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Institute of Chemistry, Faculty of Science and Technology, University of Tartu, Estonia

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Everything is theoretically impossible, until it is done.

Robert A. Heinlein

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LIST OF ORIGINAL PUBLICATIONS

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II. **Lebedev, O**.; Mäeorg, U. Metal-halogen exchange between hydrazine polyanions and α,α'-dibromo-*o*-xylene. *Organometallics* **2014**, *33*, 188–193.

III. Verendel, J. J.; Zhou, T.; Li, J.-Q.; Paptchikhine, A.; **Lebedev, O.**; Andersson, P. G. Highly selective synthesis of chiral azacycles via iridium-catalyzed hydrogenation. *J. Am. Chem. Soc.* **2010**, *132*, 8880–8881.

IV. Tšupova, S.; **Lebedev, O.**; Mäeorg, U. Combination of hydrazine polyanion strategy and ring-closing metathesis in the synthesis of heterocycles. *Tetrahedron* **2012**, *68*, 1011–1016.

Author's contribution

Paper I: Performed the major part of the experimental work. Prepared the manuscript.

Paper II: Responsible for project planning. Performed all the experimental work. Prepared the manuscript.

Paper III: Synthesized seven-membered heterocycles for asymmetric hydrogenation. Helped to prepare the manuscript.

Paper IV: Responsible for project planning. Performed a share of the experimental work. Prepared the manuscript.

ABBREVIATIONS

Ac	acetyl
All	allyl
aq	aqueous
Ar	aryl
ATR	attenuated total reflectance
BAr_F^-	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bt	benzotriazolyl
n-Bu	butyl
t-Bu	*tert*-butyl
BuLi	butyllithium
Bz	benzoyl
cat	catalyst
Cbz	benzyloxycarbonyl
Cy	cyclohexyl
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)-pyridine
DMF	dimethylformamide
DMPU	*N*,*N*′-dimethylpropylene urea or 1,3-Dimethyl-2-oxohexahydropyrimidine
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppp	1,3-bis(diphenylphosphino)propane
ESI	electrospray ionization
ESR	electron spin resonance
Et	ethyl
equiv	equivalent
FTIR	Fourier transform infrared spectroscopy
G-I	Grubbs 1st generation catalyst
G-II	Grubbs 2nd generation catalyst
HG-II	Hoveyda-Grubbs 2nd generation catalyst
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
LDA	lithium diisopropylamide
LiHDMS	lithium hexamethyldisilazide
Me	methyl
Mes	mesityl or 2,4,6-trimethylphenyl
Ms	mesyl or methylsulfonyl

MW	microwave irradiation
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
Ns	nosyl or *para*-nitrophenylsulfonyl
Ph	phenyl
Pr	1-propyl
i-Pr	2-propyl
PTC	phase transfer catalysis
RCM	ring-closing metathesis
rt	room temperature
SAMP	(S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogensulfate
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl or *para*-toluenesulfonyl

1. INTRODUCTION

Hydrazine derivatives are well-known compounds which have found their applications in pharmaceutical, agrochemical, polymer and dye industries [1]. In contrary to existing beliefs about toxicity of hydrazine derivatives, numerous natural compounds comprising N-N bond have been isolated from living organisms [2]. Many of hydrazine derivatives show remarkable biological activity inducing an interest of drug developers [3].

There are many known examples of hydrazine-based drugs from pharmaceutical industry. Historically the hydrazines bonded to an aromatic core through one or several carbons, e.g. Phenelzine or Isocarboxazid, have been used as antidepressant drugs due to their neuroprotective properties [4]. Some of hydrazine derivatives were found to be active as cyclooxygenase-2 (COX-2) inhibitors, what is essential for development of non-steroidal anti-inflammatory drugs, e.g. Celecoxib and Phenylbutazone [5]. Isoniazid is used as the medication for prevention and treatment of tuberculosis since 1950-s and still have not lost its value [1, 6]. Hydralazine, containing even two hydrazine moieties, and Cilazapril are successfully applied for treatment of hypertension [7, 8]. Hydrazine derivatives even with a very simple structure may have a strong drug potency. For example, 2-(2-Carboxyethyl)-1,1,1-trimethylhydrazinium or Mildronate, is a known cardioprotective drug [9]. In recent years some hydrazine derivatives were found to exhibit protease inhibition and anticancer properties, what opened the door for new applications. For example, Atazanavir is nowadays one of the most efficient drugs used to treat infection of human immunodeficiency virus (HIV) [10, 11]. Ibrutinib is a novel anticancer drug which was recently approved by FDA for treatment of chronic lymphosatic leukemia [12, 13]. Structures of some of the named drugs are shown on Figure 1.

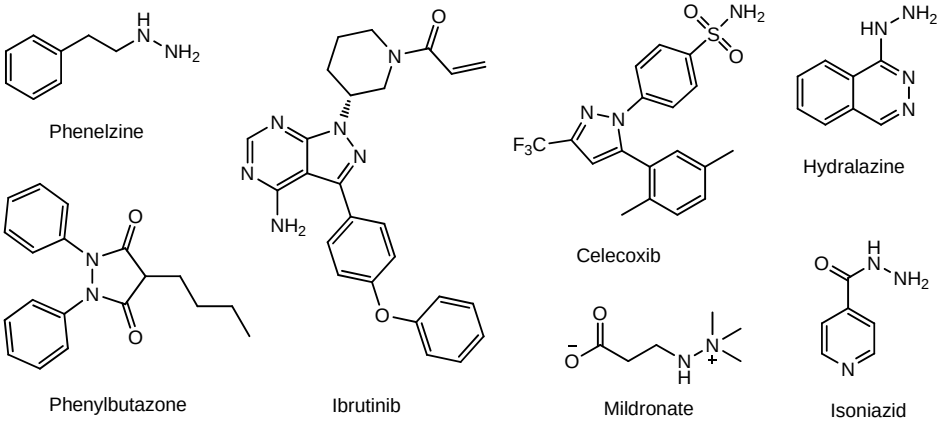


Figure 1. Some examples of hydrazine-based drugs

In addition, a significant biological activity of hydrazine derivatives has found an application in the development of new pesticides. For example, *N*-*tert*-butyl diacylated hydrazines are used in agrochemical industry as environmentally safe and selective insecticides (Figure 2) [14−16].

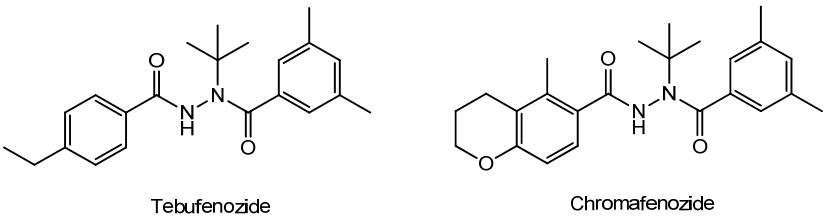


Figure 2. Some examples of hydrazine-based pesticides

As it can be seen from Figure 1, many of the abovementioned hydrazine-based drugs, e.g. Hydralazine, Ibrutinib, Celecoxib, etc., are actually heterocyclic compounds. More than 70% of all pharmaceuticals and agrochemicals contain at least one heterocyclic ring and over 90% of all pharmaceuticals have at least one nitrogen atom in their structure [17, 18]. Approximately one reaction out of seven carried out in pharmaceutical industry includes a formation of a carbon-nitrogen bond [19]. These numbers illustrate that the development of new efficient routes to nitrogen-containing molecules and particularly for heterocycles is extremely important.

In recent years a significant progress in the synthesis of multisubstituted hydrazines has been achieved. Approximately 20 years ago a first systematic strategy implying the use of orthogonally protected precursors was presented [20−21]. After introducing the significant improvements targeted to decrease the number of the involved protecting groups and to increase the efficiency of the synthesis, the orthogonal group based strategy still remained quite sluggish requiring additional protection and deprotection steps [22].

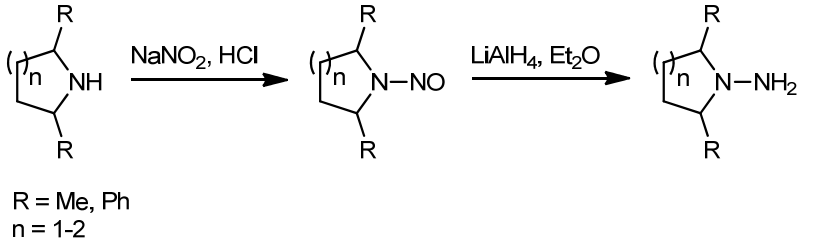
Lately, a new strategy based on the selective alkylation of hydrazine poly-anions has been demonstrated [23−25]. This approach provides fast and easy access to multisubstituted products, what makes it an excellent tool for the synthesis of cyclic hydrazines. The current thesis is a step forward in the chemistry of hydrazine polyanions focusing on the synthesis of different types of cyclic hydrazines.

2. LITERATURE OVERVIEW

2.1. Synthesis of cyclic hydrazines comprising exocyclic N-N bond

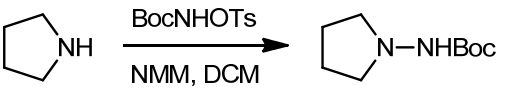
Hydrazines comprising exocyclic N-N bond may be considered as *N,N*-disubstituted hydrazines. Considering the structure, there are two possible synthesis strategies for these types of compounds. The first approach is based on the construction of the ring on the existing hydrazine core. The other strategy involves the formation of the N-N bond between the corresponding cyclic amines and a nitrogen donor. Since building of even the simplest cyclic scaffolds on the NH_2 group of a hydrazine derivative does not proceed always smoothly, the second strategy is currently dominating.

There are several existing methods for the synthesis of hydrazines from the corresponding amines [3]. The method for N-N bond formation *via* amine nitrosation by $NaNO_2$ in acidic conditions with subsequent reduction of the nitroso intermediate by $LiAlH_4$ has found its application in the synthesis of hydrazine-based heterocycles and still seems to be very popular [26−29]. G. C. Overberger was a pioneer and prepared a series of substituted *N*-amino-pyrrolidines and *N*-aminopiperidines according to this method (Scheme 1) [30−31].



Scheme 1. Synthesis of cyclic hydrazines by Overberger *et al.*

Despite the simplicity and the robustness of the nitrosation-based method, it has also a significant drawback: cyclic nitrosamines obtained as intermediates are considered to be carcinogens and mutagens [32]. Therefore, alternative *N*-amination methods are still highly welcome. The pioneering work of Collet and co-workers has demonstrated that *N*-Boc oxaziridine derivatives are powerful electrophilic aminating agents being able to convert secondary and cyclic amines to the corresponding protected hydrazines [33, 34]. Very recently, Baburaj *et al.* reported the use of BocNHOTs as a more efficient aminating agent, providing one example also for cyclic amines (Scheme 2) [35].



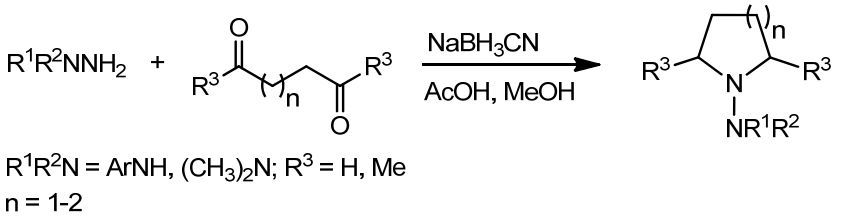
Scheme 2. *N*-amination of cyclic amines with BocNHOTs

The reaction between NH_2 group of a hydrazine derivative and bifunctional compounds seems to be an attractive strategy for designing of a cyclic frame on a hydrazine core. Dihalides look as good and readily available candidates for cyclization, but not all of them can be used to achieve good or even moderate yields for the corresponding heterocycles. Aromatic species containing two halomethyl groups have been successfully utilized for alkylation of $BocNHNH_2$ applying triethylamine as a base (Scheme 3) [36, 37]. Dibromides keep giving significantly better yields than dichlorides [38]. However, 1-(2-chloroethyl)-2-chloromethylbenzene, which contains only one additional methylene group between the benzene ring and the halide center, cannot be employed at the same conditions, affording the desired heterocycles in very poor yields [26]. So, the substitution of already one benzyl-activated halide center to an ordinary alkyl halide becomes crucial for cyclization failure. Aliphatic dibromides reacting with hydrazine hydrate provide the corresponding 5- and 6-membered rings in low to moderate yields even if a great excess of hydrazine hydrate and heating are used [30, 39, 40]. Aliphatic dimesylates show the same tendency – a huge excess of hydrazine hydrate is needed to lead the cyclization to completeness [41, 42].

Scheme 3. Cyclization of $BocNHNH_2$ with α,α'-dibromo-*o*-xylene

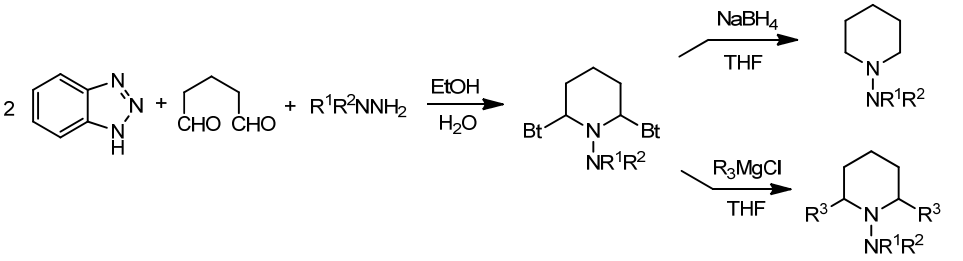
The described reaction seems to be sensitive to both electrophilicity and the position of the reaction centers. Bis(halomethyl)aromatic compounds are much stronger electrophiles than aliphatic dihalides. In addition, bis(halomethyl)-aromatic species have a rigid structure, simplifying an access to the reaction centers for a nucleophile. These factors, in turn, restrain the use of aliphatic analogues for the same purpose.

Dialdehydes and diketones have been applied for reductive alkylation of alkyl- and arylsubstituted hydrazines with a greater success (Scheme 4) [43, 44]. The reaction proceeds through the formation of imines that are reduced by $NaBH_3CN$ in one-pot fashion. The corresponding heterocycles are obtained in moderate yields.



Scheme 4. Reductive alkylation of hydrazines with dicarbonyl compounds

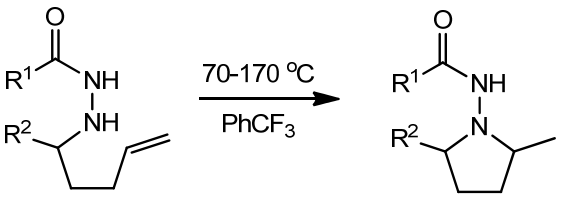
Katritzky *et al.* have significantly improved the method particularly for dialdehydes, introducing benzotriazole as a synthesis auxiliary [45]. Double condensation of benzotriazole and glutaraldehyde with different hydrazines in aqueous medium afforded *N*-substituted 2,6-bis(benzotriazolyl)piperidines. Benzotriazole moiety can be easily removed by reduction with $NaBH_4$ to provide the corresponding unsubstituted aminopiperidines in very good yields. Benzotriazole adducts may be also functionalized by the reaction with Grignard reagents to introduce alkyl- or aryl- substituents to the positions 2 and 6 in the piperidine ring (Scheme 5). The role of benzotriazole consists in the reaction with an aldehyde to form the iminium ion, which acts as an electrophile reacting with hydrazines, thus making the method similar to the classic Mannich reaction [46].



Scheme 5. Synthesis of *N*-substituted piperidines by Katritzky *et al.*

Hydrazines containing a terminal double bond on a side chain may be subjected to a ring-closure analogously with intramolecular hydroamination. Hydroamination reaction is the addition of an N-H bond to a multiple carbon-carbon bond, commonly to alkenes. The first examples of La-catalyzed intramolecular hydroamination were reported by Marks group in 1989 [47]. Since that time this relatively new and atom economical chemistry has induced a sharp interest of the scientific community [48]. In recent years, several protocols employing

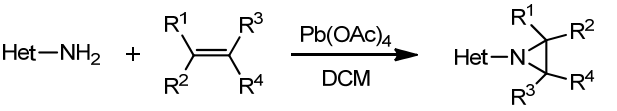
alkenyl hydrazines and being based on either transition metal-catalyzed [49, 50] or metal-free process [51−53] have appeared. For example, Loiseau *et al.* demonstrated that a variety of hydrazines undergo intramolecular hydro-hydrazination simply upon heating (Scheme 6) [52].



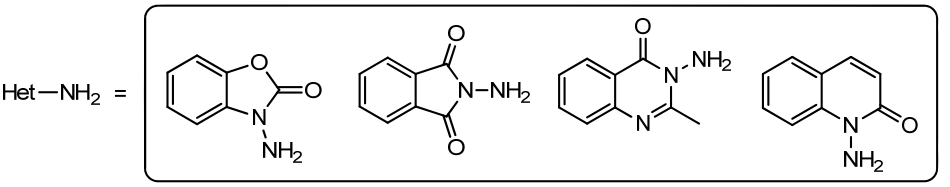
R^1 = *t*-Bu, Ar; R^2 = H, Me

Scheme 6. Intramolecular hydrohydrazination assisted by heating

Another process that involves the reaction of hydrazines and alkenes is aziridination. These nitrogen-containing strained heterocycles are of great interest because of their enormous synthetic potential and amenability to ring-opening reactions with a variety of nucleophiles [54]. Rees and co-workers first demonstrated that a variety of *N*-aminoheterocyclic compounds oxidized by $Pb(OAc)_4$ in the presence of alkenes afford the corresponding aziridines (Scheme 7) [55, 56]. The additions to *Z*- and *E*-alkenes were stereoselective. It was assumed that *N*-nitrene is involved in the reaction as an intermediate, which is generated by the oxidation of the starting hydrazine with $Pb(OAc)_4$. In recent years other chemical oxidation systems [57−59] and electrochemical solutions [60] have been reported for the synthesis of *N*-substituted aziridines.



R^1 = Me, *t*-Bu, Ph, Ac, Cl, COOMe, COOEt; R^2 = H, Me; R^3 = H, Me;
R^4 = H, Me, Cl, COOEt; R^1,R^3 = -$(CH_2)_4$-, -$(CH_2)_6$-



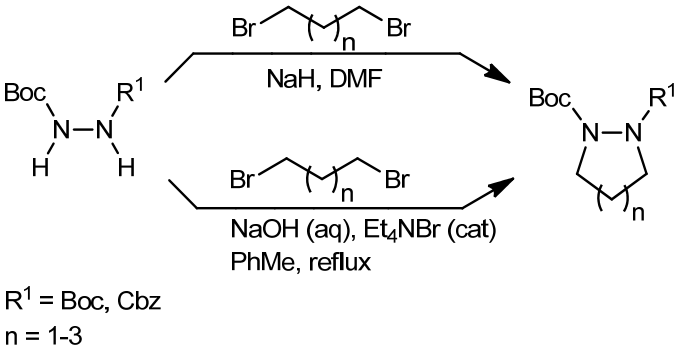
Scheme 7. Synthesis of *N*-substituted aziridines by Rees *et al.*

2.2. Synthesis of cyclic hydrazines comprising endocyclic N-N bond

The most popular way to generate pyrazolidine homologs is based on the direct alkylation of disubstituted hydrazines with dihalides. Commonly 1,2-disubstituted hydrazine derivatives are treated with 2 equiv of a strong base before addition of the alkylating agent. The first description of the synthesis of pyrazolidines is dated 1940, according to which Wittig treated PhNHNHPh with 2 equiv of MeLi in ether followed by addition of 1,3-dibromopropane [61]. Carpino *et al.* first reported the use of 2 equiv of *t*-BuOK in *t*-BuOH for deprotonation of BocNHNHBoc with subsequent addition of a dihalide [62]. Overberger *et al.* utilized 2 equiv of NaH in diglyme for the same purpose [63].

Nowadays NaH dispersion in DMF [14, 64–66] or THF [67] is frequently used for deprotonation of the starting hydrazine derivative. Commonly dibromides are employed as alkylating agents, though dimesylates [68] or ditosylates [63] may be applied as alternatives (Scheme 8). Generally reactions proceed at room temperature; however, the yields strongly depend on the ring size of the final product: whereas 5- and 6-membered rings can be mostly obtained in very good yields, a significant drop of the yield values is observed for the rings of bigger size [14].

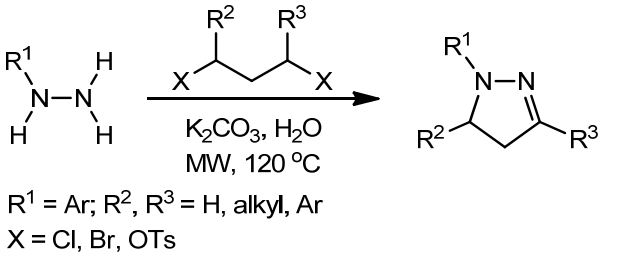
Some researchers reported that significantly milder conditions utilizing 50% NaOH aqueous solution as a base and Et_4NBr as a phase transfer catalyst may be applied for the synthesis of 5- to 7-membered rings (Scheme 8) [69, 70]. Nevertheless, elevated temperatures were required to lead the reaction to the desired extent.



Scheme 8. Commonly used methods for direct alkylation of 1,2-disubstituted hydrazines by dibromides

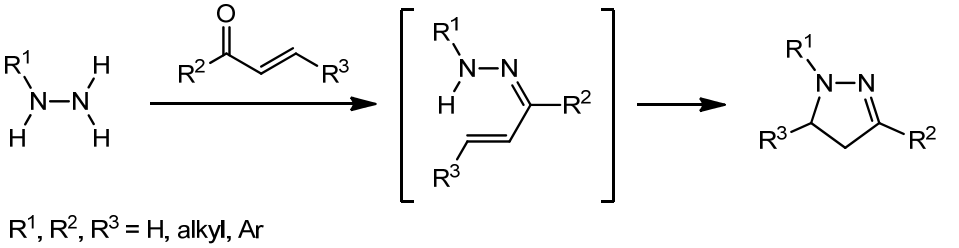
Recently Ju and Varna reported a new method of the synthesis of 2-pyrazolines which fully matches the concept of green chemistry [71]. Monosubstituted hydrazines were alkylated by dihalides or ditosylates in aqueous media under

microwave irradiation in the presence of K_2CO_3 (Scheme 9). Further stirring of the reaction mixture in contact with oxygen promoted the formation of the C=N bond. The desired products were obtained in good yields, employing a variety of dihalides. However, the method has also a limitation: apparently, hydrazines containing commonly used carbazate-type protecting groups cannot be employed due to problems with stability under the applied reaction conditions.



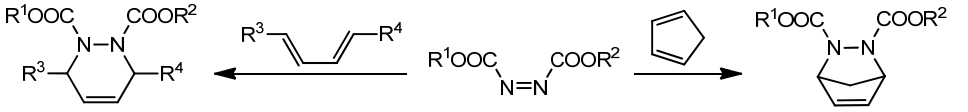
Scheme 9. Synthesis of 2-pyrazolines by Ju and Varna

The most popular way of synthesis of 2-pyrazolines is based on the reaction of hydrazines with α,β-unsaturated ketones (Scheme 10) [72–74]. This reaction was first discovered by Fischer and Knoevenagel, when they found that acrolein reacting with phenyl hydrazine affords the corresponding 2-pyrazoline instead of the expected hydrazone. Later it was confirmed that in this reaction α,β-unsaturated hydrazones are intermediates, which undergo further rearrangement [75]. Varying the structures of α,β-unsaturated ketones, it is possible to introduce different substituents into the 5-membered cycle. Recently it was reported that α,β-unsaturated ketones may be generated *in situ* from the corresponding propargyl alcohols and further coupled with hydrazines [76]. 2-pyrazolines may be easily reduced to the corresponding pyrazolidines by $LiBEt_3H$ [77, 78].



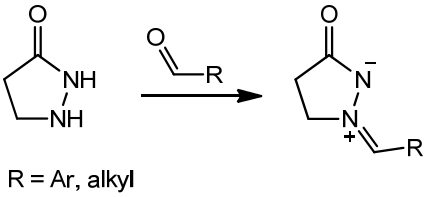
Scheme 10. Condensation of α,β-unsaturated carbonyl compounds with hydrazines

[4+2] cycloaddition of a conjugated diene and a dienophile, known as the Diels-Alder reaction, is a powerful tool for construction of 6-membered rings. Particularly, hetero-Diels-Alder reaction between azo compounds and corresponding dienes is a popular method for the synthesis of tetrahydropyridazines [79–81], which may be further reduced by H_2 on Pd/C [82] or PtO_2 [83]. Application of cyclic dienes allows to construct different fused ring systems [80, 84] (Scheme 11). The yields and the reaction times are strongly dependent on the structure of the substrates. For example, dienes containing strongly electron withdrawing groups demonstrate a tendency to have longer reaction times [82, 85]; however, the reaction rates and the yields may be significantly increased, applying microwave irradiation [85] or $La(OTf)_3$ catalysis [86]. Also, the Diels-Alder reaction is known to be stereospecific with respect to both the diene and the dienophile; therefore, 1,4-disubstituted dienes may be used to afford 3,6-disubstituted tetrahydropyridazines with the desired chirality [82, 86]. In some cases azo-compounds may be generated *in situ* by oxidation of the corresponding hydrazines with NBS [87]. The major limitation of the Diels-Alder reaction is that it is not applicable for the synthesis of cyclic systems other than 6-membered rings.



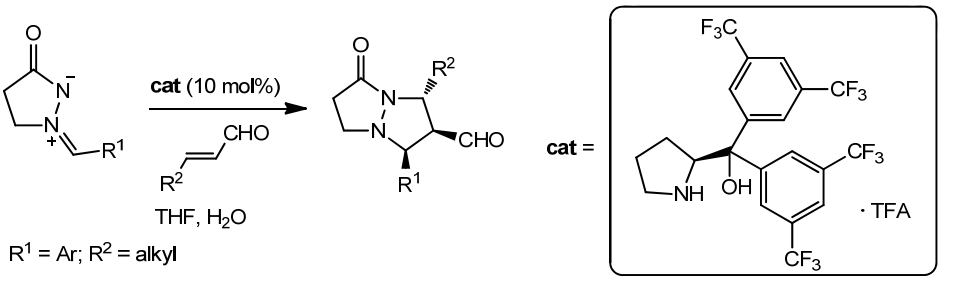
Scheme 11. Typical hetero-Diels-Alder reactions of azo compounds

Asymmetric [3+2] cycloadditions of azomethine imines with α,β-unsaturated carbonyl compounds is a powerful tool for construction of 5-membered heterocycles with the desired chirality. Azomethine imines may be easily prepared by a condensation of a suitable cyclic hydrazine with the corresponding aldehyde (Scheme 12) [88, 89], but other methods are also known [90].



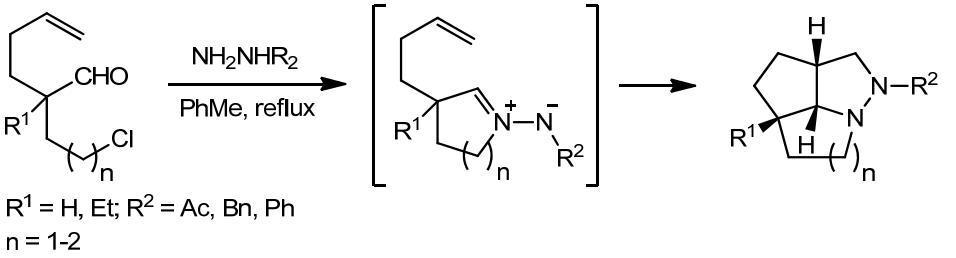
Scheme 12. Typical synthesis of cyclic azomethine imines

Enantioselective 1,3-dipolar cycloaddition of azomethine imines with olefins is reported to be efficiently catalyzed either with chiral metal complexes [91–93] or chiral secondary amines [88, 94]. For example, Chen *et al.* reported an efficient protocol for cycloaddition of azomethine imines with α,β-unsaturated aldehydes catalyzed by α,α-diarylprolinol salts to afford preferably the *exo*-cycles in good to excellent *ee* values (Scheme 13) [88].



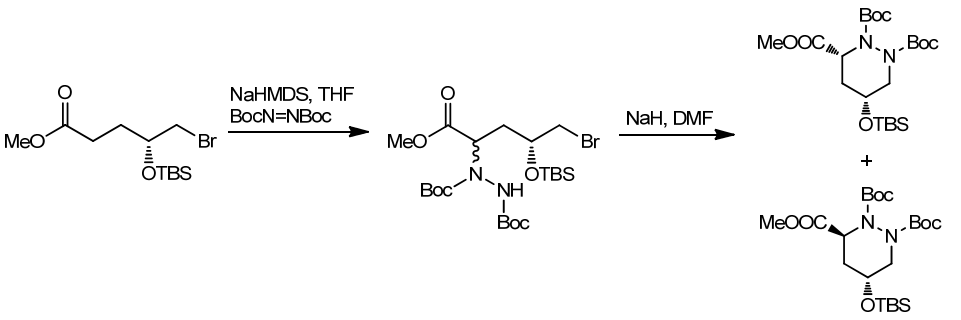
Scheme 13. Asymmetric [3+2] cycloaddition of azomethine imines with α,β-unsaturated aldehydes

In recent years the scope of this reaction has been significantly expanded. Similar [3+2] cycloaddition reactions were reported also with homoallylic alcohols [95], α,β-unsaturated nitriles [96], allenes [97] and alkynes [98] acting as dipolarophiles. Also, Guerrard *et al.* recently reported an interesting cascade one-pot reaction of chloro-enals with monosubstituted hydrazines [99]. The chemistry involved *in situ* formation of hydrazones and azomethine imines as intermediates followed by intramolecular [3+2] cycloaddition at the final step. Tricyclic fused-ring systems were obtained with good diastereoselectivity (Scheme 14).



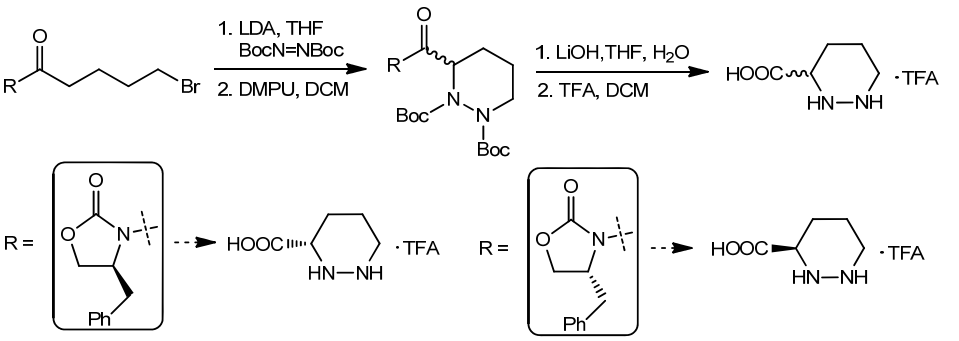
Scheme 14. Cascade one-pot reaction of chloro-enals with monosubstituted hydrazines

Hydrazination of enolates containing a halogen substituent on the side chain with azo compounds and further cyclization constitutes another method for the synthesis of hydrazine-based heterocycles. This method is especially convenient for the synthesis of biologically active piperazic acid moiety, as the corresponding 5-bromovaleric acid derivatives are readily available. The reaction starts with the deprotonation of an active methylene group with a strong base following by electrophilic hydrazination of the obtained enolate with azodicarboxylate. On the next step nucleophilic displacement of the bromide completes the cyclization (Scheme 15) [100, 101].



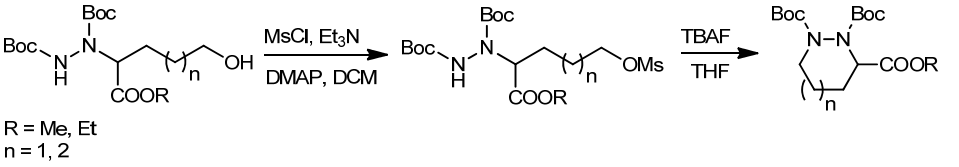
Scheme 15. Hydrazination of bromovaleryl enolate and subsequent intramolecular cyclization

In 1986, Evans and co-workers demonstrated that electrophilic hydrazination of chiral lithium enolates derived from *N*-acyloxazolidones proceeds stereoselectively, giving the hydrazide adducts in excellent yields and very high *ee* values [102]. Some years later, Hale *et al.* performed the hydrazination of chiral bromovaleryl carboxamide enolates with BocN=NBoc according to the Evans protocol. Tandem cyclization of the resulting aza anion promoted by the addition of DMPU, removal of the oxazolidone moiety by the hydrolysis with LiOH, and *N*-deprotonation with TFA afforded (*3R*)- and (*3S*)-piperazic acids with very high *ee* values (Scheme 16) [103]. Evans' chiral auxiliaries were further successfully utilized in the synthesis of more complex piperazic acid derivatives [104, 105]. Proline derivatives were also reported to be efficient chiral auxiliaries for asymmetric α-hydrazination as a key step in the synthesis of piperazic acid moiety [8, 106].



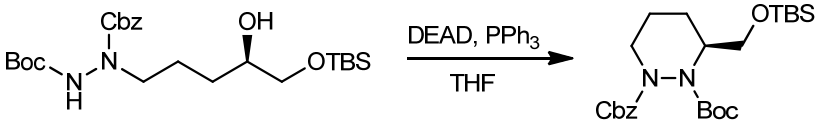
Scheme 16. Synthesis of (*3R*)- and (*3S*)-piperazic acids by Hale *et al.*

Hydrazines bearing a hydroxyl group on a side chain may be subjected to intramolecular cyclization. Commonly at first alcohols are converted to the corresponding mesylates, and further intramolecular alkylation is induced employing standard alkylation conditions, such as NaH/DMF [107] or TBAF/THF [108] (Scheme 17).



Scheme 17. Cyclization of OH-group bearing hydrazines through mesylation and intramolecular alkylation

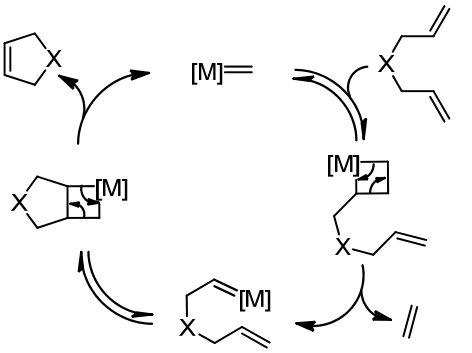
Another approach is based on a straightforward intramolecular Mitsunobu reaction without involvement of a protecting group, which was demonstrated by Aoyagi *et al*. (Scheme 18) [109]. An advantage of the Mitsunobu protocol is especially revealed if chiral alcohols are utilized, as the reaction proceeds with an inversion on the chiral center and affords the products with high enantiomeric purity.



Scheme 18. Cyclization of OH-group bearing hydrazines *via* Mitsunobu reaction

2.3. Ring-closing metathesis in the synthesis of heterocycles

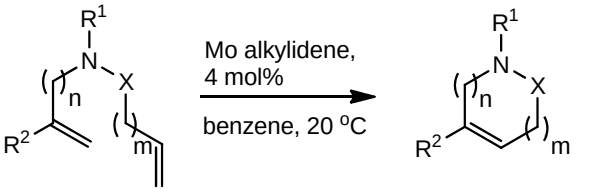
Over the last two decades ring-closing metathesis (RCM) has emerged as a very convenient tool and one of the most widely used approaches in the synthesis of carbo- and heterocycles [110]. RCM is an intramolecular olefin metathesis, yielding the medium-to-large ring and a volatile alkene, mostly ethylene. The reaction is catalyzed by metal transition complexes and driven by a continuous removal of ethylene from the reaction mixture, thus making the ring-closure reaction practically irreversible. It is generally accepted that the RCM proceeds analogously with acyclic olefin metathesis *via* metallacyclobutane and metal-carbene intermediates (Scheme 19) [111].



[M]= = active catalyst complex
X = C or heteroatom

Scheme 19. Mechanism of RCM

The first report on a successful synthesis of nitrogen heterocycles *via* RCM appeared in 1992, where Fu and Grubbs reported the use of a Mo alkylidene as a catalyst (Scheme 20) [112].



R^1 = Bn, TFA; R^2 = H, Me; X = CO, CH_2
n = 1, m = 0-2.

Scheme 20. First synthesis of nitrogen heterocycles *via* RCM

The same authors reported in 1993 a first successful application of a Ru alkylidene for the synthesis of nitrogen and oxygen heterocycles [113]. The authors mentioned that the Ru catalyst had important advantages towards the previously used Mo reagent: higher tolerance to functional groups and diminished sensitivity to oxygen and moisture.

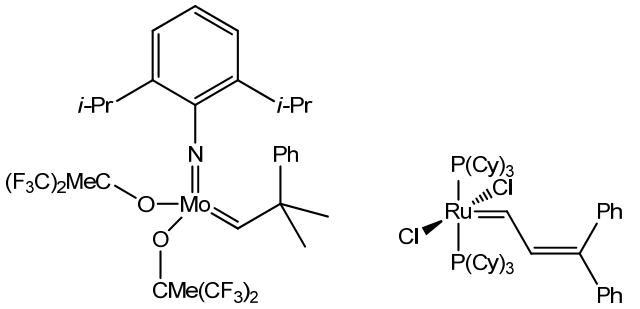


Figure 3. First catalysts used for the synthesis of nitrogen heterocycles *via* RCM by Grubbs

Since that time a variety of catalysts has been developed, mostly based on Ru [113, 114] (Grubbs type catalysts) or W [115] and Mo [116] (Schrock type catalysts). Because of the abovementioned advantages, Ru-based catalysts are most commonly employed for RCM [117]; however, Schrock type catalysts find their application in asymmetric RCM reactions due to their superior enantioselectivity [118]. The most widely used metathesis catalysts are shown in Figure 4. Grubbs and Hoveyda-Grubbs 2nd generation catalysts have a higher activity and a broader substrate scope than Grubbs 1st generation catalyst. For example, formation of cyclic disubstituted olefins from terminal dienes generally may be easily achieved by employment of Grubbs 1st generation catalyst, whereas the formation of trisubsituted cyclic olefins needs Grubbs 2nd generation catalyst [114]. Tetrasubstituted cyclic olefins may be obtained if special catalysts, for example, Hoveyda-Grubbs 2nd generation catalyst, are used [119]. Many investigators work on continuous improvement and tuning of the Ru catalysts to increase their activity and decrease the catalyst loading from common 2–5 mol% to hundreds of ppm range, and hence promoting the use of the RCM technology in industrial practice [120–122].

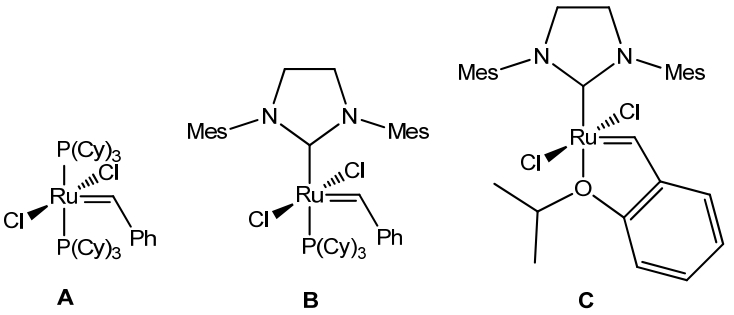
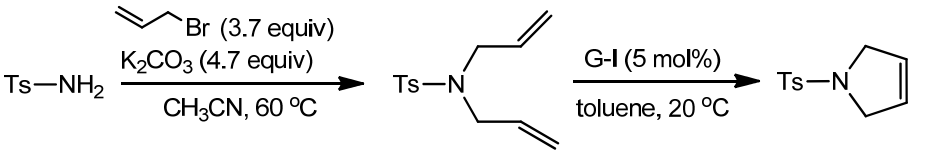


Figure 4. The most widely used RCM catalysts. (A) – Grubbs 1st generation catalyst, (B) –Grubbs 2nd generation catalyst, (C) – Hoveyda-Grubbs 2nd generation catalyst

2.3.1. RCM in the synthesis of cyclic amines

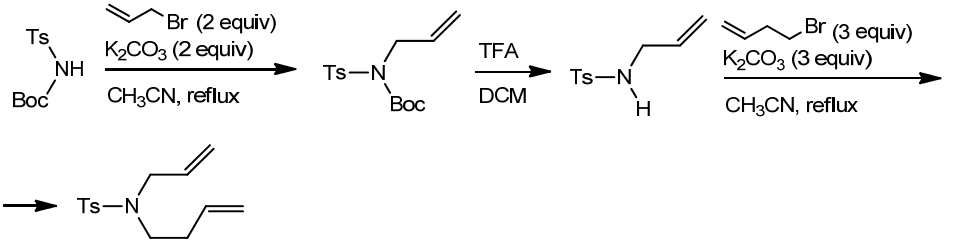
RCM is an efficient tool for construction of different cyclic frameworks, proceeding easily and cleanly, and compatible with many functional groups, such as alcohols, aldehydes and carboxylic acids [113]. Tolerance towards NH group is more challenging; therefore, electron withdrawing or bulky nitrogen protecting groups are used to prevent donor-acceptor interactions between the catalyst and the nitrogen. [123]. However, there are known examples of successful RCM in the presence of non-protected NH group as well [124]. These properties make RCM a very robust method for final cyclization step for a variety of substrates. Therefore, the main issue in the RCM strategy is the synthesis of the corresponding dienic precursors, what is in some cases a quite complicated task.

The most straightforward approach is direct introduction of two alkenyl groups on the nitrogen atom by double alkylation of amines with alkenyl halides. The simpliest case is the synthesis of symmetrical *N*-dienes, which may be prepared in a single step only by employment of 2 or more equiv of bromoalkene to 1 equiv of amine in the presence of base [125–128]. This method often affords the desired product in quantitative yield or similar. Such alkylation with further ring-closure *via* RCM is very convenient for the synthesis of heterocycles with double bond in the center of the ring, especially for 5-membered cycles because of high availability and low price of allyl bromide (Scheme 21).



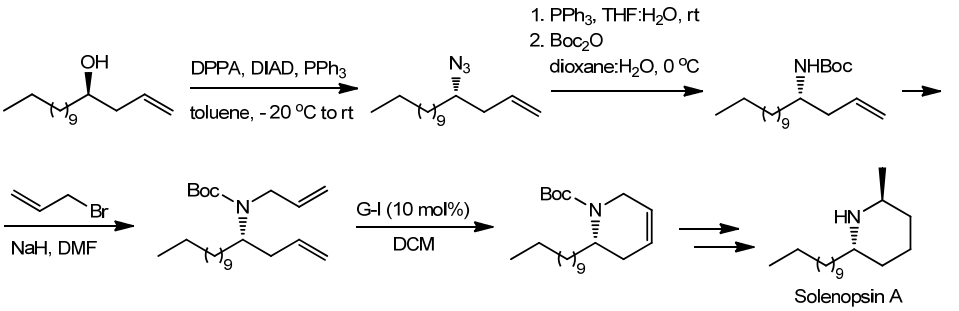
Scheme 21. Synthesis of *N,N*-diallyl-4-methylbenzenesulfonamide and subsequent RCM

In case of unsymmetrical *N*-dienes an analogous approach may be applied. Two different alkenyl groups may be introduced by double alkylation of the nitrogen with different alkenyl halides. However, this method has a significant drawback – it is quite difficult to achieve selective monoalkylation at first step of the synthesis. As a result, bis-alkylated side-products may form in significant quantities, what reduces the total yield and requires additional purification. Even sulfonamides and amines bearing strongly electron withdrawing groups, and thus being weaker nucleophiles, are reported to act not selectively [125, 129]. The problem may be overcome by introduction of a protecting group before the first alkylation step and its subsequent removal after it. For example, Terada *et al.* reported a successful synthesis of a RCM precursor in total 87% yield starting from Boc(Ts)NH_2 (Scheme 22) [130].



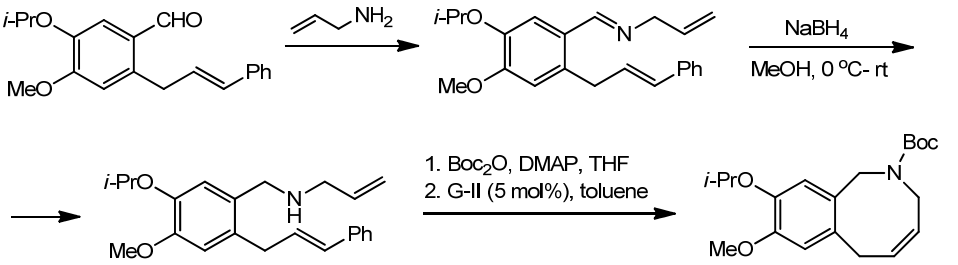
Scheme 22. Synthesis of the RCM precursor starting from Boc(Ts)NH_2

Another synthetic strategy is based on the use of alkene-bearing amines as starting materials. In this case only one alkenyl group should be attached to the substrate to generate a RCM precursor. Again, the most straightforward way is alkylation of the nitrogen with bromoalkenes, though it still requires the presence of a protecting group or the use of alkenyl amine in a big excess because of the abovementioned regioselectivity problems. Successful syntheses are reported in the presence of commonly used *N*-protecting groups, such as Ts [121, 131, 132], Ns [133], Boc [122, 128] and Cbz [134–136]. It is important to mention that a majority of alkenyl amines are not commercially available materials, thus requiring to be synthesized. Several researchers reported successful syntheses starting from unsaturated alcohols, which were converted to azides with subsequent reduction to amines [136–139]. For example, Harbindu *et al.* utilized this approach to synthesize a natural alkaloid Solenopsin A according to Scheme 23 [139].



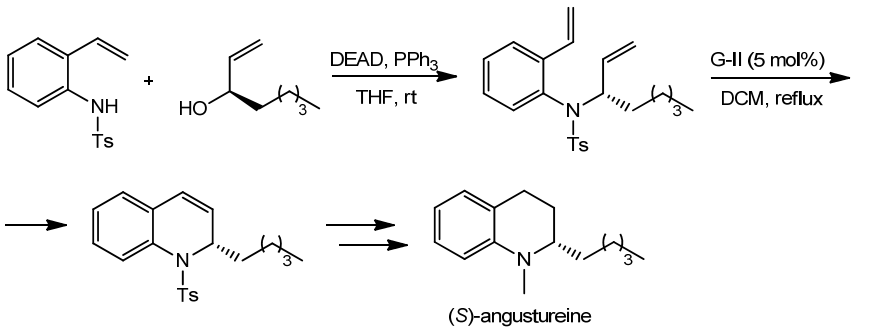
Scheme 23. Synthesis of Solenopsin A starting from (4*R*)-pentadec-1-en-4-ol

An alternative option allowing to avoid the involvement of protecting groups in the synthesis of a RCM precursor is condensation of alkene-bearing amines with unsaturated aldehydes and subsequent reduction [140] or further functionalization [141] of the obtained imine. For example, Panayides *et al.* successfully synthesized benzo-fused nitrogen heterocycles according to Scheme 24 [140].



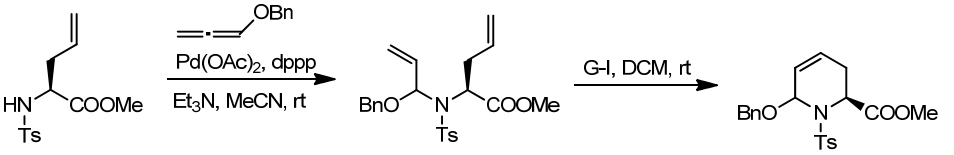
Scheme 24. Synthesis of benso-fused heterocycles starting from allyl amine and aromatic aldehyde

Unsaturated alcohols and their derivatives are also considered as good alkylating agents for the synthesis of RCM precursors. Frequently the corresponding halides are not commercially available or their synthesis is more complicated. In this case the use of sulfonates, such as mesylates [142–144] or tosylates [145, 146], which can be prepared from the corresponding alcohols in very good yields, is an excellent alternative. Also, alcohols may be successfully applied without derivatization utilizing Mitsunobu protocol [147–150]. For example, Theeraladanon *et al.* demonstrated an efficient synthesis of the alkaloid (*S*)-angustureine, where Mitsonubu reaction and further RCM were the key steps (Scheme 25) [148].



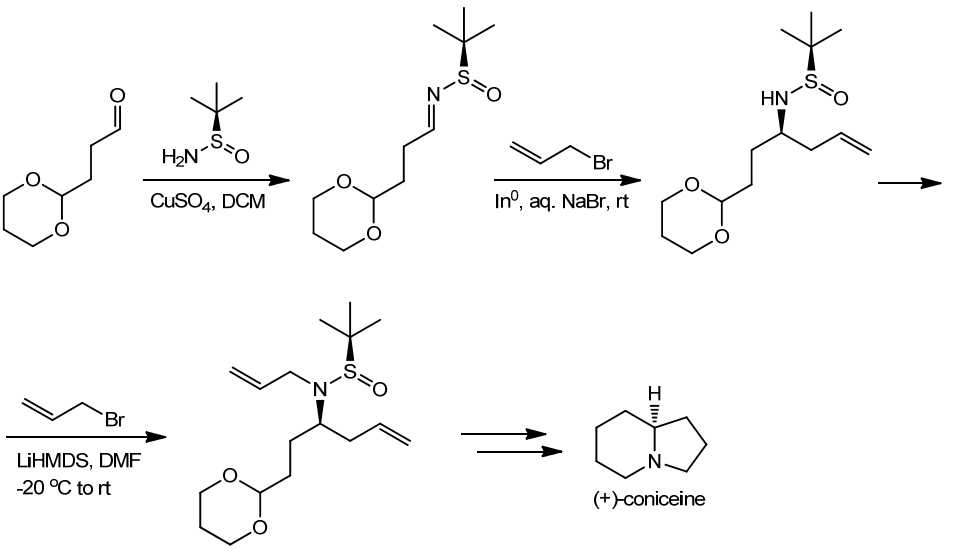
Scheme 25. Application of Mitsunobu reaction and RCM in the synthesis of (*S*)-angustureine

Another interesting approach enabling to introduce an alkenyl group with O functionality to the nitrogen was demonstrated by Tjen *et al.* for the synthesis of pipecolic acid derivatives [151]. The key step of the synthesis was amido-palladation reaction of alkoxyallenes to form the allylic *N,O*-acetals, which were further subjected to the cyclization *via* RCM (Scheme 26). Cyclic *N,O*-acetals can be converted to a variety of products, for example, quinolizidines [152] and pyrroles [153]. Recently it was shown that applying chiral *N,P*-ligands a very good stereoselectivity for Pd-mediated addition of alkoxyallenes can be achieved, what simplifies an access to a number of natural products [154].



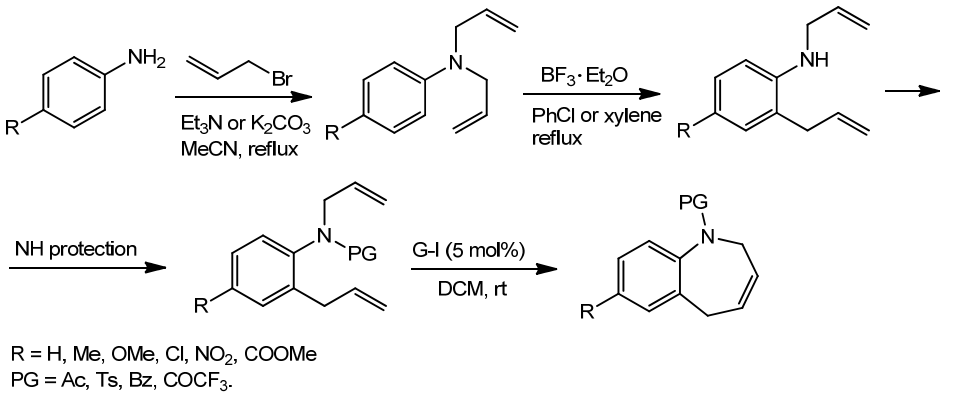
Scheme 26. Pd-mediated addition of alkoxyallenes to aminoolefins with subsequent RCM

A completely different strategy for the synthesis of RCM precursors is based on the introduction of an alkenyl group not to the nitrogen, but to the neighboring carbon atom. A very versatile method is alkylation of imines which may be easily prepared from the substrates containing carbonyl and amine centers. Also, iminium precursors can be generated *in situ* from a variety of substrates [155–158]. The alkylation may be successfully performed applying In [159–161], Mg [156, 159], Zn [159, 161], or Si [157, 158] alkylation reagents. For example, Fadeyi *et al.* successfully utilized this approach to prepare a variety of azabicyclic alkaloids [160]. An example synthesis of (+)-coniceine is shown in Scheme 27.



Scheme 27. Synthesis of (+)-coniceine by Fadeyi *et al.*

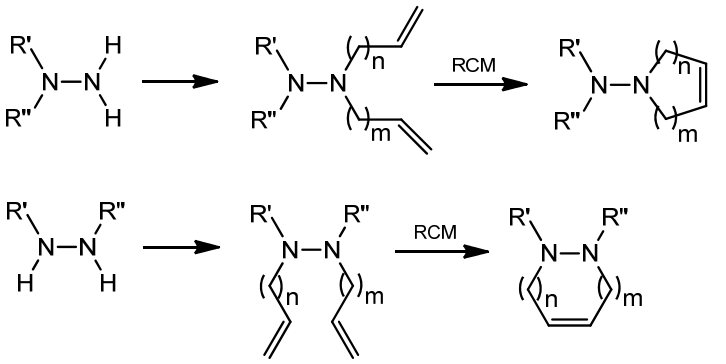
In recent years, a number of syntheses of benzazepine and benzazocine derivatives based on aza-Claizen rearrangement of allyl substituted aromatic amines and subsequent RCM have been reported [123, 126, 162]. This method is especially good for the synthesis of pharmaceutically important 7-membered 1-benzazepine rings, which may be prepared from widely available anilines in 4 simple steps only (Scheme 28) [123, 126]. A typical synthesis starts with straightforward diallylation of optionally substituted aniline. On the next step the obtained intermediate is subjected to aza-Claizen rearrangement by re-fluxing in a highly boiled solvent in the presence of a Lewis acid. Control of the reaction conditions is very important to avoid the formation of 2,6-diallyl substituted anilines as side products due to double rearrangement, what is mainly caused by overheating or overloading the Lewis acid [123, 126]. The electronic nature of the substituents in the starting anilines has very little impact on the outcome of the reaction, what is consistent with the considered nature of the reaction [126]. Suitable protection of the nitrogen and further RCM complete the design of the ring.



Scheme 28. Typical synthesis of 1-benzazepines based on aza-Claisen rearrangement

2.3.2. RCM in the synthesis of cyclic hydrazines

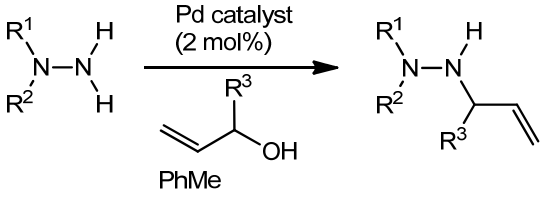
There are only few examples of RCM of the substrates comprising a hydrazine moiety can be found in literature. As hydrazines contain more reaction centers in comparison with amines, there are two types of possible heterocyclic targets, which may be obtained as a result of RCM. One way is the synthesis of *N,N*-dienehydrazines, which afford the heterocycles comprising N-N exocyclic bond after RCM. Another route is preparation of *N,N*'-dienehydrazines, what leads to the heterocycles with N-N bond inside the ring after cyclization (Scheme 29). In both cases the most challenging part in the strategy is the synthesis of dienehydrazines as the precursors for RCM.



Scheme 29. Synthesis of heterocycles comprising N-N exocyclic (above) and N-N endocyclic (below) bonds *via* RCM

Preparation of the substrates containing two different alkenyl groups on the same nitrogen is more problematic. It requires sequential selective involvement of two substituents on a free NH_2 group of the hydrazine. It is known that direct alkylation of hydrazines with alkyl halides often proceeds not selectively, having a tendency to afford overalkylated products. Therefore, using this method it is frequently quite difficult to achieve a good selectivity for monoalkylation of mono- and disubstituted hydrazines containing NH_2 group without the use of a great excess of the starting hydrazine [3]. For that reason specially designed trisubstituted hydrazine derivatives are sometimes used to ensure selective monoalkylation of the remaining NH group [20, 163, 164]. There are several known methods for the synthesis of fully orthogonally protected trisubstituted hydrazines, where protecting groups may be selectively cleaved one after another, hence opening the door for the introduction of the next substituent after removal of the desired protecting group [21, 165, 166]. However, this approach involves many additional protection and deprotection steps to reach the desired target, what makes it inconvenient in practical use.

Recently, it was demonstrated that selective monoallylation of hydrazine derivatives, what is essential for the synthesis of many RCM precursors, may be achieved applying transition metal catalysis. The first approach described by Matunas *et al.* is based on Ir-catalyzed allylation by allylic carbonates, which may be easily prepared from the corresponding allylic alcohols [167]. In 2013, Tšupova and Mäeorg reported another protocol based on Pd-catalyzed allylation by underivatized allylic alcohols (Scheme 30) [168]. In both cases different mono- and disubstituted hydrazines may be selectively monoallylated, using 1.5-2 equiv of the starting hydrazine and 2–5 mol% of the catalyst.

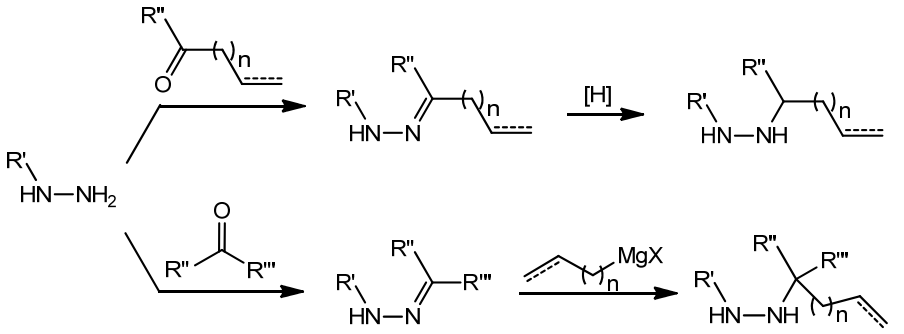


R^1 = Boc, Cbz, Ph; R^2 = Boc, H; R^3 = H, alkyl, Ar

Scheme 30. Pd-catalyzed selective *N*-allylation of hydrazines with allylic alcohols

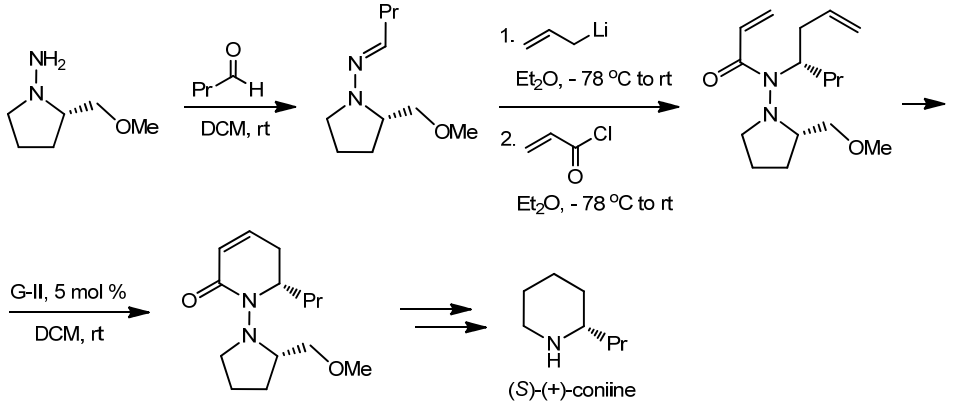
More universal and general route to alkyl hydrazines is based on the use of hydrazones. There are two general approaches for introduction of an alkenyl group to the NH_2 group of a hydrazine derivative. The first method is the condensation of an unsaturated aldehyde or a ketone with the hydrazine derivative and subsequent reduction of the obtained hydrazone by $NaBH_3CN$ [51] or $NaBH_4$ [25]. The second method is based on the functionalization of a

suitable hydrazone by an organometallic reagent containing an alkenyl group [169]. Both methods are shown in Scheme 31.



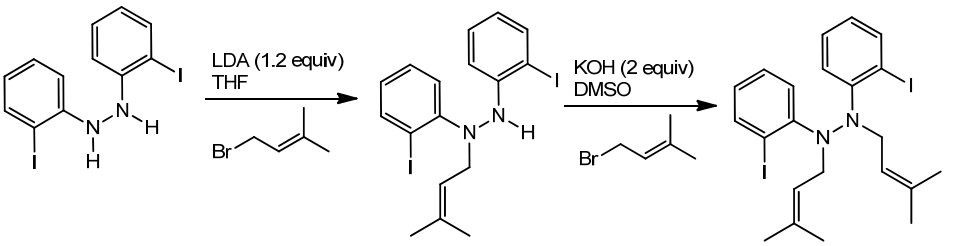
Scheme 31. Typical synthetic solutions to the problem of hydrazine monoalkylation selectivity

Hydrazone addition-RCM protocol has been successfully applied by Lebrun and co-workers for the synthesis of several piperidine alkaloids [170–173]. The key step of the syntheses was highly diastereoselective 1,2-addition of allyllithium to SAMP hydrazones, which were used as chiral auxiliaries. An example synthesis of (*S*)–(+)-coniine is depicted on Scheme 32 [170].



Scheme 32. Synthesis of (*S*)–(+)-coniine by Lebrun *et al.*

N,N'-dienehydrazines bearing the same alkenyl groups is relatively easy to obtain, applying at least 2 equiv of both a base and an alkylating agent to the starting 1,2-disubstituted hydrazine [174]. However, not all bases are expected to work [174, 175]; therefore, two-step synthesis protocol with different bases is needed in some cases to reach the target (Scheme 33) [175].

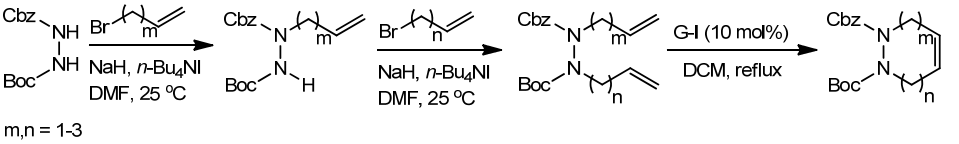


Scheme 33. Double alkylation of 1,2-bis(2-iodophenyl)hydrazine

Synthesis of *N,N*'-dienehydrazines with different alkenyl substituents is less complicated than preparation of the corresponding *N,N*-dienehydrazines, but still challenging in some cases. The discrepancy is that two different alkenyl groups should be attached to different nitrogen atoms, not to the same one. Therefore, the selectivity of the first alkylation may be controlled by the nature of the substituents in the starting hydrazine. In case the starting hydrazine derivative bears on the nitrogen atoms either groups with different electron-withdrawing properties [176] or bulky substituents [174, 175], selective monoalkylation of one nitrogen center may be achievable. If the starting material contains on the both nitrogens the substituents with the same or similar electronegativity, selective monoalkylation of the desired nitrogen may be problematic [177, 178].

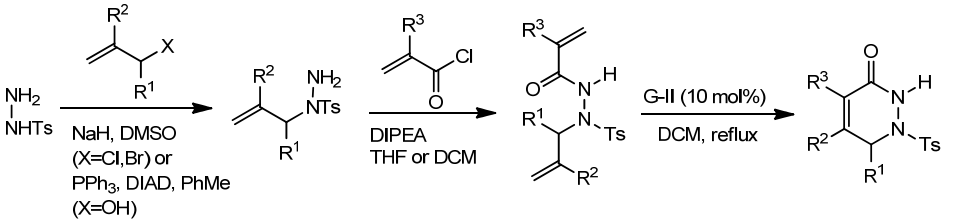
For example, Tae *et al.* prepared a series of *N,N*'-dienehydrazines by sequential alkylation of CbzNHNHBoc by different bromoalkenes in the presence of NaH and catalytic amount of *n*-Bu_4NI [178]. However, the researchers reported formation of significant amounts of dialkylation side-products (from 12% to 45%) during the first alkylation reaction, whereas the monoalkylated products were isolated in relatively low yields (from 33% to 67%). Second alkylation proceeded smoothly at the same conditions and revealed the desired products in 87–89% yield (Scheme 34).

This work was the first where the synthesis of hydrazine-based heterocycles of different ring size *via* RCM was studied. RCM was performed in DCM at 45 °C, employing 10 mol% of the Grubbs 1st generation catalyst. It was found that 6- and 7-membered rings may be obtained in yields higher than 90% even using relatively high substrate concentration (0.02 M), whereas 8-, 9- and 10-membered cycles required 3- and 4-fold dilution and twice longer reaction time to reach 70% yields (Scheme 34). In a short while, Kim *et al.* demonstrated that formation of up to 14-membered macrocycles is achievable in moderate to good yields under similar conditions [179].



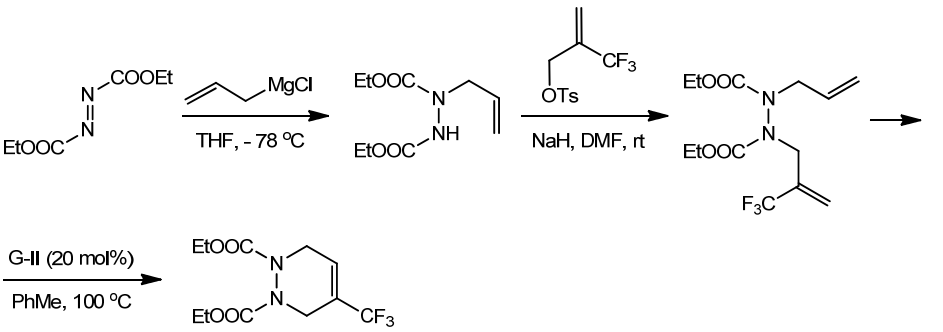
Scheme 34. Synthesis of 6- to 10-membered rings starting from CbzNHNHBoc by Tae *et al.*

Donohoe *et al.* synthesized the metathesis substrates by sequential alkylation and acylation of $TsNHNH_2$ [176]. First allylation was readily achieved at more acidic NH, using allyl chlorides or bromides in DMSO, or Mitsunobu conditions. Subsequent acylation with a range of acryloyl chlorides was performed in the presence of DIPEA either in THF or DCM. Final RCM was accomplished employing 10 mol% of Hoveyda-Grubbs 2nd generation catalyst; however, the success of cyclization was strongly dependent on the nature of olefin substituents. Formation of trisubstituted cyclic olefins containing aryl, alkoxyl or trifluoroalkyl substituents was not achievable, whereas alkyl groups were totally tolerated (Scheme 35).



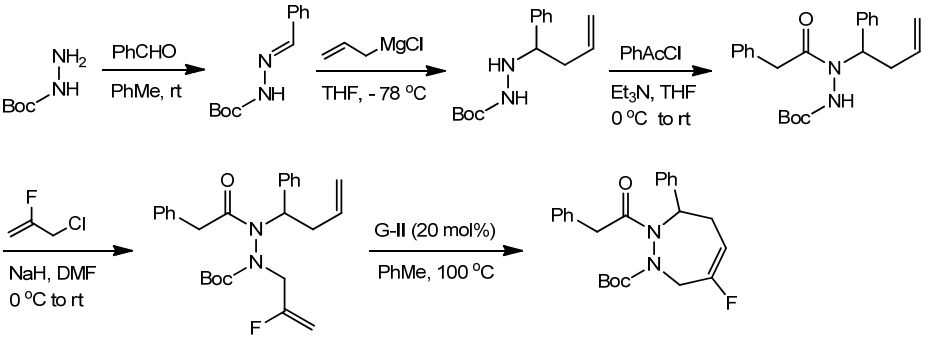
Scheme 35. Synthesis of dihydropyridazinones by Donohoe *et al.*

Versatile electrophilicity of azo compounds in general and commercial availability of many azodicarboxylates in particular make the nucleophilic addition reaction to the N=N bond one of the most attractive tools for introduction of alkyl and aryl substituents to the hydrazine moiety. Generally addition of organomagnesium, -zinc or -lithium reagents to the N=N bond proceeds smoothly and selectively with both symmetrical azo compounds [180] and unsymmetrical arylazo compounds [181]. This approach has been successfully applied by De Matteis *et al.* in the synthesis of RCM precursors with subsequent cyclization, as shown in Scheme 36 [182].



Scheme 36. Synthesis of a cyclic hydrazine starting from alkylation of diethyl azodicarboxylate by De Matteis *et al.*

As it has been discussed above, hydrazones may be efficiently alkylated through nucleophilic addition of organometallic reagents to the C=N bond with subsequent alkylation of the nitrogen to reach *N,N*-dienehydrazines. The same approach may be successfully used for the synthesis of *N,N*'-dienehydrazines if there is an option to switch the second alkylation to another nitrogen. Double allylation of hydrazones with subsequent RCM (Scheme 37) is an efficient method for the synthesis of pharmaceutically important substituted 7-membered rings, what was demonstrated by De Matteis and co-workers [182].



Scheme 37. Synthesis of a fluorinated 7-membered ring by De Matteis *et al.*

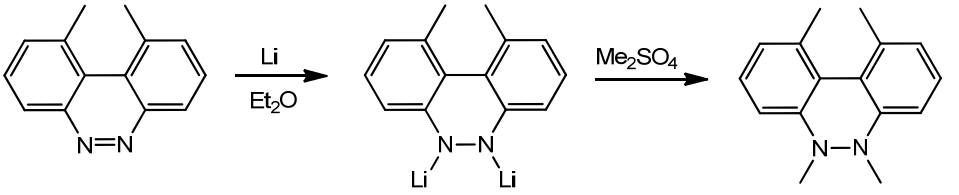
2.4. Polyanions of hydrazine derivatives

Dianions, which are molecules bearing two anionic centers, have become popular and widely used in organic synthesis. Dianion chemistry is mainly utilizing carbon-carbon or carbon-heteroatom dianions, particularly as carbon nucleophiles. [183]. The selectivity in the reactions of dianions is generally based on a significant difference of the pKa values of the corresponding reaction centers: less acidic reaction center acts a more reactive nucleophile.

2.4.1. Synthesis and properties of hydrazine polyanions

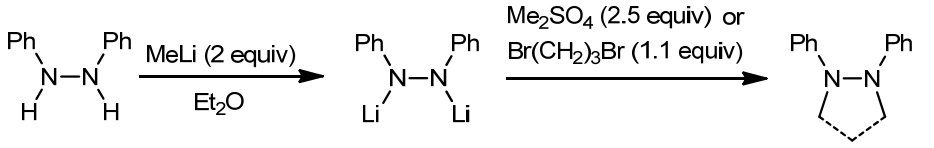
There are two main methods for metalation of hydrazine derivatives: deprotonation of NH or NH_2 group with a strong base, or addition of an alkali metal to the N=N bond of an azo compound.

The history of hydrazine dianions began in 1935, when Wittig reported the formation of dimetal adducts by shaking ether solution of 1,10-dimethyldibenzopyridazine with excess of Li or Na [184]. The dianionic nature of the obtained species was confirmed by titration. Also, the di-lithium adduct was successfully alkylated with dimethyl sulfate, thus indicating the first known example of hydrazine dianion alkylation (Scheme 38).



Scheme 38. Generation of the dianion from 1,10-dimethyldibenzopyridazine and subsequent alkylation

In 1940, Wittig reported the formation of the dianion from PhNHNHPh, applying 2 equiv of MeLi as a base [61]. The obtained dianion was also successfully alkylated by dimethyl sulfate or 1,3-dibromopropane (Scheme 39).

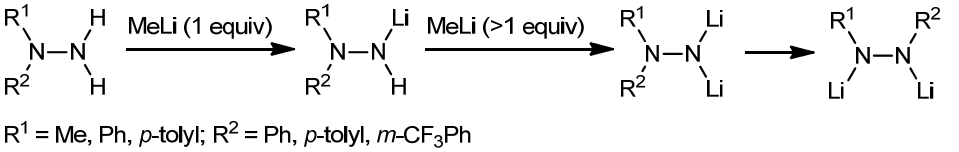


Scheme 39. Generation of the dianion from PhNHNHPh and subsequent alkylation

Thereafter many papers utilizing dianions of 1,2-diarylsubstituted hydrazines, which were obtained either by metal addition to the N=N bond [185–187] or deprotonation of the corresponding hydrazines [188], were published. Modern spectroscopy techniques, such as NMR [189] and ESR [190], and also X-ray crystallography [191] were employed to deduce the dianionic nature of the charged systems and acquire other interesting data. For example, ESR spectroscopy demonstrated that formation of the dianion from PhN=NPh and an alkali metal goes through radical anions [190].

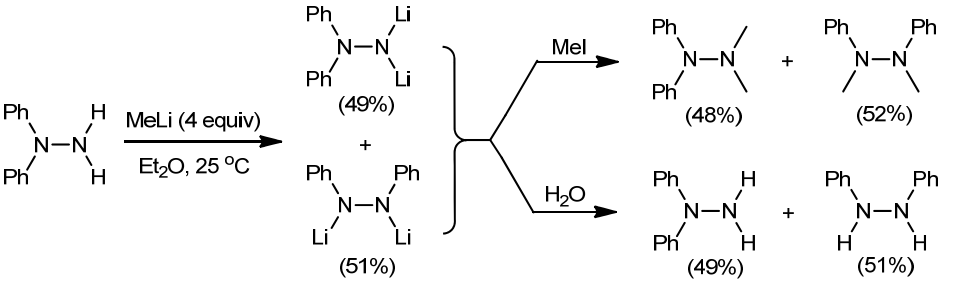
Another type of hydrazine dianions bearing double negative charge on one nitrogen was described by West and Stewart in 1970, when they studied the

rearrangement of arylhydrazines [192]. 1,1-diaryl- and 1-aryl-1-methyl-hydrazines were converted to the corresponding monoanions, but no migration of the aryl groups was observed even at 110 °C. However, if the substrates were treated with more than 1 equiv of alkyl lithium to give the corresponding dianions, the rearrangement to more stable dianionic species occurred at room temperature (Scheme 40).



Scheme 40. Anionic rearrangement of arylhydrazines

The driving force for aryl migration is the large repulsion of the two negative charges on the same nitrogen, which is relieved in the rearranged dianions. Nevertheless, the rearrangement of arylhydrazine dianions was surprisingly slow and required several days for completeness. The process was monitored by NMR due to specific resonances of the both type dianions, and it was confirmed that the original dianions were relatively stable at room temperature. The results from the direct NMR measurement and from quenching the reaction mixture with water or methyl iodide were fully consistent (Scheme 41).

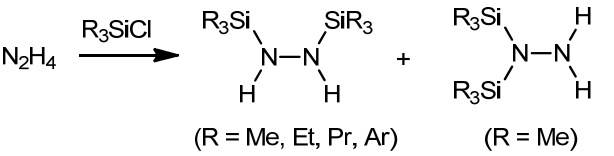


Scheme 41. Anionic rearrangement of arylhydrazines: monitoring of the progress by NMR and by quenching of the reaction mixture

It was also confirmed that aryl migration is always accompanied by the decomposition of the dianions. When 1-phenyl-1-methylhydrazine dianion was subjected to rearrangement, significant amounts of methylaniline, derived from the original dianion, and aniline, derived from the rearranged dianion, were detected. This indicates that the both type dianions undergo a slow decomposition with the breakdown of the N-N bond.

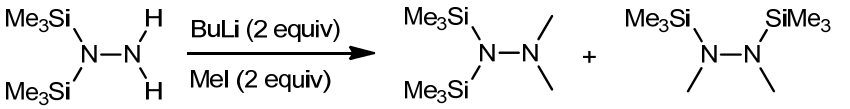
Similar investigation was performed with 1,1-dimethylhydrazine dianion; however, no rearrangement was observed.

Another branch of hydrazine dianions concerns silyl hydrazines. The history of silyl hydrazines began in the second half of 1950-s, when the first syntheses were described by Aylett and Wannagat. Aylett reported the formation of tetrasilyl hydrazine $(SiH_3)_2N\text{-}N(SiH_3)_2$ in the reaction of anhydrous hydrazine with the excess of silyl iodide [193]. Two years later, Wannagat *et al.* studied a similar reaction of anhydrous hydrazine with trialkyl- and triarylsilylchlorides [194]. The reaction afforded symmetrical disubstituted derivatives; all the attempts to isolate tri- and tetrasubstitued silylhydrazines were unsuccessful. Wannagat *et al.* reported the formation of 1,2-bis(trialkylsilyl)hydrazines as single products in all experiments, but several years later Bayley and West confirmed that the reaction affords the mixture of 1,1- and 1,2-isomers in case of Me_3SiCl (Scheme 42) [195, 196].



Scheme 42. Silylation of hydrazine

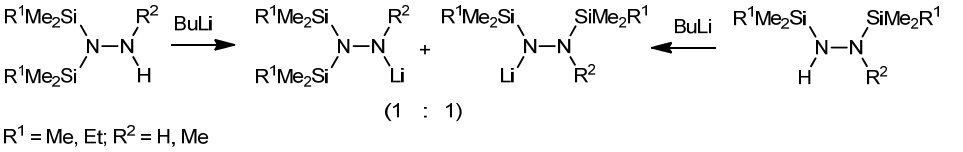
The first data on dianions of silylhydrazines appeared in 1964, when Bayley and West discovered anionic rearrangement of silylhydrazines. 1,1-bis(trimethylsilyl)hydrazine treated with 2 equiv of *n*-BuLi followed by MeI unexpectedly gave equal amounts of 1,1- and 1,2-isomers (Scheme 43) [195]. Nevertheless, initially the researchers reported the anionic rearrangement for 1,2-bis(trimethylsilyl)hydrazine. Only two years later an erroneous structure assignment was confirmed and the isomer previously had been considered as 1,2-bis(trimethylsilyl)hydrazine was verified to be the 1,1-isomer [196].



Scheme 43. Rearrangement and alkylation of 1,1-bis(trimethylsilyl)hydrazine dianion

To study the anionic rearrangement in more details, the researchers prepared a series of 1,1- and 1,2-bis(alkyldimethylsilyl)hydrazines and subjected to treatment with BuLi. It was found that the substrates containing Me_3Si and $EtMe_2Si$ substituents underwent the rearrangement to essentially equal amounts of isomers within several minutes (Scheme 44) [197]. However, a steric effect

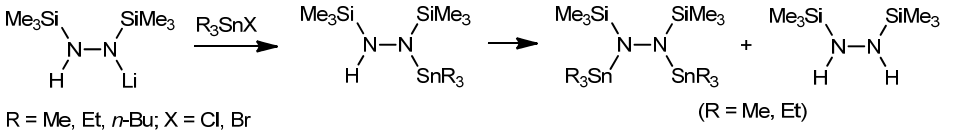
emerged in case of bulkier substituents: the substrates bearing *t*-BuMe$_2$Si group rearranged preferably to the less hindered 1,2-isomers [198].



Scheme 44. Rearrangement of silylhydrazines after treatment with BuLi

In addition to rearrangements, lithiated silyl hydrazines have a tendency to aggregate and form dimers or bigger complexes. Many of them have been isolated as single crystals, which structures were confirmed by X-ray crystallography [191, 199, 200].

Recently, stannylation of hydrazine derivatives was also reported [201]. Lithium 1,2-bis(trimethylsilyl)hydrazine reacted with Me$_3$SnCl, Et$_3$SnCl and *n*-Bu$_3$SnCl to form the corresponding mono-stannylated hydrazines. The stability of the obtained products strongly depended on their structures: whereas Me$_3$Sn and Et$_3$Sn adducts underwent a disproportionation already at room temperature, *n*-Bu$_3$Sn derivative was stable even at 150 °C (Scheme 45).

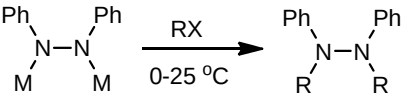


Scheme 45. Synthesis and disproportionation of stannylated hydrazines

2.4.2. Alkylation of hydrazine polyanions

As shown above, possible rearrangements have to be considered when mono- and dianions of silyl hydrazines are alkylated, what reduces their synthetic potential. Other known types of hydrazine dianions are more stable and may be exposed to further functionalization.

Some examples of alkylation of hydrazines dianions bearing two aryl or two carbamate type protecting groups have been shown before. All the cases were rather individual until Reesor and Wright reported in 1957 a first series of experiments, where the dianion prepared from azobenzene was dialkylated by different alkylating agents, including dihalides (Scheme 46) [185]. The corresponding tetrasubstituted hydrazines were obtained in good yields except the case with isopropyl halides, which afforded monoalkylated product only.

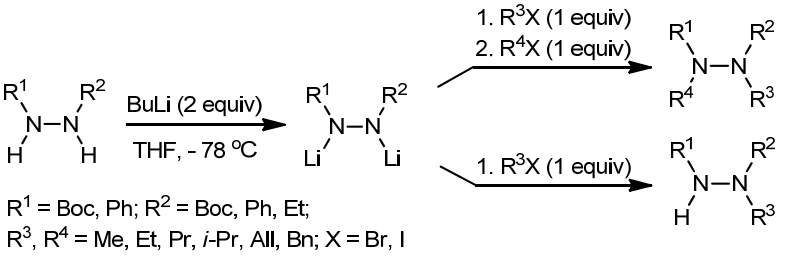


M = Li, Na, K; R = Me, Pr, Bn, -$(CH_2)_3$-, -$(CH_2)_4$-
X = Cl, Br, I

Scheme 46. Alkylation of the dianion obtained from PhN=NPh

In 2007, Bredihhin *et al.* described a method for selective alkylation of PhNHNHBoc [23]. All possible manipulations were achieved: symmetrical double alkylation, selective monoalkylation of any nitrogen, or one-pot selective alkylation of both nitrogens with different substituents (Scheme 47). The selectivity was controlled by the difference in acidities of the corresponding NH groups, which may be estimated as 5–7 pKa units [202]. This difference enabled selective alkylation of either PhNH group (in the case of the dianion) or BocNH group (in the case of the monoanion). The dianion was generated by addition of 2 equiv of BuLi to the solution of the substrate in THF and was stable in the solution at room temperature.

Later the method was expanded also to other substrates, such as EtNHNHBoc, BocNHNHBoc and PhNHNHPh [25]. The substrates containing Cbz protecting group were inapplicable in this strategy due to metalation of the benzylic CH_2. In case of symmetrical hydrazines selectivity is achievable by careful control of stoichiometry of the reagents and the temperature of the reaction mixture, as the second alkylation is always much slower than the first addition.

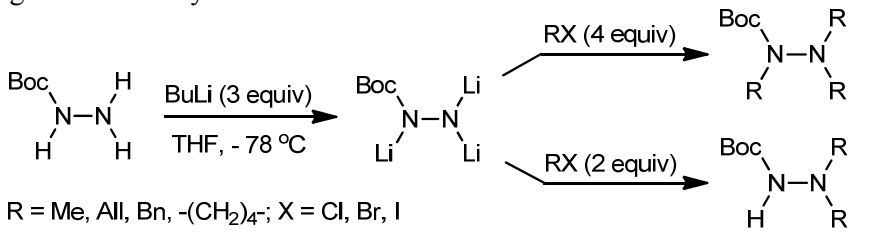


R^1 = Boc, Ph; R^2 = Boc, Ph, Et;
R^3, R^4 = Me, Et, Pr, *i*-Pr, All, Bn; X = Br, I

Scheme 47. Selective alkylation of the dianions of 1,2-disubstituted hydrazines

Bredihhin and Mäeorg described also a similar alkylation of $BocNHNH_2$ [24]. The substrate was treated with 3 equiv of BuLi to generate the trianion and allowed to react either with the excess of an alkyl halide to afford the trialkylated hydrazines, or exactly with 2 equiv of an alkyl halide to generate the 2,2-dialkylated derivatives (Scheme 48). Alkylation of $BocNHNH_2$ dianion

surprisingly provided also 2,2-dialkylated derivatives instead of the expected 1,2-dialkylated species, thus indicating equilibria between anionic hydrazines in the reaction mixture. The attempts to achieve selective monoalkylation of any nitrogen were mainly unsuccessful.



Scheme 48. Alkylation of the $BocNHNH_2$ trianion

3. AIMS OF THE STUDY

The main objectives of the current thesis were:

1) To investigate the scope and the limitations of the hydrazine polyanion strategy in the synthesis of heterocycles.

2) To study the formation of bis(hydrazines) in the reaction of hydrazine polyanions with α,α-dibromo-*o*-xylene and to investigate the mechanism of the reaction.

3) To synthesize a series of prochiral azacycles *via* RCM strategy for asymmetric hydrogenation study.

4) To study the applicability of the hydrazine polyanion strategy for the synthesis of dienehydrazines and to study the RCM reaction for the synthesis of cyclic hydrazines, including prochiral heterocycles.

5) To contribute to the development of preparative methods for the synthesis of cyclic hydrazine derivatives comprising both exocyclic and endocyclic N-N bond.

4. RESULTS AND DISCUSSION

4.1. Polyanions of hydrazines in the synthesis of heterocycles: direct alkylation

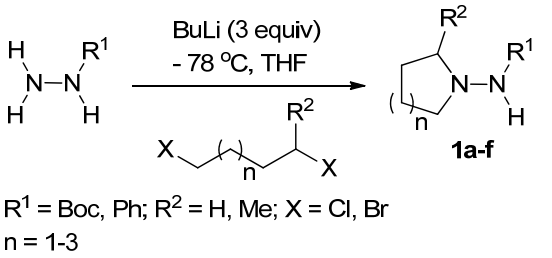
During the last two decades a significant progress in the synthesis of multisubstituted hydrazine derivatives has been achieved. Introduction of the orthogonally protected precursors, in which the protecting groups could be removed in optional order, was a substantial improvement of the methods had been used so far. This strategy gave an access to a variety of new multi-substituted hydrazines. Nevertheless, this approach was not perfect: many additional synthetic steps were required for introduction and removal of the corresponding protecting groups.

A new strategy recently developed in our research group allows a direct and selective functionalization of hydrazine derivatives based on the difference in acidities of the corresponding reaction centers. Being a quite strong base, on the other hand, hydrazine N_2H_4 may be considered as a weak acid. The acidic properties of the substituted hydrazines are obviously determined by the nature of the substituents. Increase of the electronegativity of the substituents makes the corresponding nitrogen centers more acidic. For that reason hydrazines bearing acyl substituents are more acidic than, for example, alkyl or aryl substituted derivatives [202].

Reactivity of many compounds depends on their acidity. For example, it has been demonstrated that the yields of the Mitsunobu reaction are in a good accordance with the pKa values of the applied imidodicarbonates and tosylcarbamates [203]. Knowledge of the pKa values of hydrazine derivatives may also help to predict their behavior in a similar manner. In recent years the pKa values of many hydrazine derivatives were measured experimentally or revealed from the quantum chemical calculations, enabling also to predict their properties [202, 204, 205]. Latest investigations in our research group clearly demonstrated that the reactivity of lithiated hydrazine derivatives strongly depends on their acidity.

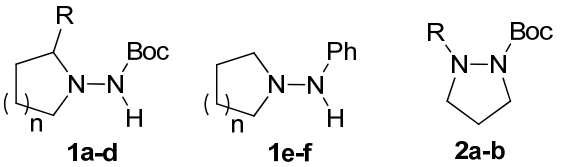
For example, $BocNHNH_2$ has two types of the nitrogen groups with different acidities. The difference between NH and NH_2 reaction centers may be roughly estimated as at least 10 pKa units [202]. Hence the reactivity of the corresponding anions should be also different, enabling selective alkylation of the NH_2 group. As it has been discussed in Section 2.4.2, $BocNHNH_2$ treated with 3 equiv of BuLi and subsequently with 2 equiv of an alkyl halide afforded the corresponding 2,2-dialkylated derivatives in good yields (Scheme 48).

This result encouraged us to prepare a series of heterocycles in a similar fashion, starting from $BocNHNH_2$ and $PhNHNH_2$ (Scheme 49). The results of our experiments are summarized in Table 1.



Scheme 49. Alkylation of $BocNHNH_2$ and $PhNHNH_2$ with dihalides

Table 1. Synthesis of heterocycles.



Entry	Product	R	n	Conditions	Yield, %
1	**1a**	H	1	$Br(CH_2)_4Cl$, 4 h, – 78 °C to rt [a]	71
2	**1a**	H	1	$Br(CH_2)_4Cl$, 4 h, – 40 °C to rt [b]	54
3	**1a**	H	1	$Br(CH_2)_4Cl$, 3 h, rt	52
4	**1b**	H	2	$Br(CH_2)_5Br$, 4 h, – 78 °C to rt [a]	41
5	**1b**	H	2	$Br(CH_2)_5Br$, 4 h, – 40 °C to rt [b]	73
6	**1b**	H	2	$Br(CH_2)_5Br$, 4 h, – 10 °C to rt [b]	63
7	**1b**	H	2	$Br(CH_2)_5Br$, 3 h, rt	52
8	**1c**	H	3	$Br(CH_2)_6Br$, 4 h, – 78 °C to rt [a]	24
9	**1c**	H	3	$Br(CH_2)_6Br$, 4 h, – 40 °C to rt [b]	41
10	**1c**	H	3	$Br(CH_2)_6Br$, 4 h, – 10 °C to rt [b]	31
11	**1d**	Me	1	$Br(CH_2)_3CH(CH_3)Br$, 4 h, – 78 °C to rt [a]	48
12	**1d**	Me	1	$Br(CH_2)_3CH(CH_3)Br$, 4 h, – 40 °C to rt [b]	52
13	**1e**		1	$Br(CH_2)_4Cl$, 2 h, rt	45
14	**1f**		2	$Br(CH_2)_5Br$, 2 h, rt	34
15	**2a**	Ph		$I(CH_2)_3I$, 30 min, rt	87
16	**2a**	Ph		$Br(CH_2)_3Br$, 1 h, rt	64
17	**2b**	Et		$I(CH_2)_3I$, 3 h, – 40 °C to rt [b]	58
18	**2b**	Et		$Br(CH_2)_3Br$, 3 h, – 40 °C to rt [b]	38

[a] The reaction mixture was stirred at – 78 °C for 1 h before being warmed up to rt in additional 1 h. [b] The dihalide was added at the indicated temperature and the reaction mixture was allowed to warm up to rt in 1 h.

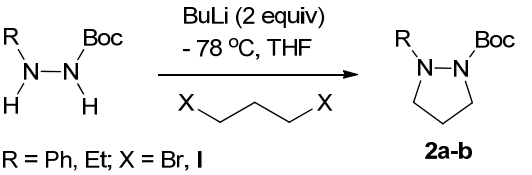
$BocNHNH_2$ trianion, which was obtained by metalation with 3 equiv of BuLi in THF at – 78 °C, may be alkylated with dihalides to form the corresponding 5-, 6- or 7-membered rings. 1,4-dibromopentane, which contains a secondary reaction center, can be also employed. However, all the attempts to synthesize a strained 4-membered azetidine ring system were unsuccessful.

From the previous experience we had already known that the efficiency of $BocNHNH_2$ trianion alkylation may depend on the temperature mode of the reaction [24]. For that reason we decided to find optimal reaction conditions for each ring system, adding dihalides at different temperatures. As it can be seen from Table 1, the yields for 5-membered rings **1a** and **1d** do not show a tendency to increase if to perform the addition of the dihalide at – 40 °C instead of – 78 °C. In turn, for the heterocycles of bigger size the addition of the dihalide and keeping the reaction mixture for 1 h at – 78 °C before slow warming up to room temperature had a negative impact on the yield values. The best yields for **1b** and **1c** were obtained when the dihalides were added at – 40 °C and the reaction mixture was slowly warmed up to room temperature. Probably, bulkier heterocycles require a higher temperature for efficient alkylation and cyclization, and maintaining the reaction mixture at – 78 °C for 1 hour may promote rather a partial destruction of the trianion than formation of the heterocycle. Shorter length halides, in turn, have a greater torsional mobility and a higher probability for reaction ends to meet, probably, even at lower temperatures. This is supported also by the results of the process monitoring by TLC: whereas formation of **1a** after 1 h was clearly visible even at – 78 °C, only traces of **1c** were detected at the same check-point. However, at – 40 °C or higher temperatures the reaction progress was faster for all heterocycles. TLC analysis indicated the consumption of the major part of $BocNHNH_2$ in first 30 min and completion of the reaction in 3–4 hours. Nevertheless, slightly lower yields were obtained for all heterocycles if dihalides were added at room temperature.

The trianion obtained from $PhNHNH_2$ seems to be a stronger base than the trianion obtained from $BocNHNH_2$. The alkylation also proceeded much faster even at low temperatures. We have tried to prepare a full range of heterocycles, but only 5- and 6-membered rings were obtained. We noticed that the formation of the heterocycles from $PhNHNH_2$ trianion was not very selective. For example, in the case of 1-bromo-4-chlorobutane the main products were **1e** and phenylpiperidazine comprising the endocyclic N-N bond. We suppose that the difference in the acidities of PhNH and NH_2 groups may be insufficient to ensure selectivity. In addition, the decrease of selectivity is obviously influenced by the difference in the bulkiness of Ph and Boc groups. Moreover, the elevated basicity of $PhNHNH_2$ trianion may promote other side reactions.

Similarly with the previous experiments, we also tried to alkylate the dianions of disubstituted hydrazines (Scheme 50). To obtain the dianions from PhNHNHBoc and EtNHNHBoc, 2 equiv of BuLi were used. These dianions yielded the corresponding 5-membered pyrazolidines **2a** and **2b**, reacting with 1,3-dibromopropane or 1,3-diiodopropane. Reactions were normally complete

within 3 h. By-products of elimination were observed if the dihalide was added to EtNHNHBoc at room temperature. This problem can be overcome by the addition of the alkylating agent at – 40 °C. Nevertheless, the reaction of PhNHNHBoc with 1,3-dihalides proceeded selectively even if the addition was made at room temperature.



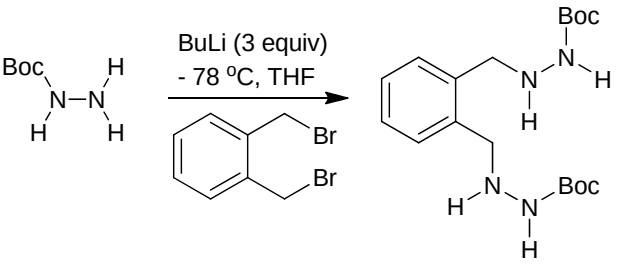
Scheme 50. Alkylation of PhNHNHBoc and EtNHNHBoc dianions with dihalides

The reaction of the dianions with 1,4-dibromobutane and 1,4-diiodobutane yielded the corresponding bis(hydrazines), in which two dianion fragments were bridged by the alkyl chain of the dihalide. We propose that the cyclization problems may be caused by steric hindrance of the Boc nitrogen.

The dianion of BocNHNHCOOEt was also obtained, using 2 equiv of BuLi. However, it precipitated from the solution and did not show any reactivity even at 50 °C.

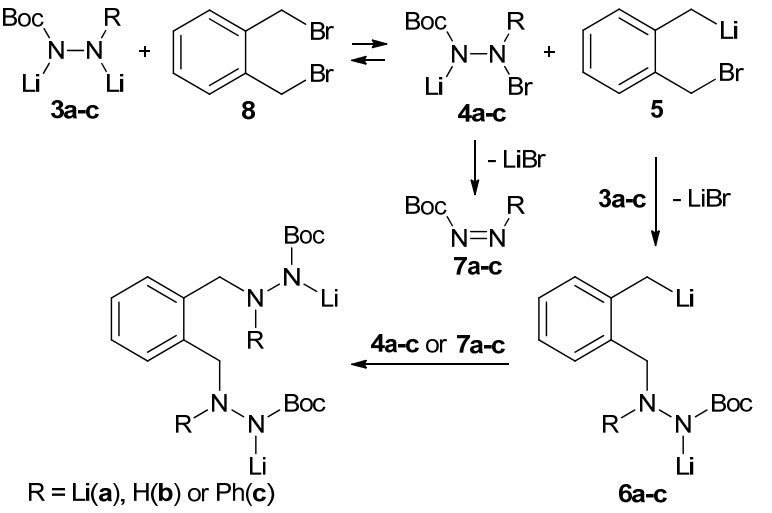
4.2. Metal-halogen exchange between hydrazine polyanions and α,α'-dibromo-*o*-xylene.

Attempting to synthesize heterocycles from $BocNHNH_2$ trianion, we encoutered one significant deviation. $BocNHNH_2$ treated with 3 equiv of BuLi and α,α'-dibromo-*o*-xylene unexpectedly afforded the product with two hydrazine fragments attached to the aromatic ring instead of the expected heterocycle (Scheme 51).



Scheme 51. Synthesis of an aromatic-bridged bis(hydrazine)

A surprising result inspired us to start searching for an explanation of the phenomenon. In our case steric hindrance unlikely can hamper the cyclization and be a reason of the formation of the non-cyclic product, as even bulkier heterocycles have been prepared utilizing similar aromatic dihalides [37]. In the obtained compound two methylene groups are bonded to the equivalent nitrogens, but of the different hydrazine molecules. As we have not found an objective reason for α,α'-dibromo-*o*-xylene for binding to two hydrazine fragments, we assumed that the reaction pathway should include the formation of an intermediate bearing two different substituents on the aromatic ring. Also, we considered that α,α'-dibromo-*o*-xylene and similar halides are among the few which react with $BocNHNH_2$ and afford the heterocycles in good yields, but at the conditions that exclude the formation of metalated hydrazines [36, 37]. This fact promoted a hypothesis that metalation of $BocNHNH_2$ is crucial for unnatural behaviour of the substrate and the key step of the process is metal-halogen exchange between the lithiated hydrazines and α,α'-dibromo-*o*-xylene. We suggested a reaction pathway, according to which the trianion **3a** and α,α'-dibromo-*o*-xylene (**8**) generate the intermediates **4a** and **5** *via* metal-halogen exchange (Scheme 52). In the next step **5** may interact with the trianion **3a**, affording the intermediate **6a** which, in turn, can react either with the intermediate **4a** or its azo form **7a**, finally completing the structure.



Scheme 52. Proposed reaction pathway

In compliance with the proposed mechanism, we expected that other lithiated hydrazines may be able to react in a similar manner. Thus, we started with screening the hydrazine dianions in the reaction with the dibromide **8**. The dianions **3b** and **3c** were generated from the corresponding hydrazines by the

treatment with 2 equiv of BuLi in THF at – 78 °C prior to the addition of the dihalide at – 45 °C. Indeed, it was found that $BocNHNH_2$ dianion furnished the same product **12** (Figure 5) with no impact on the yield and the reaction time (Table 2, Entry 2). The dianion generated from PhNHNHBoc reacted in the same manner, giving the non-cyclic bis(hydrazine) **13** in good yield (Entry 3). These experiments confirmed that the method has a broader scope and is not limited to monosubstituted hydrazines. Nevertheless, the experiment with BocNHNHBoc dianion revealed that the presence of two strong electron withdrawing groups on the both nitrogens totally blocks the metal-halogen interconversion (Entry 13).

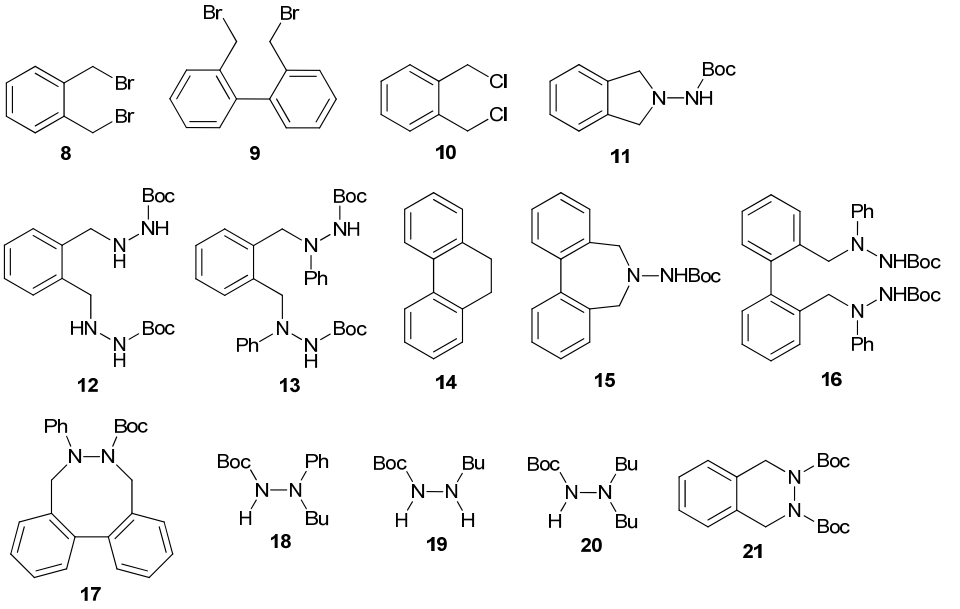


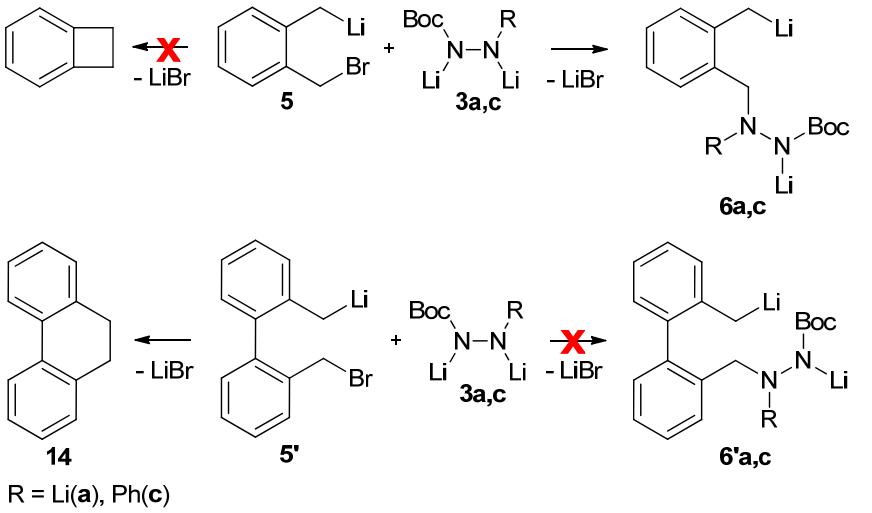
Figure 5. Compounds **8**–**21**

Table 2. Summarized results of the experiments

Entry	Starting material	Conditions	Reaction time	Isolated products (yield, %)
1	$BocNHNH_2$	3 equiv of BuLi, 1 equiv of **8**	10 min	**11** (4), **12** (44)
2	$BocNHNH_2$	2 equiv of BuLi, 1 equiv of **8**	10 min	**11** (4), **12** (42)
3	PhNHNHBoc	2 equiv of BuLi, 1 equiv of **8**	30 min	**13** (65)
4[a]	$BocNHNH_2$	3 equiv of BuLi, 1 equiv of **9**	1 h	**14** (58), **15** (30)
5	PhNHNHBoc	2 equiv of BuLi, 1 equiv of **9**	1 day	**14** (26), **16** (34), **17** (17)
6	PhNHNHBoc	3 equiv of BuLi, 1 equiv of **8**	1 day	**13** (18), **18** (27)
7[a]	PhNHNHBoc	3 equiv of BuLi, 1 equiv of **9**	1 h	**14** (61), **18** (52)
8[a]	$BocNHNH_2$	4 equiv of BuLi, 1 equiv of **8**	2 h	**19** (18)[b], **20** (21)[b]
9[a]	$BocNHNH_2$	3 equiv of BuLi, 0.5 equiv of **8**	1 day	mixture
10[c]	$BocNHNH_2$	3 equiv of BuLi, 2 equiv of **8**	10 min	**12** (40)
11	$BocNHNH_2$	2 equiv of BuLi, 0.5 equiv of **8**	10 min	**12** (62)
12	PhNHNHBoc	2 equiv of BuLi, 0.5 equiv of **8**	2 h	**13** (60)
13[a]	BocNHNHBoc	2 equiv of BuLi, 1 equiv of **8**	2 days	**21** (60)
14[a]	$BocNHNH_2$	3 equiv of BuLi, 1 equiv of **10**	1 day	**11** (30), **12** (8)
15	PhNHNHBoc	2 equiv of BuLi, 1 equiv of **10**	1 h	**13** (70)

[a] Full conversion of the starting material was not observed. [b] The yield is based on the excess of BuLi. [c] 0.76 equiv of **6** was recovered.

To prove the metal-halogen exchange process, similar reactions have been carried out with 2,2'-bis(bromomethyl)-1,1'-biphenyl (**9**). This halide is similar to **8**, and it is expected to give the analog of the intermediate **5** if the metal-halogen exchange is taking place. However, the intermediate **5'** generated from **9** was supposed to undergo self-cyclization *via* fast intramolecular alkylation to build a favorable six-membered ring system; this is in contrast to its analog **5** obtained from the dihalide **8**, for which this way is undesirable, as it would produce a strained four-membered cycle (Scheme 53). The desired carbocycle **14** was found in both reactions with $BocNHNH_2$ and PhNHNHBoc (Entries 4–5). Some similar examples of a bromine-lithium interconversion with subsequent intramolecular cyclization may be also found in literature [206, 207].

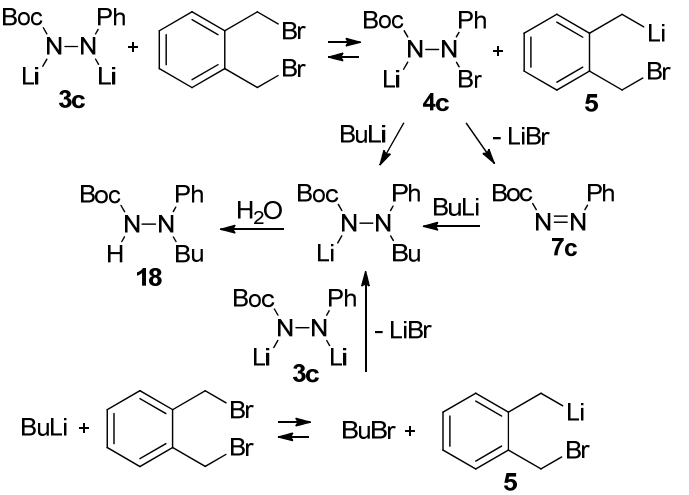


Scheme 53. Illustration of a different behavior of the intermediates **5** and **5'** generated from the dihalides **8** and **9**

The next step of our work was to confirm that hydrazine polyanions act as metal donors in the process. The determined pKa values of mono- and disubstituted hydrazines indicate that the existence of the corresponding dianions is definitely possible [202, 205]. The same conclusion may be postulated for hydrazine trianions considering the successful alkylation experiments [24] Nevertheless, full deprotonation of $BocNHNH_2$ had not been proven so far, thus making the existence of the trianion still questionable.

Our idea was to demonstrate the absence of free BuLi in the reaction mixture after 3 equiv of BuLi are added to $BocNHNH_2$ and the possibility to trap the excess of BuLi if a greater amount employed. At first we designed a model system adding 3 equiv of BuLi to PhNHNHBoc to produce the dianion **3c** with a fixed excess of BuLi. There are two theoretical possibilities for further metal-halogen exchange with the dihalides **8** or **9**. The first option is participation of the dianion **3c**, which should afford the intermediate **4c** or its azo analog **7c**, which would likely react with BuLi. Alternatively, the process may take place between BuLi and the dihalide, providing BuBr, which can alkylate the dianion. It means that in both cases the hydrazine derivative **18** is expected to form in significant quantities (Scheme 54). This hypothesis was successfully confirmed (Entries 6–7). As it may be seen from Table 2, the yield of **18** is higher if the dihalide **9** is employed. This result is consistent with the inference that the intermediate **5'** is being constantly removed from the reaction mixture *via* self-cyclization, thus suppressing possible side-reactions with BuLi or BuBr. The analogous experiments with $BocNHNH_2$ and 3 equiv of BuLi revealed no *N*-butyl derivatives, pointing out full deprotonation of the starting material (Entries 1,

4). In contrast, the use of 4 equiv of BuLi and **8** as a halide afforded the desired species **19** and **20** in total 39% yield, whereas the formation of **12** was totally suppressed (Entry 8). This experiment finally verified that free BuLi is observed only if more than 3 equiv are added to $BocNHNH_2$.



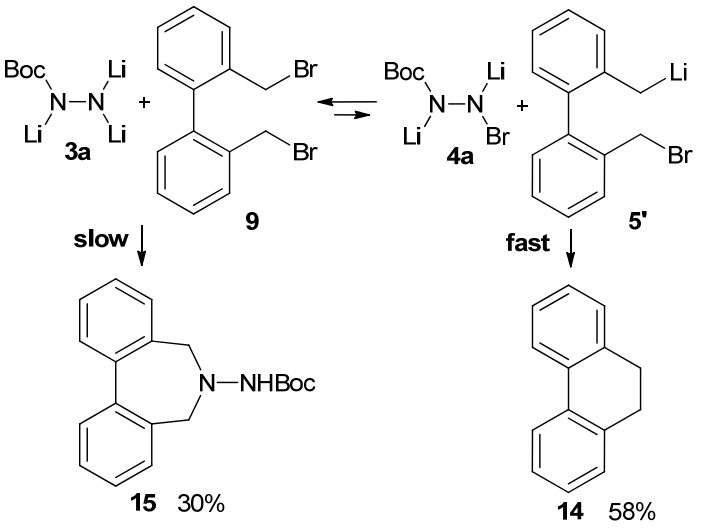
Scheme 54. Two possible ways of the formation of **18** in Entry 6

Next we studied the reactions of hydrazine polyanions with 0.5 equiv of α,α'-dibromo-*o*-xylene, which is the stoichiometric quantity for **12** and **13**. $BocNHNH_2$ trianion failed the test as only traces of the desired product **12** were observed after 10 min, and accumulation of several side-products was detected after 1 h (Entry 9). Amazingly, $BocNHNH_2$ dianion afforded **12** in 62% yield in 10 min, which is the best known result for this compound (Entry 11). The reason for such different actions for these two species is still unclear. Probably, $BocNHNH_2$ trianion has some specific feature requiring dihalide in 2-fold stoichiometric quantity. However, it was demonstrated that there is no positive impact on the yield of **12** if more than 1 equiv of **8** is added to the trianion, as the additional quantity of the dihalide remains unconsumed (Entry 10). PhNHNHBoc dianion was proven to have almost no difference reacting either with 0.5 or 1 equiv of **8** as very similar yield values for **13** were found (Entry 12).

Finally we tested hydrazine polyanions towards α,α'-dichloro-*o*-xylene (**10**). It is known that the rates of metal interconversion in chlorides are significantly lower in comparison with bromides [208]. Indeed, the experiment with $BocNHNH_2$ trianion afforded the bis(hydrazine) **12** only in 8% yield, whereas the main isolated component was the heterocyclic product **11** as a result of competing direct alkylation of the trianion (Entry 14). The reaction of PhNHNHBoc dianion with the dichloride **10** required significantly more time

than the analogous reaction with the dibromide **8**, however, it was surprisingly discovered that the yield of **13** was almost the same (Entry 15).

The obtained results encouraged us to make additional suggestions regarding the mechanism of the reaction. As it has been shown, the first step of the reaction was proven to be the metal-halogen exchange between a dianion or the trianion and α,α'-dibromo-*o*-xylene. We anticipate that it is an equilibrium process shifted to the left. We propose that if the equilibrium was shifted to the intermediates **4** and **5**, these species would likely interact with each other, giving heterocycles as main products. Nevertheless, **11** was isolated only as a minor component in entries 1 and 2. Our hypothesis is also supported by entry 4, where two competing reactions – intramolecular cyclization of the aromatic intermediate **5'** and intermolecular alkylation of the trianion – are taking place. Though the intramolecular process should be much faster, there is still a comparable amount of the heterocycle **15** formed (Scheme 55).



Scheme 55. Formation of **14** and **15** in Entry 4

An equilibrium of metal-halogen exchange may be imagined as a reflective measure of relative anion stability [209]. If the equilibrium is shifted to the left, it may be suggested that $BocNHNH_2$ trianion is a weaker base than the intermediate **5**, which is an analogue of benzyl lithium. Understanding that the pKa value of toluene is at least several units lower than the pKa value of butane [210], it is obvious that BuLi should be strong enough to deprotonate $BocNHNH_2$.

In the case of PhNHNHBoc dianion the equilibrium has to be shifted to the left even more strongly than in the case of $BocNHNH_2$ trianion. Analogously with the previous situation described above, it was also confirmed by the

experiment with the dihalide **9**. It was found that the total yield of the products of the dianion alkylation with the dihalide **9** is twice as high as the yield of the carbocycle **14**, despite the fact that the latter species is expected to form much more quickly (Entry 5). A special case is BocNHNHBoc dianion, where the equilibrium is shifted to the left so strongly that the metal-halogen interconversion is not actually taking place (Entry 13). Obviously, strong electron withdrawing properties of the Boc group make the N-Li bond more covalent, eliminating the possibility for the interchange of the metal.

The second step of the mechanism includes an interaction between the intermediate **5** and the polyanion **3**. Our confidence is based on the comparison of the reactions of $BocNHNH_2$ trianion **3a** with the dihalides **8** and **9** (Entries 1 and 4). The only difference in actions of these two dihalides lies in the failure for **9** to provide the intermediate **5'** in sufficient quantity, as it is rapidly converting to the carbocycle **14** (Scheme 53). As can be observed, knocking out this intermediate it is sufficient to terminate the process of the formation of the bis(hydrazine) at step 1, hence giving a green light for direct alkylation of the trianion **3a** (Scheme 55). It allows us to conclude that the next step of the formation of the bis(hydrazine) **12** has to include the interaction of **5** with a hydrazine derivative. Among all three candidates present in the reaction mixture, the intermediates **4a** and **7a** are inappropriate, as they would more likely afford the heterocycle **11**, which was found only as a minor component. Therefore, the most probable step is the interaction of the intermediate **5** with the trianion **3a** furnishing the trianion **6a**.

Considering the structure of **12**, the third step of the mechanism should include the reaction of the intermediate **6** with either **4** or **7**, as the polyanion **3** is not able to contribute due to the absence of possible reaction centers. It is still unknown whether **4** is stable enough to function itself or transforms to the azo form **7**; therefore, we consider both options. An absolutely analogous reaction of unsymmetrical azo compounds with alkyl lithium reagents under very similar conditions has been previously reported, and it was confirmed to be a very fast and selective process [181]. Apparently, the selectivity of the alkylation of $BocN{=}NR^1$ with R^2Li is achieved due to the greater stability of the anion $BocN^{-}\text{-}NR^1R^2$, thus being controlled thermodynamically.

The stability of the key intermediates **5** and **7a-c** is an important point. We suppose that the intermediate **5** is a stable molecule, which does not undergo intramolecular ring-closure at low temperatures. Our expectations are in a good accordance with the observations of Parham *et al.*, where a very similar intermediate has been described [211]. Apparently, the stability of the intermediates **7a-c** RN=NBoc strongly depends on the nature of the R group. If R has an aromatic origin, the stability of **7** is assured, as such compounds are well-known synthetic reagents [181]. The diazene HN=NBoc is still an unknown substance; however, a similar analogue has been recently described as an intermediate in the process proceeding at 70 °C [212]. Considering the reaction conditions, the diazene HN=NBoc may undergo a rapid deprotonation. Diazene anions, like

LiN=NBoc that is thought to be generated in the reaction of $BocNHNH_2$ trianion, are also known from the literature to be trapped as intermediates [213].

4.3. Synthesis of chiral azacycles

Chiral saturated nitrogen-containing heterocycles are present in the structures of many natural and medicinal compounds [214]. As it has been discussed earlier, RCM represents a universal approach for building cyclic frameworks of different size and structure, thus being very widely utilized for the synthesis of heterocycles. In Section 2.3 many examples for the synthesis of chiral nitrogen heterocycles *via* RCM were demonstrated. If the position of the chiral center in the ring shall be close to the nitrogen, it is generally created before the final ring-closure. However, in the case where the chiral substituent in the ring shall be distant from the nitrogen, an assymetric functionalization of the double bond after RCM may be required.

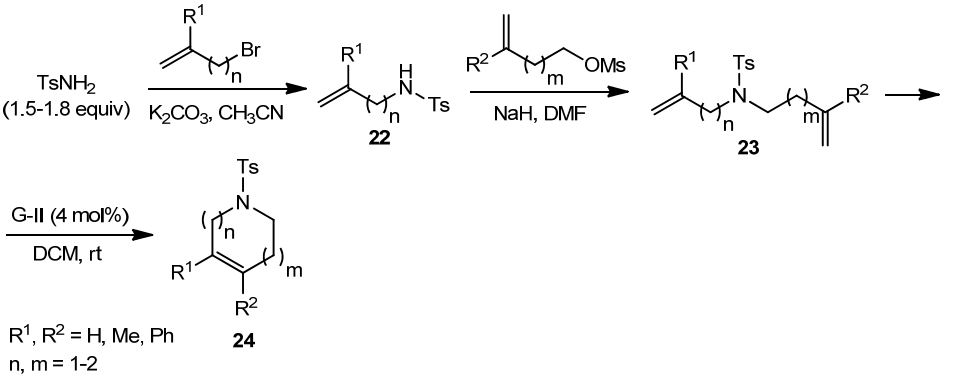
One of the most powerful approaches for the synthesis of enantiomerically enriched compounds is transition metal-catalyzed asymmetric hydrogenation [215]. Andersson and co-workers developed a series of iridium complexes with N,P-ligands, which are very efficient catalysts in asymmetric hydrogenation of an unusually wide range of prochiral alkenes [216]. We decided to expand the scope of the method also to *N*-heterocyclic olefins.

A number of 5-, 6- and 7-membered prochiral nitrogen-containing heterocycles were prepared and subjected to asymmetric hydrogenation. The biggest in size in the series 7-membered rings provided the greatest options for a variation of the positions of the double bond and the prochiral substituent. Therefore, the different types of *N*-Ts protected prochiral 7-membered rings with Me and Ph substituents were examined with a separate synthesis route for each sort of the skeleton.

Our straightforward synthesis strategy was based on the double alkylation of $TsNH_2$ by alkenyl bromides or mesylates and subsequent RCM (Scheme 56). Considering potential regioselectivity problems for the first alkylation [129], we still refused to introduce an additional protecting group, as its insertion and subsequent removal would require two more synthetic steps. Also, construction of tri- and tetrasubstituted cyclic olefins of bigger size is often limited by the availability of the corresponding alkenyl halides as building blocks. So, mesylates were used instead in the second alkylation, which can be easily prepared from more available unsaturated alcohols.

Optimizing the conditions for the alkylation of $TsNH_2$ in acetonitrile in the presence of K_2CO_3, we found that the use of $TsNH_2$ already in a slight excess eliminates the regioselectivity problem and provides exclusively the monoalkylated products. Thus, 1.5–1.8 equiv of $TsNH_2$ with respect to the alkenyl bromide were used to synthesize the monoalkylated derivatives in up to 70% yield. Considering the cheapness of $TsNH_2$, such approach is more than

reasonable from commercial point of view. The obtained products were further alkylated by freshly prepared alkenyl mesylates, using the conditions reported by Yao and Zhang [217]. Finally, RCM was performed, applying 4 mol% of Grubbs 2nd generation catalyst. The results of the experiments are summarized in Table 3.

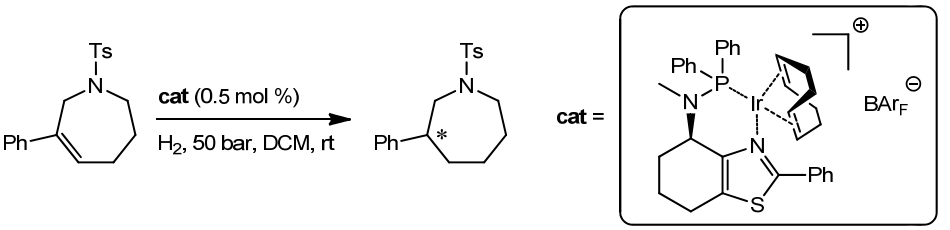


Scheme 56. Synthesis of 7-membered *N*-heterocyclic olefins

Table 3. Summarized results of the synthesis of 7-membered *N*-heterocyclic olefins

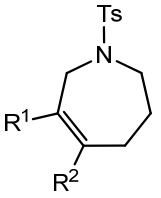
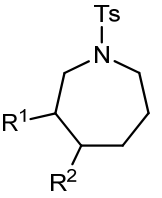
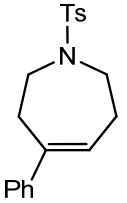
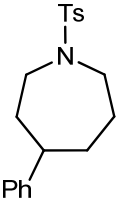
					Yield, %		
Entry	n	m	R^1	R^2	**22**	**23**	**24**
1	1	2	H	Me		48	90
2	1	2	H	Ph		80	60
3	2	1	H	Me	56	67	83
4	2	1	H	Ph		75	55
5	1	2	Me	H	64	72	62
6	1	2	Ph	H	70	54	52

The obtained Me- and Ph-substituted 7-membered rings were studied in asymmetric hydrogenation. The reactions were performed applying 0.5 mol% of the Ir catalyst under 50 bar H_2 for 15 h (Scheme 57). While Me-substituted derivatives demonstrated a moderate enantioselectivity, a very good *ee* values were obtained for the reduction of Ph-substituted olefins (Table 4). Also, it has been shown that the selectivity is not impacted by the position of the double bond.



Scheme 57. A typical example of asymmetric hydrogenation of a prochiral *N*-heterocyclic olefin

Table 4. The results of asymmetric hydrogenation of Ph-substituted 7-membered *N*-heterocyclic olefins

Substrate	Product		Conversion[a] (%)	*ee*[b] (%)
		R^1 = Ph R^2 = H	>99	98 (–)
		R^1 = H R^2 = Ph	>99	96 (–)
			>99	90 (+)

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC.

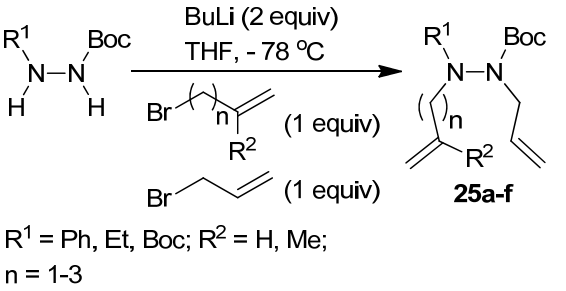
4.4. Combination of hydrazine polyanion strategy and ring-closing metathesis

Successful experiments with the synthesis of prochiral *N*-heterocyclic olefins *via* double alkylation and RCM inspired us to investigate the possibilities for preparation of analogous heterocycles with hydrazine moiety. As shown in section 2.2, the existing methods for the synthesis of the heterocycles comprising endocyclic N-N bond are good for preparation of 5- and 6-membered rings, and in some cases also 7-membered cycles. However, quite a wide range of heterocyclic targets still remains relatively unachievable.

In section 4.1 it was demonstrated that the heterocycles obtained by the alkylation of the dianions of hydrazine derivatives with dihalides were also limited to 5-membered rings. At the same time, the dianion strategy displayed its excellence in one-pot selective unsymmetrical alkylation, what makes it a

superior tool for an efficient synthesis of RCM substrates. Employment of RCM gives an access to a variety of cyclic frameworks. In section 2.3.2 the cases where RCM was applied for the synthesis of cyclic hydrazine derivatives were shown, but all of them are rather individual examples. We decided to perform a systematic study with variation of the most important synthetic parameters.

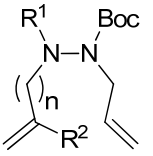
We started with symmetrical dialkylation of dianions with bromoalkenes (Scheme 58). The dianions from PhNHNHBoc, EtNHNHBoc and BocNHNHBoc were generated by the treatment with 2 equiv of BuLi in THF at –78 °C with subsequent addition of the alkylating agent. The reaction progress was monitored by TLC. The addition of 2 equiv of allyl bromide to the dianions led to a rapid formation of the monoalkylated products (1 h) and a slow formation of the dialkylated products (1–3 days) even at 40 °C (Table 5). At room temperature the reactions were incomplete. Unfortunately, we failed to introduce the alkenyl groups with a longer alkyl chain in a similar manner, obtaining the monoalkylated products with a small content of the dialkylated species. Probably, the dianion being also a strong base may promote elimination, especially in the case of 4-bromo-1-butene with formation of 1,3-butadiene, which is stabilized by conjugation and hence is thermodynamically more favored to form compared to other bromides. For 5-bromo-1-pentene we suspect that steric interactions between two long alkyl chains may also affect, as similar behaviour has been previously observed [23].



Scheme 58. Direct dialkylation of the dianions

Considering these limitations, next we tried the consecutive one-pot mono-alkylation of the both nitrogens of PhNHNHBoc dianion in order to introduce the alkenyl groups with longer or branched chain onto the Ph nitrogen, and the smaller allyl group onto the Boc nitrogen (Scheme 58). The second halide was added after the monoalkylation reaction was complete according to TLC. The corresponding products were obtained in good yields (Table 5). Again, the formation of the dialkylated products required 1–2 days at 40 °C. As expected, the introduction of the alkenyl groups with a longer alkyl chain onto the Boc nitrogen was still problematic, though a satisfactory 60% yield was obtained for 5-bromo-1-pentene if allyl bromide had been used before.

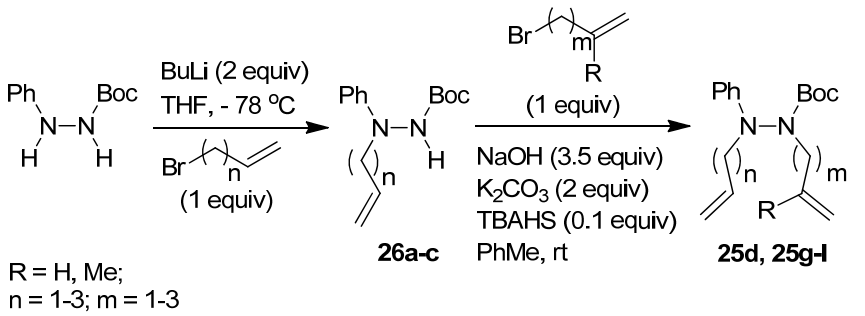
Table 5. Products of direct alkylation of the dianions



Product	R^1	R^2	n	Conditions	Yield, %
25a	Ph	H	1	AllBr (2 equiv), – 40 °C to 40 °C, 1 day	77
25b	Et	H	1	AllBr (2 equiv), – 40 °C to 40 °C, 1 day	49
25c	Boc	H	1	AllBr (2 equiv), – 40 °C to 40 °C, 3 days	81
25d	Ph	H	2	CH_2=CH(CH_2)$_2$Br, – 40 °C to rt, 1 h; AllBr, 40 °C, 2 days	60
25e	Ph	H	3	CH_2=CH(CH_2)$_3$Br, – 40 °C to rt, 1 h; AllBr, 40 °C, 2 days	81
25f	Ph	Me	1	CH_2=C(CH_3)CH_2Br, – 40 °C, to rt 1 h; AllBr, 40 °C, 1 day	80

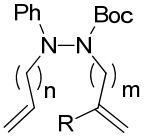
Faced with clear liminations of the dianion direct alkylation, we decided to work out another methodology to synthesize the dienehydrazines containing the substituents with a longer alkyl chain on the Boc nitrogen. At first we performed the monoalkylation of PhNHNHBoc dianion with 1 equiv of the alkylating agent (Scheme 59). The monoalkylated derivatives **26** formed within 1 h and were obtained in very good yields.

Next we started examining milder conditions for the alkylation of trisubstituted hydrazines **26**. First we tried to employ NaH as a deprotonation agent with subsequent addition of an excess of 4-bromo-1-butene, but a low conversion was observed according to TLC. Probably, elimination was the case again, as the halide and a strong base were still in contact. Therefore, we decided to switch on insoluble bases. The application of NaOH in the presence of K_2CO_3 and TBAHS as a PTC catalyst gave superior results for alkylation of **26** with different alkenyl bromides (Scheme 59). Apparently, the success was achieved due to a biphasic system of the reaction: the base and the base-sensitive compounds were in the different phases, what reduced the probability of elimination. The dialkylated products **25** were obtained in very good yields as a result of the overnight reaction. However, still some problems were observed for 4-bromo-1-butene even under these very mild conditions, indicating the incompleteness of the reactions after 1 day in certain cases. An additional 1 equiv of the halide was added to improve the reaction progress. The results of the experiments are summarized in Table 6.



Scheme 59. Monoalkylation of PhNHNHBoc dianion and further alkylation under PTC conditions

Table 6. Products of mono- and double alkylation



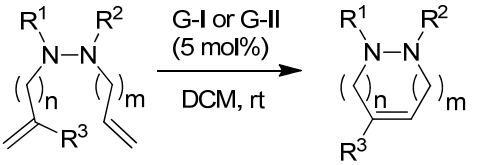
Product	R	n	m	Conditions	Yield, %
26a		1		AllBr, – 40 °C, 1 h	90
26b		2		CH_2=CH$(CH_2)_2$Br, – 40 °C, 1 h	80
26c		3		CH_2=CH$(CH_2)_3$Br, – 40 °C, 1 h	75
25d	H	2	1	AllBr (1 equiv), rt, 1 day	81[a]
25g	H	1	2	CH_2=CH$(CH_2)_2$Br (1 equiv), rt, 1 day	93[a]
25h	H	1	3	CH_2=CH$(CH_2)_3$Br (1 equiv), rt, 1 day	91[a]
25i	Me	1	1	CH_2=C$(CH_3)CH_2$Br (1 equiv), rt, 1 day	61[a]
25j	H	2	2	CH_2=CH$(CH_2)_2$Br (2 equiv), rt, 2 days	71[a]
25k	H	2	3	CH_2=CH$(CH_2)_3$Br (1 equiv), rt, 1 day	79[a]
25k	H	2	3	CH_2=CH$(CH_2)_2$Br (1 equiv) – 40 °C to rt, 1 h; CH_2=CH$(CH_2)_3$Br (1 equiv), rt, 1 day	65[b]
25l	H	3	2	CH_2=CH$(CH_2)_2$Br (2 equiv), rt, 2 days	71[a]

[a] Synthesized from the corresponding derivative **26**. [b] One-pot synthesis from PhNHNHBoc.

Though the direct dialkylation of the dianions has certain limitations, its one-pot fashion is an undeniable advantage. Testing the monoalkylation and further alkylation under PTC conditions, we observed that both reactions proceeded cleanly without formation of significant amounts of side-products. Thus, we tried to perform the same reaction sequence in a one-pot fashion without separation of the monoalkylated product and only changing the solvent after the first

step. We found that such approach had the same efficiency as two separate reactions, and hence a simplified procedure may be successfully used.

RCM studies were started with the cyclization of **25a** using Grubbs 1st generation catalyst (Scheme 60). We found that the use of 5 mol% of the catalyst seemed to be optimal for the cyclization. For example, using 2 and 5 mol% of the catalyst, the corresponding 6-membered ring **27a** was obtained in 39% yield for the overnight cyclization and 89% yield after 30 minutes, respectively. 20 mM substrate concentration was found to be suitable as no side-products were detected. Therefore, the same cyclization conditions were employed for all other dienehydrazines (Table 7).

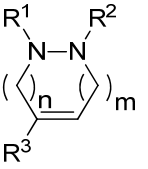


25a-l **27a-l**

R^1, R^2 = Ph, Et, Boc; R^3 = H, Me;
n, m = 1-3

Scheme 60. Ring-closing metathesis of dienehydrazines

Table 7. Products of ring-closing metathesis



Product	R^1	R^2	R^3	n	m	Conditions	Yield, %
27a	Ph	Boc	H	1	1	G-I (5 mol%), rt, 30 min	89
27b	Et	Boc	H	1	1	G-II (5 mol%), rt, 1 day	71
27c	Boc	Boc	H	1	1	G-I (5 mol%), rt, 2 h	87
27d	Ph	Boc	H	2	1	G-I (5 mol%), rt, 1 day	88
27e	Ph	Boc	H	3	1	G-I (5 mol%), rt, 1 day	94
27f	Ph	Boc	Me	1	1	G-II (5 mol%), rt, 1 day	80
27g	Ph	Boc	H	1	2	G-I (5 mol%), rt, 1 day	86
27h	Ph	Boc	H	1	3	G-I (5 mol%), rt, 1 day	81
27i	Boc	Ph	Me	1	1	G-II (5 mol%), rt, 1 day	82
27j	Ph	Boc	H	2	2	G-I (5 mol%), rt, 2 h	77
27k	Ph	Boc	H	2	3	G-I (5 mol%), rt, 1 day	54
27l	Ph	Boc	H	3	2	G-I (5 mol%), rt, 1 day	51

25b, **25f** and **25i** did not react at all in the presence of Grubbs 1st generation catalyst, so, the corresponding cycles were obtained employing Grubbs 2nd generation catalyst. Whereas this situation was predictable for the synthesis of prochiral cycles **27f** and **27i**, it was rather unexpected for **27b**. A possible explanation is that EtNHNHBoc has an accessible lone electron pair on the ethyl-bearing nitrogen, and hence is able to act as a ligand and to deactivate the catalyst. Metal-ligand interaction with Grubbs 2nd generation catalyst must be much weaker because of higher electron density on the Ru atom, which preferable complexes with a double bond and hence the ring-closed product can form.

All 6-, 7- and 8-membered rings, including the prochiral cycles, were obtained in good to excellent yields. We also noticed that the cyclization of the substrates with identical alkenyl groups proceeded more rapidly. Some decrease of the yield values for 9-membered heterocycles **27k** and **27l** was observed even when lower substrate concentrations were used for more efficient cyclization. The use of Grubbs 2nd generation catalyst did not improve the yields.

5. EXPERIMENTAL

General

All hydrazine polyanion alkylation and ring-closing metathesis reactions were performed under an inert atmosphere in oven-dried glassware. THF was freshly distilled from Na/benzophenone, DCM was freshly distilled from calcium hydride. Column chromatography was carried out on a Merck Kieselgel 60 (70–230 mesh). The structures of all synthesized compounds were confirmed by NMR and IR spectroscopy. HRMS spectra were measured for all new compounds.

^{1}H and ^{13}C NMR spectra were recorded either on an AVANCE II 200 spectrometer at 200 MHz and 50 MHz respectively (University of Tartu), or on a Varian Unity 400 spectrometer at 400 MHz and 100 MHz respectively (Uppsala University). $CDCl_3$ was used as a solvent. The chemical shifts were internally referenced to the residual solvent signals or tetramethylsilane.

IR spectra were measured on a Perkin-Elmer Spectrum BXII FTIR spectrometer using ATR technique.

HRMS spectra were measured either on a Thermo Electron LTQ Orbitrap ESI mass spectrometer, or Thermo Scientific Q Exactive mass spectrometer.

Typical procedure for alkylation of $BocNHNH_2$ trianion with aliphatic dihalides

A flask was charged with $BocNHNH_2$ (2.00 mmol, 264 mg), evacuated and backfilled with argon. Thereafter THF (14 mL) was added to dissolve the solid. The reaction mixture was cooled down to − 78 °C and 1.6 M BuLi solution in hexane (6.00 mmol, 3.75 mL) was added dropwise. The reaction mixture was allowed to warm up to − 40 °C for 15 min and the corresponding dihalide (2.00 mmol) was added. Then the reaction mixture was allowed to warm up to room temperature for 1 h. The reaction progress was monitored by TLC. After 3–4 h the reaction was mainly complete, but it was allowed to stir overnight. The reaction mixture was quenched by addition of 0.1 mL of H_2O and the solvent was evaporated under reduced pressure. To the residue 15 mL of $CHCl_3$ and anhydrous $MgSO_4$ were added. The mixture was filtered and $MgSO_4$ was washed with $CHCl_3$ (3 × 2 mL). The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica.

Typical procedure for alkylation of $BocNHNH_2$ trianion with α,α'-dibromo-*o*-xylene

A flask was charged with $BocNHNH_2$ (2.00 mmol, 264 mg), evacuated and backfilled with argon. Thereafter THF (12 mL) was added to dissolve the solid. The reaction mixture was cooled down to − 78 °C and 1.6 M BuLi solution in hexane (6.00 mmol, 3.75 mL) was added dropwise. The reaction mixture was

allowed to warm up to − 45 °C for 15 min and a solution of α,α'-dibromo-*o*-xylene (2.00 mmol, 528 mg) in THF (2 mL) was added. The reaction progress was monitored by TLC. After 10 min the reaction was complete. The reaction mixture was quenched by addition of 0.1 mL of H_2O and the solvent was evaporated under reduced pressure. To the residue 15 mL of $CHCl_3$ and anhydrous $MgSO_4$ were added. The mixture was filtered and $MgSO_4$ was washed with $CHCl_3$ (3 × 2 mL). The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica.

Typical procedure for alkylation of $BocNHNH_2$ dianion with α,α'-dibromo-*o*-xylene

The reaction was performed analogously with the previous description for $BocNHNH_2$ trianion with the only difference that 2 equiv of 1.6 M BuLi solution in hexane (4.00 mmol, 2.50 mL) were added.

Typical procedure for alkylation of PhNHNHBoc dianion with α,α'-dibromo-*o*-xylene

A flask was charged with PhNHNHBoc (1.00 mmol, 208 mg), evacuated and backfilled with argon. Thereafter THF (5 mL) was added to dissolve the solid. The reaction mixture was cooled down to − 78 °C and 1.6 M BuLi solution in hexane (2.08 mmol, 1.30 mL) was added dropwise. The reaction mixture was allowed to warm up to − 45 °C for 15 min and a solution of α,α'-dibromo-*o*-xylene (1.00 mmol, 264 mg) in THF (1 mL) was added. The reaction progress was monitored by TLC. After 30 min the reaction was complete. The reaction mixture was quenched by addition of 0.1 mL of H_2O and the volatiles were evaporated under reduced pressure. The residue was purified by column chromatography on silica.

Typical procedure for monoalkylation of $TsNH_2$ with alkenyl halides

A flask was charged with $TsNH_2$ (1.5–1.8 equiv), K_2CO_3 (1.2–1.3 equiv) and acetonitrile. The corresponding alkenyl halide (1 equiv) was added to the mixture. The mixture was heated to reflux and stirred overnight. Then the mixture was cooled down to room temperature, filtered and the volatiles were evaporated under reduced pressure. The residue was partitioned between Et_2O and H_2O. Phases were separated and the aqueous phase was extracted with Et_2O. The combined organic solutions were dried and concentrated. The residue was purified by flash chromatography on silica.

Typical procedure for alkylation of *N*-Ts-alkenes with alkenyl mesylates
A solution of *N*-Ts-alkene (1 equiv) in DMF was cooled down to 0 °C and NaH (1.3–1.4 equiv, 60% in mineral oil) was added in one portion. After H_2 evolution was finished, a solution of the corresponding alkenyl mesylate (1.3 equiv) in DMF was added. The reaction mixture was heated to 100 °C for 6 h and then cooled down to room temperature. The reaction mixture was partitioned between Et_2O and H_2O. Phases were separated and the aqueous phase was extracted with Et_2O. The combined organic solutions were dried and concentrated. The residue was purified by flash chromatography on silica.

Typical procedure for ring-closing metathesis of *N*-Ts-dienes
N-Ts-diene (1 equiv) and Grubbs 2nd generation catalyst (0.04 equiv) were dissolved in dry DCM (50–70 mL/mmol) under nitrogen. The solution was stirred at room temperature. After the reaction was complete according to TLC, the solvent was evaporated under reduced pressure and the crude material was purified by column chromatography on silica.

Typical procedure for symmetrical diallylation of hydrazine dianions
A flask was charged with the corresponding disubstituted hydrazine (1 equiv), evacuated and backfilled with argon. Thereafter THF was added to dissolve the solid. The reaction mixture was cooled down to − 78 °C and 1.6 M BuLi (2 equiv) solution in hexane was added dropwise. The reaction mixture was allowed to warm up to − 40 °C for 15 min and allyl bromide (2 equiv) was added. The reaction mixture was allowed to warm up to room temperature for 1 hour, then heated to 40 °C and stirred overnight. The reaction progress was monitored by TLC. When the reaction was complete, the volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica.

Typical procedure for selective one-pot alkylation/allylation of PhNHNHBoc dianion
A flask was charged with PhNHNHBoc (1 equiv), evacuated and backfilled with argon. Thereafter THF was added to dissolve the solid. The reaction mixture was cooled down to − 78 °C and 1.6 M BuLi (2 equiv) solution in hexane was added dropwise. The reaction mixture was allowed to warm up to − 40 °C for 15 min and the corresponding alkenyl halide (1 equiv) was added. The reaction mixture was allowed to warm up to room temperature for 1 hour. Then allyl bromide (1.1 equiv) was added, the reaction mixture was heated to 40 °C and stirred overnight. The reaction progress was monitored by TLC. When the reaction was complete, the volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica.

Typical procedure for monoalkylation of PhNHNHBoc dianion

A flask was charged with PhNHNHBoc (1 equiv), evacuated and backfilled with argon. Thereafter THF was added to dissolve the solid. The reaction mixture was cooled down to − 78 °C and 1.6 M *n*-BuLi (2 equiv) solution in hexane was added dropwise. The reaction mixture was allowed to warm up to − 40 °C for 15 min and the corresponding alkenyl bromide (1 equiv) was added. The reaction progress was monitored by TLC. After 1 h the reaction was complete. The volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica.

Typical procedure for alkylation of trisubstituted hydrazines under PTC conditions

Trisubstituted hydrazine (1 equiv) was dissolved in toluene and the corresponding alkenyl bromide (1.05 equiv) was added. The reaction was performed at room temperature under PTC conditions by adding K_2CO_3 (2 equiv), NaOH (3.5 equiv) and TBAHS (0.1 equiv) to the reaction mixture. The reaction progress was monitored by TLC. After 1 day the reaction was complete. H_2O was added and the mixture was extracted with Et_2O. The combined Et_2O solutions were evaporated under reduced pressure and the residue was purified by column chromatography on silica.

Typical procedure for ring-closing metathesis of dienehydrazines

Dienehydrazine (1 equiv) and Grubbs 1st or 2nd generation catalyst (0.05 equiv) were dissolved in dry DCM (50 mL/mmol for 6-, 7- and 8-membered rings; 80 mL/mmol for 9-membered rings) under nitrogen. The solution was stirred at room temperature. The reaction progress was monitored by TLC. After 1 day the reaction was separated. The volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica.

6. CONCLUSIONS

The current thesis describes the different strategies for the synthesis of heterocycles containing hydrazine moiety. Both types of heterocycles comprising exo- and endocyclic N-N bond were covered by the study. The central point of the approach is generation of di- and trianions of hydrazine derivatives and their sequential selective alkylation.

A number or 5-, 6- and 7-membered heterocycles were synthesized by the alkylation of $BocNHNH_2$ trianion with aliphatic dihalides. The reaction conditions were studied and optimized. This is the first known preparative method for a direct synthesis of *N*-aminoazacycles from $BocNHNH_2$ and aliphatic dihalides in good yields, thus providing an easy access to the heterocyclic targets which can be further optionally functionalized. Unfortunately, the similar alkylation of $PhNHNH_2$ trianion was not selective, affording the mixture of products. The analogous alkylation of the dianions of disubstituted hydrazines was also investigated and found applicable for the synthesis of 5-membered pyrazolidine rings.

The reaction of $BocNHNH_2$ trianion with α,α'-dibromo-*o*-xylene unexpectedly afforded an aromatic-bridged bis(hydrazine). Further a similar behaviour was observed also for the dianions of hydrazine derivatives. The method constitutes a very fast and convenient synthetic tool for the preparation of aromatic-bridged bis(hydrazines). It was experimentally confirmed that the process involves a metal-halogen interconversion between a polyanion and α,α'-dibromo-*o*-xylene or a similar halide. A possible reaction pathway was suggested and experimentally justified. To the best of our knowledge, it is the first reported example of a metal-halogen exchange on a nitrogen atom. Moreover, the metal-halogen exchange was an essential instrument, which demonstrated a possibility of existence of the trianions of monosubstituted hydrazines.

The second part of the thesis was focused on the application of the ring-closing metathesis reaction to the synthesis of nitrogen-containing heterocycles. During the preliminary study a series of prochiral *N*-heterocyclic olefins were synthesized and successfully subjected to asymmetric hydrogenation. A straightforward and commercially reasonable synthesis strategy particularly for different 7-membered azacycles was demonstrated.

A similar approach was used to expand the scope of hydrazine polyanion strategy for the synthesis of the heterocycles comprising endocyclic N-N bond. A series of dienehydrazines were prepared by sequential double alkylation of different disubstituted hydrazines. During the study it was found that one-pot double alkylation of the dianions was not applicable for the synthesis of dienehydrazines with two long alkyl chains. A problem was successfully overcome, employing a phase-transfer catalysis for the second alkylation, which can be also combined in a one-pot fashion with the monoalkylation of the dianions.

A first systematic study of the ring-closing metathesis of dienehydrazines with a variation of the most important synthetic parameters was performed. It

was found that hydrazine derivatives with different substituents can be employed, though trialkylated hydrazines may require special conditions for efficient cyclization. A number of heterocycles of different size and structure were synthesized.

In summary, hydrazine polyanion strategy was confirmed to be efficient for the synthesis of both types of cyclic hydrazines, being a good alternative to already existing methods.

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SUMMARY IN ESTONIAN

Hüdrasiinide polüanioonid: erinevad strateegiad heterotsüklite sünteesil

Käesolev dissertatsioon käsitleb kahte erinevat strateegiat hüdrasiini fragmenti sisaldavate heterotsüklite sünteesiks. Uurimistöö hõlmab kahte tüüpi heterotsükleid, mis sisaldavad nii ekso-, kui ka endotsüklilist N-N sidet. Lähenemise keskpunktiks on hüdrasiini derivaatidest di- ja trianioonide tekitamine ja nende järjestikune selektiivne alküülimine.

Töö esimese osa raames sünteesiti rida 5-, 6- ja 7-lülilisi heterotsükleid, alküleerides $BocNHNH_2$ trianiooni alifaatsete dihalogeniididega. Uuriti ja optimeeriti reaktsioonitingimusi. See on esimene kirjeldatud preparatiivne meetod, mis võimaldab N-aminoasatsüklite otsest sünteesimist heade saagistega, lähtudes $BocNHNH_2$-st ja alifaatsetest dihalogeniididest. Seega, antud meetod lihtsustab juurdepääsu erinevate heterotsüklite sünteesiblokkidele, mida saab edasi valikuliselt funktsionaliseerida. Kahjuks, sarnane $PhNHNH_2$ trianiooni alküülimine ei olnud selektiivne, andes produktide segu. Uuriti ka analoogset diasendatud hüdrasiinide dianioonide alküülimist ja leiti see olevat sobivaks 5-lüliliste pürasolidiini tsüklite sünteesiks.

$BocNHNH_2$ trianiooni reaktsioon α,α'-dibromo-*o*-ksüleeniga andis üllatavalt aromaatse sillaga bis(hüdrasiini). Hiljem näidati, et sarnane käitumine on loomulik ka hüdrasiini derivaatide dianioonidele. Antud reaktsioon on väga kiire ja mugav meetod aromaatse sillaga bis(hüdrasiinide) sünteesiks. Eksperimentaalselt kinnitati, et protsessi oluliseimaks etapiks on metall-halogeen vahetus polüaniooni ja α,α'-dibromo-*o*-ksüleeni või sarnase halogeniidi vahel. Vastavalt sellele esitati võimalik reaktsiooni mehhanism, mis oli ka eksperimentaalselt põhjendatud. Meie parimate teadmiste järgi on see esimene kirjeldatud näide, kus metall-halogeen vahetus toimub lämmastiku aatomi juures. Lisaks, osutus metall-halogeen vahetus väga kasulikuks instrumendiks, mille abil kinnitati monoasendatud hüdrasiinide trianioonide eksisteerimise võimalust.

Antud töö teine osa oli keskendatud tsüklitekke metateesi reaktsiooni rakendamisele lämmastikku sisaldavate heterotsüklite sünteesiks. Algsete uuringute käigus sünteesiti seeria prokiraalseid N-heterotsüklilisi alkeene, mis said edukalt asümmeetriliselt hüdrogeenitud. Käesolevas töös demonstreeriti lihtsat ja majanduslikult mõistlikku sünteesiteed erinevate struktuuridega 7-lüliliste asatsüklite sünteesiks.

Sarnast lähenemist kasutati hüdrasiini polüanioonide strateegia rakenduspiiride laienemiseks endotsüklilist N-N sidet sisaldavate heterotsüklite sünteesiks. Sünteesiti rida dieenhüdrasiine erinevate diasendatud hüdrasiinide topelt-alküülimisel. Uuringute käigus leiti, et meetod ei sobi kaht pikka alküülahelat sisaldavate dieenhüdrasiinide sünteesiks. Probleem lahendati edukalt faasiülekandekatalüüsi rakendamisega teise alküülimise jaoks, mida saab teha ka ühepoti sünteesi meetodiga koos dianiooni monoalküülimisega.

Teostati esimene dieenhüdrasiinide tsüklitekke metateesi süstemaatiline uurimine, varieerides tähtsamaid sünteetilisi parameetreid. Selgitati, et tsükliseerimise jaoks saab kasutada erinevaid rühmi sisaldavaid hüdrasiine, kuid trialküülitud hüdrasiinid võivad nõuda eritingimusi efektiivse tsükliseerimise jaoks. Töö tulemusena sünteesiti palju erineva suurusega ja struktuuriga heterotsükleid.

Kokkuvõteks, tõestati et hüdrasiini polüanioonide strateegia on efektiivne mõlemat tüüpi tsükliliste hüdrasiinide sünteesiks ning on hea alternatiiv juba olemasolevatele sünteesimeetoditele.

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PUBLICATIONS

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