Asymmetric Allylation of α-Ketoester-Derived *N*-Benzoylhydrazones Promoted by Chiral Sulfoxides/*N*-Oxides Lewis Bases: Highly Enantioselective Synthesis of Quaternary α-Substituted α-Allyl-α-Amino Acids

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ABSTRACT Chiral sulfoxides/*N*-oxides (*R*)-**1** and (*R*,*R*)-**2** are effective chiral promoters in the enantioselective allylation of α-keto ester *N*-benzoylhydrazone derivatives **3a-g** to generate the corresponding *N*-benzoylhydrazine derivatives **4a-g**, with enantiomeric excesses as high as 98%. Representative hydrazine derivatives **4a-b** were subsequently treated with SmI_2, and the resulting amino esters **5a-b** with LiOH to obtain quaternary α-substituted α-allyl α-amino acids **6a-b**, whose absolute configuration was assigned as (*S*), with fundament on chemical correlation and electronic circular dichroism (ECD) data. *Chirality 25:529–540, 2013.*

KEY WORDS: Asymmetric allylation; chiral sulfoxides; α-allyl-α-amino acids; quaternary carbons; Lewis bases

INTRODUCTION

The enantioselective allylation of prochiral aldehydes and ketones, imines, or hydrazones is a reaction of fundamental importance in organic synthesis owing to its capacity to generate new C–C bonds in the synthesis of complex molecules.[1] For example, enantiopure homoallylic amines are useful intermediates for the preparation of several valuable nitrogen-containing compounds.[2–12] In this regard, allyl organometallics have been used with success in imine addition reactions[13–16]; however, metal-free *organocatalyzed* allylation reactions are most attractive in terms of reagent stability and environmental concerns (so-called "green" chemistry).[17–30]

A major problem encountered in the addition of allylmetals to imines is competitive α-deprotonation.[31–33] This complication can be solved by the use of allylsilanes; nevertheless, their relatively low reactivity usually requires the use of catalysts. In particular, allyltrichlorosilanes are essentially inert to electrophilic imines in the absence of added promoters. Thus, activation of the addition reaction is usually accomplished in two ways: (1) by the use of Lewis acid catalysis, including asymmetric variants using chiral Lewis acids, which activate the imine,[34–41] and (2) by means of a Lewis base, which activates the nucleophile via coordination to the silicon atom of the allyltrichlorosilanes to generate more reactive hypervalent silicon intermediates.[41] Particularly effective Lewis bases include *N*,*N*-dimethylformamide (DMF),[42,43] hexamethylphosphoramide (HMPA),[42,43] *N*-oxides,[44–48] *P*-oxides,[49,50] and ureas,[51] including their enantiopure chiral derivatives for asymmetric catalysis.[37] It is worth mentioning that the allylation of α-hydrazo esters with BINAP dioxides is particularly efficient.[36] Furthermore, chiral sulfoxides[52–67] and C_2-symmetric bis-sulfoxides[68–76] have been used as Lewis base promoters in the enantioselective allylation of aldehydes and hydrazones with allyltrichlorosilane, which is of particular relevance in the present work.[77–86]

Recently, we reported the synthesis of novel enantiomerically pure sulfoxides according to the Andersen protocol with (*S*)-menthyl *p*-tolyl sulfinate and the dilithium derivative of 2,6-dimethylpyridine *N*-oxide.[80] In this procedure, both chiral monosulfoxide (*R*)-**1** and C_2-symmetric bis-sulfoxide (*R*,*R*)-**2** are obtained (Scheme 1). In particular, bis-sulfoxide (*R*,*R*)-**2** proved to be an efficient chiral organocatalyst in the asymmetric allylation of prochiral *N*-benzoyl hydrazones derived from both aldehydes and ketones (Scheme 2).[80]

On the other hand, the stereoselective formation of chiral quaternary centers remains a challenging subject in asymmetric synthesis[87–93]; thus, we deemed it of interest to examine the applicability of chiral bis-sulfoxide/*N*-oxide (*R*,*R*)-**2** in the enantioselective allylation of hydrazones derived from α-keto esters. If successful, this protocol will create a new quaternary center in the product, which can be derivatized to biologically active α-allyl α-amino acids (Scheme 3).[94–109]

Herein, we describe the allylation of *N*-benzoyl hydrazones derived from α-keto esters employing sulfoxide/*N*-oxides (*R*)-**1** and (*R*,*R*)-**2** as chiral organocatalysts, according to the reaction conditions recommended by Kobayashi et al.[38] Subsequent chemical manipulation of the enantioenriched hydrazine products allowed for the enantioselective synthesis of **6a-b**, two α-allyl α-amino acids derived of L-phenylglycine.

MATERIALS AND METHODS

Materials

Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Melting points were measured with a Melt-Temp 'Electrothermal' apparatus and are uncorrected. NMR spectra were recorded with a Jeol ECA 500 (500 MHz) spectrometer. IR spectra were recorded with a Varian model 640 apparatus. Mass spectra were registered with a Thermo Electron Trace-DSQ spectrometer, at 20 eV. HRMS were recorded with Jeol

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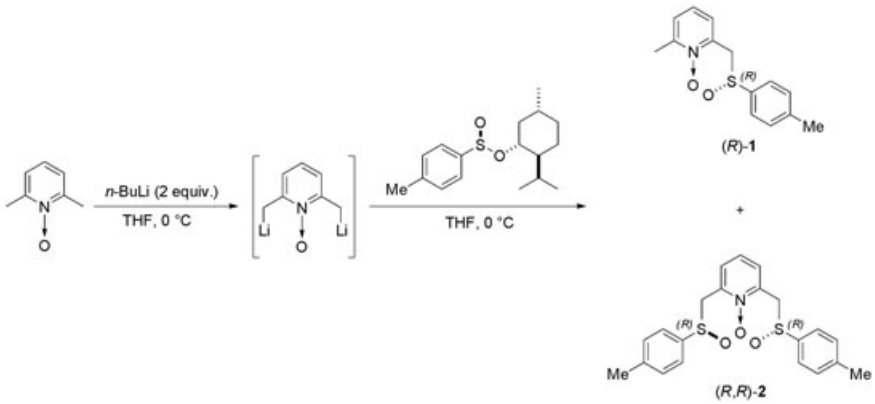
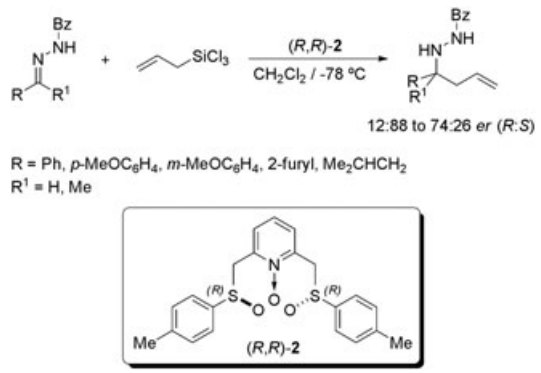
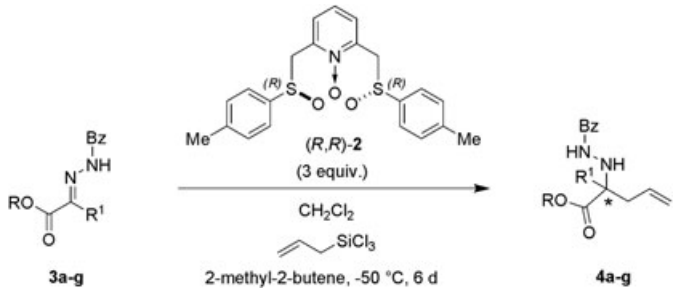


Scheme 1. Synthesis of chiral sulfoxides (*R*)-**1** and (*R,R*)-**2**.



Scheme 2. Asymmetric allylation of prochiral *N*-benzoyl hydrazones catalyzed for bis-sulfoxide (*R,R*)-**2**.



Scheme 3. Allylation of various *N*-benzoylhydrazones **3a-g** with allyltrichlorosilane under catalysis by bis-sulfoxide/*N*-oxide (*R,R*)-**2**.

JMS-SX 102a and Agilent-MSD-TOF1069A spectrometers. Elemental analyses were obtained using a Thermo-Finnigan CHNS/O 1112 apparatus. HPLC analyses were carried out with a Waters 600 E equipment fitted with a UV/Visible Waters 2487 detector and Chiralpack AD-H and Chiralcel OD-H (Daicel Chemical Ind., 0.46 x 25 cm) columns, employing hexane-*i*-PrOH mixture as mobile phase. Experimental CD spectra were recorded with a Jasco-815 spectropolarimeter using the following parameters: 1 cm quartz cells, 5 mM in MeCN or MeOH, 20 °C, data pitch 1 nm, data points 201, bandwidth 1 nm, response 1 sec, high sensitivity, scan speed 100 nm/min, 400–200 nm measurement range, and the baselines correspond to the spectra of the solvent under the same conditions. Methyl benzoylformate, ethyl glyoxalate, and ethyl pyruvate were commercially available. Methyl 2-(naphthalene-2-yl)-2-oxoacetate, methyl 2-oxo-2-(*p*-tolyl)acetate, methyl 2-(4-bromophenyl)-2-oxoacetate, and methyl 2-(4-methoxyphenyl)-2-oxoacetate were prepared according to the literature protocols.[110,111] Racemic hydrazines (**4a-e**), amino esters (**5a-b**), and amino acids (**6a-b**) were prepared as reference samples in order to establish the optical purity of the corresponding enantioenriched chiral products by HPLC.

Substrate Synthesis

(*R*)-2-Methyl-6-(*p*-tolylsulfinylmethyl)pyridine-1-oxide, (*R*)-1, and 6-bis(*p*-tolylsulfinylmethyl))-pyridine-1-oxide, (*R,R*)-2. To a solution of 2,6-dimethylpyridine *N*-oxide (0.166 g, 1.35 mmol) in 5 ml of THF at 0 °C was added dropwise a solution of *n*-BuLi in hexane (2.5 M, 1.0 ml, 2.70 mmol). The resulting mixture was stirred at 0 °C for 1 h and then transferred via cannula to a flask containing (*S*)-(−)-menthyl *p*-tolylsulfinate (1.0 g, 3.34 mmol) in 5.0 ml of THF at 0 °C. The reaction mixture was stirred for 1 h at 0 °C before quenching with aqueous saturated ammonium chloride solution. The product mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated at reduced pressure, and purified by silica gel column chromatography (EtOAc–CH_2Cl_2-*i*-PrOH, 4:4:1).

(*R*)-**1**, R_f = 0.44 (tlc 4 times) followed by crystallization from hexane to afford 0.23 g (68% yield) of monosulfoxide, mp 71–72 °C. $[\alpha]_D^{25}$ +295.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.39 (s, 3H), 2.52 (s, 3H), 4.05 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 7.137.14 (m, 1H), 7.22–7.30 (m, 4H), 7.60–7.61 (m, 2H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 18.2, 21.5, 61.7, 123.9, 125.0, 126.0, 126.3, 130.1, 141.0, 141.8, 142.8, 149.3. HRMS (ESI-TOF) calcd. for $C_{14}H_{16}NO_2S + H^+$: 262.0896; found: 262.0895.

(*R,R*)-**2**, R_f = 0.54 (tlc 4 times) followed by crystallization from CH_2Cl_2-hexane to afford 0.12 g (22% yield) of bis-sulfoxide, mp 175–176 °C. $[\alpha]_D^{25}$ +320.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.39 (s, 6H), 4.08 (d, *J* = 12.3 Hz, 2H), 4.49 (d, *J* = 12.2 Hz, 2H), 7.14–7.18 (m, 1H), 7.29–7.34 (m, 6H), 7.57-7.60 (m, 4H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 21.6, 60.8, 123.9, 124.7, 128.2, 130.1, 140.5, 142.1, 142.9. HRMS (ESI-TOF) calcd. for $C_{21}H_{21}NO_3S_2 + H^+$: 400.1038; found: 400.1036.

(Z)-Methyl 2-(2-benzoylhydrazono)-2-phenylacetate, (3a)[112]

Benzoic hydrazine (2.48 g, 18.2 mmol) was added to a stirred solution of methyl benzoylformate (3 g, 18.2 mmol) in 70 ml of a mixture of methanol-acetic acid (4:1). The resulting solution was heated to reflux for 12 h, during which time all solid dissolved. The reaction mixture was allowed to cool to room temperature, concentrated, and the residue was dissolved in ethyl acetate and washed several times with saturated aqueous sodium and potassium tartrate solution, dried (Na_2SO_4), filtered, and concentrated. The crude product was recrystallized from ethyl acetate-hexane to afford 3.5 g (68% yield) of **3a**: mp 128–129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, 2H, Ar*H*), 7.67 (br, 2H, Ar*H*), 7.59 (m, 1H, Ar*H*), 7.51 (m, 2H, Ar*H*), 7.417.39 (m, 2H, Ar*H*), 3.94 (s, 3H, C*H*$_3$).

^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 163.9, 163.5, 139.4, 134.5, 135.4, 132.7, 132.6, 129.6, 129.2, 128.9, 128.3, 127.8, 52.9.

This same procedure was followed for the preparation of *N*-benzoylhydrazones **3b-e.**

(Z)-Methyl 2-(2-benzoylhydrazono)-2-(4-methoxyphenyl) acetate, (3b)

This compound was obtained from benzoic hydrazine and methyl 2-(4-methoxyphenyl)-2-oxoacetate, purified by flash chromatography on silica gel [hexane-ethyl acetate (6:4)], and recrystallized from ethyl acetate-hexane (68% yield), mp 129–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (d, J = 7.45 Hz, 2H, Ar*H*), 7.637.49 (m, 6H, Ar*H*), 6.91 (d, J = 6.75 Hz, 1H, Ar*H*), 3.94 (s, 3H, CH_3), 3.83 (s, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 163.6, 160.8, 139.4, 132.8, 132.6, 130.6, 129.0, 127.7, 127.3, 126.7, 113.7, 55.4, 52.9. IR (cm^{-1}): 3267, 1690, 1604, 1505, 1478, 1239, 1175, 1141, 1027, 831. MS (EI) *m/z* (%): 312 (7.5) (M^+), 254 (17), 253(100). Calcd. for $C_{17}H_{16}N_2O_4$ (312.32): C 65.38, H 5.16, N 8.97; found: C 65.71, H 5.17, N 9.20.

(Z)-Methyl 2-(2-benzoylhydrazono)-2-(naphthalen-2-yl) acetate, (3c)

This compound was obtained from benzoic hydrazine and methyl 2-(naphthalen-2yl-)-2-oxoacetate, purified by flash chromatography on silica gel [hexane-ethyl acetate (9:1)], and recrystallized from ethyl acetate-hexane (55% yield), mp 115–116 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (br, 1H, Ar*H*), 7.99-7.97 (m, 2H, Ar*H*), 7.91-7.79 (m, 5H, Ar*H*), 7.61-7.56 (m, 1H, Ar*H*), 7.52-7.50 (m, 4H, Ar*H*), 3.16 (s, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 163.9, 163.6, 139.5, 133.7, 132.9, 132.7, 132.6, 131.9, 129.2, 129.0, 128.8, 127.9, 127.7, 127.1, 126.5, 126.0, 53.1. IR (cm^{-1}): 3243, 3053, 1714, 1682, 1548, 1508, 1481, 1435, 1254, 1145, 907. MS (EI) *m/z* (%): 332 (0.78) (M^+), 287(13), 272(71), 207(15), 153(100), 105(13). Calcd. for $C_{20}H_{16}N_2O_3$ (332.35): C 72.28, H 4.85, N 8.43; found: C 72.29, H 4.83, N 8.55.

(Z)-Methyl 2-(2-benzoylhydrazono)-2-p-tolylacetate, (3d)

This compound was obtained from benzoic hydrazine and methyl-2-oxo-2-*p*-tolylacetate, purified by flash chromatography on silica gel [hexane-ethyl acetate (8:2)], and recrystallized from ethyl acetate-hexane (72% yield), mp 130–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (d, J = 7.3 Hz, 2H, Ar*H*), 7.65-7.45 (m, 5H, Ar*H*), 7.20 (d, J = 8.0 Hz, 2H, Ar*H*), 3.93 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 163.6, 139.8, 132.7, 131.7, 129.0, 127.7, 52.9, 21.5. IR (cm^{-1}): 3256, 3036, 1697, 1683, 1536, 1502, 1444, 1236, 1141, 825. MS (EI) *m/z* (%): 296 (0.72) (M^+), 237(100), 105(3). Calcd. for $C_{17}H_{16}N_2O_3$ (296.32): C 68.91, H 5.44, N 9.45; found: C 68.60, H 5.19, N 9.68.

(Z)-Methyl 2-(2-benzoylhydrazono)-2-(4-bromophenyl) acetate, (3e)

This compound was obtained from benzoic hydrazine and methyl 2-(4-bromophenyl)-2-oxoacetate, purified by flash chromatography on silica gel [hexane-ethyl acetate (8:2)], and recrystallized from ethyl acetate-hexane (75% yield), mp 132–133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, J = 7.5 Hz, 2H, Ar*H*), 7.62-7.47 (m, 7H, Ar*H*), 3.94 (s, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 163.1, 133.5, 132.8, 132.4, 131.4, 130.7, 129.0, 127.8, 124.0, 53.1. IR (cm^{-1}): 3582, 3256, 1697, 1678, 1582, 1497, 1472, 1436, 1230, 1141, 1071, 984. MS (EI) *m/z* (%): 361 (0.52) (M^+), 303 (89), 302 (25), 301 (100), 105(25). HRMS (ESI-TOF) calcd. for $C_{16}H_{14}BrN_2O_3$ + H^+: 361.0182; found: 361.0180.

(Z)-Ethyl 2-(2-benzoylhydrazono)propanoate, (3f)

Benzoic hydrazine (3.52 g, 25.8 mmol), ethyl pyruvate (3 g, 25.8 mmol), and 60 ml of ethanol were heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature, concentrated, and the residue was purified by flash chromatography on silica gel CH_2Cl_2-ethyl acetate (95:5). Two products were detected, the less polar corresponding to the desired product (3 g, 57% yield), mp 81–82 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (d, J = 7.5 Hz, 2H, Ar*H*), 7.53-7.41(m, 3H, Ar*H*), 4.30 (q, J = 7.1 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 1.35 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 163.9, 163.2, 138.1, 132.6, 128.9, 127.6, 62.2, 20.3, 14.1. IR (cm^{-1}): 3238, 2997, 2360, 1682, 1576, 1518, 1486, 1269, 1181, 1141, 1024, 917. MS (EI) *m/z* (%): 235 (0.56) (M^++1), 161 (100), 105 (13). HRMS (ESI-TOF) calcd. for $C_{12}H_{14}N_2O_3 + H^+$: 235.1077; found: 235.1077.

(Z)-Ethyl 2-(2-benzoylhydrazono)acetate, (3g)[113]

Benzoic hydrazine (5.75 g, 42.2 mmol), ethyl glyoxalate 50% in toluene (10 g, 9.73 ml, 49.2 mmol) and 50 ml of ethanol were heated to 80 °C for 90 min. The reaction mixture was allowed to cool to room temperature, and the precipitated hydrazone was filtered and washed with ethanol (30 ml), toluene (300 ml), and hexane (500 ml), to give 4.7 g (43% yield) of **3g**, that was recrystallized from CH_2Cl_2-hexane, mp 141–142 °C (lit.[113] mp = 140–141 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.80 (br, 1H, CO*H*), 8.04-7.93 (m, 3H, Ar*H*, N*H)*, 7.52-7.47 (m, 1H, Ar*H*), 7.42-7.36 (m, 2H, Ar*H*), 4.31 (q, J = 6.7 Hz, 2H, CH_2), 1.21 (t, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 165.8, 163.8, 138.8, 132.5, 131.9, 128.5, 128.0, 61.5, 14.0. IR (cm^{-1}): 3127, 3041, 1736, 1660, 1598, 1555, 1344, 1213, 1133, 1084, 1031, 932. MS (EI) *m/z* (%): 220 (0.01) (M^+), 148 (9.0), 147 (100), 105 (15). HRMS (ESI-TOF) calcd. for $C_{12}H_{12}N_2O_3 + Na^+$: 243.0740; found: 243.0741.

General Procedure for the Enantioselective Allylation of Hydrazones 3a-g

To a solution of 35 mg of *N*-benzylhydrazone and bis-sulfoxide/*N*-oxide (*R,R*)-**2** (3 equiv.) in 2 ml of anhydrous CH_2Cl_2 at −78 °C was added dropwise 0.1 ml of 2-methyl-2-butene and 0.1 ml of allyltrichlorosilane. After stirring at −50°C for 48 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (2 ml) and warmed to room temperature. Three additional milliliters of saturated aqueous solution of $NaHCO_3$ were added, the CH_2Cl_2 solvent was evaporated, the aqueous phase was extracted with ethyl acetate (3 x 15 ml), and the combined organic phase was dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography with hexane-ethyl acetate-CH_2Cl_2 (3:1:1).

(S)-Methyl 2-(2-benzoylhydrazinyl)-2-phenylpent-4-enoate, (S)-4a[112]

Yield 31%, pale yellow oil. $[\alpha]_D^{25}$ = +35.9 (*c* 1.02, $CHCl_3$) [Lit.[112] $[\alpha]_D^{25}$ = −36.0 (*c* 1.15, $CHCl_3$) for the (*R*)-enantiomer]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (s, 1H, N*H*), 7.59-7.55 (m, 2H, Ar*H*), 7.47-7.43 (m, 3H, Ar*H*), 7.40-7.26, (m, 5H, Ar*H*), 5.92-5.82 (m, 1H, C*H*), 5.64 (br, 1H, N*H*), 5.21 (dd,

J = 1.1, 17 Hz, 1H, C*H*$_2$), 5.15 (dd, *J* = 1.0, 10.1 Hz, 1H, C*H*$_2$), 3.8 (s, 3H, C*H*$_3$), 3.02 (dd, *J* = 7.3, 14.2 Hz, 1H, C*H*$_2$), 2.95 (dd, *J* = 6.9, 14.3 Hz, 1H, C*H*$_2$). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 174.0, 166.2, 138.6, 132.9, 132.6, 131.7, 128.6, 128.4, 128.2, 126.8, 126.6, 119.5, 71.1, 52.5, 41.1. IR (cm^{-1}): 3278, 3070, 2950, 1728, 1637, 1578, 1523, 1431, 1229, 916, 692. MS (EI) *m/z* (%): 324 (0.85) (M^+), 283 (100), 265 (17), 223 (22), 105 (44). HRMS (ESI-TOF) calcd. for $C_{19}H_{20}N_2O_3 + H^+$: 325.1546; found: 325.1549. Enantiomeric ratio 1:99, determined by HPLC (Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1 ml/min): t_r = 30.1 min (minor, *R* enantiomer); 35.3 min (major, *S* enantiomer).

(S)-Methyl-2-(2-benzoylhydrazinyl)-2-(4-methoxyphenyl) pent-4-enoate, (S)-4b

Yield 50%, pale yellow oil. $[\alpha]_D^{25}$ = +26.5 (*c* 1.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (s, 1H, N*H*), 7.60-7.56 (m, 2H, Ar*H*), 7.48-7.43 (m, 1H, Ar*H*), 7.40-7.34, (m, 4H, Ar*H*), 6.89-6.84 (m, 2H, Ar*H*), 5.92-5.82 (m, 1H, C*H*), 5.60 (br, 1H, N*H*), 5.20-5.12 (m, 2H, C*H*$_2$), 3.78 (s, 3H, C*H*$_3$), 3.79 (s, 3H, C*H*$_3$), 2.99 (dd, *J* = 7.3, 14.3 Hz, 1H, C*H*$_2$), 2.92 (dd, *J* = 7.0, 14.2 Hz, 1H, C*H*$_2$). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 174.2, 166.2, 159.3, 133.0, 132.8, 131.7, 130.6, 128.7, 128.0, 126.9, 119.5, 113.8, 70.7, 55.3, 52.6, 41.1. IR (cm^{-1}): 3278, 3069, 2919, 1730, 1640, 1609, 1512, 1433, 1249, 1180, 1028, 919, 692. MS (EI) *m/z* (%): 355 (0.57) ($M^+ + 1$), 322 (7), 253 (100), 105 (15). HRMS (ESI-TOF) calcd. for $C_{20}H_{22}N_2O_4 + H^+$: 355.1652; found: 355.1653. Enantiomeric ratio 98:2, determined by HPLC (Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1 ml/min): t_r = 41.2 min (major, *S* enantiomer); 45.2 min (minor, *R* enantiomer).

(S)-Methyl-2-(2-benzoylhydrazinyl)-2-(naphthalen-2-yl)-pent-4-enoate, (S)-4c

Yield 25%, pale yellow oil. $[\alpha]_D^{25}$ = +13.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (s, 1H, N*H*), 7.86-7.75 (m, 4H, Ar*H*), 7.60-7.54 (m, 3H, Ar*H*), 7.51-7.46 (m, 2H, Ar*H*), 7.46-7.42 (m, 1H, Ar*H*), 7.38-7.33 (m, 2H, Ar*H*), 5.95-5.85 (m, 1H, C*H*), 5.82 (d, *J* = 6.6 Hz, 1H, N*H*), 5.22 (dd, *J* = 1.3, 17 Hz, 1H, C*H*$_2$), 5.15 (dd, *J* = 1.0, 10.2 Hz, 1H, C*H*$_2$), 3.81 (s, 3H, C*H*$_3$), 3.11 (dd, *J* = 7.4, 14.3 Hz, 1H, C*H*$_2$), 3.04 (dd, *J* = 6.7, 14.3 Hz, 1H, C*H*$_2$). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 173.8, 166.4, 136.2, 133.1, 133.0, 132.9, 132.7, 131.7, 128.7, 128.4, 128.3, 127.6, 126.9, 126.5, 126.4, 125.9, 124.5, 119.6, 71.2, 52.7, 40.9. IR (cm^{-1}): 3284, 3058, 2921, 1731, 1659, 1432, 1226, 917, 817, 749, 709, 692. MS (EI) *m/z* (%): 374 (12) (M^+), 355 (17), 315 (18), 281 (45), 272 (36), 207 (100), 153 (19), 105 (17), 83 (30). HRMS (ESI-TOF) calcd. for $C_{23}H_{22}N_2O_3 + H^+$: 375.1703; found: 375.1704. Enantiomeric ratio 1:99, determined by HPLC (Chiralcel OD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1 ml/min): t_r = 5.5 min (minor, *R* enantiomer); 6.0 min (major, *S* enantiomer).

(S)-Methyl 2-(2-benzoylhydrazinyl)-2-p-tolylpent-4-enoate, (S)-4d

Yield 35%, pale yellow oil. $[\alpha]_D^{25}$ = +29.3 (*c* 0.87, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (s, 1H, N*H*), 7.60-7.56 (m, 2H, Ar*H*), 7.49-7.44 (m, 1H, Ar*H*), 7.40-7.35, (m, 2H, Ar*H*), 7.35-7-30 (m, 2H, Ar*H*), 7.18-7-13 (m, 2H, Ar*H*), 5.82-5.93 (m, 1H, C*H*), 5.63 (d, *J* = 4.9 Hz, 1H, N*H*), 5.20 (dd, *J* = 1.1, 17 Hz, 1H, C*H*$_2$), 5.15 (dd, *J* = 0.86, 10.2 Hz, 1H, C*H*$_2$), 3.7 (s, 3H, C*H*$_3$), 3.00 (dd, *J* = 7.4, 14.3 Hz, 1H, C*H*$_2$), 2.93 (dd, *J* = 6.9, 14.3 Hz, 1H, C*H*$_2$), 2.31 (s, 3H, C*H*$_3$). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 174.1, 166.2, 138.0, 135.7, 133.0, 132.8, 131.7, 129.3, 128.7, 126.9, 126.6, 119.5, 71.0, 52.6, 41.0, 21.1. IR (cm^{-1}): 3283, 3065, 2919, 1731, 1640, 1513, 1432, 1228, 918, 708, 691. MS (EI) *m/z* (%): 338 (0.96) (M^+), 297 (76), 279 (18), 237 (100), 105 (38). HRMS (ESI-TOF) calcd. for $C_{20}H_{22}N_2O_3 + H^+$: 339.1703; found: 339.1706. Enantiomeric ratio 98:2, determined by HPLC (Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1 ml/min): t_r = 23.7 min (major, *S* enantiomer); 26.3 min (minor, *R* enantiomer).

(S)-Methyl-2-(2-benzoylhydrazinyl)-2-(4-bromophenyl) pent-4-enoate, (S)-4e

Yield 18%, pale yellow oil. $[\alpha]_D^{25}$ = +13.3 (*c* 0.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.8 (d, *J* = 6 Hz, 1H, N*H*), 7.61-7.57 (m, 2H, Ar*H*), 7.51-7.45 (m, 3H, Ar*H*), 7.42-7.37 (m, 2H, Ar*H*), 7.37- 7.33 (m, 2H, Ar*H*), 5.87-5.76 (m, 1H, C*H*), 5.61 (d, *J* = 6.4 Hz, 1H, N*H*), 5.20 (dd, *J* = 1.6, 17 Hz, 1H, C*H*$_2$), 5.16 (dd, *J* = 0.8, 10.2 Hz, 1H, C*H*$_2$), 3.8 (s, 3H, C*H*$_3$), 2.97 (dd, *J* = 7.4, 14.5 Hz, 1H, C*H*$_2$), 2.88 (dd, *J* = 7.0, 14.3 Hz, 1H, C*H*$_2$). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 173.5, 166.4, 137.8, 132.8, 132.2, 131.9, 131.6, 128.8, 128.6, 126.9, 122.4, 120.0, 70.8, 52.8, 41.2. IR (cm^{-1}): 3277, 3067, 2950, 2921, 1731, 1641, 1488, 1432, 1228, 1009, 920, 709, 691. MS (EI) *m/z* (%): 402 (0.62) (M^+-1), 370 (35), 281 (18), 207 (26), 105 (100). HRMS (ESI-TOF) calcd. for $C_{19}H_{19}BrN_2O_3 + H^+$: 403.0651; found: 403.0652. Enantiomeric ratio 1:99, determined by HPLC (Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1 ml/min): t_r = 32.1 min (minor, *R* enantiomer); 35.5 min (major, *S* enantiomer).

Ethyl 2-(2-benzoylhydrazinyl)-2-methylpent-4-enoate, 4f

Yield 64%, pale yellow oil. $[\alpha]_D^{25}$ = +17.1 (*c* 1.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (s, 1H, N*H*), 7.76-7.72 (m, 2H, Ar*H*), 7.53-7.49 (m, 1H, Ar*H*), 7.46 -7.41 (m, 2H, Ar*H*), 5.89- 5.78 (m, 1H, C*H*), 5.19 (dd, *J* = 1.4, 12.6 Hz, 1H, C*H*$_2$), 5.16 (dd, *J* = 1.6, 5.7 Hz, 1H, C*H*$_2$), 5.05 (br, 1H, N*H*), 4.27-4.16 (m, 2H, C*H*$_2$), 2.58 (dd, *J* = 7.0, 14.0 Hz, 1H, C*H*$_2$), 2.52 (dd, *J* = 7.7, 13.9 Hz, 1H, C*H*$_2$), 1.40 (s, 3H, C*H*$_3$), 1.30 (t, *J* = 7.23 Hz, 3H, C*H*$_3$). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 174.9, 166.7, 132.9, 132.1, 131.7, 128.6, 126.8, 119.6, 64.8, 61.3, 41.5, 21.2, 14.2. IR (cm^{-1}): 3275, 3073, 2980, 1726, 1640, 1448, 1302, 1217, 1150, 1024, 918, 709, 691. MS (EI) *m/z* (%): 276 (0.18) (M^+), 235 (100), 203 (16), 105 (24). HRMS (ESI-TOF) calcd. for $C_{15}H_{20}N_2O_3 + H^+$: 277.1546; found: 277.1552. Enantiomeric ratio 79:21, determined by HPLC (Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 210 nm, 1 ml/min): t_r = 18.5 min (major); 19.3 min (minor).

Ethyl 2-(2-benzoylhydrazinyl)pent-4-enoate, 4g

Yield 93%, pale yellow oil. $[\alpha]_D^{25}$ = −14.42 (*c* 1.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.0 (s, 1H, N*H*), 7.76-7.72 (m, 2H, Ar*H*), 7.54-7.47 (m, 1H, Ar*H*), 7.44-7.39, (m, 2H, Ar*H*), 5.84-5.88 (m, 1H, C*H*), 5.16-5.23 (m, 2H, C*H*$_2$), 5.10 (s, 1H, N*H*), 4.23-4.18 (m, 2H, C*H*$_2$), 3.83-3.81 (m, 1H, C*H*), 2.65-2.60 (m, 1H, C*H*$_2$), 2.50-2.44 (m, 1H, *CH*$_2$), 1.27 (t, *J* = 7 Hz, 3H, C*H*$_3$). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 172.7, 167.0, 133.0, 132.6, 132.0, 128.8, 127.0, 119.0, 62.1, 61.2, 35.3, 14.3. IR (cm^{-1}): 3213, 3064, 2982, 1727, 1644, 1452, 1317, 1188, 1016, 989, 913, 849, 697. MS (EI) *m/z* (%): 262 (0.64) (M^+), 222 (14), 221 (100), 189 (21), 150 (50). HRMS (ESI-TOF) calcd. for $C_{14}H_{18}N_2O_3 + H^+$: 263.1390; found: 263.1391. Enantiomeric ratio 32:68, determined by HPLC (Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 210 nm, 1 ml/min): t_r = 17.20 min (minor); 18.35 min (major).

(S)-Methyl 2-amino-2-phenylpent-4-enoate, (S)-5a

To a solution of hydrazine (*S*)-**4a** (120 mg, 0.37 mmol) in MeOH (0.3 ml) was added 11.1 ml (448 mg, 1.1 mmol) of SmI_2 (0.1 M in THF) at ambient temperature. The dark blue-green SmI_2 solution turned yellow. The reaction mixture was stirred for 30 min at room temperature and the solvent was removed under vacuum. The residue was treated with 1N HCl (15 ml) and diethyl ether (30 ml), the aqueous phase was neutralized with 1M NaOH, and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over $NaSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with CH_2Cl_2-ethyl acetate (8:2) to afford the desired amino ester (*S*)-**5a** in 26% yield (20 mg) as a pale yellow oil, $[\alpha]_D^{25} = -13.5$ (*c* 2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53-7.51 (m, 2H, Ar*H*), 7.36-7.33 (m, 2H, Ar*H*), 7.29-7.25 (m, 1H, Ar*H*), 5.75-5.40 (m, 1H, C*H*), 5.22-5.13 (m, 2H, CH_2), 3.71 (s, 3H, CH_3), 2.98 (dd, *J* = 6.7, 13.6 Hz, 1H, CH_2), 2.66 (dd, *J* = 7.8, 13.6 Hz, 1H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 175.8, 142.8, 133.0, 128.5, 127.6, 125.5, 120.1, 63.2, 52.6, 44.7. IR (cm^{-1}): 2951, 2923, 2849, 2363, 1729, 1434, 1215, 1143, 921, 697. MS (EI) *m/z* (%): 206 (0.05) (M^++1), 164 (94), 146 (100), 104 (3). HRMS (ESI-TOF) calcd. for $C_{12}H_{15}NO_2 + H^+$: 206.1175; found: 206.1180.

(S)-Methyl 2-amino-2-(4-methoxyphenyl)pent-4-enoate, (S)-5b

The procedure described above was followed with 368 mg (1.04 mmol) of hydrazine (*S*)-**4b**, 0.84 ml methanol, and 31.15 ml (1.26 g, 3.1 mmol) of SmI_2 (0.1 M in THF) to afford the desired amino ester (*S*)-**5b** in 21% yield (51 mg) as a pale yellow oil, $[\alpha]_D^{25} = -16.8$ (*c* 1.01, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44-7.43 (m, 2H, Ar*H*), 6.88-6.86 (m, 2H, Ar*H*), 5.72-5.63 (m, 1H, C*H*), 5.20-5.14 (m, 2H, CH_2), 3.7 (s, 3H, CH_3), 2.97 (dd, *J* = 6.7, 13.6 Hz, 1H, CH_2), 2.65 (dd, *J* = 7.9, 13.6 Hz, 1H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 176.0, 159.0, 134.9, 133.1, 126.7, 120.0, 113.8, 62.7, 55.3, 52.6, 44.8. IR (cm^{-1}): 3387, 3001, 2951, 1728, 1509, 1248, 1214, 1177, 1031, 829. MS (EI) *m/z* (%): 235 (0.03) (M^++1), 194 (100), 176 (88), 134 (5). HRMS (ESI-TOF) calcd. for $C_{13}H_{17}NO_3 + H^+$: 236.1281; found: 236.1282.

(S)-2-Amino-2-phenylpent-4-enoic acid, (S)-6a

In a 50 ml round-bottom flask was placed 20 mg (0.097 mmol) of amino ester (*S*)-**5a**, 1.5 ml of mixture THF-H_2O (3:1 *v/v*), and 9.4 mg (0.22 mmol) of $LiOH \cdot H_2O$, and the reaction mixture was stirred for 24 h at room temperature. The THF was evaporated and the aqueous residue was acidified to pH 2 with 1N HCl. The H_2O was removed under vacuum and the residue was purified by flash chromatography on silica gel with *i*-PrOH-MeOH-NH_4OH (7:2:0.5 *v/v*) to afford the desired amino acid **6a** in 54% (10 mg) as a white solid, mp 180–181 °C, $[\alpha]_D^{25} = +5.88$ (*c* 0.51, 1N HCl). 98% ee (determined by HPLC, Scheme 4) [Lit.[114] mp = 223–225 °C, $[\alpha]_D^{25} = +12.6$ (*c* 0.4, 1N HCl)]. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.60-7.53 (m, 2H, Ar*H*), 7.44-7.32 (m, 3H, Ar*H*), 5.86-5.74 (m, 1H, C*H*), 5.32-5.21 (m, 2H, CH_2), 3.10-2.96 (m, 2H, CH_2). ^{13}C NMR (125.76 MHz, CD_3OD): δ = 173.0, 138.5, 131.7, 128.4, 128.0, 125.9, 120.1, 65.8, 40.7. IR (cm^{-1}): 3080, 2977, 2360, 2341, 1658, 1587, 1538, 1363, 910, 738, 693. HRMS (ESI-TOF) calcd. for $C_{11}H_{13}NO_2 + H^+$: 192.10191; found: 192.10216. Enantiomeric ratio 99:1, determined by HPLC (Chirobiotic T, MeOH-H_2O (50:50), 210 nm, 0.7 ml/min): t_r = 6.4 min (major *S* enantiomer); 9.6 min (minor *R* enantiomer).

(S)-2-Amino-2-(4-methoxyphenyl)pent-4-enoic acid, (S)-6b

The procedure described above was followed with 45 mg (0.19 mmol) of (*S*)-**5b**, 2 ml mixture THF · H_2O (3:1 *v/v*) and 18.45 mg (0.44 mmol) of $LiOH \cdot H_2O$ to afford the desired amino acid **6b** in 54% yield (23 mg) as a white solid, mp 190–191 °C (EtOH-diethyl ether), $[\alpha]_D^{25} = -13.75$ (*c* 0.8, 1N HCl). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.48-7.46 (m, 2H, Ar*H*), 6.94-6.92 (m, 2H, Ar*H*), 5.83-5.77 (m, 1H, C*H*), 5.32-5.28 (m, 1H, CH_2), 5.24-5.22 (m, 1H, CH_2), 3.78 (s, 3H, CH_3), 3.08-3.04 (m, 1H, CH_2), 2.98-2.94 (m, 1H, CH_2). ^{13}C NMR (125.76 MHz, CD_3OD): δ = 173.0, 159.8, 131.6, 130.2, 127.3, 120.1, 113.6, 65.4, 54.4, 40.5. IR (cm^{-1}): 3734, 3127, 3039, 2936, 2360, 2340, 1582, 1516, 1375, 1256, 1032, 930, 827. HRMS (ESI-TOF) calcd. for $C_{12}H_{15}NO_3 + H^+$: 222.1124; found: 222.1126. Enantiomeric ratio 98:2, determined by HPLC (Chirobiotic T, MeOH-H_2O (50:50), 210 nm, 0.7 ml/min): t_r = 7.3 min (major *S* enantiomer); 13.2 min (minor *R* enantiomer).

General Procedure for the Nonasymmetric Allylation of the Prochiral Hydrazones, in Order to Prepare Racemic Standards

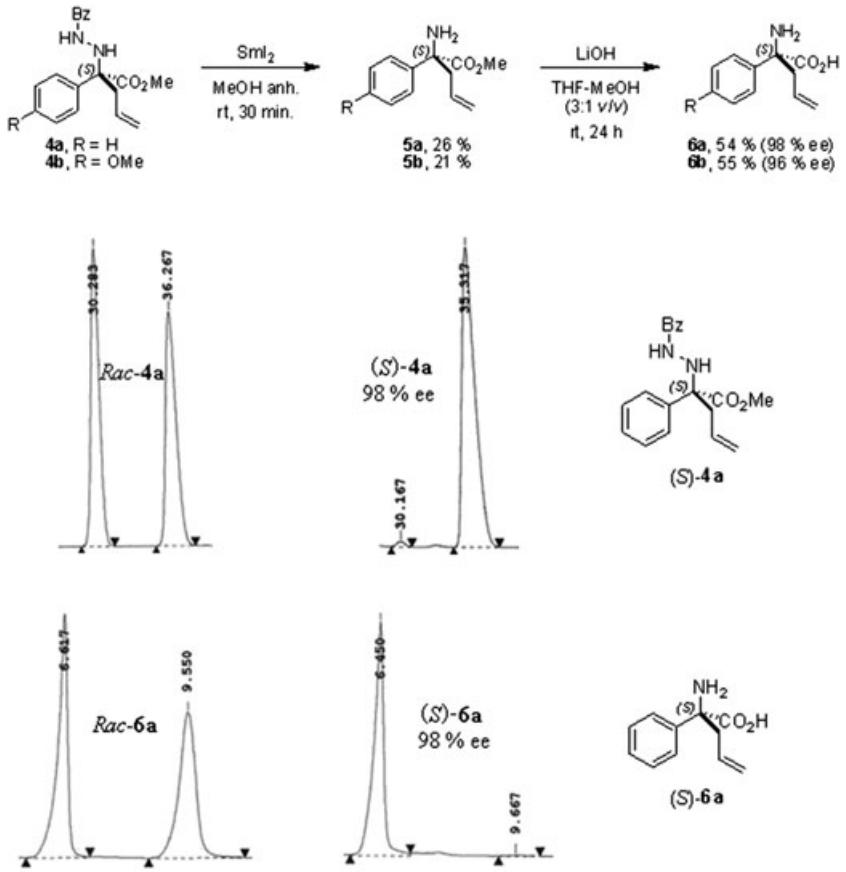
A solution of 1 mmol of hydrazone and 0.2 mmol of $InCl_3$ (dried 2 h under vacuum at 100 °C) in 5 ml of anhydrous THF was stirred for 15 min at room temperature, then allyltributylstannane (1.3 mmol) was added dropwise via syringe and stirred for 18 h at room temperature. Saturated aqueous NH_4Cl (15 ml) was added and the resulting solution was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried ($NaSO_4$), filtered, concentrated, and purified by flash chromatography on silica gel with hexane-ethyl acetate-dichloromethane (3:1:1).

Methyl 2-(2-benzoylhydrazinyl)-2-phenylpent-4-enoate, rac-4a

Yield 44%, mp 78–79 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 6.61 Hz, N*H*), 7.25-7.56 (m, 9H, Ar*H)*, 5.83-5.89 (m, 1H, C*H*), 5.63 (d, *J* = 6.6 Hz, 1H, C*H*), 5.13-5.22 (m, 2H, CH_2), 3.8 (s, 3H, CH_3), 3.0 (dd, *J* = 7.3, 14.3 Hz, 1H, CH_2), 2.93 (dd, *J* = 7.0, 14.3 Hz, 1H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 174.0, 166.2, 138.7, 133.0, 132.7, 131.7, 128.5, 128.3, 126.8, 126.7, 119.6, 71.2, 52.7, 41.1. IR (cm^{-1}): 3373, 3248, 1711, 1662, 1580, 1535, 1472, 1293, 1250, 1025, 691. MS (EI) *m/z* (%): 324 (0.68) (M^+), 283 (100), 265 (16), 223 (16), 105 (20). HRMS (ESI-TOF) calcd. for $C_{19}H_{22}N_2O_2 + H^+$: 325.1546; found: 325.1543. HPLC: Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1 ml/min, t_r = 30.2 and 36.2 min.

Methyl 2-(2-benzoylhydrazinyl)-2-(4-methoxyphenyl)pent-4-enoate, rac-4b

Yield 69%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 6.5 Hz, 1H, N*H*), 7.58-7.56 (m, 2H, Ar*H,)*, 7.46-7.44 (m, 1H, Ar*H*), 7.38-7.35 (m, 4H, Ar*H*), 6.86 (d, 2H, Ar*H*), 5.89-5.82 (m, 1H, C*H*), 5.58 (d, *J* = 6.8 Hz, 1H, N*H*), 5.21-5.13 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 2.98 (dd, *J* = 7.5, 14.25 Hz, 14.25, 1H, CH_2) 2.91 (dd, *J* = 7.0, 14.3 Hz, 1H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 174.2, 166.2, 159.3, 132.7, 131.7, 128.7, 127.9, 126.9, 119.6, 117.0, 114.1, 113.8, 70.5, 55.3, 52.6, 41.1. IR (cm^{-1}): 3282, 3073, 2952, 2923, 2360, 1731, 1639, 1610, 1511, 1433,



Scheme 4. Assignment of the absolute configuration in chiral hydrazines **4a-b** by chemical correlation with quaternary α-allyl-α-aryl-α-amino acids **6a-b**.

1250, 1180, 1032, 691. MS (EI) *m/z* (%): 354 (1) (M^+), 312 (8), 253 (100), 207 (5), 105 (17). HRMS (ESI-TOF) calcd. for $C_{20}H_{22}N_2O_4 + H^+$: 355.1652; found: 355.1651. HPLC: Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1 ml/min, t_r = 41.3 and 44.9 min.

Methyl 2-(2-benzoylhydrazinyl)-2-(naphthalen-2-yl)pent-4-enoate, rac-4c

Yield 61%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (s, 1H, N*H*), 7.84-7.76 (m, 4H, Ar*H)*, 7.58-7.55 (m, 3H, Ar*H*), 7.49-7.42 (m, 3H, Ar*H*), 7.36-7-33 (m, 2H, Ar*H*), 5.96-5.87 (m, 1H, C*H*), 5.81 (d, *J* = 6.8 Hz, 1H, N*H*), 5.24-5.14 (m, 2H, CH_2), 3.80 (s, 3H, CH_3), 3.11 (dd, *J* = 7.5, 14.4 Hz, 1H, CH_2), 3.04 (dd, *J* = 6.7, 14.3 Hz, 1H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 173.8, 166.4, 136.2, 133.1, 133.0, 132.9, 132.7, 131.8, 128.7, 128.4, 128.3, 127.6, 126.9, 126.5, 126.4, 125.9, 124.5, 119.6, 71.2, 60.5, 52.8, 40.9. IR (cm^{-1}): 3276, 3058, 2950, 2923, 1730, 1639, 1530, 1431, 1275, 1226, 1134, 918, 708, 691. MS (EI) *m/z* (%): 374 (4) (M^+), 315 (31), 282 (14), 281 (48), 273 (41), 272 (28), 207 (100), 153 (18), 105 (22). HRMS (ESI-TOF) calcd. for $C_{23}H_{22}N_2O_3 + H^+$: 375.1703; found: 375.1704. HPLC: Chiralcel OD-H, Hexane-EtOH (90:10), 254 nm, 1 ml/min, t_r = 5.46 and 6.06 min.

Methyl 2-(2-benzoylhydrazinyl)-2-p-tolylpent-4-enoate, rac-4d

Yield 66%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 6.4 Hz, 1H, *NH*), 7.58-7.56 (m, 2H, Ar*H,)*, 7.47-7.44 (m, 1H, Ar*H*), 7.39-7.31 (m, 4H, Ar*H*), 7.15 (m, 2H, Ar*H*), 5.89-5.84 (m, 1H, C*H*), 5.61 (d, *J* = 6.5 Hz, 1H, N*H*), 5.22-5.13 (m, 2H, CH_2), 3.78 (s, 3H, CH_3), 2.99 (dd, *J* = 7.2, 14.3 Hz, 1H, CH_2), 2.92 (dd, *J* = 7.1, 14.2 Hz, 1H, CH_2), 2.31 (s, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 174.1, 166.2, 138.0, 135.7, 132.8, 131.7, 129.3, 128.7, 126.9, 126.6, 119.5, 70.9, 52.6, 41.0, 21.1. IR (cm^{-1}): 3276, 3072, 2951, 2920, 1731, 1639, 1513, 1431, 1227, 1136, 707, 691. MS (EI) *m/z* (%): 338 (0.08) (M^+), 297(100), 279(22), 237(62), 203 (19), 181(11), 145(13), 105 (69). HRMS (ESI-TOF) calcd. for $C_{20}H_{23}N_2O_3 + H^+$: 339.1703; found: 339.1706. HPLC: Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1ml/min, t_r = 23.8 and 26.6 min.

Methyl 2-(2-benzoylhydrazinyl)-2-(4-bromophenyl)pent-4-enoate, rac-4e

Yield 80%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 6.35 Hz, 1H, N*H*), 7.58-7.57 (m, 2H, Ar*H*), 7.49-7.45 (m, 3H, Ar*H*), 7.40-7.33 (m, 2H, Ar*H*), 5.84-5.78 (m, 1H, C*H*), 5.60 (d, *J* = 6.8 Hz, 1H, N*H*), 5.20-5.14 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 2.96 (dd, *J* = 7.2, 14.3 Hz, 1H, CH_2), 2.87 (dd, *J* = 6.9, 14.3 Hz, 1H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 173.5, 166.4, 137.8, 132.7, 132.2, 131.9, 131.6, 128.8, 128.6, 126.9, 122.4, 120.0, 70.8, 52.8, 41.2. IR (cm^{-1}): 3272, 3071, 2951, 2920, 1731, 1640, 1488, 1432, 1228, 1075, 1009, 708, 691. MS (EI) *m/z* (%): 402 (1.58) (M^+-1), 372 (30), 371(11), 370 (36), 303 (38), 302(16), 301 (44), 281(20), 207 (40), 105 (100). HRMS (ESI-TOF) calcd. for $C_{19}H_{19}N_2O_3Br + H^+$: 403.0651; found: 403.0645. HPLC: Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 254 nm, 1ml/min, t_r = 32.2 and 35.8 min.

Ethyl 2-(2-benzoylhydrazinyl)-2-methylpent-4-enoate, rac-4f

Yield 57%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.0 (s, 1H, N*H*), 7.75-7.73 (m, 2H, Ar*H*), 7.51-7.49 (m, 1H, Ar*H*), 7.45-7.42 (m, 2H, Ar*H*), 5.86-5.79 (m, 1H, C*H*), 5.19-5.15 (m, 2H, CH_2), 5.06 (br, 1H, N*H*), 4.27-4.18 (m, 2H, CH_2), 2.58 (dd, *J* = 7.0, 14.0 Hz, 1H, CH_2), 2.52 (dd, *J* = 7.7, 14.0 Hz, 1H, CH_2), 1.40 (s, 3H, CH_3), 1.30 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 174.8, 166.6, 132.9, 132.1, 131.7, 128.6, 126.8, 119.5, 64.8, 61.3, 41.5, 21.2, 14.2. IR (cm^{-1}): 3278, 2980, 2957, 2930, 1723, 1641, 1449, 1287, 1271, 1150, 1024, 920, 711, 692. MS (EI) *m/z* (%): 276 (0.25) (M^+), 235 (39), 203 (21), 161 (7), 105 (100), 77(42). HRMS (ESI-TOF) calcd. for $C_{15}H_{20}N_2O_3 + Na^+$: 299.1366; found: 299.1367. HPLC: Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 210 nm, 1ml/min, t_r = 20.4 and 21.4 min.

Ethyl 2-(2-benzoylhydrazinyl)pent-4-enoate, rac-4g

Yield 42%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18 (s, 1H, N*H*), 7.76-7.70 (m, 2H, Ar*H*), 7.52-7.47 (m, 1H, Ar*H*), 7.44-7.38 (m, 2H, Ar*H*), 5.92-5.80 (m, 1H, C*H*), 5.23-5.07 (m, 3H, CH_2, N*H*), 4.23-4.12 (m, 2H, CH_2), 3.82 (t, *J* = 6.1 Hz, 1H, C*H*), 2.66-2.56 (m, 1H, CH_2), 2.50-2.40 (m, 1H, CH_2), 1.26 (t, *J* =7.1 Hz, 3H, CH_3). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 172.7, 167.0, 133.0, 132.7, 132.0, 128.7, 127.0, 119.0, 62.2, 61.2, 35.3, 14.3. IR (cm^{-1}): 3285, 3066, 2980, 2932, 1731, 1640, 1526, 1463, 1295, 1192, 1025, 917, 692. MS (EI) *m/z* (%): 260 (0.93) (M^+-2), 221 (17), 121 (14), 105 (100), 77 (66), 68 (39). HRMS (ESI-TOF) calcd. for $C_{14}H_{18}N_2O_3 + Na^+$: 285.1209; found: 285.1210. HPLC: Chiralpak AD-H, Hexane-*i*-PrOH (90:10), 210 nm, 1ml/min, t_r = 17.2 and 18.4 min.

Compounds *rac*-**5a** and *rac*-**5b** were obtained according to the procedure described for the preparation of (*S*)-**5a** (see above).

Methyl 2-amino-2-phenylpent-4-enoate, rac-5a

With 200 mg (0.61 mmol) of *rac*-***4a***, 0.5 ml of methanol and 18.5 ml (747 mg, 1.83 mmol) of SmI_2 (0.1 M in THF), to afford 80 mg (63% yield) of *rac*-**5a** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52-7.51 (m, 2H, Ar*H*), 7.36-7.34 (m, 2H, Ar*H*), 7.29-7.25 (m, 1H, Ar*H*), 5.72-5.65 (m, 1H, C*H*), 5.22-5.14 (m, 2H, CH_2), 3.71 (s, 3H, CH_3), 3.10-2.95 (m, 1H, CH_2), 2.67-264 (m, 1H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 175.8, 142.8, 133.0, 128.5, 127.6, 125.5, 120.1, 63.2, 52.6, 44.7. IR (cm^{-1}): 2951, 2916, 1729, 1434, 1214, 921, 697. MS (EI) *m/z* (%): 205 (0.08) (M^+), 164 (100), 146 (81), 104 (82). HRMS (ESI-TOF) calcd. for $C_{12}H_{15}NO_2 + H^+$: 206.1175; found: 206.1181.

Methyl 2-amino-2-(4-methoxyphenyl)pent-4-enoate, rac-5b

With 664 mg (1.87 mmol) of *rac*-***4b***, 1.51 ml of methanol, and 56.2 ml (2.27g, 5.62 mmol) of SmI_2 (0.1 M in THF), to afford 132 mg (30% yield) of *rac*-**5b** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44-7.43 (m, 2H, Ar*H*), 6.88-6.86 (m, 2H, Ar*H*), 5.72-5.64 (m, 1H, C*H*), 5.20-5.13 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 2.97-2.93 (m 1H, CH_2), 2.65-2.62 (m, 1H, CH_2). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 175.9, 158.9, 134.8, 133.1, 126.7, 120.0, 113.8, 62.7, 55.3, 52.6, 44.8. IR (cm^{-1}): 3386, 3001, 2951, 1727, 1509, 1248, 1214, 1173, 1031, 829. MS (EI) *m/z* (%): 235 (0.03) (M^+ +1), 194 (100), 176 (88), 134 (5). HRMS (ESI-TOF) calcd. for $C_{13}H_{17}NO_3 + H^+$: 236.1281; found: 236.1284. HPLC: Chiralcel OD-H, Hexane-*i*-PrOH (95:5), 220 nm, 1 ml/min, t_r = 15.9 and 17.7 min.

Compounds *rac*-**6a** and *rac*-**6b** were obtained according to the procedure described for the preparation of (*S*)-**6a** (see above).

2-Amino-2-phenylpent-4-enoic acid, rac-6a

With 41 mg (0.19 mmol) of *rac*-***5a***, 19.2 mg (0.46 mmol) of $LiOH \cdot H_2O$ and 2 ml of a THF-H_2O (3:1) mixture, to afford 23 mg (60% yield) of *rac*-**6a**, mp 177–179 °C (EtOH-diethyl ether). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.60-7.53 (m, 2H, Ar*H*), 7.42-7.32 (m, 2H, Ar*H*), 7.35-7.30 (m, 1H, Ar*H*), 5.82-5.74 (m, 1H, C*H*), 5.34-5.26 (m, 1H, CH_2), 5.25-5.18 (m, 1H, CH_2), 3.11-3.04 (m, 1H, CH_2), 3.02-2.95 (m, 1H, CH_2). ^{13}C NMR (125.76 MHz, CD_3OD): δ = 173.0, 138.5, 131.7, 128.4, 128.0, 125.9, 120.1, 65.8, 40.7. IR (cm^{-1}): 3080, 2977, 2360, 2341, 1587, 1538, 1500, 1363, 910, 738, 693. HRMS (ESI-TOF) calcd. for $C_{11}H_{13}NO_2 + H^+$: 192.1019; found: 192.1017. HPLC: Chirobiotic T, MeOH-H_2O (50:50), 210 nm, 0.7 ml/min. t_r = 6.6 and 9.5 min.

2-Amino-2-(4-methoxyphenyl)pent-4-enoic acid, rac-6b

100 mg (0.43 mmol) of ***rac-5b***, 41 mg (0.98 mmol) $LiOH \cdot H_2O$ and 3 ml mixture THF-H_2O (3:1), to afford 46 mg (49% yield) of *rac*-**6b**, mp 186–188 °C (EtOH-diethyl ether). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.48-7.46 (m, 2H, Ar*H*), 6.94-6.92 (m, 2H, Ar*H*), 5.83-5.75 (m, 1H, C*H*) 5.33-5.23 (m, 2H, CH_2), 3.78 (s, 3H, CH_3), 3.09-3.05 (m, 1H, CH_2), 3.00-2.96 (m, 1H, CH_2). ^{13}C NMR (125.76 MHz, CD_3OD): δ = 173.9, 159.8, 131.4, 128.8, 127.3, 120.4, 113.7, 65.2, 54.5, 40.5. IR (cm^{-1}): 3379, 3110, 3043, 2359, 1613, 1592, 1518, 1378, 1264, 1185, 821, 603. HRMS (ESI-TOF) calcd. for $C_{12}H_{15}NO_3 + H^+$: 222.1124; Found: 222.1126. HPLC: Chirobiotic T, MeOH-H_2O (50:50), 210 nm, 0.7 ml/min. t_r = 7.1 and 12.9 min.

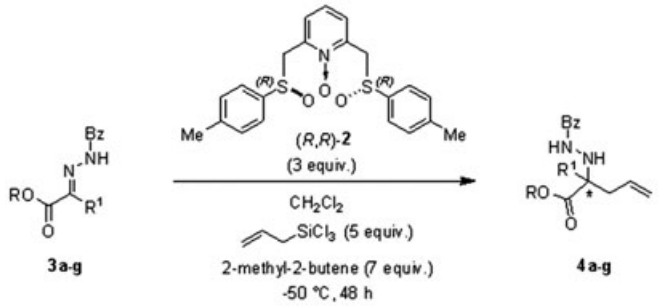
RESULTS AND DISCUSSION

Asymmetric Allylation of Prochiral Hydrazones 3a-g

Initially, the asymmetric allylation of the *N*-benzoyl hydrazone **3a** with allyltrichlorosilane was attempted in the presence of 3 equivalents of bis-sulfoxide (*R*,*R*)-**2** at −78 °C in CH_2Cl_2. However, under these reaction conditions the desired product **4a** was not observed by TLC even after 48 h (Table 1, entry 1). To obtain the desired *N*-benzoyl hydrazine, the temperature was raised to −50 °C, which led to the formation of product **4a** in 31% yield with excellent enantioselectivity, 98% ee (Table 1, entry 2). Motivated by this result, we next examined the scope of the reaction with a variety of α-keto ester derived *N*-benzoyl hydrazones **4b-g**, and the results are collected in Table 1.

As shown in Table 1, the anticipated products **4a-g** were obtained in 18 to 93% yield and with enantiomeric excesses ranging from 36–98%. In those cases proceeding in low yield, the starting material was recovered unchanged. The best enantioselectivities (ee = 96–98%) were obtained with hydrazones derived from methyl aryl-glyoxylates (Table 1, entries 2–6). The configuration of the major enantiomer of the *N*-benzoyl hydrazine **4a** was assigned as (*S*) by comparison of its optical rotation with that already assigned in the literature for the (*R*)-enantiomer.[112] By contrast, substrates **3f** and **3g**, which do not present an aromatic substituent at the imine carbon, afforded products **4f** and **4g** of low enantiopurity, probably because the steric hindrance introduced by the aryl substituent has a beneficial effect on the stereodifferentiation process at the transition state (Table 1, entries 7 and 8).

TABLE 1. Allylation of *N*-benzoylhydrazones 3a-g with allyltrichlorosilane under (*R,R*)-2 catalysis

Entry	Product	R	R^1	Yield (%)	% ee[a]
					
1[b]	**4a**	Me	Ph	—	—
2	**4a**	Me	Ph	31	98[c]
3	**4b**	Me	4-MeOPh	50	96
4	**4c**	Me	2-Naphtyl	25	98
5	**4d**	Me	4-MePh	35	96
6	**4e**	Me	4-BrPh	18	98
7	**4f**	Et	Me	64	58
8	**4g**	Et	H	93	36

[a]The enantiomeric excess was determined by chiral HPLC.
[b]At −78 °C.
[c]The absolute configuration of compound **4a** was assigned as (*S*) with base on literature precedent (Ref. 112).

In an attempt to improve the observed yields, reaction times were increased using *N*-benzoylhydrazone **3a** as a model substrate. Indeed, entries 6–8 in Table 2 show a direct correlation between reaction time and yield. Best results were found after 6 days of reaction at −50 °C.

With these precedents, monosulfoxide (*R*)-**1** was then evaluated as chiral promoter, under the best reaction conditions discovered for bis-sulfoxide (*R,R*)-**2** (Table 2). Nevertheless, six equivalents of (*R*)-**1** were required to achieve good yield (47%), while maintaining good enantiomeric excess (Entry 17 in Table 2).

When hydrazone **3a** was treated with allyltrichlorosilane in the presence of chiral sulfoxide (*R*)-**1** in 10 ml of anhydrous solvent (that is, under more diluted conditions) the desired product was not observed (Entry 11 in Table 2). Interestingly, decreasing the amount of solvent to 3 ml afforded the desired product in 70% yield and 76% ee (Entry 12 in Table 2).

With respect to the recyclability of bis-sulfoxide/*N*-oxide (*R,R*)-**2**, it is worth mentioning that this promoter can be recovered (75–85% recovery) and reused up to six times with no loss of enantiomeric purity.

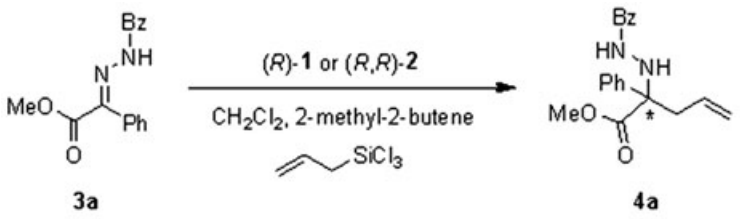
On the other hand, enantiomerically pure α-allyl α-amino acids have previously been prepared by enzymatic resolution[97,115] or by diastereoselective alkylation of chiral α-iminoesters.[116,117] In this work, (*S*)-*N*-benzoyl hydrazines **4a-b** were converted to the corresponding amino esters **5a-b** by treatment with excess SmI_2. Finally, the (*S*)-amino esters **5a-b** were hydrolyzed with LiOH to obtain the desired α-allyl α-amino acids **6a-b** related to L-phenylglycine in 54–55% yield and with very high enantiopurity (Scheme 4). The levorotatory optical activity of **6a** agrees in sign (although not in magnitude) with that reported in the literature for the (*S*)-enantiomer.[114] Thus, chemical correlation (conversion of (*S*)-**4a** to (*S*)-**6a** with retention of configuration, Scheme 4) confirms the assignment of configuration for the major product of the asymmetric allylation reported herein.

Electronic Circular Dichroism

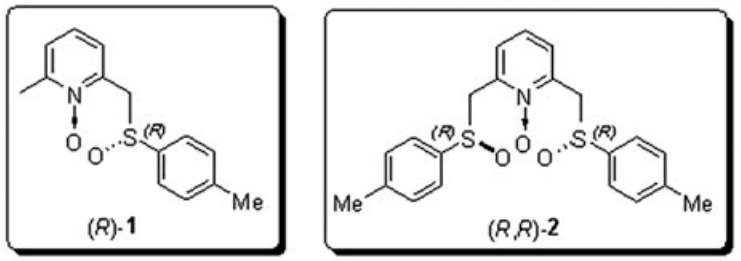
Electronic circular dichroism (ECD) is regarded as one of the most powerful techniques for the assignment of the absolute configuration (AC) of chiral compounds, principally because of its high sensitivity to the tridimensional orientation of the chromophores present in the chiral molecule.[118,119] In principle, chiral compounds with the same or similar chromophores and stereochemical environment exhibit similar ECD spectra, which is the basis for the assignment of the AC of a new chiral molecule that can be compared with those whose absolute configuration is known.[119,120] For example, Aimi and coworkers established the AC of several oxoindoles by comparison of their ECD spectra with those of known oxytryptophan derivatives.[121] In similar fashion, Tomasini and coworkers were able to establish the absolute configuration of a group of aromatic ring-substituted chiral isatins by comparison of their ECD spectra with those from known hydroxytryptophan derivatives.[122–124]

In this context, in 2004 Leighton and coworkers synthesized compound **4a** of (*R*) configuration and reported an optical rotation equal to −36.0 ($[\alpha]_D = -36.0$; *c* 1.15, $CHCl_3$),[112] which is opposite in sign to that obtained by us. Therefore, it is concluded that we had obtained (*S*) configured allylated α-allyl benzoylhydrazinyl keto ester derivative (*S*)-**4a**. Furthermore, one can anticipate that derivatives presenting similar ECD spectra should have the same configuration. Indeed, compounds **4b-e** were analyzed by ECD spectroscopy in MeCN and MeOH and the resulting spectra were compared with the ECD spectra of (*S*)-**4a**. Spectra of similar shape were recorded in both solvents (Figure 1). Allylated derivatives **4a-c** and **4e** exhibit similar negative Cotton effects in the long-wave region (300–230 nm) and a positive effect in the short-wave region (230–200 nm) in methanol, which suggests that all of them have the same stereochemistry; i.e., an (*S*) configuration.

TABLE 2. Allylation of *N*-benzoylhydrazone 3a with allyltrichlorosilane in the presence of (*R*)-1 and (*R,R*)-2 catalysts and under different reaction conditions



3a **4a**



Entry	Promoter	Promoter equivalents	Temp. (°C)	Allylsilane/butene equivalents	CH_2Cl_2 volume (ml)	Time (days)	Yield (%)	ee[a] (%)
1[b]	(*R,R*)-**2**	1	−50	2/6	2	3	—[c]	—
2[b]	(*R,R*)-**2**	1	−50	2/6	3	3	15	91
3[b]	(*R,R*)-**2**	3	−50	2/6	2	3	—[c]	—
4[b]	(*R,R*)-**2**	3	−50	2/6	5	3	17	95
5[d]	(*R,R*)-**2**	3	−24	5/7	2	3	—[e]	—
6[d]	(*R,R*)-**2**	3	−50	5/7	2	2	31	98
7[d]	(*R,R*)-**2**	3	−50	5/7	2	3	37	96
8[d]	(*R,R*)-**2**	3	−50	5/7	2	6	45	98
9[d]	(*R,R*)-**2**	3	−50	5/7	2	8	39	98
10[d]	(*R*)-**1**	3	−24	5/7	2	3	—[e]	—
11[b]	(*R*)-**1**	3	−50	5/7	10	6	—	—
12[b]	(*R*)-**1**	3	−50	5/7	3	6	70	76
13[b]	(*R*)-**1**	1	−50	2/6	3	3	61	85
14[b]	(*R*)-**1**	3	−50	2/6	3	3	40	87
15[d]	(*R*)-**1**	1	−50	5/7	2	3	20	88
16[d]	(*R*)-**1**	3	−50	5/7	2	3	45	90
17[d]	(*R*)-**1**	6	−50	5/7	2	3	47	94

[a]The enantiomeric excess was determined by chiral HPLC.
[b]These reactions were carried out with 0.65 mmol of hydrazone.
[c]It is observed low solubility of the promoter under these conditions.
[d]These reactions were carried out with 0.13 mmol of hydrazone.
[e]Decomposition of the promoter was observed at this temperature.

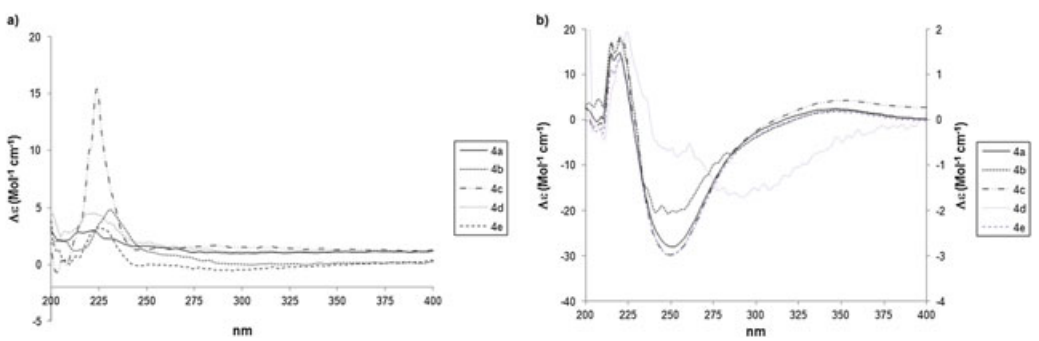


Fig. 1. Superimposed CD spectra of compounds **4a-e**. **a)** 5 mM in MeCN, 20 °C; **b)** 5 mM in methanol, 20 °C.

In the case of compound **4d**, the assignment is more tenuous due to its relatively flat, featureless ECD spectrum.

CONCLUSION

Chiral sulfoxides/*N*-oxides (*R*)-**1** and (*R,R*)-**2** are effective promoters in the enantioselective allylation of prochiral *N*-benzoylhydrazones derived from α-keto esters with allyltrichlorosilane. Enantiomerically pure α-allyl α-amino acids **6a-b** were readily prepared from **4a-b** via simple and mild synthetic procedures. The application of chemical correlation strategies, as well as ECD methodology, permitted the assignment of the (*S*) configuration of the allylated products.

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