DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
53

DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
53

NEW METHODS IN THE SYNTHESIS OF MULTISUBSTITUTED HYDRAZINES

OLGA TŠUBRIK

TARTU UNIVERSITY
PRESS

Institute of Organic and Bioorganic Chemistry, Department of Chemistry, University of Tartu, Estonia

Dissertation is accepted for the commencement of the Degree of Doctor of Philosophy in Chemistry on April 26th, 2006 by the Doctoral Committee of the Department of Chemistry, University of Tartu.

MSc Olga Tšubrik

Speciality: Organic Chemistry

Scientific advisor: Assoc. Prof. Dr. Uno Mäeorg

Opponent: Prof. Ulrich Groth (Konstanz University, Germany)

Commencement: 12 pm, June 12th, 2006, 2 Jakobi Str., room 430.

Publication of this dissertation is granted by the University of Tartu

ISSN 1406–0299
ISBN 9949–11–338–5 (trükis)
ISBN 9949–11–339–3 (PDF)

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimuse nr 281

Opportunities multiply as they are seized.
Sun-Tzu

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following papers, referred in the text by Roman numbers I–VII.

I. Combination of *tert*-Butoxycarbonyl and Triphenylphosphonium Protecting Groups in the Synthesis of Substituted Hydrazines. Tšubrik, O.; Mäeorg, U. *Org. Lett.* **2001**, 3, 2297–2299.
II. Acidity of di- and triprotected hydrazine derivatives in dimethyl sulfoxide and aspects of their alkylation. Ragnarsson, U.; Grehn, L.; Koppel, J.; Loog, O.; Tšubrik, O.; Bredikhin, A.; Maeorg, U.; Koppel, I. *J. Org. Chem.* **2005**, 70, 5916–5921.
III. Highly selective arylation of disubstituted hydrazines by pentavalent organobismuth reagents. Tšubrik, O.; Mäeorg, U.; Ragnarsson, U. *Tetrahedron Lett.* **2002**, 43, 6213–6215.
IV. Arylation of diversely substituted hydrazines using tri- and pentavalent organobismuth compounds. Tšubrik, O.; Mäeorg, U.; Ragnarsson, U. *Tetrahedron* **2004**, 60, 8363–8373.
V. Novel, efficient and regiospecific alkylation/arylation/heteroarylation of unsymmetrical azo-compounds. Tšubrik, O.; Sillard, R.; Mäeorg, U. *Synthesis* **2006**, 843–846.
VI. Addition of arylboronic acids to symmetrical and unsymmetrical azo compounds. Kisseljova, K.; Tšubrik, O.; Sillard, R.; Mäeorg, S.; Mäeorg, U. *Org. Lett.* **2006**, 8, 43–45.
VII. Copper salt catalyzed addition of triarylbismuthanes and triarylbismuth diacetates to symmetrical and unsymmetrical azo compounds. Tšubrik, O.; Kisseljova, K.; Mäeorg, U. Submitted.

Author's contribution

Paper I: Performed all the experimental work. Prepared the manuscript.

Paper II: Synthesized several substrates for pKa measurements and performed NMR analysis. Helped to prepare the manuscript.

Paper III: Responsible for project planning. Performed all the experimental work. Performed NMR analysis. Prepared the manuscript.

Paper IV: Responsible for project planning. Performed all the experimental work. Performed NMR analysis. Prepared the manuscript.

Paper V: Responsible for project planning. Performed all the experimental work. Performed NMR analysis. Prepared the manuscript.

Paper VI: Responsible for project planning. Performed several experiments. Performed NMR analysis. Prepared the manuscript.

Paper VII: Responsible for project planning. Performed half of the experiments. Performed NMR analysis. Prepared the manuscript.

ABBREVIATIONS

Ac	acetyl
acac	acetoacetonate
ACN	acetonitrile
Alloc	allyloxycarbonyl
An	anisyl (4-methoxyphenyl)
aq.	aqueous
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol, butylated hydroxytoluene
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bzl	benzyl
cat.	catalyst
Cbs	*para*-cyanobenzosulfonyl
$COIm_2$	1,1'-carbonyldiimidazole
Cp	cyclopentyl
dba	dibenzylacetone
DBAD	di-*tert*-butylazodicarboxylate
DCC	dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DIAD	diisopropylazodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNP	2,4-dinitrophenyl
DO	dioxane
dppf	diphenylphosphinoferrocene
Et	ethyl
HFIP	hexafluoroisopropyl alcohol
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
MCPBA	*meta*-clhoroperbenzoic acid
Me	methyl
Mes	2,4,6-trimethylphenyl
mp	melting point
NBS	N-bromosuccinimide
NMO	N-methylmorpholine N-oxide
NMP	N-methylpyrrolidone
NMR	nuclear magnetic resonance
Np	naphthyl
Ns	naphthalenesulfonyl

OTMS	trimethylsilyloxy
Ph	phenyl
Pht	phtaloyl
Pr	1-propyl
i-Pr	2-propyl
PTC	phase transfer catalysis
Py	pyridine
rt	room temperature
t-Bu	*tert*-butyl
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrosulfate
TBAI	tetrabutylammonium iodide
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifyl (trifluoromethylsulfonyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
Tol	tolyl
Troc	trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl
Z	benzyloxycarbonyl

FOREWORD

This thesis is devoted to various aspects of the synthesis of multisubstituted hydrazines. The challenge was taken up in early 2000 and therefore the most amazing Lego-game in my life was started. During the next years, plenty of complicated molecules were carefully constructed by cementing small building blocks onto bigger ones, which from the synthetical point of view are proper, albeit unceremonious, nicknames for substituents and precursors. The strategy of erecting durable constructions was based on the stepwise introduction of the building blocks. In order to pile up them the right way, we used tactical combination of protecting groups and electronic effects. The continuous development of one idea into another can be observed in the included papers I–VII. The results are conditionally divided into three parts.

The first part of the studies is devoted to design, synthesis and use of the new hydrazine precursor. This diprotected precursor, combined from *tert*-butoxycarbonyl and triphenylphosphonium groups, has no analogs reported previously. The first successful outcome is illustrated in the Paper I. We described the preparation of this compound and its applications, involving the systematic introduction of alkyl and acyl substituents into the hydrazine molecule. The originality of the precursor was in fact determined by the subtle tuning of its acidic properties. In turn, it compelled us to study the acidity of similar compounds and acidic hydrazines as such (Paper II).

Afterwards our interest was refocused on the introduction of aryl substituents. As a consequence, the above-mentioned precursor was used in the preparation of several multisubstituted hydrazines. These compounds were studied in respect to the arylation with triarylbismuthanes and triarylbismuth diacetates with emphasis on scope and limitations (Paper III and IV). As reported in Paper IV, we also developed a new method for direct highly selective arylation of monoacylhydrazines under very mild conditions. In fact, all these copper-catalyzed reactions fit well into the so-called Ullmann renaissance, witnessed in modern organic chemistry.

Arylation experiments gave us some observations about azo compounds, occasionally emerging here and there as side-products in hydrazine reactions. We decided to give it a try and refocused again, this time shifting from the substitution reaction to the addition, and using azo compounds as versatile starting materials. Our valour was generously rewarded. At first, we have found an unusually regiospecific nucleophilic addition to the unsymmetrical azo compounds (Paper V). In a short while, we combined copper catalysis with azo compounds. The outcome was the discovery of two new reactions (Paper VI and VII).

1. INTRODUCTION

Why hydrazines?

In order to shake common erroneous beliefs about hydrazines, such as their obligatory carcinogenicity and toxicity, I would like to invite your attention to the facts known from pharmaceutical industry. Many hydrazines with general formula $R^1R^2NNR^3R^4$ (R – H, alkyl, acyl or aryl substituent) exhibit incredible biological activity and are used in the treatment of various diseases. A few vivid examples can refer to tuberculostatic activity of isonicotinohydrazide derivatives [1, 2]. Substituted diphenylhydrazides are found to be effective pharmacophores for selective cyclooxygenase-2 (COX-2) inhibition, which is necessary in the design of novel anti-inflammattory drugs [3]. Both N^1- and N^2-propargylphenelzine exhibited ability to work as antidepressant agents [4]. Several 1-acyl-1,2-bis(methylsulfonyl)-2-(2-chloroethyl)hydrazines were found to have pronounced activity against both the P388 leukemia and solid tumors like the B16F10 melanoma, the M5076 reticulum cell sarcoma, and the M109 lung carcinoma [5]. A special class of trisubstituted hydrazines, containing aryl-, alkyl- and 4-chloro-3-sulfamoylbenzoyl groups, showed diuretic activity comparable to that of commercial indapamide [6].

Chemical structure of atazanavir (Figure 1), which represent an example of extremely useful peptidomimetics, also includes genuine hydrazine skeleton [7]. This protease inhibitor is by now one of the most potent cures for HIV-I infection (received FDA approval on June 20, 2003) and the first drug in its class that allows once-daily dosing. (Reyataz ® by Bristol-Myers Squibb Virology).

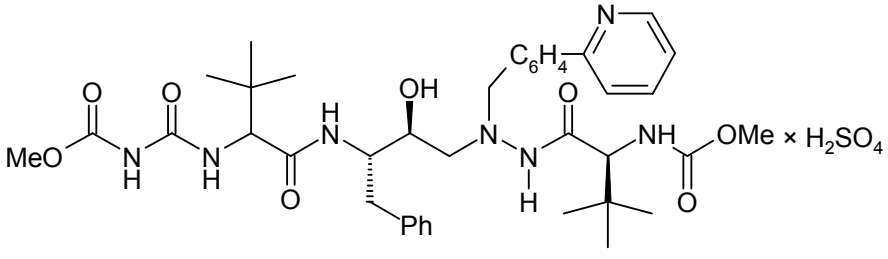


Figure 1. Structure of Atazanavir

Besides Atazanavir, there are plenty of biologically active azapeptides and azatides [8–10] (Figure 2). These compounds are synthesized from the corresponding hydrazino acids [11–13] and are mostly used in cancer treatment, designed and synthesized with the purpose of binding to target proteins in order to induce cancer cells into apoptosis (programmed cell death).

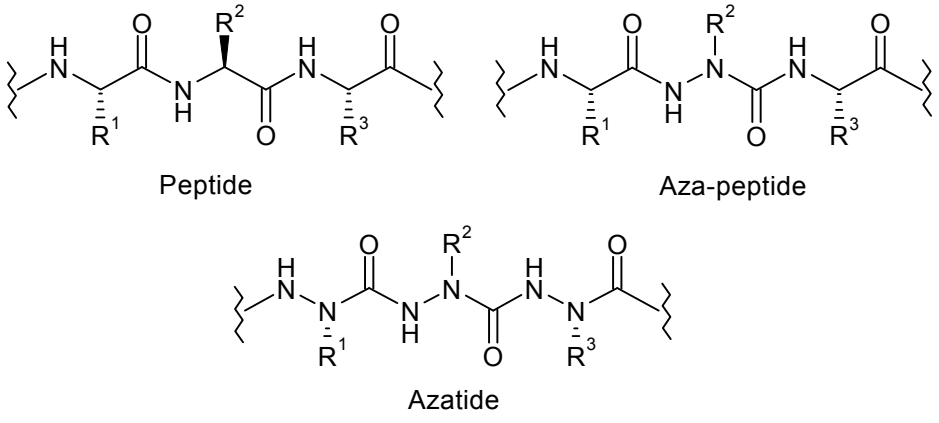


Figure 2. Peptides, aza-peptides and azatides

In addition to the employment in cure of many human maladies, the outstanding biological activity of multisubstituted hydrazines has found wide applications in the development of highly efficient pesticides [14–16].

Hydrazine derivatives were also employed in the functionalization of both peptides and oligonucleotides on the solid phase. For instant, the chemoselective reaction of α-hydrazinoacetylpeptides with activated fatty acids allows the synthesis of peptides, modified by hydrophobic chains, which enhances their transport across biological membranes [17]. Also, the glyoxylyl oligonucleotide was successfully engaged in hydrazone ligation with an α-hydrazino acetyl peptide [18]. [N,N'-tri(*tert*-butoxycarbonyl)hydrazino]acetic acid was used to introduce hydrazine function onto a surface of onion vesicles containing an aldehyde functionalized lipid [19]. This modification is important for targeting the neutral onion vectors to the tissues and controlling the delivery of drugs in vivo. New phosphoramidite building blocks were synthesized and used for the modification of oligonucleotides with hydrazides. Compared with the established amino modified nucleotides, hydrazides show enhanced reactivity at neutral and acidic buffer conditions. The obtained branched hydrazide oligonucleotides were successfully used to immobilize DNA on active electronic Nanogen chips [20].

It should be also noticed that mono- and disubstituted hydrazines have also found great use as N-N building blocks in the synthesis of heterocycles [21–23].

Despite the fact that plenty of hydrazine derivatives are already known and successfully produced in industry because of their importance as stated above, the capability of classical methods is limited to simple mono- or disubstituted molecules [24–28]. Multisubstituted hydrazines are reached by rather specific pathways [14–16, 29]. All this put obstacles in the way of facile biological screening of potent drug-wannabes. Modern drug design set high expectations

for the development of synthetic strategies and tactics. The strategy should allow the attachment of structural elements in certain positions. The required interaction with biological objects is ensured only if the compound possesses certain stereochemical configuration, thus demanding high regio- and stereoselective methods used in its preparation. The tactical toolbox has to contain general and facile procedures, which remain efficient even if those structural elements are to be modified.

Can it be done? With hydrazines? The answer is affirmative.

Classical methods, no matter how limited they were, gave us a solid foundation on which lately subtler structures could be built. For example, more than hundred years ago Gabriel used phtaloyl protection for the first time in the amine synthesis [30]. Zwierzak used two protecting groups to prepare simple dialkylhydrazines [31]. Only ten years ago, the systematic methodology was born and introduced with the design of triprotected precursor [32]. On the other hand, there would be no such strategy without Gabriel synthesis. Another example would be copper-catalyzed arylation of arylamines. Ullmann reported his discovery in the beginning of 20th century [33]. Today we can use modified versions of this approach and no original harsh conditions are required for the transformation [34–37].

Literature overview of classical and modern methods is given in the following sections. Classical strategies are discussed using specific synthetic approaches as examples. The tactical toolbox includes all the necessary derivatization protocols with the emphasis on their development and recent modifications. When we are armed with best weapons a synthetic chemist could ever have, we will proceed right to the modern strategy.

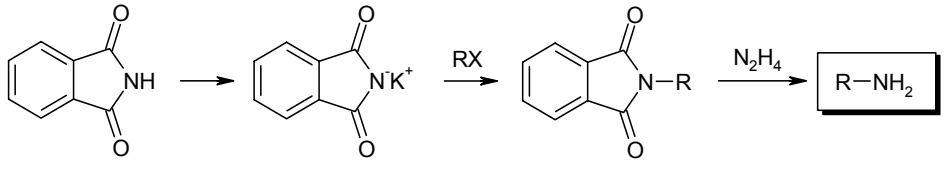
As a warning, I must say that there is no matter to think everything is utmost clear and all the synthetic riddles are solved. Besides the obvious success of the systematic methodology, which has substantially broadened our horizons, the topic still issues challenges to researchers. The introduction of an arbitrary substituent (alkyl, acyl or aryl) in arbitrary position of hydrazine molecule is far from generalized.

And so, more work awaits us ahead.

2. LITERATURE OVERVIEW AND THEORETICAL BACKGROUND

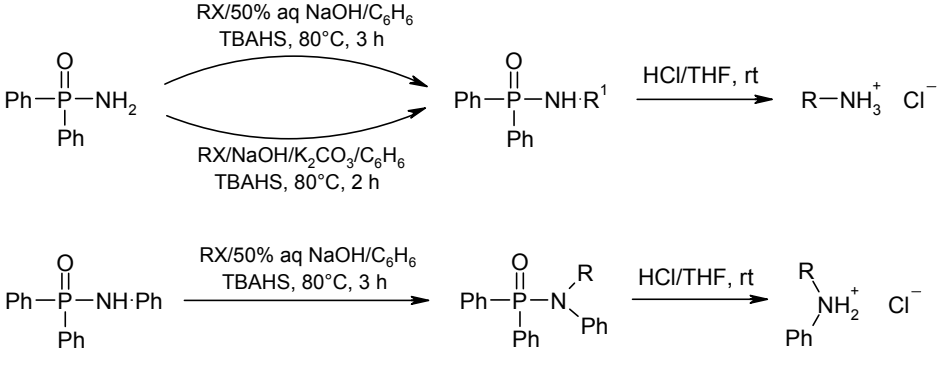
2.1. Synthesis of mono- and dialkylhydrazines by alkylation in PTC conditions

Gabriel synthesis is a classical protocol for the preparation of primary amines [30]. This method involves alkylation of protected ammonia and subsequent cleavage of phthaloyl group as depicted in Scheme 1. There are plenty of fashionable Gabriel reagents, which all in fact consist of the ammonia protected with different functional groups. Representative examples can include $(Boc)_2NH$, Z_2NH, MeOCONHBoc, BocNHZ, $(EtO)_2PONHBoc$, BocNHTs etc.



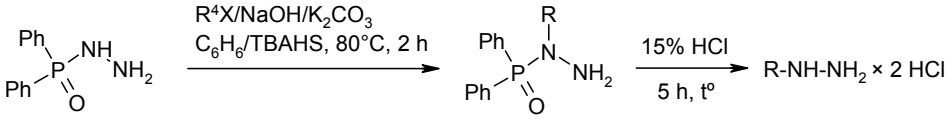
Scheme 1. The Gabriel synthesis

Zwierzak's pioneering work in phase transfer catalysis has opened new opportunities for the alkylation of nitrogen compounds. Unlike the classical Gabriel reaction, PTC alkylation does not require the formation of intermediate metal salt in stoichiomeric amount. As soon as a catalytic amount of metal salt is generated, it immediately reacts with alkylhalogenide. Using both solid-liquid and liquid-liquid PTC procedures, Zwierzak *et al* has accomplished derivatization of different amides, sulfonamides and phosphoramides as shown in Scheme 2 [31, 38–42].



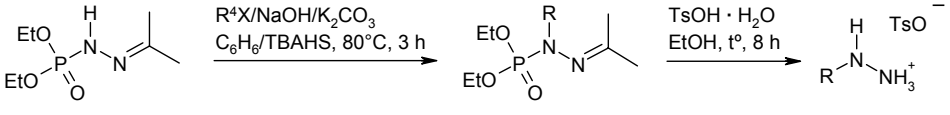
Scheme 2. Alkylation of diphenylphosphinamides

The direct conventional alkylation of hydrazine is not very efficient since the resulting monoalkylhydrazine is more reactive than N_2H_4 itself. The result is a complicated mixture of polyalkylhydrazines and quaternization products. Zwierzak *et al* prepared a series of monoalkylhydrazines, starting from diphenylphosphino-protected hydrazine and using alkylation under solid-liquid PTC conditions (Scheme 3). The alkylation proceeded in good to excellent yields (R = Me, Et, Pr, $(CH_3)_2CH$, C_4H_9, *iso*-C_4H_9, *sec*-C_4H_9, CH_2=CH-CH_2, CH≡C-CH_2, Bzl) and after cleavage the monoalkylhydrazines were isolated as salts [43].



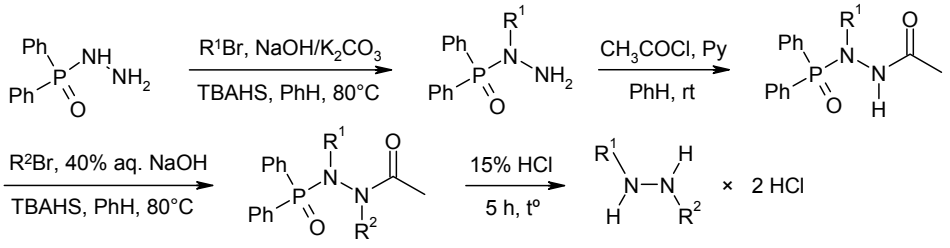
Scheme 3. Synthesis of monoalkylhydrazines

Another approach, also developed by the same research group, utilizes diethoxyphosphoryl- $(EtO)_2PO$ and 2-propylidene $(CH_3)_2CH$ protecting groups [44]. After the alkylation of the starting material under solid-liquid PTC conditions, both protecting groups are cleaved simultaneously and the corresponding hydrazines are isolated as *p*-toluenesulfonates (Scheme 4).



Scheme 4. Synthesis of monoalkylhydrazines

Zwierzak *et al* also described a method for the preparation of N,N'-dialkylhydrazines, which is based on the same principles as above. At first, diphenylphosphinic hydrazide was alkylated under usual solid-liquid conditions. Additional protecting group was then introduced by acetylation, followed by second alkylation (Scheme 5). Both protecting groups were cleaved simultaneously under acidic conditions. All the reaction steps proceeded with good yields [31].

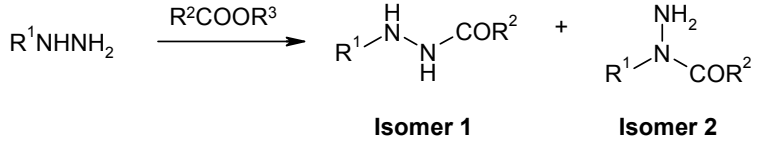


Scheme 5. Synthesis of 1,2-dialkylhydrazines

2.2. Synthesis of 1-alkyl-2-acylhydrazines

Due to the difference between the electronic effects of substituents, the nitrogen atoms in 1-acyl-2-alkylhydrazines $R^1NHNHCOR^2$ possess different properties. R^1NH-part of the molecule can be viewed as the amine functionality, whereas R^2CONH is clearly the amide functionality.

The oldest method for the preparation of 1-acyl-2-alkylhydrazines is based on the acylation of the corresponding alkylhydrazine with ester (Scheme 6). As a side-product, 1-acyl-1-alkylhydrazine is usually formed.



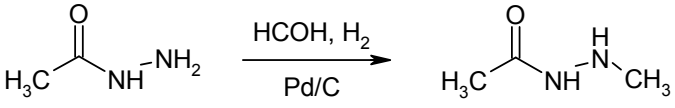
Scheme 6. Acylation of alkylhydrazine

Hinman and Fulton studied [25] the acylation of methylhydrazine with some esters and anhydrides. It was concluded that 1-acyl-2-methylhydrazine (Isomer 1) was the basic product from the reaction with ester. Another isomer was predominant in the reaction with anhydride. As the size of the acyl group of an ester was increased, the percentage of 1-acyl-2-methylhydrazine decreased and the overall rate of reaction decreased. Similar results were obtained in the experiments carried out by Theuer and Moore [26]. Methylhydrazine reacted with ethyl phenylacetate, giving the 2-methyl-1-phenylacetylhydrazine in 76% yield. In order to find kinetic justification for the experimental results, Condon investigated the acetylation of methylhydrazine [27]. The reaction with acetic anhydride was reported to give isomer 1/isomer 2 in ratio 1:38. The reaction with ethyl acetate was not so selective as the ratio was found to be ~1:3. Condon claimed the isomer ratios have resulted from kinetic control. Also, it was possible to isolate 1-acetyl-2-methylhydrazine in 96% purity by cooling the

product. The yield of the compound was lower than 40%. Therefore, the reaction with ester is simple, although slow and not very selective, which cause the problems with yield and purity.

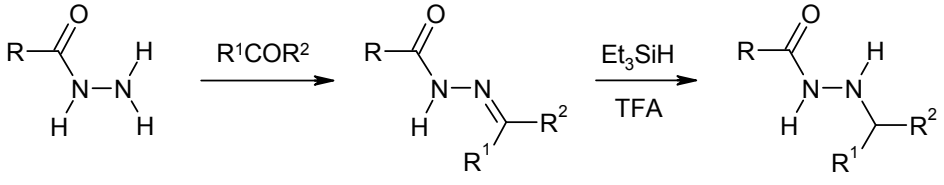
Another possibility to synthesize 1-acyl-2-alkylhydrazines is based on Leuchkart-Wallach reaction. At first, the corresponding acylhydrazine is transformed into the hydrazone, which is then reduced to the hydrazine. There are several protocols known from the literature, all of them include the same synthetic sequence.

Malz *et al* patented the procedure for the preparation of 1-acetyl-2-methylhydrazine (Scheme 7). The process demanded high pressures (up to 42 atm) and the product has only 83% purity [45].



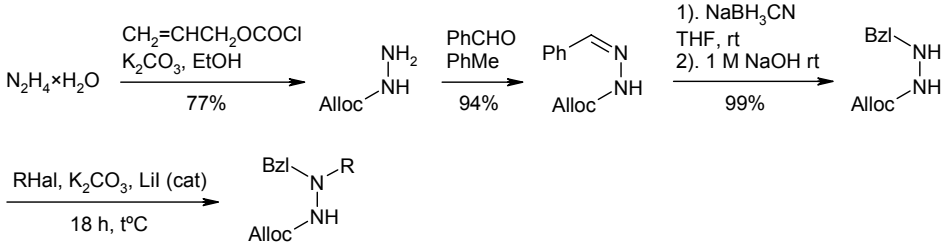
Scheme 7. Synthesis of 1-acetyl-2-methylhydrazines

Instead of gaseous hydrogen, Wu *et al* used triethylsilane as reducing agent to accomplish the so-called ionic hydrogenation of the intermediate hydrazone (Scheme 8). R = Me, Ph; R^1 = H, Me; R^2 = Ph, Bzl, *m*-$CH_3OC_6H_4$, C_5H_{11}, $(CH_3)_2CH$, cyclohexyl, Me [46].



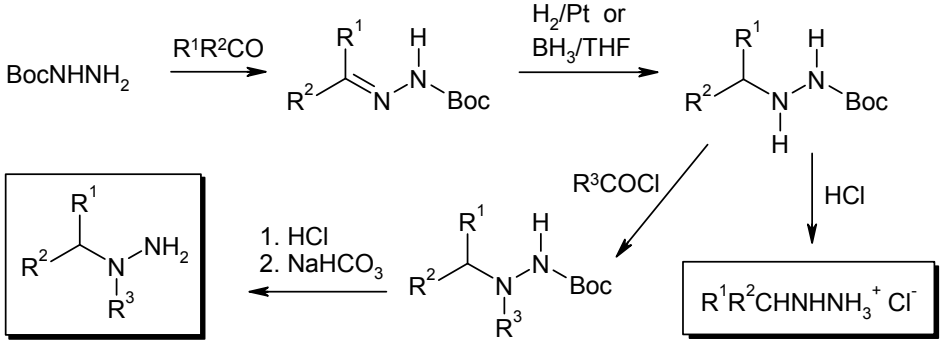
Scheme 8. Synthesis of 1-alkyl-2-acylhydrazines by ionic hydrogenation

Speckamp *et al* synthesized 1-allyloxycarbonyl-2-benzylhydrazine accordingly to the Scheme 9 [29]. The obtained compound was selectively alkylated at the benzylic nitrogen atom. For the derivatization, benzyl chloride, substituted allyl halogenides and $Me_3SiC{\equiv}CCH_2I$ were used. The yields of alkylation were in range 58–89%. The products were further used in cyclization reaction and all the strategy was aimed at the synthesis of cyclic derivatives of α-hydrazino acids.



Scheme 9. Synthesis of 1-Alloc-2-Benzylhydrazine and its alkylation

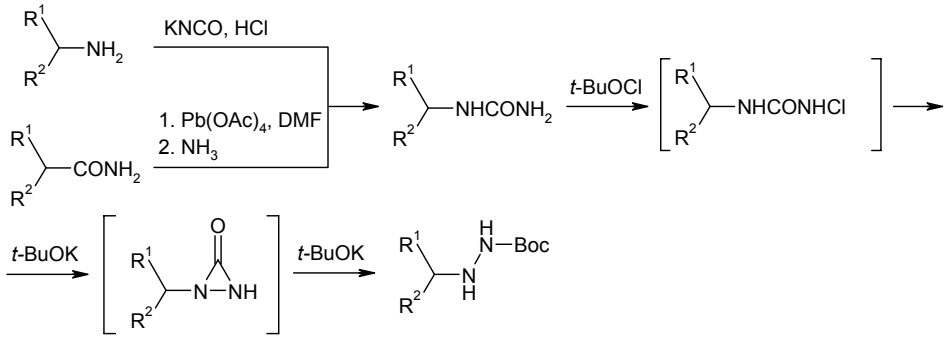
Baumgarten *et al* studied the preparation of hydrazines with secondary substituents as illustrated in Scheme 10 [47]. The commercially available *tert*-butylcarbazate was used as a starting material ($BocNHNH_2$). 1-Alkyl-2-*tert*-butoxycarbonylhydrazines were obtained in good yields. Because of the higher reactivity of the aminic nitrogen, it was possible to acylate these compounds selectively. After the Boc-group was cleaved, 1-acyl-2-alkylhydrazines were isolated in 56–77% yields. The same method offered a good opportunity to synthesize secondary monoalkylhydrazines, which were obtained as salts after treatment of 1-alkyl-2-*tert*-buroxycarbonylhydrazines with hydrochloric acid.



Scheme 10. Synthesis of hydrazines with secondary alkyl substituents

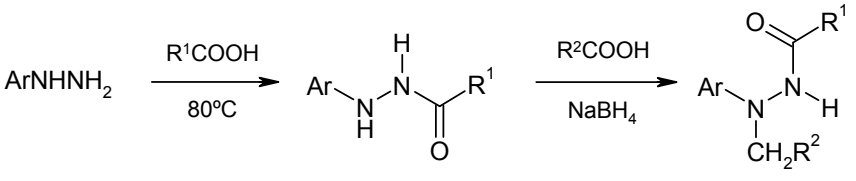
On the other hand, the reduction of the Schiff base was not stereoselective. That's why for the preparation of chiral hydrazines another strategy was employed by the same authors [47]. Either chiral amine or chiral amide were used as starting materials (Scheme 11). Alkyl substituted carbamides were subjected to rearrangement. As a result, N-N bond was formed and the corresponding 1-alkyl-2-Boc-hydrazine was obtained in 82% yield (R^1 = Ph, R^2 = CH_3). The rearrangement of *tert*-butylcarbamide furnished

$(CH_3)_3CNHNHBoc$. This compound is an interesting example of a hydrazine with tertiary alkyl substituent, which is difficult to prepare by the direct introduction of the *tert*-butyl group.



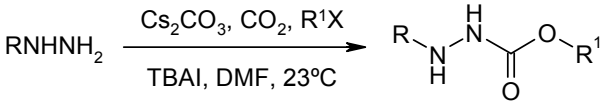
Scheme 11. Synthesis of hydrazines with secondary alkyl substituents

Verardo *et al* combined two above-described approaches into one preparative method [48]. 1-Acyl-2-arylhydrazines, readily obtained in high yield from the condensation of arylhydrazines and the appropriate liquid carboxylic acids, underwent reductive alkylation with the same or different carboxylic acid and $NaBH_4$ to give 1-acyl-2-alkyl-2-arylhydrazines in good to moderate yields (Scheme 12).



Scheme 12. Synthesis of 1-acyl-2-alkyl-2-arylhydrazines

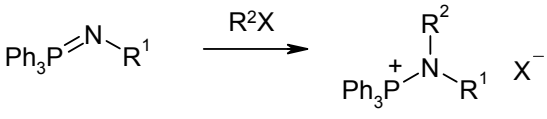
Completely different synthesis of carbazates was developed by Salvatore *et al* [49]. In the presence of cesium carbonate and tetrabutylammonium iodide alkyl- or arylhydrazine, CO_2 and an alkyl halide underwent a three-component coupling at room temperature. The methodology was highly chemoselective as depicted in Scheme 13. Racemizations were not detected when chiral alkyl bromides were used for alkylation. Carbon disulfide could be employed instead of carbon dioxide, furnishing the corresponding dithiocarbazates. The yields varied from moderate to high.



Scheme 13. Synthesis of 1-alcoxycarbonyl-2-alkylhydrazines

2.3. Alkylation of iminophosphoranes and cleavage of triphenylphosphonium group

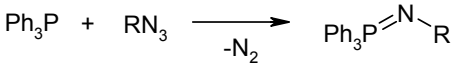
The compounds with the general formula $Ph_3P{=}N\text{-}R$ are known under the name of iminotriphenylphosphoranes or triphenylphosphinimines. The negative charge on the nitrogen atom determines the essential nucleophilicity of such molecules. Staudinger and Hauser found [50] that phosphoranes are able to react with many different nucleophiles, for instant with alkyl halogenides as outlined in Scheme 14.



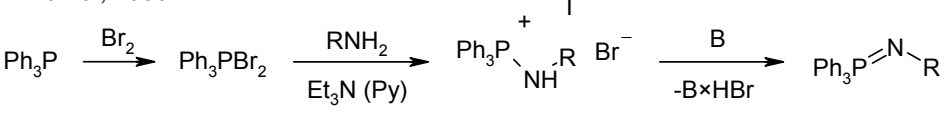
Scheme 14. Iminotriphenylphosphoranes as nucleophiles

The most important pathways for the preparation of iminotriphenylphosphoranes are given in the Scheme 15. The first method, introduced by Staudinger, is based on the reaction between alkyl (or acyl-) azide and triphenylphosphine [50]. Another approach was invented by Horner *et al* [51, 52]. This reaction sequence starts with the preparation of dibromotriphenylphosphorane, which then reacts with the corresponding amine RNH_2 in the presence of weak base (Et_3N or Py), forming triphenylphosphonium salt.

1. Staudinger, 1921

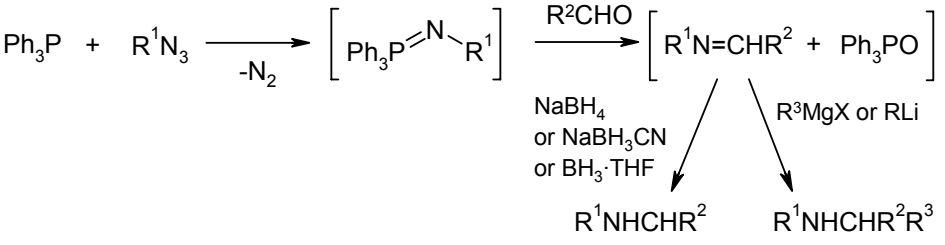


2. Horner, 1956



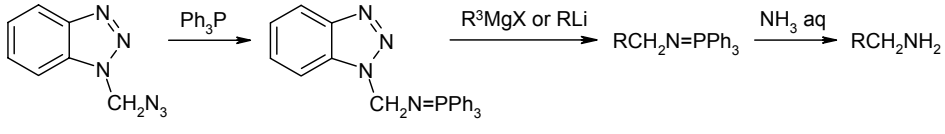
Scheme 15. The synthesis of iminotriphenylphosphoranes

Staudinger's method of the preparation of iminotriphenylphosphoranes was further successfully employed in the synthesis of primary amines. For instant, alkylazides were used by Vaultier *et al* to produce a reactive phosphorane $Ph_3P{=}NR$ as intermediate, which was subsequently hydrolyzed to amine [53]. Recently, Hemming *et al* [54] presented a high yielding one-pot solution phase and polymer-supported synthesis of a range of primary and secondary amines starting from azides and aldehydes (Scheme 16). The obtained imino-phosphorane underwent the Aza-Wittig reaction, furnishing imines. The imines were either reduced to secondary amines or subjected to the addition of organometallics. When trimethylsilyl azide was used as a starting material, primary amines have been afforded.



Scheme 16. Synthesis of primary and secondary amines via iminotriphenylphosphoranes

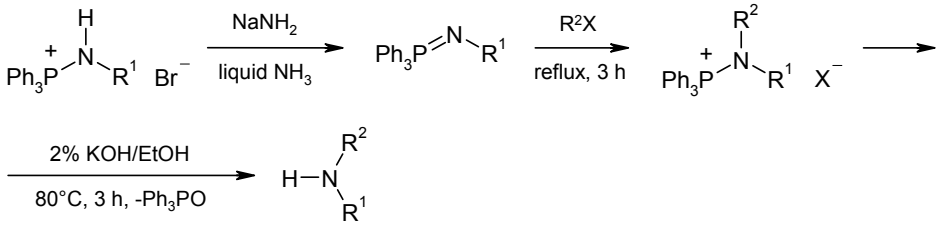
Katritzky has introduced N-triphenylphosphorylidene-1-(benzotriazol-1-yl)methylamine as a novel synthon equivalent to $^{+}CH_2NH_2$ [55]. As illustrated in Scheme 17, this rather stable phosphorane reacts smoothly with organometallics, forming another phosphorane, which is subsequently hydrolyzed to primary amines.



Scheme 17. Synthesis of primary and secondary amines via iminotriphenylphosphoranes

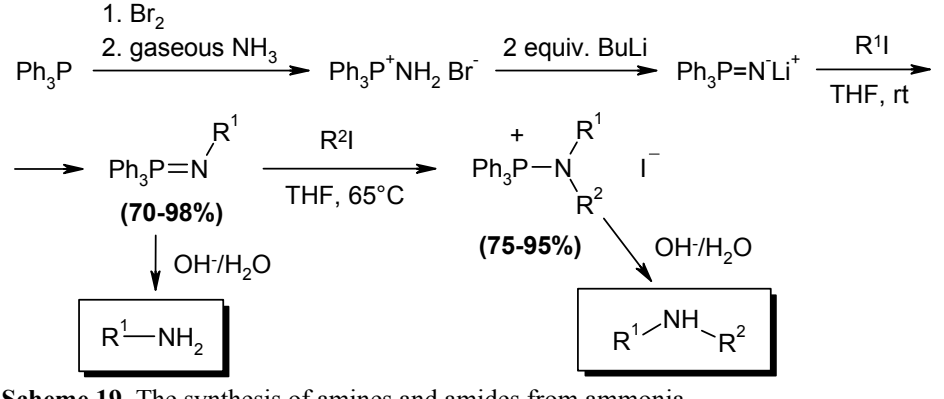
Using the same principle as Horner, Zimmer and Singh [56] developed a protocol for the synthesis of dialkylamines (Scheme 18). The phosphonium salts were prepared in benzene in the presence of triethylamine with yields 77–93% (R^1 = Me, Et, Pr, $(CH_3)_2CH$, $(CH_3)_2CHCH_2$, *tert*-Bu). Sodium amide

was used to convert salts into the corresponding phosphoranes in high yields (93–99%). It was observed that the phosphoranes with short alkyl group were highly sensitive to any humidity. The subsequent alkylation was performed by boiling phosphoranes in neat alkylhalogenides (yields 60–98%). Only MeI, MeBr and EtI could be used in this step since phosporane causes the elimination even in the case of propylhalogenides. The triphenylphosphonium group was cleaved by boiling the obtained salts with 2% KOH in ethanol for 3 h. The amines were isolated by distillation (58–66%). In a short while Zimmer has extended this technique for the preparation of dialkylamines with complicated structure (R^1 = cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and 1-adamantyl) [57].



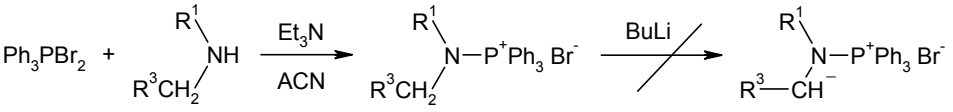
Scheme 18. The synthesis of dialkylamines

Starting from ammonia instead of amines, primary/secondary amines and amides were synthesized by Cristau *et al* [58] as depicted in Scheme 19 (R^1 = Me, Et, Pr, $(CH_3)_2CH$, *tert*-Bu, Bzl, PhCO and R^2 = Me, Et, Pr, *tert*-Bu, CH_2=CH-CH_2, Me-CH=CH-CH_2, Bzl).



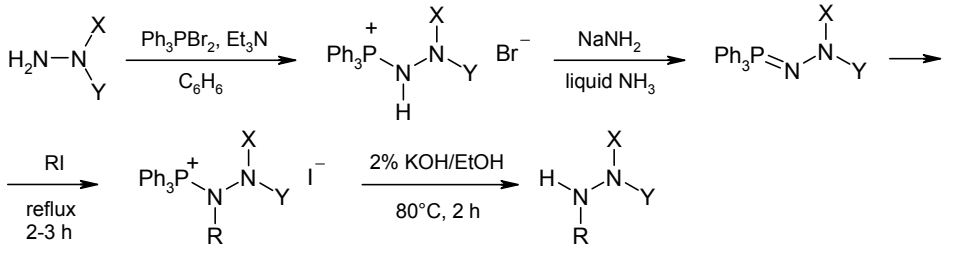
Scheme 19. The synthesis of amines and amides from ammonia

Fukui and Sudo [59] studied reaction between different dibromotriphenylphosphorane and secondary amines R^1R^2NH (R^1 = Et, Me, Ph, R^2 = Ph, Et, Bzl), including cyclic compounds such as piperidine and morfoline (Scheme 20). Acetonitrile was used as solvent. The reactions were quite slow and the yield was obviously influenced by steric hindrance (42–82%, 19% in case of PhBzlNH). The reaction of the obtained $BzlMeNP^+Ph_3\ Br^-$ with butyllithium was reported to give several decomposition products.



Scheme 20. Derivatives of secondary amines

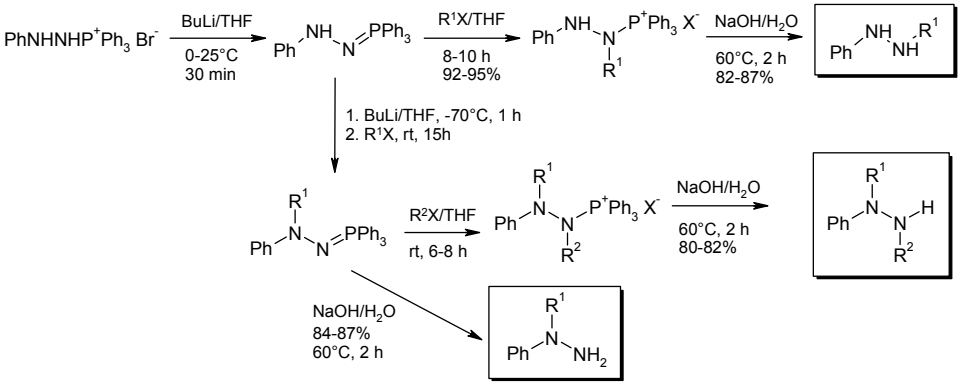
Lately, Zimmer and Singh used their own skills, perfected at the preparation of amines, to obtain trisubstituted hydrazines [60]. The yields of all the steps (Scheme 21) were high (X and Y = H, Me, Ph; R = Me, Et). Because of the precipitation of resulting phosphonium salt $NH_2NHP^+Ph_3Br^-$ from the reaction medium, no formation of possible $Br^-\ Ph_3P^+NHNHP^+Ph_3Br^-$ was detected.



Scheme 21. Synthesis of trisubstituted hydrazines

Barluenga *et al* described an elegant technique for the preparation of alkylsubstituted phenylhydrazines as illustrated on the Scheme 22 [61]. $PhNHNHP^+Ph_3\ Br^-$ is obtained in the reaction between phenylhydrazine and dibromotriphenylphoshorane. This compound is then used as a starting material for all the subsequent syntheses (R^1 = Me, Et, Bzl, CH_2=CH-CH_2). In fact, this work represents an analogue to Zwierzak's studies [31, 43, 44], where also an organophosphorus moiety was used as a protecting group (see also Section 2.3). In addition to the common alkylation of iminophosphorane, an interesting invention was demonstrated. Barluenga reported that the iminophosphorane itself could be also deprotonated by butyllithium. Then, a second alkyl group was easily introduced by the alkylation of the resulting anion. In order to

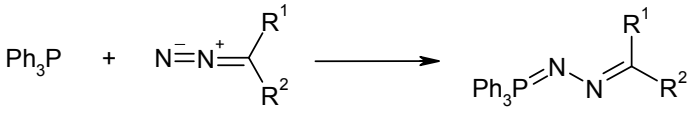
remove the triphenylphosphonium group, the obtained phoshonium salts were heated in the 2 M NaOH for 2 h.



Scheme 22. Synthesis of trisubstituted hydrazines

The analogous method was used by Song and Yee [62] to prepare disubstituted hydrazines 2-Br-4-X-$C_6H_3CH_2NHNHAr$. The synthesis started with monoarylhydrazines, which were transformed into $ArNHNHP^+Ph_3\ Br^-$. After the treatment with LiHMDS, a corresponding phosphorane was formed and alkylated with substituted benzylbromides 2-Br-4-X-$C_6H_3CH_2Br$ (X = H, F, OMe). Triphenylphosphonium group was cleaved by heating in NaOH, furnishing the desired products.

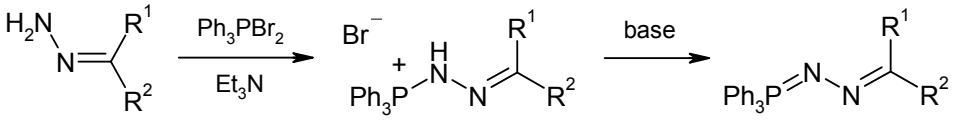
There is a special class of hydrazine derivatives which in fact represent a special type of iminophosphorane. Those compounds are triphenylphosphazines with general formula $Ph_3P{=}N{-}N{=}CR^1R^2$. There are three ways to approach triphenylphosphazines. Staudinger and Meyer [63] were the first to describe a method for the preparation of phosphazines. Their studies were continued by Bestmann and Göthlich [64]. According to these reports, phosphazine was formed during the reaction between diazoalkane $R^1R^2CN_2$ and triphenylphosphine as illustrated in Scheme 23.



Scheme 23. Synthesis of triphenylphosphazines. Method 1

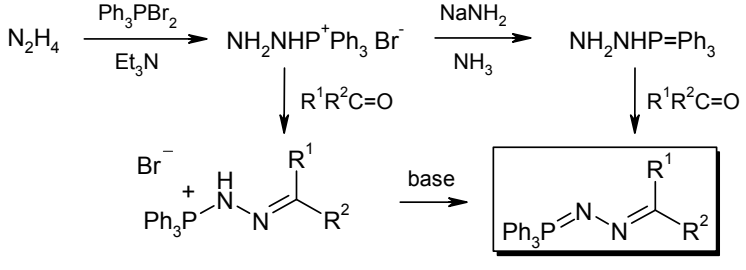
As is the case with iminotriphenylphosphoranes, their analogs triphenylphosphazines can be obtained from phosphonium salts $R^1R^2C{=}N{-}NHP^{(+)}Ph_3\ Br^{(-)}$ (see Scheme 24 and 25). Bestmann *et al* [64, 65] has

developed one-pot procedure starting directly from hydrazones (Scheme 24). After the hydrazone $R^1R^2C{=}NNH_2$ reacted with dibromotriphenylphosphorane, the intermediate phosphonium salts were not isolated but transformed into triphenylphosphazines with triethylamine. Zimmer and Singh conducted the syntheses step-by-step, isolating and characterizing the phosphonium salts. To prepare the triphenylphosphazines, sodium amide was used analogously with $RNHNHP^{+}Ph_3\ Br^{-}$ [66].



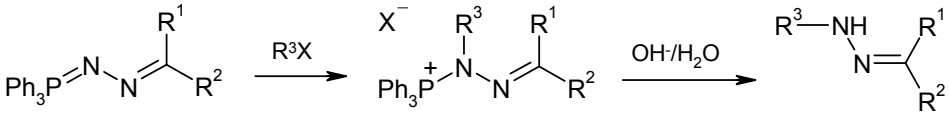
Scheme 24. Synthesis of triphenylphosphazines. Method 2

Walker and Shechter used $NH_2NHP^{+}Ph_3\ Br^{-}$ as a starting material for the preparation of phosphazines [67]. This compound was synthesized from anhydrous hydrazine and dibromotriphenylphosphorane [52, 60]. In the reaction with ketone, a new phosphonium salt was formed, which was subsequently transformed into the phosphazine by treating with a base or by chromatography on aluminium oxide. Phosphorane could also be prepared directly from $NH_2NHP^{+}Ph_3\ Br^{-}$ and sodium amide [60, 67, 68]. During the reaction with ketones or aldehydes in the presence of molecular sieves, the phosphazines $Ph_3P{=}N{-}N{=}CR^1R^2$ were formed.



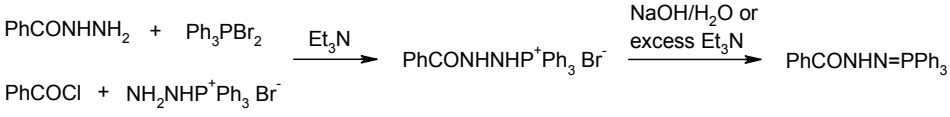
Scheme 25. Synthesis of triphenylphosphazines. Method 3

Exactly as expected from the analogy with phosphoranes, phosphazines can be alkylated (Scheme 26) [64, 66]. Triphenylphosphonium group is cleaved by stirring the obtained phosphonium salts with hot solution of Na_2CO_3. During such treatment, hydrazones are formed [64], which can be hydrolyzed to the monosubstituted hydrazines.



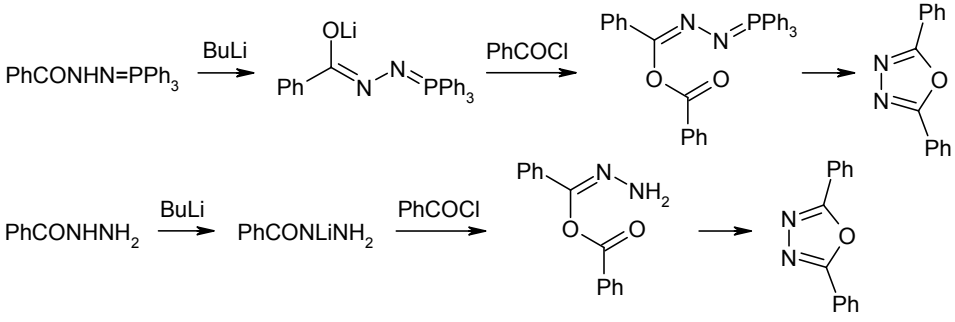
Scheme 26. Alkylation of triphenylphosphazines

In comparison with typical alkyliminophosphoranes and triphenylphosphazines, acyliminophosphoranes RCONHN=PPh_3 were not so thoroughly investigated. The same goes for the corresponding acyliminophosphonium salts RCONHNHP^+Ph_3 Br^-. The first acyliminophosphorane PhCONHN=PPh_3 was described by Horner [52], who obtained this compound in the reaction of benzoylhydrazide with dibromotriphenylphosphorane in the presence of 2 equiv Et_3N (yield 18%). Shechter and Walker [69] also prepared the salt PhCONHNHP^+Ph_3 Br^- using two independent synthetic pathways as outlined in Scheme 27.



Scheme 27. Preparation of PhCONHNHP^+Ph_3 Br^- and PhCONHN=PPh_3

Unfortunately, Shechter reported neither detailed description of experimental procedures nor NMR data, although this is utmost essential to confirm the formation of phosphorane under exposure to NaOH. Authors claimed that the phosphorane was generated in several minutes and reacted with aldehydes, forming Schiff bases RCH=NNHCOPh and triphenylphosphine oxide Ph_3PO. Also, the lithium salt of the phosphorane reacted with benzoylchloride, forming 1,3,4-oxadiazole and Ph_3PO (Scheme 28). With a high probability, under the exposure to NaOH both the phosphonium salt and the phosphorane decompose, yielding equimolar mixture of the corresponding hydrazide $PhCONHNH_2$ and Ph_3PO. Obviously, in the reaction with aldehyde benzoyl hydrazide affords imine and probably it is able to form 1,3,4-oxadiazole (Scheme 28).



Scheme 28. The formation of 1,3,4-oxadiasoles from phosphorane and hydrazides

Shechter and Merrill reported the formation of other compounds with general formula $RCONHNHP^{+}Ph_3\ Br^{-}$ (R = H, CH_3, Ph) [70]. The phosphonium salt $NH_2NHP^{+}Ph_3\ Br^{-}$ reacted with ortho-esters $RC(OCH_3)_3$, yielding intermediate compounds $Ph_3P^{+}NHN{=}CR(OCH_3)\ Br^{-}$, which were then hydrolyzed to give $RCONHNHP^{+}Ph_3\ Br^{-}$.

In addition to all this, Foucaud *et al* [71] synthesized N-imidylphosphoranes (Figure 3) using reaction between the corresponding hydrazides and Ph_3PBr_2. The transformation required 2 equiv Et_3N and 2-3 h heating in benzene. Yields were 50–79%.

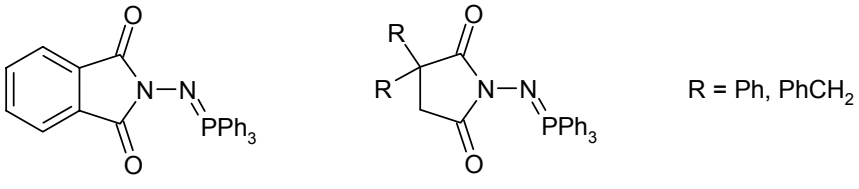


Figure 3. N-imidylphosphoranes

Frøyen [72] described the preparation of $EtOCONHNHP^{+}Ph_3\ Br^{-}$ from ethoxycarbonylhydrazine and Ph_3PBr_2 in presence of Et_3N. This is a very rare example of phosphonium salt containing alkoxycarbonyl group in its structure. The corresponding phosphorane was obtained by treatment of the salt with sodium ethoxide in anhydrous ethanol.

2.4. Acidic hydrazines and their properties

Hydrazine N_2H_4 possesses remarkable basic properties and is comparable with typical amines. On the other hand, hydrazine is a very weak NH-acid. Obviously, the acidic/basic properties of the substituted hydrazines are determined by the character of substituent. Analogously with amines and amides, alkyl/aryl substituted hydrazines belong to the class of organic bases, whereas acylsubstituted hydrazines are undoubtedly NH-acids, although weak. The increase in electronegativity of a moiety attached to NH nitrogen reflects in the increase of the NH acidity.

For the alkylation, simple amides demand to be stoichiometrically metallated with such strong bases as LDA or KH. In Section 2.1 Zwierzak's contributions to hydrazines synthesis were described, where the main idea was to start with compounds like $Ph_2PONHNH_2$ and $(EtO)_2PONHN{=}CMe_2$ [31, 43, 44]. Contrary to amides, PTC system was sufficient to metallate those Zwierzak's reagents exactly because of their increased acidity. The acidity itself was strongly influenced by electron-withdrawing diphenylphosphino group.

The same question rises in the derivatization of amino- and hydrazino-triphenylphosphonium salts, as described in Section 2.3 [60]. Normally, butyllithium or sodium amide are required for smooth deprotonation. In case of $PhNHNHP^{+}Ph_3\ Br^{-}$, it was possible to distinguish two NH protons due to the different acidities of PhNH and $NHPPh_3$ groups [61]. Furthermore, in order to convert the phosphonium salts $R^1R^2C{=}N\text{-}NHP^{(+)}Ph_3\ Br^{(-)}$ into triphenyl-phosphazines, no butyllithium is demanded. The base as weak as triethylamine is perfectly sufficient [64, 65].

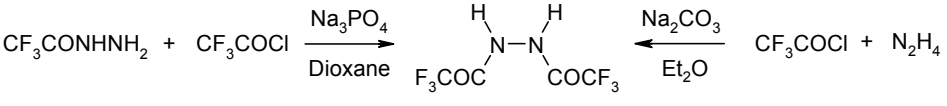
The alkylation of such acidic hydrazines as $BocNHNBoc_2$, BocNHNZBoc etc will be covered in part 2.9.3. The main idea still focuses on three electron-withdrawing groups, which substantially increase the NH acidity of the compound. As a consequence, alkylation can be successfully performed under PTC liquid-liquid conditions (30% aqueous NaOH-PhMe) [32].

Undoubtedly, it is difficult to overestimate the dependence of the reactivity on the intrinsic acidity of the hydrazines. Besides alkoxycarbonyl, acyl and triphenylphosphonium groups, there are other moieties, which could substantially affect the acidity: trifluoroacetyl, trifluoromethylsulfonyl (also known as trifyl), *p*-toluenesulfonyl, 2,4-dinitrophenyl. Their combination can also present a certain interest for researchers. In fact, highly acidic hydrazines are less well known and the preparative reactions often turned capricious. Some examples are brought below.

Ried and Franz reported that trifluoroacetylhydrazine could be obtained in the reaction between hydrazine hydrate and methyl trifluoroacetate [73]. After stirring at 0ºC in methanol, the product was isolated by distillation under reduced pressure (yield 84%). Use of 95% hydrazine [74] and ethyl trifluoroacetate instead of methyl ester [75] was also described. Recent

investigations showed that trifluoroacetylhydrazine (mp 39–40ºC) is quite unstable [76]. On standing at room temperature for several days this compound was transformed into N,N'-ditrifluoroacetylhydrazinate $N_2H_5^+$ $CF_3CONHNCOCF_3$ (mp 132–134ºC). Heating the obtained material above its melting point or redistillation yielded again pure trifluoroacetylhydrazine.

Groth synthesized 1,2-trifluoroacetylhydrazine (yield 83%) by passing gaseous trifluoroacetylchloride into the suspension of trifluoroacetylhydrazine and Na_3PO_4 in dioxane at 0ºC [75] (Scheme 29). Brown *et al* employed trifluoroacetic anhydride in the same reaction [74]; the yield is not reported. Preparation using anhydrous hydrazine, trifluoroacetyl chloride, and sodium carbonate in ether was effected with a 70% yield of product [75]. Young *et al* described synthesis of 1,2-trifluoroacetylhydrazine from anhydrous hydrazine [77]. Ethyl trifluoroacetate was used in the first step to obtain mono-trifluoroacetylhydrazine. This intermediate was not isolated and immediately reacted with trifluoroacetic anhydride, furnishing 1,2-trifluoroacetylhydrazine from anhydrous hydrazine in 92% yield.

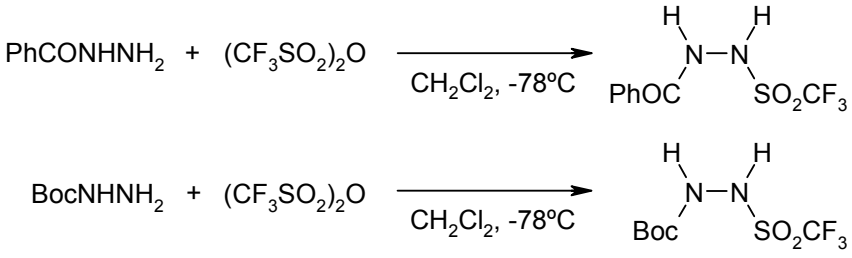


Scheme 29. Preparation of 1,2-trifluoroacetylhydrazine

Young *et al* described the preparation of azo compound $CF_3CON{=}NCOCF_3$ by oxidation $(CF_3CON)_2Hg$ by ICl in CCl_4 [77]. The yield was low and the product impure. Young also reported the synthesis of tetrakis-trifluoroacetylhydrazine. $(CF_3CON)_2Hg$ and trifluoroacetic anhydride were heated in hermetically closed bomb. However, the structure was not confirmed by any trustworthy analytical method. The same problem is with Allen's publication, who has obtained 2'-trifluoroacetyl-2,4-dinitrophenylhydrazine from DNP-hydrazine and trifluoroacetic acid [78].

All the attempts to prepare trifylhydrazine $CF_3SO_2NHNH_2$ from hydrazine and trifylchloride/fluoride were reported to be unsuccessful [79, 80]. Recent studies showed that the desired compound is not stable even at low temperatures and decomposes fastly, forming trifluorosulfinic acid or its salt [81].

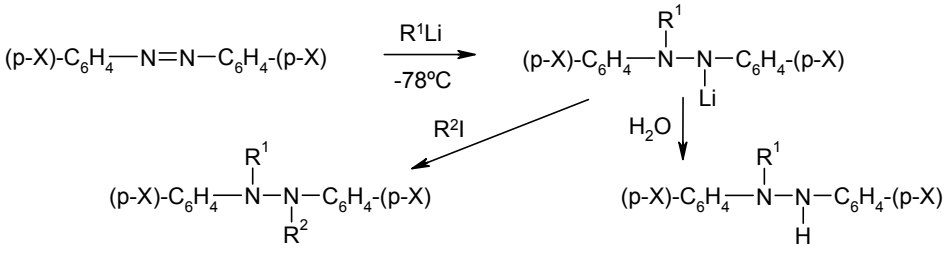
On the other hand, the compounds N-benzoyl-N'-trifylhydrazine and N-*tert*-butoxycarbonyl-N'-trifylhydrazine are known. Hendrikson and Sternbach prepared both of them by reacting the corresponding hydrazides with trifyl anhydride at –78ºC in dichloromethane as illustrated in Scheme 30 [82]. The yields of recrystallized products were respectively 93% and 50%.



Scheme 30. Preparation of N-benzoyl-N'-trifylhydrazine and N-*tert*-butoxycarbonyl-N'-trifylhydrazine

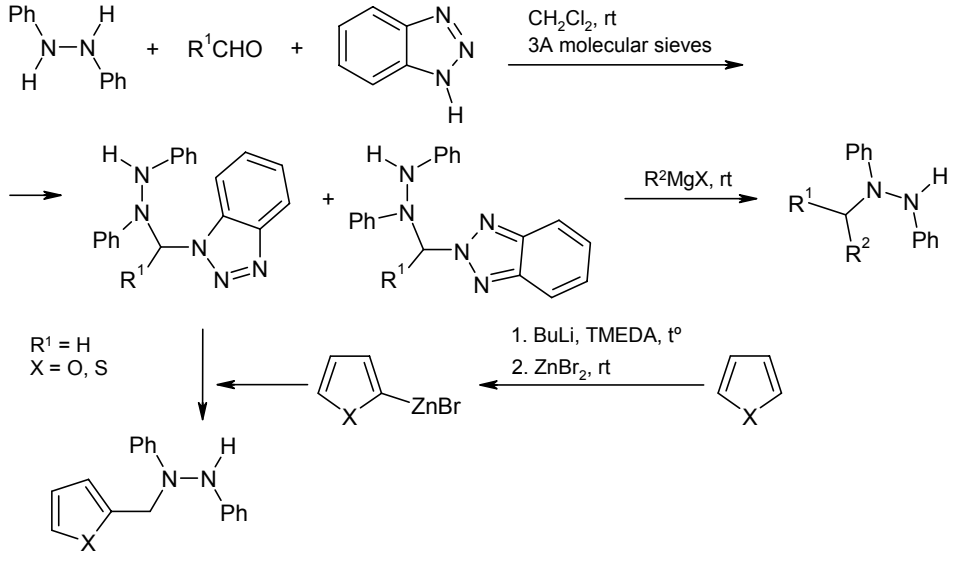
2.5. Specific methods for the synthesis of arylhydrazines

In Section 2.5, a specific synthetic method was described, designed by Barluenga and intended for the preparation of alkylsubstituted phenylhydrazines from phenylhydrazine [61]. Katritzky *et al* [83] suggested another strategy, based on the use of the extreme reactivity of azo compounds. Contrary to Barluenga approach, one does not require any protecting groups here. On the other hand, the methodology is systematic as illustrated in Scheme 31. Alkyl- or arylgroup is introduced via the addition of organometallic nucleofile to the symmetrical azo compounds (X = H, Me, Cl; R^1 = Bu, *sec*-Bu, *tert*-Bu, Ph; R^2 = Bu, Et, Me).



Scheme 31. Synthesis of arylhydrazines from azo compounds

Katritzky has also applied his well-known developments of benzotriazolyl auxiliaries [84] in the preparation of trisubstituted hydrazines as demonstrated in Scheme 32. N-(1-benzotriazolylalkyl)N,N'-diphenylhydrazine is formed as intermediate. The secondary alkyl group is constructed from both organometallic reagent and aldehyde (R = H, Et, Pr, cyclohehyl). Yields were 53–99%. The reactions are slow because the preparation of triazolyl derivative takes as long as 24–120 h.



Scheme 32. Synthesis of trisubstituted arylhydrazines

2.6. N-Arylation as "palladium chemist" does it and improves it and optimizes it

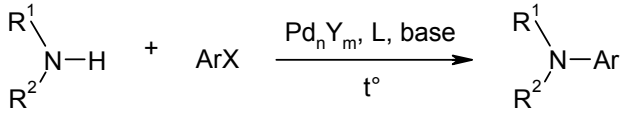
Modern palladium chemistry started in 1960 with the ingenious invention of industrial process for acetaldehyde production by air oxidation of ethylene, catalyzed by $PdCl_2$ and $CuCl_2$, which is called the Wacker process [85]. In 1965, Tsuji discovered that carbon-carbon bond formation could be achieved by reacting π-allylpalladium and π-$PdCl_2$ complexes with carbon nucleophiles such as active methylene compounds. Since then, remarkable progress has been made in organic synthesis using Pd compounds both as stoichiometric reagents and catalysts. Many transition metals are now used in organic synthesis [86, 87], but it is widely recognized that palladium is the most versatile in promoting or catalyzing reactions, particularly those involving carbon-carbon bond formation, which is not always easy to accomplish with other transition metals. The tolerance of Pd reagents to many functional groups such as carbonyl and hydroxy groups is the second important feature. Pd reagents and catalysts are not very sensitive to oxygen and moisture. Although reactions catalyzed by Pd-phosphine complexes should be carried out carefully, it is enough to apply precautions to avoid oxidation of the phosphine. Palladium is a noble metal and expensive, but it is much less expensive than platinum and osmium. Also, the toxicity of Pd has posed no big problem so far. The fact that a number of industrial processes based on Pd-catalyzed reactions have been developed and

are now operated reflects these advantages of using Pd catalysts commercially [85].

One of the most useful coupling reactions is the cross-coupling of organoboron compounds with aryl, alkenyl, and alkynyl halides, called the Suzuki-Myaura reaction. The palladium-catalyzed C-C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is referred as the well-known "Heck Reaction". In 1995 the research groups of Hartwig and Buchwald published concurrently their results on palladium-catalyzed amination of aryl halides [88, 89]. As a result of the prominent work accomplished during the last decade, the palladium-catalyzed synthesis of arylamines by the reaction of aryl halides or triflates has rapidly become valuable synthetic tool for a variety of applications [90–94].

The process can form monoalkyl- or dialkylanilines as well as mixed diaryl- or triarylamines. In addition, the chemistry can be extended to the formation of aryl ethers from aryl halides, although this process is currently less general than the synthesis of arylamines.

The C-N coupling, as outlined in Scheme 33, is substantially affected by several parameters. In most cases palladium-catalyzed reaction demands thorough optimization in order to find the reactions conditions suitable for the given substrate.



Scheme 33. N-Arylation of amine

In Scheme 33 symbol **L** denotes a ligand. Figure 4 shows structures of several organic compounds, well known for their excellent applicability as ligands in palladium catalysis. Quite often chemists use mixture of the ligand with palladium salt or palladium complex compound, denoted by Pd_nY_m. New complex compound, which actually works as a real catalyst, forms *in situ* just before the coupling reaction. In instance, $PdCl_2$, $Pd(OAc)_2$, $[Pd_2(dba)_3]$ are good starting materials. Frequently, ready-to-be-used complex compounds such as zero-valent species $Pd(Ph_3P)_4$ or $[Pd(dppf)Cl_2]$ can be employed without additional ligand.

Most ligands depicted in Figure 4 represent derivatives of phosphane, where the coordinative bond is formed owing to nonbonding electrone pair of phosphorus atoms. Generally electronic properties and sterical hindrance of the ligand L has deciding influence over the coupling reaction.

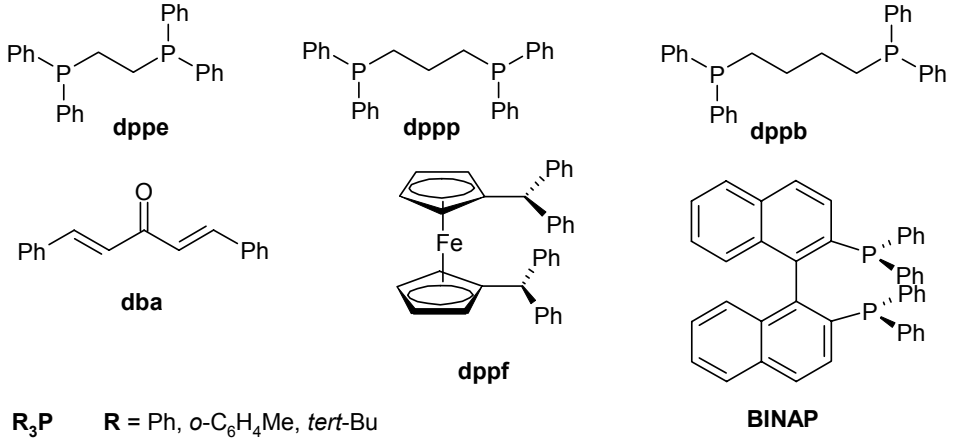
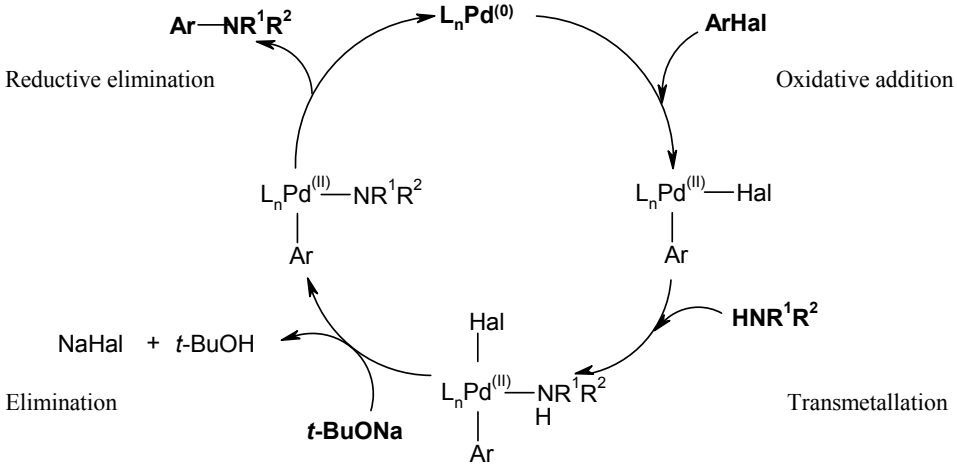


Figure 4. Some well-known ligands for palladium catalysis

The palladium catalyzed C-N coupling is characterized by the following:

- Usually the coupling demands presence of a strong base such as Me_3CONa, LiHMDS, K_2CO_3, Cs_2CO_3, Rb_2CO_3, NaH.
- Regardless of the substrate, the reaction is conducted in both polar and unpolar solvents: toluene, dioxane, dimethylformamide and dimethyl-sulfoxide.
- Normally the coupling is conducted at the boiling point of the solvent.
- Concentrations and stoichiometry of both starting materials and catalyst can also affect the reaction.
- The conversion is quite slow, taking several hours to be fully accomplished.

Possible mechanism for the catalyzed reaction cycle [91] involves the oxidative addition of the aryl halide to the Pd (0) followed by the formation of a Pd (II) species which undergoes reductive elimination to give the required product and the regenerated Pd (0) catalyst



Scheme 34. Possible mechanism for the catalyzed reaction cycle of N-arylation

As the nature of catalyst remains the most important factor to influence the reaction, in most cases the optimization of the conditions focuses on the search of the suitable ligand. Frequently the oxidative addition is the rate-limiting step of the whole catalytic cycle. The electron-rich phosphanes facilitate oxidative addition of the aryl chloride and bind tightly to the metal to prevent precipitation of the catalyst. In instance, highly active ligands were designed and successfully used for C-N coupling of aryl halides at room temperature (Figure 5) [95, 96].

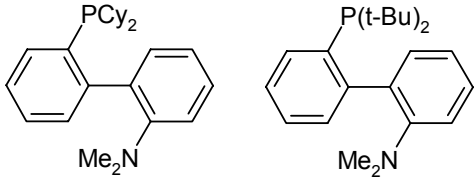
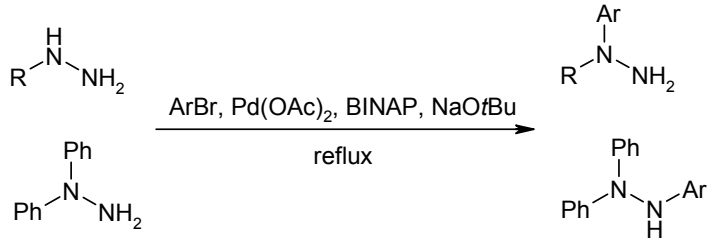


Figure 5. Highly active ligands for the amination of aryl halides

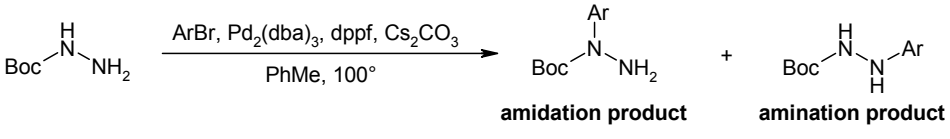
Palladium catalysis has also found applications for the N-arylation of hydrazones and hydrazines. Buchwald *et al* employed the catalytic system $Pd(OAc)_2$/BINAP for the coupling of bensophenone hydrazone $Ph_2C{=}NNH_2$ with *p*- ja *m*-substituted arylbromides [97, 98]. The process was conducted under heating at 80–100°C in toluene in the presence of Me_3CONa or Cs_2CO_3. The obtained hydrazones are useful starting materials for the Fischer indole synthesis.

Buchwald *et al* also studied the reaction of other hydrazines [98] with aryl bromides as illustrated in Scheme 35 (R = Ph, 4-F-C_6H_4, Boc and Ar = Ph, 4-Cl-C_6H_4, 4-CF_3-C_6H_4). Toluene or diisopropylamine was used as solvent. The reaction time (1–18 h) considerably varies with substrate as well as yields (24–95%).



Scheme 35. Palladium-catalyzed arylation of hydrazines

Skerlj *et al* reported the first example of an intermolecular palladium-catalyzed amidation reaction for the efficient synthesis of aryl hydrazides [99]. Substituted aryl bromides were coupled with *tert*-butoxycarbazate in the presence of palladium catalyst and base. The initial attempts with $Pd(OAc)_2$/BINAP afforded a mixture of monoarylated and diarylated products. The reaction conditions were optimized as shown in Scheme 36. Aryl bromides bearing electron-withdrawing *p*-substituents undergo the amidation reaction most efficiently while the corresponding *m*-analogs react in low yield (16–26%). Unactivated aryl bromides such as bromobenzene failed to react under the standard coupling conditions; in this case the homo-coupled product was isolated. While most aryl bromides provided the amidation product, a reversal in the regioselectivity of coupling was observed for aryl bromides with an additional substituent in the *o*-position.

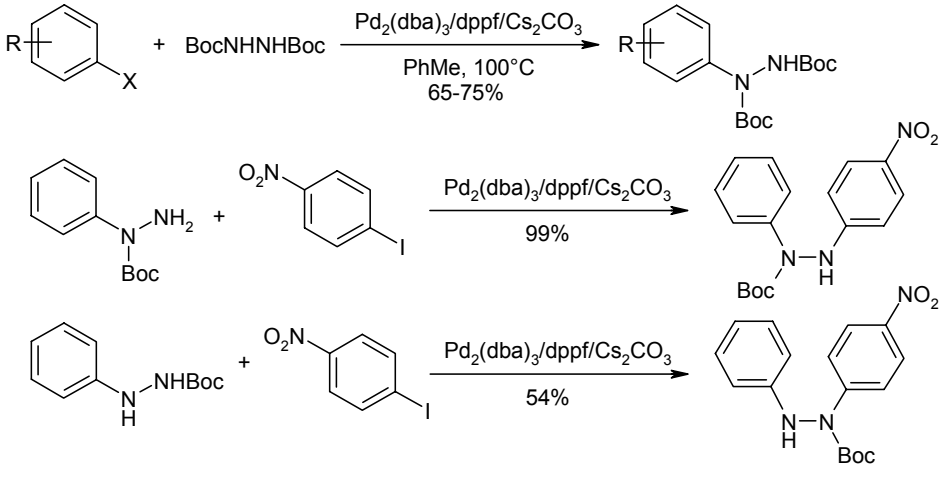


Scheme 36. Arylation of *tert*-butoxycarbazate

Arterburn *et al* synthesized protected pyridylhydrazine derivatives in a one-step palladium-catalyzed amination reaction using chelating phosphine ligands [100]. 2-Pyridyl chlorides, bromides, and triflates were effective electrophiles in these couplings. The compounds $Ph_2C{=}NNH_2$, $BocNHNH_2$ and BocNHNHBoc were used as substrates. The catalytic system $Pd(OAc)_2$/BINAP/*t*BuONa was

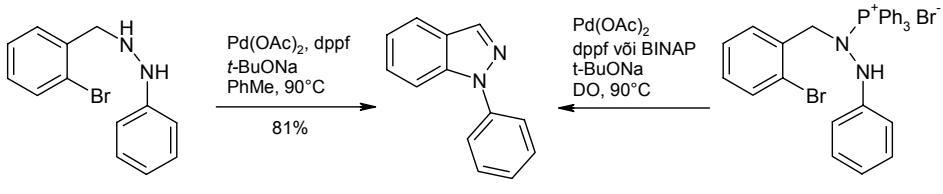
the most efficient for the benzophenone hydrazone. The conditions optimization failed for *tert*-butoxycarbazate since reaction products underwent decomposition during the isolation step. On the other hand, the protected hydrazine BocNHNHBoc was an excellent substrate for C-N bond formation under $Pd_2(dba)_3$/dppf/Cs_2CO_3. This could be useful for the synthesis of a wide variety of hydrazines via catalytic amination.

Using the reaction procedure developed by Arterburn, Cho *et al* prepared various N,N'-bis-Boc-arylhydrazines, N- and N'-Boc-diarylhydrazines as shown in Scheme 37 [101].



Scheme 37. Syntheses of Boc-protected arylhydrazines

Intramolecular amination can be useful for the synthesis of heterocycles. Song and Yee [62] synthesized 1-aryl-1*H*-indazoles by the palladium-catalyzed amination of the corresponding N-aryl-N'-(*o*-bromobenzyl)hydrazines as outlined in Scheme 38. It was further demonstrated that cyclization of [N-aryl-N'-(*o*-bromobenzyl)hydrazinato-N']-triphenylphosphonium bromides under the conditions of [$Pd(OAc)_2$/dppf/*t*BuONa/] also led to the formation of the corresponding 1-aryl-1*H*-indazoles via simultaneous N-arylation and elimination of Ph_3P group (yields 38–53%). The preparation of phosphonium salts was already discussed in Section 2.3.

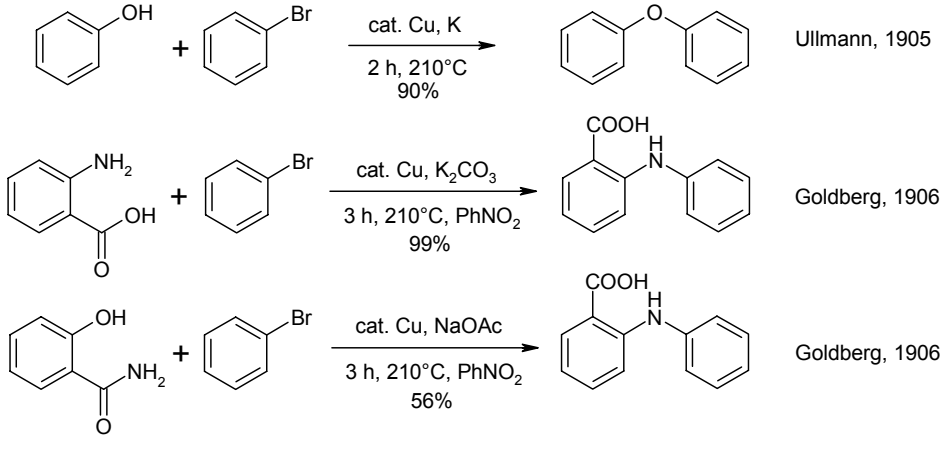


Scheme 38. Intramolecular amination

2.7. N-Arylation. The exciting era of Ullmann Reneissance

2.7.1. Classical way or classical problems?

There is a high demand for new methods to facilitate the synthesis of diaryl ethers, alkylaryl ethers, diaryl amines, alkylaryl amines, diaryl thioethers, and alkylaryl thioethers owing to their importance as structural motifs in numerous molecules with important applications. At the beginning of the last century Fritz Ullmann and Irma Goldberg started their pioneering work on copper mediated and copper-catalyzed coupling reactions, outlined in Scheme 39. They explored new ways to form aryl-C-, aryl-N and aryl-O-bonds and thus paved the way to access to huge numbers of previously inaccessible compounds. For the first time unactivated aryl halides were used as coupling components while classical nucleophilic aromatic substitution reactions required electron poor aryl halides in combination with strong nucleophiles. The results represent a general breakthrough in the field of catalysis and have to be considered the basis of all the contemporary contributions on the copper-catalyzed arylation reactions. The importance of the results described in these publications is underlined by the fact that they found their way into numerous industrial applications, such as synthesis of intermediates in pharmaceuticals, agrochemical and polymer chemistry [36].



Scheme 39. Ullmann ether synthesis, Ullmann-Goldberg amidation and Goldberg amidation

However, the harsh reaction conditions (high temperatures, strong bases, stoichiometric amounts of copper or copper salts, long reaction times) needed to effect these transformations, usually only in moderate yields, led to severe limitations in the general use of this reaction, especially on a large scale. In addition with the evolution of green chemistry, the necessity to use stoichiometric amounts of the heavy metal copper in order to obtain satisfactory yields, has to be considered as a major drawback.

As could be expected, numerous contributions of Buchwald and Hartwig, which led palladium- catalyzed cross-coupling reactions (see Section. 2.6) to the fantastic development, should have consigned copper chemistry to eternal oblivion. However, the last years witness a completely opposite effect [34–37]. A steady increase of interest in copper assisted cross-coupling chemistry is evident. The only explanation is the high cost of sophisticated palladium ligands and essential restrictions in scope of palladium-catalyzed reactions. In comparison to the palladium catalyzed reactions, the copper-catalyzed couplings also seem to be less sensitive towards the choice of the metal source. In many cases, precursors as different as copper powder and air sensitive copper (I) salts proved to be suitable for the efficient transformation. That is why copper catalysis is not too easy to get rid of.

During the last decade, copper-catalyzed coupling reactions involving organobismuth, -lead, -antimony, -silicon, -tin, -iodonium and –boron reagents have been extensively studied. The use of simple aryl source such as aryl halide has been considerably revitalized by the develoment of new procedures. And as a result, chemists now talk about Reneissance of Ullmann reactions.

2.7.2. Aryl halides as the aryl donor

The selection of ligand, the choice of the solvent and base play an important role in both palladium-catalyzed reactions and Ullmann-Goldberg aminations as well. A selection of ligand additives in the copper catalysis toolbox is outlined in Figure 6. Neutral bidentate ligands appear to be in the majority of the reaction protocols. The variety of donor combinations includes N,N-, O,O- and N,O-chelators as well as phosphines and carbenes. The wide choice of ligands implies the potential for optimization and fine-tuning of a given transformation. The required temperatures range from 80–120ºC, which excludes low boiling solvents. As in palladium-catalyzed amination, toluene is commonly used and sometimes replaced by dioxane or polar solvents such as N-methylpyrrolidone or DMF. Potassium carbonate is frequently used as base, but there are substrates which need other proton acceptors such as sodium methoxide or potassium *t*-butoxide [36].

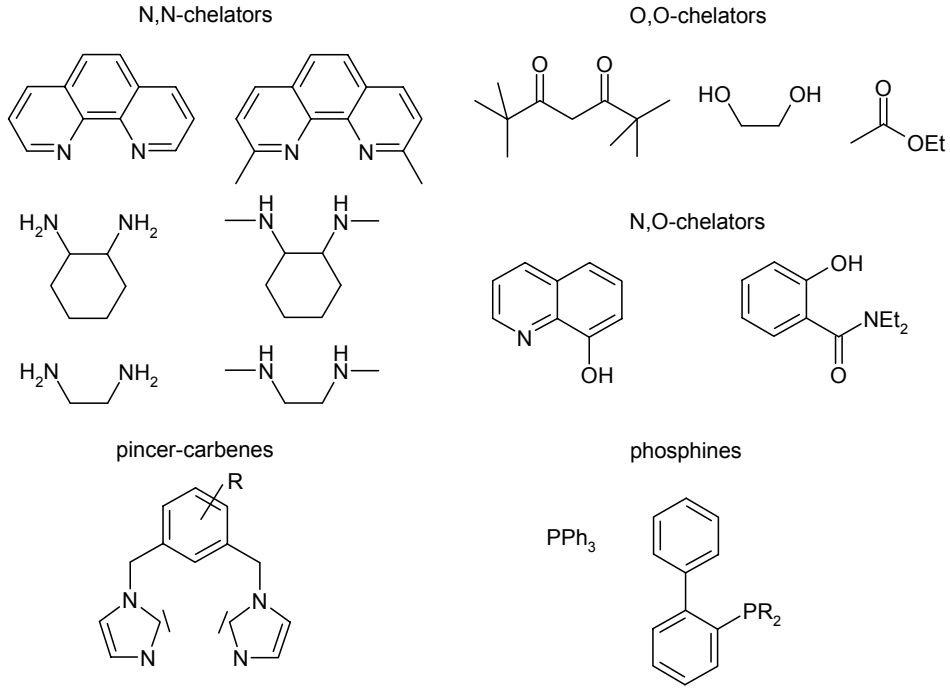
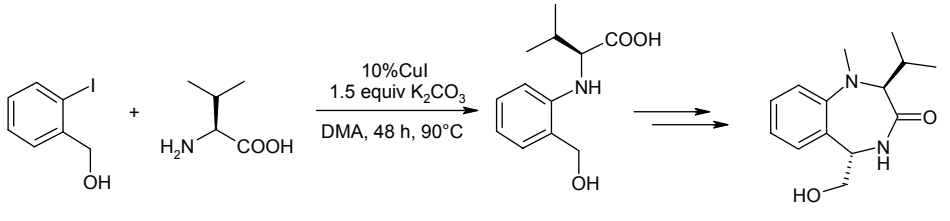


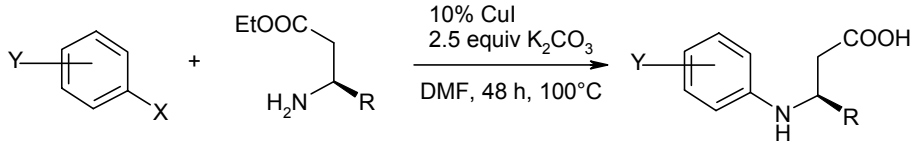
Figure 6. Ligand toolbox for copper-catalyzed amination

Coupling of optically pure α-amino acids with aryl halides was used by Ma *et al* in the synthesis of phosphokinase C activator Benzolactam V6 as illustrated in Scheme 40 [102]. Under the catalysis of CuI, enantiopure N-aryl-α-amino acids were produced with retention of configuration. The transformation was conducted at much lower temperature than typical Ullmann reaction, which indicates that an accelerating effect induced by the structure of the α-amino acids is present.



Scheme 40. α-Amino acids as chelating substrates in the Ullmann amination

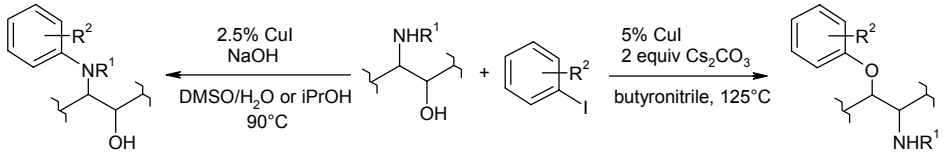
The chelating effect of the substrate was also observed in the CuI-catalyzed coupling reaction of aryl halides with β-amino acids or β-amino esters as depicted in Scheme 41[103].



Scheme 41. β-Amino acids as chelating substrates in the Ullmann amination

Goodbrand *et al* has demonstrated that the addition of the copper-binding ligand 1,10-phenantroline to the copper iodide catalyst dramatically moderates the severity of conditions required to conduct the Ullmann amination. Reactions of aryl iodides with both di- and triarylamines were rapid and clean at temperatures of 50–100ºC [104].

In addition to his magnificient contributions in the field of palladium catalysis, Buchwald has have conducted fruitful investigations of Ullmann amination [105–107]. An operationally simple C-N protocol of broad applicability was described. CuI is used as catalyst and ethylene glycol as ligand in 2-propanol. A variety of functionalized aryl iodides as well as several amines were efficiently coupled using this method. The procedure is comparably insensitive to moisture and can be performed under an air atmosphere [105]. Afterwards, methods for the preparation of *N*-aryl β-amino alcohols and *O*-aryl β-amino alcohols were described [106]. Depending on catalyst and base, the system unambiguously distinguish between the two competing reaction pathways as shown in Scheme 42. Commerically available diethylsalicylamide was found to be very efficient ligand for copper-catalyzed amination of aryl bromides with primary alkylamines [107].



Scheme 42. Copper-catalyzed arylation of β-amino alcohols

Buchwald *et al* also performed copper-catalyzed N-arylation of imidazoles using $(CuOTf)_2$·benzene as a catalyst, aryl bromides/iodides as an aryl source and Cs_2CO_3 as a base in xylenes at 110–125ºC [108]. As could be expected, addition of 1,10-phenanthroline and *trans*, *trans*-dibenzylideneacetone was

crucial to the success of the transformation. The products, N-arylimidazoles, were isolated in high yields. Further investigations of N-arylation of nitrogen heterocycles resulted in the development of an extremely general, experimentally simple, and inexpensive catalyst system based on CuI and K_3PO_4 [109]. Racemic *trans*-cyclohexanediamine was employed as a ligand. In addition to amines, amides were also successfully used for this enhanced version of Goldberg coupling reaction. A variety of heteroarylbromides such as 3-bromothiophene, 3-bromoquinoline and 3-bromopyrimidine were coupled with amides in high yields. Pyrazoles, indazole, 7-azaindole and phtalazinone were successfully transformed into corresponding N-arylated derivatives with aryl iodides. The same catalytic system was found to be very efficient for coupling of lactams, primary amides and formamides derived from primary amines with a variety of aryl iodides. The N-arylation of several multifunctional substrates (Figure 7), not compatible with the Pd-catalyzed methodology, was conducted in high yield using the same copper-based catalytic system.

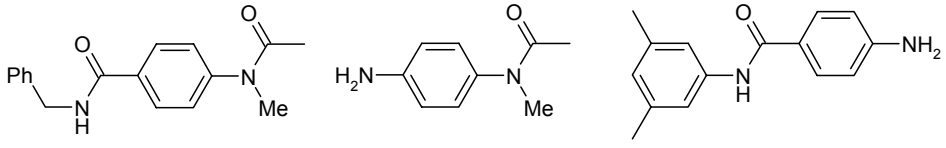
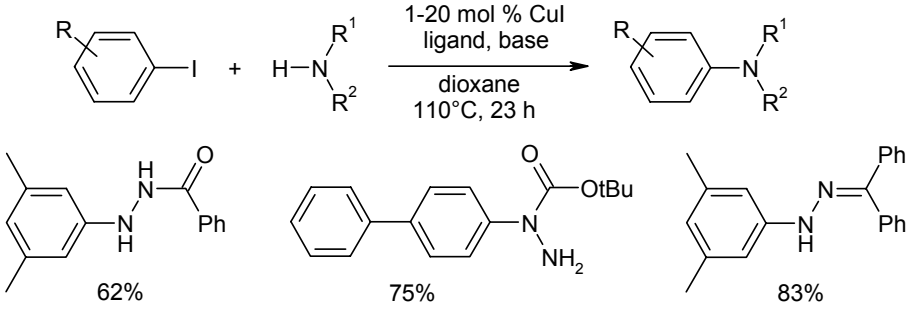


Figure 7. Substrates not compatible with Pd-cat. methodology and easily arylated under Cu catalysis

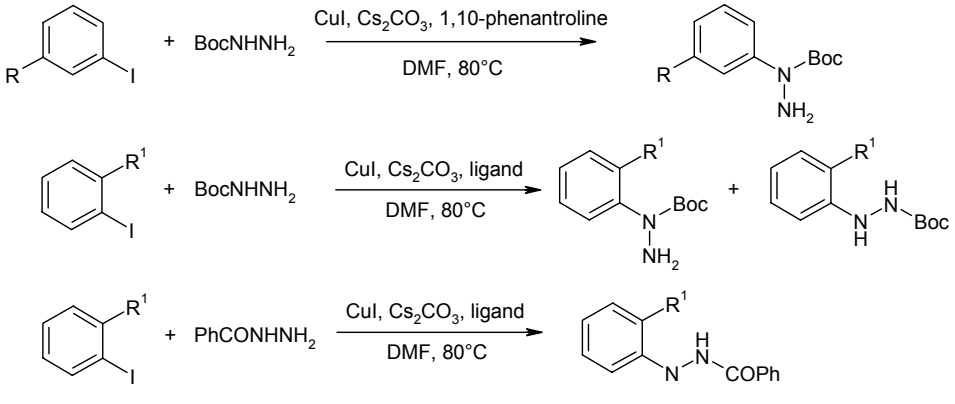
Of particular interest were substrates such as *tert*-butoxycarbazate, benzoic hydrazide and benzophenone hydrazone. As illustrated in Scheme 43, N-arylation of these compounds proceeds smoothly, affording the corresponding products in good yields.



Scheme 43. Copper-catalyzed arylation of β-amino alcohols

Effect of various diamine ligands on the efficiency of the aryl amidation reaction was thoroughly studied [110]. Thirteen chelators were tested in the reactions with 5 mol % of CuI, 10 mol % of ligand, 1.0 equiv of aryl bromide, 1.2 equiv of amide and 2 equiv of K_2CO_3. It was concluded that the degree of substitution and consequently the steric bulk play the most important role. N,N'-dimethylated 1,2-diamine ligands are considered to be the most efficient. It should be emphasized that a variety of functional groups are tolerated in the aryl amidation reaction, including nitrile, free NH_2 and aliphatic OH. Positive results were obtained even with such unactive aryl sources as aryl chlorides. Although the reactions are moderately sensitive to oxygen and have to be performed under an inert atmosphere there is no need to use glovebox techniques nor to purify the commecialy available reagents. No reduction or homo-coupling of the aryl halide, which often takes place in the Pd-catalyzed cross-coupling reactions, is normally observed.

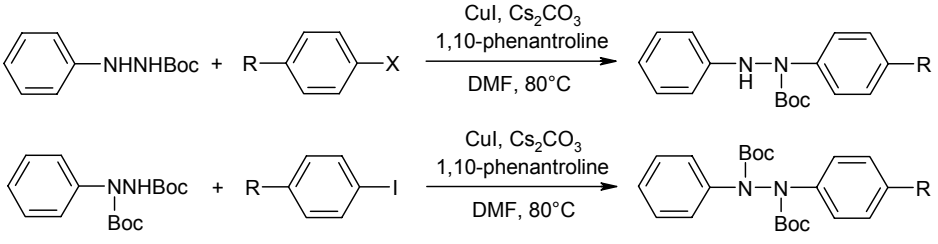
Although the copper-mediated N-arylation of *tert*-butoxycarbazate and benzoic hydrazides was already reported in previous studies [109], it was challenging to find an improved catalytic system for this transformation. Therefore Buchwald *et al* developed a convenient method for intermolecular N-arylation of hydrazides with substituted aryl iodides in the presence of copper catalyst CuI and Cs_2CO_3 as a base [111]. 1,10-Phenantroline and picolinic acid were employed as ligands. The investigation was complement to Skerlj's studies [99] of palladium-catalyzed arylation of *tert*-butoxycarbazate, where high yields were obtained only with aryl agents having electron-withdrawing substituents in the *para* position. Under copper-catalysis (CuI/Cs_2CO_3/DMF/80ºC), both electron-withdrawing and electron-donating p-substituents were tolerated and the corresponding aryl iodides were successfully coupled with *tert*-butoxycarbazate. The reaction was also carried out with a series of meta-substituted aryl iodides. As demonstrated in Scheme 44, N-arylated products were obtained regioselectively and in good yields irrespectively of the electronic properties of the substituent.



Scheme 44. Copper-catalyzed arylation of hydrazides

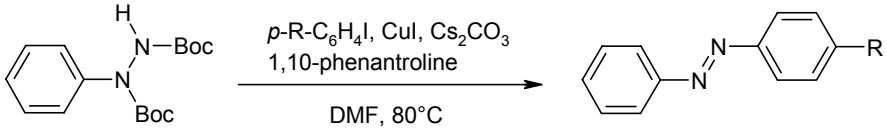
Arylation of $BocNHNH_2$ with *ortho*-substituted aryl iodides presented more challenge. A mixture of two arylation products was formed. Using a substrate with an electron-withdrawing substituent, the N'-arylated product was formed exclusively. In the coupling with benzoic hydrazide, a reversal in the regioselectivity was observed with all *ortho*-substituted aryl iodides as shown in Scheme 44.

Cho *et al* carried out copper-catalyzed N-arylation of PhNHNHBoc with substituted aryl bromides and iodides as illustrated in Scheme 45 [101]. The yields varied from moderate to high. Arylation of bis-Boc phenylhydrazine was conducted under the same conditions. Although, the yields were substantially higher if stoichiometric amounts of CuI were used instead of catalytic.



Scheme 45. Syntheses of Boc-protected arylhydrazines

The resulted di-Boc-diarylhydrazines were heated with stoichiometric amounts of CuI and Cs_2CO_3 at 110ºC in DMF, affording azobenzenes. The coupling and oxidation can be performed in one pot as shown in Scheme 46 below.

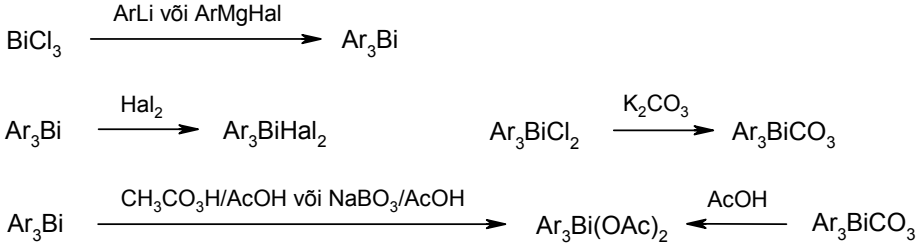


Scheme 46. Cu(I) mediated one-pot synthesis of azobenzenes

2.7.3. Organobismuth reagents as the aryl donor

The entire spectrum of organobismuth compounds is amazingly broad [112, 113]. Bismuth is present in its compounds almost exclusively in two oxidation states namely (III) and (V). There are two types of organobismuth reagents, which found a great number of synthetic applications as described below: trivalent species Ar_3Bi and pentavalent species Ar_3BiX_2 (X = Hal, OCOR, most often $OCOCH_3$). Triphenylbismuthane is commercially available inexpensive reagent. The rest of triarylbismuthanes can be readily prepared by the reaction

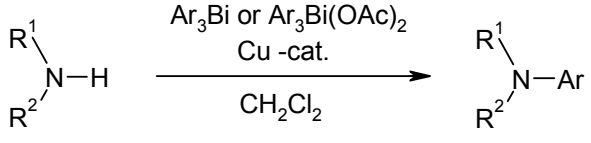
of extremely cheap bismuth (III) chloride and an organometallic compound. The most widely used organometallic reagent for this purpose is the Grignard reagent [112–114]. Triphenylbismuth diacetates, which are considered to be the most useful organobismuth species, are easily obtained by oxidation of the corresponding triarylbismuthanes by sodium perborate in acetic acid [114]. The preparation of the most important organobismuth reagents is demonstrated in Scheme 47 [112, 115].



Scheme 47. Preparation of organobismuth reagents

The contemporary era of organobismuth arylation started in 1980. To that time, C-arylation and O-arylation by Bi(V) reagents as well as oxidation was already known [116–118]. In 1981, David and Thieffry described a surprisingly simple and specific mono-O-phenylation of glycols by refluxing of the glycol with triphenylbismuth diacetate for 4–5 hours without any additives [119]. In a short while, Barton as well as Dodonov independently reported that the aryl transfer from triarylbismuth diacetates to alcohols proceeded much more smoothly (room temperature, 15 min) in the presence of catalytic amounts of copper acetate [120, 121]. These observations of a catalytic effect of copper salts on the monophenylation of glycol led to the development of new O and N-arylation methods [115, 122–124].

The basic principles of N-arylation organobismuth reagents were elaborated as a result of Dodonov and Barton fundamental investigations [125, 126–130]. The arylation of amines occurs accordingly to Scheme 48 below.

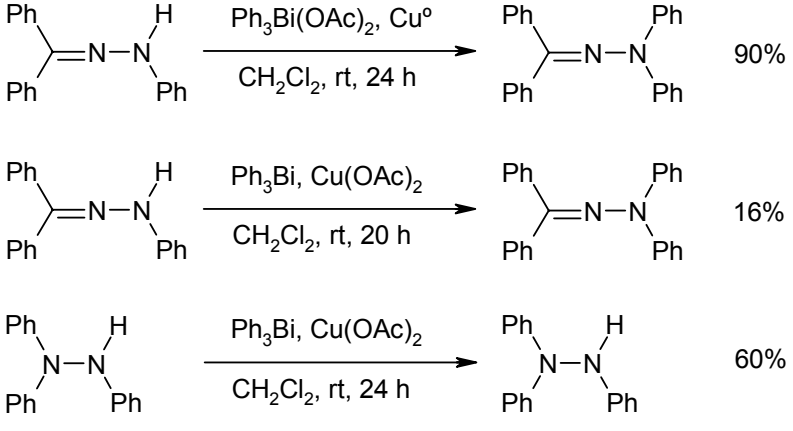


Scheme 48. Arylation of amines by organobismuth reagents

The reaction of simple primary aliphatic amines with triphenylbismuth diacetate and copper diacetate in THF at room temperature led to good yields of the obtained arylamines (69–82% based on the bismuth reagent). The process was rather slow (60–180 h). In the case of the phenylation of N,N-diphenylamine, triphenylamine was isolated in a very poor yield (<3%) [125]. When the same reaction was performed in dichloromethane, in the presence of catalytic amounts of metallic copper, the N-monophenylamines were obtained in higher yields. For instance, arylation of aniline gave diphenylamine in 96% yield in 2 h. Imines, enamines, oximes, amides, N,N,N',N'-tetramethylguanidine and semicarbazones were inert to the reagent $Ph_3Bi(OAc)_2$ + Cu°.

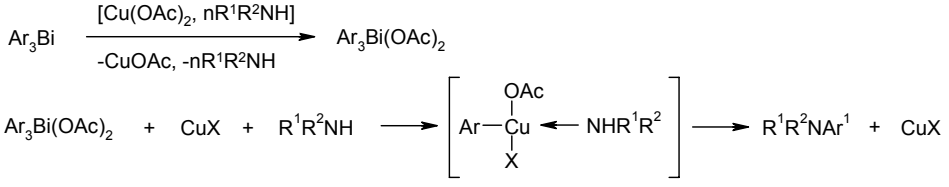
Triphenylbismuthane acted also as a versatile phenylating agent towards a variety of amines in the presence of stoichiometric amount of copper diacetate to afford high yields of the N-phenylated amines [127]. Whereas in the previously described system ($Ph_3Bi(OAc)_2$ + Cu°) the yields were mostly related to the steric hindrance of the amine, the Ph_3Bi + $Cu(OAc)_2$ system shows also a dependence on the basicity of the amine. N-butylamine gave a good yield of the N-diphenyl derivative but *p*-nitroaniline reacted poorly. The reaction was quite slow (18–24 h). It must be emphasized that in the coupling with triphenylbismuthane only copper diacylates such as $Cu(OAc)_2$ or $Cu(OCOCF_3)_2$ were efficient catalyst. Other copper compounds, such as metallic copper, copper oxides, chlorides or triflates gave no N-phenylation.

The results of some hydrazine derivatives, also used as substrates in the reaction with organobismuth reagents, are demonstrated in Scheme 49 [126, 127]. As we can see, in contrast to efficient $Ph_3Bi(OAc)_2$ (90% yield) triphenylbismuthane yielded only 16% of the product in the reaction with benzophenone hydrazone.



Scheme 49. Arylation of hydrazine derivatives

A possible mechanism, suggested by Barton, is shown in Scheme 50. The copper diacetate-amine complex is formed and reacts with Ph_3Bi to give either a phenyl copper derivative by transmetalation, followed by N-phenylation, or to yield $Ph_3Bi(OAc)_2$ which then reacts with a copper (I) species to afford a phenyl copper (III) species, which phenylates the amine [127].



Scheme 50. Possible mechanism of organobismuth N-arylation

There is an important conclusion from the mechanism, which is confirmed by experimental facts as well. The reaction with trivalent bismuth compounds demands copper (II) salt as necessary reagent in stoichiometric amount. After the oxidation to pentavalent bismuth, copper salt can act as a catalyst for N-arylation. However, in case of $Ph_3Bi(OAc)_2$, all types of copper are suitable and required only in catalytic amounts. Afterwards, the presence of aryl radical species has been studied by the use of an internal-trap containing reagent: tris(2-allyloxyphenyl)bismuth and its diacetate [128]. The intervention of radical species was excluded as cyclized products were never detected in N-arylation reaction.

In addition to amines, the selective mono-N-phenylation of α-amino acid derivatives has been performed with triphenylbismuth diacetate in the presence of a catalytic amount of copper or copper acetate [129]. Free α-amino esters reacted in 24 h, giving the corresponding products in good yields. Triphenylbismuth bis-trifluoroacetate was used to phenylate indoles [130]. Whereas C(3)-phenyl derivatives were obtained form C(3)-unsubstituted indoles, N-phenylation occurres with (C3)-substituted compounds. It should be noticed that although N-arylation demands catalyst, deprotonated amides can be arylated even without copper salt [117, 131].

In 1997, Barton *et al* reinvestigated copper-mediated phenylation of amines by Bi (V) reagents [132]. The influence of ligands bound to bismuth and the basicity of the amines have been examined. For this purpose, numerous bismuth (V) compounds were prepared. Copper pivalate was found to be very efficient catalyst since it surpassed both $Cu(OAc)_2$ and metallic copper in terms of reaction time and yield. This is probably due to its high solubility in common organic solvents, permitting homogeneous reaction.

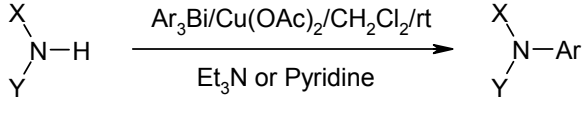
It was also demonstrated that during the course of the phenylation process, the remaining starting amine may be protonated by the liberated acid HX (from

Ar_3BiX_2), thus inhibiting further reaction. The utilization of an appropriate base allowed the efficient phenylation of more basic amines. For instance, the addition of one equivalent of N-*tert*-butyl-N'-N''-tetramethylguanidine to the reaction mixture of aniline and $Ph_3Bi(OTs)_2$ increased the yield of arylation from 50% to 80% [132]. According to the same principle, tetramethylguanidine was successfully employed as additive for copper-mediated N-arylation of various heterocycles [133].

Finet *et al* has shown that triarylbismuth diacetates can be prepared *in situ* using the oxidation of Ar_3Bi by iodobenzene diacetate under mild neutral conditions [134]. The obtained reagents were used in a one-pot copper-catalyzed arylation of anilines to afford excellent yields of diarylamines.

Steric hindrance in organobismuth reagent possess a great influence on N-arylation reactions [135]. In the case of aniline, the introduction of an ortho-methyl group on the aryl group had no effect on the yield of the obtained diarylamines. However, the reaction rate appeared slower than in the case of the unsubstituted reagent. With the substrates of low reactivity such as phthalimide, the reaction was so slow that decomposition of the bismuth reagent became predominant and the N-arylation product was isolated in modest yield. Probably, the steric hindrance is most important at the stage of the bismuth-copper transmetallation. When this transfer is facilitated by coordination of the copper species with an aniline, the steric effect induces less imortant consequences.

In 1996, Chan *et al* reported a highly efficient N-arylation method, which represents an impressive modification of Barton's procedure [136]. In contrast to Barton's results, Chan has succeeded in the N-arylation of a diversity of organic compounds such as amides, imides, ureas, carbamates and sulfonamides using triphenylbismuthane as an arylative agent (Scheme 50). The key point was the presence of a tertiary amine promoter such as triethylamine or pyridine. This amine promoter had a remarkable effect in the arylation reactions. For instance, no product was observed in the absence of promoter in the case of 4-fluorobenzamide, whereas in the presence of pyridine of triethylamine the monophenylated derivative was isolated with yield respectively 83% and 71%.

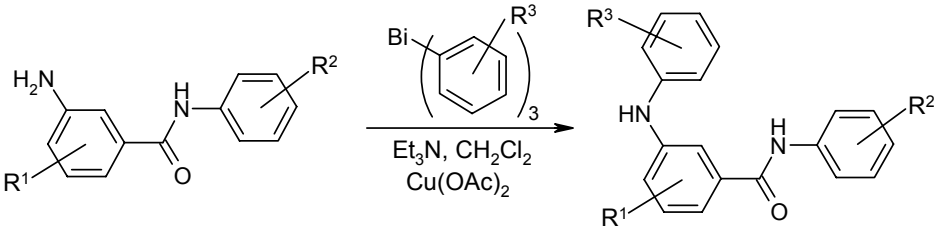


X, Y = COR, COOR, $CONR_2$, SO_2R, R, H (R = alkyl and aryl)

Scheme 50. Chan's modification

In most cases, an equimolar amount of the promoter was used. The reaction times vary in the range 5–72 h and the yields of isolated products were mostly high. The difference between using triethylamine or pyridine as a promoter is also noteworthy. It is evident that Et_3N is better at promoting amide arylation, whereas pyridine is more efficient with imides and sulfonamides. Probable, the promoter enhances the solubility and reactivity of copper acetate and various copper species involved in product formation. Promoter also buffers the reaction mixture since acetic acid is generated during the course of arylation process.

Using the original Chan's procedure, Sorenson performed regioselective N-arylation of aminobenzanilides with triarylbismuthanes [137]. The substrates contain both the amine and amide functionalities. Under these conditions coupling with aryl group occurred preferentially at the amino- rather than the amide-nitrogen of the substrate as shown in Scheme 51. An inert atmosphere was not required during the reaction and the corresponding fuctionalized diarylamines were obtained in high yields after 3–20 h of reflux in dichloromethane.



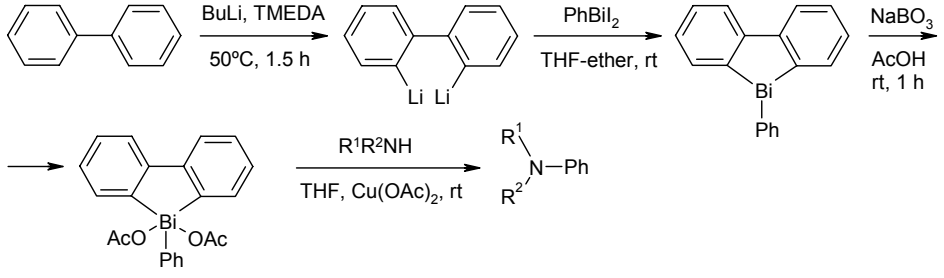
Scheme 51. Selective N-arylation of aminobenzanilides

It should be emphasized that nowadays functionalized organobismuth reagents are of special importance in N-arylation. Banfi *et al* prepared several triarylbismuthanes, containing various electron-withdrawing substituents in the *meta*-position of the aryl group (CF_3, F, Cl, OCH_3, NO_2) [138]. The obtained compounds were used in the synthesis of N-arylpiperidines functionalized both on the aromatic and piperidine ring. The N-arylation was performed in dichloromethane at room temperature in the presence of equimolar amount of copper diacetate, affording the corresponding products in 41–67% yields.

Suzuki *et a*l synthesized several water-soluble non-ionic triarylbismuthanes, containing sulfonamide and hydroxy groups in the aryl moiety [139]. Using Knochel method [140] for the preparation of functionalized aryl-Grignard reagents, containing an ester, amide or cyano group, Sugihara *et al* obtained triarylbismuthanes bearing π-accepting substituents in the aromatic ring [141]. Sharma *et al* prepared a set of organobismuthanes containing aromatic heterocycles of general formula $(2\text{-}XC_4H_3)_3Bi$ where X = S; O or NMe_2 [142]. All the

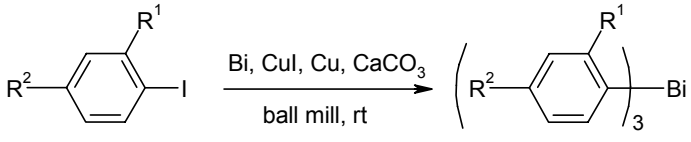
compounds were synthesized by the reaction of bismuth chloride with the corresponding heteroaryl-lithium.

Fedorov and Finet synthesized phenylbiphenyl-2,2'-ylenebismuth diacetate, which reacted with amino groups to give the products of N-phenylation [143]. This is the first example of organobismuth reagent containing different aryl groups. During arylation reaction, a selective transfer of phenyl substituent occurred as illustrated in Scheme 52.



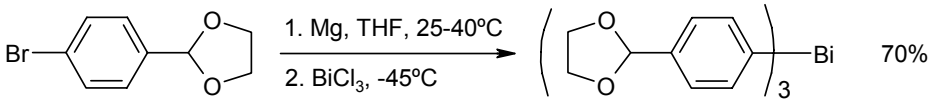
Scheme 52. Synthesis and use of phenylbiphenyl-2,2'-ylenebismuth diacetate

Recently, Suzuki *et al* reported a special route to *ortho*-functionalized triarylbismuthanes that are difficult to access by conventional procedures [144]. When an aryl iodide bearing an electron-withdrawing group at the ortho-position was milled together with bismuth shots and calcite grains in the presence of copper powder and CuI using a laboratory ball mill, the corresponding triarylbismuthane was obtained in moderate to good yield as shown in Scheme 53



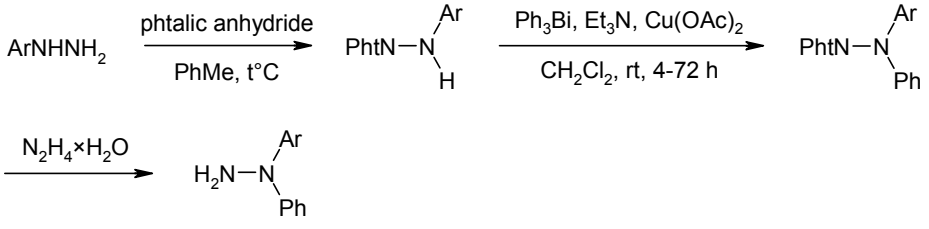
Scheme 53. The preparation of *ortho*-functionalized triarylbismuthanes

Loog and Mäeorg synthesized acetal protected 4-formylphenylbismuthane [145] as demonstrated in Scheme 54. This compound was further used for the N-arylation of trisubstituted hydrazines and this route will be described in Section 2.9.2.2.



Scheme 54. The preparation of acetal protected 4-formylphenylbismuthane

Kikugawa *et al* developed a technique for the synthesis of 1-aryl-1-phenylhydrazines, based on the use of phthaloyl protection [146] as outlined in Scheme 55. Arylhydrazines are used as starting materials. Yields of copper-mediated arylation in standard Chan's conditions were high to excellent (82–99%).



Scheme 55. Synthesis of 1-aryl-1-phenylhydrazines

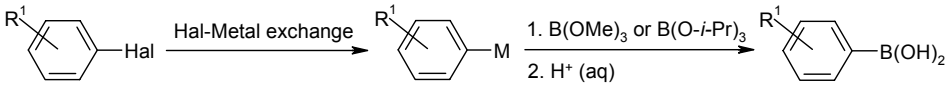
Another method for the synthesis of multisubstituted arylhydrazines, which is based on the use of several protecting groups and does not require arylhydrazines as a starting material, will be described below in Section 2.9.2.2 [147].

It is interesting to notice that in the reactions of triphenylbismuth diacetate with disubstituted hydrazines such as PhNHNHPh and $PhNHNHCPh_3$ no arylation occurs at all. Due to the significant oxidative properties of pentavalent bismuth [112], the substrates are transformed to the corresponding azo compounds, respectively PhN=NPh and $PhN{=}NCPh_3$ [116, 148].

2.7.4. Arylboronic acids as the aryl donors

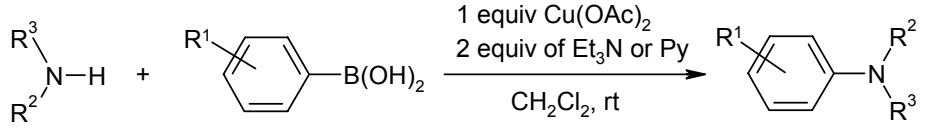
Boronic acids have become established as important reagents for plenty of useful reactions [149]. The advantages that these compounds possess over organolithium, organomagnesium and other organometallic reagents in related coupling processes are their tolerance to a wide variety of functional groups, air stability and relatively low toxicity. Boronic acids are readily handled without special precautions. Many of them are commercially available. These

compounds, including both aryl and heteroarylboronic acid can also be easily prepared by the reaction of corresponding organometallic derivative and boric acid esters as shown in Scheme 56 [149, 150].



Scheme 56. General method for the synthesis of arylboronic acid

The development of copper-catalyzed N-, O- and S-arylation using arylboronic acids as the source of the aryl group is quite recent as the first report was published by Chan in 1998 [151]. The N-arylation reaction, as outlined in Scheme 57, is conducted at room temperature and requires 2 equiv of arylboronic acid. The process is slow (18–67 h), but compatible with a variety of substituents on both reactants. Amines, anilines, amides, ureas, carbamates and sulfonamides were thus easily arylated in moderate to excellent yields. Thus, using essentially the same mild reaction conditions as in the triarylbismuth arylation [136], one can replace the bismuth reagent with the corresponding arylboronic acid, many of which are commercially available. Another advantage of using a phenylboronic acid is that it is in theory a more "aryl-economical" approach since only one of three aryl groups is transferred from the bismuth reagent under normal conditions.

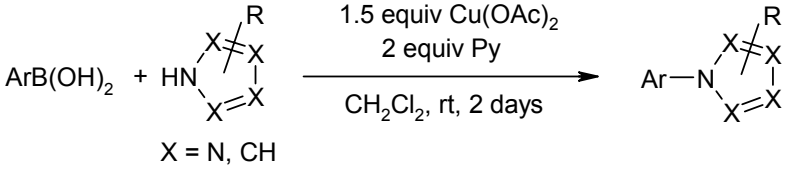


Scheme 57. N-arylation by arylboronic acids

Cundy and Forsyth evaluated the generality of this procedure, using a selection of electronically diverse arylboronic acids and variety of substrates with different NH basicity/nucleophilicity such as piperidine, butylamine, para-tertbutylaniline, acetamide and succinimide [152]. The influence of steric hindrance was observed as the *ortho*-substituted methoxyboronic acid afforded lower yields in comparison to *para*-substituted one. No substrate trend was noticed in terms of the basicity of the amine and the electronic nature of the boronic acid. Despite several unsuccessful experiments, the study highlighted the potential of the method.

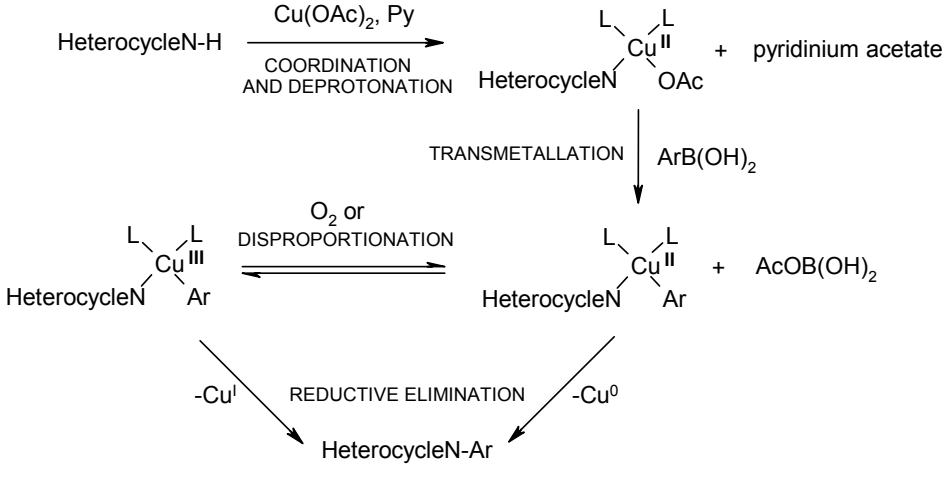
The efficiency of this new methodology was further demonstrated by Lam, Chan *et al* using aryl-heteroaryl C-N cross coupling [153]. The reaction

proceeds at room temperature exposed to air and is applicable to a variety of N-H containing heterocycles, including pyrazole, imidazole, indazole and benzimidazole (Scheme 58). The yields are mostly high (67–88%) except for less nucleophilic substrates, such as triazoles and tetrazole. Three different arylboronic acids $RC_6H_4B(OH)_2$ (R=CF_3, CH_3, CH_3O) ranging from electron-deficient to electron-rich aromatic rings were tried for the N-arylation of imidazole and pyrazole. Good yields indicate that this reaction tolerates arylboronic acids of different electronic nature.



Scheme 58. Aryl-heteroaryl C-Ncross coupling using arylboronic acids

In a short while, Lam and Chan have extended their studies to saturated heterocycles and aminopyridines [154]. The reaction was conducted in air but in the presence of 4Å mol. sieves. It was observed that for the less acidic heterocycles Et_3N seems to give slightly better yields than pyridine and for more acidic substrates pyridine was still the additive of choice. Presumably, there is a trade-off between the capability to deprotonate the heterocycle-copper (II) complex intermediate and the capability to complex the copper intermediate. This is why triethylamine acts as a better base whereas pyridine acts as a better ligand. A possible mechanism of N-arylation was suggested as outlined in Scheme 59.



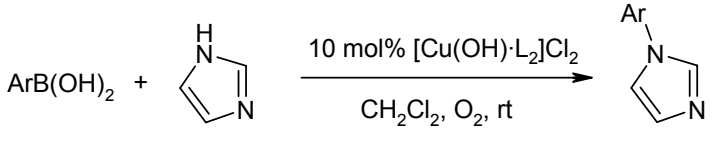
Scheme 59. Possible mechanism of N-arylation

There are many other applications for this arylation methodology. Bakkestuen and Gundersen reported efficient and regioselective synthesis of 9-arylpurines using N-arylation of purines with arylboronic acids in the presence of copper (II) acetate [155]. Phenantroline was found to be the best additive and the yields were moderate to high.

Lam *et al* reported that the arylboronic acid could be extended with a vinyl group [156]. Also, the same researchers showed that *p*-tolylboronic acid couples smoothly with a range of 15 α-aminoesters to form the N-arylated products in generally acceptable yields [157]. Although the reactions required 1–2 days for complete conversion and standard use of 2 equiv of the $ArB(OH)_2$ with the stoichiometric amount of $Cu(OAc)_2$, the process was conducted at room temperature and the products were formed with complete retention of configuration for both enantiomers. Combs *et al* described efficient examples of the solid-supported aryl and heteroaryl C-N cross-coupling reactions promoted by microwave radiation [158].

In an important development, Collmann and Zhong described the catalytic version of this N-arylation [159]. $[Cu(OH)\cdot TMEDA]_2Cl_2$ was used as catalyst for the arylation of imidazoles under the atmosphere of oxygen. The coupling proceeded without the addition of any base at room temperature. As a result, good to excellent yields of N-arylimidazoles were isolated under these mild conditions. Collmann *et al* also demonstrated that this reaction could be conducted in water instead of dichloromethane [160]. The effect of pH value was studied. When the reaction was accomplished under either acidic or basic buffer conditions, lower yields were obtained compared to that in neutral media possibly due to the deboronation reaction.

Afterwards, Collmann *et al* prepared a series of μ-hydroxo Cu (II) complexes with nitrogen chelating bidentate ligands and applied these compounds to the coupling of imidazoles with arylboronic acids [161] as shown in Scheme 60. Both sp^2-N and sp^3-N ligands were under investigation, including several bisimidazoles, phenantroline, 2,2'-pyridyl, alkylsubstituted ethylenediamines etc. Nevertheless, among the various combinations, TMEDA appeared to be the most effective ligand.



Scheme 60. Catalytic N-arylation of imidazoles

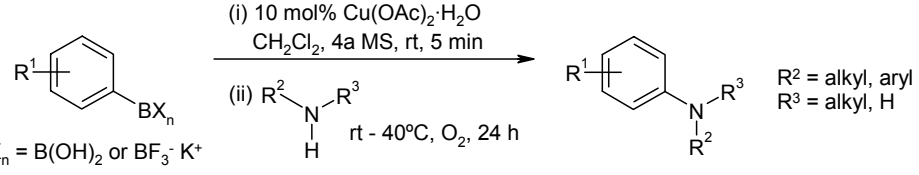
In order to improve the catalytic version of the reaction, two other systems were developed by Buchwald [162] and Lam [156]. Buchwald *et al* reported that the reaction of a number of functionalized anilines with arylboronic acids in the

presence of catalytic amount of $Cu(OAc)_2$, 2,6-lutidine as a base and myristic acid as an additive, provided the diarylamines in good yields. Alkylamines were also successfully arylated under these conditions [162]. Myristic acid probably operates by coordination to the copper center, thereby increasing the solubility of the catalyst.

Lam *et al* studied the effect of a co-oxidant in the C-N cross-coupling with arylboronic acids [156]. Several oxidants were screened such as pyridine-N-oxide, TEMPO, NMO, sodium perborate, MCPBA etc. It was demonstrated that catalytic $Cu(OAc)_2$-TEMPO in air and catalytic $Cu(OAc)_2$-O_2 appear to work for the majority of substrates, including amines and NH heterocycles.

Lan *et al* described copper-catalyzed N-arylation using arylboronic acids in methanol with no base or ligand [163]. The reaction proceeded under reflux and was accomplished in 10 min –3 h with a variety of substrates, which is much faster than that reported previously. In the presence of 10 mol% of $Cu(OAc)_2$ imides provided excellent yields of N-arylimides. Amines, amides and sulfonamides afforded the corresponding N-arylated products in moderate to good yields.

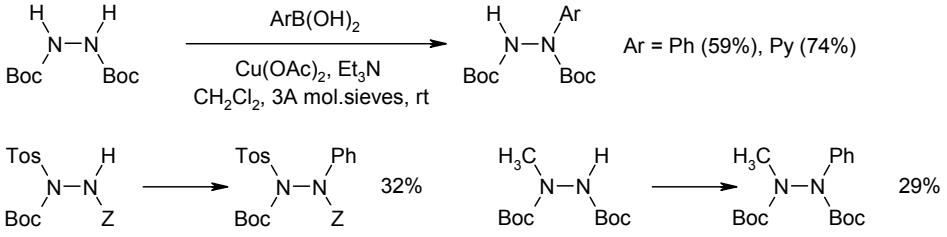
In 2003, Batey and Quach reported a ligandless and base-free Cu-catalyzed protocol for the cross-coupling of arylboronic acid and potassium aryltrifluoroborate salts with primary and secondary amines and anilines [164]. The process required catalytic amounts of $Cu(OAc)_2 \cdot H_2O$ and 4Å molecular sieves in dichloromethane at 40ºC under an atmosphere of oxygen as shown in Scheme 61. In general, phenylboronic acid gave slightly greater yields than potassium phenyltrifluoroborate, probably due to its greater solybility in dichloromethane. The successful transformation of aliphatic amines is of special importance as this is a class of nucleophiles that have been problematic under previous cross-coupling protocols with $ArB(OH)_2$. A variety of functional groups on the amines are tolerated. α-Amino acid derivatives were converted without epimerization. Anilines afforded only low to moderate yields of the unsymmetrical diarylamine products.



Scheme 61. Catalytic N-arylation with arylboronic acids and potassium aryltrifluoroborate salts

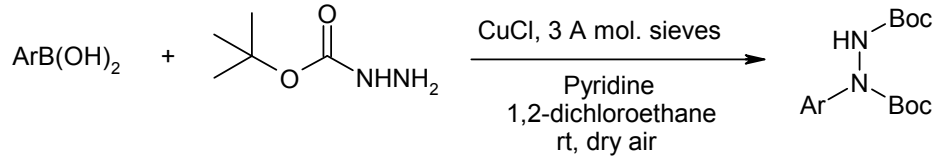
Mäeorg *et al* studied copper-mediated N-arylation of di- and trisubstituted hydrazines with arylboronic acids as outlined in Scheme 62 [165]. Under Chan conditions [151] with the addition of 3 Å molecular sieves the reaction was

slow (up to 4 days) and best yields were obtained in the arylation of 1,2-di-Boc-hydrazine. Trisubstituted hydrazines afforded low yields probably due to the significant steric hindrance.



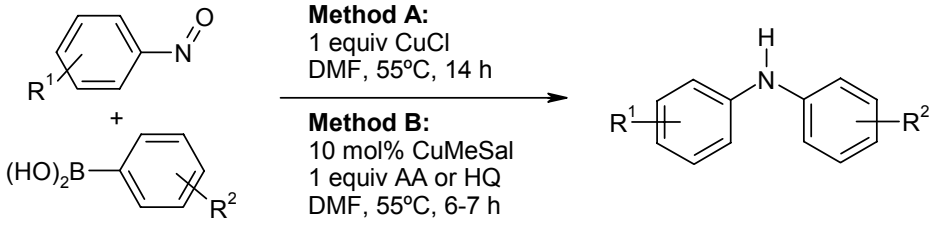
Scheme 62. N-Arylation of hydrazines with arylboronic acids

Kabalka and Guchhait studied the reaction of *tert*-butyl carbazate with arylboronic acids under the conditions of copper catalysis [166]. The result is quite unusual as no expected direct N-arylation took place as outlined in Scheme 63. Diprotected monoarylated hydrazines were isolated in good yields after 6–96 h. The process is catalyzed by 10 mol % of cuprous chloride. It is noteworthy that the reaction is insensitive to the electronic nature of the functional groups present in the arylboronic acids. A wide range of substrates included aryl, heteroaryl, and vinylboronic acids. Sterically hindered boronic acids also readily participated in the process. The results suggest that the reaction proceeds via self-coupling of the *tert*-butyl carbazate to form di-*tert*-butyl hydrazodiformate, which is then arylated by the boronic acid.



Scheme 63. Synthesis of BocArNNHBoc

Liebeskind *et al* used nitrosoarenes as substrates in coupling with arylboronic acids [167] as depicted in Scheme 64. This C-N bond formation is mediated by a stoichiometric amount of CuCl as both a catalyst and a reducing agent. Alternatively, the reaction can be catalyzed by 10 mol % of Cu(I)-3-methylsalicylate in the presence of reducing agent such as ascorbic acid or hydroquinone. Both methods A and B afford the corresponding substituted diarylamines in high yields. This procedure provides an interesting synthetic complement to existing protocols for C-N cross-coupling.



CuMeSal = Cu(I) 3-methylsalicylate; AA = ascorbic acid; HQ = hydroquinone

Scheme 64. N-arylation of nitrosoarenes with arylboronic acids

2.7.5. Other aryl donors

In addition to organobismuth compounds and arylboronic acids, there are other aryl sources proved also to be efficient reagents for the mild copper-catalyzed N-arylation. These compounds include aryl siloxanes, aryl stannanes, aryl iodonium salts and aryllead triacetates [34, 37, 124]. Examples of their use in N-arylation reactions are brought below.

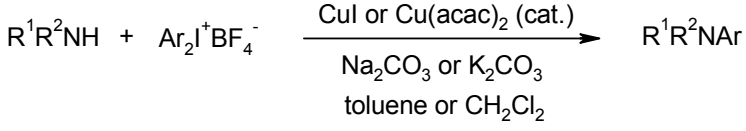
Barton *et al* were first to study copper catalysis on the phenylation of amines with ***organolead reagents*** [168]. The reaction was conducted in CH_2Cl_2 at room temperature under argon atmosphere. The arylation ability of tetravalent aryllead compounds appeared to be dependent upon the nature and number of each substituent. For instance, N-phenylation of *p*-toluidine was attempted with all possible phenyllead acetates ($PhPb(OAc)_3$, $Ph_2Pb(OAc)_2$, $Ph_3Pb(OAc)$, Ph_4Pb) under $Cu(OAc)_2$ catalysis. The yield of N-phenyl-*p*-toluidine decreased with the increasing number of phenyl substituents contained in the organolead reagent. Therefore, $PhPb(OAc)_3$ turned out to be the most efficient arylating reagent. Conversion of *p*-toluidine and other anilines were complete in 3–48 h and the yields of the corresponding N-phenyl derivatives were mostly high. Secondary aliphatic amines afforded poor yields. Arylation of benzophenone hydrazone gave only 9% of product in 48 h [168].

Furthemore, Barton *et al* found that the arylation of arylamines was unaffected by the steric hindrance of the substrates but was dependent on the arylamine basicity [169]. For instance, the yields of coupling of mesitylamine with a series of aryllead triacetates in the presence of a catalytic amount of $Cu(OAc)_2$ were high with the exception of formation of extremely hindered N-(2,4,6-trimethylphenyl)-2,4,6-trimethoxyaniline.

Avendano *et al* described N-arylation of a variety of N-heterocycles, including pyrazole, 3-methylindole, indazole, imidazole etc. with *p*-tolyllead acetate under mild conditions [170]. Yields were high and the conversion was over in 4–48 h. In a short while, Avendano also reported that carboxamides, sulfonamides, imide and hydantoin anions can be successfully arylated with the

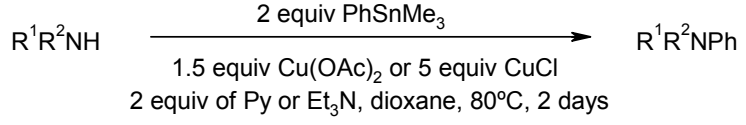
same reagent [171]. The reaction is superior to traditional methods for N-arylation of amides in that the conditions required are mild.

Kang *et al* studied the copper-catalyzed arylation of amines, azoles and amides with ***hypervalent iodonium salts*** as outlined in Scheme 65 [172]. Yields of the corresponding N-phenylated products were high except for amides which afforded poorer conversion. The advantage of this method is that it can be carried out at room temperature and with a weak base.



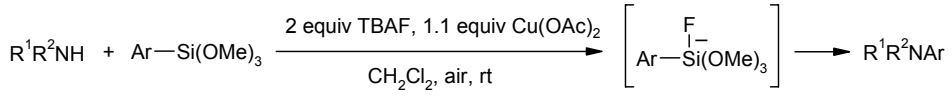
Scheme 65. N-arylation of nitrosoarenes with arylboronic acids

Commercially, a larger variery of ***arylstannanes*** are available than are aryl-boronic acids. Applicability of phenyltrimethylstannane $PhMe_3Sn$ for the copper-mediated arylation was studied as shown in Scheme 66 [154]. Unfortunately, the yields with N-H containing heterocycles were moderate and the reaction failed with most other substrates.



Scheme 66. Phenyltrimethylstannane as an arylative agent

In 2000, Lam *et al* reported the discovery of the copper-promoted C-N cross-coupling reaction with ***hypervalent aryl siloxanes*** and a variety of N-H substrates as outlined in Scheme 67 [173]. The addition of an equimolar amount of tetrabutylammonium fluoride to phenyltrimethylsiloxane generates a hypervalent siloxane species. This silicate species is a very efficient arylating agent for N-H containing substrates in the presence of cupric acetate at room temperature under atmospheric air. It is significant that no base/ligand is necessary for N-arylations with aryl siloxane. The yields were moderate to excellent depending on the substrate.



Scheme 67. N-Arylation with Aryl Trimethylsiloxane

2.8. Azo compounds

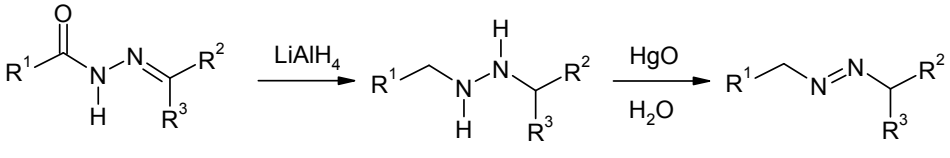
Azo compounds are known as versatile reagents in modern organic synthesis, with most striking examples including DEAD and DBAD. Such azodicarboxylates possess an attractive combination of high reactivity toward nucleophiles coupled with good shelf stability. Azoarenes have gained much interest due to their photoresponsive properties. Azoalkanes found use as progenitors of alkyl radicals by photolytic, radiolytic, and pyrolytic reactions.

2.8.1. Synthesis of azo compounds

Those azo compounds, which are not commercially available, can be prepared using three basic methods: diazocondensation, reduction of azoxy compounds or oxidation of hydrazines [174]. Diazocondensation, e.g. coupling of diazonium ion with arylamine or alcohol, is widely used for the preparation of azoarenes. A number of open chain aliphatic and also alicyclic azoxy derivatives have been successfully reduced to the azo compounds with different reagents, like Mg/MeOH and $LiAlH_4$. The reduction of substituted azoxybenzenes to azo derivatives can be also conducted with good results, using Zn/AcOH, Zn/KOH, $LiAlH_4$, $NaBH_4$.

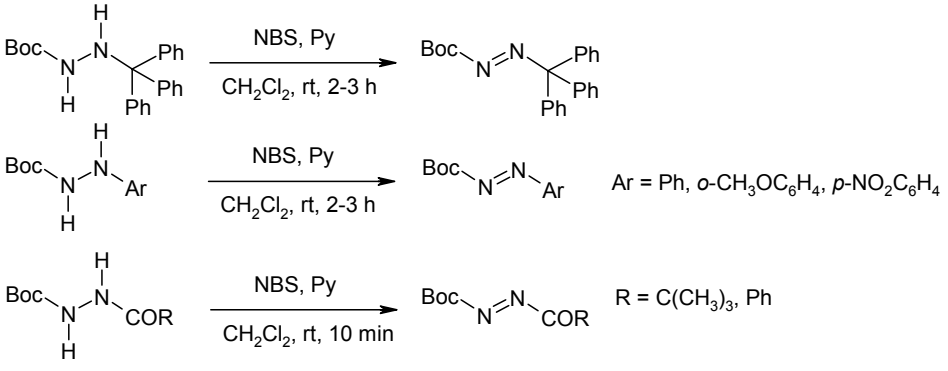
On the other hand, considerable attention has been paid to studies on the oxidation of disubstituted hydrazines to the corresponding azo compounds. The broad spectrum of available starting materials leaves no doubts in the advantages and the convenience of this protocol, compatible with many aromatic, aliphatic and acylsubstituted hydrazines.

Spialter *et al* prepared various unsymmetrical azoalkanes by oxidation of 1,2-dialkylhydrazines, which in turn were obtained from the lithium aluminium hydride reduction of acylalkylhydrazones [175]. The full synthetic pathway is illustrated in Scheme 68. Mercuric oxide was used as oxidant and the corresponding azo compounds were isolated in moderate yields (23-59%). It is interesting to notice that their boiling points are related to those of the analogous hydrocarbons.



Scheme 68. Synthesis of unsymmetrical azoalkanes

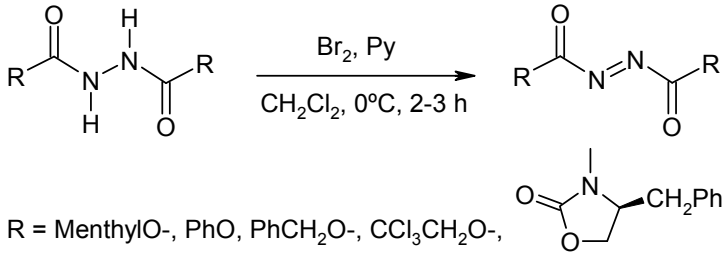
Carpino *et al* used NBS with pyridine to carry out the oxidation of disubstituted hydrazines [176]. Several *tert*-butyl aryl and acylazoformates were synthezised this way as outlined in Scheme 69. The yields of the corresponding products were high or close to quantitative. The reaction was especially fast in case of azo compound with two electron-withdrawing groups.



Scheme 69. Synthesis of azo compounds

Wang *et al* used the same oxidative system NBS/Py to perform the transformation of arylsubstituted semicarbazides $Ar^1NHCONHNHAr^2$ and carbazides ArNHNHCONHNHAr into the corresponding azo compounds [177]. The conversion was complete in 10 min at room temperature in dichloromethane, affording high yields of $Ar^1NHCON{=}NAr^2$ and ArN=NCON=NAr. Cho *et al* showed that NBS/Py can be also employed for the oxidation of diarylhydrazines $Ar^1NHNHAr^2$ into $Ar^1N{=}NAr^2$ [178]. The reaction time range from 1 h to 24 h 2 h and the yields were mostly good. However, the procedure is not compatible with the diarylhydrazine containing a methoxy group in the aromatic ring. Due to its strong electron-donating nature, bromination on the aromatic ring becomes a serious side-reaction, thus interfering with the oxidation process and decreasing the yield of the azo compound.

Starr *et al* described a very convenient oxidation method for the preparation of azodicarbonyl compounds [179]. Five representative hydrazines were converted into azo compounds using bromine and pyridine as shown in Scheme 70. Yields range from 80% to 93%.



Scheme 70. Oxidation of hydrazines using bromine

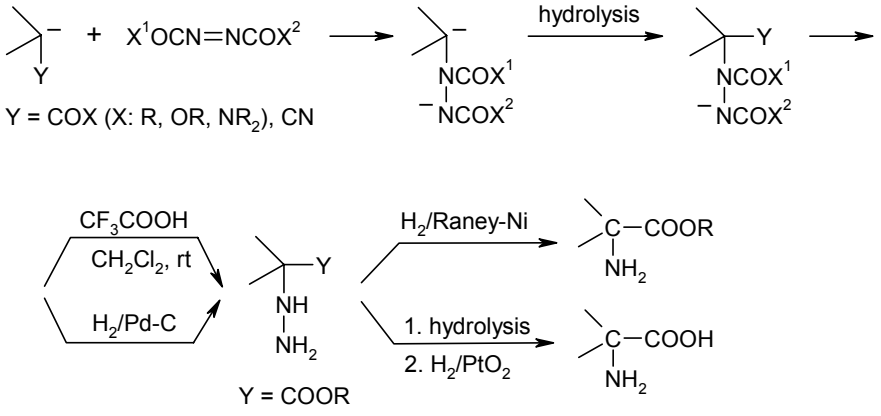
Recently, a number of new efficient oxidizing systems have been developed [180–183]. For instance, Li *et al* employed mixture $NaNO_2$-Ac_2O in order to oxidize hydrazines $Ar^1CONHNHAr^2$ into the corresponding azo compounds $Ar^1CON{=}NAr^2$ [180]. This reaction proceeds in acetone at room temperature and the conversion is complete in 0.5–1 h, affording the products in high yields. Wang *et al* used ceric ammonium nitrate in the synthesis of carbodiazones, which is a special class of azo compounds with the general formula $Ar^1N{=}NCON{=}NAr^2$ [181]. The reaction was over in 10 min with high yields.

Wang has also found that the transformation can be successfully performed even in solid state [182, 183]. According to this protocol, solid substrates are ground in agate mortar with $Fe(NO_3)_3{\cdot}9H_2O$ for 10 min, which is enough for full conversion. The method is compatible with starting materials such as PhCH=CHCONHNHAr [182] and $Ar^1NHNHCONHNHAr^2$ [183]. It is worth mentioning that in case of $Ar^1NHNHCONHNHAr^2$ only one NHNH moiety undergoes oxidation, thus affording $Ar^1N{=}NCONHNHAr^2$.

Synthesis of azobenzenes via direct oxidation of diarylhydrazines in the presence of CuI was already discussed above in Section 2.7.2 [101].

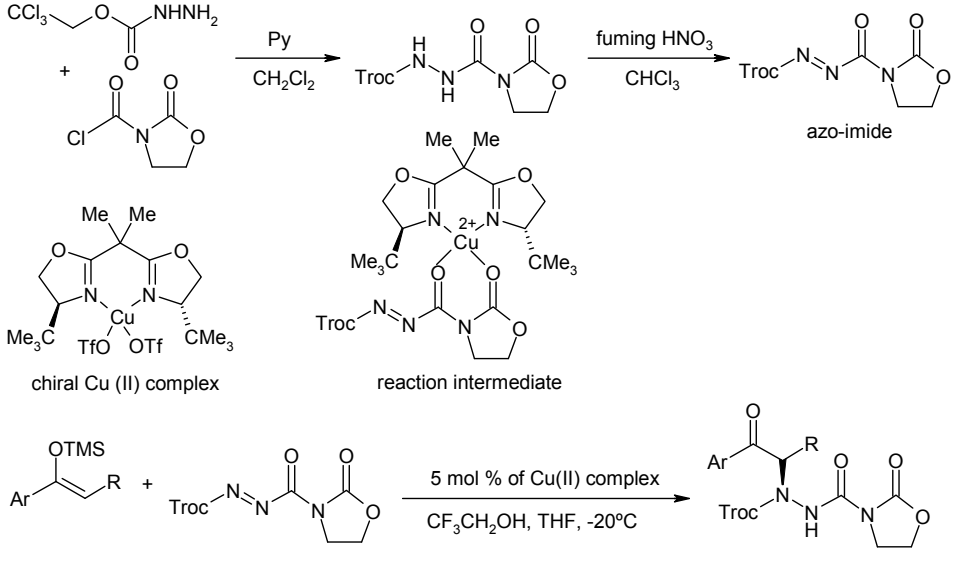
2.8.2. The big world of electrophilic amination

Because of the exceptional electrophilicity of the N=N bond, azo compounds found great use in organic synthesis. For instance, these versatile reagents are employed in such useful reactions as Mitsunobu process [185] and electrophilic amination [186]. In general, the methodology of electrophilic amination provides an important route for C-N bond formation in organic synthesis. In this process, electrophilic nitrogen carried by the reagent is transferred to a nucleophilic atom of the substrate to form Nu-N bond in the product. The reaction of diazene dicarboxylates with enolates is a particularly attractive method for preparation of α-aminocarbonyl compounds and α-aminoacids as outlined in Scheme 71. Asymmetric synthesis is possible using different methods for chiral induction [186].



Scheme 71. Preparation of α-aminocarbonyl compounds and α-aminoacids

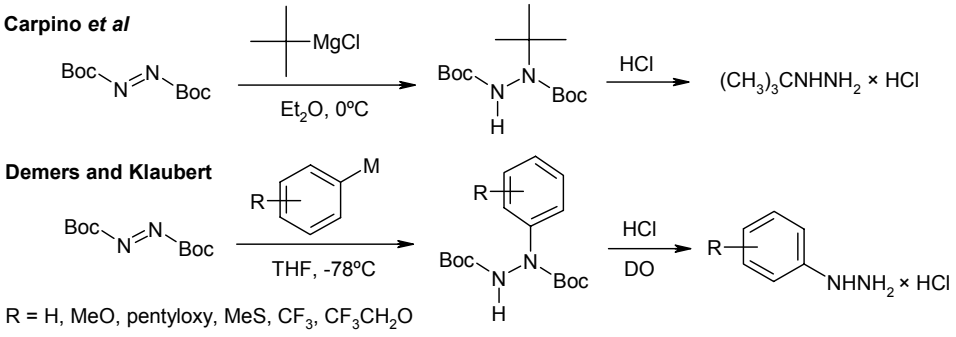
From among multiple publications in this field, a significant contribution from Evans and Johnson should be distinguished [187]. It was found that chiral Cu (II) complex catalyzes the enantioselective amination of enolsilanes with azodicarboxylate derivatives as illustrated in Scheme 72. Isomerically pure enolsilanes of arylketones, acylpyrroles, and thioesters added to the azo-imide in greater than 95% ee. In contrast to typical azo compounds used in this type of amination, this substrate is unsymmetrical. However, the addition of enolsilanes is completely regioselective on the azo component, suggesting that the substrate is being activated through the anticipated chelate.



Scheme 72. Copper-catalyzed enantioselective amination using azo-imides

In addition to enolates, azo compounds react with a number of other nucleophiles such as ***organometallics, alkenes*** and ***arenes***, yielding a variety of trisubstituted hydrazines.

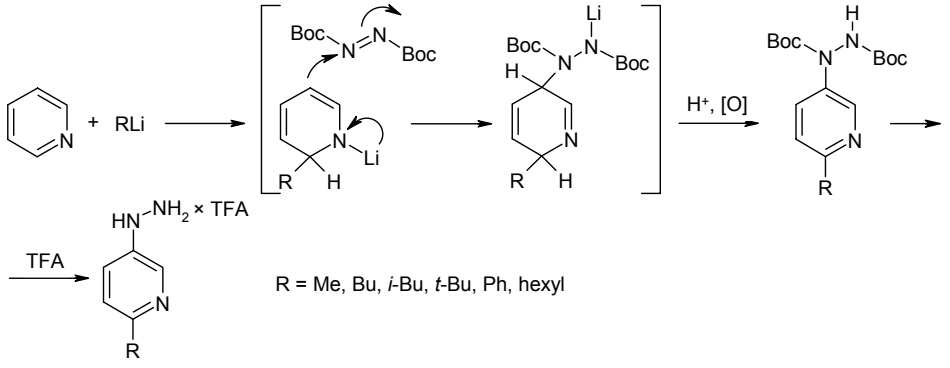
Carpino [176] *et al* prepared *tert*-butylhydrazine hydrochloride via the reaction of *tert*-butyl magnesium chloride with di-*tert*-butyl azodicarboxylate BocN=NBoc with subsequent cleavage of Boc groups by HCl (Scheme 73). Demers and Klaubert described analogous synthetic route to arylhydrazines [188]. As illustrated in Scheme 73, aryllithium and arylmagnesium bromides smoothly add to the N=N bond of di-*tert*-butyl azodicarboxylate. Subsequent acid deprotection affords good yields of several arylhydrazines. The process failed to produce electron-rich 3,4-dimethoxyphenylhydrazine.



Scheme 73. Preparation of monosubstituted hydrazines via azo compound

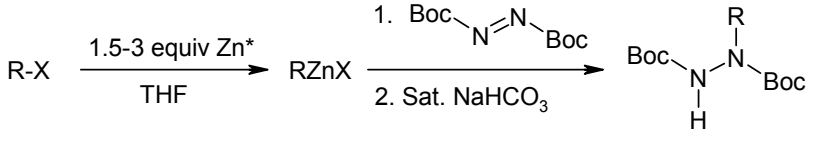
A one-pot preparative method for tri and tetrasubstituted hydrazines via azobenzenes and organolithiums, developed by Katritzky [83], was already described in Section 2.5.

Zhang and Tan described preparation of 2-alkyl- and 2-phenyl-5-hydrazinopyridines [189]. As shown in Scheme 74, nucleophilic addition of alkyl- or phenyllithium to pyridine generates a 2-substitted dihydropyridine anion that reacts with DBAD affording 2,5-disubstituted dihydropyridine. Conversion of these compounds to pyridines was accomplished by mild air oxidation. The yields range from 28% to 73%.



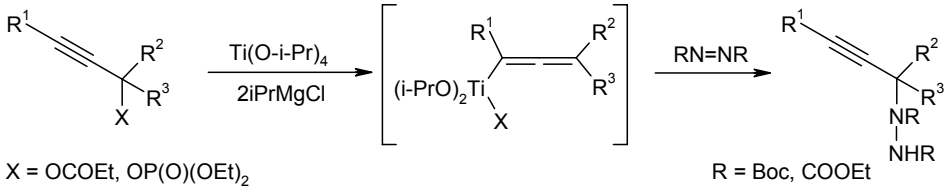
Scheme 74. Preparation of 2-alkyl- and 2-phenyl-5-hydrazinopyridines

Rieke *et al* used organozinc halides as nucleophiles in the electrophilic amination as outlined in Scheme 75 [190]. The reaction of several functionalized primary, secondary and tertiary organozinc bromides, benzylzinc bromide, functionalized arylzinc halides and one heterocyclic zinc bromide with DBAD afforded the corresponding derivatives BocRNNHBoc. Very high yields were obtained with most aliphatic substrates and good yields with aromatic substrates. Active zinc was used to prepare organozinc halides. Excellent functional group tolerance was also exhibited in the process, similar to other reactions mediated by organozinc reagents, which is a great advantage of this method.



Scheme 75. Organozinc halides as nucleophiles in the electrophilic amination

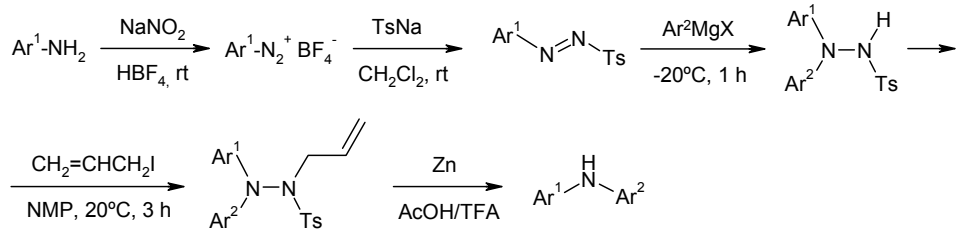
Sato *et al* used allenyltitaniums as nucleophiles in the electrophilic amination reaction [191]. Successive treatment of propargylic carbonates or phosphates with a $Ti(O\text{-}i\text{-}Pr)_4/2i\text{-}PrMgCl$ reagent and dialkyl azodicarboxylates afforded α-hydrazinoalkynes in good yields as outlined in Scheme 76. The reaction proceeded with high chiral transfer if optically active allenyltitaniums were used.



Scheme 76. Synthesis of optically active α-hydrazinoalkynes

Knochel and Sapountzis demonstrated that arylazo tosylates $Ar^1N{=}NTs$ are excellent amination reagents [192]. The synthetic pathway is illustrated in Scheme 77. Arylazo tosylates are readily prepared from primary aromatic amines in a two-step consisting of a diazotation and subsequent reaction of the resulting diazonium tetrafluoroborates with sodium *p*-toluenesulfinate. These highly electrophilic substrates were obtained in overall yields of >80%. Under mild conditions (–20ºC) arylazo tosylates react with a variety of polyfunctional arylmagnesium halides prepared by an iodine-magnesium exchange reaction. The intermediate addition products were allylated in situ and the resulted products were treated with zinc in acidic media. This one-pot procedure furnishes polyfunctionalized diarylamines in overall yields 63–86%.

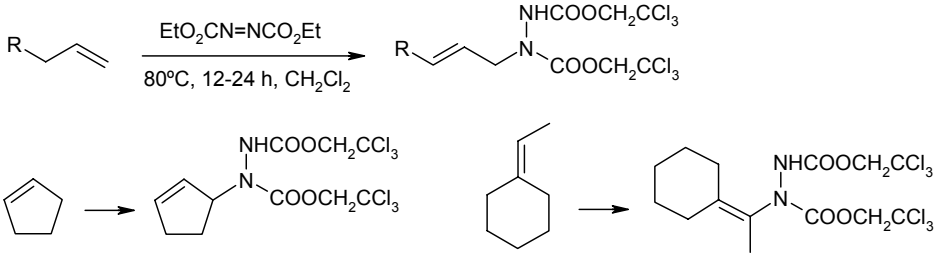
It is remarkable that addition of organometallics to the unsymmetrical azo compound is regiospecific. Steric hindrance was also not problematic, since in both the arylazo tosylates as well as in the Grignard reagent the presence of ortho substituent does not reduce the amination yield.



Scheme 77. Synthesis of diarylamines via electrophilic amination of arylazo tosylates

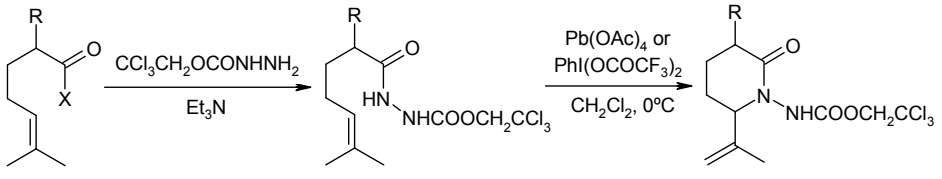
The ene reaction between ***alkenes*** and diethyl azodicarboxylate has been known for a long time [193, 194]. However, in most cases this process affords mixtures of adducts, thus lowering the yield of the desired product. Leblanc *et al* concluded that DEAD and similar azo compounds are not suitable for the selective transformation [195]. Therefore, bis(2,2,2-trichloroethyl)azodicarboxylate was chosen as a substrate and successfully employed in the ene reaction with alkenes (Scheme 78). The process has to be conducted at 80ºC in

benzene. A shift of the double bond was observed, yielding the corresponding 3-hydrazinoalkenes in high yields. For 1-methylcyclohexane a mixture of regioisomers was obtained, whereas with both 3-cyclopentene and ethylidenecyclohexane as substrates a high selectivity was observed to provide predominantly the more substituted alkene as shown in Scheme 78.



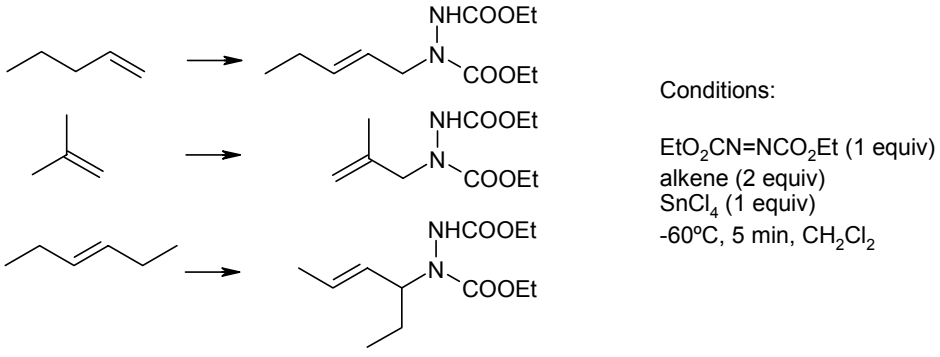
Scheme 78. Reaction of bis(2,2,2-trichloroethyl)azodicarboxylate with alkenes

In the further studies, Leblanc *et al* reported the intramolecular version of the same reaction as demonstrated in Scheme 79 [196]. Azo compound, obtained on the oxidation step, is not isolated and immediately react, giving the corresponding cyclic adduct in high yield.



Scheme 79. Intramolecular ene reaction

Heathcock and Brimble managed to run this process successfully even with diethyl azodicarboxylate [197]. Lewis acid was used to mediate the ene reaction with alkenes. The transformation was perfomed under mild conditions as shown in Scheme 80. High yields were obtained with all substrates and a shift of the double bond was observed as a result of the reaction.



Scheme 80. Lewis-acid-mediated reaction of DEAD with alkenes

Brimble and Lee designed and synthesized a chiral substrate for the ene reaction [198]. Structure of di-(-)-(1R,2S)-2-phenyl-1-cyclohexyl diazenedicarboxylate is depicted in Figure 8. The compound reacted with alkenes, affording the corresponding products in high yields and with high diastereomeric excess.

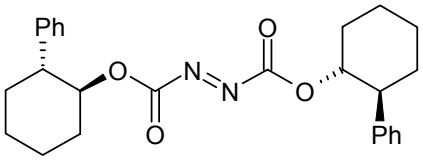
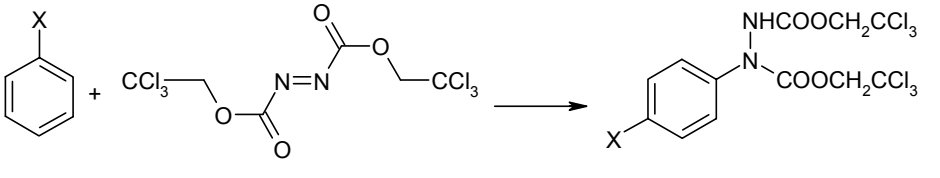


Figure 8. Structure of di-(-)-(1R,2S)-2-phenyl-1-cyclohexyl diazenedicarboxylate.

Leblanc *et al* described the amination of electron-rich ***arenes*** by an electron-deficient azodicarboxylates such as bis(2,2,2-trichloroethyl)azodicarboxylate [199]. The amination reactions were conducted in 3 M lithium perchlorate-diethyl ether or acetone solution as shown in Scheme 81. The process yields exclusively the para-isomer. However, with less-reactive substrates such as anisole, the amination required heating for several hours, whereas with poorly reactive compounds like xylene the formation of the desired the product was not observed in all.

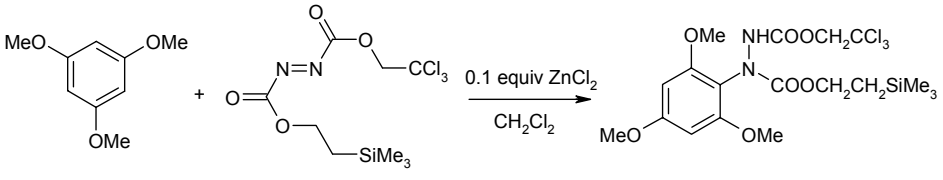


Scheme 81. Amination of arenes with bis(2,2,2-trichloroethyl)azodicarboxylate

In a short while, Leblanc and Mitchell developed more efficient protocol for the amination of arenes, using a catalytic amount of Lewis acids such as ZnI_2, $ZnCl_2$, $BF_3{\cdot}Et_2O$ in CH_2Cl_2 [200]. Under these conditions, even substrates containing both electron-withdrawing and electron-donating groups can be aminated with bis(2,2,2-trichloroethyl)azodicarboxylate in high yields. Monohydrazide compounds were produced from this process probably due to deactivation of aromatic ring by hydrazide group and preventing further amination. Besides simple arenes, both indole and 2-methylindole are compatible with the protocol, affording the corresponding 3-hydrazido compounds.

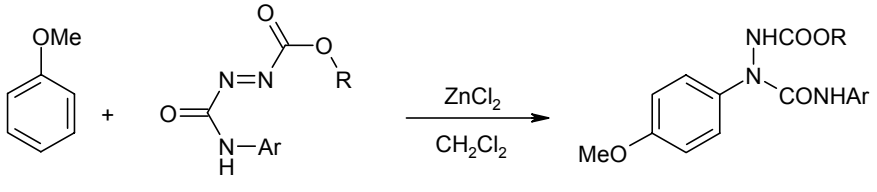
Also, it has been found that CF_3SO_3H and CF_3COOH are powerful catalysts for the amination of electron-rich arenes [201]. In presence of 3 equiv of bis(2,2,2-trichloroethyl)azodicarboxylate, a bisaminated product was obtained from anisole.

In addition to this, Leblanc and Mitchell reported an amination of arenes with an unsymmetrical 2-(trimethylsilyl)ethyl 2,2,2-trichloroethyl azodicarboxylate as outlined in Scheme 82 [200]. It was supposed that 1,3,5-trimethoxybenzene adds selectively to the more electron-deficient nitrogen of the azo reagent to yield only one hydrazide product. However, it seems there is no any satisfacting explanation for this unusual regiospecifity.



Scheme 82. Amination with 2-(trimethylsilyl)ethyl 2,2,2-trichloroethyl azodicarboxylate

Polanc *et al* synthesized several alkyl arylaminocarbonyldiazenecarboxylates ArNHCON=NCO_2R and employed these compounds in the amination of arenes [202]. The amination process was completely regioselectivive in respect to both reactants; the nitrogen atom, vicinal to the amide functionality of unsymmetrical azo compound, always attacked *para*-position in the anisole as demonstrated in Scheme 83. Amination was also performed with other arenes, affording the same regioselectivity.



Scheme 83. Amination with alkyl arylaminocarbonyldiazenecarboxylates

In addition to the catalysts mentioned above, other compounds were used to mediate similar reactions [203–206]. Catalytic amount of scandium triflate $Sc(OTf)_3$ promoted amination of a variety of arenes, including those which does not contain electron-donating group [203]. Trifluoroacetic acid catalyzed the reaction of $EtO_2CN{=}NCO_2Et$ with *p*-xylene and mesitylene. A mixture of CF_3COOH and triflic acid was especially efficient, allowing to perform amination even with electron-poor arenes such as dichlorobenzene and N-phenylphtalimide [204]. 4-Chlorobenzenesulfinic acid sodium salt reacted with TrocN=NTroc under the catalysis of triflic acid [205]. Amination of electron-rich arenes with $EtO_2CN{=}NCO_2Et$ can also be promoted with microwave irradiation in the presence of $InCl_3$-SiO_2 catalyst [206].

2.9. The new methodology in the synthesis of hydrazines

2.9.1. Hydrazine precursor – what is there so wonderful about it?

The age of the so-called "new methodology" of the synthesis of multi-substituted hydrazines started in 1996 when Mäeorg and Ragnarsson published their first work on triprotected precursors [32, 207]. Hydrazine precursor (or reagent) is a hydrazine derivative containing a combination of orthogonal protecting groups. The conception of orthogonality means that the protecting groups can be cleaved selectively one by one [208]. As demonstrated in Figure 9, normally such a precursor contains three protecting groups and only one NH hydrogen.

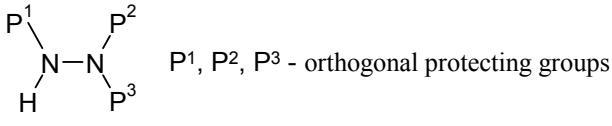
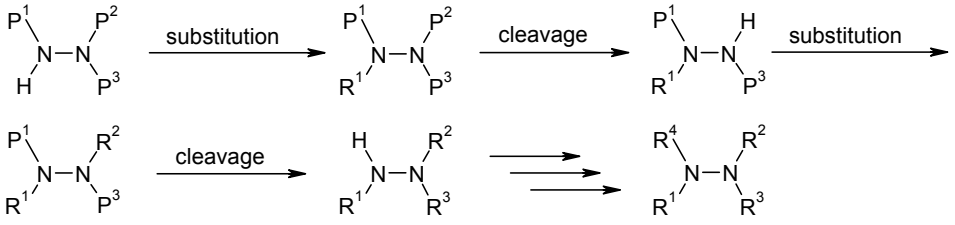


Figure 9. Structure of a hydrazine precursor

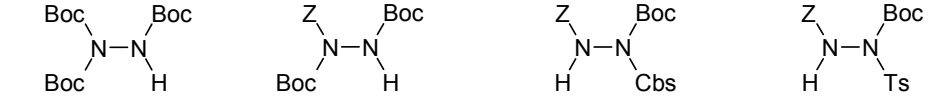
The NH-nitrogen is a reaction center for any appropriate type of substitution such as N-alkylation, N-acylation or N-arylation. If then one protecting group could be removed selectively from the intermediate, another hydrogen atom is set for the next substitution as illustrated in Scheme 84. After this systematic sequence of substitution-cleavage reactions has been performed, a tetra-substituted hydrazine derivative with four different substituents is obtained. This is how the methodology of stepwise synthesis works.



Scheme 84. Stepwise synthesis of a substituted hydrazine

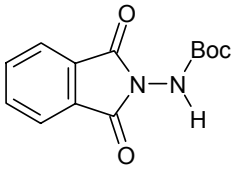
There is a number of amino protecting groups which found use in the stepwise synthesis of multisubstituted hydrazines, e.g. Boc, Z, Ts, Pht. These groups can be introduced and cleaved under rather mild conditions [208, 209]. At the same time it is possible to design a feasible orthogonal combination of them. Several hydrazine precursors, developed in the last decade, are shown in Figure 10. The precursors, white crystalline compounds with perfect shelf stability, are readily prepared from commercially available starting materials.

All of these valuable synthetic tools were involved in the preparation of a variety of multisubstituted hydrazines with excellent results [32, 210–222]. For the comparison, a monoprotected Zwierzak' reagent is also brought out in Figure 10.

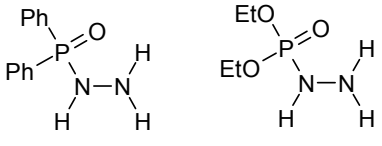


U. Ragnarsson and U. Mäeorg [32, 210-212]

U. Ragnarsson, L. Grehn *et al* [213-217]



B. Jamart-Gregoire *et al* [218-222]



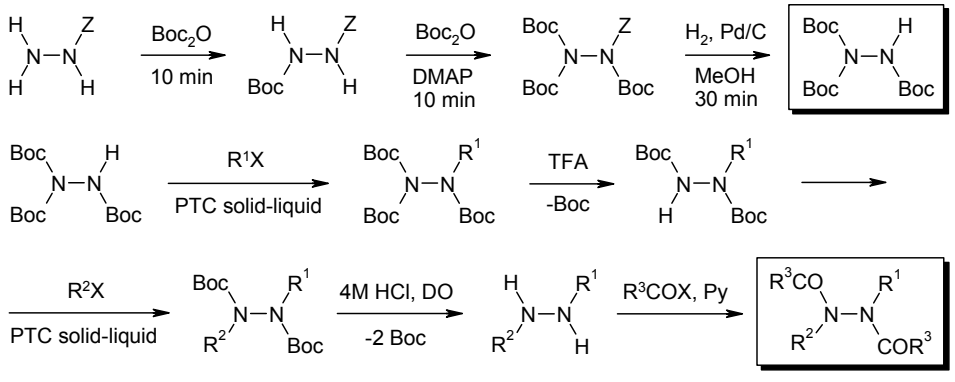
A. Zwierzak *et al* [43, 44]

Figure 10. Triprotected hydrazine precursors

2.9.2. Alkoxycarbonyl NH-protection

2.9.2.1. Introduction of alkyl- and acyl substituents

As already mentioned, in 1996 Mäeorg and Ragnarsson reported a new method for the synthesis of tetrasubstituted hydrazines [32]. Following this aprroach, it was possible to introduce three different substituent into the hydrazine molecule. The synthetic pathway starts with the preparation of hydrazine presursor – 1,1,2-tris(*tert*-butoxycarbonyl)hydrazine as shown in Scheme 85. The precursor is readily obtained in high overall yield.



Scheme 85. Synthesis of 1,1,2-tris(*tert*-butoxycarbonyl)hydrazine and its use

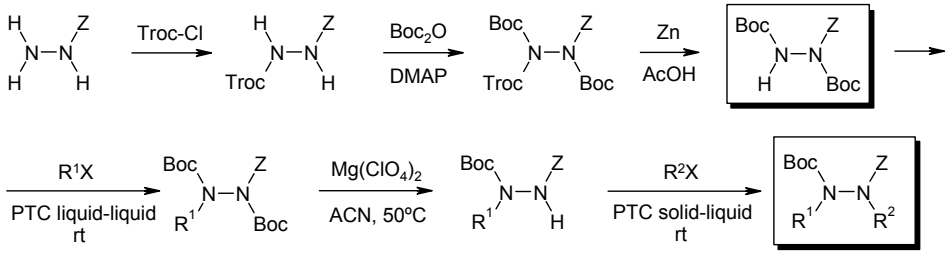
Phase transfer catalysis ($NaOH/K_2CO_3/TBAHS/C_6H_6$) was used to promote efficient N-alkylation of the precursor with primary alkyl halides (R^1 = Me, *n*-C_6H_{13}, Bzl, *p*-$NO_2C_6H_4CH_2$). The desired alkylation products were obtained in excellent yields. 2,4-$(NO_2)_2C_6H_3Cl$ and dansylchloride (dansyl i.e. 5-(dimethylamino)naphtalene-1-sulfonyl) were also successfully employed for N-derivatization under the same conditions.

Next step is crucial to the whole synthetic sequence. The key point is that the protecting Boc-groups are not identical. Two Boc-groups attached to one nitrogen atom are far more labile under cleavage conditions in comparison to a single Boc-group with no vicinal acyl neighbours. Therefore, it is possible to selectively cleave one Boc from $N(Boc)_2$ moiety with trifluoroacetic acid. As a result, another substitution site is available. Two remaining two Boc-groups, one on each nitrogen, are fully equivalent and can be removed only simultaneously. It is important that all the reaction steps proceed at room temperature and with high yields.

In a short while, Mäeorg and Ragnarsson designed alternative triprotected precursor 1,2-Boc_2-2-Z-hydrazine [210, 211]. This compound contains two Boc-groups, which are orthogonal to each other, and a Z-group, which is

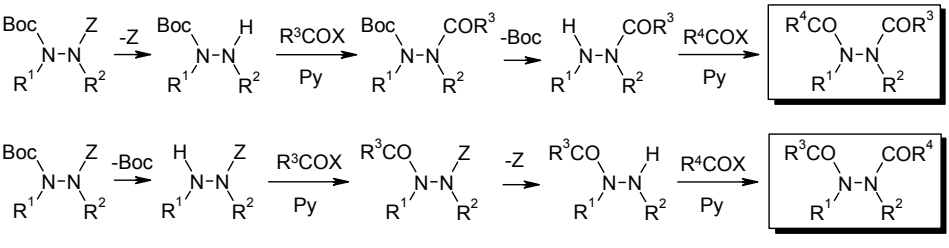
orthogonal to both Boc-groups. Thus all the protecting groups are orthogonal. Three-step preparation of the precursor is outlined in Scheme 86. The obtained compound is quite sensitive to base. In order to derivatize the precursor, it was alkylated under mildest possible, liquid-liquid PTC conditions (10–20% aq. NaOH/TBAHS/C_6H_6). The N-alkylation products were afforded in high yields (R^1 = Me, Bzl, $EtOCOCH_2$, CH_2=CH-CH_2, 2,4-$(NO_2)_2C_6H_3$, 2,4-$(NO_2)_2$-FC_6H_2, 4-$NO_2C_6H_4CH_2$, *n*-C_6H_{13}).

Catalytic amounts of $Mg(ClO_4)_2$ in ACN were sufficient to promote a smooth selective removal of one Boc-group from BocR^1NNBocZ. This method was recently applied for cleavage of *tert*-butyl imidodicarbonates and *tert*-butyl acylcarbamates [223] and worked perfectly on the corresponding hydrazine derivatives. After the selective Boc-removal, N-alkylation was performed under PTC conditions (R^2 = Bzl, Me, $EtOCOCH_2$, 4-$NO_2C_6H_4CH_2$, 2,4-$(NO_2)_2C_6H_3$).



Scheme 86. 1,2-Boc_2-2-Z-hydrazine as a precursor for multisubstituted hydrazines

The obtained BocR^1NNR^2Z contain two orthogonal groups, which can be cleaved in optional order as demonstrated in Scheme 87.



Scheme 87. Synthesis of tetrasubstituted hydrazines

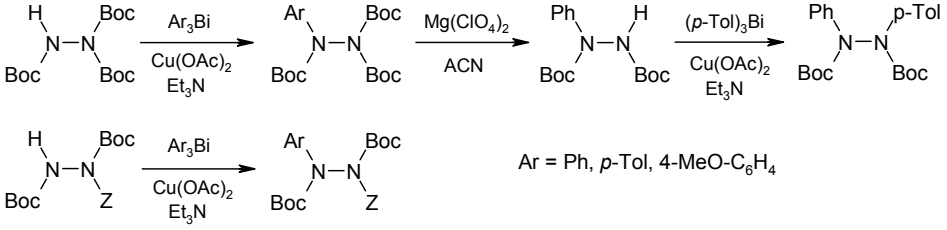
As a result, tetrasubstituted hydrazines with four different substituents were prepared in high yields (R^3CO, R^4CO = Ac, PhCO).

It is important that both 1,1,2-Boc_3-hydrazine and 1,2-Boc_2-2-Z-hydrazine undergo Michael addition with acrylonitrile CH_2=CHCN in the presence of basic catalyst [211].

2.9.2.2. Introduction of aromatic substituents

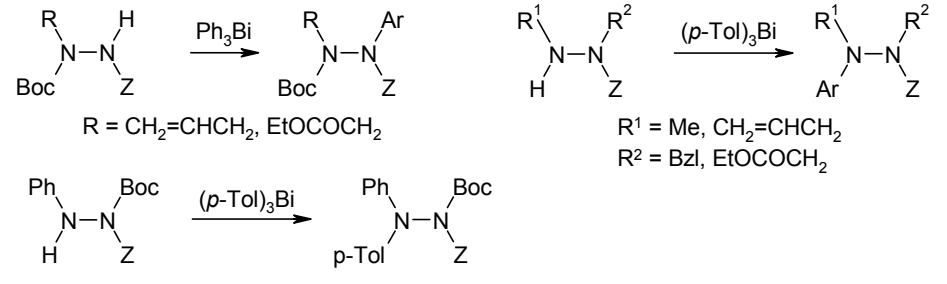
The above described synthetic methodology was tested on both 1,1,2-triBoc-hydrazine and 1,2-diBoc-1-Z-hydrazine for stepwise introduction of aromatic substituents into hydrazines [212]. In order to perform copper-mediated N-arylation with triarylbismuthanes, a versatile protocol developed by Chan was chosen [136]. In the beginning, the reaction of 1,1,2-triBoc-hydrazine with triphenylbismuthane was optimized in respect to the temperature and the stoichiometry of reagents and catalyst. As a result, the mole ratio 1.5/1.5/1.5 for the system $Ph_3Bi/Cu(OAc)_2/Et_3N$ was established. Refluxing the reagents in dichloromethane decreased the reaction time to 6 h in comparison to 23 h at room temperature.

Using these optimized conditions, a variety of hydrazine derivatives were arylated to give the corresponding monoarylated products as demonstrated in Scheme 88. No side products were detected and full conversion resulted in excellent yields.



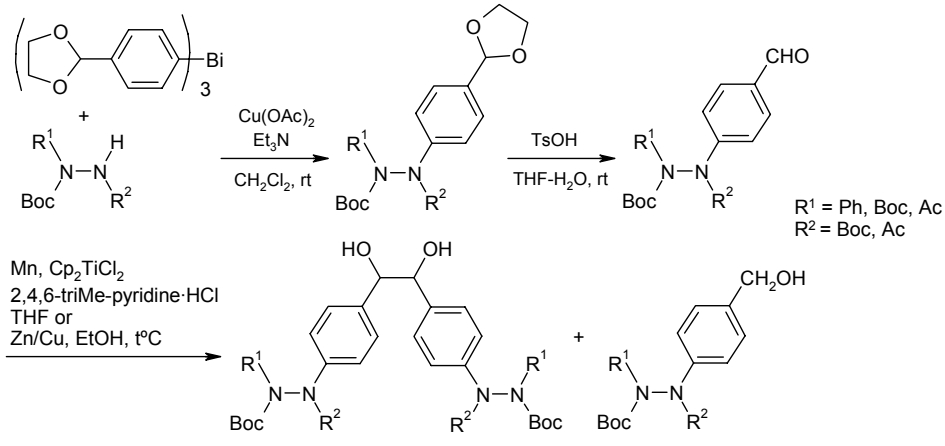
Scheme 88. N-arylation of triprotected precursors

In addition to the carbamate BocNH and ZNH arylation, the reactions were also performed on both amine and amide functions as demonstrated in Scheme 89. Excellent yields were obtained for all the substrates.



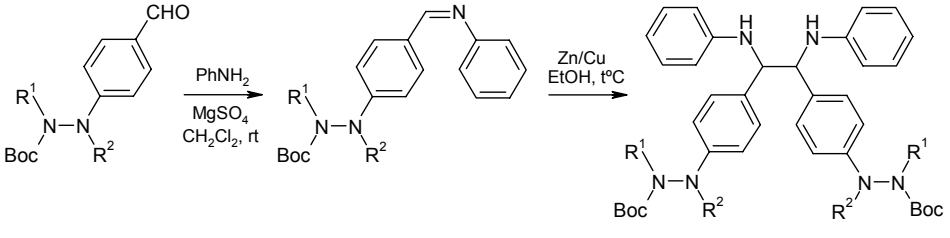
Scheme 89. N-arylation of trisubstituted hydrazine derivatives

Mäeorg and Loog have extended the stepwise substitution strategy with direct introduction of arylaldehyde functionality as outlined in Scheme 90 [145]. The preparation of the protected triarylbismuthane was already described in Section 2.7.3. Arylation of hydrazines $BocR^1NNHR$ was performed under mild conditions in the presence of $Cu(OAc)_2$ and Et_3N, affording the corresponding tetrasubstituted derivatives in high yields. The reaction time was in range from 28 h to 52 h. Acetal group removal was accomplished by treatment with catalytic amounts of *p*-toluenesulfonic acid in THF-water mixture. Under these conditions, the Boc group was not affected. Subsequent treatment with Zn/Cu in ethanol under heating resulted in the reduction of the aldehyde. In order to perform the pinacol coupling, the reductive system Mn/Cp_2TiCl_2 was used. The corresponding diols were obtained in moderate yields and with moderate to good diastereoselectivity.



Scheme 90. Synthesis and reactions of 4-formylphenylhydrazines

Formylarylhydrazine derivatives were converted into the corresponding phenylimines, which were coupled into diamines as shown in Scheme 91. However, no diastereoselectivity was observed.



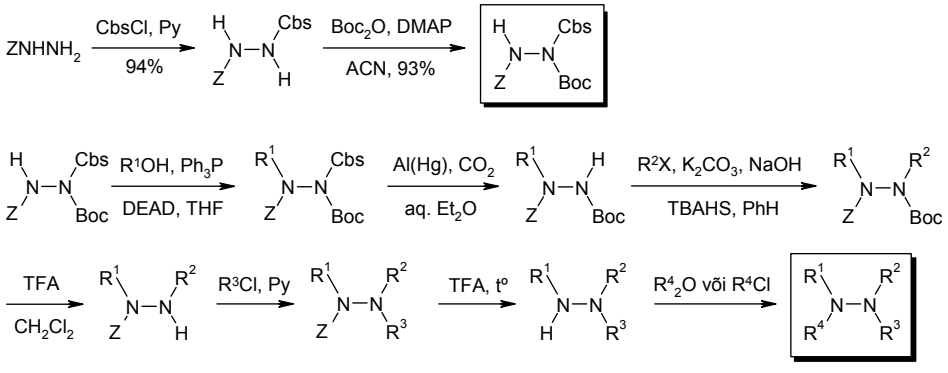
Scheme 91. Phenylimine derivatives of 4-formylphenylhydrazines

2.9.3. Sulfonyl protection

2.9.3.1. Introduction of alkyl- and acyl substituents

In continuation of efforts aiming at the systematic synthesis of multisubstituted hydrazines, Ragnarsson *et al* developed two additional hydrazine precursors, containing three different protecting groups [213, 214]. The first orthogonal combination included Z, Boc and Cbs [213]. In order to prepare such compound, Z-hydrazine was at first converted into disubstituted CbsNHNHZ with two amide functions. This allows regioselective reaction with Boc_2O at the sulfonamide nitrogen to afford the desired product as shown in Scheme 92.

The obtained triprotected precursor was subject to alkylation with alcohols under Mitsunobu conditions (R^1 = Bzl, 4-$ClC_6H_4CH_2$, (S)-EtMeCHCH$_2$, 4-$MeOC_6H_4CH_2$). The Cbs group can be cleaved under treatment with Hg-activated aluminium. The second alkylation step was accomplished under phase transfer conditions (R^2 = Me, CH_2COOEt, 2,4-$(NO_2)_2C_6H_3$, 2,4-O_2N-$C_6H_3CH_2$).

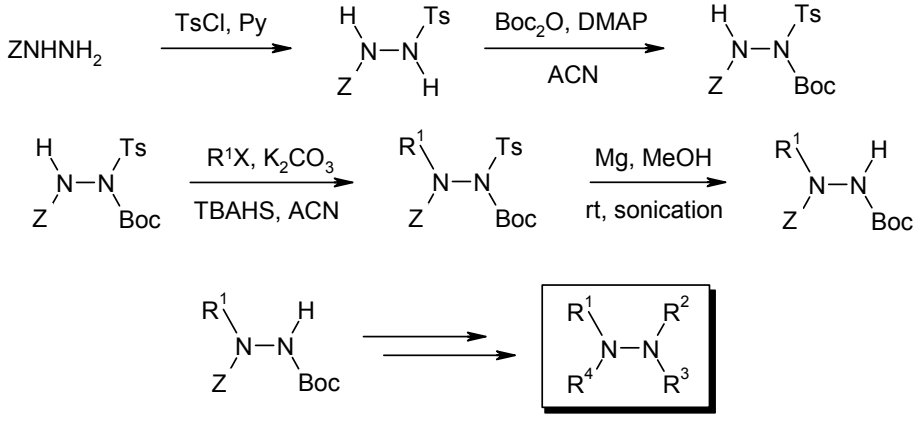


Scheme 92. Synthesis of tetrasubstituted hydrazines via sulfonyl protection

Several tetrasubstituted hydrazines with four different substituents such as two alkyl- and two acyl groups (R^3 = PhCO, 4-FC_6H_4CO, BuCO, $C_{10}H_7CO$; R^4 = Ac, $ClCH_2CO$, 4-$FC_6H_4SO_2$) were synthesized using this precursor.

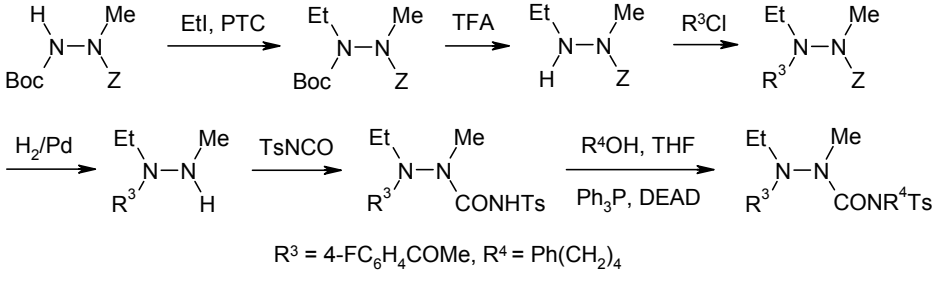
In 1997, a new cleavage method [224] for tosyl group was reported. Under sonication, magnesium in methanol successfully removed tosyl from RCONTs moiety. This remarkable find allowed using tosyl instead of Cbs. This led to the design and synthesis of the next precursor, as demonstrated in Scheme 93. The new hydrazine reagent is readily available by a convenient three-step route. The selective acylation of ZNHNHTs by Boc_2O is evidently due to the fact that the more acidic sulfonamide NH reacted preferentially. The obtained precursor could be alkylated with MeI, BzlBr or $EtOCOCH_2Br$ under very mild PTC conditions. Both alkylation and the subsequent detosylation gave almost

quantitative yields of the corresponding R^1ZN-NHBoc, which in turn could be used in the synthesis of multisubstituted hydrazines by already known protocols.

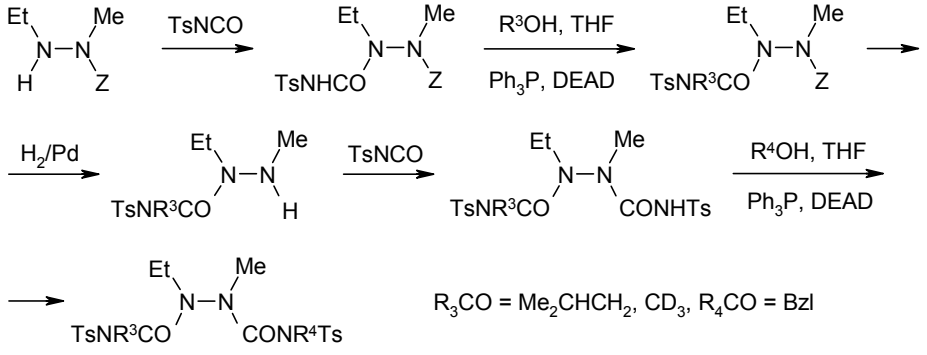


Scheme 93. Synthesis of 1-Z-2-Boc-2-Ts-hydrazine and its applications

From the above described precursor 1-Z-2-Boc-2-Ts-hydrazine, multisubstituted urea derivatives of hydrazines were synthesized as shown in Schemes 94 and 95 [215]. All the steps proceeded with high yields of the desired products.



Scheme 94. Synthesis of urea derivatives of hydrazines



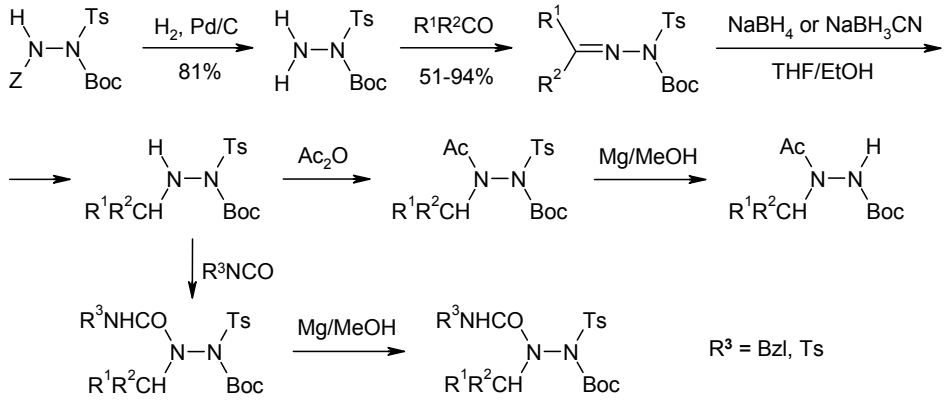
Scheme 95. Synthesis of urea derivatives of hydrazines

Ragnarsson *et al* has also demonstrated that the approach has applications in the synthesis of the library of multisubstituted hydrazines [216]. The same precursor 1-Z-2-Boc-2-Ts-hydrazine was employed in combinatorial studies, involving substitutions under competition conditions with various halides. The well-known variation in reactivity between different halides was reflected in a more-or-less product distribution. Hydrazine libraries containing up to nine components were prepared and characterized quantitatively.

It might be also important to notice that in addition to purely synthetic work, cyclic voltammetry measurements on a variety of hydrazine derivatives were carried out to study reductive removal of the sulfonyl protecting groups [225, 226]. It was found that 2-naphtalenesulfonyl moiety is cleaved by magnesium in methanol even more easily than a tosyl. Thus it can act as a useful substitute of a tosyl group for protection of amino functions.

2.9.3.2. Introduction of secondary alkyl substituents

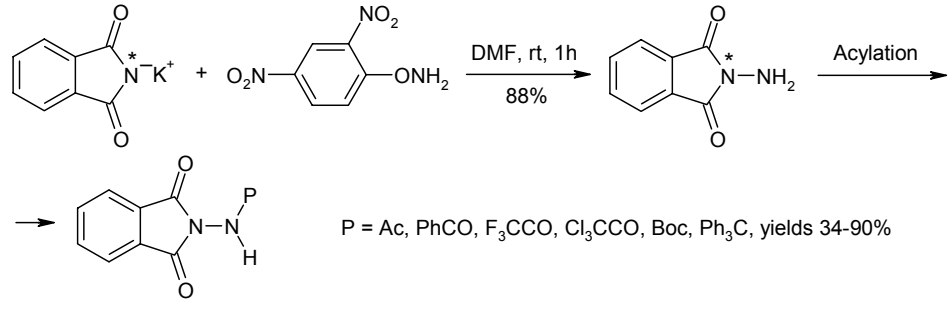
In addition to the introduction of primary alkyl and acyl groups, Ragnarsson and Grehn found another application for the precursor ZNHNTsBoc [217]. This compound was employed in the preparation of substituted hydrazines with a secondary alkyl group. As illustrated in Scheme 96, catalytic hydrogenolysis of the precursor furnished 1-Boc-1-Ts-hydrazine. It contains two orthogonal protecting groups and thus can be viewed as a new hydrazine reagent, designed specially for the Leuckart-Wallach approach. 1-Boc-1-Ts-hydrazine reacted with a representative set of the ketones to afford the corresponding ketones in high yields. The aliphatic hydrazones were readily reduced to hydrazines with $NaBH_4$, whereas the aromatic required more active $NaBH_3CN$. This method also allows to prepare various urea derivatives of hydrazines.



Scheme 96. Synthesis of hydrazines with secondary alkyl substituents

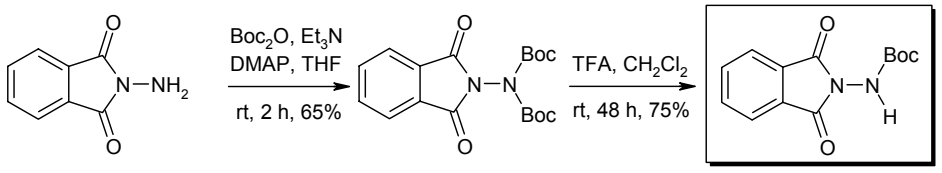
2.9.4. Phtalimide NH-protection

In 1998, Jamart-Gregoire *et al* synthesized a series of labelled *N*-(protected)aminophtalimides as illustrated in Scheme 97 [218].



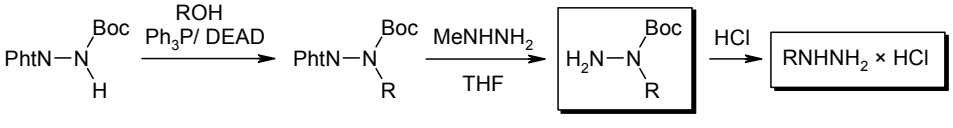
Scheme 97. Synthesis of N-(protected)aminophtalimides

As carbamates are extensively used as protecting groups for amines, it was attempted to find suitable conditions for the introduction of Boc group into N-aminophtalimide. However, neither $BocN_3$ nor BocCl afforded the desired product due to the side reactions. Successfull introduction of Boc group was achieved using Boc_2O as outlined in Scheme 98. Surprisingly, under these conditions the formation of the expected *N*-*tert*-butoxycarbonylaminophtalimide was never observed and only a derivative with two Boc groups was isolated. Therefore, TFA was used to remove one Boc group selectively.



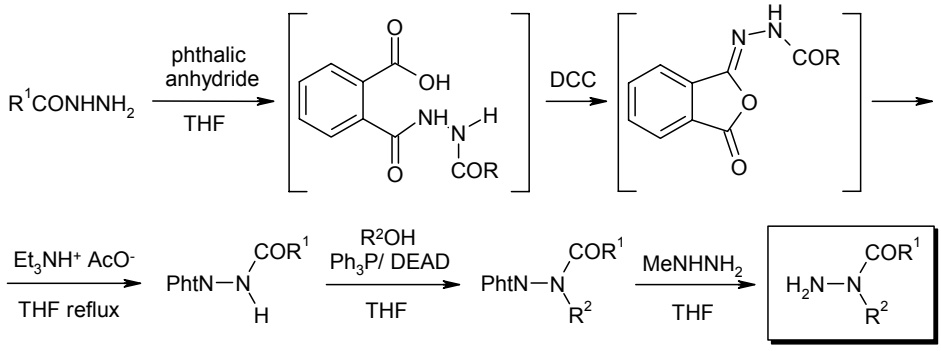
Scheme 98. Synthesis of *N-tert*-butoxycarbonylaminophtalimide

N-tert-butoxycarbonylaminophtalimide may be considered as a triprotected hydrazine since one could envisage that both the phtaloyl and the Boc groups may potentially be removed. Jamart-Gregoire *et al* demonstrated that this compound can be used as a versatile reagent for the synthesis of multisubstituted hydrazines [219]. The presence of three electron-withdrawing acyl groups increases the acidity of the hydrazinyl proton. At the same time, the incorporation of two of the three acyl groups into the phtaloyl moiety reduces steric hindrance. Therefore, an efficient two-step method has been developed for the conversion of alcohols to substituted hydrazines as shown in Scheme 99. The alkylation of *N-tert*-butoxycarbonylaminophtalimide was performed under Mitsunobu conditions, using both primary and secondary alcohols (R = Me, Bzl, CH_2=$CHCH_2$, *i*-Pr, cyclopentyl). Dephtaloylation was accomplished by methylhydrazine. As a result, 1-alkyl-1-Boc-hydrazines and monoalkylhydrazines were prepared in high yields.



Scheme 99. Synthesis of *N-tert*-butoxycarbonylaminophtalimide

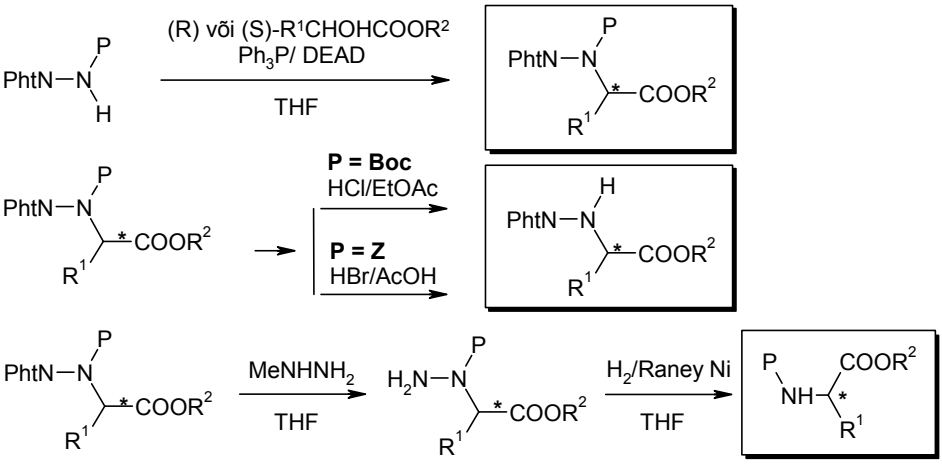
In a short while, Jamart-Gregoire *et al* suggested alternative convenient synthetic route for the preparation of a variety of N-acyl- and N-alkoxycarbonylaminophtalimides [220]. Commercially available hydrazides or carbamates were used as starting materials. The subsequent treatment with phthalic anhydride/DCC and triethylammonium acetate resulted in the formation of PhtNNHCOR in high yields as shown in Scheme 100. The obtained compounds were alkylated using the Mitsunobu protocol. Dephthaloylation readily afforded the corresponding 1-alkylhydrazides and 1-alkylcarbazates such as $BocR^2NNH_2$ and ZR^2NNH_2.



COR^1 = Boc, Z
R^1 = CF_3, Me, Ph, C_5H_4N, CHMeNHCbz, R^2 = Me, Bzl, *i*-Pr, Et, $(CH_2)_5Me$, $CH_2CH{=}CH_2$

Scheme 100. Synthesis of substituted hydrazines via phtaloyl protection

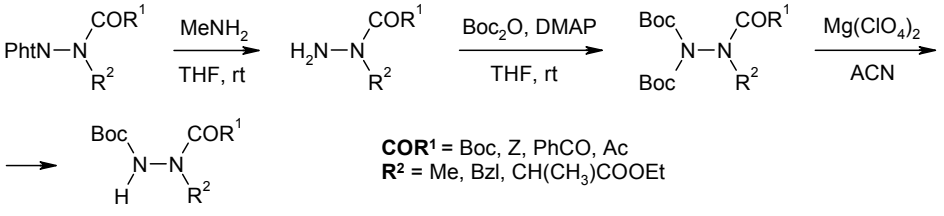
Current method was extended to include the preparation of chiral α-hydrazinoacid derivatives with high optical purity as shown in Scheme 101 [221]. Under Mitsunobu conditions, (R) and (S)-α-hydroxyesters reacted with N-alkoxycarbonylaminophtalimides, giving the corresponding products in high yields. Subsequent dephthaloylation with methylhydrazine afforded the protected α-hydrazino esters.



Scheme 101. Synthesis of chiral α-hydrazinoacid derivatives via phtaloyl protection

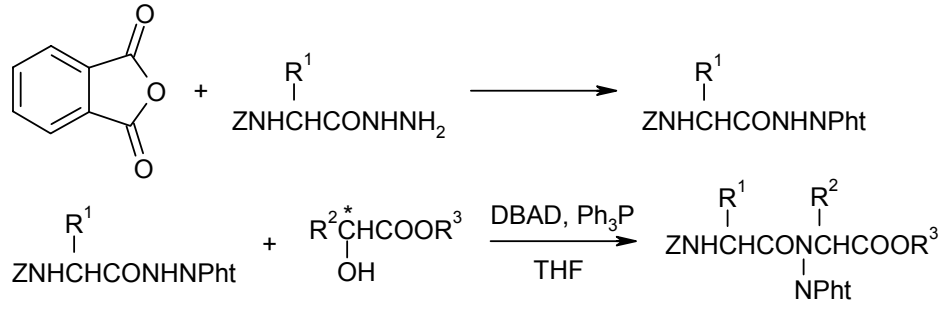
In order to determine the optical purity, Z protected α-hydrazino esters $PhtNNPCHR^1COOR^2$ (P=Z, R^1=Bzl) were subjected to hydrogenolysis in the

presence of Raney nickel. These conditions allowed simultaneous cleavage of the N-N bond, deprotection of the Z group, and transformation of the benzylester into the corresponding acid form. It was established that the conversion of the chiral α-hydroxyesters to the amino acids proceeded with complete inversion of configuration on the Mitsunobu reaction step. This is the first method, which enables the strictly systematic synthesis of chiral hydrazines.
Jamart-Gregoire and Brosse also reported an efficient one-pot protocol for the conversion of the phthaloyl group into bis-*tert*-butoxycarbonyl group under very mild conditions [222]. At first, phthaloyl protected hydrazine derivatives were subjected to deprotection with methylhydrazine as outlined in Scheme 102. Subsequently, Boc-groups were introduced by treatment with Boc_2O. To remove selectively one Boc group, catalytic amounts of magnesium perchlorate were used [223]. As a result, the protected hydrazines $BocNHNR^2COR^1$ were obtained in high to excellent yields. These compounds can be viewed as precursors to multisubstituted hydrazines.



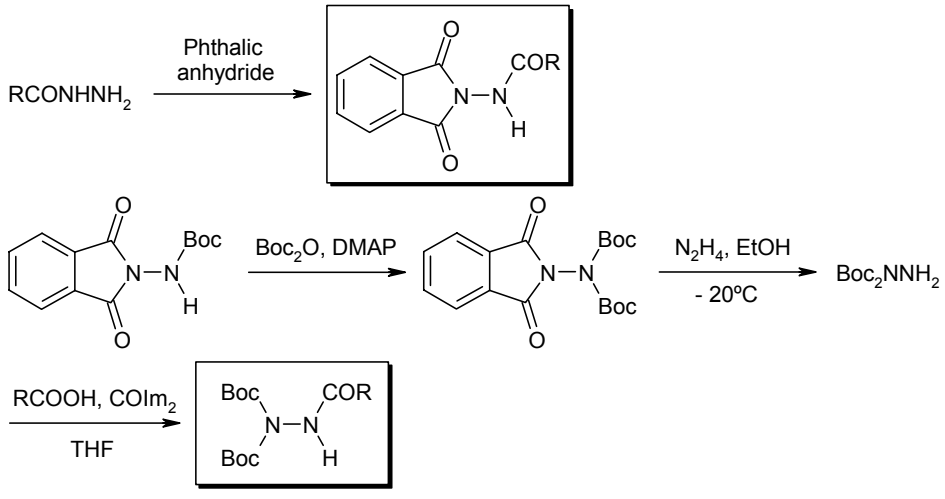
Scheme 102. Conversion of phthaloyl group into bis-*tert*-butoxycarbonyl group

N-protected phthaloylhydrazide amino acids [221] were used in further studies [227]. It was shown that the synthesis of *N*-phtalimidoamide pseudodipeptides can be performed by condensing these compounds with *a*-hydroxyesters via the Mitsunobu protocol. The reaction is outlined in Scheme 103.

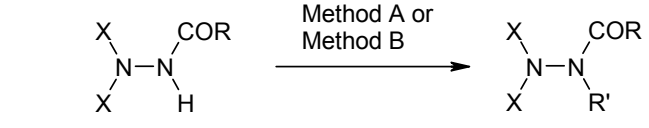


Scheme 103. Synthesis of *N*-phtalimidoamide pseudodipeptides

Alkylation reactions of trisubstituted hydrazines by Mitsunobu and PTC approaches were thoroughly investigated [228]. Starting compounds were prepared as outlined in Scheme 104. Subsequently, primary and secondary alkyl groups were introduced as shown in Scheme 105. It has been demonstrated that aminophtalimide derivatives are better acidic partners than their aminoimidodicarbonate ($NBoc_2$) analogues in both Mitsunobu and PTC protocols. Also, it seemed that PTC alkylation is more sensitive to steric hindrance than the Mitsunobu reaction.



Scheme 104. Synthesis of trisubstituted hydrazines



Method A: R'OH, DIAD, Ph_3P, THF, rt, 0.5 h

Method B: CH_3I or R'Br, K_2CO_3, $BzlEt_3NCl$, ACN, 50ºC

Scheme 105. Conversion of phthaloyl group into bis-*tert*-butoxycarbonyl group

It is important to notice that the above described phthaloyl protection was successfully applied in the solid phase synthesis of orthogonally protected chiral α-hydrazinoacids [229]. Also, several of N-protected phthaloylhydrazides aminoacides exhibited organogelation phenomenon [230].

3. AIMS OF THE STUDY

The main goals of the present thesis were:

1) To design a new hydrazine precursor, containing a combination of only two orthogonal protecting groups, to achieve selective substitution of one NH hydrogen and to evaluate the suitability of the reagent for the synthesis of multisubstituted hydrazines.

2) To contribute to the development of preparative methods for the synthesis of acidic hydrazines.

3) To study the diprotected precursor and its derivatives with respect to arylation by organobismuth reagents.

4) To study a set of mono-, di- and trisubstituted hydrazines with respect to arylation by organobismuth reagents with emphasis on scope and limitations, to explore the influence of sterical hindrance on the arylation process and to find out advantages of both pentavalent and trivalent reagents in hydrazines arylation.

5) To prepare a set of unsymmetrically substituted azo compounds, to study addition of diverse organometallic nucleophiles to these substrates and to develope new methods for introduction of secondary, primary and heteroaryl substituents into hydrazine molecule.

6) To combine a copper-catalyzed N-arylation process with addition to the N=N bond in both symmetrical and unsymmetrical azo compounds using aryl boronic acids as aryl source.

7) To combine a copper-catalyzed N-arylation process with addition to the N=N bond in both symmetrical and unsymmetrical azo compounds using organobismuth compounds as aryl source and to compare this reaction with the addition of aryl boronic acids.

4. RESULTS AND DISCUSSION

4.1. A new precursor for the synthesis of substituted hydrazines: design and applications

Design, synthesis and applications of various triprotected precursors P^1P^2N-NP^3H were described above in Section 2.9. These reagents contain orthogonal phthaloyl, alkoxycarbonyl-, or sulfonyl protecting groups, leaving only one hydrogen available for the substitution reaction. Plenty of multisubstituted hydrazines were prepared using those precursors. Completely systematic and selective reaction pathway is the obvious advantage of such methodological strategy.

On the other hand, three protecting groups demand three reaction steps for introduction and three additional steps for selective cleavage. This makes six steps in total owing to three protecting groups. No matter how high are the yield and the chemoselectivity, every step usually requires isolation and purification of all the intermediates. In other words, a lot of time is lost during the synthesis. Whether we are speaking about research work in laboratory or industrial scale in pharmaceutical industry, "time is money" (Benjamin Franklin).

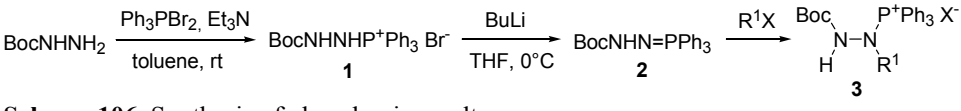
The design of a precursor with a lesser number of protecting groups presented considerable challenge. When this study was started, there were no reports on using diprotected precursors. Obviously, the key point is the selective substitution of only one hydrogen. We supposed that the selectivity could be provided by the significant differences in the nature of the protecting groups.

Triphenylphosphonium group was already used by Zimmer and Singh to conduct derivatization of several amines and hydrazines [60]. In contrast to many conventional protecting groups, this moiety possesses full positive charge. Therefore an NH moiety to which the triphenylphosphonium group is attached is more succeptible to base in comparison to ROCONH and $ArSO_2NH$. The deprotonation of Ph_3P^+NH occurs easily and leads to the formation of nucleophilic iminophosphorane.

We decided to design a precursor, containing a combination of alkoxycarbonyl and triphenylphosphonium groups. It should be pointed out that neither $PhCONHNHP^+Ph_3Br^-$ prepared by Schecter [69] nor $EtOCONHNHP^+Ph_3Br^-$ prepared by Froyen [72] was used in NH substitution reactions. *Tert*-butoxycarbonyl group was chosen because its usability in hydrazines synthesis has been already proven.

A new precursor $BocNHNHP^+Ph_3Br^-$ was prepared in a yield up to 87% from commercially available cheap starting materials such as dibromotriphenylphosphorane and *tert*-butoxycarbazate (Scheme 106). Unlike the preparation of other hydrazine reagents, only one step is required here to obtain the precursor **1**. Benzene and toluene were found to be the best solvents for the

transfromation. It is obvious that one cannot use toluene if dibromotriphenylphosphorane is to be prepared from bromine and Ph_3P. The formation of side product in substantial amounts was observed in dichloromethane [231]. According to NMR, this compound contains two identical triphenylphosphonium groups. The formation of $Br^-Ph_3P^+NHNHP^+Ph_3Br^-$ could be explained if the solubility of $BocNHNHP^+Ph_3Br^-$ in dichloromethane is taken into account. During the main reaction, $Et_3N{\times}HBr$ is generated. Triethylammonium hydrobromide can act as acid and cleave Boc group from the product $BocNHNHP^+Ph_3Br^-$, yielding $NH_2NHP^+Ph_3Br^-$. Free NH_2 reacts with unreacted dibromotriphenylphosphorane, forming $Br^-Ph_3P^+NHNHP^+Ph_3Br^-$. As $BocNHNHP^+Ph_3Br^-$ is not soluble in benzene, it completely precipitates from the reaction mixture, thus preventing Boc-cleavage.



Scheme 106. Synthesis of phosphonium salts

Because of the great difference in acidities of the NH hydrogens in $BocNHNHP^+Ph_3Br^-$, the phosphinimine $BocNHN{=}PPh_3$ is readily and selectively obtained by treatment with 1 equiv of butyllithium. The compound **2** does not need to be isolated. Therefore the alkylation was performed as a one-pot synthesis, affording phosphonium salts **3**, which precipitate from the reaction medium. In most cases the obtained products were pure by TLC and NMR. Also, an additional amount of product **3** can be precipitated by adding ethyl ether to the reaction mixture after filtration. However, this fraction is usually contaminated by triphenylphospine oxide and some polar side-product. The results are presented in Table 1.

Table 1. Alkylation of iminophosphorane $BocNHN{=}PPh_3$

N	RX	RX equiv	Addition of BuLi and RX, t°C	time h	Yield %	Total yield, % (includes product precipitated by ether)
1	BzlBr	1	0°C	24	58	–, oil
2	BzlBr	1	0°C	48	69	–, oil
3	BzlBr	1	0°C	72	69	–
4	BzlBr	1	0°C	48	77	–
5	BzlBr	1	0°C	2	51	66
6	BzlBr	1	0°C	24	72	–
7	BzlBr	1	0°C *	22	71	–
8	BzlBr	1	0°C* LDA	5	47	61
9	BzlBr	1	0°C *	5	64	76
10	BzlBr	1	0°C *	6	80	83

Table 1. Continuation

N	RX	RX equiv	Addition of BuLi and RX, t°C	time h	Yield %	Total yield, % (includes product precipitated by ether)
11	BzlBr	1	0°C *	6	77	83
12	BzlBr	1.1	0°C *	4	83	–
13	$BrCH_2COOEt$	1	0°C	20	67	85
14	$BrCH_2COOEt$	1	0°C	29	58	–
15	$BrCH_2COOEt$	1	0°C	43	64	–
16	$BrCH_2COOEt$	1	0°C *	6	78	84
17	$CH_2=CHCH_2Br$	1	BuLi at –70°C, then 1h stirring and RX at –70°C	24	56	–
18	$CH_2=CHCH_2Br$	10	BuLi at –70°C, then 1 h stirring and RX at –20°C	24	84	–
19	$CH_2=CHCH_2Br$	1	0°C	47	52	–
20	$CH_2=CHCH_2Br$	1	0°C	24	47	–
21	$CH_2=CHCH_2Br$	1	0°C *	21	60	67
22	$CH_2=CHCH_2Br$	1	0°C *	20	63	72
23	$CH_2=CHCH_2Br$	1	0°C *	7	68	71
24	$CH_2=CHCH_2Br$	1.1	0°C *	4	58	–
25	MeI	1	BuLi at –70°C, then 1h stirring and RX at –70°C	24	66	–
26	MeI	1	BuLi at –70°C, then 1h stirring and RX at –70°C	24 in total, 5 h at 50ºC	65	–
27	MeI	10	BuLi at –70°C, then 1 h stirring and RX at –20°C	24	65	–
28	MeI	1	0°C	42	70	92
29	MeI	1	0ºC	46	67	90
30	MeI	10	0°C	22	74	98
31	MeI	1	0°C	4	75	–
32	MeI	2	0°C	21	75	–
33	MeI	1	0°C	24	53	–
34	MeI	1	0°C *	21	68	75
35	$NO_2C_6H_4CH_2Br$	1	0°C *	22	50	66
36	$NO_2C_6H_4CH_2Br$	1	0°C *	22	62	79
37	n-BuI	1	0°C *	68	26	59
38	n-BuI	1	0°C *	50	33	68
39	n-BuI	10	0°C *	50	53	72
40	n-BuI	10	0°C *	50	67	82
41	n-BuI	10	0°C *	30	70	88
42	$HC\equiv CCH_2Br$	1	0°C *	7	68	73
43	$HC\equiv CCH_2Br$	1	0°C *	7	52	–
44	$HC\equiv CCH_2Br$	1	0°C * LDA	5.5	42	49
45	$HC\equiv CCH_2Br$	1	0°C *	6	63	–

* BuLi was added slowly during 30–50 min

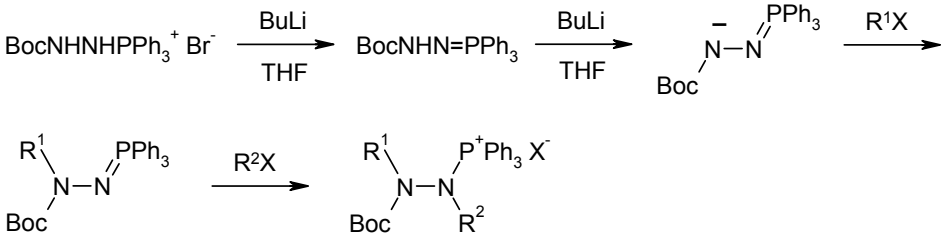
LDA was used instead of BuLi in the experiments **8** and **44**. In the experiments **28–30** ethyl ether was used instead of tetrahydrofuran to wash the precipitate on filter, resulting in the contamination of the product. In the experiments **28, 29, 31, 33** (methyl iodide), **19**, **20** (allylbromide) the reaction progress was monitored by GC. The composition of the gas phase was analyzed using the head-space technique. The most part of MeI had reacted during 2 h and the most part of CH_2=$CHCH_2Br$ had been consumed during 3–4 h. It was observed that a minor amount of alkyl halogenide always remains unreacted.

From the results presented in Table 1 it seems that the alkylation is never complete probably due to the minor decomposition of iminophosphorane during the reaction. Neither the yield nor the purity of the product **3** depends on the temperature of the BuLi addition. On the other hand, it is useful to add BuLi as slowly as possible (30–60 min). In order to avoid possible decomposition of iminophosphorane by BuLi, LDA was used as less nucleophilic base but no difference was obsrved.

Probably the lower steric hindrance of the methyl group enables the formation of the 1:1 TH solvate (calculated by intensities of signal of ^{1}H NMR spectra) in case of $BocNHNMeP^+Ph_3\ I^-$ since it was not observed in the case of other salts. Methyl iodide, benzyl bromide and ethyl bromoacetate were the most reactive alkyl halogenides. In order to obtain a good yield of butylated product, ten-fold excess of *n*-butyliodide has to be used. Secondary alkyl groups could not be introduced using the same procedure.

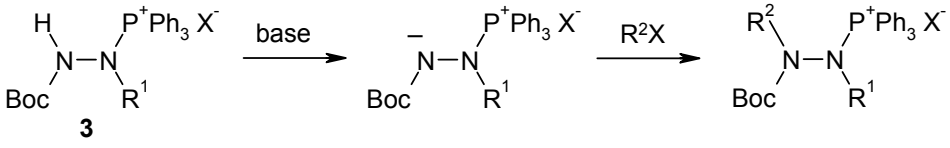
Methylation of $Br^-Ph_3P^+NHNHP^+Ph_3Br^-$, isolated as a side-product during the preparation of **1**, was performed under similar conditions. 2 equiv of BuLi were added to generate the diphosphorane Ph_3P=NN=PPh_3. Despite of it, the formation of $Ph_3P^+NHNMeP^+Ph_3\ 2X^-$ as THF solvate 1:1 was observed, which indicates that only one NH was deprotonated [231].

It is important to notice that we have also tried to use Barluenga approach [61] on the new precursor **1** as outlined in Scheme 107. Unfortunately these attempts failed probably due to the instability of deprotonated phosphinimine even at –80ºC.



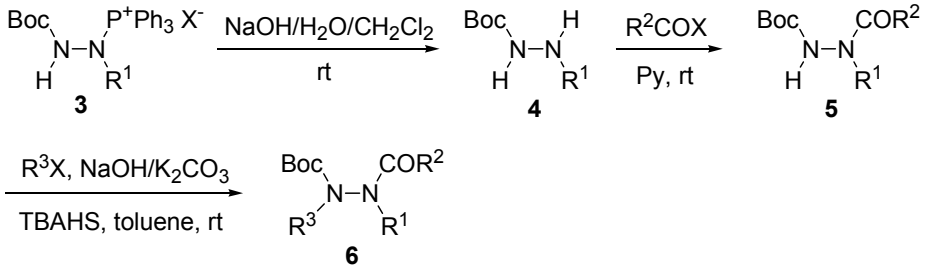
Scheme 107. Double alkylation of $BocNHNHP^+Ph_3Br^-$

We have also attempted to introduce another alkyl substituent into phosphonium salt 3 (Scheme 108). Treatment of **3** with BuLi in THF led to the decomposition of a half of the starting material. Attempts to perform alkylation in solid-liquid PTC system failed as well.



Scheme 108. Alkylation of the phosphonium salts $BocNHNR^1P^+Ph_3Br^-$

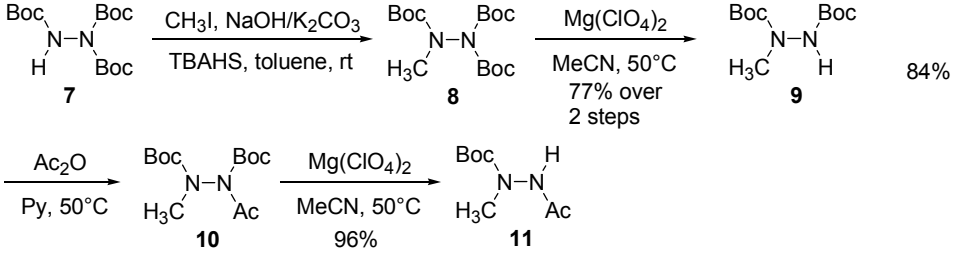
Nevertheless, we managed to find some use for the instability of the phosphonium salts **3**. In the earlier studies, removal of triphenylphosphonium group demanded several hours of heating with a strong base [60, 61]. We have found that compounds **3** can be deprotected within 2 min at room temperature in the system 2M $NaOH/CH_2Cl_2$. Probably the starting phosphonium salt acts as a phase transfer catalyst, which explains the unusually fast conversion. As a result, equimolar mixture of hydrazine **4** and triphenylphosphine oxide is obtained. Further this mixture can be acylated without prior separation into components (Scheme 109).



Scheme 109. Synthesis of hydrazine derivatives from phosphonium salts

The obtained compounds **5** can be further used for introduction of additional alkyl and acyl substituents according to already known methodology [32]. For instance, the compound **6** (R^3=allyl, R^2 = Me, R^1 = Bzl) was prepared in 87% yield by our standard PTC alkylation procedure. Deprotection of **6** with TFA and subsequent treatment with aqueous Na_2CO_3 afforded free amine $CH_2=CHCH_2NHNMeBzl$ (89%). The fourth substituent was introduced by benzoylation (PhCOCl/Py), furnishing tetrasubstituted hydrazine $CH_2=CHCH_2(PhCO)NNMeBzl$ in 70% yield [232].

It is important to emphasize that the selective substitution of the PNH hydrogen in reagent **1** is evident from the analysis of NMR spectra of products **3**. $^{3}J_{PH}$ and $^{2}J_{PC}$ values are in good agreement with previously reported experimental values [61]. To further demonstrate the regioselective alkylation of **1**, compound **11**, which is isomeric to **5a** (R^1=R^2=CH_3, BocNHNMeAc), was synthesized as illustrated in Scheme 110. The comparison of ^{1}H NMR spectra of **11** and **5a** confirm that they are isomers but not identical substances.



Scheme 110. Synthesis of BocMeNNHAc

This is the first time a diprotected precursor is described. The combination of *tert*-butoxycarbonyl and triphenylphosphonium group proved to be useful in the systematic methodology for the efficient synthesis of multisubstituted hydrazines. The NH hydrogens of the precursor are readily distinguished by base, which enables selective introduction of primary alkyl groups via phosphinimine. An extremely efficient method for removal of triphenyl-phosphonium groups is also found.

4.2. Acidic hydrazines

As described in Section 2.4, reactivity of a substrate often depends on its acidity. It was recently demonstrated that for imidodicarbonates and tosyl-carbamates there is a clear connection between their pK_a in DMSO solution and the yield of product in the Mitsunobu reaction [233]. In order to comprehend the behavior of substituted hydrazines, it would obviously be helpful to know their pK_a values. Bordwell *et al* have determined pK_a values for a variety of simple hydrazine derivatives except for N_2H_4 itself [234, 235].

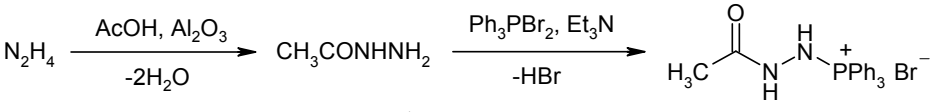
In Paper II, a number of di- and triprotected hydrazine reagents were prepared and their pK_a values were determined by potentiometric titration and quantum chemical calculations. Synthesis and acidity of several hydrazine derivatives is discussed below. The experimentally determined pKa values are brought in Table 2.

Table 2. pK_a values of several hydrazine derivatives

Compound	pK_a value
$BocNHNHP^+Ph_3Br^-$	9.9
$AcNHNHP^+Ph_3Br^-$	11.4
BocNHNHTf	8.2
$BocNHNHCOCF_3$	10.0
$CF_3CONHNH_3^+ CF_3COO^-$	16.6*

* pKa value corresponds to CF_3CONH proton.

Preparation of $BocNHNHP^+Ph_3Br^-$ was already described in 4.1. The pK_a value 9.9 corresponds to the most acidic proton in this compound, in other words $N\underline{H}P^+Ph_3$. Analogous substance $AcNHNHP^+Ph_3Br^-$ was obtained via similar reaction as illustrated in Scheme 111. At first, acetylhydrazine was prepared from hydrazine hydrate and acetic acid [28]. This reaction was catalyzed by aluminium oxide and proceeded with excellent yield. Due to the solubility problems, the reaction of acetylhydrazine with dibromotriphenylphosphorane was conducted in acetonitrile under inert atmosphere. The reaction was slow and afforded the desired compound in 48% yield. In comparison to $BocNHNHP^+Ph_3Br^-$ (pK_a = 9.9) this phosphonium salt $AcNHNHP^+Ph_3Br^-$ is a weaker acid (pK_a = 11.4).



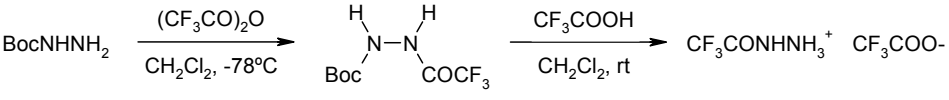
Scheme 111. Synthesis of $AcNHNHP^+Ph_3Br^-$

On the other hand, phosphonium salts may be viewed as disubstituted hydrazines and thus can be compared with similar derivatives, synthesized previously [214]. It seems that positively charged PPh_3^+ group makes these compounds more acidic than those with aromatic sulfonyl group such as TsNHNHBoc, BocNHNHCbs, BocNHNH(1-Ns), BocNHNH(2-Ns) (pK_a of those are in range 12.7–14.5). This confirms that the PPh_3^+ group has stronger electron-withdrawing properties. Presumably, it can better stabilize the zwitter-ionic species fromed on protolysis by electrostatic ion-ion interaction.

BocNHNHTf was synthesized according to the classical procedure of Hendrickson [82] as illustrated in Scheme 30. Recrystallization of crude product gave 1-*tert*-butoxycarbonyl-2-trifylhydrazine in 53% yield. Preparation of $BocNHNHCOCF_3$ was carried out analogously with the previous synthesis. As shown in Scheme 112, trifluoroacetic anhydride was used to acylate *tert*-butoxycarbazate in dichloromethane under inert atmosphere, affording

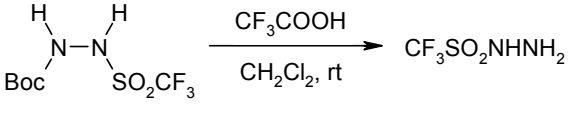
1-*tert*-butoxycarbonyl-2-trifluoroacetylhydrazine in 95% yield [236]. The pK_a values of both BocNHNHTf and $BocNHNHCOCF_3$ (respectively 8.2 and 10.0) are lower than those of disubstituted hydrazines with alkoxycarbonyl and sulfonyl group.

Deprotection of Boc-group by trifluoroacetic acid afforded derivative $CF_3CONHNH_2$ as trifluoroacetate in quantitative yield. It is important to notice that this monosubstituted hydrazine (pK_a = 16.6) is almost the same acidic as derivatives with three electron-withdrawing groups such as BocNHNTsBoc (pK_a = 16.0) and ZNHNTsBoc (pK_a = 15.5).



Scheme 112. Synthesis of 1-trifluoroacetyl-2-Boc-hydrazine and trifluoroacetylhydrazine

All attempts to synthesize $TfNHNH_2$ by similar reaction pathway have thus far been unsuccessful (Scheme 113). Possible reasons of instability have been discussed in recent publication [81].



Scheme 113. Failed synthesis of trifylhydrazine

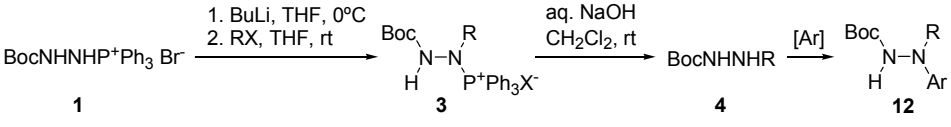
As we can see, experimentally determined pK_a values distinctly reflect structural features of substituted hydrazines. The compounds containing trifyl, trifluoroacetyl or triphenylphosphonium groups are of highest acidity among the hydrazine derivatives under study. It is also important that found pK_a values were used to estimate a rough value of pK_a of N_2H_4 in DMSO solution. Linear relationship between determined pK_a values and calculated GA values yielded the $pK_{a(DMSO)}$ of hydrazine = 36.0 ± 1. It indicates that N_2H_4 is by ca 5 units a stronger acid than ammonia.

4.3. Highly selective arylation of disubstituted hydrazines

In Paper I, we described a convenient diprotected hydrazine precursor $BocNHNHP^+Ph_3Br^-$ and demonstrated that various alkyl and acyl substituents could be introduced selectively. Recently, triarylbismuthanes were successfully used to arylate triprotected hydrazine precursors such as $BocNHNBoc_2$ and BocNHNZBoc [212], which induced us to investigate $BocNHNHP^+Ph_3Br^-$ in the same context.

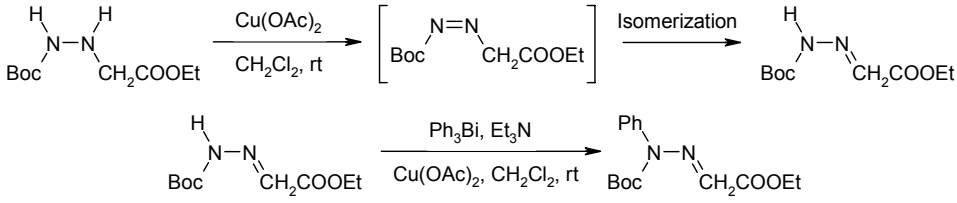
Unfortunately all attempts to arylate both the precursor $BocNHNHP^+Ph_3Br$ and obtained phosphonium salts $BocNHNRP^+Ph_3Br^-$ under Chan conditions have failed [136] due to the decomposition of the substrates. On the other hand, deprotection of phosphonium salts $BocNHNRP^+Ph_3Br^-$ easily yields disubstituted hydrazines BocNHNHR. Regioselective acylation of these compounds was already described in Paper I. Sorenson reported regioselective arylation of polyfunctional compounds, where amine and amide NH groups were clearly distinguished by arylative agent [137]. By analogy with Sorenson's results, selective arylation of compounds BocNHNHR could be expected.

A number of compounds **4**, required a starting materials, were obtained as illustrated in Scheme 114. Deprotection step afforded an equimolar mixture of **4** and Ph_3PO, which we used in the further experiments without prior separation.



Scheme 114. Arylation of BocNHNHR

At first, we tried to conduct arylation using trivalent bismuth compounds and stoichiometric amount of $Cu(OAc)_2$. Instead of arylation, we observed only slow oxidation of starting material $BocNHNHCH_2R^1$ into the corresponding hydrazone $BocNHN{=}CHR^1$. Then triethylamine was employed as promoter according to Chan protocol [136] ($Ar_3Bi/Et_3N/Cu(OAc)_2$ in molar ratio 1.5/1.5/1.5). Under these conditions both the oxidation and the N-arylation of the resulting hydrazone occurred. After 1 h, $BocNHNHCH_2COOEt$ gave 55% of hydrazone and 27% of arylation product as outlined in Scheme 115. Similar results were obtained with other substrates. Obviously, disubstituted hydrazines are oxidized by stoichiometric amount of copper (II) salt, demanded for N-arylation with Ar_3Bi. The oxidation yields intermediate azo compounds, which undergo rapid isomerization into hydrazones [237].



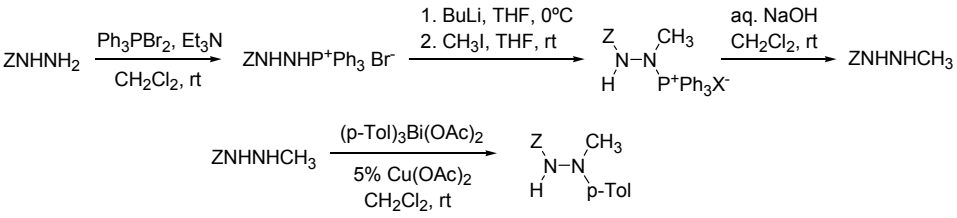
Scheme 115. Arylation of BocNHNHCH$_2$COOEt under Chan conditions

On the other hand, N-arylation with $Ar_3Bi(OAc)_2$ requires only catalytic amounts of $Cu(OAc)_2$. Apparent advantages of pentavalent over trivalent reagents were exemplified by successful arylation of compounds **4**. The reactions of BocNHNHR with 1.1 equiv of $Ar_3Bi(OAc)_2$ in the presence of 5% $Cu(OAc)_2$ were complete in 5–10 min at room temperature, affording the desired compounds **12** in high yields starting from the phosphonium salts **3** (Table 3). It is interesting that arylation eventually occurs without copper catalysis. However, in this case full conversion requires longer time or excess of bismuth reagent. Also, the reaction is tolerant to steric hindrance since excellent results were obtained upon the introduction of 1-naphthyl groups.

Table 3. Arylation of disubstituted hydrazines $R^1NHNHCOR^2$

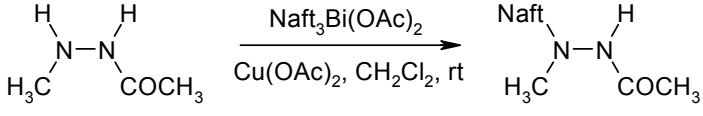
R^1	R^2CO	Ar	Yield %
$PhCH_2$	Boc	Ph	95
n-Bu	Boc	Ph	86
CH_3	Boc	1-Naphthyl	87
$HC{\equiv}CCH_2$	Boc	4-$CH_3C_6H_4$	93
$EtOCOCH_2$	Boc	4-$CH_3C_6H_4$	74
CH_3	Z	4-$CH_3C_6H_4$	82
CH_3	CH_3CO	1-Naphthyl	80
Boc	Boc	Ph	86

The next question is whether N-arylation of a disubstituted hydrazine bearing electron-donating or electron-withdrawing groups on either nitrogen is always regioselective? In order to study the scope of the reaction, a few other hydrazines substrates were tested under the same conditions. Phosphonium salt $ZNHNHP^+Ph_3Br^-$ was prepared analogously with the precursor 1, then methylated and deprotected to give $ZNHNHCH_3$ as outlined in Scheme 116. Arylation of the obtained disubstituted hydrazine furnished ZNHN(*p*-Tol)CH_3 as the only product.



Scheme 116. Synthesis of $ZNHNHCH_3$ and its arylation

To compare alcoxycarbonyl and acyl substituents, 1-acetyl-2-methylhydrazine was prepared by Condon's procedure [27] and also included in this study as an additional example of regioselective arylation (Scheme 117). NMR spectra of the product revealed E/Z isomers. As already known from earlier investigations, this phenomenon is quite typical for multisubstituted hydrazines [210, 211] and even for small hydrazine molecules such as starting 1-acetyl-2-methylhydrazine [238].



Scheme 117. Arylation of $AcNHNHCH_3$

Under these conditions, arylation of diacylated hydrazine BocNHNHBoc required Et_3N as a promotor and afforded the corresponding monoarylated product BocPhNNHBoc in 4h. In the absence of $Cu(OAc)_2$ the only product isolated from the reaction mixture was azo-compound BocN=NBoc. The formation of azo-compounds in the reaction of $Ph_3CNHNHPh$ and PhNHNHPh with Ph_3BiCO_3 has been reported earlier [116, 148] and obviously occurs here as well due to the dual nature of pentavalent bismuth compounds, behaving as arylation agents or oxidants. In the reaction of $R^1CONHNHR^2$ with $Ar_3Bi(OAc)_2$ only traces of hydrazones were detected by TLC, which means that N-arylation dominates over oxidation.

In summary, a convenient procedure for fast, smooth and clean N-arylation under very mild conditions is described. This highly selective protocol is compatible with disubstituted hydrazines of type $R^1NHNHCOR^2$.

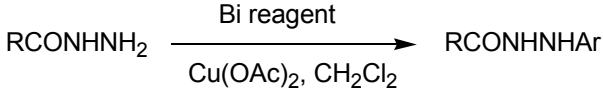
4.4. Arylation of diversely substituted hydrazines by tri- and pentavalent organobismuth reagents

In Paper III, we reported regioselective N-arylation of disubstituted hydrazines $R^1NHNHCOR^2$, derived from the precursor $BocNHNHP^+Ph_3Br^-$. Trivalent organobismuth reagents were unsuitable but could be replaced by pentavalent compounds $Ar_3Bi(OAc)_2$. On the other hand, in previous studies triarylbismuthanes were successfully used for N-arylation of triprotected precursors [212]. This compelled us to conduct a more scrupulous investigation of the scope of these two types of bismuth reagents with respect to arylation of diversely substituted hydrazines.

4.4.1. Arylation of monoacylhydrazines

Several monoacylhydrazines can be arylated under Cu or Pd catalysis [99, 100, 111], although the reactions are quite slow and require heating. By analogy with $R^1NHNHCOR^2$ (Paper III), it should be possible to arylate non-acylated nitrogen of $RCONHNH_2$ regioselectively.

Facile oxidation of hydrazides by copper compounds [239] makes it impossible to conduct N-arylation using the standard Chan procedure [136] with stoichiometric amount of $Cu(OAc)_2$. Therefore, we sought for alternative protocol that utilizes pentavalent organobismuth reagents as outlined in Scheme 118.



Scheme 118. Regioselective arylation of monoacylhydrazines

The results of optimization experiments are demonstrated in Table 4. The reaction between $(p\text{-Tol})_3Bi(OAc)_2$ and $BocNHNH_2$ occurs extremely rapidly at room temperature, producing a significant amount of azo-compound *p*-TolN=NBoc as a side-product. Substantial decrease of the temperature and the amount of copper catalyst has improved both yield and purity of the desired product. Further improvement of the procedure conditions was achieved by the addition of antioxidant BHT to the reaction mixture (entry 7). Except for entry 12 where 14% of azo-compounds were isolated, all remaining arylation experiments proceeded smoothly and only traces of side-products could be detected by TLC. The conversion was complete immediately after the addition of organobismuth reagent. No difference in both selectivity and reaction time was noticed with the bulky *o*-tolyl and 1-naphthyl bismuth reagents.

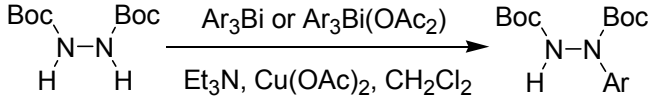
Table 4. Optimization experiments with $RCONHNH_2$ and $Ar_3Bi(OAc)_2$

Entry	RCO	Ar	$Cu(OAc)_2$, mol%	tºC	Yield, %
1[a]	Boc	*p*-Tol	5	rt	45
2	Boc	*p*-Tol	5	–84	51
3	Boc	*p*-Tol	2	–10	61
4	Boc	*p*-Tol	2	–50	75
5	Boc	*p*-Tol	20	–50	27
6	Boc	*p*-Tol	2	–91	74
7[b]	Boc	*p*-Tol	2	–60	91
8[b]	Boc	*p*-Tol	2	rt	56
9[b]	Boc	*o*-Tol	2	–60	80
10[b]	Troc	*o*-Tol	2	–60	91
11[b]	Ac	1-Np[d]	2	–60	72
12[b]	Z	An[e]	2	–60	72

[a] All $(p\text{-Tol})_3Bi(OAc)_2$ was added in one batch. In the other experiments, the solution of organobismuth reagent was added dropwise during 20–50 min. Experiments 5 and 7–12 were carried out under argon.
[b] 3% of BHT (2,6-di-*tert*-butyl-4-methyl-phenol; butylated hydroxytoluene) was added.

4.4.2. Arylation of disubstituted hydrazines

In Paper III, monophenylation of BocNHNHBoc with $Ph_3Bi(OAc)_2$ under Chan conditions was reported (4 h, 86%). Soon after we found out that Ph_3Bi gives somewhat better results (2 h, quantitative yield). A bulky 1-naphthyl group was also successfully introduced using Np_3Bi (3 h, 93%) as outlined in Scheme 119.



Scheme 119. Monoarylation of BocNHNHBoc

We decided to expand copper-catalyzed arylation of $R^1NHNHCOR^2$ with the examples including some bulky substituents such as *o*-tolyl and 2-methoxy-4-methylphenyl. As a result, several new compounds have been prepared in high yields (Table 5). Analogously with Paper III, yields are calculated over two steps starting from the corresponding phosphonium salts. The only exception was Entry 4 where we observed the formation of a side-product. Irrespectively of steric hindrance, conversion was complete in 5–10 min.

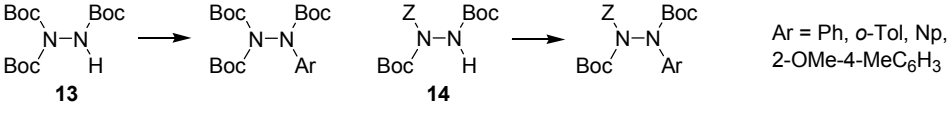
Table 5. Arylation of BocNHNHR[1] with $Ar_3Bi(OAc)_2$

Entry	Product	Yield, %
1	BocNHNMe(*o*-Tol)	86
2	BocNHNBu(*p*-Tol)	89
3	BocNHNBuAn	92
4	BocNHNBu(2-MeO-4-MeC_6H_3)	48

4.4.3. Arylation of trisubstituted hydrazines

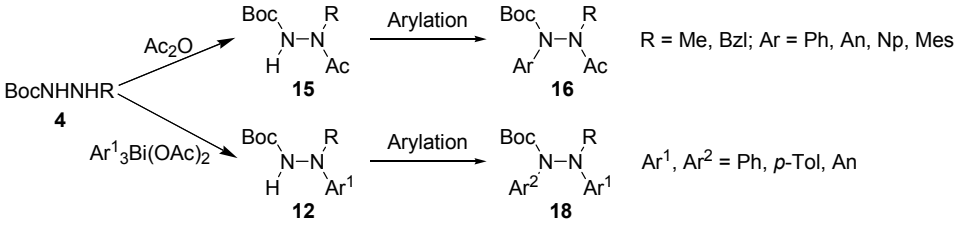
Although arylation of triprotected precursors **13** and **14** with triarylbismuthanes has been already described [212], no examples involving sterically hindered aryl groups and pentavalent organobismuth reagents have been presented. To find out whether $Ar_3Bi(OAc)_2$ offer some advantages over Ar_3Bi, precursors **13** and **14** were reacted with triphenylbismuth diacetate. Longer reaction times and lower yields (74–86% instead of quantitative yield) provide evidence in favour of triarylbismuthanes Ar_3Bi.

Introduction of bulky substituents such as *o*-tolyl and 1-napthyl was extremely slow at room temperature. After 4 days of stirring, only 26% of (*o*-Tol)BocNNBoc$_2$ was isolated form the reaction mixture. The situation changed drastically when reagents were refluxed in dichloromethane (~42ºC). Full conversion required 2–4 days, affording the corresponding *o*-tolyl, 1-naphthyl and 2-methoxy-4-methylphenyl derivatives in yields 73–100% (Scheme 120). Only the highly hindered Mes_3Bi (2,4,6-trimethylphenyl-bismuthane) failed to react completely, even at reflux. Gradual decomposition of Ar_3Bi in the reaction mixture was observed and thus compensated by additional amount of fresh reagent and catalyst.



Scheme 120. Arylation of triprotected precursors 13 and 14.

The next step was to study two less hindered substrates, derived from precursor BocNHNHP$^+$Ph$_3$Br$^-$ as demonstrated in Scheme 121. All reactions were conducted at room temperature and the results are brought in Table 6. A clear dependence of bismuthane reactivity upon steric hindrance was demonstrated when aryl bulkiness was gradually increased from p-anisyl to mesityl. In contrast to experiments with bulky precursor **13**, mesityl group was successfully introduced into hydrazine molecule.



Scheme 121. Arylderivatives originating from precursor $BocNHNHP^{+}Ph_3Br^{-}$

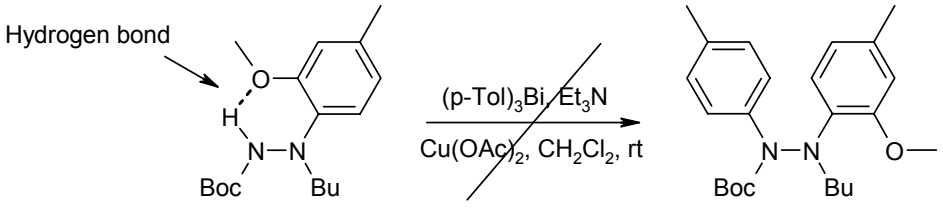
Table 6. Arylation of $BocNHNR^1Ac$ with bismuth reagents

Starting material	Arylating agent	Reaction time, h	Yield, %
BocNHNAcBzl	Ph_3Bi	9	93
BocNHNAcBzl	$Ph_3Bi(OAc)_2$	12	73
BocNHNAcBzl	Np_3Bi	46	51
BocNHNAcMe	An_3Bi	6	100
BocNHNAcMe	Np_3Bi	14	100
BocNHNAcMe	Mes_3Bi	20	56

The trisubstituted hydrazines **12** $BocNHNRAr^1$, described in Sections 4.3 and 4.4.2, could be also used as substrates in order to explore the synthesis of derivatives with two different aryl substituents (Scheme 121). Four compounds were studied with respect to arylation with triarylbismuthanes. The results are shown in Table 7. It seems that aromatic ring on the neighbouring nitrogen does not impede the arylation. However, one substrate completely failed to react with $(p\text{-Tol})_3Bi$ (Scheme 122). AM1 calculations were used to elucidate the reason of unreactivity. The afforded interatomic distance between methoxy oxygen and BocNH hydrogen indicated a possibility for a strong hydrogen bonding, which presumably block the access of triarylbismuthane.

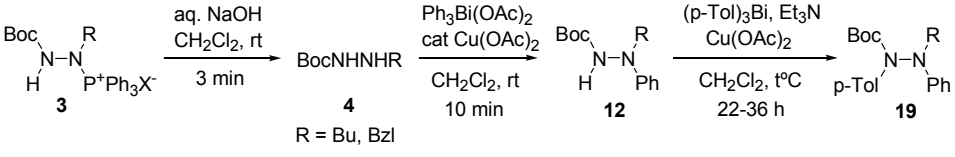
Table 7. Arylation of $BocNHNR^1Ac$ with bismuth reagents

Starting material	Arylating agent	Reaction time, h	Yield, %
BocNHNBzlPh	$(p\text{-Tol})_3Bi$	26	92
$BocNHN(CH_2COOEt)(p\text{-Tol})$	Ph_3Bi	44	80
$BocNHNBu(p\text{-Tol})$	An_3Bi	45	96
BocNHNBuAn	$(p\text{-Tol})_3Bi$	46	100



Scheme 122. An experiment failed due to hydrogen bonding

Two tetrasubstituted hydrazines were obtained from BocNHNRP^{+}Ph$_3$Br^{-} via one-pot procedure as outlined in Scheme 123. At first, triphenylphosphonium group was cleaved and the obtained BocNHNHR was reacted with triarylbismuth diacetate. After the first aryl substituent was introduced, triarylbismuthane and auxiliary reagents were added, furnishing the desired diarylated hydrazines in good yields (69–85%, calculated over three steps from phosphonium salts).



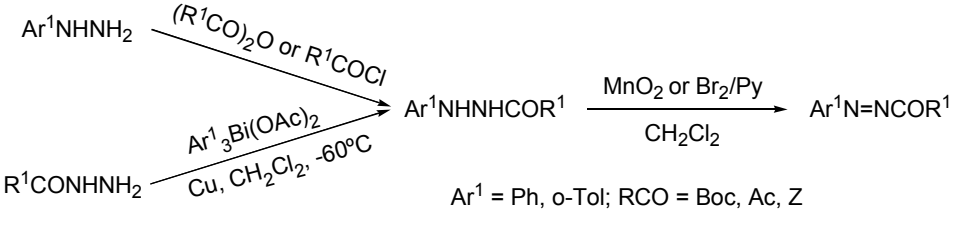
Scheme 123. Synthesis of tetrasubstituted hydrazines with two aryl groups

In conclusion, N-arylation of various hydrazine derivatives with triarylbismuthanes and triarylbismuth diacetates was studied. It appears that tri- and pentavalent organobismuth reagents complement each other with respect to the structure of substrate. Pentavalent reagents exhibit high chemoselectivity for amino over amido fnctions and thus are extremely useful for monoacylated and 2-alkyl substituted substrates. Although arylation of amidic NH in diacylated hydrazines or BocNH in trisubstituted hydrazines can be performed by both types of reagents, trivalent reagent offer some advantages. Also, sterically hindered substituents were introduced into triprotected precursors **13** and **14**. Influence of bulkiness of reagent and substrate on arylation reactivity is demonstrated.

4.5. Regiospecific alkylation/arylation/heteroarylation of unsymmetrical azo-compounds

The new methodology for the synthesis of multisubstituted hydrazines employs a set of relevant protecting groups and stepwise introduction of substituents. Each step is in fact an N-H substitution reaction: alkylation, acylation or arylation. Contrary to N-H substitution as a way to derivatize a hydrazine precursor, another approach would utilize direct addition reaction to the N=N bond. Versatile electrophilicity of azo compounds containing two alkoxycarbonyl groups (DEAD, DBAD) was already discussed in Section 2.8.2. Regioselective nucleophilic addition to unsymmetrically substituted azo compounds is less known [187, 192], although such process could be extremely promising and presented an attractive challenge.

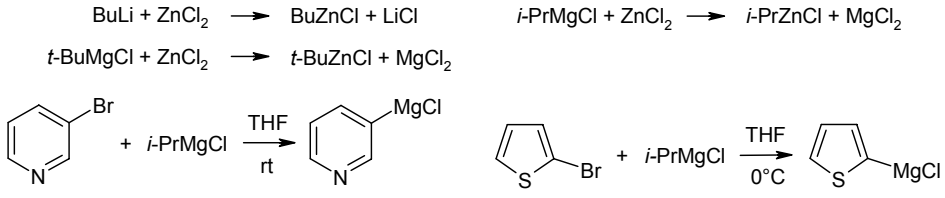
Substrates containing combination of aryl and acyl/alkoxycarbonyl groups were chosen as starting materials and prepared by two methods as demonstrated in Scheme 124. Available arylhydrazines were easily converted into the desired products by acylation (yields 80–90%). Vice versa, unavailability of the starting arylhydrazines compelled us to use highly selective catalytic arylation of alkoxycarbonylhydrazines with triarylbismuthdiacetates, already reported in Paper IV (yields 90–100%). Further oxidation by bromine-pyridine complex or manganese dioxide under very mild conditions furnished azo compounds in excellent yields. The corresponding procedures were recently described in our other paper concerning both chemical and electrochemical oxidation of di- and monosubstituted hydrazines [240].



Scheme 124. Synthesis of unsymmetrical azo compounds

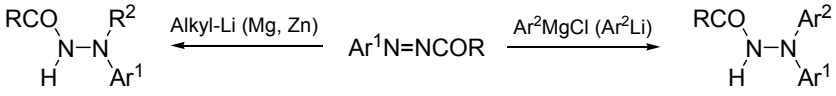
2,4-dinitrophenylhydrazine was also employed as a readily available starting material. Troc and PhCO groups were introduced by direct acylation with yields respectively 43% and 84%. Attempts to introduce Ac and Z groups failed due to the formation of undesired products. The reaction with Boc_2O was very slow and the product contaminated. Despite of the plenty of reagents we have tried (MnO_2, Br_2/Py, $NaBO_3$, PyN-oxide, MCPBA, CF_3COOOH, $H_2O_2{\times}(NH_2)_2CO$), both TrocNHNHDNP and PhCONHNHDNP were very stable to oxidation.

Organozinc nucleophiles were prepared from the corresponding organolithium or organomagnesium compounds. Metal-halogen exchange reactions were used to generate heteroarylmagnesium *in situ* (Scheme 125).



Scheme 125. Preparation of organometallic nucleophiles

The obtained azo compounds were then subjected to the addition of organometallic nucleophiles as outlined in Scheme 126. The reaction with any organometalic nucleofile was extremely fast and full conversion was achieved in 15–20 min even at –80ºC. The results of the experiments are shown in Table 8.



Scheme 126. Regioselective addition to the N=N bond

Generally, the yield and the purity increase with lowering the temperature. The regiospecificity of the addition was confirmed by the ^{1}H NMR analysis of the crude mixtures. R^{1}CONH proton is clearly distinguishable from ArNH, which should appear if the addition happens to be nonselective. The only case where we have observed nonspecific addition, was actually the reaction between *i*-PrMgCl and BocN=NPh, probably due to the extreme reactivity of such organomagnesium (PhNH proton was visible in the ^{1}H NMR of the product).

Organozinc compounds, which are easily prepared from organolithiums just before use, were the best alkylative reagents and gave no side-products. Organomagnesium reagents seem to be most convenient option for arylation.

The reasonable explanation of the unusual regiospecificity is absent. The reaction is seemingly ruled by the difference in electronegativities of R^{1}CONH and NHAr. On the other hand, it is unlikely that there is a fast equilibrium between two possible anions RCON$^{(-)}$-NRAr and RCONHN$^{(-)}$Ar at –80ºC. Despite low steric hindrance on AcNH in comparison to bulky BocNH, the last compound still gave very selective addition of alkylzinc, thus rejecting the possibility of steric control. Also, there is no difference in results with BocN=NPh and more hindered BocN=N(*o*-Tol).

Table 8. The results of the regioselective addition

Entry	Substrate	Nucleophile	Temperature, tºC	Yield, %
1	BocN=NPh	BuLi*	–100	82
2	BocN=NPh	BuLi*	–80	67
3	BocN=NPh	BuLi	–80	incomplete conversion
4	BocN=NPh	BuZnCl	–80	100
5	BocN=NPh	*i*–PrMgCl	–80	nonselective
6	BocN=NPh	*i*–PrMgCl	–100	nonselective
7	BocN=NPh	*i*-PrZnCl	–80	92
8	BocN=NPh	*t*-BuZnCl	–80	97
9	BocN=NPh	3-thienylMgCl	–80	91
10	BocN=NPh	3-PyMgCl	–80	81
11	BocN=NPh	*p*-TolMgBr	–80	81
12	BocN=NPh	*p*-TolMgBr	–100	100
13	ZN=NPh	BuLi	–80	70
14	ZN=NPh	BuZnCl	–80	85
15	ZN=NPh	*i*-PrMgCl	–80	77
16	AcN=NPh	BuZnCl	–80	96
17	AcN=NPh	*i*-PrMgCl	–80	88
18	AcN=NPh	*t*-BuZnCl	–80	54
19	BocN=N-o-Tol	BuZnCl	–80	91
20	BocN=N-o-Tol	p-TolMgCl	–80	93

* – In the experiments **1** and **2** BuLi was added to the azo compound. In the rest of experiments, the solution of azo compound was added to the organometallic nucleophile.

In conclusion, we have described a new versatile protocol for the introduction of alkyl or aryl substituents into protected azo compound. High yields and high regioselectivity are afforded under very mild conditions. The procedure is compatible with secondary and tertiary alkyl substituents as well as with primary alkyl groups. The addition is fast and rather tolerant to steric hindrance.

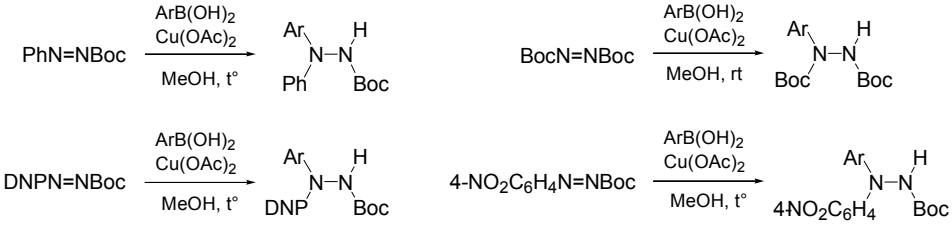
4.6. Addition of arylboronic acids to azo compounds

In Sections 2.6 and 2.7, all the important N-arylation methods were described. Most of those protocols are compatible with hydrazine NH bond. On the other hand, substituted hydrazines can also be obtained by addition of an aryl-containing nucleophile to azo compound. Besides the reactions of N=N bond, copper-catalyzed addition of arylboronic acid to N=O electrophile was resently reported by Liebeskind [167] and can be viewed as a specific case of Ullmann arylation.

Would it be possible to combine a copper-catalyzed N-arylation with addition to the N=N bond in azo compounds?

Exactly when we were going to submit Paper VI to the *Org Lett.* editorial office, an article was published by Chatani *et al* [241]. They described a parallel work on azodicarboxylates and arylboronic acids. Fortunately, we were interested in more complex hydrazines and thus our studies were not confined to symmetrical azo compounds. Therefore, we still had to say something.

The starting azo compounds were obtained using the same oxidation techniques as described in Paper V. The reactions with arylboronic acids are outlined in Scheme 127.



Scheme 127. Addition of arylboronic acids to azo compounds

The addition of phenylboronic acid to PhN=NBoc proceeded even without catalyst in refluxing methanol, although $Cu(OAc)_2$ in catalytic amounts did increase the yield with the decrease of the reaction time. From Table 9 it seems methanol is the best solvent for this transformation.

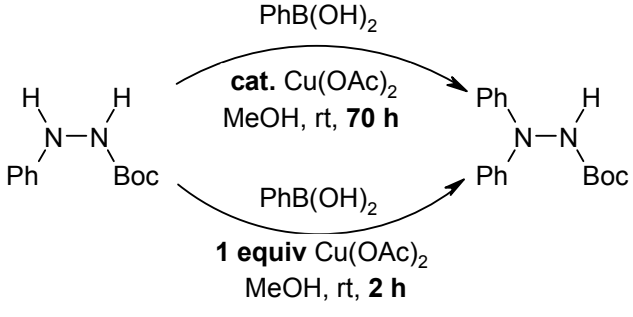
The transformation works well with substrates containing electron-withdrawing groups. As judged from reaction times, BocN=NBoc was the most active azo compound. In contrast, PhN=NPh was almost unreactive under these conditions. It is important that the addition is tolerant to steric hindrance and allows easy introduction of such bulky substituent as 1-naphthyl.

Direct copper-catalyzed N-arylation of PhNHNHBoc by $PhB(OH)_2$ was also studied as shown in Scheme 128. The reaction occurred in the presence of both catalytical and stoichiometric amount of $Cu(OAc)_2$. From the reaction times we concluded that stoichiometric arylation proceeds via oxidation of PhNHNHBoc to PhN=NBoc, followed by addition of $PhB(OH)_2$ to the resulting azo compound.

Table 9. The results of the regioselective addition

Entry	Substrate	Aryl	Solvent, tºC	Reaction time	Yield, %
1	PhN=NBoc	Ph	MeOH, 65	1.5 h	100
2	PhN=NBoc	Ph	MeOH, rt	2 h	100
3	PhN=NBoc	Ph	CH_2Cl_2, rt	16 h	93
4	PhN=NBoc	Ph	ACN, rt	6 days	45 [a]
5	PhN=NBoc	1-Naphthyl	MeOH, 65	45 min	77
6	PhN=NBoc	3-Py	MeOH, 65	6 h	65
7	PhN=NBoc	2-Thienyl	MeOH, 65	7 h	– [b]
8	PhN=NBoc	3-Thienyl	MeOH, 65	7 h	– [b]
9	BocN=NBoc	Ph	MeOH, rt	30 min	91
10	BocN=NBoc	1- Naphthyl	MeOH, rt	30 min	60
11	BocN=NBoc	3-Py	MeOH, 65	15 min	43
12	BocN=NBoc	2-Thienyl	MeOH, rt	20 min	45
13	BocN=NBoc	3-Thienyl	MeOH, rt	40 min	100
14	DNPN=NBoc	Ph	MeOH, 65	7–8 min	57 [c]
15	DNPN=NBoc	3–Py	MeOH, 65	22 h	18
16	4-$NO_2C_6H_4$N=NBoc	Ph	MeOH, 65	1 h	100
17	4-$NO_2C_6H_4$N=NBoc	1- Naphthyl	MeOH, 65	4 h	94
18	4-$NO_2C_6H_4$N=NBoc	3-Py	MeOH, 65	8 h	78
19	4-$NO_2C_6H_4$N=NBoc	2-Thienyl	MeOH, 65	16 h	– [b]
20	4-$NO_2C_6H_4$N=NBoc	3-Thienyl	MeOH, 65	36 h	59

[a] 31% of the starting material recovered
[b] Only decomposition products
[c] 21% of DNPNHNPhBoc and 21% of DNPNHNHBoc were isolated
^{1}H NMR spectra analysis was used to prove the regioselectivity of addition to ArN=NBoc by analogy with Paper V. Coupling of phenylboronic acid with DNPN=NBoc was the only experiment where another isomer was also detected and isolated (Entry 14 in Table 9).



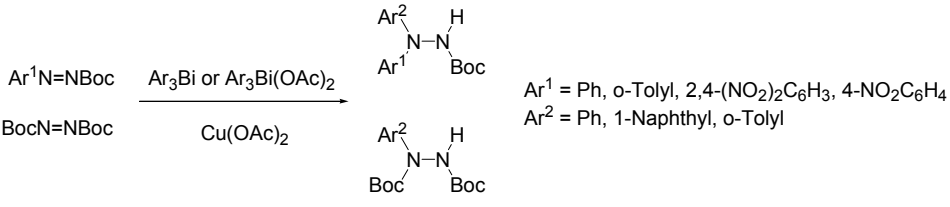
Scheme 128. Arylation of PhNHNHBoc

In conclusion, the addition of arylboronic acids to a variety of azo compounds was under systematic study. Excellent regioselectivity was observed in addition to unsymmetrical azo compounds. The reaction is a useful alternative to the method described in Paper V.

4.7. Addition of organobismuth reagents to azo compounds

In Papers III and IV we studied arylation of hydrazine NH bond with organobismuth reagents. In Paper VI we described the copper-catalyzed addition of arylboronic acids to azo compounds.

Now it was time to combine those two. We supposed that organobismuth reagents could be applicable for copper-catalyzed addition to azo compounds as shown in Scheme 129.



Scheme 129. Addition of organobismuth reagents to azo compounds.

In order to see how our hypothesis works, series of experiments were conducted using the same substrates as in Paper VI. In comparison with our previous studies, coupling with organobismuth reagents was more capricious. The reaction demanded elevated temperature and either protic solvent (methanol) or polar aprotic solvents like NMP and ACN. Coupling in methanol was accompanied by the formation of side products. The yields were higher in N-methylpyrrolidone (see Table 1 in Paper VII). With respect to both chemoselectivity and practical convenience, acetonitrile was found to be the most suitable solvent for this transformation. We have tried to use HFIP as a required proton source, but it was fully replaced by the addition of methanol later on. In some cases presence of oxygen has obviously decreased the yields and therefore all the representative experiments were conducted under argon. The results are presented in Table 10.

Table 10. Reaction in acetonitrile in the presence of 10% mol copper catalyst and 5 equiv of methanol[a]

	Azo compound	Organobismuth	Conditions	Time min	Yield %
1	PhN=NBoc	Ph_3Bi	75ºC, HFIP	20	84
2	PhN=NBoc	Ph_3Bi	70ºC	5	90
3	PhN=NBoc	Ph_3Bi	70ºC, CuCl	5	89
4	PhN=NBoc	Ph_3Bi	70ºC, $CuCl_2 \times 2H_2O$	240	89
5	PhN=NBoc	Np_3Bi	70ºC	5	74
6	PhN=NBoc	$(o\text{-Tol})_3Bi$	70ºC	10	63
7	*o*-TolN=NBoc	Ph_3Bi	70ºC	5	100
8	*o*-TolN=NBoc	Np_3Bi	70ºC	300	90
9	*o*-TolN=NBoc	$(o\text{-Tol})_3Bi$	70ºC	5	83
10	BocN=NBoc	Ph_3Bi	75ºC, HFIP	15	100
11	BocN=NBoc	Ph_3Bi	75ºC	5	90
12	BocN=NBoc	$Ph_3Bi(OAc)_2$	75ºC	30	82
13	BocN=NBoc	$(o\text{-Tol})_3Bi$	70ºC	70	72
14	BocN=NBoc	Np_3Bi	75ºC	70	76
15	DNPN=NBoc	Ph_3Bi	75ºC, HFIP	60	93
16	DNPN=NBoc	$Ph_3Bi(OAc)_2$	70ºC, HFIP	600	58
17	DNPN=NBoc	Ph_3Bi	40ºC	30	95
18	DNPN=NBoc	Ph_3Bi	60ºC	5	89
19	DNPN=NBoc	Ph_3Bi	70ºC	5	59
20	DNPN=NBoc	$Ph_3Bi(OAc)_2$	60ºC	90	87
21	DNPN=NBoc	$(o\text{-Tol})_3Bi$	70ºC	120	86
22	DNPN=NBoc	$(o\text{-Tol})_3Bi$	55ºC	360	90
23	NPN=NBoc	Ph_3Bi	70ºC, HFIP	30	94
24	NPN=NBoc	Ph_3Bi	70ºC	5	100
25	NPN=NBoc	$Ph_3Bi(OAc)_2$	60ºC	150	93
26	NPN=NBoc	Np_3Bi	70ºC	10	92
27	NPN=NBoc	$(o\text{-Tol})_3Bi$	70ºC	90	85

[a] In case HFIP is marked, then it was used instead of methanol as a proton source

In contrast to analogous coupling with arylboronic acids, this reaction of PhN=NBoc does not proceed without copper catalyst. On the other hand, coupling of $Ph_3Bi(OAc)_2$ with the most active substrate BocN=NBoc occurs at room temperature, although the conversion is not full and significant amount of side products are yielded due to the disproportionation.

From Table 10 it seems that pentavalent reagent $Ph_3Bi(OAc)_2$ does not offer advantages over trivalent Ph_3Bi. $Cu(OAc)_2$ was found to be the most efficient catalyst for the transformation. CuCl can be used as alternative, whereas other

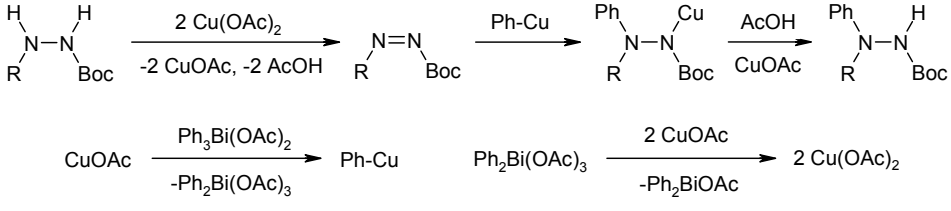
tested copper salts ($CuCl_2 \times 2H_2O$, $CuSO_4$ and copper (II) pivaloate) slowed the process down and reduced the yield.

The transfer of aryl group to ArN=NBoc from organobismuth reagent proceeds with the same regioselectivity as from arylboronic acid. In comparison with the results discussed in Paper VI, the only exception was again the reaction of DNPN=NBoc with Ph_3Bi in methanol. This addition yielded DNPNHN(Ph)Boc in 21% yield and 55% of reduction product DNPNHNHBoc. Use of acetonitrile and lower temperatures positively affect the addition reaction.

The addition is quite tolerant to steric hindrance, allowing smooth introduction of *ortho*-tolyl and 1-naphthyl substituents.

Shorter reaction time is the main advantage of this transformation over analogous coupling with arylboronic acids (Paper VI). The conversion is unusually fast under optimized conditions and is complete within minutes whereas the addition of arylboronic acids to the same substrates requires several hours. Obviously, choice of the procedure depends on the availability of the aryl source. Plenty of arylboronic acids are commercially available. In the same time, triarylbismuthanes can be readily prepared in the lab.

The results of Paper III, where we have evidenced unusually fast N-arylation of disubstituted hydrazines with pentavalent bismith reagents, could be revisioned in the light of the new observations. Presumably, copper-catalyzed N-arylation of BocNHNHR (R = alkyl) proceeds via the formation of azo compound. The speculated mechanism is demonstrated in Scheme 130. At first, the starting material is oxidized to the azo compound. The copper (I) acetate is involved in the transmetallation reaction with $Ph_3Bi(OAc)_2$, which gives phenyl copper species. After the addition to the N=N bond, the resulting copper (I) acetate is oxidized by intermediate bismuth (V) compound to its initial form $Cu(OAc)_2$ and the catalytic cycle restarts.



Scheme 130. N-arylation of BocNHNHR

In summary, a new copper salt catalyzed C-N coupling is reported. Systematic study of coupling between organobismuth reagents and azo compounds of different structure is conducted. This smooth transformation is characterized with high regioselectivity, excellent yields and short reaction time.

5. CONCLUSIONS

The following results were obtained during the present study:

- A new reagent for the systematic synthesis of multisubstituted hydrazines is described.
  - Combination of *tert*-butoxycarbonyl and triphenylphosphonium group afforded diprotected precursor with no analogs published before. Selectivity of the substitution is guaranteed by the formation of the phosphinimine.
  - A series of trisubstituted hydrazine derivatives are obtained as a result of evaluation of the new precursor.
  - An extremely efficient method for removal of triphenylphosphonium groups is found.
- Several acidic hydrazines, containing electron-withdrawing groups such as Ac, Boc, PPh_3, Tf, CF_3CO, were prepared and used in the estimation of the pK_a of hydrazine in DMSO solution.
- A highly selective protocol for the N-arylation of disubstituted hydrazines of type $R^1NHNHCOR^2$ is reported.
- A number of mono-, di- and trisubstituted hydrazines were studied with respect to arylation by triarylbismuthanes and triarylbismuth diacetates with emphasis on scope and limitations.
  - Fast, highly chemoselective copper-catalyzed arylation of acylhydrazines by triarylbismuth diacetates is reported.
  - Diacylhydrazines and trisubstituted hydrazines are more efficiently arylated by trivalent reagents.
  - Bulky substituents, such as *o*-tolyl, 1-naphthyl and 2-methoxy-4-methylphenyl were introduced into trisubstituted precursors.
  - A few tetrasubstituted hydrazines with two different aryl groups were also obtained.
- Regioselective addition of organometallic nucleofiles to the unsymmetrical azo compounds ArN=NCOR is described.
  - Primary/secondary/tertiary alkyl, aryl and heteroaryl substituents were introduced in high yields.
  - The addition is fast and sensitivity to sterical hindrance is diminished.
  - Organozinc reagents seem to be more suitable for alkylation in comparison to organolithium, while organomagnesium compounds are the reagents of choice for arylation.
- Addition of arylboronic acids to azo compounds is described.
  - Aryl- and heteroaryl substituents were introduced into hydrazine molecule, using commercially available boronic acids.

- Excellent regioselectivity was observed in addition to unsymmetrical azo compounds ArN=NBoc.
- A number of Boc-protected diarylhydrazines is obtained.

- Addition of organobismuth reagents to azo compounds is described.
  - Excellent regioselectivity was observed in addition to unsymmetrical azo compounds ArN=NBoc.
  - The addition is quite tolerant to steric hindrance. Satisfying results were obtained upon the introduction of *o*-tolyl and 1-naphthyl groups.
  - The reaction is fast and the yields under optimized conditions are mostly excellent.
  - A number of Boc-protected diarylhydrazines is obtained

REFERENCES

1. Hearn, M. J.; Joo On Kang, H.; Thai, M. *Bull. Soc. Chim. Belg.* **1997**, 106, 109–114.
2. Sinha, N.; Jain, S.; Tilekar, A.; Upadhayaya, R. S.; Kishore, N.; Sinha, R. K.; Arora, S. K. *ARKIVOC* **2005**, 9–19.
3. Sui, Z.; Guan, J., Ferro, M. P.; McCoy, K.; Wachter, M. P.; Murray, W. V.; Singer, M.; Steber, M.; Ritchie, D. M.; Argentieri, D. C. *Bioorg. Med. Chem. Lett.* **2000**, 10, 601–604.
4. Ling, L.; Urichuk, L. J.; Sloley, B. D.; Coutts, R. T.; Baker, G. B.; Shan, J. J.; Pang, P. K. T. *Bioorg. Med. Chem. Lett.* **2001**, 11, 2715–2717.
5. Shyam, K.; Penketh, P. G.; Divo, A. A.; Loomis, R. H.; Rose, W. C.; Sartorelli, A. C. *J. Med. Chem.* **1993**, 36, 3496–3502.
6. Cignarella, G.; Barlocco, D.; Landriani, L.; Pinna, G. A.; Andriuoli, G.; Dona, Giancarlo. *Farmaco* **1991**, 46, 527–538.
7. Vilme, M.; Edwards, D.; McPherson-Baker, S. *Drug Forecast* **2005**, 30, 1, 27–35.
8. Aubin, S.; Martin, B.; Delcrois, J.-G.; Arlot-Bonnemains, Y.; Baudy-Floc'h, M. *J. Med. Chem.* **2005**, 48, 330–334.
9. Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, 118, 11, 2539–2544.
10. Gante, J.; Neunhoeffer, H.; Schmidt, A. *J. Org. Chem.* **1994**, 59, 6487–6489.
11. Bonnet, D.; Grandbjean, C.; Rousselot-Pailley, P.; Joly, P.; Bourel-Bonnet, L.; Santraine, V.; Gras-Masse, H.; Melnyk. O. *J. Org. Chem.* **2003**, 68, 7033.
12. Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, 60, 7043–7046.
13. Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, 60, 5992–5994.
14. Mulvihill, M.J.; Nguyen, D. V.; MacDougall, B.; Martinez-Teipel, B.; Joseph, R.; Gallagher, J.; Weaver, D.; Gusev, A.; Chung, K.; Mathis, W. *Tetrahedron. Lett.* **2001**, 42, 7751–7754.
15. Toya, T.; Yamaguchi, K.; Endo, Y. *Biorg. Med. Chem*. **2002**, 10, 953–961.
16. Wang, Q.; Huang, R. *Tetrahedron. Lett.* **2001**, 42, 50, 8881–8883.
17. Bonnet, D.; Rommens, C.; Grass-Masse, H.; Melnyk, O. *Tetrahedron Lett*. **2000**, 41, 45–48.
18. Ollivier, N.; Ollivier, C.; Gouyette, C.; Huynh-Dinh, T.; Grass-Masse, H.; Melnyk, O. *Tetrahedron Lett.* **2002**, 43, 997–999.
19. Chenevier, P.; Grandjean, C.; Loing, E.; Malingue, F.; Angyalosi, G.; Grass-Masse, H.; Roux, D.; Melnyk, O.; Bourel-Bonnet, L. *Chem. Comm.* **2002**, 2446–2447.
20. Raddatz, S.; Müller-Ibeler, J.; Kluge, J.; Wäß, L.; Burdinski, G.; Havens, J. R.; Onofrey, T. J.; Wang, D.; Schweitzer, M. *Nucl. Acids Res.* **2002**, 30, 4793–4802.
21. Kotschy, A.; Hajós, G.; Messmer, A.; Jones, G. *Tetrahedron* **1996**, 52, 4, 1399–1410.
22. Park, K.-H.; Cox, L. J. *Tetrahedron Lett.* **2002**, 43, 3899–3901.
23. Košmrlj, J.; Kocevar, M.; Polanc, S. *Synlett* **1996**, 652–654.
24. Hinman, R. L. *J. Am. Chem. Soc.* **1956**, 78, 1645–1649.
25. Hinman, R. L; Fulton, D. *J. Am. Chem. Soc.* **1958**, 80, 1895–1900.
26. Theuer, W. J.; Moore, J. A. *J. Org. Chem.* **1964**, 29, 3734–3735.
27. Condon, F. E. *J. Org. Chem.* **1972**, 37, 23, 3608–3615.
28. Rabini, T.; Vita, G. *J. Org. Chem.* **1965**, 30, 2486–2488.

29. Rutjes, F. P. J. T.; Teerhuis, N. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1993**, 49, 8605–8628.
30. Ragnarsson, U; Grehn, L. *Acc. Chem. Res.* **1991**, 24, 10, 285–289.
31. Kluba, M.; Zwierzak, A. *Synthesis* **1981**, 537–539.
32. Mäeorg, U.; Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 22, 2626–2627.
33. Ullmann, F. *Ber. Dtsch. Chem.* Ges. **1903**, 36, 2382–2389.
34. Ley, S. V.; Thomas, A. W. *Angew. Chemie., Int. Ed. Engl.* **2003**, 42, 5400–5449.
35. Beletskaya, I. P.; Cheprakov, A. V. *Coordination Chem. Rev*. **2004**, 248, 2337–2364.
36. Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 15, 2428–2439.
37. Finet, J.-P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, 6, 597–626.
38. Zwierzak, A.; Podstawczynska, I. *Angew. Chem.* **1977**, 89, 737–738.
39. Zwierzak, A.; Slusarska, E. *Synthesis* **1980**, 717–719.
40. Zwierzak, A. *Synthesis* **1984**, 332–333.
41. Gajda, T.; Zwierzak, A. *Synthesis* **1981**, 1005–1008.
42. Gajda, T.; Koziara, A.; Zawadski, S.; Zwierzak, A. *Synthesis* **1979**, 549–552.
43. Miotkowska, B.; Zwierzak, A. *Tetrahedron. Lett.* **1978**, 47, 4731–4734.
44. Zawadski, S.; Osowska-Pasewicka, K.; Zwierzak, A. *Synthesis* **1987**, 485–487.
45. Malz, R. E.; Amidon, R. W.; Greenfield, H. U.S. 4,045,484. (Cl. 260–561 H, C 07 C 103/32).
46. Wu, P.; Peng, S.; Magrath, J. *Synthesis* **1995**, 435–438.
47. Baumgarten, H. E.; Chen, P. Y.-N.; Taylor, H. W.; Hwang, D.-R. *J. Org. Chem.* **1976**, 41, 3805–3811.
48. Verardo, G.; Toniutti, N.; Giumanini, A. G. *Can. J. Chem.* **1998**, 76, 1180–1187.
49. Fox, D. L.; Ruxer, J. T.; Oliver, J. M.; Alford, K. L.; Salvatore, R. N. *Tetrahedron Lett.* **2004**, 45, 401–405.
50. Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, 4, 861–886.
51. Horner, L.; Hoffmann, H. *Angew. Chem.* **1956**, 68, 15, 473–504.
52. Horner, L.; Oediger, H. *Lieb. Ann. Chem.* **1959**, Bd. 627, 142–162.
53. Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, 24, 8, 763–764.
54. Hemming, K.; Bevan, M. J.; Loukou, C.; Patel, S. D.; Renaudeau, D. *Synlett* **2000**, 1565–1568.
55. Katrizky, A. R.; Jiang, J.; Urogdi, L.*Tetrahedron Lett.* **1989**, 30, 25, 3303–3306.
56. Zimmer, H.; Singh, G. *J. Org. Chem.* **1963**, 28, 483–486.
57. Zimmer, H.; Jayawant, M.; Gutsch, P. *J. Org. Chem.* **1970**, 35, 8, 2826–2828.
58. Cristau, H.; Garcia, C.; Kadoura, J.; Torreilles, E. *Phosphor., Sulfur, Silicon Relat. Elem.* **1990**, 49/50, 151–154.
59. Fukui, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, 43, 4, 1160–1163.
60. Zimmer, H.; Singh, G. *J. Org. Chem.* **1964**, 29, 1579–1581.
61. Barluenga, J.; Merino, I.; Viña, S.; Palacios, F. *Synthesis* **1990**, 5, 398–400.
62. Song, J. J.; Yee, N. K. *Tetrahedron Lett.* **2001**, 42, 2937–2940.
63. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, 2, 619–635.
64. Bestmann, H. J.; Göthlich, L. *Lieb. Ann. Chem.* **1962**, 655, 1–19.
65. Bestmann, H. J.; Fritzsche, H. *Chem. Ber.* **1961**, 54, 2477–2485.
66. Singh, G.; Zimmer, H. *J. Org. Chem.* **1965**, 30, 417–420.
67. Walker, C. C.; Shechter, H. *Tetrahedron Lett.* **1965**, 20, 1447–1452.

68. Appel, R.; Schöllhorn, R. *Angew. Chem.*, **1964**, 24, 991–992
69. Walker, C. C.; Shechter, H. *J. Am. Chem. Soc.* **1968**, 90, 5626–5627.
70. Merrill, G. B.; Shechter, H. *Tetrahedron. Lett.* **1975**, 51, 4527–4530.
71. Merot, P.; Gadreau, C.; Foucaud, A. *Tetrahedron* **1981**, 37, 2295–2599.
72. Frøyen, P. *Phosphor., Sulfur, Silicon Relat. Elem.* **1991**, 57, 11–15.
73. Ried, W.; Franz, G. *Justus Liebigs Ann. Chem*. **1961**, 644, 141.
74. Brown, H. C.; Cheng, M. T.; Parcell, L. J.; Pilipovich, D. *J. Org. Chem.* **1961**, 26, 4407–4409.
75. Groth, R. H. *J. Org. Chem.* **1960**, 25, 102–105.
76. Fritz, H.; Kristinsson, H.; Mollenkopf, M.; Winker, T. *Magn. Res. Chem.* **1990**, 28, 331–336.
77. Young, J. A.; Durrell, W. S.; Dresdner, R. D. *J. Am. Chem. Soc*. **1962**, 84, 2105–2109.
78. Allen, C. F. H. *Can. J. Chem.* **1975**, 53, 865–868.
79. Powell, J. W.; Whiting, M. C. *Tetrahedron* **1959**, 7, 305–310.
80. Chamberlin, A. R.; Bond, T. F. *J. Org. Chem.* **1978**, 43, 154–155.
81. Shainyan, B. A.; Tolstikova, L. L.; Meshcheryakov, V. I.; Danilevich, Yu. S. *Russian Journal of Organic Chemistry* **2004**, 40, 1071–1075.
82. Hendrickson, J. B.; Sternbach, D. D. *J. Org. Chem.* **1975**, 40, 3450–3452.
83. Katritzky, A.; Wu, L.; Verin, S. V. *Synthesis* **1995**, 651–653.
84. Katritzky, A. R.; Qiu, G.; Yang, B. *J. Org. Chem.* **1997**, 62, 8210–8214.
85. Tsuji, J. Palladium reagents and catalysts. Innovations in Organic Synthesis. John Wiley and Sons Ltd, England. **1995**.
86. Brandsma, L; Vasilevsky, S. F.; Verkruijsse, H. D.; Application of Transition Metal Catalysis in Organic Synthesis. Springer-Verlag Berlin Heidelberg New York, **1998**.
87. Diederich, F.; Stang, J. P. Metal-catalyzed cross-coupling reactions. Wiley-VCH Verlag Gmbh, Germany, **1998**.
88. Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, 36, 3609–3612.
89. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1348–1350.
90. Hartwig, J. F. *Angew. Chem. Int. Ed. Engl*. **1998**, **37**, 2046–2067.
91. Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, **31**, 805–818.
92. Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*. Negishi, E, Ed., John Wiley & Sons, Inc., Hoboken, N. J. **2002**, 1, 1051–1096.
93. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, 65, 1144–1157.
94. Belfield, A.J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, 55, 11399–11428.
95. Wolfe, J. P.; Buchwald, S. T. *Angew. Chem. Int. Ed.* **1999**, 38, 16, 2413–2416.
96. Old, D. W; Wolfe J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, 120, 9722–9723.
97. Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, 120, 9722–9723.
98. Buchwald, S. L.; Wagaw, S.; Geis, O. F. US 6,235,936 B1. Appl. No.: 09/030,936.
99. Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, 40, 3543–3546.
100. Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, 3, 1351–1354.
101. Kim, K.-K.; Shin, J.-T.; Lee, K.-S.; Cho, C.-G. *Tetrahedron Lett.* **2004**, 45, 117–120.

102. Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, 120, 12459–12467.
103. Ma, D.; Xia, C. *Org. Lett.* **2001**, 3, 2583–2586.
104. Goodbrand, H. B.; Hu, N.-X.. *J. Org. Chem.* **1999**, 64, 670–674.
105. Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, 4, 581–584.
106. Job, G. E.; Buchwald, S. L.. *Org. Lett.* **2002**, 4, 3703–3706.
107. Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, 4, 793–796.
108. Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, 40, 2657–2660.
109. Klapars, A.; Antilla J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, 123, 7727–7729.
110. Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, 124, 7421–7428.
111. Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, 3, 23, 3803–3805.
112. Suzuki, H.; Matano, Y., Eds., Organobismuth Chemistry, Elsevier: Amsterdam, **2001**.
113. Freedman, L.; Doak, G.O. *Chem. Rev.* **1982**, 82, 15–57.
114. Combes, S.; Finet, J.-P. *Synth. Commun.* **1996**, 26, 4569–4575.
115. Finet, J.-P. *Chem. Rev.* **1989**, 89, 1487–1501.
116. Barton, D.H.R; Kitchin, J. P.; Lester D. J.; Motherwell, W. B.; Papoula, M. T. B. *Tetrahedron* **1981**, 37, Suppl. No 1, 73–79.
117. Barton, D. H. R.; Blazejewski, J.-C.; Charpiot, B.; Lester, D. J.; Motherwell, W. B.; Papoula, M. T. B. *J. Chem. Soc., Chem. Comm.* **1980**, 827–829.
118. Barton, D. H. R.; Blazejewski, J.-C.; Charpiot, B.; Lester, D. J.; Motherwell, W. B. *Chem. Soc., Chem. Comm.* **1980**, 827–829.
119. David, S.; Tieffry, A. *J. Org. Chem.* **1983**, 48, 441–447.
120. Barton, D. H. R.; Finet, J.-P.; Pichon, C. *Chem. Soc., Chem. Comm.* **1986**, 65–66.
121. Додонов, В. А.; Гущин, А. В.; Брилкина, Т. Г. *Журнал общей химии*, **1985**, 55, 2514–2519.
122. Abramovitch, R. A.; Barton, D. R.; Finet, J.-P. *Tetrahedron* **1988**, 44, 3039–3071.
123. Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, 249–267.
124. Elliott, G. I., Konopelski, J. P.. *Tetrahedron* **2002**, 57, 5683–5705.
125. Додонов, В. А.; Гущин, А. В.; Брилкина, Т. Г. *Журнал общей химии* **1985**, 55, 466–467.
126. Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1986**, 27, 3615–3618.
127. Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1987**, 28, 887–890.
128. Combes, S.; Finet, J.-P. *Tetrahedron* **1999**, 55, 3377–3386.
129. Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1989**, 30, 937–940.
130. Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1988**, 29, 1115–1118.
131. Akhtar, M. S.; Brouillette, W. J.; Waterhouse, D. V. *J. Org. Chem.* **1990**, 55, 5222–5225.
132. Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron* **1997**, 53, 12, 4137–4144.
133. Fedorov, A. Y.; Finet, J.-P. *Tetrahedron Lett.* **1999**, 40, 2747–2748.
134. Combes, S.; Finet, J.-P. *Tetrahedron* **1998**, 54, 4313–4318.
135. Fedorov, A. Y.; Combes, S.; Finet, J.-P. *Tetrahedron* **1999**, 55, 1341–1352.
136. Chan, D. M. T. *Tetrahedron Lett.* **1996**, 37, 50, 9013–9016.
137. Sorenson, R. J. *J. Org. Chem.* **2000**, 65, 7747–7749.

138. Banfi, A.; Bartoletti, M.; Bellora, E.; Bignotti, M.; Turconi, M. *Synthesis* **1994**, 775–776.
139. Matano, Y.; Aratani, Y.; Miyamatsu, T.; Kurata, H.; Miyaji, K.; Sasako, S.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2511–2517.
140. Rottländer, M.; Boymond, L.; Berillon, L.; Lepretre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Queguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, 6, 767–770.
141. Murafuji, T.; Nishio, K.; Nagasue, M.; Tanabe, A.; Aono, M.; Sugihara, Y. *Synthesis* **2000**, 1208–1210.
142. Lemus, A.; Sharma, P.; Cabrera, A.; Rosas, N.; Alvarez, C.; Gomez, E.; Sharma, M.; Cespedes, C.; Hernandez, S. *Main Group Met. Chem.* **2001**, 24, 835–839.
143. Fedorov, A. Y.; Finet, J.-P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3775–3778.
144. Urano, M.; Wada, S.; Suzuki, H. *Chem. Commun.* **2003**, 1202–1203.
145. Loog, O.; Mäeorg, U.; Ragnarsson, U. *Synthesis* **2000**, 1591–1597.
146. Aoki, Y.; Saito, Y.; Sakamoto, T.; Kikugawa, Y. *Synth. Commun.* **2000**, 30, 131–140.
147. Loog, O.; Mäeorg, U. *Synlett* **2004**, 2537–2540.
148. Suzuki, H.; Ikegami, T.; Matano, Y. *Tetrahedron Lett.* **1994**, 35, 8197–8200.
149. Hall, D. G. (Editor). Boronic acids. Preparation, application in Organic Synthesis and Medicine. Wiley-VCH, Germany, **2005**.
150. Tyrrell, E.; Brookes, P. *Synthesis* **2004**, 469–483.
151. Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, 39, 2933–2936.
152. Cundy, D. J.; Forsyth, S. A. *Tetrahedron Lett.* **1998**, 39, 7979–7982.
153. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, 39, 2941–2944.
154. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett.* **2000**, 5, 674–676.
155. Bakkestuen, A. K.; Gundersen, L.-L. *Tetrahedron Lett.* **2003**, 44, 3359–3362.
156. Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, 42, 3415–3418.
157. Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, 44, 1691–1694.
158. Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, 40, 1623–1626.
159. Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, 2, 1233–1236.
160. Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, 66, 1528–1531.
161. Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, 66, 7892–7897.
162. Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, 3, 2077–2079.
163. Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* **2004**, 1095–1097.
164. Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, 5, 4397–4400
165. Raus, L.; Tšubrik, O.; Mäeorg, U. *Proc. Estonian Acad. Sci., Chemistry* **2005**, 54, 12–15.
166. Kabalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, 5, 4129–4131.
167. Yu, Y.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2004**, 6, 2631.

168. Barton, D. H. R.; Yadav-Bhatnagar, N.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1987**, 28, 3111–3114.
169. Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2095–2102.
170. López-Alvarado, P.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **1995**, *60*, 5678–5682.
171. López-Alvarado, P.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **1996**, *61*, 5865–5870.
172. Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022–1024.
173. Lam. P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, 122, 7600–7601.
174. Newbold, Brian T. Reduction and synthetic uses of hydrazo, azo, and azoxy compounds. Chem. Hydrazo, Azo Azoxy Groups. Ed.: Patai, Saul. John Wiley and Sons, **1975**, 2, 599–641.
175. Spialter, L.; O'Brien, D. H.; Untereiner, G. L.; Rush, W. A. *J. Org. Chem.* **1965**, 30, 3278–3283.
176. Carpino, L. A.; Terry, P. H.; Crowley, P. J. *J. Org. Chem.* **1961**, 26, 4336–4340.
177. Wang, Y.-L.; Wang, X.-Y.; Li, J.-P.; Ma, D.-I.; Wang, H. *Synth. Commun.* **1997**, 27, 1737–1742.
178. Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett.* **2003**, 5, 979–982.
179. Starr, J. T.; Rai, G. S.; Dang, H.; McNelis, B. J. *Synth. Commun.* **1997**, 27, 3197–3200.
180. Li, J.-P.; Liu, P.; Xue, W.-X.; Wang, Y.-L. *J. Chin. Chem. Soc.* **2003**, 50, 433–435.
181. Xiao, J.-P.; Wang, Y.-L.; Jia, X.-S.; Wang, X.-Y.; Wang, H. *Synth. Commun.* **2000**, 30, 1807–1812.
182. Zhao, Y.-W.; Wang, Y.-L.; Wang, H.; Dun, Z.-F.; Yao, X.-Z. *Synth. Commun.* **2001**, 31, 2563–2567.
183. Wang, H.; Wang, Y.-L.; Zhang, G.; Li, J.-P.; Wang, X.-Y. *Synth. Commun.* **2000**, 31, 2563–2567.
184. Li, Y.-K., Lee, K.-S.; Cho, C.-G. *Org. Lett.* **2003**, 5, 979–982.
185. Mitsunobu, O. *Synthesis* **1981**, 1–28.
186. Erdik, E. *Tetrahedron* **2004**, 60, 8747–8782.
187. Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, 1, 595–598.
188. Demers, J. P.; Klaubert, D. H. *Tetrahedron Lett.* **1987**, 28, 4933–4934.
189. Zhan, L.; Tan, Z. *Tetrahedron Lett.* **2000**, 41, 3025–3028.
190. Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998**, 39, 9157–9160.
191. An, D. K.; Hirakawa, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, 40, 3737–3740.
192. Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, 43, 897–900.
193. Jacobson, M. B.; Arvanitis, G. M.; Eliasen, C. A.; Mitelman, R. *J. Org. Chem.* **1985**, 50, 194–201.
194. Thaler, W. A.; Franzus, B. *J. Org. Chem.* **1964**, 29, 2226–2235.
195. Leblanc, Y.; Zamboni, R.; Bernstein, M. A. *J. Org. Chem.* **1991**, 56, 1971–1972.
196. Scartozzi, M.; Grondin, R.; Leblanc, Y. *Tetrahedron Lett.* **1992**, 33, 5717–5720.
197. Brimble, M. A.; Heathcock, C. H. J. *J. Org. Chem.* **1993**, 58, 5261–5263.
198. Brimble, M. A.; Lee, C. K. Y. *Tetrahedron: Asymmetry* **1998**, 9, 873–884.

199. Zaltgendler, I; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett.* **1993**, 34, 2441–2444.
200. Mitchell, H.; Leblanc, Y. *J. Org. Chem.* **1994**, 59, 682–687.
201. Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995**, 60, 4268–4271.
202. Lenaršič, R.; Kočevar, M.; Polanc, S. *J. Org. Chem.* **1999**, 64, 2558–2563.
203. Yadav, J. S.; Reddy, B. V. S.; Veerendhar, G.; Rao, R. S.; Nagaiah, K. *Chem. Lett.* **2002**, 318–319.
204. Lee, K. Y.; Im, Y. J.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, 22, 131–132.
205. Chan, W. Y.; Berthelette, C. *Tetrahedron Lett.* **2002**, 43, 4537–4540.
206. Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Madan, C. *Synlett* **2001**, 1781–1783.
207. Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205–213.
208. Kocienski, P. J. Protecting groups. Georg Thieme Verlag Stuttgart: New York, **1994**.
209. Green, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis. John Wiley & Sons, Inc, **1999**, 518–525.
210. Mäeorg, U.; Ragnarsson, U. *Tetrahedron Lett.* **1998**, 39, 7, 681–684.
211. Mäeorg, U.; Pehk, T.; Ragnarsson, U. *Acta. Chem. Scand.* **1999**, 53, 1127–1133.
212. Loog, O.; Mäeorg, U.; Ragnarsson, U. *Synthesis* **2000**, 1591–1597.
213. Grehn, L.; Löhn, H.; Ragnarsson, U. *Chem. Commun.* **1997**, 1–2.
214. Grehn, L.; Nyasse, B.; Ragnarsson, U. *Synthesis* **1997**, 1429–1432.
215. Grehn, L.; Ragnarsson, U. *Synthesis* **1998**, 1817–1821.
216. Ragnarsson, U.; Fransson, B.; Grehn, L. *J. Chem. Soc., Perkin Trans.* 1 **2000**, 1405–1409.
217. Grehn, L.; Ragnarsson, U. *Tetrahedron* **1999**, 55, 4843–4852.
218. Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *J. Chem. Soc., Perkin Trans.* 1 **1998**, 3685–3688.
219. Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2000,** 41, 2, 205–207.
220. Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *J. Org. Chem*. **2000**, 65, 4370–4374.
221. Brosse, N.; Pinto, M.-F.; Bodiguel, J.; Jamart-Grégoire, B. *J. Org. Chem*. **2001**, 66, 2869–2873.
222. Brosse, N.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2002**, 43, 249–251.
223. Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, 34, 7873–7876.
224. Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017–1018.
225. Nyasse, B.; Grehn, L.; Maia, H. L. S.; Monteiro, L. S.; Ragnarsson, U. *J. Org. Chem.* **1999**, 64, 7135–7139.
226. Ragnarsson, U.; Grehn, L.; Maia, H. L. S.; Monteiro, L. S. *J. Chem. Res.* (S) **2000**, 6–7.
227. Brosse, N.; Grandeury, A.; Jamart-Gregoire, B. *Tetrahedron Lett.* **2002**, 43, 2009–2011.
228. Brosse, N.; Pinto, M.-F.; Jamart-Gregoire, B. *Eur. J. Org. Chem.* **2003**, 4757–4764.
229. Bouillon, I.; Brosse, N.; Vanderesse, R.; Jamart-Gregoire, B. *Tetrahedron Lett.* **2004**, 45, 3569–3572.
230. Brosse, N.; Barth, D.; Jamart-Gregoire, B. *Tetrahedron Lett.* **2004**, 45, 9521–9524.
231. Tšubrik, O. Unpublished results.

232. Cubrika, O (Tšubrik, O). *Latvijas Kimijas Zurnals* **2002**, 118.
233. Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, 56, 7172.
234. Bordwell, F. G.; Harrelson, J. A.; Lynch, T.-Y. *J. Org. Chem.* **1991**, 55, 3337–3341.
235. Zhao, Y.; Bordwell, F. G.; Cheng, J.-P.; Wang, D. *J. Am. Chem. Soc.* **1991**, 119, 9125–9129.
236. Bredikhin, A.; Tšubrik, O.; Sillard, R.; Mäeorg, U. *Synlett* **2005**, 1939–1941.
237. Hegarty, A. F. Chem. Hydrazo, Azo Azoxy Groups. Ed.: Patai, Saul. John Wiley and Sons, **1975**, Vol. 16, 643–723.
238. Tšubrik, O.; Burk, P.; Pehk, T.; Mäeorg, U. *J. Mol. Str. (Theochem)* **2001**, 546, 119–125.
239. Tsuji, J.; Nagashima, T; Qui, N. T.; Takayanagi, H. *Tetrahedron* **1980**, 36, 1311–1315.
240. Jürmann, G.; Tšubrik, O.; Tammeveski, K.; Mäeorg, U. *J. Chem. Res.* **2005**, 661–662.
241. Uemura, T; Chatani, N. *J. Org. Chem.* **2005**, *70*, 8631–8634.

SUMMARY IN ESTONIAN

Käesoleva töö tulemused on esitatud allpool:

- Kirjeldati uut reagenti polüasendatud hüdrasiinide süstemaatiliseks sünteesiks.
  - *Tert*-butoksükarbonüül- ja trifenüülfosfooniumrühmade kombinatisoon andis uue kahe kaitserühmaga prekursori, millel pole analooge. Asenduse selektriivsust garanteerib iminofosforaani teke.
  - Uue prekursori evalueerimise tulemusena sünteesiti rida triasendatud hüdrasiine.
  - Leiti erakordselt efektiivne meetod trifenüülfosfooniumrühma eemaldamiseks.
- Valmistati rida happelisi hüdrasiine, mis sisaldavad selliseid elektronegatiivseid rühmi nagu Ac, Boc, PPh_3, Tf, CF_3CO. Neid ühendeid kasutati hüdrasiini pK_a hindamiseks (DMSO lahuses).
- Töötati välja meetod diasendatud hüdrasiinide $R^1NHNHCOR^2$ kõrgselektiivseks arüülimiseks triarüülbismutdiatsetaatide abil ja vaskkatalüsaatori juuresolekul.
- Uuriti mono-, di- ja triasendatud hüdrasiinide vaskkatalüütilist N-arüülimist, võrdlemaks arüülivate reagentidena triarüülbismutaane ja triarüülbismutdiatsetaate.
  - Töötati välja kiire ja kõrgselektiivne meetod atsüülhüdrasiinide arüülimiseks triarüülbismutdiatsetaatide abil.
  - Näidati, et diatsüülhüdrasiinide ja triasendatud hüdrasiinide efektiivseks arüülimiseks sobivad kõige paremini kolmevalentse bismuti reagendid.
  - Kasutades triasendatud prekursoreid, õnnestus sisse viia steeriliselt takistatud asendajaid, näiteks *o*-tolüül-, 1-naftüül- ja 2-metoksü-4-metüülfenüülrühmi.
  - Sünteesiti rida kahe erineva arüülrühmaga tetraasendatud hüdrasiine.
- Kirjeldati metallorgaaniliste nukleofiilide regioselektiivset liitumist mittesümmeetrilistele asoühenditele ArN=NCOR.
  - Primaarsete, sekundaarsete, tertsiaarsete alküül-, arüül- ja heteroarüülasendajate sisseviimine toimub kõrgete saagistega.
  - Liitumine on kiire ning ei ole eriti tundlik steerilise takistuse suhtes.
  - Tsinkorgaanilised ühendid osutusid kõige efektiivsemateks alküülimisagentideks. Samal ajal magneesiumorgaanilised reagendid sobisid kõige paremini arüülimise jaoks.
- Kirjeldati arüülboroonhapete liitumist asoühenditele.
  - Kasutades müügilolevaid boroonhappeid, õnnestus sisse viia arüül- ja heteroarüülrühmi.
  - Liitumine mittesümmeetrilistele asoühenditele ArN=NBoc toimub suurepärase regioselektiivsusega.

- Valmistati rida Boc-kaitstud diarüülhüdrasiine.

- Kirjeldati bismutorgaaniliste ühendite liitumist asoühenditele.
  - Liitumine mittesümmeetrilistele asoühenditele ArN=NBoc toimub suurepärase regioselektiivsusega.
  - Reaktsioon ei ole eriti tundlik steerilise takistuse suhtes. Rahuldavad tulemused saadi *o*-tolüül ja 1-naftüülrühmade sisseviimisel.
  - Reaktsioon on kiire ning optimeeritud tingimustel on saagised suurepärased.
  - Valmistati rida Boc-kaitstud diarüülhüdrasiine.

ACKNOWLEDGEMENTS

First of all, without my supervisor, Assoc. Prof. Uno Mäeorg, this work would have never been done. Thank you very much for your continuous support, endless patience, warm encouragement and enthusiastic guidance.

Also, I would like to express my sincere gratitude to Prof. Ulf Ragnarsson for his support and collaboration.

I wish to thank Assoc. Prof. Rein Pullerits for organization of Estonian Chemistry Olympiads, which stimulated me on my way to become a chemist.

Thanks to all the people in Organic and Bioorganic Chemistry Institute where this work was conducted:

Ksenija Kisseljova, who was a wonderful colleague and the most hardworking student in the University,

Aleksei Bredikhin, who was a great company in the lab for several years, always diligent and extremely creative,

Eerold Vellemäe and Pavel Starkov, who were enthusiastic collaborators,

Sirje Mäeorg for help with IR analyses,

Vahur Mäemets for assisting with NMR apparatus.

I wish to thank Prof. Valentin Wittmann (University of Konstanz) for the possibility to work in his group.

Thanks to Prof. P. Trapencieris and his colleagues for help with microanalyses.

Financial support from Estonian Science Foundation (grant no. 5255 and 6706) is gratefully acknowledged.

Special thanks to my friends for their understanding and support.

And finally, I would like to thank my family for their love and encouragement.

PUBLICATIONS

Reprinted with permission from *Organic Letters*, **2001**, 3, 2297–2299, Tšubrik, O.; Mäeorg, U., Combination of *tert*-Butoxycarbonyl and Triphenylphosphonium Protecting Groups in the Synthesis of Substituted Hydrazines.

Reprinted with permission from *Journal of Organic Chemistry*, **2005**, 70, 5916–5921, Ragnarsson, U.; Grehn, L.; Koppel, J.; Loog, O.; Tšubrik, O.; Bredikhin, A.; Maeorg, U.; Koppel, I. Acidity of di- and triprotected hydrazine derivatives in dimethyl sulfoxide and aspects of their alkylation.

Reprinted with permission from *Tetrahedron Letters*, **2002**, 43, 6213–6215, Tšubrik, O.; Mäeorg, U.; Ragnarsson, U. Highly selective arylation of disubstituted hydrazines by pentavalent organobismuth reagents.

Reprinted with permission from *Tetrahedron*, **2004**, 60, 8363–8373, Tšubrik, O.; Mäeorg, U.; Ragnarsson, U. Arylation of diversely substituted hydrazines using tri- and pentavalent organobismuth compounds.

Reprinted with permission from *Synthesis*, **2006**, 60, 843–846, Tšubrik, O.; Sillard, R.; Mäeorg, U. Novel, efficient and regiospecific alkylation/arylation/heteroarylation of unsymmetrical azo-compounds..

Reprinted with permission from *Organic Letters*, **2006**, 8, 43–45, Kisseljova, K.; Tšubrik, O.; Sillard, R.; Mäeorg, S.; Mäeorg, U. Addition of arylboronic acids to symmetrical and unsymmetrical azo compounds.

Copper salt catalyzed addition of triarylbismuthanes and triarylbismuth diacetates to symmetrical and unsymmetrical azo compounds. Tšubrik, O.; Kisseljova, K.; Mäeorg, U. Submitted.

CURRICULUM VITAE

OLGA TŠUBRIK

Date and place of birth:	November 25, 1979, Tallinn, Estonia
Citizenship:	Estonian
Family Status:	Single
Address:	Institute of Organic and Bioorganic Chemistry, University of Tartu, Jakobi 2, 51014, Tartu Estonia
Phone:	+372 7375233
Fax:	+372 7375245
E-mail:	olga7@ut.ee

Education

1987–1997	Tallinn Tõnismäe Reaalkool
1997–2000	University of Tartu, Department of Chemistry Graduated as Bachelor of Science, BSc, *cum laude*
2000–2002	University of Tartu, Department of Chemistry Graduated as Master of Science, MSc (organic chemistry)
2002–2006	University of Tartu, Department of Chemistry PhD studies

Employment

2003–	Institute of Organic and Bioorganic Chemistry, University of Tartu. Research Assistant

Professional experiences and training

University of Uppsala (Sweden), 2001, August-October, in the group of Prof. Stefan Sjöberg.
University of Konstanz (Germany), 2004, January-March, in the group of Prof. Valentin Wittmann.
NORFA (Nordic Academy for Advanced Study), Druskininkai, Lithuania – course "Today's research training – tomorrow's scientific quality", 2004, June 5–12.

OY Galilaeus, Turku, Finland – a training visit to pharmaceutical company, 2004, September.

Main scientific publications

1. Tšubrik, O.; Burk, P.; Pehk, T.; Mäeorg, U. Conformational Analysis of 1-Acetyl-2-methylhydrazine. *J. Mol. Struct. (THEOCHEM)* **2001**, *546*, 119–125.
2. Tšubrik, O.; Mäeorg, U. Combination of *tert*-Butoxycarbonyl and Triphenylphosphonium Protecting Groups in the Synthesis of Substituted Hydrazines. *Org. Lett.* **2001**, *3*, 2297–2299.
3. Tšubrik, O.; Mäeorg, U.; Ragnarsson, U. Highly selective arylation of disubstituted hydrazines by pentavalent organobismuth reagents. *Tetrahedron Letters* **2002**, *43*, 6213–6215.
4. Tšubrik, O.; Mäeorg, U.; Ragnarsson, U. Arylation of diversely substituted hydrazines using tri- and pentavalent organobismuth compounds. *Tetrahedron* **2004**, *60*, 8363–8373.
5. Ragnarsson, U.; Grehn, L.; Koppel, J.; Loog, O.; Tšubrik, O.; Bredikhin, A.; Mäeorg, U.; Koppel, I. Acidity of di- and triprotected hydrazine derivatives in dimethyl sulfoxide and aspects of their alkylation. *J. Org. Chem.* **2005**, *70*, 5916–5921.
6. Bredikhin, A.; Tšubrik, O.; Sillard, R.; Mäeorg, U. Increasing the N-H acidity: Introduction of highly electronegative groups into the hydrazine molecule. *Synlett* **2005**, 1939–1941.
7. Jürmann, G.; Tšubrik, O.; Tammeveski, K.; Mäeorg, U. Investigation of the oxidation ability of the protected hydrazine derivatives. *J. Chem. Res.* **2005**, 661–662.
8. Vellemäe, E.; Tšubrik, U.; Mäeorg, S.; Mäeorg. U. Mischmetall and Zn-Cu couple as efficient reagents for the pinacol coupling of aldimines. *J. Chem. Res.* **2006**, 149–150.
9. Tšubrik, O.; Sillard, R.; Mäeorg, U. Novel, efficient and regiospecific alkylation/arylation/heteroarylation of unsymmetrical azo-compounds. *Synthesis* **2006**, 843–846.
10. Kisseljova, K.; Tšubrik, O.; Sillard, R.; Mäeorg, U. Addition of arylboronic acids to symmetrical and unsymmetrical azo compounds. *Org. Lett.* **2006**, *8,* 43–45.
11. Tšubrik, O.; Kisseljova, K.; Mäeorg, U. Copper salt catalyzed addition of triarylbismuthanes and triarylbismuth diacetates to symmetrical and unsymmetrical azo compounds. Submitted.

Participated in 15 international and 5 local conferences.

CURRICULUM VITAE

OLGA TŠUBRIK

Sündinud:	25. november, 1979, Tallinn, Estonia
Kodakondsus:	Eesti
Perekonnaseis:	vallaline
Aadress:	Orgaanilise ja Bioorgaanilise keemia instituut, Tartu Ülikool, Jakobi 2, 51014, Tartu, Eesti
Tel.:	+372 7375233
Faks:	+372 7375245
E-post:	olga7@ut.ee

Haridus

1987–1997	Tallinna Tõnismäe Reaalkool
1997–2000	Tartu Ülikool, Keemiaosakond Bakalaureusekraad, BSc, *cum laude*
2000–2002	Tartu Ülikool, Keemiaosakond Magistrikraad, MSc (orgaaniline keemia)
2002–2006	Tartu Ülikool, Keemiaosakond, doktorant

Teenistuskäik

2003–	Tartu Ülikool, Orgaanilise ja Bioorgaanilise keemia instituut Erakorraline teadur

Erialane enesetäiendus

Uppsala Ülikool (Rootsi), 2001, August-Oktoober, Prof. Stefan Sjöberg'i uurimisgrupis.
Konstanzi Ülikool (Saksamaa), 2004, Jaanuar-Märts, Prof. Valentin Wittmann'i uurimisgrupis.
NORFA (Nordic Academy for Advanced Study), Druskininkai, Leedu – osalenud kursusel "Today's research training – tomorrow's scientific quality", 2004, June 5–12.
OY Galilaeus, Turku, Soome – erialane treening farmaatsiafirmas, 2004, September.

Tähtsamad teaduspublikatsioonid

1. Tšubrik, O.; Burk, P.; Pehk, T.; Mäeorg, U. Conformational Analysis of 1-Acetyl-2-methylhydrazine. *J. Mol. Struct. (THEOCHEM)* **2001**, *546*, 119–125.
2. Tšubrik, O.; Mäeorg, U. Combination of *tert*-Butoxycarbonyl and Triphenylphosphonium Protecting Groups in the Synthesis of Substituted Hydrazines. *Org. Lett.* **2001**, *3*, 2297–2299.
3. Tšubrik, O.; Mäeorg, U.; Ragnarsson, U. Highly selective arylation of disubstituted hydrazines by pentavalent organobismuth reagents. *Tetrahedron Letters* **2002**, *43*, 6213–6215.
4. Tšubrik, O.; Mäeorg, U.; Ragnarsson, U. Arylation of diversely substituted hydrazines using tri- and pentavalent organobismuth compounds. *Tetrahedron* **2004**, *60*, 8363–8373.
5. Ragnarsson, U.; Grehn, L.; Koppel, J.; Loog, O.; Tšubrik, O.; Bredikhin, A.; Mäeorg, U.; Koppel, I. Acidity of di- and triprotected hydrazine derivatives in dimethyl sulfoxide and aspects of their alkylation. *J. Org. Chem.* **2005**, *70*, 5916–5921.
6. Bredikhin, A.; Tšubrik, O.; Sillard, R.; Mäeorg, U. Increasing the N-H acidity: Introduction of highly electronegative groups into the hydrazine molecule. *Synlett* **2005**, 1939–1941.
7. Jürmann, G.; Tšubrik, O.; Tammeveski, K.; Mäeorg, U. Investigation of the oxidation ability of the protected hydrazine derivatives. *J. Chem. Res.* **2005**, 661–662.
8. Vellemäe, E.; Tšubrik, U.; Mäeorg, S.; Mäeorg. U. Mischmetall and Zn-Cu couple as efficient reagents for the pinacol coupling of aldimines. *J. Chem. Res.* **2006**, 149–150.
9. Tšubrik, O.; Sillard, R.; Mäeorg, U. Novel, efficient and regiospecific alkylation/arylation/heteroarylation of unsymmetrical azo-compounds. *Synthesis* **2006**, 843–846.
10. Kisseljova, K.; Tšubrik, O.; Sillard, R.; Mäeorg, U. Addition of arylboronic acids to symmetrical and unsymmetrical azo compounds. *Org. Lett.* **2006**, *8,* 43–45.
11. Tšubrik, O.; Kisseljova, K.; Mäeorg, U. Copper salt catalyzed addition of triarylbismuthanes and triarylbismuth diacetates to symmetrical and unsymmetrical azo compounds. Submitted.

Osalenud 15 rahvusvahelisel ja 5 kohalikul konverentsidel.