Tetrahedron 67 (2011) 2895–2904

Contents lists available at ScienceDirect

Tetrahedron

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

Studying competitive lithiations at alpha-, *ortho*-, and benzylic positions in various *N*-protected aniline derivatives

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ARTICLE INFO

Article history:
Received 25 January 2011
Received in revised form 18 February 2011
Accepted 21 February 2011
Available online 26 February 2011

Dedicated to Professor Carmen Najera on the occasion of her 60th birthday

Keywords:
Directed metalation
Directing metalation group
Ortho-lithiation
Regioselectivity
Protecting group

ABSTRACT

The directing effects of the *t*-BuOCONH– (NHBoc) and the *t*-BuCONH– (NH–pivaloyl) groups have been investigated on a series of differently substituted anilines. Depending on the nature of the directing group and the substrate, lithiation either occurred in the *ortho*-, benzylic-, or alpha-position. In general, it was observed that ortho-lithiation is the least facile process and alpha-lithiation slightly favored compared to lithiation in the benzylic position. However, it was found that minor changes in the starting materials led to different regioselectivity in the metalation process. For example, changing substituents from methyl to ethyl can result in completely different regioselectivity. As final conclusion, a graphical guideline for lithiation experiments is presented.

1. Introduction

The methodology of directed or heteroatom-facilitated metalation, most importantly lithiation reactions, is a powerful and versatile tool in organic synthesis since many years.[1,2] It is essential for achieving regioselectivity in the synthesis of complex molecules. The use of substrates bearing suitable directing metalation groups (DMGs) offers a clean and fast way for the regioselective synthesis of polysubstituted aromatics or heteroaromatics that would be difficult to obtain through other substitution methods.[3,4] In the last decades, many examples of directed lithiation strategies (with subsequent introduction of an electrophile) have been reported and the subject was repeatedly reviewed.[3,4] Directed ortho-metalation (DOM) and directed remote metalation (DRM) are now widely applied methods in the synthesis of complex molecules, such as pharmaceuticals or natural products.[5–7] Therefore, systematic investigations toward the selectivity and substrate scope of directed metalation reactions are important since these methods can considerably facilitate complex synthesis. The synthetic chemist can nowadays choose from numerous groups promoting *ortho*-, alpha- or remote directed lithiation.[8–10] Carbamates, such as the *t*-BuOCONH (NHBoc) group and amides, such as the *t*-BuCONH (NH–pivaloyl) group have been applied as *ortho*-directing groups since 1979.[3,11] Despite the broad spectrum of available directing groups, the NHBoc– and the NH–pivaloyl-group still are of special value, because the free amino group can be regenerated during the course of a multistep reaction. While the Boc-group can be removed under relatively mild conditions[12] or reduced to the *N*-methyl-group by powerful reducing agents,[13] the pivaloyl-group requires forced hydrolyzing conditions.[14] This can lead to problems, especially when there are other hydrolytically unstable groups present in the molecule. The *ortho*-directing properties of the NHBoc– and the NH–pivaloyl-group have already been studied on a series of different substrates.[15] However, systematic studies on compounds bearing different types of protons (such as benzylic, aromatic, and *N*-alkyl hydrogens) simultaneously available for lithiation in a single molecule are not available to the best of our knowledge. Within this contribution we conducted such a comparative study on a series of aniline derivatives to elaborate how directing effects can be influenced by alkyl-substituents on the amino group or in *ortho*-position in order to be able to predict the products of lithiation reactions on higher substituted substrates (Fig. 1). Such investigations are potentially useful for a large number of synthetic chemists taking into account that many compounds, (e.g., natural products or pharmaceuticals) contain substituted anilines[16–20] and facile ways of accessing these compounds alternative to established routes are highly welcome.

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doi:10.1016/j.tet.2011.02.056

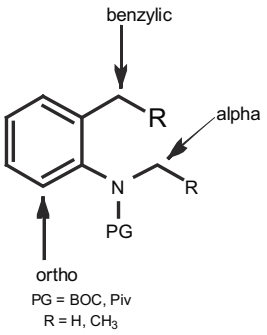
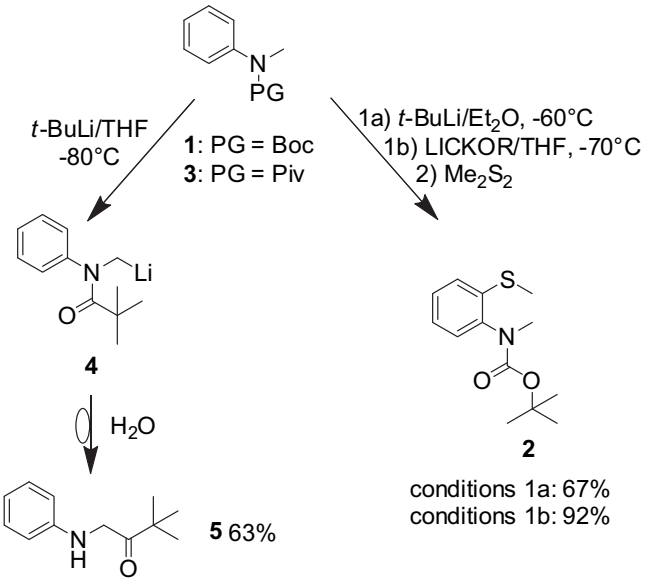


Fig. 1. Possible positions for lithiation.

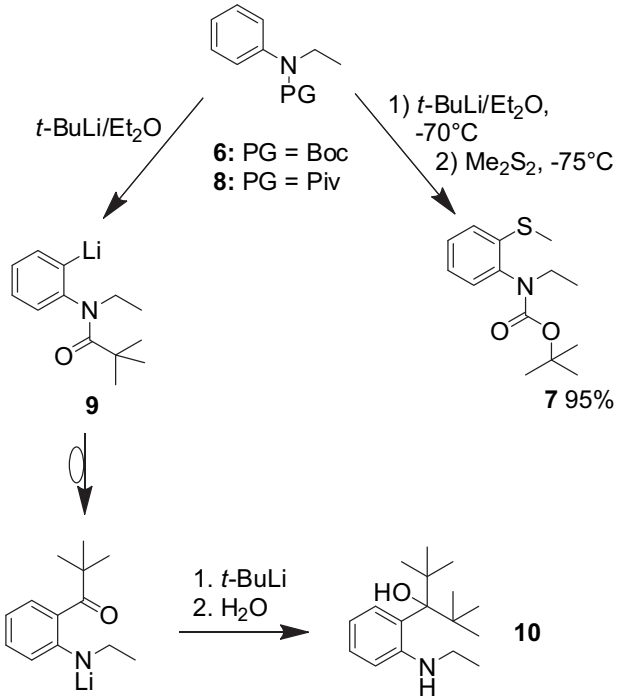
2. Results and discussion

N-Protected *N*-methylaniline was used as the first model-substrate for investigating the directed lithiation. In this compound either deprotonation at the *N*-methyl-group (alpha-lithiation) or at the benzene ring (ortho-lithiation) is possible. Lithiation of pivaloylmethylaniline **3** was described by Hellwinkel and Lämmerzahl:[21] reaction with 1.1 equiv of *t*-BuLi in THF at −80 °C was complete after 2 h and after hydrolysis 3,3-dimethyl-1-(phenylamino)-2-butanone **5** could be isolated in 63% yield. This product was formed through alpha-lithiation and subsequent migration of the pivaloyl-group (Scheme 1). Using this study as starting point, we investigated if switching from the pivaloyl to the Boc-group has an influence on the selectivity of the reaction. Lithiation of **1** with 1.2 equiv of *t*-BuLi in Et_2O at −10 °C led to decomposition of the starting material. At −60 °C, the lithiation reaction was complete after 30 min and quenching with Me_2S_2 as a fast reacting electrophile gave the ortho-lithiated product **2** in 67% yield. This shows that the lithiation was now directed into the *ortho*- rather than the alpha-position. Through lithiation with LICKOR (*t*-BuLi, KO^{t}Bu) in THF at −70 °C the yield could be improved to 92%. This already demonstrates that the nature of the directing group has a significant influence on the position of the lithiation. On *N*-protected-*N*-methylaniline, the Boc-group directs preferably into the *ortho*-position, whereas the pivaloyl-group activates the alpha-position.



Scheme 1. Lithiation studies on **1** and **3**.

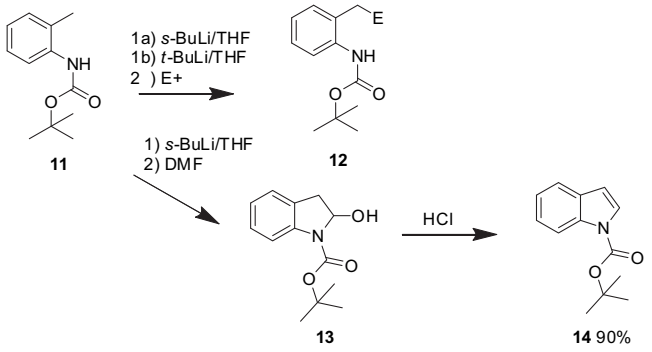
The influence of the aliphatic residue was investigated subsequently, exchanging the methyl for an ethyl group. First, the Boc-protected substrate **6** was lithiated using 1.2 equiv *t*-BuLi in Et_2O at −70 °C. Subsequent quenching with Me_2S_2 at −75 °C and warming the reaction mixture to −30 °C for 2 h gave product **7** in 95% yield, derived again from *ortho*-lithiation as could be expected (Scheme 2). Interestingly, the reaction could not be driven to completion when carrying out the lithiation at −60 °C. Switching from methyl to ethyl had no influence on the direction of lithiation when the Boc-protecting group was used. However, a different result was obtained when *N*-pivaloylethylaniline **8** was investigated in a directed lithiation reaction. For the lithiation of **8** 2.5 equiv of *t*-BuLi in Et_2O were used, because the first equivalent would very likely induce a migration of the pivaloyl-group (either into the alpha-position, as shown in the literature[21] or into the *ortho*-position if the nature of the side chain has an influence on the position of the lithiation). The remaining amount of *t*-BuLi would then attack the ketone formed in the rearrangement process. No reaction was observed at −70 °C. Only after elevating the temperature to −20 °C could the lithiation be driven to completion within 3 h. In this, case compound **10** was isolated after aqueous workup and precipitation as hydrochloride. The product was formed via ortho-lithiation, and not by alpha-lithiation as it was the case for the corresponding methyl-substrate **3**. Rearrangement of the pivaloyl-group and addition of *t*-BuLi to the resulting aromatic ketone (Scheme 2) then leads to compound **10**. Reaction with an electrophile is therefore not possible when pivaloyl is used as *N*-protecting group. Hence, a slight change from the methyl-group to an ethyl-substituent also changes the direction of the lithiation from the alpha- to the *ortho*-position.



Scheme 2. Influence of the *N*-alkyl group on the lithiation position.

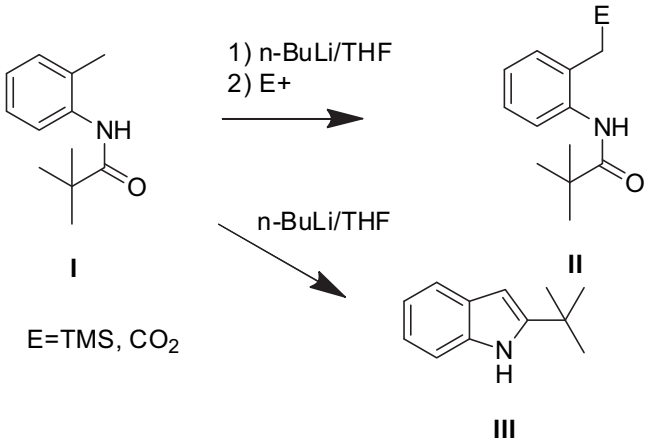
To determine the influence of an *ortho*-alkyl-group on the direction of the lithiation, experiments on derivatives of 2-methylaniline were carried out. The lithiation of Boc-protected *o*-toluidine **11** was first described by Clark et al.[22a] Reaction with 2.0 equiv of *s*- or *t*-BuLi in THF at −40 °C occurred spontaneously at the benzylic position and was finished shortly after completing the addition of the second equivalent.

Hence, electrophiles can be introduced in this position providing access to compounds **12**. Reaction with DMF led to indoline derivative **13** via attack of the negatively charged nitrogen on the initially introduced benzylic aldehyde group. After treatment with aqueous HCl **13** was converted to the Boc-protected indole **14** in 90% yield (Scheme 3). Cervantes et al.[22b] optimized the reaction conditions described by Clark et al.[22a] in order to enable introduction of substituents into the benzylic position in the first step followed by cyclization to the indole ring in a second step.[22b]



Scheme 3. Benzylic lithiation and indole formation of **11**.

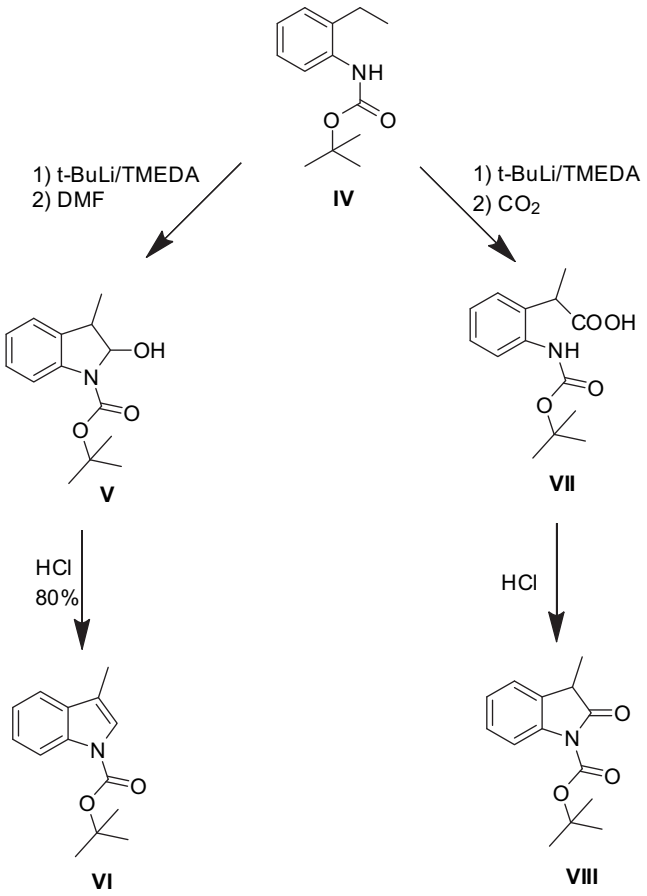
The lithiation of *N*-pivaloyl-*o*-toluidine I was described by Fuhrer and Gschwend and electrophiles (CO_2 or TMSCl) were introduced in the phenylmethyl-group (II).[23] Stirring the reaction mixture at room temperature for 16 h gave 2-(1,1-dimethylethyl)-indole III as a product of a modified Madelung-synthesis (Scheme 4).[24]



Scheme 4. Benzylic lithiation of **I**.

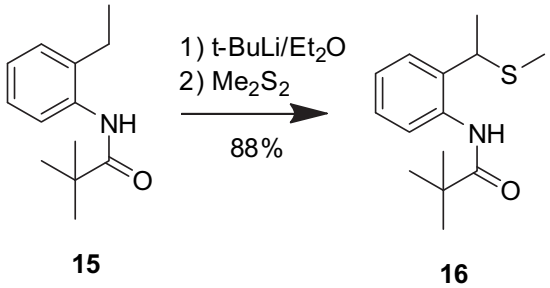
Lithiation of *N*-Boc-2-ethylaniline IV was also described by Clark et al.,[22a] however, the publication fails to give the exact reaction conditions. It rather states that *t*-BuLi/TMEDA gave best results, since lithiation seemed to be much more difficult compared to *N*-Boc-2-methylaniline. No ortho-lithiation products could be observed. Using DMF as the electrophile, *N*-Boc-protected 3-methylindole VI could be obtained in 80% yield after treatment with aqueous HCl. When using CO_2 as the electrophile, *N*-Boc-protected 3-methylindole-2(3*H*)-one VIII was obtained through acidic ring-formation. Consequently, lithiation was reported at the benzylic position only in all previous reports (Scheme 5).

Since the regioselectivity of lithiation of *N*-Boc-2-ethylaniline was established, we now investigated the regioselectivity of the metalation of *N*-pivaloly-2-ethylaniline **15**. This substrate was



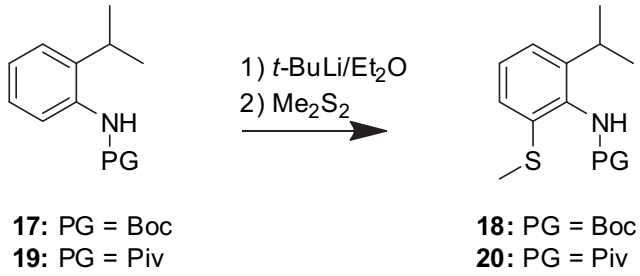
Scheme 5. Lithiations of **VI**.

reacted again with 2.5 equiv of *t*-BuLi in Et_2O at −10 °C for 3 h and quenched with Me_2S_2. Via this method 88% of **16** could be isolated (Scheme 6). Here, both the Boc- and pivaloyl-group direct into the CH_2-position of the ethyl-group; ortho-lithiation products could not be observed. Therefore, it can be concluded that benzylic positions are more readily lithiated compared to the *ortho*-position. It is also noteworthy that no migration of the pivaloyl-group was observed as it was the case for previous substrates.



Scheme 6. Benzylic lithiation of **15**.

However, changing from ethyl to isopropyl as in Boc-protected substrate **17** led to *ortho*-direction when lithiating with the improved lithiation conditions established in our group (Scheme 7).[25] After 2 h of stirring with 2.5 equiv of *t*-BuLi in Et_2O at −10 °C, there was still starting material present; addition of another equivalent of *t*-BuLi could also not drive the reaction to completion. In the crude NMR 25–30% of thioether **18** could be identified, next to starting material **17**. Again this indicates that lithiation in *ortho*-position is more sluggish than in the benzylic position. When the benzylic position is not

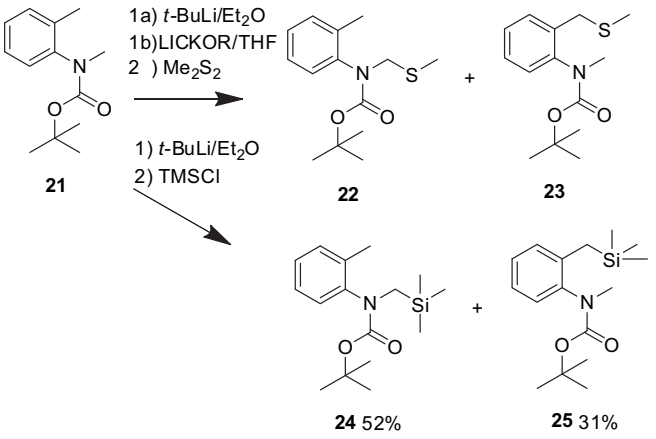


Scheme 7. Ortho-lithiation of **17** and **19**.

available for lithiation due to steric reasons, metalation can be forced into the *ortho*-position; however, the efficiency is low.

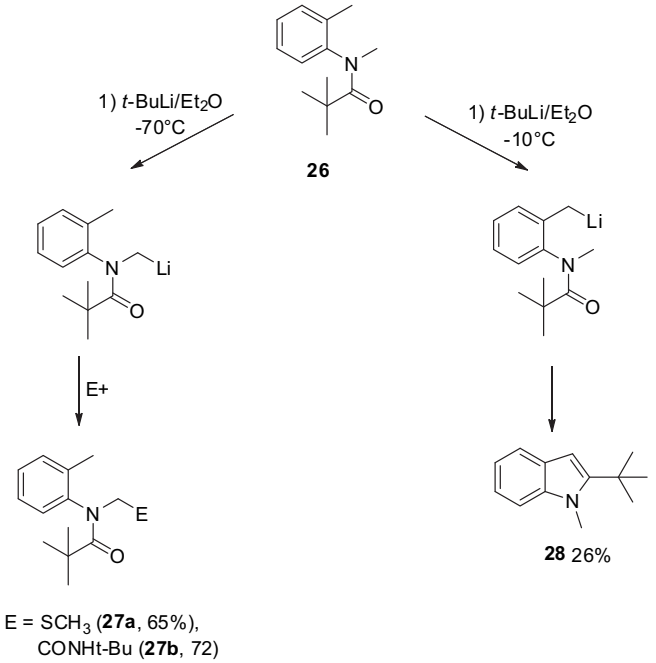
Lithiation of pivaloyl-protected **19** turned out to be a rather difficult task. Problems occurred already when trying to dissolve **19** in Et_2O. When trying to carry out the lithiation reaction in a heterogeneous mixture with 2.5 equiv of *t*-BuLi at −20 °C for 4 h and subsequent quenching with Me_2S_2 only 30% conversion to the thioether **20** could be observed. Changing the solvent from Et_2O to THF led to an even decreased conversion of 5%. The lithiation reaction was also carried out according to Fuhrer and Gschwend[23] using a mixture of Et_2O and THF in a ratio of 4:3. Upon cooling the reaction mixture, parts of starting material **19** precipitated and a maximum conversion of 20% could be obtained after several experiments. The best yield of 35% could be obtained when starting with 3.0 equiv of *t*-BuLi in Et_2O at −10 °C and addition of another equivalent of *t*-BuLi after 3 h of stirring (Scheme 7). This demonstrates again the preferred lithiation in the benzylic position. Only if lithiation at the benzylic position is blocked, ortho-lithiation can take place. The low yields can be attributed to solubility problems. Again, a migration of the pivaloyl-group was not observed.

After determining the directing effect of the individual groups for *ortho*-, alpha-, and benzylic lithiation, it was interesting to explore the lithiation of substances where all these three positions are available for lithiation simultaneously. As a first model compound Boc-protected compound **21** was used; lithiation with 1.2 equiv of *t*-BuLi in Et_2O at −70 °C and quenching with Me_2S_2 after 3 h led to the formation of two regioisomers. Alpha-lithiated product **22** (53%) was isolated as main fraction accompanied by 15% of compound **23** lithiated in the benzylic position (besides 11% of starting material **21**). Consequently, lithiation in alpha-position is slightly favored over lithiation in the benzylic position. No ortho-lithiated product was detected, indicating again that this is the least favorable position. Repeating the reaction at −30 °C led to full conversion and 60% of **22** and 27% of **23** could be obtained. Hence, elevation of the temperature also changed the ratio of the two regioisomers **22**/**23** from ~3.5:1 to ~2:1. When changing the electrophile from Me_2S_2 to TMSCl, another fast reacting electrophile, the corresponding regioisomers **24** (52%) and **25** (31%) were obtained which corresponds to a still lower selectivity (**24**/**25**—1.7:1). To determine the effect of the base, the reaction was also carried out with LICKOR. Starting material **21** was stirred with LICKOR in THF at −70 °C for 2 h and quenched with Me_2S_2. In this experiment 18% of **22** and 50% of **23** could be isolated (Scheme 8). Interestingly, changing the base caused inversion of the isomeric ratio of **22**/**23** to ~1:2.8. This can be interpreted in a way that the phenylmethyl-group is the more acidic group, because of the preferred deprotonation by LICKOR, but the complexing effect of the Boc-group in this position is inhibited for steric reasons. The complexation affects only the *N*-methyl-group, which leads to preferred deprotonation with *t*-BuLi in this position. No *ortho*-substituted product could be observed, which can be explained by the minor acidification by the Boc-group and steric factors.



Scheme 8. Alpha- and benzylic-lithiation of **21**.

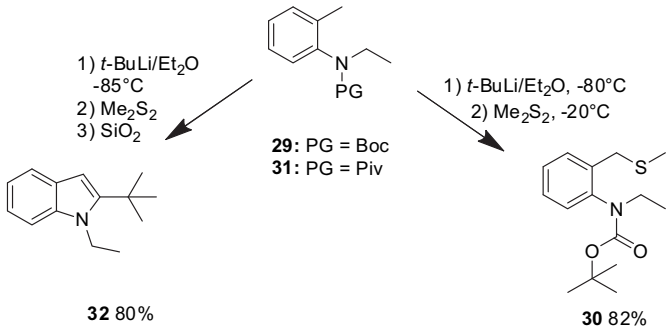
The pivaloyl-protected analog **26** was first lithiated again with *t*-BuLi in Et_2O at −70 °C for 3 h. Subsequent quenching with Me_2S_2 gave 65% of **27a**. Quenching with *tert*-butylisocyanate under the same reaction conditions gave 72% of **27b**. Both products originate from an alpha-lithiated intermediate. In contrast to findings of Hellwinkel and Lämmerzahl[21] the pivaloyl-group did not migrate into the alpha-position under these conditions. Interestingly, compound **28** was obtained without addition of an electrophile (although in low yields), which stems from a Madelung-type reaction.[24] After carrying out the reaction at −10 °C for 2 h **28** was isolated from a complex mixture in 26% yield (Scheme 9). This indicates that the initial attack of the lithiating agent occurs at the alpha-position and that the lithiation position changes to the benzylic position when applying higher reaction temperatures.



Scheme 9. Alpha- and benzylic-lithiation of **26**.

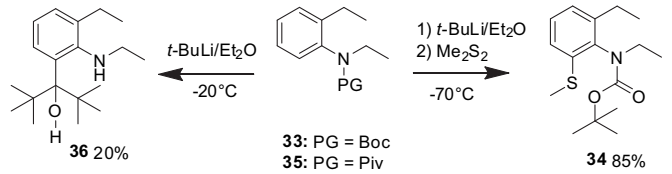
Since the *N*-methyl-position was preferred in both protected *N*,2-dimethylanilines, it was now investigated in which direction the reaction proceeds when switching to the corresponding *N*-ethyl starting materials **29** and **31**. Since the *N*-methyl substrates **1** and **3**

gave lithiation in alpha-position (Scheme 1), whereas *N*-ethyl substrates **6** and **8** led to ortho-lithiation (Scheme 2), we were interested if a similar change in selectivity could be observed also in this case. Lithiation of **29** was carried out with *t*-BuLi under the same reaction conditions as used for the lithiation of **21** (Scheme 8). Product **30**, derived from lithiation in the benzylic position, could be isolated in 83% yield. So again changing to an ethyl-group switched the selectivity, now from the alpha- to the benzylic position. Keeping in mind the previous results, this was expected, since no lithiation in the alpha-position was observed also in **6** and **8**. Moreover, the observed lithiation at the benzylic position is a logical result since it proved to be more reactive than the *ortho*-position and consequently no ortho-lithiation products were observed. Lithiation of the pivaloyl-protected analog **31** with 2.5 equiv of *t*-BuLi in Et_2O for 2 h and quenching with Me_2S_2 gave 80% of **32** again derived from lithiation in the benzylic position. So changing to the ethyl-group also increased the yield of the indole product significantly. Just like **21** (Scheme 8), **32** was formed via the attack of the species lithiated in the benzylic position at the carbonyl-group. The elimination of water to form the aromatic ring occurred by acid catalysis with SiO_2 during column chromatography (Scheme 10).



Scheme 10. Benzylic lithiation of **29** and indole formation from **31**.

Since no ortho-lithiations could be observed with *N*,2-dimethylanilines (**21** and **26**) and *N*-ethyl-2-methylaniline derivatives **29** and **31** it was investigated if longer alkyl-chains could direct the lithiation into the *ortho*-position. Lithiation of **33** was carried out with *t*-BuLi in Et_2O at −70 °C for 2 h followed by quenching with Me_2S_2. Indeed, 85% of *ortho*-substituted thioether **34** could be isolated in accordance with our rational. Also, lithiation of *N*-pivaloyl-protected *N*-ethyl-2-ethylaniline **35** with 1.2 equiv of *t*-BuLi in Et_2O at −20 °C led to compound **36** (compare to Scheme 3) derived from ortho-lithiation, however, in only 20% yield. Carrying out the experiment with 2.5 equiv *t*-BuLi improved the yield to 52% (Scheme 11). So in this case again a migration of the pivaloyl-group is induced and the initially formed ketone is attacked by *t*-BuLi also explaining the necessity for excess lithiating reagent.



Scheme 11. Ortho-lithiation of **33** and **35**.

Since the lithiation of **21** led to a mixture of products **22** and **23** (Scheme 8), one last experiment was carried out on the corresponding ethyl-substrate **37**. It was expected that no lithiation in the benzylic position would occur on this substrate and preferred lithiation will take place in the alpha-position. The same reaction conditions were chosen as for substrate **21**. The expected compound **38** derived from lithiation in alpha-position was obtained in 69% yield. In contrast to starting material **21** no product derived from lithiation in the benzylic position was observed. However, ^1H NMR analysis revealed that also *ortho*-substituted product **39** had been formed in approximately 20% yield (Scheme 10). So again a slight change in the substrate had a significant influence on the outcome of the lithiation reaction.

3. Conclusion

Fig. 2 summarizes the results of the previously described directed lithiation studies. The black wedges point to the lithiation position in case of pivaloyl as protecting group and the plain wedges in case of the Boc-protecting group. Directed lithiations previously reported in the literature are also included to provide a more comprehensive overview. Numbers in italics describe compounds with Boc as protecting group, the numbers in normal style point to compounds with the pivaloyl protecting group.

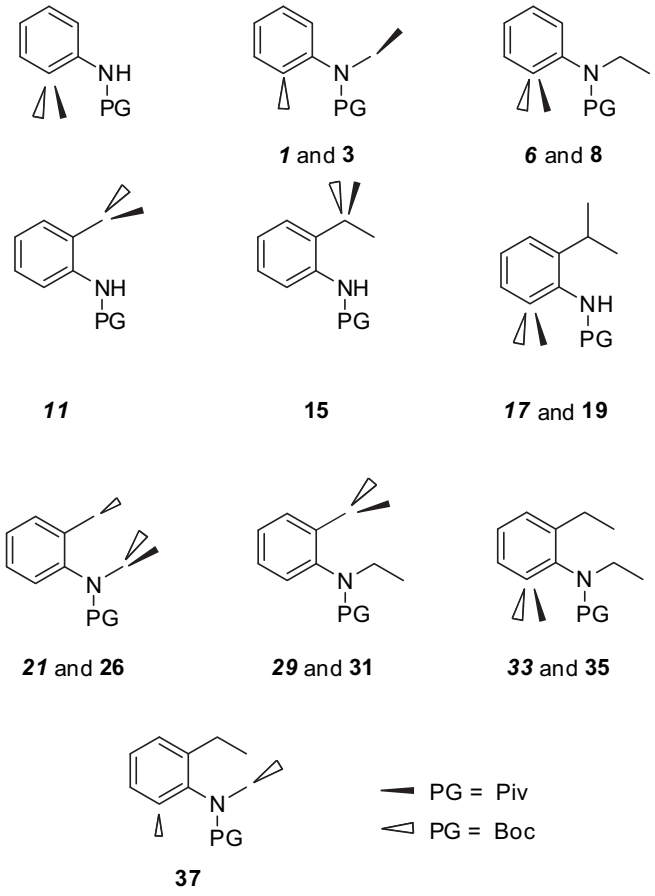


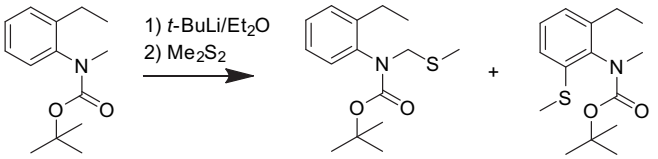
Fig. 2. Summary of directed lithiation reactions.

While unsubstituted Boc- and pivaloyl-protected anilines were selectively lithiated in *ortho*-position (Fig. 2 top left),[15] the introduction of an *N*-alkyl-group led to different results. Boc-protected **1** still gave ortho-lithiation, whereas pivaloyl-protected **3** was lithiated exclusively in the alpha-position. Elongating the *N*-alkyl chain to ethyl gave ortho-lithiation for both protecting groups (compounds **6** and **8**). Introduction of an *ortho*-alkyl-group (**11** or **15**), changed the direction of the lithiation to the benzylic position (Schemes 3 and 6). The introduction of an *ortho*-*i*-propyl-group (starting materials **17** and **19**) again led to ortho-lithiation products exclusively due to sterical reasons, however, in poor yields (Scheme 7).

The pivaloyl-group also directed the lithiation exclusively into the alpha-position in the *N*,2-dimethyl-derivative **26** (Scheme 9). With the Boc-group (**21**, Scheme 8) a mixture of alpha- and benzylic-substituted products **22** and **23** (Scheme 8) was obtained, the alpha-lithiation products being preferred. It was found that the ratio of the two products was also dependent on the temperature. Although still the major product, compound **22** was less favored at higher temperature. This could be explained by the fact that the *ortho*-methyl-group causes the Boc-group to rotate out of the ring-plane so that complexation into the ring is no longer favored. Instead, the two methyl groups are the preferred sites of attack of the lithiating agent. The ratio of the two products could be influenced by variation of the base and electrophile.

N-Protected *N*-ethyl-2-methyl derivatives **29** and **31** both gave lithiation in the benzylic position and again no lithiation on the *N*-ethyl-group (Scheme 10) was observed. On the *N*-pivaloyl starting material **31**, an intramolecular attack of the initially formed lithiated species led to the formation of indole derivative **32** (Scheme 10).

N,2-Diethyl starting materials **33** and **35** both gave lithiation in *ortho*-position since the lithiations of the ethyl groups are more sluggish than lithiation in *ortho*-position. 2-Ethyl-*N*-methyl substrate **37** gave then again preferred lithiation in the alpha-position although also *ortho*-substituted product **39** (Scheme 12) was obtained as by-product.



37 38 39

Scheme 12. Alpha- and ortho-lithiation of **37**.

4. Experimental

4.1. General

Melting points were measured on a KOFLER hot stage microscope and are uncorrected. Combustion analyses were performed in the microanalytical laboratory at the Institute for Physical Chemistry at the University of Vienna under the supervision of Mag. J. Theiner. Thin layer chromatography was performed with Merck silica gel 60 F_{245} plates. Column chromatography was performed using silica gel Merck 60. NMR spectra were recorded on a BRUKER AC 200 FT-NMR-spectrometer with TMS as an internal standard. Solvents and lithiation reagents were obtained from commercial sources. Solvents were distilled prior to use and dried if necessary.

4.2. General procedures

4.2.1. General procedure A: protection with the Boc-group. The unprotected amine (1.0 equiv) and bis(1,1-dimethylethyl) dicarbonate (1.0 equiv) were dissolved in dry THF and stirred under reflux for 16 h. The reaction mixture was extracted twice with 2 N HCl and the aqueous layer was re-extracted once with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by *Kugelrohr* distillation or vacuum distillation.

4.2.2. General procedure B: protection with the pivaloyl-group. The unprotected amine (1.0 equiv) and 1.0 equiv of triethylamine were dissolved in dry Et_2O. Then 1.0 equiv of 2,2-dimethylpropionic acid chloride dissolved in dry Et_2O was added slowly at 0 °C. The reaction mixture was then stirred at room temperature until the reaction was complete. Water was added and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed twice with water, 2 N HCl, and saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization.

4.2.3. General procedure C: lithiation with LICKOR. The substrate (1.0 equiv) and 1.0–1.2 equiv of *t*-BuOK were dissolved in dry THF and cooled. Then *t*-BuLi solution was added and the reaction mixture was warmed and stirred until the lithiation was complete. The reaction mixture was then cooled again and quenched with the desired electrophile. After warming to room temperature and stirring for 16 h, hydrolysis was either carried out with water or saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was either purified by column chromatography, vacuum distillation or *Kugelrohr* distillation.

Exact temperatures, reaction times, and amounts of reagents are specified separately for each specific compound.

4.2.4. General procedure D: lithiation with t-BuLi. Substrate (1.0 equiv) was dissolved in dry Et_2O or dry THF and cooled. Then *t*-BuLi solution was added dropwise and the reaction mixture was warmed and stirred until the lithiation was complete. Workup and purification were carried out as described in general procedure C.

Exact temperatures, reaction times, and amounts of reagents are specified separately for each specific compound.

4.3. Products protected by the Boc-group

*4.3.1. 1,1-Dimethyethyl N-methyl-N-[2-(methylthio)phenyl]carbamate (**2**).* Prepared according to general procedure C starting from **1** (0.50 g, 2.4 mmol, 1.0 equiv) and *t*-BuOK (0.27 g, 2.4 mmol, 1.0 equiv) dissolved in 6 mL of dry THF. *t*-BuLi (1.4 mL, 1.7 M solution in heptane, 2.4 mmol, 1.0 equiv) was added at −80 °C. The reaction mixture was warmed to −70 °C and stirred for 1.5 h. Subsequent quenching was carried out with Me_2S_2 (0.25 g, 2.6 mmol, 1.1 equiv), dissolved in 3 mL of dry THF. Hydrolysis with saturated NH_4Cl solution and purification by column chromatography (PE/EtOAc 15:1) gave **2** (0.56 g, 92%) as colorless oil as a mixture of rotamers. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.82; H, 7.56; N, 5.54; R_f (PE/EtOAc 5:1) 0.35; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.37 and 1.53 (2br s, 9H), 2.45 (s, 3H), 3.16 (s, 3H), 7.04–7.31 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.8 (q), 15.1 (q), 28.0 (q), 35.8 (q), 36.8 (q), 79.5 (s), 79.9 (s), 125.1 (d), 125.5 (d), 127.5 (d), 127.7 (d), 128.2 (d), 137.6 (s), 140.9 (s), 154.7 (s).

*4.3.2. 1,1-Dimethyethyl N-ethyl-N-[2-(methylthio)phenyl]carbamate (**7**).* Prepared according to general procedure D starting from **6** (0.50 g, 2.3 mmol, 1.0 equiv) dissolved in 7 mL of dry Et_2O. *t*-BuLi (1.6 mL, 1.7 M solution in heptane, 2.7 mmol, 1.2 equiv) was added at −80 °C. The reaction mixture was warmed to −30 °C and stirred for 2 h. Me_2S_2 (0.26 g, 2.7 mmol, 1.2 equiv) dissolved in 3 mL of dry Et_2O was added at −75 °C. Hydrolysis was carried out with H_2O. Title compound **7** was obtained via *Kugelrohr* distillation (80–90 °C, 0.05 mbar) as colorless oil as a mixture of rotamers (0.57 g, 95%). Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24. Found: C, 63.03; H, 8.16; N, 5.27; R_f (PE/EtOAc 5:1) 0.50; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.12 (t, 3H), 1.22–1.61 (m, 9H), 2.41 (s, 3H), 3.20–3.49 (m, 1H), 3.68–3.95 (m, 1H), 6.98–7.35 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.4 (q), 14.8 (q), 28.1 (q), 43.1 (t), 44.4 (t),

79.4 (s), 124.7 (d), 125.4 (d), 127.4 (d), 129.0 (d), 138.2 (s), 139.2 (s), 154.3 (s).

*4.3.3. 1,1-Dimethylethyl N-[2-(methylethyl)-6-(methylthio)phenyl] carbamate (**18**).* Prepared according to general procedure D starting from **17** (0.50 g, 2.1 mmol, 1.0 equiv) dissolved in 7 mL of dry Et_2O. *t*-BuLi (3.2 mL, 1.7 M solution in heptane, 5.4 mmol, 2.6 equiv) was added at −85 °C. The reaction mixture was warmed to −10 °C and stirred for 2 h. Additional *t*-BuLi (1.6 mL, 1. 7 M solution in heptane, 2.7 mmol, 1.3 equiv) was added. The reaction mixture was stirred at −10 °C for additional 2 h. Me_2S_2 (0.45 g, 4.8 mmol, 2.3 equiv) dissolved in 3 mL of dry Et_2O was added. Hydrolysis was carried out with water and the title compound **18** submitted to column chromatography (PE/EtOAc 10:1).[26] R_f (PE/EtOAc 5:1) 0.55; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.22 (d, *J*=7 Hz, 6H), 1.52 (s, 9H), 2.42 (s, 3H), 3.15–3.35 (m, 1H), 5.90 (br s, 1H), 7.01–7.35 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=15.2 (q), 23.3 (q), 27.5 (d), 28.1 (q), 79.9 (s), 122.4 (d), 122.6 (d), 126.2 (d), 131.3 (s), 138.1 (s), 147.4 (s), 154.1 (s).

*4.3.4. 1,1-Dimethylethyl N-(2-ethylphenyl)-N-[(methylthio)methyl] carbamate (**22**).* Prepared according to general procedure D starting from **21** (0.50 g, 2.3 mmol, 1.0 equiv) dissolved in 6 mL of dry Et_2O. *t*-BuLi (1.6 mL, 1.7 M solution in heptane, 2.7 mmol, 1.2 equiv) was added at −80 °C. The reaction mixture was warmed to −30 °C and stirred for 1 h. Me_2S_2 (0.26 g, 2.8 mmol, 1.3 equiv) dissolved in 3 mL of dry Et_2O was added at −80 °C. Hydrolysis was carried out with water. The title compound **22** was purified by column chromatography (PE/EtOAc 20:1) and obtained in 60% yield (0.36 g) as colorless oil as a mixture of rotamers. Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24. Found: C, 62.61; H, 8.01; N, 5.04; R_f (PE/EtOAc 5:1) 0.70; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.33 and 1.52 (2br s, 9H), 2.19 (s, 3H), 2.25 (s, 3H), 4.50 (d, *J*=14 Hz, 1H), 4.95 (d, *J*=14 Hz, 1H), 7.13–7.31 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=15.3 (q), 17.5 (q), 17.6 (q), 28.0 (q), 28.2 (q), 54.0 (t), 54.8 (t), 80.2 (s), 120.8 (d), 123.5 (d), 126.3 (d), 126.6 (d), 127.4 (d), 128.5 (d), 130.1 (d), 130.4 (d), 135.5 (s), 136.2 (s), 140.0 (s), 152.9 (s), 154.8 (2s). As by-product **23** was obtained (0.16 g, 27%).

*4.3.5. 1,1-Dimethylethyl N-methyl-N-[2-[(methylthio)methyl]phenyl] carbamate (**23**).* Prepared according to general procedure C starting from **21** (0.50 g, 2.3 mmol, 1.0 equiv) and *t*-BuOK (0.30 g, 2.7 mmol, 1.2 equiv) dissolved in 7 mL of dry THF. *t*-BuLi (1.6 mL, 1. 7 M solution in heptane, 2.7 mmol, 1.2 equiv) was added at −75 °C. The reaction mixture was warmed to −70 °C and stirred for 2 h. Me_2S_2 (0.26 g, 2.8 mmol, 1.2 equiv) dissolved in 2.5 mL of dry THF was added. Hydrolysis and purification by column chromatography (PE/EtOAc 20:1) gave **23** (0.30 g, 50%) as colorless oil as a mixture of rotamers. Anal. Calcd. For $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24. Found: C, 62.77; H, 7.79; N, 5.18; R_f (PE/EtOAc 5:1) 0.55; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.31 and 1.52 (2br s, 9H), 2.00 (s, 3H), 3.20 (s, 3H), 3.57 (d, *J*=14 Hz) and 3.69 (d, *J*=14 Hz) in total 2H, 7.03–7.30 (m, 3H), 7.36–7.50 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=15.4 (q), 28.1 (q), 33.7 (t), 37.4 (q), 79.7 (s), 127.1 (d), 127.6 (d), 127.7 (d), 129.0 (d), 135.4 (s), 142.4 (s), 154.8 (s). As by-product **22** (0.11 g, 18%) was obtained.

*4.3.6. 1,1-Dimethylethyl N-(2-methylphenyl)-N-[(trimethylsilyl) methyl]carbamate (**24**).* Prepared according to general procedure D starting from **12** (0.50 g, 2.3 mmol, 1.0 equiv). TMSCl (0.30 g, 2.8 mmol, 1.2 equiv) was used as the electrophile. Compound **24** was purified by column chromatography (PE/EtOAc 20:1) and obtained as colorless liquid in 52% yield (0.34 g) R_f (PE/EtOAc 5:1) 0.65; As by-product **25** was obtained also as colorless liquid in 31% yield (0.21 g). ^{1}H NMR (200 MHz $CDC1_3$): δ=0.02 (s, 9H), 1.25–1.59 (m, 9H), 2.22 (s, 3H), 2.88 (d, *J*=16 Hz, 1H), 3.27 (br d, *J*=16 Hz, 1H), 6.96–7.22 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−1.5 (q), 17.7 (q), 28.2 (q), 41.3 (t), 79.1 (s), 126.1 (d), 126.6 (d), 127.7 (d), 130.5 (d), 135.2 (s), 143.0 (s), 155.0 (s).

*4.3.7. 1,1-Dimethylethyl N-methyl-N-[2-[(trimethylsilyl)methyl]phenyl]carbamate (**25**).* Preparation see section 4.3.6. Colorless liquid; 31% yield (0.21 g). R_f (PE/EtOAc 5:1) 0.60; ^{1}H NMR (200 MHz $CDC1_3$): δ=0.02 (s, 9H), 1.25–1.56 (m, 9H), 2.05 (s, 2H), 3.13 (s, 3H), 6.98–7.20 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−1.1 (q), 21.2 (t), 28.1 (q), 37.3 (q), 79.5 (s), 124.7 (d), 126.5 (d), 127.6 (d), 129.6 (d), 137.7 (s), 141.3 (s), 155.6 (s).

*4.3.8. 1,1-Dimethylethyl N-ethyl-N-(2-methylphenyl)carbamate (**29**).* Starting material **6** (3.00 g, 13.6 mmol, 1.0 equiv) was dissolved in 30 mL of dry THF and cooled to −75 °C before *t*-BuLi solution (9.6 mL, 1.7 M solution in heptane, 16.3 mmol, 1.2 equiv) was added dropwise. The reaction mixture was warmed to −30 °C and stirred for 2 h. After cooling to −80 °C methyliodide (4.0 mL, 64 mmol, 9.4 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 16 h. Hydrolysis was carried out with 30 mL of water. The layers were separated and the aqueous phase was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by *Kugelrohr* distillation (90–100 °C, 0.04 mbar) gave **29** (2.81 g, 88%) as colorless crystals. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.75; H, 8.72; N, 6.00; Mp: 28–30 °C; R_f (PE/EtOAc 5:1) 0.40; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.00–1.25 (m, 3H), 1.25–1.62 (m, 9H), 2.20 (s, 3H), 3.35–3.58 (m, 1H), 3.60–3.82 (m, 1H), 6.97–7.25 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.3 (q), 13.9 (q), 17.6 (q), 28.2 (q), 44.0 (t), 45.1 (t), 79.2 (s), 126.2 (d), 126.8 (d), 128.2 (d), 130.4 (d), 135.9 (s), 140.8 (s), 154.5 (s).

*4.3.9. 1,1-Dimethylethyl N-ethyl-N-[2-[(methylthio)methyl]phenyl] carbamate (**30**).* Prepared according to general procedure D starting from **29** (0.50 g, 2.1 mmol, 1.0 equiv) dissolved in 7 mL of dry Et_2O. *t*-BuLi (1.7 mL, 1. 7 M solution in heptane, 2.6 mmol, 1.2 equiv) was added at −85 °C. The reaction mixture was warmed to −30 °C and stirred for 2 h. Me_2S_2 (0.24 g, 2.6 mmol, 1.2 equiv) dissolved in 2 mL of dry Et_2O was added at −80 °C. Hydrolysis was carried out with H_2O. Purification by column chromatography (PE/EtOAc 20:1) gave **30** (0.50 g, 83%) as colorless oil. For combustion analysis the substance was further purified by *Kugelrohr* distillation (90–100 °C, 0.05 mbar). Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98. Found: C, 64.26; H, 8.51; N, 5.00; R_f (PE/EtOAc 10:1) 0.35; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.08–1.23 (m, 3H), 1.23–1.70 (m, 9H), 1.98 and 2.04 (s, 3H), 3.23–3.45 (m, 1H), 3.63 (s, 2H), 3.70–3.95 (m, 1H), 6.97–7.35 (m, 3H), 7.45–7.53 and 7.62–7.70 (2 m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.3 (q), 13.9 (q), 17.6 (q), 28.2 (q), 44.0 (t), 45.1 (t), 79.2 (s), 126.2 (d), 126.8 (d), 128.2 (d), 130.4 (d), 135.9 (s), 140.8 (s), 154.5 (s).

*4.3.10. 1,1-Dimethylethyl N-ethyl-N-(2-ethylphenyl)carbamate (**33**).* Prepared according to general procedure A starting from *N*,2-diethylbenzolamine (0.89 g, 6.0 mmol, 1.0 equiv). Compound **33** was purified by distillation under reduced pressure (85–95 °C, 0.01 mbar) to give 90% (1.34 g) yield as colorless liquid. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.52; H, 9.33; N, 5.72; R_f (PE/EtOAc 4:1) 0.70; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.15 (t, *J*=7 Hz, 3H), 1.23 (t, *J*=7 Hz, 3H), 1.45 (s, 9H), 2.65 (q, *J*=7 Hz, 2H), 3.68 (q, *J*=7 Hz, 2H), 6.96–7.07 (m, 3H), 7.18–7.29 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.7 (q), 15.3 (q), 28.2 (q), 28.5 (t), 44.8 (t), 79.6 (s), 124.0 (d), 125.3 (d), 126.5 (d), 128.3 (d), 142.3 (s), 144.6 (s), 154.5 (s).

*4.3.11. 1,1-Dimethylethyl N-ethyl-[2-ethyl-6-(methylthio)-phenyl] carbamate (**34**).* Prepared according to general procedure D

starting from **33** (0.50 g, 2.0 mmol, 1.0 equiv) dissolved in 6 mL of dry Et_2O. *t*-BuLi (1.5 mL, 1. 7 M solution in heptane, 2.4 mmol, 1.2 equiv) was added at −80 °C. The reaction mixture was warmed to −70 °C and stirred for 3 h. Me_2S_2 (0.23 g, 2.4 mmol, 1.2 equiv) dissolved in 3 mL of dry Et_2O was added. Hydrolysis was carried out with saturated NH_4Cl. Purification by column chromatography (PE/EtOAc 10:1) gave **34** (0.51 g, 85%) as colorless crystals. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 65.05; H, 8.53; N, 4.74. Found: C, 65.08; H, 8.53; N, 4.74; Mp: 53–55 °C; R_f (PE/EtOAc 10:1) 0.40; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.07–1.20 (m, 3H), 1.21 (t, J=7 Hz, 3H), 1.28–1.63 (m, 9H), 2.40 (s, 3H), 2.62 (q, J=7 Hz, 2H), 3.18–3.50 (m, 1H), 3.70–3.95 (m, 1H), 6.85–7.21 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.4 (q), 14.0 (q), 15.4 (q), 27.9 (q), 28.1 (t), 43.2 (t), 44.6 (t), 79.3 (s), 79.8 (s), 126.2 (d), 126.9 (d), 128.6 (d), 134.5 (s), 139.5 (s), 141.4 (s), 154.4 (s).

*4.3.12. 1,1-Dimethylethyl N-(2-ethylphenyl)-N-methyl-carbamate (**37**).* NaH (0.20 g, 8.1 mmol, 1.2 equiv) was suspended in 7 mL of dry DMF. Then **15** (1.50 g, 6.8 mmol, 1.0 equiv), dissolved in 15 mL of dry DMF was added dropwise. The reaction mixture was stirred at room temperature for 2 h. Subsequently, methyliodide (1.92 g, 13.6 mmol, 2.0 equiv) was added quickly and the reaction mixture was stirred for 1 h at room temperature. DMF was removed under reduced pressure. The residue was taken up in 10 mL of water and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After distillation under reduced pressure (60–70 °C, 0.015 mbar), **27** was obtained in 92% (1.47 g) yield as colorless oil as a mixture of rotamers. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.49; H, 9.21; N, 6.06; R_f (PE/EtOAc 10:1) 0.60; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.22 (t, 3H, J=7 Hz), 1.31 and 1.51 (2br s, 9H), 2.59 (q, 2H, J=7 Hz), 3.15 (s, 3H), 7.01–7.32 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4 (q), 23.6 (t), 28.1 (q), 37.2 (q), 79.4 (s), 126.3 (d), 127.2 (d), 127.4 (d), 128.7 (d), 141.0 (s), 141.8 (2s), 155.1 (s).

*4.3.13. 1,1-Dimethylethyl N-(2-ethylphenyl)-N-[(methylthio)methyl] carbamate (**38**).* Prepared according to general procedure D starting from **37** (0.50 g, 2.1 mmol, 1.0 equiv) dissolved in 7 mL of dry Et_2O. *t*-BuLi (1.5 mL, 1.7 M solution in heptane, 2.4 mmol, 1.2 equiv) was added at −80 °C. The reaction mixture was warmed to −30 °C and stirred for 2 h. Me_2S_2 (0.24 g, 2.4 mmol, 1.2 equiv) dissolved in 3 mL of dry Et_2O was added. Hydrolysis was carried out with H_2O. Purification by column chromatography (PE/EtOAc 15:1) gave **38** (0.42 g, 70%) as colorless oil as a mixture of rotamers. For combustion analysis, the product was further purified by *Kugelrohr* distillation (80–90 °C, 0.04 mbar). Anal. Calcd for $C_{15}H_{23}NO_2S$: requires C, 64.02; H, 8.24; N, 4.98. Found: C, 64.32; H, 8.01; N, 4.95; R_f (PE/EtOAc 15:1) 0.45; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.25 (t, J=7 Hz, 3H), 1.35 and 1.52 (2br s, 9H), 2.19 (s, 3H), 2.60 (q, J=7 Hz, 2H), 4.35 (d, J=14 Hz, 1H), 5.09 (d, J=14 Hz, 1H), 7.15–7.35 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.3 (q), 15.4 (q), 23.4 (t), 28.0 (q), 54.3 (t), 80.1 (s), 126.1 (d), 127.7 (d), 128.6 (d), 129.0 (d), 139.2 (s), 141.2 (s), 154.9 (s).

4.4. Products protected by the piv-group

*4.4.1. 3-(2-(Ethylamino)phenyl)-2,2,4,4-tetramethylpentan-3-ol hydrochloride (**10**).* Prepared according to general procedure D starting from **8** (0.50 g, 2.4 mmol, 1.0 equiv) dissolved in 10 mL of dry Et_2O. *t*-BuLi (3.4 mL, 1.7 M solution in heptane, 5.4 mmol, 2.2 equiv) was added at −80 °C. The reaction mixture was warmed to −20 °C and stirred for 3 h before 10 mL of H_2O were added. After extraction and concentration, the residue was taken up in 20 mL of dry Et_2O and precipitated as hydrochloride with gaseous HCl. The colorless crystals of the title compound **10** (0.35 g, 55%) were filtered and dried. For combustion analysis, the product was recrystallized from dry THF. Anal. Calcd for $C_{17}H_{29}NO.HCl$: C, 68.09; H, 10.08; N, 4.67. Found: C, 67.88; H, 10.29; N, 4.62; Mp: 221–223 °C; R_f (PE/EtOAc 5:1) 0.8; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.11 (s, 18H), 1.23 (t, J=7 Hz, 3H), 3.06 (q, J=7 Hz, 2H), 6.73–6.88 (m, 2H), 7.06–7.18 (m, 1H), 7.44 (dd, J=10 Hz, J=2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=15.0 (q), 29.7 (q), 42.1 (s), 43.4 (t), 88.5 (s), 117.9 (d), 119.3 (d), 126.6 (d), 130.3 (d), 132.9 (s), 147.7 (s).

*4.4.2. 2,2-Dimethyl-N-[2-[(1-methylthio)ethyl]phenyl]-propanamide (**16**).* Prepared according to general procedure D starting from **15** (0.50 g, 2.4 mmol, 1.0 equiv) dissolved in 7 mL of dry Et_2O. *t*-BuLi (3.8 mL, 1. 7 M solution in heptane, 6.1 mmol, 2.5 equiv) was added at −80 °C. The reaction mixture was warmed to −30 °C and stirred for 2 h. Me_2S_2 (0.24 g, 2.4 mmol, 1.2 equiv) dissolved in 3 mL of dry Et_2O was added and the reaction mixture was warmed to room temperature and stirred over night. Hydrolysis was carried out with H_2O. Purification by *Kugelrohr* distillation (90–100 °C, 0.01 mbar) gave **16** (0.54 g, 88%) as colorless crystals. For combustion analysis the product was further purified by recrystallization from PE. Anal. Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57. Found: C, 66.93; H, 8.40; N, 5.53; Mp: 58–61 °C; R_f (PE/EtOAc 5:1) 0.40; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.35 (s, 9H), 1.68 (d, J=7 Hz, 3H), 1.93 (s, 3H), 3.97 (q, 1H), 7.01–7.39 (m, 3H), 7.95 (dd, J=8 Hz, J=1 Hz, 1H), 8.78 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.2 (q), 19.1 (q), 27.6 (q), 39.5 (s), 42.2 (d), 124.2 (d), 124.3 (d), 127.8 (d), 127.9 (d), 131.4 (s), 136.0 (s), 176.6 (s).

*4.4.3. 2,2-Dimethyl-N-[2-(1-methylethyl)-6-(methylthio)phenyl]-propanamide (**20**).* Prepared according to general procedure D starting from **19** (0.50 g, 2.4 mmol, 1.0 equiv) suspended in 11 mL of dry Et_2O. *t*-BuLi (4.0 mL, 1. 7 M solution in heptane, 6.8 mmol, 3.0 equiv) was added at −40 °C. The reaction mixture was warmed to −10 °C and stirred for 3 h. Additional 1.4 mL of *t*-BuLi solution (2.3 mmol, 1.0 equiv) were added and the reaction mixture was stirred for another 1.5 h at −10 °C. Me_2S_2 (0.64 g, 6.8 mmol, 3.0 equiv), dissolved in 3 mL of dry Et_2O was added at −75 °C. Hydrolysis was carried out with saturated NH_4Cl. Recrystallization from DIPE gave **20** in 35% (0.21 g) yield as colorless crystals. Anal. Calcd for $C_{15}H_{23}NOS$: C, 67.88; H, 8.73; N, 5.28. Found: C, 67.61; H, 8.48; N, 5.29; mp: 220–221 °C; R_f (PE/EtOAc 3:1) 0.50; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.20 (d, J=7 Hz, 6H), 1.38 (s, 9H), 2.40 (s, 3H), 2.91–3.12 (m, 1H), 6.94 (br s, 1H), 7.04 (dd, J=8 Hz, J=2 Hz, 1H), 7.12 (dd, J=6 Hz, J=2 Hz, 1H), 7.28 (dd, J=8, 6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=15.0 (q), 23.2 (q), 27.5 (q), 28.4 (d), 39.2 (s), 122.3 (d), 122.4 (d), 128.0 (d), 131.1 (s), 137.1 (s), 147.0 (s), 177.1 (s).

*4.4.4. N,2,2-Trimethyl-N-(2-methylphenyl)propanamide (**26**).* Prepared according to general procedure B starting from *N*,2-dimethylbenzolamine (5.00 g, 41.3 mmol) with the slight change that all the steps were carried out at room temperature. The product was purified by recrystallization from PE to give a yield of 93% (7.88 g) of **26** as colorless crystals. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.28; H, 9.59; N, 6.83; mp: 67–69 °C; R_f (PE/EtOAc 4:1) 0.60; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.02 (s, 9H), 2.26 (s, 3H), 3.12 (s, 3H), 7.09–7.30 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=28.8 (q), 39.4 (q), 40.5 (s), 126.4 (d), 128.0 (d), 128.8 (d), 131.1 (d), 135.7 (s), 143.7 (s), 177.9 (s).

*4.4.5. 2,2-Dimethyl-N-(2-methylphenyl)-N-[(methylthio)methyl]-propanamide (**27a**).* Prepared according to general procedure D starting from **26** (0.50 g, 2.4 mmol, 1.0 equiv) dissolved in 10 mL of dry Et_2O. *t*-BuLi (1.7 mL, 1.7 M solution in heptane, 2.9 mmol, 1.2 equiv) was added at −40 °C. The reaction mixture was warmed to −70 °C and stirred for 3 h. Me_2S_2 (0.28 g, 2.9 mmol, 1.2 equiv) dissolved in 3 mL of dry Et_2O was added at −70 °C. Hydrolysis was carried out with H_2O. Purification **27a** by column chromatography (PE/EtOAc 20:1) gave **27a** (0.40 g, 65%) as colorless oil. For

combustion analysis the product was further purified by *Kugelrohr* distillation (80–90 °C, 0.01 mbar). Anal. Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57. Found: C, 66.62; H, 8.28; N, 5.51; R_f (PE/EtOAc 5:1) 0.60; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.02 (s, 9H), 2.16 (s, 3H), 2.28 (s, 3H), 3.77 (d, J=13 Hz, 1H), 5.60 (d, J=13 Hz, 1H), 7.17–7.38 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=15.9 (q), 17.8 (q), 28.7 (q), 40.1 (s), 55.0 (t), 126.0 (d), 128.5 (d), 131.1 (d), 135.8 (s), 140.7 (s), 178.2 (s). One signal (d) overlaps with another signal.

*4.4.6. 2,2-Dimethyl N-(2,2-dimethylaminocarbonylmethylen)-N-(2-methylphenyl)propanamide (**27b**).* Prepared according to general procedure D starting from **26** (2.00 g, 9.7 mmol, 1.0 equiv) dissolved in 40 mL of dry Et_2O. *t*-BuLi (6.9 mL, 1. 7 M solution in heptane, 11.7 mmol, 1.2 equiv) was added at −80 °C. The reaction mixture was warmed to −70 °C and stirred for 2 h. Subsequently, *tert*-butylisocyanate (1.1 g, 11.7 mmol, 1.2 equiv), dissolved in 5 mL of dry Et_2O was added at −70 °C. Hydrolysis was carried out with saturated NH_4Cl solution. Recrystallization from DIPE gave **27b** (2.13 g, 72%) as colorless crystals. Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 70.87; H, 9.13; N, 9.14; mp: 128–131 °C; R_f (PE/EtOAc 5:1) 0.20; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.01 (s, 9H), 1.35 (s, 9H), 2.24 (s, 3H), 3.36 (d, J=16 Hz, 1H), 4.64 (d, J=16 Hz, 1H), 6.60 (br s, 1H), 7.17–7.30 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=17.7 (q), 28.5 (2q), 40.6 (s), 50.7 (s), 57.0 (t), 126.4 (d), 128.6 (d), 129.5 (d), 131.2 (d), 135.4 (s), 142.1 (s), 168.2 (s), 178.8 (s).

*4.4.7. 2-(1,1-Dimethylethyl)-1-ethylindole (**32**).* Prepared according to general procedure D starting from **31** (0.50 g, 2.3 mmol, 1.0 equiv) dissolved in 7 mL of dry Et_2O. *t*-BuLi (3.4 mL, 1.7 M solution in heptane, 5.7 mmol, 2.5 equiv) was added at −80 °C. The reaction mixture was warmed to −20 °C and stirred for 2 h. 10 mL of H_2O were added. Purification by column chromatography (PE/EtOAc 50:1) gave **32** (0.37 g, 80%) as pale yellow liquid. For combustion analysis the product was further purified by *Kugelrohr* distillation (100–110 °C, 0.04 mbar). Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.35; H, 9.78; N, 6.83; mp: 128–131 °C; R_f (PE/EtOAc 15:1) 0.60; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.41 (t, J=7 Hz, 3H), 1.47 (s, 9H), 4.38 (q, J=7 Hz), 6.38 (d, J=1 Hz, 1H), 7.01–7.21 (m, 2H), 7.28 (dd, J=8 Hz, J=1 Hz, 1H), 7.54 (dd, J=8 Hz, J=1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.9 (q), 30.5 (q), 32.4 (s), 39.6 (t), 98.0 (d), 109.2 (d), 119.1 (d), 120.1 (d), 120.7 (d), 127.5 (s), 137.3 (s), 148.4 (s).

*4.4.8. N-Ethyl-N-(2-ethylphenyl)-2,2-dimethylpropanamide (**35**).* Prepared according to general procedure B starting from *N*,2-diethylbenzolamine (1.40 g, 9.4 mmol). Purification by *Kugelrohr* distillation (90–100 °C, 0.03 mbar) gave **35** (1.70 g, 78%) as colorless liquid. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00 Found: C, 77.04; H, 10.13; N, 6.05; R_f (PE/EtOAc 5:1) 0.50; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.02 (s, 9H), 1.13 (t, J=7 Hz, 3H), 1.25 (t, J=7 Hz, 3H), 2.66 (q, J=7 Hz, 2H), 3.65 (q, J=7 Hz, 2H), 6.95–7.01 (m, 2H), 7.10–7.18 (m, 1H), 7.24–7.30 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=12.6 (q), 15.4 (q), 28.5 (t), 29.4 (q), 40.8 (s), 47.6 (t), 126.8 (d), 127.2 (d), 128.7 (d), 129.2 (d), 143.2 (s), 145.2 (s), 177.2 (s).

*4.4.9. 3-(3-Ethyl-2-(ethylamino)phenyl)-2,2,4,4-tetramethylpentan-3-ol (**36**).* Prepared according to general procedure D starting from **35** (0.50 g, 2.3 mmol, 1.0 equiv) dissolved in 7 mL of dry Et_2O. Then *t*-BuLi (3.3 mL, 1.7 M solution in heptane, 5.4 mmol, 2.6 equiv) was added at −70 °C. The reaction mixture was warmed to −20 °C and stirred for 4 h. Subsequently 10 mL of saturated NH_4Cl were added. Purification by column chromatography (PE/EtOAc 30:1) gave **36** (0.33 g, 52%) as colorless crystals. For combustion analysis the product was further purified by recrystallization from PE. Anal. Calcd for $C_{19}H_{33}NO$: C, 78.29; H, 11.41; N, 4.81. Found: C, 78.29; H, 11.16; N, 5.01; mp: 74.5–75.5 °C; R_f (PE/EtOAc 5:1) 0.55; ^{1}H NMR (200 MHz $CDC1_3$): δ=1.13 (s, 18H), 1.23 (t, J=7 Hz, 3H), 1.25 (t, J=7 Hz, 3H), 2.59 (q, J=7 Hz, 2H), 3.08 (q, 2H), 6.61–6.72 (m, 2H), 7.35 (dd, J=10, 1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.9 (q), 15.0 (q), 27.9 (t), 29.7 (q), 42.7 (s), 43.4 (t), 88.2 (s), 118.3 (d), 119.7 (d), 130.2 (d), 131.2 (s), 142.3 (s), 147.2 (s).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.02.056. These data include MOL files and InChiKeys of the most important compounds described in this article.

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26. The product **18** could not be separated from the substrate **17** due to identical R_f values and hence a mixture of these two compounds was isolated. According to integration of the ^{1}H NMR spectrum, 0.17 g (28%) of **18** was obtained.