Do not fear to be eccentric in opinion, for every opinion now accepted was once eccentric.

- Bertrand Russell

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Innovative synthesis of phosphonylated azaheterocycles and benzo[*c*]thiophenes

Thesis submitted in fulfillment of the requirements for the degree of Doctor (PhD) of Applied Biological Sciences: Chemistry and Bioprocess Technology

Dutch translation of the title:

Innovatieve synthese van gefosfonyleerde azaheterocyclische verbindingen en benzo[*c*]thiofenen

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Woord vooraf

Onder lichte tijdsdruk en niet bepaald voorbereid of boordevol inspiratie ben ik beginnen schrijven aan dit woord vooraf, voor vele lezers het enige relevante onderdeel van dit werk en voor zo mogelijk nog meer lezers het enige écht interessante onderdeel, al hoop ik dat ik sommigen onder jullie kan verleiden om verder ook eens een kijkje te nemen. Ik heb mijn best gedaan.

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Wouter Debrouwer

Mei 2015

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List of abbreviations

Ad	adamantyl
AMP	adenosine monophosphate
APCI	atmospheric pressure chemical ionization
APT	attached proton test
aq.	aqueous
Ar	aryl
ATP	adenosine triphosphate
ATR	attenuated total reflectance
bmim	1-butyl-3-methylimidazolium
BHT	2,6-di-*t*-butyl-4-methylphenol
Boc	*t*-butyloxycarbonyl
bp	boiling point
BINOL	1,1'-bi-2-naphthol
BPA	BINOL phosphoric acid
Bpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl
BrettPhos	2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
CAAC	cyclic (alkyl)(amino) carbene
calcd	calculated
Cbz	carboxybenzyl
CCD	charge-coupled device
CCDC	Cambridge crystallographic data centre

CLP	Classification, Labelling and Packaging regulations
COSY	correlation spectroscopy
Cy	cyclohexyl
dB	decibel
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DME	1,2-dimethoxyethane, glyme
DMF	*N*,*N*-dimethyl formamide
DMP	dimethyl phosphite
DMPTMS	dimethyl trimethylsilyl phosphite
DPAP	3,5-diphosphono-1-aminoalkylphosphonate
DNA	deoxyribonucleic acid
DPP	diphenyl phosphate
dppm	1,1-bis(diphenylphosphino)methane
dr	diastereomeric ratio
E	elimination
ECE	endothelin converting enzyme
ee	enantiomeric excess
er	enantiomeric ratio
ESI	electrospray ionization
GABA	γ-aminobutyric acid

GC	gas chromatography
GHS	Globally Harmonized System of Classification and Labeling of Chemicals
H2BC	heteronuclear 2-bond correlation spectroscopy
HATRC	heteroatom transfer radical cyclization
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple-bond correlation spectroscopy
HPLC	high-performance liquid chromatography
HOESY	heteronuclear Overhauser effect spectroscopy
HOMO	highest occupied molecular orbital
HSQC	heteronuclear single-quantum correlation spectroscopy
IAd	1,3-bis(1-adamantyl)imidazol-2-ylidene
iGluR	ionotropic glutamate receptor
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared
JohnPhos	(2-biphenyl)di-*t*-butylphosphane
kt	kamertemperatuur
LC-MS	Liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide, lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
mGluR	metabotropic glutamate receptor

MPM	(*para*-methoxyphenyl)methyl
MS	mass spectrometry *or* molecular sieves
Ms	methanesulfonyl
MSDS	material safety data sheet
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIR	near infrared
nd	not determined
NMDA	*N*-methyl D-aspartate
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	2-nitrobenzenesulfonyl
OLED	organic light-emitting diode
on	overnight (*ca.* 16 h)
OPV	organic photovoltaics
PAP	3-phosphono-1-aminoalkylphosphonate
PEP	phosphoenolpyruvate
Phth	phthaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
pmp	phosphonomethylphenylalanine

PMDTA	*N*,*N*,*N'*,*N'*,*N"*-pentamethyldiethylenetriamine
ppb	parts per billion
ppm	parts per million
PTPase	protein tyrosine phosphatase
p-TsOH	*para*-toluenesulfonic acid
RCM	ring-closing metathesis
RNA	ribonucleic acid
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
rt	room temperature
T	temperature
t	time
TAP	trialkyl phosphite
TBS	*t*-butyldimethylsilyl
*t*BuXPhos	2-di-*t*-butylphosphino-2',4',6'-triisopropylbiphenyl
TEP	triethyl phosphite
THF	tetrahydrofuran
tht	tetrahydrothiophene
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl *or* tetramethylsilane

TMSE	2-(trimethylsilyl)ethyl
TOF	time-of-flight
Tos	*para*-toluenesulfonyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
UV-VIS	ultraviolet-visible
VWD	variable wavelength detector
XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

I. Introduction and goals

Phosphorus in the form of inorganic phosphate, PO_4^{3-}, is necessary for all living beings. As such, it is incorporated in diverse structural organic and inorganic components that make up cells, organisms and entire life-forms. Adult human beings contain on average 700 g of phosphorus of which 90% is present in bones and teeth as apatite. The rest is located in tissues and extracellular fluids.[1]

Transformations that rely on the formation or cleavage of a P-O bond are omnipresent in nature.[2-3] The phosphate fraction that is not bound in bone and teeth plays a role in major biological systems and functions: DNA and RNA that contain genetic information are both phosphate esters, ATP is an important energy carrier, phosphoenolpyruvate (PEP) is a metabolic intermediate involved in glycolysis, inositol phosphates are responsible for cellular signaling, *etc.*[4-7]

Phosphonates are analogous to phosphates but one P-O single bond has been substituted by a P-C single bond. Contrary to phosphates, phosphonates are much less ubiquitous in living organisms. Nevertheless, a number of naturally occurring phosphonates have been identified and some display exquisite biological properties. Ciliatine **1** was the first phosphonate isolated from living beings: it was discovered in 1959 during an investigation on the aminoacid composition of rumen protozoa (Figure 1).[8] Later in the 20th century, fosfomycin **2** was discovered in *Streptomyces sp.* and is nowadays used as a broad-spectrum antibiotic in urinary tract infections.[9-10] Fosmidomycin **3**, a phosphonate with antimalarial activity, was also isolated from *Steptomyces* microorganisms.[11]

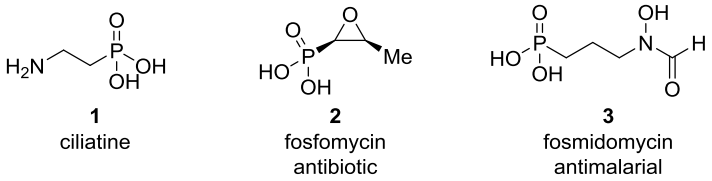
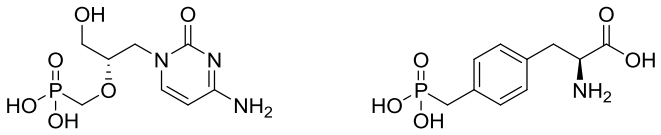


Figure 1. Naturally occurring phosphonates.

The presence of a P-C single bond in phosphonates has a dramatic influence on their reactivity. Where phosphates are prone to hydrolysis, phosphonate hydrolysis would require the breaking of a P-C bond and concomitant expulsion of a carbanion. Needless to state that this is not a favored process so as a consequence, phosphonates are more stable towards hydrolysis than phosphates.[12-13]

The large structural resemblance of phosphonates to phosphates is responsible for their biological activity.[14] Accordingly, nucleoside phosphonates have found application as antiviral drugs,[15] *e.g.* cidofovir **4**, a compound that inhibits viral DNA polymerase (Figure 2).[16-17]

Phosphonomethylphenylalanine **5** (pmp) is the phosphonate analog of phosphotyrosine, an important intermediate in signal transduction and regulation of enzymatic activity. Its non-hydrolyzable nature however is responsible for the inhibition of protein tyrosine phosphatases (PTPases).[18-19]

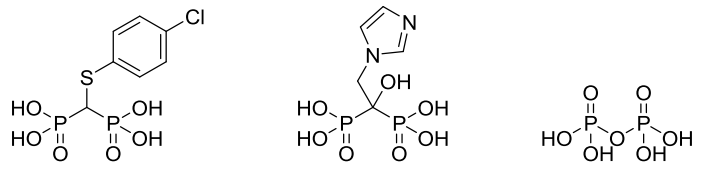


4
cidofovir
antiviral

5
pmp

Figure 2. Cidofovir and pmp.

Bisphosphonates are of importance in the treatment of osteoporosis, Paget's disease and tumor bone disease (Figure 3). These compounds are analogs of pyrophosphate **8** and hence, inhibit enzymes that employ pyrophosphate. In contrast to pyrophosphate, the P-C-P bond in bisphosphonates is hydrolytically stable. Due to their double negative charge at physiological pH, bisphosphonates display a strong affinity for Ca^{2+} ions. Thus, they accumulate in bone tissue where they can exert their activity.[20-21]



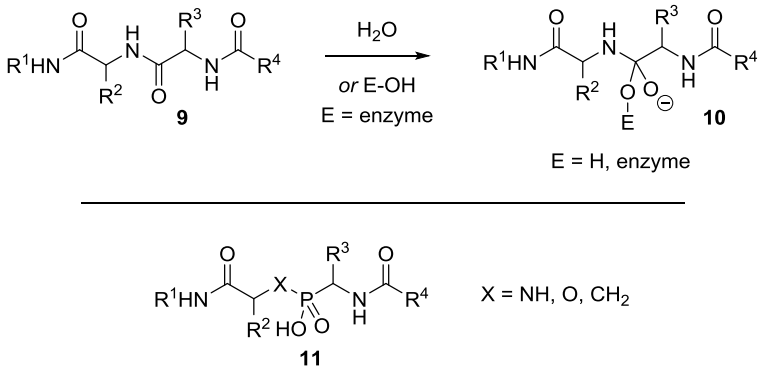
6
tiludronic acid
Skelid (Sanofi-Aventis)
Paget's disease

7
zoledronic acid
Zometa (Novartis)
osteoporosis

8
pyrophosphoric acid

Figure 3. Bisphosphonate drugs tiludronic acid and zoledronic acid, and pyrophosphoric acid.

Furthermore, phosphonates are known as bioisosteres of carboxylic acid derivatives. Indeed, they are different in shape (tetrahedral *vs*. planar), acidity (phosphoric acid is more acidic) and steric bulk (difference in atomic radii). Nevertheless, aminophosphonates **11** (X = O) are structural mimics of the transition state of amino acids during hydrolysis (Scheme 1).[18]



Scheme 1. Regular and enzymatic hydrolysis of a peptide, along with phosphonate-based transition state analogs.

The formation of a high-energy transition state **10** is usually followed by cleavage of a peptide bond. However, upon addition of phosphonates that resemble this transition state the active site of the enzyme is blocked and inhibition prevails. This approach has been most successful in the case of metalloproteases as the presence of a coordinating phosphonate moiety in the active site of the enzyme induces strong complexation with active site metals. In this light, serine proteases can become covalently phosphonylated due to attack of a serine residue onto a diphenylphosphonate and concomitant expulsion of phenol.[18, 22]

For instance, aptly substituted phosphonates inhibit HIV protease (Figure 4, **12**),[23-24] renin (**13**),[25] PTPases[26-27] and can be used in molecular imprinting.[28] Moreover, alafosfalin **14** is an antibacterial compound that contains two stereogenic centers and is easily taken up in the cell. In the cytoplasm, hydrolysis takes place and the resulting phosphonoalanine inhibits alanine racemase, an enzyme that is required for bacterial cell wall synthesis. Only one stereoisomer of alafosfalin is active.[29-30] A well-known biologically active phosphonate is glyphosate **15**, better known as Roundup. It was brought on the market by Monsanto in 1970 and is a post-emergence broad-spectrum herbicide that inhibits 5-enolpyruvoylshikimate 3-phosphate synthase, an enzyme that is responsible for the synthesis of aromatic amino acids.[13, 31] Recently, glyphosate has been reported to cause non-Hodgkin lymphoma and was classified as “probably carcinogenic to humans” (2A).[32]

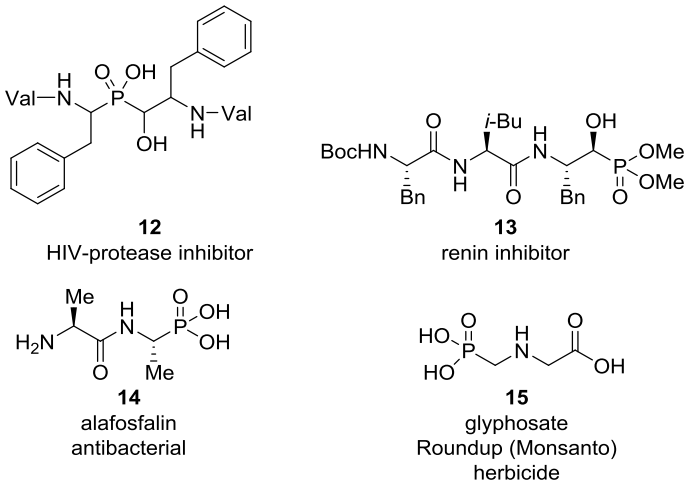


Figure 4. Inhibitors of HIV-protease and renin, alafosfalin and glyphosate.

Glutamate **16** is the main neurotransmitter in the central nervous system and operates through two main classes of receptors: ionotropic and metabotropic Glu receptors (iGluRs and mGluRs, respectively). Phosphonate analogs of glutamate are of interest for the characterization of different Glu receptor subtypes and for the treatment of central nervous system diseases such as epilepsy, Huntington's disease, Parkinson's disease, *etc.* (Figure 5). (*S*)-AP4 **17** is a group III mGluR agonist which is some tenfold more potent than Glu **16** itself. (*R*)-AP5 **18** is a potent and selective iGluR antagonist.[33-36] The cyclic (*R*)-CPP **19** is a selective and competitive *N*-methyl D-aspartate receptor (NMDA, iGluR) antagonist.[37]

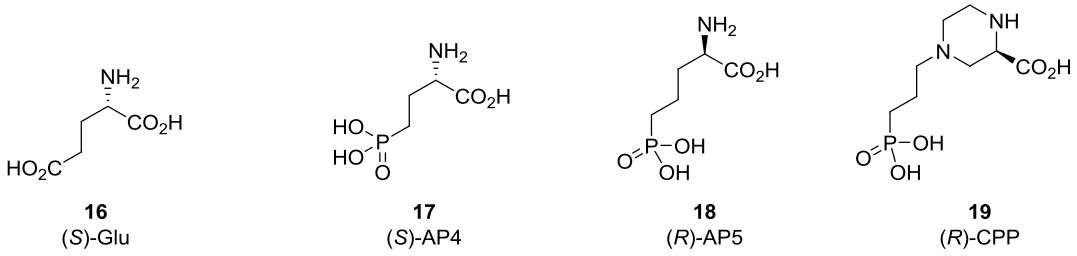


Figure 5. Glutamate and biologically active phosphonate analogs.

Cyclic aminophosphonates are conformationally restricted and as a result they have a well-defined spatial arrangement. This has for instance been exploited in the design of herbicides and endothelin converting enzyme (ECE) inhibitors (Figure 6).[38-39]

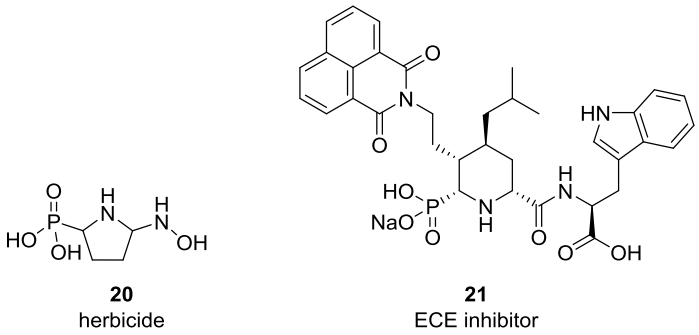
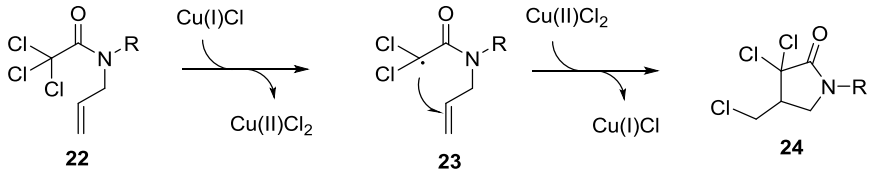


Figure 6. Biologically relevant cyclic aminophosphonates.

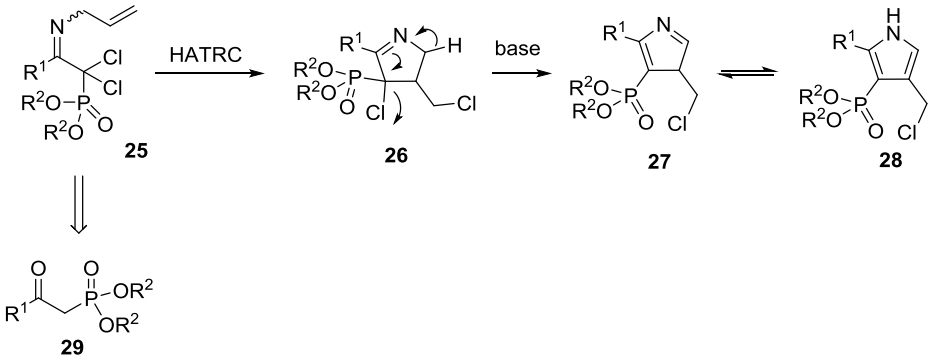
At the SynBioC Research Group of the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering at Ghent University, the interest in azaheterocyclic phosphonates has resulted in an array of novel phosphonylated compounds, for instance aziridines,[40-41] pyrrolidines,[42] 2-phosphonopyrroles,[43-44] benzazepines,[45] benzazocines,[46] tricyclic aminophosphonates,[47] oxazolidinones and imidazolidinones,[48] β-lactams,[49-51] γ-lactams,[52] benzocarbacephems,[53] tetrahydroquinolines[54] and isoindoles.[55]

Furthermore, the Heteroatom Transfer Radical Cyclization (HATRC) methodology has been applied on several occasions for the construction of pyrrolidinones,[56] pyrrolinones[57] and spiro-indoles.[58-59] In this approach, trichloroacetamides **22** with a pending alkene undergo a radical ring closure in the presence of Cu(I)Cl via abstraction of a Cl radical and recombination (Scheme 2).[60]



Scheme 2. Principle of Cu(I)-catalyzed HATRC.

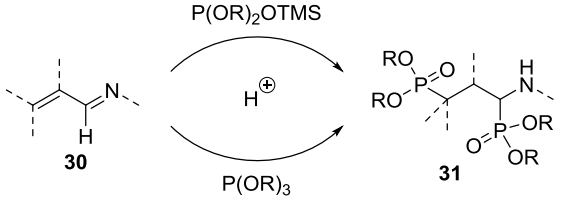
In this light the HATRC-mediated synthesis of 3-phosphonylated pyrroles was envisioned. This class of compounds has been prepared on several occasions in literature but never using the HATRC strategy.[61-65] Instead of trichloroacetamides **22**, *N*-allyl α,α-dichloroimines **25** would undergo a radical ring closure and yield 1-pyrrolines **26** (Scheme 3). Upon treatment with base, a 1,4-dehydrochlorination would take place with formation of 3*H*-pyrrole **27** which would readily isomerize and furnish the corresponding 1*H*-pyrrole **28**.[41, 66] The substrate for the ring closure could be accessed from **29** via imination and α,α-dichlorination using *N*-chlorosuccinimide (NCS).



Scheme 3. Retrosynthetic approach to phosphonylated pyrroles using HATRC.

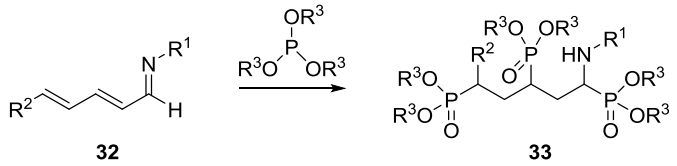
The influence of the steric and electronic nature of R^1 on the HATRC and the dehydrohalogenation will be investigated. Several bases will be evaluated for the elimination reaction to ensure optimal conditions. In this approach phosphonylated precursors will be cyclized and further derivatized in order to obtain phosphonylated azaheterocycles.

A second part of this work will focus on the addition of phosphorus nucleophiles to imine Michael acceptors. This methodology has been elaborated at the department over the past 10 years. It has been shown that α,β-unsaturated imines **30** react with dialkyl trimethylsilyl phosphites and trialkyl phosphites in a tandem fashion: a double 1,4-1,2-addition takes place with formation of 3-phosphonylated 1-aminoalkylphosphonates **31** (PAPs, Scheme 4). This method has been applied to imines,[67-68] hydrazones,[69] quinolines[54] and phenanthrolines.[70]



Scheme 4. Tandem 1,4-1,2-addition to α,β-unsaturated imines.

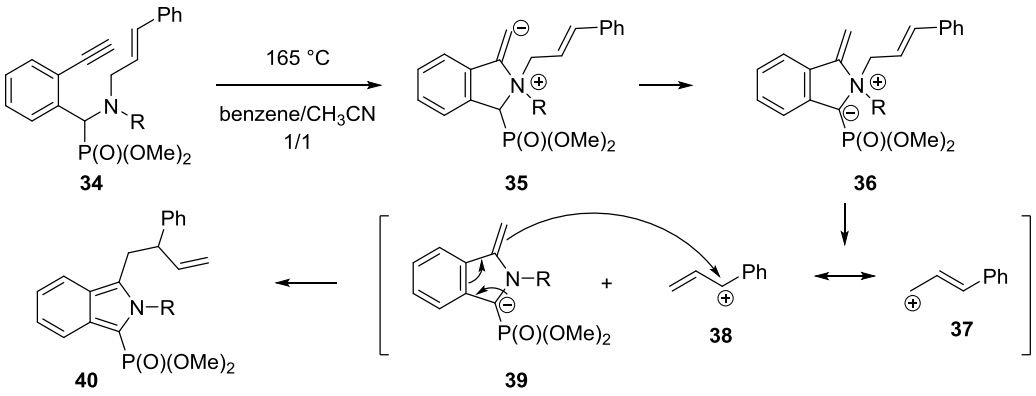
The current goal is to extend this methodology to α,β,γ,δ-diunsaturated imines **32** to try and obtain a triple 1,6-1,4-1,2-addition. This would give rise to 3,5-diphosphonylated 1-aminoalkylphosphonates **33** (DPAPs, Scheme 5). The effect of the steric and electronic nature of R^1 and R^2 will be evaluated by generating a library of these compounds. Furthermore, both silylated dialkyl phosphites as well as trialkyl phosphites will be assessed as nucleophiles.



Scheme 5. Envisioned triple addition of phosphorus nucleophiles to α,β,γ,δ-diunsaturated imines.

Once these compounds have been produced, they could be converted into their corresponding phosphonylated β-lactams.[49-50] *N*-Acylation using chloroacetyl chloride followed by deprotonation between the amine and phosphonate functional groups could result in substitution and concomitant ring closure. These β-lactams are of interest as potential antibiotics.[71]

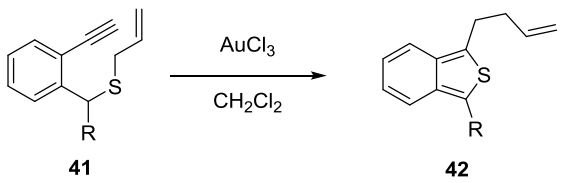
In a third part of this thesis the Au-catalyzed preparation of benzo[*c*]thiophenes will be evaluated. This project has its roots in the serendipitous preparation of phosphonylated isoindoles **40**, earlier at the department. In the course of previous research on enyne metathesis the synthesis of phosphonylated benzazepines was envisaged. However, no enyne metathesis of **34** took place but after a prolonged period at reflux temperature, a trace amount of phosphonylated isoindole **40** was formed. Optimization and mechanistic investigations revealed that a 5-*exo-dig* cyclization to **35** had taken place and was followed by immediate proton transfer and a fragmentative allyl shift at high temperature (Scheme 6).[55]



Scheme 6. Thermally induced 5-*exo-dig* cyclization and formal [1,3]-alkyl shift.

Next, it was discovered that this transformation proceeds smoothly at room temperature under $AuCl_3$-catalysis. In this case however no fragmentation takes place. Instead, a Claisen rearrangement is responsible for the molecular reorganization. This approach was further extended to cyanoisoindoles and dihydrothiazoles.[72-73] Based on this research, a Au-catalyzed preparation of benzo[*c*]thiophenes **42** is proposed (Scheme 7). Initial 5-*exo-dig* ring closure, catalyzed by $AuCl_3$, would be followed by Claisen rearrangement and aromatization. The combination of Au-catalysis

with *S*-nucleophiles is not very common, as witnessed by the literature overview of this work (*vide infra*).



Scheme 7. Proposed Au-catalyzed route to benzo[*c*]thiophenes.

These compounds are of interest mainly due to their physical properties: they could be used in organic photovoltaic systems (OPV).[74]

II. Literature overview

Homogeneous Au-catalyzed cyclization reactions of alkynes with *N*- and *S*-nucleophiles

As outlined in the Introduction and Goals, this work is a hybrid between phosphonate chemistry and heterocyclic frameworks. However, one common trait is the intention to construct cyclic molecules. Therefore, this literature overview will focus on a specific cyclization method: homogeneous Au-catalyzed cyclizations with *N*- and *S*-nucleophiles on alkynes.

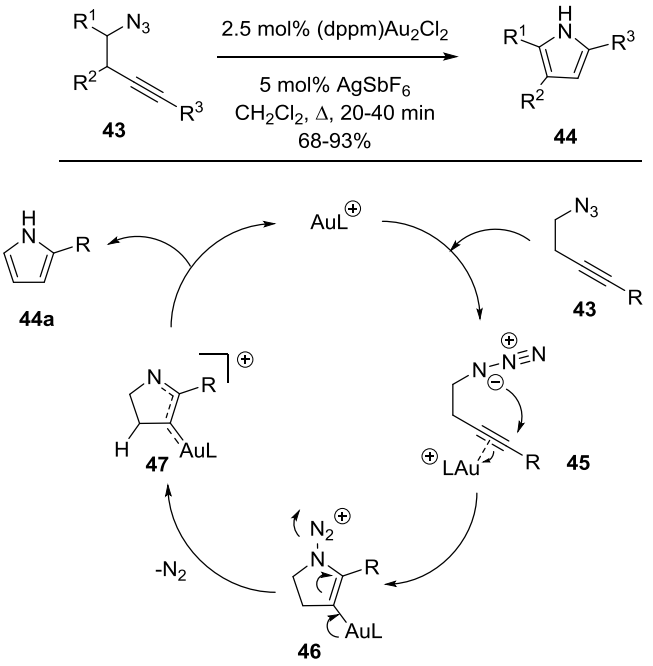
1. Homogeneous Au-catalyzed intramolecular attack of *N*-nucleophiles on alkynes

1.1 Formation of 5-membered rings

1.1.1 5-endo-dig cyclization

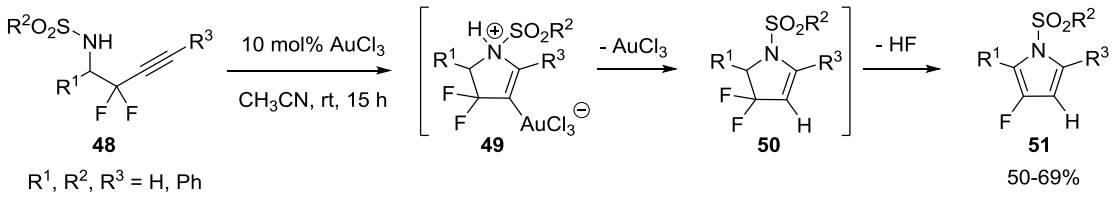
1.1.1.1 Pyrroles

In 2005 Toste and co-workers discovered an intramolecular Au(I)-catalyzed acetylenic Schmidt reaction with formation of pyrroles **44** (Scheme 8). Initial alkyne activation by the catalyst results in formation of a five-membered ring after attack of the proximal *N*-atom of the azide. Back-bonding from the metal into the electron-deficient intermediate **46** expels nitrogen gas and yields a cationic intermediate **47**, which is stabilized by electron donation from gold. The catalyst is regenerated by a formal 1,2-*H*-shift with concomitant release of a 2*H*-pyrrole, which is swiftly transformed into the desired pyrrole **44a**. Replacement of the migrating H-atom by another migrating group allowed for the synthesis of annulated pyrroles from cyclobutylmethyl azides. Heteroatoms could also act as migrating group, *e.g.* silyl ethers.[75-76] Xia and Huang performed a DFT study to investigate the operative mechanism in detail. They concluded that intermolecular proton transfer in the final tautomerization between the 2*H*- and 1*H*-pyrrole is the rate-determinig step of the overall process.[77]



Scheme 8. Au(I)-catalyzed formation of pyrroles from homopropargylic azides by an acetylenic Schmidt-reaction.

The De Kimpe group reported on the $AuCl_3$-catalyzed preparation of fluorinated pyrroles from homopropargylic amines **48** (Scheme 9). Initial Au-mediated ring closure to **49** was followed by protodeauration and furnished difluorinated 2-pyrrolines **50**. After dehydrofluorination the desired monofluorinated pyrroles **51** were obtained. Instead of using a Au-catalyst, treatment with $AgNO_3$ or bases did not result in pyrroles **51**. The sulfonyl group could be removed with the aid of a large excess of NaOH in ethanol.[78] Li and co-workers used a similar approach to produce 2,4-disubstituted pyrroles.[79]

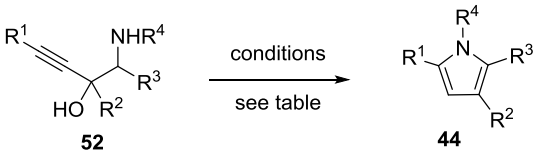


Scheme 9. $AuCl_3$-catalyzed preparation of fluorinated pyrroles.

Somewhat later, two groups simultaneously published their pyrrole syntheses starting from 2-hydroxy homopropargylic amines **52**. The Aponick group employed 2 mol% JohnPhosAuCl as a catalyst in THF whereas the Akai group applied loadings as low as 0.1 mol% of PPh_3AuCl in toluene, both in combination with AgOTf in order to generate a cationic Au(I)-catalyst (Table 1). Both transformations were very efficient with yields up to 92 and 96%, respectively. Similar to the

previous method for fluorinated pyrroles **51**, Au-catalyzed 5-*endo*-*dig* cyclization is followed by dehydration and yields pyrroles **44**. Aponick's method could be performed in an open flask, though care had to be taken to avoid water when using very low catalyst loadings.[80-81]

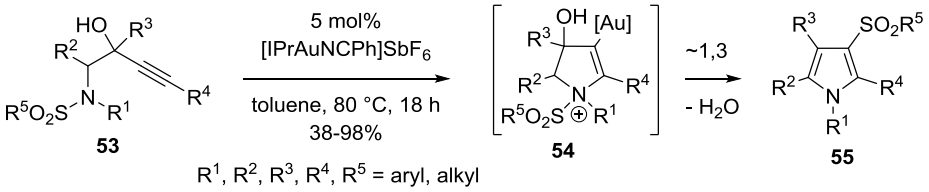
Table 1. Comparison of Aponick's and Akai's results for pyrrole synthesis from homopropargylic amines.



52 **44**

author	catalyst	conditions	R^1	R^2	R^3	R^4	yield (%)
Aponick	JohnPhosAuCl, AgOTf (2 mol%)	THF, 4Å MS, 0 °C, 10 min - 1 h	Ph	H	H	Ts	89
			Octyl	H	H	Ts	91
			Ph	H	H	Bu	91
			Ph	H	H	Bn	92
Akai	PPh_3AuCl, AgOTf (0.1 mol%)	toluene, rt, 1-9 h	$(CH_2)_2Ph$	Me	H	Boc	96
	PPh_3AuCl, AgOTf (0.5 mol%)		*t*-Bu	H	Bn	Boc	88
	PPh_3AuCl, AgOTf (0.1 mol%)		H	Me	H	Ts	92

In 2011 the Chan group discovered a domino aminocyclization/1,3-sulfonyl migration of *N*-sulfonyl aminobutynols **53**, which they further elaborated in 2013 (Scheme 10).[82] Au-assisted cyclization toward **54** is followed by dehydration and 1,3-sulfonyl migration, or the other way around. A cross-over experiment demonstrated that the migration proceeds intramolecularly. This was further witnessed by the lack of reaction of a 3-unsubstituted pyrrole (no SO_2R^5) with TsCl in the presence of the same catalyst.[83]

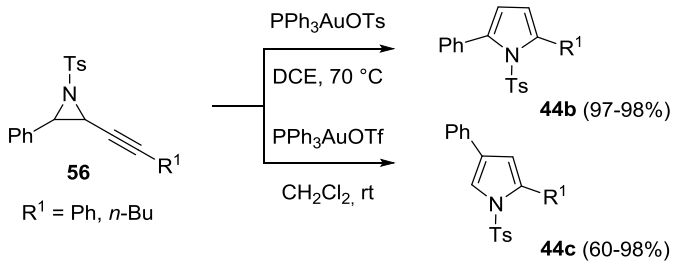


53 **54** **55**

Scheme 10. Domino aminocyclization/1,3-sulfonyl migration yielding pyrroles.

Davies and Hou also simultaneously reported their findings on the synthesis of pyrroles **44** from alkynylaziridines **56**, based on seminal work by Hashmi regarding furan synthesis (Scheme 11).[84] Davies found that the outcome of this transformation is largely dependent on the reaction

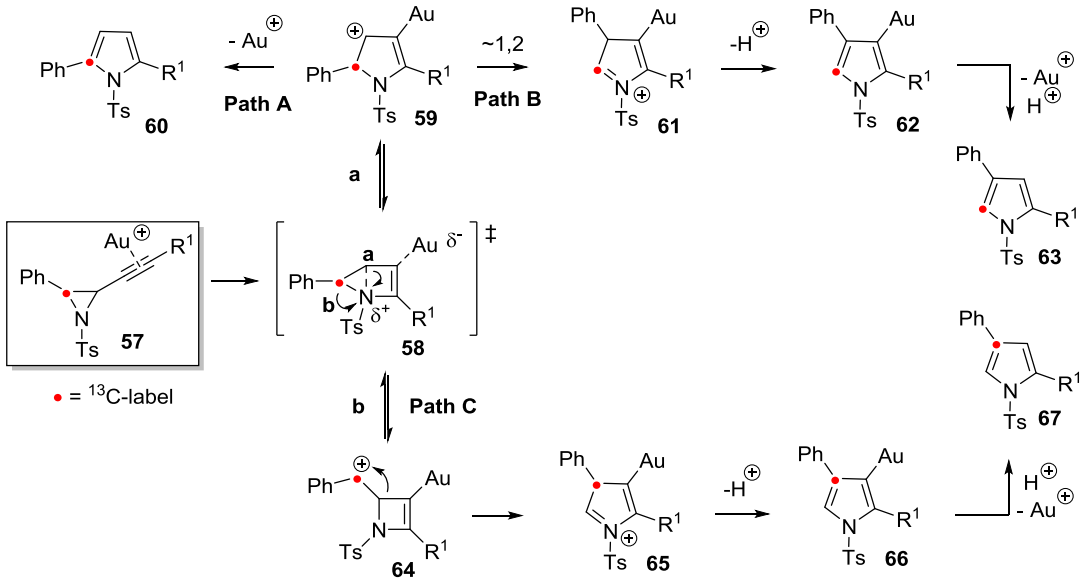
conditions. More precisely, the nature of the counterion of the Au(I) complex as well as the solvent exert a large influence. Protic or aromatic solvents give rise to 2,5-disubstituted pyrroles **44b** exclusively, while for 1,2-dichloroethane (DCE) and dichloromethane the counterion plays a large role. The weakly coordinating tosylate promotes 2,5-disubstitution while the non-coordinating triflate results in 2,4-disubstitution (**44c**).[85] Hou, on the other hand, only obtained 2,5-disubstituted pyrroles **44b** in 59-95% yields under their optimized conditions, *i.e.* $PPh_3AuCl/AgOTf$ in a 5/1 THF/MeOH mixture.[86] Liu and co-workers obtained similar results, while Liang produced spirotetrahydro-β-carbolines from aptly substituted alkynylaziridines.[87-88]



Scheme 11. Formation of 2,5- or 2,4-substituted pyrroles depending on the counterion according to Davies.

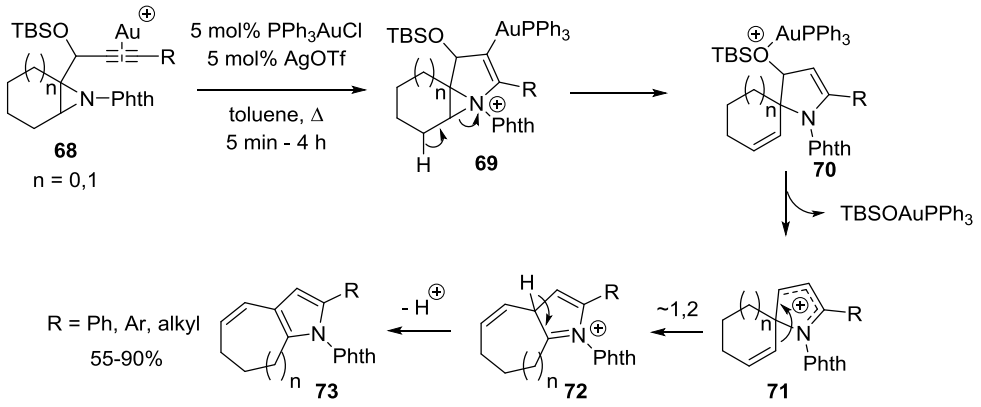
In a following paper, Davies performed an in-depth study using ^{13}C-labeling to elucidate the operative mechanism and explain the observed dichotomy (Scheme 12). Initial 4-*endo-dig* cyclization of alkynylaziridine **57** leads to a transition state **58**. This product can ring-open in two ways (**a** or **b**). When a 5-membered ring is formed (**59**) there are two possibilities: either elimination of a proton and protodeauration result in isotopomer **60** (**Path A**), or a 1,2-aryl shift takes place which ultimately leads to isotopomer **63** (**Path B**). On the other hand formation of a 4-membered ring with a benzylic cation **64** will induce a Wagner-Meerwein shift with formation of cation **65**, which eventually results in isotopomer **67** (**Path C**).[89]

Which path operates under which conditions can be predicted to a certain extent. If R^1 is an alkyl group, products from both **Path B** and **Path C** are observed, while if R^1 is a phenyl group, **Path B** is favored due to the greater mesomeric stabilization of intermediate **59**. There is an electronic effect in operation as well with regard to substitution of the phenyl group directly attached to the aziridine. Electron-rich phenyl groups will favor formation of benzylic cation **64** and 1,2-migration (**Path C** and **B**, respectively). Conversely, electron-poor phenyl moieties will favor **Path A**.[89]



Scheme 12. ^{13}C-labeling experiment to elucidate the mechanisms behind pyrrole formation.

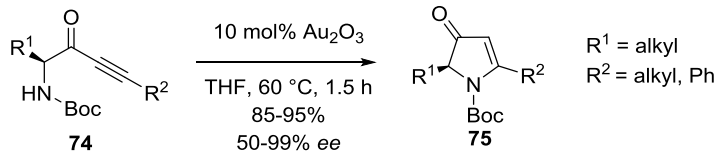
Tu and co-workers elegantly adapted Davies' method for the synthesis of cycloalkane fused pyrroles **73** (Scheme 13). After 5-*endo-dig* cyclization, the aziridinium moiety in **69** is opened with concomitant protodeauration. Elimination of the OTBS-group, assisted by the Au-catalyst, is followed by Wagner-Meerwein rearrangement and aromatization. Electron-rich and electron-poor phenyl groups are tolerated for R, as well as thiophenyl, naphthyl, alkyl and cycloalkyl moieties.[90]



Scheme 13. Preparation of fused pyrroles starting from propargylic aziridines.

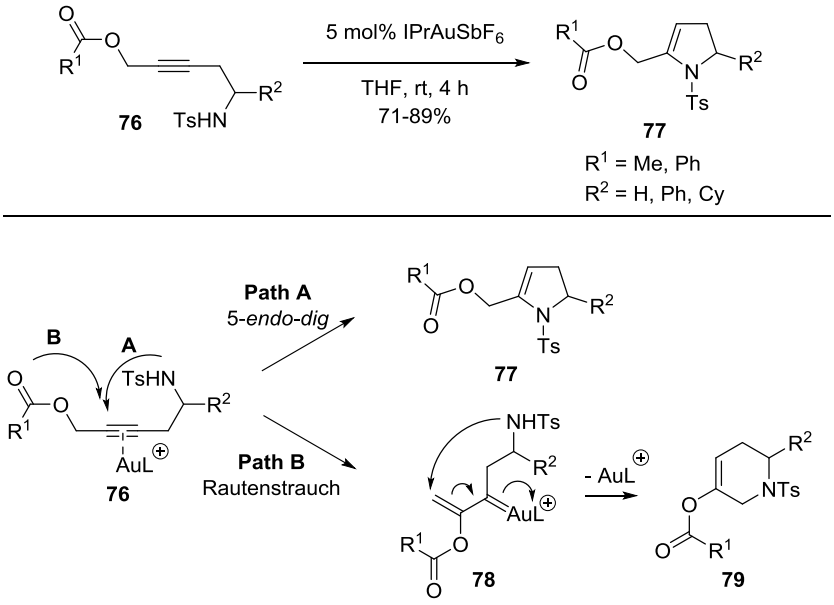
1.1.1.2 Pyrrolines

Gouault obtained substituted pyrrolin-4-ones **75** from alkynones **74** that were derived from amino acids (Scheme 14). A catalyst screening indicated that AuCl was the most efficient catalyst for the cyclization but engendered complete epimerization of the stereocenter, most likely due to a trace of HCl from the catalyst. Upon addition of K_2CO_3 or 2,6-di-*t*-butylpyridine the *ee* augmented but the best overall results were obtained with Au_2O_3 and $Au(OH)_3$.[91]



Scheme 14. Formation of pyrrolinones with retention of stereochemistry.

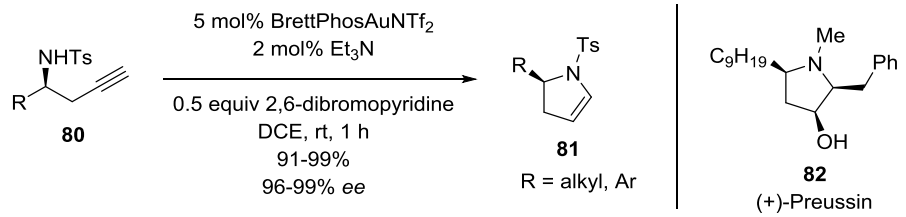
Propargylic esters **76** can undergo two types of reactions in the presence of cationic Au(I)-catalysts (Scheme 15). Either a direct 5-*endo-dig* cyclization takes place yielding pyrrolines **77**, or a stepwise Rautenstrauch rearrangement and cyclization eventually results in dehydropiperidines **79**. The Rautenstrauch rearrangement consists of 1,2-acyloxy migration with formation of a Au-carbene **78**.[92] This carbene is α,β-unsaturated and operates as a Michael-acceptor, which accounts for dehydropiperidine formation. The product ratio **77/79** was found to be strongly dependent on the applied ligand, counterion and solvent. A thorough investigation on the factors influencing product distribution was performed: the nature of the sulfonamide, the migrating group and propargylic substitution were taken into account.[93]



Scheme 15. Formation of 2-pyrrolines and competition between direct and stepwise product formation.

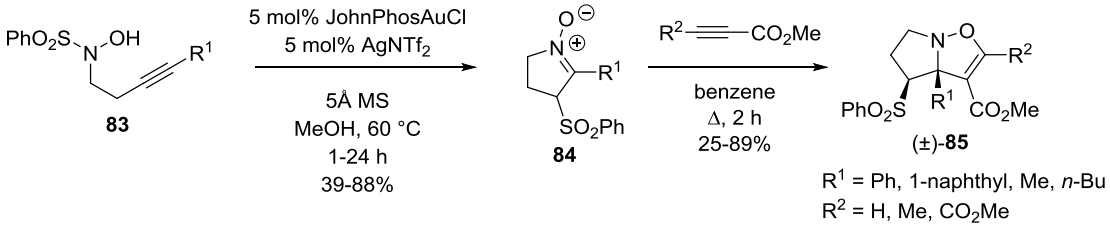
Ye and co-workers produced a library of enantioenriched dihydropyrroles **81** from chiral homopropargyl sulfonamides **80** (Scheme 16). Lack of basic additives resulted in dimerization but addition of both 2,6-dibromopyridine and a catalytic amount of Et_3N was the most efficacious method to prevent this. A ligand screening indicated that BrettPhos was most suited while the similar XPhos resulted in partial dimerization. A deuterium labeling experiment proved that the reaction proceeds through 5-*endo-dig* cyclization and not via a vinylidene intermediate. The obtained 2-

pyrrolines **81** could serve as precursors for (+)-Preussin **82**, an antifungal alkaloid.[94] Fustero employed similar substrates and obtained dimerization products using PPh_3AuCl/AgOTf as catalyst system in toluene.[95] The Hammond group developed a tandem hydroamination/cyanation approach for homopropargylic anilines. Application of 5 mol% IPrAuCl and AgOTf in dioxane under microwave irradiation gave rise to a 2-cyanopyrrolidine in the presence of TMSCN (*vide infra*, Scheme 64).[96]



Scheme 16. Formation of enantioenriched 2-pyrrolines.

Finally homopropargylic *N*-sulfonyl hydroxylamines **83** were used to generate 3-sulfonyl-1-pyrroline *N*-oxides **84** through 5-*endo*-*dig* cyclization and 1,3-sulfonyl migration (Scheme 17). The obtained nitrones reacted with dipolarophiles in a 1,3-dipolar cycloaddition to yield annulated dihydroisoxazoles **85**. The sterically demanding sulfonyl group directs the dipolarophile to the opposite face, ensuring a diastereoselective reaction. When terminal alkynes were treated with a Au(I)-catalyst, 5-*exo*-*dig* attack of the OH-group took place and was ensued by fragmentation and formation of 3-pyrrolidones.[97]

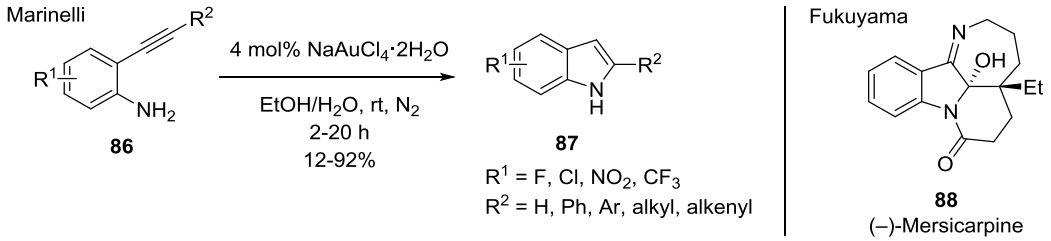


Scheme 17. Formation of 3-sulfonyl-1-pyrroline *N*-oxides and subsequent 1,3-dipolar cycloaddition.

1.1.1.3 Indoles

After pioneering work in the late 1980's by Utimoto and co-workers with regard to Pd-catalyzed hydroamination,[98] the group of Marinelli was one of the first to revisit the gold-catalyzed 5-*endo*-*dig* cyclization of 2-alkynylanilines **86** with formation of indoles **87** in 2004.[99-100] They converted a number of terminal and internal alkynes into 2-substituted indoles **87** using 4 mol% $NaAuCl_4 \cdot 2H_2O$ in an EtOH/H_2O mixture (Scheme 18). A catalyst screening indicated that Au(III) salts were more effective catalysts than Au(I), Pd(II) and Cu(II) salts.[99] This approach was employed by Fukuyama in

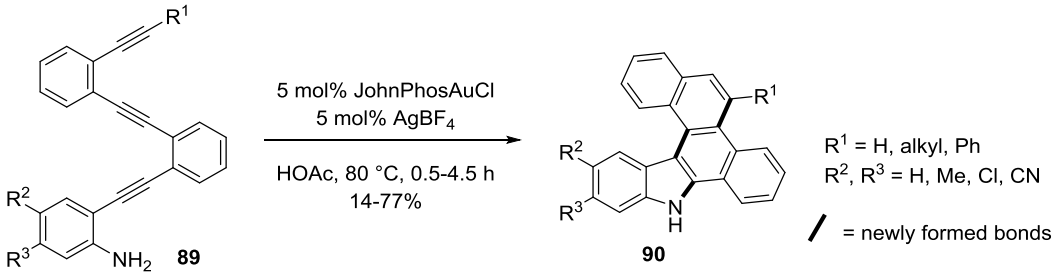
2010 in the total synthesis of (−)-Mersicarpine **88**, an alkaloid isolated from the *Kopsia* plant genus.[101] Perumal reported a one-pot cyclization and consecutive C_3-derivatization of indoles.[102-103]



Scheme 18. Au-catalyzed formation of indoles from 2-alkynylanilines.

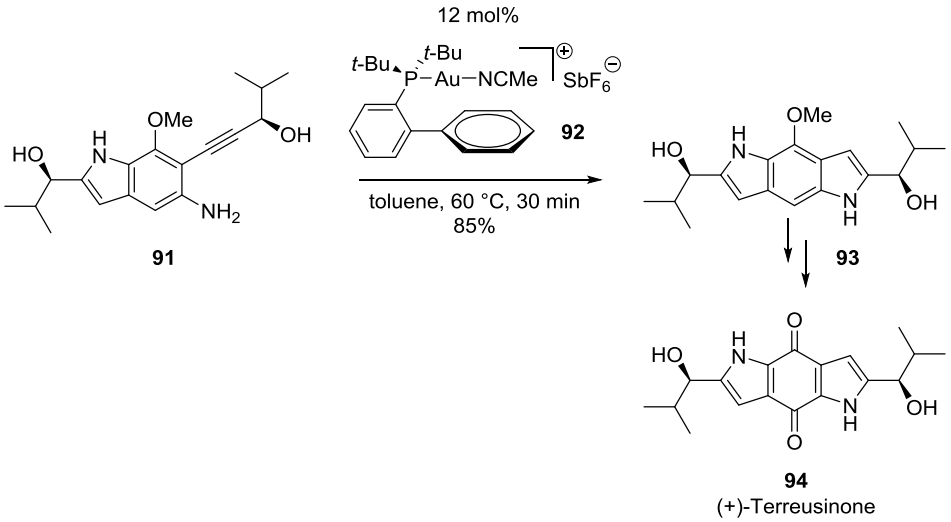
A few years later Marinelli's group reported on the identical transformation in an ionic liquid solvent system, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4). Here, application of 1 mol% $NaAuCl_4{\cdot}2H_2O$ at 50 °C for 24 h resulted in the formation of the desired indoles in 91-94% yield. The ionic liquid could be recycled up to five times along with a *n*-Bu_4NAuCl_4 catalyst without a significant loss of activity.[104]

Extension of this methodology to trienyne-containing substrates **89** led to the formation of polyaromatics such as benzo[*a*]naphtho[2,1-*c*]carbazoles **90** via a polycyclization cascade (Scheme 19). A catalyst screening had indicated that JohnPhosAuCl gave better results than XPhosAuCl and that BF_4^- was the counteranion of choice. Tetra- and pentacyclization was also possible and thiophenes could be used as tether between the alkynes to produce *S*-containing polyaromatic compounds.[105] In a similar fashion, Ohno obtained carbolines.[106]



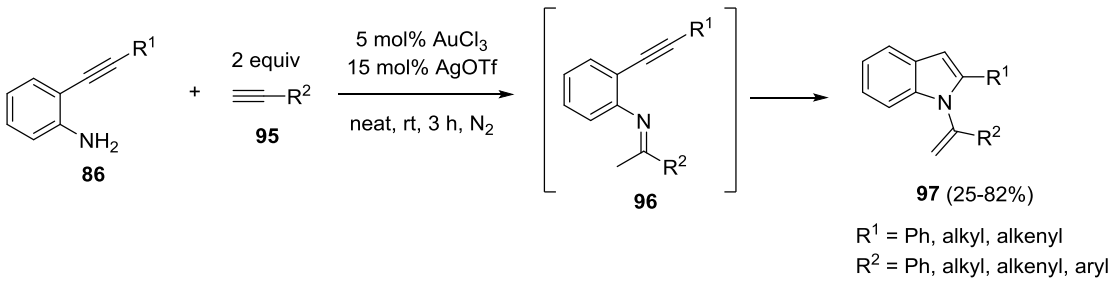
Scheme 19. Polycyclization of trienyne type anilines through hydroamination and a consecutive hydroarylation cascade.

Sperry and co-workers applied a Au(I)-catalyzed hydroamination step for the total synthesis of (+)-Terreusinone **94**, a photoprotecting dipyrrolobenzoquinone (Scheme 20). Attempted double Larock indolization failed, so a tandem Larock indolization/Au(I)-catalyzed hydroamination was employed using one of Echavarren's cationic Au-catalysts **92**.[107] A late stage oxidative demethylation furnished the desired compound.[108-109]



Scheme 20. Au(I)-catalyzed hydroamination in the total synthesis of (+)-Terreusinone.

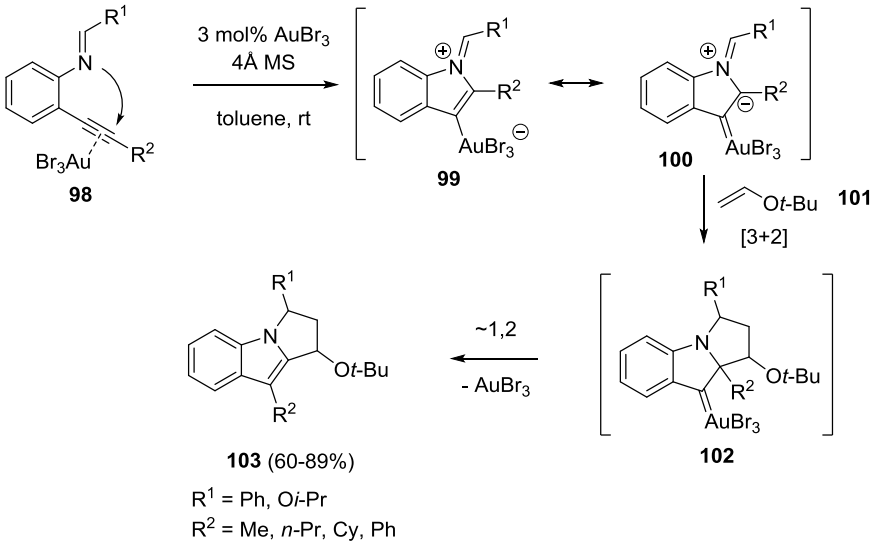
A double hydroamination reaction of *ortho*-alkynylanilines **86** with terminal alkynes **95** furnished *N*-alkenylindoles **97**, a class of compounds whose synthesis has only scarcely been described in literature. Variation of R^1 and R^2 yielded a number of *N*-vinyl indoles **97** in mediocre to excellent yields (Scheme 21).[110] The mechanism was investigated in order to establish which hydroamination reaction occurred first. Upon reaction of the corresponding *N*-unsubstituted indoles with terminal alkynes **95** in the presence of the same catalyst, no formation of *N*-vinyl indoles was detected. This suggests the intermolecular hydroamination takes place first. Imination of a suitable *ortho*-alkynylaniline with acetophenone and treatment with the same catalytic system did result in formation of the desired *N*-vinyl indoles **97**. This outcome confirmed that the intermolecular hydroamination takes place first with formation of imine **96**, and only then intramolecular hydroamination ensues.[110]



Scheme 21. Double hydroamination with formation of *N*-vinyl indoles.

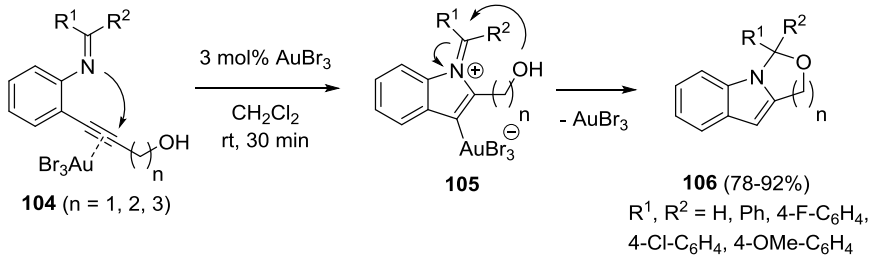
Iwasawa and co-workers transformed *N*-(*o*-alkynylphenyl)imines **98** into tricyclic indoles **103**. An azomethine ylide **100** was *in situ* generated by $AuBr_3$-mediated 5-*endo*-*dig* cyclization and carbene

formation. This 1,3-dipole then underwent a [3+2] cylcoaddition with vinyl ethers **101**, followed by 1,2-migration and regeneration of the catalyst (Scheme 22).[111]



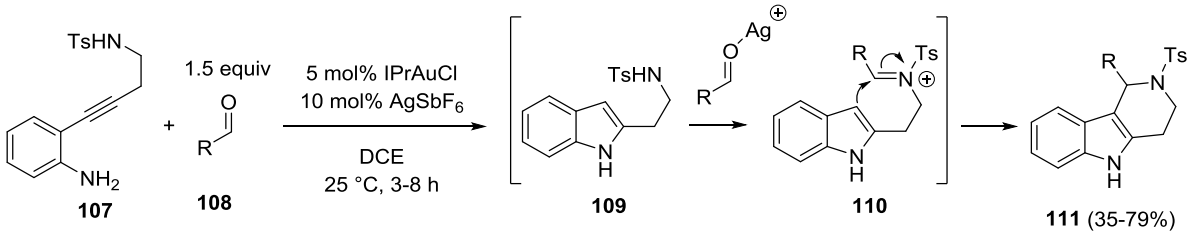
Scheme 22. Formation of tricyclic indoles from *N*-(*o*-alkynylphenyl)imines.

Similarly, Fu *et al.* employed the same substrate **104** but with a tethered nucleophile to trap the *in situ* formed iminium species **105** in a tandem reaction. This strategy gave rise to heterotricyclic indoles **106** (Scheme 23). The reaction was initiated either by 5-*endo-dig* cyclization, as depicted in Scheme 23, or by attack of the alcohol at the imine functionality.[112]



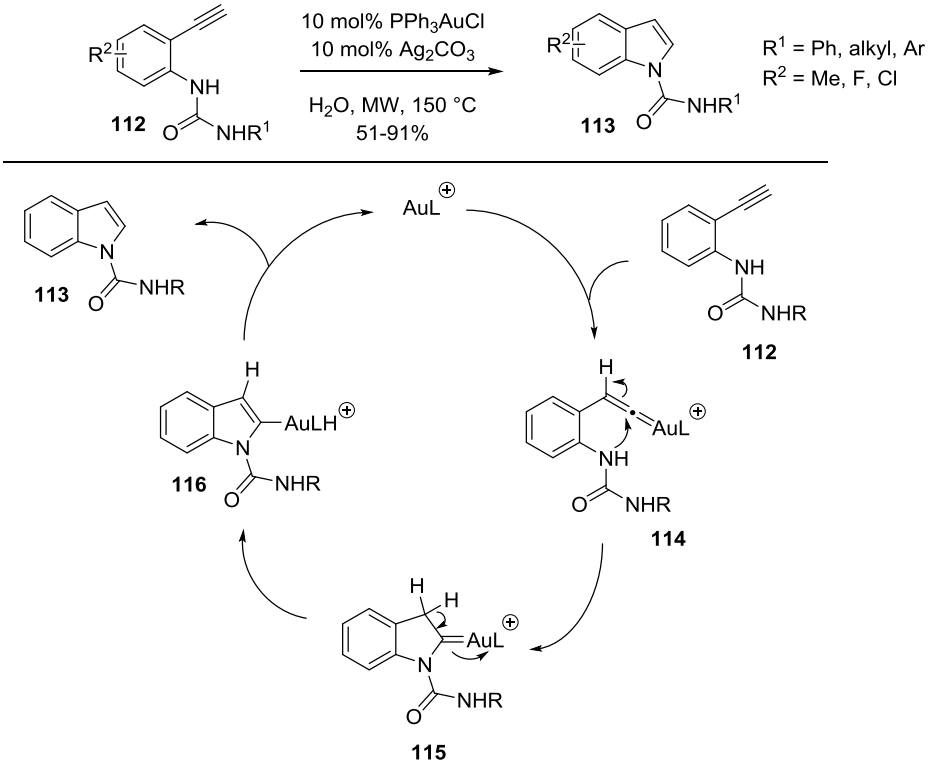
Scheme 23. Formation of ring-fused indoles.

Reddy and co-workers reported on a domino cycloisomerization/Pictet-Spengler approach for the production of tetrahydropyrido[4,3-*b*]indoles **111**. These compounds were obtained by treatment of *ortho*-alkynylanilines tethered to tosyl amides **107** with 5 mol% IPrAuCl and 10 mol% $AgSbF_6$ in the presence of benzaldehydes **108** (Scheme 24). After intramolecular 5-*endo-dig* formation of the corresponding isotryptamine **109**, the Pictet-Spengler reaction takes place and a tetrahydropyridine **111** is annulated. The authors isolated an intermediate isotryptamine **109** and treated it with $AgSbF_6$ to assess the role of its excess. The tetrahydropyrido[4,3-*b*]indole **111** was also obtained, hence concluding that the Ag-catalyst facilitates the Pictet-Spengler step.[113]



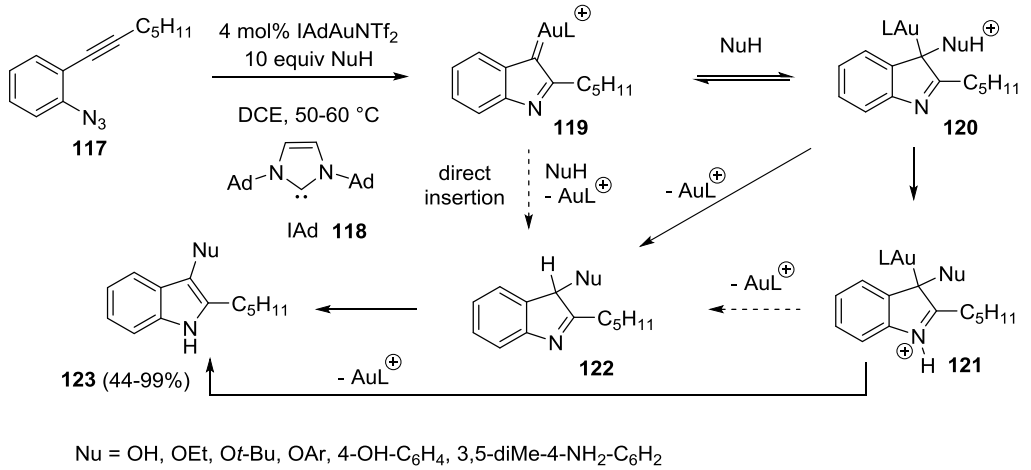
Scheme 24. Domino hydroamination/Pictet-Spengler approach to tetrahydropyrido[4,3-*b*]indoles.

In 2009 Liu reported on a Au-catalyzed green protocol for the preparation of indole-1-carboxamides **113**. The reaction was performed in water, an environmentally benign solvent, and microwave irradiation was used. This approach led to a library of indole-1-carboxamides **113** in acceptable to excellent yields (51-91%). Based on deuterium labeling experiments, a mechanism was proposed (Scheme 25). The authors suggested the intermediacy of a gold vinylidene **114**, which was then attacked intramolecularly. Tautomerization and reductive elimination yield the indole-1-carboxamide **113** and regenerate the catalyst.[114] Asensio transformed similar substrates but with internal alkynes into 2-substituted indoles using a catalytic amount of $IPrAuSbF_6$, while terminal alkynes underwent 6-*exo-dig* reaction to the corresponding pyrimidinones. They concluded that the regioselectivity was controlled by the substitution pattern of the alkyne.[115] Wu and co-workers used amidines as substrates to generate indoles.[116]



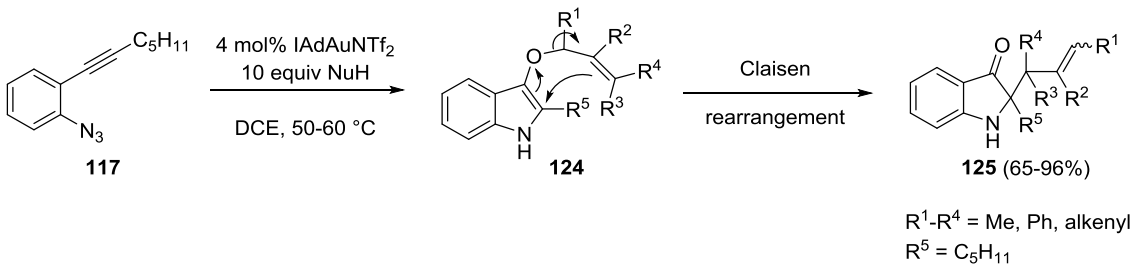
Scheme 25. Proposed mechanism for the formation of indole-1-carboxamides.

In 2011, Gagosz and Zhang simultaneously published their findings on the cyclization of 2-alkynyl arylazides **117**. In analogy to Toste's acetylenic Schmidt reaction (Scheme 8),[75] 5-*endo-dig* cyclization by the proximal *N*-atom of the azide is followed by Au-assisted expulsion of N_2-gas with formation of Au-carbene **119** (Scheme 26). Next, a number of mechanistic pathways are feasible for the nucleophilic attack. Either direct insertion takes place and **122** is formed from **119**, or the nucleophile adds to the carbene and several protodeauration mechanisms are possible. Ultimately, indole **123** is formed.[117]



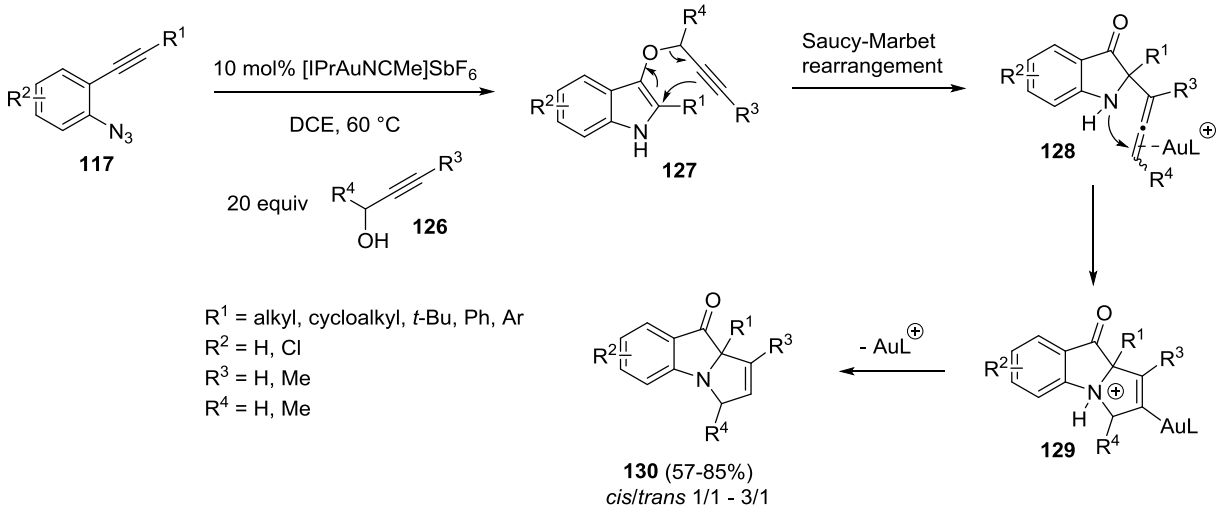
Scheme 26. Formation of indoles according to Gagosz.

When NuH is an allylic alcohol, however, the reaction does not end at **123**. A thermal or Au-mediated Claisen rearrangement takes place with formation of 3-indolinones **125** (Scheme 27).[117] Zhang's results of this indole umpolung were very similar. Upon treatment of 2-alkynyl arylazides **117** with 5 mol% $IPrAuNTf_2$ in DCE at 80 °C and 4 equivalents of nucleophile, a number of 3-substituted indoles were obtained in 49-91% yields. Use of aromatics as nucleophiles resulted in the formation of different regioisomers (*e.g. ortho* and *para* substitution). Allylalcohol also resulted in a Claisen rearrangement as depicted in Scheme 27. Installation of internal nucleophiles resulted in annulated indoles.[118]



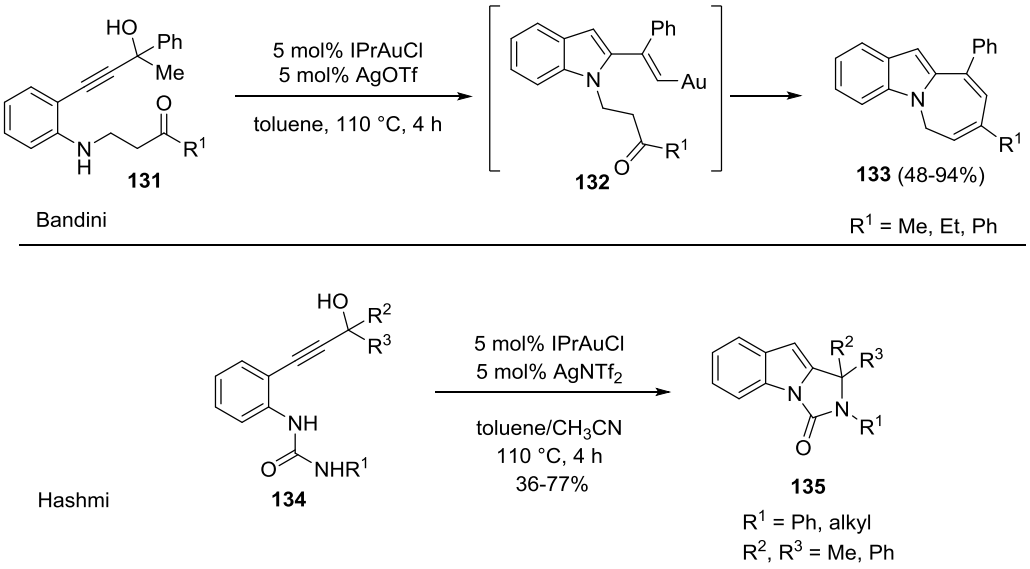
Scheme 27. Claisen rearrangement of allyloxyindoles.

In 2015 Zhang applied the same methodology to propargyl alcohols **126** instead of allyl alcohols (Scheme 28). After formal O-H insertion into the Au-carbene, **127** undergoes a thermal or Au-catalyzed Saucy-Marbet rearrangement (propargyl-Claisen rearrangement) and allene **128** is formed. The present Au-catalyst activates the allene and the indole N-H performs a 5-*endo*-*trig* cyclization. Protodeauration yields pyrroloindolones **130**.[119]



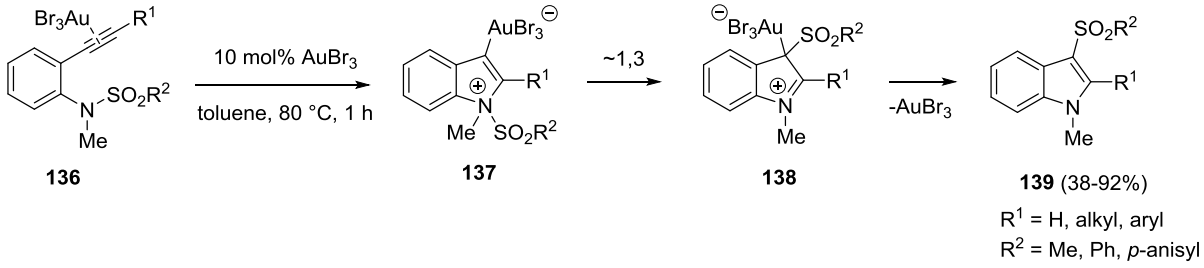
Scheme 28. Propargylation and subsequent Saucy-Marbet rearrangement.

Azepino[1,2-*a*]indoles **133** were synthesized from appropriately substituted 2-alkynylanilines **131** (Scheme 29). Initial 5-*endo*-*dig* cyclization was followed by dehydration and furnished vinylgold intermediate **132** after insertion. This nucleophilic vinylgold species **132** then added across the carbonyl function, which promoted another dehydration, 1,3-proton transfer and protodeauration.[120-121] Based on these results Hashmi and co-workers developed a method to convert ureas **134** into polycyclic indole scaffolds **135** (Scheme 29).[122]



Scheme 29. Synthesis of polycyclic indoles by Bandini and Hashmi.

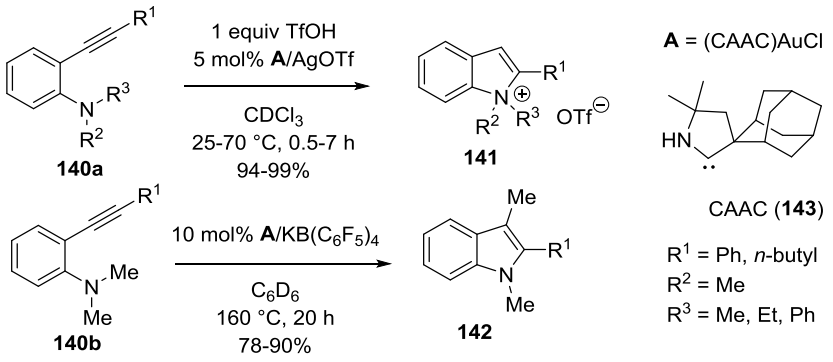
The direct preparation of 3-sulfonylindoles **139** from unsubstituted indoles by electrophilic substitution is rather challenging as the electrophilicity of a sulfonyl group is much lower than that of acyl groups and halogens.[123-124] Reaction of *ortho*-alkynylanilines **136** with a migrating group on the *N*-atom in the presence of a transition metal catalyst results in the formation of 2,3-disubstituted indoles **139**.[125-126] In this light *ortho*-alkynyl-*N*-sulfonylanilines **136** were treated with $AuBr_3$ in toluene (Scheme 30).[124, 127]



Scheme 30. Formation of 3-sulfonylindoles via $AuBr_3$-assisted aminosulfonylation.

This mechanism was supported by a crossover experiment which indicated that the migration proceeds in an intramolecular fashion. Furthermore, mixing indole with tosyl chloride and a catalytic amount of $AuBr_3$ did not result in sulfonylated indoles, suggesting that no electrophilic substitution took place. It is noteworthy that an unprecedented sulfonyl migration to the benzene ring occurred as a side reaction resulting from intramolecular 1,5- or 1,7-migration. Indium(III) bromide also catalyzed this transformation.[124]

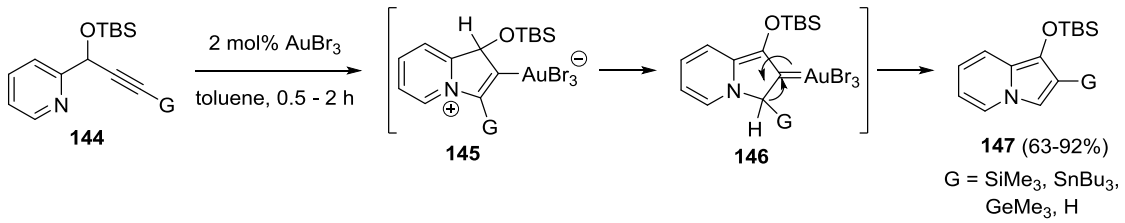
Bertrand and co-workers serendipitously discovered the catalytic hydroammoniumation and methylamination of alkynes under Au-catalysis with cyclic (alkyl)(amino) carbene (CAAC) ligands **143**. Treatment of tertiary 2-alkynylanilines **140** with TfOH and a catalytic amount of Au(I)-catalyst resulted in intramolecular hydroammoniumation (Scheme 31). Au(I)-catalyzed ring closure is followed by protodeauration in the presence of a strong acid. Treatment with TfOH without a catalyst for 3 days at 120 °C did not yield any hydroammoniumation. In addition, reaction of the same substrate at 160 °C resulted in aminomethylation of the alkyne (Scheme 31).[128]



Scheme 31. Hydroammoniumation and aminomethylation of *o*-alkynylanilines.

1.1.1.4 Indolizines

Gevorgyan and co-workers synthesized pyrrole-fused heterocycles **147** from 2-propargylpyridines **144** containing a migrating group G (Scheme 32). Isoquinolines, pyrazines, benzopyrazines and thiazoles could be employed as substrates too. In the original paper the authors invoked Au-vinylidenes as intermediates in the mechanism but DFT calculations disproved this hypothesis. Based on these calculations another mechanism was proposed which was in accordance with deuterium labeling studies. Initial 5-*endo*-*dig* cyclization was followed by an intermolecular *H*-shift with formation of a gold carbene **146**. A 1,2-shift of the migrating group then furnished the desired indolizines **147**. Interestingly, use of a Ag-catalyst instead of $AuBr_3$ also generated pyrrole-fused heterocycles but without migration of G.[129-132]

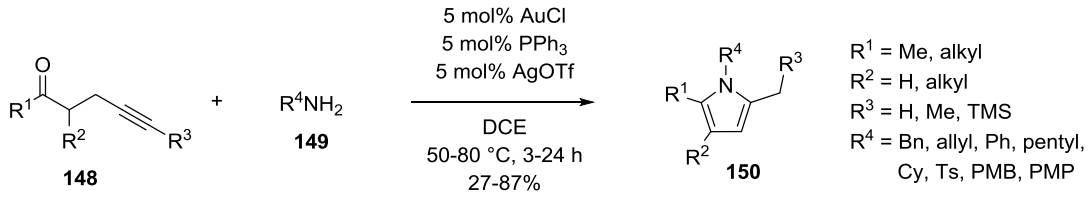


Scheme 32. Formation of indolizines with 1,2-migration.

1.1.2 5-exo-dig cyclization

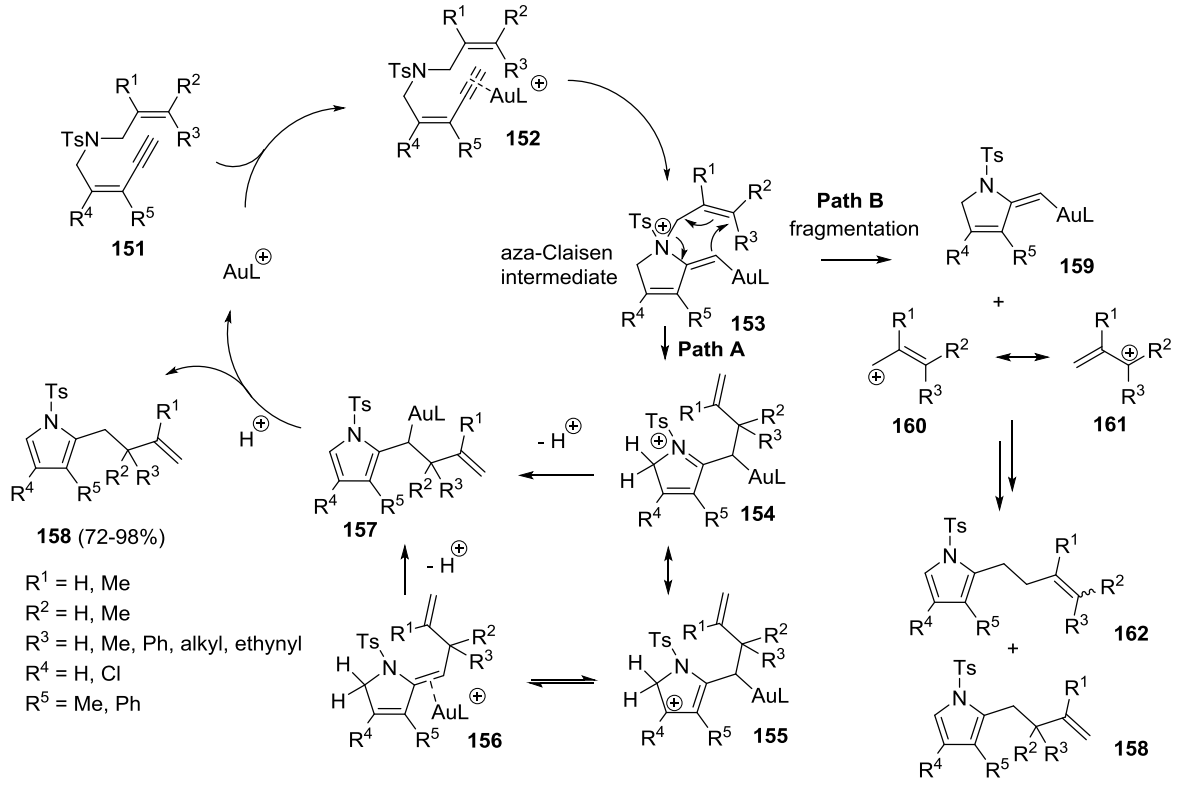
1.1.2.1 Pyrroles

After the pioneering work by Arcadi in 2001, Dake discovered a cationic Au(I)-catalyzed pyrrole synthesis starting from alkynones **148** and amines **149** (Scheme 33).[133-134] Intermolecular imination was followed by hydroamination in a 5-*exo-dig* fashion, protodeauration and isomerization. The authors compared the catalytic activity of AgOTf, AgOTf and PPh_3AuCl, and AgOTf with AuCl and PPh_3. Interestingly, the reaction proceeded with the best yields using separate addition of all three species (Scheme 14). On the other hand, AgOTf alone was usually faster, but suffered from incomplete conversion.[135]



Scheme 33. Formation of pyrroles via 5-*exo-dig* cyclization with a cationic Au(I)-catalyst.

In 2007, Gagosz and co-workers developed a cationic Au(I)-catalyzed aza-Claisen rearrangement with formation of trisubstituted pyrroles (Scheme 34). Based on the work of Fürstner, Yamamoto and Nakamura on Pt- and Au-catalyzed cycloisomerization reactions,[125-126, 136-137] and more specifically Fürstner's work on the rearrangement of allyl pentynyl ethers,[138-139] the authors envisaged the transformation of easily accessible substrates such as **151** into the corresponding pyrroles **158**. A catalyst screening indicated that the cationic $(p\text{-}CF_3Ph)_3PAuNTf_2$ was the most performant catalyst for this transformation, culminating in full conversion in under 30 minutes (2 mol% in CH_2Cl_2 at rt).[140]

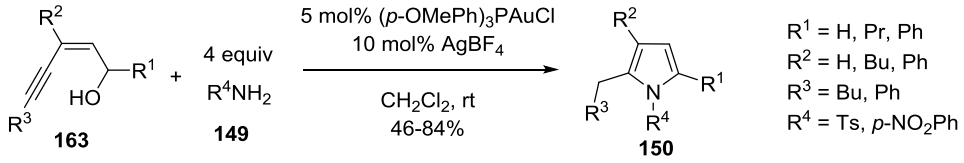


Scheme 34. Formation of homoallylic pyrroles via aza-Claisen rearrangement according to Gagosz.

With respect to the mechanism, two distinct pathways are feasible. At first, 5-*exo-dig* cyclization of the tosyl amide **152** will result in an ammonium intermediate **153** which can rearrange via two pathways. Either intramolecular aza-Claisen rearrangement takes place and **154** is formed (**Path A**), or fragmentation of the allyl ammonium moiety occurs (**Path B**). In the latter case, an allyl cation is formed and recombination engenders homoallylic pyrroles as well. However, in case of substituted allyl groups **160/161**, the allyl cation can isomerize and ultimately give rise to linear and branched homoallylic pyrroles **162/158**. If this was the prevailing mechanism, mixtures of branched and linear homoallylic groups should have been isolated (**158** and **162**, respectively). In this transformation, only one product was obtained (**158**). This observation, in combination with crossover experiments, proved that allyl migration is a concerted intramolecular process.[140]

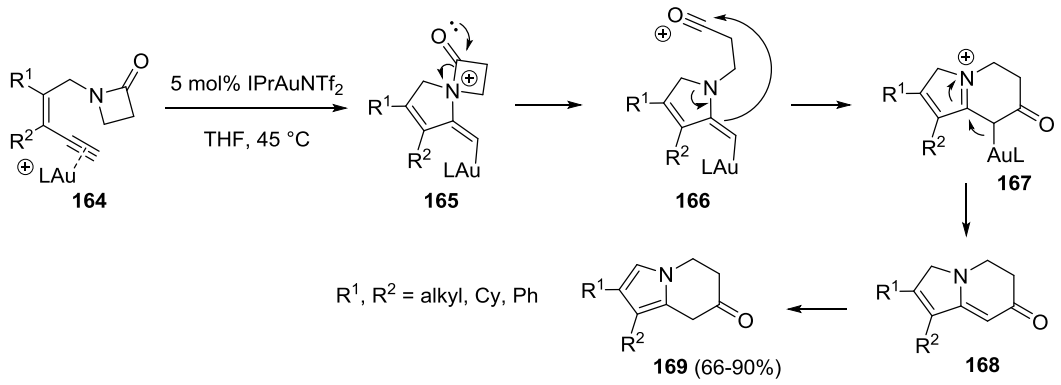
(*Z*)-enynols **163** react with amines and a cationic Au(I)-catalyst to yield pyrroles **150** in one pot. Liu and co-workers developed a Au-mediated preparation of allylic amines from allylic alcohols.[141] Based on this methodology they envisioned a one-pot consecutive amination and alkyne hydroamination with formation of substituted pyrroles **150** (Scheme 35). It is noteworthy that stepwise formation of the corresponding enynamine and cyclization resulted in lower yields. Upon addition of three extra equivalents of amine to the stepwise cyclization reaction, the yield was restored to its one-pot level.[142] Liang's group employed a very similar approach to produce

annulated pyrroles from 1-en-4-yn-3-ols. Here Au-assisted S_N2' resulted in 2-en-4-yn-1-amides which then underwent 5-*exo-dig* cyclization. $HAuCl_4 \cdot 4H_2O$ was applied in CH_3CN.[143]



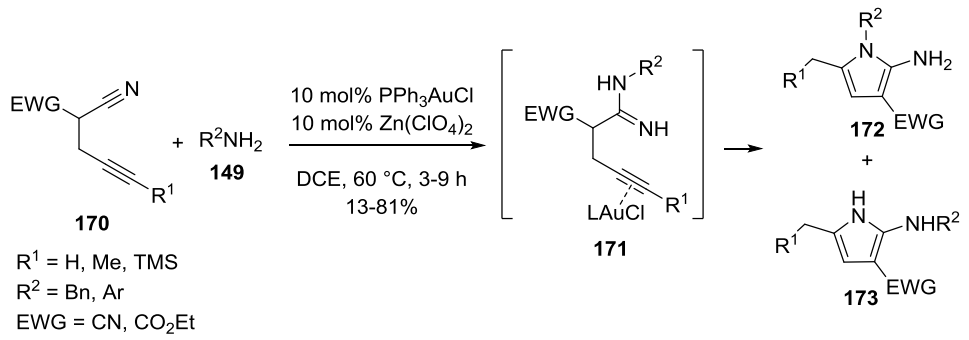
Scheme 35. One-pot formation of pyrroles from (*Z*)-enynols and amines

Zhang developed a pyrrole synthesis from *N*-(pent-2-en-4-yn-1-yl)-β-lactams **164** (Scheme 36). Cationic Au(I)-catalysts performed much better than $PtCl_2$, $PtCl_4$ or $AuCl_3$. After 5-*exo-dig* cyclization the amide bond in **165** was cleaved and a 6-membered ring was annulated. An isomerization step then yields dihydroindolizinones.[144]



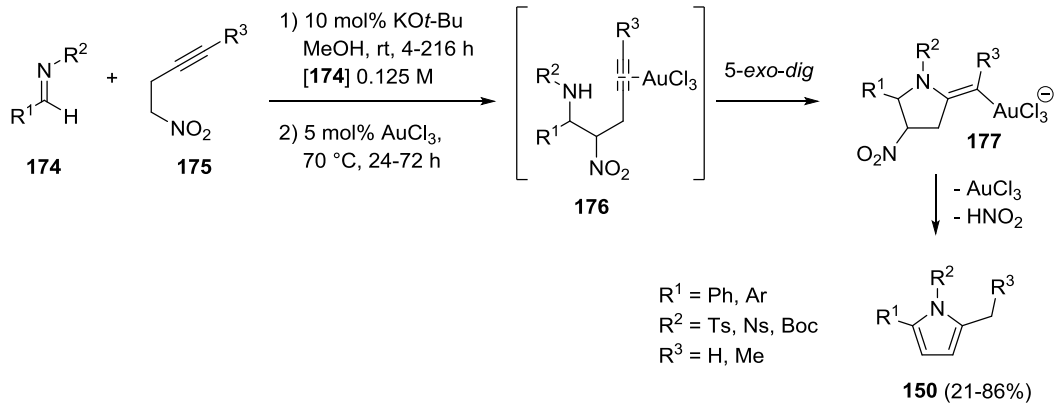
Scheme 36. Formation of annulated pyrroles according to Zhang.

Intermolecular hydroamination of 4-yne-nitriles **170** gives rise to amidines **171** which then induce 5-*exo-dig* cyclization and formation of 2-aminopyrroles (Scheme 37). The authors suggested that the Zn-catalyst was responsible for the hydroamination of the nitrile, while the Au-catalyst activated the alkyne for pyrrole formation. Mixtures of 2-amino and 2-alkylaminopyrroles **172/173** were obtained in 13-81% yield.[145]



Scheme 37. Intermolecular hydroamination of nitriles followed by intramolecular hydroamination for pyrrole synthesis.

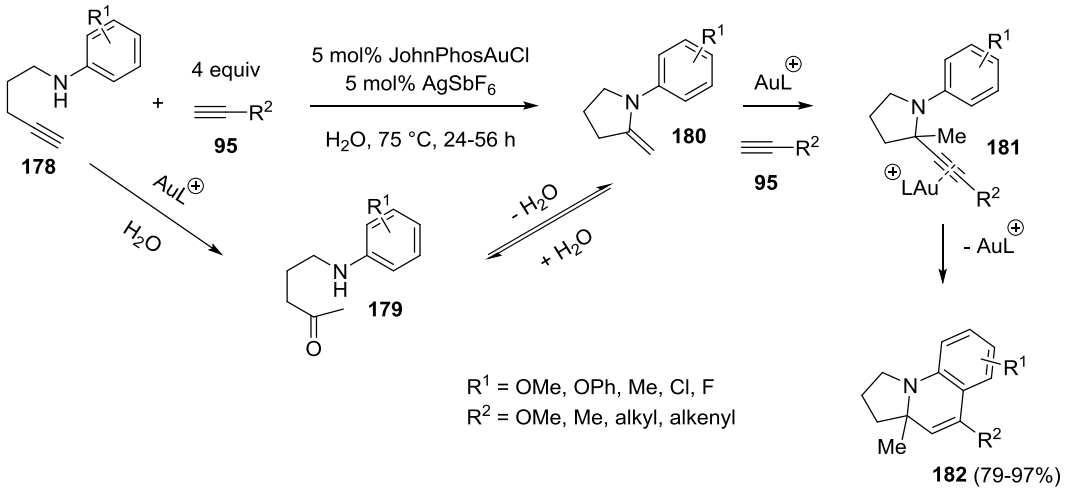
Dixon and co-workers reported a one-pot nitro-Mannich/hydroamination cascade (Scheme 38). A catalytic amount of base was sufficient to complete the nitro-Mannich reaction after which the Au-catalyst effectuated the ring closure. The presence of ligands such as PPh_3 or JohnPhos did not improve the efficiency of the catalyst.[146]



Scheme 38. Nitro-Mannich/hydroamination cascade.

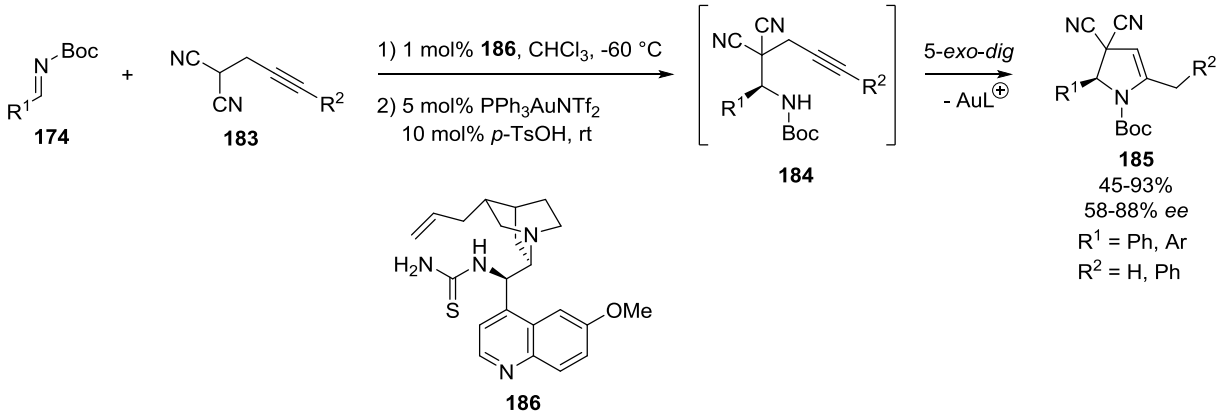
1.1.2.2 Pyrrolines and pyrrolidines

In 2008 Che and Liu reported on the tandem synthesis of tetrahydropyrrolo[1,2-*a*]quinolines **182** in water (Scheme 39). At first a 2-methylidenepyrrolidine **180** is formed via 5-*exo*-*dig* cyclization or by consecutive hydration of the alkyne and imination.[147] Next, alkyne **95** adds across the enamine and the activated alkyne is attacked via electrophilic substitution to furnish a tetrahydropyrrolo[1,2-*a*]quinoline **182**.[148] Fensterbank and co-workers treated *N*-pent-4-yn-1-yl tosylamides with PPh_3AuCl and Selectfluor and obtained mixtures of the corresponding 3-fluoro-2-methylenepyrrolidines and 3-fluoro-2-fluoromethylenepyrrolidines.[149] Lee developed novel Au(III)-oxo catalysts with bipyridine or phenanthroline ligands which proved efficacious for intramolecular hydroamination reactions.[150]



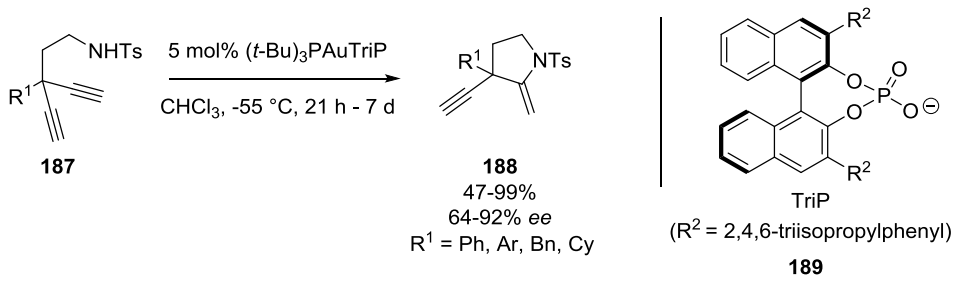
Scheme 39. Au-mediated aqueous synthesis of tetrahydropyrrolo[1,2-*a*]quinolines.

Jørgensen and co-workers developed an enantioselective one-pot Mannich/hydroamination cascade for the synthesis of pyrrolines **185** (Scheme 40). Quinidine-derived organocatalyst **186** resulted in the best *ee*'s and further optimization revealed that -60 °C was the optimal temperature for good enantiocontrol. A number of transition metals were assessed for the hydroamination reaction (Cu, Ag, Pd, Ni, Rh, Fe, Pt, Zn, In) but none were active. Au(I) and Au(III)-salts on the other hand were efficacious and the optimal catalyst was Gagosz's PPh_3AuNTf_2.[151-152]



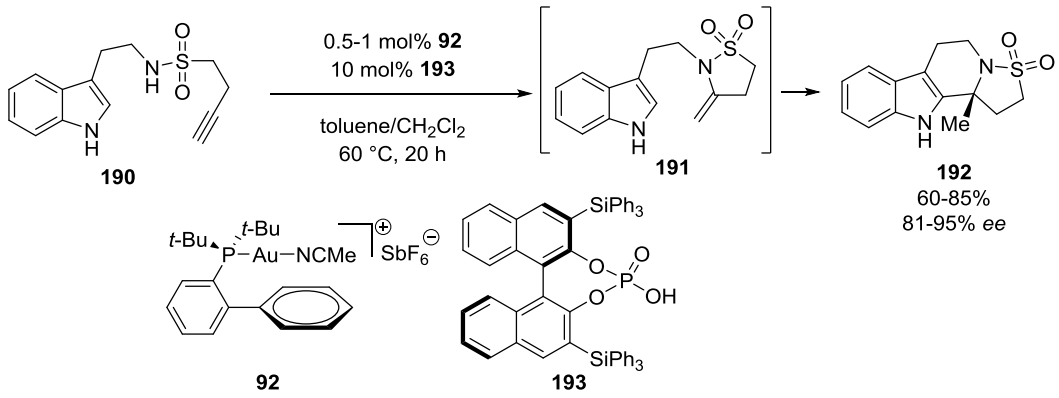
Scheme 40. Enantioselective tandem Mannich/hydroamination reaction.

The enantioselective desymmetrization of 1,4-diynamides **187** was reported by Czekelius and co-workers in 2012. Optimization of the reaction conditions revealed that cationic $(t\text{-Bu})_3PAu^+$ with a bulky BINOL phosphate counterion **189** resulted in the best yields and *ee*'s (Scheme 41). The catalyst was prepared prior to addition to the reaction, as *in situ* formation deteriorated the results.[153]



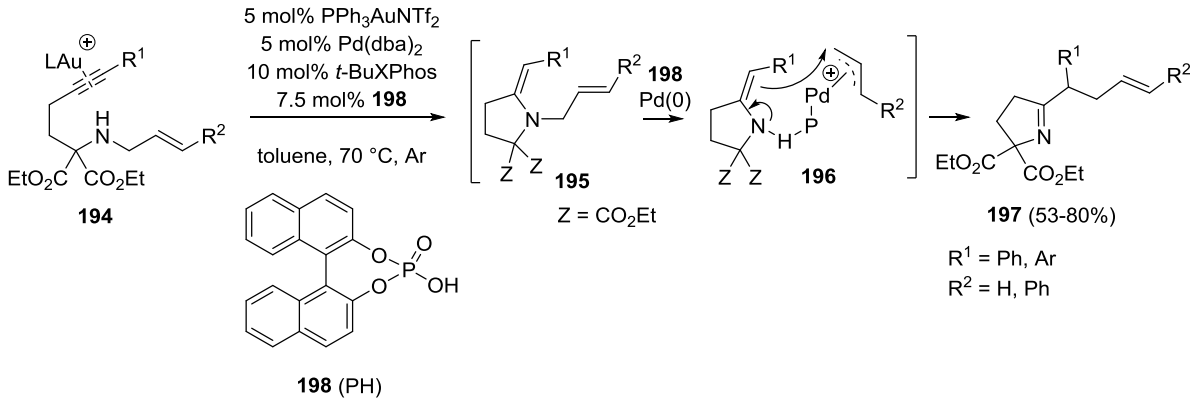
Scheme 41. Au-catalyzed desymmetrization of diynamides.

Similarly, Dixon discovered a Au- and BINOL phosphoric acid (BPA)-catalyzed enantioselective hydroamination/*N*-sulfonyliminium cyclization cascade (Scheme 42). First a 5-*exo-dig* cyclization formed an exocyclic enesulfonamide **191**, after which the chiral BPA **193** tethers the indole to the *N*-sulfoniminium moiety in an enantioselective fashion.[154]



Scheme 42. Enantioselective tandem hydroamination/cyclization according to Dixon.

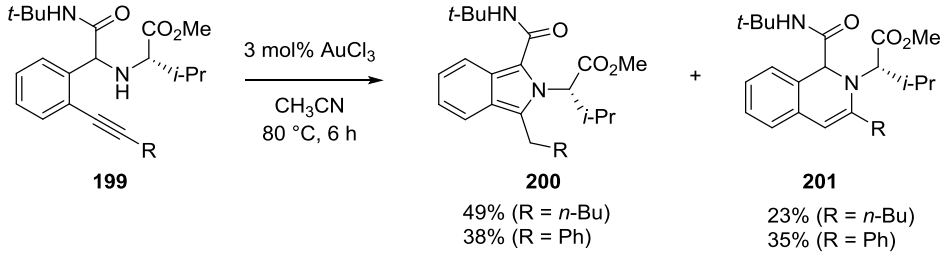
A Au/Pd/Brønsted acid ternary system catalyzed the transformation of amine-tethered 1,8-enynes **194** to 1-pyrrolines **197** (Scheme 43). After a Au-catalyzed 5-*exo-dig* cyclization yields an *N*-allylic enamine **195**, the nitrogen atom is protonated by the acid and this results in Pd-assisted fragmentation of the ammonium species. The cooperative catalysis of a Pd(0)-species and a Brønsted acid ensure the regioselective allylation at the sterically least encumbered end of the allyl fragment, yielding 1-pyrrolines **197**.[155]



Scheme 43. Relay and cooperative catalysis with a Au/Pd/Brønsted acid ternary system.

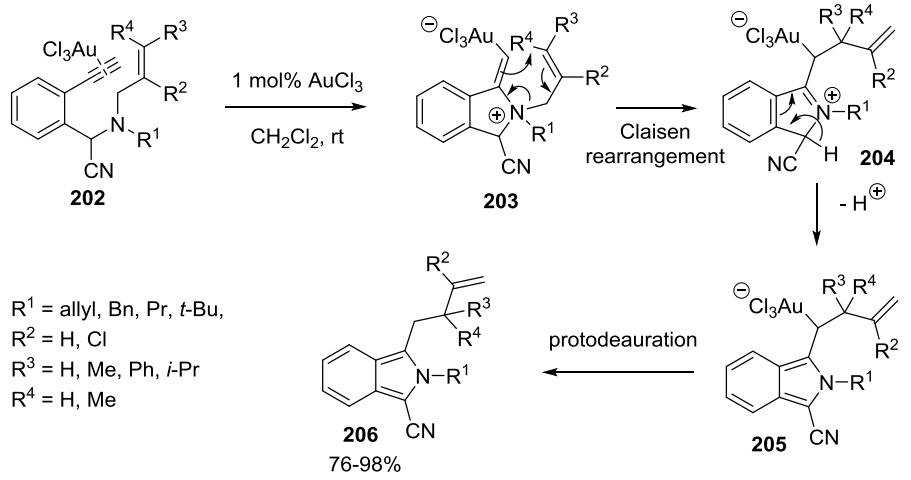
1.1.2.3 Isoindoles

Dyker reported a Au-mediated synthesis of isoindoles **200** based on (*o*-ethynylbenzyl)amines **199**. They subjected post-Ugi products **199** to treatment with $AuCl_3$ in CH_3CN at reflux for 6 hours and obtained a mixture of 5-*exo-dig* and 6-*endo-dig* product, with more 5-membered ring product present (Scheme 44).[156]



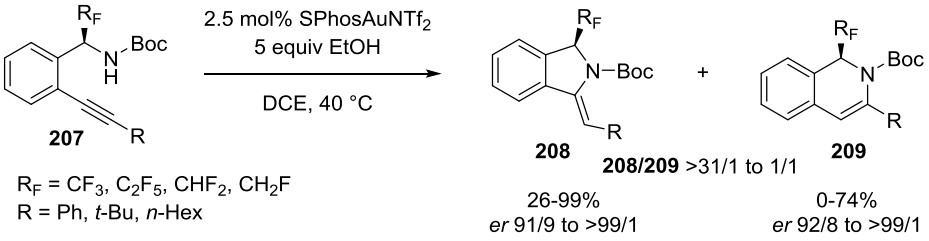
Scheme 44. Post-Ugi isoindole formation according to Dyker.

The Stevens group also published on the Au-catalyzed synthesis of isoindoles **206** (Scheme 45).[72] In this case a tertiary allylamine **202** was employed and 5-*exo-dig* cyclization was succeeded by allyl migration through an aza-Claisen rearrangement. This was proven by the fact that no linear isomer was present after the allyl migration.[140] Furthermore, upon introduction of steric constraints (instead of an allyl group and R^1, a 1,2,3,6-tetrahydropyridin-1-yl group was used) no product formation was observed, thus precluding a stepwise, fragmentative mechanism. It must be noted that the authors did observe a stepwise mechanism under microwave irradiation without the presence of any catalyst.[72]



Scheme 45. $AuCl_3$-mediated synthesis of cyanoisoindoles.

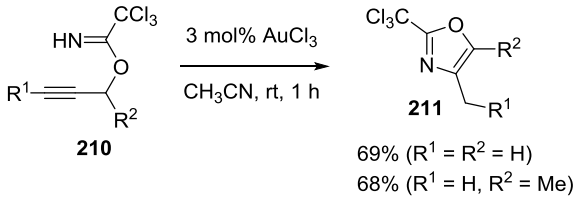
Chiral fluorinated isoindolines **208** were accessed from fluorinated (*o*-ethynylbenzyl)amines **207** using a SPhosAuNTf$_2$-catalyst. Mixtures of 5-*exo* and 6-*endo* products **208** and **209**, respectively, were obtained, but the ratio was strongly dependent on electronic factors (Scheme 46). Electron-donating R-substituents promoted 6-*endo-dig* cyclization, while the nature of the R_F group was a determining factor as well: changing R_F from C_2F_5 to CF_3 to CHF_2 to CH_2F to CH_3 to H resulted in a regioselectivity gradient from 5-*exo*- to 6-*endo-dig* products.[157]



Scheme 46. SPhosAuNTf$_2$-mediated cyclization to fluorinated isoindolines and dihydroisoquinolines.

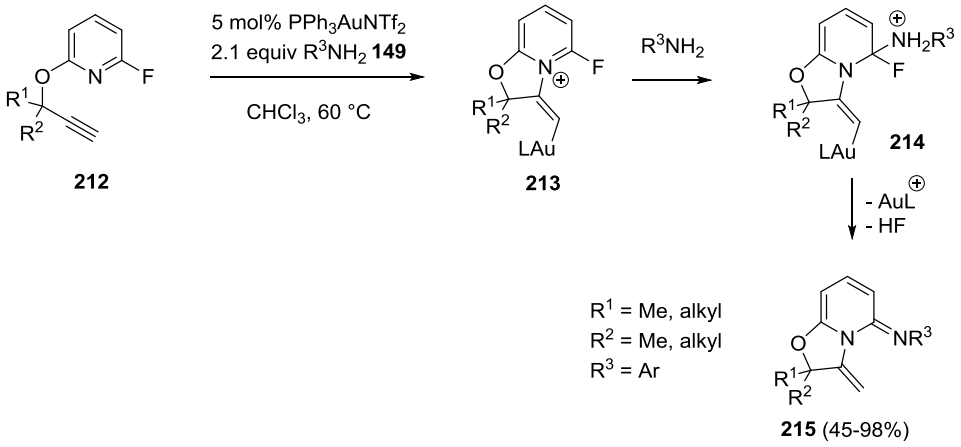
1.1.2.4 Oxazoles

In 2006 Hashmi described the conversion of propargylic trichloroacetimidates **210** to the corresponding oxazoles **211** (Scheme 47). The cyclization reaction to the oxazoline was very fast but the rate-determining step was the subsequent isomerization to the oxazole.[158] Shin and co-workers simultaneously reported a similar transformation using 5 mol% P(C_6F_5)$_3$AuCl and $AgSbF_6$ in DCE. They obtained 74-98% yields in 3-9 h at 0 °C.[159]



Scheme 47. Formation of oxazoles from propargylic trichloroacetimidates.

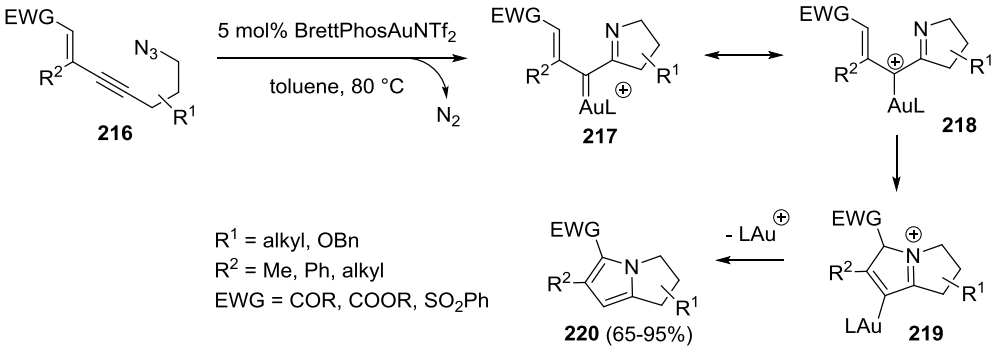
Gagosz and co-workers employed 2-propargyloxypyridines **212** for a 5-*exo*-*dig* cyclization and subsequent nucleophilic attack (Scheme 48). As an activated 2-fluoropyridinium system is present in **213**, aromatic nucleophilic substitution takes place and results in oxazolopyridine imines **215**. Upon application of an Ag-catalyst, an isomeric product is formed due to initial 6-*endo*-*dig* cyclization and rearrangement.[160]



Scheme 48. Au-catalyzed formation of oxazolopyridine imines.

1.1.2.5 Pyrrolizines

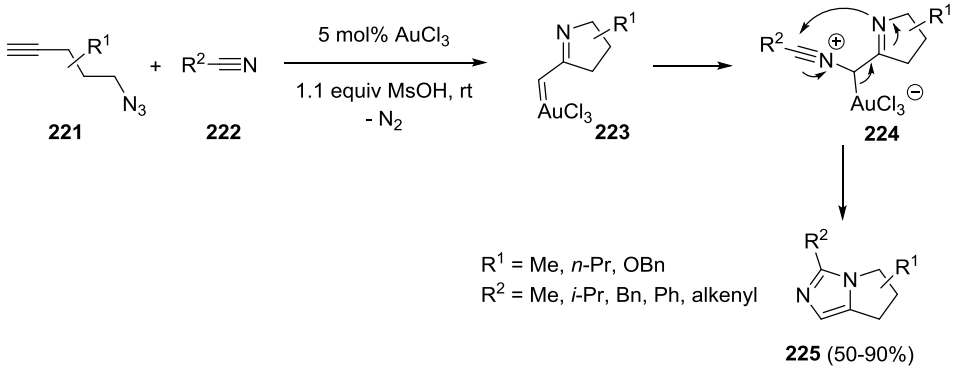
Based on Toste's acetylenic Schmidt reaction published in 2005,[75] Zhang envisaged a dihydropyrrolizine synthesis originating from a 5-*exo*-*dig* cyclization by an azide **216**. In order to direct the attack to 5-*exo*, the introduction of an electron-withdrawing C-C double bond at the distal end of the alkyne was assessed. In addition, this allowed for a consecutive electrocyclic ring closure with formation of a dihydropyrrolizine **220** (Scheme 49).[161]



Scheme 49. Formation of dihydropyrrolizines based on Toste's acetylenic Schmidt reaction.

1.1.2.6 Imidazoles

Similar to the approach for pyrrolizine formation (Scheme 49), Zhang designed a method for the synthesis of bicyclic imidazoles **225**. The reaction took place in nitrile **222** as solvent with alkylazide **221** at a concentration of 0.05 M. Formation of a Au-carbene via 5-*exo-dig* ring closure and concomitant expulsion of N_2-gas was followed by intermolecular trapping with a nitrile. Species **224** then underwent electrocyclization with formation of a bicyclic imidazole **225** (Scheme 50). The choice of the catalyst is crucial to minimize the competing Huisgen cycloaddition with formation of triazole. As the obtained products contain basic nitrogen atoms the addition of acid is necessary to prevent catalyst deactivation.[162] Propargylic amidines have been applied as substrates for the preparation of 2-fluoroalkylimidazoles, while propargylureas have not been used to this end.[163-164]

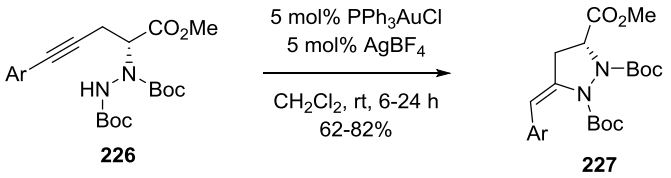


Scheme 50. Formation of bicyclic imidazoles according to Zhang.

1.1.2.7 Pyrazoles

Greck and co-workers reported on the formation of pyrazolidines **227** from homopropargylic hydrazines **226** (Scheme 51). The transformation proceeded smoothly using *in situ* generated PPh_3AuBF_4. Either PPh_3AuCl or $AgBF_4$ alone did not result in any conversion to **227**. Apart from the

anticipated 5-*exo*-*dig* ring closure, some 6-*endo*-*dig* side product was present too, depending on the substitution of the phenyl ring. More electron-rich aromatic rings promoted 6-*endo*-*dig* reaction.[165]



Ar = 4-Me-C_6H_4, 4-F-C_6H_4, 4-OMe-C_6H_4, *etc.*

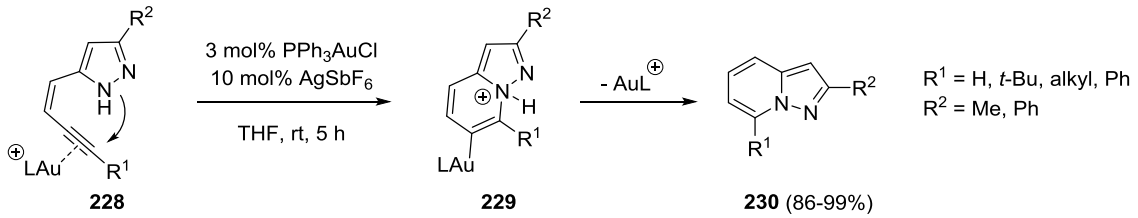
Scheme 51. Transformation of homopropargylic hydrazines into benzylidenepyrazolidines.

1.2 Formation of 6-membered rings

1.2.1 6-endo-dig cyclization

1.2.1.1 Pyrazolopyridines

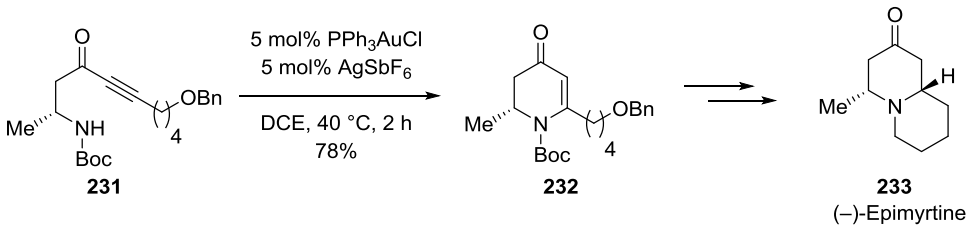
Wu and co-workers produced pyrazolo[1,5-*a*]pyridines **230** via a Au(I)-catalyzed cyclization of alkynylpyrazoles **228** (Scheme 52). Salts of Pt, Pd, Cu, Ag and Zn were evaluated for the ring closure as well but conversion was incomplete or required reflux in CH_3CN for prolonged periods of time. A combination of PPh_3AuCl and $AgSbF_6$ resulted in full conversion after 5 hours at room temperature. Iodine-mediated cyclization was possible as well and resulted in iodinated pyrazolo[1,5-*a*]pyridines which are excellent substrates for further derivatization through cross-coupling strategies.[166] It must be noted that it is probably the other tautomer of pyrazole **228** which initiates attack on the triple bond. Propargylic enamines were converted into pyridines using $NaAuCl_4 \cdot 2H_2O$ and PPh_3AuOTf by Arcadi and Wang, respectively.[167-168]



Scheme 52. Synthesis of pyrazolo[1,5-*a*]pyridines via Au-mediated 6-*endo-dig* cyclization.

1.2.1.2 Dihydropyridines

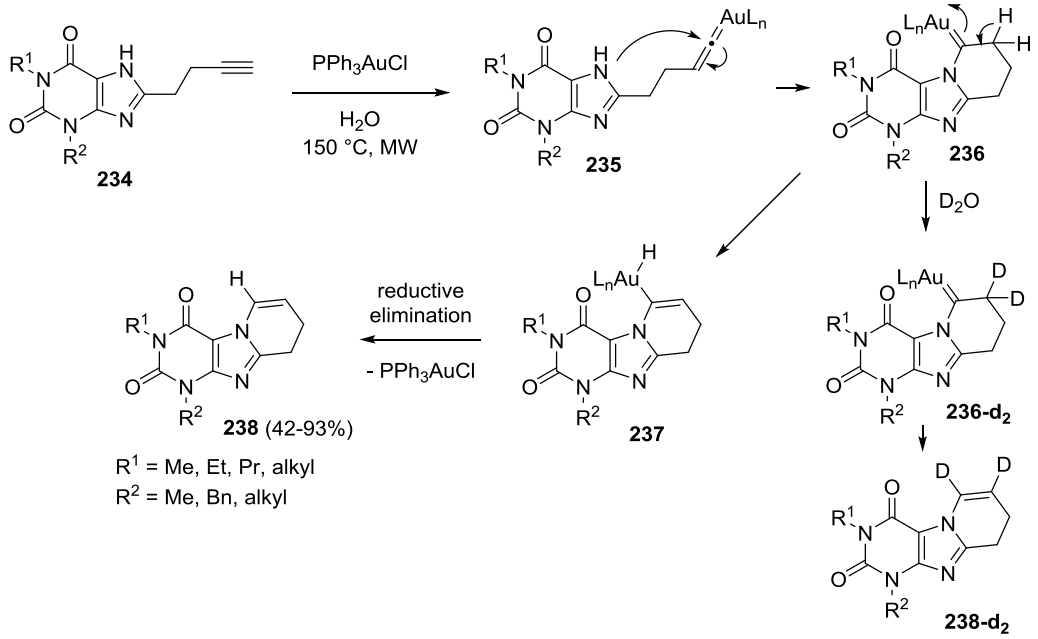
Gouault applied a Au-catalyzed hydroamination for the total synthesis of (−)-Epimyrtine **233** (Scheme 53). One advantage of this cationic Au(I)-mediated ring closure was the use of mild conditions which did not engender any racemization. In this manner the desired 6-membered ring was obtained in 78% yield.[169-170]



Scheme 53. Au-catalyzed 6-*endo-dig* ring closure in the total synthesis of (−)-Epimyrtine.

Tricyclic xanthines fused at N_7 **238** were produced by 6-*endo-dig* cyclization of alkynylxanthines **234** (Scheme 54). The authors proposed a mechanism based on deuterium labeling experiments. Initial

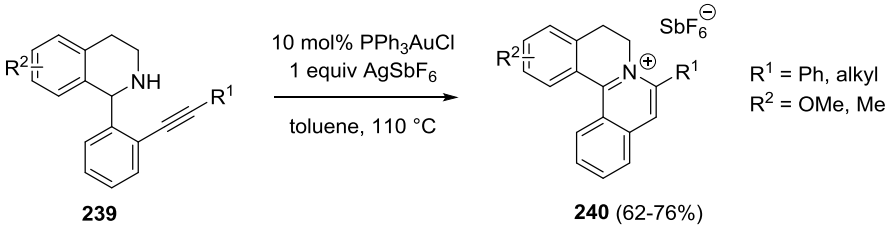
formation of a Au-vinylidene **235** results in ring closure and generation of a Au-carbene **236**. Tautomerization and reductive elimination then yield the product and regenerate the catalyst. Performing the reaction in D_2O instead of H_2O resulted in dideuterated product **238-d$_2$**. Swift H/D-exchange at the carbon in α-position to the carbene was assumed to account for the observed result. Interestingly, the use of $AgAsF_6$ as catalyst results in N_9-fused tricyclic xanthines.[171]



Scheme 54. Formation of tricyclic xanthines via Au-vinylidenes.

1.2.1.3 Quinolines

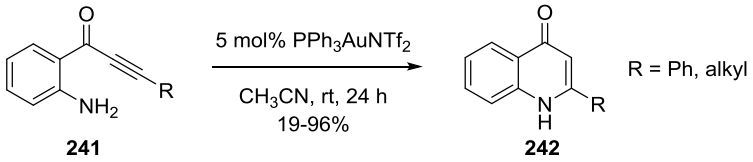
Liu and co-workers developed a method for the synthesis of tetracyclic isoquinolizinium salts **240** (Scheme 55). Au-catalyzed 6-*endo-dig* cyclization preceeded protodeauration and oxidation. The reaction only worked for internal alkynes **239** while *t*-Bu-substituted alkynes were unreactive due to steric hindrance.[172]



Scheme 55. Preparation of isoquinolizinium salts via Au(I)-mediated cyclization and oxidation.

Quinolones **242** could be obtained through hydroamination of alkynones **241** (Scheme 56). Au(I)-catalysts with phosphane ligands performed much better than with NHC ligands or other catalysts

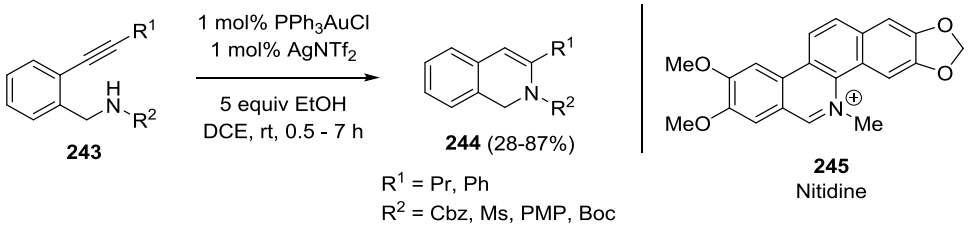
such as $PtCl_2$, $KAuCl_4$, $HAuCl_4$ or Au/C. DFT calculations revealed that amine-gold coordination was the preferred binding mode and not alkyne-gold or carbonyl-gold coordination. As such, coordination with the alkyne is some 15 kJ/mol more endothermic than with the amine. However, reaction can only take place after the catalyst has moved from the amine to the triple bond.[173] Hydroamination reactions are known to proceed via an outer sphere mechanism.[174]



Scheme 56. Quinolone formation through intramolecular hydroamination.

1.2.1.4 Dihydroquinolines and tetrahydroquinolines

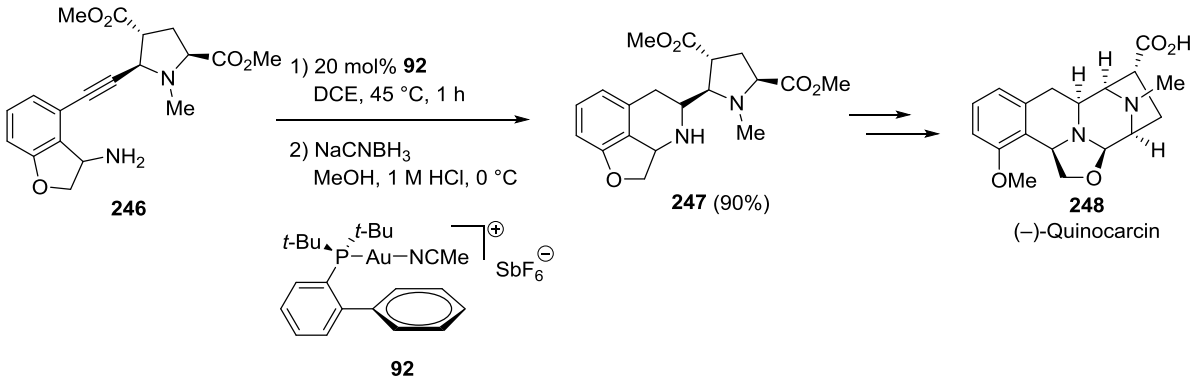
In 2008 Takemoto and co-workers reported on the intramolecular 6-*endo-dig* hydroamination of weakly basic amines **243** in the presence of a cationic Au(I)-catalyst. The reaction rate increased dramatically upon the addition of EtOH as a protic additive. The more electron-rich the amine, the better the reaction proceeded.[175] In a follow-up publication the same authors expanded the scope of the transformation by using different R^1 groups. Furthermore they succeeded in a tandem cyclization reaction when R^1 contained an acetal or Michael acceptor. In this light, a total synthesis of Nitidine **245** was achieved, a naturally occurring alkaloid with antimalaria activity (Scheme 57).[176-177] Fustero *et al*. obtained chiral perfluoroalkyl dihydroquinolines along with the corresponding isoindoles using $SPhosAuNTf_2$.[157]



Scheme 57. Formation of dihydroquinolines.

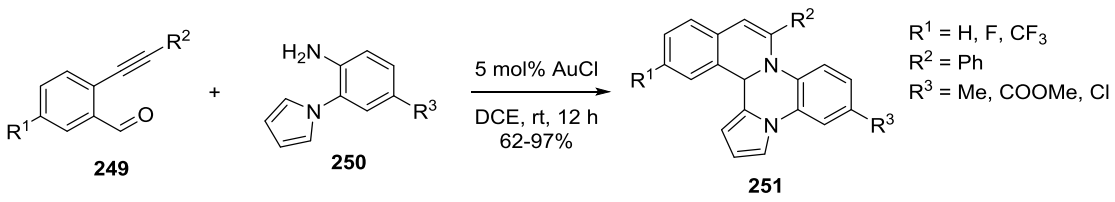
A related transformation was employed by Ohno and co-workers in the total synthesis of (−)-Quinocarcin **248** (Scheme 58). Initially, an aminomethyl group was present in the substrate instead of an amino-substituted dihydrofuran **246**. In the former case the competing 5-*exo-dig* cyclization proved very challenging to avoid. Upon introduction of steric constraints the preference for the 6-membered ring became larger. Application of a dihydrofuran tether ensured an optimal orientation for 6-*endo-dig* cyclization. In case 5-*exo-dig* cyclization would take place, this would introduce a

significant amount of ring strain into the system, accounting for the preference for 6-*endo-dig* ring closure.[178-179]



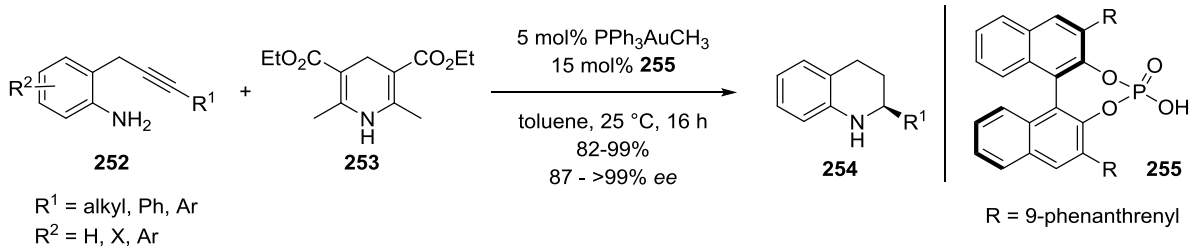
Scheme 58. Au-catalyzed hydroamination in the total synthesis of (−)-Quinocarcin.

The reaction between *o*-alkynylbenzaldehydes **249** and anilines **250** under Au-catalysis results in fused (iso)quinolines **251** (Scheme 59). First, intermolecular imination takes place and then two distinct routes are possible, though both with the same outcome: either hydroamination of the alkyne takes place first and is followed by electrophilic substitution, or electrophilic substitution preceeds the hydroamination step. Monitoring the reaction by ^{1}H-NMR indicated that hydroamination is the final step. Anilines tethered to other azaheterocycles were applied as well.[180] Saifuddin *et al.* adopted a similar approach.[181]



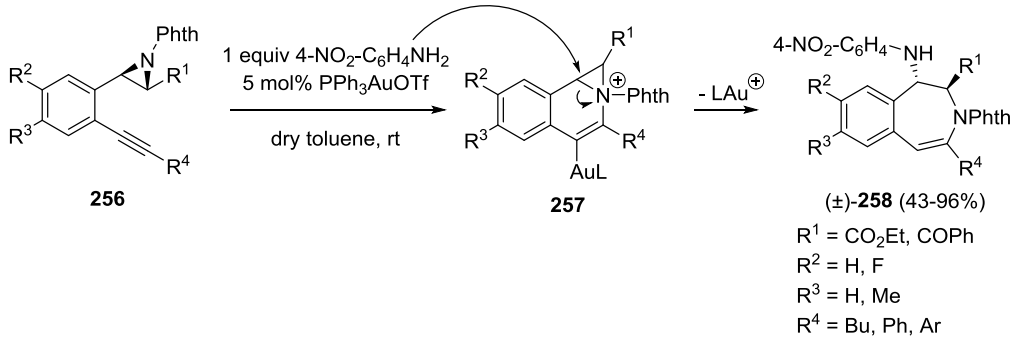
Scheme 59. Reaction between *o*-alkynylbenzaldehydes and anilines under AuCl-catalysis.

The Gong group disseminated their results on the hydroamination/asymmetric transfer hydrogenation of anilines **252** under relay catalysis of an achiral gold complex and chiral Brønsted acid **255** (Scheme 60). Application of PPh_3AuCH_3 in the presence of a Brønsted acid implies that some acid will be lost. Upon lowering the ratio of Au-catalyst/acid to 1/1 the reaction slowed down significantly, demonstrating that the acid participates by activating the *in situ* formed imine. Furthermore, a control experiment with only Au-phosphorate resulted in inferior yields and *ee*'s as compared to a binary system consisting of cationic Au(I) and a chiral Brønsted acid.[182]



Scheme 60. Intramolecular hydroamination and transfer hydrogenation.

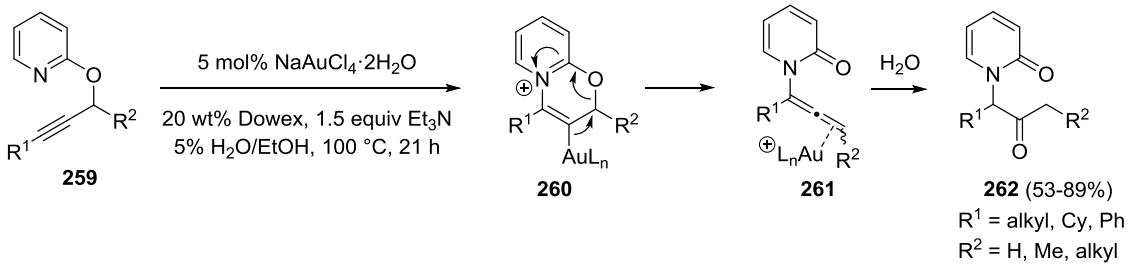
Liu and co-workers constructed 3-functionalized benzazepine skeletons **258** through ring-opening/cycloamination reactions, catalyzed by cationic Au(I)-complexes (Scheme 61). The reaction between (*o*-alkynylphenyl)aziridines **256** and PPh_3AuOTf results in 6-*endo*-*dig* ring closure. In this manner, aziridinium ion **257** is generated which is prone to ring opening by nucleophiles. An electron-poor aniline opens the aziridine regio- and diastereoselectively at C_3 which results in a 7-membered ring with a *trans*-configuration **258**. An electron-withdrawing group as R^1 was crucial to obtain regioselective ring-opening. Instead of OTf, other counterions such as SbF_6 and NTf_2 were active as well and the reaction proceeded in THF, DCE, dichloromethane, dioxane and acetonitrile. Water was also able to open the aziridine ring, resulting in a free alcohol and opening up possibilities for further derivatization.[183]



Scheme 61. Synthesis of benzazepines from (*o*-alkynylphenyl)aziridines.

1.2.1.5 Oxazines

The transformation of 2-propargyloxypyridines **259** into α-(*N*-2-pyridonyl)ketones **262** was described by Anderson and her group (Scheme 62). A 6-*endo*-*dig* ring closure was followed by rearrangement of the intermediate pyridinium **260** to an *N*-allenyl pyridine **261**. Hydrolysis resulted in the corresponding ketones **262**.[184]

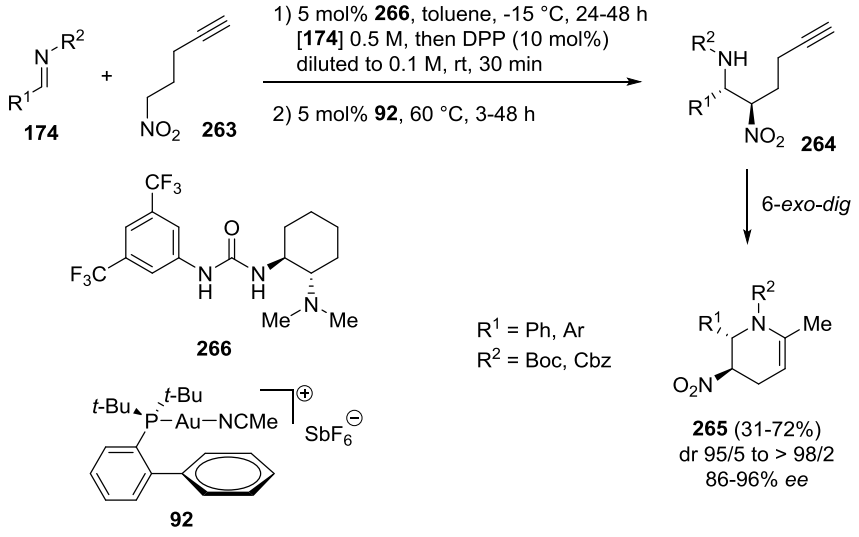


Scheme 62. Initial formation of 2*H*-oxazines and subsequent collapse and hydrolysis.

1.2.2 6-exo-dig cyclization

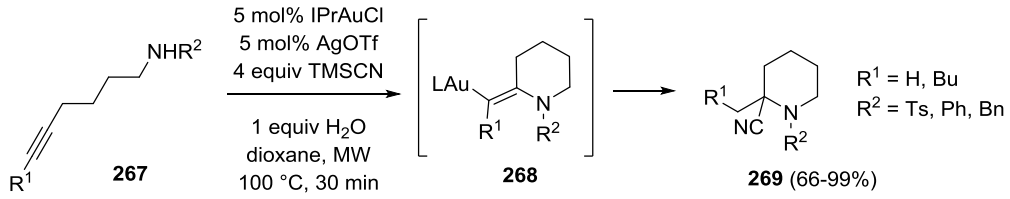
1.2.2.1 Tetrahydropyridines

After Nozaki in 1987, Müller and co-workers have performed some pioneering work on Au-catalyzed 6-*exo-dig* cyclizations with amines around the turn of the millennium but other metal catalysts gave superior yields in their hands.[185-187] Dixon extended his enantioselective nitro-Mannich/hydroamination methodology to the synthesis of tetrahydropyridines **265** (Scheme 63). After nitro-Mannich reaction, Echavarren's cationic Au(I)-catalyst **92** mediated the desired ring closure. Prior to addition of the Au-catalyst, the basic *N*-atom of the organocatalyst was protonated using diphenylphosphate (DPP) as to avoid catalyst deactivation.[188]



Scheme 63. Diastereo- and enantioselective nitro-Mannich/hydroamination cascade.

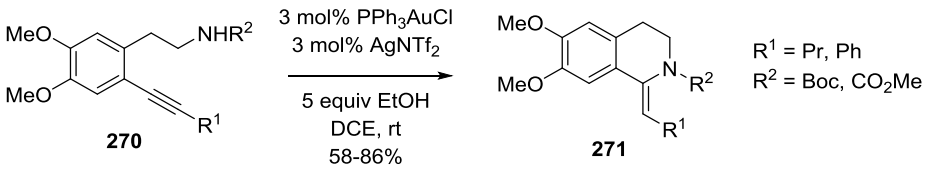
Hammond's group developed a tandem hydroamination/cyanation approach for alkynylamines **267** (Scheme 64). For non-basic amines, IPrAuOTf proved to be the most efficacious catalyst, but basic amines were transformed more efficiently with CuBr as a catalyst.[96] Brimble and co-workers performed a similar hydroamination reaction in their synthetic studies towards spiroimine marine toxins.[189]



Scheme 64. Tandem hydroamination/cyanation.

1.2.2.2 Isoquinolines

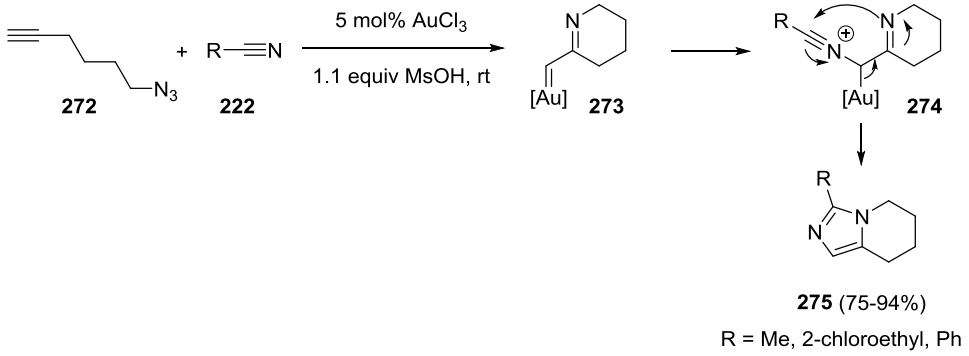
Tetrahydroisoquinolines **271** can easily be accessed from alkynylbenzenes **270** with an amine tethered to a carbon linker at a suitable distance. Takemoto adopted this methodology and synthesized 1-alkylidene-1,2,3,4-tetrahydroisoquinolines **271** (Scheme 65). The reaction with an *in situ* generated cationic Au(I)-catalyst proceeded in a highly stereoselective manner as the double bond geometry was identified as strictly *Z*. This was remarkable as the stereoselective synthesis of 1-alkylidene-1,2,3,4-tetrahydroisoquinolines **271** is often cumbersome.[175]



Scheme 65. Stereoselective tetrahydroisoquinoline synthesis using cationic Au(I)-catalysis.

1.2.2.3 Imidazoles

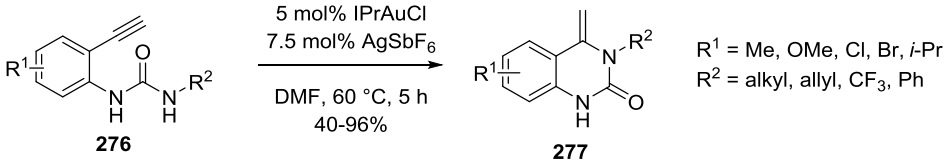
Zhang's bicyclic imidazole synthesis (Scheme 50) was also applicable to 6-membered rings (Scheme 66). The reaction was performed in nitrile **222** as solvent with alkylazide **272** at a concentration of 0.05 M. After 6-*exo*-*dig* cyclization and attack of the nitrile, the imidazole is generated. No more than 6% triazole was formed upon application of $AuCl_3$. Again, the addition of acid was required to prevent complexation of the imidazole or triazole products with the catalyst.[162]



Scheme 66. Fused imidazole synthesis from alkylazides and nitriles.

1.2.2.4 Quinazolinones

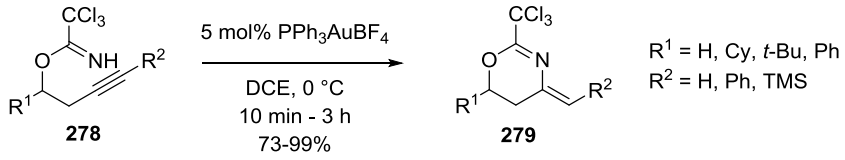
Au-catalyzed intramolecular 6-*exo*-*dig* cyclization of (*o*-ethynylphenyl)ureas **276** resulted in methylidenequinazolinones **277** (Scheme 67). Terminal alkynes underwent 5-*endo*-*dig* or 6-*exo*-*dig* ring closure depending on the catalyst system used, resulting from N_1- or N_3-attack respectively. Internal alkynes exclusively underwent 5-*endo*-*dig* cyclization. Furthermore, the applied ligand exerted a large influence as well: JohnPhos resulted in mixtures of *endo*- and *exo*- cyclization while IPr selectively gave 6-*exo*-*dig* reaction to **277**. The closely related but sterically less encumbered IMes ligand on the other hand also resulted in mixtures.[115]



Scheme 67. Au(I)-catalyzed formation of quinazolinones from aptly substituted ureas.

1.2.2.5 Dihydrooxazines

Subjecting homopropargylic imidates **278** to PPh_3AuBF_4 in DCE led to formation of dihydrooxazines **279** (Scheme 68). A large variety of functional groups was tolerated, but for R^2 = TMS reaction at room temperature and a change of ligand to P(*n*-Bu)$_3$ were required for the reaction to proceed. A catalyst screening revealed there was a considerable counterion effect: catalysts with NTf_2, SbF_6 and OTf were inactive, while BF_4 was successful.[159]

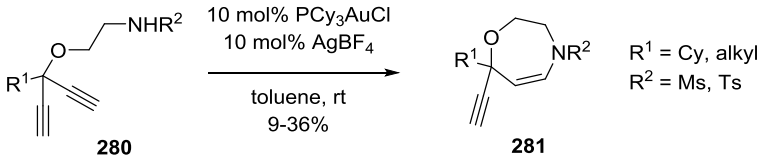


Scheme 68. Au(I)-mediated preparation of dihydrooxazines from homopropargyl trichloroacetimidates.

1.3 Formation of 7-membered rings

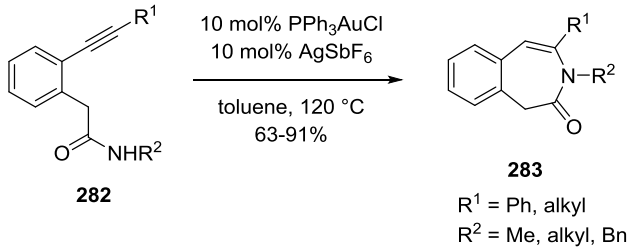
1.3.1 7-endo-dig cyclization

Czekelius and co-workers subjected 1,4-diynamides **280** to cationic Au(I) in order to produce tetrahydrooxazepines **281** (Scheme 69). The applied catalyst could not fully convert the substrates, probably due to catalyst degradation.[190]



Scheme 69. Au(I)-catalyzed 7-*endo-dig* cyclization with formation of tetrahydrooxazepines.

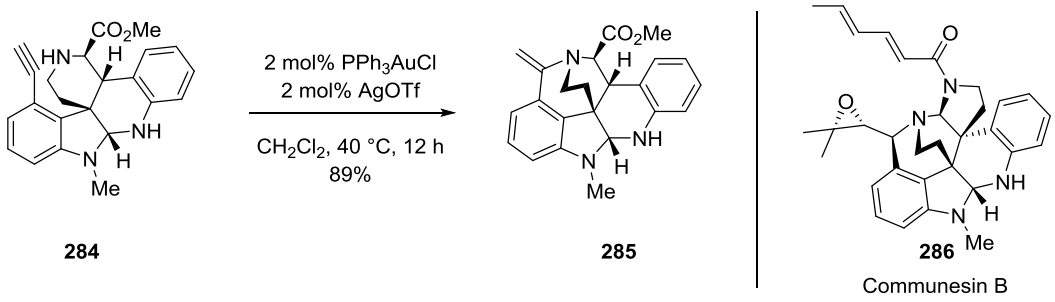
Benzazepinones **283** could be accessed through 7-*endo-dig* cyclization of amides **282** using a cationic Au(I)-catalyst (Scheme 70). It must be noted that use of $AgSbF_6$ alone also resulted in the desired 3-benzazepinones, but in combination with a Au-catalyst better yields were obtained. Furthermore, upon application of 1.2 equiv $AuBr_3$ in acetic acid the corresponding 5-bromo-3-benzazepinones were isolated. The authors suggested this was due to a highly unusual and unforeseen reductive elimination process rather than protodeauration. Addition of bromine instead of a Au-catalyst or combination of $AuBr_3$ with an oxidant did not result in any conversion.[191]



Scheme 70. Generation of benzazepinones through 7-*endo-dig* cyclization.

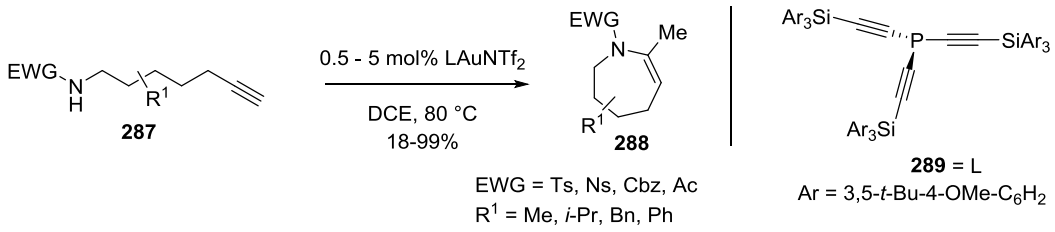
1.3.2 7-exo-dig cyclization

Funk and Crawley employed a Au(I)-catalyzed 7-*exo-dig* ring closure in their attempted synthesis of Communesin B **286**, a *Penicillium* metabolite.[192] Application of *in situ* generated PPh_3AuOTf smoothly generated the 7-membered ring in **285** (Scheme 71). It must be noted that this transformation took place spontaneously as well, albeit very slowly.[193]



Scheme 71. 7-*exo*-*dig* cyclization in the attempted total synthesis of Communesin B.

Sawamura and co-workers applied their bulky semihollow-shaped silyl-capped triethynylphosphane ligands **289** to the Au(I)-mediated construction of azepines and benzazepines **288** (Scheme 72). A regioselective 7-*exo*-*dig* cyclization takes place with formation of a tetrahydroazepine ring or dihydrobenzazepines **288**. The cavity in the ligand forces the amine into the proximity of the alkyne-Au π-complex, resulting in an entropy-based rate enhancement.[194] The Zhang group has demonstrated that $AuCl_3$ can also perform 7-*exo*-*dig* cyclizations in their work on bicyclic imidazoles (Scheme 50 and Scheme 66).[162]



Scheme 72. Au(I)-mediated 7-*exo*-*dig* cyclization by application of semihollow-shaped phosphane ligands.

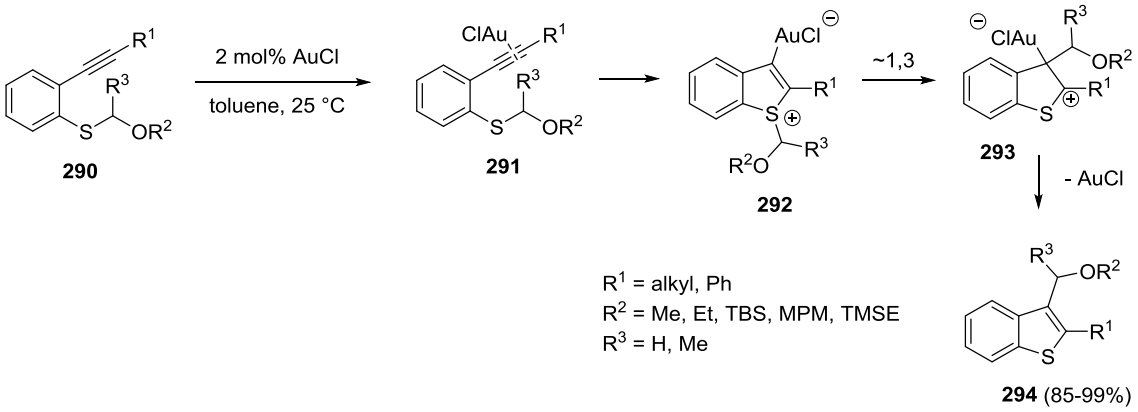
2. Homogeneous Au-catalyzed intramolecular attack of *S*-nucleophiles on alkynes

S-nucleophiles have been much less investigated than their *N*-counterparts. Nevertheless, the feasibility of combining *S*-nucleophiles with Au-catalysts as π-acids has been demonstrated. Krause and Yamamoto have described reactions between sulfides and allenes, but these transformations are outside the scope of this overview.[195-196]

2.1 Formation of 5-membered rings

2.1.1 5-endo-dig cyclization

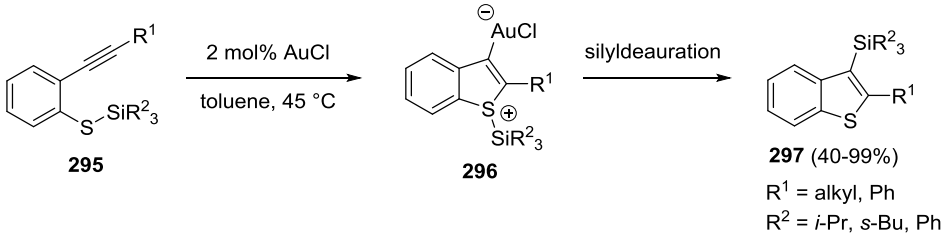
Nakamura and co-workers were the first to evaluate the Au-catalyzed intramolecular 5-*endo-dig* cycloisomerization of sulfides **290** (Scheme 73). A library of transition-metal catalysts was screened and AuCl, $AuCl_3$ and $PtCl_2$ were identified as excellent catalysts. On the contrary $AuBr_3$, $PtCl_4$, AgOTf, $InCl_3$ and some Pd- and Cu-salts were inactive in this case. An apolar solvent was required with toluene and hexane giving the best results. However, in toluene conversion was faster. Acetonitrile, THF or methanol were not suited. A mechanism was proposed: initial 5-*endo-dig* cyclization is followed by [1,3]-migration and elimination of AuCl to yield benzo[*b*]thiophenes **294**. Allyl and PMB-groups could also undergo [1,3]-migration, while a regular benzyl group could not. A crossover experiment indicated that the observed migration is an intramolecular process.[136, 197] Aponick and co-workers described a 5-*endo-dig* cyclization of homopropargyl thiols with formation of thiophenes.[80]



Scheme 73. Benzo[*b*]thiophene formation catalyzed by AuCl.

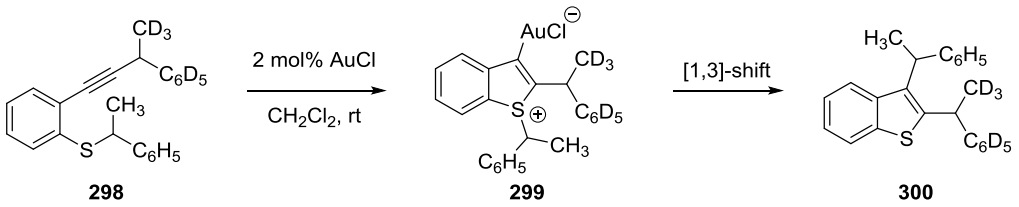
Next, the same authors investigated silyl migrating groups in a similar transformation to **297** (Scheme 74). Ring closure was followed by [1,3]-migration and silyldeauration. Interestingly, a crossover

experiment resulted in a 1/1/1/1 distribution of products: two products derived from intramolecular migration and two products derived from intermolecular migration of the silyl group. This was in contrast with the lack of crossover in the previous case (Scheme 73). The proposed reason behind these observations is the low migratory ability of silyl groups as compared to carbon migrating groups. This increased the lifetime of sulfonium **296**, hence facilitating cross-over.[197]



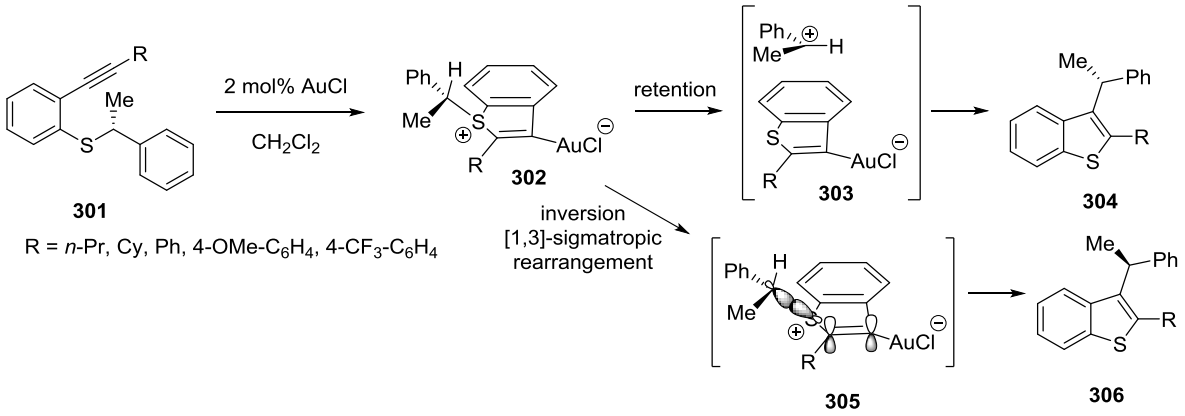
Scheme 74. Formation of 3-silylbenzo[*b*]thiophenes.

Introduction of a chiral migrating group would give more information about the precise nature of the [1,3]-migration. Treatment of chiral substrates **301** with AuCl resulted in the desired benzo[*b*]thiophenes with retention of stereochemistry (Scheme 76, *vide infra*). A deuterium labeling experiment had indicated that the migration is indeed a [1,3]-migration and not the consequence of two consecutive [1,2]-migrations (Scheme 75). If two consecutive [1,2]-shifts had occurred, scrambling of the deuterated and protonated groups would have taken place. However, this was not the case, thus corroborating a direct [1,3]-migration.[198]



Scheme 75. Deuterium labeling experiment to investigate the nature of the [1,3]-shift.

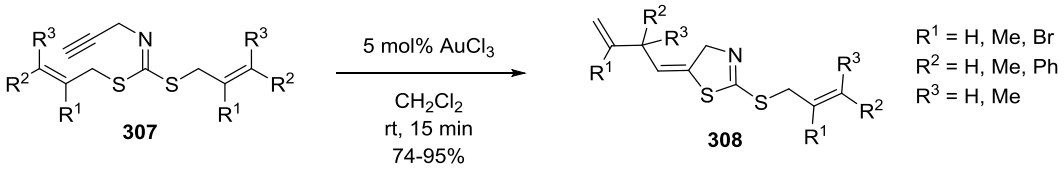
Retention of configuration in Scheme 76 suggests that a contact ion pair **303** is generated which smoothly recombines to form a new C-C bond before racemization of the stereocenter is possible. This was supported by inferior retention of stereochemistry at higher reaction temperatures due to more separation of the ion pair. The presence of an aromatic moiety in the migrating group plays an important role in light of π-π-interactions in the contact ion pair **303** (Scheme 76). In case of a sigmatropic [1,3]-shift the migration would proceed suprafacially with inversion of stereochemistry. This was not the case, so a concerted migration is unlikely.[197]



Scheme 76. Generation of a contact ion pair with retention of stereochemistry, and the unobserved sigmatropic rearrangement with inversion of stereochemistry.

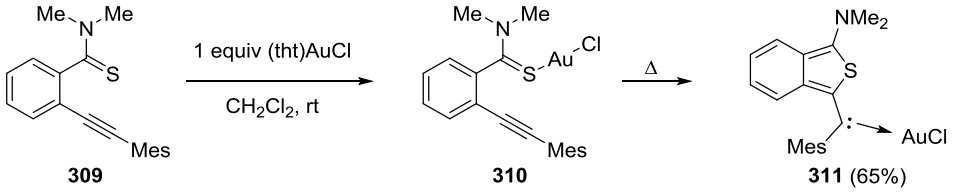
2.1.2 5-exo-dig cyclization

In 2011, the Stevens group published a $AuCl_3$-catalyzed 5-*exo*-*dig* ring closure with concomitant Claisen rearrangement for the preparation of dihydrothiazoles **308** (Scheme 77). A crossover experiment indicated that this is an intramolecular process, while selective formation of branched products **308** underlined the concerted nature of this transformation. In addition, performing the reaction in nucleophilic solvents such as methanol did not give rise to allylmethyl ethers, supporting the conclusions drawn from the crossover experiment. The exocyclic double bond in dihydrothiazoles **308** was present in the *E*-configuration according to a NOE experiment.[73]



Scheme 77. Au(III)-catalyzed cycloisomerization with formation of dihydrothiazoles.

The Bertrand group reported on one example where a *S*-atom performed a 5-*exo*-*dig* cyclization (Scheme 78). Using Au(I)Cl with a tetrahydrothiophene (tht) ligand in a stoichiometric amount, complex **310** was obtained. However, heating the reaction mixture to reflux temperature resulted in the formation of carbene **311**. This was the first example of a diarylcarbene Au-complex obtained without using a diazo precursor or an oxidative addition.[199]

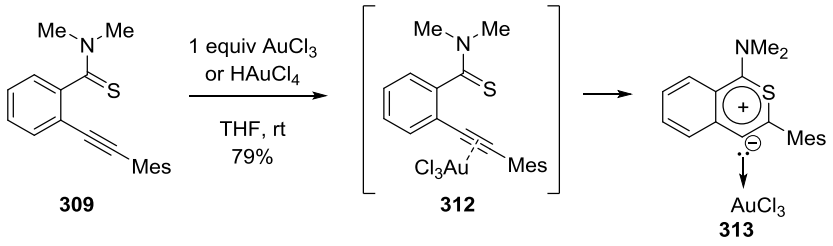


Scheme 78. Au(I)-catalyzed generation of a Au-carbene.

2.2 Formation of 6-membered rings

2.2.1 6-endo-dig cyclization

In the same report Bertrand synthesized another Au-carbene **313** via 6-*endo-dig* cyclization of a thioamide **312** (Scheme 79). This was the first metal complex with a non-*N*-containing 6-membered mesoionic carbene.[199-200]



Scheme 79. Formation of a mesoionic Au-carbene.

3. Conclusion

The Au-catalyzed cyclization reaction of *N*- and *S*-nucleophiles with alkynes is a reliable and practical manner for the construction of aza- and thiaheterocyclic compounds. The resulting mode of ring closure (*endo* vs. *exo*) is influenced by a number of factors, which in most cases allow for the selective formation of the envisioned heterocycles.

Five- and six-membered rings are the easiest cyclization products to obtain, resulting from 5-*endo*-*dig*, 5-*exo*-*dig*, 6-*endo*-*dig* or 6-*exo*-*dig* transformations. Firstly, substrate design is obviously the most determining factor in steering the regioselectivity. Both 5-*endo*-*dig* and 6-*exo*-*dig* ring closure usually occur with little formation of four- or seven-membered products, respectively, though there are exceptions (*vide supra*).

Particularly in the case where 5-*exo*-*dig* and 6-*endo*-*dig* reaction are feasible, competition between these two modes of cyclization occurs. There is no categorical recipe to exclude a cyclization mode, although some trends can be deduced from this literature overview. Terminal alkynes tend to preferentially undergo 5-*exo*-*dig* cyclization, whereas internal alkynes are more susceptible to 6-*endo*-*dig* ring closure. Furthermore, the introduction of electron-donating or electron-withdrawing substituents on the triple bond can direct the nucleophilic attack: when an electron-donating substituent is present on a triple bond, it will push the electron density of the alkyne to the distal carbon atom, thus activating the proximal (*i.e.* the *ipso*) carbon for nucleophilic attack, and *vice versa* for electron-withdrawing substituents.

Apart from substrate design, the applied catalyst can have a large impact on the mode of ring closure. This often requires a more trial-and-error approach where the oxidation state (soft Au(I) vs. hard Au(III)), the ligand (NHC's, Buchwald ligands, *etc.*) and the counterion (coordinating ability, electron-density, *etc.*) all play a crucial role in tuning the electronic and steric nature of the catalyst. When cationic Au(I)-catalysts are applied, one must keep in mind that their preparation may not be as innocent as commonly assumed due to an important "silver effect".[201-202]

The choice of solvent can exert an influence on the selectivity as well. Usually, homogeneous Au-catalysis is performed in apolar solvents such as toluene, dichloromethane and dichloroethane. However, reactions in water and other polar solvents are no exceptions.

III. Results and discussion

1. Synthetic entry into 3-phosphono-1-azabicyclo[3.1.0]hexanes

1.1 Introduction

Phosphonylated pyrroles are of interest due to their presence in bio-active molecules. Analgetic properties have been ascribed to 2-phosphonopyrroles[203] while 2-phosphonoindoles display thyromimetic (**314**),[204] anti-inflammatory (**315**)[205] and plant growth regulating qualities.[206] Furthermore, 3-carboxylpyrroles **316**, of which the phosphonates are bioisosteres, have been reported as cyclic AMP-specific phosphodiesterase inhibitors (Figure 7).[207]

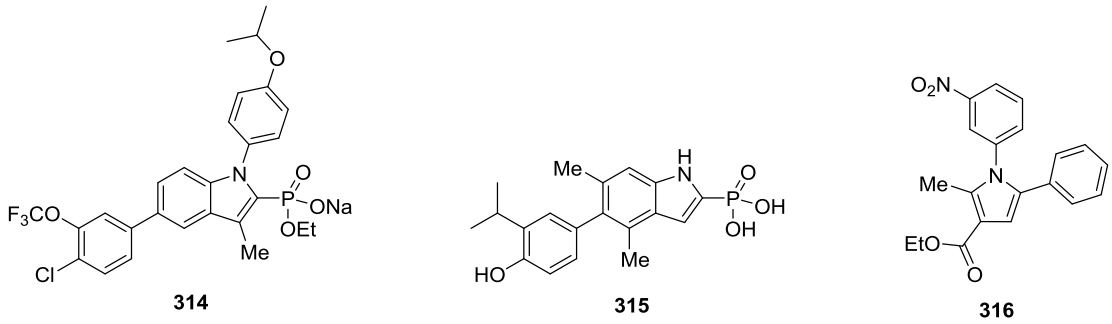
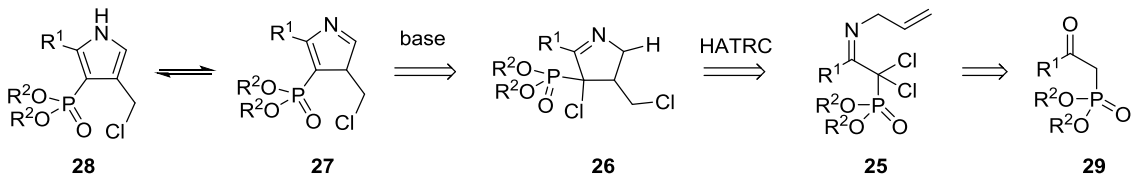


Figure 7. Examples of biologically active phosphonylated indoles and 3-carboxylpyrroles.

In continuation of the department's ongoing research on Heteroatom Transfer Radical Cyclization (HATRC) for the design of phosphonylated heterocycles,[41, 53, 59, 70, 208] and the interest in phosphonylated azadienes,[41, 66, 69] a retrosynthetic approach toward 3-phosphonopyrroles was elaborated (Scheme 80). Commercially available or easily accessible β-ketophosphonates **29** could be iminated and α,α-dichlorinated in order to generate a suitable substrate **25** for HATRC. After ring closure, a cyclic imine **26** with a leaving group in α-position could be obtained and upon treatment with base, this product would undergo a 1,4-dehydrohalogenation with formation of 3*H*-pyrrole **27**. This product would then easily equilibrate and yield the envisioned 3-phosphonylated pyrroles **28**.

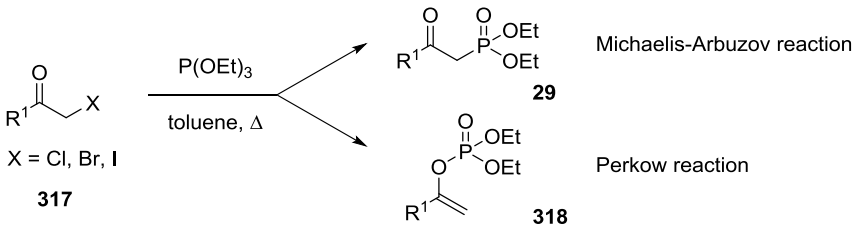


Scheme 80. Retrosynthetic approach to 3-phosphonopyrroles.

1.2 Attempted synthesis of 3-phosphonopyrroles

1.2.1 Synthesis of β-ketophosphonates 29

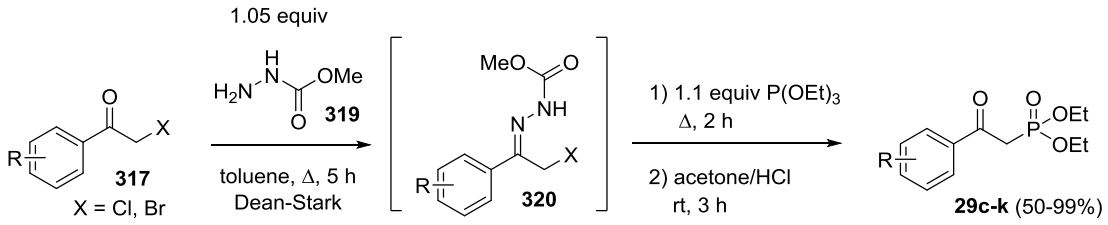
Most of the required β-ketophosphonates **29** had to be synthesized as only the derivatives with R^1 = Ph or alkyl are commercially available. In order to study the influence of the electronic properties of R^1 on the envisioned transformations we decided to use the derivatives with R^1 = Me and Ph (**29a-b**, respectively), along with a number of aptly substituted phenyl groups. Subjecting α-halo ketones **317** to classic Michaelis-Arbuzov conditions with triethyl phosphite would be the most straightforward entry in order to generate the desired β-ketophosponates **29** (Scheme 81). However, such α-halo ketones are prone to Perkow reaction, *i.e.* a side reaction arising from phosphite attack across the carbonyl function. The Perkow route yields enol phosphate esters via a zwitterionic intermediate.[209]



Scheme 81. Desired Michaelis-Arbuzov reaction and undesired Perkow reaction.

In order to avoid formation of these enol phosphates **318** during the preparation of β-ketophosphonates **29**, two literature procedures were applied: one relied on the generation of intermediate hydrazones (Method A), another employed phosphonoacetic acid (Method B). In a first approach (Method A) α-halo acetophenones **317** were converted into the corresponding hydrazones **320** (Table 2). The use of hydrazones prevented phosphite attack across the carbonyl function and favored the envisaged Michaelis-Arbuzov reaction.[209] Consecutive hydrolysis of the hydrazones in a 1/1 mixture of acetone and 2 M HCl delivered the desired β-ketophosphonates **29c-i** in good to excellent yields, as depicted in Table 2, and no Perkow-reaction was observed. Electron-poor halogen-substituted derivatives were obtained in markedly lower yields than more electron-rich derivatives (entries **29c-e** vs. **29f-h**).

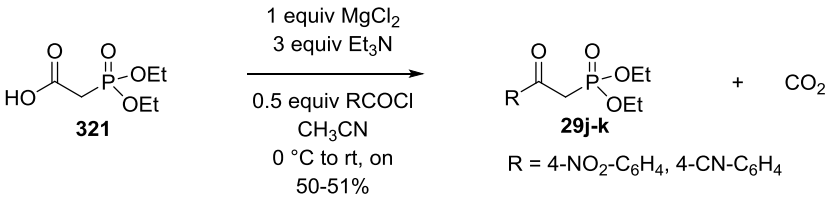
Table 2. Generation of β-ketophosphonates 29. Method A is depicted.



product	R	method	yield **29** (%)
29c	4-F	A	50[a]
29d	4-Cl	A	51[a]
29e	4-Br	A	52[a]
29f	4-OMe	A	95[a]
29g	4-Me	A	90
29h	4-Ph	A	99
29i	3-OMe	A	61[a]
29j	4-NO_2	B	51[a]
29k	4-CN	B	50[a]

[a] after column chromatography

For α-halo acetophenones with strongly electron-withdrawing groups on the phenyl ring (**29j-k**), formation of the hydrazones appeared to be troublesome, leading to severe degradation of the reaction products **320**. Hence, a different procedure using a $MgCl_2/Et_3N$ system and diethyl phosphonoacetic acid was evaluated (Method B). α-Acylation followed by decarboxylation cleanly yielded the desired electron-poor β-ketophosphonates **29j-k** (Scheme 82 and Table 2).[210] When the purity of the crude reaction product was unsatisfactory, column chromatography was performed since even small impurities caused unproportionally large amounts of side products in the following steps. Using these two methods, nine β-ketophosphonates **29c-k** of various electronic nature were obtained.



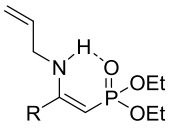
Scheme 82. Alternative synthesis of β-ketophosphonates 29 (Method B, Table 2).

1.2.2 Imination of β-ketophosphonates 29

Next, β-ketophosphonates **29** were iminated with allylamine and 5 mol% *p*-TsOH·H_2O as a catalyst under Dean-Stark conditions for 24 hours (Table 3). This transformation proceeded smoothly and resulted in the formation of a mixture of enamines **322** and imines **323**. Based on some characteristic signals in the ^{1}H-NMR spectrum the ratio of products **322**/**323** could be determined, as well as their conformation:

- the α-CH_2 signal of imines **323** is clearly visible as a doublet with $^2J_{HP}$ ≈ 22 Hz in the range of 3-4 ppm
- the α-CH signal of enamines **322** is clearly visible as a doublet of $^2J_{HP}$ ≈ 13 Hz in case of a *Z*-isomer and $^2J_{HP}$ ≈ 10-11 Hz in case of an *E*-isomer, both in the range of 3.5-4.5 ppm[211]

After reaction, a crude mixture was obtained consisting of enamines/imines **322**/**323** in ratios around 80/20 in favor of the enamines (Table 3). Only one isomer of enamine **322** prevailed, *i.e.* the *Z*-form, due to intramolecular stabilization and formation of a 6-membered ring with the phosphonate oxygen atom (Figure 8). In contrast, imines **323** were obtained in both their *E*- and *Z*-forms, most likely with the *E*-form prevailing, possibly due to the steric hindrance of the phosphonate (for exact ratios, see Table 3). However for R = Me, the conformational ratios could not be determined due to severe overlap in the ^{1}H-NMR spectrum (entry 1). It is difficult to deduce any trends with regard to the *E*/*Z* ratio from these results, even taking Hammett substituent constants into account.

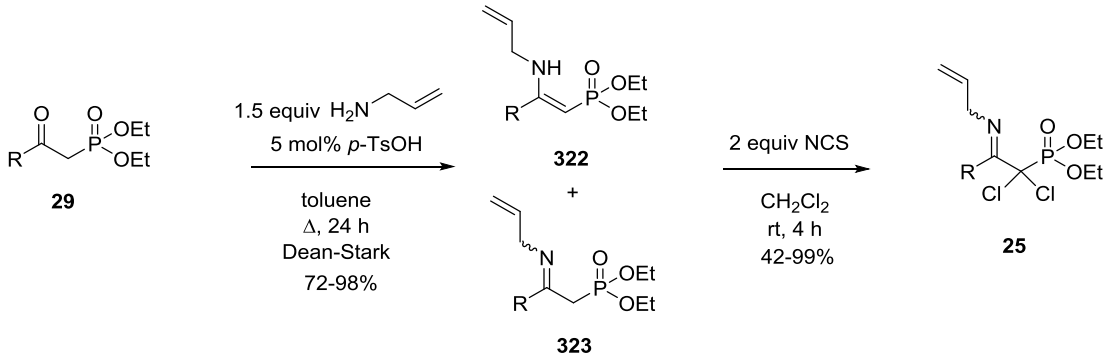


322

Figure 8. Formation of *Z*-enamines 322 due to intramolecular stabilization.

These β-enaminophosphonates **322** are versatile building blocks and accordingly, various syntheses of these molecules have been reported, *e.g.* by the addition of amines to phosphonylated alkynes[212-214] or addition of metalated dialkyl phosphonates to nitriles.[215-218] Furthermore, they can be converted into a myriad of acyclic and cyclic compounds, such as 1-aza-1,3-dienes,[219-220] pyridines[217] and pyrazoles.[219]

Table 3. Yields and conformational ratios of enamines/imines 322/323 and α,α-dichlorinated imines 25.



entry	R	yield **322** + **323** (%)	ratio **322**/**323**	ratio *E*/*Z* of **323**	yield **25** (%)
1	Me (**a**)	90	-	-	90[a]
2	Ph (**b**)	98	83/17	65/35	95
3	4-F-C_6H_4 (**c**)	89	71/29	53/47	99
4	4-Cl-C_6H_4 (**d**)	80	72/28	51/49	97
5	4-Br-C_6H_4 (**e**)	93	49/51	60/40	82
6	4-OMe-C_6H_4 (**f**)	91	73/27	59/41	92
7	4-Me-C_6H_4 (**g**)	72	74/26	73/27	96
8	4-Ph-C_6H_4 (**h**)	91	82/18	54/46	90
9	3-OMe-C_6H_4 (**i**)	98	84/16	59/41	99
10	4-NO_2-C_6H_4 (**j**)	83	50/50	93/7	42[b]
11	4-CN-C_6H_4 (**k**)	88	51/49	78/22	44[b]

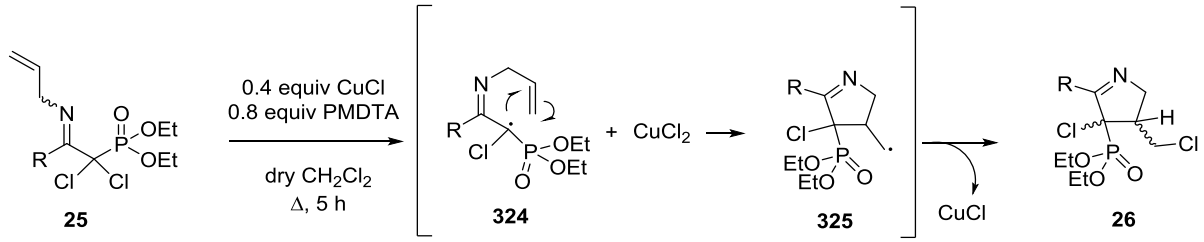
[a] *E*/*Z* ratio 3/1; [b] after column chromatography

In this work, the resulting enamine/imine **322**/**323** mixtures were α,α-dihalogenated using two equivalents of *N*-chlorosuccinimide (NCS) furnishing the α,α-dichlorinated imines **25a-k** in satisfactory yields and with high purities.[221] As chlorination proceeded through the enamine tautomer this probably ensured the *E*-form of imine **25** was obtained, though this was not explicitly determined. In addition, the steric bulk of the phosphonate and two chlorine atoms is expected to be larger than that of the R-groups, also favoring the *E*-stereomers.[222-223] These imines were present in only one isomeric form, except for **25a** (R = Me) which was present in a 3/1 *E*/*Z* mixture. No purification step was required except for the derivatives with strong electron-withdrawing groups on the phenyl ring (Table 3, entries 10-11).

1.2.3 Heteroatom Transfer Radical Cyclization

With a library of α,α-dichlorinated imines **25a-k** in hand, a HATRC was performed in order to acquire the envisaged 1-pyrrolines **26a-k** (Scheme 83).[59] Usually, copper(I) complexes mediate this free radical ring closure and their activity can be tuned by adding ligands that modify their solubility, electron density and hence, redox potential.[224] The α,α-dihalogenated imines **25a-k** were stirred with Cu(I)Cl and *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDTA) as a tridentate ligand in CH_2Cl_2 at reflux temperature. Application of other ligands such as the bidentate *N,N,N',N'*-tetramethylethylenediamine (TMEDA) gave similar results. The reaction progress was monitored using LC-MS.

Mechanistically, the HATRC starts with the abstraction of a chloride radical by a Cu(I) species which is concomitantly oxidized to Cu(II)Cl_2 (Scheme 83). The resulting organic radical can then isomerize the *E*-imine into the required *Z*-form **324** and attacks the double bond of the allyl group in a 5-*exo*-*trig* fashion, thus forming 1-pyrroline **325**.[225] No 6-*endo*-*trig* products were detected. Radical **325** then reduces the *in situ* formed Cu(II)Cl_2 back to Cu(I)Cl with generation of a chloromethyl substituent on the pyrroline **26**. After all starting material **25** was consumed (*ca.* 5 h), the crude reaction mixture was subjected to column chromatography. This yielded 1-pyrrolines **26a-k** in satisfactory yields (Table 4).



Scheme 83. Mechanism of the HATRC.

Due to the molecular reorganization caused by the radical cyclization process, two stereogenic centres were introduced into the molecule (Scheme 83, **26a-k**). Interestingly, ^{31}P-NMR analysis of the crude mixture revealed the ring closure was highly diastereoselective. Only one major peak was present, along with some small signals accounting for the minor diastereomer and some impurities. The diastereoisomeric ratios were all in the range of 90/10 and only the major diastereomer was obtained in pure form after column chromatography (Table 4).

Table 4. Diastereoisomeric ratios of the crude reaction mixtures and yields after purification.

product	R	dr[a]	yield **26** (%)
26a	Me	84/16	38
26b	Ph	90/10	93[b]
26c	4-F-C_6H_4	92/8	59
26d	4-Cl-C_6H_4	90/10	73
26e	4-Br-C_6H_4	89/11	43
26f	4-OMe-C_6H_4	85/15	45
26g	4-Me-C_6H_4	95/5	26
26h	4-Ph-C_6H_4	96/4	37
26i	3-OMe-C_6H_4	93/7	60
26j	4-NO_2-C_6H_4	93/7	23[c]
26k	4-CN-C_6H_4	95/5	14[c]

[a] based on ^{31}P-NMR integration; [b] no column chromatography necessary; [c] after first crystallization; further crystallization proved difficult so column chromatography was used if necessary

Unfortunately, the first synthesized pyrrolines **26** were not crystalline so their relative stereochemistry had to be determined using several NMR techniques. At first, a 2D-NOESY experiment demonstrated no interaction between the phosphonate ethoxy groups and H_a, possibly indicating a *trans*-configuration (Figure 9, with the chlorine and chloromethyl group *trans*). However, it is possible that due to steric crowding, the ethoxy groups turn away from the pyrroline and hence from H_a, so this experiment was inconclusive.

To tackle this issue, a heteronuclear 2D-NOESY (HOESY) experiment was performed. This is a similar technique that detects Overhauser effect between a heteroatom and protons. Accordingly such an experiment was conducted between ^{31}P and ^{1}H. In case the P and stereogenic H_a are in eachother's proximity in space, a correlation should be visible in this 2D-experiment. However, the only clear correlation visible was between the P-atom and its ethoxy groups. This experiment thus does not contradict the results from the 2D-NOESY, *i.e.* the stereogenic P and H atoms are in a relative *trans*-configuration.

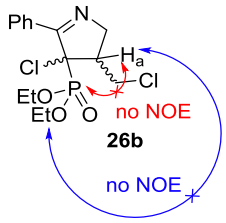


Figure 9. Absence of NOE in 26b, both between H_a and the ethoxy groups (2D-NOESY) and between H_a and the P-atom (HOESY).

Unsatisfied, we decided to try and determine the $^3J_{HP}$ coupling constant between P and H_a in **26b** in order to compare this value to literature reports and draw a conclusion with regard to the relative stereochemistry. However, this coupling constant could not straightforwardly be determined from the ^{1}H- or ^{31}P-NMR spectra (Figure 10):

- H_a couples with four adjacent hydrogens (NCH_bH_c and CH_dH_eCl) and the P-atom so in theory the signal should appear as a ddddd. This signal is visible in the ^{1}H-NMR spectrum as a multiplet.
- a ^{1}H-undecoupled ^{31}P-NMR spectrum would result in splitting of the ^{31}P-signal and possibly allow for the determination of the desired $^3J_{H_aP}$. However, coupling of P to other protons has to be taken into account.

In the ^{1}H spectrum of **26b** the only signals that couple (visibly) with ^{31}P are H_a and H_f (Figure 10, only one ethoxy moiety fully drawn). This means that coupling with ^{31}P is visible over 3 bonds and not over 4 bonds with H_b, H_c, H_d, H_e or H_g as $^4J_{HP}$ is too small or absent. Consequently, a ^{1}H-undecoupled ^{31}P-NMR spectrum would result in a ttd signal which, given the lower resolution of ^{31}P-NMR spectra, would not allow for the determination of the desired $^3J_{H_aP}$. The signals for H_f, integrating for 4H, are present in the spectra as an overlapping multiplet at *ca.* 4.0-4.2 ppm, while H_a (integrating for 1H) is present as a multiplet at *ca.* 3.2-3.4 ppm.

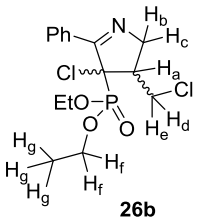


Figure 10. ^{1}H-^{31}P coupling is visible only for H_a and H_f in the ^{1}H-NMR spectrum.

These spectral properties spurred us to record a ^{1}H-undecoupled ^{31}P-NMR spectrum in which the region between 4.0-4.2 ppm of the ^{1}H spectrum was selectively irradiated. This would saturate the H_f protons and as a consequence they would not couple to P which would only leave coupling with H_a.

As such, determination of $^{3}J_{H_aP}$ from the ^{31}P-NMR spectrum should be possible. However, great care had to be taken to avoid saturation of neighbouring signals; if H_a was partially saturated as well due to too strong, unselective irradiation this would lead to incorrect results for $^{3}J_{H_aP}$.

A number of ^{1}H-undecoupled ^{31}P-NMR spectra were recorded with different intensities of decoupling irradiation to find an optimum. The corresponding ^{1}H-NMR spectra with the same intensity of irradiation were also recorded in parallel to assess whether the intensity of irradiation was sufficient or excessive. This could be quantified by comparing the integration of neighbouring signals with the aromatic signals as these were several ppm removed. The results are depicted in Figure 11 and Figure 12.

Four ^{1}H-NMR spectra are shown (Figure 11): the first spectrum (a) is a normal ^{1}H-NMR spectrum while the next three were irradiated at different intensities. The intensity of irradiation is expressed as a level of attenuation: hence, no irradiation (which results in a normal ^{1}H spectrum) is characterized by a very large attenuation of irradiation. The smaller the attenuation becomes (in dB), the stronger the irradiation of the H_f protons. This is clearly visible in the region around 4.1 ppm as the present signals become smaller until they have nearly disappeared at an attenuation of 30 dB (spectrum d). Up until 30 dB the integration of H_a (around 3.3 ppm) is unaffected but stronger irradiation at 4.1 ppm resulted in a distorted signal as well as changes in integration. We concluded that an attenuation of 35-30 dB was optimal.

The corresponding ^{31}P-NMR spectra are displayed as well (Figure 12). Without irradiation the signal is a very broad multiplet, but upon lowering the attenuation to 45 dB a doublet becomes visible while at 35 and 30 dB a clean doublet is visible. At attenuations lower than 30 dB the coupling constant $^{3}J_{H_aP}$ decreased until only a singlet signal was left, as is the case in a standard ^{1}H-decoupled ^{31}P-NMR spectrum. Based on the parallel ^{1}H-NMR spectra, $^{3}J_{H_aP}$ was calculated as the average between the coupling constants at 35 and 30 dB, *i.e.* 11.91 and 10.42 Hz, resulting in $^{3}J_{H_aP}$ = 11.2 Hz.

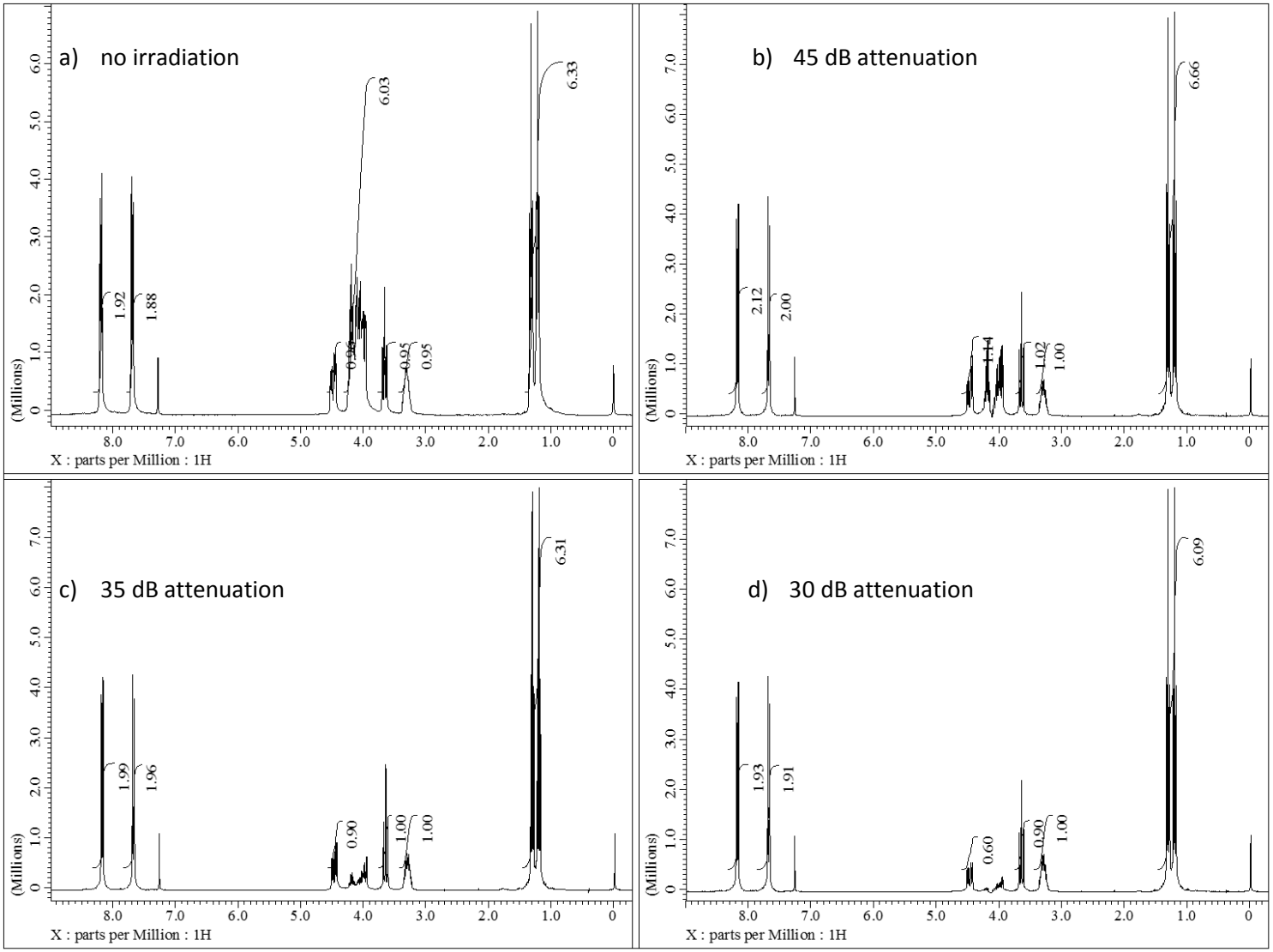


Figure 11. ^{1}H- NMR spectra (300 MHz, $CDCl_3$) of 26k without and with different intensities of irradiation at 4.1 ppm in the ^{1}H-NMR spectrum.

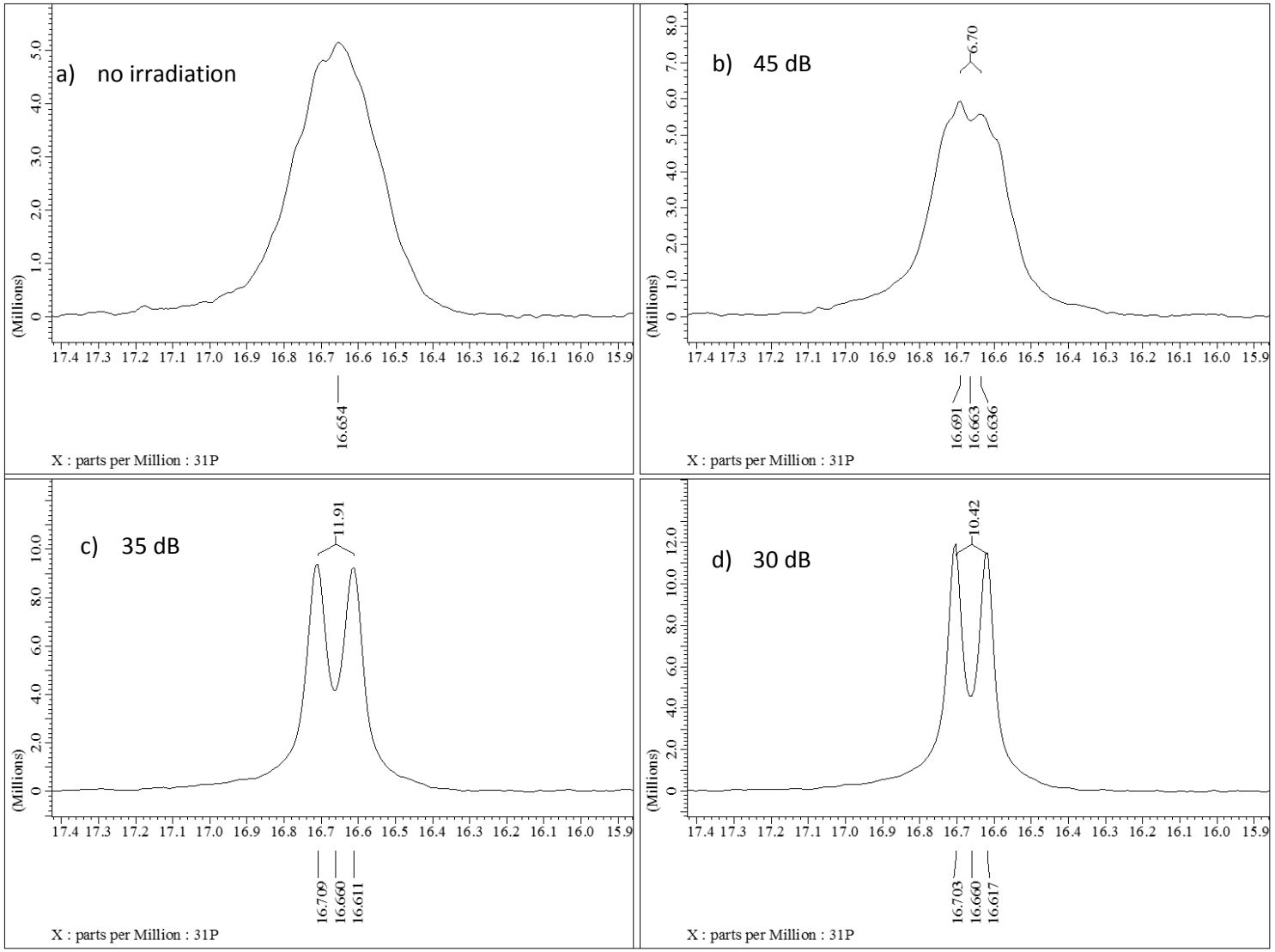
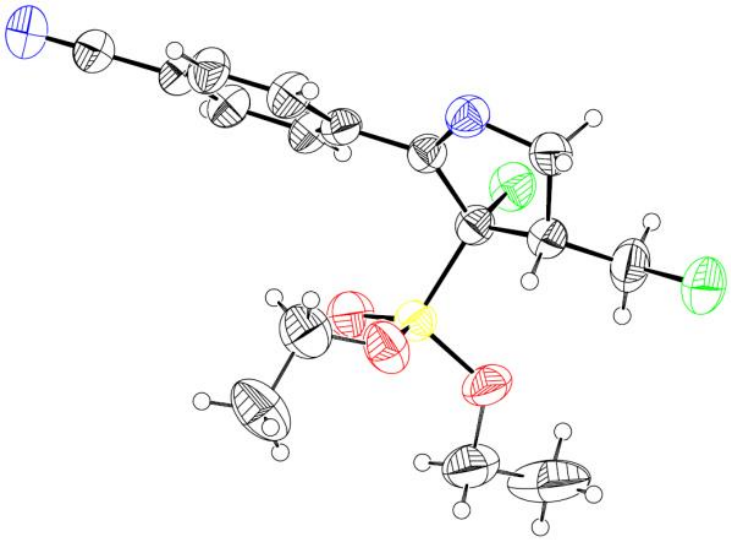


Figure 12. ^{31}P-NMR spectra (121 MHz, $CDCl_3$) of 26k without and with different intensities of irradiation at 4.1 ppm in the ^{1}H-NMR spectrum.

Literature values for $^{3}J_{HP}$ in five-membered rings have been reported as $^{3}J_{HP,trans}$ = 5.4-6.0 Hz, while $^{3}J_{HP,cis}$ = 17.2-18.0 Hz.[226] Unfortunately the coupling constant observed in **26k** lies in the middle of these two values, rendering the NMR observations inconclusive.

Fortunately, after standing on the bench for weeks two derivatives started to crystallize (**26j**, R = 4-NO_2-C_6H_4 and **26k**, R = 4-CN-C_6H_4). It must be noted that no other phosphonates synthesized in this work were crystalline so this was truly a fortunate coincidence. Crystals suited for single crystal X-ray diffraction were analyzed by Prof. Dr. Kristof Van Hecke (XStruct Bio-Inorganic group, Department of Inorganic and Physical Chemistry, Ghent University).

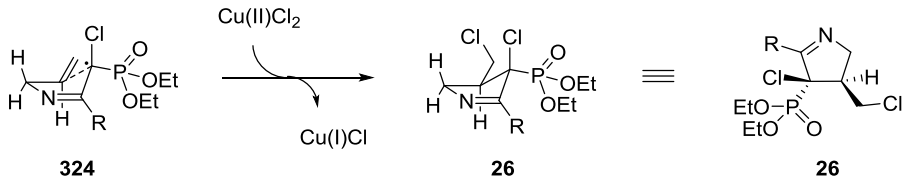
Contrary to the configuration suspected from the preliminary 2D-NOESY and HOESY NMR experiments, single crystal X-ray diffraction analyses indicated that the relative stereochemistry is *cis* (the chlorine and chloromethyl group are *cis*), with a torsion angle of -33.1(3)° between the phosphorus atom and H_a (Figure 13). The 5-membered ring is almost entirely flat. As compound **26k** crystallized in the centro-symmetric space group $P2_1/c$, both enantiomers were present in the crystal structure. Further details with regard to the crystal structures for **26j** and **26k** can be found in the experimental part of this work.



(3*R*,4*S*)-**26k** (3*S*,4*R*)-**26k**

Figure 13. Asymmetric unit of the crystal structure of 26k, showing thermal ellipsoids at the 40% probability level. Both enantiomers are present in the crystal structure. Disorder of the ethoxy groups is omitted for clarity.

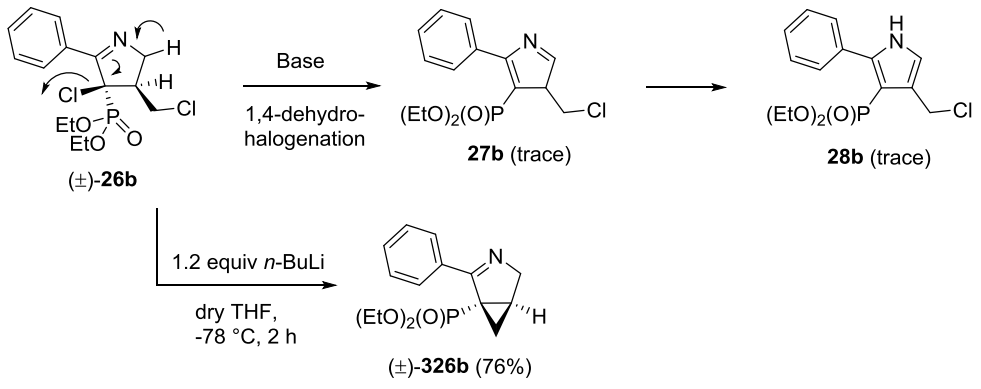
The origin of this diastereoselectivity most likely lies in steric hindrance caused by the phosphonate's bulky ethoxy substituents, as no other obvious inducing factors are present. Formation of the five-membered ring proceeds through a radical 5-*exo*-*trig* cyclization (Scheme 84). In the transition state a five-membered ring **324** is formed, with the bulky phosphonate adopting a pseudo-equatorial position. Radical ring closure is followed by recombination with a chloride radical, yielding **26**. In this manner the energetically most favorable five-membered ring is formed, being the one with the least steric repulsion in the transition state.



Scheme 84. Transition state illustrating the origin of diastereoselectivity towards the *cis*-conformers.

1.2.4 Attempted pyrrole synthesis

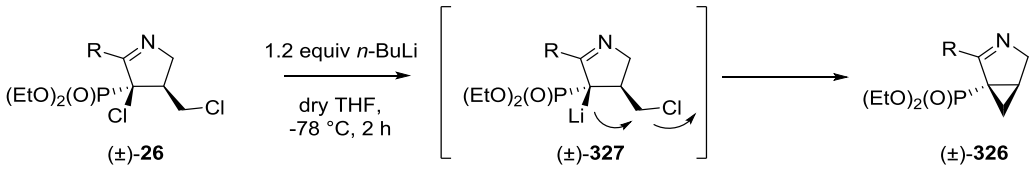
With five-membered ring **26** in hand, the initial retrosynthetic goal was to perform a 1,4-dehydrohalogenation reaction in order to ultimately obtain phosphonylated pyrroles **28** (Scheme 85).[66] As such, several bases were evaluated. Weak bases such as Et_3N or K_2CO_3 did not engender the desired elimination. Bases of intermediate strength such as KO*t*-Bu and NaH also failed to do so. The use of LiHMDS yielded a trace of pyrrole **28b** so in order to achieve complete conversion *n*-BuLi was employed. However, this resulted in the formation of an unexpected new compound instead of the envisaged pyrrole **28b**. After purification, careful NMR studies and comparison to literature spectral data,[227] the structure of this new compound was assigned as azabicyclic product **326b**.



Scheme 85. Attempted synthesis of phosphonylated pyrroles 28b through E_2.

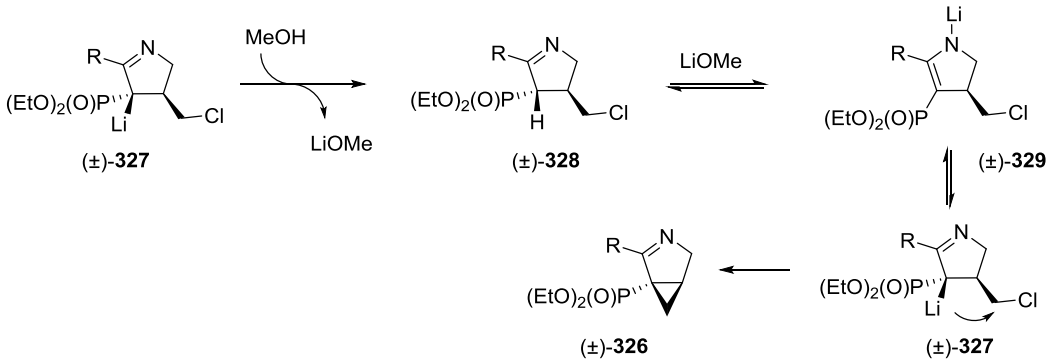
A literature search revealed that bicyclic β-aminophosphonates bearing a phosphonate moiety at the bridgehead of a bicyclic structure, such as **326b**, have only scarcely been reported.[228-232] Therefore we decided to further elaborate this route instead of the envisioned dehydrohalogenation.

A mechanism was proposed to account for the formation of azabicycle **326b**. The hypothesis was that instead of deprotonating 1-pyrroline **26b**, the alkyllithium reagent had performed a Li-Cl exchange with the tertiary chlorine atom to yield the most stable carbanion **327** (Scheme 86). This lithiated anion subsequently performed an intramolecular S_N2 affording bicycle **326b**. Although usually the formation of a tertiary carbanion should be disfavored as compared to primary carbanions, conjugation with the imine as well as the electron-withdrawing nature of the phosphonate moiety ensured that only the tertiary chlorine was exchanged, and the primary, more accessible one was left untouched.



Scheme 86. Mechanistic proposal for the formation of bicyclic phosphonates 326.

This hypothesis was proven by quenching the reaction with methanol five minutes after the addition of *n*-BuLi, as this yielded the same bicyclic product **326** (Scheme 87). Contrary, quenching the anion with acetic acid after the same time interval yielded a mixture of starting material **26**, bicycle **326** and some monochlorinated compounds, most likely **328**. Firstly, upon addition of methanol the lithiated product **327** is quenched by the acidic alcohol proton with formation of **328**. However, the *in situ* formed LiOMe is basic enough to deprotonate the β-iminophosphonate **328** and mediate the intramolecular ring closure. This deprotonation could not be accomplished by the much less basic lithium acetate. Secondly, if the primary chlorine atom had been exchanged instead of the tertiary one, lithium methoxide would not have been able to deprotonate the resulting aliphatic methyl group. Furthermore, this would imply that the primary carbanion was able to displace a tertiary leaving group, which is highly unlikely. These experiments prove that the mechanism proposed in Scheme 86 is correct: the tertiary chlorine is exchanged after the addition of *n*-BuLi and a stable aza-enolate **329** is formed. This aza-enolate then displaces the primary chlorine with formation of the annulated cyclopropane **326** moiety.



Scheme 87. Quenching of anion 327 to prove the proposed mechanism.

The other diastereoisomer of **26**, in which the tertiary chlorine and the chloromethyl group are in a *trans*-configuration, cannot directly be transformed into bicyclic product **326** as the resulting anion is too far from the chloromethyl moiety to attack. The *in situ* formation of aza-enolate **329** implies that the stereocenter at C_4 bearing the phosphonate is racemized (Scheme 87, **329**). In this case the aza-enolate **327** simply equilibrates again and the conformation required for ring closure as in **327** is attained.

1.2.5 Cyclopropanation of 26

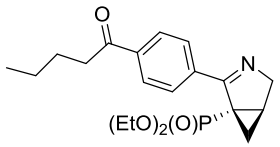
All derivatives **26a-k** were subjected to treatment with *n*-BuLi in order to form azabicycles **326**. This proceeded in acceptable yields for most derivatives (Table 5).

Table 5. Yields of cyclopropanation.

product	R	yield **326** (%)
326a	Me	-[a]
326b	Ph	76
326c	4-F-C_6H_4	49
326d	4-Cl-C_6H_4	33
326e	4-Br-C_6H_4	40[b]
326f	4-OMe-C_6H_4	51
326g	4-Me-C_6H_4	54
326h	4-Ph-C_6H_4	30
326i	3-OMe-C_6H_4	72
326j	4-NO_2-C_6H_4	20
330k	4-pentanoyl-C_6H_4	36

[a] complete degradation; [b] inseparable mixture

Treatment of **326a** with *n*-BuLi resulted in complete degradation, most likely due to α-deprotonation of the methyl group and subsequent side reactions. In the 4-Br-C_6H_4 derivative **26e** Li-Br exchange on the phenyl ring took place next to the desired Li-Cl exchange. This resulted in inseparable mixtures of brominated, chlorinated and dehalogenated products along with some cyclopropanated compound **326e**. Interestingly, Li-Cl exchange in **26d** (R = 4-Cl-C_6H_4) occurs only on the tertiary chlorine atom and not on the phenyl ring as no dehalogenated products were detected. For **26k** (R = 4-CN-C_6H_4) the simultaneous addition of *n*-BuLi to the nitrile could not be prevented, resulting in a mixture of starting material, cyclopropanated product **326k** with the nitrile intact and with a 4-pentanoyl substituent **330k** (Figure 14). Therefore, all of **26k** was converted into **330k** by adding an excess (2.2 equiv) of *n*-BuLi.



(±)-**330k**

Figure 14. Product after addition of *n*-BuLi to 26k with loss of the nitrile moiety.

1.2.6 Reduction of the imine 326

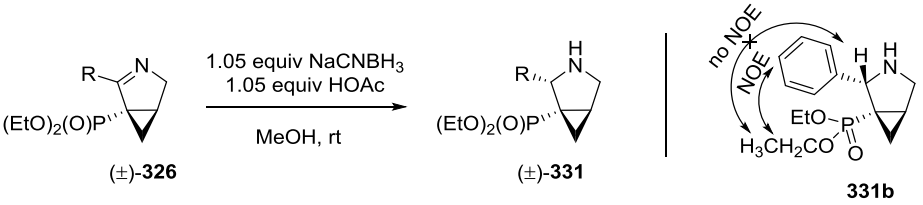
To our surprise, a reactivity study indicated that further derivatization of the imine in azabicycles **326** was extremely difficult.[233-235] Hydrolysis in neutral, acidic or alkaline medium as well as addition of alkyllithium or Grignard reagents was unsuccessful. *N*-alkylation using methyl iodide or trimethyloxonium tetrafluoroborate (Meerwein's salt) in order to activate the imine bond was ineffective, as was reduction with both $NaBH_4$ and $LiAlH_4$. However, application of equimolar amounts of $NaCNBH_3$ and acetic acid proved to be efficacious for the reduction to bicyclic pyrrolidines **331** (Table 6).[236] Reaction progress was monitored by HPLC.

The otherwise lack of reactivity of **326b-k** can be explained by steric hindrance at the imine bond caused by the bulky ethoxy groups of the phosphonate on one side, and a cyclopropane proton on the other side. These groups block the anti-bonding π*-orbitals of the imine, thus impeding attack of most species. Only the smallest nucleophiles can add on condition that the imine is suitably activated, *i.e.* by protonation.

Through this reduction, a third stereogenic centre was introduced into the molecule with high diastereoselectivity (*dr* ≥ 99/1 for all derivatives **331b-k**, based on ^{31}P-NMR). This observation may be explained by strong steric hindrance at the imine bond caused by the phosphonate. This forces the hydride to add from the less hindered side of the five-membered ring, *i.e.* the side with the

cyclopropane moiety. This results in a racemic mixture of diethyl (2-phenyl-3-azabicyclo[3.1.0]hexan-1-yl)phosphonates **331**, with the phenyl ring and the phosphonate moiety in a *cis* configuration as confirmed by 2D-NOESY. No NOE was visible between the ethoxy groups and the stereogenic NCH proton, while there was interaction between the ethoxy groups and the phenyl ring.

Table 6. Reduction of cyclic imine 326 and results from a 2D-NOESY experiment.



(±)-**326** (±)-**331** **331b**

Product	R	time (h)	yield **331** (%)
331b	Ph	1	84
331c	4-F-C_6H_4	2	74
331d	4-Cl-C_6H_4	1	85
331e	4-Br-C_6H_4	-	-[a]
331f	4-OMe-C_6H_4	16	92
331g	4-Me-C_6H_4	16	63
331h	4-Ph-C_6H_4	24	91
331i	3-OMe-C_6H_4	24	30[b]
331j	4-NO_2-C_6H_4	4	81[b]
331k	4-pentanoyl-C_6H_4	24	60[b]

[a] reduction was not performed because of impure starting material; [b] after column chromatography

A literature search indicated that in the class of 3-azabicyclo[3.1.0]hexane scaffolds, no bicycles phosphonylated at the bridgehead have been reported. The carboxylic acid derivatives on the other hand, which are bioisosteres, have been reported in patent literature and exhibit a wide range of therapeutic activities.[237] Amino acid **332** is a bicyclic GABA analog,[238] while **333** functions as a NK_1 antagonist, counteracting emesis in cancer patients receiving chemotherapy (Figure 15).[239] Coupling of the azabicyclic skeleton to larger molecules furnishes antibacterial agents **334**, antihistamines and $S1P_1$ agonists.[240-242]

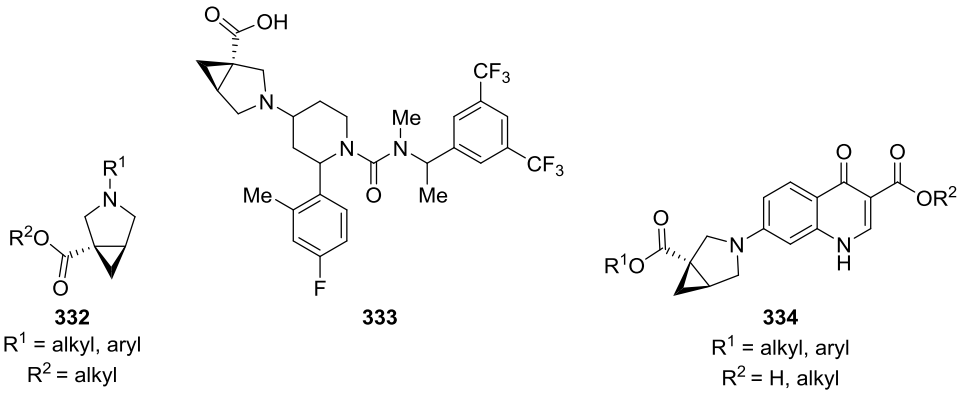


Figure 15. Biologically relevant carboxyl analogs of phosphonylated 3-azabicyclo[3.1.0]hexanes.

Furthermore, the 3-azabicyclo[3.1.0]hexane skeleton is present in bicifadine **335**, an analgesic, in boceprevir **336**, a protease inhibitor for the treatment of hepatitis C and in (+)-Duocarmycin A **337**, an antitumor alkaloid (Figure 16).[227, 243-247] The biological properties of compounds **335**-**337**, which are analogous to the synthesized azabicycles **331**, are a testimony that they are not only interesting from a synthetic point of view but they can possess interesting biological activities.

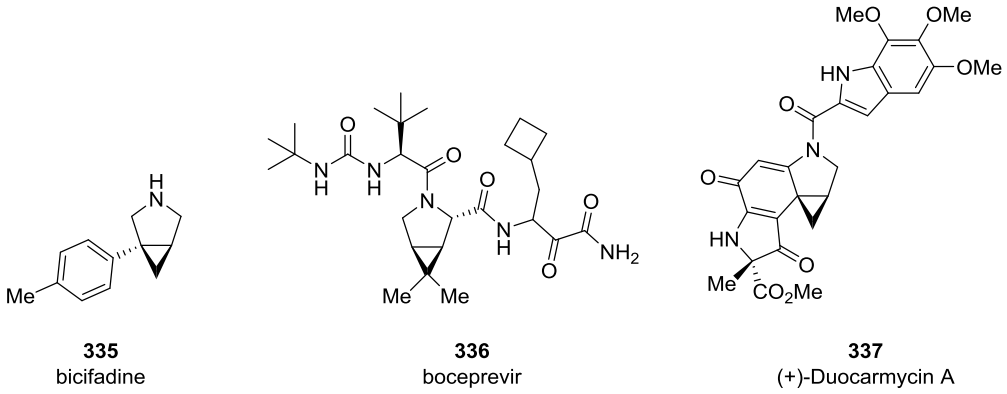


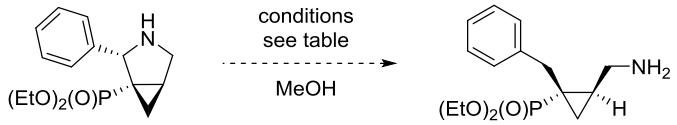
Figure 16. Biologically active 3-azabicyclo[3.1.0]hexanes.

1.2.7 Attempted ring-opening

Bicylic imines **326** have proven to be rather unreactive (*vide supra*) but the successful diastereoselective reduction of the imine towards **331** opened up some new possibilities in this reactivity study. Firstly, *N*-alkylation would lead to tertiary amines and secondly, ring-opening via intramolecular debenzylation would result in phosphonylated cyclopropanes. The latter was deemed more interesting so a number of attempts at debenzylation was made, but none resulted in the desired ring-opening to **338** (Table 7). Reactions under H_2-atmosphere with Pd/C as a catalyst resulted in only trace formation of cyclopropane at best and the addition of formic acid or acetic acid to generate the salt of **331** did not lead to improvement (entries 1-4). Application of Pearlman's

catalyst also failed, even under very large pressures up to 150 bar H_2 (entries 5-8). Finally, reaction with ammonium formate as H_2-source also failed.[248-250]

Table 7. Attempted intramolecular debenzylation of 331b with formation of phosphonylated cyclopropanes.



(±)-**331b** (±)-**338b**

entry	H_2-source	catalyst	additive	temp	time	conversion
1	1 bar H_2	20 wt% Pd/C	-	rt	18 h	-
2	5 bar H_2	20 wt% Pd/C	-	rt	24 h	trace
3	5 bar H_2	10 wt% Pd/C	5% HCOOH	rt	16 h	-
4	5 bar H_2	20 wt% Pd/C	5 equiv HOAc	rt	24 h	-
5	5 bar H_2	20 wt% $Pd(OH)_2$/C	-	rt	24 h	trace
6[a]	5 bar H_2	20 wt% $Pd(OH)_2$/C	-	rt	24 h	trace
7	50 bar H_2	20 wt% $Pd(OH)_2$/C	-	rt	2 d	-
8	150 bar H_2	20 wt% $Pd(OH)_2$/C	-	rt	3 d	-
9	5 equiv $HCOONH_4$	20% Pd/C	-	Δ	4 h	-

[a] HCl salt of **331b** was used as substrate

In another attempt, *N*-methylation of the pyrrolidine **331b** using MeI proceeded smoothly and was followed by treatment with H_2-gas under the same conditions as in entry 2, but this again resulted in full recovery of starting material. Debenzylation of this tertiary amine using 1-chloroethyl chloroformate in methanol also failed.[248]

1.3 Conclusion

In conclusion, a library of novel diethyl (2-phenyl-3-azabicyclo[3.1.0]hexan-1-yl)phosphonates **331** was synthesized in six steps from commercially available products. The required β-ketophosphonates **29** were prepared using literature procedures to circumvent the undesired Perkow reaction. This was achieved by either formation of intermediate hydrazones **320** or by use of phosphonoacetic acid, acylation and subsequent decarboxylation. Imination under Dean-Stark conditions resulted in enamines and imines **322/323**, which could smoothly be α,α-dichlorinated to **25**. Ring closure by HATRC to **26** took place in a very diastereoselective manner, due to the steric bulk of the phosphonate. Single crystal X-ray diffraction demonstrated that *cis*-pyrrolines **26** were the major

diastereomers. Subsequent treatment with bases did not result in any transformation until *n*-BuLi was evaluated. In this case however, cyclopropanation took place as a result of Li-Cl exchange and intramolecular substitution. A reactivity study indicated that these bicyclic pyrrolines **326** were very unreactive and only reduction of the imine to **331** was successful. Any further modifications failed.

At the outset of this work, phosphonylated pyrroles were the aim but an interesting and unexpected Li-Cl exchange resulted in cyclopropanation and consequently, this route was further explored.

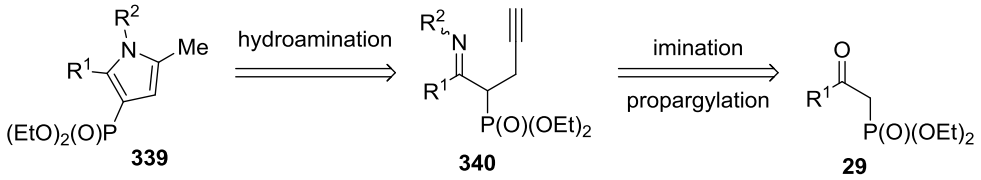
2. Preparation of tetrasubstituted 3-phosphonopyrroles through hydroamination: scope and limitations

2.1 Introduction

Our envisaged synthesis of phosphonylated pyrroles using HATRC had failed but we had not lost interest in these compounds. Therefore, another convenient synthetic methodology was sought which would enable us to prepare 3-phosphonopyrroles from β-ketophosphonates **29**.

Next to the classical Knorr, Paal-Knorr and Hantzsch pyrrole syntheses and some less prevailing name reactions such as the Barton-Zard or van Leusen transformations, multi-component reactions as well as cycloadditions have been intensively utilized for the preparation of a range of polysubstituted pyrrole cores. Another frequently applied method is the hydroamination of alkynes in order to furnish polysubstituted pyrroles using, among others,[246, 251] gold,[79, 133-134, 252] silver,[253-255] titanium[256-257] and platinum catalysts.[258-263] Only in some cases 3-pyrrolylphosphonates were obtained.[61-62, 71, 264-265] Beller and co-workers recently published a versatile Ru-catalyzed three-component reaction involving ketones, amines and vicinal diols, which is applicable to phosphonates.[266] Larionov and de Meijere reported on the formal cycloaddition of α-metalated isocyanides to acetylenes leading to pyrroles,[267-268] and Demir and Tural transformed α-cyanomethyl-β-ketophosphonates into pyrrole-3-phosphonates.[63]

Given the department's experience with transition-metal catalyzed cyclization reactions,[72-73] we envisioned a Lewis acid catalyzed cycloisomerization-type pyrrole assembly of α-propargyl imines **340** (Scheme 88). These substrates could be obtained from the already synthesized β-ketophosphonates **29** (*vide supra*, 1.2.1), in two steps by consecutive imination and α-propargylation.



Scheme 88. Retrosynthetic approach to 3-phosphonopyrroles.

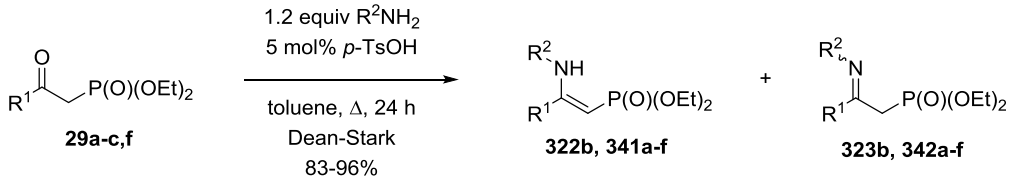
2.2 Synthesis of phosphonylated pyrroles

2.2.1 Imination of β-ketophosphonates 29

The imination of β-ketophosphonates **29a-c,f** under Dean-Stark conditions proceeded in excellent yields.[211, 269] Several amines were used in combination with various substrates to explore the scope

of the subsequent reactions (Table 8). Electron-withdrawing (**29c**) as well as electron-donating (**29f**) aromatic moieties were tolerated as R^1, while aliphatic groups could also be used (**29a**). The conversion of the β-ketophosphonates **29** was clean and quantitative. The obtained crude products consist of enamines **322b, 341a-f** and imines **323b, 342a-f** and their ratios could easily be determined by analysis of $^2J_{HP}$ in ^{1}H-NMR (see 1.2.2). The enamines **322b, 341a-f** were present in the *Z*-conformation due to intramolecular formation of a stable 6-membered ring between the NH and P=O moieties (*vide supra*, Figure 8). Conversely, imines **323b, 342a-f** were present in both their *E*-and *Z*-forms. The majority of the imines was present in the *E*-configuration due to steric hindrance between the R^2 substituent and the bulky phosphonate group.

Table 8. Preparation of phosphonylated enamines and imines. Reaction yields and conformational ratios.



substrate	product	R^1	R^2	yield **322,341 + 323, 342** (%)	ratio **322, 341 /323, 342**	*E*/*Z* ratio **323, 342**[a]
29b	**341a/342a**	Ph	Bn	95	60/40	63/37
29c	**341b/342b**	4-F-C_6H_4	Bn	92	57/43	85/15
29f	**341c/342c**	4-OMe-C_6H_4	Bn	83	70/30	55/45
29a	**341d/342d**	Me	Bn	94	63[b]/37	63/37
29b	**322b/323b**	Ph	allyl	98	83/17	65/35
29b	**341e/342e**	Ph	*n*-butyl	87	77/23	76/24
29b	**341f/342f**	Ph	Ph	96	69/31	85/15

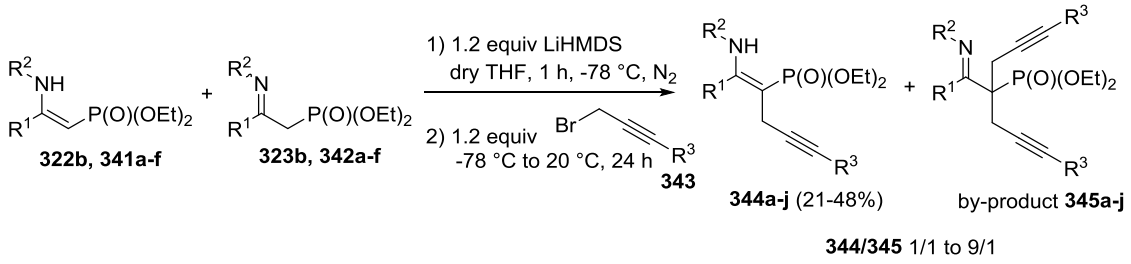
[a] based on ^{1}H- and ^{31}P-NMR; [b] the enamine **341d** is present in both the *E*- and *Z*-form, in a ratio of 2/1 respectively

2.2.2 Propargylation of 322b, 341a-f/323b, 342a-f

Next, the introduction of an alkyne moiety was achieved by treating the enamine/imine mixture **322b, 341a-f/323b, 342a-f** with LiHMDS at -78 °C, leading to the formation of the corresponding aza-enolate. This was followed by the addition of propargyl bromide **343** and allowing the reaction mixture to warm to room temperature (Table 9).

Other strong bases such as *n*-BuLi, LDA or NaH could be employed as well, but LiHMDS qualified as the most suitable base in this case: the reaction proceeded cleaner and with less generation of by-products. The reaction progress was monitored using ^{31}P-NMR spectroscopy which indicated it was difficult to obtain complete conversion. Therefore, additional base and electrophile were consecutively added until complete conversion was achieved. However, formation of bis-propargylated products **345** was inevitable. Unfortunately these compounds have retention factors that are similar to those of the desired products **344**, accounting for diminished yields after purification via column chromatography.

Table 9. Introduction of the propargylic moiety.

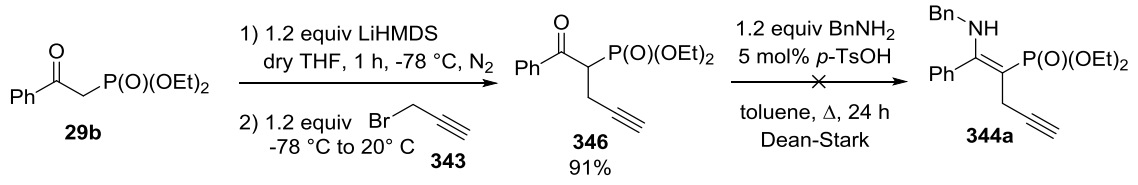


substrate	product	R^1	R^2	R^3	yield **344** (%)
341a/342a	**344a**	Ph	Bn	H	41
341b/342b	**344b**	4-F-C_6H_4	Bn	H	37
341c/342c	**344c**	4-OMe-C_6H_4	Bn	H	43
341d/342d	**344d**	Me	Bn	H	94[a]
322b/323b	**344e**	Ph	allyl	H	21
341e/342e	**344f**	Ph	*n*-butyl	H	48
341f/342f	**344g**	Ph	Ph	H	31
341a/342a	**344h**	Ph	Bn	Me	46
341a/342a	**344i**	Ph	Bn	1-naphthyl	38
341a/342a	**344j**	Ph	Bn	$SiMe_3$	45

[a] crude yield, as **344d** is unstable and degrades during column chromatography

In order to simplify the reaction sequence, we considered first propargylating the β-ketophosphonates **29** before performing the iminations. Unfortunately, the subsequent imination reaction failed, resulting in full recovery of starting material **346** (Scheme 89). This was probably due

to increased steric hindrance after introduction of the propargyl moiety, shielding the π*-orbitals at the carbonyl carbon from amine attack.



29b **343** **346** 91% **344a**

Scheme 89. Attempted imination of α-propargyl β-ketophosphonates 346.

Having synthesized terminal alkynes **344a-g**, it seemed interesting to evaluate our envisioned strategy on internal alkynes too. Especially, since they could exert both a steric and electronic effect on the future centre of reactivity, *i.e.* the triple bond.

Internal alkynes could be produced by Sonogashira coupling using terminal alkynes **344a-g** as substrates but this would require an extra step in the sequence. An alternative entry was the use of non-terminal propargyl bromides **343** with the aza-enolates obtained from **322b, 341a-f** and **323b, 342a-f**. As such, the second option employing internal propargyl bromides was adopted and a few non-terminal alkynes **344** were produced in this way (R^3 = CH_3, 1-naphthyl, $SiMe_3$, see Table 9). For R^1 = Me though (**341d/342d**), introduction of the propargyl moiety proved a lot more challenging than for the other substrates, probably due to deprotonation of the acidic methyl group. Attempted purification through column chromatography led to severe degradation, so the next step was performed using the crude product.

The thus obtained α-propargyl phosphonates **344a-j** were exclusively present as enamines, mostly in the *Z*-form although some *E*-isomer was also present. As no more α-protons were present in the ^{1}H-NMR spectra, the conformational analysis was now based on some characteristic coupling constants derived from the ^{13}C-NMR spectra:[270]

- $^3J_{CP,cis}$ ≈ 6 Hz
- $^3J_{CP,trans}$ ≈ 18 Hz

For both terminal alkynes **344a-g** and internal alkynes **344i-j** the *E*/*Z* ratio was around 1/9 while for internal alkyne **344h** the ratio was 1/4.

2.2.3 Ring closure of 344

With propargylated enamines **344a-j** in hand, we next envisioned a regioselective 5-*exo*-*dig* hydroamination reaction leading to phosphonylated pyrroles **339**. A literature search resulted in a copious amount of references regarding hydroamination catalysts, solvents and the substrate scope for the synthesis of pyrroles.[271-283]

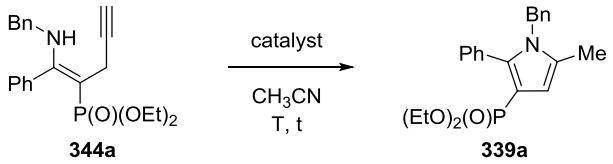
Based on our own work regarding transition metal-catalyzed cyclization reactions,[72-73, 284] several Au-catalysts were evaluated at first with **344a**, albeit with mediocre results (Table 10, entries 1-3). Formation of the desired pyrrole **339a** took place along with hydrolysis of the enamine. According to literature, application of gold chlorides under non-anhydrous conditions can lead to *in situ* hydrochloric acid formation which could account for the observed hydrolysis.[285] Indeed, 0.2 equivalents of aqueous hydrochloric acid only led to hydrolysis of the starting material and precipitation, probably due to salt formation (entry 4). Other acids such as TFA also induced hydrolysis instead of hydroamination (entry 5). Furthermore, refluxing enamine **344a** in toluene with a catalytic amount of *p*-TsOH·H_2O yielded the desired pyrrole **339a**, but given pyrrole's tendency to decompose, the room temperature catalytic approach was preferred (entry 6). It is noteworthy that in no case 6-*endo*-*dig* cyclization took place.

Gratifyingly, application of $ZnCl_2$ yielded the desired pyrrole in quantitative yield after one day while $AgNO_3$ required merely one hour (entries 7-8). Both Pd- and Cu-acetates were less suitable (entries 9-10).

Next, the catalyst loading was diminished to 5 and 1 mol% for both $ZnCl_2$ and $AgNO_3$ and the reaction times were compared (entries 11-14). For $ZnCl_2$ there was no difference in reaction time between a catalyst loading of 20 and 5 mol%. Further lowering to 1 mol% resulted in a severe decrease in reaction rate, prolonging the reaction to 144 hours. Upon application of 5 mol% $AgNO_3$ the reaction time doubled, while use of 1 mol% required 48 hours for the reaction to complete. However, prolonged exposure to $AgNO_3$ led to some slight degradation, resulting in lower yields.

As a result of these observations and as $AgNO_3$ is a factor 30 more expensive than $ZnCl_2$ (*ca.* 340 €/mol *vs.* 11 €/mol, respectively), the latter was chosen at a catalyst loading of 5 mol% for the further elaboration of the reaction scope (entry 11), in spite of the discrepancy in reaction rate. In literature, Zn-salts have often been applied for the hydroamination of alkynes.[286-297]

Table 10. Catalyst screening for pyrrole synthesis through hydroamination.



entry	catalyst	loading (mol%)	temperature (°C)	time (h)	yield **339a** (%)
1	AuCl	20	20	4	50[a]
2	$AuCl_3$	20	20	5	41[a]
3	$HAuCl_4$	20	20	4	73[a]
4	HCl_{aq}	20	20	24	0
5	TFA	20	20	24	0
6	*p*-TsOH·H_2O	10	110	48	93
7	$ZnCl_2$	20	20	24	99
8	$AgNO_3$	20	20	1	99
9	$Pd(OAc)_2$	20	20	4	23[a]
10	$Cu(OAc)_2$	20	20	24	32[a]
11	$ZnCl_2$	5	20	24	99
12	$ZnCl_2$	1	20	144	99
13	$AgNO_3$	5	20	2	94[a]
14	$AgNO_3$	1	20	48	62[a]

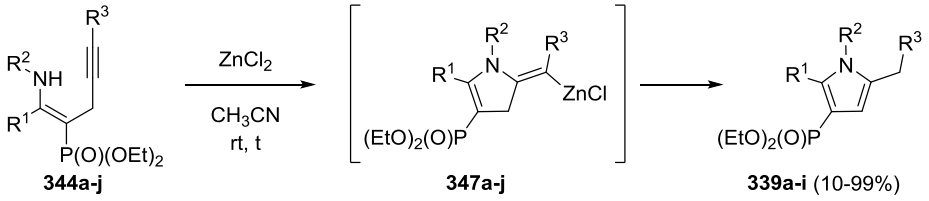
[a] after column chromatography

Having identified a suitable catalyst, a solvent screening indicated that the transformation also proceeded cleanly in more apolar solvents such as CH_2Cl_2, THF and toluene but at a slower rate (7 d). Therefore, CH_3CN remained the solvent of choice. Application of these optimized hydroamination conditions to the propargylic enamines **344** led to the desired pyrroles in good to excellent yields (Table 11). The choice of R^1 and/or R^2 does not seem to significantly influence the reaction.

However, non-terminal alkynes **344h-j** did not furnish pyrroles **339h-j** under these conditions, as only starting material was recovered after 24 hours. The reaction was therefore continued at reflux temperature (82 °C) and this did deliver the aspired pyrroles **339h-j** albeit along with hydrolysis of

the starting enamines **344h-j**. Consequently, these substrates were transformed using 20 mol% of dried $ZnCl_2$[1] in dry CH_3CN in order to speed up the pyrrole formation and counteract hydrolysis.

Table 11. Yields and reaction times for the hydroamination of enamines 344a-j with formation of the corresponding pyrroles 339a-i.[a]



344a-j **347a-j** **339a-i** (10-99%)

product	R^1	R^2	R^3	time	yield **339** (%)
339a	Ph	Bn	H	24 h	99
339b	4-F-C_6H_4	Bn	H	24 h	97
339c	4-OMe-C_6H_4	Bn	H	24 h	72[b]
339d	Me	Bn	H	45 min	10[b,c]
339e	Ph	allyl	H	20 h	89
339f	Ph	*n*-butyl	H	20 h	94
339g	Ph	Ph	H	20 h	91
339h	Ph	Bn	Me	7 d	46[b]
339i	Ph	Bn	1-naphthyl	24 h	37[b]
339j	Ph	Bn	$SiMe_3$	3 d	-

[a] conditions for terminal alkynes **344a-g**: 5 mol% $ZnCl_2$, CH_3CN, rt, air. Non-terminal alkynes **344h-j**: 20 mol% dried $ZnCl_2$, dry CH_3CN, Δ, N_2; [b] after column chromatography. [c] yield over 2 steps. Crude starting material **344g** was used and catalyst was added based on this weight, so more than 5 mol% catalyst was added which can account for the shorter reaction time

For R^3 = $SiMe_3$ though (**344j**), no pyrrole formation was detected even after 7 days reaction at reflux temperature. This may be attributed to electronic effects, as silicon is more electropositive than sp^3- and sp^2-hybridized carbon atoms and accordingly deactivates the alkyne bond for 5-*exo-dig* hydroamination. However, 6-*endo-dig* ring closure could take place in this case, but this was presumably inhibited by the sterically demanding TMS-group. For the Me and naphthyl group steric

[1] $ZnCl_2$ was dried by heating to 60 °C using an oil bath under a vacuum of *ca.* 1 mbar for 4 hours.

effects were expected to be negligible as attack takes place at the distal alkyne carbon (5-*exo*-*dig* cyclization).

2.2.4 Further derivatization of 339 via lithiation

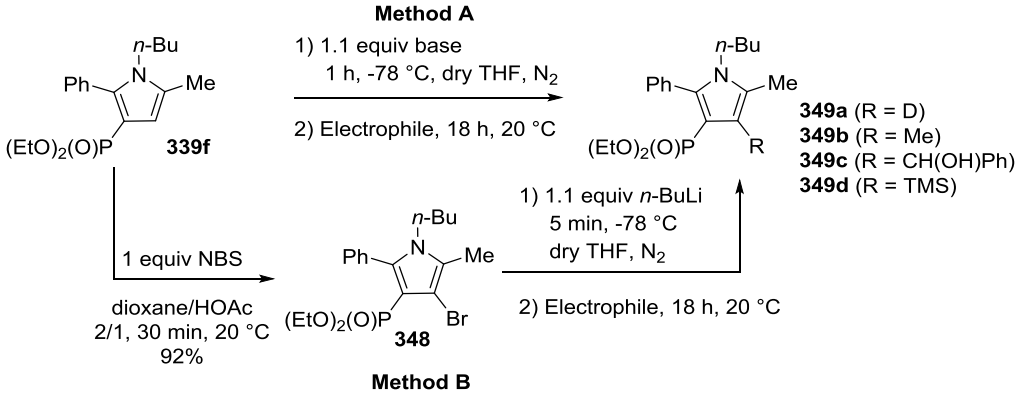
So far, a general method for the preparation of 1,2,5-substituted-3-phosphonopyrroles **339** was developed. In order to add to the versatility of the developed method, it would be interesting to be able to introduce a substituent at the 4-position as well. Retrosynthetically, this would require the use of branched propargyl halides **343,** or the obtained pyrroles **339** had to be derivatized. The first option would most likely be troublesome since branched propargyl halides are not commercially available and the introduction of the propargyl group is already the most difficult step in the synthesis. Therefore, we opted for the development of a general method for the derivatization of the obtained pyrroles **339** at the 4-position.

The most straightforward possibility was deprotonating the pyrrole C-H using a strong base followed by subsequent quenching with a suitable electrophile (Table 12, method A). In order to avoid benzylic deprotonation, **339f** was selected as substrate since it contained an aliphatic R^2 moiety on the nitrogen atom. While the presence of a methyl group in **339f** could also lead to undesired benzylic deprotonation, literature examples prove the feasibility of this approach.[298]

Initial attempts to derivatize the pyrrole **339** using *n*-BuLi were only partly successful as no complete conversion to **349** could be attained after the addition of several electrophiles. Reaction with D_2O resulted in 60% deuteration to **349a** and with the somewhat bulkier iodomethane only 21% conversion to **349b** was obtained (entries 1-2). Using benzaldehyde as an electrophile did not lead to any alkylation at all towards **349c** (entry 3). Benzaldehyde is most likely too large to approach the lithiated anion which is in the plane of the pyrrole ring and is shielded by the phosphonate group. Moreover, lack of full deuteration suggests that *n*-BuLi did not fully deprotonate the heterocycle (entry 1).

Application of stronger bases such as *s*-BuLi did lead to full deuteration, proving complete deprotonation of **339f** (entry 4). Use of iodomethane for alkylation only led to 62% conversion, which was blamed on steric hindrance, although formation of lithiated aggregates cannot be excluded (entry 5).[299] Interestingly, *t*-BuLi did not deprotonate pyrrole **339f** which again could be attributed to the sterically encumbered environment (entry 6). It is noteworthy that under these conditions no deprotonation of the methyl group on the 5-position of **339f** occurs at all, not even when using *t*-BuLi.

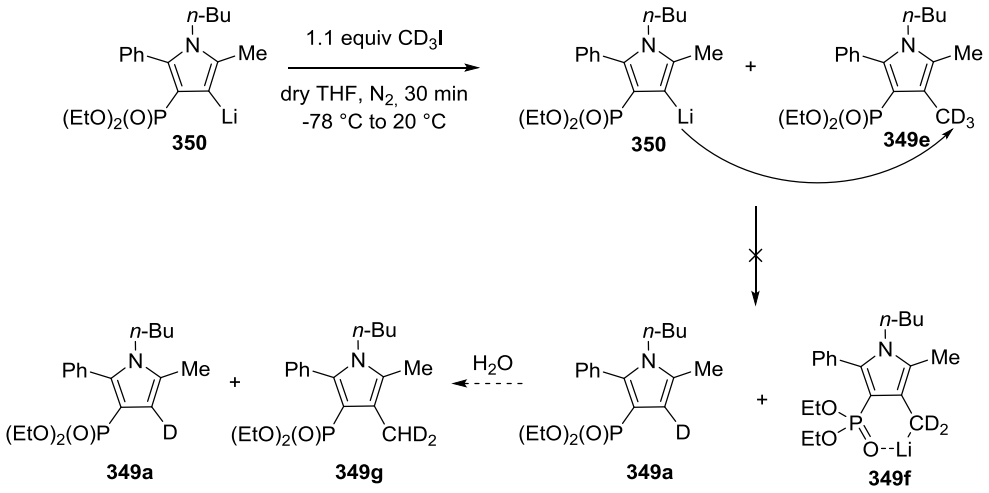
Table 12. Derivatization at the 4-position of pyrrole 339f.



entry	method	base	electrophile (equiv)	additive (equiv)	product ratio (%)	
					339f	**349**
1	A	*n*-BuLi	D_2O (excess)	-	40	60
2	A	*n*-BuLi	MeI (1.1)	-	79	21
3	A	*n*-BuLi	benzaldehyde (1.1)	-	100	0
4	A	*s*-BuLi	D_2O (excess)	-	0	100
5	A	*s*-BuLi	MeI (1.1)	-	38	62
6	A	*t*-BuLi	MeI (1.1)	-	100	0
7	B	*n*-BuLi	MeI (1.1)	-	40	60
8	B	*n*-BuLi	MeI (10)	-	31	69
9	B	*n*-BuLi	MeI (10)	AgF (1.2)	36	64
10	B	*n*-BuLi	MeI (10)	12-crown-4 (1.2)	40	60
11	B	*n*-BuLi	TMSCl (1.1)	-	98	trace
12	B	*n*-BuLi	benzaldehyde (1.1)	-	100	0
13	B	*n*-BuLi	MeI-d_3 (1.1)	-	26	74

Another effort to functionalize pyrroles **339f** involved bromination and subsequent lithium-bromine exchange (Table 12, method B).[300] The introduction of the bromine atom proceeded smoothly but attempted methylation proved just as difficult as after direct deprotonation, although method B gave cleaner results (entry 7). Even a large excess of iodomethane (entry 8) did not improve conversion, nor did the addition of AgF to precipitate AgI, or the addition of 12-crown-4 to scavenge lithium ions and counteract aggregation (entries 9-10). Introducing larger electrophiles also failed (entries 11-12). These results suggest that steric hindrance caused by the phosphonate is the factor that limits conversion.

Another possibility was that the newly introduced methyl group at the 4-position of **349e** was acidic enough to quench the remainder of the starting material **350**, thus preventing full methylation. This was probed by quenching the lithiate with iodomethane-d_3 (Scheme 90). Intermolecular deprotonation would ultimately lead to formation of deuterated pyrroles **349a** and **349g** with a CHD_2 group. However, no deuterated pyrrole **349a** was visible in ^{1}H-NMR nor LC-MS analyses. This further supports the hypothesis that steric hindrance is the limiting factor in further derivatization at the 4-position.



Scheme 90. Quench with iodomethane-d_3 to verify the hypothesis of intermolecular deprotonation after Li-Br exchange and addition of iodomethane.

2.2.5 Further derivatization via cross-coupling

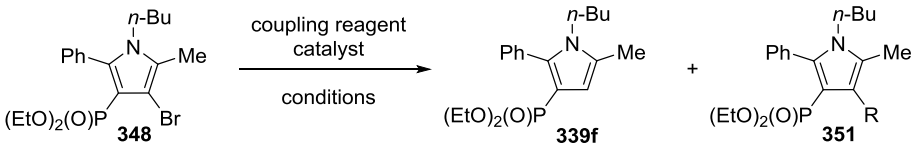
An alternative to lithiation followed by alkylation is transition metal-catalyzed cross-coupling. Admittedly, steric hindrance might equally hamper conversion in this case but the scope would be much broader. The 4-bromopyrrole **348** was subjected to standard cross-coupling procedures in order to connect the pyrrole core to a sp-, sp^2- and sp^3-hybridized carbon atom. The results are depicted in Table 13.

Attempted Sonogashira coupling yielded unreacted starting material **348** exclusively, under both conventional and microwave heating up to 130 °C (entries 1-4).[301-302] Higher temperatures were avoided to prevent thermal degradation.

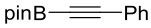
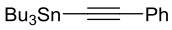
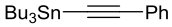
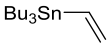
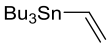
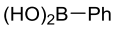
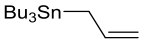
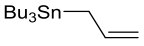
As an alternative, Suzuki coupling with 2-phenyl-1-ethynylboronic acid pinacol ester was evaluated at 130 °C under microwave irradiation.[303-305] After one hour, mainly debrominated product **339f** was recovered along with some 15% starting material **348**. This indicated that oxidative addition of the catalyst to the bromopyrrole had taken place, but the transmetalation or reductive elimination steps did not proceed (entry 5). No phenylacetylene was detected so transmetalation could not have taken

place. Prolonging the reaction time to two hours resulted in the formation of some coupled product **351** and complete consumption of the starting material **348**, along with product degradation (entry 6). However, increasing the amount of boronic ester (entry 7) or further prolonging the reaction time (entry 8) did not lead to better results.

Table 13. Transition metal-catalyzed coupling of pyrrole 348 to sp, sp^2 and sp^3 carbon atoms.



entry	coupling reagent (equiv)	catalyst	conditions	product ratio (%)[a]		
				348	**339f**	**351**
1	TMS (1.2)	2 mol% $PdCl_2(PPh_3)_2$ 1 mol% CuI	Et_3N, N_2 60 h, Δ	100	0	0
2	TMS (1.2)	2 mol% $PdCl_2(PPh_3)_2$ 1 mol% CuI	MW, Et_3N 1 h, 130 °C	100	0	0
3	TMS (1.2)	2 mol% $Pd(PPh_3)_4$ 1 mol% CuI	MW, Et_3N 1 h, 130 °C	100	0	0
4	TMS (1.2)	2 mol% $PdCl_2(PPh_3)_2$ 1 mol% CuI	1 equiv Et_3N MW, DME/H_2O 3/1 1 h, 130 °C	100	0	0
5	pinB—≡—Ph (1.3)	5 mol% $Pd(PPh_3)_4$	2 equiv Na_2CO_3 MW, DME/H_2O 3/1 1 h, 130 °C	15	85	0
6	pinB—≡—Ph (1.3)	5 mol% $Pd(PPh_3)_4$	2 equiv Na_2CO_3 MW, DME/H_2O 3/1 2 h, 130 °C	0	60	40
7	pinB—≡—Ph (3.0)	5 mol% $Pd(PPh_3)_4$	3 equiv Na_2CO_3 MW, DME/H_2O 3/1 2 h, 130 °C	degradation		

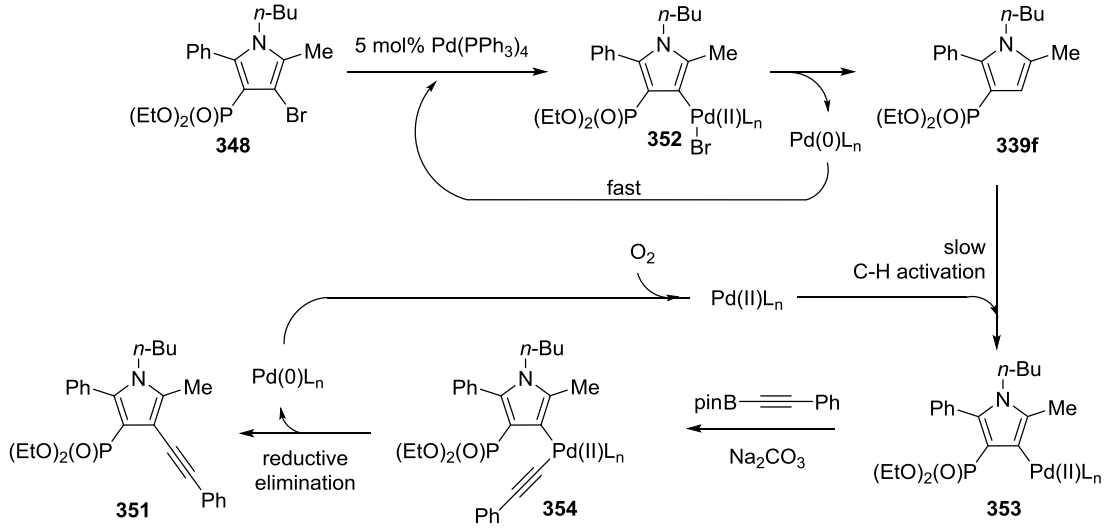
8	 (1.3)	5 mol% $Pd(PPh_3)_4$	2 equiv Na_2CO_3 MW, DME/H_2O 3/1 4 h, 130 °C	degradation		
9	 (3.0)	5 mol% $Pd(PPh_3)_4$	MW, DMF 2 h, 130 °C	40	0	60
10	 (3.0)	5 mol% $Pd(PPh_3)_4$	MW, DMF 4 h, 130 °C	25	0	75
11	 (1.2)	5 mol% $Pd(PPh_3)_4$	DMF, N_2 60 h, 100 °C	100	0	0
12	 (3.0)	5 mol% $Pd(PPh_3)_4$	MW, DMF 2 h, 130 °C	52	0	48
13	 (1.3)	5 mol% $Pd(PPh_3)_4$	2 equiv Na_2CO_3 MW, DME/H_2O 3/1 1 h, 130 °C	0	21	79 (63)[b]
14	 (3.0)	5 mol% $Pd(PPh_3)_4$	DMF, N_2 60 h, 100 °C	100	0	0
15	 (3.0)	5 mol% $Pd(PPh_3)_4$	MW, DMF 3 h, 130 °C	20	10	70 (43)[b]

[a] based on ^{1}H-NMR integration; [b] isolated yield

The results observed in entries 5-6 are peculiar and suggest another mode of action than normal cross-coupling. In entry 5, 85% debrominated product **339f** was formed and 15% starting material **348** was left. If the coupling reaction was simply blocked at the transmetalation or reductive elimination step, only 5% of debrominated pyrrole **339** would be present in the mixture. In entry 6 however, 40% of the envisioned product was formed and 60% debrominated compound **339f** remained.

These results suggest that initially, oxidative addition of the Pd(0)-species to the bromopyrrole took place as the bromine was cleaved off, after which the Pd(II)-intermediate degraded, releases **339f** and was somehow reduced to Pd(0) again (Scheme 91). This went on until all bromopyrrole had been consumed, leaving only debrominated pyrrole **339f** and the Pd(0) catalyst. As in entry 6 conversion to the desired coupled product **351** took place, debrominated product **339f** must have been able to be transformed into **351**, presumably via a C-H activation process. Oxidative addition must have been

faster than C-H activation as in entry 5 no desired product **351** was formed. C-H activation using a phosphonate, phosphate or phosphoramidate as directing group is known.[306-311] Next, oxygen that was present in the headspace might have oxidized the catalyst to Pd(II). Transmetalation with the boronate and reductive elimination then ultimately yielded coupled product **351**. However, the precise mode of action is unclear up to now and this mechanism remains speculative.



Scheme 91. Speculative mechanism based on C-H activation to account for formal Suzuki-coupling in entry 6.

Next, Stille coupling with tributyl(phenylethynyl)tin was assessed (Table 13, entries 9-10).[312-313] After two hours of microwave irradiation, 60% of coupled product **351** was observed and after four hours reaction the conversion to **351** was increased to 75%. Longer reaction times did not lead to full conversion of starting material **348**, which was chromatographically inseparable from the coupled product **351**.

Coupling of the pyrrole core to sp^2-carbon atoms was also performed by Stille coupling (entries 11-12) and Suzuki coupling (entry 13). The Stille coupling was successful only under microwave irradiation (entry 12) but the coupled product could not be isolated in analytically pure form. Suzuki coupling proceeded cleanly and resulted in the isolation of 63% **351a**. Increasing the reaction time did not lead to improved conversion to **351a**. However, the presence of debrominated product suggests that a mechanism similar to that in Scheme 91 was operative.

An sp^3-carbon was coupled to the pyrrole core in 43% isolated yield (**351b**) using allyltributyltin under microwave irradiation (entry 15) whereas conventional heating resulted exclusively in starting material (entry 14).

Overall, the best results were obtained using the Stille cross-coupling methodology. The requirement for microwave heating in these cross-coupling reactions might be attributed to the steric bulk of the

phosphonate. This hampers oxidative addition of a Pd(0) species which is often complexed to bulky phosphane ligands. Only at very high temperatures (*ca.* 130 °C) oxidative addition takes place and the coupling reaction can commence. These high temperatures might account for the degradation of certain organopalladium species (Scheme 91).

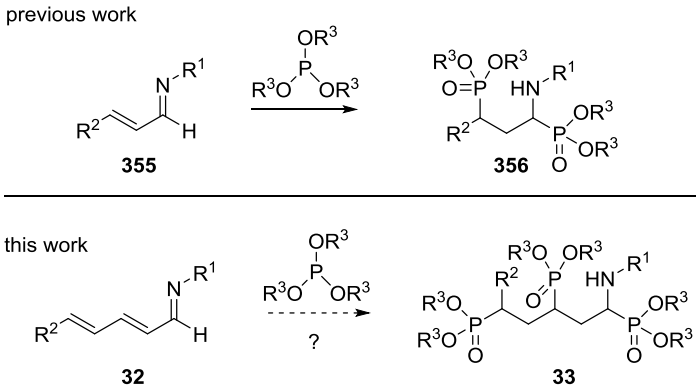
2.3 Conclusion

In conclusion, a library of 9 phosphonylated pyrroles **339** was synthesized in 3 to 4 steps depending on the substrate. Imination of β-ketophosphonates **29** was followed by α-alkylation using propargyl bromide **343** as electrophile. Full conversion was difficult to obtain and addition of extra base and electrophile resulted in mixtures of mono- and dipropargylated products. After purification, propargylated enamines **344** were obtained in the *Z*-form due to intramolecular stabilization. A catalyst screening for the hydroamination revealed that $ZnCl_2$ was the catalyst of choice and acetonitrile was the best solvent. Both terminal as well as internal alkynes could be cyclized to the corresponding pyrroles **339**, although in case of TMS-capped alkynes no reaction took place, probably due to a combination of electronic and steric factors. In addition, further derivatization of the pyrroles **339** was attempted by lithiation but this was not very successful: only deuteration resulted in full conversion while reaction with MeI and larger electrophiles was sluggish. Instead, cross-coupling strategies were evaluated which allowed coupling to sp-, sp^2- and sp^3-carbon atoms. In particular, Suzuki and Stille cross-coupling proved to be useful for further derivatization.

3. Addition of dialkyl trimethylsilyl phosphite and triethyl phosphite to α,β,γ,δ-diunsaturated imines

3.1 Introduction

In continuation of our work on tandem 1,4-1,2-phosphite addition to α,β-unsaturated imines **355**,[54, 67-70, 314] we wanted to assess the viability of a tandem 1,6-1,4-1,2-addition to suitable α,β,γ,δ-diunsaturated imines **32** (Scheme 92). Conjugate 1,6-additions (vinylogous Michael reactions) are known for C-nucleophiles, both under transition-metal catalyzed conditions as well as in an organocatalytic manner, and enantioselective variants have been reported.[315]



Scheme 92. Envisaged transformation of 32 to 33 based on previous work.

Numerous transition metals have been used to this end, of which Cu(I) has received the most attention. Cu-salts are added to transmetalate another organometallic reagent such as trialkylaluminium, Grignard reagents, diethyl zinc and organolithiums.[316-319] After initial formation of a π-complex the organocuprate undergoes addition to the unsaturated system. 1,3-Migration, or the lack of it, dictates the regioselectivity of the conjugate addition and is influenced by electronic and steric factors.[317] Pd, Ir and other metals have been reported to mediate 1,6-conjugate additions as well,[320-323] and Yamamoto even succeeded in a conjugate 1,8-addition using Pd.[321]

The approach handled in organocatalytic 1,6-conjugate addition relies on lowering the LUMO of the substrate, often by formation of an intermediate iminium ion ('vinylogous iminium ion catalysis').[324] A pending nucleophile, activated (HOMO-rising) or not, then attacks the conjugated system and is directed to the δ-position by both steric and electronic factors.[325] Application of chiral organocatalysts, *e.g.* prolinol and cinchona derivatives, has resulted in excellent remote stereocontrol.[325-329] Ooi and coworkers used triaminoiminophosphoranes, a type of phosphazenes,

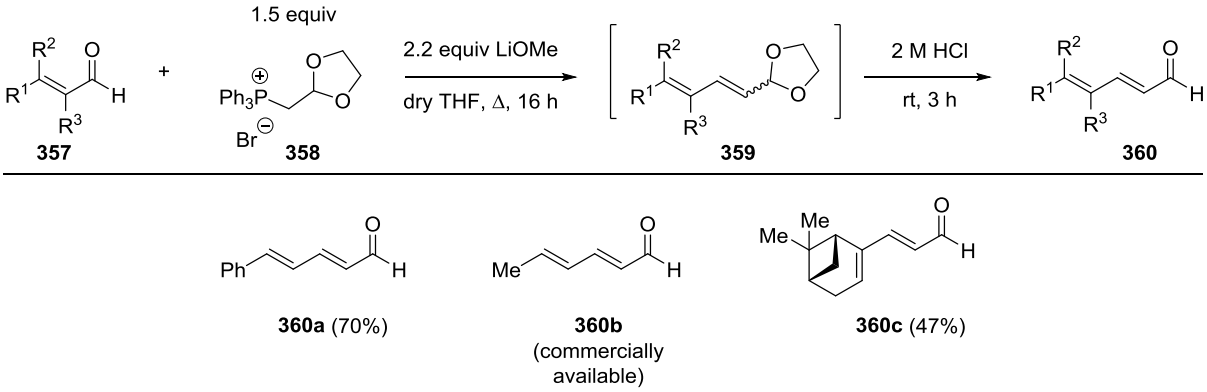
as organocatalysts which resulted in the regio-, stereo- and diastereoselective formation of 1,6- and 1,8-adducts.[324]

Selective uncatalyzed conjugate 1,6-addition has not been reported.[330] However, given the strongly nucleophilic nature of silylated phosphites and other phosphorus nucleophiles, we wanted to probe whether a tandem 1,6-1,4-1,2-addition would be feasible. Triadducts **33** are of potential biological interest as their tricarboxylic analogs display micromolar activity as agonists of ionotropic glutamate receptors (iGluRs).[331]

3.2 Attempted triphosphonylation

3.2.1 Synthesis of diunsaturated aldehydes 360

The feasibility of a tandem 1,6-1,4-1,2-addition was evaluated using both silylated phosphite nucleophiles as well as trialkyl phosphites as they both proved efficacious in previous studies. The required α,β,γ,δ-diunsaturated substrates **360** were prepared by Wittig reaction of the corresponding α,β-unsaturated aldehydes **357** according to a literature procedure, unless they were commercially available (Scheme 93).[332] After the Wittig reaction an *E*/*Z* mixture of acetals **359** was obtained but after acidic hydrolysis only *E*,*E*-isomer **360** remained and was used in the next step. Aldehydes **360** were stored under an inert atmosphere at -18 °C in the absence of light, as they were not bench-stable. In this manner two different α,β,γ,δ-diunsaturated aldehydes **360a,c** were prepared while **360b** is commercially available (Scheme 93). Aldehyde **360c** is derived from (1*R*)-(−)-myrtenal, a monoterpenoid naturally occurring in the plant *Cyperus articulatus*.[333]



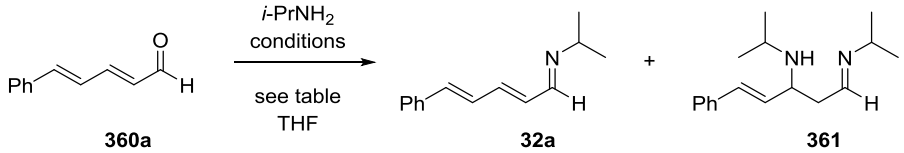
Scheme 93. Wittig reaction for the synthesis of α,β,γ,δ-diunsaturated aldehydes.

3.2.2 Imination of 360

Imination of these α,β,γ,δ-diunsaturated substrates **360** was evaluated employing *i*-$PrNH_2$ as a model amine of intermediate steric hindrance. After reaction with 1.5 equivalents of *i*-$PrNH_2$ at room

temperature it was clear that during the imination undesired conjugate addition with formation of **361** took place, accounting for superstoichiometrical yields (Table 14, entry 1). Lowering the amount of amine in combination with higher reaction temperature led to some improvement though unwanted β-amino imine **361** was still present due to difficult precise dosage of the amine (entry 2). Attempted removal of **361** by extraction using a buffer at a pH of 5.8 was successful, yet traces of hydrolysis of **32a** were present (entry 3). At a higher pH, **361** was still present while at lower pH hydrolysis of **32a** became significant. Procedures making use of the oxophilic Lewis acids $Ti(OEt)_4$ and $CuSO_4$ were evaluated but they gave rise to hydrolysis during work-up and incomplete conversion, respectively (entries 4-5). In the end a self-made 2 M stock solution of amine in THF was employed in order to avoid undesired double addition of amine (entry 6). This methodology proved efficacious and was used for all further imination reactions.

Table 14. Evaluation of different imination procedures.



360a **32a** **361**

entry	*i*-$PrNH_2$ (equiv)	additive	T (°C)	t	conversion (%)	crude yield (%)
1	1.5	2 eq. $MgSO_4$	rt	4 h	100	114[a]
2	1	2 eq. $MgSO_4$	Δ	1 h	99	105[a]
3	1	2 eq. $MgSO_4$	Δ	1 h	99	94[b]
4	1	2 eq. $Ti(OEt)_4$	Δ	20 min	100	79[c]
5	1	3 eq. $CuSO_4$	rt	16 h	80	-
6	1[d]	2 eq. $MgSO_4$	Δ	1 h	99	96

[a] yields were calculated based on the formation of **32a**; [b] acid-base extraction at pH = 5.8; [c] partial hydrolysis during work-up; [d] 2 M stock solution

Utilizing this optimized procedure, a small library of suitable imines **32** was produced using dienals **360a-c** and five different amines (Figure 17). All imines were obtained in quantitative yield, as work-up only consisted of filtration and concentration of the crude products. As these compounds are very sensitiveto hydrolysis, they were not characterized.

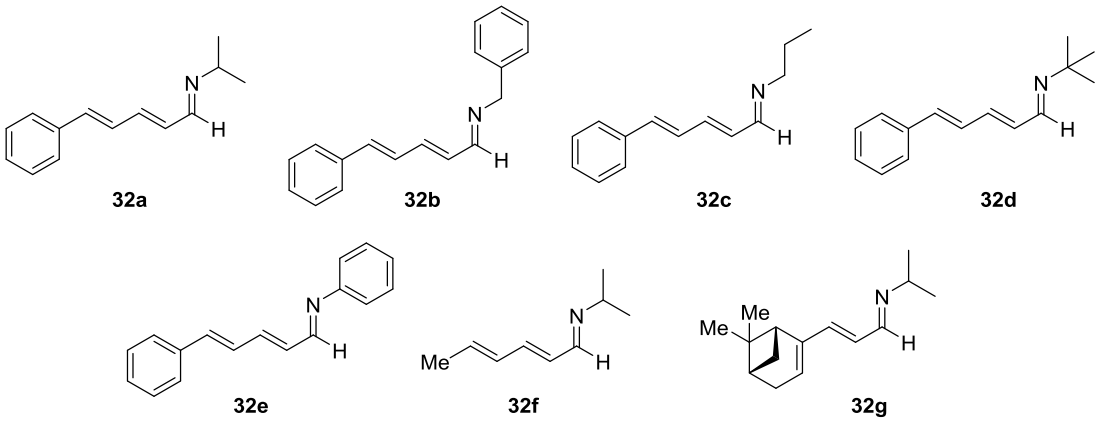


Figure 17. Synthesis of a small library of α,β,γ,δ-diunsaturated imines 32a-g.

3.2.3 Phosphite addition to 32

Subsequently, imines **32a-g** were subjected to our previously optimized conditions for a tandem 1,4-1,2-phosphite addition. In the case of α,β-unsaturated imines **355** both dimethyl trimethylsilyl phosphite (silylated phosphite, DMPTMS, Figure 18) and triethyl phosphite (TEP) could successfully perform the desired tandem 1,4-1,2-addition. Benzyl imine **32b** was used as a model substrate to minimize steric hindrance.

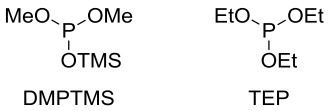


Figure 18. DMPTMS and TEP.

3.2.3.1 Dimethyl trimethylsilyl phosphite as nucleophile

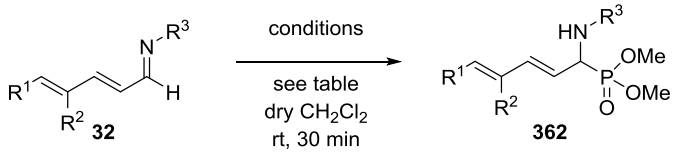
a) Synthesis

First, dimethyl trimethylsilyl phosphite was employed as a nucleophile in dry CH_2Cl_2. The same conditions as for the α,β-unsaturated substrates were employed in order to assess which positions would favor nucleophilic phosphite addition. After addition of 2 equivalents of DMPTMS to the unsaturated substrate **32b**, 0.5 equivalents of concentrated H_2SO_4 were added in a dropwise fashion (Table 15). Gratifyingly, the reaction mixture started to boil vigorously upon contact with H_2SO_4, as was the case in our previous experiments, indicating some reaction took place.[314] To our surprise, only 1,2-addition had taken place with formation of **362b**, and conversion was incomplete at 65%, despite an excess of nucleophile (entry 1). Doubling the amount of H_2SO_4 resulted in exactly the same conversion, while 2 equivalents of both H_2SO_4 and DMPTMS led to full conversion to monoadduct **362b** (entries 2-3). Addition of extra nucleophile, however, could not drive the reaction

to complete conversion (entry 4). When applying stoichiometric amounts of both nucleophile and acid, only 52% conversion could be attained (entry 5).

Extension of these reaction conditions to imines **32a-g** resulted exclusively in the formation of 1,2-addition products, *i.e.* the products of a Kabachnik-Fields reaction.[334] When more steric bulk was present at the imine functionality, more DMPTMS was required to reach complete conversion. In the case of *t*-Bu imine **32d** and *i*-Pr imine **32g** even a large excess of nucleophile was insufficient (entries 8 and 10). The other imines were completely transformed into α-aminophosphonates **362a-g**, except for **32e** (*vide infra*).

Table 15. Optimization of the addition of silylated phosphite to α,β,γ,δ-diunsaturated imines 32.



entry	substrate	DMPTMS (equiv)	H_2SO_4 (equiv)	Conversion (%)	yield **362** (%)
1	**32b**	2	0.5	65	nd
2	**32b**	2	1	65	nd
3	**32b**	2	2	100	61
4	**32b**	3	2	87	nd
5	**32b**	1	1	52	nd
6	**32a**	5	2	100	73
7	**32c**	2	2	100	81
8	**32d**	10	2	77	68
9	**32f**	5	2	100	79 (9/1)[a]
10	**32g**	5	2	89	22 (55/45)[b]

nd = not determined; [a] *E*/*Z* ratio for the distal double bond; [b] diastereomeric ratio

The isolated yields however are somewhat lower than one would expect based on the conversions due to the loss of end-product by an acid-base extraction during work-up:

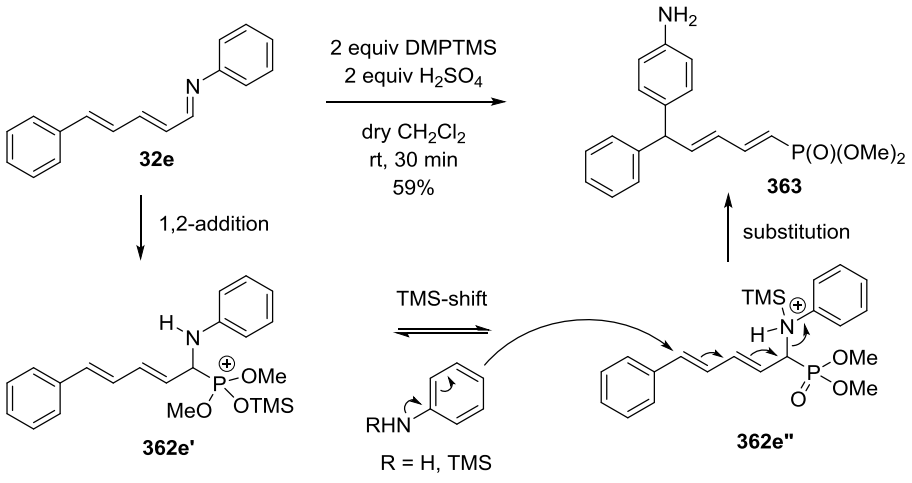
- First, the crude mixture is acidified using 2 M HCl and extracted with Et_2O. Products **362** are protonated and accumulate in the aqueous phase while the excess phosphite nucleophile remains in the organic phase. The aqueous phase is extracted twice using Et_2O. ^{31}P-NMR

analysis of the combined organic layers indicated that some product is lost in the organic phase.

- Next, the aqueous phase is rendered alkaline (pH = 14) by addition of 2 M NaOH and extracted using EtOAc. α-Aminophosphonates **362** are neutralized and return to the organic phase while the salts are washed out with the aqueous phase. ^{31}P-NMR analysis of the aqueous phase demonstrated that some product is lost during this step as well, probably due to the highly polar nature of α-aminophosphonates **362**.

Attempted direct neutralization of the crude reaction mixture using 2 M NaOH, followed by column chromatography, was unable to remove the excess phosphite from the product, necessitating the laborious and rather inefficient acid-base extraction.

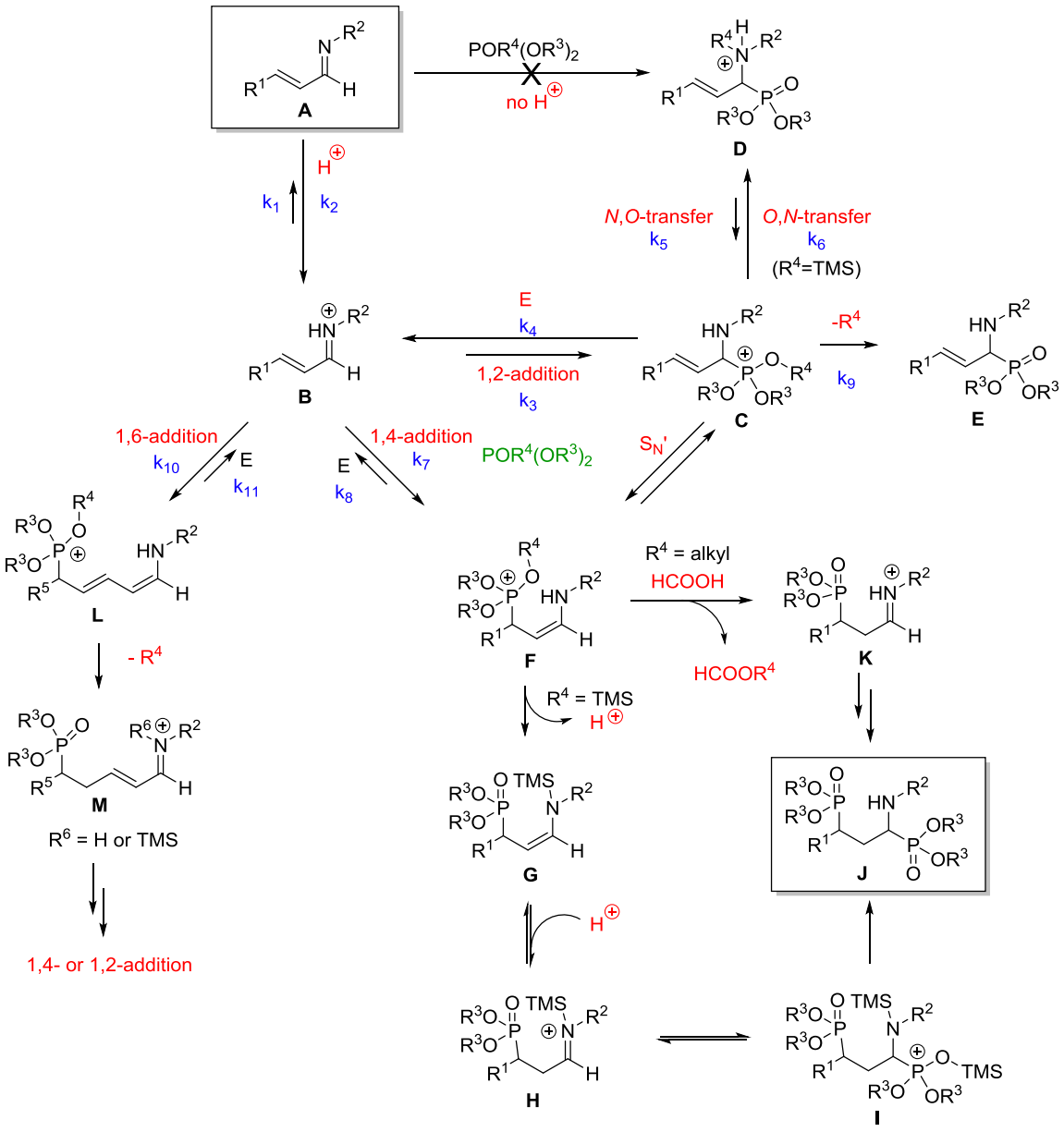
Furthermore, transformation of imine **32e** derived from **360a** and aniline resulted in complete conversion into another product, though very similar to **362**. Careful analysis of the spectra identified **363** as the compound instead of the desired α-aminophosphonate **362**, and a mechanism for its formation was proposed (Scheme 94). It starts with the desired H_2SO_4-mediated 1,2-addition of DMPTMS to **32e**. Then, a catalytic amount of aniline or *N*-TMS-aniline acts as a carbon nucleophile through its *para*-position and initiates a double S_N2' reaction on **362e"** with expulsion of *N*-TMS-aniline and formation of **363**. It is possible that a trace of aniline left from the previous imination step is responsible for this substitution reaction, as only a catalytic amount is required. This substitution was not observed for the other derivatives, perhaps because aniline is a better leaving group than aliphatic amines. Alternatively, a S_N1'-type mechanism could be operative as well, where **362e"** fragments into an aniline and a carbenium ion, which then recombines with formation of **363**. A third option was an intramolecular [5,5]-sigmatropic rearrangement.[335]



Scheme 94. Proposed mechanism for the formation of 363.

b) Mechanistic considerations

The most interesting aspect of the transformation to **362** is the lack of any 1,4- or 1,6-addition even though an excess of DMPTMS was used. Whereas α,β-unsaturated imines **355** were cleanly converted into diphosphonylated products (Scheme 92), these α,β,γ,δ-diunsaturated imines **32** only underwent 1,2-addition. It seems that an expansion of the linear unsaturated system has a dramatic effect on the reactivity of these substrates. Scheme 95 shows the elaborate reaction mechanism as it was proposed for tandem 1,4-1,2-additions to α,β-unsaturated imines using both DMPTMS and trialkyl phosphites (TAPs). It has been extended here to α,β,γ,δ-diunsaturated imines.[314]



Scheme 95. Reaction mechanism for phosphite addition to unsaturated imines.

Species **A** is first activated by protonation to **B**, otherwise no phosphite addition takes place (Scheme 95). In the case of α,β-unsaturated imines (*i.e.* our previous work), double phosphite addition takes place with the two nucleophiles, DMPTMS and TEP. Iminium **B** could first undergo both 1,2- or 1,4-addition regardless of the nucleophile, DMPTMS or TEP. Careful follow-up of the reaction progress demonstrated that 1,2-addition takes place initially with formation of **C**. This is a very unstable species and for DMPTMS, *O*-*N*-transfer of the TMS-group occurs (**C** → **D**). **D** is a resting-state and when *N*-*O*-transfer of the TMS-group takes place (**D** → **C**), **C** immediately undergoes elimination back to **B** or S_N' takes place with formation of **F**. No **E** was formed so $k_9 = 0$. If **B** is regenerated, 1,2-addition can take place again, or 1,4-addition will now proceed (**B** → **F**). **F** then equilibrates to **H** and 1,2-addition follows. For TEP the situation is somewhat different: when 1,2-addition to **B** takes place and **C** is formed, no transfer of ethyl groups or dealkylation takes place (no formation of **D** or **E**). Instead, **C** readily reverts back to **B** or S_N' takes place with formation of **F**. If **B** is regenerated, 1,4-addition can take place, also furnishing **F**. Next, dealkylation to **K** occurs and 1,2-addition takes place. In summary, α,β-unsaturated imines undergo double 1,4-1,2-addition with both nucleophiles, although 1,2-addition is usually faster but it is reversible.

In the case of α,β,γ,δ-diunsaturated imines **32** and application of DMPTMS, only 1,2-addition was observed in the end-products. This implies that **D** (which was termed a resting state) or **C** must be the only species present at the end of the reaction. As **C**, a phosphonium salt, is highly unstable and TMS-transfer with formation of **D** readily takes place, **D** is probably the only species present. Only in the case where **C** is quickly desilylated in an intermolecular fashion (**C** to **E**) could **C** be the direct source of α-aminophosphonates. This is unlikely as intramolecular TMS-shift should be faster ($k_6 >> k_9$) and no other species capable of desilylation are present in this case as compared to our previous work on the α,β-unsaturated imines **355**, where no intermolecular desilylation was observed. The conclusion is that **D** must be the only species in the reaction medium. This can only be the case if either:[314]

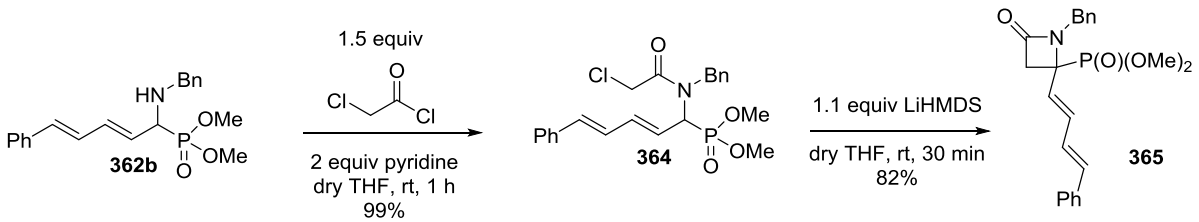
1. $k_5 \approx 0$: however, there is no obvious reason why an expansion of the unsaturated system would influence this TMS-transfer. In addition, k_5 has been shown to be very small as compared to k_6 as **D** is a resting state, so it is unlikely that such a small difference in k_5 (as compared to the previous work) would have a dramatic effect on the reaction outcome.
2. $k_3 >> k_4$: here $k_5 << k_6$ (and not $k_5 \approx 0$ as in the previous option) as was the case in the mechanism suggested for the α,β-unsaturated imines. From the moment some **C** is present (equilibrium from **D**) elimination back to **B** is possible but the equilibrium is

strongly shifted towards **C** (as k_3 is much larger than k_4, contrary to what is shown in Scheme 95) so that no 1,4-addition can occur.

The second option is more likely as the presence of an extra double bond between R^1 and the α,β-unsaturated imine (Scheme 95) might reduce the tendency of **C** to revert to **B**. Hence, the energy gained by reconjugation is not as large as for the smaller conjugated system present in α,β-unsaturated imines. Furthermore, there is no apparent reason why k_5 would equal zero instead of being very small in this case as compared to the α,β-unsaturated imines. Also, the longer lifetime of **C** could result in irreversible protonation, as an excess of H_2SO_4 is required, possibly contributing to the selectivity of the transformation (not depicted in Scheme 95). It must be said that these explanations are mere speculations and molecular modeling is currently underway to try and account for this apparent anomaly in reactivity.

c) Ring closure and further derivatization

Though they were not envisaged, the obtained α-aminophosphonates **362a-g** are interesting substrates with potential for further derivatization. In this light, benzyl derivative **362b** was smoothly acylated using chloroacetyl chloride and pyridine (Scheme 96). Next, amide **364** was treated with a slight excess of LiHMDS at room temperature in order to deprotonate the CH of the α-aminophosphonate moiety. The resulting anion could then mediate an intramolecular S_N2 of the chloride with formation of a β-lactam **365**. Due to the conjugated 4-phenylbutadiene fragment, possible delocalization of the anion followed by S_N2 of the chloride could give rise to 6- or 8-membered lactams. The experiment resulted in the formation of the corresponding phosphonylated β-lactam exclusively, indicating that conjugation did not play a role in this case.[71]

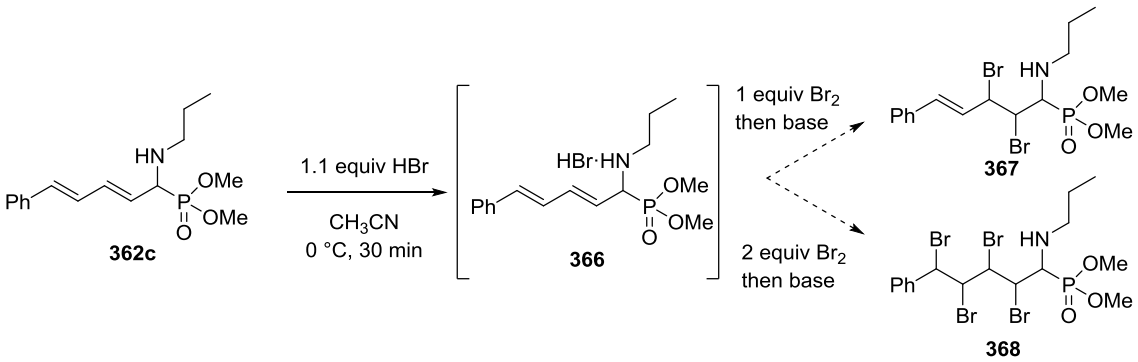


Scheme 96. Further derivatization of α-aminophosphonate 362b with formation of a phosphonylated β-lactam.

This is in agreement with the α,β-unsaturated case: the selectivity for 4-ring formation is associated with the intramolecular nature of this reaction. This is caused by hindered rotation around the C-N bond of the aminophosphonate moiety in **364**. The chloroacetyl group is preferentially oriented away from the linear unsaturated system. Hence, the transition state for 6-membered ring-formation is energetically disfavored, as much energy is required to attain it. The γ-position is more reactive in the

case of intermolecular cation trapping.[49] Phosphonylated β-lactams are of interest as potential antibiotics.[71, 336-337]

Other attempts to derivatize α-aminophosphonates **362** were carried out. In one case **362c** was treated with aqueous HBr and stirred for half an hour, before adding bromine (Scheme 97). Both the addition of 1 and 2 equivalents of bromine resulted in complex mixtures.



Scheme 97. Attempted bromination of α-aminophosphonate 362c.

3.2.3.2 Triethyl phosphite as nucleophile

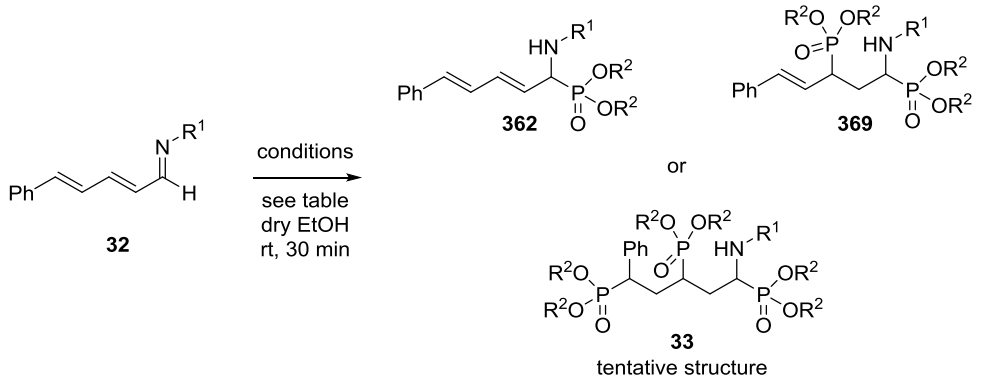
a) Synthesis

Next, triethyl phosphite (TEP) was applied as a nucleophile in dry EtOH, along with formic acid to both activate the imines and dealkylate the intermediate phosphonium ions. Without the presence of a dealkylating agent, no Arbuzov-rearrangement can take place so the unstable *in situ* generated phosphonium ions would readily collapse back (for instance **C** to **B** or **F** to **B**, Scheme 95).[338-339] As 1,2-addition is predominant at first, k_3 must be much larger than k_7, but this step is reversible and eventually 1,4-addition takes place after which **F** is then dealkylated to **K**.

As in the previous section, benzyl imine **32b** was chosen as a model substrate. Here, 3 equivalents of TEP along with 3 equivalents of formic acid were added to a solution of **32b** in dry ethanol (Table 16, entry 1). To our delight, we observed a fast and complete conversion. About 10% conversion to monoadduct **362** had taken place, but the major product was a diphosphonylated compound in 85% conversion, according to integration of the ^{31}P-NMR spectrum. Two diastereomers were present (visible as two doublets and two singlets in ^{31}P-NMR) in a 2/1 ratio but separation using column chromatography or preparative TLC proved to be extremely difficult. In the end they were separated in minute amounts using preparative HPLC. Careful NMR-analysis confirmed the structure as **369b**, with the distal double bond intact. The relative configuration of both diastereomers could be determined using 1D-NOESY spectroscopy by irradiating the CHP protons (Figure 19): the major

diastereomers have a *syn* configuration and are visible in the ^{31}P-NMR spectrum as two doublets with $^{4}J_{PP}$ = 10 Hz. The *anti* diastereomers are visible as two singlets. These results are in agreement with literature information.[340]

Table 16. Addition of P(OEt)$_3$ to α,β,γ,δ-diunsaturated imines 32.



entry	substrate	P(OEt)$_3$ (equiv)	HCOOH (equiv)	conversion (%)			*dr*[a] of **369**
				362	**369**	**33**	
1	**32b**	3	3	10	85	-	66/34
2	**32b**	6	6	-	70	-	65/35
3	**32d**	3	3	13	70	trace	43/57
4	**32d**	6	6	-	89	trace	44/56
5	**32a**	6	6	-	97	trace	60/40
6	**32a**	1	1	complex mixture			-

[a] *dr* = syn/anti, based on ^{31}P-NMR

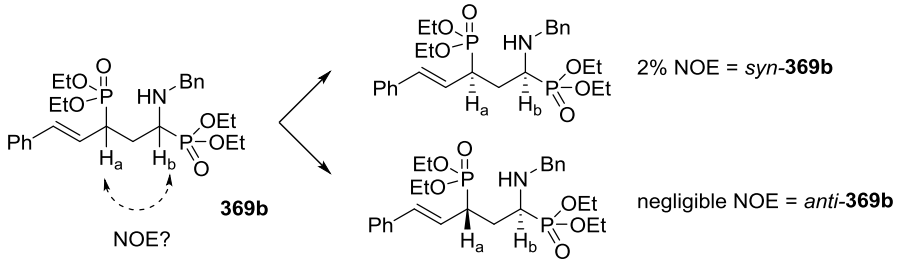


Figure 19. 1D-NOESY experiment to determine the relative configuration of both diastereomers.

Care must be taken when interpreting these results. Aminophosphonate **369b** is not a cyclic molecule and therefore its conformation is not locked, as free rotation around the single bonds can take place. This might render the conclusions drawn from the 1D-NOESY experiments doubtful. However, as **369b** contains two bulky phosphonate moieties in a 1,3-relation, its conformation is

more rigid than for sterically less-charged substrates. Moreover, it is possible that an intramolecular H-bond stabilizes the conformation between the amine and the γ-phosphonate, further impeding free rotation.[341]

The next trial (Table 16, entry 2) with 6 equivalents of nucleophile and formic acid also resulted in the formation of diphosphonylated product **369** but no monoadduct **362** was left. However, conversion was somewhat less clean. Upon treatment of *t*-Bu imines **32d** with 3 equivalents of nucleophile and acid, diphosphonylated compound **369** was again the major compound, along with some monoadduct (entry 3). Surprisingly, traces of triphosphonylated product **33** were also present according to LC-MS analysis. Doubling the amounts of reagents resulted in 89% conversion to diadduct **369** with no monoadduct present. Again some traces of triphosphonylated product **33** were detected. It is noteworthy that the *dr* for this substrate has shifted in favor of the *anti* isomers. Use of *i*-Pr imine **32a** and an excess of nucleophile and acid resulted in nearly quantitative formation of diphosphonylated product, again with a trace of triphosphonylation (entry 5). The obtained *dr* was comparable to the one for **32b** as substrate. Use of stoichiometric amounts of reagents gave rise to a complex mixture (entry 6).

b) Mechanistic considerations

The presence of trace amounts of 1,6-1,4-1,2-tandem addition products for the addition of $P(OEt)_3$ to **32d** and **32a** (*t*-Bu and *i*-Pr imine, respectively) suggests that the steric bulk of the imine is a governing factor in the regioselectivity of the addition. When the steric bulk is small, 1,4-addition will take place first (probably after reversible 1,2-addition) although 1,2-addition cannot be neglected ($k_4 > k_8$, Scheme 95). Once dealkylation of 1,4-adduct **F** has taken place to **K**, the possibility of 1,6-addition is lost and 1,2-addition will follow. Obviously, when 1,2-addition has taken place and dealkylation occurs from **C** to **E**, 1,4- or 1,6-addition will not proceed anymore.

Consequently, in order to selectively obtain 1,6-1,4-1,2-conjugate addition, the 1,6-addition must take place first ($k_{10} > k_3$ and $k_{10} > k_7$) and $k_{10} > k_{11}$, or $k_4 > k_3$ and $k_8 > k_7$ so there is plenty of **B** present whilst $k_{10} \geq k_{11}$. Once 1,6-addition has taken place, the competition between 1,4- and 1,2-addition will recommence as in the case for α,β-unsaturated imines, starting from **M** (same case as for **B**). The tendency for 1,6-addition could be stimulated by using very bulky imines that disfavor 1,2- and 1,4-addition.

Apart from steric factors, computational calculations have indicated that the orbital coefficients of the LUMO at the C_6-carbon in **370** are considerably smaller than at the C_4- and C_2-carbons according to a literature report by Hayashi *et al*. (Figure 20). Furthermore, the Mulliken and CHelpG atomic

charges demonstrate that the positive charge decreases in the order $C_2 > C_4 > C_6$. These calculations underline the difficulties to be overcome for a tandem 1,6-1,4-1,2-addition.[328] It must be noted that it is not sure that ground-state properties as calculated in this example would have a decisive influence on the transition state energies, as the transformations under consideration involve equilibria or endothermic processes leading to high-energy phosphonium salts.

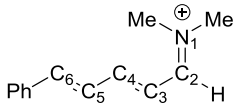


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Figure 20. Model used for the calculation of π-orbital coefficients of the LUMO and the atomic charges.

3.3 Conclusion

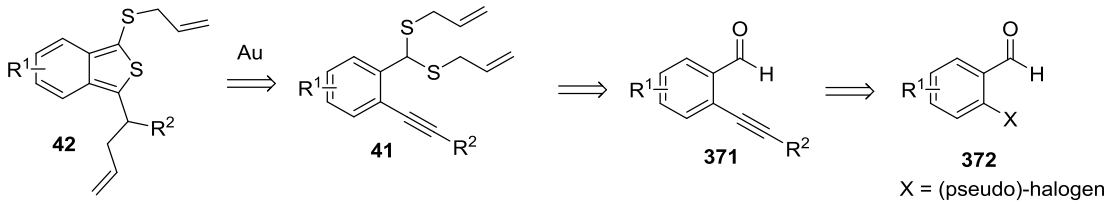
In conclusion, phosphite addition to α,β,γ,δ-diunsaturated imines **32** has been evaluated using both silylated phosphite nucleophiles as well as trialkyl phosphites. The substrates were obtained in two steps via Wittig reaction of monounsaturated aldehydes **357** followed by imination. Next, two types of phosphorus nucleophiles were added that result in aminophosphonates. Surprisingly, silylated phosphite (DMPTMS) attacked in a 1,2-fashion exclusively as opposed to the results obtained with α,β-monounsaturated imines **355** in earlier work. An attempt was made to account for this anomaly based on the extended general mechanism. Next, the obtained aminophosphonates were acylated and deprotonation resulted in intramolecular ring closure to β-lactams **365**.

On the other hand, application of triethyl phoshite mainly resulted in tandem 1,4-1,2-addition products **369**, parallel to our earlier work, while some monoaddition occurred as well. Only traces of 1,6-1,4-1,2-triaddition were found upon application of sterically hindered imines as substrates. These results were also correlated to the general mechanism in an attempt to account for the observed results.

4. Gold-superacid catalyzed preparation of benzo[*c*]thiophenes

4.1 Introduction

The department's interest in Au-catalysis was originally sparked with the discovery that phosphonoisoindoles could be produced starting from *N*-(*o*-ethynylbenzyl)-α-aminophosphonates (Scheme 6). This transformation was performed under microwave irradiation at 165 °C but it was soon found that similar transformations could be mediated by $AuCl_3$ at ambient temperature.[55, 72] Consequently, cyanoisoindoles and dihydrothiazoles were prepared from similar systems.[72-73] Based on this methodology, a three-step approach toward benzo[*c*]thiophenes **42** was proposed (Scheme 98).[140, 259-260, 342-344] Starting from *ortho*-halobenzaldehydes **372**, of which plenty of derivatives are commercially available, *ortho*-ethynylbenzaldehydes **371** could be produced via Sonogashira-coupling. These substrates could then be converted into dithioacetals **41**, which were the desired reactants to be subjected to Au-catalyzed ring closure.



Scheme 98. Retrosynthetic approach to benzo[*c*]thiophenes using Au-catalysis.

Benzo[*c*]thiophenes or isothianaphthenes **42** are of particular interest to material chemists. Most of their applications rely on their presence in oligomers or polymers, bestowing specific photochemical and -physical features on these materials.[345] They are used in the generation of organic light-emitting diodes (OLEDs),[346-350] as colorimetric fluoride anion chemosensors,[351] as chromophores for non-linear optics materials,[352] as NIR contrast agents for biomedical applications[353-354] and in transistors.[353] However, benzo[*c*]thiophene oligomers are mostly applied in organic photovoltaic cells (OPV) due to their small band gap, as a cheaper alternative to silicon based solar cells.[74, 355-365] Hitherto, benzothiophene-based OPVs with efficiencies exceeding 7% have been reported, in contrast to Si-based solar cells which display efficiencies of *ca.* 15%.[366-368]

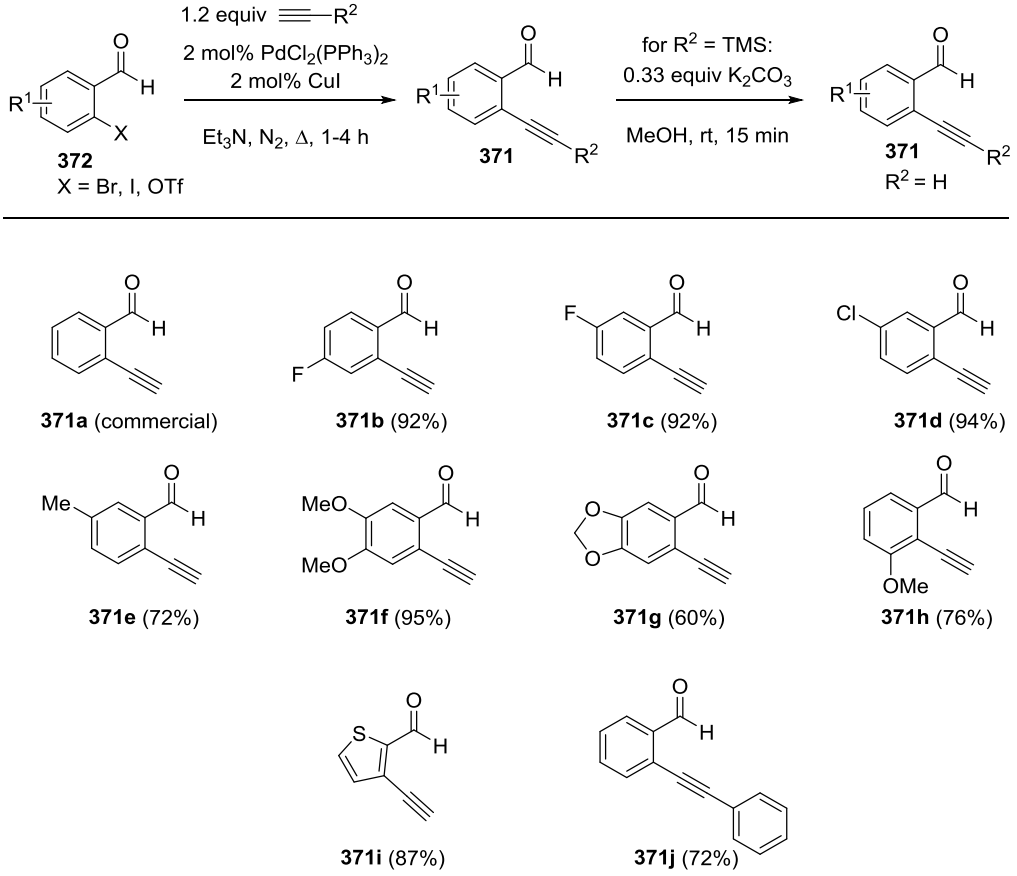
Despite the wide applicability of benzo[*c*]thiophenes in material sciences, the scope of reactions to generate them remains relatively limited. Most methods rely on thionating agents such as Lawesson's reagent or P_2S_5, which display poor atom economy.[345, 352, 354-355, 369] In other cases, the

benzene ring is annulated onto a thiophene or the corresponding dihydroisothianaphthene is oxidized to the desired isothianaphthene.[74, 347-350, 357-358, 361-364, 370]

4.2 Synthesis of benzo[*c*]thiophenes

4.2.1 Preparation of o-ethynyl aromatic aldehydes 371

A number of aptly substituted *ortho*-ethynyl benzaldehydes **371** was purchased or prepared via Sonogashira coupling, according to a literature procedure (Scheme 99).[301-302] The substrate scope was further expanded using thiophene-2-carbaldehyde **371i** and an internal alkyne **371j** instead of terminal ones. No halogenated starting material for Sonogashira coupling to **371h** was commercially available so the corresponding salicylaldehyde was triflated instead.[371] In general these coupling reactions and deprotections proceeded smoothly in excellent isolated yields.



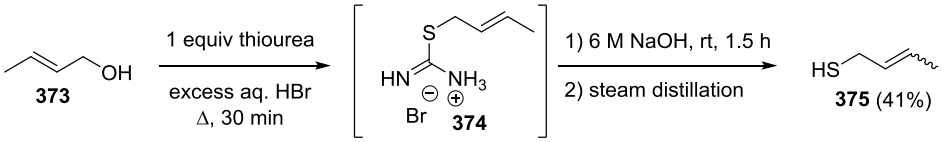
Scheme 99. Preparation of *ortho*-ethynylbenzaldehydes and 3-ethynylthiophene-2-carbaldehyde 371.

4.2.2 Dithioacetalization of 371

4.2.2.1 Precursor synthesis

Next, these aldehydes had to be converted into the corresponding diallyl thioacetals **376**. Allyl mercaptan would be used for most derivatives and crotyl mercaptan for one (**376k**). These reagents deserve some special attention: allyl mercaptan is a commercially available liquid but only in *ca.* 60% purity so purification was required. However, allyl mercaptan (bp 69 °C) has a very bad, pungent, garlic-like odor which impedes straightforward distillation (odor detection threshold 0.2 ppb; for comparison, H_2S and triethylamine have odor detection thresholds of 0.5 ppb and 5 ppb, respectively).[372] Instead, a vacuum-distillation was performed and it is imperative that the outlet of the pump is connected to two washing flasks in order to eliminate any residual allyl mercaptan (one with a 5 wt% H_2O_2 solution, another with aqueous 0.5 M NaOH). More details can be found in the experimental part of this work.

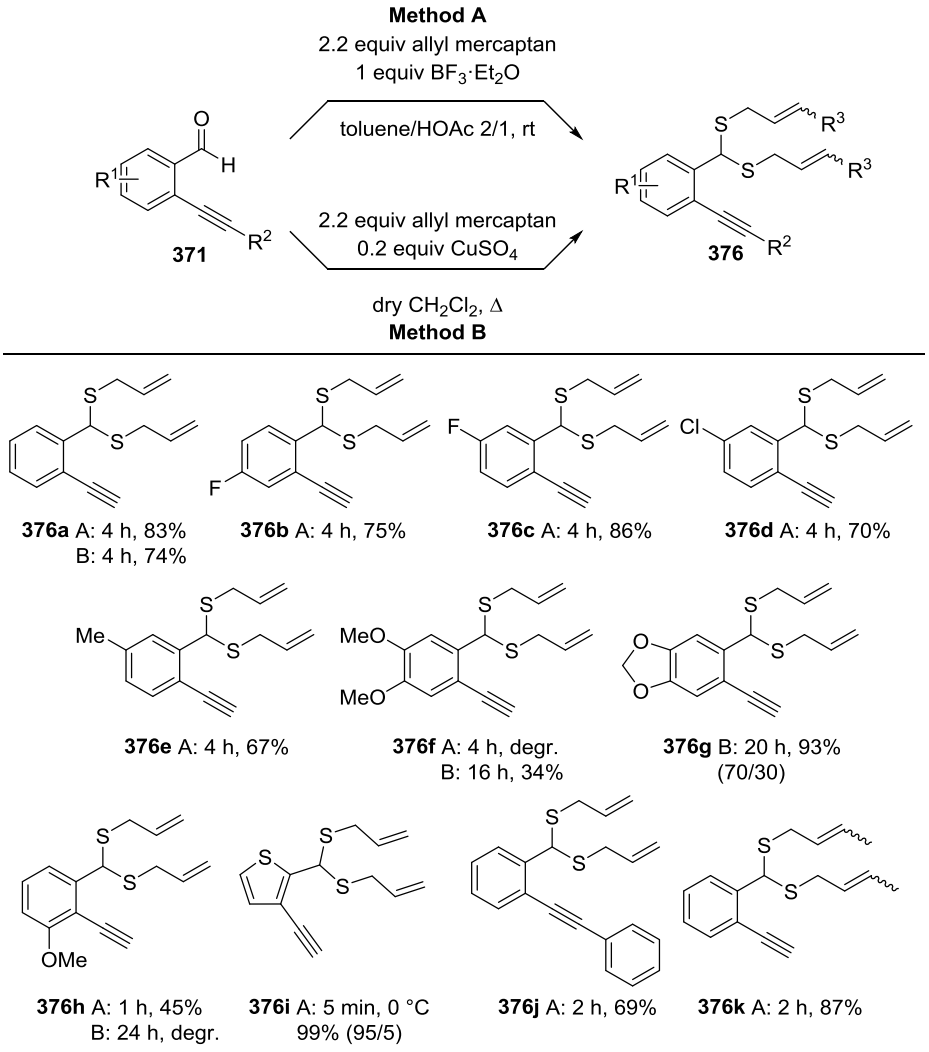
Crotyl mercaptan **375** on the other hand is not commercially available and had to be produced. Like its allyl counterpart, crotyl mercaptan has an equally terrible odor which did not facilitate its synthesis from a practical point of view. A literature procedure was followed and steam distillation resulted in crotyl mercaptan (*E*/*Z* 94/6, Scheme 100).[373]



Scheme 100. Synthesis of crotyl mercaptan 375.

4.2.2.2 Dithioacetalization

With these mercaptans in hand, aldehydes **371a-j** could be converted into the corresponding diallyl thioacetals (Scheme 101). Two literature protocols were applied: one using boron trifluoride in acetic acid (**Method A**) and one using copper sulfate in dichloromethane (**Method B**).[374-375] Electron-rich substrates were more efficiently converted using the latter protocol (**371f-g**), whereas the other substrates gave satisfactory results using the boron trifluoride-mediated transformation. Some 30% formation of the corresponding benzo[*c*]thiophene was observed for **371g** and 5% for **371i**, according to ^{1}H-NMR analysis. These mixtures were chromatographically inseparable, so the crude mixture was used as such in the following step.



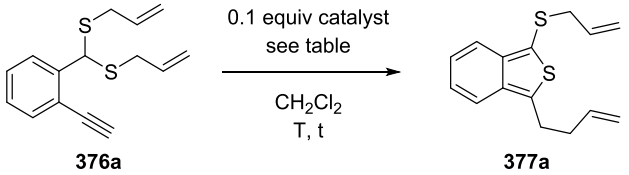
Scheme 101. Formation of diallyl thioacetals 376. Values in parentheses refer to the ratio of diallyl thioacetal/benzo[*c*]thiophene.

4.2.3 Ring closure of 376

Sulfur-containing compounds have a reputation of being difficult substrates for catalytic reactions as they can cause catalyst poisoning. Nevertheless, gold salts have been shown to be compatible with thiols or thioethers.[73, 195, 376-379] Based on our previous work on 5-alkylidenedihydrothiazoles, a gold catalyzed 5-*exo*-*dig* migratory cycloisomerization was envisioned, yet a selection of other catalytic systems was evaluated to ensure optimal reaction conditions (Table 17). No 6-*endo*-*dig* cyclization was encountered for any of the screened catalysts.

Heating diallyl thioacetal **376a**, either conventionally or by microwave irradiation, did not deliver the desired benzo[*c*]thiophene (entries 1-2). The use of iron, copper, ammonium, nickel, palladium and silver salts resulted in no conversion after 3 hours of refluxing in dichloromethane (entries 3-8). Also, the use of mild and very strong protic acids such as acetic acid, sulfuric acid and tetrafluoroboric acid as catalyst proved to be unsuccessful and resulted in full recovery of starting material (entry 9-13).

Table 17. Screening of different catalysts.



376a **377a**

entry	catalyst	temperature (° C)	time (min)	yield **377** (%)
1	-	40	1 d	-
2	-[a]	165	60	-
3	$Fe(acac)_3$	40	120	-
4	CuI	40	120	-
5	TBAB	40	120	-
6	$Ni(cod)_2$	40	180	-
7	$PdCl_2$	40	180	-
8	AgOTf	40	120	-
9	*p*-TsOH	40	180	-
10	HOAc	20	180	-
11	H_2SO_4	20	180	-
12	$HClO_4$	20	180	-
13	HBF_4	20	180	-
14	$BF_3{\cdot}Et_2O$	20	180	-
15	$CuSO_4$	20	180	-
16	$AuCl_3$	20	15	65
17	$AuBr_3$	20	15	37
18	AuCl	20	60	60
19	AuOTf	20	180	-
20	PPh_3AuCl	20	180	-
21	$HAuCl_4$	20	60	48
22	$KAuCl_4$[b]	20	180	-

[a] microwave heating; [b] anhydrous conditions

Addition of $BF_3{\cdot}Et_2O$ or $CuSO_4$ did not yield any benzo[*c*]thiophene, precluding them as ring closure catalysts in the earlier dithioacetalization step (entries 14-15 and Scheme 101, **376g** and **376i**).

When moving to the previously optimized conditions for the synthesis of 5-alkylidene-dihydrothiazoles,[73] using $AuCl_3$ in dichloromethane, full consumption of the starting material was observed at room temperature within 15 minutes. $AuBr_3$ and AuCl performed well too, albeit with a drop in isolated yield or at a slower rate (entries 16-18).

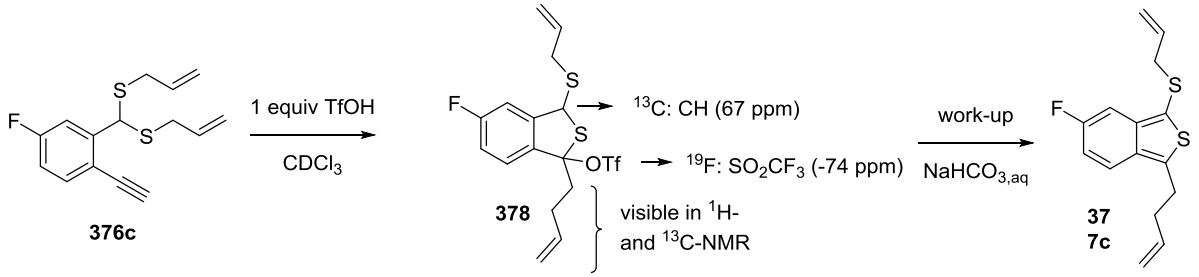
However, when other monovalent Au catalysts were used, we were surprised that no conversion took place at all (entries 19-20). This led us to believe that small amounts of hydrochloric acid, released from the catalyst by moisture, played a key role in the conversion. The acidity of HCl can be increased in the presence of $AuCl_3$, by complexation of the chloride and formation of a $HAuCl_4$ superacid.[285]

Indeed, when the substrate was treated with $HAuCl_4$, full conversion to the end product could be observed (entry 21). However, these conditions were too harsh and the end product showed appreciable degradation, resulting in an isolated yield of 48%. Upon addition of 10 mol% 2,6-di-*t*-butylpyridine as a sterically hindered base to a mixture of diallyl thioacetal **376c** (chosen for stability reasons) and 10 mol% $AuCl_3$ the reaction proceeded much slower, indicating that strongly acidic conditions are required. This was further supported by the fact that use of $KAuCl_4$ under strictly anhydrous conditions did not result in any conversion (entry 22), until moisture was introduced. It is known that alkynes can mediate the reduction of trivalent gold to a complex of monovalent gold and tetrachloroaurate.[380-382] Yet, this is unlikely to occur here as both AuCl and $KAuCl_4$ did not give better results than $AuCl_3$.

4.2.4 Mechanistic considerations

Instead of $HAuCl_4$, TfOH was selected as another superacid to verify whether it could perform the desired transformation as well.[383-384] Curiously, treatment of **376c** with 10 mol% TfOH resulted in precisely 10% conversion to the desired benzo[*c*]thiophene. Repeating the reaction with a quantitative amount of TfOH in $CDCl_3$ to allow direct NMR-analysis revealed the formation of an intermediate product, which could be converted to the corresponding benzo[*c*]thiophene by addition of Cs_2CO_3 or by aqueous work-up. Based on the crude ^1H-, ^{13}C-, ^{19}F-, COSY and HSQC NMR data of the unknown compound, we postulate having trapped an intermediate as a covalently bound triflate (Scheme 102, compound **378**). Some characteristic data to support the conclusion:

- ^{19}F-NMR: -74.32 ppm (s); -78.73 ppm (s, TfOH), -108.46 ppm (multiplet, $C_{ar}F$). The signal at -74.32 ppm corresponds to a covalently bound triflate.[385]
- ^{1}H-NMR: the alkyne proton at 3.31 ppm and the SCH_2 signals at 3.09 and 3.30 ppm of **376c** have disappeared. New signals in the range of 2-3 ppm suggest the presence of a homoallylic and S-allyllic group. These factors combined indicate the desired cyclization and 1,3-migration have taken place.
- ^{13}C-NMR: a CF_3-signal is clearly present as a quadruplet around 119 ppm. A singlet at 67 ppm corresponds to the CHS_2 carbon while signals at 42, 33 and 31 ppm correspond to a SCH_2 and the CH_2 carbons of a homoallylic group, respectively. No alkyne signals are present. These observations corroborate that cyclization and 1,3-migration have taken place, but aromatization has not as a CHS_2 proton is present.

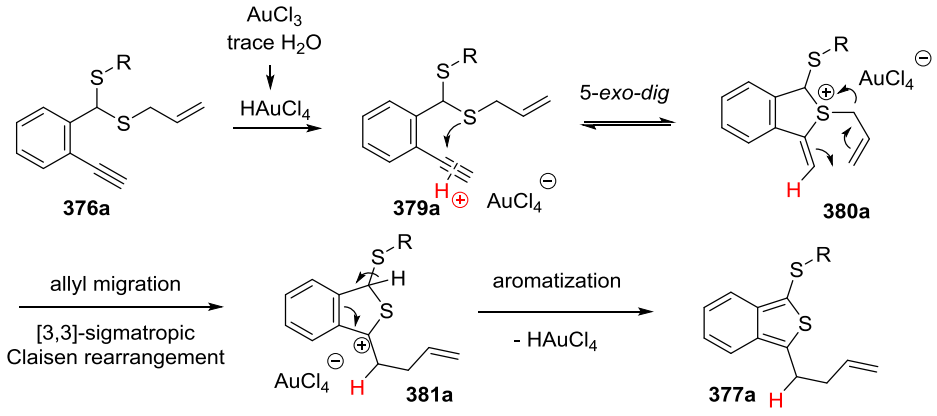


Scheme 102. Treatment of diallyl thioacetals with TfOH and generation of intermediate 378.

These observations suggest that both the strongly acidic conditions as well as the counterion play a key role in the transformation. A sufficiently strong acid is able to execute the migratory cycloisomerization but cannot catalytically form the desired benzo[*c*]thiophene **377**, as the intermediate is trapped by the counteranion. As such, the use of a catalytic amount of $AuCl_3$ under non-anhydrous conditions was selected as the best option. Due to its highly hygroscopic nature, simply weighing the catalyst in open air introduced enough moisture to generate $HAuCl_4$ for the reaction to proceed swiftly.

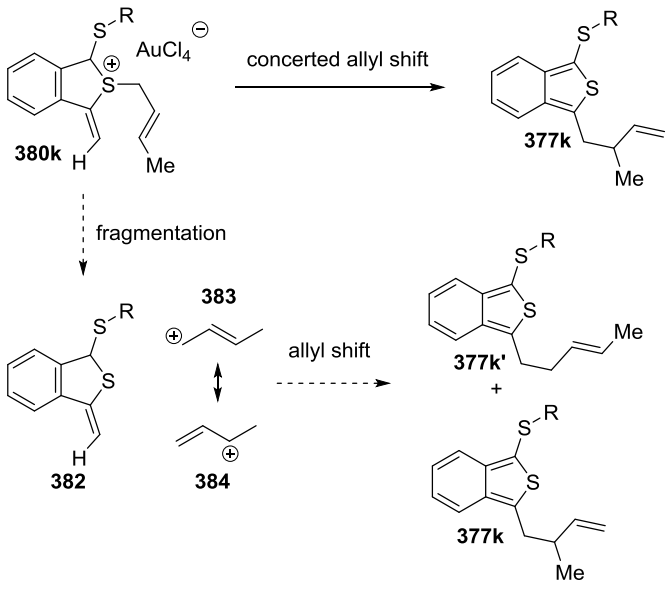
The proposed mechanism for benzo[*c*]thiophene **377** formation based on these conclusions is depicted in Scheme 103. After acidic alkyne activation by *in situ* formed $HAuCl_4$, a 5-*exo*-*dig* cyclization takes place, furnishing intermediate **380a** which readily undergoes a Claisen rearrangement to **381a**. Instead of trapping **381a**, as was the case for the TfOH-mediated transformation in Scheme 102, the $AuCl_4^-$ counteranion does not covalently bind to **381a**. This allows for consecutive aromatization to yield the desired benzo[*c*]thiophene **377a** by elimination of a proton, thus regenerating the catalyst.

However, combination of $AuCl_3$ and 2,6-di-*t*-butylpyridine also results in the formation of benzo[*c*]thiophene albeit much slower. This implies that $AuCl_3$ can mediate the transformation as well but not as fast as an appropriate superacid.



Scheme 103. Proposed mechanism of the migratory cycloisomerization.

The concerted nature of this Claisen-type rearrangement was confirmed by selective transformation of **376k** to branched **377k**, ruling out a fragmentative allyl shift as this should yield mixtures of **377k** and **377k'** (Scheme 104).[138-139]



Scheme 104. Proof of the concerted nature of the Claisen rearrangement.

4.2.5 Further optimization

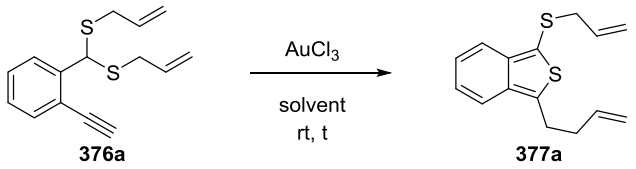
Next, a solvent screening was performed to verify whether CH_2Cl_2 indeed gave the best results in this case. Using strongly apolar solvents (Table 18, entries 1-2) resulted in very long reaction times, as did the use of highly polar solvents (entries 7-10). Solvents of intermediate polarity gave more valuable results, with yields around 40% and reaction times of 3 hours (entries 3-6). In dichloroethane (entry

5) the reaction was almost equally fast as in dichloromethane, however, product degradation occurred (which was clearly visible upon TLC analysis), resulting in an isolated yield of only 43%.

These observations established dichloromethane as the solvent of choice. The catalyst loading could be lowered to 1 mol%, maintaining an isolated yield of 65%, while lengthening the reaction time to 3 hours (entry 12). As a compromise, a catalyst loading of 5-10 mol% was applied, depending on how fast the transformation proceeded (Scheme 105).

As product stability was clearly a determining factor in order to obtain good yields, an experiment was performed using 2,6-di-*t*-butyl-4-methylphenol (BHT) as a radical scavenging additive. This attempt to further stabilize the end product proved to be unsuccessful and the reaction yield was unchanged. For all derivatives **376**, except **376j**, a conversion of ≥ 98% was achieved based on HPLC, though poor product stability led to losses during work-up and purification.

Table 18. Screening of different solvents for the Au-mediated cycloisomerization.

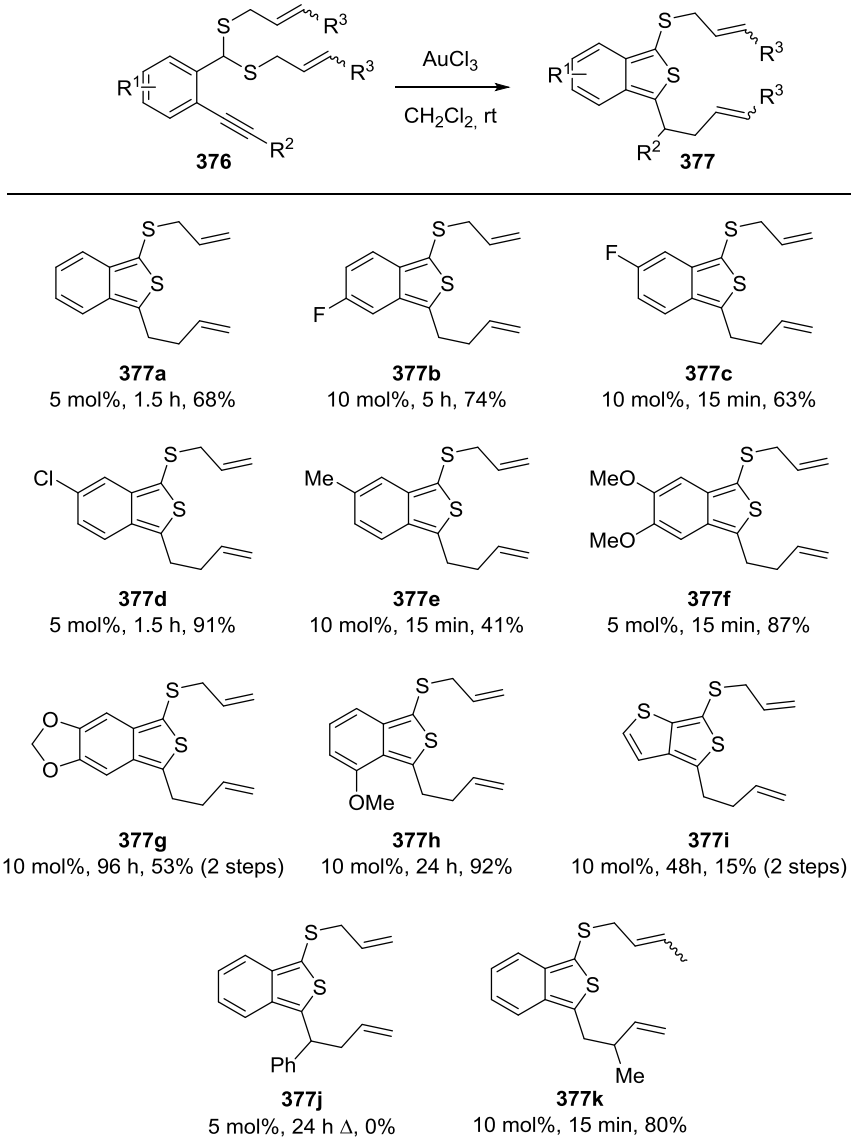


376a **377a**

entry	loading (equiv)	solvent	time (min)	yield **377a** (%)
1	0.1	Hexane	2 d	-
2	0.1	Toluene	1.5 d	56
3	0.1	EtOAc	180	40
4	0.1	DME	180	40
5	0.1	DCE	30	43
6	0.1	Acetone	180	45
7	0.1	DMF	2.5 d	23
8	0.1	CH_3CN	180	35
9	0.1	1-Pentanol	2.5 d	25
10	0.1	MeOH	2.5 d	7
11	0.1	CH_2Cl_2	15	65
12	0.01	CH_2Cl_2	180	65
13	0.05	CH_2Cl_2	15	68

Oxidative stability seemed to be the most important issue, and simple storage under air for a few weeks gave rise to sulfoxide formation. Furthermore, benzo[*c*]thiophenes **377** are prone to Diels-Alder reactions as an *o*-quinodimethane functionality is present.[386-387]

The influence of electron-withdrawing groups on the migratory cycloisomerization is mainly reflected in the improved stability of the formed benzo[*c*]thiophenes. As for electron-donating groups, there is a large discrepancy in reaction time between **376f** and **376g** for no apparent reason, while the 4-methoxybenzo[*c*]thiophene **377h** is obtained in excellent yield but only after 24 hours, possibly due to steric hindrance. Thieno[3,4-*b*]thiophene **377i** was obtained in 15% yield over 2 steps. Non-terminal alkyne **376j** could not be cyclized, not even after 48 hours of reflux with 5 mol% $AuCl_3$ in toluene, and only starting material was recovered.



Scheme 105. Ring closure of diallyl thioacetals 376. Catalyst loading, reaction time and yield are indicated.

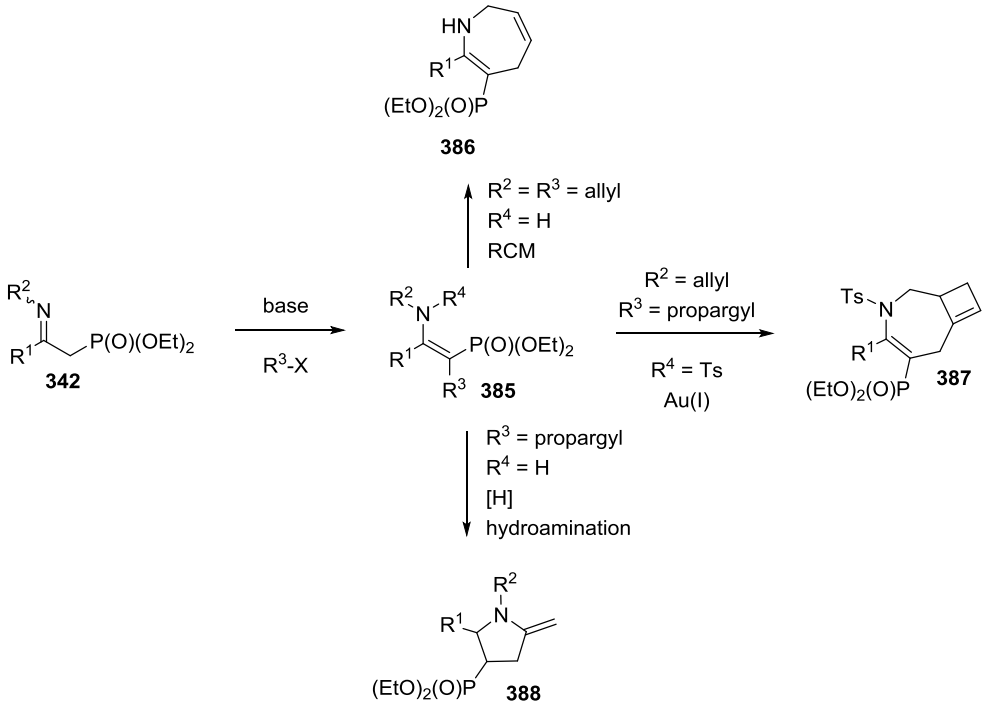
4.3 Conclusion

The methodology employed for the synthesis of isoindoles earlier at the research group could be extended to benzo[*c*]thiophenes **377**. Sonogashira coupling was followed by generation of dithioacetals **376** using allyl and crotyl mercaptan. Two methods were applied using either $CuSO_4$ or $BF_3{\cdot}Et_2O$ as Lewis acids. With thioacetals **376** in hand, a number of catalysts was evaluated for the envisioned ring closure and concomitant migration. In the end, only Au-catalysts were active and $AuCl_3$ gave the best results while acids and other metals resulted in full recovery of the starting material. However, the lack of transformation upon application of $KAuCl_4$ and the slowing down upon addition of base suggested that *in situ* formed $HAuCl_4$ was the actual catalytic species. This was further supported by the ability of TfOH to generate intermediate **378**. This observation led to the proposed mechanism: alkyne activation by a proton was followed by 5-*exo*-*dig* cyclization, then allyl migration and finally aromatization occurred. The allyl migration took place in a concerted manner, as the use of the crotyl derivative resulted exclusively in branched product, while a fragmentative mechanism would furnish both branched and linear compounds. A solvent screening indicated that dichloromethane was the solvent of choice. Application of $AuCl_3$ to all derivatives resulted in ring closure, except for internal alkynes.

IV. Perspectives

Despite the fact that the work on the phosphite additions is the only part of this thesis that was still ongoing at the end of the practical work, there are some issues from the other chapters that would be interesting to address as well. Some transformations are more relevant from a biological point of view while others are of interest for their synthetic endeavours.

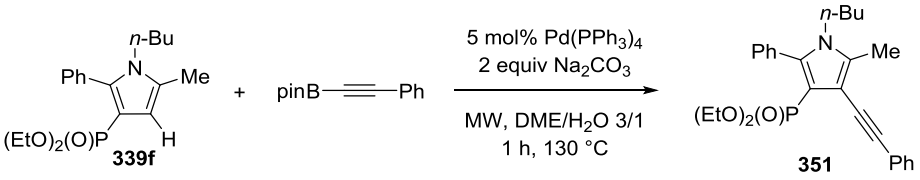
Firstly, the α-alkylation strategy employed for the generation of the 3-phosphonopyrroles permits the introduction of a wide variety of alkyl chains. Subsequent ring closure can give rise to a whole array of phosphonylated azaheterocycles with a large variation in ring size, saturation and functional groups. Ring closure through hydroamination is certainly possible, but other strategies are just as viable, *e.g.* ring-closing metathesis (RCM) or cycloaddition (Scheme 106). Ring-closing metathesis would give rise to phosphonylated dihydroazepines **386**, a scaffold that has been reported only once in literature.[388] In case R^2 = allyl and R^3 = propargyl, a 1,8-enyne is available. Such substrates are known to undergo a cationic Au(I)-mediated formal [2+2]-cycloaddition to **387**.[389-390] Moreover, reduction of the enamine **385** and subsequent hydroamination would give rise to phosphonylated pyrrolidines **388**.



Scheme 106. Opportunities for further derivatization of phosphonylated enamine building blocks.

Furthermore, during the quest for methodologies to derivatize phosphonylated pyrroles **339**, we stumbled upon a discrepancy during Suzuki coupling reactions. Comparison of the conversions after 1 hour and 2 hours under microwave irradiation suggested that the mode of action that was operative was in fact a C-H activation instead of a coupling reaction. Therefore, it would be most interesting to

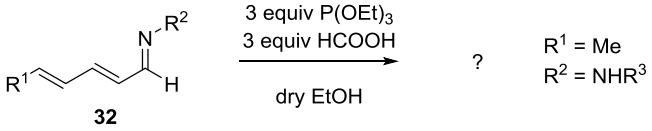
repeat this protocol with unbrominated pyrrole **339** to see if any transformation takes place (Scheme 107). If so, it has been proven that a C-H activation protocol is operative and further scrutiny would reveal whether this transformation holds any potential.



Scheme 107. Attempted C-H functionalization.

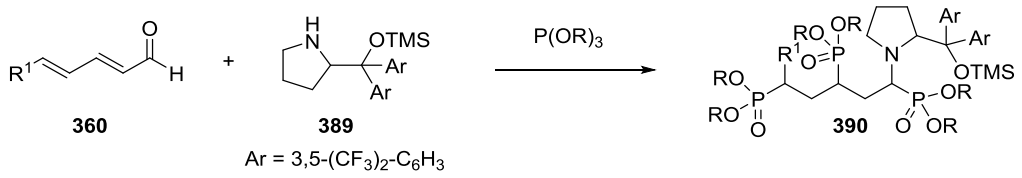
With regard to the chapter on phosphite addition, plenty of space is left for further research. First of all, the results from molecular modeling studies will point out whether it is feasible to further pursue 1,4- or 1,6-addition on α,β,γ,δ-diunsaturated imines **32** using silylated phosphite nucleophiles. These results might help to get a better understanding of the complex mechanism behind this transformation.

Anyway, there remains much work to be done using triethyl phosphite as nucleophile. *In concreto*, instead of R^1 = Ph, other substituents must be evaluated, especially unsaturated ones to probe whether the size of the conjugated system has any influence on the reaction outcome (Scheme 108). Moreover, instead of imines, hydrazones could be evaluated as substrates to verify whether the outcome parallels the results of the imines.



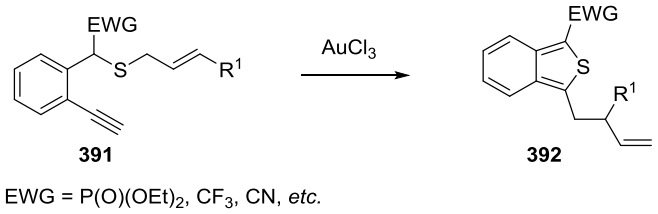
Scheme 108. Further elaboration of the addition of $P(OEt)_3$.

In any case, it would be interesting to evaluate an organocatalytic approach. For instance, the Jørgensen group has employed sterically demanding prolinol derivatives in combination with α,β,γ,δ-diunsaturated aldehydes **360** to promote 1,6-addition (Scheme 109).[391-393] If this approach is helpful in directing the nucleophiles to the δ-carbon atom, 1,4- and 1,2-addition may follow. This would lead to the incorporation of the organocatalyst, so it would in fact not be a truly catalytic approach. This methodology would open up the possibility of enantioselective phosphite addition as well.[394] On the other hand, organometallic phosphorus nucleophiles might present a possible solution.[317, 323]



Scheme 109. Application of sterically demanding prolinols as amines.

The Au-mediated preparation of benzo[*c*]thiophenes is a useful transformation but the products lack stability. Introduction of other substituents instead of the *S*-allyl moiety might alleviate this issue (Scheme 110). This could be accomplished by preparing dithioacetals and then substituting one sulfide moiety or the other way around.



Scheme 110. Preparation of more stable benzo[*c*]thiophenes.

The literature overview of this work has demonstrated that there are very little precendents of combining Au-catalysis with *S*-nucleophiles so this area might certainly be interesting to further elaborate.

V. Experimental procedures

1. General methods

Commercially available solvents and products were used as received without any purification unless otherwise stated. Reactions were performed in non-flame-dried glassware and open to the air unless otherwise noted. Inert atmosphere refers to a N_2-atmosphere.

1.1 Solvents

Dry diethyl ether (Et_2O), tetrahydrofuran (THF) and toluene were freshly distilled from sodium/benzophenone ketyl. Dry dichloromethane (CH_2Cl_2) was freshly distilled over calcium hydride (CaH_2). Dry acetonitrile (CH_3CN) was distilled over CaH_2 and stored over 4Å molecular sieves.

1.2 Pressure reactions

Reactions performed under more than 1 atmosphere H_2-pressure were performed in a thick-walled glass bottle, shielded by an iron cage in case of explosion. When more than 5 bar H_2 was used, a specialized Parr-reactor was employed at the Department of Organic and Macromolecular Chemistry, Faculty of Sciences, Ghent University.

1.3 Column chromatography

Column chromatography was performed in a glass column with silica gel (particle size 70−200 µm, pore diameter 60 Å) using appropriate mixtures of ethyl acetate (EtOAc) and hexanes. Visualisation was performed on TLC-plates using UV irradiation and oxidation by a $KMnO_4$ solution or elemental iodine.

1.4 Preparative TLC

Preparative TLC was executed with 2000 µm 20 × 20 cm TLC plates in an elution chamber using an appropriate eluent.

1.5 Gas chromatography

GC analyses were performed on an Agilent 6980 Series or an Agilent 1991J-433 gas chromatograph, connected to a FID detector, using an Alltech EC-5 capillary column (30 m x 0.25 mm) with a film thickness of 0.25 µm and He as the carrier gas.

1.6 Liquid chromatography

HPLC and HPLC-MS analyses were performed on an Agilent 1200 Series liquid chromatograph using a reversed phase column (Eclipse plus C18 column, 50 x 4.6 mm, particle size 3.5 µm, or a Supelco

Ascentis Express C18 column, 30 x 4.6 mm, particle size 2.7 µm) connected to a UV-VIS detector and an Agilent 1100 series LC/MSD type SL mass spectrometer (ESI, 70 eV) using a mass selective single quadrupole detector. A mixture of 5 mM NH_4OAc in H_2O and CH_3CN was used as eluent.

1.7 Preparative HPLC

Preparative HPLC was performed on an Agilent 1100 Series liquid chromatograph using a reversed phase column (Zorbax Eclipse XDB-C18 column, 150 x 21.2 mm, particle size 5 µm) that is thermostatized at 25 °C. The column is connected to a UV-VIS Variable Wavelength Detector (VWD). A mixture of H_2O and CH_3CN is used as eluent, with TFA or diethylamine as additives if needed.

1.8 Mass spectrometry

Low-resolution mass spectra were obtained with an Agilent 1100 series LC/MSD type SL mass spectrometer (ESI, 70 eV) using a mass selective single quadrupole detector. High-resolution mass spectra were obtained with an Agilent Technologies 6210 Time-Of-Flight (TOF) mass spectrometer (ESI or APCI).

1.9 NMR spectroscopy

High resolution ^{1}H- (300 or 400 MHz), ^{13}C- (75 or 100 MHz), ^{19}F- (282 or 376 MHz) and ^{31}P- (121 or 162 MHz) NMR spectra were recorded on a Jeol Eclipse FT 300 or a Bruker Avance III Nanobay 400 MHz spectrometer at room temperature, unless otherwise noted. Peaks were assigned with the aid of DEPT, APT, COSY, HSQC, HMBC, H2BC and NOESY experiments. Samples were dissolved in deuterated solvents with TMS as an internal standard. $CFCl_3$ was added as an internal standard for ^{19}F-NMR analyses. All chemical shifts are expressed as parts per million (ppm).

1.10 Infrared spectroscopy

IR-spectra were obtained from a Perkin-Elmer Spectrum One BX FT-IR spectrophotometer with an ATR (Attenuated Total Reflectance) accessory. Samples were analyzed in neat form and selected peaks are reported.

1.11 Melting points

Melting points of crystalline compounds were determined using a Büchi B-540 apparatus or a Wagner & Munz WME Heizbank Kofler bench.

1.12 Microwave irradiation

All microwave reactions were performed in a CEM Discover Benchmate with a continuous power output from 0 to 300 W and a self-adjusting, single mode microwave cavity. Reactions were performed in a 10 mL thick-walled Pyrex reaction vessel, closed with a snap-cap and equipped with a small magnetic stirring bar. A ramp time of maximum 5 minutes was used during which the temperature was increased from room temperature to the desired temperature. This temperature was maintained during the course of the reaction. The temperature control system used an external infrared sensor to measure the temperature on the bottom of the vessel and was used in a feedback loop with the on-board computer to regulate the temperature from 25 to 250 °C by adjusting the power output (1 W increments). The pressure control, Intellivent Pressure Control System, used 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 was performed by a rotating magnetic plate located below the bottom of the microwave cavity. After the reaction the vial was cooled down by a stream of air which decreased the temperature of the vial from approximately 150 °C to 40 °C in less than 120 s.

1.13 X-ray analysis

X-ray diffraction was performed using a Agilent Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using CuKα radiation (λ = 1.54178 Å) and ω scans. The images were interpreted and integrated with the program CrysAlisPro (Agilent Technologies). Using Olex2, the structure was solved by direct methods using the ShelXL program package. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U (eq) of the parent atoms. The amide and amine hydrogen atoms were located from a difference electron density map and were unrestrainedly refined.

All X-ray diffraction analyses were performed in collaboration with Prof. dr. Kristof Van Hecke, XStruct, Department of Inorganic and Physical Chemistry, Ghent University, Belgium.

CCDC 940960-940961 contain the supplementary crystallographic data for this work and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

2. Safety

2.1 General safety aspects

The practical work in this thesis was performed according to the SynBioC Research Group Internal Guidelines and with the aid of the internal safety document "Safety Instructions: How to work with chemicals". Wherever possible, hazardous or toxic reagents were avoided and/or substituted by safer or greener alternatives.

2.2 Specific safety aspects

A list of the risks associated with each chemical is available in the corresponding material data safety sheet (MSDS), which can be found on the website of the supplier. Therein, a classification of the hazards was made according to the European Regulation (EC) No 1272/2008 [EU-GHS/CLP], which combines the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) and Classification, Labelling and Packaging regulations (CLP). A brief overview of the chemicals employed in this work classified as **category 1**, the most severe category, of the respective hazard class will be given below, along with the GHS hazards and precautions.

Alkyllithium reagents: pyrophoric liquids, substances and mixtures which in contact with water emit flammable gases, acute toxicity after inhalation, acute and chronic hazards to the aquatic environment. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid contact with air or water and work under an inert atmosphere. In case of fire use dry sand, dry chemical- or alcohol-resistant foam to extinguish.

Alkyltin reagents: specific target organ toxicity following repeated exposure, acute and chronic aquatic toxicity. Wear protective gloves and clothing. Avoid release in the environment.

Boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$): skin corrosion, specific target organ toxicity following repeated exposure (inhalation). Avoid inhalation, wear protective gloves and clothing.

Bromine (Br_2): skin corrosion, acute aquatic toxicity. Avoid inhalation, wear protective gloves and clothing, avoid release in the environment.

Chloroacetyl chloride: skin corrosion, specific target organ toxicity following repeated exposure, acute aquatic toxicity. Avoid inhalation and release in the environment. Wear protective gloves and clothing.

Chloroform: specific target organ toxicity following repeated exposure. Avoid inhalation.

Solvents in general: acute toxicity after inhalation, specific target organ toxicity following single or repeated exposure. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing. A useful tool for solvent selection is the "**GSK solvent selection guide**" which lists a wide variety of hazards associated with specific solvent classes as well as more benign alternatives for commonly used solvents.[395-397]

Iodomethane (MeI): respiratory sensitization, skin sensitization. Avoid inhalation and wear protective gloves and clothing.

Propargyl bromide: acute toxicity after inhalation. Avoid inhalation.

H_2-gas: flammable gas, especially when compressed. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

H_2O_2: serious eye damage. Wear eye protection.

$NaCNBH_3$: acute toxicity after inhalation, flammable solid, acute and chronic hazards to the aquatic environment. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and release into the environment. Wear protective gloves and clothing.

Organic acids (acetic acid, formic acid, *para*-toluenesulfonic acid, trifluoromethanesulfonic acid): skin corrosion. Wear protective gloves and clothing.

Inorganic acids (HCl, HBr, H_2SO_4, $HClO_4$, HBF_4): skin corrosion, corrosive to metals. Wear protective gloves and clothing.

Organic bases (Et_3N, KO*t*-Bu, LDA, LiHMDS): skin corrosion. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Inorganic bases (NaOH, NaH): skin corrosion, corrosive to metals. Wear protective gloves and clothing.

Transition metal salts: acute and chronic aquatic toxicity. Avoid release in the environment.

Thiourea: skin sensitization. Wear protective gloves.

3. Synthetic procedures and spectral data

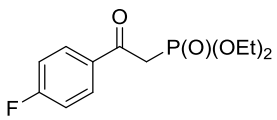
3.1 Synthetic entry into 3-phosphono-1-azabicyclo[3.1.0]hexanes

3.1.1 Synthesis of diethyl (2-oxo-2-phenylethyl)phosphonates 29

Synthesis of diethyl (2-oxo-2-phenylethyl)phosphonates **29c-i** (Method A): a mixture of substituted 2-chloroacetophenone or 2-bromoacetophenone (1 equiv) and methyl hydrazinecarboxylate (1.05 equiv) was dissolved in toluene (0.5 M) in a round-bottom flask equipped with a Dean-Stark apparatus and heated to reflux temperature for 5 h. Next, triethyl phosphite was added (1.1 equiv) and the reaction mixture was kept at reflux temperature for an additional 2 h. The solvent was evaporated *in vacuo* before redissolving the residue in a mixture of 20 mL acetone and 20 mL 2 M HCl. After 3 h of stirring at room temperature, the acetone was evaporated *in vacuo* and the residue was brought to pH 7 with 20 mL 2 M NaOH before extraction with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. If necessary, the product was purified using column chromatography. Spectral data were in agreement with literature values.

Synthesis of diethyl (2-oxo-2-phenylethyl)phosphonates **29j-k** (Method B): a mixture of diethyl phosphonoacetic acid (1 equiv) was dissolved in CH_3CN (0.5 M). $MgCl_2$ (1.2 equiv) and Et_3N (2 equiv) were added and the reaction mixture was stirred for 2 h at room temperature. Then, the suspension was cooled to 0 °C using an ice bath and an appropriate acid chloride (0.5 equiv) was dissolved in CH_3CN (1 M) and added in a dropwise fashion to the cooled solution. The reaction was allowed to slowly warm to room temperature overnight. The solvent was removed *in vacuo* and the resulting solids were redissolved in 20 mL CH_2Cl_2 and washed with 20 mL 2 M HCl. The aqueous phase was extracted with CH_2Cl_2 (3x 20 mL) and was dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was purified using column chromatography. Spectral data for **29j** were in agreement with literature values.

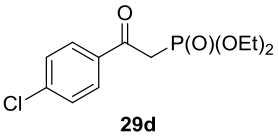
diethyl (2-(4-fluorophenyl)-2-oxoethyl)phosphonate 29c[398]



29c

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.29 (6H, t, *J* = 7.2 Hz, 2x $OCH_2\underline{CH_3}$), 3.60 (2H, d, $^2J_{HP}$ = 23.1 Hz, CH_2), 4.14 (4H, dq, $^3J_{HP}$ = 7.2 Hz, *J* = 7.2 Hz, 2x $OC\underline{H_2}CH_3$), 7.15 (2H, dd, $^3J_{HF}$ = 8.5 Hz, *J* = 8.3 Hz, 2x CH_{ar}), 8.06 (2H, dd, *J* = 8.3 Hz, $^4J_{HF}$ = 5.3 Hz, 2x CH_{ar}). **^{19}F-NMR (282 MHz, $CDCl_3$) δ** -103.88 to -103.97 (m). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 20.20. **Chromatography**: hexanes/EtOAc 3/7, R_f = 0.26. **Yield**: 50%, yellow oil.

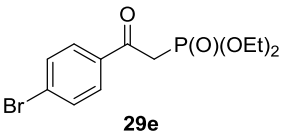
diethyl (2-(4-chlorophenyl)-2-oxoethyl)phosphonate 29d[398]



29d

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.29 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.61 (2H, d, $^2J_{HP}$ = 23.7 Hz, CH_2), 4.14 (4H, dq, $^3J_{HP}$ = 7.2 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 7.46 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}), 7.97 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 20.05. **Chromatography**: hexanes/EtOAc 3/7, R_f = 0.25. **Yield**: 51%, yellow oil.

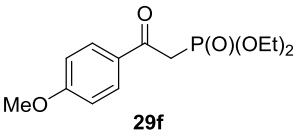
diethyl (2-(4-bromophenyl)-2-oxoethyl)phosphonate 29e[398]



29e

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.29 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.60 (2H, d, $^2J_{HP}$ = 22.6 Hz, CH_2), 4.14 (4H, dq, $^3J_{HP}$ = 7.2 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 7.63 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}), 7.89 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 20.00. **Chromatography**: hexanes/EtOAc 3/7, R_f = 0.20. **Yield**: 52%, yellow oil.

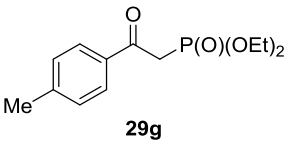
diethyl (2-(4-methoxyphenyl)-2-oxoethyl)phosphonate 29f[398]



29f

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.29 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.58 (2H, d, $^2J_{HP}$ = 22.6 Hz, CH_2), 3.88 (3H, s, OCH_3), 4.14 (4H, dq, $^3J_{HP}$ = 7.2 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 6.94 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}), 8.01 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 21.01. **Chromatography**: EtOAc, R_f = 0.20. **Yield**: 95%, colorless oil.

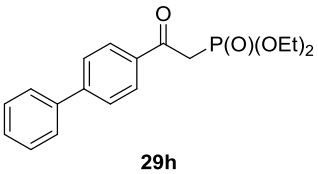
diethyl (2-oxo-2-(p-tolyl)ethyl)phosphonate 29g[398]



29g

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.28 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 2.42 (3H, s, CH_3), 3.61 (2H, d, $^2J_{HP}$ = 22.6 Hz, CH_2), 4.13 (4H, dq, $^3J_{HP}$ = 7.2 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 7.27 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}), 7.91 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 20.83. **Chromatography**: hexanes/EtOAc 1/9, R_f = 0.29. **Yield**: 90%, yellow oil.

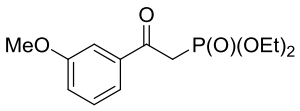
diethyl (2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)phosphonate 29h[399]



29h

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.67 (2H, d, $^2J_{HP}$ = 22.6 Hz, CH_2), 4.16 (4H, dq, $^3J_{HP}$ = 7.2 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 7.41-7.51 (3H, m, 3x CH_{ar}), 7.59-7.66 (2H, m, 2x CH_{ar}), 7.68-7.72 (2H, m, 2x CH_{ar}) 8.09-8.11 (2H, m, 2x CH_{ar}) **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 20.60. **Yield**: 99%, yellow oil.

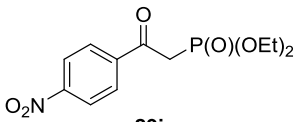
diethyl (2-(3-methoxyphenyl)-2-oxoethyl)phosphonate 29i[400]



29i

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.27 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.61 (2H, d, $^2J_{HP}$ = 22.6 Hz, CH_2), 3.84 (3H, s, OCH_3), 4.13 (4H, dq, $^3J_{HP}$ = 7.2 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 7.14 (1H, dd, *J* = 8.3 Hz, *J* = 2.8 Hz, CH_{ar}), 7.38 (1H, dd, *J* = 8.3 Hz, *J* = 8.3 Hz, CH_{ar}), 7.53 (1H, dd, *J* = 2.8 Hz, *J* = 2.8 Hz, CH_{ar}), 7.60 (1H, dd, *J* = 8.3 Hz, *J* = 2.8 Hz, CH_{ar}). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 20.54. **Chromatography**: hexanes/EtOAc 1/4, R_f = 0.17. **Yield**: 61%, yellow oil.

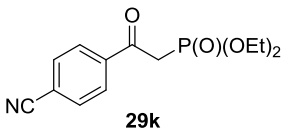
diethyl (2-(4-nitrophenyl)-2-oxoethyl)phosphonate 29j[210, 398]



29j

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, t, *J* = 7.1 Hz, 2x $OCH_2C\underline{H}_3$), 3.68 (2H, d, $^2J_{HP}$ = 23.1 Hz, CH_2), 4.16 (4H, dq, $^3J_{HP}$ = 7.4 Hz, *J* = 7.1 Hz, 2x $OC\underline{H}_2CH_3$), 8.20 (2H, d, *J* = 8.5 Hz, 2x CH_{ar}), 8.33 (2H, d, *J* = 8.5 Hz, 2x CH_{ar}) **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 19.01. **Chromatography**: hexanes/EtOAc 2/3, R_f = 0.07. **Yield**: 51%, yellow oil.

diethyl (2-(4-cyanophenyl)-2-oxoethyl)phosphonate 29k



29k

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, t, *J* = 7.1 Hz, 2x $OCH_2C\underline{H}_3$), 3.64 (2H, d, $^2J_{HP}$ = 23.1 Hz, CH_2), 4.15 (4H, dq, $^3J_{HP}$ = 7.4 Hz, *J* = 7.1 Hz, 2x $OC\underline{H}_2CH_3$), 7.79 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}), 8.13 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.1 (d, $^3J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 38.7 (d, $^1J_{CP}$ = 129.2 Hz, CH_2P), 62.7 (d, $^2J_{CP}$ = 5.8 Hz, 2x $O\underline{C}H_2CH_3$), 116.5 ($\underline{C}_{q,ar}C{\equiv}N$), 117.8 (C≡N), 129.4 (2x CH_{ar}), 132.4 (2x CH_{ar}), 139.3 ($\underline{C}_{q,ar}C{=}O$), 190.9 (d, $^2J_{CP}$ = 5.8 Hz, C=O). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 19.18. **IR (ATR, cm^{-1}) ν_{max}**: 1019 (P-O), 1051 (P-O), 1248 (P=O), 1685 (C=O), 2232 (C≡N), 2984. **MS (ESI, pos)**: *m/z* (%) 282.3/283.0 ($M+H^+$, 100/14). **HRMS**: *m/z* calcd for $C_{13}H_{16}NO_4P+H^+$ 282.0890, found 282.0899. **Chromatography**: hexanes/EtOAc 2/3, R_f = 0.11. **Yield**: 50%, yellow oil.

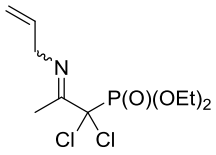
3.1.2 Synthesis of diethyl (2-(allylamino)vinyl)phosphonates 322 and diethyl (2-(allylimino)ethyl)phosphonates 323

Diethyl (2-oxoethyl)phosphonates **29a-k** were dissolved in toluene (1 M) in a round-bottom flask equipped with a Dean-Stark apparatus. Allylamine (1.5 equiv) and *p*-TsOH monohydrate (0.05 equiv) were added and the reaction mixture was heated to reflux temperature and left overnight. The reaction progress was monitored using gas chromatography. After all starting material had been consumed, the solvent was removed *in vacuo* and the residue was redissolved in diethyl ether and washed with aqueous $NaHCO_3$. The organic phase was extracted with diethyl ether (3x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

3.1.3 Synthesis of diethyl (2-(allylimino)-1,1-dichloroethyl)phosphonates 25

Diethyl (2-(allylamino)vinyl)phosphonates **322a-k** and diethyl (2-(allylimino)ethyl)phosphonates **323a-k** were dissolved in CH_2Cl_2 (1 M) and *N*-chlorosuccinimide was added (2 equiv). After 4 h, the reaction mixture was poured into 2 M NaOH and extracted (3x 20 mL CH_2Cl_2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. If necessary, the residue was purified using column chromatography.

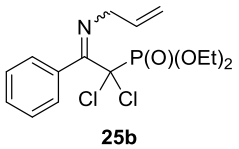
diethyl (2-(allylimino)-1,1-dichloropropyl)phosphonate 25a



25a

450 mg (1.93 mmol) of enamine/imine **322a/323a** was converted into 522 mg **25a** (1.73 mmol, 90% yield, yellow oil). This product was present in a 3/1 *E*/*Z* mixture. The spectral data for both isomers are reported (M for the major isomer, m for the minor isomer). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.36 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$, M), 1.37 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$, m), 2.16 (2x 3H, s, CH_3, M + m), 4.08 (2x 2H, d, *J* = 5.0 Hz, NCH_2, M + m), 4.25-4.42 (2x 4H, m, 2x $OC\underline{H}_2CH_3$, M + m), 5.14 (1H, dd, *J* = 10.5 Hz, *J* = 1.7 Hz, $CH=C\underline{H}_EH_Z$, M), 5.17 (1H, dd, *J* = 10.5 Hz, *J* = 1.7 Hz, $CH=C\underline{H}_EH_Z$, m), 5.25 (1H, dd, *J* = 17.1 Hz, *J* = 1.7 Hz, $CH=CH_E\underline{H}_Z$, M), 5.33 (1H, dd, *J* = 17.1 Hz, *J* = 1.7 Hz, $CH=CH_E\underline{H}_Z$, m), 5.99 (1H, ddt, *J* = 17.1 Hz, *J* = 10.5 Hz, *J* = 5.0 Hz, $C\underline{H}=CH_EH_Z$, M), 6.04 (1H, ddt, *J* = 17.1 Hz, *J* = 10.5 Hz, *J* = 5.0 Hz, $C\underline{H}=CH_EH_Z$, m). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 13.2 (d, $^3J_{CP}$ = 3.5 Hz, CH_3, M + m), 16.3 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$, M + m), 53.8 (NCH_2, M), 54.4 (NCH_2, m) 65.1 (d, $^2J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$, M), 65.5 (d, $^2J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$, m), 81.6 (d, $^1J_{CP}$ = 177.7 Hz, $PCCl_2$, m), 83.4 (d, $^1J_{CP}$ = 177.7 Hz, $PCCl_2$, M), 116.0 ($CH=\underline{C}H_2$, M), 116.5 ($CH=\underline{C}H_2$, m), 133.5 ($\underline{C}H=CH_2$, m), 133.7 ($\underline{C}H=CH_2$, M), 159.5 (C=N, m) 163.9 (C=N, M). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 10.82 (M), 8.70 (m). **IR (ATR, cm^{-1}) ν_{max}**: 1019 (P-O), 1263 (P=O), 1664, 2983. **MS (ESI, pos)**: *m/z* (%) 302.0/304.0/306.0 ($M+H^+$, 100/64/10).

diethyl (2-(allylimino)-1,1-dichloro-2-phenylethyl)phosphonate 25b

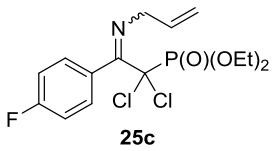


25b

3.08 g (10.43 mmol) of enamine/imine **322b/323b** was converted into 3.61 g **25b** (9.91 mmol, 95 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.37 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.86 (2H, d, *J* = 5.3 Hz, NCH_2), 4.27-4.48 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.10 (1H, dd, *J* = 10.6 Hz, *J* = 1.1 Hz, $CH=C\underline{H}_EH_Z$), 5.21 (1H, dd, *J* = 17.1 Hz, *J* = 1.4 Hz, $CH=CH_E\underline{H}_Z$), 5.90 (1H, ddt, *J* = 17.1 Hz, *J* = 10.6 Hz, *J* = 5.3 Hz, $C\underline{H}=CH_EH_Z$), 7.31-7.33 (2H, m, 2x CH_{ar}), 7.43-7.44 (3H, m, 3x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.5 (d, $^3J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 55.9 (NCH_2), 65.4 (d, $^2J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 82.0 (d, $^1J_{CP}$ = 176.5 Hz, $PCCl_2$), 116.3 ($CH=\underline{C}H_2$), 128.1 (2x CH_{ar}), 128.9 (2x CH_{ar}), 129.3 (CH_{ar}), 131.7 (d, $^3J_{CP}$ = 5.8 Hz, $C_{q,ar}$), 134.3 ($\underline{C}H=CH_2$), 166.0 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 10.96. **IR (ATR, cm^{-1}) ν_{max}**: 1017 (P-O), 1054 (P-O), 1265 (P=O), 1654, 2982.

MS (ESI, pos): *m/z* (%) 364.0/366.0/368.0 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{15}H_{20}Cl_2NO_3P+H^+$ 364.0631, found 364.0642.

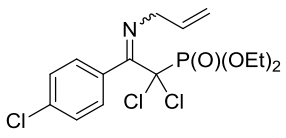
diethyl (2-(allylimino)-1,1-dichloro-2-(4-fluorophenyl)ethyl)phosphonate 25c



25c

2.42 g (7.72 mmol) of enamine/imine **322c/323c** was converted into 2.92 g **25c** (7.64 mmol, 99 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.38 (6H, t, *J* = 7.5 Hz, 2x $OCH_2C\underline{H}_3$), 3.87 (2H, dt, *J* = 5.3 Hz, *J* = 1.8 Hz, NCH_2), 4.26-4.48 (4H, m, 2x $OCH_2C\underline{H}_3$), 5.11 (1H, ddd, *J* = 10.5 Hz, *J* = 3.4 Hz, *J* = 1.8 Hz, $CH=C\underline{H}_EH_Z$), 5.20 (1H, ddd, *J* = 17.3 Hz, *J* = 3.4 Hz, *J* = 1.8 Hz, $CH=CH_E\underline{H}_Z$), 5.90 (1H, ddt, *J* = 17.3 Hz, *J* = 10.5 Hz, *J* = 5.3 Hz, $C\underline{H}=CH_EH_Z$), 7.13 (2H, dd, $^3J_{HF}$ = 8.5 Hz, *J* = 8.5 Hz, 2x CH_{ar}), 7.28-7.35 (2H, m, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.5 (d, $^3J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 55.9 (NCH_2), 65.5 (d, $^2J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 81.9 (d, $^1J_{CP}$ = 176.5 Hz, $PCCl_2$), 115.3 (d, $^2J_{CF}$ = 20.8 Hz, 2x CH_{ar}), 116.3 ($CH=\underline{C}H_2$), 127.6 ($\underline{C}_{q,ar}C=N$), 131.0 (d, $^3J_{CF}$ = 8.1 Hz, 2x CH_{ar}), 134.0 ($\underline{C}H=CH_2$), 163.1 (d, $^1J_{CF}$ = 249.2 Hz, $C_{q,ar}F$), 165.2 (C=N).**^{19}F-NMR (282 MHz, $CDCl_3$) δ** -110.98 to -110.87 (m). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 10.76. **IR (ATR, cm^{-1}) ν_{max}**: 1019 (P-O), 1052 (P-O), 1229 (P=O), 1507, 2983. **MS (ESI, pos)**: *m/z* (%) 382.0/384.0/386.0 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{15}H_{19}Cl_2FNO_3P+H^+$ 382.0536, found 382.0540.

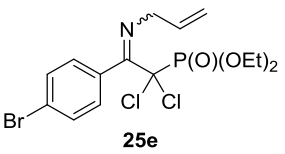
diethyl (2-(allylimino)-1,1-dichloro-2-(4-chlorophenyl)ethyl)phosphonate 25d



25d

0.63 g (1.91 mmol) of enamine/imine **322d/323d** was converted into 0.74 g **25d** (1.85 mmol, 97 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.38 (6H, t, *J* = 7.5 Hz, 2x $OCH_2C\underline{H}_3$), 3.85-3.88 (2H, m, NCH_2), 4.26-4.48 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.11 (1H, ddd, *J* = 10.4 Hz, *J* = 3.4 Hz, 1.7 Hz, $CH=C\underline{H}_EH_Z$), 5.20 (1H, *J* = 17.3 Hz, 3.4 Hz, 1.8 Hz, $CH=CH_E\underline{H}_Z$), 5.89 (1H, ddt, *J* = 17.3 Hz, *J* = 10.4 Hz, *J* = 5.2 Hz, $C\underline{H}=CH_EH_Z$), 7.26 (2H, d, *J* = 8.5 Hz, 2x CH_{ar}), 7.42 (2H, d, *J* = 8.5 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.5 (d, $^3J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 56.0 ($N\underline{C}H_2$), 65.6 (d, $^2J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 81.8 (d, $^1J_{CP}$ = 177.0 Hz, $PCCl_2$), 116.5 ($CH=\underline{C}H_2$), 128.5 (2x CH_{ar}), 130.1 (d, $^3J_{CP}$ = 5.8 Hz, $C_{q,ar}$), 130.4 (2x CH_{ar}), 134.0 ($\underline{C}H=CH_2$), 135.7 ($C_{q,ar}Cl$), 165.1 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 10.65. **IR (ATR, cm^{-1}) ν_{max}**: 1012 (P-O), 1054 (P-O), 1264 (P=O), 1487, 2982. **MS (ESI, pos)**: *m/z* (%) 398.0/400.0/402.0 ($M+H^+$, 100/97/40). **HRMS**: *m/z* calcd for $C_{15}H_{19}Cl_3NO_3P+H^+$ 398.0241, found 398.0246.

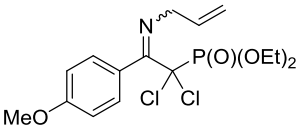
diethyl (2-(allylimino)-1,1-dichloro-2-(4-bromophenyl)ethyl)phosphonate 25e



25e

0.67 g (1.80 mmol) of enamine/imine **322e/323e** was converted into 0.65 g **25e** (1.48 mmol, 82 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.38 (6H, t, *J* = 7.2 Hz, 2x $OCH_2\underline{C}H_3$), 3.86-3.87 (2H, m, NCH_2), 4.24-4.48 (4H, m, 2x OCH_2CH_3), 5.11 (1H, ddd, *J* = 10.2 Hz, *J* = 3.3 Hz, *J* = 1.7 Hz, $CH=CH_EH_Z$), 5.20 (1H, ddd, *J* = 17.3 Hz, *J* = 3.3 Hz, *J* = 1.7 Hz, $CH=CH_EH_Z$), 5.90 (1H, ddt, *J* = 17.3 Hz, *J* = 10.2 Hz, *J* = 5.2 Hz, $CH=CH_EH_Z$), 7.20 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}), 7.58 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.6 (d, $^{3}J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 56.0 (NCH_2), 65.7 (d, $^{2}J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 81.7 (d, $^{1}J_{CP}$ = 177.7 Hz, $PCCl_2$), 116.5 ($CH=\underline{C}H_2$), 124.0 ($C_{q,ar}Br$), 130.5 ($\underline{C}_{q,ar}C=N$), 130.7 (2x CH_{ar}), 131.5 (2x CH_{ar}), 134.1 ($\underline{C}H=CH_2$), 165.1 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$)** δ 10.64. **IR (ATR, cm^{-1}) ν_{max}**: 1010 (P-O), 1054 (P-O), 1260 (P=O), 1484, 2982. **MS (ESI, pos)**: *m/z* (%) 442.0/444.0/446.0 ($M+H^+$, 62/100/45). **HRMS**: *m/z* calcd for $C_{15}H_{19}BrCl_2NO_3P+H^+$ 441.9736, found 441.9743.

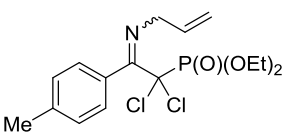
diethyl (2-(allylimino)-1,1-dichloro-2-(4-methoxyphenyl)ethyl)phosphonate 25f



25f

1.23 g (3.78 mmol) of enamine/imine **322f/323f** was converted into 1.37 g **25f** (3.48 mmol, 92 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.38 (6H, t, *J* = 7.4 Hz, $OCH_2\underline{C}H_3$), 3.85 (3H, s, OCH_3), 3.89 (2H, dt, *J* = 5.1 Hz, *J* = 1.7 Hz, NCH_2), 4.27-4.48 (4H, m, 2x $O\underline{C}H_2CH_3$), 5.10 (1H, ddd, *J* = 10.5 Hz, *J* = 3.6 Hz, *J* = 1.7 Hz, $CH=C\underline{H}_EH_Z$), 5.21 (1H, ddd, *J* = 17.3 Hz, *J* = 3.6 Hz, *J* = 1.7 Hz, $CH=CH_E\underline{H}_Z$), 5.91 (1H, ddt, *J* = 17.3 Hz, *J* = 10.5 Hz, *J* = 5.1 Hz, $C\underline{H}=CH_EH_Z$), 6.95 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}), 7.26 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^{3}J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 55.0 (OCH_3), 55.5 (NCH_2), 65.0 (d, $^{2}J_{CP}$ = 5.8 Hz, 2x $O\underline{C}H_2CH_3$), 82.3 (d, $^{1}J_{CP}$ = 176.5 Hz, $PCCl_2$), 113.3 (2x CH_{ar}), 115.9 ($CH=\underline{C}H_2$), 123.5 (d, $^{3}J_{CP}$ = 5.8 Hz, $\underline{C}_{q,ar}C=N$), 130.1 (2x CH_{ar}), 134.2 ($\underline{C}H=CH_2$), 160.1 ($\underline{C}_{q,ar}OCH_3$), 165.9 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 11.12. **IR (ATR, cm^{-1}) ν_{max}**: 1020 (P-O), 1055 (P-O), 1245 (P=O), 1509, 2981. **MS (ESI, pos)**: *m/z* (%) 394.3/396.3/398.3 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{16}H_{22}Cl_2NO_4P+H^+$ 394.0736, found 394.0744.

diethyl (2-(allylimino)-1,1-dichloro-2-(4-methylphenyl)ethyl)phosphonate 25g

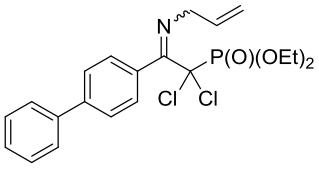


25g

1.78 g (5.75 mmol) of enamine/imine **322g/323g** was converted into 2.09 g **25g** (5.52 mmol, 96 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.37 (6H, t, *J* = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 2.39 (3H, s, CH_3), 3.87 (2H, dt, *J* = 5.1 Hz, *J* = 1.7 Hz, NCH_2), 4.27-4.51 (4H, m, 2x $O\underline{C}H_2CH_3$), 5.10 (1H, ddd, *J* = 10.4 Hz, *J* = 3.4 Hz, *J* = 1.7 Hz, $CH=C\underline{H}_EH_Z$), 5.21 (1H, ddd, *J* = 17.1 Hz, *J* = 3.4 Hz, *J* = 1.7 Hz, $CH=CH_E\underline{H}_Z$), 5.90 (1H, ddt, *J* = 17.1 Hz, *J* = 10.4 Hz, *J* = 5.1 Hz, $C\underline{H}=CH_EH_Z$), 7.22 (4H, m, 4x CH_{ar}).**^{13}C-NMR (75 MHz, $CDCl_3$) δ**

16.6 (d, $^{3}J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 21.5 (CH_3), 55.9 (NCH_2), 65.5 (d, $^{2}J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 82.2 (d, $^{1}J_{CP}$ = 176.5 Hz, $PCCl_2$), 116.3 ($CH=\underline{C}H_2$), 128.8 (2x CH_{ar}), 128.9 (2x CH_{ar}), 134.5 ($\underline{C}H=CH_2$), 139.4 ($\underline{C}_{q,ar}C=N$ + $\underline{C}_{q,ar}CH_3$), 166.3 (d, $^{2}J_{CP}$ = 2.3 Hz, C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 11.07. **IR (ATR, cm^{-1}) ν_{max}**: 1017 (P-O), 1052(P-O), 1262 (P=O), 1654, 2982. **MS (ESI, pos)**: *m/z* (%) 378.3/380.3/382.3 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{16}H_{22}Cl_2NO_3P+H^+$ 378.0787, found 378.0795.

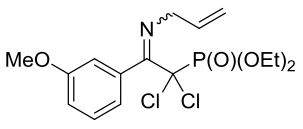
diethyl (2-([1,1'-biphenyl]-4-yl)-2-(allylimino)-1,1-dichloroethyl)phosphonate 25h



25h

1.78 g (5.75 mmol) of enamine/imine **322h/323h** was converted into 2.09 g **25h** (5.52 mmol, 90 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.38 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.92 (2H, dt, *J* = 5.1 Hz, *J* = 1.8 Hz, NCH_2), 4.28-4.50 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.12 (1H, ddd, *J* = 10.5 Hz, *J* = 3.4 Hz, *J* = 1.8 Hz, $CH=C\underline{H}_EH_Z$), 5.24 (1H, ddd, *J* = 17.2 Hz, *J* = 3.4 Hz, *J* = 1.8 Hz, $CH=CH_E\underline{H}_Z$), 5.93 (1H, ddt, *J* = 17.2 Hz, *J* = 10.5 Hz, *J* = 5.1 Hz, $C\underline{H}=CH_EH_Z$), 7.35-7.49 (5H, m, 5x CH_{ar}), 7.57-7.71 (4H, m, 4x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.6 (d, $^{3}J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 56.0 (NCH_2), 65.6 (d, $^{2}J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 82.1 (d, $^{1}J_{CP}$ = 176.5 Hz, $PCCl_2$), 116.4 ($CH=\underline{C}H_2$), 126.8 (2x CH_{ar}), 127.2 (2x CH_{ar}), 127.9 (CH_{ar}), 129.0 (2x CH_{ar}), 129.5 (2x CH_{ar}), 130.7 (d, $^{3}J_{CP}$ = 5.8 Hz, $\underline{C}_{q,ar}CN$), 134.4 ($\underline{C}H=CH_2$), 140.2 ($C_{q,ar}$), 142.2 ($C_{q,ar}$), 166.0 (d, $^{2}J_{CP}$ = 2.3 Hz, C=N) .**^{31}P-NMR (121 MHz, $CDCl_3$) δ** 10.93. **IR (ATR, cm^{-1}) ν_{max}**: 1019 (P-O), 1054 (P-O), 1262 (P=O), 1712, 2982. **MS (ESI, pos)**: *m/z* (%) 440.3/442.3/444.3 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{21}H_{24}Cl_2NO_3P+H^+$ 440.0944, found 440.0947.

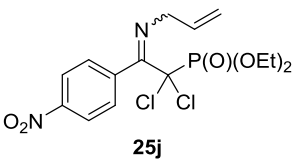
diethyl (2-(allylimino)-1,1-dichloro-2-(3-methoxyphenyl)ethyl)phosphonate 25i



25i

2.01 g (6.18 mmol) of enamine/imine **322i/323i** was converted into 2.41 g **25i** (6.12 mmol, 99 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.38 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.82 (3H, OCH_3), 3.88 (2H, dt, *J* = 5.3 Hz, *J* = 1.7 Hz, NCH_2), 4.27-4.49 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.11 (1H, dd, *J* = 10.8 Hz, *J* = 1.7 Hz, $CH=C\underline{H}_EH_Z$), 5.22 (1H, dd, *J* = 16.8 Hz, *J* = 1.7 Hz, $CH=CH_E\underline{H}_Z$), 5.91 (1H, ddt, *J* = 16.8 Hz, *J* = 10.8 Hz, *J* = 5.3 Hz, $C\underline{H}=CH_EH_Z$), 6.85-6.91 (2H, m, 2x CH_{ar}), 6.97 (1H, dd, *J* = 8.1 Hz, *J* = 2.2 Hz, CH_{ar}), 7.34 (1H, dd, *J* = 8.1 Hz, *J* = 8.1 Hz, CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.4 (d, $^{3}J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 55.2 (OCH_3), 55.8 (NCH_2), 65.3 (d, $^{2}J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 81.7 (d, $^{1}J_{CP}$ = 177.7 Hz, $PCCl_2$), 114.5 (CH_{ar}), 114.8 (CH_{ar}), 116.1 ($CH=\underline{C}H_2$), 121.1 (CH_{ar}), 129.2 (CH_{ar}), 132.8 (d, $^{3}J_{CP}$ = 5.8 Hz, $\underline{C}_{q,ar}C=N$), 134.3 ($\underline{C}H=CH_2$), 159.1 ($\underline{C}_{q,ar}OCH_3$), 165.7 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 10.96. **IR (ATR, cm^{-1}) ν_{max}**: 1019 (P-O), 1264 (P=O), 1578, 2982. **MS (ESI, pos)**: *m/z* (%) 394.3/396.3/398.3 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{16}H_{22}Cl_2NO_4P+H^+$ 394.0736, found 394.0743.

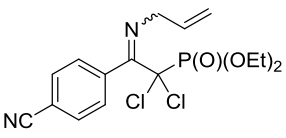
diethyl (2-(allylimino)-1,1-dichloro-2-(4-nitrophenyl)ethyl)phosphonate 25j



25j

1.78 g (5.23 mmol) of enamine/imine **322i/323i** was converted and purified by column chromatography into 0.90 g **25j** (2.20 mmol, 42 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.39 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 3.86 (2H, d, *J* = 5.4 Hz, NCH_2), 4.27-4.49 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.15 (1H, d, *J* = 11.2 Hz, $CH{=}C\underline{H}_EH_Z$), 5.20 (1H, d, *J* = 17.8 Hz, $CH{=}CH_E\underline{H}_Z$), 5.90 (1H, ddt, *J* = 17.8 Hz, *J* = 11.2 Hz, *J* = 5.4 Hz, $C\underline{H}{=}CH_EH_Z$), 7.54 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}), 8.31 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.4 (d, $^{3}J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 56.0 (NCH_2), 65.7 (d, $^{2}J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 81.0 (d, $^{1}J_{CP}$ = 175.4 Hz, $PCCl_2$), 116.6 ($CH{=}\underline{C}H_2$), 123.2 (2x CH_{ar}), 130.2 (2x CH_{ar}), 133.5 ($\underline{C}H{=}CH_2$), 138.2 (d, $^{3}J_{CP}$ = 5.8 Hz, $\underline{C}_{q,ar}C{=}N$), 148.3 ($C_{q,ar}NO_2$), 163.9 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 10.12. **IR (ATR, cm^{-1}) ν_{max}**: 1013 (P-O), 1052 (P-O), 1263 (P=O), 1347 (N-O), 1521 (N-O), 1600, 2980. **MS (ESI, pos)**: *m/z* (%) 409.0/411.0/413.0 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{15}H_{19}Cl_2N_2O_5P+H^+$ 409.0481, found 409.0492. **Chromatography**: hexanes/EtOAc 3/2, R_f = 0.11.

diethyl (2-(allylimino)-1,1-dichloro-2-(4-cyanophenyl)ethyl)phosphonate 25k



25k

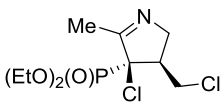
1.60 g (5.00 mmol) of enamine/imine **322k/323k** was converted and purified by column chromatography into 0.86 g **25k** (2.20 mmol, 44 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.38 (6H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.84 (2H, d, *J* = 5.0 Hz, NCH_2), 4.26-4.48 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.14 (1H, d, *J* = 11.4 Hz, $CH{=}C\underline{H}_EH_Z$), 5.19 (1H, d, *J* = 18.0 Hz, $CH{=}CH_E\underline{H}_Z$), 5.89 (1H, ddt, *J* = 18.0 Hz, *J* = 11.4 Hz, *J* = 5.0 Hz, $C\underline{H}{=}CH_EH_Z$), 7.46 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}), 7.74 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.4 (d, $^{3}J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 55.8 (NCH_2), 65.5 (d, $^{2}J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 81.0 (d, $^{1}J_{CP}$ = 176.5 Hz, $PCCl_2$), 113.3 ($\underline{C}_{q,ar}C{\equiv}N$), 116.5 ($CH{=}\underline{C}H_2$), 117.9 (C≡N), 129.8 (2x CH_{ar}), 131.8 (2x CH_{ar}), 133.6 ($\underline{C}H{=}CH_2$), 136.2 (d, $^{3}J_{CP}$ = 4.6 Hz, $\underline{C}_{q,ar}C{=}N$), 164.0 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 9.96. **IR (ATR, cm^{-1}) ν_{max}**: 1016 (P-O), 1052 (P-O), 1264 (P=O), 2232 (C≡N), 2984. **MS (ESI, pos)**: *m/z* (%) 389.0/391.0/393.0 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{16}H_{19}Cl_2N_2O_3P+H^+$ 389.0583, found 389.0597. **Chromatography**: hexanes/EtOAc 3/2, R_f = 0.10.

3.1.4 Synthesis of diethyl (4-chloro-3-(chloromethyl)-3,4-dihydro-2H-pyrrol-4-yl)phosphonates 26

In a flame-dried round-bottom flask and under a N_2-atmosphere, diethyl (2-(allylimino)-1,1-dichloroethyl)phosphonates **25a-k** were dissolved in dry CH_2Cl_2 (1 M). Cu(I)Cl (0.4 equiv) and *N,N,N',N',N"*-pentamethyldiethylenetriamine (0.8 equiv) were added and the reaction mixture was heated to reflux. The reaction progress was monitored using HPLC. After all starting material had

been consumed, the reaction mixture was poured into brine and extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases were washed with water until no more Cu salts were present (blue color of the aqueous phase disappears). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* and the residue was purified by crystallization or column chromatography. Only the major diastereoisomers could be isolated in pure form.

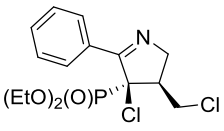
diethyl (*cis*-4-chloro-3-(chloromethyl)-5-methyl-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26a



(±)-**26a**

4.04 g (13.4 mmol) of **25a** was converted into **26a** (*dr* = 84/16). After column chromatography 1.53 g of product was obtained (5.09 mmol, 38 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.38 (6H, t, *J* = 6.9 Hz, 2x $OCH_2C\underline{H}_3$), 2.23 (3H, s, CH_3), 3.01-3.15 (1H, m, $C\underline{H}CH_2Cl$), 3.57 (1H, dd, *J* = 10.7 Hz, *J* = 10.7 Hz, $CHC\underline{H}_aH_bCl$), 3.72-3.82 (1H, m, $NC\underline{H}_aH_b$), 3.94 (1H, dd, *J* = 10.7 Hz, *J* = 4.1 Hz, $CHCH_a\underline{H}_bCl$), 4.19-4.36 (5H, m, 2x $OC\underline{H}_2CH_3$ + $NCH_a\underline{H}_b$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.4 (d, $^3J_{CP}$ = 4.6 Hz, 2x $OCH_2\underline{C}H_3$), 16.9 (CH_3), 43.9 (d, $^3J_{CP}$ = 3.5 Hz, $CH\underline{C}H_2Cl$), 46.5 ($\underline{C}HCH_2Cl$), 63.2 (d, $^3J_{CP}$ = 10.4 Hz, NCH_2), 64.2 (d, $^2J_{CP}$ = 8.1 Hz, $O\underline{C}H_2CH_3$), 64.8 (d, $^2J_{CP}$ = 8.1 Hz, $O\underline{C}H_2CH_3$), 72.0 (d, $^1J_{CP}$ = 168 Hz, PC_q) 169.2 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 16.70. **IR (ATR, cm^{-1}) ν_{max}**: 1014 (P-O), 1250 (P=O), 1643, 2983. **MS (ESI, pos)**: *m/z* (%) 302.0/304.0/306.0 ($M+H^+$, 100/64/10). **Chromatography**: hexanes/EtOAc 1/1, R_f = 0.15.

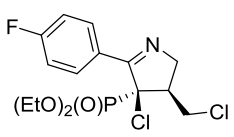
diethyl (*cis*-4-chloro-3-(chloromethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26b



(±)-**26b**

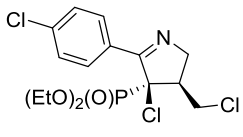
3.42 g (9.39 mmol) of **25b** was converted into **26b** (*dr* = 90/10). After column chromatography 3.18 g of product was obtained (8.73 mmol, 93 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.20 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.28 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.22-3.38 (1H, m, $C\underline{H}CH_2Cl$), 3.67 (1H, dd, *J* = 10.7 Hz, *J* = 10.7 Hz, $CHC\underline{H}_aH_bCl$), 3.96-4.23 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.45 (1H, dd, *J* = 17.1 Hz, *J* = 6.6 Hz, $NCH_a\underline{H}_b$), 7.36-7.44 (3H, m, 3x CH_{ar}), 8.02 (2H, d, *J* = 7.2 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 44.2 (d, $^3J_{CP}$ = 2.3 Hz, $CH\underline{C}H_2Cl$), 48.6 ($\underline{C}HCH_2Cl$), 63.2 (d, $^3J_{CP}$ = 10.4 Hz, NCH_2), 64.3 (d, $^2J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 64.7 (d, $^2J_{CP}$ = 8.1 Hz, $O\underline{C}H_2CH_3$), 71.2 (d, $^1J_{CP}$ = 166.1 Hz, PC_q), 128.0 (2x CH_{ar}), 129.3 (2x CH_{ar}), 130.7 (CH_{ar}), 132.8 ($C_{q,ar}$), 169.1 (d, $^2J_{CP}$ = 2.3 Hz, C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 17.11. **IR (ATR, cm^{-1}) ν_{max}**: 1012 (P-O), 1043 (P-O), 1263 (P=O), 1606, 2981. **MS (ESI, pos)**: *m/z* (%) 364.0/366.0/368.0 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{15}H_{20}Cl_2NO_3P+H^+$ 364.0631, found 364.0636. **Chromatography**: hexanes/EtOAc 1/1, R_f = 0.4.

diethyl (*cis*-4-chloro-3-(chloromethyl)-5-(4-fluorophenyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26c


(±)-**26c**

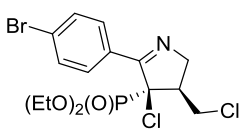
3.00 g (7.82 mmol) of **25c** was converted into **26c** (*dr* = 92/8). After column chromatography 1.77 g of product was obtained (4.61 mmol, 59 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.20 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.31 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.23-3.36 (1H, m, $C\underline{H}CH_2Cl$), 3.66 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 3.96-4.19 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.43 (1H, ddd, *J* = 17.1 Hz, *J* = 7.2 Hz, $^{4}J_{HP}$ = 1.7 Hz, $NCH_a\underline{H}_b$), 7.07 (2H, dd, *J* = 8.8 Hz, $^{3}J_{HF}$ = 8.8 Hz, 2x CH_{ar}), 8.10 (2H, dd, *J* = 8.8 Hz, $^{4}J_{FH}$ = 5.5 Hz, 2x CH_{ar}).**^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.2 (d, $^{3}J_{CP}$ = 5.8 Hz, 2x $OCH_2\underline{C}H_3$), 44.1 (d, $^{3}J_{CP}$ = 2.3 Hz, $CH\underline{C}H_2Cl$), 48.4 ($\underline{C}HCH_2Cl$), 63.1 (d, $^{3}J_{CP}$ = 9.2 Hz, NCH_2), 64.5 (d, $^{2}J_{CP}$ = 12.1 Hz, $O\underline{C}H_2CH_3$), 64.6 (d, $^{2}J_{CP}$ = 12.1 Hz, $O\underline{C}H_2CH_3$), 71.1 (d, $^{2}J_{CP}$ = 165.0 Hz, PC_q), 114.9 (d, $^{2}J_{CF}$ = 21.9 Hz, 2x CH_{ar}), 128.7 (d, $^{4}J_{CF}$ = 3.5 Hz, $\underline{C}_{q,ar}C$=N), 131.6 (d, $^{3}J_{CF}$ = 8.1 Hz, 2x CH_{ar}), 164.2 (d, $^{1}J_{CF}$ = 251.22 Hz, $C_{q,ar}F$), 167.7 (C=N). **^{19}F-NMR (282 MHz, $CDCl_3$) δ** -109.43 to -109.32 (m).**^{31}P-NMR (121 MHz, $CDCl_3$) δ** 17.08. **IR (cm^{-1}) ν_{max}**: 1012 (P-O), 1039 (P-O), 1263 (P=O), 1509, 2980. **MS (ESI, pos)**: *m/z* (%) 382.0/384.0/386.0 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{15}H_{19}Cl_2FNO_3P+H^+$ 382.0536, found 382.0543. **Chromatography**: hexanes/EtOAc 4/1, R_f = 0.15.

diethyl (*cis*-4-chloro-3-(chloromethyl)-5-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26d


(±)-**26d**

0.70 g (1.76 mmol) of **25d** was converted into **26d** (*dr* = 90/10). After column chromatography 0.51 g of product was obtained (1.28 mmol, 73 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.21 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.31 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.22-3.36 (1H, m, $C\underline{H}CH_2Cl$), 3.65 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 3.94-4.23 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.43 (1H, ddd, *J* = 17.1 Hz, *J* = 7.2 Hz, $^{4}J_{HP}$ = 1.7 Hz, $NCH_a\underline{H}_b$), 7.37 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}), 8.02 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, $^{3}J_{CP}$ = 4.6 Hz, $OCH_2\underline{C}H_3$), 44.1 (d, $^{3}J_{CP}$ = 3.5 Hz, $CH\underline{C}H_2Cl$), 48.4 ($\underline{C}HCH_2Cl$), 63.2 (d, $^{3}J_{CP}$ = 9.2 Hz, NCH_2), 64.5 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 64.7 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 71.1 (d, $^{1}J_{CP}$ = 165.0 Hz, PC_q), 128.2 (2x CH_{ar}), 130.8 (2x CH_{ar}), 131.0 ($\underline{C}_{q,ar}C$=N), 136.9 ($C_{q,ar}Cl$), 167.8 (C=N).**^{31}P-NMR (121 MHz, $CDCl_3$) δ** 17.06. **IR (ATR, cm^{-1}) ν_{max}**: 1012 (P-O), 1041 (P-O), 1263 (P=O), 1491, 2982. **MS (ESI, pos)**: *m/z* (%) 398.0/400.0/402.0 ($M+H^+$, 100/96/40). **HRMS**: *m/z* calcd for $C_{15}H_{19}Cl_3NO_3P+H^+$ 398.0241, found 398.0249. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.21.

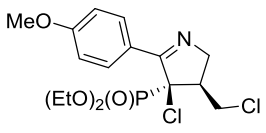
diethyl (*cis*-4-chloro-3-(chloromethyl)-5-(4-bromophenyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26e



(±)-**26e**

0.65 g (1.47 mmol) of **25e** was converted into **26e** (*dr* = 89/11). After column chromatography 0.28 g of product was obtained (0.63 mmol, 43 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.12 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.22 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.14-3.27 (1H, m, $C\underline{H}CH_2Cl$), 3.56 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 3.88-4.13 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.33 (1H, ddd, *J* = 17.2 Hz, *J* = 7.0 Hz, $^{4}J_{HP}$ = 1.7 Hz, $NCH_a\underline{H}_b$), 7.44 (2H, *J* = 8.8 Hz, 2x CH_{ar}), 7.88 (2H, *J* = 8.8 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.4 (d,$^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 44.1 (d, $^{3}J_{CP}$ = 3.5 Hz, $CH\underline{C}H_2Cl$), 48.4 ($\underline{C}HCH_2Cl$), 63.2 (d, $^{3}J_{CP}$ = 9.2 Hz, NCH_2), 64.5 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 64.7 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 71.1 (d, $^{1}J_{CP}$ = 165.0 Hz, PC_q), 125.4 ($C_{q,ar}Br$), 131.0 (2x CH_{ar}), 131.1 (2x CH_{ar}), 131.4 ($\underline{C}_{q,ar}C$=N), 167.8 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 16.97. **IR (ATR, cm^{-1}) ν_{max}**: 1010 (P-O), 1038 (P-O), 1266 (P=O), 1394, 2978. **MS (ESI, pos)**: *m/z* (%) 442.0/444.0/446.0(M+H$^+$, 62/100/45). **HRMS**: *m/z* calcd for $C_{15}H_{19}BrCl_2NO_3P+H^+$ 441.9736, found 441.9737. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.19.

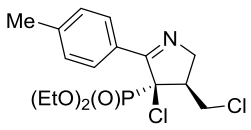
diethyl (*cis*-4-chloro-3-(chloromethyl)-5-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26f



(±)-**26f**

1.11 g (2.82 mmol) of **25f** was converted into **26f** (*dr* = 85/15). After column chromatography 0.50 g of product was obtained (1.27 mmol, 45 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.19 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.31 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.21-3.35 (1H, m, $C\underline{H}CH_2Cl$), 3.64 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 3.81 (3H, s, OCH_3), 3.91-4.22 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.39 (1H, ddd, *J* = 17.1 Hz, *J* = 7.2 Hz, $^{4}J_{HP}$ = 1.7 Hz, $NCH_a\underline{H}_b$), 6.89 (2H, d, *J* = 9.4 Hz, 2x CH_{ar}), 8.08 (2H, d, *J* = 9.4 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.2 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 44.3 (d, $^{3}J_{CP}$ = 3.5 Hz, $CH\underline{C}H_2Cl$), 48.4 ($\underline{C}HCH_2Cl$), 55.2 (OCH_3), 62.8 (d, $^{3}J_{CP}$ = 9.2 Hz, NCH_2), 64.3 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 64.5 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 71.1 (d, $^{1}J_{CP}$ = 163.8 Hz, PC_q), 113.2 (2x CH_{ar}), 124.8 ($\underline{C}_{q,ar}C$=N), 131.0 (2x CH_{ar}), 161.5 ($\underline{C}_{q,ar}OCH_3$), 167.8 (d, $^{2}J_{CP}$ = 2.3 Hz, C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 17.48. **IR (ATR, cm^{-1}) ν_{max}**: 1012 (P-O), 1177 (P-O), 1252 (P=O), 1513, 1606, 2978. **MS (ESI, pos)**: *m/z* (%) 394.0/396.0/398.0 (M+H$^+$, 100/64/11). **HRMS**: *m/z* calcd for $C_{16}H_{22}Cl_2NO_4P+H^+$ 394.0736, found 394.0740. **Chromatography**: hexanes/EtOAc 3/2, R_f = 0.23.

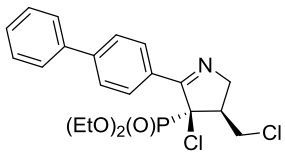
diethyl (*cis*-4-chloro-3-(chloromethyl)-5-(4-methylphenyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26g



(±)-**26g**

1.82 g (4.81 mmol) of **25g** was converted into **26g** (*dr* = 95/5). After column chromatography 0.47 g of product was obtained (1.25 mmol, 26 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.20 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.30 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.37 (3H, s, CH_3), 3.19-3.37 (1H, m, $C\underline{H}CH_2Cl$), 3.65 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 3.94-4.23 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.42 (1H, ddd, *J* = 17.1 Hz, *J* = 7.2 Hz, $^{4}J_{HP}$ = 1.7 Hz, $NCH_a\underline{H}_b$), 7.19 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}), 7.95 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 21.6 (CH_3), 44.3 (d, $^{3}J_{CP}$ = 2.3 Hz, $CH\underline{C}H_2Cl$), 48.5 ($\underline{C}HCH_2Cl$), 63.0 (d, $^{3}J_{CP}$ = 9.2 Hz, NCH_2), 64.4 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 64.7 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 71.2 (d, $^{1}J_{CP}$ = 163.8 Hz, PC_q), 128.7 (2x CH_{ar}), 129.3 (2x CH_{ar}), 129.7 ($\underline{C}_{q,ar}C$=N), 141.0 ($\underline{C}_{q,ar}CH_3$), 168.8 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 17.36**. IR (ATR, cm^{-1}) ν_{max}**: 1014 (P-O), 1096 (P-O), 1264 (P=O), 1606, 2359, 2981. **MS (ESI, pos)**: *m/z* (%) 378.3/380.3/382.3 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{16}H_{22}Cl_2NO_3P+H^+$ 378.0787, found 378.0782. **Chromatography**: hexanes/EtOAc 1/1, R_f = 0.47.

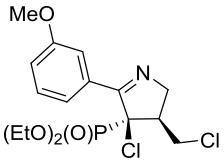
diethyl (*cis*-5-([1,1'-biphenyl]-4-yl)-4-chloro-3-(chloromethyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26h



(±)-**26h**

1.15 g (2.61 mmol) of **25h** was converted into **26h** (*dr* = 96/4). After column chromatography 0.42 g of product was obtained (0.97 mmol, 37 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.22 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.31 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 3.25-3.40 (1H, m, $C\underline{H}CH_2Cl$), 3.68 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 4.00-4.21 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.47 (1H, ddd, *J* = 17.1 Hz, *J* = 6.9 Hz, $^{4}J_{HP}$ = 1.9 Hz, $NCH_a\underline{H}_b$), 7.35-7.47 (3H, m, 3x CH_{ar}), 7.62-7.65 (4H, m, 4x CH_{ar}), 8.14-8.18 (2H, m, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.4 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 44.3 ($CH\underline{C}H_2Cl$), 48.5 ($\underline{C}HCH_2Cl$), 63.3 (d, $^{3}J_{CP}$ = 10.4 Hz, NCH_2), 64.5 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 64.7 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 71.3 (d, $^{1}J_{CP}$ = 165.0 Hz, PC_q), 126.6 (2x CH_{ar}), 127.2 (2x CH_{ar}), 127.9 (CH_{ar}), 129.0 (3x CH_{ar}), 129.9 (CH_{ar}), 131.5 ($C_{q,ar}$), 140.3 ($C_{q,ar}$), 143.3 ($C_{q,ar}$), 168.5 (d, $^{2}J_{CP}$ = 2.3 Hz, C=N).**^{31}P-NMR (121 MHz, $CDCl_3$) δ** 17.27.**IR (ATR, cm^{-1}) ν_{max}**: 1014 (P-O), 1043 (P-O), 1263 (P=O), 1602, 2980. **MS (ESI, pos)**: *m/z* (%) 440.3/442.3/444.3 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{21}H_{24}Cl_2NO_3P+H^+$ 440.0944, found 440.0949. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.29.

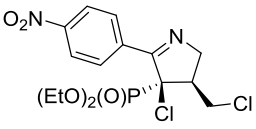
diethyl (*cis*-4-chloro-3-(chloromethyl)-5-(3-methoxyphenyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26i



(±)-**26i**

2.11 g (5.35 mmol) of **25i** was converted into **26i** (*dr* = 93/7). After column chromatography 1.27 g of product was obtained (3.21 mmol, 60 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.21 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.29 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.24-3.36 (1H, m, $C\underline{H}CH_2Cl$), 3.66 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 3.84 (3H, s, OCH_3), 3.96-4.18 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.45 (1H, dd, *J* = 17.1 Hz, *J* = 7.2 Hz, $NCH_a\underline{H}_b$), 6.99 (1H, d, *J* = 8.1 Hz, CH_{ar}), 7.30 (1H, dd, *J* = 8.1 Hz, *J* = 8.1 Hz, CH_{ar}), 7.63-7.66 (2H, m, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 44.2 (d, $^{3}J_{CP}$ = 2.3 Hz, $CH\underline{C}H_2Cl$), 48.6 ($\underline{C}HCH_2Cl$), 55.4 (OCH_3), 63.1 (d, $^{3}J_{CP}$ = 10.4 Hz, NCH_2), 64.3 (d, $^{2}J_{CP}$ = 10.4 Hz, $O\underline{C}H_2CH_3$), 64.7 (d, $^{2}J_{CP}$ = 10.4 Hz, $O\underline{C}H_2CH_3$), 71.2 (d, $^{1}J_{CP}$ = 165.0 Hz, PC_q), 114.1 (CH_{ar}), 117.0 (CH_{ar}), 121.7 (CH_{ar}), 129.0 (CH_{ar}), 133.8 ($\underline{C}_{q,ar}C$=N), 159.1 ($\underline{C}_{q,ar}OCH_3$), 168.8 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 17.21. **IR (ATR, cm^{-1}) ν_{max}**: 1013 (P-O), 1263 (P=O), 1578, 2981. **MS (ESI, pos)**: *m/z* (%) 394.3/396.3/398.3 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{16}H_{22}Cl_2NO_4P+H^+$ 394.0736, found 394.0732. **Chromatography**: hexanes/EtOAc 3/2, R_f = 0.29.

diethyl (*cis*-4-chloro-3-(chloromethyl)-5-(4-nitrophenyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26j

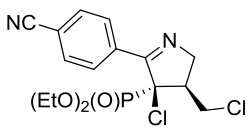


(±)-**26j**

0.60 g (1.47 mmol) of **25j** was converted into **26j** (*dr* = 93/7). After one crystallisation 0.14 g of product was obtained (0.34 mmol, 23 % yield, orange needles). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.22 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.32 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.25-3.40 (1H, m, $C\underline{H}CH_2Cl$), 3.67 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 3.97-4.25 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.50 (1H, dd, *J* = 17.6 Hz, *J* = 7.2 Hz, $NCH_a\underline{H}_b$), 8.25 (4H, s, 4x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 43.9 (d, $^{3}J_{CP}$ = 2.3 Hz, $CH\underline{C}H_2Cl$), 48.4 ($\underline{C}HCH_2Cl$), 63.6 (d, $^{3}J_{CP}$ = 9.2 Hz, NCH_2), 64.8 (d, $^{2}J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 71.1 (d, $^{1}J_{CP}$ = 163.8 Hz, PC_q), 123.0 (2x CH_{ar}), 130.5 (2x CH_{ar}), 138.5 ($\underline{C}_{q,ar}C$=N), 149.0 ($C_{q,ar}NO_2$), 167.4 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 16.59. **IR (ATR, cm^{-1}) ν_{max}**: 1011 (P-O), 1041 (P-O), 1266 (P=O), 1342 (N-O), 1518 (N-O), 1594, 2980. **MS (ESI, pos)**: *m/z* (%) 409.0/411.0/413.0 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{15}H_{19}Cl_2N_2O_5P+H^+$ 409.0481, found 409.0483. **Melting point range**: 108.0-109.0 °C. **Crystal data for compound 26j**: $C_{15}H_{19}N_2O_5PCl_2$, *M* = 409.19, monoclinic, space group $P2_1/c$ (No. 14), *a* = 9.0945(13) Å, *b* = 11.1936(9) Å, *c* = 21.398(3) Å, *β* = 120.027(18)°, *V* = 1886.0(5) Å^3, *Z* = 4, *T* = 293.15 K, ρ_{calc} = 1.441 g cm^{-3}, μ(Cu-Kα) = 4.154 mm^{-1}, *F*(000) = 848, 6793 reflections measured, 3245 unique (R_{int} = 0.0624) which were used

in all calculations. The final *R*1 was 0.0702 ($I > 2\sigma(I)$) and *wR*2 was 0.2166 (all data). One of the ethoxy groups was found to be disordered and was modeled over two positions.

diethyl (*cis*-4-chloro-3-(chloromethyl)-5-(4-cyanophenyl)-3,4-dihydro-2*H*-pyrrol-4-yl)phosphonate 26k



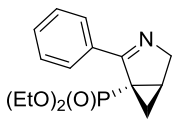
(±)-**26k**

0.85 g (2.18 mmol) of **25k** was converted into **26k** (*dr* = 95/5). After one crystallisation 0.12 g of product was obtained (0.31 mmol, 14 % yield, transparent cubic crystals). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.21 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.32 (3H, t, *J* = 6.9 Hz, $OCH_2C\underline{H}_3$), 3.24-3.37 (1H, m, $NCH_2C\underline{H}$), 3.66 (1H, dd, *J* = 10.5 Hz, *J* = 10.5 Hz, $CHC\underline{H}_aH_bCl$), 3.96-4.24 (6H, m, 2x $OC\underline{H}_2CH_3$ + $CHCH_a\underline{H}_bCl$ + $NC\underline{H}_aH_b$), 4.48 (1H, dd, *J* = 17.6 Hz, *J* = 7.2 Hz, $NCH_a\underline{H}_b$), 7.69 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}), 8.19 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^3J_{CP}$ = 4.6 Hz, $OCH_2\underline{C}H_3$), 44.0 (d, $^3J_{CP}$ = 2.3 Hz, $CH\underline{C}H_2Cl$), 48.4 ($\underline{C}HCH_2Cl$), 63.6 (d, $^3J_{CP}$ = 9.2 Hz, NCH_2), 64.8 (d, $^2J_{CP}$ = 6.9 Hz, 2x $O\underline{C}H_2CH_3$), 71.1 (d, $^1J_{CP}$ = 166.1 Hz, PC_q), 114.2 ($\underline{C}_{q,ar}C{\equiv}N$), 118.5 (C≡N), 130.1 (2x CH_{ar}), 131.7 (2x CH_{ar}), 136.7 ($\underline{C}_{q,ar}C{=}N$), 167.6 (C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 16.67. **IR (ATR, cm^{-1}) ν_{max}**: 1011 (P-O), 1039 (P-O), 1266 (P=O), 2230 (C≡N), 2984. **MS (ESI, pos)**: *m/z* (%) 389.0/391.0/393.0 ($M+H^+$, 100/64/10). **HRMS**: *m/z* calcd for $C_{16}H_{19}Cl_2N_2O_3P+H^+$ 389.0583, found 389.0595. **Melting point range**: 111.0-112.5 °C. **Crystal data for compound 26k**. $C_{16}H_{19}N_2O_3PCl_2$, *M* = 389.20, monoclinic, space group $P2_1/c$ (No. 14), *a* = 9.6158(4) Å, *b* = 11.3767(5) Å, *c* = 17.5776(7) Å, *β* = 98.092(4)°, *V* = 1903.78(14) Å^3, *Z* = 4, *T* = 293.15 K, ρ_{calc} = 1.358 g cm^{-3}, μ(Cu-Kα) = 4.007 mm^{-1}, *F*(000) = 808, 7893 reflections measured, 3369 unique (R_{int} = 0.0326) which were used in all calculations. The final *R*1 was 0.0452 ($I > 2\sigma(I)$) and *wR*2 was 0.1342 (all data). Both of the ethoxy groups were found to be disordered and were modeled over two positions.

3.1.5 Synthesis of diethyl (3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonates 326 and 330

In a round-bottom flame-dried flask and under a N_2-atmosphere, diethyl (*cis*-4-chloro-3-(chloromethyl)-3,4-dihydro-2H-pyrrol-4-yl)phosphonates **26a-k** were dissolved in dry THF (1 M). The solution was cooled to -78 °C and *n*-BuLi (1.2 equiv, however for **26k** 2.2 equiv was used) was added in a dropwise fashion. The reaction mixture was kept at -78 °C for 2 h and was then slowly warmed to room temperature. Water was added and the solution was extracted with diethyl ether (3x 10 mL). After drying the combined organic layers over $MgSO_4$, the solvent was removed *in vacuo* and the residue was purified using column chromatography.

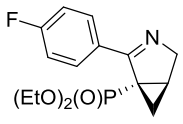
diethyl (2-phenyl-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 326b



(±)-**326b**

2.50 g (6.86 mmol) of **26b** was converted into **326b**. After column chromatography 1.53 g of product was obtained (5.21 mmol, 76 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 0.84-0.90 (1H, ~q, $PC_qC\underline{H}_aH_b$), 1.17 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.20 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.76 (1H, ddd, $^{3}J_{HP}$ = 14.6 Hz, *J* = 8.5 Hz, *J* = 4.7 Hz, $PC_qCH_a\underline{H}_b$), 2.58-2.69 (1H, m, $NCH_2C\underline{H}$), 3.91-4.03 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.10 (2H, ~t, NCH_2), 7.37-7.44 (3H, m, 3x CH_{ar}), 7.91 (2H, d, *J* = 6.6 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.2 (d, $^{3}J_{CP}$ = 4.6 Hz, $OCH_2\underline{C}H_3$), 16.3 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 19.2 ($PC_q\underline{C}H_2$), 28.7 ($NCH_2\underline{C}H$), 34.0 (d, $^{1}J_{CP}$ = 199.6 Hz, PC_q), 61.3 (d, $^{3}J_{CP}$ = 3.5 Hz, NCH_2), 62.2 (d, $^{2}J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.4 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 128.0 (2x CH_{ar}), 128.7 (2x CH_{ar}), 130.5 (CH_{ar}), 134.1 ($C_{q,ar}$), 173.1 (d, $^{2}J_{CP}$ = 8.1 Hz, C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 22.91. **IR (ATR, cm^{-1}) ν_{max}**: 1022 (P-O), 1049 (P-O), 1247 (P=O), 1596, 2982. **MS (ESI, pos)**: *m/z* (%) 294.3/295.3 ($M+H^+$, 100/16). **HRMS**: *m/z* calcd for $C_{15}H_{20}NO_3P+H^+$ 294.1254, found 294.1264. **Chromatography**: EtOAc, R_f = 0.06.

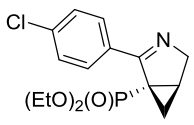
diethyl (2-(4-fluorophenyl)-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 326c



(±)-**326c**

0.18 g (0.47 mmol) of **26c** was converted into **326c**. After column chromatography 72 mg of product was obtained (0.23 mmol, 49 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 0.83-0.89 (1H, m, $PCC\underline{H}_aH_b$), 1.18 (3H, t, *J* = 7.5 Hz, $OCH_2C\underline{H}_3$) 1.21 (3H, t, *J* = 7.5 Hz, $OCH_2C\underline{H}_3$), 1.75 (1H, ddd, $^{3}J_{HP}$ = 14.5 Hz, *J* = 8.4 Hz, *J* = 4.3 Hz, $PCCH_a\underline{H}_b$), 2.54-2.69 (1H, m, $NCH_2C\underline{H}$), 3.93-4.05 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.08 (2H, ~t, NCH_2), 7.09 (2H, dd, *J* = 8.8 Hz, $^{3}J_{FH}$ = 8.8 Hz, 2x CH_{ar}), 7.94 (2H, dd, *J* = 8.8 Hz, $^{4}J_{HF}$ = 5.5 Hz, 2x CH_{ar}).**^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^{3}J_{CP}$ = 5.2 Hz, $OCH_2\underline{C}H_3$), 16.3 (d, $^{3}J_{CP}$ = 5.2 Hz, $OCH_2\underline{C}H_3$), 19.2 ($PC\underline{C}H_2$), 28.9 ($NCH_2\underline{C}H$), 33.9 (d, $^{1}J_{CP}$ = 200.8 Hz, PC_q), 61.2 (d, $^{3}J_{CP}$ = 3.5 Hz, NCH_2), 62.3 (d, $^{2}J_{CP}$ = 6 Hz, $O\underline{C}H_2CH_3$), 62.5 (d, $^{2}J_{CP}$ = 6 Hz, $O\underline{C}H_2CH_3$), 115.1 (d, $^{2}J_{CF}$ = 21.9 Hz, 2x CH_{ar}), 130.3 (d, $^{4}J_{CF}$ = 2.3 Hz, $\underline{C}_{q,ar}C$=N), 130.9 (d, $^{3}J_{CF}$ = 8.1 Hz, 2x CH_{ar}), 164.3 (d, $^{1}J_{CF}$ = 250.4 Hz, $C_{q,ar}F$), 172.0 (d, $^{2}J_{CP}$ = 8.1 Hz, C=N). **^{19}F-NMR (282 MHz, $CDCl_3$) δ** -109.92 to -109.82 (m).**^{31}P-NMR (121 MHz, $CDCl_3$) δ** 22.83. **IR (ATR, cm^{-1}) ν_{max}**: 1019 (P-O), 1047 (P-O), 1229 (P=O), 1510, 2984. **MS (ESI, pos)**: *m/z* (%) 312.3/313.3 ($M+H^+$, 100/17). **HRMS**: *m/z* calcd for $C_{15}H_{19}FNO_3P+H^+$ 312.1159, found 312.1165. **Chromatography**: EtOAc, R_f = 0.09.

diethyl (2-(4-chlorophenyl)-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 326d

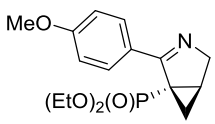


(±)-**326d**

0.15 g (0.38 mmol) of **26d** was converted into **326d**. After column chromatography 41 mg of product was obtained (0.13 mmol, 33 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 0.81-0.88 (1H, m, $PCC\underline{H}_aH_b$), 1.18 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.22 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.75 (1H, ddd, $^{3}J_{HP}$ = 14.5 Hz, *J* = 8.4 Hz, *J* = 4.4 Hz,

$PCCH_a\underline{H}_b$), 2.58-2.69 (1H, m, $NCH_2C\underline{H}$), 3.93-4.05 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.09 (2H, ~t, NCH_2), 7.38 (2H, d, *J* = 8.5 Hz, 2x CH_{ar}), 7.87 (2H, d, *J* = 8.5 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 19.2 ($PC\underline{C}H_2$), 28.9 ($NCH_2\underline{C}H$), 33.9 (d, $^1J_{CP}$ = 199.6 Hz, PC_q), 61.3 (d, $^3J_{CP}$ = 3.5 Hz, NCH_2), 62.4 (d, $^2J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.6 (d, $^2J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 128.3 (2x CH_{ar}), 130.2 (2x CH_{ar}), 132.5 ($\underline{C}_{q,ar}C$=N), 136.7 ($C_{q,ar}Cl$), 172.1 (d, $^2J_{CP}$ = 8.1 Hz, C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 22.74. **IR (ATR, cm^{-1}) ν_{max}**: 1020 (P-O), 1048 (P-O), 1247 (P=O), 1596, 2984. **MS (ESI, pos)**: *m/z* (%) 328.3/329.3/330.3 ($M+H^+$, 100/17/32). **HRMS**: *m/z* calcd for $C_{15}H_{19}ClNO_3P+H^+$ 328.0864, found 328.0868. **Chromatography**: EtOAc, R_f = 0.09.

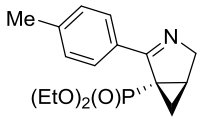
diethyl (2-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 326f



(±)-**326f**

1.13 g (2.87 mmol) of **26f** was converted into **326f**. After column chromatography 0.47 g of product was obtained (1.46 mmol, 51 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 0.81-0.87 (1H, m, $PCC\underline{H}_aH_b$), 1.20 (6H, t, *J* = 7.5 Hz, 2x $OCH_2C\underline{H}_3$), 1.74 (1H, ddd, $^3J_{HP}$ = 14.6 Hz, *J* = 8.5 Hz, *J* = 4.4 Hz, $PCCH_a\underline{H}_b$), 2.56-2.66 (1H, m, $NCH_2C\underline{H}$), 3.84 (3H, s, OCH_3), 3.93-4.03 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.06 (2H, m, NCH_2), 6.91 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}), 7.91 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}).**^{13}C-NMR (75 MHz, $CDCl_3$) δ** 15.9 (d, $^3J_{CP}$ = 4.6 Hz, $OCH_2\underline{C}H_3$), 16.0 (d, $^3J_{CP}$ = 4.6 Hz, $OCH_2\underline{C}H_3$), 18.7 ($PC\underline{C}H_2$), 28.5 ($NCH_2\underline{C}H$), 33.4 (d, $^1J_{CP}$ = 199.6 Hz, PC_q), 54.9 (OCH_3), 60.5 (d, $^3J_{CP}$ = 3.5 Hz, NCH_2), 61.8 (d, $^2J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 62.1 (d, $^2J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 113.0 (2x CH_{ar}), 126.5 ($\underline{C}_{q,ar}C$=N), 130.2 (2x CH_{ar}), 161.2 ($\underline{C}_{q,ar}OCH_3$), 171.8 (d, $^2J_{CP}$ = 6.9 Hz, C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 23.26. **IR (ATR, cm^{-1}) ν_{max}**: 1018 (P-O), 1174 (P-O), 1249 (P=O), 1514, 1607, 2918, 3429. **MS (ESI, pos)**: *m/z* (%) 324.3/325.3 ($M+H^+$, 100/17). **HRMS**: *m/z* calcd for $C_{16}H_{22}NO_4P+H^+$ 324.1359, found 324.1359. **Chromatography**: EtOAc, R_f = 0.08.

diethyl (2-(4-methylphenyl)-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 326g

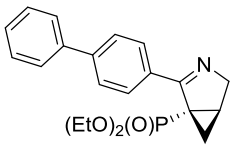


(±)-**326g**

2.70 g (7.14 mmol) of **26g** was converted into **326g**. After column chromatography 1.18 g of product was obtained (3.86 mmol, 54 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 0.83-0.88 (1H, m, $PCC\underline{H}_aH_b$), 1.14-1.26 (6H, m, 2x $OCH_2C\underline{H}_3$), 1.74 (1H, ddd, $^3J_{HP}$ = 14.3 Hz, *J* = 8.3 Hz, *J* = 4.4 Hz , $PCCH_a\underline{H}_b$), 2.38 (3H, s, CH_3), 2.61 (1H, m, $NCH_2C\underline{H}$), 3.92-4.04 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.04-4.12 (2H, m, NCH_2), 7.20 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}), 7.82 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}).**^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.2 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.3 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 19.2 ($PC\underline{C}H_2$), 21.5 (CH_3), 28.7 ($NCH_2\underline{C}H$), 33.9 (d, $^1J_{CP}$ = 201.9 Hz, PC_q), 61.1 (d, $^3J_{CP}$ = 3.5 Hz, $N\underline{C}H_2CH$), 62.2 (d, $^2J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.4 (d, $^2J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 128.7 (4x CH_{ar}), 131.3 ($\underline{C}_{q,ar}C$=N), 140.7 ($\underline{C}_{q,ar}CH_3$), 173.0 (d, $^2J_{CP}$ = 8.1 Hz, C=N).**^{31}P-NMR (121 MHz, $CDCl_3$) δ** 23.18. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1050 (P-O), 1248 (P=O), 1594, 2922. **MS (ESI, pos)**: *m/z* (%)

308.3/309.3 (M+H$^+$, 100/18). **HRMS**: *m/z* calcd for $C_{16}H_{22}NO_3P+H^+$ 308.1410, found 308.1411. **Chromatography**: EtOAc, R_f = 0.09.

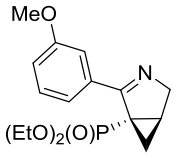
diethyl (2-([1,1'-biphenyl]-4-yl)-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 326h



(±)-**326h**

1.84 g (4.18 mmol) of **26h** was converted into **326h**. After column chromatography 0.56 g of product was obtained (1.50 mmol, 30 % yield, brown oil). **^{1}H-NMR (300 MHz, CDCl$_3$) δ** 0.85-0.92 (1H, ~q, PCC$\underline{H}_a$H$_b$), 1.21 (6H, t, *J* = 7.6 Hz, 2x OCH$_2$C$\underline{H}_3$), 1.78 (1H, ddd, $^3J_{HP}$ = 14.2 Hz, *J* = 8.9 Hz, *J* = 4.8 Hz, PCCH$_a\underline{H}_b$), 2.58-2.71 (1H, m, NCH$_2$C$\underline{H}$), 3.95-4.07 (4H, m, 2x O$\underline{C}$H$_2$CH$_3$), 4.10-4.13 (2H, ~t, NCH$_2$), 7.34-7.38 (1H, m, CH$_{ar}$), 7.45 (2H, dd, *J* = 7.3 Hz, *J* = 7.3 Hz, 2x CH$_{ar}$), 7.64 (4H, d, *J* = 8.3 Hz, 4x CH$_{ar}$), 8.01 (2H, d, *J* = 7.3 Hz, 2x CH$_{ar}$). **^{13}C-NMR (75 MHz, CDCl$_3$) δ** 16.3 (d, $^3J_{CP}$ = 5.8 Hz, OCH$_2\underline{C}$H$_3$), 16.4 (d, $^3J_{CP}$ = 5.8 Hz, OCH$_2\underline{C}$H$_3$), 19.3 (PC$\underline{C}$H$_2$), 28.8 (NCH$_2\underline{C}$H), 33.9 (d, $^1J_{CP}$ = 199.6 Hz, PC$_q$), 61.3 (d, $^3J_{CP}$ = 3.5 Hz, NCH$_2$), 62.3 (d, $^2J_{CP}$ = 5.8 Hz, O$\underline{C}$H$_2$CH$_3$), 62.5 (d, $^2J_{CP}$ = 5.8 Hz, O$\underline{C}$H$_2$CH$_3$), 126.7 (2x CH$_{ar}$), 127.2 (2x CH$_{ar}$), 127.8 (CH$_{ar}$), 128.9 (2x CH$_{ar}$), 129.3 (2x CH$_{ar}$), 133.0 (C$_{q,ar}$), 140.5 (C$_{q,ar}$), 143.2 (C$_{q,ar}$), 172.8 (d, $^2J_{CP}$ = 8.1 Hz, C=N). **^{31}P-NMR (121 MHz, CDCl$_3$) δ** 23.02. **IR (ATR, cm^{-1}) ν$_{max}$**: 1021 (P-O), 1045 (P-O), 1246 (P=O), 1594, 2982. **MS (ESI, pos)**: *m/z* (%) 370.3/371.3 (M+H$^+$, 100/23). **HRMS**: *m/z* calcd for $C_{21}H_{24}NO_3P+H^+$ 370.1567, found 370.1563. **Chromatography**: EtOAc, R_f = 0.10.

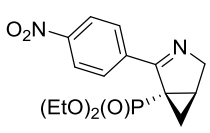
diethyl (2-(3-methoxyphenyl)-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 326i



(±)-**326i**

1.72 g (4.36 mmol) of **26i** was converted into **326i**. After column chromatography 1.01 g of product was obtained (3.14 mmol, 72 % yield, brown oil). **^{1}H-NMR (300 MHz, CDCl$_3$) δ** 0.86 (1H, ~q, PCC$\underline{H}_a$H$_b$), 1.18 (3H, t, *J* = 7.3 Hz, OCH$_2$C$\underline{H}_3$), 1.20 (3H, t, *J* = 7.3 Hz, OCH$_2$C$\underline{H}_3$), 1.75 (1H, ddd, $^3J_{HP}$ = 14.7 Hz, *J* = 8.4 Hz, *J* = 4.3 Hz, PCCH$_a\underline{H}_b$), 2.57-2.69 (1H, m, NCH$_2$C$\underline{H}$), 3.86 (3H, s, OCH$_3$), 3.93-4.04 (4H, m, 2x O$\underline{C}$H$_2$CH$_3$), 4.08 (2H, ~t, NCH$_2$), 6.99 (1H, dd, *J* = 8.1 Hz, *J* = 2.8 Hz, CH$_{ar}$), 7.31 (1H, dd, *J* = 8.1 Hz, *J* = 8.1 Hz, CH$_{ar}$), 7.48-7.54 (2H, m, 2x CH$_{ar}$). **^{13}C-NMR (75 MHz, CDCl$_3$) δ** 16.3 (d, $^3J_{CP}$ = 5.8 Hz, 2x OCH$_2\underline{C}$H$_3$), 19.2 (PC$\underline{C}$H$_2$), 28.9 (NCH$_2\underline{C}$H), 34.0 (d, $^1J_{CP}$ = 200.8 Hz, PC$_q$), 55.4 (OCH$_3$), 61.3 (d, $^3J_{CP}$ = 3.5 Hz, NCH$_2$), 62.2 (d, $^2J_{CP}$ = 6.9 Hz, O$\underline{C}$H$_2$CH$_3$), 62.5 (d, $^2J_{CP}$ = 6.9 Hz, O$\underline{C}$H$_2$CH$_3$), 113.3 (CH$_{ar}$), 117.1 (CH$_{ar}$), 121.3 (CH$_{ar}$), 129.0 (CH$_{ar}$), 135.3 ($\underline{C}_{q,ar}$C=N), 152.3 ($\underline{C}_{q,ar}$OCH$_3$), 173.0 (d, $^2J_{CP}$ = 6.9 Hz, C=N). **^{31}P-NMR (121 MHz, CDCl$_3$) δ** 22.97. **IR (ATR, cm^{-1}) ν$_{max}$**: 1018 (P-O), 1238 (P=O), 1327, 1575, 2981. **MS (ESI, pos)**: *m/z* (%) 324.3/325.3 (M+H$^+$, 100/16). **HRMS**: *m/z* calcd for $C_{16}H_{22}NO_4P+H^+$ 324.1359, found 324.1361. **Chromatography**: EtOAc, R_f = 0.18.

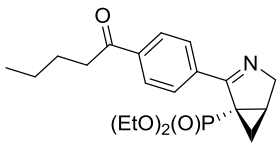
diethyl (2-(4-nitrophenyl)-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 326j



(±)-**326j**

0.38 g (0.94 mmol) of **26j** was converted into **326j**. After column chromatography 64 mg of product was obtained (0.19 mmol, 20 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 0.87-0.93 (1H, m, PCC$\underline{H}_a$H$_b$), 1.19 (3H, t, *J* = 6.9 Hz, OCH$_2$C$\underline{H}_3$), 1.23 (3H, t, *J* = 7.2 Hz, OCH$_2$C$\underline{H}_3$), 1.80 (1H, ddd, $^{3}J_{HP}$ = 13.9 Hz, *J* = 8.1 Hz, *J* = 4.3 Hz, PCCH$_a$$\underline{H}_b$), 2.69 (1H, m, NCH$_2C\underline{H}$), 3.95-4.08 (4H, m, 2x OC$\underline{H}_2$CH$_3$), 4.16 (2H, ~t, NCH$_2$), 8.10 (2H, d, *J* = 8.5 Hz, 2x CH$_{ar}$), 8.27 (2H, d, *J* = 8.5 Hz, 2x CH$_{ar}$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 16.3 (d, $^{3}J_{CP}$ = 5.8 Hz, OCH$_2$$\underline{C}H_3$), 16.4 (d, $^{3}J_{CP}$ = 6.9 Hz, OCH$_2$$\underline{C}H_3$), 19.3 (PC$\underline{C}H_2$), 29.0 (NCH$_2$$\underline{C}$H), 34.1 (d, $^{1}J_{CP}$ = 201.9 Hz, PC$_q$), 61.9 (NCH$_2$), 62.5 (d, $^{2}J_{CP}$ = 5.8 Hz, O$\underline{C}$H$_2$CH$_3$), 62.7 (d, $^{2}J_{CP}$ = 5.8 Hz, O$\underline{C}$H$_2$CH$_3$), 123.3 (2x CH$_{ar}$), 129.8 (2x CH$_{ar}$), 139.9 (C$_{q,ar}$C=N), 150.0 (C$_{q,ar}$NO$_2$), 171.5 (d, $^{2}J_{CP}$ = 9.2 Hz, C=N). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 22.17. **IR (ATR, cm^{-1}) ν_{max}**: 1018 (P-O), 1047 (P-O), 1248 (P=O), 1325 (N-O), 1519 (N-O), 1586, 2983. **MS (ESI, pos)**: *m/z* (%) 339.3/340.3 (M+H$^+$, 100/16). **HRMS**: *m/z* calcd for C$_{15}$H$_{19}$N$_2$O$_5$P+H$^+$ 339.1104, found 339.1114. **Chromatography**: EtOAc, R_f = 0.21.

diethyl (2-(4-pentanoylphenyl)-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonate 330k



(±)-**330k**

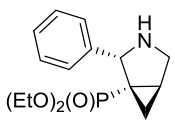
0.44 g (1.13 mmol) of **26k** was converted into **330k**. After column chromatography 0.15 g of product was obtained (0.41 mmol, 36 % yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 0.86-0.92 (1H, m, PCC$\underline{H}_a$H$_b$), 0.96 (3H, t, *J* = 7.4 Hz, CH$_3$), 1.17 (3H, t, *J* = 7.3 Hz, OCH$_2$C$\underline{H}_3$), 1.21 (3H, t, *J* = 7.3 Hz, OCH$_2$C$\underline{H}_3$), 1.41 (2H, sext, *J* = 7.4 Hz, C(O)CH$_2$CH$_2$C$\underline{H}_2$CH$_3$), 1.73 (2H, quint, *J* = 7.4 Hz, C(O)CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 1.78-1.83 (1H, m, PCCH$_a$$\underline{H}_b$), 2.61-2.71 (1H, m, NCH$_2C\underline{H}$), 2.99 (2H, t, *J* = 7.4 Hz, C(O)C$\underline{H}_2$CH$_2$CH$_2$CH$_3$), 3.92-4.05 (4H, m, 2x OC$\underline{H}_2$CH$_3$), 4.14 (2H, d, *J* = 3.9 Hz, NCH$_2$), 7.99 (4H, s, 4x CH$_{ar}$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 14.0 (CH$_3$), 16.3 (d, $^{3}J_{CP}$ = 6.9 Hz, OCH$_2$$\underline{C}H_3$), 16.4 (d, $^{3}J_{CP}$ = 6.9 Hz, OCH$_2$$\underline{C}H_3$), 19.2 (PC$\underline{C}H_2$), 22.5 (CH$_2$), 26.4 (CH$_2$), 28.9 (NCH$_2$$\underline{C}$H), 34.1 (d, $^{1}J_{CP}$ = 200.8 Hz, PC$_q$), 38.6 (CH$_2$), 61.7 (d, $^{3}J_{CP}$ = 3.5 Hz, NCH$_2$), 62.4 (d, $^{2}J_{CP}$ = 5.8 Hz, O$\underline{C}$H$_2$CH$_3$), 62.6 (d, $^{2}J_{CP}$ = 5.8 Hz, O$\underline{C}$H$_2$CH$_3$),127.8 (2x CH$_{ar}$), 129.0 (2x CH$_{ar}$), 138.1 ($\underline{C}_{q,ar}$C=N), 138.3 (C$_{q,ar}$NO$_2$), 172.5 (d, $^{2}J_{CP}$ = 9.2 Hz, C=N), 200.3 (C=O). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 22.56. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1249 (P=O), 1684 (C=O), 2931. **MS (ESI, pos)**: *m/z* (%) 378.3/379.3 (M+H$^+$, 100/16). **HRMS**: *m/z* calcd for C$_{20}$H$_{28}$NO$_4$P+H$^+$ 378.1829, found 378.1835. **Chromatography**: EtOAc, R_f = 0.16.

3.1.6 Synthesis of diethyl (2-phenyl-3-azabicyclo[3.1.0]hexan-1-yl)phosphonates 326

Diethyl (2-phenyl-3-azabicyclo[3.1.0]hex-2-en-1-yl)phosphonates **326b-d,f-j** and **330k** were dissolved in MeOH (1 M) in a round-bottom flask. Then NaCNBH$_3$ (1.05 equiv) and HOAc (1.05 equiv) were

added. The reaction progress was monitored using HPLC. After all starting material had been consumed, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with diethyl ether (3x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. All compounds were obtained in a *dr* of ≥ 99/1.

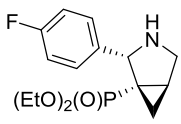
diethyl ((1*S,2*S**,5*R**)-2-phenyl-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331b**



(±)-**331b**

87 mg (0.32 mmol) of **326b** was converted into **331b**. 79 mg of product was obtained (0.27 mmol, 84 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.00 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.19-1.32 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$, 2H, m, $PCCH_2$), 1.97-2.06 (1H, m, $NHCH_2C\underline{H}$), 2.09 (1H, br s, NH), 3.16 (2H, s, $NHC\underline{H}_2$), 3.64-4.05 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.52 (1H, d, $^{3}J_{HP}$ = 3.9 Hz, $NHC\underline{H}CP$), 7.27-7.34 (3H, m, 3x CH_{ar}), 7.48 (2H, d, *J* = 6.6 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.6 ($PC\underline{C}H_2$), 16.1 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 24.8 ($NCH_2\underline{C}H$), 25.8 (d, $^{1}J_{CP}$ = 198.5 Hz, PC_q), 47.7 (d, $^{3}J_{CP}$ = 3.5 Hz, $NHCH_2$), 61.7 (d, $^{2}J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 61.9 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 63.0 (d, $^{2}J_{CP}$ = 10.4 Hz, $NH\underline{C}HCP$), 127.9 (CH_{ar}), 128.0 (2x CH_{ar}), 128.2 (2x CH_{ar}), 139.6 ($C_{q,ar}$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 28.51. **IR (ATR, cm^{-1}) ν_{max}**: 1019 (P-O), 1056 (P-O), 1234 (P=O), 1366, 2981, 3310. **MS (ESI, pos)**: *m/z* (%) 296.3/297.3 ($M+H^+$, 100/16). **HRMS**: *m/z* calcd for $C_{15}H_{22}NO_3P+H^+$ 296.1410, found 296.1416.

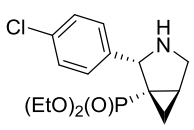
diethyl ((1*S,2*S**,5*R**)-2-(4-fluorophenyl)-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331c**



(±)-**331c**

0.48 g (1.53 mmol) of **326c** was converted into **331c**. 0.36 g of product was obtained (1.13 mmol, 74 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.02 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.23-1.30 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$, 2H, m, $PCCH_2$), 1.89-2.01 (1H, m, $NHCH_2C\underline{H}$), 2.43 (1H, br s, NH), 3.11 (2H, br s, $NHC\underline{H}_2$), 3.66-4.04 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.47 (1H, d, $^{3}J_{HP}$ = 4.4 Hz, NCHCP), 6.98 (2H, dd, *J* = 8.6 Hz,$^{3}J_{HF}$ = 8.6 Hz, 2x CH_{ar}), 7.45 (2H, dd, *J* = 8.6 Hz, $^{4}J_{HF}$ = 5.5, 2x CH_{ar}).**^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.0 ($PC\underline{C}H_2$), 15.9 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 16.3 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 24.6 ($NCH_2\underline{C}H$), 25.7 (d, *J* = 198.5 Hz, PC_q), 47.3 (d, $^{3}J_{CP}$ = 3.5 Hz, $NHCH_2$), 61.5 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 61.7 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 61.9 (d, $^{2}J_{CP}$ = 10.4 Hz, $NH\underline{C}HCP$), 114.6 (d, $^{2}J_{CF}$ = 21.9 Hz, 2x CH_{ar}), 129.4 (d, $^{3}J_{CF}$ = 8.1 Hz, 2x CH_{ar}), 135.6 (d, $^{4}J_{CF}$ = 2.3 Hz, $C_{q,ar}$), 162.2 (d, $^{1}J_{CF}$ = 245.8 Hz, $C_{q,ar}F$). **^{19}F-NMR (282 MHz, $CDCl_3$) δ** -115.20 to -115.11 (m). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 28.42. **IR (ATR, cm^{-1}) ν_{max}**: 1021 (P-O), 1058 (P-O), 1231 (P=O), 1508, 2982. **MS (ESI, pos)**: *m/z* (%) 314.3/315.3 ($M+H^+$, 100/17). **HRMS**: *m/z* calcd for $C_{15}H_{21}FNO_3P+H^+$ 314.1316, found 314.1325

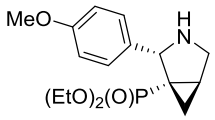
diethyl ((1*S,2*S**,5*R**)-2-(4-chlorophenyl)-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331d**



(±)-**331d**

0.20 g (0.61 mmol) of **326d** was converted into **331d**. 0.17 g of product was obtained (0.52 mmol, 85 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.05 (3H, d, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.11-1.29 (3H, m, $OCH_2C\underline{H}_3$, 2H, m, $PCCH_2$), 2.00 (1H, m, $NHCH_2C\underline{H}$), 2.53 (1H, br s, NH), 3.15 (2H, br s, $NHC\underline{H}_2$), 3.72-4.05 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.49 (1H, d, $^{3}J_{HP}$ = 3.9 Hz, $NHC\underline{H}CP$), 7.27-7.31 (2H, m, 2x CH_{ar}), 7.41-7.44 (2H, m, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.4 ($PC\underline{C}H_2$), 16.1 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 24.8 ($NCH_2\underline{C}H$) 25.7 (d, $^{1}J_{CP}$ = 198.5 Hz, PC_q), 47.5 ($NHCH_2$), 61.8 (d, $^{2}J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.0 (d, $^{2}J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.1 (d, $^{2}J_{CP}$ = 11.5 Hz, $NH\underline{C}HCP$), 128.2 (2x CH_{ar}), 129.4 (2x CH_{ar}), 133.4 ($C_{q,ar}$), 138.3 ($C_{q,ar}Cl$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 28.32. **IR (ATR, cm^{-1}) ν_{max}**: 1014 (P-O), 1021 (P-O), 1232 (P=O), 1491, 2924, 3423. **MS (ESI, pos)**: *m/z* (%) 330.3/331.3/332.3 ($M+H^+$, 100/17/32). **HRMS**: *m/z* calcd for $C_{15}H_{21}ClNO_3P+H^+$ 330.1021, found 330.1024.

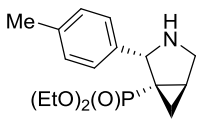
diethyl ((1*S,2*S**,5*R**)-2-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331f**:



(±)-**331f**

87 mg (0.27 mmol) of **326f** was converted into **331f**. 81 mg of product was obtained (0.25 mmol, 92 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.03 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.19-1.33 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$, 2H, m, $PCCH_2$), 1.96-2.04 (1H, m, $NHCH_2C\underline{H}$), 3.15 (2H, $NHC\underline{H}_2$), 3.71-4.09 (4H, m, 2x $OC\underline{H}_2CH_3$), 3.80 (3H, s, OCH_3), 4.52 (1H, d, $^{3}J_{HP}$ = 4.4 Hz, $NHC\underline{H}CP$), 6.86 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}), 7.41 (2H, d, *J* = 8.3 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.6 ($PC\underline{C}H_2$), 16.1 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 24.3 ($NHCH_2\underline{C}H$), 25.5 (d, $^{1}J_{CP}$ = 198.5 Hz, PC_q), 47.3 ($NHCH_2$), 55.3 (OCH_3), 61.8 (d, $^{2}J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.1 (d, $^{2}J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.5 (d, $^{2}J_{CP}$ = 11.5 Hz, $NH\underline{C}HCP$), 113.6 (2x CH_{ar}), 129.2 (2x CH_{ar}), 130.6 ($C_{q,ar}$), 159.4 ($\underline{C}_{q,ar}OCH_3$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 27.95. **IR (ATR, cm^{-1}) ν_{max}**: 1019 (P-O), 1177(P-O), 1249 (P=O), 1514, 1607, 2918, 3429. **MS (ESI, pos)**: *m/z* (%) 326.3/327.3 ($M+H^+$, 100/18). **HRMS**: *m/z* calcd for $C_{16}H_{24}NO_4P+H^+$ 326.1516, found 326.1521.

diethyl ((1*S,2*S**,5*R**)-2-(4-methylphenyl)-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331g**

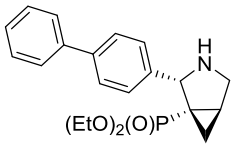


(±)-**331g**

75 mg (0.24 mmol) of **326g** was converted into **331g**. 47 mg of product was obtained (0.15 mmol, 63 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.03 (3H, t, *J* = 6.9 Hz, $OCH_2C\underline{H}_3$), 1.21-1.30 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$, 2H, m, $PCCH_2$), 1.91-2.21 (2H, m, $NHCH_2C\underline{H}$ + NH), 2.33 (3H, s, CH_3), 3.15 (2H, br s, $NHC\underline{H}_2$), 3.67-4.05 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.50 (1H, d, $^{3}J_{HP}$ = 3.9 Hz, $NHC\underline{H}CP$), 7.12 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}), 7.36 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.5 ($PC\underline{C}H_2$), 16.1 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 21.2 (CH_3), 24.9 ($NHCH_2\underline{C}H$), 25.7 (d, $^{1}J_{CP}$ = 197.3 Hz, PC_q), 47.7 (d, $^{3}J_{CP}$ = 3.5 Hz,

$NHCH_2$), 61.7 (d, $^2J_{CP}$ = 6.9 Hz, O<u>C</u>H_2CH_3), 61.9 (d, $^2J_{CP}$ = 5.8 Hz, O<u>C</u>H_2CH_3), 62.8 (d, $^2J_{CP}$ = 10.4 Hz, NH<u>C</u>HCP), 127.8 (2x CH_{ar}), 128.9 (2x CH_{ar}), 136.4 (<u>C</u>$_{q,ar}$CHN), 137.5 (<u>C</u>$_{q,ar}CH_3$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 28.62. **IR (ATR, cm^{-1}) ν_{max}**: 1020 (P-O), 1177 (P-O), 1236 (P=O), 1443, 2978. **MS (ESI, pos)**: *m/z* (%) 310.3/311.3 ($M+H^+$, 100/18). **HRMS**: *m/z* calcd for $C_{16}H_{24}NO_3P+H^+$ 310.1567, found 310.1569.

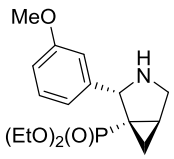
diethyl ((1*S,2*S**,5*R**)-2-([1,1'-biphenyl]-4-yl)-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331h**



(±)-**331h**

0.12 g (0.32 mmol) of **326h** was converted into **331h**. 0.11 g of product was obtained (0.30 mmol, 91 % yield, pale yellow solid). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.03 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.21-1.34 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$, 2H, m, $PCCH_2$), 1.76 (1H, br s, NH), 1.99-2.09 (1H, m, $NHCH_2C\underline{H}$), 3.19 (2H, d, *J* = 1.7 Hz, $NHC\underline{H}_2$), 3.73-4.14 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.58 (1H, d, $^3J_{HP}$ = 4.4 Hz, NHC<u>H</u>CP), 7.21-7.26 (1H, m, CH_{ar}), 7.32-7.37 (1H, m, CH_{ar}), 7.42-7.47 (2H, m, 2x CH_{ar}), 7.56 (2H, s, 2x CH_{ar}), 7.56-7.60 (3H, m, 3x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.5 (PC<u>C</u>H_2), 16.1 (d, $^3J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 24.9 ($NHCH_2\underline{C}H$), 25.9 (d, $^1J_{CP}$ = 198.5 Hz, PC_q), 47.7 (d, $^3J_{CP}$ = 3.5 Hz, $NHCH_2$), 61.8 (d, $^2J_{CP}$ = 5.8 Hz, O<u>C</u>H_2CH_3), 62.0 (d, $^2J_{CP}$ = 5.8 Hz, O<u>C</u>H_2CH_3), 62.7 (d, $^2J_{CP}$ = 10.4 Hz, N<u>C</u>HCP), 126.9 (2x CH_{ar}), 127.1 (2x CH_{ar}), 127.4 (CH_{ar}), 128.4 (2x CH_{ar}), 128.9 (2x CH_{ar}), 138.9 ($C_{q,ar}$), 140.7 ($C_{q,ar}$), 141.0 ($C_{q,ar}$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 28.59. **IR (ATR, cm^{-1}) ν_{max}**: 1017 (P-O), 1052 (P-O), 1233 (P=O), 1484, 2982. **MS (ESI, pos)**: *m/z* (%) 372.3/373.3 ($M+H^+$, 100/23). **HRMS**: *m/z* calcd for $C_{21}H_{26}NO_3P+H^+$ 372.1723, found 372.1718.

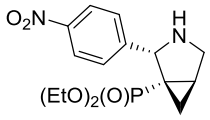
diethyl ((1*S,2*S**,5*R**)-2-(3-methoxyphenyl)-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331i**



(±)-**331i**

88 mg (0.27 mmol) of **326i** was converted into **331i**. After column chromatography 26 mg of product was obtained (0.08 mmol, 30 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.04 (3H, t, *J* = 7.3 Hz, $OCH_2C\underline{H}_3$), 1.19-1.29 (3H, t, *J* = 7.3 Hz, $OCH_2C\underline{H}_3$, 2H, m, $PCCH_2$), 1.96-2.02 (1H, m, $NHCH_2C\underline{H}$), 2.04 (1H, br s, NH), 3.16 (2H, s, $NHCH_2$), 3.69-4.16 (4H, m, 2x $OC\underline{H}_2CH_3$), 3.81 (3H, s, OCH_3), 4.51 (1H, d, $^3J_{CP}$ = 4.4 Hz, NHC<u>H</u>CP), 6.82 (1H, dd, *J* = 7.5 Hz, *J* = 4.5 Hz, CH_{ar}), 7.05-7.09 (2H, m, 2x CH_{ar}), 7.23 (1H, dd, *J* = 7.5 Hz, *J* = 7.3 Hz, CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.6 (PC<u>C</u>H_2), 16.1 (d, $^3J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 25.0 ($NHCH_2\underline{C}H$), 25.7 (d, $^1J_{CP}$ = 197.3 Hz, PC_q), 47.7 (d, $^3J_{CP}$ = 3.5 Hz, $NHCH_2$), 55.3 (OCH_3), 61.7 (d, $^2J_{CP}$ = 6.9 Hz, O<u>C</u>H_2CH_3), 61.9 (d, $^2J_{CP}$ = 5.8 Hz, O<u>C</u>H_2CH_3), 62.9 (d, $^2J_{CP}$ = 10.4 Hz, NH<u>C</u>HCP), 113.2 (CH_{ar}), 113.7 (CH_{ar}), 120.2 (CH_{ar}), 129.1 (CH_{ar}), 141.3 (<u>C</u>$_{q,ar}$CHN), 159.5 (<u>C</u>$_{q,ar}CH_3$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 28.53. **IR (ATR, cm^{-1}) ν_{max}**: 1020 (P-O), 1232 (P=O), 1438, 1602, 2981, 3308. **MS (ESI, pos)**: *m/z* (%) 326.3/327.3 ($M+H^+$, 100/17). **HRMS**: *m/z* calcd for $C_{16}H_{24}NO_4P+H^+$ 326.1516, found 326.1512. **Chromatography**: EtOAc, R_f = 0.08.

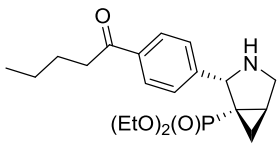
diethyl ((1*S,2*S**,5*R**)-2-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331j**



(±)-**331j**

70 mg (0.21 mmol) of **326j** was converted into **331j**. After column chromatography 58 mg of product was obtained (0.17 mmol, 81 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 1.06 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.13-1.21 (2H, m, $PCCH_2$), 1.28 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.85 (1H, br s, NH), 2.03-2.11 (1H, m, $NHCH_2C\underline{H}$), 3.22 (2H, s, $NHC\underline{H}_2$), 3.74-4.09 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.63 (1H, d, $^{3}J_{HP}$ = 4.4 Hz, $NHC\underline{H}CP$), 7.69 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}), 8.18 (2H, d, *J* = 8.8 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.5 ($PC\underline{C}H_2$), 16.2 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 25.0 ($NHCH_2\underline{C}H$), 26.1 (d, $^{1}J_{CP}$ = 200.8 Hz, PC_q), 47.4 (d, $^{3}J_{CP}$ = 3.5 Hz, $NH\underline{C}H_2$), 61.9 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 62.0 ($NH\underline{C}HCP$), 62.1 (d, $^{2}J_{CP}$ = 6.9 Hz, $O\underline{C}H_2CH_3$), 123.3 (2x CH_{ar}), 129.0 (2x CH_{ar}), 147.6 ($\underline{C}_{q,ar}CHN$), 147.9 ($\underline{C}_{q,ar}NO_2$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 27.72. **IR (ATR, cm^{-1}) ν_{max}**: 1023 (P-O), 1238 (P=O), 1347 (N-O), 1520 (N-O), 2982, 3303. **MS (ESI, pos)**: *m/z* (%) 341.3/342.3 ($M+H^+$, 100/17). **HRMS**: *m/z* calcd for $C_{15}H_{21}N_2O_5P+H^+$ 341.1261, found 341.1265. **Chromatography**: EtOAc, R_f = 0.07.

diethyl ((1*S,2*S**,5*R**)-2-(4-pentanoylphenyl)-3-azabicyclo[3.1.0]hexan-1-yl)phosphonate 331k**



(±)-**331k**

51 mg (0.14 mmol) of **330k** was converted into **331k**. After column chromatography 32 mg of product was obtained (0.08 mmol, 60 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$) δ** 0.95 (3H, t, *J* = 7.5 Hz, CH_3), 1.02 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.17-1.29 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$, 2H, m, $PCCH_2$), 1.41 (2H, sext, *J* = 7.5 Hz, $C(O)CH_2CH_2C\underline{H}_2CH_3$), 1.71 (2H, quint, *J* = 7.5 Hz, $C(O)CH_2C\underline{H}_2CH_2CH_3$), 1.85 (1H, br s, NH), 1.99-2.09 (1H, $NHCH_2C\underline{H}$), 2.95 (2H, t, *J* = 7.5 Hz, $C(O)C\underline{H}_2CH_2CH_2CH_3$), 3.19 (2H, s, $NHC\underline{H}_2$), 3.69-4.07 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.57 (1H, d, $^{3}J_{HP}$ = 4.4 Hz, $NHC\underline{H}CP$), 7.58 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}), 7.91 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ** 8.5 ($PC\underline{C}H_2$), 14.0 (CH_3), 16.1 (d, $^{3}J_{CP}$ = 5.8 Hz, $OCH_2\underline{C}H_3$), 16.5 (d, $^{3}J_{CP}$ = 6.9 Hz, $OCH_2\underline{C}H_3$), 22.6 (CH_2), 24.9 ($NHCH_2\underline{C}H$), 25.9 (d, $^{1}J_{CP}$ = 199.6 Hz, PC_q), 26.7 (CH_2), 38.5 (CH_2), 47.6 (d, $^{3}J_{CP}$ = 3.5 Hz, $NHCH_2$), 61.8 (d, $^{2}J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.0 (d, $^{2}J_{CP}$ = 5.8 Hz, $O\underline{C}H_2CH_3$), 62.5 (d, $^{2}J_{CP}$ = 11.5 Hz, $NH\underline{C}HCP$), 128.0 (2x CH_{ar}), 128.2 (2x CH_{ar}), 136.6 ($\underline{C}_{q,ar}CHN$), 145.2 ($\underline{C}_{q,ar}C=0$), 200.5 (C=O). **^{31}P-NMR (121 MHz, $CDCl_3$) δ** 28.14. **IR (ATR, cm^{-1}) ν_{max}**: 1025 (P-O), 1238 (P=O), 1681 (C=O), 2931, 3308. **MS (ESI, pos)**: *m/z* (%) 380.3/381.3 ($M+H^+$, 100/17). **HRMS**: *m/z* calcd for $C_{20}H_{30}NO_4P+H^+$ 380.1985, found 380.1978. **Chromatography**: EtOAc, R_f = 0.06.

3.2 Preparation of tetrasubstituted 3-phosphonopyrroles through hydroamination: scope and limitations

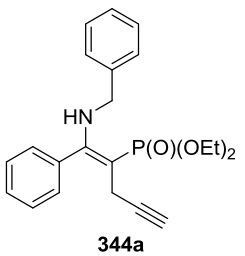
3.2.1 Synthesis of diethyl (Z)-(2-aminovinyl)phosphonates 322b,341a-f and diethyl (2-iminoethyl)phosphonates 323b,342a-f

Diethyl (2-oxoethyl)phosphonates **29a-c,f** were dissolved in toluene (1 M) in a round-bottom flask equipped with a Dean-Stark apparatus. An appropriate primary amine (1.2 equiv) and *p*-TsOH monohydrate (0.05 equiv) were added and the reaction mixture was heated to reflux temperature and left overnight. The reaction progress was monitored using gas chromatography. After all starting material had been consumed, the solvent was removed *in vacuo* and the residue was redissolved in diethyl ether and washed with aqueous $NaHCO_3$. The organic phase was extracted with diethyl ether (3x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

3.2.2 Synthesis of diethyl (Z)-(1-aminopent-1-en-4-yn-2-yl)phosphonates 344

In a flame-dried round-bottom flask, enaminophosphonates **322b,341a-f** and iminoethylphosphonates **323b,342a-f** were dissolved in dry THF (0.5 M) and placed under an inert N_2-atmosphere. The solution was cooled to -78 °C before adding LiHMDS (1.2 equiv) and was kept stirring at -78 °C for one hour. Next, a propargyl bromide solution in toluene (1.2 equiv) was added in a dropwise fashion and the reaction mixture was allowed to warm to 20 °C. Reaction progress was monitored using HPLC. If no further conversion was observed, additional LiHMDS and propargyl bromide were added until no more starting material was present. Water was added and the solution was extracted using diethyl ether (3x 20 mL). After drying the combined organic layers over $MgSO_4$, the solvent was removed *in vacuo* and the residue was purified using column chromatography. *E*/*Z* mixtures were obtained but only the peaks of the major isomers (*Z*-form) were assigned.

diethyl (*Z*)-(1-(benzylamino)-1-phenylpent-1-en-4-yn-2-yl)phosphonate 344a

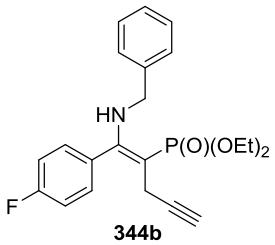


344a

317 mg (0.92 mmol) of **341a/342a** was converted into **344a**. After column chromatography, 144 mg of **344a** was obtained in a *E*/*Z* ratio of 1/9 (0.38 mmol, 41% yield, brown oil). **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 1.36 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 1.84 (1H, t, *J* = 2.2 Hz, C≡CH), 2.62 (2H, dd, $^3J_{HP}$ = 16.5 Hz, *J* = 2.2 Hz, PC_qCH_2), 3.91 (2H, d, *J* = 6.5 Hz, $NHC\underline{H}_2$), 4.11 (4H, dd, $^3J_{HP}$ = 8.3 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 7.08-7.10 (2H, m, 2x CH_{ar}), 7.19-7.26 (4H, m, 4x CH_{ar}), 7.36-7.43 (4H, m, 4x CH_{ar}), 8.30 (1H, t, *J* = 6.5 Hz, NH). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 16.4 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 18.6 (d, $^2J_{CP}$ = 10.4 Hz, $PC_q\underline{C}H_2$), 48.6 (NCH_2), 61.3 (d, $^2J_{CP}$ = 4.6 Hz, 2x $O\underline{C}H_2CH_3$), 67.0 (C≡CH), 81.8 (d, $^1J_{CP}$ = 184.6

Hz, PC_q), 84.8 (C≡CH), 126.9 (CH_{ar}), 127.1 (2x CH_{ar}), 128.4 (2x CH_{ar}), 128.5 (4x CH_{ar}), 128.9 (CH_{ar}), 134.8 (d, $^3J_{CP}$ = 17.3 Hz, $C_{q,ar}$), 140.1 ($C_{q,ar}$), 165.0 (d, $^2J_{CP}$ = 13.9 Hz, C_qN). **^{31}P-NMR (121 MHz, $CDCl_3$)** δ 27.31. **IR (ATR, cm^{-1}) ν_{max}**: 1021 (P-O), 1050 (P-O), 1205 (P=O), 1589, 1606, 2113, 2980, 3288. **MS (ESI, pos)**: *m/z* (%) 384.2/385.2 ($M+H^+$, 100/25). **HRMS**: *m/z* calcd for $C_{22}H_{26}NO_3P+H^+$ 384.1723, found 384.1734. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.26.

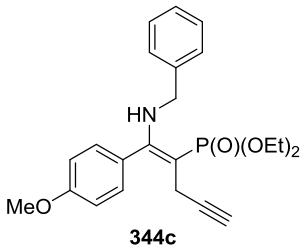
diethyl (*Z*)-(1-(benzylamino)-1-(4-fluorophenyl)pent-1-en-4-yn-2-yl)phosphonate 344b



344b

1.12 g (3.08 mmol) of **341b/342b** was converted into **344b**. After column chromatography, 0.46 g of **344b** was obtained in a *E*/*Z* ratio of 1/9 (1.14 mmol, 37% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.36 (6H, td, *J* = 7.1 Hz, $^4J_{HP}$ = 0.4 Hz, 2x $OCH_2C\underline{H}_3$), 1.85 (1H, t, *J* = 2.6 Hz, C≡CH), 2.61 (2H, dd, $^3J_{HP}$ = 16.4 Hz, *J* = 2.6 Hz, PC_qCH_2), 3.91 (2H, d, *J* = 6.6 Hz, $NHC\underline{H}_2$), 4.06-4.15 (4H, m, 2x $OC\underline{H}_2CH_3$), 7.04-7.09 (4H, m, 4x CH_{ar}), 7.19-7.26 (5H, m, 5x CH_{ar}), 8.32 (1H, t, *J* = 6.6 Hz, NH). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 16.3 (d, $^3J_{CP}$ = 7.0 Hz, 2x $OCH_2\underline{C}H_3$), 18.4 (d, $^2J_{CP}$ = 9.5 Hz, $PC_q\underline{C}H_2$), 48.4 ($NHCH_2$), 61.3 (d, $^2J_{CP}$ = 4.4 Hz, 2x $O\underline{C}H_2CH_3$), 67.2 (C≡CH), 82.7 (d, $^1J_{CP}$ = 186.2 Hz, PC_q), 84.5 (d, $^3J_{CP}$ = 1.5 Hz, C≡CH), 115.5 (d, $^2J_{CF}$ = 21.7 Hz, 2x CH_{ar}), 126.89 (CH_{ar}), 126.94 (2x CH_{ar}), 128.4 (2x CH_{ar}), 130.4 (d, $^3J_{CF}$ = 8.1 Hz, 2x CH_{ar}), 130.6 (dd, $^3J_{CP}$ = 18.1 Hz, $^4J_{CF}$ = 3.2 Hz, $C_{q,ar}$), 139.9 ($C_{q,ar}$), 162.8 (d, $^1J_{CF}$ = 248.3 Hz, $C_{q,ar}$F), 163.9 (d, $^2J_{CP}$ = 12.9 Hz, C_qN). **^{19}F-NMR (376 MHz, $CDCl_3$)** δ -112.06 to -111,99 (multiplet). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.23. **IR (ATR, cm^{-1}) ν_{max}**: 1022 (P-O), 1050 (P-O), 1205 (P=O), 1589, 1607, 2113, 2981, 3283. **MS (ESI, pos)**: *m/z* (%) 402.1/403.1 ($M+H^+$, 100/23). **HRMS**: *m/z* calcd for $C_{22}H_{25}FNO_3P+H^+$ 402.1629, found 402.1628. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.29.

diethyl (*Z*)-(1-(benzylamino)-1-(4-methoxyphenyl)pent-1-en-4-yn-2-yl)phosphonate 344c

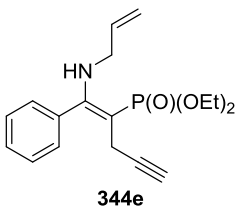


344c

1.0 g (2.67 mmol) of **341c/342c** was converted into **344c**. After column chromatography, 0.47 g of **344c** was obtained in a *E*/*Z* ratio of 1/9 (1.14 mmol, 43% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.35 (6H, td, *J* = 7.2 Hz, $^4J_{HP}$ = 0.4 Hz, 2x $OCH_2C\underline{H}_3$), 1.86 (1H, t, *J* = 2.6 Hz, C≡CH), 2.66 (2H, dd, $^3J_{HP}$ = 16.5 Hz, *J* = 2.6 Hz, PC_qCH_2), 3.84 (3H, s, OCH_3), 3.93 (2H, d, *J* = 6.5 Hz, $NHC\underline{H}_2$), 4.10 (4H, dq, $^3J_{HP}$ = 9.4 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 6.83-6.92 (2H, m, 2x CH_{ar}), 7.09-7.25 (7H, m, 7x CH_{ar}), 8.26 (1H, t, *J* = 6.5 Hz, NH). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 16.3 (d, $^3J_{CP}$ = 7.1 Hz, 2x $OCH_2\underline{C}H_3$), 18.6 (d, $^2J_{CP}$ = 9.2 Hz, $PC_q\underline{C}H_2$), 48.5 ($NHCH_2$), 55.1 (OCH_3), 61.1 (d, $^2J_{CP}$ = 4.3 Hz, 2x $O\underline{C}H_2CH_3$), 67.1 (C≡CH), 82.1 (d, $^1J_{CP}$ = 185.6 Hz, PC_q), 84.9 (d, $^3J_{CP}$ = 1.2 Hz, C≡CH), 113.8 (2x CH_{ar}), 126.8 (CH_{ar}), 126.8 (d, $^3J_{CP}$ = 17.7 Hz, $C_{q,ar}$), 127.0 (2x CH_{ar}), 128.3 (2x CH_{ar}), 129.8 (2x CH_{ar}), 140.1 ($C_{q,ar}$), 159.9 ($C_{q,ar}OCH_3$), 164.9 (d, $^2J_{CP}$ = 12.8 Hz, C_qN). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.82. **IR (ATR,**

cm^{-1}) ν_{max}: 1022 (P-O), 1050 (P-O), 1248 (P=O), 1592, 1610, 1712, 2116, 2980, 3287. **MS (ESI, pos)**: *m/z* (%) 414.2/415.2 (M+H$^+$, 100/23). **HRMS**: *m/z* calcd for $C_{23}H_{28}NO_4P+H^+$ 414.1829, found 414.1842. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.21.

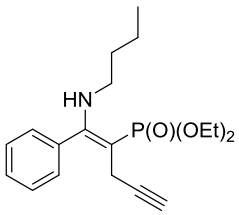
diethyl (*Z*)-(1-(allylamino)-1-phenylpent-1-en-4-yn-2-yl)phosphonate 344e



344e

300 mg (1.02 mmol) of **322b/323b** was converted into **344e**. After column chromatography, 71 mg of **344e** was obtained in a *E*/*Z* ratio of 1/9 (0.21 mmol, 21% yield, brown oil). **^{1}H-NMR (300 MHz, CDCl$_3$)** δ 1.37 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 1.86 (1H, t, *J* = 2.3 Hz, C≡CH), 2.61 (2H, dd, $^3J_{HP}$ = 16.5 Hz, *J* = 2.3 Hz, PC_qCH_2), 3.32 (2H, dd, *J* = 6.1 Hz, *J* = 5.0 Hz, $NHC\underline{H}_2$), 4.14 (4H, dq, $^3J_{HP}$ = 7.2 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 5.03 (1H, dd, *J* = 9.9 Hz, *J* = 1.1 Hz, CH=C$\underline{H}_E$H$_Z$), 5.13 (1H, dd, *J* = 17.1 Hz, *J* = 1.4 Hz, CH=CH$_E$$\underline{H}_Z$), 5.68 (1H, ddt, *J* = 17.1 Hz, *J* = 9.9 Hz, *J* = 5.0 Hz, C$\underline{H}$=CH$_E$H$_Z$), 7.29-7.33 (2H, m, 2x CH_{ar}), 7.40-7.41 (3H, m, 3x CH_{ar}), 7.96 (1H, t, *J* = 6.1 Hz, NH). **^{13}C-NMR (75 MHz, CDCl$_3$)** δ 16.3 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 18.5 (d, $^2J_{CP}$ = 10.4 Hz, $PC_q\underline{C}H_2$), 46.9 (NCH_2), 61.3 (d, $^2J_{CP}$ = 4.6 Hz, 2x $O\underline{C}H_2CH_3$), 66.9 (C≡$\underline{C}$H), 80.6 (d, $^1J_{CP}$ = 188.0 Hz, PC_q), 84.9 ($\underline{C}$≡CH), 115.3 (CH=$\underline{C}H_2$), 128.3 (2x CH_{ar}), 128.5 (2x CH_{ar}), 128.8 (CH_{ar}), 134.8 (d, $^3J_{CP}$ = 17.3 Hz, $C_{q,ar}$), 136.1 ($\underline{C}$H=CH_2), 165.0 (d, $^2J_{CP}$ = 12.7 Hz, C_qN). **^{31}P-NMR (121 MHz, CDCl$_3$)** δ, 27.47. **IR (ATR, cm^{-1}) ν_{max}**: 1021 (P-O), 1050 (P-O), 1204 (P=O), 1587, 1607, 2114, 2981, 3288. **MS (ESI, pos)**: *m/z* (%) 334.3/335.3 (M+H$^+$, 100/25). **HRMS**: *m/z* calcd for $C_{18}H_{24}NO_3P+H^+$ 334.1567, found 334.1574. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.20.

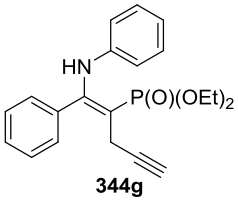
diethyl (*Z*)-(1-(butylamino)-1-phenylpent-1-en-4-yn-2-yl)phosphonate 344f



344f

418 mg (1.34 mmol) of **341e/342e** was converted into **344f**. After column chromatography, 224 mg of **344f** was obtained in a *E*/*Z* ratio of 1/9 (0.64 mmol, 48% yield, brown oil). **^{1}H-NMR (300 MHz, CDCl$_3$)** δ 0.71 (3H, t, *J* = 7.2 Hz, CH_3), 1.12-1.22 (2H, m, CH_2), 1.25-1.30 (8H, m, 2x $OCH_2C\underline{H}_3$ + CH_2), 1.78 (1H, t, *J* = 2.8 Hz, C≡CH), 2.51 (2H, dd, $^3J_{HP}$ = 16.5 Hz, *J* = 2.8 Hz, PC_qCH_2), 2.60 (2H, td, *J* = 6.6 Hz, *J* = 6.1 Hz, $NHC\underline{H}_2$), 4.04 (4H, dq, $^3J_{HP}$ = 8.6 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 7.21-7.25 (2H, m, 2x CH_{ar}), 7.29-7.36 (3H, m, 3x CH_{ar}), 7.38 (1H, t, *J* = 6.1 Hz, NH). **^{13}C-NMR (75 MHz, CDCl$_3$)** δ 13.7 (CH_3), 16.3 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 18.3 (d, $^2J_{CP}$ = 10.4 Hz, $PC_q\underline{C}H_2$), 19.8 (CH_2), 33.0 (CH_2), 44.4 (NCH_2), 61.1 (d, $^2J_{CP}$ = 4.6 Hz, 2x $O\underline{C}H_2CH_3$), 66.8 (C≡$\underline{C}$H), 79.2 (d, $^1J_{CP}$ = 188.1 Hz, PC_q), 85.0 ($\underline{C}$≡CH), 128.2 (2x CH_{ar}), 128.4 (2x CH_{ar}), 128.6 (CH_{ar}), 135.2 (d, $^3J_{CP}$ = 17.3 Hz, $C_{q,ar}$), 165.3 (d, $^2J_{CP}$ = 12.7 Hz, C_qN). **^{31}P-NMR (121 MHz, CDCl$_3$)** δ 27.88. **IR (ATR, cm^{-1}) ν_{max}**: 1022 (P-O), 1052 (P-O), 1203 (P=O), 1588, 1607, 2176, 2932, 3283. **MS (ESI, pos)**: *m/z* (%) 350.3/351.3 (M+H$^+$, 100/25). **HRMS**: *m/z* calcd for $C_{19}H_{28}NO_3P+H^+$ 350.1880, found 350.1878. **Chromatography**: hexanes/EtOAc 8/2, R_f = 0.16.

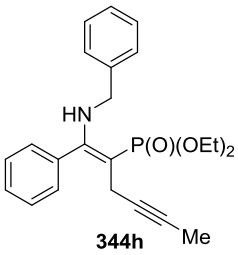
diethyl (*Z*)-(1-phenyl-1-(phenylamino)pent-1-en-4-yn-2-yl)phosphonate 344g



344g

495 mg (1.50 mmol) of **341f/342f** was converted into **344g**. After column chromatography, 172 mg of **344g** was obtained in a *E*/*Z* ratio of 1/9 (0.47 mmol, 31% yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 1.37 (6H, td, *J* = 7.2 Hz, $^{4}J_{HP}$ = 1.1 Hz, 2x $OCH_2C\underline{H}_3$), 2.01 (1H, t, *J* = 2.8 Hz, C≡CH), 2.85 (2H, dd, $^{3}J_{HP}$ = 16.5 Hz, *J* = 2.8 Hz, PC_qCH_2), 4.18 (4H, dq, $^{3}J_{HP}$ = 8.3 Hz, *J* = 7.2 Hz, 2x $OC\underline{H}_2CH_3$), 6.51 (2H, d, *J* = 8.5 Hz, 2x CH_{ar}), 6.64 (1H, d, *J* = 8.5 Hz, CH_{ar}), 6.73-6.79 (1H, m, CH_{ar}), 6.96 (2H, dd, *J* = 7.2 Hz, 2x CH_{ar}), 7.30-7.33 (2H, m, 2x CH_{ar}), 7.42-7.45 (2H, m, 2x CH_{ar}), 9.82 (1H, br s, NH). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 16.4 (d, $^{3}J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 18.8 (d, $^{2}J_{CP}$ = 8.1 Hz, $PC_q\underline{C}H_2$), 61.8 (d, $^{2}J_{CP}$ = 4.6 Hz, 2x $O\underline{C}H_2CH_3$), 68.1 (C≡CH), 84.5 (C≡CH), 88.7 (d, $^{1}J_{CP}$ = 182.3 Hz, PC_q), 121.2 (2x CH_{ar}), 121.9 (CH_{ar}), 128.9 (4x CH_{ar}), 129.2 (CH_{ar}), 129.5 (2x CH_{ar}), 134.9 (d, $^{3}J_{CP}$ = 17.3 Hz, $C_{q,ar}$), 141.5 ($C_{q,ar}$), 159.0 (d, $^{2}J_{CP}$ = 10.4 Hz, C_qN). **^{31}P-NMR (121 MHz, $CDCl_3$)** δ 25.65. **IR (ATR, cm^{-1}) ν_{max}**: 1020 (P-O), 1049 (P-O), 1242 (P=O), 1496, 1576, 1595, 2116, 2980, 3283. **MS (ESI, pos)**: *m/z* (%) 370.3/371.3 ($M+H^+$, 100/23). **HRMS**: *m/z* calcd for $C_{21}H_{24}NO_3P+H^+$ 370.1567, found 370.1566. **Chromatography**: hexanes/EtOAc 8/2, R_f = 0.22.

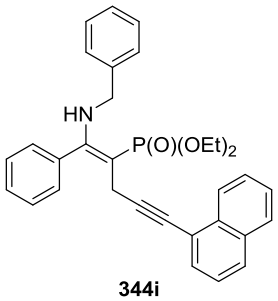
diethyl (*Z*)-(1-(benzylamino)-1-phenylhex-1-en-4-yn-2-yl)phosphonate 344h



344h

0.70 g (2.03 mmol) of **341a/342a** was converted into **344h**. After column chromatography, 0.37 g of **344h** was obtained in a *E*/*Z* ratio of 1/4 (0.93 mmol, 46% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.36 (6H, td, *J* = 7.1 Hz, $^{4}J_{HP}$ = 0.4 Hz, 2x $OCH_2C\underline{H}_3$), 1.70 (3H, t, *J* = 2.5 Hz, CH_3), 2.56 (2H, dq, $^{3}J_{HP}$ = 16.8 Hz, *J* = 2.5 Hz, PC_qCH_2), 3.90 (2H, d, *J* = 6.5 Hz, $NHC\underline{H}_2$), 4.10 (4H, dq, $^{3}J_{HP}$ = 10.2 Hz, *J* = 7.1 Hz, 2x $OC\underline{H}_2CH_3$), 7.08-7.11 (2H, m, 2x CH_{ar}), 7.19-7.25 (4H, m, 4x CH_{ar}), 7.34-7.38 (4H, m, 4x CH_{ar}), 8.25 (1H, t, *J* = 6.5 Hz, NH). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 3.6 (CH_3), 16.3 (d, $^{3}J_{CP}$ = 7.1 Hz, 2x $OCH_2\underline{C}H_3$), 18.6 (d, $^{2}J_{CP}$ = 9.5 Hz, $PC_q\underline{C}H_2$), 48.5 ($NHCH_2$), 61.2 (d, $^{2}J_{CP}$ = 4.3 Hz, 2x $O\underline{C}H_2CH_3$), 73.9 (C≡$\underline{C}CH_3$), 79.4 (d, $^{3}J_{CP}$ = 1.9 Hz, $\underline{C}\equiv CCH_3$), 82.9 (d, $^{1}J_{CP}$ = 184.3 Hz, PC_q), 126.8 (CH_{ar}), 127.0 (2x CH_{ar}), 128.3 (4x CH_{ar}), 128.5 (2x CH_{ar}), 128.7 (CH_{ar}), 134.9 (d, $^{3}J_{CP}$ = 17.9 Hz, $C_{q,ar}$), 140.1 ($C_{q,ar}$), 164.6 (d, $^{2}J_{CP}$ = 12.9 Hz, C_qN). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 27.17. **IR (ATR, cm^{-1}) ν_{max}**: 1022 (P-O), 1051 (P-O), 1204 (P=O), 1590, 1606, 2238, 2918, 3266. **MS (ESI, pos)**: *m/z* (%) 398.2/399.2 ($M+H^+$, 100/23). **HRMS**: *m/z* calcd for $C_{23}H_{28}NO_3P+H^+$ 398.1880, found 398.1887. **Chromatography**: hexanes/EtOAc 8/2, R_f = 0.29.

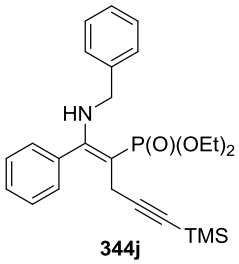
diethyl (*Z*)-(1-(benzylamino)-5-(naphthalen-1-yl)-1-phenylpent-1-en-4-yn-2-yl)phosphonate 344i



344i

0.70 g (2.03 mmol) of **341a/342a** was converted into **344i**. After column chromatography, 0.39 g of **344i** was obtained in a *E*/*Z* ratio of 1/9 (0.77 mmol, 38% yield, pale yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.34 (6H, t, *J* = 7.1 Hz, 2x $OCH_2\underline{C}H_3$), 3.00 (2H, d, $^{3}J_{HP}$ = 16.4 Hz, PC_qCH_2), 3.95 (2H, d, *J* = 6.4 Hz, $NHC\underline{H}_2$), 4.16 (4H, dq, $^{3}J_{HP}$ = 7.2 Hz, *J* = 7.1 Hz, 2x $OC\underline{H}_2CH_3$), 7.10-7.12 (2H, m, 2x CH_{ar}), 7.17-7.20 (1H, m, CH_{ar}), 7.23-7.25 (1H, m, CH_{ar}), 7.32-7.37 (3H, m, 3x CH_{ar}), 7.38-7.42 (4H, m, 4x CH_{ar}), 7.49-7.53 (3H, m, 3x CH_{ar}), 7.76 (1H, d, *J* = 8.3 Hz, CH_{ar}), 7.82-7.84 (1H, m, CH_{ar}), 8.21-8.24 (1H, m, CH_{ar}), 8.36 (1H, t, *J* = 6.4 Hz, NH). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 16.5 (d, $^{3}J_{CP}$ = 7.0 Hz, 2x $OCH_2\underline{C}H_3$), 19.8 (d, $^{2}J_{CP}$ = 9.7 Hz, $PC_q\underline{C}H_2$), 48.6 ($NHCH_2$), 61.5 (d, $^{2}J_{CP}$ = 4.4 Hz, 2x $O\underline{C}H_2CH_3$), 77.4 (C≡$\underline{C}$Ar), 82.2 (d, $^{1}J_{CP}$ = 186.1 Hz, PC_q), 95.8 (d, $^{3}J_{CP}$ = 1.6 Hz, $\underline{C}$≡CAr), 122.1 ($C_{q,ar}$), 125.4 (CH_{ar}), 126.35 (CH_{ar}), 126.43 (CH_{ar}), 126.5 (CH_{ar}), 127.0 (CH_{ar}), 127.1 (2x CH_{ar}), 127.9 (CH_{ar}), 128.3 (CH_{ar}), 128.5 (4x CH_{ar}), 128.61 (CH_{ar}), 128.62 (CH_{ar}), 129.0 (CH_{ar}), 129.8 (CH_{ar}), 133.3 ($C_{q,ar}$), 133.7 ($C_{q,ar}$), 134.9 (d, $^{3}J_{CP}$ = 17.8 Hz, $C_{q,ar}$), 140.2 ($C_{q,ar}$), 165.2 (d, $^{2}J_{CP}$ = 12.7 Hz, C_qN). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.96. **IR (ATR, cm^{-1}) ν_{max}**: 1022 (P-O), 1049 (P-O), 1205 (P=O), 1588, 1606, 2231, 2924, 3273. **MS (ESI, pos)**: *m/z* (%) 510.2/511.2 ($M+H^+$, 100/30). **HRMS**: *m/z* calcd for $C_{32}H_{32}NO_3P+H^+$ 510.2193, found 510.2182. **Chromatography**: hexanes/EtOAc 8/2, R_f = 0.16.

diethyl (*Z*)-(1-(benzylamino)-1-phenyl-5-(trimethylsilyl)pent-1-en-4-yn-2-yl)phosphonate 344j



344j

0.70 g (2.03 mmol) of **341a**/**342a** was converted into **344j**. After column chromatography, 0.42 g of **344j** was obtained in a *E*/*Z* ratio of 1/9 (0.91 mmol, 45% yield, yellow oil). However, **344j** and its bis-propargylated product **345** constitute a chromatographically inseparable mixture. As a consequence, 20% of bis-propargylated product is present (**^{31}P-NMR (162 MHz, $CDCl_3$)** δ 25.61 ppm). Spectral data are reported for 339j only. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.10 (9H, s, $SiMe_3$), 1.36 (6H, td, *J* = 7.1 Hz, $^{4}J_{HP}$ = 0.3 Hz, 2x $OCH_2\underline{C}H_3$), 2.63 (2H, d, *J* = 16.3 Hz, PC_qCH_2), 3.91 (2H, d, *J* = 6.5 Hz, $NHC\underline{H}_2$), 4.11 (4H, dq, $^{3}J_{HP}$ = 7.4 Hz, *J* = 7.1 Hz, 2x $OC\underline{H}_2CH_3$), 7.09-7.11 (2H, m, 2x CH_{ar}), 7.19-7.30 (4H, m, 4x CH_{ar}), 7.33-7.38 (4H, m, 4x CH_{ar}), 8.28 (1H, t, *J* = 6.5 Hz, NH). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 0.1 ($SiMe_3$), 16.4 (d, $^{3}J_{CP}$ = 7.2 Hz, 2x $OCH_2\underline{C}H_3$), 19.7 (d, $^{2}J_{CP}$ = 9.7 Hz, $PC_q\underline{C}H_2$), 48.5 ($NHCH_2$), 61.2 (d, $^{2}J_{CP}$ = 4.2 Hz, 2x $O\underline{C}H_2CH_3$), 82.0 (d, $^{1}J_{CP}$ = 185.7 Hz, PC_q), 82.7 (C≡$\underline{C}$$SiMe_3$), 87.1 (d, $^{3}J_{CP}$ = 1.3 Hz, $\underline{C}$≡C$SiMe_3$), 126.8 (CH_{ar}), 127.0 (2x CH_{ar}), 127.6 (CH_{ar}), 128.1 (CH_{ar}), 128.29 (CH_{ar}), 128.32 (2x CH_{ar}), 128.6 (CH_{ar}), 128.8 (CH_{ar}), 134.7 (d, $^{3}J_{CP}$ = 17.7 Hz, $C_{q,ar}$), 140.1 ($C_{q,ar}$), 165.1 (d, $^{2}J_{CP}$ = 12.7 Hz, C_qN). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.83. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1051 (P-O), 1248 (P=O), 1590, 1607, 2172, 2959, 3267. **MS (ESI, pos)**: *m/z* (%) 456.2/457.2 ($M+H^+$, 100/30).

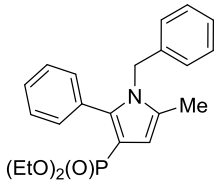
HRMS: *m/z* calcd for $C_{25}H_{34}NO_3PSi+H^+$ 456.2118, found 456.2121. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.19.

3.2.3 Synthesis of pyrroles 339

Synthesis of pyrroles **339a-g**. Propargylic enaminophosphonates **344a-g** were dissolved in CH_3CN (0.5 M) in a round-bottom flask and 5 mol% of $ZnCl_2$ was added. The reaction progress was monitored using HPLC. When all starting material had been consumed, the reaction mixture was filtered over a plug of silica (*ca.* 5 cm) to remove the catalyst. If necessary, column chromatography was performed.

Synthesis of pyrroles **339h-i**. Propargylic enaminophosphonates **344h-i** were dissolved in dry CH_3CN (0.5 M) in a round-bottom flask and 20 mol% of dried $ZnCl_2$ (4 hours at 60 °C under a 1 mbar vacuum) was added. The mixture was then heated to reflux temperature. The reaction progress was monitored using HPLC. When all starting material had been consumed, the reaction mixture was filtered over a plug of silica (*ca.* 5 cm) to remove the catalyst. If necessary, column chromatography was performed.

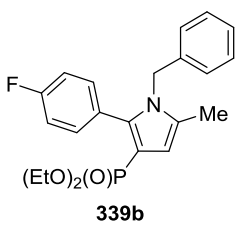
diethyl (1-benzyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)phosphonate 339a



339a

51 mg (0.13 mmol) of **344a** was converted into 50 mg of **339a** (0.13 mmol, 99% yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 1.12 (6H, t, *J* = 6.9 Hz, 2x $OCH_2C\underline{H}_3$), 2.11 (3H, s, CH_3), 3.81-4.03 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.96 (2H, s, NCH_2), 6.40 (1H, d, $^3J_{HP}$ = 4.4 Hz, CH_{ar}), 7.19-7.37 (10H, m, 10x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 12.5 (CH_3), 16.2 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 47.9 (NCH_2), 61.4 (d, $^2J_{CP}$ = 5.8 Hz, 2x $O\underline{C}H_2CH_3$), 106.5 (d, $^1J_{CP}$ = 218.1 Hz, PC_q), 111.7 (d, $^2J_{CP}$ = 11.5 Hz, CH_{ar}), 125.7 (2x CH_{ar}), 127.3 (CH_{ar}), 128.0 (2x CH_{ar}), 128.4 (CH_{ar}), 128.8 (2x CH_{ar}), 130.0 (d, $^3J_{CP}$ = 15.0 Hz, $\underline{C}_{q,ar}CH_3$), 130.8 (2x CH_{ar}), 131.9 ($C_{q,ar}$), 137.9 ($C_{q,ar}$), 139.3 (d, $^2J_{CP}$ = 23.1 Hz, $C_{q,ar}N$). **^{31}P-NMR (121 MHz, $CDCl_3$)** δ 18.89. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1053 (P-O), 1227 (P=O), 1400, 1454, 2979. **MS (ESI, pos)**: *m/z* (%) 384.3/385.3 ($M+H^+$, 100/15). **HRMS**: *m/z* calcd for $C_{22}H_{26}NO_3P+H^+$ 384.1723, found 384.1719.

diethyl (1-benzyl-2-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl)phosphonate 339b

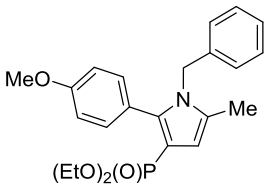


339b

100 mg (0.25 mmol) of **344b** was converted into 97 mg of **339b** (0.24 mmol, 97% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.15 (6H, t, *J* = 7.1 Hz, 2x $OCH_2C\underline{H}_3$), 2.12 (3H, s, CH_3), 3.87-3.98 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.92 (2H, s, NCH_2), 6.39 (1H, d, $^3J_{HP}$ = 3.7 Hz, CH_{ar}), 6.81-6.83 (2H, m, 2x CH_{ar}), 6.79-7.02 (2H, m, 2x CH_{ar}), 7.21-7.30 (5H, m, 5x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 12.4 (CH_3), 16.2 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 47.8 (NCH_2), 61.4 (d, $^2J_{CP}$ = 5.8 Hz, 2x $O\underline{C}H_2CH_3$), 106.7 (d, $^1J_{CP}$ = 209.0

Hz, PC_q), 111.5 (d, $^2J_{CP}$ = 12.0 Hz, CH_{ar}), 114.9 (d, $^2J_{CF}$ = 21.5 Hz, 2x CH_{ar}), 125.5 (2x CH_{ar}), 127.3 (CH_{ar}), 127.7 (d, $^4J_{CF}$ = 3.44 Hz, $C_{q,ar}$), 128.8 (2x CH_{ar}), 130.1 (d, $^3J_{CP}$ = 15.5 Hz, $\underline{C}_{q,ar}CH_3$), 132.6 (d, $^3J_{CF}$ = 8.5 Hz, 2x CH_{ar}), 137.6 ($C_{q,ar}$), 138.1 (d, $^2J_{CP}$ = 23.4 Hz, $C_{q,ar}N$), 162.8 (d, $^1J_{CF}$ = 248.1 Hz, $C_{q,ar}F$). **^{19}F-NMR (376 MHz, $CDCl_3$)** δ -113.01. **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 17.92. **IR (ATR, cm^{-1}) ν_{max}**: 1025 (P-O), 1053 (P-O), 1223 (P=O), 1392, 1480, 1529, 2981. **MS (ESI, pos)**: *m/z* (%) 402.2/403.2 ($M+H^+$, 100/25). **HRMS**: *m/z* calcd for $C_{22}H_{25}FNO_3P+H^+$ 402.1629, found 402.1635.

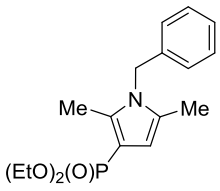
diethyl (1-benzyl-2-(4-methoxyphenyl)-5-methyl-1*H*-pyrrol-3-yl)phosphonate 339c



339c

98 mg (0.24 mmol) of **344c** was converted into **339c**. After preparative TLC, 71 mg of **339c** was obtained (0.17 mmol, 72% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.15 (6H, td, *J* = 7.1 Hz, $^4J_{HP}$ = 0.4 Hz, 2x $OCH_2\underline{CH}_3$), 2.10 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 3.83-4.02 (4H, m, 2x OCH_2CH_3), 4.94 (2H, s, NCH_2), 6.37 (1H, dq, $^3J_{HP}$ = 4.5 Hz, *J* = 0.9 Hz, CH_{ar}), 6.82-6.85 (4H, m, 4x CH_{ar}), 7.21-7.28 (5H, m, 5x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 12.4 (CH_3), 16.2 (d, $^3J_{CP}$ = 7.2 Hz, 2x $OCH_2\underline{C}H_3$), 47.7 (NCH_2), 55.2 (OCH_3), 61.3 (d, $^2J_{CP}$ = 5.3 Hz, 2x $O\underline{C}H_2CH_3$), 106.1 (d, $^1J_{CP}$ = 218.0 Hz, PC_q), 111.4 (d, $^2J_{CP}$ = 11.9 Hz, CH_{ar}), 113.3 (2x CH_{ar}), 123.9 ($C_{q,ar}$), 125.6 (2x CH_{ar}), 127.2 (CH_{ar}), 128.7 (2x CH_{ar}), 129.7 (d, $^3J_{CP}$ = 15.5 Hz, $\underline{C}_{q,ar}CH_3$), 131.9 (2x CH_{ar}), 137.9 ($C_{q,ar}$), 139.2 (d, $^2J_{CP}$ = 23.5 Hz, $C_{q,ar}$), 159.6 ($\underline{C}_{q,ar}OCH_3$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 18.45. **IR (ATR, cm^{-1}) ν_{max}**: 1025 (P-O), 1053 (P-O), 1245 (P=O), 1395, 1481, 1531, 2979. **MS (ESI, pos)**: *m/z* (%) 414.2/415.2 ($M+H^+$, 100/25). **HRMS**: *m/z* calcd for $C_{23}H_{28}NO_4P+H^+$ 414.1829, found 414.1838. **Chromatography**: EtOAc, R_f = 0.50.

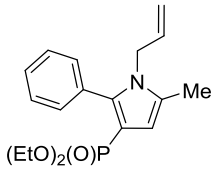
diethyl (1-benzyl-2,5-dimethyl-1*H*-pyrrol-3-yl)phosphonate 339d



339d

100 mg of crude **344d** was converted into **339d**. After preparative TLC, 10 mg of **339d** was obtained (0.03 mmol, 10% yield over 2 steps, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.32 (6H, td, *J* = 7.1 Hz, $^4J_{HP}$ = 0.4 Hz, 2x $OCH_2\underline{CH}_3$), 2.11 (3H, br s, CH_3), 2.37 (3H, d, $^4J_{HP}$ = 1.8 Hz, CH_3), 3.99-4.16 (4H, m, 2x OCH_2CH_3), 5.03 (2H, s, NCH_2), 6.14 (1H, dq, $^3J_{HP}$ = 4.2 Hz, *J* = 1.0 Hz, CH_{ar}), 6.86-6.88 (2H, m, 2x CH_{ar}), 7.25-7.33 (3H, m, 3x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 11.6 (CH_3), 12.2 (d, $^3J_{CP}$ = 1.0 Hz, CH_3), 16.4 (d, $^3J_{CP}$ = 6.8 Hz, 2x $OCH_2\underline{C}H_3$), 47.0 (d, $^4J_{CP}$ = 1.5 Hz, NCH_2), 61.3 (d, $^2J_{CP}$ = 5.0 Hz, 2x $O\underline{C}H_2CH_3$), 103.6 (d, $^1J_{CP}$ = 216.9 Hz, PC_q), 109.6 (d, $^2J_{CP}$ = 11.9 Hz, CH_{ar}), 125.6 (2x CH_{ar}), 127.4 (CH_{ar}), 128.9 (2x CH_{ar}), 129.1 (d, $^3J_{CP}$ = 15.3 Hz, $\underline{C}_{q,ar}CH_3$), 136.3 (d, $^2J_{CP}$ = 24.2 Hz, $\underline{C}_{q,ar}CH_3$), 137.0 ($C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 19.77. **IR (ATR, cm^{-1}) ν_{max}**: 1025 (P-O), 1076 (P-O), 1230 (P=O), 1410, 1519, 2980. **MS (ESI, pos)**: *m/z* (%) 322.1/323.1 ($M+H^+$, 100/15). **HRMS**: *m/z* calcd for $C_{17}H_{24}NO_3P+H^+$ 322.1567, found 322.1575. **Chromatography**: EtOAc, R_f = 0.47.

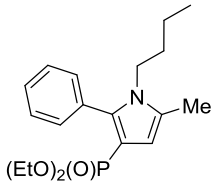
diethyl (1-allyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)phosphonate 339e



339e

80 mg (0.24 mmol) of **344e** was converted into 71 mg of **339e** (0.21 mmol, 89% yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 1.10 (6H, t, *J* = 7.2 Hz, 2x $OCH_2C\underline{H}_3$), 2.23 (3H, s, CH_3), 3.79-4.01 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.29 (2H, m, NCH_2), 4.76 (1H, d, *J* = 16.8 Hz, $CH{=}CH_E\underline{H}_Z$), 5.15 (1H, d, *J* = 10.6 Hz, $CH{=}C\underline{H}_EH_Z$), 5.80 (1H, ddt, *J* = 16.8 Hz, *J* = 10.6 Hz, *J* = 4.5 Hz, $C\underline{H}{=}CH_EH_Z$), 6.36 (1H, d, $^3J_{HP}$ = 4.4 Hz, CH_{ar}), 7.38 (5H, s, 5x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 12.2 (CH_3), 16.2 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 46.7 (NCH_2), 61.5 (d, $^2J_{CP}$ = 5.8 Hz, 2x $O\underline{C}H_2CH_3$), 105.8 (d, $^1J_{CP}$ = 219.2 Hz, PC_q), 111.3 (d, $^2J_{CP}$ = 11.5 Hz, CH_{ar}), 116.3 ($CH{=}\underline{C}H_2$), 127.9 (2x CH_{ar}), 128.5 (CH_{ar}), 129.9 (d, $^3J_{CP}$ = 16.1 Hz, $\underline{C}_{q,ar}CH_3$), 130.7 (2x CH_{ar}), 131.9 ($C_{q,ar}$), 133.9 ($\underline{C}H{=}CH_2$), 138.9 (d, $^2J_{CP}$ = 24.2 Hz, $C_{q,ar}$). **^{31}P-NMR (121 MHz, $CDCl_3$)** δ 18.99. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1054 (P-O), 1235 (P=O), 1399, 1475, 2979. **MS (ESI, pos)**: *m/z* (%) 334.3/335.3 ($M+H^+$, 100/17). **HRMS**: *m/z* calcd for $C_{18}H_{24}NO_3P+H^+$ 334.1567, found 334.1566.

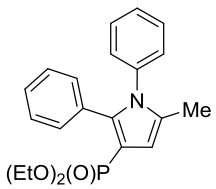
diethyl (1-butyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)phosphonate 339f



339f

100 mg (0.29 mmol) of **344f** was converted into 95 mg of **339f** (0.27 mmol, 94 % yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 0.74 (3H, t, *J* = 7.6 Hz, CH_3), 1.07-1.16 (8H, m, 2x $OCH_2C\underline{H}_3$ + CH_2), 1.45 (2H, quint, *J* = 7.6 Hz, CH_2), 2.27 (3H, s, CH_3), 3.69 (2H, t, *J* = 7.6 Hz, NCH_2), 3.78-4.01 (4H, m, 2x $OC\underline{H}_2CH_3$), 6.32 (1H, d, $^3J_{HP}$ = 3.9 Hz, CH_{ar}), 7.38 (5H, s, 5x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 12.5 (CH_3), 13.5 ($CH_2\underline{C}H_3$), 16.1 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 19.8 (CH_2), 32.9 (CH_2), 44.2 (NCH_2), 61.5 (d, $^2J_{CP}$ = 4.6 Hz, 2x $O\underline{C}H_2CH_3$), 105.4 (d, $^1J_{CP}$ = 218.1 Hz, PC_q), 111.3 (d, $^2J_{CP}$ = 12.7 Hz, CH_{ar}), 128.0 (2x CH_{ar}), 128.3 (CH_{ar}), 129.3 (d, $^3J_{CP}$ = 16.2 Hz, $\underline{C}_{q,ar}CH_3$), 130.9 (2x CH_{ar}), 132.3 ($C_{q,ar}$), 138.7 (d, $^2J_{CP}$ = 24.2 Hz, $C_{q,ar}$). **^{31}P-NMR (121 MHz, $CDCl_3$)** δ 19.21. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1054 (P-O), 1227 (P=O), 1400, 1475, 2931, 2959. **MS (ESI, pos)**: *m/z* (%) 350.3/351.3 ($M+H^+$, 100/13). **HRMS**: *m/z* calcd for $C_{19}H_{28}NO_3P+H^+$ 350.1880, found 350.1885.

diethyl (5-methyl-1,2-diphenyl-1*H*-pyrrol-3-yl)phosphonate 339g

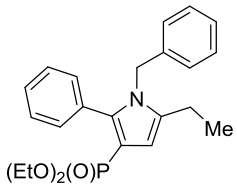


339g

75 mg (0.20 mmol) of **344g** was converted into 68 mg of **339g** (0.18 mmol, 91% yield, yellow oil). **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 1.12 (6H, t, *J* = 6.9 Hz, 2x $OCH_2C\underline{H}_3$), 2.10 (3H, s, CH_3), 3.84-4.06 (4H, m, 4x $OC\underline{H}_2CH_3$), 6.44 (1H, d, $^3J_{HP}$ = 4.4 Hz, CH_{ar}), 7.03-7.06 (2H, m, 2x CH_{ar}), 7.14-7.23 (5H, m, 5x CH_{ar}), 7.27-7.31 (3H, m, 3x CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 13.1 (CH_3), 16.2 (d, $^3J_{CP}$ = 6.9 Hz, 2x $OCH_2\underline{C}H_3$), 61.5 (d, $^2J_{CP}$ = 5.8 Hz, 2x $O\underline{C}H_2CH_3$), 106.9 (d, $^1J_{CP}$ = 218.1 Hz, PC_q), 111.7 (d, $^2J_{CP}$ = 11.5 Hz, CH_{ar}), 127.48 (2x CH_{ar}), 127.54 (CH_{ar}), 128.0 (CH_{ar}), 128.5 (2x CH_{ar}), 129.0 (2x CH_{ar}), 130.9 (2x CH_{ar}), 131.2 ($C_{q,ar}$), 131.8

($C_{q,ar}$), 138.1 ($C_{q,ar}$), 139.0 (d, $^2J_{CP}$ = 24.2 Hz, $C_{q,ar}$). **^{31}P-NMR (121 MHz, $CDCl_3$)** δ 18.81. **IR (ATR, cm^{-1}) ν_{max}**: 1023 (P-O), 1053 (P-O), 1238 (P=O), 1391, 1496, 2979. **MS (ESI, pos)**: *m/z* (%) 370.1/371.2 ($M+H^+$, 100/18). **HRMS**: *m/z* calcd for $C_{21}H_{24}NO_3P+H^+$ 370.1567, found 370.1570.

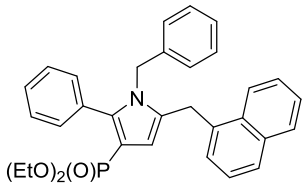
diethyl (1-benzyl-5-ethyl-2-phenyl-1*H*-pyrrol-3-yl)phosphonate 339h



339h

140 mg (0.35 mmol) of **344h** was converted into **339h**. After preparative TLC, 63 mg of **339h** was obtained (0.16 mmol, 46% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.11 (6H, td, *J* = 7.1 Hz, $^4J_{HP}$ = 0.4 Hz, 2x $OCH_2C\underline{H}_3$), 1.22 (3H, t, *J* = 7.5 Hz, $CH_2C\underline{H}_3$), 2.40 (2H, q, *J* = 7.5 Hz, $C\underline{H}_2CH_3$), 3.82-4.01 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.96 (2H, s, NCH_2), 6.44 (1H, dt, $^3J_{HP}$ = 4.7 Hz, *J* = 1.0 Hz, CH_{ar}), 6.83 (2H, d, *J* = 8.0 Hz, 2x CH_{ar}), 7.22-7.27 (4H, m, 4x CH_{ar}), 7.29-7.33 (4H, m, 4x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 12.0 (CH_3), 16.1 (d, $^3J_{CP}$ = 7.1 Hz, 2x $OCH_2\underline{C}H_3$), 19.7 (CH_2), 47.7 (NCH_2), 61.3 (d, $^2J_{CP}$ = 5.3 Hz, 2x $O\underline{C}H_2CH_3$), 106.3 (d, $^1J_{CP}$ = 218.1 Hz, PC_q), 109.7 (d, $^2J_{CP}$ = 12.3 Hz, CH_{ar}), 125.6 (2x CH_{ar}), 127.2 (CH_{ar}), 127.9 (2x CH_{ar}), 128.4 (CH_{ar}), 128.7 (2x CH_{ar}), 130.8 (2x CH_{ar}), 131.7 ($C_{q,ar}$), 136.1 (d, $^3J_{CP}$ = 15.0 Hz, $\underline{C}_{q,ar}CH_2$), 137.9 ($C_{q,ar}$), 139.1 (d, $^2J_{CP}$ = 23.2 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 18.53. **IR (ATR, cm^{-1}) ν_{max}**: 1023 (P-O), 1053 (P-O), 1229 (P=O), 1390, 2976. **MS (ESI, pos)**: *m/z* (%) 398.2/399.2 ($M+H^+$, 100/25). **HRMS**: *m/z* calcd for $C_{23}H_{28}NO_3P+H^+$ 398.1880, found 398.1884. **Chromatography**: EtOAc, R_f = 0.55.

diethyl (1-benzyl-5-(naphthalen-1-ylmethyl)-2-phenyl-1*H*-pyrrol-3-yl)phosphonate 339i



339i

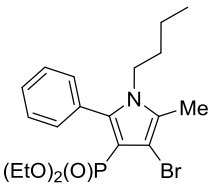
0.30 g (0.59 mmol) of **344i** was converted into **339i**. After column chromatography, 0.11 g of **339i** was obtained (0.22 mmol, 37% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.06 (6H, t, *J* = 6.8 Hz, 2x $OCH_2C\underline{H}_3$), 3.78-3.96 (4H, m, 2x $OC\underline{H}_2CH_3$), 4.16 (2H, s, CH_2), 4.98 (2H, s, NCH_2), 6.17 (1H, d, $^3J_{HP}$ = 4.5 Hz, CH_{ar}), 6.87 (2H, d, *J* = 7.4 Hz, 2x CH_{ar}), 7.17 (1H, d, *J* = 7.0 Hz, CH_{ar}), 7.25-7.47 (11H, m, 11x CH_{ar}), 7.69 (1H, d, *J* = 8.4 Hz, CH_{ar}), 7.75 (1H, d, *J* = 8.2 Hz, CH_{ar}), 7.84 (1H, d, *J* = 8.1 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 16.1 (d, $^3J_{CP}$ = 7.0 Hz, 2x $OCH_2\underline{C}H_3$), 30.3 (CH_2), 48.1 (NCH_2), 61.3 (d, $^2J_{CP}$ = 5.4 Hz, 2x $O\underline{C}H_2CH_3$), 106.9 (d, $^1J_{CP}$ = 218.2 Hz, PC_q), 113.3 (d, $^2J_{CP}$ = 12.3 Hz, CH_{ar}), 123.8 (CH_{ar}), 125.56 (CH_{ar}), 125.63 (CH_{ar}), 125.8 (2x CH_{ar}), 126.0 (CH_{ar}), 126.7 (CH_{ar}), 127.5 (2x CH_{ar}), 128.0 (2x CH_{ar}), 128.5 (CH_{ar}), 128.7 (CH_{ar}), 128.9 (2x CH_{ar}), 130.8 (2x CH_{ar}), 131.6 ($C_{q,ar}$), 132.0 ($C_{q,ar}$), 132.3 (d, $^3J_{CP}$ = 15.4 Hz, $\underline{C}_{q,ar}CH_2$), 133.9 ($C_{q,ar}$), 134.1 ($C_{q,ar}$), 137.8 ($C_{q,ar}$), 139.9 (d, $^2J_{CP}$ = 23.4 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 18.06. **IR (ATR, cm^{-1}) ν_{max}**: 1027 (P-O), 1055 (P-O), 1236 (P=O), 1453, 2928. **MS (ESI, pos)**: *m/z* (%) 510.2/511.3 ($M+H^+$, 100/35). **HRMS**:

m/z calcd for $C_{32}H_{32}NO_3P+H^+$ 510.2193, found 510.2215. **Chromatography**: hexanes/EtOAc 1/1, R_f = 0.41.

3.2.4 Synthesis of bromopyrrole 348

In a round-bottom flask pyrrole **339f** was dissolved in a 2/1 1,4-dioxane/acetic acid mixture (0.5 M), *N*-Bromosuccinimide (NBS, 1.05 equiv) was added and the reaction mixture was stirred for 30 minutes at 20 °C. The reaction mixture was poured into a 2 M NaOH solution (10 mL) and extracted with diethyl ether (3x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

diethyl (4-bromo-1-butyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)phosphonate 348



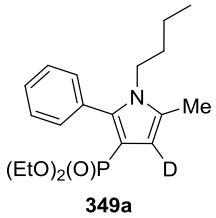
348

100 mg (0.29 mmol) of **339f** was converted into 99 mg of **348** (0.27 mmol, 92% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.74 (3H, t, *J* = 7.3 Hz, CH_3), 1.06-1.15 (8H, m, 2x $OCH_2C\underline{H}_3$ + CH_2), 1.39-1.46 (2H, m, CH_2), 2.28 (3H, d, $^5J_{HP}$ = 0.4 Hz, CH_3), 3.60-3.64 (2H, m, NCH_2), 3.78-3.87 (2H, m, $OC\underline{H}_2CH_3$), 3.92-4.01 (2H, m, $OC\underline{H}_2CH_3$), 7.30-7.33 (2H, m, 2x CH_{ar}), 7.38-7.41 (3H, m, 3x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 11.1 (CH_3), 13.4 (CH_3), 16.1 (d, $^3J_{CP}$ = 7.0 Hz, 2x $OCH_2\underline{C}H_3$), 19.7 (CH_2), 32.7 (CH_2), 45.0 (NCH_2), 61.4 (d, $^2J_{CP}$ = 5.6 Hz, 2x $O\underline{C}H_2CH_3$), 97.9 (d, $^2J_{CP}$ = 8.4 Hz, $C_{q,ar}Br$), 106.3 (d, $^1J_{CP}$ = 223.1 Hz, PC_q), 127.9 (2x CH_{ar}), 128.2 (d, $^3J_{CP}$ = 12.6 Hz, $C_{q,ar}$), 128.6 (CH_{ar}), 131.1 (2x CH_{ar}), 131.9 ($C_{q,ar}$), 139.7 (d, $^2J_{CP}$ = 21.0 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 14.12. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1057 (P-O), 1243 (P=O), 1391, 1469, 2960. **MS (ESI, pos)**: *m/z* (%) 428.1/430.1 ($M+H^+$, 98/100). **HRMS**: *m/z* calcd for $C_{19}H_{27}BrNO_3P+H^+$ 428.0985, found 428.0991.

3.2.5 Synthesis of deuterated pyrrole 349a

In a round-bottom flask pyrrole **339f** was dissolved in dry THF (0.5 M) under a N_2-atmosphere and cooled to -78 °C. A solution of *s*-BuLi (1.2 equiv) was added in a dropwise fashion and the reaction mixture was kept at -78 °C for one hour. Next, an excess of D_2O was added and the mixture was allowed to warm to room temperature, after which it was extracted with diethyl ether (3x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified using preparative TLC.

diethyl (1-butyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl-4-d)phosphonate 349a



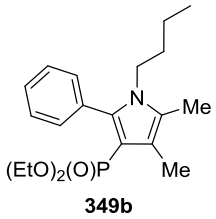
349a

127 mg (0.36 mmol) of **339f** was converted into **349a**. After preparative TLC, 72 mg of **349a** was obtained (0.21 mmol, 57% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.75 (3H, t, *J* = 7.4 Hz, CH_3), 1.07-1.16 (8H, m, 2x $OCH_2\underline{C}H_3$ + CH_2), 1.41-1.49 (2H, m, CH_2), 2.27 (3H, s, CH_3), 3.68 (2H, t, *J* = 7.8 Hz, NCH_2), 3.78-3.97 (4H, m, 2x $O\underline{C}H_2CH_3$), 7.36-7.40 (5H, m, 5x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 12.4 (d, $^{4}J_{CP}$ = 1.1 Hz, CH_3), 13.5 (CH_3), 16.0 (d, $^{3}J_{CP}$ = 7.2 Hz, 2x $OCH_2\underline{C}H_3$), 19.7 (CH_2), 32.8 (CH_2), 44.1 (NCH_2), 61.2 (d, $^{2}J_{CP}$ = 5.5 Hz, 2x $O\underline{C}H_2CH_3$), 105.6 (d, $^{1}J_{CP}$ = 218.6 Hz, PC_q), 110.9 (td, $^{1}J_{DC}$ = 25.2 Hz, $^{2}J_{CP}$ = 13.3 Hz, CD_{ar}), 127.9 (2x CH_{ar}), 128.2 (CH_{ar}), 129.1 (d, $^{3}J_{CP}$ = 15.7 Hz, $C_{q,ar}$), 130.9 (2x CH_{ar}), 132.3 ($C_{q,ar}$), 138.5 (d, $^{2}J_{CP}$ = 23.3 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 18.45. **IR (ATR, cm^{-1}) ν_{max}**: 1026 (P-O), 1055 (P-O), 1229 (P=O), 1392, 1474, 2960. **MS (ESI, pos)**: *m/z* (%) 351.3/352.3 ($M+H^+$, 100/15). **HRMS**: *m/z* calcd for $C_{19}H_{27}DNO_3P+H^+$ 351.1942, found 351.1946. **Chromatography**: EtOAc, R_f = 0.41.

3.2.6 Synthesis of methylpyrrole 349b

In a round-bottom flask pyrrole **339f** was dissolved in dry THF (1 M) under an inert N_2-atmosphere and cooled to -78 °C. A solution of *s*-BuLi (1.2 equiv) was added in a dropwise fashion and the reaction mixture was kept at -78 °C for one hour. Next, iodomethane (1.1 equiv) was added and the mixture was allowed to warm to room temperature after which it was extracted with diethyl ether (3x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using column chromatography.

diethyl (1-butyl-4,5-dimethyl-2-phenyl-1*H*-pyrrol-3-yl)phosphonate 349b



349b

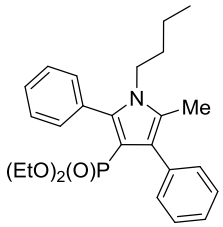
0.86 g (2.45 mmol) of **339f** was converted into **349b**. After column chromatography, 0.23 g of **349b** was obtained (0.64 mmol, 26% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.74 (3H, t, *J* = 7.3 Hz, CH_3), 1.07-1.13 (8H, m, 2x $OCH_2\underline{C}H_3$ + CH_2), 1.38-1.46 (2H, m, CH_2), 2.18 (3H, s, CH_3), 2.22 (3H, s, CH_3), 3.58 (2H, t, *J* = 7.9 Hz, NCH_2), 3.72-3.82 (2H, m, $O\underline{C}H_2CH_3$), 3.86-3.95 (2H, m, $O\underline{C}H_2CH_3$), 7.31-7.38 (5H, m, 5x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 9.9 (d, $^{3}J_{CP}$ = 1.4 Hz, CH_3), 10.8 (CH_3), 13.0 (CH_3), 16.0 (d, $^{3}J_{CP}$ = 7.1 Hz, 2x $OCH_2\underline{C}H_3$), 19.7 (CH_2), 32.9 (CH_2), 44.0 (NCH_2), 60.7 (d, $^{2}J_{CP}$ = 5.3 Hz, 2x $O\underline{C}H_2CH_3$), 105.1 (d, $^{1}J_{CP}$ = 215.2 Hz, PC_q), 117.9 (d, $^{2}J_{CP}$ = 13.0 Hz, $C_{q,ar}$), 126.0 (d, $^{3}J_{CP}$ = 16.1 Hz, $C_{q,ar}$), 127.6 (2x CH_{ar}), 128.0 (CH_{ar}), 131.1 (2x CH_{ar}), 132.8 ($C_{q,ar}$), 138.4 (d, $^{2}J_{CP}$ = 23.6 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 18.56. **IR (ATR, cm^{-1}) ν_{max}**: 1026 (P-O), 1056 (P-O), 1230 (P=O), 1246, 1393, 2930. **MS (ESI, pos)**: *m/z* (%) 364.2/365.2 ($M+H^+$, 100/22). **HRMS**: *m/z* calcd for $C_{20}H_{30}NO_3P+H^+$ 364.2036, found 364.2047. **Chromatography**: EtOAc/hexanes 3/2, R_f = 0.15.

3.2.7 Synthesis of pyrroles 351

3.2.7.1 Synthesis of pyrrole **351a**.

In a 10 mL Pyrex microwave vial equipped with a 'snap-cap' and magnetic stirrer, pyrrole **348** was dissolved in a 3/1 DME/H_2O mixture. $PhB(OH)_2$ (1.3 equiv) was added, along with Na_2CO_3 (2 equiv) and $Pd(PPh_3)_4$ (5 mol%). The vial was inserted into the microwave and the reaction was carried out at 130 °C for one hour. Afterwards, the reaction mixture was poured into water (10 mL) and extracted with diethyl ether (3x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified using preparative TLC.

diethyl (1-butyl-5-methyl-2,4-diphenyl-1*H*-pyrrol-3-yl)phosphonate 351a



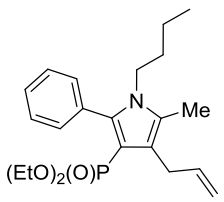
351a

96 mg (0.22 mmol) of **348** was converted into **351a**. After preparative TLC, 52 mg of **351a** was obtained (0.12 mmol, 63% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.75-0.80 (9H, m, 2x $OCH_2C\underline{H}_3$ + CH_3), 1.15 (2H, sext, *J* = 7.4 Hz, CH_2), 1.46-1.54 (2H, m, CH_2), 2.20 (3H, s, CH_3), 3.41-3.51 (2H, m, NCH_2), 3.59-3.70 (4H, m, 2x $OC\underline{H}_2CH_3$), 7.23-7.28 (1H, m, CH_{ar}), 7.34-7.48 (9H, m, 9x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 10.7 (d, $^4J_{CP}$ = 1.2 Hz, CH_3), 13.5 (CH_3), 15.7 (d, $^3J_{CP}$ = 7.3 Hz, 2x $OCH_2\underline{C}H_3$), 19.9 (CH_2), 32.9 (CH_2), 44.4 (NCH_2), 60.8 (d, $^2J_{CP}$ = 6.0 Hz, 2x $O\underline{C}H_2CH_3$), 106.0 (d, $^1J_{CP}$ = 217.6 Hz, PC_q), 124.6 (d, $^2J_{CP}$ = 12.0 Hz, $C_{q,ar}$), 126.2 (CH_{ar}), 126.9 (d, $^3J_{CP}$ = 15.0 Hz, $C_{q,ar}$), 127.6 (2x CH_{ar}), 127.8 (2x CH_{ar}), 128.2 (CH_{ar}), 130.8 (2x CH_{ar}), 131.2 (2x CH_{ar}), 132.9 ($C_{q,ar}$), 136.1 ($C_{q,ar}$), 139.0 (d, $^2J_{CP}$ = 22.9 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 17.30**. IR (ATR, cm^{-1}) ν_{max}**: 1029 (P-O), 1057 (P-O), 1228 (P=O), 1248, 1392, 2960. **MS (ESI, pos)**: *m/z* (%) 426.2/427.2 ($M+H^+$, 100/22). **HRMS**: *m/z* calcd for $C_{25}H_{32}NO_3P+H^+$ 426.2193, found 426.2195. **Chromatography**: EtOAc, R_f = 0.59.

3.2.7.2 Synthesis of pyrrole **351b**

In a 10 mL Pyrex microwave vial equipped with a 'snap-cap' and magnetic stirrer, pyrrole **348** was dissolved in DMF. Allyl tributyltin (3.0 equiv) was added, along with $Pd(PPh_3)_4$ (5 mol%). The vial was inserted into the microwave and the reaction was carried out at 130 °C for three hours. Afterwards, the reaction mixture was poured into brine (10 mL) and extracted with diethyl ether (3x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography.

diethyl (4-allyl-1-butyl-5-methyl-2-phenyl-1*H*-pyrrol-3-yl)phosphonate 351b



351b

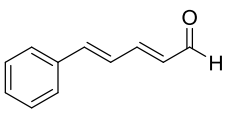
80 mg (0.19 mmol) of **348** was converted into **351b**. After column chromatography, 32 mg of **351b** was obtained (0.08 mmol, 43% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.74 (3H, t, *J* = 7.4 Hz, CH_3), 1.06-1.13 (8H, m, 2x $OCH_2C\underline{H}_3$ + CH_2), 1.39-1.43 (2H, m, CH_2), 2.17 (3H, s, CH_3), 3.48 (2H, d, *J* = 6.2 Hz, CH_2), 3.57-3.61 (2H, m, NCH_2), 3.72-3.79 (2H, m, $OC\underline{H}_2CH_3$), 3.86-3.92 (2H, m, $OC\underline{H}_2CH_3$), 4.95 (1H, ddd, *J* = 10.1 Hz, *J* = 3.5 Hz, *J* = 1.6 Hz, $CH=C\underline{H}_EH_Z$), 5.00 (1H, ddd, *J* = 17.0 Hz, *J* = 3.8 Hz, *J* = 1.6 Hz, $CH=CH_E\underline{H}_Z$), 5.99 (1H, ddt, *J* = 17.0 Hz, *J* = 10.1 Hz, *J* = 6.2 Hz, $C\underline{H}=CH_EH_Z$), 7.31-7.34 (2H, m), 7.36-7.39 (3H, m). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 10.1 (d, $^{4}J_{CP}$ = 1.5 Hz, CH_3), 13.5 (CH_3), 16.1 (d, $^{3}J_{CP}$ = 7.2 Hz, 2x $OCH_2\underline{C}H_3$), 19.8 (CH_2), 29.9 (CH_2), 32.9 (CH_2), 44.1 (NCH_2), 60.8 (d, $^{2}J_{CP}$ = 5.4 Hz, 2x $O\underline{C}H_2CH_3$), 104.7 (d, $^{1}J_{CP}$ = 215.9 Hz, PC_q), 113.5 ($CH=\underline{C}H_2$), 120.3 (d, $^{2}J_{CP}$ = 13.5 Hz, $C_{q,ar}$), 126.9 (d, $^{3}J_{CP}$ = 16.1 Hz, $C_{q,ar}$), 127.6 (2x CH_{ar}), 128.1 (CH_{ar}), 131.2 (2x CH_{ar}), 132.9 ($C_{q,ar}$), 138.36 ($\underline{C}H=CH_2$), 138.41 (d, $^{2}J_{CP}$ = 23.0 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 18.23. **IR (ATR, cm^{-1}) ν_{max}**: 1028 (P-O), 1056 (P-O), 1225 (P=O), 1246, 1395, 1466, 2929. **MS (ESI, pos)**: *m/z* (%) 390.2/391.2 ($M+H^+$, 100/22). **HRMS**: *m/z* calcd for $C_{22}H_{32}NO_3P+H^+$ 390.2193, found 390.2205. **Chromatography**: hexanes/EtOAc 7/3, R_f = 0.11.

3.3 Addition of dialkyl trimethylsilyl phosphite and triethyl phosphite to α,β,γ,δ-diunsaturated imines

3.3.1 Synthesis of α,β,γ,δ-diunsaturated aldehydes 360

In a flame-dried round-bottom flask equipped with a stirring bar a suitable α,β-unsaturated aldehyde **357** was dissolved in dry THF under an inert atmosphere. Next, (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide **358** (1.5 equiv) and LiOMe (2.2 equiv) were added and the reaction mixture was heated to reflux temperature for 16 h. A solution of 2 M HCl with a volume equal to the reaction solvent was then added to the reaction mixture at room temperature and was left to stir for 1 hour. Afterwards the THF was evaporated *in vacuo* until only the aqueous phase remained. Ethyl acetate was added and the mixture was extracted thrice using ethyl acetate. The combined organic layers were washed using $NaHCO_3$ once, dried over $MgSO_4$, filtered and concentrated *in vacuo*.[332] The crude product was then triturated using a 9/1 mixture of hexanes/EtOAc and filtered: the desired α,β,γ,δ,-diunsaturated aldehyde **360** was present in the filtrate while the residue consisted of triphenylphosphine oxide. The filtrate was concentrated *in vacuo* and purified using column chromatography. Spectral data for **360a** were in agreement with literature values.

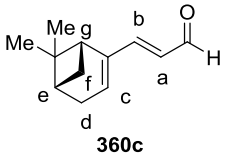
(2*E*,4*E*)-5-phenylpenta-2,4-dienal 360a[332]



360a

Cinnamaldehyde (0.29 mL, 2.32 mmol) was transformed into (2*E*,4*E*)-5-phenylpenta-2,4-dienal **360a**. After column chromatography, 257 mg was obtained (1.62 mmol, 70% yield, yellow oil). Spectral data are in accordance with reported values.[332] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 6.28 (1H, dd, *J* = 15.1 Hz, *J* = 7.9 Hz, C<u>H</u>CHO), 7.00-7.03 (2H, m, 2x CH), 7.24-7.31 (1H, m, CH), 7.33-7.41 (3H, m, 3x CH), 7.49-7.53 (2H, m, 2x CH), 9.63 (1H, d, *J* = 7.9 Hz, CHO). **Chromatography**: hexanes/EtOAc 95/5, R_f = 0.25.

(*E*)-3-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)acrylaldehyde 360c



360c

(1*R*)-(−)-Myrtenal (1.18 g, 7.73 mmol) was transformed into (*E*)-3-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)acrylaldehyde **360c**. After column chromatography, 636 mg was obtained as an *E*/*Z* mixture in a 93/7 ratio (3.61 mmol, 47% yield, yellow oil). Spectral data are given for the major isomer. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.78 (3H, s, CH_3), 1.16 (1H, d, *J* = 9.0 Hz, $CH_{d,1}$), 1.35 (3H, s, CH_3), 2.15-2.20 (1H, m, CH_g), 2.46-2.53 (3H, m, $CH_{2,f}$ + $CH_{d,2}$), 2.57 (1H, m, CH_e), 6.06 (1H, dd, *J* = 15.6 Hz, *J* = 7.8 Hz, CH_a), 6.17-6.20 (1H, m, CH_c), 7.10 (1H, d, *J* = 15.6 Hz, CH_b), 9.58 (1H, d, *J* = 7.8 Hz). **^{13}C-NMR (100 MHz,**

$CDCl_3$) δ 20.8 (CH_3), 26.0 (CH_3), 31.1 (CH_d), 32.9 ($CH_{2,f}$), 37.8 (C_q), 40.5 (CH_g), 41.4 (CH_e), 125.5 (CH_a), 136.9 (CH_c), 146.2 (C_q), 153.2 (CH_b), 194.2 (CHO). **IR (ATR, cm^{-1}) ν_{max}**: 1121, 1609 (C=C), 1678 (C=O), 2921. **MS (ESI, pos)**: *m/z* (%) 177.1/178.1 ($M+H^+$, 100/12). **Chromatography**: hexanes/EtOAc 95/5, R_f = 0.34.

3.3.2 Synthesis of α-aminophosphonates 362 and 363

3.3.2.1 Synthesis of dimethyl trimethylsilyl phosphite (DMPTMS)

In a flame-dried round-bottom flask equipped with a magnetic stirring bar dimethyl phosphite (DMP) was dissolved in dry dichloromethane under a N_2-atmosphere. Next the flask was cooled to 0 °C using an ice bath before Et_3N (1.2 equiv) was added. Then TMSCl (1.1 equiv) was added in a dropwise fashion and the reaction mixture was kept at 0 °C for 30 minutes. Afterwards the resulting suspension was filtered using an oven-dried filter and flame-dried glassware (which was allowed to cool first in a dessicator). The residue was washed using dry diethyl ether and the filtrate was concentrated *in vacuo*. The resulting suspension was again filtered using an oven-dried filter and flame-dried glassware and was washed using dry diethyl ether. The filtrate was concentrated *in vacuo*. This filtration/concentration procedure was repeated until no more salt was visibly present and a clear colorless solution was obtained. The resulting DMPTMS was stored in a flame-dried flask under a N_2-atmosphere in the freezer at -18 °C and could be kept as such without significant hydrolysis for several months. Prior to use, the exact concentration was determined using ^{1}H- and ^{31}P-NMR spectroscopy (relevant signals: DMPTMS: **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 3.40 (6H, d, $^3J_{HP}$ = 10.4 Hz, 2x OCH_3) and **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 128.1. DMP: **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 3.72 (6H, d, $^3J_{HP}$ = 11.9 Hz, 2x OCH_3) and **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 10.4).

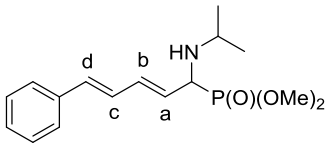
3.3.2.2 Synthesis of α,β,γ,δ-diunsaturated imines **32**

In a round-bottom flask equipped with a magnetic stirring bar, a diunsaturated aldehyde was dissolved in THF (0.3 M). Then 2 equivalents of $MgSO_4$ and 1 equivalent of a suitable amine (2 M stock solution in THF to ensure precise dosage) were added to the flask. The mixture was heated to reflux temperature and the reaction progress was monitored using ^{1}H-NMR spectroscopy. After consumption of all starting material, the $MgSO_4$ was filtered off and washed three times using dry THF. The filtrate was concentrated *in vacuo* and the resulting crude was used as such in the next step if no hydrolysis had taken place during work-up according to ^{1}H-NMR spectroscopy.

3.3.2.3 Synthesis of α-aminophosphonates **362** and **363**

In a flame-dried round-bottom flask equipped with a magnetic stirring bar α,β,γ,δ-diunsaturated imines were dissolved in dry dichloromethane under a N_2-atmosphere. Next, an appropriate amount of DMPTMS was added using a syringe. H_2SO_4 was then added via a syringe in a dropwise fashion after which the reaction mixture started to boil vigorously. The reaction progress was monitored using LC-MS and after complete consumption of the starting material, the reaction mixture was poured into 10 mL of a 2 M HCl-solution. Diethyl ether was added and the mixture was extracted thrice using diethyl ether. The resulting aqueous layer was then rendered alkaline to a pH of 14 using a 2 M NaOH solution. Next, the alkaline aqueous phase was extracted thrice using ethyl acetate (3x 10 mL). The combined ethyl acetate fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*, yielding the crude desired α-aminophosphonates **362**. The obtained products were purified using column chromatography or preparative TLC.

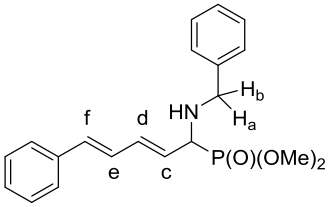
dimethyl ((2*E*,4*E*)-1-(isopropylamino)-5-phenylpenta-2,4-dien-1-yl)phosphonate 362a



362a

190 mg (0.95 mmol) of (1*E*,2*E*,4*E*)-*N*-isopropyl-5-phenylpenta-2,4-dien-1-imine **32a** was converted into **362a** using 5 equiv of DMPTMS and 2 equiv of H_2SO_4. After column chromatography, 213 mg was obtained (0.69 mmol, 73% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.01 (3H, d, *J* = 6.2 Hz, CH_3), 1.09 (3H, d, *J* = 6.2 Hz, CH_3), 2.92 (1H, sept, *J* = 6.2 Hz), 3.74 (1H, d, $^2J_{HP}$ = 21.6 Hz, *J* = 8.5 Hz, NCHP), 3.79 (3H, d, $^3J_{HP}$ = 10.5 Hz, OCH_3), 3.83 (3H, d, $^3J_{HP}$ = 10.4 Hz, OCH_3), 5.71 (1H, ddd, *J* = 15.2 Hz, *J* = 8.5 Hz, $^3J_{HP}$ = 6.3 Hz, CH_a), 6.43 (1H, ddd, *J* = 15.2 Hz, *J* = 10.5 Hz, $^4J_{HP}$ = 4.6 Hz, CH_b), 6.56 (1H, dd, *J* = 15.7 Hz, *J* = 2.1 Hz, CH_d), 6.80 (1H, dd, 15.7 Hz, *J* = 10.5 Hz, CH_c), 7.21-7.40 (5H, m , 5x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 21.5 (CH_3), 23.8 (CH_3), 46.0 (d, $^3J_{CP}$ = 15.4 Hz, NCH), 53.3 (d, $^2J_{CP}$ = 7.1 Hz, OCH_3), 53.80 (d, $^2J_{CP}$ = 7.2 Hz, OCH_3), 55.9 (d, $^1J_{CP}$ = 157.2 Hz, NCHP), 126.4 (2x CH_{ar}), 127.7 (CH_{ar}), 127.8 (d, $^4J_{CP}$ = 4.3 Hz, CH_c), 128.58 (2x CH_{ar}), 128.61 (d, $^2J_{CP}$ = 5.0 Hz, CH_a), 133.0 (d, $^5J_{CP}$ = 4.3 Hz, CH_d), 134.2 (d, $^3J_{CP}$ = 14.2 Hz, CH_b), 136.9 (d, $^6J_{CP}$ = 1.5 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.27. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1244 (P=O), 1448, 2956. **MS (ESI, pos)**: *m/z* (%) 200.0/201.0 (M-[P(O)(OMe)$_2$]$^-$, 100, 15) 310.0 (M+H$^+$, 8). **HRMS**: *m/z* calcd for $C_{16}H_{24}NO_3P+H^+$ 310.1567, found 310.1561. **Chromatography**: EtOAc, R_f = 0.17.

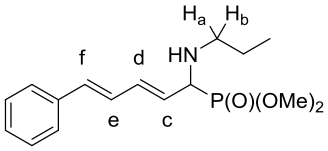
dimethyl ((2*E*,4*E*)-1-(benzylamino)-5-phenylpenta-2,4-dien-1-yl)phosphonate 362b



362b

210 mg (0.85 mmol) of (1*E*,2*E*,4*E*)-*N*-benzyl-5-phenylpenta-2,4-dien-1-imine **32b** was converted into **362b** using 2 equiv DMPTMS and 2 equiv H_2SO_4. After column chromatography, 186 mg was obtained (0.52 mmol, 61% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 3.66 (1H, dd, $^2J_{HP}$ = 19.9 Hz, *J* = 8.5 Hz, NCHP), 3.73 (1H, d, *J* = 13.4 Hz, NC$\underline{H}_aH_b$), 3.79 (3H, d, $^3J_{HP}$ = 10.5 Hz, OCH_3), 3.82 (3H, d, $^3J_{HP}$ = 10.5 Hz, OCH_3), 3.96 (1H, d, *J* = 13.4 Hz, NCH$_a\underline{H}_b$), 5.77 (1H, ddd, *J* = 15.2 Hz, *J* = 8.5 Hz, $^3J_{HP}$ = 6.4 Hz, H_c), 6.47 (1H, ddd, *J* = 15.2 Hz, *J* = 10.6 Hz, $^4J_{HP}$ = 4.6 Hz, H_d), 6.60 (1H, dd, *J* = 15.7 Hz, *J* = 1.8 Hz, H_f), 6.85 (1H, dd, *J* = 15.7 Hz, *J* = 10.6 Hz, H_e), 7.23-7.43 (10H, m, 10x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 50.9 (d, $^3J_{CP}$ = 16.3 Hz, NCH_2), 53.1 (d, $^2J_{CP}$ = 6.8 Hz, OCH_3), 53.3 (d, $^2J_{CP}$ = 7.1 Hz, OCH_3), 56.8 (d, $^1J_{CP}$ = 156.3 Hz, NCHP), 126.1 (2x CH_{ar}), 126.8 (CH_{ar}), 127.3 (d, $^2J_{CP}$ = 7.7 Hz, CH_c), 127.4 (CH_{ar}), 127.5 (d, $^4J_{CP}$ = 5.2 Hz, CH_e), 127.9 (2x CH_{ar}), 128.1 (2x CH_{ar}), 128.3 (2x CH_{ar}), 132.9 (d, $^5J_{CP}$ = 4.2 Hz, CH_f), 134.7 (d, $^3J_{CP}$ = 14.0 Hz, CH_d), 136.6 (d, $^6J_{CP}$ = 1.5 Hz, $C_{q,ar}$), 138.9 ($C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 25.91. **IR (ATR, cm^{-1}) ν_{max}**: 1025 (P-O), 1241 (P=O), 1450, 2952. **MS (ESI, pos)**: *m/z* (%) 358.2/359.2 ($M+H^+$, 100/22). **HRMS**: *m/z* calcd for $C_{20}H_{24}NO_3P+H^+$ 358.1567, found 358.1560. **Chromatography**: EtOAc, R_f = 0.37.

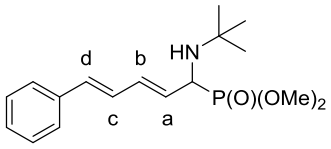
dimethyl ((2*E*,4*E*)-5-phenyl-1-(propylamino)penta-2,4-dien-1-yl)phosphonate 362c



362c

295 mg (1.48 mmol) of (1*E*,2*E*,4*E*)-*N*-propyl-5-phenylpenta-2,4-dien-1-imine **32c** was converted into **362c** using 2 equiv of DMPTMS and 2 equiv of H_2SO_4. After work-up, 370 mg was obtained (1.20 mmol, 81% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.92 (3H, t, *J* = 7.4 Hz, CH_3), 1.44-1.55 (2H, m, CH_2), 2.51 (1H, dt, *J* = 11.3 Hz, *J* = 7.0 Hz, NC$\underline{H}_aH_b$), 2.69 (1H, dt, *J* = 11.3 Hz, *J* = 7.4 Hz, NCH$_a\underline{H}_b$), 3.63 (1H, dd, $^2J_{HP}$ = 19.6 Hz, *J* = 8.6 Hz, NCHP), 3.79 (3H, d, $^3J_{HP}$ = 7.8 Hz, OCH_3), 3.82 (3H, d, $^3J_{HP}$ = 7.8 Hz, OCH_3), 5.72 (1H, ddd, *J* = 15.2 Hz, *J* = 8.6 Hz, $^3J_{HP}$ = 6.4 Hz, CH_c), 6.45 (1H, ddd, *J* = 15.2 Hz, *J* = 10.6 Hz, $^4J_{HP}$ = 4.6 Hz, CH_d), 6.57 (1H, dd, *J* = 15.7 Hz, *J* = 1.9 Hz, CH_f), 6.81 (1H, dd, *J* = 15.7 Hz, *J* = 10.6 Hz, CH_e), 7.23 (1H, dd, *J* = 7.3 Hz, *J* = 7.3 Hz, CH_{ar}), 7.32 (2H, dd, *J* = 7.3 Hz, *J* = 7.3 Hz, 2x CH_{ar}), 7.40 (2H, d, *J* = 7.3 Hz, 2x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 11.6 (CH_3), 23.0 (CH_2), 50.0 (d, $^3J_{CP}$ = 15.5 Hz, NCH_2), 53.3 (d, $^2J_{CP}$ = 7.2 Hz, OCH_3), 53.5 (d, $^2J_{CP}$ = 7.2 Hz, OCH_3), 58.6 (d, $^1J_{CP}$ = 155.6 Hz, NCHP), 126.4 (2x CH_{ar}), 127.7 (CH_{ar}), 127.8 (d, $^4J_{CP}$ = 4.3 Hz, CH_e), 128.3 (d, $^2J_{CP}$ = 7.9 Hz, CH_c), 128.6 (2x CH_{ar}), 133.0 (d, $^5J_{CP}$ = 4.3 Hz, CH_f), 134.4 (d, $^3J_{CP}$ = 14.0 Hz, CH_d), 136.9 (d, $^6J_{CP}$ = 1.9 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.00. **IR (ATR, cm^{-1}) ν_{max}**: 1025 (P-O), 1242 (P=O), 1448, 2955. **MS (ESI, pos)**: *m/z* (%) 200.1/201.0 (M-[P(O)$(OMe)_2]^-$, 100/15) 310.0/311.0 ($M+H^+$, 25/5). **HRMS**: *m/z* calcd for $C_{16}H_{24}NO_3P+H^+$ 310.1567, found 310.1562.

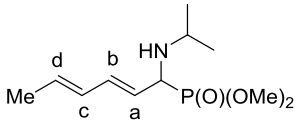
dimethyl ((2*E*,4*E*)-1-(*t*-butylamino)-5-phenylpenta-2,4-dien-1-yl)phosphonate 362d



362d

798 mg (3.74 mmol) of (1*E*,2*E*,4*E*)-*N*-*t*-butyl-5-phenylpenta-2,4-dien-1-imine **32d** was converted into **362d** using 10 equiv of DMPTMS and 2 equiv H_2SO_4. After column chromatography, 834 mg was obtained (2.58 mmol, 68% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.11 (9H, s, $(CH_3)_3$), 3.76 (3H, d, $^3J_{HP}$ = 10.4 Hz, OCH_3), 3.80 (1H, dd, $^2J_{HP}$ = 24.8 Hz, *J* = 8.4 Hz, NCHP), 3.84 (3H, d, $^3J_{HP}$ = 10.3 Hz, OCH_3), 5.81 (1H, ddd, *J* = 15.1 Hz, *J* = 7.5 Hz, $^3J_{HP}$ = 7.5 Hz, CH_a), 6.44 (1H, ddd, *J* = 15.3 Hz, *J* = 10.5 Hz, $^4J_{HP}$ = 5.0 Hz, CH_b), 6.54 (1H, dd, *J* = 15.6 Hz, *J* = 2.5 Hz, CH_d), 6.79 (1H, dd, *J* = 15.6 Hz, *J* = 10.5 Hz, CH_c), 7.22 (1H, dd, *J* = 7.3 Hz, *J* = 7.3 Hz, CH_{ar}), 7.31 (2H, dd, *J* = 7.3 Hz, *J* = 7.3 Hz, 2x CH_{ar}), 7.39 (2H, d, *J* = 7.3 Hz, 2x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 29.9 ($(CH_3)_3$), 52.1 (d, $^3J_{CP}$ = 14.5 Hz, NC_q), 53.2 (d, $^2J_{CP}$ = 7.4 Hz, OCH_3), 53.5 (d, $^1J_{CP}$ = 158.5, NCHP), 54.4 (d, $^2J_{CP}$ = 7.3 Hz, OCH_3), 126.3 (2x CH_{ar}), 127.6 (CH_{ar}), 128.1 (d, $^4J_{CP}$ = 5.0 Hz, CH_c), 128.6 (2x CH_{ar}), 131.9 (d, $^2J_{CP}$ = 6.2 Hz, CH_a), 132.6 (d, $^5J_{CP}$ = 4.9 Hz, CH_d), 132.7 (d, $^3J_{CP}$ = 13.7 Hz, CH_b), 137.0 (d, $^6J_{CP}$ = 2.1 Hz, $C_{q,ar}$). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.24. **IR (ATR, cm^{-1}) ν_{max}**: 1022 (P-O), 1053 (P-O), 1240 (P=O), 1447, 2953. **MS (ESI, pos)**: *m/z* (%) 214.1/215.1 (M-[P(O)(OMe)$_2$]$^-$, 100/18) 324.0/325.0 (M+H$^+$, 35/5). **HRMS**: *m/z* calcd for $C_{17}H_{26}NO_3P$+H$^+$ 324.1723, found 324.1725. **Chromatography**: EtOAc/hexanes 4/1, R_f = 0.14.

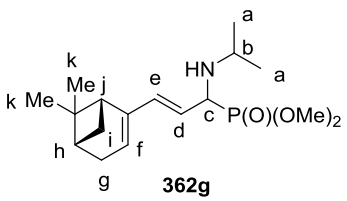
dimethyl ((2*E*,4*E*)-1-(isopropylamino)hexa-2,4-dien-1-yl)phosphonate 362f



362f

235 mg (1.72 mmol) of (1*E*,2*E*,4*E*)-*N*-isopropylhexa-2,4-dien-1-imine **32f** was converted into **362f** using 5 equiv of DMPTMS and 2 equiv of H_2SO_4. After work-up, 336 mg was obtained as an *E*/*Z* mixture in a 9/1 ratio (1.36 mmol, 79% yield, pale yellow oil). Spectral data are reported only for the major isomer. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.98 (3H, d, *J* = 6.2 Hz, CH_3), 1.06 (3H, d, *J* = 6.2 Hz, CH_3), 1.76 (3H, dd, *J* = 7.0 Hz, *J* = 1.7 Hz, CH_3), 2.88 (1H, sept, *J* = 6.2 Hz, CH), 3.64 (1H, dd, $^2J_{HP}$ = 21.2 Hz, *J* = 8.6 Hz, NCHP), 3.76 (3H, d, $^3J_{HP}$ = 10.5 Hz, OCH_3), 3.80 (3H, d, $^3J_{HP}$ = 10.4 Hz, OCH_3), 5.43 (1H, ddd, *J* = 15.0 Hz, *J* = 8.6 Hz, $^3J_{HP}$ = 6.2 Hz, CH_a), 5.72 (1H, dqd, *J* = 13.4 Hz, *J* = 7.0 Hz, *J* = 2.3 Hz, CH_d), 6.08 (1H, m, CH_c), 6.21 (1H, ddd, *J* = 15.0 Hz, *J* = 10.5 Hz, $^4J_{HP}$ = 4.5 Hz, CH_b). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 18.1 (CH_3), 21.4 (NCH$\underline{C}H_3$), 23.8 (NCH$\underline{C}H_3$), 45.8 (d, $^3J_{CP}$ = 15.6 Hz, NCH), 53.3 (d, $^2J_{CP}$ = 7.2 Hz, OCH_3), 53.7 (d, $^2J_{CP}$ = 7.2 Hz, OCH_3), 55.8 (d, $^1J_{CP}$ = 157.7 Hz, NCHP), 125.1 (d, $^2J_{CP}$ = 6.6 Hz, CH_a), 130.4 (d, $^5J_{CP}$ = 4.1 Hz, CH_d), 130.6 (d, $^4J_{CP}$ = 3.8 Hz, CH_c), 134.4 (d, $^3J_{CP}$ = 14.3 Hz, CH_b). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.67. **IR (ATR, cm^{-1}) ν_{max}**: 1024 (P-O), 1233 (P=O), 1448, 2958. **MS (ESI, pos)**: *m/z* (%) 138.1/139.1 (M-[P(O)(OMe)$_2$]$^-$, 100/10). **HRMS**: *m/z* calcd for $C_{11}H_{22}NO_3P$+H$^+$ 248.1401, found 248.1407.

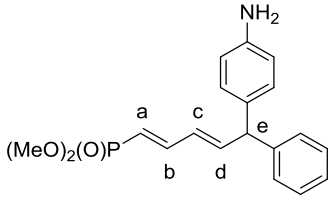
dimethyl ((*E*)-3-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)-1-(isopropylamino)allyl)phosphonate 362g



362g

185 mg (0.85 mmol) of (1*E*,2*E*)-3-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)-*N*-isopropylprop-2-en-1-imine **32g** was converted into **362g** using 5 equiv DMPTMS and 2 equiv H_2SO_4. After preparative TLC, 65 mg of **362g** was obtained of a mixture of diastereomers in a 55/45 ratio (0.20 mmol, 22% yield, yellow oil). Signals were assigned to the major (M) or minor (m) diastereomer. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 0.76 (3H, s, $CH_{3,k}$, m), 0.77 (3H, s, $CH_{3,k}$, M), 0.98 (3H, d, *J* = 6.1 Hz, NCHC$\underline{H}_{3,a}$, m), 0.99 (3H, d, *J* = 6.1 Hz, NCHC$\underline{H}_{3,a}$, M), 1.05 (3H, s, NCHC$\underline{H}_{3,a}$, m), 1.06 (3H, s, NCHC$\underline{H}_{3,a}$, M), 1.12-1.16 (2x 1H, m, $CH_{i,1}$, M+m), 1.32 (2x 3H, s, 2x $CH_{3,k}$, M+m), 2.09-2.15 (2x 1H, m, 2x CH_h, M+m), 2.27-2.39 (2x 2H, m, 2x CH_g, M+m), 2.40-2.46 (2x 1H, m, 2x $CH_{i,2}$, M+m), 2.53-2.57 (2x 1H, m, 2x CH_j, M+m), 2.82-2.94 (2x 1H, m, 2x NC$\underline{H}_b(CH_3)_2$, M+m), 3.61-3.71 (2x 1H, m, 2x NCH_cP, M+m), 3.73 (3H, d, $^3J_{HP}$ = 10.1 Hz, OCH_3, M or m), 3.75 (3H, d, $^3J_{HP}$ = 10.2 Hz, OCH_3, M or m), 3.80 (2x 3H, d, $^3J_{HP}$ = 10.4 Hz, 2x OCH_3, M+m), 5.39 (2x 1H, ddd, *J* = 15.4 Hz, *J* = 8.7 Hz, $^3J_{HP}$ = 6.5 Hz, 2x H_d, M+m), 5.57 (2x 1H, br s, 2x H_f, M+m), 6.24 (2x 1H, dd, *J* = 15.7 Hz, $^4J_{HP}$ = 4.2 Hz, 2x H_e, M+m). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 20.67, 20.70 (2x $CH_{3,k}$, M+m), 21.5, 21.6 (2x $CH_{3,a}$, M+m), 23.80, 23.82 (2x $CH_{3,a}$, M+m), 26.22 (2x $CH_{3,k}$, M+m), 31.2 (2x $CH_{2,i}$, M+m), 31.9 (2x $CH_{2,g}$, M+m), 37.7 (2x C_qMe_2, M+m), 40.9 (2x CH_h, M+m), 41.1, 41.2 (2x CH_j, M+m), 45.7, 45.8 (2x N$\underline{C}H_b$, M+m), 53.4, 53.6 (2x d, $^2J_{CP}$ = 7.2 Hz, 2x OCH_3, M+m), 53.7 (2x d, $^2J_{CP}$ = 7.2 Hz, 2x OCH_3, M+m), 56.1 (d, $^1J_{CP}$ = 157.1 Hz, NCHP, m), 56.2 (d, $^1J_{CP}$ = 157.3 Hz, NCHP, M), 120.0, 120.2 (2x d, $^2J_{CP}$ = 6.0 Hz, CH_d, M+m), 125.0, 125.1 (2x d, $^5J_{CP}$ = 4.3 Hz, CH_f, M+m), 135.3, 135.4 (2x d, $^3J_{CP}$ = 14.3 Hz, CH_e, M+m), 145.6 (d, $^4J_{CP}$ = 3.6 Hz, 2x C_q). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 26.88 (M), 26.74 (m). **IR (ATR, cm^{-1}) ν_{max}**: 1026 (P-O), 1242 (P=O), 1466, 2952. **MS (ESI, pos)**: *m/z* (%) 218.1/219.1 (M-[P(O)(OMe)$_2$]$^-$, 100/18) 328.0/329.0 (M+H$^+$, 40/8). **HRMS**: *m/z* calcd for $C_{17}H_{30}NO_3P$+H$^+$ 328.2036, found 328.2036. **Chromatography**: EtOAc, R_f = 0.38.

dimethyl ((1*E*,3*E*)-5-(4-aminophenyl)-5-phenylpenta-1,3-dien-1-yl)phosphonate 363



363

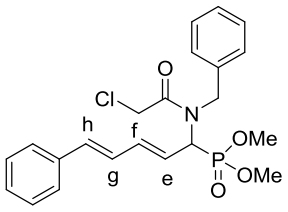
294 mg (1.26 mmol) of (1*E*,2*E*,4*E*)-*N*-phenyl-5-phenylpenta-2,4-dien-1-imine **32e** was converted into **363** using 2 equiv of DMPTMS and 2 equiv H_2SO_4. After column chromatography, 255 mg was obtained (0.74 mmol, 59% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 3.63 (2H, br s, NH_2), 3.71 (6H, d, $^3J_{HP}$ = 11.1 Hz, 2x OCH_3), 4.73 (1H, d, *J* = 7.2 Hz, CH_e), 5.55 (1H, dd, $^2J_{HP}$ = 19.5 Hz, *J* = 16.9 Hz, CH_a), 6.04 (1H, dd, *J* = 15.1 Hz, *J* = 10.7 Hz, CH_c), 6.51 (1H, dd, *J* = 15.1 Hz, *J* = 7.2 Hz, CH_d), 6.63 (2H, d, *J* = 8.2 Hz, 2x CH_{ar}), 6.93 (2H, d, *J* = 8.2 Hz, 2x CH_{ar}), 7.21-7.24

(4H, m, 3x CH_{ar} + CH_b), 7.27-7.32 (2H, m, 2x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 52.3 (d, $^2J_{CP}$ = 5.6 Hz, 2x OCH_3), 53.3 (CH_e), 114.4 (d, $^1J_{CP}$ = 191.4 Hz, CH_a), 115.2 (2x CH_{ar}), 126.6 (CH_{ar}), 128.52 (2x CH_{ar}), 128.54 (2x CH_{ar}), 129.4 (2x CH_{ar}), 130.1 (d, $^3J_{CP}$ = 27.0 Hz, CH_c), 131.9 ($C_{q,ar}$), 142.9 ($C_{q,ar}$), 145.3 ($C_{q,ar}$), 145.8 (CH_d), 149.6 (d, $^2J_{CP}$ = 6.0 Hz). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 22.20. **IR (ATR, cm^{-1}) ν_{max}**: 1021 (P-O), 1235 (P=O), 1514, 1636, 2950, 3343. **MS (ESI, pos)**: *m/z* (%) 343.9/344.9 ($M+H^+$, 100/20). **HRMS**: *m/z* calcd for $C_{19}H_{22}NO_3P+H^+$ 344.1410, found 344.1408. **Chromatography**: EtOAc, R_f = 0.12.

3.3.3 Synthesis of α-N-(2-chloroacetamido)phosphonate 364

In a flame dried round-bottom flask equipped with a magnetic stirring bar dimethyl ((2*E*,4*E*)-1-(benzylamino)-5-phenylpenta-2,4-dien-1-yl)phosphonate **362b** was dissolved in dry THF under a N_2-atmosphere. Chloroacetyl chloride (1.5 equiv) was added along with 2 equiv pyridine and the reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was poured into a saturated $NaHCO_3$-solution and extracted thrice with diethyl ether. The combined organic layers were washed with 2 M HCl, after which the resulting aqueous layer was extracted with diethyl ether again twice. The resulting combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

dimethyl ((2*E*,4*E*)-1-(*N*-benzyl-2-chloroacetamido)-5-phenylpenta-2,4-dien-1-yl)phosphonate 364



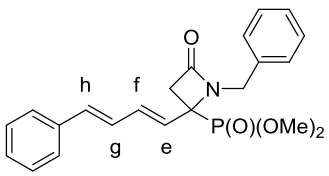
364

180 mg (0.50 mmol) of dimethyl ((2*E*,4*E*)-1-(benzylamino)-5-phenylpenta-2,4-dien-1-yl)phosphonate **362b** was converted into **364**. After work-up, 214 mg was obtained (0.495 mmol, 99% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 3.77 (3H, d, $^3J_{HP}$ = 10.8 Hz, OCH_3), 3.81 (3H, d, $^3J_{HP}$ = 10.8 Hz, OCH_3), 3.89 (1H, d, *J* = 12.7 Hz, $ClCH_aH_b$), 3.97 (1H, d, *J* = 12.7 Hz, $ClCH_aH_b$), 4.82 (1H, d, *J* = 18.3 Hz, NCH_cH_d), 4.98 (1H, d, *J* = 18.3 Hz, NCH_cH_d), 5.58 (1H, dd, $^2J_{HP}$ = 20.9 Hz, *J* = 9.4 Hz, NCHP), 5.80 (1H, ddd, *J* = 16.2 Hz, *J* = 8.1 Hz, $^3J_{HP}$ = 8.1 Hz, CH_e), 6.52-6.67 (3H, m, H_f, H_g, H_h), 7.20-7.23 (3H, m, 3x CH_{ar}), 7.27-7.38 (7H, m, 7x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 41.5 (CH_2Cl), 49.8 (NCH_2), 53.2 (d, $^2J_{CP}$ = 7.1 Hz, OCH_3), 54.0 (d, $^2J_{CP}$ = 6.6 Hz, OCH_3), 54.7 (d, $^1J_{CP}$ = 157.3 Hz, NCHP), 122.2 (CH_e), 126.0 (2x CH_{ar}), 126.6 (2x CH_{ar}), 127.2 (CH_g), 127.8 (CH_{ar}), 128.1 (CH_{ar}), 128.7 (2x CH_{ar}), 129.0 (2x CH_{ar}), 135.0 (d, $^5J_{CP}$ = 1.8 Hz, CH_h), 136.56 ($C_{q,ar}$), 136.63 ($C_{q,ar}$), 137.9 (d, $^3J_{CP}$ = 13.6 Hz, CH_f), 167.4 (d, $^3J_{CP}$ = 2.9 Hz, C=O). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 22.96. **IR (ATR, cm^{-1}) ν_{max}**: 1026 (P-O), 1051 (P-O), 1251 (P=O), 1448, 1660 (C=O), 2954. **MS (ESI, pos)**: *m/z* (%) 433.8/435.8 ($M+H^+$, 15/5). **HRMS**: *m/z* calcd for $C_{22}H_{25}ClNO_4P+H^+$ 434.1283, found 434.1267.

3.3.4 Synthesis of phosphonylated β-lactams 365

In a flame dried round-bottom flask equipped with a magnetic stirring bar 2-chloroacetamide **364** was dissolved in dry THF under a N_2-atmosphere. LiHMDS (1.1 equiv, 1 M solution) was added in a dropwise fashion and the reaction mixture was kept at room temperature for 1 hour. Then the reaction mixture was poured into water and extracted thrice using ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified using preparative TLC.

dimethyl (1-benzyl-4-oxo-2-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)azetidin-2-yl)phosphonate 365



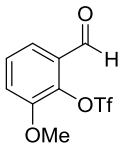
365

160 mg dimethyl ((2*E*,4*E*)-1-(*N*-benzyl-2-chloroacetamido)-5-phenylpenta-2,4-dien-1-yl)phosphonate **364** was converted into **365**. After preparative TLC, 54 mg was obtained (0.136 mmol, 37% yield, yellow oil). **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 3.02 (1H, dd, *J* = 14.6 Hz, $^3J_{HP}$ = 5.8 Hz, C=OC$\underline{H}_aH_b$), 3.43 (1H, dd, *J* = 14.6 Hz, $^3J_{HP}$ = 8.1 Hz, C=OC$H_a\underline{H}_b$), 3.72 (3H, d, $^3J_{HP}$ = 10.6 Hz, OCH_3), 3.75 (3H, d, $^3J_{HP}$ = 10.6 Hz, OCH_3), 4.41 (1H, d, *J* = 15.4 Hz, NC$\underline{H}_cH_d$), 4.63 (1H, d, *J* = 15.4 Hz, NC$H_c\underline{H}_d$), 5.81 (1H, dd, *J* = 15.5 Hz, $^3J_{HP}$ = 9.5 Hz, CH_e), 6.36 (1H, ddd, *J* = 15.5 Hz, *J* = 10.4 Hz, $^4J_{HP}$ = 3.3 Hz, CH_f), 6.42 (1H, d, *J* = 15.6 Hz, CH_h), 6.60 (1H, dd, *J* = 15.6 Hz, *J* = 10.4 Hz, CH_g), 7.22-7.42 (10H, m, 10x CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 45.9 (NCH_2), 48.0 (C=O$\underline{C}H_2$), 53.6 (d, $^2J_{CP}$ = 7.5 Hz, OCH_3), 53.9 (d, $^2J_{CP}$ = 7.2 Hz, OCH_3), 59.1 (d, $^1J_{CP}$ = 167.6 Hz, NC_qP), 126.1 (d, $^2J_{CP}$ = 6.6 Hz, CH_e), 126.6 (2x CH_{ar}), 127.1 (d, $^4J_{CP}$ =2.3 Hz, CH_g), 127.7 (CH_{ar}), 128.1 (CH_{ar}), 128.6 (2x CH_{ar}), 128.7 (2x CH_{ar}), 128.9 (2x CH_{ar}), 134.8 (d, $^3J_{CP}$ = 9.5 Hz, CH_f), 135.0 (d, $^5J_{CP}$ = 2.6 Hz, CH_h), 136.56 ($C_{q,ar}$), 136.59 ($C_{q,ar}$), 166.2 (d, $^3J_{CP}$ = 8.0 Hz, C=O). **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 23.31. **IR (ATR, cm^{-1}) ν_{max}**: 1026 (P-O), 1252 (P=O), 1751 (C=O), 2954. **MS (ESI, pos)**: *m/z* (%) 397.9/398.9 ($M+H^+$, 100/20). **HRMS**: *m/z* calcd for $C_{22}H_{24}NO_4P+H^+$ 398.1516, found 398.1513. **Chromatography**: EtOAc, R_f = 0.47.

3.4 Gold-superacid catalyzed preparation of benzo[*c*]thiophenes

3.4.1 Synthesis of 2-formyl-6-methoxyphenyl trifluoromethanesulfonate 372h

2-Hydroxy-3-methoxybenzaldehyde was triflated according to an adapted literature procedure.[371] In a round-bottom flame-dried flask, a suitable phenol (1 equiv) was dissolved in dry toluene under a N_2-atmosphere and cooled to 0 °C. Next, pyridine (2 equiv) and triflic anhydride (1.2 equiv) were added in a dropwise fashion. The mixture was then stirred at room temperature for 1 h. Then, the crude mixture was concentrated *in vacuo*. Diethyl ether was added to the residue and the mixture was neutralized using $NaHCO_3$. After extraction (3x 10 mL diethyl ether) the product was dried over $MgSO_4$ and concentrated *in vacuo*. Spectral data are in accordance with reported values.[401]



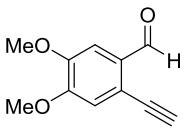
372h

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.96 (3H, s, OCH_3), 7.31 (1H, dd, *J* = 8.0 Hz, *J* = 1.6 Hz, CH_{ar}), 7.47 (1H, dd, *J* = 8.0 Hz, *J* = 8.0 Hz, CH_{ar}), 7.53 (1H, dd, *J* = 8.0 Hz, *J* = 1.6 Hz, CH_{ar}), 10.25 (1H, s, CHO). **Yield**: 90%, colorless oil.

3.4.2 Synthesis of ortho-ethynyl aromatic aldehydes 371

A number of 2-bromobenzaldehydes and 2-formyl-6-methoxyphenyl trifluoromethanesulfonate **372h** were subjected to a Sonogashira coupling and subsequent deprotection. 2-Ethynylbenzaldehyde is commercially available. Representative procedure: 5.32 g 2-bromo-4,5-dimethoxybenzaldehyde (21.2 mmol, 1 equiv), 0.30 g $PdCl_2(PPh_3)_2$ (0.43 mmol, 2 mol%) and 83 mg CuI (0.43 mmol, 2 mol%) were dissolved in 20 mL Et_3N in a 50 mL round-bottom flask under N_2-athmosphere. 3.70 mL TMS-acetylene was added in a dropwise fashion (26.0 mmol, 1.2 equiv) after which the reaction mixture was heated to reflux temperature. After completion of the reaction according to HPLC analysis, the solvent was removed *in vacuo* and the crude was then redissolved in ethyl acetate and filtered through a thick layer (*ca.* 5 cm) of Celite®. The filtrate was concentrated *in vacuo*, redissolved in methanol and 0.99 g of K_2CO_3 (7.2 mmol, 0.33 equiv) was added. As such, the reaction mixture was stirred for 15 minutes at room temperature. The solvent was removed *in vacuo* and the crude reaction mixture was dissolved in a saturated $NaHCO_3$ solution with ethyl acetate and extracted 3 times with ethyl acetate (3x 20 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. 3.83 g (20.1 mmol, 95%) of **371f** was obtained. The spectral data, if available, were in accordance with reported values. If necessary, column chromatography or recrystallization was performed.

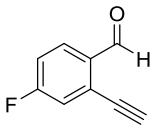
2-ethynyl-4,5-dimethxoybenzaldehyde 371f[402]



371f

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.39 (1H, s, C≡CH), 3.95 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 7.03 (1H, s, CH_{ar}), 7.41 (1H, s, CH_{ar}), 10.39 (1H, s, CHO). **Yield**: 95%, pale brown solid.

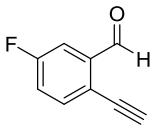
2-ethynyl-4-fluorobenzaldehyde 371b[403]



371b

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.51 (1H, s, C≡CH), 7.19 (1H, ddd, *J* = 8.7 Hz, $^3J_{HF}$ = 8.4 Hz, *J* = 2.5 Hz, CH_{ar}), 7.30 (1H, dd, $^3J_{HF}$ = 8.7 Hz, *J* = 2.5 Hz, CH_{ar}), 7.97 (1H, dd, *J* = 8.7 Hz, $^4J_{HF}$ = 5.8 Hz, CH_{ar}), 10.46 (1H, s, CHO). **Yield**: 92%, pale yellow solid.

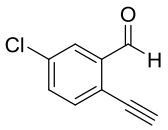
2-ethynyl-5-fluorobenzaldehyde 371c[403]



371c

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.44 (1H, s, C≡CH), 7.29 (1H, dd, $^3J_{HF}$ = 8.4 Hz, *J* = 2.8 Hz, CH_{ar}), 7.58-7.64 (2H, m, 2x CH_{ar}), 10.49 (1H, d, $^5J_{HF}$ = 3.2 Hz, CHO). **Yield**: 92%, grey solid.

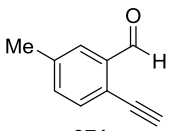
5-chloro-2-ethynylbenzaldehyde 371d[403]



371d

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.50 (1H, s, C≡CH), 7.53 (1H, dd, *J* = 8.3 Hz, *J* = 2.1 Hz, CH_{ar}), 7.56 (1H, dd, *J* = 8.3 Hz, *J* = 0.6 Hz, CH_{ar}), 7.90 (1H, dd, *J* = 2.1 Hz, *J* = 0.6 Hz, CH_{ar}), 10.48 (1H, s, CHO). **Yield**: 94%, white solid.

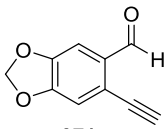
2-ethynyl-5-methylbenzaldehyde 371e



371e

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.38 (3H, s, CH_3), 3.41 (1H, s, C≡CH), 7.26 (1H, d, *J* = 8.3 Hz, CH_{ar}), 7.40 (1H, s, CH_{ar}), 7.81 (1H, d, *J* = 8.3 Hz, CH_{ar}), 10.45 (1H, s, CHO). **Yield**: 72%.

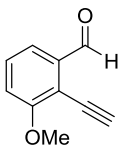
6-ethynylbenzo[*d*][1,3]dioxole-5-carbaldehyde 371g[404]



371g

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.37 (1H, s, C≡CH), 6.08 (2H, s, CH_2), 6.99 (1H, s, CH_{ar}), 7.35 (1H, s, CH_{ar}), 10.38 (1H, s, CHO). **Yield:** 60%, grey solid.

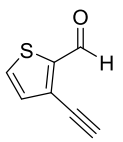
2-ethynyl-3-methoxybenzaldehyde 371h



371h

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.70 (1H, s, C≡CH), 3.96 (3H, s, OCH_3), 7.14 (1H, dd, *J* = 8.1 Hz, *J* = 0.9 Hz, CH_{ar}), 7.44 (1H, dd, *J* = 8.1 Hz, *J* = 7.9 Hz, CH_{ar}), 7.54 (1H, dd, *J* = 7.9 Hz, *J* = 0.9 Hz, CH_{ar}), 10.55 (1H, s, CHO). **Yield**: 76%, grey solid.

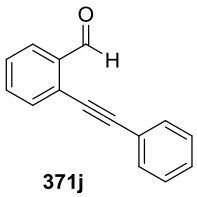
3-ethynylthiophene-2-carbaldehyde 371i[403]



371i

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.46 (1H, s, C≡CH), 7.22 (1H, d, *J* = 5.0 Hz, CH_{ar}), 7.68 (1H, dd, *J* = 5.0 Hz, *J* = 1.3 Hz, CH_{ar}), 10.15 (1H, d, *J* = 1.3 Hz, CHO). **Yield**: 87%, yellow solid.

2-(phenylethynyl)benzaldehyde 371j[405]



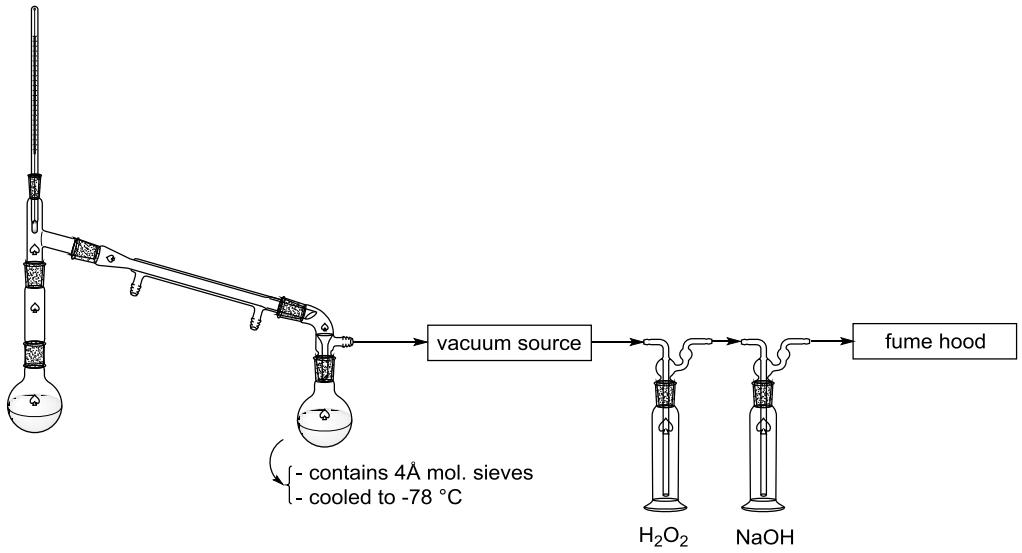
371j

Instead of TMS-acetylene, phenylacetylene was used for the Sonogashira coupling. Evidently, no K_2CO_3-treatment was performed. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.38-7.41 (3H, m, 3x CH_{ar}), 7.44-7.48 (1H, m, CH_{ar}), 7.55-7.67 (4H, m, 4x CH_{ar}), 7.96 (1H, d, *J* = 8.2 Hz, CH_{ar}), 10.66 (1H, d, *J* = 0.8 Hz, CHO). **Yield**: 72%, yellow oil.

3.4.3 Synthesis of diallyl thioacetals 376

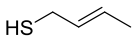
3.4.3.1 Distillation of allyl mercaptan

Commercially available allyl mercaptan is only *ca.* 60% pure so a purification step before use was essential. The setup as depicted in the figure below was used, due to the very pungent, unpleasant odor of the product: a round-bottom flask filled with allyl mercaptan was equipped with a vigreux column, a thermometer and a standard distillation piece. To this distillation piece, a water cooler was connected and the distillate was collected in a flame-dried round-bottom flask filled with 4Å molecular sieves that was cooled to -78 °C. A pump was attached to the setup and all connections were sealed with vacuum grease. The outlet of the pump was connected to two washing flasks, the first one containing a 5 wt% H_2O_2 solution and the other one containing a 0.5 M NaOH solution, in order to oxidize or deprotonate any residual allyl mercaptan and avoid spreading of the odor. Evidently, the distillation was performed in a working fume hood. After the distillation, all glassware was cleaned using a H_2O_2 solution. Allyl mercaptan was obtained as a colorless, clear liquid (bp 33-35 °C, 380 mbar) and was stored at -18 °C under an inert atmosphere.



3.4.3.2 Synthesis of crotyl mercaptan **375**

Crotyl mercaptan **375** (but-2-ene-1-thiol) was prepared according to a literature procedure.[373] A mixture of crotyl alcohol (10 g, 0.139 mol), thiourea (1 equiv, 12.5 g, 0.139 mol) and 20 mL 48% HBr were heated to reflux for 30 minutes. Then, the reaction mixture was treated with 250 mL 6 M NaOH for 1.5 h at room temperature. Next, the resulting mixture was subjected to steam distillation The same precautions as with the distillation of allyl mercaptan were taken due to the very pungent odor of the product. After distillation and separation in a separatory funnel, 6 mL of crude crotyl mercaptan was obtained in an *E*/*Z* ratio of 94/6 (5.07 g, 58 mmol, 41% yield). Crotyl mercaptan was stored at -18 °C under an inert atmosphere. Crotyl mercaptan was assumed to have the same density as crotyl alcohol (0.845 g/mL).



375

Spectral data are reported for the *E*-isomer only. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.43 (1H, br s, SH), 1.66-1.68 (3H, m, CH_3), 3.11-3.13 (2H, m, SHC$\underline{H}_2$), 5.56-5.59 (2H, m, C$\underline{H}$=C$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 17.5 (CH_3), 26.8 (SCH_2), 126.7 (CH=$\underline{C}$HCH$_3$), 130.2 ($\underline{C}$H=CHCH$_3$). **Yield**: 41%, colorless liquid.

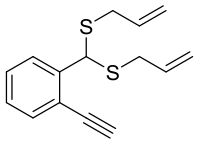
3.4.3.3 Synthetic procedures

Method A: representative example: in a 25 mL round-bottom flask 0.4 g (3.1 mmol, 1 equiv) 2-ethynylbenzaldehyde **371a** and 0.5 g (6.8 mmol, 2.2 equiv) freshly distilled allyl mercaptan (380 mbar, 33-35 °C – CAUTION: very pungent smell, take precautions during distillation, *vide supra*) were dissolved in 4 mL toluene and 2 mL acetic acid. The flask was cooled to 0 °C and 0.44 g (3.1 mmol, 1 equiv) $BF_3{\cdot}OEt_2$ was added in a dropwise fashion. The reaction mixture was stirred at room temperature and the progress was monitored using HPLC. After completion, it was diluted with 8 mL dichloromethane and washed three times with water (8 mL). After drying over $MgSO_4$ and removal of

the volatiles, the crude product was purified by means of column chromatography. 0.67 g (2.57 mmol, 83%) of **376a** was obtained.

Method B: representative example: in a 25 mL round-bottom flask 0.2 g (1.1 mmol, 1 equiv) 2-ethynyl-4,5-dimethoxybenzaldehyde **371f** and 34 mg (0.21 mmol, 0.2 equiv) anhydrous Cu(II)SO_4 were dissolved in 10 mL dry dichloromethane under N_2-atmosphere. 0.19 mL (2.31 mmol, 2.2 equiv) freshly distilled allyl mercaptan (380 mbar, 33-35 °C – CAUTION: very pungent smell, take precautions during distillation, *vide supra*) was added to this flask in a dropwise fashion and the reaction mixture was heated to reflux temperature. The reaction progress was monitored using HPLC. After completion, the mixture was poured into water and extracted thrice using dichloromethane (3x 10 mL). After drying over $MgSO_4$ and removal of the volatiles, the crude was purified by means of column chromatography. 0.12 g (0.37 mmol, 34%) of **376f** was obtained.

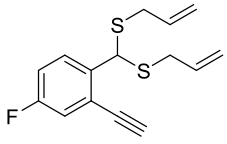
((2-ethynylphenyl)methylene)bis(allylsulfane) 376a, prepared by method A



376a

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.09 (2H, dd, *J* = 13.9Hz, *J* = 7.2Hz, 2x SC$\underline{H}_a\underline{H}_b$), 3.29 (2H, dd, *J* = 13.9 Hz, *J* = 7.2 Hz, 2x SC$H_a\underline{H}_b$), 3.33 (1H, s, C≡CH), 5.08 (2H, dd, *J* = 9.9 Hz, *J* = 1.1 Hz, 2x CH=C$\underline{H}_E H_Z$), 5.14 (2H, dd, *J* = 16.9 Hz, *J* = 1.1 Hz, 2x CH=C$H_E\underline{H}_Z$), 5.47 (1H, s, CHS_2), 5.81 (2H, ddt, *J* = 16.9Hz, *J* = 9.9Hz, *J* = 7.2 Hz, 2x C$\underline{H}$=C$H_E H_Z$), 7.21 (1H, dd, *J* = 7.7 Hz, CH_{ar}), 7.37 (1H, dd, *J* = 7.7 Hz, CH_{ar}), 7.46 (1H, d, *J* = 7.7 Hz, CH_{ar}), 7.76 (1H, d, *J* = 7.7 Hz, CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 35.6 (2x SCH_2), 48.3 (CHS_2), 81.3 (C≡CH), 82.9 (C≡C), 117.8 (2x CH=$\underline{C}H_2$), 121.0 ($\underline{C}_{q,ar}$C≡CH), 127.6 (CH_{ar}), 128.5 (CH_{ar}), 129.5 (CH_{ar}), 132.8 (CH_{ar}), 133.7 (2x $\underline{C}$H=CH_2), 142.8 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1634 (CH=CH_2), 3288 (C≡CH). **MS (ESI, pos)**: *m/z* (%) 187.1 (M-[SCH_2CH=CH_2]$^-$, 75). **HRMS**: *m/z* calcd for $C_{15}H_{16}S_2$+H^+ 261.0771, found 261.0765. **Chromatography**: hexanes/EtOAc 98/2. R_f = 0.21. **Yield**: 83%, yellow oil.

((2-ethynyl-4-fluorophenyl)methylene)bis(allylsulfane) 376b, prepared by method A

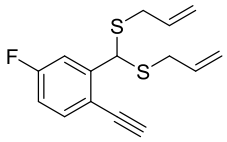


376b

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.08 (2H, dddd, *J* = 13.7 Hz, *J* = 7.0 Hz, *J* = 1.2 Hz, *J* = 0.9 Hz, 2x SC$\underline{H}_a\underline{H}_b$), 3.29 (2H, dddd, *J* = 13.7 Hz, *J* = 7.3 Hz, *J* = 1.2 Hz, *J* = 0.9 Hz, 2x SC$H_a\underline{H}_b$), 3.36 (1H, s, C≡CH), 5.08 (2H, dddd, *J* = 9.9 Hz, *J* = 1.4 Hz, *J* = 0.9Hz, *J* = 0.9 Hz, 2x CH=C$\underline{H}_E H_Z$), 5.13 (2H, ddt, *J* = 17.0Hz, *J* = 1.4 Hz, *J* = 1.2 Hz, 2x CH=C$H_E\underline{H}_Z$), 5.40 (1H, s, CHS_2), 5.79 (2H, dddd, *J* = 17.0 Hz, *J* = 9.9 Hz, *J* = 7.3 Hz, *J* = 7.0 Hz, 2x C$\underline{H}$=C$H_E H_Z$), 7.09 (1H, ddd, *J* = 8.6 Hz, $^3J_{HF}$ = 8.4Hz, *J* = 2.7 Hz, CH_{ar}), 7.14 (1H, dd, $^3J_{HF}$ = 8.9 Hz, *J* = 2.7 Hz, CH_{ar}), 7.75 (1H, dd, *J* = 8.6 Hz, $^4J_{HF}$ = 5.7 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 35.5 (2x SCH_2), 47.4 (CHS_2), 80.1 (C≡CH), 83.7 (C≡C), 117.0 (d, $^2J_{CF}$ = 21.5Hz, CH_{ar}), 117.8 (2x CH=$\underline{C}H_2$), 119.0 (d, $^2J_{CF}$ = 23.4 Hz, CH_{ar}), 122.6 (d, $^3J_{CF}$ = 9.6 Hz, $C_{q,ar}$), 130.4 (d, $^3J_{CF}$ = 8.9 Hz, CH_{ar}), 133.6 (2x $\underline{C}$H=CH_2), 138.4 (d,

$^4J_{CF}$ = 3.3 Hz, $\underline{C}_{q,ar}CHS_2$), 161.3 (d, $^1J_{CF}$ = 247.7 Hz, $C_{q,ar}F$). **^{19}F-NMR (376 MHz, $CDCl_3$)** δ -114.52 to -114.59 (m). **IR (ATR, cm^{-1}) ν_{max}**: 1265, 1487, 1578, 1635 ($CH=CH_2$), 2912, 3081, 3296. **MS (ESI, pos)**: *m/z* (%) 205.0 (M-[$SCH_2CH=CH_2$]$^-$, 100). **HRMS**: *m/z* calcd for $C_{12}H_{10}FS^+$ (M-[$SCH_2CH=CH_2$]$^-$) 205.0482, found 205.0478. **Chromatography**: hexanes/EtOAc 99/1. R_f = 0.21. **Yield**: 75%, yellow oil.

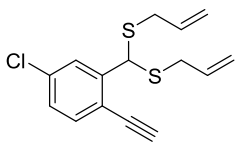
((2-ethynyl-5-fluorophenyl)methylene)bis(allylsulfane) 376c, prepared by method A



376c

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.09 (2H, dd, *J* = 13.7 Hz, *J* = 7.2 Hz, 2x $SC\underline{H}_aH_b$), 3.30 (2H, dd, *J* = 13.7 Hz, *J* = 7.2 Hz, 2x $SCH_a\underline{H}_b$), 3.31 (1H, s, C≡CH), 5.08 (2H, dd, *J* = 9.9 Hz, *J* = 1.6 Hz, 2x $CH=C\underline{H}_EH_Z$), 5.13 (2H, dd, *J* = 17.1 Hz, *J* = 1.1 Hz, 2x $CH=CH_E\underline{H}_Z$), 5.40 (1H, d, $^5J_{HF}$ = 1.7 Hz, CHS_2), 5.80 (2H, ddt, *J* = 17.1 Hz, *J* = 9.9 Hz, *J* = 7.2 Hz, 2x $C\underline{H}=CH_EH_Z$), 6.93 (1H, ddd, $^3J_{HF}$ = 8.3 Hz, *J* = 8.3 Hz, *J* = 2.7 Hz, CH_{ar}), 7.44 (1H, dd, *J* = 8.3 Hz, $^4J_{HF}$ = 5.5 Hz, CH_{ar}), 7.50 (1H, dd, $^3J_{HF}$ = 9.6 Hz, *J* = 2.7 Hz, $C_{q,ar}CH_{ar}CF$). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 35.6 (2x SCH_2), 47.9 (CHS_2), 80.4 ($\underline{C}$≡CH), 82.6 (C≡$\underline{C}$H), 115.3 (d, $^2J_{CF}$ = 23.1 Hz, CH_{ar}), 115.7 (d, $^2J_{CF}$ = 24.2 Hz, CH_{ar}), 117.1 (d, $^4J_{CF}$ = 2.3 Hz, $\underline{C}_{q,ar}C$≡CH), 118.0 (2x CH=$\underline{C}H_2$), 133.5 (2x $\underline{C}H=CH_2$), 134.6 (d, $^3J_{CF}$ = 9.2 Hz, CH_{ar}), 145.4 (d, $^3J_{CF}$ = 6.9 Hz, $\underline{C}_{q,ar}CHS_2$), 163.1 (d, $^1J_{CF}$ = 250.4 Hz, $C_{q,ar}F$). **^{19}F-NMR (282 MHz, $CDCl_3$):** δ -108.48 to -108.55 (m). **IR (ATR, cm^{-1}) ν_{max}**: 1633 ($CH=CH_2$), 3301 (C≡CH). **MS (ESI, pos)**: *m/z* (%): 205.0 (M-[$SCH_2CH=CH_2$]$^-$, 100). **HRMS**: *m/z* calcd for $C_{15}H_{15}FS_2$+H^+ 279.0677, found 279.0672. **Chromatography**: hexanes/EtOAc 98/2. R_f = 0.23. **Yield**: 86%, pale yellow oil.

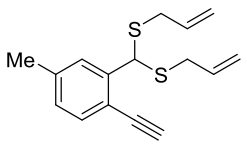
((5-chloro-2-ethynylphenyl)methylene)bis(allylsulfane) 376d, prepared by method A



376d

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.09 (2H, dddd, *J* = 13.7 Hz, *J* = 7.1 Hz, *J* = 1.2 Hz, *J* = 0.8 Hz, 2x $SC\underline{H}_aH_b$), 3.30 (2H, dddd, *J* = 13.7 Hz, *J* = 7.4 Hz, *J* = 1.2 Hz, *J* = 0.8 Hz, 2x $SCH_a\underline{H}_b$), 3.35 (1H, s, C≡CH), 5.08 (2H, dddd, *J* = 9.9 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, *J* = 0.8 Hz, 2x $CH=C\underline{H}_EH_Z$), 5.14 (2H, dddd, *J* = 17.0 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, *J* = 0.8 Hz, 2x $CH=CH_E\underline{H}_Z$), 5.37 (1H, s, CHS_2), 5.80 (2H, dddd, *J* = 17.0 Hz, *J* = 9.9 Hz, *J* = 7.4 Hz, *J* = 7.1 Hz, 2x $C\underline{H}=CH_EH_Z$), 7.20 (1H, dd, *J* = 8.3 Hz, *J* = 2.2 Hz, CH_{ar}), 7.38 (1H, d, *J* = 8.3 Hz, CH_{ar}), 7.76 (1H, d, *J* = 2.2 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 35.6 (2x SCH_2), 47.7 (CHS_2), 80.2 ($\underline{C}$≡CH), 83.7 (C≡$\underline{C}$H), 118.0 (2x CH=$\underline{C}H_2$), 119.4 ($C_{q,ar}$), 128.0 (CH_{ar}), 128.7 (CH_{ar}), 133.4 (2x $\underline{C}H=CH_2$), 133.8 (CH_{ar}), 135.5 ($C_{q,ar}$), 144.3 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1475, 1588, 1634 ($CH=CH_2$), 2914, 3081, 3293. **MS (ESI, pos)**: *m/z* (%): 221.0 (M-[$SCH_2CH=CH_2$]$^-$, 100). **HRMS**: *m/z* calcd for $C_{12}H_{10}ClS^+$ (M-[$SCH_2CH=CH_2$]$^-$) 221.0186, found 221.0185. **Chromatography**: hexanes/EtOAc 99/1. R_f = 0.09. **Yield**: 70%, yellow oil.

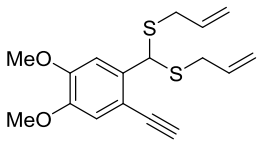
((2-ethynyl-5-methylphenyl)methylene)bis(allylsulfane) 376e, prepared by method A



376e

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.31 (3H, s, CH_3), 3.08 (2H, dd, *J* = 13.5 Hz, *J* = 7.2 Hz, 2x $SC\underline{H}_aH_b$), 3.28 (2H, dd, *J* = 13.5 Hz, *J* = 7.2 Hz, 2x $SCH_a\underline{H}_b$), 3.29 (1H, s, C≡CH), 5.07 (2H, dd, *J* = 9.9 Hz, *J* = 1.6 Hz, 2x $CH=C\underline{H}_EH_Z$), 5.13 (2H, dd, *J* = 16.9 Hz, *J* = 1.6 Hz, 2x $CH=CH_E\underline{H}_Z$), 5.42 (1H, s, CHS_2), 5.80 (2H, ddt, *J* = 16.9 Hz, *J* = 9.9 Hz, *J* = 7.2 Hz, 2x $C\underline{H}=CH_EH_Z$), 7.19 (1H, d, *J* = 8.3 Hz, CH_{ar}), 7.27 (1H, s, CH_{ar}), 7.64 (1H, d, *J* = 8.3 Hz, CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 21.0 (CH_3), 35.5 (2x SCH_2), 48.0 (CHS_2), 81.4 ($\underline{C}$≡CH), 82.4 (C≡$\underline{C}$H), 117.8 (2x $CH=\underline{C}H_2$), 120.8 ($\underline{C}_{q,ar}C$≡CH), 128.4 (CH_{ar}), 130.5 (CH_{ar}), 133.2 (CH_{ar}), 133.8 (2x $\underline{C}H=CH_2$), 137.5 ($\underline{C}_{q,ar}CH_3$), 139.4 ($\underline{C}_{q,ar}CHS_2$). **MS (ESI, pos)**: *m/z* (%): 201 (M-[$SCH_2CH=CH_2$]$^-$, 100). **HRMS**: *m/z* calcd for $C_{16}H_{18}S_2+H^+$ 275.0928, found 275.0921. **IR (ATR, cm^{-1}) ν_{max}**: 1634 ($CH=CH_2$), 3305 (C≡CH). **Chromatography**: hexanes/EtOAc 98/2. R_f = 0.19. **Yield**: 67%, yellow oil.

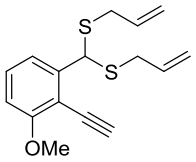
((2-ethynyl-4,5-dimethoxyphenyl)methylene)bis(allylsulfane) 376f, prepared by method B



376f

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.10 (2H, dddd, *J* = 13.6 Hz, *J* = 7.0 Hz, *J* = 1.2 Hz, *J* = 1.0 Hz, 2x $SC\underline{H}_aH_b$), 3.25 (1H, s, C≡CH), 3.27 (2H, dddd, *J* = 13.6 Hz, *J* = 7.3 Hz, *J* = 1.2 Hz, *J* = 1.0 Hz, 2x $SCH_a\underline{H}_b$), 3.87 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 5.08 (2H, dddd, *J* = 9.9 Hz, *J* = 1.5 Hz, *J* = 1.0 Hz, *J* = 1.0 Hz, 2x $CH=C\underline{H}_EH_Z$), 5.15 (2H, dddd, *J* = 17.0 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, *J* = 1.2 Hz, 2x $CH=CH_E\underline{H}_Z$), 5.42 (1H, s, CHS_2), 5.82 (2H, dddd, *J* = 17.0 Hz, *J* = 9.9 Hz, *J* = 7.3 Hz, *J* = 7.0 Hz, 2x $C\underline{H}=CH_EH_Z$), 6.90 (1H, s, CH_{ar}), 7.26 (1H, s, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 35.6 (2x SCH_2), 48.0 (CHS_2), 56.0 (2x $C_qO\underline{C}H_3$), 81.3 (C≡$\underline{C}$H), 81.3 ($\underline{C}$≡CH), 110.8 (CH_{ar}), 112.8 ($C_{q,ar}$), 114.2 (CH_{ar}), 117.7 (2x $CH=\underline{C}H_2$), 133.6 (2x $\underline{C}H=CH_2$), 135.8 ($C_{q,ar}$), 148.1 ($C_{q,ar}$), 150.3 ($C_{q,ar}$). **MS (ESI, pos)**: *m/z* (%): 247.1 (M-[$SCH_2CH=CH_2$]$^-$, 75), 321.1 (M+H$^+$, 25). **HRMS**: *m/z* calcd for $C_{17}H_{20}O_2S_2+H^+$ 321.0978, found 321.0976. **IR (ATR, cm^{-1}) ν_{max}**: 1505, 1601, 1634 ($CH=CH_2$), 2912, 3280. **Chromatography**: hexanes/EtOAc 9/1. R_f = 0.20. **Yield**: 34%, brown oil.

((2-ethynyl-3-methoxyphenyl)methylene)bis(allylsulfane) 376h, prepared by method A

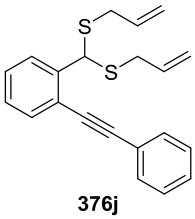


376h

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.10 (2H, dddd, *J* = 13.5 Hz, *J* = 7.0 Hz, *J* = 1.2 Hz, *J* = 0.9 Hz, 2x $SC\underline{H}_aH_b$), 3.29 (2H, dddd, *J* = 13.5 Hz, *J* = 7.3 Hz, *J* = 1.2 Hz, *J* = 0.9 Hz, 2x $SCH_a\underline{H}_b$), 3.58 (1H, s, C≡CH), 3.90 (3H, s, OCH_3), 5.07 (2H, dddd, *J* = 10.0 Hz, *J* = 1.5 Hz, *J* = 0.9 Hz, *J* = 0.9 Hz, 2x $CH=C\underline{H}_EH_Z$), 5.15 (2H, dddd, *J* = 17.0 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, *J* = 1.2 Hz, 2x $CH=CH_E\underline{H}_Z$), 5.47 (1H, s, CHS_2), 5.81 (2H, dddd, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 7.3 Hz, *J* = 7.0 Hz, 2x $C\underline{H}=CH_EH_Z$), 6.81 (1H, dd, *J* = 7.9 Hz, *J* = 1.3 Hz, CH_{ar}), 7.33 (1H, dd, *J* = 7.9 Hz, *J* = 7.9 Hz, CH_{ar}), 7.37 (1H, dd, *J* = 7.9 Hz, *J* = 1.3 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 35.5 (2x SCH_2), 48.1 (CHS_2), 56.1 (OCH_3), 77.4 ($\underline{C}$≡CH), 87.2 (C≡$\underline{C}$H), 109.5 (CH_{ar}), 110.1 ($C_{q,ar}$), 117.8 (2x $CH=\underline{C}H_2$), 120.6

(CH_{ar}), 130.1 (CH_{ar}), 133.7 (2x $\underline{C}H=CH_2$), 144.4 ($C_{q,ar}$), 160.6 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1270, 1468, 1573, 1633 ($CH=CH_2$), 2913, 3265. **MS (ESI, pos)**: *m/z* (%): 217.1 (M-[$SCH_2CH=CH_2$]$^-$, 90), 291.1 ($M+H^+$, 10). **HRMS**: *m/z* calcd for $C_{13}H_{13}OS^+$ (M-[$SCH_2CH=CH_2$]$^-$) 217.0682, found 217.0683. **Chromatography**: hexanes/EtOAc 96/4. R_f = 0.23. **Yield**: 45%, yellow oil.

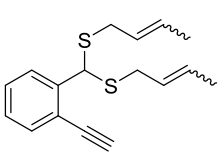
((2-(phenylethynyl)phenyl)methylene)bis(allylsulfane) 376j, prepared by method A



376j

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.10 (2H, dddd, *J* = 13.7 Hz, *J* = 7.1 Hz, *J* = 1.3 Hz, *J* = 1.0 Hz, 2x $SC\underline{H}_aH_b$), 3.32 (2H, dddd, *J* = 13.7 Hz, *J* = 7.3 Hz, *J* = 1.2 Hz, *J* = 0.9 Hz, 2x $SCH_a\underline{H}_b$), 5.02 (2H, dddd, *J* = 10.0 Hz, *J* = 1.5 Hz, *J* = 1.0 Hz, *J* = 0.9 Hz, 2x $CH=C\underline{H}_EH_Z$), 5.15 (2H, dddd, *J* = 17.0 Hz, *J* = 1.5 Hz, *J* = 1.3 Hz, *J* = 1.2 Hz, 2x $CH=CH_E\underline{H}_Z$), 5.54 (1H, s, CHS_2), 5.81 (2H, dddd, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 7.3 Hz, *J* = 7.1 Hz, 2x $C\underline{H}=CH_EH_Z$), 7.23-7.27 (1H, m, CH_{ar}), 7.34-7.40 (4H, m, 4 x CH_{ar}), 7.49-7.55 (3H, m, 3 x CH_{ar}), 7.77 (1H, dd, *J* = 7.9 Hz, *J* = 1.1 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 35.5 (2x SCH_2), 48.2 (CHS_2), 87.1 ($\underline{C}\equiv C$), 94.8 ($C\equiv\underline{C}$), 117.8 (2x $CH=\underline{C}H_2$), 122.1 ($C_{q,ar}$), 123.2 ($C_{q,ar}$), 127.7 (CH_{ar}), 128.5 (3 x CH_{ar}), 128.6 (CH_{ar}), 129.0 (CH_{ar}), 131.5 (2x CH_{ar}), 132.2 (CH_{ar}), 133.8 (2x $\underline{C}H=CH_2$), 141.7 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1422, 1442, 1491, 1636 ($CH=CH_2$), 2978. **MS (ESI, pos)**: *m/z* (%): 263.1 (M-[$SCH_2CH=CH_2$]$^-$, 80). **HRMS**: *m/z* calcd for $C_{18}H_{15}S^+$ (M-[$SCH_2CH=CH_2$]$^-$) 263.0889, found 263.0886. **Chromatography**: hexanes/EtOAc 98/2. R_f = 0.26. **Yield**: 69%, yellow oil.

((2-ethynylphenyl)methylene)bis(but-2-en-1-ylsulfane) 376k, prepared by method A



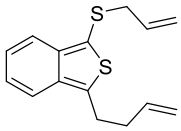
376k

This compound was obtained as a mixture of *E*/*Z* stereoisomers in a 9/1 *E,E*/*E,Z* ratio, according to ^{1}H-NMR integration. Spectral data are reported for the *E,E* isomer. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.68 (6H, dd, *J* = 6.1 Hz, *J* = 1.1 Hz, 2x CH_3), 3.02 (2H, ddd, *J* = 13.5 Hz, *J* = 6.8 Hz, *J* = 1.0 Hz, 2x $SC\underline{H}_aH_b$), 3.23 (2H, ddd, *J* = 13.5 Hz, *J* = 7.3 Hz, *J* = 0.9 Hz, 2x $SCH_a\underline{H}_b$), 3.31 (1H, s, $C\equiv CH$), 5.39-5.56 (5H, m, 4 x CH= + CHS_2), 7.21 (1H, ddd, *J* = 7.7 Hz, *J* = 7.7 Hz, *J* = 1.3 Hz, CH_{ar}), 7.37 (1H, ddd, *J* = 7.7 Hz, *J* =7.7 Hz, *J* = 1.3 Hz, CH_{ar}), 7.45 (1H, dd, *J* = 7.7 Hz, *J* = 1.0 Hz, CH_{ar}), 7.77 (1H, d, *J* = 7.7 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 17.8 (2x CH_3), 34.7 (2x SCH_2), 47.6 (CHS_2), 81.4 ($\underline{C}\equiv CH$), 82.1 ($C\equiv\underline{C}H$), 120.9 ($\underline{C}_{q,ar}C\equiv CH$), 126.5 (2x CH=), 127.4 (CH_{ar}), 128.4 (CH_{ar}), 128.8 (2x CH=), 129.4 (CH_{ar}), 132.7 (CH_{ar}), 142.6 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1220, 1444, 1475, 1665 (CH=CH), 2915. **MS (ESI, pos)**: *m/z* (%): 201.0 (M-[$SCH_2CH=CHCH_3$]$^-$, 95). **HRMS**: *m/z* calcd for $C_{13}H_{13}S^+$ (M-[$SCH_2CH=CHCH_3$]$^-$) 201.0733, found 201.0733. **Chromatography**: hexanes/EtOAc 99/1. R_f = 0.19. **Yield**: 87%, yellow oil.

3.4.4 Synthesis of benzo[c]thiophenes 377

Representative example: 400 mg ((2-ethynylphenyl)methylene)bis(allylsulfane) **376a** (1.54 mmol, 1 equiv) was dissolved in 3 mL dichloromethane in a round-bottom flask and 5 mol% $AuCl_3$ was added. The reaction progress was monitored using TLC and HPLC. In case of a very slow reaction, another 5 mol% $AuCl_3$ was added to the reaction mixture, bringing the total to 10 mol% catalyst. After all starting material had been consumed, the crude reaction mixture was filtered over a small plug of silica gel using ethyl acetate. The filtrate was concentrated *in vacuo* and the resulting oil was purified by means of column chromatography. 0.27 g (1.05 mmol, 68%) of **377a** was obtained.

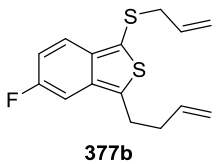
1-(allylthio)-3-(but-3-en-1-yl)benzo[*c*]thiophene 377a



377a

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.53 (2H, tddd, *J* = 7.6 Hz, *J* = 6.6 Hz, *J* = 1.4 Hz, *J* = 1.2 Hz, $C_qCH_2C\underline{H}_2$), 3.25 (2H, t, *J* = 7.6 Hz, $C_qC\underline{H}_2$), 3.36 (2H, ddd, *J* = 7.4 Hz, *J* = 1.2 Hz, *J* = 0.8 Hz, $SC\underline{H}_2$), 4.82 (1H, ddt, *J* = 17.0 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 4.93 (1H, ddt, *J* = 9.9 Hz, *J* = 1.5 Hz, *J* = 0.8 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.02 (1H, ddt, *J* = 10.3 Hz, *J* = 1.7 Hz, *J* = 1.2 Hz, $CH=C\underline{H}_ECH_Z$), 5.08 (1H, ddt, *J* = 17.0 Hz, *J* = 1.7 Hz, *J* = 1.4 Hz, $CH=CH_E\underline{H}_Z$), 5.85 (1H, ddt, *J* = 17.0 Hz, *J* = 9.9 Hz, *J* = 7.4 Hz, $SCH_2C\underline{H}$), 5.86 (1H, ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.6 Hz, $C_qCH_2CH_2C\underline{H}$), 7.03 (1H, ddd, *J* = 8.7 Hz, *J* = 6.3 Hz, *J* = 1.0 Hz, CH_{ar}), 7.11 (1H, ddd, *J* = 8.7 Hz, *J* = 6.3 Hz, *J* = 1.0 Hz, CH_{ar}), 7.52 (1H, dd, *J* = 8.7 Hz, *J* = 1.0 Hz, CH_{ar}), 7.74 (1H, dd, *J* = 8.7 Hz, *J* = 1.0 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 27.5 ($C_qC\underline{H}_2$), 35.7 ($C_qCH_2C\underline{H}_2$), 42.5 (SCH_2), 116.0 ($CH=C\underline{H}_2$), 117.8 ($SCH_2CH=C\underline{H}_2$), 118.2 ($C_{q,ar}$), 120.2 (CH_{ar}), 121.0 (CH_{ar}), 122.6 (CH_{ar}), 124.3 (CH_{ar}), 133.8 ($SCH_2C\underline{H}$), 135.6 ($C_{q,ar}$), 137.1 ($C\underline{H}=CH_2$), 139.8 ($C_{q,ar}$), 142.4 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1638 ($CH=CH_2$), 1691 ($CH=CH_2$). **MS (ESI, pos)**: *m/z* (%): 277.1 ($C_{15}H_{16}OS_2+H^+$ (S=O), 100). **HRMS**: *m/z* calcd for $C_{15}H_{16}OS_2+H^+$ (S=O) 277.0715, found 277.0712. **Chromatography**: hexanes. R_f = 0.31. **Yield**: 68%, orange oil.

1-(allylthio)-3-(but-3-en-1-yl)-5-fluorobenzo[*c*]thiophene 377b

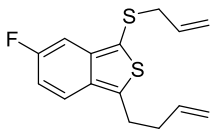


377b

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.51 (2H, tddd, *J* = 7.6 Hz, *J* = 6.7 Hz, *J* = 1.4 Hz, *J* = 1.3 Hz, $C_qCH_2C\underline{H}_2$), 3.16 (2H, t, *J* = 7.6 Hz, C_qCH_2), 3.35 (2H, ddd, *J* = 7.4 Hz, *J* = 1.1 Hz, *J* = 0.8Hz, SCH_2), 4.81 (1H, ddt, *J* = 17.1 Hz, *J* = 1.4 Hz, *J* = 1.1 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 4.92 (1H, ddt, *J* = 9.8 Hz, *J* = 1.4 Hz, *J* = 0.8 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.03 (1H, ddt, *J* = 10.3 Hz, *J* = 1.6 Hz, *J* = 1.3 Hz, $CH=C\underline{H}_ECH_Z$), 5.08 (1H, ddt, *J* = 17.0 Hz, *J* = 1.6 Hz, *J* = 1.4 Hz, $CH=CH_E\underline{H}_Z$), 5.84 (1H, ddt, *J* = 17.1 Hz, *J* = 9.8 Hz, *J* = 7.4 Hz, $SCH_2C\underline{H}$), 5.86 (1H, ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, $C_qCH_2CH_2C\underline{H}$), 6.94 (1H, ddd, *J* = 9.4 Hz, $^3J_{HF}$ = 8.3 Hz, *J* = 2.3 Hz, CH_{ar}), 7.07 (1H, ddd, $^3J_{HF}$ = 10.3 Hz, *J* = 2.3 Hz, *J* = 0.6 Hz, CH_{ar}), 7.70 (1H, ddd, *J* = 9.4 Hz, $^4J_{HF}$ = 5.5 Hz, *J* = 0.6 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 27.5 ($C_{q,ar}C\underline{H}_2$), 35.5 ($C_{q,ar}CH_2C\underline{H}_2$), 42.6 ($SCH_2$), 102.2 (d, $^2J_{CF}$ = 22.5 Hz,

CH_{ar}), 116.1 (CH=$\underline{C}H_2$), 116.5 (d, $^2J_{CF}$ = 29.5 Hz, CH_{ar}), 118.0 ($SCH_2CH=\underline{C}H_2$), 119.9 ($C_{q,ar}$), 122.9 (d, $^3J_{CF}$ = 10.0 Hz, CH_{ar}), 133.6 ($SCH_2\underline{C}H$), 134.7 (d, $^3J_{CF}$ = 9.0 Hz, $C_{q,ar}$), 136.9 ($\underline{C}H=CH_2$), 137.8 (d, $^4J_{CF}$ = 9.4 Hz, $C_{q,ar}$), 139.9 ($C_{q,ar}$), 159.7 (d, $^1J_{CF}$ = 244.9 Hz, $C_{q,ar}$F). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ -119.75 to -119.81 (m). **IR (ATR, cm^{-1}) ν_{max}**: 1175, 1222, 1508, 1626 (CH=CH_2), 1693 (CH=CH_2), 2918. **MS (ESI, pos)**: *m/z* (%): 279.1 (M+H$^+$, 100). **HRMS**: *m/z* calcd for $C_{15}H_{15}FOS_2$+H$^+$ (S=O) 295.0621, found 295.0621. **Yield**: 74%, pale yellow oil.

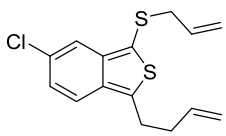
3-(allylthio)-1-(but-3-en-1-yl)-5-fluorobenzo[*c*]thiophene 377c



377c

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.52 (2H, m, $C_qCH_2C\underline{H}_2$), 3.23 (2H, t, *J* = 7.6 Hz, C_qCH_2), 3.33 (2H, d, *J* = 7.7 Hz, $SC\underline{H}_2$), 4.80 (1H, d, *J* = 16.7 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 4.92 (1H, d, *J* = 9.9 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.03 (1H, d, *J* = 9.9 Hz, $CH=C\underline{H}_ECH_Z$), 5.08 (1H, d, *J* = 17.1 Hz, $CH=CH_E\underline{H}_Z$), 5.77-5.93 (2H, m, $SCH_2C\underline{H}$ + $CH_2CH_2C\underline{H}$) 6.86 (1H, ddd, *J* = 9.5 Hz, $^3J_{HF}$ = 8.3Hz, *J* = 2.2Hz, $C\underline{H}_{ar}$), 7.31 (1H, dd, $^3J_{HF}$ = 9.9 Hz, *J* = 2.2 Hz, CH_{ar}), 7.49 (1H, dd, *J* = 9.5 Hz, $^4J_{HF}$ = 5.2 Hz, $C\underline{H}_{ar}$). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 27.8 ($C_{q,ar}\underline{C}H_2$), 35.7 ($C_{q,ar}CH_2\underline{C}H_2$), 42.5 ($SCH_2$), 103.2 (d, $^2J_{CF}$ = 23.1 Hz, CH_{ar}), 115.1 (d, $^2J_{CF}$ = 28.8 Hz, CH_{ar}), 116.3 (CH=$\underline{C}H_2$), 116.9 (d, J_{CF} = 9.2 Hz, $C_{q,ar}$), 118.0 ($SCH_2CH=\underline{C}H_2$), 122.1 (d, $^3J_{CF}$ = 9.2 Hz, $\underline{C}H_{ar}$), 133.2 ($C_{q,ar}$), 133.8 ($SCH_2\underline{C}H$), 136.9 ($\underline{C}H=CH_2$), 141.4 ($C_{q,ar}$), 142.5 (d, $^4J_{CF}$ = 9.2 Hz, $C_{q,ar}$), 161.2 (d, $^1J_{CF}$ = 246.9 Hz, $C_{q,ar}$F). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ -117.3. **IR (ATR, cm^{-1}) ν_{max}**: 1625 (CH=CH_2), 1696 (CH=CH_2). **MS (ESI, pos)**: *m/z* (%): 279.1 (M+H$^+$, 100). **HRMS**: *m/z* calcd for $C_{15}H_{15}FS_2$+H$^+$ 279.0672, found 279.0666. **Chromatography**: hexanes. R_f = 0.25. **Yield**: 63%, pale yellow oil.

3-(allylthio)-1-(but-3-en-1-yl)-5-chlorobenzo[*c*]thiophene 377d

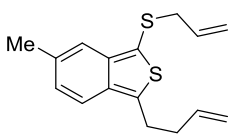


377d

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.50 (2H, tddd, *J* = 7.6 Hz, *J* = 6.6 Hz, *J* = 1.4 Hz, *J* = 1.2 Hz, $C_qCH_2C\underline{H}_2$), 3.22 (2H, t, *J* = 7.6 Hz, C_qCH_2), 3.34 (2H, ddd, *J* = 7.4 Hz, *J* = 1.2 Hz, *J* = 0.8 Hz, SCH_2), 4.81 (1H, ddt, *J* = 17.0 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 4.94 (1H, ddt, *J* = 10.0 Hz, *J* = 1.5 Hz, *J* = 0.8 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.02 (1H, ddt, *J* = 10.3 Hz, *J* = 1.7 Hz, *J* = 1.2 Hz, $CH=C\underline{H}_ECH_Z$), 5.07 (1H, ddt, *J* = 17.0 Hz, *J* = 1.7 Hz, *J* = 1.4 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 5.84 (1H, ddt, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 7.4 Hz, $SCH_2C\underline{H}$), 5.84 (1H, ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.6 Hz, $C_qCH_2CH_2C\underline{H}$), 6.96 (1H, dd, *J* = 9.2 Hz, *J* = 1.9 Hz, CH_{ar}), 7.44 (1H, dd, *J* = 9.2 Hz, *J* = 0.8 Hz, CH_{ar}), 7.72 (1H, dd, *J* = 1.9 Hz, *J* = 0.8 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 27.6 ($C_{q,ar}\underline{C}H_2$), 35.6 ($C_{q,ar}CH_2\underline{C}H_2$), 42.5 ($SCH_2$), 116.2 (CH=$\underline{C}H_2$), 117.9 ($C_{q,ar}$), 118.0 ($SCH_2CH=\underline{C}H_2$), 119.5 ($CH_{ar}$) , 121.3 ($CH_{ar}$) , 124.1 ($CH_{ar}$), 131.4 ($C_{q,ar}$), 133.6 ($SCH_2\underline{C}H$), 133.7 ($C_{q,ar}$), 136.8 ($\underline{C}H=CH_2$), 141.1 ($C_{q,ar}$), 142.3 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1219, 1273, 1425, 1604, 1638 (C=CH_2), 1698 (C=CH_2), 2918,

3078. **MS (ESI, pos)**: *m/z* (%): 295.0 ($M+H^+$, 100). **HRMS**: *m/z* calcd for $C_{15}H_{15}ClS_2+H^+$ = 295.0377, found = 295.0370. **Yield**: 91%, orange oil.

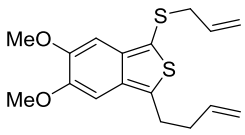
3-(allylthio)-1-(but-3-en-1-yl)-5-methylbenzo[*c*]thiophene 377e



377e

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s, CH_3), 2.51 (2H, m, $C_qCH_2C\underline{H}_2$), 3.20 (2H, t, *J* = 7.4 Hz, C_qCH_2), 3.34 (2H, d, *J* = 7.2 Hz, SCH_2), 4.81 (1H, d, *J* = 17.1 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 4.91 (1H, d, *J* = 9.1 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.02 (1H, d, *J* = 11.0 Hz, $CH=C\underline{H}_EH_Z$), 5.08(1H, d, *J* = 17.1 Hz, $CH=CH_E\underline{H}_Z$), 5.76-5.95 (2H, m, $SCH_2C\underline{H}$ + $C_qCH_2CH_2C\underline{H}$), 6.95 (1H, d, *J* = 8.9Hz, CH_{ar}), 7.24 (1H, s, CH_{ar}), 7.63 (1H, d, *J* = 8.9 Hz, CH_{ar}). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ 21.8 (CH_3), 27.5 ($C_{q,ar}\underline{C}H_2$), 35.7 ($C_{q,ar}CH_2\underline{C}H_2$), 42.6 ($SCH_2$), 115.9 ($CH_2CH_2CH=\underline{C}H_2$), 117.8 ($SCH_2CH=\underline{C}H_2$), 118.1 ($C_{q,ar}$), 118.3 ($C_{q,ar}\underline{C}H_{ar}$), 120.6 ($C_{q,ar}\underline{C}H_{ar}$), 127.6 ($CH_{ar}$), 132.1 ($C_{q,ar}$), 133.9 ($SCH_2\underline{C}H$), 136.0 ($C_{q,ar}$), 137.3 ($\underline{C}H=CH_2$), 138.0 ($C_{q,ar}$), 141.4 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1638 ($CH=CH_2$). **MS (ESI, pos)**: *m/z* (%): 291 ($C_{16}H_{18}OS_2+H^+$ (S=O), 100). **Chromatography**: hexanes. R_f = 0.30. **Yield**: 41%, yellow oil.

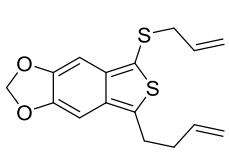
1-(allylthio)-3-(but-3-en-1-yl)-5,6-dimethoxybenzo[*c*]thiophene 377f



377f

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.51 (2H, tddd, *J* = 7.7 Hz, *J* = 6.6 Hz, *J* = 1.8 Hz, *J* = 1.5 Hz, $C_qCH_2C\underline{H}_2$), 3.14 (2H, t, *J* = 7.7 Hz, $C_qC\underline{H}_2$), 3.34 (2H, ddd, *J* = 7.4 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, $SC\underline{H}_2$), 3.92 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.87 (1H, ddt, *J* = 17.0 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 4.94 (1H, ddt, *J* = 9.9 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.03 (1H, ddt, *J* = 10.3 Hz, *J* = 1.8 Hz, *J* = 1.5 Hz, $CH=C\underline{H}_EH_Z$), 5.10 (1H, ddt, *J* = 17.1 Hz, *J* = 1.8 Hz, *J* = 1.5 Hz, $CH=CH_E\underline{H}_Z$), 5.87 (1H, ddt, *J* = 17.0 Hz, *J* = 9.9 Hz, *J* = 7.4 Hz, $SCH_2C\underline{H}$), 5.89 (1H, ddt, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 6.6 Hz, $C_qCH_2CH_2C\underline{H}$), 6.65 (1H, s, CH_{ar}), 6.96 (1H, s, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 27.6 ($C_{q,ar}\underline{C}H_2$), 35.3 ($C_{q,ar}CH_2\underline{C}H_2$), 42.4 ($SCH_2$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 97.0 ($CH_{ar}$), 98.0 ($CH_{ar}$), 114.7 ($C_{q,ar}$), 115.8 ($CH=\underline{C}H_2$), 117.7 ($SCH_2CH=\underline{C}H_2$), 131.1 ($C_{q,ar}$), 134.0 ($SCH_2\underline{C}H$), 136.2 ($C_{q,ar}$), 137.3 ($\underline{C}H=CH_2$), 139.0 ($C_{q,ar}$), 149.2 ($C_{q,ar}$), 150.6 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1230, 1352, 1490, 1638 ($CH=CH_2$), 1682 ($CH=CH_2$), 2932. **MS (ESI, pos)**: *m/z* (%): 337.1 ($C_{17}H_{20}O_3S_2+H^+$ (S=O), 66), 321.1 ($M+H^+$, 33). **HRMS**: *m/z* calcd for $C_{17}H_{20}O_3S_2+H^+$ (S=O) 337.0927, found 337.0928. **Yield**: 87%, brown oil.

5-(allylthio)-7-(but-3-en-1-yl)thieno[3',4':4,5]benzo[1,2-*d*][1,3]dioxole 377g

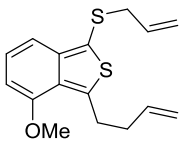


377g

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.47 (2H, tddd, *J* = 7.7 Hz, *J* = 6.7 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, $C_qCH_2C\underline{H}_2$), 3.08 (2H, t, *J* = 7.7 Hz, $C_qC\underline{H}_2$), 3.32 (2H, ddd, *J* = 7.4 Hz, *J* = 1.1 Hz, *J* = 0.8 Hz, $SC\underline{H}_2$), 4.85 (1H, ddt, *J* = 16.9 Hz, *J* = 1.4 Hz, *J* = 1.1 Hz,

$SCH_2CH=CH_E\underline{H}_Z$), 4.93 (1H, ddt, *J* = 9.9 Hz, *J* = 1.4 Hz, *J* = 0.8 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.01 (1H, ddt, *J* = 10.3 Hz, *J* = 1.7 Hz, *J* = 1.2 Hz, $CH=C\underline{H}_EH_Z$), 5.07 (1H, ddt, *J* = 17.1 Hz, *J* = 1.7 Hz, *J* = 1.5 Hz, $CH=CH_E\underline{H}_Z$), 5.84 (1H, ddt, *J* = 16.9 Hz, *J* = 9.9 Hz, *J* = 7.4 Hz, $SCH_2C\underline{H}$), 5.85 (1H, ddt, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, $C_qCH_2CH_2C\underline{H}$), 5.95 (2H, s, OCH_2O), 6.72 (1H, s, CH_{ar}), 6.99 (1H, s, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 27.7 ($C_{q,ar}\underline{C}H_2$), 35.4 ($C_{q,ar}CH_2\underline{C}H_2$), 42.3 ($SCH_2$), 94.8 ($CH_{ar}$), 96.0 ($CH_{ar}$), 101.2 ($OCH_2O$), 115.5 ($C_{q,ar}$), 115.9 ($CH=\underline{C}H_2$), 117.7 ($SCH_2CH=\underline{C}H_2$), 132.3 ($C_{q,ar}$), 133.8 ($SCH_2\underline{C}H=CH_2$), 136.6 ($C_{q,ar}$), 137.1 ($\underline{C}H=CH_2$), 140.4 ($C_{q,ar}$), 147.4 ($C_{q,ar}$), 148.8 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1213, 1336, 1594, 1638 ($C=CH_2$), 1684 ($C=CH_2$), 2360, 2901. **MS (ESI, pos)**: *m/z* (%): 305.0 ($M+H^+$, 100). **HRMS**: calcd for $C_{16}H_{16}O_2S_2+H^+$ 305.0665, found 305.0665. **Chromatography**: hexanes/EtOAc 99/1. R_f = 0.16. **Yield**: 53% (2 steps), yellow oil.

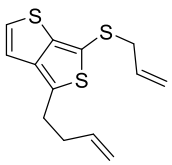
1-(allylthio)-3-(but-3-en-1-yl)-4-methoxybenzo[*c*]thiophene 377h



377h

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.51 (2H, tddd, *J* = 7.7 Hz, *J* = 6.7 Hz, *J* = 1.3 Hz, *J* = 1.3 Hz, $C_qCH_2C\underline{H}_2$), 3.34 (2H, ddd, *J* = 7.3 Hz, *J* = 1.0 Hz, *J* = 1.0 Hz, $SC\underline{H}_2$), 3.42 (2H, t, *J* = 7.7 Hz, $C_qC\underline{H}_2$), 3.90 (3H, s, OCH_3), 4.82 (1H, ddt, *J* = 17.1 Hz, *J* = 1.4 Hz, *J* = 1.0 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 4.93 (1H, ddt, *J* = 9.9 Hz, *J* = 1.4 Hz, *J* = 1.0 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.00 (1H, ddt, *J* = 10.3 Hz, *J* = 1.9 Hz, *J* = 1.3 Hz, $CH=C\underline{H}_EH_Z$), 5.06 (1H, ddt, *J* = 17.1 Hz, *J* = 1.9 Hz, *J* = 1.3 Hz, $CH=CH_E\underline{H}_Z$), 5.84 (1H, ddt, *J* = 17.1 Hz, *J* = 9.9 Hz, *J* = 7.3 Hz, $SCH_2C\underline{H}$), 5.89 (1H, ddt, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, $C_qCH_2CH_2C\underline{H}$), 6.22 (1H, d, *J* = 7.2 Hz, CH_{ar}), 6.99 (1H, dd, *J* = 8.7 Hz, *J* = 7.2 Hz, CH_{ar}), 7.31 (1H, d, *J* = 8.7 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 30.1 ($C_{q,ar}\underline{C}H_2$), 36.6 ($C_{q,ar}CH_2\underline{C}H_2$), 42.2 ($SCH_2$), 55.0 ($O\underline{C}H_3$), 98.84 ($CH_{ar}$), 113.5 ($CH_{ar}$), 115.4 ($CH=\underline{C}H_2$), 116.6 ($C_{q,ar}$), 117.8 ($SCH_2CH=\underline{C}H_2$), 124.9 ($\underline{C}H_{ar}$), 128.3 ($C_{q,ar}$), 133.9 ($SCH_2\underline{C}H$), 137.8 ($\underline{C}H=CH_2$), 141.8 ($C_{q,ar}$), 144.9 ($C_{q,ar}$), 155.1 ($C_{q,ar}$OMe). **IR (ATR, cm^{-1}) ν_{max}**: 1428, 1528, 1614, 1638 ($CH=CH_2$), 1695 ($CH=CH_2$), 2911. **MS (ESI, pos)**: *m/z* (%): 217.1 ($M-[SCH_2CH=CH_2]^-$, 60). **HRMS**: calcd for $C_{16}H_{18}O_2S_2+H^+$ (S=O) 307.0821, found 307.0827. **Yield**: 92%, brown oil.

6-(allylthio)-4-(but-3-en-1-yl)thieno[3,4-*b*]thiophene 377i

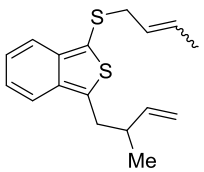


377i

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.46 (2H, tddd, *J* = 7.6 Hz, *J* = 6.6 Hz, *J* = 1.5 Hz, *J* = 1.3 Hz, $C_qCH_2C\underline{H}_2$), 3.04 (2H, t, *J* = 7.6 Hz, $C_qC\underline{H}_2$), 3.41 (2H, ddd, *J* = 7.3 Hz, *J* = 1.2 Hz, *J* = 1.1 Hz, $SC\underline{H}_2$), 4.95 (1H, ddt, *J* = 16.8 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, $SCH_2CH=CH_E\underline{H}_Z$), 4.99 (1H, ddt, *J* = 10.2 Hz, *J* = 1.5 Hz, *J* = 1.1 Hz, $SCH_2CH=C\underline{H}_EH_Z$), 5.02 (1H, ddt, *J* = 10.3 Hz, *J* = 1.7 Hz, *J* = 1.3 Hz, $CH=C\underline{H}_ECH_Z$), 5.07 (1H, ddt, *J* = 17.1 Hz, *J* = 1.7 Hz, *J* = 1.5 Hz, $CH=CH_EC\underline{H}_Z$), 5.84 (1H, ddt, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 6.6Hz, $C_qCH_2CH_2C\underline{H}$), 5.88 (1H, ddt, *J* = 16.8 Hz, *J* = 10.2 Hz, *J* = 7.3 Hz, $SCH_2C\underline{H}$), 6.82 (1H, d, *J* = 5.6 Hz, CH_{ar}), 7.21 (1H, d, *J* = 5.6 Hz, SCH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ

28.9 ($C_{q,ar}\underline{C}H_2$), 35.5 ($C_{q,ar}CH_2\underline{C}H_2$), 41.0 ($SCH_2$), 113.6 ($C_{q,ar}$), 116.0 ($CH=\underline{C}H_2$), 116.7 ($CH_{ar}$), 118.0 ($SCH_2CH=\underline{C}H_2$), 130.9 ($CH_{ar}$), 133.7 ($SCH_2\underline{C}H$), 136.1 ($C_{q,ar}$), 137.0 ($\underline{C}H=CH_2$), 144.4 ($C_{q,ar}$), 146.4 ($C_{q,ar}$). **IR (ATR, cm^{-1}) ν_{max}**: 1220, 1425, 1639 ($C=CH_2$), 1841, 2913, 3077. **MS (ESI, pos)**: *m/z* (%): 267.1 ($M+H^+$, 25), 283.1 ($C_{13}H_{14}OS_3+H^+$ (S=O), 100). **HRMS**: calcd for $C_{13}H_{14}OS_3+H^+$ (S=O) 283.0280, found 283.0276. **Chromatography**: hexanes/EtOAc 98/2. R_f = 0.24. **Yield**: 15% (2 steps), orange oil.

1-(but-2-en-1-ylthio)-3-(2-methylbut-3-en-1-yl)benzo[*c*]thiophene 377k

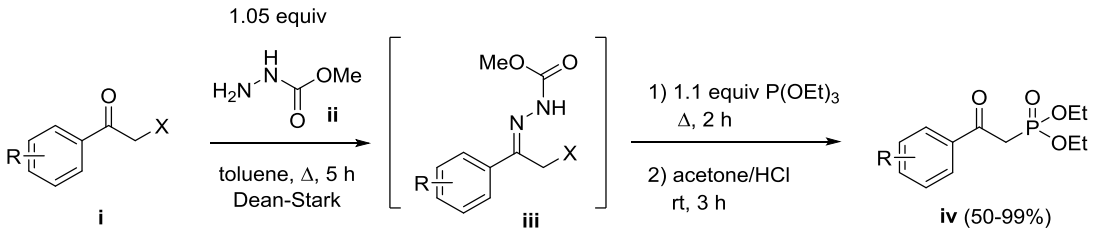


377k

This compound was obtained as a mixture of *E*/*Z* stereoisomers in a 9/1 *E*/*Z* ratio, according to ^{1}H-NMR integration. Spectral data are reported for the *E*-isomer only. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 1.06 (3H, d, *J* = 7.0 Hz, $C\underline{H}_3CH$), 1.51 (3H, ddt, *J* = 6.5 Hz, *J* = 1.5 Hz, *J* = 0.8 Hz, $CH=CHC\underline{H}_3$), 2.61 (1H, sept, *J* = 7.0 Hz, $CH_3C\underline{H}$), 3.09 (1H, dd, *J* = 14.8 Hz, *J* = 7.0 Hz, $C\underline{H}_aH_b$), 3.20 (1H, dd, *J* = 14.8 Hz, *J* = 7.0 Hz, $CH_a\underline{H}_b$), 3.29 (2H, d, *J* = 7.5 Hz, SCH_2), 4.95 (1H, dm, *J* = 10.6 Hz, $CH=C\underline{H}_EH_Z$), 4.99 (1H, ddd, *J* = 17.1 Hz, *J* = 1.4 Hz, *J* = 1.4 Hz, $CH=CH_E\underline{H}_Z$), 5.10 (1H, dqt, *J* = 15.0 Hz, *J* = 6.5 Hz, 1.0 Hz, $CH=C\underline{H}CH_3$), 5.48 (1H, dtq, *J* = 15.0 Hz, *J* = 7.5 Hz, *J* = 1.5 Hz, $C\underline{H}=CHCH_3$), 5.82 (1H, ddd, *J* = 17.1 Hz, *J* = 10.6 Hz, *J* = 7.0 Hz, $C\underline{H}=CH_EH_Z$), 7.01 (1H, ddd, *J* = 8.7 Hz, *J* = 6.4 Hz, *J* = 1.0 Hz, CH_{ar}), 7.10 Hz (1H, ddd, *J* = 8.7 Hz, *J* = 6.4 Hz, *J* = 1.0 Hz, CH_{ar}), 7.50 (1H, d, *J* = 8.7 Hz, CH_{ar}), 7.71 (1H, d, *J* = 8.7 Hz, CH_{ar}). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 17.7 (CH_3), 19.6 (CH_3), 35.0 (CH_2), 40.1 (CH), 41.9 (SCH_2), 113.7 ($CH=\underline{C}H_2$), 118.9 ($C_{q,ar}$), 120.3 (CH_{ar}), 121.0 (CH_{ar}), 122.5 (CH_{ar}), 124.0 (CH_{ar}), 126.4 ($\underline{C}H=CHCH_3$), 129.2 ($CH=\underline{C}HCH_3$), 136.1 ($C_{q,ar}$), 138.3 ($C_{q,ar}$), 142.3 ($C_{q,ar}$), 143.0 ($\underline{C}H=CH_2$). **IR (ATR, cm^{-1}) ν_{max}**: 1220, 1444, 1665 ($C=CH_2$), 2915, 3288. **MS (ESI, pos)**: *m/z* (%): 289.0 ($M+H^+$, 100). **HRMS**: calcd for $C_{17}H_{20}S_2+H^+$ 289.1079, found 289.1083. **Chromatography**: hexanes. R_f = 0.23. **Yield**: 80%, yellow oil.

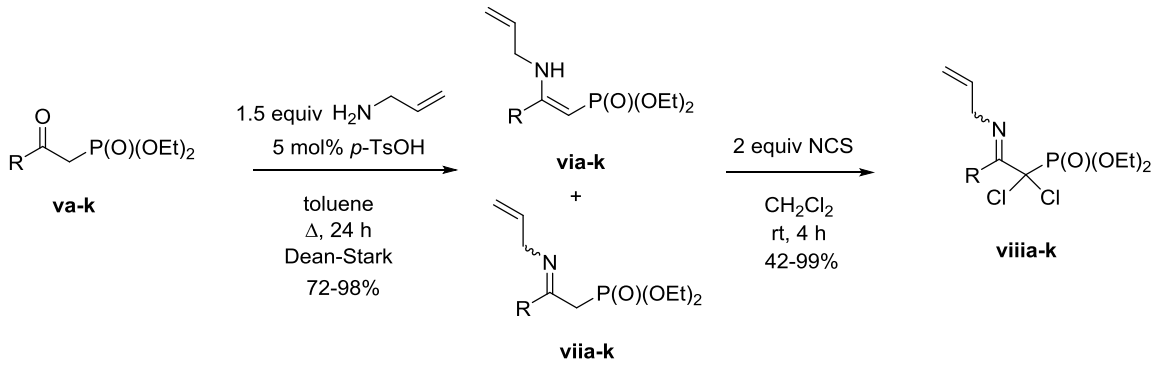
VI. Summary

Due to the experience in the SynBioC research group with the heteroatom transfer radical cyclization (HATRC) methodology and due to the interesting biological properties of aminophosphonates, a synthetic route toward 3-phosphonopyrroles was designed with a HATRC key step. The required β-ketophosphonates **iv** were synthesized by a Michaelis-Arbuzov reaction on α-haloketones **i**. In order to prevent Perkow reaction, *i.e.* a side reaction leading to enol phosphates, the α-haloketones were transformed into the corresponding hydrazones **iii** (Scheme 111). For very electron-poor substrates another method was adopted to prevent Perkow reaction, based on acylation of phosphonoacetic acid and subsequent decarboxylation.



Scheme 111. Formation of β-ketophosphonates.

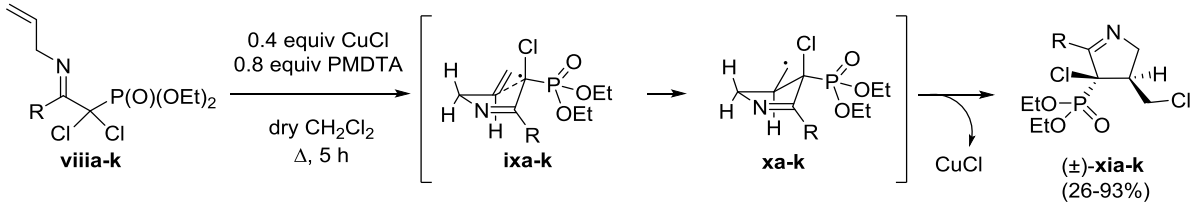
After Michaelis-Arbuzov reaction and hydrolysis, the obtained β-ketophosphonates **iv** were subjected to imination under Dean-Stark conditions (Scheme 112). This smoothly resulted in a mixture of the desired enamines **vi** and imines **vii**, in a ratio of 1/1 to 4/1. The enamines were solely present in the *Z*-form due to intramolecular H-bond formation. The imines occurred in both their *E*- and *Z*- forms in a ratio of 1/1 to 9/1. Next, the crude mixtures were subjected to treatment with NCS which cleanly resulted in α,α-dichlorination to **viii**.



Scheme 112. Imination and α,α-dichlorination.

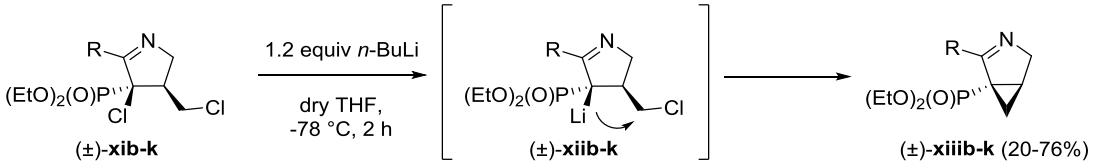
With *N*-allyl α,α-dichloroimines **viii** in hand, the HATRC was evaluated and resulted in the generation of the desired 1-pyrrolines **xi** (Scheme 113). Interestingly, this transformation proceeded with a large diastereoselectivity (9:1). After purification, only the major diastereomer was left and quite some effort was devoted to the determination of the relative stereochemistry. A 2D-NOESY experiment

showed no NOE between the phosphonate ethoxy groups and the CH of the pyrroline, while a heteronuclear NOESY (HOESY) did not render further information either. In an effort to determine the $^{3}J_{HP}$ coupling constant, a number of ^{1}H-undecoupled ^{31}P-NMR spectra were recorded in which the interfering protons were saturated. This indicated that $^{3}J_{HP}$ was 11.2 Hz. Unfortunately, this result did not provide unambiguous information about the relative configuration of the products. Luckily however, the two last synthesized derivatives were crystalline and with the aid of single crystal X-ray diffraction, the relative configuration was assigned as *cis*. The reason for this was most likely the bulky phosphonate adopting a pseudo-equatorial position in the transition state **ix**, minimizing steric repulsion with the other substituents.



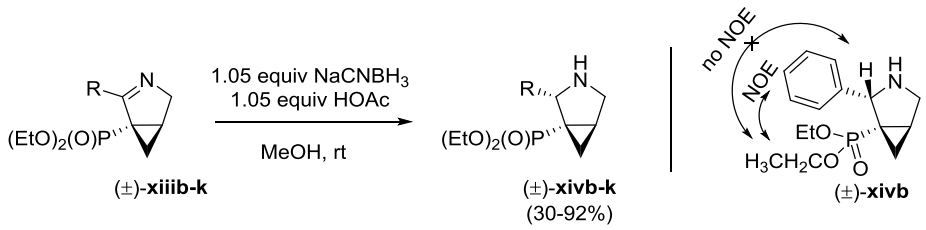
Scheme 113. HATRC with formation of *cis*-diastereomers xi.

Next, treatment with base would result in 1,4-dehydrohalogenation and formation of the envisioned 3-phosphonopyrroles. However, only starting material was recovered after treatment with a number of bases. Upon application of *n*-BuLi though, a new product was formed and surprisingly, it was not the anticipated pyrrole. Instead, the structure was elucidated as bicycle **xiii** and a possible mechanism for its formation was proposed (Scheme 114). Instead of performing the desired 1,4-dehydrohalogenation, a Li-Cl exchange had occurred (**xii**) after which intramolecular elimination resulted in cyclopropanation. As this conversion was innovative, it was further pursued in spite of the originally envisoned pyrrole synthesis.



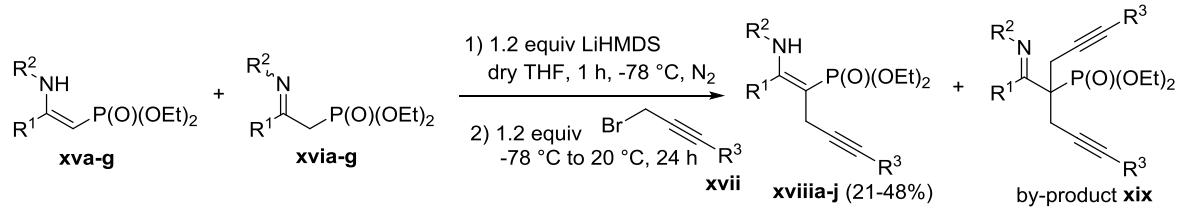
Scheme 114. Unforeseen cyclopropanation through Li-Cl exchange.

The imine bond was reduced with $NaCNBH_3$ and HOAc which resulted in azabicyclo[3.1.0]hexanes **xiv** (Scheme 115). A 2D-NOESY experiment indicated that this reduction also proceeded in a very diastereoselective manner. This was most likely due to the bulky phosphonate group. After reduction, intramolecular debenzylation was attempted in order to generate phosphonylated aminomethyl cyclopropanes. However, all attempts in this direction failed.



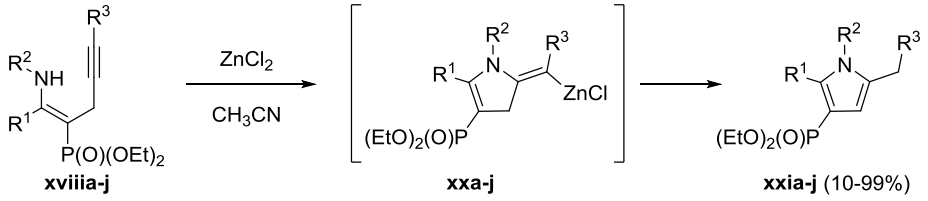
Scheme 115. Reduction of the imine and 2D-NOESY.

As the envisioned 3-phosphonopyrrole synthesis had failed, another synthetic route was devised starting from the same β-iminophosphonates, based on π-acid catalysis. As was the case in the first attempt, imination proceeded smoothly and again a mixture of enamines **xv** and imines **xvi** was obtained. Next, introduction of a propargyl group was attempted by generation of the corresponding aza-enolate using LiHMDS and quenching with propargyl bromide **xvii** (Scheme 116). This method proved fruitful, but it was difficult to obtain full conversion. Addition of extra base and electrophile resulted in mixtures of mono- and dipropargylated products **xviii** and **xix**. Compounds **xviii** were present as enamines in the *Z*-form due to intramolecular H-bond formation.



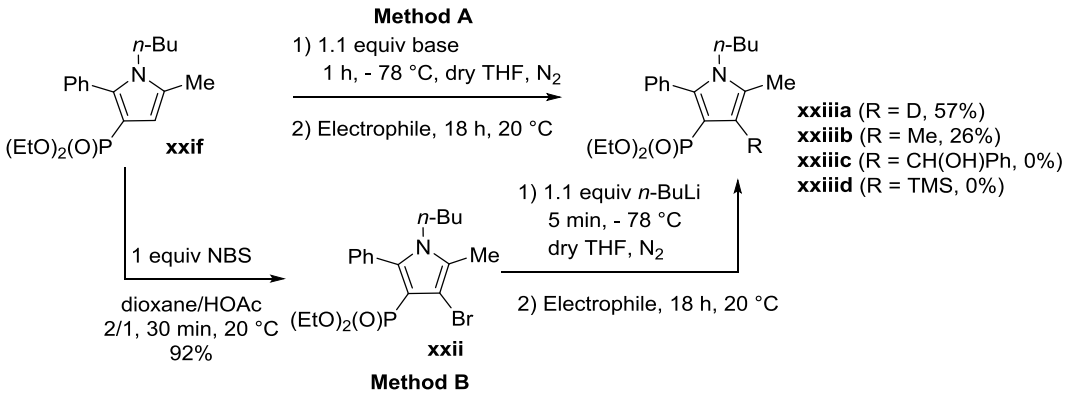
Scheme 116. Introduction of a propargyl group.

After purification, a number of π-acids were evaluated for the envisioned hydroamination of **xviii**. Both 20 mol% $ZnCl_2$ and $AgNO_3$ were efficacious catalysts but $AgNO_3$ was much faster. However, upon decreasing the catalyst loading the reaction time augmented and some degradation occurred in the case of $AgNO_3$. This observation, in combination with the much higher price of Ag than Zn, resulted in the choice for 5 mol% $ZnCl_2$ as π-acidic catalyst. This worked smoothly for terminal alkynes, but internal alkynes were much more reluctant towards hydroamination. A higher catalyst loading of 20 mol% was required as well as reflux temperature to effectuate ring closure. Using this hydroamination approach, a library of phosphonylated pyrroles **xxi** was synthesized (Scheme 117).



Scheme 117. Hydroamination catalyzed by $ZnCl_2$.

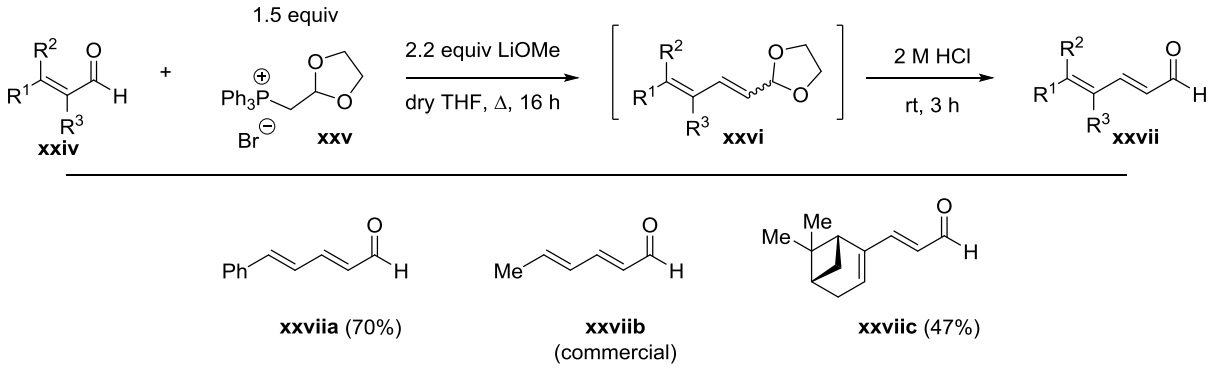
In order to further derivatize pyrroles **xxi**, lithiation of the aromatic ring followed by quenching with electrophiles was evaluated. This was done either directly using organolithium bases to deprotonate the pyrrole **xxi** or via bromination (**xxii**) and subsequent Li-Br exchange (methods A and B, Scheme 118). The latter approach was somewhat cleaner but in all cases it was very difficult to alkylate the pyrrole ring. Full deuteration to **xxiiia** was accomplished but reaction with other electrophiles than D_2O did not lead to full conversion. This was most likely due to steric hindrance caused by the vicinal bulky phosphonate group.



Scheme 118. Derivatization by lithiation.

Finally, brominated pyrroles **xxii** were subjected to a number of cross-coupling reactions under microwave irradiation. Sonogashira coupling failed, but Suzuki and Stille coupling reactions were more effective and resulted in coupling to sp-, sp^2- and sp^3-carbons. Nevertheless complete conversion was difficult to attain and chromatography was necessary to separate the products from residual starting material. In case of Suzuki coupling, there are indications that the actual mechanism was in fact a C-H activation instead of cross-coupling.

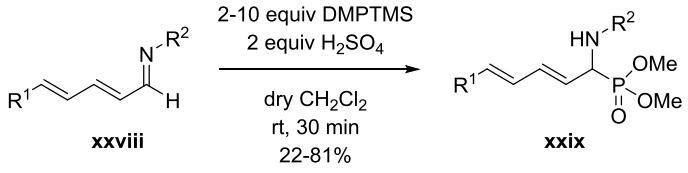
In a third part of this work the diphosphonylation of α,β-unsaturated aliphatic and aromatic imines was further extended to α,β,γ,δ-diunsaturated imines. In order to do so, the corresponding aldehyde precursors **xxvii** were required. These compounds were prepared by Wittig reaction from commercially available short-chain aldehydes **xxiv** like cinnamaldehyde (Scheme 119). The intermediate acetals existed as mixtures of *E*- and *Z*-isomers **xxvi** but after hydrolysis of the acetal, the desired *E*,*E*-product **xxvii** was obtained.



Scheme 119. Wittig reaction for the generation of diunsaturated aldehydes xxvii.

Subsequently these diunsaturated aldehydes **xxvii** were iminated. Employing standard conditions with $MgSO_4$ and an excess of amine resulted in imination but a considerable amount of 1,6- or 1,4-addition had taken place as well. Other imination procedures using $CuSO_4$ or $Ti(OEt)_4$ did not result in improvement. $MgSO_4$-mediated imination with 1 equivalent of amine was selected as the most suitable method.

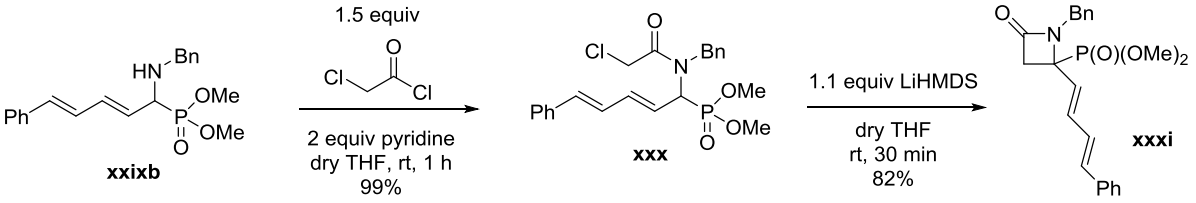
With α,β,γ,δ-diunsaturated imines **xxviii** in hand, the triaddition of two types of phosphorus nucleophiles was evaluated. First, dimethyl trimethylsilyl phosphite (DMPTMS) was applied as nucleophile in the presence of H_2SO_4 (Scheme 120). Surprisingly, this resulted in the clean conversion of diunsaturated imines into diunsaturated aminophosphonates **xxix**. No 1,6- or 1,4-addition had taken place, regardless of the steric bulk or electronic nature of R^2. Also, for the three types of substrates **xxviiia-c**, the R^1 group had no effect whatsoever on 1,6- or 1,4-addition with DMPTMS. In case R^2 = Ph though, 1,2-addition was followed by intermolecular substitution or a [5,5]-sigmatropic rearrangement and an isomeric compound was obtained. These results stand in sharp contrast to the previous work conducted at the department on phosphite addition to α,β-unsaturated imines.



Scheme 120. 1,2-addition of DMPTMS.

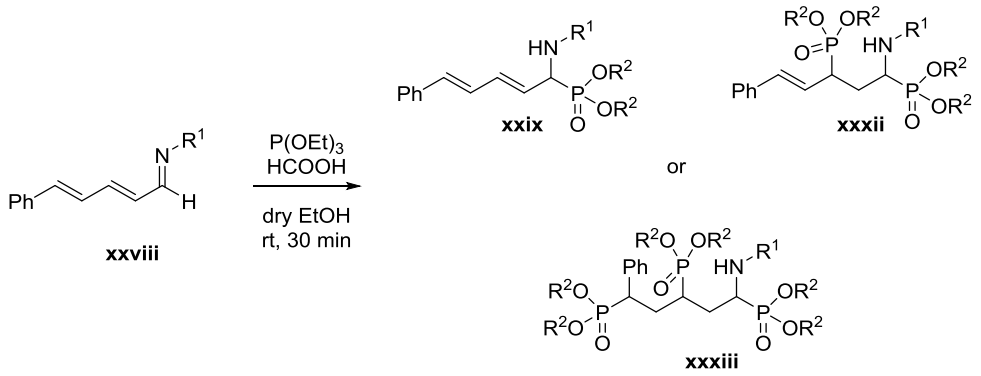
Based on the proposed mechanism for the tandem 1,4-1,2-addition, an explanation was sought to account for the lack of any 1,4- or 1,6-addition in this case. However, at this stage this is rather speculative and molecular modeling studies are underway to support the hypothesis.

The obtained aminophosphonates **xxix** were further acylated using chloroacetyl chloride (Scheme 121). Subsequent deprotonation and intramolecular substitution resulted in the formation of a phosphonylated β-lactam **xxxi** in good yield. Other attempts at derivatization of **xxix** failed.



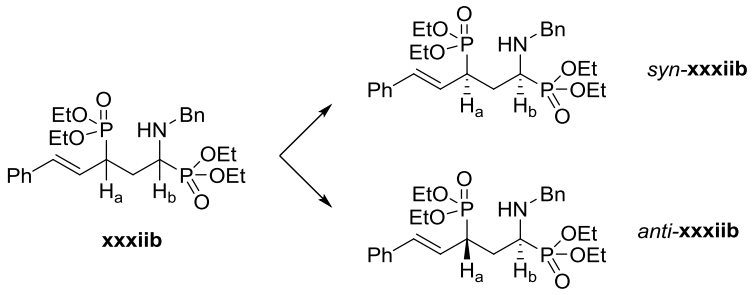
Scheme 121. Acylation of xxixb and formation of a β-lactam.

Upon application of another phosphorus nucleophile, *i.e.* triethyl phospite, instead of DMPTMS the result was rather different. In this case tandem 1,4-1,2-addition occurred, yielding **xxxii** as the major product (Scheme 122). Some monoadduct **xxix** was also present and in case of a sterically demanding R^1-group, traces of a triaddition product, possibly **xxxiii**, were formed. However, in all cases diphosphonylation to **xxxii** was the major pathway. This stands in sharp contrast to the addition of DMPTMS, where only monoaddition arose.



Scheme 122. Addition of triethyl phosphite to α,β,γ,δ-diunsaturated imines xxviii.

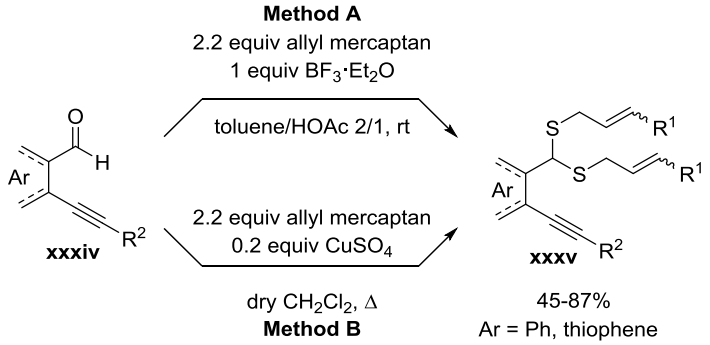
As a result of the diphosphonylation, two pairs of diastereomers were present in a 2/1 ratio for **xxxiib**. They were separated using preparative HPLC and the major diastereomer was assigned a *syn*-configuration based on a NOE experiment.



Scheme 123. Identification of *syn*- and *anti*-isomers.

The final part of this work aimed at preparing benzo[*c*]thiophenes using Au as a π-acid for a cycloisomerization. A number of halogen- or triflate-substituted benzaldehydes were subjected to Sonogashira coupling using TMS-acetylene or phenylacetylene. In case of TMS-protected substrates, the silyl group was cleaved off in order to produce terminal alkynes.

Next, these aromatic aldehydes **xxxiv** were converted into their corresponding diallyl thioacetals **xxxv** (Scheme 124). This was achieved using allyl or crotyl mercaptan in combination with a Lewis acid.



Scheme 124. Generation of dithioacetals.

With these compounds **xxxv** in hand, the envisioned Au-mediated cyclization toward benzo[*c*]thiophenes **xxxx** could be evaluated. A large number of catalysts was assessed and revealed that 5 mol% $AuCl_3$ was the most suited catalyst for this transformation. AuCl, $AuBr_3$ and $HAuCl_4$ also catalyzed the reaction but other monovalent Au-catalysts did not. Addition of 2,6-di-*t*-butylpyridine considerably slowed down the reaction while the use of $KAuCl_4$ under anhydrous conditions did not result in any conversion. These observations suggested that a trace of $HAuCl_4$ was formed *in situ* from $AuCl_3$ and moisture, as is known from literature.

In this case other superacids might also be able to catalyze this transformation, so the reaction was evaluated with TfOH. Surprisingly, this led to the formation of an intermediate that could be

converted into the desired benzo[*c*]thiophene upon work-up (Figure 21). Based on a number of spectral data, the intermediate was identified as **xxxvi**.

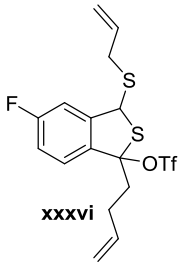
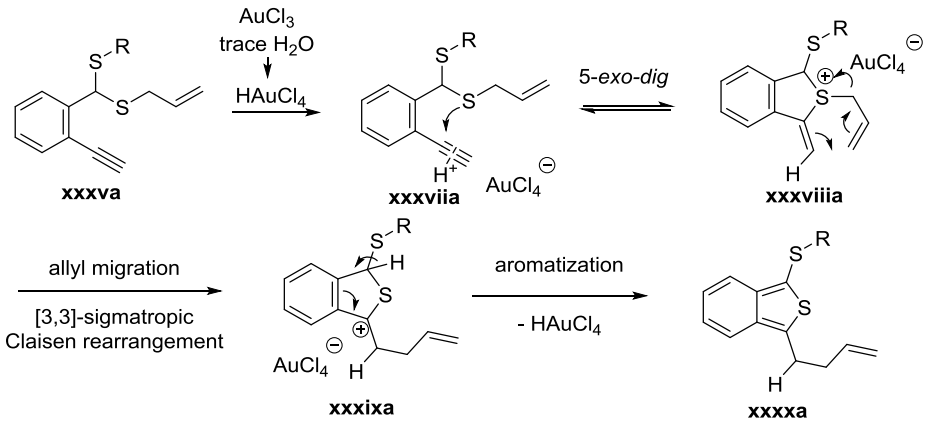


Figure 21. Isolated intermediate after treatment of xxxvc with TfOH.

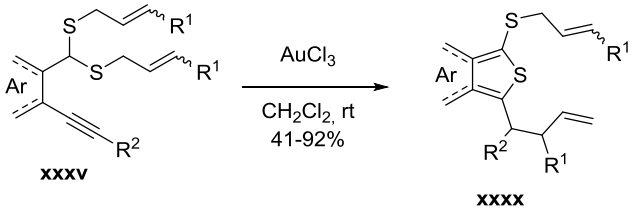
These observations suggested that a sufficiently strong acid could mediate the ring closure as well as the allyl migration, but a stoichiometric amount of acid was required as aromatization did not occur spontaneously. A solvent screening revealed that dichloromethane resulted in the best yields.

Based on this scrutiny, a mechanism was proposed for the transformation of diallyl thioacetals **xxxv** into benzo[*c*]thiophenes **xxxx** (Scheme 125). *In situ* generation of $HAuCl_4$ results in activation of the alkyne. Ring closure takes place in a 5-*exo*-*dig* fashion and is followed by a Claisen rearrangement. The concerted nature of this rearrangement was proven by using the crotyl derivative instead of the allyl group. This resulted solely in a branched product instead of a mixture of branched and linear products, which means no fragmentation took place. After allyl migration, aromatization takes place and the catalyst is regenerated.



Scheme 125. Mechanism of benzo[*c*]thiophene formation.

This transformation succeeded for all terminal alkynes (Scheme 126). Subjecting internal alkyne **xxxvj** to these optimized conditions however resulted in full recovery of starting material.



Scheme 126. Preparation of a library of benzo[*c*]thiophenes.

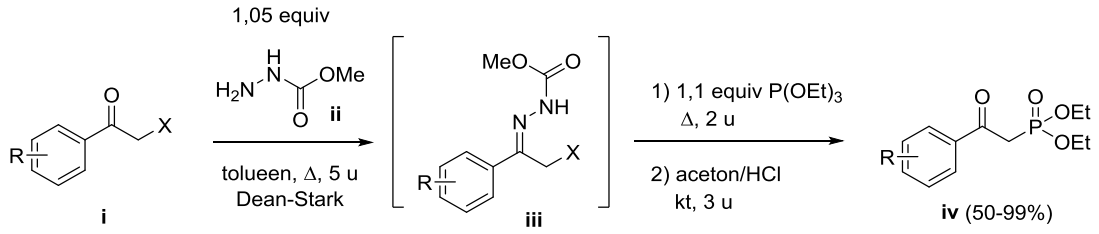
In summary, this work has resulted in the synthesis of 93 novel compounds and the development of innovative entries to aza- and thiaheterocyclic compounds. The retrosynthetically envisioned synthesis of phosphonylated pyrroles based on the chemistry of phosphono-azadienes failed but resulted in the discovery of an unexpected lithium-halogen exchange on an sp^3-carbon. In addition, this led to an intramolecular cyclopropanation with formation of an azabicyclic framework, which is difficult to straightforwardly access. Therefore, this methodology was explored and subsequently, another approach to phosphonylated pyrroles was developed based on a transition-metal catalyzed intramolecular hydroamination of phosphonylated alkynamines. This time the outlined strategy proved fruitful and tetrasubstituted pyrroles were obtained. Further derivatization of the pyrrole ring proved feasible employing Pd-based cross-coupling reactions.

Apart from these classes of unsaturated *N*-heterocycles, phosphonylated β-lactams could be accessed too. The results of the extension of earlier developed tandem phosphite addition reactions to α,β,γ,δ-diunsaturated imines surprisingly depended on the type of nucleophile. The obtained α-aminophosphonates could smoothly be converted into β-lactams. Finally, one class of thiaheterocycles was prepared using a Au-mediated cycloisomerization strategy from commercially available benzaldehydes. Scrutiny of the catalyst system and isolation of an intermediate revealed that a Au-assisted proton-driven mechanism was operative.

In retrospect, four classes of transformations were studied and in every chapter a number of valuable results were obtained, either from a synthetic or mechanistic viewpoint. Many of these results have engendered new opportunities or raised other questions, which ensure plenty of room for the further elaboration of certain parts of this work.

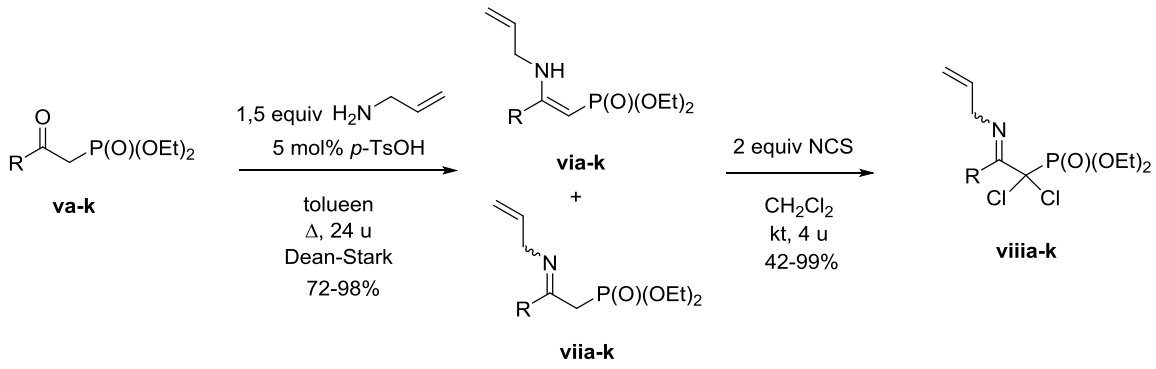
VII. Samenvatting

Gezien de ervaring in de SynBioC onderzoeksgroep omtrent de heteroatoom transfer radicalaire cyclisatie (HATRC) methodologie en gezien de interessante biologische eigenschappen van aminofosfonaten, werd een synthetische route tot 3-fosfonopyrrolen ontworpen met als belangrijkste stap een HATRC. De bereiding van het startmateriaal voor de HATRC werd uitgevoerd in drie stappen (Schema 1). De benodigde β-ketofosfonaten **iv** werden gesynthetiseerd uit α-haloketonen **i** gebruik makend van een Michaelis-Arbuzov reactie. Om de ongewenste Perkow reactie tegen te gaan, *i.e.* een nevenreactie die leidt tot enolfosfaten, werden de α-haloketonen **i** getransformeerd tot de overeenkomstige hydrazonen **iii**. Voor erg elektronarme substraten werd een andere methode aangewend om Perkow reactie te voorkomen, gebaseerd op de acylering van fosfonoazijnzuur en de daaropvolgende decarboxylering.



Schema 1. Vorming van β-ketofosfonaten.

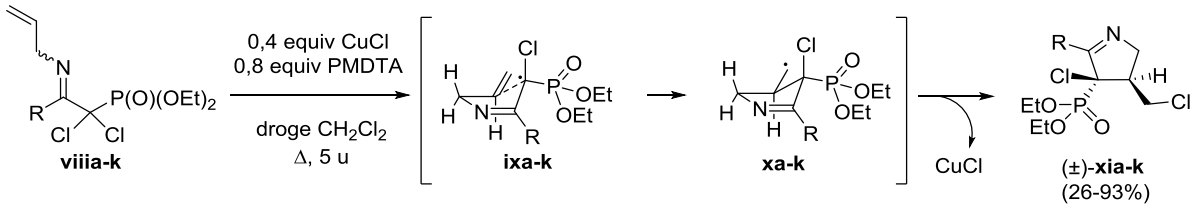
Na Michaelis-Arbuzov reactie en hydrolyse werden de bekomen β-ketofosfonaten **iv** onderworpen aan iminering onder Dean-Stark condities (Schema 2). Dit resulteerde vlot in een mengsel van de gewenste enamines **vi** en imines **vii**, in een verhouding van 1/1 tot 4/1. De enamines **vi** waren enkel aanwezig in de *Z*-vorm omwille van intramoleculaire H-brugvorming. De imines **vii** werden gevormd in zowel de *E*- als *Z*-vorm in een verhouding van 1/1 tot 9/1. Vervolgens werden de ruwe mengsels behandeld met NCS, wat resulteerde in α,α-dichlorering tot imines **viii**.



Schema 2. Iminering en α,α-dichlorering.

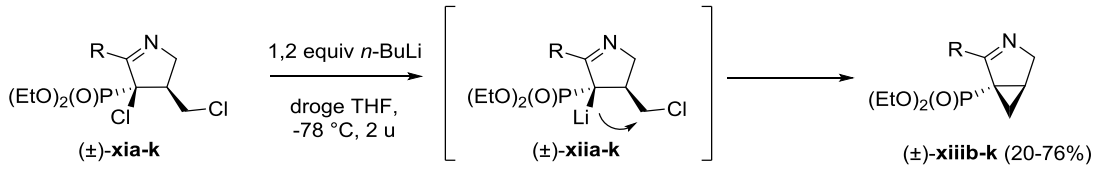
Met deze *N*-allyl α,α-dichloorimines **viii** ter beschikking werd de HATRC geëvalueerd, hetgeen resulteerde in de vorming van de gewenste 1-pyrrolines **xi** (Schema 3). Opmerkelijk was het feit dat

deze transformatie doorging met een grote diastereoselectiviteit (9/1 verhouding). Na opzuivering bleef enkel het major diastereomeer over en werd geprobeerd de relatieve stereochemie te achterhalen. Een 2D-NOESY experiment toonde geen NOE aan tussen de ethoxygroepen van het fosfonaat en de CH van het pyrroline, terwijl een heteronucleaire NOESY (HOESY) ook geen extra infomatie verschafte. In een poging om $^{3}J_{HP}$ te bepalen werd een aantal ^{1}H-onontkoppelde ^{31}P-NMR spectra opgenomen waarin de overlappende protonen verzadigd werden. Hieruit werd geconcludeerd dat $^{3}J_{HP}$ 11.2 Hz was. Jammer genoeg kon dit resultaat geen uitsluitsel geven over de relatieve configuratie van de producten. Gelukkig, echter, waren de twee laatst gesynthetiseerde derivaten kristallijn en wees X-straaldiffractie uit dat de relatieve configuratie van **xi** *cis* was. Dit was hoogstwaarschijnlijk te wijten aan de pseudo-equatoriale positie van het bulky fosfonaat in de transitietoestand **ix**, om de sterische repulsie met de andere substituenten te minimaliseren.



Schema 3. HATRC met vorming van *cis*-diastereomeren.

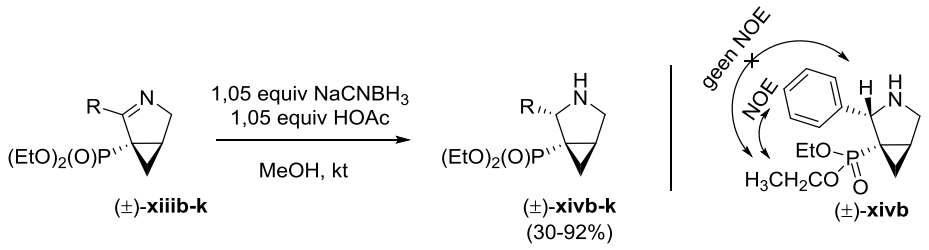
Vervolgens zou behandeling van **xi** met base moeten resulteren in een 1,4-dehydrohalogenering en vorming van de beoogde 3-fosfonopyrrolen. Echter, na behandeling met een aantal basen werd enkel startmateriaal gerecupereerd. Na gebruik van *n*-BuLi echter werd een nieuw product gevormd, maar niet het verhoopte pyrrool (Schema 4). In de plaats werd de structuur bepaald als bicyclisch product **xiii** en een mogelijk mechanisme voor de vorming hiervan werd voorgesteld. Niet de gewenste 1,4-dehydrohalogenering maar een Li-Cl uitwisseling tot **xii** had plaatsgevonden waarna intramoleculaire substitutie resulteerde in cyclopropanering. Gezien deze conversie innovatief was, werd ze verder uitgewerkt ten koste van de oorspronkelijk beoogde pyrroolsynthese.



Schema 4. Onvoorziene cyclopropanering door middel van Li-Cl uitwisseling.

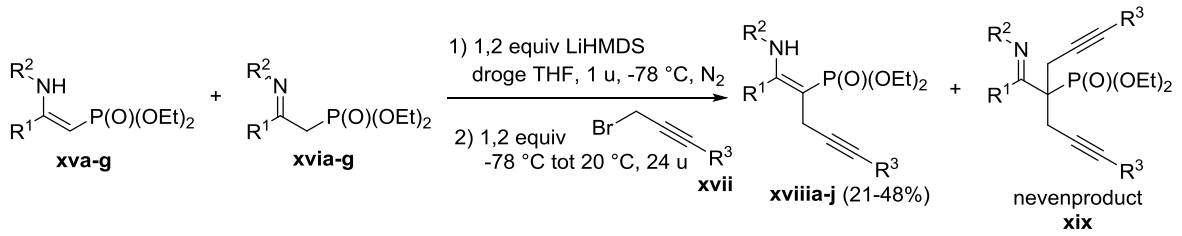
Vervolgens werd de iminebinding gereduceerd met $NaCNBH_3$ en HOAc, hetgeen resulteerde in azabicyclo[3.1.0]hexanen **xiv** (Schema 5). Een 2D-NOESY experiment toonde aan dat deze reductie evenzeer doorging op een erg diastereoselectieve manier. Dit was hoogstwaarschijnlijk opnieuw te wijten aan de grote fosfonaatgroep. Na reductie werd gepoogd een intramoleculaire debenzylering

te bewerkstelligen om zo gefosfonyleerde aminomethylcyclopropanen te bekomen. Echter, alle pogingen in deze richting faalden.



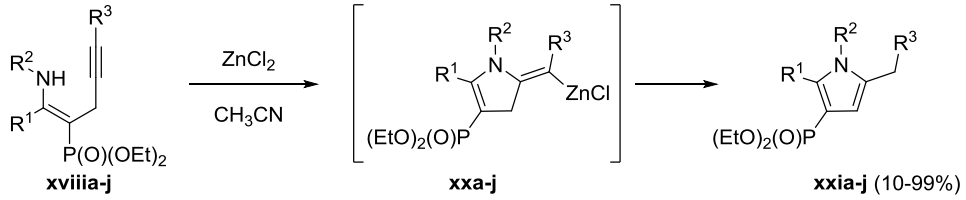
Schema 5. Reductie van het imine en 2D-NOESY.

Aangezien de beoogde synthese van 3-fosfonopyrrolen had gefaald, werd een andere syntheseroute ontworpen gebaseerd op π-zuur katalyse. Net zoals in de voorgaande poging verliep de iminering vlot en werd opnieuw een mengsel van enamines **xv** en imines **xvi** bekomen. Vervolgens werd gepoogd een propargylgroep te introduceren door het overeenkomstige aza-enolaat te genereren met behulp van LiHMDS en te quenchen met propargyl bromide **xvii** (Schema 6). Deze methode was succesvol maar het was moeilijk om volledige conversie te bekomen. Additie van extra base en elektrofiel resulteerde in mengsels van mono- en digepropargyleerde producten **xviii** en **xix**. Deze verbindingen **xviii** waren aanwezig als enamines in de *Z*-vorm ten gevolge van intramoleculaire H-brugvorming.



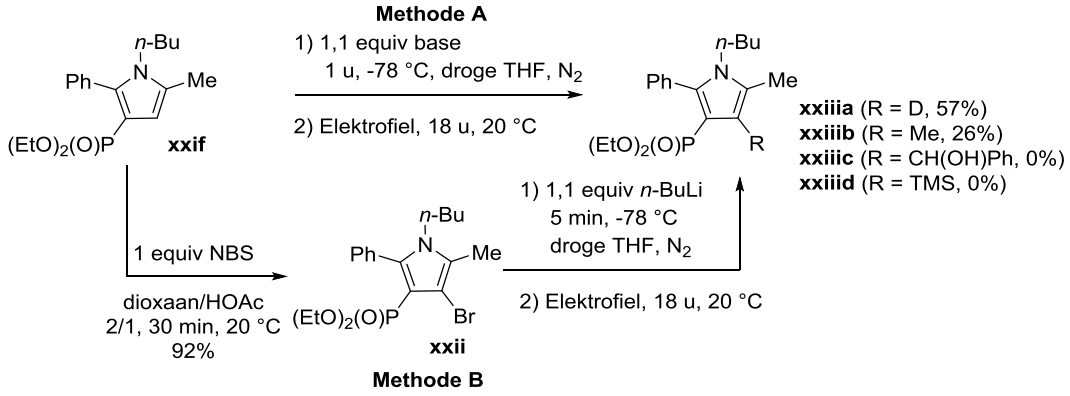
Schema 6. Introductie van een propargylgroep.

Na opzuivering werd een aantal π-zuren geëvalueerd voor de beoogde hydroaminering van **xviii**. Zowel 20 mol% $ZnCl_2$ als $AgNO_3$ waren effectief als katalysator maar $AgNO_3$ was veel sneller. Echter, bij het verminderen van de hoeveelheid katalysator nam de reactietijd toe en trad enige degradatie op in het geval van $AgNO_3$. Deze observatie, in combinatie met de veel hogere kostprijs van Ag dan Zn, resulteerde in de keuze voor 5 mol% $ZnCl_2$ als π-zure katalysator. Deze methode werkte vlot voor terminale alkynen maar interne alkynen waren minder reactief. Een grotere hoeveelheid katalysator alsook refluxtemperatuur waren nodig om de ringsluiting te bewerkstelligen. Gebruik makend van deze hydroaminering werd een bibliotheek gefosfonyleerde pyrrolen gesynthetiseerd (Schema 7).



Schema 7. Hydroaminering gekatalyseerd door $ZnCl_2$.

Om de pyrrolen **xxi** verder te derivatiseren werd de aromatische ring achtereenvolgens gelithieerd en gequencht met elektrofielen (Schema 8). Dit werd ofwel direct uitgevoerd door deprotonering met behulp van organolithiumbasen, ofwel via bromeren tot **xxii** en daaropvolgende Li-Br uitwisseling (methodes A en B). De laatste aanpak bleek iets zuiverder maar in alle gevallen was het erg moeilijk om de pyrroolring te alkyleren. Volledige deuterering werd bekomen maar reactie met andere elektrofielen dan D_2O leidde niet tot volledige conversie. Dit had waarschijnlijk te maken met de sterische hinder die veroorzaakt werd door de grote vicinale fosfonaatgroep.

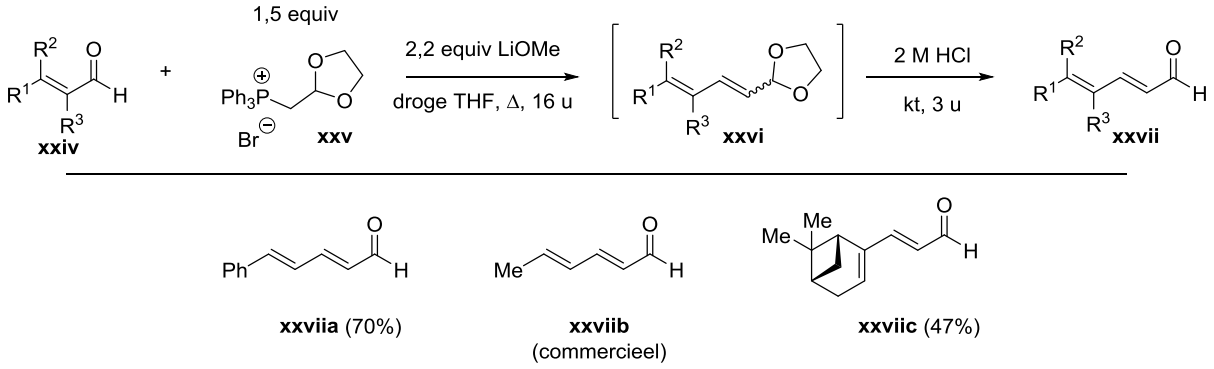


Schema 8. Derivatisering door lithiëring.

Uiteindelijk werden de gebromeerde pyrrolen **xxii** onderworpen aan een aantal koppelingsreacties onder microgolfbestraling. Sonogashirakoppeling faalde, maar Suzuki- en Stillekoppeling waren efficiënter en resulteerden in koppeling met sp-, sp^2- en sp^3-koolstofatomen. Desondanks was het moeilijk om volledige conversie te bekomen en was chromatografie vereist om de producten te scheiden van het residuele startmateriaal. In geval van de Suzukikoppeling zijn er aanwijzingen dat het eigenlijke werkingsmechanisme veeleer een C-H activatie was dan een koppelingsreactie.

In een derde gedeelte van dit werk werd de difosfonylering van α,β-onverzadigde alifatische en aromatische imines verder uitgebreid naar α,β,γ,δ-dionverzadigde imines. Daartoe waren de overeenkomstige aldehydeprecursoren **xxvii** nodig. Deze verbindingen werden gesynthetiseerd aan de hand van een Wittig reactie uitgaande van commercieel beschikbare kortketen aldehyden **xxiv**

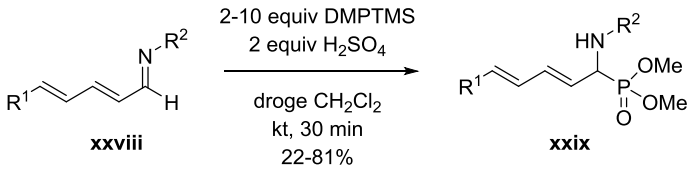
zoals cinnamaldehyde (Schema 9). De intermediaire acetalen bestonden als mengsels van *E*- en *Z*-isomeren **xxvi** maar na acetaalhydrolyse werd uitsluitend het gewenste *E*,*E*-isomeer **xxvii** bekomen.



Schema 9. Wittig reactie voor de vorming van dionverzadigde aldehyden.

Vervolgens konden deze dubbel onverzadigde aldehyden **xxvii** geïmineerd worden. Gebruik makend van standaardcondities met $MgSO_4$ en een overmaat amine werden imines bekomen naast een aanzienlijke hoeveelheid 1,6- of 1,4-adduct. Andere imineringsprocedures gebruik makend van $CuSO_4$ of $Ti(OEt)_4$ resulteerden niet in een verbetering. De methode gebruik makend van $MgSO_4$ in combinatie met 1 equivalent amine werd geselecteerd als de meest geschikte methode.

Met deze α,β,γ,δ-dionverzadigde imines **xxviii** ter beschikking werd de drievoudige additie van twee types fosfornucleofielen geëvalueerd. Eerst werd dimethyl trimethylsilyl fosfiet (DMPTMS) gebruikt als nucleofiel in de aanwezigheid van H_2SO_4. Verrassend genoeg resulteerde dit in een vlotte conversie van dionverzadigde imines in dionverzadigde aminofosfonaten **xxix** (Schema 10). Geen 1,6- of 1,4-additie had plaatsgevonden, ongeacht de sterische bulk of de elektronsiche aard van R^2. Bovendien had de R^1 groep voor geen enkele van de drie types substraten een invloed op 1,6- of 1,4-additie met DMPTMS. Echter, voor R^2 = Ph werd 1,2-additie gevolgd door intermoleculaire substitutie of [5,5]-sigmatrope omlegging en werd een isomere verbinding bekomen. Deze resultaten staan in schril contrast tot het vorige werk over fosfietaddities aan α,β-onverzadigde imines dat werd uitgevoerd aan de onderzoeksgroep.

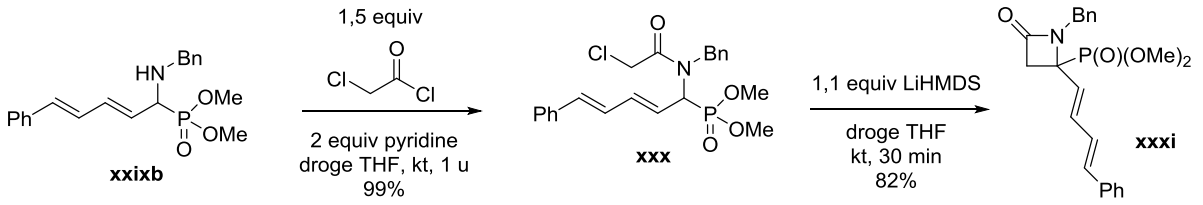


Schema 10. 1,2-additie van DMPTMS.

Gebaseerd op het voorgestelde mechanisme voor de tandem 1,4-1,2-additie werd een verklaring gezocht voor het gebrek aan 1,4- of 1,6-additie in dit geval. Hoewel, momenteel is dit speculatief en

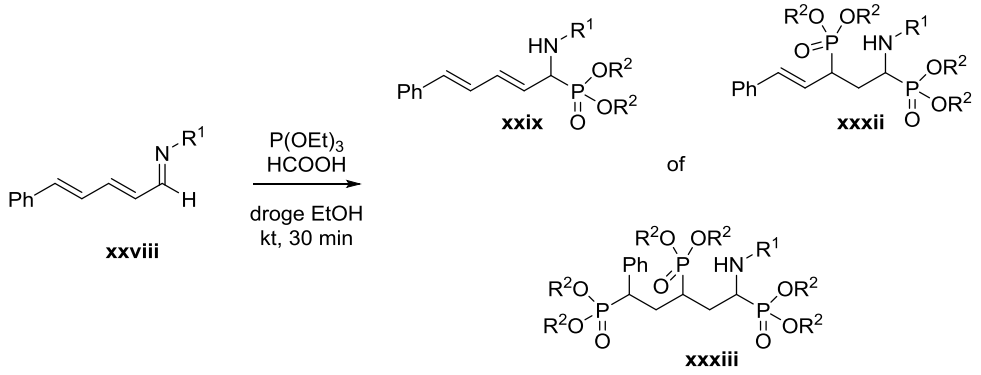
moleculaire modellering studies worden op dit ogenblik uitgevoerd om de hypothese te ondersteunen.

De bekomen aminofosfonaten **xxix** werden verder geacyleerd met behulp van chlooracetyl chloride (Schema 11). Daaropvolgende deprotonering en intramoleculaire substitutie resulteerden in de vorming van een gefosfonyleerd β-lactam **xxxi** in een goed rendement. Andere pogingen om **xxix** verder te derivatiseren, faalden.



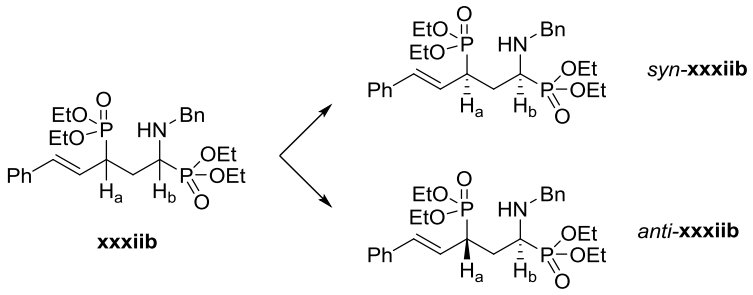
Schema 11. Acylering van xxixb en vorming van een β-lactam xxxi.

Bij gebruik van een ander fosfornucleofiel, zijnde triëthyl fosfiet in plaats van DMPTMS, was het resultaat enigszins anders (Schema 12). In dit geval trad tandem 1,4-1,2-additie op en **xxxii** was het majorproduct. Er was eveneens wat monoadduct **xxix** aanwezig en bij sterisch gehinderde R-groepen werd een spoor triadduct, mogelijks **xxxiii**, waargenomen. Echter, in alle gevallen was difosfonylering tot **xxxii** de voornaamste reactieweg. Dit stond in schril contrast met de additie van DMPTMS, waar alleen monoadditie tot **xxix** optrad.



Schema 12. Additie van triëthyl fosfiet aan onverzadigde imines xxviii.

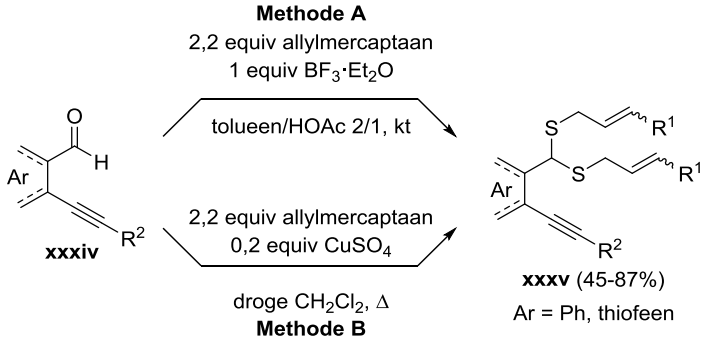
Als gevolg van de difosfonylering waren twee paren diastereomeren aanwezig in een 2/1 verhouding voor **xxxiib**. Ze werden gescheiden met behulp van preparatieve HPLC en het major diastereomeer werd de *syn*-configuratie toegewezen gebaseerd op een NOE experiment (Schema 13).



Schema 13. Identificatie van *syn*- en *anti*-isomeren.

Het laatste deel van dit werk beoogde de bereiding van benzo[*c*]thiofenen met behulp van Au als π-zuur voor een cycloisomerisatie. Een aantal benzaldehydes gesubstitueerd met een halogeen of een triflaat in *ortho*-positie werd onderworpen aan Sonogashirakoppeling gebruik makend van TMS-acetyleen of fenylacetyleen. In het geval van TMS-beschermde substraten werd de silylgroep verwijderd om terminale alkynen te bekomen.

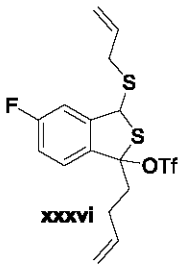
Vervolgens werden deze aromatische aldehyden **xxxiv** omgezet in hun overeenkomstige diallyl thioacetalen (Schema 14). Dit werd bereikt gebruikmakend van allyl- of crotylmercaptaan in combinatie met een Lewiszuur.



Schema 14. Vorming van dithioacetalen.

Met deze verbindingen **xxxv** ter beschikking kon de beoogde Au-gekatalyseerde cyclisatie tot benzo[*c*]thiofenen **xxxx** geëvalueerd worden. Een groot aantal aan katalysatoren werd getest en dit toonde aan dat 5 mol% $AuCl_3$ de meest geschikte katalysator was voor deze transformatie. AuCl, $AuBr_3$ en $HAuCl_4$ katalyseerden de reactie ook, maar andere monovalente Au-species deden dit niet. Additie van 2,6-di-*t*-butylpyridine vertraagde de reactie aanzienlijk terwijl het gebruik van $KAuCl_4$ onder droge omstandigheden niet resulteerde in enige omzetting. Deze observaties suggereerden dat een spoor $HAuCl_4$ *in situ* gevormd was uitgaande van $AuCl_3$ en vocht, zoals beschreven in de literatuur.

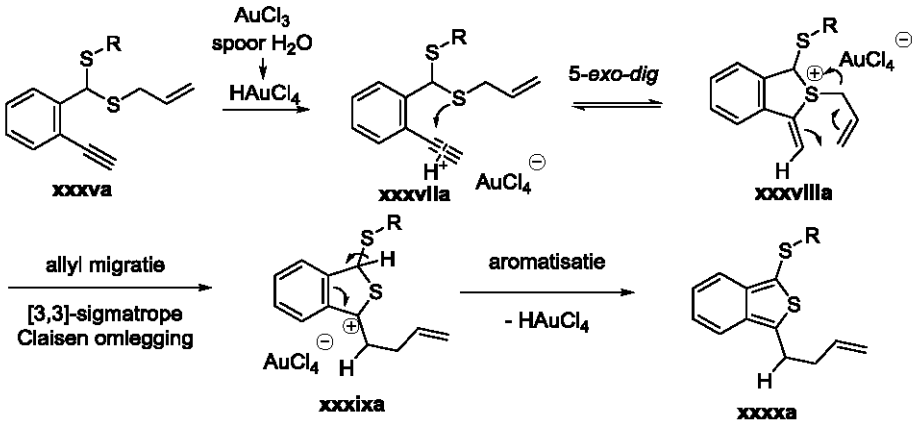
In dit geval konden andere superzuren deze omzetting mogelijks ook katalyseren, dus werd de reactie met TfOH geëvalueerd. Verrassend genoeg leidde dit tot de vorming van een intermediair dat kon omgezet worden tot het beoogde benzo[*c*]thiofeen bij opwerking. Gebaseerd op een aantal spectrale data werd het intermediair geïdentificeerd als **xxxvi** (Figuur 1).



Figuur 1. Geïsoleerd intermediair na behandeling van xxxvc met TfOH.

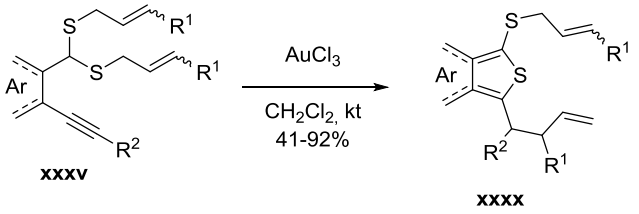
Deze observaties suggereerden dat een voldoende sterk zuur de ringsluiting en allylmigratie kon bewerkstelligen, maar dat een stoichiometrische hoeveelheid zuur nodig was aangezien aromatisering niet spontaan optrad. Een solventscreening toonde aan dat dichloormethaan het meest geschikte solvent was.

Gebaseerd op deze analyse werd een mechanisme voorgesteld voor de omzetting van diallyl thioacetalen **xxxv** naar benzo[*c*]thiofenen **xxxx** (Schema 15). *In situ* vorming van $HAuCl_4$ resulteert in activering van het alkyn. Ringsluiting treedt op via 5-*exo*-*dig* cyclisatie en wordt gevolgd door een Claisen omlegging. De geconcerteerde aard van deze omlegging werd bewezen door het crotylderivaat te gebruiken in plaats van een allylderivaat. Dit resulteerde selectief in een vertakt product in plaats van een mengsel van vertakt en lineair product, hetgeen aantoont dat geen fragmentatie plaatsgreep. Na allylmigratie treedt aromatisering op en wordt de katalysator geregenereerd.



Schema 15. Mechanisme van benzo[*c*]thiofeenvorming.

Deze transformatie slaagde voor alle terminale alkynen (Schema 16). Intern alkyn **xxxvj** blootstellen aan deze geoptimaliseerde contities, echter, resulteerde alleen in recuperatie van startmateriaal.



Schema 16. Bereiding van een bibliotheek aan benzo[*c*]thiofenen.

Samengevat heeft dit werk geresulteerd in de synthese van 93 nieuwe verbindingen en de ontwikkeling van innovatieve toetredingen tot aza- en thiaheterocyclische verbindingen. De retrosynthetisch beoogde synthese van gefosfonyleerde pyrrolen gebaseerd op de chemie van de fosfonoazadiënen faalde, maar heeft geresulteerd in de ontdekking van een onverwachte lithium-halogeen uitwisseling op een sp^3-koolstof. Bovendien heeft dit geleid tot een intramoleculaire cyclopropanering met vorming van een azabicyclisch skelet dat anders moeilijk te bekomen is. Bijgevolg werd een andere toenadering tot gefosfonyleerde pyrrolen ontwikkeld gebaseerd op een transitie-metaal gekatalyseerde intramoleculaire hydroaminering van gefosfonyleerde alkynamines. Dit keer was de beoogde strategie succesvol en tetragesubstitueerde pyrrolen werden bekomen. Verdere derivatisatie van de pyrroolring was mogelijk gebruik makend van Pd-gebaseerde koppelingsreacties.

Naast deze klassen onverzadigde *N*-heterocyclische verbindingen konden gefosfonyleerde β-lactamen ook gemaakt worden. De resultaten van de uitbreiding van eerder ontwikkelde tandem fosfietadditiereacties aan α,β,γ,δ,-dionverzadigde imines hingen verrassend genoeg af van het type nucleofiel. De bekomen α-aminofosfonaten konden vlot worden omgezet naar β-lactamen. Tot slot werd een klasse thiaheterocyclische verbindingen gesynthetiseerd gebruik makend van Au-gekatalyseerde cycloisomerisatie uitgaande van commercieel beschikbare benzaldehydes. Nauwkeurige analyse van het katalytisch systeem en isolering van een intermediair toonde aan dat een Au-geassisteerd proton-gedreven mechanisme werkzaam was.

Terugblikkend op dit werk werden vier klassen aan transformaties bestudeerd en in elk hoofstuk werd een aantal waardevolle resultaten behaald, vanuit een synthetisch of mechanistisch standpunt. Veel van deze resultaten hebben nieuwe opportuniteiten voortgebracht of andere vragen opgeroepen, die meer dan genoeg ruimte laten voor de verdere uitwerking van bepaalde delen van dit werk.

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Curriculum vitae

PERSONALIA

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EDUCATION

2011-2015 PhD student (FWO aspirant)

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PhD Thesis: "Innovative synthesis of phosphonylated azaheterocycles and benzo[*c*]thiophenes"

Promoter: Prof. Dr. ir. Christian Stevens

2009-2011 Master in Bioscience Engineering: Chemistry & Bioprocess Technology (graduated with greatest distinction)

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2009 Internship at Proviron Fine Chemicals NV (Oostende, August-September)

2006-2009 Bachelor in Bioscience Engineering: Chemistry and Food Technology

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2004-2006 Immaculata Instituut, De Panne (Latin-Sciences)

2000-2004 Sint-Bernarduscollege, Nieuwpoort (Latin)

SCIENTIFIC PUBLICATIONS

INTERNATIONAL PEER-REVIEWED JOURNALS (A1)

1. **Wouter Debrouwer**, Ruben A. J. Seigneur, Thomas S. A. Heugebaert, Christian V. Stevens. Gold superacid-catalyzed preparation of benzo[*c*]thiophenes, *Chem. Commun.* **2015**, *51*, 729-732.
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2. Frederik E. A. Van Waes, **Wouter Debrouwer**, Thomas S. A. Heugebaert, Christian V. Stevens. On the discovery and development of tandem 1,4- and 1,2-addition of phosphites to 1-azadienes, *Arkivoc* **2014** *(i)*, 386-427.

3. Iris Wauters, **Wouter Debrouwer**, Christian V. Stevens. Preparation of phosphines through C–P bond formation, *Beilstein J. Org. Chem.* **2014**, *10*, 1064–1096.

4. **Wouter Debrouwer**, Thomas S. A. Heugebaert, Christian V. Stevens. Preparation of tetrasubstituted 3−phosphonopyrroles through hydroamination: scope and limitations, *J. Org. Chem.* **2014**, *79*, 4322−4331.
   Highlighted in *Synfacts* **2014,** *10*, 0801.

5. **Wouter Debrouwer**, Thomas S. A. Heugebaert, Kristof Van Hecke, Christian V. Stevens. Synthetic entry into 1-phosphono-3-azabicyclo[3.1.0]hexanes, *J. Org. Chem.* **2013**, *78*, 8232−8241. Featured Article.

6. Ann De Blieck, Saron Catak, **Wouter Debrouwer**, Józef Drabowicz, Karen Hemelsoet, Toon Verstraelen, Michel Waroquier, Veronique Van Speybroeck, Christian V. Stevens. Diphosphonylation of aromatic diazaheterocycles and theoretical rationalization of product yields, *Eur. J. Org. Chem.* **2013**, *6*, 1058–1067.

BOOKS (B2)

7. **Wouter Debrouwer**, Iris Wauters, Christian V. Stevens. Methods for the introduction of the phosphonate moiety into complex organic molecules. *In press*, John Wiley & Sons.

ACTIVE PARTICIPATION AT CONFERENCES

1. 18th Sigma-Aldrich Symposium (SAS), December 4-5, 2014, Blankenberge, Belgium.
   Poster presentation: **Wouter Debrouwer**, Ruben A. J. Seigneur, Thomas S. A. Heugebaert, Christian V. Stevens. Gold superacid-catalyzed synthesis of benzo[*c*]thiophenes.

2. 14th Belgian Organic Synthesis Symposium (BOSS XIV), July 13-18, 2014, Louvain-La-Neuve, Belgium.
   Poster presentation: **Wouter Debrouwer**, Thomas S. A. Heugebaert, Christian V. Stevens. Preparation of tetrasubstituted 3-phosphonopyrroles through hydroamination and subsequent cross-coupling: Scope and limitations.

3. 20th International Conference on Phosphorus Chemistry (ICPC 2014), June 28-July 2, 2014, Dublin, Ireland.
   Poster presentation: **Wouter Debrouwer**, Thomas S. A. Heugebaert, Christian V. Stevens. Preparation of tetrasubstituted 3-phosphonopyrroles through hydroamination: scope and limitations.

4. 16th Sigma-Aldrich Symposium (SAS), December 6-7, 2012, Spa, Belgium.
   Poster presentation: **Wouter Debrouwer**, Christian V. Stevens. A concise new entry to phosphonylated azabicycles.

5. 12th international symposium on selected problems of chemistry of acyclic and cyclic heteroorganic compounds, November 15, 2012, Częstochowa, Poland.
   Oral Presentation: New entries to phosphonylated azaheterocycles.

6. 15th international symposium on advances in the chemistry of heteroorganic compounds, November 16, 2012, Łódź, Poland.
   Oral Presentation: New entries to phosphonylated azaheterocycles.

7. 19th International Conference on Phosphorus Chemistry (ICPC 2012), July 8-12, 2012, Rotterdam, The Netherlands.

   Poster presentation: Ann De Blieck, Saron Catak, **Wouter Debrouwer**, Toon Verstraelen, Józef Drabowicz, Veronique Van Speybroeck, Michel Waroquier, Christian V. Stevens. Diphosphonylation of aromatic diazaheterocycles and theoretical rationalization of product yields.

Yes, in 1917, when Albert Einstein established the theoretic foundation for the laser in his paper “Zur Quantentheorie der Strahlung,” his fondest hope was that the resulting device be “bitchin’.”

- Sheldon Cooper