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PAPER

New domino radical synthesis of aminoalcohols promoted by $TiCl_4$–Zn/*t*-BuOOH system: selective hydroxyalkylation of amines in alcohol or in cyclic ether cosolvents†‡

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We report a new and fast domino synthesis of aminoalcohols under mild conditions. The free-radical reaction of aliphatic and aromatic amines with alcohol cosolvents is promoted by means of the $TiCl_4$–Zn/*t*-BuOOH system. According to the proposed mechanism, the amine reacts with two molecules of alcohol in an electrophilic–nucleophilic cascade process. This procedure, if compared with the $TiCl_3$/*t*-BuOOH-mediated protocol previously reported, appears to be more selective, of more general applicability and affords the desired products in higher yields. Besides, with the same catalytic system it was possible to promote the reaction of primary arylamines with two molecules of cyclic ether, leading to the formation of a wider range of functionalized aminoalcohols.

Introduction

1,2-Aminoalcohols are important building blocks extensively employed for the synthesis of a wide range of derivatives in medicinal chemistry,[1] for the production of chiral auxiliaries or chiral catalysts to be used in asymmetric synthesis[2] and, as organic ligands, for materials syntheses by sol–gel processing.[3]

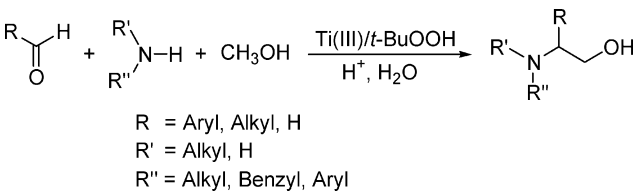
In the last decade many protocols have been developed for the selective asymmetric synthesis of these compounds, mainly following two alternative approaches: the Sharpless aminohydroxylation of olefins catalyzed by transition metal salts[4,5] and the hydroxyalkylation of amines *via* nucleophilic addition to ethylene and propylene oxides.[6]

Nevertheless, these syntheses often require expensive reagents and multi-step procedures under highly controlled operating conditions, whereas the growing demand of waste and energy consumption minimization calls for the development of new one-pot more-bond-forming processes (domino or cascade reactions)[7] starting from simple and cheap materials.

For this reason, the nucleophilic radical addition to imines, mediated by transition metal salts, has often represented an important alternative to the classical ionic procedures, leading to the formation of a wide range of polyfunctional amines under milder and more environmentally benign conditions.[8,9]

Following the radical route to 1,2-aminoalcohols, in 2008 Tomioka and coworkers reported the nucleophilic addition to preformed imines by means of acyloxymethyl radicals, generated from the corresponding iodomethyl esters by action of dimethylzinc or triethylborane.[10]

In the same year, as a part of our ongoing interest in promoting one-pot transformations mediated by $TiCl_3$/hydroperoxide systems,[11,12] we showed that an amine, an aldehyde and methanol could be readily assembled under aqueous conditions through a free radical multicomponent reaction, requiring neither the preformation of the imine nor the protection of the amino group (Scheme 1).[13]



Scheme 1 $TiCl_3$/*t*-BuOOH mediated hydroxymethylation of imines generated *in situ*.

Although these radical approaches do not show enantioselectivity, both the enantiomers (whose configuration may be easily assigned by NMR)[14] could be isolated in their pure form by means of the several methods reported in the literature.[15]

More recently, we reported that the $TiCl_3$/*t*-butyl hydroperoxide (*t*-BuOOH) system, when operating in an alcoholic solvent different from methanol, was able to promote the cascade reaction of primary and secondary arylamines with an aldehyde generated *in situ* from the corresponding alcohol, leading to 1,2-aminoalcohols in good yields (Scheme 2).[16]

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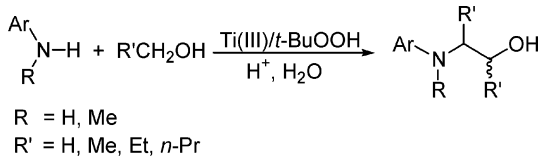
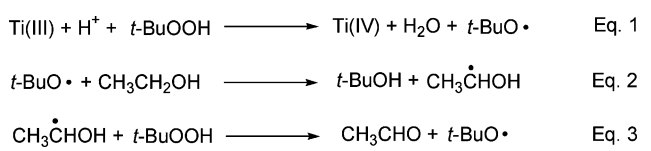
† In memory of Athel Beckwith for his fundamental and significant contribution to the Renaissance of free radical chemistry.

‡ Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of compounds **2*e–f***, **3*b–c***, **3*e–f***, **5*b–c***, **6*a–c*** and **7*a–c***. See DOI: 10.1039/c1ob05191a



Scheme 2 Radical domino approach to 1,2-aminoalcohols from arylamines and alcohols triggered by $TiCl_3$/*t*-BuOOH.

The efficiency of this process was ascribed to the strong nucleophilic character of α-hydroxyalkyl radicals (ketyls), formed according to eq. 1 and 2 (Scheme 3): in fact, the higher reducing potential of ketyls under aqueous acidic conditions[17] enabled the formation of the corresponding aldehydes by oxidative action of the hydroperoxide present in the reaction medium (eq. 3, Scheme 3).

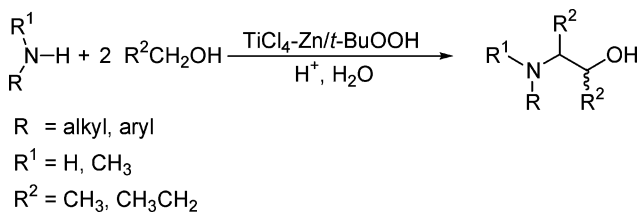


Scheme 3 Ti(III)/*t*-BuOOH triggered *in situ* generation of aldehydes.

Nevertheless, this protocol showed two main drawbacks: (i) it was limited to arylamines, while aliphatic amines were unreactive; (ii) yields were very high only when operating in the presence of ethanol (EtOH), due to the lower reducing potential of *n*-propanol (PrOH) and, in general, of alcohols bearing longer aliphatic chains.[18]

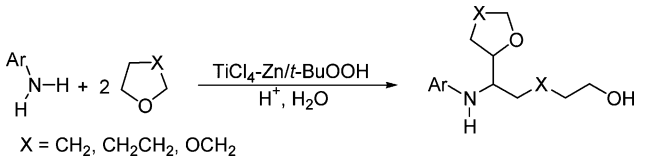
At the same time, we showed that the use of the couple $TiCl_4$–Zn, in place of $TiCl_3$, allowed the facile carbamoylation of ketimines generated *in situ*.[19]

While investigating the general applicability of the above mentioned $TiCl_4$–Zn/hydroperoxide system in solvents different from formamide, we were surprised to detect traces of aldehyde when an alcoholic solvent was used. This observation encouraged us to further look into this reaction in the absence of additional aldehydes or ketones. As a result, we now report that the $TiCl_4$–Zn/hydroperoxide system allows to assemble aliphatic and aromatic amines with two molecules of EtOH or PrOH, affording the corresponding 1,2-aminoalcohols in unexpected excellent yields, in spite of the reducing environment (Scheme 4).



Scheme 4 Radical domino reaction between of an amine with two molecules of alcohol, triggered by $TiCl_4$–Zn/*t*-BuOOH.

Moreover, we here show that the same catalytic system is able to promote the reaction of two molecules of cyclic ethers with one molecule of primary arylamine, to afford aminoalcohols through the consecutive electrophilic amination to imines *via* ring opening of the ether, followed by a nucleophilic radical addition (Scheme 5).



Scheme 5 Radical domino reaction of a primary arylamine with two molecules of cyclic ether triggered by $TiCl_4$–Zn/*t*-BuOOH.

Results and discussion

The reaction of amines in alcoholic solvents

The results of the reaction of aliphatic and aromatic amines with alcoholic solvents (R^2CH_2OH) mediated by the $TiCl_4$–Zn/*t*-BuOOH system are shown in Table 1 (left column) and are compared with those (right column) obtained by the $TiCl_3$/*t*-BuOOH system.[16]

p-Methoxyaniline (PMP-NH_2, **1*a***) was selected as a model substrate and its reaction in ethanol solvent was fully investigated (entries 1–5), since the easy removal of PMP group leads to unprotected amino-derivatives.[20]

First experiments were conducted in the presence of H_2O_2 in order to reproduce the catalytic system previously reported in the carbamoylation of ketimines.[19] As already observed for radical reactions promoted by hydroperoxide redox decomposition,[16] the hydroxyl radicals generated *in situ* led to the desired product **2*a*** in poor yield (26%) and poor selectivity, probably because of enthalpic reasons (entry 1). In fact, by simply replacing H_2O_2 with *t*-BuOOH (entry 2), we observed a complete selectivity in **2*a*** and a significant improvement of yield (50%), which however was still too low as compared with the results reported with the previous protocol.[16] We ascribed this behavior to the lower acidity of the reaction medium under the new conditions, while it is well known that redox potential of ketyls increases on decreasing the pH.[17] To verify this hypothesis and with the aim of improving the efficiency of the new protocol, we added a small amount of acetic acid (AcOH) to the reaction mixture and succeeded in increasing the yield up to 95%, even higher than that reported with the $TiCl_3$/*t*-BuOOH system (entry 3).

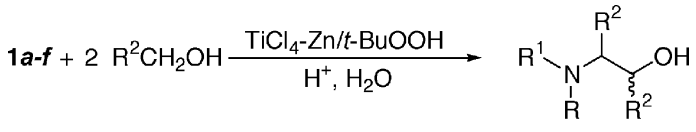
By operating in the absence of Zn or $TiCl_4$, the reaction afforded a complex mixture of products with only traces of **2*a*** (entries 4 and 5).

More interesting, by carrying out the same reaction in propanol solvent (entry 6), it was possible to achieve product **3*a*** in 87% yield, in spite of the lower reducing potential of the corresponding ketyl radical. On the contrary, no significant improvement was observed when operating in *n*-butanol as a solvent (entry 7); in fact, in spite of complete conversion of the starting amine, in this case the reaction afforded a mixture of products providing the desired derivative **4*a*** with poor selectivity.

In a general procedure, a homogeneous solution of alcohol/acetic acid (10/1) containing an amine **1*a–f*** (Fig. 1) and a 1 M CH_2Cl_2 solution of $TiCl_4$ was stirred at 0 °C under N_2 atmosphere. After 30 min, Zn powder (*ca.* 300 mg) was suspended in the reaction medium and an aqueous 80 wt% *t*-BuOOH solution, diluted in the same alcoholic solvent, was added dropwise over 1 h.

A possible reaction mechanism is proposed in Scheme 6. The Zn metal has a unique role in continuously converting Ti(IV) to Ti(III)

Table 1 Reaction of aliphatic and aromatic amines **1*a–f*** in alcoholic solvents



2*a-f*, 3*a-f*, 4*a*

				Yield, %[a] (yield, %)[b]	
entry	Amine	R^2-CH_2OH	Product	$TiCl_3$/*t*-BuOOH[c]	$TiCl_4$–Zn/*t*-BuOOH[d]
1	**1*a***	CH_3-	**2*a***	60[e,f]	26[e]
2	**1*a***	CH_3-	**2*a***	80[f]	50
3	**1*a***	CH_3-	**2*a***	80[f]	95 (89)[g]
4	**1*a***	CH_3-	**2*a***	80[f]	traces[h]
5	**1*a***	CH_3-	**2*a***	80[f]	traces[i]
6	**1*a***	CH_3CH_2-	**3*a***	59[f]	87 (80)
7	**1*a***	$CH_3CH_2CH_2$-	**4*a***	37[f]	35 (24)[j]
8	**1*b***	CH_3-	**2*b***	70[f]	96 (88)
9	**1*b***	CH_3CH_2-	**3*b***	12	82 (76)
10	**1*c***	CH_3-	**2*c***	82[f]	63 (57)
11	**1*c***	CH_3CH_2-	**3*c***	10	61 (52)
12	**1*d***	CH_3-	**2*d***	82[f]	36 (30)[j]
13	**1*d***	CH_3CH_2-	**3*d***	49[f]	50 (44)[j]
14	**1*e***	CH_3-	**2*e***	no product[f]	95 (91)
15	**1*e***	CH_3CH_2-	**3*e***	no product[f]	94 (88)
16	**1*f***	CH_3-	**2*f***	no product[f]	80 (75)
17	**1*f***	CH_3CH_2-	**3*f***	no product[f]	52 (43)

[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; yields based on converted amines were always ≥ 90%: the remaining material is mainly unreacted imine. [b] Yield of isolated products. [c] The aqueous 15 wt% $TiCl_3$ solution is added dropwise to the alcoholic solution of **1** and *t*-BuOOH. [d] The aqueous 80 wt% *t*-BuOOH solution is added dropwise to the alcoholic solution of **1** and TiC_4 in the presence of Zn powder. [e] H_2O_2 was used instead of *t*-BuOOH. [f] Data from ref. 16 [g] Acetic acid added. [h] No Zn. [i] No $TiCl_4$. [j] Complete conversion of the imine, poor selectivity.

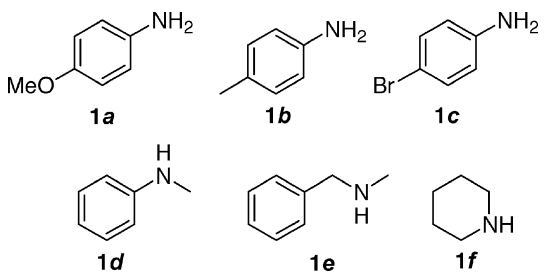
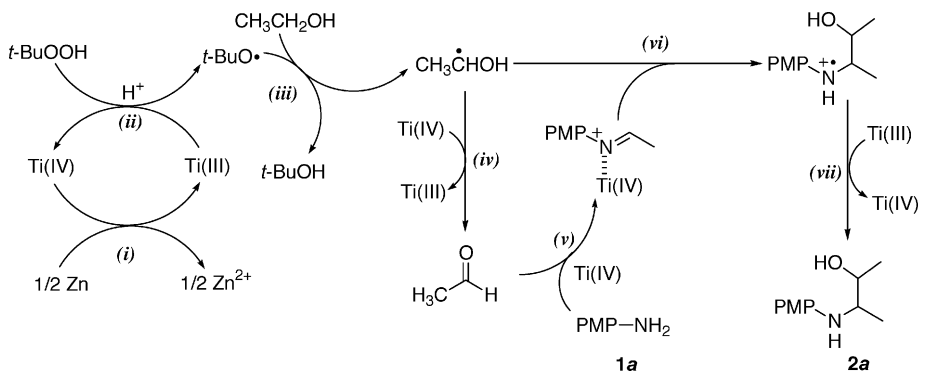


Fig. 1 Representative amines **1*a–f***.

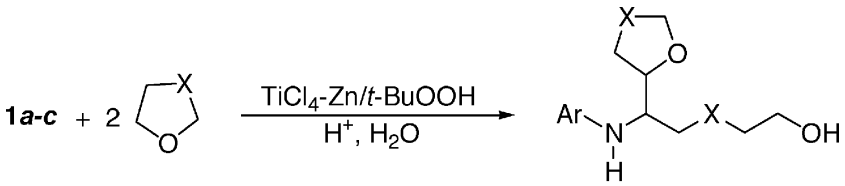
(path i). The violet Ti(III) acts, in turn, both as a radical initiator and as a radical terminator: in the first case, it promotes the formation of *tert*-butoxyl radical (*t*-BuO•) from the corresponding hydroperoxide (path ii) and in the latter case, it causes the reduction of the aminium radical intermediate (path vii). In both cases, the orange Ti(IV) is regenerated, prolonging the radical chain and justifying the colour oscillation, according to which the reaction looks like a titration and can be easily monitored and interrupted when a pale orange is barely maintained upon further addition of Zn.

t-Butoxy radical is able to promote the formation of ketyl radicals *via* α-H atom abstraction from the corresponding alcohols (path iii).[21] As previously discussed, ketyls can be easily oxidized to the corresponding carbonyl derivatives under aqueous acidic conditions.



Scheme 6 Proposed catalytic cycle for the reaction of PMP-NH_2 **1*a*** with EtOH, triggered by $TiCl_4$–Zn/*t*-BuOOH system.

Table 2 Reaction of primary arylamines **1*a–c*** in cyclic ether solvents



5*a-c*, 6*a-c*, 7*a-c*

Entry	Amine	X	Product	Yield, %[a] (yield, %)[b] $TiCl_3$/*t*-BuOOH[c]	Yield, %[a] (yield, %)[b] $TiCl_4$–Zn/*t*-BuOOH[d]
1	**1*a***	CH_2	**5*a***	96	96 (86)
2	**1*a***	CH_2CH_2	**6*a***	<5	76 (70)
3	**1*a***	OCH_2	**7*a***	no product	36 (32)
4	**1*b***	CH_2	**5*b***	22	84 (79)
5	**1*b***	CH_2CH_2	**6*b***	no product	70 (62)
6	**1*b***	OCH_2	**7*b***	no product	56 (50)
7	**1*c***	CH_2	**5*c***	no product	73 (68)
8	**1*c***	CH_2CH_2	**6*c***	no product	88 (83)
9	**1*c***	OCH_2	**7*c***	no product	55 (50)

[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; yields based on converted amines were always ≥ 90%: the remaining material is mainly unreacted imine. [b] Yield of isolated products. [c] The aqueous 15 wt% $TiCl_3$ solution is added dropwise to the alcoholic solution of **1** and *t*-BuOOH [d] The aqueous 80 wt% *t*-BuOOH solution is added dropwise to the alcoholic solution of **1** and TiC_4 in the presence of Zn powder.

However, while *t*-BuOOH proved to be responsible for ketyl oxidation in the $TiCl_3$/hydroperoxide mediated process[16] (Scheme 3, eq. 3), under our new reaction conditions the sole species capable of promoting the redox process is Ti(IV) (path iv).

The aldehyde, once formed, reacts with the amine present in solution under the coordinating effect of Ti(IV), affording the corresponding imine (path v). In addition, Ti(IV), being a strong Lewis acid, increases the electrophilicity of the C=N bond, activating the imine towards the selective nucleophilic radical addition by a second ketyl radical, driven by a marked polar effect (path vi).[22]

A series of amines was tested in order to verify the general scope of the reaction (Fig. 1). Primary arylamines **1*b*** and **1*c*** also led to the formation of the respective products **2*b***, **2*c***, **3*b*** and **3*c*** in good to excellent yields (Table 1, entries 8–11), while *N*-methylaniline **1*d*** was too reactive under our operating conditions, so that the complete conversion was not matched by a good selectivity (entries 12 and 13).

Finally, contrary to what is observed in the presence of the $TiCl_3$/*t*-BuOOH system, the aliphatic amines *N*-methyl benzylamine **1*e*** and piperidine **1*f*** easily reacted in both EtOH and PrOH, affording the corresponding products in high yields, while general aliphatic amines competed with the alcoholic solvent in the oxidative step, leading to the formation of mixtures of products.

The reaction of amines in cyclic ether solvents

In 2005, Tomioka and co-workers reported an intriguing dimethylzinc initiated radical reaction of two molecules of tetrahydrofuran (THF) with primary arylamines, leading to the formation of aminoalcohols in good yields.[23]

According to the proposed mechanism, the reaction proceeds *via* two consecutive steps. At first, the α-alkoxyalkyl radical, generated by α-hydrogen atom abstraction by a methyl radical, is oxidized to an electrophilic α-alkoxyalkyl cation, which then undergoes nucleophilic substitution by an amine nitrogen, affording the corresponding imine *via* ring opening. Subsequently, the imine reacts with a second nucleophilic α-alkoxyalkyl radical, providing a one-pot route for the synthesis of aminoalcohols.

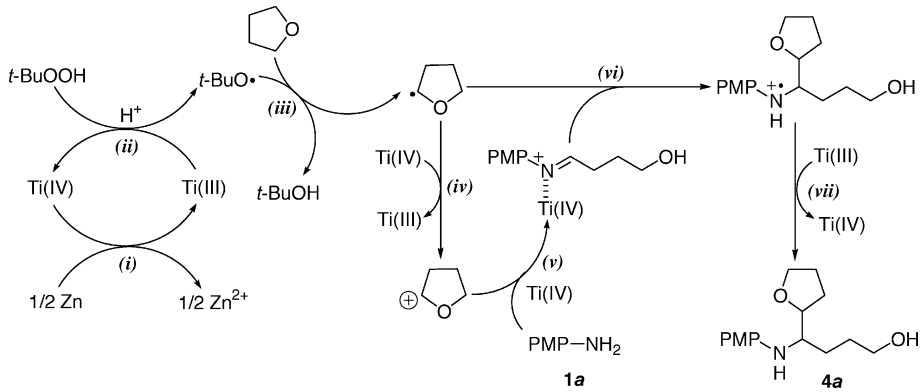
On this basis, with the aim of mimicking the domino approach in alcohol, we investigated the reactivity of primary arylamines in cyclic ether solvent and the results are reported in Table 2.

Indeed, we succeeded in obtaining the desired products in good to excellent yields under very mild conditions, with a protocol which seems to be more efficient and convenient compared with Tomioka's procedure: in fact, while the dimethylzinc process requires very long reaction times, high amounts of radical initiator and only THF afforded the desired product in high yields, on the contrary, our approach resulted of general applicability, not only with THF (**5*a–c***, entries 1, 4 and 7), but also with the less reactive cyclic ethers, like tetrahydropyran (THP) and dioxane, which led to the formation of the corresponding aminoalcohols (**6*a–c***, entries 2, 5 and 8 and **7*a–c***, entries 3, 6 and 9 respectively) in just three hours.

Once again, we compared the $TiCl_3$/*t*-BuOOH system with the $TiCl_4$–Zn/*t*-BuOOH one, the latter always being the most efficient in terms of the scope of the reaction.

Aliphatic and secondary aromatic amines were too reactive under our operating conditions, affording a mixture of several side products.

The general procedure was similar to that reported for the domino reaction in alcoholic solvents and the proposed mechanism (Scheme 7) is consistent with that described by Tomioka, the α-alkoxyalkyl radical being generated by α-hydrogen atom abstraction by *t*-BuO$^\bullet$ (path iii) and subsequently converted to the corresponding cation by the oxidative intervention of Ti(IV) (path iv).



Scheme 7 Proposed catalytic cycle for the reaction of PMP-NH_2 **1*a*** with THF, triggered by the $TiCl_4$–Zn/*t*-BuOOH system.

Conclusions

This investigation allowed us to develop an advantageous methodology for the synthesis of aminoalcohols by a simple radical domino approach promoted by the $TiCl_4$–Zn system and *t*-BuOOH.

Titanium species may be considered the regulators of the overall radical process. In the initiation step, Ti(III) promotes the redox decomposition of the hydroperoxide, leading to the generation of the radical species; in the propagation step Ti(IV) behaves both as an efficient oxidant, favouring the formation of the imine by oxidation of the ketyl radicals generated *in situ* in the presence of an amine, and as a strong Lewis acid, increasing the electrophilicity of the carbon atom in the α position to the nitrogen and activating the imine toward the addition of a second ketyl radical; finally, in the termination step Ti(III) has the role of reducing the aminium radical intermediate.

This protocol appears to be more efficient than the $TiCl_3$/*t*-BuOOH system previously reported by our group, since, when conducted in the presence of alcoholic solvent, it provides the desired products in higher yields and a wider range of amines resulted reactive.

Furthermore, we also demonstrated that this system could be successfully applied to cyclic ether solvents, affording a different class of aminoalcohols with a procedure which was more convenient and of more general application than the previously reported protocols.

Experimental

General

All materials were purchased from commercial suppliers without further purification. All reactions were performed at room temperature (20 °C) under an atmosphere of nitrogen. The following solutions were used: 1 M solution of $TiCl_4$ in CH_2Cl_2, 35 wt% aqueous solution of H_2O_2, 15 wt% acidic aqueous solution of $TiCl_3$ and 80 wt% aqueous solution of *t*-BuOOH.

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 a 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. Mass spectra were alternatively performed with a GC-MS instrument, using a gas chromatograph equipped with an SBP-1 fused silica column (30 m×0.2 mm i.d., 0.2 μm film thickness) and helium as a carrier gas.

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.

General procedure for the synthesis of aminoalcohols starting from amines 1*a–f* in alcoholic or cyclic ether solvent triggered by $TiCl_4$–Zn/*t*-BuOOH

A aqueous 80 wt% *t*-BuOOH solution (5 mmol, *ca.* 0.5 mL), diluted in 4.5 mL of alcohol (EtOH or PrOH) or cyclic ether (THF, THP or dioxane), was added dropwise to a well stirred homogeneous solution of the same solvent (10 mL) containing the amine (2 mmol), $TiCl_4$ (2.5 mmol) and AcOH (1 mL), with Zn powder in suspension (300 mg, *ca.* 5 mmol). The reaction looks like a titration which proceeds with periodic changes of color from orange to violet, and *t*-BuOOH was added until a pale orange was barely maintained upon further addition of Zn. At this point, the reaction was quenched with 5 mL of H_2O and added to a 30% aqueous NH_3 solution until basic pH (a white precipitate of Ti(IV) hydroxide was observed) and extracted with EtOAc (3 × 50 mL). The solution was then washed twice with 5 mL of H_2O in order to remove the remaining formamide, which is insoluble in $CHCl_3$ but very soluble in H_2O. The organic layers were then dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography of the crude residue afforded the desired products **2**, **3**, **4**, **5**, **6** and **7**. Yields of isolated products are based on the starting amine.

General procedure for the synthesis of aminoalcohols starting from amines 1*a–f* in alcoholic or cyclic ether solvent triggered by $TiCl_3$/*t*-BuOOH.

To 10 mL of a well stirred homogeneous solution of alcohol (EtOH or PrOH) or cyclic ether (THF, THP or dioxane) containing primary arylamines **1*a–f*** (2 mmol) and the hydroperoxide (5 mmol of 80% *t*-BuOOH, *ca.* 0.5 mL), a 15 wt% $TiCl_3$ solution was added dropwise such that a pale blue color was just maintained to ensure the complete decomposition of the peroxide. The solvent was removed *in vacuo* 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.

Isolation and characterization of the products

All the reaction products **2*a–f***, **3*a–f***, **4a**, **5*a–c***, **6*a–c*** and **7*a–c*** were isolated and fully characterized by MS, ^{1}H and ^{13}C NMR and HRMS (see ESI for compound spectra‡).

3-(4-Methoxy-phenylamino)-butan-2-ol, 2*a*[16]. Diastereoisomers **A** and **B** were isolated by FCC (Hexane/EtOAc, 7/3); total yield 89%. Diastereoisomer **A** (R_f major: 0.37); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3415, 2972, 1736, 1601, 1513, 1222, 737 cm^{-1}; ^{1}H 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; Diastereoisomer **B** (R_f minor: 0.33); FTIR (liquid film) ν_{max} 3415, 2972, 1736, 1601, 1513, 1222, 737 cm^{-1}; ^{1}H 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.

3-*p*-Tolylamino-butan-2-ol, 2*b*[16]. Diastereoisomers **A** and **B** have been isolated by FCC (Hexane/EtOAc, 8/2); total yield 88%. Diastereoisomer **A** (R_f major: 0.37); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3396, 2973, 1617, 1520, 1300, 809 cm^{-1}; ^{1}H 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; Diastereoisomer **B** (R_f minor: 0.33); FTIR (liquid film) ν_{max} 3396, 2973, 1617, 1520, 1300, 809 cm^{-1}; ^{1}H 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.

3-(4-Bromo-phenylamino)-butan-2-ol, 2*c*[16]. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 65/35) in a ratio 77/23; total yield 57%; appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3405, 2975, 1736, 1594, 1496, 757 cm^{-1};^{1}H 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 (2 C, **A** + **B**), 115.5, 115.9, 132.0 (2 C, **A** + **B**), 146.1, 146.4; MS (*m*/*z*): 244 (6), 242 (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**).

3-(Methyl-phenyl-amino)-butan-2-ol, 2*d*[16]. Diastereoisomers **A** and **B** were isolated by FCC (Hexane/EtOAc, 6/4); total yield 30%. Diastereoisomer **A** (R_f major = 0.37); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3355, 3019, 1583, 1216, 758 cm^{-1}; ^{1}H 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; Diastereoisomer **B** (R_f minor = 0.33); appearance pale yellow liquid; FTIR (liquid film) ν_{max} 3355, 3019, 1583, 1216, 758 cm^{-1}; ^{1}H 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.

3-(Benzyl(methyl)amino)butan-2-ol, 2*e*. Crude reaction ≥ 95%, no purification necessary to obtain the mix of the two diastereoisomers **A** and **B** in a ratio 1/1; appearance colourless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm) 0.95 (3H, CH_3, d, J = 6.4 Hz), 1.07 (3H, CH_3, d, J = 6.4 Hz), 1.15 (3H, CH_3, d, J = 6.4 Hz), 1.22 (3H, CH_3, d, J = 6.4 Hz), 2.12 (3H, NCH_3, s), 2.19 (3H, NCH_3, s), 2.47 (1H, CH, m), 2.56 (1H, CH, m), 3.41 (1H, CH, d, J = 13.4 Hz), 3.52 (1H, CH, m), 3.57 (1H, CH, d, J = 13.4 Hz), 3.62 (1H, CH, d, J = 13.4 Hz), 3.65 (1H, CH, d, J = 13.4 Hz), 3.88 (1H, CH, m), 7.23–7.34 (10H, 10Ar, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 7.4, 8.9, 19.3, 19.9, 35.7, 38.3, 58.0, 59.1, 62.9, 65.0, 67.2, 68.2, 126.9, 127.1, 128.2, 128.3, 128.6, 128.8, 138.8, 139.5; ESI-MS *m*/*z* 194 [M + H], 216 [M + Na]; HRMS calcd. for $C_{12}H_{19}NO$: 193.1467; found 193.1472 (mix **A** + **B**).

3-(Piperidin-1-yl)butan-2-ol, 2*f*. Crude reaction ≥ 80%, no purification necessary to obtain mix of the two diastereoisomers **A** and **B** in a ratio 1/1; appearance colourless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm) 0.86 (3H, CH_3, d, J = 6.4 Hz), 0.97 (3H, CH_3, d, J = 6.9 Hz), 1.11 (6H, $2CH_3$, m), 1.41–1.45 (4H, $2CH_2$, m), 1.51–1.61 (8H, $4CH_2$, m), 2.13–2.38 (4H, 2CH+2CH, m), 2.45–2.58 (6H,2CH+2CH+4CH, m), 3.21 (br, sign exc. with D_2O), 3.38 (1H, CH, m), 3.88 (1H, CH, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 0.8, 0.9, 19.3, 19.5, 24.5, 24.7, 26.5, 26.5, 51.5, 64.1, 66.5, 66.9, 66.9; ESI-MS *m*/*z*158 [M + H], 180 [M + Na]; HRMS calcd. for $C_9H_{19}NO$: 157.1467; found 157.1459 (mix **A** + **B**).

4-(4-Methoxy-phenylamino)-hexan-3-ol, 3*a*[16]. Diastereoisomer **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 80%. Diastereoisomer **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 (2 C, **A** + **B**), 61.4, 61.6, 73.9, 74.3, 115.0 (2 C, **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-(*p*-Tolylamino)hexan-3-ol, 3*b*. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 6/4) in a ratio 3 : 2; appearance colourless liquid; total yield 76%, ^1H NMR ($CDCl_3$) δ (ppm) 0.98–1.08 (12 H, 4 CH_3, m) 1.44–1.62 (4H, $2CH_2$, m, **A**), 1.65–1.77 (4H, $2CH_2$, m, **B**), 2.29 (6H, $2CH_3$, s), 3.21–3.25 (1H, CH, m, **A**), 3.31–3.35 (1H, CH, m, **B**), 3.53–3.57 (1H, CH, m, **A**), 3.65–3.69 (1H, CH, m, **B**), 6.62–6.64 (4H, 2CH Ar **A** + 2CH Ar **B**, m), 7.01–7.03 (4H, 2CH Ar **A** + 2CH Ar **B**, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 10.3, 10.6, 10.7, 11.1, 20.3, 22.9, 25.2, 25.9, 27.0, 59.7, 59.8, 74.3, 74.5, 113.8, 126.6, 126.7, 129.9, 146.1, 146.5; ESI-MS m/z 208 [M + H], 230 [M + Na]; HRMS calcd for $C_{13}H_{21}NO$: 207.1623; found 207.1615 (mix **A** + **B**).

4-(4-Bromophenylamino)hexan-3-ol, 3*c*. The mix of diastereoisomers A and B (R_f 0.35) in a 1 : 1 ratio was isolated by FCC (Hexane/EtOAc 6 : 4); total yield 52%; appearance pale yellow liquid; ^1H NMR (DMSO) δ (ppm) 0.78 (3H, CH_3, t, J = 7.5 Hz), 0.82 (3H, CH_3, t, J = 7.3 Hz), 0.83 (3H, CH_3, t, J = 7.5 Hz), 0.85 (3H, CH_3, t, J = 7.4 Hz), 1.21–1.78 (12H, 4 CH_2, m) 3.03–3.08 (1H, CH, m), 3.17–3.40 (3H, CH, m) 6.51–6.53 (4H, CH Ar, d, J = 8.8 Hz) 7.10– 7.12 (4H, CH Ar, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 10.1, 10.5, 10.5, 10.9 22.7, 25.1, 26.0, 26.9, 58.8, 59.2, 74.3, 74.4, 109.9, 116.6, 131.8, 145.4; MS (m/z) 271 (8) 212 (100); HMRS calcd for $C_{12}H_{18}BrNO$: 271.0572, found 271.0569 (mix **A+B**).

4-(Methyl-phenyl-amino)-hexan-3-ol, 3*d*[16]. Diastereoisomers **A** and **B** were isolated by FCC (Hexane/EtOAc, 8/2); total yield 44%. Diastereoisomer **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, CHAr, 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; Diastereoisomer **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.

3-(Benzyl(methyl)amino)hexan-3-ol, 3*e*. Crude reaction ≥ 95%, no purification necessary to obtain mix of the two diastereoisomers **A** and **B** in a 1/1 ratio; appearance colourless liquid; ^1H NMR ($CDCl_3$) δ (ppm) 1.00 (3H, CH_3, t, J = 7.4 Hz), 1.01 (3H, CH_3, t, J = 7.4 Hz), 1.03 (3H, CH_3, t, J = 7.4 Hz), 1.06 (3H, CH_3, t, J = 7.4 Hz), 1.26–1.75 (8H, 4 CH_2, m), 2.21 (3H, CH_3, s), 2.24 (3H, CH_3, s), 2.33–2.38 (1H, CH, m), 2.56–2.60 (1H, CH, m), 3.23–3.32 (1H, CH, m), 3.55–3.59 (1H, CH, m), 3.61 (1H, CH benz, d, J = 13.4 Hz), 3.64 (1H, CH benz, d, J = 13.4 Hz), 3.71 (1H, CH benz, d, J = 13.4 Hz), 3.78 (1H, CH benz, d, J = 13.4 Hz), 7.22–7.31 (10H, CH Ar, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 10.2, 11.2, 12.3, 13.7, 18.7, 19.1, 23.1, 26.5, 26.7, 26.9, 36.1, 38.7, 59.3, 59.9, 68.4, 69.8, 71.5, 73.0, 126.9, 127.1, 128.2, 128.4, 128.5, 128.8, 139.2, 140.0; ESI-MS m/z 222 [M + H], 244 [M + Na]; HRMS calcd for $C_{14}H_{23}NO$: 221.1780; found 221.1786 (mix **A** + **B**).

4-(Piperidin-1-yl)hexan-3-ol, 3*f*. Diastereoisomers **A** and **B** were isolated by FCC ($CHCl_3$–MeOH, 8/2); total yield 43%. Diastereoisomer **A** (R_f major = 0.38); appearance colourless liquid; ^1H NMR ($CDCl_3$) δ (ppm) 0.99 (3H, CH_3, t, J = 7.4 Hz), 1.04 (3H, CH_3, t, J = 7.4 Hz), 1.24–1.34 (4H, m, 2 CH_2), 1.45–1.49 (2H, m, CH_2), 1.54–1.67 (4H, m, $2CH_2$), 2.11–2.16 (1H, m, CH), 2.45–2.50 (2H, m, CH_2), 2.72–2.78 (2H, m, CH_2), 3.15–3.20 (1H, m, CH); ^{13}C NMR ($CDCl_3$) δ (ppm) 10.2, 13.7, 19.3, 24.6, 26.7, 27.1, 51.2, 70.6, 71.3. ESI-MS m/z 186 [M + H], 208 [M + Na]; Diastereoisomer **B** (R_f minor = 0.32); appearance colourless liquid;^1H NMR ($CDCl_3$) δ (ppm) 0.96 (3H, CH_3, t, J = 7.3 Hz), 1.00 (3H, CH_3, t, J = 7.3 Hz), 1.26–1.31 (1H, m, CH), 1.41–1.49 (4H, m, $2CH_2$), 1.55–1.70 (5H, m, $2CH_2$ + 1CH), 2.40–2.45 (1H, m, CH), 2.53–2.59 (2H, m, CH_2), 2.65–2.71 (2H, m, CH_2), 3.48–3.52 (1H, m, CH); ^{13}C NMR ($CDCl_3$) δ (ppm) 11.5, 12.4, 18.6, 24.6, 26.1, 26.7, 52.3, 70.2, 72.4. ESI-MS m/z 186 [M + H], 208 [M + Na]; HRMS calcd for $C_{11}H_{23}NO$: 185.1780; found 185.1773 (mix **A** + **B**).

5-(4-Methoxy-phenylamino)-octan-4-ol, 4*a*[16]. Diastereoisomer **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 24%. Diastereoisomer **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 (2 C, **A** + **B**), 14.5 (2 C, **A** + **B**), 19.4, 19.7, 19.8, 20.0, 32.6, 35.2 (2 C, **A** + **B**), 36.6, 56.1 (2 C, **A** + **B**), 59.4, 60.1, 72.6, 73.5, 115.3 (2 C, **A** + **B**), 115.4 (2 C, **A** + **B**), 142.8, 143.2, 152.6 (2 C, **A** + **B**); MS (*m/z*) 251(3), 178 (100); HRMS calcd for $C_{15}H_{25}NO_2$: 251.1885; found 251.1877.

4-(4-Methoxyphenylamino)-4-(tetrahydrofuran-2-yl)butan-1-ol, 5*a*[23]. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 2/8) in a 1/1 ratio; total yield 86%; appearance brown liquid; ^1H NMR ($CDCl_3$) δ (ppm): 1.42–1.96 (m, 8H), 3.29–3.37 (m, 1H), 3.59–3.77 (m, 3H), 3.74 (s, 3H), 3.81–4.00 (m, 2H), 6.56–6.65 (m, 2H), 6.74–6.76 (m, 2H). ^{13}C NMR: 25.9, 26.1, 28.0, 28.1, 28.2, 29.4, 29.56, 29.60, 55.75, 55.78, 56.5, 58.4, 62.9 (overlap), 68.3, 68.6, 80.8, 81.2, 114.6, 114.9, 115.0, 115.6, 142.0, 142.5, 151.9, 152.4. IR: 3380, 1510, 1040. MS: 265 (M^+), 194 ($M^+ - C_4H_7O$), 107 ($C_6H_4OCH_3$), 71 (C_4H_7O). HRMS: calcd for $C_{15}H_{23}NO_3$, 265.1678; found, 265.1671 (mix **A** + **B**).

4-(Tetrahydrofuran-2-yl)-4-(p-tolylamino)butan-1-ol, 5*b*[23]. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 2/8) in a 1/1 ratio; total yield 79%; appearance brown liquid; ^1H NMR ($CDCl_3$) δ (ppm) 1.50–1.89 (16H, CH, m), 2.14 (6H, 2CH_3, s), 3.28 (2H, CH, m), 3.53 (4H, CH,m), 3.61–3.69 (2H, CH, m), 3.73–3.84 (3H, CH, m), 3.89–3.94 (1H, CH, m), 5.69 (sb, NH), 6.45 (2H, Ar, d, J = 8.4 Hz), 6.49 (2H, Ar; d, J = 8.4 Hz), 6.87 m (4H, Ar, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 20.1, 20.2, 25.8, 26.0, 28.0, 28.1, 28.2, 29.3, 29.4, 29.5, 55.6, 57.2, 62.7, 62.7, 68.1, 68.5, 80.8, 51.5, 113.0, 113.7, 129.6, 129.7, 132.5, 132.9, 145.7, 146.0; ESI-MS *m/z* 250 [M + H], 272 [M + Na]; HRMS: calcd for $C_{15}H_{23}NO_2$, 249.1729; found, 249.1722 (mix **A** + **B**).

4-(4-Bromophenylamino)-4-(tetrahydrofuran-2-yl)butan-1-ol, 5*c*. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 6/4) in a 1/1 ratio; total yield 68%; appearance colourless liquid; ^1H NMR ($CDCl_3$) δ (ppm) 1.39–1.46 (1H, CH, m), 1.52–1.59 (3 H, CH_2 + CH, m), 1.64–1.77 (6H, 3 CH_2, m), 1.82–1.94 (6H, 3 CH_2, m), 3.39–3.42 (2H, CH_2, m), 3.51–3.54 (4 H, 2 CH_2, m), 3.67–3.79 (3H, m), 3.84–3.89 (2H, m), 3.92–3.97 (1H, m), 4.71 (2H, 2 OH, br, sign. exch. with D_2O), 6.53–6.58 (4H, CH Ar, m), 7.11–7.14 (4H, CH Ar, m). ^{13}C NMR ($CDCl_3$) δ (ppm) 17.2, 17.4, 19.1, 19.4, 20.0, 20.4, 20.6, 20.9, 47.2, 48.0, 53.4, 59.6, 59.8, 73.1, 74.0, 98.5, 105.7, 105.9, 123.0, 123.1, 140.2. ESI-MS *m/z* 313, 315 [M + H], 335, 337 [M + Na]; HRMS: calcd for $C_{14}H_{29}BrNO_2$, 313.0677; found, 313.0684 (mix **A** + **B**).

5-(4-Methoxyphenylamino)-5-(tetrahydro-2*H*-pyran-2-yl)-pentan-1-ol, 6*a*. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 6/4) in a 1/1 ratio; total yield 70%; appearance pale orange liquid; ^1H NMR ($CDCl_3$) δ (ppm) 1.36–1.77 (22H, 20CH_2+2CH_a, m), 1.90 (2H, 2CH_b, m), 3.17 (2H, 2CH, m), 3.30 (2H, 2CH_a, m), 3.39 (2H, 2CH_b, m), 3.59 (4H, 2CH_2, m), 3.72 (3H, OCH_3, s), 3.72 (3H, OCH_3, s), 3.99 (2H, 2CH, m), 6.53 (2H, 2Ar, d, J = 8.9 Hz), 6.55 (2H, 2Ar, d, J = 8.9 Hz) 6.72–6.75 (4H, 4Ar, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6, 22.7, 23.4, 23.6, 26.2, 26.2, 28.1, 28.6, 30.3, 31.6, 32.8, 55.8, 55.8, 57.8, 58.6, 62.7, 68.7, 78.8, 79.9, 114.0, 115.0, 115.1, 142.6, 142.9, 151.5, 151.9; MS (*m/z*): 293 (9), 208 (100), 190 (5), 134 (9), 85 (13), 41 (12). HRMS: calcd for $C_{17}H_{27}NO_3$, 293.1991; found, 293.1985 (mix **A** + **B**).

5-(*p*-Tolylamino)-5-(tetrahydro-2*H*-pyran-2-yl)pentan-1-ol, 6*b*. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 8/2) in a 1/1 ratio; total yield 62%; appearance pale orange liquid; ^1H NMR ($CDCl_3$) δ (ppm) 1.29–1.41 (12H, 6 CH_a, m), 1.44–1.53 (10H, 5 CH_a, m), 1.67–1.74 (2H, CH_a, m), 2.13 (6H, 2CH_3, s), 3.13–3.18 (2H, CH, m), 3.20–3.37 (4H, m), 3.49–3.52 (4H, m), 3.88–3.93 (2H, 2 CH, m), 6.42 (4H, 4 CH Ar, m), 6.85–6.87 (4H, 4 CH Ar, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.1, 22.5, 22.7, 23.3, 23.4, 26.1, 27.9, 28.6, 30.3, 31.6, 32.7, 56.9, 57.6, 62.5, 68.6, 78.8, 80.8, 112.7, 113.5, 125.4, 126.0, 129.6, 146.0, 146.2; ESI-MS *m/z* 278 [M+ H], 300 [M + Na]; HRMS calcd for $C_{17}H_{27}NO_2$, 277.2042; found 277.2049 (mix **A** + **B**).

5-(4-Bromophenylamino)-5-(tetrahydro-2*H*-pyran-2-yl)pentan-1-ol, 6*c*. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 6/4) in a 1/1 ratio; total yield 83%; appearance pale orange liquid; ^1H NMR ($CDCl_3$) δ (ppm) 1.33–1.87 (24H, 12 CH_2, m), 3.18–3.45 (6H, 3 CH_2, m), 3.59–3.65 (4H, CH_2 + 2CH, m), 3.96–4.01 (2H, 2 CH, m), 6.43–6.47 (4H, 4CH Ar, m), 7.18–7.21 (4H, 4CH Ar, m);^{13}C NMR ($CDCl_3$) δ (ppm): 22.6, 22.7, 23.3, 23.5, 26.1, 26.2, 28.3, 28.5, 30.4, 31.8, 32.8, 56.9, 57.4, 62.7, 68.8, 7.6, 80.0, 107.7, 108.2, 114.2, 114.8, 131.9, 147.3, 147.6; ESI-MS *m/z* 341, 343 [M + H], 363, 365 [M + Na]; HRMS calcd for $C_{16}H_{24}BrNO_2$, 341.0990; found 341.0996 (mix **A** + **B**).

2-(2-(1,4-Dioxan-2-yl)-2-(4-methoxyphenylamino)ethoxy)ethanol, 7*a*. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 4/6) in a 1/1 ratio; total yield 32%; appearance pale orange liquid; ^1H NMR ($CDCl_3$) δ (ppm) 3.31 (2H, CH, m), 3.41–3.54 (10H, CH, m), 3.56–3.62 (10H, CH, m), 3.64 (6H, OCH_3, s), 3.66–3.73 (4H, CH, m), 3.80 (1H, CH, dt, J = 10.1, 2.8 Hz), 3.86 (1H, CH, dd, J = 11.5, 2.0 Hz), 6.50 (2H, 2CH Ar, d, J = 8.7 Hz), 6.51 (2H, 2CH Ar, d, J = 8.9 Hz), 6.68 (4H, 4CHAr; d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 54.5, 55.6, 55.7, 55.8, 61.5, 61.6, 66.3, 66.5, 66.7, 67.0, 68.6, 68.7, 69.5, 69.7, 72.3, 72.4, 74.6, 75.2, 114.7, 114.9, 115.0, 115.5, 141.2, 141.4, 152.3, 152.6; MS (*m/z*): 297 (21), 222 (32), 210 (67), 148 (100), 136 (41), 117 (19), 107 (14), 77 (19), 45 (32); ESI-MS *m/z*. 298 [M + H], 320 [M + Na], 336 [M + K]; HRMS calcd for $C_{15}H_{23}NO_5$, 297.1576; found 297.1583 (mix **A** + **B**).

2-(2-(1,4-Dioxan-2-yl)-2-(*p*-tolylamino)ethoxy)ethanol, 7*b*. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 5/5) in a 1/1 ratio; total yield 50%; appearance pale orange liquid; ^1H NMR ($CDCl_3$) δ (ppm) 2.14 (6H, 2 CH_3, s), 3.37–3.41 (4H, 2CH_2, m), 3.47 (4H, 2CH_2, m), 3.50–3.54 (4H, 2CH_2, m), 3.57–3.64 (10H, m), 3.67–3.73 (4H, m), 3.81–3.86 (2H, 2 CH, m), 6.44–6.47 (4H, 4CH Ar, m), 6.87–6.89 (4H, 4CH Ar, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 20.2, 53.5, 54.7,

61.5, 61.6, 66.3, 66.4, 66.7, 67.0, 68.7, 68.8, 69.5, 69.6, 72.4, 74.4, 75.3, 113.2, 114.0, 126.7, 129.8, 144.8, 144.9; ESI-MS *m/z*. 282 [M + H], 304 [M + Na], 320 [M + K]; HRMS calcd for $C_{15}H_{23}NO_4$: 281.1627; found 281.1632 (mix **A** + **B**)

2-(2-(1,4-Dioxan-2-yl)-2-(4-bromophenylamino)ethoxy)ethanol, 7*c*. The mix of the diastereoisomers **A** and **B** (R_f 0.35) was isolated by FCC (Hexane/EtOAc, 5/5) in a 1/1 ratio; total yield 50%; appearance pale orange liquid; ^{1}H NMR (DMSO) δ (ppm) 3.33–3.63 (24H, 12CH_2, m), 3.70–3.78 (24H, 12CH_2, m), 4.48 (1H, OH, exch. with D_2O, J = 5.6 Hz), 4.51 (1H, OH, exch. with D_2O, J = 5.3 Hz), 5.50 (1H, NH, exch. with D_2O, J = 8.1 Hz), 5.59 (1H, NH, exch. with D_2O, J = 8.1 Hz), 6.59–6.62 (4H, 4 CH Ar, m), 7.15–7.17 (4H, 4 CH Ar, m); ^{13}C NMR ($CDCl_3$) δ (ppm) 53.3, 54.2, 60.3, 61.5, 61.6, 66.3, 66.4, 66.6, 67–0, 68.6, 68.7, 69.2, 69.4, 72.4, 74.2, 75.1, 109.0, 109.3, 114.6, 115.1, 131.9, 132.0, 146.2; ESI-MS *m/z* 345, 347 [M + H], 367, 369 [M + Na]; HRMS calcd for $C_{14}H_{20}BrNO_4$: 345.0576; found 345.0570 (mix **A** + **B**).

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