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A new asymmetric synthesis of 2,6-*cis*-diarylated piperidines

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ABSTRACT

A new synthetic approach to a variety of enantioenriched 2,6-*cis*-diarylated piperidines has been developed. This new methodology hinges upon the diastereoselective reduction of enantioenriched endocyclic enecarbamates obtained through a two step sequence involving a Suzuki–Miyaura cross coupling reaction between an aminovinyl phosphate and a variety of (hetero)aromatic boronic acids.

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1. Introduction

The piperidine ring system is one of the most common heterocyclic units found in a wide range of alkaloids, drugs and drug candidates, which possess a broad spectrum of interesting biological activities.[1] In particular, enantiopure 2,6-*cis*-disubstituted compounds represent 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 **1**, which is an active ingredient in the venom of fire ants, has been reported to inhibit designated neuronal nitric oxide synthase (nNOS) (see Fig. 1).[2]

(−)-Lobeline **2**, the major alkaloid of *Lobelia inflata*, has been shown to inhibit dopamine uptake into synaptic vesicles via an interaction with the tetrabenazine (TBZ) binding site on VMATZ.[3] Bicyclic (−)-pumiliotoxin C **3** was first isolated from *Dendrobates pumilio*, which possesses a *cis*-fused perhydroquinoline skeleton and is a potent neurotoxin that acts as a noncompetitive blocker for acetylcholine receptor channels.[4] Indolizidine alkaloid (+)-monomorine I **4** is a trail pheromone of the Pharaoh's ant *Monomorium pharaonis* L.[5] (−)-Lasubine II **5** which is isolated from the leaves of the *Lagerstroemia subcostata koehne*, is a rare quinolizidine alkaloid bearing an aryl group alpha to the nitrogen on the piperidine ring.[6] In addition, *meso*-2,6-*cis*-diheteroarylated

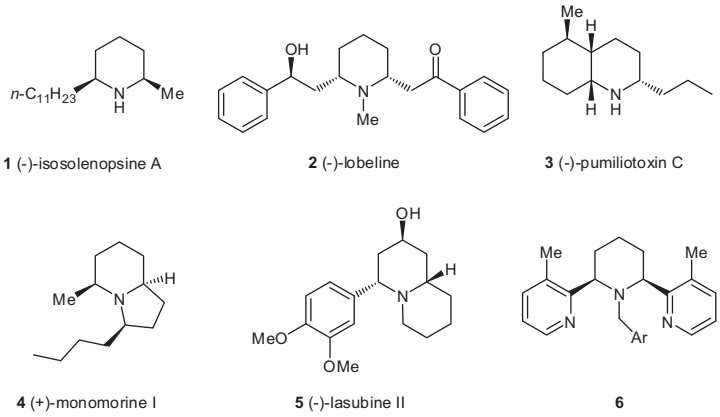

Figure 1. Examples of naturally occurring and synthetic pharmacologically active 2,6-*cis*-disubstituted piperidines.

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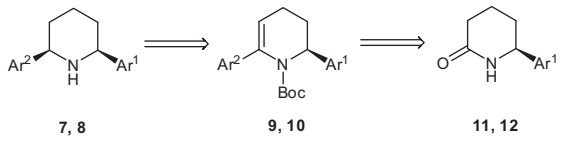
compounds such as **6** have been shown to bind to chemokine receptors, including CXCR4 and CCR5, and demonstrate protective effects against the infection of target cells by a human immunodeficiency virus (HIV).[7] Consequently, the important bioactivities of these compounds have stimulated the development of new synthetic approaches and considerable effort has been devoted to the preparation of enantiopure 2,6-*cis*-dialkylated piperidines.[8] Paradoxically, to the best of our knowledge, only one synthesis of enantiopure 2,6-*cis*-diarylated piperidines has been reported so far. Thus, Szymoniak et al.[8j] 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.

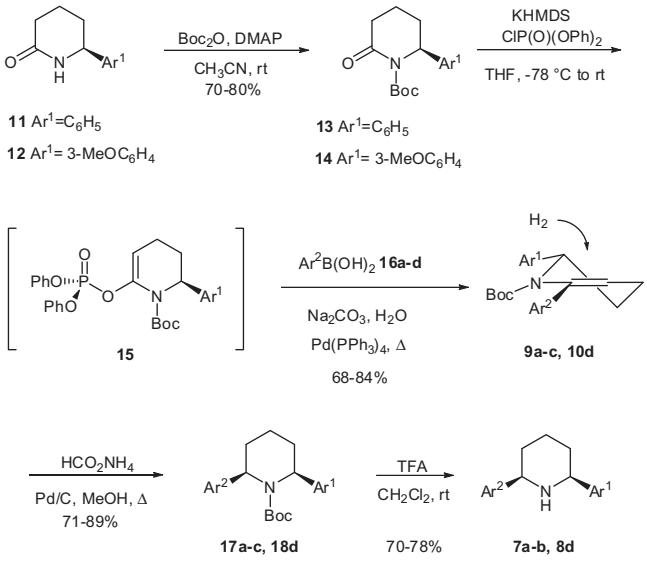
2. Results and discussion

We have developed a new synthetic approach to a variety of enantiopure 2,6-*cis*-diarylated piperidines, which relies upon the diastereoselective reduction of endocyclic enecarbamates **9** and **10** as the key step (retrosynthetic Scheme 1). These highly conjugated models would be obtained through a two step sequence involving a Suzuki cross coupling reaction from the enantioenriched 6-arylpiperidin-2-ones **11** and **12**.



Scheme 1. Retrosynthetic analysis of enantioenriched 2,6-*cis*-diarylated piperidines.

The new synthetic route, depicted in Scheme 1, requires the preliminary elaboration of chiral piperidinones **11** and **12** bearing an aryl group alpha to nitrogen (Scheme 2). These enantioenriched lactams (ee >96%) can be easily prepared in four steps from glutaric anhydride via a reported procedure[9] and then protected by reaction with Boc_2O to furnish carbamates **13** and **14**. The *N*-Boc group was initially used as an electron withdrawing protecting group since it could be easily removed under acidic conditions. We assumed that these cyclic protected lactams 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.,[10] several groups have used constitutionally diverse enol phosphates in a variety of cross-coupling reactions.[11] Coudert et al. developed a new and efficient methodology, which allows access to a wide range of nitrogen heterocycles based upon a Suzuki–Miyaura cross coupling between lactam derived enol phosphates and boronic acids.[12] Exposure of protected chiral lactams **13** and **14** to KHMDS at −78 °C provided the corresponding potassium enolate which was intercepted by reaction with diphenyl phosphoryl chloride to give the sensitive aminovinyl phosphates **15**, 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 (hetero)aromatic boronic acids **16a–d** 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 **9a–c** and **10d**. With this reliable route to these enecarbamates in hand, the diastereoselective reduction of the endocyclic carbon–carbon double bond of these highly conjugated compounds was initiated. Assuming a pseudoequatorial aryl group orientation and Fürst–Plattner control (*trans*-diaxial addition) for the reduction of **9** and **10** we expected that the 2,6-*cis* relative stereochemistry should be observed via catalytic hydrogenation of these enecarbamates.[8i] As anticipated, the antiperiplanar addition of hydrogen from the less hindered face of the half-chair-like privileged conformation of **9** and **10** gave diastereomers **17** and **18** with a high level of selectivity. It should be noted that the reduction of enecarbamate **9c** was less stereoselective. Indeed, two inseparable diastereoisomers detectable by ^1H NMR spectroscopy were obtained, probably due to the presence of the less hindered furyl group in our model. Finally, removal of the protecting group was achieved cleanly under acidic conditions by treatment of the carbamates **17a–b**, **18d** with trifluoroacetic acid to afford the targeted virtually enantiopure *cis*-2,6-diarylated piperidines **7a–b**, **8d**. The absolute and relative configurations of **7a–b**, **8d** were inferred by comparison of the specific rotation with the literature data, for example, $[\alpha]_D^{20}$ = +14.9 for (2*R*,6*S*)-**7a** (*c* 0.95, MeOH), lit.[8j] −14.5 for (2*S*,6*R*)-**7a** (*c* 1.00, MeOH) (see Table 1).



Scheme 2. Asymmetric synthesis of 2,6-diarylated piperidines **7**, **8**.

3. Conclusion

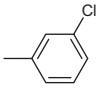
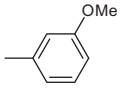
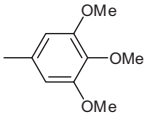
We have developed a flexible and efficient route for the stereoselective synthesis of 2,6-*cis*-diarylated piperidines. This new methodology hinges upon the diastereoselective reduction of enantioenriched endocyclic enecarbamate obtained through a two step sequence involving a Suzuki–Miyaura cross coupling reaction between an aminovinyl phosphate and a variety of (hetero)aromatic boronic acids. The extension of this approach to other scaffolds is in progress in our laboratory.

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 and are 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.

Table 1
Compounds **9a–c**, **10d**, **17a–c**, **18d**, **7a**, **b**, **8d** prepared

Entry	Ar[1]	Ar[2]	Compound	Yield[a] (%)	Compound	Yield[a] (%)	de[b] (%)	Compound	Yield[a] (%)	de[b] (%)
1			**9a**	74	**17a**	85	>96	**7a**	70	>96
2			**9b**	84	**17b**	71	>96	**7b**	78	>96
3			**9c**	71	**17c**	77	84			
4			**10d**	68	**18d**	89	>96	**8d**	72	>96

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

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 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) and ethanol (EtOH) were distilled over magnesium turnings, CH_2Cl_2 over CaH_2 and toluene over sodium.

4.2. Typical procedure for the preparation of *N*-Boc lactams 13 and 14

A solution of 6-arylpiperidin-2-one **11** or **12**[9] (3 mmol), di-*tert*-butyl dicarbonate (720 mg, 3.3 mmol), and 4-dimethylaminopyridine (36 mg, 0.3 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 12 h. Water (20 mL) was then added and the resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using EtOAc/hexanes (20:80) as eluent to give **13** or **14**.

4.2.1. (6*S*)-2-Oxo-6-phenylpiperidine-1-carboxylic acid *tert*-butyl ester 13

578 mg (70%); mp 84–85 °C; $[\alpha]_D^{20} = -19.6$ (*c* 0.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.25 (s, 9H, 3 × CH_3), 1.69–1.76 (m, 2H, CH_2), 1.85–1.98 (m, 1H, CH_2), 2.12–2.19 (m, 1H, CH_2), 2.53–2.68 (m, 2H, CH_2), 5.22 (t, *J* = 5.4 Hz, 1H, NCH), 7.20–7.38 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 171.6 (CO), 151.9 (CO), 142.3, 83.0, *CH* 128.7 (2 × CH), 127.4, 125.7 (2 × CH), 60.7 (NCH), CH_2 34.6, 31.7, 17.3, CH_3 27.5 (3 × CH_3). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.66; H, 7.92; N, 5.28.

4.2.2. (2*S*)-2-(3-Methoxyphenyl)-6-oxopiperidine-1-carboxylic acid *tert*-butyl ester 14

733 mg (80%); oil; $[\alpha]_D^{20} = -20.8$ (*c* 1.44, $CHCl_3$), ^{1}H NMR ($CDCl_3$): 1.28 (s, 9H, 3 × CH_3), 1.65–1.83 (m, 2H, CH_2), 1.88–1.99 (m, 1H, CH_2), 2.08–2.23 (m, 1H, CH_2), 2.45–2.67 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.19 (t, *J* = 5.4 Hz, 1H, NCH), 6.73–6.82 (m, 3H, H_{arom}), 7.26 (t, *J* = 7.9 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 171.6 (CO), 159.7 (CO), 154.8, 144.2, 82.9, *CH* 129.6, 118.0, 112.6, 111.5, 60.7 (NCH), CH_2 34.5, 31.6, 17.6, CH_3 55.3, 27.5 (3 × CH_3). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.80; H, 7.68; N, 4.45.

4.3. Typical procedure for the synthesis of enecarbamates 9a–c, 10d

To a solution of *N*-Boc lactams **13** and **14** (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 under stirring a solution of KHMDS (6 mL, 0.5 M in toluene, 3 mmol). After 30 minutes 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 in vacuo yielded the aminovinyl phosphates **15** as a yellow oil, which was used directly for the next coupling step. To a stirred solution of crude **15** (2 mmol) in THF (20 mL) maintained under nitrogen atmosphere, were added 2 M aqueous Na_2CO_3 solution (2 mL, 4 mmol), $Pd(PPh_3)_4$ (120 mg, 5 mol %) and the appropriate aromatic boronic acid (3 mmol). The mixture was stirred for 2 h at reflux, and then 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 EtOAc/hexanes (40:60) as eluent to afford compounds **9a–c**, **10d**.

4.3.1. (2*S*)-6-(3-Chlorophenyl)-2-phenyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 9a

547 mg (74%); mp 70–71 °C; $[\alpha]_D^{20} = -88.7$ (*c* 0.78, $CHCl_3$), ^{1}H NMR ($CDCl_3$): 1.13 (s, 9H, 3 × CH_3), 2.14–2.32 (m, 4H, 2 × CH_2), 5.36 (t, *J* = 3.6 Hz, 1H, NCH), 5.72 (t, *J* = 3.5 Hz, 1H, CH), 7.19–7.26 (m, 4H, H_{arom}), 7.31–7.43 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 154.5 (CO), 142.9, 140.7, 137.3, 133.5, 81.4, *CH* 129.3, 128.5 (2 × CH), 127.0, 126.9, 126.3 (2 × CH), 125.5, 123.4, 116.7, 55.0 (NCH), CH_2 27.5, 20.5, CH_3 27.8 (3 × CH_3). Anal. Calcd for $C_{22}H_{24}ClNO_2$: C, 71.44; H, 6.54; N, 3.79. Found: C, 71.15; H, 6.40; N, 3.98.

4.3.2. (2*S*)-6-(2-Methoxyphenyl)-2-phenyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 9b

614 mg (84%); oil; $[\alpha]_D^{20} = -122.9$ (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.05 (s, 9H, 3 × CH_3), 2.06–2.26 (m, 4H, 2 × CH_2), 3.73 (s, 3H, OCH_3), 5.14 (t, *J* = 3.6 Hz, 1H, NCH), 5.67 (t, *J* = 3.5 Hz, 1H, CH), 6.77–6.88 (m, 2H, H_{arom}), 7.15–7.34 (m, 5H, H_{arom}), 7.58 (d, *J* = 7.5 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 156.2 (CO), 154.1, 141.7, 135.7, 130.5, 80.2, *CH* 128.8, 128.1 (2 × CH), 127.9, 126.8 (2 × CH), 126.6, 120.4, 114.5, 109.9, 54.8 (NCH), CH_2 27.3, 20.7, CH_3 55.6, 27.7 (3 × CH_3). Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.91; H, 7.30; N, 3.95.

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4.3.3. (2*S*)-6-Furan-2-yl-2-phenyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 9c

461 mg (71%); oil; $[\alpha]_D^{20} = -96.3$ (*c* 0.83, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.28 (s, 9H, 3 × CH_3), 1.93–2.25 (m, 3H, 2 × CH_2), 2.35–2.45 (m, 1H, CH_2), 5.40 (t, *J* = 3.6 Hz, 1H, NCH), 5.69 (t, *J* = 3.4 Hz, 1H, CH), 6.28 (d, *J* = 3.3 Hz, 1H, H_{arom}), 6.38 (dd, *J* = 3.3–1.8 Hz, 1H, H_{arom}), 7.19–7.46 (m, 6H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 152.4 (CO), 139.9, 136.5, 128.4, 80.8, *CH* 128.3 (2 × CH), 126.6, 126.0 (2 × CH), 125.8, 114.8, 110.9, 104.7, 54.6 (NCH), CH_2 27.1, 20.1, CH_3 27.8 (3 × CH_3). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.71; H, 7.19; N, 4.15.

4.3.4. (2*S*)-2-(3-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 10d

619 mg (68%); oil; $[\alpha]_D^{20} = -90.5$ (*c* 1.89, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.17 (s, 9H, 3 × CH_3), 2.21–2.35 (m, 4H, 2 × CH_2), 3.76 (s, 3H, OCH_3), 3.83 (s, 6H, 2 × OCH_3), 3.84 (s, 3H, OCH_3), 5.37 (t, *J* = 3.3 Hz, 1H, NCH), 5.63–5.69 (br s, 1H, CH), 6.61 (s, 2H, H_{arom}), 6.67 (dd, *J* = 2.4–7.7 Hz, 1H, H_{arom}), 7.02–7.07 (m, 2H, H_{arom}), 7.23–7.29 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 159.6 (CO), 154.5, 152.9 (2 × C), 142.7, 138.4, 137.0, 134.3, 80.9, *CH* 129.3, 118.7, 115.5, 113.0, 111.5, 102.3 (2 × CH), 54.9 (NCH), CH_2 27.6, 20.5, CH_3 61.0, 56.0 (2 × OCH_3), 55.2, 27.8 (3 × CH_3). Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.72; H, 7.13; N, 2.92.

4.4. Typical procedure for the synthesis of carbamates 17a–c, 18d

A suspension of compounds **9a**–**c**, **10d** (1 mmol) in MeOH (15 mL) was stirred with activated Pd/C (10 mg, 10 mol %) and a solution of HCO_2NH_4 (252 mg, 4 mmol) in distilled water (2 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 left an oily product, which was purified by chromatography on silica gel using EtOAc/hexanes (60:40) as eluent to give **17a**–**c**, **10d**.

4.4.1. (2*R*,6*S*)-2-(3-Chlorophenyl)-6-phenylpiperidine-1-carboxylic acid *tert*-butyl ester 17a

316 mg (85%); mp 86–87 °C; $[\alpha]_D^{20} = -51.6$ (*c* 0.41, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.17 (s, 9H, 3 × CH_3), 1.38–1.47 (m, 2H, CH_2), 1.79–2.24 (m, 4H, 2 × CH_2), 5.17–5.28 (m, 2H, 2 × NCH), 7.17–7.35 (m, 9H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 156.2 (CO), 148.1, 144.7, 127.9, 79.7, *CH* 128.2 (2 × CH), 126.8, 126.1 (2 × CH), 125.6 (4 × CH), 55.4 (NCH), 55.2 (NCH), CH_2 28.2, 27.3, 14.4, CH_3 28.0 (3 × CH_3). Anal. Calcd for $C_{22}H_{26}ClNO_2$: C, 71.05; H, 7.05; N, 3.77. Found: C, 70.92; H, 7.12; N, 3.99.

4.4.2. (2*R*,6*S*)-2-(2-Methoxyphenyl)-6-phenylpiperidine-1-carboxylic acid *tert*-butyl ester 17b

261 mg (71%); oil; $[\alpha]_D^{20} = -16.4$ (*c* 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.11 (s, 9H, 3 × CH_3), 1.34–1.45 (m, 2H, CH_2), 1.83–2.18 (m, 3H, 2 × CH_2), 2.25–2.37 (m, 1H, CH_2), 3.84 (s, 3H, OCH_3), 5.36 (br s, 1H, NCH), 5.52 (br s, 1H, NCH), 6.84 (dd, *J* = 8.1–0.9 Hz, 1H, H_{arom}), 6.93 (td, *J* = 7.5–0.9 Hz, 1H, H_{arom}), 7.16–7.33 (m, 7H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 156.4 (CO), 155.9, 145.8, 131.6, 79.3, *CH* 128.6, 128.2 (2 × CH), 127.1, 126.0, 125.5 (2 × CH), 120.0, 110.2, 54.8 (NCH), 51.4 (NCH), CH_2 28.9, 26.7, 14.5, CH_3 55.2, 28.0 (3 × CH_3). Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.28; H, 8.12; N, 3.63.

4.4.3. (2*R*,6*S*)-2-Furan-2-yl-6-phenylpiperidine-1-carboxylic acid *tert*-butyl ester 17c

252 mg (77%); oil; $[\alpha]_D^{20} = -20.5$ (*c* 0.16, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.24 (s, 9H, 3 × CH_3), 1.43–1.56 (m, 2H, CH_2), 1.78–1.93 (m, 1H, CH_2), 1.98–2.21 (m, 3H, 2 × CH_2), 4.99 (br s, 1H, NCH), 5.36 (br s, 1H, NCH), 6.12–6.15 (m, 1H, H_{arom}), 6.33–6.35 (m, 1H, H_{arom}), 7.20–7.35 (m, 6H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 156.6 (CO), 156.1, 143.6, 79.9, *CH* 140.9, 128.5 (2 × CH), 126.3, 125.6 (2 × CH), 110.3, 105.9, 55.5 (NCH), 49.8 (NCH), CH_2 28.9, 25.2, 15.2, CH_3 28.1 (3 × CH_3). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.42; H, 7.63; N, 4.33.

4.4.4. (2*S*,6*R*)-2-(3-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)piperidine-1-carboxylic acid *tert*-butyl ester 18d

407 mg (89%); oil; $[\alpha]_D^{20} = -38.4$ (*c* 3.4, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.22 (s, 9H, 3 × CH_3), 1.39–1.48 (m, 2H, CH_2), 1.83–2.25 (m, 4H, 2 × CH_2), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 6H, 2 × OCH_3), 5.18–5.32 (m, 2H, 2 × NCH), 6.51 (s, 2H, H_{arom}), 6.77 (dd, *J* = 8.0–2.4 Hz, 1H, H_{arom}), 6.83–6.92 (m, 2H, H_{arom}), 7.22–7.29 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 159.7 (CO), 156.2, 153.1, (2 × C), 146.3, 140.4, 136.3, 79.7, *CH* 129.3, 118.0, 114.7, 111.1, 102.6 (2 × CH), 55.8 (NCH), 55.2 (NCH), CH_2 28.1 (2 × CH_2), 14.4, CH_3 60.9, 56.0 (2 × OCH_3), 54.8, 27.6 (3 × CH_3). Anal. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 68.19; H, 7.95; N, 3.19.

4.5. Typical procedure for the synthesis of 2,6-diarylpiperidines 7a–b, 8d

To a solution of compounds **17a**–**b**, **18d** (0.3 mmol) in CH_2Cl_2 (2 mL) at room temperature was added trifluoroacetic acid (0.35 mL, 4.5 mmol). After stirring for 3H, the reaction mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated in vacuo to provide an oily product, which was purified by chromatography on silica gel using hexanes/Et_2O (90:10) as eluent.

4.5.1. (2*R*,6*S*)-2-(3-Chlorophenyl)-6-phenylpiperidine 7a

57 mg (70%); oil; $[\alpha]_D^{20} = +14.9$ (*c* 0.95, MeOH), lit.[8j] $[\alpha]_D^{20} = -14.5$ (*c* 1, MeOH) for the (2*S*,6*R*)-enantiomer; ^1H NMR ($CDCl_3$): 1.32–1.62 (m, 3H, 2 × CH_2), 1.66–1.83 (m, 3H, 2 × CH_2), 1.89–1.95 (m, 1H, NH), 3.62–3.75 (m, 2H, 2 × NCH), 7.17–7.40 (m, 9H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 144.1 (2 × C), 132.5, *CH* 130.0, 128.8, 127.6, 127.4, 127.2 (4 × CH), 125.4, 62.9 (NCH), 62.6 (NCH), CH_2 35.2, 35.1, 26.2. Anal. Calcd for $C_{17}H_{18}ClN$: C, 75.13; H, 6.68; N, 5.15. Found: C, 75.01; H, 6.55; N, 5.32.

4.5.2. (2*R*,6*S*)-2-(2-Methoxyphenyl)-6-phenylpiperidine 7b

62 mg (78%); mp 63–64 °C, lit.[8j] 68 °C; $[\alpha]_D^{20} = -17.0$ (*c* 1.18, MeOH); ^1H NMR ($CDCl_3$): 1.36–1.96 (m, 6H, 3 × CH_2), 3.76 (s, 3H, OCH_3), 3.82 (dd, *J* = 11.1–2.5 Hz, 1H, NCH), 4.13 (dd, *J* = 11.1–2.2 Hz, 1H, NCH), 6.78 (d, *J* = 8.2 Hz, 1H, H_{arom}), 6.89 (t, *J* = 7.4 Hz, 1H, H_{arom}), 7.08–7.17 (m, 2H, H_{arom}), 7.23 (t, *J* = 7.2 Hz, 2H, H_{arom}), 7.37 (d, *J* = 7.1 Hz, 2H, H_{arom}), 7.53 (dd, *J* = 7.5–1.6 Hz, 1H, H_{arom}) [NH not observed]; ^{13}C NMR ($CDCl_3$): *C* 156.6, 146.2, 133.7, *CH* 128.3 (2 × CH), 127.6, 127.0 (2 × CH), 126.9 (2 × CH), 120.8, 110.1, 55.3 (NCH), 55.2 (NCH), CH_2 34.9, 32.2, 25.9, CH_3 62.9. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.01; H, 7.80; N, 5.36.

4.5.3. (2*S*,6*R*)-2-(3-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)piperidine 8d

77 mg (72%); oil; $[\alpha]_D^{20} = -53.0$ (*c* 0.1, MeOH); ^1H NMR ($CDCl_3$): 1.45–1.64 (m, 2H, CH_2), 1.78–1.86 (m, 2H, CH_2), 1.94–2.05 (m, 2H, CH_2), 3.72–3.81 (m, 2H, 2 × NCH), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.88 (s, 6H, 2 × OCH_3), 6.70 (s, 2H, H_{arom}), 6.78 (dd, *J* = 8.1, 2.6 Hz, 1H, H_{arom}), 7.03–7.06 (m, 2H, H_{arom}), 7.22–7.28 (m, 1H,

H_{arom}) [NH not observed]; ^{13}C NMR ($CDCl_3$): *C* 129.6, 153.1 (2 × C), 147.4, 141.7, 136.7, *CH* 129.3, 119.1, 112.5, 112.1, 103.5 (2 × CH), 63.0 (NCH), 62.6 (NCH), CH_2 34.8, 34.6, 25.8, CH_3 60.8, 56.1 (2 × OCH_3), 55.2. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.35; H, 7.85; N, 3.84.

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