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Communications

Conjugate Addition Reactions of Chiral (*E*)-Crotylsilanes: Application to an Asymmetric [3 + 2] Cyclopentane Annulation

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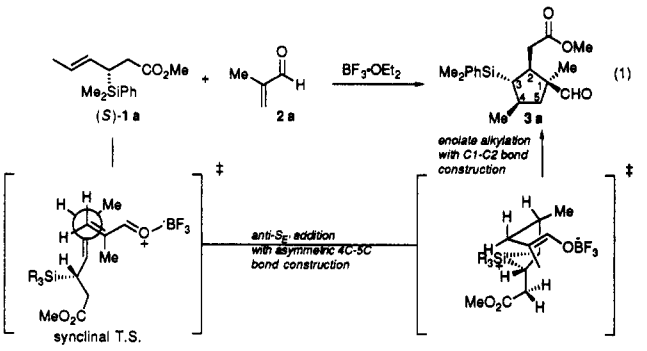
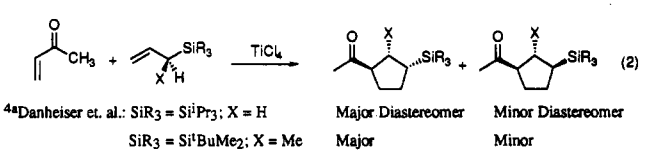
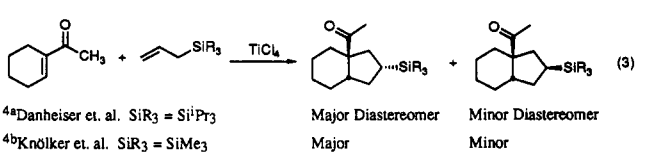
Summary: Functionalized (*E*)-crotylsilanes **1** undergo Lewis acid promoted conjugate addition reactions with α-substituted enals and methyl vinyl ketone **2** to produce tetrasubstituted cyclopentanes **3** with high levels of diastereoselection. The reaction is believed to proceed by an initial 1,4-addition which is followed by a 1,2-silyl migration and a final cyclization step involving the derived boron enolate resulting in the construction of the cyclopentanoid product.

Lewis acid promoted asymmetric addition reactions of chiral (*E*)-crotylsilanes with acetals and aldehydes have been shown to proceed with high levels of diastereoselection to form highly functionalized homoallylic ethers,[1] tetrahydrofurans,[2] and γ-alkoxy-α-amino acid synthons.[3] These asymmetric reaction processes are initiated by a simple bimolecular reaction which is consistent with an anti-S_E' process. In studies designed to further probe the utility of the these organosilane reagents we have learned that they undergo asymmetric conjugate addition reactions with α-substituted α,β-unsaturated enals and methyl vinyl ketone **2** resulting in the formation of tetrasubstituted cyclopentanes in highly scalemic form. The present annulation process is illustrated in eq 1.



Recent reports by Danheiser,[4a] Knölker,[4b] and others have documented the fact that allylsilanes function as effective three-carbon components with methyl vinyl ketone and 1-acetylcyclohexene in a related [3 + 2] annulation promoted by titanium tetrachloride. Relevant examples of those studies are summarized in eqs 2 and 3.





(1) (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.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790–5792.

(2) (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.

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

(4) (a) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094–6097 and references cited therein. Related Lewis acid promoted [3 + 2] annulations involving achiral allylsilanes and stannanes with enones have also been reported; see: (b) Knölker, H.-J.; Jones, P. G.; Pannek, J.-B. *Synth. Lett.* **1990**, 429–430. (c) Allylations of α,β-unsaturated alkoxycarbene–iron complexes: Herndon, J. W. *J. Am. Chem. Soc.* **1987**, *109*, 3165–3166. (d) Snider, B. B.; Zhang, Q. *J. Org. Chem.* **1991**, *56*, 4908–4913.

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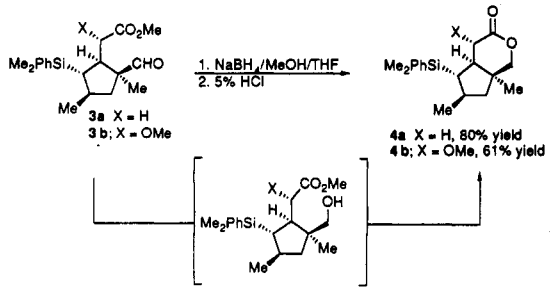
Here we describe preliminary results from our study of this reaction which constitutes a formal silicon directed [3 + 2] carbon annulation resulting in the asymmetric synthesis of functionalized cyclopentanes. This method of cyclopentane construction continues to extend our developing chiral allylsilane bond based construction methodology to include the complementary conjugate addition reaction, and together with our earlier reports concerning additions to aldehydes and acetals perhaps represents a general strategy for asymmetric C–C bond construction. In the realization of the asymmetric version of the [3 + 2] cyclopentane annulation we have found that (3*S*,4*E*)-methyl 3-(dimethylphenylsilyl)hexenoate (**1a**), underwent a conjugate addition and cyclization[5] with 2-methylacrolein (**2a**) promoted by $BF_3{\cdot}OEt_2$ (2.0 equiv) in CH_2Cl_2 (0.45 M, rt, 8 h) affording the tetrasubstituted cyclopentane **3a** in 93% isolated yield with nearly complete stereocontrol.[6] Important aspects of the present annulation include the high levels of diastereoselection; the dimethylphenylsilyl group (DMPS) and carbonyl groups emerge in a trans-1,3-relationship while the methylene group bearing the methyl ester arises cis to the aldehyde on the cyclopentane ring.[7] Consistent with our earlier report concerning the asymmetric tetrahydrofuran annulation, the 1,2-silyl migration step is favored over the conventional elimination pathway (Sakurai reaction).[8] The proposed reaction pathway for the formation of the tetrasubstituted cyclopentane begins with a conjugate addition shown proceeding through a synclinal model transition state[9] with the Lewis acid–aldehyde complex in an s-trans configuration (eq 1).[10] We believe that the positioning of the BF_3–aldehyde complex favors addition to the face of the π-bond which leads to a transition state that develops less torsional strain between the vinyl methyl of the crotylsilane and the methyl group of the aldehyde.[11] As illustrated in eq 1 with (3*S*)-**1a**, an enantioselective conjugate addition to the α,β-enal **2a** produces a boron enolate and a β-silyl carbocation (represented as a bridged silinium ion) stabilized through the $\sigma \rightarrow \pi$ conjugation of the adjacent C–Si bond.[12] A 1,2-cationic migration of the DMPS group[13] is followed by a highly stereoselective cyclization step involving the derived enolate producing the tetrasubstituted cyclopentane **3** with the aldehyde group and the carbon bearing the methyl ester in a cis-1,2 relation about the carbocyclic ring. As illustrated by our reaction pathway, the cyclization step involving the derived enolate occurs with inversion at the C2-carbon (cyclopentane numbering) bearing the bridged silinium ion species.[3,7] The potential synthetic utility of the annulation is further increased by the fact that the cyclopentanes are equipped with a DMPS group, a known hydroxyl group synthon, and functionalized with a quaternary carbon center at C1 and a methyl acetic acid ester at C2.[14]

Having confirmed that the annulation product was indeed cyclopentane derived, we surveyed a series of related α,β-enals and methyl vinyl ketone to complete the first phase of our studies concerning asymmetric conjugate addition reactions. The results of the asymmetric [3 + 2]



(5) (a) (3*S*,4*E*)-Methyl 3-(dimethylphenylsilyl)hexenoate (**1a**) $[\alpha]^{23}_D$ = −17.0° (*c* = 1.0 CH_2Cl_2) was prepared with an ee of 93% from (3*S*)-(*E*)-1-(dimethylphenylsilyl)-1-buten-3-ol by an ortho ester Claisen rearrangement [$MeC(OMe)_3$, cat. propionic acid, toluene reflux] in 85% isolated yield; cf. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743. (b) (2*R*,3*R*,4*E*)-Methyl 2-methoxy-3-(dimethylphenylsilyl)hexenoate (**1b**) $[\alpha]^{23}_D$ = −12.5° (*c* = 1.0 CH_2Cl_2) and (2*S*,3*S*,4*E*)-methyl 2-methoxy-3-(dimethylphenylsilyl)hexenoate (**1c**) $[\alpha]^{23}_D$ = +14.0° (*c* = 1.0 CH_2Cl_2) were prepared by an Ireland–Claisen rearrangement as previously reported; cf. Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3438–3431. (c) (3*S*,4*E*)-Methyl 4-methyl-3-(dimethylphenylsilyl)hexenoate (**1d**) $[\alpha]^{24}_D$ = −20.6° (*c* = 2.3 CH_2Cl_2), was prepared from (*S*)-(*E*)-1-(dimethylphenylsilyl)-2-methyl-1-buten-3-ol by an ortho ester Claisen rearrangement [$MeC(OMe)_3$, cat. propionic acid, toluene reflux] in 65% yield (96% ee, cf. Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 999–1002). Ee determination of the claisen products **1a** and **1d** was accomplished by a Mosher analysis using the method of Trost et al. (cf. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovek, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374) on the (*R*)-*O*-acetyl mandelate esters of the primary alcohols derived from the reduction of the methyl ester of the (*E*)-crotylsilanes. Methyl ester reduction of **1a** and **1b** with $LiAlH_4$ (1.0 equiv/THF/0 °C) followed by esterification of the derived primary alcohol with (*R*)-*O*-acetyl mandelic acid [1.5 equiv/DCC (1.5 equiv)/cat. DMAP/CH_2Cl_2] [cf. Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548–3551] afforded the new mandelate esters in 91% and 95% yields, respectively (two steps).

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

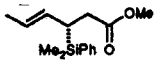
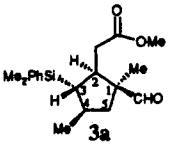
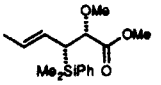
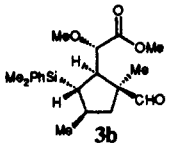
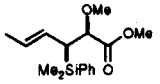
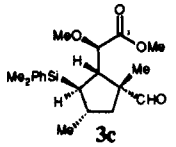
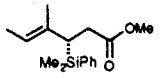
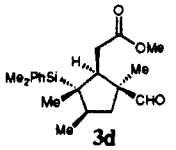
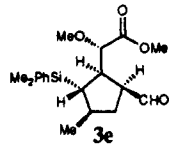
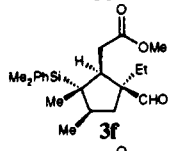
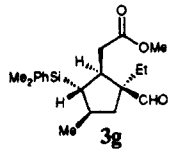
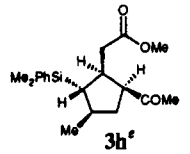
(7) The stereochemical assignment of the major diastereomers as the 1,2-*cis*-2,3-*cis*-cyclopentanes **3a–h** was determined by careful NMR analysis utilizing homonuclear decoupling, multiple-difference NOE, and 2D-NOE experiments. Additional evidence corroborating the stereochemical assignments was obtained for cases **3a** and **3b**. The $NaBH_4$ reduction (1.0 equiv, MeOH/THF (4:1), 0 °C → rt, 30 min, then 5% HCl and extractive isolation) of the illustrated aldehydes produced the cis-fused bicyclic lactones **4a** and **4b**, respectively, see supplementary material for details.

(8) The absolute stereochemical assignment of the cyclopentane products is based on the fact that electrophilic substitution reactions of optically active allylsilanes proceed through an anti S_E' mechanism (anti attack). For example, in the present study we have made the assumption that the illustrated crotylsilanes **1** follow the same mechanistic pathway, the (1*S*,3*S*,4*S*,5*R*) cyclopentane products are derived from the (2*R*,3*R*,4*E*)-crotylsilane **1b**, and the (1*R*,3*R*,4*R*,5*S*) stereoisomers are derived from the (2*S*,3*S*,4*E*)-crotylsilane **1c**. Optical purities of the product cyclopentanes were determined by ^1H NMR (400 MHz) analysis of the addition products after chromatography on SiO_2 (plug) to remove any unreacted olefin and are based on the fact that nearly complete stereocontrol is observed for the crotylsilanes. The ee was determined to be 96% and refers to product ratios obtained from an anti S_E' addition for the trans-3,4-substitution on the derived cyclopentanes. These asignments are based on the fact that the C2-stereocenter of the (*E*)-crotylsilanes **1b** and **1c** does not show any appreciable signs of epimerization (see ref 1a) under the described reaction conditions. As a consequence, it serves as a stereochemical indicator which allows the detection of any stereochemical defect associated with the formation of the other diastereomer which would be derived from a syn-S_E'. For discussions concerning the mechanism and stereochemistry of S_E'-type reactions, see: (a) 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. (b) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962–4963. (c) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Wilson, T. M. *Tetrahedron* **1989**, *45*, 1053–1065.

(9) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, 64, 1413–1423. For recent reviews concerning stereoselective conjugate addition see: (a) Oare, D. A.; Heathcock, H. C. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.: John Wiley and Sons: New York, 1989; Vol. 19, pp 227–407. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series, No. 9; Pergamon: Oxford, 1992. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806. For Lewis acid catalyzedintramolecular additions of certain allylsilanes and stannanes to aldehydes, a synclinal arrangement of the reacting olefins has been postulated [cf. Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655–1560].

(10) The solution structure of 2-methylacrolein–boron trifluoride complex: Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945–6948.

Table I. Asymmetric [3 + 2] Cyclopentane Annulation

entry	crotylsilane	α,β-unsaturated aldehyde/ketone	reaction condns[a] (T (°C)/time (h))	major diast[b]	% yield[c]	diast ratio (C1:C2)[d]
1	 **1a**	 **2a**	rt/8	 **3a**	93	>30:1
2	 **1b**	**2a**	rt/12	 **3b**	73	>30:1
3	 **1c**	**2a**	rt/12	 **3c**	73	>30:1
4	 **1d**	**2a**	rt/7	 **3d**	65	>30:1
5	**1b**	 **2b**	rt/5.5	 **3e**	62	>30:1
6	**1d**	 **2c**	rt/7	 **3f**	51	>30:1
7	**1a**	**2c**	rt/7	 **3g**	81	>30:1
8	**1a**	 **2d**	−10–0/10	 **3h**[e]	56	6:1

[a] All reactions were carried out in CH_2Cl_2 using 0.45 mmol of (*E*)-crotylsilane, 3 equiv of α,β-unsaturated aldehyde/ketone, 2 equiv of $BF_3{\cdot}OEt_2$. [b] Assignment of stereochemistry is based on 2D-NOE and multiple difference NOE. [c] All yields are based on pure material isolated by chromatography on SiO_2. [d] Ratio of diastereomeric products were determined by ^1H NMR (400 MHz, 93.94 KG) operating at a S/N ratio of >200:1. [e] The conjugate addition/elimination product (Sakurai reaction) was isolated in 31% yield.

cyclopentane annulation are summarized in Table I. For the cases examined in this study, $BF_3{\cdot}OEt_2$ (2.0 equiv) in CH_2Cl_2 at room temperature was determined to be the most effective combination for efficient conversion to the cyclopentane products. In the reactions with the α-substituted aldehydes methylacrolein (**2a**) and ethylacrolein (**2c**) with (*E*)-crotylsilanes **1a–1d**,[5] good levels of diastereo- and enantioselection were generally exhibited, producing the tetrasubstituted cyclopentanes **3a** through **3f** with cis/trans ratios reaching 30:1 as determined by ^1H-NMR analysis (entries 1–7). The addition of silane **1b**, to acrolein afforded the trans-1,3-substituted silyl-functionalized cyclopentane **3e** in 62% yield. In contrast, lower levels of selectivity in the cyclization step (6:1 cis-1,2/trans-1,2) were observed in the reaction of **1a** with methyl vinyl

(11) One consequence of this transition state model is the implication that employing β-substituted enones (electrophilic olefin bearing a stereogenic center at the β-position) should produce pentasubstituted cyclopentanes with similar levels of diastereoselection. The sense of diastereoselection in the initial C–C bond construction will be determined by the preference in the orientation of the reacting π-bonds in the transition state which may be determined through minimization of nonbonding interactions between the substituents of the crotylsilane and electrophilic olefin.

(12) For reviews of synthetic applications of organosilane chemistry, see: (a) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57–575. (b) Majetich, G. In *Organic Synthesis: Theory and Application*, Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, pp 173–240. (c) Birkofer, L.; Stuhl, O. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley and Sons Ltd.: New York, 1989; Chapter 10. (d) Panek, J. S. In *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 596–593.

(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.

(14) With certain tetrahydrofurans we have demonstrated that the DMPS group can be exchanged for a hydroxyl group with retention of configuration (cf. ref 2a) employing $Hg(OAc)_2$,CH_3CO_2H/CH_3CO_3H (cf. Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229–4232).

ketone (**2d**) (entry 8). The initial reaction temperature was decreased to −10 °C to improve the overall yield and to insure the efficient and clean conversion to the cyclopentane product.

In conclusion, the asymmetric addition of chiral (*E*)-crotylsilanes to α,β-unsaturated enals and methyl vinyl ketone constitutes a remarkably simple procedure for the construction of nearly optically pure, tetrasubstituted cyclopentanes. Interesting features of this Lewis acid-mediated cyclopentane synthesis include the high levels of diastereoselection and the ease of the 1,2-silyl migration directing the second C–C bond construction step and cyclization. Further studies of these organosilane reagents in asymmetric transformations including addition reaction to β-substituted enones and α,β-unsaturated acylsilanes are in progress.

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Supplementary Material Available: General experimental procedures for the cyclopentane annulation and relative stereochemical assignments as well as spectral data for all reaction products (4 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.