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CHIRAL LITHIO FORMAMIDINES. ARE THEY CONFIGURATIONALLY STABLE?

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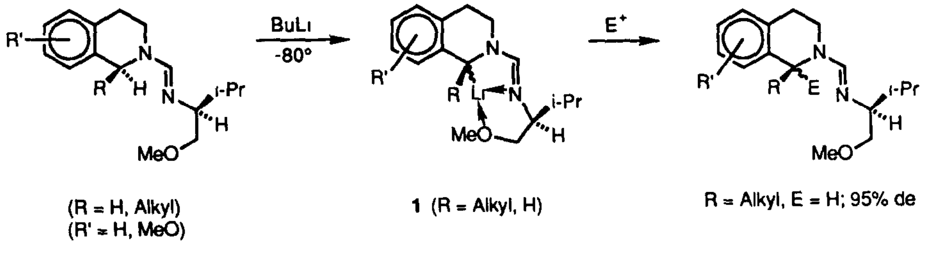
Summary: Metalation and alkylation of an optically active 1-methyl isoquinoline in the presence of an achiral formamidine leads to completely racemic material.

Ever since Letsinger and Traynham[1] showed that octyllithium prepared from S-(+)-2-iodooctane and butyllithium at -70°C lost 80% of its optical activity when quenched with CO_2, there has been considerable interest in the configuration stability of carbanions.[2] The earliest report of a configurationally stable organolithium came from Walborsky[3] who showed clearly that certain cyclopropyllithiums retained 95% of their absolute configuration. Thus, cyclopropyl, vinyl, and α-heteroatom carbanions of lithium were eventually all shown to exhibit considerable stability toward inversion.[4] Studies to substantiate this behavior have come mainly from NMR experiments and it is generally agreed that configurational stability will be considerable if either strain and/or chelation effects are involved.

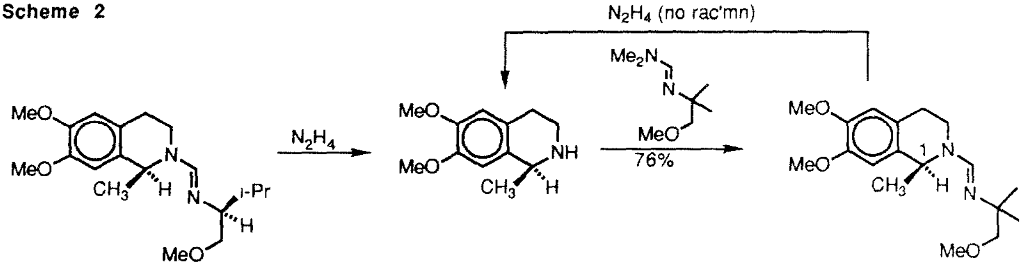
The use of lithiated chiral formamidines has been adequately demonstrated to afford chiral α-substituted amines (Scheme 1) in high enantiomeric purity.[5] However, the exact nature of this process, accompanied by a high degree of stereoselectivity, is still an open question. We have, along with others,[6] assumed with good reason, that the highly selective alkylations are due to the C-Li bond in the formamidine **1** possessing considerable covalency (Scheme 1). If the C-Li bond in **1** is indeed strong enough to inhibit inversion of the carbanion, and if the adjacent nitrogen and oxygen ligands are providing stabilizing influences, then one can ask the question: Is the lithio

Scheme 1



derivative **1** (R = alkyl) able to maintain its absolute configuration if the stereogenic center in the auxiliary is replaced by a symmetric carbon? In other words, all the factors (i e , ring conformation chelation) will remain the same except we will replace the isopropyl group and hydrogen with two methyl groups. With these conditions in place, will the alkylation step (E^+) still provide the high diastereofacial selectivity? We felt this would be a meaningful test[7] of configurational stability and shed some light on the nature of the C-Li bond [8]

Scheme 2



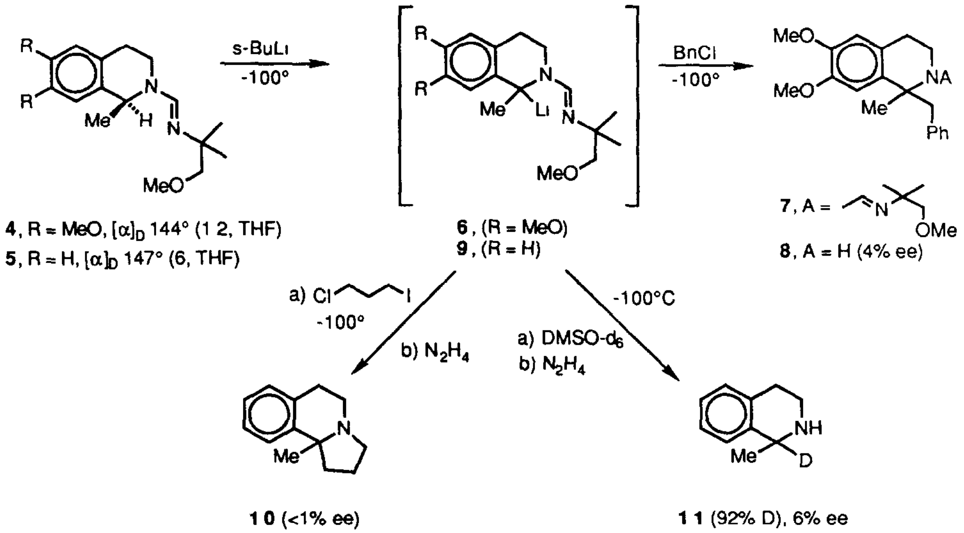
2, $[\alpha]_D$ 107° (94% de)

3, $[\alpha]_D$ -63° (94%)

4, $[\alpha]_D$ 144°

We initiated this study by first preparing **2** through alkylation of the lithiated formamidine with methyl iodide. This reaction has already been studied in detail using the *t*-butoxy group as the chiral auxiliary[9] which gave **2** in 94-97% de. The 94% de observed for **2** was to act as the benchmark for further reactions in Scheme 2. Removal of the chiral auxiliary (hydrazine-EtOH-HOAc) gave the alkaloid salsolidine **3**,[9] which was 94% optically pure by virtue of its specific rotation Since use of methoxy formamidines now allows deprotonation of 3°-carbons,[5] the configurational stability of the resulting 3°-carbanion or carbon-lithium pair could be evaluated In this regard, we reinstated the **achiral** auxiliary derived from 2-methyl 2-aminopropanol[5] by simple exchange of dimethylamine in hot toluene This produced the optically active 1-methyl formamidine isoquinoline **4**, in 76-80% yield. The latter is now a single enantiomer, enriched to the level of 94% ee and the methyl group at C-1 is the only stereogenic center in the molecule To assure that no racemization had occurred in transforming **3** to **4**, hydrazinolysis of **4** returned the 1-methylisoquinoline **3** with less than 1% variation in its specific rotation

Metalation of **4** at -78°C with *s*-BuLi generated the red anion solution of **6** which was kept at -100°C while benzyl chloride was introduced Alkylation gave **7**, ($[\alpha]_D$ 2.8°) which after hydrazinolysis furnished the 1,1-disubstituted isoquinoline **8** possessing $[\alpha]_D$ 1.4°. Based on



4, R = MeO, $[\alpha]_D$ 144° (1 2, THF)
5, R = H, $[\alpha]_D$ 147° (6, THF)
6, (R = MeO)
9, (R = H)
7, A = (N=CH–N–C(Me)₂CH₂OMe)
8, A = H (4% ee)
10 (<1% ee)
11 (92% D), 6% ee

specific rotations (THF), the optical purity went from 94% in **3** to 4% in **8** (based upon $[\alpha]_D$ 25 0° (1.6, THF) for **8** at 86% ee).[5] Further confirmation of the low enantiomeric purity of **8** was obtained by chiral HPLC analysis (Chiracel OJ, 3:1 hexane-i-PrOH, 1 mL/min) which gave an integrated peak ratio of 49.8:48.6. Thus **8** was indeed close to being racemic and this indicated that even at -100°C, the C-Li bond is too weakly associated to prevent any inversion. Furthermore, if the C-1 methyl in **6** was attached to a trigonal carbon (or mainly so) the rotation of the N-C=N-moiety in the formamidine would lead to enantiomers, which would also explain the racemic-like nature of **8**. Not totally satisfied with this behavior, we performed two additional experiments to assess configurational stability. The isoquinoline **5** (99+% ee), prepared as described above and from earlier studies,[10] was metalated with *n*-BuLi and then alkylated with 1-chloro-3-iodopropane followed by hydrazinolysis to the pyrroloquinoline **10** $[\alpha]_D$ =0-1°. Since the latter was prepared[11] in 75% ee using a chiral auxiliary, we were able to assess the level of survival of the carbanion, which was obviously very poor. The lithiated isoquinoline **9** was also treated with DMSO-d_6 to give 92% D incorporation (NMR) at -100°C but, once again removal of the achiral formamidine showed $[\alpha]_D$ -4.2° (2, THF) which amounts to ~6% optical purity.[10] The residual optical activity is no doubt due to unmetalated **5** (~8%) and once again convinced us that there was little configurational stability in these lithiated formamidines, due to poor levels of covalent character in the C-Li bond.[12]

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