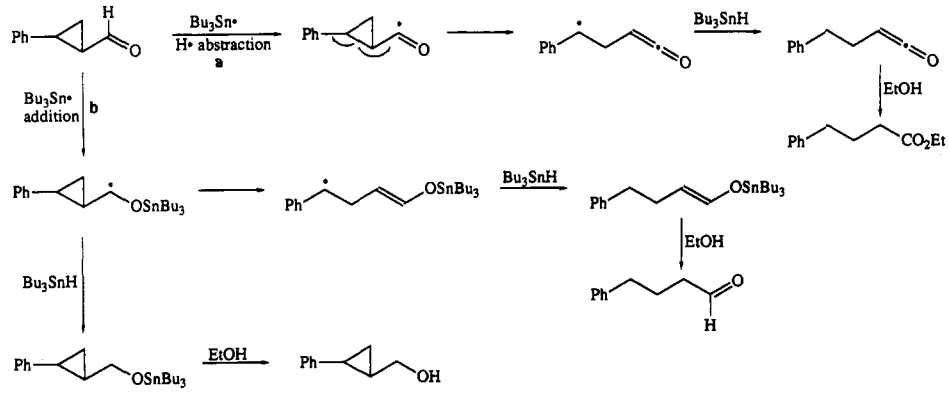
Scheme IV. Potential Pathways for the Reaction of 2-Phenylcyclopropanecarboxaldehyde with Tributyltin Radicals



the xanthate methylthio radical (related to Scheme II). ^{119}Sn NMR was used to confirm that the addition mechanism was correct in this case as well.

Experimental Section

NMR spectra were recorded either on a Varian XLA-400 (400 MHz) spectrometer or a Varian Gemini-300 (300-MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Electron impact mass spectra were obtained at 70 eV on a V6 70-250SE chromatomass spectrometer with a HP cross-linked methyl silicone capillary column. All reagents were from Aldrich Chemical Co., Inc., and were used without further purification.

Reduction of Aldehydes with Tributyltin Hydride or Deuteride (General Procedure). Equimolar amounts of the reagents (5 mmol) in benzene (15 mL) and a catalytic amount of AIBN (5 mol %) were heated in a bath at 80 °C for 4 h. The mixture was cooled and passed through a short silica gel column (elution with ethanol), and the eluent was analyzed by GC or GC-mass.

***trans*-(2-Phenylcyclopropyl)carbinol.** The procedure of Sneen et al.[10] was followed starting from *trans*-2-phenylcyclopropanecarboxylic acid, and the product was obtained as a colorless oil: bp 140–141 °C (13.5 mmHg) (lit.[11] 144 °C (14 mmHg); lit.[10] bp 90 °C (0.3 mmHg)); ^1H NMR ($CDCl_3$) δ 0.70–0.90 (m, 2 H), 1.15–1.50 (m, 1 H), 1.55–1.85 (m, 1 H), 2.80 (s, OH), 3.45 (d, 2 H), 6.80–7.35 (m, 5 H).

***trans*-(2-Phenylcyclopropyl)carboxaldehyde.** The alcohol (5.9 g, 40 mmol) was oxidized with pyridinium chlorochromate (15.1 g, 70 mmol) in CH_2Cl_2 (100 mL) at room temperature (1.5 h) by the method of Corey and Suggs.[12] The aldehyde was extracted with ether from the reaction mixture and distilled to give the product as a colorless oil (3.5 g, 60%), 93–95 °C (5 mmHg), 2,4-dinitrophenylhydrazone, mp 181–182 °C (from alcohol) (lit.[11] mp 179–180 °C (from benzene)): ^1H NMR ($CDCl_3$) δ 1.25–1.80 (m, 2 H), 1.95–2.25 (m, 1 H), 2.35–2.75 (m, 1 H), 6.90–7.40 (m, 5 H), 9.27 (d, 1 H) (same as lit.[13]); HRMS (EI) calcd for $C_{10}H_{10}O$ 146.0732, found 146.0737. This product was readily oxidized in air to the corresponding carboxylic acid.

Hex-5-enal. 5-Hexenol (3.0 g, 30 mmol) was oxidized by pyridinium chlorochromate (9.5 g, 45 mmol) by the method of Corey and Suggs.[12] A colorless liquid (1.8 g, 60%) was obtained after distillation at 48–50 °C (50 mmHg) (lit.[14] distillation 118–118.5 °C): ^1H NMR δ 1.60–2.50 (m, 6 H), 4.80–5.10 (m, 2 H), 5.50–5.95 (m, 1 H), 9.78 (t, J = 1.4, 1 H) (same as ref 15).

4-Phenylbutanal. 4-Phenyl-1-butanol (1.5 g, 10 mmol) was oxidized by pyridinium chlorochromate (3.5 g, 16 mmol) by the method of Corey and Suggs.[12] A colorless liquid was obtained (0.8 g, 57%) after distillation at 65–67 °C (3 mmHg). The product oxidized rapidly to the carboxylic acid upon exposure to air: ^1H NMR δ 2.00–2.11 (m, 2 H), 2.45–2.55 (m, 2 H), 2.73 (t, J = 7.6 Hz, 2 H), 7.25–7.40 (m, 5 H), 9.80 (t, J = 1.4 Hz, 1 H); ^{13}C NMR δ 24.1, 35.4, 43.5, 126.5, 128.8, 128.9, 141.7, 202.8. Anal. Calcd for $C_{10}H_{12}O$: C, 81.08; H, 8.27. Found: C, 80.90; H, 8.27. 2,4-Dinitrophenylhydrazone, mp 105–107 °C (lit.[16] mp 106–107 °C). Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.87; N, 17.07. Found: C, 58.48; H, 4.88; N, 17.03.

Ethyl 4-Phenylbutanoate. 4-Phenylbutanoic acid (3.28 g, 20 mmol) was heated to reflux for 10 h in ethyl alcohol (10 mL) with a catalytic amount of sulfuric acid. After distillation at 105–106 °C (3 mmHg) (lit.[17] distillation 139 °C (15 mmHg), 80 °C (0.5 mmHg)) the product was obtained as a colorless liquid (3.1 g, 80%): ^1H NMR δ 1.23 (t, 3 H), 1.90–2.00 (m, 2 H), 2.30 (t, 2 H), 2.65 (t, 2 H), 4.10 (q, 2 H), 7.13–7.25 (m, 5 H); ^{13}C NMR δ 14.7, 27.0, 34.1, 35.6, 60.7, 126.4, 128.8, 128.9, 141.9, 173.9. Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.13; H, 8.29.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM32634) for financial support of this research.

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Silver(I)/Peroxydisulfate-Induced Oxidative Decarboxylation of Amino Acids. A Chemical Model for a Possible Intermediate in the Monoamine Oxidase-Catalyzed Oxidation of Amines

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Amino acids are known to undergo oxidative decarboxylation to give (after hydrolysis) the corresponding aldehyde by reaction with potassium peroxydisulfate ($K_2S_2O_8$) and catalytic silver(I)[1] or with silver(II) picolinate.[2] The mechanisms of these reactions, however, are not clear. In the case of the stoichiometric silver(II) reactions, where a cyclic complex can form, a concerted (electrocyclic) mechanism (Scheme I, 1) has been suggested, although a radical mechanism was not excluded.[2] The mechanism for

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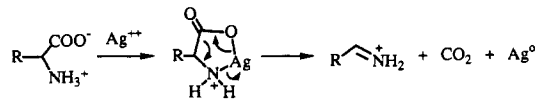
Scheme I. Oxidative Decarboxylation of Amino Acids by Silver(II) Picolinate



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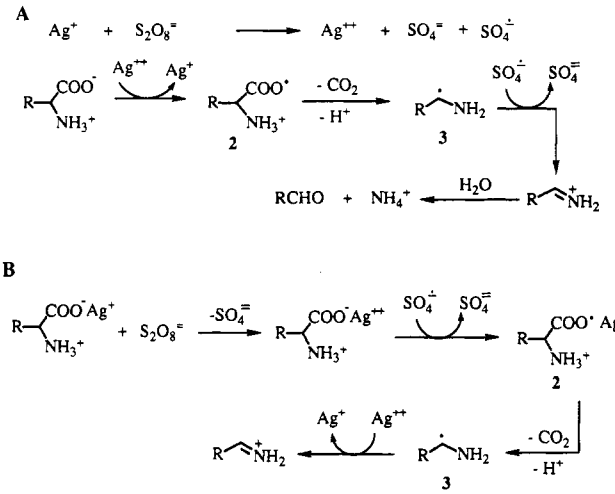
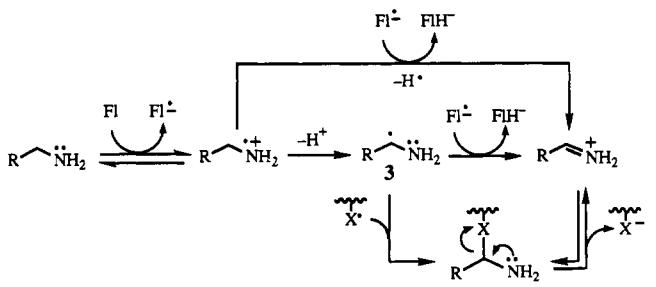
Scheme II. Possible Oxidative Decarboxylation Mechanisms for Amino Acids by $Ag^+/S_2O_8^{2-}$



Scheme III. Proposed Mechanism for Monoamine Oxidase[a]



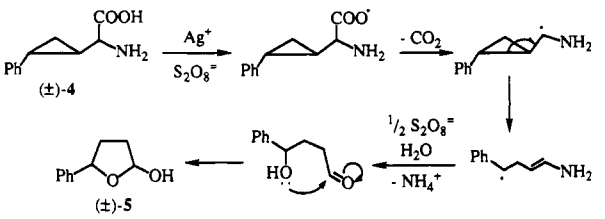
[a] Fl represents the flavin cofactor.

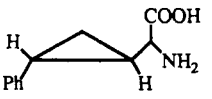
oxidative decarboxylation induced by peroxydisulfate ion with catalytic silver(I) may involve radical intermediates (Scheme II, 2 and 3).[3]

We sought to test the concerted versus radical mechanisms for these two oxidation systems because we were interested in utilizing a chemical model system that could be carried out in aqueous buffer at physiological pH and temperature for the reactions catalyzed by the enzyme monoamine oxidase. Monoamine oxidase catalyzes the oxidative deamination of a variety of amine neurotransmitters and hormones and has been proposed to involve the intermediacy of an α-amino radical (Scheme III, 3).[4] Consequently, if one of these silver-induced oxidations of an amino acid really proceeded via the α-amino radical 3, it would be an excellent model reaction for the proposed intermediate in this enzyme-catalyzed reaction.

The mechanisms in Scheme II involve a radical intermediate, and the standard approach for detection of radical intermediates has been the application of the cyclopropylcarbinyl rearrangement.[5] The rate of cyclopropylcarbinyl ring cleavage has been determined[6] to be about 10^8 s^{-1}, so if a radical is generated adjacent to the cyclopropane ring, it is expected that ring cleavage products would be produced. A concerted mechanism, however, would lead to the corresponding cyclopropanecarboxaldehyde without intermediacy of the cyclopropylcarbinyl radical. More reactive radical probes have been developed so that cyclopropane ring cleavage becomes more favorable than other reactions, e.g., second electron transfer.[7] One such probe is the 2-phenylcyclopropyl substituent; the (*trans*-2-phenylcyclopropyl)carbinyl radical cleaves at a rate of 1.8×10^{11} s^{-1} at 20 °C.[7a] In this note we report the synthesis and oxidative decarboxylation of 2-(2-phenylcyclopropyl)glycine ((±)-4), which was designed to test the mechanisms for silver(I)/peroxydisulfate and silver(II) picolinate oxidation of amino acids and to determine if an α-amino radical is an important intermediate in either reaction.

Scheme IV. Possible Mechanism for the Formation of 2-Hydroxy-5-phenyltetrahydrofuran





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Results and Discussion

(±)-2-(*trans*-2-Phenylcyclopropyl)glycine (4) was synthesized by Strecker synthesis methodology from *trans*-2-phenylcyclopropanecarboxaldehyde, which gave (±)-4 in an overall yield of 34%.

Treatment of 4 with Ag(I) and peroxydisulfate ions resulted in the formation of 2-hydroxy-5-phenyltetrahydrofuran (Scheme IV, 5) which was synthesized by an independent route. The formation of 5 suggests the generation of an intermediate cyclopropylcarbinyl radical. A mechanism to account for the formation of 5 is shown in Scheme IV. Because of the lability of 5 only a 23% yield was recovered; 7% of 5-phenyl-γ-butyrolactone, which is the oxidation product of 5 also was obtained. Little or none of *trans*-2-phenylcyclopropanecarboxaldehyde, the product of two-electron oxidation of 4, was detected. This is consistent with a radical mechanism of action for this reagent.

Treatment of 4 with Ag(II) picolinate, however, gave exclusively *trans*-2-phenylcyclopropanecarboxaldehyde, which suggests that no α-amino radical was generated and supports the concerted mechanism (Scheme I) previously proposed.[2] The difference in the reagents may be that the addition of Ag(II) to the amino acid results in the formation of a five-membered ring (Scheme I, 1) that undergoes electrocyclic conversion to the iminium ion, CO_2, and silver metal at 70 °C. When the reaction was carried out at 40 °C, conditions used with the Ag(I)/peroxydisulfate system, no reaction occurred. When the Ag(I)/

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peroxydisulfate reaction was carried out at 70 °C, there was no difference in the resultant products of that reaction. Therefore, it is not the temperature that makes a difference in the pathways. Addition of picolinic acid to the Ag(I)/peroxydisulfate system gave no products either at 40 °C or at 70 °C, presumably because only a catalytic amount of silver(I) is used in this method and the metal is converted stoichiometrically to silver metal. When picolinic acid was added to a reaction containing a stoichiometric amount of silver(I) and peroxydisulfate followed by addition of amino acid, then many side products were formed in addition to 2-phenylcyclopropanecarboxaldehyde. It appears that the picolinic acid is important to the electrocyclic pathway, but it is not essential, because silver(II) oxide also is effective for the conversion of amino acids to aldehydes.[2]

The results described here suggest that the oxidative decarboxylation of amino acids by peroxydisulfate ion and catalytic silver(I) to the corresponding aldehyde at 40 °C in aqueous medium is a viable model system for the reaction catalyzed by monoamine oxidase.

Experimental Section

Reagents. All reagents are from Aldrich Chemical Co., Inc., except for potassium peroxydisulfate and silver acetate which were purchased from Mallinckrodt, Inc.

General Methods. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian XLA-400 (400 MHz) spectrometer; chemical shifts are expressed as parts per million (δ) downfield from tetramethylsilane. Mass spectra were obtained on a V6 70-250SE chromatomass spectrometer with a HP cross-linked methyl silicone capillary column.

***(trans*-2-Phenylcyclopropyl)carbinol.** The procedure of Sneen et al.[8] was followed, and the product was obtained as a colorless oil: bp 140–141 °C (13.5 mmHg) (lit.[9] bp 144 °C (14 mmHg); lit.[8] bp 90 °C (0.3 mmHg)); ^{1}H NMR ($CDCl_3$) δ 0.70–0.90 (m, 2 H), 1.15–1.50 (m, 1 H), 1.55–1.85 (m, 1 H), 2.80 (s, O-H), 3.45 (d, 2 H), 6.80–7.35 (m, 5 H).

***trans*-2-Phenylcyclopropanecarboxaldehyde.** The (*trans*-2-phenylcyclopropyl)carbinol (5.9 g, 40 mmol) was oxidized with pyridinium chlorochromate (15.1 g, 70 mmol) in CH_2Cl_2 (100 mL) at room temperature (1.5 h) by the method of Corey and Suggs.[10] The aldehyde was extracted with ether from the reaction mixture and distilled to give the product as a colorless oil (3.5 g, 60%): bp 93–95 °C (5 mmHg); 2,4-dinitrophenylhydrazone, mp 181–182 °C (from alcohol) (lit.[9] mp 179–180 °C (from benzene)); ^{1}H NMR ($CDCl_3$) δ 1.25–1.80 (m, 2 H), 1.95–2.25 (m, 1 H), 2.35–2.75 (m, 1 H), 6.90–7.40 (m, 5 H), 9.27 (d, 1 H) (same as lit.[11] data); HRMS (EI) calcd for $C_{10}H_{10}O$ 146.0732, found 146.0737. This product was readily oxidized in air to the corresponding carboxylic acid.

2-(2-Phenylcyclopropyl)glycine (4). A pressure bottle was charged with a cold saturated solution of ammonium chloride (6 mL), concentrated aqueous ammonia (6 mL), and sodium cyanide (1.5 g, 30 mmol) in water (3 mL). After being cooled to 0 °C a solution of *trans*-2-phenylcyclopropanecarboxaldehyde (3.7 g, 25 mmol) in methanol (5 mL) was added. The sealed bottle was shaken overnight, and then the water and ammonia were evaporated in vacuo at 30–40 °C. The residue was heated in refluxing concentrated hydrochloric acid (12 mL) for 3 h, and then the mixture was distilled in vacuo to dryness. The hydrochloride salt of the amino acid was dissolved in methanol and treated with triethylamine (15 mL). White crystals (2.6 g, 54%) were obtained which were recrystallized from methanol: mp 235–237 °C; ^{1}H NMR (D_2O, F_3CCOOD) δ 1.00–1.55 (m, 2 H), 2.00–2.35 (m, 1 H), 3.30–3.65 (m, 1 H), 6.95–7.35 (m, 5 H). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.33. Found: C, 68.75; H, 6.84; N, 7.22.

2-Methoxy-3-carbomethoxy-5-phenyltetrahydrofuran. The procedure of Korte and Machleidt[12] was followed as described by Loewen et al.[13] The mixture of isomers was obtained as a colorless oil (3.2 g, 45%): bp 125–127 °C (0.5 mmHg) (lit.[13] bp 125 °C (0.5 mmHg)); ^{1}H NMR ($CDCl_3$) δ 2.05–2.30 (m, 1 H), 2.40–2.75 (m, 2 H), 3.40–3.80 (m, 6 H), 4.70–5.65 (m, 2 H), 7.20–7.55 (m, 5 H).

2-Methoxy-3-carboxy-5-phenyltetrahydrofuran. This compound was prepared from the corresponding methyl ester by the procedure of Loewen et al.[13] (0.7 g, 35%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.60 (m, 3 H), 2.30–2.50 (m, 3 H), 4.90–5.40 (m, 2 H), 7.20–7.40 (m, 5 H). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.53; H, 6.27.

2-Hydroxy-5-phenyltetrahydrofuran (5). 2-Methoxy-3-carboxy-5-phenyltetrahydrofuran (0.44 g, 2 mmol) was heated in refluxing 0.5 N HCl (20 mL) under nitrogen for 20 h as described by Loewen et al.[13] The product was extracted with ether and purified on silica gel (cyclohexane–ether, 5:1), resulting in a colorless oil (0.20 g, 64%). The NMR spectrum showed a 1:1 mixture of the cis and trans isomers: ^{1}H NMR ($CDCl_3$) δ 1.70–2.60 (m, 4 H), 4.95–5.05 (m, 0.5 H), 5.23 (t, 0.5 H), 5.60 (d, 0.5 H), 5.70–5.75 (m, 0.5 H), 7.20–7.50 (m, 5 H); mass spectrum (m/z) 164, 147, 117, 107, 79, 58; HRMS (EI) calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0842. This compound was air sensitive, oxidizing to 5-phenyl-γ-butyrolactone.

Silver(II) Picolinate. This compound was obtained by the method Hampson et al.[2] Picolinic acid (6.15 g, 50 mmol) was dissolved in water, and silver nitrate (4.25 g, 25 mmol) was added followed by potassium peroxydisulfate (3.38 g, 12.5 mmol). The mixture was stirred for 48 h, and the red precipitate that formed was filtered and dried in vacuo (8.8 g, 100%).

Reaction of 4 with Silver(I) Peroxydisulfate. Amino acid 4 (1.0 g, 5 mmol), potassium peroxydisulfate (1.6 g, 6 mmol), and a catalytic amount of silver(I) acetate (0.05 g, 0.08 mmol) in water (40 mL) and $CHCl_3$ (100 mL) were stirred at 40 °C under nitrogen. The completion of the reaction was determined by iodometric titration of the peroxydisulfate ions; the reaction was stopped at 95% conversion of peroxydisulfate (about 4 h). The organic phase was separated and passed through a short silica gel column (elution with chloroform), and the eluant was analyzed by GC and NMR spectroscopy. The major product (23%) obtained was a 1:1 mixture of the cis and trans isomers of 5-phenyl-2-hydroxytetrahydrofuran. The corresponding γ-butyrolactone (7%) also was obtained, which was shown to be derived from 5-phenyl-2-hydroxytetrahydrofuran. The product was identical (NMR, GC) with the synthesized compound as described above.

Reaction of 4 with Silver(II) Picolinate. The procedure was the same as that described by Hampson et al.[2] The amino acid (4) (0.4 g, 2 mmol) and silver(II) picolinate (1.4 g, 4 mmol) in water (40 mL) were stirred with under reflux at 70 °C for 1 h, and then the reaction product was extracted into benzene and distilled in vacuo (93–95 °C (5 mmHg)), giving *trans*-2-phenylcyclopropanecarboxaldehyde as the major product (0.20 g, 75%). No 2-hydroxy-5-phenyltetrahydrofuran was detected.

Acknowledgment. Financial support of this research by the National Institutes of Health (GM 32634) is gratefully acknowledged.

Registry No. 4, 143169-59-9; *cis*-5, 143123-92-6; *trans*-5, 143123-93-7; $K_2S_2O_8$, 7727-21-1; AgOAc, 563-63-3; (*trans*-2-phenylcyclopropyl)carbinol, 936-98-1; *trans*-2-phenylcyclopropanecarboxaldehyde, 34271-31-3; 2-methoxy-3-carbomethoxy-5-phenyltetrahydrofuran, 38624-35-0; silver(II) picolinate, 22721-95-5; 5-phenyl-γ-butyrolactone, 69814-97-7; 2-methoxy-3-carboxy-5-phenyltetrahydrofuran, 143123-94-8; monoamine oxidase, 9001-66-5.

Supplementary Material Available: ^{1}H and ^{13}C NMR and mass spectra of 2-hydroxy-5-phenyltetrahydrofuran (5) (3 pages).

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Diastereoselective Additions of Chiral (*E*)-Crotylsilanes to in Situ Generated Oxonium Ions: A Direct Asymmetric Synthesis of Functionalized Homoallylic Ethers

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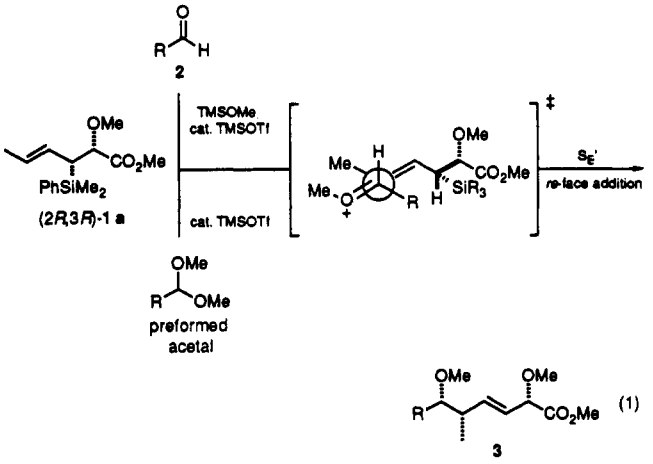
Received June 2, 1992

In recent reports from our laboratory, we have described the use of functionalized (*E*)-crotylsilanes as carbon nucleophiles in highly diastereo- and enantioselective addition reactions to preformed acetals and aldehydes. Those studies resulted in the development of a useful strategy for the asymmetric construction of homoallylic ethers,[1] tetrahydrofurans,[2] and γ-alkoxy-α-amino acid synthons,[3] subunits of many polyketide, and amino acid derived natural products. In experiments designed to optimize these reaction conditions, we have determined that the enantioselective condensation reactions can be performed by using a documented procedure for the in situ generation of an oxonium ion.[4] The action of a Lewis acid, (trimethylsilyl)trifluoromethanesulfonate (TMSOTf) and a silyl ether (Me_3SiOR) reagent cleanly promotes the asymmetric addition from the corresponding aldehyde (eq 1).[4d,e]



This note describes the results of our experiments concerning the asymmetric synthesis of homoallylic ethers employing the illustrated chiral (*E*)-crotylsilanes with the in situ generation of an oxonium ion from an achiral aldehyde. Thus, combining the chiral (*E*)-crotylsilane reagent **1** with an aldehyde **2** and the trimethylsilyl ether, TMSOMe[5] or TMSOBn,[5] followed by the Lewis acid, TMSOTf produced the homoallylic ether **3**. In most cases excellent levels of disastereo- and enantioselection were achieved, presumably through the oxonium ion species illustrated in the eq 1.

Key features of this process include the fact that highly functionalized homoallylic ethers are constructed in a three-component, one-pot operation with generally useful levels of stereoselection. Operationally, the reaction is simplified by removing the requirement for a preformed acetal.[6] In this regard, for the cases employing trimethylsilyl benzyl ether as the alkoxy exchange reagent, a benzyl moiety is installed on the secondary homoallylic ether without loss of diastereoselection (entries 3–9, Table I). The potential utility of such transformations is rather obvious, in the context of organic synthesis a protection step is removed from a reaction sequence. With regard to acyclic diastereoselective reaction processes the present study demonstrates that our developing chiral allylsilane bond construction methodology can be extended to include the in situ generation and capture of an oxonium ion.[4]

A summary of Lewis acid catalyzed addition reactions of **1a–d** to aldehydes **2a–i** is given in Table I. The diastereomerically pure *syn*- and *anti*-(*E*)-crotylsilanes employed in this study were prepared as previously reported.[7,8] For all the cases examined, the product homoallylic ethers **3** were obtained by mixing equimolar quantities of the silane reagent **1**, aldehyde **2**, and the trimethylsilyl ether at −78 °C followed by the addition of 0.2–1.0 equiv of TMSOTf. The resulting reaction mixture was then warmed to the indicated temperature (Table I) for 8–24 h with stirring to afford, after extractive isolation, **3a–i** in good to excellent yield. The reactions generally proceed with high levels of diastereoselection for the formation of the syn-C5,C6 isomer and are consistent with an anti-$S_{E'}$ mechanism as previously reported for intermolecular additions of chiral allylsilanes (entries 3–9).[9] The aliphatic and branched aldehydes (entries 1–6) were less reactive than the aromatic aldehydes (entries 7–9) and generally required higher temperatures and longer reaction times to ensure efficient conversion. The reactions of the aliphatic aldehydes, acetaldehyde, and valeraldehyde were nonselective (entries 1 and 2).

Stereochemical Assignment. Assignment of stereochemistry for the major C5,C6-syn isomer is based on comparison of the vicinal coupling constants between the C5/C6 stereogenic centers. In four cases, authentic sam-

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(9) The antiperiplanar transition state for intermolecular chiral allysilane additions was originally proposed by Kumada and co-workers: (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962–4963. For Lewis acid catalyzed intramolecular 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*, 1655–1660). (b) Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 2865–2868. For diastereoselective $S_{E'}$ additions of optically active allenylstannanes, see: Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 3211–3213.

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