Article:
Talk, R., El-Tunsi, A., Robertson, C. et al. (2019) Regioselective lithiation and electrophilic quench of N-Boc-3-phenyltetrahydroisoquinoline. European Journal of Organic Chemistry, 2019 (31-32). pp. 5294-5301. ISSN: 1434-193X

https://doi.org/10.1002/ejoc.201900238

Regioselective lithiation and electrophilic quench of *N*-Boc-3-phenyltetrahydroisoquinoline

Ruaa A. Talk,[a] Ashraf El-Tunsi,[a] Craig C. Robertson,[a] and Iain Coldham*[a]

Abstract: Tetrahydroisoquinolines are found in many natural products and drug compounds and a convenient method to access 1-substituted derivatives is to carry out lithiation at C-1 followed by trapping with an electrophile. Here we explore the feasibility of lithiation at C-3 by using a substrate with a benzylic proton on both sides of the nitrogen atom such that lithiation with *n*BuLi could occur at either C-1 or C-3 of the tetrahydroisoquinoline. The regioselectivity in the lithiation was determined using the substrate *N*-*tert*-butoxycarbonyl (Boc)-3-phenyltetrahydroisoquinoline. The lithiation could be followed by in situ ReactIR spectroscopy and the rate of rotation of the carbamate group was determined (barrier to rotation was approximately $\Delta G^{\ddagger}$ 58 kJ/mol at –50 °C). Subsequent trapping of the organolithium with an electrophile gave a mixture of two regioisomeric products with a preference for reaction at C-1. This led to the isolation of 1,3-disubstituted tetrahydroisoquinolines with *trans* relative stereochemistry. Removal of the Boc group from the nitrogen atom gave secondary and tertiary amine products.

Introduction

The tetrahydroisoquinoline ring system is an important scaffold in natural products and biologically active compounds.[1] Alkyl, benzyl or other functional groups at C-1 and/or C-3 of this ring system provide the most common substitution pattern. In contrast, tetrahydroisoquinolines with an aryl group at C-3 are relatively uncommon. Some examples are canadine (tetrahydroberberine)[2] and coralydine,[3] which are protoberberine alkaloids, and the *N*-methyl D-aspartate (NMDA) receptor antagonist dizocilpine (MK801) (Figure 1).[4]

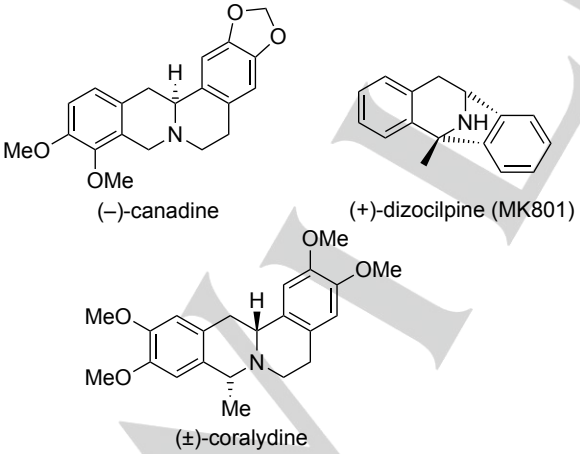
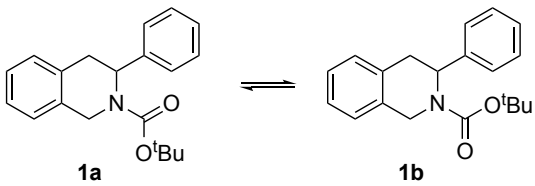


Figure 1. Examples of 3-aryltetrahydroisoquinolines.

There are many routes for the synthesis of tetrahydroisoquinoline derivatives, in particular the Pictet–Spengler and Bischler–Napieralski reactions that involve cyclization starting from a 2-arylethylamine.[5] Methods that employ the parent isoquinoline or 3,4-dihydroisoquinoline ring systems have been developed by using reduction or nucleophilic addition.[6] Alternatively, metallated tetrahydroisoquinolines can act as nucleophiles to react with electrophiles.[7] We found that the *N*-*tert*-butoxycarbonyl (Boc) group, popularised by Beak and co-workers,[8] is effective at allowing lithiation at C-1 with *n*BuLi in THF,[9] particularly if the reaction is conducted at –50 °C rather than –78 °C, as this allows faster rotation of the Boc group to which the *n*BuLi is coordinated.[10,11]

In our earlier work, we found that lithiation occurs at the benzylic position (C-1) on treatment of *N*-Boc-tetrahydroisoquinoline with *n*BuLi.[9] We were interested to determine the regioselectivity when an aryl group was located at C-3. The substrate selected was *N*-Boc-3-phenyltetrahydroisoquinoline **1** (rotamers **1a** and **1b**, Scheme 1) and this has a benzylic C–H on both sides of the *N*-Boc group (at C-1 and C-3). Therefore it is feasible that lithiation could occur at either C-1 or C-3. If rotation of the Boc group in compound **1** is fast then coordination of BuLi would allow lithiation at either C-1 or C-3 and the ratio of regioisomers of the lithiated–trapped product would reflect the preference for lithiation at one of these positions. However, if rotation of the Boc group is slow relative to lithiation, then the ratio of the regioisomeric products after trapping with an electrophile should reflect the ratio of the rotamers **1a** and **1b** (since lithiation occurs only after coordination of BuLi to the carbonyl oxygen atom).[10,11] We describe here the regioselectivity in this lithiation–trapping chemistry.



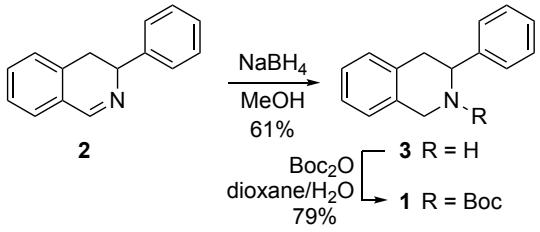
Scheme 1. Rotamers of *N*-Boc-3-phenyltetrahydroisoquinoline **1**.

Results and Discussion

The target compound *N*-Boc-3-phenyltetrahydroisoquinoline **1** was prepared by reduction then Boc protection of the known 3-phenyl-3,4-dihydroisoquinoline **2** (Scheme 2).[12] The ^{1}H NMR spectrum of *N*-Boc-3-phenyltetrahydroisoquinoline **1** in D8-THF showed a mixture of rotamers at low temperature with a ratio

[a] *Dr R. A. Talk, Mr A. El-Tunsi, Dr C. C. Robertson, Prof I. Coldham*
Department of Chemistry, University of Sheffield
Brook Hill, Sheffield S3 7HF, UK
E-mail: i.coldham@sheffield.ac.uk
https://www.sheffield.ac.uk/chemistry/staff/profiles/iain_coldham
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc

1.2:1. Coalescence of the two *tert*-butyl singlets occurred at just below room temperature and a broad peak for the *tert*-butyl group was observed at room temperature (Figure 2). Line shape analysis of these data (see SI) led to rate constants from which an Eyring plot revealed approximate activation parameters of $\Delta H^{\ddagger}$ 61 kJ/mol and $\Delta S^{\ddagger}$ 16 J/K/mol (assuming 1:1 ratio of rotamers). Hence the barrier to rotation can be estimated as $\Delta G^{\ddagger}$ ~58 kJ/mol at –50 °C, with a half-life for rotation (**1a** ⇆ **1b**) of only about 5 sec at –50 °C.



Scheme 2. Preparation of tetrahydroisoquinoline **1**.

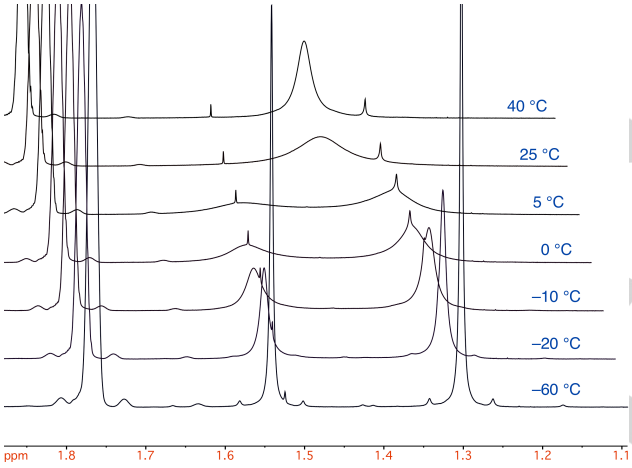


Figure 2. Variable temperature ^{1}H NMR spectra of **1** in D8-THF (showing region 1.85–1.10 ppm, peak at 1.76 ppm for THF).

Lithiation of *N*-Boc-3-phenyltetrahydroisoquinoline **1** using *n*BuLi in THF occurred rapidly at –50 °C. This was verified by *in situ* IR (ReactIR) spectroscopy (Figure 3).[13] Two peaks could be observed for the carbonyl stretch of the lithiated intermediate (at 1642 and 1632 cm^{-1}), probably relating to lithiation at C-1 and at C-3.

On the basis of the VT-NMR and IR spectroscopic studies, the lithiation of *N*-Boc-3-phenyltetrahydroisoquinoline **1** was carried out by using *n*BuLi in THF at –50 °C for 4 min, followed by addition of a variety of electrophiles (Scheme 3). Good yields of a range of different substituted products were obtained and in all cases a mixture of the 1- and 3-substituted products (**4** and **5**) were formed.

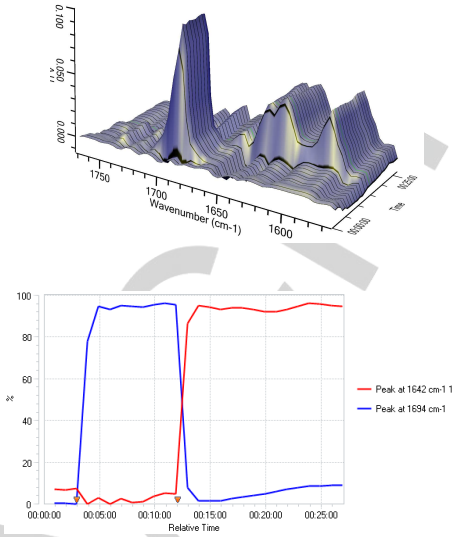
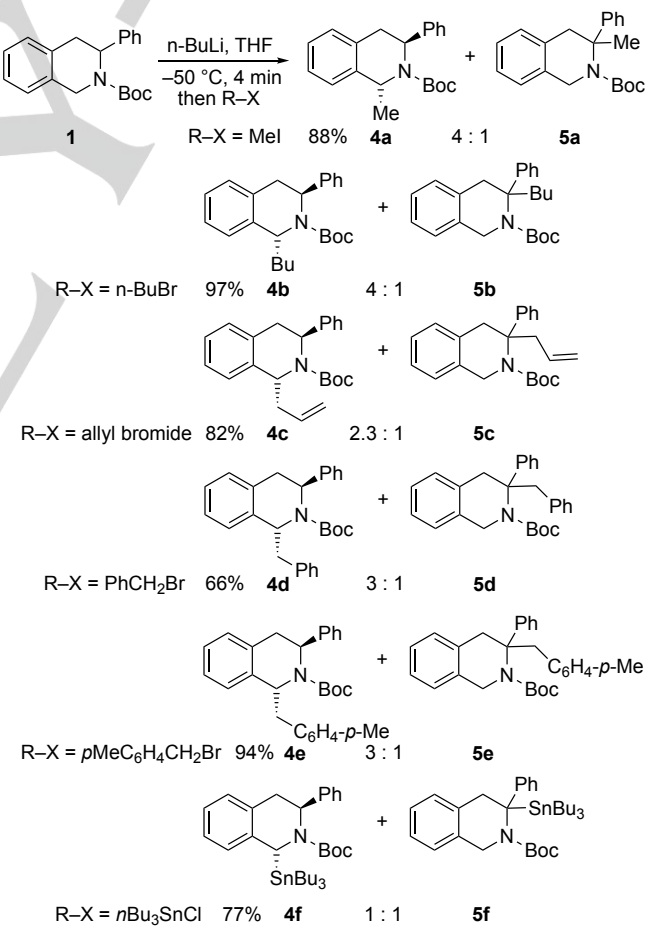


Figure 3. ReactIR spectra for lithiation of tetrahydroisoquinoline **1** with *n*BuLi added at 12 min in THF at –50 °C; $\nu_{C=O}$ at 1694 cm^{-1} for **1** and $\nu_{C=O}$ at 1642 (and 1632) cm^{-1} for lithiated **1** (Time in h:min:sec).



Scheme 3. Lithiation–substitution of tetrahydroisoquinoline **1**.

The ratio of these products was typically around 3:1 in favour of reaction at C-1, suggesting that rotation of the Boc group (ratio of rotamers 1.2:1) is faster than lithiation. The preference for lithiation at C-1 may be due to steric reasons or possibly due to a slightly greater acidity at this position. In all cases, the C-1 substituted products **4** were obtained as a single stereoisomer. For product **4a** this was determined to be the *trans* isomer by single crystal X-ray analysis (Figure 4).[14]

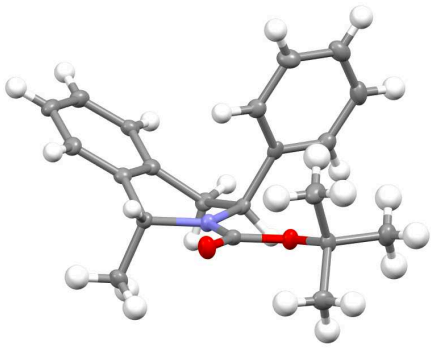
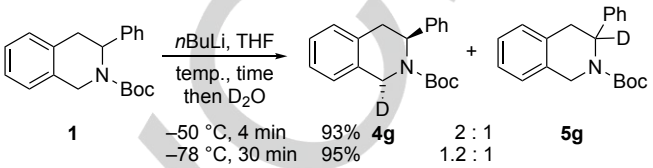


Figure 4. Crystal structure for **4a** with thermal ellipsoids at 50% calculated displacement parameter.

To further investigate the regioselectivity in the lithiation–trapping of *N*-Boc-3-phenyltetrahydroisoquinoline **1** and to avoid any steric effects of the electrophile, we trapped the organolithium intermediates with D_2O. This gave the same two regioisomeric products (**4g** and **5g**, 93% yield, Scheme 4). The ratio of the regioisomers was 2:1 (C-1 to C-3) which was similar to that for the products on using alkyl halide electrophiles. The reactivity of the electrophile does have some effect on the selectivity, as can be seen from the small differences in the ratio of the regioisomers (Scheme 3). It is possible that the best ratios (4:1), obtained for iodomethane and bromobutane as the electrophiles (to give predominantly **4a** and **4b** respectively), could be due to the poorer reactivity of these electrophiles[11c] and slower reaction at the more hindered C-3 position. The α-amino-organolithiums at C-1 and at C-3 could potentially be interconverting and these are likely to react at different rates with the different electrophiles. An attempt to verify this was made by reacting the stannane **4f** with *n*BuLi (THF, –50 °C) followed by addition of MeI. Although tin–lithium exchange occurred, no methylated product was isolated. The same experiment with the 3-stannyl compound **5f** at –50 °C gave only the recovered stannane. However, on warming this mixture to room temperature tin–lithium exchange took place and addition of MeI gave the 3-methylated product **5a** as the only observable isomer (90% yield). These results are inconclusive but suggest that there is no conversion of the 3-lithiated intermediate to the 1-lithiated intermediate under the reaction conditions.

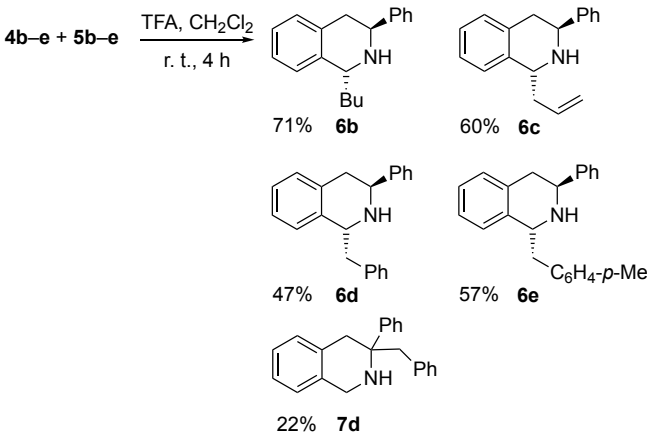
At the lower temperature of –78 °C, the rate of rotation of the Boc group is reduced and the half-life for rotation can be calculated to be approximately 11 min. Lithiation is more rapid than rotation at this temperature, so the ratio of the organolithium intermediates should match the ratio of rotamers (1.2:1). Indeed, on quenching the mixture of organolithiums formed at –78 °C with D_2O, the deuterated products **4g** and **5g** were formed in high yield as a 1.2:1 mixture (Scheme 4). Carrying out the lithiation–trapping at 0 °C gave the same ratio of products as that found at –50 °C, indicating that at –50 °C or at higher temperatures the Boc group is rotating faster than lithiation.



Scheme 4. Lithiation–deuteration of tetrahydroisoquinoline **1**.

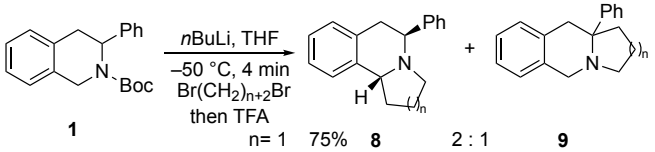
It is possible that the size of the base could affect the ratio of regioisomers. However, on using *s*BuLi in THF at –50 °C, the products **4d** and **5d** had very similar levels of selectivity (62%, 3:1). Likewise, on using Schlosser's base (*n*BuLi + KO*t*Bu) these products were formed in 66% yield with a ratio of 4:1 in favour of **4d**. We also explored incorporating the additive TMEDA in the solvents THF, Et_2O, or cyclopentyl methyl ether but these too gave almost identical results (to using *n*BuLi in THF), with the products **4a** and **5a** being formed in high yields (89–93%) and with the same regioselectivity (ratio 4:1 in favour of **4a**).

As mentioned above, the product **4a** could be isolated by recrystallisation, although we generally did not separate the mixture of regioisomers. The mixtures of **4b–e** and **5b–e** were treated with trifluoroacetic acid (TFA) to remove the Boc group. With the mixture of **4d** and **5d** we were able to isolate the amines **6d** and **7d** (Scheme 5). In the other cases, it was only possible to isolate the amines **6b**, **6c** and **6e**. The product **6e** was recrystallised and the stereochemistry was confirmed as *trans* by single crystal X-ray analysis (see SI),[13] which matched that obtained for product **4a** (Figure 4). Other products are assumed to have the same *trans* stereochemistry.



Scheme 5. Removal of the Boc group from the carbamate **4** and **5**.

As further examples, we prepared the tricyclic products **8**–**11** by lithiation of tetrahydroisoquinoline **1** followed by trapping with 1,3-dibromopropane or 1,4-dibromobutane and then treatment with TFA (Scheme 6). In both cases the regioisomeric products could be separated by column chromatography. These products have potential biological activity for example as anti-depressants and compound **8** has been screened as an antagonist of tetrabenazine-induced ptosis and as an inhibitor of dopamine, norepinephrine, and serotonin uptake.[15,16]



1

n= 1 75% **8** 2 : 1 **9**

n= 2 87% **10** 2.6 : 1 **11**

Scheme 6. Preparation of the tricyclic amines **8** and **9**.

Conclusions

The regioselectivity in the lithiation and trapping of *N*-Boc-3-phenyltetrahydroisoquinoline was investigated and found to give a mixture of products that favour reaction at C-1. The barrier to rotation of the carbamate was determined and the half-life was found to be several minutes at –78 °C but only a few seconds at –50 °C. This has implications for the selectivity as at the lower temperature the ratio of regioisomeric products matched the ratio of carbamate rotamers (about 1.2:1). This indicated that the lithiation occurs more quickly than the rotation at –78 °C. However at –50 °C and above, lithiation was slower than rotation and this allowed higher selectivities in the reaction (ratio of regioisomers up to 4:1). This selectivity is likely a result of the less hindered environment at C-1 although bases with different steric bulk gave similar results. The products from substitution at C-1 were found to have *trans* stereochemistry. It was possible to remove the Boc group using acid to give a selection of bicyclic and tricyclic amine products.

Experimental Section

***tert*-Butyl 3-Phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 1:** Di-*tert*-butyl dicarbonate (0.4 g, 1.9 mmol) was added to 3-phenyltetrahydroisoquinoline **3** (3.0 g, 19 mmol) in water–dioxane (3 mL, 1:2) at 0 °C. After 4 h, the mixture was allowed to warm to room temperature. After 16 h, the mixture was extracted with Et_2O (3 × 20 mL) then the extracts were washed with saturated brine solution (20 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by flash column chromatography on silica, eluting with petrol–EtOAc (97:3), gave the carbamate **1** (0.5 g, 79%) as an amorphous solid; m.p 70–73 °C; R_f 0.23 [petrol–EtOAc (90:10)]; FTIR ν_{max} (film)/cm^{-1} 3005, 2975, 1690, 1455; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.25–7.14 (9H, m, ArH), 5.38 (1H, br s, CH), 4.85 (1H, d, *J* 16 Hz, CH), 4.31–4.27 (1H, m, CH), 3.36–3.31 (1H, m, CH), 3.14–3.10 (1H, m, CH), 1.40 (9H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, some aromatic signals could not be observed) δ = 155.2, 142.4, 133.8, 128.2, 126.9, 126.8, 126.4, 126.0, 80.0, 54.4, 43.8, 35.9, 28.4; HRMS (ES) Found: MNa^+, 332.1614. $C_{20}H_{23}NO_2Na$ requires MNa^+ 332.1626; LRMS *m/z* (ES) 332 (100%, MNa^+).

3-Phenyl-1,2,3,4-tetrahydroisoquinoline 3: $NaBH_4$ (3.6 g, 96 mmol) was added in portions to a solution of the imine **2** (9.9 g, 47.8 mmol, prepared according to the literature[12]) in methanol (100 mL) at 0 °C. After 3 h, aqueous NaOH (20 mL, 2 M) was added and the solvent was evaporated. The residue was extracted using CH_2Cl_2 (2 × 150 mL), dried ($MgSO_4$), evaporated and the residue was purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (92:8), to give the amine **3** (6.1 g, 61%) as an oil; R_f 0.21 [CH_2Cl_2–MeOH (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$,) δ = 7.47–7.45 (1H, m, ArH), 7.41–7.37 (2H, m, 2 × ArH), 7.33–7.30 (2H, m, 2 × ArH), 7.20–7.10 (4H, m, 4 × ArH), 4.31 (1H, d, *J* 16 Hz, CH), 4.21 (1H, d, *J* 16 Hz, CH), 4.07–4.03 (1H, m, CH), 3.02–3.00 (2H, m, 2 × CH), 1.90 (1H, br s, NH). Data in accordance with the literature.[17]

***tert*-Butyl (1*R*,3*S*)-1-Methyl-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 4a and *tert*-Butyl 3-Methyl-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 5a:**

*n*BuLi (0.2 mL, 0.5 mmol, 2.5 M in hexane) was added to the carbamate **1** (100 mg, 0.32 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 4 minutes, iodomethane (0.07 mL, 1.2 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (95:5), to give the carbamates **4a** and **5a** (92 mg, 88%), ratio 4:1.

Carbamate **4a** could be recrystallised from hexane–CH_2Cl_2 to give cubes (75 mg); R_f 0.41 [petrol–EtOAc (90:10)]; FTIR ν_{max} (film)/cm^{-1} 3000, 2920, 1690, 1455; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.21–7.20 (2H, m, 2 × ArH), 7.11–7.06 (4H, m, 4 × ArH), 6.89–6.83 (3H, m, 3 × ArH), 5.50–5.19 (2H, m, 2 × CH), 3.59–3.55 (1H, m, CH), 2.87–2.83 (1H, m, CH), 1.52 (3H, d, *J* 7 Hz, CH_3), 1.19 (9H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.0, 145.1, 140.0, 131.7, 128.5, 127.6, 127.0, 126.9, 126.1, 125.9, 125.5, 79.6, 56.6, 52.4, 36.0, 28.5 & 28.1, 14.1; HRMS (ES) Found: MNa^+, 346.1790. $C_{21}H_{25}NO_2Na$ requires MNa^+ 346.1783; LRMS *m/z* (ES) 346 (100%, MNa^+); CCDC 1889261.

Carbamate **5a** was an oil (17 mg); R_f 0.41 [petrol–EtOAc (80:20)]; FTIR ν_{max} (film)/cm^{-1} 3000, 2920, 1690, 1455; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.32–7.27 (8H, m, 8 × ArH), 7.09–7.08 (1H, m, 1 × ArH), 4.91 (1H, d, *J* 15 Hz, CH), 4.67 (1H, d, *J* 15 Hz, CH), 3.06 (1H, d, *J* 14.5 Hz, CH), 2.83 (1H, d, *J* 14.5 Hz, CH), 1.67 (3H, s, CH_3), 1.09 (9H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, C=O could not be observed) δ = 149.6, 136.0, 135.8, 127.9, 127.4, 127.1, 126.7, 126.0, 125.8, 124.5, 79.8, 60.3, 48.0, 46.3, 28.0, 25.2; HRMS (ES) Found: MNa^+, 346.1789. $C_{21}H_{25}NO_2Na$, requires MNa^+; 346.1780, LRMS *m/z* (ES) 346 (100%, MNa^+).

Alternatively, carbamate **5a** was formed from the stannane **5f** (67 mg, 0.13 mmol) in THF (2 mL) by addition of *n*BuLi (0.05 mL, 0.13 mmol, 2.5 M in hexane) at room temperature. After 5 min, iodomethane (0.02 mL, 0.34 mmol) was added. MeOH (1 mL) was added and the solvent was evaporated. The residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (95:5), gave the carbamate **5a** (32 mg, 90%) as an oil; data as above.

***tert*-Butyl 1-Butyl-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 4b and *tert*-Butyl 3-Butyl-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 5b:**

*n*BuLi (0.24 mL, 0.6 mmol, 2.5 M in hexane) was added to the carbamate **1** (120 mg, 0.4 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 4 minutes, 1-bromobutane (0.13 mL, 1.2 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (95:5), to give the carbamates **4b** and **5b** (140 mg, 97%), ratio 4:1 as an inseparable mixture, as an oil; R_f 0.57 [petrol–EtOAc (80:20)]; FTIR ν_{max} (film)/cm^{-1} 3005, 2955, 2925, 1685, 1170; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.21–7.07 (6H, m, 6 × ArH), 6.89–6.80 (3H, m, 3 × ArH), 5.48–5.19 (1.6H, m, CH), 4.99–4.96 (0.2H, m, CH), 4.34 (0.2H, d, *J* 14.5 Hz, CH), 3.65–3.57 (0.8H, m, CH), 3.35 (0.2H, d, *J* 14.5 Hz, CH), 2.89–2.52 (1H, m, CH), 2.19–2.03 (1H, m, CH), 1.68–1.60 (1H, m, CH), 1.47–1.11 (16H, m, 7 × CH, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.1, 145.3, 138.3, 136.0, 135.6, 133.8 & 133.5, 132.2, 128.7 & 128.6, 128.2 & 128.1, 128.0 & 127.9, 127.6, 127.4, 127.3, 127.1 & 127.0, 126.5 & 126.4, 126.2, 126.1, 125.6, 125.5 & 125.4, 124.7, 124.5, 76.6 & 76.5, 62.3, 57.9 & 57.0, 56.6 & 55.9, 46.9, 44.4, 43.7 & 43.1, 40.6 & 39.9, 37.0, 36.2, 29.3 & 28.9, 28.5 & 28.3, 28.0, 27.3 & 26.6, 23.2 & 22.7, 14.2, 14.1; HRMS (ES) Found: MNa$^+$, 388.2240. $C_{24}H_{31}NO_2Na$ requires MNa$^+$ 388.2247; LRMS *m/z* (ES) 388 (100%, MNa$^+$).

***tert*-Butyl 3-Phenyl-1-(prop-2-en-1-yl)-3,4-dihydro-1H-isoquinoline-2-carboxylate 4c and *tert*-Butyl 3-Phenyl-3-(prop-2-en-1-yl)-1,4-dihydroisoquinoline-2-carboxylate 5c:**

*n*BuLi (1.0 mL, 2.4 mmol, 2.4 M in hexane) was added to the carbamate **1** (500 mg, 1.6 mmol) in dry THF (8 mL) at –50 ºC under nitrogen. After 4 minutes, allyl bromide (0.42 mL, 2.9 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (90:10), to give the carbamates **4c** and **5c** (460 mg, 82%), ratio 2.3:1 as an inseparable mixture, as an oil; R_f 0.58 [petrol–EtOAc (80:20)]; FTIR ν_{max} (film)/cm^{-1} 2970, 2945, 2930, 1690, 1495, 1170; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.24–7.07 (6H, m, 6 × ArH), 6.89–6.80 (3H, m, 3 × ArH), 5.94–5.88 (0.3H, m, CH), 5.81–5.72 (0.7H, m, CH), 5.53–5.15 (2H, m, 2 × CH), 5.04–4.97 (1.7H, m, CH), 4.27 (0.3H, d, *J* 14.5 Hz, CH), 3.61–3.53 (1H, m, CH), 3.41 (0.3H, d, *J* 14.5 Hz, CH), 2.92–2.76 (1.7H, m, CH), 2.68 (0.3H, d, *J* 14.5 Hz, CH), 2.50–2.43 (0.7H, m, CH), 1.18–1.13 (9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.1, 145.2, 134.8, 128.5, 127.7, 127.6, 127.5, 127.3, 127.2, 126.3, 126.2, 125.8, 125.5, 125.4, 124.4, 119.0, 117.6, 79.9, 79.7, 61.9, 60.4, 58.0, 57.0, 56.8, 56.6, 56.0, 46.8, 44.1, 43.8, 41.8, 36.4, 36.2, 28.6, 28.1, 27.6; HRMS (ES) Found: MNa$^+$, 372.1942. $C_{23}H_{27}NO_2Na$ requires MNa$^+$ 372.1943; LRMS *m/z* (ES) 372 (100%).

***tert*-Butyl 1-Benzyl-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 4d and *tert*-Butyl 3-Benzyl-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 5d:**

*n*BuLi (0.3 mL, 0.7 mmol, 2.4 M in hexane) was added to the carbamate **1** (150 mg, 0.48 mmol) in dry THF (3 mL) at –50 ºC under nitrogen. After 4 minutes, benzyl bromide (0.4 mL, 1.4 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (90:10), to give the carbamates **4d** and **5d** (150 mg, 82%), ratio 3:1 as an inseparable mixture, as an oil; R_f 0.28 [petrol–EtOAc (90:10)]; FTIR ν_{max} (film)/cm^{-1} 2970, 2930, 2920, 1685, 1495, 1170; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.36–7.03 (9H, m, 9 × ArH), 6.96–6.67 (5H, m, 5 × ArH), 5.47–5.42 (0.75H, m, CH), 5.29–5.23 (0.75H, m, CH), 5.05 (0.25H, d, *J* 15 Hz, CH), 4.18 (0.25H, d, *J* 15 Hz, CH), 3.48 (0.25H, d, *J* 15 Hz, CH), 3.39–3.30 (1H, m, CH), 3.20–2.96 (1.75H, m, CH), 2.79 (0.25H, d, *J* 15 Hz, CH), 2.70–2.62 (0.75H, m, CH), 1.29–1.18 (9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.1 & 154.6, 145.2, 144.0, 138.1 & 137.9, 137.7, 136.7, 136.4 & 136.2, 135.2 & 135.0, 132.6 & 132.2, 131.2, 130.1, 129.9, 128.3 & 128.2, 128.0, 127.9, 127.6 & 127.5, 127.4, 127.3, 127.1, 127.0 & 126.9, 126.7 & 126.6, 126.4, 126.2 & 126.1, 126.0, 125.8 & 125.7, 125.5, 125.3, 125.1, 124.4, 80.3 & 80.1, 79.7, 62.7, 59.6 & 58.7, 56.6 & 56.1, 46.3 & 44.3, 43.7 & 43.4, 42.8 & 42.7, 36.1 & 36.0, 29.7, 28.7 & 28.4, 28.2 & 28.1; HRMS (ES) Found: MH$^+$, 422.2083. $C_{27}H_{29}NO_2Na$ requires MNH$^+$ 422.2096; LRMS *m/z* (ES) 422 (100%, MNa$^+$).

***tert*-Butyl 1-[(4-Methylphenyl)methyl]-3-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate 4e and *tert*-Butyl 3-[(4-Methylphenyl)methyl]-3-phenyl-1,4-dihydroisoquinoline-2-carboxylate 5e:**

*n*BuLi (0.6 mL, 1.4 mmol, 2.4 M in hexane) was added to the carbamate **1** (300 mg, 0.96 mmol) in dry THF (6 mL) at –50 ºC under nitrogen. After 4 minutes, 4-methylbenzyl bromide (500 mg, 2.9 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (95:5), to give the carbamates **4e** and **5e** (370 mg, 94%), ratio 3:1 as an inseparable mixture, as an oil; R_f 0.3 [petrol–EtOAc (90:10)]; FTIR ν_{max} (film)/cm^{-1} 3025, 2970, 2925, 1690, 1120; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.26–7.02 (8H, m, 8 × ArH), 6.93–6.69 (5H, m, 5 × ArH), 5.49–5.42 (0.75H, m, CH), 5.29–5.22 (0.75H, m, CH), 5.07 (0.25H, d, *J* 15 Hz, CH), 4.15 (0.25H, d, *J* 15 Hz, CH), 3.49 (0.25H, d, *J* 15 Hz, CH), 3.62–2.94 (2.75H, m, CH), 2.79 (0.25H, d, *J* 15 Hz, CH), 2.71–2.60 (0.75H, m, CH), 2.37 (0.75H, s, CH_3), 2.34 (2.25H, s, CH_3), 1.30–1.19 (9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 155.1 & 154.6, 145.3, 144.1, 136.9 & 136.6, 136.3, 136.2, 135.7 & 135.6, 135.4, 135.0 & 134.8, 134.5, 132.6 & 132.3, 131.1, 129.9 & 129.7, 129.0, 128.7 & 128.6, 128.4, 128.2, 127.8, 127.7, 127.6, 127.3 & 127.2, 127.1 & 127.0, 126.3, 126.1, 126.0, 125.8, 125.5 & 125.3, 125.1, 124.4, 80.3 & 80.0, 79.7, 62.7, 59.6 & 58.7, 56.6 & 56.1, 46.3 & 43.9, 43.0, 42.7 & 42.4, 36.2 & 36.0, 29.7, 28.7 & 28.4, 28.2 & 28.1, 21.2, 21.1; HRMS (ES) Found: MNa$^+$, 436.2227. $C_{28}H_{31}NO_2Na$ requires MNa$^+$ 436.2247; LRMS *m/z* (ES) 436 (100%, MNa$^+$).

***tert*-Butyl 3-Phenyl-1-(tributylstannyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate 4f and *tert*-Butyl 3-Phenyl-3-(tributylstannyl)-1,4-dihydroisoquinoline-2-carboxylate 5f:**

*n*BuLi (0.47 mL, 1.2 mmol, 2.5 M in hexane) was added to the carbamate **1** (300 mg, 1.0 mmol) in dry THF (6 mL) at –50 ºC under argon. After 4 minutes, Bu_3SnCl (0.8 mL, 2.9 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (3 mL) was added. The solvent was evaporated and the residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (99:1), to give the carbamates **4f** and **5f** (460 mg, 79%), ratio 1:1.

Carbamate **4f** was an oil (233 mg); R_f 0.5 [petrol–EtOAc (95:5)]; FTIR ν_{max} (film)/cm^{-1} 3005, 2975, 1685, 1515, 1150; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.14–6.80 (9H, m, 9 × ArH), 5.46–5.23 (2H, m, CH), 3.16–2.98 (2H, m, CH), 1.77–1.49 (9H, br, *t*-Bu), 1.40–1.33 (12H, m, 3 × CH_2CH_2), 1.14–0.85 (15H, m, 3 × CH_2 and 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.9, 144.6, 140.6, 129.9, 128.2, 127.8, 126.8, 126.3, 125.9, 124.2, 123.3, 79.5, 55.7, 50.1, 37.2, 29.0, 28.4, 27.6, 13.8, 11.0; HRMS

(ES) Found: MNa^+, 622.2706. $C_{32}H_{49}NO_2{}^{120}SnNa$ requires MNa^+ 622.2683; LRMS *m/z* (ES) 622 (100%, MNa^+).

Carbamate **5f** was an oil (227 mg); R_f 0.67 [petrol–EtOAc (95:5)]; FTIR ν_{max} (film)/cm^{-1} 3005, 2975, 1685, 1515, 1150; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.23–6.89 (9H, m, 9 × ArH), 4.83 (1H, d, *J* 16 Hz, CH), 4.19 (1H, d, *J* 16 Hz, CH), 3.61 (1H, d, *J* 16 Hz, CH), 3.43 (1H, d, *J* 16 Hz, CH), 1.59 (9H, s, *t*-Bu), 1.41–1.25 (12H, m, 3 × CH_2CH_2), 0.89–0.73 (15H, m, 3 × CH_2 and 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, one aromatic CH overlapping) δ = 157.2, 144.8, 134.8, 133.4, 128.7, 128.1, 126.1, 125.8, 124.8, 124.0, 80.4, 56.0, 43.8, 36.3, 29.1, 28.5, 27.7, 13.8, 13.3; HRMS (ES) Found: MNa^+, 622.2706. $C_{32}H_{49}NO_2{}^{120}SnNa$ requires MNa^+ 622.2683; LRMS *m/z* (ES) 622 (100%, MNa^+).

tert-Butyl 3-Phenyl-3,4-dihydro(1-$^2H_1$)-1H-isoquinoline-2-carboxylate 4g _tert_-Butyl 3-Phenyl-1,4-dihydro(3-^{2}H)isoquinoline-2-carboxylate 5g:

*n*BuLi (0.2 mL, 0.5 mmol, 2.4 M in hexane) was added to the carbamate **1** (100 mg, 0.32 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 4 minutes, D_2O (0.02 mL, 1.0 mmol) was added. The mixture was allowed to warm slowly to room temperature and the solvent was evaporated. The residue was purified by flash column chromatography on silica, eluting with petrol–EtOAc (99:1), to give the carbamates **4g** and **5g** (93 mg, 93%), ratio 2:1 as an inseparable mixture, as an oil; R_f 0.23 [petrol–EtOAc (90:10)]; FTIR ν_{max} (film)/cm^{-1} 3005, 2975, 2925, 1690, 1160; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.20–7.04 (9H, m, ArH), 5.25 (0.65H, br s, CH), 4.77 (0.35H, d, *J* 16 Hz, CH), 4.17–4.15 (1H, m, CH), 3.22–3.20 (1H, m, CH), 3.02–2.98 (1H, m, CH), 1.30 (9H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, one aromatic signal could not be observed) δ = 155.3, 142.8, 134.4, 133.8, 128.2, 126.9, 126.8, 126.4, 126.0, 80.0, 54.4, 43.4 (t, *J* 22 Hz), 35.0, 28.4; HRMS (ES) Found: MNa^+, 333.1682. $C_{20}H_{22}DNO_2Na$ requires MNa^+ 333.1684; LRMS *m/z* (ES) 333 (100%, MNa^+); Found: C, 76.91; H, 7.57; N, 4.07. $C_{20}H_{22}DNO_2$ requires C, 77.39; H, 7.79; N, 4.51.

1-Butyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline 6b:

Trifluoroacetic acid (0.06 mL, 0.5 mmol) was added to a mixture (ratio 4:1) of the carbamates **4b** and **5b** (100 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (10 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Purification by flash column chromatography on silica, eluting with petrol–EtOAc (95:5), gave the amine **6b** (51 mg, 71%) as an oil; R_f 0.45 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 3315, 2955, 2920, 1490, 1450; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.51–7.48 (2H, m, 2 × ArH), 7.42–7.38 (2H, m, 2 × ArH), 7.34–7.30 (1H, m, ArH), 7.20–7.11 (4H, m, 4 × ArH), 4.28–4.24 (1H, m, CH), 4.15–4.12 (1H, m, CH), 3.01–2.99 (2H, m, 2 × CH), 2.15 (1H, br s, NH), 1.99–1.93 (1H, m, CH), 1.77–1.71 (1H, m, CH), 1.52–1.28 (7H, m, 4 × CH and CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.5, 139.3, 134.5, 129.0, 128.6, 127.4, 127.0, 126.8, 126.1, 125.8, 56.4, 51.6, 37.7, 36.4, 29.2, 22.6, 14.1; HRMS (ES) Found: MH^+, 266.1902. $C_{19}H_{24}N$, requires MH^+; 266.1909, LRMS *m/z* (ES) 266 (100%, MH^+).

3-Phenyl-1-(prop-2-en-1-yl)-1,2,3,4-tetrahydroisoquinoline 6c:

Trifluoroacetic acid (0.2 mL, 2.6 mmol) was added to a mixture (ratio 2.3:1) of the carbamates **4c** and **5c** (460 mg, 1.3 mmol) in CH_2Cl_2 (12 mL) at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (10 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Purification by flash column chromatography on silica, eluting with petrol–EtOAc (65:35), gave the amine **6c** (170 mg, 60%) as an oil; R_f 0.37 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 3350, 2955, 2920, 1630, 1490; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.48–7.46 (2H, m, 2 × ArH), 7.41–7.37 (2H, m, 2 × ArH), 7.34–7.30 (1H, m, ArH), 7.20–7.12 (4H, m, 4 × ArH), 5.92 (1H, dddd, *J* 15, 9, 6, 3 Hz, CH), 5.21–5.16 (2H, m, 2 × CH), 4.33–4.14 (2H, m, 2 × CH), 3.09–2.96 (2H, m, 2 × CH), 2.77–2.68 (1H, m, CH), 2.62–2.56 (1H, m, CH), 2.22 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.3, 138.0, 135.9, 134.8, 129.0, 128.6, 127.4, 127.0, 126.9, 126.3, 125.8, 118.4, 55.7, 51.6, 41.3, 37.8; HRMS (ES) Found: MH^+, 250.1593. $C_{18}H_{19}N$ requires MNH^+ 250.1590; LRMS *m/z* (ES) 250 (100%, MNa^+).

1-Benzyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline 6d and 3-Benzyl-3-phenyl-2,4-dihydro-1H-isoquinoline 7d:

Trifluoroacetic acid (0.05 mL, 0.6 mmol) was added to a mixture (ratio 3:1) of the carbamates **4d** and **5d** (120 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (5 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Purification by flash column chromatography on silica, eluting with petrol–EtOAc (75:25), gave the amines **6d** and **7d** (65 mg, 69%) as a separable mixture (ratio 2:1):

Amine **6d** (44 mg) as an oil; R_f 0.2 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (film)/cm^{-1} 3330, 3060, 3020, 1500; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.50–7.47 (2H, m, 2 × ArH), 7.39–7.16 (12H, m, 12 × ArH), 4.44–4.37 (2H, m, 2 × CH), 3.26–3.20 (1H, m, CH), 3.16–3.10 (1H, m, CH), 3.06–3.00 (2H, m, 2 × CH), 2.03 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.1, 139.1, 137.9, 134.8, 129.3, 129.1, 128.8, 128.6, 127.5, 127.3, 126.9, 126.5, 126.4, 125.8, 58.4, 51.8, 42.9, 38.2; HRMS (ES) Found: MH^+, 300.1719. $C_{22}H_{21}N$ requires MH^+ 300.1746; LRMS *m/z* (ES) 300 (100%, MH^+). Amine **6d** is known but no data were reported.[18]

Amine **7d** (21 mg) as an oil; R_f 0.2 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 3330, 3060, 3020, 1500; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.35 (2H, m, 2 × ArH), 7.28–7.06 (9H, m, 9 × ArH), 6.88–6.87 (3H, m, 3 × ArH), 4.00 (1H, d, *J* 16 Hz, CH), 3.79 (1H, d, *J* 16 Hz, CH), 3.25 (1H, d, *J* 16 Hz, CH), 3.11–3.01 (3H, m, 3 × CH), 1.79 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.2, 136.7, 135.1, 134.0, 130.6, 129.1, 128.0, 127.7, 127.2, 126.5, 126.4, 125.9, 125.7, 125.6, 58.2, 50.8, 44.4, 36.8; HRMS (ES) Found: MH^+, 300.1717. $C_{22}H_{21}N$ requires MH^+ 300.1746; LRMS *m/z* (ES) 300 (100%, MH^+).

(1*S*,3*R*)-1-(4-Methylbenzyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline 6e:

Trifluoroacetic acid (0.13 mL, 1.8 mmol) was added to a mixture (ratio 3:1) of carbamates **4e** and **5e** (370 mg, 0.9 mmol) in CH_2Cl_2 (10 mL) at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (5 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Purification by flash column chromatography on silica, eluting with petrol–EtOAc (60:40), gave the amine **6e** (160 mg, 57%) as plates; m.p 71–73 °C; R_f 0.4 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 3315, 3020, 2920, 1515, 1490; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.48–7.46 (2H, m, 2 × ArH), 7.40–7.37 (2H, m, 2 × ArH), 7.34–7.22 (4H, m, 4 × ArH), 7.18–7.13 (5H, m, 5 × ArH), 4.40–4.37 (2H, m, 2 × CH), 3.21–3.15 (1H, m, CH), 3.11–2.98 (3H, m, 3 × CH), 2.35 (3H, s, CH_3), 1.94 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.1, 138.0, 136.1, 135.9, 134.7, 129.5, 129.2, 129.1, 128.6, 127.5, 127.3, 126.9, 126.4, 125.8, 58.4, 51.8, 42.5, 38.2, 21.1; HRMS (ES) Found: MH^+, 314.1914.

$C_{23}H_{23}N$ requires MH^+ 314.1903; LRMS *m/z* (ES) 314 (100%, MH^+); CCDC 1889262.

(5*S*,10b*R*)-5-Phenyl-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinoline 8 and 10a-Phenyl-1H,2H,3H,5H,10H-pyrrolo[1,2-b]isoquinoline 9:

*n*BuLi (0.24 mL, 0.57 mmol, 2.4 M in hexane) was added to the carbamate **1** (150 mg, 0.48 mmol) in dry THF (3 mL) at –50 ºC under nitrogen. After 4 minutes, $Br(CH_2)_3Br$ (0.14 mL, 1.44 mmol) was added. The mixture was allowed to warm slowly to room temperature and the solvent was evaporated. To this mixture (220 mg) was added trifluoroacetic acid (2.6 mL, 0.2 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (20 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (95:5), gave the amines **8** and **9** (86 mg, 75%) as separable regioisomers (ratio 2:1):

Amine **8** (56 mg) as a gum; R_f 0.22 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 3000, 2990, 2950, 1450; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.34 (4H, m, 4 × ArH), 7.32–7.28 (1H, m, ArH), 7.25–7.13 (4H, m, 4 × ArH), 4.23 (1H, t, *J* 8 Hz , CH), 3.88 (1H, dd, *J* 9.5, 4 Hz, CH), 3.15–3.08 (1H, m, CH), 3.02–2.97 (1H, m, CH), 2.88–2.83 (1H, m, CH), 2.80–2.74 (1H, m, CH), 2.42–2.34 (1H, m, CH), 1.92–1.80 (2H, m, 2 × CH), 1.61–1.50 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.1, 138.6, 134.8, 128.4, 127.8, 127.7, 127.2, 126.2, 126.1, 126.0, 60.8, 60.5, 52.4, 38.6, 32.0, 23.1; HRMS (ES) Found: MH^+, 250.1591. $C_{18}H_{19}N$ requires MH^+ 250.1590; LRMS *m/z* (ES) 250 (100%, MH^+).

Amine **9** (30 mg) as a gum; R_f 0.25 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 2950, 2920, 1600, 1450; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.56 (1H, m, 1 × ArH), 7.32–7.10 (8H, m, 8 × ArH), 3.90 (1H, d, *J* 16 Hz, CH), 3.79 (1H, d, *J* 16 Hz, CH), 3.24 (1H, t, *J* 7.5 Hz, CH), 3.14 (1H, d, *J* 16 Hz, CH), 2.95 (1H, d, *J* 16 Hz, CH), 2.70 (1H, q, *J* 7.5 Hz, CH), 2.15–2.09 (1H, m, CH), 1.85–1.69 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.4, 136.5, 135.4, 128.4, 127.9, 126.5, 126.4, 126.0, 125.8, 125.4, 65.4, 53.0, 50.0, 41.6, 36.7, 22.1; HRMS (ES) Found: MH^+, 250.1591. $C_{18}H_{19}N$ requires MH^+ 250.1589; LRMS *m/z* (ES) 250 (100%, MH^+). Data in accordance with the literature.[19]

(6*S*,11b*R*)-6-Phenyl-1H,2H,3H,4H,6H,7H,11bH-pyrido[2,1-a]isoquinoline 10 and 11a-Phenyl-1H,2H,3H,4H,6H,11H-pyrido[1,2-b]isoquinoline 11:

*n*BuLi (0.24 mL, 0.57 mmol, 2.4 M in hexane) was added to the carbamate **1** (150 mg, 0.48 mmol) in dry THF (3 mL) at –50 ºC under nitrogen. After 4 minutes, $Br(CH_2)_4Br$ (0.17 mL, 1.44 mmol) was added. The mixture was allowed to warm slowly to room temperature and the solvent was evaporated. To this mixture (240 mg) was added trifluoroacetic acid (2.7 mL, 0.2 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature. After 4 h, the solvent was evaporated and aqueous NaOH (5 mL, 1 M) was added. After 1 h, the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (95:5), gave the amines **10** and **11** (110 mg, 87%) as separable regioisomers (ratio 2:1):

Amine **10** (80 mg) as a gum; R_f 0.22 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 3005, 2970, 1480; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.32 (3H, m, 3 × ArH), 7.21–7.15 (6H, m, 6 × ArH), 4.24 (1H, t, *J* 6 Hz, CH), 3.60–3.44 (2H, m, 2 × CH), 3.10–2.97 (2H, m, 2 × CH), 2.45–2.39 (1H, m, CH), 2.15–2.12 (1H, m, CH), 1.89–1.86 (1H, m, CH), 1.73–1.60 (2H, m, 2 × CH), 1.50–1.43 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.9, 139.5, 133.6, 128.7, 128.6, 128.1, 127.4, 126.2, 125.7, 125.5, 60.3, 57.7, 52.3, 36.0, 31.2, 25.0, 23.3; HRMS (ES) Found: MH^+, 264.1748. $C_{19}H_{21}N$ requires MH^+ 264.1747; LRMS *m/z* (ES) 264 (100%, MH^+).

Amine **11** (30 mg) as a gum; R_f 0.54 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 2960, 2940, 1450; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.55 (2H, m, 2 × ArH), 7.28–7.13 (5H, m, 5 × ArH), 7.10–7.05 (1H, m, ArH), 6.87–6.85 (1H, m, ArH), 3.83 (1H, d, *J* 17 Hz, CH), 3.58 (1H, d, *J* 17 Hz, CH), 3.41 (1H, d, *J* 17 Hz, CH), 3.02 (1H, d, *J* 17 Hz, CH), 2.88–2.83 (2H, m, 2 × CH), 1.88–1.78 (3H, m, 3 × CH), 1.72–1.61 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.0, 134.2, 133.6, 128.7, 128.1, 126.7, 126.5, 126.4, 125.9, 125.7, 58.9, 53.4, 49.3, 40.2, 26.2, 25.9, 21.1; HRMS (ES) Found: MH^+, 264.1748. $C_{19}H_{21}N$ requires MH^+ 264.1745; LRMS *m/z* (ES) 264 (100%, MH^+).

Acknowledgements

We thank the Iraqi Government, the Ministry of Higher Education & Scientific Research Libya, and the University of Sheffield for support. We would like to thank the reviewers for their comments and suggestions.

Keywords: Alkylation • Carbanions • Lithiation • Nitrogen heterocycles • Quaternary centers

[1] J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669–1730.

[2] G. Mari, S. Catalani, E. Antonini, L. De Crescentini, F. Mantellini, S. Santeusanio, P. Lombardi, A. Amicucci, S. Battistelli, S. Benedetti, F. Palma, *Bioorg. Med. Chem.* **2018**, *26*, 5037–5044.

[3] M. Chaumontet, R. Piccardi, O. Baudoin, *Angew. Chem. Int. Ed.* **2009**, *48*, 179–182.

[4] a) G. Ellison, *Brain Res. Rev.* **1995**, *20*, 250–267; b) P. Kovacic, R. Somanathan, *Oxid. Med. Cell. Longev.* **2010**, *3*, 13–22.

[5] a) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370; b) C. E. Puerto Galvis, V. V. Kouznetsov, *Synthesis* **2017**, *49*, 4535–4561.

[6] For recent examples, see a) H. Zhou, Y. Liu, S. Yang, L. Zhou, M. Chang, *Angew. Chem. Int. Ed.* **2017**, *56*, 2725–2729; b) T. Yang, G. Gu, X. Zhang, *Chem. Commun.* **2018**, 7247–7250; c) J. Flores-Ferrándiz, N. Carter, M. J. González-Soria, M. Wasinska, D. Gill, B. Maciá, V. Caprio, *Org. Biomol. Chem.* **2018**, *16*, 6961–6968; d) C. Hargitai, T. Nagy, J. Halász, G. Simig, B. Volk, *Molecules* **2018**, *23*, 1280/1–1280/11; e) X. Guo, Y. Okamoto, M. R. Schreier, T. R. Ward, O. S. Wenger, *Chem. Sci.* **2018**, *9*, 5052–5056; f) G. Oss, S. D. de Vos, K. N. H. Luc, J. B. Harper, T. V. Nguyen, *J. Org. Chem.* **2018**, *83*, 1000–1010; g) L. Zeng, B. Huang, Y. Shen, S. Cui, *Org. Lett.* **2018**, *20*, 3460–3464.

[7] a) D. Seebach, J.-J. Lohmann, M. A. Syfrig, M. Yoshifuji, *Tetrahedron* **1983**, *39*, 1963–1974; b) A. I. Meyers, L. M. Fuentes, Y. Kubota, *Tetrahedron* **1984**, *40*, 1361–1370; c) K. Rein, M. Goicoechea-Pappas, T. V. Anklekar, G. C. Hart, G. A. Smith, R. E. Gawley, *J. Am. Chem. Soc.* **1989**, *111*, 2211–2217; d) S. Adam, X. Pannecoucke, J. C. Combret, J. C. Quirion, *J. Org. Chem.* **2001**, *66*, 8744–8750; e) S. V. Kessar, P. Singh, R. Vohra, N. P. Kaur, K. N. Singh, *J. Chem. Soc., Chem. Commun.* **1991**, 568–570; f) G. M. Coppola, *J. Heterocyclic Chem.* **1991**, *28*, 1769–1772; g) M. R. Ebden, N. S. Simpkins, D. N. A. Fox, *Tetrahedron* **1998**, *54*, 12923–12952; h) J. C. Liermann, T. Opatz, *J. Org. Chem.* **2008**, *73*, 4526–4531; i) K. N. Singh, P. Singh, E. Sharma, Y. S. Deol, *Synthesis* **2014**, *46*, 1739–1750; j) L. Benmekhbi, F. Fouafi, T. Roisnel, J.-P. Hurvois, *J. Org. Chem.* **2016**, *81*, 6721–6739; k) A. Monsees, S. Laschat, I. Dix, P. G. Jones, *J. Org. Chem.*

1998, *63*, 10018–10021. For a sila derivative, see l) S. J. Barraza, S. E. Denmark, *J. Am. Chem. Soc.* **2018**, *140*, 6668–6684.

[8] P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560.

[9] a) X. Li, D. Leonori, N. S. Sheikh, I. Coldham, *Chem. Eur. J.* **2013**, *19*, 7724–7730; b) X. Li, I. Coldham, *J. Am. Chem. Soc.* **2014**, *136*, 5551–5554; c) R. A. Talk, A. Duperray, X. Li, I. Coldham, I. *Org. Biomol. Chem.* **2016**, *14*, 4908–4917.

[10] a) N. S. Sheikh, D. Leonori, G. Barker, J. D. Firth, K. R. Campos, A. J. H. M. Meijer, P. O'Brien, I. Coldham, *J. Am. Chem. Soc.* **2012**, *134*, 5300–5308; b) E. J. Cochrane, D. Leonori, L. A. Hassall, I. Coldham, *Chem. Comm.* **2014**, *50*, 9910–9913; c) E. J. Cochrane, L. A. Hassall, I. Coldham, *J. Org. Chem.* **2015**, *80*, 5964–5969; d) T. Aeyad, J. D. Williams, A. J. H. M. Meijer, I. Coldham, *Synlett* **2017**, *28*, 2765–2768; e) N. Carter, X. Li, L. Reavey, A. J. H. M. Meijer, I. Coldham, *Chem. Sci.* **2018**, *9*, 1352–1357; f) T. Aeyad, C. G. Jones, I. Coldham, *Eur. J. Org. Chem.* **2018**, *23*, 5289–5296.

[11] a) G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos, P. O'Brien, *J. Org. Chem.* **2011**, *76*, 5936–5953; b) A. M. Fournier, C. J. Nichols, M. A. Vincent, I. H. Hillier, J. Clayden, *Chem. Eur. J.* **2012**, *18*, 16478–16490; c) J. D. Firth, P. O'Brien, L. Ferris, *J. Am. Chem. Soc.* **2016**, *138*, 651–659; d) J. D. Firth, P. O'Brien, L. Ferris, *J. Org. Chem.* **2017**, *82*, 7023–7031.

[12] R. D. Larsen, R. A. Reamer, E. G. Corley, P. Davis, E. J. J. Grabowski, P. J. Reider, I. Shinkai, *J. Org. Chem.* **1991**, *56*, 6034–6038.

[13] For examples of *in situ* IR (ReactIR) spectroscopy with organolithiums, see a) R. C. Mykura, S. Veth, A. Varela, L. Dewis, J. J. Farndon, E. L. Myers, V. K. Aggarwal, *J. Am. Chem. Soc.* **2018**, *140*, 14677–14686; b) A. M. Fournier, C. J. Nichols, M. A. Vincent, I. H. Hillier, J. Clayden, *Chem. Eur. J.* **2012**, *18*, 16478–16490; c) D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260–7261; d) V. Capriati, S. Florio, R. Luisi, F. M. Perna, A. Spina, *J. Org. Chem.* **2008**, *73*, 9552–9564; e) D. J. Pippel, G. A. Weisenburger, N. C. Faibish, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 4919–4927.

[14] For X-ray data of compounds **4a** and **6e**, see CCDC 1889261 and CCDC 1889262 respectively.

[15] B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Costanzo, S. O. Nortey, C. R. Schneider, P. E. Setler, *J. Med. Chem.* **1987**, *30*, 1433–1454.

[16] The *cis* stereoisomer of tricyclic product **10** has been prepared in 10 steps: see ref. 3.

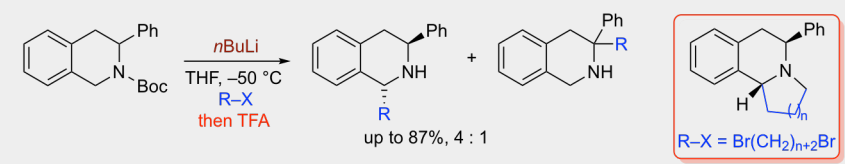
[17] F. Foubelo, C. Gómez, A. Gutiérrez, M. Yus, *J. Het. Chem.* **2000**, *37*, 1061–1064.

[18] R. Kojima, T. Shiragami, K. Shima, M. Yasuda, T. Majima, *Chem. Lett.* **1997**, 1241–1242.

[19] A. J. Y. Lan, R. O. Heuckeroth, P. S. Mariano, *J. Am. Chem. Soc.* **1987**, *109*, 2738–2745.

Entry for the Table of Contents

FULL PAPER



The regioselectivity in the lithiation–trapping of *N*-*tert*-butoxycarbonyl (*N*-Boc)-3-phenyltetrahydroisoquinoline was studied, including the use of React-IR and VT-NMR spectroscopy ($\Delta G^{\ddagger}$ 58 kJ/mol at –50 °C for Boc rotation). The major product was the *trans*-1-substituted isomer using a range of electrophiles. The Boc group could be removed with acid to give bicyclic and tricyclic tetrahydroisoquinolines.

Organolithium reactions

*R. A. Talk, A. El-Tunsi, C. C. Robertson, I. Coldham**

Page No. – Page No.

Regioselective lithiation and electrophilic quench of *N*-Boc-3-phenyltetrahydroisoquinoline