Synthesis of *N*-Heterocycles via Intramolecular Reductive Cyclizations of ω-Nitroalkenes

Dissertation zur Erlangung des Doktorgrades der Naturwissenschaften (Dr. rer. nat.)

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Die vorliegende Arbeit wurde unter der Leitung von Herrn Prof. Dr. Uwe Beifuss am Institut für Chemie der Universität Hohenheim in der Zeit von Januar 2004 bis Januar 2007 durchgeführt.

I wish to express my sincere gratitude and appreciation to *Prof. Dr. Uwe Beifuss* for his supervision, invaluable support and encouragement throughout this research. Without his advice and endless interest, this study could not have been carried out and completed.

To my parents!

PRELMINARY REMARKS

The work presented in this thesis was carried out under the supervision of Prof. Dr. Uwe Beifuss at the Institute of Chemistry, University of Hohenheim, from January 2004 to January 2007. Parts of the results have already been published in international peer reviewed journals:

1a ELENA MERIŞOR, JÜRGEN CONRAD, IRIS KLAIBER, SABINE MIKA, UWE BEIFUSS "Triethyl phosphite-mediated domino reaction: direct conversion of ω-nitroalkenes into *N*-heterocycles"
Angew. Chem. Int. Ed. **2007***, 46,* 3353–3355.

1b ELENA MERIŞOR, JÜRGEN CONRAD, IRIS KLAIBER, SABINE MIKA, UWE BEIFUSS "Triethylphosphit-vermittelte Dominoreaktion: Direkte Umwandlung von ω-Nitroalkenen in *N*-Heterocyclen"
Angew. Chem. **2007***, 119,* 3417–3419.

2 ELENA MERIŞOR, JÜRGEN CONRAD, SABINE MIKA and UWE BEIFUSS
"Microwave-assisted reductive cyclization of *N*-allyl 2-nitroanilines. A new approach to substituted 1,2,3,4-tetrahydroquinoxalines"
Synlett **2007**, 2033–2036.

3 ELENA MERIŞOR and UWE BEIFUSS
"From the study of naturally occurring *N*-allylated phenazines towards new Pd-mediated transformations"
Tetrahedron Lett. **2007**, *48*, 8383–8387.

4 MARIO TIETZE, ALBERTO IGLESIAS, ELENA MERIŞOR, JÜRGEN CONRAD, IRIS KLAIBER and UWE BEIFUSS
"Efficient methods for the synthesis of 2-hydroxyphenazine based on the Pd-catalyzed N-arylation of aryl bromides"
Org. Lett. **2005**, *7*, 1549–1552.

or have been presented at international (or national) scientific conferences:

1 ELENA MERIŞOR and UWE BEIFUSS
"Microwave assisted cyclization of allyl 2-nitrophenyl ethers – synthesis of 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines"
XXII EUROPEAN COLLOQUIUM on HETEROCYCLIC CHEMISTRY, Bari (Italy), 2–6 Sept. **2006**.

2 ELENA MERIŞOR
"Microwave assisted cyclization of allyl 2-nitrophenyl ethers – synthesis of 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines"
11. TAG der ORGANISCHEN CHEMIE, Stuttgart (Germany), 13 Oct. **2006**.

3 ELENA MERIŞOR, CHANDI C. MALAKAR and UWE BEIFUSS
"Microwave assisted cyclization of ω-nitroalkenes – synthesis of saturated *N*-heterocycles"
GDCH, Ulm (Germany), 16–19 Sept. **2007**.

Organization of the Dissertation:

The dissertation is divided into 9 chapters:

Chapter **1** presents an introduction into nitroaromatic compounds and their importance.
Chapter **2** is subdivided into four parts and describes the deoxygenation reaction of nitro-aromatic compounds and the synthesis of various *N*-heterocycles.
Chapter **3** presents the aim of the presented work.
Chapter **4** describes a new domino reaction of ω-nitroalkenes mediated by triethyl phosphite and the synthesis of substituted 3,4-dihydro-2*H*-1,4-benzoxazines; it is identical with the articles published in *Angew. Chem. Int. Ed.* **2007**, *46*, 3353–3355, respectively in *Angew. Chem.* **2007**, *119*, 3417–3419, including an experimental part as supporting information.

Chapter **5** is in form identical with publication no. 2 and is focused on the synthesis of 1,2,3,4-tetrahydroquinoxalines as an application of the newly developed domino reaction.
Chapter **6** is identical with publication no. 3 and concerns the synthesis of different saturated *N*-heterocycles via palladium-catalyzed *N*-heteroannulation of nitroaromatics in the presence of carbon monoxide.
Chapter **7** shows the final overview of the work in English.
Chapter **8** gives the final overview of the work in German.
Chapter **9** presents all the citations used for preparing this thesis.

Chemical structures are numbered consecutively, the designation of the cross-links has been unified as the references, too.

Concerning the co-authors:

Prof. Dr. Uwe Beifuss was the supervisor of this work and was always available for scientific discussions. He was involved in preparing the manuscripts throughout the whole process of publication and was responsible for all aspects of publication and is the corresponding author of all publications.

Dr. Jürgen Conrad advised on all analytical processes, assisted in the interpretation of spectral data and was always available for scientific discussions. He measured all of the NMR samples on the 500 MHz Varian ^{Unity}Inova.

Sabine Mika measured all NMR samples on the 300 MHz Varian ^{Unity}Inova. She was also always open for scientific discussions.

Iris Klaiber measured all samples for MS, HR-MS and GC-MS spectra and assisted in the interpretation of spectral data; she was also always available for scientific discussions.

TABLE OF CONTENTS

1 INTRODUCTION

Heterocycles and implicit *N*-heterocycles are very important organic compounds and are becoming ever more important in all aspects of pure and applied chemistry. Isolation from natural sources, development of new synthetic methodology or finding modern applications of many heterocycles in chemistry, the pharmaceutical field, medicine or industry are subjects intensively studied and described by chemists, biologists and researchers. Heterocycles are not only very abundant in organic chemistry, but are also important for their chemical, biological and technological significance.

There is a vast number of heterocycles, many of them being natural products or known as vitamins, antibiotics, alkaloids, hormones, drugs, dyes, herbicides, stabilizing agents, corrosion inhibitors, sensitizers. Synthesis of heterocycles and *N*-heterocycles is a challenging target for every researcher. Sources for the synthesis of *N*-heterocycles can be nitro compounds, amino compounds, nitriles or their derivatives containing a nitrogen atom.

Nitroaromatics have a remarkable synthetic importance and their utilization in organic synthesis as useful starting materials for the preparation of various *N*-heterocycles has been intensively studied by chemists. Historically, they are known as explosives (especially aromatic nitro compounds), propellants and precursors of azo dyes. At the same time, they are very important reagents for the synthesis of complex target molecules. Nitroaromatics form an important group of recalcitrant xenobiotics. Only few aromatic compounds, bearing one nitro group as substituent on the aromatic ring, are produced as secondary metabolites by micro-organisms. However, relatively few micro-organisms have been described as being able to use nitroaromatic compounds as a nitrogen and /or carbon and energy source. The majority of the nitroaromatics in the biosphere are industrial chemicals such as explosives, dyes, polyurethane foams, herbicides, insecticides and solvents.

Many organic reactions are carried out by exploiting the activating effect of the nitro group. Because of its facile transformation into various functional groups, the importance of nitro compounds in the synthesis of complex molecules has been widely extended. Aromatic nitro compounds are good precursors to introduce such nitrogen substituents as NH_2, CN or to the generation of such highly active intermediates as the nitrenes; this is the reason why they are frequently used as starting material for synthesizing a large variety of *N*-heterocycles.

As far as the chemistry of the nitroaromatics is concerned, all its aspects have been extensively debated – including the chemical, physical and spectroscopic features, as well as the synthetic properties and their theoretical study.

So far, reductive cyclizations of nitroaromatics have been predominantly employed to synthesize indoles, carbazoles and related *N*-heteroaromatics.[1a] The best known methods include the synthesis of indoles according to Leimgruber-Batcho, Bartoli, Reissert,[1b] the Cadogan cyclization and the transition metal catalyzed reductive *N*-heteroannulation of *o*-nitrostyrenes.[1c]

2 DEOXYGENATION AND HETEROANNULATION OF NITROAROMATICS

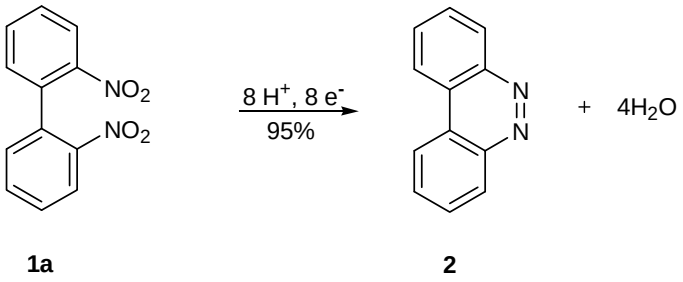
The deoxygenation and heteroannulation of nitroaromatics to various *N*-heterocycles has been known since 1898, using mono- or dinitroaromatics and it can take place in a single or in two steps.[2] A variety of reducing agents have been used, different reaction mechanisms have been taken into consideration, different theories have been proposed and different reactive intermediates have been suggested. A classification of the deoxygenation and cyclization of nitroaromatics reactions can be made, starting with the early studies regarding the use of reducing agents, then the decade during which tervalent phosphorous reagents were used, followed by the current decade, when metal catalysts are used.

2.1 Early stage-intramolecular cyclization of nitroaromatics

One of the earliest methods of synthezising *N*-heterocycles is the *N*-heteroannulation of ω-nitroketones under reductive conditions, first reported by Störmer and Brockerhof.[2] Depending on the reaction conditions and substrates, the cyclization of ω-nitroketones was realized in a one-step reaction using reducing agents such as Sn or $SnCl_2$/HCl.

It has been assumed that the nitro group was reduced to the amino group. The addition of the amino group to the carbonyl group is then followed by an intramolecular ring closure occurring with the elimination of water; the imine intermediate was reduced to the corresponding amine under the reaction conditions.[2]

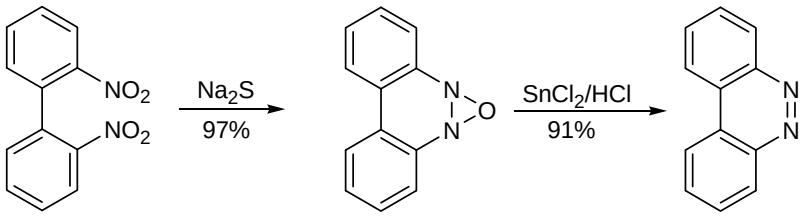
Wohlfart[3] has described the one stage *N*-heteroannulation of 2,2'-dinitrodiphenyl **1a** by electrolytic reduction to yield 3,4-benzocinnoline **2** (Eq 1).



1a **2**

Equation 1 Cyclization of 2,2'-dinitrodiphenyl **1a** by electrolytic reduction.

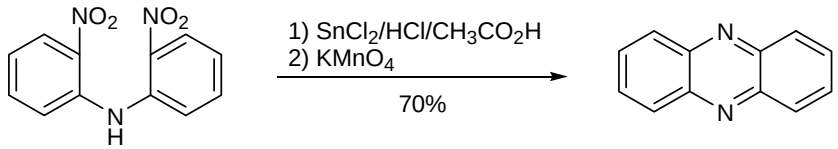
Unlike Wohlfart, Ullmann[4] and King[5] described the synthesis of 3,4-benzocinnoline **2** by a two stage reduction of 2,2'-dinitrodiphenyl **1a** involving 3,4-benzocinnoline *N*-oxide **3** as intermediate. The first reduction step to the 3,4-benzocinnoline *N*-oxide **3** was carried out with sodium sulphide (Na_2S) and then the intermediate, 3,4-benzocinnoline *N*-oxide **3** was reduced with stannous chloride in acidic conditions (or by electrochemical reduction) to the final product (Scheme 1).[4]



1a **3** **2**

Scheme 1 The two step cyclization of 2,2'-dinitrodiphenyl **1a** via 3,4-benzocinnoline *N*-oxide **3**.

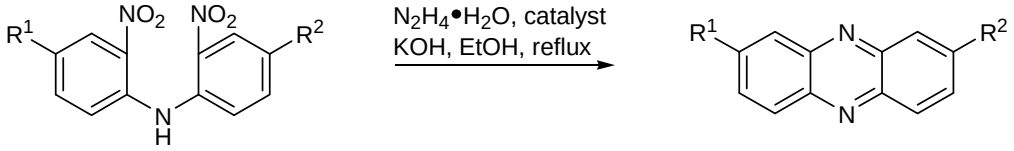
Similar results were also reported by Thomson[6] who used Zn dust and acetic acid as reducing agents during the second step; lithium aluminium hydride was also used to perform both reductions, including the reduction step of the intermediate 3,4-benzocinnoline *N*-oxide **3** to the final product **2**. Eckert and Steiner[7a] studied the cyclization reaction of 1,1'-nitroanthrimide; they concluded that, as regards reduction in basic conditions, oxyanthrimide was formed via ammonia elimination, while in acidic conditions, indanthrene derivatives were formed. Eckert and Steiner[7b] also synthesized phenazine **4a** using 2,2'-dinitrodiphenyl amine **5a** as starting material (Eq 2). 2,2'-Dinitrodiphenyl amine **5a** was first reduced with stannous chloride ($SnCl_2$) and then the resulting reaction mixture oxidized with hydrogen peroxide or other oxidative reagents ($KMnO_4$, $FeCl_3$, MnO_2); 2,2'-diaminodiphenyl amine has not been isolated.



5a **4a**

Equation 2 Cyclization of 2,2'-dinitrodiphenyl amine **5a** to phenazine **4a**.

The one-step reductive cyclization of substituted 2,2'-dinitrodiphenyl amines **5a**,**b** under mild reduction conditions[8] in alkaline media yields phenazine derivatives **4a**,**b** (Eq 3).
Ru/C[8] or Raney-Ni[8, 9] were used as catalysts. 1,6-Dimethoxy-phenazines[10, 11] have been prepared in a similar way.

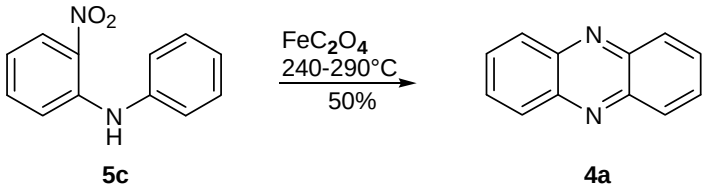


5a ($R^1 = R^2 = H$) 5% Ru/C **4a** 40%
5b (R^1 = Cl, R^2 = H) 5% Ru/C or Raney-Ni **4b** 74-76%

Equation 3 Synthesis of phenazines **4a**,**b** via one step intramolecular cyclization.

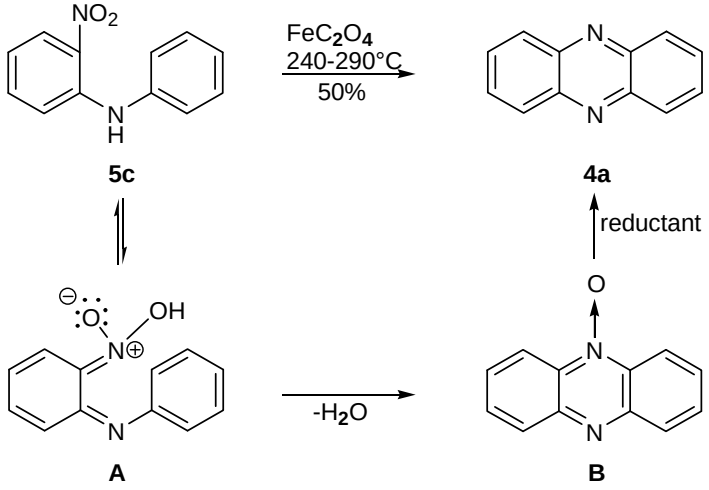
Tomlinson[12] described the formation of phenazines via a two-stage reaction, through the reduction of the nitro compound with zinc dust and acetic acid (Zn/CH_3CO_2H) and then the oxidation of the resulting solution with mild oxidising agents such as $FeCl_3$ or H_2O_2.
Waterman and Vivian[13] first suggested the possibility of synthesizing an *N*-heterocycle by acting on a nitro compound in order to obtain the direct ring closure, using the method for the preparation of phenazines developed by Heiler[14]. The deoxygenation of nitroaromatics described by Waterman and Vivian was realized using reducing agents such as metallic iron[13] or FeC_2O_4 and granulated lead[15-17] and it was the most widely used method to synthesize phenazines. The conclusion was that the entire procedure of reduction of the 2-nitrodiphenyl amine **5c** to the amino compound followed by oxidation of the primary amino group to the phenazine ring can be replaced by a new reaction: a reduction of the nitro group which offers no possibility for amine formation, which, however, under the reaction conditions results in direct ring closure. Phenazines were obtained from 2-nitrodiphenyl amine **5c** by reductive cyclization with Fe or FeC_2O_4.[13]

The reaction takes place easily and the products are quite stable so that different reductants with a wide activity range allow the formation of phenazine **4a** (Eq 4) and of some of its substitution products. Yields as high as 50% were obtained.



Equation 4 One step cyclization reaction of 2-nitrodiphenyl amine **5c** to phenazine **4a**.

No dihydrophenazines were detected as intermediates and there is reasonable doubt that this type of deoxygenation reaction of nitroaromatics actually involves a nitrene intermediate. The mechanism of the reaction has been widely discussed.[18-20] Suschitzky[19a] suggested an uncatalyzed cyclization reaction via an *aci*-form (**A**) of the nitroderivative, which then eliminates water. The formed *N*-oxide intermediate (**B**) is reduced further to the final product (Scheme 2).

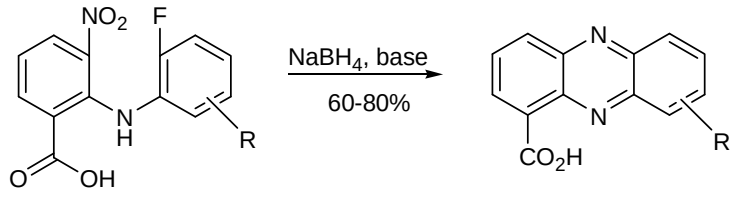


Scheme 2 The proposed mechanism for the phenazine **4a** synthesis.

Smolinsky[19b] proposed that nitroaromatics in diphenylether or in the presence of FeC_2O_4 follow the *aci*-form route. It seems that even in the absence of FeC_2O_4, nitroaromatics capable of forming *aci*-form cyclize by this route with water elimination. The conclusion was that deoxygenation of nitroaromatics via FeC_2O_4 does not involve a nitrene intermediate.

Substituents on the same ring as the nitro group are not affected but the substituents in the second benzene ring are frequently eliminated during the cyclization.[19-23] Other reducing reagents were used for the reductive cyclization reaction, e.g. $NaBH_4$[24, 25] or sulphur,[23]

oleum[8, 26] or KOH[8, 27] to give phenazines or phenazine *N*-oxides. Reductive cyclizations of 2-nitrodiphenylamines have been achieved in alkaline and acidic media and can also occur via the replacing of nucleophiles via aromatic nucleophilic substitution. The reductive cyclization of substituted *N*-(2'-fluorophenyl)-3-nitroanthranilic acids **5d** under alkaline conditions provides a synthetic route by reductive ring closure exclusively to the fluoro-substituted carbon to yield 6-, 8-, and 9-substituted phenazine-1-carboxylic acids in good yields (Eq 5). This ring closure occurs via S_NAr displacement of fluoride[28] using different bases (NaOMe, NaOEt, NaOH).



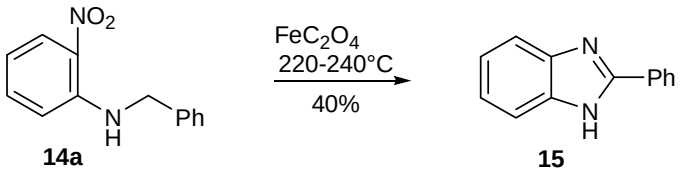
5d **4c**

Equation 5 One step cyclization of *N*-(2'-fluorophenyl)-3-nitroanthranilic acids **5d**.

The method of intramolecular cyclization of nitroaromatics in the presence of reducing agents ($LiAlH_4$, Ra-Ni/N_2H_4, Na_2S or Zn/NH_3) was extended to the preparation of heteroaromatic systems[6, 29, 30] of type **6-9** or **10-13** (Fig 1). Starting with the proper dinitroaromatics, the intramolecular cyclization reaction occurred in the presence of the reducing agents, yielding partly or completely reduced compounds **6-13**.[29, 30]

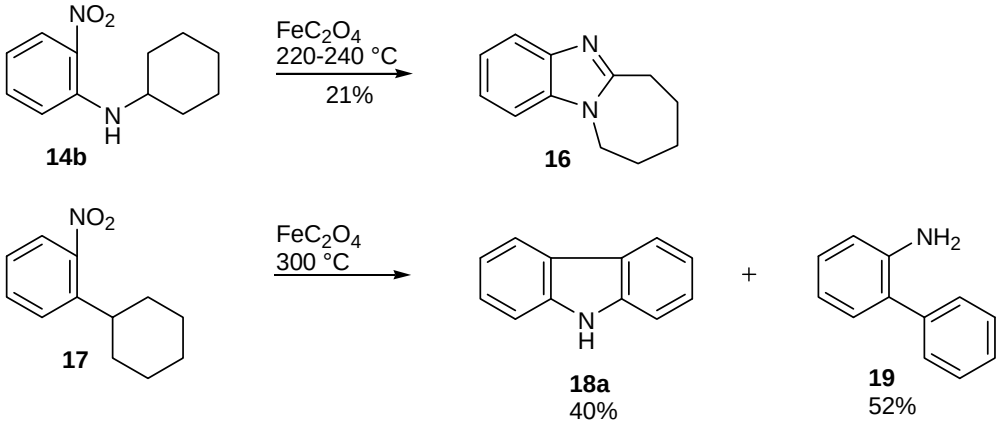
Figure 1 The structures of *N*-heterocycles **6-13** synthesized via cyclization of dinitroaromatics.

o-Nitroanilines with at least one methylene or methine group attached to the basic nitrogen also lead to a reductive cyclization reaction.[19] The pyrolysis of this type of compounds produced partly reduced heteroaromatic systems. Cyclization to a saturated C-H bond takes place in the presence of FeC_2O_4 at high temperatures, when *N*-benzyl-2-nitroaniline **14a** is converted to 2-phenylbenzimidazole **15** (Eq 6).



Equation 6 Pyrolysis of *N*-benzyl-2-nitroaniline **14a** to 2-phenylbenzimidazole **15**.

A ring expansion was observed in the case of *N*-cyclohexyl-*o*-nitroaniline **14b** that yields hexahydroazepino-1',2'-1,2-benzimidazole **16** by deoxygenation, while 2-cyclohexyl-1-nitro-benzene **17** gives carbazole **18a** and the 2-amino biphenyl **19**[19b] (Scheme 3).



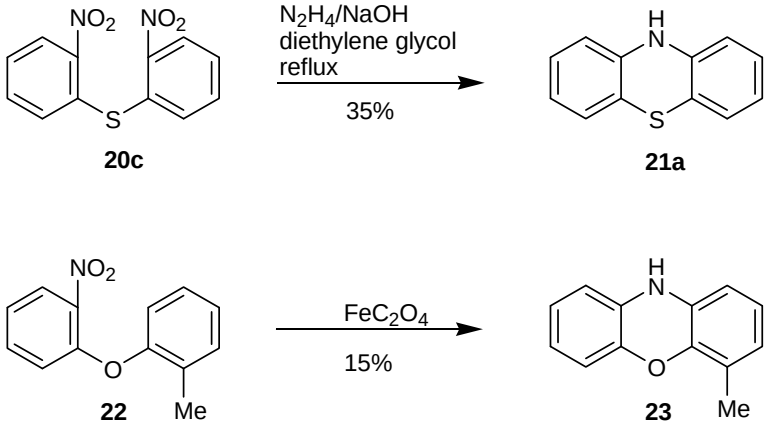
Scheme 3 Deoxygenations of nitroaromatics **14b** and **17** using FeC_2O_4 as a reductive reagent.

The deoxygenation of 2-cyclohexyl-1-nitrobenzene **17** was realized in the presence of ferrous oxalate[13] at a higher temperature. Probably the oxidation of the cyclohexyl group to a phenyl group and aromatization undergoes at such a high temperature and precedes cyclization[19b] (*o*-aminobiphenyl is known to undergo thermal conversion to carbazole[19c]). It should be noted that carbazole **18a** was also formed in 27% yield, in the absence of ferrous oxalate.

A mechanism was formulated by loss of one molecule of water from the nitro compound, probably reacting in its *aci*-form to give an intermediate *N*-oxide. The Wohl-Aue reaction[31] (phenazine *N*-oxides are obtained by heating anilines with nitrobenzenes) displays a compelling similarity. On this account, the function of the reductant, is to act as an oxygen acceptor converting the *N*-oxide into the final product.[19] This type of reaction can lead to the generation of nitrenes, as transitory reactive reaction intermediates. Probably the first synthesis of nitrogen containing heterocycles wherein a nitrene intermediate was reported by Brown *et al*. in 1951.[32]

Loudon[33] *et al*. showed that quinolones and indole derivatives are formed readily by the interaction of aromatic nitro groups and *ortho*-side-chains. By contrast, the displacement of an *ortho*-substituent frequently occurs when a diaryl derivative containing two *ortho* nitro groups is reduced in an alkaline solution. 2,2-dinitrodiphenyl amine **5a** is converted to phenazine **4a** by sodium sulphide.[34] Similarly, phenothiazine **21a** is obtained from the reaction of 2,2'-dinitrodiphenyl sulphide **20c** with hydrazine in one step (Scheme 4).[35a]

4-Methylphenoxazine **23** was obtained from 4'-methyl-2-nitrodiphenyl ether **22** with ferrous oxalate.[35b]



Scheme 4 The synthesis of phenothiazine **21a** and 4-methylphenoxazine **23** via a one-step reaction.

As has already been shown, the reductive cyclization of nitroaromatics has been realized by a number of research groups, using several reducing agents, different reaction conditions and different nitroaromatic substrates. Therefore a large number of *N*-heterocycles were synthesized.

The phenazine class and their derivatives were definitely the most synthesized *N*-heterocycles, using the reductive methods on the available starting materials.

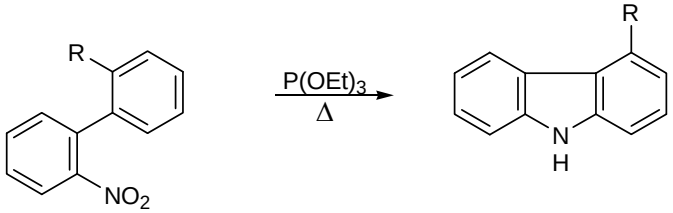
FeC_2O_4, the source of active ferrous oxide, was the most efficient and used reagent in the synthesis of *N*-heterocycles, especially in the synthesis of phenazine derivatives.

The oxidizing action of the nitro group, frequently a complicating factor in the reactions of nitrobenzene derivatives, takes effect in various ways. The centres which undergo oxidation may be contained totally or partly in the nitro compound or may be external to it: the nitro-group itself may be completely or partly reduced. When the nitro group and a suitable side-chain are *ortho* to each other, heterocyclic ring formation can occur. More commonly the ring formation occurs after the nitro group has been reduced (partly or totally).

2.2 Cyclization of nitroaromatics employing tervalent phosphorous reagents

During their investigations regarding the chemistry of tervalent phosphorus compound, Cadogan[36] *et al.* discovered that the nitroaromatics react with tervalent phosphorus compounds (trialkyl or triarylphosphines, trialkyl phosphites) to yield the corresponding quinquivalent phosphate derivatives, in which the nitro group is deoxygenated and a heterocyclic nitrogen ring is formed. The products derived from the reactions of nitroaromatics are similar to the products obtained from the thermal and photochemical reactions of azides and azirines.[37] Triethyl phosphite is the most commonly used deoxygenating reagent and solvent, while triphenyl phosphine, phosphorous trihalides, diethoxy methylphosphine have been used less frequently.[38] Depending on the structure of the substrate and reaction conditions, the deoxygenated fragments have also been isolated as azoxy compounds,[39, 40, 41] derivatives of phosphorimidic acid[39, 42] and as tars.[36b, 42] The deoxygenation of aromatic nitro compounds by trivalent phosphorous compounds has been extensively developed not only by Cadogan, but also by Sundberg.[43]

Sundberg demonstrated the close similarities between the azide decomposition and the deoxygenation of nitroaromatics. He concluded that a reactive electron deficient nitrogen atom develops at some stage during the deoxygenation of nitroaromatics. For the deoxygenation of nitroaromatics a variety of intermediates have been suggested, but the general conclusion was the fact that the product pattern is almost identical to that observed by decomposing azides and azirines. Since the discovery of the reaction in 1962, the reduction of nitro compounds by triethyl phosphite and related reagents has been recognised as a general route to a wide variety of nitrogen containing heterocycles including for example carbazoles[36, 44a] or benz[*a*]carbazoles.[44b, c] The deoxygenation of 2-nitrobiphenyl **1b** or 2'-bromo-2-nitrobiphenyl **1c** under reflux conditions with triethyl phosphite yielded carbazoles **18a**,**b**[36] (Eq 7). Functional groups such as esters, halides, alkyl and methoxy groups are tolerated under the reaction conditions and carbazoles are formed in good yields.[45]



1b R = H 83% **18a**
1c R = Br 77% **18b**

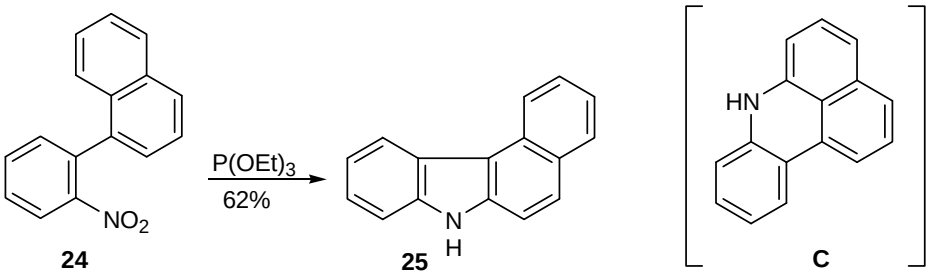
Equation 7 $P(OEt)_3$ mediated cyclizations of **1b**,**c** under thermal conditions.

A recent application of the Cadogan procedure using $P(OEt)_3$ and nitrobiaryls, is the synthesis of the tetracyclic pyridocarbazole alkaloid *ellipticine*[36c] which shows antitumor activity.

The reductive cyclization of 2-nitrobiphenyls to substituted carbazoles was also recently reported by Freeman[36d] *et al*, using a modified Cadogan procedure. Instead of triethyl phosphite, a slight excess of triphenylphosphine (PPh_3) was used as reducing agent in a suitable solvent as *o*-dichlorobenzene (*o*-DCB) at reflux (180 °C). This method avoids the formation of *N*-alkoxy or *N*-alkylated byproducts.[36b]

More recently[36e] another reductive cyclization method of 2-nitrobiphenyls to carbazoles has been reported, using triphenylphosphine as reducing agent in the presence of dichloro-dioxomolybdenum (VI) complex as catalyst. Good yields have been obtained using this method that tolerates a wide range of functional groups such as alkyls, ethers, carbonyls, halogens and carboxylic esters and also avoids the formation of *N*-alkylated[36b] side products.

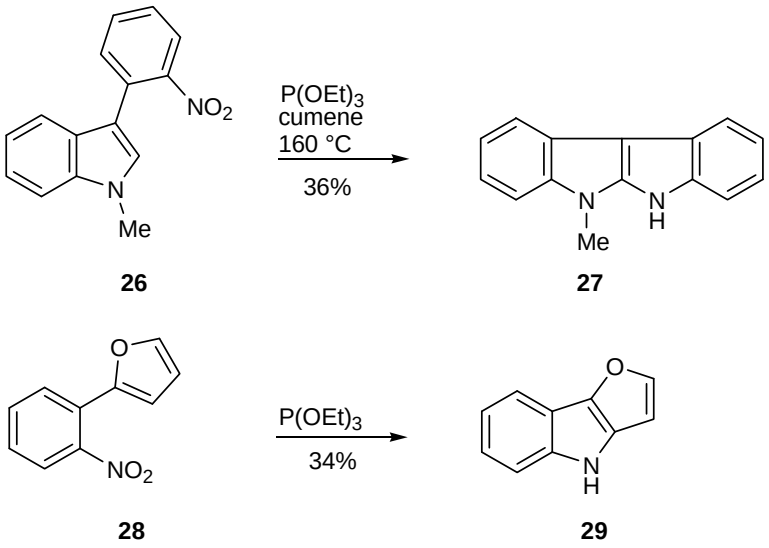
1-(2'-Nitrophenyl)naphthalene **24** which presents two possible sites of ring closure cyclized to [3,4]-benzocarbazole **25** (Eq 8). Heteroannulation to the 8-position of the naphthalene forming a six member ring benzacridine (**C**) was not observed.[36b]



24 **25** **C**

Equation 8 The synthesis of [3,4]-benzocarbazole **25**.

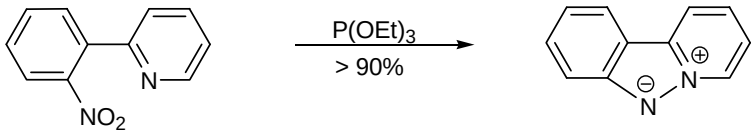
Heteroaromatic rings as furan, pyridine, indole and isoquinoline were used instead of a phenyl group, reacting in a similar way to *o*-nitrobiaryls. For example, indolo[2,3-*I*]indole[46] **27** and 4*H*-furo-[3,2-*b*]indole[47, 48] **29** have been prepared from the corresponding substrates via thermal deoxygenation by triethyl phosphite (Scheme 5).



26 **27** **28** **29**

Scheme 5 The synthesis of indolo[2,3-*l*]indole **27** and 4*H*-furo-[3,2-*b*]indole **29**.

From 2-*o*-nitrophenylpyridine **30** and 2 moles of triethyl phosphite under reflux conditions pyrido-[1,2-*b*]indazole **31**[36a] was obtained in over 90% yield, rather than the alternative product of ring closure, *δ*-carboline (Eq 9). The cyclization reaction occurred exclusively at the relatively electron-rich pyridine nitrogen atom presumably by the attack of an electron-deficient nitrogen intermediate. Such a ring closure at nitrogen in a conjugated *δ*-position has been exploited as a convenient route to indazoles and triazoles.[36b]

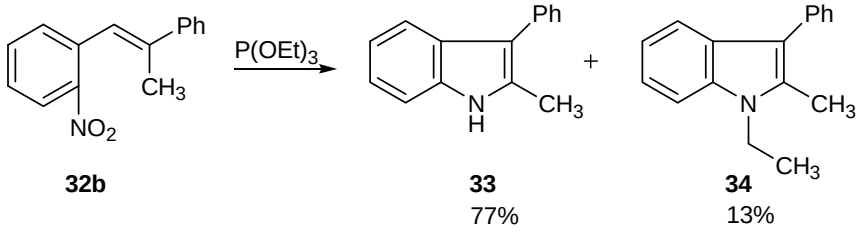


30 **31**

Equation 9 Synthesis of pyrido-[1,2-*b*]indazole **31**.

On the other hand 4-*o*-nitrophenylpyridine, via deoxygenation with triethyl phosphite in similar conditions, gives a ring closure at a C-atom of the benzene ring forming azacarbazole norharm (40% yield).[45a] A variety of indoles can be formed by the deoxygenation of *o*-nitrostyrenes using triethyl phosphite.[36a, 42, 45] For example, indole-2-carboxylates,[49] 2-cyanoindole,[50] and 2-(2-pyridyl)indole[51] have been prepared via thermal cyclization of nitroaromatics in the presence of triethyl phosphite. It was shown that both, *cis* and *trans*-2-nitrostilbene form 2-phenyl-indole.[36a, 42] Sundberg[52a] reported that deoxygenation of *β*,*β*-disubstituted *o*-nitrostyrenes with triethyl phosphite yields indole derivatives and might

give rise to rearranged deoxygenation products. The yields varied for the different nitrostyrenes, as did the nature of accompanying byproducts. In general, low to average yields of indoles are obtained from *β*,*β*-disubstituted *o*-nitrostyrenes. A study of the migratory aptitude was performed by Sundberg and Kotchmar.[52b] An example is the formation of 2-methyl-3-phenyl-indole **33**[52a] (Eq 10) from *α*-methyl-2'-nitrostilbene **32b** that underwent deoxygenation with rearrangement; 1-ethyl derivative **34** is presumed to be formed from **33** by alkylation with triethyl phosphate developed during the deoxygenation.[36b, 42, 52a, 53] The preferential migration of phenyl vs. methyl has established (by the stereochemical configuration of the nitrostilbene) an expected course for the migration to a cationic centre.[52c]

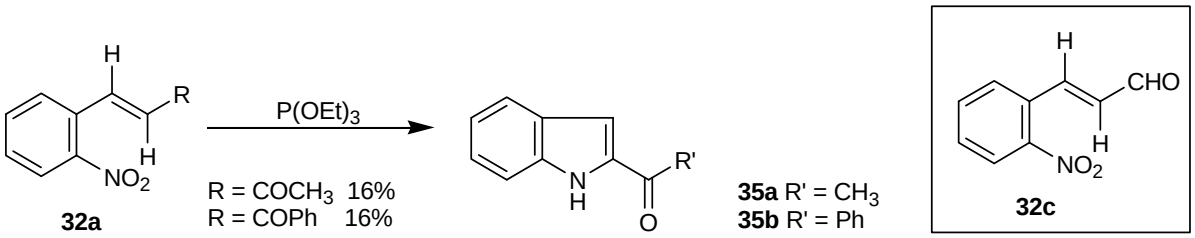


32b **33** 77% **34** 13%

Equation 10 Synthesis of 2-methyl-3-phenylindole **33** and *N*-ethyl-2-methyl-3phenylindole **34**.

Relatively low yields of indoles, biindoles, *N*-ethoxy derivatives, rearrangement and fragmentation products were observed for keto substituted styrenes.[42, 54, 55]

2-Acetylindoles **35a-b** have been prepared via deoxygenation of *β*-substituted *o*-nitrostyrenes in lower yields than *β*-alkyl-*o*-nitrostyrenes (Eq 11) and serve as precursors to the synthesis of the dimeric indole alkaloids.[56] The pyrolysis of the corresponding azides is usually more effective for the formation of 2-acylindoles and gives better yields in comparison. *N*-ethoxy indoles are frequently isolated in small amounts from deoxygenation reactions of 2-nitrostyrene derivatives.[54, 55, 57]



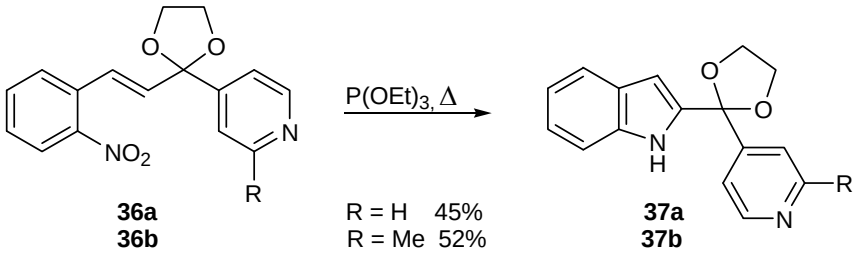
32a **35a** R' = CH_3 **35b** R' = Ph **32c**

Equation 11 The synthesis of 2-acetylindoles **35**.

When the carbonyl group of the *o*-nitrochalcone **32c** (R = CHO) is protected via its ethylene glycol ketal, a mixture of products such as indoles, 1-ethoxyindoles, 2-substituted indoles and 3-substituted indoles (via rearrangements), as well as 2-acylindoles[55] were isolated, too.

The formation of the cleavage products indole and 1-ethoxyindole is supposed to be a result of the fragmentation processes initiated by the development of electron deficiency at C-3 of the developing indole ring. The fragmentation might be favoured by the oxygen atoms of the dioxolane ring and by the aryl substituent.

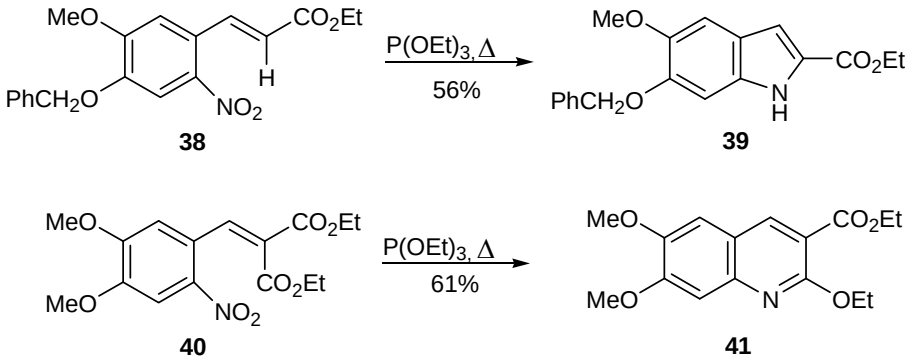
Gribble[58] *et al* described that substrates of type **36** form the corresponding 2-substituted indoles **37** as the sole products, only in average yields (Eq 12).



36a **36b** **37a** **37b**

Equation 12 The cyclization of 2-nitrostyrene ketals **36a**,**b**.

In an earlier paper, Ogasawara[44c] described the formation of quinoline derivatives from compounds having a carboxyl group in a ***Z*** configuration with the *o*-nitrophenyl skeleton. One year later, Ogasawara[59] agreed with Sundberg's[36a] theory that the indole derivatives[45a] are formed when both, 2-nitrophenyl and carboxyl groups, are in relation to ***E*** configuration and showed that the compounds with the reverse configuration yielded quinoline derivatives. Deoxygenation of ethyl 4-benzyloxy-3-methoxy-2-nitrocinnamate **38** and 4,5-dimethoxy-2-nitrobenzylidenemalonate **40** with an excess of triethyl phosphite (5 mol) at reflux (170 °C) produced indole and quinoline derivatives, respectively (Scheme 6).

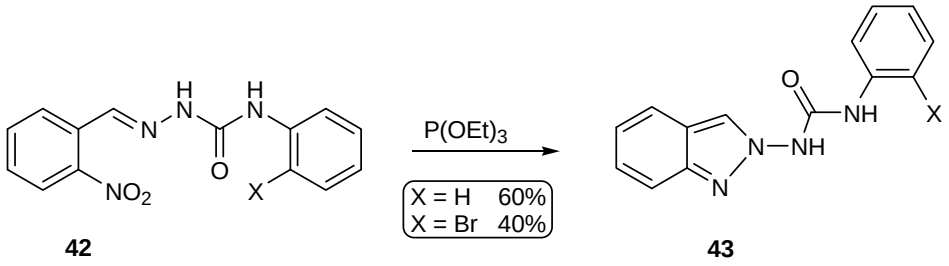


38 **39** **40** **41**

Scheme 6 The synthesis of the indole derivative (**39**) and the quinoline derivative (**41)**.

Indolocarbazoles,[60a] or indolo-[2,3-*a*]carbazoles,[60b,c] highly biologically active alkaloids, have been prepared via thermal deoxygenation of nitrocarbazole derivatives or terphenyl

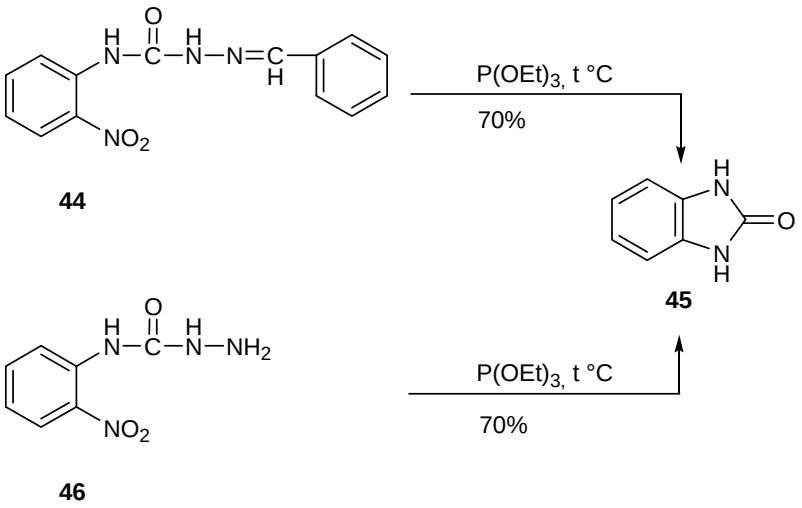
compounds with triethyl phosphite or triphenyl phosphine, respectively. Potential intermediates for indolocarbazole alkaloids are 2,2'-biindoles,[61] prepared in very good yields (90-95%) via deoxygenation of 2-vinyl indole derivatives, as well as diindolo-carbazoles.[62] *N*-Heterocycles other than indoles and carbazoles can be prepared via deoxygenation reactions related to those of azides. Thus, *β*-carbolines[63] were prepared from 4-*o*-nitro-phenylpyridine derivatives in contrast to the results reported by Sundberg,[36a] using 2-*o*-nitro-phenylpyridines; at that time this constituted the first example of nitrene insertion into the carbonyl C (aromatic) - C bond. Anthranils[53] were formed from 2-nitrochalcones or directly from 2-nitrobenzophenone, indazoles[36b] from *o*-nitroanils or isoindazoles[64] from semicarbazones. The preparation of 1-isoindol-2-yl-3-phenylurea **43** from phenyl semicarbazone **42** (Eq 13) is mediated by an excess of triethyl phosphite. A nitrene intermediate is mentioned as the active species and can cyclise to form: 1) a five-membered ring, an isoindazole or 2) a six-membered ring nitrogen heterocycle, a 1,2,3-benzotriazine, depending on the site of attack (nitrene inserts into the N-H bond).[64]



42 **43**

Equation 13 The synthesis of 1-isoindol-2-yl-3-phenylurea **43**.

2*H*-benzotriazoles[36b] were prepared from their corresponding precursors 2-nitroazobenzenes while benzotriazolo-naphthotriazines from naphthotriazines.[65] The reaction of 1-benzal-4-(*o*-nitrophenyl)semicarbazone **44** with triethyl phosphite as well as the deoxygenation of *o*-nitrophenyl semicarbazide **46** under similar conditions yielded benzimidazole-2-one **45** (Scheme 7) instead of a 1,2,4-triazine.[64] This is an example of the preference of the nitrene cyclization to form a five-membered ring in triethyl phosphite mediated reaction of compounds, having the appropriate nucleophilic centre in *ortho* position to the nitro aryl group. The formation of benzimidazole-2-one **45** is possible via a nucleophilic attack at the C=O group for the substrate **46** while, in turn, a phosphoramidate intermediate (**D**) (Fig 2) is supposed to be formed through the reduction of the nitro group (in the case of the substrate **44**) and further transformed into the final product, under reaction conditions.[64]



Scheme 7 The synthesis of benzimidazole-2-one **45**.

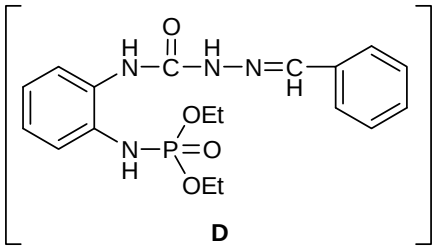
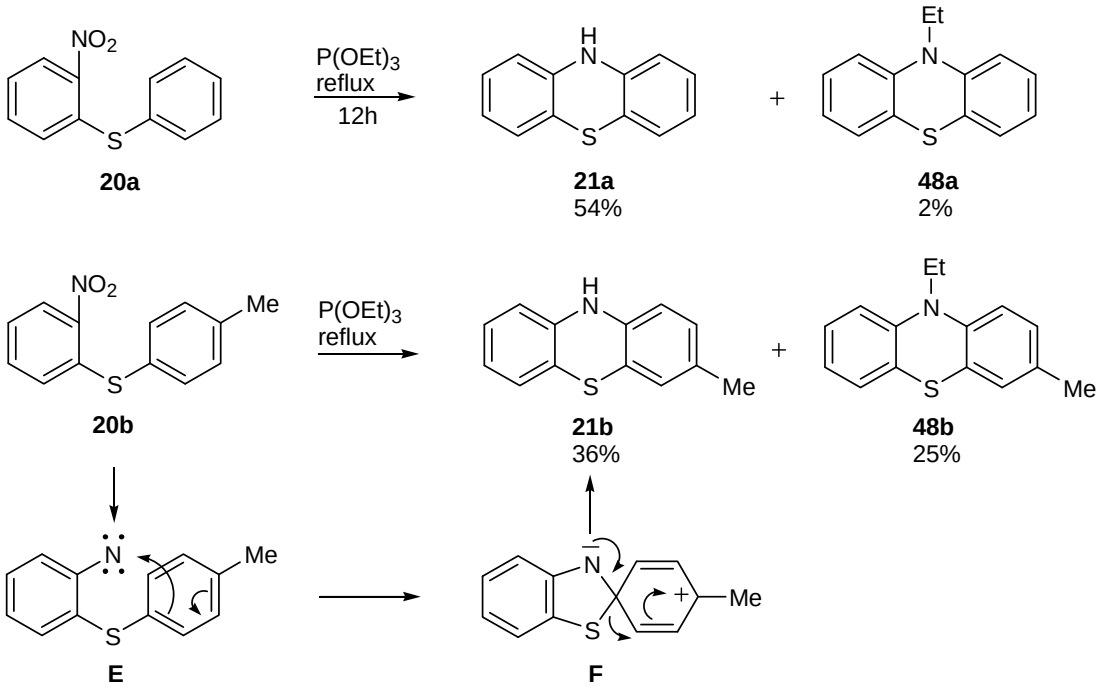


Figure 2 Phosphoramidate intermediate (**D**).

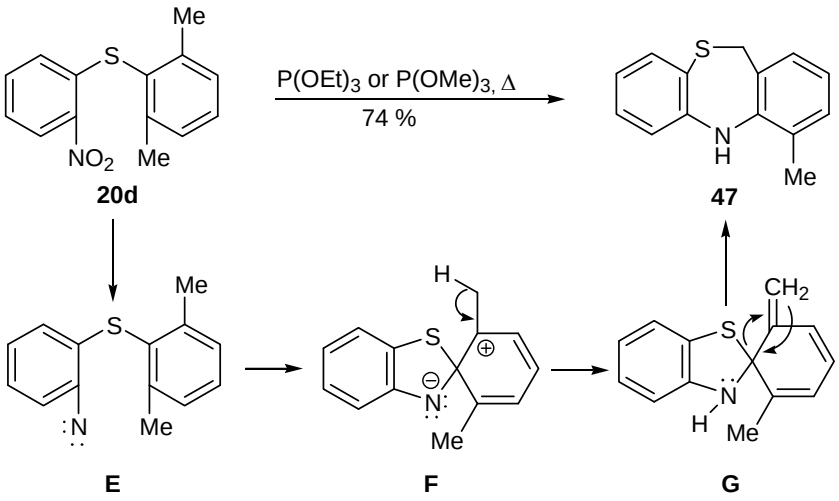
Benzimidazoles[66] were prepared from a large variety of nitroaromatics via phosphorous reagents; 1,2-benzoxazoles[53] are similarly obtained, while the formation of benzo[1,3]oxazoles[67] is reported as having place via nitrene insertion into the C=O group. Phenothiazines **21**,[53, 68a, 69, 70a] or 1,4-thiazepines **47**[70a] derivatives are formed by reductive cyclization of 2-nitrodiaryl sulphides **20a**.

Cadogan[53] reported that by refluxing 2-nitrodiphenyl sulphide **20a** in an excess of triethyl phosphite, phenothiazine **21a** was isolated in a yield of 54%, while the corresponding *N*-ethylated byproduct **48a** in a just 2% yield. After detailed investigations, Cadogan[68a] reported two years later that cyclization of 4'-methyl-2-nitrodiphenyl sulphide **20b** yields 3-methylphenothiazine **21b** and its *N*-ethyl derivative **48b** via a molecular rearrangement. This type of reaction proceeds through the rearrangement of a first five member intermediate (**F**), formed by electrophilic attack of the singlet nitrene (**E**) first formed, at the electron rich 1'-position. The products are derived from spirocyclic intermediates (**F**), not from direct nitrene (**E**) insertion.[68a, 70a] *N*-ethyl-3-methylphenothiazine **48b** was produced by the ethylation of the first formed phenothiazine **21b** (Scheme 8).



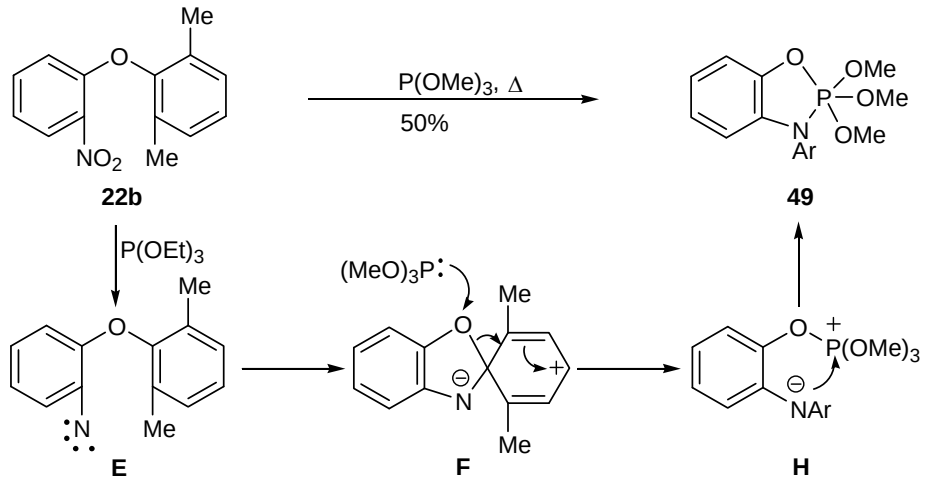
Scheme 8 Synthesis of phenotiazine **21a** and 3-methylphenothiazine **21b**.

An aromatic rearrangement[70a] involving a nitrene (**E**) was observed in the deoxygenation of 2-nitrophenyl-2',6'-dimethylphenyl sulphide **20d** and the implicit synthesis of 1,4-thiazepine ring. A spirointermediate (**F**) was taken into account for the rearrangement occurred during the thermal decomposition in a molecule in which both essential *o*-positions are blocked with methyl groups. The nitrene intermediate (**E**) attacks the adjacent benzene ring at the nucleophilic 1'-position to give the five-membered intermediate (**F**) which then undergoes a sigmatropic rearrangement (Scheme 9).



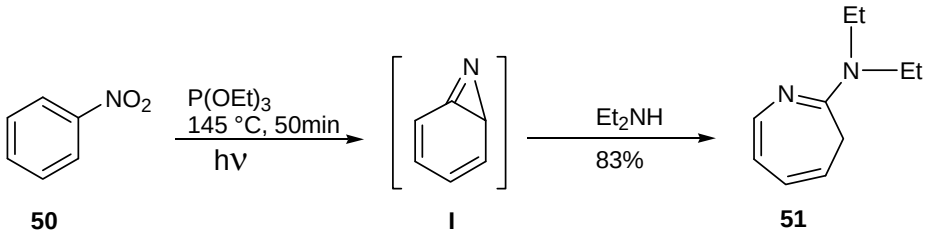
Scheme 9 Synthesis of 5,11-dihydrodibenzo-[b,e]-1,4-thiazepine **47**.

In the case of *o*-nitrodiaryl ethers **22b** it is also assumed that a spirodiene intermediate (**F**) exists, even if it reverts to aromaticity via a nucleophilic attack by tervalent phosphorus on the bridgehead oxygen, with the isolation of a phosphorane system **49** in 50% yield (Scheme 10).[70b] Interesting results were obtained years later with similar substrates, *o*-nitrophenyl naphtyl ethers, when spirodienyl intermediates and different rearrangements were reported.[70c]



Scheme 10 The synthesis of aminotetroxyphosphorane **49**.

Seven-membered ring nitrogen heterocycles were also formed via the reductive cyclization of nitroaromatics. Thermal reductions of simple nitrobenzenes in excess of triethyl phosphite led to phosphonylated 3*H*-azepines[68b] in low yields, while photolysis of nitrobenzenes, nitrotoluenes and nitromesitylenes in excess of triethyl phosphite with diethyl amine led to 3*H*-azepines.[71, 72a] The photochemical deoxygenation of nitrobenzene **50** (Scheme 11) in the presence of triethyl phosphite leads to the formation of 2-diethylamino-3*H*-azepine **51** via ring expansion to the intermediate of type (**I**), which under reaction conditions resulted in the final product, azepine (**51**).



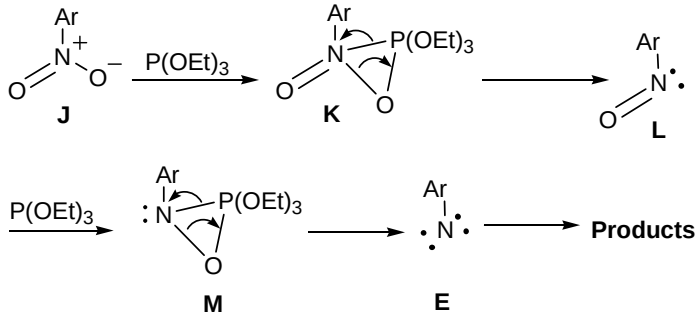
Scheme 11 The synthesis of 2-diethylamino-3*H*-azepine **51**.

Sundberg[72b] *et al* also reported that the irradiation of nitroaromatics (nitrobenzenes) solutions in triethyl phosphite results in oxygen transfer reactions at room temperature with a formation of a mixture of products such as phosphates, phosphorimidates, anilines and pyridines.

The formation of pyridine derivatives was explained by including another type of rearrangement. In a further publication,[72c] Sundberg also showed that the presence of acetic acid (5% by volume) in triethyl phosphite solutions of nitroaromatics at photochemical deoxygenation, affects the nature of the reaction products to a large extent. His conclusion was that arylnitrenes as singlet species are relatively basic species and can be converted to arylnitrenium ions. Thus the presence of acetic acid led to products formed from a nucleophilic aromatic substitution process.[72d]

Suzuki[73] *et al* reported that the reduction of *o*-nitrodiphenylamines by triethyl phosphite also involves an aromatic rearrangement via arylnitrenes, allowing dihydrophenazines. The dihydrophenazines initially formed by triethyl phosphite are transformed into the respective phenazines by autooxidation.

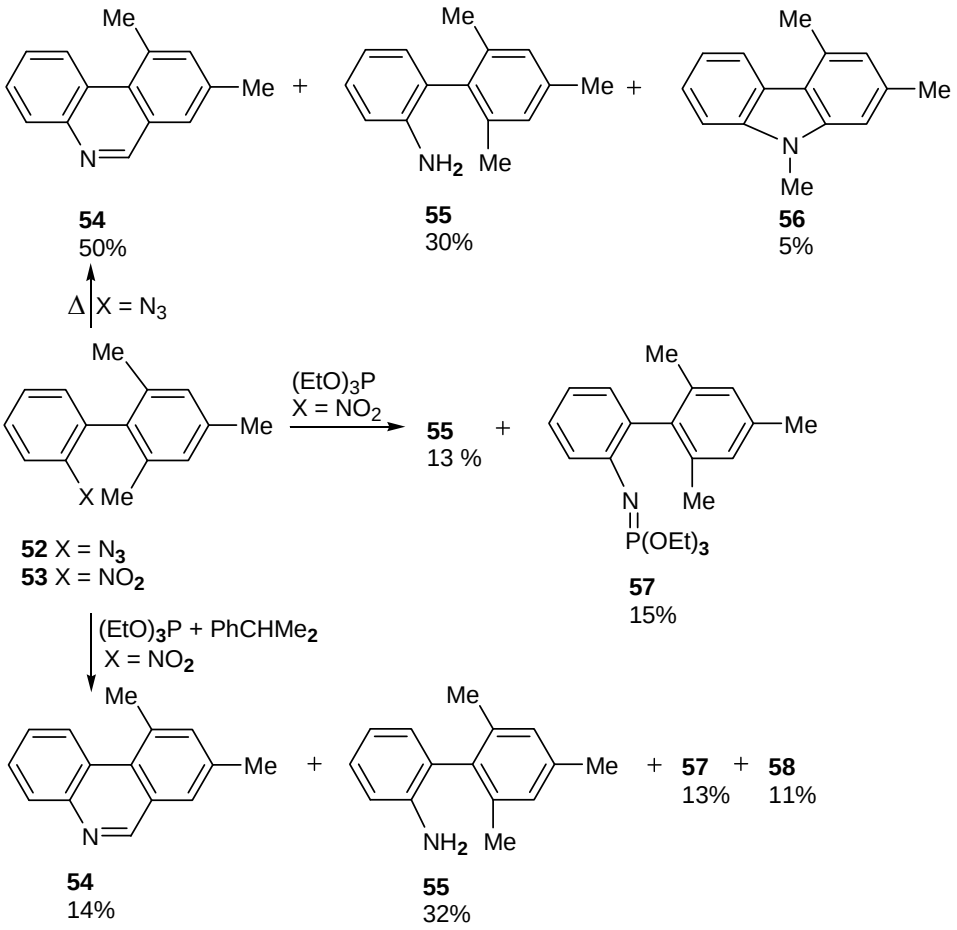
Some conclusions should be drawn regarding the cyclization of nitroaromatics with triethyl phosphite: the reduction of nitro compounds with triethyl phosphite is generally considered to take place in two steps.[74, 75] The first step is represented by a reduction of the nitro group to a nitroso compound (**L**) via an electrophilic attack of the phosphorus atom at the nucleophilic oxygen atom in a concerted mechanism, involving the intermediate (**K**). The second step consists in the complete deoxygenation to the nitrene (**E**) that participates in the final step (Scheme 12).



Scheme 12 The deoxygenation of nitroaromatics via a nitrene, in a concerted mechanism.

The conclusion, that arylnitrenes are intermediates in the deoxygenation of nitroaromatics using tervalent phosphorous compounds, is based on the similarity of the nature and proportion of the isolated products in deoxygenating reactions to those found in the photolysis of arylazides.[75] The proposal that nitrene is the intermediate in the latter step has been supported by identifying products obtained from hydrogen abstraction and insertion reactions with C-H bonds in the deoxygenation reaction of 2'-azide-2,4,6-trimethylbiphenyl **52**, or 2-nitro-2,4,6-trimethylbiphenyl **53** with triethyl phosphite (Scheme 13).[38, 71, 74] The formation of the products **54**, **55** and **56** via the decomposition of the azide **52** at 230 °C has been attributed to a nitrene participation.[74b] A nitrene intermediate is taken into account by

Abramovitch,[76c] too. Heating 2,4,6-trimethyl-2'-nitrobiphenyl **53** with $FeC_2O_4 \cdot 2H_2O$ in the absence of a solvent, 8,10-dimethylphenanthridine **54** was isolated in a yield of 23%, while the amino compound **55** was isolated in a yield of 27%. When the reaction was performed in a solvent such as hexadecane, the yield of the amino compound **55**, increased to 42% yield, while the yield of the phenanthridine **54** decreased to 15% yield. In this case, the hydrogen abstraction from the solvent may also be possible. No other products could be identified or isolated. Abramovitch's conclusion was that the hydrogen abstraction by the nitrene must take place from methyl groups of another molecule and therefore at the surface of the reagent Fe^{+2}, possibly. The formation of the corresponding amine **55** and triethyl-*N*-(2,4,6-trimethyl-biphenyl-2-yl) phosphorimidate **57** from the deoxygenation of 2,4,6-trimethyl-2'-nitro-biphenyl **53** also suggests a nitrene formation and its reaction with the excess of triethyl phosphite.[71] The products **54** and **56** were not detected under these reaction conditions, maybe because their formation would have involved the energetically less favourable insertion into strong bonds, in competition with the easier pathway involving coupling with an excess of the phosphite present. In addition to **55** and **57**, the deoxygenation of nitrobiaryl **53** in cumene gives 8,10-dimethyl-phenanthridine **54** and bi-α-cumyl **58**.



Scheme 13 *E*xperiments for the elucidation of the reaction mechanism.

The formation of bi-*α*-cumyl **58** can be explained by dimerization of *α*-cumyl radicals, produced by the abstraction of a hydrogen atom from cumene via a *triplet* nitrene.[71a]

In addition to those shown above, Feuer[74a] *et al* have isolated as byproduct diethyl *N*-(2,4,6-trimethylbiphenyl-2-yl)phosphoramidate **59** (Fig 3); as shown by Cadogan,[71a] **59** may be formed from triethyl *N*-(2,4,6-trimethyl-biphenyl-2-yl)phosphorimidate **57** via hydrolysis.

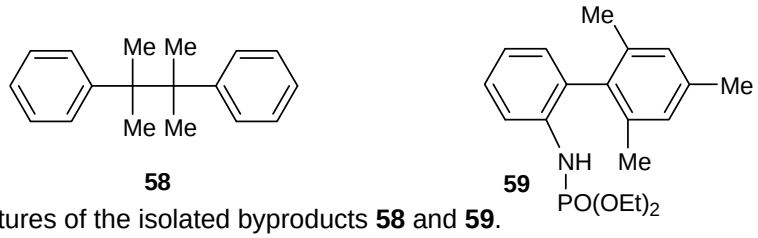
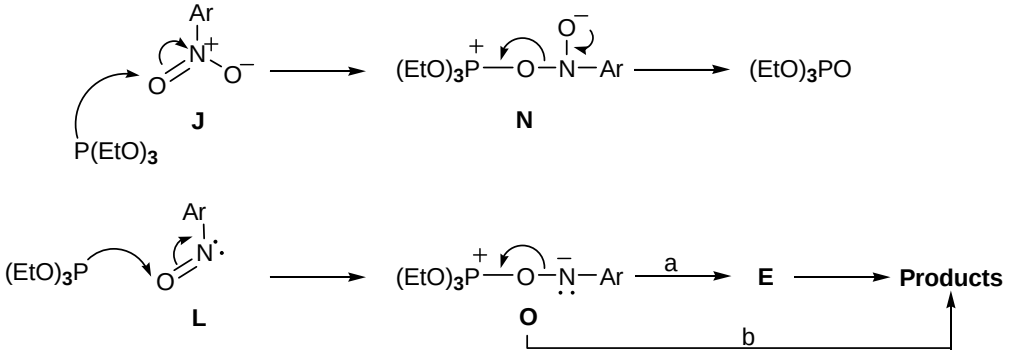


Figure 3 The structures of the isolated byproducts **58** and **59**.

It has also been proposed that the reactions occurring via nitrene intermediate in the intramolecular cyclization of the nitroso or nitroaromatics and triethyl phosphite, generally take place in several steps via a non concerted mechanism.[36b, 39, 69] The nucleophilic attack of the phosphorous atom takes place on both nitro and nitroso-oxygen (Scheme 14); it is supposed that the nitro group is deoxygenated to the nitroso group which in its turn, is reduced very rapidly to the final product. From the intermediate (**O**), different reaction products are isolated via two ways, including a nitrene intermediate (**E**), or directly via a non-nitrene route. The nitrene hypothesis is supported by the similarity in behaviour of simple 2-nitrobiaryls or 2-nitrophenylpyridine **30**.[36a] Against the nitrene hypothesis is the fact that the nitrene obtained from 2-azido-2,4,6-trimethyl-biphenyl **52** undergoes a C-H insertion reaction at an *ortho*-methyl group to yield 8,10-dimethylphenanthridine **54** (Scheme 13), whereas the corresponding reduction by triethyl phosphite resulted in a tar. It is possible therefore that these reductions of nitroaromatics via triethyl phosphite can take place without the intermediacy of a nitrene.

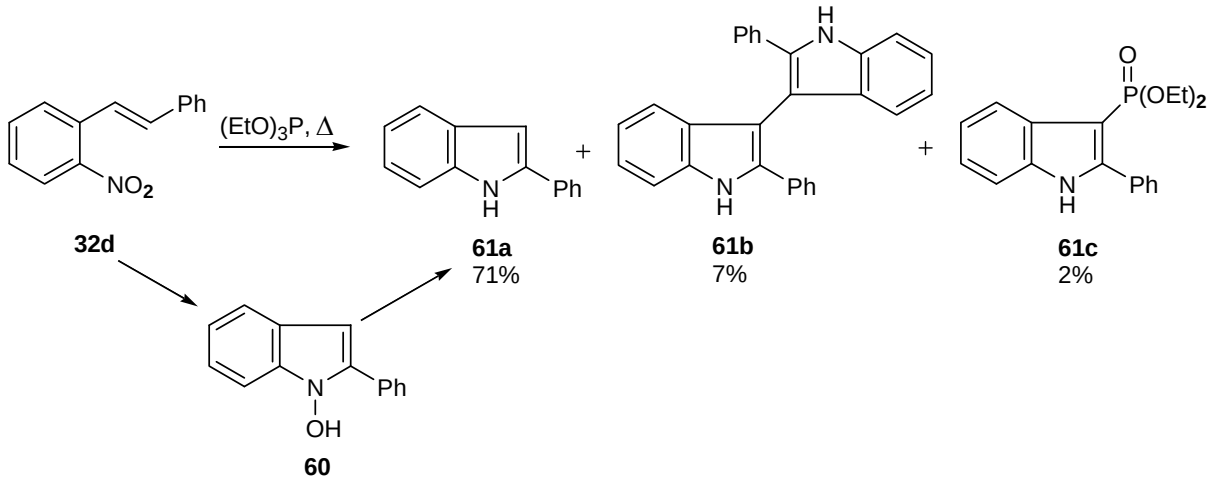


Scheme 14 The deoxygenation of nitro- and nitrosoaromatics in a non-concerted mechanism:

a) via nitrene route;

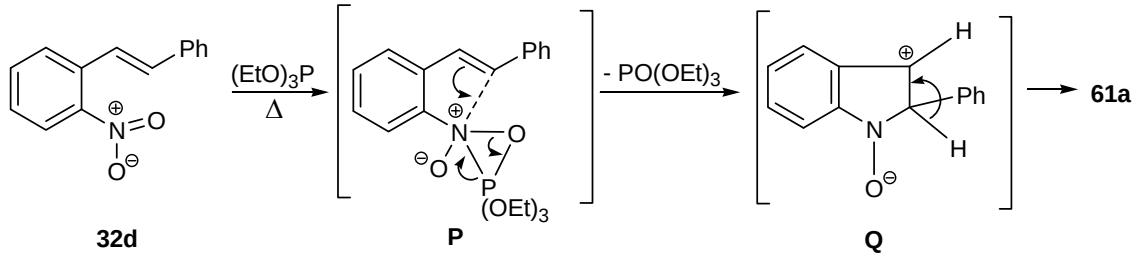
b) b) via non-nitrene route.

On the other hand, it has also been reported that similar deoxygenative reactions by means of triethyl phosphite are sequenced by a concerted mechanism in which the nitrene does not participate.[53, 76 - 78] For example, the formation of 2-phenylindole **61a** in a 71% yield from trans-*o*-nitro-stilbene **32d** with triethyl phosphite does not actually involve nitrene and the cyclization reaction occurs before the completion of deoxygenation.[42, 52a] Such a reaction involves a C-N bond formation, concurrently with or after the first deoxygenating step, via the intermediate, *N*-hydroxy-2-phenylindole **60** (Eq 14). When heated with triethyl phosphite under similar conditions, the intermediate **60** was converted in a 79% yield to the main product **61a**, demonstrating that it might be formed during the deoxygenative reduction of the substrate **32d**, but would be converted mainly to **61a**.



Equation 14 Synthesis of 2-phenylindole **61a**.

It has been supposed that in a concerted mechanism, the nitro group is nucleophilically attacked by the phosphorous atom. The cyclization and C-N bond formation have occurred simultaneously with the formation of a zwitterionic intermediate (**Q**) before the completion of deoxygenation. These rearrangements are possible and therefore *N*-hydroxyl products can be formed.



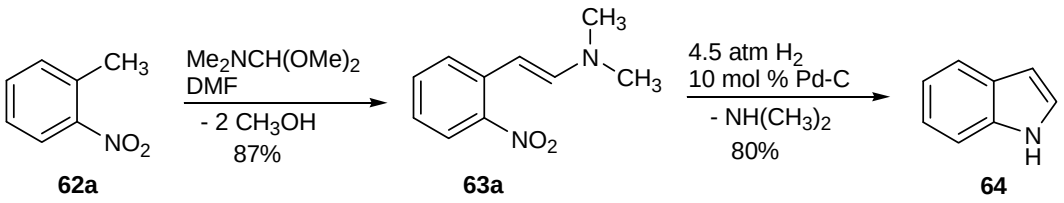
Scheme 15 The deoxygenation of nitroaromatics in a concerted mechanism via the non-nitrene route.

Hahn[77c] has reported that during the kinetic investigations of tetraazapentalenes the formation a four member cyclic transition state is involved, in a concerted mechanism, with non-nitrene participation.

The presence of a nitrene or non-nitrene intermediate in the deoxygenative reactions of nitroaromatics via tervalent phosphorous compounds, is an intriguing matter but it is a fact that this type of reaction permits a synthesis of a large number of *N*-heterocycles.

2.3 The Leimgruber-Batcho indole synthesis

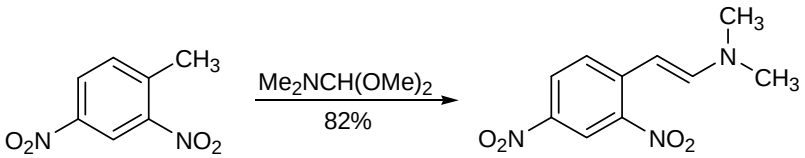
The reductive cyclization of nitroaromatics is also employed to construct indoles via a method described by Leimgruber and Batcho,[79] a very useful tool for the synthesis of natural products, too. The Leimgruber and Batcho indole synthesis is a two-step reaction that produces indoles from *o*-nitrotoluene **62a**. Leimgruber and Batcho introduced an efficient indole synthesis based on the condensation of *o*-nitrotoluene **62a** with *N,N*-dimethyl-formamide dimethyl acetal (*DMFDMA*), followed by the reductive cyclization of the resulting ***E*-*β*-dimethylamino-2-nitrostyrene **63a** (Scheme 16).



Scheme 16 The two-step synthesis of indole **64** via Leimgruber-Batcho method.

The reaction includes two steps: the first step is represented by the formation of an enamine in which the nitro group is not involved and the second step consists of the reduction of the nitro group to the amino group simultaneously with the *N*-heteroannulation to the indole formation. This reaction sequence (and modifications therefore) has been utilized for the preparation of many structurally substituted indoles.

For the Leimgruber-Batcho synthesis, the original basis has been Meerwein's observation[80] that 2,4-dinitrotoluene **62b** can be condensed with dimethylformamide diethyl acetal to give an enamine **63b** (Eq 15). The intermediate enamines are electronically related to push–pull olefins, having an electron–withdrawing nitro group conjugated to an electron–donating group.



62b **63b**

Equation 15 The formation of [2-(2,4-dinitrophenyl)-vinyl]-dimethyl amine **63b**.

Subsequently, Bredereck[81] *et al.* reported that 2-nitrotoluene **62a** can also be converted to the enamine **63a** by condensation with bis(dimethylamino)^{t}butoxymethane. The original Leimgruber-Batcho publications[79] described other reagents (*N*,*N*-dimethylformamide, dimethyl and diethyl acetals, *N*-formylpyrrolidine dimethyl acetal and *N*-formylpiperidine dimethyl acetal) which are able to carry out this type of transformation.[82] Leimgruber-Batcho also described a number of methods for the reductive cyclization of β-dimethylamino-2-nitro-styrenes to indoles. The hydrogen and palladium/carbon, Raney nickel, the hydrazine, the iron/acetic acid, the sodium dithionite, the ferrous sulphate-ammonia in different organic solvents are effective reducing agents.[79]

Somei [83–86] *et al*. have demonstrated the utility of $TiCl_3$ as a reducing agent in the Leimgruber-Batcho synthesis. This reagent displays several desirable features: its ability to reduce the nitro groups,[87] its acidic nature which promotes hydrolysis of the enamines to phenylacetaldehydes thereby facilitating intramolecular cyclization, and the possibility of controlling the reduction level by means of the regulation of its amount.

The Leimgruber-Batcho synthesis has several advantages over almost all the other routes of synthesizing indoles:

- A large variety of substituted indoles can easily be prepared in high yields,
- The reductive cyclization to the indole can be achieved under relatively mild conditions,
- The regiospecificity of the method allows the introduction of substituents at the carbon atoms C-4, C-5, C-6 or C-7,
- Indoles unsubstituted in the 2 and/or 3 position are obtained directly.

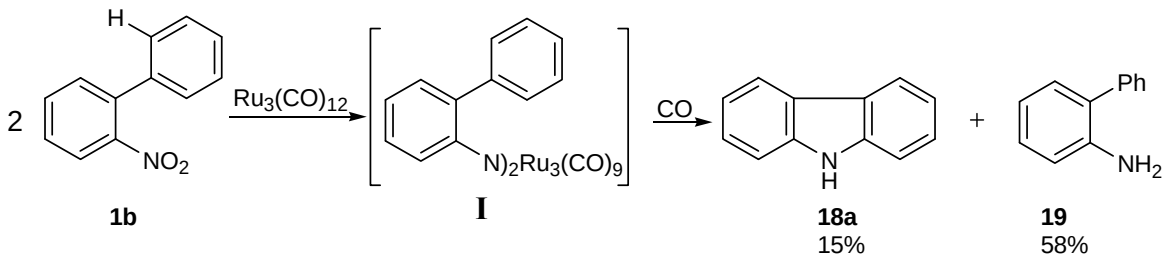
The major disadvantages of the Leimgruber-Batcho synthesis is the inaccessibility of multiple substituted 2-nitrotoluenes. This is a good example of a reaction that was widely used in industry; many indoles are pharmacologically active, so a good indole synthesis is important for the pharmaceutical industry. The process has become a popular alternative to the Fischer indole synthesis because many starting *o*-nitrotoluenes are commercially available or easily prepared.

2.4 Metal catalyzed *N*-heteroannulations of nitroaromatics

Reductive carbonylation of nitroaromatics in the presence of metal complexes has been intensively investigated in the last years. Transition metal catalyzed reactions, wherein nitrene insertion type products are isolated, produced the highest growing area of *N*-heterocyclic synthesis. The remarkable character of the transition metal complexes using different ligands, additives or various reaction conditions offers advantages in comparison with the conventional methods. Deoxygenations of nitroaromatics and reductive *N*-heteroannulations catalyzed by transition metals in the presence of CO can be formally considered as nitrenoid in character. This seems, however, to be most likely an over simplification of very complex metal mediated reactions. The products formed using transition metals are the same or similar to those that can be found starting from more conventional sources of nitrenes. Usually, metal catalyzed reactions of nitroaromatics exhibit a higher degree of selectivity, higher yields and short reaction times, compared to reactions using tervalent phosphorous compounds. An array of transition metal catalysts have been used to prepare a variety of indoles or carbazoles.[1c]

Carbazoles can be prepared by reductive carbonylation of *o*-nitrobiphenyl **1b**; the reaction is catalyzed by $Ru_3(CO)_{12}$[88a,b], $Fe(CO)_5$[89] or Pd(II).[88c] The reaction of 2-nitrobiphenyl **1b** with $Ru_3(CO)_{12}$ in the presence of carbon monoxide produced the carbazole **18a**. The insertion into the aromatic C-H bond to give carbazole is believed to bear evidence for the intermediate formation of a *singlet* nitrene species, a ruthenium bound nitrene **I**. It has been proposed that in this reaction the intermediate is $Ru_3(\mu_3\text{-}NC_6H_4\text{-}o\text{-}C_6H_5)_2(CO)_9$, a cluster in which the nitrene ligand is triply bridged with the ruthenium atoms. The intermediate species is quite stable and its decomposition at 220 °C yields the reaction products. The structure of **I** was determined by X-ray crystallography. 2-aminobiphenyl **19** was isolated as a byproduct (Scheme 17).[88]

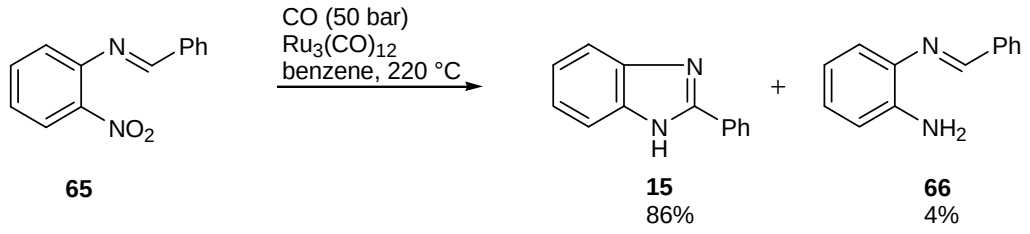
2-Nitrobiphenyl **1b** has also been deoxygenated using iron pentacarbonyl ($Fe(CO)_5$) and CO, yielding 2-aminobiphenyl **19** in a yield of 58% and carbazole **18a** in a yield of 15%.[89]



Scheme 17 The formation of the carbazole **18a** by $Ru_3(CO)_{12}$.

When the nitrene acceptor moiety is fully substituted in the *ortho* positions, phenanthridines (**54**) together with the amine (**55**) as reduction products were observed under the above mentioned reaction conditions[74a, 76c] (see scheme 13, page 19).

A number of disilanes deoxygenate nitroaromatics. The reaction of 2-nitrobiphenyl **1b** with hexamethyldisilane (Si_2Me_6, 240 °C) yields carbazole **18a** (42%) together with a small amount of 2-aminobiphenyl **19**. A higher yield was obtained using benzo-1,1,2,2-tetramethyl-disilacyclopentene.[90] The deoxygenation of 2-(2'-nitrophenyl)pyridine **30** using ferrous oxalate at 300 °C has taken place not at a pyridine nuclear carbon, but at the pyridine nitrogen atom to give pyrido-[1,2-b]indazole **31** in good yields.[13, 91] Similar results were obtained using $P(OEt)_3$ as reducing agent when pyrido-[1,2-b]indazole **31** was isolated in a yield of 90% (see equation 9, page 11).[76c] This result parallels that of the corresponding azide. A nitrene intermediate was suggested, but other pathways could not be ruled out. A number of non-nitrene pathways have been proposed.[19, 74] It has been shown that $Ru_3(CO)_{12}$ has been used as a catalyst in the deoxygenation of *o*-nitrobiphenyl to carbazole, but it has also been used in the reductive carbonylation of *o*-nitroazo derivatives to give the corresponding benzotriazoles in solvents such as *o*-dichlorobenzene or *o*-xylene (180-200 °C, 70-80 atm). Conversion and selectivity are markedly increased by the addition of a base such as Et_3N, which acts as a deoxygenating agent of the nitro group.[92] $Ru_3(CO)_{12}$ is a very efficient catalyst for deoxygenation of 2-nitro-*N*-(phenylmethylene)-benzeneamine **65** to yield the corresponding 2-phenylbenzimidazole **15** (Eq 16). The corresponding amines are the main byproducts. The reducing action of CO is confirmed by the detection of CO_2 in the solution at the end of the reaction (IR evidence).[93] The side formation of the amine is very likely due to the hydrogen abstraction by the intermediate nitrene from the solvent or from the traces of water present in the medium.

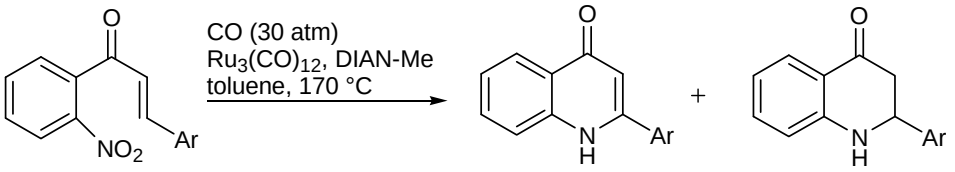


65 **15** 86% **66** 4%

Equation 16 $Ru_3(CO)_{12}$ mediated synthesis of 2-phenylbenzimidazole **15**.

The same benzimidazoles are also obtained starting from *o*-nitroanilines and the corresponding aldehydes, in the presence of the catalyst, $Ru_3(CO)_{12}$.[93] On the other hand, the formation of amine **66** as a byproduct is rather common for this type of catalytic reaction,[94]

particularly when ruthenium complexes are used as catalysts. The use of $Ru_3(CO)_{12}$ as deoxygenating catalyst of nitroaromatics is also reported for the synthesis of six-membered *N*-heterocycles. A case in point is represented by the synthesis of 2-aryl-4(1*H*)-quinolone **68a** (Eq 17) by the reductive cyclization of 2-nitrochalcone **67a** with CO, catalyzed by $Ru_3(CO)_{12}$ in ethanol-water, in the presence of bis(*p*-tolylimino)-acenaphthalene (DIAN-Me).[95] This is in contrast to the reactions of 2-azidochalcones forming 2,1-benzoisoxazoles and 3-aryl-4-(1*H*)-quinolinones.[96]

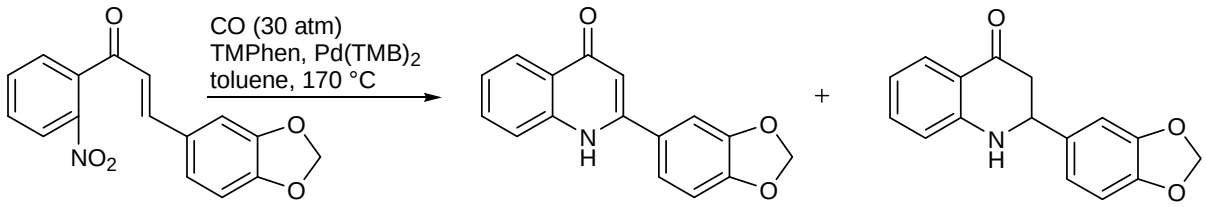


67a **68a** 57% **69a** 43%

Equation 17 The synthesis of 2-aryl-4-(1*H*)-quinolone **68a**.

Bis(*p*-tolylimino)acenaphthalene (DIAN-Me) and 3,4,7,8-tetramethyl-1,10-phenanthroline (TMPhen) were used as ligands for the metal. A synthesis of the quinoline alkaloid *graveoline* was accomplished employing palladium bis-(2,4,6-trimethylbenzoate) as the catalyst in the presence of carbon monoxide. In addition to the *graveoline* **68b**, a fair amount of the 2,3-dihydroderivative **69b** was also isolated (Eq 18).[97]

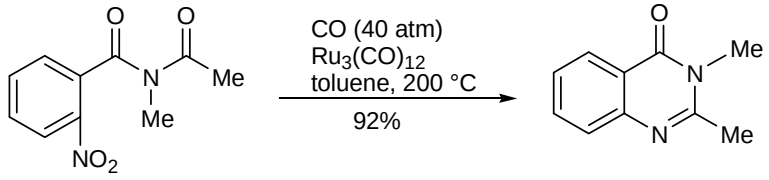
It was shown that the formation of 4-(1*H*)-quinolinones may not involve the initial reduction of the nitro group to the corresponding amino group as shown by Cenini *et al*.[98]



67b **68b** 78% **69b** 16%

Equation 18 The synthesis of graveoline **68b**.

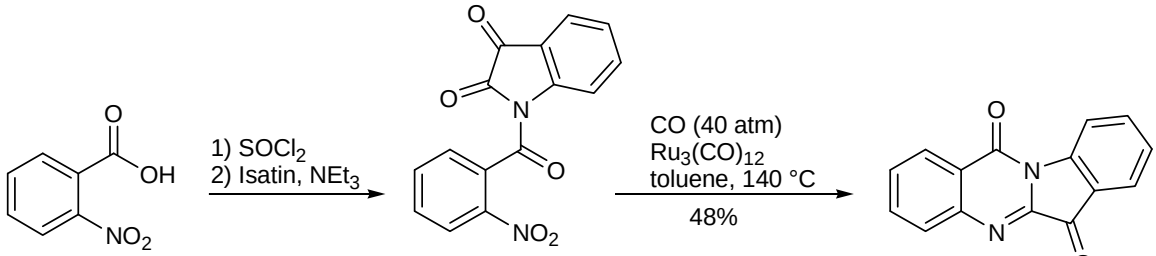
Watanabe[99] *et al.* have demonstrated the potential of several transition metal complexes in the reductive cyclization reactions. In particular, ruthenium catalysts were found to effectively transform *N*-(2-nitrobenzoil) amides **70** to 4-(3*H*)-quinazolinone derivatives **71** (Eq 19).



70 **71**

Equation 19 The synthesis of 2,3-dimethyl-4-(3*H)*-quinazolinone **71**.

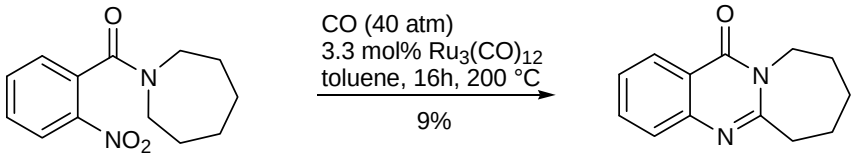
This reaction was used in the synthesis of the antibiotic tryptanthrine (**74**) (Scheme 18).



72 **73** **74**

Scheme 18 Synthesis of the antibiotic tryptanthrine (**74**).

The insertion into a saturated methylene was also observed, albeit in a low 9% yield (Eq 20). All of these reactions are again thought to proceed via a metal bound nitrene intermediate.

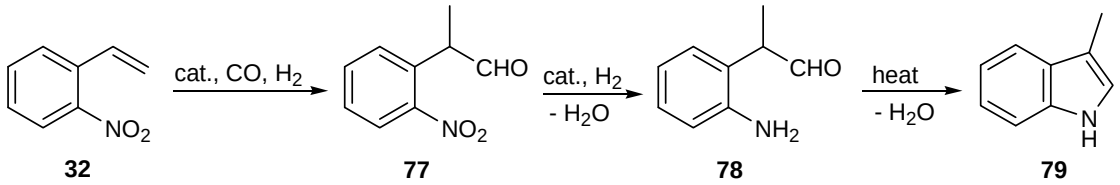


75 **76**

Equation 20 The synthesis of azacycloheptano-[2,1-b]-4(3*H*)-quinazolinone **76**.

A variety of transition metal catalysts have been used to prepare indoles by reductive cyclizations of nitroaromatics. It was shown that from the deoxygenation of *o*-nitrostyrenes by triethyl phosphite an intramolecular cyclization of nitrene occurred simultaneously with the formation of indoles.[42] Moreover, under hydroformylation conditions, supported rhodium being used as a catalyst, 2-nitrostyrene **32** is directly converted into skatole in ca. 70% yield, by a reaction involving: the formation of 2-(*o*-nitrophenyl)propionaldehyde **77** by homogeneous catalysis, the reduction of the nitro group by heterogeneous catalysis to **78** and then ring closure and thermal dehydration to **79** (Scheme 19).[100] The hydroformylation of styrene derivatives with rhodium complexes shows a high selectivity for formation of

branched-chain rather than terminal aldehydes, because of the strong orienting effect of the aromatic ring.



Scheme 19 The synthesis of skatole (**79**).

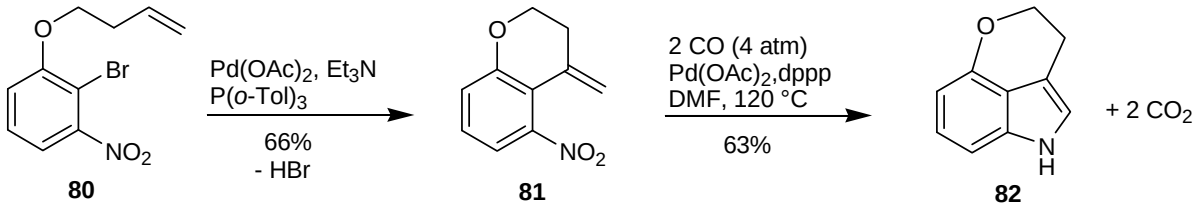
Complexes such as $RhCl(PPh_3)_3$ and $RhCl(CO)(PPh_3)_2$ lead to the conversion of 2-nitrostyrene derivatives even under high pressure and high temperatures, while clusters such as $Rh_4(CO)_{12}$ and $Rh_6(CO)_{16}$ are quite ineffective. The most active catalysts were produced in situ from supported rhodium precursors such as Rh/Al_2O_3 and Rh/C.[100]

Cenini[101] *et al* have described the use of metal carbonyls such as $Fe(CO)_5$, $Ru_3(CO)_{12}$ and $Rh_6(CO)_{16}$ to afford indole derivatives via the deoxygenation of *o*-nitrostyrene derivatives under carbon monoxide pressure. The side products were the corresponding amines. A variety of palladium,[102] iron, ruthenium, rhodium, platinum, nickel and tin complexes have all been successfully employed. Watanabe[103] has described the synthesis of indoles by the carbonylation of *o*-nitrostyrenes, catalyzed by $PdCl_2(PPh_3)_2/SnCl_2$ under milder conditions (100 °C) in yields ranging between 62-75%. The carbonylation of *o*-substituted nitrostyrenes with $Pd(TMB)_2$/TMPhen as a catalytic system gives the corresponding indoles in very good yields and selectivities. In some cases, some byproducts such as biindoles were reported.[102] Both Pd(0) and Pd(II) species enter the catalytic cycle and it is likely that the former species is the actual catalyst for the annulations. A wide variety of functional groups are tolerated under the reaction conditions. The observation that, both triflates and bromides remain intact on the indole molecules, is particularly interesting.[101a, 104] Both (***Z***/***E***) stereoisomers of 2-nitrostyrene afford 2-phenyl indoles in comparable yields, as was observed using triethyl phosphite. Once more, this result points to a common mechanism for the metal catalyzed reactions and those employing phosphorous reagents. In the presence of CO and a palladium-phosphine catalytic system, indoles were obtained in average to good yields. Best results were obtained using palladium diacetate together with PPh_3 as the catalytic system (4 atm CO, acetonitrile, 70 °C).[104] Hegedus[105] *et al*. have reported that Pd(II) complexes catalyze oxidative *N*-heterocyclization of 2-aminostyrene or 2-allylaniline derivatives to various indoles, including the ergot alkaloids. The *N*-heteroannulation of the nitroaromatics forming indole derivatives does not proceed by the initial reduction of the nitro group to an amine,

followed by a Hegedus type indole synthesis via an amino-palladation *β*-hydride elimination sequence. There are a number of indications to support an opposite theory; the amine route would require a Pd(II) catalyst which has to be regenerated by an added oxidant. But no oxidant is added; in fact the reaction conditions used are highly reductive.

Ragaini[98] *et al*. concluded in a mechanistic study that the formation of anilines plays a very little role in the formation of indoles.

Söderberg[106] *et al*. described a new route to fused indoles via two consecutive Pd(II) catalyzed reactions: an intramolecular Heck reaction followed by a mild and very efficient palladium catalyzed reductive *N*-heterocyclization. *N*-heterocyclization of 2-bromo-3-nitro-(3-butenyloxy)benzene **80** to indole derivative **82** is taken as an example (Scheme 20).



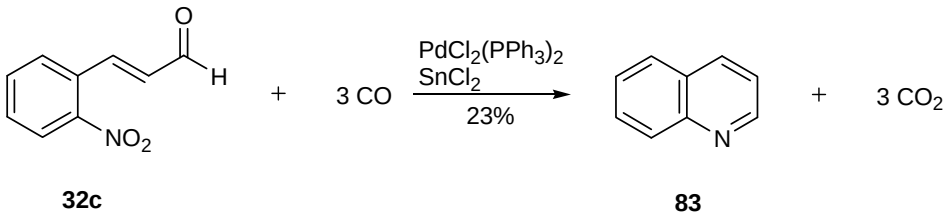
Scheme 20 The synthesis of indole derivative **82** via two consecutive palladium catalyzed reactions.

Using this route, it should be possible to assemble indoles having a variety of ring sizes anchored to the 3- and 5-position of the indole nucleus. Considering the high tolerance of a number of functional groups of the two reactions, both carbon and heteroatom substituents should be possible in (or attached to) the additional ring.

Using this methodology, some mushroom metabolites, indole derivatives, isolated from two species of European Basidomycetes (*Tricholoma virgatum* and *Tricholoma sciodes)* have been synthesized.[107]

For *β*,*β*-disubstituted styrenes an alkyl shift, similar to the triethyl phosphite mediated reactions, can be observed.[88a] In comparison with the reaction mediated by triethyl phosphite, the reactions mediated by transition metals usually give higher yields of indoles from *β*,*β*-disubstituted styrenes, without the formation of indoline-3-ones or dimerization products. In the reaction of 2-nitrocinnamaldehyde **32c** only quinoline **83** was isolated in a 23% yield and the corresponding indole was not obtained at all (Eq 21).[103b]

Indium similarly mediates reductive cyclization of 2-nitrochalcones to quinolines.[103c]

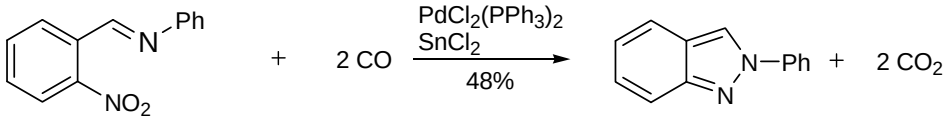


32c **83**

Equation 21 The synthesis of quinoline **83**.

Elemental selenium is an efficient catalyst for the carbonylation and the reductive *N*-hetero-cyclization of 2-nitrostyrenes with carbon monoxide, giving the corresponding indoles in moderate to good yields.[108]

A new synthetic approach to the natural product arcyriaflavin-A, based on a nitrene insertion, has been reported.[108b] A number of additional heterocyclic compounds have been prepared by transition metal catalyzed reductive *N*-heteroannulation of *o*-nitroaromatics. For example, 1-phenyl-2*H*-indazole **85** was synthesized from *N*-(2-nitrobenzylidene)amine **84** (Eq 22).

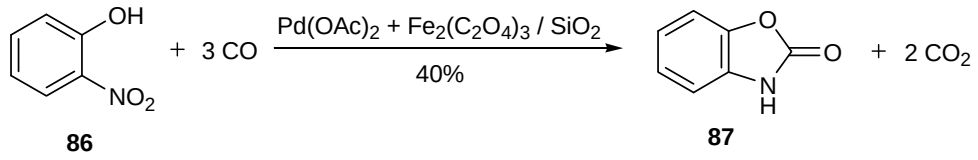


84 **85**

Equation 22 The synthesis of 1-phenyl-2*H*-indazole **85**.

To synthesize indazoles from *N*-(2-nitro-benzylidene)amines under carbon monoxide pressure, different transition metal catalysts were used such as: $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PtCl_2(PPh_3)_2$, $NiCl_2(PPh_3)_2$, $RhCl(PPh_3)_3$, $RuCl_2(PPh_3)_3$.[103b, 109] It is interesting to note that 2*H*-indazoles are not formed to any appreciable amount upon reacting with $Ru_3(CO)_{12}$.[98]

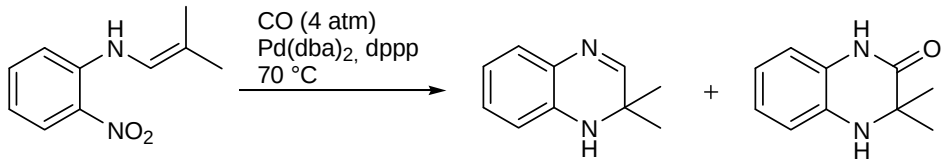
Other *N*-heterocycles were synthesized by transition metal-catalyzed reductive *N*-hetero-annulation of different nitroaromatics in the presence of carbon monoxide. For example $Fe(CO)_5$/CO were also used for the cyclization of 2,2'-dinitrobiphenyl **1a** to 3,4-benzo-cinnoline **2**, or for the reductive cyclization of 2-nitrobiphenyl **1b** to the carbazole **18a**.[110] $Ru_3(CO)_{12}$ was used as a catalyst for the synthesis of carbazoles, too.[88a] The catalytic synthesis of 1,4-dihydro-2*H*-3,1-benzoxyzin-2-one derivatives by reductive carbonylation of *o*-nitrobenzyl alcohols was reported by Cenini.[111] Concerning the selectivity of the reaction, it has been shown that Pd(II) is by far superior compared to the ruthenium catalyst in this type of reaction.[111] Mixed metal cluster-derived heterogeneous bimetallic catalysts such as Fe-Pd were used for the carbonylation of *o*-nitrophenol **86** to benzoxazol-2-one **87** (Eq 23).[112]



86 **87**

Equation 23 The synthesis of benzoxazol-2-one **87**.

Söderberg[113] has also shown the use of Pd(0) species with different ligands in the reductive deoxygenations of nitroaromatics. The reaction of enamines with carbon monoxide in the presence of a Pd(0) and 1,3-bis-(diphenylphosphino)propane forms mixtures of 1,2-dihydro-quinoxalines and 3,4-dihydroquinoxalines.[113a] He also described the synthesis of 1,2-dihydro-4(3*H*)-carbazolones via a reductive *N*-heteroannulation step using Pd(0) as a catalyst.[113b] A case in point is that of enamine **88** to yield 3,3-dimethyl-3,4-dihydro-quinoxaline **89** and 3,3-dimethyl-3,4-dihydro-1*H*-quinoxaline-2-one **90** (Eq 24).[113a] The addition of a catalytic amount of 1,10-phenanthroline to the reaction mixture substantially improved the yield of products.



88 **89** 71% **90** 11%

Equation 24 The synthesis of 3,3-dimethyl-1,2-dihydroquinoxaline **89** and 3,3,-dimethyl-3,4-dihydro-quinoxaline **90**.

New synthetic methods using transition metals as catalysts or metal complexes continue to appear. Transition metal catalyzed synthetic methods have been attempted over the past years in intramolecular *N*-heteroannulations of nitroaromatics. Transition metals offered convenient and efficient ways for the formation of the C-N bond and, therefore, for the construction of a large variety of *N*-heterocycles or of structural cores of many biological active compounds. *N*-heterocycles comprise the skeleton of many natural products; consequently there is a high demand for developing new, efficient, easily accessible ways for their synthesis. The palladium-catalyzed *N*-heteroannulations are of a great interest in organic synthesis because they can induce a very good regio- and stereoselectivity and often allow the formation of *N*-heterocyclic systems in one or two steps. The cyclization reactions catalyzed by Pd(0) or Pd (II) species have been extended to the synthesis of many common ring systems over the past 20 years.

3 AIM OF THE WORK

A classic synthetic method for the construction of *N*-heterocycles involving a new C-N bond formation is the deoxygenation of nitroaromatics.[1c] As shown in chapter 2, a variety of *N*-heterocycles have been formed via the deoxygenation and intramolecular reaction of different mono- or dinitroaromatics. However, little is known about the reductive cyclization reactions of nitroaromatics yielding saturated *N*-heterocycles. To create an ideal synthesis, a process able to generate multiple bonds in one pot is being explored. Nevertheless, in organic syntheses it is necessary to isolate and synthesize the intermediate species. A more efficient strategy in organic synthesis is the use of domino[114] processes, knowing that the domino reactions often display high regio-, chemo-, and stereoselectivity, that can easily be conducted and worked up and that permit the synthesis of complex molecules in a few steps. This type of reaction possesses many advantages: the entire process is carried out without adding any reagent or catalyst, without changing reaction conditions and without isolating any intermediates. Therefore reaction steps are saved by eliminating the need to isolate the intermediates. This way, the amount of waste can be reduced.

The focus of this work is on the creation and development of a new domino process using easily accessible ω-nitroalkenes as starting material to synthesize saturated *N*-heterocycles in a one-step process. Allyl 2-nitrophenyl ethers **91a-k**, **92**, **93**, allyl 2-nitrophenyl tertiary anilines **94a-d**, allyl 2-nitrophenyl secondary anilines **95a-d**, **96** and 2-(4,4-dimethyl-3-butene)nitrobenzene **97** (Fig 4) are examples of ω-nitroalkenes that were considered as starting materials for the production of saturated *N*-heterocycles in a single step.

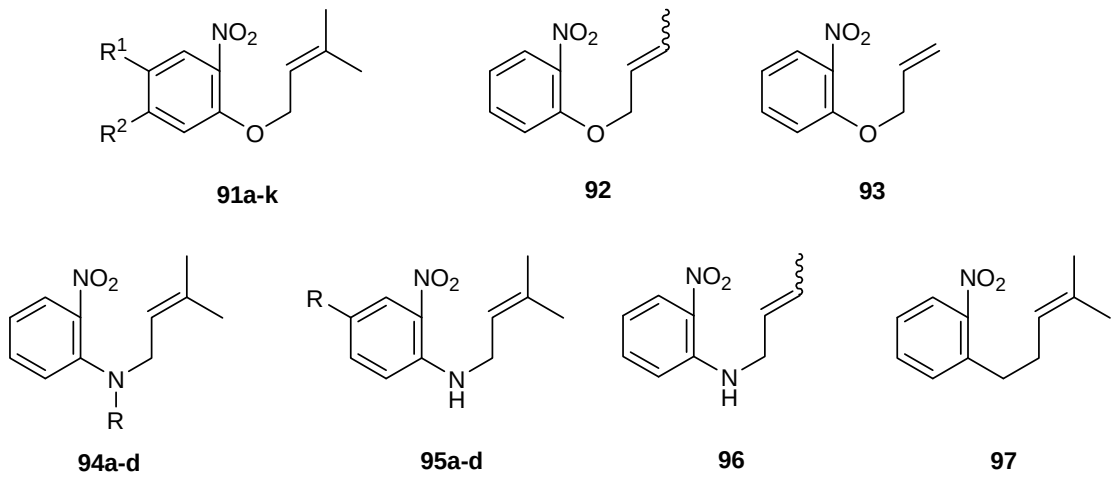


Figure 4 ω-Nitroalkenes to be used as starting material for the domino reaction.

Concerning the formation of a new C-N bond from nitroaromatics, **1)** the potential of the nitroso ene reaction has by no means been exhausted.[115]

2) In particular, methods for the single-step generation of the nitroso group from easily accessible precursors are lacking. The nitroso compounds are often unstable and therefore must be prepared in situ from nitroaromatics. The nitroso ene reaction has been used as a key step in the total synthesis of several natural products.

3) In addition, the primary product of the nitroso ene reaction is a *N*-hydroxyl amine instead of the much more interesting amine.

4) The objective of this work was also to couple the nitroso ene reaction and two reductions to create a new domino process. The nitroso derivatives generated in the former reaction step would undergo a cyclization reaction and involve a hydrogen transfer to give an intermediate *N*-hydroxyl amine. The new C-N bond formation is followed by reduction of the *N*-hydroxyl amine to yield the final *N*-heterocycle.

To obtain the corresponding saturated *N*-heterocycles from the above mentioned starting materials, excess of triethyl phosphite might be used as a reagent and/or solvent.

5) Other alkyl phosphites like triisopropyl phosphite and trimethyl phosphite should be taken in consideration in the domino reaction.

6) The yields and selectivities should also be compared to that obtained in the cyclization reactions mediated by triethyl phosphite.

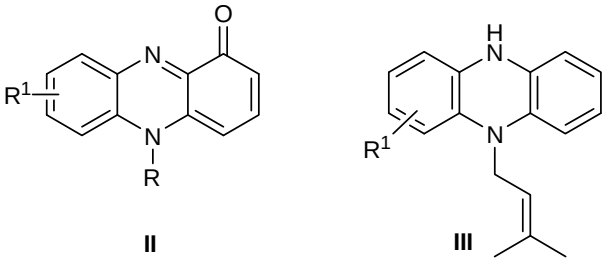
In order to obtain insight into the new domino process with triethyl phosphite as a reagent, the following aspects had to be investigated more closely:

a) Variation of the olefin part of the ω-nitroalkenes used as starting materials; prenyl, crotyl and allyl derivatives have been considered as variations of the alkene part of the ω-nitroalkenes,
b) Variation of the substituents on the aromatic nucleus,
c) Performance of the new domino process under both thermal and microwave conditions,
d) Comparison of the results obtained under thermal and microwave conditions,
e) Analysis of the influence of different organic solvents on the course of the *N*-heteroannulation reaction under both conditions,
f) Observing the reaction times, the yields obtained and the types of products formed.

7) Identification and characterization of the main products and byproducts using the required spectroscopic methods.
8) Carrying out investigations regarding the possible reaction mechanism.
9) Carrying out investigations regarding the scope of the new domino process.
10) Finding new reagents to conduct the domino reaction to saturated *N*-heterocycles.

More recently developed methods for the synthesis of *N*-heterocycles involving the *N*-heteroannulation from nitroaromatics include transition metal-mediated reductive cyclization with CO.[1c] It is known that this type of deoxygenation reaction catalyzed by metals has advantages over the more conventional methods and usually exhibit a higher degree of selectivity compared to the reactions using tervalent phosphorus compounds. Carbon monoxide is important in the reduction of the nitroaromatics, because it both leads to aromatic amines, carbamates, isocyanates and ureas and it acts as a reductant in intramolecular *N*-heteroannulations.[116] Transition metal catalyzed reactions have been recognized as powerful tools for the development of domino reactions and are in the focus of sustained investigations in contemporary inorganic and organometallic chemistry. A wide variety of catalysts have been used, a special place being occupied by the catalytic system palladium / phenanthroline, that catalyzes a number of organic reactions and has a wide range of synthetic applications.

Our goal was also to synthesize *N*-allylated phenazinones of type **II** and *N*-allylated phenazines of type **III** (Fig 5) since they display remarkable biological activities[117, 118] and only few synthesis methods are reported.[119]

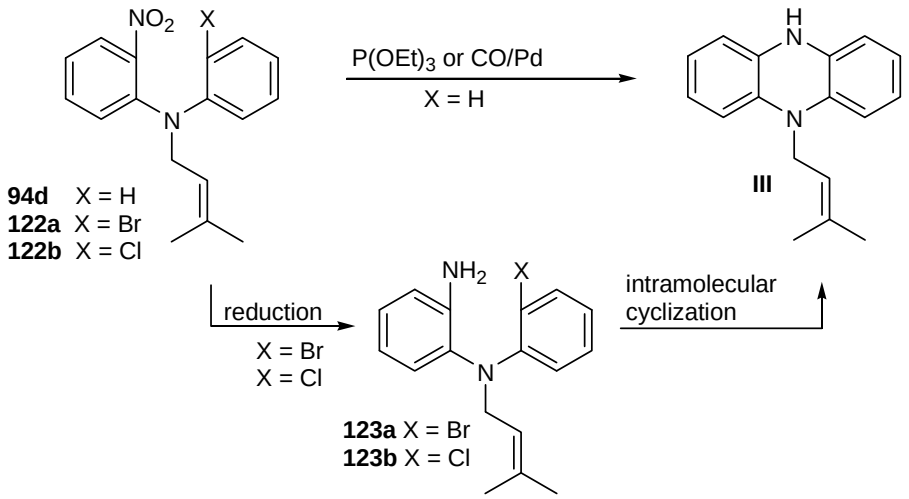


II **III**

Figure 5 *N*-substituted phenazinones **II** and *N*-substituted phenazines **III**.

According to the presumed retrosynthesis (see Scheme 35) our idea was to synthesize *N*-allylated phenazinones via one-step or two-steps reactions, including modern synthetic methods such as the Buchwald-Hartwig[120] *N*-arylation of aryl halides or deoxygenation of the nitro group and *N*-heterocyclization using a catalytic system such as CO-Pd(II).

For this purpose, the Buchwald-Hartwig reaction had to be performed for different substrates using a combination of Pd(0), *rac*-BINAP, Cs_2CO_3 as base and toluene as solvent;[121] *N*-allyl 2-nitrodiphenylamine **94d** had to be considered a key precursor to the possible direct ring closure via the deoxygenation reaction to the compound of type **III**; the tertiary amines **122a**,**b** had to be considered key precursors for a two-step cyclization reaction to yield **III**, via the reduction of the nitro group to the amino group (**123a**,**b**), followed by a possible intramolecular cyclization as shown in Scheme 21.



Scheme 21 Theoretical routes to synthesize phenazinones of type **III**.

An additional proposal of this work was to replace $P(OEt)_3$ in the domino reaction and to conduct further experiments on the ω-nitroalkenes of type **91** and **94** in the presence of CO, using Pd(0) as the active catalyst.

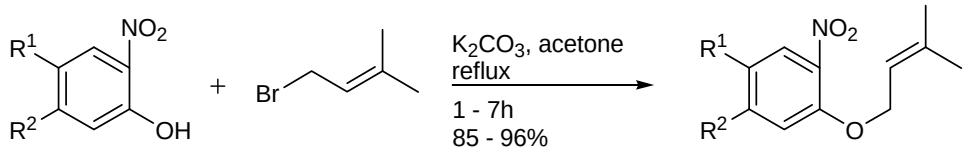
Different ligands, additives, solvents and reaction conditions might be studied and the results had to be compared with those obtained with triethyl phosphite in the domino reaction.

4 SYNTHESIS OF 3-ISOPROPENYL-3,4-DIHYDRO-2*H*-1,4-BENZOXAZINES

4.1 Synthesis of allyl 2-nitrophenyl ethers 99a-k

Allyl 2-nitrophenyl ethers **91a-k** have been taken into account in order for the one-step transformation to yield saturated *N*-heterocycles. The advantage is that allyl 2-nitrophenyl ethers are easily prepared in good yields (85-96%) from the commercially available substituted 2-nitrophenols **86a-k**. Substituted 2-nitrophenols **86a-k** were treated under standard conditions in acetone at reflux with an excess of prenyl bromide **99a**, in the presence of a mild base (K_2CO_3);[122] the reaction times varied from 0.5 to 7 h (Table 1).

Table 1 Synthesis of 2-nitrophenyl ethers **91a-k**.



86a-k **99a** **91a-k**

Entry	**86**	R^1	R^2	*t* [h]	Product **91** (yield [%])
1	**a**	H	H	6	89
2	**b**	Me	H	7	95
3	**c**	OMe	H	6	96
4	**d**	F	H	0.5	93
5	**e**	Cl	H	7	95
6	**f**	Br	H	0.5	87
7	**g**	CO_2Me	H	3.5	86[a]
8	**h**	H	Me	6	90
9	**i**	H	F	0.5	90
10	**j**	H	CO_2Me	2	85[a]
11	**k**	Cl	Me	1	87

[a] Yields were determined over two steps reaction

1) In order to obtain a new domino transformation, the triethyl phosphite was the best choice among other alkyl phosphites [$(MeO)_3P$, (^{i}PrO)$_3$P)]. The one step *N*-heterocyclization of allyl 2-nitrophenyl ethers **91a-k** generated 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines **100a-k** (55-64%), and the byproducts, 4-etyhl-3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines **101a**, **b**,**d**,**e**,**f**,**k** (1-6%).

2) To reduce the reaction time, the allyl 2-nitrophenyl ethers **91a-k** have been subjected to irradiation under microwave conditions, as an alternative protocol. All the results are presented below in a form identical to the publication **1a**,**b** (see list of publications).

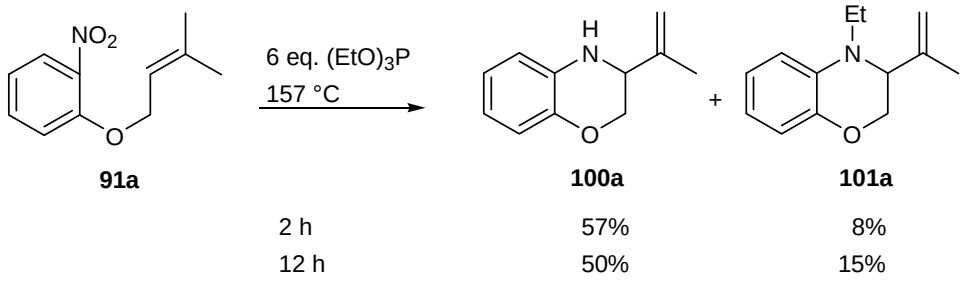
4.2 Triethyl phosphite-mediated domino reaction: direct conversion of ω-nitroalkenes into *N*-heterocycles

Dedicated to Professor Lutz F. Tietze on the occasion of his 65th birthday

The development of new synthetic methods for *N*-heterocycles is an important topic of research in organic synthesis because of their potential application as pharmaceuticals.[123] So far, reductive cyclizations of nitro compounds[1a] have been predominantly employed to construct indoles and related *N*-heteroaromatics. The best known methods include the synthesis of indoles following the procedures of Leimgruber-Batcho,[1b,124] Bartoli[1b,125] and Reissert,[1b] the transition-metal-catalyzed reductive *N*-heteroannulation of *o*-nitrostyrenes[104, 103b] and the Cadogan cyclization.[126] Still little is known about their application to the synthesis of saturated *N*-heterocycles. Another method for the reductive cyclization of aromatic nitro compounds is the transformation of ω-nitro ketones under reducing conditions.[2b] In addition, the potential of the nitroso ene reaction for the formation of C-N bonds has by no means been exhausted.[115] In particular, there is a lack of methods for the one-step generation of the nitroso group from easily accessible precursors. Furthermore, the primary product of the nitroso ene reaction is a hydroxylamine instead of the much more interesting amine. Our aim was to join the nitroso ene reaction and two reduction reactions to create a novel domino process.[114] To this end, the nitro group of a ω-nitroalkene was first to be reduced to give the corresponding nitroso group which then, as the enophile, should undergo an intramolecular ene reaction with the alkene to produce the corresponding hydroxylamine. Final reduction of the NOH group would then deliver the cyclic amine.

Here we describe the reductive cyclization of ω-nitroalkenes to saturated *N*-heterocycles in a single step. As an example, we chose the transformation of allyl 2-nitrophenyl ethers **91** into substituted 3,4-dihydro-2*H*-1,4-benzoxazines **100**, since this structural element occurs in numerous biologically active compounds.[127] A further advantage of allyl 2-nitrophenyl ethers is that they are accessible from the most simple substrates in a single step and in high yields. After some preliminary experiments, which included Pd-catalyzed reactions with CO, we found that this novel domino process can best be accomplished with phosphites. For example, 3,3-dimethylallyl-2-nitrophenyl ether (**91a**) was heated with triethyl phosphite $(EtO)_3P$ to

reflux for two hours, to give 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**100a**) as the main product in 57% yield (Scheme 22).



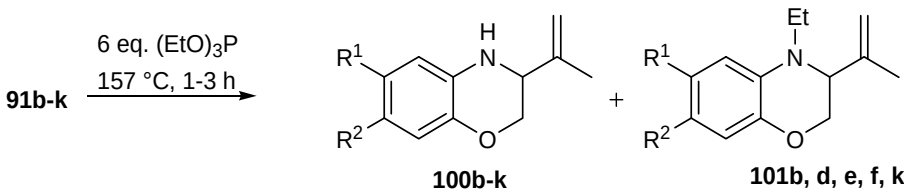
Scheme 22 Domino reaction of **91a** with $(EtO)_3P$ under thermal conditions.

The *N*-ethyl derivative of **100a**, 4-ethyl-3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**101a**) was formed as a side product in 8% yield. Longer reaction times (12 h) decreased the yield of **100a** to 50%, but increased the yield of **101a** to 15%.

We assumed that **101a** is formed by *N*-ethylation of **100a** with triethyl phosphate $(EtO)_3PO$, which was produced by oxidation of $(EtO)_3P$. This assumption was corroborated by the experimental finding that **100a** was recovered unchanged after heating in $(EtO)_3P$ (reflux, 8 h), whereas heating **100a** with $(EtO)_3PO$ (reflux, 6 h) gave **101a** in 70% yield. The formation of *N*-alkylated side products was also observed with other phosphites such as trimethyl and triisopropyl phosphite.

In addition, we investigated whether the new transformation could also be applied to allyl 2-nitrophenyl ethers that were substituted in their aromatic nucleus. The cyclization precursors **91b-k** were synthesized from the reaction of the corresponding substituted *o*-nitrophenols with prenyl bromide under standard conditions (K_2CO_3, acetone, reflux) in yields of 85-96 %. The precursors **91b-k** were heated with $(EtO)_3P$ (reflux 1-3h) to give 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines **100b-k** as the main products with yields of 52-64% (Table 2). Again, in about half the cyclizations, *N*-ethylation was observed as a side reaction to give the substituted 4-ethyl-3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines **101b**,**d**,**e**,**f**,**k** (yields of 1 to 6%).

Table 2 Domino reaction of **91b-k** with $(EtO)_3P$ under thermal conditions.

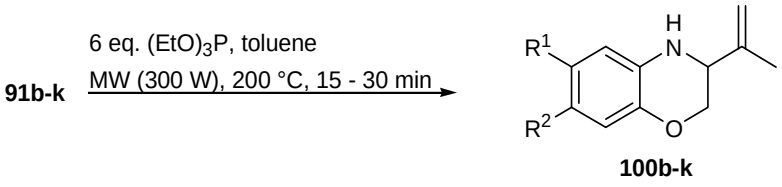


No.	**91**	R^1	R^2	*t* [h]	Product **100** (yield [%])[a]	Product **101** (yield [%])[a]
1	**b**	Me	H	3	63	5
2	**c**	OMe	H	1	60	-
3	**d**	F	H	1	52	6
4	**e**	Cl	H	1	64	3
5	**f**	Br	H	1	55	2
6	**g**	CO_2Me	H	2	58	-
7	**h**	H	Me	1	57	-
8	**i**	H	F	2	58	-
9	**j**	H	CO_2Me	1.5	60	-
10	**k**	Cl	Me	1	60	1

[a] Yields refer to isolated, analytically pure product.

As one of the well-known advantages of the use of microwaves (MW) is reaction acceleration,[128] we repeated the cyclization of **91a** under microwave conditions (300 W, 200 °C). Although the reaction time could be reduced from 2 h to 30 min it was not possible to suppress the formation of **101a**, in 13% yield, along with **100a** in 47% yield. Finally, we examined the effect of solvents on the course of the reaction. **91a** was treated with $(EtO)_3P$ in toluene under both thermal (closed vial, 200 °C, 3 h) and microwave conditions (closed vial, 300 W, 200 °C, 30 min). Surprisingly, both conditions led to exclusive formation of **100a** in 45 and 55%, yields respectively. Similar results were obtained with solvents like cumene and *o*-dichlorobenzene. As a result of the suppression of the side product **101a,** the higher yield of **100a,** and the shorter reaction time, the reductive cyclizations of **91b-k** were repeated under microwave conditions in toluene, too (Table 3). All cyclizations proceeded with complete selectivity within 15 - 30 min with formation of **100b-k** in yields of 57-65%. The results demonstrate that halide and ester functionalities are well tolerated in these transformations.

Table 3 Domino reaction of **91b-k** with $(EtO)_3P$ in toluene under microwave conditions.

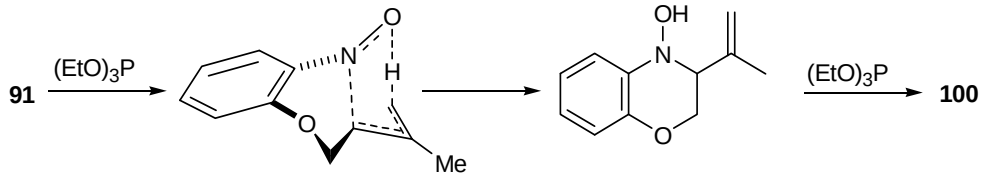


100b-k

No.	**91**	R^1	R^2	*t* [min]	Product **100** (yield [%])[a]
1	**b**	Me	H	20	57
2	**c**	OMe	H	30	58
3	**d**	F	H	15	60
4	**e**	Cl	H	20	63
5	**f**	Br	H	20	64
6	**g**	CO_2Me	H	20	60
7	**h**	H	Me	25	58
8	**i**	H	F	25	61
9	**j**	H	CO_2Me	25	60
10	**k**	Cl	Me	20	65

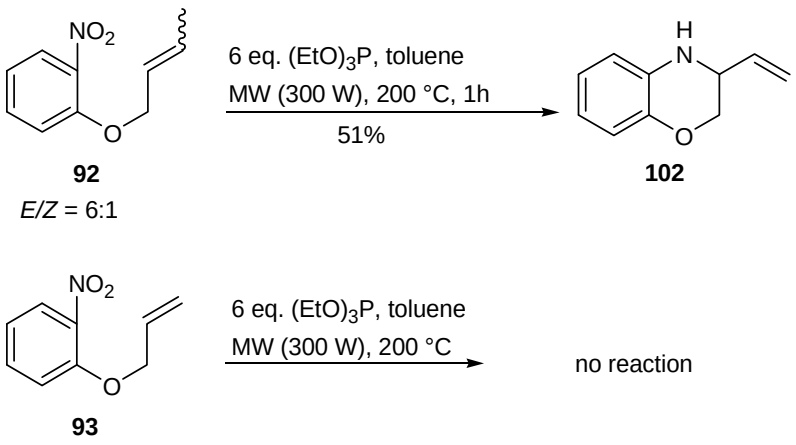
[a] Yields refer to isolated, analytically pure product.

We considered both an intramolecular nitroso ene reaction[115] and the reaction of a nitrene[1c] as the reaction mechanism. In the case of a nitroso ene reaction, the nitro group must be reduced to a nitroso group, which then reacts as an enophile intramolecularly with the 2-methylpropenyl group to form the hydroxylamine. Finally, the hydroxylamine would be reduced to give the amine **100** (Scheme 23).



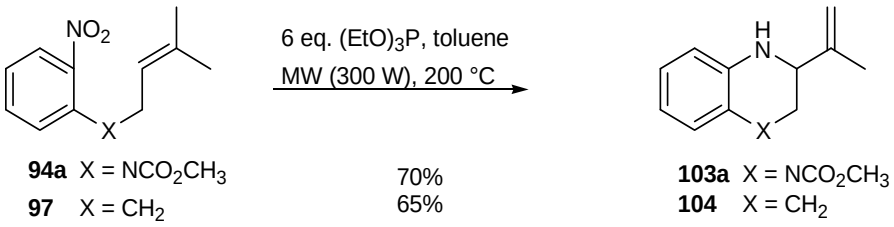
Scheme 23 Potential reaction mechanism

The finding that the 3-methylallyl ether **92** led to the formation of **102** in 51% yield, whereas the allyl ether **93** without any terminal methyl group does not react at all (Scheme 24) supports both mechanisms. Even though we cannot make a definite statement about the mechanism, since both high yields of cyclization products **100** were achieved and the products that would be expected from nitrenes were not observed, we assume the nitroso ene pathway is operating.



Scheme 24 Investigations into the reaction mechanism.

Notably the new reductive cyclization is not only an effective means to construct the 3,4-dihydro-2*H*-1,4-benzoxazine skeleton, but also may be extended to the one-step synthesis of 1,2,3,4-tetrahydroquinoxalines **103a** and 1,2,3,4-tetrahydroquinolines **104**(Scheme 25).



Scheme 25 One-step synthesis of 1,2,3,4-tetrahydroquinoxaline (**103a**) and 1,2,3,4-tetrahydroquinoline (**104**).

Here we describe the first domino reaction in which ω-nitroalkenes are converted into saturated *N*-heterocycles. The reductive cyclization reaction mediated by triethyl phosphite allows access to substituted 3,4-dihydro-2*H*-1,4-benzoxazines, 1,2,3,4-tetrahydroquinoxalines, and 1,2,3,4-tetrahydroquinolines. Investigations into the scope and mechanism of this reaction are ongoing.

Experimental Section

Cyclization of **91** under microwave conditions: Precursor **91** (1 mmol), $(EtO)_3P$ (6 mmol), and toluene (3 mL) were sealed in a septum reaction vial (10 mL) and irradiated with microwaves (Discover™ CEM; 2450 MHz; 300 W; 200 °C; 15- 30 min). After removal of $(EtO)_3P$ and

$(EtO)_3PO$ (10^{-1} mbar), the residue was taken up in EtOAc (25 mL) washed with brine (3 x 20 mL). After drying over $MgSO_4$ and concentration in vacuum, the residue was purified by flash chromatography on silica gel (petroleum ether / EtOAc, 20 : 1).

Keywords: benzoxazines · cyclization · domino reactions · ene-reaction · microwaves

4.3 Supporting Information. Triethyl phosphite-mediated domino reaction: direct conversion of ω-nitroalkenes into *N*-heterocycles

General Methods

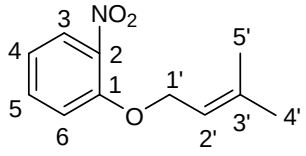
All starting materials were purchased from commercial suppliers (Sigma-Aldrich Chemical Co., Across Organics and Lancaster Organics) and were used without further purification unless otherwise indicated. All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. Temperatures are reported as inner temperatures. Microwave assisted reactions were performed with a Discover™ single mode cavity microwave synthesizer (CEM Corp.), producing continuous irradiation at 2450 MHz. The average power of the radiation was approximately 300 W for all reactions performed at 200 °C. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on Alugram SIL G/UV $_{254}$ (Macherey and Nagel). Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in an ethanolic vanillin solution followed by heating. Products were purified by Kugelrohr distillation or by flash chromatography on silica gel 60 M, 230-400 mesh (Macherey & Nagel). Melting points were determined on a Büchi melting point apparatus B-545 with open capillary tubes and are uncorrected. IR spectra were measured on a Perkin-Elmer *Spectrum One* (FT-IR-spectrometer). UV/VIS spectra were recorded with a Varian Cary 50. ^{1}H (^{13}C) NMR spectra were recorded at 300 (75.4) MHz on a Varian ^{Unity}Inova spectrometer using $CDCl_3$ as a solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.27/77.28 ($CDCl_3$) relative to TMS as internal standards. HSQC-, HMBC- and COSY-spectra were recorded on a Varian ^{Unity}Inova at 300 MHz. Coupling constants *J* [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Low-resolution electron impact mass spectra (EI-LRMS) and exact mass electron impact mass spectra (EI-

HRMS) were obtained at 70 eV on a Finnigan MAT 8200 instrument. Gas-chromatography mass spectra were done on a Thermo Polaris Q equipped with a Varian Trace GC Ultra and a column DB5 (TGC/50/5/10/280). The intensities are reported as percentages relative to the base peak after the corresponding *m/z* value. Elemental analyses were carried out by F. Hambloch, Institut für Organische Chemie, Universität Göttingen, or were obtained from the Institut für Organische Chemie, Universität Stuttgart.

General procedure for the preparation of prenyl 2-nitrophenyl ethers 91a-k[122]

50 mmol 2-nitrophenol, 50 mmol prenyl bromide, 50 mmol anhydrous potassium carbonate and 50 mL acetone were placed in a flask and heated under reflux with stirring. After cooling the reaction mixture was poured into 150 mL water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 2M sodium hydroxide solution and dried over anhydrous potassium carbonate. After removal of the solvent in vacuum the crude product was purified by Kugelrohr distillation or by flash chromatography on SiO_2.

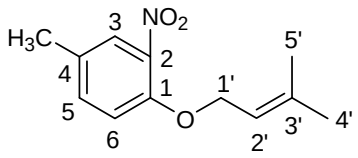
1-(3'-Methyl-but-2'-enyloxy)-2-nitro-benzene (91a)[129]



91a

Yield: 89%. **B.p.** = 153 °C/1-2 mbar. $\mathbf{R_f}$ = 0.32 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 2975 cm^{-1}, 2914 (CH_2, CH_3), 1605, 1520 (C=C), 1350 (C-NO_2), 1275 and 1236 (C-O), 1164, 974 (C-H), 741 (1,2-disubstitution). **UV/VIS** (EtOH): λ_{max} (log ε) = 205 nm (4.09), 258 (3.51), 317 (3.36). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.76 (s, 3H, 4'-H), 1.81 (s, 3H, 5'-H), 4.69 (brd, ^3J = 6.6 Hz, 2H, 1'-H), 5.48 (tq, ^3J = 6.6. Hz, ^4J = 1.1. Hz, 1H, 2'-H), 7.03 (d, 1H, 6-H), 7.09 (t, 1H, 4-H), 7.52 (td, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 1H, 5-H), 7.83 (dd, ^3J = 8 Hz, ^4J = 1.7 Hz, 1H, 3-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.29 (C-5'), 25.74 (C-4'), 66.54 (C-1'), 115.03 (C-6), 118.55 (C-4), 120.11 (C-2'), 125.53 (C-3), 133.83 (C-5), 139.11 (C-2), 140.37 (C-3'), 152.18 (C-1). **MS** (70 eV, EI): *m/z* (%) = 207 (2) [M^+], 192 (1), 175 (2), 139 (9), 123 (9), 106 (10), 92 (3), 78 (13), 69 (100), 67 (90).

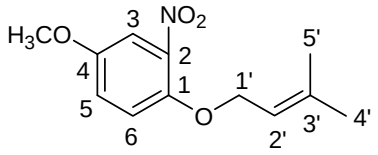
4-Methyl-1-(3'-methyl-but-2'-enyloxy)-2-nitrobenzene (91b)



91b

Yield: 95%. $\mathbf{R_f}$ = 0.27 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 2976 cm^{-1} and 2926 (CH_2, CH_3), 1623 (C=C), 1525 (C=C), 1350 (C-NO_2), 1278, 1255 and 1235 (C-O), 1159, 1085, 977, 808, 671. **UV/VIS** (EtOH): λ_{max} (log ε) = 292 nm (3.88). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.76 (s, 3H, 5'-H, CH_3), 1.81 (s, 3H, 4'-H, CH_3), 2.36 (s, 3H, CH_3), 4.66 (brd, ^3J = 6.6 Hz, 2H, 1'-H), 5.49 (brt, ^3J = 6.6 Hz, 1H, 2'-H), 7.01 (d, ^3J = 8.5 Hz, 1H, 6-H), 7.31 (dd, ^3J = 8.5 Hz, ^4J = 1.4 Hz, 1H, 5-H), 7.65 (brs, 1H, 3-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.5 (C-5'), 20.4 (CH_3), 26.0 (C-4'), 66.9 (C-1'), 115.5 (C-6), 119.0 (C-2'), 125.9 (C-3), 130.4 (C-4), 134.7 (C-5), 139.1 (C-3'), 140.2 (C-2), 150.3 (C-1). **MS** (70 eV, EI): *m/z* (%) = 221 (1) [M^+], 153 (50), 137 (2), 123 (2), 107 (3), 95 (2), 77 (9), 69 (100), 53 (14). **Elemental analysis** (%) calcd for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33; found: C 65.39, H 6.91, N 6.40.

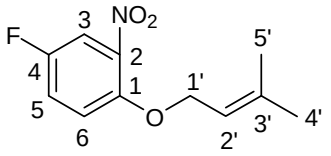
4-Methoxy-1-(3'-methyl-but-2'-enyloxy)-2-nitro-benzene (91c)



91c

Yield: 96%. $\mathbf{R_f}$ = 0.27 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 2970 cm^{-1}, 2936, 2913, 2839 (CH_2, CH_3), 1525 (C=C), 1496, 1349 (C-NO_2), 1276 and 1216 (C-O), 1035, 976, 914, 808, 769. **UV/VIS** (EtOH): λ_{max} (log ε) = 356 nm (3.37), 220 (4.26). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.75 (s, 3H, 5'-H), 1.80 (s, 3H, 4'-H), 3.84 (s, 3H, OMe), 4.64 (brd, ^3J = 6.6 Hz, 2H, 1'-H), 5.48 (brt, ^3J = 6.6 Hz, 1H, 2'-H), 7.07 (d, ^3J = 9.1 Hz, 1H, 6-H), 7.12 (dd, ^3J = 9.1 Hz, ^4J = 2.8 Hz, 1H, 5-H), 7.38 (d, ^4J = 2.8 Hz, 1H, 3-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.5 (C-5'), 26.0 (C-4'), 56.2 (OMe), 67.8 (C-1'), 109.9 (C-3), 117.7 (C-6), 119.2 (C-2'), 120.9 (C-5), 139.2 (C-3'), 140.7 (C-2), 146.7 (C-1), 153.2 (C-4). **GCMS** (70 eV, EI): *m/z* (%) = 237 (1) [M^+], 221 (1), 205 (3), 169 (100), 139 (4), 124 (5), 111 (7), 79 (6), 67 (6). **Elemental analysis** (%) calcd for $C_{12}H_{15}NO_4$: C 60.75, H 6.37, N 5.90; found: C 61.03, H 6.44, N 5.95.

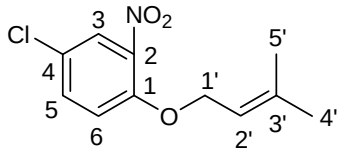
4-Fluoro-1-(3'-methyl-but-2'-enyloxy)-2-nitro-benzene (91d)



91d

Yield: 93%. **M.p.** = 36.4 °C. $\mathbf{R_f}$ = 0.30 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3089 cm^{-1}, 2978, 2917 (CH_2 and CH_3), 1529 (C=C), 1494 (C=C), 1349 (C-NO_2), 1267 (C-O), 1197 (C-F), 976, 939, 811, 774. **UV** (EtOH): λ_{max} (log ε) = 474 nm (1.71), 299 (3.42), 228 (3.92). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.75 (s, 3H, 5'-H), 1.80 (s. 3H, 4'-H), 4.67 (brd, ^3J = 6.7 Hz, 2H, 1'-H), 5.47 (brt, ^3J = 6.7 Hz, ^4J = 1.1 Hz, 1H, 2'-H), 7.09 (dd, ^3J = 9.4 Hz, 1H, 6-H), 7.27 (ddd, ^3J = 9.2 Hz, $^3J_{H\text{-}F}$ = 7.3 Hz, ^4J = 2.9 Hz, 1H, 5-H), 7.57 (dd, $^3J_{H\text{-}F}$ = 7.3 Hz, ^4J = 3.1 Hz, 1H, 3-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.53 (C-5'), 26 (C-4'), 67.59 (C-1'), 112.93 (d, C-3, $^2J_{C\text{-}F}$ = 27 Hz), 117.05 (d, C-6, $^3J_{C\text{-}F}$ = 7.8 Hz), 118.65 (C-2'), 121.06 (d, C-5, $^2J_{C\text{-}F}$ = 22.8 Hz), 139.79 (C-3'), 140.2 (brs, C-2), 149.02 (d, C-1, $^4J_{C\text{-}F}$ = 2.8 Hz), 155.47 (d, C-4, $^1J_{C\text{-}F}$ = 243 Hz). **MS** (70 eV, EI): *m/z* (%) = 225 (1) [M^+], 193 (1), 157 (2), 82 (3), 69 (100), 53 (5), 41 (75). **HRMS** (EI, M^+): calcd for $C_{11}H_{12}FNO_3$: 225.0801; found: 225.0763. **Elemental analysis** (%) calcd for $C_{11}H_{12}FNO_3$: C 58.66, H 5.37, N 6.22; found: C 58.50, H 5.15, N 6.03.

4-Chloro-1-(3'-methyl-but-2'-enyloxy)-2-nitro-benzene (91e)

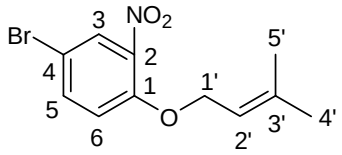


91e

Yield: 95%. **M.p.** = 55 °C. $\mathbf{R_f}$ = 0.30 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 2975 cm^{-1}, 2935, 2915 and 2881 (CH_2, CH_3), 1607 (C=C), 1526 (C=C), 1481, 1348 (C-NO_2), 1272 and 1234 (C-O), 1117 (C-Cl), 972, 885, 811, 719. **UV** (EtOH): λ_{max} (log ε) = 335 nm (3.37), 220 (4.35). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.77 (s, 3H, 5'-H), 1.82 (s, 3H, 4'-H), 4.69 (brd, ^3J = 6.7 Hz, 2H, 1'-H), 5.4 (brt, ^3J = 6.7 Hz, ^4J = 1.1 Hz, 1H, 2'-H), 7.06 (d, ^3J = 9.1 Hz, 1H, 6-H), 7.49 (dd, ^3J = 9.1 Hz, ^4J = 2.5 Hz, 1H, 5-H), 7.83 (d, ^4J = 2.5 Hz, 1H, 3-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.6 (C-5'), 26.0 (C-4'), 67.2 (C-1'), 116.6 (C-6), 118.4 (C-2'), 125.4 (C-4), 125.7 (C-3), 133.9 (C-5), 139.9 (C-3'), 140.6 (C-2), 151.1 (C-1). **MS** (70 eV, EI): *m/z* (%) = 173 (2) [M^+ - 68], 156 (1), 140 (1), 128 (1), 112 (1), 98 (3), 69 (100), 63 (15), 54 (8), 41

(67), 27 (8). **Elemental analysis** (%) calcd for $C_{11}H_{12}ClNO_3$: C 54.67, H 5.00, N 5.80, Cl 14.67; found: C 54.67, H 5.01, N 5.77, Cl 14.57.

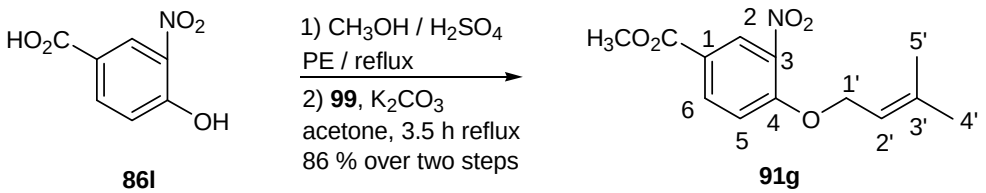
4-Bromo-1-(3'-methyl-but-2'-enyloxy)-2-nitro-benzene (91f)



91f

Yield: 87%. **M.p.** = 66 °C. $\mathbf{R_f}$ = 0.5 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 2968 cm^{-1}, 2910 (CH_2 and CH_3), 1606, 1524 (C=C), 1357 (C-NO_2), 1277 and 1256 (C-O), 1100 (C-Br), 988, 977, 876, 810, 782. **UV** (EtOH): λ_{max} (log ε) = 476 nm (2.70), 307 (3.33), 221 (4.33). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.77 (s, 3H, 4'-H), 1.82 (s, 3H, 5'-H), 4.69 (brd, ^3J = 9 Hz, 2H, 1'-H), 5.47 (brt, ^3J = 6.7 Hz, ^4J = 1.1 Hz, 1H, 2'-H), 7.00 (brd, ^3J = 9 Hz, 1H, 6-H), 7.62 (dd, ^3J = 9 Hz, ^4J = 5.5 Hz, 2.5 Hz, 1H, 5-H), 7.97 (d, 1H, ^4J = 2.4 Hz, 3-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.60 (C-4'), 20.02 (C-5'), 67.15 (C-1'), 111.93 (C-4), 116.99 (C-6), 118.37 (C-2'), 128.49 (C-3), 136.81 (C-5), 140.03 (C-3'), 141.00 (C-2), 151.62 (C-1). **MS** (70 eV, EI): *m/z* (%) = 287/ 285 (4), 219/ 217 (5), 69 (100), 63 (5), 41 (38), 28 (14). **HRMS** (EI, M^+): calcd for $C_{11}H_{12}BrNO_3$: 285.0001; found: 285.0013. **Elemental analysis** (%) calcd for $C_{11}H_{12}BrNO_3$: C 46.18, H 4.23, N 4.90; found: C 45.91, H 4.02, N 5.11.

4-(3'-Methyl-but-2'-enyloxy)-3-nitro-benzoic acid methyl ester (91g) was prepared in two steps starting from 4-hydroxy-3-nitrobenzoic acid **86l**. After esterification with methanol according to a known procedure[130] the 4-hydroxy-3-nitrobenzoic acid methyl ester was prenylated to yield **91g**.

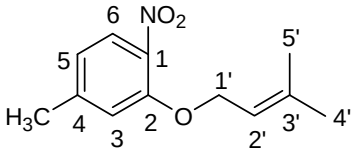


86l **91g**

Yield: 86% (over two steps). **M.p.** = 110 °C. $\mathbf{R_f}$ = 0.41 (SiO_2, PE/TBME = 3 : 1). **IR** (ATR): $\tilde{\nu}$ = 3086 cm^{-1} and 2959 (CH_2 and CH_3), 1715 (C=O), 1615 (C=C), 1529 (C=C), 1434, 1343 (C-NO_2), 1266, and 1237 (C-O), 1160, 954, 822, 756, 697. **UV (**EtOH): λ_{max} (log

ε) = 316 nm (2.96), 242 (4.25). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.78 (s, 3H, 5'-H), 1.82 (s, 3H, 4'-H), 3.95 (s, 3H, OCH_3), 4.76 (brd, ^3J = 6.6 Hz, 2H, 1'-H), 5.49 (brt, ^3J = 6.6 Hz, ^4J = 1.1 Hz, 1H, 2'-H), 7.12 (brd, ^3J = 8.9 Hz, 1H, 5-H), 8.20 (dd, ^3J = 8.9 Hz, ^4J = 2.2, Hz, 1H, 6-H), 8.49 (d, ^4J = 2.2, Hz, 1H, 2-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.6 (C-5'), 26.0 (C-4'), 52.6 (OCH_3), 67.1 (C-1'), 114.5 (C-5), 118.0 (C-2'), 122.4 (C-1), 127.4 (C-2), 135.2 (C-6), 139.9 (C-3'), 140.3 (C-3), 155.6 (C-4), 165.2 (C=O). **MS** (70 eV, EI): *m/z* (%) = 265 (8) [M^+], 233 (4), 206 (13), 166 (15), 120 (3), 91 (2), 69 (100), 41 (28). **HRMS** (EI, M^+): calcd for $C_{13}H_{15}NO_5$: 265.0950; found: 265.0929. **Elemental analysis** (%) calcd for $C_{13}H_{15}NO_5$: C 58.86, H 5.70, N 5.28; found: C 58.56, H 5.51, N 5.02.

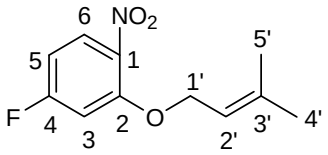
4-Methyl-2-(3'-methyl-but-2'-enyloxy)-1-nitrobenzene (91h)



91h

Yield: 90%. **R_f** = 0.24 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 2986 cm^{-1}, 2917 (CH_2, CH_3), 1605 (C=C), 1589 (C=C), 1513, 1492, 1343 (C-NO_2), 1274 (C-O), 1176, 1089, 986, 839 (C-H alkene), 815, 752. **UV** (EtOH): λ_{max} (log ε) = 326 nm (2.51), 267 (3.63), 214 (4.21). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.77 (s, 3H, 5'-H), 1.81 (s, 3H, 4'-H), 2.42 (s, 1H, Me), 4.67 (brd, ^3J = 6.6 Hz, 2H, 1'-H), 5.51(brt, ^3J = 6.6 Hz, ^4J = 1.1 Hz, 1H, 2'-H), 6.82 (brd, ^3J = 8.5 Hz, 1H, 5-H), 6.89 (brs, 1H, 3-H), 7.80 (d, ^3J = 8.3 Hz, 1H, 6-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.6 (C-5'), 22.2 (CH_3), 26.0 (C-4'), 66.7 (C-1'), 115.8 (C-3), 118.9 (C-2'), 121.1 (C-5), 126.0 (C-6), 138.11 (C-1), 139.2 (C-3'), 145.7 (C-4), 152.7 (C-2). **MS** (70 eV, EI): *m/z* (%) = 221 (5) [M^+], 189 (8), 153 (20) [M^+-68], 137 (8), 121 (4), 77 (3), 69 (100), 41 (42). **HRMS** (EI, M^+): calcd for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1048. **Elemental analysis** (%) calcd for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33; found: C 65.44, H 6.85, N 6.45.

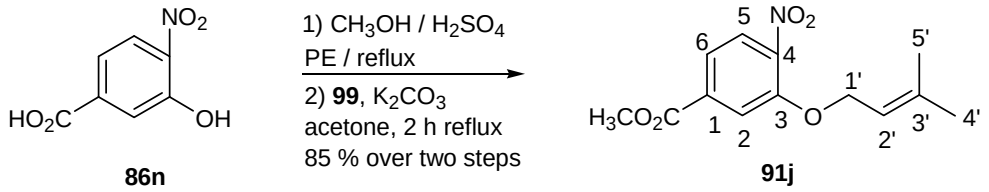
4-Fluoro-2-(3'-methyl-but-2'-enyloxy)-1-nitro-benzene (91i)



91i

Yield: 90%. **M.p.** = 31.5 °C. $\mathbf{R_f}$ = 0.25 (PE/CH_2Cl_2 = 3 : 1). **IR** (ATR): $\tilde{\nu}$ = 3091 cm^{-1}, 2976, 2916 (CH_2 and CH_3), 1618 (C=C), 1587 and 1521 (C=C), 1348 (C-NO_2), 1279 (C-O), 1168 (C-F), 1087, 837 (C-H alkene), 749. **UV** (EtOH): λ_{max} (log ε) = 440 nm (1.91), 313 (3.46), 257 (3.52), 212 (4.24). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.78 (s, 3H, 4'-H), 1.82 (s, 3H, 5'-H), 4.69 (brd, ^3J = 6.6 Hz, 2H, 1'-H) , 5.5 (brt, ^3J = 6.6 Hz, ^4J = 1.1 Hz, 1H, 2'-H), 6.72 (ddd, ^3J = 9.3 Hz, $^3J_{H-F}$ = 7.3 Hz, ^4J = 2.4 Hz, 1H, 5-H), 6.83 (dd, $^3J_{H-F}$ = 10.5 Hz, ^4J = 2.5 Hz, 1H, 3-H), 7.95 (dd, ^3J = 9.1 Hz, $^4J_{H-F}$ = 6.1 Hz, 1H, 6-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.61 (C-4'), 26.03 (C-5'), 67.20 (C-1'), 102.9 (d, $^2J_{C-F}$ = 26.8 Hz, C-3), 107.38 (d, $^2J_{C-F}$ = 23.6 Hz, C-5), 118.12 (C-2'), 128.23 (d, $^3J_{C-F}$ = 11.5 Hz C-6), 136.63 (brs, C-1), 140.16 (C-3'), 154.77 (d, C-2, $^3J_{C-F}$ = 11.3 Hz), 165.82 (d, $^1J_{C-F}$ = 255 Hz, C-4). **MS** (70 eV, EI): *m/z* (%) = 225 (4) [M^+], 209 (1), 193 (2), 157 (5), 141 (6), 124 (4), 96 (5), 69 (100), 41 (78). **HRMS** (EI, M^+): calcd for $C_{11}H_{12}FNO_3$: 225.0801; found: 225.0770. **Elemental analysis** (%) calcd for $C_{11}H_{12}FNO_3$: C 58.66, H 5.37, N 6.22; found: C 58.41, H 5.47, N 6.11.

3-(3'-Methyl-but-2'-enyloxy)-4-nitro-benzoic acid methyl ester (91j) was prepared in two steps starting from 3-hydroxy-4-nitrobenzoic acid **86n**. After esterification with methanol according to a known procedure[130] the 4-hydroxy-3-nitrobenzoic acid methyl ester was prenylated to yield **91j**.

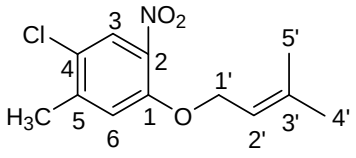


86n **91j**

Yield: 85% over two steps. **M.p.** = 78 °C. $\mathbf{R_f}$ = 0.46 (SiO_2, PE/TBME = 3 : 1). **IR** (ATR): $\tilde{\nu}$ = 2940 cm^{-1} (CH_2 and CH_3), 1725 (C=O), 1609 (C=C), 1582, 1515 (C=C), 1436, 1337 (C-NO_2), 1288, 1225 and 1976 (C-O), 995, 962, 834 (C-H alkene), 745. **UV** (EtOH): λ_{max} (log ε) = 327 nm (3.46), 256 (3.65), 234 (3.95). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.80 (s, 3H, 4'-H), 1.82 (s, 3H, 5'-H), 3.98 (s, 3H,OMe), 4.75 (brd, ^3J = 6.6 Hz , 2H, 1'-H), 5.49 (brt, ^3J = 6.6 Hz, ^4J = 1.1 Hz, 1H, 2'-H), 7.68 (dd, ^3J = 8.41 Hz, ^4J = 1.3 Hz, 1H, 6-H), 7.77 (brs, ^4J = 1.2 Hz, 1H, 2-H), 7.83 (d, ^3J = 8.4 Hz, 1H, 5-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.60 (C-4'), 26.0 (C-5'), 53.0 (OMe), 67.1 (C-1'), 116.3 (C-2), 118.3 (C-2'), 121.4 (C-6), 125.4 (C-5), 134.8 (C-1), 140.1 (C-3'), 143.1 (C-4), 151.9 (C-3), 165.5 (C=O). **MS** (70 eV, EI): *m/z* (%) = 265 (3) [M^+], 234 (2), 197 (4) [M^+-68], 136 (2), 119 (4), 91 (2), 69 (100), 53 (2), 41 (38).

HRMS (EI, M^+): calcd for $C_{13}H_{15}NO_5$: 265.0950; found: 265.0915. **Elemental analysis** (%) calcd for $C_{13}H_{15}NO_5$: C 58.86, H 5.70, N 5.28; found: C 58.56, H 5.51, N 5.02.

4-Chloro-5-methyl-1-(3'-methyl-but-2'-enyloxy)-2-nitrobenzene (91k)



91k

Yield: 87%. **M.p. =** 62-63 °C. $\mathbf{R_f}$ = 0.3 (PE/EtOAc = 20:1). **IR** (ATR): $\tilde{\nu}$ = 2977 cm^{-1}, 2937, 2916, 2881 and 2856 (CH_2 and CH_3), 1609 (C=C), 1506 (C=C), 1376 (C-NO_2), 1340, 1261, 1250, 1176 (C-O), 1103, 959, 853, 829 (C-H alkene), 758, 709. **UV** (EtOH): λ_{max} (log ε) = 464 nm (2.60), 316 (3.44), 222 (4.27). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.78 (s, 3H, 5'-H), 1.82 (s, 3H, 4'-H), 2.45 (s, 3H, CH_3), 4.67 (brd, ^3J = 6.7 Hz , 2H, 1'-H), 5.48 (brt, ^3J = 6.7 Hz, ^4J = 1.1 Hz, 1H, 2'-H), 6.97 (s, 1H, 6-H), 7.90 (s, 1H, 3-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 18.59 (C-5'), 21.06 (CH_3), 26.05 (C-4'), 67.71 (C-1'), 117.55 (C-6), 118.55 (C-2'), 125.50 (C-4), 126.25 (C-3), 138.34 (C-2), 139.78 (C-3'), 143.43 (C-5), 151.22 (C-1). **MS** (70 eV, EI): *m/z* (%) = 257/ 255 (1) [M^+], 190 (2), 187 (35), 69 (100), 41 (3). **HRMS** (EI, M^+): calcd for $C_{12}H_{14}ClNO_3$: 255.0662; found: 255.0685. **Elemental analysis** (%) calcd for $C_{12}H_{14}ClNO_3$: C 56.37, H 5.52, N 5.48; found: C 56.14, H 5.30, N 5.27.

General procedure for the Domino reaction of 91a-k under thermal conditions

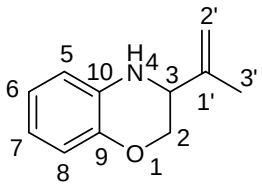
A mixture of 1 mmol **91** and 6 mmol triethyl phosphite was refluxed under argon for 0.5-3 h. After removing triethyl phosphate and triethyl phosphate by distillation under reduced pressure the remaining residue was purified by flash chromatography on silica gel using PE/EtOAc = 20 : 1 as eluent.

General procedure for the Domino reaction of 91a-k under microwave conditions

A 10 mL process vial was charged with a mixture of 1 mmol **91**, 6 mmol triethyl phosphite and 3 mL toluene. The vial was sealed, placed into the cavity of the microwave reactor and irradiated with microwaves at 200 °C for 15–30 min. After removing triethyl phosphate and triethyl phosphate by distillation under reduced pressure the remaining residue was diluted

with EtOAc (25 mL) and washed with brine (3 x 20 mL). The organic layer was dried over magnesium sulphate and the solvent was removed under reduced pressure. The remaining residue was purified by flash chromatography over silica gel using PE/EtOAc = 20 : 1 as eluent.

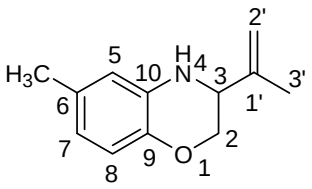
3-Isopropenyl-3,4-dihydro-*2H*-1,4-benzoxazine (100a)[131]



100a

R_f = 0.55 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3364 cm^{-1} (NH), 2976 and 2876 (CH_2, CH_3), 1607, 1590 (C=C), 1498, 1275 and 1205 (C-O), 1047, 1009, 903, 738. **UV** (EtOH): λ_{max} (log ε) = 297 nm (3.57), 248 (3.79). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.86 (s, 3H, 3'-H), 3.96 (overlapped, 1H, 3-H), 3.97 (dd, ^3J = 7.6 Hz, ^2J = 16.8 Hz , 1H, 2-H), 4.31 (dd, ^3J = 8.2 Hz, ^2J = 16.4 Hz, 1H, 2-H), 5.05 (brs, 2H, 2'-H), 5.15 (brs, 2H, 2'-H), 6.70, 6.71, 6.80, 6.81 (overlapped, 4H, 5-H, 6-H, 7-H, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.8 (C-3'), 55.4 (C-3), 68.7 (C-2), 113.6 (C-2'), 115.9 (C-5), 116.8 (C-8), 119.5 (C-7), 121.7 (C-6), 133.40 (C-10), 142.85 (C-1'), 143.97 (C-9). **MS** (70 eV, EI): *m/z* (%) = 175 (100) [M^+], 160 (12), 144 (16), 134 (82), 120 (17), 106 (18), 77 (12), 65 (13), 52 (17), 39 (18). **HRMS** (EI, M^+): calcd for $C_{11}H_{13}NO$: 175.0997; found: 175.0984. **Elemental analysis** (%) calcd for $C_{11}H_{13}NO$: C 75.40, H 7.48, N 7.99; found: C 75.42, H 7.51, N 8.02.

3-Isopropenyl-6-methyl-3,4-dihydro-*2H*-1,4-benzoxazine (100b)

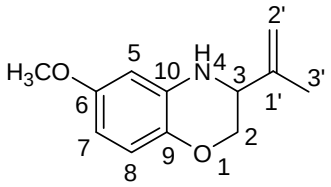


100b

R_f = 0.40 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3362 cm^{-1} (NH), 2975, 2918 and 2871 (CH_2 and CH_3), 1595 (C=C), 1513, 1474 (C-H), 1357, 1304, 1262 and 1210 (C-O), 903, 796. **UV** (EtOH): λ_{max} (log ε) = 302 nm (3.58), 249 (3.73), 212 (4.49). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, 3'-H), 2.25 (s, 3H, CH_3), 3.96 (overlapped, 1H, 3-H), 3.98 (dd, ^3J = 7.6 Hz, ^2J = 16.8 Hz , 1H, 2-H), 4.25 (dd, ^3J = 7.5 Hz, ^2J = 16.4 Hz, 1H, 2-H), 5.03 (brs, 1H,

2'-H), 5.13 (brs, 1H, 2'-H), 6.50 (m, 1H, 7-H), 6.51 (brs, 1H, 5-H), 6.73 (d, ^{3}J = 8.6 Hz, 1H, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.80 (C-3'), 20.98 (CH_3), 55.47 (C-3), 68.9 (C-2), 113.3 (C-2'), 116.05 (C-5), 116.46 (C-8), 119.5 (C-7), 131.2 (C-6), 133.4 (C-10), 141.7 (C-9), 143.1 (C-1'). **GCMS** (70 eV, EI): *m/z* (%) = 189 (100) [M^+], 174 (14), 160 (20), 148 (52), 134 (21), 120 (28), 103 (9), 91 (13), 77 (14), 65. **Elemental analysis** (%) calcd for $C_{12}H_{15}NO$: C 76.16, H 7.99, N 7.40; found: C 76.00, H 8.08, N 7.52.

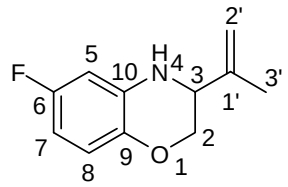
3-Isopropenyl-6-methoxy-3,4-dihydro-2*H*-1,4-benzoxazine (100c)



100c

R_f = 0.39 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3364 cm^{-1} (NH), 2933 and 2833 (CH_2 and CH_3), 1615 (C=C), 1509 (C=C), 1258 and 1200 (C-O), 1166, 1046, 1033, 903, 826, 784. **UV** (EtOH): λ_{max} (log ε) = 305 nm (3.76), 243 (3.75). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, 3'-H), 3.76 (s, 1H, OMe), 3.87 (dd, ^{3}J = 7.1 Hz, 1H, 2-H), 3.90 (overlapped, 1H, 3-H), 4.24 (dd, ^{3}J = 7.1 Hz, 1H, 2-H), 5.03 (brs, 1H, 2'-H), 5.12 (brs, 1H, 2'-H), 6.26 (dd, ^{3}J = 8.7 Hz, ^{4}J = 2.8 Hz, 1H, 7-H), 6.27 (brs, 1H, 5-H), 6.75 (brd, ^{3}J = 9.3 Hz, 1H, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.79 (C-3'), 55.52 (C-3), 55.85 (OCH_3), 68.72 (C-2), 101.34 (C-5), 103.84 (C-7), 113.3 (C-2'), 116.95 (C-8), 134.17 (C-10), 138.05 (C-9), 143.06 (C-1'), 154.8 (C-6). **GCMS** (70 eV, EI): *m/z* (%) = 205 (100) [M^+], 190 (10), 174 (14), 164 (28), 150 (34), 136 (8), 123 (6), 91 (3), 79 (5), 68 (4). **Elemental analysis** (%) calcd for $C_{12}H_{15}NO_2$: C 70.22, H 7.37, N 6.82; found: C 70.14, H 7.35, N 6.82.

6-Fluoro-3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine (100d)

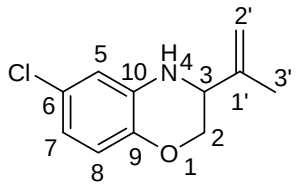


100d

R_f = 0.37 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3382 cm^{-1} (NH), 2979, 2923, 2877 (CH_2 and CH_3), 1622 and 1507 (C=C), 1306, 1203 (C-O), 1157 (C-F), 967, 833, 747. **UV** (EtOH): λ_{max} (log ε) = 302 nm (3.71), 246 (3.84), 206 (4.44). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85

(s, 3H, 3'-H), 3.91 (overlapped, 1H, 3-H), 3.92 (dd, ^{3}J = 7.1 Hz, 1H, 2-H), 4.25 (dd, ^{3}J = 7.1 Hz, 1H, 2-H), 5.05 (brs, 1H, 2'-H), 5.11 (brs, 1H, 2'-H), 6.36 (dt, ^{3}J = 8.4 Hz, $^{3}J_{H\text{-}F}$ = 8.4 Hz, ^{4}J = 2.9 Hz, 1H, 7-H), 6.40 (brdd, $^{3}J_{H\text{-}F}$ = 9.8 Hz, ^{4}J = 2.9 Hz, 1H, 5-H), 6.75 (dd, ^{3}J = 8.6 Hz, $^{4}J_{H\text{-}F}$ = 5.4 Hz, 1H, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.73 (C-3'), 55.2 (C-3), 68.5 (C-2), 101.95 (d, $^{2}J_{C\text{-}F}$ = 27 Hz, C-5), 104.65 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz, C-7), 113.60 (C-2'), 117.05 (d, $^{3}J_{C\text{-}F}$ = 9.8 Hz, C-8), 134.40 (brd, $^{3}J_{C\text{-}F}$ = 11.2 Hz, C-10), 139.74 (d, $^{4}J_{C\text{-}F}$ = 2.11 Hz, C-9), 142.72 (C-1'), 158.09 (d, $^{1}J_{C\text{-}F}$ = 236 Hz, C-6). **MS** (70 eV, EI): *m/z* (%) = 193 (100) [M^+], 178 (11), 162 (14), 152 (68), 138 (30), 124 (15), 96 (11), 69 (55), 41 (37). **HRMS** (EI, M^+): calcd for $C_{11}H_{12}FNO$: 193.0903; found: 193.0900. **Elemental analysis** (%) calcd for $C_{11}H_{12}FNO$: C 68.38, H 6.26, N 7.25; found: C 68.46, H 6.32, N 7.21.

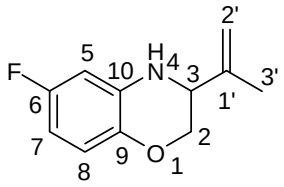
6-Chloro-3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine (100e)



100e

R_f = 0.33 (PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3377 cm^{-1} (NH), 2981, 2926, and 2877 (CH_2 and CH_3), 1606 (C=C), 1494, 1286 and 1203 (C-O), 1086 (C-Cl), 904, 841, 793. **UV** (EtOH): λ_{max} (log ε) = 307 nm (3.68), 254 (3.86), 215 (4.57). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.84 (s, 3H, 3'-H), 3.91 (dd, ^{3}J = 7.3 Hz , 1H, 2-H), 3.93 (overlapped, 1H, 3-H), 4.26 (dd, ^{3}J = 7.3 Hz, 1H, 2-H), 5.04 (brs, 1H, 2'-H), 5.10 (brs, 1H, 2'-H), 6.62 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.5 Hz, 1H, 7-H), 6.65 (d, ^{4}J = 2.3 Hz, 1H, 5-H), 6.74 (d, ^{3}J = 8.3 Hz, 1H, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.73 (C-3'), 55.09 (C-3), 68.65 (C-2), 113.69 (C-2'), 114.92 (C-5), 117.61 (C-8), 118.49 (C-7), 126.38 (C-6), 134.66 (C-10), 142.38 (C-9), 142.6 (C-1'). **MS** (70 eV, EI): *m/z* (%) = 211/ 209 [M^+] (100), 194 (24), 178 (23), 170 (44), 168 (75), 154 (69), 140 (24), 127 (11), 104 (10), 99 (9), 77 (16), 68 (15), 41 (17). **HRMS** (EI, M^+): calcd for $C_{11}H_{12}ClNO$: 209.0607; found: 209.0588. **Elemental analysis** (%) calcd for $C_{11}H_{12}ClNO$: C 63.01, H 5.77, N 6.68; found: C 62.93, H 5.86, N 6.67.

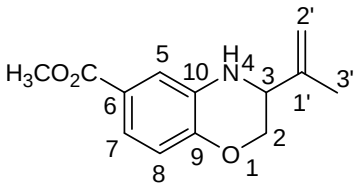
6-Bromo-3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine (100f)



100f

R_f = 0.58 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3375 cm^{-1} (NH), 2977, 2921, 2877 (CH_2 and CH_3), 1601 and 1491(C=C), 1281, 1202 (C-O), 1010, 903, 792. **UV** (EtOH): λ_{max} (log ε) = 308 nm (3.66), 254 (3.79), 214 (4.53). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.84 (s, 3H, 3'-H), 3.91 (overlapped, 1H, 3-H), 3.94 (dd, ^3J = 7.5 Hz, 1H, 2-H), 4.27 (dd, ^3J = 7.5 Hz, 1H, 2-H), 5.05 (brs, 1H, 2'-H), 5.11 (brs, 1H, 2'-H), 6.78 (dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 1H, 7-H), 6.81 (d, ^4J = 2.2 Hz, 1H, 5-H), 6.69 (d, ^3J = 8.6 Hz, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.75 (C-2'), 55.07 (C-3), 68.57 (C-2), 113.67 (C-6), 113.81 (C-2'), 117.89 (C-5), 118.12 (C-8), 121.6 (C-7), 134.88 (C-10), 142.47 (C-1'), 142.97 (C-9). **MS** (70 eV): *m/z* (%) = 255/ 253 (100) [M^+], 238 (8), 224 (10), 212 (50), 198 (14), 174 (5), 144 (6), 133 (15), 105 (13), 78 (11), 41 (10). **HRMS** (EI, M^+): calcd for $C_{11}H_{12}BrNO$: 253.0102; found: 253.0104. **Elemental analysis** (%) calcd for $C_{11}H_{12}BrNO$: C 51.99, H 4.76, N 5.51; found: C 52.06, H 4.82, N 5.46.

3-Isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxylic acid methyl ester (100g)

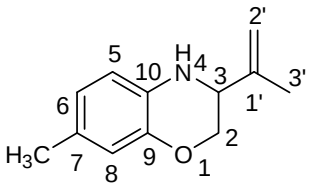


100g

M.p. = 92 °C. **R_f** = 0.41 (SiO_2, PE/TBME = 3 : 1). **IR** (ATR): $\tilde{\nu}$ = 3342 cm^{-1} (NH), 2944, 2840 (CH_2 and CH_3), 1689 (C=O), 1587 (C=C), 1491, 1438, 1303, 1210 (C-O), 1124, 1001, 911, 768. **UV** (EtOH): λ_{max} (log ε) = 327 nm (3.55), 267 (3.80), 239 (4.46). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, 3'-H), 3.88 (s, 3H, OCH_3), 3.92, (overlapped, 1H, 3-H), 4.00 (dd, ^3J = 9.9 Hz, 1H, 2-H), 4.33 (dd, ^3J = 10.2 Hz, 1H, 2-H), 5.06 (brs, 1H, 2'-H), 5.13 (brs, 1H, 2'-H), 6.83 (brd, ^3J = 8.2 Hz, 1H, 8-H), 7.40 (brs, 1H, 5-H), 7.42 (dd, ^3J = 8.2 Hz, ^4J = 2.1 Hz, 1H, 7-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.76 (C-3'), 52.08 (OMe), 54.95 (C-3), 69.09 (C-2), 113.78 (C-2'), 116.46 (C-8), 116.81 (C-5), 121.22 (C-7), 123.53 (C-6), 133.44 (C-10), 142.47 (C-1'), 147.87 (C-9), 167.30 (C=O). **MS** (70 eV, EI): *m/z* (%) = 233 (100)

[M^+], 218 (11), 202 (11), 192 (63), 178 (14), 144 (4), 132 (5), 104 (6), 77 (2), 93 (3), 51 (2), 41 (3). **HRMS** (EI, M^+): calcd for $C_{13}H_{15}NO_3$: 233.1052; found: 233.1057. **Elemental analysis** (%) calcd for $C_{13}H_{15}NO_3$: C 66.94, H 6.48, N 6.01; found: C 66.65, H 6.48, N 5.92.

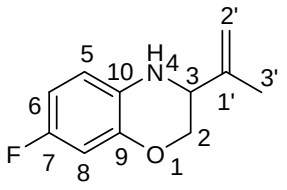
3-Isopropenyl-7-methyl-3,4-dihydro-*2H*-1,4-benzoxazine (100h)



100h

R_f = 0.50 (PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3356 cm^{-1} (NH), 2975, 2917 (CH_2 and CH_3), 1588 (C=C), 1512 (C=C), 1294 and 1278 (C-O), 1153, 1135, 1048, 903, 797. **UV** (EtOH): λ_{max} (log ε) = 303 nm (3.53), 249 (3.80), 212 (4.55). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, 3'-H), 2.26 (s, 3H, CH_3), 3.92 (overlapped, 1H, 3-H), 3.97 (dd, ^3J = 9.6 Hz, 1H, 2-H), 4.28 (dd, ^3J = 9.6 Hz, 1H, 2-H), 5.04 (brs, 1H, 2'-H), 5.14 (brs, 1H, 2'-H), 6.59 (d, ^3J = 7.9 Hz, 1H, 5-H), 6.63 (m, 1H, 8-H), 6.67 (m, 1H, 6-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.87 (C-3'), 20.84 (CH_3), 55.51 (C-3), 68.97 (C-2), 113.40 (C-2'), 115.6 (C-5), 117.31 (C-6), 122.19 (C-8), 128.8 (C-7), 131.11 (C-10), 143.11 (C-1'), 143.79 (C-9). **GCMS** (70 eV, EI): *m/z* (%) = 189 (100) [M^+], 174 (14), 158 (20), 148 (71), 134 (16), 120 (30), 103 (8), 91 (17), 77 (20), 65 (11), 41 (2). **Elemental analysis** (%) calcd for $C_{12}H_{15}NO$: C 76.16, H 7.99, N 7.40; found: C 76.28, H 8.01, N 7.54.

7-Fluoro-3-isopropenyl-3,4-dihydro-*2H*-1,4-benzoxazine (100i)

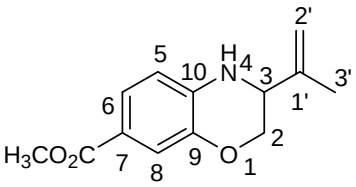


100i

R_f = 0.29 (SiO_2, PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3367 cm^{-1} (NH), 2981, 2881 (CH_2 and CH_3), 1606, 1503 (C=C), 1296 and 1252 (C-O), 1144, 1129 and 1111 (C-F), 1014, 906, 844, 792. **UV** (EtOH): λ_{max} (log ε) = 304 nm (3.54), 244 (3.70), 208 (4.48). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, 3'-H), 3.89 (overlapped, 1H, 3-H), 3.97 (dd, ^3J = 10.2 Hz, 1H, 2-H), 4.29 (dd, ^3J = 10.2 Hz, 1H, 2-H), 5.05 (brs, 1H, 2'-H), 5.13 (brs, 1H, 2'-H), 6.54 (dt, ^3J = 8.4 Hz, $^3J_{H\text{-}F}$ = 8.4 Hz, ^4J = 2.8 Hz, 1H, C-6), 6.59 (dd, $^3J_{H\text{-}F}$ = 9.2 Hz, ^4J = 2.8 Hz, 1H, C-8),

6.61 (dd, ^{3}J = 8.3 Hz, $^{4}J_{H\text{-}F}$ = 5.3 Hz, 1H, C-5). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.84 (C-3'), 55.22 (C-3), 69.09 (C-2), 104.31 (d, $^{2}J_{C\text{-}F}$ = 25.8 Hz, C-8), 108.31 (d, $^{2}J_{C\text{-}F}$ = 22.5 Hz, C-6), 113.61 (C-2'), 115.75 (d, $^{3}J_{C\text{-}F}$ = 9.22 Hz, C-5), 129.8 (d, $^{4}J_{C\text{-}F}$ = 1.6 Hz, C-10), 142.68 (C-1'), 144.36 (d, $^{3}J_{C\text{-}F}$ = 11.5 Hz, C-9), 156.63 (d, $^{1}J_{C\text{-}F}$ = 236 Hz, C-7). **MS** (70 eV, EI): *m/z* (%) = 193 (100) [M^+], 178 (15), 162 (16), 152 (95), 138 (16), 124 (12), 111 (8), 97 (6), 83 (5), 69 (7), 41 (5). **HRMS** (EI, M^+): calcd for $C_{11}H_{12}FNO$: 193.0903; found: 193.0900. **Elemental analysis** (%) calcd for $C_{11}H_{12}FNO$: C 68.38, H 6.26, N 7.25; found: C 68.17, H 6.28, N 7.16.

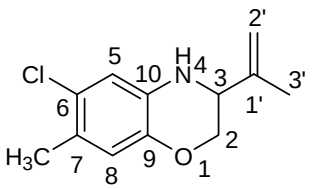
3-Isopropenyl-3,4-dihydro-*2H*-1,4-benzoxazine-7-carboxylic acid methyl ester (100j)



100j

M.p. = 81 °C. **R_f** = 0.38 (SiO_2, PE/TBME = 3 : 1). **IR** (ATR): $\tilde{\nu}$ = 3372 cm^{-1}, 3344 (NH), 2987, 2843 (CH_2, CH_3), 1687 (C=O), 1602 and 1519 (C=C), 1438, 1427, 1324, 1280 and 1233 (C-O), 1099, 1015, 899, 762. **UV** (EtOH): λ_{max} (log ε) = 318 nm (4.27), 238 (4.02), 212 (4.34). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, 3'-H), 3.87 (s, 3H, OMe), 3.92 (dd, ^{3}J = 9.5 Hz, 1H, 2-H), 3.95 (overlapped, 1H, 3-H), 4.29 (dd, ^{3}J = 9.5 Hz, 1H, 2-H), 5.06 (brs, 1H, 2'-H), 5.10 (brs, 1H, 2'-H), 6.65 (d, ^{3}J = 8.2 Hz, 1H, 5-H), 7.51 (d, ^{4}J = 1.9 Hz, 1H, 8-H), 7.55 (dd, ^{3}J = 8.2 Hz, ^{4}J = 1.9 Hz, 1H, 6-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.67 (C-3'), 51.91 (OMe), 55.22 (C-3), 68.32 (C-2), 113.73 (C-2'), 113.95 (C-5), 118.15 (C-8), 119.93 (C-7), 124.34 (C-6), 138.49 (C-10), 142.56 (C-9), 142.6 (C-1'), 167.32 (C=O). **MS** (70 eV, EI): *m/z* (%) = 233 (100) [M^+], 218 (8), 202 (26), 192 (74), 178 (10), 160 (4), 150 (4), 133 (5), 104 (5), 78 (5), 41 (3). **HRMS** (EI, M^+): calcd for $C_{13}H_{15}NO_3$: 233.1052; found: 233.1044. **Elemental analysis** (%) calcd for **$C_{13}H_{15}NO_3$**: C 66.94, H 6.48, N 6.01; found: C 66.80, H 6.47, N 5.94.

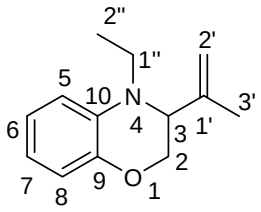
6-Chloro-3-isopropenyl-7-methyl-3,4-dihydro-*2H*-1,4-benzoxazine (100k)



100k

R_f = 0.40 (SiO_2, PE/EtOAc, 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3373 cm^{-1} (NH), 2976, 2919, 2878 (CH_2 and CH_3), 1619 and 1502 (C=C), 1295, 1208, 1157 (C-O), 1129 (C-Cl), 970, 906, 864. **UV** (EtOH): λ_{max} (log ε) = 310 nm (3.67), 252 (3.85), 215 (4.58). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, 3'-H), 2.25 (s, 3H, CH_3), 3.90 (overlapped, 1H, 3-H) 3.96 (dd, ^2J = 8.1 Hz, ^3J = 1.6 Hz, 1H, 2-H) 4.26 (dd, ^2J = 8.1 Hz, ^3J = 1.6 Hz, 1H, 2-H), 5.05 (brs, 1H, 2'-H), 5.12 (brs, 1H, 2'-H), 6.68 (s, 1H, 8-H) 6.72 (s, 1H, 5-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.36 Me), 19.85 (C-3'), 55.26 (C-3), 68.67 (C-2), 113.87 (C-2'), 115.90 (C-5), 118.68 (C-8), 126.19 (C-6 or C-7), 126.57 (C-6 or C-7), 131.69 (C-10), 142.55 (C-9), 142.55(C-1'). **MS** (70 eV, EI): *m/z* (%) = 225/ 223 (100) [M^+], 210 (3), 208 (9), 192 (8), 182 (56), 168 (10), 154 (5), 118 (5), 91 (4), 77 (6), 69 (4), 41 (8). **HRMS** (EI, M^+): calcd for $C_{12}H_{14}ClNO$: 223.0764; found: 223.0751. **Elemental analysis** (%) calcd for $C_{12}H_{14}ClNO$: C 64.43, H 6.31, N 6.26; found: C 64.41, H 6.33, N 6.09.

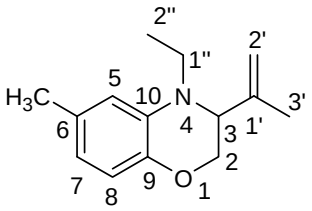
4-Ethyl-3-isopropenyl-3,4-dihydro-*2H*-1,4-benzoxazine (101a)



101a

R_f = 0.83 (PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3068 cm^{-1}, 2972, 2930, 2873 (CH_2, CH_3), 1604 (C=C), 1497(C=C), 1258, 1247 and 1214 (C-O), 1058, 900, 807, 735. **UV** (EtOH): λ_{max} (log ε) = 303 nm (3.64), 256 (3.94). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.15 (t, ^3J = 7.1 Hz, 3H, 2"-H) 1.78 (s, 3H, 3'-H), 3.21 (dq, ^2J = 14.8 Hz, ^3J = 7.1 Hz, 1H, 1"-H), 3.51 (dq, ^2J = 14.8 Hz, ^3J = 7.1 Hz, 1H, 1"-H), 3.87 (brt, ^3J =3.6 Hz, 1H, 3-H), 4.06 (dd, ^2J = 10.8 Hz, ^3J = 4.2 Hz, 1H, 2-H), 4.21 (dd, ^2J = 10.8 Hz, ^3J = 4.2 Hz, 1H, 2-H), 4.94 (brs, 1H, 2'-H), 5.00 (brs, 1H, 2'-H), 6.61 (ddd, ^3J = 7.3 Hz, ^3J = 7.3 Hz, ^4J = 1.5 Hz, 1H, 7-H), 6.75 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz, 1H, 5-H), 6.82 (dd, ^3J = 7.81 Hz, ^4J = 1.5 Hz, 1H, 8-H), 6.89 (ddd, ^3J = 7.3 Hz, ^3J = 7.3 Hz, ^4J = 1.6 Hz, 1H, 6-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 11.3 (C-2"), 19.1 (C-3'), 42.6 (C-1"), 61.0 (C-2), 67.3 (C-3), 111.5 (C-5), 114.4 (C-2'), 116.5 (C-7, C-8), 122.3 (C-6), 135.0 (C-10), 143.4 (C-1'), 144.1 (C-9). **MS** (70 eV, EI): *m/z* (%) = 203 (96) [M^+], 188 (35), 162 (100), 146 (7), 120 (21), 92 (5), 77 (8), 65 (14), 41 (17). **HRMS** (EI, M^+): calcd for $C_{13}H_{17}NO$: 203.1310; found: 203.1306. **Elemental analysis** (%) calcd for $C_{13}H_{17}NO$: C 76.81, H 8.43, N 6.89; found: C 76.88, H 8.53, N 6.77.

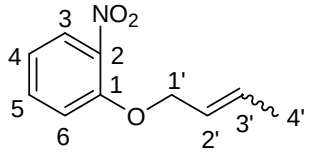
4-Ethyl-3-isopropenyl-3,4-dihydro-*2H*-1,4-benzoxazine (101b)



101b

R_f = 0. 42 (PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 2971 cm^{-1}, 1920, 2870 (CH_2 and CH_3), 1610, 1508 (C=C), 1214 (C-O), 1084, 1063, 900, 794. **UV** (EtOH): λ_{max} (log ε) = 307 nm (3.70), 257 (3.91), 215 (4.48). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.16 (t, ^3J = 7.3 Hz, 3H, 2"-H), 1.78 (s, 3H, 3'-H), 2.30 (s, 3H, Me), 3.21 (dq, ^2J = 14.7 Hz, ^3J = 7.3 Hz, 1H, 1"-H), 3.50 (dq, ^2J = 14.7 Hz, ^3J = 7.3 Hz, 1H, 1"-H_b), 3.85 (brt, ^3J = 3.6 Hz, 1H, 3-H), 4.03 (dd, ^2J = 10.7 Hz, ^3J = 4.2 Hz, 1H, 2-H), 4.19 (dd, ^2J = 10.7 Hz, ^3J = 4.2 Hz, 1H, 2-H), 4.95 (brs, 1H, 2'-H), 5.00 (brs, 1H, 2'-H), 6.43 (brd, ^3J = 8.1 Hz, 1H, 7-H), 6.57 (d, ^4J = 1.7 Hz, 1H, 5-H), 6.71 (d, ^3J = 8.1 Hz, 1H, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 11.32 (C-2"), 19.16 (C-3'), 21.56 (CH_3), 42.67 (C-1"), 61.06 (C-3), 67.34 (C-2), 112.22 (C-5), 114.38 (C-2'), 116.26 (C-8), 117.08 (C-7), 131.66 (C-6), 134.51 (C-10), 142.04 (C-9), 143.49 (C-1'). **GCMS (**70 eV, EI): *m/z* (%) = 217 (100) [M^+], 202 (41), 186 (20), 176 (76), 160 (24), 134 (38), 122 (15), 107 (10), 91 (12), 77 (14), 65 (5). **Elemental analysis** (%) calcd for $C_{14}H_{19}NO$: C 77.38, H 8.81, N 6.45; found: C 77.58, H 8.87, N 6.30.

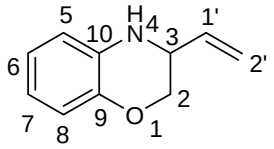
3-Methyl-allyl 2-nitrophenyl ether (92)[132]



92

R_f = 0.30 (PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3027 cm^{-1} (C-H arom.), 2919, 2890 (CH_2 and CH_3), 1605, 1520 (C=C), 1349 (C-NO_2), 1274, 1250 and 1230 (C-O), 1165, 1088, 964, 855 (C-H alkene), 741 (1,2-disubstituted). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.78 (brd, ^3J = 6.4 Hz, 3H, 4'-H), 4.63 (brd, ^3J = 6.7 Hz, 2H, 1'-H), 5.74 (m, 1H, 3'-H), 5.93 (sextet , ^3J = 15.6 Hz, 1H, 2'-H), 7.03 (d, ^3J = 7.6 Hz, 1H, 6-H), 7.10 (ddd, ^3J = 8.5 Hz, 1H, 4-H), 7.52 (ddd, ^3J = 8.7 Hz, ^4J = 1.6 Hz, 1H, 5-H), 7.84 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1H, 3-H). **GCMS** (70 eV, EI): *m/z* (%) = 193 (1) [M^+], 139 (40), 123 (4), 109 (5), 93 (2), 81 (4), 63 (10), 55 (100), 39 (17), 29 (21).

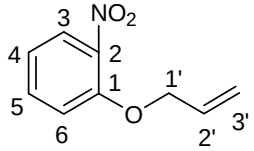
3-Vinyl-3,4-dihydro-*2H*-1,4-benzoxazine (102)



102

R_f = 0.40 (PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3366 cm^{-1} (NH), 2981, 2921, 2872 (CH_2 and CH_3), 1766, 1607 and 1590 (C=C), 1309, 1274, 1205 (C-O), 1036, 989, 922, 738. **UV** (EtOH): λ_{max} (log ε) = 297 nm (3.50), 247 (3.73). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.9 (overlapped, 1H, 2-H), 4 .05 (overlapped, 1H, 3-H), 4.25 (dd, ^3J = 9.8 Hz, 1H, 2-H), 5.29 (brd, ^3J = 10.3 Hz, 1H, 2'-H), 5.42 (brd, ^2J = 17.2 Hz, 1H, 2'-H), 5.87 (m, 1H, 1'-H), 6.66 (dd, ^3J = 7.7 Hz, 1H, 8-H), 6.71 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, 7-H) 6.78 - 6.83 (overlapped, 2H, 5-H and 6-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 52.19 (C-3), 69.09 (C-2), 115.7 (C-8), 116.8 (C-5), 118.2 (C-2'), 119.2 (C-7), 121.7 (C-6), 133.2 (C-10), 135.6 (C-1'), 143.8 (9). **MS (**70 eV, EI): *m/z* (%) = 161 (100) [M^+], 146 (15), 134 (38), 132 (18),130 (42), 120 (38), 106 (17), 93 (7), 79 (20), 65 (18), 52 (30), 41 (6), 39 (21). **HRMS** (EI, M^+): calcd for $C_{10}H_{11}NO$: 161.0840; found: 161.0850. **Elemental analysis** (%) calcd for $C_{10}H_{11}NO$: C 74.51, H 6.88, N 8.69; found: C 74.20, H 6.96, N 8.73.

Allyl-(2-nitrophenyl)-ether (93)[133]



93

Yield = 90 %. **R_f** = 0.20 (PE/EtOAc = 20 : 1). **IR** (ATR): $\tilde{\nu}$ = 3020 cm^{-1} (C-H arom.), 2919, 2887 (CH_2 and CH_3), 1605, 1520 (C=C), 1349 (C-NO_2), 1250 and 1230 (C-O), 1165, 964, 857 (C-H alkene), 741 (1,2-disubstituted). **UV** (EtOH): λ_{max} (log ε) = 215 nm (2.33), 258 (2.41). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 4.71 (d, ^2J = 4.9 Hz, 2H, 1'-H), 5.36 (brd, 1H, 3'-H), 5.52 (brd, 1H, 3'-H), 6.06 (octet, 1H, 1'-H), 7.05 (dd, ^3J = 8 Hz, ^4J = 1.5 Hz, 1H, 6-H), 7.1 (dd, ^3J = 8.6 Hz, ^4J = 1.5 Hz, 1H, 4-H), 7.5 (ddd, ^3J = 8.6 Hz, ^4J = 1.5 Hz, 1H, 5-H), 7.8 (dd, ^3J = 8 Hz, ^4J = 1.5 Hz, 1H, 3-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 70.2, 115.1, 118.6, 120.7, 125.9, 131.9, 134.2, 152.1. **MS** (70 eV, EI): *m/z* (%) = 179 (6) [M^+], 139 (2), 123 (29), 106 (13), 92 (3), 78 (4), 63 (11), 43 (100), 33 (4), 24 (2).

4.4 Discussion of the spectral data for the compounds 100a-k

The IR spectra of the compounds **100a-k** all show the characteristic absorption band of the (N-H) bond at 3340 – 3390 cm^{-1}, while this absorption band was not observed in the case of the compounds **101a**,**b**,**d**,**e**,**f**,**k**.

General Discussion of the 1,4-Oxazine Moiety on the Compounds 100a-k

The presence of the chiral centre at the C-3 position leads to the existence of diastereotopic protons of the methylene group at the C-2 position as shown in Figure 6a.

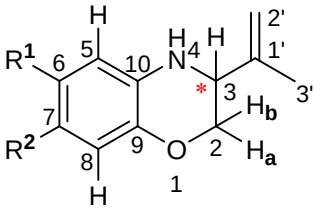


Figure 6a The structure assignment of the 1,4-oxazine moiety for the compounds **100a-k**.

Table **4** shows the ^{1}H and ^{13}C NMR chemical shifts of the position 2 and 3 of the compounds **100c**,**e**,**g**,**i**,**k** on the 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines skeleton.

Table 4 Selected NMR ^{1}H and ^{13}C data of the compounds **100c**,**e**,**g**,**i**,**k**

No.	**100**	2-H_a δ (ppm)	2-H_b δ (ppm)	C-2 δ (ppm)	3-H δ (ppm)	C-3 δ (ppm)
1	**c**	3.88	4.24	68.72	3.92	55.52
2	**e**	3.91	4.26	68.65	3.93	55.09
3	**g**	4.00	4.33	69.09	3.92	54.95
4	**i**	3.97	4.29	69.09	3.89	55.22
5	**k**	3.95	4.25	68.67	3.90	55.26

In all compounds the two protons 2-H_a and 2-H_b appear as doublet of doublets each at δ = 3.88 – 4.00 ppm and δ = 4.24 – 4.33 ppm, respectively. A strong coupling of $^{2}J \approx 16.5$ Hz indicates the geminal coupling between 2-H_a and 2-H_b, whereas a coupling size of ≈ 7.5 Hz shows the vicinal coupling to the overlapped 3-H atom, appearing in the range of δ = 3.89 – 3.93 ppm.

Generally, the C-2 signals of **100c**, **e**, **g**, **i**, **k** appear in the range of δ = 68.65 – 69.09 ppm, while the C-3 signals appear in the range of δ = 54.95 – 55.52 ppm.

Discussion of Spectral Data of the Aromatic Part on the Compound 100c

The compound **100c** (Fig 6b) is taken as an example:

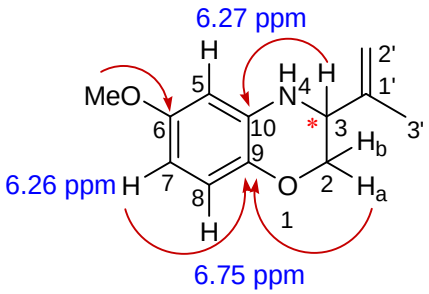


Figure 6b The structure assignment of the compound **100c**

The aromatic ABM splitting system consisted of the protons with signals at δ = 6.26 ppm (dd, ^{3}J = 8.7 Hz, ^{4}J = 2.8 Hz), δ = 6.27 ppm (brs, ^{4}J = 2.8 Hz) and δ = 6.75 ppm (brd, ^{3}J = 8.7 Hz). The assignment of each ^{13}C-resonance as well as the connectivities of the individual ^{1}H spin systems (1,4-oxazine and aromatic moieties) have been performed by gHSQC and gHMBC.

5 SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOXALINES

5.1 Microwave-assisted reductive cyclization of *N*-allyl 2-nitroanilines. A new approach to substituted 1,2,3,4-tetrahydroquinoxalines

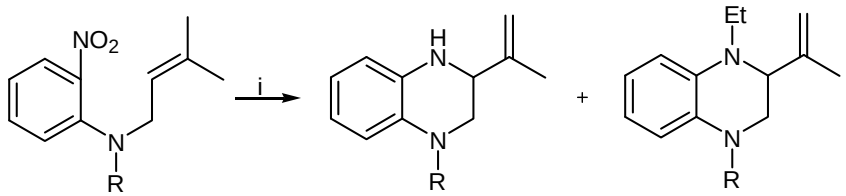
(Reprinted with permission from: Merisor, E.; Conrad, J.; Mika, S.; Beifuss, U. *Synlett* **2007**, 2033.

Abstract: *N*-Allyl 2-nitrophenyl amines can be efficiently cyclized to yield alkenyl-1,2,3,4-tetrahydroquinoxalines in a single reaction step by means of a new microwave-assisted reductive domino process.

Key words: cyclizations, domino reactions, ene reactions, microwaves, tetrahydroquinoxalines

The applications of 1,2,3,4-tetrahydroquinoxalines as promising prostaglandin D2 receptor antagonists[134] and vasopressin V2 receptor antagonists[135] underline the importance of this heterocyclic skeleton for the development of new pharmaceuticals. Due to their role as model compounds for tetrahydrofolic acid the synthesis of 1,2,3,4-tetrahydroquinoxalines is also important in the field of bioorganic chemistry.[136] Despite the marked interest in 1,2,3,4-tetrahydro-quinoxalines there are only a limited number of synthetic methods available. A classic strategy to 1,2,3,4-tetrahydroquinoxalines is the reduction of suitably substituted quinoxalines.[137] Alternatively, more recent approaches to 1,2,3,4-tetrahydroquinoxalines include the metal-mediated reaction between substituted 1,2-diaminobenzenes with 1,4-butene diol or acetates[138] as well as the Lewis acid promoted addition of allyl stannanes to *o*-quinonediimines.[139] Suitably substituted nitroarenes are not only used as a substrate for tetrahydroquinoxaline syntheses in a domino reduction/Michael addition,[140] but are also employed in other domino processes.[141-143] Altogether there is a strong demand for new and efficient methods for the synthesis of the 1,2,3,4-tetrahydroquinoxaline skeleton. Recently, we discovered a new domino process that allows the transformation of allyl 2-nitrophenyl ethers into substituted 3,4-dihydro-*2H*-1,4-benzoxazines in a single synthetic operation.[144] Whether a new synthetic method is able to gain major importance will greatly depend on its scope and limitations. Here we report on the successful application of this new reductive domino process to the preparation of substituted 1,2,3,4-tetrahydroquinoxalines. First, the easily accessible protected *N*-allyl 2-nitroanilines **94a-d** were reacted with triethyl phosphite [$(EtO)_3P$] under argon. After heating under reflux for 2–12 h the 3-isopropenyl-1,2,3,4-tetrahydroquinoxalines **103a-d**[145] were isolated as the main products with yields ranging from 55 to 60% (Scheme

26, Table 5). In these reactions, 4-ethyl-3-isopropenyl-1,2,3,4-tetrahydroquinoxalines **105a**,**b**,**d**[146] were also formed as side products in small amounts (2–6%) (Scheme 26, Table 5).



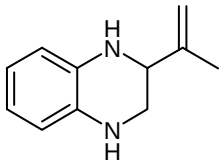
94 **103** **105**

Scheme 26 Reductive cyclization of protected *N*-prenyl 2-nitroanilines **94** under thermal conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) 6 eq. $(EtO)_3P$, reflux 2-12h.

Table 5 Synthesis of 3-Isopropenyl-1,2,3,4-tetrahydroquinoxalines **103** and **105** under thermal conditions in neat $(EtO)_3P$.

Entry	**94**	R	Time (h)	**103**	Yield (%) of **103**	**105**	Yield (%) of **105**
1	**a**	CO_2Me	2	**a**	60	**a**	6
2	**b**	CO_2Bn	2	**b**	59	**b**	4
3	**c**	CO_2t-Bu	2	**c**	55 [a]	**c**	-
4	**d**	Ph	12	**d**	57	**d**	<2

[a] In addition, **106** (12%, Figure 7) was isolated

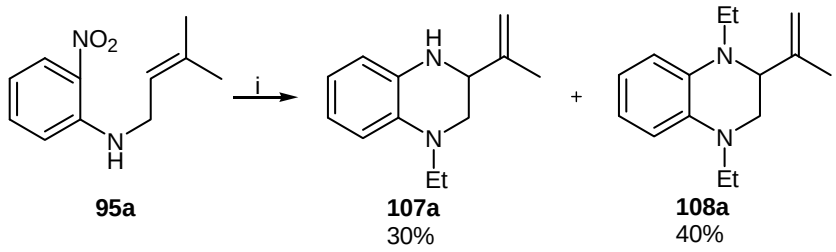


106

Figure 7

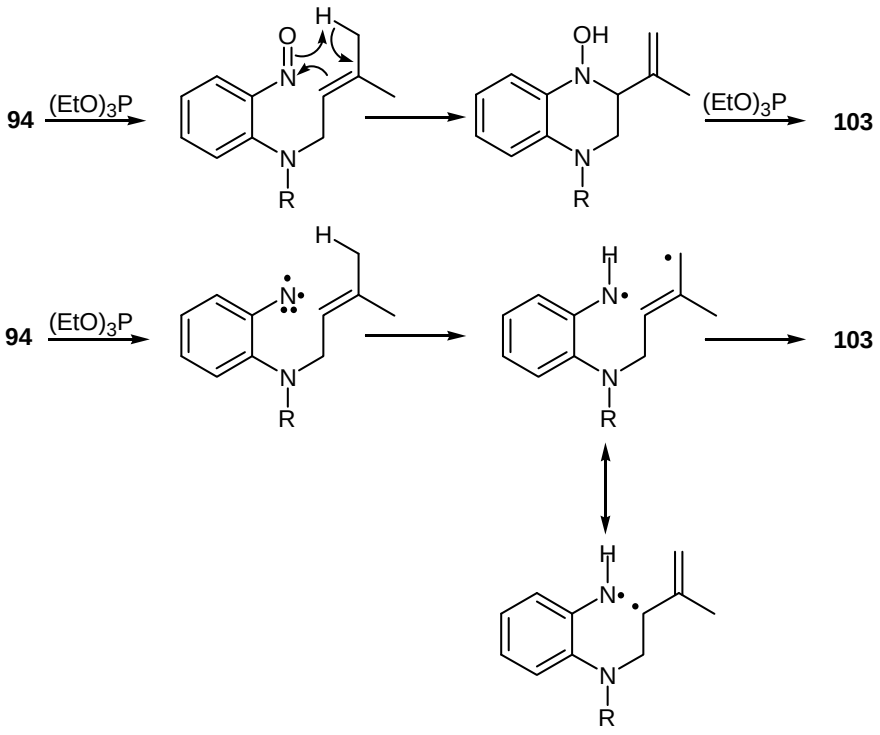
It is assumed that the formation of these *N*-ethylated compounds is due to the ethylation of **103** with $(EtO)_3PO$, which is produced during the reaction by oxidation of $(EtO)_3P$. The conversion of *tert*-butyl carbamate **94c** is unusual since the BOC group is partially cleaved under the reaction conditions. Apart from 55% yield of **103c**, an additional 12% yield of the 2-isopropenyl-1,2,3,4-tetrahydroquinoxaline (**106**; Fig 7) was isolated.

In contrast, the transformation of the unprotected *N*-prenyl 2-nitroaniline (**95a**) with $(EtO)_3P$ under thermal conditions exclusively gave *N*-ethylated products, namely 1-ethyl-3-isopropenyl-1,2,3,4-tetrahydroquinoxaline (**107a,** 30% yield) and 1,4-diethyl-2-isopropenyl-1,2,3,4-tetrahydroquinoxaline (**108a**, 40% yield) (Scheme 27).



Scheme 27 Reductive cyclization of the unprotected *N*-prenyl 2-nitroaniline (**95a**) under thermal conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) 6 eq. $(EtO)_3P$, reflux 12 h.

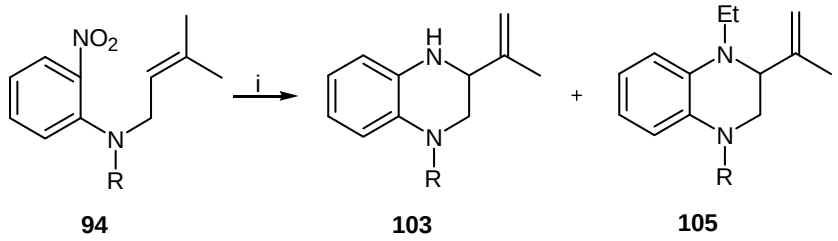
Both an intramolecular nitroso ene reaction[115] and the reaction of a nitrene[1c, 71b] may be considered as the reaction mechanism (Scheme 28). With a nitroso ene reaction we may assume that the reaction of the protected *N*-prenyl 2-nitroanilines **94** with phosphite starts with the reduction of the nitro group. The nitroso group so formed then undergoes an intramolecular ene reaction with the 2-methylpropenyl group of the molecule, resulting in the formation of a cyclic hydroxyl amine that is finally reduced by the phosphite to yield the cyclic amine **103**. In the case of a nitrene mechanism we assume that the nitro group is first reduced to the corresponding nitrene, which then abstracts an hydrogen atom from the 2-methyl-propenyl group and yields both an NH radical and a mesomerically stabilized propenyl radical, which undergo intramolecular cyclization to give **103** (Scheme 28).[147]



Scheme 28 Possible reaction mechanisms.

On the basis of these results we examined whether (a) the reaction times of the reductive cyclization and, (b) the proportion of *N*-ethylated products could be decreased by conducting the domino reactions of **94** and **95** under microwave conditions.[128] Recently, Dehaen et al. have reported on the Cadogan cyclization under microwave conditions.[148]

It turned out that indeed the reaction times of the reductive cyclization of *N*-allyl 2-nitroanilines could be dramatically shortened in some cases (Scheme 29, Table 6 and Scheme 30, Table 7). For example, the reaction time required to transform **95d** could be reduced from 12 hours to 30 min (Scheme 29, Table 6, entry 4).



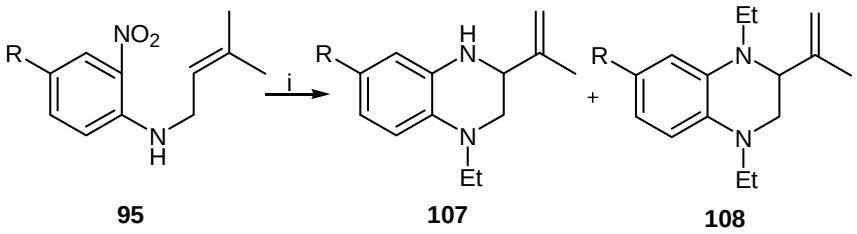
Scheme 29 Reductive cyclization of protected *N*-prenyl 2-nitroanilines **94** under microwave conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) 6 eq. $(EtO)_3P$, MW (300 W), 200 °C.

Table 6 Synthesis of 3-Isopropenyl-1,2,3,4-tetrahydroquinoxalines **103** and **105** under microwave conditions in neat $(EtO)_3P$.

Entry	**94**	R	Time (min)	**103**	Yield (%) of **103**	**105**	Yield (%) of **105**
1	**a**	CO_2Me	35	**a**	60	**a**	4
2	**b**	CO_2Bn	35	**b**	58	**b**	4
3	**c**	CO_2t-Bu	35	**c**	36 [a]	**c**	-
4	**d**	Ph	30	**d**	56	**d**	<2

[a] In addition, **106** (28%, Figure 7) was isolated

In contrast, the formation of the *N*-ethylated products could not be suppressed by using microwaves, as can be shown by the cyclizations of **94a-d** and, even more noticeably, by the transformation of **95a-d** which exclusively yield the mono- and diethylated products **107a-d** and **108a-d**, resp. (Scheme 30, Table 7). The reactions of **95a-d** also demonstrate that the reductive domino process tolerates substrates which are substituted at the aromatic nucleus.



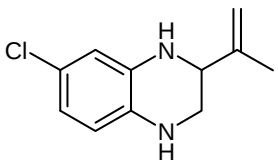
95 **107** **108**

Scheme 30 Reductive cyclization of the unprotected *N*-prenyl 2-nitroanilines **95a-d** under microwave conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) 6 eq. $(EtO)_3P$, MW (300 W), 200 °C.

Table 7 Synthesis of substituted 1,2,3,4-tetrahydroquinoxalines **107** and **108** under microwave conditions in neat $(EtO)_3P$.

Entry	**95**	R	Time (min)	**107**	Yield (%) of **107**	**108**	Yield (%) of **108**
1	**a**	H	35	**a**	40	**a**	23
2	**b**	Me	35	**b**	46	**b**	21
3	**c**	OMe	35	**c**	45	**c**	17
4	**d**	Cl [a]	35	**d**	26	**d**	4

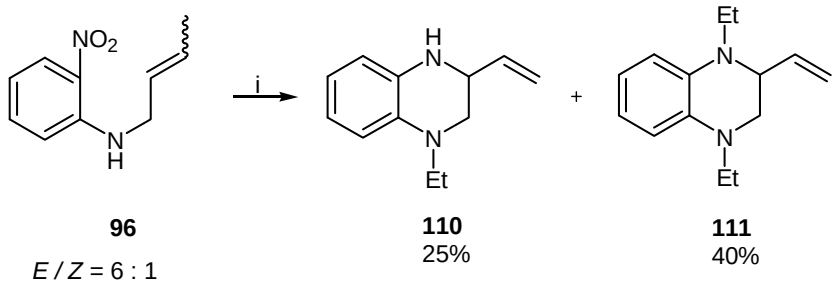
[a] In addition, **109** (38%; Figure 8) was isolated



109

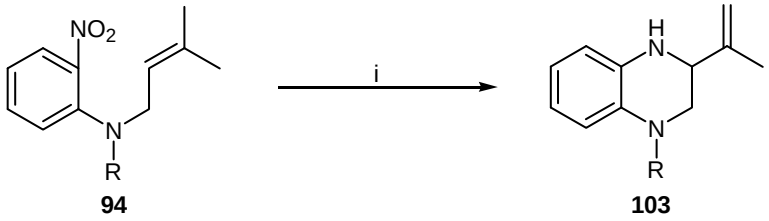
Figure 8

Furthermore the question arose whether the presence of a dimethyl allyl group is essential to the cyclization process or whether it can be achieved with a crotyl group instead. Heating the *N*-crotyl 2-nitroaniline (**96**) with triethyl phosphite $(EtO)_3P$ led to the formation of 1-ethyl-3-vinyl-1,2,3,4-tetrahydroquinoxaline (**110**) in 25% yield and 1,4-diethyl-2-vinyl-tetrahydro-quinoxaline **111** in a yield of 40% (Scheme 31). This clearly demonstrates that variation of the allylic component also works.



Scheme 31 Reductive cyclization of the unprotected *N*-crotyl 2-nitroaniline **96** under thermal conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) 6 eq. $(EtO)_3P$, reflux 12 h.

Finally, the influence of solvents on the reaction was studied. After some experimentation $(EtO)_3P$ in toluene was identified as the most suitable combination for this type of cyclization. When, for example, **94a** was reacted with $(EtO)_3P$ in toluene under microwave conditions, the heterocycle **103a** could be isolated in good yield (70%) after 35 min. These reaction conditions[149] lead to the exclusive production of **103a**, while formation of the *N*-ethylated side product **105a** is completely suppressed (Scheme 32, Table 8, entry 1). Similarly good results were observed with the reductive cyclizations of **94b-d** (Scheme 32, Table 8, entries 2-4).



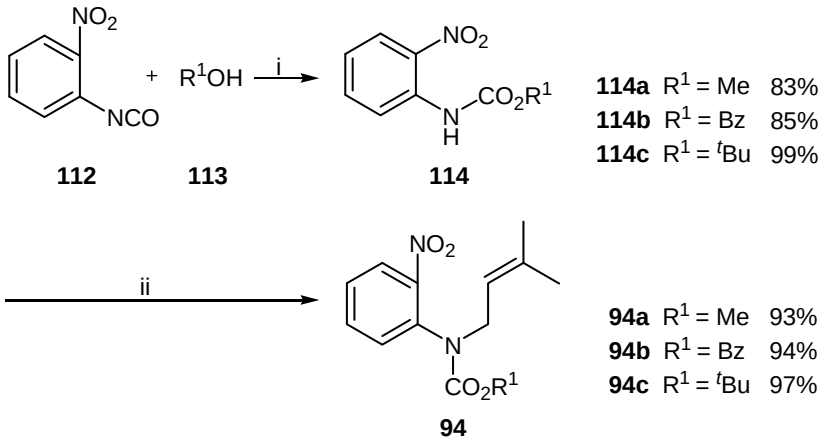
Scheme 32 Reductive cyclization of protected *N*-prenyl 2-nitroanilines **94** in $(EtO)_3P$/toluene. *Reagents and conditions*: (i) 6 eq. $(EtO)_3P$, toluene, MW (300 W), 200 °C.

Table 8 Synthesis of Substituted 3-Isopropenyl-1,2,3,4-tetrahydroquinoxalines **103a-d** under microwave conditions in $(EtO)_3P$/toluene.

Entry	**94**	R	Time (min)	**103**	Yield (%) of **103**
1	**a**	CO_2Me	35	**a**	70
2	**b**	CO_2Bn	35	**b**	67
3	**c**	CO_2t-Bu	35	**c**	36 [a]
4	**d**	Ph	35	**d**	60

[a] In addition, **106** (28%; Figure 7) was isolated

Again, the cyclization of **94c** is an exception since partial cleavage of the Boc group of **103c** also occurs under these reaction conditions (Scheme 32, Table 8, entry 3). Surprisingly, the secondary 2-nitroanilines **95a-d** did not react under these conditions at all; the substrates could be retrieved unchanged after 1 h irradiation at 200 °C. The same holds true for the *N*-crotyl 2-nitroaniline (**96**). Another benefit of the novel tetrahydroquinoxaline synthesis is the easy accessibility of the substrates. Compounds of type **94** could be obtained in high yields by reacting 2-nitrophenylisocyanate (**112**) with the alcohols **113a-c** (CH_3OH, BnOH, *t*-BuOH) to give **114a-c**[150], followed by allylation of the carbamates **114a-c** with prenyl bromide (**99a**)[151, 152] (Scheme 33).



112 **113** **114**

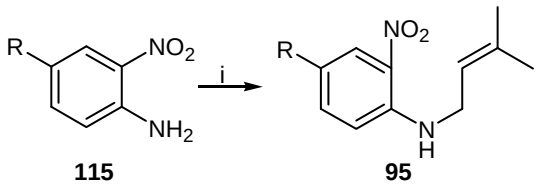
114a R^1 = Me 83%
114b R^1 = Bz 85%
114c R^1 = ^{t}Bu 99%

94

94a R^1 = Me 93%
94b R^1 = Bz 94%
94c R^1 = ^{t}Bu 97%

Scheme 33 Preparation of protected *N*-prenyl 2-nitroanilines **94a-c**. *Reagents and conditions*: (i) petroleum ether, reflux; (ii) NaH, DME, 0°C or *t*-BuOK, THF, - 78 °C, **99a**, r.t.

The approach to the secondary amines **95a-d** is even more simple in that they can be obtained in one step by reaction of the corresponding substituted 2-nitroanilines **115a-d** with prenyl bromide (**99a**) in very good yields (Scheme 34).[153]



115 **95**

95a R = H 82%
95b R = Me 92%
95c R = OMe 92%
95d R = Cl 93%

Scheme 34 Preparation of unprotected secondary 2-nitroanilines **95a-d**. *Reagents and conditions*: (i) benzene, reflux, 50 % NaOH, **99a**, $PhCH_2N^+Et_3Cl^-$.

In summary, the efficient conversion of *N*-allyl 2-nitroanilines into substituted 1,2,3,4-tetrahydroquinoxalines by means of a $(EtO)_3P$ – mediated reductive domino reaction has been presented.

Acknowledgment

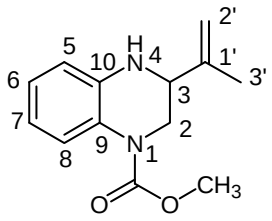
We thank Mrs. I. Klaiber and Dr. R. Frank for recording of spectra.

5.2 Experimental section

General procedure for the synthesis of alkenyl-1,2,3,4-tetrahydroquinoxalines under microwave conditions:

A solution of 1 mmol **94a**, 6 mmol $(EtO)_3P$ and 3 mL toluene in a 10 mL septum sealed reaction vial was irradiated with microwaves (Discover^{TM} by CEM; 2450 MHz; 300 W; 200 °C) After removal of $(EtO)_3P$ and $(EtO)_3PO$ (10^{-1} mbar) the residue was taken up in EtOAc (25 mL) and washed with brine (3 x 20 mL). The residue obtained after drying over $MgSO_4$ and after concentration in vacuo was purified by flash chromatography on silica gel (PE-EtOAc, 20:1).

Selected Data for 103a:



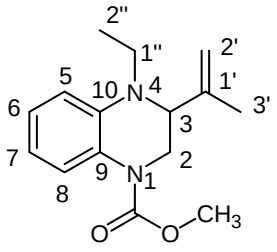
103a

Figure 9

R_f = 0.40 (PE/EtOAc = 20:1). **IR** (ATR): $\tilde{\nu}$ = 3376 cm^{-1} (NH), 2952, 2854 (CH_3 and CH_2), 1691 (C=O), 1604, 1501 (C=C), 1435, 1382 and 1372 (COO^-), 1232, 1211, 1146 and 1061, (=C-O-C), 900, 760, 741. **UV/Vis** (EtOH): λ_{max} (log ε) = 307 nm (2.48), 253 (2.40), 220 (2.34).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, 3'-H_3), 3.58 (dd, ^2J = 12.3 Hz, ^3J = 6.2 Hz, 1H, 2-H), 3.81 (s, 3H, OCH_3), 3.98 (dd, ^3J = 6.2 Hz, ^3J = 3.4 Hz, 1H, 3-H), 4.02 (dd, ^2J = 12.3 Hz, ^3J = 3.3 Hz, 1H, 2-H), 4.98 (bs, 1H, 2'-H), 5.05 (bs, 1H, 2'-H), 6.65 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, 5-H), 6.70 (ddd, ^3J = 8.2 Hz, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 1H, 7-H), 6.97 (ddd, ^3J = 7.9 Hz, ^3J = 7.4 Hz, ^4J = 1.4 Hz, 1H, 6-H), 7.48 (bs, 1H, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.57 (C-3'), 45.25 (C-2), 53.24 (OCH_3), 56.72 (C-3), 112.87 (C-2'), 114.4 (C-5), 116.9 (C-7), 123.9 (C-9), 124.61 (C-8), 125.4 (C-6), 137.09 (C-10), 144.3 (C-1'), 155.3 (C=O). **MS** (70 eV, EI): *m/z* (%) = 232 (100) [M^+], 218 (8), 199 (14), 191 (40), 173 (21), 157 (18), 131 (40), 106 (7), 77 (7). **Elemental analysis** (%) calcd for $C_{13}H_{16}N_2O_2$: C 67.22, H 6.94, N12.06. Found: C 67.43, H 7.01, N 11.99.

Selected Data for 105a:



105a

Figure 10

R_f = 0.59 (PE/EtOAc = 20:1). **IR** (ATR): $\tilde{\nu}$ = 2980 cm^{-1}, 2958 (CH_3 and CH_2), 1702 (C=O), 1602, 1504 (C=C), 1438, 1375 and 1344 (COO^-), 1217, 1190, 1145, 1062 (=C-O-C), 899, 733. **UV/Vis** (EtOH): λ_{max} (log ε) = 310 nm (2.49), 258 (2.41), 223 (2.35). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.17 (t, ^3J = 7.1 Hz, 3H, 2''-H_3), 1.80 (s, 3H, 3'-H_3), 3.15-3.27 (overlapped, 2H, 1''-H_2), 3.52 (dd, ^2J = 13.1 Hz, ^3J = 7.1 Hz, 1H, 2-H), 3.76 (s, 3H, OCH_3), 3.94 (t, ^3J = 7.1 Hz, 1H, 3-H), 4.37 (dd, ^2J = 12.9 Hz, ^3J = 7.1 Hz, 1H, 2-H), 4.81 (bs, 1H, 2'-H), 4.93 (bs, 1H, 2'-H), 6.62 (dd, ^3J = 8.1 Hz, ^4J = 1.1 Hz, 1H, 5-H), 6.75 (ddd, ^3J = 8.1 Hz, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 1H, 7-H), 7.06 (ddd, ^3J = 8.1 Hz, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 1H, 6-H), 7.4 (bs, 1H, 8-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 11.76 (C-2''), 19.60 (C-3'), 43.50 (C-1''), 43.82 (C-2), 53.12 (OCH_3), 62.76 (C-3), 110.56 (C-2'), 113.5 (C-5), 115.1 (C-7), 124.3 (C-9), 124.7 (C-8), 125.8 (C-6), 137.9 (C-10), 143.06 (C-1'), 155.4 (C=O). **MS** (70 eV, EI): *m/z* (%) = 260 (100) [M^+], 245 (16), 231 (26), 219 (58), 213 (12), 190 (34), 171 (20), 159 (30), 131 (27), 119(6), 92 (3), 77 (12), 41 (3), 28 (3). **HRMS** (EI, M^+): calcd for $C_{15}H_{20}N_2O_2$: 260.1525; found: 260.1507.

6 PALLADIUM CATALYZED CYCLIZATIONS OF NITROAROMATICS

From the study of naturally occurring *N*-allylated phenazines towards new Pd-mediated transformations

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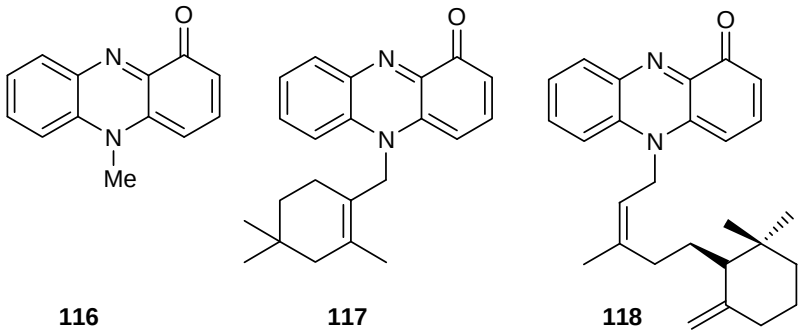
Abstract – New Pd-mediated reductive heteroannulations of *N*-allyl diphenylamines accessible through Pd-catalyzed *N*-arylation and of *O*-allylethers are reported.

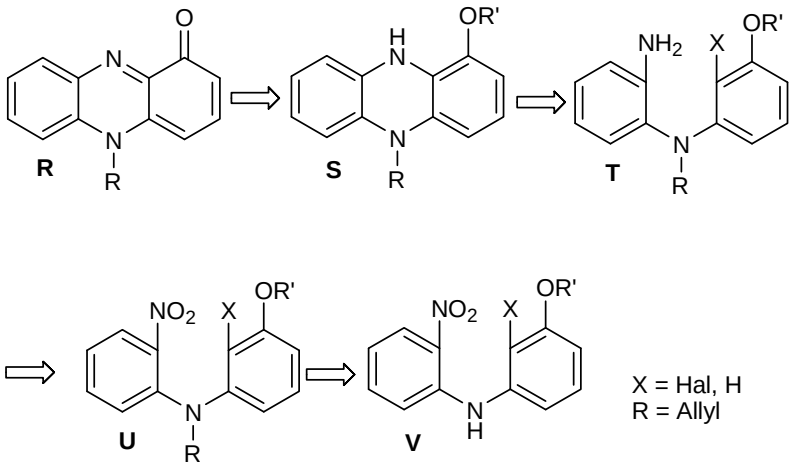
Currently we know more than 100 naturally occurring phenazines, which, due to the diversity of their biological activities, have gained a lot of popularity.[154] Most of them are *C*-substituted compounds. In addition, a small number of naturally occurring *N*-alkylated and *N*-allylated phenazine derivatives are known. Apart from the *N*-alkylated phenazinones represented by the structurally most simple pyocyanin **116**,[155] there are, in particular, the *N*-allylated phenazinones like lavanducyanin (WS-9659 B) **117**[117] and phenazinomycin **118**.[118] The latter was isolated by Ōmura *et al.* from the mycelial extracts of *Streptomyces* sp. WK-2057.[118a] It exhibits in vivo antitumor activity against experimental murine tumor cells and cytotoxic activity against adriamycin resistant P388 leukaemia cells. [118b] The total synthesis of **118** was reported by Kitahara, using low-yield *N*-allylation under high pressure conditions. [119]



116 **117** **118**

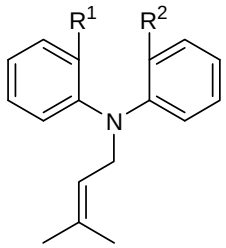
Against this background we envisaged performing an alternative synthesis of *N*-allylated phenazinones according to the retrosynthesis depicted in Scheme 35. The initial idea was to start the synthesis with a diphenylamine **V**, which was to be *N*-allylated. The reduction of **U** (X = Hal) was expected to deliver **T** (X = Hal), which in turn should be transformed into **S** by intramolecular *N*-arylation according to Buchwald-Hartwig.[120a] Alternatively, the reductive cyclization of **U** (X=H) according to the method by Holliman[24] would deliver **S** in one

synthetic step. Deprotection of the phenolic OH group, followed by oxidation, should finally give the *N*-allylated phenazinone **R**.



Scheme 35 Retrosynthesis of *N*-allylated phenazinones.

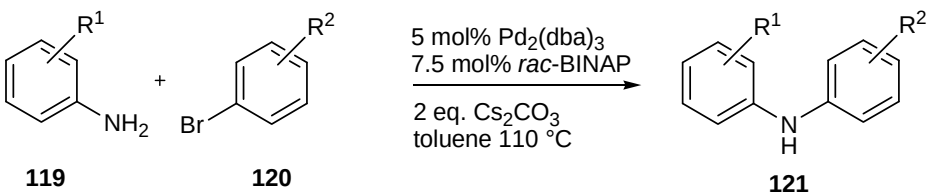
First, we focussed on the synthesis of the tertiary *o*-nitro-substituted diphenylamines **122a-b** and **94d** and their conversion into the corresponding anilines **123a-b** and **98**, respective.



122a $R^1 = NO_2$, R^2 = Br
122b $R^1 = NO_2$, R^2 = Cl
94d $R^1 = NO_2$, R^2 = H

123a $R^1 = NH_2$, R^2 = Br
123b $R^1 = NH_2$, R^2 = Cl
98 $R^1 = NH_2$, R^2 = H

Intermolecular *N*-arylation reactions of the Buchwald-Hartwig type[120a] were used to synthesize the secondary diphenylamines **121a-c**, the precursors of the anilines **122a-b**, **94d** and **123a-b** and **98**, respectively. The reactions between the *o*-substituted anilines **119a-e** and aryl bromides **120a-d** were achieved by combining the catalyst $Pd_2(dba)_3$, the ligand *rac*-BINAP, the base Cs_2CO_3 and toluene as a solvent. Under these conditions, diphenylamines **121** were isolated with yields ranging from 57% to 99% (Table 9).[121] Reaction times varied between 12 and 17 h.

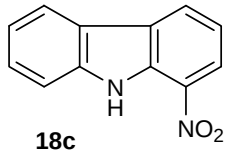


119 **120** **121**

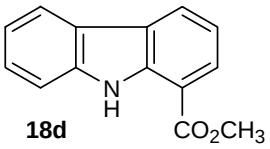
Table 9 Synthesis of diphenylamines **121a-f**

Entry	**119**	R^1	**120**	R^2	**121**	Yield **121** (%)
1	**a**	*o*-NO_2	**a**	*o*-Br	**a**	68
2	**b**	*o*-Cl	**b**	*o*-NO_2	**b**	99
3	**c**	*o*-H	**b**	*o*-NO_2	**c**	98
4	**d**	*o*-Br	**b**	*o*-NO_2	**-** [a]	-
5	**d**	*o*-Br	**c**	*p*- NO_2	**d**	58
6	**d**	*o*-Br	**d**	*o*-CO_2CH_3	**e** [b]	80
7	**e**	*o*-Br-*p*-CN	**b**	*o*-NO_2	**f**	57

[a] 1-Nitrocarbazole (**18c**) was isolated in 90% yield.
[b] In addition, 15% of **18d** was isolated.



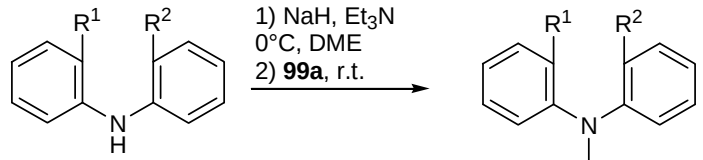
18c



18d

In two cases, cyclization to the corresponding carbazoles was observed.[156] Most noticeably, the reaction between **119d** and **120b** exclusively produces nitrocarbazole **18c** in 90% yield. In contrast, the reaction of **119d** and **120d** yields a mixture of diphenylamine **121e** (80%) and carbazole **18d** (15%).

Then the secondary diphenylamines **121a-c** were transformed into the corresponding tertiary amines **122a-b** and **94** by *N*-allylation with prenyl bromide **99a** in yields from 90% to 97% (Scheme 36).



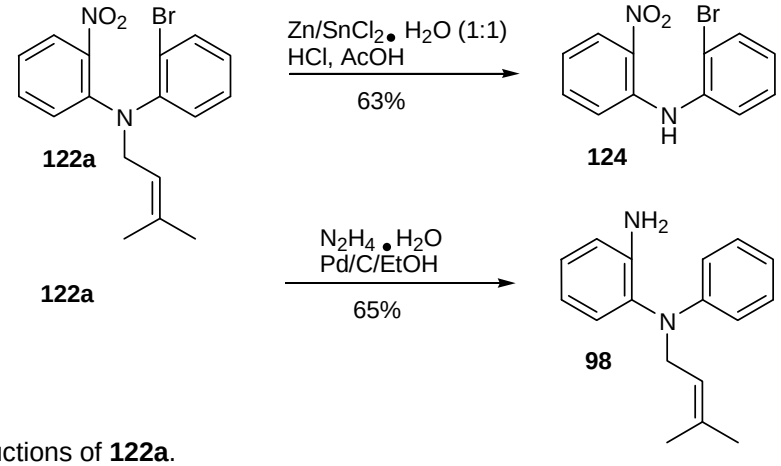
121a $R^1 = NO_2$, R^2 = Br 96% **122a**
121b $R^1 = NO_2$, R^2 = Cl 90% **122b**
121c $R^1 = NO_2$, R^2 = H 97% **94d**

Scheme 36 Synthesis of tertiary diphenylamines **122a-b** and **94d**.

This transformation was achieved by deprotonation of **121a-c** with a slight excess of NaH in dimethoxyethane at 0 °C followed by treatment with an excess of prenyl bromide **99a** at room temperature.[151]

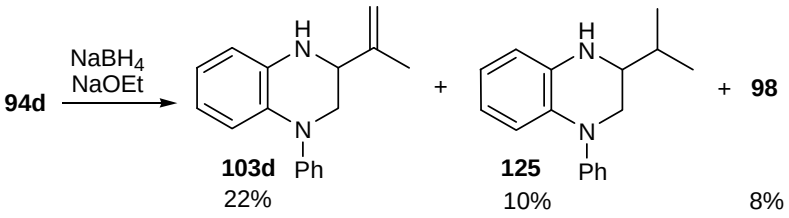
The next goal was to reduce the nitro compounds **122a-b** and **94d** to the corresponding anilines **123a-b** and **98**. However, unexpected problems occurred with the reduction of the

nitro groups of **122a** and **122b**. For example, treatment of 1 eq. of **122a** with 2.5 eq. of a 1**:**1-mixture of Zn and $SnCl_2 \cdot 2H_2O$ as reducing agents under acidic conditions[153] (37% HCl in concd CH_3CO_2H) did not only lead to the reduction of the nitro group but also to *N*-deallylation. The *o*,*o'*-disubstituted diphenylamine **124** was formed exclusively in a yield of 63% (Scheme 37). On the other hand, the reaction of 1 eq. of **122a** with a large excess of $N_2H_4 \cdot H_2O$ (13 equiv) in the presence of 2.5 mol% Pd/C[157] resulted in both reduction of the nitro group and cleavage of the bromo substituent, so compound **98** was isolated in 65% yield (Scheme 37).



Scheme 37 Reductions of **122a**.

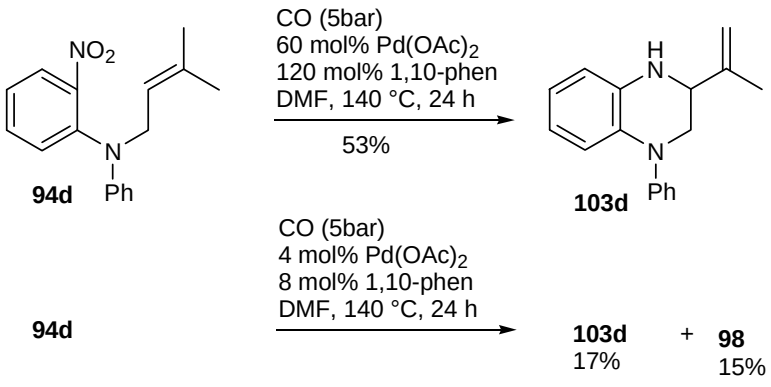
Clean conversion of **122a-b** into **123a-b** also failed with various other reducing agents, including $NH_4OH/(NH_4)_2Fe(SO_4)_2$,[158] $Cu(acac)_2/NaBH_4$,[159] In/NH_4Cl,[160] Zn/CH_3CO_2H,[12] Fe/HCl,[161] $FeCl_3 \cdot 6H_2O/NH_2\text{-}N(CH_3)_2$[162] and SmI_2.[163] Thus, we focussed on the reduction of **94d** to **98** and the reductive cyclization of **98c**, respectively. A classical procedure for the reductive cyclization of *o*-nitrodiphenylamines to phenazines in a single step is Holliman´s method[24] using of a mixture of $NaBH_4$ and NaOEt in excess as the reducing agent. Surprisingly, no phenazine was formed when **94d** was treated with 2.5 eq. $NaBH_4$ and a 5*N* ethanolic solution of NaOEt. Instead, a mixture of 3-isopropenyl-1-phenyl-1,2,3,4-tetrahydro-quinoxaline **103d** (22%), 3-isopropyl-1-phenyl-1,2,3,4-tetrahydroquinoxaline **125** (10%) and the amine **98** (8%) was isolated (Scheme 38).



Scheme 38 Reductive cyclization of **94d** using $NaBH_4$/NaOEt as a reagent.

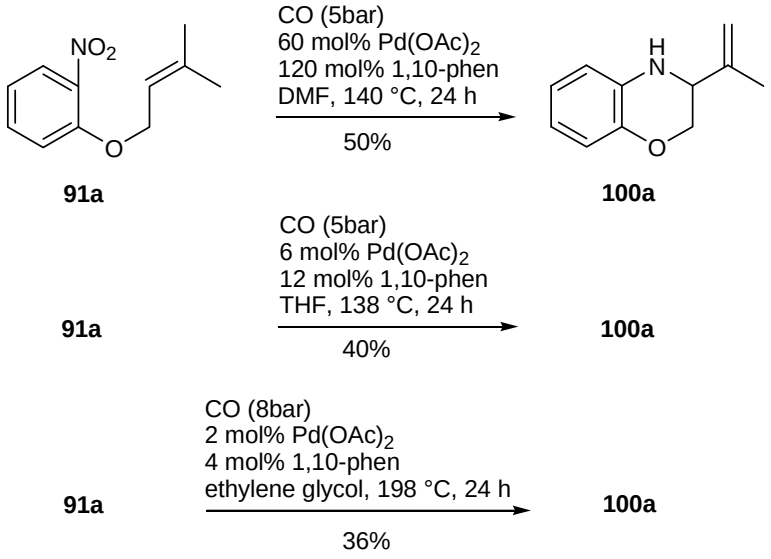
Despite the modest yield of 22% of 3-isopropenyl-1-phenyl-1,2,3,4-tetrahydroquinoxaline **103d** the conversion of an ω-nitroalkene into an alkenyl-substituted *N*-heterocycle in a single synthetic step is of general interest as this transformation represents a new reductive domino process.[114] In the course of our studies we tried to establish reagents and reaction conditions capable of increasing the yields of the annulation products. This objective was reached by using phosphites as the reagents.[144, 164] For example, compound **103d** was obtained in a yield of 57% upon heating **94d** with $(EtO)_3P$ under reflux. In this and all the other cases investigated, $(EtO)_3P$ had to be used in excess. It was this excess that triggered the search for catalytic alternatives.

The past years have shown that the synthesis of *N*-heterocycles can be achieved by transition metal-catalyzed *N*-heteroannulations of aromatic nitro compounds in the presence of CO.[1c] Particularly well known is the Pd-catalyzed reductive *N*-heteroannulation of *o*-nitrostyrenes to indoles.[1c, 102, 103a, 104] Even if this annulation can be performed with complexes of other metals like Ru,[1c, 93, 95] Rh,[1c, 100] or Fe,[1c] it is the Pd complexes that are undoubtedly the most important catalysts. So we set out to investigate the reductive cyclization of the ω-nitroalkene **94d** into the saturated *N*-heterocycle **103d** by Pd-catalyzed reactions with CO. First we concentrated on the combination of $Pd(OAc)_2$ as a catalyst, 1,10-phenanthroline as a ligand and CO as a reductant. We found that reductive cyclization of the ω-nitroalkene **94d** can be realized in a single step by using 60 mol% of $Pd(OAc)_2$, 120 mol% of 1,10-phenanthroline and CO (5 bar).[165] Under these conditions the 1,2,3,4-tetrahydroquinoxaline **103d** was isolated in 53% yield (Scheme 39). But although we managed a reduction of $Pd(OAc)_2$ to 4 mol% and of 1,10-phenanthroline to 8 mol%, the product yield dropped: only 17% of **103d** were formed under these conditions, accompanied by 15% of the tertiary diphenylamine **98** (GC-MS) (Scheme 39).



Scheme 39 Pd-mediated *N*-heteroannulation of **94d**.

In order to find out whether this new one-step Pd-mediated *N*-heteroannulation of ω-nitroalkenes can also be applied to the synthesis of other heterocycles we turned our attention to the conversion of allyl 2-nitrophenyl ethers. Reaction of 3,3-dimethylallyl-2-nitrophenyl ether **91a** with CO (5 bar, 140 °C) in the presence of 60 mol% $Pd(OAc)_2$ and 120 mol% 1,10-phenanthroline produced 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine **100a** in 50% yield (Scheme 40).

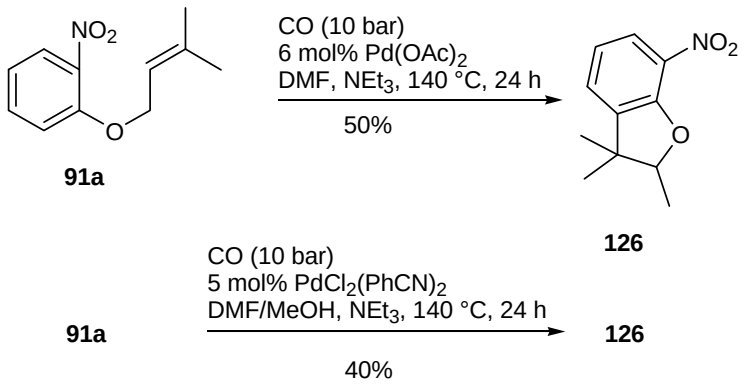


***Scheme* 40** Synthesis of benzoxazine **100a**.

In the case of **91a** the amounts of $Pd(OAc)_2$ and 1,10-phenanthroline could be reduced to 6 mol% and 12 mol%, respectively, when the reaction was performed with CO (10 bar) in tetrahydrofurane (138 °C). Under these conditions **100a** was obtained in 40% yield. With ethylene glycol as the solvent as little as 2 mol% $Pd(OAc)_2$ and 4 mol% 1,10-phenanthroline was sufficient to catalyze the reductive cyclization of **91a** with CO (8 bar). After 24 h at 198 °C **100a** was isolated in 36% yield. The remarkably strong influence of the solvent on the course of this reaction is supported by the finding that no cyclization occurred in xylene (145 °C, 10 bar), and many products were formed (TLC) in acetonitrile (140 °C, 10 bar CO).

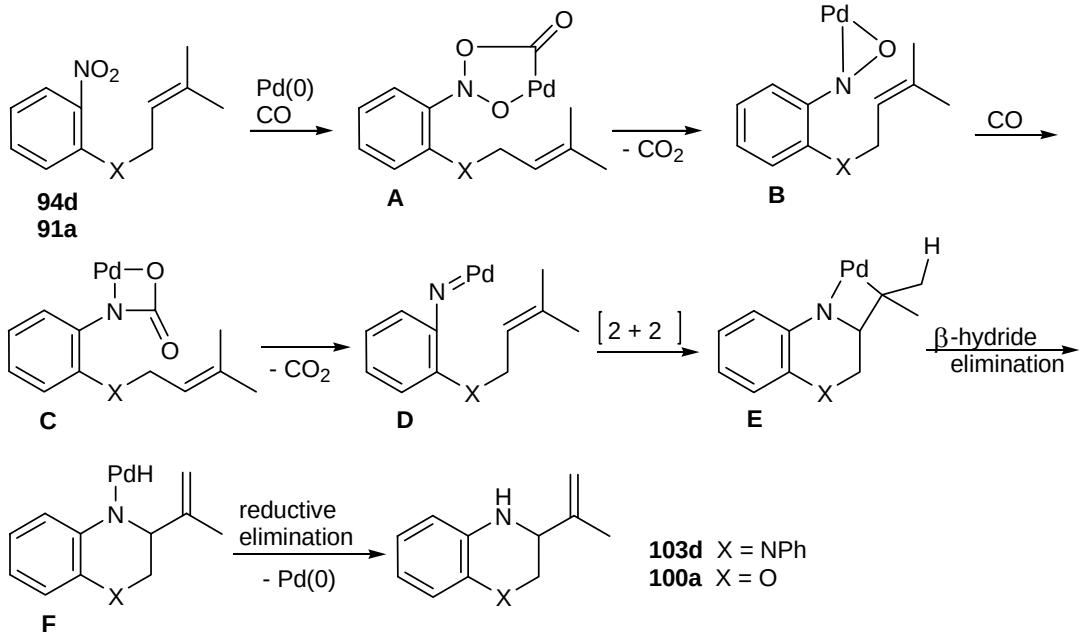
Finally, the Pd-catalyzed transformation of **100a** with CO (10 bar) was also examined under basic conditions with NEt_3 (10 equiv) in DMF or DMF/MeOH. Surprisingly, 2,3,3-trimethyl-7-nitro-2,3-dihydro-benzofuran **126** was the only cyclization product formed. Yields ranged from 40% to 50% (Scheme 41).[166] Formation of **126** implicates that the cyclization proceeds without the participation of the nitro group in **91a**. As a side product 2-nitrophenol was

isolated with yields of 10% and 15%, respectively. It probably originates from deallylation of **91a**.



Scheme 41 Synthesis of benzofuran **126**.

Currently, we can only speculate on the mechanism of the Pd-mediated reductive *N*-heteroannulation of ω-nitroalkenes with CO.[113a, 113b] We assume that the process starts with the metal-mediated deoxygenation of **94d** and **91a**, respectively. Reaction of the nitro group with CO would first yield **A** leading to the metal-bound nitrosamine **B** and the formation of CO_2. Repeated insertion of CO would give the metalla-cyclobutanone **C**, which in turn decomposes to yield the metal-bound nitrene **D** and CO_2. A formal intramolecular [2+2] cycloaddition between the Pd-bound nitrene and the alkene would give the tricycle **E**. The next step involves the formation of the bicyclic intermediate **F** by means of ß-hydride elimination. Finally, reductive elimination would not only deliver the products **103d** and **100a**, respectively, but also regenerate the Pd(0) catalyst (Scheme 42).



Scheme 42 Possible reaction mechanism for the Pd-mediated *N*-heteroannulation.

In summary, new Pd-mediated reductive heteroannulations have been achieved starting from *N*-allyl diphenylamines and *O*-allylethers yielding saturated heterocycles.

Acknowledgements

We thank Dr. J. Conrad, Mrs. S. Mika, Dr. R. Frank and Mrs. I. Klaiber for recording of NMR, UV and MS spectra.

General procedure for the cyclization reaction with CO

A Berghof PTFE liner was charged with (0.166 g, 0.589 mmol) **94d** dissolved in 5 mL DMF and inserted into a Berghof pressure reactor HR-100. A mixture of $Pd(OAc)_2$ (80 mg, 0.356 mmol) and 1,10-phenanthroline (128 mg, 0.71 mmol) dissolved in 50 mL DMF was added. The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (5 bar) and heated at 140 °C for 24 h. The reaction mixture was cooled to rt, the catalyst filtered off and washed with H_2O. Extraction with EtOAc (3 x 50 mL) was followed by drying of the organic phase over $MgSO_4$ and removal of the solvent under reduced pressure. The residue was purified by flash column chromatography (PE/EtOAc = 20**:**1).

7 SUMMARY

Heterocycles are widely distributed in nature, constitute the largest group of organic compounds and are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances, being used as intermediates in organic synthesis, as pharmaceutical, agrochemical or veterinary products.

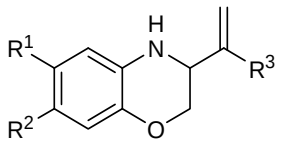
Many of them are of fundamental importance to living systems, since they represent key components of biological processes.[1b, 123, 167] New methods for the construction of heterocycles are not only of major interest to all synthetic chemists involved in the synthesis of biologically active compounds, but in general to all those working in the field of life sciences. This holds particularly true if these methods serve to expand familiar methodological devices in the synthetic arsenal.

In the synthesis of heterocycles, domino reactions play a crucial role as a method used to improve synthetic efficiency and to give access to a multitude of compounds. The domino reaction is a process involving two or more bond-forming transformations occurring in a sequential mode. The quality and importance of a domino reaction can be correlated to the number of bonds generated and the increase of complexity.[114]

During the last years microwave heating has become a convenient and broadly used tool in organic synthesis, its most popular application being the synthesis of heterocycles.[128] Under microwave irradiation, chemical reactions usually proceed faster, in higher yields and with fewer byproducts.

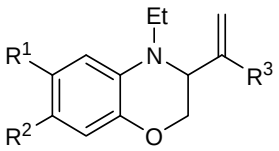
Transition metal catalysts have developed into excellent reagents in organic synthesis to form C–C and C–heteroatom bonds.[1c] The domino reactions, the microwave techniques and the transition metal catalysis have all been used together in the present work as shown in publications no. 1 – 3.

7.1 A new domino reaction of allyl 2-nitro-phenylethers **91a-k**, **92** and 1-(4-methyl-pent-3-enyl)-2-nitrobenzene **97** mediated by triethyl phosphite and implicitly the synthesis of the substituted 3,4-dihydro-2*H*-1,4-benzoxazines **100a-k**, **102**, *N*-ethyl 3,4-dihydro-2*H*-1,4-benzoxazines **101a**,**b**,**d**,**e**,**f**,**k**, and 2-isopropenyl-1,2,3,4-tetrahydroquinoline **104**, respectively (Fig 11) is described in article no. 1 (see list of publications).

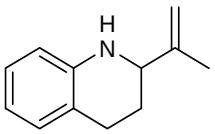


102, $R^1 = R^2 = R^3 = H$

100a-k



101a, **b**, **d**, **e**, **f**, **k**



104

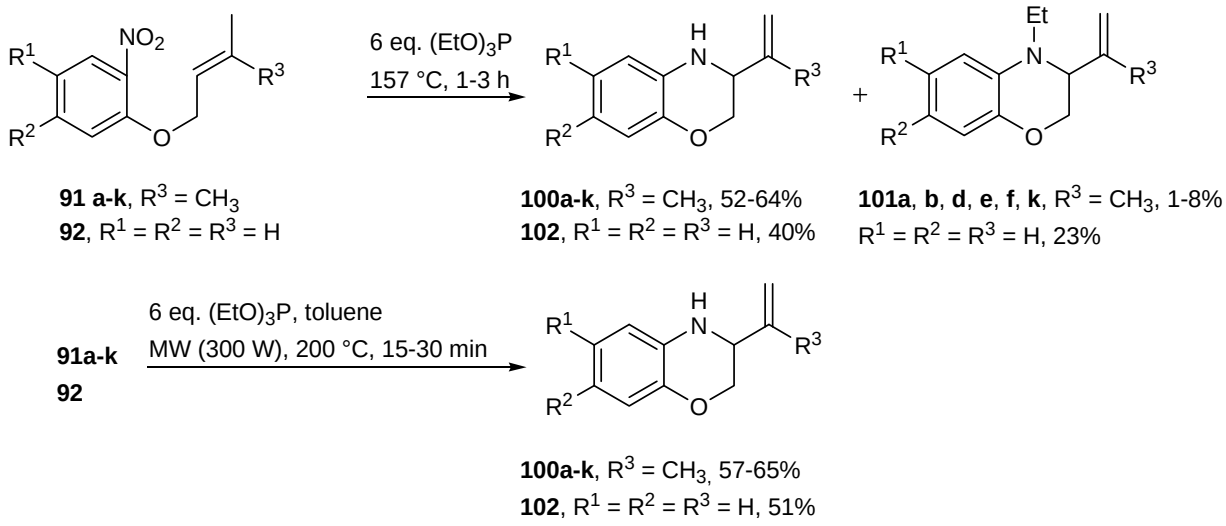
100	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
c	OMe	H	Me
d	F	H	Me
e	Cl	H	Me
f	Br	H	Me
g	CO_2Me	H	Me
h	H	Me	Me
i	H	F	Me
j	H	CO_2Me	Me
k	Cl	Me	Me

101	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
d	F	H	Me
e	Cl	H	Me
f	Br	H	Me
k	Cl	Me	Me

Figure 11 3,4-dihydro-2*H*-1,4-benzoxazines **100a-k**, **101a**,**b**,**d**,**e**,**f**,**k**, **102**, and 1,2,3,4-tetrahydro-quinoline **104**.

Under thermal conditions with an excess of triethyl phosphite, the cyclization of the allyl 2-nitrophenyl ethers **91a-k** and **92** occurred with the formation of substituted 3,4-dihydro-2*H*-1,4-benzoxazines **100a-k**, **102** and substituted *N*-ethyl 3,4-dihydro-2*H*-1,4-benzoxazines **101a**,**b**,**d**,**e**,**f**,**k** (Scheme 43). The results demonstrate that a range of substituents on the aromatic nucleus is well tolerated in these transformations.

The cyclization reactions under microwave conditions (300 W, 200 °C) have taken place in a shorter time and the reaction times could be reduced from hours to minutes. Unfortunately, it was not possible to suppress the formation of the byproducts **101** using pure triethyl phosphite as reagent and solvent. Using toluene as solvent, the formation of the byproducts could be completely suppressed (Scheme 43; for R^1, R^2 and R^3 in **91**, **100** and **101**, see also Scheme 22, Table 2).



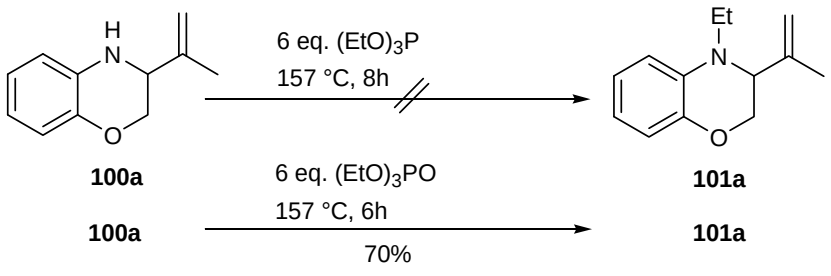
91 **100**	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
c	OMe	H	Me
d	F	H	Me
e	Cl	H	Me
f	Br	H	Me
g	CO_2Me	H	Me
h	H	Me	Me
i	H	F	Me
j	H	CO_2Me	Me
k	Cl	Me	Me

101	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
d	F	H	Me
e	Cl	H	Me
f	Br	H	Me
k	Cl	Me	Me

Scheme 43 Domino reactions of the substrates **91a-k** and **92** under thermal and microwave conditions.

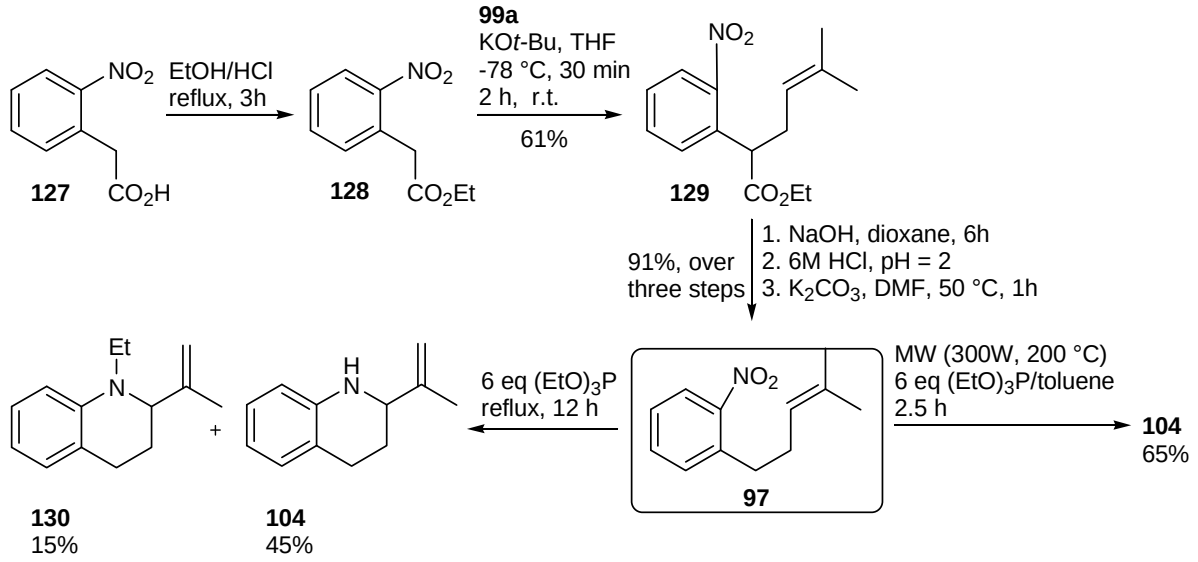
The byproducts **101** have been formed by *N*-ethylation of the main products **100** with triethyl phosphate, produced by oxidation of triethyl phosphite under reaction conditions.

The formation of the compound **101a** from **100a** is taken as an example (Scheme 44).



Scheme 44 *N*-ethylation of **100a** to **101a** produced by triethyl phosphate.

The 2-isopropenyl-1,2,3,4-tetrahydroquinoline **104** has been prepared from the commercially available 2-nitrophenyl acetic acid **127** in six steps; the domino reaction of the compound **97** mediated by triethyl phosphite occurred selectively when the reaction was carried out in toluene under microwave conditions (**104** was isolated in 65% yield, Scheme 45).



Scheme 45 Synthesis of 2-isopropenyl-1,2,3,4-tetrahydroquinoline **104**.

The compounds **100a-k**, **101a**,**b**,**d**,**e**,**f**,**k**, **102** and **104** have been analyzed by conventional methods such as NMR, LR-MS, HR-MS, EA, UV and IR spectroscopy.

7.2 The synthesis of 1,2,3,4-tetrahydroquinoxalines **103a-d**, **105a-d**, **107a-d**, **108a-d** and **110**, **111** (Fig 12) has been described in the publications 1 and 2 (see list of publications) as a successful application of the triethyl phosphite mediated domino reaction of ω-nitroalkenes.

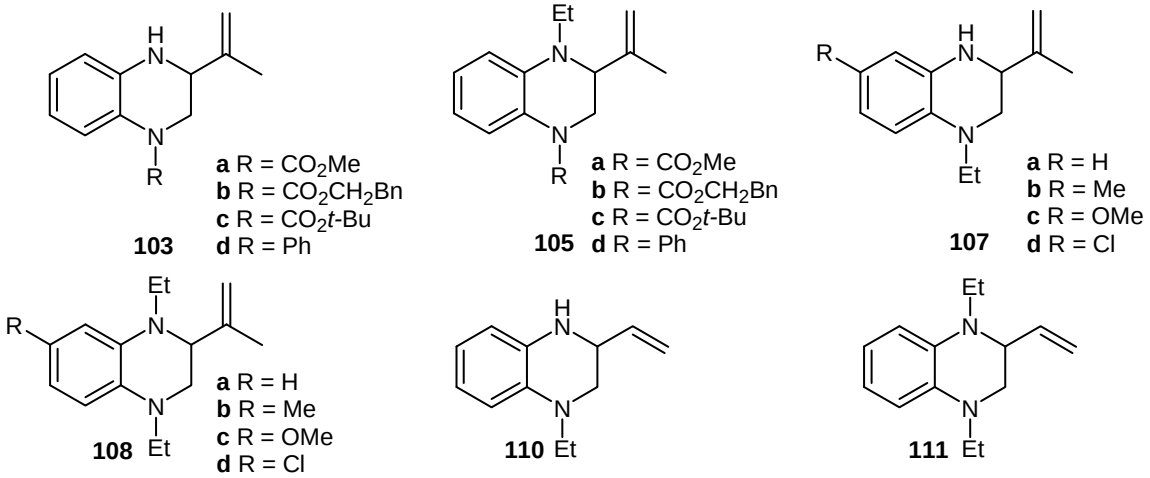
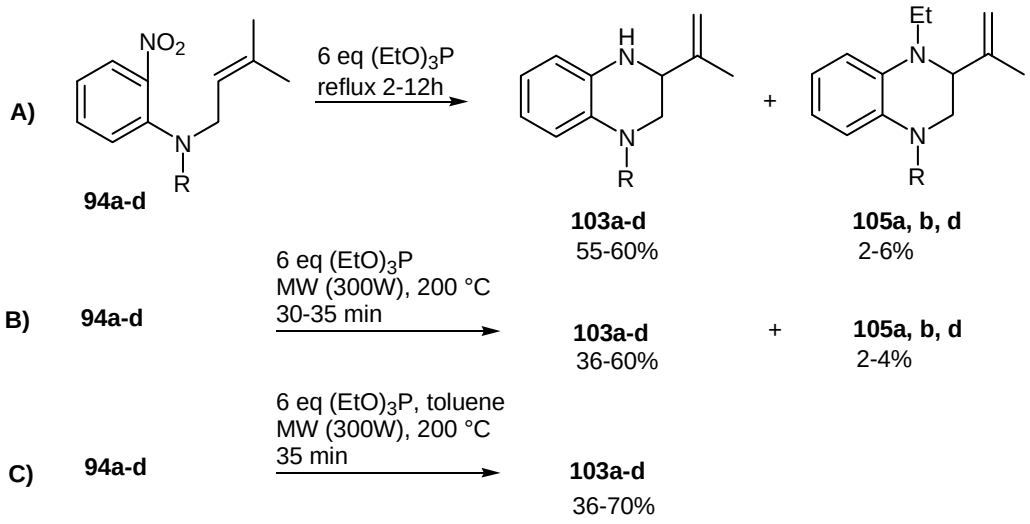


Figure 12 1,2,3,4-tetrahydroquinoxalines synthesized via domino reaction

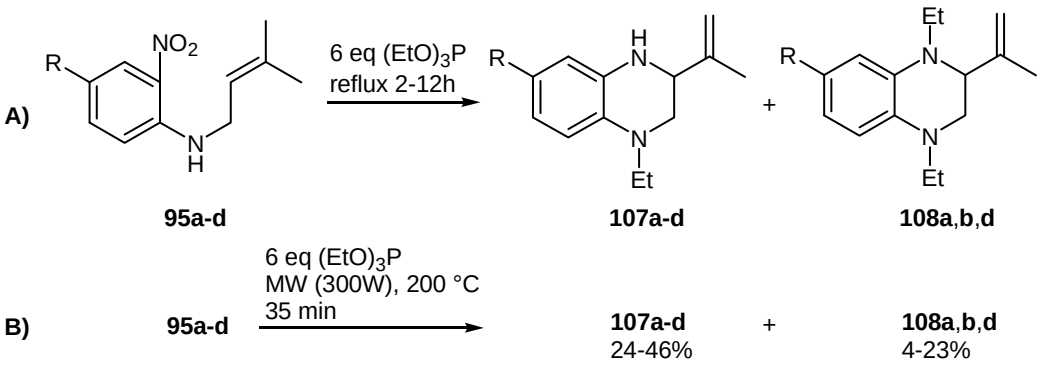
By heating the tertiary *N*-prenyl 2-nitroanilines **94a-d** under reflux, the 3-isopropenyl-1,2,3,4-tetrahydroquinoxalines **103a-d** were isolated together with the monoalkylated compounds **105a**,**b**,**d** as byproducts in small amounts (Scheme 46, Equation A). Similar results were obtained under microwave conditions in pure triethyl phosphite, where the *N*-monoethylation could not be suppressed (Scheme 46, Equation B). The domino reaction of **94a-d** mediated by triethyl phosphite in toluene led to the exclusive formation of **103a-d** (Scheme 46, Equation C).



94, 103, 105	R
a	CO_2Me
b	CO_2CH_2Bn
c	CO_2t-Bu
d	Ph

Scheme 46 Reductive cyclization of protected *N*-prenyl 2-nitroanilines **94a-d**; **A)** under thermal conditions in neat $(EtO)_3P$; **B)** under microwave conditions in neat $(EtO)_3P$; **C)** under microwave conditions in a mixture of $(EtO)_3P$/toluene.

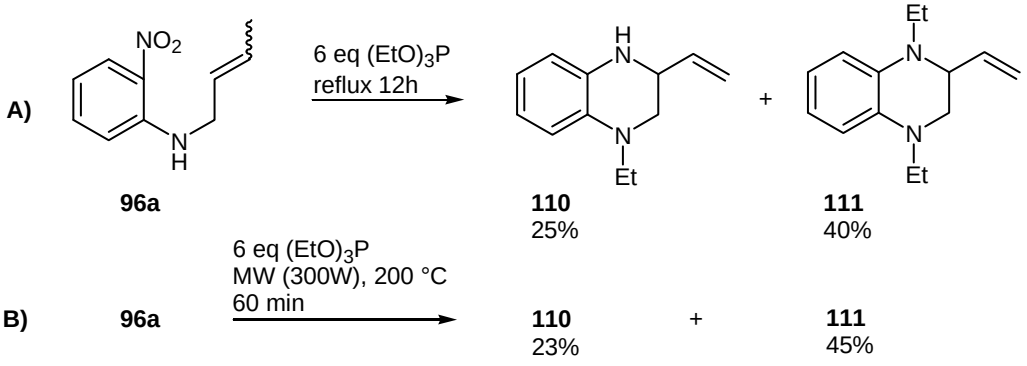
In contrast, the transformation of the unprotected *N*-prenyl 2-nitroanilines **95a-d** by heating with $(EtO)_3P$ under reflux (Scheme 47, Equation A) or by irradiation under microwave conditions in pure $(EtO)_3P$ (Scheme 47, Equation B) exclusively yielded the mono- and diethylated derivatives, **107a-d** and **108a**,**b**,**d**. The unprotected *N*-prenyl 2-nitroanilines **95a-d** and the unprotected *N*-crotyl 2-nitroanilines **96a** did not react under microwave conditions in a mixture of $(EtO)_3P$/toluene.



95, 107, 108	R
a	H
b	Me
c	OMe
d	Cl

Scheme 47 Reductive cyclization of unprotected *N*-prenyl 2-nitroanilines **95a-d**.

The reactions of **95a-d** demonstrate that the reductive domino process tolerates substrates substituted at the aromatic nucleus, while the reaction of **96a** and the synthesis of the corresponding vinyl-1,2,3,4-tetrahydroquinoxalines **110** and **111** demonstrate that the variation of the allylic component is also possible (Scheme 48).



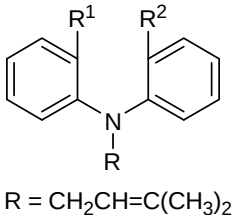
Scheme 48 Reductive cyclization of the unprotected *N*-crotyl 2-nitroanilines **96a**.

The 1,2,3,4-tetrahydroquinoxaline derivatives **103a-d**, **105a**,**b**,**d**, **107a-d**, **108a-d** and **110**, **111** have been characterized by employing conventional spectroscopic methods.

7.3 The reductive cyclizations reported here are transition metal-catalyzed domino processes without precedent and represent a new method for the synthesis of saturated *O*- and *N*-heterocycles.[169]

Transition metal-catalyzed domino reactions play an important role in the synthesis of heterocycles. A well known example is the Pd-catalyzed cyclization of *o*-nitrostyrenes using CO as reductant.[1c] The corresponding transition metal-catalyzed cyclizations of 2-nitro-benzenamines or *N*-allyl *o*-nitroaromatics are known.[113, 168]

First, the main target was the synthesis of the tertiary *o*-nitro-substituted diphenylamines **122a**,**b** and **94d** and their reductive conversion into the corresponding anilines **123a**,**b** and **98**, respectively (Fig 13).



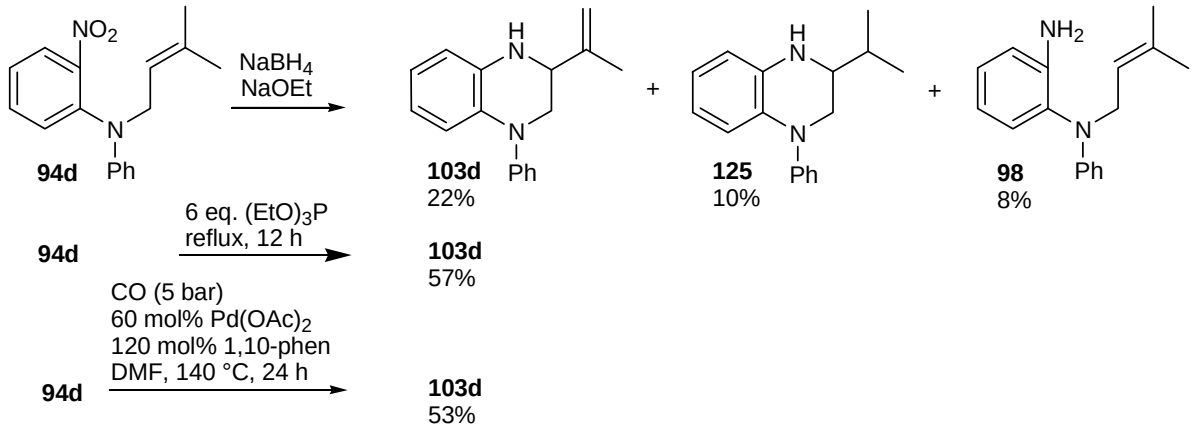
122a $R^1 = NO_2$, R^2 = Br
122b $R^1 = NO_2$, R^2 = Cl
94d $R^1 = NO_2$, R^2 = H

123a $R^1 = NH_2$, R^2 = Br
123b $R^1 = NH_2$, R^2 = Cl
98 $R^1 = NH_2$, R^2 = H

Figure 13 Potential substrates for the synthesis of phenazinone **II**.

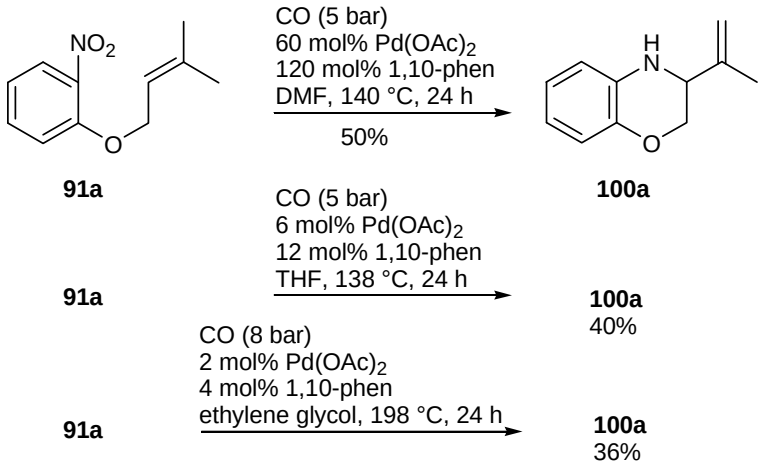
Using a mixture of $NaBH_4$/NaOEt, **94d** was converted to 3-isopropenyl-1-phenyl-1,2,3,4-tetrahydroquinoxaline **103d** in 22% yield (Scheme 49); despite the modest yield, the conversion of an ω-nitroalkene into a saturated *N*-heterocycle in a single synthetic step is of general interest as this transformation represents a new reductive domino process.[144] To increase the yields of the cyclization products, phosphites have been used as reagents.[144, 164] For example, compound **103d** was obtained in a yield of 57% upon heating **94d** with an excess of $(EtO)_3P$. This excess of $(EtO)_3P$ triggered the search for catalytic alternatives.

It was found that reductive cyclization of the ω-nitroalkene **94d** can be realized in a single step by using $Pd(OAc)_2$ (60 mol%), 1,10-phenanthroline (120 mol%) and CO (5 bar) (Scheme 49). With the reduction of $Pd(OAc)_2$ to 4 mol% and of 1,10-phenanthroline to 8 mol%, the reaction still proceeded, but the product yield of **103d** dropped to 17%.



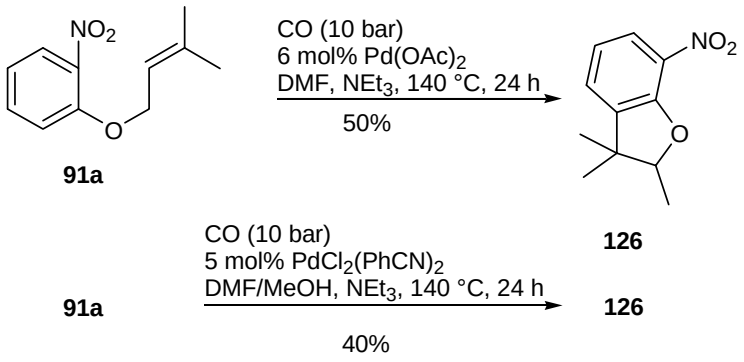
Scheme 49 Cyclization reactions of **94d** under different reaction conditions.

Further, the main attention was focused on the conversion of allyl 2-nitrophenyl ethers, namely **91a**. Analogous reaction of *O*-allyl 2-nitrophenyl ether **91a** with CO in the presence of $Pd(OAc)_2$ and 1,10-phenanthroline yields the corresponding 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine **100a**. The cyclization reaction was performed with catalytic amounts of $Pd(OAc)_2$ by varying the solvent (Scheme 50).



Scheme 50 Cyclization reactions of **91a** to **100a**.

Finally, the Pd-catalyzed transformation of **91a** with CO was also examined under basic conditions. Surprisingly, the Pd-catalyzed reaction of the *O*-allyl 2-nitrophenyl ether **91a** delivered a 2,3,3-trimethyl-7-nitro-2,3-dihydrobenzofuran **126** as the main product in the presence of triethylamine as a base (Scheme 51).



Scheme 51 Synthesis of benzofuran **126** under basic conditions.

In conclusion, the current work describes a new triethyl phosphite mediated domino reaction of ω-nitroalkenes,[144, 164] which in one step cyclize to the corresponding saturated *N*-heterocycles. The one-step domino reaction described in this work includes a three-step reaction, a nitroso-ene reaction being coupled with two reduction reactions. A new C-N bond is formed and saturated *N*-heterocycles are synthesized. The microwave irradiation of the ω-nitroalkenes has been developed as an alternative protocol, having the advantage that the formation of byproducts can be suppressed and the reaction times reduced. The reductive cyclization reaction mediated by triethyl phosphite allows preparation of a series of saturated *N*-heterocycles such as substituted 3,4-dihydro-2*H*-1,4-benzoxazines, 1,2,3,4-tetrahydro-quinoxalines and 1,2,3,4-tetrahydroquinolines.

The newly developed domino reaction can also occur under CO pressure using metal catalysts, allowing the formation of saturated *N*-heterocycles.[169] Since the reductive cyclizations reported in this work are transition metal-catalyzed domino processes without precedent, they could be of significant interest to the field of synthetic chemistry and "Life Sciences".

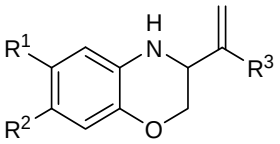
The spectroscopic properties of the entire range of the synthesized compounds have been determined.

8 ZUSAMMENFASSUNG

Heterocyclen sind in der Natur weit verbreitet, bilden die größte Gruppe an organischen Verbindungen und gehören zu den am häufigsten anzutreffenden Grundgerüsten in Medikamenten und pharmazeutisch relevanten Substanzen. Viele Heterocyclen haben eine große Bedeutung als Zwischenprodukte in der organischen Synthese. Hauptsächlich werden sie als Pharmazeutika, als Agrarchemikalien oder in Produkten für die Veterinärmedizin eingesetzt. Eine Reihe von Heterocyclen hat grundlegende Bedeutung in lebenden Systemen, wo sie als Schlüsselkomponenten in biologischen Prozessen eine Rolle spielen.[1b, 123, 167] Neue Methoden zum Aufbau von Heterocyclen sind von maßgeblichem Interesse nicht nur für alle Synthetiker, die sich mit dem Aufbau biologisch aktiver Verbindungen beschäftigen, sondern allgemein auch für alle diejenigen, die auf dem Gebiet der "Life Sciences" arbeiten. Dies gilt speziell dann, wenn diese Methoden dazu dienen, das vertraute synthetische Arsenal um neue Methoden zu erweitern. In der Synthese von Heterocyclen spielen Dominoreaktionen eine sehr wichtige Rolle als Methoden zur Verbesserung der Synthese-Effizienz und für den Zugang zu einer Vielzahl von verschiedenartigen Produkten. Bei Dominoreaktionen handelt es sich um Prozesse, bei denen zwei oder mehr Umsetzungen stattfinden, bei denen sich chemische Bindungen bilden. Der Wert und die Bedeutung einer Dominoreaktion können mit der Anzahl der neu geknüpften Bindungen und dem Anstieg der Komplexität in direkte Verbindung gebracht werden.[114] Das Erhitzen mittels Mikrowellen hat sich in den letzten Jahren zu einem bequemen und oft verwendeten Werkzeug in der organischen Synthese entwickelt; die Synthese von Heterocyclen ist einer der am stärksten bearbeiteten Bereiche der Mikrowellen-Chemie.[128] Bei Bestrahlung mit Mikrowellen laufen chemische Reaktionen in der Regel schneller, mit höheren Ausbeuten und weniger Nebenprodukten ab. Ebenso stellen Übergangsmetall-Katalysatoren ausgezeichnete Werkzeuge in der organischen Synthese bei der Knüpfung von C-C-Bindungen sowie Bindungen zwischen Kohlenstoff und Heteroatomen dar.[1c] Dominoreaktionen, Mikrowellen-Technik und Übergangsmetall-Katalyse fanden in der vorliegenden Arbeit allesamt Anwendung, wie die Veröffentlichungen Nr. 1 – 3 zeigen.

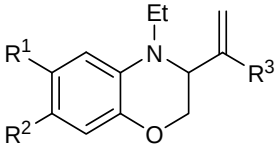
8.1 Der erste Teil dieser Untersuchungen beschreibt eine neue Dominoreaktion der Allyl-2-nitrophenylether **91a-k**, **92** und 1-(4-Methyl-pent-3-enyl)-2-nitrobenzol **97** in der durch Triethylphosphit vermittelten Synthese der substituierten 3,4-Dihydro-2*H*-1,4-benzoxazine

100a-k, **102**, der *N*-Ethyl-3,4-dihydro-2*H*-1,4-benzoxazine **101a**,**b**,**d**,**e**,**f**,**k** sowie des 2-Isopropenyl-1,2,3,4-tetrahydrochinolins **104** (Abb. 11).

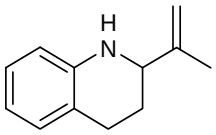


100a-k, $R^3 = CH_3$

102, $R^1 = R^2 = R^3 = H$



101a, **b**, **d**, **e**, **f**, **k**, $R^3 = CH_3$



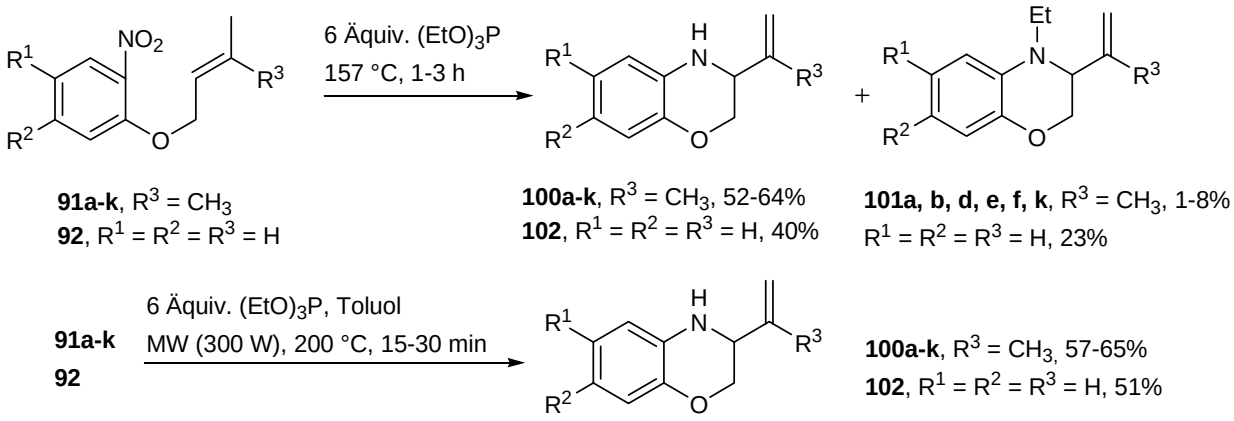
104

100	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
c	OMe	H	Me
d	F	H	Me
e	Cl	H	Me
f	Br	H	Me
g	CO_2Me	H	Me
h	H	Me	Me
i	H	F	Me
j	H	CO_2Me	Me
k	Cl	Me	Me

101	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
d	F	H	Me
e	Cl	H	Me
f	Br	H	Me
k	Cl	Me	Me

Abb. 11 3,4-Dihydro-2*H*-1,4-benzoxazine **100a-k**, **101a**,**b**,**d**,**e**,**f**,**k**, **102** und 1,2,3,4-Tetrahydrochinolin **104**.

Der Ringschluss der Allyl-2-nitrophenylether **91a-k** und **92** verlief unter thermischen Bedingungen und mit einem Überschuss von Triethylphosphit unter Ausbildung der substituierten 3,4-Dihydro-2*H*-1,4-benzoxazine **100a-k** sowie **102** und der substituierten *N*-Ethyl-3,4-dihydro-2*H*-1,4-benzoxazine **101a**,**b**,**d**,**e**,**f**,**k** (Schema 43). Die Ergebnisse zeigen, dass eine gewisse Bandbreite an Substituenten am aromatischen Ring in diesen Umsetzungen zulässig ist. Die Cyclisierung unter Mikrowellen-Bedingungen (300 W, 200°C) findet schneller statt, wodurch die Reaktionszeiten von Stunden auf Minuten reduziert werden konnten. Allerdings war es nach wie vor nicht möglich, die Bildung der Nebenprodukte **101** bei Verwendung von reinem Triethylphosphit als Reagenz und Lösungsmittel zu unterdrücken. Durch die zusätzliche Verwendung von Toluol als Lösungsmittel kann die Bildung von Nebenprodukten unterdrückt werden (Schema 43; für R^1, R^2 und R^3 in **91**, **100** und **101**, siehe auch Schema 22 und Tabelle 2).

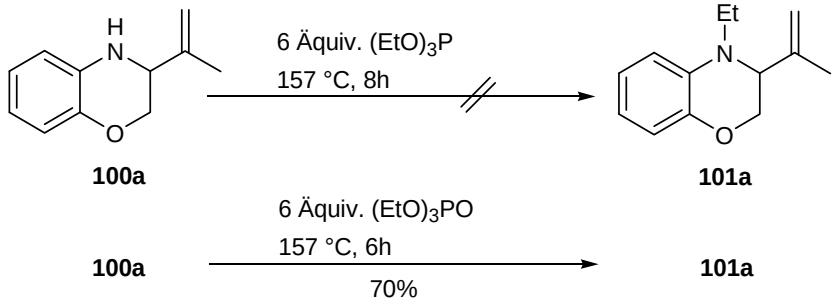


91 **100**	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
c	OMe	H	Me
d	F	H	Me
e	Cl	H	Me
f	Br	H	Me
g	CO_2Me	H	Me
h	H	Me	Me
i	H	F	Me
j	H	CO_2Me	Me
k	Cl	Me	Me

101	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
d	F	H	Me
e	Cl	H	Me
f	Br	H	Me
k	Cl	Me	Me

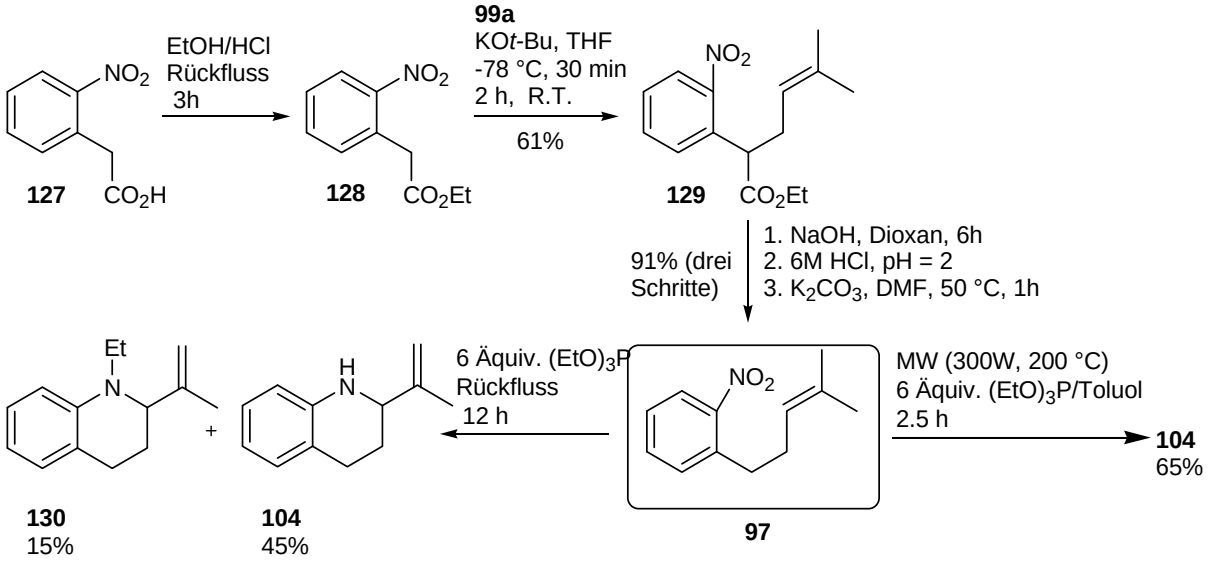
Schema 43 Dominoreaktionen der Edukte **91a-k** und **92** unter thermischen und Mikrowellen-Bedingungen.

Die Nebenprodukte **101** wurden durch die Ethylierung der Hauptprodukte **100** mit Triethylphosphat gebildet, welches das Produkt der Oxidation von Triethylphosphit ist. Die Bildung der Verbindung **101a** aus **100a** soll als Beispiel dienen (Schema 44).



Schema 44 *N*-Ethylierung von **100a** zu **101a** unter Einsatz von Triethylphosphat.

2-Isopropenyl-1,2,3,4-tetrahydrochinolin **104** wurde aus der käuflichen 2-Nitrophenyl-essigsäure **127** in sechs Schritten hergestellt; die Domino-Reaktion der Verbindung **97** mittels Triethylphosphit verläuft selektiv, wenn sie in Toluol unter Mikrowellen-Bedingungen durchgeführt wird (**104** wurde in 65% Ausbeute isoliert, Schema 45).



Schema 45 Synthese von 2-Isopropenyl-1,2,3,4-tetrahydrochinolin **104**.

Die Verbindungen **100a-k**, **101a**,**b**,**d**,**e**,**f**,**k**, **102** und **104** wurden mit Standardmethoden wie NMR, LR-MS, HR-MS, EA, UV- und IR-Spektroskopie charakterisiert.

8.2 Die Synthese der 1,2,3,4-Tetrahydrochinoxaline **103a-d**, **105a-d**, **107a-d**, **108a-d** sowie **110** und **111** (Abb. 12) wurde als eine erfolgreiche Anwendung der neuen Triethyl-phosphit-vermittelten Dominoreaktion von ω-Nitroalkenen beschrieben, die wiederum ursprünglich in den Veröffentlichungen 1 und 2 vorgestellt worden war.

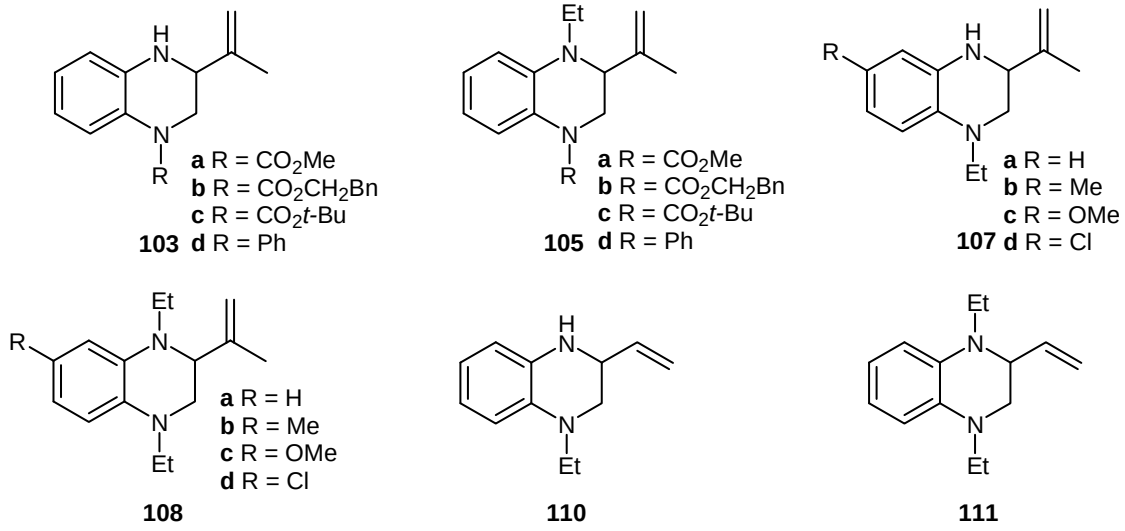
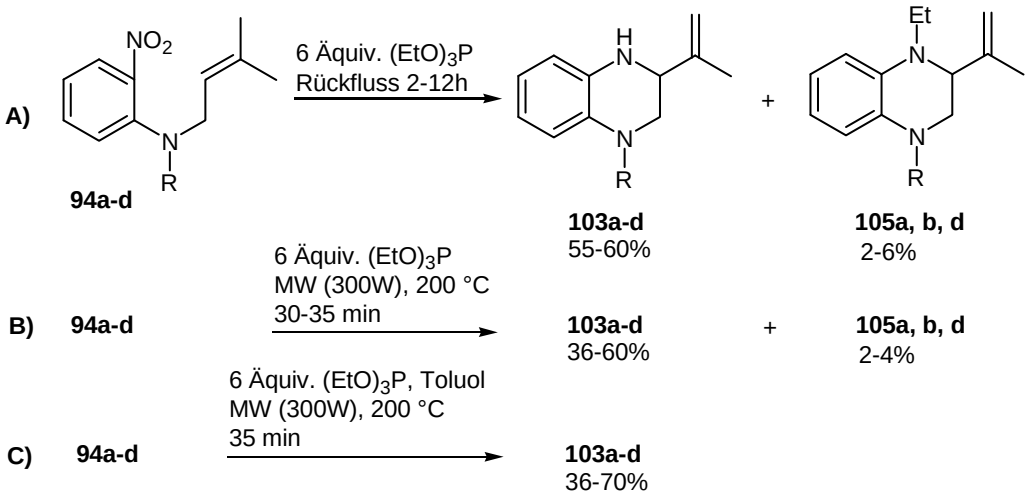


Abb. 12 Durch Dominoreaktion synthetisierte 1,2,3,4-Tetrahydrochinoxaline.

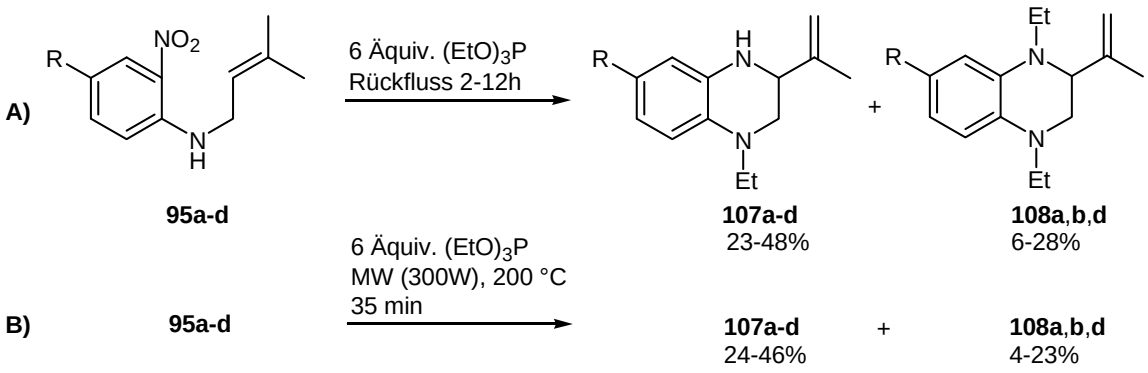
Nachdem die tertiären *N*-Prenyl-2-nitroaniline **94a-d** unter Rückfluss erhitzt worden waren, wurden die 3-Isopropenyl-1,2,3,4-tetrahydrochinoxaline **103a-d** und in geringen Mengen die monoalkylierten Verbindungen **105a**,**b**,**d** als Nebenprodukte erhalten (Schema 46, Gleichung A). Ähnliche Ergebnisse wurden unter Mikrowellen-Bedingungen in reinem Triethylphosphit erzielt, allerdings konnte die *N*-Monoethylierung unter diesen Bedingungen nicht unterdrückt werden (Schema 46, Gleichung B). Die durch Triethylphosphit in Toluol vermittelte Domino-reaktion von **94a-d** führte ausschließlich zur Bildung von **103a-d**, während die Bildung der *N*-ethylierten Nebenprodukte **105a-d** vollständig unterdrückt wurde (Schema 46, Gleichung C).



94, 103, 105	R
a	CO_2Me
b	CO_2CH_2Bn
c	CO_2t-Bu
d	Ph

Schema 46 Reduktive Cyclisierungen der tertiären *N*-Prenyl-2-nitroaniline **94a-d**; **A)** unter thermischen Bedingungen in reinem $(EtO)_3P$; **B)** unter Mikrowellen-Bedingungen in reinem $(EtO)_3P$; **C)** unter Mikrowellen-Bedingungen in einer Mischung aus $(EtO)_3P$/Toluol.

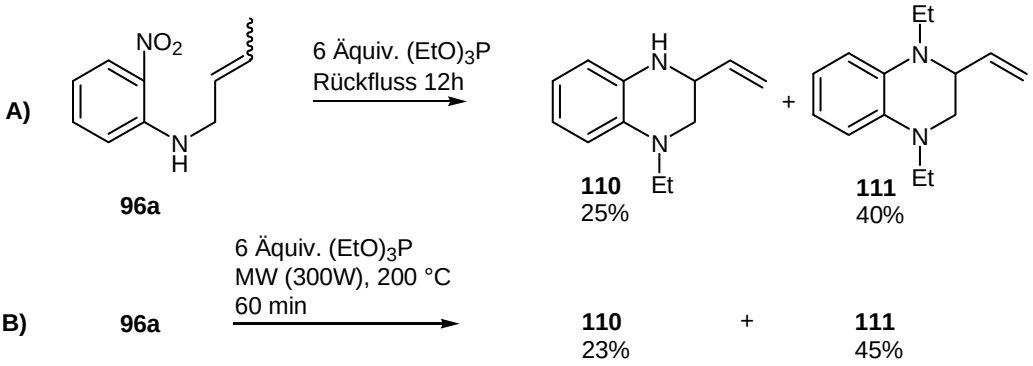
Im Gegensatz hierzu ergab die Umwandlung der ungeschützten *N*-Prenyl-2-nitroaniline **95a-d** durch Erhitzen mit Triethylphosphit unter Rückfluss (Schema 47, Gleichung A) oder durch Bestrahlung unter Mikrowellen-Bedingungen in reinem Triethylphosphit (Schema 47, Gleichung B) ausschließlich die monoethylierten Verbindungen **107a-d** bzw. die zweifach ethylierten 1,2,3,4-Tetrahydrochinoxalin-Derivate **108a**,**b**,**d**. Die ungeschützten *N*-Prenyl-2-nitroaniline **95a-d** und die ungeschützten *N*-Crotyl-2-nitroaniline **96** reagierten unter Mikrowellen-Bedingungen in einer Lösung von Triethylphosphit in Toluol nicht.



95, 107, 108	R
a	H
b	Me
c	OMe
d	Cl

Schema 47 Reduktive Cyclisierungen der sekundären *N*-Prenyl-2-nitroaniline **95a-d**.

Die Reaktionen von **95a-d** zeigen, dass der reduktive Dominoprozess mit am aromatischen Ring substituierten Edukten funktioniert, während die Reaktion von **96a** und die Synthese der entsprechenden Vinyl-1,2,3,4-tetrahydrochinoxaline **110** bzw. **111** zeigen, dass auch die allylische Komponente mit Erfolg variiert werden kann (Schema 48).



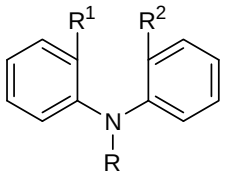
Schema 48 Reduktive Cyclisierungen des *N*-Crotyl-2-nitroanilins **96a**.

Die 1,2,3,4-Tetrahydrochinoxaline **103a-d**, **105a**,**b**,**d**, **107a-d**, **108a-d** sowie **110** und **111** wurden mit Standardmethoden wie NMR, LR-MS, HR-MS, EA, UV- und IR-Spektroskopie charakterisiert.

8.3 Die reduktiven Cyclisierungen, über die hier berichtet wird, stellen bislang nicht bekannte metall-katalysierte Dominoprozesse dar und somit eine neue Methode zur Synthese von *O*- und *N*-Heterocyclen.[169]

Durch Übergangsmetalle katalysierte Dominoreaktionen spielen in der Synthese von Heterocyclen eine wichtige Rolle. Ein bekanntes Beispiel ist die Pd-katalysierte Cyclisierung von *o*-Nitrostyrolen mit CO als Reduktionsmittel.[1c] Andererseits sind auch die entsprechenden durch Übergangsmetalle katalysierten Cyclisierungen von 2-Nitroamino-benzolen oder *N*-Allyl-*o*-nitroaromaten bekannt.[113, 168]

In dieser Arbeit wird von der Synthese der tertiären *o*-Nitro-substituierten Diphenylamine **122a**,**b** und **94d** sowie ihrer Umwandlung in die entsprechenden Aniline **123a**,**b** bzw. **98** berichtet (Abb. 13).



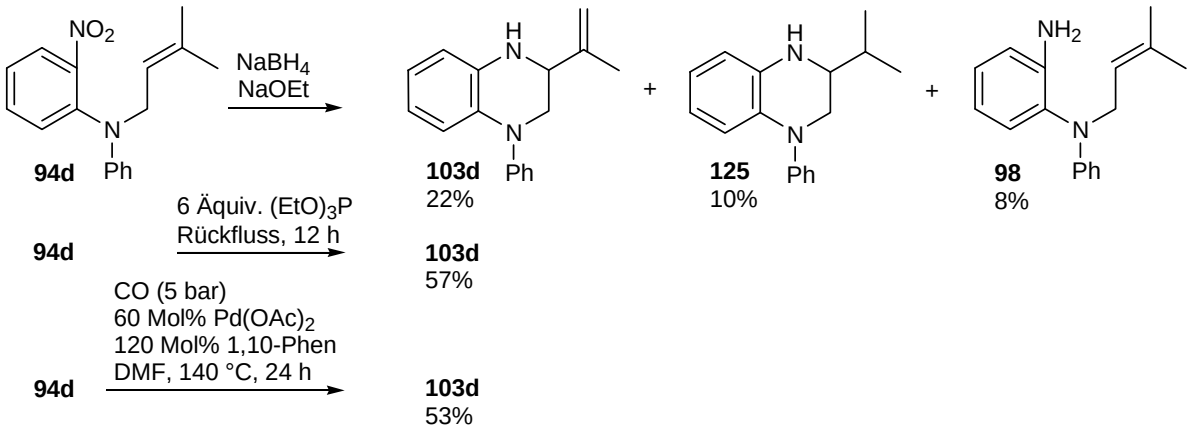
122a $R^1 = NO_2$, R^2 = Br
122b $R^1 = NO_2$, R^2 = Cl
94d $R^1 = NO_2$, R^2 = H

123a $R^1 = NH_2$, R^2 = Br
123b $R^1 = NH_2$, R^2 = Cl
98 $R^1 = NH_2$, R^2 = H

Abb. 13 Potentielle Edukte für die Synthese der Phenazinone **II**.

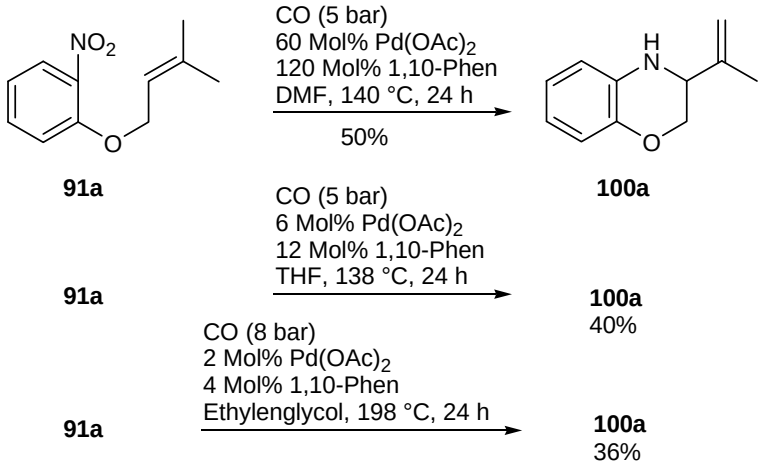
Bei der Behandlung von **94d** mit einer Mischung aus $NaBH_4$ und NaOEt wurde 3-Isopropenyl-1-phenyl-1,2,3,4-tetrahydrochinoxalin **103d** mit 22% Ausbeute (Schema 49) isoliert; trotz der bescheidenen Ausbeute ist die Umwandlung eines ω-Nitroalkens in einen Alkenyl-*N*-heterocyclus in einem einzigen Syntheseschritt insofern von allgemeinem Interesse, als diese Umwandlung einen neuen reduktiven Dominoprozess darstellt.[144] Zur Steigerung der Ausbeuten an *N*-Heterocyclisierungsprodukten wurden Phosphite als Reagenzien verwendet.[144, 164] Beispielsweise wurde die Verbindung **103d** in einer Ausbeute von 57% erhalten, indem **94d** mit einem Überschuss von $(EtO)_3P$ unter Rückfluss erhitzt wurde. Der zu Nebenprodukten führende Überschuss war es, der die Suche nach alternativen Reagenzien auslöste. Es stellte sich heraus, dass z.B. die reduktive Cyclisierung des ω-Nitroalkens **94d** in einem einzigen Schritt unter Verwendung von $Pd(OAc)_2$ (60 Mol-%), 1,10-Phenanthrolin (120 Mol-%) und CO (5 bar) durchgeführt werden konnte (Schema 49). Wenn die Menge an $Pd(OAc)_2$ auf 4 Mol-% und die Menge an 1,10-Phenanthrolin auf 8 Mol-% reduziert wurde, sank gleichzeitig auch die Ausbeute an **103d** auf 17%.

In allen mit Pd/CO durchgeführten Versuchen konnte jedoch keine signifikante Verbesserung der Ausbeute erhalten werden.



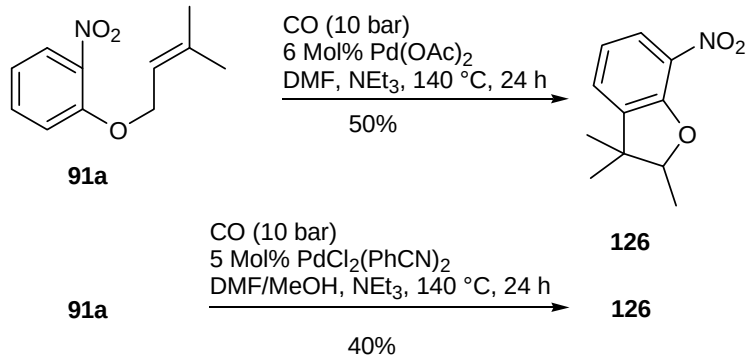
Schema 49 Cyclisierungsreaktionen von **94d** unter verschiedenen Reaktionsbedingungen.

Weiter wurde das Augenmerk auf die Umwandlung von Allyl-2-nitrophenylethern, wie etwa **91a**, gerichtet. Dabei zeigte sich, dass die analoge Reaktion des *O*-Allyl-2-nitrophenylethers **91a** mit Kohlenmonoxid in Gegenwart von $Pd(OAc)_2$ und 1,10-Phenanthrolin das entsprechende 3-Isopropenyl-3,4-dihydro-2*H*-1,4-benzoxamin **100a** ergab. Weiterhin konnten durch Änderung des Lösungsmittels die Cyclisierungen mit katalytischen Mengen an $Pd(OAc)_2$ durchgeführt werden (Schema 50).



Schema 50 Cyclisierungsreaktionen von **91a** zu **100a**.

Abschließend wurde die Pd-katalysierte Umwandlung von **91a** mit CO auch unter basischen Bedingungen untersucht. Dabei lieferte überraschenderweise die Reaktion des *O*-Allyl-2-nitrophenylethers **91a** das 2,3,3-Trimethyl-7-nitro-2,3-dihydrobenzofuran **126** als Hauptprodukt in Gegenwart von Triethylamin als Base (Schema 51).



Schema 51 Synthese des Benzofurans **126** unter basischen Bedingungen.

Als Fazit lässt sich festhalten, dass die hier vorgestellte Arbeit eine neue durch Triethylphosphit vermittelte Dominoreaktion von ω-Nitroalkenen beschreibt,[144, 164] mit deren Hilfe die Cyclisierung zu entsprechenden gesättigten N-Heterocyclen in einem Schritt gelingt. Die einstufige Dominoreaktion umfasst insgesamt drei Reaktionen, und zwar eine Nitroso-En-Reaktion, die mit zwei Reduktionen gekoppelt ist. Eine neue C-N-Bindung wird gebildet und gesättigte N-Heterocyclen werden hergestellt. Die Bestrahlung der ω-Nitroalkene mit Mikrowellen wurde als ein alternatives Reaktionsprotokoll entwickelt. Es hat den Vorteil, dass die Bildung von Nebenprodukten unterdrückt wird und die Reaktionszeiten deutlich verkürzt werden können. Die reduktive, durch Triethylphosphit vermittelte Cyclisierung erlaubt die Herstellung einer Reihe von gesättigten *N*-Heterocyclen wie substituierten 3,4-Dihydro-2*H*-1,4-benzoxazinen, 1,2,3,4-Tetrahydrochinoxalinen und 1,2,3,4-Tetrahydro-chinolinen.

Die neu entwickelte Dominoreaktion kann auch unter Druck in CO unter Einsatz von Übergangsmetallkatalysatoren ablaufen, was zur Bildung von gesättigten Heterocyclen führt.[169] Da die hier vorgestellten reduktiven Cyclisierungen bislang nicht untersuchte metall-katalysierte Dominoprozesse darstellen, könnten sie großes Interesse im Bereich der synthetischen Chemie und der "Life Sciences" erregen.

Alle synthetisierten Produkte wurden mit Standardmethoden wie NMR, LR-MS, HR-MS, EA, UV- und IR-Spektroskopie vollständig charakterisiert.

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ABBREVIATIONS

A	absorbance
ac	acetyl
acac	acetylacetonate
aq	aqueous
BOC	butoxycarbonyl
br	broad (NMR)
calcd	calculated
concd	concentrated
COSY	Correlated Spectroscopy
d	doublet (NMR)
DCB	dichlorobenzene
dd	doublet of doublets (NMR)
δ	chemical shift
Δ	heating
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMFDMA	*N,N*-dimethylformamide dimethyl acetal
dq	doublet of quartets (NMR)
dt	doublet of triplets (NMR)
EA	elemental analysis (Elementaranalyse)
EI	Electron Impact Mass Spectrometry
e^-	electron
ε	absorption coefficient
eq	equation
equiv	equivalent
Et	ethyl
eV	electron volt (MS)
GC	Gas Chromatography
h	hour(s)
HMBC	Heteronuclear Multiple-Bond Spectroscopy
HMQC	Heteronuclear Multiple-Quantum Spectroscopy
HRMS	High Resolution Mass Spectrometry

HSQC	Heteronuclear Single Quantum Spectroscopy
Hz	Hertz
IR	Infrared Spectroscopy
J	coupling constant (NMR)
λ	wavelength (cm)
LRMS	Low Resolution Mass Spectrometry
M^+	molecular ion
m	multiplet (NMR)
Me	methyl
min	minute
mL	milliliters
mol	mole(s)
mp	melting point
MS	Mass Spectrometry
MW	microwave
m/z	mass/charge ratio
NMR	Nuclear Magnetic Resonance Spectroscopy
NOE	Nuclear Overhauser Spectroscopy
NOESY	Nuclear Overhauser Enhancement Spectroscopy
$\tilde{\nu}$	wavenumber (cm^{-1})
o	*ortho*
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
R_f	ratio of fronts (TLC)
ROESY	Rotating-frame nuclear Overhauser Enhancement Spectroscopy
rt	room temperature
s	singlet (NMR)
soln	solution
t	triplet (NMR)
t-Bu	*tert*-butyl
t-BOC	*ter*t-butoxycarbonyl
t-BuOH	*tert*-butanol

THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TOCSY	Total Correlated Spectroscopy
TMS	tetramethylsilane
UV	Ultraviolet Spectroscopy
UV-VIS	Ultraviolet Visible Spectroscopy

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