HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 129 - 173. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2013, Accepted, 26th August, 2013, Published online, 6th September, 2013
DOI: 10.3987/REV-13-SR(S)3

HYDRAZINES AND AZO-COMPOUNDS IN THE SYNTHESIS OF HETEROCYCLES COMPRISING N-N BOND

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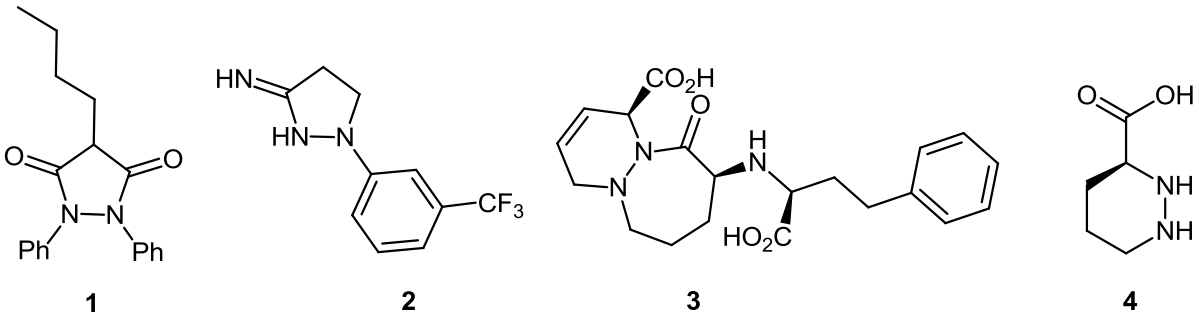
We would like to dedicate this work to professor Viktor Snieckus, on the occasion of his 77th birthday and in thanks for his years of contribution to Baltic chemistry.

Abstract – The synthesis of nitrogen containing heterocycles is of great importance in modern science, owing to their valuable biological properties, and endocyclic hydrazinocycles are no exception. There are methods that enable the transformation of amines to hydrazines, however the use of hydrazine derivatives and azo-compounds as starting materials is both logical and straightforward. In this review we aimed to summarize the methods that use simple hydrazines and azo-compounds for the synthesis of these heterocycles. We begin with simple stoichiometric alkylation of hydrazines and later on move to catalytic systems. Finally, we provide an overview of the advances in the field of azomethine imines chemistry.

CONTENTS

1. INTRODUCTION

Hydrazine containing heterocycles are a varied class of compounds and many of them show remarkable biological activity. They are used as anti-inflamatory drugs (e.g. phenylbutazone **1**),[1] COX (e.g. **2**)[2] and ACE (e.g. Cilazapril **3**)[3] inhibitors, pesticides,[4] dyes.[5] Piperazic acid **4** is an important building block and was used in the synthesis of sanglifehrin A[6] and its analogues,[7] verucopeptin,[8] and antitumor agents (+)-azinothricinand (+)-kettapeptin.[9]



1 2 3 4

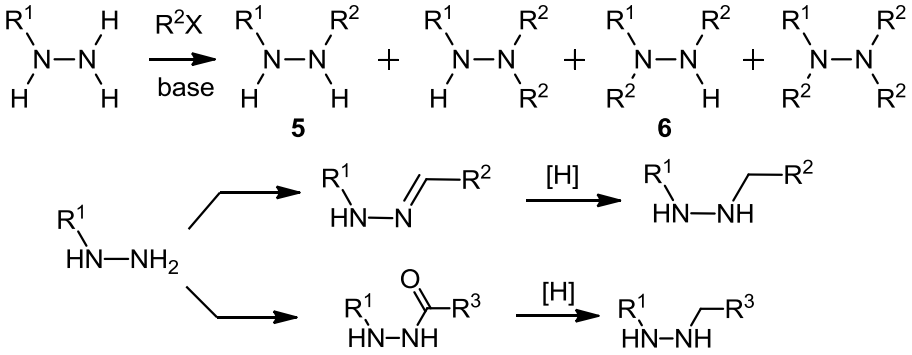
Figure 1. Some biologically active hydrazine derivatives

Owing to the importance of these compounds, methods of synthesizing of them are necessary. This review aims to summarize the synthetic methods that use hydrazines or azo-compounds as starting materials.

2. GENERAL CONSIDERATIONS OF HYDRAZINE ALKYLATION

The alkylation of hydrazines face challenges linked to selectivity.[10] If a protecting group strategy is employed, the reactions proceed very cleanly, but in poor overall atom economy, which makes it ill-suited to a modern synthetic chemist's mindset.[11] Of far greater interest, if more difficult to achieve is the monoalkylation of monosubstituted hydrazines. When performing direct alkylation, the major product

is usually hydrazine **6** (a product of 1,2-disubstitution), which often limits the synthesis of 1,2-disubstituted hydrazines **5** to reductive aminations of carbonyl compounds[12] or an acylation which is subsequently followed by reduction (Scheme 1).[13] In the last few years, several protocols employing iridium[10] and palladium[14] catalysis were developed for the selective monoallylation of mono- and disubstituted hydrazines, however catalytic alkylations of hydrazines remain still widely unexplored.



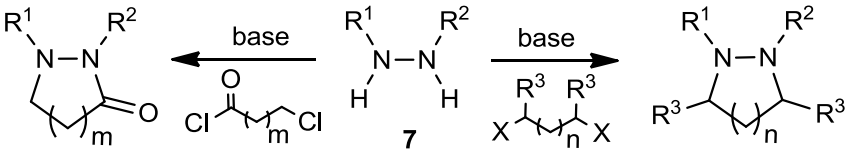
Scheme 1. Direct alkylation of hydrazines. Reductive alkylation and acylation/reduction as replacement of selective monoalkylation

The most widely used protocol for the alkylation of hydrazines is the deprotonation of hydrazine with NaH in DMF, subsequently followed by the addition of an alkylating agent. An excess of a mild bases, such as K_2CO_3,[15] or mixtures containing NaOH[16] or Cs_2CO_3[17] could be used. It was shown that the reaction depends on the solubility of the base,[18] which suggests that phase-transfer catalysis (PTC) might be useful. Indeed, the PTC approach enables the use of milder conditions, while being less sensitive to steric hindrance,[19] and therefore can be more widely used.

The Mitsunobu approach is very useful as well: especially when a chiral starting alcohol is used, since the reaction proceeds with an inversion at the stereocenter. This enables the synthesis of enantiomerically pure products (in contrast to PTC which generates racemic products).[20] A limitation of the Mitsunobu reaction is its sensitivity to the acidity of the hydrazines employed: should the pK_a of the starting hydrazine exceed 14 it will be insufficiently active to participate in the reaction.[21]

3. DIRECT ALKYLATION AND ACYLATION OF HYDRAZINES

Probably the most straightforward method to synthesize cyclic hydrazines is the alkylation of disubstituted hydrazines **7** by dihalides. This method was first mentioned by Overberger[22] and still widely used for the synthesis of aliphatic cycles, since suitably protected hydrazines are readily available.

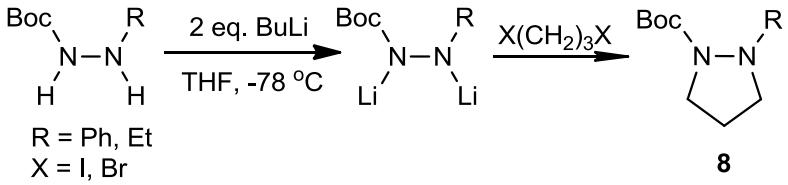


R^1=CO_2Et, Boc, R^2 = CO_2Et, Cbz, Boc, Ph, R^3 = H, Me,
X = Br, OTs,
n = 1-4, m = 1-2

Scheme 2. Direct alkylation of hydrazines

The direct alkylation of hydrazine starts with its deprotonation, usually by a NaH dispersion in DMF or diglyme (Scheme 2).[23] The most common alkylating agents are dibromides (both primary, and in some cases, secondary), though ditosylates[24] have been used as a cheaper alternative. Reaction yields depend on the size of the generated ring, and examples of the preparation of 5- to 8-membered cycles are found in literature. Similarly, by using a milder base (K_2CO_3) and 3-chloropropanoyl chloride or 4-chlorobutanoyl chloride, the analogous acylation/alkylation of hydrazines was also performed (Scheme 2).[25] PTC conditions are also applicable for cyclizations: NaOH and catalytic Et_4NBr in aqueous medium, with heating was used to generate 5- to 7-membered cycles in good yields (78-95%).[26]

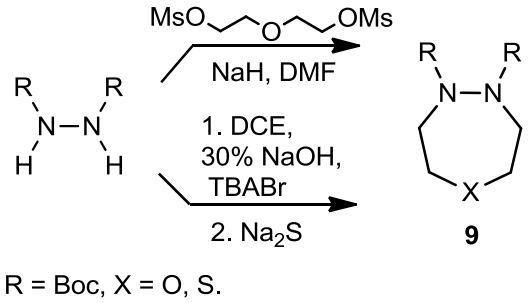
Pyrazolidines **8** could be obtained easily from disubstituted hydrazines by using dihalopropane for the alkylation via the polyanion strategy,[27] however attempts to prepare larger heterocycles failed (Scheme 3).[28]



R = Ph, Et
X = I, Br

Scheme 3. Use of dianions for the synthesis of heterocycles

Very similarly, the dimesylates obtained from 2,2'-oxydiethanol could be used for alkylation. Thiadiazepane **9** was obtained by performing an alkylation using 2 equiv of dichloroethane, under mild PTC conditions and then refluxing with Na_2S in EtOH to generate the desired cycle **9** (Scheme 4).[29]

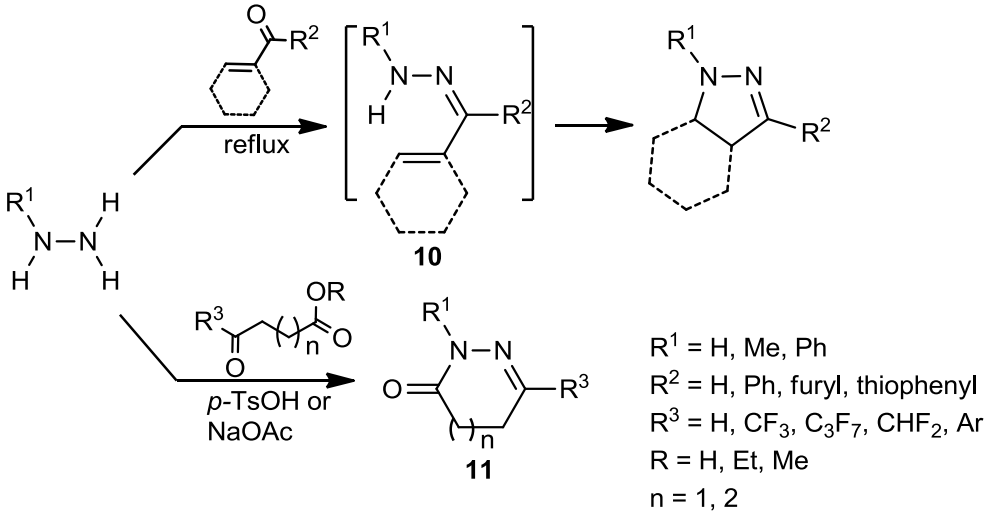


Scheme 4. Synthesis of thiazepane by alkylation of hydrazine

Acylations have also been performed by using carboxylic acids in conjunction with coupling agents, as was shown by Bihel *et al.*[30] For example, 2-(carboxymethyl)benzoic acid ester was condensed with a 1,2-disubstituted hydrazine, the first step was the condensation of benzoic acid with hydrazine which was achieved through the use of HBTU and, in a second step, acylation with ester occured.

4. CONDENSATION OF HYDRAZINES WITH CARBONYL COMPOUNDS

Cyclic systems are accessible from carbonyl compounds, providing a functionality reactive to the hydrazine's NH group is available after the hydrazone formation.[31] The rearrangement of unstable hydrazones **10** formed in the reaction of hydrazines with α,β-unsaturated ketones, discovered by Fisher and Knoevenagel is such an example.[32] However its main limitations are long reaction times and moderate yields (31-54%).

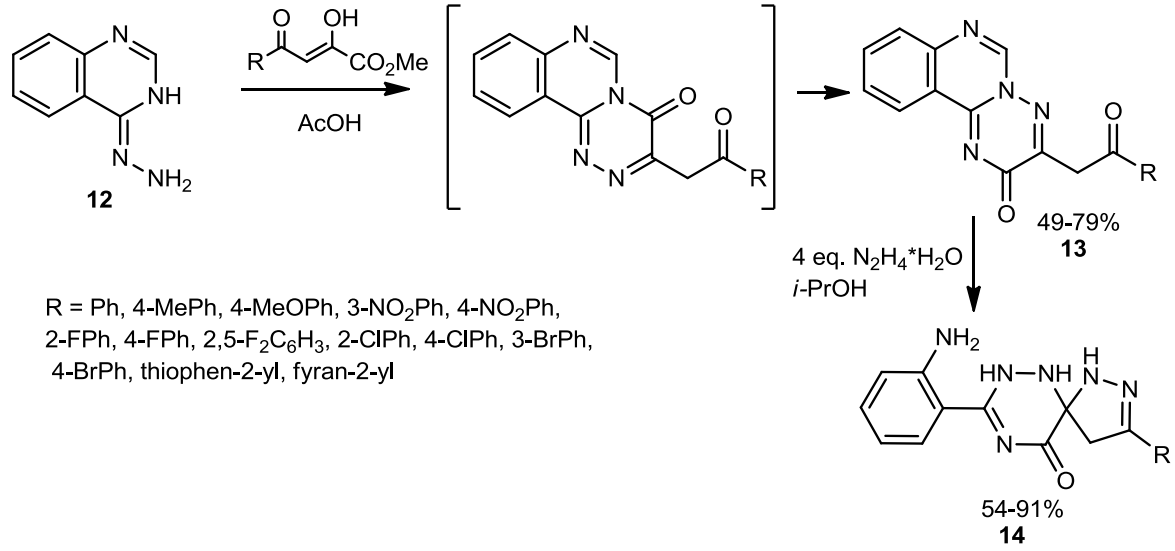


Scheme 5. Reactions of hydrazines with carbonyl compounds

The obtained pyrazolines can be reduced with H_2 on Pd/C,[32] or with $LiBEt_3H$ leading to pyrazolidines.[33] Ketoesters have been cyclized with arylhydrazines upon heating with *p*-TsOH as catalyst.[34] The reflux of hydrazine hydrate in EtOH with aldoesters and *p*-TsOH yielded 6- to 8-membered cyclic hydrazines **11**.[35]

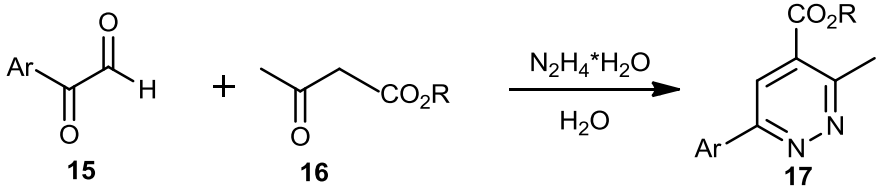
Ketoacids could also participate in the same type of reactions, giving dihydropyridazin-3(2*H*)-one derivatives upon reflux in EtOH with hydrazine hydrate[36] (Scheme 5) or with addition of NaOAc (which accelerates the reaction).[37] Reactions proceed slowly (1-2 days),[38] and the obtained cyclic structures bear imine bonds which could undergo further reaction, such as reduction by $NaBH_3CN$.[39] In principle, cycles containing π-bound prochiral carbon could be interesting substrates for asymmetric reduction, though this remains unexplored at the time of writing.

The treatment of 4-hydrazinoquinazoline **12** with 2,4-diketoesters, after cyclization and a Dimroth-like rearrangement leads to a build-up of 2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-one core **13** (Scheme 6). The reflux of obtained compound with hydrazine hydrate in *i*-PrOH resulted in the formation of spiro-heterocycles **14**.[40]



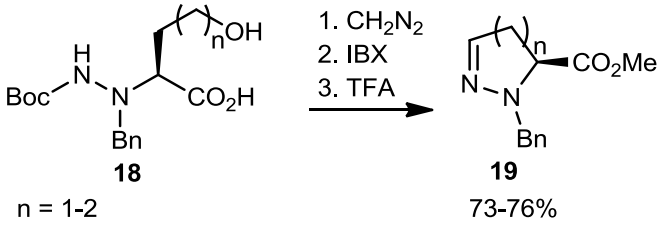
Scheme 6. Reaction of a hydrazone with 2,4-diketoester

Hydrazine could also be employed in cyclizing 2-hydroxy-1,4-diketones: in a reported procedure, ketoesters **16** were reacted with glyoxals **15** and in the presence of hydrazine cyclized to pyridazines **17** (Scheme 7).[41]



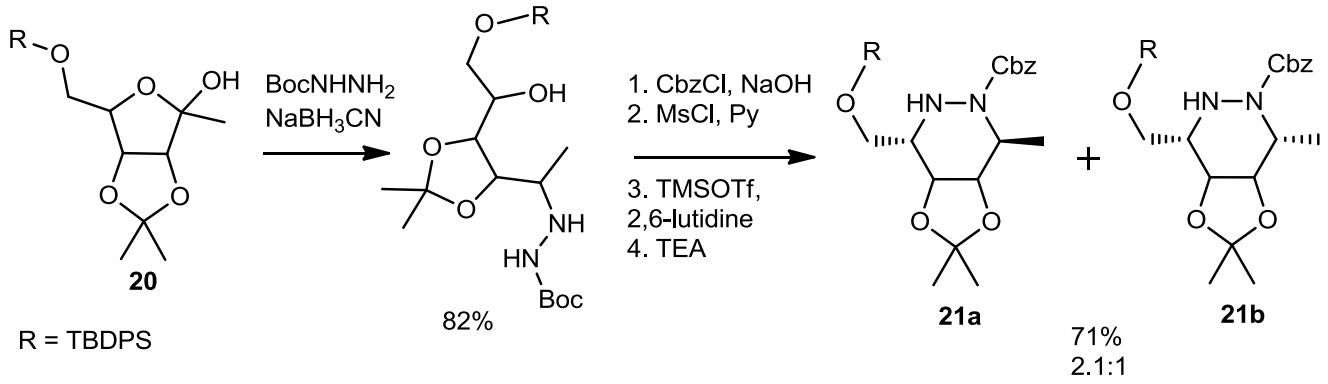
Scheme 7. Three-component reaction between glyoxal, ketoesters and hydrazine

The intramolecular formation of a hydrazone employing a substituted hydrazine, bearing an aldehyde in its side-chain, could be envisioned as an another method of cyclization. For example, aldohydrazines for cyclization were generated by the oxidation of alcohol **18** using a periodane such as IBX, in the reported case, the cyclization yields to derivatives of **19** (Scheme 8).[42]



Scheme 8. Intramolecular hydrazone formation

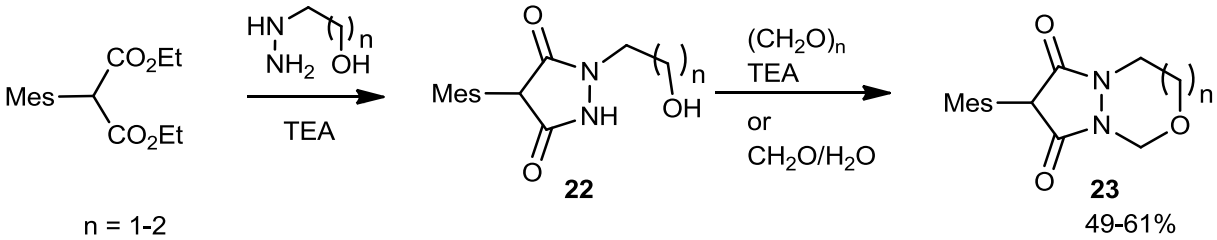
A sequentional proccess can be employed, in this example, a reductive hydrazination with hemiacetal **20** and subsequent mesylation of OH functionality were done. Then an intramolecular alkylation of the NH produced cyclic hydrazines **21**, though the synthesis generated a mixture of 2 diastereomers (Scheme 9).[43]



Scheme 9. Synthesis of hydrazinocycles from sugar derivative

5. MANNICH-TYPE REACTION

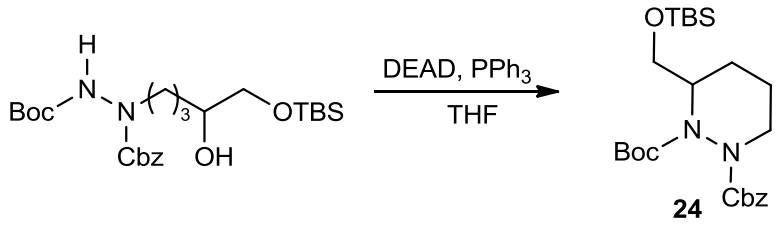
Hydrazines **22**, bearing a hydroxyl group on their side-chain can participate in a condensation with formaldehyde. The 1,3,4-oxadiazinane or 1,3,4-oxadiazepane **23** cores were prepared by heating with paraformaldehyde or formaline (Scheme 10).[50]



Scheme 10. Mannich reaction with hydrazine derivative

6. MITSUNOBU REACTION

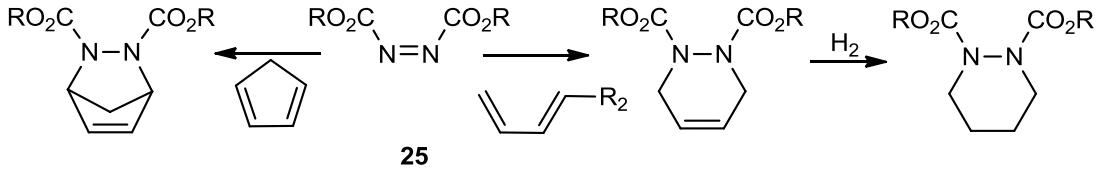
Mitsunobu chemistry is well developed for hydrazine alkylation, however to the best of our knowledge, was only once it was used for cyclization, generating **24** (Scheme 11).[44]



Scheme 11. Mitsunobu reaction

7. DIELS-ALDER REACTION WITH AZO COMPOUNDS

Azodicarboxylates **25** are among most reactive dienophiles, so the rate of hydrazine Diels-Alder reaction is mostly dependent on the employed diene, with reaction times varying from 1 hour to several days, in normally good yields.[45,46]



Scheme 12. Diels-Alder reaction of azo-compounds

Both acyclic[46,47] and cyclic[47,48] dienes are known to couple with azo-compounds, however the reaction is limited, in that it only allows for the synthesis of 6-membered rings (Scheme 12). Piperidazines can be further reduced with Pd/C or PtO_2 as hydrogenation catalysts[47] or subjected to other types of reactions by capitalizing on the reactivity of its double bonds: racemic and stereoselective Rh-catalyzed hydroboration yielding to **26**,[48] formation of *cis*-diols **27** (oxidation with Os-reagents)[49] and *trans*-diols **28** via an epoxydation with dimethoxyoxirane[50] or by using TFD directly[50] or generated *in situ*.[51] Additionnaly, the formation of aminoalcohols **29**,[49,52] bromination to **30**[53] and the hydroxyfluorination to **31**[54] have all been reported (Figure 2).

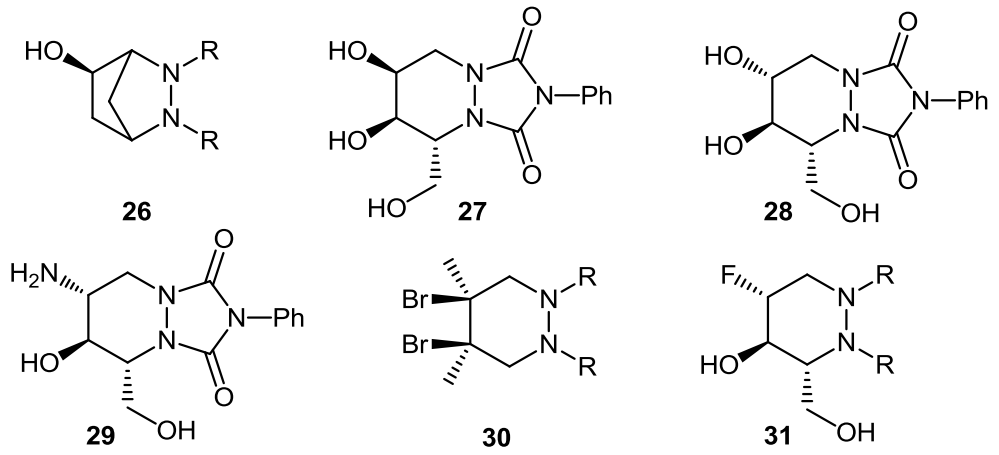
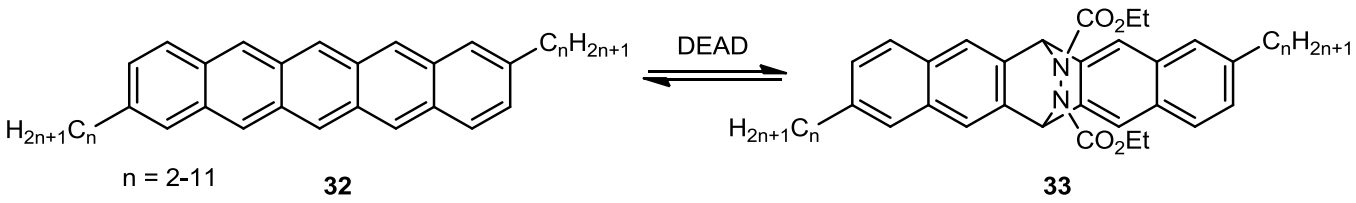


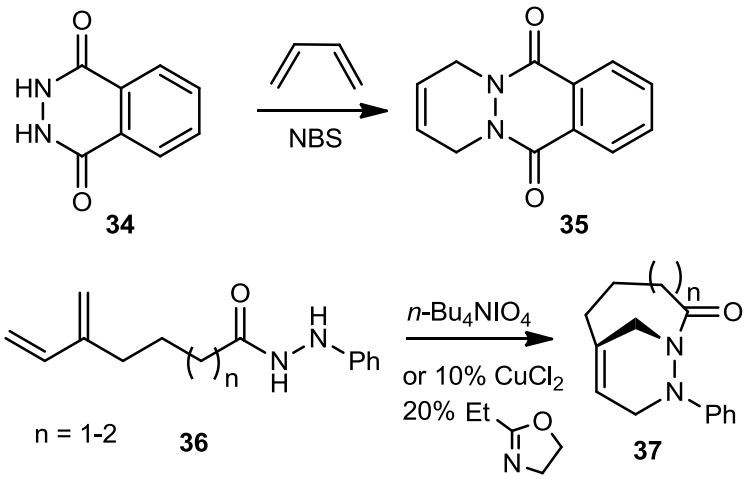
Figure 2. Selected compounds obtained from Diels-Alder reaction

The Diels-Alder reaction of DEAD with 2,9-dilakylpentacenes **32** proceeded smoothly in refluxing toluene (37-63% yields), as shown in Scheme 13.[55] The obtained compounds **33** are stable at room temperature, but underwent a retro-Diels-Alder reaction when heated to 300 °C.



Scheme 13. Diels-Alder reaction between pentacenes and azodicarboxylate

The azo-compounds used as starting materials for hetero-Diels-Alder reactions can be generated *in situ* via the oxidation of hydrazines. Phthalazinedione **34** was treated with NBS and a diene to give the corresponding cycloadduct **35**.[56] Azo-diene for intramolecular Diels-Alder reaction could be obtained from hydrazide **36** by oxidation with TBA-IO_4, the Diels-Alder trapping of obtained azo-compounds gives bicyclic hydrazines **37** (55-78%).[57] *In situ* oxidation was accomplished also by means of an aerobic Cu(II)-catalysis; in the example shown for this transformation, the bicyclic hydrazine **37** was obtained in excellent yield (Scheme 14).[58]



Scheme 14. One-pot dienophile generation and Diels-Alder reaction

The facial selectivity of the Diels-Alder reaction was investigated, using *cis*-3,5-cyclohexadiene-1,2-diol derivatives as dienes.[59] In the case of azo-dienophiles, most reactions gave *anti*-products **39**-**40** (Table 1). The formation of some *syn*-products **38** was explained by hydrogen bonding between OH groups of the diene and the dienophile (Figure 3).

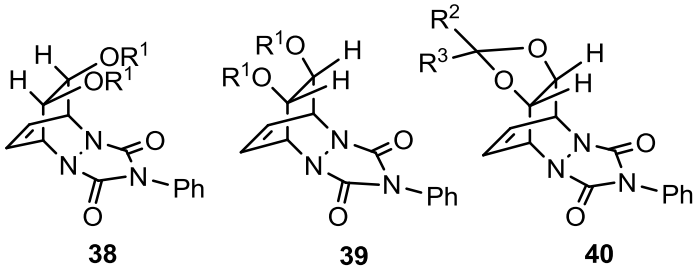
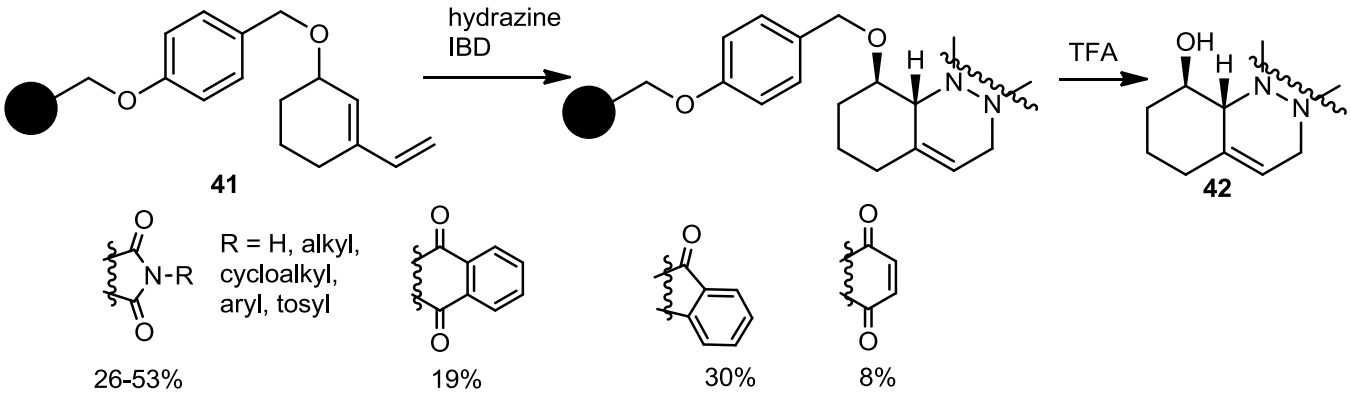


Figure 3. Products of Diels-Alder reaction between cis-3,5-cyclohexadiene-1,2-diol derivatives and azo compounds

Table 1. Facial selectivity of the Diels-Alder reaction

compound nr	R^1 or R^2/R^3	syn : anti
38	H	76 : 24
39	TMS	0 : 100
39	Ac	12 : 88
40	Me/Me	0 : 100
40	H/Ph	0 : 100
40	Ph/H	0 : 100

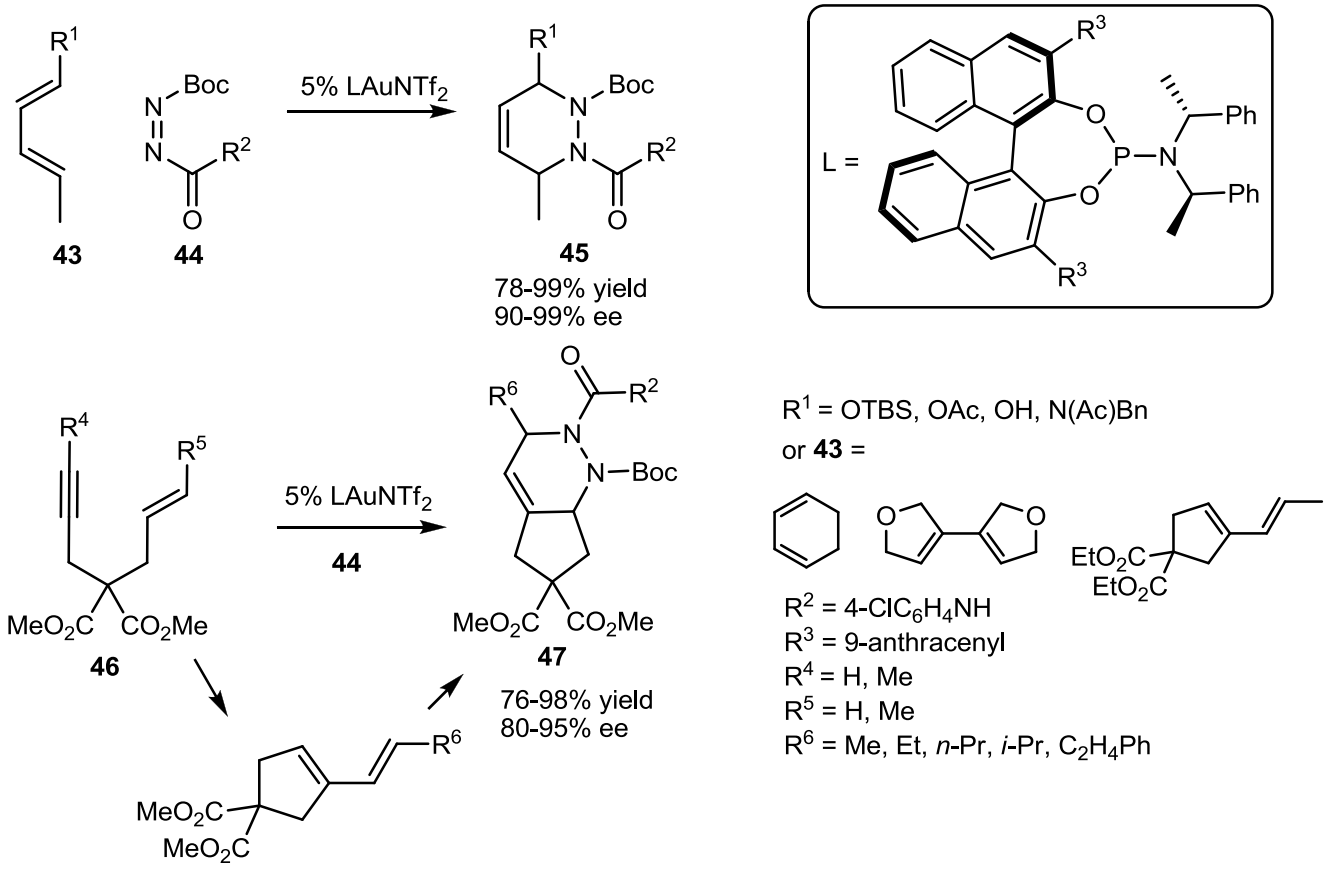
It was shown, that the aza-Diels-Alder reaction could be done with Wang-resin-bound dienes **41**.[60] This was performed in three steps: *in situ* generation of azo-compound, cyclization and hydrolytic removal of the product **42** from resin to give yields in the range 8-53%. However, the simple isolation of the products is advantageous in this case. Aromatic triazolediones give the best yields in this reaction (Scheme 15).



Scheme 15. Diels-Alder reaction with resin-bound dienes

Enantioselective Diels-Alder reaction

Though some previous achievements in this area are reviewed elsewhere,[61] the field has advanced in the past six years. Among the most recent advances, cationic gold(I) bearing chiral phosphoramitide ligands were shown to catalyze enantioselective hetero-Diels-Alder reaction.[62] These reactions tolerate a variety of different dienes (**43**) and proceed in toluene at -78 °C to give cycloadducts **45** in excellent yields and enantioselectivity. More interestingly, cascade gold-catalyzed enyne cycloisomerization/Diels-Alder reaction proceeds very efficiently for a variety of enynes **46** to give **47** in very good yields and *ee*-s (Scheme 16). In enyne isomerization, the gold-catalyst acts as a π-acid and the Diels-Alder reaction is affected by gold acting as a σ-acid. By these means, the coordination of heteroatom to Au lowers the LUMO energy of dienophile.



Scheme 16. Gold-catalyzed Diels-Alder reaction and cascade cycloisomerization/Diels-Alder reaction

Proton driven Diels-Alder reaction

Dialkyldiimines **48**-**49** in contrast with azodicarboxylates are poor dienophiles for Diels-Alder reaction, so the protonation of dialkylazocompounds was shown to facilitate the reaction greatly.[63] When the α-proton of the azo-compound is abstractable, the protonation would lead to a rearrangement to a hydrazone, but in the cyclic dialkyldiimines this reaction is suppressed due to strain in putative hydrazone. Therefore, protonated cyclic dilakylazocompounds could be used in Diels-Alder reactions. The bicyclic compounds **50** could be synthesized in this manner (Figure 4). It is useful to keep in mind that reduction of Diels-Alder adducts sometimes lead to retro-Diels-Alder reaction and reduction with diimine is shown to proceed better than catalytic hydrogenation.[64]

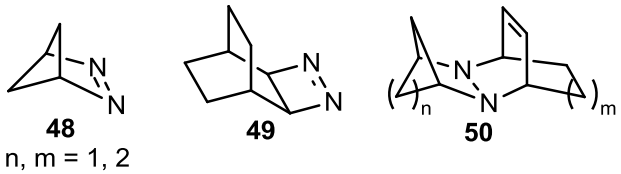
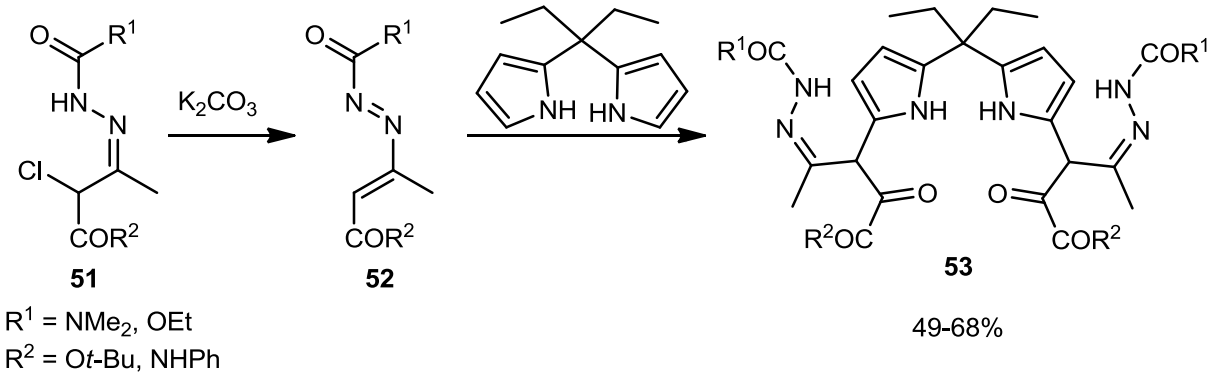


Figure 4. Starting azo-compounds and hydrazine obtained from Diels-Alder reaction

Inverse azo-Diels-Alder reaction

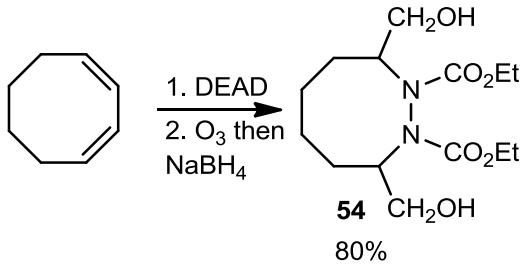
The hydrazine moiety could be incorporated into a cycle via Diels-Alder reactions, when the starting azo-compound **52** is part of a diene.[65] Azo-alkenes are obtained by treatment of β-chlorohydrazone **51** with base, and can be reacted with methoxystyrene to generate cyclic hydrazone.[66] Interestingly, pyrrole could be used as a dienophile in the reaction with azoalkenes. In this case non-cyclic products **53** are obtained (Scheme 17). Similarly, the use of tetrazines as cyclic azo-derivatives lead to inverse Diels-Alder adducts.[67]



Scheme 17. Inverse Diels-Alder reaction with azo-compounds

Tandem Diels-Alder and other transformations

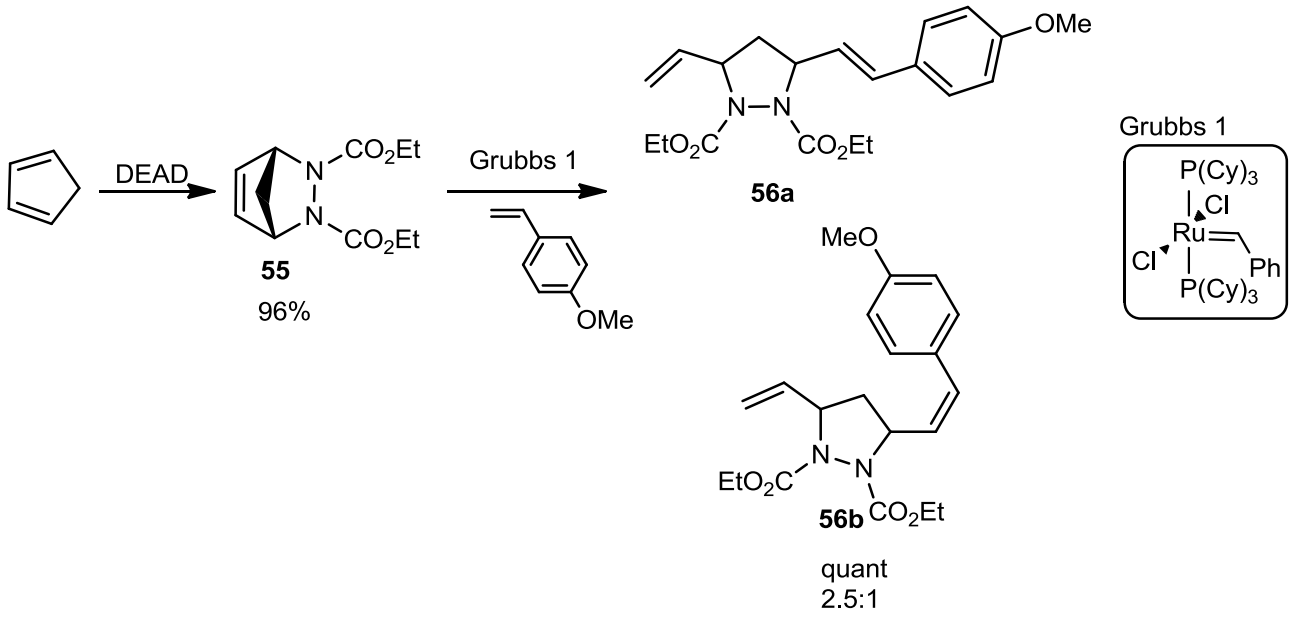
A tandem Diels-Alder reaction and ozonolysis, which would be followed by a reduction was envisioned as a synthetic method towards linear diamino diols.[68] Additionally, following a similar method, N-N endocycles are also accessible (Scheme 18). After the Diels-Alder coupling, a reductive ozonolysis was performed to yield diether **54**, the reaction was very sensitive to temperature and as such it was necessary to carefully control it.



Scheme 18. Sequential Diels-Alder reaction and ozonolysis with azo-compounds

Ellis and King suggested combining the Diels-Alder reaction with a sequential ring-opening cross metathesis to produce cyclic hydrazines (Scheme 19).[69] In the case of [2.2.1] bicycle **55**, the reaction furnished the desired diene **56** as a 2.5:1 mixture of the *E* and *Z* isomers in nearly quantitative yield.

These results were obtained by the slow addition of alkenes to a dichloromethane solution containing Grubbs' first generation catalyst, but when a mixture of alkenes and Grubbs' catalyst were stirred in benzene, oligomers were formed instead. As always, the ring strain is the driving force of this ring opening metathesis reaction, as the less strained [2.2.2] bicycles don't react.

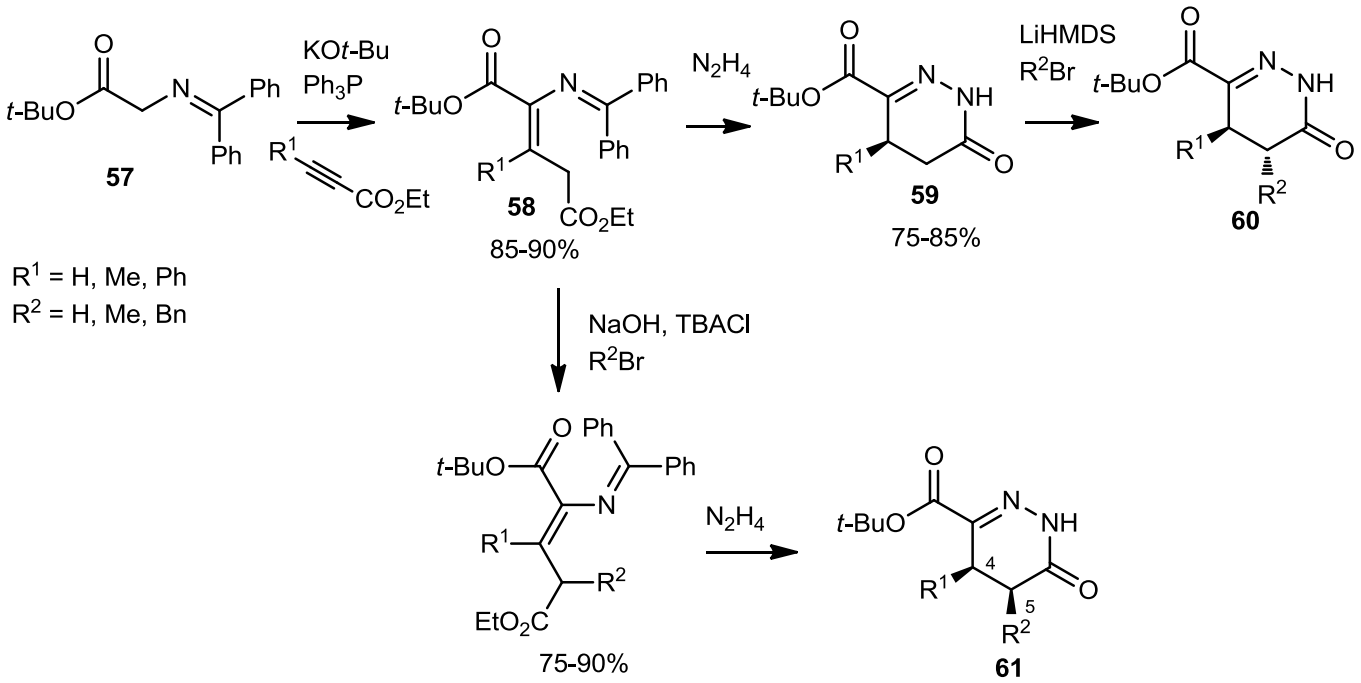


Scheme 19. Sequential Diels-Alder reaction and ring-opening cross metathesis with azo-compounds

8. SYNTHESIS OF PIPERAZIC ACID AND ITS DERIVATIVES

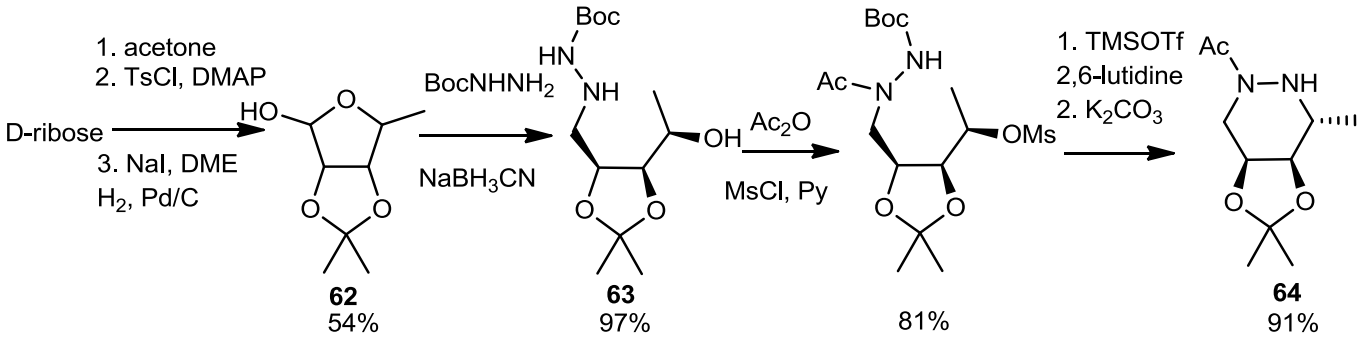
Piperazic acid **4** and its derivatives are important compounds. Their skeleton is often found in biologically active compounds and therefore it is important to have methods for the stereoselective synthesis of piperazic acid and its derivatives, that can be readily scaled up.

Gomez de la Oliva *et al.* performed the synthesis of **59**, shown in Scheme 20.[70] It consisted of the addition of imine **57** to alkynoates followed by a cyclization using hydrazine hydrochloride in the presence of NaOAc in boiling EtOH. Substituents in the 5-position could be introduced in the intermediate **58** under PTC conditions, whereupon the *cis*-product **61** is obtained after cyclization. Alternatively, cyclic compounds **59** could be alkylated, giving rise to *trans*-products **60**. The resulting dihydropyridazinones **59** were deprotonated with LiHMDS to allow an alkylation of the carbon. Furthermore, the obtained protected cyclic hydrazones could be reduced with $NaBH_3CN$ in methanol to tetrahydropyridazines. Noticeably, the stereoselectivity of the reduction is dictated by the substituent on the 4-position of the ring, as the hydride attack occurred from the opposite site giving rise to 3,4-*cis* isomers from compound **61** (de > 98%).



Scheme 20. Synthesis of 6-oxopiperazic acid from imine

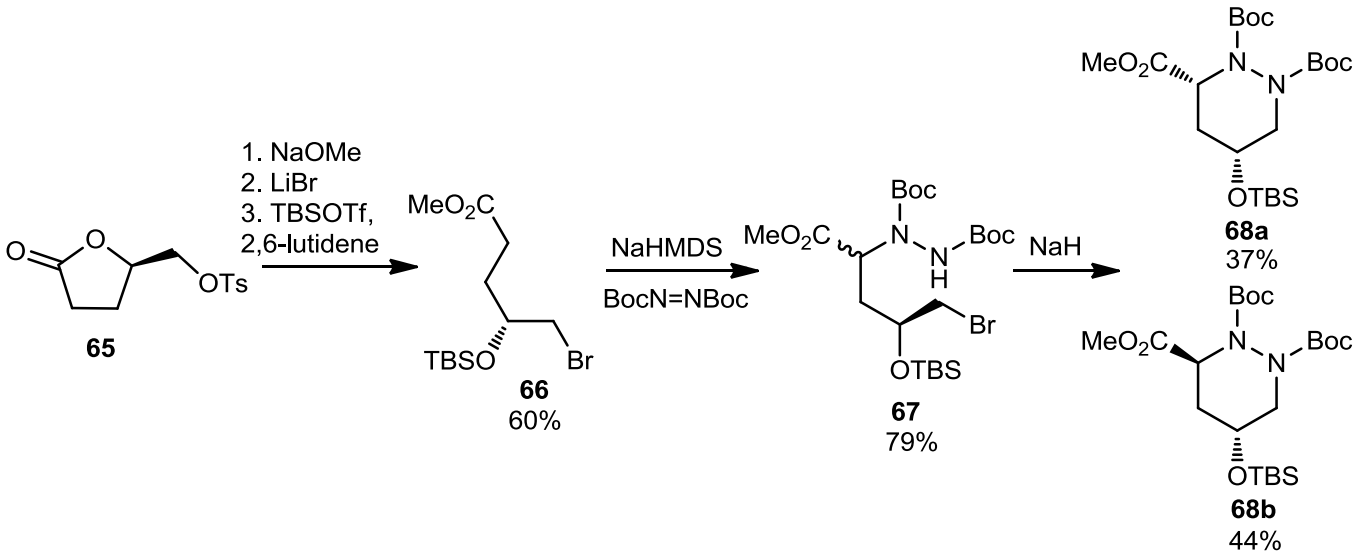
Azafagomine analogue of L-fucose was prepared according to Scheme 21. To begin with, D-ribose was protected with acetone and tosylated, subsequently underwent the Finkelstein reaction to generate the iodide and finally hydrogenated to **62**. The reductive amination of the obtained hemiacetal **62** with $BocNHNH_2$ gave a disubstituted hydrazine **63** which after protection/deprotection steps was cyclized by an intramolecular alkylation of hydrazine, with mesylate and using K_2CO_3 as a base, to give compound **64** and after deprotection 4,5-dihydroxy-3-methylhexahydropyridazine.[71]



Scheme 21. Cyclization of D-ribose derived substrate

In the work of Danishefsky and coworkers,[72] the synthesis started from **65**, which was obtained from D-glutamic acid (Scheme 22). Then **65** was converted to a hydroxyl ester via the epoxy ester. After a protection of the hydroxyl group (**66**), the ester was deprotonated and treated with BocN=NBoc which

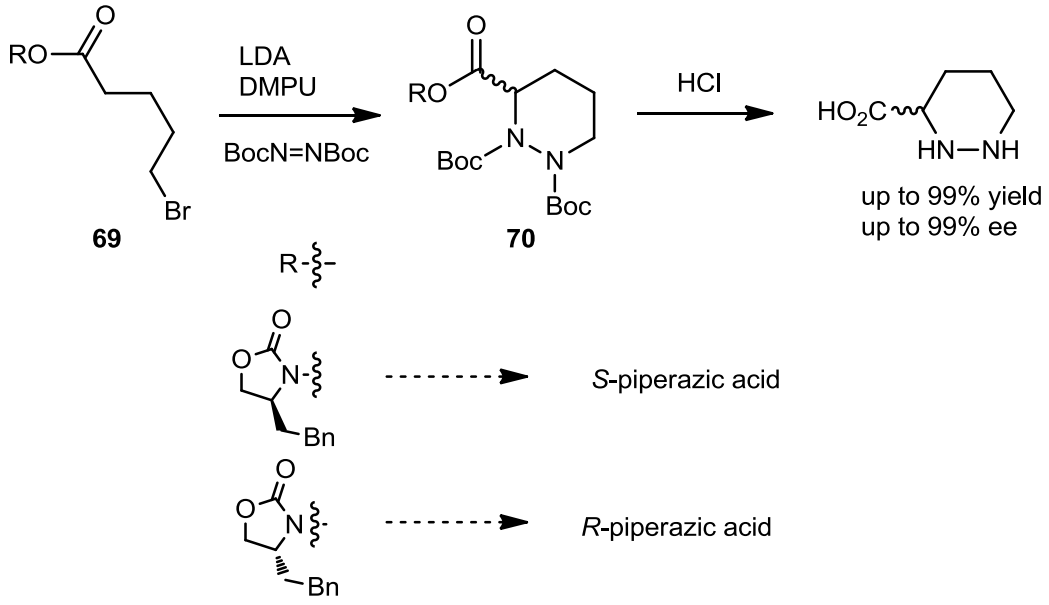
lead to the trisubstituted hydrazine **67,** bearing Br on its side chain. A treatment of the obtained compound with NaH in DMF supplied the desired cycle **68** as a 1:1 mixture of two isomers.



Scheme 22. Hydrazination/cyclization of *D*-glutamic acid derived substrate

Synthesis with Evans chiral auxiliaries

Jogiya and coworkers reported the first synthesis of piperazic acid using (*R*)-4-benzyloxazolidin-2-one as chiral auxiliary.[73]



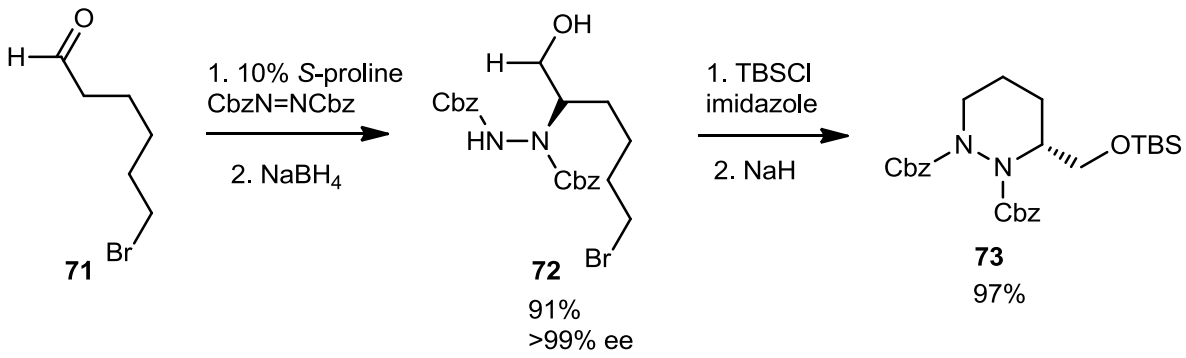
Scheme 23. Cyclizations with Evans oxazolidinones as chiral auxiliaries

After deprotonation of the oxazolidinone, using BuLi, and an acylation with 5-bromovaleryl chloride to give **69**, an electrophilic hydrazination with BocN=NBoc was performed. The obtained lithium

aza-enolate was cyclized using an excess of DMPU (26 eq.) as additive to give **70** (Scheme 23). After hydrolysis, 67% of the auxiliary was recovered. Additionally, a synthesis employing another oxazolidine, (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one was attempted. In this case the *S*-piperazic acid was obtained in 88-93% *ee*, however thanks to an easier work-up procedure and the possibility to separate the *R* isomer by recrystallization, this method has remained attractive. It was shown that catalytic amounts of tetrabutylammonium halide (15 mol %) could induce cyclization of aza-enolate to **70**. Furthermore, cyclization was observed without additives when a THF/DCM/hexane mixture was used as a solvent and the reaction warmed to room temperature. However, probably due to long reaction times (up to 18 h), an erosion of *ee* was observed. A similar DMPU-induced cyclization procedure was used in the work of Coats and coworkers,[74] with cyclization product **70** obtained this way in 99% yield.

Proline-catalyzed reactions

The (*S*)-proline catalyzed hydrazination of 6-bromohexanal **71** with BocN=NBoc was shown to proceed in excellent yield and > 99% *ee*.[75] The cyclization of the obtained hydrazine **72** via deprotonation with NaH in DMF gave the desired cyclic product **73**, which after hydrolysis, oxidation and deprotection provided (*R*)-piperazic acid. It was also shown that this procedure could be scaled up (Scheme 24).

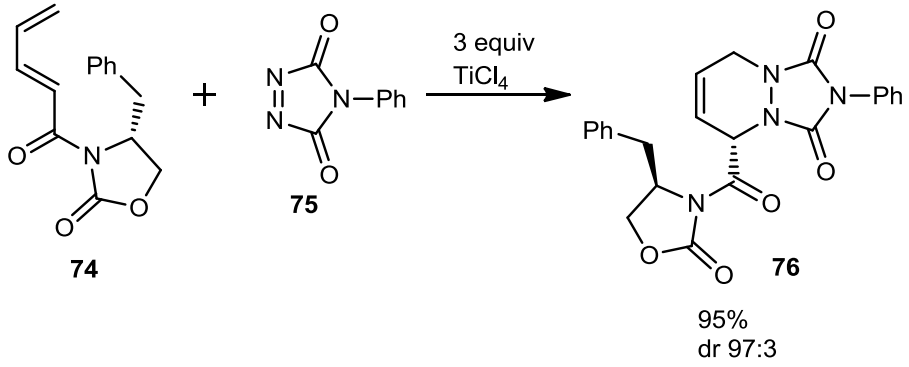


Scheme 24. Sequential proline-catalyzed hydrazination/cyclization

Aza-Diels-Alder reaction for the synthesis of piperazic acid

As it shown above, the Diels-Alder reaction is widely used for the synthesis of 6-membered cycles, and its variation with aza-compounds used as dienophile is valuable for the synthesis of piperazine derivatives. The reaction with dienophile **75** was modified to generate cycles **76** in a stereoselective manner.[76] Evans auxiliary was used with diene **74**, but gave rise to almost racemic mixture. It was found that $TiCl_4$ exerted a tremendous effect on the reaction (Scheme 25). The use of 3 equiv of $TiCl_4$ gave **76** with a diastereomeric ratio of 97:3 with 95% isolated yield. In this reaction, 2 equiv of $TiCl_4$ complex with the dienophile and the third equivalent is chelated by the diene (**74**), ensuring high diastereoselectivity. The reduction of **76**, followed by a reductive cleavage of the chiral auxiliary, the manipulation of protecting

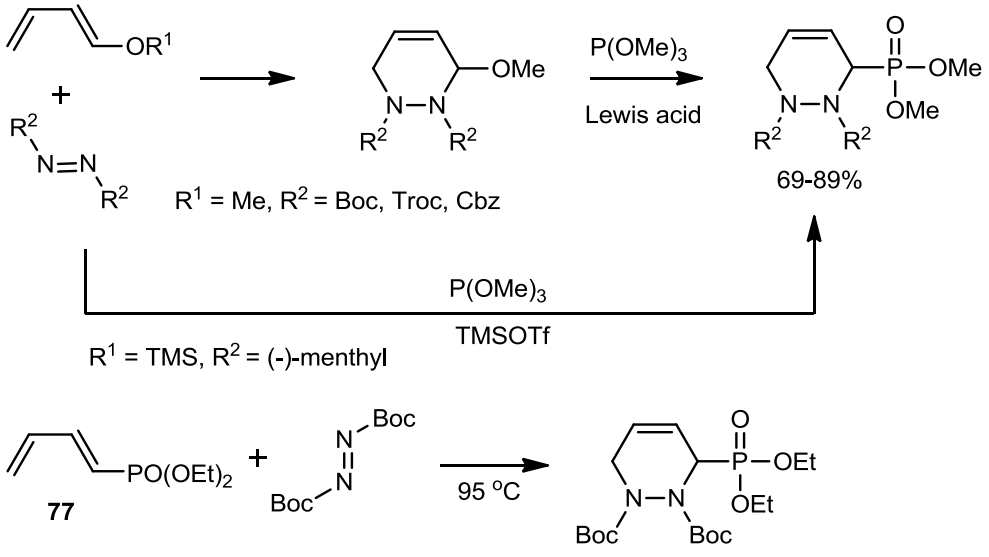
groups on nitrogen and oxidation of the obtained alcohol gave di-Cbz-(*S*)-piperazic acid. However direct conversion of **76** to piperazic acid proved itself impossible due to the lack of solubility of the starting material.



Scheme 25. Diastereoselective Diels-Alder reaction with $TiCl_4$

Piperazinephosporic acids and phosphonates

In the report by Yoshifuji and coworkers,[77] 1-methoxybutadiene was reacted with azo compounds and after successive Lewis acid-assisted phosphorylation, hydrogenation and hydrolysis, racemic piperidazine-3-phosphonic acid was obtained. An alternative synthesis of (*S*)-piperidazine-3-phosphonic acids was accomplished: (buta-1,3-dien-1-yloxy)trimethylsilane was used as diene and di-(−)-menthyl azodicarboxylate as dienophile in the presence of TMSOTf and $P(OMe)_3$.[78] After hydrolysis the two isomers, arose from phosphorylation (in a ratio 2:1), were separated by column chromatography (Scheme 26, top). Marchard-Brynaert *et al.*[79] reported a method for the synthesis of aminophosphonates, making use of the aza-Diels-Alder reaction between BocN=NBoc and 1-diethoxyphosphorylbyta-1,3-diene **77** under microwave activation (Scheme 26, bottom).

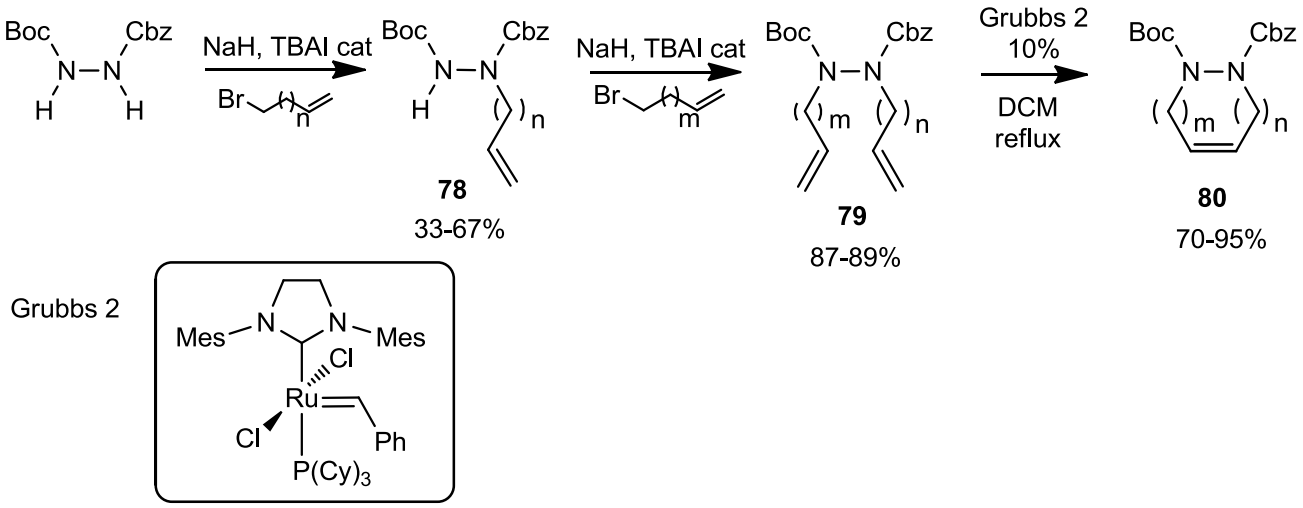


Scheme 26. Synthesis of piperazinephosphonates

2-Phosphonated dienes could be obtained from Peterson synthesis and it was shown that Diels-Alder reaction (77% yield) is also possible in this case.[80]

9. RING CLOSING METATHESIS OF HYDRAZINES FOR THE SYNTHESIS OF ENDOCYCLES

There are only a few examples of Ring Closing Metathesis (RCM) of 1,2-disubstituted hydrazines in literature, a possible reason could be the problematic synthesis of the substrates.

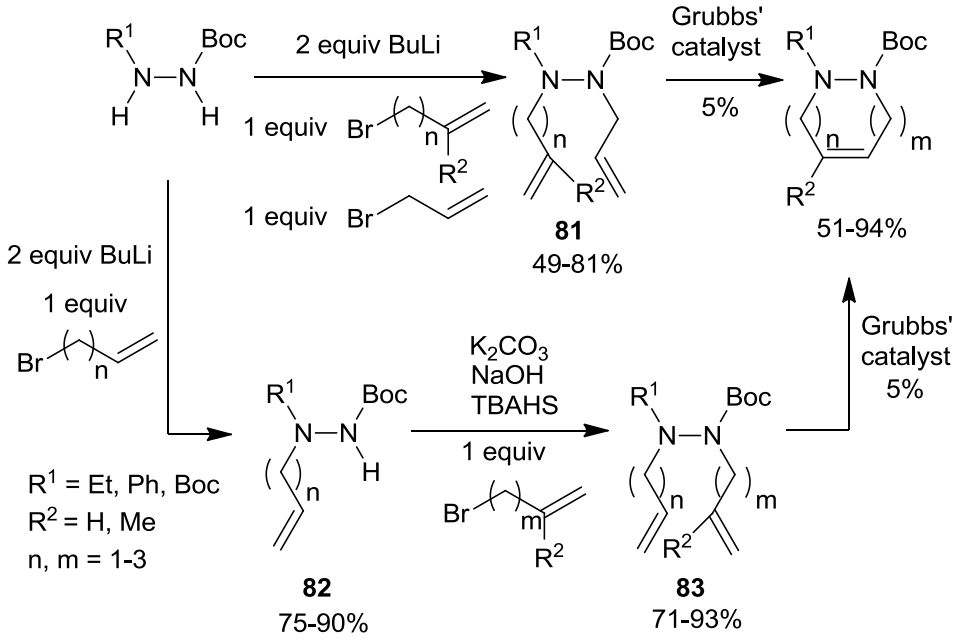


Scheme 27. Synthesis of hydrazinocycles by Tae *et al.*

In Tae and Hahn's work,[81] dienes were prepared by the 2-step sequential alkylation of diprotected hydrazines. Cbz-NHNH-Boc was used as starting material, NaH as a base and bromide bearing olefins as alkylating agents (Scheme 27). The first alkylation to **78** encountered problems with its selectivity, yielding a mixture of monoalkylated and dialkylated hydrazines due to insufficient difference in acidity between the two N-H groups (estimated to be less than 0.4 units of pKa).[22] However the second alkylation supplied the desired dienes **79** in good yields. The RCM employed 10 mol % of Grubbs first generation catalyst, with more diluted DCM solutions and longer reaction times for larger cycles. The 6- to 10-membered cycles **80** were obtained in good to excellent yields. Three examples of ring-closing enyne metathesis were also shown to give corresponding 6- to 8-membered cycles in good yields (70-99%).

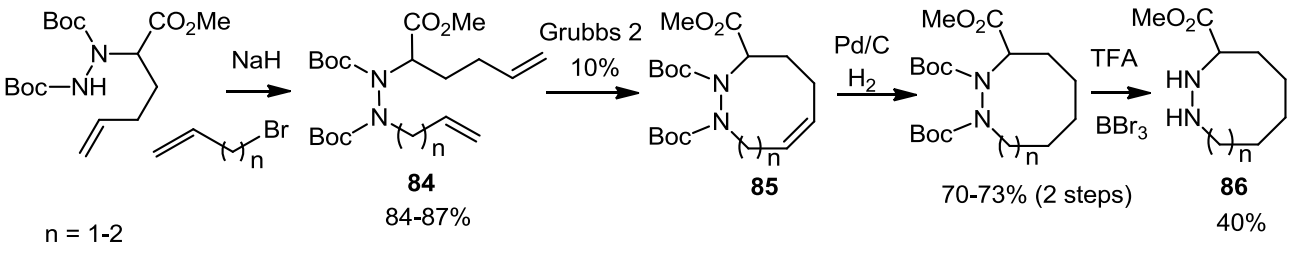
The polyanion strategy was also applied for the synthesis of RCM precursors.[82] Various hydrazines with allyl substituent on the Boc-bearing nitrogen **81** were prepared by the double alkylation of dianions, but difficulties appeared with an increase in the chain length of the substituents. Therefore a 2-step strategy was devised: a monoalkylation of the dianion to **82**, followed by a second alkylation under PTC

conditions were conducted, which resulted in the synthesis of hydrazinic dienes **83** with different substitution pattern. Further reaction by RCM furnished 6- to 9-membered heterocycles in good yields using either Grubbs' first or second generation catalysts (Scheme 28).



Scheme 28. Dianions of hydrazines and RCM for the synthesis of hydrazinocycles

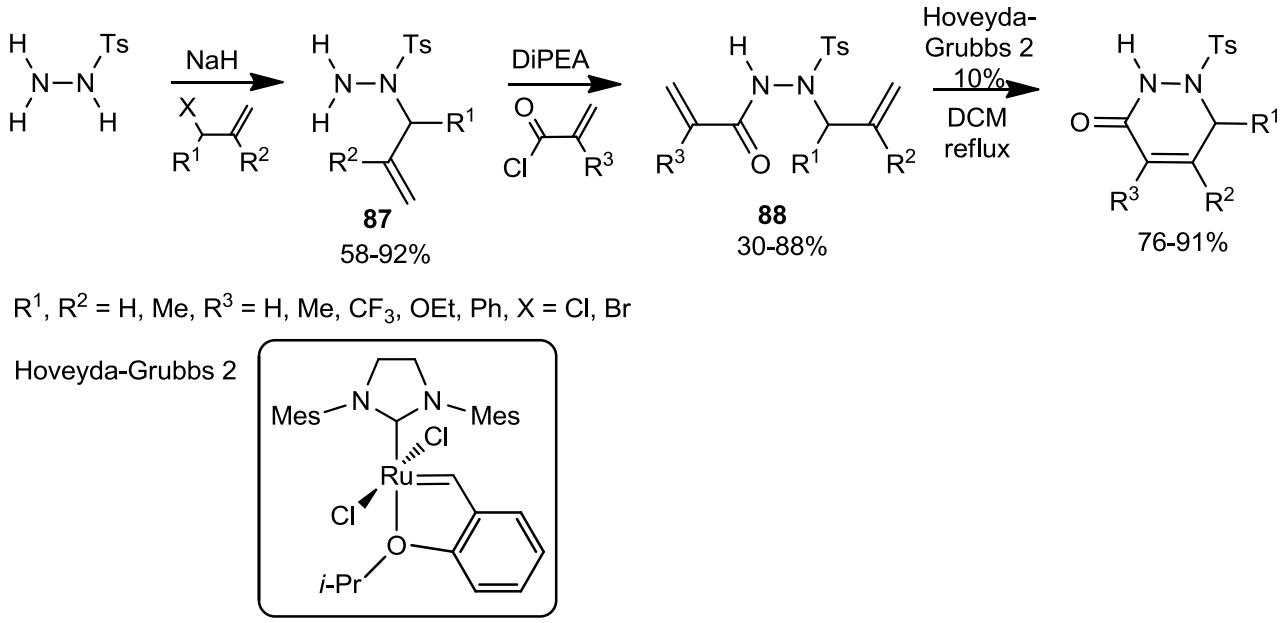
Ring closing metathesis was recently applied to the synthesis of hydrazinoacids (Scheme 29). The tetrasubstituted hydrazinic dienes **84** were obtained by the alkylation of the trisubstituted hydrazine with bromides, using NaH in DMF. Products **85** having undergone the metathesis using Grubbs second generation catalyst, were used to synthesize hydrazino acids **86** by reduction, deprotection and finally hydrolysis.[83]



Scheme 29. Synthesis of cyclic hydrazinoacids by RCM

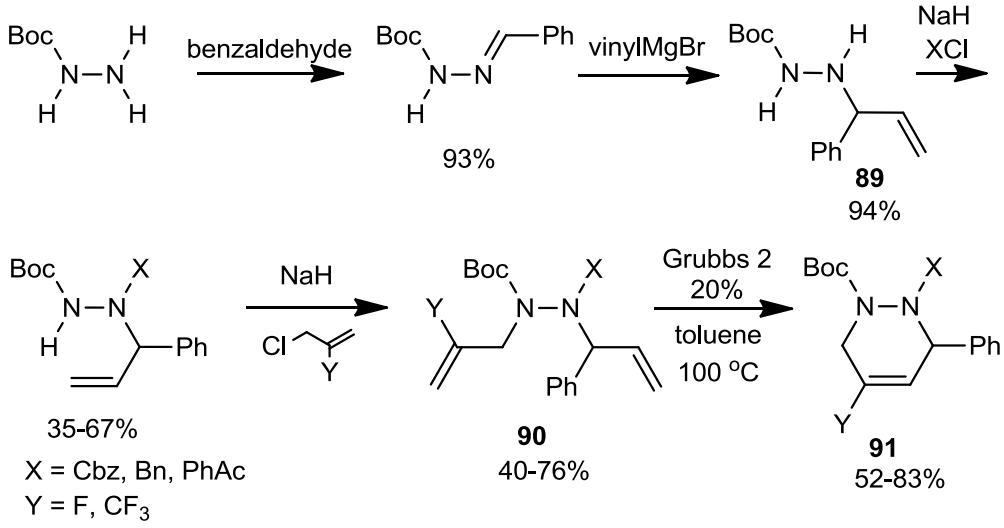
Callens *et al.* prepared the metathesis substrates by sequential allylation and acylation of hydrazines. The yield of the first step was good for all reported compounds, and the efficiency of the acylation of **87** to **88** depended strongly on the bulk of substituent R^3 (Scheme 30). The RCM worked well with substrates with

low steric hindrance employing Hoveyda-Grubbs second generation catalyst, but attempts to cyclize sterically demanding substrates failed.[84]



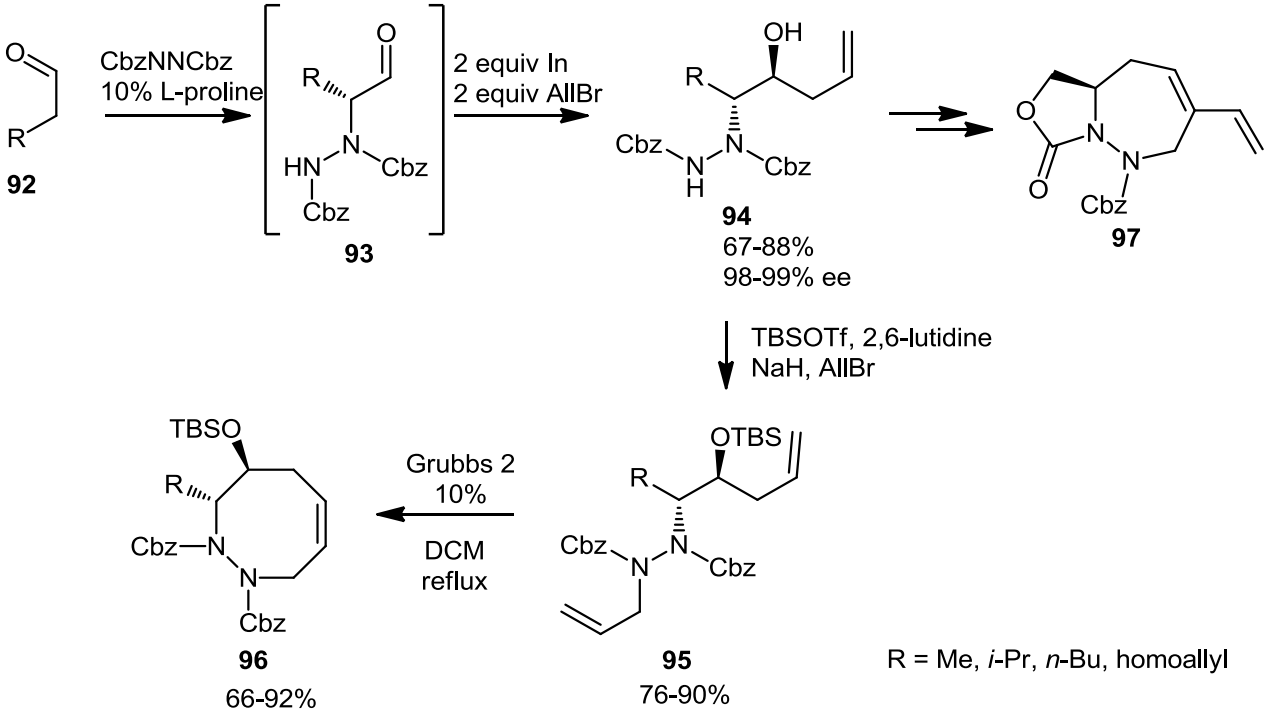
Scheme 30. Synthesis of dihydropyridazinones

Rutjes *et al.* (Scheme 31) started from $BocNHNH_2$ which upon condensation with benzaldehyde and successive coupling with vinylmagnesium bromide gave allylated hydrazine **89**. It was protected and after treatment with NaH, alkylated with chlorides or tosylates to **90**. Yields for the second alkylation were 40-76%. The ring-closure was performed with 20% Grubbs second generation catalyst at 100 °C and gave differently fluorinated pyridazines **91** with 52-83% yield.[85] The requirement for high catalyst loadings in this reaction could be linked to the difficulty of the metathesis of electron-deficient double bonds.



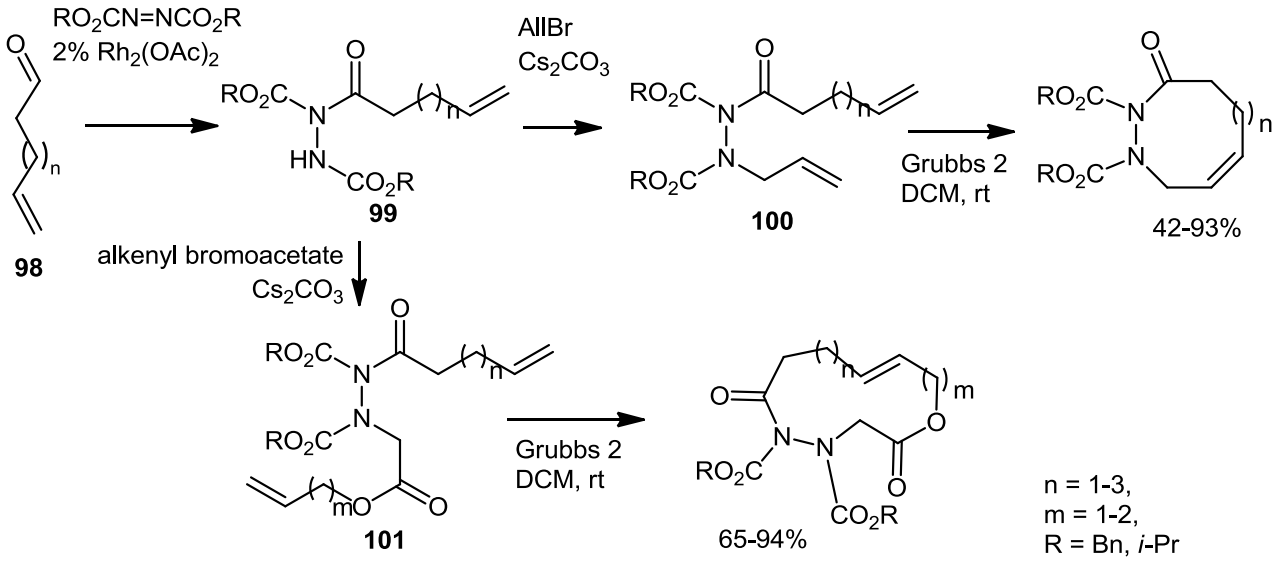
Scheme 31. Synthesis of fluorinated dihydropyridazines

In a report by Tae *et al.* (Scheme 32), RCM substrates **95** were prepared by (*S*)-proline catalyzed amination of aldehydes **92** with azo-compounds, followed by indium-mediated allylation of **93**. The obtained hydrazinic alkene **94** was protected with TBSOTf, subjected to deprotonation with NaH and either alkylation with allyl or propargyl bromide, or acylation with acroyl chloride. The coupling of both alkenes to hydrazine proceeded with good yields (67 to 90%) and the obtained dienes **95** were cyclized with 10% of Grubbs first generation catalyst in refluxing DCM, to furnish 8-membered cycles **96** in 66 to 92% yield. An example of enyne metathesis gave the desired cyclic diene **97** in 75% yield. Despite the long synthesis of dienes, the advantage of this strategy is that proline catalyzed amination coupled with In allylation opens up a route towards the synthesis of enantioenriched cycles (98-99% *ee*), from achiral starting material.[86]



Scheme 32. Synthesis and RCM of enantioenriched dienes

Kim and Lee[87] reported a double RCM strategy with the subsequent reductive cleavage of the N-N bond to form macrocycles. They, however, mainly focused on the first RCM (Scheme 33). The preparation of dienes started with the Rh-catalyzed coupling of unsaturated aldehydes **98** to azo-compounds, followed by an allylation of **99** with allyl bromide (to **100**) or alkenyl esters of bromoacetic acid (to **101**) using Cs_2CO_3 in DMF as base. Attempts to perform the RCM were successful and gave 8- to 13-membered cyclic compounds with 42-93% yields. Enyne metathesis proceeded more sluggishly. 12- and 13-membered cycles products were obtained as mixture of *E* and *Z* isomers, with a preference for *Z*-products, which is consistent with RCM mechanism.



Scheme 33. Rh-catalyzed coupling with azo-compounds for the synthesis of RCM precursors

RCM was also used as a key step in the synthesis of analogues of Sanglifehrin.[88] The macrocyclization to yield 22-membered cycle on Figure 5 proceeded with Grubbs' first generation catalyst in 47-57% yield.

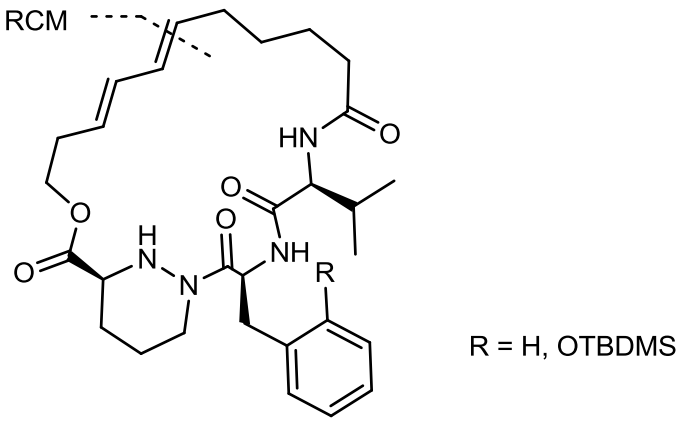
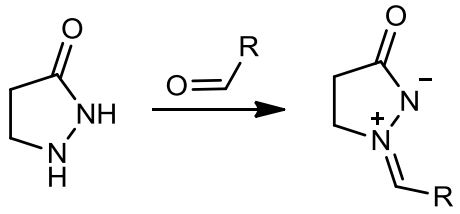


Figure 5. Sanglifehrin analogue obtained via RCM macrocyclization

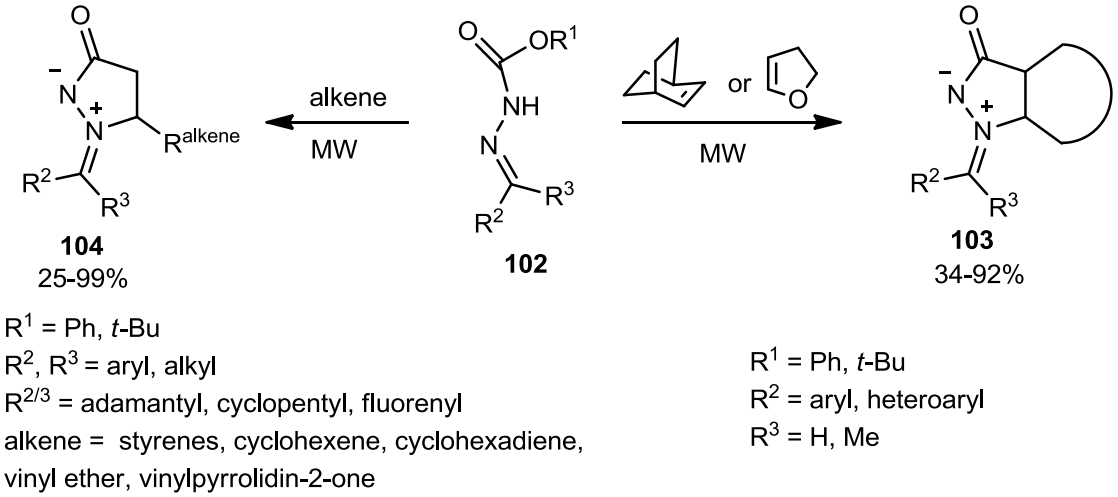
10. FORMATION OF AZOMETHINE IMINES FROM HYDRAZINES

A general synthetic scheme for the formation of azomethine inimes (Scheme 34) is showed below. As can be seen from this scheme, azomethine imines are derivatives of hydrazines.



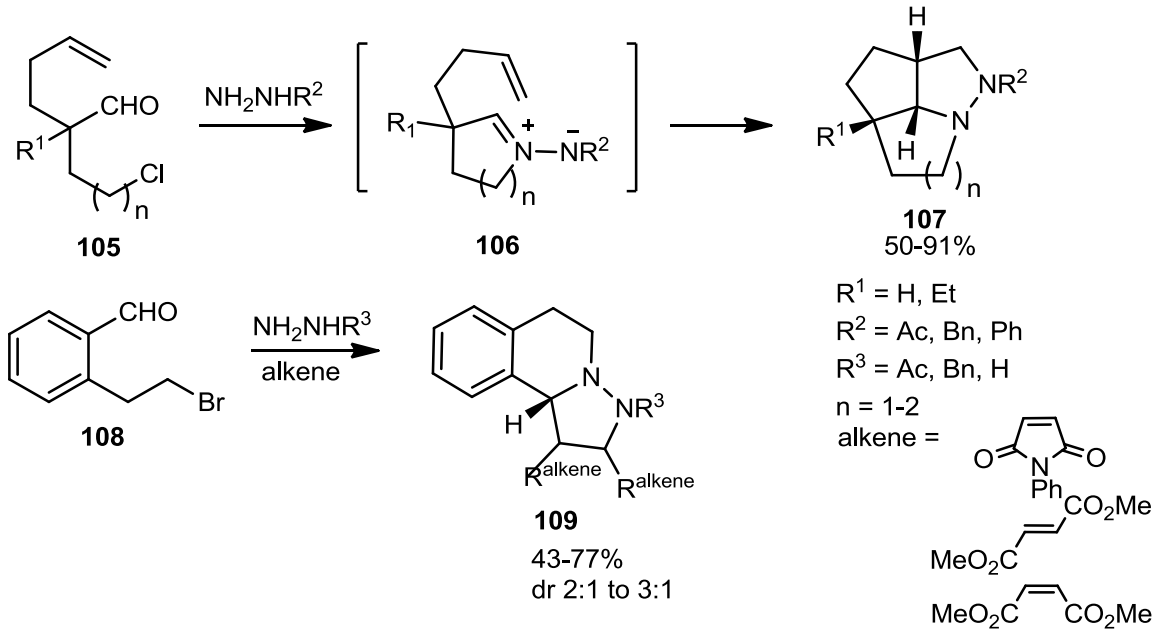
Scheme 34. General synthesis of N-N cyclic azomethine imines

The synthesis of azomethine imines has been reviewed elsewhere,[89] however some recent developments are discussed below. Recently, a new route starting from alkenes was reported (Scheme 35). Hydrazones **102** are starting compounds for these reactions. When treated with alkenes under microwave irradiation, they form N-N cyclic azomethine imines **103-104**. These reactions proceed with different leaving groups and hydrazone substituents, but the best yields are achieved for bulky substituents. Additionally different alkenes, dienes, styrenes and dihydrofurans are tolerated. Despite the use of an excess of alkene, a probable explanation for the non-occurrence of the competing [3+2] cycloaddition (see below) is steric shielding.[90]



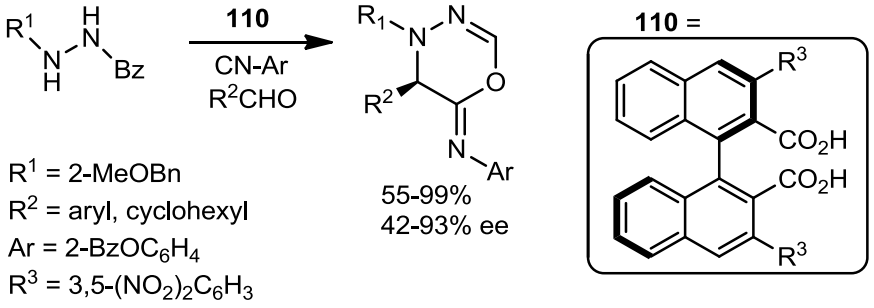
Scheme 35. Synthesis of azomethine imines from alkenes and hydrazones

In a cascade process, azomethine imines **106** were formed and cyclized into a system of 3 fused rings **107** (Scheme 36, top). For this, chloro-enals **105** were treated with monosubstituted hydrazines in presence of DiPEA in boiling toluene. The formation of hydrazone and alkylation was followed by [3+2] cycloaddition to the azomethine imine **106** which furnished the aforementioned product. Analogously, 2-(2-bromoethyl)benzaldehyde **108** was treated with monosubstituted hydrazines in the presence of alkenes, which gave products **109**.[91]



Scheme 36. Cascade azomethine imine formation/[3+2] cycloaddition

Acyclic azomethine imines (formed *in situ* from aldehydes and disubstituted hydrazines) underwent an Ugi-type reaction with isocyanides. Catalyst **110** was used in *m*-xylene, giving products in excellent yield and *ee*. Aromatic aldehydes with different aryl-isocyanides are excellent substrates for this reaction (Scheme 37).[92]



Scheme 37. Formation and cyclization of acyclic azomethine imines

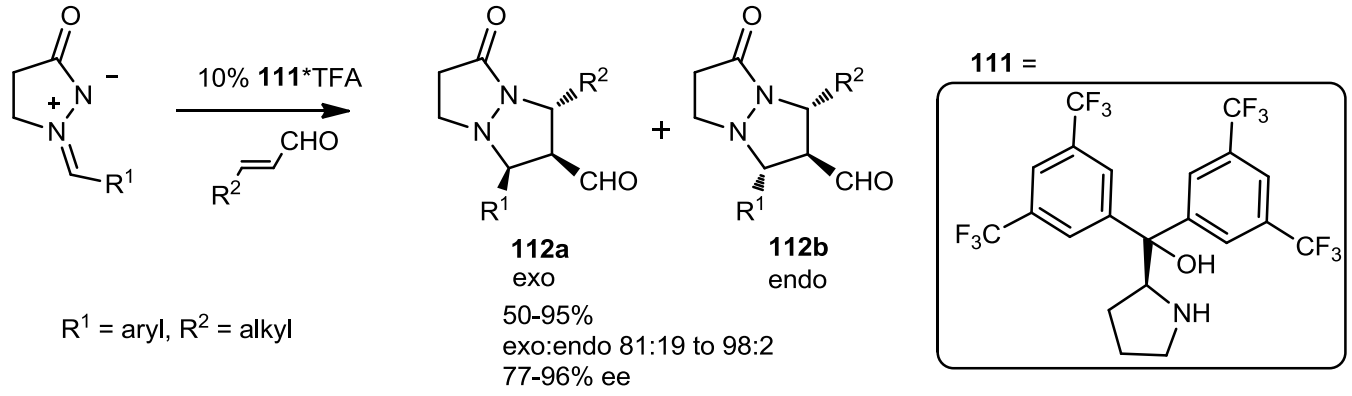
11. CYCLIZATIONS WITH AZOMETHINE IMINES TO FORM 5-MEMBERED CYCLES

Though partly within the scope of this paper, the enantioselective copper-catalyzed [3+2] cycloadditions have already been reviewed elsewhere and consequently will not be dealt with.[93]

Cyclizations with N-N cyclic Azomethine imines

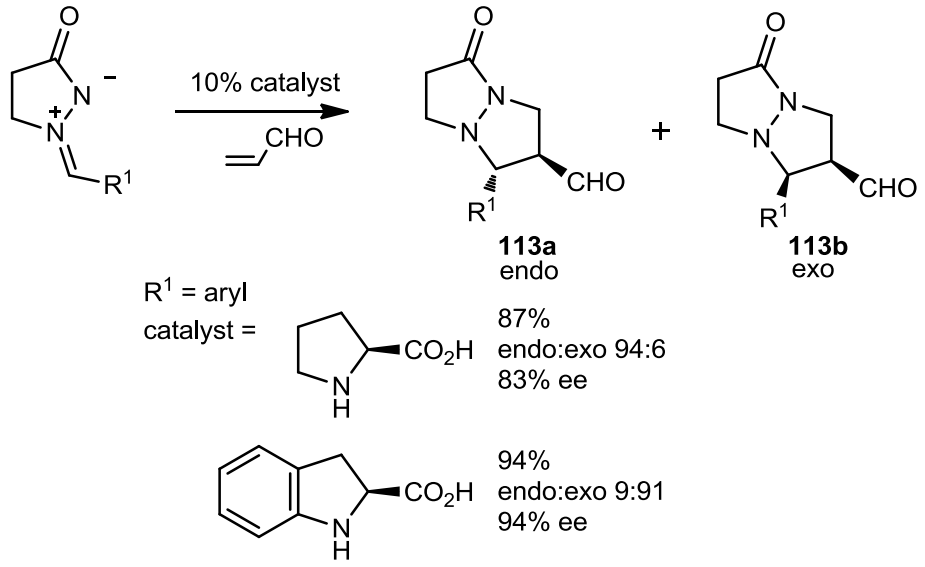
The stereoselective [3+2] cycloadditions of azomethine imines with α,β-unsaturated aldehydes catalyzed by chiral secondary amines were reported.[94] In this strategy, an acrylaldehyde derivative reacts with a chiral amine to form an iminium compound, which then participates in a cycloaddition, which enables

stereoselective reactions. Amine **111** (10 mol %) with TFA (10 mol %) as additive in wet THF proved to be optimal catalytic system. Azomethine imines derived from aromatic aldehydes participate in the reaction with ketones bearing β-aliphatic substituents, giving bicycles **112** in good yields and in preference to *exo*-cycles (81:19 to 98:2). *Exo*-cycles were synthesized in good to excellent *ee*-s. Cinnamaldehyde didn't participate in this reaction (Scheme 38).



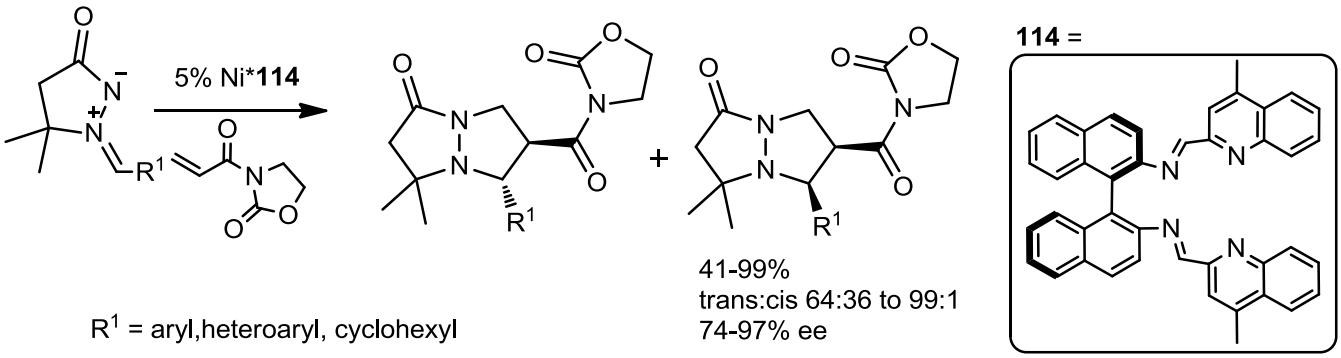
Scheme 38. Cycloaddition of N-N cyclic azomethine imines catalyzed by chiral amine

Similar reactions of unsubstituted acrolein and azomethine imines catalyzed by (*S*)-proline were demonstrated to provide the *endo*-product **113a** preferentially. The use of azomethine imines derived from aromatic aldehydes, and therefore differently substituted, was probed but *ee*-s drop dramatically for aliphatic azomethine imines. Interestingly, when (*S*)-indoline-2-carboxylic acid is used as a catalyst, the formation of the *exo*-product **113b** is observed with excellent selectivities and *ee*-s (Scheme 39). Finally it was shown that in the presence of (*S*)-proline **113a** isomerize to **113b** (92:8 to 6:94 after 65 h).[95]



Scheme 39. [3+2] Cyclization catalyzed by proline derivatives

Reactions between azomethine imines and 3-acryloyl-2-oxazolidinone catalyzed by Ni(II)-binaphthyldiimine complexes were shown to proceed with high eneatioselectivity (Scheme 40).[96] A selection of different aromatic azomethine imines proved effective in this cyclization, giving good yields as well as good to excellent *dr*-s and *ee*-s. Sterically encumbered nickel-intermediates allow only *Si*-attack of azomethine imine to 3-acryloyl-2-oxazolidinone, which is the source of the enantioselectivity (Figure 6).



Scheme 40. Ni-catalyzed [3+2] cycloaddition with N-N cyclic azomethine imines

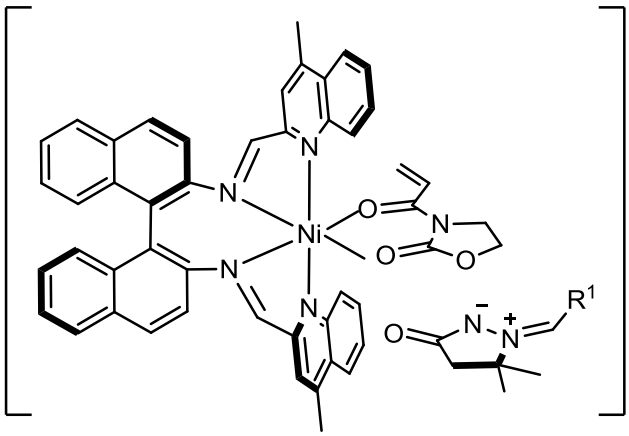
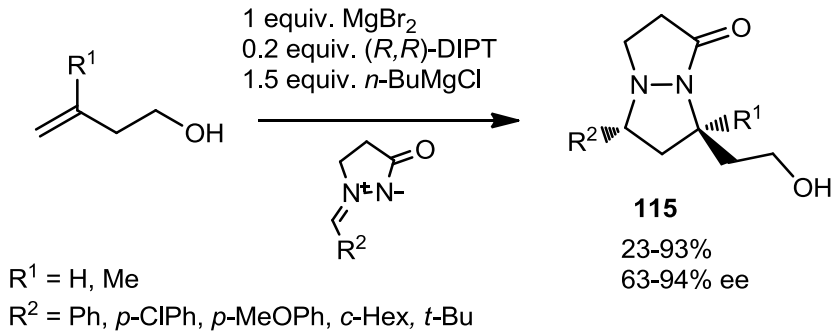


Figure 6. Intermediate, responsible for stereoselectivity in Ni-catalyzed cycloaddition

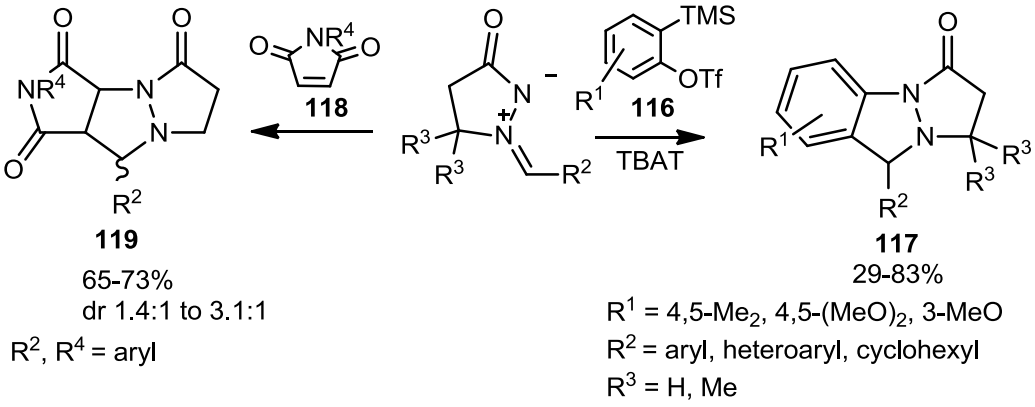
Homoallylic alcohols were used as cyclization partners in an asymmetric form of this reaction (Scheme 41), in which 20 mol % of (*R,R*)-diisopropyl tartrate and 1.5 equivalents of Grignard reagent were employed. As a result, cyclization products **115** were obtained with good yields and good *ee*-s.[97]



Scheme 41. Cycloaddition of homoallylic alcohols to azomethine imines

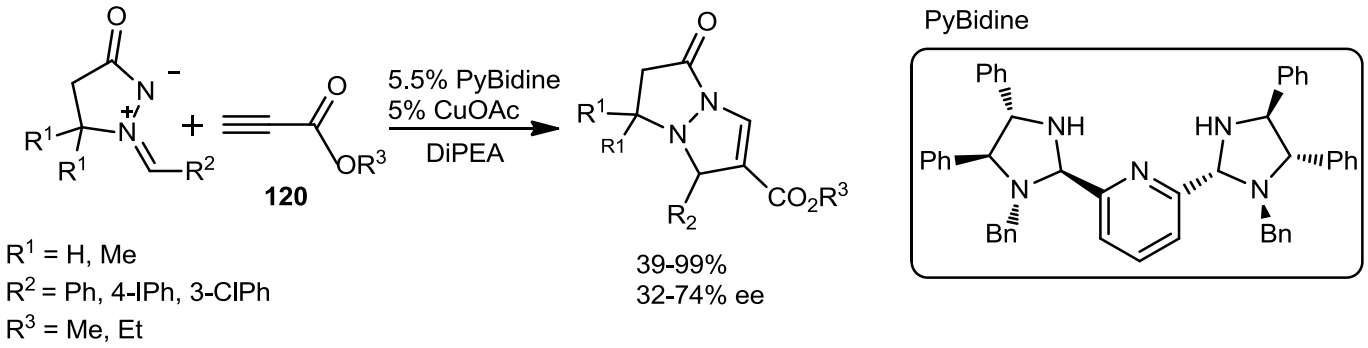
Arynes have also been cyclized with azomethine imines.[98] It was observed that benzynes are formed from **116** when treated with 1.25 eq. of TBAT, and that the reaction with azomethine imines yields aryl-fused tricyclic systems **117**. Reactions with three arynes were attempted, and gave average yields, but a wide variety of azomethine imines could be used in those reactions. Surprisingly, aliphatic azomethine imines generate products in better yields (Scheme 42, right).

N-Arylmaleimides **118** could also serve as partners for [3+2] cyclization with azomethine imines (Scheme 42, left). A variety of maleimides that bore different substitution patterns were reacted with azomethine imines in non-catalytic process, to form tricyclic systems **118** as a mixture of *cis* and *trans* isomers (1:1.4 to 1:3.1 respectively) in good overall yields.[99]



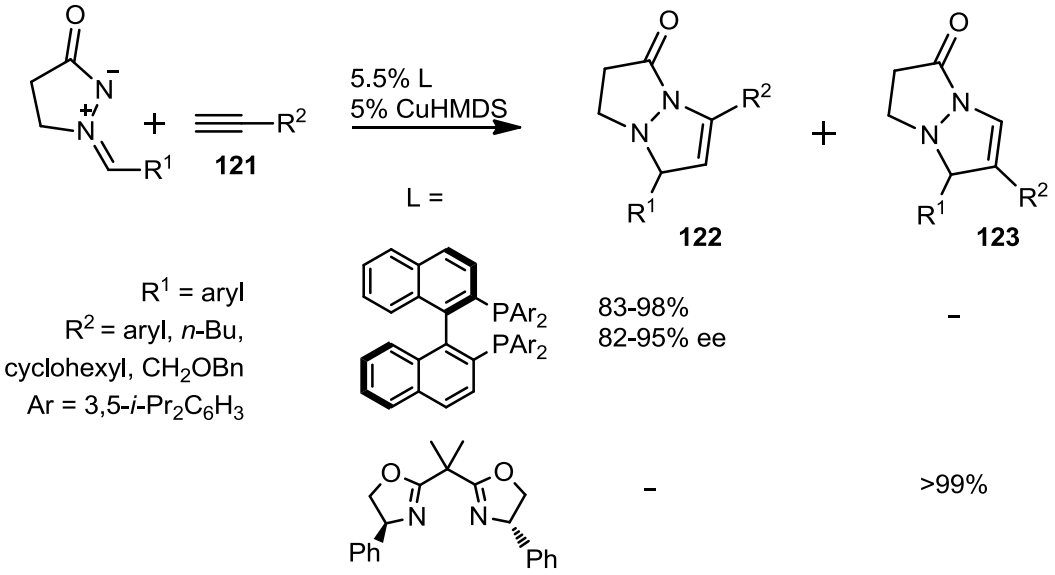
Scheme 42. Cyclizations of azomethine imines with maleimides and arynes

Alkynes constitute another class of compounds that can be used as partners for these reactions (Scheme 43). A copper catalyst was used to cyclize propiolates **120** with azomethine imines. A selection of bases was screened and the best *ee* (74%) was obtained with DiPEA at -20 °C.[100]



Scheme 43. Cu-catalyzed coupling of azomethine imines with propiolates

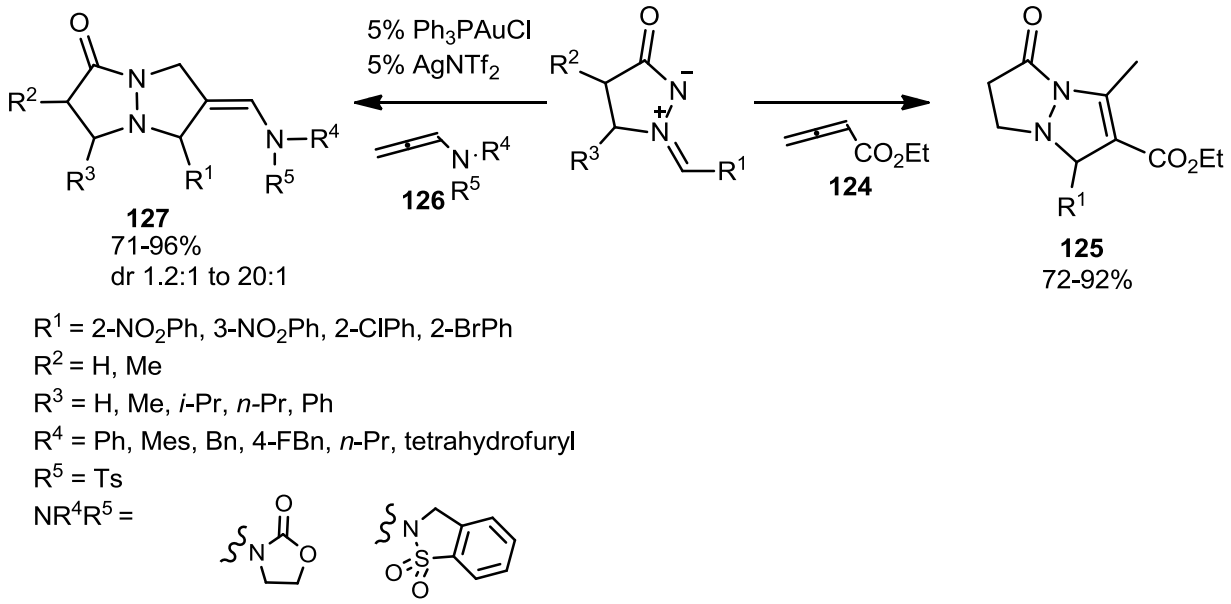
When arylacetylenes **121** were used with AgHMDS and racemic BINAP as catalyst in THF at 40 °C, the 5,7-substituted product **122** was formed. Excellent yields were obtained for aromatic azomethine imines and arylacetylenes. An asymmetric version of this reaction was designed, and CuHMDS with (*S*)-DIP-BINAP was used to generate excellent yields and *ee*-s for aromatic and aliphatic alkynes and azomethine imines. It was postulated that Cu-acetylenide forms in the reaction, which adds to azomethine imine and leads to a subsequent intramolecular cyclization. Interestingly, the use of BOX ligands lead to an inversion of chemoselectivity, giving 5,6-disubstituted products **123** (Scheme 44).[101]



Scheme 44. Cu-catalyzed cyclizations with arylacetylenes

In a final example of [3+2] cycloadditions, allenes were reacted with azomethine imines. The use of ethyl allenoate **124** in conjunction with aromatic azomethine imines in a thermal process, generated **125** in 73-92% yields.[102] Similarly Au(I) catalysis, lead to the formation of **127** when employing allenyl amines **126** as starting materials in reaction with azomethine imines. It was found that cationic $Ph_3PAuOTf$ is the best catalyst, and that when used in DCM for wide variety of aromatic aldehyde derived azomethine

imines along with allenyl amines bearing an electron-withdrawing group on nitrogen. Yields are usually good to excellent and good *dr* were achieved (Scheme 45).[103]

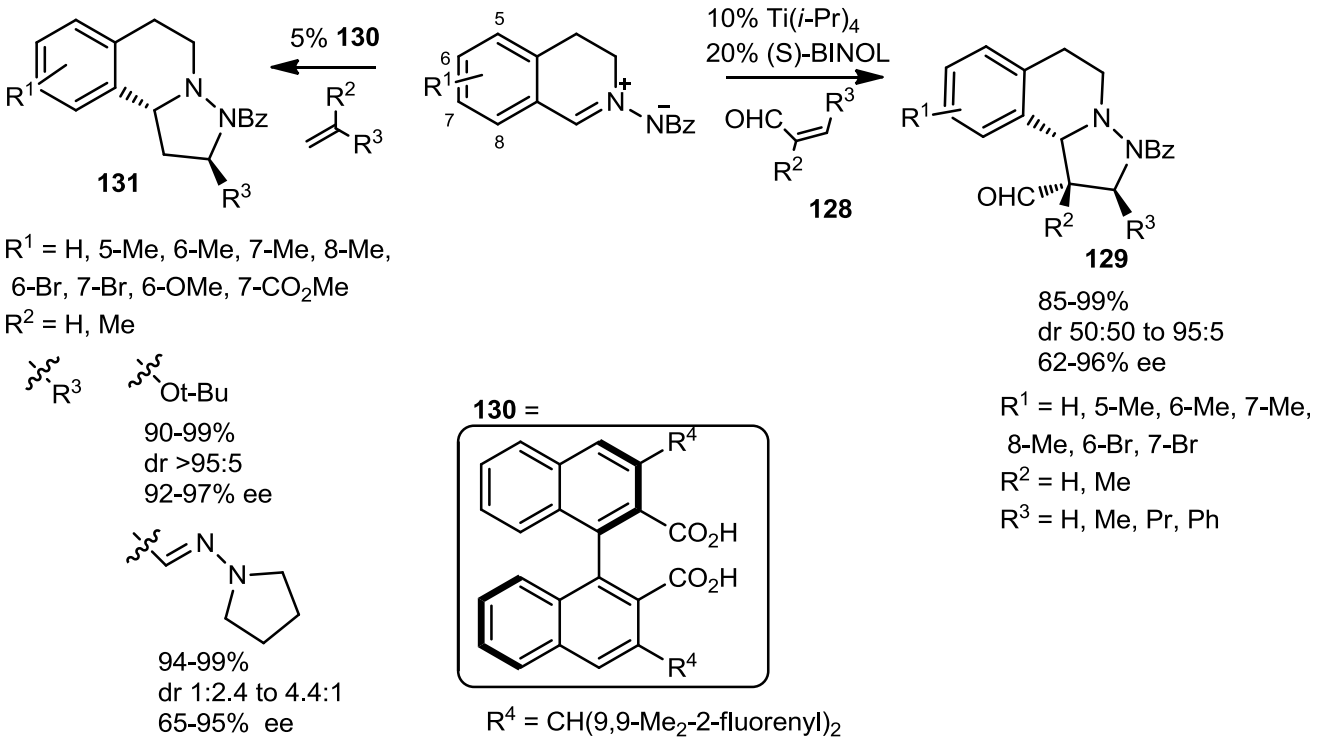


Scheme 45. Reactions of N-N cyclic azomethine imines with allenes

Cyclizations with C-N cyclic azomethine imines

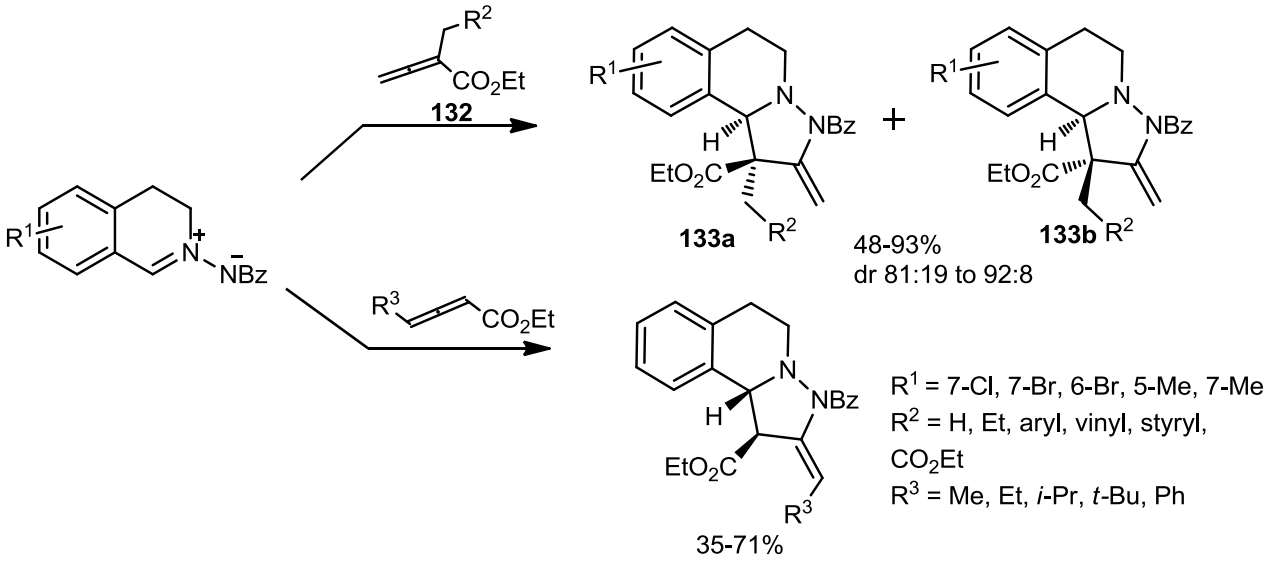
Enals **128** were used for [3+2] cycloadditions with C-N cyclic azomethine imines by Maruoka and coworkers. A catalytic system of Ti(O*i*-Pr)$_4$ (10%) with (*S*)-BINOL gave the best *exo*:*endo* ratio (>95:1) and 92% *ee* of **129**. It was determined by screening that substitutions on the aryl moiety of azomethine imine were tolerated and that aromatic, aliphatic and cyclic unsaturated aldehydes are good partners in this reaction. The enantiomeric excess is affected by the substitution in the 8-position of the azomethine imine, additionally it was found that unsubstituted acrylaldehyde lead to reduced *ee* compared to other groups. The diastetreoselectivity was affected negatively by having a methyl group in the 7-position in comparison with hydrogen (Scheme 46, right).[104]

Following another investigation by Maruoka and coworkers, it was determined that vinyl *tert*-butyl ether is also a suitable candidate for cycloadditions. With catalyst **130**, the reaction proceeded with a variety of azomethine imines to provide **131** in excellent yields and *ee*-s. Although a different catalyst was employed, (*E*)-*N*-allylidenepyrrolidin-1-amine followed the same pathway, but with a much reduced *exo*:*endo* ratio compared to vinyl ether (Scheme 46, left).[105]



Scheme 46. Reactions with C-N cyclic azomethine imines with alkenes

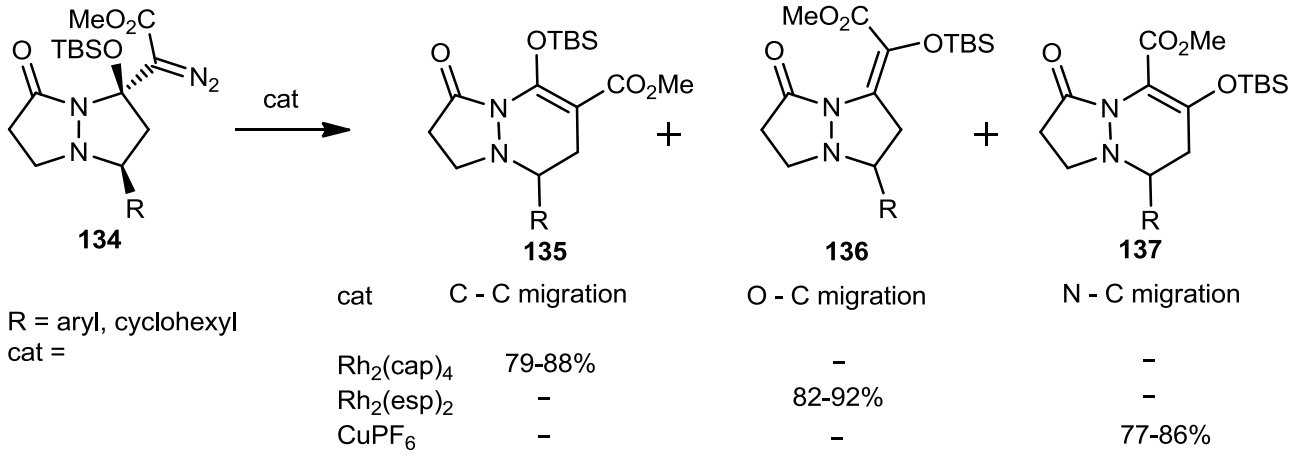
Finally, allenes have also been used for cyclization.[103] The heating of β'-arylsubstituted allenoates **132** with azomethine imines in *i*-PrOH gave products **133** in very good yields and *dr*-s ranging from 81:19 to 92:8. Furthermore, screening showed that substitutions of the aryl moiety of the azomethine imine also were tolerated (Scheme 47).



Scheme 47. Reactions of C-N cyclic azomethine imines with allenes

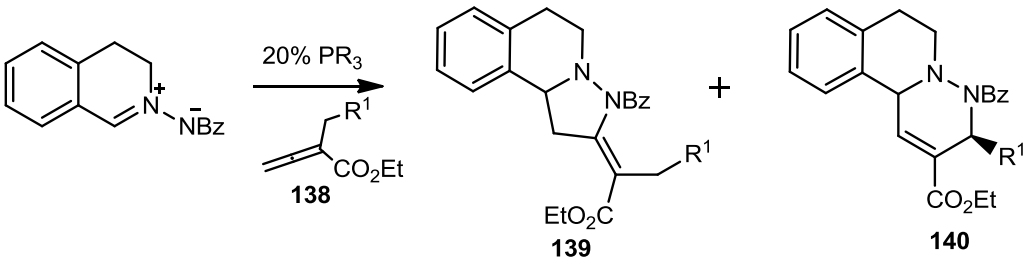
Tandem reactions

Very recently the formation of β-methylene-β-silyloxy-β-amido-α-diazoacetates **134** from azomethine imines was achieved by using Lewis acid catalysis. These reactions proceeded with excellent yields for a variety of azomethine imines derived from aromatic aldehydes. Some decreases in yields were observed for non-aromatic R substituents (Scheme 48). It was observed that in some cases a 1,2-migration occurred, giving rise to the formation of 6-membered rings, provided that **134** included a suitably substituted quaternary carbon in the 5-position. The migration reactions were highly dependent on the catalyst employed, as can be seen in Scheme 47 (C-C migration with formation of **135**, O-C migration with formation of **136** or N-C migration with formation of **137**). Firstly, $Rh_2(TFA)_4$ and $Rh_2(cap)_4$ gave the C-C migration and **135** as major product. Secondly, $Rh_2(esp)_2$ furnished O-C migration. Finally, Cu catalysts showed themselves superior for the N-C migration: while Rh catalysts always gave a mixture of products (in 88:12 to 81:19 **135**:**137** ratio), $CuPF_6$ gave N-C products **136** only (regardless of substituents).[106]



Scheme 48. Rh and Cu catalyzed reactions of bicyclic diazo-compound

The chemoselectivity depends on the phosphane catalyst employed and the structure of allenoate **138**, when they are used in cyclizations with C-N cyclic azomethine imines. It was shown that with PMe_3 as catalyst, [3+2] cycloaddition is preferable, albeit in lower yields of **13** for aromatic allenoates, and PBu_3 favors [3+3] cycloaddition with aromatic allenoates (Scheme 49 and Table 2).[107] An analogous trend is observed in another report with N-N cyclic azomethine imines.[108]

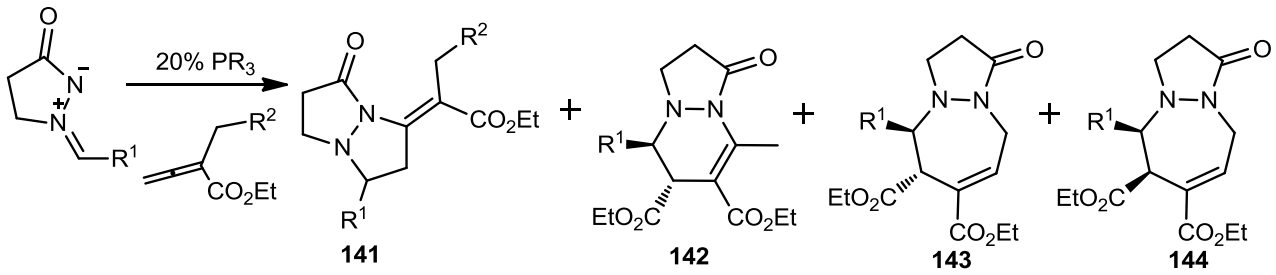


Scheme 49. Phosphane-dependent chemoselectivity of C-N cyclic azomethine imine cyclizations

Table 2. Products of phospane-catalyzed cycloadditions

R	R^1	major product	yield
Me	H, Me, Et, *i*-Pr, *t*-Bu	**139**	60-93%
Me	Ph, 2-MePh, 3-MePh, 4-MePh, 4-FPh, 3-ClPh, 4-ClPh, 4-BrPh	**139**	18-92%
Bu	H, Me, Et, *i*-Pr, *t*-Bu	**139**	62-89%
Bu	Ph, 2-MePh, 3-MePh, 4-MePh, 4-FPh, 3-ClPh, 4-ClPh, 4-BrPh	**140**	42-90%

Cycloaddition was observed for β'-unsubstituted phenyl or alkyl enoates in a [3+2] manner to give **141**. Notably the presence of a second -CO_2Et group in the allene lead to a change in reactivity based on the catalyst's alkyl chain length: with PBu_3, [3+4] cycloaddition to **143-144** was preferred, whereas with PMe_3 [3+2] and [3+3] cycloadditions proceeded with same efficiency. Whichever catalyst was employed, for all reactions a mixture of products were obtained (Scheme 50 and Table 3).

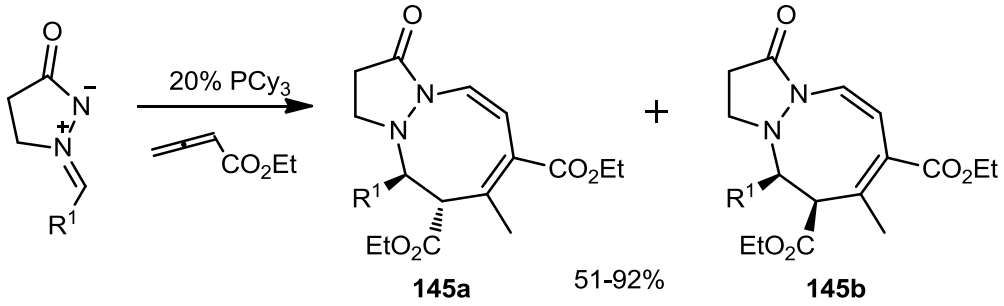


Scheme 50. Cycloadditions with N-N cyclic azomethine imines catalyzed by PMe_3 and PBu_3

Table 3. Yields of different products depending on catalysts for cycloadditions with N-N cyclic azomethine imines

R^3	R^1	R^2	**141**	**142**	**143**	**144**
Bu	aryl	H	50-99%	-	-	-
Me	aryl	alkyl, aryl, vinyl, styryl	30-99%	-	-	-
Bu	aryl	CO_2Et	6%	23%	48%	15%
Me	aryl	CO_2Et	40%	42%	7%	5%

Finally, when PCy_3 was used as catalyst, a [3+2+3] cycloaddition was observed, with ethyl allenoate giving mixtures of two isomeric products **145** in very good combined yields (Scheme 51).

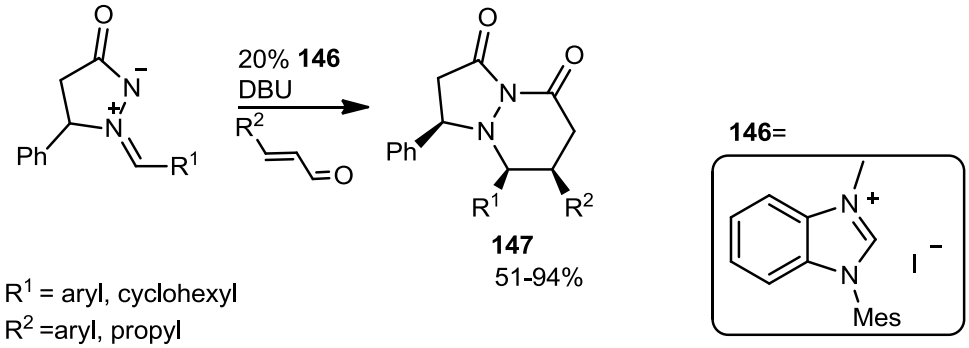


Scheme 51. PCy_3-catalyzed cycloaddition of allenoate with azomethine imine

12. [3+3] AND OTHER CYCLIZATIONS OF AZOMETHINE IMINES TO FORM LARGER CYCLES

6-membered rings from N-N cyclic azomethine imines

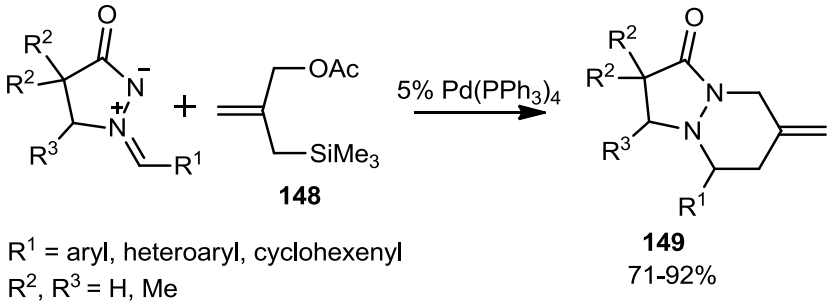
Chan and Scheidt [109] showed that 2-enals with *N*-heterocyclic carbenes (NHC) form Breslow ene-intermediate, which can add to the azomethine imine double bond and after a subsequent cyclization form a hexahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one core **147**. It was necessary to employ 20 mol % of the NHC formed from **146** and DBU in boiling DCM to conduct the reaction. Short reaction times were sufficient to generate products **147** with excellent diastereoselectivity (*dr* >20:1 in all cases). Different azomethine imines derived from aromatic aldehydes are tolerated, and a variety of enals could be used in this reaction, though non-aromatic ones give rise to lower yields (Scheme 52).



Scheme 52. NHC-catalyzed [3+3] cycloaddition

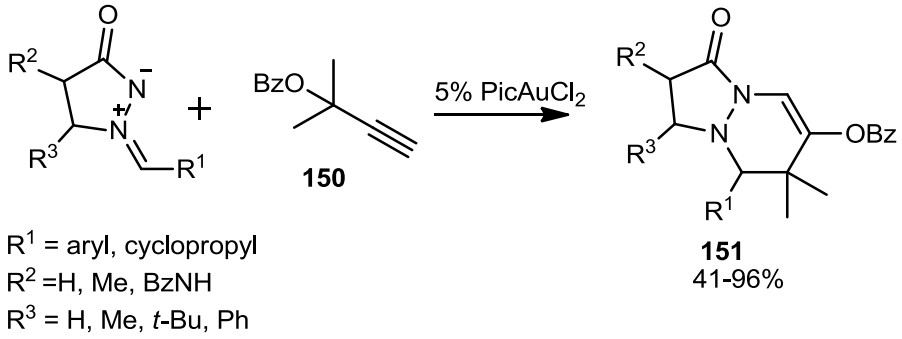
Research conducted by Shintani and Hayashi[110] showed that the trimethylenemethane generated from **148** is a suitable partner for [3+3] cycloadditions with azomethine imines in presence of Pd-catalysts. It was found that $Pd(PPh_3)_4$ in DCM was the best catalytic system, generating

7-methylene-5-phenylhexahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one **149** in 81% yield. Different azomethine imines derived from aromatic aldehydes made for good substrates (Scheme 53).



Scheme 53. Reaction between trimethylenemethane and N-N cyclic azomethine imine

Toste *et al.*[111] demonstrated the use of Au(III)-catalysts in the [3+3]-cyclization of propargyl esters **150** (Scheme 54). After a 1,2-shift and the formation of carbenoid intermediate from propargyl ester, reaction with azomethine imine takes place, giving rise to **151**. Following screening, it was found that $PicAuCl_2$ in DCM at 0 ^{o}C proved to be the best catalytic system for this reaction. Reactions occurred between 2-methylbut-3-yn-2-yl benzoate and a variety of azomethine imines, allowing for different substitution on pyrazolidin-3-one ring, for aromatic aldehydes based azomethine imines.

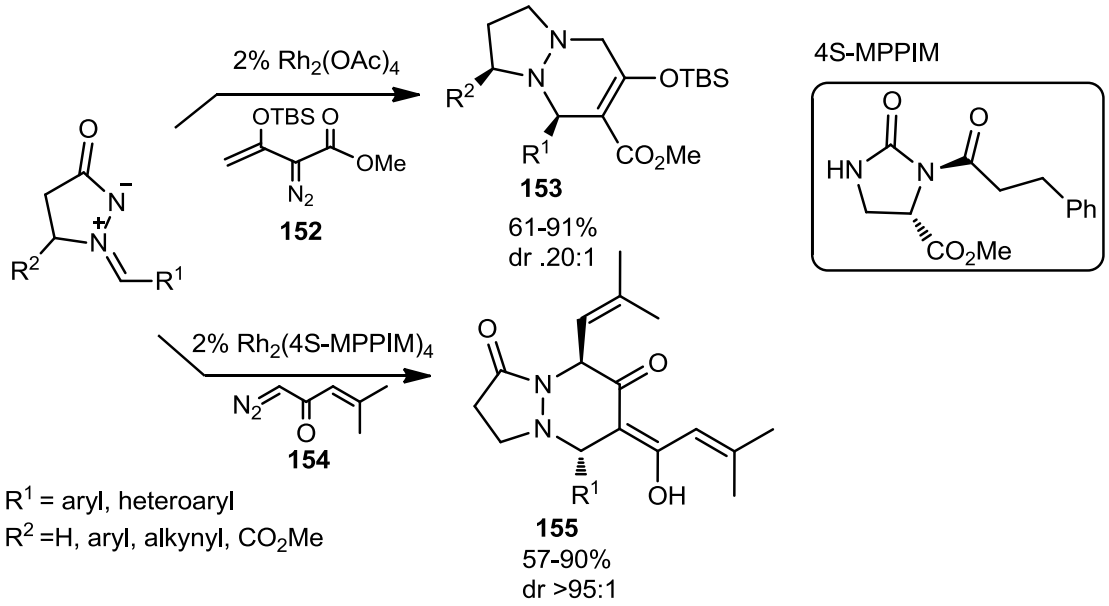


Scheme 54. Au-catalyzed reaction between azomethine imines and propargyl benzoate

Diazo compounds could be used as partners in cycloadditions with azomethine imine, if a Rh-catalyst is utilized. Enoldiazoacetates **152** with $Rh_2(OAc)_4$ generate carbenoid intermediates which are reactive towards nucleophilic side of the dipole. If a carbene addition occurs, the N-N bond cleavage furnishes diimine compounds. Should the vinylogous addition to azomethine imine take place, the cyclization to **153** occurs. Aryl and ester substitution on the position 5 of the azomethine imine favors cycloaddition path. These reactions occur with excellent yields for aryl R^1 groups, whereas cyclohexyl leads to a drop in yield implying that electronics are more at play than sterics (Scheme 55, top).[112]

If a diazoketone **154** is used, then a formal [3+2+1] cyclization happens.[113] In this case it is proposed that the Rh catalyst acts as a Lewis acid on the azomethine imine, rather than generating a carbene from the

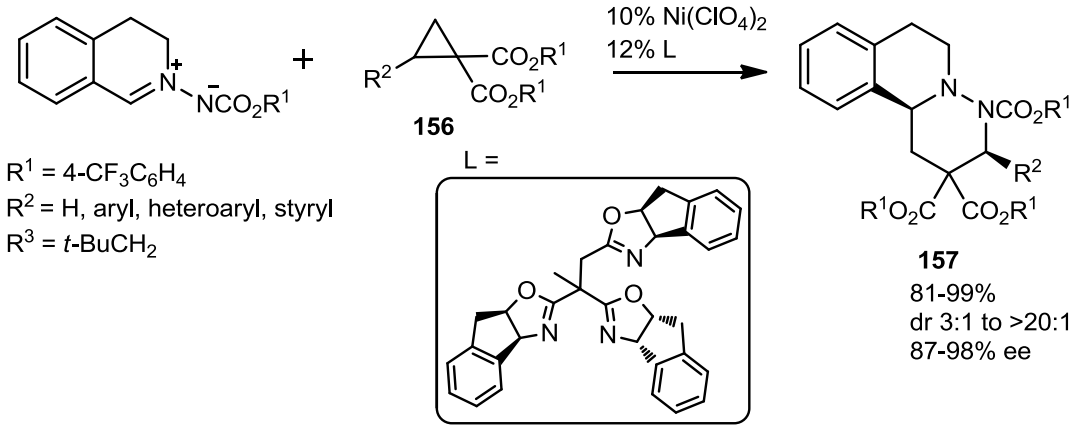
diazoketone. Then a stepwise diazoketone addition and N_2 extrusion occurs, to finally generate the 6-membered cyclization product **155**. The reaction is applicable to different azomethine imines furnishing products in good yields and with very good *dr* (Scheme 55, bottom).



Scheme 55. Rh-catalyzed reactions of azomethine imines with diazocompounds

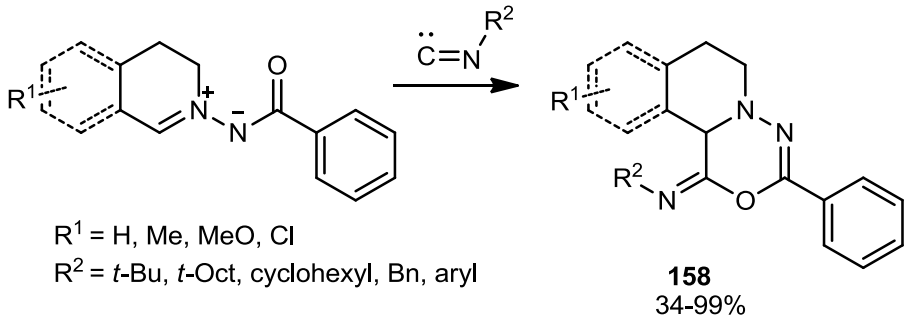
6-membered rings from N-C cyclic azomethine imines

Charette *et al.*[114] showed that aromatic C-N cyclic azomethine imines could be reacted with 1,1-cyclopropane diesters **156** to give [3+3] cycloaddition products. Using $Ni(ClO_4)_2$ as Lewis acid catalyst, a selection of substituted cyclopropanes reacted with azomethine imine, giving the fused tricyclic products **157**. The transfer of chirality doesn't occur from the cyclopropanes. It is proposed instead that the diester chelates to the Ni-catalyst and then the nuclephilic end of the azomethine imines dipole attacks the cyclopropane, after which, the obtained enol cyclizes with imine function. However, when a BOX ligand was used, a strereoselective process takes place (Scheme 56).



Scheme 56. Ni-catalyzed [3+3] cyclizations with C-N cyclic azomethine imines

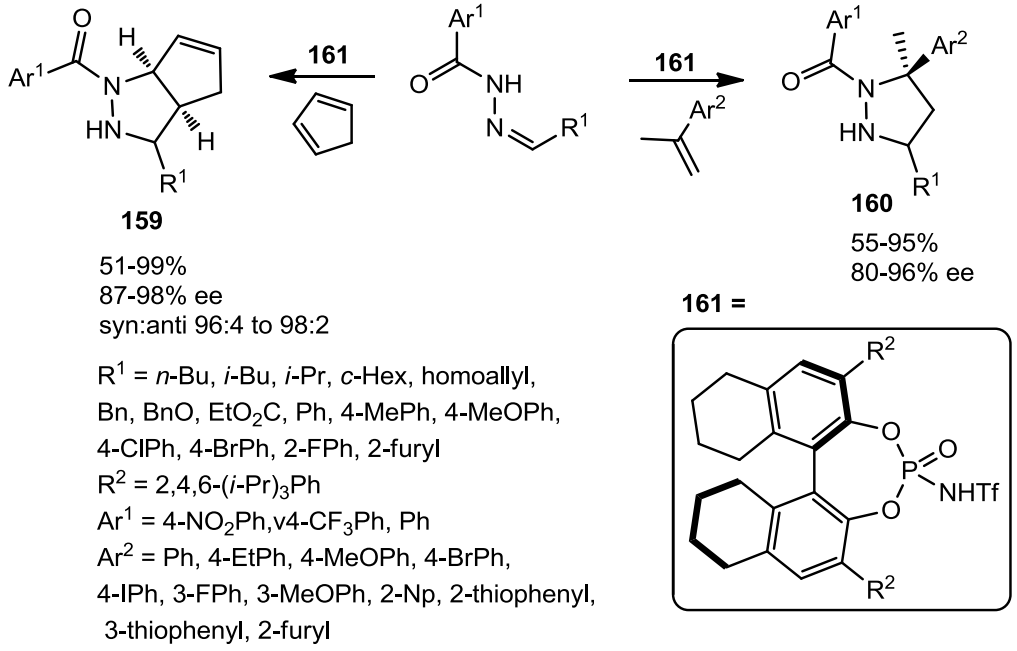
The [5+1] cycloaddition can occur between N-C cyclic N'-acyl azomethine imines and isocyanides.[115] This transformation doesn't require catalysts, as one of the resonance forms of azomethine imine could be considered as an "isocyanophile". The products **158** are obtained in good to excellent yields with different aliphatic and aromatic isocyanides and substitution on benzoate and 3,4-dihydroisoquinoline are tolerated. Azomethine imine (even without a fused aromatic ring) also react readily and N-N cyclic azomethine imines are not reactive in this transformation (Scheme 57).



Scheme 57. [5+1] Cyclization between C-N cyclic azomethine imine and isocyanides

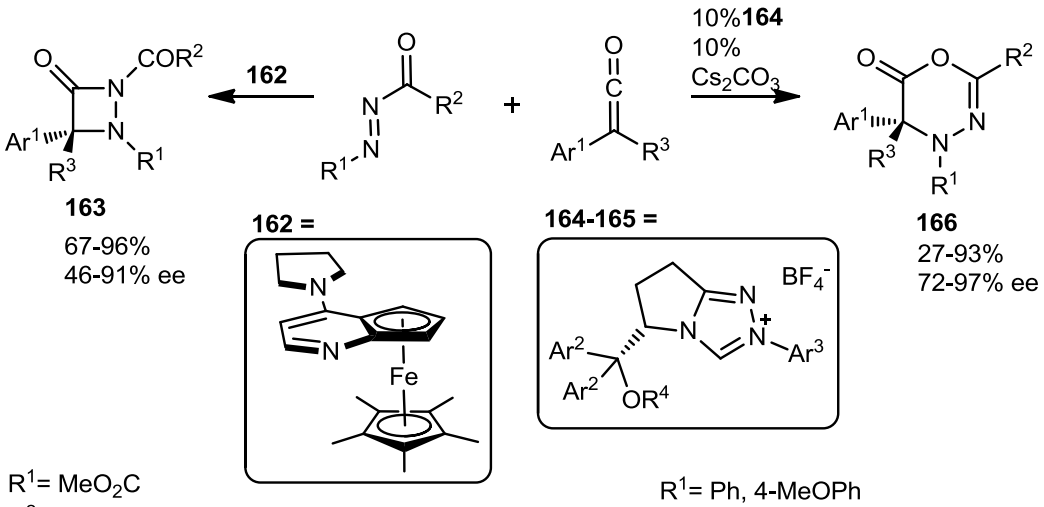
13. OTHER CYCLIZATIONS

Hydrazones were reported to cyclize with alkenes to yield pyrazolidines **159**-**160**. [116] In this case, chirality was induced by using binol-based *N*-trifylphosphoramide **161** as a catalyst. This reaction tolerates both aromatic and aliphatic hydrazones as well as different alkenes, to give good *ee*-s and *syn*:*anti* ratios (Scheme 58).



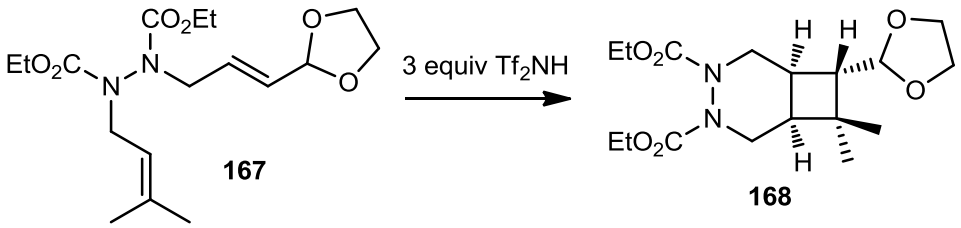
Scheme 58. Enantioselective pyrazolidine formation

Ketenes can also react with azo-compounds to give cyclic hydrazines. Interestingly, when ferrocene derivative **162** was used as catalyst, an enantioselective [2+2] cycloaddition occurs, giving rise to products **163**.[117] On the other hand, with the NHC-catalyst **164**, a [4+2] cycloaddition occured, producing **166**. Finally, a similar catalyst **165** gave the opposite enantiomer of the product **166** (Scheme 59).[118]



Scheme 59. Enantioselective cycloadditions between ketenes and azo-compounds

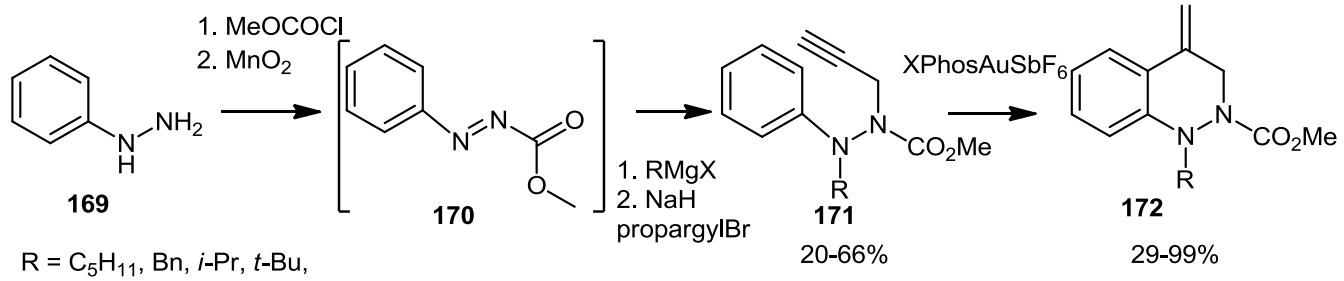
Recently a cationic [2+2] cycloaddition was reported for hydrazines.[119] Cycloaddition substrate **167** was prepared by the double alkylation of hydrazine with allylic bromides, using NaH for deprotonation. Furthermore, the reaction proceeded upon addition of Lewis or Brønsted acids, with $SnCl_4$ being the most effective, leading to the desired cyclic product **168** as single diastereomer (Scheme 60).



Scheme 60. [2+2] Cationic cyclization of a hydrazinic diene

14. OTHER TRANSITION METAL CATALYZED CYCLIZATIONS

In Gagosz' group a protocol for the Au(I)-catalyzed arylation of hydrazine containing substrates was developed (Scheme 61).[120] The substrate synthesis started with phenyl-hydrazine **169**, which was protected, then oxidized with MnO_2 to azo-compound **170**. Subsequently it was subjected to a Grignard reagent, followed by propargylation. The obtained hydrazines **171** were exposed to a cationic Au(I) catalyst (in 4 mol % loading) to furnish *exo*-methylene tetrahydrocinnolines **172** in excellent yields and in short reaction times. This reaction is applicable for differently substituted aromatics, whereas *meta*-substituted compounds give 1:1 mixture of the 2 regioisomers **173** and **174**and *ortho*-substitution results in the mixture of *exo* and *endo* products **175** and **176** (Figure 7).



Scheme 61. Synthesis of exo-methylene tetrahydrocinnolines

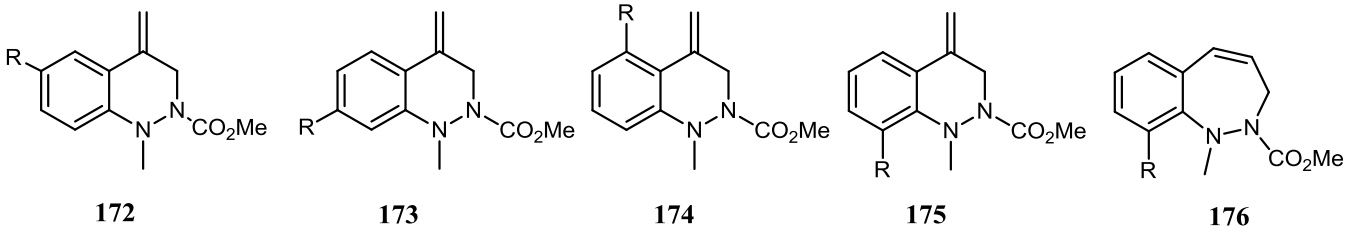


Figure 7. Compounds obtained from Au-catalyzed cycloisomerization

15. SUMMARY

In this review we aimed to summarize methods for the synthesis of endocyclic hydrazines starting from acyclic hydrazines and azo-compounds. Of particular interest, section 8 shows methods of enantioselective synthesis of piperazic acid, which is an important building block for the synthesis of biologically active molecules. Additionally, the application of transition-metal catalysis to hydrazine chemistry was highlighted. And finally, recent advances in the field of azomethine imines were reviewed.

16. ACKNOWLEDGEMENTS

This work was supported by Estonian Science Foundation (Grant nr. 8794), the European Regional Development Fund (Center of Excellence ‘‘Mesosystems: Theory and Applications’’, TK114) and the Estonian Science Targeted Project no. SF0180032s12. We would like to thank Alban Cadu (Uppsala University, Sweden) for proof-reading the manuscript.

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