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Asymmetric Synthesis of *trans*-2,5-Disubstituted Pyrrolidines from Enantiopure Homoallylic Amines. Synthesis of Pyrrolidine (−)-197B

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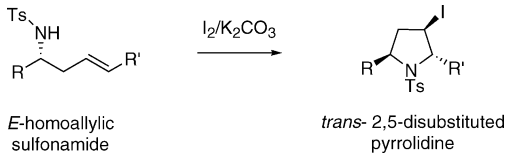

Iodocyclization of sulfinimine-derived enantiopure homoallylic sulfonamides affords *trans*-2,5-disubstituted 3-iodopyrrolidines and represents valuable methodology for the asymmetric synthesis of this important heterocyclic ring system.

The *trans*-2,5-disubstituted pyrrolidine ring system is found in numerous natural products, medicinally relevant molecules, and the pyrrolizidine and indolizidine alkaloids.[1,2] Enantiopure C_2-symmetrical *trans*-2,5-disubstituted pyrrolidines have found utility as organocatalysts,[3] as chiral ligands for asymmetric catalysis,[3] and as chiral auxiliaries.[4] Although many racemic syntheses of this ring system have been reported,[5] fewer general methods are available for their preparation in enantiomerically pure form.[1c,d,6−8] Furthermore, many of these methods are target specific, require difficult separations of diastereoisomers, and are multistep. These methods also necessitate enantiomerically pure starting materials, which can be difficult to obtain. For these reasons the development of new methods for the concise asymmetric synthesis of this class of heterocycles continues to be an important challenge.

In this context we describe an iodocyclization of sulfinimine-derived enantiopure homoallylic sulfonamides that represents a valuable new route for the asymmetric synthesis of *trans*-2,5-disubstituted pyrrolidines (Scheme 1). Our work was inspired by the studies of Knight et al., who explored the racemic system.[9] In their research these workers reported that racemic *E*-homoallylic sulfonamides underwent the iodocyclization reaction with I_2/K_2CO_3 to give *trans*-2,5-disubstituted pyrrolidines in high yield and selectivity. However, the Z-homoallylic sulfonamides or multisubstituted examples resulted in poor yields and lower selectivity.

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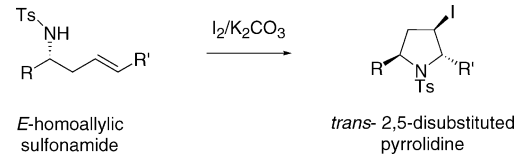
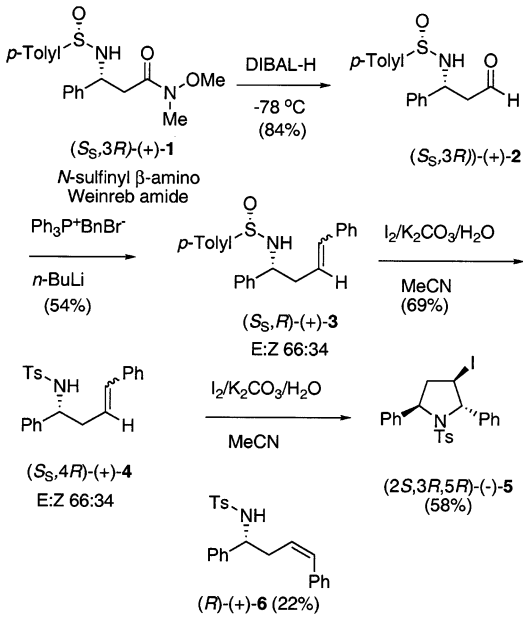
SCHEME 1



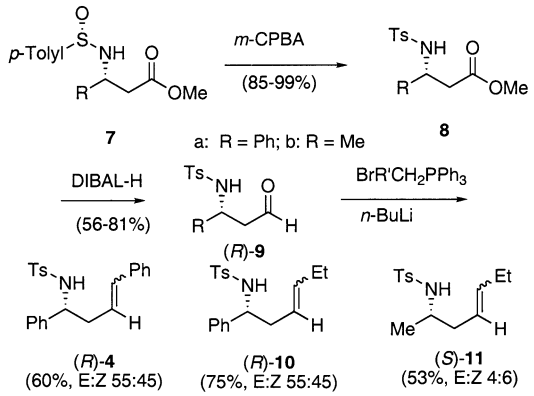
SCHEME 2



A general method for the asymmetric synthesis of *trans*-2,5-disubstituted pyrrolidines using the iodocyclization protocol requires easy access to structurally diverse enantiopure homoallylic sulfonamides. However, most of the methods reported for the asymmetric synthesis of homoallylic amines appear to be of limited scope and restricted to examples containing terminal olefins.[10] Furthermore, many examples of substituted homoallylic amines do not provide convenient access to the requisite *N*-sulfonyl derivatives.[11]

Recently we introduced a general method for the asymmetric synthesis of β-amino carbonyl compounds, including β-amino aldehydes, that involves the use of sulfinimine-derived *N*-sulfinyl β-amino Weinreb amides (Scheme 2).[12,13] This method involves the selective reduction of sulfinimine-derived *N*-sulfinyl β-amino Weinreb amides with DIBAL-H. Thus treatment of Weinreb amide (S_S,3*R*)-(+)-**1** with 5 equiv of DIBAL-H at −78 °C afforded *N*-sulfinyl β-amino aldehyde (S_S-3*R*)-(+)-**2** in 84%.

SCHEME 3



The aldehyde was next treated with 5.0 equiv of the Wittig reagent generated from *n*-butyllithium and benzyltriphenylphosphonium bromide to give the homoallylic sulfinamide (S_S,4*R*)-(+)-**3** as an inseparable 66:34 mixture of *E* and *Z* isomers.[14] The ^{1}H NMR chemical shifts of the two vinyl protons centered at δ 6.47 (J = 16 Hz) and δ 6.6 (J = 11 Hz) for the *E* and *Z* isomers, respectively, were used to establish the *E*:*Z* ratio. Next the mixture of homoallylic sulfinamides (+)-**3** was treated with 3.0 equiv of I_2, along with 3.0 equiv of K_2CO_3 in aqueous acetonitrile (Scheme 2). However, none of the expected 3-iodopyrrolidine **5** was detected, but rather the *N*-sulfinyl group in **3** was oxidized to the corresponding homoallylic sulfonamide (*R*)-**4** in 69% yield, again as an inseparable mixture of 66:34 *E*:*Z* isomers. Longer reactions times also failed to give the iodocyclization product **5**. However, when **4** was resubjected to the iodocyclization protocol, (2*S*,3*R*,5*R*)-(−)-**5** was obtained in 58% yield as the major isomer of a 95:5 mixture. The *Z*-homoallylic amide (*S*)-(+)-**6** was isolated in 22% yield (Scheme 2). The structure of (−)-**5** was established by conversion into the known (2*R*,5*R*)-(+)-2,5-diphenylpyrrolidine (**13**) as outlined below. In (+)-**6** the vinyl proton centered at δ 6.6 (J = 11.7 Hz) is consistent with its structure.

Because *N*-sulfinyl β-amino aldehydes slowly decompose after several days at 0 °C, it was found to be more efficient to prepare the requisite *N*-tosyl β-amino aldehydes **9** by selective DIBAL-H reduction of the corresponding *N*-tosyl β-amino esters (*R*)-**8** (Scheme 3). Oxidation of the *N*-sulfinyl β-amino esters **7** with 5.0 equiv of *m*-CPBA gave **8** in 85−99% yield. Although the *N*-tosyl β-amino aldehydes (*R*)-**9** were stable to chromatography, they were also observed to slowly decompose on storage after several days. For this reason, they were quickly transformed into the corresponding homoallylic sulfonamides **4**, **10**, and **11** by treatment with the appropriate nonstabilized Wittig reagent at −78 °C. In all cases mixtures of inseparable *E*:*Z* isomers were obtained.

Subjecting the homoallylic sulfonamide mixtures to the iodocyclization protocol $I_2/K_2CO_3/H_2O$/MeCN afforded the corresponding 3-iodo *trans*-2,5-disubstituted pyrrolidines **5** along with the unreacted *Z*-homoallylic sulfonamides **6** (Scheme 4, Table 1). Although modest yields of the 3-iodopyrrolidines **5** were obtained because mixtures of the *E*:*Z* homoallylic sulfonamide were employed, it is important to note that it was not necessary to purify the precursor sulfonamide. However, the

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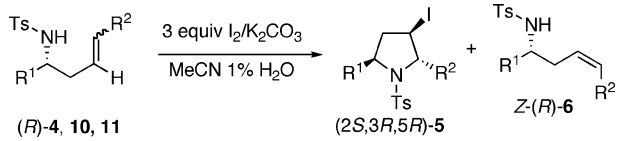
SCHEME 4



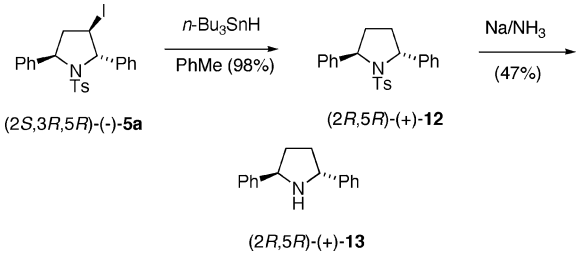
a: $R^1 = R^2$ = Ph; **b**: R^1 = Ph, R^2 = Et; **c**: R^1 = Me; R^2 = Et

TABLE 1. Iodocyclization of Homoallylic Sulfonamides to 3-Iodopyrrolidines 5 and Z-Homoallylic Sulfonamides

entry	homoallylic sulfonamide R^1, R^2 (*E*:*Z*)	**5** (% yield)[a] [dr][b]	**6** (% yield)[a]
1	**4** $R^1 = R^2$ = Ph (55:45)	**5a** (40) [88:12]	**6a** (45)
2	**10** R^1 = Ph; R^2 = Et (55:45)	**5b** (46) [>95:5]	**6b** (31)
3	**11** R^1 = Me; R^2 = Et (4:6)	**5c** (39) [>95:5]	**6c** (49)
4	**11** R^1 = Me; R^2 = Et (8:2)[c]	**5c** (71) [>95:5]	**6c** (20)

[a] Isolated yield of major product. [b] Determined by ^{1}H NMR. [c] Prepared using photoisomerization and PhSSPh.

SCHEME 5



fact that the starting homoallylic sulfonamide is not completely transformed into product could be a liability in a long synthetic sequence. To address this issue we briefly explored the radical-induced photoisomerization of the *Z*-olefin in (*R*)-**11** to the *E* isomer.[15] Photolysis of the 4:6 *E*:*Z* mixture of **11** at 300 nm in the presence of 2 equiv of phenyl disulfide for 6 h in cyclohexane improved the *E*:*Z* ratio to 8:2. Iodocyclization of (*R*)-**11** (8:2 *E*:*Z*) afforded **5c** in 71% isolated yield (Table 1, entry 4).

The *trans* relationship of the 2- and 5-substituents in **5a** was confirmed by treatment of (2*S*,3*R*,5*R*)-(−)-**5a** with tributyltin hydride to give (2*R*,5*R*)-2,5-diphenyl-1-tosylpyrrolidine (**12**) in nearly quantitative yield (Scheme 5). Reductive removal of the *N*-tosyl group with Na/NH_3 (liq) afforded (2*R*,5*R*)-(+)-2,5-diphenylpyrrolidine (**13**) with properties identical to literature values.[16] Pyrrolidine (+)-**13** is a popular chiral auxiliary with C_2-symmetry, and the homoallylic sulfonamide iodocyclization protocol represents a potentially general method for the asymmetric synthesis of this valuable class of auxiliaries and ligands.[3−5]

As shown in Table 1, *E*-homoallylic sulfonamides were the only active partner in the iodocyclization reaction with *Z*-homoallylic sulfonamides inert to the cyclization conditions. The lack of reactivity of the *Z*-homoallylic sulfonamides **6** can be explained in terms of the chairlike transition states depicted in Figure 1. The existing A[1,3] strain in transition state **TS-A** for

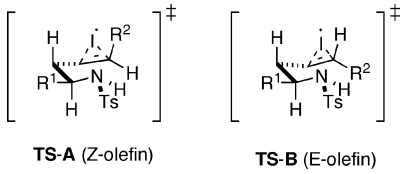


FIGURE 1.

the *Z*-olefin compare to those in **TS-B** for the *E*-olefin makes the latter lower in energy. This results in the exclusive reaction of the *E*-homoallylic sulfonamide under the reaction conditions to produce the *trans*-2,5-pyrrolidines **5**. The poorer diastereoselectivity observed in the iodocyclization of homoallylic sulfonamides having a phenyl group on the terminal carbon for R^2 = Ph (Table 1, entry 1) could be explained by extra stabilization of a benzylic carbocation, which could result in isomerization. In a related study, Harding et al. reported that equilibration of the products from amidomercuration of δ-alkenylcarbamates resulted in scrambling in the product.[5b]

The utility of our new *trans*-2,5-disubstituted pyrrolidine synthesis is highlighted by a total asymmetric synthesis of (−)-pyrrolidine 197B (**22**), *trans*-2-*n*-butyl-5-*n*-pentylpyrrolidine (Scheme 6). In addition to many other alkaloids (−)-pyrrolidine 197B (**22**) has been detected in the poison frogs of the family *Dendrobates histrionicus*[1a,f] and in the venom of fire ants of the genus *Solenopsis* and *Monomorium latinode*.[17] These alkaloids exhibit a wide range of biological activities including hemolytic and antibiotic activity,[18] but because they are isolated in only minute quantities the biological properties of the majority of these alkaloids remains unknown. A single asymmetric synthesis of (−)-197B has been reported by Machinaga and Kibayashi.[19] Their synthesis required in excess of 16 steps starting from C_2-symmetric diepoxides derived from D-mannitol.

Our synthesis of (−)-197B begins with the preparation of the *E*-homoallylic sulfonamide (*R*)-**18** from (*R*)-(−)-*N*-(pentylidine)-*p*-toluenesulfinamide (**14**), using the standard conditions. This procedure affords (*R*)-**18** in 50% yield for the four-step sequence (Scheme 6). The modest *E*:*Z* ratio of **18** from the Wittig reaction was improved by photoisomerization. Irradiation of compound (*R*)-**18** at 300 nm in the presence of 2.0 equiv of PhSSPh improved the *E*:*Z* isomer ratio from 54:46 to 85:15 with an isolated yield of 84%. When (*R*)-**18** was subjected to the iodocyclization protocol, the major diastereoisomer of pyrrolidine (+)-**20** was isolated in 82% yield along with 10% of the Z-olefin (*R*)-(+)-**19**. Finally, deiodination of (+)-**20** with Bu_3SnH gave pyrrolidine (−)-**21** in quantitative yield, which was followed by removal of the *N*-tosyl group with Na/NH_3 (liq) to give the target (−)-pyrrolidine 197B (**22**) in 62% yield (Scheme 6). Although the spectral properties of (−)-**22** were in agreement with literature values, our specific rotation of −25.3 was considerably larger than the value of −5.8 reported by Kibayashi and co-workers.[19b] This group also prepared the *N*-benzoyl derivative of the enantiomer of **22**. Their specific rotation was +125.5, whereas ours was considerable higher at −231.5.[19b] These discrepancies suggests that racemization may

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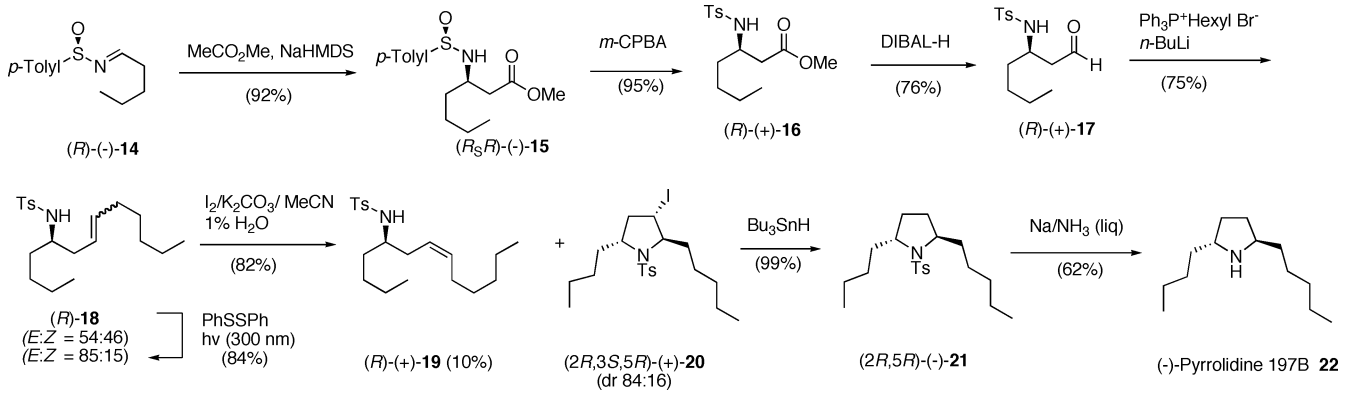
SCHEME 6



have occurred in the earlier preparations of this material. Attempts to make the Mosher amide of (−)-**22** were unsuccessful.

In conclusion, we have developed a useful stereoselective synthesis of enantiopure *trans*-2,5-pyrrolidine derivatives from homoallylic sulfonamides using iodocyclization. The homoallylic sulfonamides were prepared from readily available sulfinimine-derived β-amino aldehydes using the Wittig reaction and were obtained as *E*:*Z* mixtures. Because only the *E*-homoallylic sulfonamides undergo the cyclization reaction, it was not necessary to separate *E*:*Z* sulfonamide mixtures. The utility of this methodology was highlighted in the total asymmetric synthesis of toxic frog/fire ant venom alkaloid (−)-197B (**22**).

Experimental Section

(S_S,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino *N*-Methoxy-*N*-methyl-3-phenylpropionamide (**1**),[12] (S_S,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-3-phenyl-propionaldehyde (**2**),[12] (S_S,*R*)-(+)-Methyl 3-(*p*-toluenesulfinylamino)-3-phenylpropanoate (**7a**),[12] and (S_S,3*S*)-(+)-Methyl *N*-(*p*-Toluenesulfinyl)-3-aminobutanoate (**7b**)[12] were prepared as previously described.

(S_s,4*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-amino-1,4-diphenylbut-1-en (3). In an oven-dried, one-neck, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed benzyltriphenylphosphonium bromide (0.676 g, 1.56 mmol) in THF (6 mL). The solution was cooled to 0 °C, *n*-BuLi (0.610 mL, 1.53 mmol, 1.6 M in hexanes) was added, and the solution was stirred for 1 h at room temperature. At this time the reaction mixture was cooled to −78 °C, and a solution of (+)-**2** (0.088 g, 0.305 mmol) in THF (2 mL) was added via cannula. After consumption of starting material as judged by TLC (2.5 h at 0 °C), the reaction mixture was quenched with water (1 mL) at 0 °C, warmed to room temperature, and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (2 × 5 mL), dried ($MgSO_4$), and concentrated. Chromatography (50% Et_2O/hexane) gave 0.06 g (54%) of a colorless oil as an inseparable 66:34 *E*:*Z* mixture: $[\alpha]^{20}_D$ +76.4 (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$) major isomer δ 2.46 (s, 3H), 2.74 (m, 2H), 4.41 (d, J = 3.0 Hz, 1H), 4.73 (m, 1H), 6.06 (dt, J = 7.6, 15.5 Hz, 1H), 6.41 (d, J = 15.9 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 7.19−7.53 (m, 12H), 7.64 (m, 2H); minor isomer δ 2.88 (m, 2H), 4.32 (bs, 1H), 4.68 (m, 1H), 5.61 (m, 1H), 6.57 (d, J = 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) major isomer δ 21.4, 42.2, 57.7, 125.1, 125.5, 126.3, 127.5, 128.6, 128.7, 128.8, 129.59, 129.6, 134.0, 141.3, 141.46, 141.5, 142.3; minor isomer δ 37.3, 57.9, 127.0, 127.2, 127.7, 127.9, 128.0, 128.3, 132.3, 137.0; IR (film) 3193, 3058, 3027, cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{23}H_{23}NONaS$ (M + Na) 384.139806, found 384.1391.

(*R*)-(+)-*N*-(1,4-Diphenylbut-3-enyl)-4-methylbenzenesulfonamide (4). In an oven-dried one-neck round-bottom flask equipped with a magnetic stirring bar and argon inlet was placed (+)-**3** (0.015 g, 0.042 mmol) and K_2CO_3 (0.02 g, 0.145 mmol) in MeCN (1 mL) and H_2O (0.01 mL). The solution was stirred for 30 min at room temperature, and I_2 (0.032 g, 0.145 mmol) was added. After consumption of starting material as judged by TLC analysis (1 h at room temperature), the mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 mL). The resulting clear yellow solution was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (10% EtOAc/hexane) gave 0.011 g (69%) of a colorless oil: $[\alpha]^{20}_D$ +72.4 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$) major isomer δ 2.27 (s, 3H), 2.52 (dt, J = 0.8, 7.1 Hz, 2H), 4.34 (m, 1H), 4.98 (d, J = 6.4 Hz, 1H), 5.74 (dt, J = 7.4, 16.0 Hz, 1H), 6.29 (d, J = 15.6 Hz, 1H), 6.91−7.25 (m, 12H), 7.49 (d, J = 8.0 Hz, 2H); minor isomer δ 2.27 (s, 3H), 2.66 (m, 2H), 4.83 (d, J = 6.8 Hz, 1H), 5.35 (dt, J = 7.2, 12.0 Hz, 1H), 6.4 (d, J = 11.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) major isomer δ 21.8, 41.6, 57.9, 124.8, 126.6, 126.9, 127.46, 127.5, 127.8, 128.8 (2C), 129.8, 134.4, 137.1, 137.8, 141.0, 143.5; minor isomer δ 30.7, 36.5, 58.3, 127.0, 127.4, 127.86, 127.9, 128.7, 129.0, 129.7, 132.7, 140.7, 143.4; IR (film) 3279, 3061, 2928, 2858, cm^{-1}; HRMS calcd for $C_{23}H_{23}NO_2SNa$ (M + Na) 400.1347, found 400.1352.

(2*S*,3*R*,5*R*)-(−)-3-Iodo-2,5-diphenyl-1-tosylpyrrolidine (5). In an oven-dried one-neck round-bottom flask equipped with a magnetic stirring bar and argon inlet was placed (+)-**4** (0.027 g, 0.072 mmol) and K_2CO_3 (0.033 g, 0.239 mmol) in MeCN (1 mL) and H_2O (0.01 mL), the solution was stirred for 30 min at room temperature, and I_2 (0.061 g, 0.239 mmol) was added. After consumption of starting material as judged by TLC analysis (3 h at room temperature), the mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 mL). The resulting clear solution was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (10% EtOAc/hexane) gave 0.021 g (58%) of a light yellow solid as a mixture of inseparable diastereoisomers in a ratio of 95:5 and 0.006 g (22%) of *Z*-homoallylic sulfonamide (+)-**6**: mp 164−165 °C; $[\alpha]^{20}_D$ −7.9 (*c* 0.067, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H), 2.45 (dt, J = 5.2, 15.2 Hz, 1H), 3.15 (m, 1H), 4.28 (dt, J = 8.6, 8.6 Hz, 1H), 5.19 (dd, J = 5.7, 9.6 Hz, 1H), 5.3 (d, J = 4.5 Hz, 1H), 6.85−7.36 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 21.5, 25.0, 45.9, 65.3, 77.2, 127.1, 127.3, 127.7, 128.1, 128.3, 128.7, 128.8, 128.9, 138.3, 139.0, 139.8, 142.4; IR (film) 3031, 2921 cm^{-1}; HRMS calcd for $C_{23}H_{22}NO_2SINa$ (M + Na) 526.0314, found 526.0321. **(*R*,*Z*)-(+)-1,4-Diphenyl-*N*-tosyulbut-3-en-1-amine (6):** $[\alpha]^{20}_D$ +42.7 (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.81 (m, 2H), 4.47 (q, J = 6.8 Hz, 1H), 4.77 (d, J = 6.9 Hz, 1H), 5.48 (m, 1H), 6.56 (d, J = 11.7 Hz, 1H), 7.08−7.40 (m, 12H), 7.56 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 36.2, 58.0, 126.7, 127.2, 128.5, 128.7, 129.3, 132.4, 136.8, 137.5, 138.3, 139.0,

139.8, 140.3, 142.4, 143.1; IR (film) 3276, 3026, 2923 cm^{-1}; HRMS calcd for $C_{23}H_{23}NO_2SNa$ (M + Na) 400.1347, found 400.1349.

Typical Procedure for the Preparation of *N*-Tosyl *β*-Amino Esters. (*R*)-(+)-Methyl 3-(4-Methylphenylsulfonamido)-3-phenylpropanoate (8a). In an oven-dried one-neck round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**7a** (0.157 g, 0.496 mmol) in CH_2Cl_2 (10 mL). The solution was cooled to 0 °C, *m*-CPBA (0.144 g, 1.984 mmol) was added, and the solution was stirred for 1.5 h at 0 °C. At this time the reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (5 mL), diluted with $CHCl_3$ (10 mL), and saturated aqueous $NaHCO_3$ (5 mL) was added. The solution was stirred vigorously with warming to room temperature, and the organic phase was dried ($MgSO_4$) and concentrated to provide 0.140 g (85%) of a white solid: mp 100−101 °C; $[\alpha]^{20}_D$ +50.6° (*c* 1.62, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.87 (q, J = 15.6 Hz, 2H), 3.62 (s, 3H), 4.80 (q, J = 6.5 Hz, 1H), 5.89 (d, J = 8.1 Hz, 1H), 7.15−7.3 (m, 7H), 7.67 (d, J = 8.7 Hz, 2H); ^{13}C NMR($CDCl_3$) δ 21.5, 41.2, 51.9, 54.4, 126.4, 127.2, 127.8, 128.6, 129.5, 137.5, 139.4, 143.3, 171.1; IR (film) 3280, 1739 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO_4Na$ (M + Na) 356.0932, found 356.0927.

(*S*)-(−)-Methyl 3-(4-Methylphenylsulfonamido)butanoate (8b). Chromatography (20% Et_2O/hexane) gave 0.247 g (88%) of a colorless oil: mp 78−79 °C; $[\alpha]^{20}_D$ −22.4 (*c* 1.16, $CHCl_3$) [lit.[20] mp 78−79 °C, $[\alpha]^{20}_D$ −27.4 (*c* 0.71, $CHCl_3$)]. Spectral properties were consistent with literature values.

Typical Procedure for the Preparation of *N*-Tosyl *β*-Amino Aldehydes. (*R*)-(+)-4-Methyl *N*-(3-Oxo-1-phenylpropyl)benzenesulfonamide (9a). In an oven-dried round-bottom one-neck flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**8a** (0.222 g, 0.667 mmol) in toluene (7 mL). The solution was cooled to −78 °C, and DIBAL-H (0.670 mL, 0.667 mmol, 1.0 M solution in CH_2Cl_2) was added dropwise. After consumption of starting material as judged by TLC analysis (5 h at −78 °C), the reaction mixture was quenched with by addition of saturated aqueous $NaKC_4H_4O_6{\cdot}H_2O$ (Rochell salt) (5 mL), diluted with EtOAc (10 mL), and vigorously stirred with warming to room temperature. The organic phase was dried ($MgSO_4$) and concentrated. Chromatography (50% Et_2O/hexane) gave 0.090 g (56%) of a colorless oil and 0.095 g (43%) of starting material: $[\alpha]^{20}_D$ +41.3° (*c* 1.37, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.06 (m, 2H), 4.86 (q, J = 6.8 Hz, 1H), 5.52 (d, J = 7.2 Hz, 1H), 7.13 (m, 2H), 7.24 (m, 5H), 7.65 (d, J = 8.4 Hz, 2H), 9.70 (t, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 50.1, 53.3, 126.5, 127.2, 128.0, 128.8, 129.6, 137.1, 139.3, 143.5, 199.6; IR (film) 3254, 1726 cm^{-1}; HRMS calcd for $C_{16}H_{17}NO_3SNa$ (M + Na) 326.0827, found 326.0820.

(*S*)-(−)-4-Methyl *N*-(4-Oxobutan-2-yl)benzenesulfonamide (9b). Chromatography (20% EtOAc/hexane) gave 0.227 g (81%) of a colorless oil and 0.047 g (15%) of starting material: $[\alpha]^{20}_D$ −22.0 (*c* 1.98, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 6.6 Hz, 3H), 2.46 (s, 3H), 2.65 (m, 2H), 3.81 (septet, J = 6.8 Hz, 1H), 5.51 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.8 (d, J = 8.1 Hz, 2H), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.6, 45.5, 50.4, 127.1, 129.9, 137.7, 143.7, 200.9; IR (film) 3275, 2978, 2739, 1715 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{11}H_{15}NO_3NaS$ (M + Na) 264.067035, found 264.0668.

Typical Procedure for the Preparation of Homoallylic Sulfonamide. (*R*)-(+)-*N*-(1,4-Diphenylbut-3-enyl)-4-methyl-benzensulfonamide (4). In an oven-dried one-neck round-bottom flask, equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed benzyltriphenylphosphonium bromide (1.49 g, 3.43 mmol) in THF (18 mL). The solution was cooled to 0 °C, *n*-BuLi (2.14 mL, 3.43 mmol, 1.6 M in hexanes) was added, and the solution was stirred for 1 h at room temperature. At this time the reaction mixture was cooled to −78 °C, and a solution of (+)-**9a** (0.20 g, 0.686 mmol) in THF (3 mL) was added. After consumption of starting material as judged by TLC analysis (2.5 h at −78 °C), the reaction mixture was quenched with H_2O (1 mL) at 0 °C, warmed to room temperature, and extracted with EtOAc (3 mL). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (20% Et_2O/hexane) gave 0.15 g (61%) of a colorless oil as an inseparable 55:45 *Z*:*E* mixture of isomers: $[\alpha]^{20}_D$ +23.9° (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$) major isomer δ 2.41 (s, 3H), 2.66 (t, J = 6.8 Hz, 2H), 4.48 (pent, J = 6.8 Hz, 1H), 5.03 (d, J = 6.8 Hz, 1H), 5.89 (dt, J = 15.6, 7.5 Hz, 1H), 6.43 (d, J = 15.9 Hz, 1H), 7.0−7.34 (m, 12H), 7.64 (m, 2H); minor isomer δ 2.42 (s, 3H), 2.80 (m, 2H), 5.14 (d, J = 6.9 Hz, 1H), 5.50 (dt, J = 11.7, 7.0 Hz, 1H), 6.54 (d, J = 11.1 Hz, 1H), 7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) major isomer δ 21.5, 41.2, 58.0, 124.5, 126.3, 126.6, 127.1, 127.2, 127.54, 128.4, 128.51, 128.52, 129.37, 134.1, 136.77, 140.6, 143.2; minor isomer δ 36.2, 57.6, 126.5, 127.05, 127.51, 127.6, 127.7, 128.3, 128.53, 128.7, 129.43, 132.4, 136.78, 140.3, 143.1; IR (film) 3279, 3061, 3028, 2928, 2858 cm^{-1}; HRMS calcd for $C_{23}H_{23}NO_2SNa$ (M + Na) 400.1347, found 400.1352.

(*R*)-(+)-4-Methyl *N*-(1-phenylhex-3-enyl)benzenesulfonamide (10). Following the typical procedure, (+)-**9a** (0.137 g, 0.452 mmol), triphenylphosphoranepropylbromide (0.871 g, 2.26 mmol), and *n*-BuLi (0.904 mL, 2.26 mmol) were employed. Chromatography (20% Et_2O/hexane) gave 0.111 g (75%) of a colorless oil as an inseparable 45:55 *Z*:*E* mixture of isomers: $[\alpha]^{20}_D$ +59.9 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) major isomer δ 0.97 (t, J = 5.9 Hz, 3H), 1.99 (sextet, J = 7.5 Hz, 2H), 2.43 (m, 1H), 2.44 (s, 3H), 2.53 (q, J = 7.7 Hz, 1H), 4.38 (m, 1H), 5.15 (m, 2H), 5.54 (m, 1H), 7.13−7.23 (m, 7H), 7.64 (d, J = 7.8 Hz, 1H); minor isomer δ 0.93 (t, J = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) major isomer δ 15.9, 21.8, 25.9, 41.2, 57.8, 123.7, 126.95, 126.98, 127.5, 128.6, 129.7, 137.7, 140.9, 141.3, 143.4; minor isomer δ 14.4, 21.0, 35.6, 58.1, 123.3, 127.7, 128.7, 136.2, 137.9; IR (film) 2849, 2917, 1329, 1157 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{19}H_{22}INO_2NaS$ (M + Na) 478.031373, found 478.0330.

(*S*)-(−)-*N*-(hept-4-en-2-yl)-4-methylbenzenesulfonamide (11). Following the typical procedure, (−)-**9c** (0.274 g, 1.137 mmol), triphenylphosphoranepropylbromide (2.23 g, 5.799 mmol), and *n*-BuLi (2.3 mL, 5.685 mmol) were employed. Chromatography (20% Et_2O/hexane) gave 0.162 g (53%) of a colorless oil as an inseparable 4:6 *E*:*Z* mixture of isomers: $[\alpha]^{20}_D$ −31.4 (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$) major isomer δ 0.83 (t, J = 7.5 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.86 (m, 2H), 1.96 (m, 1H), 2.04 (m, 1H), 2.35 (s, 3H), 3.22 (m, 1H), 4.69 (d, J = 7.6 Hz, 1H), 5.04 (m, 1H), 5.36 (m, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.69 (m, 2H); minor isomer δ 0.84 (t, J = 7.5 Hz, 3H), 1.0 (d, J = 6.6 Hz, 3H), 4.64 (d, J = 7.2 Hz, 1H), 5.14 (m, 1H), 5.43 (m, 1H); ^{13}C NMR ($CDCl_3$) major isomer δ 14.5, 21.0, 21.4, 21.8, 35.0, 50.2, 123.8, 127.5, 130.0, 135.6, 138.5, 143.5; minor isomer δ 13.9, 21.7, 25.9, 40.5, 50.0, 124.0, 136.9; IR (film) 3279, 2967, 2933, 1329, 1184 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{14}H_{21}NO_2NaS$ (M + Na) 290.119071, found 290.1195.

Typical Procedure for the Iodocyclization of Homoallylic Sulfonamide. (2*S*,3*R*,5*R*)-(−)-3-Iodo-2,5-diphenyl-1-(*p*-tolylsulfonyl)-pyrrolidine (5a). In an oven-dried, one-neck, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**4** (0.053 g, 0.147 mmol) and K_2CO_3 (0.0648 g, 0.44 mmol) in CH_3CN (1.5 mL) and H_2O (0.016 mL), the solution stirred for 30 min at room temperature, and I_2 (0.112 g, 0.440 mmol) was added. After consumption of the starting material as judged by TLC analysis (3 h at room temperature), the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (1:9 Et_2O/hexanes) gave 0.024 g (40%) of a white solid as inseparable mixture of diastereomers in a ratio of 88:12 and 0.024 g (45%) of recovered *Z* homoallylic sulfonamide **6a**: mp 163−164 °C; $[\alpha]^{20}_D$ −10.3° (*c* 0.76, $CHCl_3$); ^1H NMR ($CDCl_3$) major isomer δ 2.26 (s, 3H), 2.45

(20) Wang, J.; Hou, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1919.

(dt, J = 15.0, 5.4 Hz, 1H), 3.16 (dt, J = 14.4, 8.6 Hz, 1H), 4.28 (dt, J = 7.5, 4.7 Hz, 1H), 5.20 (dd, J = 8.9, 5.5 Hz, 1H), 5.34 (d, J = 4.2 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.1−7.4 (m, 12H); Minor isomer δ 2.57 (m, 1H), 2.74 (m, 1H), 4.12 (m, 1H), 5.21 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 24.9, 45.8, 65.2, 77.1, 126.6, 127.2, 126.9, 127.7, 128.1, 128.4, 128.6, 128.7, 138.2, 138.9, 139.7, 142.3; IR (film) 3031, 2921 cm^{-1}; HRMS calcd for $C_{23}H_{22}NO_2SINa$ (M + Na) 526.0314, found 526.0321.

(*R*,*Z*)-(+)-*N*-(1,4-Diphenylbut-3-enyl)-4-methylbenzenesulfonamide (6a): $[\alpha]^{20}_D$ +28.8° (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.74 (m, 2H), 4.41 (q, J = 7.4 Hz, 1H), 5.69 (dt, J = 11.1, 7.5 Hz, 1H), 6.10 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 11.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 7.05−7.35 (m, 10H), 7.62 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 36.2, 58.0, 126.7, 127.2, 128.5, 128.7, 129.3, 132.4, 136.8, 137.5, 138.3, 139.0, 139.8, 140.3, 142.4, 143.1; IR (film) 3276, 3026, 2923 cm^{-1}; HRMS calcd for $C_{23}H_{23}NO_2SNa$ (M + Na) 400.1347, found 400.1349.

(2*S*,3*R*,5*R*)-(+)-2-Ethyl-3-iodo-5-phenyl-1-tosylpyrrolidine (5b). Chromatography (20% Et_2O/hexane) gave 0.031 g (46%) of a yellow oil and 0.015 g (31%) of recovered *Z*-homoallylic sulfonamide **6b**: $[\alpha]^{20}_D$ +3.7 (*c* 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7.4 Hz, 3H), 1.67 (m, 1H), 2.12 (m, 1H), 2.24 (s, 3H), 2.37 (m, 1H), 3.18 (ddd, J = 9.7, 16.1, 7.4 Hz, 1H), 4.34 (m, 2H), 4.80 (dd, J = 9.8, 5.6 Hz, 1H), 6.87−7.0 (m, 5H), 7.17 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 11.0, 21.4, 21.7, 26.5, 46.4, 62.9, 76.7, 127.5, 127.8, 128.2, 129.0, 129.8, 138.5, 139.2, 142.7; IR (film) 2849, 2917, 1329, 1157 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{19}H_{22}INO_2NaS$ (M + Na) 478.031373, found 478.0330.

Upon irradiation of the C-5 proton at δ 4.8, a positive NOE was observed on the C-4 proton at δ 3.18 (5.25%), confirming the *cis* relationship between the C-5 proton and the C-4 proton and determining the C-4 proton at δ 3.18 as H_α of two methylene C-4 protons. Upon irradiation of the C-4 proton H_α at δ 3.18, positive NOEs were observed on the C-5 proton at δ 4.8 (7.87%) and on the C-3 proton at δ 4.34 (5.55%), confirming the *cis* relationship between the C-5 proton and the C-3 proton. Upon irradiation of the C-2 methyl at δ 1.0, a positive NOE was observed on the C-5 proton at δ 4.80 (3.21%), confirming the *trans* relationship between the C-2 proton and the C-5 proton.

(*R*,*Z*)-(+)-4-Methyl-*N*-(1-phenylhex-3-enyl)benzenesulfonamide (6b): $[\alpha]^{20}_D$ +47.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.70 (t, J = 7.5 Hz, 3H), 1.74 (quint, J = 7.4 Hz, 1H), 2.20 (s, 3H), 2.32 (m, 2H), 4.14 (q, J = 7.0, 1H), 4.67 (d, J = 6.0 Hz, 2H), 4.88 (m, 1H), 5.28 (m, 1H), 6.94 (m, 7H), 7.39 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.0, 21.8, 35.6, 58.1, 123.2, 127.0, 127.5, 127.7, 128.7, 129.7, 136.3, 137.9, 140.9, 143.4; IR (film) 3278, 2964, 1622, 1325, 1184 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{19}H_{23}NO_2NaS$ (M + Na) 352.1347, found 352.1346.

(2*S*,3*R*,5*S*)-(+)-2-Ethyl-3-iodo-5-methyl-1-tosylpyrrolidine (5c). Chromatography (20% Et_2O/hexane) gave 0.026 g (39%) of a yellow oil and 0.022 g (49% recovery) of recovered *Z*-homoallylic sulfonamide **6c**: $[\alpha]^{20}_D$ +2.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.5 Hz, 3H), 1.42 (d, J = 6.5 Hz, 3H), 1.47 (m, 1H), 2.06 (m, 1H), 2.10 (m, 1H), 2.43 (s, 3H), 2.87 (ddd, J = 8.5, 15.0, 6.5 Hz, 1H), 4.15 (m, 1H), 4.21 (dd, J = 3.0, 10.0 Hz, 1H), 4.26 (dt, J = 6.5, 1.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.1, 21.2, 21.9, 28.5, 44.1, 56.16, 56.2, 76.3, 127.9, 130.0, 140.2, 143.7; IR (film) 2971, 2932, 2876, 1457, 1338, 1157 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{14}H_{20}INO_2NaS$ (M + Na) 416.015723, found 416.0148.

Upon irradiation of the C-2 methyl at δ 0.96, a positive NOE was observed on the C-3 proton at δ 4.26 (6.4%), confirming *trans* relationship between the C-2 proton and C-3 proton. Upon irradiation of the C-5 methyl at δ 1.42, a positive NOE was observed on the C-2 proton at δ 4.15 (2.0%), confirming a *trans* relationship between the C-5 proton and C-2 proton.

(*S*,*Z*)-(−)-*N*-(Hept-4-en-2-yl)-4-methylbenzenesulfonamide (6c): $[\alpha]^{20}_D$ −31.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.8, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.94 (dq, J = 1.5, 7.5 Hz, 2H), 2.12 (q, J = 6.5 Hz, 2H), 2.43 (s, 3H), 3.32 (quint, J = 6.8 Hz, 1H), 4.46 (d, J = 7.5 Hz, 1H), 5.13 (m, 1H), 5.46 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.8, 21.3, 21.8, 35.2, 35.3, 50.41, 123.9, 127.8, 130.3, 136.1, 138.6, 143.9; IR (film) 3279, 2967, 2933, 1329, 1184 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{14}H_{21}NO_2NaS$ (M + Na) 290.119071, found 290.1195.

Photolysis of (*S*)-(−)-*N*-(Hept-4-en-2-yl)-4-methylbenzenesulfonamide and Its Iodocyclization. In an oven-dried one-neck round-bottom flask, equipped with magnetic stirring bar and rubber septum, was placed PhSSPh (0.082 g, 0.375 mmol) and the mixture of 4:6 *E*:*Z* isomers of (−)-**11** (0.082 g, 0.375 mmol) in cyclohexane (3 mL). The solution was irradiated by mercury lamp (300 nm, 450 W) for 6 h with stirring. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with EtOAc (3 mL), and the organic phases were dried ($MgSO_4$) and concentrated. Chromatography (20% Et_2O/hexane) provided 0.004 g (80%) of a colorless oil as an inseparable 8:2 *E* and *Z* mixture of **11**. Following the typical procedure for the iodocyclization, (−)-**11** (0.04 g, 0.150 mmol, *E*:*Z* 8:2), K_2CO_3 (0.062 g, 0.45 mmol), and I_2 (0.114 g, 0.45 mmol) were employed. Chromatography (10% Et_2O/hexane) gave 0.042 g (71%) of a yellow oil and 0.008 g (20%) of recovered *Z*-homoallylic sulfonamide **6c**.

(2*R*,5*R*)-(+)-2,5-Diphenyl-1-tosylpyrrolidine (12). In an oven-dried, argon-purged 25-mL, one-neck flask attached to reflux condenser and equipped with stir bar was placed toluene (5 mL), (−)-**5a** (0.047 g, 0.096 mmol), and Bu_3SnH (0.255 mL, 0.96 mmol). The reaction mixture was refluxed at 130 °C for 4 h at which time the solvent and excess Bu_3SnH were evaporated off under reduced pressure. Chromatography (3:17 Et_2O/hexanes) afforded 0.034 g (98%) of a colorless oil: $[\alpha]^{20}_D$ +116.6° (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 2H), 2.32 (s, 3H), 2.62 (m, 2H), 5.27 (d, J = 7.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8 Hz, 2H), 7.16−7.27 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 34.0, 65.3, 65.5, 127.0, 127.5, 127.6, 128.9, 129.4, 139.1, 142.8, 143.5; IR (film) 3027, 2961, 2922, cm^{-1}; HRMS calcd for $C_{23}H_{23}NO_2SNa$ (M + Na) 400.1347, found 400.1354.

(2*R*,5*R*)-(+)-2,5-Diphenylpyrrolidine (13). In an oven-dried, argon-purged 50-mL, three-neck round-bottom flask equipped with a magnetic stir bar and dry ice condenser and cooled to −78 °C was collected NH_3 (~10 mL). Sodium metal (~0.9 g) was added, and the solution was stirred for 15 min. At this time (+)-**15** (0.021 g, 0.058 mmol) in THF (3 mL) was then added dropwise. The reaction was quenched after 30 min by addition of solid NH_4Cl (1.3 g), and the NH_3 was allowed to evaporate by warming to room temperature. Water (10 mL) was then added, and the solution was extracted with Et_2O (2 × 5 mL), dried ($MgSO_4$), and evaporated. Chromatography (1:9 EtOAc/hexanes) afforded 0.0053 g (47%) of clear film: $[\alpha]^{20}_D$ +102.1° (*c* 0.47, $CHCl_3$), [lit.[16b] $[\alpha]^{20}_D$ +104.5 (*c* 1.00, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 1.97 (m, 2H), 2.43 (m, 2H), 2.7−3.2 (s, br, 1H), 4.59 (t, J = 7.0 Hz, 2H), 7.26 (t, J = 7.3 Hz, 2H), 7.34 (t, J = 7.3 Hz, 4H), 7.43 (d, J = 7.5 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 35.1, 62.4, 126.3, 127.2, 128.6, 144.4; IR (film) 3400, 2921, 2851 cm^{-1}; HRMS calcd for $C_{16}H_{18}N$ (M + H) 224.1439, found 224.1436.

(*R*)-(−)-*N*-(Pentenylidene)-*p*-toluenesulfonamide (14). In a 100-mL round-bottom, one-neck flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed valeraldehyde (0.422 mL, 3.852 mmol), $Ti(OEt)_4$ (0.377 mL, 12.84 mmol), and (*R*)-(−)-*p*-toluenesulfonamide (0.298 g, 2.568 mmol) in CH_2Cl_2 (40 mL), and the solution was stirred for 2.5 h at 0 °C. At this time the reaction mixture was quenched with water (10 mL) and filtered through Celite, rinsing with CH_2Cl_2 (20 mL), and the organic phases concentrated. Chromatography (35% Et_2O/hexane) gave 0.550 g (96%) of a colorless oil: $[\alpha]^{20}_D$ −292.9 (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3H), 1.31 (sextet, J = 7.4 Hz, 2H), 1.55 (m, 2H), 2.36 (s, 3H), 2.44 (m, 2H), 7.26 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H), 8.18 (t, J = 4.95 Hz,

1H); ^{13}C NMR ($CDCl_3$) 13.1, 20.7, 21.6, 26.8, 35.0. 123.9, 129.1, 141.2, 143.7, 166.8; IR (film) 2957, 2931, 2872 cm^{-1}; HRMS calcd for $C_{12}H_{18}NOS$ (M + H) 224.1109, found 224.1108.

(R_S,*R*)-(−)-Methyl-*N*-(*p*-toluenesulfinyl)-3-aminopehtanoate (15). In an oven-dried, 100-mL, round-bottom one-neck flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed NaHMDS (3.6 mL, 3.57 mmol, 1.0 M solution in THF) in ether (20 mL). The solution was cooled to −78 °C, and anhydrous $MeCO_2Me$ (0.283 mL, 3.57 mmol) was added dropwise via syringe. After the solution was stirred for 1 h at this temperature, (−)-**14** (0.53 g, 2.377 mmol) in Et_2O (4 mL) was added via cannula. The resulting mixture was stirred for 2 h at −78 °C and quenched with saturated aqueous NH_4Cl (5 mL) at this temperature. The solution was warmed to room temperature, diluted with H_2O (10 mL), and extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. Chromatography (50% Et_2O/hexane) gave 0.648 g (92%) of a colorless oil as a single diastereomer: $[\alpha]^{20}_D$ − 89 (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.83 (d, J = 6.6 Hz, 3H), 1.2−1.7 (m, 6H), 2.32 (s, 3H), 2.51 (m, 2H), 3.57 (s, 4H), 4.59 (d, J = 9.0 Hz, 1H), 7.2 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.3, 22.3, 28.2, 35.5, 40.4, 51.6, 52.5, 76.7, 125.5, 129.4, 141.1, 142.3, 171.9; IR (film) 3210, 2955, 2862, 1734, 1050 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{15}H_{23}NO_3NaS$ (M + Na) 320.129635, found 320.1303.

(*R*)-(+)-Methyl 3-(4-methylphenylsulfonamido)heptanoate (16). In an oven-dried, 100-mL one-neck round-bottom, flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (*Rs*,*R*)-(−)-methyl-*N*-(*p*-toluenesulfinyl)-3-aminopheptanoate **15** (0.645 g, 2.172 mmol) in CH_2Cl_2 (43 mL). The solution was cooled to 0 °C, and *m*-CPBA (0.614 g, 6.515 mmol) was added. The reaction mixture was stirred for 3 h at 0 °C, quenched with saturated aqueous $Na_2S_2O_3$ (5 mL), diluted with $CHCl_3$ (20 mL), and stirred vigorously. The organic phases were dried ($MgSO_4$) and concentrated. Chromatography (50% Et_2O/hexane) gave 0.647 g (95%) of a colorless oil: $[\alpha]^{20}_D$ +21.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 6.8 Hz, 3H), 1.19 (m, 4H), 1.46 (m, 2H), 2.37−2.52 (m, 5H), 3.55 (m, 1H), 3.64 (s, 3H), 5.44 (d, J = 9.0 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.5, 22.2, 27.8, 34.5, 38.9, 50.7, 51.7, 127.1, 129.7, 138.1, 143.4, 171.8; IR (film) 3288, 2956, 1330, 1160 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{15}H_{23}NO_4NaS$ (M + Na) 336.12455, found 336.1251.

(*R*)-(+)-4-Methyl *N*-(1-oxoheptan-3-yl)benzenesulfonamide (17). In an oven-dried, 50-mL, round-bottom one-neck flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (*R*)-(+)-**16** (0.645 g, 2.061 mmol) in toluene (21 mL). The solution was cooled to −78 °C, and then DIBAL-H (2.1 mL, 2.1 mmol, 1.0 M solution in CH_2Cl_2) was added dropwise. The reaction mixture was stirred for 3 h at −78 °C and quenched with aqueous Rochell salt (5 mL) at −78 °C. The resulting mixture was warmed to room temperature, diluted with EtOAc (10 mL), and stirred vigorously until the solution becomes two clear layers. Chromatography (35% Et_2O/hexane) provided 0.432 g (76%) of a colorless oil and 0.125 g (19%) of starting material: $[\alpha]^{20}_D$ +24.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.76 (d, J = 6.6 Hz, 3H), 1.14 (m, 5H), 1.42 (m, 2H), 2.44 (s, 3H), 2.62 (d, J = 5.7 Hz, 1H), 3.64 (m, 1H), 5.45 (bs, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 9.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 21.5, 22.1, 27.7 34.7, 48.8, 49.5, 127.1, 129.8, 137.8, 143.6, 201.0; IR (film) 3281, 2957, 2735, 1719, 1327, 1159 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{14}H_{21}NO_3NaS$ (M + Na) 306.113985, found 306.1132.

(*R*)-(+)-4-Methyl *N*-(tridec-7-en-5-yl)benzenesulfonamide (18). In an oven-dried, 50-mL, round-bottom one-neck flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed hexyltrophenylphosphonium bromide (0.65 g, 1.52 mmol) in THF (5 mL), and *n*-BuLi (0.6 mL, 1.52 mmol, 2.5 M solution in hexane) was added dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature and cooled to −78 °C, and a solution of (*R*)-(+)-**17** (0.086 g, 0.304 mmol) in THF (1 mL) was added. The reaction mixture stirred for 8 h at −78 °C, quenched with H_2O (1 mL), warmed to room temperature, extracted with EtOAc (2 × 5 mL), dried ($MgSO_4$), and concentrated. Chromatography (20% Et_2O/hexane) gave 0.08 g (75%) of a colorless oil as an inseparable 54:46 *E* and *Z* mixture. In an oven-dried, one-neck, round-bottom flask equipped with a magnetic stirring bar and rubber septum was placed the *E* and *Z* mixture of (+)-**18** (0.077 g, 0.219 mmol) and PhSSPh (0.096 g, 0.439 mmol) in cyclohexane (4 mL). The reaction mixture was irradiated by mercury lamp (300 nm, 450 W) for 6 h with stirring, quenched with saturated aqueous $NaHCO_3$ (1 mL), and extracted with EtOAc (5 mL) The organic phases were dried ($MgSO_4$) and concentrated. Chromatography (20% Et_2O/hexane) provided 0.065 g (84%) of a colorless oil as an inseparable 85:15 *E* and *Z* mixture: $[\alpha]^{20}_D$ +24.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.73 (t, J = 6.6 Hz, 3H), 0.81 (t, J = 7.0 Hz, 3H), 1.01−1.39 (m, 12H), 1.82 (m, 2H), 1.94 (t, J = 6.2 Hz, 2H), 2.35 (s, 3H), 3.13 (m, 1H), 4.41 (d, J = 8.0 Hz, 1H), 5.02 (m, 1H), 5.27 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 21.8, 22.7, 22.8, 27.9, 29.6, 31.7, 32.9, 34.7, 38.1, 54.0, 124.7, 127.5, 129.8, 135.5, 138.8, 143.4; IR (film) 2917, 2849 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{20}H_{33}NO_2NaS$ (M + Na) 374.212971, found 374.2136.

(2*R*,3*S*,5*R*)-(+)-5-Butyl-3-iodo-2-pentyl-1-tosylpyrrolidine (20). Following typical procedure for the iodocyclization, (+)-**18** (0.062 g, 0.177 mmol, *E*:*Z* 85:15), K_2CO_3 (0.073 g, 0.531 mmol), and I_2 (0.135 g, 0.531 mmol) were employed. Chromatography (5% Et_2O/hexane to 20% Et_2O/hexane) gave 0.069 g (82%) of a yellow oil as a separable 84:16 mixture of diastereomers and 0.006 g (10%) of recovered *Z* homoallylic sulfonamide. Major diastereomer: $[\alpha]^{20}_D$ +52.8 (*c* 3.6, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 0.79 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H), 1.0 (m, 2H), 1.15−1.3 (m, 9H), 1.74 (m, 1H), 1.88 (m, 1H), 1.89 (s, 3H), 2.1 (ddd, J = 6.6, 8.6, 15.2 Hz, 1H), 2.19 (m, 2H), 3.79 (dt, J = 1.9, 6.7 Hz, 1H), 3.88 (m, 1H), 4.37 (dd, J = 1.7, 8.1, 1H), 6.83 (m, 2H), 7.98 (m, 2H); ^{13}C NMR (C_6D_6) δ 14.5, 14.6, 21.5, 22.9, 23.1, 23.3, 26.6, 29.5, 32.3, 34.0, 35.3, 40.6, 60.7, 74.8, 127.9, 129.8, 141.9, 143.0; IR (film) 2956, 2927, 2859, 1339, 1156 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{20}H_{32}INO_2NaS$ (M + Na) 500.109623, found 500.1099.

The C-4 proton H_β at δ 2.1 was assigned from COSY spectrum and NOE experiments. Upon irradiation of the C-4 proton H_β at δ 2.1, a positive NOE was observed on the C-3 proton at δ 3.79 (9.3%) and on the C-5 proton at δ 3.88 (11.2%), confirming the *cis* relationship between the C-3 proton and the C-5 proton. The *trans* relationship between the C-2 proton and the C-3 proton was confirmed by the *trans* vicinal coupling constant of J = 6.7 of the C-3 proton at δ 3.79 originating from coupling between the C-3 proton and the C-2 proton.

(*R*,*Z*)-(+)-4-Methyl-*N*-(tridec-7-en-5-yl)benzenesulfonamide (19): $[\alpha]^{20}_D$ +18.8 (*c* 2.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.5 Hz, 3H), 0.94 (t, J = 6.6 Hz, 3H), 1.16−1.53 (m, 12H), 1.84 (m, 2H), 2.08 (m, 2H), 2.48 (s, 3H), 3.29 (sext, J = 6.8 Hz, 1H), 4.61 (d, J = 8.1 Hz, 1H), 5.22 (m, 1H), 5.49 (m, 1H), 7.35 (d, J = 7.8 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 21.6, 22.4, 22.6, 27.4, 27.6, 29.3, 31.6, 32.6, 34.3, 53.9, 123.8, 127.2, 129.6, 133.7, 138.3, 143.2; IR (film) 2917, 2849 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{20}H_{33}NO_2NaS$ (M + Na) 374.212971, found 374.2136.

Upon irradiation of one of the alkenyl protons at δ 5.49, a positive NOE was observed on the other alkenyl proton at δ 5.22 (2.9%), confirming the *Z* geometry of olefin.

(2*R*,5*R*)-(−)-2-Butyl-5-pentyl-1-tosylpyrrolidine (21). In an oven-dried, 10-mL, round-bottom one-neck flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**20** (0.037 g, 0.078 mmol) in dry toluene (4 mL) and Bu_3SnH (0.194 mL, 0.73 mmol), and the reaction mixture was refluxed for 1 h at 125 °C. The resulting mixture was cooled to room temperature and concentrated. Chromatography (10% Et_2O/hexane) provided 0.027 g (99%) of a colorless oil: $[\alpha]^{20}_D$ −43.5 (*c* 2.7,

$CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.79 (t, $J = 7.2$ Hz, 3H), 0.81 (t, $J = 7.2$ Hz, 3H), 1.0−1.40 (m, 12H), 1.60 (m, 2H), 1.86 (m, 4H), 2.37 (s, 3H), 3.75 (m, 2H), 7.21 (m, 2H), 7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.3, 16.8, 21.7, 22.9, 26.4, 26.9, 28.4, 29.0, 29.5, 32.0, 34.0, 34.2, 62.1, 127.3, 129.8, 140.6, 142.8; IR (film) 2957, 2927, 1342, 1156 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{20}H_{33}NO_2NaS$ (M + Na) 374.212971, found 374.2134.

(−)-Pyrrolidine 197B (22). In a 25-mL, two-neck, round-bottom flask equipped with a magnetic stirring bar, a rubber septum, argon inlet, and an acetone−dry ice cooled coldfinger condenser, cooled to −78 °C, was passed NH_3 (g) until approximately 7 mL of liquid NH_3 (1/3 of flask volume) was collected. A solution of (−)-**21** (0.023 g, 0.066 mmol) in THF (3 mL) was added, and enough Na was introduced until a permanent deep navy blue color persisted. After 1.5 h of stirring at −78 °C, the reaction mixture was quenched by addition of solid NH_4Cl (∼1 g), and the excess NH_3 was removed by passing argon through the solution with warming to room temperature. At this time the residue was diluted with Et_2O (5 mL) and water (2 mL). The solution was extracted with ether (2 × 10 mL), and the combined organic phases were dried ($MgSO_4$). Since the product was volatile, the organic phase was concentrated carefully at 0 °C. Chromatography ($CHCl_3$/MeOH−NH_3 10:1) gave 0.008 g (62%) of a yellow oil: $[\alpha]^{20}_D$ −25.3 (*c* 0.6, $CHCl_3$) [lit.[19b] $[\alpha]^{25}_D$ −5.8 (*c* 0.61, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 0.87 (m, 6H), 1.22−1.47 (m, 16H), 1.93 (m, 2H), 2.1 (bs, 1H), 3.1 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.43, 23.0, 23.2, 27.4, 29.9, 32.4, 32.8 (2C), 37.1, 37.4, 58.5 (2C); IR (film) 2955, 2926, 2860 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{13}H_{28}N$ (M + H) 198.222175, found 198.2218, *m*/*e* calcd for $C_{13}H_{26}N$ (M − H) 196.206525, found 196.2061. Spectral properties are consistent with literature values.[19b]

(2*R*,5*R*)-(−)-*N*-Benzoyl-2-butyl-5-pentylpyrrolidinine. In an oven-dried, 5-mL round-bottom one-neck flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (−)-**22** (0.02 g, 0.01 mmol) in CH_2Cl_2 (1 mL) and 20% aqueous K_2CO_3 (1 mL, 1.45 mmol) at 0 °C. The solution was stirred for 5 min, and benzoyl chloride (0.012 mL, 0.1 mmol) was added. After being stirred for 1 h at 0 °C, the reaction mixture was dissolved in Et_2O (3 mL), and the organic phase was washed with brine (2 × 2 mL), dried ($MgSO_4$), and concentrated. Chromatography (5% EtOAc/hexane) provided 0.01 g (33%) of a colorless oil: $[\alpha]^{20}_D$ −231.5 (*c* 0.1, $CHCl_3$) [lit.[19b] enantiomer, $[\alpha]^{27}_D$ +125.5 (*c* 1.0, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 0.55, 0.64 (1:1 ratio, total 6H, t, $J = 7.0$, 7.2 Hz, respectively, due to rotamers), 0.66−1.11 (m, 10H), 1.26 (m, 3H), 1.63 (m, 2H), 1.84−2.07 (m, 3), 3.89, 4.19 (1:1 ratio, total 2H, m, due to rotamers), 7.3 (m, 3H), 7.4 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 14.3, 21.2, 22.5, 22.9, 26.1, 26.5, 26.9, 28.6, 29.0, 32.1, 33.1, 33.4, 34.6, 34.8, 58.0, 59.7, 59.9, 105.5, 127.3, 128.5, 129.7, 140.0, 170.6. Spectral properties were consistent with literature values.[19b]

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Note Added after ASAP Publication. There were errors in the Abstract/TOC graphic and Scheme 1 in the version published ASAP February 24, 2006; the corrected version was published ASAP February 27, 2006.

Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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