Asymmetric C−N Bond Constructions via Crotylsilane Addition Reactions: A Stereocontrolled Route to Dipeptide Isosteres

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Received December 19, 1996[⊗]

Abstract: A new approach to the asymmetric synthesis of *(E)*-olefin dipeptide isosteres is described based on asymmetric C−N bond constructions resulting from nitronium tetrafluoroborate (NO_2BF_4) promoted electrophilic nitrations of chiral (*E*)-crotylsilanes and from a copper(I)-catalyzed enantioselective aziridination of chiral (*E*)-crotylsilanes. The silane reagents undergo efficient *anti*-S_E' additions to the nitrogen-based electrophiles to give the (*E*)-olefin isosteres in >96% de. The topological bias is principally controlled by the facial bias of the silane reagent. The scope of the methodology was explored via several related crotylsilane derivatives. The (*E*)-olefin isosteres are nonhydrolyzable, rigid analogs of the peptide linkage in biologically active peptides. The new methodology will facilitate the preparation and study of peptidomimetics since the crotylsilane reagents allow for incorporation of a wide range of functionality on the resulting isosteres.

Introduction

Replacement of the amide bond linkage with an *(E)*-olefin is a proven useful configurationally biased structural mimic for the construction of peptide linkages in a number of different enzyme inhibitors.[1] These analogs of biologically active peptides offer distinct advantages over the naturally occurring compounds including lower enzymatic degradation, increased oral bioavailability, and a prolonged duration of action.[2] The amide linkage is the primary target for enzymatic degradation of peptide and peptide-like substances; therefore structural modifications at this site may lead to enhanced metabolic stability. A combination of factors make such suitably functionalized molecules less susceptible to unwanted biodegradation. These factors include the absence of hydrogen bonding potential and unlike an amide bond inability to undergo proteolytic cleavage at the peptide linkage. In addition, it is known that key factors in the degree of bioactivity of the peptides are the chemical nature and stereochemistry of the associated α-amino acid side chains.[1a] Although hydrogen-bonding involving the amide linkage to the enzyme active site is important in bioactivity, the olefinic isostere may still achieve excellent binding recognition with a target enzyme. A comparison between the contributing resonance structures of the amide linkage and the incorporated *(E)*-olefin isostere produced is illustrated in Figure 1. Recently, interest has emerged in peptidomimetics of inverso D-peptides which are resistant to the action of cellular proteases thereby making these isosteres attractive for incorporation into potential drug candidates.[3]

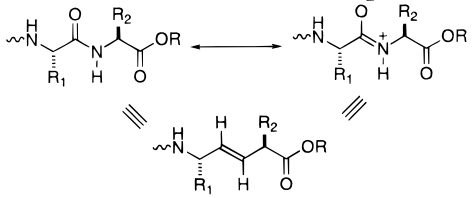

Figure 1. Comparison of contributing resonance structures of the amide linkage with the olefinic isostere.

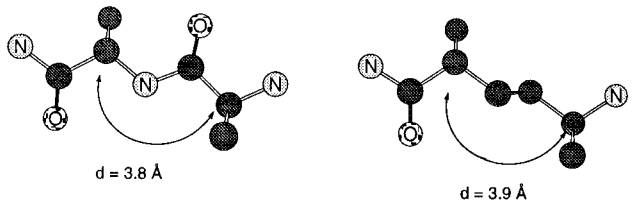

Figure 2. Comparison of the three-dimensional structure of the amide linkage with the olefin isostere.[4i]

(*E*)-Olefin isosteres have been shown to be useful replacements for the amide linkage in drug candidates as the (*E*)-CR═CH group closely approximates the bond lengths, angles, and rigidities of the natural parent amide (Figure 2). These peptide mimetics require the generation of a stereocenter at the α-position of a 5-amino-3-hexenoic acid derivative; therefore any successful chemical synthesis of dipeptide isosteres must

† Recipient of a Graduate Fellowship from the Organic Chemistry Division of American Chemical Society 1996−1997, sponsored by Organic Syntheses Inc.

⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1997.

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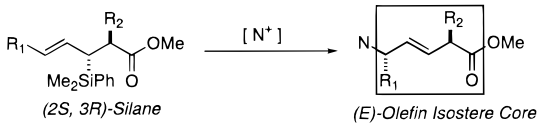


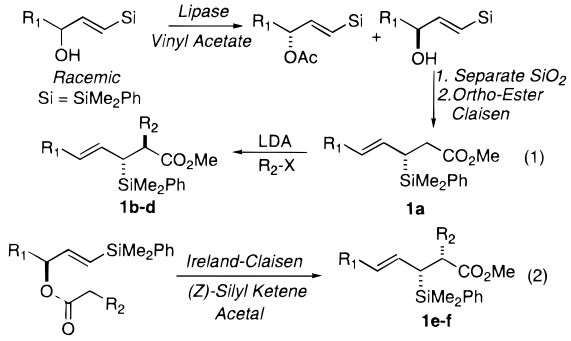
Figure 3. Access of isostere core via crotylsilylation reaction.

address an (*E*)-selective olefination process and also allow for the stereoselective introduction of the α-side chains of the amino acids associated with P_1-P_1' positions of the dipeptide. The lack of general efficient syntheses of *(E)*-olefins bearing bis-allylic stereocenters has impeded their development as peptidomimetics and reports describing highly stereoselective approaches to these isosteric units are rare.[4] These methods generally rely on the use of modified amino acid derivatives as the source of absolute chirality which typically leads to difficulties in the introduction of the second α-side chain of the associated amino acid. Ibuka and co-workers[5] have reported that boron trifluoride·organocopper reagents can be used for the introduction of the α-side chains of the (*E*)-olefin isostere. The reaction is thought to proceed by an *anti*-S_N2' displacement pathway on the δ-amino-γ-mesyloxy-α,β-unsaturated esters and represents a highly stereoselective process for the introduction of one of the isostere side chains. However, a multistep process was required to access the starting unsaturated ester. Recently, Wipf and co-workers[4i] have accessed this class of peptide mimetics by an *anti*-S_N2' alkylation of chiral *N*-acylaziridines with organocuprate reagents. In those cases, the cuprate additions were found to be prone to several side reactions and varying levels of diastereoselection.

Recent efforts in our laboratories have demonstrated that chiral (*E*)-crotylsilanes act as useful carbon nucleophile equivalents in highly diastereo- and enantiospecific condensation reactions with aldehydes, acetals, and certain electrophilic alkenes. These experiments have culminated in efficient methods for the asymmetric synthesis of functionalized homoallylic ethers, tetrahydrofurans, γ-alkoxy-α-amino acid synthons, and tetrasubstituted cyclopentanes.[6] The dipeptide isostere core, characterized by an *(E)*-olefin bordered on either side by alkyl substituted stereocenters on the peptide backbone, closely resembles the general structural type of products accessed by allylsilane/electrophile additions (Figure 3). The reaction results in the simultaneous introduction of a new *(E)*-double bond and both side chains (R_1 and R_2) with high levels of diastereo- and enantioselection. Due to the facile access to the isostere core that the crotylsilylation methodology affords, we became interested in the asymmetric synthesis of dipeptide isosteres. Although we had previously reported the construction of pseudo *C2*-symmetric isosteres by asymmetric Lewis acid promoted additions to *s*-trioxane,[7] a more general and direct approach to the isosteres would be realized by asymmetric C−N bond construction.

Our exploration has led to new asymmetric syntheses of *(E)*-olefin dipeptide isosteres which utilize a chiral allylsilane bond construction methodology involving additions of chiral (*E*)-crotylsilanes to nitrogen-based electrophiles. This methodology is capable of solving the problems of stereocontrol in the installation of the (*E*)-double bond and introduction of a variety of alkyl, alkoxy, and allyl groups (amino acid side chains) in either a *syn* or *anti* stereochemical relationship. Thus, the development of a highly stereoselective general route to these *(E)*-olefin isosteres would be considered a valuable contribution to organic synthetic methodology. This advance would also constitute an important contribution to the general design considerations for peptide mimetics.

Scheme 1[a]



(E)-Crotylsilane[a]	R_1	R_2
(3*R*) - **1a**	Me	H
(2*R*, 3*S*) - **1b**	Me	Me
(2*R*, 3*S*) - **1c**	Me	allyl
(2*R*, 3*S*) - **1d**	^{i}Pr	Me
(2*R*, 3*R*) - **1e**	Me	Me
(2*R*, 3*R*) - **1f**	Me	OMe

[a] The absolute stereochemistry of the silanes used in these examples is indicated in parentheses, although either antipode is accessible. For a detailed preparation of the silanes, see ref 8.

Synthesis of the Chiral Crotylsilanes. The synthesis of the silane reagents (**1a**−**f**), as summarized in Scheme 1, centers around an ortho-ester Claisen rearrangement for the elaboration of the illustrated (*E*)-vinylsilanes to the crotyl derivatives. The entire process begins with enantiomerically enriched (*R,E*)- and (*S,E*)-vinylsilanes derived from enzymatic resolutions (*Pseudomonas* lipase) of the corresponding racemic secondary alcohols.[8] The sigmatropic rearrangements are highly enantio- and diastereoselective and stereoselective with respect to the configuration of the disubstituted (*E*)-double bond, which is produced exclusively. The corresponding *anti*- and *syn*-β-substituted crotylsilanes are produced by either a diastereoselective *anti*-alkylation of the unsubstituted crotylsilane (eq 1) or an Ireland−Claisen rearrangement of the appropriate (*E*)-vinyl silane (eq 2).

Results and Discussion

Asymmetric C−N Bond Construction. In order to expand this methodology to encompass the preparation of a general class of dipeptide isosteres, we needed to address the issue of asymmetric C−N bond construction in the chiral (*E*)-crotylsilane system to prepare the required allylic nitrogen compounds. In addition to the synthesis of dipeptide isosteres, such a transformation would constitute a facile synthetic route to chiral allylic amine synthons. We have previously disclosed a method to these synthons based on nitronium tetrafluoroborate (NO_2-BF_4) electrophilic nitrations of chiral (*E*)-crotylsilanes.[9] Formation of the allylic nitro group takes place with complete stereocontrol. The chirality of the emerging nitro-bearing center solely originates from and is controlled by the nature of the silyl stereocenter and is consistent with an *anti*-S_E' addition

(5) (a) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370−4382.
(6) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.
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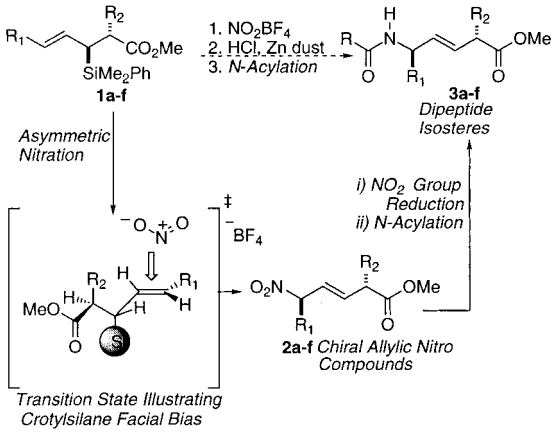
(8) Synthesis of the chiral silane reagents: Beresis, R. T.; Solomon, J. S.; Yang, M. J.; Jain, N. F.; Panek, J. S. *Org. Synth.* In press.
(9) Beresis, R. T.; Masse, C. E.; Panek, J. S. *J. Org. Chem.* **1995**, *60*, 7714−7715.

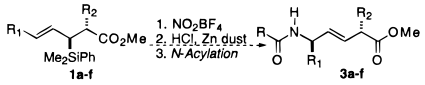
Scheme 2

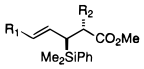
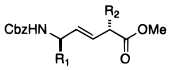
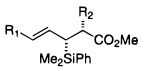
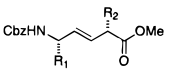


process. The absolute stereochemical assignment of the nitro compounds was established by conversion of the appropriate isostere to *L*-Cbz-alanine.[10] Subsequent reduction of the allylic nitro compounds using Zn/HCl furnishes the allylic amines.[11] The crude amines were *N*-acylated with carbobenzoxy chloride to yield the allylic carbamates as the desired isosteres **3a**−**f** in good overall yields with high levels of stereoselectivity[12] and excellent levels of 1,4-remote asymmetric induction (Scheme 2). This concise stereocontrolled route to these isosteres may increase their availability for drug discovery programs. The results of this dipeptide isostere synthesis are summarized in Table 1. The overall yield for the three-step sequence is comparable to existing methods for the asymmetric synthesis of this class of isostere,[4] and the synthetic sequence is short and operationally straightforward.

Prior to our work in this area, only one example of the reaction of a nitronium cation with an allyl metal reagent has been reported. Olah and Rochin have previously demonstrated the feasibility of this type of electrophilic substitution through nitration of unfunctionalized and achiral allylsilanes.[13] In our examples, solid NO_2BF_4[14] (1.1 equiv) in anhydrous CH_2Cl_2 was determined to be the most effective nitrating agent-solvent combination for efficient electrophilic substitution and formation of the allylic nitro compounds in yields ranging between 50 and 66%. The modest yields in the nitration step were primarily due to partial desilylation of the starting crotylsilane induced by the presence of free fluoride ion in solution. The amount of competing desilylation was partially reduced by allowing the mixture to slowly warm to room temperature over 10 h and diluting with an aqueous saturated $NaHCO_3$ solution. The allylic nitro compounds proved to be especially labile and were subject to partial decomposition during column chromatography on silica gel and under basic conditions. Due to competing nitration of the aromatic ring,[15] attempts to carry out the asymmetric nitration reaction on substrates containing benzyl substituents failed. Reduction was ultimately accomplished using Zn/HCl in methanol at 0 °C which cleanly afforded the allylic amines in crude yields on the order of 95%. The crude amines were immediately *N*-acylated with carbobenzoxy chloride (Cbz-Cl) followed by purification by chromatography on silica gel to give the allylic carbamate isosteres.

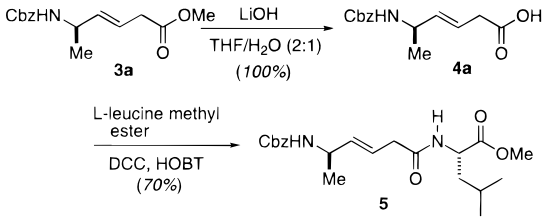
Table 1. Asymmetric Synthesis of (*E*)-Olefin Dipeptide Isosteres



(*E*)-crotylsilane entry(abs. stereochem) (R_1, R_2)	major product (overall % yield **3**[a]; de[b])
	
1. **1a** (3*R*); (Me, H)	(5*R*)-**3a** (41; > 30:1)
2. **1b** (2*R*, 3*S*); (Me, Me)	(2*S*, 5*R*)-**3b** (25; > 30:1)
3. **1c** (2*R*, 3*S*); (Me, allyl)	(2*S*, 5*R*)-**3c** (30; > 30:1)
4. **1d**[c] (2*R*, 3*S*); (^{i}Pr, Me)	(2*S*, 5*R*)-**3d** (25; > 30:1)
	
5. **1e** (2*R*, 3*R*); (Me, Me)	(2*S*, 5*S*)-**3e** (45; > 30:1)
6. **1f** (2*R*, 3*R*); (Me, OMe)	(2*S*, 5*S*)-**3f** (41; > 30:1)

[a] Overall yield for the 3 step-sequence based on pure materials isolated by chromatography (SiO_2). [b] Ratios of products were determined by ^{1}H NMR (400 MHz) operating at S/N of >200:1. [c] Silane **1d** was prepared by an analogous Claisen strategy starting from 4-methyl-1-pentyn-3-ol, see experimental for details.

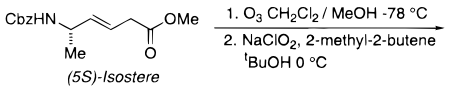
Scheme 3

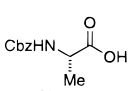


Application to the Synthesis of a Thermolysin Peptidomimetic. The potential utility of this technology was illustrated with a short synthesis of a structural mimetic of the tripeptide sequence Cbz-Ala[Ψ(*E*)-CH═CH]Gly-Leu-OMe. Our interest in this structural class arises from a recent report demonstrating potent inhibition of the zinc endopeptidase thermolysin by similar peptidomimetics.[4j] The synthesis of the tripeptide analog **5** was accomplished by methyl ester hydrolysis of isostere **3a** using lithium hydroxide followed by coupling of the derived acid **4a** with the methyl ester of L-leucine as illustrated in Scheme 3.

Asymmetric Aziridination. This asymmetric nitration of chiral (*E*)-crotylsilanes with NO_2BF_4 provides access to both natural and unnatural analogs of peptide sequences by choice

(10) The absolute stereochemistry of the allylic nitro compounds has been established by conversion of the (5*S*)-isostere to synthetic Cbz-L-alanine via the following sequence. Comparison to the natural amino acid (Fluka) derivative unambiguously established the absolute stereochemistry of these compounds (see Supporting Information for experimental details).





$[\alpha]^{23}_D$ (synthetic) = +3.36° (c = 1.13, $CHCl_3$)
$[\alpha]^{23}_D$ (natural) = +3.35° (c = 1.0, $CHCl_3$)

(11) Numerous conditions were surveyed to cleanly effect nitro group reduction including transfer hydrogenation, $CoCl_2 \cdot 6H_20/NaBH_4$, iron/acetic acid, and $NaBH_4$/S, all of which resulted in complex mixtures.

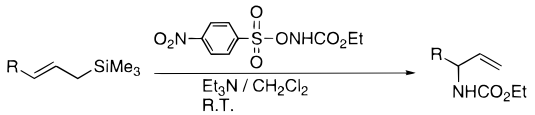
(12) All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data.

(13) Olah, G.; Rochin, C. *J. Org. Chem.* **1987**, *52*, 701−702.

(14) NO_2BF_4 is commercially available from Aldrich Chemical Co.

(15) The crude ^{1}H NMR of these substrates indicated substantial desilation and displayed a *para*-substituted splitting pattern of the aromatic protons.

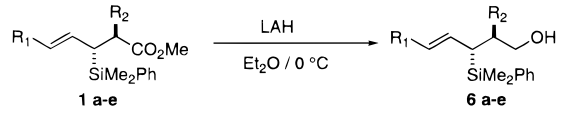
Scheme 4



of the chirality of the starting allylsilane reagent and provides a highly diastereo- and enantiospecific method for the asymmetric synthesis of (*E*)-olefin dipeptide isosteres. Despite the concise nature of the asymmetric nitration protocol, we had envisioned a more efficient approach to this class of isosteres via a direct asymmetric aziridination of the chiral (*E*)-crotylsilanes. Our expectation for high levels of acyclic stereocontrol in the aziridination process stems from the ability of the stereocenter bearing the silicon group to direct addition to one of the π-faces of the adjacent olefin. Additionally, the σ-donating silicon group will activate the aziridine ring by $\sigma \rightarrow \sigma^*$ orbital overlap, which will stabilize the emerging β-carbocation in the ring opening process to afford the allylic amine derivative.

The development of catalytic enantiospecific nitrogen-group transfer processes to alkenes has recently emerged as a promising method for the construction of functionalized aziridines, whose utility has been well documented in organic synthesis.[16] In the seminal publication, Kwart and Kahn[17] reported the copper-bronze catalyzed aziridination reactions of cyclohexene with benzenesulfonylazide. Evans and co-workers then made the critical discovery that low-valent copper complexes catalyze the aziridination of various types of olefins using the nitrene source of (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI═NTs).[18] Subsequently, the Jacobsen group[19] as well as the Evans group[20] disclosed methods for the asymmetric aziridination of unfunctionalized olefins utilizing chiral copper-(I)-based catalyst systems. These methodologies demonstrated the feasibility of a catalytic asymmetric variant of the reaction analogous to the well-known methods for enantioselective cyclopropanation.[21] The potential utility of allylsilane substrates in an aziridination reaction had been reported by Fioravanti and co-workers who reported the successful addition of the nitrene precursor *N*-{[4-nitrophenyl)sulfonyl]oxy}carbamate to achiral allyltrimethylsilanes to produce allylic amine derivatives (Scheme 4).[22] However, an asymmetric variant of this allylsilane aziridination has not been reported to our knowledge despite the utility that such a methodology would enjoy. The chiral allylic amines produced after subsequent desilylation of the chiral aziridine intermediates are of significant biological interest as peptidomimetics for pharmaceutical applications. The possibility of a catalytic, enantiospecific method for the construction of dipeptide isosteres led us to explore this idea as a viable method for the efficient aziridination of (*E*)-crotylsilanes.

Scheme 5



We now wish to disclose the scope of a copper (I)-catalyzed olefin aziridination of chiral (*E*)-crotylslianes using PhI═NTs[23] as the nitrene precursor. Our initial investigation into the aziridination was centered around the optimization of reaction solvent and catalyst as well as reaction temperature. In accord with the observations of Evans and co-workers,[18] the use of acetonitrile as solvent at room temperature proved to be optimum; however, the choice of a copper catalyst was unexpectedly critical. Copper(I) triflate (Cu(I)OTf) was found to be the optimal catalyst in terms of reaction turnover as compared to other copper(I) and copper(II) sources such as Cu-$(MeCN)_4ClO_4$,[24] $Cu(MeCN)_4PF_6$,[25] $Cu(acac)_2$,[25] and $Cu(OTf)_2$.[25] Achiral copper(I) bis-imine catalysts were also found to be less effective than Cu(I)OTf despite the fact that such bis-imine ligands have been shown to accelerate the aziridination of certain olefins.[19] The use of 10 mol % Cu(I)OTf in acetonitrile at room temperature was found to be the optimal catalyst load-solvent combination for the aziridination of the chiral (*E*)-crotylsilanes. Initial attempts at the aziridination using the chiral (*E*)-crotylsilyl esters (**1**) resulted in poor levels of diastereoselection in the resulting *N*-tosyl allylic amines. The lack of diastereoselectivity was attributed to poor olefin facial bias in the binding of the ester-bearing silanes to the copper species.[26] In order to increase the binding affinity of the crotylsilanes to the copper species and therefore increase the diastereoselectivity of the aziridination, the ester functionality of the silanes was reduced to the corresponding chiral silyl alcohols (**6a**−**f**) as illustrated in Scheme 5 for a substrate possessing *anti* stereochemistry.

Subjection of the silyl alcohols to the aziridination conditions described above afforded the *N*-tosylallylic amines with high levels of diastereoselection and in moderate yields. Presumably, the stronger binding affinity of the silyl alcohols to the copper species allows for superior facial bias in the delivery of the nitrene source to the olefin of the silane. In this case, the silane may function as an internal ligand/substrate that binds to the copper-nitrenoid intermediate thereby directing the tosylnitrene to the olefin of the silyl alcohol. The present study illustrates the utility of these chiral silane reagents in the development of an effective one-step method for the asymmetric synthesis of (*E*)-olefin dipeptide isosteres. Five (*E*)-crotylsilanes (**6a**−**e**) were examined to establish the viability of this approach for the synthesis of a series of dipeptide isosteres. The synthesis of the individual dipeptide isosteres is shown in Scheme 6 and is illustrated with a substrate possessing *anti* stereochemistry. The chiral silane reagents undergo a rapid copper(I)-catalyzed aziridination with PhI═NTs at room temperature to directly afford the *N*-tosylallylic amines (**7a**−**e**) which are isolated as chromatographically pure materials. The absolute stereochemistry of the allylic *N*-tosylamines was established by correlation to the known allylic nitro compounds.[27] Presumably, the first addition products are the aziridines which undergo desilylation to afford the allylamines; however, analysis of the crude reaction mixtures showed only the presence of the desired allylic amines along with starting silane and small amounts of desilylated

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(17) Kwart, H.; Kahn, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1951−1953.

(18) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744−6746.

(19) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326−5327.

(20) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329.

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(22) Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Raimondi, S.; Tardella, P. A. *Tetrahedron Lett.* **1993**, *34*, 4101−4104.

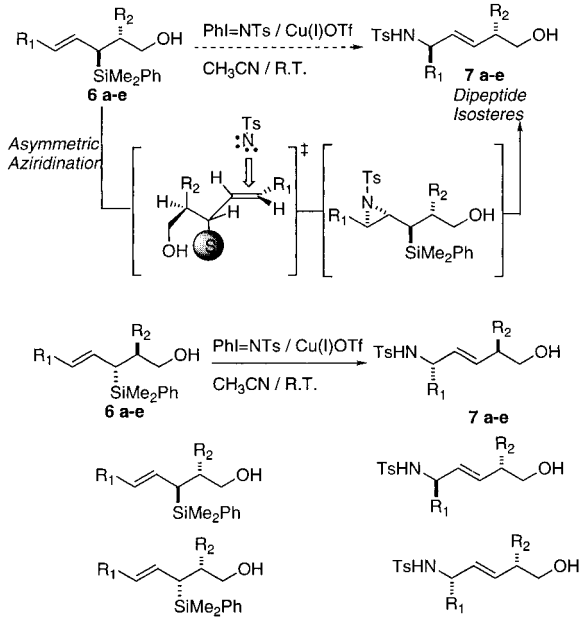
(23) The PhI═NTs was prepared according to Yamada et al. (Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem Lett.* **1975**, 361−362) with modifications as described in the Experimental Section.

(24) Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90−92.

(25) Commercially available from Aldrich Chemical Co.

(26) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889−5890.

Scheme 6

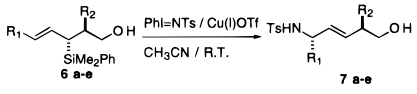


substrate. The overall sequence yields the desired isosteres in moderate yields with high levels of stereoselectivity and excellent levels of 1,4-remote asymmetric induction. The results of the asymmetric aziridination reactions are summarized in Table 2.

The modest yields in the aziridination reaction were primarily due to the catalyst turnover rate which resulted in the recovery of silyl alcohol as well as small amounts of desilylation product induced by the presence of triflate ion in solution. In these examples, solid PhI═NTs (1.0 equiv) in anhydrous acetonitrile (0.4 M) with 10 mol % Cu(I)OTf was determined to be the most effective aziridinating agent concentration-catalyst load for the efficient preparation of the *N*-tosylallylic amines. The starting silyl alcohols were readily recovered by flash chromatography and could be recycled into the aziridination reaction after being recharged with catalyst. The aziridination methodology allows for the facile introduction of a variety of alkyl or alkoxy side chains into the dipeptidomimetic. It should also be pointed out that this approach can be applied to the preparation of all four possible diastereomers of the Ψ[CH═CH] dipeptides in a stereocontrolled fashion by the proper selection of the silane reagent.

A Substrate Directed Process. The observation of significantly enhanced diastereoselectivity in the aziridination process upon introduction of a bis-homoallylic alcohol functionality implicated a preassociation of the silane with the aziridinating reagent. Several examples of such a hydroxyl-directed aziridination process have been reported using an *N*-aminoquinazolone nitrene source.[28] In the examples shown in Table 2, the hydroxyl group seems to reinforce the sense of diastereoselection by working synergistically with the topology of the (*E*)-olefin substrate. We have previously noted similiar hydroxyl directing effects in the epoxidations of these silyl alcohols with *m*-CPBA or $VO(acac)_2$-TBHP.[29] In an effort to determine the effect of the coordination ability of the silane substrate on the diastereoselectivity of the aziridination, several derivatives of silyl alcohol **6c** were prepared and subjected to the aziridination conditions (Scheme 7). The *tert*-butyldiphenylsilyl (TBDPS) ether and the methyl ether derivatives (**6f**−**g**) of the silyl alcohol-**6c** were prepared to probe the mechanism of the aziridination.[30] Aziridination of the TBDPS-ether substrate (**6f**) resulted in a 2:1 mixture of diastereomeric *N*-tosylallylic amine isosteres. This result was consistent with the level of diastereoselection obtained for the ester-bearing silane reagents (**1**). Aziridination of the methyl ether substrate (**6g**) which is capable of more effective coordination than the TBDPS ether resulted in a 4:1 mixture of diastereomeric *N*-tosylallylic amine isosteres. Clearly, the alcohol functionality has a pronounced effect on the diastereoselectivity of the aziridination which may implicate a need for a secondary coordination of the silane substrates to the copper-

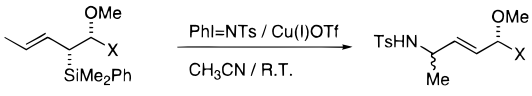
Table 2. Asymmetric Aziridination of (*E*)-Crotylsilanes



(*E*)-crotylsilane entry(abs. stereochem) (R_1, R_2)	major product (% yield **7**[a]; de[b])
1. **6a** (3*R*); (Me, H)	(5*R*)-**7a** (65; > 30:1)
2. **6b** (2*R*, 3*S*); (Me, Me)	(2*S*, 5*R*)-**7b** (64; > 30:1)
3. **6c** (2*R*, 3*R*); (Me, OMe)	(2*S*, 5*S*)-**7c** (63; > 30:1)
4. **6d** (2*R*, 3*R*); (Me, Me)	(2*S*, 5*S*)-**7d** (65; > 30:1)
5. **6e**[c] (3*S*); (^{i}Pr, H)	(5*S*)-**7e** (60; > 30:1)

[a] Overall yield for the sequence based on recovered silane. [b] Ratios of products were determined by ^{1}H NMR (400 MHz) operating at S/N of >200:1. [c] Silane **6e** was prepared by an analogous Claisen strategy starting from 4-methyl-1-pentyn-3-ol, see experimental section for details.

Scheme 7[a]

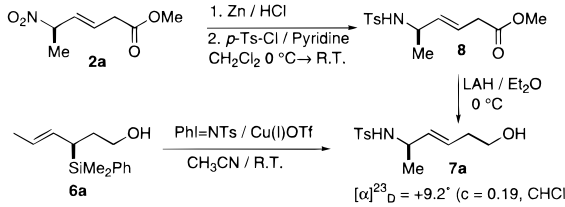


X	*Silane*	*Diastereoselection*[a]	*% Yield*[b]
CO_2Me	**1f**	1 : 1	67
$CH_2OTBDPS$	**6f**	2 : 1	64
CH_2OMe	**6g**	4 : 1	65
CH_2OH	**6a**	>30 : 1	65

[a]Ratio determined by ^{1}H NMR of crude reaction mixture [b] Yield based on recovered silane.

[a] Ratio determined by ^{1}H NMR of crude reaction mixture. [b] Yield based on recovered silane.

(27) Proof of the absolute stereochemistry of the allylic *N*-tosylamines was obtained by correlation of the known allylic nitro compound **2a** to the allylic *N*-tosylamine **7a** via the following sequence: (see Supporting Information for experimental details).



(28) (a) Atkinson, R. S.; Kelley, B. J. *J. Chem. Soc., Chem. Commun.* **1988**, 624−625. (b) Atkinson, R. S.; Kelley, B. J.; McNocolas, C. *J. Chem Soc., Chem. Commun.* **1988**, 562−564. (c) Atkinson, R. S.; Kelley, B. J. *J. Chem. Soc., Perkin Trans. I* **1989**, 1515−1519.

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(30) See the Experimental Section for the preparation of silanes **6f** and **6g**.

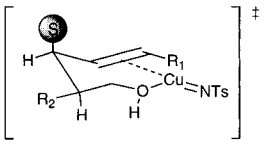

Figure 4. Representation of the hydroxyl-assisted aziridination of the silane reagents.

nitrenoid species. Our experiments seem to be consistent with a substrate-directable aziridination process.[31]

In an attempt to characterize the silane bound to the copper catalyst, crystals were grown from an acetonitrile solution of 1:1 Cu(I)OTf and silane **6d** by diffusion of ether into the acetonitrile solution at −20 °C. Subsequent X-ray crystallographic analysis revealed the crystals consisted of $[Cu(MeCN)_4]OTf$ which were surface coated with the silane ligand. This result allows us to conclude that the silyl alcohols (**6a**−**e**) do not participate in binding to the copper(I) species in the solid state. Although no mechanistic interpretation can be made at this point, it is possible that the silane ligand binds to the Cu(III)-nitrenoid intermediate prior to aziridination of the olefin. A plausible representation of the hydroxyl-assisted aziridination transition state is shown in Figure 4 and involves simultaneous coordination of the (*E*)-olefin and alcohol functionalities of the silane reagent in a chair-like conformation.

Conclusions

In conclusion, asymmetric C−N bond constructions resulting from nitronium tetrafluoroborate (NO_2BF_4) promoted electrophilic nitrations of chiral (*E*)-crotylsilanes and by a PhI═NTs/copper (I)-catalyzed enantiospecific aziridination of chiral (*E*)-crotylsilanes provide a highly diastereo- and enantiospecific method for the asymmetric synthesis of (*E*)-olefin dipeptide isosteres and continue to expand the scope and utility of this developing chiral allylsilane methodology. Further experiments aimed at the characterization of the silane bound to the copper species will be reported in due course.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz and 67.5 MHz, respectively, unless specified otherwise. Methylene chloride (CH_2Cl_2) and pyridine were distilled from calcium hydride prior to use. The zinc dust utilized had a mesh size of 325. Anhydrous acetonitrile (CH_3CN) was purchased from Aldrich and used as received. Anhydrous methanol (MeOH) was purchased from J. T. Baker and used as received. Copper(I) trifluoromethanesulfonate benzene complex ($Cu(I)OTf{\cdot}C_6H_6$) was purchased from Aldrich and used as received. All reactions were carried out in oven-dried glassware under a dry argon atmosphere. Analytical thin layer chromatography was performed on Whatman Reagent 0.25 mm silica gel 60-Å plates.

Representative Experimental Procedure for the NO_2BF_4 Additions Illustrated for the Reaction of (3*R*)-(*E*)-Methyl-3-(dimethylphenyl)silyl-hex-4-enoate with Nitronium Tetrafluoroborate (2a). A solution of **1a**[8] (6.3 g, 24.0 mmol) in 120 mL of CH_2Cl_2 (0.2 M) was slowly added to a stirred suspension of nitronium tetrafluoroborate (NO_2BF_4) (3.65 g, 26.4 mmol, 1.1 equiv) in 260 mL of CH_2Cl_2 (0.1 M) at −78 °C. The reaction mixture was allowed to warm to room temperature over 10 h under vigorous stirring and subsequently quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford crude **2a** as an oil. Purification on SiO_2 (10% EtOAc/PE) afforded **2a** as a yellow oil, 2.0 g (50%, 4.1 g theoretical): ^1H NMR (400 MHz, $CDCl_3$) δ 5.98−5.79 (m, 2H), 5.03 (m, 1H), 3.67 (s, 3H), 3.12 (d, 2H, J = 6.4 Hz), 1.62 (d, 3H, J = 6.4 Hz).

Representative Procedure for the Reduction and *N*-Acylation of the Allylic Nitro Compounds. (5*R*)-(*E*)-Methyl-5-(*N*-benzyloxy)-amino-hex-3-enoate (3a). A solution of **2a** (0.5 g, 2.9 mmol) in absolute methanol (10 mL) at 0 °C was treated with zinc dust (0.38 g, 5.8 mmol, 2.0 equiv). Under vigorous stirring, concentrated aqueous HCl (1.5 mL) was added dropwise to the cooled solution (0 °C). The reaction mixture was subsequently filtered through Celite, washed thoroughly with CH_2Cl_2 (15 mL), and neutralized with 3 N NaOH. The neutralized solution was extracted further with CH_2Cl_2 (2 × 15 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford a light yellow oil, 0.4 g. To a solution of the crude amine (0.4 g, 2.9 mmol) in 15 mL of CH_2Cl_2 was added pyridine (5.8 mmol, 0.5 mL, 2.0 equiv), and the solution was cooled to 0 °C. A solution of benzylchloroformate (5.8 mmol, 0.83 mL, 2.0 equiv) in 6 mL of CH_2Cl_2 was added via a dropping funnel to the cooled solution over a 1 h period. The reaction was quenched with a saturated aqueous NH_4Cl solution (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification on SiO_2 (15% EtOAc/PE) afforded **3a** as a yellow oil, 0.58 g (78%, two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.80−5.63 (m, 2H), 5.21 (s, br, 2H), 4.69 (br, 1H), 3.64 (s, 3H), 2.97 (d, 2H, J = 6.4 Hz), 1.29 (d, 3H, J = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.6, 155.7 (d, J = 83.0 Hz), 154.5, 135.3, 128.6, 128.5, 128.4, 128.3, 128.2, 71.1, 68.4, 65.3, 51.8, 37.3; IR (neat) ν_{max} 3056, 2980, 2953, 1795, 1734, 1499, 1217; CIMS (NH_3 gas) 279, 278, 234, 162, 142, 127, 108, 91, 35; CIHRMS M + H^+ (calculated for $C_{15}H_{20}NO_4$): 278.1393, found: 278.1392; $[\alpha]^{23}_D$ = +1.72° (c = 1.5, $CHCl_3$).

(2*S*,5*R*)-(*E*)-Methyl-5-(*N*-benzyloxy)amino-2-methyl-hex-3-enoate (3b): ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.73−5.56 (m, 2H), 5.22 (s, br, 2H), 4.79 (br, 1H), 3.63 (s, 3H), 3.04 (m, 1H), 1.28 (d, 3H, J = 7.6 Hz), 1.16 (d, 3H, J = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.6, 155.7 (d, J = 83.0 Hz), 154.4, 135.3, 128.8, 128.6, 128.5, 128.3, 128.2, 71.0, 68.3, 58.0, 51.8, 42.3, 17.0; IR (neat) ν_{max} 3035, 2981, 2953, 1795, 1736, 1499, 1217; CIMS (NH_3 gas) 293, 292, 264, 248, 156 141, 108, 91; CIHRMS M + H^+ (calculated for $C_{16}H_{22}NO_4$): 292.1549, found: 292.1538; $[\alpha]^{23}_D$ = −11.3° (c = 1.4, $CHCl_3$).

(2*S*,5*R*)-(*E*)-Methyl-5-(*N*-benzyloxy)amino-2-allyl-hex-3-enoate (3c): ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.68−5.60 (m, br, 2H), 5.22−5.16 (m, 4H), 5.02−4.96 (m, 1H), 4.78 (br, 1H) 3.63 (s, 3H), 3.02 (m, br, 1H), 2.40 (m, br, 1H), 2.19 (m, br, 1H), 1.28 (d, 3H, J = 6.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.5, 155.7 (d, J = 83.0 Hz), 154.4, 135.3, 130.5, 128.8, 128.6, 128.3, 117.2, 71.1, 68.4, 51.8, 48.5, 36.5, 17.0; IR (neat) ν_{max} 3046, 2981, 2953, 1795, 1734, 1642, 1588, 1499, 1224; CIMS (NH_3 gas) 334, 318, 290, 248, 272, 269, 268, 258, 252, 227, 226, 225, 224, 182 167, 108; CIHRMS M + H^+ (calculated for $C_{18}H_{24}NO_4$): 318.1706, found: 318.1713; $[\alpha]^{23}_D$ = +22.1° (c = 1.0, $CHCl_3$).

(2*S*,5*R*)-(*E*)-Methyl-5-(*N*-benzyloxy)amino-2-methyl-hept-3-enoate (3d): ^1H NMR (400 MHz, $CDCl_3$) **4d** exists as a 2:1 mixture of rotamers at room temperature. (The major rotamer is reported) δ 7.34−7.25 (m, 5H), 5.66 (dd, 1H, J = 15.6 Hz, 8.0 Hz), 5.60 (s, 1H), 5.40 (dd, 1H, J = 14.8 Hz, 8.0 Hz), 5.25−5.12 (m, 2H), 4.07 (s, 1H), 3.61 (s, 3H), 3.08−3.01 (m, 1H), 1.85−1.76 (m, 1H), 0.90 (d, 3H, J = 6.4 Hz), 0.86 (d, 3H, J = 6.8 Hz), 0.81 (d, 3H, J = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.6, 155.1 (d, J = 145.6 Hz), 134.1, 128.8, 128.6, 128.5, 128.4, 128.3, 127.9, 70.2, 69.1, 51.8, 42.6, 29.4, 19.4, 17.0; IR (neat) ν_{max} 3000, 1805, 1750, 1470, 1400, 1240; CIMS (NH_3 gas) 109.1, 184.2, 214.2, 248.2, 274.2, 338.2; CIHRMS M + H^+ (calculated for $C_{18}H_{26}NO_4$) 320.1862, found 320.1889; $[\alpha]^{23}_D$ = +1.0° (c = 0.1, $CHCl_3$).

(2*S*,5*S*)-(*E*)-Methyl-5-(*N*-benzyloxy)amino-2-methyl-hex-3-enoate (3e): ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.30 (m, 5H), 5.72−5.59 (m, 2H), 5.20 (s, br, 2H), 4.80 (br, 1H), 3.63 (s, 3H), 3.06 (m, 1H), 1.28 (d, 3H, J = 6.8 Hz), 1.15 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.6, 155.9 (d, J = 83.0 Hz), 154.6, 135.3, 128.8, 128.6, 128.5, 128.4, 128.3, 71.1, 68.3, 58.0, 51.9, 42.3, 17.0; IR (neat) ν_{max} 3035, 2981, 2953, 1794, 1737, 1499, 1218; CIMS (NH_3 gas) 308, 292, 288, 262, 246, 165, 156, 141, 108, 105, 91, 35; CIHRMS M + H^+

(31) For an excellent and comprehensive review of substrate-directable reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

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(calculated for $C_{16}H_{21}NO_4$): 292.1548, found: 292.1515; $[\alpha]^{23}_D = +2.6°$ ($c = 0.38$, $CHCl_3$).

(2*S*,5*S*)-(*E*)-Methyl-5-(*N*-benzyloxy)amino-2-methoxy-hex-3-enoate (3f): ^{1}H NMR (400 MHz, C_6D_6) δ 7.08−6.93 (m, 5H), 6.05 (s, 1H), 5.72 (dd, 1H, $J = 15.6$ Hz, 6.0 Hz), 4.94−4.74 (m, 4H), 4.21 (s, 1H), 3.19 (s, 3H), 3.00 (s, 3H), 1.02 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.5, 154.9, 135.2, 134.1, 128.7, 128.5, 128.4, 128.2, 127.8, 80.1, 71.0, 68.3, 57.1, 56.7, 52.2; IR (neat) ν_{max} 3000, 1810, 1760, 1470, 1400, 1230; CIMS (NH_3 gas) 91, 157, 262, 304, 338; CIHRMS M + H^+ (calculated for $C_{16}H_{22}NO_5$) 308.1498, found 308.1505; $[\alpha]^{23}_D = +8.3°$ ($c = 0.40$, $CHCl_3$).

Experimental Procedure for Peptide Coupling: *N*-((*E*)-(5*R*)-5-(*N*-benzyloxycarbonyl)amino-3-hexenoyl)-L-leucine Methyl Ester (5). Acid **4a** (0.014 g, 0.053 mmol) was dissolved in 1 mL of CH_2Cl_2 (0.05 M) and cooled to 0 °C. L-Leucine methyl ester (0.011 g, 0.06 mmol, 1.1 equiv) was added to the reaction mixture followed by HOBT (0.72 mg, 0.0053 mmol, 0.1 equiv) and DCC (0.013 g, 0.06 mmol, 1.1 equiv). The resulting white suspension was allowed to warm to room temperature under stirring over 24 h. The suspension was then diluted with CH_2Cl_2, recooled to 0 °C, filtered through Celite, and concentrated *in vacuo*. Purification on SiO_2 (70% EtOAc/PE) afforded **5** as a white solid, 0.015 g (70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5H); 6.61 (br, 1H); 6.09 (d, 1H, $J = 8.4$ Hz); 5.73 (m, 2H); 5.17 (s, 2H); 4.72 (m, 1H); 4.58 (m , 1H); 3.70 (s, 3H); 3.43 (m, 1H); 2.96 (d, 2H, $J = 4.8$ Hz); 1.70−1.41 (m, 2H); 1.31 (d, 3H, $J = 7.6$ Hz); 1.20−1.02 (m, 1H); 0.90 (d, 6H, $J = 4.0$ Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.8, 170.6, 157.2, 135.9, 134.1, 128.5, 128.3, 128.1, 124.9, 67.9, 52.4, 41.4, 39.6, 33.8, 24.9, 24.8, 22.8, 21.9, 16.4; IR (KBr) ν_{max} 3306, 2955, 2929, 1744, 1717, 1651; CIMS (NH_3 gas) 391, 386, 364, 324, 308, 240, 181, 156, 141, 108, 92, 91; CIHRMS M^+ (calculated for $C_{21}H_{30}N_2O_4$): 374.2206, found: 374.2217; $[\alpha]^{23}_D = +22.5°$ ($c = 0.36$, $CHCl_3$).

Modified Experimental Procedure for the Synthesis of (*N*-(*p*-Toluenesulfonyl)imino)phenyliodinane. A solution of *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and potassium hydroxide (1.40 g, 25.0 mmol, 2.5 equiv) in 40 mL of anhydrous MeOH (0.25 M) was cooled to −10 °C. To this solution was added (diacetoxy)iodobenzene (3.87 g, 12.0 mmol, 1.2 equiv), and the reaction mixture was allowed to warm to room temperature over 3 h under vigorous stirring. After 3 h, the reaction mixture was diluted with 150 mL of distilled water to give a precipitate which was filtered and washed with Et_2O (20 mL) to yield yellow crystals. The yellow crystals (2.80 g, 75%) were dried under reduced pressure. No further purification steps were performed as the iodinane exhibited an acceptable ^{1}H NMR and FTIR spectral properties.[23]

Representative Experimental Procedure for the Reduction of the Chiral (*E*)-Crotylsilyl Esters. (3*R*)-(*E*)-3-(Dimethylphenylsilyl)-4-hexenol (6a). A solution of **1a**[8] (2.0 g, 8.06 mmol) in 30 mL of anhydrous Et_2O (0.25 M) was cooled to 0 °C. To this solution was added lithium aluminum hydride (LAH) (0.31 g, 8.06 mmol, 1.0 equiv) and the reaction mixture was stirred vigorously at 0 °C for 0.5 h. The reaction mixture was quenched dropwise with saturated aqueous NH_4Cl (30 mL), and the mixture was extracted with Et_2O (2 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification on SiO_2 (5% EtOAc/PE → 20% EtOAc/PE gradient elution) afforded **6a** as a pale yellow oil, 1.85 g (98%, 1.89 g theoretical); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2H), 7.34−7.31 (m, 3H), 5.31−5.18 (m, 2H), 3.64−3.59 (m, 1H), 3.55−3.49 (m, 1H), 1.80−1.74 (m, 1H), 1.68−1.60 (m, 1H), 1.63 (d, 3H, $J = 5.6$ Hz), 1.55−1.45 (m, 1H), 1.34 (br, 1H), 0.25 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 137.6, 134.0, 131.2, 128.9, 127.6, 123.8, 62.7, 31.7, 29.2, 18.0, −4.5, −5.4; IR (neat) ν_{max} 3446, 3069, 2959, 1952, 1653, 1249; CIMS (NH_3 gas) 250.1, 233.1, 205.0, 189.1, 152.0, 135.0, 91.1; CIHRMS M^+ (calculated for $C_{14}H_{22}SiO$): 234.1440, found: 234.1423; $[\alpha]^{23}_D = +12.57°$ ($c = 1.40$, $CHCl_3$).

(2*R*,3*S*)-(*E*)-3-(Dimethylphenylsilyl)-2-methylhex-4-enol (6b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.47 (m, 2H), 7.35−7.32 (m, 3H), 5.38−5.27 (m, 2H), 3.37−3.32 (m, 2H), 1.98−1.95 (m, 1H), 1.80−1.78 (m, 1H), 1.67 (d, 3H, $J = 4.8$ Hz), 0.82 (d, 3H, $J = 6.8$ Hz), 0.31 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 138.5, 133.9, 128.8, 127.6, 127.4, 125.6, 68.1, 35.5, 34.7, 18.1, 14.0, −3.3, -3.9; IR (neat) ν_{max} 3382, 3069, 2960, 1952, 1653, 1248; CIMS (NH_3 gas) 249.1, 209.1, 189.1, 152.1, 135.1, 96.1; CIHRMS M + H^+ (calculated for $C_{15}H_{25}SiO$): 249.1675, found: 249.1693; $[\alpha]^{23}_D = -5.5°$ ($c = 1.21$, $CHCl_3$).

(2*R*,3*R*)-(*E*)-3-(Dimethylphenylsilyl)-2-methoxy-hex-4-enol (6c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.47 (m, 2H), 7.34−7.32 (m, 3H), 5.28−5.21 (m, 2H), 3.64−3.60 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 2.8$ Hz), 3.51−3.46 (dd, 1H, $J_1 = 5.2$ Hz, $J_2 = 5.2$ Hz), 3.20 (s, 3H), 3.19−3.17 (m, 1H), 2.24 (t, 1H), 1.85 (br, 1H), 1.63 (d, 3H, $J = 5.2$ Hz), 0.32 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 138.1, 134.0, 128.8, 127.6, 127.5, 126.0, 82.3, 61.7, 56.3, 35.3, 18.1, −3.0, -3.2; IR (neat) ν_{max} 3432, 3014, 2960, 2094, 1653, 1246; CIMS (NH_3 gas) 264.2, 236.1, 181.1, 152.1, 135.1, 98.1; CIHRMS M + H^+ (calculated for $C_{15}H_{25}SiO_2$): 265.1546, found: 265.1594; $[\alpha]^{23}_D = +25.4°$ ($c = 1.14$, $CHCl_3$).

(2*R*,3*R*)-(*E*)-3-(Dimethylphenylsilyl)-2-methylhex-4-enol (6d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.38−7.31 (m, 3H), 5.29−5.26 (m, 2H), 3.52−3.48 (dd, 1H, $J_1 = 4.0$ Hz, $J_2 = 4.8$ Hz), 3.38−3.34 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 6.0$ Hz), 1.77−1.65 (m, 2H), 1.64 (d, 3H, $J = 4.4$ Hz), 0.86 (d, 3H, $J = 6.0$ Hz), 0.29 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 139.0, 133.9, 130.1, 128.8, 127.6, 124.9, 67.5, 37.3, 36.5, 18.0, 0.0, −2.4, −3.5; IR (neat) ν_{max} 3371, 2958, 2930, 1726, 1249; CIMS (NH_3 gas) 247.1, 209.1, 171.1, 152.1, 135.1, 96.1; CIHRMS M + H^+ (calculated for $C_{15}H_{25}SiO$): 249.1675, found: 249.1700; $[\alpha]^{23}_D = -2.75°$ ($c = 1.20$, $CHCl_3$).

(3*S*)-(*E*)-3-(Dimethylphenylsilyl)-6-methylhept-4-enol (6e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2H), 7.34−7.31 (m, 3H), 5.27−5.12 (m, 2H), 3.63−3.51 (m, 2H), 2.24−2.19 (m, 1H), 1.77−1.61 (m, 2H), 1.56−1.50 (m, 1H), 1.36 (br, 1H), 0.92 (d, 6H, $J = 6.4$ Hz), 0.26 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 137.5, 137.0, 134.0, 128.9, 127.6, 127.1, 62.9, 31.7, 31.3, 29.2, 22.9, 22.8, -4.6, −5.4; IR (neat) ν_{max} 3389, 2958, 2929, 2082, 1653, 1248; CIMS (NH_3 gas) 259.2, 217.1, 189.1, 185.1, 152.1, 135.0; CIHRMS M + H^+ (calculated for $C_{16}H_{27}SiO$): 263.1831, found: 263.1807; $[\alpha]^{23}_D = -9.80°$ ($c = 1.53$, $CHCl_3$).

Note: Silane **6e** is prepared from an analogous hydrosilation/Lipase resolution/ortho-ester Claisen methodology as reported in ref 8 starting from racemic 4-methyl-1-pentyn-3-ol.[32]

Experimental Procedure for the Synthesis of (2*R*, 3*R*)-(*E*)-1-*tert*-Butyl-diphenylsilyloxy-3-(dimethylphenylsilyl)-2-methoxyhex-4-ene (6f). A solution of **6c** (0.2 g, 0.76 mmol) in 1.5 mL of DMF (0.5 M) was cooled to 0 °C. To this solution was added imidazole (0.16 g, 2.28 mmol, 3.0 equiv) followed by *tert*-butyldiphenylsilyl chloride (0.21 g, 0.76 mmol, 1.0 equiv). The reaction mixture was allowed to warm to room temperature over 12 h of vigorous stirring and subsequently quenched with H_2O. The mixture was extracted with Et_2O (3 × 25 mL), washed with saturated aqueous NaCl (3 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification on SiO_2 (PE) afforded **6f** as a colorless oil, 0.372 g (97%, 0.382 g theoretical): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.30 (m, 15H), 5.12−5.10 (m, 2H), 3.70−3.67 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 2.4$ Hz), 3.59−3.55 (dd, 1H, $J_1 = 5.6$ Hz, $J_2 = 5.2$ Hz), 3.28 (s, 3H), 3.22−3.21 (m, 1H), 2.09 (t, 1H), 1.53 (d, 3H, $J = 4.0$ Hz), 1.01 (s, 9H), 0.28 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 138.9, 135.7, 135.6, 134.8, 134.2, 133.7, 129.7, 129.5, 128.9, 128.5, 127.7, 127.6, 127.3, 124.7, 83.8, 65.7, 57.9, 36.5, 31.6, 26.8, 22.7, 19.2, 18.1, 14.1, -2.7; IR (neat) ν_{max} 3441, 3071, 2931, 2109, 1653, 1245; CIMS (NH_3 gas) 555.2, 520.2, 391.2, 377.1, 274.1, 196.2; CIHRMS M + H^+ (calculated for $C_{31}H_{43}Si_2O_2$): 503.2801, found: 503.2829; $[\alpha]^{23}_D = -8.3°$ ($c = 0.68$, $CHCl_3$).

Experimental Procedure for the Synthesis of (2*R*,3*R*)-(*E*)-1-Methoxy-3-(dimethylphenylsilyl)-2-methoxyhex-4-ene (6g). A solution of **6c** (0.2 g, 0.76 mmol) in 7.6 mL of CH_2Cl_2 (0.1 M) was cooled to 0 °C. To this solution was added proton sponge (0.49 g, 2.28 mmol, 3.0 equiv) and trimethyloxonium tetrafluoroborate (0.34 g, 2.28 mmol, 3.0 equiv). The reaction mixture was allowed to warm to room temperature over 4 h of vigorous stirring and subsequently diluted with 1 N $NaHSO_4$ (20 mL). The mixture was filtered through Celite and washed thoroughly with Et_2O. The filtrate was extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification on SiO_2 (5% EtOAc/PE) afforded **6g** as a yellow oil, 0.148 g (70%, 0.212 g theoretical): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.32−7.30 (m, 3H), 5.22−5.20 (m, 2H), 3.43−3.40 (m, 1H), 3.30−3.26 (m, 2H), 3.25 (s, 3H), 3.24 (s, 3H), 2.12 (t, 1H), 1.62 (d, 3H, $J =$

2.0 Hz), 0.31 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 138.2, 134.2, 128.7, 128.3, 127.4, 125.3, 81.4, 74.1, 58.9, 57.0, 36.3, 18.1, -2.8, −2.9; IR (neat) ν_{max} 3427, 3070, 2958, 2110, 1712, 1251; CIMS (NH_3 gas) 301.1, 296.1, 233.1, 193.1, 175.1, 161.1; CIHRMS M+NH_4^+ (calculated for $C_{16}H_{30}SiNO_2$): 296.2046, found: 296.2081; $[\alpha]^{23}_D = +14.6$ °C (c = 0.51, $CHCl_3$).

Representative Experimental Procedure for the Aziridination of the Chiral (*E*)-Crotylsilyl Alcohols. (5*R*)-(*E*)-(*N*-(*p*-Toluenesulfonyl)amino)hex-3-enol (7a). To a solution of **6a** (0.136 g, 0.581 mmol) in 1.5 mL of CH_3CN (0.4 M) was added (*N*-(*p*-toluenesulfonyl)imino)-phenyliodinane (PhI═NTs) (0.217 g, 0.581 mmol, 1.0 equiv), and the heterogeneous mixture was stirred under argon. To this heterogeneous mixture was added Cu(I)OTf·C_6H_6 (0.029 g, 0.0581 mmol, 10 mol%). The reaction mixture was stirred at room temperature for 1 h to yield a homogeneous yellow solution. Direct purification of reaction mixture on SiO_2 (PE → 50% EtOAc/PE gradient elution) afforded **7a** as a yellow oil, 0.048 g (31%, 0.156 g theoretical, 65% based on recovered silane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 8.8 Hz), 7.27 (d, 2H, J = 8.0 Hz), 5.41−5.35 (m, 2H), 4.48 (br, 1H), 3.82−3.80 (m, 1H), 3.55−3.51 (m, 2H), 2.40 (s, 3H), 2.16−2.11 (m, 2H), 1.14 (d, 3H, J = 6.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.3, 137.8, 134.0, 129.6, 127.7, 127.1, 61.5, 51.3, 35.3, 21.9, 21.5; IR (neat) ν_{max} 3448, 2109, 1684, 1653, 1635, 1319, 1159; CIMS (NH_3 gas) 287.1, 270.1, 130.1, 81.1; CIHRMS M^+ (calculated for $C_{13}H_{19}NO_3S$): 270.1086, found: 270.1185; $[\alpha]^{23}_D = +9.2°$ (c = 0.19, $CHCl_3$).

(2*S*,5*R*)-(*E*)-5-(*N*-(*p*-toluenesulfonyl)amino)-2-methylhex-3-enol (7b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 5.33−5.31 (m, 2H), 4.56 (d, 1H, J = 7.2 Hz), 3.86−3.82 (m, 1H), 3.41−3.37 (m, 1H), 3.30−3.25 (m, 1H), 2.40 (s, 3H), 2.21−2.18 (m, 1H), 1.63 (br, 1H), 1.15 (d, 3H, J = 6.4 Hz), 0.86 (d, 3H, J = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.3, 138.0, 133.5, 132.1, 129.6, 127.2, 67.0, 51.2, 38.9, 22.1, 21.5, 16.0; IR (neat) ν_{max} 3456, 2090, 1653, 1600, 1319; CIMS (NH_3 gas) 284.1, 213.0, 198.0, 189.0, 155.0, 95.1; CIHRMS M + H^+ (calculated for $C_{14}H_{22}NO_3S$): 284.1320, found: 284.1340; $[\alpha]^{23}_D = +9.0°$ (c = 0.48, $CHCl_3$).

(2*S*,5*S*)-(*E*)-5-(*N*-(*p*-Toluenesulfonyl)amino)-2-methoxyhex-3-enol (7c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.4 Hz), 5.58−5.53 (dd, 1H, J_1 = 6.0 Hz, J_2 = 6.4 Hz), 5.32−5.26 (dd, 1H, J_1 = 7.6 Hz, J_2 = 7.2 Hz), 4.63 (d, 1H, J = 7.2 Hz), 3.91−3.87 (m, 1H), 3.58−3.53 (m, 1H), 3.39−3.36 (m, 2H), 3.19 (s, 3H), 2.40 (s, 3H), 2.12 (br, 1H), 1.17 (d, 3H, J = 6.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.5, 137.8, 135.8, 129.7, 127.6, 127.1, 81.9, 64.9, 56.5, 50.8, 21.9, 21.5; IR (neat) ν_{max} 3471, 2088, 1718, 1636, 1326, 1160; CIMS (NH_3 gas) 300.1, 268.1, 250.1, 189.1, 129.1, 97.1; CIHRMS M^+ (calculated for $C_{14}H_{22}NO_4S$): 300.1269, found: 300.1265; $[\alpha]^{23}_D = -3.4°$ (c = 0.35, $CHCl_3$).

(2*S*,5*S*)-(*E*)-5-(*N*-(*p*-toluenesulfonyl)amino)-2-methylhex-3-enol (7d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 2H, J = 8.4 Hz), 7.28 (d, 2H, J = 8.0 Hz), 5.33−5.26 (m, 2H), 4.52 (d, 1H, J = 6.0 Hz), 3.78−3.77 (m, 1H), 3.42−3.37 (m, 1H), 3.30−3.24 (m, 1H), 2.40 (s, 3H), 2.21−2.20 (m, 1H), 1.63 (br, 1H), 1.15 (d, 3H, J = 6.8 Hz), 0.85 (d, 3H, J = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.5, 138.5, 134.0, 133.5, 129.6, 127.2, 67.1, 51.6, 39.3, 22.1, 21.5, 16.0; IR (neat) ν_{max} 3430, 2094, 1643, 1600, 1322, 1158; CIMS (NH_3 gas) 283.1, 219.1, 181.1, 153.1, 151.1, 135.1, 82.9; CIHRMS M^+ (calculated for $C_{14}H_{21}NO_3S$): 283.1242, found: 283.1608; $[\alpha]^{23}_D = -32.4°$ (c = 0.25, $CHCl_3$).

(5*S*)-(*E*)-5-(*N*-(*p*-Toluenesulfonyl)amino)-6-methylhept-3-enol (7e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 5.37−5.35 (m, 1H), 5.25−5.20 (m, 1H), 4.68 (d, 1H, J = 7.6 Hz), 3.82−3.80 (m, 1H), 3.59−3.43 (m, 2H), 2.39 (s, 3H), 2.20−2.11 (m, 1H), 1.73−1.64 (m, 2H), 0.81 (d, 3H, J = 1.6 Hz), 0.79 (d, 3H, J = 2.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.2, 130.3, 129.4, 128.9, 127.2, 61.8, 56.2, 33.0, 31.2, 21.5, 18.5, 18.3, 17.9; IR (neat) ν_{max} 3431, 2961, 2927, 2089, 1646, 1321, 1305, 1159; CIMS (NH_3 gas) 315.1, 298.1, 255.0, 254.0, 224.0, 189.0, 127.1; CIHRMS M + H^+ (calculated for $C_{15}H_{24}NO_3S$): 298.1478, found: 298.1445; $[\alpha]^{23}_D = -8.5°$ (c = 0.71, $CHCl_3$).

(5*R*)-(*E*)-Methyl-5-(*N*-(*p*-toluenesulfonyl)amino)hex-3-enoate (8): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 6.60 (br, 1H), 5.70−5.30 (m, 1H), 5.45−5.30 (m, 1H), 4.38 (m, 1H), 3.65 (s, 3H), 2.80 (d, 2H, J = 6.4 Hz), 2.40 (s, 3H), 1.14 (d, 3H, J = 6.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 144.4, 131.2, 129.5, 129.3, 124.4, 58.3, 51.8, 37.3, 21.6, 18.0; IR (neat) ν_{max} 3369, 1738, 1597, 1348, 1168, 1090; CIMS (NH_3 gas) 298.2, 282.2, 142.1, 127.1, 110.1, 91.1; CIHRMS M + H^+ (calculated for $C_{14}H_{20}NO_4S$): 298.1113, found: 298.1093; $[\alpha]^{23}_D = -29.5°$ (c = 0.21, $CHCl_3$).

Acknowledgment. This work has been financially supported by the National Institutes of Health (RO1CA56304).

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JA964364W