Direct Amino-Crotylsilylation of Achiral Acetals and Aldehydes: Asymmetric Synthesis of Homoallylic Amines and Functionalized Pyrrolidines

James S. Panek* and Nareshkumar F. Jain

Department of Chemistry, Metcalf Center for Science and Engineering, Boston University, Boston, Massachusetts 02215

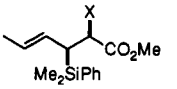
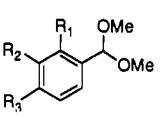
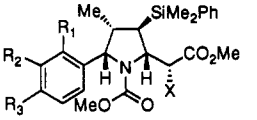
Received November 12, 1993 (Revised Manuscript Received March 25, 1994®)

Summary: The condensation between chiral (*E*)-crotylsilanes 1 and *in situ*-generated achiral *N*-acylimines produces homoallylic *N*-acylamines 3 or tetrasubstituted *N*-acylpyrrolidines 4 with high levels of diastereoselection.

Interest in biologically and synthetically important acyclic and cyclic amines with well-defined stereochemistry has often contributed to the development of new reaction methodology for their synthesis. Methodology designed for the stereoselective synthesis of β-amino acid synthons has evolved from simple diastereoselection processes involving the use of achiral enol derivatives and allylmetals in addition to achiral imines and *N*-acyliminium ions to asymmetric condensations utilizing chiral imines.[1] The purpose of this paper is to report the results of our experiments concerning the utility of chiral (*E*)-crotylsilanes in addition to achiral imines resulting in the enantioselective construction of homoallylic amines (β-amino acid synthons) and pyrrolidines. This study represents the first asymmetric addition of a chiral allylsilane to *in situ*-generated imines.[2]

Here, we describe an efficient procedure for the direct asymmetric amino-crotylsilylation and a [3 + 2] pyrrolidine annulation from the derived imines utilizing achiral aldehydes and acetals (Scheme 1, eqs 1 and 2). We have used these silane reagents previously in asymmetric electrophilic substitution[3] and related annulation reactions.[4] In a similar manner, the silane reagents 1 can be used in highly diastereo- and enantioselective additions to *in situ*-generated *N*-acylimines 2 under mild conditions (−78 → −20 °C). Our experiments have shown that when the reaction temperature is lowered, *N*-carbamoylpyrrolidines 4 are produced from aryl acetals or aldehydes. On the other hand, only acyclic homoallylic carbamates were detected and isolated when the reaction temperature was immediately warmed to −20 °C.[5]

Table I. Asymmetric Synthesis of Homoallylic *N*-Acylamines and *N*-Acylpyrrolidines

entry	silane	acetal/ aldehyde	major product (%, syn/anti)[a]
			
1	**1a**; (3*R*), X = H	**2a**; R = Ph	**3a** (87, >30:1)[b]
2	**1b**; (2*S*,3*S*), X = OMe	**2a**	**3b** (79, >9:1)[b]
3	**1c**; (*anti*,2*R*,3*S*), X = Me	**2a**	**3c** (73, >30:1)[b]
4	**1a**; (3*R*), X = H	**2b**; R = $BnOCH_2CH_2$	**3d** (65, >30:1)[b]
5	**1a**; (3*R*), X = H	**2c**; R = $BnOCH_2$	**3e** (87, >30:1)[b]
		RCHO	
6	**1a**; (3*R*), X = H	**2d**; R = ^{i}Pr	**3f** (68, >30:1)[b]
7	**1a**; (3*R*), X = H	**2e**; R = ^{t}Bu	**3g** (72, >30:1)[b]
			
8	**1a**; (3*R*), X = H	**2a**; $R_1 = R_2 = R_3 = H$	**4a** (68, >30:1)[c]
9	**1b**; (2*S*,3*S*), X = OMe	**2a**	**4b** (72, 20:1)[c]
10	**1b**; (2*S*,3*S*), X = OMe	**2f**; $R_1 = R_2 = H$, R_3 = Cl	**4c** (47, 20:1)[c]
11	**1b**; (2*S*,3*S*), X = OMe	**2g** $R_1 = R_2$ = OMe, $R_3 = H$	**4d** (53, 10:1)[c]

[a] Based on pure material isolated by chromatography (SiO_2). Ratios were determined by ^{1}H NMR. [b] Run in CH_2Cl_2 (0.3 M) from −78 → −20 °C, 24–32 h using $BF_3{\cdot}OEt_2$ (3.0 equiv) for aldehydes and (2.0 equiv) for acetals. [c] Run in CH_2Cl_2 (0.3 M) from −100 → −78 °C, 12–24 h using $BF_3{\cdot}OEt_2$ (2.0 equiv).

On the basis of previous studies we projected that the silane reagents would show useful levels of selectivity in Lewis acid catalyzed additions to imine derivatives. The results of those experiments describing the enantioselective condensation and pyrrolidine annulation with the derived imines are given in Table 1. The experiments have shown that the silane reagents **1a–c**[6] exhibit high levels of diastereo- and enantioselectivity in the electrophilic substitution reactions with a variety of imine derivatives. The reactions generally proceed with high levels of diastereoselection (>30:1 syn/anti), and in many examples, ^{1}H NMR analysis could not detect the minor *anti*-diastereomer.[7] Slightly lower diastereoselectivity (9–

® Abstract published in *Advance ACS Abstracts*, April 15, 1994.

(1) Reviews: Imines: (a) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, pp 975–1006. (b) *N*-Acylimines: Hiemstra, H.; Speckamp, N. W. In *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1047–1082. (c) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447–1465.

(2) Reports concerning simple disatereoselective reactions of achiral allylmetals with imine derivatives, see: (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031–5033. (b) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146–147. (c) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115–3121. (d) Wuts, P. G. M., Jung, Y. W. *Tetrahedron Lett.* **1986**, *27*, 2079–2082. (e) For an example of a chiral allylboronation, see: Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, 2000–2008. (f) Double stereodifferentiating reactions with chiral imines: Hattori, K.; Miyata, M.; Yammamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151–1152.

(3) (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594–6600. (b) Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755–5758. (c) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 999–1002. (d) Panek, J. S.; Yang, M.; Muler, I. *J. Org. Chem.* **1992**, *57*, 4063–4064.

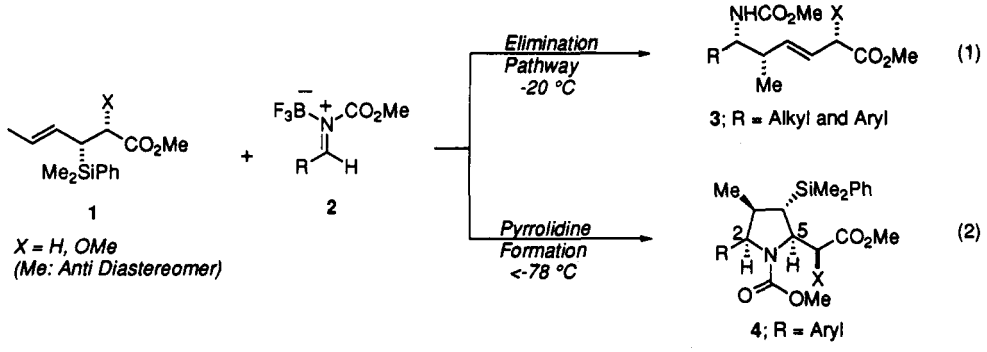
(4) (a) Tetrahydrofurans: Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868–9870. (b) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1993**, *58*, 809–811. (c) Tetrasubstituted cyclopentanes: Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1993**, *58*, 2345–2348. (d) Δ^2-Isoxazolines: Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898–7899. Related [3 + 2] annulations involving achiral allylsilanes: (e) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094–6097. (f) Knölker, H.-J.; Jones, P. G.; Pannek, J.-B. *Synlett* **1990**, 429–430. (g) Herndon, J. W. *J. Am. Chem. Soc.* **1987**, *109*, 3165–3166. (h) Snider, B. B.; Zhang, Q. *J. Org. Chem.* **1991**, *56*, 4908–4913.

(5) Our experiments indicate that the pyrrolidines derived from arylimines are the kinetic products as they are efficiently produced at low temperatures (<−78 °C). However, at elevated temperatures (ca. −20 to −10 °C) only the acyclic products are detected indicating that at warmer temperatures the elimination pathway predominates.

(6) (a) *anti*-Silane reagents see: Panek, J. S.; Beresis, R.; Xu, F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341–7344. (b) *syn*-Silane reagents see: Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431–3438.

0022-3263/94/1959-2674$04.50/0

Scheme 1



10:1 syn:anti) was observed for cases involving the α-methoxy (*E*)-crotylsilanes, entries 2 and 11 (Table 1).

Discovery of the pyrrolidine annulation was made using the (*E*)-crotylsilane (*3R*)-**1a** with benzaldehyde dimethyl acetal (1.2 equiv) and methyl carbamate (1.25 equiv) in CH_2Cl_2 (0.3 M, $-100 \rightarrow -78$ °C, 12 h). The homoallylic amine **3a** and the annulated pyrrolidine **4a** were obtained as a 1:12 mixture after the reaction mixture was diluted with a solution of $NaHCO_3$ and extractive isolation (eq 2). Chromatography afforded **4a** in 68% isolated yield and 6% of the acyclic amine, each as a single diastereomer (Table 1, entry 8).[7,8] The assumption that both products are formed through a common mechanistic pathway is supported by correlation experiments; treatment of the isolated pyrrolidines **4a** and **4b** with BF_3·OEt_2 (1.0 equiv, -10 °C) generated the acyclic products **3a** and **3b** in high yield. Having verified an efficient, controllable [3 + 2] pyrrolidine annulation of **1a**, we surveyed a series of acetals and (*E*)-crotylsilanes to determine the generality. The results obtained from those experiments have led us to conclude that only the more reactive arylimines are effective in the formation of the pyrrolidines. Alkyl or branched acetals/aldehydes required higher temperatures in the initial condensation and did not produce the annulated pyrrolidines.

The isolation of the 2,5-cis isomer is consistent with the stepwise mechanism proposed to rationalize the formation of related tetrahydrofurans and cyclopentanes; initial C–C bond construction occurs by an anti-S_E' addition.[4,8] The stabilized β-silyl carbocation is illustrated rearranging through a bridged siliranium ion; this migration promotes the cyclization step, as it proceeds with inversion at the C5 position (eq 2).[9]

In summary, the use of chiral (*E*)-crotylsilanes in condensation reactions with C=N π bonds provides a highly stereoselective process for the formation of homoallylic amines, a new asymmetric pyrrolidine annulation, and continues to expand the scope of our developing chiral allylsilane methodology.

Acknowledgment. Financial support was obtained from the National Institutes of Health (CA47249 and CA56304) and the donors of the Petroleum Research Fund, administered by the American Chemical Society (ACS-PRF No. 25590).

Supplementary Material Available: General experimental procedures as well as spectral data for all addition and annulation products (7 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.

(7) All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^1H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data.

(8) (a) The relative stereochemical assignment of the homoallylic amines was based on analogy from the ^1H-NMR coupling constant analysis of the derived cyclic carbamate of **3a**; see supplementary material for details. Assignment of the pyrrolidine products as the cis-2,5-trans-3,4 stereoisomer was based on 1D homonuclear decoupling, multiple difference NOE, 2D-NOE experiments, and correlation experiments; see supplementary material for details. (b) The absolute stereochemistry of the homoallylic carbamates was assigned by correlation with (2*S*,3*S*)-3-methylaspartic acid [lit. $[\alpha]^{23}_D = +13.5$ (*c* 1.5 5 N HCl): McClarin, J. A.; Dressel, L. A.; Legg, J. I. *J. Am. Chem. Soc.* **1976**, *98*, 4150–4154] obtained from a resolution of *erythro* and *threo* isomers. Synthetic material [$[\alpha]^{23}_D = +11.22$ (*c* 1.5 5 N HCl)] was obtained in four steps from **3d**; see supplementary material for details.

(9) Brook, A. G.; Bassindale, A. R. In *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. II, pp 190–192.