Diastereoselective Addition of Prochiral Metallo Enolates to Chiral 1-Acylpyridinium Salts

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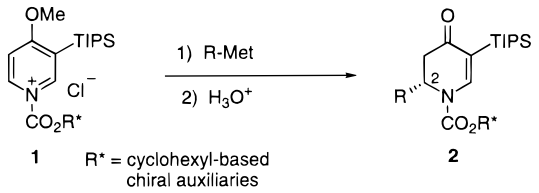
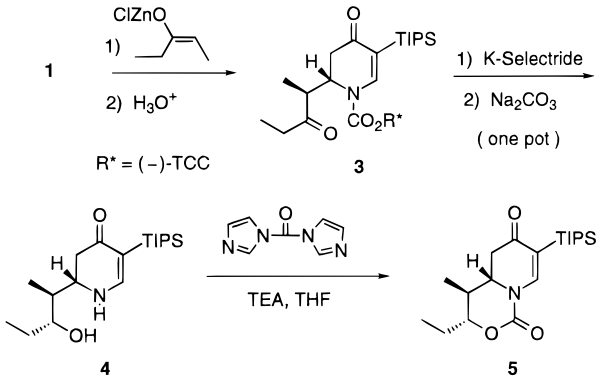
The addition of Grignard reagents,[1] or certain other organometallics,[2] to chiral 1-acylpyridinium salts **1** gives synthetically useful 2-substituted 1-acyl-2,3-dihydro-4-pyridones **2**. The utility



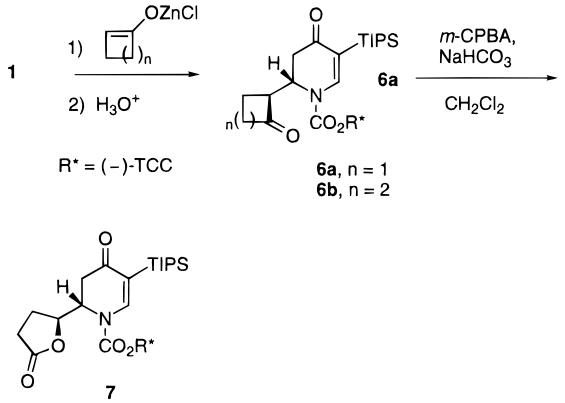
of heterocycles **2** as chiral building blocks has prompted us to investigate their preparation with various functionality and stereocenters in the C-2 side chain. We have reported that the addition of zinc or magnesium enolates of methyl ketones to **1** provides 2-(2-oxoalkyl)-2,3-dihydro-4-pyridones in good yield and high diastereoselectivity (90−94% de).[3] The stereostructure of an enolate (*E*/*Z*) can often determine the relative configuration (syn/anti) of two new chiral centers in a product derived from its addition to an electrophile having diastereotopic faces. To ascertain if this diastereoselective process would operate by means of a chiral 1-acylpyridinium salt as the electrophile, we initiated a study on the reaction of **1** with prochiral zinc enolates of ketones and lactones.

Following the procedure developed for the analogous methyl ketone reactions,[3] the zinc *E*-enolate of 3-pentanone (3 equiv, LDA; ZnCl)[4] was added to chiral salt **1** (R* = (−)-*trans*-2-(α-cumyl)cyclohexyl, (−)-TCC)[5] in THF/toluene at −78 °C. An 83% yield of dihydropyridone **3** was isolated after chromatography (Scheme 1). The reaction was found to be quite general, as cyclobutanone and cyclopentanone enolates gave similar results (57% and 82%, respectively). In all cases the major product was the anti isomer, crystalline and easily separated from minute amounts of minor diastereomers by means of radial preparative-layer chromatography (silica gel, EtOAc/hexanes). Not only can two stereogenic centers be simultaneously and stereoselectively incorporated into a highly functionalized heterocycle with the use of this method, but subsequent reduction of the side-chain ketone

Scheme 1



Scheme 2



with K-Selectride (THF, −78 °C) occurs with high diastereoselectivity (>96% de) to give an enantiopure dihydropyridone containing three contiguous stereocenters. In this manner ketone **3** was reduced to alcohol **4** (69%), which was converted to cyclic carbamate **5** with 1,1′-carbonyldiimidazole (TEA, THF, reflux; 85%). The relative stereochemistry of **5** was determined by ^{1}H NMR analysis. As shown in Scheme 2, the cyclobutane derivative **6a** was converted to lactone **7** via the Baeyer−Villiger reaction. This chemoselective oxidation proceeded in 91% yield in the presence of the enone moiety of **6a** which was protected by the C-5 TIPS group. The stereochemistry of **6a** and **7** was confirmed by single-crystal X-ray analysis of **7**.[6] This two-step sequence allows the stereoselective preparation of a dihydropyridone (i.e., **7**) containing a hydroxy-derivative in the α-position of the C-2 side chain. A more direct route to α-oxygenated C-2 side chain derivatives was investigated (Scheme 3). Zinc enolates of ketones **8**[7] and **9**[8] were added to pyridinium salt **1** to give dihydropyridones **10** and **11** with enolate facial selectivities of 9/1 and 4/1, respectively. The major diastereomers were again easily isolated by radial preparative-layer chromatography and shown to possess the stereochemistry depicted as determined by single-crystal X-ray analysis.[6,9] Interestingly, the enolate of ketone **8** (*E*-enolate) gives the anti (2*S**,2′*S**) isomer **10** (60%), whereas the analogous reaction using ketone **9** (mainly *Z*-enolate due to chelation)[10] leads predominately to the syn (2*S**,2′*R**) product **11** (55%) as determined by X-ray analysis.[6] Thus, the stereochemistry at C-2 can be set by the proper choice of the auxiliary, (+)- or (−)-

(1) (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807 and references cited therein.

(2) (a) Comins, D. L.; Foti, C. J.; Libby, A. H. *Heterocycles* **1998**, *48*, 1313. (b) Comins, D. L.; Stolze, D. A.; Thakker, P.; McArdle, C. L. *Tetrahedron Lett.* **1998**, *39*, 5693.

(3) (a) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035. (b) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851.

(4) We assume that the *E*/*Z* ratio of the zinc enolate is similar to that reported for the lithium enolate (*E*/*Z* = 70/30) prepared using LDA, see: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(5) (a) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656. (b) (+)- and (−)-TCC alcohols are available from Aldrich Chemical Co.

(6) Details can be found in the Supporting Information.

(7) Available from Aldrich Chemical Co.

(8) Araki, Y.; Nagasawa, J.; Yoshiharu, I. *J. Chem. Soc., Perkin Trans. 1* **1981**, 12.

(9) The reactions and X-ray analyses were carried out using racemic material. The absolute stereochemistry depicted by the structures is relative to R* being (−)-TCC.

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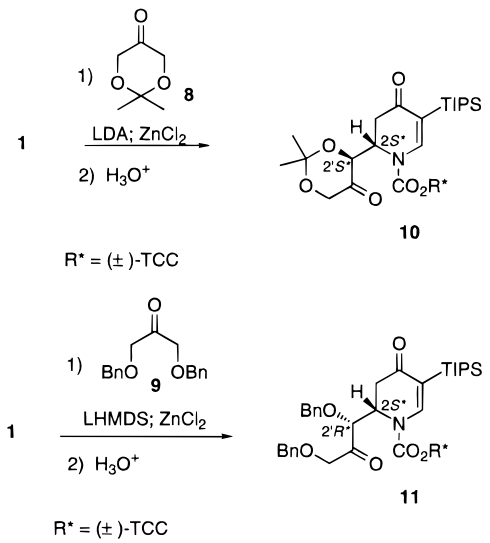
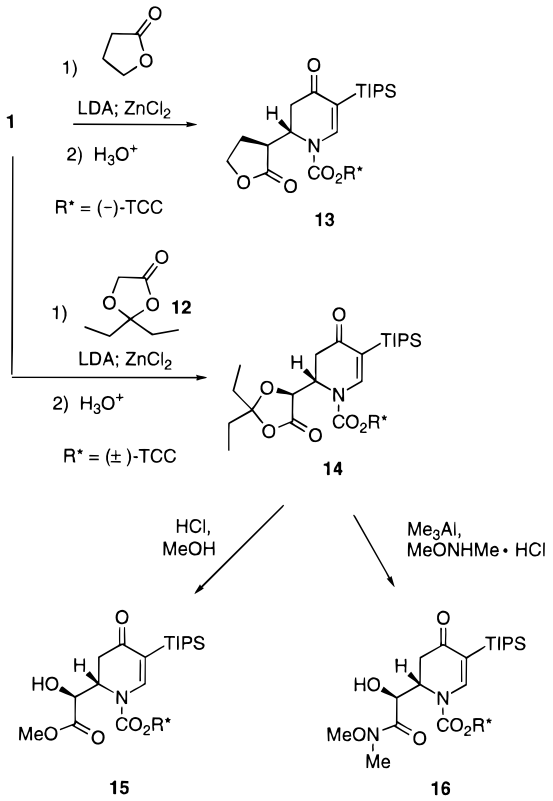
Scheme 3



Scheme 4



TCC,[5] and the stereochemistry at C-2′ can be controlled by using an enolate with the appropriate geometry. To determine if lactone anions give analogous results to the cyclic ketone series, the zinc enolates of γ-butyrolactone and dioxolanone **12**[11] were added to **1** (Scheme 4). Dihydropyridones **13** and **14** were isolated as white solids in 75 and 85% yields, respectively. No other diastereomers were found upon purification of the crude products. The stereochemistry of **13** and **14** was determined to be anti by ^{1}H NMR and single-crystal X-ray analysis.[6] The *E*-enolate facial selectivity can be explained by assuming an acyclic transition state with a synclinal orientation as depicted in Figure 1. This TS-conformation may be favored due to reduced nonbonded interactions with the pyridinium ring and electrostatic attraction of the positively charged nitrogen and the negative enolate oxygen.[12] The anti-product selection observed in the *E*-enolate reactions of *N*-acylpyridinium salt **1** is analogous to that found in the diastereoselective reactions of prochiral trialkylsilyl enol ethers with *N*-acyliminium ions as reported by Heaney and co-workers.[13] This stereoselection is in contrast to the syn-selective Me_3SiOTf-mediated reaction of enolsilanes with acetals[14] and the Lewis acid-catalyzed reaction of *N*-benzyloxycarbonyl-2-methoxypyrrolidine with 3-methyl-2-trimethylsiloxyfuran,[15] which have been proposed to proceed via acyclic extended transition states.[16]

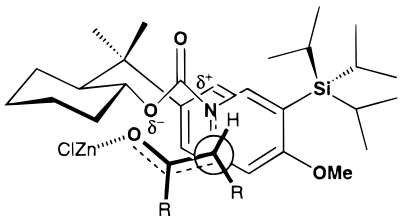


Figure 1. Transition state for *E*-enolate addition to **1**.

To examine the usefulness of lactone **14** as a synthetic building block, it was treated with anhydrous HCl in methanol (reflux, 2 h). A very clean reaction occurred providing a 97% yield of hydroxyester **15**. The Weinreb's amide **16** was also prepared from **14** (Me_3Al, MeONHMe•HCl, CH_2Cl_2) in 97% yield.[17] These reactions, and those reported above in the ketone series, demonstrate that functional groups in the C-2 side chain can undergo useful synthetic transformations in the presence of the dihydropyridone ring system. The application of this chemistry and the utility of these highly functionalized dihydropyridones (**7**, **10**−**11**, **13**−**16**) as chiral building blocks for natural product synthesis are under study in our laboratories.

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) and the Petroleum Research Fund (ACS-PRF No. 28394-AC) for financial support of this research. NMR and mass spectra and X-ray structures (**7**, **10**, **14**) were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grant CHE-9121380). X-ray analysis of **11** was performed at the crystallography laboratory of the University of Delaware.

Supporting Information Available: Experimental procedures for **3**, **14**−**16** and spectroscopic data for **3**−**7**, **10**−**11**, and **13**−**16**, ^{1}H and ^{13}C NMR spectra of **4**, **5**, and **15**, ORTEP plots and X-ray data for **7**, **10**−**11**, and **14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Trapping of the enolate (LiHMDS, THF, −78 °C) with TMSCl gave *E*/*Z* silyl enol ethers in a ratio of 3/97. For a discussion on the stereochemistry of enolate formation, see: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, Chapter 2, pp 111−206.

(11) Fairbanks, A. J.; Sinaÿ, P. *Tetrahedron Lett.* **1995**, *36*, 893.

(12) An acyclic TS is proposed based on an apparent low-energy conformation that does not favor a chelate; however, some sort of chelation control cannot be ruled out at this time. This TS model suggests that due to steric interactions *E*-enolates should be more reactive than Z-enolates. This difference in reactivity may explain the high diastereoselectivity obtained on reaction of **1** with the zinc enolate of 3-pentanone (3 equiv) which is likely a 70/30 mixture of *E* and *Z* isomers.

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(16) For examples of prochiral enolate additions to imines, see: Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 893.

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