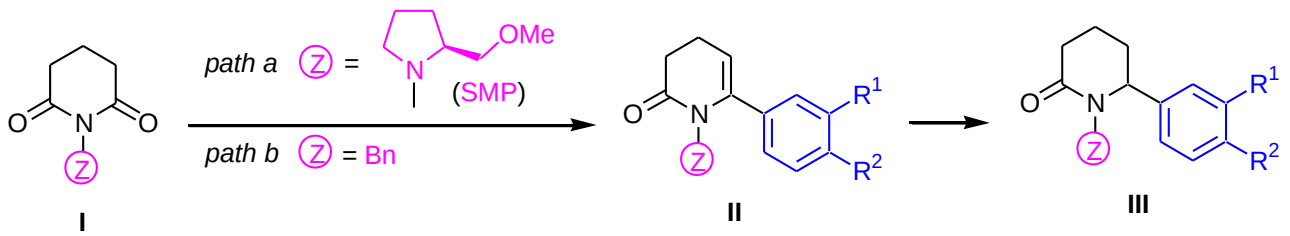
Stereocontrolled generation of C-arylated carbon center α to nitrogen atom in six-membered azaheterocycles. Alternative strategies.

Romain Sallio,[a] Stéphane Lebrun,[a] Francine Agbossou-Niedercorn,[b] Christophe Michon,[b] Eric Deniau[a,*]

[a]*Université Lille Nord de France - USTL, LCOP, EA CMF 4478, Bâtiment C3(2), F-59655 Villeneuve d'Ascq Cedex, France.*
[b]*Université Lille Nord de France - CNRS, UCCS UMR 8181, ENSCL, CCM-CCCF, Bât C7, BP 90108, 59652 Villeneuve d'Ascq Cedex, France.*

*Eric.Deniau@univ-lille1.fr

Abstract: Piperidin(on)es represent the core unit of a wide range of alkaloids and biologically active compounds and in particular, 6-(het)aryl substituted compounds play an important role as key targets for the pharmaceutical industry. The stereocontrol of carbon centers embedded in the azaheterocycle is a permanent synthetic task for organic chemists. In this regard we have developed two alternative and conceptually new synthetic approaches to a variety of 6-arylated piperidinones **III** that is based upon the asymmetric reduction of endocyclic enamides **II** readily accessible from imides **I**, as the key step. The stereoselectivity of the reduction process could be controlled either by the use of a (*S*)-methylprolinol chiral auxiliary (Z = SMP, *path a*) or by ligand/catalyst chirality transfer (Z = Bn, *path b*). Varying degrees of success were observed for these conceptually different approaches.



Keywords: *Enelactams, asymmetric hydrogenation, piperidinones, diastereoselectivity, enantioselectivity*

Introduction

Piperidinones and their derivatives have attracted much attention from the scientific community since they represent the core unit of a wide range of alkaloids and biologically active compounds [1] and additionally they can serve a key role as advanced intermediates prior to their conversion to piperidines [2]. Typical examples include the spiro indane **1** which is an antagonist of CGRP receptors involved in the treatment or prevention of migraine [3], the indoloisoquinolinone **2** which displays antimalarial activity [4], the NK1 antagonist **3** [5] and the acylpiperidone **4** which has been reported as α1a receptor antagonist for treatment of benign prostatic hypertrophy [6] (Fig. 1). Consequently the development of short, versatile and efficient procedures for the stereocontrolled preparation of these aza-heterocycles and their oxo derivatives constitutes an area of current interest and alternative methods are currently the object of intensive synthetic endeavor.

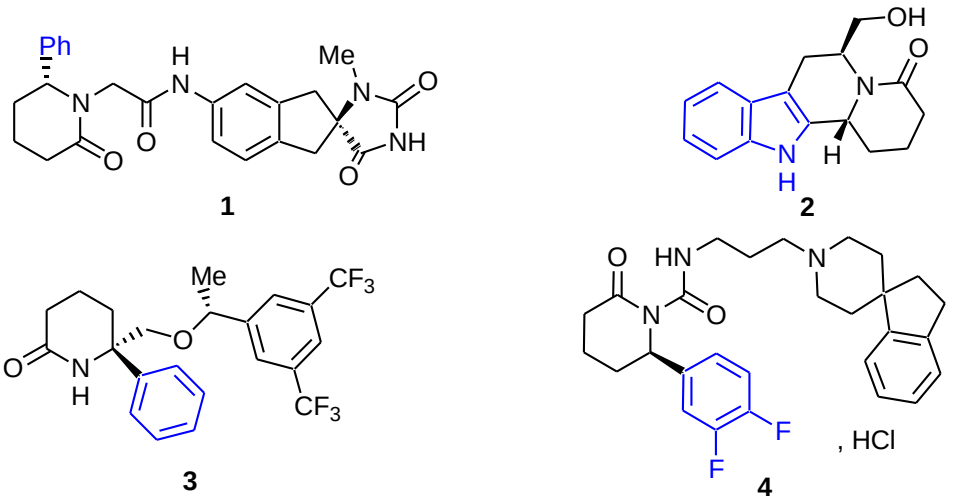
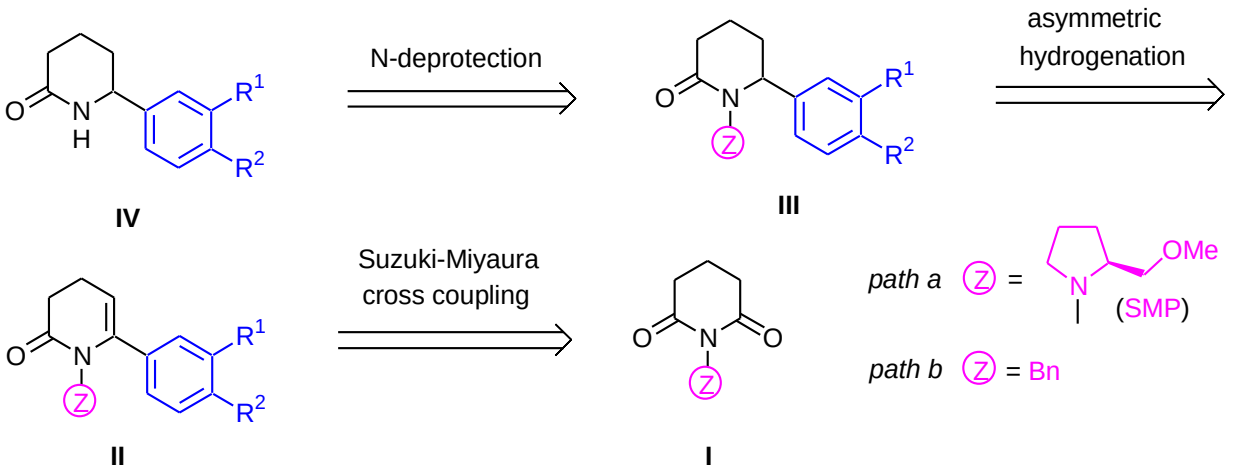


Figure 1. Examples of pharmacologicaly active enantiopure 6-(het)arylated piperidinones.

Results and Discussion

1. Our alternative strategies

We have developed two alternative and conceptually new synthetic approaches to a variety of 6-arylated piperidinones **IV** that hinge upon the asymmetric reduction of endocyclic enamides **II** as the key step (retrosynthetic scheme 1).

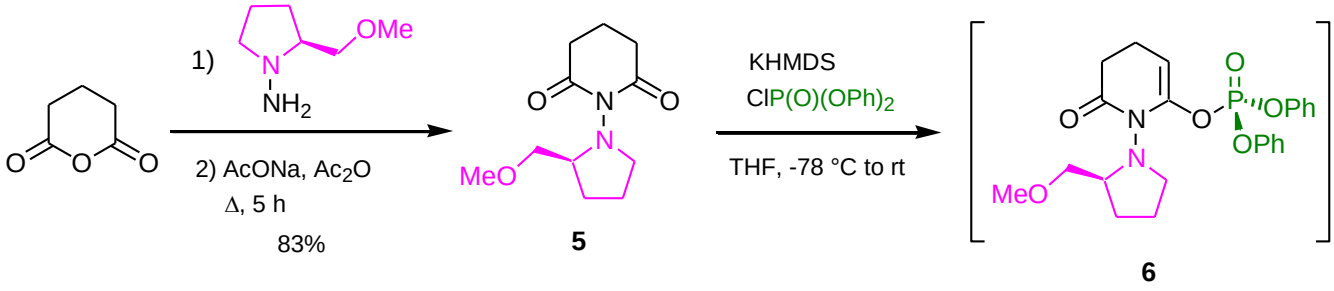


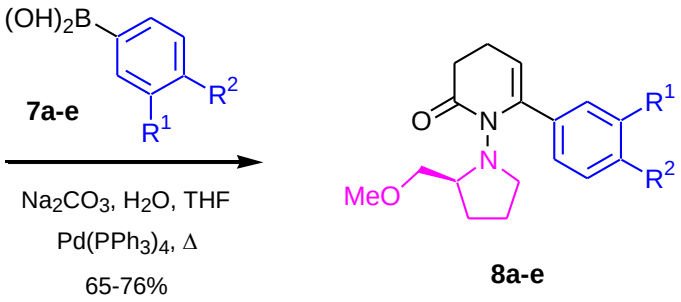
Scheme 1. Retrosynthetic analyses to targeted compounds.

These highly conjugated models would be obtained from the N-protected imides **I** and the stereoselectivities of the transformations should be controlled either by the use of a (*S*)-Methylprolinol chiral auxiliary (Z=SMP, *path a*) [7] or by the ligand/catalyst chirality transfer (Z=Bn, *path b*). N-deprotection of the saturated compounds **III** should then result in the formation of the desired enantiopure lactamic heterocycles **IV**.

2. Elaboration of hydrazide precursors 8a-e involved in path a

Initially the cyclic imide precursor **5** was easily assembled by condensation between glutaric anhydride and (*S*)-aminomethylprolinol (SAMP). Subsequent installation of an additional aryl unit was secured through a palladium-mediated Suzuki-Miyaura cross coupling reaction (scheme 2).





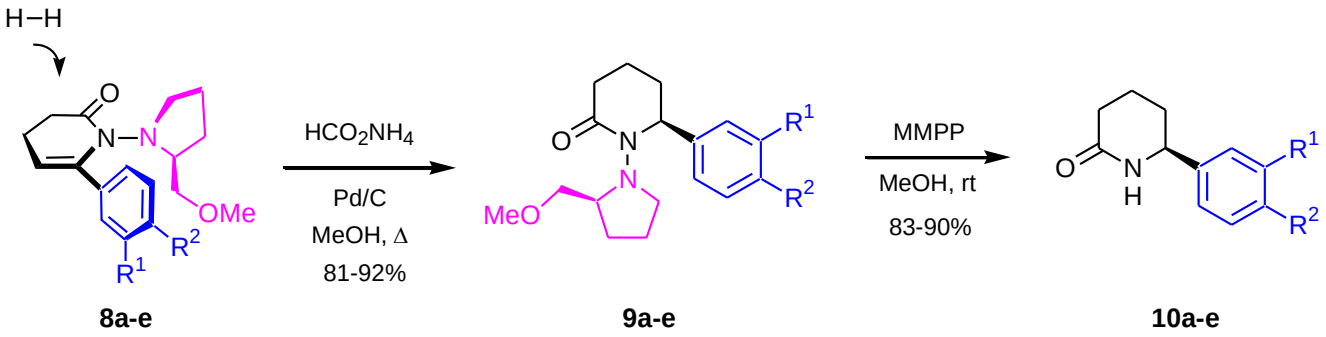
8	R^1	R^2	Yield (%)
a	H	H	72
b	H	F	65
c	H	OMe	70
d	OMe	OMe	76
e	OCH_2O		75

Scheme 2.

3. Asymmetric hydrogenation of enehydrazides 8a-e. Access to enantioenriched NH free 6-arylated piperidinones 10a-e.

A high level of diastereoselectivity in the reduction of the unsaturated compounds **8a-e** was observed by making use of Pd/C with ammonium formate (scheme 3). One can reasonably assume that high facial selectivity might be ascribed to addition of hydrogen on the preferred conformer of the enehydrazides **8a-e**. Hence, antiperiplanar addition of hydrogen occurs preferentially from the less hindered face of **8a-e**, providing the diastereomers **9a-e** with a high level of selectivity (scheme 3, table).

Removal of the auxiliary was subsequently cleanly achieved under oxidizing conditions by treatment of the hydrazides **9a-e** with magnesium mono-peroxyphthalate hexahydrate (MMPP) to afford the targeted 6-arylpiperidin-2-ones **10a-e** free of the chiral auxiliary. The absolute configuration of **10a-e** was inferred by comparison of the specific rotation with the literature data, e.g. $[\alpha]_D$ = −58.0 for (*S*)-**10a** (*c* 0.54 in $CHCl_3$), lit. +58.2 for (*R*)-**10a** (*c* 1.0 in $CHCl_3$).

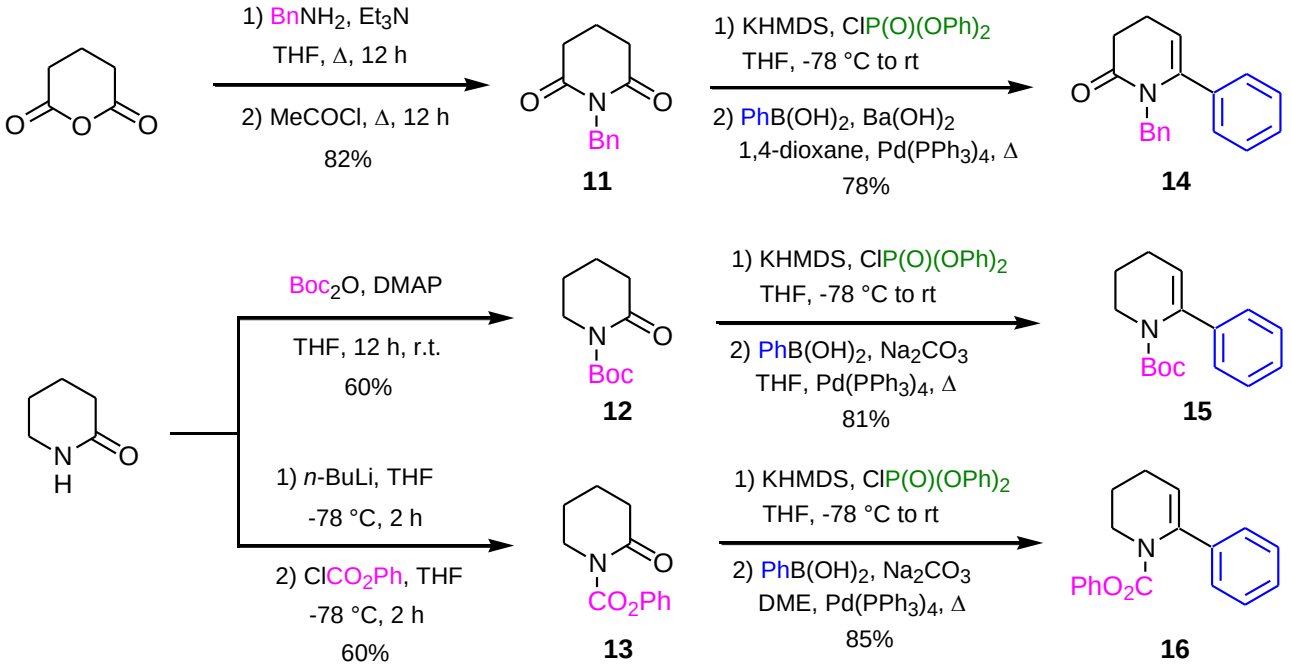


9	R^1	R^2	Yield (%)	d.e. (%)	10	R^1	R^2	Yield (%)	e.e. (%)
a	H	H	89	>96	**a**	H	H	88	>96
b	H	F	86	>96	**b**	H	F	85	>96
c	H	OMe	87	>96	**c**	H	OMe	83	>96
d	OMe	OMe	92	>96	**d**	OMe	OMe	90	>96
e	OCH_2O		81	>96	**e**	OCH_2O		86	>96

Scheme 3.

4. Elaboration of the unsaturated lactam precursors 14-16 involved in the alternative synthetic approach (path b).

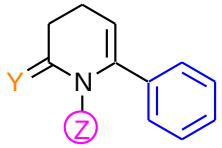
The highly functionalized models **14-16** chosen for this study were easily obtained from the parent lactam or anhydride precursor followed by Suzuki-Miyaura cross coupling reaction (Scheme 4).



Scheme 4.

5. Asymmetric hydrogenation of cyclic enamide and enecarbamates 14-16.

A variety of catalysts and ligands were screened for the asymmetric reduction of the unsaturated precursors **14-16** (scheme 5, table).

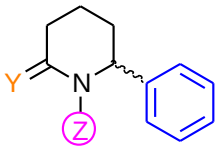


14-16

H_2, catalyst

solvent, time

heating



17-19

	Y	Z
14, 17	O	Bn
15, 18	H_2	Boc
16, 19	H_2	CO_2Ph

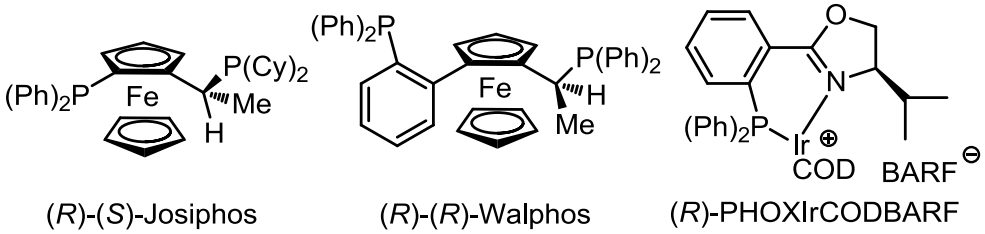
Scheme 5.

Table. Screening of catalysts for the hydrogenation of enamides **14-16** into **17-19**.

Entry	Reagent	Catalyst	solvent	P(H_2) (bar)	T (°C)	Time (h)	Yield (%)	E.e (%)
1	**14**	10% Pd/C	EtOH	1	20	16	100	-
2	**14**	(*R*)-(*S*)-Josiphos (2.2 mol%) + $[IrCODCl]_2$ (2.2 mol%)	THF	20	20	16	10	<5
3	**14**	(*S*)-BINAP-$Ru(OAc)_2$ (2 mol%)	MeOH	55	50	16	10	<5
4	**14**	(*S*)-BINAP-$Ru(OAc)_2$ (2 mol%)	CH_2Cl_2	55	50	16	5	<5
5	**14**	(*R*)-BINAP (1mol%) + $[RhCOD]_2BF_4$ (1 mol%)	MeOH	50	60	16	22	<5
6	**15**	10% Pd/C	EtOH	1	20	16	100	-
7	**15**	(*R*)-(*S*)-Josiphos (2.2 mol%) + $[IrCODCl]_2$ (2.2 mol%)	THF	50	20	16	0	-
8	**15**	(*R*)-BINAP (1mol%) + $[RhCOD]_2BF_4$ (1 mol%)	*i*PrOH	100	70	64	50	<5
9	**15**	(*R*)-BINAP (5mol%) + $[Rh(OH)COD]_2$ (1 mol%)	EtOH	65	70	16	15	<5
10	**15**	(*R*)-(*R*)-Walphos (5mol%) + $[Rh(OH)COD]_2$ (1 mol%)	*i*PrOH	115	70	64	30	<5
11	**16**	10% Pd/C	EtOH	1	20	16	100	-
12	**16**	(*R*)-(*S*)-Josiphos (2.2 mol%) + $[IrCODCl]_2$ (2.2 mol%)	THF	20	20	16	0	-
13	**16**	(*R*)-PHOX-IrCODBARF (1 mol%)	CH_2Cl_2	50	20	16	0	-
14	**16**	(*R*)-BINAP (1mol%) + $[RhCOD]_2BF_4$ (1 mol%)	*i*PrOH	50	70	64	60	<5
15	**16**	(*S*)-BINAP-$Ru(OAc)_2$ (2 mol%)	MeOH	45	50	64	0	-

The catalytic study started with the preparation of racemic samples. Whereas the Pd/C catalyzed hydrogenation of enamides **14-16** delivered the racemic amides **17-19** quantitatively (Table 4, entries 1, 6, 11) the screening of other catalysts led to rather disappointingly results. Poor yields were indeed observed upon hydrogenation of compounds **14-16** using Ir(I) catalyst. Thus compound **17** was obtained in poor yield and without enantioselectivity whereas substrates **15** and **16** could not be hydrogenated (entries 7, 12, 13). These results are in strong contrast with those reported by Zhou et al. who hydrogenated N-alkylated five-membered cyclic enamines by making use of Ir(I) catalysts with high yields and enantioselectivities [8]. Hydrogenation of enamides **14** and **16** using Ru(II) catalysts proved also to be unfruitful, with **14** being hydrogenated in low yield and enantioselectivity and **16** remaining unreacted (entries 3, 4, 15). The use of Rh(I) catalysts enabled better hydrogenation reactions for enamides **14-16**. Whereas the

combined use of (*R*)-BINAP and $[RhCOD]_2BF_4$ led to hydrogenation of compound **14** in modest 22% yield (entries 5), the use of same catalyst with close reaction conditions enabled compounds **15** and **16** to be hydrogenated in 50 and 60% yield respectively (entries 8, 14). However, in each case, almost no enantioselectivity was obtained. For the hydrogenation of enamide **15**, the change for $[Rh(OH)COD]_2$ and Walphos ligand (Fig. 2) decreased the yield of **18** to 30% and did not improve enantioselectivity (table 3, entries 9, 10.



(*R*)-(*S*)-Josiphos (*R*)-(*R*)-Walphos (*R*)-PHOXIrCODBARF

Figure 2. Some ligands and catalyst used in this study.

Conclusion

In conclusion two alternative synthetic approaches for the stereoselective synthesis of 6-arylated piperidin-2-ones have been developed. The first one was 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 endocyclic enehydrazide precursors. Rather disappointing results were however observed through the alternative catalytic hydrogenation process applied to structurally related N-alkyl or acyl precursors. These compounds were indeed hydrogenated with varying degrees of success but always with low enantioselectivity

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