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ensCM CHIMIE Montpellier

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FACULTY OF CHEMISTRY

DEPARTMENT OF BIOORGANIC CHEMISTRY

Ph.D. Thesis

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„β-Enaminones, alkenylphosphonates and alkenylphosphinates as substrates in cyclization reactions"

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For my Family

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EXPERIMENTAL SECTION

ABBREVIATIONS

Units

°C	Celsius degrees
g, mg	gram, milligram
L, mL	litr, millilitr
mol, mmol	mole, millimole
eq, equiv.	equivalent
m/z	mass-to-charge ratio
ppm	parts per million
Hz, MHz	hertz, megahertz

Chemical groups

Ac	acetyl
AIBN	azobisisobutyronitrile
All	allyl
PTSA	*p*-toluenesulfonic acid
Ar	aryl
Bn	benzyl
Cbz (or Z)	benzyl carbamate
cod	1,5-cyclooctadiene
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DMAP	4-dimethylaminopyridine
dmpe	1,2-Bis(dimethylphosphino)ethane
DMF	dimethylformamide
DPEphos	Bis(2-diphenylphosphinophenyl)ether
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDA	ethylenediamine
Et	ethyl
EWG	electrowithdrawing group
i-Pr	isopropyl
Me	methyl
n-Bu	butyl (linear)
n-BuLi	*n*-butyllithium
n-Pent	pentyl (linear)
NuH	nucleophile
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
t-Bu	*tert*-butyl
t-BuOK	potassium *tert*-butylate
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran

TBS	*tert*-butyldimethylsilyl
TBTP	tetraphenylphosphonium tetraphenylborate
TMS	trimethylsilyl
Triphos	Bis(diphenylphosphinoethyl)phenylphosphine
Ts	tosyl
xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Instruments and analysis

TLC	thin layer chromatography
COSY	Correlation spectroscopy
ESI	ionization par electrospray
FT-IR	Fourrier transform Infrared spectroscopy
GC	gas chromatography
HMQC	Heteronuclear Multiple Quantum Correlation
HRMS	high resolution mass spectrometry
MS	mass spectrometry
NOESY	Nuclear Overhauser Effect Spectroscopy
Mp	melting point
NMR	nuclear magnetic resonance
UV	ultraviolet
s	singulet
d	doublet
t	triplet
q	quadruplet
quint	quintuplet
sext	sextuplet
hept	heptuplet
m	multiplet
brs	broad singlet
dd	double of doublets
dt	double of triplets
δ	chemical shift
J	coupling constant

Other abbreviations

aq.	aqueous
cat.	catalytic quantity
Δ	heating
ee	enantiomeric excess
h	hour
min	minute
NuH	nucleophil
R_f	retention value
SN	nuclephilic substitution
rt	room temperature
MW	microwaves irradiation

GENERAL INTRODUCTION

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, they are found in numerous natural products and molecules biogically active. Therefore, they value is very precious in medicinal chemistry and agrochemistry. The importance of those structures draws significant attention of the scientists. For this reason, the research focuses on the development of new, atom-economical methodologies. Search for the selective and efficient tools towards synthesis of heterocycles led, among the other methods, to the application of transition metal catalysis. Catalytic quantity of palladium, rhodium, platinum, copper, gold or iron allow the formation of carbon-carbon bond or carbon-heteroatom efficiently and selectively.

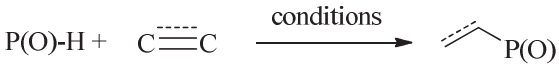
The work described herein will focus on the two heterocyclic synthetic pathways. The first one lays in the organophosphorus chemistry. In ***Chapter I***, numerous methodologies towards the synthesis of phosphonates and phosphinates will be explained. The significance of metal-catalyzed hydrophosphonylation/hydrophosphinylation reactions will be described. ***Chapter II*** stands for the experimental exploration of metal-catalyzed intramolecular and intermolecular P-C bond formation.

In ***Chapter III*** the attention will be turned to the base-catalyzed Cbz-protected β-enaminones and their subsequent implementation in the cyclization reaction towards 2,4,6-trisubstituted pyrimidines.

Chapter I

EXPLORING INTERMOLECULAR HYDROPHOSPHINYLATION AND HYDROPHOSPHONYLATION

The following chapter describes the scope of the metal-catalyzed reactions, which provide the phosphinates and phosphonates from unsaturated C-C bonds (*Scheme 1.1*).



Scheme 1.1

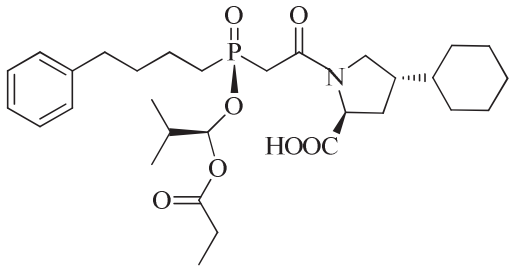
In the light of existing literature, the following objectives will be considered:

- the introduction of the term of hydrophosphonylation and hydrophosphinylation (*Scheme1.1*),
- the elucidation of the reaction mechanisms,
- the application of the catalytic systems to prepare useful products.

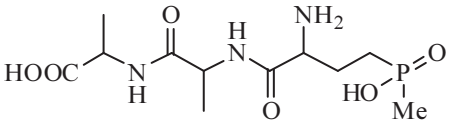
1. The significance of organophosphorous compounds.

The remarkable importance of the organophosphorous compounds is well-established in medicine, agriculture or nanotechnology. For that reason, it has become crucial to search for new atom-economical methods that provide new families of organophosphorous structures. Structures with P-C bond, including phosphinates and phosphonates, provide drugs (antibacterial, antiviral and antitumor agents, compounds against osteoporosis) and pesticides. Many others appeared to be anticorrosive agents, dispersants, detergents and plastic components. Phosphorus-containing flame retardants are widely used in standard and engineering plastics, polyurethane foams, thermosets, coatings, and textiles. We may say that organophosphorus chemistry touches every area of human life. Some of the most known and useful structures are shown below.[1]

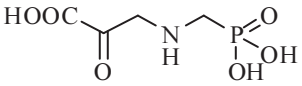
[1] a) Mastalerz P., Kafarski P., *Aminophosphonic and Aminophosphinic Acids*, J Wiley & Sons Ed., **2000**, *1*, 1; b) Fields S. C., *Tetrdahedron*, **1999**, *55,* 12237; c) Kafarski P., Lejczak B., *Phosphorous, Sulfur and Silicon*, **1991**, *63*, 193



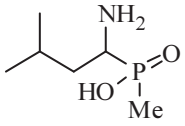
Fosinopril ® Angiotensin converting enzyme (ACE) inhibitor



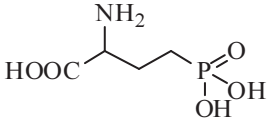
Bialaphos - natural herbicide



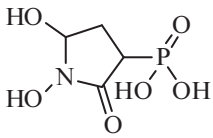
Glyphosate Roundup® - herbicide



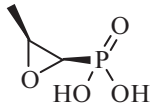
Analogue of leucine -
Leucine aminopeptidase inhibitor



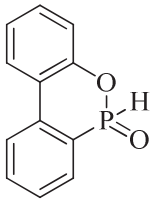
L-phosphinothricin Basta® - herbicide



SF-2312
Antibiotic from *Micromonospora*



Fosfonomycin - antibiotic from:
Streptomyces fradiae,
Streptomyces wedmorensis,
Streptomyces viridochromogenes



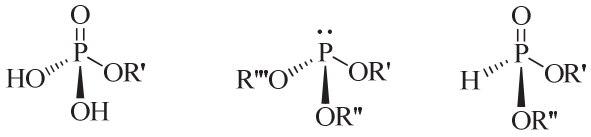
DOPO - fire retardant

2. The nature and reactivity of phosphinylidene group P(O)H towards unsaturated carbon linkages.

The classical methodologies for the synthesis of organophosphorous compounds focus on the implementation of Grignard reactions,[2] Michaelis-Arbuzov reaction[3] and radical additions of H-P compounds.[4] However, in the past 15 years, the attention has turned to metal-catalyzed addition of H-P(O) species to unsaturated carbon compounds, which has been found to be a powerful alternative.[5] This tool proved to be much more efficient in terms of regioselectivity and stereoselectivity and is being continuously developed.

2.1. Advantages of *H*-phosphonates in the synthesis and their chemical nature.

Amongst three classes of phosphorous compounds shown in **Figure 1.1** *H*-phosphonates **1.3** are found to be unique.[6]



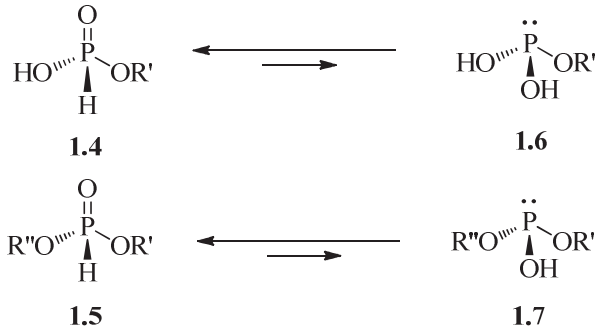
1.1 **1.2** **1.3**

Figure 1.1

Species **1.3** are pentavalent tetracoordinated phosphorous compounds. They possess kind of a dualism in themselves. Having a tetrahedral geometry and a P=O group present, they resemble very much to class of phosphate compounds **1.1**. Those features make us believe in their electophilic nature with the electrophilic center on the phosphorous atom. However, their character can be changed as phosphonate species **1.3** exist in two tautomeric forms between P(V) (**1.4** and **1.5, Figure 1.2**) and P(III) (**1.6** and **1.7**, **Figure 1.2**). The trivalent P(III) (phosphite derivatives) **1.2** (**Figure 1.1**), on the contrary, present a

[2] Pirat J-L., Virieux D., Drag M., Sobecki M., Midrier C., Filippini D., Volle J.-N., *Synthesis,* **2011**, 15, 2490
[3] a) Arbusov B. Z., *Pure Appl. Chem*., **1964**, *9*, 307; b) C. Wasilewski A., Antczak K., *Synthesis*, **1981**, 540; c) Falbe J., Paatz R., Korte F. *Chem Ber*., **1965**, *98*, 2312;d) Gali H., Karra S. R., Reddy V. S., Katti K. V., *Angew. Chem. Int. Ed.*, **1999**, *38*, 2020
[4] a) Deprele S., Montchamp J.-L., J. Org. Chem., **2001**, *66*, 6745; b) Han L.-B., Zhao C.-Q., *J. Org. Chem*, **2005**, *70*, 10121; c) Antczak M., Montchamp J.- L., *Synthesis*, **2006**, 3080; d) Leca D., Fensterbank L., Lacote E., Malacria M., *Chem. Soc. Rev*., **2005**, *34*, 858
[5] For recent reviews on metal-catalyzed additions see: a) Xu Q., Han L.-B.,*J. Organomet. Chem*., **2011**, *696*, 130; b) Tanaka M., *Top. Organomet. Chem*., **2011**; c) Coudray L., Montchamp J.-L., **2008**, Eur. *J. Org. Chem*., 3601

nucleophilic nature due to the lone pair on the phosphorous center. A tetracoordonate phosphonate (**1.4** and **1.5)** and tricoordinated phosphite (**1.6** and **1.7**) stay in equilibrium although it is shifted to the left (almost in 99%), as the P=O group guarantees better thermodynamic stability. However, this can be modified by treating the phosphite form with a suitable reagent (for example silylating agent[7]), which shifts the equilibrium to the right. Therefore, the nucleophilic nature of phosphorous atom is dominant and it can react with soft electrophiles. Compounds **1.3** are also more resistant to oxidation when compared to compounds **1.2** and they gain better stability under acidic conditions. Thus, they were found to be convenient to handle from a synthetic viewpoint.[4]



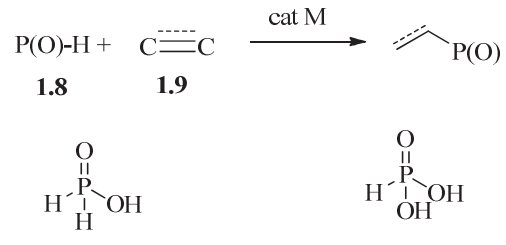
1.4 **1.6**

1.5 **1.7**

Figure 1.2

2.2. The general scope of metal-catalyzed H-P(O) addition to unsaturated carbon carbon linkages.

Hydrophosphinylation and hydrophosphonylation stands for the reaction of H-P(O) **1.8** addition to unsaturated carbon linkages **1.9** as shown in *Scheme 1.2.*



1.8 **1.9**

Hypophosphorous acid (H_3PO_2, HPA, phosphinic acid) — **1.10**

Phosphorous acid (H_3PO_3, phosphonic acid) — **1.11**

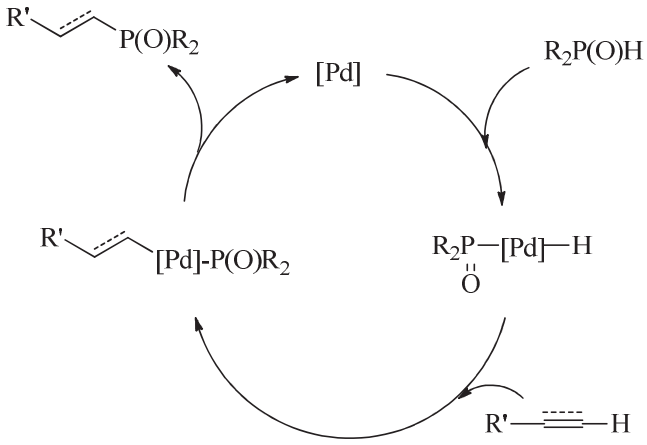
[6] Stawinski J., Kraszewski A.*, Acc. Chem. Res*., **2002**, 35, 952, b) Walker B. J., Organophosphorous Chemistry, **1972**, *Penguin Books*

[7] Boyd A. E., Boyd M. E. K., Loh V. M. Jr., *Tetrahedron. Lett*., **1996***, 37*, 1651; Keith J., Boyd A. E., Regan A., C,. *Tetrahedron Lett*., **1994**, *35*, 4223

Scheme 1.2

Particularly, the term hydrophosphinylation concerns the addition of a hypophosphorous acid **1.10** and its derivatives to unsaturated carbon linkages, whereas hydrophosphonylation (or sometimes called hydrophosphorylation) stands for the addition of phosphorous acid **1.11** and its derivatives.

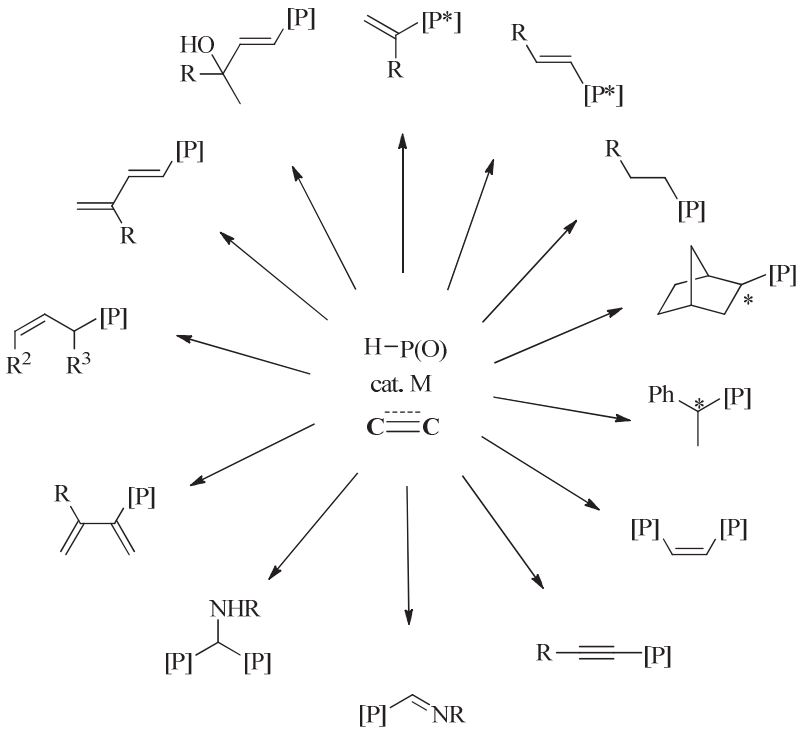
Over the years, research groups put utmost efforts to find the most efficient systems and to develop regioselective and stereoselective procedures. Methodologies based on palladium, rhodium, and nickel catalysis have been providing new classes of compounds implicated widely in biological field.[8] Their great importance comes out with the possibilities of regioselective and stereoselective course of these reactions, which is often crucial in terms of biological significance. The supposed general catalytic cycle with a palladium source in *Scheme 1.3* shows that the transition metals can undergo an oxidative addition into the P-H bond, followed by hydropalladation of the insaturation and, finally, end up with a reductive elimination to form C-P(O) bond.[5] Catalytic mechanisms will be widely explained in the following sections.



Scheme 1.3

The general scope of the developed methodologies is exposed in the *Scheme 1.4*.[5] Enantioselective versions of this reaction are highly desirable.

[8] Coudray L., Pennebaker A. F., Montchamp J.-L., *Bioorg. Med. Chem*., **2009**, *17*, 7680

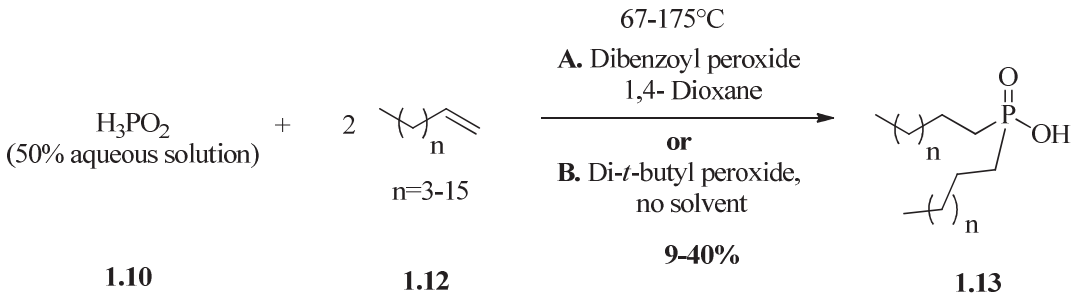


cat. M= Ni, Pd, Rh, Cu
[P]= $P(O)R_2$, $P(O)(OR)_2$, P(O)(OR)Ph, P(O)(pinacolato), $P(pinacolato)_2$
[P]=[P] or a chiral P-stereogenic phopshorous species

Scheme 1.4

2.3. Radical additions of H-P(O) to unsaturated carbon linkages.

Before the metal-catalyzed additions will be widely explored, it is worth to recall that the radical additions of phosphinylidene group H-P(O) across the double and triple bonds have been known in the literature much earlier than the metal-catalyzed procedures. The addition of hypophosphorous acid **1.10** to olefins **1.12** under radical conditions was described by Williams and Hamilton in 1955 (*Scheme 1.5*).[9]

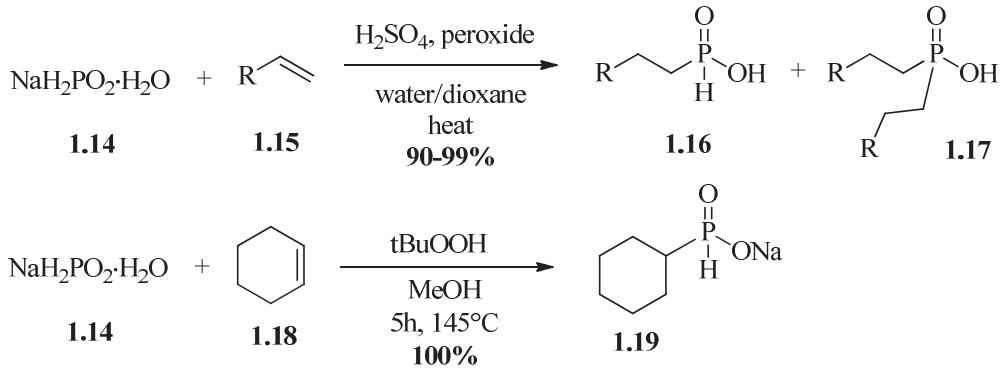


1.10 **1.12** **1.13**

Scheme 1.5

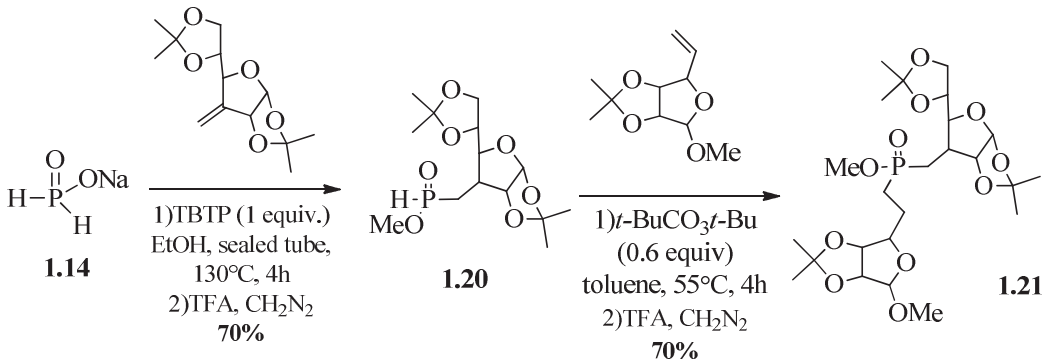
[9] Williams R. H., Hamilton L. A., *J. Am. Chem. Soc.* **1955**, *77*, 3411

The method afforded disubstituted phosphinic acids **1.13** in rather poor yields.[9] This work was extended by Nifant'ev[10] (*Scheme 1.6*), who developed the most known method for the radical preparation of phosphinic acids. Sodium hypophosphite **1.14** has been used in Nifant'ev radical reactions providing the products in very good yields (*Scheme 1.6*). Unfortunately, the linear alkenes give the mixture of mono- and disubstituted phosphinic acids **1.16** and **1.17**. However, in case of cyclohexene **1.18** only monosubstitution of the product **1.18** is observed.



Scheme 1.6

Although Nifant'ev method has been used for decades, the application of sodium hypophosphite **1.14** encounters numerous obstacles, such as its low solubility in organic solvents, the need for high initiation temperatures and large amounts of initiator. That makes the reaction impractical. In spite of this, some individual applications gave interesting results. Particularly, the radical process for the synthesis of a DNA-dimer analog **1.21** as described by Piettre (*Scheme 1.7*).[11]



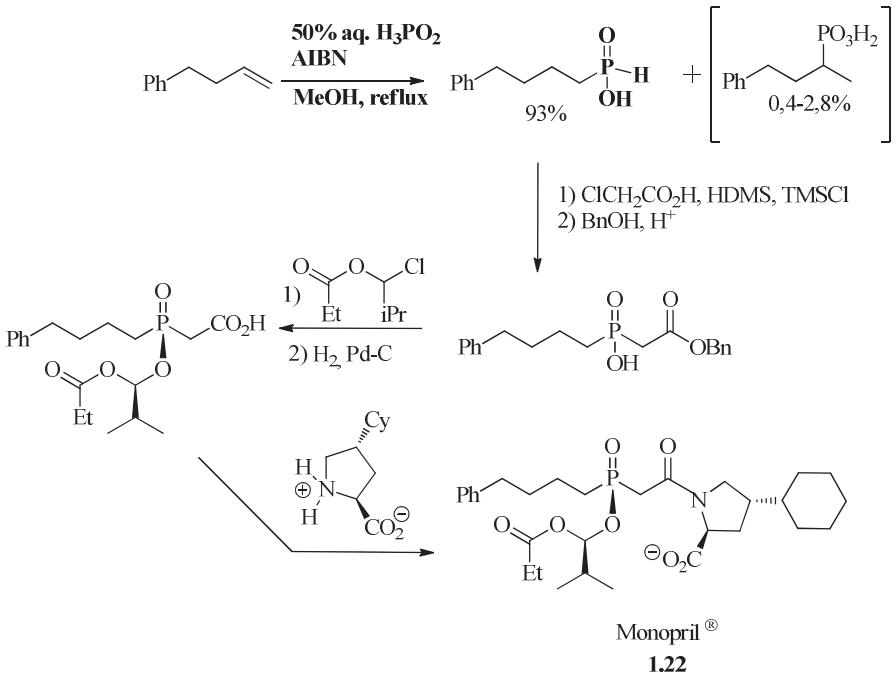
Scheme 1.7

[10] Nifant'ev E. E., Magdeeva R. K., Shchepet'eva N. P., *J. Gen. Chem. USSR*, **1980**, 50, 1416; b) Nifant'ev, E. E.; Koroteev, M. P. *J. Gen. Chem. USSR,* **1967**, *37*, 1366; c) Karanewsky D. S., Badia M. C., Cushman D. W., DeForrest J. M., Dejneka T., Loots M. J., Perri M. G., Petrillo E. W., Powell J. R., *J. Med. Chem*., **1988**, 31, 204

[11] Dubert O., Gautier A., Condamine E., Piettre S. R., *Org. Lett*., **2002**, *4*, 359

It is shown in the second step that the monosubstituted phosphinate **1.20** underwent subsequent radical addition in a good yield of 70%. This is an example of the radical chain reactions of hypophosphorous compound, which are generally inefficient.[12]

Modified conditions of Nifant'ev reaction are currently used industrially for the side-chain preparation of the drug Monopril® **1.22** (*Scheme 1.8* **in bold**).

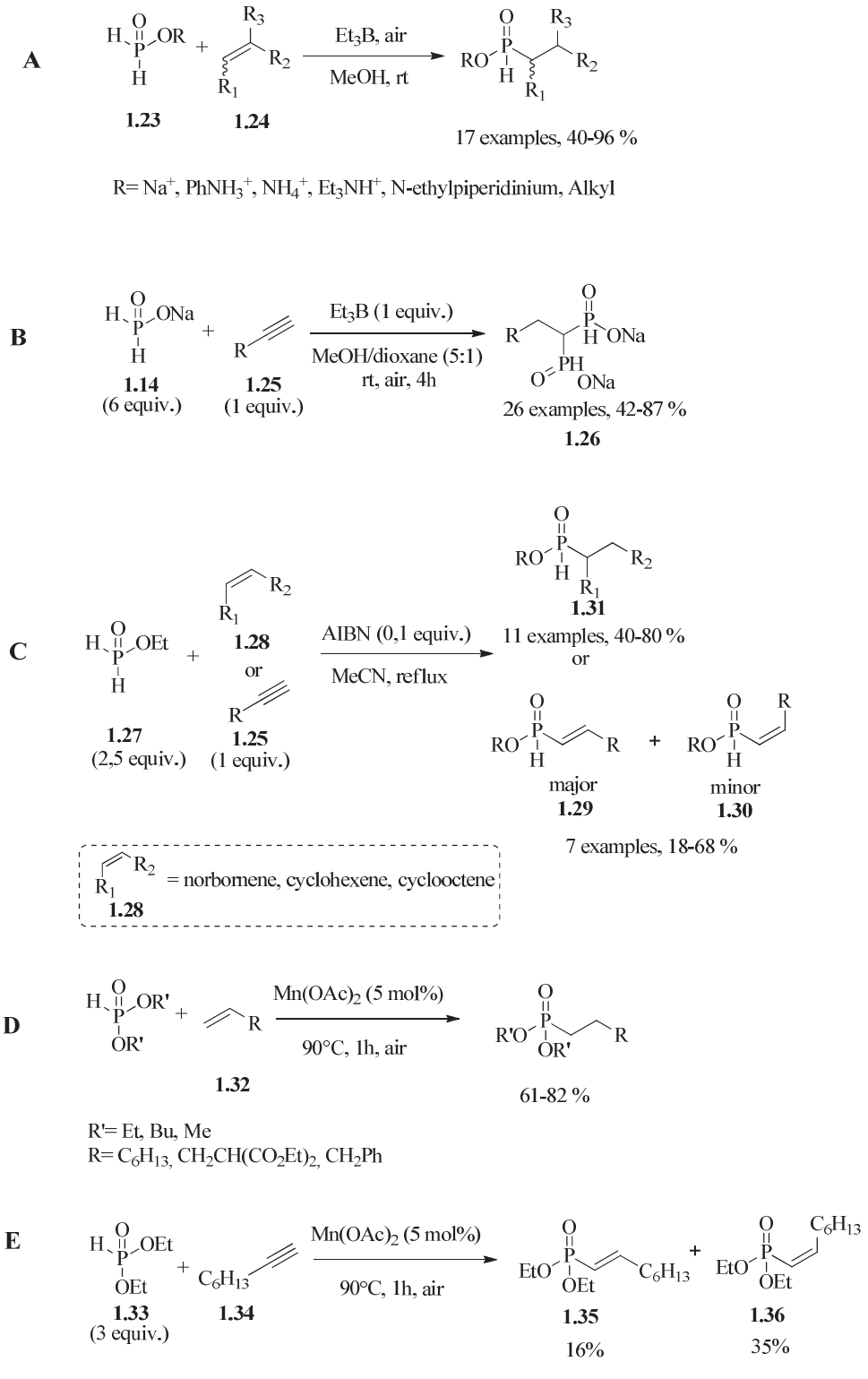


Scheme 1.8

Search for more general and modern methods for the radical additions led to the application of a trialkylboranes and air as the initiator at room temperature[4a,13](*Scheme 1.9,* **A** and **B**) or AIBN initiator in refluxing acetonitrile[4c](*Scheme 1.9,* **C**) or hydrophosphonylation catalyzed by Mn(III) under air (*Scheme 1.9,* **D** and **E**).[14] However, all these methods suffer from serious limitations. The most convenient route is the radical addition of hypophosphorous derivatives **1.23** under neutral conditions and at room temperature by using triethylborane and air as the initiator (*Scheme 1.9*, **A)**.[4a] The reaction has a broad scope in terms of alkene **1.24** and phosphinate reagents **1.23**. Good selectivity for monoaddition is observed, even when an excess of the alkene **1.24** is employed. Sodium, anilinium, ammonium and even alkyl phosphinates are all useful reagents to hydrophosphinylate alkenes **1.24** under radical conditions. However, alkynes **1.25** treated with this method afford only

[12] Jessop C. M., Parsons A. F., Routledge A., Irvine D. J., *Eur. J. Org. Chem*., **2006**, 1547.
[13] Antczak M. I., Montchamp J.-L., *Synthesis,* **2006**, 18, 3080
[14] Ishii Y., Sakaguchi S., Iwahama T., Nakano A., Tayama O., *J. Org. Chem*, **2004**, *69*, 5494

1,1-bis-*H*-phosphinates **1.26** which makes this reaction impractical when monosubstituted alkenes are expected (*Scheme 1.9*, **B**).[13]



Scheme 1.9

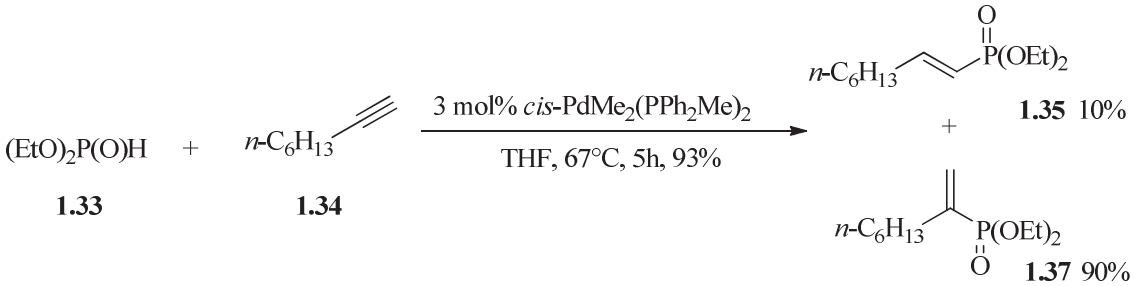
The methodology with AIBN (*Scheme 1.9,* **C**) requires the preparation of thermally-resistant alkyl phosphinates **1.27** by using toxic alkoxysilane esterification method.[15]Although the cyclic alkenes react in good yields **1.28**, hydrophosphinylation of alkynes **1.25** affords the mixture of isomers. Finally, the hydrophosphonylation with $Mn(OAc)_2$ is efficient only in terms of alkene substrate **1.32** (*Scheme 1.9,* **D)**.[14] The authors suggested that Mn^{II} is oxidized by oxygen from air to Mn^{III}, which catalyzes the addition. When an alkyne **1.34** is subjected for the reaction, the two stereoisomers **1.35** and **1.36** are formed (*Scheme 1.9*, **E**).[14]

Although much progress has been made in the field of the radical additions of phosphinylidene group across the double and triple bonds, those methods still need improvements. That leaves a large area for the application of metal-catalyzed reaction in terms of regio- and stereocontrolled ones.

3. Metal-catalyzed addition of H-P(O) to the alkynes.

3.1. First successful metal-catalyzed addition of H-P(O) group to alkynes.

Back to 1996, the group of Tanaka reported palladium-catalyzed hydrophosphonylation of alkynes for the first time.[16] An example of the reaction is shown in the *Scheme 1.10*.

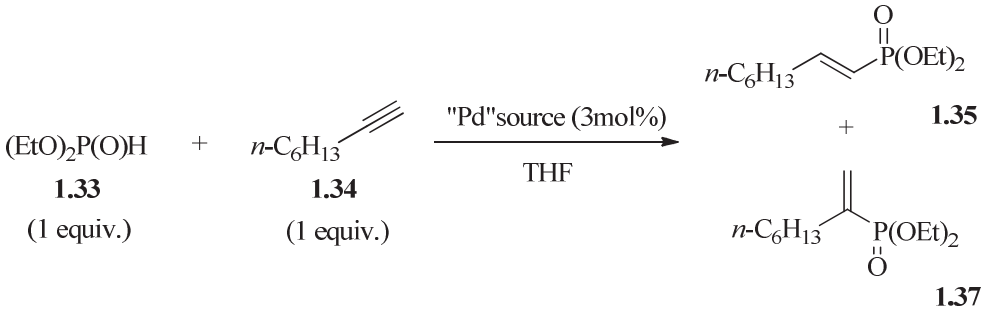


Scheme 1.10

This method offers numerous advantages. It gives the access to various alkenylphosphonates (8 examples) in 41-95% yields. It also allows decent regioselectivity with a 90/10 ratio of the Markovnikov α-adduct **1.37**. The internal alkynes also reacted, although slower. The reaction of 4-octyne in the same conditions as indicated in *Scheme 1.10* lead to the *cis*-isomer in 82% within 65h. It is noteworthy that any olefinic substrate subjected to these conditions remained unreactive.[16]

[15] Deprele S., Montchamp J.-L., *J. Organomet. Chem*., **2002**, *643-644*, 154
[16] Han L.-B., Tanaka M., *J. Am. Chem. Soc,* **1996**, *118*, 1571

Amongst different catalytic systems tested for this reaction, shown in *Scheme 1.11*, Tanaka *et al*. concluded that the efficiency of the Pd(0) catalyst depends on the nature of the ligand.



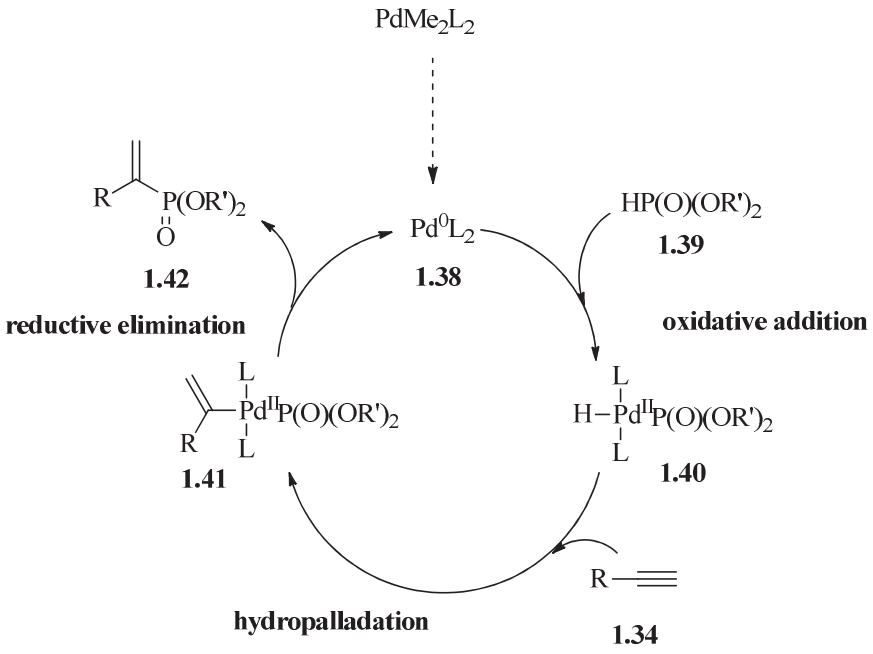
Entry	"Pd" source	Time (h)	Yield (ratio 1.35/1.37)
1.	$Pd(PPh_3)_4$	18h	89% (14/ 86)
2.	*cis*-$PdMe_2(PPh_3)_2$	17h	73% (15/ 85)
3.	*cis*-$PdMe_2(PPh_2Me)_2$	13h	92% (11/ 89)
4.	*cis*-$Pd(CH_2{=}CH_2)(PPh_3)_2$	6h	93% (9/91)

Scheme 1.11

As *Scheme 1.11* shows the efficient catalysts, it has to be mentioned that Pd(II) complexes such as $PdMe_2(PEt_3)_2$, $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ and $PdCl_2(PhCN)_2$ are inactive probably due to their difficult reduction to the corresponding Pd(0) complexes.[16]

Tanaka *et al.* proposed the first catalytic cycle shown in *Scheme 1.12*. Firstly, Pd^0 catalyst **1.38** is generated. Then, the oxidative addition to H-P(O)(OR')$_2$ **1.39** takes place with formation of the complex **1.40**. The hydropalladation of an alkyne **1.34** leads to complex **1.41**.and the reductive elimination affords product **1.42**. That methodology gives the branched products, which cannot be formed under radical conditions (**Section 2.3**).[16]

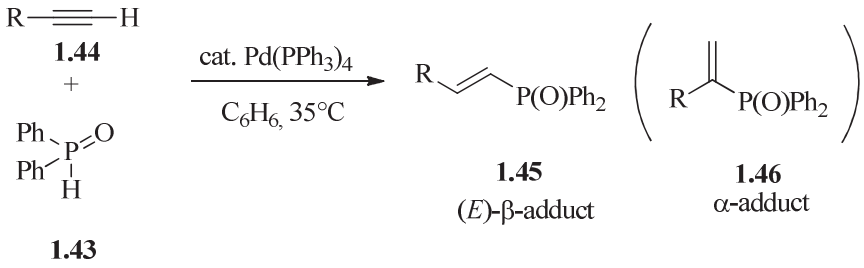
This revolutionary work gave the start for the next 15 years of intense research on new synthetic methodologies and mechanistic studies.



Scheme 1.12

3.2. Metal-catalyzed addition of secondary phosphine oxides $R_2P(O)H$ to alkynes.

The following works of Tanaka and his group revealed for the first time the possibility of conducting the reaction of metal-catalyzed hydrophosphinylation.[17] For this purpose, the secondary phosphine oxide $Ph_2P(O)H$ **1.43** (*Scheme 1.13*) was used. Although the hydrophosphonylation described in **Section 3.1** showed predominance of the Markovnikov α-adducts **1.42**, herein, a change in the regioselectivity was reported. The use of $Pd(PPh_3)_4$ complex provides the best regioselectivity (>95/5 of ratio) in favor of the *anti*-Markovnikov (*E*)-β-adduct **1.45** (*Scheme 1.13*). Internal alkynes also reacted, but slower and with heating.[17]

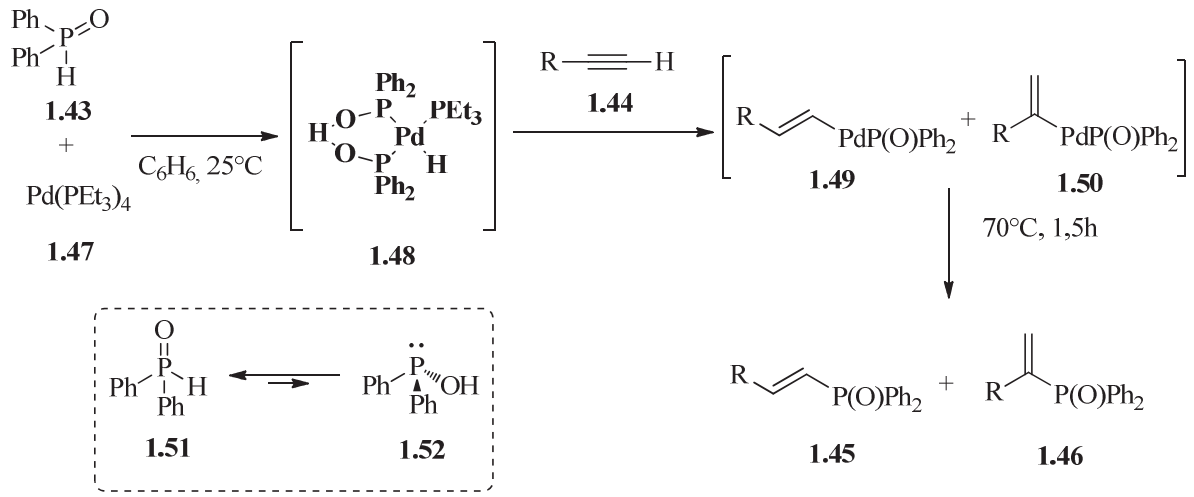


Scheme 1.13

For the purpose of mechanistic studies, the separate experiment was set as shown in *Scheme 1.14.* Mixture of diphenylphosphine oxide **1.43** with $Pd(PEt_3)_4$ **1.47** in benzene was

[17] a) Han L.-B., Hua R., Tanaka M., *Angew. Chem. Int. Ed.* **1998**, *37*, 94; b) Han L.-B., Choi N., Tanaka M., *Organometallics* **1996,** *15*, 3259

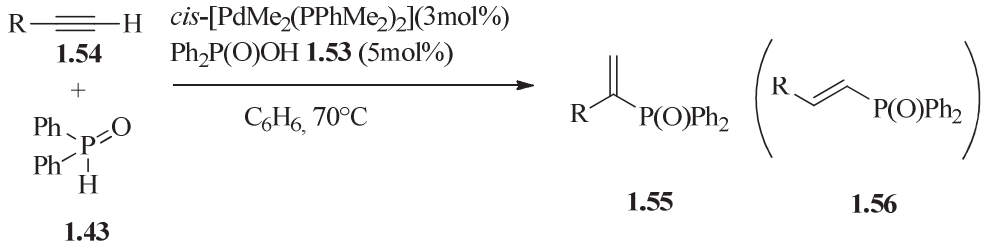
followed by NMR spectroscopy uncovering the molecular structure of the intermediate being *cis*-PdH[P(O)Ph_2][PPh-(OH)][PEt_3] complex **1.48**.[17]



Scheme 1.14

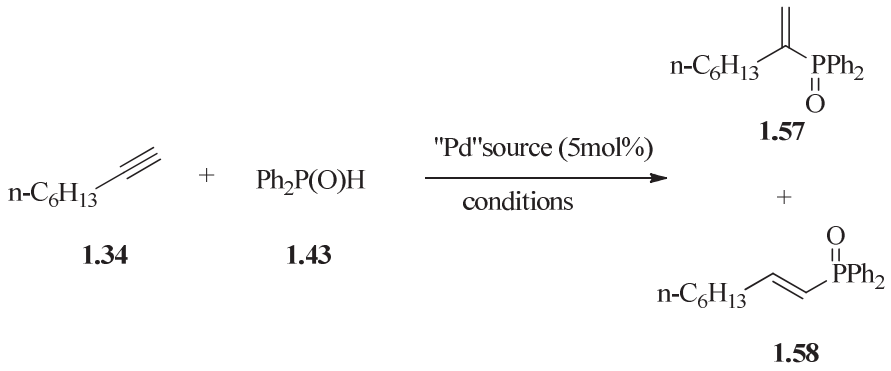
Tanaka has proved that two $Ph_2P(O)H$ **1.43** molecules reacted with the metal. One, undergoing oxidative addition whereas the other coordinating in tautomeric form P(III), $Ph_2P(OH)$ **1.52**. The authors strongly suggested that hydropalladation (addition of H-Pd) was favored over phosphinylpalladation (addition of Pd-P).[17]

Apparently, the regioselectivity of above reaction can be changed. This can be achieved with the addition of diphenylphosphinic acid **1.53** (*Scheme 1.15*).[17]



Scheme 1.15

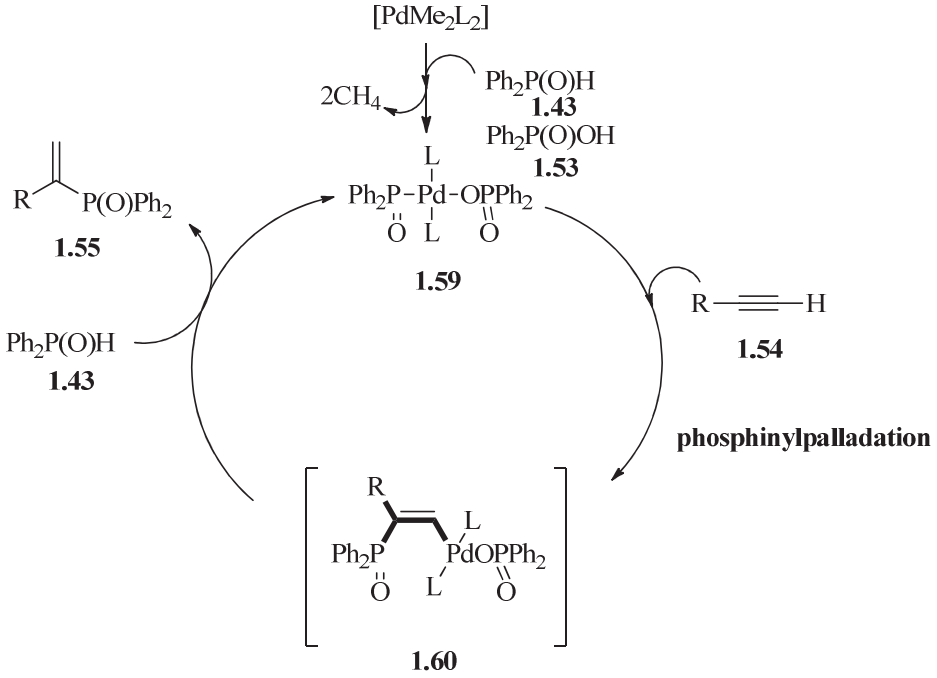
In this case, small amounts of $Ph_2P(O)(OH)$ **1.53** in the reaction mixture changed totally the regioselectivity, increased the yields and enhanced the catalytic activity (entry **6** with previously inactive [$PdMe_2$(dmpe)], *Scheme 1.16*).[17]



Entry	"Pd" source	Yield [%] (ratio 1.57/1.58) with $Ph_2P(O)(OH)$ 1.53	Yield [%] (ratio 1.57/1.58) without $Ph_2P(O)(OH)$ 1.53
1.	$Pd(PPh_3)_4$	89 (33/67)	54 (92/ 8)
2.	*cis*-$PdMe_2(PPh_3)_2$	73 (37/73)	69 (91/9)
3.	*cis*-$PdMe_2(PPh_2Me)_2$	100 (84/16)	56 (90/10)
4.	*cis*-$PdMe_2(PPhMe_2)_2$	93 (95/5)	75 (88/12)
5.	$PdMe_2(PEt_3)_2$	95 (91/9)	51 (87/13)
6.	$PdMe_2$(dmpe)	93 (92/8)	0

Scheme 1.16.

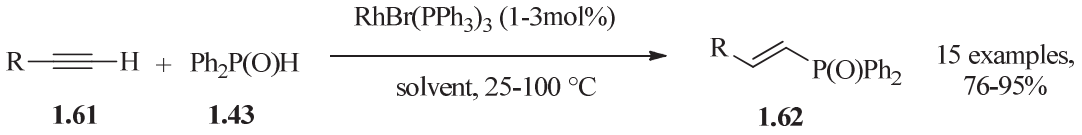
These results draw attention to the significant role of OH group of $Ph_2P(O)(OH)$ **1.53**. The catalytic cycle suggested by Tanaka presented in *Scheme 1.17* is supported by his NMR study. [17]



Scheme 1.17

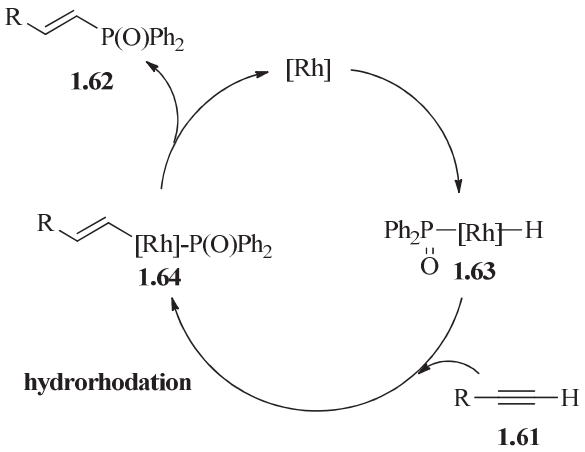
It is believed that complex **1.59** is formed. Under these conditions the phosphinylpalladation of the alkyne **1.54** takes place and leads to intermediate **1.60**. Subsequently, the protonolysis of **1.60** with $Ph_2P(O)H$ **1.43** affords α-adduct **1.55** and simultaneous regeneration of the catalyst.[17]

Rhodium catalyzed hydrophosphinylation with secondary phosphine oxide **1.43** was also developed.[18] If previous methods always gave mixtures of regioisomers and reaction requires extended times, rhodium catalysts improved the efficiency of hydrophosphinylation *Scheme 1.18.*



Scheme 1.18

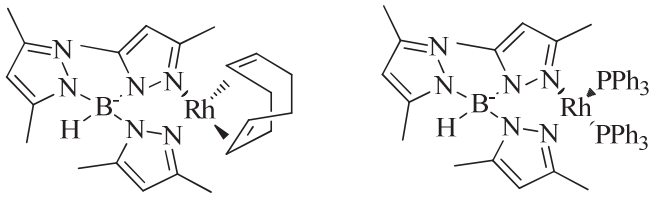
Rhodium catalysts enabled the formation of (*E*)- alkenylphosphine oxides **1.62** in 76-92% yields (both aliphatic and aromatic terminal alkynes with various functionalities reacted readily). All catalysts of the Wilkinson-type, $RhX(PPh_3)_3$ (where X stands for Cl, Br or I), exhibit a high catalytic activity at ambient temperature unlike $RhCl(CO)\text{-}(PPh_3)_2$ and $RhH(CO)(PPh_3)_3$, which are unreactive below 80 °C. A good catalytic activity was also exhibited by $[Rh\text{-}(cod)Cl]_2$. The proposed mechanism in *Scheme 1.19*, supported by NMR data, involves oxidative addition of the P-H bond forming complex **1.63**, subsequent hydrorhodation of an alkyne **1.61** leads to complex **1.64**, and reductive elimination step affords the product **1.62**.[18]



Scheme 1.19

[18] Han L.-B., Zhao Ch.-Q., Tanaka M., *J. Org. Chem*. **2001**, *66*, 5929

Rhodium-catalyzed hydrophosphinylation can be performed with secondary phosphine oxides by using of rhodium pyrazoylborate complexes **1.65 and 1.66** (**Figure 1.3**).[19]

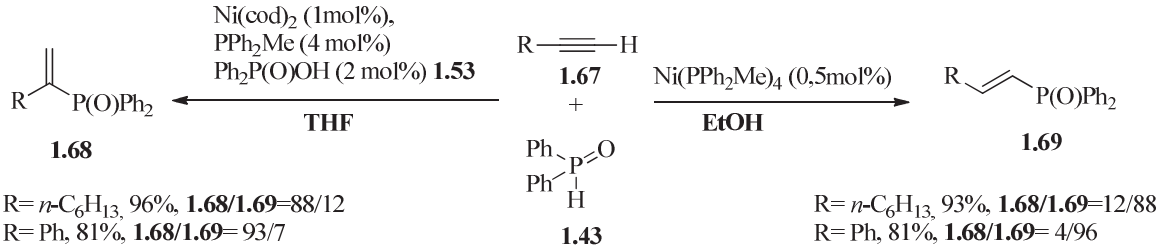


1.65 **1.66**

Figure 1.3

Compared to the Wilkinson catalysts these complexes are weakly effective with yields from 17 to 61% limited to the small range of terminal alkynes (5 examples).[19]

The addition of $R_2P(O)H$ to alkynes can also be achieved using nickel catalysts, which are found to be an efficient alternative to very expensive Rh and Pd sources (*Scheme 1.20*)[20] Using various phosphine ligands, nickel(0) catalyzes the addition of a variety of H-P(O) to alkynes **1.67** even at room temperature. The selectivity of the reaction enhances its advantage: by changing the solvent, both the Markovnikov **1.68** or the *anti*-Markovnikov adducts **1.69** can be generated. When the reaction is conducted in the presence of a small amount of $Ph_2P(O)OH$ **1.53** in THF, α-adducts **1.68** are the major products with up to 93/7 of selectivity. On the other hand, when the reaction is carried out in EtOH in the absence of **1.53**, the result is reverse and leads to products **1.69**.[20]



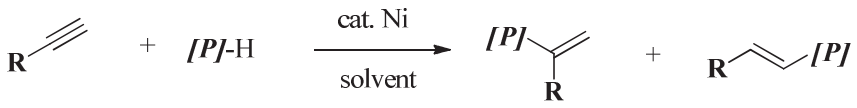
Scheme 1.20

The catalyst's activity is determined by the steric hindrance of the ligands. Particularly, PPh_2Bu as a ligand works well, whereas a bulkier PPh_2i-Pr promotes the reaction sluggishly. The less sterically hindered, but more basic $PPhMe_2$ and $PPhEt_2$ work more efficiently than PPh_2Me to give nearly quantitative yields of the products **1.68** and **1.69**. The

[19] Van Rooy S., Cao C., Patrick B. O., Lam A., Love J. A, *Inorganica Chimica Acta*, **2006**, *359*, 2918
[20] Han L.-B., Zhang C., Yazawa H., Shimada S., *J. Am. Chem.Soc,* **2004**, *126*, 5080

addition fails when bulky ligands like $PPhCy_2$ are used. The yield is decreasing in an order from PMe_3 to PEt_3 and PBu_3. $P(t\text{-}Bu)_3$ fails to promote the reaction. The corresponding palladium, platinum, and rhodium complexes do not catalyze this addition when similar reaction conditions are applied.[21]

Scheme 1.21 shows the scope of the reaction. *H*-phosphinate Ph(EtO)P(O)H, diphenylphosphine oxide $Ph_2P(O)H$ and alkyl *H*-phosphonate $(MeO)_2P(O)H$ can be successfully added to both aliphatic and aromatic unsaturated species **1.70** in very good yields.[21]



1.70 **1.71** **1.72** **1.73**

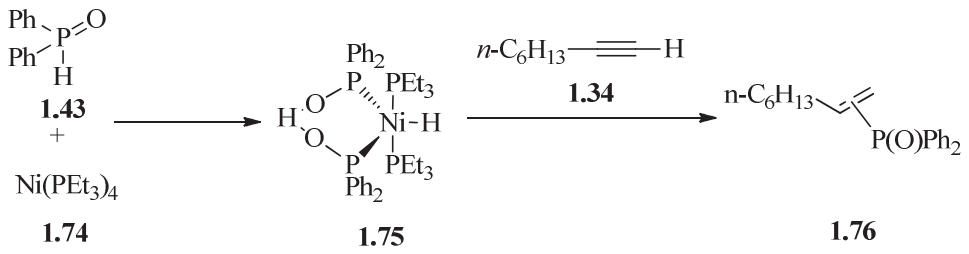
Entry	R	*[P]*	Solvent	Yield [%] (ratio 1.72/1.73)
1.	Ph	$(MeO)_2P(O)H$	EtOH	91 (1/ **99**)
2.	Ph	$(MeO)_2P(O)H$	THF	72 (**90**/10)
3.	*n*-C_6H_{13}	Ph(EtO)P(O)H	EtOH	95 (5/**95**)
4.	*n*-C_6H_{13}	Ph(EtO)P(O)H	THF	93 (**92**/8)
5.	Ph	Ph(EtO)P(O)H	EtOH	87 (1/**99**)
6.	Ph	Ph(EtO)P(O)H	THF	89 (**94**/6)
7.	*n*-C_6H_{13}	$Ph_2P(O)H$	EtOH	96 (12/**88**)
8.	*n*-C_6H_{13}	$Ph_2P(O)H$	THF	93 (**88**/12)
9.	Ph	$Ph_2P(O)H$	EtOH	81 (6/**94**)
10.	Ph	$Ph_2P(O)H$	THF	79 (**93**/7)

Scheme 1.21

Mechanistic studies of the reaction indicate that, similarly to Pd (*Scheme 1.14*), nickel inserts into H-P(O) bond to form a five-coordinated hydridonickel complex **1.75** (*Scheme 1.22*), which is much more reactive toward 1-octyne **1.34** than its Pd analog (*Scheme 1.22*).[17]

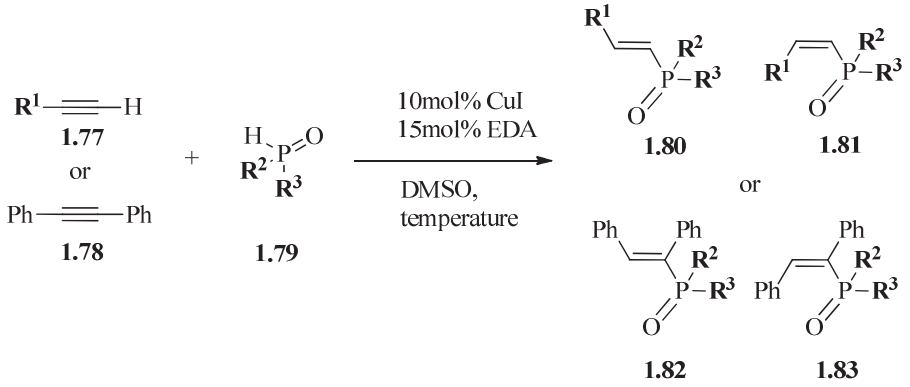
[21] a) Han L.-B.; Tanaka, M. *Chem. Commun*. **1999**, 395; b) Han L.-B.; Zhao, C.-Q.; Onozawa S.-Y.; Goto, M.; Tanaka, M. *J. Am. Chem. Soc*. **2002**, *124*, 3842;c) Zhao, C.-Q.; Han, L.-B.; Goto, M.; Tanaka, M. *Angew. Chem., Int. Ed*. **2001**, *40*, 1929;

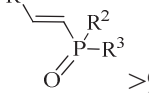
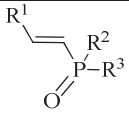
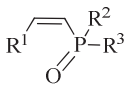
The higher catalytic activity of the nickel complex is probably due to the higher reactivity of the corresponding hydrido nickel intermediates **1.75**.[21]



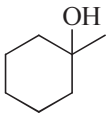
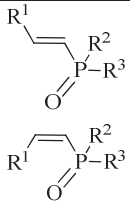
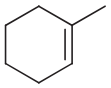
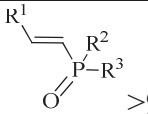
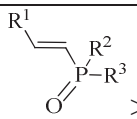
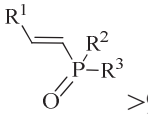
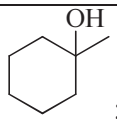
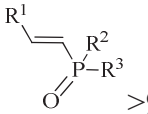
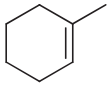
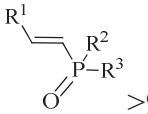
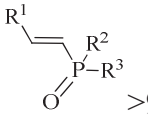
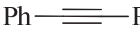
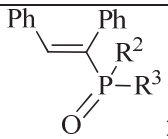
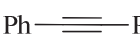
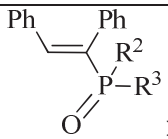
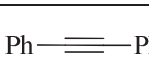
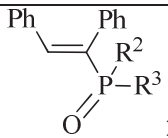
Scheme 1.22

The addition of H-phosphine oxides to alkynes can be achieved also by copper-catalyzed reaction, which is a convenient and inexpensive way to alkenylphosphinates *Scheme 1.23*.[22]



Entry	**R^1; R^2; R^3**	**T[°C]; Time**	**Products** ratio	**Yield [%]**
1.	Ph; R^2= R^3=Ph	60; 3h	 >99	**90**
2.	*n*-C_6H_{13}; R^2= R^3=Ph	90; 12h	 85  15	**67**

[22] Niu M., Fu H., Jiang Y., Zhao Y., *Chem. Comm*., **2007**, 272

3.	 ; R^2= R^3=Ph	60; 9h	 90 10	**75**
4.	 ; R^2= R^3=Ph	60; 10h	 >99	**65**
5.	Ph; R^2= R^3=$PhCH_2$	60; 18h	 >99	**66**
6.	n-C_6H_{13}; R^2= R^3= $PhCH_2$	90; 18h	 >99	**72**
7.	 ; R^2= R^3= $PhCH_2$	60; 18h	 >99	**64**
8.	 ; R^2= R^3= $PhCH_2$	60; 18h	 >99	**61**
9.	Ph; R^2=Ph, R^3=OEt	90; 10h	 >99	**70**
10.	 ; R^2= R^3= Ph	60; 3h	 >99	**trace**
11.	 ; R^2= R^3= Ph	100; 12h	 >99	**60**
12.	 ; R^2= R^3= $PhCH_2$	100; 12h	 >99	**79**

Scheme 1.23

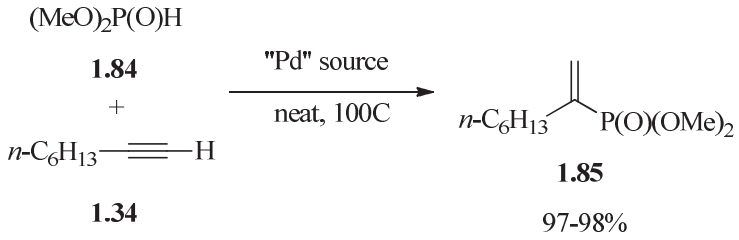
Hydrophosphinylation occurs regioselectively and stereoselectively under indicated conditions and in very good yields. The yields depend mainly on the steric properties of the P(O)H compounds **1.79** and alkynes **1.77** and **1.78** (*Scheme 1.23*). Terminal alkynes lead to *anti* Markovnikov adducts **1.80** and **1.81** by the regioselective addition of the phosphorous atom at the terminal carbon of the triple bond. However, *cis* and *trans* isomers can be

observed (Entry 2 and 3, *Scheme 1.23*). The internal alkynes remain less active (Entry 10, *Scheme 1.23*) and higher temperature has to be applied.[22]

3.3. Metal-catalyzed addition of $(RO)_2P(O)H$ and $R^1(OR^2)P(O)H$ to alkynes.

The role of nickel catalysts for the addition of $(RO)_2P(O)H$ to triple bonds was already mentioned in **Section 3.2.** These methodologies describe the hydrophosphonylation leading to the *anti*-Markovnikov adducts.

The palladium-catalyzed reactions are found to be useful as well, which is shown in *Scheme 1.24*.[23] This method affords Markovnikov products **1.85**, which cannot be reached under radical conditions (**Section 2.3**).



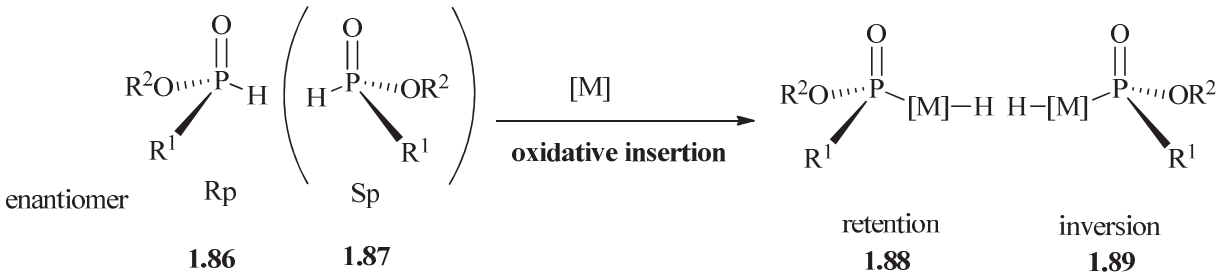
$Pd_2(dba)_3$ / $PPh_2(CH_2)_3PPh_2$ (0.5 mol% Pd, Pd/P = 1/2), 20 h, 99% yield
$Pd(OAc)_2$ /$PPh_2(CH_2)_3PPh_2$ (0.05 mol% Pd, Pd/P = 1/3), 24 h, 92% yield

Scheme 1.24

The phosphine ligand is crucial to determine the catalyst's efficiency. A bidentate phosphine $Ph_2P(CH_2)_nPPh_2$ (for n= 3 or 4) is the best one for this reaction. The combination of these ligands with commercially available palladium sources such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ gave very good results. With low catalyst loadings (0.5mol%) high yields of the Markovnikov adduct **1.85** can be obtained.[23]

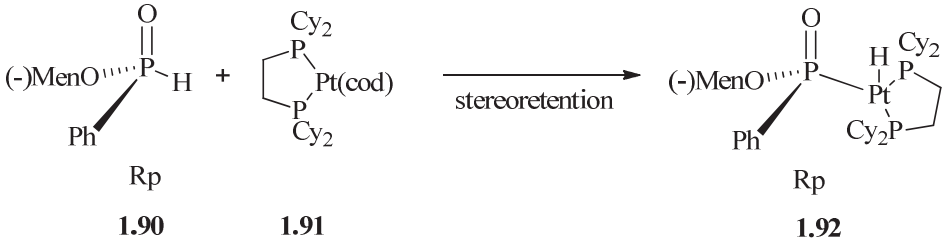
Exploring the stereochemistry of the oxidative addition of optically pure *H*-phosphinate **1.86** bearing a chiral P- stereogenic center answers the question of retention or inversion of configuration at the phosphorus during catalysis (*Scheme 1.25*).[21,24]

[23] Ananikov V. P., Khemchyan L. L., Beletskaya I. P., *Synlett*, **2009**, 15, 2375
[24] a) Korpium O., Lewis R.A., Chickos J., Mislow K., *J. Am. Chem. Soc*., **1968**, *90*, 4842; b) Farnham W.B., Murray R.K., Mislow K., *J. Am. Chem. Soc*., **1970**, *92*, 5809; c) Xu Q., Zhao C.-Q., Han L.-B., *J. Am. Chem. Soc*. **2008**, *130*, 12648;



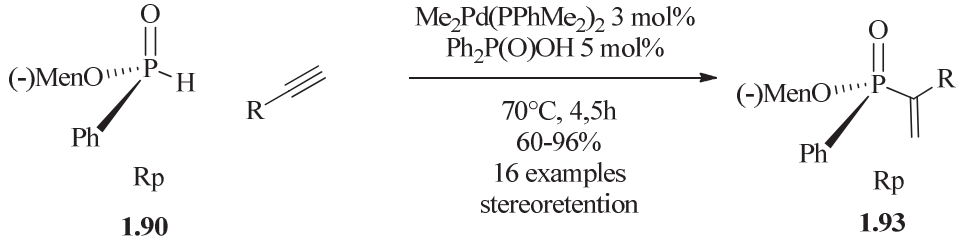
Scheme 1.25

An experiment with (R_P)-Menthyl phenylphosphinate **1.90** as the substrate shows, that the oxidative addition to a platinum(0) complex **1.91** proceeds readily with complete retention of configuration at the phosphorus center to give hydridoplatinum complex **1.92** (*Scheme 1.26)*.[24]



Scheme 1.26

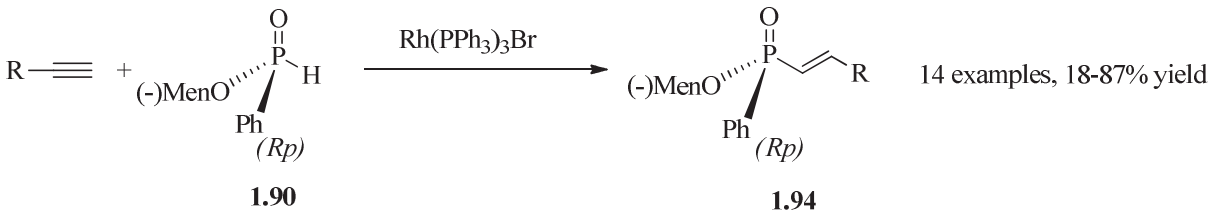
Examination of **1.90** with palladium catalyst results in a stereospecific addition to alkynes with retention of configuration leading to the branched products **1.93** (*Scheme 1.27*).[24]



Scheme 1.27

In comparison to Pd catalysis, rhodium catalyzed methodology yields optically pure (*E)*-adducts **1.94** with also retention of configuration as shown in *Scheme 1.28*.[25,26]

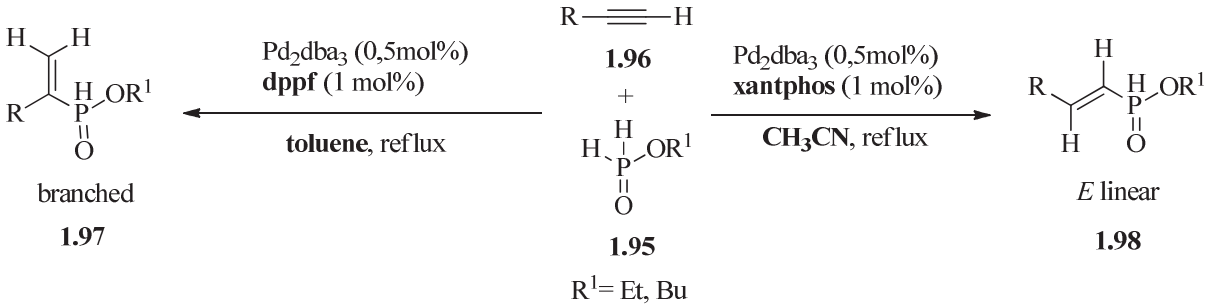
[25] a) Xu Q., Han L.-B., *J. Org. Chem*., **2011**, *696*, 130, b) L.-B. Han, C.-Q. Zhao, M. Tanaka, Pat. 3777397 JP 2006.
[26] Pietrusiewicz K.M., Zablocka M*., Chem. Rev*., **1994**, *94*, 1375.



Scheme 1.28

3.4. Metal-catalyzed addition of (OR)P(O)H2 to alkynes.

The palladium-catalyzed hydrophosphinylation of terminal alkynes **1.96** (*Scheme 1.29)* can selectively form either the branched 2-alkenyl- *H*-phosphinates **1.97** or the linear (*E*)-1-alkenyl-*H*-phosphinates **1.98**, depending on the ligand and solvent (*Scheme 1.29*).[27]



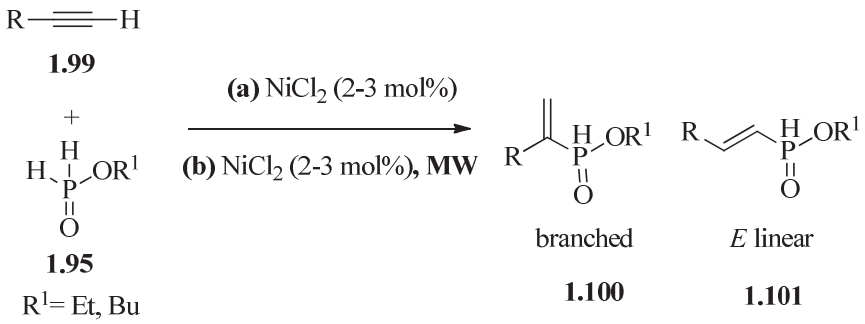
Scheme 1.29

The screening of various ligands and conditions showed that the use of **dppf** as a ligand in **toluene** allows the branched isomers **1.97**, while **xantphos** and **acetonitrile** lead to linear isomers **1.98**. It is worth to note that the selectivity for the linear isomer **1.98** decreases from xantphos, to DPEphos and dppf. This could be possibly due to the decreasing ligand's bite angle (111°, 102° and 99° respectively).[28] Apart from the ligand, solvent stands as an important factor. This might be explained by drawing attention to electronic effects on reactive intermediates with terminal alkynes when polar acetonitrile is used as a solvent. Moreover, the structure of the alkyne **1.96** also plays a role. The more electron-donating substituents incline towards the formation of the branched isomers **1.97** (for example cyclopropylacetylene), but the electron-withdrawing ones like phenylacetylene favor the linear *H*-phosphinates **1.98**.[27]

[27]Belabassi Y., Bravo-Altamirano K., Montchamp J.-L., *J. Organomet. Chem*., **2011**, *696*, 106
[28] Birkholz M.-N., Freixa Z., van Leeuwen P.W.N.M., *Chem. Soc. Rev*. **2009**, *38*, 1099

The hydrophosphinylation with nickel catalysts, particularly, nickel chloride, leads to the alkylphosphinates **1.100** and **1.101** (23 examples) in very good yield (32-100%), in the absence of added ligand (*Scheme1.30*).[29] However, the regiocontrol is significantly lower compared to Pd- catalyzed reaction. The reason lays in the higher reactivity of both terminal and internal alkynes with $ROP(O)H_2$ under nickel catalysis than under palladium catalysis.[27] In the absence of significant steric or electronic biases, the nickel-catalyzed hydrophosphinylation leads to regioisomeric mixtures.

It is worth to note that phenylacetylene gives a 1:1 mixture when following the conditions indicated in the pathway **(a)** in *Scheme 1.30*, but under microwave irradiation (pathway **(b),** *Scheme 1.30*), a slightly better branched to linear ratio was obtained (2.5:1). The reasons for this slight difference remain unclear.[29]



Scheme1.30

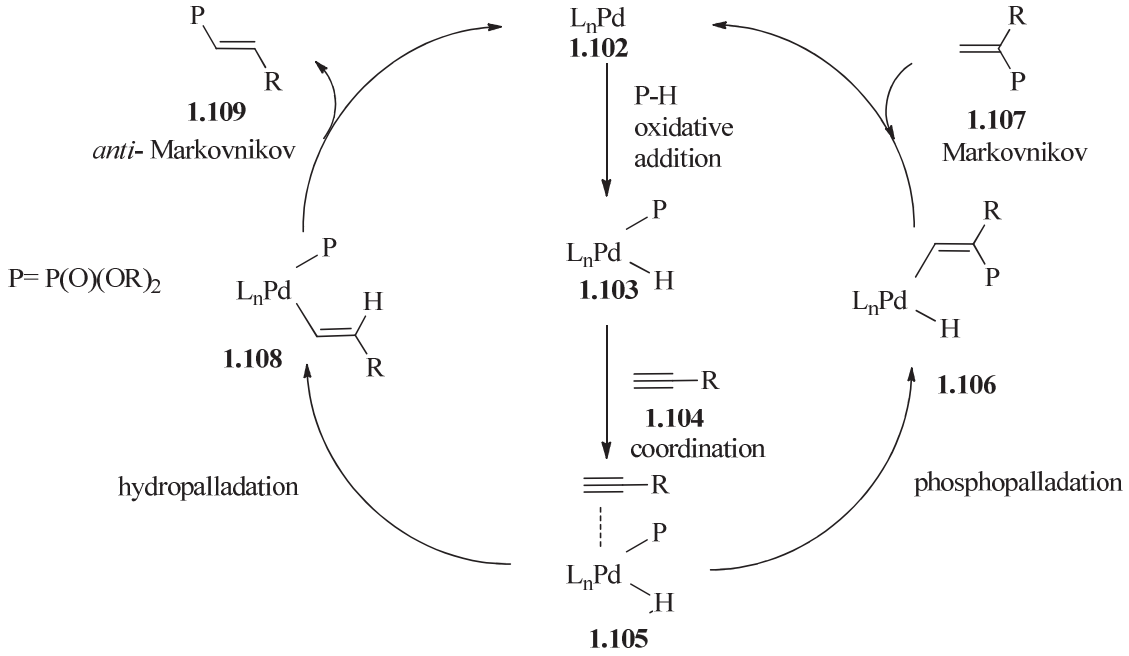
3.5. Mechanistic insight into Pd-catalyzed addition of $(RO)_2P(O)H$.

If most of the papers propose the possible mechanisms involved in the metal-catalyzed additions of H-P(O) to unsaturated carbon linkages none of them give straight and clear answer. A central question lies in the addition to the alkyne moiety since it can proceed by either [M]–H addition (process of hydrometalation) or [M]–P addition (phosphometalation) resulting in the formation of respectively, the linear or branched alkene. Moreover, the reductive elimination of the [M]-P complex (Formation of the P-C bond), which can be rate-determining step, has not been well studied either. Palladium complexes have been explored most intensively and Tanaka suggested that it proceeded by hydropalladation (**Section 3.1**).[5,16] The exception was marked in case of secondary phosphine oxide $Ph_2P(O)H$ with additional presence of $Ph_2P(O)OH$.[17] The authors proposed in that case a mechanism *via*

[29] Ribière P., Bravo-Altamirano K., Antczak M.I., Hawkins J.D., Montchamp J.-L., *J. Org. Chem*, **2005**, *70*, 4064

phosphinylpalladation process (**Section 3.2**). Although the presumable catalytic cycles have been presented in this manuscript, they suffer from a lack of firm proof. Another question arises from the regioselectivity issue. There are branched-selective or linear-selective methods of additions to alkynes, but in most of the cases, the products are the mixtures of isomers difficult to separate.

Just recently, the mechanism of the Pd-catalyzed addition of $(RO)_2P(O)H$ to terminal triple bonds has been explored by the group of Beletskaya.[30] The general idea of possible mechanistic pathway is shown in *Scheme 1.31*. The authors suggested that the Markovnikov products **1.107** are formed via phosphometalation, whereas anti-Markovnikov **1.109** compounds are the result of hydrometalation.

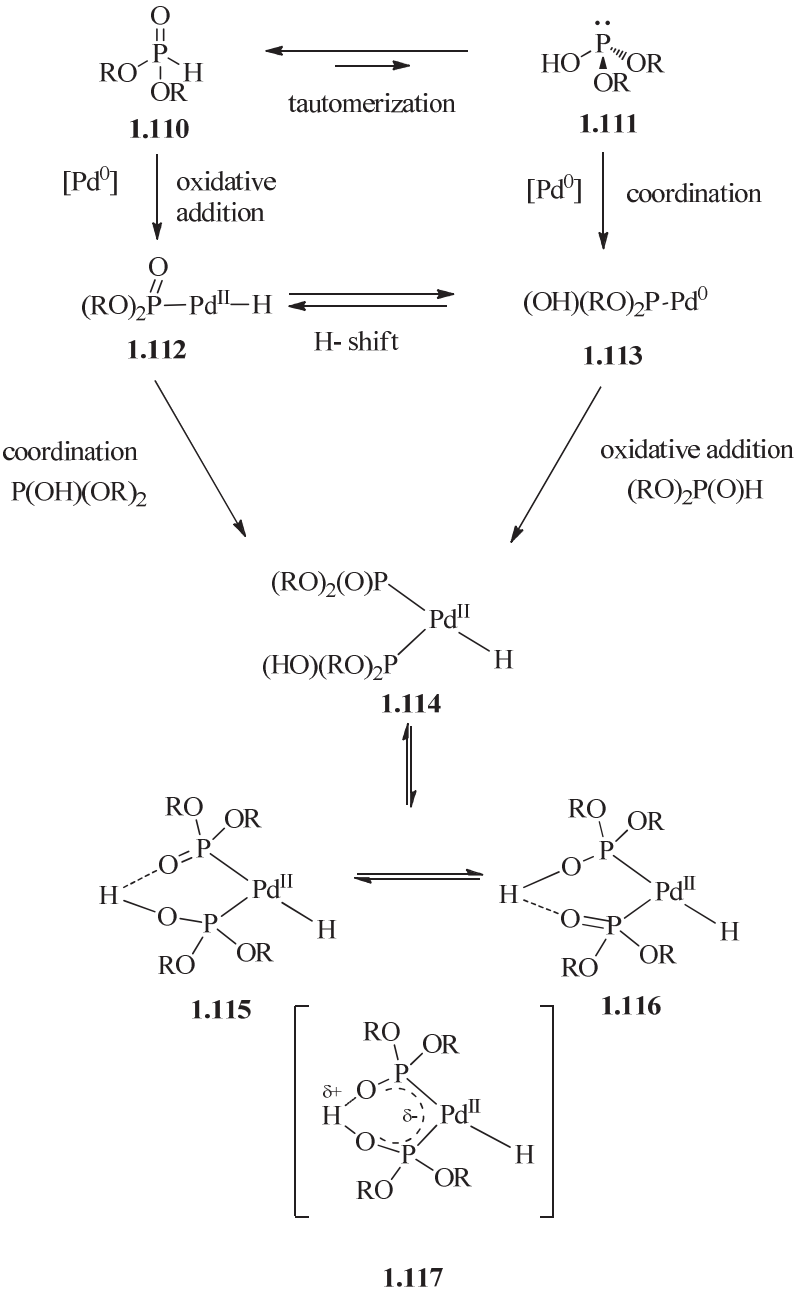


Scheme 1.31

This assumption is in the contradiction with certain papers of Tanaka's group. They thought of forming both products, branched and linear, *via* hydropalladation pathway.[5,16] However, there is no mechanistic studies to prove it. Additionally, the calculations made by Beletskaya do not solve this problem as well.[31] In the light of the literature data, there is no reliable computational work explaining mechanistic insight.

[30] Ananikov V. P., Ivanova J., Khemchyan L. L., Beletskaya I. P., *Eur. J. Org. Chem*. **2012**, 3830
[31] a) Ananikov V. P., Makarov A. V., Beletskaya I. P., *Eur. J. Org. Chem*. **2011**, 17, 12623, b) Ananikov V. P., Beletskaya I. P., *Chem. Asian. J.*. **2011**, 6, 1423

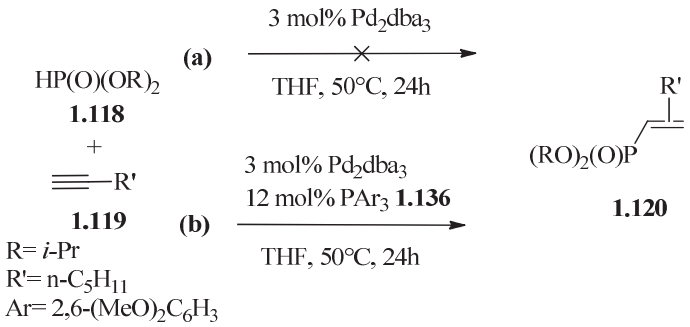
The reagents having the P(O)-H bond not only undergo oxidative addition. They can also behave as a ligand and launch other transformations, mainly due to the tautomerization of the P(O)H group resulting from the equilibria between **1.110** and **1.111,** *Scheme 1.32* (**Section 2.1**). The simplified oxidative addition step in *Scheme 1.31* gets complicated as shown in *Scheme 1.32*. The example is given with *H*-phosphonate **1.110**.[30]



Scheme 1.32

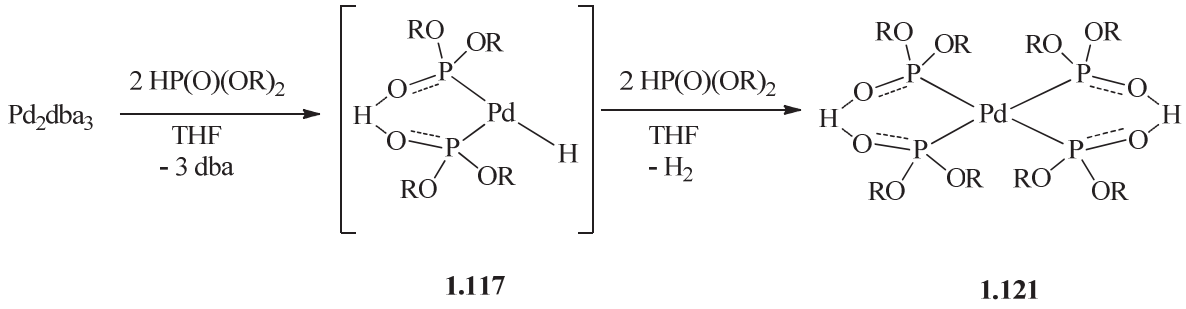
As shown in the *Scheme 1.32*, the palladium complex **1.114** can form an intramolecular hydrogen bond to form species **1.117** (it has been observed also in Tanaka's work, described in **Section 3.2**. *Scheme 1.14*).

In the recent work of Beletskaya, it has been experimentally proved that Pd-catalyzed addition of $(i\text{-PrO})_2P(O)H$ to the triple bond of alkynes cannot proceed without phosphine ligand PAr_3 **1.136** (*Scheme 1.33,* run **(a)** and **(b)**).[30]



Scheme 1.33

However, an experiment taken without alkyne **1.119** and PAr_3 ligand **1.136** shows formation of the complex with *H*-phosphonate, but not as species **1.117** (*Scheme 1.34*). The additional oxidative step results in formation of complex **1.121** instead of expected **1.117**.[30]

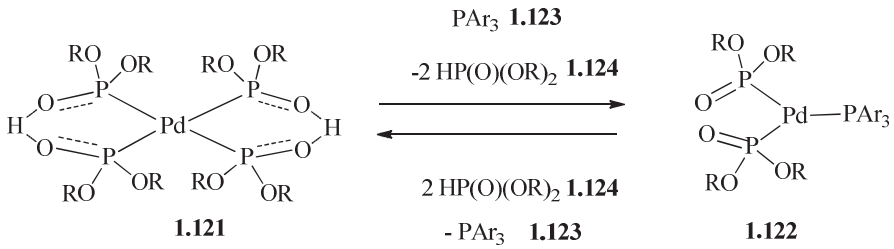


Scheme 1.34

Decomposition of hydride complexes accompanied by hydrogen evolution is a known reaction in the case of P–H.[32] It seems that during the oxidative addition stage, the formation of hydride complex **1.117** is a slow step, followed by a relatively fast step leading to detectable complex **1.121** (*Scheme 1.34*). In *Scheme 1.33* run **(a)**, obviously**,** the complex **1.121** (*Scheme 1.34*) is inactive in the reaction mixture**.** However, when PAr_3 **1.123** is added to the complex **1.121** an equilibrium is established between **1.121** and **1.122** (*Scheme 1.35*).

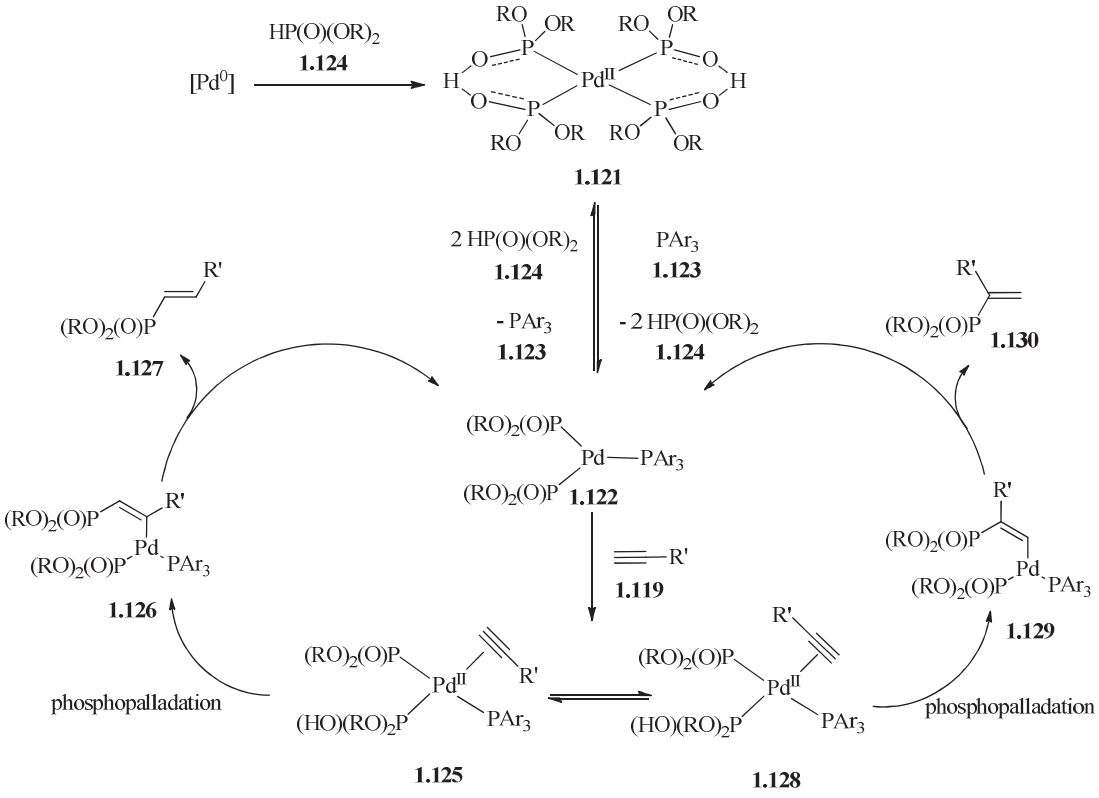
[32] a) Glueck D. S., *Top.Organomet. Chem*. **2010**, *31*, 65; b) Ananikov V. P., Khemchyan L. L., Beletskaya I. P., Starikova Z. A., *Adv. Synth. Catal*.,**2010**, *352*, 2979; c) Mizuta T., Miyaj C. i, Katayama T., Ushio J., Kubo K., Miyoshi K., *Organometallics* **2009**, *28*, 539; d) Coudray L., Montchamp J.-L., *Eur. J. Org. Chem*. **2008**, 3601; e) Delacroix O., Gaumont A. C., *Curr. Org.Chem*. **2005**, *9*, 1851; f) Tanaka M., *Top. Curr. Chem.* **2004**, *232*, 25

This equilibrium can be easily manipulated by changing the concentration of PAr_3 **1.123**. Despite the higher concentration of *H*-phosphonate **1.124** compared to PAr_3 **1.123**, the introduction of a much better ligand like PAr_3 shifts the equilibrium to the right. The interaction between **1.121** and the phosphine ligands **1.123** results in **1.122**, which is active in the reaction mixture leading to formation of the product (*Scheme 1.33* run **(b)**).[30] It has to be highlighted that in this case, there is no possibility for the addition across the alkyne *via* hydropalladation (no Pd-H bond). The only possibility lies in the phosphopalladation. That means that the reaction in *Scheme 1.33* run **(b)** goes via phosphopalladation of alkyne **1.119.**



Scheme 1.35

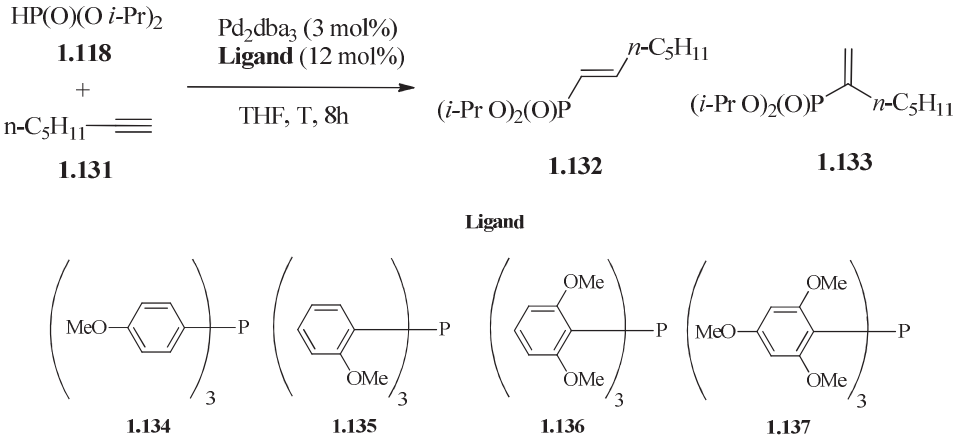
Beletskaya suggests the following catalytic cycle (*Scheme 1.36*).[30]



Scheme 1.36

Following the cycle, complex **1.121** is inactive because all positions of the four-coordinate Pd complex are taken by phosphorus ligands. This do not allow the coordination to the alkyne **1.126** (*Scheme 1.36*). The presence of PAr_3 **1.123** let the complex **1.121** convert into **1.122.** The species **1.122**, in the contrary to **1.121**, have a coordination vacancy, so the binding of the alkyne **1.119** is possible and complexes **1.125** and **1.128** are formed. Those complexes differ in terms of the orientation of the R' group of alkyne **1.119** (*Scheme 1.36*). Then, phosphopalladation of alkyne **1.119** leads to the complex **1.126** and further, to formation of the *anti*-Markovnikov product **1.127**, whereas phosphopalladation of **1.128** generates complex **1.129** and end up with the Markovnikov product **1.130**.[30]

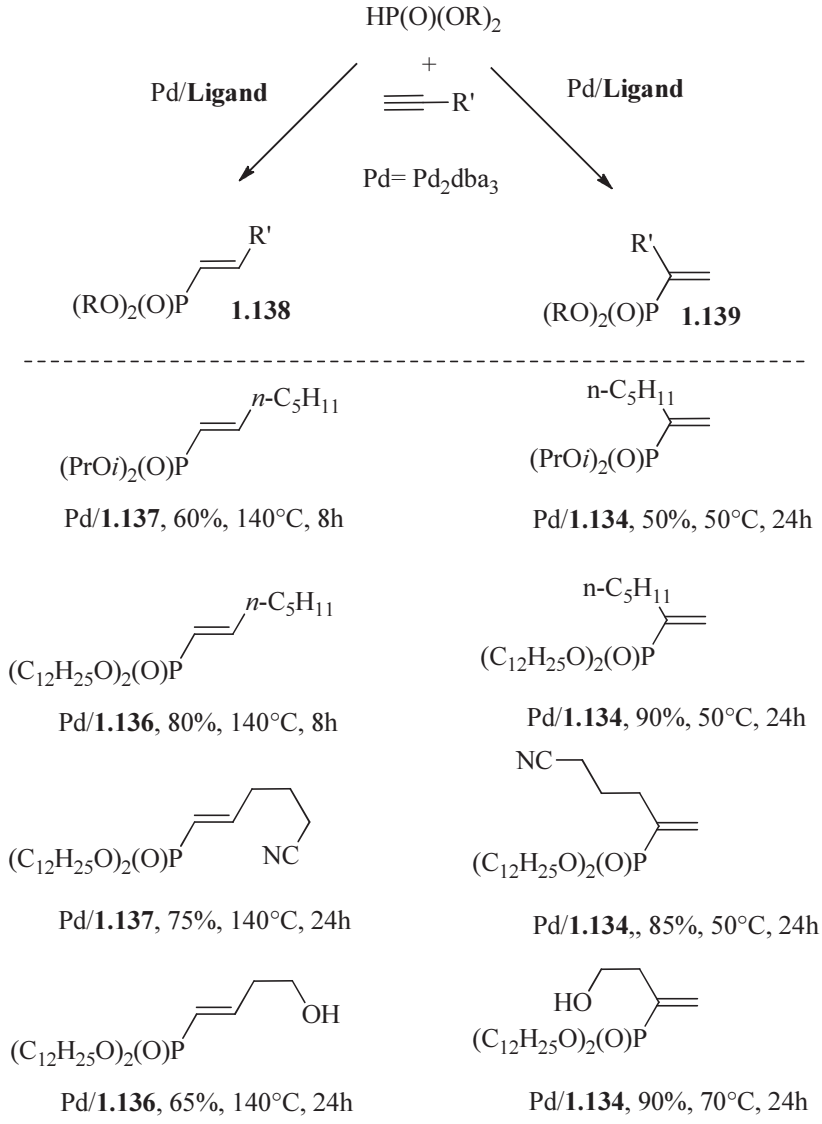
Beletskaya and co-workers described new methodology of palladium-catalyzed hydrophosphonylation based on the results described above. Her group investigated a new catalytic system by exploring the possibilities of use of various PAr_3 **1.123** ligands, some of the trials are shown in *Scheme 1.37*. It is shown, that the best yield of branched product **1.133** is achieved by using *p*-MeO-substituted ligand **1.134** (*Scheme 1.37*, entry 1). Change to *o*-MeO-substituted ligand **1.135** (*Scheme 1.37*, entry 2) results in poor yield. The presence of 2,6- $(MeO)_2$- and 2,4,6- $(MeO)_3$- substituted ligands **1.136** and **1.137** led to the linear products **1.132** but with moderate selectivity and in higher temperature (*Scheme 1.37*, entries 3-4).[30]



Entry	Ligand	T[°C] Time= 8h	Yield [%]	Product selectivity 1.132/1.133
1.	**1.134**	50	56	0:100
2.	**1.135**	50	21	0:100
3.	**1.136**	140	81	84:16
4.	**1.137**	140	70	80:20

Scheme 1.37

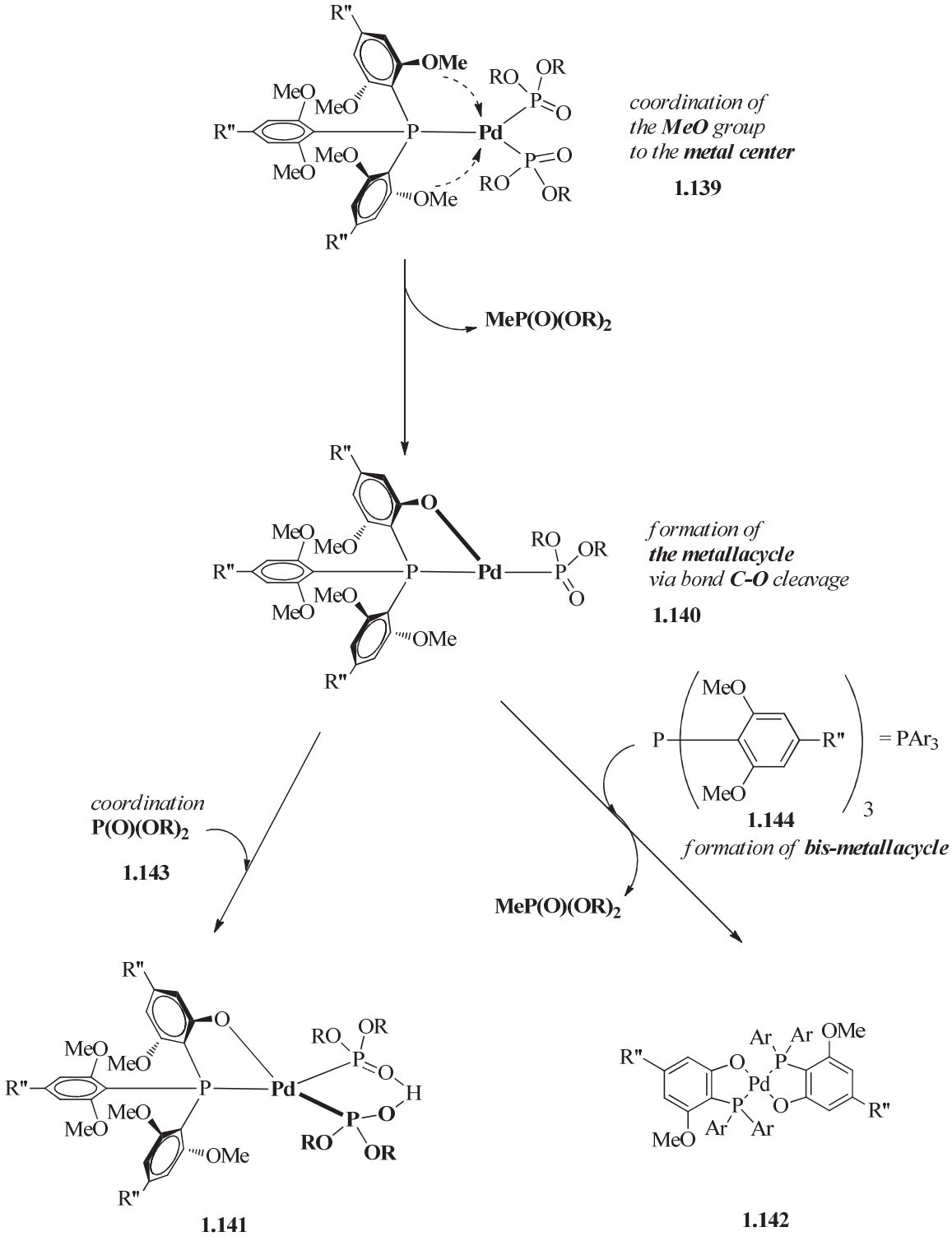
The reaction of different *H*-phosphonates with various alkynes resulted in the series of products **1.138** in 60–85% yield and products **1.139** in 50–90% yields with some examples given in *Scheme 1.38*.[30]



Ligands 1.134-1.137 as indicated in *Scheme 1.37*

Scheme 1.38

There is an evidence that the MeO group of the ligands **1.134-1.137** coordinates to the metal center of **1.139** *via* C–O bond breakage and formation of metallacycle **1.140** (*Scheme 1.39*).



Scheme 1.39

Metal complex **1.141** occurs when the phosphorus reagent **1.143** is coordinated to the complex **1.140**. The coordination of **1.140** to the second phosphine ligand **1.144** leads to the formation of bis-metallacycle **1.142**. It is suggested that in the catalytic addition reaction, complex **1.140** might be the intermediate in the catalytic cycle. Considering complex **1.142**, it

is thought to degradatde in reaction conditions. However, this is not yet confirmed in the light of the existing knowledge.[30]

Beletskaya proposed that for the ligands **1.134-1.137** (*Scheme 1.39*) two pathways are possible towards the formation of vinylphosphonates. In **Figure 1.4**, there are four possibilities of alkyne alignment. The conformers **1.145** and **1.147** have restricted rotation resulted from the coordination of the aryl group of phosphine ligand. The figures **1.146** and **1.148** have unrestricted rotation without coordination.[30]

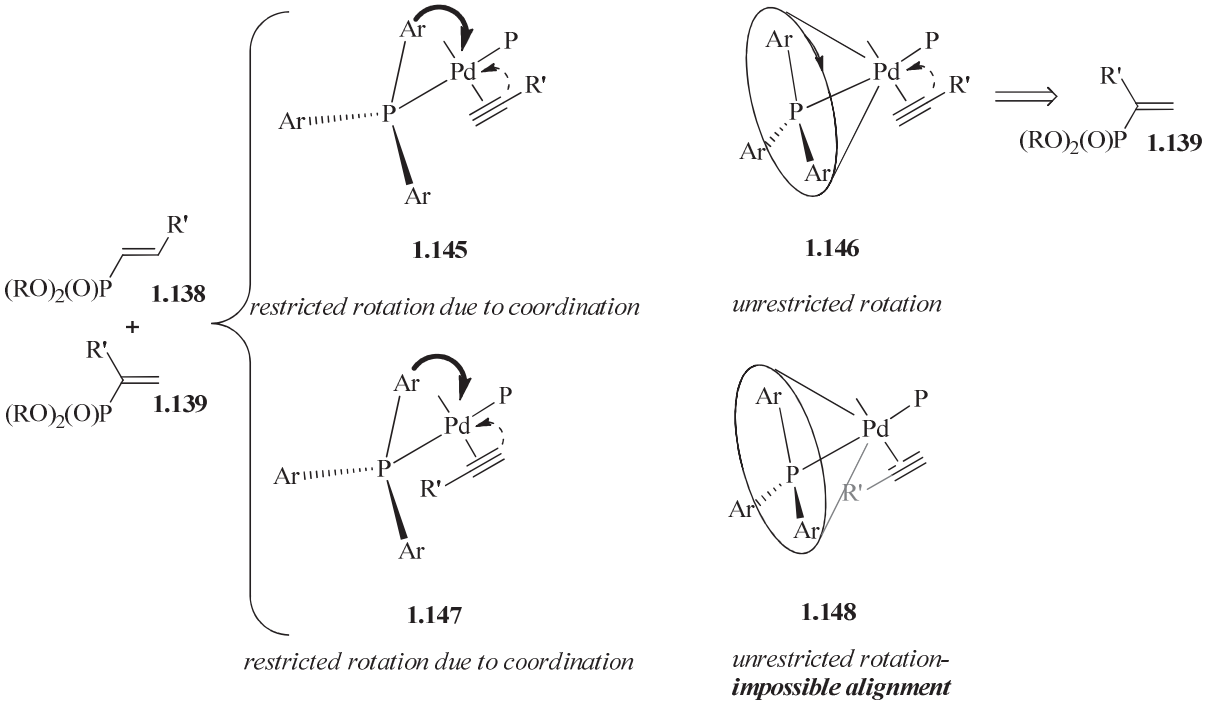


Figure 1.4 Arrows show steric contacts

With restricted rotation around the Pd–P bond (**Figure 1.4**, **1.145** and **1.147**) the catalytic reaction gives a mixture of **1.138** and **1.139**, with **1.138** being the dominant (*Scheme 1.38*). The overall **1.138/1.139** selectivity of the products for these ligands depends on the nature of both the alkyne and the *H*-phosphonate. The pathway leading to **1.138** is not possible for ligands with unrestricted rotation around the Pd–P bond (**Figure 1.4, 1.148**), whereas **1.139** should be accessible according to possible alignment of the alkyne and the PAr_3 ligand (**Figure 1.4, 1.146**). For that reason, selective formation of **1.139** can be obtained with complexes formed from the P(4-$MeOC_6H_4$)$_3$ ligand **1.134** (*Scheme 1.37*) in high selectivity and high yields (*Scheme 1.38*).[31]

3.6. Conclusions.

In the light of existing literature there are still numerous questions to answer about the catalytic mechanism of P(O)-H addition to alkenes and alkynes. Most of the publications (with the biggest contribution of Tanaka *et al.*) incline towards the hydrometalation process, but these assumptions are not confirmed. Beletskaya suggests that both processes (phosphometalation and hydrometalation) are taking part in the overall catalytic cycle. However, it is not consistent with the group's mechanistic calculations. Due to the specific reactivity known for phosphorous reagents, the calculations led to rather complex picture and controversial conclusions about the reaction mechanism. The lack of mechanistic knowledge makes it difficult to accomplish rational design of new catalytic procedures for synthetic purposes. However, the group of Beletskaya achieved excellent results by developing new catalytic systems that offers significant control of regioselectivity of the addition reaction by adjusting the positions of the methoxy groups in PAr_3 ligand. This recent report has definitely an impact on the development of new strategies for more sophisticated methodologies.

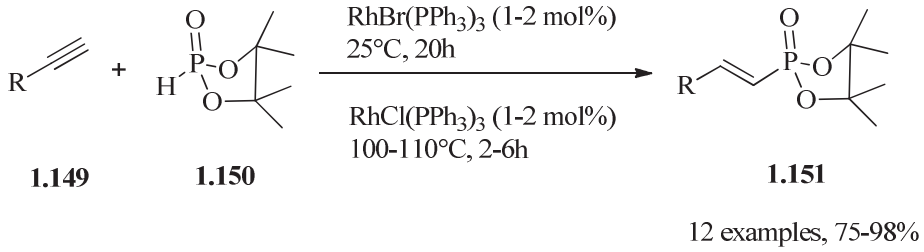
4. Hydrophosphonylation with pinacol phosphonate.

4.1. Developed methodologies, reactivity and mechanistic insights.

The reactivity of five-membered cyclic (pinacolato)P(O)H **1.150**, 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide, is much more remarkable than other acyclic *H*-phosphonates described previously in this manuscript, especially in terms of the metal-catalyzed additions.[33]

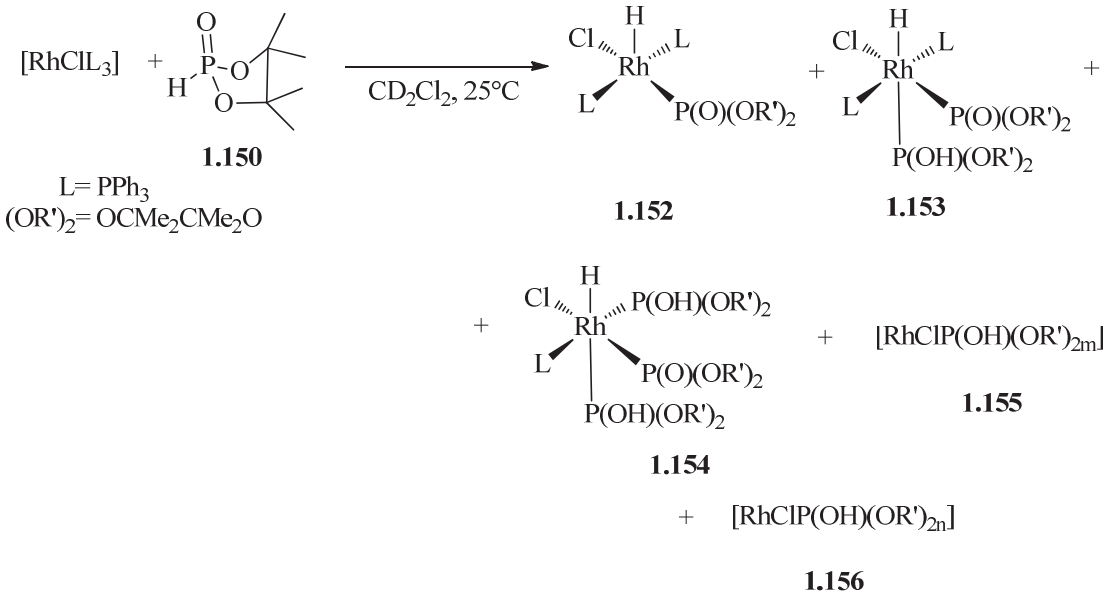
Starting from rhodium-catalyzed reactions *Scheme 1.40*, (pinacolato)P(O)H **1.150** can be added to the alkynes even at room temperature to produce the (*E)*-alkenylphosphonates **1.151** with high selectivity.[33]

[33] (a) Han L.-B., Mirzaei F., Zhao C.-Q., Tanaka M., *J. Am. Chem. Soc*., **2000**, *122*, 5407; b) Ajellal N., Thomas C.M., Carpentier J.-F., *Adv. Synth. Catal.* **2006**, *348*, 1093; c) Alnasleh B.K., Sherrill W.M., Rubin M., *Org. Lett*., **2008**, *10*, 3231



Scheme 1.40

Variety of functional groups of **1.149** are tolerable, namely: chloro, cyano, hydroxyl, thienyl and silyl. As in rhodium-catalyzed hydrophosphinylation of secondary phosphine oxides (**Section 3.2**, *Scheme 1.19*), catalytic cycle involves an oxidative insertion of Rh(I) into the H-P(O) bond.[34] Spectroscopic studies describe an interesting behavior of rhodium complexes as shown in the *Scheme 1.41.*[35]

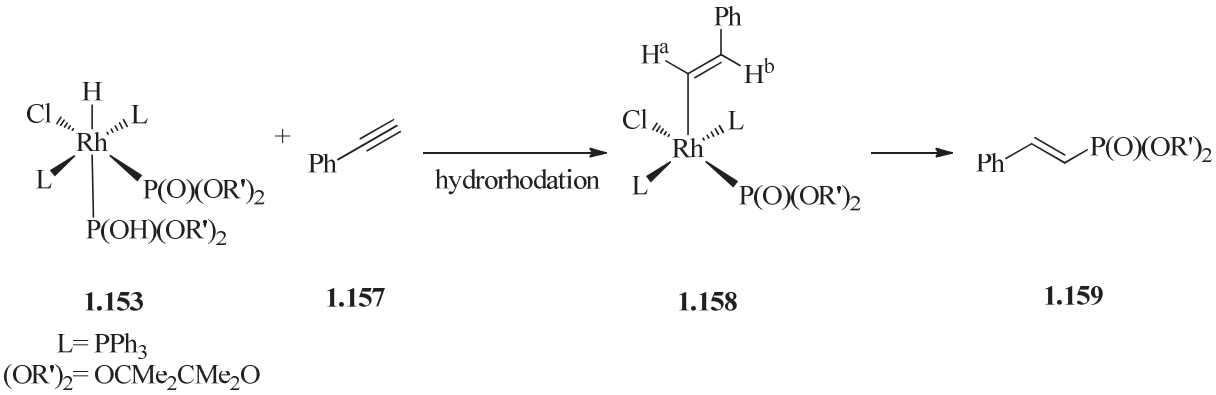


Scheme 1.41

Apparently, the formation of three Rh^{III} complexes **1.152-1.154** occurs. Their ratio varies along with the reaction time changing from the value of 1/2.5/0.31 after 3.5 h to 1/4.82/3.36 after 22h. Obviously, that indicates an equilibrium among them and is significantly dependent on the (picolato)P(O)H and Rh catalyst ratio, all together with the choice of a solvent. It was proven, that large excess of P(O)H donor suppresses coordination

[34](a) Roundhill D. M., Sperline R. P., Beaulieu W. B., *Coord. Chem. Rev*. **1978**, *26*, 263; (b) Bennett M. A., Mitchell T. R. B., *J. Organomet. Chem*. **1985**, *295*, 223; c) Varshney A., Gray G. M., *J. Organomet. Chem*. **1990**, *391*, 415.
[35] Zhao C.-Q., Han L.-B., Goto M., Tanaka M., *Angew. Chem. Int. Ed.,* **2001***, 113*, 10

of PPh_3 and thus enhances the generation of complexes **1.155** and **1.156**. They are inactive towards hydrophosphonylation. The process is very much solvent-dependent. For that reason, acetone was chosen because it maintains high concentration of active complex **1.154** regardless the excess of phospholane oxide **1.150**. The mixture of complexes **1.155** and **1.156** was observed in parallel experiment in toluene. In conclusion, complexes **1.152-1.154** are reactive towards hydrorhodation (the addition across triple bond) leading to the intermediate **1.158**. Subsequent reductive elimination produces efficiently the product **1.159** *Scheme 1.42*.[35]



1.153 **1.157** **1.158** **1.159**

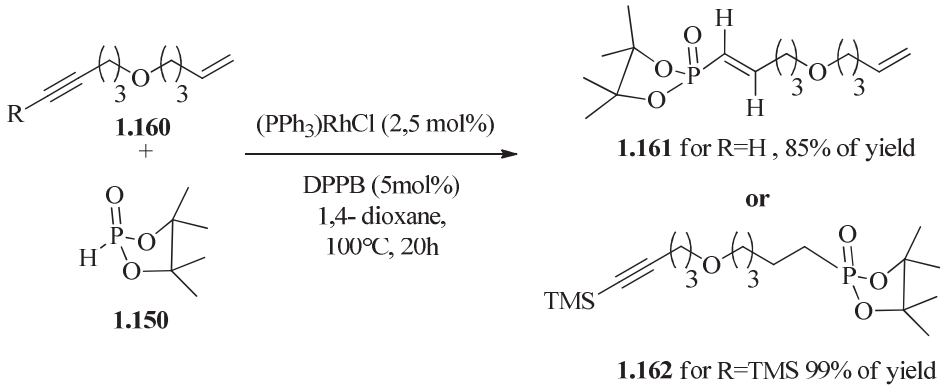
L= PPh_3
$(OR')_2$= $OCMe_2CMe_2O$

Scheme 1.42

The (pinacolato)P(O)H **1.153** plays significant role in the metal-catalyzed selective hydrophosphonylation reactions not only towards alkynes, but also terminal alkenes, which remain one of the very few examples of such reactivity.[36]

Under conditions indicated in *Scheme 1.43*, the compound **1.161** is achieved as the sole product with enyne **1.160** when R= H. The other end of the molecule (double bond) remains intact. However, the substitution of the alkyne **1.160** with a TMS group prevents parallel addition and favors the hydrophosphonylation of the double bond producing exclusively compound **1.162**.[36]

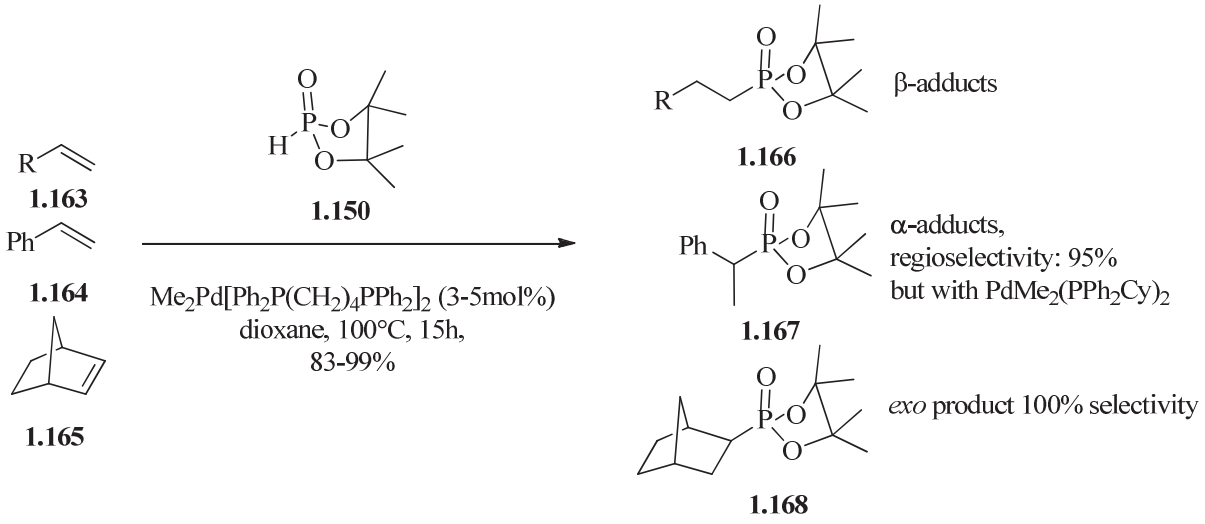
[36] Reichwein J. F., Patel M. C., Pagenkopf B. L., *Org. Lett*. **2001**,*3*, 4303



Scheme 1.43

Under the same conditions, *trans* internal double bonds remain intact, and only terminal alkenes react.[36]

The Pd-catalyzed hydrophosphonylation of alkenes **1.163** has been explored as well (*Scheme 1.44*).[37] *Anti*-Markovnikov products **1.166** are mainly obtained under the indicated conditions. Styrene **1.164** is an exception giving α- adduct **1.167**. Noteworthy, internal cyclic alkenes can also react and norbornene **1.165** gives the best results. Reaction with pentene also proceeds in good yield (87%), although slower (48h). On the contrary, cyclohexene reacts with poor yield of 37% within 48h. Obviously, the ring strain plays significant role here, thus the more exposed double bond is, the better reactivity is achieved.[37]



Scheme 1.44

[37]Han L.-B., Mirzaei F., Zhao Ch.-Q., Tanaka M., *J. Am. Chem. Soc.,* **2000**, *122*, 5407

Under similar conditions acyclic **1.171** and six-membered cyclic hydrogen phosphonates **1.169** and **1.170** remain unreactive (**Figure 1.5**) proving that pinacolato phospholene oxide **1.150** has remarkable properties.[37]

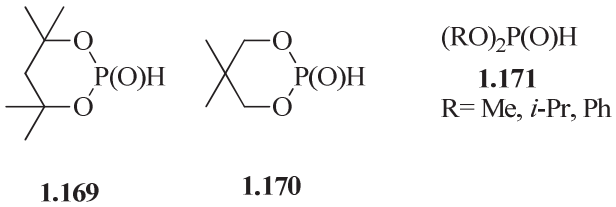
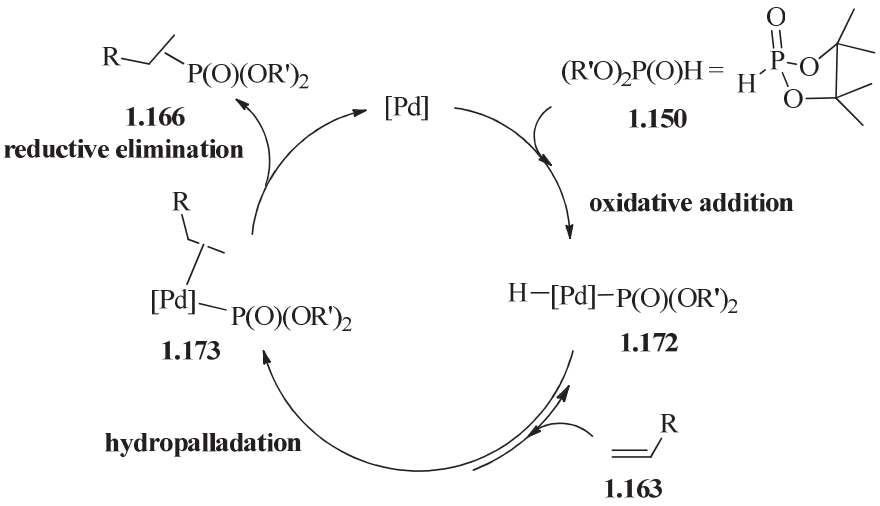


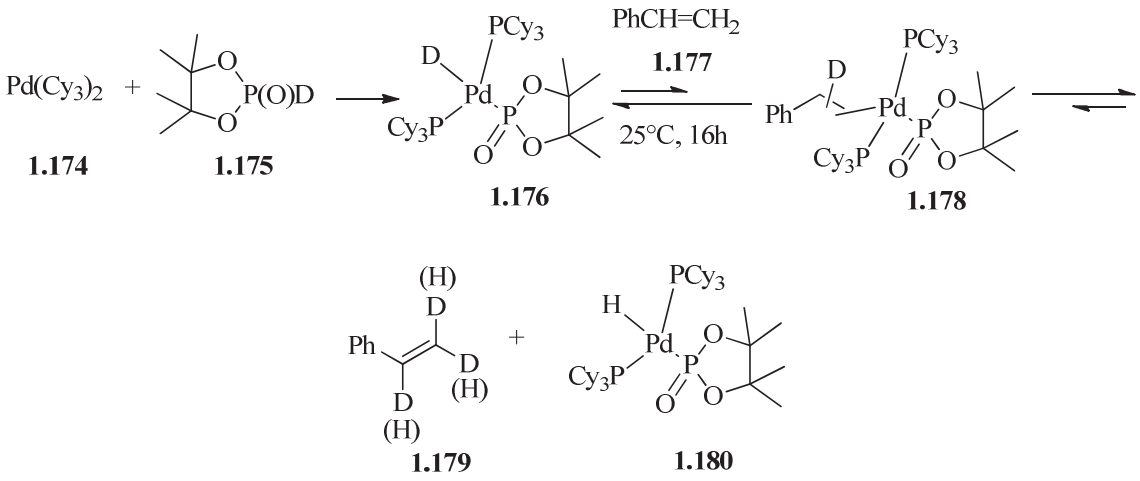
Figure 1.5

Mechanistic elucidation of the reaction is shown in *Scheme 1.45*. The hydrophosphorylation takes place as follows. Firstly, oxidative addition of **1.150** to Pd takes place with the formation of **1.172**, then the hydropalladation of **1.163** leads to **1.173.** Finally, the reductive elimination affords **1.166** adduct with regeneration of the palladium catalyst.[37]



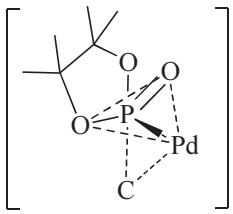
Scheme 1.45

Moreover, there is a rapid equilibrium between species **1.172** and **1.173** indicated in *Scheme 1.45***.** The authors claim that the reductive elimination of **1.166** from **1.173** is slow as compared with the backward reaction to **1.172** *via β*-hydrogen elimination. The separate H- D isotope effect experiments carried out by the group of Tanaka suggest that the hydropalladation is a facile process (*Scheme 1.46*). This assumption is supported by the fact of the presence of the deuterated styrene **1.179** in the reaction mixture and by ^{31}P NMR spectroscopy. At the same time, no product was observed. This suggests that the reductive elimination step might be rate-determining in this process.[37]



Scheme 1.46

Nevertheless, under conditions indicated in *Scheme 1.45* (pinacolato)P(O)H **1.150** does react providing the products **1.166** whereas all the other phosphonate reagents fail. (**Figure 1.5**). The remarkable synthetic properties of **1.150** can be explained by its tendency to lead to a trigonal bipyramidal-like transition state **1.181** that might appear upon catalysis (**Figure 1.6**).[37]



1.181

Figure 1.6

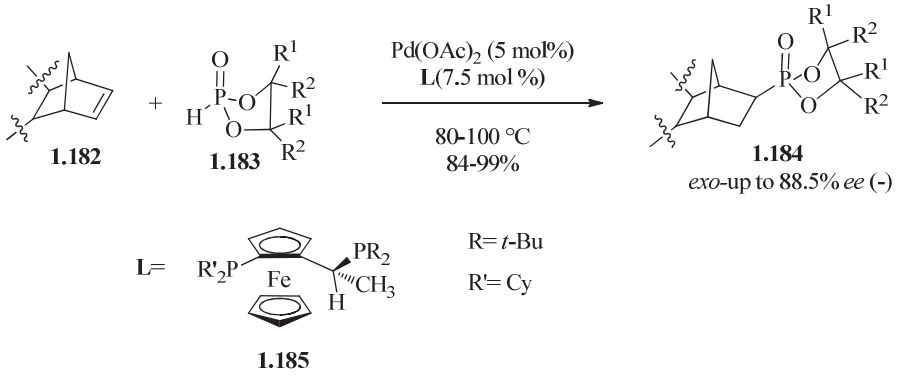
It is suggested that the ring occupies an apical and equatorial position with an O-P-O angle of 90° releasing its strain. The internal O-P-O ring angle of pinacol phosphonate **1.150** is estimated to be 99°, and it makes a difference of circa 5° less than the angles of its acyclic analogues. This can contribute to acceleration of the reductive elimination step.[37]

4.2. Metal-catalyzed assymetric addition of pinacol phosphonates to cyclic alkenes.

Pd-catalyzed hydrophosphonylation with pinacol phospholene oxides and alkenes can be perfomed in an asymmetric version to give optically active phosphonates.[38]

Methodology of palladium-catalyzed enantioselective addition to norbornenes **1.182** involves Josiphos ligand **1.185** (*Scheme 1.47*).[38]

[38] a) Xu Q., Han L.-B., *Org. Lett*. **2006**, *8*, 2099, b) Shulyupin M.O., Francio G., Beletskaya I.P., Leitner W., *Adv. Synth. Catal*., **2005**, *347*, 667; c) Barta K., Francio G., Leitner W., Lloyd-Hones G.C., Shepperson I.R., *Adv. Synth. Catal*. **2008**, *350*, 2013



Scheme 1.47

The steric bulkiness of the bidentate ligand is crucial to control the enantioselectivity of the reaction. It has been experimentally proved that higher enantiomeric excess *ee* comes along with the bulkier Josiphos ligands in the following order of substituents: *t*-Bu> Cy> Ph. Ligand **L 1.185** shown in *Scheme 1.47* gave the best result yielding 88.5% *ee* of the adduct in a model reaction with non-modified pinacol phosphonate **1.150** and norbornene **1.90** (**Figure 1.7**).[38]

Apart from the steric bulkiness of the ligands, the steric hindrance of the substrates is another important issue (**Figure 1.7**).

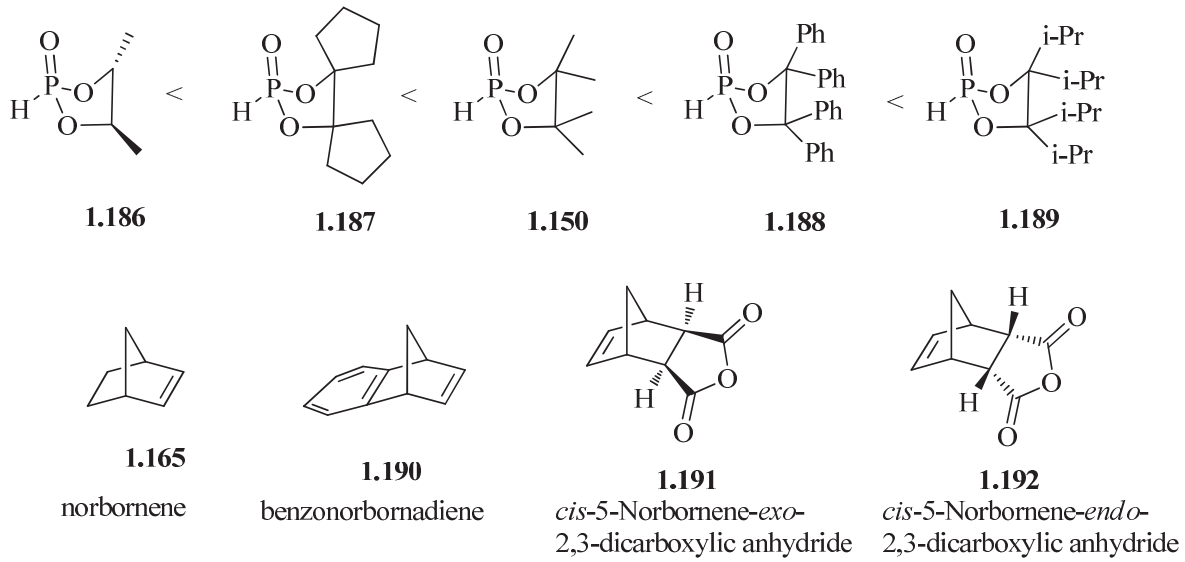
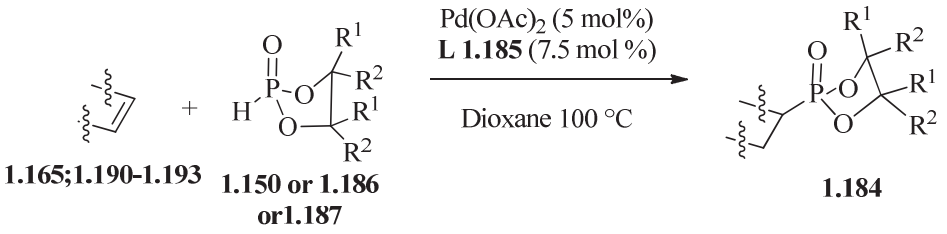


Figure 1.7

Pinacol phosphonates **1.150** and **1.186-1.189** were subjected to the reaction together with the substituted norbornenes **1.165** and **1.190-1.192** (*Scheme 1.48,* **Figure 1.7**). The increasing steric hindrance in order of **1.186** < **1.187** < **1.150** induces the increasing order of the corresponding product enantiomeric excess *ee* (*Scheme 1.48*).[38] The tendency of improving the *ee* of the adduct correlates with bulkier substituents, but *H*-phosphonates **1.188**

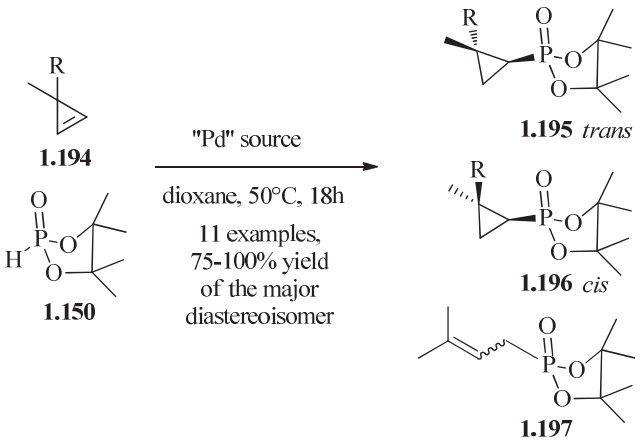
and **1.189** (**Figure 1.7**) remain inactive under the same conditions. However, good enantioselectivity can be achieved with norbornenes **1.190** and **1.191**. As indicated in the *Scheme 1.48*, species **1.192** (*endo* isomer of **1.191**), is inactive towards hydrophosphinylation and it is possibly due to the steric hindrance of the *endo*- dicarboxylic anhydride moiety.[38]



Entry	Substrates	Time [h]	Yield [%]	Product 1.184 *ee* [%]
1.	**1.186+ 1.165**	10	99	72.5(-)
2.	**1.187+ 1.165**	15	99	77.6(-)
3.	**1.150+ 1.190**	86	84	73.2(-)
4.	**1.150+ 1.191**	108	99	87.1(+)
5.	**1.150+ 1.192**	53	---	---

Scheme 1.48

Metal-catalyzed hydrophosphonylation of cyclopropenes was achieved by Rubin *et al*. (*Scheme 1.49*).[39]



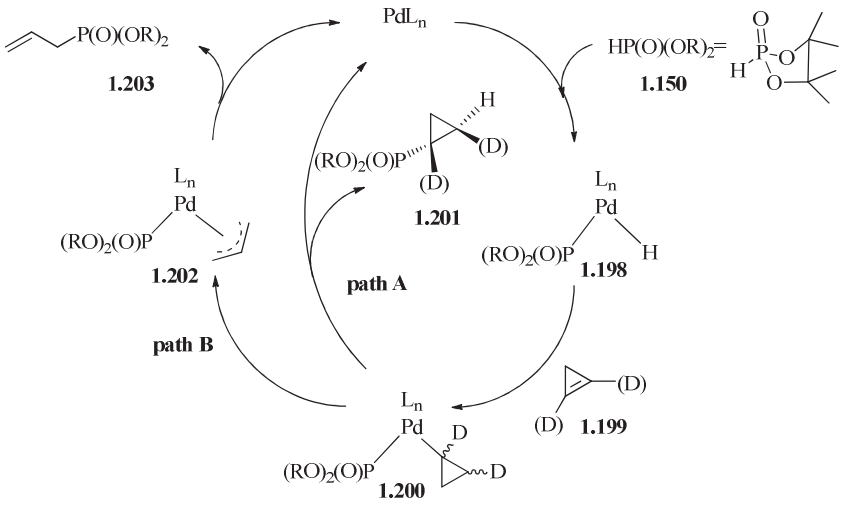
R	Catalyst	Yield [%] (1.195/1.196)	Yield (1.197) [%]
Ph	$Pd(PPh_3)_4$	89 (19/1)	6
COOMe	Pd_2dba_3/dppf	97 (9/1)	0

Scheme 1.49

Noteworthy, thermal or radical variation of this reaction did not proceed. However in the presence of Pd catalysts, as shown in the table of *Scheme 1.49*, the addition of P(O)H

[39] Rubin M., Sherill W. M., Alnasleh B. K., *Org. Lett*., **2008**, *10*, 3231

group occurs under mild conditions forming three products **1.195-1.197**. Reaction affords the isomeric mixture of the desired products **1.195** and **1.196**, with preference to the *trans* adduct. The scope of the reaction involves different functionalized cyclopropenes. Proposed mechanistic pathway is presented below. It was supported by an experiment with a deuterium labeled cyclopropene (*Scheme 1.50*).[39]



Scheme 1.50

The oxidative addition of palladium to P- H bond of **1.150** produces palladium hydride species **1.198**. Subsequently, the addition of the cyclopropene **1.199** leads to the cyclopropylpalladium complex **1.200**, which undergoes reductive elimination (**path A**) and affords product- cyclopropylphosphonate **1.201**. This reaction is *syn*-specific. The formation of allylphosphonate **1.203** is rationalized in the alternative **path B**. It requires higher temperatures. Species **1.200** undergo ring cleavage via *β*-carbon elimination.[40] The resulting $^{3}\eta$-allylpalladium species **1.202** afford, after reductive elimination, allylphosphonate **1.203**.[39]

4.3. Conclusion

All of the above reactions take advantage of the exceptional reactivity of the five-membered *H*-phosphonates. These metal-mediated additions of H-P(O) to alkenes are far from being general, especially if compared with the corresponding metal-catalyzed additions of H-P(O) to carbon-carbon triple bonds. Alkenes with other H-P(O) compounds cannot

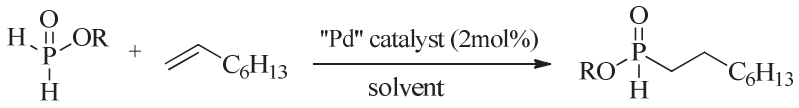
[40] Rubin M.; Rubina M.; Gevorgyan V. *Chem. Rev.* **2007**, *107*, 3117

undergo reaction under similar conditions and, in fact, the radical initiated H-P(O) bonds additions to alkenes are more general and convenient (**Section 2.2**).[41]

5. H-P(O) addition to alkenes. Developed methodologies and elucidation of mechanisms

The metal-catalyzed additions of H-P(O) compounds to carbon double bonds is a bigger challenge than the additions to triple bonds. This field is still dominated by radical methodologies (**Section 2.2**), which suffer from the lack of regiocontrol and stereocontrol. Therefore, it is of interest to develop new metal-catalyzed methods that would provide the full control of resulting products. Especially enantioselective procedures are desired. Until now, only pinacol phosphonate **1.150**, amongst the H-phosphonates, is reactive towards inactivated alkenes (**Section 4)**.

In the light of existing literature, the hydrophosphinylation with the unsubstituted phosphinic acid and its derivatives **1.204** found the application in the addition of H-P(O) to alkenes.[42] The work of Montchamp *et al*. proved that hypophosphorous acid and its esters **1.204** add to alkenes in the presence of palladium catalysts (*Scheme 1.51*).[42]



1.204 **1.205** **1.206**

Entry	R	Solvent (reflux, t= 12-16h)	Catalyst	Yield 1.206* [%]
1.	Butyl	CH_3CN	$Cl_2Pd(PPh_3)_2$/MeLi	65
2.	Butyl	THF	$Cl_2Pd(PPh_3)_2$/MeLi	100
3.	Butyl	toluene	$Cl_2Pd(PPh_3)_2$/MeLi	78
4.	Butyl	toluene	$Cl_2Pd(PPh_3)_2$/MeLi	86
5.	Butyl	toluene (rt)	$Cl_2Pd(PPh_3)_2$/MeLi	18
6.	Butyl	CH_3CN	Pd_2dba_3/dppf	86
7.	Butyl	CH_3CN	Pd_2dba_3/xantphos	100
8.	Butyl	CH_3CN	Pd_2dba_3/xantphos	90
9.	Butyl	CH_3CN	Pd_2dba_3/DPEphos	100
10.	Ethyl	toluene	$Cl_2Pd(PPh_3)_2$/MeLi	86
11.	Ethyl	THF	$Cl_2Pd(PPh_3)_2$/MeLi	70
12.	Ethyl	CH_3CN	Pd_2dba_3/xantphos	92

[41] a) Rauhut M.M., Currier H.A., Semse A.M. l, Wystrach V.P., *J. Org. Chem*. **1961**, *26*, 5138; b) Rauhut M.M., Hechenbleikner I., Currier H.A., Schaefer F.C., Wystrach V.P., *J. Am. Chem. Soc*. **1959**, 81, 1103; c) L.-B. Han, C.-Q. Zhao, *J. Org. Chem*. **2005**, 70, 10121;
[42] Deprele. S., Montchamp J.-L., *J. Am. Chem. Soc*., **2002**, *124*, 9386

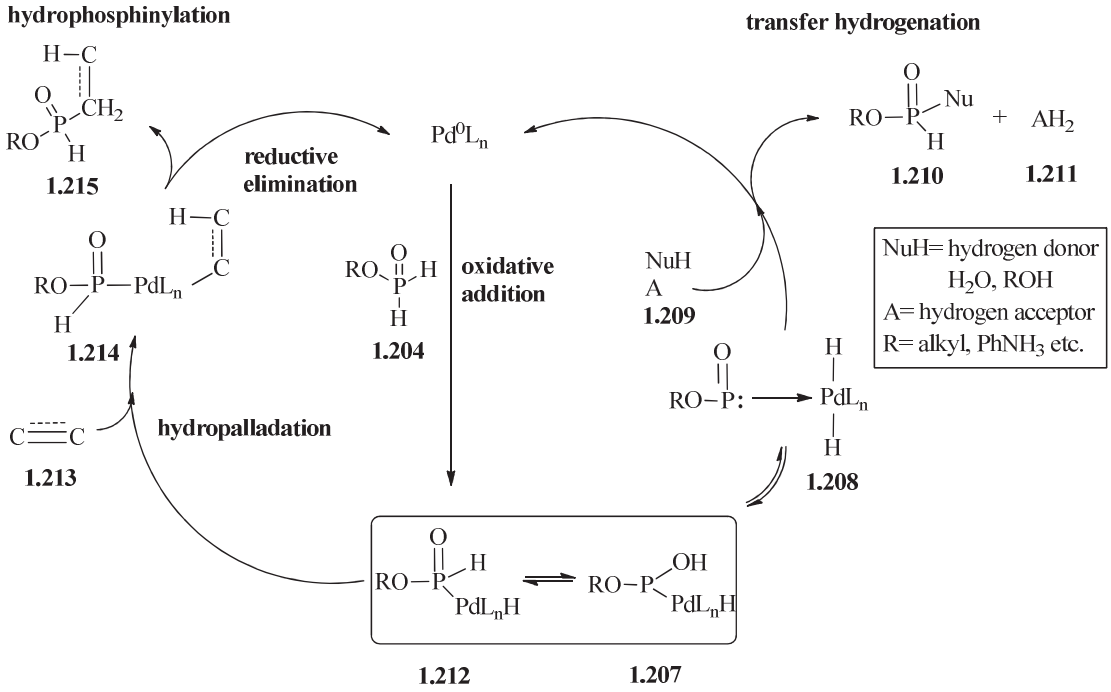
13.	Methyl	CH_3CN	Pd_2dba_3/DPEphos	100
14.	$PhNH_3$	DMF (80°C)	Pd_2dba_3/xantphos	93
15.	H	CH_3CN (rt)	Pd_2dba_3/xantphos	100
16.	H	H_2O,CH_3CN (rt)	Pd_2dba_3/xantphos	79

*** Determined by ^{31}PNMR of the crude reaction and integration of all the resonance**

Scheme 1.51

Table in *Scheme 1.51* exposes the most efficient catalytic systems to carry out the hydrophosphinylation. Four systems are found to be particularly useful: $Cl_2Pd(PPh_3)_2$/MeLi in toluene, THF, or acetonitrile and Pd_2dba_3/xantphos (or DPEphos, or dppf) in acetonitrile.

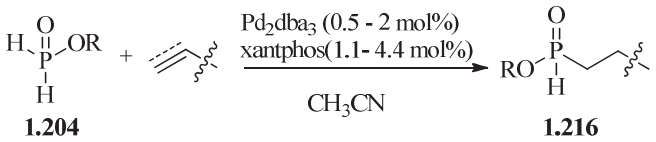
Possible pathways for catalytic reaction are presented in *Scheme 1.52*.



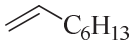
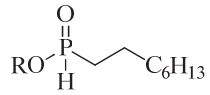
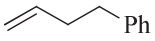
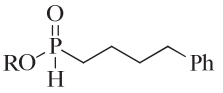
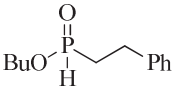
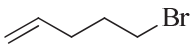
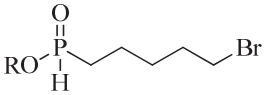
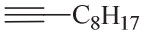
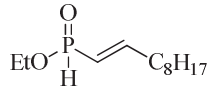
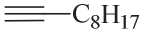
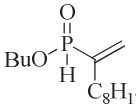
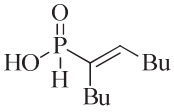
Scheme 1.52

Hydrophosphinylation remains the major pathway, even in the presence of alcohol or water excess **1.209**, which might lead to transfer hydrogenation[43] through trapping complex **1.212** and form **1.207** (*Scheme 1.52*). Actually, the reaction of aqueous H_3PO_2 with Pd_2dba_3/xantphos takes place at room temperature (Table, entry 16, *Scheme 1.51*), which clearly indicates the selectivity of this system favoring the hydrophosphinylation over the reduction (transfer hydrogenation). The mechanism that has been proposed is similar to the palladium-catalyzed hydrophosphonylation (**Section 3.1**). It proceeds through insertion of Pd(0) into a P-H bond to form **1.212.** Then the hydropalladation of alkene or alkyne **1.213**

leads to species **1.214** and the reductive elimination affords the product **1.215**. The competitive step of the transfer hydrogenation (**1.208** leading to **1.210)** is probably too slow to occur. In *Scheme 1.53*, several representative examples of the hydrophosphinylation are shown.[42]



1.204 **1.216**

Entry	Substrate	Product	1.216: R, Yield ^{31}PNMR [%] (isolated yield[%])
1.			R= Bu, **89**(76) R= H, **100**(67)
2.			R= Et **100**(84) R= H **81**(75)
3.			**100**(69) *linear/branched= 4.4/1
4.			R= Et **100**(61) R= H **100**(83)
5.			**75**(70) *linear/branched= 3.7/1
6.		 *$Cl_2Pd(PPh_3)_2$/MeLi (3mol%) in toluene (reflux)	**70** *branched only
7.			**100**(88)

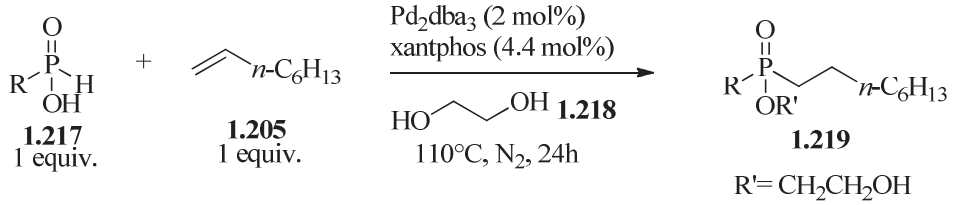
Scheme 1.53

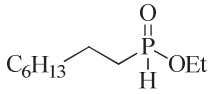
The system of Pd_2dba_3/xantphos is found to be very efficient, with catalyst load of 1 mol % or less (0.02 mol % still delivers a good yield of adduct after 24 h). As shown in *Scheme 1.53*, the reaction proceeds in good to excellent yields with various alkenes and alkynes as

[43] **Review**: (a) Johnstone, R. A. W.; Wilby, A. H. *Chem. Rev.* **1985**, *85*, 129. **Examples** (b) Khai, B. T.; Arcelli, A. *J. Org. Chem.* **1989**, *54*, 949.(c) Brigas, A. F.; Johnstone, R. A. W. *Tetrahedron* **1992**, *48*, 7735. (d) Marques, C. A.; Selva, M.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 529

substrates. The entry 6 (Table, *Scheme 1.53*) shows the branched vinylphosphinate as the sole product of the reaction with catalytic system consisting of $Cl_2Pd(PPh_3)_2$/MeLi in toluene (the possible influence of the solvent, **Section 3.4**, *Scheme 1.29*). The linear product is the major component with Pd_2dba_3/xantphos (Table, *Scheme 1.53*, entry 5). Noteworthy, species **1.210** are unreactive toward alkenes, and disubstitution is not observed. The same situation occurs with the products, *H*-phosphinic esters **1.215**. They remain intact under the reaction conditions and the formation of disubstituted phosphinic esters $R_2P(O)(OR)$ is not observed.[42]

The extension of the methodology that involves alkenes was not achieved until 2011. The same group developed the method for disubstituted phosphinic acids (*Scheme 1.54*).[44]



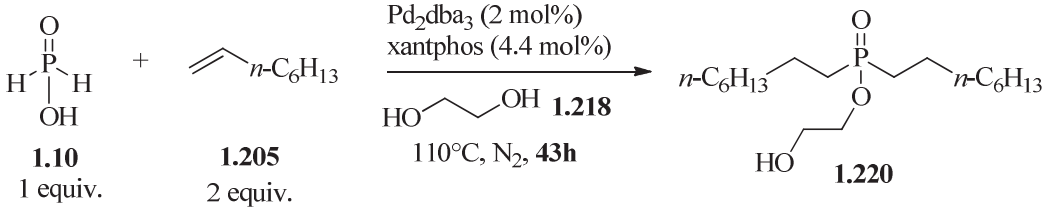
Entry	R Substrate 1.217	Yield 1.219 [%]
1.	Ph	56
2.	$Ph(CH_2)_4$	71
3.	$Ph(CH_2)_4$	57 *without xantphos
4.	$Ph(CH_2)_4$	63 *in propylene glycol R'= $CH_2CH_2CH_2OH$
5.	$BnO(CH_2)_3$	65
6.	C_8H_{17}	53
7.		54

Scheme 1.54

The monosubstituted acids **1.217** undergo the addition to 1- octene **1.205** in the presence of Pd_2dba_3/xantphos and ethylene glycol **1.218**. The disubstituted 2-hydroxyethyl phosphinate esters **2.119** are obtained in moderate yields 53-71% just after extraction process. Noteworthy,

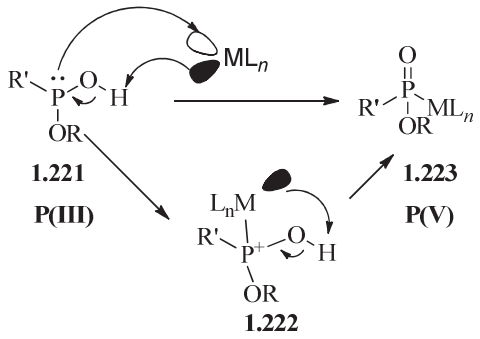
[44] Montchamp J.-L., Petit C, Fecourt F., *Adv. Synth. Catal*., **2011**, *353*, 1883

hypophosphorous acid **1.10** can be subjected to the reaction with 2 equivalents of 1-octene **1.205** to afford disubstituted phosphinate ester **2.220** although it requires prolonged reaction time (*Scheme 1.55*). It has to be highlighted, that the application of ethylene glycol **1.218** is crucial for the reaction. Its role is not fully understood but without this reagent, the reaction does not proceed. This is probably connected with the tautomerization of the monosubstituted phosphinic acid **1.217**.[44]



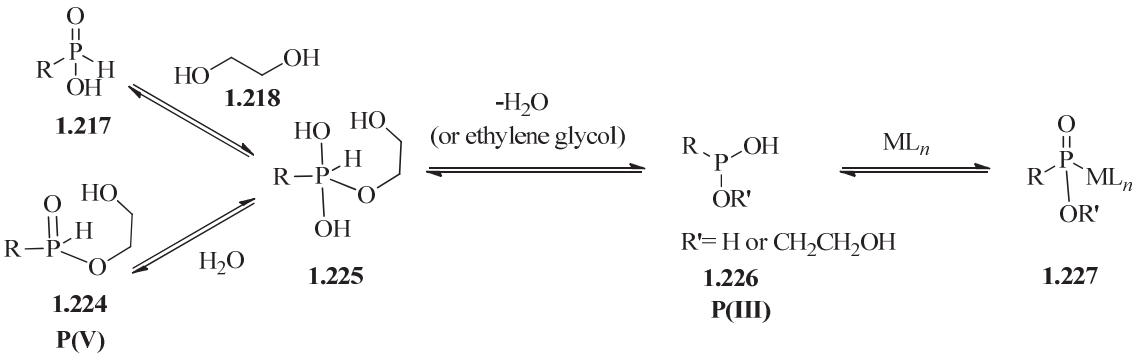
Scheme 1.55

The mechanism for the oxidative addition proposed by Montchamp proceeds through concerted or stepwise processes from the P(III) form **1.221**(*Scheme 1.56*). Particularly, through complexation of the phosphorous lone pair to the metal **1.223** is formed. According to the authors, the key reactivity lies in the tautomeric equilibrium and the availability of the P(III) **1.221** form in order to achieve the oxidative addition is crucial here. P(III) tautomer **1.221** of unsubstituted phosphinic acids or esters (for R'=H, *Scheme 1.56*) is more available than in the case of alkyl-H-phosphinates (for R'=alkyl, *Scheme 1.56*). Therefore, monosubstitution occurs readily, but second substitution cannot be observed under the same conditions.[44]



Scheme 1.56

Additionally, decomposition of the catalyst was observed during the disubstitution reaction (*Scheme 1.54*). For this reason, an overall rate of hydrophosphinylation plays also an important role. It has to be able to compete with the parallel loss of catalyst. Ethylene glycol is thought to increase the concentration of the P(III) tautomer of monosubstituted phosphinic acids *Scheme 1.57*.[44]



Scheme 1.57

The authors suspect that ethylene glycol **1.218** provokes the formation of phosphorane intermediate **1.225.** In the first place, 2-hydroxyethyl ester **1.224** is stabilized by hydrogen bonding and can undergo nucleophilic attack by H_2O to form **1.225**. Next, the phosphorane **1.225** possibly loses H_2O leading to P(III) tautomer **1.226** which allows the insertion of the metal **1.127.** The role of ethylene glycol is not confirmed in the light of existing literature.[44]

6. Conclusion to bibliographic studies.

The first chapter was devoted to the intermolecular hydrophosphinylation and hydrophosphonylation. The chapter described various methods of P(O)-H additions to unsaturated carbon-carbon bonds, which have been described in the literature. Numerous metal-catalyzed methodologies have been developed. However, as it has been highlighted, that the mechanism of these additions remains not fully understood. Therefore, the regiocontrol and the stereocontrol of the reaction are more difficult to achieve. The groups of Tanaka, Beletskaya and Montchamp contribute to the subject with the biggest amount of studies. Recent report of Beletskaya shows impressive strategy for designing new ligands for hydrophosphonylation of alkynes. However, the field still needs improvements. Especially in the additions to alkenes, which are a little-developed area. The asymmetric version of hydrophosphonylation is only known when using cyclic pinacolato(O)PH compound as substrate. No intramolecular hydrophosphonylation nor hydrophosphinylation have been reported until now. That indicates the requirements for future studies, and also highlights their challenging character from the synthetic viewpoint.

Chapter II

EXPLORING EXPERIMENTALLY INTER- AND INTRAMOLECULAR HYDROPHOSPHINYLATION AND HYDROPHOSPHONYLATION

1. The goal of the project.

As an objective for the proposed project, we planned to develop an asymmetric and catalytic synthesis of cyclic phosphonic and phosphinic acids and their derivatives of general formula shown in **Figure 2.1**.

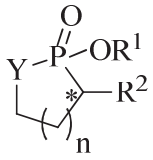


Figure 2.1

The target heterocycles would have 5 or 6 membered ring and possess P=O (phosphinyl) group integrated within. The group R^1 stands for the hydrogen atom or the alkyl esters, whereas the group R^2 is thought to be an aryl or alkyl substituent. We intended to obtain the target molecules in a diastereocontrolled manner. For this reason, we have chosen intramolecular hydrophosphinylation and hydrophosphonylation reactions, catalyzed by palladium complexes with non-chiral ligands like xantphos chosen as a model catalyst (**I Figure 2.2**). Subsequently, more sophisticated chiral ligands (examples in the **II Figure 2.2**) had been planned to be used, in order to achieve enantiocontrol of the outcoming products (**Figure 2.1**).

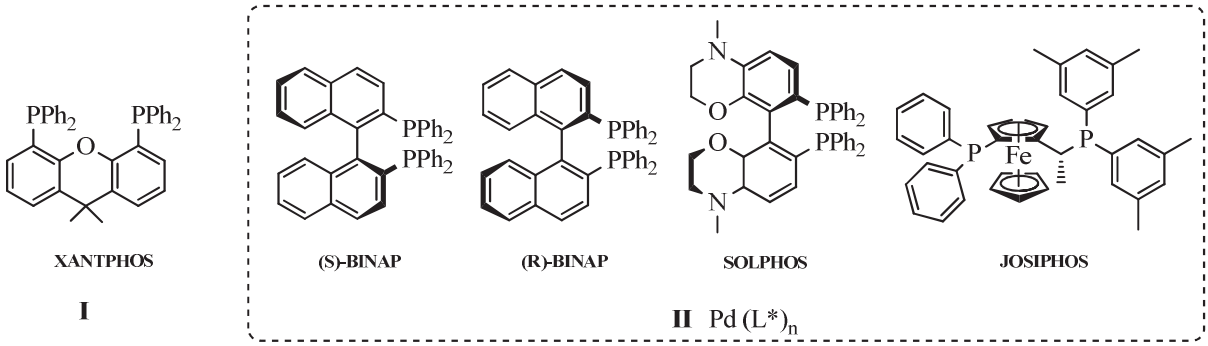
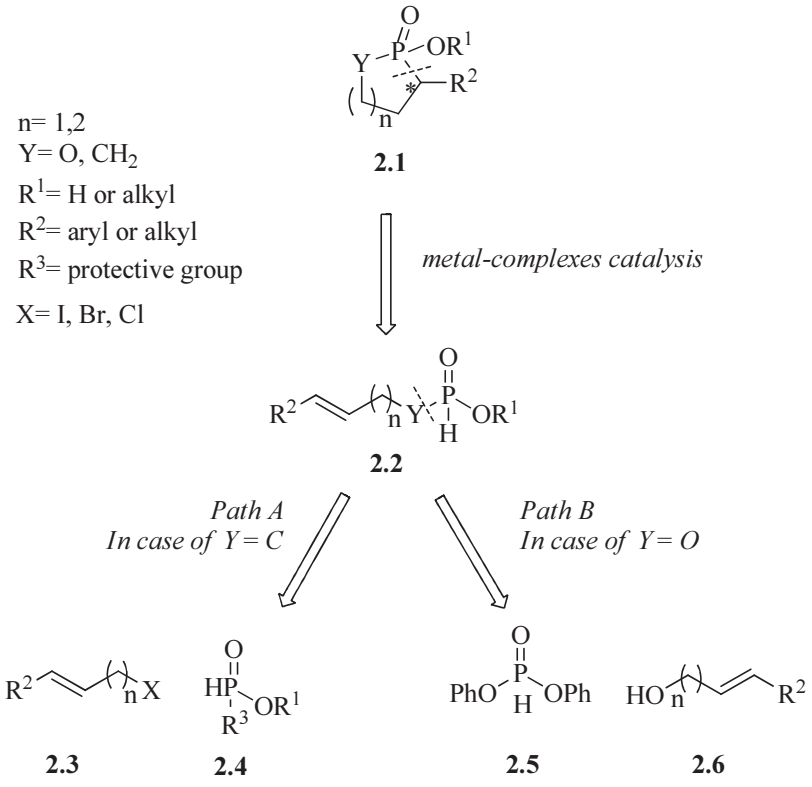


Figure 2.2

Metal-catalyzed intramolecular hydrophosphinylation and hydrophosphonylation have not been described in the literature so far, in the contrary to its intermolecular reactions described in ***Chapter I***. Additionally, only little is known about the asymmetric additions of P(O)-H to unactivated alkenes (***Chapter I,*** **Section 4**). The development of this methodology might be very interesting from a chemical and biological points of view.

2. Retrosynthetic analysis.

The synthetic strategy to access **2.1** (*Scheme 2.1*) was based mainly on the divergent intermolecular approaches of hydrophosphonylation and hydrophosphinylation, known in the literature and described in ***Chapter I***. We assumed that metal catalysis, especially the palladium chemistry, would be the most suitable. The retrosynthetic plan is presented in *Scheme 2.1*.

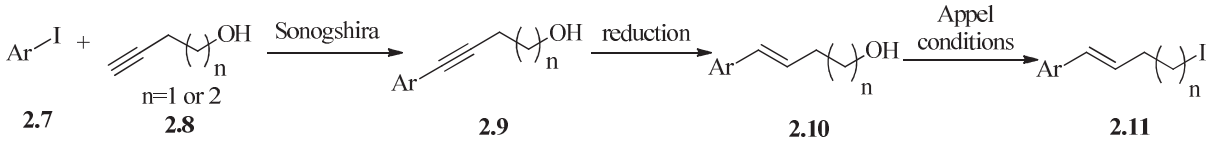


Scheme 2.1

The general strategy drawn herein required synthons for the target molecules. In case of *Path A* (*Scheme 2.1*) synthesis of compounds **2.2** that have internal double carbon-carbon bond as a *trans*-isomer, with the P(O)H group on the other end of molecule were designed. We had assumed, that the easiest way to synthesize **2.2** would be to prepare the compounds **2.3** and subject them to the reaction with the protected phosphinic acid **2.4.** The retrosynthetic

Path B (*Scheme 2.1*) requires the preparation of the unsaturated phosphonic acid and its derivatives by the transesterification of diphenyl phosphite **2.5** with the corresponding alkenyl alcohols **2.6.**[45]

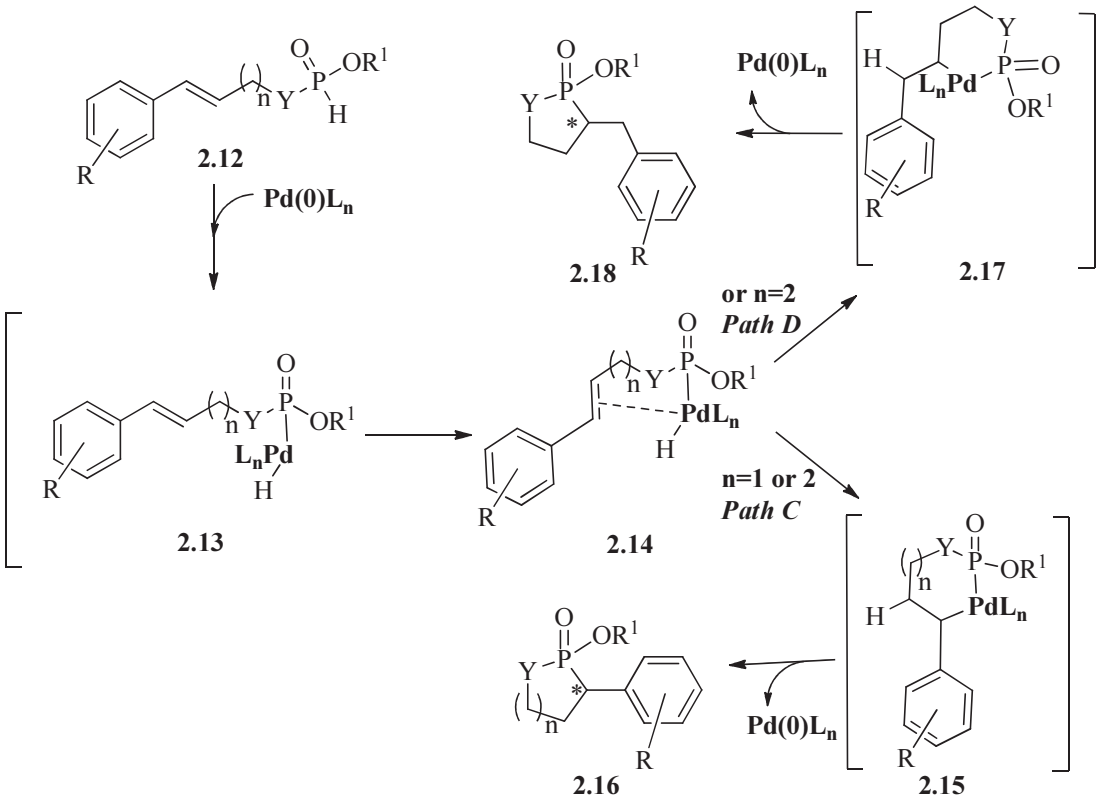
In order to prepare compounds **2.3** (*Path A*, *Scheme 2.1*), we envisioned to perform a Sonogashira coupling between aryl iodide **2.7** and alkynyl alcohols **2.8**, followed by reduction the product **2.9** to an alkene **2.10** as it is shown in *Scheme 2.2*. Further substitution under Appel reaction conditions[46] would allow to access the synthons **2.3** as the unsaturated iodides **2.11**.



Scheme 2.2

The choice of the aryl group and *trans*- isomer is important the future cyclization (*Scheme 2.1*). First, the possible steric effects were taken into consideration. Affording pure *trans*-isomer after the reduction of compound **2.9**, would support the formation of the possible intermediates during the catalysis of cyclization reaction. Second, the presence of an aryl group, would ease the cyclization process *via* mesomeric stabilization. Adapting the mechanistic knowledge from the literature research (***Chapter I***), the expected mechanism of the reaction is shown in *Scheme 2.3*. Palladium (0) complex is supposed to undergo the oxidative addition-insertion into the P-H bond of the molecule **2.12** and subsequently coordinate to the double bond **2.13**. The following step splits in two possible situations depending on the regioselectivity. In case of **n=1 or 2** of substrate **2.12**, the formation of the complex **2.15** and a reductive elimination are supposed to take place leading to the formation of the product **2.16** (*Path C, Scheme 2.3*). However, in case of **n=2**, the mechanism might follow the *Path D* yielding complex **2.17**, which should lead to the product **2.18** (*Path D, Scheme 2.3*).

[45] Kraszewski A., Sobkowski M,. Stawinski J., Kers I., Kers A., **1995**, *Synthesis*, 427
[46] Appel R., *Angew. Chem*. **1975**, *87,* 863; Appel R., *Angew. Chem. Int. Ed.*, **1975**, *14*, 801



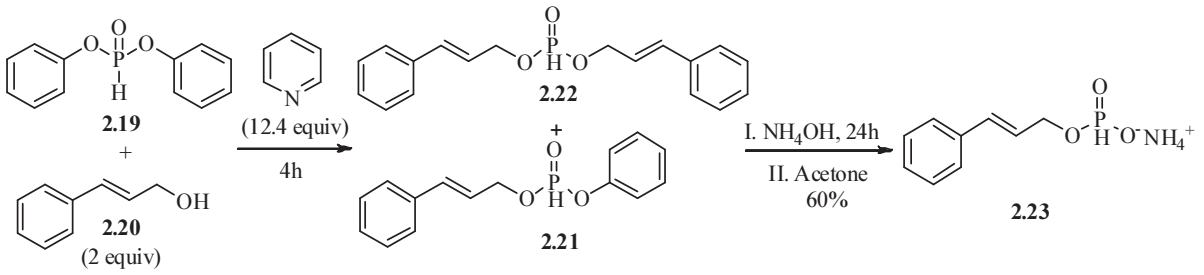
Scheme 2.3

3. Preparation of *H*-phosphonate and attempts of intramolecular hydrophosphonylation.

In this section, the preparation of ammonium cinnamyl *H*-phosphonate is described together with the subsequent attempts of Pd (0)-catalyzed cyclization reaction.

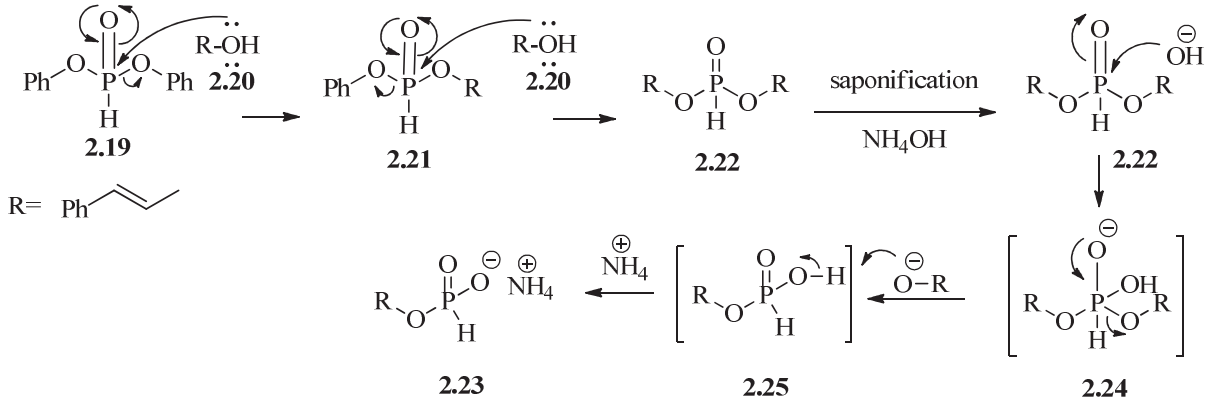
3.1. Transesterification reaction and hydrolysis towards cinnamyl H-phosphonic acid.

In order to prepare the *H*-phosphonates we applied the method developed by Stawiński and Kraszewski.[45] First, transesterification of diphenyl *H*-phosphonate **2.19** with cinnamyl alcohol **2.20** followed by hydrolysis with concentrated ammonium hydroxide (*Scheme 2.4*). After 24h, the reaction mixture was evaporated and the residue dissolved in acetone to afford the precipitation of **2.23** in 60% of yield.



Scheme 2.4

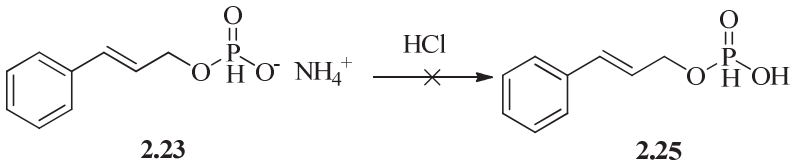
This convenient procedure afforded the first starting material in moderate yield. The course of reaction was followed by means of ^{31}P NMR. After the 3h all starting material **2.19** was consumed and NMR analysis indicated the presence of **2.21** and **2.22** ($CDCl_3$: 5.87 ppm and 8.07 ppm respectively). The extension of the reaction time to 6h indicated the presence of **2.22** as the sole product. The next step (the addition of NH_4OH and formation of phosphinic acid salts) took 24h and the signal at 6.29 ppm (in D_2O) indicated the formation of ammonium *H*-phosphonate **2.23**. The reaction mechanism is shown in *Scheme 2.5*. In the first step, the double transesterification of diphenyl *H*-phosphonate **2.19** by cinnamyl alcohol **2.20** leads to the **2.22**. The saponification allows the addition of OH^- to the compound **2.22**. Since the anion of cinnamyl alcohol is a good base and it deprotonates the intermediate phosphonic acid **2.25**. Finally, the ammonium phosphate **2.23** is formed.



Scheme 2.5

A further step was envisioned to achieve the cinnamyl *H*-phosphonic acid **2.25**. Unfortunately, the acidification of the compound **2.23** with hydrochloric acid was troublesome. The application of various concentrations of the HCl did not afford the desired cinnamyl *H*-phosphonic acid **2.25** (*Scheme 2.6*). In fact, it led to the decomposition of the compound **2.23**, which is indicated by the presence of phosphonic acid in the reaction

mixture. At this point, we could conclude that the cinammyl *H*-phosphonic acid **2.25** is not a stable compound and cannot be isolated.

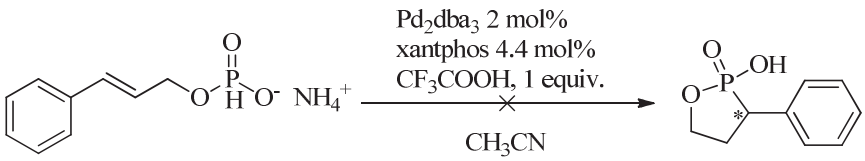


2.23 **2.25**

Scheme 2.6

3.2 Attempt of Pd(0)-Catalyzed cyclization of ammonium cinnamyl *H*-phosphonate.

Regardless the conclusion coming from the unsuccessful isolation of cinnamyl *H*-phosphonate **2.23,** we decided to try to generate the free acid **2.25** *in situ* in the presence of trifluoroacidic acid and palladium catalyst (Pd_2dba_3/xantphos) (*Scheme 2.7*).



2.23 **2.26**

Scheme 2.7

Unfortunately, we did not observe any reaction. As indicated by ^{31}P NMR ,the constant presence of starting material **2.23** without any formation of the product **2.26** was seen.

Thus, either the formation of free acid **2.25** is crucial for the catalysis or the applied catalytic system is unsuitable. The next effort undertaken was to use alkyl *H*-phosphinic acids (**Figure 2.3**) as they are believed to be more stable due to the presence of P-C bond.

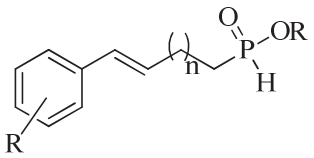


Figure 2.3

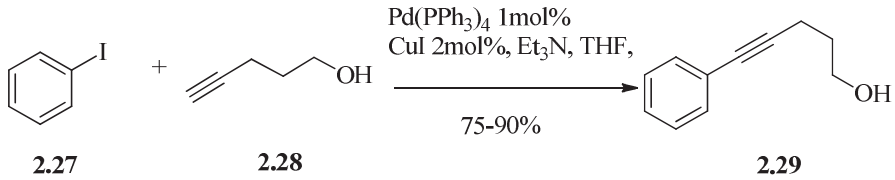
4. Preparation of *H*-phosphinates and attempts of intramolecular hydrophosphinylation.

Simultaneously to the synthesis of ammonium cinnamyl *H*-phosphonate **2.23**, we elaborated the synthetic pathway to *H*-phosphinates (**Figure 2.3**). In this section, the results in this area will be described as well as the efforts for intramolecular hydrophosphinylation catalyzed by palladium (0) species.

4.1. Preparation of unsaturated *H*-phosphinates.

4.1.1. Performance of Sonogashira/reduction sequence.

In the first step, we had chosen commercially available iodobenzene **2.27** and pent-4-yn-1-ol **2.28** as substrates to perform the Sonogashira reaction.[47]

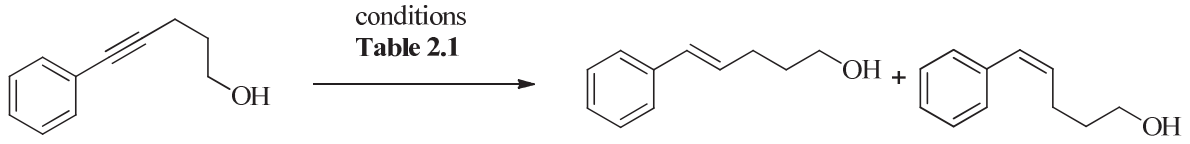


2.27 **2.28** **2.29**

Scheme 2.8

With the tetrakis(triphenylphosphine)palladium(0)catalyst and copper iodide in the presence of a triethylamine, the reaction proceeds very well giving 5-phenylpent-4-yn-1-ol **2.29** in 75- 90% of yield. Whereas this procedure gives excellent result, the reduction of the compound **2.29** came out to be difficult, due to the formation of a mixture of isomers (*Scheme 2.8*, **Table 2.1**).

[47] Liu G., Stahl S. S., J. Am. Chem. Soc. **2007**, *129*, 6328



2.29 **2.30** **2.31**

Scheme 2.9

Entry	Conditions: Reagent/Solvent/Time	Yield[a] [%]	Product selectivity 2.30/2.31
1.	2.5 eq $LiAlH_4/N_2$, THF 0°C/24h[47]	50-60%	2:1
2.	3,5 eq $LiAlH_4/N_2$, THF:diglyme(5:1) 0-100°C/[48]	60%	1.5:1
3.	1.2 eq Red-Al ®/N_2, THF -20- reflux/2h[49]	65%	2:1
4.	4 eq Li/N_2, THF	NR[b]	---

[a] isolated yield [b]no reaction

Table 2.1

Although different conditions were applied, all of them produce an unseparable mixture of *E/Z* isomers. In terms of yields, which are moderate, the Red-Al® (sodium bis(2-methoxyethoxy) aluminium hydride, (**Figure 2.4**) was of choice providing products in 65% with the 2:1 selectivity of *E/Z* (entry 3, **Table 2.1**).

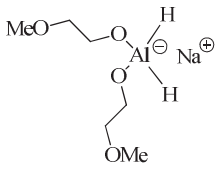


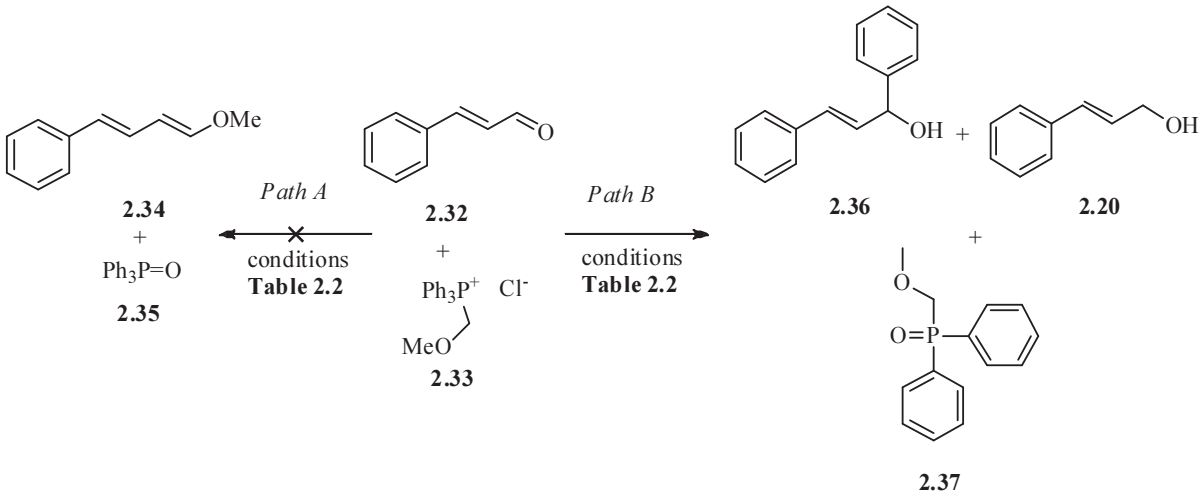
Figure 2.4

The use of $LiAlH_4$ (entries 1-2) resulted in 2:1 or 1.5:1 mixtures a Li(0)-mediated reduction(entry 4) failed (**Table 2.1**). The known fact that iodine in the presence of light catalyzes conversion of *Z* into *E* isomers was applied here. Thus, keeping mixture in the toluene with iodine in the presence of light resulted in transformation of *Z* isomer into more stable *E* form, improved the yield of *E* isomer **2.30** to 80%. Finally, unsatisfactory results of the reduction prompted us to find another synthetic way to obtain **2.30**.

[48] Rossi R.; Carpita A., *Synthesis*, **1977**, 561
[49] Crousse B., Mouad A., Linstrumelle G. *Synlett*, **1997**, 992

4.1.2. Wittig reaction of cinnamyl aldehyde

In order to obtain pure *E*-isomers of *H*-phosphinates **2.2** (*Scheme 2.1*), we envisioned to perform a Wittig reaction with *trans*-cinnamyl aldehyde as substrate. We thought that this versatile reaction would be suitable for the elongation of the chain, without changing the stereochemistry of aldehyde **2.34** (*Path A, Scheme 2.10*). The product of this reaction **2.34,** regardless stereochemistry of the formed second double bond, would be suitable for further transformations. Surprisingly, Wittig reaction of cinnamyl aldehyde with methylmethoxytriphenylphosphonium chloride **2.33** gave unexpected results (*Path B, Scheme 2.10)*. **Table 2.2** shows the obtained results under application of various bases.



Scheme 2.10

Entry	Conditions (Solvent: THF) Base	Yield[a] of 2.36 [%]
1.	2 eq *n*-BuLi	11 %/
2.	DBU 2 eq NaH	10 %
3.	1,1 eq DBU	NO[b]

[a] isolated yield [b]no reaction

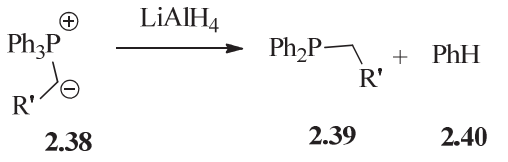
Table 2.2

Applying a typical procedure for Wittig reaction, all starting material was consumed and four new compounds were formed as showed by TLC analysis (entry 1 and 2 **Table 2.2**). Purification by column chromatography enabled to separate compounds seen as first two spots as one fraction in a form of yellow oil, which provided rather complex spectra. However, the formation of crystals was observed and their spectroscopic analysis revealed the structure of **2.37**. Compounds seen as third and fourth spots turned out to be allylic alcohol **2.36** and cinnamyl alcohol **2.20**, respectively (*Scheme 2.10*). The use of a weaker base, such

as DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) base did not lead to the formation of any product and only starting material **2.32** was recovered (entry 3).

4.1.3. Discussion of the course of Wittig reaction of cinnamyl aldehyde with methylmethoxytriphenylphosphonium chloride

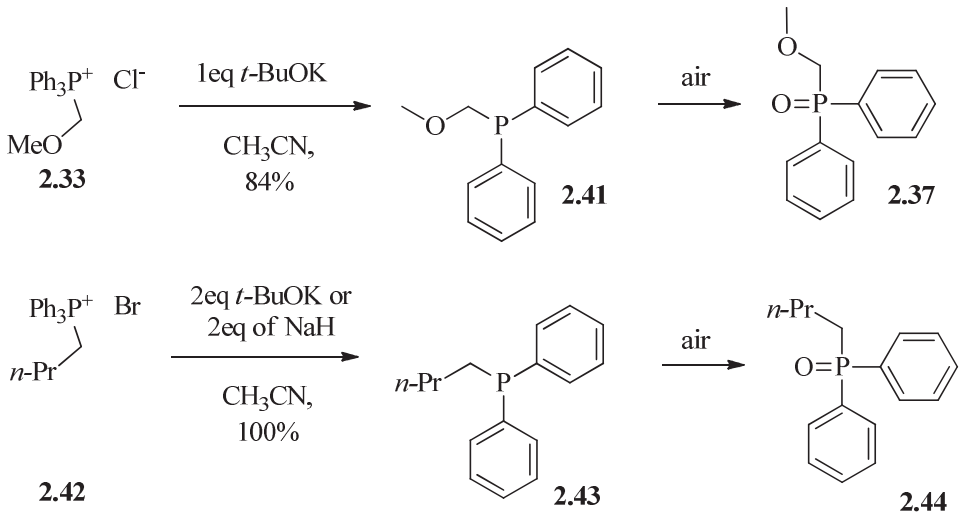
The unusual transfer of a phenyl group of Wittig reagent to cinnamyl aldehyde required some explanation. However, this reaction came out to be inefficient considering the very poor yields of product **2.37** (**Table 2.1**). A literature survey gave no answer, although some information about methylmethoxydiphenylphosphine oxide **2.37** was obtained (*Scheme 2.10*).[50] As a matter of fact, the loss of one phenyl group from triphenylphosphonium ylides **2.38** is known.[51] When a reducing agent like lithium aluminum hydride is present in the reaction mixture, the formation of phosphines **2.39** is observed (*Scheme 2.11*). This mechanism of the ylide reduction is not well understood.[51]



Scheme 2.11

However, in our case (*Scheme 2.10*) the presence of **2.37** in the reaction mixture cannot be explained by application of reducing agent. It was found that the group of Banejee *et al*. encountered similar problem (*Scheme 2.12*).[50]

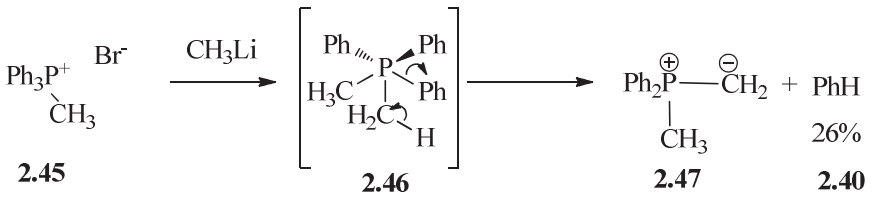
[50] Ngwendson J. N., Schultze C. M., Bollinger J. W., Banerjee A., *Can. J. Chem*., **2008**, *86*, 668
[51] Walker B. J., Organophosphorous Chemistry, **1972**, *Penguin Books*



Scheme 2.12

It was observed, that under inert atmosphere, phosphines **2.41** and **2.43** are formed. On the other hand, in the presence of the air a white solid of phosphine oxides **2.37** and **2.44** precipitated. As in case of ylides **2.38** (*Scheme 2.11*) little is known about the possible mechanism of this reaction.[50]

The alkylmetal reagents react with the phosphonium salts by a deprotonation of the α-hydrogen atom, but an addition at the phosphorous atom is also observed (*Scheme 2.13*).[51] In this case, when methyltriphenylphosphonium bromide **2.38** is treated with methyllithium in ether, apart from the formation of ylide **2.47**, 26% of benzene **2.40** is also produced. The mechanism drawn in *Scheme 2.13* is, however, not certain.[51]

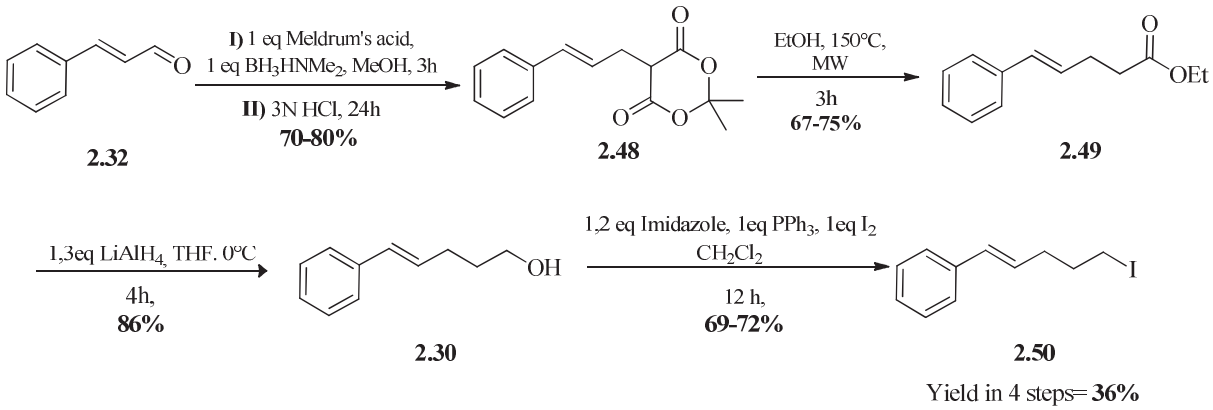


Scheme 2.13

In light of those information, the mechanism of our reaction (*Scheme 2.10*) remains unsolved. Both aspects, the loss of the phenyl group and its transfer to cinnamyl aldehyde to form allylic alcohol **2.36** with simultaneous reduction to cinnamyl alcohol **2.20** are, so far, a not explainable.

4.1.4. Four step synthesis of (E)-(5-iodopent-1-en-1-yl)benzene

Because simple efforts to obtain (*E*)-isomers of substrates (**Section 4.1.1** and **4.1.2**) for further cyclization reactions were inefficient, we turned our attention to multistep synthesis shown in *Scheme 2.14*.[52] Although this four-step procedure requires the use of column chromatography for purifications, we obtained the desired iodide **2.50** in 36% overall yield and used it as a synthon for the next transformations..

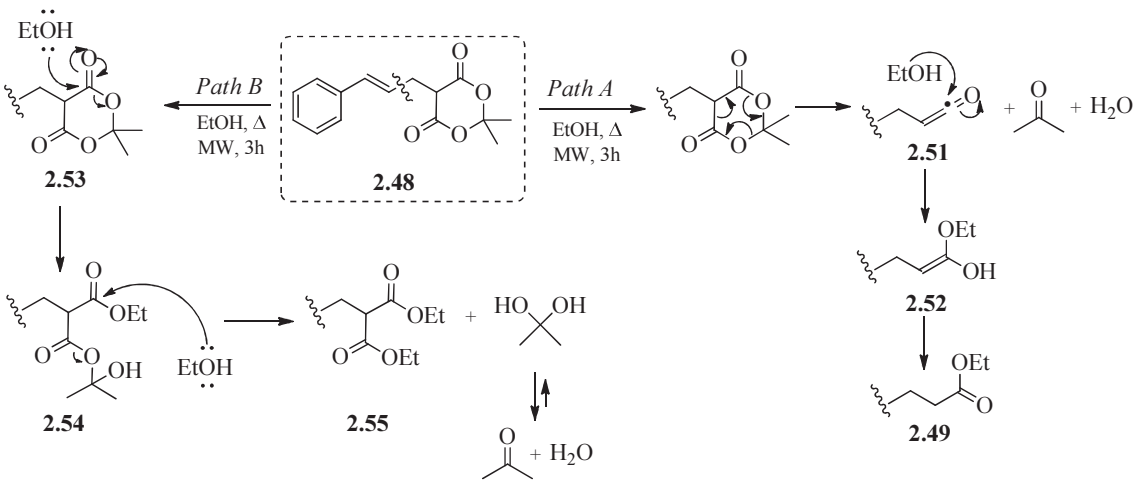


Scheme 2.14

In the first step, *trans*-cinnamyl aldehyde **2.32** underwent Knoevenagel condensation-hydroboronation reaction, which constitutes an efficient way to synthesize the monoalkylated dicarbonyls.[52] The resulting compound **2.48** was subsequently transesterified and decarboxylated in ethanol using microwave irradiation (MW), which yields two compounds **2.49** and **2.55** (*Scheme 2.14*, *Scheme 2.15*).

The diester **2.55** is formed probably due to the insufficient temperature in the microwave reactor. We have noticed that *Path A*, the pericyclic reaction leading to the formation of a ketene intermediate **2.51**, acetone and CO_2 is favored under high heating (*Scheme 2.15*). Ethanol subsequently adds to the ketene **2.51**, and finally generates the ester **2.49**. When the temperature is below 140°C up to 60% of product **2.55** can be obtained (*Path B, Scheme 2.15*). The first step is followed by addition of ethanol to the one of the two carbonyl groups, and then elimination of hemiacetal moiety, which leads to the formation of the intermiediate **2.54**. The addition of second ethanol molecule to remaining carbonyl group affords the diester **2.55** with the simultaneous elimination of *gem*-propanediol which is in equilibrium with acetone.

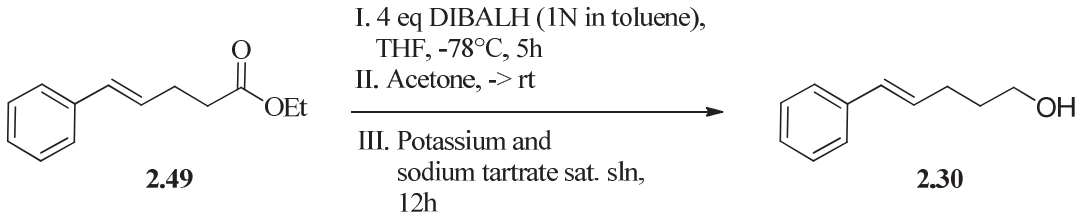
[52]a) Hrubowchak, D. M., Smith, F. X. *Tetrahedron Lett.* **1983**, *24*, 4951; b) Bélanger G., Lévesque F., Pâquet J., Barbe G., *J. Org. Chem.*, **2005**, *70*, 291



Scheme 2.15

A temperature of 150-155°C (13 Bars) could however be reached under microwave heating and product **2.49** was eventually isolated in 67-75% of yield after column chromatography.

In the next step (*Scheme 2.14*), the reduction of carboxylate with a lithium aluminium hydride leads to alcohol **2.30**. We also tried the reduction with DIBALH reagent. Although the yield of 86% could be achieved, following this procedure required harsh conditions and a longer reaction time (*Scheme 2.16*) compared to the simple $LiAlH_4$ protocol.



Scheme 2.16

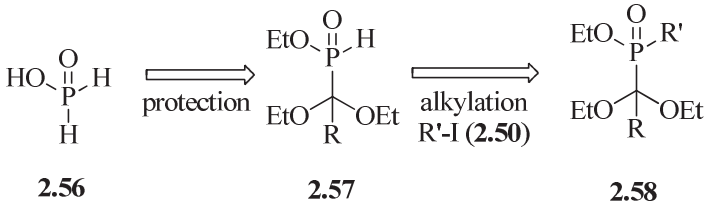
Finally, in a fourth step alcohol **2.30** was iodinated under Appel reaction conditions, to provide product **2.50** in *circa* 70% (*Scheme 2.14*).

By this multistep synthesis, we thus obtained a convenient substrate **2.50** for further transformations.

4.1.5. Protection of hypophosphorous acid

The (*E*)-(5-iodopent-1-en-1-yl)benzene **2.50** obtained in previous section is an appropriate substrate to alkylate the phosphinic acid **2.56**. However, hypophosphorous acid

2.56 needs to be protected for that reason (*Scheme 2.17*). Therefore, we decided to synthesize monoalkylphosphinates **2.57**,[53] also called Ciba Geigy reagents.

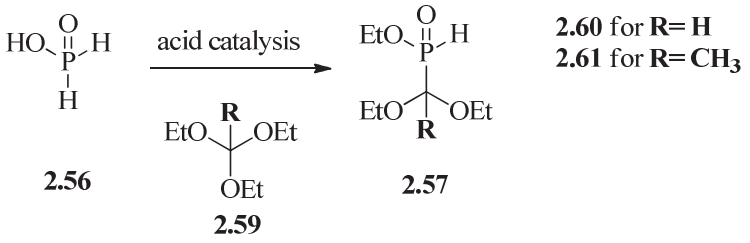


Scheme 2.17

The method to prepare monoalkylphosphinates was described for the first time by Gallagher and Honegger.[53] It requires the use of anhydrous hypophosphorous acid HPA (white crystals below 18°C).

Unfotunately, anhydrous HPA is not commercially available and was obtained by the dehydratation of commercial 50% aqueous HPA by a long, careful evaporation of water under reduced pressure. The temperature stands as an extremely important factor here. If the elimination of water is performed above 40°C for a long time, it may lead to disproportionation of this acid with the formation of pyrophoric phosphines (usually observed by the change of the color to yellow).[54]

The crystalline, dry HPA was protected by the method of Gallagher (*Scheme 2.18*).[53]



Scheme 2.18

The reaction takes place in the presence of triethyl orthoformate or triethyl orthoacetate (2.2 equivalents) **2.59** and a catalytic amount of *p*-toluenesulphonic acid (PTSA)[53] or boron trifluoride diethyl etherate (BF_3OEt_2) or trifluoroacetic acid (TFA).[55] The reaction time is a very important issue here. Our first trials with the catalytic acids did not afford the corresponding compounds **2.57** and we observed the secondary products described

[53] a)Gallagher M. J., Honegger H., *Tetrahedron Lett*. **1977**, *18*, 34, 2987;b) Gallagher M. J. and Honegger H., *Aust. J. Chem.,* **1980**, *32*, 287
[54] Kosolapoff G. M., Powell S. J., *J. Am. Chem. Soc*., **1950**, *72*, 4291
[55] Fougere C., Guenin E., Hardouin J, Lecouvey M, *Eur. J. Org. Chem*, **2009**, 6048

by Gallagher after 6h of reaction time, which were identified by their chemical shift in ^{31}P NMR spectra (**Figure 2.5**). These structures result from the reaction between two molecules of **2.57**.

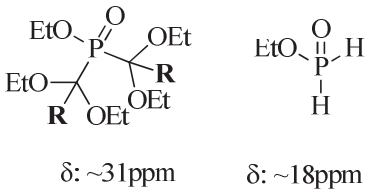
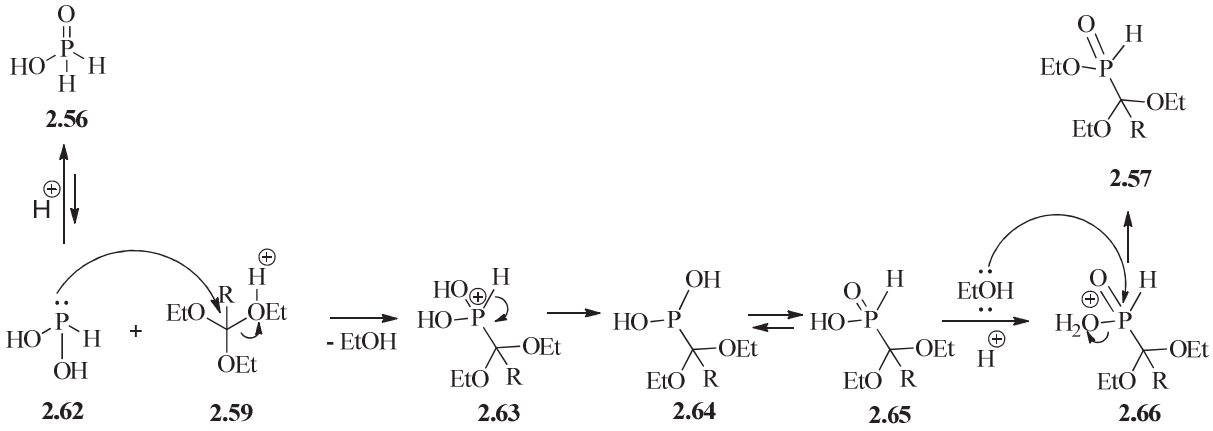


Figure 2.5

The monitoring of the reaction by ^{31}P NMR revealed that the desired product is formed after 1h (**2.61**) or 3h (**2.60**) as monitored by presence of ^{31}P NMR signals at 28 ppm for **2.60** and 31 ppm for **2.61** (*Scheme 2.18*). The reaction must be quenched just after, otherwise the degradation of the products can be clearly observed with the decreasing signal of primary product and simultaneous rise of the peaks from the secondary products (**Figure 2.5**). The mechanism leading to the formation of primary products **2.57** is drawn in *Scheme 2.19*.

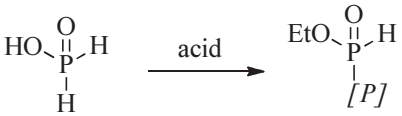


Scheme 2.19

In acid medium, the P(V)/P(III) equilibrium allows the formation of compound **2.62** and the subsequent substitution of ethoxy group of **2.59**. Then, after deprotonation of **2.63** and a shift of the P(III)/P(V) equilibrium to the right, and compound **2.65** is generated. The protonation of the OH moiety of species **2.65** allows the addition of ethanol and elimination of water to afford the product **2.57**.

Amongst all the mentioned acids tested as catalysts, TFA came out to be the most efficient giving a clean and fast reaction (entry 3, **Table 2.3**). The use of PTSA is not convenient, because it needs to be additionally dehydrated and recrystalized before the reaction, which makes the overall procedure time-consuming. Additionally it provides the product in rather poor yield (entry 1). Considering BF_3OEt_2 etherate, the reagent itself is not easy to handle due to its air-sensitivity and the yield of the reaction is moderate (entry 2).

Unfortunately, the distillation of the products was also troublesome, because all of the obtained compounds are sensitive to air and heating. Thus, the application of very strong vacuum was essential (30-40 μBars, 75°C).



2.56 **2.57**

[P] protective group

Entry	Acid [2.2 eq]	Average yield **2.57**[a] [%]
1.	PTSA	30-40
2.	BF_3 EtO_2	40
3.	TFA	70-85

[a] isolated yields

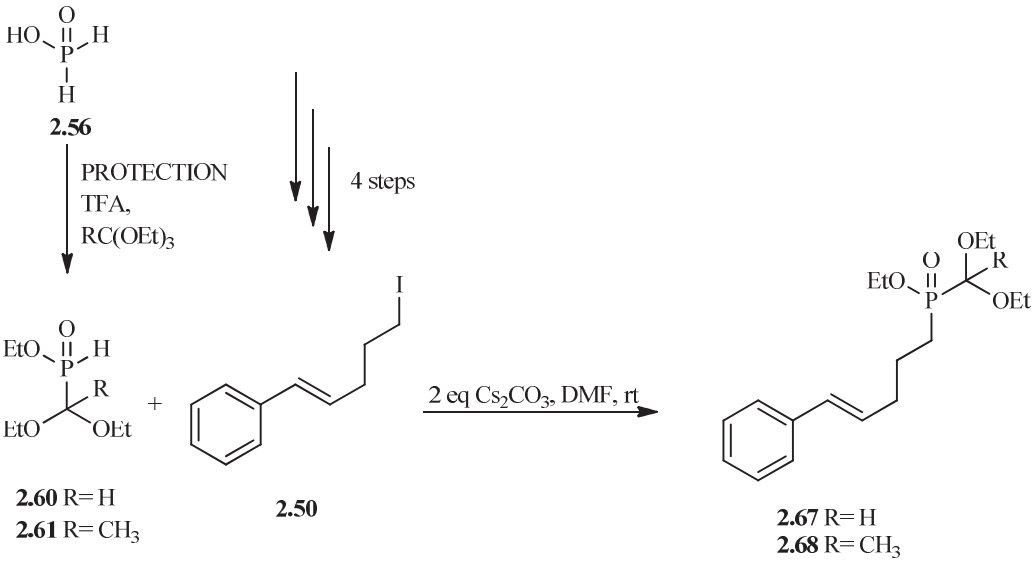
Table 2.3

In summary, the TFA procedure was selected for this transformation since it provides substrates in good yields for the following step.

4.1.6. Cs_2CO_3-promoted synthesis of protected (E)-ethyl (5-phenylpent-4-en-1-yl)phosphinates

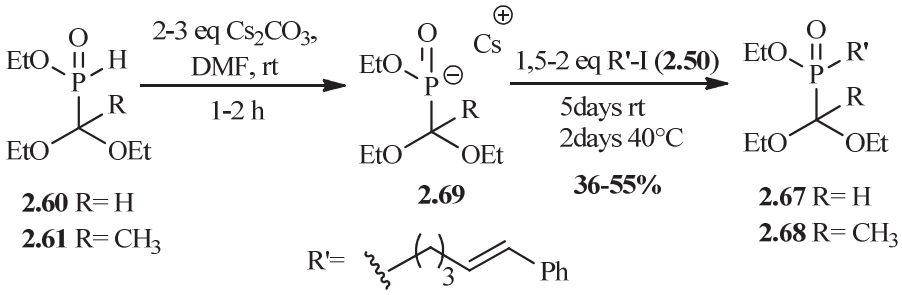
In order to prepare the products **2.67** or **2.68** (*Scheme 2.20*) we decided to use cesium carbonate as a promoting agent[56] since such bases have been widely used in alkylation reactions.[57]

[56] Cohen J. R., Fox D. L., Eubank, F.,Salvatore R. N., *Tetrahedron Lett*., **2003**, *44*, 8617
[57] a) Parrish, J. P.; Dueno, E. E.; Kim, S.-I.; Jung K. W. *Synth. Commun*., **2000**, *30*, 2687;b) Salvatore, R. N.; Flanders, V. L.; Ha, D.; Jung, K. W. *Org. Lett*. **2000**, *2*, 2797



Scheme 2.20

Literature data on the alkylation reactions of *H*-phosphinates with the inactivated halides is quite scarce.[58] We applied the modified procedure originally developed by Salvatore *et al*.[56] for *H*-phosphonate esters. In the presence of cesium carbonate at room temperature, *H*-phosphinate anion **2.69** (*Scheme 2.21*) can be generated *in-situ* from Giba Geigy agent **2.60** or **2.61**. Subsequent alkylation of anion **2.69** with alkyl halide **2.50** in anhydrous DMF produced the corresponding phosphinates **2.67** or **2.68**.



Scheme 2.21

It result was somehow disappointing, since the yield of this reaction could not exceed 55 % leading to an overall yield of 19% for this five step sequence. Additionally, the reaction time is very long and the purification by column chromatography was troublesome due to the high polarity of the products **2.67** or **2.68.** Moreover ,many minor by-products (probable resulting from degradation of the anion **2.60** or **2.61** considering its sensitivity and long

[58] a)Tappe F. M. J., Trepohl V. T., Oestreich M., *Synthesis*, **2010**, 3037;b) Abrunhosa-Thomas I., Sellers C. E., Montchamp J.-L., *J. Org. Chem*., **2007**, *72*, 2851

reaction time) were impossible to separate (except of the excess of starting material **2.60**). Alternative methods came out to be even less efficient (**Table 2.4**).

Entry	Conditions	Yield[a] **2.68**
1.	Na (3eq.), THF, Ar bubbling, 25°C, 24h [55]	25%
2.	LiHMDS (1eq), THF, Ar, -78°C to rt, 5h[58]	30%

[a] isolated yields

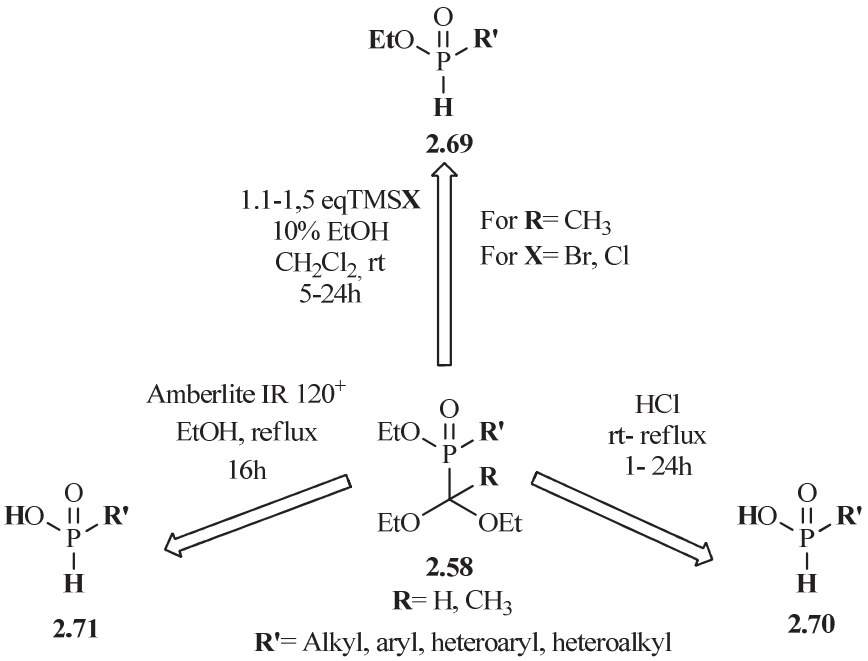
Table 2.4

Summing up this step, the reaction with cesium carbonate provides a pure product but is very time-consuming and affords poor to moderate yields after a tedious purification. Nonetheless, after the preparation of desired compounds **2.67** and **2.68** in satisfactory quantities, we carried on to the next step.

4.1.7. Deprotection of (E)-ethyl(diethoxymethyl)(5-phenylpent-4-en-1-yl)phosphinate and (E)-ethyl (diethoxyethyl)(5-phenylpent-4-en-1-yl)phosphinate

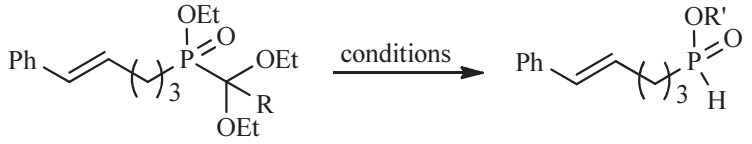
The use of compounds such as **2.58** known as Ciba-Geigy reagents and their deprotection was widely described.[59] Three classical approaches for this deprotection are shown in *Scheme 2.22*.

[59] For **deprotection with Amberlite** a): Montchamp J.-L., Coudray L., *Eur. J. Org. Chem*, **2009**, 4646; For **deprotection with HCl**: c) Froestl W., Mickel S. J., Hall R. G., von Sprecher G., Strub D., Baumann P. A., Brugger F., Gentsch C., Jaekel J., Olpe H.-R., Rihs G., Vassout A., Waldmeier P. C., Bittiger H., *J. Med. Chem.* **1995**, *38*, 3297; For **deprotection with TMSCl/EtOH**: d) Yamagishi T., Haruki T., Yokomatsu T., *Tetrahedron*, **2006**, *62*, 9210; e) Yamagishi T., Miyame T., Yokomatsu T. Shibuya S., *Tetrahedron Lett.,* **2004**, 6713; f)Reck F., Marmor S., Fisher S., Wuonola M. A., *Bioorg. Med. Chem. Lett*., **2001**, 1451; g) Froestl W., Mickel S. J., von Sprecher G., Diel P. J., Hall R. G., Maier L., Strub D., Melillo V., Baumann P. A., Bernasconi R. , Brugger F., Gentsch C., Hauser K., Jaekel J., Karlsson G., Klebs K., Maitre L., Marescaux C., Pozza M., Schmutz M., Steinmann M. W., van Riezen H., Mondadori C., Olpe H.-R., Vassout A., Waldmeier P. C., Bittiger H., *J. Med. Chem.* **1995**, *38*, 3313



Scheme 2.22

These methods afford deprotected *H*-phosphinic acids **2.69** or *H*-phosphinates **2.70** and **2.71**. The use of hydrochloric acid usually leads to the formation of *H*-phosphinic acids **2.70**. It relies on the use of varying concentrations of hydrochloric acid at different temperatures. The use of Amberlite IR 120^+ resin was described only by the group of Montchamp.[59] It leads to the formation of the acids **2.71.** Finally, the deprotection with TMSX followed by hydrolysis of trimethylsilyl groups by EtOH allows the generation of milder acidic conditions and it leads to the formation of the ester **2.69**. The **Table 2.5** shows the results of experiments carried out in order to obtain **2.72** and **2.73.**



2.67 R= H
2.68 R= CH_3

2.72 R'= Et
2.73 R'= H

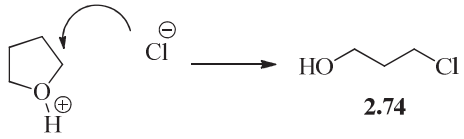
Scheme 2.23

Entry	Substrate	Conditions (t=24h)	Product, yield [a]
1.	**2.67**	4N HCl/ THF/reflux,	**2.73,** NI[b]
2.	**2.67**	HCl conc. /50°C,	**2.73,** NI[b]
3.	**2.67**	5N HCl/reflux,	NR [c]
4.	**2.67**	TMSCl/EtOH/$CHCl_3$,	**2.72,** NR[c]
5.	**2.68**	TMSCl/EtOH/$CHCl_3$	**2.72,** 20% [d]
6.	**2.68**	**4N HCl/reflux**	**2.73, 50%**[e]
7.	**2.68**	**Toluene, PTSA/80°C**	**2.73, 70%**[e]
8.	**2.68**	Amberlite IR 120^+, EtOH	**2.72,** 40%

[a] isolated yields[b]not isolated [c] no reaction [d]after purification with column chromatography [e]dried under vaccum

Table 2.5

In the first attempt of deprotection of *(E)*-ethyl (diethoxyethyl)(5-phenylpent-4-en-1-yl)phosphinate **2.67**, we used 4N hydrochloric acid. In order to obtain homogenic mixture THF was used (entry 1, **Table 2.5**). The reaction followed by TLC indicated that the starting material **2.67** was completely consumed. The ^{31}PNMR spectrum also indicated the formation of the deprotected compound **2.73** (no signal of starting material **2.67** at 46 ppm, signals from P-H product **2.73** at 38.117 ppm and 33.461 ppm**)**. However, the ^{1}H NMR spectrum of the crude substrate was complex. Beside the signals of product **2.73**, a product arising from a ring opening rection of THF was probably identified (*Scheme 2.24*). Signals on the ^{1}H NMR spectrum are indeed in agreement with 3-chloropropan-1-ol **2.74.**

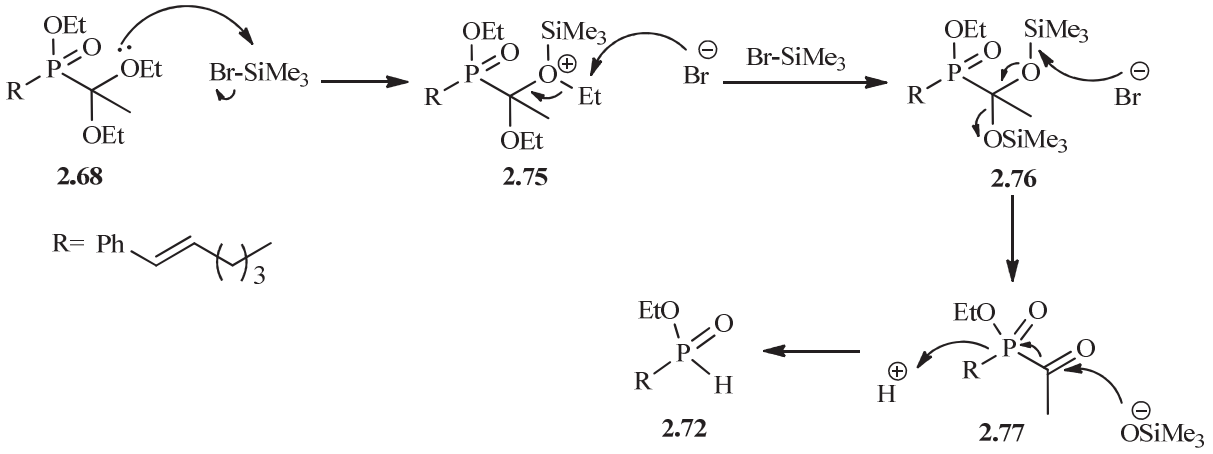


2.74

Scheme 2.24

Additionally, the products are very polar compounds, which makes the reactions difficult to follow by TLC. Therefore, ^{31}P NMR was found to be the most convenient tool. In the next attempt, we used concentrated hydrochloric acid without any solvent (entry 2). Unfortunately, we obtained a complex ^{31}P NMR spectrum, which showed the signals from the product **2.73** together with a range of smaller unidentified signals ranging from 37 ppm to 51 ppm (^{31}P NMR). Therefore, we abandoned the use of concentrated hydrochloric acid. We may

conclude that it is too strong acid for preparation of compound **2.73** and leads to hydrolysis products **2.73**. The use of 5N hydrochloric acid failed to deprotect **2.67**, and we could see only the starting material. Thus, we decided to apply conditions that would provide ester **2.72**. Therefore, TMSCl in chloroform was used (entry 4), even though the literature mentions that the protection with the acetal group (**2.58** R=H, *Scheme 2.22*) is difficult to remove and actually, no reaction occured.[59] For this reason, in the next attempt (entry 5), we used the same conditions but this time with compound **2.68** protected as a ketal. In this case, we obtained the desired compound **2.72**. The proposed mechanism of this reaction is shown in *Scheme 2.25*.



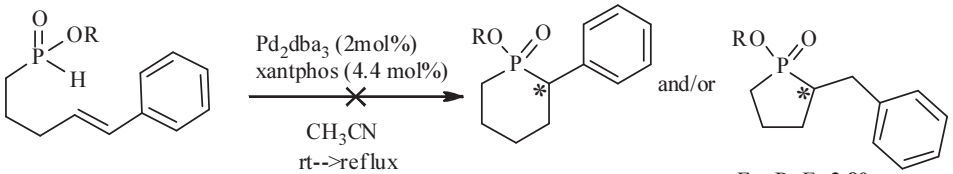
Scheme 2.25

Unfortunately, compound **2.72** was difficult to handle. It is both water and organic - soluble and the yield after purification on column chromatography led was only 20%. Some pure material **2.72** was however ready for the cyclization. Moreover acid **2.73** was obtained from **2.68** by hydrolysis with hydrochloric acid (entry 6). In this case, the strong vaccum had to be applied to remove the solvent and other volatile products. Also the use of PTSA in toluene afforded the acid **2.73** in good yield of 70% (entry 7). Finally, the deprotection with Amberlite in EtOH also led to compound **2.68** in 40% of yield.

Summing up, the compound **2.68** having ketal group came out to be convenient substrate for deprotection. The ester **2.72** and acid **2.73** were obtained in the quantities that allowed to proceed to the step of cyclization.

4.2. Attempts of Pd (0)-Catalyzed cyclization of (*E*)-(5-phenylpent-4-en-1-yl)phosphinic acid

The products **2.72** and **2.73** were subjected to cyclization as shown in the *Scheme 2.26.*



For R=Et **2.72**
For R=H **2.73**

For R=Et **2.78**
For R=H **2.79**

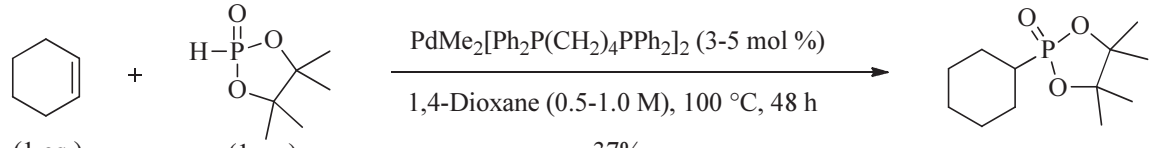
For R=Et **2.80**
For R=H **2.81**

The reaction of intramolecular hydrophosphinylation was performed in the presence of $Pd_2(dba)_3$ and xantphos, which is the typical catalytic system for the intermolecular version.[60] Unfortunately, desired product was not observed. Only starting materials were observed (for both reactions, with ester **2.72** and acid **2.73**). Reactions were performed several times to confirm this finding leading each time to the same result. Also application of Pd_2dba_3/dppf was also used but gave no reaction as well. Unfortunately, we were not able to recover starting materials because of their polarity and the presence of catalysts in the mixture. Screening for other catalysts was limited because of the limited quantity of starting materials **2.72** or **2.73,** which were obtained in 6 steps with 10-14% of overall yield. The starting hypothesis which was that intramolecular processes should be easier than the corresponding intermolecular reactions proved wrong in this case. Most probably the lack of reaction results from P(III) and P(V) tautomerization, as indicated by Montchamp.[61] We can assume that the tautomer PIII is not thermodynamically favored to carry out the oxidative addition. From ***Chapter I*** we know that only terminal alkenes (not internal ones as in case of our starting material **2.72** and **2.73**) could undergo hydrophosphinylation under the standard conditions. Therefore, we shifted our interest towards the development of new catalytic systems by using new ligands of palladium. As the preparation of the substrates for intramolecular pathway is complex, we first chose the appropriate substrates that are commercially available and test them in intermolecular reactions.

[60] Deprele. S., Montchamp J.-L., *J. Am. Chem. Soc.*, **2002**, *124*, 9386
[61] Montchamp J.-L., Petit C, Fecourt F., *Adv. Synth. Catal*., **2011**, *353*, 1883

5. Attemps of Pd-catalyzed intermolecular hydrophosphonylation with cyclohexene and pinacol phosphonate.

The previous sections showed unsuccessful Pd-catalyzed reactions of intramolecular hydrophosphinylation and hydrophosphonylation. Therefore, we decided to improve the catalytic possibilities of palladium complexes in the intermolecular pathway. The addition of pinacol phosphonate **2.83** on cyclohexene **2.82** was chosen as a model reaction. This reaction was actually performed by Tanaka *et al.* in 2000 (*Scheme 2.27*).[62] The choice of cyclohexene is justified by the fact, that it is a difficult substrate for metal-catalyzed additions of P(O)-H group. Hydrophosphonylation with $H(O)P(OAlk)_2$ and alkenes fails to afford the product in general (***Chapter I***). Hydrophosphinylation with $H_2P(O)(OEt)$ under standard conditions (Pd_2dba_3/xantphos) results in 10% yield only.[63] Hydrophosphonylation with pinacol phosphonate **2.83** led to 37% yield of **2.84** within 48h under Tanaka conditions. It was achieved by Pd complex which is not commercially available, therefore, less convenient to handle. Therefore, it was a good starting point for our search towards new efficient catalytic system. The efficiency of various catalysts that will be screened will be evaluated in terms of reaction rate and yields determined by ^{31}P NMR.



2.82 **2.83** **2.84**

Scheme 2.27

We decided to turn to new phosphine ligands that were developed in the past several years but not tested in the field of hydrophosphonylation and hydrophosphinylation. In particular, the Buchwald group has developed a series of bulky electron-rich phosphines that were very efficient in various C–C, C–N, and C–O bond formations.[64] The SPhos and XPhos ligands have proven to be universal ligands for Suzuki-Miyaura reactions.[65] Therefore, we decide to test them to see if they could be useful in the field of P-C bond formation. The work was

[62] Han L.-B., Mirzaei F., Zhao C.-Q., Tanaka M., *J. Am. Chem. Soc*., **2000**, *122*, 5407
[63] Montchamp J.-L., *J. Organomet. Chem*., **2005**, *690*, 2388
[64] For general reviews on Buchwald's phosphines, see: a) Mauger, C. C.; Mignani, G. A. *Aldrichimica Acta* **2006**, *39*, 17; b) Schlummer, B.; Scholz, U. *Adv. Synth. Catal*., **2004**, *346*, 1599.
[65] Billingsley, K.; Buchwald, S. L., *J. Am. Chem. Soc*., **2007**, *129*, 3358

performed in co-operation with dr. Sophie Rousseaux during her practice in the AM_2N laboratory of Professor Jean-Marc Campagne.

In the following studies we took the various palladium (0) and (II) sources shown in **Figure 2.6**.

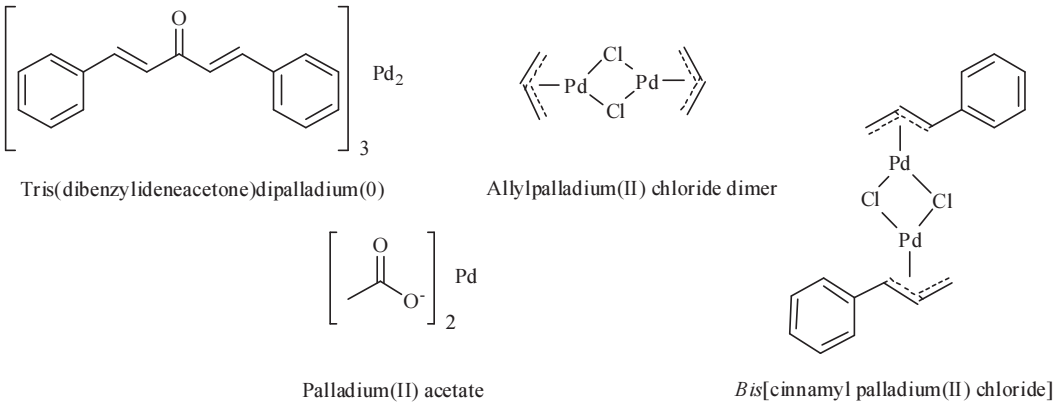


Figure 2.6

Next, we chose the commercially available ligands presented in the **Figure 2.7**.

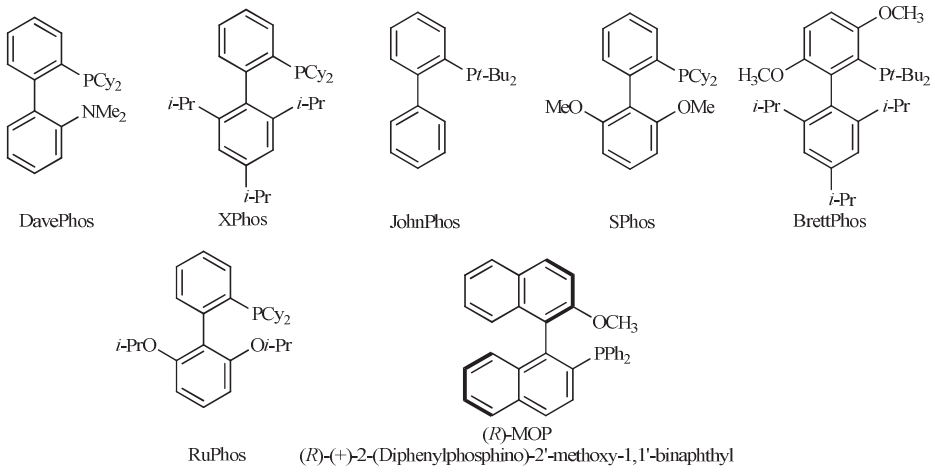
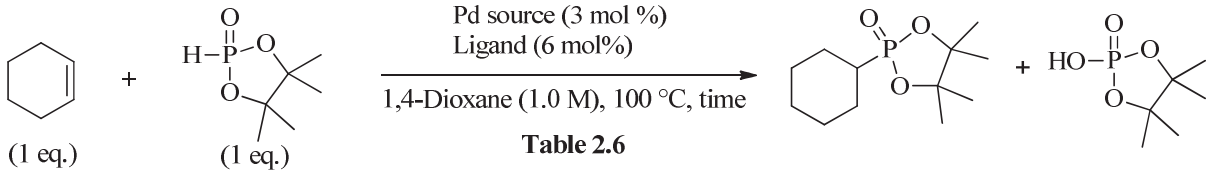


Figure 2.7

These different ligands and pre-catalyst were screened for the reaction between pinacol phosphonate **2.83** on cyclohexene **2.82** (*Scheme 2.28*) and the results are presented in the **Table 2.6**. All reactions were monitored by ^{31}P NMR.



Scheme 2.28

E.	Pd	Ligand	Solvent/T/	time	Ratio [a] **2.83/2.84/2.85**	Product, yield [a]
1	Pd_2dba_3	xantphos,	Dioxane	40h	1:0:trace	-
2	Pd_2dba_3	PPh_3	Dioxane	40h	1:trace:0.53	-
3	$Pd(OAc)_2$	xantphos	Dioxane	40h	1:0.07:0.32	5%
4	Pd_2dba_3	JohnPhos	Dioxane	40h	1:0:0.11	-
5	Pd_2dba_3	DavePhos	Dioxane	40h	1:0.04:0.21	3%
6	$Pd(OAc)_2$	DavePhos	Dioxane	40h	1:0.11:0.31	7%
7	$Pd(OAc)_2$	JohnPhos	Dioxane	40h	1:0:0.11	-
8	$Pd(OAc)_2$	XPhos	Dioxane	62h	1:0.03:0.33	2%
9	$[Pd(allyl)Cl]_2$	DavePhos	Dioxane	62h	1:0.15:0.81	8%
10	$[Pd(allyl)Cl]_2$	DavePhos	Dioxane	20h	1:0.17:0.22	12%
11	$Pd(OAc)_2$	SPhos	Dioxane	62h	1:0.39:0.60	20%
12	**$[Pd(allyl)Cl]_2$**	**SPhos**	**Dioxane**	**20h**	**1:1.79:1.23**	**44%**
13	-	SPhos	Dioxane	40h	1:0:0	-
14	$[Pd(allyl)Cl]_2$	SPhos	Dioxane, 80°C	26h	1:0.05:0.11	3%
15	$[Pd(allyl)Cl]_2$	SPhos	Toluene	62h	1:0.12:0.49	7%
16	$[Pd(allyl)Cl]_2$	PPh_3	Dioxane	26h	1:0.07:0.29	5%
17	$[Pd(allyl)Cl]_2$	PPh_3	Dioxane	40h	1:0.09:0.32	7%

18	$[Pd(allyl)Cl]_2$	BrettPhos	Dioxane	26h	1:0.02:0.24	2%
19	$[Pd(allyl)Cl]_2$	(*R*)-MOP	Dioxane	24h	1:0.08:0.22	6%
20	**$[Pd(allyl)Cl]_2$**	**SPhos**	**DCE**	**15h**	**1:0.60:0.21**	**33%**
21	**$[Pd(allyl)Cl]_2$**	**SPhos**	**DCE**	**15h**	**1:0.72:0.27**	**36%**
22	$[Pd(allyl)Cl]_2$	RuPhos	DCE	16h	1:0.09:0.24	7%
23	$[Pd(cinnamyl)Cl]_2$	SPhos	DCE	16h	1:0.42:0.41	23%

[a]determined by ^{31}PNMR

Table 2.6

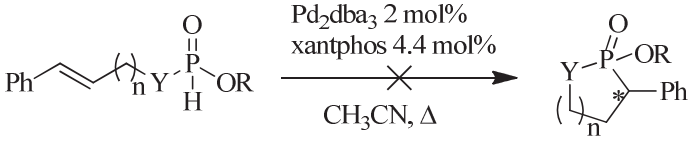
The screening begun with the implementation of catalytic system developed by Montchamp for hydrophosphinylation reaction (entry 1, **Table 2.6**).[60] However, Pd_2dba_3/xantphos in distilled dioxane failed to form the product **2.84**. The combination of palladium source (Pd_2dba_3 or $Pd(OAc)_2$) with different ligands like xantphos, PPh_3, DavePhos, JohnPhos or XPhos did not lead to any significant change in the yield of **2.84** (entries 2-9). On the other hand, we could notice the formation of pinacol phosphate **2.85** each time. This side-product of metal-catalyzed hydrophosphonylation has not been reported in the literature before. Nevertheless, we continued the screening with other catalytic systems. The change to $[Pd(allyl)Cl]_2$ with DavePhos (entries 9 and 10) gave a small improvement in the yield **2.84** (12% within 20h). We reached 20% yield in case of $Pd(OAc)_2$/SPhos system, but with a long reaction time of 62h (entry 11). The first significant improvement was observed with $[Pd(allyl)Cl]_2$/SPhos (entry 12), since a 44% yield of product **2.84** was obtained after 20h. Simultaneously, we could observe the oxidation by-product **2.85** in 30% yield. At that point, a control experiment was performed, using SPhos in the absence of palladium catalyst (entry 13). Neither the expected product **2.84** nor the oxidation product **2.85** were formed, which demonstrates that both processes are palladium-catalyzed. Decreasing temperature (entry 14) or switching the solvent to toluene (entry 15) delivered the product **2.84** in decreased yields. Therefore, the high temperature and solvent are important issues in terms of reaction efficiency. The use of $[Pd(allyl)Cl]_2$ and PPh_3 or BrettPhos or (*R*)-MOP proved (entries 16-19), that the SPhos ligand is the most efficient one. Changing the solvent to 1,2-dichloroethene (DCE) still using $[Pd(allyl)Cl]_2$/SPhos led to the formation of the product **2.84** in 36% within 15h (entry 20 and reproductive trial: entry 21). It is worth to note, that **2.85**

yield had decreased to 13%. Therefore, the use of the apolar, aprotic dichloroethane gave the best score until now. The catalytic system $[Pd(allyl)Cl]_2$/RuPhos (entry 22) did not improve the yield of **2.84**, nor did the change of the palladium source to $[Pd(cinnamyl)Cl]_2$ (entry 23).

In conclusion to that section, various palladium catalytic systems were tested in the hydrophosphonylation reaction of cyclohexene with pinacol phosphonate. Among the different combinations of Pd source, ligands and solvents, the use of $[Pd(allyl)Cl]_2$ as pre-catalyst along with SPhos as a ligand in dichloroethene delivered cyclohexyl pinacol phosphonate **2.84** with the best yield. Although 36% yield of the reaction does not stand for an improvement when compared to Tanaka's result, we significantly decreased the reaction time from 48h to 15h. Additionally, the catalysts are commercially available and therefore, more convenient to handle. Moreover, the work explored the possibilities of Buchwald ligands in the field of P-C bond formation. Until now, none of those ligands has been used in the field of hydrophosphonylation. The catalytic system $[Pd(allyl)Cl]_2$/SPhos in DCE has never been reported. It might find possible application in hydrophosphonylation reactions. Therefore, those studies have valuable prospects. The future perspective would involve the extension of the alkene substrates and the possible application in intramolecular hydrophosphonylation/hydrophosphinylation.

6. Conclusion to *Chapter II*

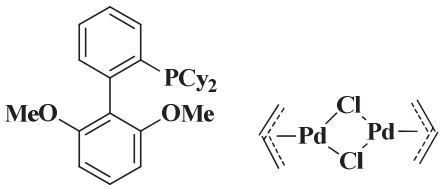
In ***Chapter II*** we explored experimentally intramolecular and intermolecular hydrophosphonylation and hydrophosphinylation. The appropriate substrates were synthesized. Transesterification reaction led to ammonium cinnamyl H-phosphonate in 60% yield. The preparation of (*E*)-ethyl(diethoxymethyl)(5-phenylpent-4-en-1-yl)phosphinate and (*E*)-ethyl (diethoxyethyl)(5-phenylpent-4-en-1-yl)phosphinate were obtained in complex six-step synthesis in 10-14% overall yield. Unfortunately, the attempts of intramolecular cyclization failed under standard conditions.



n= 1,2
Y= O, CH_2
R= H or alkyl or NH_4^+

We explain that fact by a difficult P(III)/P(V) tautomerization. We can assume that the tautomer P(III) is not thermodynamically favored to carry out the oxidative addition.

The last part of ***Chapter II*** was devoted to intermolecular hydrophosphonylation of pinacol phosphonate on cyclohexene. Numerous attempts were performed in order to develop new catalytic systems. We tested different palladium sources together with Buchwald ligands. The combination of $[Pd(allyl)Cl]_2$ with SPhos in dichloroethene was the most efficient and delivered cyclohexyl pinacol phosphonate in 36% yield in 15h.



SPhos **Allylpalladium(II) chloride dimer**

This result in encouraging and can be a good starting point for future experiments leading to the development of novel catalytic systems for hydrophosphonylation and hydrophosphinylation reactions, including intramolecular approach.

Chapter III

EXPLORING THE POTENTIAL OF N-PROPARGYLIC HYDROXYLAMINES IN THE STEREOSELECTIVE SYNTHESIS OF CBZ-PROTECTED *β*-ENAMINONES AND THE SYNTHESIS OF PYRIMIDINES.

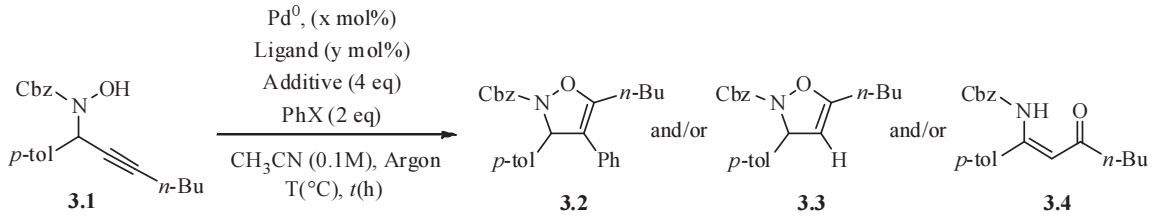
This Chapter describes studies conducted in the laboratory of Professor Jean-Marc Campagne. Firstly, the palladocyclization/cross coupling reaction towards trisubstituted isoxazoles will be described. Then, the results of the synthesis of *β*-enaminones will be described and its application in the synthesis of 2,4,6-trisubstituted pyrimidines.

1. Palladocyclization/cross coupling reaction towards trisubstituted isoxazoles.

During my work on palladium-catalyzed reactions of hydrophosphonylation and hydrophosphinylation, I had a chance to cooperate with Eric Gayon. I witnessed and discussed his work on the transition-metal catalyzed uninterrupted four-step sequence to access trisubstituted isoxazoles.[66] In particular, we were interested by the step of the annulation/cross coupling step of *N*-propargylic hydroxylamine **3.1** with iodobenzene. The conditions tested and shown below with the interpretation were performed by Eric Gayon, Ophelie Quinonero and Sebastien Lemouzy. My small contribution is exposed in entries 3 and 4 (*Scheme 3.1*, **Table 3.1**).[66]

The entry 1 was carried out in the presence of iodobenzene under the conditions reported by Yang.[67] This reaction affords 2,3-dihydroisoxazole **3.2** in 85% yield after 72h in 50°C. As it was interesting to shorten the reaction time, the reaction was carried out in acetonitrile in reflux (entry 2) which effected in the formation of the mixture of three products namely isoxazoline **3.2**, its disubstituted analog **3.3** and *β*-enaminone **3.4** in the 4/1/1 ratio. The formation of the by-products **3.3** and **3.4** was intriguing enough to decide to track down the synthetic pathway and the involved mechanisms.

[66] Gayon E., Quinonero O., Lemouzy S., Vrancken E., Campagne J.-M., *Org. Lett*., **2011**, *13*, 6418
[67] Zhan Z.-P., Yu J.-L., Liu H.-J., Cui Y.-Y., Yang R.-F., Yang W.-Z., Li J.-P., *J. Org. Chem.,* **2006**, *71*, 8298



Scheme 3.1

Entry	Pd(0) ([x mol%]), Ligand ([y mol%])	PhX (2 eq)	Additive (4 eq)	T(°C)	*t* (h)	**3.2**/**3.3**/**3.4**[a] (Yield, %)[b]
1	Pd_2dba_3 (5), bpy (10)	PhI	K_2CO_3	50	72	1/0/0 (85/-/-)
2	Pd_2dba_3 (5), bpy (10)	PhI	K_2CO_3	Reflux	1	4/1/1 (33/5/13)
3	-	-	K_2CO_3	50	20	0/0/1 (-/-/**89**)
4	Pd_2dba_3 (5), bpy (10)	-	K_2CO_3	50	20	0/9/1 (-/**73**/7)
5	$Pd(PPh_3)_4$ (10)	PhI	K_2CO_3	50	20	0/3/1 (-/58/19)
6	$Pd(PPh_3)_4$ (10)	-	K_2CO_3	50	20	0/1.5/1 (-/41/30)
7	$Pd(PPh_3)_4$ (10)	PhI	-	50	72	NR
8	Pd_2dba_3 (5), bpy (10)	PhI	-	50	72	NR
9	Pd_2dba_3 (5), bpy (10)	PhI	DMAP	50	72	NR
10	Pd_2dba_3 (5), bpy (10)	PhI	Imidazole	50	72	NR
11	Pd_2dba_3 (5), bpy (10)	PhI	Propylene oxide	50	72	NR
12	Pd_2dba_3 (5), bpy (10)	PhI	Et_3N	50	40	1/0/0 (75/-/-)
13	Pd_2dba_3 (5), bpy (10)	PhBr	K_2CO_3	50	40	0/4.5/1 (-/50/11)
14	Pd_2dba_3 (10), bpy (20)	PhI	K_2CO_3	50	20	1/0/0 (**86**/-/-)

[a] Determined by the ^1H NMR spectroscopy of the crude [b] Isolated yield. NR = No Reaction.

Table 3.1

Therefore, in the control reaction (entry 3) *N*-propargylic hydroxylamine **3.1** was tested only in the presence of 4 equivalents of K_2CO_3. The result was very promising from synthetic point of view, as the formation of *β*-enaminone **3.4** was observed in 89% yield without the smallest trace of cyclization products **3.2** and **3.3**.[66] The development of this transformation will be evaluated in details in the **Section 2** and **Section 3 (*Chapter III*)**.

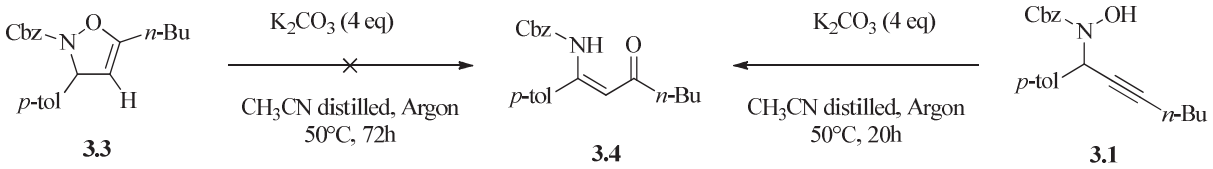
Another control reaction (entry 4) was performed in the presence of the catalytic system Pd_2dba_3/bpy (2,2'-bipyridine) and in the absence of iodobenzene. This reaction results in the formation of 3,5-disubstituted isoxazoline **3.3** in 73% yield accompanied by traces of the *β*-enaminone **3.4** (7%). The use of the tetrakis(triphenylphosphine)palladium(0) in the

presence or in the absence of iodobenzene affords isoxazoline **3.3** in majority together with the *β*-enaminone **3.4** (entries 5-6).[66]

We were interested in the role of the base in this transformation. In the absence of K_2CO_3, no reactivity can be observed (entries 7-8). The same situation is encountered when moderate bases like imidazole or DMAP (4-dimethylaminopyridine) are employed (entries 9-12). However, the use of triethylamine leads to the formation of the product **3.2** in 75% yield (entry 12). The application of the bromobenzene affords the compound **3.3** in 50% yield (entry 13).

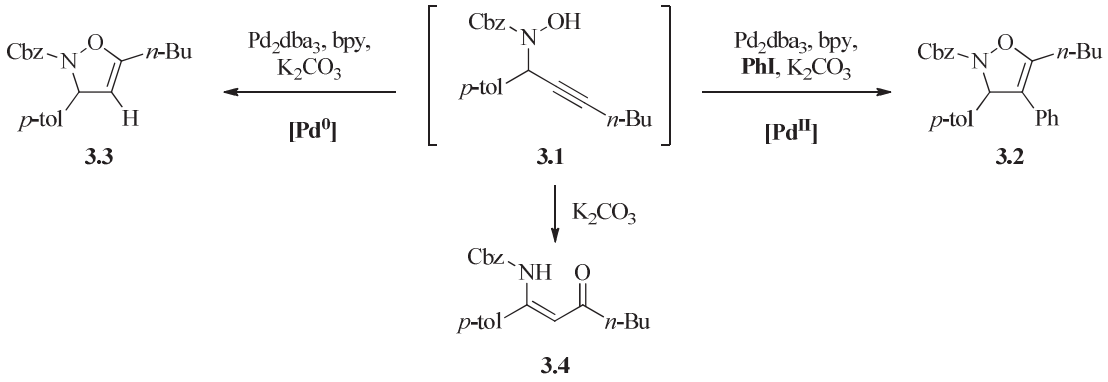
Finally, the increased quantity of the catalysts [Pd_2dba_3 (10 mol%)/bpy (20mol%)] decreased the reaction time to 20h affording of compound **3.4** in 86% yield (entry 14).

In order to cross out the possibility of *β*-enaminone being the result of the opening of the isoxazoline **3.2** under basic conditions of the reaction, we set the trial with pure **3.3** in acetonitrile in the presence of K_2CO_3 (*Scheme 3.2*). Under these conditions, no reaction was observed proving that the compound **3.2** is not the intermediate of enaminone **3.4**, but the separate product promoted by the base on *N*-propargylic hydroxylamine **3.1** (*Scheme 3.2*).



Scheme 3.2

After those studies, we can conclude, that three competing pathways take place in the reaction mixture leading to products **3.2**, **3.3** and **3.4**. Amongst them, one led to the formation of *β*-enaminone, which is the slowest and is base-catalyzed. The other two are Pd-catalyzed and led to the cyclization products **3.2** and **3.3** (*Scheme 3.3*).

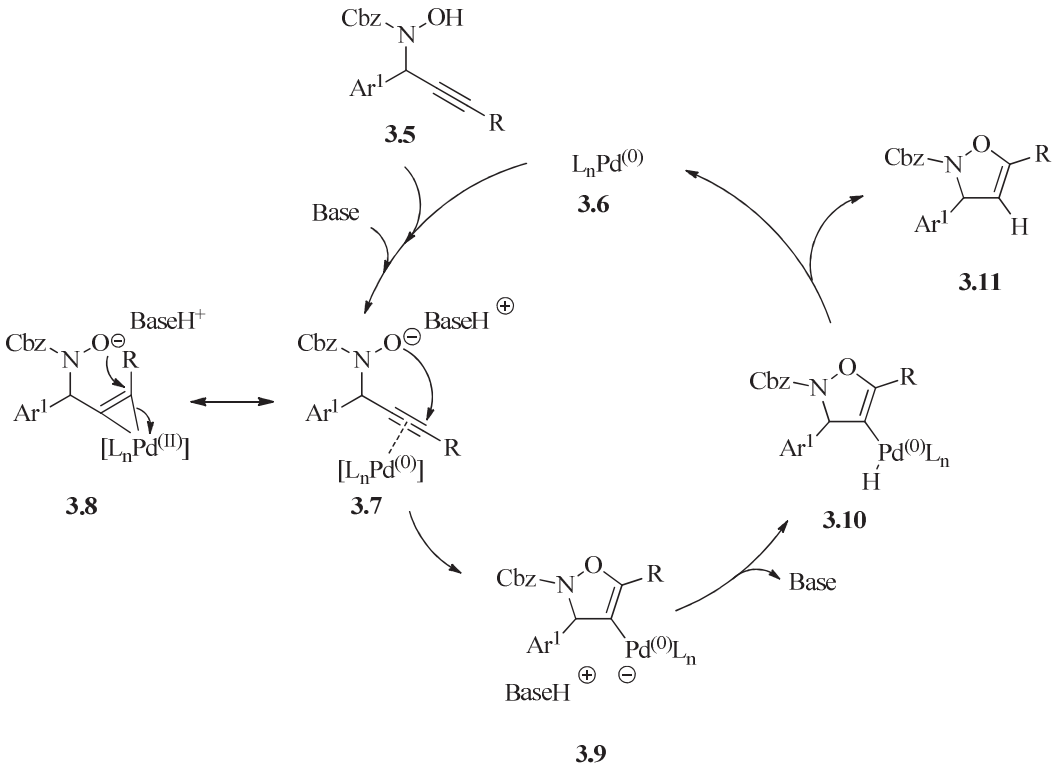


Scheme 3.3

The formation of isoxazoline 3,5-disubstituted **3.2** is the first, to our knowledge, example of π-activation of the unsaturation by Pd(0)-catalysis. In fact, numerous publications describe the π-activation of double and triple bonds by Pd(II) complexes.[68] Additionally, the group of Norrby *et al.* performed calculations providing the information that alkynes can be excellent ligands for Pd(0).[69] The interactions between d orbitals of Pd(0) with π* orbitals of the triple bond will allow the metal to concede a part of his electronic density by back-donation, leading to a significant stabilization of the various Pd(0)-alkyne complexes. In our case, the coordination of the triple bond of *N*-propargylic hydroxylamine **3.1** by Pd(0) allows to activate the unsaturation of **3.1** and promote the attack of internal nucleophile leading to 3,5-disubstituted isoxazole. **3.3**.

[68]a) Rubin M., Sromek A. W., Gevorgyan V., *Synlett*, **2003**, 2265; b) Zeni G., Larock R. C., *Chem. Rev.*, **2006**, *106*, 4644; c) Conreaux D., Bouyssi D., Monteiro N., Balme G., *Curr. Org. Chem.*, **2006**, *10*, 1325; d). D'Souza D. M, Müller T. J. J., *Chem. Soc. Rev.*, **2007**, *36*, 1095

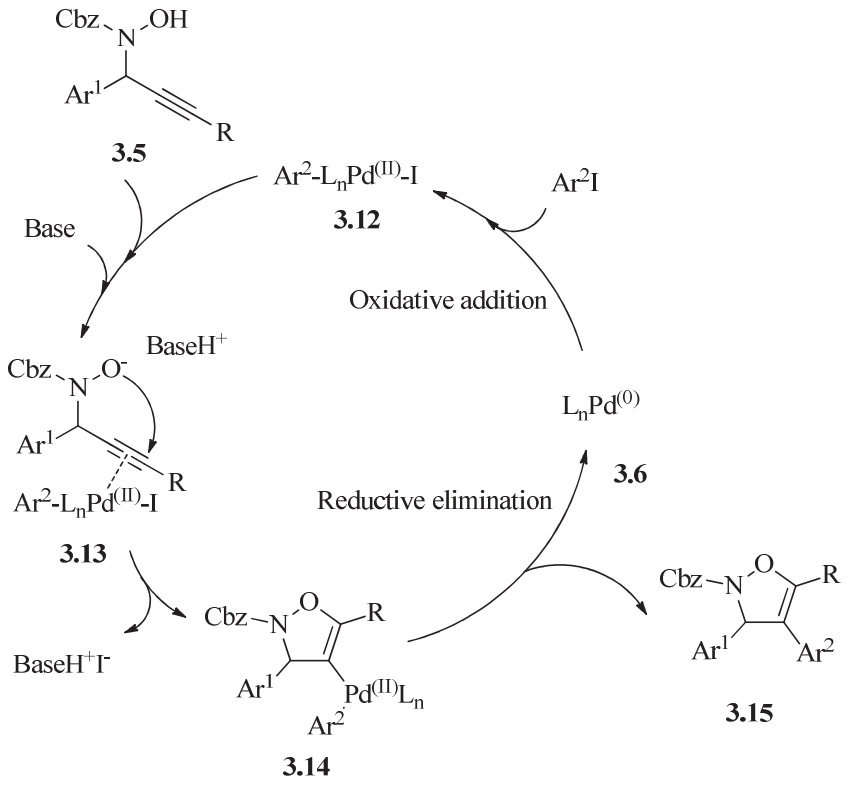
[69] Ahlquist M., Fabrizi G., Cacchi S., Norrby P.-O., *Chem. Commun.*, **2005**, 33, 4196



Scheme 3.4

It seems to be difficult to describe the nature of the mechanism of this reaction, as little is known about the Pd(0) activation of triple and double bonds. However, the hypothesis can be proposed (*Scheme 3.4*). The obligatory presence of the base in this reaction indicates that the first step relays on the deprotonation of *N*-propargylic hydroxylamine **3.5**. The coordination of triple bond by the complex of Pd(0) leads to the formation of the complex η^2-palladium(0) **3.7** or η^2-palladacyclopropene **3.8.** The attack of the internal nuclephile *via* 5-*endo*-dig cyclization affords vinyl-palladate **3.9**. The protonation of this species gives the complex of palladium(0) vinyl hydride **3.10** which, after proto-demetalation affords disubstituted isoxazoline **3.11** with the regeneration of the catalyst **3.6** (*Scheme 3.3*).

The formation of 3,4,5-trisubstituted isoxazoline **3.2** is Pd(II) catalyzed. It does not occur until the ligand (bpy) is coordinated to the complex of palladium and not until the oxidative insertion is facilitated by the aryl iodide. In fact, in case of the use of bromobenzene, oxidative insertion seems to be abandoned and the Pd(0)-catalyzed process is favored.



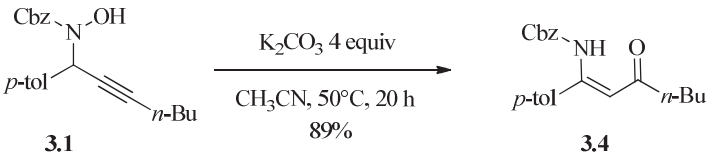
Scheme 3.5

The complex of C_{sp^2}-palladium(II) **3.12** generated *in-situ* coordinates to the triple bond of **3.5** to form complex η^2-palladium(II) **3.13** which induces the intramolecular nucleophilic attack *via* the 5-*endo*-dig cyclization (after deprotonation of hydroxylamine). The reductive elimination of the complex σ-vinyl-palladium(II) **3.14** allows the regeneration of the catalysts **3.6** and the formation of the product **3.15** (*Scheme 3.5*).

The work described above is part of the transition-metal catalyzed uninterrupted four-step sequence to access 3,4,5-trisubstituted isoxazoles[66] conducted by Eric Gayon in the laboratory of Professor Jean-Marc Campagne. Full approach of this sequence has been published recently[66] and will not be discussed herein. However, the discovery of the isomerization of *N*-propargylic hydroxylamines into *β*-enaminones was carried out by Eric Gayon with my contribution and the following sections will focus on the development of the methodology based on that rearrangement.

In the framework of the reaction shown in *Scheme 3.1* we observed the formation of the *β*-enaminones from *N*-propargylic hydroxylamines in the presence of the excess potassium carbonate (*Scheme 3.6*). We were intrigued by this unexpected rearrangement and we decided

to follow these studies in order to understand the mechanism of this isomerisation, origins of the selectivity and explore its scope and limitations.



Scheme 3.6

The next **Section 2** ***Chapter III*** recalls the known procedures towards *β*-enaminones and mentions their different application. The development of the methodology will be described in the **Section 3**. The extension of that studies resulted in the synthesis of 2,4,6-trisubstituted pyrimidines and this will be described in the **Section 4**.

2. Structure, significance and reactivity of β-enaminones.

The group of compounds named *β*-enaminones can be presented as a general formula shown in **Figure 3.1.** Those organic molecules possess in their structure a conjugated system composed of the motif N-C=C-C=O, which is crucial for their reactivity.

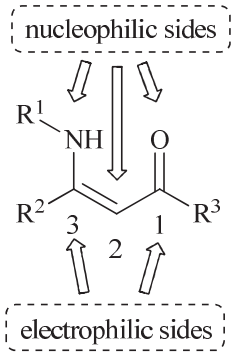


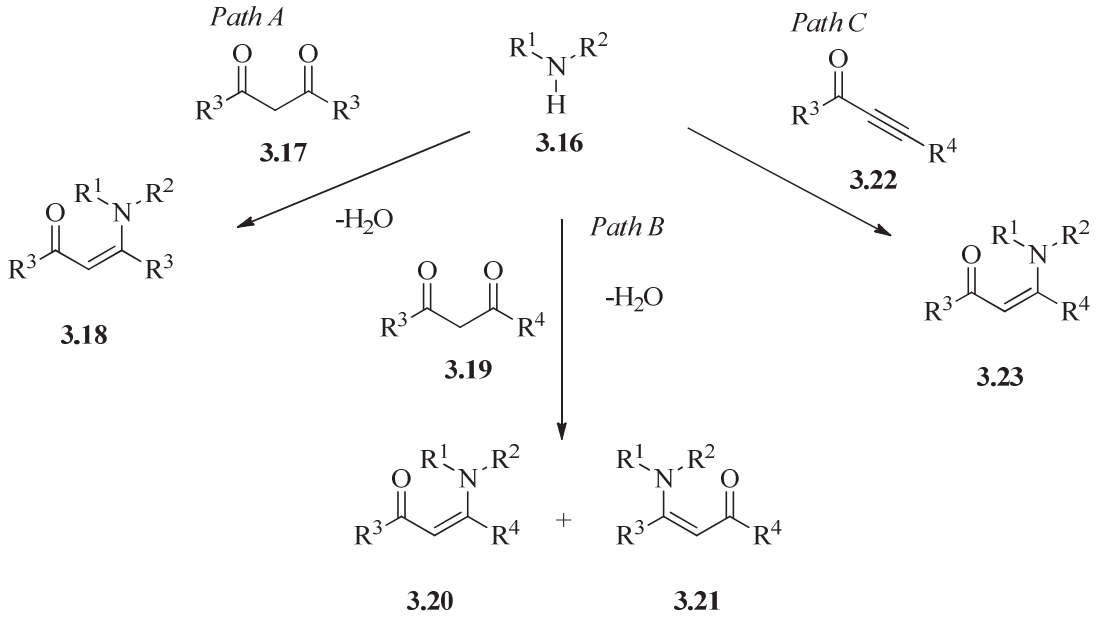
Figure 3.1

The nature of these compounds lays in their ambivalent character. They exibit the ambident nucleophilicity of enamines (C2 or N), whereas C-1 and C-2 presents the ambident electrophilicity of enones (**Figure 3.1**). Those divergent features make *β*-enaminones and their derivatives useful synthetic tools, implemented in various organic chemistry fields as it will be presented in the following sections.[70]

[70] a) Greenhill J. V., *Chem. Soc. Rev.*, **1977**, *6*, 277. b) Elassar A.-Z. A., El-Khairb A. A., *Tetrahedron*, **2003**, *59*, 8463

2.1. Common methods to access *β*- enaminones.

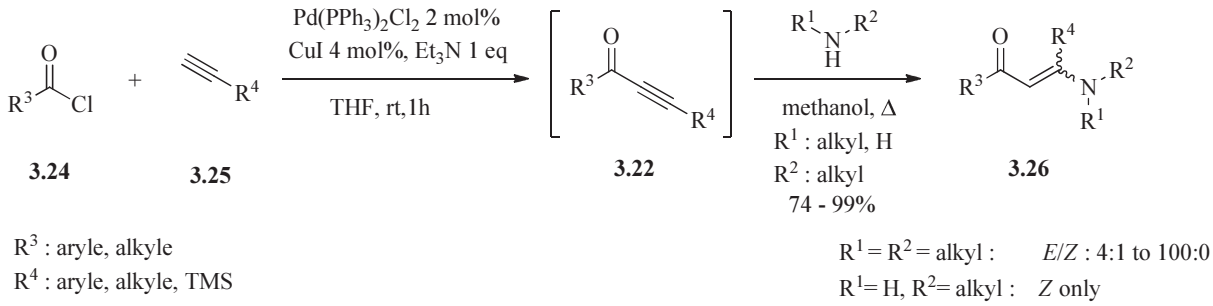
In the light of existing literature, numerous methodologies affording *β*-enaminones can be found. The best-known one relays on the direct condensation of ammonia or primary and secondary amines (general formula **3.16** *Scheme 3.7***)** with the derivatives of 1,3- dicarbonyls (**3.17** or **3.19** *Scheme 3.7*).[71] However, efficiency of this methodology depends on the substituents R^3 and R^4 of the dicarbonyl substrate **3.17** or **3.19**, resulting in the differences in electrophilicity. Two cases should be taken into the consideration. In the first case, symmetric dicarbonyl **3.17** is taken (*Path A***,** *Scheme 3.7*) so the reaction leads to the sole product. In the second case (*Path B*, *Scheme 3.7*), if the electrophilic difference between R^3 and R^4 of **3.19** is significant, the nucleophilic attack of the amine will occur on the carbonyl group, which is stronger electrophile and this result in one product (or **3.20** or **3.21**). Finally, the regioselectivity is lost if there is too small difference in electrophilicity and the mixture of regioisomers **3.20** and **3.21** is obtained. This inconvenience can be efficiently omitted by the methodology shown in *Path C* (*Scheme 3.7*), where propargylic ketones **3.22** undergo Michael addition giving *β*-enaminones **3.23** regioselectively.[72]



Scheme 3.7

[71] Dixon K., J. Greenhill V., *J. Chem. Soc., Perkin Trans.2*, **1974**, 164
[72] a) Bowden K., Braude E. A., Jones E. R. H., Weedon B. C. L., *J. Chem.* Soc., **1946**, 45; b) Winterfeldt E., Nelke J. M., *Chem. Ber.,* **1968**, *101*, 2381

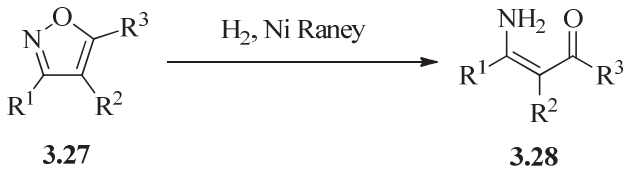
An example of *Path C* is shown in *Scheme 3.8*.[73] Firstly, performing Sonogashira reaction gives the family of alkynones **3.22** *in situ*. Then, Michael addition of various amines leads to the corresponding enaminones **3.26**.



Scheme 3.8

The stereoselectivity of final products depends on the structure of the amine. Primary amines as the substrates led exclusively to the *Z* stereochemistry (due to the existence of possible intramolecular hydrogen bond), whereas (*E*)-*β*-enaminones can be achieved from secondary amines (*Scheme 3.8*).[73]

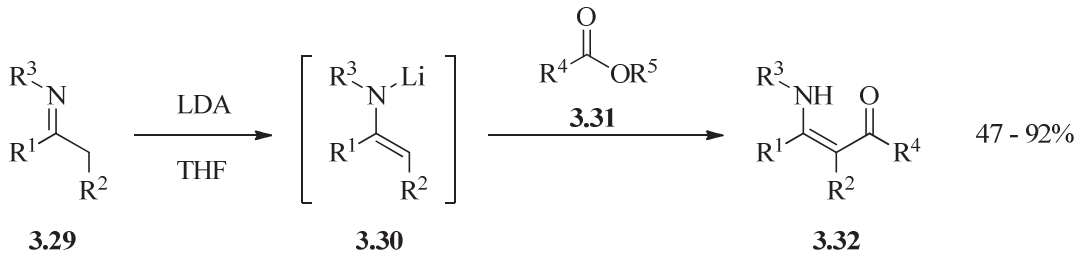
Another methodology describing the synthesis of *β*- enaminones **3.28** includes the reduction of N-O bond of isoxazoles **3.27** in the presence of Raney nickel (*Scheme 3.9*).[74]



Scheme 3.9

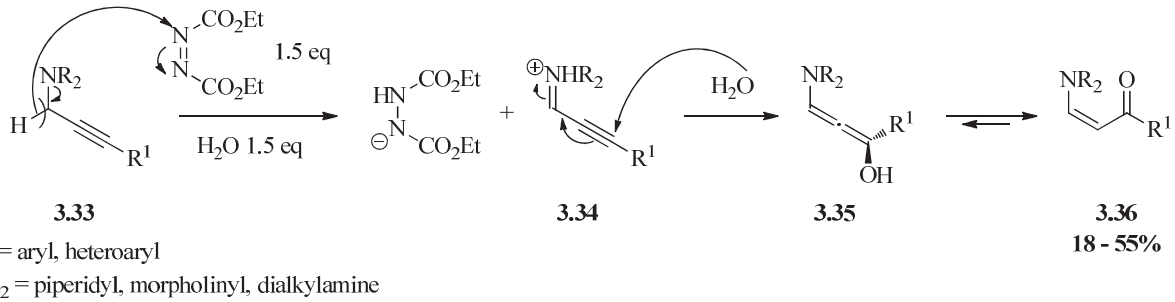
Efficient method to access *β*-enaminones was also demonstrated by Bartoli *et al*.[75] Products **3.32** were obtained by the addition of N-lithiated enamines **3.30** to the esters **3.31** (*Scheme 3.10*).

[73] Karpov A.S., Müller T. J. J., *Synthesis*, **2003**, *18*, 2815
[74] a) Stagno D'Alcontres G., *Gazz. Chem. Ital.*, **1950**, *80*, 441;b) Kochetkov N. K., Sokolov S. D., *Adv. Heterocycl. Chem.*, **1963**, *2*, 365; c) Sainsbury M., Trost B. M., Ed.; *Comprehensive Organic Synthesis*; Pergamon: New York, **1991**; *8*, 644; d) Baraldi G., Barco A., Benetti S., Pollini G. P., Simoni D., *Synthesis*, **1987**, 857
[75] Bartoli G., Cimarelli C., Palmieri G., Bosco M., Dalpozzo R., *Synthesis*, **1990**, *10*, 895



Scheme 3.10

Recently, Xu and Li described stereoselective synthesis of (*Z*)-*β*-enaminones from propargylic amines **3.33** promoted by diethyl azodicarboxylate (DEAD) under mild conditions without a solvent (*Scheme 3.11*).[76] According to the authors, DEAD allows the abstraction of the hydride in α position of nitrogen atom of the propargylic amine **3.33** to generate propargylic iminium **3.34**. Conjugated addition of water allows the formation of allenol **3.35**, which, after the tautomerization, leads to the disubstituted *β*-enaminone **3.36** (*Scheme 3.11*).[76]



Scheme 3.11

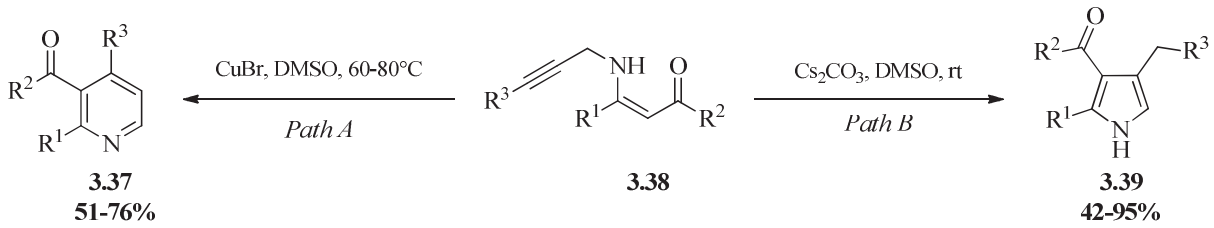
2.2. Divergent application of *β*-enaminones.

β-Enaminones have found numerous applications on the field of the heterocyclic chemistry.[77]In particular, in 2008, Cacchi and Fabrizi described the selective method to obtain

[76] Xu X., Du P., Cheng D., Wang H., Li X., *Chem. Commun*., **2012**,*48*, 1811

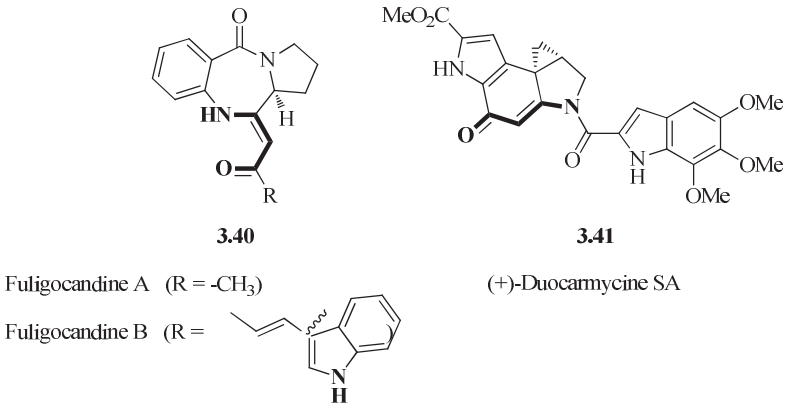
[77] a) Lue P., Greenhill J. V., *Adv. Heterocycl. Chem.* **1997**, *67*, 215;b) Hantzsch A., *Liebigs Ann. Chem.*, **1882**, *215*, 1; c) Dondoni A., Massi A., Minghini E., Sabbatini S., Bertolasi V., *J. Org. Chem.*, **2003**, *68*, 6172; d). Nenitzescu C. D, *Bull. Soc. Chim. Romania*, **1929**, *11*, 37; e) Littell R., Morton G., Allen G. R., *J. Am. Chem. Soc.*, **1970**, *92*, 12, 3740; f) Barun O., Chakrabarti S., Ila H., Junjappa H., *J. Org. Chem.*, **2001**, *66*, 4457; g) Neumann J. J., Suri M., Glorius F., *Angew. Chem. Int. Ed.*, **2010**, *49*, 7790;h) Stahl P., Kissau L., Mazitschek R., Huwe A., Furet P., Giannis A., Waldmann H., *J. Am. Chem. Soc.* **2001**, *123,* 11586

pyridines **3.37** and pyrroles **3.39** starting from the same N-propargylic β-enaminone **3.38** (*Scheme 3.12*).[78]



Scheme 3.12

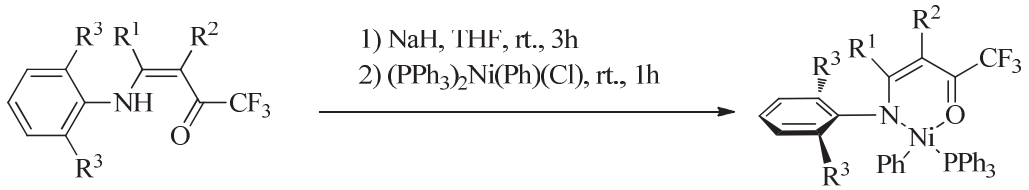
We can also observe the impact of β-enaminones in the total synthesis of natural products.[79] In particular, the motif of β-enaminones can be noticed in alkaloids, like the Fuligocandines **3.40** and Duocarmycine SA [80] **3.41**, which possess anti-cancer properties (*Scheme 3.13*).



Scheme 3.13

Coordination chemistry also finds β-enaminones useful.[81] For example, Brookhart *et al.* synthesized a new complex of nickel (II) **3.43** from trifluoromethylated β-enaminones **3.42**. These complexes came out to be efficient in the polymerization of ethylene (*Scheme 3.14*).[82]

[78] Cacchi S., Fabrizi G., Filisti E., *Org. Lett.*, **2008**, *10*, 13, 2629
[79] a) Caprathe B. W., Jaen J. C., Wise L. D., Heffner T. G., Pugsley T. A., Meltzer L. T., Parvez M., *J. Med. Chem.*, **1991**, *34*, 2736; b) Gatta F., Del Giudice M. R., Pomponi M., Marta M., *Heterocycles*, **1992**, *34*, 991; c) Cimarelli C., Palmieri G., *J. Org. Chem.*, **1996**, *61*, 5557; d) Harris M. I. N. C., Braga A. C. H., *J. Braz. Chem. Soc.*, **2004**, *15*, 971; e) Salama N. N., Eddington N. D., Payne T. L., Wilson K. R., Scott K. R., *Curr. Med. Chem.,* **2004**, *11*, 2093
[80] Boger D. L., *Chemtracts: Org. Chem.* **1991**, *4*, 5, 329
[81] a) Cindrić M., Vrdoljak V., Strukan N., Brbot-Šaranović A., Novak P., Kamenar B., *Inorg. Chim. Acta*, **2004**, *357*, 931; b) Bartoli G., Cimarelli C., Marcantoni E., Palmieri G., Petrini M., *J. Org. Chem.*, **1994**, *59*, 5328; c) Szydłowska J., Krówczyński A., Górecka E., Pociecha D., *Inorg. Chem.* **2000**, *39,* 4879
[82] Zhang L., Brookhart M., White P. S., *Organometallics*, **2006**, *25*, 1868



3.42 **3.43**

Scheme 3.14

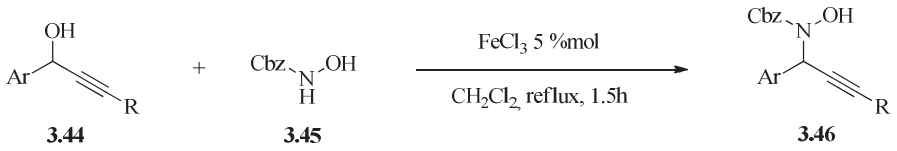
3. Rearrangement of propargylic hydroxylamines. Stereoselective access to Cbz-protected β-enaminones.

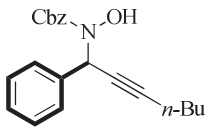
The work described herein is devoted to the methodology of the stereoselective synthesis of (*Z*)-*β*-enaminones. It was conducted by Eric Gayon with my participation. This considers synthesis of *β*-enaminones (**3.84-3.88**, **3.92)** and pyrimidines (**3.155-3.158**, **3.162**), as well as the re-synthesis of the starting materials, N-propargylic hydroxylamines (**3.47**, **3.54, 3.56-3.59, 3.63**).

3.1. The synthesis of N-propargylic hydroxylamines.

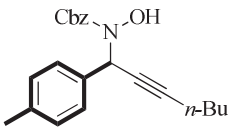
In order to carry out the rearrangement, the family of N-propargylic hydroxylamines were synthesized using the method of the propargylic substitution described by Zhan.[83] Hydroxylamine **3.44** reacts with propargylic alcohols **3.45** in the presence of catalytic amounts of iron(III) chloride giving the corresponding N- propargylic hydroxylamines **3.46**.

[83] Zhan Z.-P., Yu J.-L., Liu H.-J., Cui Y.-Y., Yang R.-F., Yang W.-Z., Li J.-P., *J. Org. Chem.,* **2006**, *71*, 8298





3.47
93%



3.48
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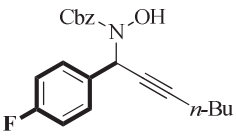

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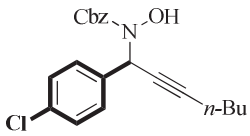

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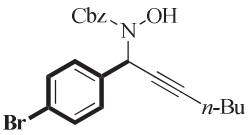

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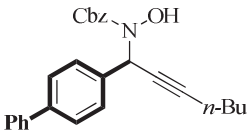

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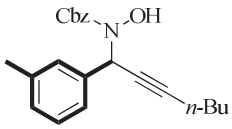

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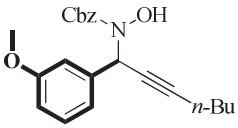

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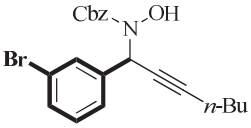

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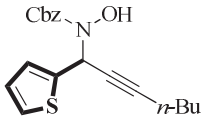

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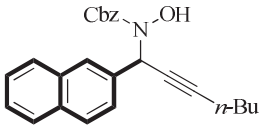

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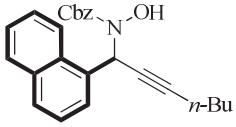

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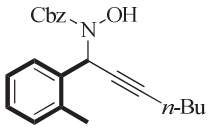

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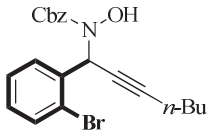

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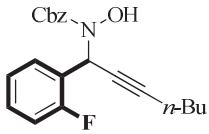

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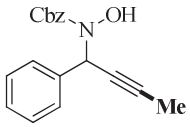

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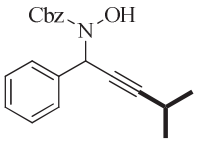

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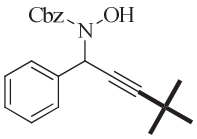

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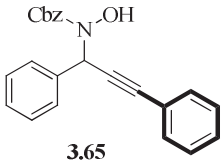

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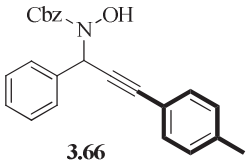

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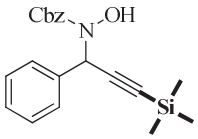


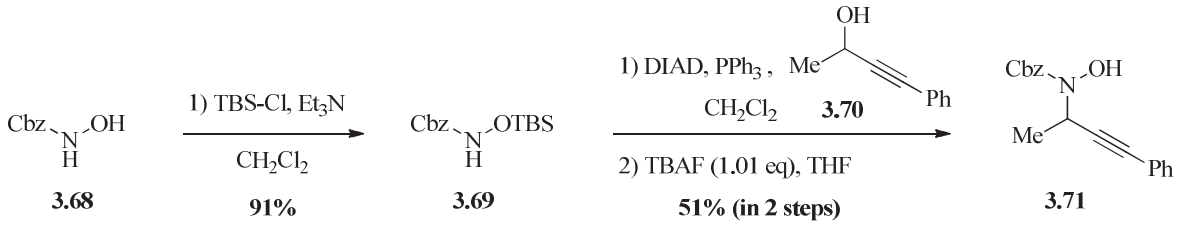
3.67
87%

The products were obtained in very good to excellent yields (62- 94%). Starting material with either the substitution in aromatic ring (**3.48- 3.61**) or the substitution of propargylic position (**3.62- 3.67**) reacted smoothly.

In order to evaluate the effect of the substituent of propargylic moiety, we also have envisioned the synthesis of *N*-propargylic hydroxylamines substituted at the propargylic position with the alkyl groups.

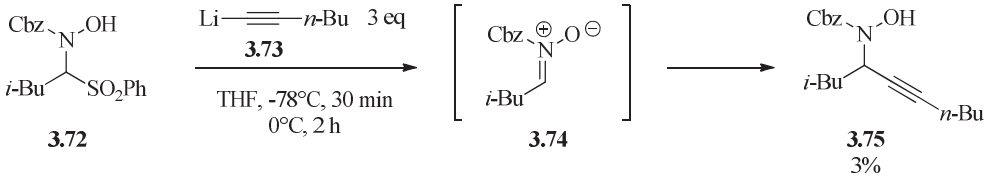
The method described above, is efficient only for the synthesis of the derivatives substituted with aromatic groups (which is necessary for the stabilization of carbocation

intermediate). Therefore, we set Mitsunobu reaction between hydroxylamine **3.68** and a propargylic alcohol **3.70**, followed by the desilylation in the presence of TBAF, which gave the desired product **3.71** (*Scheme 3.15*). The protection of hydroxylamine **3.69** by silyl group is essential to conduct this reaction.



Scheme 3.15

In order to obtain the second derivative, namely compound **3.75** substituted by aliphatic groups,[84] we set the reaction with the sulfonylcarbamate **3.72**. Treating **3.72** with an excess of lithium acetylide **3.73** led to the formation of numerous products with the propargylic hydroxylamine obtained **3.75** in 3% yield. Significant quantity of benzylic alcohol ($PhCH_2OH$) observed in the crude H^1NMR spectrum shows that the deprotection of the intermediates occured (*Scheme 3.16*).

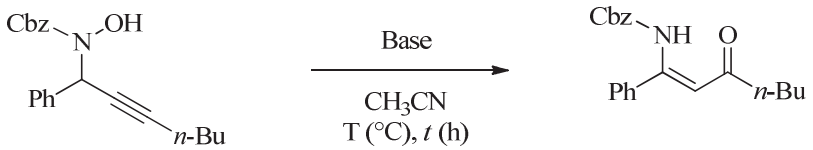


Scheme 3.16

3.2. Optimization of the reaction towards (*Z*)-β-enaminone.

We chose benzyl hydroxyl(1-phenylhept-2-yn-1-yl)carbamate **3.47** as a model substrate. Reactions were conducted in acetonitrile using various bases (*Scheme 3.17*, **Table 3.2**).

[84] Guinchard X., Vallée Y., Denis J.-N., *Org. Lett.*, **2005**, *7*, 23, 5147



3.47 **3.76**

Scheme 3.17

Entry	Base	Equiv.Base	T (°C)	*t* (h)	Yield 3.76 [a] (%)
1	K_2CO_3	4	50	20	71
2	Et_3N	4	50	20	NR
3	NaOH	4	50	1	28
4	NaOH	1	50	1	75
5	**NaOH**	**0,1**	**50**	**1**	**86**
6	NaOH	0,1	rt	12	78
7	K_2CO_3	0,1	50	8	59

[a] Isolated yield NR= no reaction

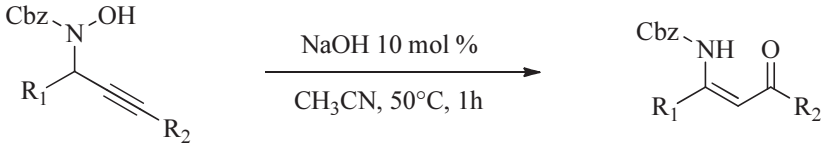
Table 3.2

In the presence of the excess of K_2CO_3 (4 equivalents), β-enaminone **3.76** can be isolated in 71% yield after 20h at 50°C (entry 1). Triethylamine (4 equivalents) does not promote the rearrangement and the starting material was recovered (entry 2). The conversion of hydroxylamine **3.47** with 4 equivalents of NaOH resulted in 28% of yield (entry 3). That was accompanied by the formation of side-products. Therefore, we decided to decrease the quantity of NaOH to 1 equivalent, which resulted in the increase of yield to 75% (entry 4).

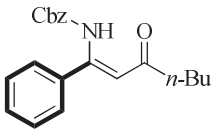
In fact, the rearrangement takes place even in the presence of 0.1 equivalent of NaOH providing the product in 86% yield (entry 2). This reaction can be even conducted at room temperature, although the reaction time extends to 12h (entry 6). At the end, we tried again the reaction with K_2CO_3, but with only 0,1 equivalent. The reaction needed 8h to obtain **3.76** in moderate yield of 59% (entry 7).

3.3. Synthesis of (Z)-β-enaminones.

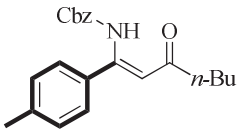
The synthesized substrates were subjected to the conversion to β-enaminones (*Scheme 3.18*) under the optimized conditions. In the first place, we were interested in the influence of the substituents present in the aromatic ring.



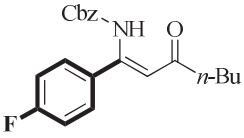
Scheme 3.18



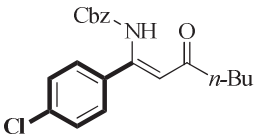
3.76
86%



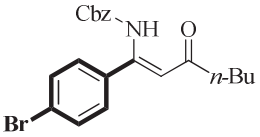
3.77
90%



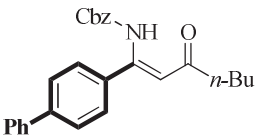
3.78
71%



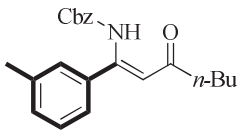
3.79
80%



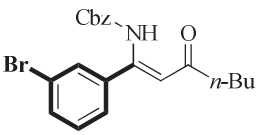
3.80
87%



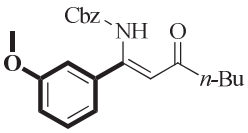
3.81
61%



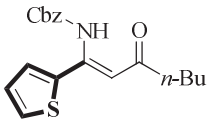
3.82
71%



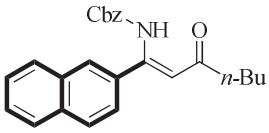
3.83
52%



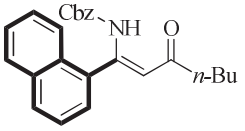
3.84
66%



3.85
45%



3.86
58%



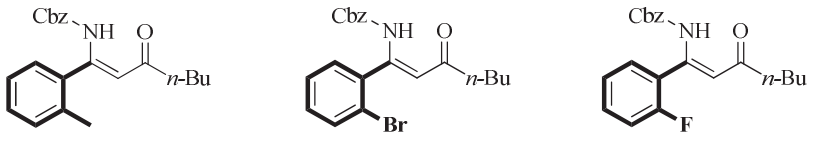
3.87
29%

The Cbz-protected β-enaminones **3.76-3.86** were obtained in good to excellent yields (52-90%). The reaction tolerates well the presence of withdrawing and donating groups either in *para* or *meta* positions. Even the presence of thiophene leads to the product in satisfactory yield (**3.85**, 45%).

However, some limitations can be also observed. The hindered substituents at *ortho* position of the aromatic ring lead to the significant decrease of the product yield (58% of **3.86** vs 29% of **3.87**).

Moreover, the presence of methyl substituent or bromine at *ortho* position of the aromatig ring of the starting hydroxylamines does not provide the corresponding products

3.88 and **3.89**, whereas fluorine is tolerated and **3.90** was obtained in 84% yield (*Scheme 3.19*).



3.88 NR

3.89 NR

3.90 84%

Scheme 3.19

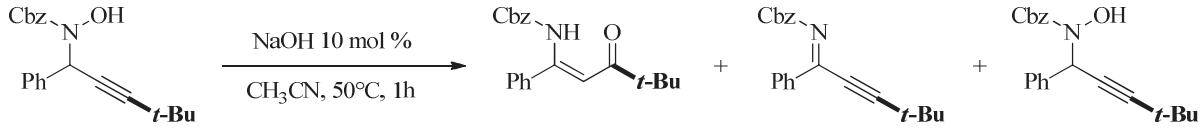
Furthermore, we evaluated the reaction capability of hydroxylamines with sibstituents at acetylenic position. As the result, the methyl and *iso*-propyl substituents are well-tolerated leading to enaminones **3.91** and **3.92** (*Scheme 3.20*).

3.91 75%

3.92 63%

Scheme 3.20

However, in case of *tert*-butyl group, hydroxylamine **3.64** was observed as the trace in H^1NMR spectrum of the crude product. In fact, the reaction leads to the formation of propargylic imine **3.94** isolated in 41% of yield, accompanied by 46% of starting material and hydroxylamine **3.64** (*Scheme 3.21*).



3.64

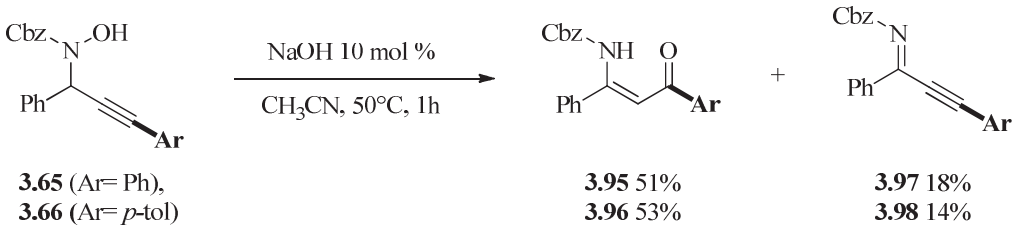
3.93 traces

3.94 41%

3.64 46%

Scheme 3.21

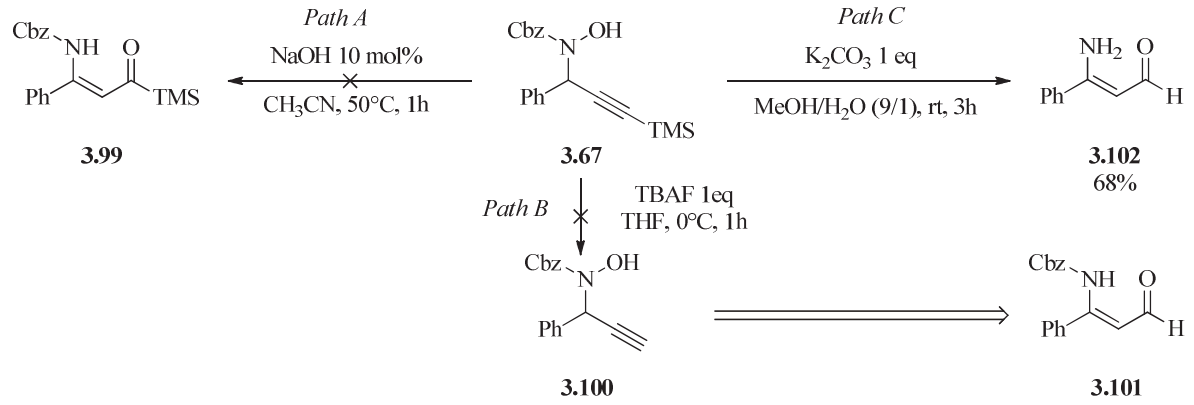
When initial acetylenic position is substituted by the phenyl group as in **3.65** or *p*-tolyl group as in **3.66**, the enaminones **3.95** or **3.96** are obtained in 51% and 53% yield respectively (*Scheme 3.22*). Corresponding propargylic imines **3.97** (18%) or **3.98** (14%) are also formed. Mechanistic approach explaining the appearance of propargylic imines will be discussed in **Section 3.4**.



3.65 (Ar= Ph), **3.66** (Ar= *p*-tol) — **3.95** 51%, **3.96** 53% — **3.97** 18%, **3.98** 14%

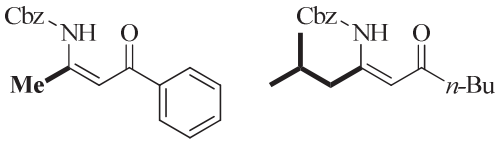
Scheme 3.22

The presence of TMS group at acetylenic position does not provide the corresponding product **3.99** (*Path A*, *Scheme 3.23*) under typical conditions (NaOH 10 mol%. 50°C, 1h). Therefore, we thought of testing this reaction with propargylic hydroxylamine **3.100** having terminal alkyne group which would provide, after isomerisation, *β*-enaminal **3.101** (*Scheme 3.23*). The first trial of the desilylation of **3.67** in the presence of TBAF (1equivalent) led only to the degradation of the starting material (*Path B*, *Scheme 3.23*). However, using K_2CO_3 in the mixture of methanol/water afford vinylogous formamide **3.102** in 68% of yield (*Path C*, *Scheme 3.23*).



Scheme 3.23

Unfortunately, when the aryl substituent at propargylic position is replaced by the alkyl group no reactivity is observed under typical conditions (NaOH, 50°C, 1h). Even the implementation of stronger bases (KOH, NaOH/15-Crown-5) in stoichiometric quantities does not provide the enaminones **3.103** and **3.104**, and only starting materials can be recovered (*Scheme 3.24*).



3.103 NR **3.104** NR

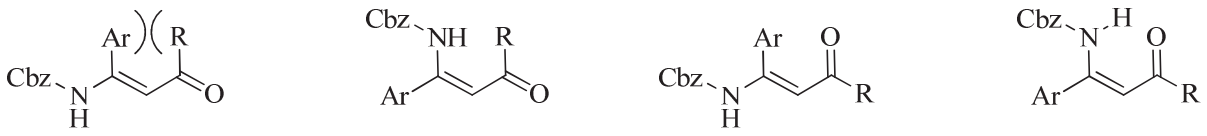
Scheme 3.24

Summing up the performed experiments, we can conclude that the isomerization does not take place in the presence of mild bases like triethylamine. The application of the strong bases like K_2CO_3 or NaOH is essential to deprotonate benzylic position, which is leading to the formation of desired enaminones. Moreover, the substitution of the aromatic ring at *para* and *meta* positions is well-tolerated. However, the rearrangement is sensitive to the *ortho* substituted substrates. Another important issue is the steric hindrance generated by the *tert*-butyl group at acetylenic position. It does not provide the corresponding enaminone, but leads to the formation of the propargylic imine. Phenyl and *para*-tolyl groups in the same position also led to formation of propargylic imines as the minor products.

Propargylic position has to be substituted by aromatic group in order to undergo isomerization. In fact, when alkyl groups are present in this position, propargylic proton is not sufficiently acidic to provoke the rearrangement and no reaction occurs.

3.4. Structure determination and potential mechanism of the reaction.

Acyclic *β*-enaminones can exist in four different conformations. Amongst those conformers, only *cis*-s-*cis* isomer **3.108** allows the formation of a hydrogen bond between NH and oxygen of the carbonyl group (*Scheme 3.25*).



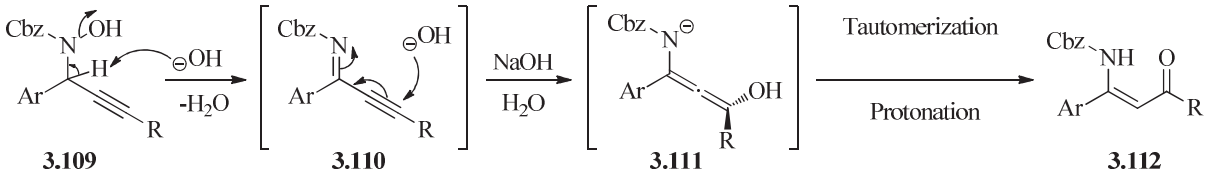
trans-s-*trans* **3.105** *cis*-s-*trans* **3.106** *trans*-s-*cis* **3.107** *cis*-s-*cis* **3.108**

Scheme 3.25

The calculations by DFT carried out by Gilli *et al*. show, that in β-enaminones with disubstituted double bond, the NH · · · O hydrogen bond induces higher stability of *cis*-s-*cis*

isomer from 3,5 kcal/mol to 6,5 kcal/mol when compared to other conformers.[85] In order to extend this field to the trisubstituted *β*-enaminones, the calculations were performed by Doctor Hélène Gérard form Pierre and Marie Curie University in Paris. It was shown, that the higher stability of *cis*-s-*cis* conformer is due to the presence of the hydrogen bond (4.0 kcal/mol) and due to the decreased steric hindrance between Ar and R groups (3 kcal/mol) within *cis*-s-*cis* **3.108** and *trans-s-trans* **3.105**, *Scheme 3.25.*

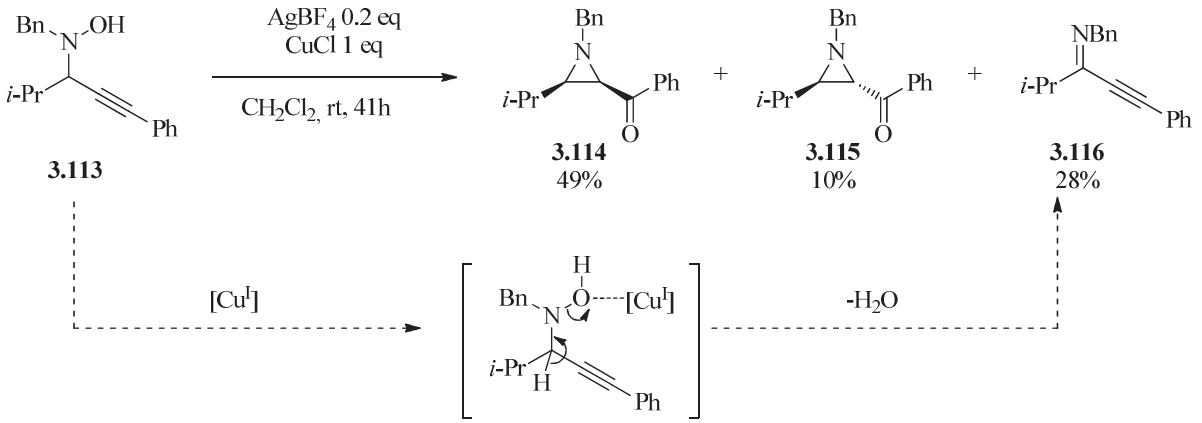
The studies of the isomerisation presented above give an idea of the mechanism of the formation of *Z-β*-enaminones. Firstly, the formation of the propargylic imines (when acetylenic position is occupied by *tert*-butyl or aryl group) indicates that the process can be initiated by the *β*-elimination of the hydroxyl group provoked by the base (**3.109-3.110**, *Scheme 3.26*). The Michael addition of the hydroxyl anion (concerted or subsequent) to the conjugated imine **3.110** would afford allenolate **3.111**, which, after tautomerization and protonation, would lead to *β*-enaminones.



Scheme 3.26

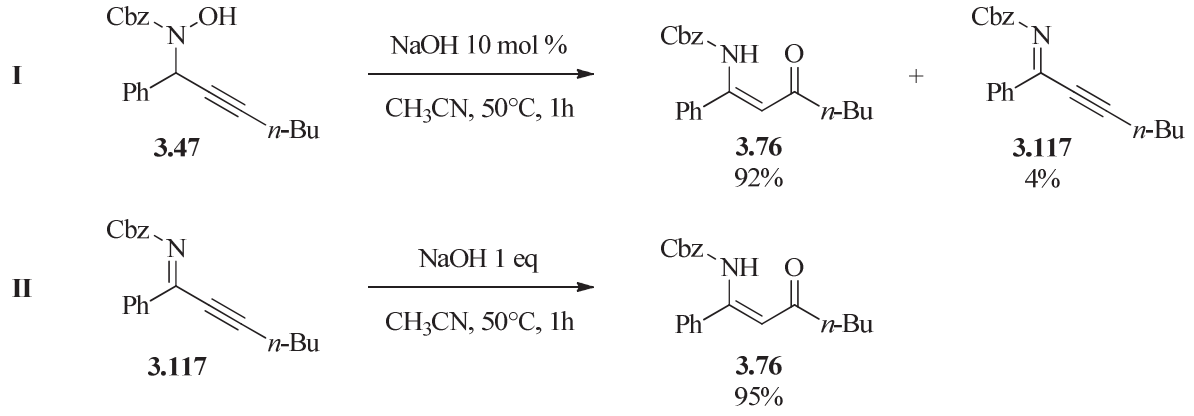
The first step of this process is cleavage of N-O bond. This transformation is interesting and scarcely described in the literature.[86] However, similar elimination was observed recently by Ukaji *et al*.[87] upon synthesis of acylaziridines **3.114** and **3.115** promoted by the copper (I) salt (*Scheme 3.27*). Hydroxylamine **3.113** has been transformed into the propargylic imine **3.116** by the dehydratation promoted by copper (I) salt in rather poor yield of 28% (*Scheme 3.27*).

[85] a) Gilli P., Bertolasi V., Ferretti V., Gilli G., *J. Am. Chem. Soc.,* **2000,** *122,* 10405; b) Sanz P., Mó O., Yáñez M., Elguero J., *J. Phys. Chem. A,* **2007,** *111,* 3585
[86] Padwa A., Koehler K. F., *Chem. Comm.,* **1986**, 789.
[87] Wada N., Kaneko K., Ukaji Y., Inomata K., *Chem. Lett.,* **2011**, *40*, 440



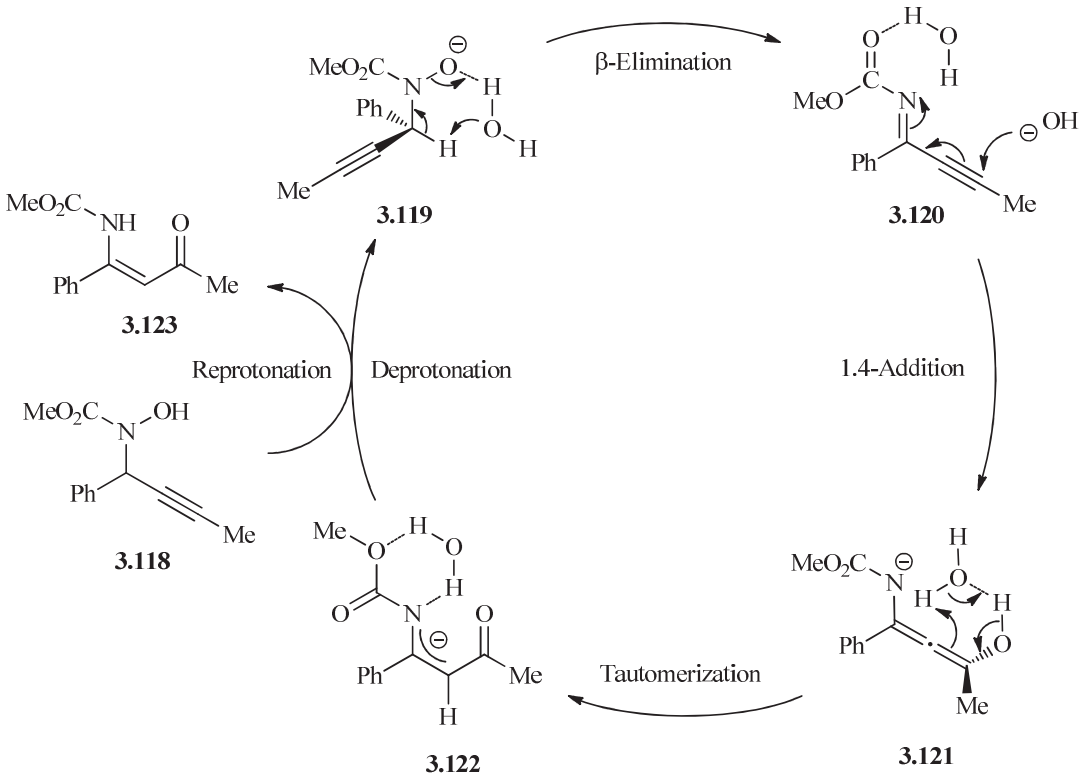
Scheme 3.27

In order to prove experimentally that the first step actually takes place *via* the formation of propargylic imine, we set an experiment with 1,77g of **3.47** in our typical conditions. It resulted in 1.63g of enaminone **3.76** (92%) accompanied by 70 mg of propargylic imine (4%) (**I**, *Scheme 3.28*). Then, the isolated conjugated imine **3.117** was mixed with NaOH (1 equivalent) to give enaminone **3.76** in 95% yield (**II**, *Scheme 3.28*).



Scheme 3.28

This result confirms that the 1,4-addition of hydroxyl anion to propargylic imine **3.117** is the second step of the process. When the steric hindrance of acetylenic position becomes significant (Ar = Ph, R = *t*-Bu), or when the β-elimination of the OH moiety lead to the fully conjugated propargylic imines (Ar = Ph, R = Ph, *p*-tol), the addition step is not favoured.



Scheme 3.29

This mechanism has been confirmed by the DFT calculations performed by Professor Hélène Gérard. In order to reduce the number of degrees of freedom of the starting material and the intermediates, a model of propargylic hydroxylamine **3.118** with C(O)OMe (instead of Cbz group) was studied (*Scheme 3.29*).

After the deprotonation of the propargylic hydroxylamine **3.118**, corresponding anion **3.119** undergoes *syn* elimination leading to the propargylic imine **3.120**. In the following step, 1,4- addition of the hydroxyl anion affords allenolate **3.121**. As for the anion **3.119**, the most stable entity proved to be the charged species **3.121** (stabilized by mesomeric effect) associated with a water molecule. This water molecule allows the tautomerization by simultaneous deprotonation of the hydroxyl group and the protonation of the central allenic carbon leading to the anionic structure **3.122**. The energy barrier between *Z* isomer and *E* isomers of the last structure values 5.7 kcal/mol facilitating the isomerization. The reprotonation of **3.122** by the starting material or water molecule afford enaminone **3.123** (*Scheme 3.29*).

The profile of the global energy presents the relative energies (in kcal/mol) of all of the structures described before (**Figure 3.2**).

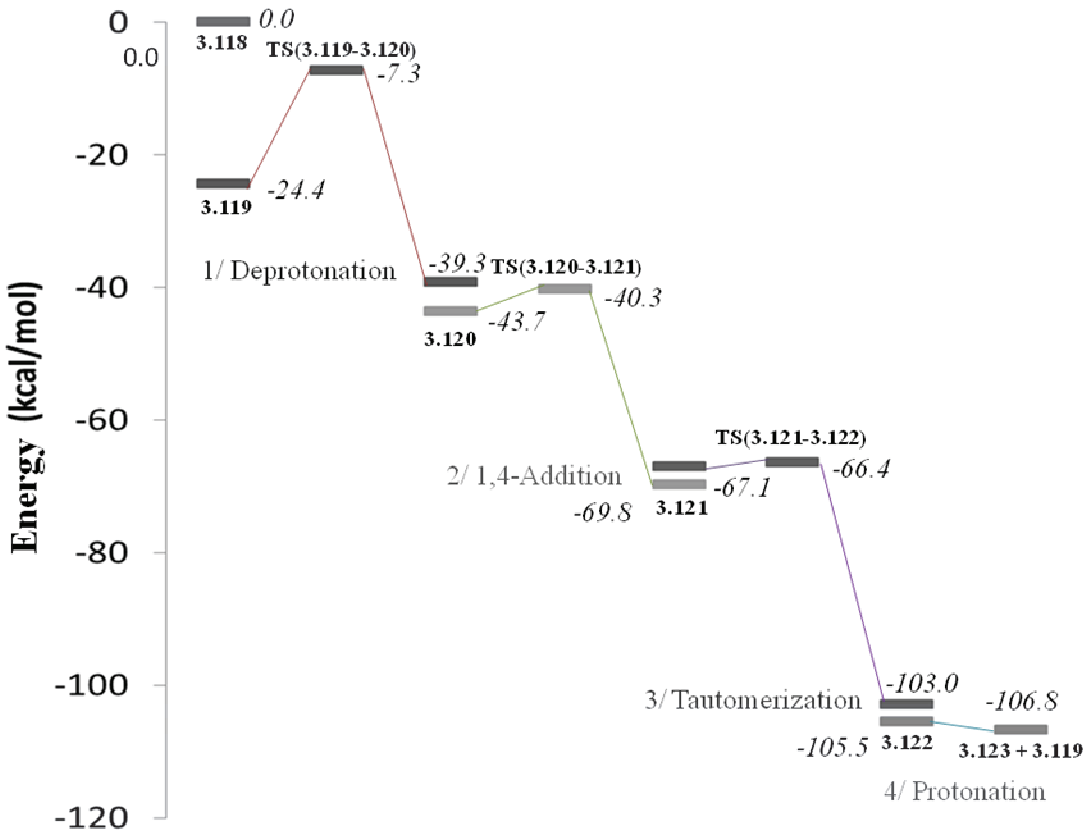
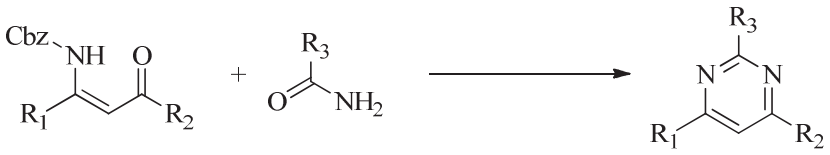


Figure 3.2

In conclusion, the catalytic and stereoselective isomerization of *N*-propargylic hydroxylamines leading to (*Z*)-*β*-enaminones takes place in the simple and efficient conditions (NaOH 10 mol%, 50°C, 1h). During our studies on this reaction, we observed the formation of propargylic imines, which enlightened some mechanistic points of this transformation. The experimental results together with the calculations allow us to rationalize this transformation and to propose the four-step catalytic cycle. The first one being the *β*-elimination of the hydroxyl group, which *syn* course is mediated by the water molecule. The second step is the conjugated addition of the hydroxyl anion followed by the third step, namely tautomerization and the last one, the fourth step being the reprotonation.

4. Synthesis of 2,4,6-trisubstituted pyrimidines.

After studies on the isomerization of N-propargylic hydroxylamines into (Z)-β-enaminones, we examined the synthetic utility of those structures. In particular, we were wondering if (*Z*)-β-enaminones can undergo the reaction of cyclocondensation in the presence of carboxylic amides to form 2,4,6-trisubstituted pyrimidines (*Scheme 3.30*).

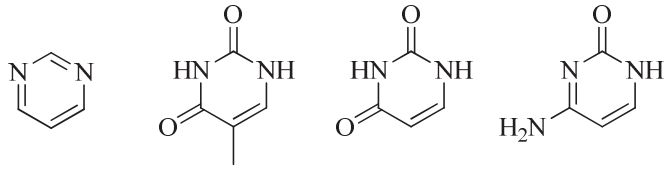


Scheme 3.30

This section will describe the results of this research with a short introduction considering pyrimidines, their reactivity and the synthetic application.

4.1. Pyrimidines. Common synthetic methods and the application.

Pyrimidines **3.124** are nitrogen heterocycles that belong to the family of diazines (*Scheme 3.31*). They are present in numerous important structures. For example, three nucleobases found in nucleic acids: uracil (U) **3.125**, thymine (T) **3.126**, and cytosine (C) **3.127**, are pyrimidine derivatives (*Scheme 3.31*).

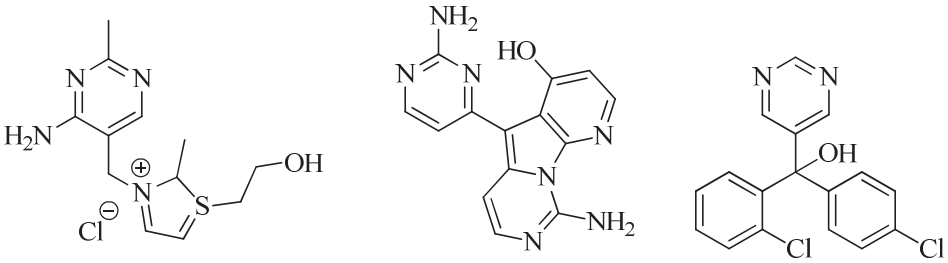


3.124 Pyrimidine | **3.125** Thymine | **3.126** Uracil | **3.127** Cytosine

Scheme 3.31

Pyrimidines are integral part of various natural products found in plants, fungi and animals.[88] For example, they are present in vitamin B1 (thiamine **3.128**), or in the alkaloid Varioline B **3.129** isolated from the antarctic sponge *Kirkpatrickia varialosa,* which possess antiviral and cytostatic activity.[89] Nonetheless, they found much application in numerous medical drugs and sanitary products, like Fenarimol® **3.130**, which is a fungicide (*Scheme 3.32*).[90]

[88] Lagoja I. M., *Chem. Biodivers.*, **2005**, *2*, 1
[89] Perry N. B., Ettouati L., Litaudon M., Blunt J. W., Munro M. H. G., Parkin S., Hope H., *Tetrahedron*, **1994**, *50*, 3987
[90] *Pesticide Manual*, **1997**, British Crop Protection Council.



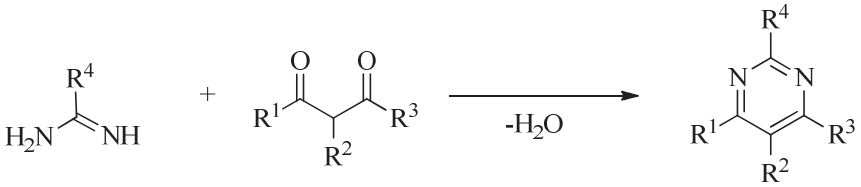
3.128
Thiamine (Vitamin B_1)

3.129
Varioline B

3.130
Fenarimol

Scheme 3.32

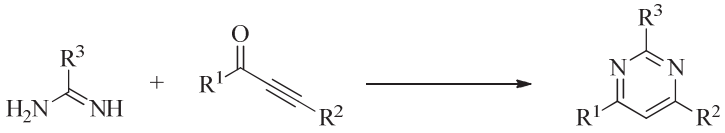
The methods that afford pyrimidines are diverse.[91] Amongst them, the synthesis described by Pinner is the most common.[92] It relays on the double condensation of amidines **1.131** with 1,3-dicarbonyls **3.132**, which can be acid or base catalyzed (*Scheme 3.33*).



3.131 **3.132** **3.133**

Scheme 3.33

Another common method was developed by El-Rayyes *et al*. It affords various 2,4,6-trisubstituted pyrimidines by addition of amidines **3.134** to propargylic ketones **3.135** or alkynones (*Scheme 3.34*).[93]



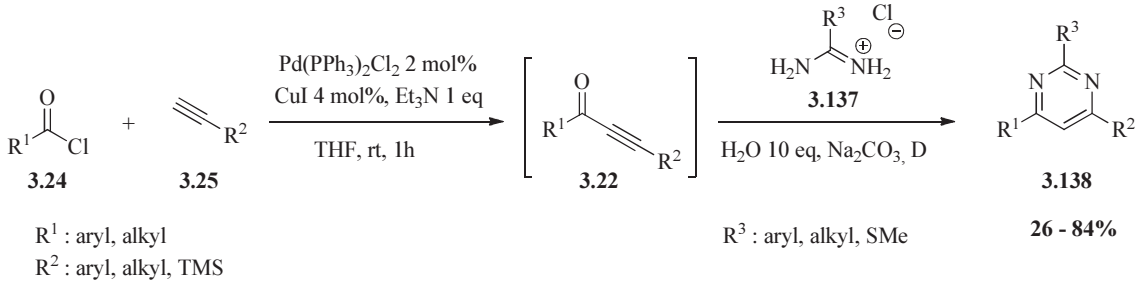
3.134 **3.135** **3.136**

Scheme 3.34

The extension of the above, described by Muller *et al*., who re-introduced it in one-pot version.[94] Alkynones **3.22**, firstly generated *in situ* by Sonogashira coupling, undergo Michael

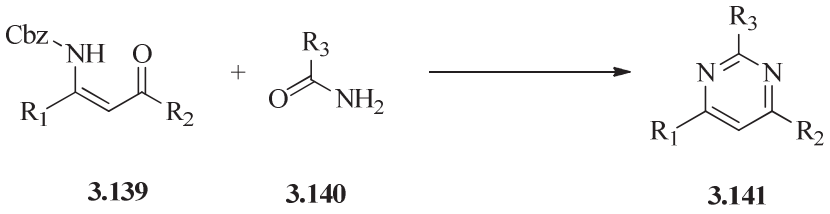
[91] Joule J. A., Mills K., Smith G. F., *Heterocyclic chemistry*, Chapman & Hall, **1995**
[92] Pinner A., *Ber. Dtsch. Chem. Ges.*, **1885**, *18*, 759
[93] a) Baddar F. C., Al-Hajjar F. H., El-Rayyes N. R., *J. Heterocycl. Chem.*, **1976**, *13*, 257; b) Adlington R. M., Baldwin J. E., Catterick D., Pritchard G. J., *J. Chem. Soc., Perk. Trans. 1* **1999**, 855
[94] Karpov A.S., Müller T. J. J., *Synthesis*, **2003**, *18*, 281

addition to various amidines **3.137** to achieve corresponding pyrimidines in 26- 84% of yield (*Scheme 3.35*).



Scheme 3.35

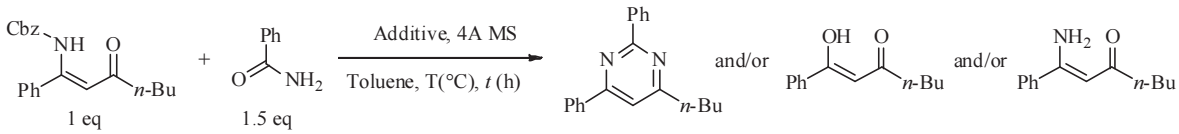
So far, (*Z*)-*β*-enaminones, although they serve as synthons towards numerous compounds (**Section 2.2**), have never been used for the synthesis of pyrimidines. Therefore, we were interested in setting the reaction of cyclocondensation between previously synthesized (*Z*)-*β*-enaminones **3.139** and carboxylic amides **3.140** in order to obtain 2,4,6-trisubstituted pyrimidines **3.141** (*Scheme 3.36*).



Scheme 3.36

4.2. Optimization of the methodology.

We had chosen (*Z*)-benzyl(3-oxo-1-phenylhept-1-en-1-yl)carbamate **3.76** and benzamide **3.142** as the model substrates and we subjected them to the reaction in toluene in the presence of various bases or acids. The results are described in the **Table 3.3**.



Entry	Additive ([eq])	T (°C)	*t* (h)	**3.143/3.144/3.145** [a]	Yield **3.143** [b] (%)
1	PTSA (0.1)	reflux [c]	72	1/1/0	Not determined [d]
2	MeONa (1)	130°C [e]	1	1/0/1	30
3	DBU (1)	130°C [e]	1	1/0/2.8	14
4	*t*-BuOK (1)	130°C [e]	1	30/0/1	51 [f]
5	*t*-BuOK (1.5)	130°C [e]	1	10/0/1	76
6	***t*-BuOK (2)**	**130°C** [e]	**1**	**12/0/1**	**80**

[a] Ratio between **3.143**, **3.144**, **3.145 determined by** ^{1}HNMR of crude material [b] Isolated yield [c] Reaction conducted with Dean-Stark apparatus for 0.2 mmol of **3.76** [d] Crude mixture of, **3.143** and **3.144** is inseparable by chromatography[e] Reaction conducted in the closed Wheaton® reactors for 0.2 mmol de **3.76**[f] 35% of enaminone **3.76** which did not react was recovered. NR = No reaction.

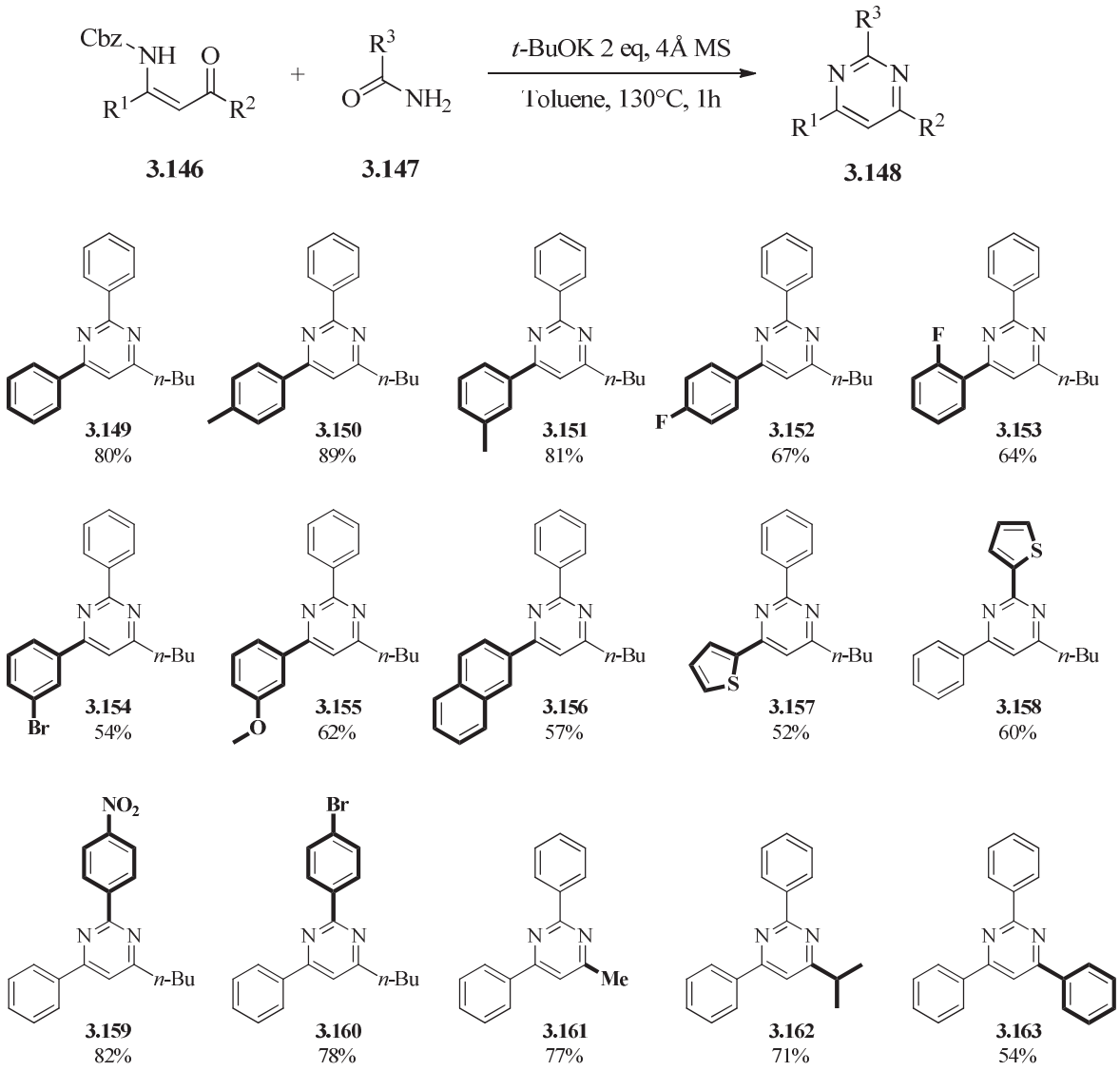
Table 3.3

The first cyclocondensation was carried out in the acidic conditions, in the presence of catalytic quantity of PTSA. We obtained the mixture of **3.143** and **3.144** in the 1:1 ratio together with the starting material and other side-products, which were not identified (entry 1). The purification of the pyrimidine **3.143** (by column chromatography) was troublesome due to the similar polarity of product **3.143** and 1,4-diketone (tautomeric form of enol **3.144**). For this reason, we tried to apply the conditions that would let us avoid the formation of enol **3.144** and we set the reaction under basic conditions. In fact, the reaction conducted in the presence of sodium methoxide led to the formation of compounds **3.143** and **3.145** in 1:1 ratio. Species **3.145** is the deprotected vinylogous amide. This time, the pyrimidine **3.143** was isolated in 30% of yield (entry 2). Encouraged by this result, we decided to use more hindered base like DBU and *t*-BuOK in order to avoid competitive deprotection of enaminone **3.143**. Unfortunately, the application of DBU gave complex mixture and pyrimidine **3.143** could be isolated in 14% of yield (entry 3). The reaction with *t*-BuOK, on the other hand, afforded the product **3.143** in 51% together with 35% of enaminone **3.76**, which did not react (entry 4). Following this result, we set the reactions with the excess of the base (entries 5-6). Finally, the reaction led to the formation of **3.143** in 80% of yield in the presence of 2 equivalents of *t*-

BuOK. Only traces of the vinylogous amide **3.145** could be detected in the crude material (entry 6).

4.3. Synthesis of 2,4,6-trisubstituted pyrimidines.

Once the optimal conditions were determined, we were interested in the enlargement of the scope of this reaction of cyclocondensation.[95] Enaminones **3.146** with various substituents led to the formation of corresponding pyrimidines **3.148** in 52-89% yield (*Scheme 3.37*).



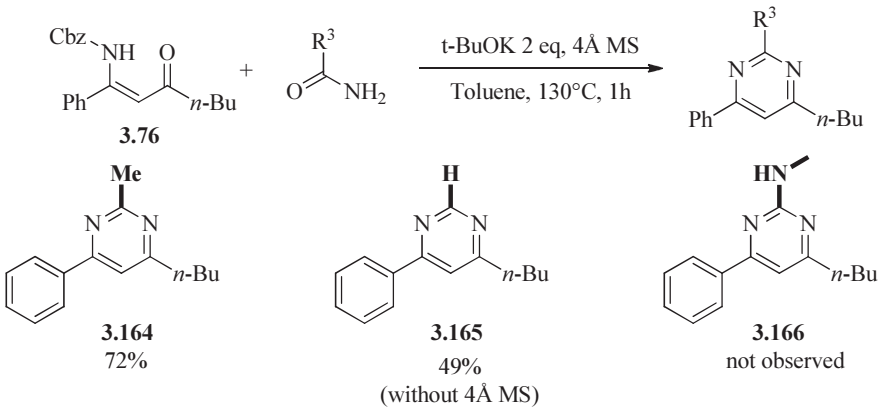
Scheme 3.37

[95] Gayon E., Szymczyk M., Gérard H., Vrancken E,. Campagne J.-M., *J. Org. Chem*., **2012**, 77 (20), 9205

Therefore, enaminones with halogen atoms (F, Br) in *ortho*, *meta* and *para* positions are well-tolerated. Tiophenyl groups present in both starting materials also lead efficiently to the products **3.157** and **3.158** in 52% and 60% of yield respectively.

The nature of the R^2 of the carbonyl group of the enaminone has little influence on the yield of the transformation. The use of *β*-amino-chalcone **3.95** led to the formation of 2,4,6-triphenylpyrimidine **3.163** in moderate yield of 54% (*Scheme 3.37*).

The cyclocondesation carried out with aromatic and heteraromatic carboxamides proceeded efficiently. Therefore, we decided to extend the scope of the reaction to non-aromatic amides. For this reason, acetamide and formamide were chosen as substrates for the reaction with enaminone **3.76** and this approach also led to the corresponding pyrimidines in good yields (**3.164**, 72% and **3.165**, 49%) (*Scheme 3.38*). Noteworthy, the reaction with formamide was conducted without molecular sieves 4Å because formamide absorbs on the molecular sieves decreasing the yield (23% of **3.165** versus 49% without 4Å MS). Finally, the trial of cyclocondensation between *N*-methyl-urea and enaminone **3.76** was carried out. Unfortunately, 2-amino-pyrimidine **3.166** was not observed in this case. It is probable that due to the presence of second nitrogen, electrophile of the carbonyl of urea might be inactivated. In this case, the cyclocondensation between nitrogen of enaminone and the carbonyl group of urea could not produce **3.166** (*Scheme 3.38*).



Scheme 3.38

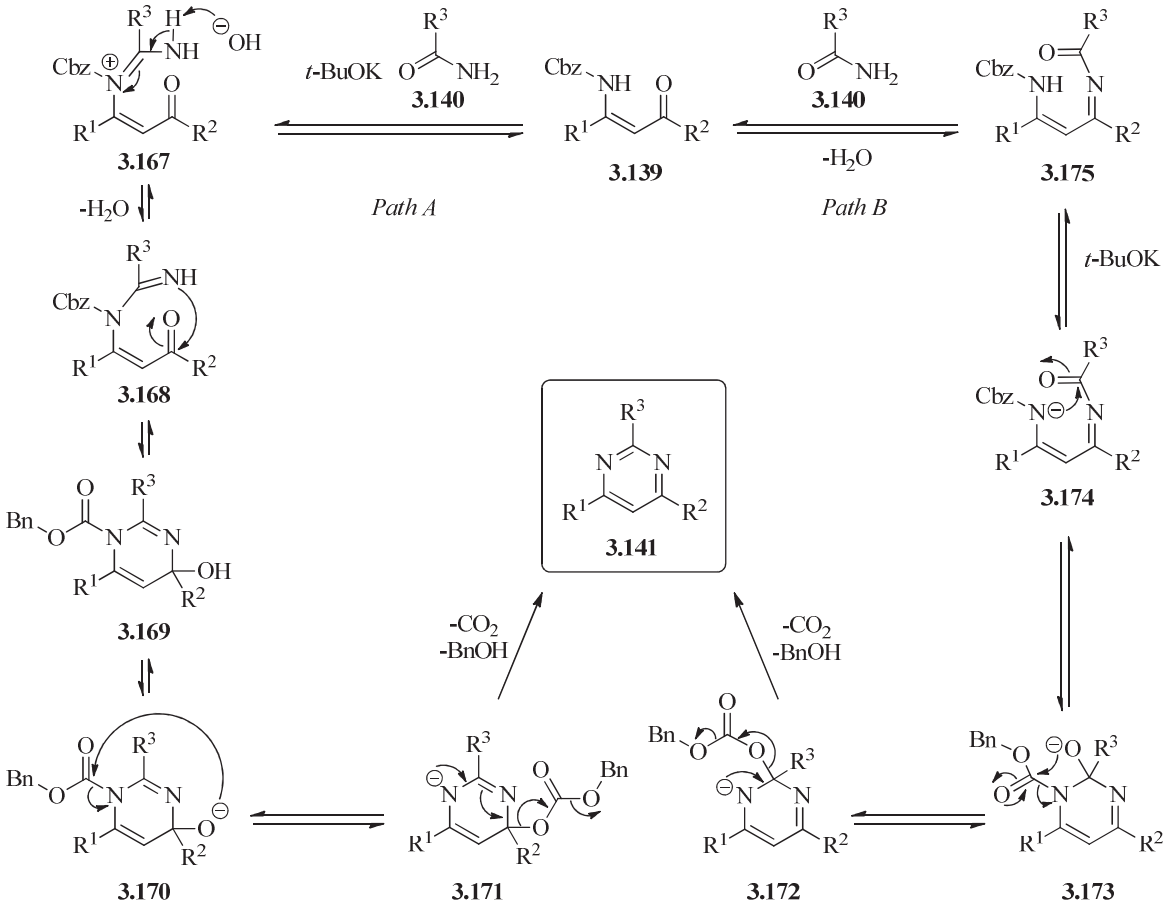
In conclusion, this methodology allows an efficient access to various 2,4,6-trisubstituted starting from the simple and not expensive reagents like carboxylic amides.

4.4. The potential mechanisms of the synthesis of pyrimidines.

To justify the mechanism of the formation of pyrimidines, two different paths have to be considered regarding the initial step. In the first option, the mechanism follows the condensation of the nitrogen of enaminone **3.139** with the carbonyl of amide **3.140 (***Path A*, *Scheme 3.39*). The second version stands for the mechanism that involves the condensation of nitrogen of amide **3.140** with the carbonyl of enaminone **3.139** in the first step (*Path B Scheme 3.39*).

In case of *Path A*, the condensation of the enaminone nitrogen with amide carbonyl would lead to the formation of iminium ion **3.167**, which is in equilibrium with amidine **3.168**. The attack of the imine nitrogen on the carbonyl carbon atom would lead to hemi-aminal **3.169**. The transposition of the Cbz group (intra or intermolecular) would provide the species **3.171**, which after aromatization/decarboxylation/dealkoxylation would afford pyrimidines **3.141.**

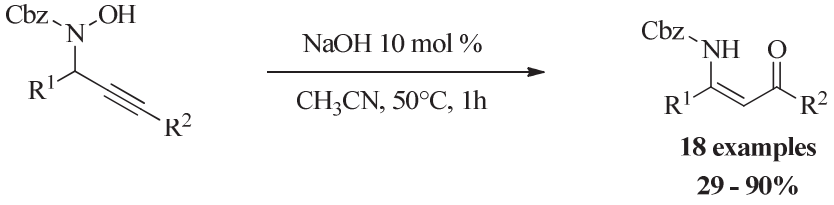
In case of *Path B*, the first step would relays on the condensation of amide nitrogen **3.140** with the enaminone carbonyl of **3.139** to form **3.175**. The deprotonation of NH would enhance its nucleophilic character and induce the attack of the carbonyl carbon leading to the hemi-aminal **3.174**. Transposition and elimination of Cbz would afford the desired product **3.141.**



Scheme 3.39

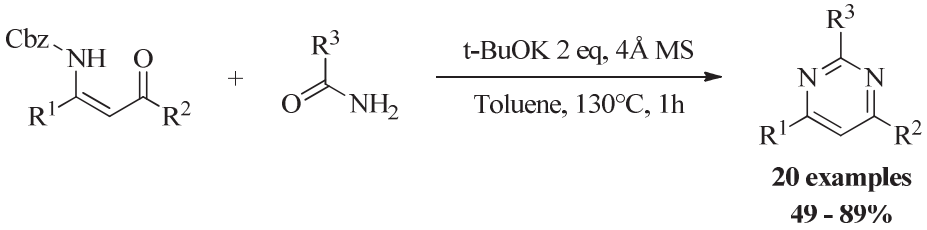
5. Conclusion.

We have described a new method of the synthesis of β-enaminones *via* the base-catalyzed isomerization of the *N*-propargylic hydroxylamines. This reaction proceeds under mild conditions and afford enaminones in good yields. Substitution of propargylic fragment with aromatic group (R^1 = aryl, heteroaryl) is necessary for the rearrangement to take place and it is the principal limitation of this reaction (*Scheme 3.40*).



Scheme 3.40

Having enaminones in hands we were able to implement them for elaboration of new pathway for the synthesis of 2,4,6-trisubstituted pyrimidines. This reaction has a large scope and tolerates various carboxylic amides (R^3= aryl, heteroaryl, vinyl, alkyl, H). Unfortunately, the its mechanistic pathway still remains unclear. To complete these studies, it would be interesting to investigate the formation of different intermediates by molecular modeling in order to achieve its better understanding (*Scheme 3.41*).

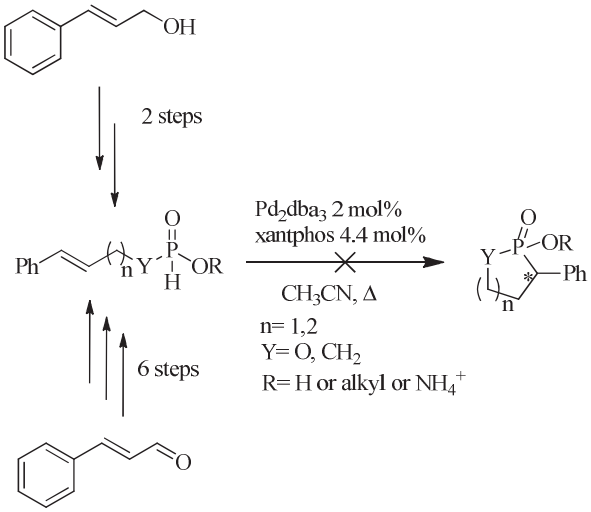


Scheme 3.41

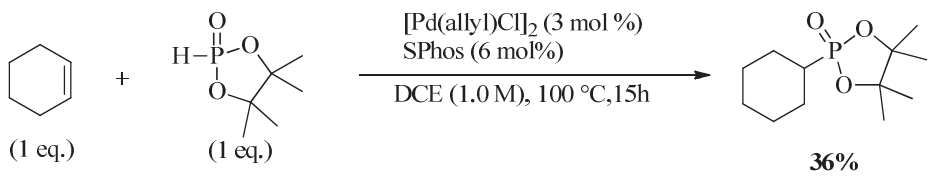
GENERAL CONCLUSION

The goal of this work relied on the cyclization reactions of *β*- enaminones, alkenylphosphinates and alkenylphosphonates.

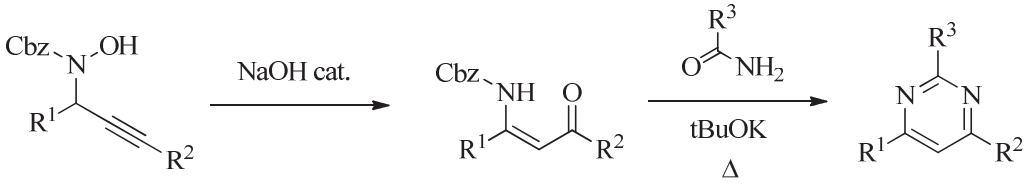
The first part was devoted to organophosphorus chemistry. We intended to develop the method for palladium(0)-catalyzed intramolecular hydrophosphinylation and hydrophosphonylation. The appropriate substrates, alkenyl *H*-phosphinates and alkenyl *H*-phosphonate were synthesized. However, the attempts of cyclization failed under standard conditions. This fact proves, that the area of intramolecular hydrophosphonylation/hydrophosphinylation stands for a great challenge for synthetic chemists. Until now, it remains unknown in the literature.



The efforts towards development of new catalytic systems for P-C bond formation revealed the possibilities of Buchwald ligands. Particularly, the combination of $[Pd(allyl)Cl]_2$ with SPhos in refluxing 1,2 dichloroethane found to be the most efficient to catalyze the reaction of cyclohexene with pinacol phosphonate. This is actually a good starting point for the future experiments. The extended screening might lead to the development of efficient catalytic system that would be checked on various alkenes in intermolecular and intramolecular approach.



The second part of this work was devoted to base-catalyzed rearrangement of N-propargylic hydroxylamines towards the stereoselective formation of Cbz-protected *β*-enaminones. The experimental results were supported by the molecular modeling calculations leading to the reliable proposal of the mechanism for this isomerization. The synthetic potential of Cbz-protected *β*-enaminones was demonstrated in their application in the new synthetic pathway towards 2,4,6-trisubstituted pyrimidines.



Experimental section:

General considerations

Physical data and spectroscopic measurements

^{1}H NMR spectra were recorded on a BRUKER Ultra shield 400 plus (400 MHz) instrument. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform (7.26 ppm) or acetone-d_6 (2.05 ppm) or DMSO-d_6 (2.50 ppm) or D_2O (4.79 ppm). Coupling constants are expressed in Hertz (Hz). The following abbreviations were used to express the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), sext (sextet), sept (septet), dd (double doublet), dt (double triplet), m (multiplet), brs (broad singlet).

^{13}C NMR spectra were recorded on the same instrument at 100.6 MHz. The chemical shifts are expressed in parts per million (ppm), reported from the central peak chloroform (77.0 ppm) or acetone-d_6 (206.26 ppm) or DMSO-d_6 (39.52 ppm).

The assignments were obtained using one dimensional NMR techniques (^{1}H, ^{13}C, ^{13}C-J-mod) or two dimensional ones (^{1}H-^{1}H : COSY and NOESY, or ^{1}H-^{13}C : HMQC and HMBC). The assignment was made according to the numbering indicated on each figure.

^{31}P NMR spectra were recorded on the same instrument at 161.97 MHz. The chemical shifts are expressed in parts per million (ppm)

Infrared Spectra (**IR**) were obtained on a PERKIN-ELMER FT-IR Spectrum 1000 or on a PERKIN-ELMER FT-IR ATR Spectrum 100 instruments and are reported in terms of frequency of absorption (cm^{-1}). The measure was realized by film on silicon plates (FT-IR Spectrum 1000) or neat (FT-IR ATR Spectrum 100).

Mass Spectra (**MS**):

Low resolution spectra, the spectrometer used was for electro spray ionization (ESI): WATERS QTof-I spectrometer. High resolution spectra were performed by electrospray ionization (ESI): Laboratoire Mesures Physiques of University Montpellier II.

Chromatography

Thin Layer Chromatography (**TLC**) was performed on precoated plates of silica gel 60 F_{254} Merck. Visualization was performed with UV light then phosphomolybdic acid solution, 2,4-dinitrophenyl hydrazine solution, anisaldehyde solution, or permanganate solution followed by heating as developing tool.

- Phosphomolybdic acid solution (**PMA**) was prepared using phosphomolybdic acid hydrate (10 g) in absolute ethanol (100 mL).

- 2,4-Dinitrophenyl hydrazine solution (**2,4-DNPH**) was prepared dissolving 2,4-dinitrophenyl hydrazine (12 g) in a mixture of concentrated sulfuric acid (60 mL), water (80 mL) and ethanol (200 mL).

- **Ninhydrin** was prepared by dissolving ninhydrin (0.3 g) in *n*-butanol (100 ml) and acetic acid (3 mL).

- Permanganate solution (**$KMnO_4$**) was prepared in water (200 mL) with $KMnO_4$ (1.5 g), K_2CO_3 (10g) and 10% NaOH solution (1.25 mL).

- **Vanillin** was prepared by dissolving vanillin (15 g) in ethanol (250 mL) and concentrated sulfuric acid (2.5 mL, slow addition).

- ***p*-Anisaldehyde** was prepared by dissolving *p*-anisaldehyde (15 g) in ethanol (250 mL) and concentrated sulfuric acid (2.5 mL, slow addition).

Flash Chromatography was performed using silica gel 60A 35-70µm SDS column.

Purification of solvent and reagents

Solvents were purified before using by classical techniques:

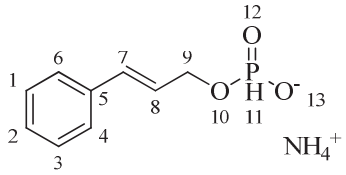
- Pyridine was distilled over calcium hydride then stocked over 4Å MS
- Tetrahydrofuran (**THF**) was distilled over sodium-benzophenone.
- Dichloromethane (**DCM**) was distilled over calcium hydride.

- Toluene was distilled over sodium.
- Dioxane was distilled over sodium-benzophenone or over molecular sieves.
- Dimehtylformamide was distilled over calcium hydride and stored over molecular sieves.
- Acetonitrile was purified by distillation over calcium hydride then stocked over 4Å MS and degassed with argon prior of use.

Other reagents were used as provided by chemical companies without purification unless otherwise noticed. All air and/or water sensitive reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents. All corresponding glassware was carefully dried under vacuum with a flameless heat gun

Experimental section: Chapter II

ammonium cinnamyl phosphonate (2.23)



$C_9H_{14}NO_3P$
215,19 g.mol^{-1}
orange crystals

In a 50-mL round bottom flask, equipped with a magnetic stirrer bar, diphenyl *H*-phosphonate **2.19** (1,17 g, 5 mmol, 1 equiv) was added to the solution of *trans* cinnamyl alcohol **2.20** (1.342 g, 10 mmol, 2 equiv) in pyridine (5 mL, 62mmol, 12.4 equiv) under argon. The reaction mixture was stirred at rt for 6 h. Then, 25% aq ammonium hydroxide (15 mL) was added and the reaction mixture was left with stirring for the next 24h. After that time, the solvent mixture was evaporated under reduced pressure and the residue was dissolved in acetone (50 mL) to afford crystalline solid. The mixture was filtered off and washed with diethyl ether to give 645 mg of ammonium cinnamyl phosphonate **2.23**. **Yield: 60%**
Mp= 166-168°C

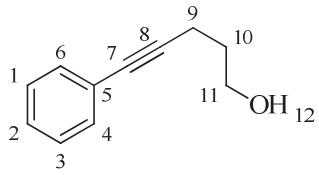
Spectral Data

^{1}H NMR (400 MHz, D_2O) δ (ppm): 7.27- 7.56 (m, 5H, H_{Ar}), 6.71 (d, *J* = 15.82 Hz, 1H, H_7), 6.38 (td, *J* = 7.3Hz, *J*=15.7Hz, 1H, H_8), 4.53 (ddd, *J* = 1.2 Hz, *J*= 5.8 Hz, *J*=9.2 Hz, 2H, H_9), 6.76 (d, $^{1}J_{HP}$= 636.4Hz,1H, H_{11})

^{13}C NMR (100 MHz, D_2O) δ (ppm): 136.4 (1C, C_{Ar}), 133.8 (1C, C_7), 128.6 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 127.9 (C_2), 123.8 (C_8), 73.3 (C_9)

^{31}P NMR (161 MHz, D_2O) δ (ppm): 6.29 (dt, ^{1}J=636.3 Hz, ^{3}J=9.35Hz)

5-phenylpent-4-yn-1-ol (2.29)



$C_{11}H_{12}O$
160.21 g.mol^{-1}
yellow oil

In a 25-mL round bottom flask, equipped with a magnetic stirrer bar, $Pd(PPh_3)_4$ (42 mg, 0.044 mmol, 0.01 equiv) and CuI (147 mg, 0.045 mmol, 0.021 equiv) were added to the solution of iodobenzene **2.27** (0.96 mL, 8.6 mmol, 2equiv) and 5-hydroxy pentyne **2.28** (0.4 mL, 4.3 mmol, 1equiv) in triethylamine (12.4 mL, 90 mmol, 21 equiv) and THF (2 mL) under argon. The reaction mixture was stirred at rt for 12 h. The mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel using cyclohexane/EtOAc as the eluent (90/10 → 50/50) to give 620 mg of 5-phenylpent-4-yn-1-ol **2.29**. **Yield: 90%**

R_f (silica, cyclohexane/ethyl acetate: 50/50) = 0.6 (UV)

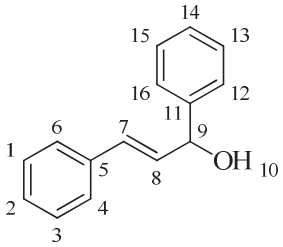
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26- 7.40 (m, 5H, H_{Ar}), 3.84 (t, *J* = 6.0 Hz, 2H, H_{11}), 2.50 (t, *J* = 6.9 Hz, 2H, H_9), 1.83 (p, *J* = 7.1 Hz, 2H, H_{10}), 1.62 (s,1H, H_{12}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 128.4 (3C, C_{Ar}), 128.3 (2C, C_{Ar}), 122.7 (C_5), 103.1 (C_8), 83.5 (C_7), 61.6 (C_{11}), 31.8 (C_{10}), 14.7 (C_9)

The spectral data are consistent with those of the literature.

(*E*)-1,3-diphenylprop-2-en-1-ol (2.36)



$C_{15}H_{14}O$
210,27 g.mol^{-1}
yellow oil

In a 250-mL well-dried Schlenk flask, equipped with a magnetic stirrer bar, 87 mL of THF was introduced, followed by the addition of methylmethoxytriphenylphosphonium chloride **2.33** (4.8 g, 14 mmol, 1.5 equiv) under argon. The system was cooled to -78°C. Then, *n*-BuLi was added *via* syringe (11.25 mL, 18 mmol, 1,6M in hexanes). The reaction was left for 1h in 0°C. After that time, the system was cooled to -78°C again and cinnamyl aldehyde **2.32** was added dropwise (1.1 mL, 9 mmol, 1 equiv). The reaction was left with stirring for 24h in rt. Then, the reaction mixture was concentrated and extracted with Et_2O/water (3 times). The residue was concentrated and purified by column chromatography on silica gel using cyclohexane/Et_2O as the eluent (100/0 → 50/50) to give 231 mg of (*E*)-1,3-diphenylprop-2-en-1-ol **2.36**. **Yield: 11%**

R_f (silica, cyclohexane/diethyl ether: 70/30) = 0.3 (UV)

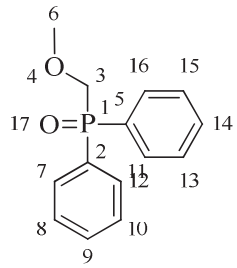
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22- 7.44 (m, 10H, H_{Ar}), 6.69 (d, *J*=15.9Hz, 1H, H_8) 6.38 (dd, *J*=6.5Hz, *J*=15.9Hz, 1H, H_7) 5.38 (d, *J*=6.5Hz, 1H, H_9), 2.13 (s, 1H, H_{10})

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 142.6 (C_{11}), 136.4 (C_5), 131.4 (C_7), 130.4 (C_8), 128.511 (2C, C_{Ar}), 128.447 (2C, C_{Ar}), 127.7 (2C, `C_{Ar}), 126.5 (2C, C_{Ar}), 126.2 (2C, C_{Ar}), 75.02 (C_9)

The spectral data are consistent with those of the literature.

(methoxymethyl)diphenylphosphine oxide (2.37)



$C_{14}H_{15}O_2P$
246,24 g.mol^{-1}
white crystals

Product obtained in the same procedure described for (*E*)-1,3-diphenylprop-2-en-1-ol **2.36** Purification by column chromatography led to the mixture of two compounds. After the time, crystals were formed in the flask from oil residue. Isolation of a small amount allowed the identification of the compound **2.37.**

R_f (silica, cyclohexane/diethyl ether: 70/30) = 0.8 (UV)

Spectral Data

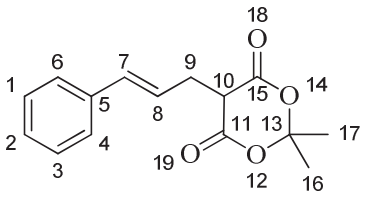
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82- 7.78 (m, 4H, H_{Ar}), 7.57- 7.54 (m, 2H, H_{Ar}), 7.50-7.46 (m, 4H, H_{Ar}), 4.22 (d, *J*=6.4Hz, 2H, H_3) 3.45 (s, 3H, H_6)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 142.6 (C_{11}), 136.4 (C_5), 131.4 (C_7), 130.4 (C_8), 128.511 (2C, C_{Ar}), 128.447 (2C, C_{Ar}), 127.7 (2C, `C_{Ar}), 126.5 (2C, C_{Ar}), 126.2 (2C, C_{Ar}), 75.02 (C_9)

^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm): 27.15 (s)

The spectral data are consistent with those of the literature.

5-cinnamyl-2,2-dimethyl-1,3-dioxane-4,6-dione (2.48)



$C_{15}H_{16}O_4$
260,29 g.mol^{-1}
white powder

In a 500-mL round bottom flask equipped with a magnetic stirrer bar, Meldrum's acid (9.51 g. 66.0 mmol, 1 equiv) was added to a solution of $BH_3 \cdot NHMe_2$ complex (3.88 g, 66 mmol, 1 equiv) in MeOH (60 mL) at rt in water bath. Then, *trans*-cinnamaldehade **2.32** (8.32 mL. 66 mmol, 1 equiv) was added dropwise *via* syringe. After 5h, the reaction mixture was transferred to the 1L erlenmeyer flask and 160mL of water was added to the reaction mixture. The formation of white solid was observed. In the next step, 240 mL of 3N HCl was added and the reaction mixture was left with stirring for the next 12h. After that time, the suspension was filtered off and dried in dessicator over P_2O_5 to give 12.11 g of 5-cinnamyl-2,2-dimethyl-1,3-dioxane-4,6-dione **2.48**. **Yield: 70%**

R_f (silica, Cyclohexane/Ethyl acetate: 50/50) = 0.2 (UV)

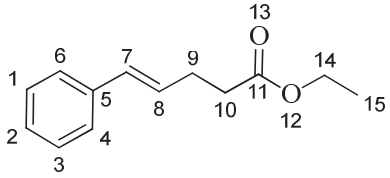
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40- 7.21 (m, 5H, H_{Ar}), 6.64 (d, J = 15.3 Hz, 1H, H_7), 6.28 (dt, J = 7.4 Hz, 1H, H_7), 3.67 (t, J = 5.1 Hz, 1H, H_{10}), 3.07-3.01 (m, 2H, H_9), 1.79 (s, 3H), 1.74 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.0 (2C, $C_{11,}$ C_{15}), 136.4 (C_5), 126.7 (2C, C_{Ar}), 126.6 (2C, C_{Ar}), 126.4 (C_7), 122.4 (C_8), 104.6 (C_{13}), 52.8 (C_{10}), 31.5 (C_9), 27.4 (3C), 27.3 (3C)

The spectral data are consistent with those of the literature.

(*E*)-ethyl 5-phenylpent-4-enoate (2.49)



$C_{13}H_{16}O_2$
204,26 g.mol^{-1}
Pale yellow oil

In a 80 mL reactor vessel compound **2.48** (4 g, 19.6 mmol, 1 equiv) was placed and suspended in EtOH (32.5 mL, 0.56 mol, 28 equiv.). The reactor vessel was subjected to microwaves for 3h in 150°C. After that time, the reactor was cooled to rt and the mixture was evaporated. The resulting crude material was purified by column chromatography on silica gel using pentene/Et_2O as the eluent (100/0 → 80/20) to give 1.76 g of (*E*)-ethyl 5-phenylpent-4-enoate **2.49**. **Yield: 56%**

R_f (silica, pentene/diethyl ether: 80/20) = 0.62 (UV)

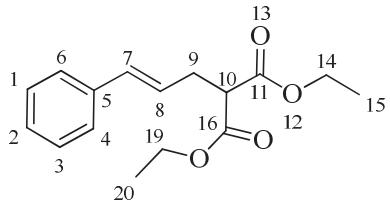
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39- 7.20 (m, 5H, H_{Ar}), 6.51 (d, *J* = 15.7 Hz, 1H, H_7), 6.23 (dt, *J* = 15.7, 6.7 Hz, 1H, H_7), 4.17 (q, *J* = 7.0 Hz, 2H, H_{14}), 2.63-2.35 (m, 4H, H_9, H_{10}), 1.24 (t, J= 7.0 Hz 3H, H_{15})

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.1 (C_{11}), 136.8 (C_5), 130.8 (C_8), 128.5 (4C, C_{Ar}), 126.8 (C_7), 125.8 (C_{Ar}), 61.6 (C_{14}), 34.3 (C_9), 28.2 (C_9), 14.3 (C_{15})

The spectral data are consistent with those of the literature.

diethyl 2-cinnamylmalonate (2.55)



$C_{16}H_{20}O_4$
276,33 g.mol^{-1}
Yellow oil

In a 80 mL reactor vessel compound **2.48** (4 g, 19.6 mmol, 1 equiv) was placed and suspended in EtOH (32.5 mL, 0.56 mol, 28 equiv.). The reactor vessel was subjected to microwaves for 3h in 150°C. After that time, the reactor was cooled to rt and the mixture was evaporated. The resulting crude material was purified by column chromatography on silica gel using pentene/Et_2O as the eluent (100/0 → 80/20) to give 0.6 g of (*E*)-ethyl 5-phenylpent-4-enoate **2.55**. **Yield: 11%**

R_f (silica, pentene/diethyl ether: 80/20) = 0.4 (UV)

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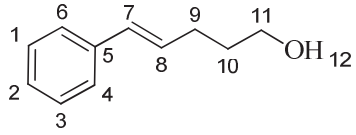
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37- 7.22 (m, 5H, H_{Ar}), 6.45 (d, *J* = 15.3 Hz, 1H, H_7), 6.24 (dt, *J* = 7.4 Hz, 1H, H_7), 4.18 (q, *J* = 7.1 Hz, 4H, H_{14}, H_{19}), 3.48 (t, J=6.2, 1H, H_{10}), 2.55 (t, J= 7.7, 2H, H_9), 1.24 (t, J= 7.0 Hz 6H, $H_{15,}$ H_{20})

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.1 (2C, C_{11} C_{16}), 136.7 (C_5), 128.4 (4C, C_{Ar}), 126.7 (C_7), 125.7 (C_{Ar}), 122.7 (C_8), 61.6 (C_{14} C_{19}), 53.3 (C_{10}), 29.2 (C_9), 14.3 (C_{15} C_{20})

HRMS (ESI+) m/z: 277,1404 calcd for $C_{16}H_{20}O_4$: 277.1401.

(*E*)-5-phenylpent-4-en-1-ol (2.30)



$C_{11}H_{14}O$
162,23 g.mol^{-1}
Yellow oil

In a 250-mL round bottom flask equipped with a magnetic stirrer bar, $LiAlH_4$ (0.427 g. 11.25 mmol, 2.5 equiv) was placed in THF (42 mL) in rt under argon. The system was cooled to 0°C and then, (*E*)-ethyl 5-phenylpent-4-enoate **2.49** (0.721 g, 4.5 mmol, 1 equiv) was added dropwise *via* syringe. After 5h, the reaction mixture was quenched with wet THF. The product was extracted with diethyl ether/water (3 times) and the organic layer was washed with brine, dried with $MgSO_4$ and concentrated. Purification by column chromatography (pentane/ethyl acetate) afforded 584 g of (*E*)-5-phenylpent-4-en-1-ol **Yield: 80%**

R_f (silica, pentane/ethyl acetate: 60/40) = 0.5 (UV)

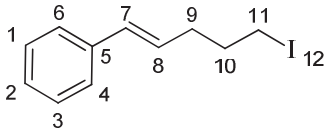
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.60- 7.18 (m, 5H, H_{Ar}), 6.53 (d, *J* = 16.0 Hz, 1H, H_7), 6.23 (dt, *J* = 7.4 Hz, 1H, H_8), 3.82 (dt, *J* = 7.0 Hz, 2H, H_{11}), 2.32 (q, *J* = 5.1 Hz, 1H, H_{10}), 3.07-3.01 (m, 2H, H_9), 1.79 (s, 3H), 1.74 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 130.4 (C_5), 130.1 (C_{Ar}), 128.5 (C_7), 127.2 (C_{Ar}), 125.9 (C_8), 62.4 (C_{11}), 32.2 (C_{10}), 29.3 (C_9),

The spectral data are consistent with those of the literature.

(*E*)-(5-iodopent-1-en-1-yl)benzene (2.50)



$C_{11}H_{13}I$
272,13 g.mol^{-1}
Yellow oil

In a 250-mL round bottom flask equipped with a magnetic stirrer bar, compound **2.30** was placed (1.263g, 7.79 mmol, 1equiv) together with PPh_3 (2.042 g. 7.79 mmol, 1 equiv) and imidazole (0.636 g, 9.34 mmol, 1.2 equiv) in CH_2Cl_2 (22 mL). The system was cooled to 0°C and then, iodine (1.976 g, 7.79 mmol, 1 equiv) was added. The solution was stirred overnight at rt. Then, the reaction mixture was filtrated and concentrated. The purification with column chromatography afforded 1.33 g of (E)-(5-iodopent-1-en-1-yl)benzene **2.50 Yield: 62%**

R_f (silica, pentane: 100) = 0.9 (UV)

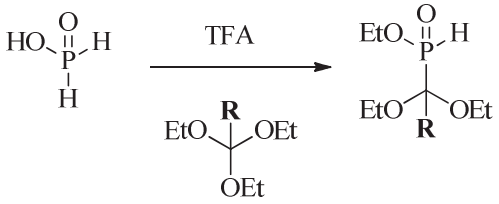
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42- 7.21 (m, 5H, H_{Ar}), 6.51 (d, *J* = 15.5 Hz, 1H, H_7), 6.19 (dt, *J* = 15.5 Hz *J* = 7.0 Hz, 1H, H_8), 3.26 (t, *J* = 7.0 Hz, 2H, H_{11}), 2.33 (q, *J* = 7.1 Hz, 2H, H_9), 2.05 (q, *J* = 7.0 Hz 2H, H_{10})

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.4 (C_5), 129.1 (C_{Ar}), 128.5 (C_7), 127.2 (C_{Ar}), 125.9 (C_8), 34.5 (C_9), 31.3 (C_{10}), 7.3 (C_{11})

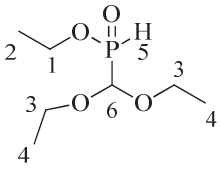
The spectral data are consistent with those of the literature.

Procedure for the synthesis of Ciba-Geigy reagents:



In a 250-mL round bottom flask equipped with a magnetic stirrer bar, anhydrous hypohposphorous acid was placed with trifluoroacetic acid (0.2 eq). Then, **(A)** triethylorthoformate (**R**=H) or **(B)** triethylorthoacetate (**R**=CH_3) was added (2.2 equiv). After 3h for **(A)** or 1h for **(B)** the reaction mixture was evaporated under pressure during 30 min in 40°C. The residue was dissolved in chloroform (100 mL) and washed with saturated solution of sodium hydrogen carbonate (3x 100 mL). The organic phase was dried over MgSO4, filtrated and evaporated under reduced pressure.

ethyl (diethoxymethyl)phosphinate (2.60)



$C_7H_{17}O_4P$
196,18 $g.mol^{-1}$
colorless oil

Yield: 70-85%
Distillation: 75°C (3 mm Hg)

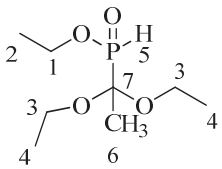
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.90 (d, $^1J_{PH}$=554.1 Hz,1H, H_5), 4.70 (d, $^2J_{PH}$ =9.0 Hz, 1H, H_6), 4.23 (q, $^3J_{HH}$ = 7,5 Hz, 2H, H_2), 3.80-3.60 (m,4H, H_3), 1.38 (t, $^3J_{HH}$ = 7.2 Hz, 3H, H_2), 1.24 (t, $^3J_{HH}$ = 7.2 Hz, 6H, H_4)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 100.4 (d, C_6, J_{PC}=154.0 Hz), 65.6 (C_1), 63.2 (C_3), 16.5 (C_2), 15.3 (C_4)

^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm): 28 (dt, $^1J_{PH}$=554.1 Hz, $^2J_{PH}$ =9.0 Hz)

ethyl (1,1-diethoxyethyl)phosphinate (2.61)



$C_7H_{17}O_4P$
210,21 g.mol^{-1}
colorless oil

Yield: 75-85%
Distillation: 65°C (3 mm Hg)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.90 (d, $^1J_{PH}$=549.2 Hz,1H, H_5), 4.19-4.16 (m, 2H,H_1), 3.73-3.62 (m,4H, H_3), 1.46 (d, $^3J_{PH}$ = 16.0 Hz, 3H, H_6), 1.34 (t, $^3J_{HH}$ = 7.5 Hz, 3H, H_4), 1.18 (m, 6H, H_4)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 101 (C_7), 63.8 (C_1), 57.9 (d, $^3J_{PC}$=62.7 Hz, C_3), 19.1 (d, $^2J_{PC}$=12.5 Hz, C_6), 16.5 (C_2), 15.5 (C_4)

^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm): 31 (dt, $^1J_{PH}$=542.0 Hz, $^2J_{PH}$ =9.0 Hz)

Procedure for the Cs_2CO_3-promoted synthesis of protected phosphinates

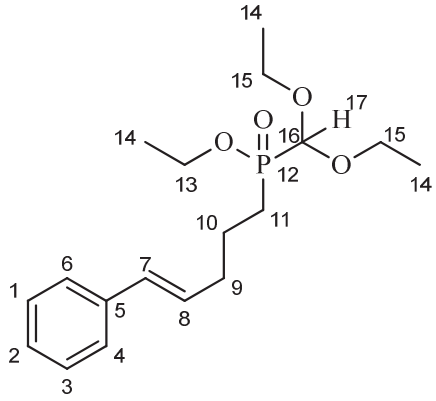
2.60 R= H
2.61 R= CH_3

2.50

2.67 R= H
2.68 R= CH_3

In a 100-mL round bottom flask equipped with a magnetic stirrer bar, compound **2.60** or **2.61** (1 equiv) was placed in DMF (0.2N) under argon. Then, Cs_2CO_3 was added (2 equiv) and reaction mixture was left with stirring for 2 hrs. After that time, compound **2.50** was added (1.5 equiv) and reaction mixture was left with stirring for 5 days in rt. Then, the reaction mixture was dissolved in ethyl acetate (50 mL) and washed with water (3x 30 mL). The organic phase was dried over $MgSO_4$, filtrated and evaporated under reduced pressure. The resulting crude material was purified by column chromatography on silica gel using pentene/ethyl acetate as the eluent (100/0 → 0/100).

(E)-ethyl (diethoxymethyl)(5-phenylpent-4-en-1-yl)phosphinate (2.67)



$C_{18}H_{29}O_4P$
340,39g.mol^{-1}
yellowish oil

Yield: 46%
R_f (silica, ethyl acetate: 100) = 0.3 (UV)

Spectral Data

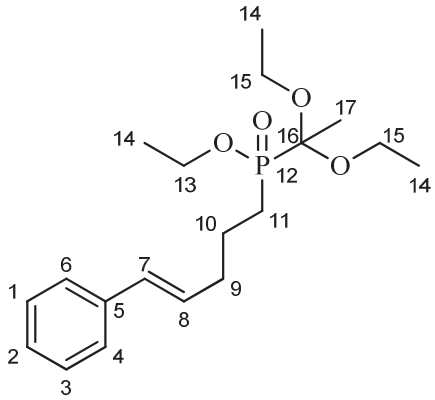
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34-7.28 (m, 4H, H_{Ar}), 7.20-7.17 (m, 1H, H_{Ar}), 6.39 (d, J=15.8Hz, 1H, H_7) 6.16 (td, J=6.9Hz, J=15.8Hz, 1H, H_8), 4.66 (d, J=6.8Hz, 1H, H_{17}) 4.17 (m, 2H, H_{13}), 3.85 (m, 2H, H_{15}) 3.69 (m, 2H, H_{15}) 2.30 (q, J=6.5Hz, 2H, H_9), 1.82 (m, 4H, H_{11}, H_{10}), 1.33 (q, J=6.9Hz, 3H, H_{14}) 1.24 (dt, J=0.8Hz, J=7.0Hz, 6H, H_{14})

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.5 (C_5), 129.2 (C_{Ar}), 128.4 (C_7), 127.1 (C_{Ar}), 125.8 (C_8), 101 (d, $C_{16,}$ $^1J_{PC}$=140.5 Hz), 65.4 (C_{13}), 61.2 (C_{15}), 34.5 (C_9), 31.3 (C_{10}), 27.2 ($C_{11,}$ $^1J_{PC}$=89.5 Hz)16.5 (C_{14})

^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm): 46 (s)

HRMS (ESI+) m/z: 340,2003 calcd for $C_{18}H_{29}O_4P$: 340.1800

(E)-ethyl (1,1-diethoxyethyl)(5-phenylpent-4-en-1-yl)phosphinate (2.68)



$C_{19}H_{31}O_4P$
354,42 g.mol^{-1}
yellow oil

Yield: 55%
R_f (silica, ethyl acetate: 100) = 0.3 (UV)

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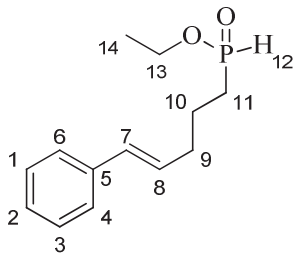
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37-7.29 (m, 4H, H_{Ar}), 7.19-7.16 (m, 1H, H_{Ar}), 6.38 (d, *J*=15.7 Hz, 1H, H_7) 6.13 (td, J=6.9 Hz, J=15.7 Hz, 1H, H_8), 4.17 (m, 2H, H_{13}), 3.85 (m, 2H, H_{15}) 3.68 (m, 2H, H_{15}) 2.29 (q, *J*= 6.5Hz, 2H, H_9), 1.82 (m, 4H, $H_{11,}$ H_{10}), 1.48 (d, $^3J_{PH}$=15.5 Hz, 3H, H_{17}), 1.33 (q, J=6.9Hz, 3H, H_{14}) 1.23 (dt, *J*=0.8 Hz, *J*=7.0 Hz, 6H, H_{14})

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.5 (C_5), 129.2 (C_{Ar}), 128.4 (C_7), 127.1 (C_{Ar}), 125.8 (C_8), 101 (d, $C_{16,}$ $^1J_{PC}$=140.5 Hz), 65.4 (C_{13}), 61.2 (C_{15}), 34.8 (C_9), 31.3 (C_{10}), 27.2 ($C_{11,}$ $^1J_{PC}$=89.5 Hz), 20.55 (d, $^1J_{PC}$=11.2 Hz, C_{17}) 16.4 (C_{14})

^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm): 48 (s)

HRMS (ESI+) m/z: 355,3897 calcd for $C_{19}H_{31}O_4P$: 355.3900

(E)-ethyl (5-phenylpent-4-en-1-yl)phosphinate (2.72)



$C_{13}H_{19}O_2P$
238,26 g.mol^{-1}
yellow oil

In a 10-mL round bottom flask equipped with a magnetic stirrer bar, compound **2.68** (100 mg, 0.3 mmol, 1 equiv) was placed in $CHCl_3$ (3.6 ml). Then, TMSCl was added (0.06 ml, 0.45 mmol, 1.5 equiv) and EtOH (10%, 0.36 ml). The reaction was left with stirring for the next 24 hrs. After that time, the solution was evaporated and purified by column chromatography on silica gel in pentane/ethyl acetate (50/50 → 0/100) to give (*E*)-ethyl (5-phenylpent-4-en-1-yl)phosphinate **2.72** in 20% yield.

R_f (silica, ethyl acetate: 100) = 0.1 (UV)

Spectral Data

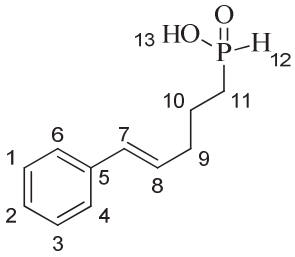
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34-7.28 (m, 4H, H_{Ar}), 7.20-7.17 (m, 1H, H_{Ar}), 7.05 (d, $^1J_{PH}$ = 520 Hz, 1H, H_{12}), 6.39 (d, *J*=15.8Hz, 1H, H_7) 6.16 (td, *J*=6.9Hz, *J*=15.8Hz, 1H, H_8), 4.18 (q, J= 6.0, 1H, H_{13}), 4.10 (q, J= 6.0, 1H, H_{13}), 2.30 (q, *J*=6.5Hz, 2H, H_9), 1.82 (m, 4H, $H_{11,}$ H_{10}), 1.33 (t, *J*=6.0Hz, 3H, H_{14})

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.2 (C_5), 129.4 (C_{Ar}), 128.3 (C_7), 127.2 (C_{Ar}), 125.8 (C_8), 65.4 (C_{13}), 34.5 (C_9), 31.3 (C_{10}), 27.6 ($C_{11,}$ $^1J_{PC}$=89.5 Hz),16.4 (C_{14})

^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm): 38 (two singlets)

HRMS (ESI+) m/z: 239.1102 calcd for $C_{13}H_{19}O_2P$: 239.1009

(*E*)-(5-phenylpent-4-en-1-yl)phosphinic acid (2.73)



$C_{11}H_{15}O_2P$
210,21 g.mol^{-1}
yellow oil

In a 10-mL round bottom flask equipped with a magnetic stirrer bar, compound **2.68** (100 mg, 0.3 mmol, 1 equiv) was placed in 3N HCl (2 ml). The reaction was left with stirring for the next 24 hrs. After that time, the solution was evaporated to give 32 mg (*E*)-ethyl (5-phenylpent-4-en-1-yl)phosphinate **2.73** in 50% yield.

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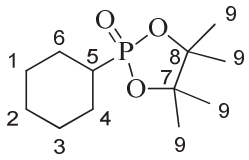
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.97 (s, 1H, H_{13}) 7.35-7.28 (m, 4H, H_{Ar}), 7.20-7.17 (m, 1H, H_{Ar}), 7.21 (d, $^1J_{PH}$ = 559 Hz, 1H, H_{12}), 6.38 (d, *J*=15.8Hz, 1H, H_7) 6.13 (td, *J*=6.9Hz, *J*=15.8Hz, 1H, H_8), 2.30 (q, *J*=6.5Hz, 2H, H_9), 1.88 (m, 4H, $H_{11,}$ H_{10})

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.2 (C_5), 129.4 (C_{Ar}), 128.3 (C_7), 127.2 (C_{Ar}), 125.8 (C_8), 65.4 (C_{13}), 34.5 (C_9), 31.3 (C_{10}), 29.1 ($C_{11,}$ $^1J_{PC}$=542.5 Hz),16.4 (C_{14})

^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm): 35 (s)

HRMS (ESI+) m/z: 211.2102 calcd for $C_{18}H_{29}O_4P$: 211.2098

2-cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide (2.84)



$C_{12}H_{23}O3P$
246,28 g.mol^{-1}
White powder

Representative experimental procedure (entry 21) for Table 2.6 in *Chapter II.*
In the 5 ml screw cap vial $[Pd(allyl)Cl]_2$ (2.2 mg, 0.006 mmol, 0.015 equiv), SPhos (9.9 mg, 0.024 mmol, 0.06 equiv) and pinacol phosphonate (66 mg, 0.4 mmol, 1 equiv) were placed. Then, the system was evacuated and backfilled with argon (3 times). In the next step, DCE (0.4 ml) and cyclohexene (41 µl, 0.4 mmol, 1equiv) were added. The reaction was stirred at 100°C for 15h. After this time period, the reaction was analyzed by ^{31}PNMR. The signals showed product **2.84** in 36%. Product **2.84** was isolated by column chromatography (pentane/ethyl acetate, 40/60) and verified by **^{1}H NMR.**

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^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.95-1.62 (m, 6H, $H_{1\text{-}6}$), 1.47 (s, 6H,H_9), 1.35 (s, 6H,H_9),1.12-1.30 (m, 5H)

^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm): 45 (s)

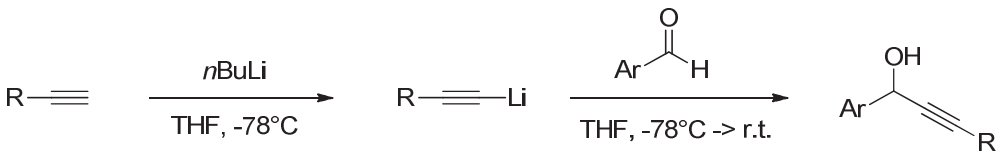
The spectral data are consistent with those of the literature.

Experimental section: Chapter III

Propargylic alcohols

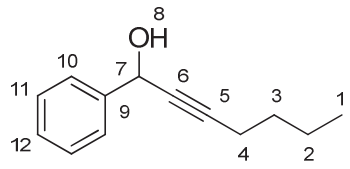
General procedure A

for the preparation of propargylic alcohols



An anhydrous and purged with N_2 round-bottom flask equipped with a magnetic stirrer bar was charged with THF (20 mL) and the corresponding alkyne (10 mmol, 1 equiv). The resulting solution was cooled to -78°C and then *n*-butyllithium (1.6 M in hexanes, 10 mmol, 1 equiv) was added via syringe. The solution was stirred for 10 min at -78°C and was allowed to warm to room temperature for 30 min. Thun, the mixture was cooled at -78°C and the corresponding aldehyde was added (10 mmol, 1 equiv). The resulting reaction mixture was warmed up to room temperature and stirred for an additional 2 h. Upon completion, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated in *vacuo* and purification of the crude material via chromatography on silica gel (cyclohexane/Et_2O) afforded corresponding propargylic alcohol.

1-Phenylhept-2-yn-1-ol (A.1)



$C_{13}H_{16}O$
188.26 g.mol^{-1}
Pale yellow oil

Compound **A.1** was prepared according to the previously described general procedure A (10 mmol scale) starting from 1-hexyne and benzaldehyde. Purification was carried out by flash chromatography on silica gel (cyclohexane/Et_2O: 95/5 → 85/15). **Yield: 89%**

R_f (silica, pentane/Et_2O: 9/1) = 0.3 (UV/PMA)

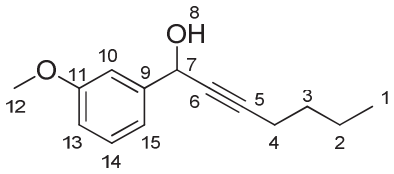
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (t, *J* = 7.3 Hz, 3H, H_1), 1.38 - 1.57 (m, 4H, H_2 and H_3), 2.19 (s, 1H, H_8), 2.28 (dt, *J* = 2.0 Hz and *J* = 7.1 Hz, 2H, H_4), 5.45 (t, *J* = 2.0 Hz, 1H, H_7), 7.3 - 7.56 (m, 5H, H_{10}, H_{11} and H_{12}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.5 (C_1), 18.4 (C_4), 21.9 (C_2), 30.6 (C_3), 64.7 (C_7), 79.8 (C_6), 87.6 (C_5), 126.5 (2C, C_{Ar}), 128.1 (C_{Ar}), 128.4 (2C, C_{Ar}), 141.2 (C_9).

The spectral data are consistent with those of the literature.

1-(3-methoxyphenyl)hept-2-yn-1-ol (A.2)



$C_{14}H_{18}O_2$
218.29 g.mol^{-1}
Pale yellow oil

Compound **A.2** was prepared according to the previously described general procedure A (5 mmol scale) starting from 1-hexyne and *m*-anisaldehyde. Purification was carried out by flash chromatography on silica gel (petroleum ether/ethyl acetate: 9/1). **Yield: 89%**

R_f (silica, pentane/ethyl acetate: 9/1) = 0.4 (UV/PMA)

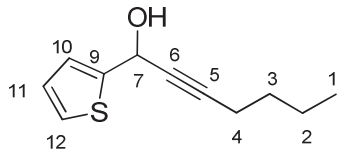
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (t, *J*= 7.2 Hz, 3H, H_1), 1.37 - 1.58 (m, 4H, H_2 and H_3), 2.17 (brs, 1H, H_8), 2.28 (dt, *J* = 2.0 Hz and *J* = 7.0 Hz, 2H, H_4), 3.82 (s, 3H, H_{12}), 5.42 (s, 1H, H_7), 6.86 (ddd, *J* = 1.2 Hz, *J* = 2.4 Hz, *J* = 8.3 Hz, 1H, H_{15}), 7.10 - 7.14 (m, 2H, H_{10} and H_{13}), 7.25 - 7.31 (m, 1H, H_{14}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.5 (C_1), 18.5 (C_4), 22.0 (C_2), 30.6 (C_3), 55.2 (C_{12}), 64.4 (C_7), 79.8 (C_6), 87.6 (C_5), 112.0 (C_{Ar}), 113.9 (C_{Ar}), 118.9 (C_{Ar}), 129.5 (C_{Ar}), 142.9 (C_{12}), 159.7 (C_9).

The spectral data are consistent with those of the literature.

1-(thiophen-2-yl) hept-2-yn-1-ol (A.3)



$C_{11}H_{14}OS$
194.29 $g.mol^{-1}$
Pale yellow oil

The compound **A.3** was prepared according to the previously described general procedure A (5 mmol scale) starting from 1-hexyne and 2-thiophene carboxaldehyde. Purification was carried out by flash chromatography on silica gel (pentane/ethyl acetate). **Yield: 92%**

R_f (silica, Pentane/Et_2O) = 0.2 (UV/PMA)

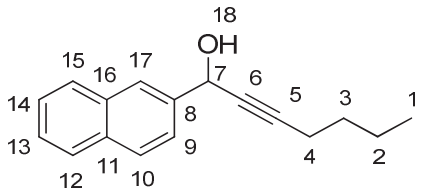
Spectral Data

NMR ^{1}H (400 MHz, $CDCl_3$) δ (ppm): 0.93 (t, *J* = 7.2 Hz, 3H, H_1), 1.39 - 1.57 (m , 4H, H_2 and H_3), 2.28 (dt, *J* = 1.2 Hz and *J* = 7.0 Hz, 2H, H_4), 2.50 (d, *J* = 6.8 Hz, 1H, OH), 5.63 (d, *J* = 6.5 Hz, 1H, H_7), 6.97 (dd, *J* = 3.5 Hz and *J* = 5.0 Hz, 1H, H_{11}), 7.15 (d, *J* = 3.5 Hz, 1H, H_{10}), 7.28 (d, *J* = 5.1 Hz, 1H, H_{12}).

NMR ^{13}C (100 MHz, $CDCl_3$) δ (ppm): 13.6 (C_1), 18.4 (C_4), 22.0 (C_2), 30.5 (C_3), 60.4 (C_7), 79.4 (C_6), 87.1 (C_5), 125.3 (C_{Ar}), 125.8 (C_{Ar}), 126.7 (C_{Ar}), 145.5 (C_9).

The spectral data are consistent with those of the literature.

2-(naphthalen-2-yl)hept-2-yn-1-ol (A.4)



$C_{17}H_{18}O$
238.32 g.mol^{-1}
Pale yellow oil

The compound **A.4** was prepared according to the previously described general procedure A (10 mmol scale) starting from 1-hexyne and 2-Naphthaldehyde. Purification was carried out by flash chromatography on silica gel (cyclohexane/Et_2O: 95/5 → 85/15). **Yield: 92%**

R_f (silica, pentane/Et_2O: 9/1) = 0.2 (UV/PMA)

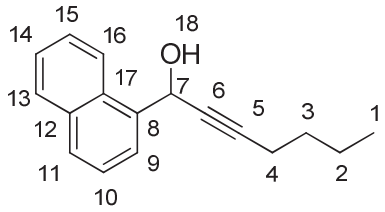
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.94 (t, *J*= 7.2 Hz, 3H, H_1), 1.41 - 1.60 (m, 4H, H_2 and H_3), 2.31 (dt, *J* = 2.0 Hz and *J* = 7.1 Hz, 2H, H_4), 2.34 (brs, 1H, H_{18}), 5.62 (brs, 1H, H_7), 7.47 - 7.53 (m, 2H, H_{Ar}), 7.66 (dd, *J* = 1.8 Hz and *J* = 8.5 Hz, 1H, H_9), 7.83 - 7.89 (m, 3H, H_{Ar}), 7.99 (brs, 1H, H_{17}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.6 (C_1), 18.5 (C_4), 22.0 (C_2), 30.6 (C_3), 64.9 (C_7), 79.9 (C_6), 87.9 (C_5), 124.7 ($CH_{,}$ C_{Ar}), 125.3 ($CH_{,}$ C_{Ar}), 126.1 ($CH_{,}$ C_{Ar}), 126.2 ($CH_{,}$ C_{Ar}), 127.6 ($CH_{,}$ C_{Ar}), 128.1 ($CH_{,}$ C_{Ar}), 128.4 ($CH_{,}$ C_{Ar}), 133.1 ($C_{q,}$ C_{Ar}), 133.2 ($C_{q,}$ C_{Ar}), 138.6 (C_{Ar}, C_8).

The spectral data are consistent with those of the literature.

1-(naphthalen-2-yl)hept-2-yn-1-ol (A.5)



$C_{17}H_{18}O$
238.32 g.mol^{-1}
Pale yellow oil

The compound **A.5** was prepared according to the previously described general procedure A (10 mmol scale) starting from 1-hexyne and 1-Naphthaldehyde. Purification was carried out by flash chromatography on silica gel (Cyclohexane/Et_2O: 95/5 → 85/15). **Yield: 92%**

R_f (silica, Pentane/Et_2O: 9/1) = 0.2 (UV/PMA)

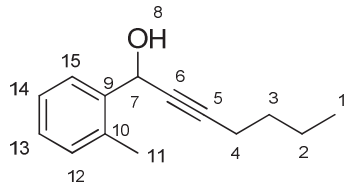
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (t, *J*= 7.0 Hz, 3H, H_1), 1.42 - 1.46 (m, 2H, H_2), 1.52 - 1.57 (m, 2H, H_3), 2.30 (t, *J* = 7.0 Hz, 2H, H_4), 2.37 (brs, 1H, H_{18}), 6.12 (brs, 1H, H_7), 7.47 - 7.56 (m, 3H, H_{Ar}), 7.83 - 7.89 (m, 3H, H_{Ar}), 8.31 – 8.33 (brs, 1H, H_{16}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9 (C_1), 18.9 (C_4), 22.3 (C_2), 30.9 (C_3), 63.3 (C_7), 79.9 (C_6), 88.6 (C_5), 124.3 (CH, C_{Ar}), 124.7 (CH, C_{Ar}), 125.5 (CH, C_{Ar}), 126.1 (CH, C_{Ar}), 126.5 (CH, C_{Ar}), 128.9 (CH, C_{Ar}), 129.4 (CH, C_{Ar}), 130.8 (C_q, C_{Ar}), 134.3 (C_q, C_{Ar}), 136.5 (C_{Ar}, C_8).

The spectral data are consistent with those of the literature.

1-*o*-tolylhept-2-yn-1-ol (A.6)



$C_{14}H_{18}O$
202.29 g.mol^{-1}
Pale yellow oil

The compound **A.6** was prepared according to the previously described general procedure A (10 mmol scale) starting from 1-hexyne and *o*-tolualdehyde. Purification was carried out by flash chromatography on silica gel (Cyclohexane/Et_2O: 95/5 → 85/15). **Yield: 92%**

R_f (silica, Pentane/ Et_2O: 9/1) = 0.3 (UV/PMA)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (t, *J* = 7.2 Hz, 3H, H_1), 1.37 - 1.56 (m, 4H, H_2 and H_3), 1.9 (b, 1H, H_8), 2.27 (dt, *J* = 2 Hz and *J* = 7.1 Hz, 2H, H_4), 2.44 (s, 3H, H_{11}), 5.61 (s, 1H, H_7), 7.16 - 7.24 (m, 3H, H_{12} and H_{13} and H_{14}), 7.64 - 7.67 (m, 1H, H_{15}).

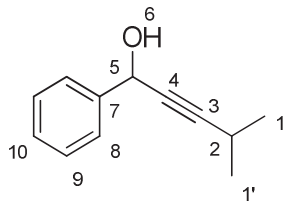
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.5 (C_1), 18.51 (C_4), 18.9 (C_{11}), 21.9 (C_2), 30.6 (C_3), 62.6 (C_7), 79.5 (C_6), 87.4 (C_5), 126.1 (C_{Ar}), 126.3 (C_{Ar}), 128.1 (C_{Ar}), 130.6 (C_{Ar}), 135.8 (C_{Ar}), 138.9 (C_{Ar}).

IR (FT-IR) cm^{-1}: 3333, 2959, 2930, 2856, 1491, 1460, 1380, 1325, 1281, 1247, 1214, 1177, 1133, 1096, 989, 747, 632.

MS (EI) *m/z*: 202 (38, [$M^{+\bullet}$]), 187 (100), 155 (18), 145 (85), 128 (31), 115 (48), 105 (21), 91 (64), 77 (15), 65 (17), 53 (9), 41 (12).

HRMS (ESI+) *m/z*: 203.1416 calcd for $C_{14}H_{18}O + H^+$: 203.1436.

4-methyl-1-phenylpent-2-yn-1-ol (A.7)



$C_{12}H_{14}O$
174.23 g.mol^{-1}
Colorless oil

The compound **A.7** was prepared according to the previously described general procedure A (10 mmol scale) starting from 3-methylbut-1-yne and benzaldehyde. Purification was carried out by flash chromatography on silica gel (Cyclohexane/Et_2O: 95/5). **Yield: 90%**

R_f (silica, Pentane/Et_2O: 9/1) = 0.3 (UV/PMA)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.21 (d, *J* = 6.9 Hz, 6H, H_1 and $H_{1'}$), 2.08 (d, *J* = 3.3 Hz, 1H, H_6), 2.65 (dsept, *J* = 1.8 Hz and *J* = 6.9 Hz, 1H, H_2), 5.45 (s, 1H, H_5), 7.30 - 7.40 (m, 3H, H_{10} and H_8), 7.53 - 7.56 (m, 2H, H_9).

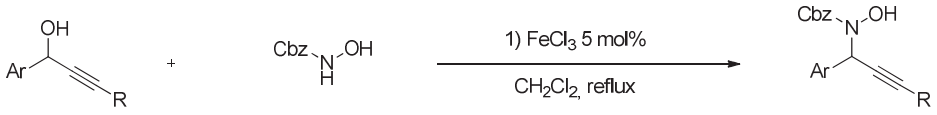
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.5 (C_2), 22.8 (C_1), 64.7 (C_5), 79.0 (C_4), 93.0 (C_3), 126.6 (2C, C_{Ar}), 128.1 (C_{Ar}), 128.5 (2C, C_{Ar}), 141.2 (C_7).

The spectral data are consistent with those of the literature.

N-Propargylic hydroxylamines

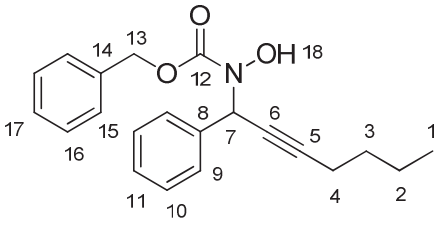
General procedure B

for the preparation of propargylic hydroxylamines (3.47 – 3.67)



To a solution of the corresponding propargylic alcohol (1 equiv) in dichloromethane (2.5 mL) was added benzyl hydroxy carbamate (1 equiv) and $FeCl_3$ (5 mol%, 0.05 equiv) and the mixture was refluxed for 90 min. After reaction completion (TLC monitoring), the mixture was concentrated under vacuum and the crude material was purified by flash chromatography on silica gel to give the corresponding propargylic hydroxylamine.

benzyl hydroxy(1-phenylhept-2-yn-1-yl)carbamate (3.47)



$C_{21}H_{23}NO_3$

337.41 g.mol^{-1}

Pale yellow solid

The compound **3.47** was prepared according to the previously described general procedure B (2 mmol scale) starting from 1-phenylhept-2-yn-1-ol **A.1** and benzyl hydroxycarbamate. Purified by flash chromatography on silica gel (Pentane/Ethyl acetate : 88/12). **Yield: 93%**

R_f (silica, pentane/ethyl acetate: 9/1) = 0.25 (UV/PMA)
Mp: 58-59 °C (Et_2O/pentane)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (t, *J* = 7.3 Hz, 3H, H_1), 1.39 - 1.59 (m, 4H, H_2 & H_3), 2.29 (dt, *J* = 2.2 Hz and *J* = 7.1 Hz, 2H, H_4), 5.26 (s, 2H, H_{13}), 5.59 (brs, 1H, H_{18}), 6.13 (t, *J* = 2.1 Hz, 1H, H_7), 7.29 - 7.42 (m, 8H, H_{Ar}), 7.50 - 7.56 (m, 2H, H_{Ar}).

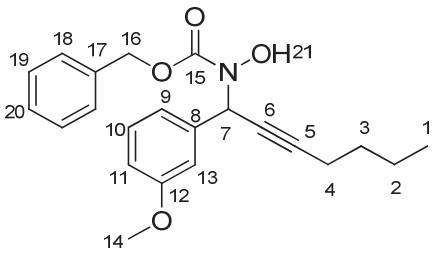
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.6 (C_1), 18.5 (C_4), 22.0 (C_2), 30.6 (C_3), 55.9 (C_7), 68.4 (C_{13}), 74.5 (C_6), 87.1 (C_5), 127.9 (3C, C_{Ar}), 128.1 (C_{Ar}), 128.2 (C_{Ar}), 128.4 (4C, C_{Ar}), 128.6 (C_{Ar}), 135.6 (C_q, C_{Ar}), 136.2 (C_q, C_{Ar}), 157.1 (C_{12}).

IR (ATR, neat) ν (cm^{-1}): 3225, 2957, 2928, 2872, 2859, 2222, 1959, 1704, 1495, 1481, 1453, 1443, 1394, 1346, 1290, 1097, 1030, 959, 763, 743, 713, 694, 636, 608.

MS (ESI+) *m/z*: 675 (15, $[2M+H]^+$), 508 (45), 464 (100), 338 (50, $[M+H]^+$), 320 (15), 261 (20).

HRMS (ESI+) *m/z*: 338.1742 calcd for $C_{21}H_{23}NO_3 + H^+$: 338.1756.

benzyl hydroxy(1-(3-methoxyphenyl)hept-2-yn-1-yl)carbamate (3.54)



$C_{22}H_{25}NO_4$

367.44 g.mol^{-1}

Orange oil

The compound **3.54** was prepared according to the previously described general procedure B (2 mmol scale) starting from 1-(3-methoxyphenyl)hept-2-yn-1-ol **A.2** and benzyl hydroxycarbamate. Purified by flash chromatography on silica gel (petroleum ether/ethyl acetate : 85/15). **Yield: 78%**

R_f (silica, pentane/ethyl acetate: 85/15) = 0.3 (UV/PMA)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (t, *J* = 7.3 Hz, 3H, H_1), 1.39 - 1.60 (m, 4H, H_2 and H_3), 2.29 (dt, *J* = 2.2 Hz and *J* = 7.0 Hz, 2H, H_4), 3.76 (s, 3H, H_{14}), 5.23 (s, 2H, H_{15}), 6.11 (t, *J* = 2.1 Hz, 1H, H_7), 6.33 (brs, 1H, H_{21}), 6.84 (ddd, *J* = 0.7 Hz, *J* = 2.4 Hz and *J* = 8.1 Hz, 1H, H_{11}), 7.10 - 7.15 (m, 2H, H_{Ar}), 7.25 (t, *J* = 8.1 Hz, 1H, H_{10}), 7.30 - 7.41 (m, 5H, H_{Ar}).

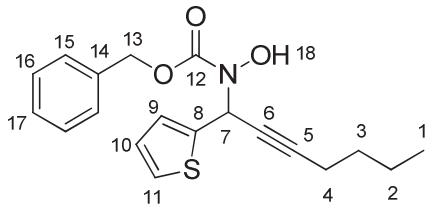
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.5 (C_1), 18.4 (C_4), 21.9 (C_2), 30.6 (C_3), 55.1 (C_{14}), 55.6 (C_7), 68.3 (C_{16}), 74.7 (C_6), 87.3 (C_5), 113.5 (C_{Ar}), 113.8 (C_{Ar}), 120.2 (C_{Ar}), 128.1 (2C, C_{Ar}), 128.2 (C_{Ar}), 128.5 (2C, C_{Ar}), 129.3 (C_{Ar}), 135.6 (C_q, C_{Ar}), 137.9 (C_q, C_{Ar}), 157.1 (C_{14}), 159.5 (C_{15}).

IR (ATR, neat) ν (cm^{-1}): 3305, 2957, 2933, 2872, 1703, 1601, 1586, 1489, 1454, 1433, 1404, 1350, 1279, 1223, 1159, 1093, 1043, 755, 737, 719, 695, 639.

MS (ESI+) *m/z*: 568 (50), 401 (100), 368 (15, $[M+H]^+$), 350 (20), 291 (80), 201 (50).

HRMS (ESI+) *m/z*: 368.1854 calcd for $C_{22}H_{25}NO_4 + H^+$: 368.1862.

benzyl hydroxy(1-(thiophen-2-yl)hept-2-yn-1-yl)carbamate (3.56)



$C_{19}H_{21}NO_3S$

343.44 g.mol^{-1}

Yellow oil

The compound **3.56** was prepared according to the previously described general procedure B (3 mmol scale) starting from 1-(thiophen-2-yl)hept-2-yn-1-ol **A.3** and benzyl hydroxycarbamate. Purified by flash chromatography on silica gel (Pentane/Ethyl acetate : 9/1). **Yield: 86%**

R_f (silica, pentane/ethyl acetate: 85/15) = 0.45 (UV/PMA)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (t, *J* = 7.2 Hz, 3H, H_1), 1.38 - 1.58 (m, 4H, H_2 & H_3), 2.27 (dt, *J* = 2.2 Hz and *J* = 7.0 Hz, 2H, H_4), 5.24 (s, 2H, H_{13}), 6.00 (brs, 1H, H_{18}), 6.28 (brs, 1H, H_7), 6.95 (dd, *J* = 3.5 Hz and *J* = 5.1 Hz, 1H, H_{10}), 7.16 (td, *J* = 1.1 Hz and *J* = 3.5 Hz, 1H, H_9), 7.26 (td, *J* = 1.2 Hz and *J* = 5.2 Hz, 1H, H_{11}), 7.31 - 7.41 (m, 5H, H_{Ar}).

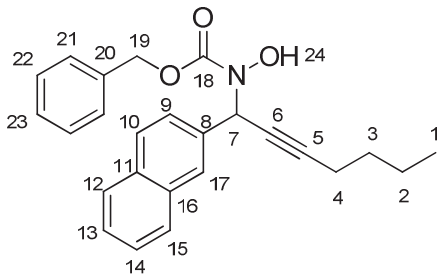
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.6 (C_1), 18.4 (C_4), 21.9 (C_2), 30.5 (C_3), 51.7 (C_7), 68.5 (C_{13}), 74.7 (C_6), 86.7 (C_5), 126.0 (C_{11}), 126.6 (C_{10}), 127.0 (C_9), 128.2 (2C, C_{Ar}), 128.4 (C_{17}), 128.5 (2C, C_{Ar}), 135.4 (C_q, C_{Ar}), 139.8 (C_q, C_{Ar}), 156.9 (C_{12}).

IR (ATR, neat) ν (cm^{-1}): 3307, 2955, 2928, 2869, 1646, 1444, 1395, 1345, 1296, 1254, 1092, 932, 912, 820, 756, 695.

MS (ESI+) *m/z*: 344 (10, $[M+H]^+$), 319 (25), 295 (15), 214 (15), 177 (100).

HRMS (ESI+) *m/z*: 344.1339 calcd for $C_{19}H_{21}NO_3S + H^+$: 344.1320.

benzyl hydroxy(1-(naphthalen-2-yl)hept-2-yn-1-yl)carbamate (3.57)



$C_{25}H_{25}NO_3$

387.47 g.mol^{-1}

Orange oil

The compound **3.57** was prepared according to the previously described general procedure B (2 mmol scale) starting from 1-(naphthalen-2-yl)hept-2-yn-1-ol **A.4** and benzyl hydroxycarbamate. Purified by flash chromatography on silica gel (pentane/ethyl acetate : 9/1 → 85/15). **Yield: 91%**

R_f (silica, Pentane/Ethyl acetate: 85/15) = 0.4 (UV/PMA)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (t, *J* = 7.3 Hz, 3H, H_1), 1.42 - 1.63 (m, 4H, H_2 and H_3), 2.35 (dt, *J* = 2.2 Hz and *J* = 7.0 Hz, 2H, H_4), 5.28 (s, 2H, H_{19}), 5.62 (brs, 1H, H_{24}), 6.28 (brs, 1H, H_7), 7.31 - 7.44 (m, 5H, H_{Ar}), 7.46 - 7.52 (m, 2H, H_{Ar}), 7.59 (dd, *J* = 1.8 Hz and *J* = 8.5 Hz, 1H, H_{Ar}), 7.80 - 7.86 (m, 3H, H_{Ar}), 8.03 (brs, 1H, H_{Ar}).

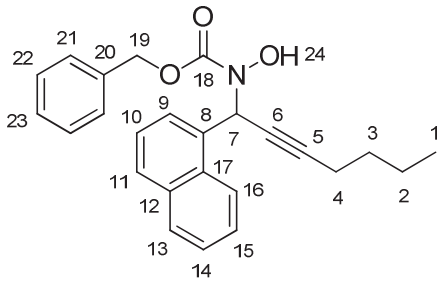
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.6 (C_1), 18.5 (C_4), 22.0 (C_2), 30.7 (C_3), 56.0 (C_7), 68.5 (C_{13}), 74.6 (C_6), 87.9 (C_5), 125.5 (C_{Ar}), 126.2 (C_{Ar}), 126.3 (2C, C_{Ar}), 127.3 (C_{Ar}), 127.6 (C_{Ar}), 128.1 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 128.4 (C_{Ar}), 128.6 (C_{Ar}), 133.1 (C_q, C_{Ar}), 133.2 (C_q, C_{Ar}), 133.7 (C_q, C_{Ar}), 135.6 (C_q, C_{Ar}), 157.2 (C_{18}).

IR (ATR, neat) ν (cm^{-1}): 3290, 3059, 2957, 2932, 2871, 1700, 1455, 1402, 1349, 1288, 1093, 808, 782, 739, 695.

MS (ESI+) *m/z*: 608 (90), 564 (50), 388 (10, $[M+H]^+$), 370 (30), 311 (100).

HRMS (ESI+) *m/z*: 388.1919 calcd for $C_{25}H_{25}NO_3 + H^+$: 388.1913.

benzyl hydroxy(1-(naphthalen-1-yl)hept-2-yn-1-yl)carbamate (3.58)



$C_{25}H_{25}NO_3$

387.47 g.mol^{-1}

Brown oil

The compound **3.58** was prepared according to the previously described general procedure B (2 mmol scale) starting from 1-(naphthalen-2-yl)hept-2-yn-1-ol **A.5** and benzyl hydroxycarbamate. Purified by flash chromatography on silica gel (pentane/ethyl acetate : 9/1). **Yield: 62%**

R_f (silica, pentane/ethyl acetate: 9/1) = 0.3 (UV/PMA)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (t, *J* = 7.3 Hz, 3H, H_1), 1.42 - 1.52 (m, 2H, H_2), 1.54 - 1.63 (m, 2H, H_3), 2.34 (dt, *J* = 2.0 Hz and *J* = 7.1 Hz, 2H, H_4), 5.23 (s, 2H, H_{19}), 5.73 (brs, 1H, H_{24}), 6.83 (brs, 1H, H_7), 7.32 - 7.43 (m, 5H, H_{Ar}), 7.44 - 7.52 (m, 3H, H_{Ar}), 7.81 - 7.87 (m, 2H, H_{Ar}), 8.02 - 8.08 (m, 2H, H_{Ar}).

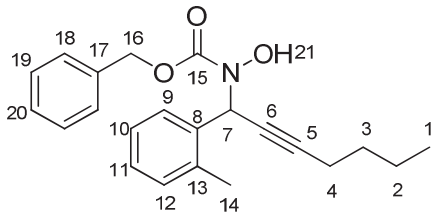
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.6 (C_1), 18.5 (C_4), 22.0 (C_2), 30.6 (C_3), 53.3 (C_7), 68.3 (C_{13}), 74.7 (C_6), 88.0 (C_5), 123.0 (C_{Ar}), 125.0 (C_{Ar}), 125.7 (C_{Ar}), 126.5 (C_{Ar}), 127.9 (C_{Ar}), 128.1 (2C, C_{Ar}), 128.3 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.7 (C_{Ar}), 129.3 (C_{Ar}), 130.6 (C_q), 131.2 (C_q), 133.7 (C_q), 135.7 (C_q), 157.0 (C_{18}).

IR (ATR, neat) ν (cm^{-1}): 3297, 2956, 2931, 2871, 1948, 1703, 1455, 1398, 1347, 1296, 1278, 1095, 797, 790, 778, 754, 737, 696.

MS (ESI+) *m/z*: 608 (10), 388 (5, $[M+H]^+$), 311 (20), 221 (100).

HRMS (ESI+) *m/z*: 388.1920 calcd for $C_{25}H_{25}NO_3 + H^+$: 388.1913.

benzyl hydroxy(1-(*o*-tolyl)hept-2-yn-1-yl)carbamate (3.59)



$C_{22}H_{25}NO_3$

351.44 g.mol^{-1}

Viscous orange oil

The compound **3.59** was prepared according to the previously described general procedure B (1 mmol scale) starting from 1-*o*-tolylhept-2-yn-1-ol **A.6** and benzyl hydroxycarbamate. Purified by flash chromatography on silica gel (pentane/ethyl acetate : 88/12). **Yield: 70%**

R_f (silica, Pentane/Ethyl acetate : 85/15) = 0.4 (UV/PMA)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (t, *J* = 7.3 Hz, 3H, H_1), 1.40 - 1.60 (m, 4H, H_2 & H_3), 2.30 (dt, *J* = 2.4 Hz and *J* = 7.2 Hz, 2H, H_4), 2.31 (s, 3H, H_{14}), 5.22 (s, 2H, H_{16}), 6.11 (brs, 1H, H_{21}), 6.22 (t, *J* = 2.0 Hz, 1H, H_7), 7.12 - 7.16 (m, 1H, H_{Ar}), 7.20 - 7.25 (m, 2H, H_{Ar}), 7.33 - 7.41 (m, 5H, H_{Ar}), 7.81 - 7.85 (m, 1H, H_{Ar}).

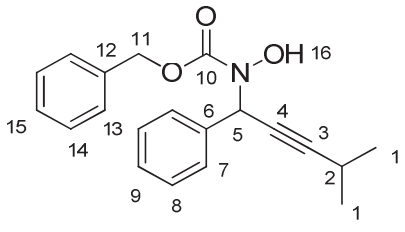
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.5 (C_1), 18.4 (C_4), 18.8 (C_{14}), 21.9 (C_2), 30.6 (C_3), 53.3 (C_7), 68.1 (C_{16}), 74.9 (C_6), 87.2 (C_5), 125.7 (C_{Ar}), 128.0 (2C, C_{Ar}), 128.2 (C_{Ar}), 128.3 (C_{Ar}), 128.4 (2C, C_{Ar}), 129.6 (C_{Ar}), 130.2 (C_{Ar}), 134.1 (C_q, C_{Ar}), 135.7 (C_q, C_{Ar}), 136.3 (C_q, C_{Ar}), 157.1 (C_{15}).

IR (ATR, neat) ν (cm^{-1}): 3263, 3034, 2960, 2868, 1675, 1655, 1487, 1463, 1455, 1410, 1346, 1296, 1259, 1093, 1079, 1016, 946, 797, 744, 729, 695, 629.

MS (ESI+) *m/z*: 536 (70), 519 (25), 492 (45), 459 (15), 369 (25), 352 (75, $[M+H]^+$), 334 (20), 308 (50), 275 (100), 216 (30), 203 (30).

HRMS (ESI+) *m/z*: 352.1909 calcd for $C_{22}H_{25}NO_3 + H^+$: 352.1913.

benzyl hydroxy(4-methyl-1-phenylpent-2-yn-1-yl)carbamate (3.63)



$C_{20}H_{21}NO_3$

323.39 g.mol^{-1}

Pale yellow solid

The compound **3.63** was prepared according to the previously described general procedure B (1 mmol scale) starting from 4-methyl-1-phenylpent-2-yn-1-ol **A.7** and benzyl hydroxycarbamate. Purified by flash chromatography on silica gel (pentane/ethyl acetate : 88/12). **Yield: 88%**

R_f (silica, pentane/ethyl acetate: 9/1) = 0.25 (UV/PMA)
Mp: 78-79 °C (Et_2O/pentane)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.21 (d, *J* = 6.9 Hz, 3H, H_1), 1.22 (d, *J* = 6.9 Hz, 3H, H_1), 2.66 (septd, *J* = 2.0 Hz and *J* = 6.8 Hz, 1H, H_2), 5.26 (s, 2H, H_{11}), 5.60 (brs, 1H, H_{16}), 6.13 (d, *J* = 1.8 Hz, 1H, H_5), 7.28 - 7.42 (m, 8H, H_{Ar}), , 7.50 - 7.55 (m, 2H, H_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.6 (C_2), 22.9 (2C, C_1), 55.7 (C_5), 68.4 (C_{11}), 73.7 (C_4), 93.0 (C_3), 127.9 (3C, C_{Ar}), 128.1 (C_{Ar}), 128.2 (C_{Ar}), 128.4 (4C, C_{Ar}), 128.5 (C_{Ar}), 135.6 (C_q, C_{Ar}), 136.2 (C_q, C_{Ar}), 157.1 (C_{10}).

IR (ATR, neat) ν (cm^{-1}): 3300, 2967, 2927, 2877, 2255, 1967, 1888, 1754, 1655, 1495, 1448, 1415, 1349, 1288, 1099, 1030, 956, 883, 752, 739, 698, 634.

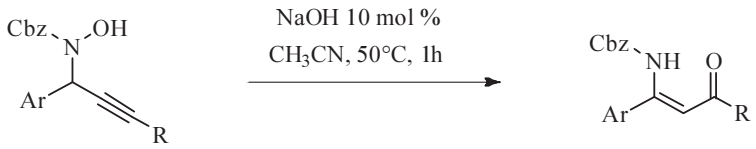
MS (ESI+) *m/z*: 647 (10, $[2M+H]^+$), 491 (10), 480 (20), 436 (100), 324 (98, $[M+H]^+$), 306 (25), 247 (25), 157 (20).

HRMS (ESI+) *m/z*: 324.1592 calcd for $C_{20}H_{21}NO_3 + H^+$: 324.1600.

β-Enaminones

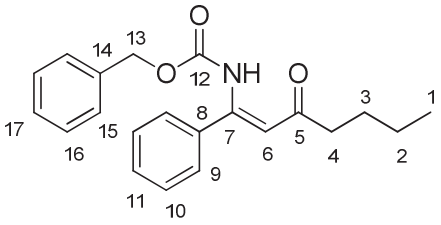
General procedure C

for the preparation of β-enaminones (3.76 – 3.87, 3.89 – 3.93, 3.95-3.96)



In a 5-mL wheaton reactor, equipped with a magnetic stirrer bar, the corresponding propargylic hydroxylamine (0.2 mmol, 1 equiv), acetonitrile (2 mL) and sodium hydroxyde powder (0.02 mmol, 0.1 equiv) were added by turn and the mixture was heated at 50°C for 1h. Thus, the reaction mixture was filtered through a silica gel pad and eluted with ethyl acetate, the filtrate was concentrated, and the residue was purified by flash chromatography on silica gel to give the corresponding β-enaminone.

(Z)-benzyl (3-oxo-1-phenylhept-1-en-1-yl)carbamate (3.76)



$C_{21}H_{23}NO_3$

337.41 g.mol^{-1}

Pale yellow oil

The compound **3.76** was prepared according to the previously described general procedure C starting from benzyl (1-phenylhept-2-yn-1-yl)(hydroxy)carbamate **3.47**. Purified by flash chromatography on silica gel (pentane/Et_2O: 92/8). **Yield: 86%**

R_f (silica, pentane/Et_2O: 9/1) = 0.35 (UV/PMA/Vanillin)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (t, *J* = 7.2 Hz, 3H, H_1), 1.29 - 1.41 (m, 2H, H_2), 1.55 - 1.67 (m, 2H, H_3), 2.47 (t, *J* = 7.0 Hz, 2H, H_4), 5.07 (s, 2H, H_{13}), 5.57 (s, 1H, H_6), 7.28 - 7.46 (m, 10H, H_{Ar}), 11.58 (brs, 1H, NH).

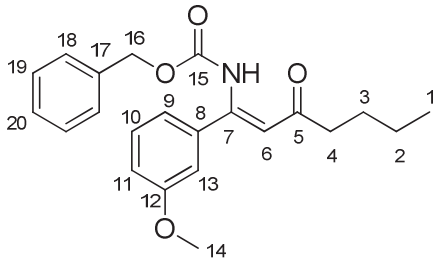
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9 (C_1), 22.4 (C_2), 26.9 (C_3), 43.5 (C_4), 67.4 (C_{13}), 107.2 (C_6), 127.5 (2C), 128.0 (2C), 128.3 (2C), 128.4 (C_{Ar}), 128.5 (2C, C_{Ar}), 129.8 (C_{Ar}), 135.5 (C_q, C_{Ar}), 135.6 (C_q, C_{Ar}), 152.8 (C_q, C_{Ar}), 154.5 (C_q, C_{Ar}), 202.6 (C_5)

IR (ATR, neat) ν (cm^{-1}): 2958, 2928, 2870, 1750, 1642, 1589, 1573, 1495, 1473, 1280, 1195, 1119, 1047, 765, 750, 694.

MS (ESI+) m/z: 675 (5, $[2M+H]^+$), 505 (10), 338 (100, $[M+H]^+$), 320 (15), 294 (10).

HRMS (ESI+) m/z: 338.1747 calcd for $C_{21}H_{23}NO_3 + H^+$: 338.1756.

(Z)-benzyl (1-(3-methoxyphenyl)-3-oxohept-1-en-1-yl)carbamate (3.84)



$C_{22}H_{25}NO_4$

367.44 g.mol^{-1}

Pale yellow oil

The compound **3.84** was prepared according to the previously described general procedure C starting from benzyl (1-(3-methoxyphenyl)hept-2-yn-1-yl)(hydroxy)carbamate **3.54**. Purified by flash chromatography on silica gel (petroleum ether/Et_2O: 9/1). **Yield: 66%**

R_f (silica, pentane/Et_2O: 9/1) = 0.3 (UV/PMA/Vanillin)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.94 (t, *J* = 7.2 Hz, 3H, H_1), 1.32 - 1.43 (m, 2H, H_2), 1.58 - 1.68 (m, 2H, H_3), 2.48 (t, *J* = 7.2 Hz, 2H, H_4), 3.81 (s, 3H, H_{14}), 5.09 (s, 2H, H_{16}), 5.60 (s, 1H, H_6), 6.92 - 7.46 (m, 3H, H_{Ar}), 7.28 - 7.39 (m, 6H, H_{Ar}), 11.55 (brs, 1H, NH).

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -114.1.

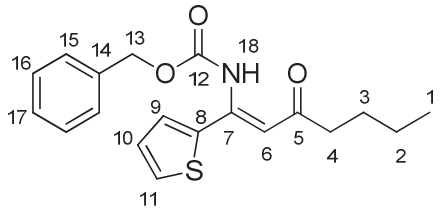
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.8 (C_1), 22.3 (C_2), 26.7 (C_3), 43.4 (C_4), 55.2 (C_{14}), 67.3 (C_{16}), 107.0 (C_6), 113.1 (C_{Ar}), 115.1 (C_{Ar}), 119.8 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 128.4 (2C, C_{Ar}), 128.9 (C_{Ar}), 135.4 (C_q, C_{Ar}), 136.9 (C_q, C_{Ar}), 152.6 (C_q, C_{Ar}), 154.0 (Cq, C_{Ar}), 159.1 (C_q, C_{Ar}), 202.4 (C_5).

IR (ATR, neat) ν (cm^{-1}): 3066, 3033, 2957, 2932, 1749, 1644, 1574, 1464, 1287, 1223, 1191, 1134, 1039, 880, 785, 755, 733, 695.

MS (ESI+) m/z: 368 (100, $[M+H]^+$), 324 (20).

HRMS (ESI+) m/z: 368.1855 calcd for $C_{22}H_{25}NO_4 + H^+$: 368.1862.

(Z)-benzyl (3-oxo-1-(thiophen-2-yl)hept-1-en-1-yl)carbamate (3.85)



$C_{19}H_{21}NO_3S$

343.44 g.mol^{-1}

Red oil

The compound **3.85** was prepared according to the previously described general procedure C (1 mmol scale) starting from benzyl hydroxy(1-(thiophen-2-yl)hept-2-yn-1-yl)carbamate **3.56** and benzyl hydroxycarbamate. Purified by flash chromatography on silica gel (pentane/ Et_2O : 92/8). **Yield: 45%**

R_f (silica, pentane/Et_2O: 9/1) = 0.4 (UV/Vanillin)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.94 (t, *J* = 7.3 Hz, 3H, H_1), 1.32 - 1.42 (m, 2H, H_2), 1.58 - 1.67 (m, 2H, H_3), 2.48 (t, *J* = 7.6 Hz, 2H, H_4), 5.13 (s, 2H, H_{13}), 5.78 (s, 1H, H_6), 7.06 (dd, *J* = 3.7 Hz and *J* = 5.0 Hz, 1H, H_{10}), 7.33 (td, *J* = 1.2 Hz and *J* = 3.7 Hz, 1H, H_9), 7.34 - 7.38 (m, 5H, H_{Ar}), 7.42 (dd, *J* = 1.2 Hz and *J* = 5.0 Hz, 1H, H_{11}), 11.45 (s, H_{18}).

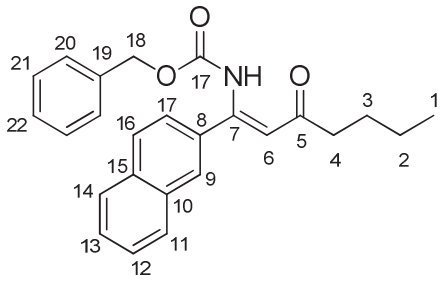
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.8 (C_1), 22.3 (C_2), 26.7 (C_3), 43.4 (C_4), 67.4 (C_{13}), 107.2 (C_6), 127.2 (C_{10}), 128.0 (C_{Ar}), 128.2 (2C, C_{Ar}), 128.3 (C_{Ar}), 128.4 (2C, C_{Ar}), 129.2 (C_{Ar}), 135.4 (C_q, C_{Ar}), 136.5 (C_q, C_{Ar}), 146.9 (C_q, C_{Ar}), 152.8 (C_{12}), 202.2 (C_5).

IR (ATR, neat) ν (cm^{-1}): 2957, 2930, 1749, 1639, 1582, 1464, 1455, 1191, 1267, 1191, 1134, 1109, 694.

MS (ESI+) *m/z*: 344 (100, $[M+H]^+$), 300 (30).

HRMS (ESI+) *m/z*: 344.1313 calcd for $C_{19}H_{21}NO_3S + H^+$: 344.1320.

(Z)-benzyl (1-(naphthalen-2-yl)-3-oxohept-1-en-1-yl)carbamate (3.86)



$C_{25}H_{25}NO_3$

387.47 g.mol^{-1}

Pale yellow oil

The compound **3.86** was prepared according to the previously described general procedure C starting from benzyl (1-(naphthalen-2-yl)hept-2-yn-1-yl)(hydroxy)carbamate **3.57**. Purified by flash chromatography on silica gel (petroleum ether/Et_2O: 92/8). **Yield: 58%**

R_f (silica, pentane/Et_2O: 9/1) = 0.4 (UV/Vanillin)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.98 (t, *J* = 7.6 Hz, 3H, H_1), 1.36 - 1.47 (m, 2H, H_2), 1.64 - 1.73 (m, 2H, H_3), 2.53 (t, J = 7.2 Hz, 2H, H_4), 5.11 (s, 2H, H_{18}), 5.72 (s, 1H, H_6), 7.28 - 7.36 (m, 5H, H_{Ar}), 7.48 - 7.58 (m, 3H, H_{Ar}), 7.81 - 7.95 (m, 4H, H_{Ar}), 11.71 (brs, 1H, NH).

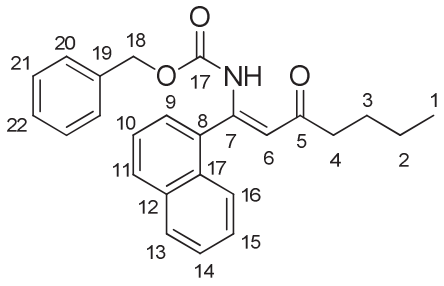
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.8 (C_1), 22.3 (C_2), 26.7 (C_3), 43.4 (C_4), 67.4 (C_{18}), 107.4 (C_6), 125.1 (C_{Ar}), 126.4 (C_{Ar}), 126.7 (C_{Ar}), 126.9 (C_{Ar}), 127.3 (C_{Ar}), 127.7 (C_{Ar}), 128.1 (C_{Ar}), 128.2 (C_{Ar}), 128.3 (2C, C_{Ar}), 128.4 (2C, C_{Ar}), 132.7 (C_q, C_{Ar}), 133.2 (C_q, C_{Ar}), 133.8 (C_q, C_{Ar}), 135.4 (C_q, C_{Ar}), 152.8 (C_q, C_{Ar}), 154.3 (C_q, C_{Ar}), 202.4 (C_5).

IR (ATR, neat) ν (cm^{-1}): 3060, 2958, 2931, 2872, 1747, 1641, 1584, 1478, 1463, 1361, 1284, 1191, 1135, 1109, 1047, 906, 814, 726, 695, 646.

MS (ESI+) m/z: 388 (100, $[M+H]^+$), 370 (20), 148 (20).

HRMS (ESI+) m/z: 388.1920 calcd for $C_{25}H_{25}NO_3 + H^+$: 388.1913.

(Z)-benzyl (1-(naphthalen-1-yl)-3-oxohept-1-en-1-yl)carbamate (3.87)



$C_{25}H_{25}NO_3$

387.47 g.mol^{-1}

Pale yellow oil

The compound **3.87** was prepared according to the previously described general procedure C starting from benzyl (1-(naphthalen-1-yl)hept-2-yn-1-yl)(hydroxy)carbamate **3.58**. Purified by flash chromatography on silica gel (pentane/Et_2O: 92/8). **Yield: 29%**

R_f (silica, pentane/Et_2O: 9/1) = 0.4 (UV/PMA/Vanillin)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (t, *J* = 7.2 Hz, 3H, H_1), 1.32 - 1.44 (m, 2H, H_2), 1.60 - 1.68 (m, 2H, H_3), 2.48 (t, J = 7.2 Hz, 2H, H_4), 4.92 (s, 2H, H_{18}), 5.59 (s, 1H, H_6), 7.15 - 7.21 (m, 2H, H_{Ar}), 7.27 - 7.32 (m, 3H, H_{Ar}), 7.40 (dd, *J* = 1.1 Hz and *J* = 7.1 Hz, 1H, H_9), 7.45 - 7.54 (m, 3H, H_{Ar}), 7.81 - 7.94 (m, 3H, H_{Ar}), 12.05 (brs, 1H, NH).

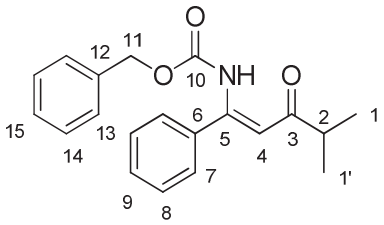
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9 (C_1), 22.4 (C_2), 26.8 (C_3), 43.4 (C_4), 67.3 (C_{18}), 107.0 (C_6), 124.4 (C_{Ar}), 124.9 (C_{Ar}), 125.3 (C_{Ar}), 126.0 (C_{Ar}), 126.7 (C_{Ar}), 128.1 (2C, C_{Ar}), 128.2 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.5 (C_{Ar}), 129.4 (C_{Ar}), 131.0 (C_q, C_{Ar}), 132.9 (C_q, C_{Ar}), 133.7 (C_q, C_{Ar}), 135.3 (C_q, C_{Ar}), 152.0 (C_q, C_{Ar}), 153.4 (C_q, C_{Ar}), 202.9 (C_5).

IR (ATR, neat) ν (cm^{-1}): 3062, 2957, 2930, 2871, 1754, 1642, 1591, 1575, 1477, 1286, 1200, 1179, 1140, 1092, 801, 776, 697.

MS (ESI+) m/z: 388 (100, $[M+H]^+$), 344 (10), 320 (15), 288 (25), 214 (10), 187 (10).

HRMS (ESI+) m/z: 388.1920 calcd for $C_{25}H_{25}NO_3 + H^+$: 388.1913.

(Z)-benzyl (4-methyl-3-oxo-1-phenylpent-1-en-1-yl)carbamate (3.92)



$C_{20}H_{21}NO_3$

323.39 g.mol^{-1}

Pale yellow oil

The compound **3.92** was prepared according to the previously described general procedure C starting from benzyl hydroxy(4-methyl-1-phenylpent-2-yn-1-yl)carbamate **3.63**. Purified by flash chromatography on silica gel (Pentane/Et_2O: 92/8). **Yield: 63%**

R_f (silica, pentane/Et_2O: 9/1) = 0.4 (UV/PMA/Vanillin)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.15 (d, *J* = 7.2 Hz, 6H, H_1 and $H_{1'}$), 2.65 (sept., *J* = 7.2 Hz, 1H, H_2), 5.08 (s, 2H, H_{11}), 5.61 (s, 1H, H_4), 7.27 - 7.48 (m, 10H, H_{Ar}), 11.61 (brs, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.7 (2C, C_1 and $C_{1'}$), 40.3 (C_2), 66.4 (C_{11}), 104.9 (C_4), 126.5 (2C, C_{Ar}), 127.0 (2C, C_{Ar}), 127.2 (2C, C_{Ar}), 127.3 (C_{Ar}), 127.5 (2C, C_{Ar}), 128.7 (C_{Ar}), 135.5 (C_q, C_{Ar}), 135.7 (C_q, C_{Ar}), 151.8 (C_q, C_{Ar}), 154.1 (C_q, C_{Ar}), 205.1 (C_3).

IR (ATR, neat) ν (cm-1): 3065, 3034, 2969, 2872, 1749, 1639, 1604, 1587, 1573, 1495, 1462, 1286, 1194, 1174, 1129, 1069, 1048, 906, 726, 694.

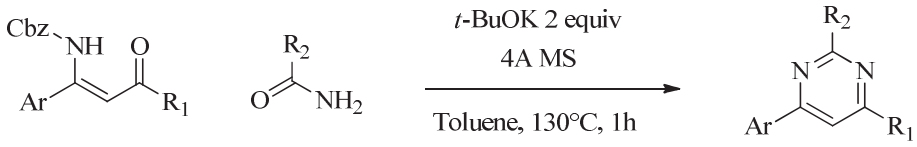
MS (ESI+) m/z: 647 (5, $[2M+H]^+$), 324 (100, $[M+H]^+$), 306 (50), 280 (45), 262 (10).

HRMS (ESI+) m/z: 324.1599 calcd for $C_{20}H_{21}NO_3 + H^+$: 324.1600.

Pyrimidines

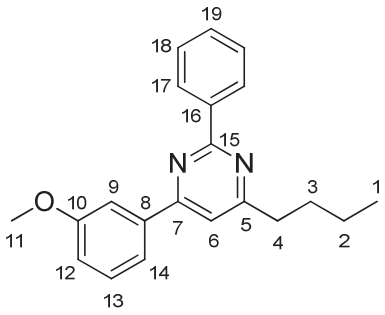
General procedure D

for the preparation of pyrimidines (3.149 - 3.163)



In a 5mL Wheaton® reactor (screw top V-Vials® with open-top cap) equipped with a magnetic stirrer bar, the corresponding vinylogous amide (0.2 mmol, 1 equiv), the corresponding amide (0.3 mmol, 1.5 equiv), 4 Å MS (70 mg) and potassium tert-butoxide (0.4 mmol, 2 equiv) toluene (2 mL) were introduced by turn and the mixture was heated at 130 °C for 1h. The reaction mixture was then filtered through a silica gel pad and eluted with ethyl acetate. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel to give the corresponding pyrimidine.

4-butyl-6-(3-methoxyphenyl)-2-phenylpyrimidine (3.155)



$C_{21}H_{22}N_2O$

318.41 g.mol^{-1}

Pale yellow oil

The compound **3.155** was prepared according to the previously described general procedure D starting from (Z)-benzyl (1-(3-methoxyphenyl)-3-oxohept-1-en-1-yl)carbamate **3.54** and benzamide. Purified by flash chromatography on silica gel (petroleum ether/Et_2O: 97/3). **Yield: 62%**

R_f (silica, pentane/Et_2O: 95/5) = 0.6 (UV/Vanillin)

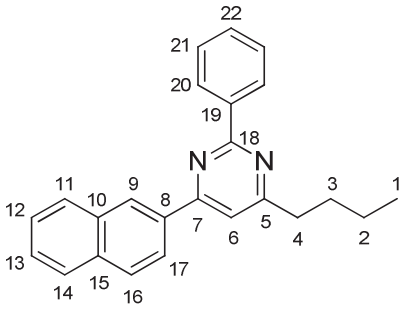
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.01 (t, *J* = 7.6 Hz, 3H, H_1), 1.43 - 1.54 (m, 2H, H_2), 1.82 - 1.91 (m, 2H, H_3), 2.89 (t, *J* = 7.6 Hz, 2H, H_4), 3.94 (s, 3H, H_{11}), 7.07 (dd, *J* = 2.5 Hz and *J* = 8.2 Hz, 1H, H_{12}), 7.42 - 7.47 (m, 2H, H_9 and H_{14}), 7.48 - 7.56 (m, 3H, H_{Ar}), 7.77 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 7.84 (brs, 1H, H_{Ar}), 8.60 - 8.65 (m, 2H, H_{17}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9 (C_1), 22.5 (C_2), 30.9 (C_3), 37.9 (C_4), 55.4 (C_{11}), 112.6 (C_{Ar}), 113.5 (C_{Ar}), 116.1 (C_{Ar}), 119.5 (C_{Ar}), 128.3 (2C, C_{Ar}), 128.4 (2C, C_{Ar}), 129.8 (C_{Ar}), 130.4 (C_{Ar}), 138.2 (C_q, C_{Ar}), 138.9 (C_q, C_{Ar}), 160.1 (C_q, C_{Ar}), 163.4 (C_q, C_{Ar}), 164.1 (C_q, C_{Ar}), 171.6 (C_q, C_{Ar}).

IR (ATR, neat) ν (cm^{-1}): 3066, 2955, 2930, 2870, 1587, 1568, 1531, 1463, 1368, 1253, 1045, 858, 756, 691, 673, 636.
MS (ESI+) m/z: 319 (100, $[M+H]^+$).
HRMS (ESI+) m/z: 319.1805 calcd for $C_{21}H_{22}N_2O + H^+$: 319.1810.

4-butyl-6-(naphthalen-2-yl)-2-phenylpyrimidine (3.156)



$C_{24}H_{22}N_2$

338.44 g.mol^{-1}

Yellow oil

The compound **3.156** was prepared according to the previously described general procedure D starting from (Z)-benzyl (1-(naphthalen-2-yl)-3-oxohept-1-en-1-yl)carbamate **3.57** and benzamide. Purified by flash chromatography on silica gel (Petroleum ether/Et_2O: 98/2). **Yield: 57%**

R_f (silica, pentane/Et_2O: 95/5) = 0.8 (UV/Vanillin)

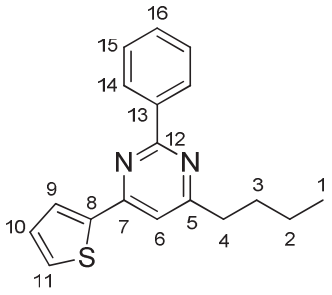
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.04 (t, *J* = 7.6 Hz, 3H, H_1), 1.46 - 1.57 (m, 2H, H_2), 1.85 - 1.95 (m, 2H, H_3), 2.93 (t, *J* = 8.0 Hz, 2H, H_4), 7.50 - 7.62 (m, 6H, H_{Ar}), 7.89 - 8.05 (m, 3H, H_{Ar}), 8.35 (d, *J* = 8.4 Hz, 1H, H_9), 8.66 - 8.74 (m, 3H, H_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.0 (C_1), 22.5 (C_2), 31.0 (C_3), 38.0 (C_4), 113.6 (C_6), 124.2 (C_{Ar}), 126.4 (C_{Ar}), 127.1 (C_{Ar}),127.2 (C_{Ar}), 127.7 (C_{Ar}), 128.3 (2C, C_{Ar}), 128.4 (2C, C_{Ar}), 128.5 (C_{Ar}), 128.9 (C_{Ar}), 130.4 (C_{Ar}), 133.3 (C_q, C_{Ar}), 134.5 (C_q, C_{Ar}), 134.7 (C_q, C_{Ar}), 138.3 (C_q, C_{Ar}), 163.5 (C_q, C_{Ar}), 164.3 (C_q, C_{Ar}), 171.6 (C_q, C_{Ar}).

IR (ATR, neat) ν (cm^{-1}): 3060, 2954, 2927, 2858, 1587, 1568, 1531, 1373; 1173, 854, 817, 758, 694, 656.
MS (ESI+) m/z: 339 (100, $[M+H]^+$).
HRMS (ESI+) m/z: 339.1861 calcd for $C_{24}H_{22}N_2 + H^+$: 339.1861.

4-butyl-2-phenyl-6-(thiophen-2-yl)pyrimidine (3.157)



$C_{18}H_{18}N_2S$

294.41 g.mol^{-1}

Yellow oil

The compound **3.157** was prepared according to the previously described general procedure D starting from (Z)-benzyl (3-oxo-1-(thiophen-2-yl)hept-1-en-1-yl)carbamate **3.56** and benzamide. Purified by flash chromatography on silica gel (Pentane/Et_2O: 98/2). **Yield: 52%**

R_f (silica, pentane/Et_2O: 95/5) = 0.7 (UV/Vanillin)

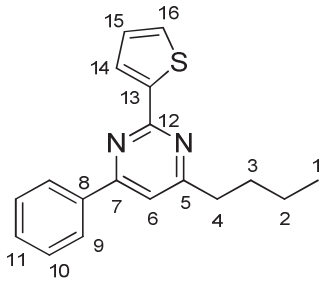
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (t, *J* = 7.2 Hz, 3H, H_1), 1.42 - 1.52 (m, 2H, H_2), 1.79 - 1.88 (m, 2H, H_3), 2.85 (t, *J* = 8 Hz, 2H, H_4), 7.17 (dd, *J* = 3.9 Hz and *J* = 4.8 Hz, 1H, H_{10}), 7.30 (s, 1H, H_6), 7.44 - 7.56 (m, 4H, H_{Ar}), 7.82 (d, *J* = 3.2 Hz, 1H, H_{Ar}), 8.57 (dd, *J* = 1.9 Hz and *J* = 7.6 Hz, 2H, H_{14}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9 (C_1), 22.5 (C_2), 30.9 (C_3), 37.8 (C_4), 111.5 (C_6), 126.8 (C_{Ar}), 128.1 (C_{Ar}), 128.3 (2C, C_{Ar}), 128.4 (2C, C_{Ar}), 129.5 (C_{Ar}), 130.4 (C_{Ar}), 137.8 (Cq, C_{Ar}), 143.3 (C_q, C_{Ar}), 158.7 (C_q, C_{Ar}), 164.1 (C_q, C_{Ar}), 171.4 (C_q, C_{Ar}).

IR (ATR, neat) ν (cm^{-1}): 2955, 2927, 2858, 1720, 1588, 1570, 1528, 1432, 1373, 1269, 1235, 1172, 1026, 856, 756, 694.
MS (ESI+) m/z: 295 (100, $[M+H]^+$).
HRMS (ESI+) m/z: 295.1261 calcd for $C_{18}H_{18}N_2S + H^+$: 295.1269.

4-butyl-6-phenyl-2-(thiophen-2-yl)pyrimidine (3.158)



$C_{18}H_{18}N_2S$

294.41 $g.mol^{-1}$

Pale yellow oil

The compound **3.158** was prepared according to the previously described general procedure D starting from (Z)-benzyl(3-oxo-1-phenylhept-1-en-1-yl)carbamate **3.47** and 2-thiophenecarboxamide. Purified by flash chromatography on silica gel (pentane/Et_2O: 97/3). **Yield: 60%**

R_f (silica, pentane/Et_2O: 95/5) = 0.75 (UV/Vanillin)

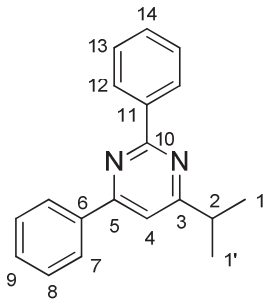
Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (t, *J* = 7.6 Hz, 3H, H_1), 1.42 - 1.52 (m, 2H, H_2), 1.78 - 1.88 (m, 2H, H_3), 2.84 (t, *J* = 7.6 Hz, 2H, H_4), 7.17 (dd, *J* = 3.7 Hz and *J* = 5.0 Hz, 1H, H_{15}), 7.37 (s, 1H, H_6), 7.48 (dd, *J* = 1.2 Hz and *J* = 5.0 Hz, 1H, H_{16}), 7.50 - 7.56 (m, 3H, H_{Ar}), 8.14 (dd, *J* = 1.2 Hz and *J* = 3.6 Hz, 1H, H_{14}), 8.17 - 8.21 (m, 2H, H_9).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9 (C_1), 22.4 (C_2), 30.8 (C_3), 37.7 (C_4), 112.8 (C_6), 127.1 (2C, C_{Ar}), 128.0 (C_{Ar}), 128.6 (C_{Ar}), 128.8 (2C, C_{Ar}), 129.3 (C_{Ar}), 130.6 (C_{Ar}), 137.0 (C_q, C_{Ar}), 144.2 (C_q, C_{Ar}), 161.1 (C_q, C_{Ar}), 163.6 (C_q, C_{Ar}), 171.7 (C_5).

The spectral data are consistent with those of the literature.

4-isopropyl-2,6-diphenylpyrimidine (3.162)



$C_{19}H_{18}N_2$

274.36 g.mol^{-1}

Pale yellow oil

The compound **3.162** was prepared according to the previously described general procedure D starting from (Z)-benzyl (4-methyl-3-oxo-1-phenylpent-1-en-1-yl)carbamate **3.63** and benzamide. Purified by flash chromatography on silica gel (Pentane/Et_2O: 98/2). **Yield: 71%**

R_f (silica, pentane/Et_2O: 95/5) = 0.8 (UV/Vanillin)

Spectral Data

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.44 (t, *J* = 6.8 Hz, 6H, H_1 and $H_{1'}$), 3.15 (sept., *J* = 6.8 Hz, 1H, H_2), 7.48 (s, 1H, H_4), 7.49 - 7.58 (m, 6H, H_{Ar}), 8.24 (dd, *J* = 2.0 Hz and *J* = 8.0 Hz, 2H, H_7), 8.66 (dd, *J* = 2.0 Hz and *J* = 8.0 Hz, 2H, H_{12}).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.9 (2C, C_1 and $C_{1'}$), 36.3 (C_2), 111.5 (C_4), 127.2 (C_{Ar}, 2C), 128.4 (C_{Ar}, 4C), 128.8 (C_{Ar}, 2C), 130.3 (C_{Ar}), 130.5 (C_{Ar}), 137.6 (C_q, C_{Ar}), 138.3 (C_q, C_{Ar}), 163.9 (C_q, C_{Ar}), 164.0 (C_q, C_{Ar}), 176.3 (C_3).

IR (ATR, neat) ν (cm^{-1}): 2961, 2924, 2866, 1590, 1568, 1531, 1496, 1373, 756, 692, 633.

MS (ESI+) m/z: 275 (100, $[M+H]^+$).

HRMS (ESI+) m/z: 275.1551 calcd for $C_{19}H_{18}N_2 + H^+$: 275.1548.

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