Asymmetric Synthesis and Synthetic Utility of 2,3-Dihydro-4-pyridones

Daniel L. Comins

Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204 USA

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Dihydropyridones of the type **1** are versatile synthetic building blocks due to their facile preparation, the functionality present, their availability in either antipode, good air stability, and the ease of introducing ring substituents in a regio- and stereocontrolled manner. The utility of these heterocycles in alkaloid synthesis has been demonstrated in our laboratories and others. Short, stereocontrolled syntheses of piperidine, indolizidine, quinolizidine, and *cis*- and *trans*-decahydroquinoline alkaloids have been reported using 2,3-dihydro-4-pyridones as chiral building blocks [1].

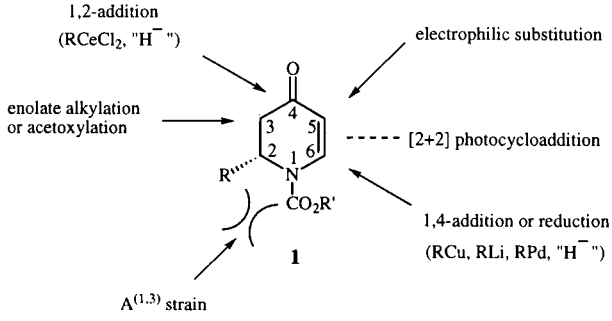


Figure 1. The Versatile *N*-Acyl-2,3-dihydro-4-pyridones.

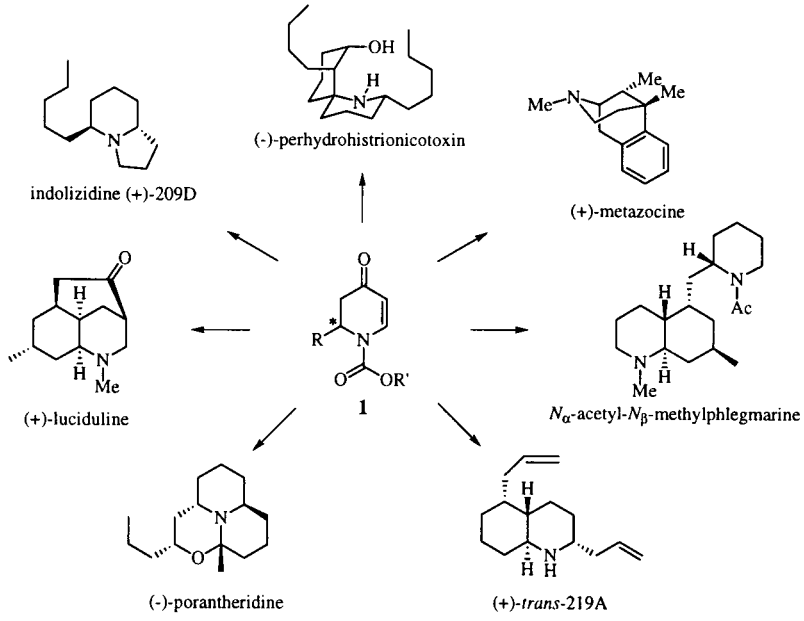
We have developed methods for preparing heterocycles **1** enantiopure *via* the addition of Grignard reagents or metallo enolates to chiral 1-acylpyridinium salts [2]. The synthetic potential of this asymmetric synthesis has been demonstrated by us in the enantioselective syntheses of several alkaloids such as those depicted in Scheme 1 [1a, 3].

Although the total synthesis of complex alkaloids using dihydropyridone intermediates is a major part of our research program, this lecture will mainly cover reactions of dihydropyridones and the preparation of small molecules.

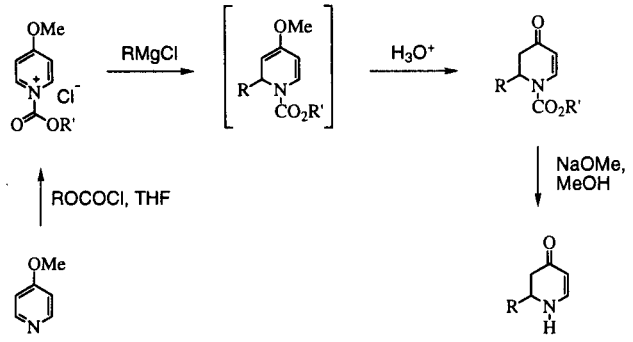
Several years ago we reported that the addition of Grignard reagents to 1-acyl-4-methoxypyridinium salts gives racemic dihydropyridones, *i.e.* **1**, on workup with aqueous acid (Scheme 2) [4]. Although we explored some of the chemistry of these unique heterocycles, it was not until our development of a practical asymmetric route for their synthesis that an extensive program developed. Our asymmetric synthesis of dihydropyridones is shown in Scheme 3. The chiral pyridinium salt **2** is formed *in situ* from 4-methoxy-3-(triisopropylsilyl)pyridine and (-)- or (+)-*trans*-2-(α-cumyl)cyclohexyl chloroformate (TCC chloroformate) [5]. Addition of a Grignard reagent followed by aqueous workup provides dihydropyridones **3** with diastereoselectivities generally ranging from 85 to

Scheme 1

2,3-Dihydro-4-pyridones as Building Blocks for Alkaloid Synthesis



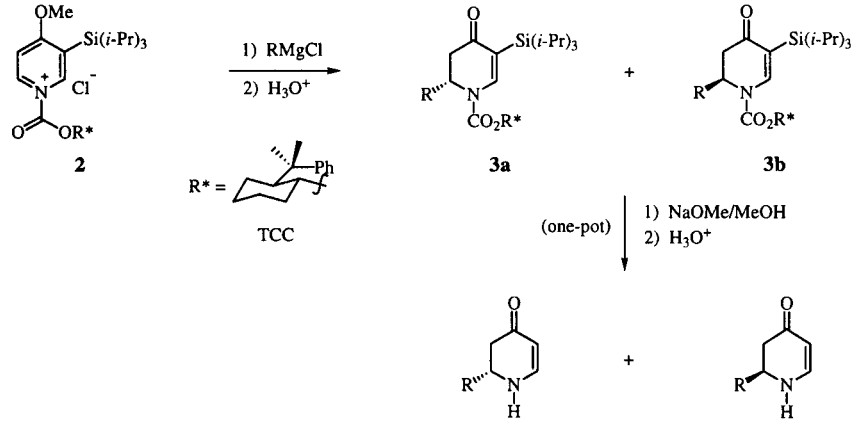
Scheme 2
Synthesis of Racemic 2,3-Dihydro-4-pyridones



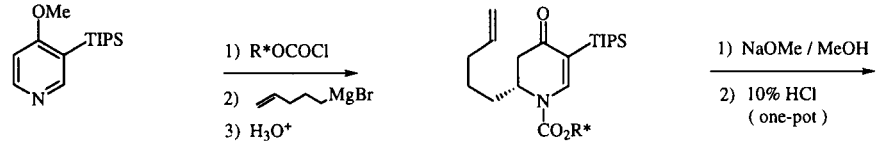
95%. Purification by recrystallization or chromatography gives the major diastereomer as an air stable white solid. In most cases, it is desireable to remove and recover the chiral auxiliary, cleave the triisopropylsilyl group, and reprotect the nitrogen as a carbamate. A typical sequence is depicted in Scheme 4. The enantiopure dihydropyridone building block **7** is prepared in high yield from pyridine **4** in three synthetic steps. The heterocycle **7** is a good example of a dihydropyridone building block for it contains useful functionality in the C-2 side-chain as well as in the ring.

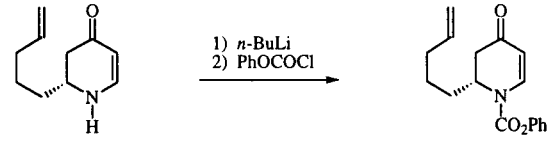
To enhance the versatility of dihydropyridones **1** as synthetic intermediates, we have developed methods to add substituents at various positions of the ring. The C-3 position can be alkylated *via* an enolate. The axial orientation

Scheme 3
Synthesis of Enantiopure 2,3-Dihydro-4-pyridones



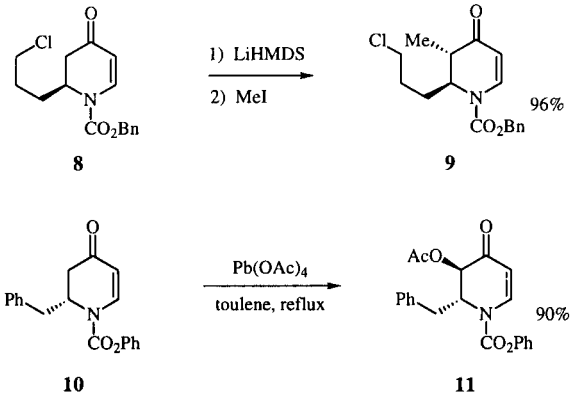
Scheme 4





of the C-2 substituent directs enolate alkylation at C-3 to occur from the axial direction providing *trans*-2,3-disubstituted products, *i.e.*, **9** (Scheme 5). A highly stereoselective acetoxylation at the C-3 position can be effected in high yield with lead tetraacetate in refluxing toluene (80-98%) [6]. A typical example (**10** → **11**) is shown in Scheme 5.

Scheme 5
Reactions at C3



8 **9** **10** **11**

In the presence of cerium chloride, alkyllithiums add to **1** at C-4 to give tertiary alcohols in high yield. The addition is highly stereoselective for the carbonyl face opposite the C-2 axial substituent. For example, dihydropyridone **12** and butyllithium/cerium chloride gives alcohol **13** in high yield [7] (Scheme 6). Alcohols of this type are acyliminium ion precursors which can be elaborated into more highly substituted piperidine derivatives [8]. If **13** is treated with bipyridinium chlorochromate (BPCC), an oxidative rearrangement occurs to give 5,6-dihydro-2-pyridone **14**. This conversion constitutes a new method for the preparation of synthetically useful enantiopure heterocycles like **14** [7].

Luche reduction of dihydropyridone **15** provides the C-4 alcohol **16**. This reaction is general for dihydropyridones of this type, and the equatorial alcohol is the major product. The resulting alcohol can be easily converted to an alkyl ether, *i.e.*, **17**, in high yield. Alcohols and ethers like **16** and **17** are useful acyliminium ion precursors [8].

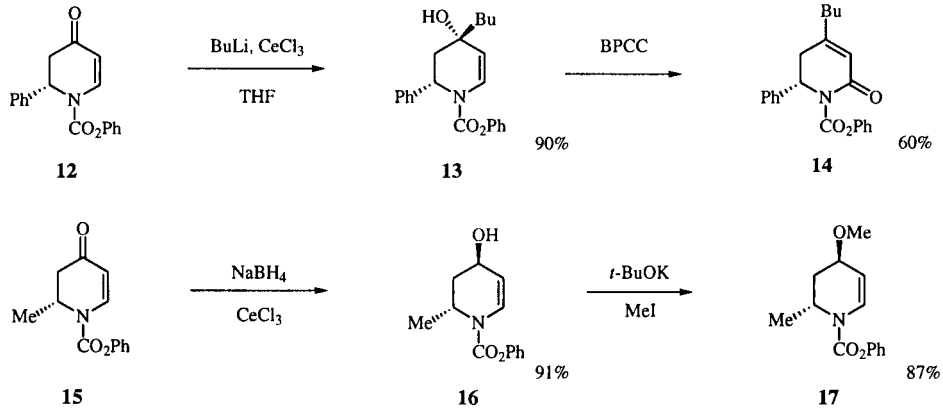
The C-5 position of dihydropyridones **1** can be substituted *via* the iodide. On treatment with *N*-iodosuccinimide, dihydropyridone **18** is converted to iodide **19** in high yield (Scheme 7). These vinyl iodides (**19**) are good substrates for transition metal catalyzed *ipso* substitution reactions. For example, **19** can be efficiently converted to alkyne **20** or C-5 ester **21** *via* palladium-catalyzed reactions [9].

A nucleophile can be added to the C-6 position of **1** *via* conjugate addition [1a]. In the presence of copper bromide and boron trifluoride etherate, Grignard reagent **22** adds to dihydropyridone **7** to provide the *cis*-2,6-disubstituted piperidone **23** (Scheme 8). Under these conditions the stereoselectivity is very high (>10:1). The 5,6-double bond of dihydropyridones **1** can be reduced in high yield with L-Selectride, K-Selectride, or zinc/acetic acid. Catalytic hydrogenation generally results in over reduction.

The C-6 position of **1** can be substituted by a two-step process. Conjugate addition of a Grignard reagent in the presence of chlorotrimethylsilane and copper bromide gives silyl enol ether **26** (Scheme 9). Crude **26** was treated with palladium acetate in acetonitrile to provide dihydropyridone **27** in high yield. This conversion is quite general and convenient [10]. Another method for preparing 2,6-disubstituted 2,3-dihydro-4-pyridones uses directed lithiation. Dihydropyridine **28** is converted to dihydropyridone **29** by C-6 lithiation with *n*-butyllithium followed by dimethyl disulfide and acidic workup [11].

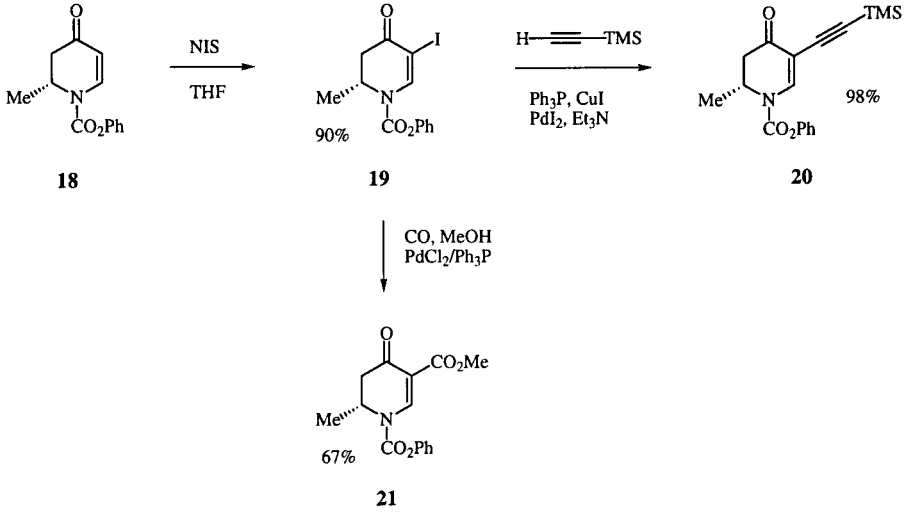
Recently, we investigated the Mukaiyama-Michael reaction of dihydropyridone **30** (Scheme 10). Ketene silyl

Scheme 6
Reactions at C4



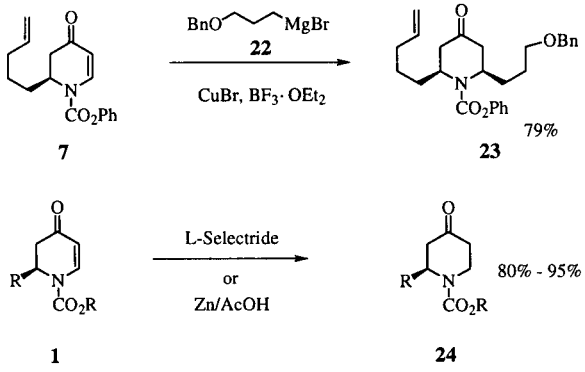
12 **13** **14** **15** **16** **17**

Scheme 7
Reactions at C5



18 19 20 21

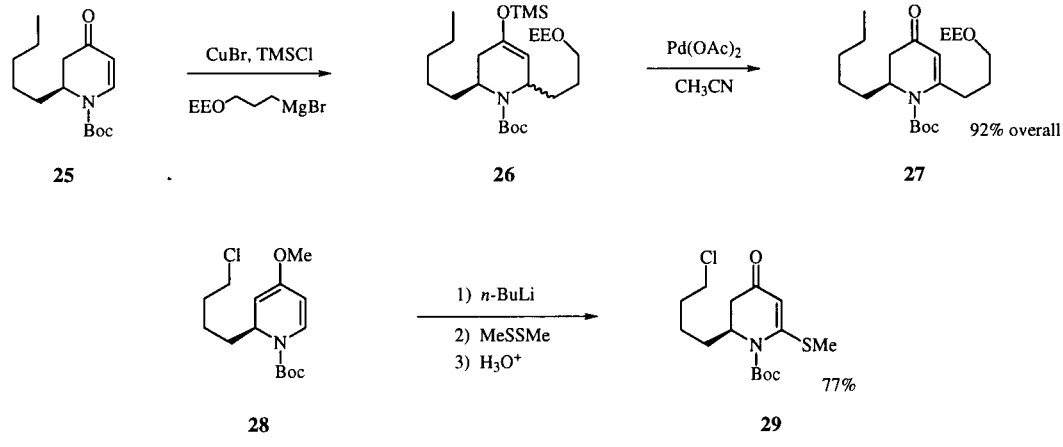
Scheme 8
Reactions at C6



7 23 1 24

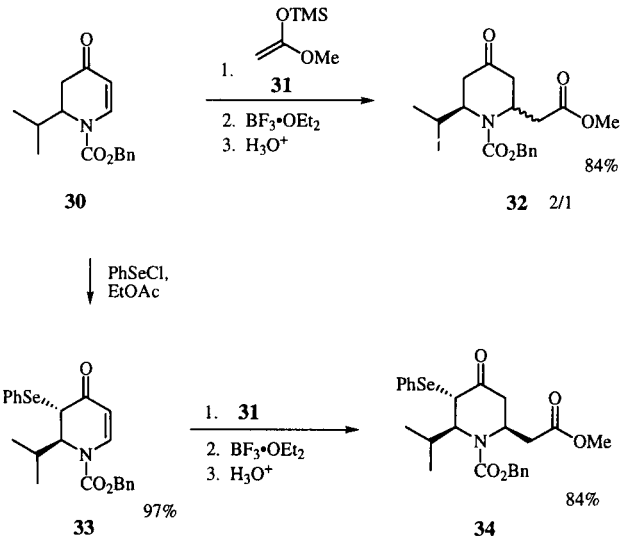
acetal **31** added to **30** in the presence of boron trifluoride etherate to give piperidones **32** as an inseparable 2/1 mixture of diastereomers. To circumvent the poor stereoselectivity, a removable group was introduced at the C-3 position. Dihydropyridone **30** was treated with phenylselenyl chloride to give **33** in near quantitative yield. The Mukaiyama-Michael reaction of **33** afforded piperidone **34** as the sole isolated product. The *cis*-C-2,6 stereochemistry was confirmed by free-radical reduction to provide *cis*-piperidone **35** in high yield (Scheme 11). The presence of the C-3 axial substituent rendered the reaction completely facial selective. This methodology was used in a regio- and stereoselective synthesis of *cis*-2,6-disubstituted 1,2,5,6-tetrahydropyridines. Piperidone **34** was reduced under Luche conditions to afford alcohols **36**,

Scheme 9
Reactions at C6 - cont.



25 26 27 28 29

Scheme 10
Mukaiyama-Michael Reactions

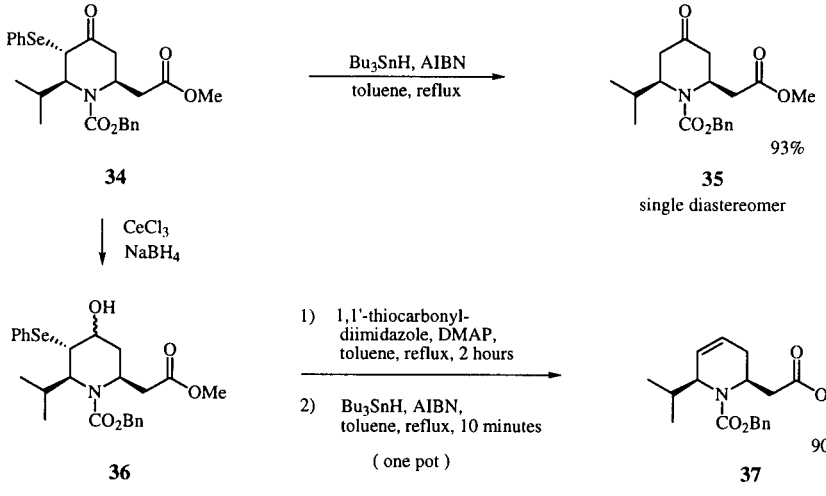


which were converted to tetrahydropyridine **37** by a one pot procedure. Conversion of **36** to the corresponding thiocarbamates *in situ*, followed by addition of tributyltin hydride and AIBN (cat.), provided a 90% yield of **37**.

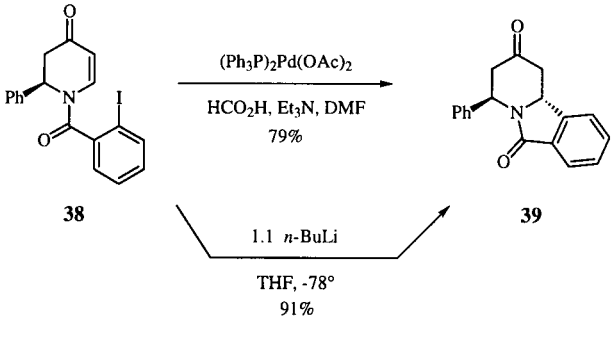
Addition reactions at C-6 can be carried out in an intramolecular fashion. Dihydropyridone **38** undergoes a stereoselective intramolecular Heck reaction to give tricyclic heterocycle **39** in good yield [13] (Scheme 12). Anionic cyclization of **38** also gives **39** stereoselectively in excellent yield [14]. This methodology was utilized in a five-step, asymmetric synthesis of indolizidine 209D (**42**) as shown in Scheme 13.

The 2,3-dihydro-4-pyridones are excellent substrates for [2+2] photocycloaddition reactions. We have been exploring intramolecular photochemical reactions of chiral dihydropyridones in the context of natural product synthesis. An interesting example is shown in Scheme 14. Dihydropyridone **43** on photolysis in acetone gives a high yield of cycloadduct **44** with good facial selectivity (> 7:1). Treatment of **44** with samarium iodide effects cyclobutane

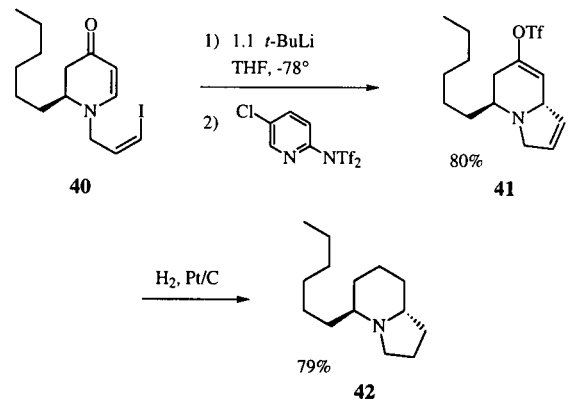
Scheme 11



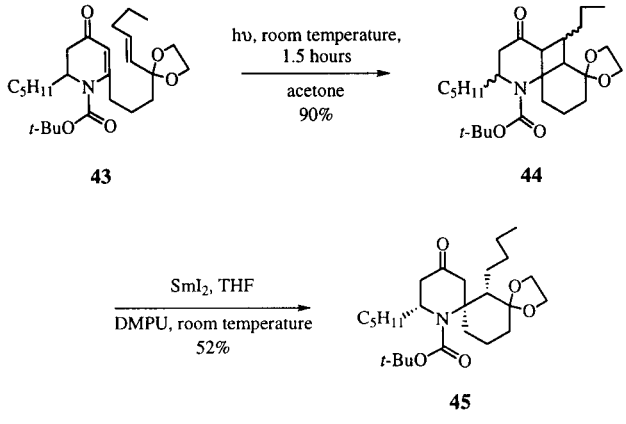
Scheme 12



Scheme 13



Scheme 14
Intramolecular [2 + 2] Photocycloaddition



43 44 45

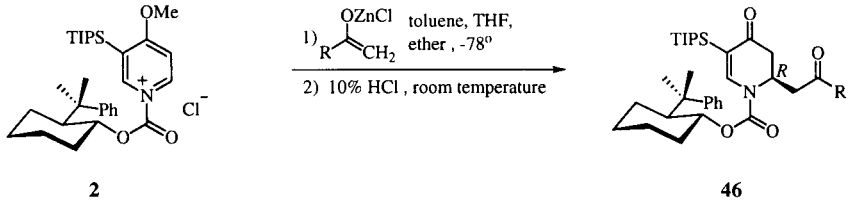
ring opening to afford spirocyclic ketone **45**. This methodology was utilized in our asymmetric synthesis of (-)-perhydrohistrionicotoxin [15].

The utility of heterocycles **1** as chiral building blocks prompted us to investigate their preparation with various functionality and stereocenters in the C-2 side chain. As shown in Scheme 15, zinc or magnesium enolates of methyl ketones add to chiral pyridinium salt **2** to provide 2-(2-oxoalkyl)-2,3-dihydro-4-pyridones in high yield and excellent stereoselectivity [16].

Prochiral metallo enolates of ketones and lactones add to **2** with a high degree of diastereoselectivity forming two new chiral centers in the process [17]. Several heterocycles containing two or three chiral centers and various functionality in the side chain have been prepared as shown in Schemes 16-20.

An α-hydroxyalkyl C-2 piperidine side chain is present in several biologically active alkaloids (Scheme 21). We have developed a stereocontrolled route to this type of piperidine unit using iodocarbocyclization reactions of dihydropyridone derivatives. This study has led to the enantioselective syntheses of the piperidine natural prod-

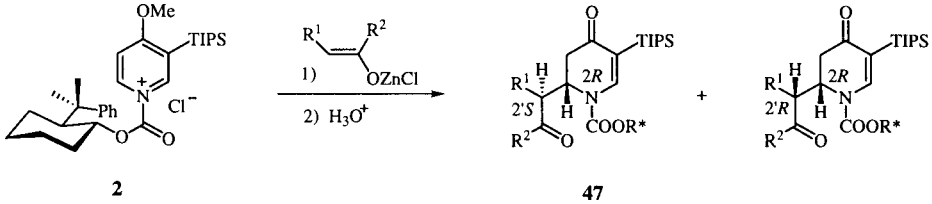
Scheme 15



2 46

Ketone	R	Yield, %	*de*, %
Acetone	Methyl	83	95
Acetophenone	Phenyl	86	92
2-Pentanone	*n*-Propyl	82	89
5-Hexen-2-one	4-Butenyl	80	94

Scheme 16
Addition of *E*-Enolates to Chiral 1-Acylpyridinium Salts

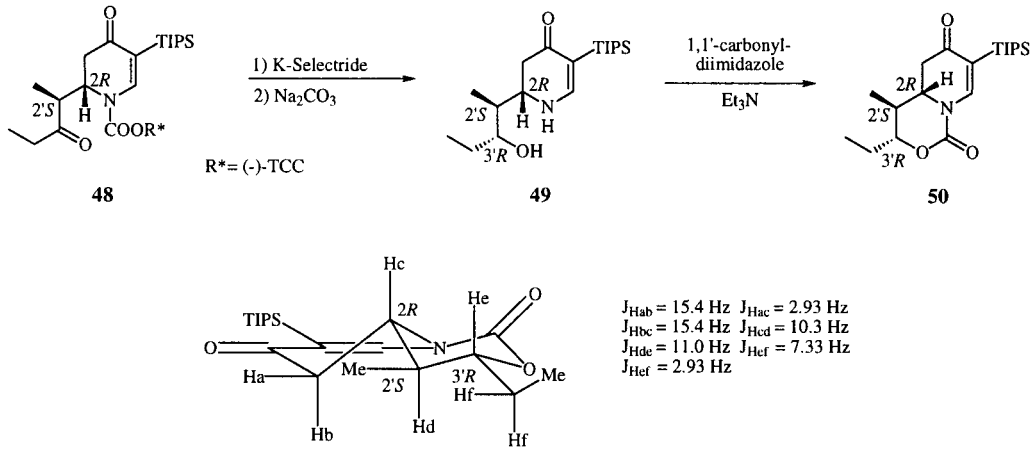


2 47

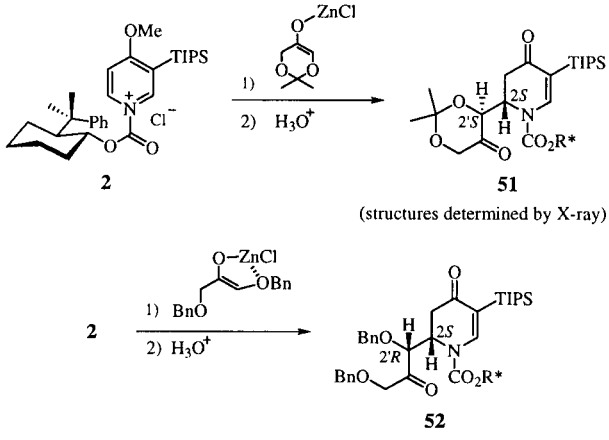
2*R*, 2'*S* (major) + 2*S*, 2'*R* + 2*S*, 2'*S* 2*R*, 2'*R*

R¹ R²	2*R*, 2'*S* (Major)		(2*S*, 2'*R* + 2*S*, 2'*S* 2*R*, 2'*R*)	Yield, % (Major)
—$CH_2CH_2CH_2$—	88	:	12	82
—$CH_2CH_2CH_2CH_2$—	86	:	14	79
Me Et	92	:	8	83

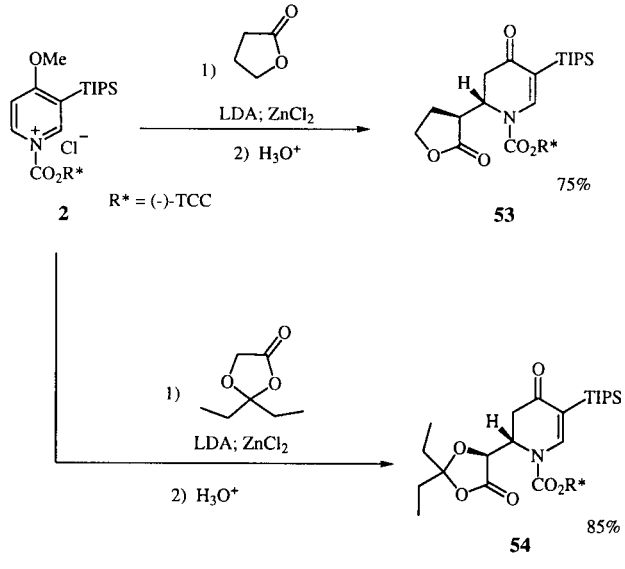
Scheme 17



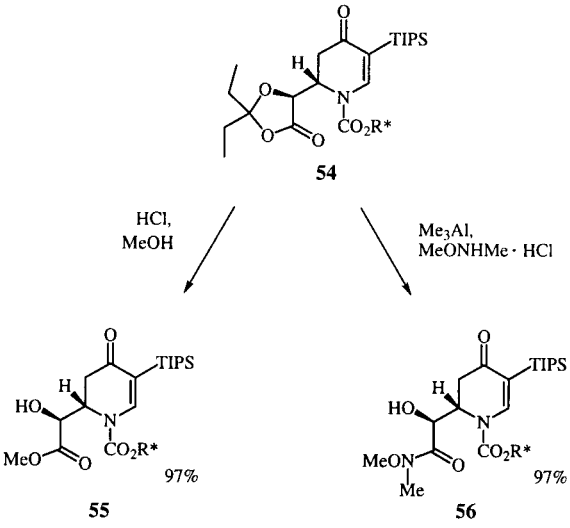
Scheme 18



Scheme 19



Scheme 20

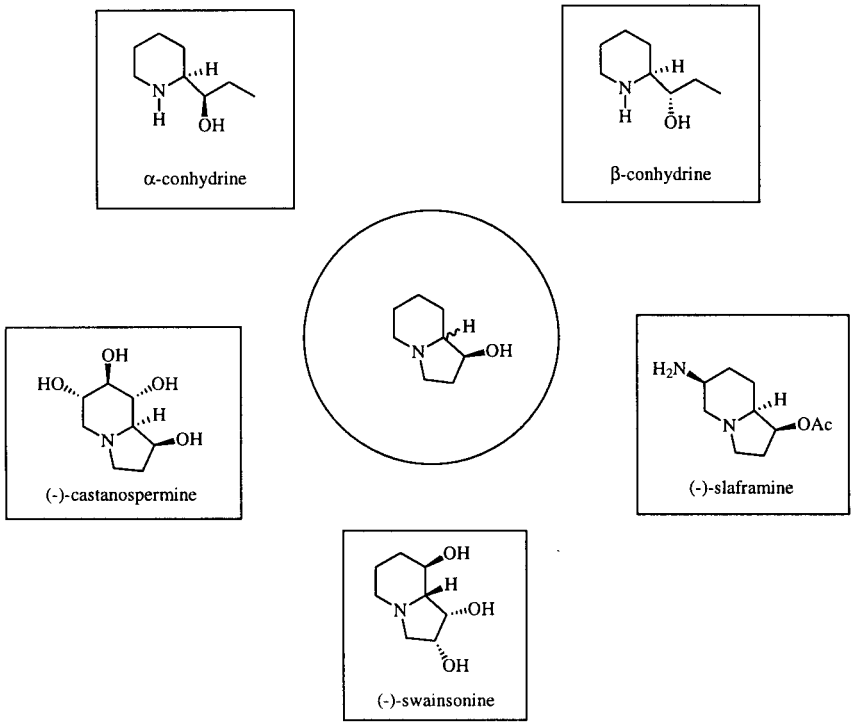


ucts, (+)-β-conhydrine (**60**) and (+)-α-conhydrine (**63**) (Schemes 22-23). The iodocarbocyclization reaction leading to enantiopure heterocycles **59** is completely stereoselective.

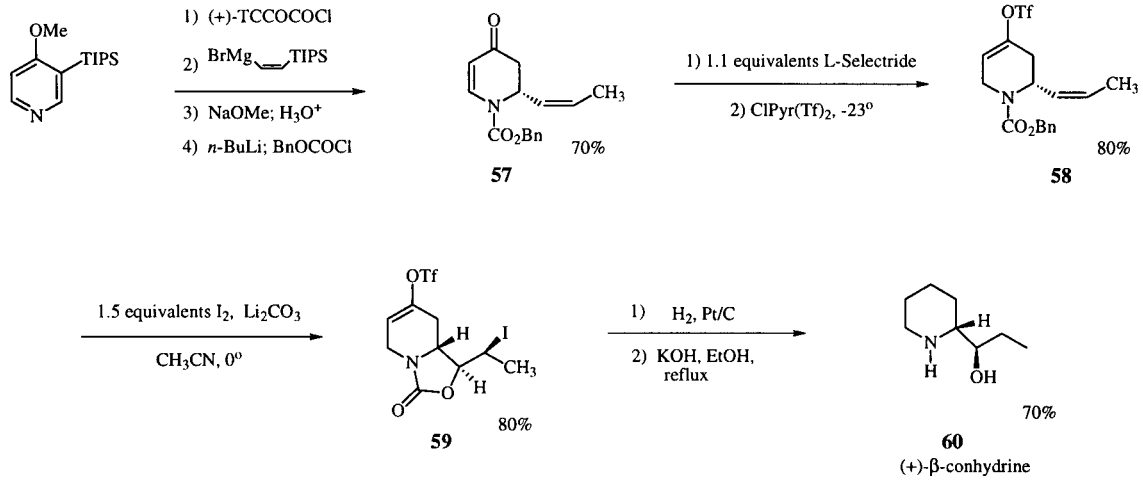
Using a similar strategy, an approach to slaframine (**64**) was investigated. The intermediate **69** was prepared stereoselectively and in good overall yield using a phenylselenyl chloride induced carbocyclization as a key step. This cyclization was also completely stereoselective (Scheme 24).

In summary, *N*-acyl-2,3-dihydro-4-pyridones **1** are versatile building blocks for asymmetric synthesis. Given the abundance of piperidine-containing natural products and biologically active compounds, the development of a general method to prepare enantiopure substituted piperidines is of considerable significance. The enantiopure heterocy-

Scheme 21



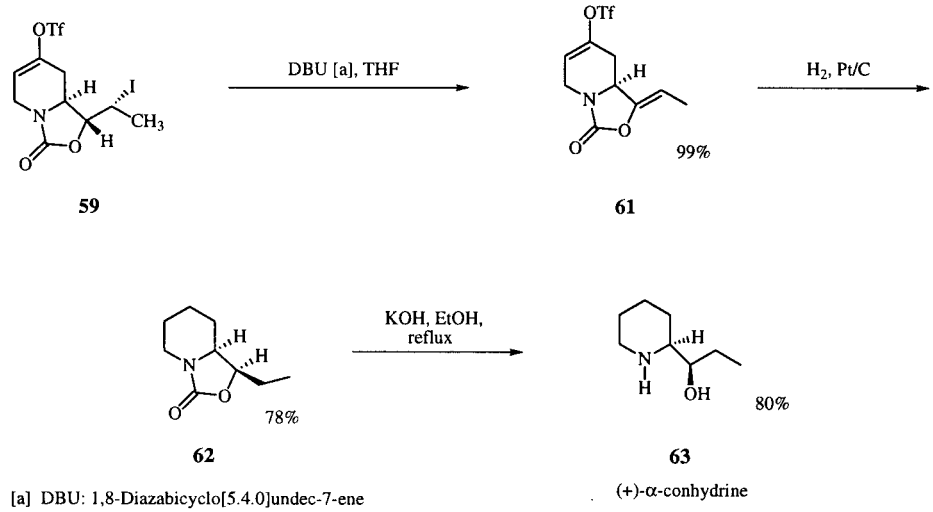
Scheme 22
Synthesis of (+)-β-Conhydrine
via Iodocyclocarbamation



cles **1** and their derivatives have the potential to be used as precursors to indolizidines, quinolizidines, perhydroquinolines, various substituted piperidines, indole alkaloids, pipecolic acids, benzomorphans, peptide mimics, scaffolds for combinatorial chemistry, and ligands for asymmetric reactions. The considerable synthetic utility of these heterocycles prompt us to continue studying their asymmetric synthesis and to develop new, concise strategies for their use as intermediates for the enantioselective preparation of alkaloids and biologically active compounds.

Scheme 23

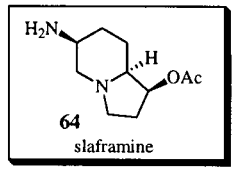
Synthesis of (+)-α-Conhydrine
via Iodocyclocarbamation

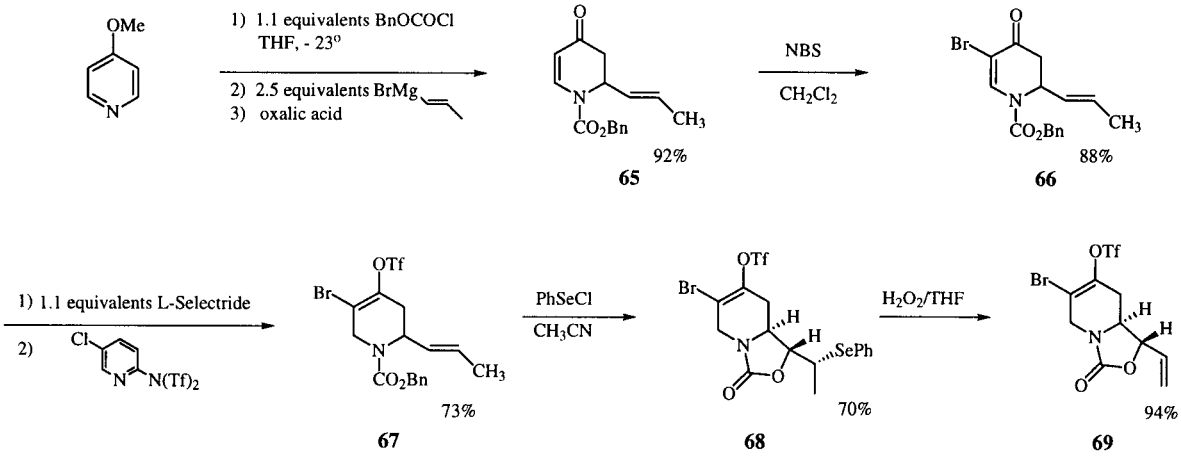


[a] DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

Scheme 24

Progress Towards Slaframine





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