Anionic Cyclizations of Chiral 2,3-Dihydro-4-pyridones: A Five-Step, Asymmetric Synthesis of Indolizidine 209D

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As part of a program directed at studying the synthesis and synthetic utility of chiral dihydropyridones,[1] we are investigating annulation reactions of *N*-acyl-2,3-dihydro-4-pyridones of the type **1** using the Heck and anionic cyclization methods. Although the Heck reaction is effective,[2] the anionic cyclization appears to be of broader synthetic utility. To effect an anionic cyclization of **1**, lithium−halogen exchange in the presence of the enaminone system was considered. Since the metal−halogen exchange of an aryl iodide is extremely rapid, it will tolerate certain carbonyl functions such as ketones, esters, and amides.[3] Although *N*-alkylenaminones have been reported to undergo intermolecular 1,2- or 1,4-addition with Grignard or organolithium reagents,[4] the intramolecular anionic 1,4-addition to *N*-acylenaminones of the type **1** was unexplored. In addition to the possibility of competing 1,2- and 1,4-addition to the enone of **1**, the *N*-acyl group is quite reactive[1] and attack at this carbonyl would complicate the anionic cyclization step. A clean conversion and a high degree of stereoselectivity during the anionic cyclization would be required to make the method attractive for use in natural product synthesis. Since *N*-acyl-2,3-dihydro-4-pyridones of various structure are readily available,[1b] we initiated a study to explore the potential of anionic cyclizations of **1**. Our preliminary results, and application of a related anionic cyclization in a concise asymmetric synthesis of indolizidine alkaloid 209D, are reported herein.

The required *N*-acyldihydropyridones **1** were prepared by adding a Grignard reagent to 1-acylpyridinium salt **3,** formed in situ from 4-methoxypyridine and 2-iodobenzoyl chloride (THF, −42 °C, 30 min), as shown in Scheme 1.[2] The anionic cyclization[3] was carried out by adding 1.1 equiv of *n*-butyllithium to the dihydropyridone **1** in THF at −78 °C. After 30 min, the reaction was quenched with aqueous sodium bicarbonate to give high yields (86−91%) of *trans*-indolizidinones **2** as shown in Table 1. The reactions appear by NMR analysis to be completely stereoselective for the trans isomer and free of byproducts resulting from *n*-butyllithium addition to the dihydropyridone. The stereoselectivity of this reaction is in contrast to, and therefore compliments, the intermolecular polar addition to C-2 substituted *N*-acyl-2,3-dihydro-4-pyridones which affords *cis*-2,6-disubsubstituted 4-piperidones. The analogous cyclization of the *N*-benzyl derivative **5**, prepared from pyridinium salt **4**, also occurred under similar conditions to give **6** in 50% yield (Scheme 2). Again, none of the cis diastereomer corresponding to **6** could be detected by ^{1}H NMR analysis. It is noteworthy that an analogous cyclization attempt on **5** using a Heck reaction failed, and only dehalogenated product was isolated.[2] Also, radical cyclization of the bromide corresponding to **5** is reported to give poor diastereoselectivity (3:1) in favor of **6**.[5]

A dihydropyridone anionic cyclization of the type depicted in Scheme 2 was utilized in a very concise synthesis of the poison-dart frog alkaloid,[6] (+)-indolizidine 209D **(11)**, as shown in Scheme 3. The 1-acylpyridinium salt, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[7] and (1*S*,2*R*,4*S*)-2-(1-methyl-1-phenylethyl)-4-(2-propyl)cyclohexanol (CPC),[8] was

Scheme 1

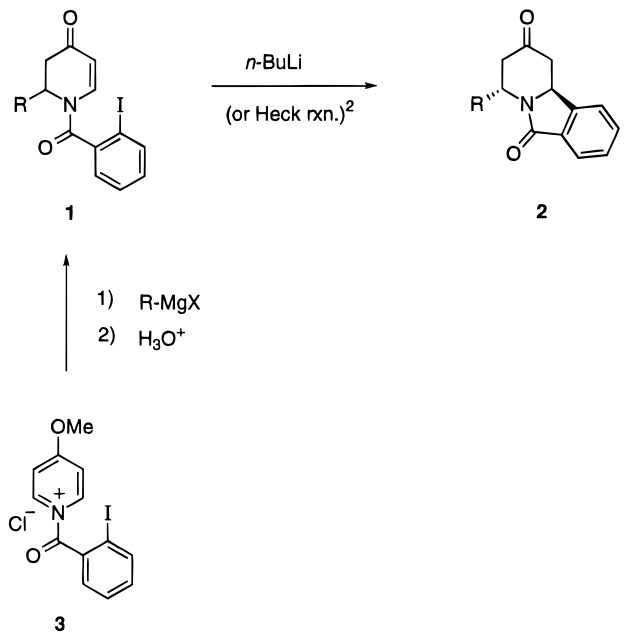
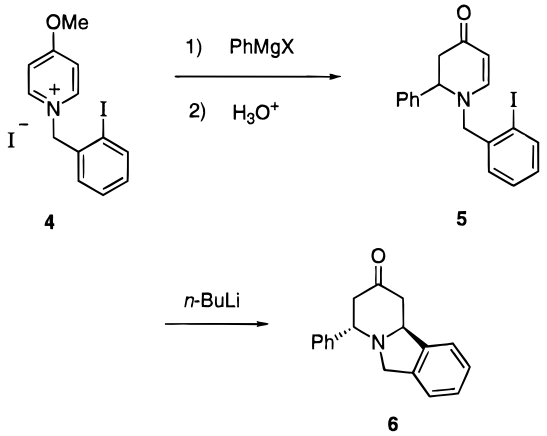


Table 1. Anionic Cyclizations of Dihydropyridones **1**

entry	R[a]	product	yield,[b] %
1	Ph	**2a**	91
2	c-hex	**2b**	86
3	vinyl	**2c**	89
4	HC≡C	**2d**	88
5	C_4H_9C≡C	**2e**	86

[a] The reactions were carried out on a 0.5 mmol scale in THF and quenched at −78 °C with saturated aqueous $NaHCO_3$. [b] Yield of product obtained from radial preparative-layer chromatography (silica gel, EtOAc/hexanes).

Scheme 2



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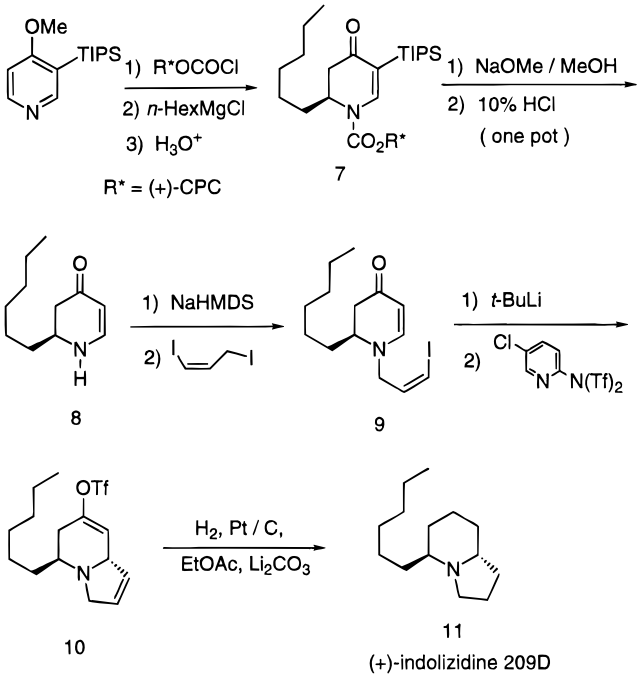
Scheme 3



treated with *n*-hexylmagnesium bromide to give dihydropyridone **7** in 87% yield after chromatography (silica gel, 4% EtOAc/hexane). HPLC analysis of the crude product showed that the reaction proceeded in 92% diastereomeric excess. Removal of the chiral auxiliary (>95% recovery) and the C-5 triisopropylsilyl group provided enantiopure **8** in 86% yield as an oil $[[\alpha]_D^{24}$ −336 (*c* 0.27, CH_2Cl_2)] via a one-pot reaction.[9] *N*-Alkylation of **8** was effected in 74% yield by deprotonation (NaHMDS, THF, −78 °C, 30 min) and addition of (*Z*)-1,3-diiodopropene[10] (−78 °C → 0 °C) to give vinyl iodide **9**. Lithium−halogen exchange and subsequent anionic cyclization occurred on addition of *tert*-butyllithium (1.1 equiv, THF, −78 °C, 1 h) to **9**. In this case, *tert*-butyllithium was used in place of *n*-butyllithium to avoid byproducts resulting from dehydrohalogenation and alkylation by the in situ formed *n*-butyl iodide. The intermediate ketone enolate was trapped with *N*-(5-chloro-2-pyridyl)triflimide[11] to provide an 80% yield of vinyl triflate **10,** which was determined to be enantiomerically pure by chiral column HPLC. The anionic cyclization was again highly stereospecific as only the trans diastereomer **10** could be detected by ^{1}H NMR analysis. Catalytic hydrogenation directly reduced **10** to (+)-indolizidine 209D **(11)** in 79% yield $[[\alpha]_D^{24}$ +10.1 (*c* 0.42, CH_2Cl_2)] [lit.[4b] $[\alpha]_D$ + 8.0 (*c* 1.0, CH_2Cl_2)].[12,13]

In summary, a stereoselective anionic cyclization of 2-substituted 1-acyl- or 1-alkyl-2,3-dihydro-4-pyridones to give *trans*-indolizidinones has been developed. The method was utilized in a five-step, highly stereocontrolled asymmetric synthesis of alkaloid **11**, which was carried out with an overall yield of 35%. Work is in progress on the enantioselective synthesis of other indolizidine and related alkaloids using this concise, practical strategy.

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Supporting Information Available: Experimental details for the preparation of **2b** and **7**−**11**, physical properties and spectroscopic data for **2b,d,e** and **7**−**11**, and ^{1}H and ^{13}C NMR spectra of **2d, 8**−**10** (20 pages). See any current masthead page for ordering information and Internet access instructions.

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(12) The spectral properties of (+)-**11** were in agreement with those reported.[6b] See table of spectral data in the Supporting Information.
(13) All new compounds were spectroscopically characterized and furnished satisfactory elemental analyses (C, H, N ±0.4%) or high-resolution mass spectra. Details are provided in the Supporting Information.