Tetrahedron Letters, Vol. 33, No. 13, pp. 1697-1700, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

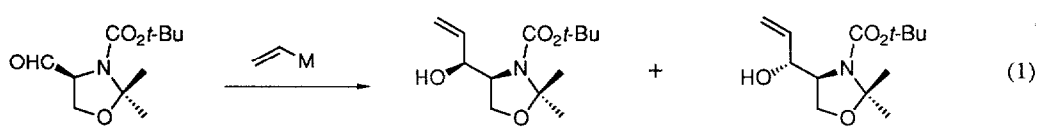
DIASTEREOSELECTIVE ADDITION OF VINYL ORGANOMETALLIC REAGENTS TO L-SERINAL

Robert S. Coleman*,[1a] and Andrew J. Carpenter[1b]

Department of Chemistry and Biochemistry
University of South Carolina
Columbia, South Carolina 29208

Abstract: *An examination of the diastereoselective addition of vinyl organometallic reagents to* N-*BOC* L-*serinal acetonide (**1**) to afford mixtures of* syn-**2** *and* anti-**2** *is presented. Vinylzinc chloride in nonpolar solvents was found to add to the aldehyde carbonyl of* **1** *with 6:1* syn/anti *stereoselectivity in excellent yields.*

In the course of synthetic studies on the antitumor agents azinomycins A and B,[2] we were confronted with the task of adding a vinyl anion to Garner's L-serinal derivative **1**[3] in a formal chelation-controlled sense[4] to afford *syn*-**2** (equation 1). Examination of prior usage of **1** as a chiral synthon[5-7] revealed that typical vinyl nucleophiles (*e.g.*, vinylmagnesium bromide[5c]) add to the aldehyde carbonyl group of **1** in a Felkin-Ahn sense[8] to afford *anti*-**2** as the predominant product. In a single example of a *syn*-selective addition of a vinyl nucleophile, Garner and co-workers observed that the vinylalane obtained by hydroalumination of 1-pentadecyne with $(i\text{-Bu})_2$AlH adds to **1** with modest 2:1 *syn/anti* diastereoselectivity.[5b] Herold has also demonstrated that the addition of acetylide anions to **1** selectively affords either the corresponding *syn*- and *anti*-products depending upon choice of metal.[7] This work led us to formulate a process involving the addition of vinyl organometallic reagents possessing a suitable coordinating metal in order to provide selective access to *syn*-**2**. The ability to add vinyl nucleophiles to **1** with either *syn*- or *anti*-selectivity is relevant to published work describing the use of **1** as a starting material for the synthesis of *threo*- and *erythro*-sphingosines and other natural products bearing the 2-amino-1,3-diol subunit.[5-7] Herein, we detail our observations on the diastereoselective addition of vinyl organometallic reagents to **1** and report the first reagent system for the synthesis of *syn*-**2** with good levels of diastereoselectivity.



1 *syn*-**2** *anti*-**2** (1)

The results of our investigation are presented in Table 1. In accord with literature precedence,[5,6] we observed modest to good *anti*-selectivity in the addition of commercially available THF solutions of vinylmagnesium bromide (entry 1) or vinyllithium (entry 2) to aldehyde **1**. For entries 3-10, aldehyde **1** was precomplexed with the Lewis acid at -78°C, and the vinyl nucleophile was then added to the reaction mixture. As evidenced by entries 3-6, Lewis acids had little effect on the diastereoselectivity of the reaction in polar solvents (*i.e.*, THF), although precomplexing aldehyde **1** with $TiCl_4$ in toluene or Et_2O prior to addition of a commercial THF solution of vinyllithium led to a slight increase in the proportion of *syn*-**2**. Surmising that chelation-controlled addition to **1** would be hampered by the presence of a Lewis basic solvent such as THF, we prepared vinyllithium *in situ* from an ethereal solution of vinyl bromide and *tert*-butyllithium in pentane (2.0 equiv, -78°C, 15-30 min). As expected (entry 8), $TiCl_4$ precomplexed to aldehyde **1** in CH_2Cl_2 solution affected very slight *syn*-selectivity using freshly prepared vinyllithium in pentane/Et_2O solution. In the presence of $ZnCl_2$, both vinyllithium in pentane/Et_2O and commercial vinylmagnesium bromide in THF/Et_2O produced increased proportions of *syn*-**2** from aldehyde **1** (entries 9-10). Likewise, modest increases in the proportion of *syn*-**2** were observed with lithium divinylcuprate (entry 11; prepared from CuI and 2 equiv commercial vinyllithium in THF) and the reagent formed from vinyllithium and Et_2AlCl in pentane/Et_2O (entry 12), although neither of the reaction conditions produced a synthetically useful level of diastereoselectivity.

Upon careful examination of the results detailed in entries 1-12, the reagent system consisting of vinylzinc chloride (prepared from vinyllithium and 1.0 equiv $ZnCl_2$ in pentane/Et_2O)[9] and aldehyde **1** precomplexed to 1.0 equiv $ZnCl_2$ in Et_2O was formulated, and was found to afford *syn*-**2** with 6:1 diastereoselectivity. Surprisingly, excess $ZnCl_2$ was found to be without effect on the diastereoselectivity of the reaction (compare entries 13 and 14), and the reagent prepared from equimolar quantities of vinyllithium and $ZnCl_2$ was found to routinely afford a 6:1 mixture of *syn*-**2**/*anti*-**2** in excellent yields (70-90%).[9]

The results presented in Table 1 are difficult to reconcile with previously published analyses.[5-7] Whereas the addition of non-chelating reagents such as vinyllithium or vinylmagnesium bromide apparently proceeds by Felkin-Ahn transition state[8] **A** to afford *anti*-**2**, reagent systems capable of forming a cyclic chelate between the aldehyde carbonyl and the *tert*-butoxycarbonyl group do not appear to proceed by chelated transition state **B**.[4] Thus, the simple picture of metal chelation shown in **B** is not consistent with our results. The lack of chelation control by $ZnCl_2$ in the addition of vinyllithium (entry 9) compared with the high levels of apparent chelation exhibited by vinylzinc chloride (entries 13-14) argues further against simple chelation model **B**. Our results are more consistent with a coordinated delivery of nucleophile (*i.e.*, entries 10-14) by a transition state such as **C**. The reagent precomplexes with the carbamate carbonyl, and is thereby delivered to the opposite face of the aldehyde carbonyl to afford *syn*-**2**. Thus, it may be that transition state **B** is difficult to form or is easily disrupted, a result that is consistent with previous work.[5-7]

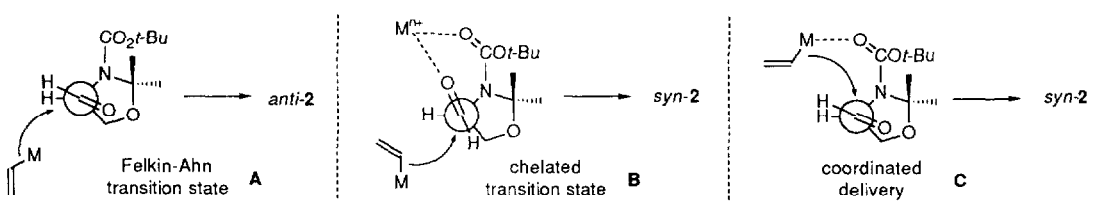
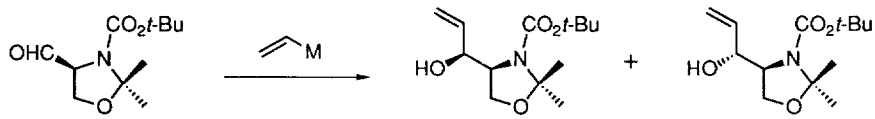


TABLE - Diastereoselective Addition of Vinyl Organometallic Reagents



1 *syn*-**2** *anti*-**2**

entry	vinyl nucleophile	solvent, temperature	equiv	Lewis acid	solvent	syn/anti[a]
1	MgBr	THF, -78°C	3.0	none	THF	1 : 3
2	Li	THF, -78°C	1.6	none	THF	1 : 5
3	MgBr	THF, -78°C	3.0	1.0 equiv $BF_3{\cdot}OEt_2$	Et_2O	1 : 4
4	Li	THF, -78°C	3.0	1.0 equiv Et_2AlCl	hexane	1 : 5
5	Li	THF, -78°C	3.0	1.0 equiv $TiCl_4$	THF	1 : 5
6	Li	THF, -78°C	3.0	1.0 equiv $TiCl_4$	toluene	1 : 2
7	Li	pent/Et_2O, -78°C	3.0	1.0 equiv $TiCl_4$	Et_2O	1 : 3
8	Li	pent/Et_2O, -78°C	3.0	1.0 equiv $TiCl_4$	CH_2Cl_2	1 : 1
9	Li	pent/Et_2O, -78°C	3.0	1.0 equiv $ZnCl_2$	Et_2O	1 : 3
10	MgBr	THF/Et_2O, -78°C	3.0	1.0 equiv $ZnCl_2$	Et_2O	1 : 1
11	$_2$CuLi	THF, -78°C	1.5	none	THF	1 : 1.5
12	$AlEt_2$	pent/Et_2O, -78°C	3.0	none	Et_2O	1.5 : 1
13	ZnCl	pent/Et_2O, -78°C	3.0	1.0 equiv $ZnCl_2$	Et_2O	6 : 1
14	ZnCl	pent/Et_2O, -78°C	1.5-3.0	none	Et_2O	6 : 1

[a]Ratio determined by ^1H NMR integration of the terminal vinylic resonances.

The results presented in Table 1 represent the first evidence that vinyl nucleophiles can be added to aldehyde **1** with synthetically useful levels of *syn*-selectivity. The reagent formed from *in situ*-prepared vinyllithium and $ZnCl_2$ in an Et_2O/pentane solvent system was found to provide *syn*-**2** with 6:1 diastereoselectivity in excellent yields.[9] This particular example solves a long-standing problem in the area of sphingosine chemistry, wherein the ability to add vinylic organometallic reagents to α-aminoaldehydes with controlled *syn*- or *anti*-diastereoselectivity would provide direct access to *threo*- and *erythro*-sphingosines.[5-7] Furthermore, a stereoselective and high-yielding route to *syn*-**2** is of considerable value in our laboratory for construction of the C8-C13 fragment of azinomycins A and B.[2]

Acknowledgments We would like to thank the American Cancer Society (JFRA-319) and the Camille and Henry Dreyfus Foundation (NF-89-18) for their generous support of this work. NMR spectra were obtained on instruments purchased with funds from the National Science Foundation (CHE-8411172 and CHE-8904942) and the National Institutes of Health (S10-RR02425).

REFERENCES AND NOTES

1. (a) Recipient of a Camille and Henry Dreyfus Foundation Distinguished New Faculty Award (1989-1994) and an American Cancer Society Junior Faculty Research Award (1991-1993). (b) Recipient of a U.S. Department of Education Predoctoral Fellowship.
2. Coleman, R.S.; Carpenter, A.J., unpublished results.
3. Garner, P.; Park, J.M. *Org. Synth.* **1991**, *70*, 18.
4. (a) For a review on the use of α-amino aldehydes in synthesis, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) See also: Reetz, M.T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556.
5. (a) Garner, P.; Park, J.M. *J. Org. Chem.* **1990**, *55*, 3772. (b) Garner, P.; Park, J.M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395. (c) Garner, P.; Park, J.M. *J. Org. Chem.* **1988**, *53*, 2979. (d) Garner, P.; Park, J.M. *J. Org. Chem.* **1987**, *52*, 2361. (e) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609. (f) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.
6. Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354.
7. Casiraghi, G.; Colombo, L.; Rassu, G.; Peitro, S. *J. Chem. Soc., Chem. Commun* **1991**, 603. Mori, K.; Matsuda, H. *Liebigs Ann. Chem.* **1991**, 529. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439. Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4151. Dondoni, A.; Fantin, G.; Fagagnolo, M. *Tetrahedron Lett.* **1990**, *31*, 6063. Nakagawa, M.; Tsuruoka, A.; Yoshida, J.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1990**, 603. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1990**, 854. Kahne, D.; Yang, D.; Lee, M.D. *Tetrahedron Lett.* **1990**, *31*, 21. Casiraghi, G.; Colombo, L.; Rassu, G.; Fava, G.G.; Belicchi, M.F. *Tetrahedron* **1990**, *55*, 3772. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *Tetrahedron Lett.* **1989**, *30*, 5325. Nimkar, S.; Menaldino, D.; Merrill, A.H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *J. Chem. Soc., Chem. Commun.* **1988**, 10. Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919. Radunz, H.E.; Devant, R.M.; Eiermann, V. *Liebigs Ann. Chem.* **1988**, 1103.
8. Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Ahn, N.T. *Top. Curr. Chem.* **1980**, *88*, 145. See also reference 4b.
9. **(4*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-[(1*R*)-1-hydroxy-2-propenyl]oxazolidine (*syn*-2).** A solution of vinyl bromide (43.6 mL, 1.5 M in Et_2O, 65.4 mmol, 1.5 equiv) in Et_2O (50 mL) was cooled to -78°C under N_2 and treated with a solution of *tert*-butyllithium (62.2 mL, 2.1 M in pentane, 130.7 mmol, 3.0 equiv) *via* syringe over 15 min. The pale yellow solution was allowed to warm to 0°C and was stirred for 1 h before recooling to -78°C. A solution of $ZnCl_2$ (65.4 mL, 1.0 M in Et_2O, 65.4 mmol, 1.5 equiv) was added and the reaction mixture was again allowed to warm to 0°C and was stirred for 1 h before being recooled to -78°C. The resulting solution of vinylzinc chloride was added *via* cannula over 1 h to a -78°C solution of aldehyde **1**[3] (10.0 g, 43.6 mmol) in dry Et_2O (50 mL). The reaction mixture was allowed to warm to 24°C and was stirred for 3-4 h. The reaction mixture was quenched by the addition of satd. aqueous NH_4Cl (150 mL) and was extracted with EtOAc (3 x 250 mL). The combined organic extracts were washed with satd. aqueous NaCl (2 x 250 mL), and were dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless oil. Purification of the residue by flash chromatography (5.6 x 15 cm silica, 10-30% EtOAc/hexanes) afforded **2** (9.5 g, 11.2 g theor., 85%) as a 6:1 mixture of diastereomers favoring the *syn*-isomer. Oxazolidine **2** exists as a pair of rotamers that interconvert slowly at 25°C. Consequently, ^1H NMR spectra exhibit doubling and line broadening of certain resonances.[5] *Syn*-**2** was characterized:[5c] ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1H, C*H*=CH_2), 5.36 and 5.30 (s, 1H, CH=C*H*H), 5.24 and 5.20 (s, 1H, CH=CH*H*), 4.31 (br s, 1H, CHO*H*), 4.20 (br m, 1H, C*H*OH), 4.0-3.8 (br m, 3H, C4-H and C5-H), 1.57 (s, 3H, C2-CH_3), 1.48 (m, 12H, C2-CH_3 and $C(CH_3)_3$); IR (neat) ν_{max} 3453, 2979, 2937, 1699, 1457, 1393, 1258, 1173, 1097, 1053, 991, 924, 852, 769, 668 cm^{-1}; CIMS, *m/e* (relative intensity) 258 (M^+ + 1, 10), 202 (59), 184 (56), 172 (25), 158 (56), 144 (base), 126 (29), 100 (77), 57 (95); HRMS, *m/e* calcd for $C_{12}H_{20}NO_4$ ($M^+ - CH_3$): 242.1392; found: 242.1392.

(Received in USA 20 December 1991)