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Efficient radical domino approach to β-aminoalcohols from arylamines and alcohols triggered by Ti(III)/*t*-BuOOH

Raffaele Spaccini, Alessandra Ghilardi, Nadia Pastori, Angelo Clerici, Carlo Punta *, Ombretta Porta *,†

Dipartimento di Chimica, Materiali e Ingegneria Chimica "G. Natta", Politecnico di Milano, Sezione Chimica,Via Mancinelli 7, I-20131 Milano, Italy

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ABSTRACT

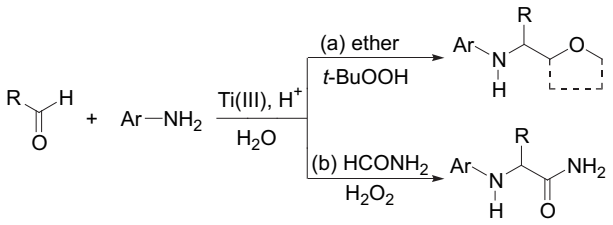
We report that an aqueous Ti(III)/*t*-BuOOH system promotes the efficient domino radical reaction of arylamines with alcohol cosolvents leading to β-aminoalcohols in good yields, in less than ten minutes at room temperature. The free-radical mechanism according to which the amine reacts with two molecules of the alcohol is discussed.

1. Introduction

The development of new processes involving one-pot more bond-forming transformations (domino or cascade reactions)[1] are particularly fascinating towards the goal of decreasing waste and minimizing handling, while increasing molecular complexity from simple starting materials.

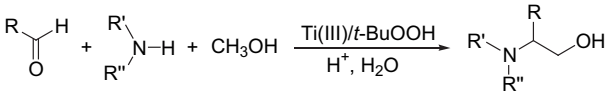
This intriguing approach has been widely applied in the field of nucleophilic free-radical addition to imines mediated by transition metal derivatives, allowing the development of more attractive synthetic routes[2,3] as compared with the classical ionic ones, which often require multi—step procedures, expensive reagents, long reaction times and highly controlled operating conditions.

In this context, in the last years we have reported that the Ti(III)/hydroperoxide [*t*-BuOOH or H_2O_2] system promotes both a radical Mannich-type reaction leading to β-aminoethers (Scheme 1, path a)[4] and a radical Strecker-type synthesis of α-aminoamides (Scheme 1, path b),[5] starting from an aldehyde and an amine in ether or formamide cosolvent, respectively.



Scheme 1. Radical versions of the Mannich reaction (a) and of the Strecker synthesis (b).

More recently, we have found that an amine, an aldehyde and methanol can be readily assembled in one-pot under very mild conditions through a free radical multicomponent reaction, by using the same promoting system, to afford 1,2-aminoalcohols in fair to excellent yields (Scheme 2).[6]



R = Aryl, Alkyl, H
R' = Alkyl, H
R'' = Alkyl, Benzyl, Aryl

Scheme 2. Hydroxymethylation of imines generated in situ mediated by $TiCl_3$/*t*-BuOOH system.

* Corresponding authors. Tel.: +39 0223993026; fax: +39 0223993180.
E-mail address: carlo.punta@polimi.it (C. Punta).
† Deceased May 3, 2008.

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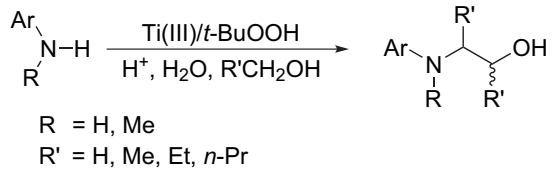
As a part of our ongoing interest in exploiting the roles of titanium salts in promoting one-pot multi-step transformations, we now report that an aqueous-acidic Ti(III)/*t*-BuOOH system that when used in combination with an alcoholic solvent different from methanol, triggers cascade reactions with primary and secondary arylamines, leading to β-aminoalcohols in good yields, under very simple experimental conditions (Scheme 3).



Scheme 3. Radical domino approach to β-aminoalcohols from arylamines and alcohols triggered by Ti(III)/*t*-BuOOH.

The chemical outcome of this process depends on the simultaneous roles played not only by the metal ions [Ti(III) and Ti(IV)], but also by the alcoholic solvent and *t*-BuOOH in generating useful concentrations of the reactive partners involved in subsequent C–N and C–C bond-forming transformations, leading to β-aminoalcohols. These derivatives are suitable intermediates for the synthesis of unnatural amino acids, β-blockers, insecticidal agents, antibiotics and chiral auxiliaries or chiral catalysts for asymmetric synthesis.[7,8]

2. Results and discussion

α-Hydroxyalkyl radicals (ketyls) are easily generated via α-H atom abstraction from the corresponding alcohols by either hydroxyl[9] or *tert*-butoxyl[10] radicals, which in turn are formed by reduction of the hydroperoxides with Ti(III) ion, according to paths *i*-*ii* of Scheme 4 (shown for *t*-BuOOH and ethanol).

As shown by their redox potentials[11] (Table 1, 3rd column), ketyls have a strong nucleophilic character, which determines their fast oxidation. In this contest, we have recently reported[12] that, under aqueous acidic conditions, they are stronger reducing agents than Ti(III) ion itself towards aromatic aldehydes. Thus, it follows that ketyls may well compete with the metal ion in reducing the hydroperoxide (Scheme 4, path *iii*) leading to the oxidation product of the alcohol and further *tert*-butoxyl radical in a chain reaction.

Table 1
Stoichiometry of the titration of *t*-BuOOH with an aqueous Ti(III) solution in different solvents

Entry	Solvent	E°_{red} (V)[a]	Ti(III) (mmol)	Ratio Ti(III)/*t*-BuOOH[b]
1	MeOH	−0.74	3.6	0.90
2	EtOH	−0.94	2.2	0.55
3	*i*-PrOH	−1.06	1.4	0.35
4	MeCOOH	—	7.8	1.95

[a] Taken from Ref. 11.
[b] 4.0 mmol of *t*-BuOOH in 10 mL of solvent were titrated with an aqueous 15 % $TiCl_3$ solution.

If the intervention of path *iii* were to occur and suitable concentrations of both the aldehyde and the ketyl could be settled, then, on the basis of our previous findings,[4,5] the addition of an amine **1** in the Ti(III)/*t*-BuOOH/CH_3CH_2OH system would produce a domino reaction leading to 1,2-aminoalcohols **2** in one-pot.

Initial experiments designed to confirm the intervention of path *iii* are reported in Table 1. As can be seen from these data, there is an obvious linear correlation (r^2=0.998) between the redox potentials of the alcohol-derived radicals and the amount of Ti(III) ion required to titrate *t*-BuOOH in the absence of added amine (Fig. 1).

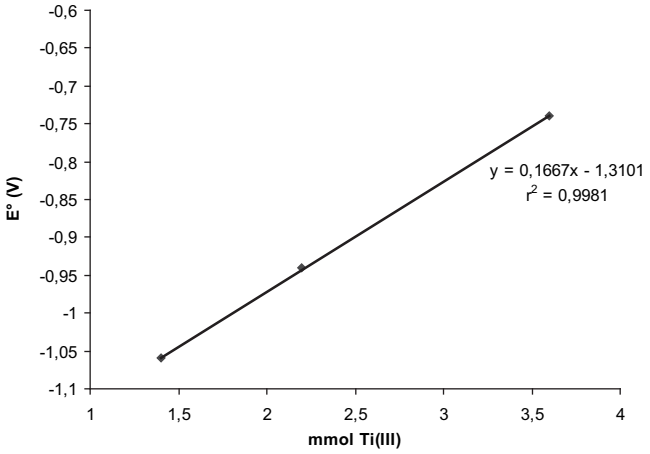
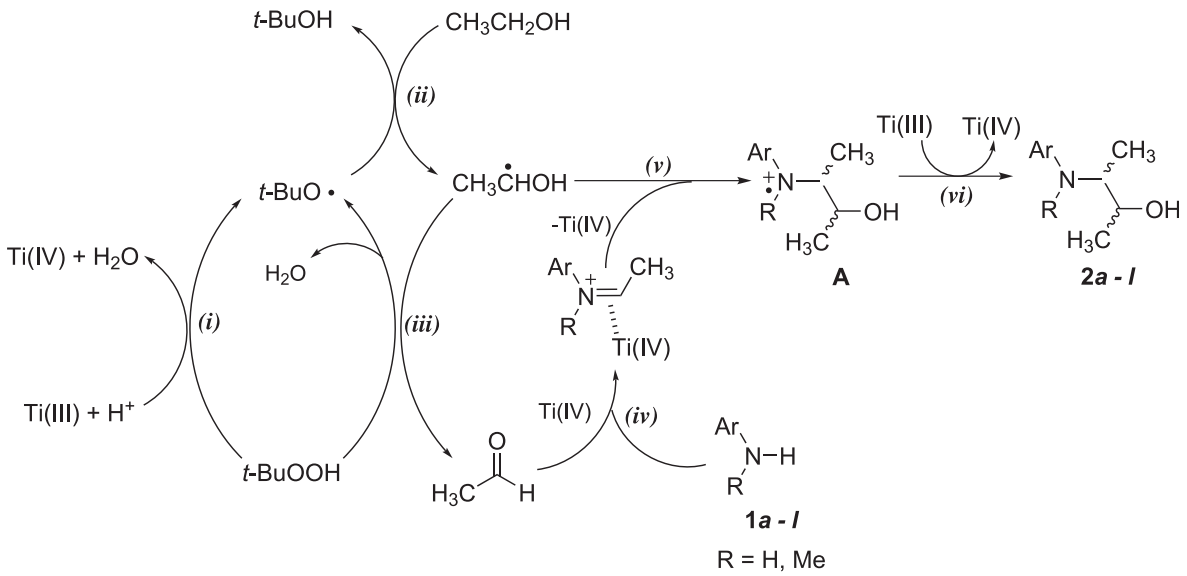


Figure 1. Stoichiometry of the titration of *t*-BuOOH with an aqueous Ti(III) solution in different solvents.



Scheme 4. Proposed catalytic cycle of primary and secondary aromatic amines with ethanol triggered by *t*-BuOOH/Ti(III) system.

The stronger the reducing power of the ketyl, the more it competes with the Ti(III) ion in reducing the hydroperoxide, as it would be expected. The intervention of reaction *iii* is even more clearly demonstrated by comparison of experiments in entries 1–3 with the one in entry 4. Acetic acid (entry 4) is considerably less reactive than alcohols towards *t*-butoxyl radical H-atom abstraction[13] and the resulting radical, having electrophilic character, does not take part in a chain reaction with the peroxide. Thus, termination according to Eq. 1 is the preferred reaction and almost 2 equiv of Ti(III) are requested to titrate the peroxide. The overall stoichiometry occurs according to the Eq. 2 in AcOH solution, whereas in alcoholic solution the stoichiometry is mainly given by Eq. 3, in which the reaction, initiated by the path *i*, is propagated by the path *iii* of the Scheme 4.

$$t\text{-}BuO^{\bullet} + Ti(III) \xrightarrow{H^+} t\text{-}BuOH + Ti(IV) \quad (1)$$

$$t\text{-BuOOH} + 2\text{Ti(III)} + 2\text{H}^+ \rightarrow t\text{-BuOH} + 2\text{Ti(IV)} + \text{H}_2\text{O} \quad (2)$$

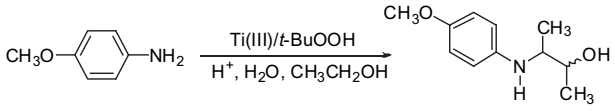
$$t\text{-BuOOH} + \text{RCH}_2\text{OH} \rightarrow t\text{-BuOH} + \text{RCHO} + \text{H}_2\text{O} \quad (3)$$

The length of this chain process, as well as the more complex chain process of Scheme 4, is relatively low, due to the fast reaction of Eq. 1. Thus, the best results can be obtained by keeping low the stationary concentration of the Ti(III) salt during the reaction.

On the basis of these results and with the aim of optimize the reaction conditions, ethanol was firstly used as a model solvent and *p*-methoxy aniline (PMP—NH_2) **1a** as a representative primary arylamine, since the protective PMP group can be further removed according to different methodologies.[14]

As shown in Table 2, the most satisfactory yield of **2a** (80%) was obtained by adding dropwise an aqueous acidic 15% $TiCl_3$ solution to a homogeneous mixture of **1a** (2 mmol) and *t*-BuOOH (4 mmol of a 80% aqueous solution) in 10 mL of ethanol under N_2 at room temperature.

Table 2
Efficiency of *t*-BuOOH in the reaction of primary aromatic amine **1a** with ethanol in the presence of $TiCl_3$



1a **2a**

Entry	*t*-BuOOH:**1a**	**2a** (yield %)[a]	Ratio *t*-BuOOH/**2a**
1	2.0	80 (50)[b]	~2:1
2	1.0	44	~2:1
3	0.5	27	~2:1
4	0.5+CH_3CHO[c]	38	~1:1

[a] Yields, determined by ^{1}H NMR of the crude reaction mixture with an internal standard, refer to the starting amine; the *syn* : *anti* ratio is always 1:1.
[b] *t*-BuOOH is added dropwise to an aqueous solution of **1a** and Ti(III).
[c] 1.0 equiv of acetaldehyde were added to the reaction mixture before Ti(III) addition.

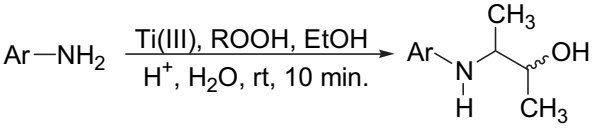
The reaction proceeded like a titration and was complete within ten minutes, e.g., by the time at which the last drop of the blue Ti(III) reducing solution was not longer discharged, imparting a pale violet colour to the reaction mixture.

The 2:1 ratio between the equivalents of *t*-BuOOH and of the product **2a** strongly supports the reaction mechanism suggested in Scheme 2. Moreover, when acetaldehyde is directly added to the reaction solution (Table 2, entry 4), *t*-BuOOH has the unique role of generating the ketyl radical, which fast adds to the preformed imine, and only one equivalent of hydroperoxide per equivalent of product is required.

Finally, by reversing the order of addition, **2a** was obtained only in 50% yield. In fact, in this case the reaction of Eq. 1 is favoured.

With the optimized conditions in hand, we sent out to examine the scope of the reaction. The results of Table 3 show that the reactivity was general for a broad range of arylamines, including both electron-donating and electron-withdrawing substituents on the aromatic ring. The reaction was very clean and arylamines **1a**–**k** afforded the corresponding 3-aminobutan-2-ols **2a**–**k** as the only reaction products in a ca. 1:1 mixture of diastereoisomers, which in most cases were separated by silica gel column chromatography.

Table 3
Ti(III)/Peroxides mediated reaction of primary aromatic amines with ethanol



1a-k **2a-k**

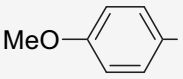
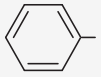
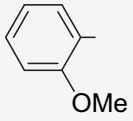
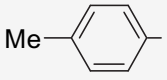
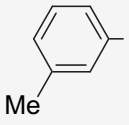
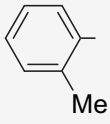
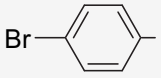
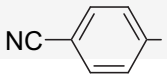
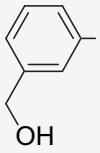
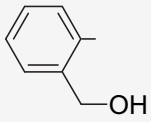
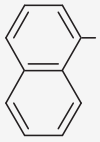
Ar–NH_2 (**1**)	Ar–	**2** (Yield %)[a,b] Method I[c] (*t*-BuOOH)	Method II[d] (H_2O_2)
1a		80	60
1b		75	—
1c		45	40
1d		77	57
1e		78	55
1f		70	45
1g		82	70
1h		80	—

Table 3 (*continued*)

Ar–NH_2 (**1**)	Ar–	**2** (Yield %)[a,b] Method I[c] (*t*-BuOOH)	Method II[d] (H_2O_2)
1*i*		47	—
1*j*		52	—
1*k*		48	—

[a] See footnote a of Table 2.
[b] Selectivity is in all cases>90%. The remaining material is mainly unreacted imine.
[c] Method I: the aqueous Ti(III) solution is added dropwise to the ethanol solution of **1** and *t*-BuOOH.
[d] Method II: the aqueous Ti(III) solution is added dropwise to the ethanol solution of **1** and H_2O_2.

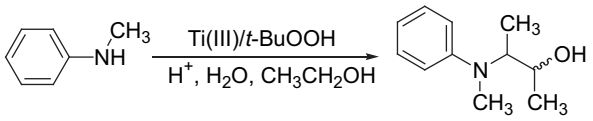
The independence of the reaction from the electronic nature of the substituent (for example **2a** and **2h** were obtained in similar yield) suggests that the polarization of the imine, induced by Ti(IV) nitrogen complexation[4,5] (Scheme 4, *path iv*), overcomes the substituent effect.

On the contrary, steric effects seem to play a key role in these kind of processes, as already observed for the direct hydroxymethylation of imines.[6] In fact, in the case of *ortho*-substituted anilines the chemical yields were lower.

We also checked the applicability of the method to aliphatic amines, but any attempt was unsuccessful, while benzylamine was rapidly oxidized to benzaldehyde before being able to form the corresponding imine with the acetaldehyde generated in situ (the benzylic C–H bond is much more reactive than the α C–H bonds in hydrogen abstraction from alcohols by electrophilic radicals).

Next, the reactivity of *N*-methylaniline **1l**, chosen as representative secondary amine, was tested in ethanol under the optimized reaction conditions. The results, reported in Table 4, clearly show

Table 4
Efficiency of *t*-BuOOH in the reaction of secondary aromatic amine **1l** with ethanol



1*l* **2*l***

Entry	*t*-BuOOH:**1l**	**2l** [a](Yield %)	Ratio *t*-BuOOH/**2l**
1	2.0	82	~2:1
2	1.0	74	~1:1
3	0.5	50	~1:1
4	0.5+CH_3CHO[b]	92	~1:2
5	0.25+CH_3CHO[b]	50	~1:2

[a] See footnote a of Table 2.
[b] 1.0 equiv of acetaldehyde were added to the reaction mixture before Ti(III) addition.

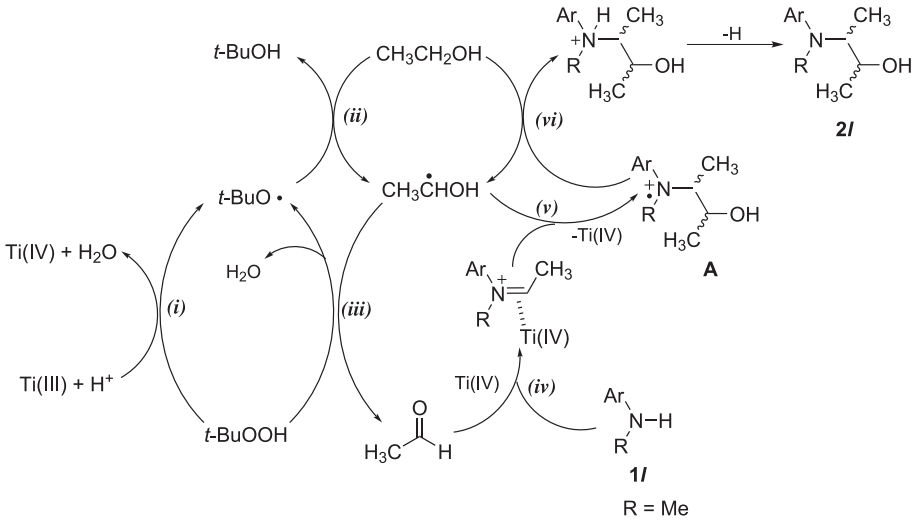
that, contrary to the observation in the presence of primary amines (Table 2, entries 2 and 3), 1 equiv of *t*-BuOOH was sufficient to afford 1 equiv of the desired product **2l** (Table 4, entries 2 and 3).

The requirement for a lower amount of *t*-BuOOH can be explained by considering the intervention of a competitive oxidation step mediated by the aminium cation radical **A** chain carrier (Scheme 5). It is well-known[15] that aminium radicals, in the presence of a suitable substrate, may undergo intermolecular hydrogen abstraction in highly acidic media.

According to this evidence, when R≠H, radical **A** should be able to abstract the hydrogen from the alcoholic solvent (Scheme 5, *path vi*), affording the corresponding α-hydroxyalkyl radical. Thus, after an initiation step, *t*-BuOOH seems to have the unique role of oxidizing the ketyl radical to the corresponding aldehyde, while **A** is responsible for the formation of new ketyl radicals.

Moreover, when 1 equiv of acetaldehyde was directly added to the reaction mixture, the ratio *t*-BuOOH:**2l** became 1:2 (Table 4, entries 4 and 5). Again, this result is in contrast with what observed with primary amine **1a** (Table 2, entry 4), and it confirms the superimposition of a second competitive route leading to the formation of the ketyl radical.

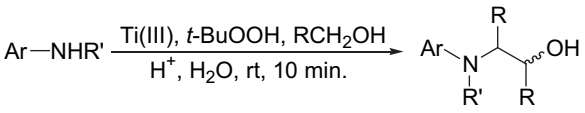
In order to extend the methodology to the synthesis of a wider range of β-aminoalcohols, we also examined the reactivity of **1a** and **1l**, chosen as representative primary and secondary aromatic amines, respectively, in different alcoholic solvents (Table 5). Methanol was, in both cases, the less reactive (Table 5, entries 1 and 6), due to the weaker reducing power of the corresponding ketyl radical (Table 1, entry 1). A considerable increase in the yields was



Scheme 5. Proposed catalytic cycle of primary and secondary aromatic amines with ethanol triggered by *t*-BuOOH/Ti(III) system.

observed in the presence of ethanol, while the moderate yields in **4a**–**4l** and **5a**–**5l**, obtained with *n*-propanol and *n*-butanol, respectively (Table 5, entries 3, 4, 8 and 9) were probably due to an enhanced steric hindrance around the carbon in α-position respect to the nitrogen. No reaction was observed in *iso*-propanol.

Table 5
Reaction of a primary (**1a**) and a secondary (**1l**) aromatic amine in different alcoholic solvents



1*a*, 1*l* **2-5*a*, 2-5*l***

Entry	Amine	R-CH_2OH	Product	Product (yield %)[a,b]	
				Method I[c] (*t*-BuOOH)	Method II[d] (H_2O_2)
1	**1a**	H–	**3a**	13	—
2	**1a**	CH_3–	**2a**	80[e]	46[e]
3	**1a**	CH_3CH_2–	**4a**	59	30
4	**1a**	$CH_3CH_2CH_2$–	**5a**	37	20
5	**1a**	$(CH_3)_2CH$–	No reaction	—	—
6	**1l**	H–	**3l**	31	—
7	**1l**	CH_3–	**2l**	82[f]	67
8	**1l**	CH_3CH_2–	**4l**	49	40
9	**1l**	$CH_3CH_2CH_2$–	**5l**	25	15

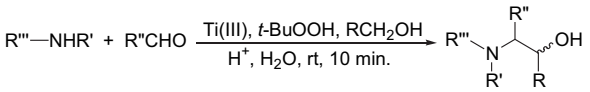
[a] See footnote a of Table 2.
[b] Selectivity is in all cases>90%. The remaining material is mainly unreacted imine.
[c] Method I: the aqueous Ti(III) solution is added dropwise to the ethanol solution of **1** and *t*-BuOOH.
[d] Method II: the aqueous Ti(III) solution is added dropwise to the ethanol solution of **1** and H_2O_2.
[e] Data from Table 3 for comparison.
[f] Data from Table 4 for comparison.

In all the examples, *t*-BuOOH proved to be more effective than H_2O_2 in terms of recovery of the desired products. Two main factors contribute to lower yields with H_2O_2; the •OH radical is less selective than *t*-BuO• in the abstraction from alcohols and H_2O_2 is a stronger oxidant than *t*-BuOOH, such that the oxidation of the ketyl radical is favoured compared to its addition on the iminium bond.

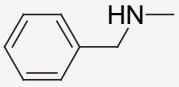
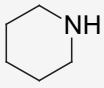
Finally, with the aim of applying this procedure to the synthesis of more complex β-aminoalcohols, we also investigated the possibility of inhibiting the 'domino reaction' in favour of a one-pot multicomponent process, carried out in the presence of an aldehyde different from that deriving by the direct oxidation of ketyl radicals generated in situ ('multicomponent reaction'). According to this last procedure, we have already reported the good results obtained with the selective hydroxymethylation of imines, generated in situ from a wide range of aldehydes, using methanol as alcoholic solvent.[6] In this case, the 'domino reaction' affords poor conversions (Table 5, entries 1 and 6) and cannot be considered competitive with the 'multicomponent reaction'. On the contrary, as we have already shown, primary alcohols with longer aliphatic chains easily undergo the domino reaction, affecting the selectivity in the desired products.

The best results, reported in Table 6, were obtained by operating with a fixed excess of aldehyde (2.5 equiv with respect to the amine), favouring the formation of the desired imines in solution.

Table 6
Radical addition of alcohols to aldimines generated in situ



1 **6-9**

Entry	Amine	R-CH_2OH	R′CHO	Product yield[a] (%)
1	**1a**	CH_3–	CH_3CH_2–	**6a**:75
2	**1a**	CH_3–	CH_3CH_2–	**6a**:41[b]
3	**1a**	CH_3CH_2–	$CH_3CH_2CH_2$–	**7a**:44
4	**1a**	$CH_3CH_2CH_2$–	CH_3–	**8a**:41
5	 **1*m***	CH_3–	H–	**9m**:54
6	 **1*n***	CH_3–	H–	**9n**:32

[a] Yields, determined by ^{1}H NMR of the crude reaction mixture with an internal standard, are referred to the starting amine.
[b] *t*-BuOOH is added dropwise to an aqueous solution of **1a**, prionaldehyde and Ti(III) in ethanol.

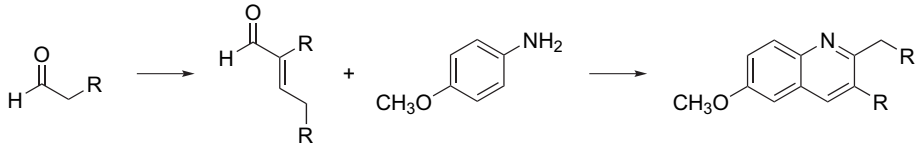
This amine/aldehyde ratio proved to be the best compromise to obtain the highest selectivity in 'multicomponent reaction' product. In fact, with a lower amount of aldehyde, the 'domino reaction' was predominant while, with a higher excess, the aldol condensation occurred, promoted by the strong acidic medium, leading to secondary transformations, among which the most significative was the well-known Doebner–Miller reaction[16] (Scheme 6).

By reversing the order of addition of Ti(III) and *t*-BuOOH (Table 6, entry 2), the selectivity increased but yields ~~in~~ on the desired products were poor. Moreover, also aliphatic amines **1m** and **1n**, which resulted unreactive towards the 'domino reaction', afforded the 'multicomponent reaction' products **9m** and **9n** in the presence of formaldehyde in moderate yields. Also in these cases the reactions were sensitive to the steric hindrance.

3. Conclusions

We have developed a new methodology for the synthesis of β-aminoalcohols by a simple radical domino approach promoted by titanium salts and *t*-BuOOH (Scheme 4). Titanium species play a multiple key role. In the lower oxidation state, TI(III) ion acts as a radical initiator inducing the decomposition of *t*-BuOOH to the corresponding alkoxyl radical (path *i*), which is responsible for the formation of the ketyl radical by hydrogen abstraction from the alcohol (path *ii*); Ti(III) ion also acts as a radical terminator in the reduction of the final aminium radical intermediate (path *vi*).

In the higher oxidation state, Ti(IV) ion behaves as a strong Lewis acid promoting the formation of the imine in aqueous medium (path *iv*) and its activation towards the ketyl radical addition,



Scheme 6. Doebner–Miller reaction.

by increasing the electrophilicity of the carbon atom of the C=N bond (path *v*).

In this cascade reaction *t*-BuOOH not only participates to the formation of the α-hydroxyalkyl radicals (path *ii*), but it also converts in part ketyls to the corresponding aldehydes (path *iii*), which are involved in the formation of the imines (path *v*).

This methodology was extended to a wide range of aromatic amines in the presence of different alcoholic solvents. Moreover, it was possible to find the ideal conditions for the synthesis of β-aminoalcohols in the presence of aldehydes different from those directly deriving by oxidation of the ketyls generated in situ, promoting a one-pot multicomponent reaction.

The reaction does not require either preformation of the imine or protection of the amino group and may be easily conducted under aqueous conditions. The mild operating conditions (room temperature under atmospheric pressure), the cheap and commercially available starting materials and the very short reaction times (~20 min) make this procedure competitive with the classic ionic ones for the synthesis of β-aminoalcohols.

4. Experimental

4.1. General

All materials were purchased from commercial suppliers without further purification. All reactions were performed at room temperature (20 °C) under atmosphere of nitrogen. Formaldehyde was 36%(T) in water solution. The following aqueous solutions were used: acidic 15 wt % of $TiCl_3$, 80 wt % of *t*-BuOOH and 35 wt % of H_2O_2.

NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C, in $CDCl_3$ or DMSO and chemical shifts were presented in parts per million (δ) using TMS as reference. ESI-MS were performed with an Esquire 3000 plus ion-trap mass spectrometer equipped with an ESI source. Tandem mass spectra were obtained by CID with helium collision gas after isolation of the precursor ion. Flash column chromatography was performed by using 40–63 μm silica gel packing; the eluent was chosen in order to move the desired components to R_f=0.35 on analytical TLC Here we report the procedures for the synthesis of **2a** and **2l** as representative β-aminoalcohols starting from primary and secondary aromatic amines respectively, and of **6a** as representative β-aminoalcohol deriving from the one-pot multicomponent approach.

4.2. Procedure for the domino synthesis of β-aminoalcohol 2a starting from primary aromatic amine 1a and ethanol

To a well stirred homogeneous solution of ethanol (10 mL) containing 4-methoxyaniline **1a** (246 mg, 2 mmol) and the hydroperoxide [*Method I*: 5 mmol of *t*-BuOOH; *Method II*: 5 mmol of H_2O_2], a 15 wt % $TiCl_3$ solution was added dropwise such that a pale blue colour was just maintained to ensure the complete decomposition of the peroxide. The alcoholic cosolvent was removed in *vacuum* and a 30% aqueous NH_3 solution was added to the leftover solution until basic pH was achieved (a white precipitate of Ti(IV) hydroxide was observed) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water (2×5 mL), dried over Na_2SO_4 and then concentrated. The resulting crude material was purified by flash chromatography (Hexane/EtOAc,7/3) and 310 mg (1.6 mmol) of **2a** were recovered; total yield 80% (*Method I*) based on the starting amine [60%, 1.2 mmol: *Method II*].

4.3. Procedure for the domino synthesis of β-aminoalcohol 2l starting from secondary aromatic amine 1l and ethanol

With the exception of the amount of hydroperoxide required [*Method I*: *t*-BuOOH (2.5 mmol); *Method II*: H_2O_2 (2.5 mmol), both procedure and work up were analogous as for primary aromatic amines. The resulting crude material was purified by flash chromatography (Hexane/EtOAc, 6/4) and 286 mg (1.6 mmol) of **2l** were recovered; total yield 82% (*Method I*) based on the starting *N*-methylaniline (214 mg, 2 mmol) [67%, 1.3 mmol: *Method II*].

4.4. Procedure for the one-pot multicomponent synthesis of β-aminoalcohol 6a starting from amine 1a, acetaldehyde and ethanol

To a well stirred homogeneous solution of ethanol (10 mL) containing 4-methoxyaniline (246 mg, 2 mmol), acetaldehyde (220 mg, 282 μL, 5 mmol) and *t*-BuOOH (5 mmol) a 15 wt % $TiCl_3$ solution was added dropwise such that a pale blue colour was just maintained to ensure the complete decomposition of the peroxide. Work up was as previously described. The resulting crude material was purified by flash chromatography (Hexane/EtOAc, 7/3) and 315 mg (1.5 mmol) of **6a** were recovered; total yield 75% based on the starting amine.

4.5. Spectroscopic data

*4.5.1. 3-(4-Methoxy-phenylamino)-butan-2-ol (**2a**).* Diasteroisomers **A** and **B** were isolated by FCC (Hexane/EtOAc,7/3); total yield 80%. Diast **A** (R_f major: 0.37); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3415, 2972, 1736, 1601, 1513, 1222, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.11 (3H, CH_3, d, J=6.6 Hz), 1.25 (3H, CH_3, d, J=6.1 Hz), 3.16 (1H, CH, m), 3.56 (1H, CH, m), 3.75 (3H, OCH_3, s), 6.65–6.67 (2H, CH Ar, d, J=8.9 Hz), 6.77–6.79 (2H, CH Ar, d, J=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 17.0, 19.3, 55.7, 57.9, 71.2, 114.9, 116.3, 141.6, 152.9; MS (*m*/*z*): 195 (12), 177 (3), 150 (100), 135 (15), 108 (9), 92 (6); HRMS calcd for $C_{11}H_{17}NO_2$: 195.1259; found 195.1265; diast **B** (R_f minor: 0.33); FTIR (liquid film) ν_{max} 3415, 2972, 1736, 1601, 1513, 1222, 737 cm^{-1}; ^1H NMR ($CDCl_3$) 1.11 (3H, CH_3, d, J=6.6 Hz), 1.18 (3H, CH_3, d, J=6.6 Hz), 3.37 (1H, CH, m), 3.74 (3H, OCH_3, s); 3.97 (1H, CH, m), 6.66–6.67 (2H, CH Ar, d, J=8.9 Hz), 6.76–6.78 (2H, CH Ar, d, J=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.0, 18.9, 55.73, 55.67, 68.5, 114.9, 116.2, 140.4, 153.0; MS (*m*/*z*): 195 (12), 177 (3), 150 (100), 135 (15), 108 (9), 92 (6); HRMS calcd for $C_{11}H_{17}NO_2$: 195.1259; found 195.1252.

*4.5.2. 3-(Phenylamino)butan-2-ol (**2b**).* Crude product, purity ≥95%: no purification necessary to obtain a mix of the two diasteroisomers **A** and **B** in a ratio 1/1; total yield 75%; appearance yellow liquid; FTIR (liquid film) ν_{max} 3394, 2972, 1620, 1522, 1280, 785.cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm), 1.09 (3H, CH_3, d, J=6.4 Hz), 1.10 (3H, CH_3, d, J=6.2 Hz), 1.14 (3H, CH_3, d, J=6.4 Hz), 1.19 (3H, CH_3, d, J=6.2 Hz), 3.07 (1H, br sign with D_2O ex), 3.28 (1H, CH, dq, J=12.6, 6.2 Hz), 3.40 (1H, CH, m), 3.58 (1H, CH, dq, J=12.4, 6.2 Hz), 3.89 (1H, CH, m), 6.58 (2H, 2Ar′H, d, J=8.1 Hz), 6.62 (2H, 2Ar′H, d, J=8.1 Hz), 6.68 (2H, 2×Ar′H, m), 7.11 (4H, 2×2Ar′H, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.6, 16.6, 18.5, 18.9, 53.1, 55.2, 68.2, 70.58, 113.7, 113.6, 117.0, 117.5, 128.8 (2C, **A**+**B**), 146.8, 147.2; MS (*m*/*z*): 165 (8), 147 (3), 120 (100), 92 (5); HRMS calcd for $C_{10}H_{15}NO$: 165.1154; found 165.1147 (mix **A**+**B**).

*4.5.3. 3-(2-Methoxy-phenylamino)-butan-2-ol (**2c**).* The mix of the diasteroisomers **A** and **B** (R_f=0.35) was isolated by FCC (Hexane/EtOAc, 65/35) in a ratio 77/23; total yield 45%; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3415, 2972, 1736, 1601, 1513, 1222, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.15 (3H, CH_3 **A**, d, J=6.4 Hz), 1.16 (3H, CH_3 **B**, d, J=6.7 Hz), 1.21 (3H, CH_3 **B**, d, J=6.7 Hz), 1.26 (3H, CH_3 **A**, d, J=6.4 Hz), 3.32 (1H, CH **A**, m), 3.46–3.52 (1H, CH **B**, m), 3.69 (1H, CH **A**, m), 3.84 (3H, OCH_3 **B**+**A**, s), 3.98–4.03 (1H, CH **B**, m), 6.67–6.71 (2H, 2CH Ar **B**, m), 6.72–6.76 (2H, CH Ar **A**, m), 6.80 (1H, CH Ar **B**+**A**, m), 6.83–6.88 (1H, CH Ar **B**+**A**, m); ^{13}C NMR

($CDCl_3$) δ (ppm) 14.4, 17.1, 18.8, 19.3, 53.8, 55.4 (2C, **A**+**B**), 55.9, 68.8, 71.3, 109.8 (2C, **A**+**B**), 111.1, 111.7, 117.0, 117.4, 121.2 (2C, **A**+**B**), 137.0, 137.3, 147.2, 147.6; MS (*m*/*z*): 195 (12), 180 (3), 151(10), 150 (100), 120 (45); HRMS calcd for $C_{11}H_{17}NO_2$: 195.1259; found 195.1253 (mix **A**+**B**).

*4.5.4. 3-p-Tolylamino-butan-2-ol (**2d**).* Diasteroisomers **A** and **B** have been isolated by FCC (Hexane/EtOAc, 8/2); total yield 77%. Diast **A** (R_f major: 0.37); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3396, 2973, 1617, 1520, 1300, 809 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.12 (3H, CH_3, d, *J*=6.4 Hz), 1.24 (3H, CH_3, d, *J*=6.4 Hz), 2.23 (3H, CH_3, s), 3.25 (1H, CH, m), 3.60 (1H, CH, m), 6.60–6.62 (2H, CH Ar, d, *J*=8.7 Hz), 6.97–6.99 (2H, CH Ar, d, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 17.1, 19.4, 20.3, 56.8, 71.2, 114.8, 127.7, 129.8, 145.2; MS (*m*/*z*): 179 (10), 164 (2), 146 (1), 118 (9), 91 (15); HRMS calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1314; diast. **B** (R_f minor: 0.33); FTIR (liquid film) ν_{max} 3396, 2973, 1617, 1520, 1300, 809 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.11 (3H, CH_3, d, *J*=6.7 Hz), 1.18 (3H, CH_3, d, *J*=6.7 Hz), 2.23 (3H, CH_3, s), 3.39–3.45 (1H, CH, m), 3.91–3.97 (1H, CH, m), 6.55–6.57 (2H, CH Ar, d, *J*=8.4 Hz), 6.96–6.98 (2H, CH Ar, d, *J*=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm)14.2, 18.9, 20.3, 54.3, 68.7,. 114.2, 127.8, 129.8, 144.8; MS (*m*/*z*): 179 (10), 164 (2), 146 (1), 118 (9), 91 (15); HRMS calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1301.

*4.5.5. 3-m-Tolylamino-butan-2-ol (**2e**).* The mix of the diasteroisomers **A** and **B** (R_f=0.35) was isolated by FCC (Hexane/EtOAc, 8/2) in a ratio 7/3; total yield 78%; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3396, 2973, 1617, 1520, 1300, 809 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.12 (3H, CH_3 **B**, d, *J*=6.7 Hz), 1.14 (3H, CH_3 **A**, d, *J*=6.2 Hz), 1.19 (3H, CH_3 **B**, d, *J*=6.7 Hz), 1.24 (3H, CH_3 **A**, d, *J*=6.2 Hz), 2.26 (3H, CH_3 **B**, s), 2.27 (3H, CH_3 **A**, s), 3.30 (1H, CH **A**, m), 3.43–3.49 (1H, CH **B**, m), 3.61 (1H, CH **A**, m), 3.92–3.98 (1H, CH **B**, m), 6.43–6.59 (3H, 3CH Ar **A**+**B**, m), 7.03–7.08 (1H, CH Ar **A**+**B**, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.2, 17.2, 19.0, 19.5 (2C, **A**+**B**), 21.5 , 53.9 , 56.2 , 68.8 , 71.2 , 111.0 , 111.6 , 114.7, 115.2, 118.8, 119.3, 129.2 (2C, **A**+**B**), 139.1 (2C, **A**+**B**), 147.2, 147.5; MS (*m*/*z*): 179 (9), 134 (100), 118 (9), 91 (16), 65 (10), 45 (4); HRMS calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1307 (mix **A**+**B**).

*4.5.6. 3-o-Tolylamino-butan-2-ol (**2f**).* The mix of the diasteroisomers **A** and **B** (R_f=0.35) was isolated by FCC (Hexane/EtOAc, 85/15) in a ratio 1/1; total yield 70%; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3396, 2973, 1617, 1520, 1300, 809 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.16 (3H, CH_3, d, *J*=6.4 Hz), 1.17 (3H, CH_3, d, *J*=6.4 Hz), 1.21 (3H, CH_3, d, *J*=6.4 Hz), 1.26 (3H, CH_3, d, *J*=6.4 Hz), 2.14 (6H, 2 CH_3, s), 3.38 (1H, CH, m), 3.49–3.55 (1H, CH, m); 3.69 (1H, CH, m); 3.95–4.01 (1H, CH, m); 6.62–6.71 (4H, CH Ar, m); 7.02–7.12 (4H, CH Ar, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.3, 17.4, 17.5, 17.6, 19.1, 19.5, 53.5, 55.6, 68.8, 71.2, 110.9, 111.5, 117.3, 117.7, 122.5, 123.0, 127.1 (2C, **A**+**B**), 130.4 (2C, **A**+**B**), 145.1, 145.5; MS (*m*/*z*): 179 (9), 134 (100), 118 (13), 91 (15); HRMS calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1303 (mix **A**+**B**).

*4.5.7. 3-(4-Bromo-phenylamino)-butan-2-ol (**2g**).* The mix of the diasteroisomers **A** and **B** (R_f=0.35) was isolated by FCC (Hexane/EtOAc, 65/35) in a ratio 77/23; total yield 82%; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3405, 2975, 1736, 1594, 1496, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.12 (3H CH_3 **B**, d, *J*=6.7 Hz), 1.14 (3H CH_3 **A**, d, *J*=6.4 Hz), 1.20 (3H CH_3 **B**, d, *J*=6.7 Hz), 1.24 (3H CH_3 **A**, d, *J*=6.4 Hz), 3.27 (1H, CH **A**, m), 3.38–3.44 (1H, CH **B**, m), 3.65 (1H, CH **A**, m), 3.90–3.96 (1H, CH **B**, m), 6.48–6.51 (2H, 2CH Ar **B**, d, *J*=9.0 Hz), 6.52–6.55 (2H, 2CH Ar **A**, d, *J*=9.0 Hz), 7.21–7.26 (4H, 2CH Ar **B**+2CH Ar **A**, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.9, 17.1, 19.2, 19.7, 54.0, 56.1, 68.9, 71.1, 109.5 (2C, **A**+**B**), 115.5, 115.9, 132.0 (2C, **A**+**B**), 146.1, 146.4; MS (*m*/*z*): 245 (6), 243 (6), 201 (13), 200 (95), 198 (100), 119 (42), 118 (50), 91 (14); HRMS calcd for $C_{10}H_{14}BrNO$: 243.0259; found 243.0266 (mix **A**+**B**).

*4.5.8. 4-(2-Hydroxy-1-methyl-propylamino)-benzonitrile (**2h**).* The mix of the diasteroisomers **A** and **B** (R_f=0.35) was isolated by FCC (Hexane/EtOAc, 45/55) in a ratio 1/1; total yield 80%; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3373, 2975, 2931, 2212, 1607, 1525, 1342, 1173 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.16–1.25 (12H, 4CH_3, m), 1.82 (1H, br sign., D_2O ex), 2.09 (1H, br sign., D_2O ex), 3.42 (1H, CH, m), 3.51 (1H, CH, m), 3.80 (1H, CH, m), 3.97 (1H, 1CH, m), 4.37 (1H, br sign., D_2O ex), 4.46 (1H br sign., D_2O ex) 6.57 (4H, 4Ar′H, m) 7.38 (4H, 4Ar′H, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.9, 17.7, 20.0, 20.5, 53.2, 54.2, 71.7, 69.5, 98.9 (2C, **A**+**B**), 113.1, 113.2, 120.8 (2C, **A**+**B**), 134.1 (2C, **A**+**B**), 151.0, 151.6; MS (*m*/*z*): 190 (7), 145 (100), 102 (10); HRMS calcd for $C_{11}H_{14}N_2O$: 190.1106; found 190.1115 (mix **A**+**B**).

*4.5.9. 3-(3-Hydroxymethyl-phenylamino)-butane-2-ol (**2i**).* Diasteroisomers **A** and **B** were isolated by FCC ($CHCl_3$/MeOH: 1/9); total yield 47%. Diast **A** (R_f major=0.36); FTIR (liquid film) ν_{max} 3355, 2973, 1607, 1489 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.10 (3H, CH_3, d, *J*=6.4 Hz), 1.19 (3H, CH_3, d, *J*=6.4 Hz), 3.31 (1H, CH, m), 3.66 (1H, CH, m), 3.50–3.70 (2H, br sign., D_2O ex), 4.53 (2H, CH_2, s), 6.59 (1H, Ar′H d, *J*=7.9 Hz), 6.6–6.72 (2H, 2Ar′H, m), 7.11 (1H, Ar′H, dd, J_1=J_2=7.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 16.7, 19.4, 56.2, 64.9, 70.7, 113.3, 113.7, 117.2, 129.3, 142.4, 147.0; MS (m/z) (*m*/*z*): 195(8) 150 (26), 132 (100), 117 (21), 91 (47); HRMS calcd for $C_{11}H_{17}NO_2$: 195.1259; found 195.1251; diast **B** (R_f minor=0.33); FTIR (liquid film) ν_{max} 3355, 2973, 1607, 1489 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.12 (3H, CH_3, d, *J*=6.6 Hz), 1.20 (3H, CH_3, d, *J*=6.6 Hz), 1.70–2.15 (2H, br sign., D_2O ex), 3.49 (1H, CH, qd, *J*=3.9, 6.6 Hz), 3.96 (1H, CH, qd, *J*=3.9, 6.6 Hz), 4.58 (2H, CH_2, s), 6.55 (1H, Ar′H, d, *J*=8.0 Hz), 6.64–6.68 (2H, 2Ar′H, m), 7.14 (1H, ArH, dd, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.5, 19.4, 54.0, 65.8, 69.2, 112.5, 113.3, 116.5, 129.9, 142.6, 148.0; MS (*m*/*z*): 195 (8) 150 (26), 132 (100), 117 (21), 91 (47); HRMS calcd for $C_{11}H_{17}NO_2$: 195.1259; found 195.1253.

*4.5.10. 3-(2-Hydroxymethyl-phenylamino)-butan-2-ol (**2j**).* The mix of the diasteroisomers **A** and **B** (R_f=0.35) was isolated by FCC ($CHCl_3$/Hexane/MeOH, 6/3/1) in a ratio 1/1; total yield 52%; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3395, 3019, 2977, 1607, 1515, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) δ 1.15 (9H, 3CH_3, m), 1.24 (3H, CH_3, d, *J*=6.6 Hz), 2.59 (1H, br sign., D_2O ex), 2.85 (1H, br sign., D_2O ex), 3.38 (1H, CH, qd, *J*=3.1, 6.3 Hz), 3.51 (1H, CH, qd, *J*=3.1, 6.6 Hz), 3.67 (1H, CH, qd, *J*=3.1, 6.6 Hz) 3.96 (1H, CH, qd, *J*=3.1, 6.3 Hz), 4.55–4.63 (4H, 2×CH_2, m) 6.64–6.69 (3H, 3Ar′H, m), 6.75 (1H, ArH, d, *J*=8.3 Hz), 7.03 (2H, 2Ar′H, m), 7.16–7.20 (2H, 2Ar′H, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.4, 17.5, 19.1, 19.9, 53.6, 55.4, 64.8, 64.9, 68.7, 71.7, 112.3, 112.4, 117.2, 117.3, 125.3, 125.5, 129.7 (2C, **A**+**B**), 129.9 (2C, **A**+**B**), 146.9, 147.5; MS (*m*/*z*): 195 (8), 150 (26), 132 (100), 117 (21), 91 (47); HRMS calcd for $C_{11}H_{17}NO_2$: 195.1259; found 195.1250 (mix **A**+**B**).

*4.5.11. 3-(Naphthalen-1-ylamino)-butan-2-ol (**2k**).* The mix of the diasteroisomers **A** and **B** (R_f=0.35) was isolated by FCC (Hexane/EtOAc, 3/7) in a ratio 44/66; total yield 48%; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3425, 2974, 1726, 1580, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.26 (6H, CH_3 **A**+**B** , m), 1.28 (3H, CH_3 **A**, d, *J*=6.4 Hz), 1,32 (3H, CH_3 **B**, d, *J*=6.2 Hz), 3.56 (1H, CH **B**, qd, *J*=12.5, 6.4 Hz), 3.66 (1H, CH **A**, m), 3.83 (1H, CH **B**, qd, *J*=12.3, 6.1 Hz), 4.09 (1H, CH **A**, m), 6.64 (1H, Ar′H **A**, d, *J*=7.56 Hz), 6.71 (1H, Ar′H **B**, d, *J*=7.28 Hz), 7.24 (2H, 2Ar′H, m), 7.29–7.35 (2H, 2Ar′H, m), 7.41–7.45 (4H, 4Ar′H, m), 7.76–7.84 (4H, 4Ar′H, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.9, 17.1, 19.2, 19.8, 53.6, 55.5, 68.7, 71.4, 105.5, 106.1, 117.7, 118.0, 119.9, 123.9 (2C, **A**+**B**), 124.2, 124.7, 124.8, 125.7 (2C, **A**+**B**), 126.5 (2C, **A**+**B**), 128.7, 128.8, 134.5, 134.6, 142.3, 142.7; MS (*m*/*z*): 215 (16),

170 (100), 154 (16), 127 (17), 115 (13); HRMS calcd for $C_{14}H_{17}NO$: 215.1310; found 215.1317 (mix **A**+**B**).

*4.5.12. 3-(Methyl-phenyl-amino)-butan-2-ol (**2l**).* Diasteroisomers **A** and **B** were isolated by FCC (Hexane/EtOAc ,6/4); total yield 82%. Diast **A** (R_f major=0.37); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3355, 3019, 1583, 1216, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.01 (3H, CH_3, d, J=6.7 Hz), 1.25 (3H, CH_3, d, J=5.9 Hz), 2.70 (3H, CH_3, s), 3.16 (1H, br sign., D_2O ex), 3.51 (1H, CH, dq, J=9.3, 6.7 Hz), 3.76 (1H, CH, dq, J=9.3, 5.9 Hz), 6.83 (1H, CH Ar, t, J=7.5 Hz), 6.95 (2H, CH Ar, d, J=8.5 Hz), 7.23 (2H, CH Ar, dd, J=7.5, 8.5 Hz);^{13}C NMR ($CDCl_3$) δ (ppm) 11.5, 19.3, 30.8, 64.0, 67.8, 116.2, 119.1, 129.0, 151.2; MS (*m*/*z*): 179 (5), 164 (1), 134 (100), 104 (14), 77 (21); HRMS calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1306; diast **B** (R_f minor=0.33); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3355, 3019, 1583, 1216, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.19 (3H, CH_3, d, J=6.7 Hz), 1.22 (3H, CH_3, d, J=6.7 Hz), 1.87 (1H, br sign., D_2O ex), 2.75 (3H, CH_3, s), 3.69 (1H, CH, dq, J=6.7 Hz), 3.89 (1H, CH, dq, J=6.7 Hz), 6.71 (1H, CH Ar, t, J=7.2 Hz), 6.79 (2H, CH Ar, d, J=8.02 Hz), 7.22 (2H, CH Ar, dd, J=7.2, 8.0 Hz);^{13}C NMR ($CDCl_3$) δ (ppm) 12.8, 21.1, 31.9, 59.5, 70.4, 113.2, 116.8, 129.1, 150.2; MS (*m*/*z*): 179 (5), 164 (1), 134 (100), 104 (14), 77 (21); HRMS calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1303.

*4.5.13. 2-(4-Methoxyphenylamino)ethanol (**3a**).* Ref. 6. Purified by FCC (Hexane/EtOAc, 3/7) (R_f=0.35); total yield 13%; pale yellow liquid; FTIR (liquid film) ν_{max} 3352, 2925, 1602, 1238, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.01 (2H,NH and OH, br.s, ex D_2O), 3.24 (2H, CH_2, t, J=5.2 Hz); 3.74 (3H, OCH_3, s); 3.80 (2H, CH_2, t, J=5.2 Hz); 6.65 (2H, CH Ar, d, J=8.8 Hz); 6.78 (2H, CH Ar, d, J=8.8 Hz). ^{13}C $CDCl_3$ δ (ppm): 47.6, 55.7, 61.0, 114.9, 115.2, 141.5, 152.9. EIMS *m*/*z* (added HCOOH 0.1%) 169 (M^++1, 88), 168 (100), 151 (16), 150 (56), 136 (7), 123 (32), 119 (12); HMRS calcd for $C_9H_{13}NO_2$: 167.0946; found 167.0949.

*4.5.14. 4-(4-Methoxy-phenylamino)-hexan-3-ol (**4a**).* Diasteroisomer **A** (R_f major=0.36) and a mix of diastereoisomers **A** and **B** (R_f minor=0.34) in a ratio 25/75 were isolated by FCC (Hexane/EtOAc, 6/4); total yield 59%. Diast. **A**; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3413, 2968, 1730, 1600, 1513, 1228, 732 cm^{-1}; ^1H NMR $CDCl_3$ δ (ppm) 0.92 (3H, CH_3, t, J=7.3 Hz), 1.00 (3H, CH_3, t, J=7.28 Hz), 1.43–1.56 (2H, CH_2, m), 1.59–1.71 (2H, CH_2, m), 3.06–3.11 (1H, CH, dt, J=5.3, 7.3 Hz), 3.45–3.49 (1H, CH, dq, J=3.9, 5.3 Hz), 3.74 (3H, OCH_3, s), 6.61–6.64 (2H, CH Ar, m, J=8.9 Hz), 6.75–6.77 (2H, CH Ar, m, J=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 10.1, 10.4, 24.8, 26.9, 55.8, 61.2, 74.3, 115.0, 115.7, 142.1, 152.6; MS (*m*/*z*) 223 (6), 206 (12), 194 (2), 176 (6), 164 (100), 134 (15); HRMS calcd for $C_{13}H_{21}NO_2$: 223.1572; found 223.1581; mix **A** and **B** (ratio 25/75); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3413, 2968, 1730, 1600, 1513, 1228, 732 cm^{-1}; ^1H NMR $CDCl_3$ δ (ppm) 0.92 (3H, CH_3 **A**, t, J=7.3 Hz), 0.96 (3H, CH_3 **B**, t, J=7.3 Hz), 1.00 (3H, CH_3 **A**, t, J=7.3 Hz), 1.01 (3H, CH_3 **B**, t, J=7.3 Hz), 1.42–1.68 (8H, $2CH_2$ **A**+$2CH_2$ **B**, m), 3.08–3.12 (1H, CH **A**, dt, J=5.3, 7.3 Hz), 3.22 (1H, CH **B**, dt, J=4.5, 8.4 Hz), 3.47–3.52 (1H, CH **A**, dt, J=3.9, 5.3 Hz), 3.63–3.67 (1H, CH **B**, dt, J=3.6, 7.8 Hz), 3.74 (3H, OCH_3 **B**, s), 3.76 (3H, OCH_3 **A**, s), 6.66–6.69 (4H, CH Ar **A**+**B**, m), 6.76–6.78 (4H, CH Ar **A**+**B**, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 10.1, 10.4, 10.7, 11.1, 22.7, 24.8, 26.9, 25.7, 55.8 (2C, **A**+**B**), 61.4, 61.6, 73.9, 74.3, 115.0 (2C, **A**+**B**), 115.8, 116.0, 141.4, 141.9, 152.8, 152.9; MS (*m*/*z*) 223 (6), 206 (12), 194 (2), 176 (6), 164 (100), 134 (15); HRMS calcd for $C_{13}H_{21}NO_2$: 223.1572; found 223.1569 (mix **A**+**B**).

*4.5.15. 5-(4-Methoxy-phenylamino)-octan-4-ol (**5a**).* Diasteroisomer **A** (R_f major=0.37) and a mix of diastereoisomers **A** and **B** (R_f minor=0.35) in a ratio 3/7 were isolated by FCC (Hexane/EtOAc, 7/3); total yield 37%. Diast. **A**; appearance pale orange liquid; FTIR (liquid film) ν_{max} 3418, 3018, 2960, 1512, 1216 cm^{-1}; ^1H NMR $CDCl_3$ δ (ppm) 0.88 (3H, CH_3, t, J=7.1 Hz), 0.94 (3H, CH_3, t, J=7.1 Hz), 1.25–1.63 (8H, $4CH_2$, m), 3.11–3.15 (1H, CH, m), 3.50–3.54 (1H, CH, m), 3.74 (3H, OCH_3, s), 6.61 (2H, 2ArH, d, J=9.0 Hz), 6.75 (2H, 2ArH, d, J=9.0 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.4, 14.5, 19.4, 19.7, 35.2, 36.6, 56.1, 60.1, 73.5, 115.3, 115.4, 143.1, 152.6; MS (*m*/*z*) 251(3), 178 (100); HRMS calcd for $C_{15}H_{25}NO_2$: 251.1885; found 251.1889; mix **A** and **B**; appearance pale orange liquid; FTIR (liquid film) ν_{max} 3418, 3018, 2960, 1512, 1216 cm^{-1}; ^1H NMR $CDCl_3$ δ (ppm) 0.87 (3H, CH_3 **A**, t, J=7.1 Hz), 0.90 (3H, CH_3 **B**, t, J=7.1 Hz), 0.93 (3H, CH_3 **A**, t, J=7.1 Hz), 0.95 (3H, CH_3 **B**, t, J=7.1 Hz), 1.25–1.60 (16H, $4CH_2$ **A**+$4CH_2$ **B**, m), 3.11–3.15 (1H, CH **A**, m), 3.27–3.31 (1H, CH **B**, m), 3.50–3.54 (1H, CH **A**, m), 3.69–3.73 (1H, CH **B**, m), 3.73 (3H, OCH_3 **A**+OCH_3 **B**, s), 6.59 (2H, 2ArH **A**+2ArH **B**, d, J=8.8 Hz), 6.76 (2H, 2ArH **A**+2ArH **B**, d, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.4 (2C, **A**+**B**), 14.5 (2C, **A**+**B**), 19.4, 19.7, 19.8, 20.0, 32.6, 35.2 (2C, **A**+**B**), 36.6, 56.1 (2C, **A**+**B**), 59.4, 60.1, 72.6, 73.5, 115.3 (2C, **A**+**B**), 115.4 (2C, **A**+**B**), 142.8, 143.2, 152.6 (2C, **A**+**B**); MS (*m*/*z*) 251(3), 178 (100); HRMS calcd for $C_{15}H_{25}NO_2$: 251.1885; found 251.1877.

*4.5.16. 2-(N-methyl-N-phenyl)ethanol (**3l**).* Ref. 6. Purified by FCC (Hexane/EtOAc, 6/4) (R_f=0.35); pale yellow liquid; total yield 31%. FTIR (liquid film) ν_{max} 3374,1595,1500, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.17 (1H, OH br.s, ex D_2O); 2.93 (3H, CH_3, s); 3.43 (2H, CH_2, t, J=5.70 Hz); 3.76 (2H, CH_2, t, J=5.70 Hz); 6.69–6.83 (3H, 3CH Ar, m), 7.19–7.26 (2H, 2CH Ar, m); ^{13}C $CDCl_3$ δ (ppm): 38.8, 55.4, 60.0, 113.1, 117.3, 129.2, 150.0. EIMS *m*/*z* 151 (M^+16), 132 (1), 120 (100), 104 (18), 77 (25). HMRS calcd for $C_9H_{13}NO$: 151.0997; found 151.0995.

*4.5.17. 4-(Methyl-phenyl-amino)-hexan-3-ol (**4l**).* Diasteroisomers **A** and **B** were isolated by FCC (Hexane/EtOAc, 8/2); total yield 49%. Diast **A** (R_f major=0.37); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3627, 3425, 2969, 1598, 1505, 1216, 755; ^1H NMR $CDCl_3$ δ (ppm) 0.75 (3H, CH_3, t, J=7.6 Hz), 1.07 (3H, CH_3, t, J=7.6 Hz), 1.42–1.49 (1H, CH, m), 1.52–1.59 (2H, CH_2, m), 1.66–1.75 (1H, CH, m), 2.78 (3H, CH_3, s); 3.51–3.58 (2H, CH_2, m), 6.75 (1H, CH Ar, t, J=7.3 Hz), 6.89–6.91 (2H, CH Ar, m, J=8.9 Hz), 7.20–7.24 (2H, CH Ar, m, J=7.3, 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 9.8, 11.5, 21.9, 26.7, 30.6, 66.9, 72.4, 114.2, 117.8, 129.1, 152.3; MS (*m*/*z*) 207 (3), 190 (2), 178 (3), 148 (100), 132 (13), 77 (13); HRMS calcd for $C_{13}H_{21}NO$: 207.1623; found 207.1630; diast **B** (R_f minor=0.34); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3627, 3425, 2969, 1598, 1505, 1216, 755; ^1H NMR $CDCl_3$ δ (ppm) 0.84 (3H, CH_3, t, J=7.3 Hz), 0.94 (3H, CH_3, t, J=7.3 Hz), 1.28–1.37 (1H, CH, m), 1.54–1.72 (3H, CH_2+OH, m, D_2O ex), 1.83–1.93 (1H, CH, m), 2.76 (3H, CH_3, s), 3.56–3.64 (1H, CH_2, m), 6.66 (1H, CH Ar, t, J=7.3 Hz), 6.77–6.79 (2H, CH Ar, m, J=8.9 Hz), 7.18–7.23 (2H, CH Ar, m, J=7.3, 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 10.3, 11.3, 21.5, 27.7, 31.3, 64.0, 75.7, 112.4, 116.1, 129.1, 151.1; MS (*m*/*z*) 207 (3), 190 (2), 178 (3), 148 (100), 132 (13), 77 (13); HRMS calcd for $C_{13}H_{21}NO$: 207.1623; found 207.1620.

*4.5.18. 5-(Methyl-phenyl-amino)-octan-4-ol (**5l**).* Diasteroisomers **A** and **B** were isolated by FCC (Hexane/$CHCl_3$/Et_2O, 6/3/1); total yield 25%. Diast. **A** (R_f major=0.37); appearance pale orange liquid; FTIR (liquid film) ν_{max} 3423, 3018, 2960, 1598, 1505, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 0.79 (3H, CH_3, t, J=7.1 Hz), 0.97 (3H, CH_3, t, J=7.1 Hz), 1.04–1.23 (2H, CH_2, m), 1.40–1.64 (6H, $3CH_2$, m), 2.76 (3H, OCH_3, s), 3.59–3.61 (2H, 2CH, m), 6.75 (1H, ArH, t, J=7.3 Hz), 6.88 (2H, 2ArH, d, J=8.9 Hz), 7.22 (2H, 2 ArH, dd, J=7.3, 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.0, 14.2, 18.9, 20.0, 30.5, 31.1, 36.2, 65.6, 70.9, 114.2, 117.8, 129.1, 152.2; MS (*m*/*z*) 235 (2), 192 (3), 162 (100); HRMS calcd for $C_{15}H_{25}NO$: 235.1936; found 235.1941; diast **B** (R_f minor=0.35); appearance pale orange liquid; FTIR (liquid film) ν_{max} 3423, 3018, 2960, 1598, 1505, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 0.85–0.90 (6H, 2 CH_3, m), 1.21–1.34 (4H, $2CH_2$, m), 1.49–1.53 (2H, CH_2, m), 1.66–1.75 (2H, CH_2, m), 2.76 (3H, CH_3, s), 3.68–3.73 (2H, 2CH, m) 6.66 (1H, ArH, t, J=7.3 Hz), 6.76 (2H, 2 ArH, d, J=8.9 Hz), 7.20 (2H, 2 ArH, dd, J=7.3, 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.9,

14.1, 19.1, 19.9, 30.7, 31.5, 36.9, 62.3, 74.0, 112.3, 116.0, 129.1, 151.0; MS (*m*/*z*) 235 (2), 192 (3), 162 (100); HRMS calcd for $C_{15}H_{25}NO$: 235.1936; found 235.1944.

*4.5.19. 3-(4-Methoxyphenylamino)pentan-2-ol (**6a**).* Diasteroisomers **A** and **B** were isolated by FCC (Hexane/EtOAc, 7/3); total yield 65%. Diast **A** (R_f major=0.37); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 2967, 2933, 2976, 2833, 1511, 1464, 1230, 1037 m^{-1}; ^1H NMR ($CDCl_3$) δ (ppm), 0.90 (3H, CH_3, t, *J*=7.5 Hz), 1.23 (3H, CH_3, d, *J*=6.0 Hz), 1.43 (1H, CH_{ab}, m), 1.65 (1H, CH_{ab}, m), 3.01 (3H, CH, NH, OH, br sign., D_2O ex), 3.70 (1H, CH, m), 3.72 (3H, OH_3, s) 6.61 (2H, 2Ar′H, d, *J*=8.9 Hz), 6.74 (2H, 2Ar′H, d, *J*=8.9 Hz); ^{13}C CDCl3 δ (ppm): 10.5, 20.1, 24.9, 55.9, 63.0, 69.3, 115.1, 115.5, 142.9, 152.5; ESI-MS *m*/*z* 210 [M^++H], 232 [M+Na]; HRMS calcd for $C_{12}H_{19}NO_2$: 209.1416; found 209.1412; diast **B** (R_f minor=0.34); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 2965, 2933, 2976, 2833, 1511, 1464, 1230, 1037 m^{-1}; ^1H NMR ($CDCl_3$) δ (ppm), 0.95(3H, CH_3, t, *J*=7.5 Hz), 1.16 (3H, CH_3, d, *J*=6.7 Hz), 1.43 (1H, CH_{ab}, m), 1.57 (1H, CH_{ab}, m), 2.87 (br sign., D_2O ex), 3.20 (1H, CH, m), 3.72 (3H, OCH_3, s) 3.91 (1H, CH, m), 6.63 (2H, 2Ar′H, d, *J*=8.9 Hz), 6.76 (2H, 2Ar′H, d, *J*=8.9 Hz); ^{13}C CDCl3 δ (ppm): 11.2, 18.5, 23.7, 55.9, 61.9, 68.5, 115.1, 115.4, 142.8, 152.4; ESI-MS *m*/*z* 210 [M^++H], 232 [M+Na]; HRMS calcd for $C_{12}H_{19}NO_2$: 209.1416; found 209.1418.

*4.5.20. 4-(4-Methoxyphenylamino)heptan-3-ol (**7a**).* Diasteroisomers **A** and **B** were isolated by FCC (Hexane/EtOAc, 8/2); total yield 44%. Diast **A** (R_f major=0.36); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 2967, 2933, 2974, 2828, 1511, 1460, 1232, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 0.89 (3H, CH_3, t, *J*=7.0 Hz), 1.01 (3H, CH_3, t, *J*=7.3 Hz), 1.23–1.68 (6H, $3CH_2$, m), 3.16 (1H, CH, m), 3.45 (1H, CH, m), 3.74 (3H, OCH_3, s) 6.63 (2H, 2Ar′H, d, *J*=8.7 Hz), 6.77 (2H, 2Ar′H, d, *J*=8.7 Hz); ^{13}C CDCl3 δ (ppm) 10.2, 14.2, 19.3, 26.9, 34.9, 55.7, 59.2, 74.9, 114.9, 115.1, 142.8, 152.3; ESI-MS *m*/*z* 238 [M^++H], 260 [M+Na]; HRMS calcd for $C_{14}H_{23}NO_2$: 237.1729; found 237.1736; diast **B** (R_f minor=0.33); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 2967, 2933, 2974, 2828, 1511, 1460, 1232, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 0.91 (3H, CH_3, t, *J*=7.0 Hz), 1.02 (3H, CH_3, t, *J*=7.3 Hz), 1.21–1.59 (6H, $3CH_2$, m), 3.30(1H, CH, m), 3.62 (1H, CH, m), 3.74 (3H, OCH_3, s) 6.62 (2H, 2Ar′H, d, *J*=8.6 Hz), 6.76 (2H, 2Ar′H, d, *J*=8.6 Hz); ^{13}C CDCl3 δ (ppm) 10.6, 14.1, 19.7, 25.6, 32.1, 55.7, 58.9, 74.1, 114.9, 115.2, 142.8, 152.3; ESI-MS *m*/*z* 238 [M^++H], 260 [M+Na]; HRMS calcd for $C_{14}H_{23}NO_2$: 237.1729; found 237.1725.

*4.5.21. 2-(4-Methoxyphenylamino)hexan-3-ol (**8a**).* Diasteroisomers **A** and **B** were isolated by FCC (Hexane/EtOAc, 7/3); total yield 41%. Diast **A** (R_f major=0.35); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 2959, 2930, 2872, 1512, 1464, 1233, 1037 cm^{-1}; ^1H NMR (DMSO ex D_2O) δ (ppm), 0.82 (3H, CH_3, t, *J*=6.8 Hz), 1.00 (3H, CH_3, d, *J*=6.8 Hz), 1.12–1.41 (4H, $2CH_2$, m), 3.26 (1H, CH, m), 3.44 (1H, CH, m), 3.61 (3H, OCH_3, s) 6.55 (2H, 2Ar′H, d, *J*=8.9 Hz), 6.69 (2H, 2Ar′H, d, *J*=8.9 Hz); ^{13}C CDCl3 δ (ppm): 14.0, 17.1, 18.8, 35.7, 55.7, 56.2, 74.7, 114.9, 116.4, 141.2, 152.9; ESI-MS *m*/*z* 224 [M^++H], 246 [M+Na]; HRMS calcd for $C_{13}H_{21}NO_2$: 223.1572; found 223.1574; diast **B** (R_f minor=0.32); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 2959, 2930, 2872, 1512, 1464, 1233, 1037 cm^{-1}; (DMSO ex D_2O) δ (ppm), 0.85 (3H, CH_3, t, *J*=6.7 Hz), 0.98 (3H, CH_3, d, *J*=6.7 Hz), 1.21–1.45 (4H, $2CH_2$, m), 3.20 (1H, CH, m), 3.44 (1H, CH, m), 3.61 (3H, OCH_3, s) 6.51 (2H, 2Ar′H, d, *J*=8.9 Hz), 6.68 (2H, 2Ar′H, d, *J*=8.9 Hz); ^{13}C CDCl3 δ (ppm): 13.9 , 14.1 , 29.6, 35.6, 53.9, 55.7, 72.4, 115.0, 115.5, 141.3, 152.5; ESI-MS *m*/*z* 224 [M^++H], 246 [M+Na]; HRMS calcd for $C_{13}H_{21}NO_2$: 223.1572; found 223.1577.

*4.5.22. 1-(Benzyl(methyl)amino)propan-2-ol (**9m**).* The product vas isolated by FCC (Hexane/CH_2Cl_2/MeOH/NH_3, 6/3,5/0,5/10^{-3}) (R_f minor=0.35); appearance colourless oil; total yield 54%. FTIR (liquid film) ν_{max} 3439, 2974–2800, 1454, 1216, 1065, 1025, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm), 1.12 (3H, CH_3, d, *J*=6.1 Hz), 2.23 (3H, CH_3, s), 2.30 ($1H_a$, CH_{ab}, dd, *J*=12.2, 3.3 Hz) 2.38 ($1H_b$, CH_{ab}, dd, *J*=12.2, 10.0 Hz), 3.45 ($1H_a$, CH_{ab}, d, *J*=12.2 Hz), 3.58 (1H, OH, brs), 3.66 ($1H_b$, CH_{ab}, d, *J*=12.2 Hz), 3.87 (1H, CH, m), 7.23–7.34 (5H, 5Ar′H, m); ^{13}C CDCl3 δ (ppm): 20.4, 42.3, 62.9, 63.4, 65.4, 127.6, 128.7, 129.4, 138.7; ESI-MS *m*/*z* 180[M^++H], 202 [M^++Na]; HRMS calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1307.

*4.5.23. 1-(piperidin-1-yl)propan-2-ol (**9n**).* The product was isolated pure from the reaction; appearance yellow liquid; total yield 32%. FTIR (liquid film) ν_{max} 3375, 2933, 1666, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm), 1.02 (3H, CH_3, d, *J*=6.7 Hz), 1.35 (2H, CH_2, m), 1.48 (4H, $2\times CH_2$, m), 2.07 ($1H_b$, CH_{ab}, t, *J*=12.2 Hz), 2.16 ($1H_a$, CH_{ab}, m), 2.21 ($2H_a$, CH_{ab}, m), 2.50 ($2H_b$, CH_{ab}, m), 3.61 (1H, br sign. D_2O ex), 73.7 (1H, CH, m); ^{13}C CDCl3 δ (ppm): 19.9, 24.1, 25.9, 54.5, 62.1, 66.3; ESI-MS *m*/*z* 144 [M^++H], 166 [M^++Na]; HRMS calcd for $C_8H_{17}NO$: 143.1310; found 143.1315.

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Supplementary data

Supplementary data (^1H and ^{13}C spectra of compounds **2a**–**l**, **3a**, **3l**, **4a**, **4l**, **5a**, **5l**, **6a**, **7a**, **8a** and **9m**–**n** and general procedure) associated with this article can be found in the online version. Supplementary data associated with this article can be found in the online version doi:10.1016/j.tet.2010.01.039.

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