Lateral Lithiation of *N'*-(2-Methylbenzyl)-*N*,*N*-dimethylurea and *N*-(2-Methylbenzyl)pivalamide: Synthesis of Tetrahydroisoquinolines

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Abstract: Lithiation of *N'*-(2-methylbenzyl)-*N*,*N*-dimethylurea and *N*-(2-methylbenzyl)pivalamide with two mole equivalents of *t*-BuLi at -78 °C takes place on the nitrogen and on the methyl group at position 2. The lithium reagents thus obtained react with a variety of electrophiles to give the corresponding side-chain substituted derivatives in high yields. Dehydration of the products obtained from reactions with carbonyl compounds in some cases gives the corresponding tetrahydroisoquinolines in excellent yields, while in other cases dehydration takes place within the substituted side chain to produce the corresponding alkenes in excellent yields.

Key words: lateral lithiation, isoquinolines, *N'*-(2-methylbenzyl)-*N*,*N*-dimethylurea, *N*-(2-methylbenzyl)pivalamide, synthesis, dehydration

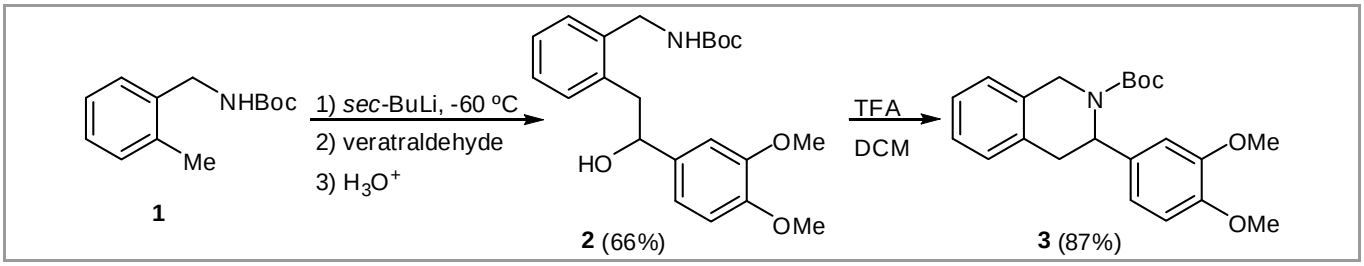
Lithiation of benzylic alkyl groups that are *ortho*- to a directing metallating group is an important methodology in organic synthesis.[1-3] Such lateral lithiation of benzenoid aromatics requires a stabilising group capable of either delocalising negative charge or stabilising an organolithium by coordination.[1] Nitrogen-based stabilising groups placed on the *ortho*-position have been used for a number of lateral lithiations of simple aromatics and heterocycles.[4-8]

Tetrahydroisoquinolines are important compounds, many of which have useful biological properties,[9-16] and there is therefore considerable interest in their syntheses. For example, recent syntheses of tetrahydroisoquinolines have included the use of reactions such as Pictet-Spengler,[17] Bischler-Napieralski,[18] intramolecular Horner,[19] Friedel-Crafts[20] and others.[21] Another potentially useful approach to the synthesis of 1,2,3,4-tetrahydroisoquinolines involves lithiation of *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine (**1**) with *sec*-BuLi at -60 °C to give the corresponding lithium intermediate, which on reaction with veratraldehyde produces **2** in 66% yield (Scheme 1). Treatment of **2** with trifluoroacetic acid (TFA) gives the corresponding tetrahydroisoquinoline **3** in 87% yield.[22]

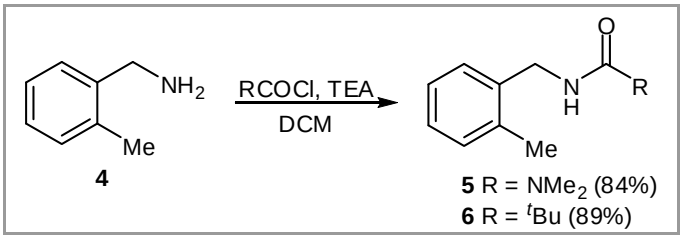
However, the cyclization appears to require the presence of the 4-methoxy group in the electrophile, presumably through stabilization of the intermediate carbenium ion in the cyclization step. The corresponding unsubstituted phenyl compound (when benzaldehyde was used as the electrophile) failed to cyclise under similar, or even more strongly acidic, conditions. Also, no cyclization took place when other carbonyl compounds, *e.g*. benzophenone and cyclohexanone, were used.[22]

We were interested to see whether this latter approach could be made more general as a synthesis of tetrahydroisoquinoline derivatives by using a different substituent on nitrogen. Based on our previous experience,[7,8,23] we decided to attempt lateral lithiation of pivaloyl- and dimethylaminocarbonyl-substituted 2-methylbenzylamine, followed by reaction with appropriate electrophiles and subsequent cyclization. The dimethylamino and *tert*-butyl groups in these compounds might be expected to render the NH group, respectively, more and less nucleophilic in the cyclization step. We now report the successful lateral lithiation and substitution of *N'*-(2-methylbenzyl)-*N*,*N*-dimethylurea and *N*-(2-methylbenzyl)pivalamide using *t*-Buli at -78 °C. In most of the cases tried, the urea derivatives indeed cyclised successfully to tetrahydroisoquinoline derivatives, whereas the pivaloyl derivatives mostly yielded 2-alkenylbenzylamine derivatives.

N'-(2-Methylbenzyl)-*N*,*N*-dimethylurea (**5**) and *N*-(2-methylbenzyl)pivalamide (**6**) were synthesised in high yields from reactions of 2-methylbenzylamine (**4**) with pivaloyl chloride and dimethylcarbamoyl chloride, respectively, in dichloromethane (DCM) in the presence of triethylamine (TEA) as a base (Scheme 2).

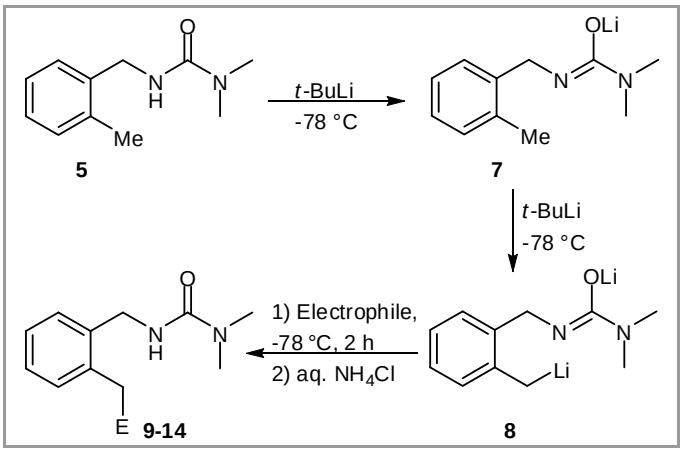


Scheme 1 Synthesis of substituted tetrahydroisoquinoline **3**



Scheme 2 Synthesis of *N*-substituted 2-methylbenzylamines **5** and **6**

Lateral lithiation of *N'*-(2-methylbenzyl)-*N*,*N*-dimethylurea (**5**) was carried out with *t*-BuLi (2.2 mole equivalents) at –78 °C in THF. Addition of the first mole of *t*-BuLi provided the monolithium reagent **7** as a yellow solution and the second mole produced a dilithium reagent (presumed to be **8**) as a reddish brown solution (Scheme 3). The dilithium reagent was allowed to react with a range of electrophiles under identical conditions. Following work-up the crude products were purified by column chromatography to give the corresponding substituted derivatives **9-14** (Scheme 3) in high yields (Table 1).



Scheme 3 Synthesis of **9-14** *via* lithiation and substitution of **5**

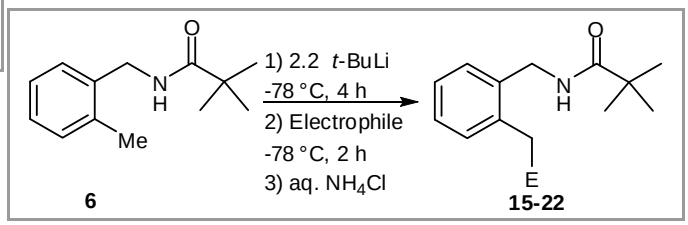
Table 1 Synthesis of *N'*-(2-(substituted methyl)benzyl)-*N*,*N*-dimethylureas **9-14** according to Scheme 3

Product	Electrophile	E	Yield (%)[a]
9	PhCHO	PhCH(OH)	77
10	4-MeOC$_6$H$_4$CHO	4-MeOC$_6$H$_4$CH(OH)	79
11	PhCOMe	PhCH(OH)Me	74
12	Ph$_2$CO	Ph$_2$C(OH)	76
13	EtI	Et	82
14	D$_2$O	D	83

[a] Yield of isolated product after purification by column chromatography.

As can be seen from Table 1, the process is successful with a variety of different electrophiles. The ^{1}H NMR spectra of compounds **9-11** showed that the signals of the two protons of each of the two CH$_2$ groups appeared separately, verifying that they are diastereotopic.

Lateral lithiation of *N*-(2-methylbenzyl)pivalamide (**6**) under similar conditions followed by reactions with a range of electrophiles also gave the corresponding substituted derivatives **15-22** (Scheme 4) in good yields (Table 2).



Scheme 4 Synthesis of **15-22** *via* lithiation and substitution of **6**

The yields of pure products were high in all cases and the process was general to produce various side-chain substituted derivatives. The ^{1}H NMR spectra of compounds **15-17** also showed diastereotopicity for the two hydrogens of each of the two CH$_2$ groups. The structure of one product (**15**) was confirmed by X-ray crystallography (Figure 1).

Table 2 Synthesis of *N*-(2-(substituted methyl)benzyl)pivalamides **15-22** according to Scheme 4

Product	Electrophile	E	Yield (%)[a]
15	PhCHO	PhCH(OH)	84
16	4-MeOC$_6$H$_4$CHO	4-MeOC$_6$H$_4$CH(OH)	89
17	PhCOMe	PhC(OH)Me	80
18	Ph$_2$CO	Ph$_2$C(OH)	88
19	(CH$_2$)$_5$C=O	(CH$_2$)$_5$C(OH)	76
20	MeI	Me	87
21	EtI	Et	88
22	D$_2$O	D	85

[a] Yield of isolated product after purification by column chromatography.

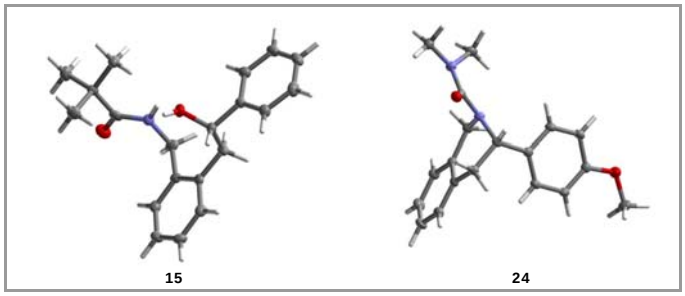
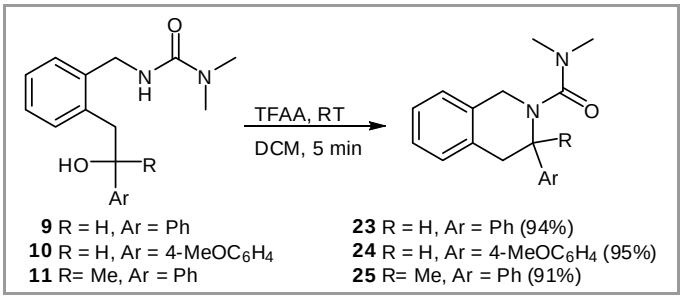


Figure 1 X-ray crystal structures of compounds **15** and **24**

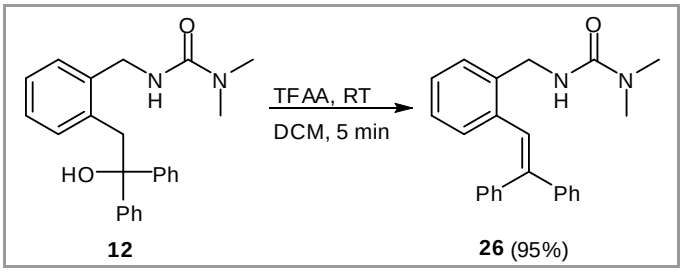
The next step was to investigate cyclization to the corresponding tetrahydroisoquinolines of appropriate compounds produced from lithiations of both **5** and **6**. Indeed, dehydration of compounds **9-11** took place smoothly and rapidly on treatment with trifluoroacetic anhydride (TFAA) at room temperature in DCM for 5 minutes to produce the corresponding substituted tetrahydroisoquinolines **23-25**, respectively, in excellent yields (Scheme 5).



Scheme 5 Synthesis of substituted tetrahydroisoquinolines **23-25** *via* dehydration

The ^{1}H NMR spectra of compounds **23-25** showed the expected diastereotopicity for the two pairs of hydrogens at positions 1 and 4 of the isoquinoline rings and the structure of compound **24** was confirmed by X-ray crystallography (Figure 1).

However, reaction of **12** with TFAA proceeded in a different manner to produce **26** in 95% yield (Scheme 6). The structure of **26** was confirmed by X-ray crystallography (Figure 2).



Scheme 6 Synthesis of **26** *via* dehydration of **12**

In this case the intermediate formed is a doubly benzylic cation that is perhaps both more stable and more hindered than those produced from **9-11**. It appears that loss of a proton from the α-position is easier than cyclization, leading to the corresponding alkene **26**. Even leaving the reaction mixture for longer with TFAA (and TFA produced *in situ*), in the hope that the alkene would protonated and cyclize, failed to produce the tetrahydroisoquinoline. However, in the majority of cases tried, cyclization to give tetrahydroisoquinolines was successful, indicating that the use of the dimethylaminocarbonyl-substituted 2-methylbenzylamine is preferable to use of the previously reported Boc-protected substrate.

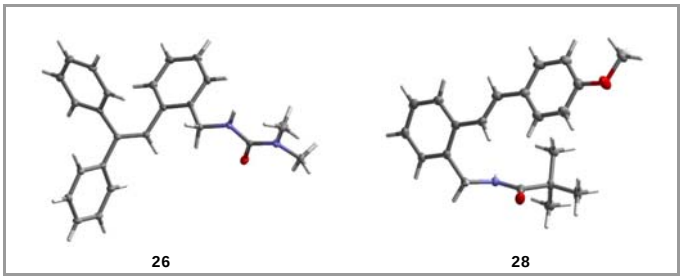
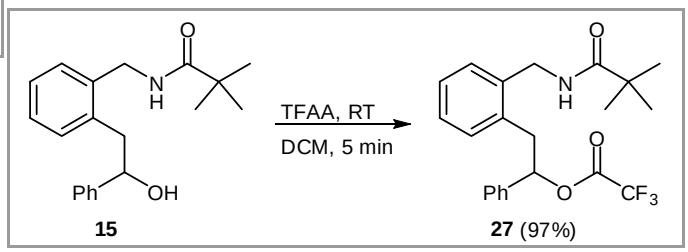


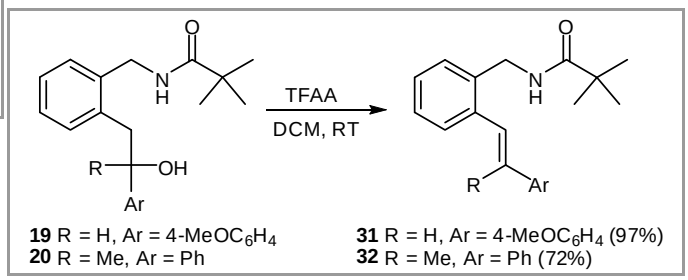
Figure 2 X-ray crystal structures of compounds **26** and **28**

By contrast, reactions of the corresponding pivaloyl derivatives did not lead to tetrahydroisoquinolines. For example, reaction of **15** with TFAA at room temperature in DCM for 5 minutes gave *N*-(2-(2-phenyl-2-trifluoroacetoxyethyl)benzyl)pivalamide (**27**) in 97% yield (Scheme 7).



Scheme 7 Synthesis of **26** *via* dehydration of **15**

Treatment of **16** and **17** with TFAA under similar conditions gave the corresponding unsaturated derivatives **28** and **29**, respectively (Scheme 8). Compounds **28** and **29** were produced in 97 and 14% yield, respectively, when the reaction time was 5 minutes. The yield of **29** was improved to 72% when the reaction time was 1 h. Neither **28** nor **29** cyclized to their corresponding tetrahydroisoquinolines even when the mixtures were left to stir for 8 h.

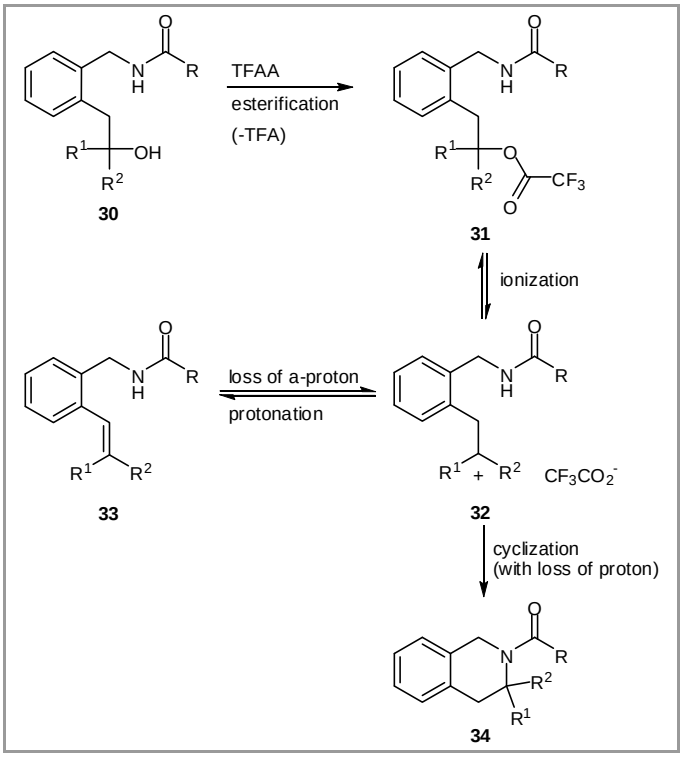


Scheme 9 Synthesis of **31** and **32** *via* dehydration of **19** and **20**, respectively

According to their ^{1}H NMR spectra, both **28** and **29** were single geometrical isomers. The structure of **28** was shown by X-ray crystallography (Figure 2) to be the *E*-isomer. A Nuclear Overhauser Effect (NOE) experiment for **29** clearly showed that when the C=CMe proton signal (δ = 2.05 ppm) was irradiated the signal corresponding to H-3 (δ = 7.46 ppm) was enhanced, showing that compound **29** was also the *E*-isomer.

The results of the attempted dehydration reactions can be rationalized by the processes outlined in Scheme 9, according to which the first step would be to form a trifluoroacetate ester **31** from the alcohol **30**. In a situation where the driving force for ionization is low (*e.g.* R^1 = Ph, R^2 = H or R^1 = H, R^2 = alkyl) and the NHCOR group is relatively non-nucleophilic (*e.g.* R = ^{t}Bu), under the mild reaction conditions used the reaction may stop at compound **31**, allowing the isolation of compound **27** (*i.e.* **31** with R^1 = Ph, R^2 = H, R = ^{t}Bu), for example.

However, when the cation **32** is more stable (*e.g*. R^1 = Ph, R^2 = Ph, Me or R^1 = 4-$MeOC_6H_4$, R^2 = H), **31** does not survive the reaction conditions. The cation **32** can lose a proton either to form an alkene **33** or cyclise to form a tetrahydroisoquinoline **34**. Alkene formation is favoured when the NHCOR group is not very nucleophilic (*e.g* R = ^{t}Bu) or when cyclization is sterically hindered (*e.g*. R^1 = R^2 = Ph, even when R = NMe_2). Cyclization is favoured when the NHCOR group is relatively more nucleophilic (*e.g*. R = NMe_2). In principle, reprotonation of **33** to give back cation **32** would be expected to be easier than reprotonation of **34**. Therefore, it might be possible to convert **33** into **34** in acid conditions. However, under the mild conditions used here the alkenes **33** appeared to be stable and no cyclizations were observed. Therefore, if the ultimate goal is a cyclised product, it is important to use a sufficiently nucleophilic NHCOR group such as $NHCONMe_2$, for which the cyclised product **34** is the normal product when the cationic centre is not too hindered.



Scheme 9 Possible processes involved during hydration experiments

A simple, efficient and general procedure that allows lateral lithiation and substitution of 2-methylbenzylamine derivatives has been demonstrated to provide various side-chain (methyl) substituted derivatives in high yields. Dehydration of the products from reactions of the urea derivatives with aldehydes and ketones using trifluoroacetic anhydride generally gives the corresponding tetrahydroisoquinolines in excellent yields. However, when a bulky group, such as hydroxydiphenylethyl, is present at position 2, cyclization is not successful and dehydration takes place instead to produce a 2-alkenylbenzylamino derivative in high yield. *N*-2-(2-Hydroxy-2-arylalkyl)benzyl)pivalamides are not cyclised under such conditions. Instead, esterification of the hydroxyl group with TFAA or dehydration to give the corresponding alkenes takes place to give high yields of the corresponding products. The results have been rationalised in terms of a common set of reaction intermediates.

General Methods: Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C measurements. Chemical shifts δ are reported in parts per million (ppm) relative to TMS and coupling constants *J* are in Hz and have been rounded to the nearest whole number. ^{13}C multiplicities were revealed by DEPT signals. Assignments of signals are based on integration values, coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution mass spectra were recorded on a Quattro II spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) at 50 eV by the use of NH_3 as ionization gas. Accurate mass data were obtained on a MAT900 instrument. Electrospray (ES) analyses were performed on a ZQ4000 spectrometer in positive and negative ionisation modes. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Microanalyses were performed by Warwick analytical service at the University of Warwick. The X-ray single-crystal diffraction data were collected on a Nonius Kappa CCD diffractometer using graphite-monochromated Mo-K_α, (λ = 0.710 73 Å) radiation. Crystal and structure refinement data are shown the supporting information. The structures were solved by direct methods using SHELXS-96[24] and refined with all data on F^2 full-matrix least squares using SHELXL-97.[25] Non-hydrogen atoms were generally refined anisotropically. Hydrogen atom positions were located from difference Fourier maps and a riding model with atomic displacement parameters 1.2 times (1.5 times for methyl groups) those of the atom to which they are bonded was used for subsequent refinements. Full crystallographic data have been deposited with the CCDC, reference numbers 737412, 737414, 737416 and 737417, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif. Column chromatography was carried out using Fischer Scientific silica 60A (35-70 micron). Alkyllithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham.[26] Other chemicals were obtained from Aldrich Chemical Company and used without further purification. THF was distilled from sodium benzophenone ketyl. Other solvents were purified by standard procedures.[27]

N'-(2-Methylbenzyl)-*N*,*N*-dimethylurea (5)

A stirred mixture of 2-methylbenzylamine (**4**; 4.84 g; 40.0 mmol), dimethylcarbamoyl chloride (4.83 g, 45 mmol) and triethylamine (8 mL) in DCM (60 mL) was heated under reflux for 1 h. The mixture was poured onto H_2O (50 mL) and the organic layer was separated, washed with H_2O (2 x 25 mL), and dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The solid obtained was purified by crystallization from EtOAc/Et_2O (1/3) to give pure **5** as a white crystalline solid.

6.45 g (33.6 mmol, 84%); Mp: 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.01 (m, 4 H, Ar), 4.48 (br, exch., 1 H, NH), 4.31 (br, 2 H, CH_2), 2.82 [s, 6 H, $N(CH_3)_2$], 2.26 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (C=O), 137.5 (C-1), 136.8 (C-2), 130.8 (C-3), 128.8 (C-6), 127.9 (C-4), 126.5 (C-5), 43.6 (CH_2), 36.7 [$N(CH_3)_2$], 19.45 (CH_3).

MS (EI): *m/z* (%) = 192 (35) $[M]^+$, 177 (5), 148 (7), 120 (49), 105 (88), 104 (94) 91 (40), 77 (40), 72 (100), 65 (17), 46 (16), 44 (46), 42 (16).

MS (CI): *m/z* (%) = 210 (4) $[M + NH_4]^+$, 193 (100) $[MH]^+$, 122 (14), 120 (20), 103 (15), 89 (12), 52 (27), 46 (39), 44 (16).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{11}H_{17}N_2O$: 193.1335; found: 193.1335.

IR (FT): = 3317, 2925, 1635, 1533, 1353, 1231 cm^{-1}.

_N_-(2-Methylbenzyl)pivalamide (6)

To a cooled solution (0 °C) of **4** (4.84 g, 40.0 mmol) and triethylamine (6 mL) in DCM (100 mL) pivaloyl chloride (5.3 g, 44.3 mmol) was slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at 0 °C for an extra 1 h. The mixture was poured onto H_2O (100 mL) and the organic layer was separated, washed with H_2O (2 x 50 mL), and dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The solid obtained was purified by crystallization from Et_2O–hexane (2:1) to give pure **6** as white crystals.

7.30 g (35.6 mmol, 89%); Mp: 108–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07–7.02 (m, 4 H, H-3, H-4, H-5 and H-6), 5.65 (br, exch., 1 H, NH), 4.29 (d, *J* = 5 Hz, 2 H, CH_2), 2.17 (s, 3 H, CH_3), 1.09 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (C=O), 136.9 (C-1), 136.6 (C-2), 130.9 (C-3), 128.8 (C-6), 128.1 (C-4), 126.6 (C-5), 42.3 (CH_2), 39.2 [$C(CH_3)_3$], 28.0 [$C(CH_3)_3$], 19.3 (CH_3).

MS (EI): *m/z* (%) = 205 (17) $[M]^+$, 105 (78), 91 (23), 77 (30), 57 (100).

MS (CI): *m/z* (%) = 411 (16) $[2 M + 1]^+$, 223 (24) $[M + NH_4]^+$, 206 (100) $[MH]^+$.

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{13}H_{20}NO$: 206.1539; found: 206.1542.

IR (FT): 3316, 2959, 1637, 1538, 1221, 1005 cm^{-1}.

_N_-(2-Substituted methyl)benzylamines 9-14 and 15-22

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of **5** or **6** (2.0 mmol) in anhydrous THF (20 mL) under N_2. The mixture was stirred at -78 °C for 4 h, to ensure the complete formation of the dilithium reagent, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at –78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; Et_2O-hexane, 1:3) to give pure product as a white solid. The yields obtained are recorded in Tables 1 and 2.

***N'*-(2-(2-Hydroxy-2-phenylethyl)benzyl)-*N*,*N*-dimethylurea (9)**

0.46 g (1.54 mmol, 77%); Mp 116–117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.12 (m, 10 H, Ph, H-3, H-4, H-5, H-6 and NH), 5.44 (br s, exch., 1 H, OH), 4.82 (dd, *J* = 4, 9 Hz, 1 H, CH), 4.33 (d, *J* = 14 Hz, 1 H, CH_aH_bNH), 4.25 (d, *J* = 14 Hz, 1 H, CH_aH_bNH), 3.02 (dd, *J* = 9, 14 Hz, 1 H, CH_aH_bCH), 2.88 (dd, *J* = 4, 14 Hz, 1 H, CH_aH_bCH), 2.75 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C=O), 144.8 (C-1), 138.5 (C-1 of Ph), 137.7 (C-2), 130.7 (C-3), 130.4 (C-6), 128.9 (C-3/C-5 of Ph), 128.1 (C-4), 128.0 (C-5), 127.3 (C-4 of Ph), 126.2 (C-2/C-6 of Ph), 76.1 (CH), 43.3 (CH_2), 42.5 (CH_2), 36.6 [$N(CH_3)_2$].

MS (EI): *m/z* (%) = 299 (6) $[M + 1]^+$, 298 (1) $[M]^+$, 281 (51), 280 (14), 209 (33), 208 (100).

MS (CI): *m/z* (%) = 316 (3) $[M + NH_4]^+$, 299 (100) $[MH]^+$, 282 (26), 281 (100), 193 (44), 179 (12), 106 (41), 89 (64), 52 (68), 46 (78).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{18}H_{23}N_2O_2$:299.1754; found: 299.1755.

IR (FT): 3230, 2938, 16310, 1586, 1530, 1212, 1018 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.50; H, 7.47; N, 9.40.

***N'*-(2-(2-(Hydroxy-2-(4-methoxyphenyl)ethyl)benzyl)-*N*,*N*-dimethylurea (10)**

0.52 g (1.58 mmol, 79%); Mp 108–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.29–7.22 (m, 5 H, H-3, H-4, H-5, H-6 and NH), 6.89 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.32 (s, exch., 1 H, OH), 4.88 (dd, *J* = 4, 9 Hz, 1 H, CH), 4.44 (d, *J* = 14 Hz, 1 H, CH_aH_bNH), 4.35 (d, *J* = 14 Hz, 1 H, CH_aH_bNH), 3.81 (s, 3 H, OCH_3), 3.12 (dd, *J* = 9, 14 Hz, 1 H, CH_aH_bCH), 2.94 (dd, *J* = 4, 14 Hz, 1 H, CH_aH_bCH), 2.85 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (C=O), 158.9 (C-4 of 4-methoxyphenyl), 138.4 (s, C-1), 137.8 (s, C-2), 137.0 (s, C-1 of 4-methoxyphenyl), 130.7 (C-3), 130.4 (C-6), 128.1 (C-4), 127.4 (C-2/C-6 of 4-methoxyphenyl), 127.3 (C-5), 114.2 (C-3/C-5 of 4-methoxyphenyl), 75.7 (CH), 55.7 (OCH_3), 43.3 (CH_2), 42.5 (CH_2), 36.6 [$N(CH_3)_2$].

MS (EI): *m/z* (%) = 328 (2) $[M]^+$, 311 (100), 310 (51), 308 (20), 265 (63).

MS (CI): *m/z* (%) = 328 (3) $[M]^+$, 327 (3), 312 (17), 311 (100), 240 (11), 193 (28), 179 (14), 154 (28), 137 (22), 135 (17), 106 (58), 89 (81), 63 (20).

MS (ES^+): *m/z* (%) = 351 (58) $[M + Na]^+$, 329 (2) $[MH]^+$, 312 (22), 311 (100).

MS (ES^-): *m/z* (%) = 328 (14) $[M]^-$, 327 (100).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{19}H_{25}N_2O_3$: 329.1860; found: 329.1864.

IR (FT): 3314, 2933, 1632, 1530, 1510, 1243, 1024 cm^{-1}.

***N'*-(2-(2-Hydroxy-2-phenylpropyl)benzyl)-*N*,*N*-dimethylurea (11)**

0.45 g (1.47 mmol, 74%); Mp 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.26–7.22 (m, 3 H, H-3/H-5 and H-4 of Ph), 7.17 (d, *J* = 8 Hz, 1 H, H-3), 7.14 (br, exch., 1 H, NH), 7.08 (app. t, *J* = 8 Hz, 1 H, H-5), 6.99 (app. t, *J* = 8 Hz, 1 H, H-4), 6.74 (d, *J* = 8 Hz, 1 H, H-6), 5.35 (s, exch., 1 H, OH), 4.31 (d, *J* = 14 Hz, 1 H, CH_aH$_b$NH), 4.23 (d, *J* = 14 Hz, 1 H, CH$_a$$H_b$NH), 3.09 (d, *J* = 14 Hz, 1 H, CH_aH$_b$COH), 3.04 (d, *J* = 14 Hz, 1 H, CH$_a$$H_b$COH), 2.78 [s, 6 H, N($CH_3$)$_2$], 1.6 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C=O), 148.5 (C-1 of Ph), 139.6 (C-1), 135.8 (C-2), 132.3 (C-3), 130.2 (C-6), 128.5 (C-3/C-5 of Ph), 127.4 (C-4 of Ph), 127.1 (C-5), 126.5 (C-4), 125.4 (C-2/C-6 of Ph), 75.4 (C-OH), 46.6 (CH_2), 43.2 (CH_2), 36.7 [N(CH_3)$_2$], 30.3 (CH_3).

MS (EI): *m*/*z* (%) = 312 (1) [M]$^+$, 295 (12), 294 (10), 222 (25), 207 (32), 206 (100).

MS (CI): *m*/*z* (%) = 313 (33) [MH]$^+$, 297 (24), 296 (20), 295 (100), 235 (13), 193 (78), 179 (9), 138 (39), 106 (42), 89 (78), 52 (58), 46 (67), 44 (24).

HRMS-CI: *m*/*z* [MH]$^+$ calcd for $C_{19}H_{25}N_2O_2$: 313.1911; found: 313.1912.

IR (FT): 3329, 2928, 1611, 1531, 1246, 1026 cm^{-1}.

***N'*-(2-(2-Hydroxy-2,2-diphenylethyl)benzyl)-*N*,*N*-dimethylurea (12)**

0.57 g (1.52 mmol, 76%); Mp 119–120 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.41 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 7.27 (app. t, *J* = 8 Hz, 4 H, H-3/H-5 of 2 Ph), 7.19–6.86 (m, 6 H, H-3, H-4, H-5, H-6 and H-4 of 2 Ph), 6.66 (t, *J* = 6 Hz, exch., 1 H, NH), 5.83 (s, exch., 1 H, OH), 3.99 (d, *J* = 6 Hz, 2 H, CH_2NH), 3.68 (s, 2 H, CH_2COH), 2.79 [s, 6 H, N(CH_3)$_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.5 (C=O), 148.5 (C-1 of 2 Ph), 140.9 (C-1), 135.4 (C-2), 131.8 (C-3), 128.0 (C-6), 127.9 (C-3/C-5 of 2 Ph), 126.8 (C-2/C-6 of 2 Ph), 126.6 (C-4 of 2 Ph), 126.0 (C-4), 125.4 (C-5), 77.8 (C-OH), 42.9 (CH_2), 41.3 (CH_2), 36.3 [N(CH_3)$_2$].

MS (EI): *m*/*z* (%) = 374 (2) [M]$^+$, 357 (11), 268 (100), 252 (16), 239 (12), 206 (25).

MS (CI): *m*/*z* (%) = 375 (12) [MH]$^+$, 374 (6) [M]$^+$, 373 (5), 359 (33), 357 (89), 286 (10), 257 (12), 200 (81), 193 (100), 183 (71), 179 (17), 118 (24), 106 (55), 89 (87), 63 (15).

MS (ES$^+$): *m*/*z* (%) = 397 (100) [M + Na]$^+$, 375 (4) [MH]$^+$, 358 (13), 357 (69), 270 (14), 269 (52), 191(34), 89 (78).

MS (ES$^-$): *m*/*z* (%) = 374 (2) [M]$^-$, 373 (8), 191 (100), 146 (9), 118 (21), 87 (25).

HRMS-CI: *m*/*z* [M + NH_4]$^+$ calcd for $C_{24}H_{30}N_3O_2$: 392.2333; found: 392.2330.

IR (FT): 3331, 2927, 1621, 1531, 1246, 1026 cm^{-1}.

***N'*-(2-Propylbenzyl)-*N*,*N*-dimethylurea (13)**

0.36 g (1.64 mmol, 82%); Mp 59–61 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.05 (m, 4 H, H-3, H-4, H-5 and H-6), 4.58 (br, exch., 1 H, NH), 4.33 (br, 2 H, CH_2NH), 2.80 [s, 6 H, N(CH_3)$_2$], 2.54 (t, *J* = 7 Hz, 2 H, CH_2CH$_2$CH$_3$), 1.53 (app. sextet, *J* = 7 Hz, 2 H, CH_2CH$_3$), 0.89 (t, *J* = 7 Hz, 3 H, CH$_2$CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (C=O), 141.3 (C-1), 137.1 (C-2), 129.9 (C-3), 129.1 (C-6), 127.8 (C-4), 126.5 (C-5), 42.9 (CH_2NH), 36.6 [N(CH_3)$_2$], 34.9 (CH_2CH$_2$CH$_3$), 24.8 (CH_2CH$_3$), 14.5 (CH$_2$CH_3).

MS (EI): *m*/*z* (%) = 220 (31) [M]$^+$, 177 (13), 148 (10), 132 (47), 117 (82), 105 (53), 91 (22), 89 (34), 77 (24), 72 (100), 65 (15), 46 (23), 44 (69), 42 (33).

MS (CI): *m*/*z* (%) = 441 (12) [2 M + 1]$^+$, 238 (13) [M + NH_4]$^+$, 221 (100) [MH]$^+$.

HRMS-CI: *m*/*z* [MH]$^+$ calcd for $C_{13}H_{21}N_2O$: 221.1648; found: 221.1648.

IR (FT): 3325, 2957, 1631, 1529, 1375, 1227 cm^{-1}.

***N'*-(2-Deuteriomethylbenzyl)-*N*,*N*-dimethylurea (14)**

0.32 g (1.66 mmol, 83%); Mp 73–75 °C (Mp of undeuteriated analogue 73–75 °C[28]).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.12 (m, 4 H, H-3, H-4, H-5 and H-6), 4.61 (br, exch., 1 H, NH), 4.42 (br, 2 H, CH_2NH), 2.91 [s, 6 H, N(CH_3)$_2$], 2.31 (seen as three lines, 1:1:1, because of coupling to D, 2 H, CH_2D).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (C=O), 137.5 (C-1), 136.8 (C-2), 130.8 (C-6), 128.7 (C-3), 127.8 (C-5), 126.5 (C-4), 43.6 (CH_2NH), 36.6 [N(CH_3)$_2$], 19.4 (seen as three lines, 1:1:1, because of coupling to D, CH_2D).

MS (EI): *m*/*z* (%) = 194 (15) [M + 1]$^+$, 193 (43), 149 (11), 121 (37), 106 (71), 105 (66), 92 (21), 78 (24), 77 (21), 72 (100), 46 (32), 44 (79), 42 (27).

MS (CI): *m*/*z* (%) = 211 (17) [M + NH_4]$^+$, 195 (23), 194 (100) [MH]$^+$, 52 (20).

HRMS-CI: *m*/*z* [MH]$^+$ calcd for $C_{11}H_{16}DN_2O$: 194.1398; found: 194.1398.

IR (FT): 3315, 2926, 1622, 1537, 1512, 1376, 12.35, 1027 cm^{-1}.

***N*-(2-(2-Hydroxy-2-phenyethyl)benzyl)pivalamide (15)**

0.52 g (1.67 mmol, 84%); Mp 133–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 9 H, Ph, H-3, H-4, H-5 and H-6), 6.69 (br app. t, exch., 1 H, NH), 4.94 (dd, 1 H, *J* = 9, 4 Hz, CH), 4.53 (dd, *J* = 6, 14 Hz, 1 H, CH_aH$_b$NH), 4.33 (dd, *J* = 2, 14 Hz, 1 H, CH$_a$$H_b$NH), 3.10 (dd, *J* = 9, 14 Hz, 1 H, CH_aH$_b$CH), 3.01 (dd, *J* = 4, 14 Hz, 1 H, CH$_a$$H_b$CH), 2.78 (br, exch., 1 H, OH), 1.19 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (C=O), 144.6 (C-1), 137.7 (C-1 of Ph), 137.6 (C-2), 130.8 (C-3), 130.3 (C-6), 128.9 (C-3/C-5 of Ph), 128.3 (C-4 of Ph), 128.1 (C-4), 127.4 (C-5), 126.2 (C-2/C-6 of Ph), 76.2 (CH), 42.5 (CH_2), 41.8 (CH_2), 39.1 [*C*(CH_3)$_3$], 28.0 [C(*C*H$_3$)$_3$].

MS (EI): *m*/*z* (%) = 311 (6) [M]$^+$, 295 (31), 294 (100), 278 (8).

MS (CI): *m/z* (%) = 329 (9) $[M + NH_4]^+$, 313 (13) $[MH + 1]^+$, 312 (78) $[MH]^+$, 294 (100), 234 (8), 206 (12), 205 (17), 192 (7), 119 (10), 102 (9).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{20}H_{26}NO_2$: 312.1958; found: 312.1955.

IR (FT): 3314, 2971, 1627, 1542, 1367, 1216, 1055 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.21; H, 8.14; N, 4.54.

_N_-(2-(2-Hydroxy-2-(4-methoxyphenyl)ethyl)benzyl)pivalamide (16)

0.61 g (1.79 mmol, 89%); Mp 124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.28–7.20 (m, 4 H, H-3, H-4, H-5 and H-6), 6.88 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.83 (br, exch., 1 H, NH), 4.87 (dd, *J* = 4, 9 Hz, 1 H, CH), 4.49 (dd, *J* = 6, 14 Hz, 1 H, CH_aH$_b$NH), 4.30 (dd, *J* = 4, 14 Hz, 1 H, CH$_a$$H_b$NH), 3.80 (s, 3 H, OCH_3), 3.22 (br, exch., 1 H, OH), 3.07 (dd, *J* = 9, 14 Hz, 1 H, CH_aH$_b$CH), 2.94 (dd, *J* = 4, 14 Hz, 1 H, CH$_a$$H_b$CH), 1.17 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8 (C=O), 159.4 (C-4 of 4-methoxyphenyl), 137.9 (C-1), 137.5 (C-2), 137.0 (C-1 of 4-methoxyphenyl), 130.8 (C-3), 130.2 (C-6), 128.2 (C-4), 127.6 (C-2/C-6 of 4-methoxyphenyl), 127.3 (C-5), 114.2 (C-3/C-5 of 4-methoxyphenyl), 75.7 (CH), 55.7 (OCH_3), 42.5 (CH_2), 41.9 (CH_2), 39.01 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 341 (5) $[M]^+$, 324 (63), 323 (79), 308 (5), 266 (21), 254 (13), 238 (100).

MS (CI): *m/z* (%) = 357 (4) $[M + NH_4]^+$, 342 (8) $[MH]^+$, 341 (20) $[M]^+$, 325 (24), 324 (100), 251 (4), 234 (6), 205 (7), 154 (8), 119 (15), 102 (7), 52 (10).

MS (ES^+): *m/z* (%) = 364 (19) $[M + Na]^+$, 324 (33), 223 (100).

MS (ES^-): *m/z* (%) = 340 (12) $[M - 1]^-$, 205 (12) 204 (100), 100 (28).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{21}H_{28}NO_3$: 342.2064; found: 342.2065.

IR (FT): 3321, 2954, 1629, 1555, 1463, 1370, 1220, 1035 cm^{-1}.

_N_-(2-(2-Hydroxy-2-phenylpropyl)benzyl)pivalamide (17)

0.52 g (1.60 mmol, 80%); Mp 135–137 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.35 (t, *J* = 8 Hz, 2 H, H-3/H-5 of Ph), 7.30–7.26 (m, 2 H, H-4 of Ph and H-6), 7.20 (app. dt, *J* = 2, 8 Hz, 1 H, H-4), 7.12 (app. dt, *J* = 2, 8 Hz, 1 H, H-5), 6.87 (dd, *J* = 2, 8 Hz, 1 H, H-3), 6.55 (br app. t, exch., 1 H, NH), 4.44 (dd, *J* = 5, 14 Hz, 1 H, CH_aH$_b$NH), 4.37 (dd, *J* = 5, 14 Hz, 1 H, CH$_a$$H_b$NH), 3.17 (d, *J* = 14 Hz, 1 H, CH_aH$_b$COH), 3.12 (d, *J* = 14 Hz, 1 H, CH$_a$$H_b$COH), 2.42 (s, exch., 1 H, OH), 1.68 (s, 3 H, CH_3COH), 1.21 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (C=O), 149.2 (C-1 of Ph), 138.7 (C-1), 135.8 (C-2), 132.4 (C-3), 130.0 (C-6), 128.5 (C-3/C-5 of Ph), 127.5 (C-4), 127.3 (C-4 of Ph), 127.2 (C-2/C-6 of Ph), 125.4 (C-5), 75.5 (C-OH), 46.6 (CH_2), 41.7 (CH_2), 39.1 [*C*$(CH_3)_3$], 30.3 (*C*H_3COH), 29.5 [C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 325 (1) $[M]^+$, 308 (77), 307 (34), 292 (12), 282 (23), 264 (31), 248 (19), 229 (60), 222 (100).

MS (CI): *m/z* (%) = 343 (2) $[M + NH_4]^+$, 326 (34) $[MH]^+$, 309 (36), 308 (100), 248 (5), 306 (17), 205 (22), 138 (7), 119 (9), 102 (9), 52 (7).

HRMS-CI: *m/z* $[MH^+]$ calcd for $C_{21}H_{28}NO_2$: 326.2115; found: 326.2115.

IR (FT): 3324, 2964, 1623, 1493, 1242, 1025 cm^{-1}.

_N_-(2-(2-Hydroxy-2,2-diphenylethyl)benzyl)pivalamide (18)

0.68 g (1.76 mmol, 88%); M.p: 94–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 11 H, 2 Ph and H-6), 7.17 (app. dt, *J* = 2, 8 Hz, 1 H, H-4), 6.97 (app. dt, *J* = 2, 8 Hz, 1 H, H-5), 6.56 (dd, *J* = 2, 8 Hz, 1 H, H-3), 6.38 (br t, exch., 1 H, NH), 4.36 (d, *J* = 5 Hz, 2 H, CH_2NH), 3.75 (s, 2 H, CH_2COH), 2.72 (s, exch., 1 H, OH), 1.18 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 178.6 (100 MHz, C=O), 147.1 (C-1 of 2 Ph), 139.0 (C-1), 134.8 (C-2), 132.3 (C-3), 129.7 (C-6), 128.5 (C-4), 128.3 (C-3/C-5 of 2 Ph), 127.6 (C-4 of 2 Ph), 127.2 (C-5), 126.8 (C-2/C-6 of 2 Ph), 79.0 (C-OH), 43.8 (CH_2), 42.3 (CH_2), 39.1 [*C*$(CH_3)_3$], 29.5 [C(*C*$H_3)_3$].

MS (EI): *m/z* (%) = 370 (7), 284 (12), 269 (39), 268 (100), 252 (13).

MS (CI): *m/z* (%) = 405 (5) $[M + NH_4]^+$, 388 (18) $[MH]^+$, 387 (33) $[M]^+$, 370 (100), 310 (11), 285 (5), 257 (7), 223 (12), 206 (41), 200 (52), 183 (17), 119 (29), 102 (12), 52 (16).

ES^+–MS: *m/z* (%) = 410 (23) $[M + Na]^+$, 370 (72), 270 (22), 269 (100), 191 (47), 102 (49), 91 (47).

MS (ES^-): *m/z* (%) = 388 (3) $[MH]^-$, 387 (21) $[M]^-$, 386 (100).

HRMS-CI: *m/z* $[M + NH_4]^+$ calcd for $C_{26}H_{33}N_2O_2$: 405.2537; found: 405.2534.

IR (FT): 3310, 2933, 1635, 1531, 1449, 1227, 1020 cm^{-1}.

_N_-(2-((1-Hydroxycyclohexyl)methyl)benzyl)pivalamide (19)

0.46 g (1.52 mmol, 76%); Mp 93–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.09 (m, 4 H, H-3, H-4, H-5 and H-6), 6.77 (br t, exch., 1 H, NH), 4.41 (br d, 2 H, CH_2NH), 2.75 (s, 2 H, CH_2COH), 1.86 (br s, exch., 1 H, OH), 1.51-1.43 [m, 10 H, $(CH_2)_5$], 1.10 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (C=O), 138.6 (C-1), 136.3 (C-2), 132.3 (C-3), 130.3 (C-6), 127.4 (C-4), 127.3 (C-5), 72.2 (C-1 of cyclohexyl), 45.0 (CH_2NH), 42.2 (*C*H_2COH), 39.1 [*C*$(CH_3)_3$], 38.3 (C-2/C-6 of cyclohexyl), 28.0 [C(*C*$H_3)_3$], 26.1 (C-4 of cyclohexyl), 22.4 (C-3/C-5 of cyclohexyl).

MS (EI): *m/z* (%) = 303 (7) $[M]^+$, 286 (39), 285 (87), 270 (12), 260 (100), 242 (40), 228 (77), 218 (71).

MS (CI): *m/z* (%) = 321 (3) $[M + NH_4]^+$, 304 (100) $[MH]^+$, 286 (58), 205 (9), 119 (5), 52 (11).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{19}H_{30}NO_2$: 304.2271; found: 304.2272.

IR (FT): 3341, 2929, 1634, 1529, 1449, 1208 cm^{-1}.

***N*-(2-Ethylbenzyl)pivalamide (20)**

0.38 g (1.74 mmol, 87%); Mp: 64–65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.08 (m, 4 H, H-3, H-4, H-5 and H-6), 5.69 (br t, exch., 1 H, NH), 4.37 (d, *J* = 5 Hz, 2 H, C*H*$_2$NH), 2.58 (q, *J* = 7 Hz, 2 H, C*H*$_2$CH$_3$), 1.14 (t, *J* = 7 Hz, 3 H, CH$_2$C*H*$_3$), 1.13 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (C=O), 143.0 (C-1), 135.9 (C-2), 129.3 (C-3), 129.2 (C-6), 128.4 (C-4), 126.6 (C-5), 41.8 (CH$_2$NH), 39.1 [*C*(CH$_3$)$_3$], 28.0 [C(*C*H$_3$)$_3$], 25.7 (*C*H$_2$CH$_3$), 15.8 (CH$_2$*C*H$_3$).

MS (ES$^+$): *m/z* (%) = 237 (15) [M + NH$_4$]$^+$, 220 (100) [MH]$^+$.

HRMS-ES$^+$: *m/z* [MH]$^+$ calcd for $C_{14}H_{22}NO$: 220.1696; found: 220.1694.

IR (FT): 3331, 2963, 1632, 1531, 1217, 1008 cm^{-1}.

***N*-(2-Propylbenzyl)pivalamide (21)**

0.41 g (1.76 mmol, 88%); Mp 66–67 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.08 (m, 4 H, H-3, H-4, H-5 and H-6), 5.68 (br t, exch., 1 H, NH), 4.37 (d, *J* = 5 Hz, 2 H, C*H*$_2$NH), 2.52 (t, *J* = 7 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.53 (app. sextet, *J* = 7 Hz, 2 H, C*H*$_2$CH$_3$), 1.14 [s, 9 H, C(CH$_3$)$_3$], 0.98 (t, *J* =7 Hz, 3 H, CH$_2$C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C=O), 141.5 (C-1), 136.1 (C-2), 130.1 (C-3), 129.2 (C-6), 128.1 (C-4), 126.6 (C-5), 41.8 (CH$_2$NH), 39.1 [*C*(CH$_3$)$_3$], 34.9 (*C*H$_2$CH$_2$CH$_3$), 28.0 [C(*C*H$_3$)$_3$], 24.8 (*C*H$_2$CH$_3$), 15.8 (CH$_2$*C*H$_3$).

MS (EI): *m/z* (%) = 233 (9) [M]$^+$, 204 (5), 190 (4), 133 (14), 132 (97), 117 (100), 105 (81), 91 (24), 57 (49).

MS (CI): *m/z* (%) = 251 (45) [M + NH$_4$]$^+$, 334 (100) [MH]$^+$, 206 (18), 132 (20), 119 (8), 102 (6).

MS (ES$^+$): *m/z* (%) = 251 (7) [M + NH$_4$]$^+$, 234 (42) [MH]$^+$, 133 (17), 114 (18), 106 (32), 105 (100), 104 (95).

HRMS-CI: *m/z* [MH]$^+$ calcd for $C_{15}H_{24}NO$: 234.1852; found: 234.1852.

IR (FT): 3331, 2963, 1633, 1530, 1363, 1218, 1008 cm^{-1}.

***N*-(2-Deuteriomethylbenzyl)pivalamide (22)**

0.35 g (1.70 mmol, 85%); Mp 108–109 °C (Mp of undeuteriated analogue 108–109 °C[28]).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.09 (m, 4 H, H-3, H-4, H-5 and H-6), 5.70 (br t, exch., 1 H, NH), 4.34 (d, *J* = 5 Hz, 2 H, C*H*$_2$NH), 2.21 (seen as three lines, 1:1:1, because of coupling to D, 2 H, CH$_2$D), 1.14 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (C=O), 136.9 (C-1), 136.5 (C-2), 131.0 (C-3), 128.8 (C-6), 128.1 (C-4), 126.6 (C-5), 42.3 (CH$_2$NH), 39.2 [*C*(CH$_3$)$_3$], 28.1 [C(*C*H$_3$)$_3$], 19.1 (seen as three lines, 1:1:1, because of coupling to D, CH$_2$D).

MS (EI): *m/z* (%) = 207 (4) [M + 1]$^+$, 206 (13) [M]$^+$, 109 (2), 107 (20), 106 (60), 105 (37), 92 (10), 78 (12), 57 (92).

MS (CI): *m/z* (%) = 224 (12) [M + NH$_4$]$^+$, 208 (32) [MH + 1]$^+$, 207 (100) [MH]$^+$.

HRMS-CI: *m/z* [MH]$^+$ calcd for $C_{13}H_{19}DNO$: 207.1602; found: 207.1602.

IR (FT): 3328, 2924, 1612, 1532, 1238, 1024 cm^{-1}.

Synthesis of 23-29

Trifluoroacetic anhydride (0.5 mL, excess) was added to a stirred solution of the appropriate substituted benzylamine **9-12** or **15-17** (0.50 g) in DCM (10 mL) at room temperature. The mixture was stirred for 5 min at room temperature (1 h in the case of compound **17**). The reaction mixture was quenched with H_2O (10 mL). The organic layer was separated, washed with aq. sat. $NaHCO_3$ (10 mL) and H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:3) to give pure the product.

2-Dimethylaminocarbonyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (23)

0.44 g (94%); Mp 96–98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.08 (m, 9 H, H-5, H-6, H-7, H-8 and Ph), 4.78 (dd, *J* = 4, 9 Hz, 1 H, H-3), 4.31 (d, *J* = 14 Hz, 1 H, H-1a), 4.21 (d, *J* = 14 Hz, 1 H, H-1b), 2.96 (dd, *J* = 9, 14 Hz, 1 H, H-4a), 2.83 (dd, *J* = 4, 14 Hz, 1 H, H-4b), 2.72 [s, 6 H, N(CH$_3$)$_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 144.5 (C-4a), 137.9 (C-8a), 137.2 (C-1 of Ph), 130.0 (C-8), 129.6 (C-4 of Ph), 129.3 (C-3/C-5 of Ph), 128.9 (C-5), 128.2 (C-6), 127.5 (C-7), 126.9 (C-2/C-6 of Ph), 76.3 (C-3), 43.5 (C-1), 42.6 (C-4), 38.1 [N(CH$_3$)$_2$].

MS (EI): *m/z* (%) = 280 (2) [M]$^+$, 208 (4), 192 (44), 177 (6), 148 (7), 120 (18), 104 (100), 91 (25), 77 (61), 72 (66), 44 (26).

MS (CI): *m/z* (%) = 299 (62) [M + NH$_4$]$^+$, 281 (72) [MH]$^+$, 271 (9), 193 (22), 179 (15), 118 (16), 106 (32), 89 (36), 72 (7), 63 (12), 46 (100).

HRMS-CI: *m/z* [MH]$^+$ calcd for $C_{18}H_{21}N_2O$: 281.1648; found: 281.1647.

FT–IR: 2935, 1636, 1523, 1512, 1455, 1203, 1174, 1037 cm^{-1}.

2-Dimethylaminocarbonyl-3-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (24)

0.45 g (95%); Mp 102–103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.07 (m, 3 H, H-6, H-7 and H-8), 7.04 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.90 (d, *J* = 8 Hz, 1 H, H-5), 6.69 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.18 (dd, *J* = 3, 6 Hz, 1 H, H-3), 4.34 (d, *J* = 16 Hz, 1 H, H-1a), 4.00 (d, *J* = 16 Hz, 1 H, H-1b), 3.65 (s, 3 H, OCH$_3$), 3.36 (dd, *J* = 6, 16 Hz, 1 H, H-4a), 3.13 (dd, *J* = 3, 16 Hz, 1 H, H-4b), 2.80 [s, 6 H, N(CH$_3$)$_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2 (C=O), 158.9 (C-4 of 4-methoxyphenyl), 134.3 (C-4a), 133.1 (C-8a), 129.1 (C-1 of 4-methoxyphenyl), 128.7 (C-8), 128.4 (C-2/C-6 of 4-methoxyphenyl), 127.2 (C-5), 126.4 (C-6), 126.2 (C-7), 114.1 (C-3/C-5 of 4-methoxyphenyl), 55.6 (OCH$_3$), 54.0 (C-3), 46.3 (C-1), 39.0 [N(CH$_3$)$_2$], 32.2 (C-4).

MS (EI): *m/z* (%) = 310 (12) $[M]^+$, 266 (9), 238 (32), 222 (62), 202 (15), 189 (23), 178 (11), 165 (13), 121 (31), 104 (100), 91 (17), 72 (93), 44 (17).

MS (CI): *m/z* (%) = 311 (100) $[MH]^+$, 89 (17), 52 (33), 46 (28).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{19}H_{23}N_2O_2$: 311.1754; found: 311.1751.

FT–IR: 2958, 1618, 1510, 1399, 1370, 1348, 1242, 1173, 1033 cm^{-1}.

2-Dimethylaminocarbonyl-3-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (25)

0.43 g (91%); Mp 122–124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.04 (m, 8 H, H-6, H-7, H-8 and Ph), 6.89 (d, *J* = 8 Hz, 1 H, H-5), 4.28 (d, *J* = 16 Hz, 1 H, H-1a), 4.14 (d, *J* = 16 Hz, H-1b), 3.42 (d, *J* = 16 Hz, 1 H, H-4a), 3.23 (d, *J* = 16 Hz, 1 H, H-4b), 2.82 [s, 6 H, $N(CH_3)_2$], 1.59 (s, CH_3C).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6 (C=O), 147.7 (C-1 of Ph), 135.6 (C-4a), 134.1 (C-8a), 129.4 (C-5), 128.8 (C-3/C-5 of Ph), 127.9 (C-6), 127.1 (C-7), 126.5 (C-4 of Ph), 125.6 (C-8), 125.5 (C-2/C-6 of Ph), 59.4 (C-3), 49.8 (C-4), 43.6 (C-1), 39.8 [$N(CH_3)_2$], 28.1 (CH_3C).

MS (EI): *m/z* (%) = 294 (22) $[M]^+$, 279 (24), 222 (52), 206 (100).

MS (CI): *m/z* (%) = 295 (100) $[MH]^+$, 222 (7), 193 (8), 89 (12), 52 (28), 46 (52).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{19}H_{23}N_2O$: 295.1805; found: 295.1807.

FT–IR: 2973, 1645, 1522, 1492, 1381, 1361, 1174, 1107 cm^{-1}.

***N'*-(2-(2,2-Diphenylethenyl)benzyl)-*N*,*N*-dimethylurea (26)**

0.45 g (95%); Mp 106–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.05 (m, 13 H, H-5, H-6, CH and 2 Ph), 6.87 (app. t, *J* = 8 Hz, 1 H, H-4), 6.83 (t, *J* = 6 Hz, exch., 1 H, NH), 6.71 (d, *J* = 8 Hz, 1 H, H-3), 4.31 (d, *J* = 6 Hz, 2 H, CH_2), 2.77 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (C=O), 143.0 (C-1 of 2 Ph), 142.9 (*C*=CH), 140.0 (C-1), 136.0 (C-2), 130.7 (C-3/C-5 of 2 Ph), 129.7 (C-3), 128.7 (C-4 of 2 Ph), 128.6 (C-4), 127.9 (C-2/C-6 of 2 Ph), 127.6 (C-5), 127.0 (C-6), 126.1 (C=*C*H), 42.2 (CH_2), 36.2 [$N(CH_3)_2$].

MS (EI): *m/z* (%) = 356 (12) $[M]^+$, 312 (7), 284 (10), 268 (100), 252 (8), 206 (12), 178 (13), 167 (33), 152 (18), 91 (13), 72 (71), 44 (22).

MS (CI): *m/z* (%) = 374 (100) $[M + NH_4]^+$, 357 (81) $[MH]^+$, 331 (6), 301 (5), 276 (7), 167 (15), 118 (19), 106 (25), 89 (33), 46 (100).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{24}H_{25}N_2O$: 357.1961; found: 357.1960.

FT–IR: 3316, 2958, 1637, 1538, 1352, 1230 cm^{-1}.

Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.90; H, 6.89; N, 7.63.

***N*-(2-(2-Phenyl-2-trifluoroacetoxyethyl)benzyl)pivalamide (27)**

0.63 g (97%); Mp 127–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.07 (m, 9 H, H-3, H-4, H-5, H-6 and Ph), 6.01 (dd, *J* = 6, 8 Hz, 1 H, CH), 5.80 (br app. t, exch., 1 H, NH), 4.38 (dd, *J* = 6, 15 Hz, 1 H, CH_aH_bNH), 4.29 (dd, *J* = 6, 15 Hz, 1 H, CH_aH_bNH), 3.24 (dd, *J* = 8, 15 Hz, 1 H, CH_aH_bCH), 3.19 (dd, *J* = 6, 15 Hz, 1 H, CH_aH_bCH), 1.13 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (C=O), 156.9 (seen as a quartet because of coupling to F, CF_3C=O), 137. 8 (C-1), 137.1 (C-1 of Ph), 134.5 (C-2), 131.6 (C-3), 129.9 (C-4), 129.5 (C-5), 129.4 (C-6), 129.3 (C-3/C-5 of Ph), 128.3 (C-4 of Ph), 126.7 (C-2/C-6 of Ph), 114.8 (seen as a quartet because of coupling to F, CF_3), 80.9 (CH), 41.5 (CH_2NH), 39.9 (CH_2CH), 39.1 [$C(CH_3)_3$], 27.9 [$C(CH_3)_3$].

MS (EI): *m/z* (%) = 407 (4) $[M]^+$, 310 (4), 294 (85), 293 (100), 278 (3).

MS (CI): *m/z* (%) = 425 (60 $[M + NH_4]^+$, 408 (5) $[MH]^+$, 329 (11), 312 (42), 294 (100), 192 (10), 119 (19), 52 (16).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{22}H_{25}F_3NO_3$: 408.1781; found: 408.1789.

FT–IR: 3313, 2933, 1635, 1531, 1462, 1227, 1030, 1020, 1000 cm^{-1}.

(*E*)-*N*-(2-(4-Methoxystyryl)benzyl)pivalamide (28)

0.46 g (97%); Mp 113–115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8 Hz, 1 H, H-3), 7.37 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.24 (app. dt, *J* = 2, 8 Hz, 1 H, H-4), 7.18–7.12 (m, 2 H, H-5 and H-6), 7.06 (d, *J* = 16 Hz, 1 H, C*H*=CH), 6.88 (d, *J* = 16 Hz, 1 H, CH=C*H*), 6.80 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.67 (br t, exch., 1 H, NH), 4.50 (d, *J* = 5 Hz, 2 H, CH_2), 3.74 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1 (C=O), 159.9 (C-4 of 4-methoxyphenyl), 137.4 (C-1), 135.6 (C-2), 130.9 (C-5), 130.4 (C-1 of 4-methoxyphenyl), 130.2 (C-6), 128.7 (C-4), 128.4 (C-2/C-6 of 4-methoxyphenyl), 127.7 (C-3), 126.2 (*C*H=CH), 123.5 (CH=*C*H), 114.5 (C-3/C-5 of 4-methoxyphenyl), 55.7 (OCH_3), 42.7 (CH_2), 39.1 [$C(CH_3)_3$], 27.9 [$C(CH_3)_3$].

EI–MS: *m/z* (%) = 323 (10) $[M]^+$, 222 (88), 207 (21), 191 (22), 165 (15), 115 (13), 57 (100).

CI–MS: *m/z* (%) = 341 (12) $[M + NH_4]^+$, 324 (100) $[MH]^+$, 222 (7), 119 (18), 52 (17).

HRMS-CI: *m/z* $[M + NH_4]^+$ calcd for $C_{21}H_{29}N_2O_2$: 341.2224; found: 341.2225.

FT–IR: 2961, 1628, 1512, 1453, 1225, 1037 cm^{-1}.

Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.89; H, 7.81; N, 4.30.

(*E*)-*N*-(2-(2-Phenylprop-1-enyl)benzyl)pivalamide (29)

0.34 g (72%); Mp 85–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8 Hz, 1 H, H-3), 7.31-7.18 (m, 8 H, H-4, H-5, H-6 and Ph), 6.79 (s, 1 H, CH), 5.76

(br t, exch., 1 H, NH), 4.38 (d, *J* = 6 Hz, 2 H, CH_2), 2.05 (s, 3 H, CH_3C=CH), 1.06 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C=O), 143.2 (C-1), 139.0 (C-2), 137.7 (C-1 of Ph), 136.9 (CH=*C*-CH_3), 130.5 (C-5), 129.0 (C-6), 128.8 (C-3/C-5 of Ph), 128.5 (C-4), 128.3 (C-3), 128.2 (C-4 of Ph), 127.4 (C-2/C-6 of Ph), 126.3 (*C*H=C-CH_3), 42.5 (CH_2), 39.1 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$], 17.6 (CH=C-*C*H_3).

EI–MS: *m/z* (%) = 307 (7) $[M]^+$, 222 (4), 206 (38), 191 (18), 178 (8), 165 (6), 128 (15), 115 (8), 91 (22), 77 (8), 57 (100), 41 (58).

CI–MS: *m/z* (%) = 325 (23) $[M + NH_4]^+$, 308 (100) $[MH]^+$, 206 (6), 119 (32), 102 (22), 52 (60).

HRMS-CI: *m/z* $[MH]^+$ calcd for $C_{21}H_{26}NO$: 308.2009; found: 308.2006.

FT–IR: 3329, 2921, 1638, 1539, 1357, 1210 cm^{-1}.

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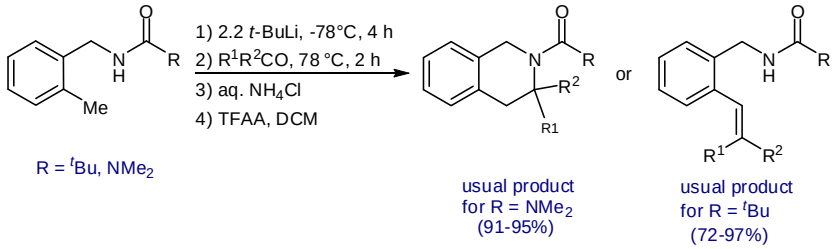

Lateral Lithiation of 2-Methylbenzylamines

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