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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Synthesis of 1,1-Disubstituted Tetrahydroisoquinolines by Lithiation and Substitution, with in Situ IR Spectroscopy and Configurational Stability Studies

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Supporting Information

ABSTRACT: Lithiation of *N*-Boc-1-phenyltetrahydroisoquinolines was optimized by in situ IR spectroscopy. The kinetics for rotation of the carbamate group and for the enantiomerization of the organolithium were determined. The organolithium is configurationally stable at low temperature, and the asymmetric synthesis of 1,1-disubstituted tetrahydroisoquinolines can be achieved with high yields and high enantiomer ratios. The chemistry was applied to the preparation of FR115427 and provides a way to recycle the undesired enantiomer in the synthesis of solifenacin.

1-Substituted 1,2,3,4-tetrahydroisoquinolines are found in many important biologically active natural products and pharmaceutical compounds.[1] For example, solifenacin **1** (Figure 1) is a potent selective muscarinic M_3 receptor antagonist with

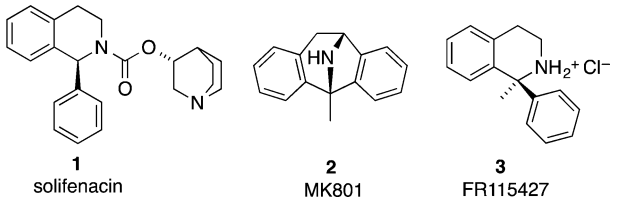


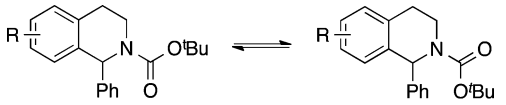
Figure 1. Some hydrogenated isoquinoline drugs.

urinary antispasmodic properties.[2] 1,1-Disubstituted tetrahydroisoquinolines have received much less attention, but this arrangement is present in drug compounds such as MK801 (dizocilpine) **2** and (+)-FR115427 **3**, which are noncompetitive antagonists of the *N*-methyl-D-aspartate (NMDA) subclass of receptors for the excitatory amino acid L-glutamate in brain tissue.[3]

One approach to 1,1-disubstituted tetrahydroisoquinolines uses the Pictet–Spengler reaction involving a 3-hydroxyphenethylamine and a ketone.[4] There are only a few asymmetric approaches, such as the alkylation of 1-cyanotetrahydroisoquinolines using a chiral phase-transfer catalyst,[5] or the lithiation–alkylation of a 1-alkyl-tetrahydroisoquinoline bearing a chiral formamidine auxiliary.[6] Meyers and co-workers found that 1-lithio-1-methyltetrahydroisoquinolines bearing an *N*-formamidine group racemize rapidly.[7] Likewise, we have found that *N*-Boc-1-lithiotetrahydroisoquinoline is configurationally labile even at −100 °C.[8] In contrast, lithiation of *N*-Boc-2-phenylpiperidine (or pyrrolidine) gives an organolithium that is configurationally stable at −50 °C for a few minutes.[9] With only a few methods known for the synthesis of 1,1-disubstituted tetrahydroisoquinolines, we were interested in studying the lithiation and electrophilic quench of *N*-Boc-1-phenyltetrahydroisoquinolines and the configurational stability of the intermediate organolithium species.

This paper describes the successful optimization of the lithiation of two *N*-Boc-1-phenyltetrahydroisoquinolines by in situ IR spectroscopy.[10] This method provides information on the extent of lithiation over time due to the directing effect of the carbonyl group (only rotamer **4a** can be lithiated at the 1-position by BuLi, Scheme 1). The rates of Boc rotation of **4** and

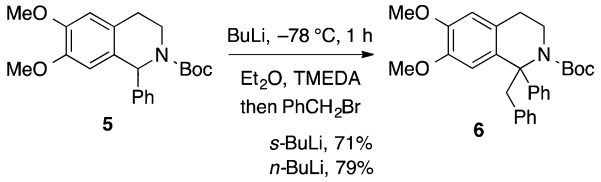
Scheme 1. Rotamers of *N*-Boc-1-phenyltetrahydroisoquinoline



of enantiomerization of the lithiated intermediate have been determined. High enantiomer ratios of 1,1-disubstituted products can be obtained, indicating substantial configurational stability of the organolithium intermediate.

Treatment of racemic 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline, which was synthesized according to a literature procedure,[11] with Boc_2O in THF gave *N*-Boc-6,7-dimethoxy-1-phenyltetrahydroisoquinoline **5** (89% yield). Initially, lithiation of **5** was carried out using *sec*-BuLi, Et_2O, TMEDA at −78 °C (Scheme 2). After 1 h, addition of benzyl bromide gave a good yield of the 1,1-disubstituted tetrahy-

Scheme 2. Initial Studies of the Lithiation–Substitution of *rac*-5



Received: January 24, 2014
Published: April 2, 2014

   dx.doi.org/10.1021/ja500485f | *J. Am. Chem. Soc.* 2014, 136, 5551–5554

droisoquinoline **6**. However, the strong base *sec*-BuLi was not a requirement, as *n*-BuLi was found to result in a similar yield (79% of **6**).

The good yields obtained in this chemistry indicate that the Boc group is able to rotate sufficiently rapidly at −78 °C to allow lithiation at the benzylic position. Despite this, we carried out optimization of the lithiation using in situ IR spectroscopy. A solution of *rac*-**5** in Et_2O/TMEDA or THF/TMEDA at −78 °C exhibited a peak at $\nu_{C=O}$ 1695 cm^{-1} (see Supporting Information). Upon addition of *n*-BuLi, a new peak formed at 1645 cm^{-1}, which was assigned to $\nu_{C=O}$ in the lithiated intermediate. The IR spectra showed that there was rapid (less than 4 min) but partial lithiation at −78 °C, and this required about 1 h to progress to completion (see Supporting Information). The solvent THF alone can be suitable for lithiation,[8,12] and we were pleased to find that TMEDA could be avoided by simply using THF at −50 °C. At this temperature, the rotation of the Boc group is fast and lithiation was complete within a few minutes (Figure 2 and Supporting Information).

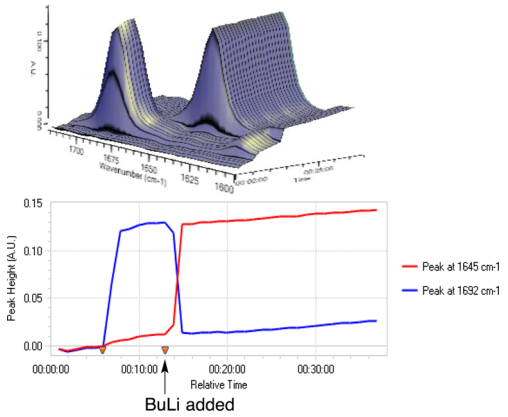


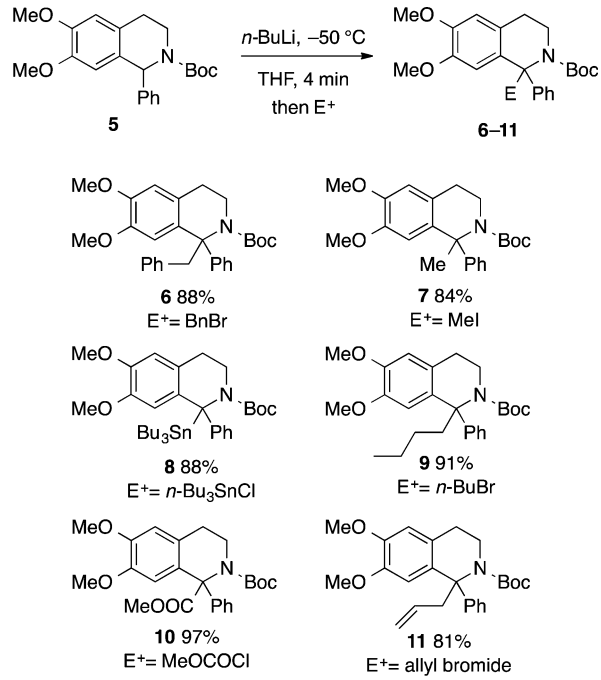
Figure 2. In situ IR 3-D and 2-D plots of the lithiation of **5** with *n*-BuLi at −50 °C in THF. Blue line represents intensity of C=O stretching frequency of **5** (1692 cm^{-1}) and red line of lithiated **5** (1645 cm^{-1}) over time (in min).

Based on the results from the in situ IR spectroscopic studies, we conducted the lithiation of *rac*-**5** using *n*-BuLi in THF at −50 °C for 4 min. A range of electrophiles was explored, and 1,1-disubstituted tetrahydroisoquinolines *rac*-**6**−**11** were obtained in 81−97% yield (Scheme 3). These conditions represent an improvement over those given in Scheme 2.

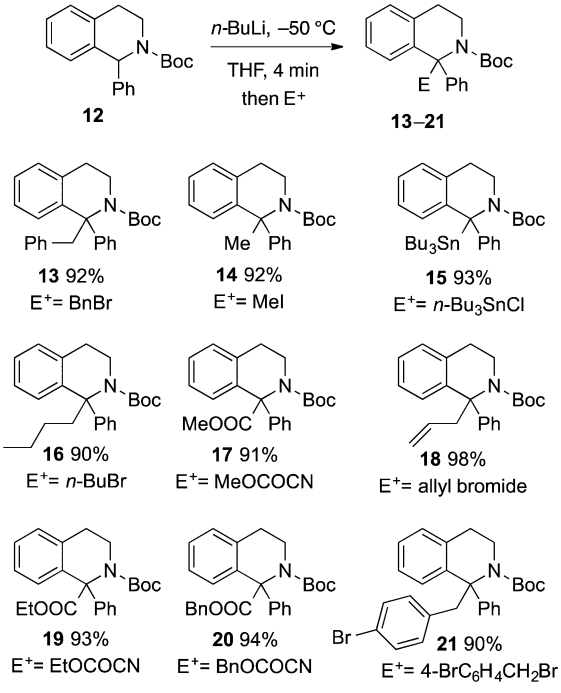
Our attention then switched to *N*-Boc-1-phenyltetrahydroisoquinoline **12**. The lithiation of racemic **12** was conducted under the same conditions as for **5** (THF, −50 °C, 4 min). A range of electrophiles was screened, and excellent yields (90−98%) of *rac*-**13**−**21** were obtained (Scheme 4).

To obtain the kinetics for rotation of the Boc group, variable temperature ^1H NMR spectroscopy studies were conducted (see Supporting Information). Coalescence of the signals (ratio 1.3:1) for the proton at the 1-position of racemic *N*-Boc-1-phenyltetrahydroisoquinoline **12** in D_8-THF occurred at about 25 °C. Using line shape analysis (see Supporting Information) gave approximate activation parameters $\Delta H^{\ddagger}$ 56.7 kJ/mol and $\Delta S^{\ddagger}$ −9.2 J/K·mol. The half-life for rotation of the Boc group in **12** can therefore be determined to be $t_{1/2}$ ~9 s at −50 °C, and ~14 min at −78 °C. The barrier to rotation of the Boc

Scheme 3. Lithiation−Substitution of (±)-5



Scheme 4. Lithiation−Substitution of (±)-12

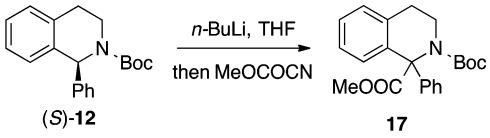


group in **12** is slightly lower than that for *N*-Boc-tetrahydroisoquinoline.[8]

The configurational stability of the organolithium formed by deprotonation of enantioenriched tetrahydroisoquinoline **12**[enantiomer ratio (er) ≥99:1 by CSP HPLC] was investigated. Table 1 shows the results of the lithiation of (*S*)-**12**[13] with *n*-BuLi in THF at different temperatures followed by addition of MeOCOCN. Based on the literature,[7,8] we anticipated that the intermediate organolithium would be configurationally unstable, so we were surprised that enantiomerically enriched product **17** was obtained even at

dx.doi.org/10.1021/ja500485f | J. Am. Chem. Soc. 2014, 136, 5551−5554

Table 1. Lithiation−MeOCOCN Quench of (*S*)-12 (Er 99:1) at Different Temperatures



entry	temp (°C)	time (min)	yield (%)[a]	er[b]
1	−78	30	94	96:4
2	−50	4	95	91:9
3	−20	30	91	84:16
4	0	30	89	52:48

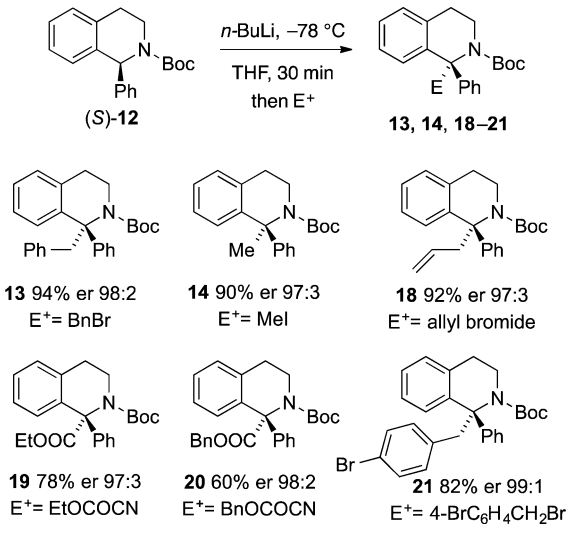
[a]Yields after chromatography. [b]Er by CSP-HPLC.

−20 °C (Table 1, entries 1−3). A temperature of 0 °C for approximately 30 min is required for racemization (Table 1, entry 4). High er was obtained at −78 °C (Table 1, entry 1). The yield of this reaction was high, indicating sufficiently fast rotation of the Boc group. The high configurational stability presumably arises from the slow movement of the lithium cation (which is likely coordinated to the carbonyl oxygen atom) across the space occupied by the phenyl group.

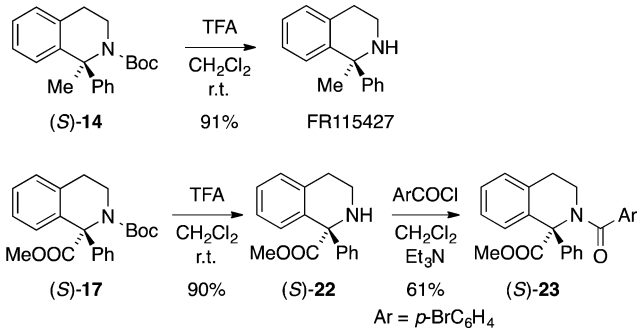
Experiments were conducted to determine the rate of inversion of the organolithium. By measuring the er of product **17** over time, first order plots and an Eyring plot at three temperatures (see Supporting Information) gave approximate activation parameters $\Delta H^{\ddagger}$ 118 kJ/mol and $\Delta S^{\ddagger}$ 132 J/K·mol. These equate to a half-life for inversion of the organolithium $t_{1/2}$ ~73 min at −10 °C. The large positive entropy of activation for inversion implies desolvation or solvent reorganization perhaps due to movement of the large Boc group during conducted tour of the lithium to the opposite face.[14]

In addition to product **17** (94%, er 96:4), 1,1-disubstituted products **13**, **14**, and **18**−**21** were obtained in high yield and high er at −78 °C (Scheme 5). By using MeOH as the electrophile, the starting material (*S*)-**12** was recovered (83% yield) with er 98:2, demonstrating that protonation occurs with retention of configuration. The absolute configuration of the product **14** was determined by removal of the Boc group with trifluoroacetic acid (TFA), which gave the NMDA antagonist FR115427, er 91:9 (Scheme 6). Removal of the Boc group

Scheme 5. Lithiation−Substitution of (*S*)-12



Scheme 6. Synthesis of FR115427 and Ester 23

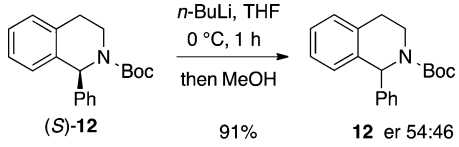


from the product **17** using TFA gave the amine **22**, and subsequent amide formation with 4-bromobenzoyl chloride gave compound **23** (Scheme 6). Single crystal X-ray analysis of compound **23** revealed that lithiation−trapping with MeOCOCN had occurred with retention of configuration (see Supporting Information). The absolute configuration of the other compounds in Scheme 5 is based on assumed retention at the organolithium center.

Trapping the enantioenriched organolithium with the electrophile *n*-BuBr under the same conditions gave the product **16** as a racemate (82% yield). Reaction of the organolithium with BuBr was found to be slow and occurs only on warming, such that racemization competes with electrophilic quench.

(*S*)-(+)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline is a key intermediate in the preparation of the urinary antispasmodic drug solifenacin **1**.[2] Industrially, classical resolution is used to obtain the (*S*) enantiomer from the racemic secondary amine. Asymmetric reduction, kinetic resolution, and deracemization have been used as methods to prepare enantioenriched (*S*)-1-phenyltetrahydroisoquinoline.[15] A method to recycle one enantiomer using oxidation and then reduction has been reported.[16] Our chemistry provides a method to recycle either enantiomer through racemization of the *N*-Boc-1-lithio derivative which is configurationally unstable at high temperature, as shown for the enantiomer (*S*)-**12** (Scheme 7). Lithiation at 0 °C followed by addition of MeOH after 1 h gave the (mostly) racemized compound **12** (91% yield, er 54:46).

Scheme 7. Racemization of (*S*)-12 (Er 99:1)



In conclusion, the lithiation of 1-phenyltetrahydroisoquinoline has been optimized by in situ IR spectroscopy. 1,1-Disubstituted tetrahydroisoquinolines can be prepared with high yields at −50 °C in THF in less than 5 min. The kinetics for rotation of the carbamate group and for the enantiomerization of the organolithium were determined. Lithiated (*S*)-*N*-Boc-1-phenyltetrahydroisoquinoline is configurationally stable at low temperature, and electrophilic quench provides high yields of highly enantioenriched 1,1-disubstituted tetrahydroisoquinolines. The chemistry was applied successfully to a synthesis of FR115427 and to racemization of *N*-Boc-1-phenyltetrahydroisoquinoline, which could have application to

dx.doi.org/10.1021/ja500485f | J. Am. Chem. Soc. 2014, 136, 5551−5554

recycle the undesired (*R*) enantiomer in the industrial synthesis of the drug solifenacin.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and compound characterization data, plus copies of NMR spectra and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Sheffield and the China Scholarship Council/Department for Business Innovation & Skills (UK-China Scholarships for Excellence). We are grateful to Susan Bradshaw for help with the NMR spectroscopic studies, Harry Adams for the single crystal X-ray analysis, and Miloš Ružič at Krka Group for a sample of (*S*)-1-phenyltetrahydroisoquinoline.

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