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Cyclic *cis*-1,3-diamines derived from bicyclic hydrazines: Synthesis and applications

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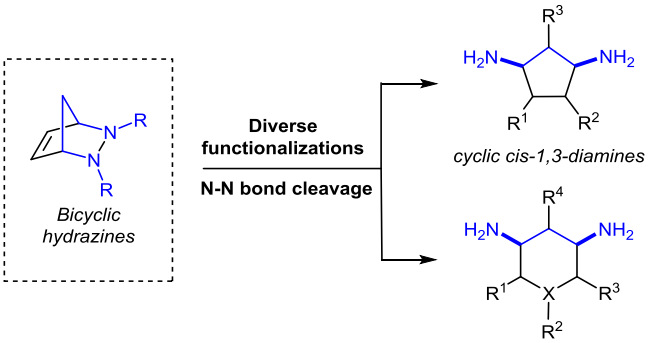

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Abstract Cyclic *cis*-1,3-diamines are versatile building blocks frequently found in natural molecules or biologically active compounds. In comparison with widely studied 1,2-diamines, and despite their chemical similarity, 1,3-diamines have been investigated less intensively probably because of a lack of general synthetic procedures giving access to these compounds with good levels of chemo- , regio- and stereocontrol. In this account we will give a general overview of the biological interest of cyclic *cis*-1,3-diamines. We will then describe the synthesis and potential applications of these compounds with a particular focus on the work realized in our laboratory.

1 Introduction
2 Biological relevance of the *cis*-1,3-diamine motif
3 Classical synthetic strategies towards *cis*-1,3-diamines
4 N-N bond cleavage of bicyclic hydrazines: a versatile method to access *cis*-1,3-diamines
4.1 Preparation of five-membered cyclic *cis*-1,3-diaminoalcohols
4.2 Access to fluorinated 1,3-*cis*-diaminocyclopentanes
4.3 Synthesis of *cis*-1,3-diaminocyclohexitols
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5 Applications of cyclic *cis*-1,3-diamines
5.1 Small molecular RNA binders
5.2 Fluorinated 1,3 diamino cyclopentanes as NMR probes
6 Concluding remarks

Key words cyclic *cis*-1,3-diamines; bicyclic hydrazines; fragments RNA ligands and probes; N-N bond cleavage; hydroxylation; fluorination; reductive amination

1. Introduction

Although cyclic 1,2-diamine moieties are recognized as important motives commonly used as building blocks in synthetic chemistry or as ligands in catalysis, [1] their cyclic 1,3-diamine analogues have received much less attention. [2] As a matter of fact, there is still a need for diversity-oriented general procedures providing practical access to cyclic 1,3-diamines with good regio- and stereo-control. This lack of general methods, compared to the variety of strategies developed to access the cyclic 1,2-diamine motif, limits considerably the applications of these compounds in different research fields. Even today, 1,3-diamine containing substrates can therefore be considered important targets in organic chemistry.

Since the early 2000s, our group has been interested in the design of efficient stereoselective routes to 1,3-diamines, with a particular attention to five- and six-membered cyclic compounds showing *cis*-substitution patterns (Figure 1). Our original goal was to explore the chemical space of these motives, regardless of their potential applications. The challenge was mostly synthetic : how to install a 1,3 diamine motif onto a functionalized five or six-membered ring, in a simple and versatile manner, with a control of the relative, and/or absolute configuration of the stereogenic centers of these densely functionalized scaffolds. Application of these synthetic methods for the design of compounds with interesting properties (mostly biological ones) has also been the focus of our studies during the last ten years.

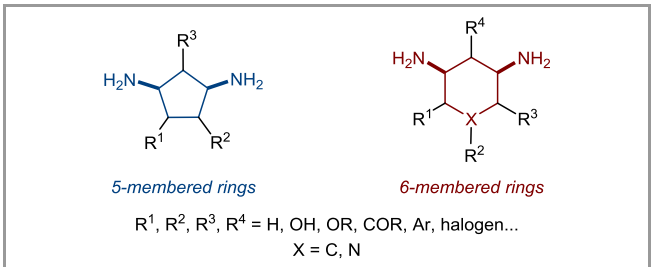


Figure 1 General structure of five- and six-membered cyclic *cis*-1,3-diamines

In this account article we will firstly present the biological relevance of cyclic *cis*-1,3-diamines. We will also briefly describe the few synthetic approaches that can be followed to access these systems. We will then report our efforts towards the development of new general methods for preparing such derivatives on synthetically useful scales *via* a key strategy involving the N-N bond cleavage of bicyclic hydrazines. We will finally describe the use of the cyclic *cis*-1,3-diamine compounds synthesized in our laboratory as RNA binders and probes.

2. Biological relevance of cyclic *cis*-1,3-diamines

Various substrates incorporating five-membered cyclic *cis*-1,3 diamine moieties have been reported to possess interesting biological activities.[3] Some selected examples are described in Figure 2, and include compounds showing antifungal,[4] analgesic or anti-inflammatory activities[5] as well as potential therapeutic agents against different human diseases. Among them figure a melanin-concentrating hormone (MCH) receptor antagonist that may be used for the treatment of obesity and other metabolic syndromes,[6] mammalian Janus Kinase 1 (JAK1) inhibitors which could be employed to cure patients affected by myelofibrosis,[7] and a neuronal nitric oxide synthase (NOSs) inhibitor that may help to prevent neurodegenerative conditions such as rheumatoid arthritis, Alzheimer's disease, and Parkinson's disease.[8] Pyrimidine carbocyclic nucleosides have finally been reported to possess interesting tumor cell growth inhibitory activities (Figure 2).[9]

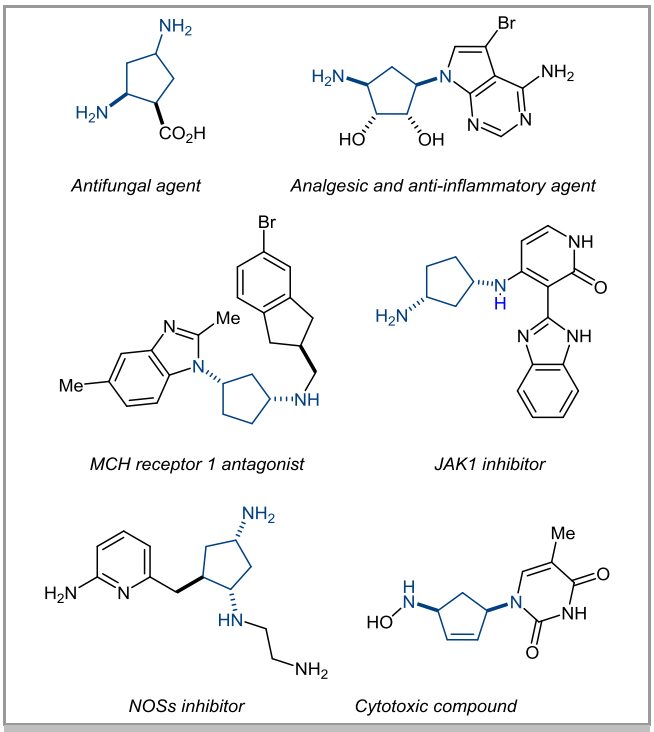


Figure 2 Biologically active compounds incorporating five-membered cyclic *cis*-1,3-diamine moieties.

Six-membered cyclic *cis*-1,3-diamine-containing molecules may also present intriguing biological properties, and many of these compounds are, for this reason, described in patent applications.[10] Few examples of such substrates are depicted in Figure 3, and include a dipeptidyl peptidase-4 (DPP-4) inhibitor useful for the treatment of type 2 diabetes,[11] a protein kinase modulator,[12] as well as a spleen tyrosine kinase (Syk) inhibitor that may serve to treat inflammatory and autoimmune disorders.[13] In addition, sugar derivatives showing the six-membered cyclic *cis*-1,3-diamine motif have been used to develop stimuli-responsive liposomes for drug delivery (Figure 3).[14]

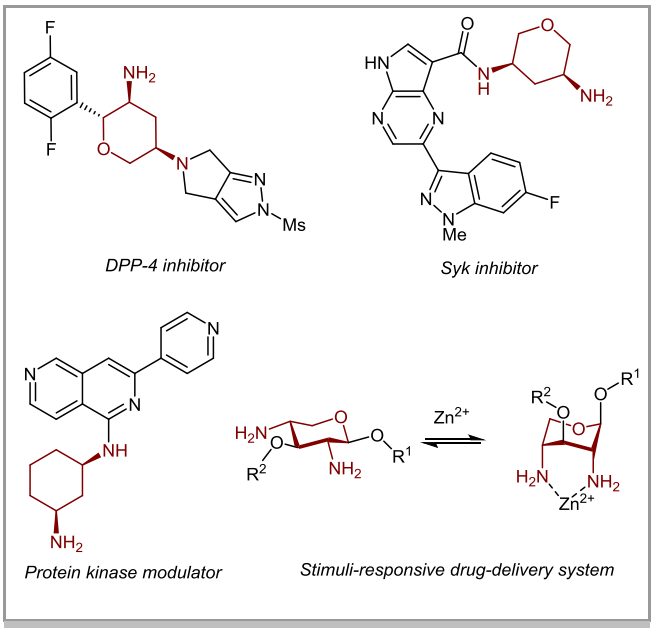


Figure 3. Biologically active compounds incorporating six-membered cyclic *cis*-1,3-diamine moieties.

Aminoglycosides irreversibly bind to the 16S ribosomal RNA of prokaryotes and prevent bacterial protein synthesis. Extensive studies including NMR investigations[15] and X-ray crystallographic studies[16] have highlighted the key interactions provided by the cis 1,3 diamine motif present in all these natural products. Several analogues of the aminoglycoside antibiotics, and in particular of their central core (2-DOS, Figure 4), have been reported over the years. As their parent compounds, these derivatives can show interesting antibacterial properties (Figure 4).[17]

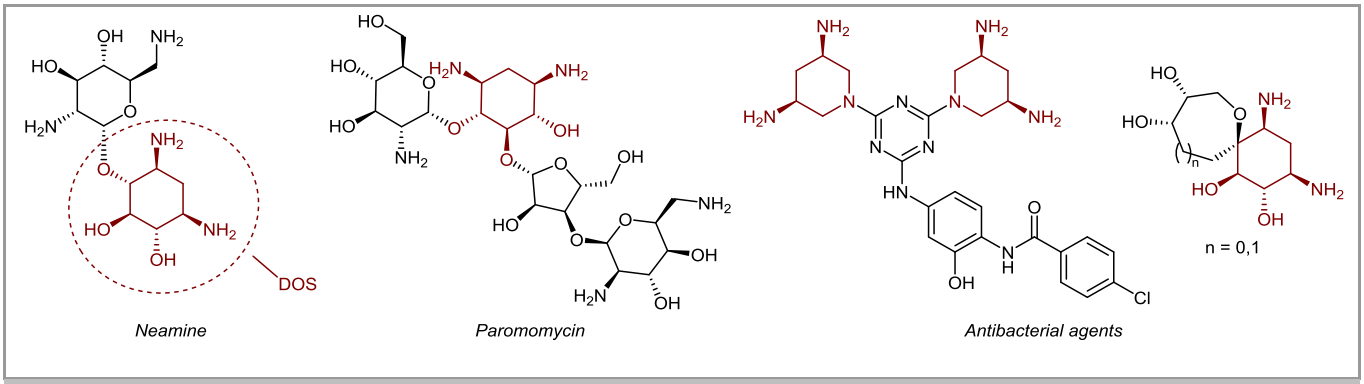


Figure 4 Biologically active compounds incorporating six-membered cyclic cis-1,3-diamine moieties.

3. Classical synthetic strategies towards *cis*-1,3-diamines

Over the years, cyclic *cis*-1,3-diamines have been prepared following various approaches. In many cases, different strategies have been used to introduce the amine functionalities onto the desired compounds, one after the other, using linear pathways that require two or more consecutive synthetic steps. The most commonly used methods to achieve these syntheses include epoxide ring-opening reactions,[18] nucleophilic substitutions,[3b,19] palladium-catalyzed allylic aminations,[20] oxime reductions,[19c,21] Curtius rearrangements,[22] intramolecular Henry reactions,[23] ring opening of cyclic sulfates,[24] and the reduction of aromatic nitro compounds[25] (Figure 5).

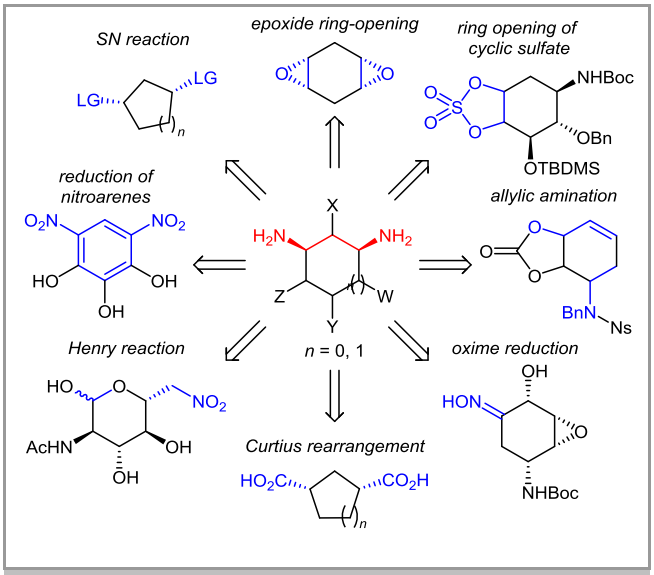
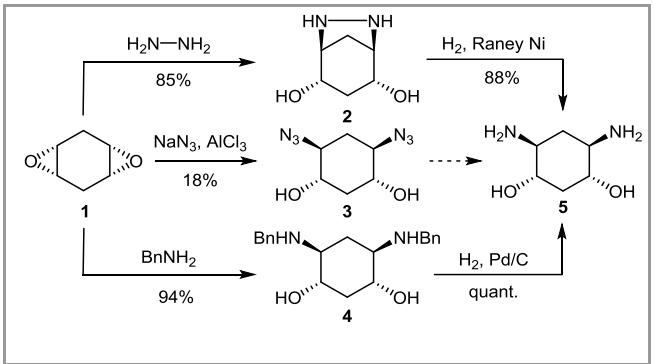


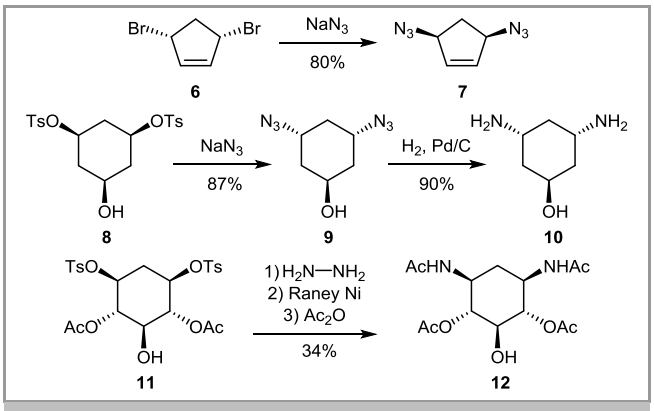
Figure 5 Synthetic strategies to access cyclic *cis*-1,3-diamines

Interestingly, only few of these methods enable to simultaneously install the two amino groups in a single synthetic step.



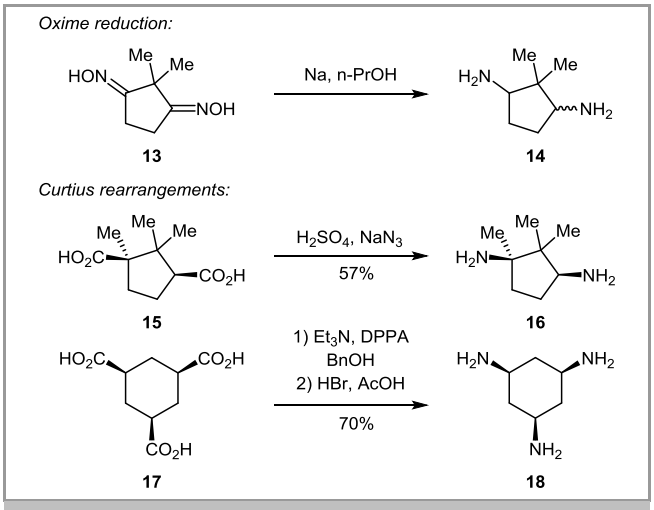
Scheme 1 Examples of epoxide ring-opening reactions

Epoxide ring-opening reactions in the presence of hydrazine,[26] benzylamine[27] or sodium azide[28] can for example be used to form six membered cyclic *cis*-1,3-diamines after a simple reduction of the reaction products (Scheme 1). Nucleophilic substitutions have been successfully employed to introduce two nitrogen-containing functional groups at once, both on five-[29] and six-membered cyclic compounds (Scheme 2).[30]



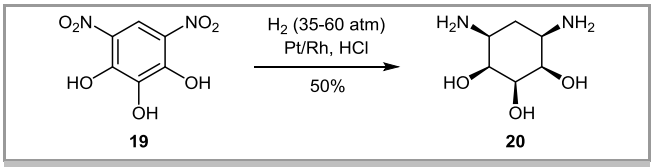
Scheme 2 Examples of nucleophilic substitutions

Examples of oxime reductions[31] and Curtius rearrangements[32] have also been reported as ways to functionalize both five- and six-membered rings with two amino groups at the same time (Scheme 3). In some cases, however, the former method does not allow to control the selectivity of the reactions and mixtures of stereoisomers (*cis*- an *trans*- 1,3 diamines) are obtained.[31]



Scheme 3 Selected examples of oxime reductions and Curtius Rearrangements.

Six-membered cyclic *cis*-1,3-diamines can finally be prepared starting from di-nitrobenzenes simply by converting the two NO_2 groups into the corresponding amine functions and concomitantly dearomatizing the aromatic group to form a fully saturated ring (Scheme 4).[25] Quite harsh conditions are however required to perform the two reductions in a single synthetic step. Other nitrogen-containing aromatic compounds (e.g. imines or 1,3-benzenediamines) can be submitted to a reductive dearomatization as well.[25a,33]



Scheme 4 Example of nitroarene reduction

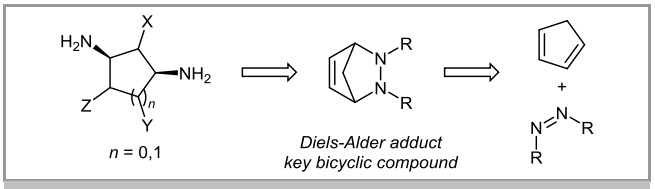
All of these transformations generally proceed with low levels of stereocontrol. Mixtures of *cis*- and *trans*-1,3 diamines are

therefore frequently obtained in moderate to good yields as main reaction products.

Taking the above mentioned examples into account, it appears clear that cyclic *cis*-1,3-diamines, and in particular five-membered rings, can hardly be synthesized in a straightforward manner with high levels of relative or absolute stereocontrol. The development of new rapid and versatile processes leading to the stereoselective formation of this class of compounds therefore still remains an important challenge for synthetic organic chemists.

4. N-N bond cleavage of bicyclic hydrazines: a versatile method to access cis-1,3-diamines

A less common but intriguing approach to prepare cyclic *cis*-1,3-diamines is based on the reductive cleavage of the N–N bond in bicyclic systems containing an hydrazine subunit. These key compounds can easily be synthesized through a Diels-Alder cycloaddition starting from cyclopentadiene and using differently substituted diazo compounds as dienophile counterparts (Scheme 5).

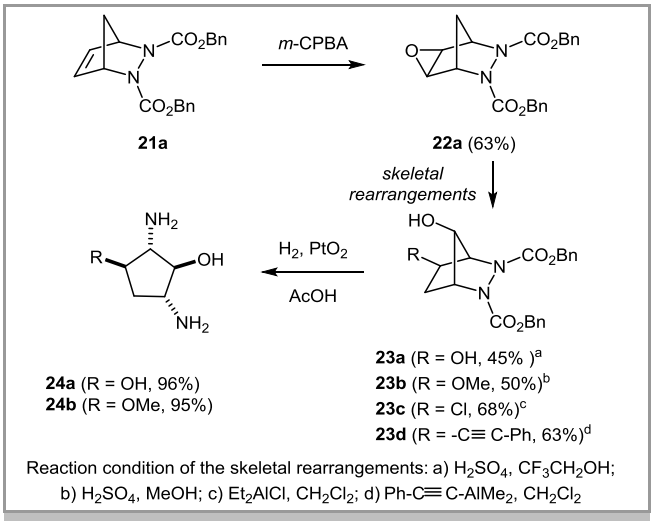


Scheme 5 Access to cyclic *cis*-1,3-diamines using Diels-Alder reactions and N-N bond cleavages as key synthetic steps.

First reported in the eighties,[34] this method allows the formation of the two C-N bonds in a single synthetic step with a total control of their relative (*syn*) configuration. By appropriate functionalization of key Diels-Alder cycloadducts, over the past few years, we have been able to adapt this procedure to the preparation of both five- and six-membered cyclic *cis*-1,3-diamines. In the next sections we will give an overview of the different scaffolds that were synthesized in our group using this convenient strategy.

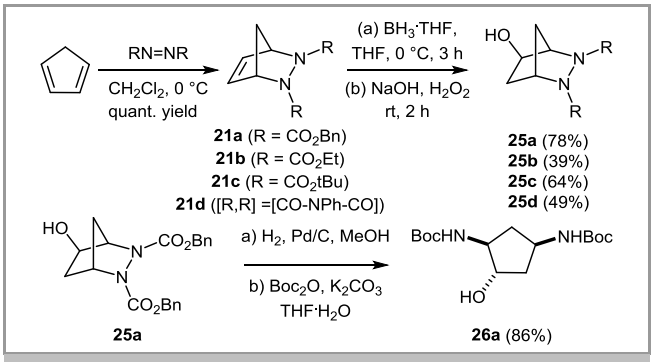
4.1 Preparation of five-membered cyclic *cis*-1,3-aminoalcohols

Various five-membered cyclic *cis*-1,3-diaminoalcohols have been successfully synthesized in few steps starting from readily available compounds and using the nitrogen-nitrogen bond cleavage of hydrazines described above as a key reaction. A first series of compounds was prepared through the epoxidation of the bicyclic adduct **21a**, easily obtained via a Diels-Alder cycloaddition between cyclopentadiene and dibenzyl azodicarboxylate (Scheme 6).[35] The acid-catalyzed rearrangement of epoxide **22a**, and subsequent nucleophilic attack, led to the formation of substituted bicyclic hydrazines **23a-d** in a regio- and stereoselective manner (Scheme 6).[36] Different reaction conditions were used to perform this transformation. Treatment of the epoxide **22a** with sulfuric acid in a non-nucleophilic solvent (trifluoroethanol) allowed the functionalization of the bicyclic system with an additional hydroxyl group. A methoxy substituent was added onto the molecule under similar conditions when methanol was employed as the solvent. Lewis acid activated reactions in the presence of organoaluminum reagents led to the formation of new carbon-halogen or carbon-carbon bonds. All the observed skeletal rearrangements allowed the control of the relative configuration of four contiguous stereocenters in a single operation, and were supposed to proceed via the formation of an aziridinium intermediate.[36] As a last synthetic step, hydrogenolysis over platinum oxide under acidic conditions of the hydrazine bond afforded the desired aminocyclopentanes **24a,b** in almost quantitative yield (Scheme 6).



Scheme 6 Synthesis of cyclic *cis*-1,3-diaminocyclitols through epoxidation, skeletal rearrangement and reductive cleavage of bicyclic hydrazines.

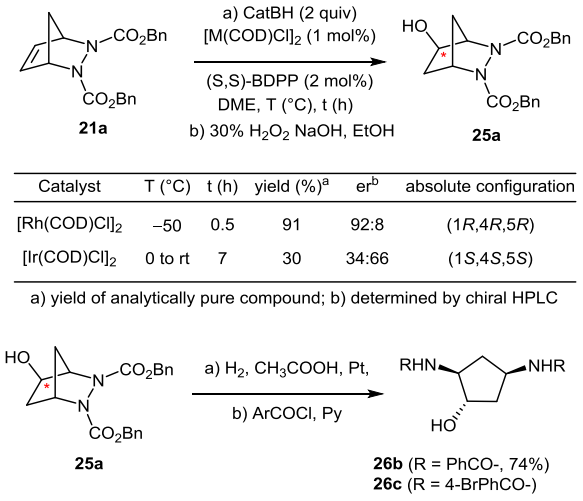
The hydroboration of different Diels-Alder adducts (**21a-d** Scheme 7) was also investigated with the aim to prepare a second series of cyclic *cis*-1,3-diaminoalcohols. Treatment of the bicyclic compounds with BH_3•THF followed by oxidative workup afforded the corresponding hydroxylated racemic products **25a-d** in moderate to good yields (Scheme 7). A reductive cleavage of the hydrazine bond was then used as the key step to access hydroxylated *N*-protected cyclic *cis*-1,3-diamines (Scheme 7).[37]



Scheme 7 Synthesis of cyclic cis-1,3-diamines through hydroboration and reductive cleavage of bicyclic hydrazines.

Asymmetric hydroborations were studied as well. In this case, a reversal of the enantioselectivity of the reaction was observed in the presence of chiral diphosphine ligands and Rh- or Ir-based catalysts.[37] Treatment of *meso* hydrazine **21a** with catecholborane (CatBH), $[Rh(COD)Cl]_2$, and (*S*,*S*)-BDPP in DME afforded the corresponding hydroxylated product **25a** in 90% yield and 84% *ee*. The absolute configuration of this compound (1*R*,4*R*,5*R*) was confirmed by X-ray analysis after reductive

cleavage of the N-N bond and subsequent protection of the final diamino alcohol as *p*-bromo dibenzamide (Scheme 8).[37] Interestingly, when $[Ir(COD)Cl]_2$ was employed as catalyst to promote the hydroboration, the hydroxylated derivative of opposite configuration (1*S*,4*S*,5*S*) was isolated as the major product (Scheme 8). Differently substituted *meso* hydrazines behave similarly under the same experimental conditions.[37] In an effort to rationalize the reaction mechanism, two different insertion pathways were invoked to explain the systematic reversal of enantioselectivity observed with the two transition metal complexes. While the use of $[Rh(COD)Cl]_2$ was supposed to involve a key Rh-H migratory insertion step, we suggested that a metal-boron insertion could be favored when using the $[Ir(COD)Cl]_2$ catalyst.[37]

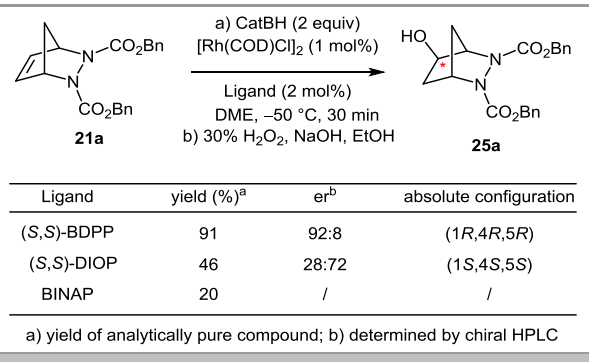


Catalyst	T (°C)	t (h)	yield (%)[a]	er[b]	absolute configuration
$[Rh(COD)Cl]_2$	–50	0.5	91	92:8	(1*R*,4*R*,5*R*)
$[Ir(COD)Cl]_2$	0 to rt	7	30	34:66	(1*S*,4*S*,5*S*)

a) yield of analytically pure compound; b) determined by chiral HPLC

Scheme 8 Asymmetric hydroborations compound **21a** with Rh- or Ir-based catalysts and subsequent reductive cleavage of the hydrazine bond

Chiral diphosphines also play an essential role in controlling the seterochemical outcome of the asymmetric hydroboration (Scheme 9).

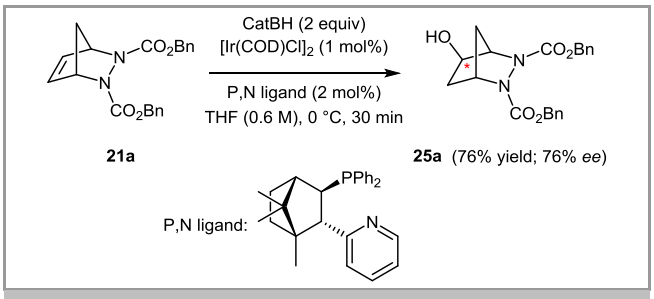


Ligand	yield (%)[a]	er[b]	absolute configuration
(*S*,*S*)-BDPP	91	92:8	(1*R*,4*R*,5*R*)
(*S*,*S*)-DIOP	46	28:72	(1*S*,4*S*,5*S*)
BINAP	20	/	/

a) yield of analytically pure compound; b) determined by chiral HPLC

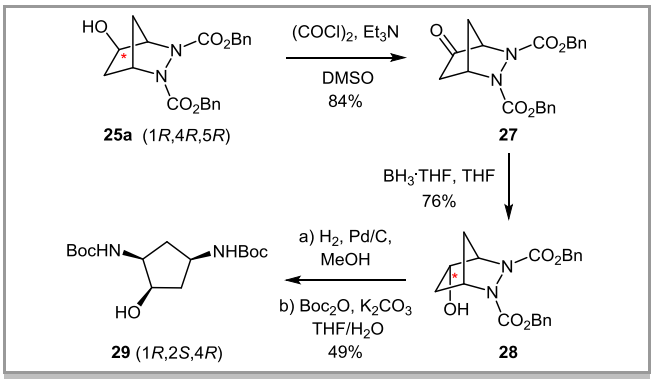
Scheme 9 Asymmetric hydroborations compound **21a** with $[Rh(COD)Cl]_2$ in the presence of different diphosphine ligands.

Indeed, alcohols of opposite absolute configuration were obtained while promoting the reaction with $[Rh(COD)Cl]_2$, simply by replacing the (S,S)-BDPP ligand with (S,S)-DIOP (Scheme 9).[37] However, a racemic product was isolated in low yield in the presence of BINAP (Scheme 9).[37a] P,N-ligands could be used in place of diphosphines with the $[Ir(COD)Cl]_2$ catalyst, and, in this case, the desired hydroxylated product **25a** was isolated in a better yield and in a higher enantiomeric excess (Scheme 10).[38]



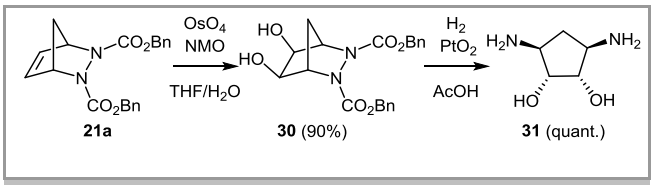
Scheme 10 Asymmetric hydroborations compound **21a** with $[Ir(COD)Cl]_2$ and P,N-ligands

As confirmed by NMR analysis, the hydroboration of bicyclic hydrazines exclusively led to the formation of *exo* alcohols.[37] The inaccessibility of the endo face, probably hindered by a pseudo axial carbamate, was confirmed by many unsuccessful trials of alcohol inversion by S_N2 type mechanisms. To obtain an all-*cis* diamino alcohol, the enantioenriched hydroxylated hydrazine **25a** was converted to the corresponding ketone by Swern oxidation (Scheme 11). Subsequent reduction of the carbonyl group, followed by N–N bond cleavage and protection of the free amino groups as N-*tert*-butyl-carbamates led to the formation of the enantioenriched compound **29** in a good overall yield (Scheme 11).[39]



Scheme 11 Synthesis of an all-*cis* diamino alcohol

In order to prepare dihydroxylated products, bicyclic hydrazine **21a** was finally engaged in a reaction with osmium tetroxide to afford hydrazine **30** in 90 % yield (Scheme 12). The reductive cleavage of the N-N bond of this compound successfully leaded to the formation of diaminodiol **31**, which could be isolated in a quantitative yield (Scheme 12).

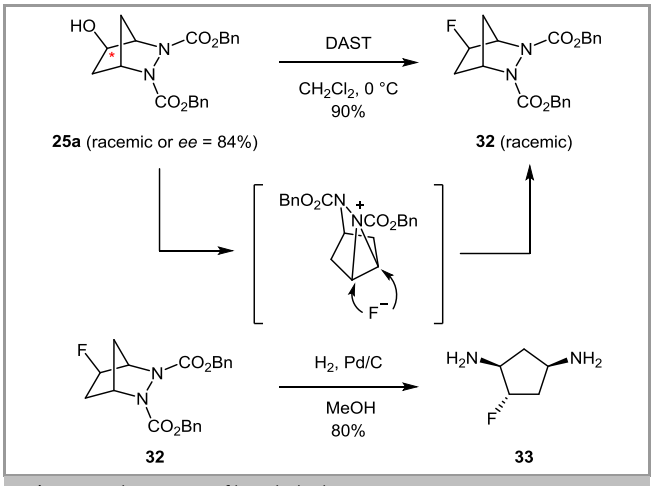


Scheme 12 Synthesis of diaminodiol **31**

4.2 Access to fluorinated 1,3-*cis*-diaminocyclopentanes

The introduction of a fluorine atom onto organic compounds can significantly influence their physicochemical properties and is nowadays considered as a classical strategy to tune their biological activities.[40] In this context, we naturally became interested in the possibility to develop practical ways to prepare fluorine-containing cyclic *cis*-1,3-diamines in an enantio- and/or diastereoselective manner by using the reductive cleavage of hydrazine as a key step. One of the objectives was to tune the acidity of the amines in order to modify their affinity with RNA (see infra), another one was to use fluorinated diamines as tools for ^{19}F NMR.

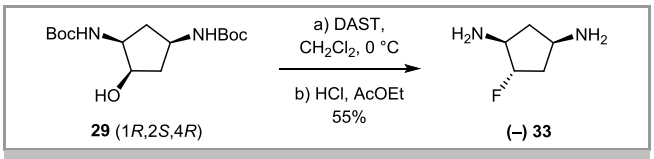
Fluorinated 1,3-*cis*-diaminocyclopentanes were successfully synthesized starting from racemic or enantioenriched hydroxylated bicyclic hydrazine **25a**.[39] Treatment of this compound with N,N-diethylaminosulfur trifluoride (DAST) led to the formation of the corresponding fluorinated bicycle **32**, which was isolated as a single diastereomer (Scheme 13). The formation of a transient aziridinium was taken into account to explain the retention of the relative configuration observed after the reaction. The formation of this transient *meso* species was confirmed when a racemic product was isolated starting from the enantioenriched hydrazine (*ee* = 84%, Scheme 13). N-N bond cleavage of hydrazine **rac-32** ultimately afforded the racemic fluorinated *cis*-1,3-diamine **33** in 80% yield (Scheme 13).



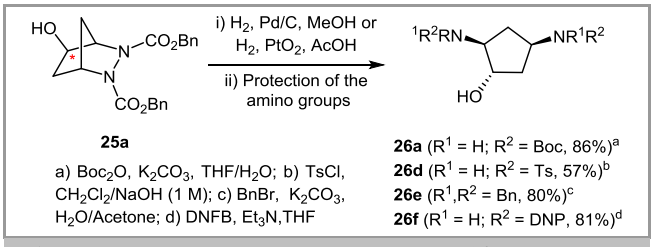
Scheme 13 Fluorination of bicyclic hydrazine **25a**

With the aim to avoid the racemisation process and to isolate enantioenriched product (–)-**33**, the all-*cis* Boc protected amino-alcohol **29** (non-racemic compound with a 1*R*,2*S*,4*R* absolute configuration) was next submitted to the fluorination reaction with DAST. This step proceeded with a complete inversion of the configuration at the carbon atom bearing the leaving group,[39] any anchimeric participation of the nitrogen protecting group being precluded by the *cis* relationship existing between the -OH and -NHBoc functions (Scheme 14).

An alternative synthetic pathway was envisaged to access an all-*cis* enantioenriched fluorinated compound. The hydroxylated bicyclic hydrazine **25a** was reductively cleaved and the two amines were protected with four different protective groups (Scheme 15).

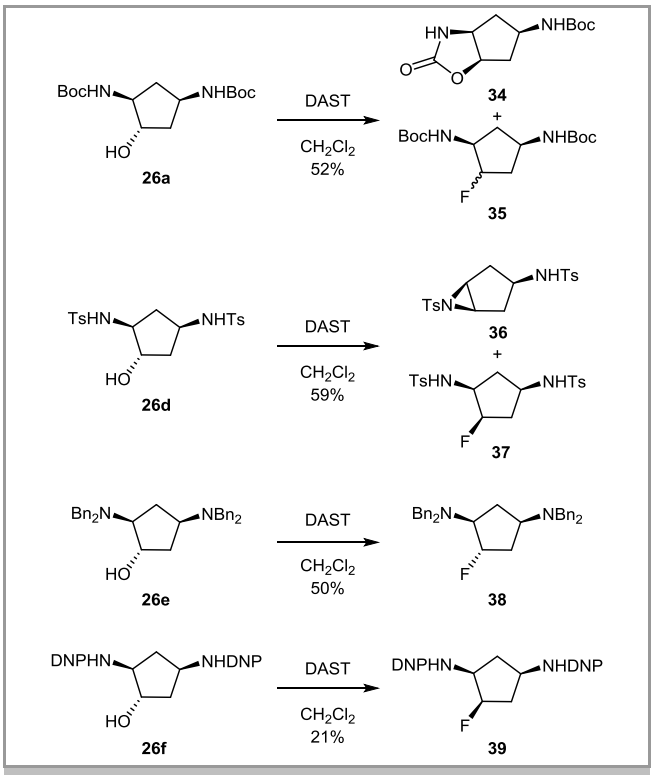


Scheme 14 Synthesis of enantioenriched fluorinated 1,3-*cis*-diaminocyclopentane (–)-**33**.



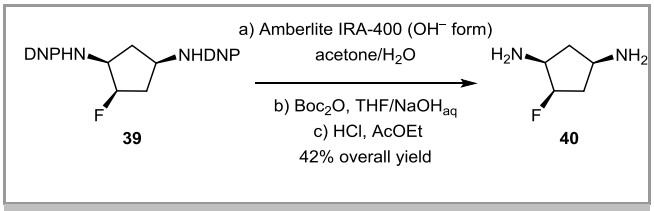
Scheme 15 Synthesis of protected diaminoalcohols **26a,d-f**

The fluorination of these derivatives was then studied. The nature of the protective groups on the nitrogen atoms was found to significantly influence the outcome of this transformation. Indeed, Boc and tosyl groups actively participated to the reaction, leading to the formation of oxazolidinone **34** and *meso* aziridine **36** as the major products (Scheme 16). On the contrary, tetrabenzyl derivative **26e** was converted into the corresponding racemic *trans* fluorinated compound **38** through a transient *meso* aziridinium intermediate (Scheme 16). Only 2,4-dinitrophenyl (DNP) groups allowed the fluorination reaction to proceed with full inversion of configuration at the stereocenter bearing the leaving group. The enantioenriched compound **39** could be obtained in this case, albeit in a low 21% yield (Scheme 16).



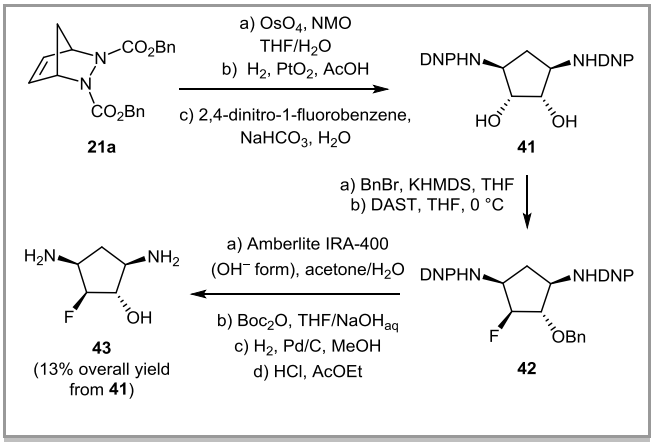
Scheme 16 Fluorination reactions of differently-protected cyclic diamino compounds.

A sequence of deprotection/protection/deprotection was lastly required to isolate the pure fluorinated diamino compound **40** (hydrochloride form) starting from compound **39** (Scheme 17).[39]



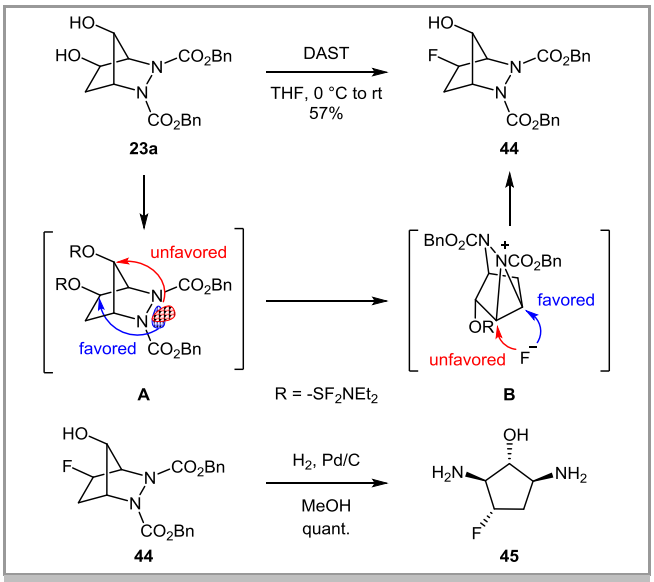
Scheme 17 Access to pure fluorinated free amino compound **40**

Fluorinated cyclic cis-1,3-diamines bearing a hydroxyl group at different positions can also be prepared starting from the bicyclic hydrazines.[39] A 1,2,3,4-tetrasubstituted cyclopentane could indeed be synthesized via the dihydroxylation of compound **21a**, followed by a reductive cleavage of its hydrazine moiety and subsequent protection of the resulting free amines with DNP groups (Scheme 18). O-monobenzylation of diol **41**, and consequent reaction with DAST delivered the protected fluorinated tetrasubstituted cyclopentane **42** as a single diastereomer (Scheme 18). A final sequence of deprotection/protection/deprotection reactions enabled to obtain product **43** in its hydrochloride form (Scheme 18).



Scheme 18 Synthesis of 1,2,3,4-tetrasubstituted cyclopentane **43**

A 1,2,4,5-tetrasubstituted cyclopentane was finally obtained starting from bicycic hydrazine **23a**. This compound was prepared *via* the epoxidation of derivative **21a** and subsequent skeletal rearrangement as described in section 4.1 (Scheme 6). The treatment of hydrazine **23a** with DAST delivered product **44** in a chemo- and diastereoselective manner. To explain the remarkable selectivity of the fluorination reaction, a mechanism involving the activation of both hydroxyl groups was postulated. The restricted conformational freedom of the carbamates caused by the presence of the hydroxymethylene group was supposed to force the nitrogen lone pairs of the hydrazine to be either in a pseudo equatorial or in a pseudo *endo* axial position (intermediate A, Scheme 19). Stereoelectronic effects were therefore assumed to favor the departure of the leaving group located on the ethylene bridge. Steric hindrance generated by the second activated hydroxyl group (intermediate B, Scheme 19) was finally invoked to account for the excellent regioselectivity of the final ring-opening step (Scheme 19). Control experiments were realized to support the proposed mechanism.[39]

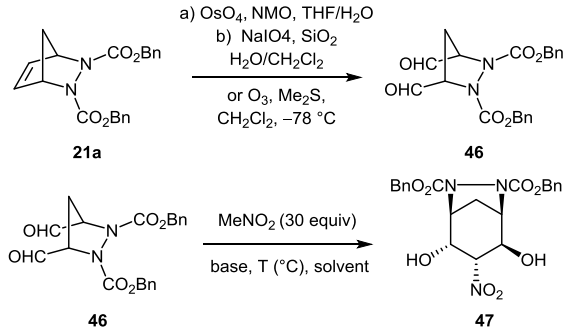


Scheme 19 Synthesis of 1,2,4,5-tetrasubstituted cyclopentane **45**

In the last synthetic step, compound **44** was successfully submitted to hydrogenolysis to isolate fluorinated cyclic *cis*-1,3-diamine **45** in quantitative yield (Scheme 19).

4.3 Synthesis of *cis*-1,3-diaminocyclohexitols

The synthetic potential of diazabicyclo[2.2.1] heptane scaffold is not limited to the synthesis of 5-membered rings. It is indeed possible to access to 6-membered rings by a one atom homologation playing with the reactivity of the double bond. Recently, the versatile reactivity of hydrazine **21a** has been exploited in our laboratory to access various *cis*-1,3-diaminocyclohexitols.[41] Bicyclic compound **21a** was either submitted to ozonolysis or engaged in a two-step dihydroxylation–oxidative cleavage sequence to form *meso* dialdehyde **46** in a straightforward fashion (Scheme 20). The cyclization of this derivative by treatment with nitromethane was then investigated. Different conditions were screened to perform the double nitroaldol condensation. No reaction was observed in the presence of NaOH (Scheme 20). The desired product **47** could be formed in low yield when using sodium alkoxide (Scheme 20). In this case, the basic conditions were supposed to promote a cleavage of the benzylcarbamates, as traces of benzyl alcohol were detected by ^{1}H NMR of the crude reaction mixture. Compound **47** was finally obtained in a high yield when running the reaction with trimethylamine,[41] and using nitromethane as the solvent. Interestingly, cyclic product **47** was formed as a single diastereomer, although six possible isomers could theoretically be obtained through the condensation. The ring-homologation of bicyclic hydrazine **21a** thus enabled to control the relative configuration of five contiguous stereogenic centers in a single operation. The relative configuration of derivative **47** was determined through NMR studies (^{1}H and ^{13}C experiments, correlation and NOE spectroscopy).[41] To explain the observed selectivity, dialdehyde **46** was supposed to react by keeping a Cs symmetrical conformation, and the cyclisation was thought to proceed under thermodynamic control.

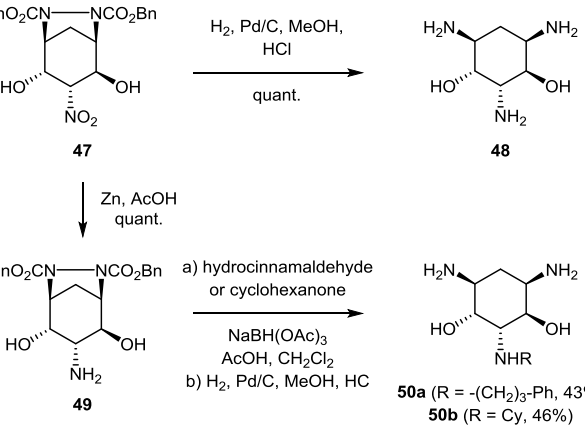


Base	Solvent	T (°C)	yield (%)[a]
2M NaOH (0.04 equiv)	MeOH/H_2O	10	/
MeONa (0.1 equiv)	MeOH	rt	26
EtONa	EtOH	rt	16
Et_3N (0.15 equiv)	$MeNO_2$	rt	78

a) overall yield from compound **21a**

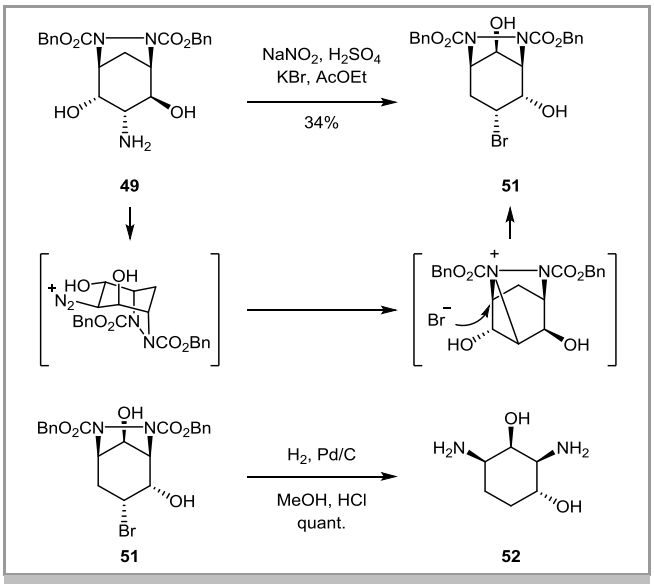
Scheme 20 Nitroaldol condensation reactions

Hydrogenolysis under acidic conditions led to the full reduction of bicycle **47**, and delivered *cis*-1,3-diaminocyclohexitol **48** in a quantitative yield (Scheme 21). The nitro function of derivative **47** could also be reduced in a selective manner by treatment with zinc in acetic acid (Scheme 21). Reductive aminations with aldehydes or ketones could be used to functionalize product **49**. The N-N hydrazine bond of the resulting bicycles was finally cleaved to obtain N-substituted triaminocyclohexitols **50a,b** in a good overall yield (Scheme 21).



Scheme 21 Functionalization of bicyclic hydrazine **47**

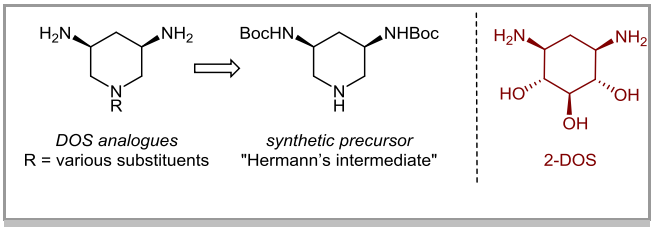
Acid-catalyzed skeletal rearrangements were also investigated starting from hydrazine **47**.[41] Despite our many efforts, the expected hydroxylated product could never been obtained. However, a brominated adduct was isolated when the reaction was conducted in the presence of a bromine source (Scheme 22). The formation of a transient azetidinium followed by a selective ring opening was proposed to explain the formation of the rearranged product **51**. Hydrogenolysis of this derivative finally afforded diamine **52** in a quantitative yield as its hydrochloride salt (Scheme 22).



Scheme 22 Synthesis and reactivity of brominated derivative **51**

4.4 Formation of cyclic *cis*-3,5-diamino-piperidines

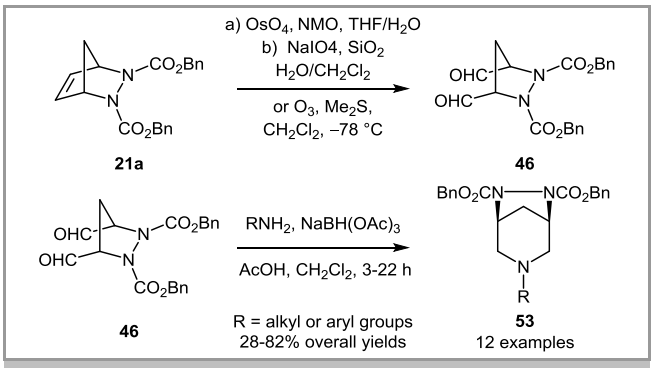
Meso cis-3,5-diaminopiperidines can be considered as valuable building blocks for the preparation of 2-deoxystreptamine (DOS) analogues since libraries of compounds can rapidly be prepared simply by functionalizing the piperidine nitrogen atom as reported by Hermann and co-workers (Scheme 23).[42]



Scheme 23 Importance of the *meso cis*-3,5-diaminopiperidine scaffold

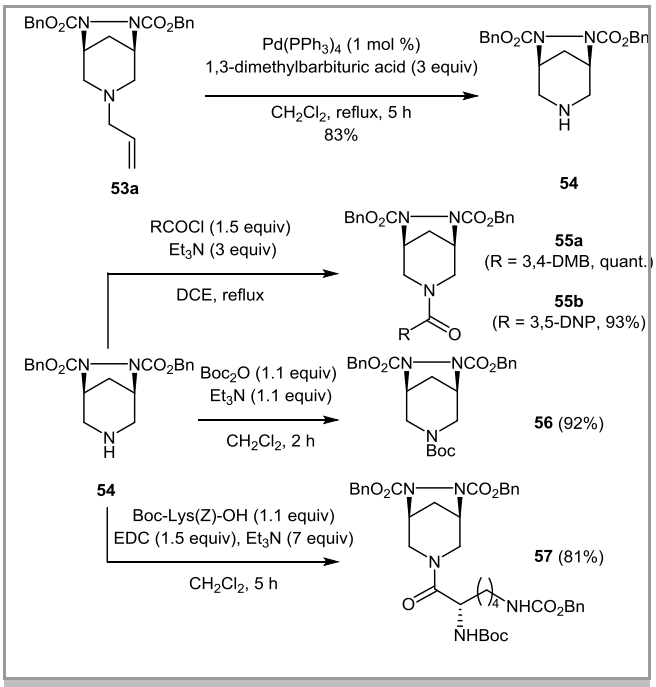
However, previously reported syntheses of this class of compounds rely on tedious high-pressure hydrogenation steps. In addition, the selective derivatization of the piperidine nitrogen atom in the presence of *cis*-3,5-diamino groups also revealed to be problematic under certain experimental conditions. In our ongoing work on the preparation of cyclic *cis*-1,3 diamines, we considered the possibility overcome these synthetic limitations by exploiting the reactivity of bicyclic hydrazines to develop a new general approach to access N-substituted *cis*-3,5-diaminopiperidines.

Starting from hydrazine **21a**, dihydroxylation and oxidative cleavage (or alternatively ozonolysis) were again preformed to prepare the relatively unstable key dialdehyde **46**. This compound was then directly submitted to a series of double reductive amination reactions in the presence of various amine derivatives (Scheme 24).[43] Aliphatic or aromatic amines readily reacted in the presence of $NaBH(OAc)_3$ under acidic reaction conditions. Diamines could also be engaged in this transformation. Remarkably, this method allowed the introduction of a stereocenter α to the piperidine nitrogen without racemization.[43]



Scheme 24 Development of double reductive amination reactions

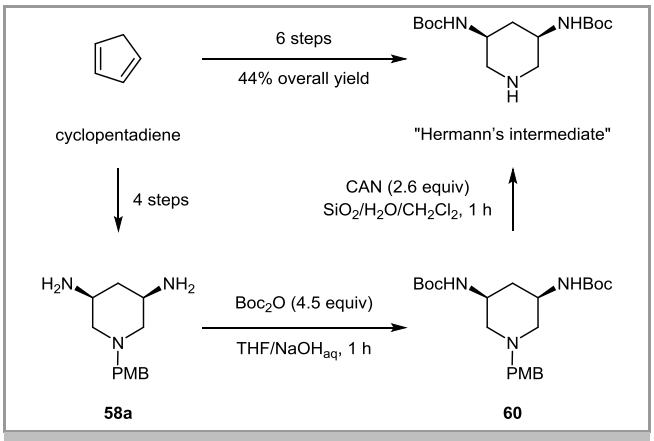
With the aim to access acylated triazabicyclo[3,2,1]octanes, product **53a**, showing an allylic substituent at the piperidine nitrogen atom, was treated with palladium-tetrakis(triphenylphosphine) to form a NH-free bicyclic heterocycle (**54**, Scheme 25). This compound smoothly underwent acylation, peptidic coupling, or carbamoylation to afford the corresponding N-acylated products **55a,b**, **56** and **57** in high yields (Scheme 25).



Scheme 25 Synthesis of acylated triazabicyclo[3,2,1]octanes

Differently functionalized bicyclic hydrazines **53**, **55**, and **56** were successfully submitted to hydrogenolysis in the presence of Pd- or Pt-based catalysts to generate the final *cis*-3,5-diaminopiperidines **58a,f** and **59a,b** in good to quantitative yields (Scheme 26). In most cases, the reaction conditions had to be tuned in order to avoid catalyst poisoning or to prevent over-reduction of the (hetero)aromatic rings that frequently decorate the synthesized molecules.

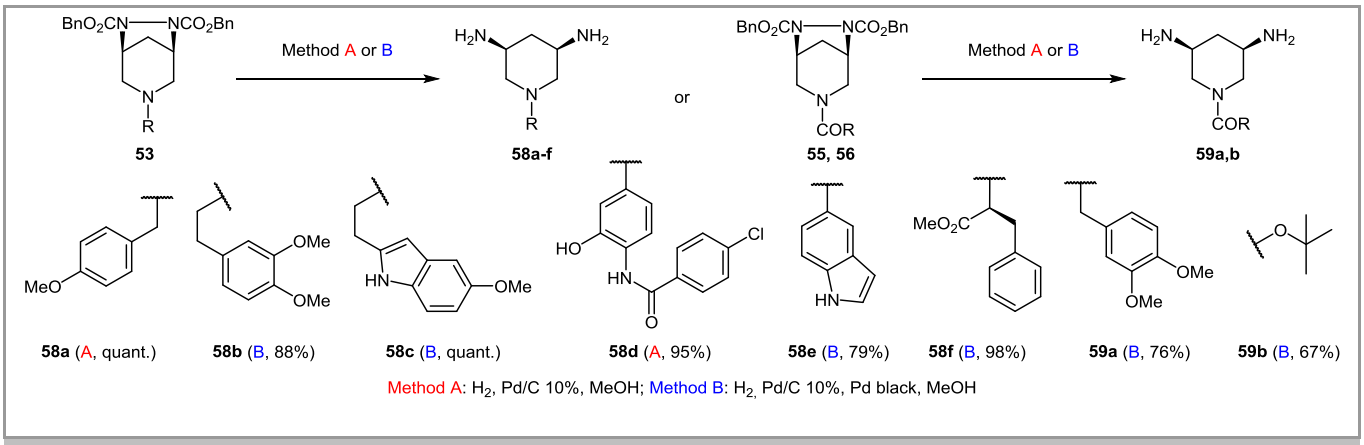
Our strategy could finally be used to prepare Hermann's intermediate,[43] without any high pressure reduction step (Scheme 27). The free NH_2- groups of product **58a** were indeed easily protected by treatment with Boc_2O. The resulting derivative **60** reacted with CAN in the last step of the synthetic sequence to yield the desired Boc-protected *cis*-3,5-diaminopiperidine in 58% yield (44% overall yield from cyclopentadiene, Scheme 27).



Scheme 27 Synthesis of Hermann's intermediate

5 Applications of cyclic cis-1,3-diamines

All the synthetic transformations of bicyclic hydrazines described above enable a large coverage of chemical space around the cyclic 1,3 diamine motif. As briefly explained in section 2, this motif can be found in several classes of compounds possessing interesting biological properties. Among them, we focused our attention on aminoglycosides. The cyclic *cis*-1,3 diamines synthesized in our laboratory are structural mimetics of 2-deoxystreptamine (DOS), the central core of aminoglycosides. These natural products can be viewed as valuable "RNA friendly" molecules.



Scheme 26 Examples of hydrogenolysis of hydrazines **53**, **55** and **56**.

RNA is an essential biomolecule which is involved in the regulation of many cell processes.[44] As a result, RNA is nowadays considered as an attractive target in drug discovery.[45] In this context, the development of small molecules capable of binding specific RNA structures represent a major challenge for organic chemists. We therefore decided to explore the possibility to use our compounds as building blocks for the design of new RNA ligands and probes.

5.1 Small molecular RNA binders

Functional sites within the genomic RNA of HIV-1 have emerged as promising targets for new antiviral approaches.[46] $tRNA^{Lys3}$ is the natural primer of HIV-1. In virions, $tRNA^{Lys3}$ interacts with the genomic RNA and forms a complex that recruits the reverse transcriptase, the enzyme responsible for viral replication.

We become interested in identifying small compounds capable of interacting with $tRNA^{Lys3}$ in order inhibit the reverse-transcription initiation complex.[47]However, the rational design of selective binders of $tRNA^{Lys3}$ is a difficult task since its shape is very similar to that of other RNA molecules. This is reflected in the fact that only low-affinity structure-specific peptide ligands could be identified by following a combinatorial approach.[48]

Taking advantage of well-known crystallographic[49] and NMR data,[50] our group undertook a fragment based approach[51] to access new ligands of $tRNA^{Lys3}$. A NMR spectroscopic screening was performed with a focused library of organic compounds (prepared in-house or commercially available).[52] Binding of these compounds to the target induced detectable changes in the 1D NMR spectra of $tRNA^{Lys3}$ (imino region, δ=10–15 ppm), and allowed us to identify racemic cyclic cis-1,3-diamine **61** (DACP) and kynuramine (**62**) as new RNA ligands (Figure 6).

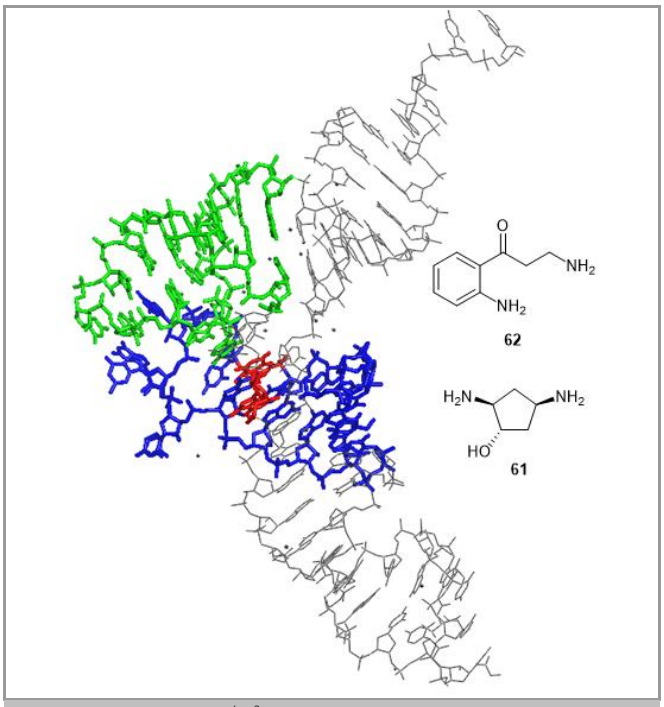


Figure 6 Mapping on $tRNA^{Lys\,3}$ structure (PDB code 1FIR) of the binding zones of compound **61** (Blue, T-arm) and compound **62** (green, D-arm). G15 and m7G46 are depicted in red.

2D HMQC experiments with ^{15}N-labeled tRNA allowed us to determine the NMR chemical shift mapping of the two ligands on $tRNA^{Lys3}$. At least two binding sites were observed for compound **61** (one in the T-stem and the other near the D-arm, the binding to the D arm being observed at higher concentration of the ligand). On the contrary, derivative **62** was found to specifically interact with the D-stem (Figure 6). Two nucleotides (G15 and m7G46) resulted to be affected by the binding of both compounds (Figure 6). NMR titrations were employed to calculate the apparent dissociation constants of the new RNA ligands (2 mM and 5 mM respectively).

A qualitative specificity study was also realized by analyzing the NMR spectroscopic footprints of compounds **61** and **62** with other nucleotide sequences ($tRNA_f^{Met}$ and $tRNA_m^{Met}$ of *E. coli*). Interestingly, derivative **62** showed some sequence-specific binding.[52] This result encouraged us to investigate the affinity between $tRNA^{Lys3}$ and various kynuramine analogues. Despite

showing a close resemblance with the structure of derivative **62**, commercially available compounds **63-68** (Figure 7) were not detected to bind to tRNA^{Lys3} in chemical shift perturbations (CSP) experiments.

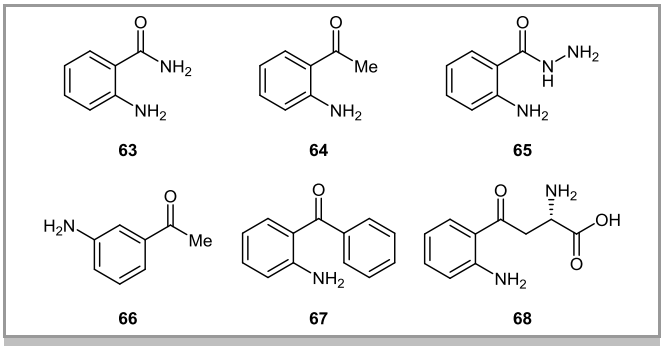
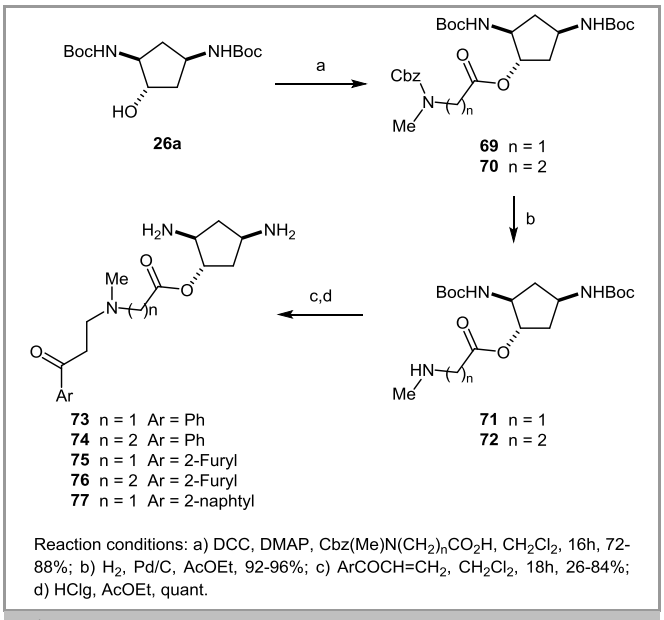


Figure 7 Commercially available analogues of kynuramine **62** that do not bind to tRNA^{Lys3}

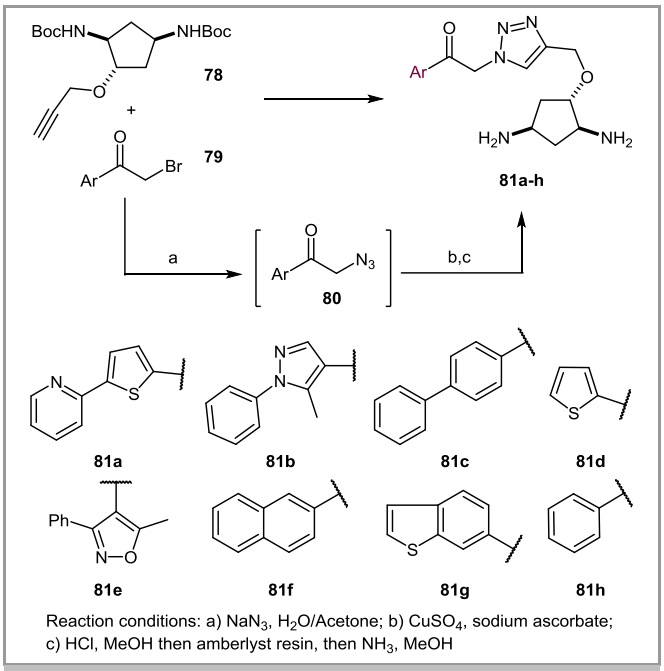
The covalent linkage of kynuramine-like fragments to diamine-containing compound **61** was investigated next in order to improve the binding affinity of our RNA ligands. Short aminoester were first used as linkers with the aim to design D-arm binders.[52] Five representative linked products (**73-77**) were prepared in four steps starting from cyclic *cis*-1,3-diamine **26a** (Scheme 28).

Under stoichiometric conditions, clear CPS was observed when comparing the NMR footprints of ligands **73**, **74** and **77** on the target tRNA^{Lys3} and the 2D TROSY spectra of ^{15}N-labeled tRNA.[52] The new binders also showed a reinforced selectivity for the D-arm of tRNA^{Lys3}, although interactions with the T-stem were observed at higher RNA:ligand ratios. The dissociation constant of derivative **77** was estimated tacking advantage of its florescence properties, and a value in the micromolar range could be determined (K_d = 8 μM). The considerably improved affinity and reinforced selectivity of ligand **77** in comparison with those of fragments **61** and **62** clearly demonstrated the validity of the fragment based approach for the design of new RNA binders. However, ligands **73-77** proved to have a relatively low stability as their linker arms could undergo retro-Michael reactions.



Scheme 28 Connection of kynuramine-like fragments and cyclic *cis*-1,3-diamine compounds with short aminoester linkers.

The linkage strategy was reinvestigated with 3+2 cycloaddition reaction for connecting the fragments through a 1,4-triazole motif. A second series of RNA binders (**81a-h**) was synthesized in a straightforward manner using a practical one-pot procedure (Scheme 29). These compounds were isolated in 6% to 66% overall yield after catch-and release purification on sulfonic acid resin.[52] Binding of ligands **81a-h** to tRNA^{Lys3} was monitored by using TROSY NMR spectroscopy. Improved affinity and reinforced selectivity for the D-arm was again observed. Fluorescence binding assays revealed that the use of a 1,4-triazole-based linker afforded better RNA binders, as compounds **81a**, **81c** and **81f** showed enhanced affinity and selectivity when compared to derivative **77** (Table 1).



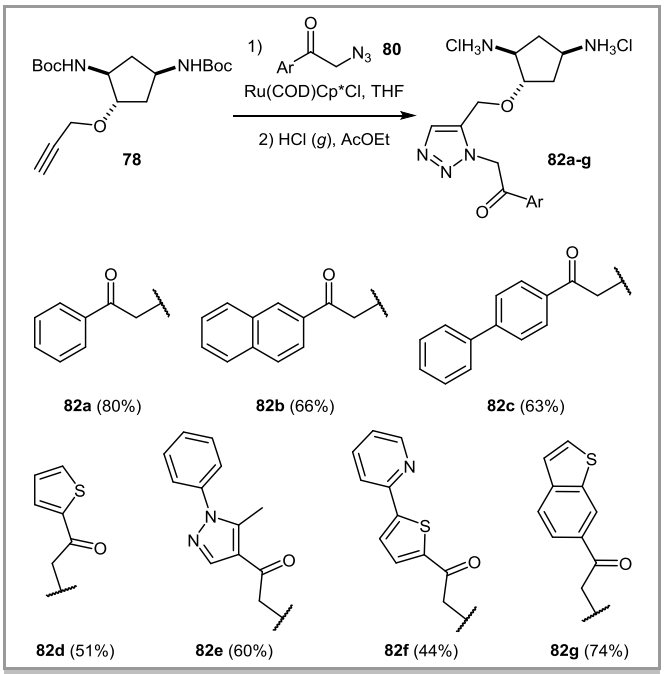
Scheme 29 Connection of kynuramine-like fragments and cyclic cis-1,3-diamine compounds with 3+2 cycloaddition reactions

The stereospecificity of the binding was also evaluated by studying the interaction of $tRNA^{Lys3}$ with the two enantiomers of compound **81f**. Both racemic or enantiomerically pure compounds **81f** binds to the same region of tRNA with similar strength (Table 1).

Table 1 Comparison of binding affinities of fragments **61**, **62** and RNA ligands **77**, **81a**, **81c**, **81f**.

Entry	Compound	K_d (μM)	Method	Binding site
1	**61**	1000	NMR	T arm, D arm
2	**62**	5000	NMR	D arm
3	**77**	8	Fluorescence	D arm, then T arm
4	**81a**	6	Fluorescence	D arm
5	**81c**	1.2	Fluorescence	D arm
6	**81f**	1.8	Fluorescence	D arm
7	(2*R*)-**81f**	1.2	Fluorescence	D arm
8	(2*S*)-**81f**	1.1	Fluorescence	D arm

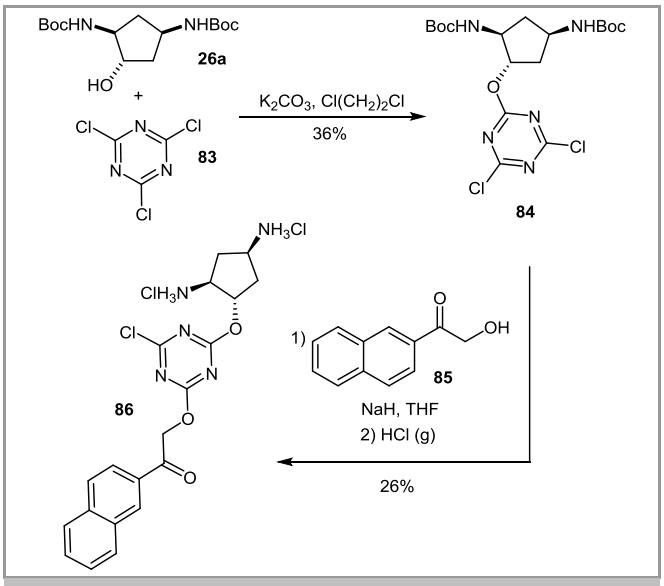
To gain a deeper insight into the influence of the linker on the binding properties of our ligands, we envisioned the possibility to replace the 1,4-triazole moiety with its 1,5- isomer, and thus shortening the distance between the two fragments without modifying the chemical nature nor the size of the linking arm.
A ruthenium-catalyzed azide-alkyne cycloaddition reaction (RuAAC),[53] was successfully used to synthesize the desired compounds starting form fragments **78** and **80** (Scheme 30).[54]
Fluorescence-quenching assays were employed to estimate the dissociation constants of ligands **82a-g** to $tRNA^{Lys3}$. Altering the orientation of the two fragments was found to entail a modest increase of the K_d values.[52,54] However, selectivity was lost as NMR studies clearly showed that all ligands could bind to both the T and D stem of $tRNA^{Lys3}$.[54]



Scheme 30 Connection of kynuramine-like fragments and cyclic cis-1,3-diamine compounds with RuAAC reactions.

Interestingly, the binding interactions of ligand **82b** with the T stem differed from those observed for compound **77**. Since the interaction with the T stem was not detected in the presence of compound **81f**, showing a 1,4 triazole moiety,[54] we concluded that rigid linkers capable of imposing a long distance between the two fragments should prove essential in the design of site selective binders.

To confirm this assumption we finally synthesized a ligand incorporating a triazine linker, a good mimic of the 1,4-triazole motif (Scheme 31).[54]



Scheme 31 Synthesis of ligand **86** incorporating a triazine linker

Cyclic *cis*-1,3-diamine **26a** and α-hydroxy-naphtylacetophenone **85** were chosen as aliphatic and aromatic fragments, and could be connected to cyanuric chloride **83** through successive substitution reactions (Scheme 31). As depicted by NMR TROSY experiments, the resulting triazine-containing ligand **86** proved to selectively interact with the D stem of $tRNA^{Lys3}$ (K_d = 1.4 μM).[54] This last result allowed as to unequivocally confirm that, together with the nature of the connected fragments, the linker characteristics play a key role in controlling the binding selectivity of our ligands and have to be taken into account when designing new RNA binders.

5.2 Fluorinated 1,3 diamino cyclopentanes as NMR probes

The use of cyclic 1,3 diamines as key components for the design of RNA binders being validated, we then explored the possibility to use fluorinated diaminocyclopentanes (Figure 9) as chiral sensitive NMR probes for studying RNA structures and dynamics as well as spy reporters in binding assays.

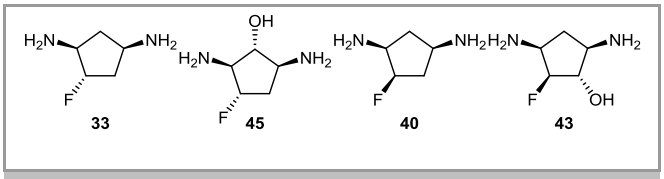


Figure 8 Fluorinated NMR probes

^{19}F NMR is indeed known to be very sensitive, and the fluorine shielding parameters are also known to strongly rely on local environment. The interaction of compound **33** (racemic or enantioenriched) with tRNA^{Lys3} was investigated first by ^{19}F NMR. Because compound **33** is only a millimolar RNA binder, the exchange between the free and bound forms was confirmed to be in the fast regime on the NMR timescale. Thus, each enantiomer led to a single ^{19}F NMR signal. However, although the two enantiomers bind to tRNA^{Lys3} with the same dissociation constant (around 1 mM), and on the same binding site,[55] they form diastereomeric complexes with the chiral RNA. As a consequence, two different averaged resonance shifts of the ^{19}F NMR signal could be detected for each enantiomer of derivative **33** in the presence of tRNA^{Lys3}. The use of racemic derivative **33** led to a complete NMR resolution with a split of 0.5 ppm (Figure 9). The interaction of racemic compounds **45**, **40** and **43** (Figure 8) with tRNA^{Lys3} was then investigated under similar conditions. Shifts and/or resolution of the fluorine resonances were observed for all compounds but with lower resolution.[55]

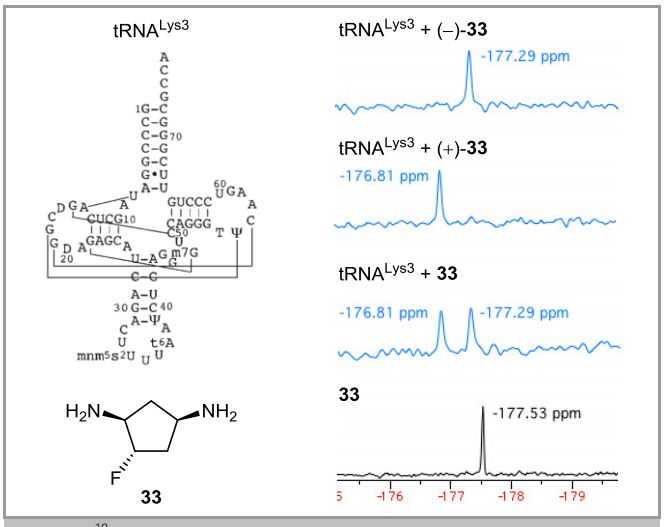


Figure 9 ^{19}F-NMR of fluorinated diaminocyclopentane **33** alone (black) and with tRNA^{Lys3} (tRNA/ ligand ratio = 16:1, blue). The samples were dissolved in a 10 mM KPO_4 buffer (pH = 6.5) and the spectra were registered at 293K.

Interestingly, a smaller signal splitting was detected by fluorine NMR when the racemic probe **33** was mixed with a short oligonucleotide sequence mimicking the T-arm hairpin of tRNA^{Lys3}, and no splitting was observed in the presence of the tRNA^{Lys3} D-arm sequence, highlighting the sensitivity of fluorinated probes to the tertiary structure of RNA. Sensitivity to secondary structure was also confirmed by thermal denaturation experiments. [55]

Ligand-based fluorine NMR screening is a powerful method for binding constant measurements, popularized by Dalvit and co-workers.[56] As 1,3 diamino cyclopentanes could mimic DOS, the central core of aminoglycosides, we assessed compound **33** as a fluorinated reporter against a 23-nucleotide hairpin mimicking the decoding A-site of 16S ribosomal RNA, the natural target of aminoglycosides.[57] Competition binding experiments were conducted by monitoring the ^{19}F chemical shift of the reporter. As exemplified in Figure 10 with neamine, chemical shift variation as well as splitting modification could be observed by increasing competitor concentration, leading to the dissociation constant measurement of the non-fluorinated ligand. Interestingly, observation of a splitting signal variation ensures that chemical shift variations are the direct consequence of the displacement of the racemic probe bound to its chiral target.

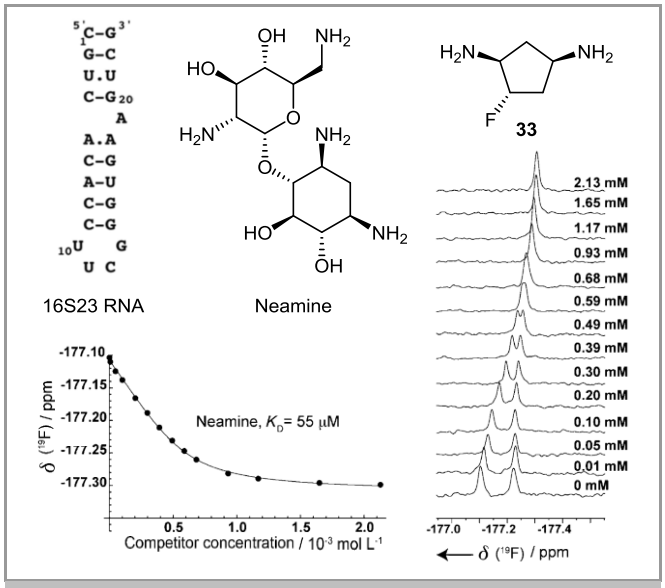


Figure 10 Competition experiments towards 16S23 RNA using compound **33** as the spy probe and neamine as a ligand : ^{19}F NMR spectra of compound **33** (0.7 mM) mixed to 16S23 RNA (0.3 mM) in KPO_4 buffer pH 6.5 containing 50 mM KCl, at 293°K, with increasing concentration neamine.

6 Concluding remarks

In this account article, we have described our efforts in setting up a general access to cyclic *cis*-1,3-diamines. We have shown that bicyclic hydrazines, easily available at a multigram scale, can lead to a large variety of five- and six-membered rings incorporating the *cis*-1,3-diamine motif in a few synthetic steps. All the transformations can be conducted on a large scale, and delivers intermediates and final substituted diamines in a regio- and stereoselective fashion. This systematic chemical space exploration around the cyclic *cis*-1,3-diamine motif provides numerous valuable fragments and building blocks. We have illustrated the interest of this strategy in the field of RNA binders, with the design of ligands and probes. We have no doubt that potential applications of cyclic *cis*-1,3-diamines are not restricted to this field, and we hope that our work will contribute to further developments in other areas of research.

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Biosketches

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