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# Recent Progress Using Chiral Formamidines In Asymmetric Syntheses*

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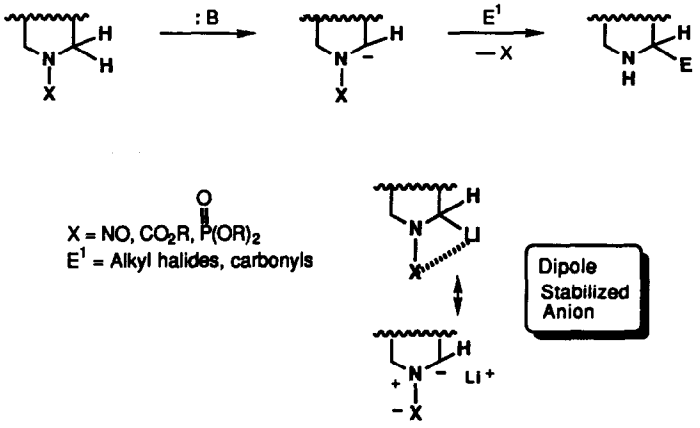
***Abstract:*** *The ability to generate a carbanion next to nitrogen in a chiral environment has led to a number of useful asymmetric routes to alkaloids and related substances. Mechanistic studies have been conducted to understand the nature of these alkylations.*

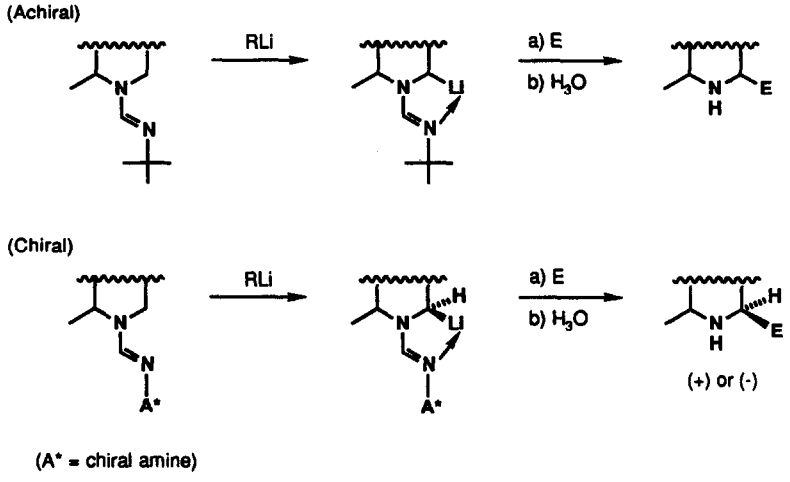
During the past decade a number of laboratories have addressed the problem of generating a carbanion adjacent to nitrogen.[1-4] The solution to this problem lay in the notion that activation of the nitrogen with a suitable electron-withdrawing group would both increase the kinetic acidity of an α-proton and stabilize the carbanion by chelation (Scheme 1). This concept of preparing anions has been termed by Beak as "dipole-stabilized" and has since been the subject of considerable discusssion.[5]




Scheme 1

*Taken from a lecture presented on May 4, 1991 at Yale University on the occasion of Professor Harry H. Wasserman's 70th Birthday. The author wishes to extend good wishes to his dear friend for many additional birthdays.

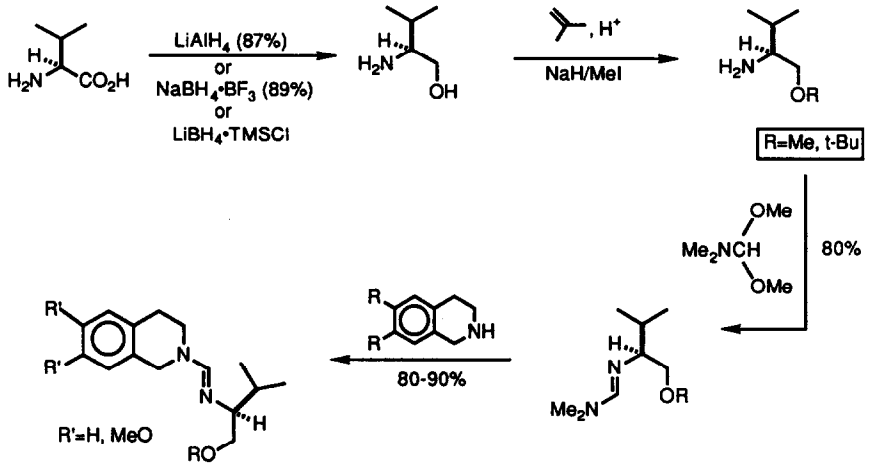
In 1980 we reported[6] that the achiral formamidine moiety was yet another dipole stabilized activating group and allowed the formation of α-amino carbanions which could be elaborated to α-alkyl amines (Scheme 2). However, it was soon recognized that the possibility existed to introduce a chiral element into these formamidines by simply affixing the appropriate group to the nitrogen. Were this to become a feasible task then the opportunity may arise to not only alkylate a carbanion adjacent to nitrogen but to do so with attending absolute stereochemistry - not a trivial feat (Scheme 2).




Scheme 2

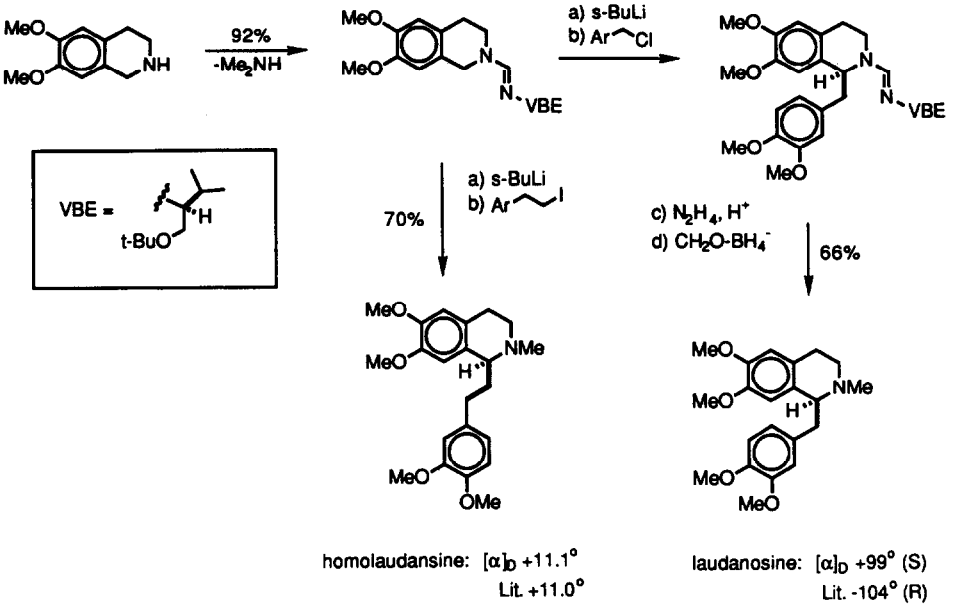
Our attempts to perform this heretofore unprecedented synthetic operation has proven quite successful and some of the early work will be briefly descibed. First of all, the chiral auxiliary utilized in this sequence has been almost always derived from amino acids (e.g. S-valine) and reduced with various hydride agents to the amino alcohol (Scheme 3). The reason for the different hydrides shown is due mainly to the slightly different characteristics of each amino alcohol produced. After reduction, the hydroxyl group is masked either as a tert-butyl ether or a methyl

ether. This choice of ethers is very important since both formamidine ethers are useful for deprotonation of an adjacent methylene group but only the methyl ether allows deprotonation of an adjacent tertiary proton. This will be disussed later in this article. Once the chiral alkoxy amine had been prepared it was transformed into the simple dimethylamino formamidine using DMF-acetal. This material is now the pivotal reagent to introduce the chiral formamidine into any secondary amine.[7] In Scheme 3 the attachment of the chiral formamidine onto the dimethoxytetrahydroisoquinoline is seen as a typical example and occurs in good yield.



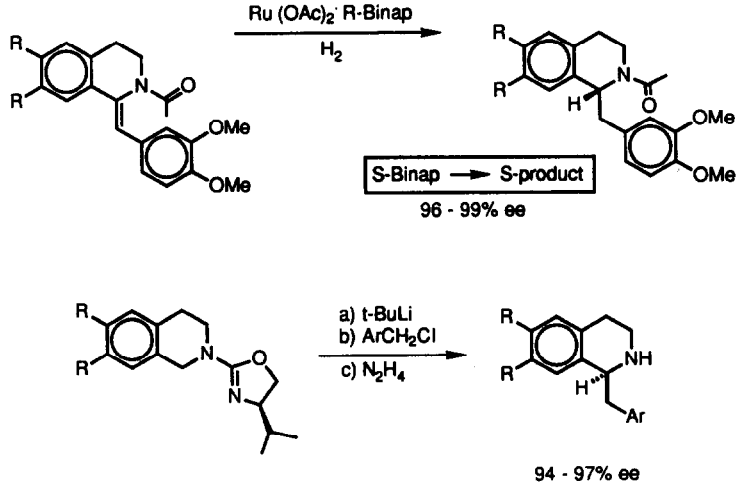

Scheme 3

The metalation and alkylation of the isoquinoline formamidine has been shown to proceed in an efficient manner and the removal of the chiral auxiliary (recoverable if desired) leads to an asymmetric total synthesis[8] of various isoquinoline alkaloids both in good yield and with very high enantiomeric excess(ee) as depicted in Scheme 4. Though only two are shown here we have prepared a number of others including reticuline,[9] isopavine,[10] aporphines,[11] and dextromethorphan.[12]




Scheme 4

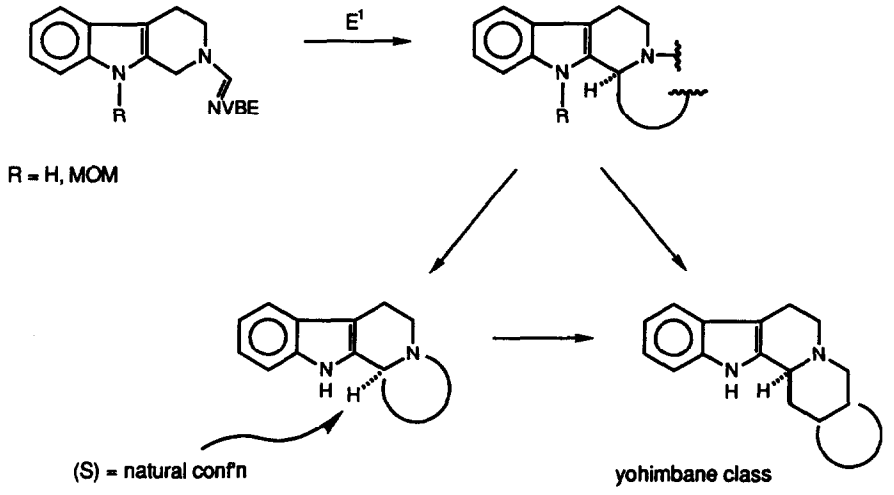
In the last several years there have been considerable advances from other laboratories toward asymmetric routes to isoquinoline alkaloids and two of them are outlined in Scheme 5. The recent use of chiral ruthenium catalysts by Noyori and co-workers[13] has demonstrated that several




Scheme 5

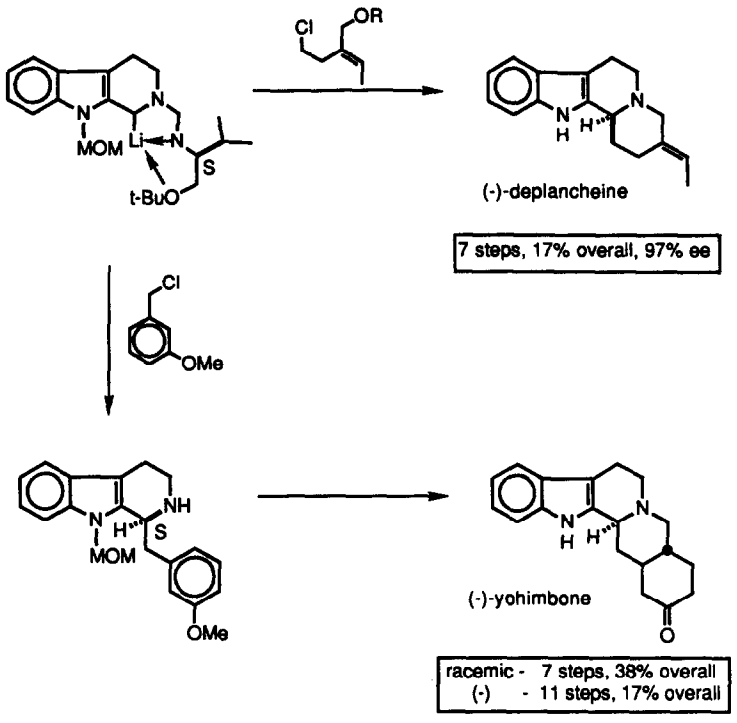
enamides containing a prochiral center can be transformed into saturated derivatives in very high ee and thus provide isoquinoline alkaloids in an efficient manner. The use of chiral oxazolines, in much the same fashion as the formamidines are employed, were readily metalated and alkylated affording a variety of isoquinoline alkaloids in high ee.[14]

The chiral formamidines were also shown to have considerable versatility for the synthesis of other alkaloidal frameworks. In fact a review will appear shortly focusing on the variety of different systems which may be accessed in high enantiomeric purity.[15] It is noteworthy however to mention briefly two indole alkaloids which were the subject of a very efficient asymmetric total synthesis. The rationale for various indole derivatives follows from the sequence outlined in Scheme 6. Thus starting with β-carboline and affixing the chiral formamidine auxiliary, metalation




Scheme 6

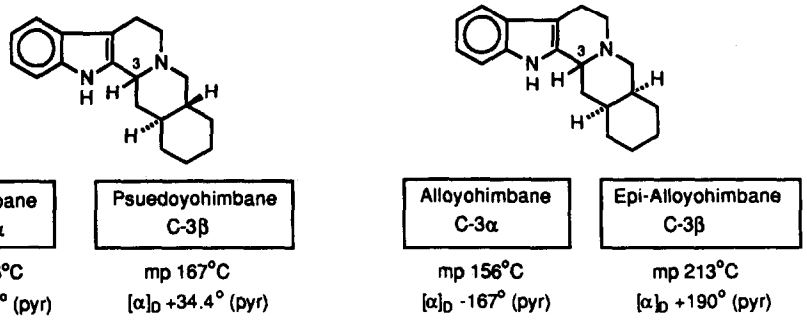
and alkylation with suitable electrophiles can lead to the tetracyclic or pentacyclic ring system by several routine steps. By use of the above strategy two indole alkaloids, deplancheine[16] and yohimbone,[17] were reached in complete enantiomeric purity and in remarkably few synthetic steps (Scheme 7). The scheme shows the single starting material employed and the indole nitrogen protected as its MOM derivative, which is then alkylated with the appropriate electrophile. The syntheses were completed using a few known steps.




Scheme 7

Quite recently we reported another entry into the indole alkaloids by use of intramolecular Diels-Alder reactions on the aracemic[18] alkylated β-carbolines. Thus an entry into yohimbanes was now possible. The yohimbanes are comprised of four stereochemically different isomers (Scheme 8) with each possessing an enantiomeric pair - thus there are eight distinct compounds.

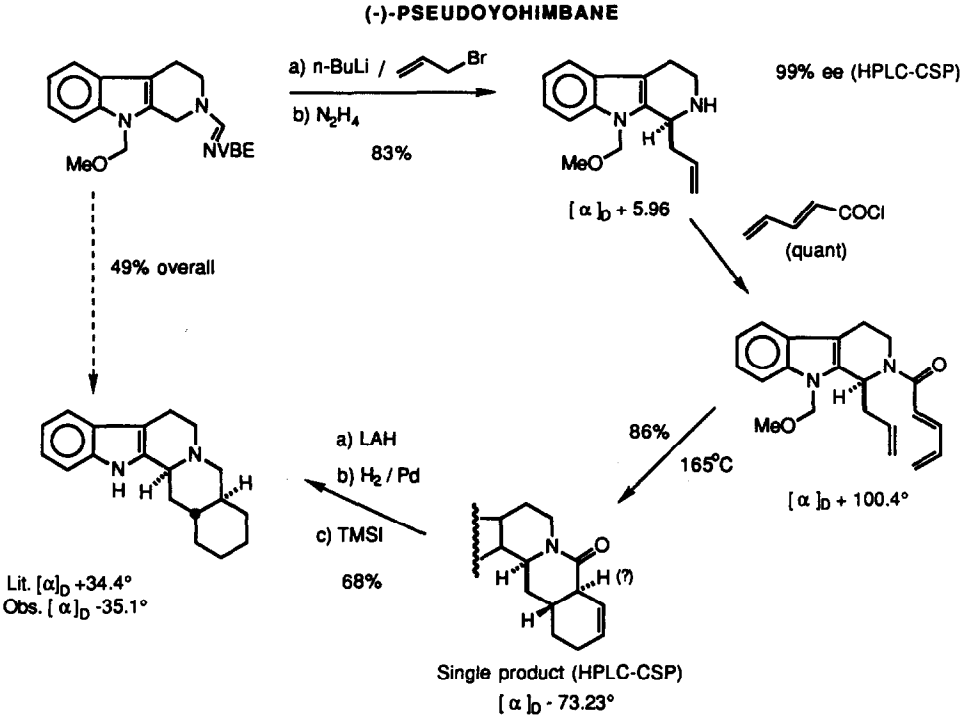
**YOHIMBANES**




| Yohimbane C-3α | Psuedoyohimbane C-3β | Alloyohimbane C-3α | Epi-Alloyohimbane C-3β |
|---|---|---|---|
| mp 206°C | mp 167°C | mp 156°C | mp 213°C |
| $[\alpha]_D$ -118° (pyr) | $[\alpha]_D$ +34.4° (pyr) | $[\alpha]_D$ -167° (pyr) | $[\alpha]_D$ +190° (pyr) |

Scheme 8

The syntheses of these pentacyclic alkaloids have drawn considerable attention as judged by the number of total syntheses reported over the period 1956-1990.[18] All the total syntheses reported were those involving racemic alkaloids but recently there have been several successful efforts culminating in aracemic products.[19] The recent total synthesis of (-)psuedoyohimbane (Scheme 9), which gave the title compound in 49% overall yield in seven steps from the β-carboline formamidine, is an example of the efficiency of this method.[20] The key feature in this approach is the reverse demand Diels-Alder cycloaddition which proceeded in 86% yield when subjected to heating (165°). The remainder of the steps are shown in the scheme and require no further

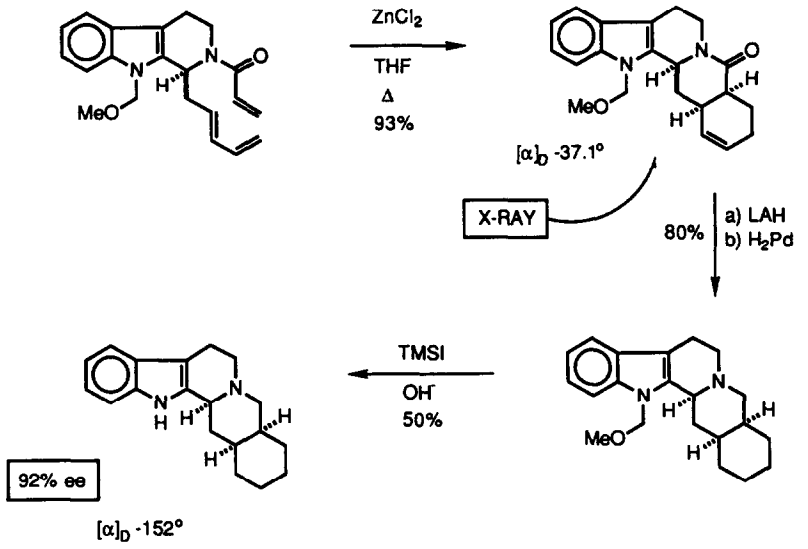



Scheme 9

comment. In the same report[20] the asymmetric total synthesis of (-)alloyohimbane was described involving a slight modification of the sequence above. By alkylating the carboline formamidine with the 2,4-pentadienyl chloride in place of allyl chloride and acylation with acroyl chloride, the

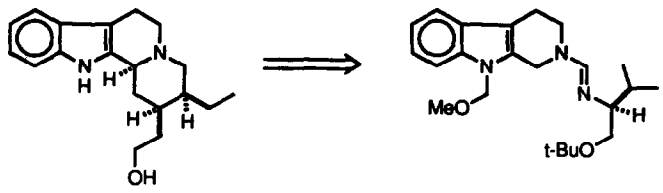
Diels-Alder precursor was efficiently prepared (Scheme 10). With normal electronics in place, the Diels-Alder reaction proceeded in refluxing THF and afforded the pentacyclic system in 93% yield as a single diastereomer. Obviously, the pure stereocenter resulting from the formamidine alkylation provided the necessary stereochemical bias for clean cycloaddition. The stereochemistry was confirmed by X-ray determination of the pentacyclic lactam which then served as the precursor, after three routine steps, to alloyohimbane.

**(-)-ALLOYOHIMBANE**



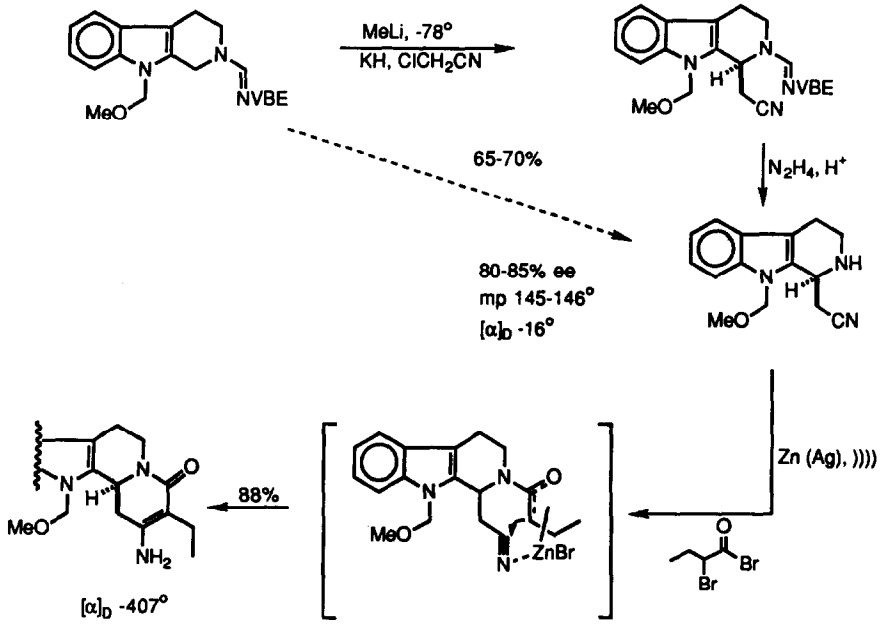

Scheme 10

An asymmetric total synthesis of the indole alkaloid Corynantheidol (Scheme11) was reported by our group in 1991.[21] The tetracyclic system, a subject of several elegant total syntheses,[22] was a viable target, we felt, for the formamidine methodology. Again the β-carboline properly equipped as the chiral formamidine would serve as the "jumping-off" point. In the route to



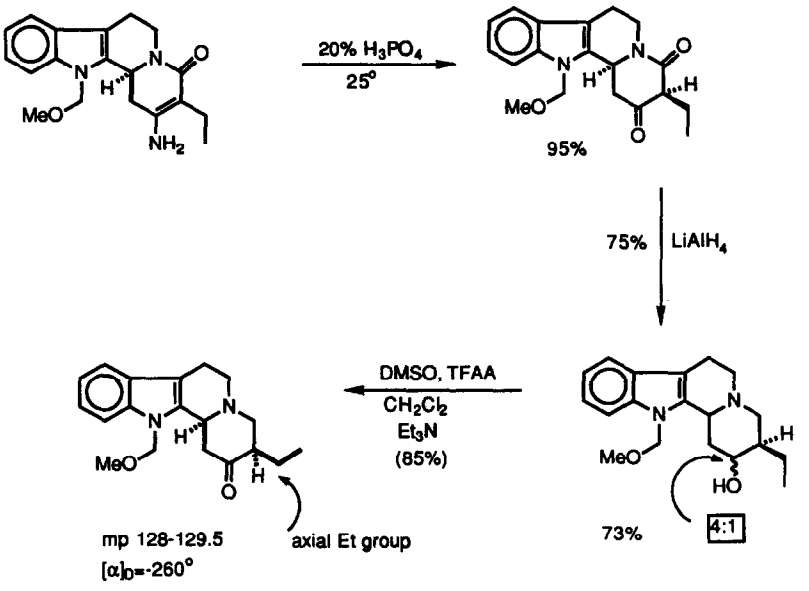
Scheme 11

Corynantheidol (Scheme 12) the chiral formamidine (VBE=Valinol-t-butyl ether) was alkylated, via its lithio carbanion, with chloroacetonitrile to provide, after formamidine removal, the cyanomethyl β-carboline in 65-70% yield and 80-85% ee. The stereoselectivity was a bit lower than most earlier alkylations but the rate of alkylation with the highly reactive electrophile ($ClCH_2CN$) is probably responsible. The core ring for the target was quickly constructed through a nice variation as well as a significant improvement in the seldom used and very old (1901) Blaise reaction affording the aminovinyl lactam in good yield. With the tetracyclic ring system in place and the ethyl substituent



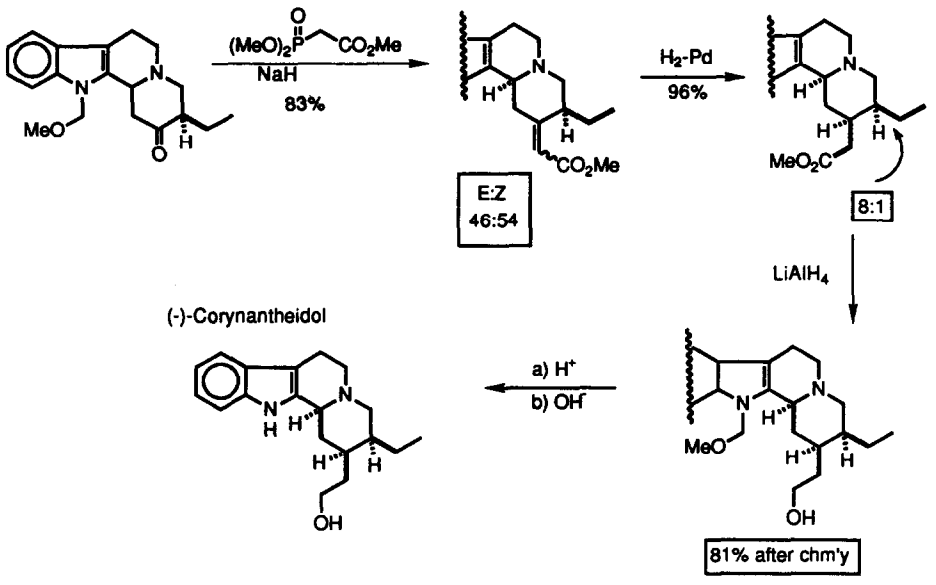

Scheme 12

also incorporated, the aminovinyl lactam was hydrolyzed to the diketone and, as shown in Scheme 13, the latter was transformed into the carbinol mixture by reduction with lithium aluminum hydride.



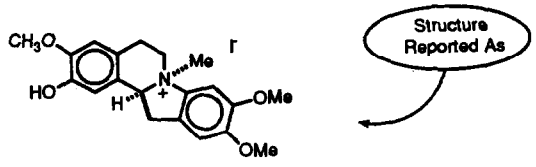

Scheme 13

This was of no consequence since oxidation gave a single tetracyclic ketone which was shown to possess the correct stereochemistry (axial) for the ethyl group. The synthesis of corynantheidol was completed as described in Scheme 14. Thus, the well known Horner-Emmons-Wadsworth olefination gave the unsaturated esters which were reduced to the acetic esters, but as an 8 to 1 mixture. Presumably some epimerization occurred during the reduction. This mixture was rectified after the hydride reduction to the carbinol and chromatographic purification. Removal of the MOM group gave the alkaloid, which was identical in all respects with the natural material.



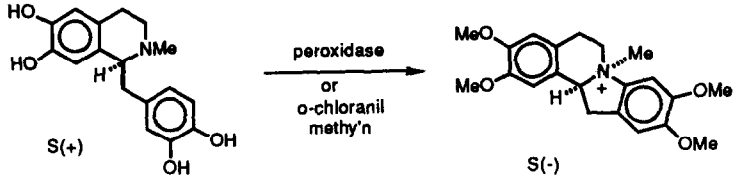

Scheme 14

One of the unsung advantages of an asymmetric synthesis is the ability to reach the final target, natural or unnatural, with **predictable** absolute stereochemistry. Because of this inherent advantage, a check now exists for confirming or questioning the assigned absolute configuration of many, if not all, of the known natural substances. Although not mentioned earlier, we found in our synthesis of deplancheine[15] and in our synthesis of schizandrin[23] by another type of asymmetric method, that absolute configurations of these substances were misassigned. Now we describe another case where our synthetic sortie into a natural product gave us not only the natural material in high ee but uncovered a subtle process which led three research groups into misassigning the absolute configuration. We recently sought as a target to demonstrate the formamidine versatility, the alkaloid Cryptausoline (Scheme 15). The structure and absolute stereochemistry appeared to



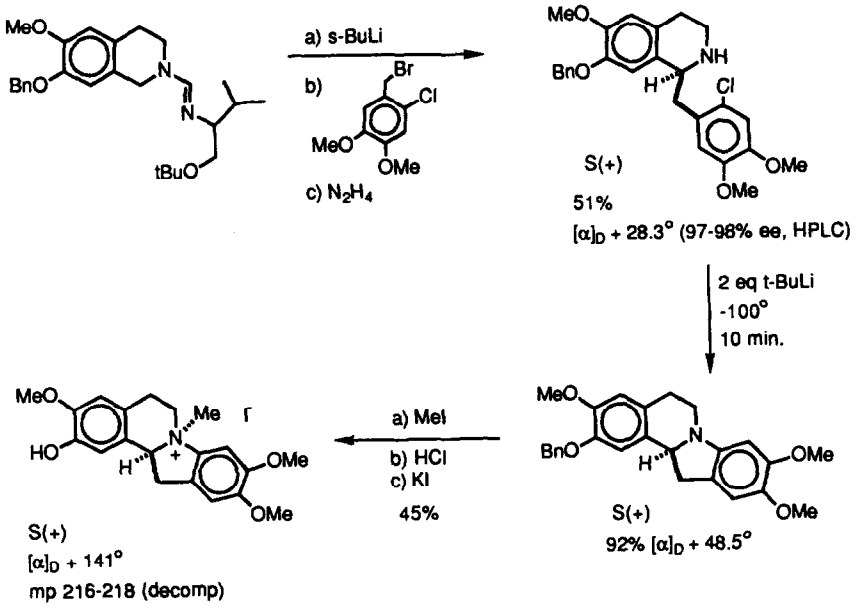

$[\alpha]_D$ -151° (c 0.4, EtOH)
mp 214° (decomp)

**Stereochemistry Related To:**




Scheme 15

be on firm ground since several groups had studied its properties, synthesis, and biogenetic origin from well known precursors; S-laudanosoline.[24] We embarked on what appeared to us to be a quick and facile approach to the alkaloid.[25] Thus, the properly equipped isoquinoline (Scheme 16) was metalated and alkylated with the o-chlorobenzyl bromide such that the 1-benzylated




Scheme 16

isoquinoline was reached in 51% overall yield with an ee of greater than 98%. The benzyne was then generated and cyclization ensued to give the tetracyclic dibenzopyrrocoline in excellent yield. To reach the final natural material, quaternization followed by benzyl ether cleavage gave cryptaustoline which matched all the physical data except one - the sign of the rotation! The dilemma lay in the fact that both the earlier workers (Scheme15) and our own synthesis began by employing the S-benzylated isoquinolines. If the oxidative route in Scheme 15 was affecting the lone stereocenter then racemic material would be expected, yet this was not the case. The asymmetric route (Scheme 16) appears unlikely to have resulted in reversal of stereochemistry, for if nothing else, strong base could have affected the benzylic proton but this, too, would lead to racemic material. The CD spectra were taken of all the key synthetic intermediates (Fig. 1) and showed no change in the sense of stereochemistry throughout the sequence. The problem,

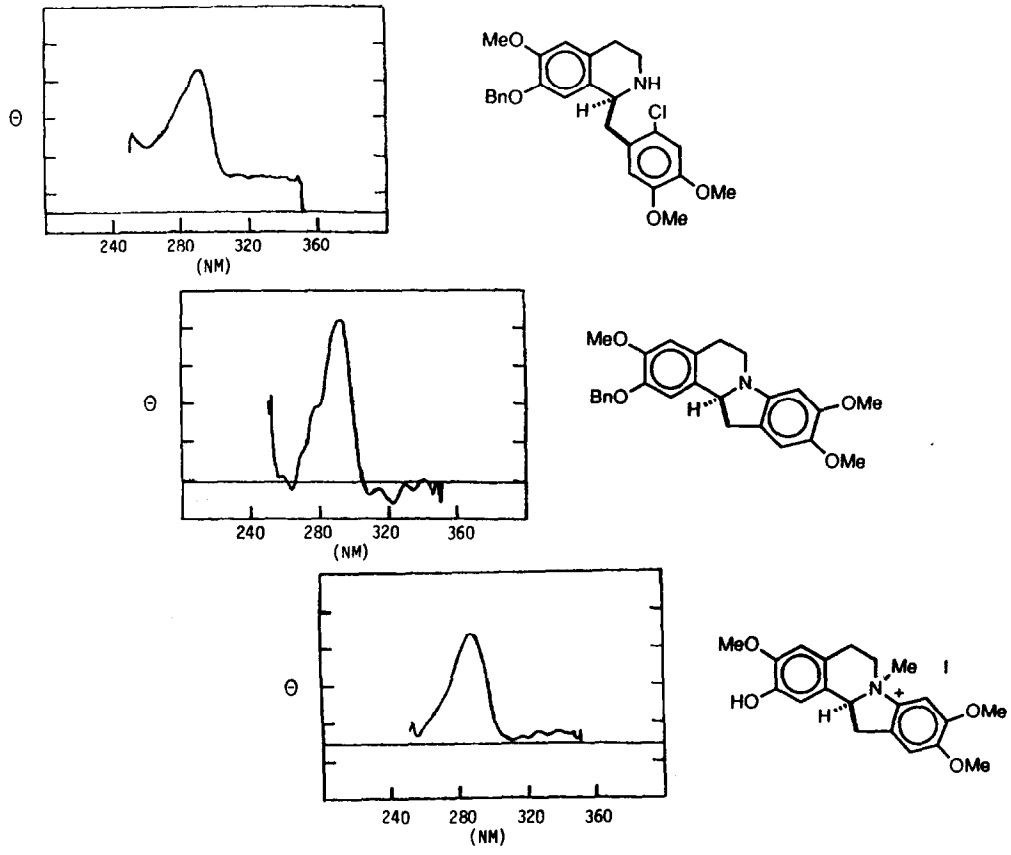
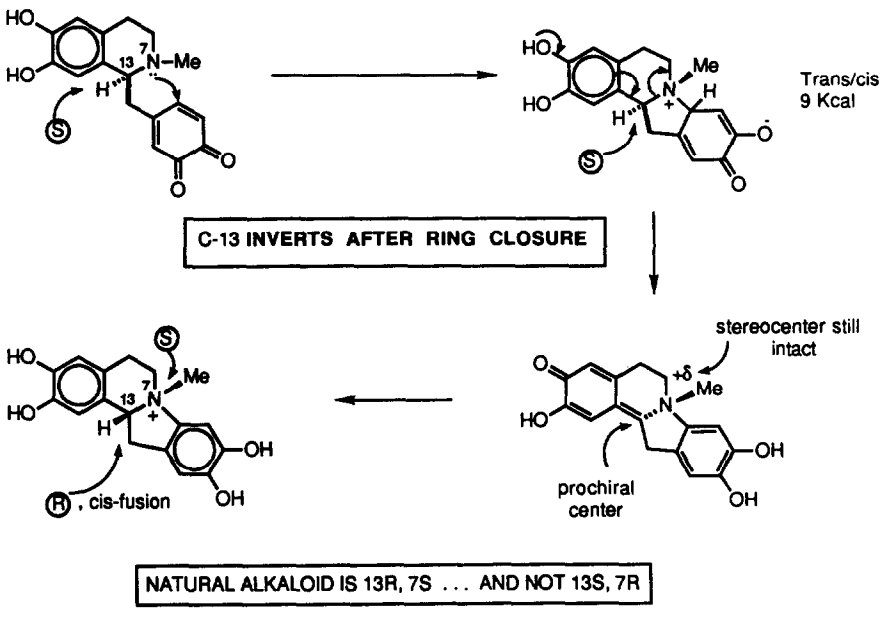



Figure 1

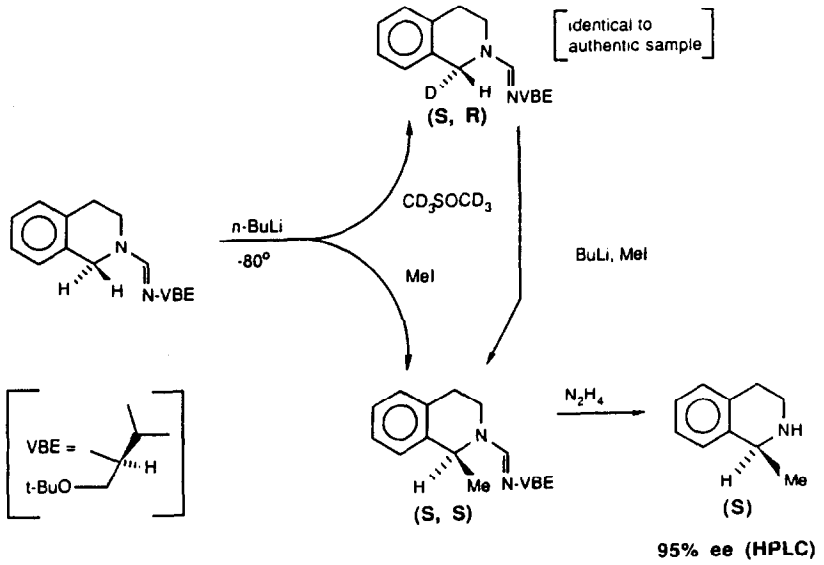
therefore, must lie with the oxidative route to cryptaustoline shown in Scheme 15. Molecular mechanics provided a clue to the discrepency in the absolute configuration. It seems that ring closure as shown in Scheme 17 leads initially to a **trans**-fused ring by virtue of the oxidative coupling. Molecular dynamic annealing (BIOGRAPH) indicated significant ring strain (ca 9Kcal) over the **cis**-fused system. Thus, this must have provided the driving force for an inversion pathway, destroying the benzylic stereocenter originally present in the starting material. However, the newly formed quaternary ammonium center, or a rigid 9-membered ring, acts as the "memory" to preserve absolute stereochemical integrity and a yet unknown pathway to the more stable **cis**-product results. It is currently not clear which route is taken to accomplish the inversion, and studies using labeling experiments are in progress. Although the asymmetric synthesis based on formamidines was successfully implemented, it led to the wrong and unnatural enantiomer - the true natural material must have the R-configuration at the benzylic carbon. That the N-methyl and the benzylic proton are known to be **cis** was already confirmed by the earlier workers.[24]




Scheme 17

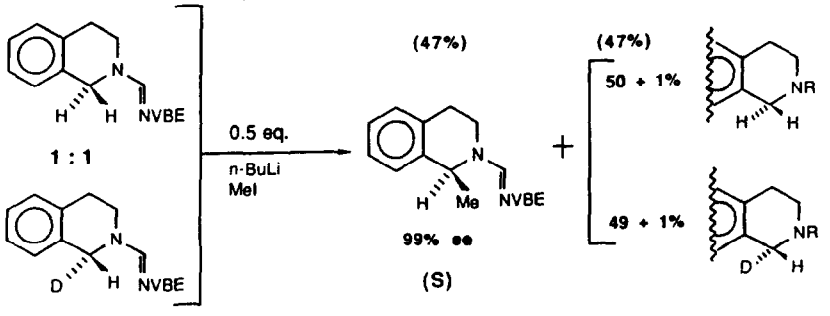
## MECHANISTIC STUDIES

A considerable amount of effort (since 1983) has gone into sorting out the factors responsible for the high degree of stereoselectivity observed in these formamidine alkylations. However, it has only been very recently that a sound mechanistic rationale based on experimental data has been presented.[26] Ironically, it was the recent ability to generate a $3^0$ anion which would ultimately provide quaternary carbons adjacent to nitrogen that provided the key to the plausible mechanism we are now able to present. The salient features of this process will now be presented, as they are currently understood, and appear to agree with all the experimental facts. With regard to the deprotonation step (Scheme 18) it was shown that only the α-proton is removed[27] when n-butyllithium is added to the chiral formamidine isoquinoline. This was explicitly shown when DMSO-$d^6$ was introduced into the lithiated formamidine and gave the α-D product which was identical to an authentic sample of (R)-1-D isoquinoline.[27] However, when methyl iodide (or any other alkyl halide) was added to the lithio salt, the alkyl group entered from the β-face to afford the S-enantiomer. Of further interest is the fact that the deuterium alone was cleanly removed when




Scheme 18

the mono-deutero isoquinoline was again treated with n-butyllithium-methyl iodide. Here the product was the S-enantiomer, devoid of any deuterium, and the methylated isoquinoline produced in greater than 95%ee. This seemingly blatant disregard of the butyl lithium for the isotopic distribution indicated that only the atom on the α-face of the isoquinoline is removable regardless whether it is proton or deuteron. This interesting behavior led to another experiment designed to confirm whether or not an isotope effect was operating in the deprotonation step. In Scheme 19 a head-to-head competition study was performed using an equimolar mixture of the deutero and protio chiral formamidines and 0.5 equivalents of n-butyllithium. After 15 min the reaction mixture was quenched with excess methyl iodide and the mixture analyzed. The results confirmed what was suspected based on the above (Scheme18) - namely that the 50% yield of the methylated product contained no deuterium and the recovered 50% of unreacted starting materials showed a 50-50 mixture of H and D isoquinoline. Thus the base completely ignored the presence of the stronger CD bond and deprotonated both compounds with equal facility. If there was no measurable isotope effect in the deprotonation of the α-face then the rate determining step must be in the formation of the complex prior to deprotonation (which may also include the energy necessary to deaggregate the butyllithium.

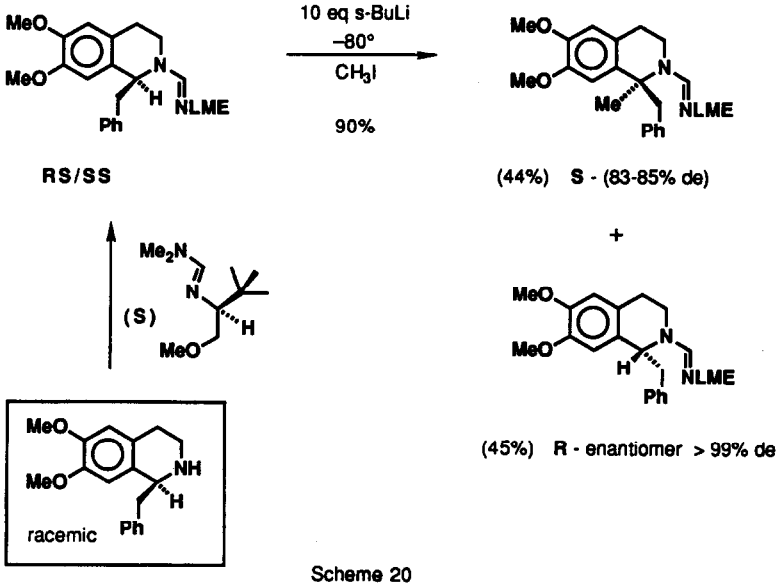



**Conclusion: Metalation step cannot be rate determining**

Scheme 19

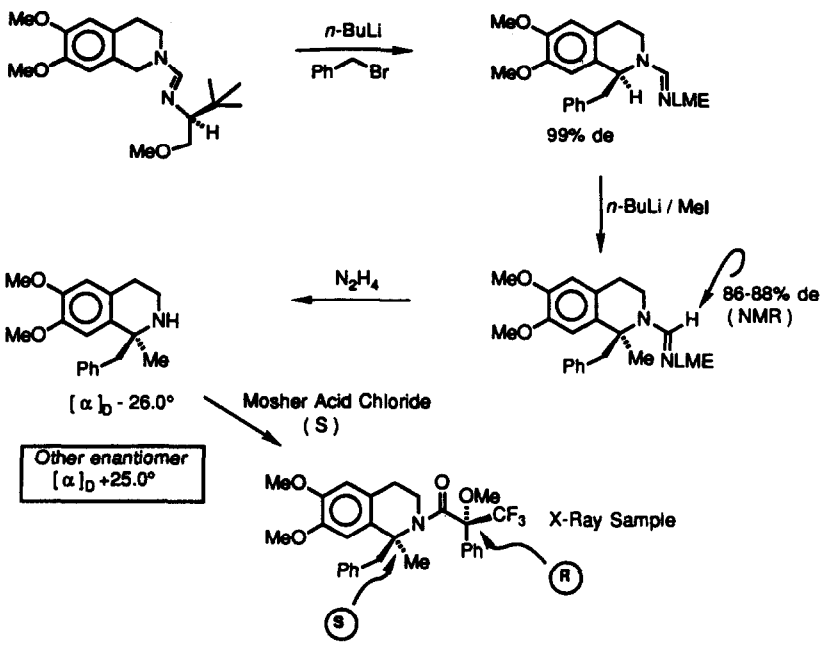
We now turn to the other aspect of this asymmetric proccess - namely the nature of the alkylation step. All that was known until recently was that even though deprotonation takes place from the α-face, alkylation occurs from the β-face. The next major clue to the alkylation step came when it was shown that metalation of the **racemic** methoxy formamidine, derived from tert-leucinol

(Scheme 20) with excess s-butyllithium and followed by introduction of methyl iodide, gave the quaternary substituted isoquinoline in 44% yield and with 85% diastereoselectivity.[28] Also obtained was a 45% yield of the (R)-benzyl isoquinoline in greater than 98% ee. This showed unequivocally that a kinetic resolution had cleanly taken place and only the enantiomer that possessed a proton on the α-face was both metalated and alkylated with respectable diastereoselectivity. It was the first example of a quaternary carbon being generated adjacent to nitrogen with attending stereocontrol. The alkylation was again repeated so that a sequential




Scheme 20

alkylation could occur and determine whether or not it was both synthetically useful and stereochemically predictable (Scheme 21). The tert-leucinol derived auxiliary was sequentially metalated and alkylated - first with benzyl bromide to give monobenzylated material in 99% ee, and then with methyl iodide to give the quaternary product in 82% yield. The % de was assessed (by NMR of the vinyl proton of the formamidine) and found to be 85-88%. Reversing the sequence of alkylation gave, after hydrazine mediated formamidine removal, the optical antipode in roughly




Scheme 21

equal enantiomeric excess. The Mosher amide was prepared as a crystalline product and this was subjected to a single crystal X-ray analysis (Fig 2). The stereochemistry that appeared from the

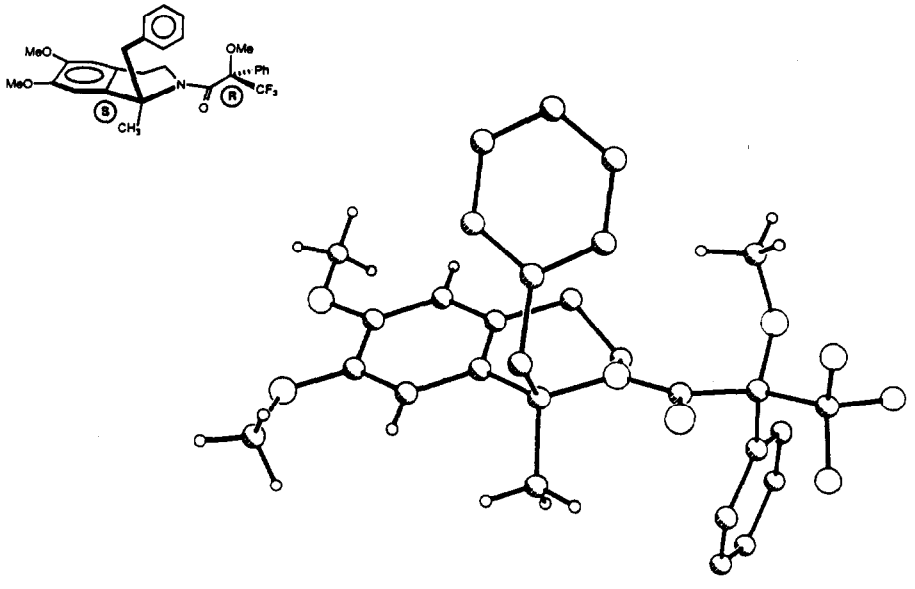


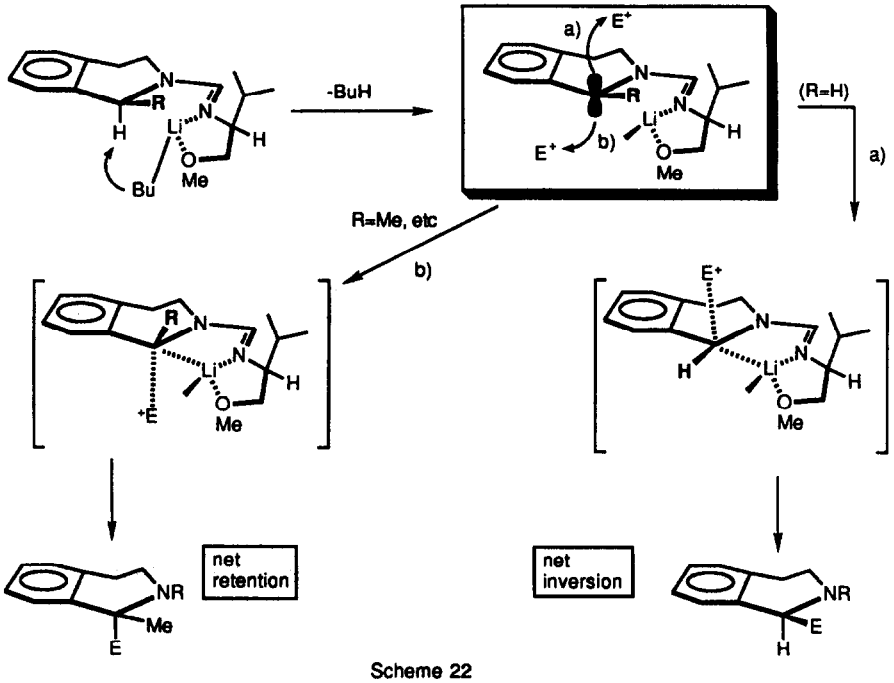
Figure 2

X-ray study showed that the second alkylation had proceeded, not from the β-face as before, but predominantly from the α-face. Scheme 22 summarizes the facts and status thus far,that is:

a) All deprotonations take place from the α-face.

b) Alkylation on 2° carbanion occurs from the β-face with very high selectivity (>99%) with net inversion.

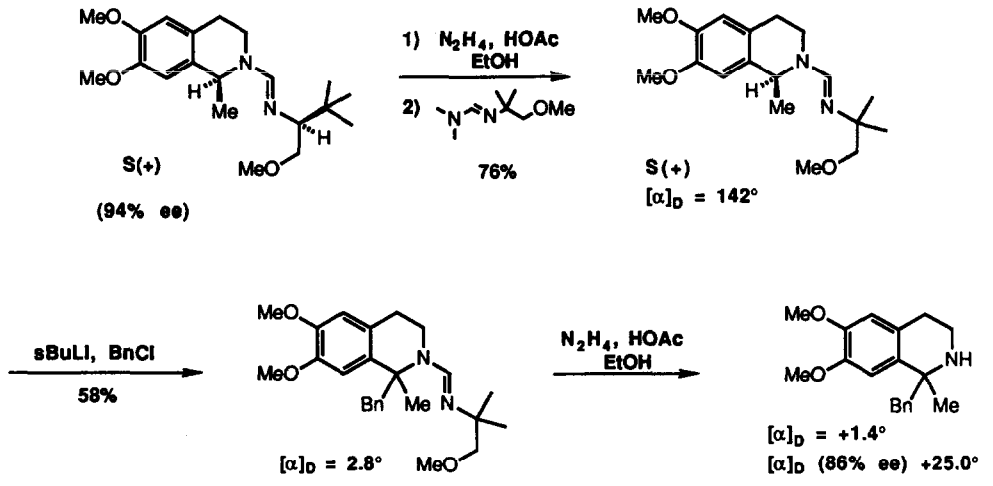
c) Alkylation on 3° carbanion occurs from the α-face with reasonably high selectivity (90-93%) with net retention.




Scheme 22

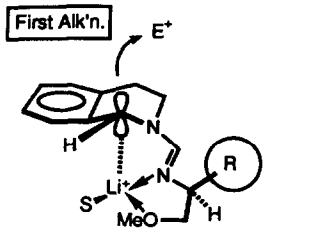
The question then arose as to whether or not the carbanion was inverting as a covalent linkage during the alkylation or whether it was a free carbanion capable of equilibrating to the most stable conformation just prior to alkylation. If the two separate alkylations were conformation controlled, it should be possible to assess this property. First, the configurational stability of the carbanion was addressed (Scheme 23). By replacing the chiral auxiliary on the isoquinoline of known enantiomeric purity (94% de) with an achiral auxiliary containing all the proper ligands, we

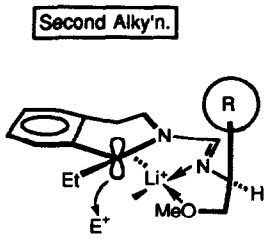
proceeded to metalate and alkylate with benzyl chloride. After removal of the auxiliary the resulting quaternary substituted isoquinoline was found to be virtually racemic.[29] Thus, the carbanion generated from the stereocenter with 94% purity was unable to retain its configuration even at the -80-100° C where the metalation and alkylation occurred. If, as stated above, the alkylation of these anions may be conformationally controlled and they are free to invert as shown by




Scheme 23

Scheme 23, steric factors should play a role. In this regard, a series of formamidine isoquinolines with chiral auxiliaries of varying size were prepared (Scheme 24).[26] The stereoselectivity of the alkylation (first alkylation) were examined as function of the size of the R-group on the auxiliary. As seen from Table on the left, varying the size of R has relatively little effect on the diastereoselectivity although the % de does fall to 66-70% with the small methyl in the alanine-derived auxiliary. On the other hand the %de in the second alkylation is more strongly affected by changes in the size of R. In fact, with R=methyl, there is virtually no selectivity in the alkylation, and with R=phenyl, the selectivity drops to half its value from the tert-butyl case.




| R | E | % de |
|---|---|---|
| Me | BnCl | 66-70 |
| Ph | BnCl | 80-85 |
| *i*-Pr | BuI | 94-97 |
| *t*-Bu | Et | 97-99 |

small effect

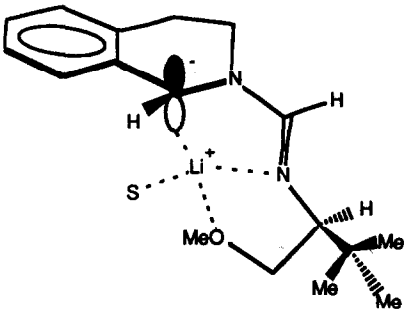
large effect

| R | E | % de |
|---|---|---|
| Me | BnCl | 4-5 |
| Ph | BuI | 40-43 |
| *i*-Pr | MeI | 70-80 |
| *t*-Bu | BnCl | 83-88 |

Scheme 24

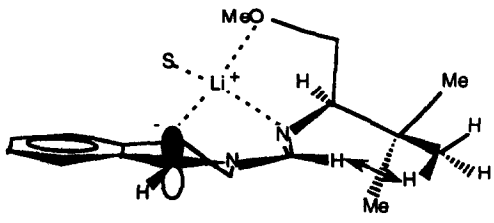
This experimental data, along with molecular mechanics computational data (Dreiding forcefield),[30] allows for a model depicting the process to be presented. In Scheme 25, two of the most populated conformations for the lithio anion in the **first alkylation** are shown as Cα and Cβ; the chelate on the α-face and the chelate on the β-face respectively. Molecular mechanics indicate that Cα is more stable than Cβ by 2.3 kcal/mole due to repulsive steric interaction between the vinyl H and the methyl-H of the t-butyl group. Also, when the t-butyl group on the chiral auxiliary is replaced by methyl (as in the left hand table, Scheme 24), the repulsive interaction still exists (ca 2-2.4 kcal) such that Cα continues to be favored. This is consistent with the experimental results stated earlier which indicated that changing the size of the R group has relatively little effect on stereoselectivity. In the second alkylation, where the hydrogen at the carbanionic center is replaced by a methyl group, Cα is destabilized by >2 kcal/mole bringing both conformation (Cα and Cβ) to approximately the same energy. This is seen as a result of repulsive interaction between the methyl group and the methyl of the tert-butyl group. The repulsion in Cβ as seen in the first alkylation is still present during the second alkylation. Although the experimental results show that α-alkylation in the latter is the dominant route taken, the computational data seem to underestimate the relative stabilities of Cα and Cβ. The poorer selectivity (80-85% de), in the second alkylation require an energy difference of ca 1 kcal/mole, a value that is below the meaningful limits of the computational system.

**First Alkylation**



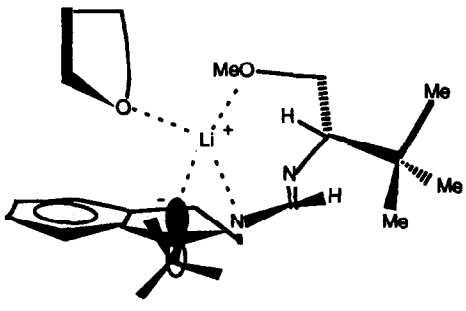

$C_\alpha$

$\Delta E = 2.3$ kcal/mol



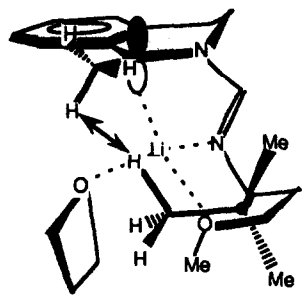

$C_\beta$

**Second Alkylation**




$C_\beta$

$\Delta E \cong 0$




$C_\alpha$

Scheme 25

In summary, the asymmetric synthesis using chiral formamidines has in recent years continued to demonstrate their value and also provide some intriguing mechanistic behavior. Further studies are continuing in this area and only time will tell if additional useful chemistry will be forthcoming.

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