Tetrahedron 68 (2012) 10151–10156

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Free-radical hydroxymethylation of ketimines generated in situ: a one-pot multicomponent synthesis of β,β-disubstituted-β-aminoalcohols

Bianca Rossi, Nadia Pastori, Angelo Clerici, Carlo Punta *

Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano, P.zza Leonardo da Vinci 32, 20133 Milano, Italy

ARTICLE INFO

Article history:
Received 12 July 2012
Received in revised form 10 September 2012
Accepted 25 September 2012
Available online 29 September 2012

Keywords:
Aminoalcohols
Ketimine
Multicomponent reaction
Free-radical addition
$TiCl_4$
Zn

ABSTRACT

We report how an acidic $TiCl_4$–Zn/*t*-BuOOH system is able to promote the one-pot multicomponent synthesis of β,β-disubstituted-β-aminoalcohols via nucleophilic addition of a hydroxymethyl radical to activated ketimines generated in situ in methanol solvent. While ketimines are generally recognized as less reactive and less stable when compared with aldimines, Ti(IV) plays a key role in facilitating their formation and in enhancing their electrophilic character. As a consequence, the reaction occurs at room temperature and under non-anhydrous conditions in just 1 h, without requiring either the preformation of the ketimine or protection of the amino group. The scope of the reaction is widely explored and a possible mechanism is discussed.

1. Introduction

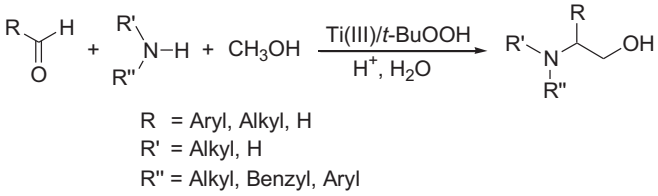
The vicinal amino alcohol functionality is present in a wide range of naturally occurring and synthetic molecules. In particular, β-aminoalcohols find extensive use as fundamental building blocks for the synthesis of drugs,[1] receptor modulators,[2] and fungistatic molecules.[3]

Among the several methodologies reported for the synthesis of these compounds, the commonly followed approaches are epoxide ring opening with amines,[3a,4] the aminohydroxylation of terminal C=C bonds[5] and the hydrogenation of α-amino esters.[6]

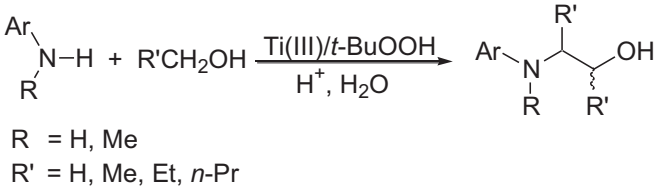
Nevertheless, in the last decade the nucleophilic addition of carbon centered radicals to imine derivatives has been shown to be a suitable alternative for obtaining substituted amines of chemical and biological relevance.[7,8]

In 2008 we reported how the $TiCl_3$/*t*-BuOOH system was able to promote the one-pot multicomponent free-radical synthesis of β-aminoalcohols by selective hydroxymethylation of aldimines generated in situ (Scheme 1).[9]

More recently we have also shown that, by operating in the absence of an aldehyde and in an alcoholic solvent, a similar system is able to promote a domino reaction, leading to the formation of α,β-disubstituted-β-aminoalcohols (Scheme 2).[10]



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



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

Since it is well known that the substitution pattern of the moiety significantly affects the biological activity of amino alcohols,[11] we wanted to investigate the applicability of our free-radical approach to the one-pot synthesis of β,β-disubstituted-β-aminoalcohols, by promoting the direct hydroxymethylation of ketimines generated in situ.

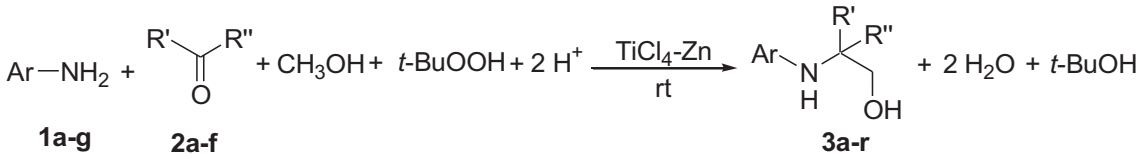
* Corresponding author. Tel.: +39 0223993026; fax: +39 0223993180; e-mail address: carlo.punta@polimi.it (C. Punta).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.09.107

The extension of the protocol to ketimines is not obvious, as they are generally recognized to be less reactive toward nucleophilic substitution (poor electrophilicity of the C=N bond) and less stable in aqueous medium, when compared with aldimines,[12] usually requiring preformation and anhydrous operating conditions during the reductive addition, in order to inhibit fast hydrolysis.

We recently succeeded in developing the selective carbamoylation of ketimines from formamide, via a previously reported protocol for the analogous functionalization of aldimines,[13] by replacing the aqueous $TiCl_3$ with stoichiometric amounts of an anhydrous $TiCl_4$ solution in CH_2Cl_2 in the presence of Zn powder and H_2O_2.[14]

As a part of our ongoing investigation on the general applicability of the above mentioned protocol in solvents different from formamide, herein we report the selective synthesis of β,β-disubstituted-β-aminoalcohols by the one-pot assembly of a primary aryl amine and a ketone in methanol solvent, promoted by the $TiCl_4$–Zn/*t*-BuOOH system (Scheme 3).



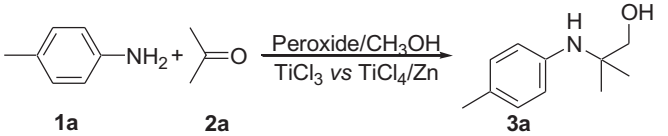
Scheme 3. $TiCl_4$–Zn/*t*-BuOOH mediated hydroxymethylation of imines generated in situ.

To the best of our knowledge, this represents the first example of direct radical hydroxymethylation of ketimines generated in situ under aqueous conditions.

2. Results and discussion

The results related to the optimization of the reaction conditions are reported in Table 1 using *p*-toluidine **1a** and acetone **2a** as the representative aniline and ketone, respectively.

Table 1
Radical addition of methanol to ketimines generated in situ from *p*-toluidine and acetone[a]



Entry	$TiCl_3$ (mmol)	$TiCl_4$ (mmol)	Zn (mmol)	Hydroperoxide	**3a** Yield[b] (%)
1	8	—	—	*t*-BuOOH	8
2[c]	—	1.7	5	H_2O_2	11
3	—	1.7	5	*t*-BuOOH	46
4	—	3.4	10	*t*-BuOOH	75
5	—	1.7	—	*t*-BuOOH	—
6	—	—	5	*t*-BuOOH	—
7[d]	1	3.4	—	*t*-BuOOH	10

[a] Compound **1a** (2 mmol) was reacted with 5 mmol of **2a** in 10 mL of methanol.
[b] Yield determined by ^1H NMR spectroscopy with acetophenone added as an internal standard to the crude reaction mixture after work up.
[c] Complete conversion.
[d] *t*-BuOOH (1 mmol) was added.

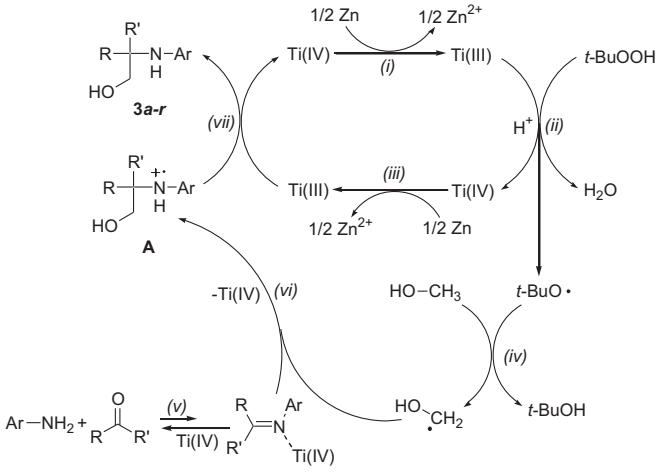
As expected, the use of the aqueous $TiCl_3$/*t*-BuOOH system was detrimental for the reaction, affording poor results in terms of conversion (Table 1, entry 1). This result reflected the low stability of ketimines under non-anhydrous conditions, as explained before.

A first attempt to apply the $TiCl_4$–Zn/H_2O_2 system, previously disclosed for the selective carbamoylation of ketimines, led to complete conversion of the starting aniline, due to the expected higher stability of the imine, but with very low selectivity for the desired product (entry 2). This behavior was ascribed to the high oxidizing power of hydrogen peroxide, which was able to convert the ketyl radical, generated by hydrogen abstraction from methanol, in to formaldehyde.[10] This latter competed with acetone, leading to the formation of the corresponding aldimine and the related products of mono- and di-substitution.[9]

To verify this hypothesis, we wanted to investigate the action of the milder oxidant *tert*-butyl hydroperoxide (*t*-BuOOH) under our operating conditions. Indeed, the desired product was obtained in 46% yield by simply replacing H_2O_2 with *t*-BuOOH (entry 3), while a further increase of the yield up to 75% was obtained by operating with double the amount of $TiCl_4$ and Zn with respect to the reported procedure (entry 4).

The reaction proceeded with changes of color from orange to violet, proving the periodic variation of the oxidation state of titanium ion from III (typical violet solution) to IV (typical orange color), while in the absence of both Zn (entry 5) and $TiCl_4$ (entry 6) no reaction was observed.

This behavior suggests the possible reaction mechanism reported in Scheme 4. Ti(III) (violet solution) is oxidized to Ti(IV) (orange solution) by both the hydroperoxide (path *ii*), leading to the formation of *tert*-butoxyl radical, and the aminium radical intermediate **A** (path *vii*). Ti(IV) is then reduced to Ti(III) by Zn, so prolonging the redox cycle and justifying the color oscillation. The *tert*-butoxyl radical is, in turn, responsible for the formation of the hydroxymethyl radical by hydrogen abstraction from methanol (path *iv*), while Ti(IV) acts as a Lewis acid, promoting the formation of the ketimine and enhancing its electrophilic character (path *v*–*vi*).



Scheme 4. Reaction mechanism.

Even if aminyl radicals are known to be excellent H-atom abstractors,[15] intermediate **A** seems not to be significantly involved in hydroxymethyl radical formation, undergoing faster reduction to the final product by means of Ti(III). In fact, if **A** would undergo

hydrogen abstraction from methanol, just tiny amounts of hydroperoxide would have been sufficient to promote the free-radical chain. Nevertheless, when the $TiCl_3$/*t*-BuOOH system was employed in catalytic amounts, in the presence of an excess of $TiCl_4$ to guarantee the coordination effect of the Lewis acid, poor results were observed in terms of converted material (Table 1, entry 6).

The intervention of the aminyl radical in the hydrogen abstraction step was previously observed by our group in the presence of secondary *N*-methyl aniline, when applying the $TiCl_3$/*t*-BuOOH system in alcoholic solvent to promote the domino synthesis of α,β-disubstituted-β-aminoalcohols.[10a] In that case, reaction stoichiometry required just 1 equiv of hydroperoxide per mmol of aniline, against the 2 equiv necessary when reacting primary aryl amines (Scheme 2).

With these results in hand, we wanted to explore the scope of the reaction by testing a range of aryl amines bearing different substituents on the aromatic ring (**1a**–**h**, Fig. 1) in the presence of both acyclic (**2a**–**c**, Fig. 2) and cyclic (**2d**–**f**, Fig. 2) ketones. The results reported in Tables 2 and 3, respectively, clearly demonstrate the general efficiency of the protocol.

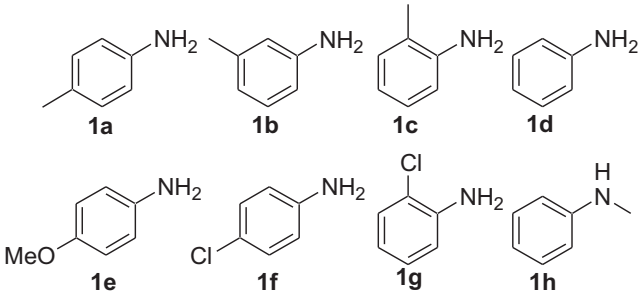


Fig. 1. Representative aryl amines **1a**–**h**.

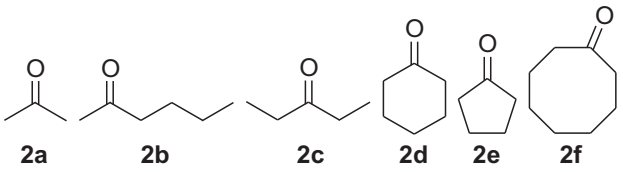


Fig. 2. Representative ketones **2a**–**f**.

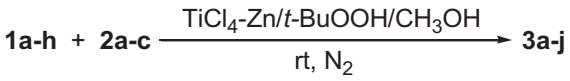
In analogy with what was observed for hydroxymethylation of aldimines[9] and carbamoylation of ketimines,[14] steric hindrance around the C=N bond negatively affected the reaction. Yields progressively decreased when the position of substituents on the aromatic ring of aryl amines was changed from *para* to *meta* and *ortho* (entries 1–3, Tables 2 and 3).

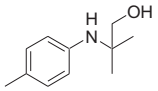
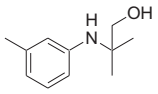
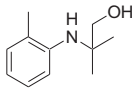
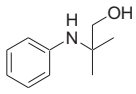
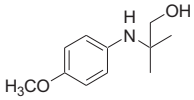
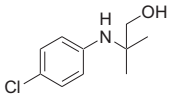
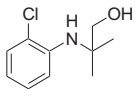
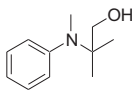
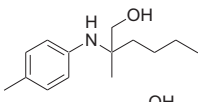
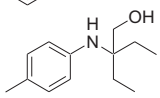
For the same reasons, the efficiency of the reaction progressively decreased by increasing the length of the ketone side-chains (entries 9 and 10, Table 2) or the size of the ring of cyclic ketones, like for cyclooctanone (entry 10, Table 3).

The reaction is relatively insensitive to the polar nature of the substituents on the aromatic ring of aniline, indicating that the polarization of the C=N bond induced by Ti(IV) complexation overcomes the substituent effect.

Any attempt to extend the protocol to secondary *N*-methyl aniline **1h** afforded a mixture of side products (entry 8, Table 2). Indeed, fast demethylation of **1h** occurred, leading to the formation of aniline **1d** and formaldehyde. The latter favored the formation of aldimines with both **1h** and **1d**, introducing competitive electron-poor substrates suitable for nucleophilic radical addition. Thus,

Table 2
Radical hydroxymethylation of ketimines generated from aryl amines and acyclic ketones[a]



Entry	1	2	3 Yield[b], % (yield[c], %)
1	**1a**	**2a**	 **3a**: 68 (75)
2	**1b**	**2a**	 **3b**: 52 (58)
3	**1c**	**2a**	 **3c**: 32 (40)
4	**1d**	**2a**	 **3d**: 71 (78)
5	**1e**	**2a**	 **3e**: 59 (65)
6	**1f**	**2a**	 **3f**: 64 (70)
7	**1g**	**2a**	 **3g**: 47 (52)
8[d]	**1h**	**2a**	 **3h**: — (20)
9	**1a**	**2b**	 **3i**: 60 (65)
10	**1a**	**2c**	 **3j**: 17 (22)

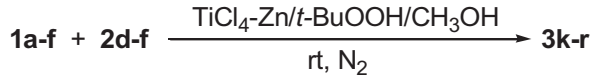
[a] The molar ratio of **1**/**2**/TiCl4/Zn was 1:2.5:1.7:5.
[b] Yield of isolated products are based on the starting amine; yields based on converted amines were always ≥90%.
[c] Yield determined by ^{1}H NMR spectroscopy with acetophenone added as an internal standard to the crude reaction mixture after work up.
[d] Selectivity for the desired product was lower than 30%. See Fig. 3.

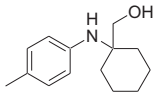
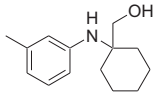
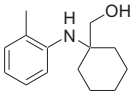
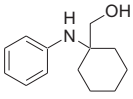
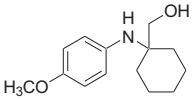
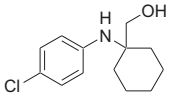
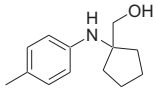
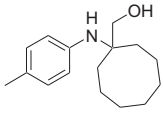
besides the desired product **3h**, derivatives **3s**–**u** were also found in the final crude mixture (Fig. 3). Furthermore, **1d** also reacted with the excess of acetone leading to the formation of significative amounts of **3d**.

3. Conclusions

In conclusion, the protocol reported herein represents a novel synthesis of a new class of β,β-disubstituted-β-aminoalcohols. These derivatives, most of which have never been synthesized before, were prepared in a one-pot manner by simply assembling a ketone, a primary aryl amine and methanol at room temperature

Table 3
Radical hydroxymethylation of ketimines generated from aryl amines and cyclic ketones[a]



Entry	1	2	3 Yield[b], % (yield[c], %)
1	**1a**	**2d**	 **3k**: 69 (77)
2	**1b**	**2d**	 **3l**: 60 (65)
3	**1c**	**2d**	 **3m**: 53 (59)
4	**1d**	**2d**	 **3n**: 57 (59)
5	**1e**	**2d**	 **3o**: 65 (73)
6	**1f**	**2d**	 **3p**: 88 (96)
9	**1a**	**2e**	 **3q**: 58 (65)
10	**1a**	**2f**	 **3r**: 27 (35)

[a] The molar ratio of **1**/**2**/$TiCl_4$/Zn was 1:2.5:1.7:5.
[b] Yield of isolated products are based on the starting amine; yields based on converted amines were always ≥90%.
[c] Yield determined by ^1H NMR spectroscopy with acetophenone added as an internal standard to the crude reaction mixture after work up.

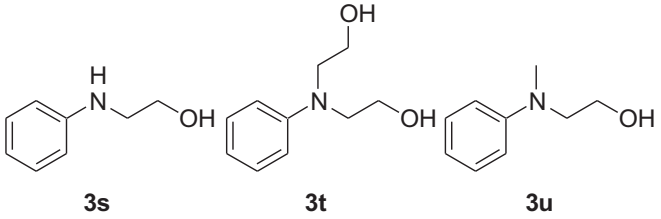


Fig. 3. Side products **3s**–**u** deriving from **1h**.

under non-anhydrous conditions in just 1 h, without requiring ether preformation of ketimine or protection of the amino group. Only a very bulky substituent at the C atom of the intermediate ketimine or in the *ortho* position on the aromatic ring of anilines depresses the yield of **3**.

Further investigations will be devoted to the optimization of this protocol in order to extend the methodology to a wider range of alcohols and ethers, inhibiting the competitive domino reaction, which tends to occur in the presence of these sources of nucleophilic radicals.[10]

4. Experimental section

4.1. General experimental methods

All materials were purchased from commercial suppliers and used without further purification. All reactions were performed at room temperature (20 °C) under atmosphere of nitrogen. The following solutions were used: 1 M solution of $TiCl_4$ in CH_2Cl_2 and 80 wt % solution of *t*-BuOOH. NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C. 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 carrier gas. IR spectra were obtained by Varian 640 high-performance FTIR spectrometer. Melting points were measured on Köppfler apparatus and are uncorrected.

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.

4.2. General procedure for the synthesis of β,β-disubstituted-β-aminoalcohols starting from aryl amines and ketones

An aqueous 80 wt % solution of *t*-BuOOH (10 mmol, ca. 1.24 mL), diluted in methanol (9 mL), was added dropwise to a well stirred homogeneous solution of methanol (10 mL) containing aryl amine (2 mmol), cyclic or acyclic ketone (5 mmol), $TiCl_4$ (1.7 mmol), 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, *t*-BuOOH was added until a pale orange was barely maintained. At this point, a second portion of $TiCl_4$ (1.7 mmol) and Zn powder in suspension (300 mg, ca. 5 mmol) was added and *t*-BuOOH was added again dropwise until the solution reached a stable orange color. The reaction was then quenched with of H_2O (5 mL) and added with 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 combined organic layers were then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography of the crude residue afforded the hydroxymethylamine **3** as the last eluted products.

Yields of isolated products are based on the starting amine.

*4.2.1. 2-Methyl-2-(p-tolylamino)propan-1-ol (**3a**).* Purification by FCC (Hex/AcOEt 1:2, R_f=0.35) afforded a yellow oil (243.6 mg, 68% isolated yield); FTIR (liquid film) ν_{max} 3390, 2969, 2921, 1616, 1512, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.19 (s, 6H, 2× CH_3); 2.26 (s, 3H, CH_3); 3.47 (s, 2H, CH_2); 3.47 (s, 2H, CH_2); 6.71–6.74 (m, 2H, 2CH Ar); 6.98–7.00 (m, 2H, 2CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.1, 25.0, 55.4, 69.4, 120.5, 129.5, 130.2, 143.0; GC–MS (*m*/*z*): 148 (100), 179 (5.6), 106 (11.6). HRMS (EI): M^+, calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1315.

*4.2.2. 2-Methyl-2-(m-tolylamino)propan-1-ol (**3b**).* Purification by FCC (CH_2Cl_2/AcOEt 1:1, R_f=0.35) afforded an orange oil (207.8 mg, 52% isolated yield); FTIR (liquid film) ν_{max} 3381, 2969, 2926, 1606, 1487 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23 (s, 6H, 2× CH_3), 2.27 (s, 3H, CH_3), 2.93 (s br, 1H, OH, exchange D_2O), 3.51 (s, 2H, CH_2), 6.59–6.60 (m, 2H, 2CH Ar), 6.65–6.67 (m, 1H, CH Ar); 7.03–7.08 (m, 1H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.3, 25.1, 55.0,

68.9, 116.0, 119.9, 120.9, 129, 138.8, 145.8; GC–MS (*m*/*z*): 149 (100), 179 (9.52), 164 (4.76). HRMS (EI): M^+, calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1317.

*4.2.3. 2-Methyl-2-(o-tolylamino)propan-1-ol (**3c**).* Purification by FCC (CH_2Cl_2/AcOEt 1:1, R_f=0.35) afforded an orange oil (114.6 mg, 32% isolated yield); FTIR (liquid film) ν_{max} 3400, 2969, 2930, 1514, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.31 (s, 6H, 2× CH_3); 2.20 (s, 3H, CH_3); 3.60 (s, 2H, CH_2); 6.73–6.77 (m, 1H, CH Ar); 6.88–6.90 (m, 1H, CH Ar); 7.07–7.11 (m, 2H, 2CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.0, 18.3, 25.2, 55.2, 69.3, 116.3, 118.7, 125.1, 127.0, 130.2, 141.3; GC–MS (*m*/*z*): 148 (100), 179 (5), 164 (0.9); HRMS (EI): M^+, calcd for $C_{11}H_{17}NO$: 179.1310; found 179.1308.

*4.2.4. 2-Methyl-2-(phenylamino)propan-1-ol (**3d**).* Crude product, purity ≥95%: no purification necessary to afford a yellow oil (234.4 mg, 71% isolated yield); R_f=0.40 on analytical TLC with Hex/AcOEt 1:1 eluent; FTIR (liquid film) ν_{max} 3379, 2970, 2931, 2874, 1668, 1601, 1497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27 (s, 6H, 2× CH_3); 2.58 (s br, 1H OH, exchange D_2O); 3.55 (s, 2H, CH_2); 6.80–6.88 (m, 3H, 3CH Ar); 7.18–7.21 (m, 2H, 2CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.7, 55.2, 69.1, 119.0, 119.8, 128.8, 145.9; ESI-MS *m*/*z* 166 [M^++H], 188 [M^++Na]. HRMS (EI): M^+, calcd for $C_{10}H_{15}NO$: 165.1154; found 165.1144.

*4.2.5. 2-(4-Methoxyphenylamino)-2-methylpropan-1-ol (**3e**).* Purification by FCC (CH_2Cl_2/AcOEt/MeOH 2.7:6.4:0.9, R_f=0.36) afforded white needles. Mp 59–61 °C (230.2 mg, 59% isolated yield); FTIR (liquid film) ν_{max} 3424, 2967, 2929, 2888, 1610, 1510, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.05 (s, 6H, 2× CH_3); 3.33 (s, 2H, CH_2); 3.67 (s, 3H, OCH_3); 6.67–675 (m, 4H, 4CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.8, 55.4, 55.7, 69.0, 114.2, 123.7, 138.4, 155.1; GC–MS (*m*/*z*): 164 (100), 180 (0.9), 195 (9.1), 149 (9.1), 108 (14.5). HRMS (EI): M^+, calcd for $C_{11}H_{17}NO_2$: 195.1259; found 195.1266.

*4.2.6. 2-(4-Chlorophenylamino)-2-methylpropan-1-ol (**3f**).* Purification by FCC (CH_2Cl_2/AcOEt 6.5:3.5, R_f=0.35) afforded a pink oil (254.8 mg, 64% isolated yield); FTIR (liquid film) ν_{max} 3384, 2971, 2932, 1597, 1492, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23 (s, 6H, $2CH_3$); 3.51 (s, 2H, CH_2); 6.70–6.73 (m, 2H, 2CH Ar); 7.11–7.13 (m, 2H, 2CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.9, 55.5, 69.2, 120.1, 124.9, 128.9, 144.6; GC–MS (*m*/*z*): 168 (100), 199 (5), 127 (11). HRMS (EI): M^+, calcd for $C_{10}H_{14}ClNO$ (^{35}Cl): 199.0764; found 199.0758.

*4.2.7. 2-(2-Chlorophenylamino)-2-methylpropan-1-ol (**3g**).* Purification by FCC (Hex/AcOEt 7.5:3.5, R_f=0.36) afforded a yellow oil (187.1 mg, 47% isolated yield); FTIR (liquid film) ν_{max} 3391, 2971, 2933, 1596, 1514, 1468, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.32 (s, 6H, 2× CH_3); 3.60 (s, 2H, CH_2); 6.69–6.74 (m, 1H, CH Ar); 6.94–6.97 (m, 1H, CH Ar); 7.08–7.12 (m, 1H, CH Ar); 7.27–7.29 (m, 1H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.9, 55.5, 69.1, 117.0, 122.7, 127.3, 129.5, 142.4; GC–MS (*m*/*z*): 199 (6), 170 (31), 168 (100), 127 (10). HRMS (EI): M^+, calcd for $C_{10}H_{14}ClNO$ (^{35}Cl): 199.0764; found 199.0754.

*4.2.8. 2-Methyl-2-(p-tolylamino)hexan-1-ol (**3i**).* Purification by FCC (Hex/AcOEt 4:6, R_f=0.34) afforded white crystal. Mp 44–46 °C (265.4 mg, 60% isolated yield); FTIR (liquid film) ν_{max} 3420, 2952, 2924, 2856, 1615, 1511, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (m, 3H, CH_3); 1.27 (s, 3H, CH_3); 1.27–1.38 (m, 4H, 2× CH_2); 1.46–1.62 (m, 2H, CH_2); 2.29 (s, 3H, CH_3); 3.48 (d, 1H, CH, *J*=10.8 Hz); 3.59 (d, 1H, CH, *J*=10.8 Hz); 6.72–6.75 (m, 2H, 2CH Ar); 7.00–7.03 (m, 2H, 2CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9, 20.4, 22.7, 23.1, 25.6, 36.9, 57.9, 67.4, 119.5, 129.5, 143.1; GC–MS (*m*/*z*): 190 (100), 221 (0.5), 164 (8), 134 (6). HRMS (EI): M^+, calcd for $C_{14}H_{23}NO$: 221.1780; found 221.1771.

*4.2.9. 2-Ethyl-2-(p-tolylamino)butan-1-ol (**3j**).* Purification by FCC (Hex/AcOEt 4:6, R_f=0.33) afforded a colorless oil (70.4 mg, 17% isolated yield); FTIR (liquid film) ν_{max} 3390, 2966, 2936, 2878, 1616, 1514, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (t, 6H, 2× CH_3, *J*=7.5 Hz); 1.51–1.57 (2d, 4H, $2CH_2$, J_1=J_2=7.5 Hz); 2.27 (s, 3H, CH_3); 3.56 (s, 2H, CH_2); 6.71–6.73 (m, 2H, 2CH Ar); 6.99–7.01 (m, 2H, 2CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 7.4, 20.4, 25.7, 60.8, 64.6, 118.9, 129.2, 129.6, 143.2; GC–MS (*m*/*z*): 176 (100), 207 (6). HRMS (EI): M^+, calcd for $C_{13}H_{21}NO$: 207.1623; found 207.1629.

*4.2.10. (1-(p-Tolylamino)cyclohexyl)methanol (**3k**).* Purification by FCC (Hex/AcOEt 9:1, R_f=0.34) afforded a pale orange oil (302.5 mg, 69% isolated yield); FTIR (liquid film) ν_{max} 3390, 2930, 2857, 1615, 1513, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33–1.60 (m, 8H, 8CH Cyc); 1.75–1.79 (m, 2H, 2CH Cyc); 2.28 (s, 3H, CH_3); 3.05 (s br, 1H OH, exchange D_2O); 3.57 (s, 2H, CH_2); 6.75 (m, 2H, CH Ar); 7.01 (m. 2H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.4, 21.5, 25.8, 33.0, 57.4, 67.4, 119.5, 129.5, 129.5, 142.6; GC–MS (*m*/*z*): 188 (100), 219 (6.4), 106 (9). HRMS (EI): M^+, calcd for $C_{14}H_{21}NO$: 219.1623; found 219.1615.

*4.2.11. (1-(m-Tolylamino)cyclohexyl)methanol (**3l**).* Purification by FCC (Hex/AcOEt 6:4, R_f=0.35) afforded an orange oil (263 mg, 60% isolated yield); FTIR (liquid film) ν_{max} 3398, 2930, 2856, 1604, 1517, 1486, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.32–1.60 (m, 8H, CH-Cyc); 1.80–1.85 (m, 2H, CH-Cyc), 2.29 (s, 3H, CH_3); 2.90 (s br, 1H OH, exchange D_2O); 3.60 (s, 2H, CH_2); 6.61–6.62 (m, 2H, CH Ar); 6.66–6.68 (m, 1H, CH Ar); 7.05–7.09 (m, 1H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.4, 25.8, 32.9, 57.2, 67.5, 115.4, 119.2, 120.5, 128.8, 168.7, 145.4; ESI-MS *m*/*z* 220 [M^++H], 242 [M^++Na]; HMRS HRMS (EI): M^+, calcd for $C_{14}H_{21}NO$: 219.1623; found 219.1628.

*4.2.12. (1-(o-Tolylamino)cyclohexyl)methanol (**3m**).* Purification by FCC (Hex/AcOEt 8:2, R_f=0.35) afforded a yellow oil (232.3 mg, 53% isolated yield); FTIR (liquid film) ν_{max} 3440, 2930, 2856, 1515, 1480, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29–1.58 (m, 8H, CH-Cyc); 1.88–1.94 (m, 2H, CH-Cyc), 2.21 (s, 3H, CH_3); 3.63 (s, 2H, CH_2); 6.68–6.71 (m, 1H, CH Ar); 6.80–6.82 (m, 1H, CH Ar); 7.00–7.05 (m, 2H, 2CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.0, 18.3, 25.2, 55.2, 69.3, 79.7, 116.3, 118.7, 125.1, 127.0, 130.2, 141.3; GC–MS (*m*/*z*): 219 (8), 188 (100), 106 (10). HRMS (EI): M^+, calcd for $C_{14}H_{21}NO$: 219.1623; found 219.1631.

*4.2.13. (1-(Phenylamino)cyclohexyl)methanol (**3n**).* Purification by FCC (Hex/AcOEt 7:3, R_f=0.35) afforded a pale orange oil (233.9 mg, 57% isolated yield); FTIR (liquid film) ν_{max} 3400, 2931, 2856, 1600, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33–1.62 (m, 8H, CH-Cyc); 1.82–1.86 (m, 2H, CH-Cyc), 2.86 (s br, 1H OH, exchange D_2O); 3.62 (s, 2H, CH_2); 6.81–6.87 (m, 3H, CH Ar); 7.18–7.22 (m, 2H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.5, 25.9, 33.1, 57.4, 67.7, 118.6, 119.8, 129.1, 145.6; GC–MS (*m*/*z*): 205 (11), 174 (100), 93 (22). HRMS (EI): M^+, calcd for $C_{13}H_{19}NO$: 205.1467; found 205.1475.

*4.2.14. (1-(4-Methoxyphenylamino)cyclohexyl)methanol (**3o**).* Purification by FCC (CH_2Cl_2/AcOEt 6:4, R_f=0.34) afforded white crystals. Mp 73–75 °C (305.7 mg, 65% isolated yield); FTIR (liquid film) ν_{max} 3287, 2940, 1609, 1509, 1461 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ (ppm): 1.19–1.29 (m, 1H, CH Cyc); 1.36–1.58 (m, 7H, 7CH Cyc); 1.61–1.67 (m, 2H, 2CH Cyc); 3.30 (s, 2H, $1CH_2$) 3.65 (s, 3H, CH_3); 4.00 (s br, 1H, NH, exchange with D_2O); 4.39 (t, 1H,

OH, exchange with D_2O); 6.68–6.60 (m, 2H, CH Ar); 6.68–6.75 (m, 2H, CH Ar); ^{13}C NMR (100 MHz, DMSO) δ (ppm): 21.4, 25.9, 32.2, 55.4, 56.8, 66.2, 114.2, 121.2, 140.2, 152.8; GC–MS (*m*/*z*): 235 (12.5), 204 (100), 108 (23.1), 122 (11.9), 115 (1.6). HRMS (EI): M^+, calcd for $C_{14}H_{21}NO_2$: 235.1572; found 235.1576.

*4.2.15. (1-(4-Chlorophenylamino)cyclohexyl)methanol (**3p**).* Purification by FCC (Hex/AcOEt 6:4, R_f=0.35) afforded a pale yellow oil (420 mg, 88% isolated yield); FTIR (liquid film) ν_{max} 3407, 2931, 2856, 1596, 1492, 1462, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.32–1.51 (m, 8H, 8CH Cyc); 1.70–1.76 (m, 2H, 2CH Cyc); 3.50 (s, 2H, CH_2); 6.64–6.66 (m, 2H, CH Ar); 7.03–7.06 (m. 2H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.5, 25.8, 33.0, 57.6, 67.5, 119.7, 124.7, 129.0, 144.2; GC–MS (*m*/*z*): 208 (100), 239 (6.4). HRMS (EI): M^+, calcd for $C_{13}H_{18}ClNO$ (^{35}Cl): 239.1077; found 239.1077.

*4.2.16. (1-(p-Tolylamino)cyclopentyl)methanol (**3q**).* Purification by FCC (Hex/AcOEt 75:25, R_f=0.35) afforded a pale yellow oil (238.0 mg, 58% isolated yield); FTIR (liquid film) ν_{max} 3391, 2953, 2868, 1616, 1514, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.66–1.86 (m, 8H, 8CH Cyc); 2.27 (s, 3H, CH_3); 3.64 (s, 2H, CH_2); 6.63–6.65 (m, 2H, CH Ar); 6.99–7.01 (m, 2H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.3, 24.4, 36.0, 65.8, 66.5, 116.7, 127.9, 129.6, 143.4; GC–MS (*m*/*z*): 174 (100), 205 (5), 158 (4). HRMS (EI): M^+, calcd for $C_{13}H_{19}NO$: 205.1467; found 205.1468.

*4.2.17. (1-(p-Tolylamino)cyclooctyl)methanol (**3r**).* Purification by FCC (Hex/AcOEt 3:7, R_f=0.35) afforded white crystal. Mp 93–95 °C (133.5 mg, 27% isolated yield); FTIR (liquid film) ν_{max} 3419, 2920, 2848, 1616, 1509, 1474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49–1.70 (m, 14H, 14CH Cyc); 2.28 (s, 3H, CH_3); 2.97 (s br, 1H OH, exchange D_2O); 3.50 (s, 2H, CH_2); 6.73–6.75 (m, 2H, CH Ar); 7.11–7.02 (m. 2H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.4, 21.9, 25.3, 28.3, 30.7, 61.4, 65.3, 120.4, 129.5, 130.0, 142.7; GC–MS (*m*/*z*): 216 (100), 247 (2). HRMS (EI): M^+, calcd for $C_{16}H_{25}NO$: 247.1936; found 247.1931.

Acknowledgements

We thank MIUR for continual support of our free-radical (PRIN 2008, project 2008KRBLP5_003) and organic (FIRB-Future in Research 2008, project RBFR08XH0H_001) chemistry.

Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of compounds **3a**–**r**) associated with this article can be found in the online version. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.09.107.

References and notes

1. (a) Yadav, J. S.; Reddy, A. R.; Narsaiah, A. V.; Reddy, B. V. S. *J. Mol. Catal. A* **2007**, *261*, 207–212; (b) Corey, E. J.; Zhang, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931–1934; (c) Bose, D. S.; Narsaiah, A. V. *Bioorg. Med. Chem.* **2005**, *3*, 627–630; (d) Meinzer, A.; Breckel, A.; Thaher, B. A.; Manicone, N.; Otto, H. H. *Helv. Chim. Acta* **2004**, *87*, 90–105.
2. US2010/0093788A1
3. (a) Mancilla, G.; Durán-Patrón, R. M.; Marcías-Sánchez, A. J.; Collado, I. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6820–6822; (b) Thevissen, K.; Hillaert, U.; Meert, E. M. K.; Chow, K. K.; Cammuea, B. P. A.; Calenbergh, S. V.; François, I. E. J. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3728–3730.
4. (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421–431; (b) Dhakshinamoorthy, A.; Alvaro, M.; Garcia, H. *Chem.—Eur. J.* **2010**, *16*, 8530–8536.
5. (a) Markò, I. E.; Svendsen, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Yamamoto, H., Pfaltz, A., Eds.; Springer: Berlin, 1999; vol. II, p 713; (b) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169–1173.
6. Studer, M.; Burkhardt, S.; Blaser, H. U. *Adv. Synth. Catal.* **2001**, *343*, 802–808.
7. For reviews in the field see: (a) Friestad, G. K. *Eur. J. Org. Chem.* **2005**, 3157–3172; (b) Yamada, K.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874–2886; (c) Akindele, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345–355; (d) Pastori, N.; Gambarotti, C.; Punta, C. *Mini-Rev. Org. Chem.* **2009**, *6*, 184–195; (e) Miyabe, H.; Yoshioka, E.; Kohtani, S. *Curr. Org. Chem.* **2010**, *14*, 1254–1264.
8. For some recent examples see: (a) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, *8*, 87–89; (b) Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5729–5732; (c) Yamada, K.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805–3808; (d) Ueda, M.; Miyabe, H.; Torii, M.; Kimura, T.; Miyata, O.; Naito, T. *Synlett* **2010**, 1341–1344; (e) Friestad, G. K.; Ji, A.; Korapla, C. S.; Qin, J. *Org. Biomol. Chem.* **2011**, *9*, 4039–4043; (f) Yamada, K.; Konishi, T.; Nakano, M.; Fuji, S.; Cadou, R.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2012**, *77*, 1547–1553.
9. Clerici, A.; Ghilardi, A.; Pastori, N.; Punta, C.; Porta, O. *Org. Lett.* **2008**, *10*, 5063–5066.
10. (a) Spaccini, R.; Ghilardi, A.; Pastori, N.; Clerici, A.; Punta, C.; Porta, O. *Tetrahedron* **2010**, *66*, 2044–2052; (b) Prosperini, S.; Pastori, N.; Ghilardi, A.; Clerici, A.; Punta, C. *Org. Biomol. Chem.* **2011**, *9*, 3759–3767.
11. Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576.
12. (a) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985–1987; (b) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324–3327; (c) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2006**, *71*, 2099–2106; (d) Friestad, G. K.; Ji, A. *Org. Lett.* **2008**, *10*, 2311–2313.
13. Cannella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* **2006**, *128*, 5358–5359.
14. Pastori, N.; Greco, C.; Clerici, A.; Punta, C.; Porta, O. *Org. Lett.* **2010**, *12*, 3898–3901.
15. (a) Alder, W. R. *J. Chem. Soc., Perkin Trans. 2* **1986**, 277–284; (b) Chow, Y. L.; Dane, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev.* **1978**, *78*, 243–274; (c) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337–350.