CHEMISTRY
A EUROPEAN JOURNAL

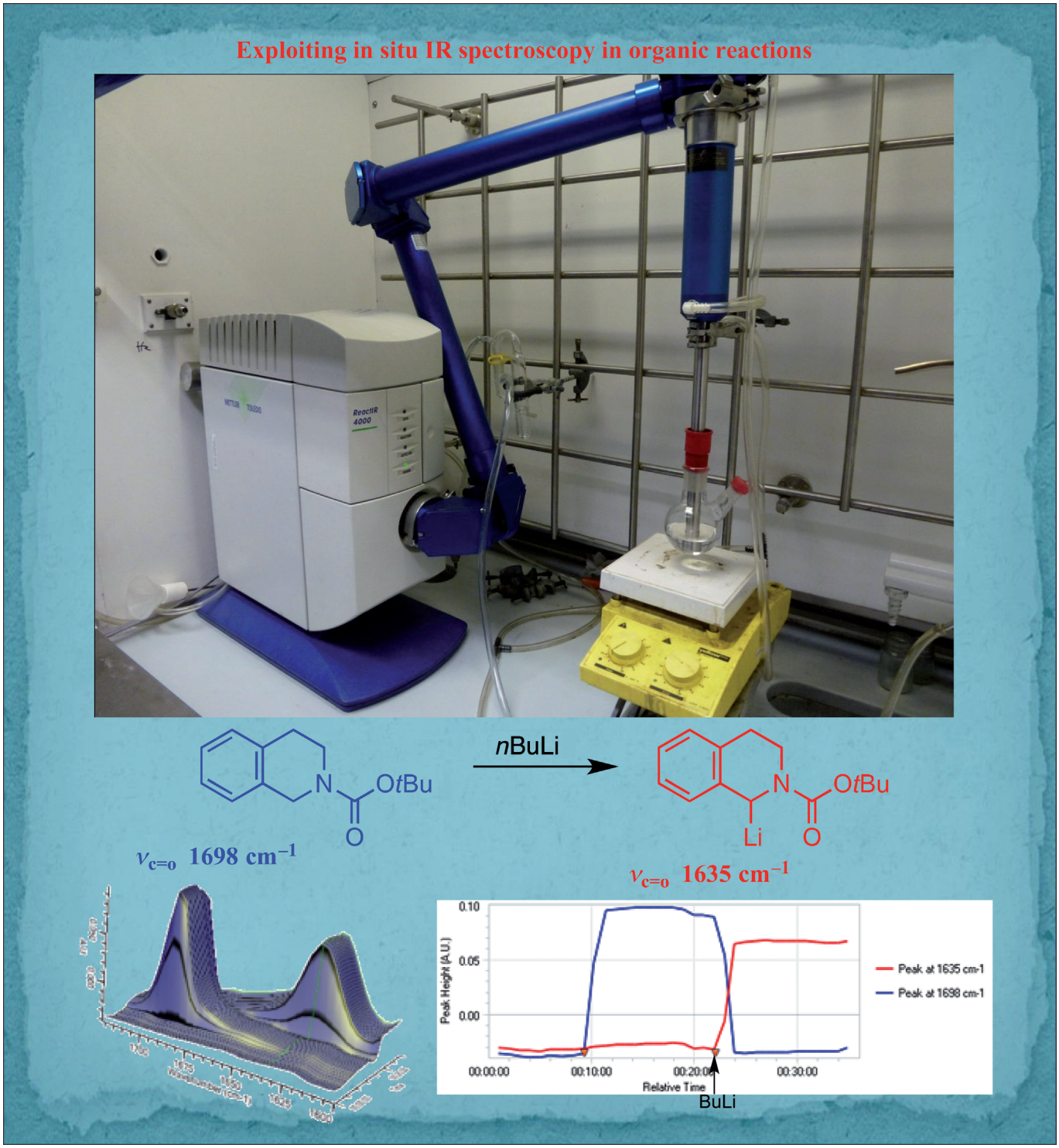
FULL PAPER

DOI: 10.1002/chem.201301096

Synthesis of 1-Substituted Tetrahydroisoquinolines by Lithiation and Electrophilic Quenching Guided by In Situ IR and NMR Spectroscopy and Application to the Synthesis of Salsolidine, Carnegine and Laudanosine

Xiabing Li, Daniele Leonori, Nadeem S. Sheikh, and Iain Coldham*[a]

In memory of Robert E. Gawley



Abstract: The lithiation of *N*-*tert*-butoxycarbonyl (*N*-Boc)-1,2,3,4-tetrahydroisoquinoline was optimized by in situ IR (ReactIR) spectroscopy. Optimum conditions were found by using *n*-butyllithium in THF at −50 °C for less than 5 min. The intermediate organolithium was quenched with electrophiles to give 1-substituted 1,2,3,4-tetrahydroisoquinolines. Monitoring the lithiation by IR or NMR spectroscopy showed that one rotamer reacts quickly and the barrier to rotation of the Boc group was determined by variable-temperature NMR spectroscopy and found to be about 60.8 kJ mol^{-1}, equating to a half-life for rotation of approximately 30 s at −50 °C. The use of (−)-sparteine as a ligand led to low levels of enantioselectivity after electrophilic quenching and the "poor man's Hoffmann test" indicated that the organolithium was configurationally unstable. The chemistry was applied to *N*-Boc-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and led to the efficient synthesis of the racemic alkaloids salsolidine, carnegine, norlaudanosine and laudanosine.

Keywords: alkaloids · carbanions · heterocyclic compounds · IR spectroscopy · metalation

Introduction

The tetrahydroisoquinoline moiety is a very common feature in natural products. 1-Substituted 1,2,3,4-tetrahydroisoquinolines are the most abundant class of such alkaloids and comprise a core ring system from which many structural groups are derived. Some of these are quite complex[1] but even simple derivatives possess a wide range of biological activities. For example, 1-methyl-1,2,3,4-tetrahydroisoquinoline, which exists in mammalian brains, is connected to the pathogenesis of Parkinson's disease.[2] 1-Phenyl- and 1-benzyl-1,2,3,4-tetrahydroisoquinoline are dopamine receptor antagonists.[3] The tetrahydroisoquinolines salsolidine and laudanosine (Figure 1) inhibit the uptake of 5-hydroxytryptamine by human blood platelets[4] and affect the cardiovascular system,[5] respectively. Synthetic tetrahydroisoquinolines form the basis of several pharmaceutical drugs, including solifenacin (which has urinary antispasmodic properties)[6] and noscapine (an antitussive agent; Figure 1).[7]

Classical approaches to the preparation of 1-substituted 1,2,3,4-tetrahydroisoquinolines involve the Pictet–Spengler and Bischler–Napieralski reactions, starting from β-arylethylamines.[8] Alternative approaches include the addition of nucleophiles to, or reduction of, 3,4-dihydroisoquinolines.[8,9] An interesting approach involves lithiation of 1,2,3,4-tetrahydroisoquinolines followed by electrophilic quenching; typically, *tert*– or *sec*-butyllithium have been used as the base, for example, in reports by Seebach and co-workers using *N*-pivaloyl (N−CO*t*Bu) 1,2,3,4-tetrahydroisoquinolines,[10] by Meyers and co-workers using formamidines (N−CN*t*Bu),[11] or by Katritzky and Akutagawa using the *N*-lithiocarboxylate salt (N−CO_2Li).[12]

Diastereoselective substitutions have been reported with chiral formamidines,[13] oxazolines,[14] or a sugar-derived auxiliary.[15] Activation of *N*-methyl-1,2,3,4-tetrahydroisoquinoline for lithiation is possible by prior complexation of the amine with BF_3 or BH_3.[16] One of the most versatile nitrogen substituents for adjacent lithiation is the *tert*-butoxycarbonyl (Boc) group, developed by Beak and co-workers.[17] In an isolated report, Coppola used *tert*-butyllithium in a mixture of THF and tetramethylethylenediamine (TMEDA) at −78 °C for 40 min for the lithiation of *N*-Boc-1,2,3,4-tetrahydroisoquinoline followed by trapping with iodomethane or a benzyl bromide.[18]

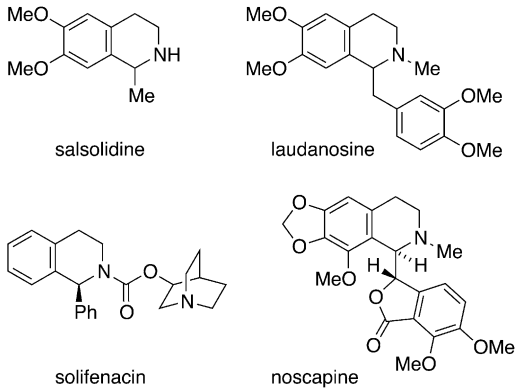


Figure 1. Some biologically active 1,2,3,4-tetrahydroisoquinolines.

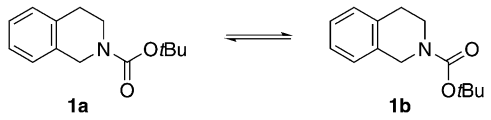
Following our work with *N*-Boc-pyrrolidine and piperidine, we became interested in the lithiation of 1,2,3,4-tetrahydroisoquinolines.[19,20] In particular, we wanted to investigate whether it was necessary to use a strong base, what the best conditions (temperature, time and solvent) were for the lithiation, and whether a range of electrophiles could be introduced. We were also interested in whether any asymmetry could be induced by using a chiral ligand, and hence the extent of the configurational stability of *N*-Boc-1-lithio-1,2,3,4-tetrahydroisoquinoline. In addition, we wanted to apply the chemistry to the synthesis of some 1-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids.

Herein, we describe our successful optimisation of the lithiation conditions, which makes use of in situ IR and ^{1}H NMR spectroscopic monitoring of the reaction.[21] Recently, we reported the benefit of using these techniques to optimise the lithiation of *N*-Boc-2-phenylpyrrolidine and pi-

[a] X. Li, Dr. D. Leonori, Dr. N. S. Sheikh, Prof. I. Coldham
Department of Chemistry, University of Sheffield
Brook Hill, Sheffield S3 7HF (UK)
Fax: (+44) 114-222-9346
E-mail: i.coldham@sheffield.ac.uk

Supporting information (experimental details) for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201301096.

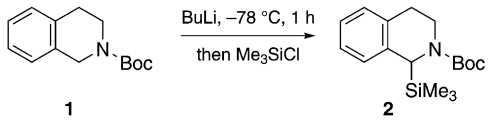
peridine.[22] Monitoring with ReactIR provides information on the extent of lithiation at different temperatures over different time periods and therefore on the rate of interconversion of the *N*-Boc rotamers. This is important, as the carbonyl group directs the lithiation by complexation to the base,[23] so that only rotamer **1a** (Scheme 1) is able to undergo subsequent benzylic lithiation at the 1-position. We report herein the spectroscopic analysis of *N*-Boc-1,2,3,4-tetrahydroisoquinoline **1**, which reveals the conformation of this compound and the rate of rotation of the Boc group that is critical to achieve efficient metallation. This has led to improved metallation conditions and we have applied these to the total synthesis of several tetrahydroisoquinoline alkaloids.



Scheme 1. Rotamers of *N*-Boc-1,2,3,4-tetrahydroisoquinoline.

Results and Discussion

The tetrahydroisoquinoline **1** was prepared in high yield by simple treatment of 1,2,3,4-tetrahydroisoquinoline with Boc_2O in THF (0 °C, 2 h, 96 % yield). For the deprotonation, we opted to avoid the hazardous reagent *tert*-butyllithium and to screen other bases and conditions. The electrophile trimethylsilyl chloride (TMSCl) was used for these studies (Scheme 2).



Scheme 2. Lithiation, then TMSCl quenching of *N*-Boc-1,2,3,4-tetrahydroisoquinoline.

The bases *s*BuLi and *n*BuLi were tested by using various solvents, with or without the additive TMEDA, at −78 °C for 1 h. In all cases (Table 1), similar yields of the product **2** were obtained. The base *n*BuLi (Table 1, entries 4–10) gave similar results to reactions with *s*BuLi (Table 1, entries 1–3), demonstrating that the metallation takes place without the need for the stronger base. In addition, it appears that the use of TMEDA is unnecessary to promote this reaction (compare Table 1, entries 4 and 8) at least when using THF as the solvent. There was a noticeable reduction in the yield after the use of a short reaction time of 1 min (Table 1, entry 9), although there was no significant improvement from the use of a longer reaction time of 2 h (Table 1, entry 10).

Table 1. Initial optimisation of the lithiation followed by TMSCl quenching reaction of **1** at −78 °C.

Entry	Base[a]	Solvent	Additive[a]	Yield [%]
1	*s*BuLi	THF	TMEDA	56
2	*s*BuLi	Et_2O	TMEDA	63
3	*s*BuLi	PhMe	TMEDA	47
4	*n*BuLi	THF	TMEDA	62
5	*n*BuLi	2-methylTHF	TMEDA	55
6	*n*BuLi	PhMe	TMEDA	51
7	*n*BuLi	Et_2O	–	30
8	*n*BuLi	THF	–	52
9[b]	*n*BuLi	THF	–	35
10[c]	*n*BuLi	THF	–	54

[a] 1.2–1.3 equivalents. [b] Lithiation time: 1 min. [c] Lithiation time: 2 h.

Attempts to improve reaction yields by using this type of optimization by stepwise variation of the conditions are typical of the approach taken by synthetic chemists when developing new methodology. The use of *n*BuLi or *s*BuLi at −78 °C in THF, or in Et_2O/TMEDA, is typical of organolithium reactions, however, these conditions may not be optimal.[24] To gain a better insight into what is happening in solution, and thereby aid the identification of more suitable conditions, we used in situ monitoring of the reaction by spectroscopy. The reaction of *N*-Boc-tetrahydroisoquinoline **1** is well suited to in situ IR spectroscopy because of the ease of monitoring the carbonyl stretching frequency and the shift of this peak as a result of coordination of the carbonyl oxygen atom with the metal.

Tetrahydroisoquinoline **1** exhibited a peak for $\nu_{C=O}$ at 1696 cm^{-1} in the IR spectrum. On addition of *n*BuLi, there was rapid (< 2 min) but partial loss of this peak, followed by further slow (> 1 h) loss over time (Figure 2). At the same time, a new peak for $\nu_{C=O}$ at 1635 cm^{-1} was rapidly produced at first and then further slow formation occured over the same time frame.

The partial rapid lithiation followed by slow further lithiation can be seen clearly in the 2D plot in Figure 2 ($\nu_{C=O}$ at 1635 cm^{-1}). This result indicates that there is slow rotation of the Boc group at −78 °C and that this limits the rate of metallation at this temperature. This can be explained by the rapid lithiation of the rotamer **1a** together with slow rotation of **1b** and thus further lithiation of **1a** as it forms.

To improve the rate of metallation, the reaction was carried out at −50 °C and the IR plots are shown in Figure 3. At this temperature, the rotation of the Boc group must be rapid as the reaction is complete within a few minutes, even with *n*BuLi as the base. At the higher temperature of 0 °C, lithiation was again rapid but the organolithium was unstable and decomposed.

To gain further insight into the effect of the rotamers on the lithiation, we investigated the reaction by using ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum of **1** in [D_8]THF at −45 °C, the signals for the rotamers of the benzylic CH_2 were clearly separated, at $\delta = 4.55$ and 4.52 ppm, and were found to exist in a 51:49 ratio (Figure 4c). Addition of *n*BuLi at −45 °C resulted in the rapid loss of one of these peaks (Figure 4b) followed by the loss of the other

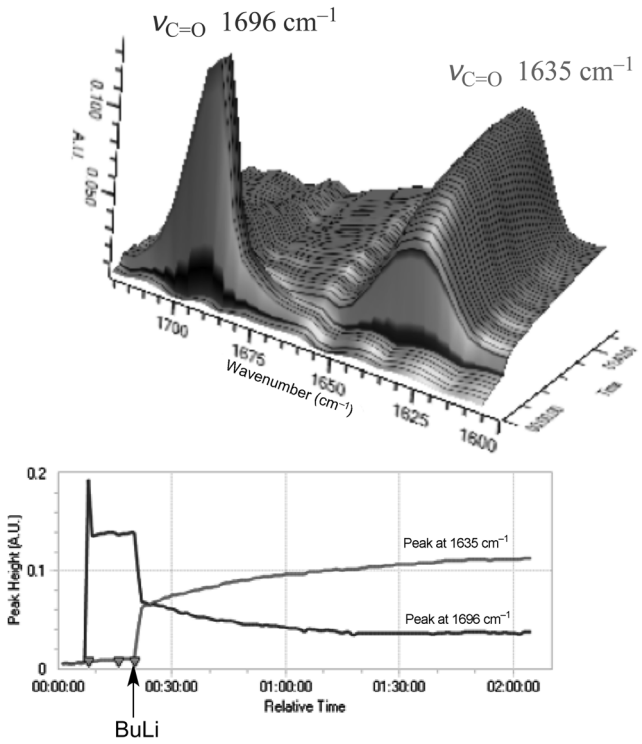


Figure 2. In situ IR 3D and 2D plots of the lithiation of **1** at −78 °C in THF/TMEDA. One line represents the intensity of the C=O stretching frequency of **1** (1696 cm^{-1}), while the other represents that of lithiated **1** (1635 cm^{-1}) over time.

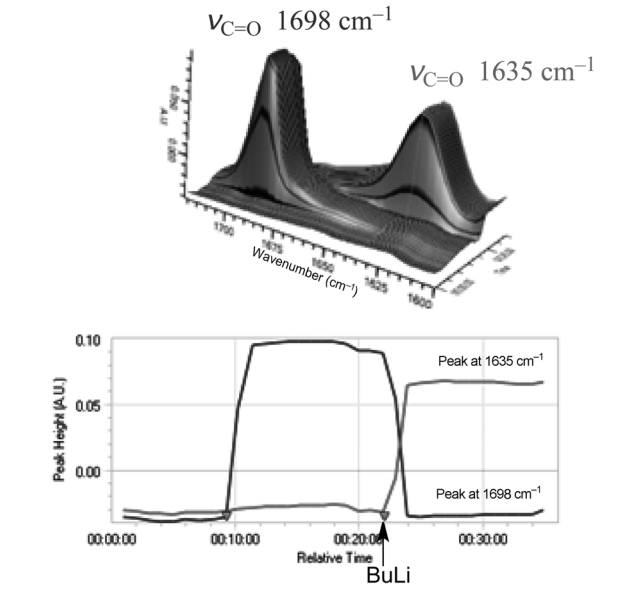


Figure 3. In situ IR 3D and 2D plots of the lithiation of **1** at −50 °C in THF. One line represents the intensity of the C=O stretching frequency of **1** (1698 cm^{-1}), while the other represents that of lithiated **1** (1635 cm^{-1}) over time.

peak (Figure 4a). This experiment fits with the in situ IR spectroscopic data, supporting the theory that only one rotamer is lithiated and there is rotation between the rotamers. In a separate experiment without BuLi, a sample of tetrahydroisoquinoline **1** in [D$_8$]THF was warmed to observe coalescence of the signals for the benzylic protons, which occurred at about 5.5 °C (see the Supporting Information). From this coalescence temperature and the difference in chemical shift between the rotamers at low temperature, it can be determined that the barrier for rotation, $\Delta G^{\neq}$, is 60.8 kJmol^{-1} at 5.5 °C. Assuming similar barriers at lower temperatures (see the Supporting Information), the half-life ($t_{1/2}$) for rotation of the Boc group in **1** was estimated to be about 30 s at −50 °C. In contrast, the half-life for rotation of the Boc group in **1** was estimated to be about 50 min at −78 °C. These results, gained by ^{1}H NMR spectroscopy, are consistent with those from the in situ IR spectroscopy and experimental data.

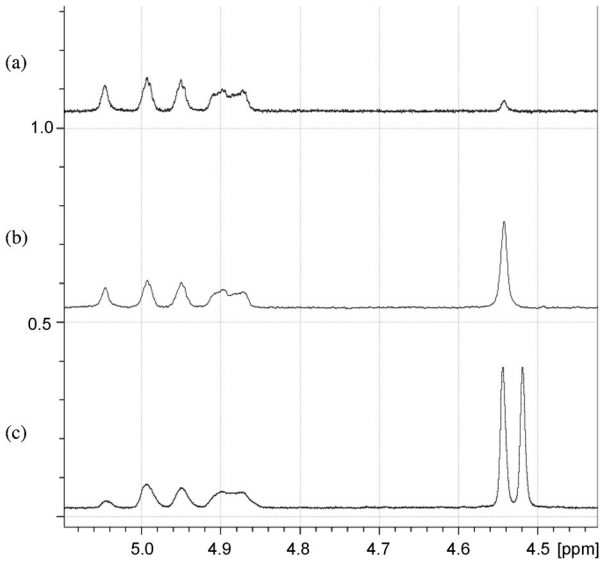
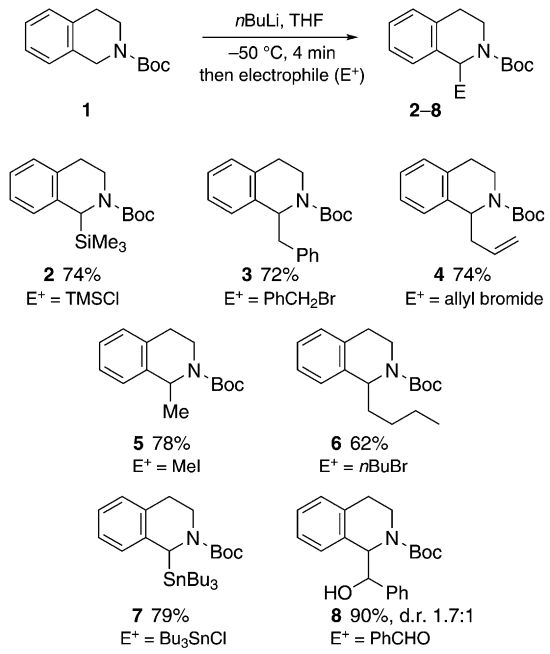


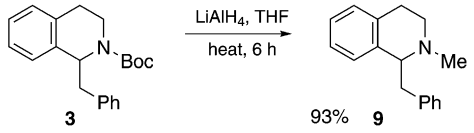
Figure 4. Partial ^{1}H NMR spectra of **1** on addition of *n*BuLi in [D$_8$]THF at −45 °C. Signals at ≈4.5 ppm for the benzylic protons of c) the two rotamers of **1**; b) compound **1** and *n*BuLi after immediate acquisition; and a) compound **1** and *n*BuLi, after about 1 min.

On the basis of the aforementioned spectroscopic data, we opted to conduct the lithiation of tetrahydroisoquinoline **1** by using *n*BuLi in THF without TMEDA at −50 °C for 4 min. Addition of the electrophile TMSCl then gave tetrahydroisoquinoline **2** in an improved yield (74% yield after purification by column chromatography) in comparison with the conditions described in Table 1. Other electrophiles were used under the same conditions and the results are given in Scheme 3.

The electrophilic quenching of lithiated compound **1** was successful with a variety of electrophiles, including benzyl bromide, allyl bromide, iodomethane and 1-bromobutane, giving the racemic products **3**–**6** (Scheme 3). The electrophile tributyltin chloride provided stannane product **7**, and the use of benzaldehyde gave a separable mixture of the diastereomeric alcohols **8** in high yield. Reduction of the Boc group of tetrahydroisoquinoline **3** with LiAlH$_4$ gave product **9** with the secoaporphine alkaloid structure (Scheme 4).



Scheme 3. Lithiation, then quenching of *N*-Boc-1,2,3,4-tetrahydroisoquinoline **1**.

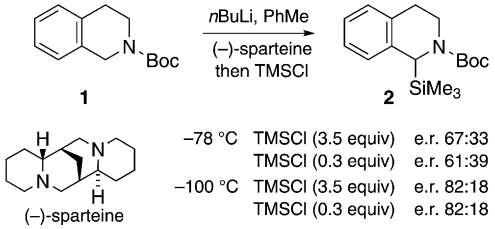


Scheme 4. Reduction of tetrahydroisoquinoline **3**.

There are currently no reports on the configurational stability of *N*-Boc-1-lithiotetrahydroisoquinoline and we were interested in whether the chiral organolithium could be generated in enantiomerically enriched form and whether it could maintain its configuration. An alternative approach to enantiomerically enriched products would be to promote a dynamic resolution,[25] should the organolithium be configurationally unstable, which is the finding for related compounds.[26]

To probe the configurational stability of the organolithium formed by deprotonation of tetrahydroisoquinoline **1**, we used Beak's version of the Hoffmann test, sometimes referred to as the "poor man's Hoffmann test" due to the lack of requirement for a chiral electrophile.[27] In this test, the organolithium is complexed with a chiral ligand and then reacted with an excess of the electrophile. The enantiomeric ratio (e.r.) of the product is then compared with the same product formed by using the same chiral ligand and a substoichiometric amount of the electrophile. If the enantiomeric ratios are different then this indicates that the organolithium has configurational stability on the timescale of the reaction with the electrophile.

Tetrahydroisoquinoline **1** was treated with *n*BuLi and the chiral ligand (−)-sparteine in toluene (to avoid any competing solvation with ethereal solvents). Addition of the electrophile TMSCl gave the product **2** with similar or the same e.r. by using stoichiometric (3.5 equiv) or substoichiometric (0.3 equiv) amounts of the electrophile, even at very low temperature (Scheme 5; enantiomeric ratio determined by



Scheme 5. Probing the configurational stability of the organolithium.

CSP HPLC). The moderate enantioselectivity in the formation of **2** therefore likely arises from rapidly interconverting organolithium•(−)-sparteine complexes and a slightly faster reaction of one of these diastereomeric complexes with TMSCl (dynamic kinetic resolution). Unfortunately, attempts to obtain enantioenriched products such as **5** or **7** by using the electrophiles MeI or Bu_3SnCl resulted in only poor enantiomeric ratios (e.r. $\leq$ 60:40).

The similar enantiomeric ratios with stoichiometric or substoichiometric amounts of the electrophiles indicate that *N*-Boc-1-lithiotetrahydroisoquinoline is configurationally labile in toluene and that even at −100 °C the enantioselectivity arises from the faster reaction of one diastereomeric complex. As the activation barriers for the reaction should be different for different complexes, it may be possible to find a chiral ligand that would promote good enantioselectivity through dynamic resolution. We screened the ligands shown in Figure 5 for the resolution of *N*-Boc-1-lithiotetrahydroisoquinoline, although all reactions resulted in essentially racemic products by using TMSCl as the electrophile.

Many tetrahydroisoquinoline alkaloids contain hydroxy or alkoxy substituents on the aromatic ring and these could influence the reactivity and/or configurational stability of the organolithium intermediate in this chemistry. We therefore prepared the 6,7-dimethoxytetrahydroisoquinoline derivative **10** for comparison with compound **1**.

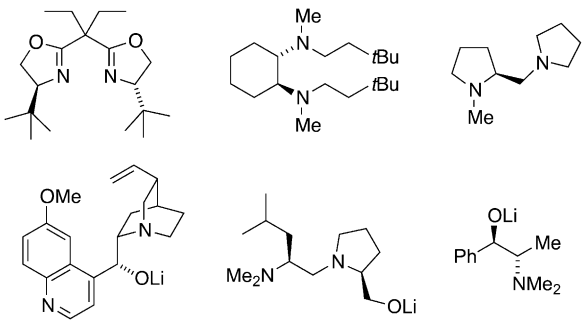
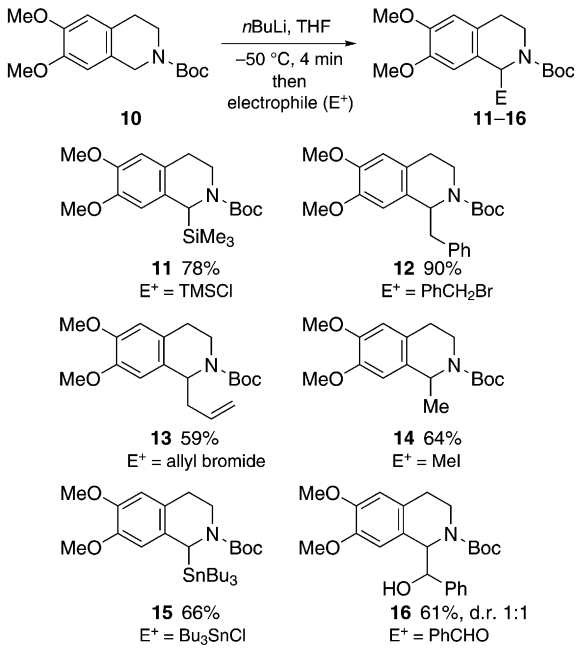


Figure 5. Chiral ligands screened for the dynamic resolution. Ligand and lithiated **1** at −78 °C in PhMe or Et_2O, followed by addition of TMSCl gave product **2** with e.r. values of 50:50–57:43.

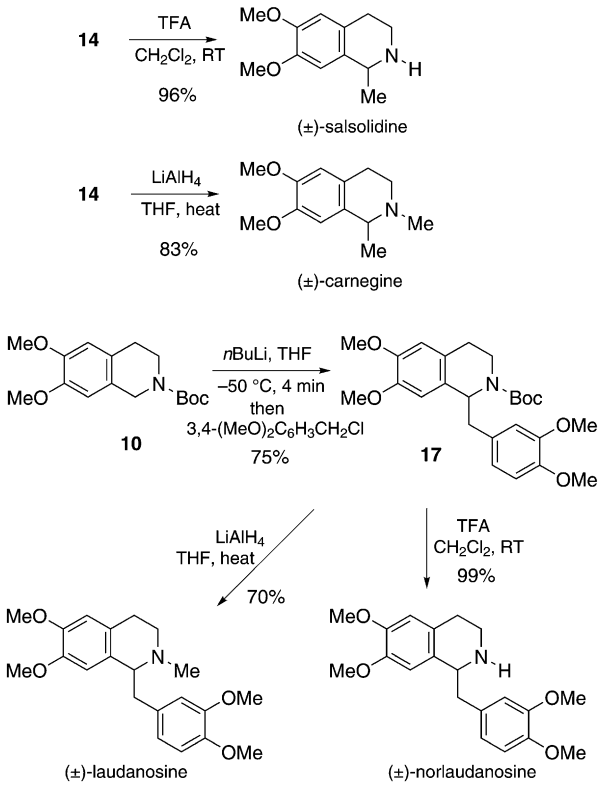
The organolithium derived from deprotonation of **10** was found to be configurationally unstable, in the same way as the deprotonated tetrahydroisoquinoline **1**. Hence, similar enantiomeric ratios of the product **11** were obtained on lithiation of **10** with *n*BuLi in PhMe and (−)-sparteine with addition of stoichiometric (3.5 equiv) or substoichiometric (0.3 equiv) amounts of the electrophile TMSCl. In this case, the selectivities were poorer (e.r. ≈70:30 at −100 °C and e.r. ≈55:45 at −78 °C) than those with tetrahydroisoquinoline **1**. Obtaining similar enantiomeric ratios under stoichiometric and substoichiometric conditions indicates that the organolithium is not configurationally stable even at −100 °C.

The racemic lithiation of tetrahydroisoquinoline **10** appeared to follow similar kinetics to that of the unsubstituted tetrahydroisoquinoline **1**, so we conducted the reaction at −50 °C for 4 min and screened a range of electrophiles (Scheme 6). Good yields of 1-substituted products **11**–**16** were obtained by using the electrophiles TMSCl, Bu_3SnCl, alkyl halides or benzaldehyde. The diastereoisomers of product **16** were separable by column chromatography.



Scheme 6. Lithiation, then quenching of *N*-Boc-tetrahydroisoquinoline **10**.

Finally, we applied this chemistry to the synthesis of some tetrahydroisoquinoline alkaloids (Scheme 7). Product **14** was deprotected with trifluoroacetic acid (TFA) to give (±)-salsolidine in excellent yield. Alternatively, reduction by heating with $LiAlH_4$ gave (±)-carnegine. Treatment of tetrahydroisoquinoline **10** with *n*BuLi in THF at −50 °C for 4 min, followed by addition of 3,4-dimethoxybenzyl chloride gave product **17**, which was deprotected with TFA to give (±)-norlaudanosine or reduced with $LiAlH_4$ to give (±)-laudanosine. The spectroscopic data for these products matched those in the literature.[28]



Scheme 7. Synthesis of tetrahydroisoquinoline alkaloids.

Conclusion

We have found that the simple base *n*BuLi is capable of deprotonating *N*-Boc-tetrahydroisoquinoline and *N*-Boc-6,7-dimethoxytetrahydroisoquinoline in THF at −50 °C in less than 5 min. The resulting organolithium compounds react with a variety of electrophiles to give 1-substituted tetrahydroisoquinoline products. The kinetics for rotation of the carbamate group were determined by NMR spectroscopy and the use of in situ IR spectroscopy allowed the optimisation of the lithiation reaction. The organolithium compounds are configurationally labile, even at −100 °C in toluene, and only low levels of asymmetric induction were obtained by using a chiral ligand, presumably through a dynamic kinetic resolution pathway. The chemistry was applied successfully to the total synthesis of several tetrahydroisoquinoline alkaloids.

Acknowledgements

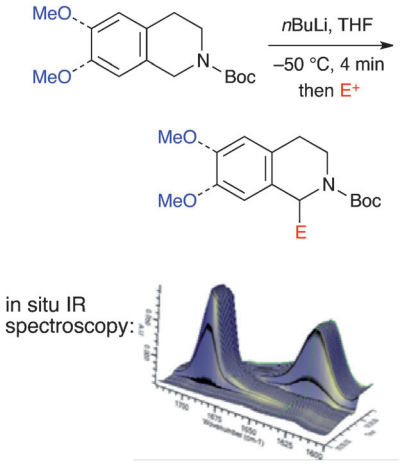
We thank the China Scholarship Council and the Department for Business Innovation & Skills (UK–China Scholarships for Excellence Programme), the EPSRC (EP/E012272/1 and EP/F000340/1) and the University of Sheffield for support of this work. Simon Sedehizadeh is thanked for preliminary studies and we are grateful to Brian Taylor for help with the NMR spectroscopic studies.

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

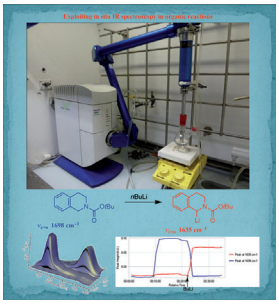
[2] T. Yamakawa, S. Ohta, *Biochem. Biophys. Res. Commun.* **1997**, *236*, 676–681.
[3] a) P. S. Charifson, S. D. Wyrick, A. J. Hoffman, R. M. A Simmons, J. P. Bowen, D. L. McDouglad, R. B. Mailman, *J. Med. Chem.* **1988**, *31*, 1941–1946; b) N. Cabedo, I. Berenguer, B. Figadere, D. Cortes, *Curr. Med. Chem.* **2009**, *16*, 2441–2467.
[4] For a review on salsolidine, see: T. S. Kaufman, *Tetrahedron: Asymmetry* **2004**, *15*, 1203–1237.
[5] S. Chuliá, M. D. Ivorra, C. Lugnier, E. Vila, M. A. Noguera, P. D'Ocon, *Br. J. Pharmacol.* **1994**, *113*, 1377–1385.
[6] P. Abrams, K.-E. Andersson, *BJU Int.* **2007**, *100*, 987–1006.
[7] J. Kamei, *Curr. Pulmonol. Pulmonary Pharmacol.* **1996**, *9*, 349–356.
[8] M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370.
[9] For reduction, see, for example: a) M. Chang, W. Li, X. Zhang, *Angew. Chem.* **2011**, *123*, 10867–10869; *Angew. Chem. Int. Ed.* **2011**, *50*, 10679–10681; b) M. Ruzic, A. Pecavar, D. Prudic, D. Kralj, C. Scriban, A. Zanotti-Gerosa, *Org. Process Res. Dev.* **2012**, *16*, 1293–1300; c) F. Berhal, Z. Wu, Z. Zhang, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett.* **2012**, *14*, 3308–3311, and references therein.
[10] a) J.-J. Lohmann, D. Seebach, M. A. Syfrig, M. Yoshifuji, *Angew. Chem.* **1981**, *93*, 125–126; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 128–129; b) D. Seebach, J.-J. Lohmann, M. A. Syfrig, M. Yoshifuji, *Tetrahedron* **1983**, *39*, 1963–1974; c) D. Seebach, M. A. Syfrig, *Angew. Chem.* **1984**, *96*, 235–236; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 248–249; d) D. Seebach, I. M. P. Huber, M. A. Syfrig, *Helv. Chim. Acta* **1987**, *70*, 1357–1379. See also, e) A. J. Burton, J. P. Graham, N. S. Simpkins, *Synlett* **2000**, 1640–1642.
[11] A. I. Meyers, S. Hellring, W. T. Hoeve, *Tetrahedron Lett.* **1981**, *22*, 5115–5118.
[12] A. R. Katritzky, K. Akutagawa, *Tetrahedron* **1986**, *42*, 2571–2574.
[13] a) A. I. Meyers, L. M. Fuentes, Y. Kubota, *Tetrahedron* **1984**, *40*, 1361–1370; b) A. I. Meyers, D. A. Dickman, M. Boes, *Tetrahedron* **1987**, *43*, 5095–5108; c) A. I. Meyers, J. S. Warmus, M. A. Gonzalez, J. Guiles, A. Akahane, *Tetrahedron Lett.* **1991**, *32*, 5509–5512.
[14] a) R. E. Gawley, G. Hart, M. Goicoechea-Pappas, A. L. Smith, *J. Org. Chem.* **1986**, *51*, 3076–3078; b) 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; c) K. S. Rein, R. E. Gawley, *J. Org. Chem.* **1991**, *56*, 1564–1569; d) R. E. Gawley, P. S. Zhang, *J. Org. Chem.* **1996**, *61*, 8103–8112; e) R. E. Gawley, G. A. Smith, *Arkivoc* **2011**, *v*, 167–179; f) for a dihydrothiazoline, see K. Nain Singh, P. Singh, A. Kaur, *Synth. Commun.* **2006**, *36*, 3339–3343.
[15] S. Adam, X. Pannecoucke, J. C. Combret, J. C. Quirion, *J. Org. Chem.* **2001**, *66*, 8744–8750.
[16] a) S. V. Kessar, R. Vohra, N. P. Kaur, *Tetrahedron Lett.* **1991**, *32*, 3221–3224; b) S. V. Kessar, P. Singh, R. Vohra, N. P. Kaur, K. N. Singh, *J. Chem. Soc. Chem. Commun.* **1991**, 568–570; c) M. R. Ebden, N. S. Simpkins, D. N. A. Fox, *Tetrahedron* **1998**, *54*, 12923–12952.
[17] P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560.
[18] a) G. M. Coppola, *J. Heterocycl. Chem.* **1991**, *28*, 1769–1772; see also: b) J. Jiang, R. J. DeVita, M. T. Goulet, M. J. Wyvratt, J.-L. Lo, N. Ren, J. B. Yudkovitz, J. Cui, Y. T. Yang, K. Cheng, S. P. Rohrer, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1795–1798.
[19] a) N. J. Ashweek, P. Brandt, I. Coldham, S. Dufour, R. E. Gawley, F. Haeffner, R. Klein, G. Sanchez-Jimenez, *J. Am. Chem. Soc.* **2005**, *127*, 449–457; b) I. Coldham, J. J. Patel, G. Sanchez-Jimenez, *Chem. Commun.* **2005**, 3083–3085; c) I. Coldham, S. Dufour, T. F. N. Haxell, J. J. Patel, G. Sanchez-Jimenez, *J. Am. Chem. Soc.* **2006**, *128*, 10943–10951; d) T. I. Yousaf, R. L. Williams, I. Coldham, R. E. Gawley, *Chem. Commun.* **2008**, 97–98; e) I. Coldham, J. J. Patel, S. Raimbault, D. T. E. Whittaker, H. Adams, G. Y. Fang, V. K. Aggarwal, *Org. Lett.* **2008**, *10*, 141–143; f) I. Coldham, D. Leonori, *J. Org. Chem.* **2010**, *75*, 4069–4077.
[20] a) I. Coldham, P. O'Brien, J. J. Patel, S. Raimbault, A. J. Sanderson, D. Stead, D. T. E. Whittaker, *Tetrahedron: Asymmetry* **2007**, *18*, 2113–2119; b) I. Coldham, J. J. Patel, S. Raimbault, D. T. E. Whittaker, *Chem. Commun.* **2007**, 4534–4536; c) I. Coldham, S. Raimbault, P. T. Chovatia, J. J. Patel, D. Leonori, N. S. Sheikh, D. T. E. Whittaker, *Chem. Commun.* **2008**, 4174–4176; d) I. Coldham, D. Leonori, *Org. Lett.* **2008**, *10*, 3923–3925; e) I. Coldham, D. Leonori, T. K. Beng, R. E. Gawley, *Chem. Commun.* **2009**, 5239–5241; f) I. Coldham, S. Raimbault, D. T. E. Whittaker, P. T. Chovatia, D. Leonori, J. J. Patel, N. S. Sheikh, *Chem. Eur. J.* **2010**, *16*, 4082–4090; g) H. H. Ince, B. Dedeoglu, S. Gul, V. Aviyente, I. Coldham, *Mol. Phys.* **2012**, *110*, 353–359.
[21] For reports of the use of in situ IR spectroscopy to monitor reactions of organolithium compounds, see ref. [22] and: a) D. J. Pippel, G. A. Weisenburger, N. C. Faibish, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 4919–4927; b) J. L. Rutherford, D. Hoffmann, D. B. Collum, *J. Am. Chem. Soc.* **2002**, *124*, 264–271; c) L. Gupta, A. C. Hoepker, K. J. Singh, D. B. Collum, *J. Org. Chem.* **2009**, *74*, 2231–2233; d) D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260–7261; e) G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos, P. O'Brien, *J. Org. Chem.* **2011**, *76*, 5936–5953; f) D. Lumpi, C. Wagner, M. Schöpf, E. Horkel, G. Ramer, B. Lendl, J. Fröhlich, *Chem. Commun.* **2012**, *48*, 2451–2453; g) J. Lefranc, A. M. Fournier, G. Mingat, S. Herbert, T. Marcelli, J. Clayden, *J. Am. Chem. Soc.* **2012**, *134*, 7286–7289; h) A. M. Fournier, C. J. Nichols, M. A. Vincent, I. H. Hillier, J. Clayden, *Chem. Eur. J.* **2012**, *18*, 16478–16490.
[22] 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.
[23] a) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356–363; b) C. M. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256–2276; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225; c) V. H. Gessner, C. Daschlein, C. Strohmann, *Chem. Eur. J.* **2009**, *15*, 3320–3334.
[24] G. Barker, P. O'Brien, K. R. Campos, *Org. Lett.* **2010**, *12*, 4176–4179.
[25] I. Coldham, N. S. Sheikh in *Topics in Stereochemistry, Vol. 26, Stereochemical Aspects of Organolithium Compounds* (Eds.: R. E. Gawley, J. S. Siegel), Verlag Helvetica Chimica Acta, Zürich, **2010**, pp. 253–293.
[26] a) A. I. Meyers, J. Guiles, J. S. Warmus, M. A. Gonzalez, *Tetrahedron Lett.* **1991**, *32*, 5505–5508; b) K. S. Rein, Z.-H. Chen, P. T. Perumal, L. Echegoyen, R. E. Gawley, *Tetrahedron Lett.* **1991**, *32*, 1941–1944; c) see also ref. [14b].
[27] S. Thayumanavan, A. Basu, P. Beak, *J. Am. Chem. Soc.* **1997**, *119*, 8209–8216.
[28] a) F. Werner, N. Blank, T. Opatz, *Eur. J. Org. Chem.* **2007**, 3911–3915; b) A. B. J. Bracca, T. S. Kaufman, *Tetrahedron* **2004**, *60*, 10575–10610; c) F. Louafi, J.-P. Hurvois, A. Chibani, T. Roisnel, *J. Org. Chem.* **2010**, *75*, 5721–5724; d) D. Mujahidin, S. Doye, *Eur. J. Org. Chem.* **2005**, 2689–2693.

Received: March 21, 2013
Published online: ■■ ■■, 0000

Carbanions



Spectroscopic optimization: Optimum conditions for the lithiation of tetrahydroisoquinolines were established by in situ IR and NMR spectroscopy. The use of *n*-butyllithium in THF at −50 °C for less than 5 min is preferable to the reaction at −78 °C. The organolithium was quenched with electrophiles to give 1-substituted tetrahydroisoquinoline products (see scheme).



Tetrahydroisoquinolines
Monitoring progress in organic reactions is possible by in situ IR spectroscopy. This is particularly suited to organometallic chemistry in which the metal coordinates to a carbonyl group, changing the carbonyl stretching frequency on reaction. This technique was used to optimize the lithiation of *N*-Boc-tetrahydroisoquinolines.