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Synthesis of Enantiomerically Enriched Amino Sulfide Building Blocks from Acyclic Chiral Amino Allylsilanes†

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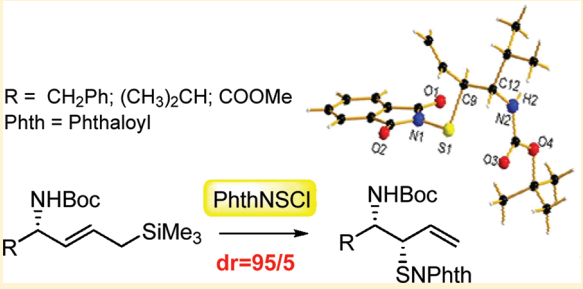
Supporting Information

ABSTRACT: An efficient synthesis of various protected *syn*-β-sulfenyl amides is described. These are prepared from the corresponding enantiopure amino allylsilanes which are in turn obtained from naturally occurring amino acids. The key step for introduction of the sulfur substituent is a diastereoselective electrophilic sulfodesilylation which is carried out with phthalimidesulfenyl chloride. The resulting homochiral β-phthalimidesulfenyl amines with an allylic sulforated stereogenic center are useful building blocks, as they represent a starting point for subsequent functional manipulations.



INTRODUCTION

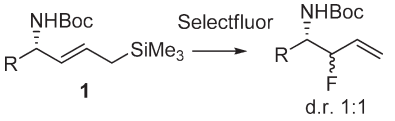
Chiral β-sulfenyl amines of high diastereomeric and enantiomeric purity are of great interest in synthetic organic chemistry; in particular, they have gained considerable attention as N,S-ligands in asymmetric catalysis.[1,2] Heterobidentate N,S-ligands have proved to be very effective in enantioselective palladium-catalyzed allylic substitution reactions,[3,4] for the enantioselective addition of dialkylzinc reagents to prochiral carbonyl compounds,[5] in the enantioselective conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds,[6] and in iridium(I)-catalyzed asymmetric hydrogenation reactions.[7,8] Furthermore, the β-sulfenyl amine unit has been found in a number of important biologically active molecules. For instance, it is a characteristic structural motif in marine alkaloids of the Ecteinascidine family which have been established as an important class of anticancer agents.[9]

Several methods for the synthesis of *vic*-sulfenyl amines have been described in the literature,[10−15] including those starting from natural α-amino acids in an ex-chiral-pool synthesis,[7,16−18] the simple regio- and stereoselective ring-opening of aziridines with thiols,[19−25] and the SAMP/RAMP-hydrazone methodology which leads to both anti-configured enantiomers.[26]

As a part of a research program aimed at the synthesis of new enantiomerically enriched building blocks via amino acids modification, we turned our interest to the development of a new procedure to prepare new chiral units containing the *vic*-amino sulfide moiety. Following our recent results,[27] we focused on chiral amino allylsilanes.

It is well recognized that allylsilanes are perhaps the most useful type of silyl nucleophiles, as they react with a wide variety of electrophiles,[28] including sulfenyl halides.[29] In addition, when they are chiral, they can undergo asymmetric transformations with a high degree of stereochemical control.[30]

Scheme 1. Electrophilic Fluorodesilylation of Amino Allylsilanes with Selectfluor



As far as amino allylsilanes are concerned, we have shown that they can react smoothly with electrophiles such as 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) to give structurally diverse fluorinated amines[31] in high yield but in a roughly 1:1 diastereomeric mixture (Scheme 1). This was in agreement with previous findings, as electrophilic fluorodesilylation of chiral acyclic allylsilanes has been reported as a high-yielding process, albeit with a poor level of diastereocontrol.[32,33] Likewise, we deemed that β-sulfenyl amines could be obtained by electrophilic sulfodesilylation of allylsilanes, and to prove this, the reactivity of phthalimidesulfenyl chloride with our substrates was tested.

Phthalimidesulfenyl chloride (PhthNSCl, Phth = phthaloyl) **2** can be easily obtained by the cleavage of *N*,*N*′-dithiobis(phthalimide) and displays a highly electrophilic character, because of the presence of the phthalimide substituent. Although it represents a convenient source of electrophilic sulfur,[34−36] its reactivity with allylsilanes has not been studied so far.

Herein, we describe the application of electrophilic sulfodesilylation of acyclic homochiral amino allylsilanes **1**, carried out using phthalimidesulfenyl chloride **2**, to prepare enantiopure

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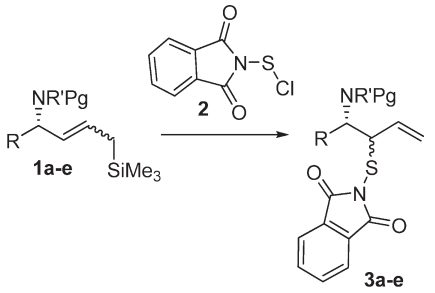
Scheme 2. Electrophilic Sulfodesilylation of Amino Allylsilanes with Phthalimidesulfenyl Chloride



β-amino sulfides **3** with an allylic monosulforated stereogenic center (Scheme 2). These novel compounds are valuable synthetic intermediates, as several synthetic pathways for the subsequent chemical manipulation of the sulfenimido group as well as of the double bond can be exploited.

RESULTS AND DISCUSSION

The enantiopure chiral *E*-allylsilanes that we employed were prepared as reported,[27,31] starting from amino aldehydes **4a**−**d** by addition of vinylmagnesium bromide followed by esterification with acetyl chloride, to obtain the corresponding acetates **5a**−**d** with good yields. Silylcuprate displacement of the allylic acetate afforded the desired *E*-amino allylsilanes **1a**−**d** in good yield and without racemization (Scheme 3).

Sulfodesilylation of allylsilanes **1a**−**d** using phthalimidosulfenyl chloride occurred smoothly in CH_2Cl_2 at −78 °C (Table 1), affording the corresponding allylic phthalimidosulfenyl amines in a 95/5 diastereomeric mixture with a good chemical yield. The reaction takes place regioselectively: the site of attack of sulfur is at C-γ (C-3), and the resulting intermediate undergoes rapid loss of the silyl group, allowing for the formation of a product with a net transposition of the double bond. A reaction temperature increase (entry 2) caused a less clean reaction, significantly lowering the final yield. A different N-protective group such as the tosyl group in **1d** did not change the stereochemical reaction outcome (entry 5).

When the *Z*-allylsilane **1f** (R = CH_2Ph), prepared by the reduction of the corresponding propargylamine,[37] was used as a substrate, a lower yield and stereoselectivity were observed (entry 7). Finally, starting from the amino acid **1c**, a new unnatural sulfur-containing unsaturated amino acid, in its protected form (**3c**) was obtained and fully characterized.

The syn relative stereochemistry of the major diastereoisomer was unambiguously determined by the X-ray crystallographic analysis of **3b**, which was crystallized from chloroform. Compound **3b** crystallizes in the orthorhombic crystal system (space group $P2_12_12_1$). N1−S1 and S1−C9 bond length of 1.690(2) and 1.847(3) Å, respectively, fall in the typical range observed for similar structures containing the phthalimidesulfenyl group (mean values = 1.692 and 1.825 Å).[35,38−41] The N1−S1−C9 bond angle equals 100.4(1)°, rather close to the mean literature value of 102°. An intermolecular hydrogen bonding between the amino proton H2 and the oxygen atom O2 from one carbonyl moiety on the phthalimidesulfenyl substituent of the neighboring molecule is present in the lattice, and a chain of molecules is formed along the *a* axes.[42] The synclinal conformation of the two substituents at C9 and C12 is confirmed by the S1−C9−C12−N2 torsion angle: 59.95(4)°. The absolute configuration of the major diastereoisomer is thus determined as (2*S*,3*S*).

The diastereotopic faces of the double bond in homochiral allylsilanes have been reported to show a surprisingly high facial selectivity in some reactions with electrophiles.[43] For instance, the electrophilic sulfodesilylation of (*E*)-trimethyl(4-phenylpent-2-enyl)silane **7** with phenylsulfenyl chloride (PhSCl)[29] has been found to occur with a high level of stereocontrol leading to a 95/5 dr, according to a preferred anti attack of the electrophile with respect to the bulkier substituent (Scheme 4).

In contrast, with our substrates the stereochemical course of the reaction seems to be controlled by the presence of the amino group since its ability at forming an intermolecular hydrogen bonding (as found in the crystal lattice of **3b**) may direct the attack of the electrophile (Scheme 4), assisting the formation of the diastereoisomer *syn*-(**3a**−**c**), where the amino and the sulfur groups are on the same side.

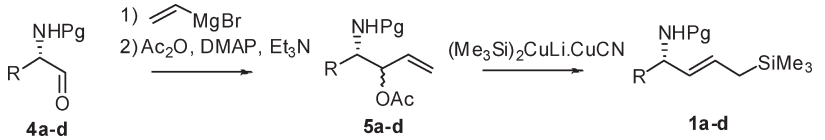
Interactions between a substrate and reagent due to the presence of functional groups are frequently responsible for the stereochemical reaction outcome, particularly when polar groups are present or hydrogen bond formation is possible.[44] Accordingly, when N-methylated-*t*-Boc-amine **1e** was prepared by reaction of **1b** with NaH in THF and methylation with MeI[45] and used as starting material, almost no diastereoselectivity was observed (Table 1, entry 6).

Table 1. Sulfodesilylation of Allylsilanes with Phthalimidesulfenyl Chloride

entry[a]	allylsilane	product	yield (%)[b]	dr anti/syn[c]
1	**1a**	**3a**	62	5/95
2[d]	**1a**	**3a**	35	5/95
3	**1b**	**3b**	80	<5/95
4	**1c**	**3c**	42	5/95
5	**1d**	**3d**	87	5/95
6	**1e**	**3e**	67	60/40[e]
7	**1f**[f]	**3a**	31	30/70
8	**7**	**8**	74	90/10

[a] Reaction conditions: −78 °C, CH_2Cl_2, 1 h. [b] Isolated compound. [c] By integration of ^{1}H NMR signals. [d] RT, CH_2Cl_2. [e] The relative configuration of major diastereoisomer was not determined. [f] *Z*-Allylsilane (Pg = Boc, R = CH_2Ph).

Scheme 3. Synthesis of Enantiopure *E*-Amino Allylsilanes 1a−d



a *E*, R = CH_2Ph, Pg = Boc **b** *E*, R = $(CH_3)_2CH$, Pg = Boc
c *E*, R = COOMe, Pg = Boc **d** *E*, R = CH_2Ph, Pg = Ts

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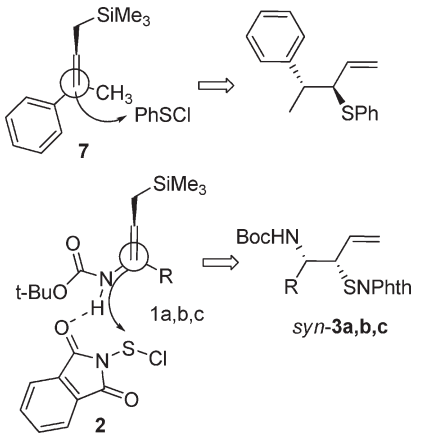
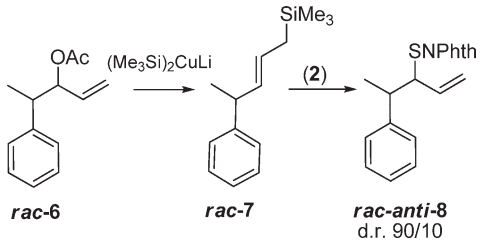
Scheme 4. Stereocontrol in the Sulfenylation Step with Phenylsulfenyl Chloride and Phthalimidesulfenyl Chloride



Scheme 5. Sulfodesilylation of Racemic (*E*)-2-Phenyl-5-trimethylsilyl-3-pentene *rac*-7 with Phthalimidesulfenyl Chloride



However, sulfodesilylation of racemic **7**, obtained from acetate **6** following the usual procedure (Scheme 5), led to the allyl sulfide **8** with high anti diasteroselectivity (Table 1, entry 8), as already observed in the known reaction with phenylsulfenyl chloride.[29]

Again, the relative stereochemistry of the major diastereoisomer was unambiguously determined as (3*R*4*R*)/(3*S*4*S*) by X-ray diffraction of *rac*-**8**, which crystallizes in the centrosymmetric space group $P_{21/c}$ as a pseudoracemate mixture. In the asymmetric unit, both enantiomers are present in a disordered manner. In particular it was possible to unambiguously locate the phenylsulfenyl group, while the remaining organic parts are disordered between two positions with a calculated occupancy factor of almost 50%. The bond distances and angles fall in the same range as those observed for **3b** and are therefore not discussed in detail.[42]

In order to rationalize the observed selectivities, we carried out calculations using DFT methods, at the PBE1PBE[46]//6-31+G(d,p) level of theory with the Gaussian 09 package.[47] We first performed geometry optimizations using allylsilane **1b** as a model substrate.

Two different conformations were found as energy minima on the potential energy surface (PES), considering the relative orientation of the trimethylsilyl and *t*-Bu substituents: in the first one the TMS and *t*-Bu substituents are in a cisoid conformation with respect to the C═C double bond, while in the other one they are in a transoid spatial disposition. The energy

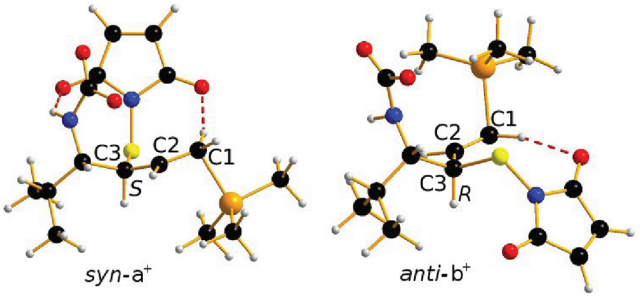


Figure 1. Intermediates *syn*-$\mathbf{a}^+$ and *anti*-$\mathbf{b}^+$. Isopropyl and *t*-Boc groups are hidden for clarity. Color code: C, black; H, white; O, red; N, blue; Si, orange; S, yellow.

difference between the two conformers is only 0.4 kcal/mol, the latter being slightly more stable; consequently, both are accessible at −78 °C. The charge distribution on the alkene carbon atoms was determined by an NBO[48] calculation on the transoid optimized geometry. A slightly higher electron density on the C-γ (C3) of the allylsilane moiety was found, this carbon being indeed the one involved in the new C−S bond formation. Furthermore, the NBO investigation confirms the well-known ability of silanes at stabilizing adjacent negative charges.[49−52] A simplified model system, created by replacing the peripheral aryl group on the phthalimide with a simpler alkene moiety was taken into account for the following calculations, in order to reduce the computational time. As it is well-known that the electrophilic addition to a C═C double bond may occur through a three-centered cyclic intermediate,[53,54] a similar process was envisaged to rationalize the sulfenylimide attack on the alkene moiety of **1b**. Under this perspective, in the starting geometry for the optimization, the electrophile was located at a distance of 3 Å from the C═C double bond, investigating two possible routes: a syn- or a anti- attack with respect to the NHBoc group, which would lead to the *syn*-$\mathbf{a}^+$ and *anti*-$\mathbf{b}^+$ intermediates and to the (3*S*,4*S*) and (3*S*,4*R*) diastereomers, respectively (see Figure 1).

Syn-$\mathbf{a}^+$ was found to be the most stable intermediate (by 1.2 kcal/mol) where an intramolecular NH···O═C hydrogen bond, which is responsible for such stabilization, is present. Because the transition states are product-like, the difference in energy between transition states (TS) can be inferred to be larger or of the same order of the difference found for the intermediates. Therefore, the presence of this hydrogen bond can be the driving force that directs the electrophile approach to the C═C bond and explains the regioselectivity observed experimentally. Finally, the intermediates display a C_1−Si bond lengthening (from 1.90 Å in the starting conformer to 2.09 Å in both *syn*-$\mathbf{a}^+$ and *anti*-$\mathbf{b}^+$, Figure 1) and the consequent adjacent C_1−C_2 bond shortening (from 1.49 to 1.38 Å), toward the formation of a new C═C double bond. Remarkably, in both optimized geometries we found that the C_1−H···O═C distance is short (equal to 2.01 Å, see Figure 1). The interaction between the oxygen and the proton on C_1 stabilizes the cationic character on the silicon atom, being responsible for a more acidic character on the C_1 atom with the concomitant formation of a partially positive charge on the $SiMe_3$ group. To evaluate the strength of such an interaction with a computational experiment, we optimized two conformers of a simplified model of the addition product where the N-Boc moiety was replaced by a hydrogen atom and one carbonyl group of the imide was replaced with a methylene. The

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Scheme 6. Sulfodesilylation of 1a with Phenylsulfenyl Chloride

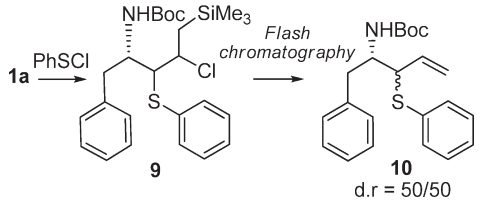
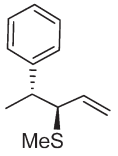
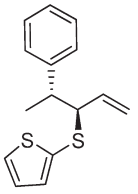
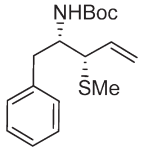
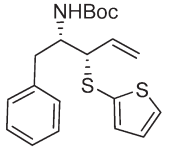
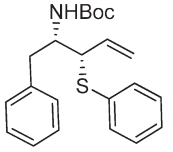


Table 2. Reactivity of Phthalimidosulfides 3a and 8 with Nucleophiles

Entry	Substrate	Base	Product	Yield (%)[a]
1	**8**	MeLi (1.2eq)	 *rac*-**11**	88
2	**8**	 (1.2eq)	 *rac*-**12**	90
3	**3a**	MeLi (2eq)	 **13**	50
4	**3a**	 (2eq)	 **14**	78
5	**3a**	PhLi (2eq)	 *syn*-**10**	87

[a] Isolated Compound.

conformer with the hydrogen bond was found to be more stable by ca. 7.0 kcal/mol. Although probably overestimated and based on a very simplified model, this value suggests that a C−H···O═C interaction is strong enough to favor the $SiMe_3$ displacement because of its more cationic character.

Indeed, when allylsilane **1a** was reacted with phenylsulfenyl chloride, a different reactivity and selectivity was observed compared with **2**. A mixture of the two diastereoisomers corresponding to the addition product **9** was found by ^{1}H NMR spectroscopic analysis of the crude mixture (Scheme 6) and no elimination occurred, even over a longer reaction time. However, when the crude was purified by flash chromatography, elimination took place[55] and a 1:1 diastereomeric mixture of phenyl sulfide **10** was finally recovered.

Finally, because allyl sulfides are valuable and versatile intermediates, we decided to study the reactivity of the S−N bond of phthalimidosulfides **3a** and **8** with bases. The reaction was carried out at −78 °C in THF using methyl-, 2-thienyl-, and phenyllithium. The results obtained are collected in Table 2. In all cases, a clean displacement of the phthalimide group was observed, affording the corresponding unsymmetrical sulfides **10**−**14** in high yield. This confirmed the labile nature of the S−N bond and the ability of phthalimide to act as a sulfide "protecting group".[56]

CONCLUSIONS

Syn-β-sulfenyl amines of high diastereomeric and enantiomeric purity have been prepared from the corresponding enantiopure amino allylsilanes by electrophilic sulfodesilylation with phthalimidesulfenyl chloride. The relative syn stereochemistry of the major diastereoisomer was determined unambiguously by X-ray crystallographic analysis.

The stereochemical course of the reaction seems to be controlled by the presence of the amino group in the substrate and its ability to form an intermolecular hydrogen bond with the carbonyl of the phthalimido group. The presence of such an interaction has been confirmed by theoretical calculations. Following this procedure, a new sulfur-containing unsaturated amino acid has been obtained in its protected form and fully characterized. Finally a clean displacement of the phthalimide group has been accomplished by reaction with organolithium nucleophiles, giving the corresponding unsymmetrical sulfides in high yield.

EXPERIMENTAL SECTION

General. All air-sensitive reactions were performed using Schlenk techniques.[57] Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl, and CH_2Cl_2 was stored under nitrogen over 4 Å molecular sieves. HMPA was distilled from CaH_2 at reduced pressure and stored on KOH under nitrogen atmosphere. Petroleum ether, unless specified, is the 40−70 °C boiling fraction. Allylsilanes **1a**−**c**,[27] acetate **6**,[43] aldehyde **4d**,[58] and $Me_3SiCuLi\cdot LiCN$[27] were prepared according to literature methods.

^{1}H NMR spectra were recorded at 200, 300, or 400 MHz, and ^{13}C NMR spectra were recorded at 50.3, 75.5, or 100.6 MHz. Chemical shifts were referenced to the residual solvent peak ($CHCl_3$, δ 7.26 ppm, and C_6H_6, δ 7.16 ppm, for ^{1}H NMR; $CHCl_3$, δ 77.0 ppm, and C_6H_6, δ 128.06 ppm, for ^{13}C NMR). When a diastereomeric mixture is present, only the signals of the major diastereoisomer are reported. Mass spectra were obtained at a 70 eV ionization potential and are reported in the form m/z (intensity relative to base = 100). IR spectra were recorded in $CHCl_3$ solution on KBr and are expressed in cm^{-1}. Polarimetric measurements were performed in $CHCl_3$ solution at λ = 589 nm, and the temperature is specified case by case.

X-ray. X-ray data were collected at ambient temperature (293 K) on an Oxford Diffraction XCALIBUR 3 diffractometer equipped with a CCD area detector using Mo K_α radiation (λ = 0.7107 Å). The program used for the data collection was CrysAlis CCD 1.171.[59] Data reduction was carried out with the program CrysAlis RED 1.17,[60] and the absorption correction was applied with the program ABSPACK 1.17. Direct methods implemented in Sir97[61] were used to solve the structures, and the refinements were performed by full-matrix least-squares against F^2 implemented in SHELX97.[62]

Computational Details. The model systems were optimized at the hybrid density functional theory (DFT) level, using the PBE1PBE functional (known as PBE0).[46] All the DFT calculations were carried out using the Gaussian 09 package.[47] For all of the fully optimized structures, calculations of vibrational frequencies were performed to confirm their nature as stationary point. The basis set was used for the 6-31G, with the important addition of the polarization functions (d, p) for all atoms, including the hydrogens. The intramolecular charge distribution was determined by an NBO[48] charges analysis carried out on the optimized geometries.

*Synthesis of (S)-4-(4-Methylphenylsulfonamido)-5-phenylpent-1-en-3-yl Acetate (**5d**).* Aldehyde **4d** (605 mg, 2.0 mmol) was dissolved in THF (12 mL), cooled at 0 °C, and reacted with vinylmagnesium bromide (1 M in ether, 5.0 mL, 5.0 mmol). The solution was stirred at room temperature overnight and then diluted with ether (20 mL) and hydrolyzed with a NH_4Cl saturated aqueous solution (20 mL). After extraction with ethyl acetate (3 × 10 mL), the organic phase was collected, dried, and evaporated to afford the intermediate alcohol (646 mg, 1.9 mmol, 97%) which was then dissolved into CH_2Cl_2 (15 mL) and reacted overnight with triethylamine (0.30 mL, 2.0 mmol), acetic anhydride (0.20 mL, 2.0 mmol), and DMAP (15 mg, 0.01 mmol). The reaction mixture was diluted with CH_2Cl_2 (15 mL), hydrolyzed with a $NaHCO_3$ saturated solution (30 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over Na_2SO_4 and finally evaporated to dryness. The crude product was filtered over a silica gel column to afford a 2:1 diastereomeric mixture of **5d** (391 mg, 54%) as a white solid which was used for the subsequent step without further purification. Eluent: petroleum ether−ethyl acetate 1:1, R_f = 0.62. (**5d**, major diastereomer) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.61 (d, 2H, J = 8.2 Hz), 7.21−7.16 (m, 7H), 5.84−5.55 (m, 2H), 5.33−5.05 (m, 3H), 3.85−3.65 (m, 1H), 2.82−2.58 (m, 2H), 2.38 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.6, 142.9, 137.5, 136.3, 135.9, 129.3, 128.9, 128.5, 128.3, 126.8, 118.7, 73.9, 57.7, 38.2, 21.5, 20.9.

*rac-(E)-Trimethyl(4-phenylpent-2-enyl)silane (**7**).* Trimethylsilylcyanocuprate was prepared using hexamethyldisilane (1.56 g, 10.7 mmol), HMPA (3.10 mL), MeLi (3.30 mL, 5.3 mmol), and CuCN (261 mg, 2.9 mmol), cooled at −78 °C, and reacted with a solution of 4-phenylpent-1-en-3-yl acetate **6** (496 mg, 2.4 mmol) in THF (5 mL). After 30 min, the reaction mixture was hydrolyzed with NH_4Cl/NH_4OH buffer solution and extracted with Et_2O. The ethereal phase was then washed with brine, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography. Purification gave **7** (447 mg, 84%) as a colorless oil. E/Z = 85/15. Eluent: petroleum ether−ethyl acetate 20:1, R_f = 0.41. (*rac*-**7**) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.39−7.18 (m, 5H), 5.52−5.47 (m, 2H), 3.53−3.42 (m, 1H), 1.44−1.40 (m, 2H), 1.33 (d, 3H, J = 7.3 Hz), −0.01 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 146.8, 133.7, 128.3, 127.1, 125.8, 125.2, 42.7, 22.9, 22.0, −1.6; MS (m/z): 218 (M^+, 7), 73 (100). Elemental analysis: Calcd for $C_{14}H_{22}Si$: C, 76.99; H, 10.15. Found: C, 76.88; H, 10.18.

*(E,S)-4-Methyl-N-[1-phenyl-5-(trimethylsilyl)pent-3-en-2-yl]benzenesulfonamide (**1d**).* Trimethylsilylcyanocuprate was prepared using hexamethyldisilane (260 mg, 0.4 mmol), HMPA (0.45 mL), MeLi (0.55 mL, 0.9 mmol), and CuCN (42 mg, 0.5 mmol) cooled at −78 °C and reacted with a solution of allylacetate **5d** (133 mg, 0.4 mmol) in THF (1 mL). After 30 min, the reaction mixture was hydrolyzed with NH_4Cl/NH_4OH buffer solution and extracted with Et_2O. The ethereal phase was then washed with brine, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography. Purification gave **1d** (91 mg, 67%) as a 90/10 E/Z mixture of diastereoisomrs. Colorless oil. Eluent: petroleum ether:ethyl acetate 5:1, R_f = 0.35. (**1d**, major diastereoisomer) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.64 (d, 2H, J = 8.4 Hz), 7.26−7.03 (m, 7H), 5.40−5.24 (m, 1H), 5.01 (dd, 1H, J = 15.2 Hz, J = 6.8 Hz), 4.69 (bd, 1H, J = 7.0 Hz), 3.98−3.87 (m, 1H), 2.82−2.70 (m, 2H), 2.39 (s, 3H), 1.28−1.16 (m, 2H), −0.14 (s, 9H); ^{13}C NMR (50 MHz, CDCl3) δ: 142.7, 137.7, 136.7, 129.8, 129.3, 128.2, 127.0, 126.9, 126.8, 126.3, 57.2, 42.8, 22.7, 21.5, 2.0; MS (m/z): 372 (M^+ − 15, 2), 73 (100). Elemental analysis: Calcd for $C_{21}H_{29}NO_2SSi$: C, 65.07; H, 7.54; N, 3.61. Found: C, 65.13; H, 7.51; N, 3.63.

*(S,E)-tert-Butyl Methyl(2-methyl-6-(trimethylsilyl)hex-4-en-3-yl)carbamate (**1e**).* *N*-Boc-allylsilane **1b** (42 mg, 0.15 mmol) and methyl iodide (0.10 mL, 1.5 mmol) were dissolved in THF (1.5 mL) and reacted with a 60% mineral oil dispersion of NaH (59 mg, 1.5 mmol), under stirring. After 24 h at room temperature, the reaction was quenched with ethyl acetate (2 mL) and H_2O (8 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and ethyl acetate (2 × 10 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (10 mL), a 5% solution of $Na_2S_2O_4$ (15 mL), and brine (10 mL) and then dried over Na_2SO_4. Purification by flash chromatography gave **1e** (41 mg, 93%) as a colorless oil. Eluent: petroleum ether−ethyl acetate 10:1, R_f = 0.45. (**1e**) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.58−5.53 (m, 1H), 5.23 (dd, 1H, J = 8.1 Hz, J = 7.7 Hz), 4.11−3.87 (bm, 1H), 2.67 (bs, 3H), 1.80−1.65 (m, 1H), 1.44 (s, 9H), 1.25−1.19 (m, 2H), 0.86 (d, 3H, J = 3.7 Hz), 0.82 (d, 3H, J = 3.3 Hz), −0.02 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 155.9, 130.5, 126.0, 78.9, 65.2(b), 37.8 (b), 29.7, 28.6; 22.7, 20.3, 19.5, −1.9. MS (m/z): 284 (M^+ − 15, 6), 73 (100). Elemental analysis: Calcd for $C_{16}H_{33}NO_2Si$: C, 64.16; H, 11.10; N,4.68. Found: C, 64.18; H, 11.16; N, 4.65. $[\alpha]^{24}_D$ = −32.3 (c = 2.8; $CHCl_3$).

Sulfodesilylation of Allylsilanes: General Procdeure. Allylsilanes **1a**−**f** (1 equiv) were dissolved in dry CH_2Cl_2 (0.1 M). The solution was cooled at −78 °C, and then phthalimidesulfenyl chloride **2** (1.1 equiv) was added in portions. The reaction was left at −78 °C for 1 h, and then the mixture was warmed up to room temperature and quenched with water. The aqueous layer was extracted with CH_2Cl_2, and the organic phases were collected, washed with a $NaHCO_3$ saturated solution, and then dried over Na_2SO_4. After solvent evaporation, the crude product was purified by flash chromatography.

*(2S,3S)-3-[(1,3-Dioxoisoindolin-2-yl)sulfanyl]-1-phenylpent-4-en-2-yl Carbamic Acid tert-Butyl Ester (**3a**).* Allylsilane **1a** (150 mg, 0.5 mmol) was reacted with phthalimidesulfenyl chloride **2** (106 mg, 0.5 mmol). Purification gave **3a** (122 mg, 62%) as a 95/5 mixture of diastereoisomers. Eluent: petroleum ether−ethyl acetate: 5:1. R_f = 0.33 (3:1). White solid. Mp 178−179 °C. (**3a**) IR (KBr): ν 3420, 3022, 1785, 1740, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ: 7.91−7.75 (m, 4H), 7.28−7.17 (m, 5H), 5.78−5.69 (dt, 1H, J = 16.8 Hz, J = 9.8 Hz), 5.06−4.90 (m, 3H), 4.16−4.05 (m, 2H), 3.06−3.00 (m, 1H), 2.84−2.79 (m, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$ 100.6 MHz) δ: 168.4, 167.9, 154.9, 134.5, 134.2, 133.6, 132.0, 129.5, 126.6, 123.8, 123.5, 120.9, 79.6, 57.5, 53.4, 39.1, 28.3; MS m/z: 347 (1), 57 (100). Elemental analysis: Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 5.98; N, 6.39. Found: C, 65.66; H, 6.03. N, 6.43. $[\alpha]^{26}_D$ = −22.1 (c = 1.0, $CHCl_3$).

*(3S,4S)-2-Methyl-4-[(1,3-dioxoisoindolin-2-yl)sulfanyl]hex-5-en-3-yl Carbamic Acid tert-Butyl Ester (**3b**).* Allylsilane **1b** (131 mg, 0.5 mmol) was reacted with phthalimidesulfenyl chloride **2** (108 mg, 0.5 mmol). Purification gave **3b** (144 mg, 80%). Eluent: petroleum ether−ethyl acetate: gradient (6:1−4:1) R_f = 0.44. White solid. Mp 145−148 °C. (**3b**) IR (KBr): ν 3429, 3017, 1778, 1739, 1714, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$

400 MHz) δ: δ: 7.88−7.73 (m, 4H), 5.78−5.69 (dt, 1H, J = 16.8 Hz, J = 9.8 Hz), 4.89−4.82 (m, 3H), 4.17−4.12 (t, 1H, J = 9.8 Hz), 3.84−3.78 (m, 1H), 1.87−1.81 (m, 1H), 1.44 (s, 9H), 0.99 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 168.2, 155.4, 134.5, 134.3, 131.9, 123.5, 119.4, 79.4, 57.7, 56.6, 31.2, 28.4, 20.0, 16.6; MS m/z: 279 (11), 149 (100). Elemental analysis: Calcd for $C_{20}H_{26}N_2O_4S$: C, 61.52; H, 6.71; N, 7.17. Found: C, 61.46; H, 6.83; N, 7.13. $[\alpha]^{23}_D$ = +2.3 (c = 1.0, $CHCl_3$).

*(2S,3S)-Methyl 2-(tert-Butoxycarbonylamino)-3-(1,3-dioxoisoindolin-2-ylthio)pent-4-enoate (**3c**).* Allylsilane **1c** (18 mg, 0.1 mmol) was reacted with phthalimidesulfenyl chloride **2** (14 mg, 0.1 mmol). Purification gave **3c** (10 mg, 42%) as a 95/5 mixture of diastereoisomers. Eluent: Petroleum ether:ethyl acetate: 5:1. R_f = 0.31. White solid. Mp 45−48 °C. (**3c**) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.95−7.91 (m, 2H), 7.81−7.66 (m, 2H), 5.93 (bd, 1H, J = 9.0 Hz), 5.75−5.69 (m, 1H), 5.38 (bd, 1H, J = 17.0 Hz), 5.27 (bd, 1H, J = 10.2 Hz), 4.74−4.69 (m, 1H), 4.65−4.60 (m, 1H), 3.46 (s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.2, 167.8, 155.5, 134.6, 131.7, 130.3, 123.9, 122.2, 80.4, 54.8, 54.5, 52.5, 28.4. MS m/z: 347 (1), 57 (100). Elemental analysis: Calcd for $C_{19}H_{22}N_2O_6S$: C, 56.15; H, 5.46; N, 6.89. Found: C, 56.21; H, 5.44; N, 6.93. $[\alpha]^{23}_D$ = −39.2 (c = 0.5, $CHCl_3$).

*(2S,3S)-N-(3-(1,3-Dioxoisoindolin-2-ylthio)-1-phenylpent-4-en-2-yl)-4-methylbenzenesulfonamide (**3d**).* Following the general procedure, allylsilane **1d** (59 mg, 0.15 mmol) was reacted with phthalimidesulfenyl chloride **2** (36 mg, 0.2 mmol. Purification gave **3d** (66 mg, 87%) as a 95/5 mixture of diastereoisomers . Eluent: hexane−ethyl acetate: gradient (4:1−2:1). R_f = 0.37 (2:1). White solid. Mp 168−170 °C. (**3d**): IR (KBr): ν 3018, 1778, 1741, 1715, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94−7.92 (m, 2H), 7.81−7.79 (m, 2H), 7.51−7.49 (m, 2H), 7.21−7.19 (m, 3H), 7.12−7.09 (m, 2H), 7.08−7.05 (m, 2H), 5.62 (ddd, 1H, J = 19.3 Hz, J = 10.2 Hz, J = 7.8 Hz), 5.16−5.11 (m, 2H), 4.02 (dd, 1H, J = 9.2 Hz, J = 4.7 Hz), 3.77−3.71 (m, 1H), 3.13 (dd, 1H, J = 13.9 Hz, J = 6.4 Hz); 2.66 (dd, 1H, J = 13.9 Hz, J = 6.9 Hz); 2.36 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.0, 143.2, 137.2, 136.1, 134.8, 131.9, 131.2, 129.6 (2C), 128.7, 126.9 (2C), 124.0, 122.1, 57.1, 38.2, 29.8, 21.6; MS (m/z): 353 (9), 91 (100). Elemental analysis: Calcd for $C_{26}H_{24}N_2O_4S_2$: C, 63.39; H, 4.91; N, 5.69. Found: C, 63.45; H, 5.03; N, 5.74. $[\alpha]^{30}_D$ = −62.0 (c = 2.3, $CDCl_3$).

*[3S,4(R,S)]-tert-Butyl-4-(1,3-dioxoisoindolin-2-ylthio)-2-methylhex-5-en-3-yl(methyl)carbamate (**3e**).* Following the general procedure, allylsilane **1e** (45 mg, 0.15 mmol) was reacted with phthalimidesulfenyl chloride **2** (34 mg, 0.2 mmol) for 1 h. Purification gave **3e** (37 mg, 63%) as a 60/40 mixture of diastereoisomers. Eluent: petroleum ether/ethyl acetate = 8/1 R_f = 0.22. White gummy solid. (**3e**, major diastereoisomer) IR (KBr): ν 3019, 1775, 1742, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.87−7.85 (m, 2H), 7.76−7.74 (m, 2H), 5.81−5.69 (m,1H), 4.88−4.73 (m, 2H), 4.22 (t, 1H, J = 9.7 Hz), 4.10−4.06 (m, 1H), 2.94 (s, 3H), 1.99−1.91 (m, 1H), 0.87 (d, 6H, J = 6.7 Hz) 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.4, 155.9, 135.8, 134.3, 132.2, 123.5, 118.4, 79.7, 59.9, 56.8, 30.7, 29.6, 28.3, 20.5, 18.8. MS m/e: 331(1), 57 (100). Elemental analysis: Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.93. Found: C, 62.42; H, 6.96. N, 6.88.

*[(3S,4S),(3R,4R)]-2-(4-Phenylpent-1-en-3-ylthio)isoindoline-1,3-dione (**8**).* Following the general procedure, allylsilane **7** (146 mg, 0.7 mmol) was reacted with phthalimidesulfenyl chloride **2** (157 mg, 0.8 mmol). Purification gave **8** (160 mg, 74%) as a 90/10 racemic mixture of diastereoisomers. Eluent: petroleum ether−ethyl acetate 10:1, R_f = 0.18. White oil. The relative configuration of the major diastereoisomer was established by X-ray analysis. (*rac,anti*-**8**) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89−7.87 (m, 2H), 7.75−7.73 (m, 2H), 7.31−7.25 (m, 2H), 7.21−7.16 (m, 3H), 5.56 (dt, 1H, J = 16.8 Hz, J = 10.2 Hz), 4.70 (dd, 1H, J = 0.4 Hz, J = 1.6 Hz), 4.61 (dd, 1H, J = 16.8 Hz, J = 1.6 Hz), 4.10 (dd, 1H, J = 10.2 Hz, J = 8.4 Hz), 3.12 (dq, 1H, J = 7.1 Hz, J = 1.4 Hz); 1.49 (d, 3H, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.0, 143.0, 135.5, 134.5, 132.1, 128.6, 127.7, 126.9, 123.7, 118.8, 61.0, 42.3, 19.9. MS (m/z): 323 (M^+, 1), 59 (100). Elemental analysis: Calcd for $C_{19}H_{17}NO_2S$, C, 70.56; H, 5.30; N, 4.33. Found: C, 70.47; H, 5.27. N, 4.29.

General Procedure of Reaction of Phtalimido Sulfides with Nucleophiles. Phthalimidosulfide **3a** or **8** (1 equiv) was dissolved in dry THF (0.1 M). The solution was cooled at −78 °C, and then MeLi (1.6 M in THF), 2-thienyllithium (1.0 M in THF), or phenyllithium (1.8 M in nBu_2O) was added with a syringe. After 30 min, at −78 °C the reaction mixture was diluted with Et_2O and quenched with a NH_4Cl saturated solution. The organic phase was extracted with Et_2O (three times), washed with fresh portions of the same solution and brine, and then dried with Na_2SO_4. Solvent removal gave the crude product which was purified by flash chromatography.

*[(3S,4S),(3R,4R)]-Methyl(4-phenylpent-1-en-3-yl)sulfane (**11**).* Following the general procedure, a solution of sulfide **8** (48 mg, 0.15 mmol) in THF (1.5 mL) was reacted with MeLi (1.6 M in THF) (0.12 mL, 0.2 mmol). Purification gave a 90/10 diastereomeric mixture of racemic **11** (25 mg, 88%). Eluent: petroleum ether−ethyl acetate 8:1, R_f = 0.69. Colorless oil. (**11**) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.33−7.17 (m, 5H); 5.47 (dt, 1H, J = 9.9 Hz, J = 16.8 Hz); 5.03−4.58 (m, 2H); 3.19 (dd, 1H, J = 7.7 Hz, J = 9.9 Hz); 3.03−2.90 (m, 1H); 1.97 (s, 3H); 1.42 (d, 3H, J = 6.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 143.8; 136.7; 128.0; 127.8; 126.4; 115.6; 57.8; 43.8; 19.7; 14.5. MS (m/z): 192 (M^+, 8); 87 (M^+ − $PhCH\cdot CH_3$, 100). Elemental analysis: Calcd for $C_{12}H_{16}S$: C, 74.94; H, 8.39. Found: C, 75.05; H, 8.43.

*[(3S,4S,)(3R,4R)]-2-(4-Phenylpent-1-en-3-ylthio)thiophene (**12**).* Following the general procedure, a solution of sulfide **8** (40 mg, 0.1 mmol) in THF (1.5 mL) was reacted with thiophen-2-yllithium (1.0 M in THF, 0.15 mL, 0.15 mmol). Purification gave a 95/5 diastereomeric mixture of racemic **12** (29 mg, 90%). Eluent: petroleum ether−ethyl acetate 10:1, R_f = 0.75. Yellow oil. (**12**) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35−7.18 (m, 6H); 7.07 (dd, 1H, J = 1.1 Hz J = 3.5 Hz); 6.97 (dd, 1H, J = 1.1 Hz J = 5.3 Hz); 5.55 (dt, 1H, J = 10.0 Hz, J = 16.8 Hz); 4.83 (dd, 1H, J = 1.5 Hz, J = 10.0 Hz); 4.64 (dd, 1H, J = 16.8 Hz, J = 0.8 Hz); 3.54 (dd, 1H, J = 8.0 Hz, J = 9.6 Hz); 3.10−3.01 (m, 1H); 1.49 (d, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.4; 136.6; 135.3; 132.7; 129.9; 128.1; 128.1; 127.3; 126.6; 116.6; 62.9; 43.3; 20.0. MS (m/z): 260 (M^+, 13); 155 (M^+ − $PhCH\cdot CH_3$, 100). Elemental analysis: Calcd for $C_{15}H_{16}S_2$, C, 69.18; H, 6.19. Found: C, 69.23; H, 6.21.

*(2S,3S)-tert-Butyl 3-(Methylthio)-1-phenylpent-4-en-2-ylcarbamate (**13**).* A solution of phthalimidosulfide **3a** (51 mg, 0.1 mmol) in THF (1.5 mL) was reacted with MeLi (1.6 M in THF, 0.15 mL, 0.2 mmol). Purification gave **13** (18 mg, 50%) as a single diastereoisomer. Eluent: petroleum ether−ethyl acetate 10:1, R_f = 0.30. Colorless oil. (**13**) IR (KBr): ν 3434, 1689 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.33−7.20 (m, 5H); 5.72 (dt, 1H, J = 9.9 Hz, J = 16.8 Hz); 5.21−5.00 (bd, 1H, J = 9.9 Hz); 5.67−4.21 (bd, 1H, J = 16.8 Hz); 4.64 (bd, 1H, J = 8.8 Hz); 4.17−4.02 (m, 1H); 3.19 (dd, 1H, J = 5.1 Hz, J = 9.9 Hz); 3.05 (dd, 1H, J = 6.0 Hz, J = 13.8 Hz); 2.76 (dd, 1H, J = 13.8 Hz, J = 7.7 Hz); 2.00 (s, 3H); 1.40 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 155.2; 137.8; 135.3; 129.3; 128.3; 126.3; 117.4; 79.3; 54.4; 53.7; 38.2; 28.3; 14.1. MS (m/z): 251 (M^+ − *t*-Bu, 1); 91 ($PhCH_2^+$, 23); 57 (100). Elemental analysis: Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.46; H, 8.23; N, 4.54. $[\alpha]^{24}_D$ = −31.1 (c = 0.9; $CHCl_3$).

*(2S,3S)-tert-Butyl 1-Phenyl-3-(thiophen-2-ylthio)pent-4-en-2-ylcarbamate (**14**).* A solution of phthalimidosulfide **3a** (27 mg, 0.1 mmol) in THF (1.5 mL) was reacted with thiophen-2-yllithium (1.0 M in THF, 0.12 mL, 0.1 mmol). Purification gave **14** (18 mg, 78%) as a 95/5 diastereoisomeric mixture. Eluent: petroleum ether−ethyl acetate 13:1, R_f = 0.36. Colorless oil. (**14**) IR (KBr): ν 3646, 3081, 1635 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.37−7.20 (m, 6H); 7.13 (bd, 1H J = 3.3 Hz); 6.98 (dd, 1H, J = 3.3 Hz, J = 5.1 Hz), 5.78 (dt, 1H, J = 9.7 Hz, J = 16.9 Hz); 5.08 (bd, 1H, J = 9.7 Hz); 4.92−4.81 (m, 1H); 4.66 (bd, 1H,

J = 8.1 Hz); 4.17−4.02 (m, 1H); 3.56 (dd, 1H, J = 5.5 Hz, J = 9.5 Hz); 3.13 (dd, 1H, J = 13.5 Hz, J = 5.9 Hz); 2.79 (bdd, 1H, J = 13.5 Hz, J = 7.7 Hz); 1.39 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 155.1; 137.7; 135.8; 135.1; 130.4; 129.3; 128.3(2C); 127.6; 126.4; 118.3; 79.4; 58.9; 54.2; 38.4; 28.3. MS (m/z): 284 (M^+ − Bn, 1.6); 91 (100). Elemental analysis: Calcd for $C_{20}H_{25}NO_2S_2$: C, 63.96; H, 6.71; N, 3.73. Found: C, 64.03; H, 6.72; N, 3.76. $[\alpha]^{24}_D$ = +17.8 (c = 0.7; $CHCl_3$)

*(2S,3S)-tert-Butyl 1-Phenyl-3-(phenylthio)pent-4-en-2-ylcarbamate (**10**).* Phthalimido sulfide (**3a**) (22 mg, 0.05 mmol) in THF (1.5 mL) was reacted with phenyllithium (1.8 M in n-Bu_2O, 0.06 mL, 0.1 mmol). Purification gave **10** (16 mg, 87%) as a single diastereoisomer. Eluent: petroleum ether−ethyl acetate 4:1, R_f = 0.51. White solid. Mp 54−58 °C. (**10**) IR (KBr): ν 3433, 3063, 1706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39−7.17 (m, 10H); 5.80 (dt 1H, J = 9.3 Hz, J = 16.8 Hz); 5.05 (d, 1H, J = 9.6 Hz); 4.94 (d, 1H, J = 16.6 Hz); 4.69 (bd, 1H, J = 8.7 Hz); 4.19−4.11 (m, 1H); 3.76 (dd, 1H, J = 4.4 Hz, J = 8.9 Hz); 3.11 (dd, 1H, J = 14.2 Hz, J = 6.2 Hz); 2.83−2.75 (m, 1H); 1.38 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 155.2; 137.8; 135.6; 133.9; 132.8; 129.3; 128.9; 128.4; 127.3; 126.4; 117.8; 79.4; 55.7; 54.9; 38.3; 28.3. MS (m/z): 369 (1); 91 (30); 57 (100). Elemental analysis: Calcd for $C_{22}H_{27}NO_2S$: C, 71.51; H, 7.36; N, 3.79. Found: C, 71.58; H, 7.34; N, 3.81. $[\alpha]^{23}_D$ = −17.2 (c = 0.3; $CHCl_3$)

■ ASSOCIATED CONTENT

Supporting Information. X-ray data for **3b** and **8**, computational details, and ^{1}H and ^{13}C NMR spectra of compounds **7**, **1d**, **1e**, **3a**, **3b**, **3c**, **3d**, **3e**, **8**, **11**, **12**, **13**, **14**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

†This work is dedicated to Prof. Alfredo Ricci in recognition of his career as researcher, chemist, and teacher.

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