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The synthesis of 3-methyl- and 3,4-dimethyltetrahydroisoquinolines by intramolecular hydroamination with *n*-butyllithium

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Abstract—The synthesis of 3-methyltetrahydroisoquinolines and 3,4-dimethyltetrahydroisoquinolines from aromatic aminoalkenes using intramolecular hydroamination reactions, mediated by sub-stoichiometric amounts of *n*-butyllithium, is described.

The tetrahydroisoquinoline (THIQ) skeleton is one of Nature's most popular motifs as evinced by the large number of natural products that have this organic component in their structure.[1–4] Some representative examples of these include the naphthylisoquinoline alkaloids, for example korupensamine B **1** and michellamine B **2**,[5] and saframycin A **3**[2] (Fig. 1). As a result, numerous THIQ alkaloids and their synthetic analogues possessing useful pharmacological properties have been studied. A topical example of this is 1-MeTHIQ **4**, a simple compound with activity against endogenous Parkinson's disease.[6]

We have been interested in the synthesis of analogues of alkaloids **1** and **2**,[7,8] and recently disclosed a novel mercury-mediated method for the synthesis of the *N*-acetyl-1,3-dimethyltetrahydroisoquinoline portion of these molecules.[9–11] This novel approach utilized an intramolecular amidomercuration-reduction to form the tetrahydroisoquinoline ring system. Examples of hydroamination[12–16] reactions are becoming increasingly more important in academic and industrial applications and include a recent paper describing the use of organolanthanides as catalysts to synthesize 1-substituted THIQs.[17] This letter has prompted us to disclose our work towards 3-methyl- and 3,4-dimethyl-THIQs utilizing an intramolecular hydroamination reaction mediated by sub-stoichiometric amounts of *n*-butyllithium.[18]

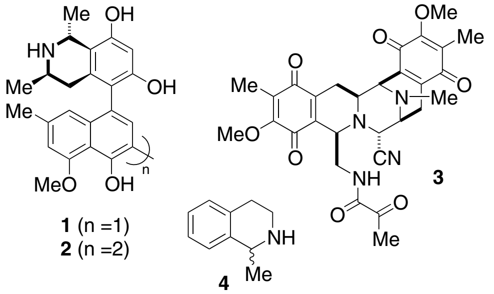

Figure 1. Topical examples of THIQs.

The initial experimental work involved in this project entailed the synthesis of the *ortho*-allylbenzylamines **6a–d** (Scheme 1). This was accomplished by performing a standard two-step reductive amination procedure on precursor **5**.[19] The amines **6a–d** were thus obtained in excellent yields and high purity without chromatography.

We next considered the use of hydroamination methodology, of which there are a plethora of recent literature examples,[20] to form the THIQ nucleus. In our hands, work based on that accomplished by Seijas et al.[21] and Beller and co-workers[22] on the intermolecular transamination of styrenes with amines utilizing *n*-butyllithium as catalyst gave interesting results.[23] The *ortho*-allylated benzylamines **6a–d** were thus treated with sub-stoichiometric quantities of *n*-butyllithium at 60 °C (Scheme 2). To our satisfaction, the THIQs **7a–d** were obtained in reasonable yields after purification by chromatography.[24] To the best of our knowledge this represents

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Keywords: Tetrahydroisoquinolines; Hydroamination; *n*-Butyllithium.

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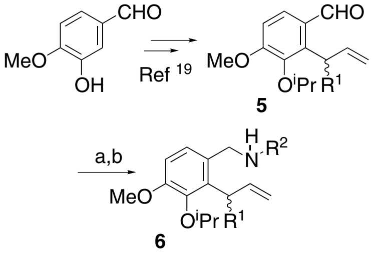
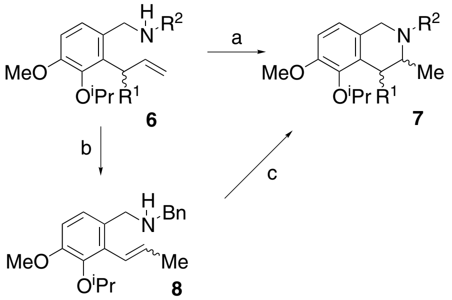


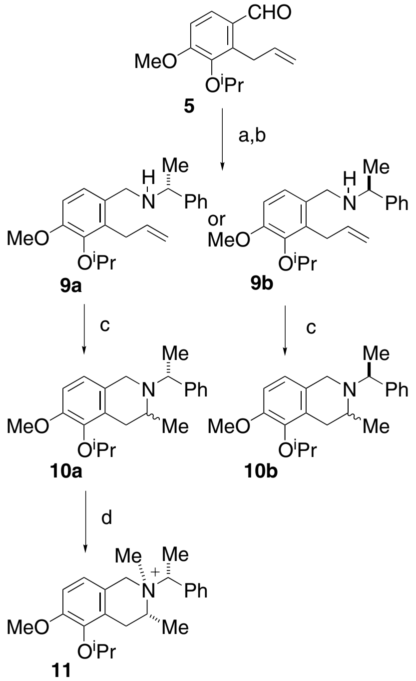
Scheme 1. Reagents and conditions: (a) R^2NH_2, *p*-TSA, benzene or toluene, Dean–Stark apparatus, reflux, 18 h; (b) $NaBH_4$, MeOH, H_2O (1 drop), 0 °C, 1 h, yields over two steps: **6a**, $R^1 = H$, $R^2 = Bn$, 99%; **6b**, $R^1 = H$, $R^2 = n$-Pr, 99%; **6c**, $R^1 = Me$, $R^2 = Bn$, 92%; **6d**, $R^1 = Me$, $R^2 = n$-Pr, 97%.



Scheme 2. Reagents and conditions: (a) *n*-BuLi (2 × 16 mol%), rt, 6 h, then 60 °C, 18 h, yields: **7a**, $R^1 = H$, $R^2 = Bn$, 87%, **7b**, $R^1 = H$, $R^2 = n$-Pr, 65%, **7c**, $R^1 = Me$, $R^2 = Bn$, 63% (5:1 *cis*:*trans*),[26] **7d**, $R^1 = Me$, $R^2 = n$-Pr, 62% (*cis*:*trans* ratio not determined); (b) for **6a**, $R^1 = H$, $R^2 = Bn$, *n*-BuLi (2 × 16 mol%), rt, 18 h, 96%; (c) *n*-BuLi (16 mol%), 60 °C, 18 h.

the first application of this particular methodology towards the synthesis of THIQs. Of interest was that when similar reaction conditions were employed using substrate **6a** at ambient temperature, isomerized compound **8** was isolated in good yield. This suggests that the initial step could involve isomerization of the allyl group to the thermodynamically more stable styrene compound followed by the intramolecular transamination. This possibility is also supported by the work of Marks coworkers[17] and Molander and Pack,[25] in which styrenes are converted into THIQs by way of intramolecular hydroamination using lanthanide catalysts. Subsequent treatment of styrene **8** with *n*-butyllithium at 60 °C then afforded the expected product **7a**.

A point of interest is that this approach to THIQs afforded 3,4-dimethyl compounds **7c** and **7d** in moderate yields.[26] A subsequent literature search revealed that there are only a few published approaches to this type of 3,4-dialkyl THIQs.[27–29]



Scheme 3. Reagents and conditions: (a) (*R*)- or (*S*)-1-phenylethylamine, *p*-TSA, benzene or toluene, Dean–Stark apparatus, reflux, 18 h; (b) $NaBH_4$, MeOH, H_2O (1 drop), 0 °C–rt, 18 h, yields over two steps: (*R*)-**9a**, 89%; (*S*)-**9b**, 98%; (c) *n*-BuLi (2 × 16 mol%), rt, 6 h, then 60 °C, 18 h, yields: (1′*R*)-**10a**, 75%, (1′*S*)-**10b**, 79%; (d) MeI, recrystallized from MeOH/EtOAc.

At this point we attempted to see if the strategy described in this letter was suitable for the stereoselective synthesis of THIQs (Scheme 3). To this end, the precursor **5** was readily converted into the amines (*R*)-**9a** and (*S*)-**9b**, both containing the chiral 1-phenylethyl group. Compounds (*R*)-**9a** and (*S*)-**9b** were then individually subjected to *n*-butyllithium, but disappointingly this only gave a mixture of diastereomers with no diastereoselectivity bias. Careful inspection of the ^{1}H NMR spectra of (1′*R*)-**10a** and (1′*S*)-**10b** confirmed that the cyclizations involving the chiral benzylamine derivatives were unselective under these conditions.

Quaternization of diastereomeric mixture **10a** with methyl iodide gave a solid from which 3-(1′*R*, *R*)-**11** was recrystallized (MeOH/EtOAc). A single crystal X-ray structural determination was then done to confirm the postulated structure (Fig. 2).[30]

In summary, we have demonstrated the first examples of intramolecular hydroaminations using sub-stoichiometric amounts of *n*-butyllithium to afford the ubiquitous

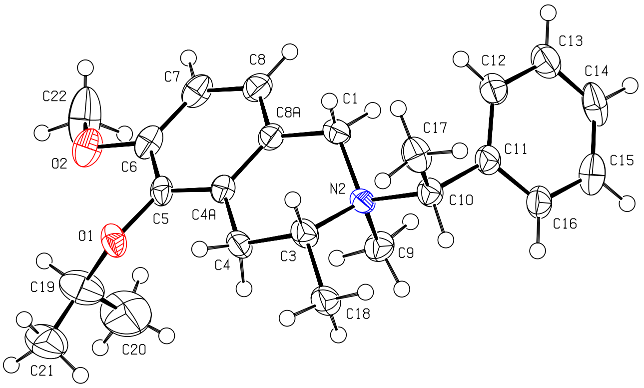


Figure 2. ORTEP diagram of the X-ray crystal structure of compound **11** (iodide counter-ion not shown and ellipsoids at 50% probability).

THIQ skeleton. Further studies will now focus on the application of this methodology to the synthesis of simple natural products as well as the investigation of related methods to invoke stereoselectivity in the hydroamination reactions.

Acknowledgements

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