Convenient, Benign and Scalable Synthesis of 2- and 4-Substituted Benzylpiperidines

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A short, scalable and environmentally benign synthesis of 2- and 4-substituted benzylpiperidines has been developed. The method is based on the temperature-programmed consecutive deoxygenation and heteroaromatic ring saturation of aryl(pyridin-2-yl)- and aryl(pyridin-4-yl)methanols and aryl(pyridin-4-yl)methanones in the presence of Pd/C catalyst. The crucial roles of the temperature, the acidity and the substrate structure in the change of selectivity have been demonstrated by isolation of several substituted aryl(piperidine)methanols. The carbinols and ketones were prepared from commercially available pyridinecarbaldehydes or 4-cyanopyridine and substituted bromobenzenes via organometallic intermediates.

Introduction

Substituted benzylpiperidines are common building blocks of pharmaceutically important compounds.[1] For example, 2-benzylpiperidines are known dopamine receptor antagonists,[2] 4-benzylpiperidine derivatives are used as selective *N*-methyl-D-aspartate (NMDA) antagonists,[3] and their high affinities for several other central nervous system receptors such as $5HT_{1A}$ or $5HT_2$, are also known from the literature.[4]

Two strategies have been followed in the literature for the preparation of 2- and 4-benzylpiperidine derivatives. One of these methods is based on the coupling of the aromatic moiety with a pyridine derivative followed by the saturation of the heteroaromatic ring. Benzylpyridines have been synthesized by Friedel−Crafts acylation,[5] catalytic carbonylation,[6] or organometallic reactions,[3] followed by reduction of the formed aryl(pyridinyl)methanones with hydrazine.[3,5] Organometallic synthesis of aryl(pyridinyl)methanols[7] and consecutive deoxygenation with Zn,[8] SmI_2,[9] in situ generated Me_3SiI,[10] or Pd/C-catalysed reduction[11] are also known methods for the preparation of benzylpyridine derivatives. The same structure has also been built up by consecutive arylation of benzyl cyanide with 2-chloropyridine, basic hydrolysis and decarboxylation.[12]

The above-mentioned procedures usually do not deal with the saturation of the pyridine ring. In other articles hydrogenation of benzylpyridines has been accomplished in the presence of Pt,[13] PtO_2 [3,12] and Raney nickel.[14] Although palladium on carbon has been used for the saturation of pyridine derivatives in many cases, there is just one example where this catalyst is used for the heteroaromatic ring saturation of benzylpyridine.[15]

In the other kind of procedures the piperidine moiety is coupled with an aromatic (or benzylic) group. In this case, there are no common methods for the synthesis of 2- and 4-benzylpiperidines. For example, 2-benzylpiperidine derivatives have been synthesized by the lithium aluminium hydride reduction of 2-benzyl-3,4,5,6-tetrahydropyridine,[16] or by ruthenium-catalyzed intramolecular hydroamination of the corresponding aminoalkynes.[17] Substituted 4-benzylpiperidines have been obtained from the corresponding aryl(piperidinyl)methanones by deoxygenation with hydrazine,[5] triethylsilane[4] or consecutive sodium borohydride/hydrogen iodide/phosphorus reduction[18] in five to six steps, or by the Wittig reaction of benzylphosphonium bromide and *N*-benzyl-4-piperidone and catalytic saturation of the olefinic double bond.[19] Recently, a novel multistep synthesis of several benzylpiperidines has been published. The key steps of the synthesis involve the cyclization of imines bearing an allylsilane moiety in the side-chain followed by a palladium-catalyzed cross-coupling reaction.[20]

The disadvantages of the above-mentioned methods are the use of sophisticated (and consequently expensive) and/

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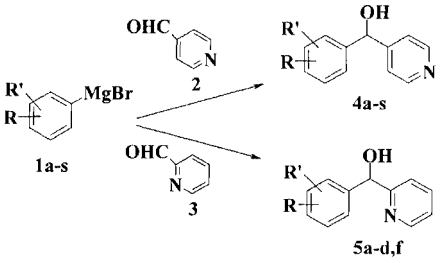
or dangerous reagents and conditions, low overall yields and production of significant amount of environmentally dangerous side products. In most cases, lack of flexibility towards preparation of different benzylpiperidines with the same reaction sequence is also a strong limitation of their application.

In order to search for a scalable, environmentally benign and general procedure for preparation of 2- and 4-benzylpiperidines, we reinvestigated our previously developed two-step synthesis of 3-benzylpiperidines.[21]

Results and Discussion

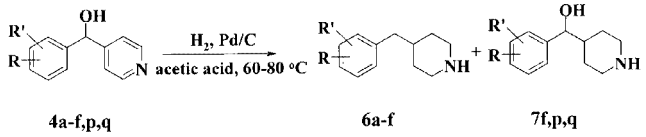
According to our synthetic strategy, a series of Grignard reagents (**1a**−**s**), prepared in situ from the corresponding substituted bromobenzenes in tetrahydrofuran, were treated with readily available pyridine-4-carbaldehyde (**2**) and pyridine-2-carbaldehyde (**3**), respectively (Scheme 1). Subsequent deoxygenation of the benzylic position and parallel saturation of the pyridine ring of compounds **4a**−**s**, **5a**−**d** and **5f** were attempted using a Pd/C catalyst.



a: R = 4-MeO, R' = H; **b**: R = 3-MeO, R' = H; **c**: R = 2-MeO, R' = H; **d**: R = 4-Me, R' = H; **e**: R = (2,2-dimethyl-2,3-dihydrobenzofuran-5-yl), R' = H; **f**: R = 3-CF_3, R' = H; **g**: R = 4-F, R' = H; **h**: R = 3-F, R' = H; **i**: R = 3-Me, R' = H; **j**: R = 2-Me, R' = H; **k**: R = 4-Et, R' = H; **l**: R = 3-Me, R' = 4-Me; **m**: R = 3-F, R' = 4-MeO; **n**: R = 5-F, R' = 2-Me; **o**: R = 3-EtO, R' = H; **p**: R = 3-F, R' = 5-F; **q**: R = 3-MeO, R' = 5-CF_3; **r**: R = 3-CF_3, R' = 5-CF_3, **s**: R = 3-OBn, R' = H

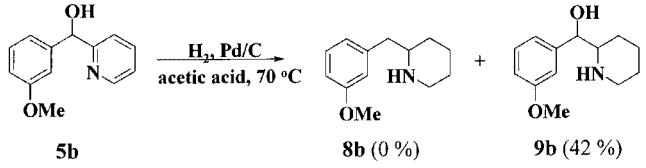
Scheme 1

In the cases of compounds **4a**−**e**, the previously developed method — hydrogenation in glacial or aqueous acetic acid at 60−80 °C — resulted in the formation of **6a**−**e** as sole products (Scheme 2, Table 1) in good yields. However, mixtures of the desired benzylpiperidines (**6f**) and about 5−10% of substituted aryl(piperidinyl)methanols (**7f**) were formed when a trifluoromethyl group was present in the carbinol **4**; aryl(piperidinyl)methanols **7p**,**q** were the sole products upon reduction of **4p**,**q** in warm glacial acetic acid (Scheme 2, Table 1).



Scheme 2

Hydrogenation of compound **5b** under the above-mentioned conditions gave similar results: instead of the desired product **8b**, only (3-methoxyphenyl)(piperidin-2-yl)methanol (**9b**) was formed (Scheme 3). It should be mentioned that our attempts to dehydroxylate **7p**,**q** or **9b** in acetic acid at higher temperature and with prolonged reaction times failed.



Scheme 3

In a separate experiment, the rate of hydrogen consumption during reduction of **4a** at atmospheric pressure was also determined. Figure 1 shows that the process contains two separate, consecutive steps. Consumption of 1 equiv. of hydrogen (dehydroxylation) can be observed at 25−35 °C;

Table 1. Hydrogenation of compounds **4** and **5** in acetic acid at 60−80 °C

Intermediate from Grignard reaction Compound	Yield[a]	Conditions of hydrogenation	Products of hydrogenation Compounds	Ratio[b]	Yield[a]
4a	80%	AcOH, 1 bar, 75 °C	**6a** + **7a**	100:0	83%
4b	86%	AcOH, 10 bar, 80 °C	**6b** + **7b**	100:0	68%
4c	75%	AcOH, 1 bar, 75 °C	**6c** + **7c**	100:0	91%
4d	74%	AcOH, 1 bar, 60 °C	**6d** + **7d**	100:0	89%
4e	37%	AcOH, 10 bar, 60 °C	**6e** + **7e**	100:0	48%
4f	87%	AcOH, 1 bar, 60 °C	**6f** + **7f**	95:5	93%
		AcOH, 10 bar, 70 °C	**6f** + **7f**	90:10	57%
4p	72%	AcOH, 1 bar, 70 °C	**6p** + **7p**	0:100	74%
4q	52%	AcOH, 1 bar, 75 °C	**6q** + **7q**	0:100	89%
5b	64%	AcOH, 10 bar, 70 °C	**8b** + **9b**	0:100	42%

[a] Yields of the isolated, purified products. [b] Product ratios were determined from the ^{1}H NMR spectra of the products.

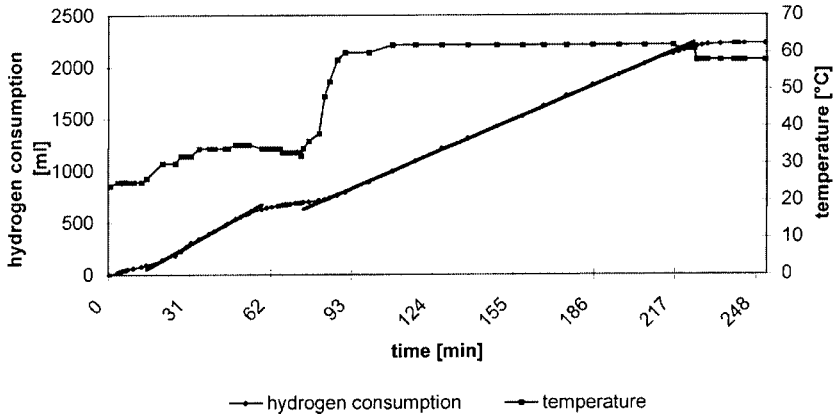
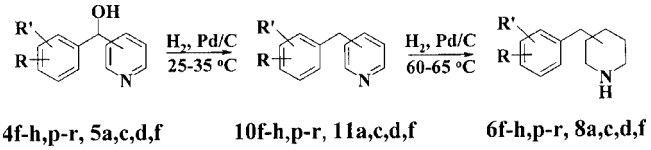


Figure 1. Time- and temperature-dependent hydrogen consumption during Pd/C-catalysed reduction of **4a** in glacial acetic acid

ring saturation (consumption of 3 equiv. of hydrogen) starts at higher temperature.

On the basis of these experimental results we concluded that the position of the benzylic group in the pyridine ring, as well as the nature of the substituent on the aromatic group, have a strong effect on the rate of dehydroxylation in the benzylic position. If this process is slow because of steric and/or electronic factors, pyridine-ring saturation occurs before dehydroxylation and carbinols of type **7** or **9** are formed. Under the applied conditions these carbinols, bearing only one neighbouring aromatic ring, are stable enough against further reductive dehydroxylation.

Consequently, we should finish dehydroxylation before ring saturation is started. According to this goal we determined the optimum conditions for stepwise dehydroxylation and pyridine-ring saturation using the same Pd/C catalyst. The rate of dehydroxylation increased significantly upon addition of strong mineral acids (H_2SO_4 or HCl) in protic solvents (acetic acid, ethanol or methanol) at ambient (25−35 °C) temperature. The benzylpyridines **10f**−**h**, **10p**−**r**, **11a**,**c**,**d** and **11f** were isolated in satisfactory to good yields after purification by fractional vacuum distillation. Then, in a separate reaction, all of these compounds were transformed into the corresponding piperidine derivatives **6** and **8** (Scheme 4, Table 2).



4f-h,p-r, 5a,c,d,f **10f-h,p-r, 11a,c,d,f** **6f-h,p-r, 8a,c,d,f**

Scheme 4

The separation and stepwise intermediate purification of the two reactions may cause waste of material, therefore we have also developed a "one-pot" version of the process. Dehydroxylation of the substrates was accomplished with hydrogen in a vigorously stirred mixture of a protic solvent and mineral acid at 20−30 °C in the presence of Pd/C catalyst and, after consumption of 1 equiv. of hydrogen gas, the temperature of the reaction mixture was increased to 60−65 °C for pyridine-ring saturation. Using this temperature-programmed reduction process a series of Grignard adducts (**4a**−**d**,**f**,**i**−**o**, **5a** and **5f**) were transformed into the desired products (**6a**−**d**,**f**,**i**−**o**, **8a** and **8f**) in good yield (Table 3).

Table 2. Two-step hydrogenation of compounds **4** and **5**

Intermediate from Grignard reaction		First reduction step		Second reduction step	
Compound	Yield[a]	Conditions	Product (yield)[a]	Conditions	Product (yield)[a]
4f	87%	$MeOH/H_2SO_4$, 1 bar, 25 °C	**10f** (55%)	AcOH, 10 bar, 60 °C	**6f** (53%)
4g	85%	$MeOH/H_2SO_4$, 1 bar, 30 °C	**10g** (70%)	AcOH, 10 bar, 60 °C	**6g** (83%)
4h	49%	$MeOH/H_2SO_4$, 1 bar, 30 °C	**10h** (70%)	AcOH, 10 bar, 60 °C	**6h** (67%)
4p	72%	$AcOH/H_2SO_4$, 1 bar, 30 °C	**10p** (89%)	AcOH, 10 bar, 60 °C	**6p** (91%)
4q	52%	$AcOH/H_2SO_4$, 1 bar, 35 °C	**10q** (84%)	AcOH, 10 bar, 65 °C	**6q** (88%)
4r	49%	$AcOH/H_2SO_4$, 1 bar, 35 °C	**10r** (91%)	AcOH, 10 bar, 65 °C	**6r** (95%)
5a	83%	$MeOH/H_2SO_4$, 1 bar, 25 °C	**11a** (77%)	AcOH, 10 bar, 65 °C	**8a** (57%)
5c	72%	$MeOH/H_2SO_4$, 1 bar, 25 °C	**11c** (79%)	AcOH, 10 bar, 65 °C	**8c** (66%)
5d	89%	$MeOH/H_2SO_4$, 1 bar, 25 °C	**11d** (87%)	AcOH, 10 bar, 65 °C	**8d** (82%)
5f	96%	$MeOH/H_2SO_4$, 1 bar, 25 °C	**11f** (66%)	AcOH, 10 bar, 65 °C	**8f** (80%)

[a] Yields of the isolated, purified products.

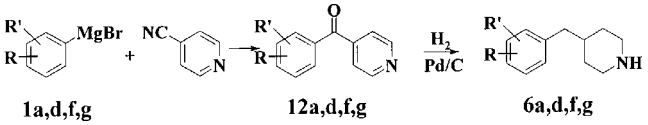
Table 3. Temperature-programmed "one-pot" hydrogenation of compounds **4** and **5**

Starting material[a]	Conditions of hydrogenation	Product of hydrogenation	
		Compound	Yield[b]
4a (80%)	EtOH/HCl, 1 bar, 30 °C then 60 °C	**6a**	82%
4b (86%)	EtOH/H_2SO_4, 10 bar, 20 °C then 60 °C	**6b**	42%
4c (75%)	EtOH/HCl, 1 bar, 30 °C then 65 °C	**6c**	82%
4d (74%)	EtOH/HCl, 1 bar, 30 °C then 65 °C	**6d**	86%
4f (87%)	EtOH/HCl, 1 bar, 30 °C then 65 °C	**6f**	71%
4i (88%)	AcOH, 10 bar, 20 °C then 60 °C	**6i**	67%
4j (95%)	AcOH, 10 bar, 20 °C then 60 °C	**6j**	70%
4k (67%)	EtOH/HCl, 1 bar, 30 °C then 60 °C	**6k**	86%
4l (76%)	EtOH/HCl, 1 bar, 30 °C then 60 °C	**6l**	83%
4m (91%)	EtOH/HCl, 1 bar, 30 °C then 60 °C	**6m**	76%
4n (96%)	EtOH/HCl, 1 bar, 30 °C then 60 °C	**6n**	80%
4o (86%)	EtOH/HCl, 1 bar, 30 °C then 60 °C	**6o**	77%
5a (83%)	EtOH/HCl, 1 bar, 30 °C then 60 °C	**8a**	62%
5f (96%)	EtOH/HCl, 1 bar, 30 °C then 60 °C	**8f**	77%

[a] Yields of Grignard reactions (**1** → **4** or **5**) are given in parentheses. [b] Yields of the isolated, purified products.

Reduction of **4a**−**d** and **4f** in glacial acetic acid at 60−80 °C gave the desired products (**6a**−**d** and **6f**) in similar or better yields (Table 1) than those of the temperature-programmed "one-pot" method (Table 3), the big advantage of this latter process being the safe, side-product-free preparation of benzylpiperidines in every case. A good example is the reduction of compound **4f** in acetic acid where 5 or 10% of (piperidin-4-yl)[3-(trifluoromethyl)phenyl]methanol (**7f**) was formed (depending on the temperature), whereas **6f** was obtained by the temperature-programmed "one-pot" method.

To check the scope and limitations of our new Pd/C catalysed "temperature-programmed consecutive reduction method" several substituted aryl(pyridin-4-yl)methanones (**12a**,**d**,**f**,**g**) were synthesized from 4-cyanopyridine and substituted bromobenzenes according to a literature method[3] (Scheme 5, yields are given in Table 4). Compounds **12** are the oxidized analogues of our carbinols **7**. Hydrogen consumption during reduction of **12a** at atmospheric pressure can be seen in Figure 2. The three parts of the hydrogen



1a,d,f,g 12a,d,f,g 6a,d,f,g

Scheme 5

consumption curve represent the three consecutive reactions: reduction of the carbonyl group to an alcohol, dehydroxylation of the diarylmethanol-type intermediate (both reactions at 30 °C) and pyridine-ring saturation. On the basis of these measurements preparative-scale transformations of **12a**,**d**,**f**,**g** into **6a**,**d**,**f**,**g** were carried out at 10 bar pressure in methanol/sulfuric acid solvent using our temperature-programmed method. Yields are given in Table 4.

A known metabolitic reaction of aromatic compounds is hydroxylation of the phenyl ring in different positions. In the literature, these pharmacologically important hydroxy-containing derivatives have been synthesized by demethylation of the corresponding methoxy derivative with a highly corrosive, concentrated aqueous hydrogen bromide solution. To demonstrate the flexibility of our new method we synthesized [3-(benzyloxy)phenyl](pyridin-4-yl)methanol (**4s**) from 3-bromophenol by benzylation and Grignard addition to pyridine-4-carbaldehyde (Scheme 1). Starting from **4s** (Scheme 6), the temperature-programmed reduction could provide two different products (**6t** or **10t**). When we kept the temperature at 30 °C until 2 equiv. of hydrogen gas had reacted with the substrate, debenzylation of the 3-benzyloxyphenyl group occurred parallel with dehydroxylation of the (pyridin-4-yl)methanol moiety of **4s**, providing 4-[(3-hydroxyphenyl)methyl]pyridine (**10t**). This compound was either isolated or allowed to react with a further 3 equiv. of hydrogen gas by increasing the temperature of the

Table 4. Temperature-programmed "one pot" hydrogenation of compounds **12**

Starting material[a]	Conditions of hydrogenation	Product of hydrogenation	
		Compound	Yield[b]
12a (58%)	MeOH/H_2SO_4, 10 bar, 30 °C then 60 °C	**6a**	83%
12d (51%)	MeOH/H_2SO_4, 10 bar, 30 °C then 60 °C	**6d**	67%
12f (57%)	MeOH/H_2SO_4, 10 bar, 30 °C then 60 °C	**6f**	78%
12g (52%)	MeOH/H_2SO_4, 10 bar, 30 °C then 50 °C	**6g**	94%

[a] Yields of Grignard reactions for preparation of compounds **12** are given in parentheses. [b] Yields of the isolated, purified products.

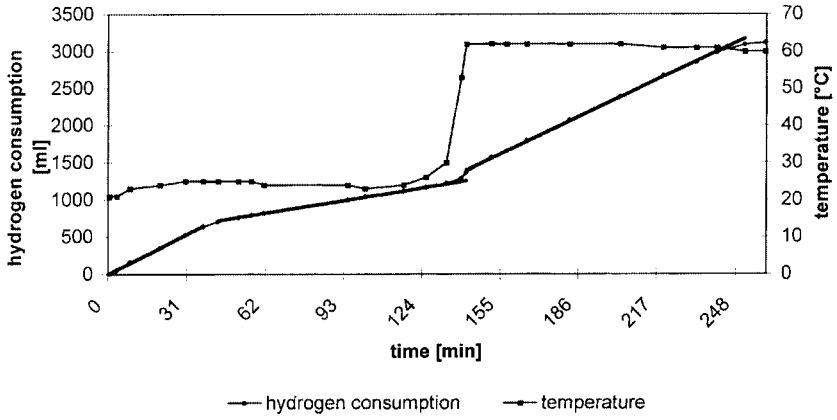
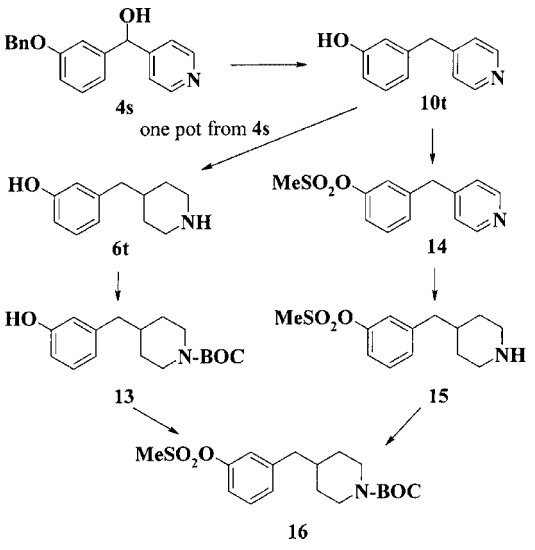


Figure 2. Time- and temperature-dependent hydrogen consumption during Pd/C-catalysed reduction of **12a** at atmospheric pressure in ethanol/sulfuric acid solvent



Scheme 6

reaction mixture to 60−65 °C. In the latter case 4-[(3-hydroxyphenyl)methyl]piperidine (**6t**) was isolated in good yield. The pyridine and piperidine derivatives (**10t** and **6t**) can be transformed into other compounds of pharmacological interest (such as the mesylates **15** and **16**). When the pharmacologically useful group on the aromatic ring is susceptible to catalytic reduction, the product (**16**) should be synthesized from **6t** via intermediate **13**. When the group on the aromatic ring is not susceptible to hydrogenation, it is better to transform **10t** into the corresponding intermediate **14** and subsequently saturate the pyridine ring (intermediate **15**). To demonstrate our idea we produced mesylate **16** in both ways.

Conclusion

A convenient new method has been developed for the preparation of 2- and 4-substituted benzylpiperidines by addition of substituted phenylmagnesium bromide to pyridine-2- or -4-carbaldehyde or 4-cyanopyridine followed by deoxygenation and heteroaromatic ring saturation in the presence of Pd/C catalyst. Isolation of several substituted aryl(piperidinyl)methanols demonstrated the crucial role of the temperature. Therefore, a temperature-programmed consecutive deoxygenation/heteroaromatic ring saturation process has been developed and a series of known and new 2- and 4-substituted benzylpiperidines have been synthesized with this method starting from aryl(pyridinyl)methanols. In the light of the literature data we realized that 4-benzylpiperidine derivatives have more practical applications than 2-benzylpiperidines and so we have reported here more examples of the synthesis of 4-benzylpiperidines, although the presented examples on preparation of 2-benzylpiperidines demonstrates the general applicability of our new method.

Experimental Section

General Remarks: All commercial starting materials were purchased from Fluka AG or Merck-Schuchardt and were used without further purification. Tetrahydrofuran was dried by distillation from sodium wire after the characteristic blue colour of in-situ-generated sodium diphenylketyl had been found to persist. All Grignard reactions were carried out under dry argon. ^{1}H NMR spectra were recorded in [D_6]DMSO or $CDCl_3$ solution at 300 or 500 MHz (Varian Innova Spectrometers). ^{13}C NMR spectra were recorded in the same solutions at 75 or 125 MHz. Chemical shifts are referenced to tetramethylsilane (δ = 0 ppm) and coupling constants are given in Hz. Melting points were determined using a Büchi capillary melting point apparatus. IR spectra of solids were recorded as KBr pellets, and IR spectra of oils were recorded as thin films on NaCl plates with a Perkin−Elmer Spectrum 1000 FT-IR spectrophotometer. GC-MS analyses were recorded with a Finnigan Mat/Automass II GC/MS. The gas chromatograph was equipped with a DB-5 capillary column (30 m × 0.25 mm i.d., 0.25 μm film). The temperature program was 45 °C (3 min) to 300 °C at 10 °C/min, hold 15 min. Compounds **4a**−**d**,**g**,**i**,**j**, **5a**−**d**,**f**, **6a**,**b**,**d**,**f**-**h**,**j**, **8a**,**d**, **9b**, **10a**,**f**, **11a**,**c**,**d** are known and their characterization data can be found in the Supporting Information.

General Procedure for the Preparation of Aryl(pyridinyl)methanols 4 and 5: At 20 °C, a solution of **2** or **3** (200 mmol, 18.9 mL) in tetrahydrofuran (100 mL) was added to the Grignard reagent (**1a**−**s**) prepared from the corresponding bromobenzene

(210 mmol) and magnesium turnings (205 mmol, 4.94 g) in tetrahydrofuran (300 mL). After 10 h of stirring, 80 mL of saturated ammonium chloride solution was poured into the reaction mixture, the phases were separated, and the tetrahydrofuran solution was dried and concentrated in vacuo. The residue was treated with hexane or ethyl acetate to give carbinols **4a**−**s**, **5a**−**d**,**f**.

(2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)(pyridin-4-yl)methanol (4e): White solid; m.p. 181−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 6 H), 2.94 (s, 2 H), 5.72 (s, 1 H), 5.92 (s, 1 H), 6.64 (m, 1 H), 7.13 (m, 1 H), 7.20 (m, 1 H), 7.29 (m, 1 H), 8.03 (m, 1 H), 8.40 (m, 1 H), 8.83 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9 (2 C), 42.3, 72.9, 87.1, 109.7, 122.1 (2 C), 125.6, 127.4, 128.7, 130.1, 149.3 (2 C), 152.5, 158.1 ppm. IR (KBr pellet): $\tilde{\nu}$ = 2913, 2430, 1616, 1488, 1445, 1251, 1085 cm^{-1}. $C_{16}H_{17}NO_2$ (255.32): calcd. C 75.27, H 6.71, N 5.49; found C 75.02, H 6.92, N 5.32.

(Pyridin-4-yl)[3-(trifluoromethyl)phenyl]methanol (4f): Pale-yellow solid; m.p. 113−114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.04 (br. s, 1 H), 5.81 (s, 1 H), 7.27−7.32 (m, 2 H), 7.39−7.56 (m, 3 H), 7.64 (s, 1 H), 8.31−8.37 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 74.1, 121.4 (2 C), 123.4 (q, J = 3.8 Hz), 123.9 (q, J = 285.2 Hz), 124.9 (q, J = 3.6 Hz), 129.2, 130.1, 131.1 (q, J = 28.3 Hz), 143.9, 149.4 (2 C), 152.7 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3096, 1328, 1184, 1168, 1120, 1072 cm^{-1}. $C_{13}H_{10}F_3NO$ (253.23): calcd. C 61.66, H 3.98, N 5.53; found C 61.57, H 3.81, N 5.37.

(3-Fluorophenyl)(pyridin-4-yl)methanol (4h): Pale-yellow solid; m.p. 120−121 °C. ^{1}H NMR (300 MHz, DMSO): δ = 5.77 (d, J = 4.2 Hz, 1 H), 6.28 (d, J = 4.2 Hz, 1 H), 7.05−7.10 (m, 1 H), 7.21−7.27 (m, 2 H), 7.32−7.43 (m, 3 H), 8.48−8.54 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 72.4 (d, J = 1.6 Hz), 113.0 (d, J = 21.7 Hz), 114.0 (d, J = 20.9 Hz), 121.3 (2 C), 122.4 (d, J = 2.6 Hz), 130.4 (d, J = 8.1 Hz), 147.4 (d, J = 6.7 Hz), 149.5 (2 C), 153.8, 162.2 (d, J = 242.3 Hz) ppm. IR (KBr pellet): $\tilde{\nu}$ = 2841, 1605, 1448, 1343, 1258, 1134, 1050, 1005 cm^{-1}. $C_{12}H_{10}FNO$ (203.22): calcd. C 70.92, H 4.96, N 6.89; found C 71.07, H 4.83, N 6.95.

(4-Ethylphenyl)(pyridin-4-yl)methanol (4k): Pale-yellow solid; m.p. 104−105 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.13 (t, J = 7.1 Hz, 3 H), 2.54 (q, J = 7.1 Hz, 2 H), 5.71 (s, 1 H), 6.12 (d, J = 2.4 Hz, 1 H), 7.13−7.18 (m, 2 H), 7.28−7.34 (m, 2 H), 7.36−7.40 (m, 2 H), 8.46−8.50 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 15.6, 27.8, 73.0, 121.2 (2 C), 126.4 (2 C), 127.7 (2 C), 141.7, 142.8, 149.4 (2 C), 154.3 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3128, 1600, 1416, 1064, 1046, 1000 cm^{-1}. $C_{14}H_{15}NO$ (213.28): calcd. C 78.84, H 7.09, N 6.57; found C 78.71, H 7.22, N 6.51.

(3,4-Dimethylphenyl)(pyridin-4-yl)methanol (4l): Pale-yellow solid; m.p. 183−184 °C. ^{1}H NMR (300 MHz, DMSO): δ = 2.17 (s, 3 H), 2.18 (s, 3 H), 5.61 (d, J = 3.9 Hz, 1 H), 5.96 (d, J = 3.9 Hz, 1 H), 7.05 (s, 2 H), 7.12 (s, 1 H), 7.31−7.36 (m, 2 H), 8.43−8.48 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 19.0, 19.5, 73.0, 121.2 (2 C), 123.9, 127.5, 129.4, 135.1, 136.0, 141.8, 149.4 (2 C), 154.4 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3136, 1604, 1496, 1416, 1344, 1056 cm^{-1}. $C_{14}H_{15}NO$ (213.28): calcd. C 78.84, H 7.09, N 6.57; found C 78.69, H 6.98, N 6.72.

(3-Fluoro-4-methoxyphenyl)(pyridin-4-yl)methanol (4m): Pale-yellow solid; m.p. 140−142 °C. ^{1}H NMR (300 MHz, DMSO): δ = 3.81 (s, 3 H), 5.70 (d, J = 3.6 Hz, 1 H), 6.19 (d, J = 3.6 Hz, 1 H), 7.07−7.25 (m, 3 H), 7.37−7.41 (m, 2 H), 8.48−8.52 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 56.0, 72.1, 113.7, 113.9, 121.1 (2 C), 122.5 (d, J = 3.3 Hz), 137.5 (d, J = 5.4 Hz), 146.2 (d, J = 10.5 Hz), 149.5 (2 C),151.3 (d, J = 242.4 Hz), 153.9 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3136, 1608, 1520, 1276, 1224, 1120, 1032 cm^{-1}. $C_{13}H_{12}FNO_2$ (233.24): calcd. C 66.95, H 5.19, N 6.01; found C 67.09, H 5.27, N 5.90.

(5-Fluoro-2-methylphenyl)(pyridin-4-yl)methanol (4n): Pale-yellow solid; m.p. 148−149 °C. ^{1}H NMR (300 MHz, DMSO): δ = 2.20 (s, 3 H), 5.85 (d, J = 3.9 Hz, 1 H), 6.22 (d, J = 3.9 Hz, 1 H), 6.97−7.05 (m, 1 H), 7.14−7.24 (m, 2 H), 7.28−7.32 (m, 2 H), 8.48−8.54 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 13.5, 65.4, 108.9 (d, J = 20.4 Hz), 109.1 (d, J = 20.5 Hz), 116.5 (2 C), 126.3, 127.1 (d, J = 7.6 Hz), 139.5 (d, J = 6.9 Hz), 144.9 (2 C), 147.5, 155.9 (d, J = 241.0 Hz) ppm. $C_{13}H_{12}FNO$ (217.24): calcd. C 71.88, H 5.57, N 6.45; found C 71.68, H 5.71, N 6.33.

(3-Ethoxyphenyl)(pyridin-4-yl)methanol (4o): Pale-yellow solid; m.p. 109−110 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.30 (t, J = 7.1 Hz, 3 H), 3.99 (q, J = 7.1 Hz, 2 H), 5.67 (d, J = 4.2 Hz, 1 H), 6.11 (d, J = 4.2 Hz, 1 H), 6.75−6.81 (m, 1 H), 6.91−6.98 (m, 2 H), 7.17−7.25 (m, 1 H), 7.36−7.41 (m, 2 H), 7.45−7.52 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 14.6, 62.9, 73.0, 112.5, 112.9, 118.4, 121.1 (2 C), 129.4, 146.0, 149.4 (2 C), 154.0, 158.5 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3056, 1600, 1448, 1260, 1144, 1048 cm^{-1}. $C_{14}H_{15}NO_2$ (229.27): calcd. C 73.45, H 6.67, N 6.29; found C 73.45, H 6.67, N 6.29.

(3,5-Difluorophenyl)(pyridin-4-yl)methanol (4p): Pale-yellow solid; m.p. 165−168 °C. ^{1}H NMR (300 MHz, DMSO): δ = 5.77 (d, J = 4.2 Hz, 1 H), 6.39 (d, J = 4.2 Hz, 1 H), 7.04−7.18 (m, 3 H), 7.40−7.45 (m, 2 H), 8.48−8.54 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 72.0, 102.6 (t, J = 25.7 Hz), 109.2 (dd, J = 9.3, J = 24.9 Hz, 2 C), 121.2 (2 C), 149.1 (t, J = 8.4 Hz), 149.6 (2 C), 152.9, 162.3 (dd, J = 245.0, J = 12.9 Hz, 2 C) ppm. IR (KBr pellet): $\tilde{\nu}$ = 3088, 1624, 1600, 1456, 1304, 1120 cm^{-1}. $C_{12}H_9F_2NO$ (221.21): calcd. C 65.16, H 4.10, N 6.33; found C 65.27, H 4.28, N 6.47.

[3-Methoxy-5-(trifluoromethyl)phenyl](pyridin-4-yl)methanol (4q): Pale-yellow solid; m.p. 143−144 °C. ^{1}H NMR (300 MHz, DMSO): δ = 3.82 (s, 3 H), 5.82 (d, J = 4.2 Hz, 1 H), 6.34 (d, J = 4.2 Hz, 1 H), 7.12 (s, 1 H), 7.29 (s, 1 H), 7.33 (s, 1 H), 7.40−7.45 (m, 2 H), 8.49−8.53 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 55.7, 72.3, 109.1 (q, J = 3.8 Hz), 114.8 (q, J = 4.0 Hz), 116.3, 121.2 (2 C), 124.0 (q, J = 270.8 Hz), 130.4 (q, J = 31.4 Hz), 147.7, 149.7 (2 C), 153.3, 159.7 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3128, 1600, 1360, 1168, 1128, 1048 cm^{-1}. $C_{14}H_{12}F_3NO_2$ (283.25): calcd. C 59.37, H 4.27, N 4.95; found C 59.15, H 4.21, N 4.78.

[3,5-Bis(trifluoromethyl)phenyl](pyridin-4-yl)methanol (4r): Pale-yellow solid; m.p. 139−141 °C. ^{1}H NMR (300 MHz, DMSO): δ = 6.00 (d, J = 3.9 Hz, 1 H), 6.58 (d, J = 3.9 Hz, 1 H), 7.40−7.48 (m, 2 H), 8.01 (s, 1 H), 8.10 (s, 2 H), 8.50−8.55 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 71.6, 121.1 (2 C), 123.7 (q, J = 271.1 Hz, 2 C), 126.9 (2 C), 130.4 (q, J = 32.6 Hz, 2 C), 147.8 (2 C), 149.8 (2 C), 152.5 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3136, 1608, 1376, 1280, 1172, 1128 cm^{-1}. $C_{14}H_9F_6NO$ (321.22): calcd. C 52.30, H 2.82, N 4.36; found C 52.16, H 2.78, N 4.48.

[3-(Benzyloxy)phenyl](pyridin-4-yl)methanol (4s): White solid; m.p. 157−158 °C. ^{1}H NMR (500 MHz, DMSO): δ = 5.07 (s, 2 H), 5.68 (d, J = 4.3 Hz, 1 H), 6.10 (d, J = 4.3 Hz, 1 H), 6.86−6.90 (m, 1 H), 6.95−6.98 (m, 1 H), 7.05−7.08 (m, 1 H), 7.20−7.25 (m, 1 H), 7.29−7.34 (m, 1 H), 7.35−7.40 (m, 4 H), 7.41−7.45 (m, 2 H), 8.44−8.49 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 69.1, 73.0, 112.9, 113.4, 118.8, 121.2 (2 C), 127.7 (2 C), 127.8, 128.4 (2 C), 129.4, 137.0, 146.05, 149.4 (2 C), 153.9, 158.3 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3128, 1600, 1452, 1264, 1048, 732 cm^{-1}. $C_{19}H_{17}NO_2$

(291.35): calcd. C 78.33, H 5.88, N 4.81; found C 78.50, H 6.05, N 4.93.

Hydrogenations: Hydrogenations at atmospheric pressure were carried out in a conventional atmospheric-pressure apparatus equipped with a magnetically driven stirrer (Medimex). Hydrogenations under pressure were carried out in a stainless-steel autoclave (Technoclave, Budapest, Hungary) equipped with a magnetic stirrer.

Method A: A mixture of 10% Pd/C catalyst (0.5 g) and an acetic acid solution (100 mL) of **4a**−**f**,**p**,**q**, **5b** (10 mmol) was hydrogenated (pressure and temperature are given in Table 1) until consumption of the hydrogen gas stopped. The catalyst was then filtered off, the solution was concentrated in vacuo and the residue was then dissolved in 20% hydrochloric acid (2 mL) and concentrated again in vacuo. Treatment of the acetic-acid-free residue with acetone or diethyl ether (50 mL) gave the corresponding piperidine hydrochloride derivative in pure form.

4-[(2-Methoxyphenyl)methyl]piperidine Hydrochloride (6c·HCl): White solid; m.p. 164−166 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.34−1.51 (m, 2 H), 1.59−1.70 (m, 2 H), 1.70−1.87 (m, 1 H), 2.50 (d, J = 7.2 Hz, 2 H), 2.66−2.84 (m, 2 H), 3.11−3.24 (m, 2 H), 3.77 (s, 3 H), 6.82−6.92 (m, 1 H), 6.93−7.00 (m, 1 H), 7.06−7.13 (m, 1 H), 7.15−7.24 (m, 1 H), 8.97−9.16 (br. m, 1 H), 9.22−9.36 (br. m, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 28.2 (2 C), 33.8, 35.9, 42.9 (2 C), 55.3, 110.8, 120.1, 127.3, 127.5, 130.6, 157.2 ppm. IR (KBr pellet): $\tilde{\nu}$ = 2951, 2795, 2465, 1586, 1495, 1455, 1242, 1031 cm^{-1}. $C_{13}H_{20}ClNO$ (241.76): calcd. C 64.58, H 8.34, N 5.79, Cl 14.66; found C 64.50, H 8.65, N 5.51, Cl 14.45.

4-[(2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)methyl]piperidine Hydrochloride (6e·HCl): White solid; m.p. 218 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 6 H), 1.60−1.68 (m, 3 H), 1.79−1.86 (m, 2 H), 2.50 (d, J = 4.8 Hz, 2 H), 2.73−2.85 (m, 2 H), 2.97 (s, 2 H), 3.40−3.46 (m, 2 H), 6.63 (d, J = 7.8 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.88 (s, 1 H), 9.30 (br. s, 1 H), 9.61 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3 (2 C), 28.7 (2 C), 36.7, 41.8, 42.9, 44.2 (2 C), 86.6, 109.1, 125.6, 127.2, 128.3, 130.3, 157.2 ppm. IR (KBr pellet): $\tilde{\nu}$ = 2959, 2430, 1488, 1445, 1370, 1252, 1150, 1087 cm^{-1}. $C_{16}H_{24}ClNO$ (281.83): calcd. C 68.19, H 8.58, N 4.97, Cl 12.58; found C 67.96, H 8.75, N 4.78, Cl 12.74.

(Piperidin-4-yl)[3-(trifluoromethyl)phenyl]methanol Hydrochloride (7f·HCl): White solid; m.p. 179−181 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.38−1.59 (m, 3 H), 1.72−1.88 (m, 2 H), 2.67−2.81 (m, 2 H), 3.14−3.27 (m, 2 H), 4.48 (dd, J = 4.9, 5.3 Hz, 1 H), 5.65 (d, J = 4.9 Hz, 1 H), 7.54−7.68 (m, 4 H), 8.98 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 23.7, 25.0, 40.5, 42.8, 42.9, 74.6, 122.9 (q, J = 3.8 Hz), 126.7 (q, J = 3.7 Hz), 124.4 (q, J = 270.6 Hz), 128.7 (q, J = 31.4 Hz), 129.0, 130.7, 145.5 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3408, 2947, 2478, 1592, 1454, 1332, 1120 cm^{-1}. $C_{13}H_{17}ClF_3NO$ (295.73): calcd. C 52.79, H 5.79, N 4.74, Cl 11.99; found C 52.65, H 5.62, N 4.83, Cl 11.71.

(3,5-Difluorophenyl)(piperidin-4-yl)methanol Hydrochloride (7p·HCl): White solid; m.p. 188−190 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.33−1.56 (m, 3 H), 1.66−1.84 (m, 2 H), 2.63−2.82 (m, 2 H), 3.13−3.27 (m, 2 H), 4.40 (d, J = 5.7 Hz, 1 H), 5.61 (br. s, 1 H), 6.97−7.17 (m, 3 H), 8.88 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 23.8, 25.2, 40.5, 42.9, 43.0, 74.3, 102.1 (t, J = 25.5 Hz), 109.5 (dd, J = 24.8, J = 9.8 Hz, 2 C), 149.2 (t, J = 7.5 Hz), 162.2 (dd, J = 243.8, J = 12.8 Hz, 2 C) ppm. IR (KBr pellet): $\tilde{\nu}$ = 3375, 2947, 2476, 1596, 1454, 1323, 1120 cm^{-1}. $C_{12}H_{16}ClF_2NO$ (263.71): calcd. C 54.65, H 6.12, N 5.31, Cl 13.44; found C 54.73, H 6.01, N 5.44, Cl 13.21.

[3-Methoxy-5-(trifluoromethyl)phenyl](piperidin-4-yl)methanol Hydrochloride(7q·HCl): White solid; m.p. 201−202 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.32−1.54 (m, 3 H), 1.64−1.87 (m, 2 H), 2.68−2.82 (m, 2 H), 3.15−3.27 (m, 2 H), 3.83 (s, 3 H), 4.45 (dd, J = 4.9, J = 5.3 Hz, 1 H), 5.60 (d, J = 4.9 Hz, 1 H), 7.11 (s, 1 H), 7.16 (s, 1 H), 7.23 (s, 1 H), 8.78 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 23.3 (2 C), 24.8, 42.4, 42.6, 55.3, 74.2, 108.4 (q, J = 3.5 Hz), 114.8 (q, J = 3.8 Hz), 116.1, 123.8 (q, J = 270.8 Hz), 129.6 (q, J = 31.3 Hz), 147.1, 159.1 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3345, 2717, 1603, 1461, 1603, 1461, 1341, 1111 cm^{-1}. $C_{14}H_{19}ClF_3NO_2$ (325.75): calcd. C 51.62, H 5.88, N 4.30, Cl 10.61; found C 51.48, H 5.96, N 4.41, Cl 10.61.

Method B: A mixture of 10% Pd/C catalyst (2 g) and a solution (250 mL) of **4a**,**f**,**g**,**p**,**r**, **5a**,**c**,**d**,**f** (40 mmol) was hydrogenated at atmospheric pressure (solvent and temperature are given in Table 2) until consumption of the hydrogen gas slowed down. The catalyst was then filtered off, the solution was concentrated in vacuo and the residue was treated with 10% sodium hydroxide solution (40 mL) and extracted with dichloromethane (200 mL). The extract was washed with water (3 × 50 mL), dried with sodium sulfate, and concentrated in vacuo. If the crude product was not pure (checked by GC-MS) it was purified by fractional vacuum distillation.

4-[(4-Fluorophenyl)methyl]pyridine (10g): Colorless oil; b.p. 94−96 °C/0.1 Torr. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 2 H), 6.94−7.03 (m, 2 H), 7.04−7.15 (m, 4 H), 8.47−8.52 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.0, 115.2 (d, J = 21.2 Hz, 2 C), 123.8 (2 C), 130.2 (d, J = 7.8 Hz, 2 C), 134.3 (d, J = 3.2 Hz), 149.5, 149.6 (2 C), 161.4 (d, J = 243.5 Hz) ppm. IR (film): $\tilde{\nu}$ = 3031, 1602, 1508, 1415, 1224, 1158 cm^{-1}. $C_{12}H_{10}FN$ (187.22): calcd. C 76.98, H 5.38, N 7.48; found C 77.15, H 5.21, N 7.61.

4-[(3-Fluorophenyl)methyl]pyridine (10h): Colorless oil; b.p. 89 °C/0.2 Torr. ^{1}H NMR (300 MHz, DMSO): δ = 4.00 (s, 2 H), 7.01−7.07 (m, 3 H), 7.25−7.29 (m, 2 H), 7.31−7.40 (m, 1 H), 7.46−7.51 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.2, 113.0 (d, J = 20.6 Hz), 115.4 (d, J = 21.3 Hz), 123.6 (2 C), 124.2 (d, J = 2.0 Hz), 129.7 (d, J = 8.3 Hz), 140.9 (d, J = 7.3 Hz), 148.7, 149.3 (2 C), 162.4 (d, J = 244.6 Hz) ppm. IR (film): $\tilde{\nu}$ = 3032, 1600, 1488, 1416, 1252, 1136 cm^{-1}. $C_{12}H_{10}FN$ (187.22): calcd. C 76.98, H 5.38, N 7.48; found C 76.81, H 5.51, N 7.56.

4-[(3,5-Difluorophenyl)methyl]pyridine (10p): Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.94 (s, 2 H), 6.62−6.74 (m, 3 H), 7.07−7.12 (m, 2 H), 8.51−8.56 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.5, 102.0 (t, J = 25.2 Hz), 111.6 (dd, J = 24.6, J = 8.9 Hz, 2 C), 123.9 (2 C), 142.5 (t, J = 9.1 Hz), 148.1, 149.8 (2 C), 163.0 (dd, J = 247.4, J = 12.8 Hz, 2 C) ppm. IR (film): $\tilde{\nu}$ = 1624, 1600, 1456, 1416, 1120, 992 cm^{-1}. $C_{12}H_9F_2$ (205.21): calcd. C 70.21, H 4.42, N 6.83; found C 70.42, H 4.57, N 6.75.

4-{[3-Methoxy-5-(trifluoromethyl)phenyl]methyl}pyridine (10q): Colorless oil; b.p. 114−116 °C/0.1 Torr. ^{1}H NMR (300 MHz, DMSO): δ = 3.84 (s, 3 H), 4.07 (s, 2 H), 7.12 (s, 1 H), 7.20 (s, 1 H), 7.23 (s, 1 H), 7.29−7.33 (m, 2 H), 8.49−8.53 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.6, 55.0, 108.5 (d, J = 3.5 Hz), 117.6, 118.1, 123.6 (q, J = 270.9 Hz), 123.8 (2 C), 131.8 (q, J = 31.8 Hz), 141.2, 148.5, 149.6 (2 C), 159.8 ppm. IR (film): $\tilde{\nu}$ = 1599, 1468, 1358, 1249, 1172, 1125, 1055 cm^{-1}. $C_{14}H_{12}F_3NO$ (267.25): calcd. C 62.92, H 4.53, N 5.24; found C 62.80, H 4.61, N 5.11.

4-{[3,5-Bis(trifluoromethyl)phenyl]methyl}pyridine (10r): Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (s, 2 H), 7.33−7.37 (m, 2 H), 7.96 (s, 1 H), 8.06 (s, 2 H), 8.50−8.54 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 39.1, 120.4, 123.3 (q, J = 271.1 Hz, 2 C), 124.1 (2 C), 129.8 (2 C), 130.5 (q, J = 32.4 Hz, 2 C), 143.22, 148.6, 149.9 (2 C) ppm. IR (film): $\tilde{\nu}$ = 1600, 1376, 1284, 1176, 1132 cm^{-1}. $C_{14}H_9F_6N$ (305.22): calcd. C 55.09, H 2.97, N 4.59; found C 55.22, H 2.87, N 4.41.

2-{[3-(Trifluoromethyl)phenyl]methyl}pyridine (11f): Colorless oil; b.p. 117 °C/0.1−0.2 Torr. ^{1}H NMR (300 MHz, DMSO): δ = 4.21 (s, 2 H), 7.20−7.26 (m, 1 H), 7.33−7.38 (m, 1 H), 7.49−7.63 (m, 3 H), 7.65−7.69 (m, 1 H), 7.69−7.76 (m, 1 H), 7.49−7.53 (m, 1 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 42.9, 121.2, 122.5 (q, J = 3.6 Hz), 122.7, 123.8 (q, J = 272.4 Hz), 124.9 (q, J = 3.6 Hz), 128.6 (q, J = 30.9 Hz), 128.9, 132.7, 136.4, 140.8, 148.8, 159.4 ppm. IR (film): $\tilde{\nu}$ = 1592, 1332, 1120, 1072, 704 cm^{-1}. $C_{13}H_{10}F_3N$ (237.22): calcd. C 65.82, H 4.25, N 5.90; found C 65.71, H 4.13, N 5.97.

Method C: A mixture of 10% Pd/C catalyst (0.5 g) and an acetic acid solution (100 mL) of **10f**−**h**,**p**,**r**, **11a**,**c**,**d**,**f** (10 mmol) was hydrogenated at 10 bar (temperatures are given in Table 2) until consumption of the hydrogen gas stopped. The catalyst was then filtered off, the solution was concentrated in vacuo and the residue was dissolved in 20% hydrochloric acid (2 mL) and concentrated again in vacuo. Treatment of the acetic-acid-free residue with acetone or diethyl ether (50 mL) gave the corresponding piperidine hydrochloride derivative in pure form.

4-[(3,5-Difluorophenyl)methyl]piperidine Hydrochloride (6p·HCl): White solid; m.p. 215 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.25−1.42 (m, 2 H), 1.62−1.73 (m, 2 H), 1.74−1.93 (m, 1 H), 2.57 (d, J = 7.2 Hz, 2 H), 2.72−2.84 (m, 2 H), 3.16−3.26 (m, 2 H), 6.92−7.10 (m, 3 H), 8.65 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 27.8 (2 C), 34.5, 40.9, 42.8 (2 C), 101.5 (t, J = 25.6 Hz), 112.1 (dd, J = 16.6, J = 7.4 Hz, 2 C), 144.4 (t, J = 9.2 Hz), 162.3 (dd, J = 244.1, J = 13.2 Hz, 2 C) ppm. IR (KBr pellet): $\tilde{\nu}$ = 2952, 1624, 1600, 1460, 1120, 992 cm^{-1}. $C_{12}H_{16}ClF_2N$ (247.72): calcd. C 58.18, H 6.51, N 5.65, Cl 14.31; found C 58.33, H 6.35, N 5.42, Cl 14.54.

4-{[3-Methoxy-5-(trifluoromethyl)phenyl]methyl}piperidine Hydrochloride (6q·HCl): White solid; m.p. 184−185 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.33−1.50 (m, 2 H), 1.63−1.74 (m, 2 H), 1.77−1.94 (m, 1 H), 2.61 (d, J = 7.2 Hz, 2 H), 2.70−2.84 (m, 2 H), 2.14−3.24 (m, 2 H), 3.83 (s, 3 H), 7.07 (s, 1 H), 7.09 (s, 1 H), 7.13 (s, 1 H), 9.10 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 27.9 (2 C), 34.8, 41.1, 42.8 (2 C), 55.5, 108.0 (q, J = 3.8 Hz), 117.7 (q, J = 3.8 Hz), 119.0, 124.1 (q, J = 270.9 Hz), 130.1 (q, J = 31.3 Hz), 142.9, 159.5 ppm. IR (KBr pellet): $\tilde{\nu}$ = 2954, 2801, 1603, 1468, 1356, 1247, 1126, 1056 cm^{-1}. $C_{14}H_{19}ClF_3NO$ (309.77): calcd. C 54.28, H 6.18, N 4.54, Cl 11.44; found C 54.47, H 5.98, N 4.68, Cl 11.65.

4-{[3,5-Bis(trifluoromethyl)phenyl]methyl}piperidine Hydrochloride (6r·HCl): White solid; m.p. 209 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.33−1.50 (m, 2 H), 1.62−1.73 (m, 2 H), 1.81−1.99 (m, 1 H), 2.72 (m, 4 H), 3.16−3.26 (m, 2 H), 7.94 (s, 1 H), 7.96 (s, 2 H), 8.99 (s,br 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 27.8 (2 C), 34.8, 40.5, 42.8 (2 C), 119.8 (br), 123.4 (q, J = 271.1 Hz, 2 C), 129.9 (2 C), 130.1 (q, J = 32.3 Hz, 2 C), 143.4 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3488, 1380, 1280, 1160, 1124, 896 cm^{-1}. $C_{14}H_{16}ClF_6N$ (347.74): calcd. C 48.36, H 4.64, N 4.03, Cl 10.20; found C 48.57, H 4.72, N 4.21, Cl 10.05.

2-[(2-Methoxyphenyl)methyl]piperidine Hydrochloride (8c·HCl): White solid; m.p. 166 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.28−1.50 (m, 2 H), 1.52−1.75 (m, 4 H), 2.76−2.85 (m, 2 H), 3.01 (dd, J = 13.2, 5.4 Hz, 1 H), 3.15−3.25 (m, 2 H), 3.80 (s, 3 H), 6.88−6.95 (m, 1 H), 6.98−7.03 (m, 1 H), 7.14−7.20 (m, 1 H), 7.23−7.30 (m, 1 H), 8.97 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 21.5, 21.6, 27.4, 33.3, 43.8, 55.4, 55.6, 110.9, 120.4, 124.0, 128.4, 130.9, 157.3 ppm. IR (KBr pellet): $\tilde{\nu}$ = 2952, 1332, 1168, 1128, 1080 cm^{-1}. $C_{13}H_{20}ClNO$ (241.76): calcd. C 64.58, H 8.34, N 5.79 Cl 14.66; found C 64.52, H 8.29, N 5.83, Cl 14.79.

2-{[3-(Trifluoromethyl)phenyl]methyl}piperidine Hydrochloride (8f·HCl): White solid; m.p. 150−152 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.30−1.77 (m, 6 H), 2.76−2.95 (m, 2 H), 3.16−3.37 (m, 3 H), 7.56−7.67 (m, 4 H), 9.12 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 21.5, 21.6, 27.3, 38.4, 43.8, 56.4, 123.6 (q, J = 3.8 Hz), 124.2 (q, J = 270.6 Hz), 125.8 (q, J = 3.8 Hz), 129.3 (q, J = 31.4 Hz), 129.6, 133.6, 137.9 ppm. IR (KBr pellet): $\tilde{\nu}$ = 2952, 1332, 1168, 1128, 1080, 704 cm^{-1}. $C_{13}H_{17}ClF_3N$ (279.74): calcd. C 55.82, H 6.13, N 5.01, Cl 12.67; found C 55.75, H 6.25, N 4.92, Cl 12.54.

Method D: A mixture of 10% Pd/C catalyst (2 g) and a solution (250 mL) of **4a**−**d**,**f**,**i**−**o**, **5a**,**f**, **12a**,**d**,**f**,**g** (40 mmol) was hydrogenated (pressure and solvents are given in Tables 3 and 4) at ambient temperature until the appropriate amount of hydrogen gas necessary to obtain benzylpyridine (1 or 2 equiv.) had been consumed. The temperature of the reaction mixture was then increased to 60−65 °C. After the consumption of another 3 equiv. of hydrogen gas, the catalyst was filtered off and the solution was concentrated in vacuo. The residue was treated with 10% NaOH solution (40 mL) and extracted with dichloromethane (200 mL). The extract was washed with water (3 × 50 mL), dried with sodium sulfate and the solvents were evaporated. If the products were bases (**6k**−**o**), the crude products were purified by fractional vacuum distillation. If the products were hydrochloride salts (**6a**−**d**,**f**,**g**,**i**,**j**, **8a**,**f**), the residues were dissolved in 20% hydrochloric acid (8 mL) and concentrated again in vacuo.

4-[(3-Methylphenyl)methyl]piperidine (6i): Colorless oil; b.p. 86−88 C/0.2 Torr. ^{1}H NMR (300 MHz, DMSO): δ = 0.94−1.10 (m, 2 H), 1.42−1.60 (m, 3 H), 1.80−2.50 (br. s, 1 H), 2.26 (s, 3 H), 2.31−2.40 (m, 2 H), 2.39−2.44 (d, J = 7.2 Hz, 2 H), 2.82−2.90 (m, 2 H), 6.89−6.99 (m, 3 H), 7.10−7.17 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 33.4 (2 C), 38.3, 43.6, 46.6 (2 C), 126.0, 126.3, 127.8, 129.8, 137.4, 140.3 ppm. IR (film): $\tilde{\nu}$ = 3427, 2914, 1673, 1517, 1486, 1442, 1284 cm^{-1}. $C_{13}H_{19}N$ (189.30): calcd. C 82.48, H 10.12, N 7.40; found C 82.66, H 9.95, N 7.61.

4-[(4-Ethylphenyl)methyl]piperidine (6k): Colorless oil; b.p. 96−98 °C/0.023 Torr. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06−1.22 (m, 2 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.52−1.70 (m, 4 H), 2.45−2.58 (m, 4 H), 2.61 (q, J = 7.1 Hz, 2 H), 2.98−3.07 (m, 2 H), 7.02−7.13 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6, 28.4, 32.6 (2 C), 38.1, 43.1, 46.3 (2 C), 127.7 (2 C), 129.1 (2 C), 137.4, 141.8 ppm. IR (film): $\tilde{\nu}$ = 2916, 2733, 1513, 1446, 1318, 1259, 1141 cm^{-1}. $C_{14}H_{21}N$ (203.33): calcd. C 82.70, H 10.41, N 6.89; found C 82.53, H 10.62, N 6.72.

4-[(3,4-Dimethylphenyl)methyl]piperidine (6l): Colorless oil; b.p. 94−96 °C/0.023 Torr. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06−1.20 (m, 2 H), 1.51−1.67 (m, 4 H), 2.22 (s, 3 H), 2.23 (s, 3 H), 2.42−2.58 (m, 4 H), 2.98−3.06 (m, 2 H), 6.87 (dd, J = 7.8, 1.5 Hz, 1 H), 6.92 (d, J = 1.5 Hz, 1 H), 7.03 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 19.8, 32.8 (2 C), 38.2, 43.2, 46.4 (2 C), 126.5, 129.4, 130.5, 133.9, 136.3, 137.8 ppm. IR (film): $\tilde{\nu}$ = 2918, 2731, 1464, 1411, 1258, 1138, 1060 cm^{-1}. $C_{14}H_{21}N$ (203.33): calcd. C 82.70, H 10.41, N 6.89; found C 82.85, H 10.28, N 6.98.

4-[(3-Fluoro-4-methoxyphenyl)methyl]piperidine (6m): White solid; b.p. 114−116 °C/0.038 Torr; m.p. 38−39 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03−1.20 (m, 2 H), 1.49−1.70 (m, 4 H), 2.42−2.58 (m, 4 H), 2.99−3.08 (m, 2 H), 3.86 (s, 3 H), 6.79−6.90 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.0 (2 C), 38.0, 42.5, 46.4 (2 C), 55.9, 112.8 (d, J = 1.6 Hz), 116.2 (d, J = 17.6 Hz), 124.2 (d, J = 3.3 Hz), 133.3 (d, J = 5.9 Hz), 145.3 (d, J = 10.6 Hz), 152.1 (d, J = 243.5 Hz) ppm. IR (KBr pellet): $\tilde{\nu}$ = 2919, 2844, 1519, 1445, 1275, 1224, 1128, 1028 cm^{-1}. $C_{13}H_{18}FNO$ (223.29): calcd. C 69.93, H 8.13, N 6.27; found C 70.12, H 8.23, N 6.15.

4-[(5-Fluoro-2-methylphenyl)methyl]piperidine (6n): Colorless oil; b.p. 98 °C/0.015 Torr. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10−1.27 (m, 2 H), 1.52−1.68 (m, 3 H), 1.78 (br. s, 1 H), 2.24 (s, 3 H), 2.46−2.58 (m, 4 H), 2.98−3.98 (m, 2 H), 6.73−6.82 (m, 2 H), 7.02−7.10 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 32.7 (2 C), 36.9, 40.7, 46.3 (2 C), 112.6 (d, J = 20.5 Hz), 116.4 (d, J = 20.5 Hz), 131.3 (d, J = 7.7 Hz), 131.6, 140.6 (d, J = 6.9 Hz), 161.0 (d, J = 241.6 Hz) ppm. IR (film): $\tilde{\nu}$ = 3275, 2974, 2735, 1591, 1495, 1449, 1246, 1150 cm^{-1}. $C_{13}H_{18}FN$ (207.29): calcd. C 75.33, H 8.75, N 6.75; found C 75.59, H 8.89, N 6.88.

4-[(3-Ethoxyphenyl)methyl]piperidine (6o): Colorless oil; b.p.108−112 °C/0.03 Torr. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04−1.20 (m, 2 H), 1.39 (t, J = 7.0 Hz, 3 H), 1.53−1.70 (m, 4 H), 2.44−2.57 (m, 4 H), 2.96−3.06 (m, 2 H), 4.00 (q, J = 7.0 Hz, 2 H), 6.67−6.74 (m, 3 H), 7.12−7.19 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 33.2 (2 C), 38.0, 43.5, 46.4 (2 C), 62.8, 111.0, 115.2, 121.1, 128.6, 141.7, 158.5 ppm. IR (film): $\tilde{\nu}$ = 2922, 2737, 1583, 1448, 1257, 1049 cm^{-1}. $C_{14}H_{21}NO$ (219.33): calcd. C 76.67, H 9.65, N 6.39; found C 76.46, H 9.51, N 6.53.

4-[(3-Hydroxyphenyl)methyl]piperidine Hydrochloride (6t·HCl): A mixture of 10% Pd/C catalyst (1 g) and an ethanol solution (200 mL) of **4s** (20 mmol) and H_2SO_4 (23 mmol) was hydrogenated at ambident temperature until 2 equiv. of hydrogen gas had been consumed (formation of **10t**), and then the temperature of the reaction mixture was increased to 60−65 °C. After the consumption of another 3 equiv. of hydrogen gas, the catalyst was filtered off and 30% hydrogen chloride solution (4.3 mL) was added to the solution. The solvent was removed in vacuo. Recrystallization from ethanol (40 mL) gave **6t·HCl** (2.63 g, 61.6%) as a white solid. M.p. 214 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.25−1.42 (m, 2 H), 1.63−1.83 (m, 3 H), 2.43 (d, J = 7.1 Hz, 2 H), 2.71−2.84 (m, 2 H), 3.15−3.25 (m, 2 H), 6.55−6.60 (m, 3 H), 7.03−7.10 (m, 1 H), 8.80 (br. s, 1 H), 9.30 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 28.1 (2 C), 34.9, 41.8, 42.9 (2 C), 113.0, 115.9, 119.6, 129.1, 140.8, 157.4 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3216, 2824, 1584, 1438, 800, 704 cm^{-1}. $C_{12}H_{18}ClNO$ (227.74): calcd. C 63.29, H 7.97, N 6.15; found C 63.37, H 7.79, N 6.32.

4-[(3-Hydroxyphenyl)methyl]pyridine (10t): A mixture of 10% Pd/C catalyst (1 g) and an ethanol solution (200 mL) of **4s** (20 mmol) and H_2SO_4 (23 mmol) was hydrogenated at 30 °C until the consumption of 2 equiv. of hydrogen gas. The catalyst was filtered off and the solution was concentrated in vacuo. The residue was treated with 5% sodium hydrogen carbonate solution (60 mL), and extracted with dichloromethane (3×30 mL). The combined extracts were washed with water (10 mL), dried with magnesium sulfate, filtered, and the solvents evaporated to dryness. Recrystallization from ethanol/water (80 mL, 2:1) gave **10t** (2.9 g, 78%) as a white solid. M.p. 98−101 °C. ^{1}H NMR (500 MHz, DMSO): δ = 3.87 (s, 2 H), 6.59−6.64 (m, 2 H), 6.65−6.68 (m, 1 H), 7.07−7.12 (m, 1 H), 7.20−7.23 (m, 2 H), 8.44−8.48 (m, 2 H), 9.30 (s, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 40.2, 113.4, 115.7, 119.5, 124.2 (2 C), 129.6, 140.9, 149.6 (2 C), 150.1, 157.5 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3032, 1608, 1584, 1488, 1288, 1008 cm^{-1}. $C_{12}H_{11}NO$ (186.24): calcd. C 77.39, H 5.95, N 7.52; found C 77.27, H 5.87, N 7.66.

***N*-(*tert*-Butoxycarbonyl)-4-[(3-hydroxyphenyl)methyl]piperidine (13):** Triethylamine (2.12 g, 21 mmol) was added to a solution of **6t·HCl** (4.46 g, 20 mmol) in dichloromethane (90 mL). The mixture was cooled to 0 °C before addition of di-*tert*-butyl dicarbonate (4.8 g, 22 mmol). Stirring was maintained at room temperature overnight. The mixture was then washed with cold water (2 × 30 mL). The organic layer was dried with sodium sulfate, filtered and the solvent was evaporated. The residue was treated with hexane to yield piperidine **13** (5.1 g, 87.6%) as a white solid. M.p. 144 °C. ^{1}H NMR (300 MHz, DMSO): δ = 0.90−1.07 (m, 2 H), 1.38 (s, 9 H), 1.48−1.70 (m, 3 H), 2.40 (d, J = 7.2 Hz, 2 H), 2.55−2.72 (m, 2 H), 3.85−3.95 (m, 2 H), 6.53−6.60 (m, 3 H), 7.01−7.08 (m, 1 H), 9.20 (s, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 28.1 (3 C), 31.6 (2 C), 37.3, 42.2, 43.3 (br., 2 C), 78.4, 112.8, 115.9, 119.7, 129.0, 141.4, 153.9, 157.2 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3232, 2936, 1652, 1600, 1440, 1280, 1160, 1120 cm^{-1}. $C_{17}H_{25}NO_3$ (291.39): calcd. C 70.07, H 8.65, N 4.81, found C 70.23, H 8.47, N 4.87.

4-{[3-(Mesyloxy)phenyl]methyl}pyridine (14): Triethylamine (2.02 g, 20 mmol) was added to a solution of **10t** (1.82, 10 mmol) in dichloromethane (20 mL). The mixture was cooled to 0 °C and mesyl chloride (1.87 g, 12 mmol) was added slowly. Stirring was maintained at room temperature overnight. The mixture was then washed with cold water (2 × 15 mL). The organic layer was dried with sodium sulfate, filtered and concentrated to dryness to give **14** as a yellow oil (1.35 g, 51.3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.13 (s, 3 H), 3.99 (s, 2 H), 7.07−7.20 (m, 5 H), 7.33−7.40 (m, 1 H), 8.49−8.56 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.0, 40.3, 119.8, 122.3, 123.8 (2 C), 127.7, 129.9, 141.1, 148.6, 149.1, 149.6 (2 C) ppm. IR (film): $\tilde{\nu}$ = 3032, 1600, 1416, 1372, 1180, 1128 cm^{-1}. $C_{13}H_{13}NO_3S$ (263.32): calcd. C 59.30, H 4.98, N 5.32, S 12.18; found C 59.21, H 5.09, N 5.23, S 12.35.

***N*-(*tert*-Butoxycarbonyl)-4-{[3-(mesyloxy)phenyl]methyl}piperidine (16):** Triethylamine (1.51 g, 15 mmol) was added to a solution of the benzylpiperidine **13** (2.18 g, 7.5 mmol) in dichloromethane (20 mL). The mixture was cooled to 0 °C and mesyl chloride (1.03 g, 9 mmol) was added slowly. Stirring was maintained at room temperature overnight. The mixture was washed with cold water (2 × 15 mL). The organic layer was dried with sodium sulfate, filtered, and the solvents were evaporated to dryness to give **16** as a yellow oil (2.5 g, 90%). This compound can also be prepared from **14**. Method C was used for saturation of the pyridine ring; then triethylamine (0.9 g, 8.93 mmol) was added to a solution of the crude product (**15**) of the hydrogenation, (2.6 g, 8.5 mmol) in dichloromethane (30 mL). The mixture was cooled to 0 °C before addition of di-*tert*-butyl dicarbonate (2.22 g, 10.2 mmol). Stirring was maintained at room temperature overnight. The mixture was then washed with water (2 × 15 mL). The organic layer was dried with sodium sulfate, filtered and concentrated to dryness to give **16** as a yellow oil (1.8 g, 54.3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06−1.22 (m, 2 H), 1.45 (s, 9 H), 1.55−1.75 (m, 3 H), 2.56 (d, J = 7.1 Hz, 2 H), 2.58−2.70 (m, 2 H), 3.14 (s, 3 H), 4.01−4.15 (m, 2 H), 7.06−7.14 (m, 3 H), 7.29−7.36 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.1 (3 C), 31.5 (2 C), 37.0, 37.6, 42.4, 43.3 (br., 2 C), 78.9, 119.1, 122.3, 127.8, 129.4, 142.5, 149.0, 154.4 ppm. IR (film): $\tilde{\nu}$ = 2936, 1688, 1424, 1368, 1244, 1180, 1128 cm^{-1}. $C_{18}H_{27}NO_5S$ (369.49): calcd. C 58.51, H 7.37, N 3.79, S 8.68; found C 58.73, H 7.61, N 3.91, S 8.89.

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