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Lewis acid complexed azacarbanions: Novel reactive intermediates of wide synthetic utility

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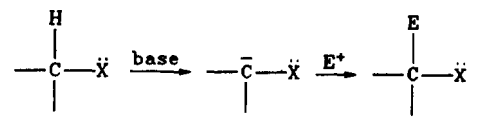
Abstract. The concept of facilitating α-deprotonation of tertiary amines by complexation with Lewis acids is described. Treatment of BF_3- amine complexes with strong bases resulted in deprotonation at benzylic, allylic, vinylic, α-pyridyl and unactivated primary or secondary carbons. Reaction with electrophiles afforded easy access to compounds with isoquinoline, morphinane and quinuclidine frameworks.

The present work was initiated to meet a specific gap in heteroatom stabilized carbanion chemistry, i.e. a viable methodology for α-deprotonation of tertiary amines(1). Reaction of heteroatom stabilized carbanions with electrophiles has been extensively used in organic syntheses for regioselective formation of new carbon-carbon bonds. Unlike S, P, O, B etc., this procedure presents difficulties with N which does not appreciably stabilize an adjoining negative charge [Scheme 1].

SCHEME 1



P, S, O, Halogens, B, Si increase C–H acidity
N is an exception

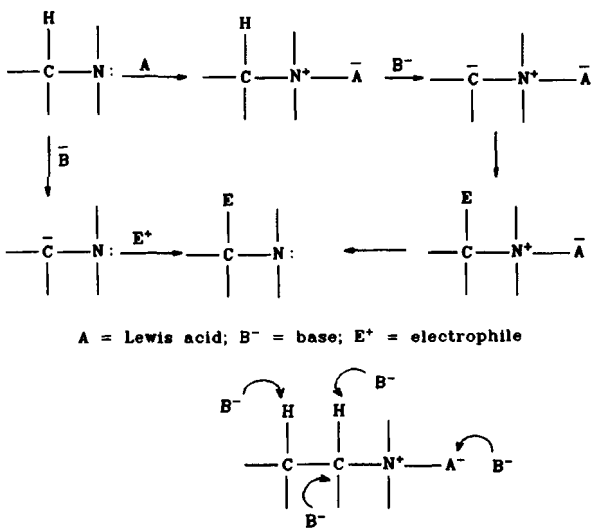
Another complication with amines is that the counterion of the base used for α-deprotonation can form cyclic chelates leading to increased thermodynamic or kinetic acidity at non-adjacent sites. The general problem can be overcome in case of primary and secondary amines by attaching to the nitrogen atom an activating/protecting group which stabilizes an α-carbanion. Many such groups have been introduced over the last two decades(1). In contrast very little progress has been made for tertiary amines where, in absence of a labile hydrogen, the scope for attaching an activating group is limited. Quaternization of nitrogen is not helpful due to ingression of Hoffmann elimination(2). N-Oxides have proved useful in quinuclidine elaboration but this method also fails if nitrogen is not located on a bridge-head, again due to a rapid elimination(3). In face of this situation some circuitous methods have been developed to access tertiary azacarbanions(1).

Our approach to the problem was simple. It was envisaged that the dipole generated on complexing an amine with a Lewis acid may promote α-deprotonation. After reaction with the electrophile, the

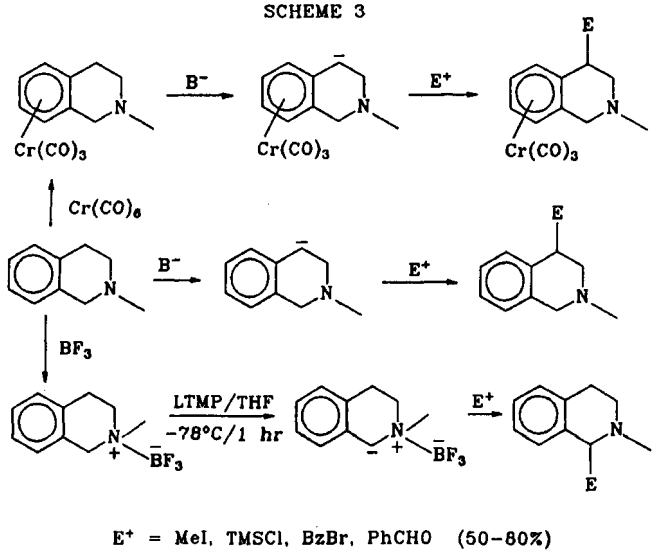
complex could be expected to break up during aqueous work up (Scheme 2). The whole sequence could be carried out in one pot, and the prospect of avoiding covalent attachment-detachment steps of conventional approaches was very appealing. The concept may sound a bit fanciful in view of the expected reaction of the Lewis acid with the deprotonating base. In fact, besides the target α-proton there are three other competing sites(Scheme 2). Some differentiation amongst these could, perhaps, be introduced in terms of hardness-softness or steric mismatch(4).

The idea was tested with N-methyl-tetrahydroisoquinoline which is a classic example of the difficulties encountered in α-deprotonation. Its treatment with butyllithium results in deprotonation at the benzylic position away from nitrogen. This trend persists in its chromium carbonyl complex(5). However, addition of an equivalent of BF_3-etherate, before exposure to base, caused a dramatic reversal of deprotonation selectivity. Reaction with various electrophiles afforded 1-substituted products in good yield(1)[Scheme 3].

SCHEME 2



SCHEME 3

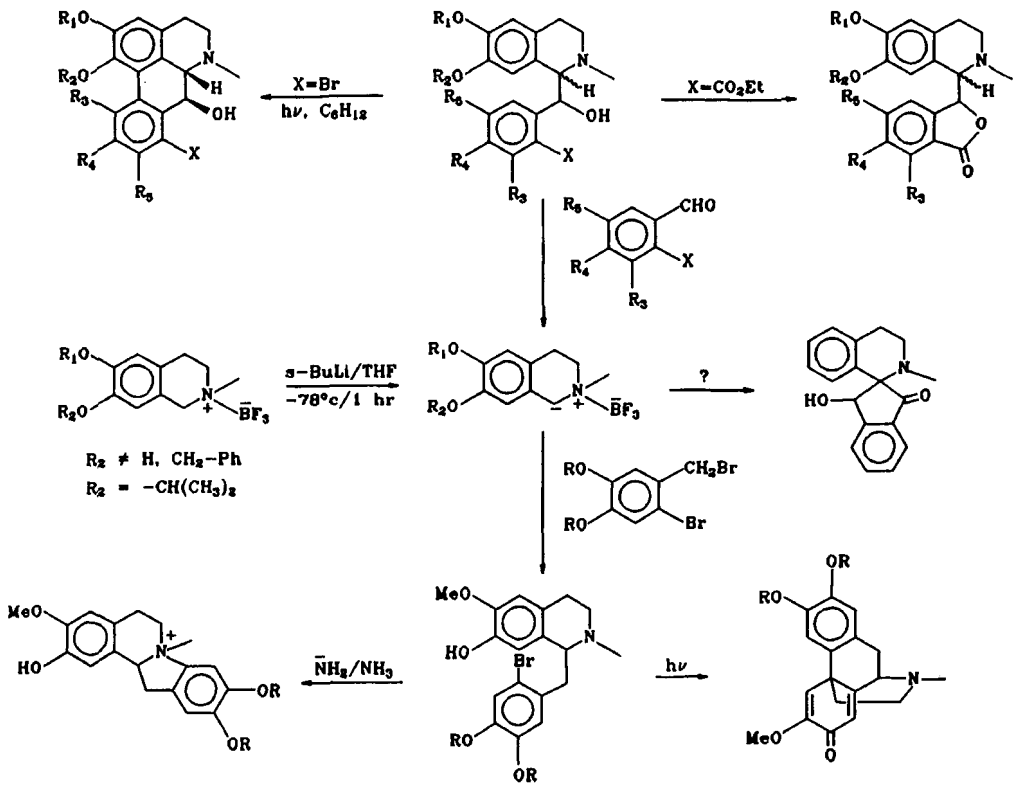


The above mentioned results opened up easy routes to a variety of alkaloids, using cylcization procedures developed earlier by us and others(6)[Scheme 4]. Only two points need to be mentioned: a) alkoxy substituents depress acidity of benzylic protons and a stronger base is needed, b) isopropyl protection of phenolic function is necessary as the conventional benzyloxy group introduces a competing acidic site.

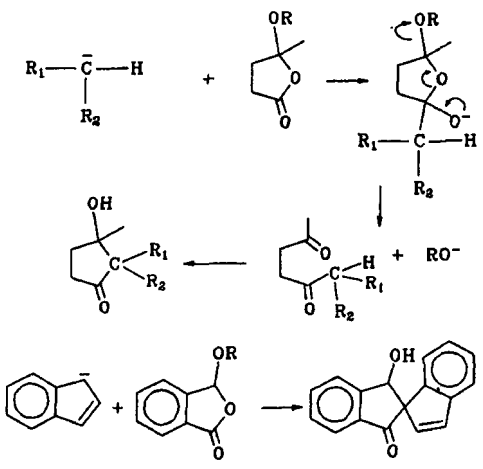
A more challenging task was synthesis of spiroalkaloids as no method was available for construction of a functionalized cyclopentane ring from a carbanion in one step. We introduced γ-alkoxy lactones as a four carbon building block for this purpose. This synthon has a protected carbonyl end and an open carboxylic end. Addition to the open terminus can trigger deprotection of the other and set it up for aldol cyclization (Scheme 5). The reaction of indenyl lithium with ethoxyphthalide indeed gave a mixture of isomeric alcohols which on PCC oxidation afforded fredericamycin A core diketone(7).

The phthalide B, needed for the synthesis of spiro alkaloids was secured from easily accessible aldehyde A. Its reaction with the carbanion gave a mixture of isomeric hydroxy ketones equilibrating to the more

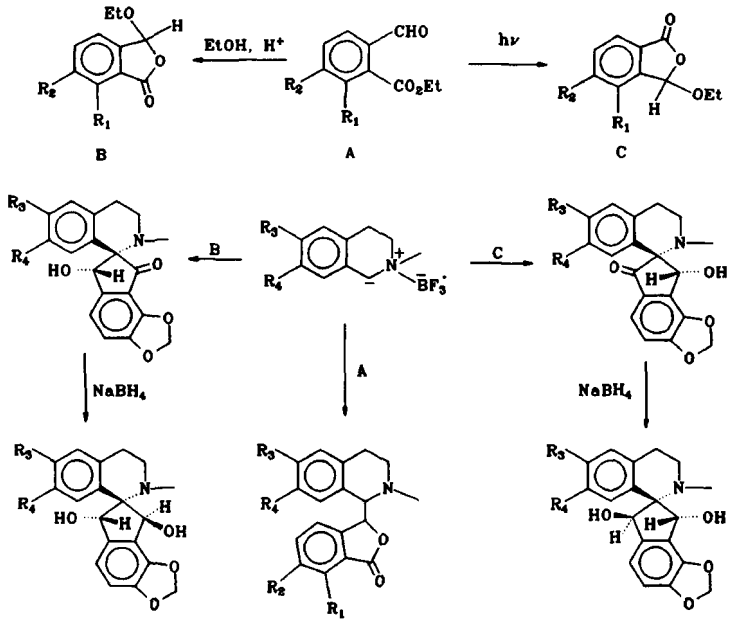
SCHEME 4



SCHEME 5



SCHEME 6

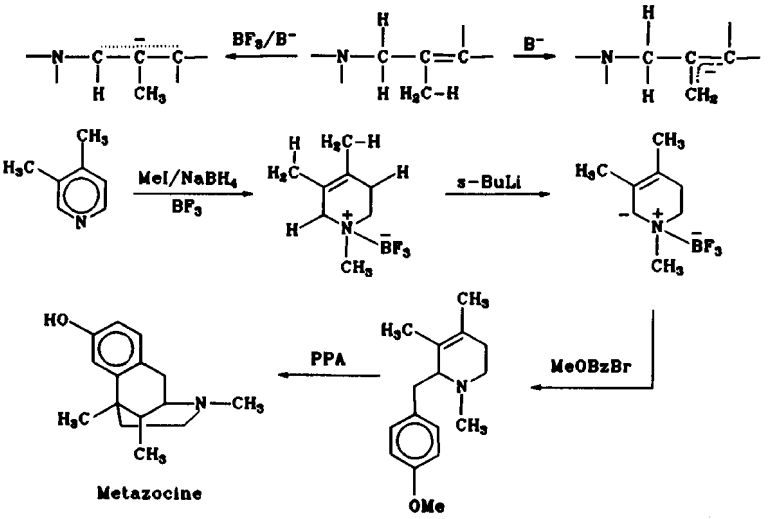


stable hydrogen bonded isomer. The reduction with sodium borohydride occurred exclusively from the less hindered face. To access compounds with the opposite stereochemistry, advantage was taken of a photorearrangement of A to phthalide C in which the original oxidation levels are reversed(7)[Scheme 6].

It was of interest to see if the normally observed regioselectivity in deprotonation of allylic amines can be reversed. In our synthesis of metazocine(1), the key intermediate had four allylic protons, out of which the two methyl protons were intrinsically more acidic. Yet, we were able to direct metallation to the site

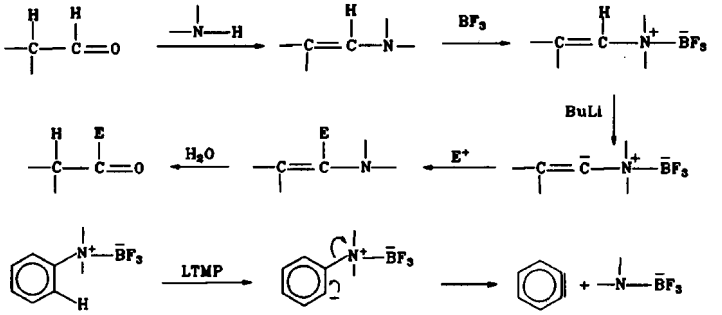
α to nitrogen by BF_3 complexation. The drug dextrophan could be similarly obtained from isoquinoline in four steps only[Scheme 7].

SCHEME 7



Deprotonation of vinyl and aryl carbons using BF_3 complexation is shown in Scheme 8. These sequences amount to an acyl anion equivalent and a method for aryne formation.

SCHEME 8



BF_3 complexation idea proved very useful in α metallation of pyridines, a well known problem of heterocyclic chemistry. Although some direct and indirect procedures for effecting this metallation are known, the present procedure is the method of choice in terms of ease and versatility(8)[Scheme 9].

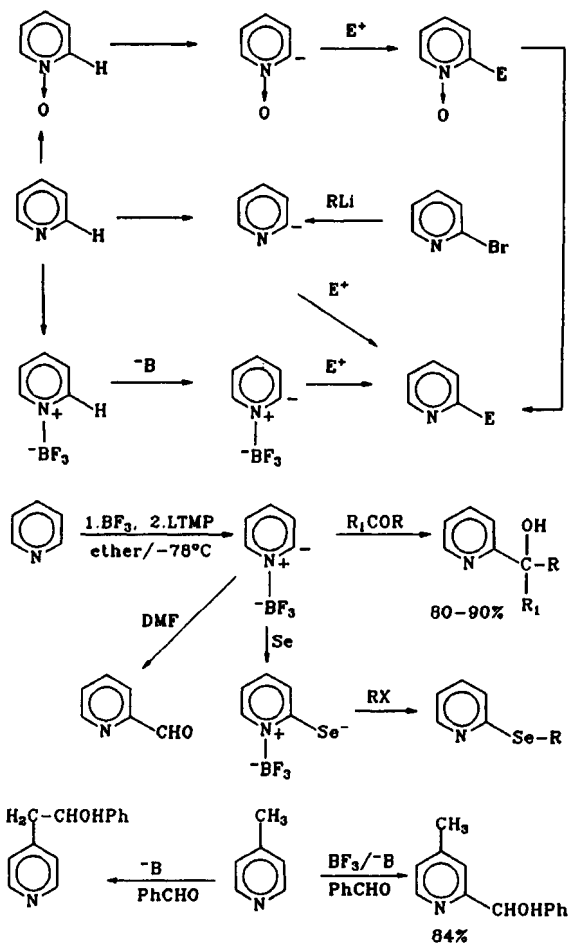
Deprotonation of unactivated methyl groups α to nitrogen was found to proceed smoothly after BF_3 complex formation, under conditions in which there was no reaction otherwise(9)[Scheme 10].

Finally, amines with unactivated secondary carbons were investigated, as ring deprotonation has been considered to be a severe test of any methodology. A stronger base was required for this purpose and our results are shown in Scheme 11. Extension to quinuclidine and DABCO was also possible, opening up easy access to quinine type alkaloids, antiarrhythmic agents and new chelating compounds of interest in asymmetric synthesis(10).

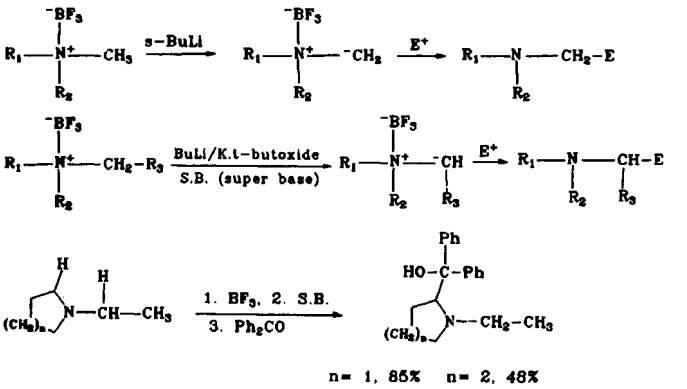
In Scheme 12 are shown various types of electrophiles which have been successfully reacted with azacarbanions.

Some work on enantioselective deprotonation, comparison of BF_3 with other Lewis acids, detailed structure of intermediates formed and delineation of the reasons for the success of this approach has also been undertaken.

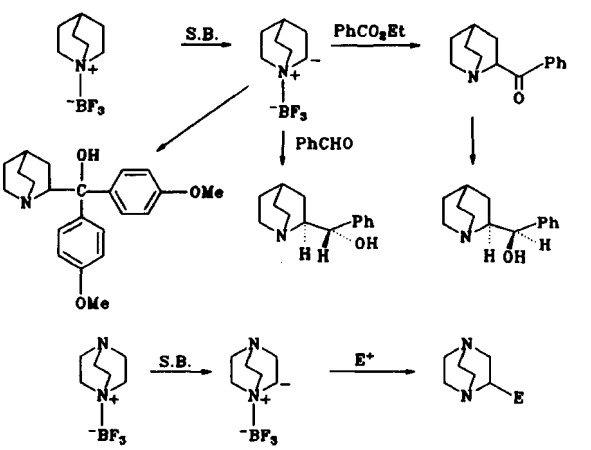
SCHEME 9



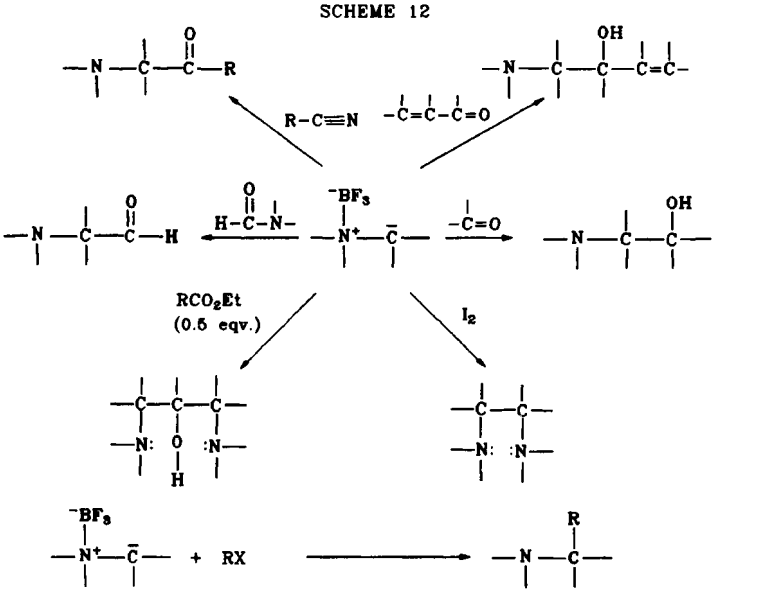
SCHEME 10



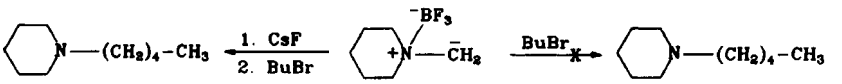
SCHEME 11



SCHEME 12



RX= MeI, BzBr, TMSCl, Ph-S-S-Ph, Ph-Se-Se-Ph



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