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A free radical Mannich type reaction: selective α-CH aminomethylation of ethers by Ti(III)/*t*-BuOOH system under aqueous acidic conditions

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Abstract—*tert*-Butoxy radical, generated by Ti(III)-one electron reduction of *tert*-butylhydroperoxide, selectively abstracts an α-H atom from ethers. The resulting α-ethereal radicals add to the C-atom of methylene iminium salts, formed in situ under aqueous acidic conditions, leading to a one-pot aminomethylation of ethers at room temperature. The aminoalkylation of ethers is also considered and the role of the metal ion is discussed.

1. Introduction

The classical Mannich aminomethylation of R–H acidic substrates is one of the most important carbon–carbon bond forming reaction in organic chemistry.[1] Aminomethylation of nucleophilic radicals, formed by H-atom abstraction from R–H substrates, would represent the radical version of the classical Mannich reaction with the substantial difference such that the functional groups directly bonded to the reactive carbon atoms in R–H must have opposite polarity.

Whereas electron-withdrawing groups (EWG) are suitable for the ionic addition, electron-donor groups (EDG) favour the nucleophilic radical addition to methylene-iminium salts. As a consequence, the type of products accessible by the classical and the radical-type Mannich reactions would be complementary concerning the polarity of the substituents in β-position to the amino groups (Fig. 1).

Recently,[2–7] the carbon–nitrogen double bond has attracted significant attention as an excellent acceptor of nucleophilic radicals, however, only water-resistant imine derivatives may be used in aqueous radical reactions.

As a consequence, studies involving the reductive intermolecular radical addition to water-sensitive simple aldimines are scattered[2,8] in comparison to those dealing with various C═N containing functional groups, such as oxime ethers, glyoxylic oxime ethers, *N*-sulfonylimines, hydrazones and nitrones.[3–7] These substrates are less sensitive to hydrolysis than the former and show higher radical addition rates due to extra-stabilisation in the addition transition state.[9]

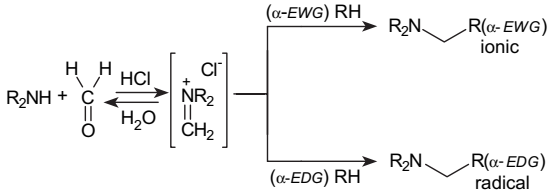

Figure 1. Classical and radical-type Mannich reaction.

Even more so, studies concerning intermolecular radical addition to highly water-sensitive and easily polymerisable[10] formaldehyde-imines and formaldehyde-iminium salts, generated in situ either in anhydrous organic solvents or in aqueous co-solvents, have not attracted the organic chemists' attention.

We report here that the exceptional coordinative properties of Ti(IV) make feasible the addition of α-ether radicals to the C-atom of methylene iminium salts and formaldehyde-imines formed in situ under aqueous conditions, leading to α-aminomethylation of ethers in a free radical Mannich type reaction (Fig. 1).

2. Results and discussion

Our recent studies[8d,e] have shown that, under aqueous conditions, a phenyl radical, generated by Ti(III)-induced

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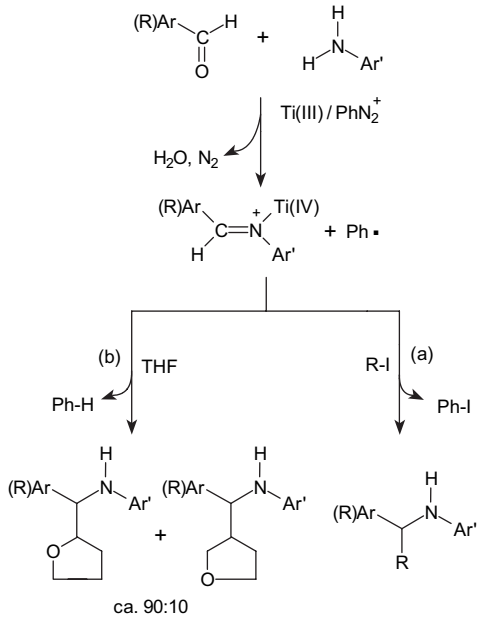
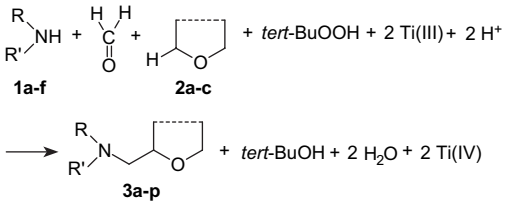
decomposition of phenyldiazonium cation, abstracts either an iodine-atom from alkyl iodides (Scheme 1, path a) or an α-H atom from ethers (Scheme 1, path b), leading to a one-pot addition of nucleophilic alkyl or α-alkoxyalkyl radicals to the C-atom of aldimines, formed in situ and activated towards radical addition by Ti(IV)–N complexation.



Scheme 1. Ti(III)/PhN_2^+ mediated radical addition to aldimines.

Continuing our research on the manifold roles simultaneously played by Ti(III) and Ti(IV) ions in promoting tandem radical one-pot multicomponent reactions, we report here that the aqueous acidic $TiCl_3$/*t*-BuOOH system is a more practical, efficient and selective radical precursor of α-alkoxyalkyl radicals from ethers[11] than the previously reported $TiCl_3/PhN_2^+$ system[8e] and that even methylene iminium salts and formaldehyde-imines may be successfully used as radical acceptors. In fact, notwithstanding the aqueous medium, these species are formed in situ in an adequate concentration to make the subsequent addition of α-ether radicals preparatively advantageous for the synthesis of 1,2-aminoethers **3**.

According to the stoichiometry of Scheme 2, the Ti(III)/*t*-BuOOH system readily assembles, in 30 min at room temperature, an amine **1**, formaldehyde and an ether **2** leading to **3**.



Scheme 2. Ti(III)/*t*-BuOOH mediated α-aminomethylation of ethers.

After a survey to optimise the reaction conditions, we found that the reaction rapidly occurs at 20 °C by dropwise addition (30 min) of *t*-BuOOH (4 mmol of a 80% aqueous solution) to a homogeneous solution containing amine **1** (2 mmol), formaldehyde (7 mmol of a 40% aqueous solution) and $TiCl_3$ (8 mmol, ca. 8 mL of a 15 wt % in 30 wt % HCl solution) in 10 mL of glacial CH_3COOH and 10 mL of the ether **2** under investigation.[12] The reaction can be followed like a titration and it is over when the blue colour of $TiCl_3$ is completely discharged to give a homogeneous yellow solution.

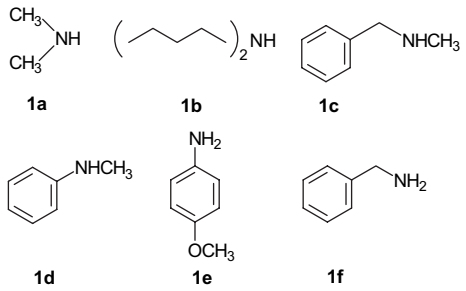


Figure 2. Representative amines **1a**–**f**.

Under these conditions, we tested the reaction of a number of representative amines **1a**–**f** (Fig. 2) in the presence of either THF (**2a**), 1,4-dioxane (**2b**) or Et_2O (**2c**) as co-solvents.

Secondary aliphatic and aromatic amines **1a**–**d** gave the expected products **3a**–**k** in fair to good isolated yields (Table 1).

This one-pot three component reaction proved to be so clean that with low boiling amines **1a**–**b**, no chromatographic separation was required in order to obtain the spectroscopically pure 1,2-aminoethers **3a**–**e** (^{1}H NMR purity of the crude residue was ≥95%, entries 1–5). Pure **3f**–**k** (entries 6–11) were obtained after chromatographic separation from the unreacted amines **1c**–**d**.

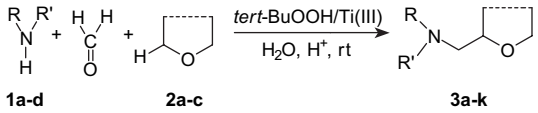
When *p*-methoxyaniline **1e** (PMP–NH_2) was used, as a representative primary aromatic amine,[13] under the reaction conditions adopted for secondary amines (e.g., molar ratio **1e**/HCHO, 1:3.5), the reaction went on and bis-adducts **4l**–**n** were obtained in addition to the desired products **3l**–**n** (Table 2, entries 1, 3 and 5).

However it was possible to control the selective formation of **3l**–**n** by decreasing the amount of formaldehyde to 0.5 equiv (Table 2, entries 2, 4 and 6). The use of **3l**–**n**, as a starting amine component under the conditions developed for secondary amines, led to bis-derivatives **4l**–**n** in ca. 70% isolated yields. The primary aliphatic amine **1f**, under all the experimental conditions tested, gave only the bis-adduct **4p** (Table 2, entry 7).

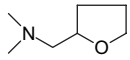
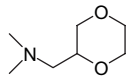
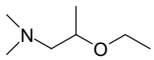
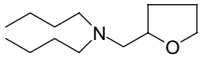
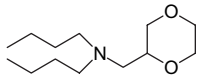
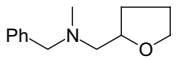
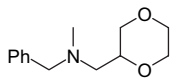
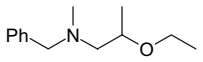
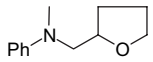
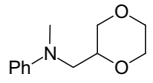
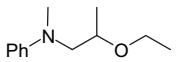
It should be underlined that the product arising from the addition of β-THF radical (Scheme 1) to the C-atom of the imine was not obtained in every case, showing that the Ti(III)/*t*-BuOOH system is more selective than Ti(III)/PhN_2^+ in abstracting a H-atom from THF.

To extend the scope of the reaction from aminomethylation to aminoalkylation and aminoarylation of ethers, we checked the applicability of the method to acetaldehyde,

Table 1. Mannich radical-type addition of ethers **2a–c** to in situ generated methylene iminium salts[a]



1a-d **2a-c** **3a-k**

Entry	Product	**3** yield %[b]
1		**3a**: 88
2		**3b**: 65
3		**3c**: 40
4		**3d**: 55
5		**3e**: 55
6		**3f**: 60 (65)
7		**3g**: 75 (81)
8		**3h**: 54 (63)
9		**3i**: 70 (81)
10		**3j**: 70 (84)
11		**3k**: 50 (65)

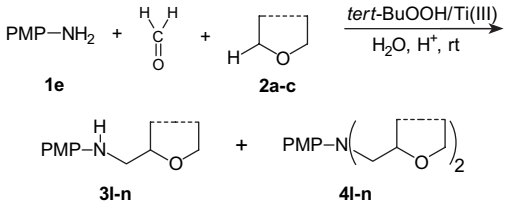
[a] Molar ratio of **1**:HCHO:*t*-BuOOH:Ti(III) was 1:3.5:2:4.
[b] Isolated yields are based on the starting amine **1** (2 mmol); yields in brackets have been determined by ^{1}H NMR with an appropriate internal standard added to the crude reaction mixture; yield of **3**, based on the converted **1**, were always >90%.

p-bromobenzaldehyde, *p*-tolualdehyde, *p*-anisaldehyde, benzaldehyde and cyclohexylaldehyde, but of all the amines screened (Fig. 2) only the primary aromatic amine **1e** gave the desired THF-adducts **3q–v** (Table 3) as a 1:1 mixture of diastereomers with no traces of bis-adduct **4**.

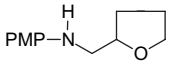
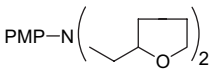
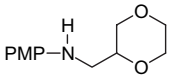
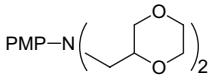
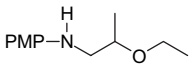
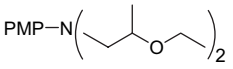
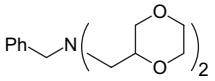
The fact that any attempt to apply this radical addition to in situ generated alkylidene or arylidene iminium ions proved to be unsuccessful implies that steric factors are relevant to the course of the reaction, as they are for the classical Mannich reaction.

In Table 3, the yields of **3l** and **3q–v**, obtained with the present method (**A**), are compared with those previously obtained[8e] by using, under comparable experimental conditions, the Ti(III)/PhN$_2^+$ method (**B**) and the yields of **3t–v** are also compared with those reported by Tomioka[8c] in a three component reaction with the use of dimethylzinc as a radical initiator (**C**).

Table 2. Mannich radical-type addition of ethers **2a–c** to an equilibrium mixture of PMP–NH$_2$ (**1e**) and formaldehyde under different experimental conditions

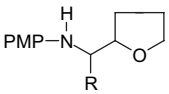


1e **2a-c** **3l-n** **4l-n**

Entry	Product; yield %[a]	
1[b]	 **3l** (30)	 **4l** (34)
2[c]	**3l** 68 (80)	**4l** (6)
3[b]	 **3m** (41)	 **4m** (24)
4[c]	**3m** 70 (86)	**4m** (5)
5[b]	 **3n** (36)	 **4n** (30)
6[c]	**3n** 68 (80)	**4n** (6)
7[d]		 **4p** (30)

[a,b] See footnotes a and b of Table 1, respectively.
[c] Molar ratio of **1e**/HCHO/*t*-BuOOH:Ti(III) was 1:0.5:2:4; yields are based on the starting HCHO.
[d] Benzylamine **1f** was used; molar ratio of **1f**/HCHO was 1:0.5.

Table 3. Addition of THF to an equilibrium mixture of PMP–NH$_2$ (**1e**) and aldehydes (R–CHO) by using different radical initiators

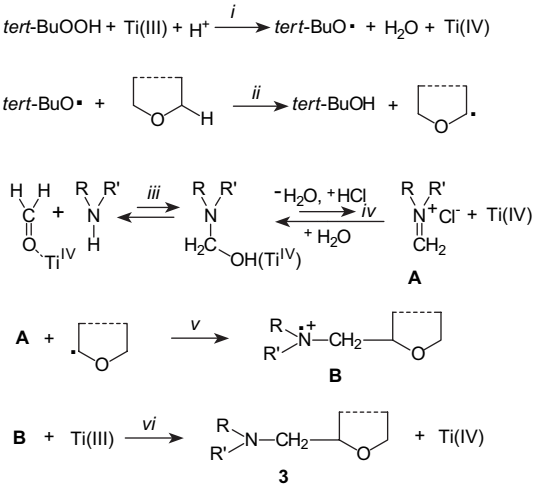
Product **3** 	Molar ratio R–CHO/**1e**	Radical initiator,[a] **3** yield %[b]		
		A (30 min)	**B** (3 h)	**C** (time)
R=H, **3l**	1:1	72	58	—
R=CH_3, **3q**	2:1	80 (90)[c]	55+9[d]	—
R=*p*-Br-C_6H_4, **3r**	1:1.5	63 (70)[c]	55+7[d]	—
R=*p*-CH_3-C_6H_4, **3s**	1:1.5	74 (85)[c]	47+8[d]	—
R=*p*-$OCH_3C_6H_4$, **3t**	1:1.5	80 (89)[c]		57 (45 h)
R=C_6H_5, **3u**	1:1.5	70 (79)[c]	51+9[d]	74 (22 h)
R=cyclohexyl, **3v**	2:1	80 (95)[c]	64	44 (138 h)

[a] **A**: Ti(III)/*t*-BuOOH (this work); **B**: Ti(III)/PhN$_2^+$ (Ref. 8e); **C**: Me_2Zn/air (Ref. 8c).
[b] Isolated yields.
[c] ^{1}H NMR yields with an appropriate internal standard.
[d] β-THF adduct.

other routes in a number of ways: shorter reaction times, titration-like reaction, cheaper and easier to handle radical source and higher-yielding reaction with wide applicability.

2.1. Mechanistic considerations

The sequence of steps *i*–*vi* reported in Scheme 3 would represent a reasonable rationale of the reaction. The one-electron reduction of *t*-BuOOH by Ti(III) ion gives the *tert*-butoxy radical (*i*) which selectively abstracts an α-H atom from the ether generating an α-ethereal radical (*ii*).



Scheme 3. Mechanistic rationale.

Owing to its nucleophilic character, the α-ethereal radical adds to the C-atom of the methylene iminium salt **A** (*v*) (or to the C-atom of the Ti(IV)-complexed imine) formed in situ by a series of equilibrium reactions (*iii*, *iv*). The resulting electrophilic aminium radical **B** is then readily reduced (*vi*) to the final product **3** by a second equivalent of Ti(III).

The H-atom abstraction from ethers by *tert*-butoxy radical (*i*) is a fast process[14] due to a favourable enthalpy balance,[15] and to polar effects, but the series of equilibria involved in the formation of **A** under aqueous conditions[16] (*iii*, *iv*) should be by far shifted to the left. In fact, for the conditions under which the classical Mannich reaction is most commonly performed (aqueous formaldehyde solution), elevated temperature and long reaction time are necessary for generation of a sufficient concentration of **A**.

In the modern variant of the Mannich reaction the methylene iminium ion, rather than being generated under equilibrium conditions, is separately preformed upon exclusion of moisture or generated in situ starting from iminium ion equivalents that permit an aprotic solvent to be used under milder reaction conditions and shorter reaction time.[1]

In view of this, the salient feature of the present radical Mannich type reaction is that aminoethers **3** are formed in good yields at room temperature in ca. 30 min, notwithstanding the aqueous medium (volume ratio H_2O/ether/CH_3COOH, ca. 1:1:1).

A plausible explanation is that Ti(IV) ion, owing to its high oxophilicity, coordinates the carbonyl oxygen, thereby preparing the aldehyde for reaction with the amine (*iii*), and that the transfer of the oxygen atom from the carbon to Ti(IV) makes equilibrium *iv* less unfavourable.

The fast[17] and irreversible step *v* further contributes to shift the total equilibrium to the side of product, rendering the process preparatively advantageous with either formaldehyde, aliphatic or aromatic aldehydes.

Finally, it must be pointed out that, in sharp contrast with the substituent effects found in acid-catalysed condensation of aromatic amines with aromatic aldehydes,[18] the yields of **3s**,**t** are higher than those of **3r** and **3u** (Table 3); however, this experimental finding strongly supports the rationale of Scheme 3.

Under our conditions, an electron-releasing group on the aromatic ring of the aldehyde would increase the equilibrium concentration of the Ti(IV)-complexed aldehyde and would favour the Ti(IV)-assisted loss of water from the intermediate hemiaminal (Scheme 3, paths *iii* and *iv*, ArCHO instead of HCHO).

Beside, the increased basic strength of the imine, brought about by an electron-donor substituent on the aldehyde,[19] would increase the equilibrium concentration of the Ti(IV)-complexed imine, which is the reactive counterpart of the incoming nucleophilic radical (Scheme 1).

3. Conclusions

The success of this one-pot reaction is mainly due to the multiple role played by titanium, which in its lower oxidation state acts both as a radical initiator and as a radical terminator, while in its higher oxidation state acts as a Lewis acid and dehydrating agent providing a relatively high concentration of the iminium salts (or of complexed aldimines), even under aqueous conditions.

Despite the simplicity of 1,2-aminoethers moiety, the synthesis of these compounds is often difficult[20,21]and this new method provides an easy entry to both *N*-aryl[21] and *N*-alkyl aminoethers starting from cheap and readily available reagents under very mild reaction conditions. Further studies are currently under investigation with the aim to extend the aminomethylation and aminoalkylation reaction to other nucleophilic radicals.

4. Experimental

4.1. General

All reactions were performed under N_2 at room temperature (20 °C). NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C, measured in $CDCl_3$ and chemical shifts were presented in parts per million (δ). The following aqueous solutions were used: 37% solution of formaldehyde (Aldrich); 80% solution of *tert*-butylhydroperoxide (Fluka); 15% solution $TiCl_3$ (C. Erba). Flash column chromatography was performed by using 40–63 μm silica gel packing. Silica gel 60 F_{254} (1 mm) plates were used for PLC.

4.2. Typical procedure for ether addition to formaldehyde-iminium salts formed in situ

t-BuOOH (4 mmol of a 80% aqueous solution), diluted in 5 mL of CH_3COOH and 5 mL of the ether **2** under investigation, was added dropwise in 30 min to a stirred homogeneous solution containing the amine **1** (2 mmol), formaldehyde (7 mmol, ca. 0.56 mL of a 37% aqueous solution) and $TiCl_3$ (8 mmol, ca. 8 mL of a 15 wt % in 30 wt % HCl solution) in: (a) 10 mL of CH_3COOH and 10 mL of THF or Et_2O; (b) 15 mL of 1,4-dioxane. The end of the reaction was shown by a rapid change of colour from blue to yellow. Work up was as follows with low boiling amines **1a**–**b**: the reaction mixtures were directly added to a 30% aqueous NH_3 solution until pH=9 and extracted with Et_2O (3× 50 mL); the combined extracts layers, washed with water and dried over Na_2SO_4, were carefully concentrated in vacuo (20 mmHg) at room temperature; the crude residues left over resulted to be ^{1}H NMR spectroscopically pure **3a**–**e**. Work up was as follows with amines **1c**–**f**: the reaction mixtures were concentrated in vacuo to eliminate most of the ether and CH_3COOH; the crude residues left were dissolved in EtOAc (50 mL) and added a 30% aqueous NH_3 solution basic pH=9; the organic layers were separated and the aqueous layers were further extracted with EtOAc (2×50 mL); the combined organic layers were then washed with water, dried over Na_2SO_4 and concentrated in vacuo. Purification of the resulting crude materials by FCC gave adducts **3** and/or **4**.

4.2.1. Typical procedure for THF addition to aldimines formed in situ (Table 3). The procedure was as above with the exception of the molar ratio *p*-methoxyaniline **1e**/aldehyde employed: (a) 4 mmol of aliphatic aldehydes were reacted with 2 mmol of **1e**; (b) 2 mmol of aromatic aldehydes were reacted with 3 mmol of **1e**. Work up was as the one reported for amines **1c**–**f**.

4.3. Spectroscopic data

4.3.1. Dimethyl-(tetrahydrofuran-2-yl-methyl) amine (3a). The crude residue left over (227 mg) was **3a** (^{1}H NMR purity≥95%, 88% yield, pale yellow oil). IR (liquid film) ν_{max} 3000–2870, 1630, 1069 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.43–1.54 (1H, CH_2, m), 1.81–1.90 (2H, CH_2, m), 1.95–2.03 (1H, CH_2, m), 2.29 (6H, $2CH_3$, s), 2.31 (1H, CH_2–N, dd, J=12.7, 4.4 Hz), 2.43 (1H, CH_2–N, dd, J=12.7, 7.5 Hz), 3.71–3.76 (1H, CH_2–O, m), 3.87 (1H, CH_2–O, ddd, J=8.3, 7.0, 6.5 Hz), 3.98 (1H, CH–O, qd, J=7.5, 4.4 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.3 (CH_2), 30.1 (CH_2), 45.9 ($2CH_3$), 64.1 (CH_2–N), 67.8 (CH_2–O), 76.9 (CH–O) ppm. EIMS (*m*/*z*) 129 (M^+, 6), 58 (M−THF, 100). HRMS calcd for $C_7H_{15}NO$: 129.11536; found 129.11527.

4.3.2. Dimethyl-(1,4-dioxan-2-yl-methyl) amine (3b).[22] The crude residue left over (195 mg) was pure **3b** (^{1}H NMR purity≥95%, 65% yield, pale yellow oil). IR (liquid film) ν_{max} 2960–2854, 1615, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.22 (1H, CH_2–N, dd, J=12.9, 4.2 Hz), 2.30 (6H, $2CH_3$, s), 2.43 (1H, CH_2–N, dd, J=12.9, 7.5 Hz), 3.28 (1H, CH_2–O, dd, J=11.9, 10.3 Hz), 3.60 (1H, CH_2–O, dd, J=11.9, 3.4 Hz), 3.69–3.80 (5H, $2CH_2$–O+CH–O, m) ppm. ^{13}C NMR ($CDCl_3$) δ 46.0 ($2CH_3$), 60.6 (CH_2–N), 66.5 (CH_2–O), 66.6 (CH_2–O), 69.9 (CH_2–O), 73.2 (CH–O) ppm. EIMS (*m*/*z*) 145 (M^+, 5), 58 (M−1,4-dioxane, 100), 42 (10). HRMS calcd for $C_7H_{15}NO_2$: 145.1103; found 145.1099.

4.3.3. Dimethyl-(2-ethoxypropyl) amine (3c). The crude residue left over (105 mg) was pure **3c** (^{1}H NMR purity≥95%, 40% yield, yellow oil). IR (liquid film) ν_{max} 2960–2852, 1620, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, CH_3, d, J=6.2 Hz), 1.19 (3H, CH_3, t, J=6.7 Hz), 2.24 (1H, CH_2–N, dd, J=12.7, 5.1 Hz), 2.27 (6H, $2CH_3$–N, s), 2.43 (1H, CH_2–N, dd, J=12.7, 6.7 Hz), 3.44–3.51 (1H, CH, m), 3.52–3.62 (2H, CH_2–O, m) ppm. ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_3), 18.4 (CH_3), 46.0 ($2CH_3$–N), 63.7 (CH_2–O), 65.3 (CH_2–N), 73.2 (CH–O) ppm. EIMS (*m*/*z*) 131 (M^+, 2), 58 (M−Et_2O, 100). HRMS calcd for $C_7H_{17}NO$: 131.13101; found 131.13098. According to the literature procedure,[23] quaternisation of **3c** with MeI in anhydrous Et_2O afforded the ethyl ether of β-methylcholine (80%) as white crystals: mp 97–99 °C (lit.[23] 99 °C).

4.3.4. Dibutyl-(tetrahydrofuran-2-yl-methyl) amine (3d). The crude residue left over was pure **3d** (235 mg, ^{1}H NMR purity≥95%, 55% yield, colourless oil). IR (liquid film) ν_{max} 2975–2860, 1467, 1077, 1070 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, $2CH_3$, t, J=7.2 Hz), 1.25–1.34 (4H, $2CH_2$, m), 1.37–1.45 (4H, $2CH_2$, m), 1.49–1.58 (1H, CH_2, m), 1.79–1.90 (2H, CH_2, m), 1.93–2.01 (1H, CH_2, m), 2.41–2.57 (6H, $3CH_2N$, m), 3.69–3.74 (1H, CH_2–O, m), 3.82–3.88 (1H, CH_2–O, m), 3.95 (1H, CH–O, quintet, J=6.5 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 14.0 ($2CH_3$), 20.6 ($2CH_2$), 25.4 (CH_2), 29.2 ($2CH_2$), 30.2 (CH_2), 54.6 (CH_2–N), 58.9 (CH_2–N), 67.8 (CH_2–O), 77.8 (CH–O) ppm. EIMS (*m*/*z*) 213 (M^+, 10), 142 (M−THF, 100), 100 (50). HRMS calcd for $C_{13}H_{27}NO$: 213.2093; found 213.2090.

4.3.5. Dibutyl-(1,4-dioxan-2-yl-methyl) amine (3e). The crude residue left over was pure **3e** (252 mg, ^{1}H NMR purity≥95%, 55% yield, pale yellow oil). IR (liquid film) ν_{max} 2955–2790, 1462, 1107 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, $2CH_3$, t, J=7.2 Hz), 1.23–1.34 (4H, $2CH_2$, m), 1.34–1.43 (4H, $2CH_2$, m), 2.33–2.49 (6H, $3CH_2N$, m), 3.27 (1H, CH_2–O, dd, J=11.6, 9.8 Hz), 3.55–3.64 (1H, CH–O, m), 3.65–3.77 (4H, $2CH_2$–O, m), 3.85 (1H, CH_2O, dd, J=11.6, 2.6 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 14.0 ($2CH_3$), 20.6 ($2CH_2$), 29.3 ($2CH_2$), 54.9 (CH_2–N), 55.9 (CH_2–N), 66.6 (CH_2–O), 66.8 (CH–O), 70.7 (CH_2–O), 74.0 (CH–O) ppm. EIMS (*m*/*z*) 229 (M^+, 10), 142 (M−1,4-dioxane, 100), 100 (50). HRMS calcd for $C_{13}H_{27}NO_2$: 229.2042; found 229.2038.

4.3.6. *N*-Benzyl-*N*-(tetrahydrofuran-2-yl-methyl)-*N*-methyl amine (3f). Purification of the crude residue by flash column chromatography ($CHCl_3$ and then EtOAc) gave **3f** (246 mg, 60% yield, colourless oil). IR (liquid film) ν_{max} 2945–2788, 1495, 1453, 1066, 739, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.48–1.57 (1H, CH_2, m), 1.79–1.87 (2H, CH_2, m), 1.93–2.01 (1H, CH_2, m), 2.29 (3H, N–CH_3, s), 2.47 (1H, CH_2–N, dd, J=12.9, 4.9 Hz), 2.53 (1H, CH_2–N, dd, J=12.9, 6.7 Hz), 3.55 (1H, CH_2–N, d, J=12.93 Hz), 3.62 (1H, CH_2–N, d, J=12.93 Hz), 3.70–3.75 (1H, CH_2–O, m), 3.81–3.87 (1H, CH_2–O, m), 4.02–4.09 (1H, CH_2–O, m),

7.21–7.34 (5H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 25.4 (CH_2), 30.2 (CH_2), 42.9 (CH_3–N), 61.6 (CH_2–N), 62.7 (CH_2–N), 67.9 (CH_2–O), 77.4 (CH–O), 126.9 (CH), 128.1 (2CH), 129.1 (2CH), 138.8 (C) ppm. EIMS (*m*/*z*) 205 (M^+, 10), 134 (M−THF, 80), 91 ($PhCH_2$, 100). HRMS calcd for $C_{13}H_{19}NO$: 205.1467; found 205.1464.

4.3.7. *N*-Benzyl-*N*-(1,4-dioxan-2-yl-methyl)-*N*-methylamine (3g). Purification of the crude residue by flash column chromatography ($CHCl_3$ and then EtOAc) gave **3g** (332 mg, 75% yield, yellow oil). IR (liquid film) ν_{max} 2955–2790, 1495, 1452, 1119, 1107, 741, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, CH_3, s), 2.33 (1H, CH_2, dd, J=12.9, 5.7 Hz), 2.45 (1H, CH_2, dd, J=12.9, 6.2 Hz), 3.24 (1H, CH_2–O, dd, J=11.4, 9.8 Hz), 3.47 (1H, CH_2–Ph, AB system, J=13.4 Hz), 3.55 (1H, CH–O, m), 3.56 (1H, CH_2–Ph, AB system, J=13.4 Hz), 3.64–3.82 (5H, 3CH_2–O, m), 7.2–7.26 (1H, Ph H, m), 7.26–7.31 (4H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 43.1 (CH_3–N), 58.2 (CH_2–N), 62.8 (CH_2–N), 66.4 (CH_2–O), 66.6 (CH_2–O), 70.16 (CH_2–O), 73.5 (CH–O), 126.9 (CH), 128.1 (CH), 128.9 (3CH), 138.6 (C) ppm. EIMS (*m*/*z*) 221 (M^+, 5), 134 (M−1,4-dioxane, 80), 91 ($PhCH_2$, 100). HRMS calcd for $C_{13}H_{19}NO_2$: 221.14158; found 221.14141.

4.3.8. *N*-Benzyl-*N*-(2-ethoxypropyl)-*N*-methylamine (3h). Purification of the crude residue by flash column chromatography ($CHCl_3$ and then EtOAc) gave **3h** (224 mg, 54% yield, yellow oil). IR (liquid film) ν_{max} 2989–2868, 1494, 1453, 1120, 740, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, CH_3, d, J=6.2 Hz), 1.18 (3H, CH_3, t, J=7.0 Hz), 2.23 (3H, N–CH_3, s), 2.34 (1H, CH_2–Ph, dd, J=12.7, 5.9 Hz), 2.51 (1H, CH_2–Ph, dd, J=12.7, 6.0 Hz), 3.47–3.60 (5H, CH–O+CH_2O+CH_2–N, m), 7.19–7.23 (1H, Ph H, m), 7.26–7.33 (4H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 15.63 (CH_3), 18.6 (CH_3), 43.0 (N–CH_3), 62.9 (CH_2–N), 63.0 (CH_2–N), 63.8 (CH_2–O), 73.6 (CH–O), 126.8 (CH), 128.0 (2CH), 128.9 (2CH), 139.3 (C) ppm. EIMS (*m*/*z*) 207 (M^+, 5), 134 (M−Et_2O, 80), 91 ($PhCH_2$, 100). HRMS calcd for $C_{13}H_{21}NO$: 207.16231; found 207.16225.

4.3.9. *N*-Methyl-*N*-(tetrahydrofuran-2-yl-methyl) aniline (3i). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 9:1) gave **3i** (260 mg, 68% yield, pale yellow oil). IR (liquid film) ν_{max} 2941–2869, 1599, 1507, 1369, 1067, 747, 692 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.53–1.62 (1H, CH_2, m), 1.80–2.0 (3H, 2CH_2, m), 2.99 (3H, N–CH_3, s), 3.40 (2H, CH_2–N, d, J=5.7 Hz), 3.74 (1H, CH_2–O, td, J=8.2, 6.2 Hz), 3.88 (1H, CH_2–O, td, J=8.2, 6.2 Hz), 4.11 (1H, CH–O, quintet, J=5.7 Hz), 6.69 (1H, Ph H, t, J=7.2 Hz), 6.74 (2H, Ph H, d, J=8.0 Hz), 7.21 (2H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 25.6 (CH_2), 29.6 (CH_2), 39.2 (CH_3–N), 57.1 (CH_2–N), 67.8 (CH_2–O), 77.7 (CH–O), 112.3 (2CH), 116.4 (CH), 129.1 (2CH), 149.5 (C) ppm. EIMS (*m*/*z*) 191 (M^+, 15), 120 (M−THF, 100), 104 (10), 77 (20). HRMS calcd for $C_{12}H_{17}NO$: 191.13101; found 191.13095.

4.3.10. *N*-(1,4-Dioxan-2-yl-methyl)-*N*-methyl-*N*-phenylamine (3j). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 8.5:1.5) gave **3j** (290 mg, 70% yield, yellow oil). IR (liquid film) ν_{max} 2957, 2854, 1599, 1506, 1110, 1107, 746, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.94 (3H, N–CH_3, s), 3.27 (1H, CH_2, AB system, J=15.2, 5.9 Hz), 3.34 (1H, CH_2, AB system, J=15.2, 5.9 Hz), 3.35 (1H, CH_2–O, dd, J=11.4, 9.8 Hz), 3.55–3.78 (6H, 2CH_2–O+2CH–O, m), 6.69–6.72 (3H, Ph H, m), 7.19–7.23 (2H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 39.4 (CH_3), 54.3 (CH_2–N), 66.4 (CH_2–O), 66.6 (CH_2–O), 69.7 (CH_2–O), 73.9 (CH–O), 112.3 (2CH), 116.6 (CH), 129.1 (2CH), 149.3 (C) ppm. EIMS (*m*/*z*) 207 (M^+, 20), 120 (M−1,4-dioxane, 100), 104 (10), 77 (20). HRMS calcd for $C_{12}H_{17}NO_2$: 207.12593; found 207.12580.

4.3.11. *N*-(2-Ethoxypropyl)-*N*-methyl-*N*-phenylamine (3k). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 95:5) gave **3k** (193 mg, 50% yield, pale yellow oil). IR (liquid film) ν_{max} 2955, 2925, 1506, 1115, 746, 687 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, CH_3, t, J=7.0 Hz), 1.14 (3H, CH_3, d, J=6.2 Hz), 2.98 (3H, CH_3, s), 3.28 (1H, CH_2–N, ABX system, J=15.0, 5.2 Hz), 3.35 (1H, CH_2–N, ABX system, J=15.0, 7.0 Hz), 3.39 (1H, CH_2–O, qd, J=7.0, 9.3 Hz), 3.55 (1H, CH_2–O, qd, J=7.0, 9.3 Hz), 3.69 (1H, CH–O, ddq, J=5.2, 6.2, 7.0 Hz), 6.64–6.70 (3H, Ph H, m), 7.20 (2H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 15.7 (CH_3), 18.1 (CH_3), 39.5 (CH_3), 58.7 (CH_2–N), 64.5 (CH_2–O), 73.6 (CH–O), 111.9 (CH), 115.9 (CH), 129.0 (3CH), 149.3 (C) ppm. EIMS (*m*/*z*) 193 (M^+, 20), 120 (M−Et_2O, 100), 104 (5), 77 (20). HRMS calcd for $C_{12}H_{19}NO$: 193.1466; found 193.1462.

4.3.12. *N*-(4-Methoxyphenyl)-*N*-(1-tetrahydrofuran-2-yl-methyl) amine (3l).[21] Purification of the crude residue by flash column chromatography (hexane/EtOAc, 6:4) gave **3l** (282 mg, 68% yield based on the starting HCHO, 2 mmol, pale yellow oil). IR (liquid film) ν_{max} 3380, 2949–2832, 1514, 1235, 1071, 1037, 820 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.6–1.68 (1H, CH_2, m), 1.87–1.95 (2H, CH_2, m), 1.97–2.03 (1H, CH_2, m), 3.02 (1H, CH_2–N, dd, J=12.1, 3.9 Hz), 3.73 (3H, OCH_3, s), 3.7–3.8 (1H, CH_2–O, m), 3.85–3.90 (1H, CH_2–O, m), 4.07–4.14 (1H, CH–O, m), 6.60 (2H, Ar H, d, J=9.0 Hz), 6.77 (2H, Ar H, d, J=9.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.8 (CH_2), 29.1 (CH_2), 49.3 (CH_2–N), 55.8 (OCH_3), 68.0 (CH_2–O), 77.6 (CH–O), 114.5 (2CH), 114.9 (2CH), 142.6 (C–N), 152.3 (C–O) ppm. EIMS (*m*/*z*) 207 (M^+, 5), 136 (M−THF, 100). HRMS calcd for $C_{12}H_{17}NO_2$: 207.12593; found 207.12582.

4.3.13. *N*-(4-Methoxyphenyl)-*N*,*N*-bis-(tetrahydrofuran-2-yl-methyl) amine (4l). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 6:4) gave **4l** contaminated with **3l**; further purification by PLC (hexane/THF, 9:1) afforded pure **4l** (116 mg, 20% yield based on the starting aniline, 2 mmol, thick oil). ^{1}H NMR ($CDCl_3$) δ 1.51–1.60 (2H, CH_2, m), 1.81–2.0 (6H, 3CH_2, m), 3.42 (4H, 2CH_2, m), 3.71 (2H, 2CH, m), 3.74 (3H, CH_3, s), 3.86 (2H, CH_2, m), 4.08 (2H, CH_2, m), 6.79 (4H, Ar H, s) ppm. ^{13}C NMR ($CDCl_3$) δ 25.5 (2CH_2), 29.7 (CH_2), 29.76 (CH_2), 55.7 (2CH_2–N), 56.6 (OCH_3), 67.8 (2CH_2–O), 77.4 (2CH–O), 114.7 (2CH), 115.3 (2CH), 135.1 (C–N), 151.8 (C–O) ppm. EIMS (*m*/*z*) 291 (M^+, 10), 276 (M−Me, 10), 220 (M−THF, 100). HRMS calcd for $C_{17}H_{25}NO_3$: 291.18344; found 291.18330.

4.3.14. *N*-(1,4-Dioxan-2-yl-methyl)-*N*-(4-methoxyphenyl) amine (3m). Purification of the crude residue by flash

column chromatography (hexane/EtOAc/MeOH, 8:1:1) gave **3m** as a yellow solid, mp 55–58 °C (312 mg, 70% yield based on the starting HCHO, 2 mmol). IR (Nujol) ν_{max} 3375, 2960–2800, 1513, 1240, 1108 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.03 (1H, CH_2–N, dd, J=12.7, 7.2 Hz), 3.11 (1H, CH_2–N, dd, J=12.7, 4.1 Hz), 3.43 (1H, CH_2–O, dd, J=11.6, 10.1 Hz), 3.55–3.65 (2H, CH_2–O, m), 3.73 (3H, OCH_3, s), 3.75–3.83 (4H, $2CH_2$–O, m), 6.58 (2H, Ar H, d, J=9.1 Hz), 6.77 (2H, Ar H, d, J=9.1 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 46.2 (CH_2–N), 55.8 (OCH_3), 66.5 (CH_2–O), 66.7 (CH_2–O), 69.4 (CH_2–O), 73.9 (CH–O), 114.6 (2CH), 115.0 (2CH), 142.2 (C–N), 152.6 (C–O) ppm. EIMS (*m*/*z*) 223 (M^+, 20), 136 (M−1,4-dioxane, 100). HRMS calcd for $C_{12}H_{17}NO_3$: 223.1208; found 223.1210.

4.3.15. *N*,*N*-Bis-(1,4-dioxan-2-yl-methyl)-*N*-(4-methoxyphenyl) amine (4m). Purification of the crude residue by flash column chromatography (hexane/EtOAc/MeOH, 8:1:1) afforded **4m** contaminated with **3m**; further purification by PLC (hexane/THF, 85:15) gave pure **4m** as a white solid, mp 88–93 °C. IR (Nujol) ν_{max} 1513, 1258, 1102 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.19 (1H, CH_2–N, dd, J=15.0, 5.2 Hz), 3.26–3.36 (5H, m), 3.57–3.68 (6H, m), 3.75 (3H, OCH_3, s), 3.74–3.80 (6H, m), 6.73 (2H, m), 6.82 (2H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 54.4 (CH_2–N), 54.8 (CH_2–N), 55.7 (OCH_3), 66.5 ($2CH_2$–O), 66.6 ($2CH_2$–O), 69.7 (CH_2–O), 69.8 (CH_2–O), 73.4 (CH–O), 73.7 (CH–O), 114.8 (CH), 114.9 (CH), 115.8 (CH), 116.1(CH), 142.7 (C–N), 152.5 (C–O) ppm. EIMS (*m*/*z*) 323 (M^+, 20), 236 (M−1,4-dioxane, 60), 150 (M−2(1,4-dioxane), 100). HRMS calcd for $C_{17}H_{25}NO_5$: 323.17327; found 323.17314.

4.3.16. *N*-(2-Ethoxypropyl)-*N*-(4-methoxyphenyl) amine (3n). Purification of the crude residue by flash column chromatography (hexane/THF, 9:1) gave **3n** (293 mg, 70% yield based on the starting HCHO, 2 mmol, pale yellow oil). IR (liquid film) ν_{max} 3376, 2970–2873, 1515, 1241, 1110 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.195 (3H, CH_3, d, J=6.2 Hz), 1.20 (3H, CH_3, t, J=7.0 Hz), 2.98 (1H, CH_2–N, dd, J=12.4, 7.2 Hz), 3.14 (1H, CH_2–N, dd, J=12.4, 3.9 Hz), 3.42 (1H, CH_2–O, qd, J=7.0, 9.3 Hz), 3.60 (1H, CH_2–O, qd, J=7.0, 9.3 Hz), 3.63–3.69 (1H, CH–O, m), 3.73 (3H, OCH_3, s), 6.59 (2H, Ar H, d, J=8.8 Hz), 6.77 (2H, Ar H, d, J=8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_3), 17.8 (CH_3), 50.4 (CH_2–N), 55.7 (OCH_3), 63.8 (CH_2), 73.5 (CH–O), 114.5 (2CH), 114.9 (2CH), 142.6 (C–N), 152.2 (C–O) ppm. EIMS (*m*/*z*) 209 (M^+, 10), 194 (M^+-CH_3, 5), 136 (M−Et_2O, 100). HRMS calcd for $C_{12}H_{19}NO_2$: 209.1415; found 209.1420.

4.3.17. *N*,*N*-Bis-(2-ethoxypropyl)-*N*-(4-methoxyphenyl) amine (4n). Purification of the crude residue by flash column chromatography (hexane/THF, 9:1) afforded **4n** as a thick oil (first eluted fraction). IR (liquid film) ν_{max} 2973, 2873, 1514, 1241, 1102, 1042 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.11–1.15 (12H, $4CH_3$, m), 3.21 (1H, CH_2–N, dd, J=15.0, 4.9 Hz), 3.30 (1H, CH_2–N, dd, J=15.0, 5.4 Hz), 3.36–3.58 (6H, CH_2–N+$2CH_2$–O, m), 3.67 (2H, 2CH, sextuplet, J=6.1 Hz), 3.74 (3H, OCH_3, s), 6.69 (2H, Ar H, m), 6.80 (2H, Ar H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 15.7 ($2CH_3$), 18.3 ($2CH_3$), 55.7 (OCH_3), 58.4 (CH_2–N), 58.7 (CH_2–N), 64.4 (CH_2), 64.41 (CH_2), 73.1 (CH–O), 73.3 (CH–O), 114.3 (2CH), 114.8 (2CH), 143.1(C–N), 151.2 (C–O) ppm. EIMS (*m*/*z*) 295 (M^+, 20), 222 (M−Et_2O, 100), 178 (80). HRMS calcd for $C_{12}H_{29}NO_3$: 295.2147; found 295.2144.

4.3.18. Benzyl-*N*,*N*-bis-(1,4-dioxan-2-yl-methyl) amine (4p). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 8:2) afforded **4p** (184 mg, 30% yield, thick oil). IR (liquid film) ν_{max} 2955, 2852, 1495, 1452, 1266, 1107 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.45–2.60 (4H, $2CH_2$–N, m), 3.19 (1H, CH_2–N, dd, J=11.4, 10.6 Hz), 3.25 (1H, CH_2–N, dd, J=11.4, 9.8 Hz), 3.50–3.58 (2H, 2CH, m), 3.64–3.82 (12H, $6CH_2O$, m), 7.22–7.33 (5H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 56.2 (2CH–N), 60.4 (CH_2–N), 66.5 ($2CH_2$–O), 66.7 ($2CH_2$–O), 70.3 ($2CH_2$–O), 127.1 (CH), 128.3 (2CH), 129.9 (CH), 139.1 (C) ppm. EIMS (*m*/*z*) 307 (M^+, 10), 220 (M−1,4-dioxane, 80), 134 (M−2(1,4-dioxane), 50), 91 ($PhCH_2$, 100). HRMS calcd for $C_{17}H_{25}NO_4$: 307.1783; found 307.1780.

4.3.19. *N*-(4-Methoxyphenyl)-*N*-(1-tetrahydrofuran-2-yl-ethyl) amine (3q).[8e] Purification of the crude reaction mixture by FCC (hexane/EtOAc, 7:3) afforded **3q** (354 mg, 80%) as a 1:1 mixture of diastereomers. Less polar isomer: ^1H NMR ($CDCl_3$) δ 1.18 (3H, CH_3, d, J=6.5 Hz), 1.71–1.79 (1H, CH_2, m), 1.85–1.95 (3H, $2CH_2$, m), 3.40 (1H, CH–N, dq, J=4.6, 6.5 Hz), 3.5 (1H, NH, br), 3.73 (3H, OCH_3, s), 3.76 (1H, CH–O, m), 3.88 (2H, CH_2–O, m), 6.60 (2H, Ar H, d, J=8.8 Hz), 6.76 (2H, Ar H, d, J=8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 17.8 (CH_3), 26.1 (CH_2), 28.2 (CH_2), 52.8 (CH–N), 55.8 (OCH_3), 68.4 (CH_2–O), 82.3 (CH–O), 115.0 (2CH), 115.2 (2CH), 141.4 (C–N), 152.2 (C–O) ppm. EIMS *m*/*z* 221 (M^+, 15), 150 (M−THF, 100). HRMS calcd for $C_{13}H_{19}NO_2$: 221.1416; found 221.1415. More polar isomer: ^1H NMR ($CDCl_3$) δ 1.14 (3H, CH_3, d, J=6.5 Hz), 1.66–1.74 (1H, CH_2, m), 1.84–1.98 (3H, $2CH_2$, m), 3.2 (1H, NH, br), 3.44 (1H, CH–N, dq, J=4.4, 6.5 Hz), 3.73 (3H, OCH_3, s), 3.77 (1H, CH–O, m), 3.83–3.93 (2H, CH_2–O, m), 6.60 (2H, Ar H, d, J=8.8 Hz), 6.75 (2H, Ar H, d, J=8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 15.7 (CH_3), 25.9 (CH_2), 28.0 (CH_2), 53.2 (CH–N), 55.7 (OCH_3), 68.4 (CH_2–O), 81.9 (CH–O), 114.9 (2CH), 115.4 (2CH), 141.6 (C–N), 152.2 (C–O) ppm. EIMS (*m*/*z*) 221 (M^+, 12), 150 (M−THF, 100).

4.3.20. *N*-[4-Bromophenyl(tetrahydrofuran-2-yl)methyl]-*N*-(4-methoxyphenyl) amine (3r).[8e] Purification by FCC (hexane/EtOAc, 75:25) gave **3r** (456 mg, 63%) as a 1:1 mixture of diastereomers, which were separated by PLC (hexane/EtOAc, 8:2). Less polar isomer: ^1H NMR ($CDCl_3$) δ 1.73–1.98 (4H, $2CH_2$, m), 3.68 (3H, OCH_3, s), 3.79 (1H, m), 3.90 (1H, t, J=6.2 Hz), 3.95 (1H, q, J=6.8 Hz), 4.10 (1H, d, J=6.8 Hz), 4.5 (1H, NH, br), 6.44 (2H, Ar′H, d, J=8.6 Hz), 6.66 (2H; Ar′H, d, J=8.6 Hz), 7.29 (2H, Ar H, d, J=8.6 Hz), 7.44 (2H, Ar H, d, J=8.6 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_2), 28.6 (CH_2), 55.6 (OCH_3), 62.6 (CH–N), 68.5 (CH_2–O), 82.5 (CH–O), 114.6 (2CH), 115.3 (2CH), 121.1 (C–Br), 129.1 (2CH), 131.6 (2CH), 140.6 (C), 141.1 (C–N), 152.3 (C–O) ppm. EIMS *m*/*z* 363–361 (M^+, 10), 292–290 (M−THF, 100). HRMS calcd for $C_{18}H_{20}NO_2Br$: 361.0677; found 361.0679. More polar isomer: ^1H NMR ($CDCl_3$) δ 1.57–1.82 (4H, $2CH_2$, m), 3.66 (3H, OCH_3, s), 3.79 (2H, OCH_2, m), 4.17 (1H, OCH, m), 4.31 (1H, CH–N, d, J=4.1 Hz), 4.4–4.6

(1H, NH, br), 6.45 (2H, Ar′H, d, J=8.5 Hz), 6.65 (2H, Ar′H, d, J=8.5 Hz), 7.24 (2H, Ar H, d, J=8.0 Hz), 7.40 (2H, Ar H, d, J=8.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.5 (CH_2), 27.3 (CH_2), 55.6 (OCH_3), 61.3 (CH–N), 68.7 (CH_2–O), 81.8 (CH–O), 114.7 (2CH), 115.4 (2CH), 121 (C–Br), 129.5 (2CH), 131.4 (2CH), 139.3 (C), 140.9 (C–N), 152.4 (C–O) ppm. EIMS (*m*/*z*) 363–361 (M^+, 20), 292–290 (M−THF, 100).

4.3.21. *N*-(4-Methoxyphenyl)-*N*-[4-methylphenyl-(tetrahydrofuran-2-yl)methyl] amine (3s).[8e] Purification by FCC (hexane/EtOAc, 8:2) of the crude mixture gave **3s** (440 mg, 74%) as a 1:1 mixture of diastereomers. Less polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.73–1.93 (4H, $2CH_2$, m), 2.30 (3H, CH_3, s), 3.66 (3H, OCH_3, s), 3.79 (1H, CH_2, m), 3.90 (1H, CH_2, m), 4.01 (1H, CH, q, J=6.7 Hz), 4.09 (1H, CH, d, J=6.7 Hz), 6.50 (2H, Ar′H, d, J=9.0 Hz), 6.65 (2H, Ar′H, d, J=9.0 Hz), 7.11 (2H, Ar H, d, J=8.0 Hz), 7.28 (2H, Ar H, d, J=8.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3), 25.7 (CH_2), 28.8 (CH_2), 55.7 (OCH_3), 63.3 (CH–N), 68.5 (OCH_2), 82.9 (OCH), 114.7 (2CH), 115.6 (2CH), 127.3 (2CH), 129.3 (2CH), 136.9 (C), 138.4 (C), 141.6 (C–N), 152.4 (C–O) ppm. EIMS (*m*/*z*) 297 (M^+, 12), 226 (M−THF, 100). HRMS calcd for $C_{19}H_{23}NO_2$: 297.1728; found 297.1730. More polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.54–1.68 (1H, CH_2, m), 1.69–1.87 (3H, CH_2+CH, m), 2.30 (3H, CH_3, s), 3.66 (3H, OCH_3, s), 3.7–3.85 (2H, CH_2, m), 4.22 (1H, OCH, m), 4.33 (1H, CH–N, d, J=4.2 Hz), 6.51 (2H, Ar′H, d, J=8.9 Hz), 6.65 (2H; Ar′H, d, J=8.9 Hz), 7.09 (2H, Ar H, d, J=7.7 Hz), 7.25 (2H, Ar H, d, J=7.7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3), 25.6 (CH_2), 27.1 (CH_2), 55.6 (OCH_3), 61.7 (CH–N), 68.7 (OCH_2), 82.1 (OCH), 114.5 (2CH), 115.6 (2CH), 127.6 (2CH), 129.0 (2CH), 136.7 (2C), 141.0 (C–N), 152.3 (C–O) ppm. EIMS (*m*/*z*) 297 (M^+, 10), 226 (M−THF, 100).

4.3.22. *N*-(4-Methoxyphenyl)-*N*-[4-methoxyphenyl-(tetrahydrofuran-2-yl)methyl] amine (3t).[8c] Purification by FCC (hexane/EtOAc, 8:2) of the crude mixture gave **3t** (500 mg, 80%) as a 1:1 mixture of diastereomers. Less polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.74–1.81 (2H, CH_2, m), 1.82–1.95 (2H, CH_2, m), 3.68 (3H, OCH_3, s), 3.79 (3H, OCH_3, s), 3.79–3.84 (1H, CH_2, m), 3.87–3.94 (1H, CH_2, m), 3.99 (1H, CH, q, J=6.7 Hz), 4.08 (1H, CH, d, J=6.7 Hz), 4.5 (1H, NH, br s), 6.50 (2H, Ar H, d, J=8.9 Hz), 6.67 (2H, Ar H, d, J=8.9 Hz), 6.86 (2H, Ar′ H, d, J=8.7 Hz), 7.33 (2H, Ar H, d, J=8.7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_2), 28.7 (CH_2), 55.2 (OCH_3), 55.7 (OCH_3), 62.7 (CH–N), 68.4 (OCH_2), 83.1 (OCH), 114.0 (2CH), 114.7 (2CH), 115.2 (2CH), 128.3 (2CH), 133.8 (C), 142.2 (C–N), 152.1 (C–O) ppm. More polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.58–1.66 (1H, CH_2, m), 1.72–1.80 (3H, $2CH_2$, m), 3.68 (3H, OCH_3, s), 3.74–3.83 (2H, CH_2, m), 3.78 (3H, OCH_3, s), 4.20 (1H, CH, dt, J=4.2, 7.2 Hz), 4.33 (1H, CH, d, J=4.2 Hz), 4.4 (1H, NH, br s), 6.49 (2H, Ar H, d, J=9.1 Hz), 6.67 (2H, Ar H, d, J=9.1 Hz), 6.84 (2H, Ar′ H, d, J=8.7 Hz), 7.29 (2H, Ar′ H, d, J=8.7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.6 (CH_2), 27.2 (CH_2), 55.1 (OCH_3), 55.7 (OCH_3), 61.0 (CH–N), 68.7 (OCH_2), 82.3 (OCH), 113.7 (2CH), 114.6 (2CH), 115.2 (2CH), 128.7 (2CH), 132.3 (C), 141.7 (C–N), 152.0 (C–O), 158.7 (C=O) ppm. EIMS (*m*/*z*) 313 (M^+, 10), 242 (M−THF, 100).

4.3.23. *N*-(4-Methoxyphenyl)-*N*-[phenyl(tetrahydrofuran-2-yl)methyl] amine (3u).[8c,e] Purification by FCC (hexane/EtOAc, 8:2) of the crude mixture gave **3u** (400 mg, 70%) as a 1:1 mixture of diastereomers. Less polar isomer: yellow solid mp 74–5 °C (hexane/Et_2O). ^{1}H NMR ($CDCl_3$) δ 1.7–2.0 (4H, $2CH_2$, m), 3.67 (3H, OCH_3, s), 3.80 (1H, OCH_2, m), 3.90 (1H, OCH_2, m), 4.04 (1H, OCH, m), 4.13 (1H, PhCH, d, J=6.9 Hz), 4.7 (1H, NH, br), 6.51 (2H, Ar′H, d, J=8.8 Hz), 6.65 (2H; Ar′H, d, J=8.8 Hz), 7.24–7.35 (3H, Ph H, m), 7.41 (2H, Ph H, m) ppm. HRMS calcd for $C_{18}H_{21}NO_2$: 283.1572; found 283.1568. More polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.53–1.67 (1H, CH_2, m), 1.70–1.86 (3H, $2CH_2$, m), 3.67 (3H, OCH_3, s), 3.78 (2H, OCH_2, m), 4.26 (1H, OCH, m), 4.37 (1H, PhCH, d, J=4.0 Hz), 4.7 (1H, NH, br), 6.54 (2H, Ar′H, d, J=8.8 Hz), 6.65 (2H; Ar′H, d, J=8.8 Hz), 7.24–7.35 (3H, Ph H, m), 7.36–7.40 (2H, Ph H, m) ppm. EIMS (*m*/*z*) 283 (M^+, 15), 212 (M−THF, 100).

4.3.24. *N*-[Cyclohexyl(tetrahydrofuran-2-yl)methyl]-*N*-(4-methoxyphenyl) amine (3v).[8c,e] Purification by FCC (hexane/EtOAc, 9:1) afforded **3v** (463 mg, 80%) as a 1:1 mixture of diastereoisomers. Less polar isomer: ^{1}H NMR ($CDCl_3$) δ 0.98–1.24 (5H, cyclohex, m), 1.55–1.64 (2H, m), 1.68–1.75 (3H, m), 1.80–1.86 (5H, m), 3.06 (1H, CH–N, dd, J=2.1, 6.3 Hz), 3.73 (3H, OCH_3, s), 3.75 (1H, CH, m), 3.87 (1H, CH_2, m), 4.11 (1H, CH_2, m), 6.55 (2H, Ar H, d, J=9.0 Hz), 6.73 (2H, Ar H, d, J=9.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 26.0 (CH_2), 26.3 (CH_2), 26.4 ($2CH_2$), 29.2 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 41.9 (CH), 55.7 (OCH_3), 61.3 (CH–N), 68.8 (CH_2–O), 78.6 (CH–O), 113.6 (CH), 113.8 (CH), 114.8 (CH), 114.9 (CH), 143.0 (C–N), 151.3 (C–O) ppm. EIMS (*m*/*z*) 289 (M^+, 12), 218 (M−THF, 100), 136 (30), 122 (10). HRMS calcd for $C_{18}H_{27}NO_2$: 289.2042; found 289.2039. More polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.02–1.15 (2H, qd, J=12.3, 3.3 Hz), 1.18–1.31 (3H, m), 1.62–1.75 (6H, cyclohex, m), 1.75–1.96 (4H, $2CH_2$, m), 3.17 (1H, CH–N, dd, J=3.4, 6.1 Hz), 3.73 (4H, CH+OCH_3, m+s), 3.83 (1H, CH, m), 3.90 (1H, CH, m), 6.59 (2H, Ar H, d, J=9.0 Hz), 6.73 (2H, Ar H, d, J=9.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.8 (CH_2), 26.3 (CH_2), 26.5 ($2CH_2$), 27.4 (CH_2), 28.8 (CH_2), 30.9 (CH_2), 40.4 (CH), 55.8 (OCH_3), 63.1 (CH–N), 68.0 (CH_2–O), 80.0 (CH–O), 114.9 (4CH), 141 (C–N), 151.9 (C–O) ppm. EIMS (*m*/*z*) 289 (M^+, 10), 274 (M−CH_3, 8), 218 (M−THF, 100), 136 (30), 122 (15).

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of compounds **3a**–**n** and **4l**–**p**) associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.014.

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