Asymmetric [3 + 2] Δ^2-Isoxazoline Annulation by Electrophilic Substitution of (*E*)-Crotylsilanes with Nitrosium Tetrafluoroborate

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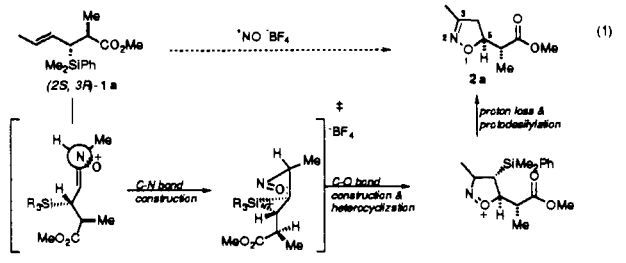
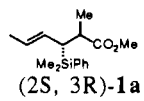
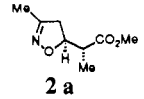
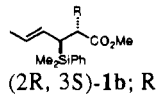
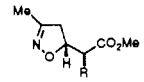
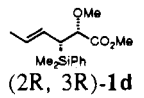
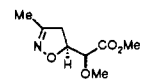
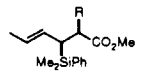
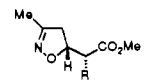
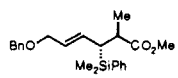
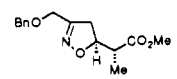
The development of stereoselective 1,3-dipolar cycloadditions of nitrile oxides has broadened the synthetic utility of Δ^2-isoxazolines.[1] The utility of this heterocycle is derived from its ready conversion to useful synthetic intermediates, β-hydroxy ketones[2] and γ-amino alcohols.[3] Advances in reaction design that provide more efficient and selective methods for the construction of these heterocycles may be regarded as useful contributions to the field of asymmetric synthesis. In support of this notion, only a limited number of examples are available concerning the asymmetric 1,3-dipolar cycloadditions of nitrile oxides that proceed with high levels of diastereoselection.[4] This paper describes an efficient and simple procedure for the asymmetric synthesis of functionalized Δ^2-isoxazolines utilizing our chiral allylsilane bond construction methodology. The reaction represents and extension of related studies from our laboratory involving Lewis-acid-promoted additions of chiral (*E*)-crotylsilanes to activated π bonds, producing highly functionalized homoallylic ethers,[5] tetrahydrofurans,[6] γ-alkoxy-α-amino acid synthons,[7] and tetrasubstituted cyclopentanes.[8] The annulation illustrated with (*E*)-crotylsilane **1a** and nitrosium tetrafluoroborate ($^+NO^-BF_4$) proceeds under mild reaction conditions (–80 °C → room temperature), producing functionalized Δ^2-isoxazolines with high enantiomeric purity (eq 1).



In a related [3 + 2] annulation, Danheiser has shown that allenylsilanes can be used as carbon nucleophiles to produce substituted isoxazoles.[9] The present study considerably extends the original findings as it: (1) documents the participation of chiral (*E*)-crotylsilanes[10] in the electrophilic substitution to $^+NO^-BF_4$, (2) results in the asymmetric construction of 3,5-disubstituted Δ^2-isoxazolines, and (3) demonstrates the issues of relative and internal asymmetric induction. The isoxazoline annulation was initiated when silane **1a** was added to a suspension of $^+NO^-BF_4$ (2.0 equiv) in CH_2Cl_2 (0.30 M, –80 °C, → room temperature, 5 h). After the reaction was quenched with a solution of $NaHCO_3$, the Δ^2-isoxazoline **2a** was isolated in 65% yield (eq 1) without the formation of acyclic products.[11] In agreement with the precedented stereochemical course of electrophilic substitution reactions of chiral allylsilanes, the initial C–N bond construction takes place by an *anti*-$S_{E'}$ addition.[5,12] The developing β-silyl carbocation (shown as a bridged silenium ion)[13] is stabilized through the $\sigma \rightarrow$ p conjugation of the adjacent C–Si bond, which facilitates the cyclization step, as it proceeds with inversion at the

Table I. Asymmetric Synthesis of Δ^2-Isoxazolines

silane	major product[a]	yield (%)[b]	ratio diast[c]
 (2S, 3R)-**1a**	 **2a**	65	20:1
 (2R, 3S)-**1b**; R = Me	 **2b**	65	20:1
(2R, 3S)-**1c**; R = Bn	**2c**	72	>40:1
 (2R, 3R)-**1d**	 **2d**	75	40:1
 (2S, 3S)-**1e**; R = Me	 **2e**	63	12:1[d]
(2S, 3S)-**1f**; R = OBn	**2f**	65	20:1
(2S, 3S)-**1g**; R = OAc	**2g**	72	>40:1
 (2S, 3R)-**1h**	 **2h**	54	20:1

[a] Run in CH_2Cl_2 (0.3 M) from –80 °C → room temperature, 5 h. [b] Based on pure material isolated by chromatography (SiO_2). [c] Ratios were determined by ^1H NMR. [d] Ratio is consistent with the starting silane (12:1 *syn*:*anti*), see ref 10b.

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(1) Reviews, see: (a) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1069–1109. (b) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719–736. (c) Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, p 291.

(2) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826–5833, and references cited therein.

(3) (a) Jäger, V.; Müller, V. *Tetrahedron Lett.* **1982**, *23*, 4777–4780. (b) Jäger, V.; Buss, V. *Liebigs Ann. Chem.* **1980**, 101–120. (c) Jäger, V.; Müller, V.; Paulus, E. F. *Tetrahedron Lett.* **1985**, *26*, 2997–3000.

(4) (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Chem. Soc., Chem. Commun.* **1987**, 529–530. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1988**, *44*, 4645–4652. (c) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555–3558.

(5) (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*, 294–296.

(6) (a) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868–9870. (b) Panek, J. S.; Beresis, R. *J. Org. Chem.* **1993**, *58*, 809–811.

(7) Panek, J. S.; Yang, M.; Muler, I. *J. Org. Chem.* **1992**, *57*, 4063–4064.

(8) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1993**, *58*, 2345–2348.

(9) (a) Danheiser, R. L.; Becker, D. A. *Heterocycles* **1987**, *25*, 277–281. (b) Propargylsilanes: Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094–6097. (c) Review: Panek, J. S. In *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991, Vol. 1, pp 579–627.

(10) (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.

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

(12) Review: (a) Fleming, I. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 563–593. For a discussion concerning the mechanisms and stereochemistry of $S_{E'}$-type reactions, see: (b) Matassa, V. G.; Jenkins, P. R.; Kumin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* **1989**, *29*, 321–343, and references cited therein; (c) The absolute stereochemical assignment of the isoxazoline products is based on the electrophilic substitution reaction proceeding through an *anti*-$S_{E'}$ mechanism, see supplementary material for details.

(13) 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.

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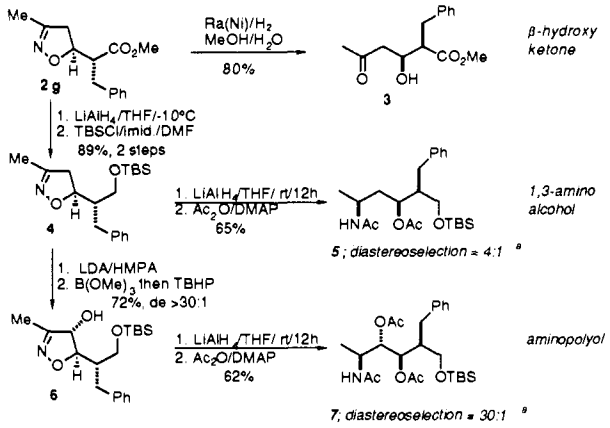
Scheme I[a]



[a] Stereochemical assignments are based on analogy with hydride reductions of related systems *cf.* refs 2 and 3.

C5 position. Heterocyclization with C–O bond formation produces the intermediate Δ^1-isoxazoline, which after loss of the C3 proton and subsequent protodesilylation results in the formation of the Δ^2-isoxazoline ring system.

The results of the annulation are summarized in Table I. For these examples, $^+NO^-BF_4$ (2.0 equiv) in anhydrous CH_2Cl_2 was determined to be the most effective nitrosating agent–solvent combination for efficient conversion to the isoxazoline. A series of α-substituted *syn*- and *anti*-(*E*)-crotylsilanes were surveyed to determine the utility of these reagents in the heteroannulation. The silane reagents exhibited high levels of diastereoselection, producing the Δ^2-isoxazolines **2a–h** with ee values reaching 96% as determined by ^1H NMR analysis.[12c]

The synthon equivalency for the formation of β-hydroxy ketones and amino alcohols is illustrated in Scheme I. Reductive opening with Raney Ni produced the *syn*-β-hydroxy ketone **3** as a single diastereomer. $LiAlH_4$ reduction of **4** and **6** afforded the 1,3-amino alcohols **5** and **7**, consistent with literature precedent.[3] As projected, the substrate-directed reaction involving the C4-hydroxylated isoxazoline **6** was found to be highly selective, whereas **4** exhibited moderate selectivity.

In conclusion, the [3 + 2] annulation with chiral (*E*)-crotylsilanes provides a highly stereoselective process for the formation Δ^2-isoxazolines, complementing the well-established 1,3-dipolar cycloaddition methodology.

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Supplementary Material Available: General experimental procedures; spectral data, and ^1H and ^{13}C NMR spectra for all annulation products (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. Ordering information is given on any current masthead page.