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1-Alkoxyamino-2-nitroalkanes as Key Building Blocks for a Chemo- and Diastereoselective Synthesis of a New Type of Polyfunctionalized *N*-Alkoxypiperidine

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A highly efficient conversion of β-nitrostyrenes into a new kind of functionalized *N*-alkoxy-2-hydroxypiperidine in two steps was developed, giving excellent yields and diastereoselectivity. The prepared compounds are the first examples of *N*-alkoxy-2-hydroxypiperidines. The synthetic approach involved the conjugate addition of alkoxyamines to β-nitrostyrenes, followed by Michael addition of the isolated nitroalkoxyamines to α,β-unsaturated carbonyl compounds, and intramolecular addition of the alkoxyamino group to the carbonyl functionality of the (non-isolated) adducts. Although three stereogenic centers are formed, only one diastereoisomer was detected. This unprecedented sequence of reactions can also be performed in a one-pot fashion.

Introduction

Both naturally occurring (e.g., nojirimycin) and synthetic (e.g., noeuromycin, miglitol) polyhydroxylated piperidines have been shown to be specific and potent inhibitors of glycosidases and they possess great potential to treat a variety of carbohydrate-mediated diseases such as diabetes, viral infections including HIV, and cancer metastasis.[1–3] Most of the methodologies described for the synthesis of these compounds and chemically modified analogues, which can be regarded as imino sugars, start from carbohydrates and require a large number of steps. Therefore, the development of new strategies that allow the stereoselective synthesis of hydroxylated piperidines starting from non-carbohydrate precursors constitutes an area of current interest.[4–7] Recently, hydroxylated 2-arylpiperidines have been shown to act as inhibitors of rhamnosyl-processing enzymes and to be potentially useful against tuberculosis.[8] In general, functionalized piperidines and the synthetic methodologies used for their preparation are of considerable interest.[9]

Nitroalkenes have attracted significant interest in recent years as Michael acceptors,[10] because of the activating effect of the nitro group, as well as its easy transformation into a number of functional groups.[11] There are a few reports on the direct addition reaction of amines to nitro-olefins;[12] however, very little attention has focused on the addition of alkoxyamines to nitro-olefins,[13] and nothing has been described about the addition of 1,2-nitro-*N*-alkoxyamines to α,β-unsaturated carbonyl compounds. For these reasons, we have explored the scope and limitations of this reaction to determine whether 1,2-nitro-*N*-alkoxyamines can act as nucleophiles in conjugate additions through the *N*-alkoxyamino group or through the nitronate anion, and to study the effect of changing an amino group to the significantly less basic alkoxyamino group. In fact, the pK_a of protonated alkoxyamines are some 5–6 orders of magnitude less than the parent amines.[14]

Furthermore, the formation of new bonds in the addition of *N*-alkoxy-1,2-nitroamines to α,β-unsaturated carbonyl compounds involves the generation of new stereogenic centers, which has important implications for the design of catalytic and stereoselective reactions for the synthesis of organic molecules with several stereogenic centers and constitutes a continuing challenge for synthetic chemistry.[15,16]

Results and Discussion

In this context, we have prepared a variety of *N*-alkoxy-1-aryl-2-nitroethanamines **3a**–**f** in high yields (72–89%) by addition of alkoxyamine hydrochlorides **2a** and **2b** to β-nitrostyrenes **1a**–**c** at room temperature in methanol containing triethylamine (Table 1).

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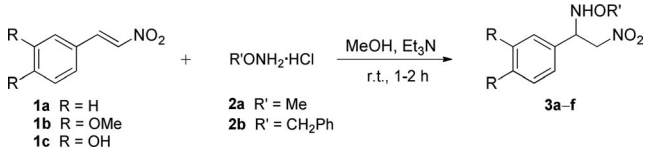
Table 1. Synthesis of *N*-alkoxy-2-nitro-1-arylethanamines **3a**–**f**.



Entry	Compound	R	R′	Yield [%][a]
1	**3a**	H	Me	89
2	**3b**	H	Bn	87
3	**3c**	OMe	Me	72
4	**3d**	OMe	Bn	84
5	**3e**	OH	Me	75
6	**3f**	OH	Bn	82

[a] Yield of pure isolated product.

We also studied the coupling of nitroalkoxyamine **3a** with methyl vinyl ketone (**4a**) under a range of reaction conditions to explore the feasibility and chemoselectivity of this Michael addition (Table 2). The reaction did not work either in the absence of catalyst, or in the presence of PL-CO_3 resin, a polymer-bound equivalent of carbonate designed for neutralization or for the scavenging of acids, using different catalyst/substrate ratios (Table 2, entry 1). Although nitroalkanes have been found to give good yields in Michael additions by the use of a catalytic amount (10 mol-%) of cetyltrimethylammonium hydroxide (CTAOH),[17] this reaction, when carried out at room temperature under solvent-free conditions (Table 2, entry 2), led to the formation of a complex mixture together with starting nitro derivative **3a**.

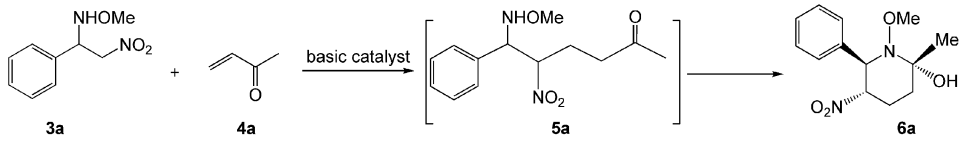
Furthermore, potassium fluoride supported on alumina (KF/Al_2O_3) under solvent-free conditions has been reported to be an efficient catalyst for Michael addition of nitroalkanes to electron-deficient alkenes.[18,19] However, in our hands, the reaction of **3a** and **4a** promoted by alumina doped with KF (Table 2, entry 3), led to the formation of by-products together with unconsumed starting material. In contrast, the reaction did take place in neat alumina,[20] and **6a** was obtained in 33% yield (Table 2, entry 4).

We also tested the reaction using, as recyclable promoters, the macroreticular ion-exchange resins Amberlyst A-21 and Amberlyst A-27, which were previously described[21,22] as efficient catalysts in the conjugate addition of nitroalkanes to α,β-unsaturated derivatives in the absence of any solvent. Piperidine **6a** could be obtained (38% yield) using the weakly basic resin A-21, but not with the strongly basic resin A-27 (Table 2, entries 5 and 6).

We tested commercial ISOLUTE Si-carbonate [silica trimethylammonium carbonate; Si-TMA(CO_3^{2-})$_{0.5}$], which is a bound equivalent of tetramethylammonium carbonate that is traditionally used as a quaternary anion-exchanger, in the reaction. This supported base has been described as an eco-friendly and recyclable catalyst that can be used to generate nitronate species.[23] The use of 20 mol-% of this catalyst at room temperature (Table 2, entry 8) was found to be the best (59%) reaction conditions for the synthesis of **6a**.

Strong organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 1 equiv.) or 1,1,3,3-tetramethylguanidine (TMG; 10 mol-%), in homogeneous solutions[24] in acetonitrile, gave good yields of **6a** (78 and 79%, respectively, Table 2, entries 11 and 12). Similarly, potassium *tert*-butox-

Table 2. Base-catalyzed synthesis of *N*-alkoxypiperidine **6a** from *N*-alkoxy-2-nitro-1-arylamines **3a**.



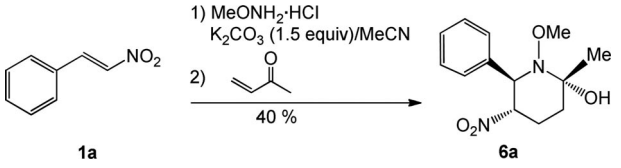
Entry	Basic catalyst	Temp. [°C]	Time [h]	Solvent	Yield [%][a]
1	PL-CO_3 resin[b] (catalyst/substrate, 10, 20, or 30 mol-%)	room temp.	6	solvent-free	–[c]
2	CTAOH[d] (aqueous 10%, 0.3 mL/mmol; 10 mol-%)	room temp.	56	solvent-free	–[c]
3	KF-Al_2O_3 (200 mg/mmol)	room temp.	2	solvent-free	–[c]
4	Al_2O_3 (200 mg/mmol)	room temp.	4	solvent-free	33
5	Amberlyst A-21 (0.5 g/mmol)	room temp.	56	solvent-free	38
6	Amberlyst A-27 (0.5 g/mmol)	room temp.	56	solvent-free	–[c]
7	Isolute[e] (catalyst/substrate, 10 mol-%)	room temp.	4	solvent-free	46
8	Isolute[e] (catalyst/substrate, 20 mol-%)	room temp.	8	solvent-free	59
9	Isolute[e] (catalyst/substrate, 20 mol-%)	60	4	solvent-free	32
10	Isolute[e] (catalyst/substrate, 30 mol-%)	room temp.	23	solvent-free	55
11	DBU (1 equiv.)	room temp.	24	CH_3CN	78
12	TMG[f] (catalyst/substrate, 10 mol-%)	room temp.	22	CH_3CN	79
13	*t*BuOK (catalyst/substrate, 30 mol-%)	room temp.	28	THF	63
14	K_2CO_3 (1 equiv.)	room temp.	6	CH_3CN	86
15	K_2CO_3 (0.2 equiv.)	room temp.	6	CH_3CN	67
16	K_2CO_3 (1 equiv.)	room temp.	9	EtOAc	37

[a] Yield of pure isolated product. [b] Tetraalkylammonium carbonate, polymer-bound. [c] Unconsumed starting material and formation of by-products. [d] Ethyltrimethylammonium hydroxide. [e] Silica trimethylammonium carbonate. [f] 1,1,3,3-Tetramethylguanidine.

ide in tetrahydrofuran (THF) (30 mol-%) afforded **6a** in 63% yield (Table 2, entry 13). These bases are known to promote *aza*-Michael addition of a range of amines to electron-poor alkenes;[25,26] however, the action of these bases on **3a** chemoselectively promoted the Michael addition through a carbanion stabilized by the nitro group.

The best result (86%, Table 2, entry 14) was obtained using potassium carbonate (1 equiv.) as heterogeneous promoter in acetonitrile. When less potassium carbonate was used, the yield dropped to 67% (Table 2, entry 15), whereas when only the solvent was changed, the drop in yield was even worse (37%; Table 2, entry 16).

It is important to note that the synthesis of **6a** could be carried out even in a one-pot fashion, directly from β-nitrostyrene (Scheme 1). Reaction with methoxyamine hydrochloride in methanol containing K_2CO_3 (1.5 equiv.), followed by addition, after 22 h, of methyl vinyl ketone to the reaction mixture gave **6a** (40% overall yield) after 2 h of reaction at room temperature.



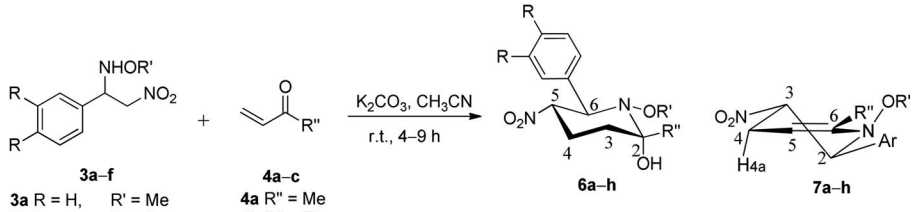
Scheme 1. One-pot synthesis of piperidine **6a** from β-nitrostyrene.

These reactions led to the formation of 2-hydroxypiperidine **6a**, most likely through the γ-nitro-δ-alkoxyamino ketone **5a** (not detected), formed by the conjugate addition of **3a** to **4a**, followed by intramolecular addition of the alkoxyamino group to the carbonyl functionality. The lower nucleophilicity of the alkoxyamino group, compared with that of the amino group, enables the activated methylene of **3a** to act as a Michael donor, thus explaining the remarkable chemoselectivity of 1,2-nitro-*N*-alkoxyamines in reaction with α,β-unsaturated ketone **4a**.

It is also remarkable that, during these reaction sequences, although three stereogenic centers were generated in the product piperidine **6a**, only one diastereomer was observed in the ^1H and ^{13}C NMR spectra, corresponding to the racemate. The vicinal coupling constants of **6a** ($J_{3a,4a}$ = 12.3, $J_{4a,5}$ = 12.3, $J_{5,6}$ = 10.4 Hz) were consistent with a chair conformation with the nitro and the phenyl groups in equatorial positions. A NOESY experiment on **6a** allowed the unequivocal assignment of the configuration at C-2; strong cross-peak correlations were observed between OH and axial H-6, and between the methyl group and both equatorial and axial H-3. The arrangement of the hydroxyl group in the axial position is in agreement with the reduced steric demand of the hydroxyl group compared with the methyl group, and with the anomeric effect.[27,28] The *trans*-diequatorial arrangement of the bulky aryl and nitro substituents might be explained by the high acidity of the hydrogen atom at the carbon bearing the nitro group and subsequent base-catalyzed isomerization at C-5 to give the more stable diastereoisomer.

A series of *N*-alkoxypiperidines **6a**–**d**, **6g**, and **6h** have been prepared in good to high yield (Table 3) from nitroalkoxyamines **3a**–**d** and alkyl vinyl ketones **4a** or **4b** or acrolein **4c**, using the conditions optimized for the synthesis of **6a** (K_2CO_3, acetonitrile). These compounds, which are the first examples of *N*-alkoxy-2-hydroxypiperidines, were found to be more stable than 2-hydroxypiperidines previously described,[29] probably due to the lower basicity of the alkoxyamino moiety. When the reaction was performed on alkoxyamines **3e** or **3f**, only extensive decomposition was observed, whereas just one diastereoisomer was detected by

Table 3. K_2CO_3-promoted synthesis of *N*-alkoxypiperidines **6** and **7** from *N*-alkoxy-2-nitro-1-arylamines **3a**–**d**, α,β-unsaturated aldehydes, and ketones **4a**–**c**.



Entry	Michael donor	Michael acceptor	Piperidine	R	R′	R′′	Time [h]	Ratio	Yield [%][a]
1	**3a**	**4a**	**6a/7a**	H	Me	Me	6	96:4	86
2	**3b**	**4a**	**6b/7b**	H	Bn	Me	5	97:3	78
3	**3c**	**4a**	**6c/7c**	OMe	Me	Me	4	86:14	83
4	**3d**	**4a**	**6d/7d**	OMe	Bn	Me	4	96:4	83
5	**3e**	**4a**	**6e**	OH	Me	Me	9	–	–[b]
6	**3f**	**4a**	**6f**	OH	Bn	Me	9	–	–[b]
7	**3c**	**4b**	**6g/7g**	OMe	Me	Et	9	95:5	70
8	**3b**	**4c**	**6h/7h**	H	Bn	H	8	99:1	58

[a] Yield after column chromatography. [b] Extensive range of by-products formed.

NMR for **6a**–**h**. The equatorial positions of the aryl, alkyl, and nitro groups were confirmed by the vicinal coupling constants and by NOE experiments (Figure 1). The β-substituted enone (*E*)-hexan-4-en-3-one did not work well with *N*-alkoxy amine **3a**; no reaction was observed after 24 h at room temperature, which was possibly due to the steric hindrance involved in the Michael addition.

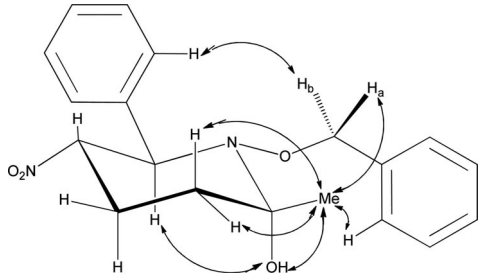


Figure 1. Significant NOE correlations of *N*-alkoxypiperidine **6b** in $CDCl_3$.

A small amount of *N*-alkoxytetrahydropyridines **7a**–**h** was detected in the NMR spectra of the corresponding piperidines (Table 3). These tetrahydropyridines were presumably formed by a dehydration reaction that took place during chromatographic purification. The dehydration might have occurred through an iminium cation, according to the facile dehydration reported for the hemiaminal moiety in aza-sugars.[30] The proton vicinal coupling constants of **7a**–**h** ($J_{2,3}$ = 9.2–9.4, $J_{3,4a}$ = 9.2–9.4 Hz) are in agreement with a half-chair conformation $^3H_2$ (Table 3).

Conclusions

In summary, we have developed an unprecedented, mild, high-yielding conversion of β-nitrostyrenes into a new class of functionalized *N*-alkoxypiperidines by a base-catalyzed, two-step procedure involving 1-alkoxyamino-2-nitroalkane intermediates. Although three stereogenic centers are formed, only one diastereomer was detected. Moreover, the synthesis can be performed in a one-pot procedure in satisfactory overall yield. Given that this procedure enables a new route to stable 2-hydroxypiperidines bearing a versatile nitro group, this sequence is likely to find interesting synthetic applications.

Experimental Section

General: ^{1}H (300 and 500 MHz) and ^{13}C (75.5 and 125.7 MHz) NMR spectra were recorded with Bruker Avance-300 and Avance-500 spectrometers. The assignments of ^{1}H and ^{13}C signals were confirmed by homonuclear COSY and heteronuclear 2D correlated spectra, respectively. Mass spectra (EI and CI) were recorded with a Micromass AutoSpec-Q mass spectrometer. IR spectra were recorded with a Perkin–Elmer FTIR Paragon 500 spectrometer using thin films on NaCl and KBr plates. Only the characteristic peaks are quoted. TLC was performed with aluminum pre-coated sheets (Merck, Silica Gel 60 F_{254}); spots were visualized by UV light or oxidized in $KMnO_4$ solution ($NaOH/KMnO_4/K_2CO_3/H_2O$, 1:6:40:600). Column chromatography was performed using Silica Gel 60 (Merck, 70–230 mesh ASTM).

General Procedure for the Synthesis of *N*-Substituted 1-Aryl-2-nitroethanamines 3a–f: To a solution of β-nitroestyrenes **1a**–**c** (3.3 mmol) in MeOH (10 mL), alkoxyamine hydrochloride **2a**–**b** (3.3 mmol) and triethylamine (3.3 mmol, 0.47 mL) were added. The reaction mixture was stirred at room temp. for 1–2 h. The solvent was removed under vacuum, and the residue was purified as described below to afford **3a**–**f**.

***N*-Methoxy-2-nitro-1-phenylethanamine (3a):** Reaction time 1 h; purification by column chromatography (hexane/EtOAc, 10:1); yield 585 mg, 89%; yellowish oil; R_f = 0.32 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5 H, PhH), 5.88 (d, $J_{1,NH}$ = 4.2 Hz, 1 H, NH), 4.89 (dd, $J_{1,2a}$ = 7.8, $J_{2a,2b}$ = 12.2 Hz, 1 H, 2a-H), 4.77 (ddd, $J_{1,2b}$ = 4.9 Hz, 1 H, 1-H), 4.60 (dd, $J_{2b,1}$ = 4.9, $J_{2b,2a}$ = 12.2 Hz, 1 H, 2b-H), 3.52 (3 H, OCH_3) ppm. ^{13}C MNR (75.5 MHz, $CDCl_3$): δ = 135.9, 129.2, 127.7 (Ph), 78.0 (C-2), 63.1 (C-1), 62.9 (OCH_3) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3252, 2916, 1732, 1556, 1455, 1377 cm^{-1}. MS (EI): *m*/*z* (%) = 196 (5) $[M]^+$. HRMS (EI): calcd. for $C_9H_{12}N_2O_3$ $[M]^+$ 196.0848; found 196.0849.

***N*-Benzyloxy-2-nitro-1-phenylethanamine (3b):** Reaction time 1 h; purification by column chromatography (hexane/EtOAc, 10:1); yield 782 mg, 87%; yellowish oil; R_f = 0.15 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 10 H, 2 × PhH), 5.85 (d, $J_{1,NH}$ = 4.3 Hz, 1 H, NH), 4.87 (dd, $J_{1,2a}$ = 7.7, $J_{2a,2b}$ = 11.8 Hz, 1 H, 2a-H), 4.81 (ddd, $J_{1,2b}$ = 4.7 Hz, 1 H, 1-H), 4.70, 4.65 (2 × d, J = 11.6 Hz, 1 H each, CH_2Ph), 4.57 (dd, $J_{2b,1}$ = 4.7, $J_{2b,2a}$ = 11.8 Hz, 1 H, 2b-H) ppm. ^{13}C MNR (75.5 MHz, $CDCl_3$): δ = 137.1, 135.9, 129.2, 129.1, 128.8, 128.6, 128.3, 127.8 (2 × Ph), 78.0 (C-2), 77.2 (*C*H_2Ph), 63.2 (C-1) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3245, 3031, 2918, 1555, 1455, 1378 cm^{-1}. MS (EI): *m*/*z* (%) = 272 (10) $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{16}N_2O_3$ $[M]^+$ 272.1161; found 272.1161.

1-(3,4-Dimethoxyphenyl)-*N*-methoxy-2-nitroethanamine (3c): Reaction time 2 h; purification by column chromatography (hexane/EtOAc, 5:1); yield 609 mg, 72%; yellowish oil; R_f = 0.23 (hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.90–6.82 (m, 3 H, ArH), 5.83 (d, $J_{1,NH}$ = 3.3 Hz, 1 H, NH), 4.86 (dd, $J_{1,2a}$ = 7.7, $J_{2a,2b}$ = 12.2 Hz, 1 H, 2a-H), 4.71 (ddd, $J_{1,2b}$ = 5.2 Hz, 1 H, 1-H), 4.57 (dd, $J_{2b,1}$ = 5.2, $J_{2b,2a}$ = 12.2 Hz, 1 H, H-2b), 3.89, 3.87 (2 × s, 3 H each, 2 × OMe), 3.52 (3 H, $NOCH_3$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 149.7, 149.4, 128.2, 120.1, 111.5, 110.7 (Ar), 78.3 (C-2), 62.9 (C-1), 62.8 ($NOCH_3$), 56.1, 56.0 (2 × OCH_3) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3249, 2959, 2917, 2841, 2255, 1733, 1552, 1464, 1375 cm^{-1}. MS (EI): *m*/*z* (%) = 256 (22) $[M]^+$. HRMS (EI): calcd. for $C_{11}H_{16}N_2O_5$ $[M]^+$ 256.1059; found 256.1048.

***N*-Benzyloxy-1-(3,4-dimethoxyphenyl)-2-nitroethanamine (3d):** Reaction time 2 h; purification by column chromatography (hexane/EtOAc, 5:1); yield 921 mg, 84%; yellowish oil; R_f = 0.39 (hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.4–6.8 (m, 8 H, ArH, PhH), 5.81 (br. s, 1 H, NH), 4.85 (dd, $J_{1,2a}$ = 7.6, $J_{2a,2b}$ = 12.1 Hz, 1 H, 2a-H), 4.74 (m, $J_{1,2b}$ = 5.3 Hz, 1 H, 1-H), 4.70, 4.64 (2 × d, J = 11.6 Hz, 1 H each, CH_2Ph), 4.54 (dd, $J_{2b,1}$ = 5.3, $J_{2b,2a}$ = 12.1 Hz, 1 H, 2b-H), 3.86 (s, 6 H, 2 × OCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 149.6, 149.3, 137.1, 128.7, 128.5, 128.2, 120.1, 111.4, 110.8 (Ar, Ph), 78.2 (C-2), 77.1 (*C*H_2Ph), 62.9 (C-1), 56.03, 56.01 (2 × OCH_3) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3251, 2954, 2919, 2853, 2254, 1732, 1555, 1464, 1377 cm^{-1}. MS (EI): *m*/*z* (%) = 332 (13) $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{20}N_2O_5$ $[M]^+$ 332.1372; found 332.1381.

1-(3,4-Dihydroxyphenyl)-*N*-methoxy-2-nitroethanamine (3e): Reaction time 2 h; purification by column chromatography (hexane/EtOAc, 2:1); yield 565 mg, 75%; yellowish oil; R_f = 0.18 (hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84–6.74 (m, 3 H, ArH), 5.59 (br. s, 3 H, 2 × OH, NH), 4.83 (dd, $J_{1,2a}$ = 7.4, $J_{2a,2b}$ = 12.1 Hz, 1 H, 2a-H), 4.66 (dd, $J_{1,2b}$ = 5.4 Hz, 1 H, 1-H), 4.55 (dd, $J_{2b,1}$ = 5.4, $J_{2b,2a}$ = 12.1 Hz, 1 H, 2b-H), 3.52 (3 H, OCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.3, 144.0, 128.6, 120.5, 115.9, 114.8 (Ar), 78.1 (C-2), 62.9 (C-1), 62.6 (OCH_3) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3320, 2953, 2921, 2847, 1717, 1553, 1445, 1379 cm^{-1}. MS (EI): *m*/*z* (%) = 228 (8) $[M]^+$. HRMS (EI): calcd. for $C_9H_{12}N_2O_5$ $[M]^+$ 228.0746; found 228.0757.

***N*-Benzyloxy-1-(3,4-dihydroxyphenyl)-2-nitroethanamine (3f):** Reaction time 2 h; purification by column chromatography (hexane/EtOAc, 2:1); yield 823.4 mg, 82%; yellowish oil; R_f = 0.57 (CH_2Cl_2/MeOH, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, PhH), 6.76–6.68 (m, 3 H, ArH), 5.84 (br. s, 3 H, 2 × OH, NH), 4.78 (dd, $J_{1,2a}$ = 7.4, $J_{2a,2b}$ = 12.3 Hz, 1 H, 2a-H), 4.69, 4.65 (2 × d, *J* = 11.5 Hz, 1 H each, CH_2Ph), 4.64 (dd, $J_{1,2b}$ = 5.5 Hz, 1 H, 1-H), 4.49 (dd, $J_{2b,1}$ = 5.5, $J_{2b,2a}$ = 12.3 Hz, 1 H, 2b-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.4, 144.0, 136.9, 128.9, 128.7, 128.4, 128.2, 120.5, 116.0, 114.9 (Ar, Ph), 78.4 (C-2), 77.1 (*C*H_2Ph), 62.6 (C-1) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3495, 3032, 2957, 2918, 2871, 1554, 1454, 1378 cm^{-1}. MS (EI): *m*/*z* (%) = 304 (2) $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{16}N_2O_5$ $[M]^+$ 304.1059; found 304.1054.

General Procedure for the Synthesis of Racemic *N*-Alkoxypiperidines 6a–h: To a solution of **3a**–**d** (1 mmol) in CH_3CN (3 mL), K_2CO_3 (1 mmol) was added, then **4a**–**c** (1.1 mmol) was slowly added dropwise. The reaction mixture was stirred at room temp. for 4–9 h. Once the reaction was completed (reaction monitored by TLC), the solvent was removed under reduced pressure and the residue was suspended in CH_2Cl_2 and washed with water. The collected organic layers were dried ($MgSO_4$), concentrated, and the residue was purified as described below to afford **6a**–**h**.

(2*R,5*S**,6*R**)-1-Methoxy-2-methyl-5-nitro-6-phenylpiperidin-2-ol (6a) and (2*R**,3*S**)-1-(Methoxy)-6-methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydropyridine (7a):** Reaction time 6 h; purification by column chromatography (EtOAc/hexane, 1:6); yield 229 mg, 86%; colorless foam; **6a/7a** ratio 96:4; R_f = 0.41 (EtOAc/hexane, 1:2). Data for **6a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.30 (m, 5 H, PhH), 4.75 (m, 1 H, 5-H), 4.53 (d, $J_{5,6}$ = 10.4 Hz, 1 H, 6-H), 3.02 (s, 3 H, OCH_3), 2.94 (br. s, 1 H, OH), 2.49 (dtd, $J_{4a,4e}$ = 14.0, $J_{4a,3a}$ = 12.3, $J_{4a,5}$ = 12.3, $J_{4a,3e}$ = 4.2 Hz, 1 H, 4a-H), 2.08 (m, $J_{4e,5}$ = 4.4, $J_{4e,3a}$ = 4.4, $J_{4e,3e}$ = 3.0 Hz, 1 H, 4e-H), 2.05 (m, 1 H, 3e-H), 1.78 (m, $J_{3a,3e}$ = 15.0 Hz, 1 H, 3a-H), 1.51 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 136.7, 128.6, 128.4, 128.4 (Ph), 88.4 (C-5), 86.9 (C-2), 66.1 (C-6), 63.8 (OMe), 33.3 (C-3), 28.1 (Me), 25.5 (C-4) ppm. Data for **7a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.07 (td, $J_{3,4a}$ = 9.2, $J_{2,3}$ = 9.2, $J_{3,4e}$ = 5.7 Hz, 1 H, 3-H), 4.70 (m, 1 H, 5-H), 4.65 (d, 1 H, 2-H), 2.80 (m, $J_{4a,4e}$ = 16.7, $J_{4a,5}$ = 2.7, $J_{4a,Me}$ = 2.3 Hz, 1 H, 4a-H), 1.92 (m, 3 H, CH_3) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 100.0 (C-5), 83.8 (C-3), 67.6 (C-2), 63.5 (OMe), 28.2 (Me) ppm. IR (NaCl, Nujol): $\tilde{\nu}_{max}$ = 3544, 3061, 2923, 2815, 1738, 1557, 1455, 1374 cm^{-1}. MS (EI): *m*/*z* (%) = 266 (8) $[M]^+$. HRMS (EI) for **6a**: calcd. for $C_{13}H_{18}N_2O_4$ $[M]^+$ 266.1267; found 266.1270.

(2*R,5*S**,6*R**)-1-(Benzyloxy)-2-methyl-5-nitro-6-phenylpiperidin-2-ol (6b) and (2*R**,3*S**)-1-(Benzyloxy)-6-methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydropyridine (7b):** Reaction time 5 h; purification by column chromatography (EtOAc/hexane, 1:9); yield 264 mg, 78%; white solid; m.p. 98–100 °C; **6b/7b** ratio 97:3; R_f = 0.51 (EtOAc/hexane, 1:2). Data for **6b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–6.70 (m, 10 H, 2 × PhH), 4.84 (m, 1 H, 5-H), 4.64 (d, $J_{5,6}$ = 10.6 Hz, 1 H, 6-H), 4.37, 3.92 (2 × d, *J* = 9.1 Hz, 1 H each, CH_2Ph), 2.93 (br. s, 1 H, OH), 2.53 (dtd, $J_{4a,4e}$ = 14.0, $J_{4a,3a}$ = 12.4, $J_{4a,5}$ = 12.4, $J_{4a,3e}$ = 4.3 Hz, 1 H, 4a-H), 2.13 (m, 1 H, 4e-H), 2.09 (m, 1 H, 3e-H), 1.85 (m, $J_{3a,3e}$ = 13.8 Hz, 1 H, 3a-H), 1.61 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 136.6, 135.4, 129.2, 128.9, 128.51, 128.46, 128.4 (2 × Ph), 88.4 (C-5), 87.1 (C-2), 78.3 (*C*H_2Ph), 66.2 (C-6), 33.4 (C-3), 28.3 (CH_3), 25.6 (C-4) ppm. Data for **7b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.14 (td, $J_{3,4e}$ = 5.8, $J_{3,4a}$ = 9.2, $J_{2,3}$ = 9.2 Hz, 1 H, 3-H), 4.74 (m, 1 H, 5-H), 4.70 (d, $J_{2,3}$ = 9.2 Hz, 1 H, 2-H), 4.32, 4.14 (2 × d, *J* = 9.5 Hz, 1 H each, CH_2Ph), 2.81 (m, $J_{4a,4e}$ = 16.6, $J_{4a,5}$ = 2.5, $J_{4a,Me}$ = 2.5 Hz, 1 H, 4a-H), 1.96 (m, 3 H, CH_3) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 100.3 (C-5), 83.5 (C-3), 78.1 (*C*H_2Ph), 68.0 (C-2), 19.0 (C-4) ppm. IR (NaCl, Nujol): $\tilde{\nu}_{max}$ = 3583, 2924, 2855, 1738, 1558, 1458, 1376 cm^{-1}. MS (EI): *m*/*z* (%) = 324 (4) $[M]^+$. HRMS (EI) for **6b**: calcd. for $C_{19}H_{22}N_2O_4$ $[M]^+$ 342.1580; found 324.1570.

(2*R,5*S**,6*R**)-6-(3,4-Dimethoxyphenyl)-1-methoxy-2-methyl-5-nitropiperidin-2-ol (6c) and (2*R**,3*S**)-2-(3,4-Dimethoxyphenyl)-1-methoxy-6-methyl-3-nitro-1,2,3,4-tetrahydropyridine (7c):** Reaction time 4 h; purification by column chromatography (EtOAc/hexane, 1:4 → 1:3); yield 114 mg, 83%; colorless foam; **6c/7c** ratio 86:14; R_f = 0.18 (EtOAc/hexane, 1:2). Data for **6c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00–6.80 (m, 3 H, ArH), 4.73 (m, 1 H, 5-H), 4.46 (d, $J_{5,6}$ = 10.4 Hz, 1 H, 6-H), 3.90, 3.87 (2 × s, 3 H each, 2 × $ArOCH_3$), 3.08 (s, 3 H, $NOCH_3$), 2.88 (br. s, 1 H, OH), 2.49 (dtd, $J_{4a,4e}$ = 14.0, $J_{4a,3a}$ = 12.5, $J_{4a,5}$ = 12.5, $J_{4a,3e}$ = 4.4 Hz, 1 H, 4a-H), 2.08 (m, 1 H, 4e-H), 2.02 (m, 1 H, 3e-H), 1.77 (m, 1 H, 3a-H), 1.51 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 149.2, 148.7, 128.9, 121.4, 111.8, 110.8 (Ar), 88.6 (C-5), 87.0 (C-2), 65.9 (C-6), 63.9 ($NOCH_3$), 56.1, 56.0 (2 × $ArOCH_3$), 33.3 (C-3), 28.1 (CH_3), 25.5 (C-4) ppm. Data for **7c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.06 (td, $J_{3,4e}$ = 5.7, $J_{3,4a}$ = 9.3, $J_{3,2}$ = 9.3 Hz, 1 H, 3-H), 4.73 (m, 1 H, 5-H), 4.53 (d, $J_{2,3}$ = 9.3 Hz, 1 H, 2-H), 3.17 (s, 3 H, $NOCH_3$), 2.80 (m, $J_{4a,4e}$ = 16.7, $J_{4a,3}$ = 2.5, $J_{4a,Me}$ = 2.5 Hz, 1 H, 4a-H), 1.91 (m, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 100.2 (C-5), 84.1 (C-3), 67.5 (C-2), 63.7 ($NOCH_3$), 28.6 (CH_3), 26.1 (C-4) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3504, 2942, 1731, 1550, 1512, 1444, 1376, 1262 cm^{-1}. MS (EI): *m*/*z* (%) = 326 (27) $[M]^+$. HRMS (EI) for **6c**: calcd. for $C_{15}H_{22}N_2O_6$ $[M]^+$ 326.1478; found 326.1485.

(2*R,5*S**,6*R**)-1-(Benzyloxy)-6-(3,4-dimethoxyphenyl)-2-methyl-5-nitropiperidin-2-ol (6d) and (2*R**,3*S**)-1-(Benzyloxy)-2-(3,4-dimethoxyphenyl)-6-methyl-3-nitro-1,2,3,4-tetrahydropyridine (7d):** Reaction time 4 h; purification by column chromatography (EtOAc/hexane, 1:5 → 1:1); yield 103 mg, 83%; colorless foam; **6d/7d** ratio 96:4; R_f = 0.28 (EtOAc/hexane, 1:2). Data for **6d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–6.75 (m, 8 H, ArH, PhH), 4.83 (m, 1 H, 5-H), 4.56 (d, $J_{5,6}$ = 10.4 Hz, 1 H, 6-H), 4.39, 3.87 (2 × d, *J* = 8.9 Hz, 1 H each, CH_2Ph), 3.89 (s, 6 H, 2 × $ArOCH_3$), 2.92 (br. s, 1 H, OH), 2.51 (dtd, $J_{4a,4e}$ = 13.5, $J_{4a,3a}$ = 12.6, $J_{4a,5}$ = 12.6, $J_{4a,3e}$ = 4.5 Hz, 1 H, 4a-H), 2.12 (m, 1 H, 4e-H), 2.06 (m, 1 H, 3e-H), 1.83 (m, 1 H, 3a-H), 1.61 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 149.5, 149.0, 129.0, 112.2, 111.0 (Ar), 135.5, 129.2, 128.5, 128.4 (Ph), 88.4 (C-5), 87.1 (C-2), 78.3 (*C*H_2Ph), 66.0 (C-6), 56.1 (2 × $ArOCH_3$), 33.4 (C-3), 28.3 (CH_3), 25.6 (C-4) ppm. Data for **7d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.13 (td, $J_{3,4e}$ = 5.8, $J_{3,4a}$ = 9.4, $J_{3,2}$ = 9.4 Hz, 1 H, 3-H), 4.61 (d, $J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 4.29, 4.17 (2 × d, *J* = 9.6 Hz, 1 H each, CH_2Ph), 2.80 (m, $J_{4a,4e}$ = 16.6, $J_{4a,5}$ = 2.5, $J_{4a,Me}$ = 2.5 Hz, 1 H, 4a-H), 1.96 (m, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 100.8 (C-5), 84.5 (C-3), 78.2

(CH_2Ph), 67.8 (C-2) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3464, 2928, 1545, 1513, 1458, 1361, 1251 cm^{-1}. MS (EI): *m*/*z* (%) = 402 (2) $[M]^+$. HRMS (EI) for **6d**: calcd. for $C_{21}H_{26}N_2O_6$ $[M]^+$ 402.1791; found 402.1771.

(2*R,5*S**,6*R**)-6-(3,4-Dimethoxyphenyl)-2-ethyl-1-methoxy-5-nitropiperidin-2-ol (6g) and (2*R**,3*S**)-2-(3,4-Dimethylphenyl)-6-ethyl-1-methoxy-3-nitro-1,2,3,4-tetrahydropyridine (7g):** Reaction time 9 h; purification by column chromatography (EtOAc/hexane, 1:5); yield 102 mg, 70%; yellowish syrup; **6g**/**7g** ratio 95:5; R_f = 0.21 (EtOAc/hexane, 1:2). Data for **6g**: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.08–6.75 (m, 3 H, ArH), 4.75 (m, 1 H, 5-H), 4.49 (d, $J_{5,6}$ = 10.6 Hz, 1 H, 6-H), 3.90, 3.87 (2 × s, 3 H each, 2 × ArOCH_3), 3.04 (s, 3 H, NOCH_3), 2.76 (s, 1 H, OH), 2.47 (dtd, $J_{4a,3a}$ = 12.4, $J_{4a,5}$ = 12.4, $J_{4a,4e}$ = 13.9, $J_{4a,3e}$ = 4.7 Hz, 1 H, 4a-H), 2.11 (m, 1 H, 4e-H), 2.03 (m, 1 H, 3e-H), 1.82 (m, 3 H, 3a-H, CH_2CH$_3$), 1.02 (t, $J_{CH2,CH3}$ = 7.5 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 149.1, 148.6, 129.2, 122.1, 111.3, 110.3 (Ar), 89.2 (C-5), 88.4 (C-2), 66.0 (C-6), 63.6 (NO*C*H$_3$), 56.1, 55.9 (2 × ArO*C*H$_3$), 33.4 (C-3), 29.4 (*C*H$_2$CH$_3$), 25.2 (C-4), 8.6 (CH_2CH_3) ppm. Data for 7**g**: ^1H NMR (300 MHz, $CDCl_3$): δ = 5.07 (td, $J_{3,4a}$ = 9.4, $J_{2,3}$ = 9.4, $J_{3,4e}$ = 5.7 Hz, 1 H, 3-H), 4.80 (m, 1 H, 5-H), 4.65 (d, $J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 3.17 (s, 3 H, NOCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 86.4 (C-3), 68.3 (C-2), 63.4 (OCH_3), 27.1 (*C*H$_2$CH$_3$), 23.0 (C-4) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3054, 2936, 1706, 1549, 1516, 1464, 1370, 1263 cm^{-1}. MS (EI): *m*/*z* (%) = 340 (10) $[M]^+$. HRMS (EI) for **6g**: calcd. for $C_{16}H_{24}N_2O_6$ $[M]^+$ 340.1634; found 340.1628.

(2*R,5*S**,6*R**)-1-(Benzyloxy)-5-nitro-6-phenylpiperidin-2-ol (6h) and (2*R**,3*S**)-1-(Benzyloxy)-3-nitro-2-phenyl-1,2,3,4-tetrahydropyridine (7h):** Reaction time 8 h; purification by column chromatography (EtOAc/hexane, 1:5); yield 158 mg, 58%; syrup; **6h**/**7h** ratio 99:1; R_f = 0.41 (EtOAc/hexane, 1:2). Data for **6h**: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.52–6.77 (m, 10 H, 2 × PhH), 5.01 (m, 1 H, 2-H), 4.79 (ddd, $J_{4a,5}$ = 11.7, $J_{5,6}$ = 10.4, $J_{4e,5}$ = 3.8 Hz, 1 H, 5-H), 4.68 (d, $J_{6,5}$ = 10.4 Hz, 1 H, 6-H), 4.37, 4.14 (2 × d, *J* = 9.9 Hz, 1 H each, CH_2Ph), 3.21 (s, 1 H, OH), 2.52 (dtd, $J_{4a,4e}$ = 14.1, $J_{4a,3a}$ = 12.0, $J_{4a,3e}$ = 4.1 Hz, 1 H, 4a-H), 2.14 (m, 2 H, 4e-H, 3e-H), 1.87 (m, 1 H, 3a-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 136.2, 129.1, 128.9, 128.7, 128.6, 128.4 (Ph), 88.4 (C-5), 81.1 (C-2), 76.0 (*C*H$_2$Ph), 64.0 (C-6), 27.0 (C-4), 24.1 (C-3) ppm. Data for **7h**: ^1H NMR (500 MHz, $CDCl_3$): δ = 6.29 (m, 1 H, 6-H), 5.12 (td, $J_{3,4a}$ = 9.5, $J_{2,3}$ = 9.2, $J_{3,4e}$ = 6.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 100.9 (C-3) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3468, 2937, 2876, 1552, 1455, 1372 cm^{-1}. MS (EI): *m*/*z* (%) = 328 (1) $[M]^+$. HRMS (EI) for **6h**: calcd. for $C_{18}H_{20}N_2O_4$ $[M]^+$ 328.1423; found 328.1424.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all new compounds.

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