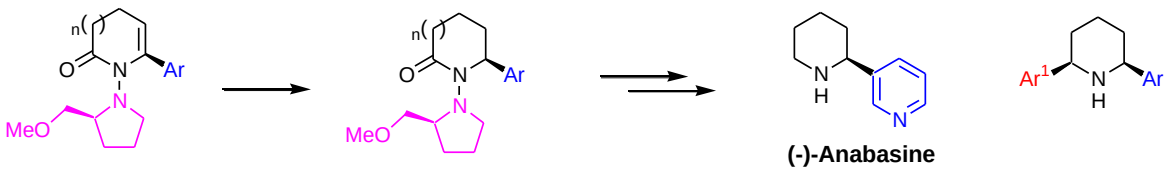
Asymmetric synthesis of α to nitrogen substituted azaheterocycles. Application to the total synthesis of *S*-(-)-Anabasine.

Romain Sallio,[a,b] Stéphane Lebrun,[a,b] Nicolas Gigant,[c] Isabelle Gillaizeau,[c] Eric Deniau[a,b,*]

[a]*Université Lille Nord de France, 59000 Lille, France*
[b]*Université Lille 1, UCCS-CCM-CASECO UMR 8181 CNRS, Bâtiment C3(2), F-59655 Villeneuve d'Ascq Cedex, France.*
[c]*Université d'Orléans, Institut de Chimie Organique et Analytique (ICOA), UMR 7311, Rue de Chartres, F-45067 Orléans Cedex 2, France.*

*Eric.Deniau@univ-lille1.fr

Abstract: Chiral azaheterocycles substituted α to nitrogen represent the core unit of a wide range of alkaloids and biologically active compounds. They also play an important role as key targets for the pharmaceutical industry. Consequently, the stereocontrol of carbon centers embedded in these azaheterocycles is a permanent synthetic task for organic chemists. In this regard, we have developed an alternative and conceptually new synthetic approach to a variety of 2-heteroaryl cyclic amines and 6-aryl piperidin-2-ones which is based upon the asymmetric reduction of chiral endocyclic enenydrazides bearing a (*S*)-methylprolinol chiral auxiliary (SMP). This new synthetic methodology has then been illustrated by the total synthesis of *S*-(-)-Anabasine and the stereoselective synthesis of *cis*-2,6-diarylated piperidines in high yields and high level of enantioselectivity.



Keywords: chiral enehydrazides, enol phosphates, cross-coupling reactions, asymmetric hydrogenation, (*S*)-(-)-Anabasine, *cis*-2,6-diarylated piperidines

Introduction

Simple cyclic amines like piperidines or azepines for example have been the target of many synthetic chemists because of these nitrogen-containing compounds are among the most ubiquitous heterocycles in nature with a wide spectrum of potential biological activities. [1] Indeed this type of framework is frequently found both in alkaloids and “privileged structures” for medicinal agents and no fewer than 33 pyrrolidine or piperidine derivatives were on the top 200 prescription list of drugs in 2010 in the US market. [2] Simple enantiopure 2-heteroaryl cyclic amines have become attractive scaffolds. They exhibit significant biological activities and have been recently employed in the design of new pharmacophores with therapeutical potential pathologies and representative examples are drawn in Figure 1. For instance, these scaffolds are present in the natural products (-)-nicotine **I** or (-)-anabasine **II,** which are found in the Tree Tobacco and reported as nicotinic acetylcholine agonists [3] In addition, the benzofurane derivative **III** displays high affinity ligands for the a4b2 nAChR, [4] and azepane framework **IV** has been recently reported as prophylactic or therapeutic agent for cancer. [5]

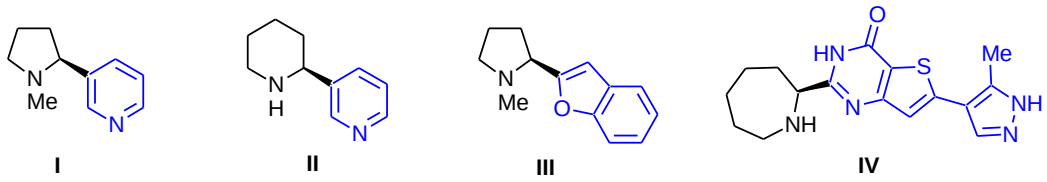
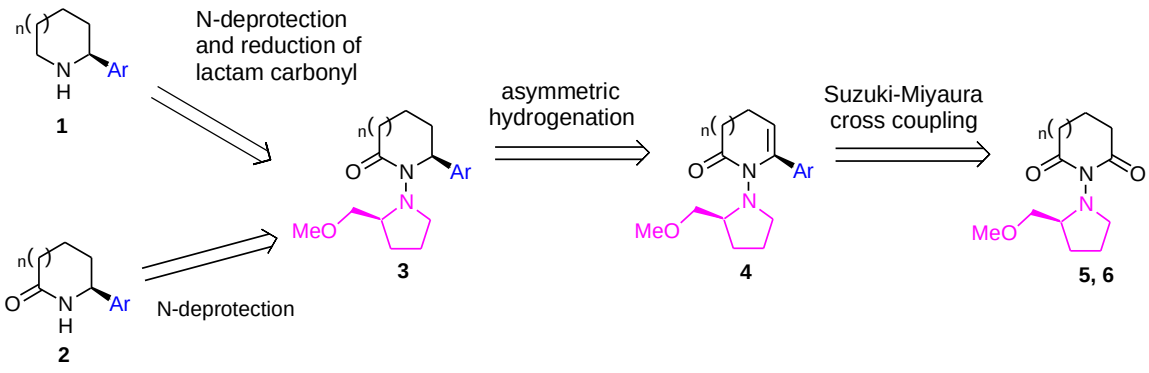


Figure 1. Examples of synthetic pharmacologically active 2-heteroaryl cyclic amines (**I-IV**).

Consequently, the important bioactivities of these compounds have stimulated the development of new synthetic approaches and considerable efforts have been mainly devoted to the enantioselective preparation of 2-heteroarylated cyclic amines and *cis*-2,6-dialkylated piperidines. [6] Existing approaches for synthesizing cyclic amines with asymmetric centers in C2 position are often and mainly based on one the following processes as key step: ring-closed metathesis with disubstituted branches linked to a chiral amine, [7] asymmetric direct α-functionalization of the corresponding saturated cyclic amines, [2] asymmetric hydrogenation [8] or allylboration [9] of cyclic imines, addition to pyridinium salts bearing a chiral auxiliary,[10] and catalyzed asymmetric of diethylzinc to imines. [11] Consequently, introducing a specific heteroaryl group in a stereoselective fashion thanks to a flexible synthetic method of the center alpha to nitrogen is still in demand and this study is particularly in connection with our ongoing project on the development of efficient methodologies to generate original collections of new nitrogen-containing molecules. [12] Our conceptually new synthetic methodology, which is described in the retrosynthetic Scheme 1, is mainly based on the Pd-catalyzed coupling with phosphate derivatives. Indeed we envisioned that enamides **4** would be constructed by a monovinylphosphate which would be subjected itself to Suzuki or Stille coupling reactions. Reduction of the C=C bond would be secured by asymmetric hydrogenation thanks to the (*S*)-methylprolinol chiral auxiliary (SMP). [13] Finally ultimate reductive N-N bond cleavage should give 6-substituted piperidin-2-ones **2** and reductive N-N bond cleavage with concomitant reduction of the lactam carbonyl functionality should give us the chiral cyclic amines **1**.

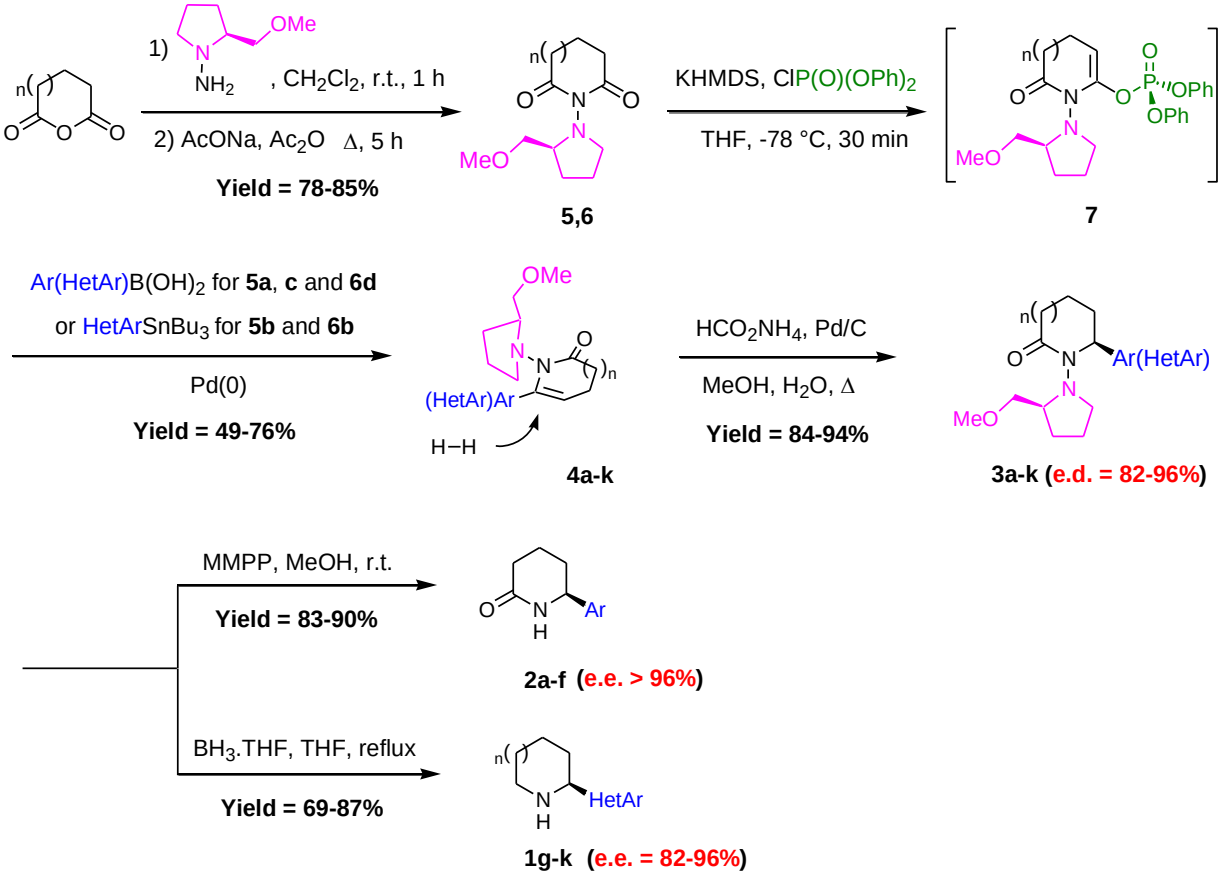


Scheme 1. Retrosynthesis strategy of chiral cyclic amines **1** and piperidones **2**.

Results and Discussion

1. Asymmetric synthesis of 2-heteroaryl cyclic amines 1 and 6-aryl piperidin-2-ones 2 :

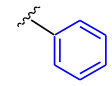
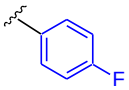
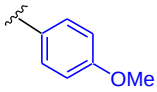
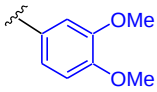
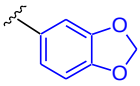
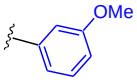
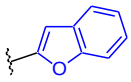
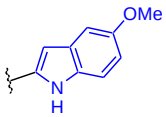
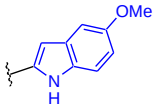
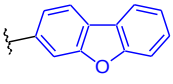
The new synthetic route, depicted in Scheme 2, required the preliminary elaboration of the chiral hydrazides **5,6**, which were easily prepared by condensation between the corresponding cyclic anhydride and (S)-AminoMethylProlinol (SAMP). [14] Treatment of protected imides **5,6** with KHMDS in the presence of diphenylchlorophosphate in THF gave us the monovinylphosphate **7** which was carried over to the next step without further purification after traditional work-up. The desired enamides **4a-k** were obtained in good yields over two steps by applying traditional Stille or Suzuki-Miyaura coupling conditions. Indeed the Stille coupling was performed with the appropriated tin reagents in the catalytic presence of $Pd(PPh)_4$ and LiCl in THF under reflux. Regarding it, the Suzuki-Miyaura reaction was achieved by using boronic acids in combination with a catalytic amount of $PdCl_2(PPh_3)_2$, aqueous Na_2CO_3 and some drops of ethanol in refluxing THF.
Based on the efficient method developed in our laboratory for the asymmetric synthesis of 5-arylmethylpirrolidin-2-ones, [15] we anticipated that a high level of diastereoselectivity in the reduction of the unsaturated compounds **4a-k** could be ensured by the use of Pd on C with ammonium formate. As can be seen from Table 1, the formation of compounds **3a-k** occurs with a high level of diastereoselection (d.e.=82-96%). According to our previously reported results, [15] one can reasonably assume that the high facial selectivity might be ascribed to the addition of hydrogen on the preferred conformer of the enehydrazides **4a-k**. Hence, antiperiplanar addition of hydrogen should occur preferentially from the less hindered face of **4a-k**, providing the diastereomers (*S*)-**3a-k** with a high level of selectivity. This hypothesis was corroborated by the comparison of the ^1H and ^{13}C NMR spectra of 6-phenylpiperidin-2-one **3a** with its previously described epimer. [16]



Scheme 2. Asymmetric synthesis of 2-heteroaryl cyclic amines **1g-k** and 6-aryl piperidin-2-ones **2a-f**

Ultimate treatment of (*S*)-**3a-k** with magnesium monoperoxyphtalate (MMPP) [17] triggered off the exclusive cleavage of the chiral appendage and this operation delivered very satisfactory yields of the enantiopure 6-arylpiperidin-2-ones (*S*)-**2a-f** free of the chiral auxiliary. The absolute configuration of **2a-f** was inferred by comparison of the specific rotation with the literature data, for example $[\alpha]_D^{20}$ –58.0 for (*S*)-**2a** (*c* 0.54 in $CHCl_3$), lit. [18] +58.2 for (*R*)-**2a** (c 1.0, $CHCl_3$). Treatment with the borane-THF complex [19] of (*S*)-**3a-k** followed by aqueous alkaline work up effected reductive N–N bond cleavage with the concomitant reduction of the lactam carbonyl group to conclude the synthesis and afford the desired enantioenriched 2-heteroaryl cyclic amines (*S*)-**1g-k**.

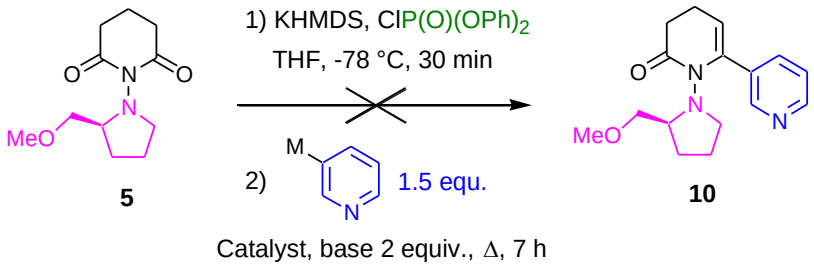
Table 1. Yields of the intermediates **3** and **4** and the 6-aryl piperidin-2-ones **2a,f** and the 2-heteroaryl cyclic amines **1g-k**.

entry	1-4	n	Het(Ar)	4	3		2		1	
				Yield (%)	Yield (%)	De[b] (%)	Yield[a] (%)	Ee[c] (%)	Yield[a] (%)	ee[c] (%)
1	**a**	1		72	89	>96	88	>96		
2	**b**	1		65	86	>96	85	>96		
3	**C**	1		70	87	>96	83	>96		
4	**d**	1		76	92	>96	90	>96		
5	**e**	1		75	81	>96	86	>96		
6	**f**	1		72	90	>96	85	>96		
7	**g**	1		54	88	86			80	86
8	**h**	1		57	**94**	82			87	82
9	**i**	1		49	85	84			69	84
10	**j**	2		67	84	>96			82	>96
11	**k**	2		72	88	>96			79	>96

[a] Isolated yields after purification by column chromatography. [b] Determined by ^{1}H NMR spectroscopy. [c] In correlation to the value of the corresponding hydrazides **3a-k** assuming that the deprotection takes place without detectable racemisation.

2. Application to the total synthesis of (–)-Anabasine 8:

With this feasible methodology in hand we then turned our attention to the total synthesis of the exemplary representative natural product (*S*)-(–)-anabasine **8** which belongs to the large group of piperidine alkaloids containing a 3-pyridyl substituent in the 2-position within the piperidine ring. Although structurally not very complex, only a limited number of stereocontrolled total syntheses of this natural product have been reported. [20] According to the previously described procedure, we first planned to synthesise the enehydrazide precursor **10** equipped with a pyridin-3-yl unit from the parent chiral imide **5** (Scheme 3). Somewhat disappointingly, imide **5** was completely unamenable to the cross-coupling reaction conditions likely to give access to the required 6-hetarylated compound **10** even after considerable experimentation with various catalysts, bases and solvents (Table 2).



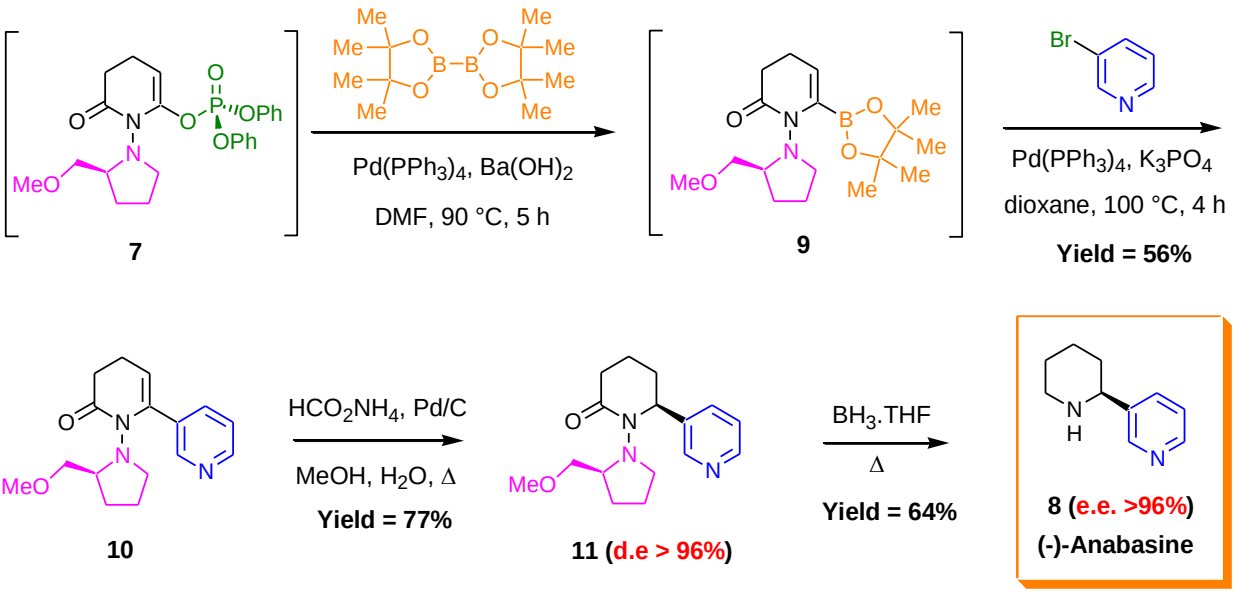
Scheme 3. Cross-coupling reaction to give 6-hetaryated compound **10**

Table 2. Conditions for the cross-coupling reaction.

Entry	M	Catalyst	Base or additive	Solvent
1	$B(OH)_2$	$Pd(PPh_3)_4$	Na_2CO_3	THF, H_2O
2	$B(OH)_2$	$PdCl_2(PPh_3)_2$	Na_2CO_3	DME, H_2O
3	$B(OH)_2$	$PdCl_2(PPh_3)_2$	Cs_2CO_3	DMF
4	$B(OH)_2$	$Pd(PPh_3)_4$	K_3PO_4	Dioxane
5	$SnBu_3$	$Pd(PPh_3)_4$	LiCl	THF

One can reasonably assume that this failure is attributable to the lack of reactivity of electron poor boronic acids towards Suzuki-Miyaura cross-coupling reactions. Consequently, we decided to adopt an alternative and complementary strategy for the installation of the pyridine-3-yl unit depicted in Scheme 4 which is based upon an umpolung of the phosphate electrophile by α-borylation. [21] Following a procedure reported by Occhiato et al., [21a] the conversion of vinyl phosphate **7** into the corresponding boronate **9** was first realized by the Pd-catalysed coupling with commercial bis(pinacolato)diboron. The best protocol was that which used $Pd(PPh_3)_4$ as a catalyst with finely powdered $Ba(OH)_2$ as a base, in anhydrous DMF at 90 °C. The reaction was complete in 5 h, furnishing aminovinyl boronate **9** which was carried over to the next step without further purification. The heterocyclic boronate **9** was then successfully engaged in a Suzuki-Miyaura cross-coupling reaction to furnish the targeted enehydrazide **10**. Catalytic hydrogenation using Pd on C with ammonium formate proceeded uneventfully to provide an excellent yield of the corresponding cyclic hydrazide (*S*,*S*)-**11**. NMR spectroscopic investigations after chromatographic separation indicated the presence of a single diastereomer, thus confirming the high level of diastereoselectivity observed in the catalytic hydrogenation of the unsaturated compound **10**.

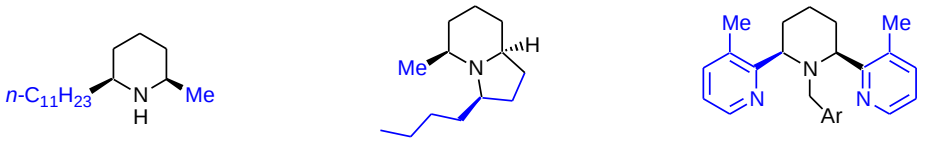
Treatment with the borane-THF complex of (*S*,*S*)-**11** effected reductive N-N bond cleavage with the concomitant reduction of the lactam carbonyl group to afford the targeted natural product **8** (Scheme 4). The absolute configuration of the stereogenic center was confirmed to be (*S*) from the sign of the specific rotation of **8,** and the enantiopurity of our synthetic (*S*)-(–)-anabasine **8** was clearly established from the optical rotation and spectroscopic data that matched with those reported for the natural product. [20b]



Scheme 4. Enantioselective total synthesis of (-)-Anabasine **8**

3. Application to the synthesis of enantiopure *cis*-2,6-diarylated piperidines 12a-d:

Cis-2,6-disubstituted compounds represent also a subclass of naturally occurring piperidines that have been extensively studied and play an important role as key targets for the pharmaceutical industry. For example, (-)-isosolenopsine A **V** which is an active ingredient in the venom of fire ants has been reported to inhibit designated neuronal nitric oxide synthase (nNOS). [22] Indolizidine alkaloid (+)-monomorine I **VI** is a trail pheromone of the Pharaoh's ant *monomorium pharaonis* L. [23] *Meso*-2,6-*cis*-diheteroarylated compounds such as **VII** have been shown to bind to chemokine receptors, including CXCR4 and CCR5, and demonstrate protective effects against infection of target cells by a human immunodeficiency virus (HIV). [24]



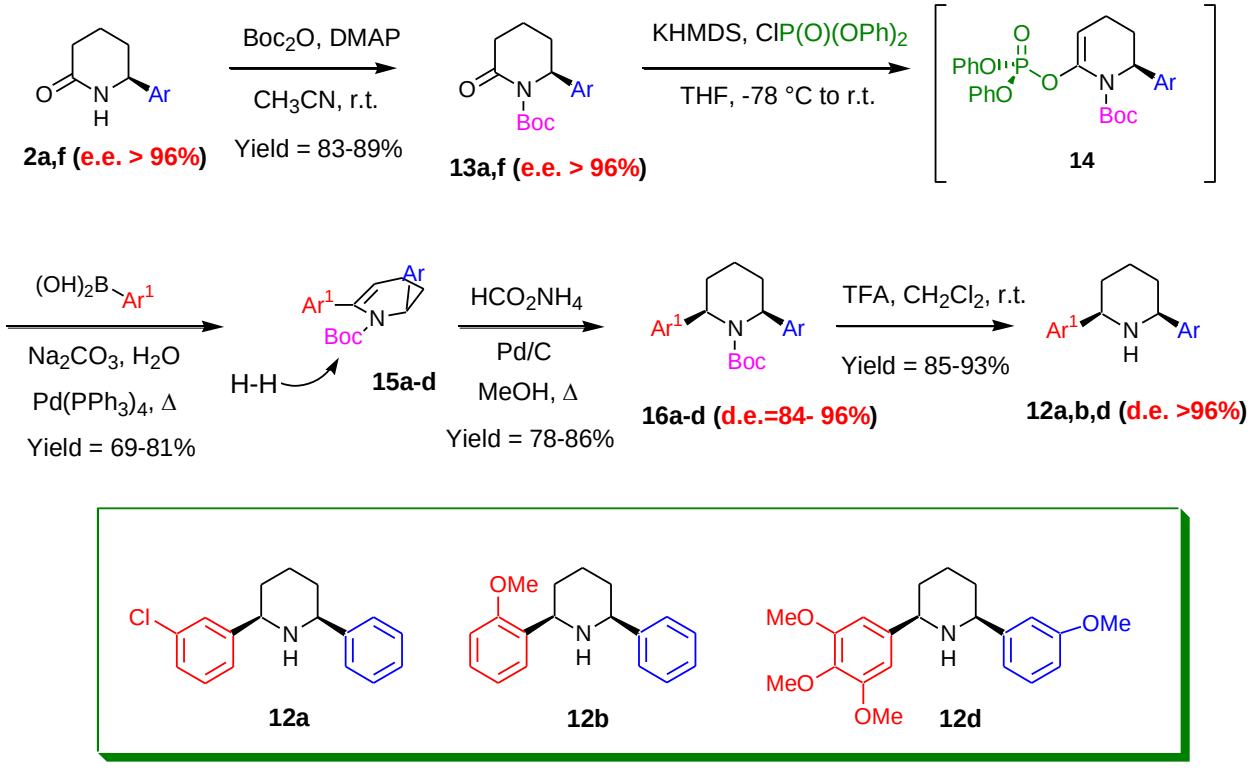
V (-)-Isosolenopsine A **VI** (+)-Monomorine I **VII**

Figure 2. Examples of synthetic pharmacologically active *cis*-2,6-disubstituted piperidines (**V-VII**).

To the best of our knowledge, only one synthesis of enantiopure *cis*-2,6-diarylated piperidines has been reported so far. Thus Szymoniak et al. [6j] developed an efficient methodology which allows access to these chiral piperidines based upon a sequential hydrozirconation/acylation followed by a diastereoselective intramolecular reductive amination starting from a *N*-Boc protected chiral homoallylic amine.

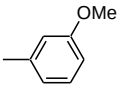
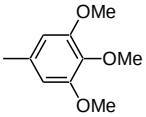
This new synthetic route, depicted in scheme 5, required the preliminary elaboration of the chiral piperidin-2-ones **2a,f** bearing an aryl group alpha to nitrogen (scheme 2). Protection of the nitrogen by reaction with Boc_2O furnish carbamates **13a,f**. The *N*-Boc group was initially used as an electron withdrawing protecting group since it could be easily removable under acidic conditions. Exposure of protected chiral lactams **13a,f** to KHMDS at -78 °C provided the corresponding potassium enolate which was intercepted by reaction with diphenyl phosphoryl chloride to deliver the sensitive aminovinyl phosphates **14** which were then used for the next step without further purification. These highly reactive electrophilic species were then allowed to react with a variety of aromatic boronic acids in the presence of $Pd(PPh_3)_4$ catalyst and Na_2CO_3 in refluxing THF to lead to the formation of a series of 2,6-diarylated cyclic chiral enecarbamates **15a-d**. With a reliable route to these enecarbamates in hand, the diastereoselective reduction of the endocyclic carbone-carbone double bond of these highly conjugated compounds was initiated.

Antiperiplanar addition of hydrogen from the less hindered face of the half-chair-like privileged conformation of **15a-d** then providing the diastereomers **16a-d** with a high level of selectivity (table 3). It should be noted that reduction of enecarbamate **15c** was less stereoselective. Indeed, two inseparable diastereoisomers detectable by ^1H NMR were obtained, probably due to the presence of a less hindered furyl group in our model. Finally, removal of the protecting group was cleanly achieved under acidic conditions by treatment of the carbamates **16a,b,d** with trifluoroacetic acid to afford the targeted virtualy enantiopure *cis*-2,6-diarylated piperidines **12a,b,d**. The absolute and relative configuration of **12a,b,d** was inferred by comparison of the specific rotation with the literature data, e.g. $[\alpha]_D$ = +14.9 for (2*R*,6*S*)-**12a** (*c* 0.95 in MeOH), lit. –14.5 for (2*S*,6*R*)-**12a** (*c* 1.00 in MeOH). [9j]



Scheme 5. Asymmetric synthesis of *cis*-2,6-diarylated piperidines **12a,b,d**.

Table 3. Yields of the intermediates **15a-d** and **16a-d** and the *cis*-2,6-diarylated piperidines **12a,b,d**

Entry	Ar	Ar^1		Yield (%)[a]		Yield (%)[a]	*d.e.* (%)[b]		Yield (%)[a]	*d.e.* (%)[b]
1			**15a**	74	**16a**	85	>96	**12a**	70	>96
2			**15b**	84	**16b**	71	>96	**12b**	78	>96
3			**15c**	71	**16c**	77	84			
4			**15d**	68	**16d**	89	>96	**12d**	72	>96

[a]After purification. [b]Determined by ^{1}H NMR spectroscopy

Conclusion

In conclusion, a new strategy have been developed and successfully employed in the asymmetric synthesis of 2-heteroaryl cyclic amines and 6-aryl piperidin-2-ones. The key step is based upon an intramolecular chirality transfer from a variety of models equipped with a methoxymethylpyrrolidine temporary activating agent. This methodology enriches the repertoire of asymmetric methods relying on the Enders chiral auxiliary since high yields and enantioselectivities were observed upon hydrogenation of arylated and heroarylated endocyclic enehydrazide precursors. The utility of our synthetic protocol is illustrated by the total synthesis of *S*-(-)-Anabasine, alkaloid extracted from *Nicotiana glauca* and the stereoselective synthesis of *cis*-2,6-diarylated piperidines. Extension of this approach to other scaffolds is in progress in our laboratory.

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