Directed Lithiation of *N*′-[2-(4-Methoxyphenyl)ethyl]-*N*,*N*-dimethylurea and *tert*-Butyl [2-(4-Methoxyphenyl)ethyl]carbamate

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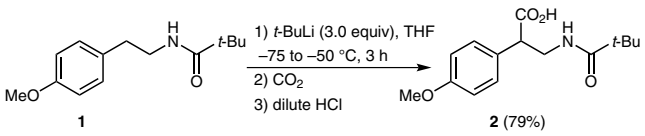
Abstract: *N*′-[2-(4-Methoxyphenyl)ethyl]-*N*,*N*-dimethylurea and *tert*-butyl [2-(4-methoxyphenyl)ethyl]carbamate are doubly lithiated on the nitrogen and *ortho* to the directing metalating group at –20 to 0 °C with three mole equivalents of *n*-BuLi in anhydrous THF. Reactions of the dilithium reagents produced in situ with various electrophiles give high yields of the corresponding substituted products. In the case of the urea, side-products due to lithiation and substitution on one of the methyl groups of the urea unit are obtained in low yields (0–17%).

Key words: directed lithiation, side-chain lithiation, *N*′-[2-(4-methoxyphenyl)ethyl]-*N*,*N*-dimethylurea, *tert*-butyl [2-(4-methoxyphenyl)ethyl]carbamate, electrophile

Many biologically active compounds, such as dopamine, adrenaline, and mescaline, possess a phenylethylamine unit bearing an oxygen substituent on the phenyl ring, and selective methods for synthesis of such derivatives are of considerable interest. Lithiation reactions[2,3] can be important in the development of clean and environmentally friendly processes for the regioselective substitution of aromatic compounds. In particular, lithiation often takes place proximal to a directing metalating group (DMG), which typically possess an oxygen or nitrogen atom.[4] Use of such DMGs to facilitate lithiation, followed by reactions of the organolithium intermediates obtained in situ with electrophiles, has therefore found wide application in a variety of synthetic transformations to produce substituted aromatics or heterocycles.[5,6]

In connection with other work on the use of lithium reagents in organic synthesis,[7,8] we have reported a detailed study of the regioselective lithiation and substitution of various substituted phenylamines and benzylamines,[9,10] in which different products were sometimes formed, depending on the nature of the lithium reagent used, the nature of the directing group, and/or the reaction conditions.

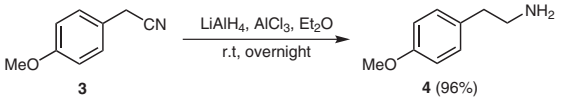
Recently, we have been interested in regioselective lithiation and substitution of phenethylamine derivatives and found that directed lithiation of *N*-[2-(4-methoxyphenyl)ethyl]pivalamide (**1**) with *n*-BuLi at –20 to 0 °C in THF occurred smoothly and cleanly on the ring next to the DMG.[11] This is in sharp contrast with results reported by Simig and Schlosser.[12] They found that lithiation of **1** using *t*-BuLi at –75 to –50 °C, followed by treatment with carbon dioxide, resulted in carboxylation at the CH_2 next to the 4-methoxyphenyl ring (α-lithiation) to give **2** in 79% yield (Scheme 1).



Scheme 1 Lithiation of **1** followed by reaction with CO_2 as reported by Simig and Schlosser[12]

We wished to investigate the possibility of ring lithiation of *N*′-[2-(4-methoxyphenyl)ethyl]-*N*,*N*-dimethylurea and *tert*-butyl [2-(4-methoxyphenyl)ethyl]carbamate under similar reaction conditions to those used with the pivalamide, since such derivatives do not necessarily behave in a similar manner. We now report that we have been able to establish conditions for a high-yielding and general ring-substitution process.

2-(4-Methoxyphenyl)ethanamine (**4**) was synthesized from the corresponding nitrile **3** based on a literature procedure.[13] Reduction of **3** with lithium aluminum hydride (2.2 equiv) in the presence of aluminum chloride (0.75 equiv) in diethyl ether at room temperature overnight provided **4** in 96% yield without the need of further purification (Scheme 2).



Scheme 2 Synthesis of 2-(4-methoxyphenyl)ethanamine (**4**)

N′-[2-(4-Methoxyphenyl)ethyl]-*N*,*N*-dimethylurea (**5**) and *tert*-butyl [2-(4-methoxyphenyl)ethyl]carbamate (**6**) were synthesized, in 97 and 92% yield, respectively, based on a literature procedure for analogous compounds[7] involving the reaction of **4** with dimethylcarbamoyl chloride or di-*tert*-butyl dicarbonate in dichloromethane in the presence of triethylamine for one hour under reflux (Scheme 3).

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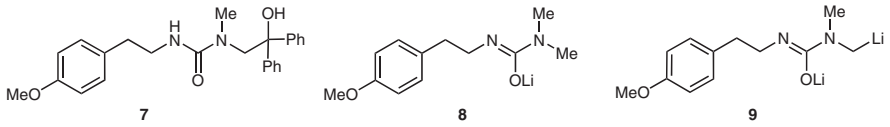
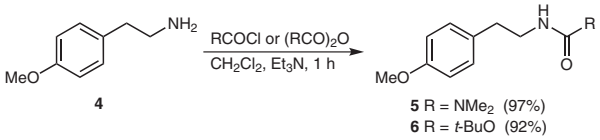


Figure 1 Structures of compound **7** and lithium intermediates **8** and **9**



Scheme 3 Synthesis of substituted 2-(4-methoxyphenyl)ethanamines **5** and **6**

Initially, **5** was lithiated with *n*-BuLi (3 molar equiv) in anhydrous THF under a nitrogen atmosphere at –78 °C for two hours, then benzophenone (1.4 mol equiv) was added. Following workup, the starting material was recovered quantitatively, indicating that no C-lithiation had taken place under such conditions. The reaction was repeated with *t*-BuLi under identical conditions. The crude product was separated by column chromatography to give a new product, *N*-(2-hydroxy-2,2-diphenylethyl)-*N*′-[2-(4-methoxyphenyl)ethyl]-*N*-methylurea (**7**, Figure 1), obtained in 5% yield along with recovered **5** (89%). Compound **7** was clearly obtained via the intermediacy of dilithium species **9**, produced in situ from lithium reagent **8** (Figure 1).

In an attempt to improve the yield of **7** the reaction was repeated with *n*-BuLi (2.4 equiv) at a higher temperature (–30 to –20 °C). The crude product was purified by column chromatography (silica gel; hexane–Et_2O, 1:1 by volume) to give the starting material **5** (61%), the methyl-substituted product **7** (13%), and *N*′-{2-[2-(hydroxydiphenylmethyl)-4-methoxyphenyl]ethyl}-*N*,*N*-dimethylurea (**10**, Figure 2) in 22% yield. Product **10** would have arisen from reaction of benzophenone with the dilithium reagent **11** (Figure 2), produced in situ from **8**. The identity of product **10** was confirmed by its X-ray crystal structure (Figure 3).

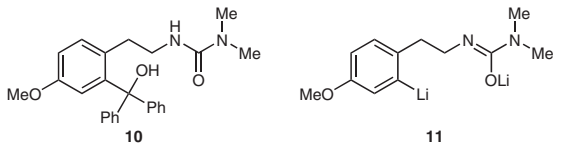


Figure 2 The structures of product **10** and its dilithium intermediate **11**

Several experiments were conducted in an attempt to find conditions under which **10** could be produced as the only product by varying the molar equivalents and type of lithium reagent, reaction time, and reaction temperature (Table 1). Excellent overall yields of up to 98% could be produced at 0 °C, but mixtures of **7** and **10** were always produced.

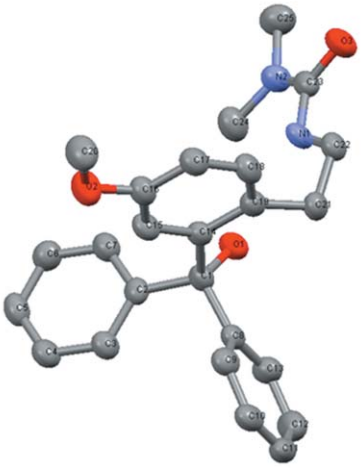


Figure 3 X-ray crystal structure of compound **10**

Some general trends can be deduced from the results in Table 1. At low temperature (–78 °C), no lithiation takes place with *n*-BuLi and only a low yield of lithiation–substitution product (specifically **7**) is obtained after two hours with the more reactive *t*-BuLi. At –30 to –20 °C, both reagents bring about lithiation, but the reaction appears to be slow, yielding about 35% of products after a two-hour lithiation period with just a small excess of lithiating agent (2.4 equiv instead of the theoretical 2.0). Both reagents show a small preference for lithiation on the ring (ratio **10**/**7** = 1.7 with *n*-BuLi and 1.3 with *t*-BuLi). Use of a larger excess of lithiating agent (3.3 equiv) understandably results in higher levels of lithiation (around 70% after 2 h), but also in greater selectivity for ring-lithiation (ratio **10**/**7** = 3.2 with *n*-BuLi and 2.1 with *t*-BuLi), which is less easy to understand. Perhaps use of the larger quantity of reagent resulted in a quicker temperature rise, so that more of the reaction occurred at the higher end of the temperature range, at which the selectivity for **10** appears to be greater. Alternatively, perhaps the rate equation for ring lithiation involves a higher order in lithiating agent than the rate equation for *N*-methyl lithiation, so that it would be favored to a greater extent at higher concentration of organolithium. At –20 to 0 °C, the yields were better still and the selectivity was greater too with *n*-BuLi (ratio **10**/**7** = 12.1). The best yields were achieved at 0 °C, and at that temperature higher selectivity was also recognizable with *t*-BuLi. Thus, it is clear that the general trend is that the yields and selectivity for formation of **10** increase as the temperature increases and with larger quantities of alkyllithium. In terms of selectivity for formation of **10**, *n*-BuLi is better than *t*-BuLi. From experiments conducted

Table 1 Lithiation of **5** Followed by Reaction with Benzophenone under Various Reaction Conditions

Entry	RLi (mol equiv)	Time (h)	Temp (°C)	Yield (%)[a] of **7**	Yield (%)[a] of **10**
1	*n*-BuLi (3.3)	2	−78	–	–[b]
2	*t*-BuLi (3.3)	2	−78	5	–[b]
3	*n*-BuLi (2.4)	2	−30 to −20[c]	13	22
4	*t*-BuLi (2.4)	2	−30 to −20[c]	16	20
5	*n*-BuLi (3.3)	2	−30 to −20[c]	18	57
6	*t*-BuLi (3.3)	2	−30 to −20[c]	22	46
7	*n*-BuLi (3.3)	2	−20 to 0	7	85
8	*t*-BuLi (3.3)	2	−20 to 0	27	55
9	*n*-BuLi (2.4)	2	0	9	38
10	*t*-BuLi (2.4)	2	0	16	28
11	*t*-BuLi (3.3)	1	0	21	62
13	*n*-BuLi (3.3)	0.25	0	10	40
14	*n*-BuLi (3.3)	1	0	12	69
15	*n*-BuLi (3.3)	2	0	15	83
16	*t*-BuLi (3.3)	2	0	23	75

[a] Isolated yield after separation by column chromatography.
[b] Starting material **5** was recovered (90–96%).
[c] Initial addition of BuLi was at –60 °C.

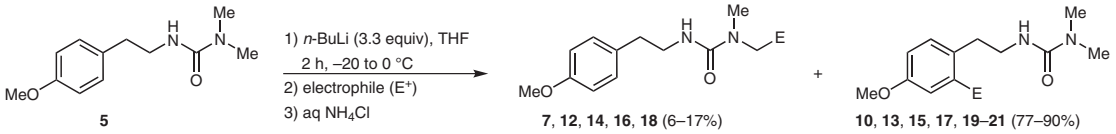
under similar conditions for different periods of time the evidence for equilibration of the intermediate organolithium species is not strong, but if it is occurring it appears that **10** is the more favored species at 0 °C.

No conditions were found under which only one product could be obtained in good yield. However, product **10** could be produced as the major product under conditions where the yield of **7** was low. The best conditions found involved use of *n*-BuLi (3.3 equiv) as the lithium reagent at –20 to 0 °C for at least two hours (Table 1, Entry 7).

It was of interest to see if the reaction with other electrophiles would be useful and general. Consequently, reactions of **5** under the conditions described above (Table 1, entry 7) were carried out with various other electrophiles [4′-methoxyacetophenone, cyclohexanone, benzaldehyde, 4-(dimethylamino)benzaldehyde, dimethylformamide, and iodoethane] (Scheme 4). Each reaction was conducted under identical conditions. The crude products were separated by column chromatography (silica gel; Et_2O–hexane 1:1 by volume), to give the corresponding substituted derivatives **12**–**21** in high overall yields (Table 2). The ^1H NMR spectra of compounds **12**, **13** and **16**–**19** showed diastereotopicity for the CH_2 protons.

As can be seen from Table 2, lithiation and substitution of **5** gave mixtures of two products in which ring substitution products were the major ones. The combined yields were typically around 95%. It appears that directed lithiation and substitution of **5** were achieved in high yields (77–90%) under the conditions tried, along with side-products due to methyl substitution in lower yields (0 to 17%). When iodoethane and dimethylformamide were used as electrophiles no *N*-methyl-substitution products were isolated, while in the case of iodoethane as an electrophile a side-product involving N-alkylation was obtained.

When DMF was used as electrophile the isolated yield of ring-substitution product was 90% and in the case of iodoethane the combined yields of products involving ring substitution including the side-product **22** (Figure 4)

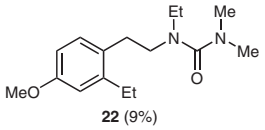


Scheme 4 Lithiation and substitution of *N*′-[2-(4-methoxyphenyl)ethyl]-*N*,*N*-dimethylurea (**5**)

Table 2 Lithiation and Substitution of **5** under Various Reaction Conditions (Scheme 4)

Electrophile	E	Product (%)[a]	
		Side-chain	*ortho*
Ph_2CO	$Ph_2C(OH)$	**7** (7)	**10** (85)
4-$MeOC_6H_4COMe$	4-$MeOC_6H_4C(OH)(Me)$	**12** (12)	**13** (82)
$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**14** (17)	**15** (77)
PhCHO	PhCH(OH)	**16** (6)	**17** (82)
4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	**18** (10)	**19** (80)
Me_2NCHO	CHO	–	**20** (90)
EtI	Et	–	**21** (86)[b]

[a] Yield of the isolated pure product after column chromatography.
[b] Diethyl derivative **22** was produced as a side-product in 9% yield.



22 (9%)

Figure 4 The structure of compound **22**

amounted to 95%. On the other hand, 17% of *N*-methyl-substitution product was isolated from the reaction with cyclohexanone, so that the maximum quantity of ring-substitution product formed in that case, even allowing for any losses, could have been not higher than 83%. These differences appear to be too great to be explained by accidental differences in experimental conditions and cannot be explained simply by failure to isolate all of one or other of the products, so the most likely explanation is that there is equilibration between the two intermediate organolithium species **8** and **11**. The equilibrium position would favor **11** and a highly reactive electrophile such as cyclohexanone might trap the equilibrium mixture sufficiently rapidly to produce more-or-less the proportions of products that reflect the two lithium species in the equilibrium mixture. However, a relatively unreactive electrophile that reacted more rapidly with **11** than with **8** would remove **11** from the mixture, thereby allowing the equilibrium to shift by conversion of **8** into more **11**, resulting ultimately in the production of a significantly higher yield of ring-substitution product. This would explain the 95% production of ring-substitution products in the case of iodoethane as electrophile. The result is in sharp contrast with the early results reported by Simig and Schlosser[12] for the α-lithiation of *N*-[2-(4-methoxyphenyl)ethyl]pivalamide (**1**; Scheme 1), since in this case no α-substitution was observed at all.

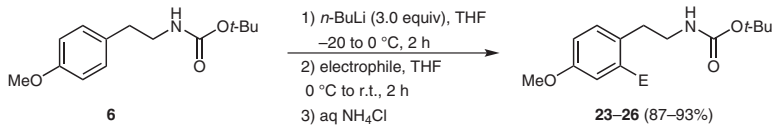
Lithiation of **6** was carried out with *n*-BuLi under the standard conditions that were used for **5**, followed by reaction with various electrophiles (benzophenone, 4′-methoxyacetophenone, dimethylformamide, and iodoethane) (Scheme 5). Each reaction was conducted under identical conditions and then quenched by the addition of aqueous NH_4Cl. Afterwards, the crude products were separated by column chromatography (silica gel; Et_2O–hexane, 1:1) to give the corresponding substituted derivatives **23**–**26** (Scheme 5) in high yields (Table 3). Clearly there was no *N*-methyl group to be lithiated in this instance, but it is noteworthy that again no α-substitution was detected.

In conclusion, *N*′-[2-(4-methoxyphenyl)ethyl]-*N*,*N*-dimethylurea (**5**) and *tert*-butyl (2-(4-methoxyphenyl)ethyl)carbamate (**6**) undergo lithiation with *n*-BuLi at –20 to 0 °C, followed by treatment with various electrophiles, to give high yields of the corresponding substituted products having the substituent *ortho* to the directing group. Side-products were obtained in low yields from the urea derivative as a result of substitution at one of the methyl groups.

Table 3 Synthesis of Substituted Derivatives **23**–**26** from Lithiation and Substitution of **6** (Scheme 5)

Product	Electrophile	E	Yield (%)[a]
23	Ph_2CO	$Ph_2C(OH)$	89
24	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	93
25	Me_2NCHO	CHO	87
26	EtI	Et	90

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



Scheme 5 Lithiation and substitution of *tert*-butyl [2-(4-methoxyphenyl)ethyl]carbamate (**6**)

Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV500 spectrometer operating at 500 MHz for ^{1}H and 125 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 Waters GCT Premier spectrometer and high-resolution mass spectra were recorded on a Waters LCT Premier XE instrument. IR spectra were recorded on a Jasco FT/IR-660 plus instrument by dissolving the product in $CHCl_3$, applying droplets on a NaCl plate and allowing the solvent to evaporate. The structure of **10** was solved by direct methods using SHELXS-96[14] and refined with all data on F^2 full-matrix least squares using SHELXL-97.[15] 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.[16] 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.[17]

2-(4-Methoxyphenyl)ethanamine (4)

A solution of $AlCl_3$ (6.70 g, 50 mmol) in anhydrous Et_2O (50 mL) was added to $LiAlH_4$ (5.70 g, 150.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min. A solution of 2-(4-methoxyphenyl)acetonitrile (**3**; 10.00 g, 68.0 mmol) in anhydrous Et_2O (15 mL) was added to the mixture at 0 °C. The reaction mixture was stirred overnight at r.t. The mixture was diluted with Et_2O (25 mL) and quenched with H_2O (100 mL). After acidifying the solution with concd H_2SO_4, it was basified with aq 6 M NaOH. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **4** (9.86 g, 65.3 mmol, 96%) as a white crystalline solid; mp 113–115 °C.

IR (FT): 3319–3201, 2959, 1512 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.75 (d, *J* = 8 Hz, 2 H, H-3/H-5), 3.69 (s, 3 H, OCH_3), 2.83 (t, *J* = 7 Hz, 2 H, C*H*$_2$NH$_2$), 2.59 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar), 1.22 (br, D_2O exch, 2 H, NH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1 (s, C-4), 139.9 (s, C-1), 129.7 (d, C-2/C-6), 113.9 (d, C-3/C-5), 55.2 (q, OCH_3), 43.7 (t, CH_2NH_2), 39.2 (t, *C*H$_2$Ar).

MS (ES$^+$): *m*/*z* (%) = 151 (50, [M]$^+$), 134 (20), 122 (100), 107 (62), 91 (90), 77 (91).

HRMS (ES$^+$): *m*/*z* [M$^+$] calcd for $C_9H_{13}NO$: 151.0997; found: 151.1000.

***N′*-[2-(4-Methoxyphenyl)ethyl]-*N*,*N*-dimethylurea (5)**

A stirred mixture of **4** (9.86 g, 65.2 mmol), dimethylcarbamoyl chloride (8.41 g, 78.3 mmol), and Et_3N (9.89 g, 97.8 mmol) in CH_2Cl_2 (100 mL) was heated under reflux for 1 h. The mixture was allowed to cool and the solid formed was collected by filtration and then washed with H_2O (2 × 25 mL). The solid was purified by crystallization from hexane to give pure **5** (14.04 g, 63.3 mmol, 97%) as a white crystalline solid; mp 80–82 °C.

IR (FT): 3341, 2933, 1634, 1538, 1357 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.85 (d, *J* = 8 Hz, 2 H, H-3/H-5), 4.42 (br, D_2O exch, 1 H, NH), 3.80 (s, 3 H, OCH_3), 3.45 (t, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.86 [s, 6 H, N(CH$_3$)$_2$], 2.76 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C-4), 158.2 (s, C=O), 131.5 (s, C-1), 129.7 (d, C-2/C-6), 114.0 (d, C-3/C-5), 55.2 (q, OCH_3), 42.3 (t, CH_2NH), 36.1 [q, N(CH$_3$)$_2$], 35.5 (t, *C*H$_2$Ar).

MS (EI): *m*/*z* (%) = 222 (80, [M]$^+$), 190 (25), 177 (40), 134 (100), 72 ([Me$_2$NCO$^+$], 98).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{18}N_2O_2$: 222.1368; found: 222.1374.

***tert*-Butyl [2-(4-Methoxyphenyl)ethyl]carbamate (6)**

To a cooled (0 °C) solution of **4** (5.00 g, 33.1 mmol) and Et_3N (5.02 g, 49.7 mmol) in CH_2Cl_2 (50 mL) was slowly added di-*tert*-butyl dicarbonate (8.67 g, 39.7 mmol) in a dropwise manner. The cooling bath was removed and the reaction mixture was stirred for 1 h at r.t. The mixture was poured onto H_2O (50 mL). The organic layer was separated, washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The solid obtained was purified by crystallization from hexane to give pure **6** (7.98 g, 31.8 mmol, 96%) as a white solid; mp 68–70 °C.

IR (FT): 3360, 2932, 1682, 1540, 1365 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 9 Hz, 2 H, H-2/H-6), 6.87 (d, *J* = 9 Hz, 2 H, H-3/H-5), 4.54 (br, D_2O exch, 1 H, NH), 3.81 (s, 3 H, OCH_3), 3.36 (app q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.76 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar), 1.46 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C-4), 155.9 (s, C=O), 131.0 (s, C-1), 129.7 (d, C-2/C-6), 114.0 (d, C-3/C-5), 79.2 [s, *C*(CH$_3$)$_3$], 55.3 (q, OCH_3), 42.0 (t, CH_2NH), 35.3 (t, *C*H$_2$Ar), 28.4 [q, C(*C*H$_3$)$_3$].

MS (EI): *m*/*z* (%) = 251 (3, [M]$^+$), 218 (22), 195 (58), 177 (90), 151 (78), 122 (100), 85 (98), 65 (88).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{14}H_{21}NO_3$: 251.1521; found: 251.1519.

Lithiation and Substitution of *N′*-[2-(4-methoxyphenyl)ethyl]-*N*,*N*-dimethylurea (5) and *tert*-Butyl [2-(4-methoxyphenyl)ethyl]carbamate (6); General Procedure

A solution of *n*-BuLi in hexane (1.85 mL, 1.6 M, 2.97 mmol) was added to a stirred solution of **5** (0.20 g) or a solution of *n*-BuLi in hexane (1.62 mL, 1.6 M, 2.60 mmol) was added to a stirred solution of **6** (0.20 g) at –20 °C in anhydrous THF (15 mL) under a N_2 atmosphere in each case. The mixture was stirred at 0 °C for 2 h. The mixture was re-cooled to –60 °C and the electrophile (1.26 mmol), in anhydrous THF (5 mL) if solid, neat otherwise, was added. The reaction mixture was stirred for 2 h at r.t. The mixture was quenched with sat. aq NH_4Cl (20 mL) and diluted with Et_2O (20 mL). The organic layer was separated, washed with H_2O (2 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; hexane–Et_2O, 1:1 by volume) to give pure products.

***N*-(2-Hydroxy-2,2-diphenylethyl)-*N*′-[2-(4-methoxyphenyl)ethyl]-*N*-methylurea (7)**
Yield: 0.025 g (0.060 mmol, 7%); colorless oil.

IR (FT): 3336, 2952, 1611, 1511, 1301, 1246 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7 Hz, 4 H, H-2/H-6 of 2 C_6H_5), 7.24 (app t, *J* = 7 Hz, 4 H, H-3/H-5 of 2 C_6H_5), 7.18–7.13 (m, 2 H, H-4 of 2 C_6H_5), 7.00 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.75 (d, *J* = 8 Hz, 2 H, H-3/H-5), 6.52 (br, D_2O exch, 1 H, OH), 4.38 (t, D_2O exch, *J* = 7 Hz, 1 H, NH), 4.05 (s, 2 H, CH_2COH), 3.70 (s, 3 H, OCH_3), 3.36 (app q, *J* = 7 Hz, 2 H, CH_2NH), 2.67 (t, *J* = 7 Hz, 2 H, CH_2Ar), 2.16 (s, 3 H, NCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6 (s, C-4), 158.2 (s, C=O), 145.8 (s, C-1 of 2 C_6H_5), 131.1 (s, C-1), 129.8 (d, C-2/C-6), 128.0 (d, C-2/C-6 of 2 C_6H_5), 126.9 (d, C-4 of 2 C_6H_5), 126.5 (d, C-3/C-5 of 2 C_6H_5), 114.0 (d, C-3/C-5), 78.6 (s, C-OH), 61.0 (t, CH_2COH), 55.2 (q, OCH_3), 42.4 (t, CH_2NH), 36.8 (q, NCH_3), 35.1 (t, CH_2Ar).

MS (EI): *m*/*z* (%) = 386 (40, $[M - H_2O]^+$), 298 (80), 182 (83), 121 (97), 83 (100).

HRMS (EI): *m*/*z* $[M - H_2O]^+$ calcd for $C_{25}H_{26}N_2O_2$: 386.1994; found: 386.1989.

***N*′-{2-[2-(Hydroxydiphenylmethyl)-4-methoxyphenyl]ethyl}-*N*,*N*-dimethylurea (10)**
Yield: 0.30 g (0.76 mmol, 85%); white solid; mp 157–159 °C.

IR (FT): 3227, 2952, 1620, 1541, 1318, 1242 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.16 (m, 10 H, 2 C_6H_5), 7.08 (d, *J* = 8 Hz, 1 H, H-6), 6.69 (dd, *J* = 3, 8 Hz, 1 H, H-5), 6.14 (d, *J* = 3 Hz, 1 H, H-3), 4.87 (s, D_2O exch, 1 H, OH), 4.72 (br, D_2O exch, 1 H, NH), 3.52 (s, 3 H, OCH_3), 3.23 (app q, *J* = 7 Hz, 2 H, CH_2NH), 2.73 [s, 6 H, $N(CH_3)_2$], 2.50 (t, *J* = 7 Hz, 2 H, CH_2Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7 (s, C-4), 156.9 (s, C=O), 147.3 (s, C-1 of 2 C_6H_5), 146.8 (s, C-2), 132.6 (d, C-6), 130.9 (s, C-1), 127.8 (d, C-3/C-5 of 2 C_6H_5), 127.7 (d, C-2/C-6 of 2 C_6H_5), 127.0 (d, C-4 of 2 C_6H_5), 117.0 (d, C-3), 111.9 (d, C-5), 82.4 (s, COH), 54.9 (q, OCH_3), 42.6 (t, CH_2NH), 36.0 [q, $N(CH_3)_2$], 33.5 (t, CH_2Ar).

MS (EI): *m*/*z* (%) = 386 (25, $[M - H_2O]^+$), 316 (98), 285 (99), 209 (97), 165 (100), 83 (98).

HRMS (EI): *m*/*z* $[M - H_2O]^+$ calcd for $C_{25}H_{26}N_2O_2$: 386.1994; found: 386.1992.

***N*′-[2-Hydroxy-2-(4-methoxyphenyl)propyl]-*N*-[2-(4-methoxyphenyl)ethyl]-*N*-methylurea (12)**
Yield: 0.04 g (0.10 mmol, 12%); colorless oil.

IR (FT): 3327, 2933, 1611, 1543, 1300, 1247 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-$MeOC_6H_4$), 7.11 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.88 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$MeOC_6H_4$), 6.85 (d, *J* = 8 Hz, 2 H, H-3/H-5), 5.24 (br s, D_2O exch, 1 H, OH), 4.78 (br, D_2O exch, 1 H, NH), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.67 (d, *J* = 15 Hz, 1 H, C$H_a$$H_b$-COH), 3.51–3.37 (m, 2 H, CH_2NH), 3.28 (d, *J* = 15 Hz, 1 H, CH_aH_bCOH), 2.78–2.75 (m, 2 H, CH_2Ar), 2.48 (s, 3 H, NCH_3), 1.55 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3 (s, C-4), 158.4 (s, C-4 of 4-$MeOC_6H_4$), 158.2 (s, C=O), 138.5 (s, C-1 of 4-$MeOC_6H_4$), 131.2 (s, C-1), 129.8 (d, C-2/C-6), 126.5 (d, C-2/C-6 of 4-$MeOC_6H_4$), 114.0 (d, C-3/C-5 of 4-$MeOC_6H_4$), 113.4 (d, C-3/C-5), 75.4 (s, COH), 62.8 (t, CH_2COH), 55.3 (q, OCH_3), 55.2 (q, OCH_3), 42.3 (t, CH_2NH), 37.1 (q, NCH_3), 35.2 (t, CH_2Ar), 27.2 (q, CH_3).

MS (EI): *m*/*z* (%) = 354 (6, $[M - H_2O]^+$), 222 (77), 177 (94), 135 (97), 121 (100), 107 (55), 91 (70), 77 (87).

HRMS (EI): *m*/*z* $[M - H_2O]^+$ calcd for $C_{21}H_{26}N_2O_3$: 354.1943; found: 354.1951.

***N*′-(2-{2-[1-Hydroxy-1-(4-methoxyphenyl)ethyl]-4-methoxyphenyl}ethyl)-*N*,*N*-dimethylurea (13)**
Yield: 0.27 g (0.73 mmol, 82%); white solid; mp 137–140 °C.

IR (FT): 3342, 2933, 1633, 1537, 1299, 1246 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.28 (s, D_2O exch, 1 H, OH), 7.25 (d, *J* = 8 Hz, 2 H, H-2/H-6 of 4-$MeOC_6H_4$), 7.19 (d, *J* = 3 Hz, 1 H, H-3), 7.12 (d, *J* = 8 Hz, 1 H, H-6), 6.82–6.80 (m, 3 H, H-5 and H-3/H-5 of 4-$MeOC_6H_4$), 4.58 (br, D_2O exch, 1 H, NH), 3.84 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.25 (m, 1 H, C$H_a$$H_b$NH), 3.04 (m, 1 H, CH_aH_bNH), 2.82 [s, 6 H, $N(CH_3)_2$], 2.64 (m, 1 H, C$H_a$$H_b$Ar), 2.45 (m, 1 H, CH_aH_bAr), 1.90 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C-4), 158.2 (s, C-4 of 4-$MeOC_6H_4$), 157.4 (s, C=O), 146.6 (s, C-2), 141.4 (s, C-1 of 4-$MeOC_6H_4$), 132.6 (d, C-6), 130.3 (s, C-1), 126.4 (d, C-2/C-6 of 4-$MeOC_6H_4$), 113.7 (d, C-3), 113.3 (d, C-3/C-5 of 4-$MeOC_6H_4$), 111.6 (d, C-5), 76.5 (s, COH), 55.28 (q, OCH_3), 55.22 (q, OCH_3), 42.5 (t, CH_2NH), 36.1 [q, $N(CH_3)_2$], 33.1 (q, CH_3), 33.0 (t, CH_2Ar).

MS (EI): *m*/*z* (%) = 354 (60, $[M - H_2O]^+$), 312 (45), 266 (100), 253 (93), 222 (50), 163 (90), 134 (98), 83 (99).

HRMS (EI): *m*/*z* $[M - H_2O]^+$ calcd for $C_{21}H_{26}N_2O_3$: 354.1943; found: 354.1936.

***N*-[(1-Hydroxycyclohexyl)methyl]-*N*′-[2-(4-methoxyphenyl)ethyl]-*N*-methylurea (14)**
Yield: 0.048 g (0.15 mmol, 17%); colorless oil.

IR (FT): 3348, 2931, 1633, 1539, 1245 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 9 Hz, 2 H, H-2/H-6), 6.78 (d, *J* = 9 Hz, 2 H, H-3/H-5), 4.97 (br, D_2O exch, 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.36 (app q, *J* = 7 Hz, 2 H, CH_2NH), 3.15 (s, 2 H, CH_2COH), 2.82 (s, 3 H, NCH_3), 2.69 (t, *J* = 7 Hz, 2 H, CH_2Ar), 1.54–1.18 (m, 10 H, *c*-Hex).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3 (s, C-4), 158.2 (s, C=O), 131.5 (s, C-1), 129.8 (d, C-2/C-6), 114.0 (d, C-3/C-5), 73.0 (s, C-1 of *c*-Hex), 60.6 (t, CH_2COH), 55.3 (q, OCH_3), 42.3 (t, CH_2NH), 37.8 (q, NCH_3), 35.7 (t, CH_2Ar), 35.3 (t, C-2/C-6 of *c*-Hex), 25.8 (t, C-4 of *c*-Hex), 22.0 (t, C-3/C-5 of *c*-Hex).

MS (EI): *m*/*z* (%) = 320 (12, $[M]^+$), 222 (98), 177 (89), 150 (11), 134 (100), 121 (97), 99 (83), 77 (81).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{28}N_2O_3$: 320.2100; found: 320.2100.

***N*′-{2-[2-(1-Hydroxycyclohexyl)-4-methoxyphenyl]ethyl}-*N*,*N*-dimethylurea (15)**
Yield: 0.22 g (0.69 mmol, 77%); colorless oil.

IR (FT): 3349, 2932, 1634, 1538, 1245 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8 Hz, 1 H, H-6), 6.87 (d, *J* = 3 Hz, 1 H, H-3), 6.78 (dd, *J* = 3, 8 Hz, 1 H, H-5), 4.97 (br s, D_2O exch, 1 H, OH), 4.28 (br, D_2O exch, 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.37 (app q, *J* = 7 Hz, 2 H, CH_2NH), 3.07 (t, *J* = 7 Hz, 2 H, CH_2Ar), 2.77 [s, 3 H, $N(CH_3)_2$], 1.78–1.18 (m, 10 H, *c*-Hex).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9 (s, C-4), 157.7 (s, C=O), 142.3 (s, C-2), 133.2 (d, C-6), 129.8 (s, C-1), 114.0 (d, C-5), 111.1 (d, C-3), 74.5 (s, C-1 of *c*-Hex), 55.2 (q, OCH_3), 43.9 (t, CH_2NH), 38.5 (t, CH_2Ar), 36.3 [q, $N(CH_3)_2$], 35.3 (t, C-2/C-6 of *c*-Hex), 25.4 (t, C-4 of *c*-Hex), 22.1 (t, C-3/C-5 of *c*-Hex).

MS (ES): *m*/*z* (%) = 384 (20, $[M + MeCNNa]^+$), 359 (22, $[M + K]^+$), 343 (100, $[M + Na]^+$).

HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{28}N_2O_3$ + Na: 343.1998; found: 343.1995.

***N*-(2-Hydroxy-2-phenylethyl)-*N*′-[2-(4-methoxyphenyl)ethyl]-*N*-methylurea (16)**
Yield: 0.016 g (0.050 mmol, 6%); colorless oil.

IR (FT): 3338, 2932, 1639, 1541, 1246 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7 Hz, 1 H, H-4 of C_6H_5), 7.29–7.25 (m, 4 H, H-2/H-3/H-5/H-6 of C_6H_5), 7.05 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.78 (d, *J* = 8 Hz, 2 H, H-3/H-5), 4.82 (dd, *J* = 3, 8 Hz, 1 H, CH), 4.65 (br, D_2O exch, 1 H, NH), 4.60 (br, D_2O exch, 1 H, OH), 3.72 (s, 3 H, OCH_3), 3.47 (dd, *J* = 7, 15 Hz, 1 H, CH_aH$_b$-CHOH), 3.45–3.33 (m, 3 H, CH$_a$$H_b$CHOH and C$H_2$NH), 2.70 (app t, *J* = 7 Hz, 2 H, CH_2Ar), 2.58 (s, 3 H, NCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0 (s, C-4), 158.2 (s, C=O), 142.4 (s, C-1 of C_6H_5), 131.2 (s, C-1), 129.8 (d, C-2/C-6), 128.4 (d, C-3/C-5 of C_6H_5), 127.5 (d, C-4 of C_6H_5), 125.8 (d, C-2/C-6 of C_6H_5), 114.0 (d, C-3/C-5), 73.9 (d, CHOH), 58.3 (t, *C*H$_2$CHOH), 55.2 (q, OCH_3), 42.3 (t, CH_2NH), 36.0 (q, NCH_3), 35.3 (t, *C*H$_2$Ar).

MS (EI): *m*/*z* (%) = 329 (17, $[M + H]^+$), 222 (100), 207 (17), 190 (32), 178 (90), 150 (9), 134 (99), 121 (97), 105 (93), 91 (96).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{25}N_2O_3$: 329.1865; found: 329.1875.

_N′_-(2-{2-[Hydroxy(phenyl)methyl]-4-methoxyphenyl}ethyl)-_N_,_N_-dimethylurea (17)
Yield: 0.24 g (0.73 mmol, 82%); colorless oil.

IR (FT): 3337, 2927, 1630, 1537, 1249 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 7 Hz, 2 H, H-2/H-6 of C_6H_5), 7.26 (app t, *J* = 8 Hz, 2 H, H-3/H-5 of C_6H_5), 7.20–7.17 (m, 2 H, OH and H-4 of C_6H_5), 7.00 (d, *J* = 8 Hz, 1 H, H-6), 6.79 (d, *J* = 3 Hz, 1 H, H-3), 6.70 (dd, *J* = 3, 8 Hz, 1 H, H-5), 6.04 (s, 1 H, CH), 4.48 (br, D_2O exch, 1 H, NH), 3.66 (s, 3 H, OCH_3), 3.43–3.25 (m, 2 H, CH_2NH), 2.87 (ddd, *J* = 6, 8, 14 Hz, 1 H, CH_aH$_b$Ar), 2.76 [s, 6 H, $N(CH_3)_2$], 2.64 (app dt, *J* = 8, 14 Hz, 1 H, CH$_a$$H_b$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C-4), 158.3 (s, C=O), 143.5 (s, C-1 of C_6H_5), 135.1 (s, C-2), 131.3 (d, C-6), 129.0 (s, C-1), 128.3 (d, C-3/C-5 of C_6H_5), 127.3 (d, C-4 of C_6H_5), 126.8 (d, C-2/C-6 of C_6H_5), 113.7 (d, C-3), 113.0 (d, C-5), 72.7 (d, CH), 55.2 (q, OCH_3), 42.5 (t, CH_2NH), 36.2 [q, $N(CH_3)_2$], 32.8 (t, *C*H$_2$Ar).

MS (EI): *m*/*z* (%) = 328 (40, $[M]^+$), 310 (93), 282 (50), 265 (24), 238 (100), 209 (96), 194 (88), 149 (89), 134 (58), 121 (87), 105 (83), 77 (95).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{24}N_2O_3$: 328.1787; found: 328.1787.

_N_-{2-[4-(Dimethylamino)phenyl]-2-hydroxyethyl}-_N′_-[2-(4-methoxyphenyl)ethyl]-_N_-methylurea (18)
Yield: 0.030 g (0.09 mmol, 10%); colorless oil.

IR (FT): 3371, 2926, 1611, 1520, 1349, 1245 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8 Hz, 2 H, H-2/H-6 of 4-$Me_2NC_6H_4$), 7.05 (d, *J* = 8 Hz, 2 H, H-2/H-6), 6.79 (d, *J* = 8 Hz, 2 H, H-3/H-5), 6.65 (d, *J* = 8 Hz, 2 H, H-3/H-5 of 4-$Me_2NC_6H_4$), 6.57 (br, D_2O exch, 1 H, OH), 4.73 (br dd, *J* = 2, 8 Hz, 1 H, CH), 4.70 (br, D_2O exch, 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.48 (dd, *J* = 8, 15 Hz, 1 H, CH_aH$_b$CHOH), 3.42 (s, 3 H, NCH_3) 3.39 (app q, *J* = 7 Hz, 3 H, CH_2NH), 3.27 (dd, *J* = 3, 15 Hz, 1 H, CH$_a$$H_b$CHOH), 2.87 [s, 6 H, $N(CH_3)_2$], 2.70 (app t, *J* = 7 Hz, 2 H, CH_2Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1 (s, C-4), 157.9 (s, C=O), 150.3 (s, C-4 of 4-$Me_2NC_6H_4$), 131.4 (s, C-1), 130.0 (s, C-1 of 4-$Me_2NC_6H_4$), 129.8 (d, C-2/C-6), 126.7 (d, C-2/C-6 of 4-$Me_2NC_6H_4$), 114.0 (d, C-3/C-5), 112.5 (d, C-3/C-5 of 4-$Me_2NC_6H_4$), 73.6 (d, COH), 58.2 (t, *C*H$_2$CHOH), 55.2 (q, OCH_3), 42.4 (t, CH_2NH), 40.6 [q, $N(CH_3)_2$], 36.0 (q, NCH_3), 35.4 (t, *C*H$_2$Ar).

MS (EI): *m*/*z* (%) = 371 (14, $[M]^+$), 353 (92), 232 (95), 176 (51), 134 (100), 121 (82), 91 (26), 77 (32).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{29}N_3O_3$: 371.2209; found: 371.2209.

_N′_-(2-{2-[(4-(Dimethylamino)phenyl)(hydroxy)methyl]-4-methoxyphenyl}ethyl)-_N_,_N_-dimethylurea (19)
Yield: 0.26 g (0.72 mmol, 80%); colorless oil.

IR (FT): 3361, 2926, 1612, 1521, 1351, 1245 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 (d, *J* = 8 Hz, 1 H, H-6), 6.95 (d, *J* = 8 Hz, 2 H, H-2/H-6 of 4-$Me_2NC_6H_4$), 6.70 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.55 (d, *J* = 8 Hz, 2 H, H-3/H-5 of 4-$Me_2NC_6H_4$), 6.50 (d, *J* = 2 Hz, 1 H, H-3), 6.02 (s, D_2O exch, 1 H, OH), 5.96 (s, 1 H, CH), 4.24 (app. t, D_2O exch, *J* = 7 Hz, 1 H, NH), 3.64 (s, 3 H, OCH_3), 3.53 (dddd, *J* = 1, 2, 7, 14 Hz, 1 H, CH_aH$_b$NH), 3.18 (app ddd, *J* = 5, 12, 14 Hz, 1 H, CH$_a$$H_b$NH), 2.90–2.82 [m, 7 H, CH_aH$_b$Ar and 4-(CH_3)$_2$NC$_6$H$_4$], 2.77 [s, 6 H, $N(CH_3)_2$], 2.63 (ddd, *J* = 2, 5, 16 Hz, 1 H, CH_aH$_b$Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.6 (s, C-4), 157.5 (s, C=O), 149.6 (s, C-4 of 4-$Me_2NC_6H_4$), 137.4 (s, C-2), 132.0 (s, C-1 of 4-$Me_2NC_6H_4$), 130.7 (s, C-1), 129.5 (d, C-2/C-6 of 4-$Me_2NC_6H_4$), 126.8 (d, C-6), 113.3 (d, C-3), 112.7 (d, C-5), 112.0 (d, C-3/C-5 of 4-$Me_2NC_6H_4$), 77.4 (d, COH), 55.3 (q, OCH_3), 40.6 (t, CH_2NH), 40.3 [q, 4-(*C*H$_3$)$_2$NC$_6$H$_4$], 38.8 [q, $N(CH_3)_2$], 27.8 (t, *C*H$_2$Ar).

MS (EI): *m*/*z* (%) = 353 (83, $[M – H_2O]^+$), 308 (67), 281 (100), 264 (64), 236 (42), 165 (31), 83 (45), 72 (65).

HRMS (EI): *m*/*z* $[M – H_2O]^+$ calcd for $C_{21}H_{27}N_3O_2$: 353.2103; found: 353.2114.

_N′_-[2-(2-Formyl-4-methoxyphenyl)ethyl]-_N_,_N_-dimethylurea (20)
Yield: 0.20 g (0.81 mmol, 90%); colorless oil.

IR (FT): 3346, 2932, 1700, 1685, 1540, 1362 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.38 (s, 1 H, CHO), 7.58 (d, *J* = 2 Hz, 1 H, H-3), 7.35 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.88 (d, *J* = 8 Hz, 1 H, H-6), 4.48 (br D_2O exch, 1 H, NH), 3.85 (s, 3 H, OCH_3), 3.39 (app q, *J* = 7 Hz, 2 H, CH_2NH), 2.80 [s, 6 H, $N(CH_3)_2$], 2.73 (t, *J* = 7 Hz, 2 H, CH_2Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.9 (d, CHO), 160.63 (s, C=O), 160.61 (s, C-4), 140.7 (s, C-2), 140.5 (s, C-1), 136.5 (d, C-6), 128.4 (d, C-5), 112.0 (d, C-3), 55.8 (q, OCH_3), 42.1 (t, CH_2NH), 36.3 [q, $N(CH_3)_2$], 35.4 (t, *C*H$_2$Ar).

MS (AP): *m*/*z* (%) = 251 (100, $[M + H]^+$), 224 (9), 206 (10), 135 (22), 124 (13), 84 (6).

HRMS (AP): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O_3$: 251.1760; found: 251.1764.

_N′_-[2-(2-Ethyl-4-methoxyphenyl)ethyl]-_N_,_N_-dimethylurea (21)
Yield: 0.19 g (0.77 mmol, 86%); colorless oil.

IR (FT): 3381, 2932, 1634, 1531, 1246 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 8 Hz, 1 H, H-6), 6.69 (d, *J* = 3 Hz, 1 H, H-3), 6.62 (dd, *J* = 3, 8 Hz, 1 H, H-5), 4.37 (br, exchangeable, 1 H, NH), 3.72 (s, 3 H, OCH_3), 3.34 (app q, *J* = 7 Hz, 2 H, CH_2NH), 2.80 [s, 6 H, $N(CH_3)_2$], 2.72 (t, *J* = 7 Hz, 2 H, CH_2Ar), 2.60 (q, *J* = 8 Hz, 2 H, CH_2CH$_3$), 1.15 (t, *J* = 8 Hz, 2 H, CH$_2$CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.34 (s, C-4), 158.27 (s, C=O), 132.7 (s, C-2), 131.1 (s, C-1), 130.6 (d, C-6), 114.4 (d, C-5), 111.0 (d, C-3), 55.2 (q, OCH_3), 41.9 (t, CH_2NH), 36.2 [q, $N(CH_3)_2$], 32.5 (t, *C*H$_2$Ar), 25.7 (t, *C*H$_2$CH$_3$), 15.8 (q, CH$_2$*C*H$_3$).

MS (AP): *m*/*z* (%) = 251 (100, $[M + H]^+$), 206 (8), 163 (5), 135 (10), 90 (4).

HRMS (AP): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_2$: 251.1760; found: 251.1771.

_N′_-Ethyl-_N′_-[2-(2-ethyl-4-methoxyphenyl)ethyl]-_N_,_N_-dimethylurea (22)
Yield: 0.025 g (0.090 mmol, 10%); colorless oil.

IR (FT): 2935, 1652, 1505, 1251 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 8 Hz, 1 H, H-6), 6.67 (d, *J* = 3 Hz, 1 H, H-3), 6.62 (dd, *J* = 3, 8 Hz, 1 H, H-5), 3.71 (s, 3 H, OCH_3), 3.19–3.10 (m, 4 H, ArCH$_2$CH_2N and NCH_2CH$_3$), 2.73 [s,

6 H, $N(CH_3)_2$], 2.71 (q, J = 7 Hz, 2 H, $ArCH_2CH_3$), 2.60 (t, J = 7 Hz, 2 H, $ArCH_2CH_2N$), 1.16 (t, J = 7 Hz, 3 H, NCH_2CH_3), 1.05 (t, J = 7 Hz, 3 H, $ArCH_2CH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3 (s, C=O), 158.3 (s, C-4), 143.7 (s, C-2), 131.5 (s, C-1), 130.7 (d, C-6), 114.3 (d, C-5), 111.0 (d, C-3), 55.2 (q, OCH_3), 49.2 (t, $ArCH_2CH_2N$), 43.5 (t, NCH_2CH_3), 38.7 [q, $N(CH_3)_2$], 30.6 (t, $ArCH_2CH_2N$), 25.7 (t, $ArCH_2CH_3$), 15.4 (q, $ArCH_2CH_3$), 13.5 (q, NCH_2CH_3).

MS (EI): m/z (%) = 278 (17, $[M]^+$), 220 (22), 205 (64), 162 (25), 129 (60), 85 (100), 72 (80).

HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{26}N_2O_2$: 278.1994; found: 278.1991.

***tert*-Butyl {2-[2-(Hydroxydiphenylmethyl)-4-methoxyphenyl]ethyl}carbamate (23)**
Yield: 0.30 g (0.70 mmol, 89%); colorless oil.

IR (FT): 3351, 2977, 1620, 1541, 1318, 1242 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.14 (m, 10 H, 2 C_6H_5), 7.02 (dd, J = 2, 8 Hz, 1 H, H-5), 6.80 (d, J = 8 Hz, 1 H, H-6), 6.24 (d, J = 2 Hz, 1 H, H-3), 5.18 (s, D_2O exch, 1 H, OH), 4.37 (br, D_2O exch, 1 H, NH), 3.50 (s, 3 H, OCH_3), 3.10 (br app q, 2 H, CH_2NH), 2.60 (t, J = 7 Hz, 2 H, CH_2Ar), 1.33 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C-4), 155.8 (s, C=O), 146.6 (s, C-1 of 2 C_6H_5), 135.7 (s, C-2), 131.0 (s, C-1), 130.6 (d, C-6), 127.8 (d, C-3/C-5 of 2 C_6H_5), 127.7 (d, C-2/C-6 of 2 C_6H_5), 127.0 (d, C-4 of 2 C_6H_5), 114.0 (d, C-3), 112.5 (d, C-5), 82.0 (s, COH), 79.1 [s, $C(CH_3)_3$], 55.9 (q, OCH_3), 41.8 (t, CH_2NH), 35.4 (t, CH_2Ar), 28.5 [q, $C(CH_3)_3$].

MS (ES^+): m/z (%) = 456 (100, $[M + Na]^+$), 416 (5), 205 (2).

HRMS (ES^+): m/z $[M + Na]^+$ calcd for $C_{27}H_{31}NO_4$ + ^{23}Na: 456.2151; found: 456.2141.

***tert*-Butyl (2-{2-[(4-(Dimethylamino)phenyl)(hydroxy)methyl]-4-methoxyphenyl}ethyl)carbamate (24)**
Yield: 0.29 g (0.73 mmol, 93%); white solid; mp 179–181 °C.

IR (FT): 3361, 2974, 1612, 1520, 1364, 1248 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-$Me_2NC_6H_4$), 7.07 (br, 1 H, H-3), 6.98 (dd, J = 1, 8 Hz, 1 H, H-5), 6.73 (d, J = 8 Hz, 1 H, H-6), 6.62 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-$Me_2NC_6H_4$), 5.88 (br, D_2O exch, 1 H, NH), 4.45 (br, D_2O exch, 1 H, OH), 3.70 (s, 3 H, OCH_3), 3.25 (app q, J = 7 Hz, 2 H, CH_2NH), 2.85 [s, 6 H, $N(CH_3)_2$], 2.64 (t, J = 7 Hz, 2 H, CH_2Ar), 1.36 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9 (s, C-4), 155.4 (s, C=O), 149.9 (s, C-4 of 4-$Me_2NC_6H_4$), 132.6 (s, C-2), 131.4 (s, C-1 of 4-$Me_2NC_6H_4$), 131.0 (s, C-1), 128.4 (d, C-6), 127.9 (d, C-3), 127.6 (d, C-2/C-6 of 4-$Me_2NC_6H_4$), 112.4 (d, C-3/C-5 of 4-$Me_2NC_6H_4$), 110.9 (d, C-5), 79.2 [s, $C(CH_3)_3$], 72.0 (d, CH), 55.6 (q, OCH_3), 41.9 (t, CH_2NH), 40.6 [q, $N(CH_3)_2$], 35.5 (t, CH_2Ar), 28.5 [q, $C(CH_3)_3$].

MS (ES^+): m/z (%) = 400 (69, $[M]^+$), 384 (88), 310 (99), 296 (37), 284 (70), 267 (28), 255 (96), 240 (100), 224 (31), 148 (48), 134 (98), 120 (44), 104 (16), 83 (93).

HRMS (ES^+): m/z $[M]^+$ calcd for $C_{23}H_{32}N_2O_4$: 400.2366; found: 400.2362.

***tert*-Butyl [2-(2-Formyl-4-methoxyphenyl)ethyl]carbamate (25)**
Yield: 0.19 g (0.68 mmol, 87%); colorless oil.

IR (FT): 3359, 2927, 1680, 1606, 1499, 1358, 1244 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.37 (s, 1 H, CHO), 7.57 (d, J = 2 Hz, 1 H, H-3), 7.32 (br app d, J = 8 Hz, 1 H, H-5), 6.87 (d, J = 8 Hz, 1 H, H-6), 4.50 (br, D_2O exch, 1 H, NH), 3.84 (s, 3 H, OCH_3), 3.25 (app q, J = 7 Hz, 2 H, CH_2NH), 2.70 (t, J = 7 Hz, 2 H, CH_2Ar), 1.35 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.7 (d, CHO), 160.6 (s, C-4), 155.8 (s, C=O), 136.3 (s, C-2), 131.3 (s, C-1), 128.4 (d, C-6), 124.8 (d, C-5), 112.0 (d, C-3), 79.3 [s, $C(CH_3)_3$], 55.7 (q, OCH_3), 41.7 (t, CH_2NH), 35.1 (t, CH_2Ar), 28.4 [q, $C(CH_3)_3$].

MS (ES^+): m/z (%) = 597 (57, $[2 M + K]^+$), 581 (100, $[2 M + Na]^+$), 343 (63, $[M + MeCNNa]^+$), 318 (60, $[M + K]^+$), 302 (23, $[M + Na]^+$), 287 (18).

HRMS (ES^+): m/z $[M + Na]^+$ calcd for $C_{15}H_{21}NO_4$ + ^{23}Na: 302.1368; found: 302.1375.

***tert*-Butyl [2-(2-Ethyl-4-methoxyphenyl)ethyl]carbamate (26)**
Yield: 0.19 g (0.71 mmol, 90%); colorless oil.

IR (FT): 3355, 2932, 1610, 1501, 1365, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.91–6.89 (m, 2 H, H-3 and H-5), 6.70 (d, J = 8 Hz, 1 H, H-6), 4.46 (br, D_2O exch, 1 H, NH), 3.73 (s, 3 H, OCH_3), 3.26 (br app q, 2 H, CH_2NH), 2.64 (t, J = 7 Hz, 2 H, CH_2Ar), 2.54 (q, J = 7 Hz, 2 H, CH_2CH_3), 1.37 [s, 9 H, $C(CH_3)_3$], 1.11 (t, J = 7 Hz, 3 H, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0 (s, C-4), 155.9 (s, C=O), 132.8 (s, C-2), 130.7 (s, C-1), 129.5 (d, C-6), 126.8 (d, C-3), 110.3 (d, C-5), 79.1 [s, $C(CH_3)_3$], 55.4 (q, OCH_3), 42.0 (t, CH_2NH), 35.4 (t, CH_2Ar), 28.4 [q, $C(CH_3)_3$], 23.2 (t, CH_2CH_3), 14.2 (q, CH_2CH_3).

MS (ES^+): m/z (%) = 279 (45, $[M]^+$), 223 (91), 206 (48), 162 (100), 135 (87), 121 (47), 105 (36), 85 (99).

HRMS (ES^+): m/z $[M]^+$ calcd for $C_{16}H_{25}NO_3$: 279.1834; found: 279.1835.

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Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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