The Addition of Metallo Enolates to Chiral 1-Acylpyridinium Salts. An Asymmetric Synthesis of (−)-Sedamine

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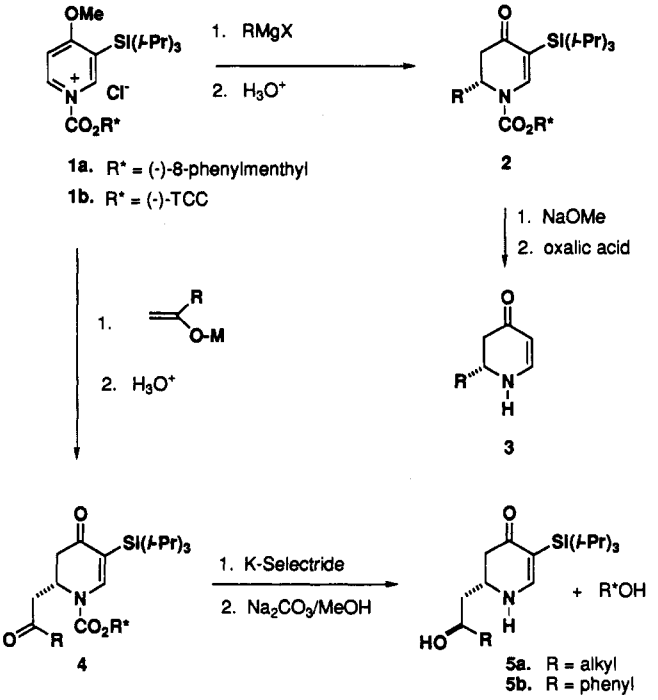
Summary: Synthetically useful 2-(2-oxoalkyl)-2,3-dihydro-4-pyridones are prepared in high diastereomeric excess by addition of ketone metallo enolates to chiral 1-acyl-4-methoxypyridinium salts.

The reaction of chiral 1-acylpyridinium salt **1a** with a Grignard reagent gives 1-acyl-2-alkyl-2,3-dihydro-4-pyridones **2** with high diastereoselectivity (76–94% de).[1,2] The dihydropyridones **3** are prepared in one step from **2** and are useful chiral building blocks for various alkaloids[2,3] (Scheme I). The considerable potential of this asymmetric synthesis prompted us to investigate the addition of other nucleophiles that would provide additional functionality in the C-2 side chain of **3**. Previously, we reported the addition of metallo enolates to achiral 1-acylpyridinium salts to give racemic 1,2- and 1,4-dihydropyridines,[4] and a related reaction using silyl enol ethers was studied by Akiba and co-workers.[5] The asymmetric counterpart to these reactions could have significant value in the enantioselective synthesis of alkaloids and natural products. We describe herein our preliminary studies on the addition of metallo enolates of ketones to chiral pyridinium salts of the type **1** and the application of this methodology to the asymmetric synthesis of the piperidine alkaloid, (−)-sedamine.

The 1-acylpyridinium salts were prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[1] and the chloroformate of readily available (−)-*trans*-2-(α-cumyl)cyclohexanol (TCC)[6] or (−)-8-phenylmenthol[7] (Scheme I). Metallo enolates of ketones were prepared using standard procedures and added to the chiral 1-acylpyridinium salt to give dihydropyridones **4** on acidic workup. The results of the initial study using 2-pentanone are given in Table I. The best results with regard to yield and diastereoselectivity were found using zinc or magnesium enolates (entries e–h). The reactions of three other zinc enolates were examined (entries i–k) and found to give good yields of dihydropyridones **4** in 90–94% de. The absolute

Scheme I



stereochemistry of the newly formed stereogenic center was determined to be *R* by single-crystal X-ray analysis of **4b**. The sense of asymmetric induction is the same as observed in the analogous reaction using Grignard reagents.[1,2]

The side-chain ketone carbonyl of **4** can be reduced with excellent control of stereochemistry by using K-Selectride (Aldrich) (THF, −78 °C). In this manner, **4b** (R = Ph) gave alcohol **5b** in 84% yield and >98% de after hydrolysis of the crude reduction product with Na_2CO_3/MeOH. The carbinol carbon of **5b** possessed the *S* configuration as determined by single-crystal X-ray analysis. The chiral auxiliary ((−)-TCC) was recovered in 95% yield at this stage. To demonstrate the potential of this sequence for the synthesis of natural products, we converted **5b** into the piperidine alkaloid, (−)-sedamine (**10**), as shown in Scheme II.[8]

The TIPS group of **5b** was removed in 89% yield on treatment with aqueous 10% HCl/THF (1/4, 45 min, rt) to give **6** [mp 106–107 °C; $[\alpha]^{26}_D$ +284° (*c* 0.67, $CHCl_3$)]. Reduction of the dihydropyridone ring and N-methylation were carried out as follows. Cyclic carbamate **7** [mp 205–206 °C; $[\alpha]^{23}_D$ +274° (*c* 0.60, $CHCl_3$)] was prepared from **6** in 88% yield on reaction with 1,1′,-carbonyldiimidazole (TEA, THF, reflux). Conjugate reduction using L-Se-

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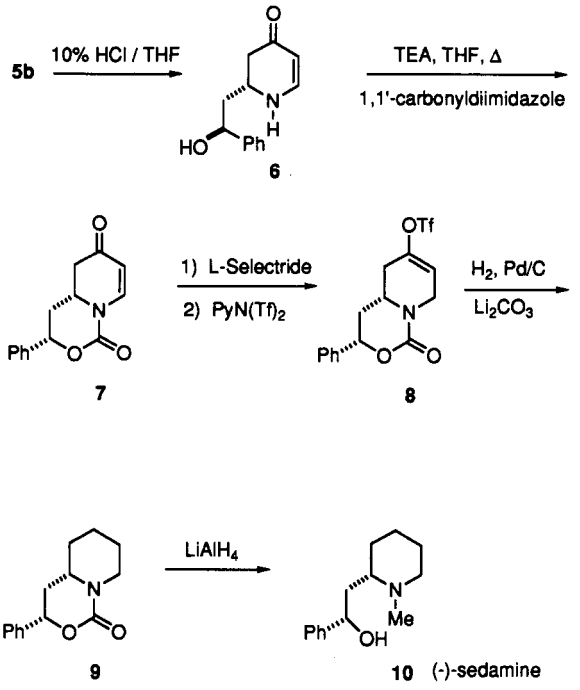
Table I. Addition of Ketone Enolates to Chiral Pyridinium Salts 1

entry[a]	chiral salt	R	MX[b]	solvent tol:Et_2O:THF	product	yield,[d] %	de,[e] %
a	**1b**	*n*-propyl	$Ti(i\text{-}PrO)_3$	1:0:1	4a	38	90
b	**1b**	*n*-propyl	$TiCl_3$	1:0:1	4a	42	65
c	**1b**	*n*-propyl	$SnCl_3$	2:0:1	4a	49	68
d	**1b**	*n*-propyl	Li	1:0:1	4a	73	82
e	**1b**	*n*-propyl	ZnCl	1:1:0	4a	74	90
f	**1b**	*n*-propyl	ZnCl	3:1:1	4a	86	89
g	**1a**	*n*-propyl	ZnCl	3:1:1	4a[c]	89	92
h	**1b**	*n*-propyl	MgBr	1:0:1	4a	82	94
i	**1b**	phenyl	ZnCl	3:1:1	4b	82	90
j	**1b**	methyl	ZnCl	3:1:1	4c	83	93
k	**1b**	*n*-butenyl	ZnCl	3:1:1	4d	80	94

[a] The reactions were generally performed on a 1.0 mmol scale using 1.0 equiv of pyridinium salt 1 and 3.0 equiv of the metallo enolate. [b] The metallo enolates were generated from the lithium enolate by metal exchange. [c] R* = (−)-8-phenylmenthyl. [d] Yield of products obtained from radial preparative-layer chromatography. [e] The diastereomeric excess (de) was determined by HPLC.

Scheme II



lectride[9,10] (Aldrich) and trapping with *N*-(2-pyridyl)-triflimide[10] provided a 62% yield of the vinyl triflate **8**. Chemoselective reduction of the vinyl triflate group using catalytic hydrogenation[11] (H_2, Pd/C, Li_2CO_3, EtOAc) gave a 95% yield of piperidine **9** [mp 127–129 °C; $[\alpha]^{23}_D$ −11.4° (*c* 0.5, $CHCl_3$)]. Treatment of **9** with LAH (THF, reflux, 1 h) provided (−)-sedamine[12] (**10**) in 80% yield[13–15] [mp 59–60 °C; $[\alpha]^{25}_D$ −86.8° (*c* 0.53, EtOH) [lit.[12] mp 59–61 °C; $[\alpha]_D$ −87.8° (*c* 0.1, EtOH)]].

The application of this methodology toward the asymmetric synthesis of other piperidine-containing natural products is underway in our laboratories.

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Supplementary Material Available: Experimental details for the preparation of **4b** (R = Ph), **5b**, and **6–10**, ORTEP plots of the X-ray structures of **4b** and **5b**, and listings giving full spectroscopic and analytical characterization of **4a–d**, **5b**, and **6–10** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) The spectral properties of (−)-**10** were in agreement with reported data.[12,13]

(15) All new compounds were spectroscopically characterized and furnished satisfactory elemental analyses (C, H, N ± 0.4%). Details are provided in the supplementary material.