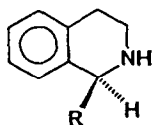


A MECHANISTIC MODEL FOR ASYMMETRIC ALKYLATION OF CHIRAL DIPOLE STABILIZED ANIONS

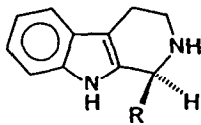
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Summary: Stereoselective deprotonation, deuteration, and alkylation of chiral formamidines are described.

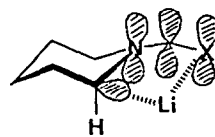
We have recently described an unprecedented asymmetric synthesis of 1-substituted tetrahydroisoquinolines 1¹ and tetrahydro- β -carbolines 2² via the lithio anion of their respective chiral formamidines. This highly efficient route to isoquinoline and indole alkaloids, in their natural configuration, led us to probe the underlying factors responsible for this subtle process which provides chiral products in greater than 95% ee.



(S)-1



(S)-2



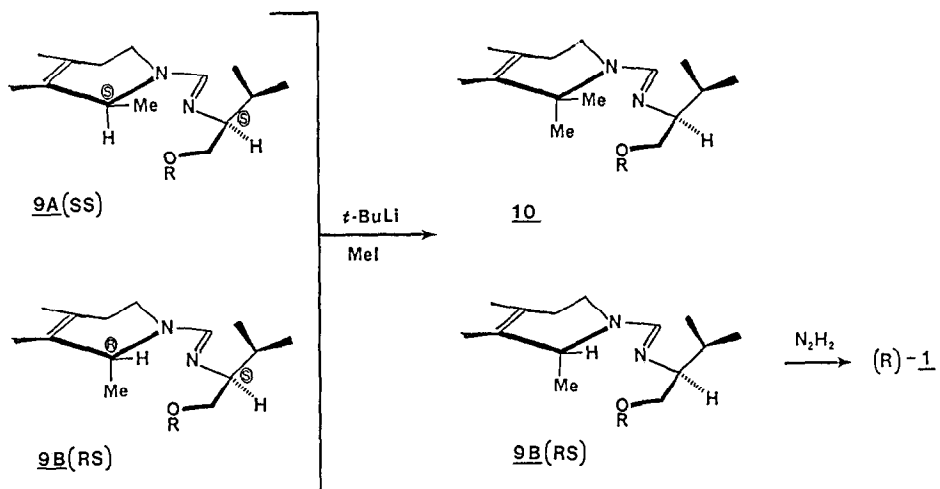
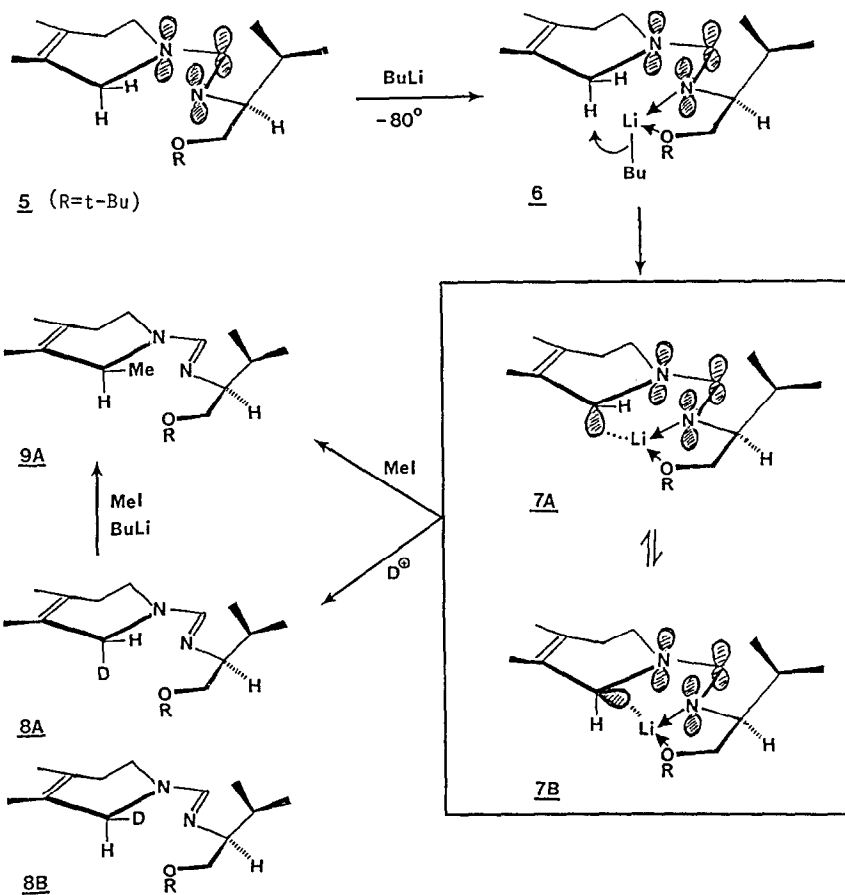
3 (X = NR, O)

The alkylation of racemic α -amino carbanions is now a well-known transformation based on the dipole-stabilized carbanions investigated by Fraser³, Seebach⁴, Beak⁵, and our own laboratory.⁶ However, the use of chiral dipole stabilized moieties to induce asymmetric alkylation adjacent to nitrogen has only been reported with formamidines. It may be safely assumed from the studies of Beak, Houk, and Schleyer⁷, Bach⁸, and others⁶ that α -lithio amino carbanions are most stable when the carbanion orbital is orthogonal to the non-bonded orbitals as shown in 3.

In the present report, we describe the highly stereospecific deprotonation and alkylation of two systems - 1(R=H) and 2(R=H) - both of which exhibit very similar behavior in the asymmetric alkylation to the (S)-alkylated derivatives, 1 and 2. When either system, depicted by partial structure 5, was metalated (*n*-BuLi, 1.1 equiv, THF, -78°), and treated with methyl iodide the major (>95% de) product was 9A. Furthermore, when the anion was quenched with D₂O, or MeOD, the monodeuterated product was formed (98 + %D) which contained a 70:30 mixture⁹ of deuterium epimers 8A,8B. However, when 5 is metalated and quenched with DMSO-d₆, only a single deuterated product 8A was obtained.⁹ Although in the latter case, these results do not unambiguously confirm that proton abstraction was stereoselective, only that a single deuterio product 8A was formed, additional studies

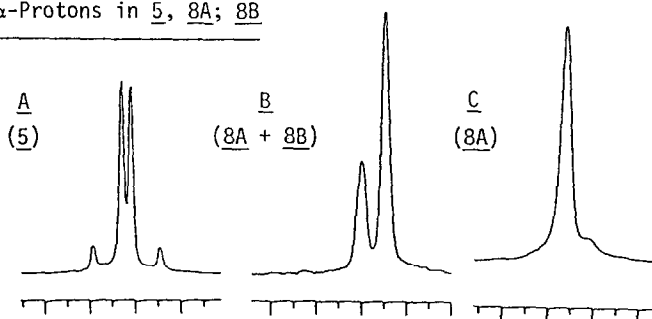
showed that proton removal is indeed stereospecific. For example, metalation of the single deuteriated product 8A followed by methyl iodide gave 9A which, after removal of the formamidine moiety with hydrazine, gave the (S)-1-methyl products 1 or 2 (R = Me) in 86-93% ee, devoid of deuterium within the limits of NMR detection (1-2%).¹⁰ The deuterium in 8A was, therefore, cleanly removed by the base, in spite of any expected isotope effect. Further support for the specific proton removal was acquired when a 1:1 mixture¹¹ of 1-methyl diastereomers (S,S) and (R,S)-9 was treated with 1.1 equiv t-butyllithium in THF at -78°. Weaker bases did not remove the 3°-proton in 9. Addition of methyl iodide followed by work-up with D₂O gave 46-50% yields of the geminal dimethyl derivative (S)-10 and 45-50% recovery of the protio methyl product, (R,S)-9B. Verification of the R-configuration at the C-methyl position in both 1 and 2 was obtained by the chiral column developed by Pirkle which cleanly separated the R and S enantiomers and these were assigned by their order of elution.¹²

The results given above appear to be consistent with the process depicted by 5 to 9A if one assumes that 5 is in its most favored conformation. Given this assumption, the protons in 5 are "equatorial" and "axial" as shown, and after butyl lithium coordination¹³ from the bottomside, the "axial" proton is removed. The kinetic acidity of the axial proton, activated by the π system, is greater than the "equatorial" proton.¹⁴ The resulting carbanion 7A is shown as sp³ capable of inversion to 7B. The latter should be more favored (as in 3) yet π -delocalization in 7A is sacrificed. Addition of methyl iodide occurs with retention on 7B or via an S_E2 mechanism from the back lobe of 7A to give 9A ("equatorial" methylation). Quenching 7A,B with D₂O or MeOD gives non-selective deuteriation to 8A or 8B, but DMSO-d₆ gives only 8A. This may be the result of oxygen coordination to lithium from the underside followed by intramolecular D-transfer to 8A. When 8A is again metallated and alkylated only the "axial" D is removed (as in 6 to 7A,7B) and methyl iodide is again introduced in the equatorial site, 9A. The specific metallation of the epimeric pair 9A,9B is totally consistent with this picture. Only the "axial" proton (9A) is capable of being removed. An experiment to further confirm the "inversion" after proton removal was performed on 9A. If the axial proton is indeed removed, reprotonation should give the epimer 9B. However, pure 9A gave after BuLi-D₂O (or DMSO-d₆) a 60:40 mixture of 9A,9B. Thus the tertiary anion from 9A does not completely invert or protonate as specifically as the secondary anion from 5. This overall behavior now forms the basis for rationalizing additional asymmetric alkylations in related systems.



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9. The pro-S and pro-R protons in **5** (270 MHz) appear as an AB quartet (Fig. 1) and after deuteration can be integrated readily to show the 70:30 mixture (B). The stereoselective deuteration to **8A** is also seen (C).

Figure 1. - α -Protons in **5**, **8A**; **8B**

10. When the 70S:30R mixture of deuterated diastereomers of **8(A,B)** was metalated and treated with methyl iodide, the (S)-methyl product **9A** was the only stereoisomer obtained, but contained 70% D and 30% H.
11. Prepared by treating (+)-1-methyl-1,2,3,4-tetrahydroisoquinoline with the (S)-valine t-butyl ether (ref 1b) to give a 1:1 mixture (two CH₃ doublets, of equal intensity, are readily discernible at 270 MHz).
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14. In those amines which do not possess benzylic or allylic activation, no metalation occurs in the presence of the chiral auxiliary.

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