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Alternative strategies for the stereoselective synthesis of enantioenriched 6-arylated piperidin-2-ones

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ABSTRACT

Two alternative synthetic approaches to a variety of enantioenriched 6-arylated piperidin-2-ones have been developed. The first one is based on the hydrogenation of suitably arylated chiral cyclic enehydrazides. The second approach relies on the asymmetric catalytic hydrogenation of the corresponding N-alkylated precursors.

1. Introduction

Piperidines 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] Although less prominent in nature,[2] the corresponding lactams (piperidinones) have received increasing interest as they serve a key role as advanced intermediates prior to their conversion to piperidines.[3]

Simple enantiopure 6-(het)aryl substituted compounds have been studied extensively and play an important role as key targets for the pharmaceutical industry. Typical examples are shown in Figure 1 and include the spiro indane **1**, which is an antagonist of CGRP receptors involved in the treatment or prevention of migraine;[4] the indoloisoquinolinone **2** which displays antimalarial activity,[5] the NK1 antagonist **3**[6] and the acylpiperidone **4** which has been reported as an α1a receptor antagonist for the treatment of benign prostatic hypertrophy.[7] 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. Organic chemists have at their disposal a variety of synthetic strategies for the asymmetric synthesis of 6-arylated piperidin-2-ones, but varying degrees of success have been achieved with regard to their stereoselectivities. The control of the stereogenic center alpha to nitrogen in these

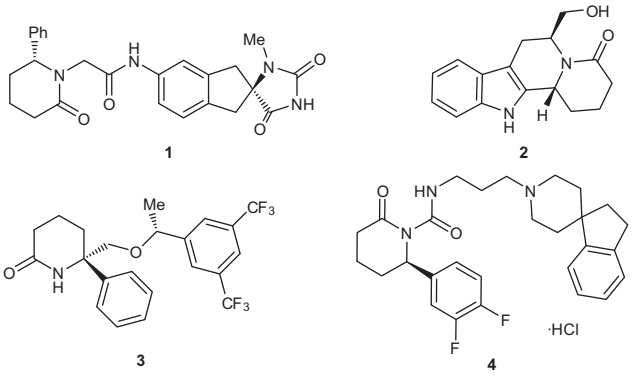

Figure 1. Examples of pharmacologically active enantiopure 6-(het)arylated piperidinones.

lactams can be achieved by different chemical processes such as (i) the diastereoselective nucleophilic additions to chiral sulfinimines[8] or SAMP hydrazones;[9] (ii) the diastereoselective aza-Michael addition of a chiral lithium amide to an α,β-unsaturated Weinreb amide;[10] (iii) the Ir-catalyzed enantioselective hydrogenation of *N*-arylimines;[11] (iv) the enantioselective catalytic vinylogous Mannich reaction of sulfonylimines;[12] and (v) the diastereoselective α-amidoalkylation reaction of Meyers' bicyclic lactams.[13]

2. Results and discussion

We have developed two alternative and conceptually new synthetic approaches to a variety of 6-arylated piperidinones that rely

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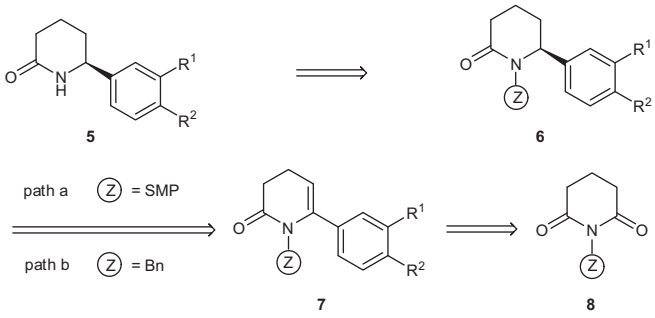
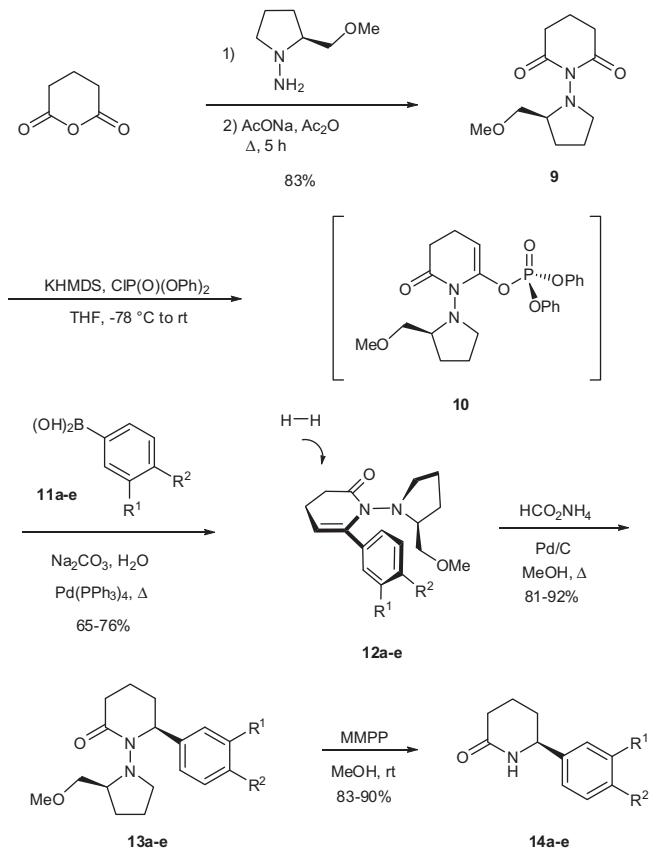
on the asymmetric reduction of endocyclic enamides **7** as the key step (Scheme 1). These highly conjugated models could be obtained via a two step sequence involving a Suzuki cross coupling reaction from the *N*-protected imides **8**. The stereoselectivities of the transformations should be controlled either by the use of a (*S*)-methylprolinol chiral auxiliary (Z = SMP, path a)[14] or by the ligand/catalyst chirality (Z = Bn, path b). The N-deprotection of the saturated compounds **6** should then result in the formation of the desired enantiopure lactam heterocycles **5**.



Scheme 1. Retrosynthetic analysis of chiral 6-arylated piperidinones.

The new synthetic route, depicted in Scheme 2, required the preliminary elaboration of the chiral hydrazide **9**, which was easily prepared by a condensation between glutaric anhydride and (*S*)-AminoMethylProlinol (SAMP).[15] We assumed that these cyclic imides would possess the appropriate functionality required for the connection of an additional aryl unit through a palladium-mediated Suzuki–Miyaura cross-coupling reaction. Since the pioneering work of Oshima et al.,[16] several groups have used constitutionally diverse enol phosphates in a variety of cross-coupling reactions.[17] Exposure of compound **9** to KHMDS in THF at −78 °C provided the corresponding potassium enolate, which was intercepted by reaction with diphenyl phosphoryl chloride. Standard work-up gave the sensitive vinyl phosphate **10**, which was then used for the next step without further purification. Hence, compound **10** was allowed to react in refluxing THF with a variety of boronic acids **11a–e** in the presence of $Pd(PPh_3)_4$ catalyst and Na_2CO_3, which led to the formation of a series of cyclic enehydrazides **12a–e**, which were substituted with different aryl groups alpha to the nitrogen. With a reliable route to these enehydrazides in hand, studies addressing the enantioselective preparation of substituted piperidinones **14a–e** were initiated.



Scheme 2. Asymmetric synthesis of 6-arylated piperidinones **14a–e**.

Based on the efficient method developed in our laboratory for the asymmetric synthesis of 5-arylmethylpirrolidin-2-ones,[18] we anticipated that a high level of diastereoselectivity in the reduction of the unsaturated compounds **12a–e** could be ensured by the use of Pd on C with ammonium formate. As can be seen from Table 1, the formation of compounds **12a–e** occurs with a high level of diastereoselection. According to our previously reported results,[18] one can reasonably assume that the high facial selectivity might be ascribed to the addition of hydrogen on the preferred conformer of the enehydrazides **12a–e**. Hence, antiperiplanar addition of hydrogen should occur preferentially from the less hindered face of **12a–e**, providing the diastereomers **13a–e** 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 **13a** with its previously described epimer.[9a]

Finally, removal of the auxiliary was achieved cleanly under oxidizing conditions by the treatment of hydrazides **13a–e** with magnesium mono-peroxyphthalate hexahydrate (MMPP)[19] to afford the targeted 6-arylpiperidin-2-ones **14a–e** free of the chiral auxiliary. The absolute configuration of **14a–e** was inferred by comparison of the specific rotation with the literature data, for example $[\alpha]_D = -58.0$ for (*S*)-**14a** (*c* 0.54, $CHCl_3$), lit.[10] +58.2 for (*R*)-**14a** (*c* 1.0, $CHCl_3$).

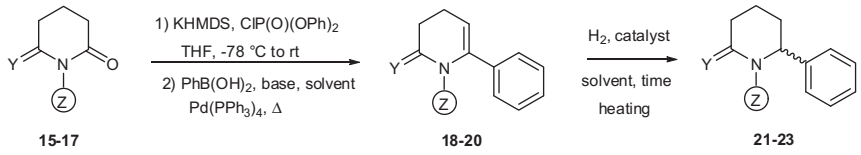
For the alternative synthetic approach based on the catalytic hydrogenation of the structurally related N-alkylated models, compound **18** was initially chosen as the model study. In order to check the scope and limitations (Table 3 and below), we subsequently extended our study to *N*-Boc and *N*-CO_2Ph enamines **19** and **20**. Precursors **18–20** could be a priori assembled through a variety of procedures,[20] but we opted for a two step sequence involving a Suzuki–Miyaura cross coupling reaction from the *N*-protected imide **15** and lactams **16–17** (Scheme 3).

Asymmetric hydrogenations of cyclic enamides studied and focused mainly on structures containing an exocyclic C=C bond.[21] However, to the best of our knowledge, the asymmetric hydrogenation of 6-arylated dihydropyridin-2-ones has not been previously reported on. Hence, we started our catalytic study with the preparation of racemic samples. Whereas the Pd/C catalyzed hydrogenation of enamides **18–20** gave the racemic amides **21–23** quantitatively (Table 2, entries 1, 6, 11), the screening of other catalysts led to rather disappointingly results. Poor yields were observed upon hydrogenation of compounds **18–20** using an Ir(I) catalyst. Thus compound **21** was obtained in poor yield and without enantioselectivity whereas substrates **19** and **20** could not be hydrogenated (entries 2, 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.[22] Hydrogenation of enamides **18** and **20** using Ru(II) catalysts also proved to be unsuccessful, with **18** being hydrogenated in low yields and enantioselectivity and **20** remaining unreacted (entries 3, 4, 15). The use of Rh(I) catalysts enabled better hydrogenation reactions for enamides **18–20**. Whereas the combined use of (*R*)-BINAP

Table 1
Compounds **12a–e**, **13a–e**, **14a–e** prepared

Entry	R^1	R^2	Compound	Yield[a] (%)	Compound	Yield[a] (%)	de[b] (%)	Compound	Yield (%)[a]	ee[c] (%)
1	H	H	**12a**	72	**13a**	89	>96	**14a**	88	>96
2	H	F	**12b**	65	**13b**	86	>96	**14b**	85	>96
3	H	OMe	**12c**	70	**13c**	87	>96	**14c**	83	>96
4	OMe	OMe	**12d**	76	**13d**	92	>96	**14d**	90	>96
5	OCH_2O		**12e**	75	**13e**	81	>96	**14e**	86	>96

[a] After purification.
[b] Determined by ^1H NMR spectroscopy.
[c] In correlation to the de value of the corresponding hydrazides **13a–e** assuming that the deprotection step takes place without detectable racemization.[9a]



Scheme 3. Synthesis of compounds **18–23**.

Table 2
Compounds **18–23** prepared

Entry	Z	Y	Compound	Base	Solvent	Time (h)	Yield (%)	Compound
1	Bn	O	**18**	$Ba(OH)_2$	1,4-Dioxane	12	78	**21**
2	Boc	H_2	**19**	Na_2CO_3	THF	2	81	**22**
3	CO_2Ph	H_2	**20**	Na_2CO_3	DME	0.5	85	**23**

Table 3
Screening of catalysts for the hydrogenation of enamides **18–20** into **21–23**.

Entry	Reagent	Catalyst	Solvent	$P(H_2)$ (bar)	T (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1[c]	**18**	10% Pd/C	EtOH	1	20	16	100	—
2[d]	**18**	(*R*)-(*S*)-Josiphos (2.2 mol %) + $[IrCODCl]_2$ (2.2 mol %)	THF	20	20	16	10	<5
3	**18**	(*S*)-BINAP-Ru$(OAc)_2$ (2 mol %)	MeOH	55	50	16	10	<5
4	**18**	(*S*)-BINAP-Ru$(OAc)_2$ (2 mol %)	CH_2Cl_2	55	50	16	5	<5
5[e]	**18**	(*R*)-BINAP (1 mol %) + $[RhCOD]_2BF_4$ (1 mol %)	MeOH	50	60	16	22	<5
6[c,f]	**19**	10% Pd/C	EtOH	1	20	16	100	—
7[g]	**19**	(*R*)-(*S*)-Josiphos (2.2 mol %) + $[IrCODCl]_2$ (2.2 mol %)	THF	50	20	16	0	—
8[f]	**19**	(*R*)-BINAP (1 mol %) + $[RhCOD]_2BF_4$ (1 mol %)	*i*PrOH	100	70	64	50	<5
9	**19**	(*R*)-BINAP (5 mol %) + $[Rh(OH)COD]_2$ (1 mol %)	EtOH	65	70	16	15	<5
10[h]	**19**	(*R*)-(*R*)-Walphos (5 mol %) + $[Rh(OH)COD]_2$ (1 mol %)	*i*PrOH	115	70	64	30	<5
11[c]	**20**	10% Pd/C	EtOH	1	20	16	100	—
12[g]	**20**	(*R*)-(*S*)-Josiphos (2.2 mol %) + $[IrCODCl]_2$ (2.2 mol %)	THF	20	20	16	0	—
13[i]	**20**	(*R*)-PHOX-IrCODBARF (1 mol %)	CH_2Cl_2	50	20	16	0	—
14	**20**	(*R*)-BINAP (1 mol %) + $[RhCOD]_2BF_4$ (1 mol %)	*i*PrOH	50	70	64	60	<5
15	**20**	(*S*)-BINAP-Ru$(OAc)_2$ (2 mol %)	MeOH	45	50	64	0	—

[a] Isolated yield.
[b] measured by chiral HPLC on Regis™ (*S,S*)-Whelk 01, (80/20) *n*-hexane/*i*-PrOH, 1 ml/min, 200 nm.
[c] Forty milligrams of Pd/C for 0.4 mmol of substrate and 20 ml EtOH.
[d] Performed with 5 mol % I_2.
[e] Performed with 60 mol % Cs_2CO_3; same result without.
[f] Same result for seven-membered ring compounds.
[g] same result at 60 °C or with CH_2Cl_2.
[h] Performed with 60 mol % Cs_2CO_3.
[i] Same result at 70 °C in TCE.

and $[RhCOD]_2BF_4$ led to hydrogenation of compound **18** in a modest 22% yield (entry 5), the use of the same catalyst with close reaction conditions enabled compounds **19** and **20** to be hydrogenated in 50% and 60% yields, respectively (entries 8, 14). However, in each case, almost no enantioselectivity was obtained. For the hydrogenation of enamide **19**, the change for $[Rh(OH)COD]_2$ and Walphos ligand (Fig. 2) decreased the yield of **22** to 30% and did not improve the enantioselectivity (Table 3, entries 9, 10).

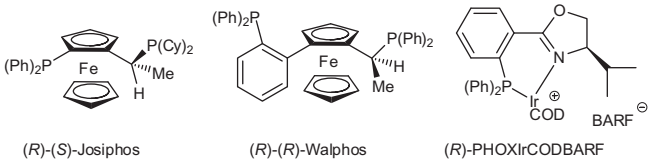


Figure 2. Some ligands and catalyst used herein.

3. Conclusion

In conclusion, two alternative synthetic approaches for the stereoselective synthesis of 6-arylated piperidin-2-ones have been developed. The first one is based on 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 the 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 hydrogenated with varying degrees of success but always with low enantioselectivity and there is still a strong incentive for the development of this conceptually different synthetic approach to the target compounds.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. NMR spectra were recorded on a Bruker AM 300 spectrometer. They were referenced against internal tetramethylsilane; coupling constants (*J*) are given in Hz and rounded to the nearest 0.1 Hz. IR absorption spectra were run on a Perkin-Elmer 881. Optical rotations were recorded on Perkin Elmer 343 digital polarimeter at 589 nm. HPLC analyses were performed on a Hitachi-VWR LaChromElite L-2000. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. Flash chromatography was performed on Sorbent Technologies 32–63 μm 60 Å silica gel. Reactions were monitored by thin layer chromatography with Sorbent Technologies 0.20 mm silica gel 60 Å plates. Dry glassware was obtained by oven-drying and assembly under an inert gas. Dry nitrogen was used as the inert atmosphere. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Methanol (MeOH), ethanol (EtOH), and isopropanol (*i*PrOH) were distilled over magnesium turnings, CH_2Cl_2 over CaH_2, and toluene over sodium.

4.2. Typical procedure for the preparation of imide 9

(*S*)-1-Amino-2-methoxymethylpyrrolidine (SAMP, 5.2 g, 0.04 mol) was added to a suspension of glutaric anhydride (0.04 mol, 4.56 g) in CH_2Cl_2 (100 mL). The mixture was then stirred at room temperature for 1 h. Acetic anhydride (5.6 mL, 0.06 mol) and a catalytic amount of sodium acetate (30 mg) were subsequently added and the mixture was refluxed for 5 h. The reaction mixture was cooled to 0 °C and stirred with a 5% aqueous $NaHCO_3$ solution (50 mL) for 30 min. The aqueous layer was separated and extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel using EA/hexanes (50:50) as eluent to afford **9** as an oil.

4.2.1. 1-((S)-2-Methoxymethylpyrrolidin-1-yl)-piperidine-2,6-dione 9

Oil; $[\alpha]_D^{20} = +3.9$ (*c* 1.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.41–1.51 (m, 1H), 1.69–1.95 (m, 5H), 2.52–2.56 (m, 4H), 3.02–3.23 (m, 7H), 3.51–3.60 (m, 1H); ^{13}C NMR ($CDCl_3$): **C** 172.5 (CO), 171.4 (CO), **CH** 59.5, **CH_2** 76.4, 50.9, 34.2, 33.3, 27.1, 22.4, 16.6, **CH_3** 58.6. Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.43; H, 8.26; N, 12.59.

4.3. Typical procedure for the preparation of enehydrazides 12a–e

To a solution of imide **9** (2 mmol, 450 mg) and diphenyl phosphoryl chloride (0.62 mL, 3 mmol) in anhydrous THF (30 mL) cooled at −78 °C and under a nitrogen atmosphere, was added dropwise under stirring a solution of KHMDS (6 mL, 0.5 M in toluene, 3 mmol). After 30 min at −78 °C, water (20 mL) was added and the resulting mixture was extracted with Et_2O (2 × 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under vacuum yielded **10** as a yellow oil, which was directly used for the next coupling step.

To a stirred solution of crude **10** (2 mmol) in THF (20 mL) maintained under a nitrogen atmosphere, were added a 2 M aqueous Na_2CO_3 solution (2 mL, 4 mmol), $Pd(PPh_3)_4$ (120 mg, 5 mol %), and aromatic boronic acid **11a–e** (3 mmol). The mixture was stirred for 2 h at reflux, and then it was diluted with water (2 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to give an orange oil, which was purified by flash column chromatography using EA/hexanes (40:60) as eluent to afford 6-arylated dihydropyridinones **12a–e**.

4.3.1. (*S*)-1-(2-Methoxymethylpyrrolidin-1-yl)-6-phenyl-3,4-dihydro-1*H*-pyridin-2-one 12a

Mp 100–101 °C; $[\alpha]_D^{20} = -99.3$ (*c* 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.21–1.32 (m, 1H), 1.41–1.56 (m, 1H), 1.88–2.05 (m, 2H), 2.12–2.27 (m, 1H), 2.38–2.61 (m, 3H), 2.80–2.88 (m, 1H), 3.02–3.11 (m, 2H), 3.20 (s, 3H, OCH_3), 3.48–3.55 (m, 1H), 3.72–3.84 (m, 1H), 5.18 (t, *J* = 7.0 Hz, 1H), 7.27–7.33 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.8 (CO), 146.6, 137.5, **CH** 127.9 (2CH), 127.4, 127.3 (2 × CH), 107.3, 60.8, **CH_2** 76.1, 51.9, 34.0, 28.2, 22.9, 19.7, **CH_3** 58.6. Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.35; H, 7.83; N, 9.60.

4.3.2. 6-(4-Fluorophenyl)-1-((S)-2-methoxymethyl-pyrrolidin-1-yl)-3,4-dihydro-1*H*-pyridin-2-one 12b

Mp 125–126 °C; $[\alpha]_D^{20} = -120.8$ (*c* 1.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.19–1.36 (m, 1H), 1.45–1.57 (m, 1H), 1.89–2.08 (m, 2H), 2.17–2.31 (m, 1H), 2.35–2.71 (m, 3H), 2.88 (dd, *J* = 6.1, 9.3 Hz, 1H), 2.94–2.99 (m, 1H), 3.04 (dd, *J* = 5.9, 9.3 Hz, 1H), 3.20 (s, 3H, OCH_3), 3.43–3.53 (m, 1H), 3.74–3.85 (m, 1H), 5.16 (dd, *J* = 3.1, 6.4 Hz, 1H), 6.96–7.04 (m, 2H, H_{arom}), 7.22–7.33 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.7 (CO), 162.1 (d, *J* = 255 Hz), 145.6, 133.5, **CH** 129.5 (d, *J* = 8.0 Hz, 2 × CH), 114.3 (d, *J* = 21.5 Hz, 2 × CH), 107.3, 60.7, **CH_2** 76.0, 52.0, 34.0, 28.1, 22.9, 19.7, **CH_3** 58.8. Anal. Calcd for $C_{17}H_{21}FN_2O_2$: C, 67.09; H, 6.95; N, 9.20. Found: C, 67.18; H, 7.06; N, 9.10.

4.3.3. 6-(4-Methoxyphenyl)-1-((*S*)-2-methoxymethylpyrrolidin-1-yl)-3,4-dihydro-1*H*-pyridin-2-one 12c

Oil; $[\alpha]_D^{20} = -56.2$ (*c* 2.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.20–1.29 (m, 1H), 1.32–1.56 (m, 1H), 1.84–2.02 (m, 2H), 2.11–2.23 (m, 1H), 2.28–2.66 (m, 3H), 2.84 (dd, *J* = 6.4, 9.2 Hz, 1H), 2.94–3.07 (m, 2H), 3.16 (s, 3H, OCH_3), 3.42–3.53 (m, 1H), 3.71–3.78 (m, 1H), 3.76 (s, 3H, OCH_3), 5.09 (dd, *J* = 3.1, 6.4 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H, H_{arom}), 7.18 (d, *J* = 8.7 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.9 (CO), 158.9, 146.2, 130.0, **CH** 129.2, 112.8, 106.6, 60.7, **CH_2** 76.1, 51.9, 34.1, 28.2, 22.8, 19.7, **CH_3** 58.6, 55.2. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.20; H, 7.67; N, 8.97.

4.3.4. 6-(3,4-Dimethoxyphenyl)-1-((*S*)-2-methoxy-methylpyrrolidin-1-yl)-3,4-dihydro-1*H*-pyridin-2-one 12d

Mp 85–86 °C; $[\alpha]_D^{20} = -105.2$ (*c* 1.97, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.18–1.23 (m, 1H), 1.37–1.52 (m, 1H), 1.81–1.98 (m, 2H), 2.06–2.19 (m, 1H), 2.35–2.64 (m, 3H), 2.72–2.83 (m, 1H), 2.93–3.08 (m, 2H), 3.17 (s, 3H, OCH_3), 3.38–3.51 (m, 1H), 3.65–3.73 (m, 1H), 3.82 (s, 6H, 2 × OCH_3), 5.16 (t, *J* = 7.1 Hz, 1H), 6.72–6.85 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.8 (CO), 148.3, 147.6, 146.2, 130.2, **CH** 120.4, 111.3, 110.0, 106.7, 60.6, **CH_2** 76.0, 51.8, 34.0, 28.1, 22.8, 19.6, **CH_3** 58.6, 55.8, 55.7. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.85; H, 7.46; N, 8.21.

4.3.5. 6-Benzo[1,3]dioxol-5-yl-1-((*S*)-2-methoxy-methylpyrrolidin-1-yl)-3,4-dihydro-1*H*-pyridin-2-one 12e

Mp 148–149 °C; $[\alpha]_D^{20} = -83.0$ (*c* 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.23–1.35 (m, 1H), 1.48–1.61 (m, 1H), 1.90–2.06 (m, 2H), 2.13–2.25 (m, 1H), 2.32–2.67 (m, 3H), 2.94 (dd, *J* = 6.3, 9.3 Hz, 1H), 2.98–3.06 (m, 1H), 3.10 (dd, *J* = 5.6, 9.3 Hz, 1H), 3.22 (s, 3H, OCH_3), 3.43–3.52 (m, 1H), 3.72–3.84 (m, 1H), 5.14 (dd, *J* = 2.9, 6.4 Hz, 1H), 5.96 (d, *J* = 3.3 Hz, 1H), 5.98 (d, *J* = 3.3 Hz, 1H), 6.74–6.78 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.9 (CO), 146.9, 146.7, 146.0, 131.5, **CH** 121.4, 108.5, 107.4, 107.1, 60.8, **CH_2** 101.0, 76.1, 52.0, 34.1, 28.3, 22.9, 19.6, **CH_3** 58.7. Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.26; H, 6.83; N, 8.23.

4.4. Typical procedure for the preparation of cyclic hydrazides 13a–e

A suspension of compounds **12a**–**e** (2 mmol) in MeOH (30 mL) was stirred with activated Pd/C (10%, 30 mg) and a solution of HCO_2NH_4 (500 mg, 8 mmol) in distilled water (5 mL) was then added. The reaction mixture was refluxed for 4 h, filtered on Celite™, and diluted with water. Extraction with CH_2Cl_2 (3 × 20 mL), drying over $MgSO_4$, and concentration under vacuum gave an oily product, which was purified by chromatography on silica gel using EA/hexanes (60:40) as eluent to give **13a**–**e**.

4.4.1. 1-((*S*)-2-Methoxymethylpyrrolidin-1-yl)-(*S*)-6-phenylpiperidin-2-one 13a

Oil, $[\alpha]_D^{20} = -56.2$ (*c* 2.89, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.51–1.68 (m, 3H), 1.71–1.92 (m, 3H), 2.07–2.25 (m, 2H), 2.35–2.61 (m, 4H), 2.96 (s, 3H, OCH_3), 3.08–3.17 (m, 2H), 3.51–3.63 (m, 1H), 4.71 (t, *J* = 5.3 Hz, 1H), 7.19–7.46 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.5 (CO), 142.8, **CH** 128.3 (2 × CH), 127.4, 127.3 (2 × CH), 61.0, 59.8, **CH_2** 75.2, 51.0, 33.5, 32.0, 27.5, 23.3, 16.5, **CH_3** 58.5. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.86; H, 8.12; N, 9.69.

4.4.2. (*S*)-6-(4-Fluorophenyl)-1-((*S*)-2-methoxy-methylpyrrolidin1-yl)piperidin-2-one 13b

Oil; $[\alpha]_D^{20} = -45.2$ (*c* 1.43, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.53–1.66 (m, 3H), 1.71–1.88 (m, 3H), 2.10–2.23 (m, 2H), 2.38–2.65 (m, 4H), 3.03 (s, 3H, OCH_3), 3.08–3.16 (m, 2H), 3.53–3.65 (m, 1H), 4.69 (t, *J* = 4.8 Hz, 1H), 7.03–7.11 (m, 2H, H_{arom}), 7.18–7.27 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.6 (CO), 162.0 (d, *J* = 250.0 Hz), 138.5 (d, *J* = 7.4 Hz), **CH** 128.9 (d, *J* = 7.6 Hz, 2CH), 115.1 (d, *J* = 21.5 Hz, 2CH), 61.0, 59.8, **CH_2** 75.3, 51.0, 33.5, 32.0, 27.6, 23.5, 16.6, **CH_3** 58.6. Anal. Calcd for $C_{17}H_{23}FN_2O_2$: C, 66.64; H, 7.57; N, 9.14. Found: C, 66.76; H, 7.41; N, 9.20.

4.4.3. (*S*)-6-(4-Methoxyphenyl)-1-((*S*)-2-methoxymethylpyrrolidin-1-yl)piperidin-2-one 13c

Mp 94–95 °C; $[\alpha]_D^{20} = -27.4$ (*c* 1.29, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.50–1.62 (m, 3H), 1.75–1.88 (m, 3H), 2.06–2.21 (m, 2H), 2.35–2.60 (m, 4H), 3.05 (s, 3H, OCH_3), 3.07–3.13 (m, 2H), 3.51–3.59 (m, 1H), 3.82 (s, 3H, OCH_3), 4.63 (t, *J* = 4.5 Hz, 1H), 6,86 (d, *J* = 8.6 Hz, 2H, H_{arom}), 7.13 (d, *J* = 8.6 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.4 (CO), 158.8, 134.6, **CH** 128.4 (2 × CH), 113.5 (2 × CH), 60.9, 59.5, **CH_2** 75.1, 50.7, 33.6, 32.0, 27.7, 23.2, 16.6, **CH_3** 58.3, 55.4. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.78; H, 8.12; N, 8.98.

4.4.4. (*S*)-6-(3,4-Dimethoxyphenyl)-1-((*S*)-2-methoxymethylpyrrolidin-1-yl)piperidin-2-one 13d

Mp 96–97 °C; $[\alpha]_D^{20} = -67.3$ (*c* 1.64, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.48–1.60 (m, 3H), 1.68–1.89 (m, 3H), 2.05–2.18 (m, 2H), 2.35–2.56 (m, 4H), 2.94 (s, 3H, OCH_3), 3.05–3.11 (m, 2H), 3.44–3.53 (m, 1H), 3.83 (s, 6H, 2 × OCH_3), 4.65 (t, *J* = 5.2 Hz, 1H), 6.67 (s, 1H, H_{arom}), 6,73 (d, *J* = 8.2 Hz, 2H, H_{arom}), 6.82 (d, *J* = 8.2 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.6 (CO), 148.8, 148.2, 135.2, **CH** 119.3, 110.7, 110.3, 61.3, 59.7, **CH_2** 75.5, 51.0, 33.4, 32.2, 27.6, 23.5, 16.6, **CH_3** 58.6, 55.9, 55.8. Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.22; H, 8.12; N, 7.98.

4.4.5. (*S*)-6-Benzo[1,3]dioxol-5-yl-1-((*S*)-2-methoxymethylpyrrolidin-1-yl)piperidin-2-one 13e

Oil; $[\alpha]_D^{20} = -53.9$ (*c* 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.54–1.63 (m, 3H), 1.73–1.87 (m, 3H), 2.04–2.18 (m, 2H), 2.36–2.60 (m, 4H), 3.07 (s, 3H, OCH_3), 3.09–3.18 (m, 2H), 3.58–3.63 (m, 1H), 4.64 (t, *J* = 4.4 Hz, 1H), 5.95 (d, *J* = 3.0 Hz, 1H), 5.97 (d, *J* = 3.0 Hz, 1H), 6.68–6.83 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 169.5 (CO), 147.8, 146.8, 136.5, **CH** 120.4, 107.9, 107.7, 60.8, 59.7, **CH_2** 101.1, 75.3, 50.9, 33.4, 31.9, 27.5, 23.4, 16.6, **CH_3** 58.3. Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.18; H, 7.36; N, 8.60.

4.5. Typical procedure for the preparation of piperidinones 14a–e

To a solution of lactam **13a**–**e** (1 mmol) in MeOH (40 mL) was added MMPP (2.5 mmol, 1.24 g). The reaction mixture was stirred at room temperature until no starting material remained (TLC monitoring). The mixture was then poured into CH_2Cl_2 (150 mL) and treated with a saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were washed successively with water (30 mL), brine (30 mL) and finally dried over $MgSO_4$. Evaporation of the solvent furnished an oily product, which was purified by flash column chromatography using EA as eluent. The product was finally recrystallized from Et_2O to give **14a**–**e**.

4.5.1. (*S*)-6-Phenylpiperidin-2-one 14a

Mp 116–117 °C, lit.[10] 115–117 °C; $[\alpha]_D^{20} = -58.0$ (*c* 0.54, $CHCl_3$), lit.[10] $[\alpha]_D^{20} = +58.2$ (*c* 1.1, $CHCl_3$) for the (*R*)-enantiomer; ^1H ($CDCl_3$): 1.57–1.66 (m, 1H), 1.69–1.78 (m, 1H), 1.81–1.98 (m, 1H), 2.03–2.17 (m, 1H), 2.37–2.52 (m, 2H), 4.55 (dd, *J* = 4.5–9.1 Hz, 1H), 6.14 (br s, 1H, NH), 7.27–7.39 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 172.5 (CO), 142.5, **CH** 128.8 (2 × CH), 127.9, 126.1 (2 × CH), 57.7, **CH_2** 32.1, 31.2, 19.6.

4.5.2. (*S*)-6-(4-Fluorophenyl)piperidin-2-one 14b

Mp 98–99 °C; $[\alpha]_D^{20} = -47.2$ (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.51–1.63 (m, 1H), 1.66–1.77 (m, 1H), 1.79–1.91 (m, 1H), 1.97–2.06 (m, 1H), 2.27–2.48 (m, 2H), 4.47 (dd, *J* = 4.6, 9.0 Hz, 1H), 5.95 (br s, 1H, NH), 6.94–7.03 (m, 2H, H_{arom}), 7.16–7.25 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 171.4 (CO), 161.5 (d, *J* = 247.0 Hz), 136.9 (d, *J* = 3.2 Hz), **CH** 126.7 (d, *J* = 7.2 Hz, 2 × CH), 114.7 (d, *J* = 2 1.6 Hz, 2 × CH), 56.3, **CH_2** 32.1, 30.8, 19.4. Anal. Calcd for $C_{11}H_{12}FNO$: C, 68.38; H, 6.26; N, 7.25. Found: C, 66.48; H, 6.37; N, 7.15.

4.5.3. (*S*)-6-(4-Methoxyphenyl)piperidin-2-one 14c

Mp 135–136 °C, lit.[12] 134–136 °C; $[\alpha]_D^{20} = -58.8$ (*c* 1.90, $CHCl_3$), lit.[12] $[\alpha]_D^{20} = +58.0$ (*c* 0.5, $CHCl_3$) for the (*R*)-enantiomer; ^1H NMR

($CDCl_3$): 1.57–1.72 (m, 1H), 1.74–1.82 (m, 1H), 1.85–1.97 (m, 1H), 2.01–2.12 (m, 1H), 2.32–2.51 (m, 2H), 3.80 (s, 3H, OCH_3), 4.49 (dd, J = 4.2, 9.0 Hz, 1H), 6.08 (br s, 1H, NH), 6,89 (d, J = 8.6 Hz, 2H, H_{arom}), 7.22 (d, J = 8.6 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 172.5 (CO), 159.2, 134.6, **CH** 127.3 (2 × CH), 114.1 (2 × CH), 57.3, **CH_2** 32.2, 31.2, 19.7, **CH_3** 55.3.

4.5.4. (*S*)-6-(3,4-Dimethoxyphenyl)piperidin-2-one 14d

Mp 124–125 °C; $[\alpha]_D^{20} = -43.1$ (c 2.16, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.55–1.64 (m, 1H), 1.68–1.76 (m, 1H), 1.81–1.88 (m, 1H), 1.94–2.07 (m, 1H), 2.27–2.49 (m, 2H), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.42 (dd, J = 4.3, 9.0 Hz, 1H), 6.32 (br s, 1H, NH), 6.68–6.81 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 172.6 (CO), 149.1, 148.5, 135.0, **CH** 118.3, 111.1, 108.9, 57.4, **CH_2** 32.2, 31.1, 19.7, **CH_3** 55.9 (2 × OCH_3). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.48; H, 7.17; N, 5.80.

4.5.5. (*S*)-6-Benzo[1,3]dioxol-5-ylpiperidin-2-one 14e

Mp 136–137 °C; $[\alpha]_D^{20} = -59.1$ (c 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.55–1.68 (m, 1H), 1.72–1.80 (m, 1H), 1.84–1.94 (m, 1H), 1.99–2.08 (m, 1H), 2.37–2.46 (m, 2H), 4.46 (dd, J = 4.4, 9.0 Hz, 1H), 5.97 (s, 2H), 6.22 (br s, 1H, NH), 6.72–6.81 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 172.4 (CO), 148.0, 147.2, 136.5, **CH** 119.4, 108.3, 106.5, 57.5, **CH_2** 101.2, 32.2, 31.2, 19.6. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.57; H, 5.89; N, 6.58.

4.6. Procedures for the preparation of 15, 16, 17

Imide **15**,[23] and acylated lactams **16**[24] and **17**[17a] were prepared according to previously described procedures.

4.7. Procedures for the preparation of 18, 19, 20

To a solution of compounds **15, 16, 17** (2 mmol) and diphenyl phosphoryl chloride (0.62 mL, 3 mmol) in anhydrous THF (30 mL) cooled at −78 °C and under nitrogen atmosphere, was added dropwise with stirring a solution of KHMDS (6 mL, 0.5 M in toluene, 3 mmol). After 30 min at −78 °C, water (20 mL) was added and the resulting mixture was extracted with Et_2O (2 × 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under vacuum yielded the vinyl phosphates as yellow oils, which were used directly in the next coupling step.

To a stirred solution of crude vinyl phosphates (2 mmol) in 1,4-dioxane for **18**, THF for **19** or DME for **20** (20 mL) maintained under a nitrogen atmosphere, were added $Ba(OH)_2$ (685 mg, 4 mmol) for **18** or 2 M aqueous Na_2CO_3 (2 mL, 4 mmol) for **19** and **20**, $Pd(PPh_3)_4$ (120 mg, 5 mol %) and phenyl boronic acid (365 mg, 3 mmol). The mixture was stirred at reflux for 12 h for **18**, 2 h for **19** or 0.5 h for **20**, and then it was diluted with water (2 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to give an orange oil which was purified by flash column chromatography using EA/hexanes (40:60) as eluent to afford compounds **18**,[25] **19**,[26] **20**.[17a]

4.7.1. 1-Benzyl-6-phenyl-3,4-dihydropyridin-2(1*H*)-one 18

Mp 40–41 °C; ^1H NMR ($CDCl_3$): 2.30–2.42 (m, 2H), 2.68 (t, J = 7.2 Hz 2 H), 4.73 (s, 2H), 5.35 (t, J = 4.6 Hz, 1H), 6.88–7.02 (m, 2H, H_{arom}), 7.13–7.39 (m, 8H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 172.4 (CO), 156.7, 142.6, 135.8, **CH** 129.5, 128.4 (2 × CH), 128.1 (2 × CH), 127.4 (2 × CH), 127.0, 115.6 (2 × CH), 111.3, **CH_2** 46.2, 32.0, 19.7.

4.8. Typical procedure for the catalytic hydrogenation of 18–20 into 21–23

In a stainless steel autoclave, compounds **18–20** (0.4 mmol) were dissolved in the selected dry solvent (3 mL) under a nitrogen atmosphere and a solution of the selected catalyst in the same solvent (2 mL) was then added. The autoclave was purged 3 times with H_2 gas and finally pressurized at the chosen pressure. Heating (water bath) and stirring (magnetic stirring plate) were started and the reaction time was counted since the desired temperature was reached. After 16 h or 64 h of reaction, the autoclave was cooled and then the H_2 gas pressure was released. The reaction mixture was filtered on a pad of Celite™ and then washed with EA (2 × 10 mL). The combined organic layers were concentrated under vacuum to leave an oily product which was purified by chromatography on silica gel using EA/hexanes mixtures as eluent. HPLC analyses were performed by using Regis™ (*S*,*S*)-Whelk 01 chiral column *n*-hexane/*i*-PrOH, 80:20, flow rate 1 mL min^{-1}, detection: UV 200 nm. Retention times were: 38.0 and 55.0 min for compound **21**,[25] 7.6 and 31.5 min for compound **22**,[27] 30.7 and 43.9 min for compound **23**.

4.9. 1-Benzyl-6-phenylpiperidin-2-one 21

Oil; ^1H NMR ($CDCl_3$): 2.45–2.56 (m, 4H), 3.27–3.35 (m, 2H), 4.36 (s, 2H), 5.61 (br d, 1H), 7.05–7.32 (m, 10 H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 170.8 (CO), 141.1, 137.3, **CH** 128.6 (2 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 127.6, 127.3, 126.7 (2 × CH), 59.6, **CH_2** 47.7, 32.3, 31.8, 19.6.

4.9.1. 2-Phenylpiperidine-1-carboxylic acid phenyl ester 23

Mp 63–64 °C; ^1H NMR ($CDCl_3$): 1.72–2.23 (m, 6H), 2.95–3.03 (m, 1H), 4.02–4.18 (m, 1H), 5.63 (t, J = 6.3 Hz, 1H), 7.03–7.32 (m, 10 H, H_{arom}); ^{13}C NMR ($CDCl_3$): **C** 154.9 (CO), 151.7, 139.7, **CH** 129.4 (2 × CH), 128.9 (2 × CH), 126.9 (2 × CH), 126.7, 125.3, 121.9 (2 × CH), 54.2, **CH_2** 41.2, 28.2, 25.6, 19.4. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.70; H, 6.89; N, 4.81.

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