New Synthetic Methodology *en route* to Asymmetric Piperidine Alkaloids

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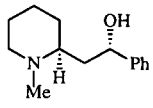
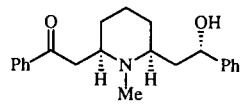
Sedamine **1** and Lobeline **2** are members of a large and variable group of alkaloids found particularly in the *Lobelia* and *Sedum* species [1]. They have particularly useful biological properties, cognition enhancement having been long recognized. For example, Appalachian Lobelia (also known as Indian tobacco) was known to American Indians and smoked for just such a purpose. As part of a program aimed at synthesizing the whole range of alkaloidal types in this group and testing them as potential anti-Alzheimer agents, we have investigated practicable approaches to all the series. Thus, we required a general method for piperidines with one or two arms (2- or 2,6-), *cis* or *trans* disposed, all types of terminal groups (R, R' = various alkyl, phenyl and ethoxyl, symmetrically or unsymmetrically disposed) and all combinations of oxidation levels in the arms. Additional double bonds or hydroxyl groups in the ring, and in particular, all aspects of chirality, were targeted as synthetic goals (**3**).



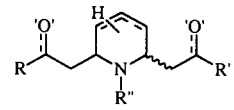
Sedamine

1



Lobeline

2



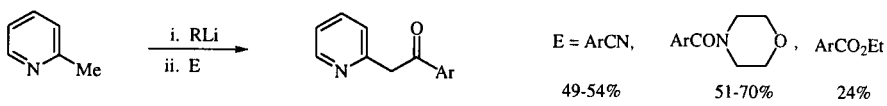
3

Several syntheses of both racemic [2] and enantiomeric [3] sedamine have appeared in the literature, but mostly using lengthy and impractical routes. Also a few syntheses of lobeline analogues (but *not* of lobeline itself), one featuring enantio-selection, have also appeared [4]. We chose to use pyridines as the starting point. The synthesis of 2-phenacylpyridines and analogous structures with aliphatic side-arms has been approached in the literature by metalation of α-picoline followed by treatment with, for example, a benzonitrile [5a] or benzoate ester [5b], yields of the products being moderate to good. We first studied the scope of this reaction, including the use of benzoylmorpholides (Scheme 1). The reaction proved reasonable for the 2-phenacyl derivatives but was not effective for 2,6-diphenacyl analogues despite numerous different approaches such as sequential metalation/quenching cycles. Presumably the second metalation could occur at the same site as the first to give mixtures.

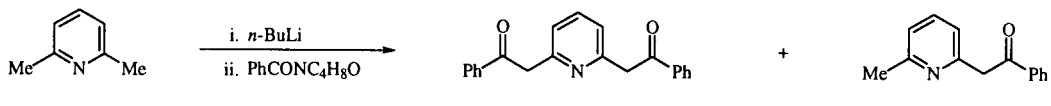
Seeking for a superior method we next explored a new protocol, utilizing the known reactivity of Vilsmeier reagents with enamines as the model [6]. 2-Halopyridinium and 2,6-dihalopyridinium salts may be viewed as 'pseudo-Vilsmeier reagents' (Scheme 2). As such they should react with enamines. Indeed, this was found to be an effective process. 2-Fluoro- and 2-chloropyridine were readily quaternized while 2,6-difluoro- and 2,6-dichloropyridine required methyl triflate for quarernization, all the reactions proceeding in almost quantitative yield (Scheme 2) and being able to be conducted *in situ*. Treatment of the fluoro-salts with acetophenone enamine (either morpholine or pyrrolidine enamine, the latter being more reactive) proceeded smoothly to yield the mono- or diphenacylpyridinium salts, best isolated as hexafluorophosphates. Alternatively, the enaminopyridinium salts could be reduced with sodium borohydride to give the tetrahydropyridines.

The phenacylpyridiniums were efficiently demethylated using the highly effective new method [7] of brief heating

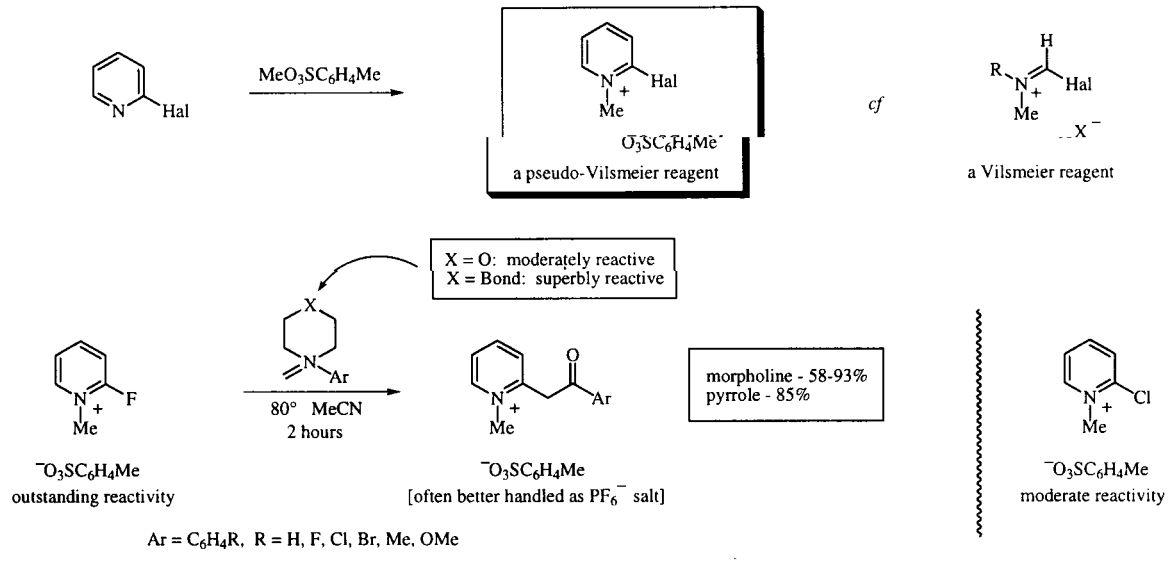
Scheme 1



Ar = *o*, *m*, and *p*-halo, methyl, methoxy

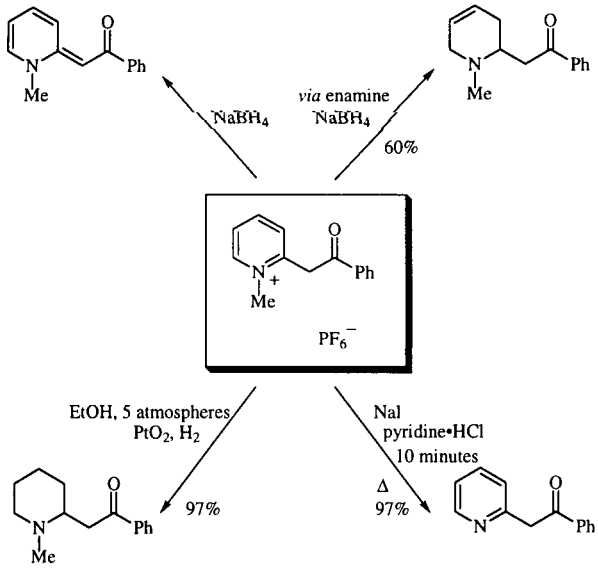


Scheme 2



in refluxing pyridinium chloride (4:1 molar ratio) to give the pyridines or could be easily hydrogenated using platinum oxide and hydrogen to give racemic sedaminone or lobelanine (Scheme 3). The corresponding chloropyridinium salts were much less reactive and required a base to optimize yields. In a similar way a range of enamines were utilized to give a variety of analogous and useful intermediates. Thus, acetone enamines were effective, but other nonsymmetrical ketone derivatives were problematic since mixtures were likely. To overcome this problem we utilized the highly useful and easily made 1,1-dimorpholinoethene [8], which on workup yielded pyridylmorpholides. This amide reacted effciently with organolithiums to give another range of sedaminone analogues (Scheme 4).

Scheme 3

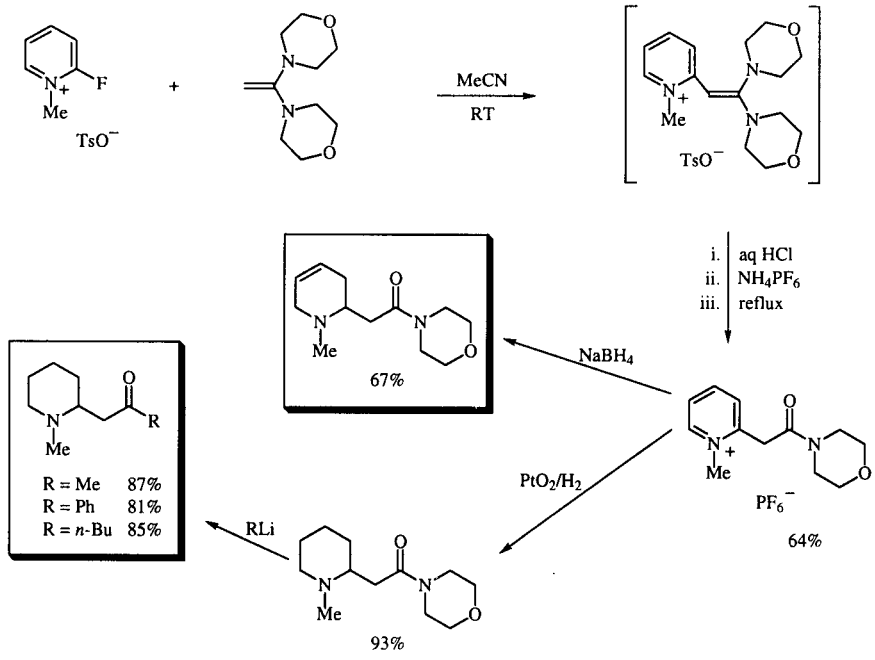


The corresponding formation of symmetrically and unsymmetrically substituted 2,6-pyridyl derivatives is illustrated in Scheme 5, which underlines the remarkable versatility of this approach. Efficient one-pot stepwise substitution proceeds cleanly.

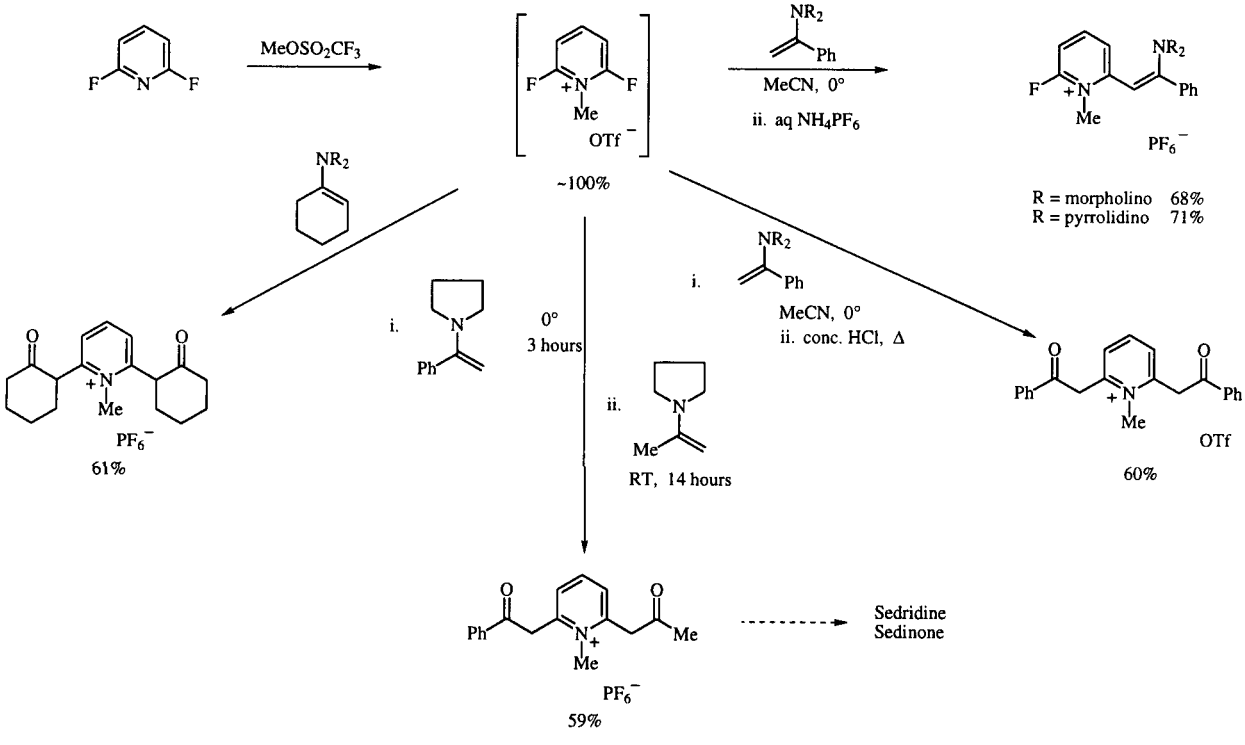
The major remaining challenge, now having to hand an excellent route to all kinds of versatile pyridine and piperidine precursors to the target alkaloids was the introduction of enantio-selection. We have tackled this problem in two novel ways. The first is illustrated in Scheme 6 and involves kinetic resolution of the derived acetates utilizing a lipase. This method may be applied to both pyridyl and piperidinyl derivatives and proceeds with high enantio-selection. Both the [*R*]- and [*S*]-2-pyridyl-1-phenylethanols were readily hydrogenated to give the easily separated corresponding (+)- and (-)-norsedamine and norallosedamine (70:30), respectively, and these products converted efficiently into (+)- and (-)-sedamine and allosedamine with formaldehyde and sodium cyanoborohydride (Scheme 7) [9].

We also examined a catalytic reduction that would allow total conversion of keto precursors into the corresponding enantiomeric alcohols. Although Bakers' yeast, *B*-chlorodiisopinocampheylborane (DIP-chloride) and various Noyori-type catalysts were not very effective, we envisaged the use of an enantiomerically pure Lewis acid might complex with the ketopyridine (or ketopiperidine) ligand, thereby introducing facial selection into the subsequent reduction. After much work this process proved remarkably effective, as illustrated in Scheme 8. The

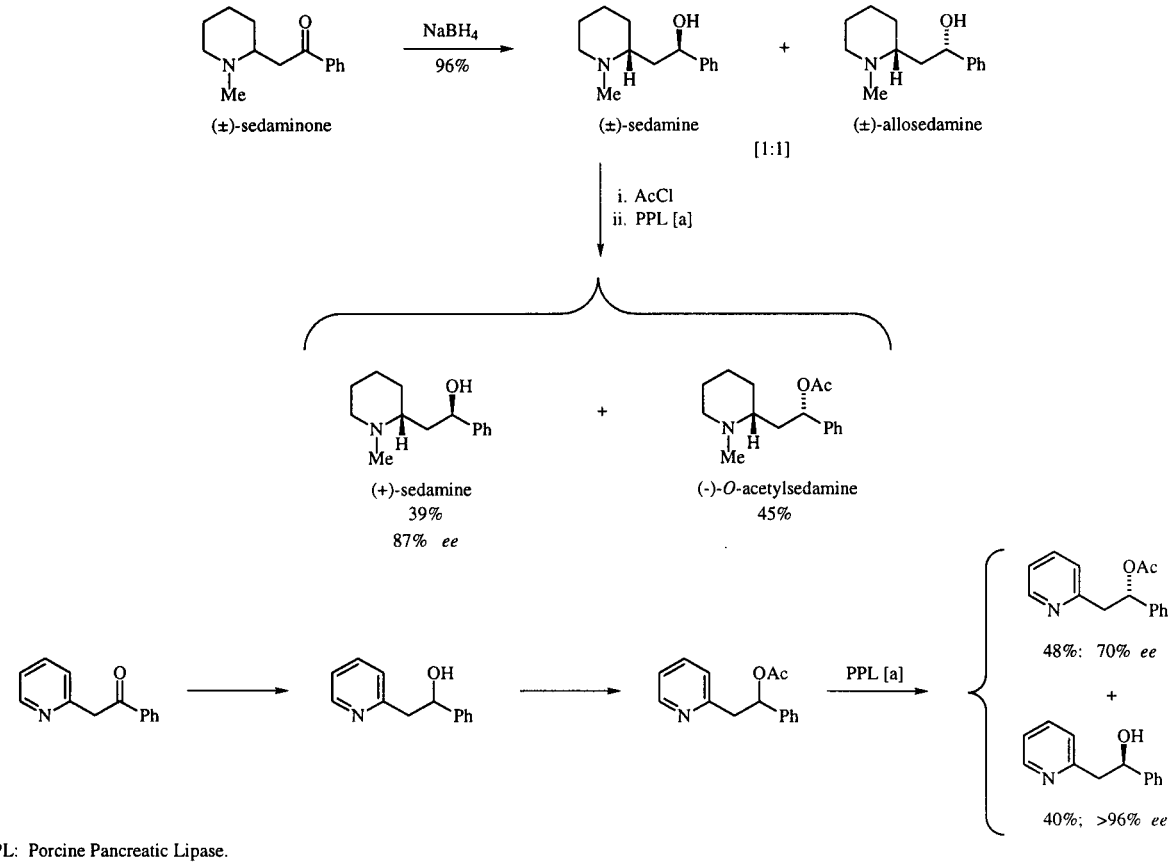
Scheme 4



Scheme 5

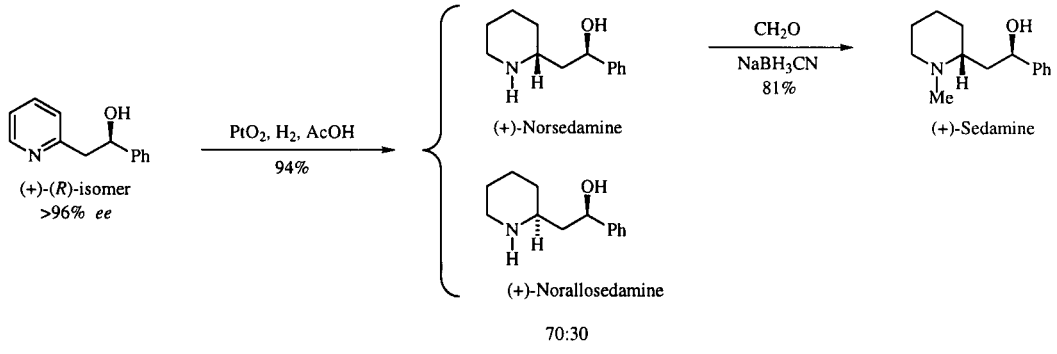


Scheme 6



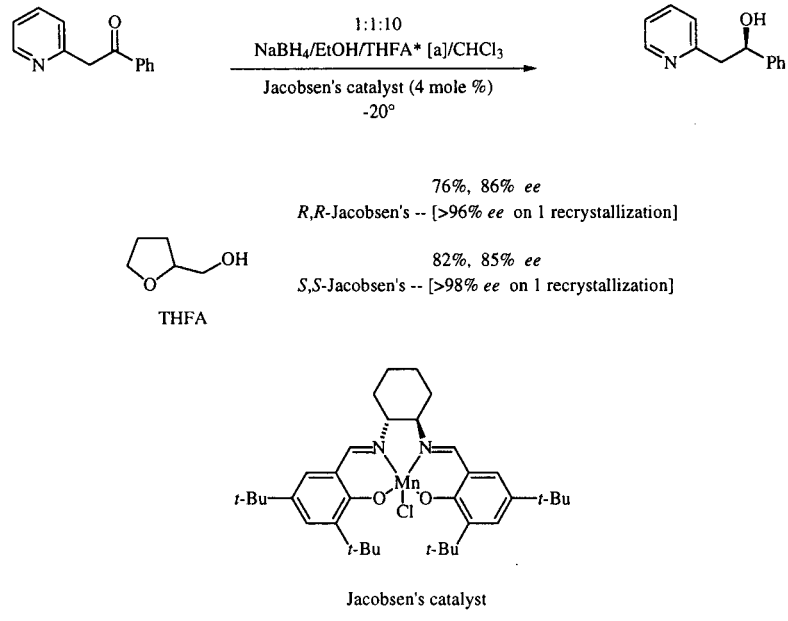
[a] PPL: Porcine Pancreatic Lipase.

Scheme 7



Also repeated for (-)-(S)-isomer (>98% *ee*)

Scheme 8

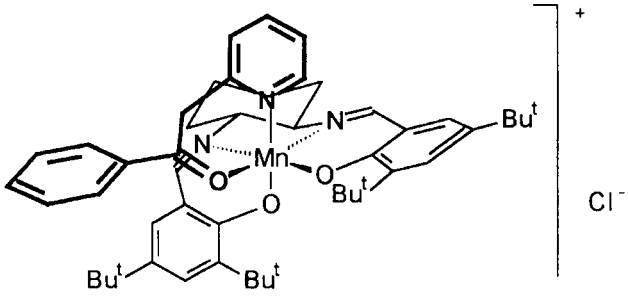


Jacobsen's catalyst

[a] THFA: Tetrahydrofurfuryl Alcohol.

method required Mukaiyama's 'modified' (chloroform soluble) sodium borohydride, and Jacobsen's manganese catalyst at 4 mole% loading. A possible mechanism for the complexation is illustrated in Scheme 9.

Scheme 9



The full exploitation of this methodology awaits further work, particularly the synthesis of the 'two-armed' series.

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