A Novel Highly Stereoselective Synthesis of 2,3-Disubstituted *3H*-Quinazoline-4-one Derivatives

Paul Zhichkin*[†], Edward Kesicki[‡], Jennifer Treiberg[‡], Lisa Bourdon[†], Matthew Ronsheim[†], Hua Chee Ooi[‡], Stephen White[‡], Angela Judkins[‡], and David Fairfax[†].

Albany Molecular Research, Inc., 21 Corporate Circle P.O. Box 15098, Albany, New York, 12212 and ICOS Corp., 22021 20th Ave SE, Bothell, WA, 98021.

pavelz@albmolecular.com

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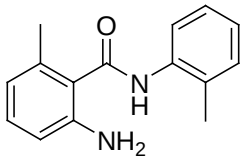
General: Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton and carbon nuclear magnetic resonance spectra were obtained on a Bruker AC 300, Bruker AV 300 or Bruker DPX 300 spectrometer at 300 MHz for proton and 75 MHz for carbon, or on a Varian Mercury VX 400 spectrometer at 400 MHz for proton and 100 MHz for carbon, or on a Bruker AMX 500 spectrometer at 500 MHz for proton and 125 MHz for carbon. Spectra are given in ppm (δ) and coupling constants, *J*, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton and carbon spectra. High resolution mass spectra were obtained on a TOF mass spectrometer using electrospray ionization at the Center for Functional Genomics, University at Albany (Albany, NY). Elemental analyses were performed by Quantitative Technologies, Inc. (Whitehouse, NJ).

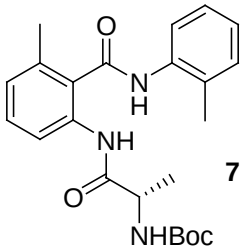
Synthesis of 2-amino-6-methyl-*N*-*o*-tolylbenzamide (1).



1

6-Methylanthranilic acid (10.0 g, 66.2 mmol) was heated at reflux with a mixture of thionyl chloride (20 mL, 32.6 g, 274 mmol) and toluene (100 mL). After 1 h the reaction was concentrated in vacuo, and the resulting residue was dissolved in THF (100 mL). *o*-Toluidine (21 mL, 21.0 g, 196 mmol) was added dropwise maintaining the internal temperature at 5–10 °C. The reaction mixture was then heated at reflux for 18 h. After this time the reaction mixture was cooled to ambient temperature, quenched with 10% aqueous K_2CO_3 (100 mL) and stirred vigorously for 15 min. The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure. The resulting solid was purified by flash chromatography on silica gel eluting with a gradient from 10:90 to 70:30 ethyl acetate/hexanes to afford **1** (14.5 g, 91%) as a light off-white solid: mp 110-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.9 Hz, 1H), 7.37 (br s, 1H), 7.27-7.20 (m, 2H), 7.13-7.04 (m, 2H), 6.61 (d, *J* = 1.5 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 4.14 (br s, 2H), 2.43 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.69, 144.9, 135.4, 135.3, 130.7, 130.3, 129.4, 126.8, 125.5, 123.2, 122.9, 120.4, 114.0, 20.3, 18.1. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.72; H, 6.80; N, 11.53.

Synthesis of *tert*-butyl (*S*)-1-[3-methyl-2-(*o*-tolylcarbamoyl)phenylamino]-1-oxopropan-2-ylcarbamate (7).

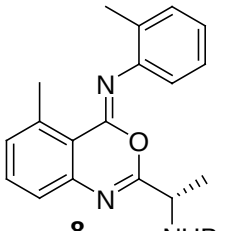


7

A solution of **1** (2.40 g, 10.0 mmol), Boc-L-alanine (2.06 g, 10.5 mmol) and 1-hydroxy-7-azabenzotriazole (1.36 g, 10.0 mmol) in DMF (16 mL) was treated with 1-ethyl-3-[3-dimethylamino)propyl]carbodiimide hydrochloride (2.50 g, 13.0 mmol), and the reaction was stirred for 18 h at room temperature. After this time the solvent was evaporated in vacuo (0.3 mmHg) at 40 °C on a rotary evaporator. The resulting residue was suspended

in a mixture of water (100 mL) and CH_2Cl_2 (20 mL), and the suspension was filtered. The filter cake was washed with CH_2Cl_2 (10 mL) followed by 10% aqueous K_2CO_3 (10 mL) and water (2 × 10 mL) and dried in vacuo to afford **7** (2.72 g, 66%) as a white solid: mp 190-192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.86 (s, 1H), 9.26 (s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.18-7.08 (m, 5H), 4.11 (br t, J = 6.9 Hz, 1H), 2.43 (s, 3H), 2.28 (s, 3H), 1.33 (s, 9H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.0, 165.9, 155.3, 135.8, 135.0, 134.7, 132.5, 130.5, 130.3, 128.9, 126.4, 126.1, 125.8, 125.7, 120.7, 78.3, 50.7, 28.1, 19.8, 18.2, 17.7. HRMS Calcd for $C_{23}H_{29}N_3O_4$+H: 412.2236. Found: 412.2239.

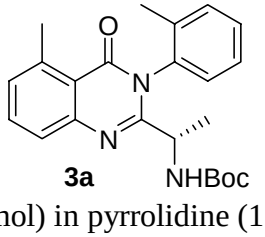
Synthesis of *tert*-butyl (*S*)-1-(5-methyl-4-(*o*-tolylimino)-4*H*-benzo[d][1,3]oxazin-2-yl)ethylcarbamate (8).



8

Bromine (125 μL, 390 mg, 2.43 mmol) was added to a solution of PPh_3 (630 mg, 2.40 mmol) in CH_2Cl_2 (12 mL). The solution was stirred for 30 min, and triethylamine (0.84 mL, 0.613 g, 6.07 mmol) was added followed by **6** (822 mg, 2.00 mmol). Boiling of the solvent was observed as a result exothermic reaction. After the exotherm subsided, the reaction was heated at reflux for a further 1.5 h. After this time the solution was cooled to room temperature and extracted with saturated aqueous $NaHCO_3$ (2 × 25 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel eluting with 50% solution of ethyl acetate in hexanes containing 1% triethylamine to give **8** (786 mg, 26%) as a brown wax: mp 47-50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, J = 7.7 Hz, 1H), 7.29-7.21 (m, 3H), 7.17 (t, J = 8.0 Hz, 1H), 7.02 (td, J = 7.4, 1.2 Hz, 1H), 6.92 (dd, J = 8.9, 1.0 Hz, 1H), 5.22 (br s, 1H), 4.39 (br t, J = 6.5 Hz, 1H), 2.85 (s, 3H), 2.22 (s, 3H), 1.44 (s, 9H), 1.32 (d, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 154.9, 144.7, 144.5, 143.5, 140.6, 132.5, 131.4, 130.3, 129.2, 126.1, 124.5, 123.8, 120.3, 117.6, 79.8, 48.5, 28.4, 24.2, 19.6, 18.4. HRMS Calcd for $C_{23}H_{27}N_3O_3$+H: 394.2130. Found: 394.2130.

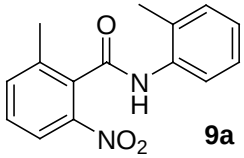
Conversion of 8 into *tert*-butyl (*S*)-1-(5-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3a).



3a

A solution of **8** (194 mg, 0.494 mmol) in pyrrolidine (1.0 mL) was stirred overnight at room temperature. After this time the solvent was evaporated; the resulting residue was dissolved in isopropyl acetate (20 mL), and the solvent was evaporated again. A 1% solution of acetic acid in acetonitrile (10 mL) was added, and the mixture was refluxed for 30 min. The reaction was then concentrated to a residue, which was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford **3a** (104 mg, 94%) with 96% ee. For the general procedure of ee determination and characterization of **3a** see the general procedure below.

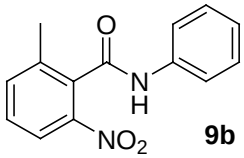
Synthesis of 2-methyl-6-nitro-*N*-*o*-tolylbenzamide (9a).



9a

A mixture of 2-methyl-6-nitrobenzoic acid (2.00 g, 11.0 mmol), toluene (15 mL) and thionyl chloride (3.0 mL, 4.89 g, 41.0 mmol) was heated at reflux for 2 h. The reaction was then concentrated at 45 °C under reduced pressure, and THF (30 mL) was added to the resulting residue, followed by *N*,*N*-diisopropylethylamine (5.0 mL, 3.7 g, 28.7 mmol) and *o*-toluidine (1.2 mL, 1.2 g, 11.2 mmol). After the exothermic reaction subsided, the reaction mixture was stirred at ambient temperature for a further 2 h. The solution was treated with 10% aqueous K_2CO_3 (30 mL); the THF layer was separated, washed with brine and evaporated in vacuo. The solid residue was triturated with 2:1 ethyl acetate/hexanes (20 mL) and dried under vacuum to afford **9a** (2.66 g, 89%) as a light brown solid. The obtained material contained 10% by weight of *N*,*N*-diisopropylethylamine hydrochloride. A small sample was recrystallized from toluene and characterized: mp 121-122 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H); 7.76 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.25 (m, 2H), 7.15 (t, *J* = 7.4, 1H), 2.49 (s, 3H, overlaps with DMSO signal), 2.27 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.2, 145.9, 137.2, 136.2, 135.6, 132.8, 132.3, 130.4, 129.5, 126.0, 125.8, 125.4, 121.8, 18.7, 17.8. Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.36; H, 5.13; N, 10.26.

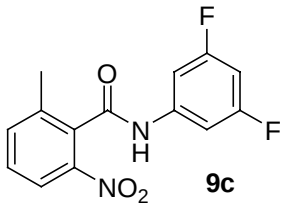
Synthesis of 2-methyl-6-nitro-*N*-phenylbenzamide (9b).



9b

A mixture of 2-methyl-6-nitrobenzoic acid (8.00 g, 44.0 mmol), toluene (95 mL) and thionyl chloride (33.0 mL, 22.0 g, 185 mmol) was heated at reflux for 2 h. The reaction was then concentrated at 45 °C under reduced pressure, and THF (80 mL) was added to the resulting acid chloride. With cooling in an ice/water bath, *N*,*N*-diisopropylethylamine (23 mL, 17.0 g, 132 mmol) and aniline (4.0 mL, 4.1 g, 44.0 mmol) were added. After this addition was complete, the reaction mixture was stirred at ambient temperature overnight. The mixture was then concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL). This solution was washed with 10% aqueous citric acid (100 mL), dried over Na_2SO_4 and concentrated in vacuo to afford **9b** (11.3 g, quantitative yield) as an off-white solid: mp 146-148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.76–7.60 (m, 3H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.3, 146.2, 139.2, 137.6, 136.7, 133.0, 130.1, 129.2, 124.3, 122.2, 120.0, 19.0; Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.63; H, 4.43; N, 10.79.

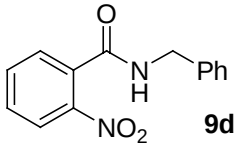
Synthesis of *N*-(3,5-difluorophenyl)-2-methyl-6-nitrobenzamide (9c).



9c

Following the procedure for the preparation of **9b**, the acid chloride prepared from 2-methyl-6-nitrobenzoic acid (10.0 g, 55.0 mmol) was reacted with 3,5-difluoroaniline (7.10 g, 55.0 mmol) in refluxing THF for 6 h. Final purification by flash chromatography on silica gel, eluting with 25% ethyl acetate in hexanes, afforded **9c** (9.28 g, 58%) as a brown solid: mp 158-160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.36 (dd, J = 2.2, 9.5 Hz, 2H), 7.00 (tt, J = 9.4, 2.3 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.5, 162.5 (dd, J = 243.6, 15.2 Hz), 145.6, 141.1 (t, J = 13.6 Hz), 137.3, 136.6, 131.9, 130.1, 121.9, 102.3 (dd, 19.3, 9.9 Hz), 99.1 (t, J = 26.1), 18.4. Anal. Calcd for $C_{14}H_{10}F_2N_2O_3$: C, 57.54; H, 3.45; N, 9.59. Found: C, 57.71; H, 3.48; N, 9.55.

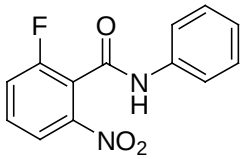
Synthesis of *N*-benzyl-2-nitrobenzamide (9d).[1]



9d

Benzylamine (13 mL, 12.7 g, 119 mmol) was added dropwise to a solution of 2-nitrobenzoyl chloride (10.0 g) in CH_2Cl_2 (100 mL), maintaining the internal temperature at 15–25 °C. The reaction was then stirred at ambient temperature for 30 min and diluted with water (100 mL). The organic layer was separated, extracted with 10% aqueous citric acid (100 mL) followed by saturated aqueous $NaHCO_3$ (100 mL), dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was dissolved in toluene (50 mL) at 70 °C, and this solution was then cooled to room temperature. Hexanes (100 mL) were added, and the suspension was cooled to 0 °C and filtered. The filter cake was dried in vacuo to afford **9d** (11.5 g, 84%) as a light brown solid: mp 121-122 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (t, J = 5.7 Hz, 1H), 8.04 (dd, J = 7.9, 1.0 Hz, 1H), 7.80 (td, J = 7.4, 1.1 Hz, 1H), 7.72-7.64 (m, 2H), 7.36 (m, 4H), 7.27 (m, 1H), 4.46 (d, J = 6.0 Hz, 2H).

Synthesis of 2-fluoro-6-nitro-*N*-phenylbenzamide (9f).



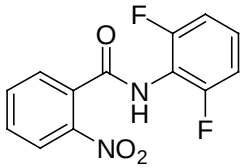
9f

2-Fluoro-6-nitrobenzoic acid (100 g, 0.540 mol) was suspended in a mixture of DMF (5 mL) and CH_2Cl_2 (600 mL). A 2 M solution of oxalyl chloride in CH_2Cl_2 (410 mL, 0.820 mol) was added dropwise over 30 min. After 1 h an aliquot was removed and analyzed by ^{1}H NMR spectroscopy. The spectroscopy showed that complete conversion to the acid chloride had occurred. The reaction mixture was concentrated under reduced pressure to give an orange syrup, which contained a small amount of solid material. The acid chloride was used in the next reaction without additional purification.

A mixture of aniline (49 mL, 50.2 g, 0.540 mol) and $NaHCO_3$ (90.0 g, 1.08 mmol) with 1,4-dioxane (250 mL) and water (250 mL) was cooled to 6 ºC in an ice bath. A solution of the acid chloride prepared above in 1,4-dioxane (80 mL) was added over 10 min.

During this addition the temperature reached a maximum of 27 ºC. The reaction mixture was stirred overnight and then quenched by addition of water (1.2 L). After stirring for an additional 15 min, the solid was collected by filtration, washed with water and dried in a vacuum oven at 50 ºC to give **9f** (139 g, 99%) as a beige solid: mp 163-165 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (br s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.81-7.88 (m, 1H), 7.79 (dd, J = 8.2, 5.8 Hz, 1H), 7.72 (dd, J = 8.4, 1.0 Hz, 2H), 7.41 (t, J = 8.0 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.1, 158.6 (d, J = 249.5 Hz), 146.4 (d, J = 5.3 Hz), 138.6, 131.8 (d, J = 9.2 Hz), 129.0, 124.3, 122.4 (d, J = 22.1 Hz), 121.7 (d, J = 23.7 Hz), 120.6 (d, J = 3.1 Hz), 119.6. Anal. Calcd for $C_{13}H_9FN_2O_3$: C, 60.00; H, 3.49; N, 10.77. Found: C, 59.91; H, 3.14; N, 10.68.

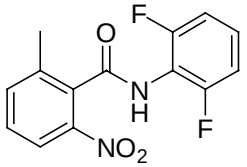
Synthesis of *N*-(2,6-difluorophenyl)-2-nitrobenzamide (9g).



9g

A solution of 2-nitrobenzoyl chloride (25.0 g, 135 mmol) in 1,4-dioxane (50 mL) was added dropwise to a solution of 2,6-difluoroaniline (36 mL, 43.5 g, 337 mmol) in 1,4-dioxane (350 mL). The resulting yellow suspension was stirred at ambient temperature overnight. After this time the reaction was diluted with water (400 mL) and stirred for 30 min. The solids were then collected by filtration, washed with water and dried in vacuo to afford **9g** (33.4 g, 97%) as a white solid: mp 184-186 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H); 8.15 (d, J = 8.0 Hz, 1H), 7.89 (dt, J = 7.5, 1.0 Hz, 1H), 7.83-7.74 (m, 2H); 7.48-7.37 (m, 1H), 7.22 (t, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.4, 157.8 (dd, J = 249.9, 5.0 Hz), 146.9, 133.9, 131.44, 131.40, 129.3, 128.6 (t, J = 9.5 Hz), 124.3, 113.7 (t, J = 16.8 Hz), 112.0 (dd, J = 17.9, 5.0 Hz). Anal. Calcd for $C_{13}H_8F_2N_2O_3$: C, 56.12; H, 2.90; N, 10.07; F, 13.66. Found: C, 56.22; H, 2.85; N, 10.07; F, 13.29.

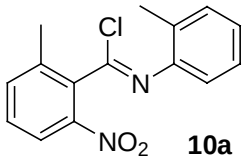
Synthesis of *N*-(2,6-difluorophenyl)-2-methyl-6-nitrobenzamide (9h).



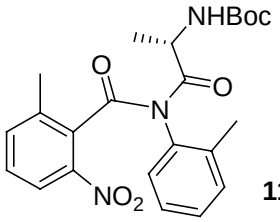
9h

Thionyl chloride (121 mL, 1.66 mol) was added dropwise to a solution of 2-nitro-6-methyl benzoic acid (100 g, 552 mmol) in THF (1.2 L), and the reaction was stirred at ambient temperature for 18 hours. After this time the mixture was concentrated in vacuo, and the resulting acid chloride was dissolved in 1,4-dioxane (250 mL). This solution was added dropwise to a solution of 2,6-difluoroaniline (178 mL, 214 g, 1.66 mol) in 1,4-dioxane (750 mL). The reaction was then stirred at ambient temperature overnight. Addition of water (1.2 L) resulted in a brown precipitate, which was collected by filtration, washed with water and dried in vacuo to afford **9h** (71.7 g, 45%) as a light brown solid: mp184-186 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (br s, 1H), 7.37 (br s, 1H), 8.06-8.04 (m, 1H), 7.76-7.74 (m, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.44-7.37 (m, 1H), 7.21 (t, J = 8.0 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 158.7 (dd, J = 250.3, 5.3 Hz), 146.7, 138.2, 137.0, 132.7, 130.6, 129.2 (t, J = 9.6 Hz), 122.5, 114.3 (t, J = 17.2 Hz), 112.7 (dd, J = 18.3, 4.6 Hz), 19.3. Anal. Calcd for $C_{14}H_{10}F_2N_2O_3$: C, 57.54; H, 3.45; N, 9.59. Found: C, 57.60; H, 3.08; N, 9.47.

Synthesis of 2-methyl-6-nitro-*N*-*o*-tolylbenzimidoyl chloride (10a) and *tert*-butyl (*S*)-1-(2-methyl-6-nitro-*N*-*o*-tolylbenzamido)-1-oxopropan-2-ylcarbamate (11a).



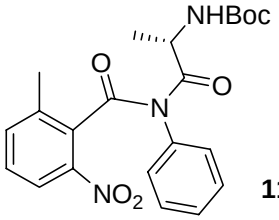
10a



11a

A mixture of **9a** (1.50 g, 5.55 mmol), toluene (15 mL), thionyl chloride (3.0 mL, 4.86 g, 40.8 mmol) and DMF (20 μL) was refluxed for 2.5 h. The resulting solution was concentrated under reduced pressure at 45 °C to afford crude **10a** as a yellow air-sensitive oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.25 (overlaps with $CHCl_3$ signal, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 2.62 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 145.2, 137.7, 136.3, 132.5, 130.6, 129.9, 129.1, 126.4, 125.8, 122.5, 119.2, 19.5, 18.0. This material was dissolved in CH_2Cl_2 (4.0 mL) and added to a solution of Boc-L-alanine (873 mg, 4.26 mmol) and *N*,*N*-diisopropylethylamine (1.5 mL, 1.1 g, 8.5 mmol) in CH_2Cl_2 (6 mL) at 0–5 °C. The reaction mixture was stirred for 1 h at this temperature and then warmed to room temperature overnight. The resulting solution was washed with 10% aqueous citric acid (2 × 15 mL) followed by saturated aqueous $NaHCO_3$ (10 mL), dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography on silica gel eluting with 20% ethyl acetate in hexanes afforded **11a** (1.80 g, 88%) as a light brown foam: mp 72-74 °C; according to the ^{1}H and ^{13}C NMR spectra the obtained material is a mixture of several rotamers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.2-8.0 (m, 1H), 7.8-7.2 (m, 6H), 5.02 (d, *J* = 8.9 Hz, 0.2H), 4.9-4.7 (m, 0.8H), 4.21 (br s, 0.6H), 4.05 (br s, 0.4H, overlaps with ethyl acetate signal), 2.52 (s, 0.6H), 2.48 (s, 3.5H), 2.45 (s, 1.5H), 2.38 (s, 0.4H), 1.27 (s, 9H), 1.18 (d, *J* = 6.9 Hz, 0.7H), 1.12 (d, *J* = 6.9 Hz, 1.4H), 1.04 (d, *J* = 6.9 Hz, 0.3H), 0.99 (d, *J* = 6.6 Hz, 0.6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 175.7, 175.6, 168.3, 168.0, 167.8, 155.4, 154.8, 154.4, 145.2, 144.9, 144.0, 138.6, 137.1, 136.5, 136.4, 136.3, 135.0, 134.1, 131.8, 130.1, 130.0, 129.9, 129.5, 129.2, 128.8, 128.7, 128.6, 128.4, 127.6, 127.4, 127.1, 122.2, 121.9, 121.8, 79.9, 79.8, 49.5, 49.1, 28.1, 21.0, 19.9, 19.7, 19.2, 19.1, 18.9, 18.5, 18.3, 18.1, 17.7, 17.6, 16.4. Anal. Calcd for $C_{23}H_{27}N_3O_6$: C, 62.57; H, 6.16; N, 9.52. Found: C, 62.59; H, 6.15; N, 9.49.

Synthesis of *tert*-butyl (*S*)-1-(2-methyl-6-nitro-*N*-phenylbenzamido)-1-oxopropan-2-ylcarbamate (11b).

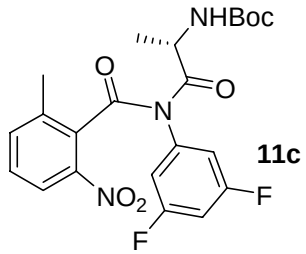


11b

The procedure for the preparation of **11a** has been followed, starting with **9b** (2.00 g, 7.81 mmol) and Boc-L-alanine (1.57 g, 8.28 mmol). Final purification by flash chromatography on silica gel eluting with a gradient from 100% hexanes to 50% ethyl acetate in hexanes, afforded **11b** (2.39 g, 80%) as an off-white solid: mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.61–7.43 (m, 8H), 4.87 (br m, 1H), 4.22 (br s, 1H), 2.45 (s, 3H), 1.38 (s, 9H), 1.21–1.10 (br m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 168.5, 155.2, 154.6, 144.7, 144.0, 136.3, 136.0, 135.1, 134.8, 130.0, 130.7, 129.2,

128.6, 121.7, 79.9, 49.4, 28.2, 18.9, 18.6, 17.2. Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.90; N, 9.83. Found: C, 61.81; H, 5.90; N, 9.77.

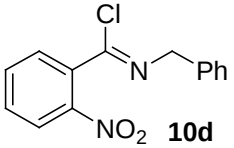
Synthesis of *tert*-butyl (*S*)-1-(*N*-(3,5-difluorophenyl)-2-methyl-6-nitrobenzamido)-1-oxopropan-2-ylcarbamate (11c).



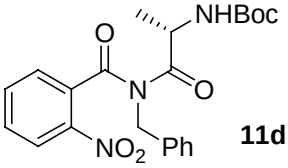
11c

The procedure for the preparation of **11a** has been followed, starting with **9c** (6.35 g, 21.7 mmol) and Boc-L-alanine (4.93 g, 26.0 mmol). Final purification by trituration with methanol afforded **11c** (6.35 g, 63%) as an off-white solid: mp 184-188 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br d, *J* = 5.6 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.45 (br t, *J* = 7.1 Hz, 1H), 7.30-6.90 (m, 3H), 5.00-4.65 (br m, 1H), 4.13 (br s, 1H), 2.45 (s, 3H), 1.38 (s, 9H), 1.25-1.00 (br m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 168.2, 163.4 (dd, *J* = 252.3, 14.9 Hz), 155.3, 144.5, 144.0, 138.5, 137.0, 136.4, 136.1, 134.5, 129.1, 128.8, 122.0, 121.8, 113.4 (d, *J* = 19.1 Hz), 105.8 (t, *J* = 25.5 Hz), 80.2, 49.4, 28.2, 18.9, 17.0. Anal. Calcd for $C_{23}H_{27}N_3O_6$: C, 57.02; H, 5.00; N, 9.07. Found: C, 57.25; H, 4.70; N, 9.04.

Synthesis of *N*-benzyl-2-nitrobenzimidoyl chloride (10d) and *tert*-butyl (*S*)-1-(*N*-benzyl-2-nitrobenzamido)-1-oxopropan-2-ylcarbamate (11d).



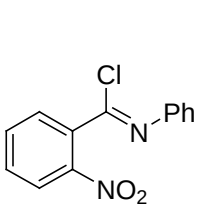
10d



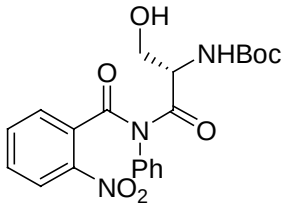
11d

Following the procedure for the preparation of **10a**, **9d** (2.56 g, 10.0 mmol) was converted into crude **10d** (2.87 g, >100%) as a yellow air-sensitive oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.9 Hz, 1H), 7.66 (m, 2H), 7.59 (m, 1H), 7.58-7.25 (m, 5H), 4.89 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 138.6, 137.1, 133.2, 130.9, 130.3, 128.6, 127.9, 127.4, 124.4, 58.1. Crude **10d** (550 mg, 2.00 mmol) was then reacted with Boc-L-alanine (400 mg, 2.12 mmol) following the procedure for the preparation of **11a**. Purification by flash chromatography on silica gel eluting with 33% ethyl acetate in hexanes afforded **11d** (611 mg, 74% over two steps) as a light brown foam: mp 55-58 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.8 Hz, 1H), 7.56 (m, 2H), 7.28 (m, 3H), 7.18 (br m, 3H), 5.07 (br m, 4H), 1.43 (s, 9H), 1.25 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 169.3, 155.2, 144.5, 136.2, 134.2, 130.0, 128.8, 128.0, 127.7, 127.0, 126.9, 124.5, 80.0, 50.6, 48.3, 28.3, 18.1. Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.90; N, 9.83. Found: C, 61.53; H, 6.06; N, 9.55.

Synthesis of 2-nitrobenzimidoyl chloride[2] (10e) and *tert*-butyl (*S*)-3-hydroxy-1-(2-nitro-*N*-phenylbenzamido)-1-oxopropan-2-ylcarbamate (11e).



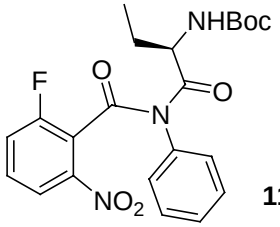
10e



11e

N-Benzyl-2-nitrobenzamide (6.70 g, 27.7 mmol) was converted into crude **10e** (6.55 g, 91%) as a yellow air-sensitive oil as described above for the preparation of **10a**. A small sample of **10e** was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.81-7.71 (m, 2H), 7.63 (td, *J* = 7.7, 1.5 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H, overlaps with $CHCl_3$ signal), 7.09 (d, *J* = 7.7 Hz, 2H). Crude **10e** (977 mg, 3.74 mmol) was then reacted with Boc-L-serine (400 mg, 2.12 mmol) using the procedure for the preparation of **11a**. Purification by flash chromatography on silica gel eluting with 60% ethyl acetate in hexanes afforded **11e** (572 mg, 40% over two steps) as a yellow oil, which decomposes when stored at room temperature: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.52-7.36 (m, 7H), 5.41 (br d, *J* = 6.7 Hz, 1H), 4.90 (m, 1H), 3.99-3.92 (m, 1H), 3.86-3.78 (m, 1H), 2.02 (m, 1H, overlaps with EtOAc signal), 1.42 (s, 9H). HRMS Calcd for $C_{21}H_{23}N_3O_7$+H: 430.1614. Found: 430.1633.

Synthesis of *tert*-Butyl (*R*)-1-(2-fluoro-6-nitro-*N*-phenylbenzamido)-1-oxobutan-2-ylcarbamate (11f).



11f

Thionyl chloride (7.25 mL, 100 mmol) followed by DMF (0.05 mL) were added to **9f** (5.20 g, 20.0 mmol). The reaction mixture was then heated to reflux for 1.5 h. After this time the reaction was cooled to room temperature and concentrated under reduced pressure. Toluene (3 × 50 mL) was added and removed three times under reduced pressure to give the crude imidoyl chloride **10f** as a dark brown gum. Because of its instability, **10f** was used directly in the next step without purification or characterization.

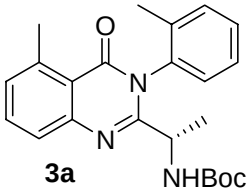
A solution of the **10f** prepared above in CH_2Cl_2 (20 mL) was added over 15 min to a solution of Boc-D-α-Abu-OH (4.47 g, 22.0 mmol) and triethylamine (3.1 mL, 2.22 g, 22.0 mmol) in CH_2Cl_2 (20 mL) at 0 ºC. Once this addition was complete, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After 23 h at room temperature, additional Boc-D-α-Abu-OH (2.03 g, 10 mmol) and a solution of triethylamine (1.4 mL, 1.01 g, 10.0 mmol) in CH_2Cl_2 (10 mL) were added. After an additional 2 h, the reaction mixture was filtered and the filtrate was washed with 0.1 M aqueous hydrochloric acid (3 × 50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL) and water (3 × 50 mL). The organic layer was then dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The resulting brown foam was suspended in toluene and the insoluble material was filtered off. The filtrate was purified by flash chromatography on silica gel, eluting first with toluene, then with 22% ethyl acetate in hexanes and finally with 50% ethyl acetate in hexanes to give **11f** (4.88 g, 55%) as a pale yellow solid: mp 118-120 ºC; the ^{1}H and ^{13}C NMR spectra indicated a mixture of

rotamers; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.0 Hz, 1H), 7.85-7.80 (m, 1H), 7.76-7.71 (m, 1H), 7.56-7.37 (m, 5H), 7.21 (d, J = 7.4 Hz, 0.8H), 6.83 (br s, 0.2H), 4.10 (br s, 1H), 1.70 (br s, 1H), 1.45 (br s, 1H), 1.39 (s, 1.8H), 1.35 (s, 7.2H), 0.72 (br s, 3H), ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.2, 174.1, 163.4, 158.9, 158.3, 155.7, 154.5, 144.4, 138.5, 136.3, 131.5, 129.7, 129.5, 128.9, 128.7, 124.2, 122.6 (d, J = 21.4 Hz), 122.3, 120.5, 119.5, 78.9, 78.3, 77.9, 55.9, 28.2, 28.1, 24.2, 23.2, 10.6. Anal. Calcd for $C_{22}H_{24}FN_3O_6$: C, 59.32; H, 5.43; N, 9.43. Found: C, 59.53; H, 5.29; N, 9.51.

General procedure for ee determination for compounds 3a-3d and 3g-3h.

Compound **3** (0.2 mmol) was dissolved in a mixture of CH_2Cl_2 (0.5 mL) and trifluoroacetic acid (0.5 mL). After stirring for 30 min, the solvents were evaporated under reduced pressure at room temperature. (Note: Prolonged exposure of the quinazoline to strong acids causes partial racemization, and the time of contact with such acids should be minimized.) The residue was dissolved in CH_2Cl_2 (10 mL), and the solution was extracted with 10% aqueous K_2CO_3 (10 mL). The organic layer was then separated, dried over Na_2SO_4 and concentrated in vacuo. A 3-mg sample of the resulting amine was dissolved in $CHCl_3$ (0.7 mL), and (*R*)-1-(1-naphthyl)ethyl isocyanate (3 μL) was added. Another 3-mg sample was similarly reacted with racemic 1-(1-naphthyl)ethyl isocyanate. After 18 h at room temperature the HPLC traces of both samples were compared. HPLC analyses were obtained using a Hypersil 5μ C18 BDS column (250 x 4.6 mm, Phenomenex), 1 mL/min flow and UV detection at 254 nm. Isocratic 60:40 acetonitrile/0.1% TFA in water method was used for the samples derived from **3a**,**c** and **d** and isocratic 50:50 acetonitrile/0.1% TFA in water method was used for the samples derived from **3b**,**g** and **h**. (Note: In the case of **3a**, HPLC peak of the excess 1-(1-naphthyl)ethyl isocyanate overlapped with the peaks of the reaction products. Ethanolamine (30 μL) was added in order to quench the isocyanate, and after 2 h the HPLC analysis was conducted again.)

Synthesis of *tert*-butyl (*S*)-1-(5-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3a).

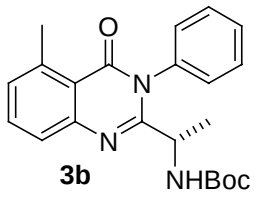


3a

A flask with a suspension of zinc powder (650 mg, 10.0 mmol) in acetic acid (4.0 mL) was placed in a water bath (20 °C), and **3a** (441 mg, 1.00 mmol) was added. After the initial heat evolution, the reaction mixture was stirred at room temperature for 3.5 h. After this time the mixture was filtered, and the filter cake was washed with acetic acid (2 × 2 mL) followed by CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated in vacuo, and the resulting residue was dissolved in CH_2Cl_2 (10 mL). The solution was washed with saturated $NaHCO_3$ (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford **3a** (228 mg, 58%) as a white solid: mp 130-137 °C; $[\alpha]_D$ = -10.3° (*c* 0.14, MeOH, 25 °C), >99% ee; according to the ^{1}H and ^{13}C NMR spectra, the obtained material is a mixture of two atropisomers in 60:40 ratio: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (td, J = 7.7, 2.7 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.40 (m, 3H), 7.29 (br s, 0.4H), 7.24 (d, J = 7.2 Hz, 1H), 7.16 (d, J = 8.5 Hz, 0.6H), 5.74 (m, 1H), 4.57 (br t, J = 6.7 Hz, 0.4H), 4.32 (quintet, J = 6.9 Hz, 0.6H), 2.83 (s, 3H), 2.15 (s, 1.2H), 2.13 (s, 1.8H), 1.42

(s, 9H), 1.30 (d, *J* = 6.6 Hz, 1.8H), 1.18 (d, *J* = 6.7Hz, 1.2H); NMR (125 MHz, $CDCl_3$) δ 162.2, 161.9, 157.6, 157.2, 154.7, 154.6, 148.9, 148.8, 141.8, 136.2, 136.1, 133.7, 132.0, 131.4, 129.8, 129.65, 129.61, 128.7, 128.6, 127.8, 127.2, 125.0, 119.6, 119.4, 79.6, 47.6, 28.41, 28.37, 23.06, 23.04, 21.4, 20.0, 17.8, 17.5. Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 70.19; H, 6.92; N, 10.68.

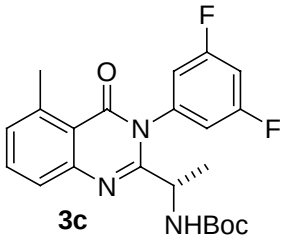
Synthesis of *tert*-butyl (*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3b).



3b

To zinc powder (3.82 g, 58.8 mmol) suspended in acetic acid (10 mL) a solution of **11b** (1.50 g, 3.92 mmol) in acetic acid was added portionwise over 1 h. After 2 h at room temperature, more zinc powder (1.27 g, 19.5 mmol) was added, and the reaction was stirred for a further 1 h. The procedure for the preparation of **3a** was then followed. Final purification by flash chromatography on silica gel eluting with a gradient from 100% hexanes to 40% ethyl acetate in hexanes, afforded **3b** (900 mg, 60%) as a white solid: mp 164–166 ºC; $[\alpha]_D$ = -4.63° (*c* 0.2, MeOH, 25 °C), 98% ee; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.48 (m, 5H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.29–7.19 (m, 2H, overlaps with $CHCl_3$ signal), 5.68 (br s, 1H), 4.50 (m, 1H), 2.82 (s, 3H), 1.42 (s, 9H), 1.26 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 149.2, 142.1, 136.7, 134.1, 130.8, 130.0, 129.8, 129.4, 129.0, 125.8, 119.9, 80.0, 48.1, 28.8, 23.4, 21.2; Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.43; H, 6.65; N, 10.82.

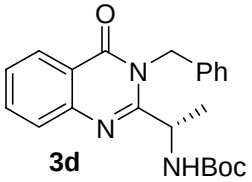
Synthesis of *tert*-butyl (*S)* 1-(3-(3,5-difluorophenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3c).



3c

To a solution of **11c** (1.00 g, 2.16 mmol) in acetic acid (30 mL), zinc powder (3.40 g, 52.3 mmol) was added. After stirring for 13 h, the procedure for the preparation of **3a** was followed. Final purification by flash chromatography on silica gel, eluting with 25% ethyl acetate in hexanes, afforded **3c** (357 mg, 40%) as a white solid: mp 151-153 ºC; $[\alpha]_D$ = +7.2° (*c* 0.13, MeOH, 25 °C), 94% ee; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (t, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 6.9 Hz, 1H, overlaps with $CHCl_3$ signal), 7.00 (m, 2H), 6.87 (d, *J* = 7.9 Hz), 5.51 (br d, *J* = 7.2 Hz, 1H), 4.47 (quintet, *J* = 7.0 Hz, 1H), 2.81 (s, 3H), 1.41 (s, 9H), 1.33 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (*J* = 251.7, 13.3 Hz), 163.2 (*J* = 251.7, 13.3 Hz), 162.4, 156.4, 154.8, 148.5, 141.7, 138.5 (t, *J* = 12.2 Hz), 134.08, 130.01, 125.6, 119.2, 113.0 (d, *J* = 23.5 Hz), 105.6 (t, *J* = 25.1 Hz), 79.9, 28.3, 23.0, 20.7; Anal. Calcd for $C_{22}H_{23}F_2N_3O_3$: C, 63.60; H, 5.58; N, 10.12. Found: C, 63.82; H, 5.61; N, 9.98.

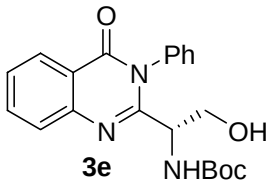
Synthesis of *tert*-butyl (*S*)-1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3d).



3d

11d (300 mg, 0.703 mmol) was reduced by zinc powder (450 mg, 7.03 mmol) in acetic acid (4 mL) using the procedure for the preparation of **3a**. Final purification by flash chromatography on silica gel eluting with 25% ethyl acetate in hexanes afforded **3d** (188 mg, 71%) as a white solid: mp 123-125 °C; $[\alpha]_D$ = -179.0° (*c* 0.11, MeOH, 25 °C), >99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.76 (td, *J* = 7.6, 1.2 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.32-7.26 (m, 5H, overlaps with $CHCl_3$ signal), 5.74 (d, *J* = 15.9Hz, 1H), 5.58 (d, *J* = 8.2 Hz, 1H), 5.33 (d, *J* = 15.8 Hz, 1H), 5.04 (quintet, *J* = 7.2 Hz, 1H), 1.43 (s, 9H), 1.22 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 158.2, 154.9, 147.0, 136.2, 134.4, 128.9, 127.8, 127.2, 127.1, 127.0, 120.7, 79.9, 47.5, 46.2, 28.4, 21.1. Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.39; H, 6.72; N, 10.85.

Synthesis of *tert*-butyl (*R*)-2-hydroxy-1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3e).

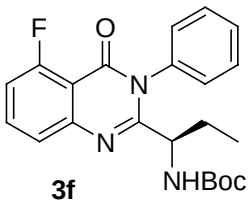


3e

Zinc powder (165 mg, 2.53 mmol) was added to a solution of **11e** (286 mg, 0.667 mmol) in acetic acid (3.5 mL), and the mixture was stirred for 6 h. The procedure for the preparation of **3a** was then followed. Final purification by flash chromatography on silica gel, eluting with 50% ethyl acetate in hexanes, afforded **3e** (145 mg, 57%) as a white solid: mp 80-83 °C, $[\alpha]_D$ = -6.7° (*c* 0.06, MeOH, 25 °C), 94% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.79 (t, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.59-7.51 (m, 4H), 7.35 (dd, *J* = 7.8, 2.2 Hz, 1H), 7.27 (m, 1H, overlaps with $CHCl_3$ signal), 5.58 (br s, 1H), 4.59 (br s, 1H), 3.86 (d, *J* = 11.2 Hz, 1H), 3.75 (m, 1H), 3.47 (br s, 1H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 155.2, 154.8, 146.3, 135.8, 134.8, 130.2, 129.9, 129.7, 129.1, 128.8, 128.3, 127.6, 127.3, 127.2, 121.3, 120.0, 80.2, 64.2, 52.3, 28.3. HRMS Calcd for $C_{21}H_{25}N_3O_4$+H: 382.1767. Found: 382.1778.

The ee of compound **3e** was determined as follows. A 4-mg sample of **3e** was reacted with (*S*)-2-methoxy-2-phenylacetyl chloride (10 μL) in CH_2Cl_2 (0.3 mL)/pyridine (0.1 mL). Another 4-mg sample was similarly reacted with racemic 2-methoxy-2-phenylacetyl chloride. After 5 h at room temperature, the HPLC traces of both samples were compared. HPLC analyses were obtained using a Hypersil 5μ C18 BDS column (250 x 4.6 mm, Phenomenex), 1 mL/min flow and UV detection at 254 nm. Isocratic 50:50 acetonitrile/0.1% TFA in water method was used.

Synthesis of *tert*-butyl (*R*)-1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propylcarbamate (3f).

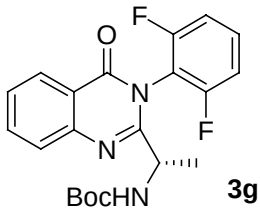


3f

11f (445 mg, 1.00 mmol) was dissolved in acetic acid (5 mL). Zinc dust (393 mg, 6.00 mmol) was added in three portions with 5 min intervals. Each addition was associated with a slight temperature increase (ranging from 3 to 6 ºC). After 17.5 h the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (15 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 15 mL), water (2 x 15 mL) and brine (15 mL). The organic solution was dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The resulting light brown foam was purified by flash chromatography on silica gel eluting with 17% ethyl acetate in hexanes to afford **3f** (267 mg, 67%) as a colorless solid: mp 114-116 ºC; 97% ee; the ^{1}H NMR spectrum indicated the presence of two rotational isomers (~9:1 ratio), which coalesce when the spectrum is acquired at 50 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (dt, *J* = 8.2, 5.8 Hz, 1H), 7.62-7.49 (m, 5H), 7.39 (br d, *J* = 8.2 Hz, 1H), 7.30 (dd, *J* = 10.7, 8.2 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 0.9H), 6.71 (br s, 0.1H), 3.97-3.92 (m, 1H), 1.76-1.68 (m, 1H), 1.59-1.48 (m, 1H), 1.33 (br s, 8.1H), 1.23 (br s, 0.9H), 0.63 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5 (d, *J* = 264.0 Hz), 159.1, 158.3 (d, *J* = 3.6 Hz), 155.5, 149.1, 136.0, 135.4 (d, *J* = 11.4 Hz), 129.6, 129.3, 129.1 (br s), 128.7, 123.0 (d, *J* = 4.0 Hz), 113.2, (d, *J* = 20.6 Hz), 110.2 (d, *J* = 5.3 Hz), 78.1, 54.1, 28.2, 25.7, 10.8. Anal. Calcd for $C_{22}H_{24}FN_3O_3$: C, 66.48; H, 6.09; N, 10.57. Found: C, 66.30; H, 5.96; N, 10.47.

The ee of compound **3f** was determined as follows. A sample of **3f** was analyzed by chiral HPLC and compared with a mixture of the R & S enantiomers which were analyzed under identical conditions. Chiralpak AD, 4.6 x 150 mm, 20ºC, 90:10 hexanes:isopropanol, 1 mL/min. The ee was calculated from the area under the respective peaks @ 230 nm and was determined to be >98%.

Synthesis of *tert*-butyl (*S*)-1-(3-(2,6-difluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3g).

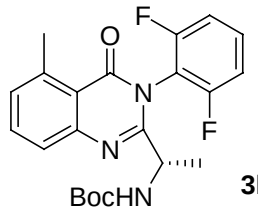


3g

To a suspension of **9g** (30.0 g, 108 mmol) in THF (300 mL) at 0 ^{o}C was added KHMDS (0.5M solution in toluene, 216 mL, 108 mmol). The reaction was then removed from the cooling bath and stirred for 10 min, after which time Boc-L-Ala-OSu (31.0 g, 108 mmol) was added. After 1 h at ambient temperature, the reaction was concentrated in vacuo, and the residue was dissolved in ethyl acetate (600 mL). The solution was then washed with water (3 × 200 mL), aqueous 0.5 M hydrochloric acid (200 mL) and brine (100 mL). The organic layer was concentrated in vacuo to give imide **11g** as a yellow foam, which was dissolved directly in acetic acid (600 mL). Zinc dust (42.3 g, 647 mmol) was added to this solution in three portions over 2 h. After this addition was complete, the reaction was stirred at ambient temperature overnight. The procedure for the preparation of **3a** was then followed. Final purification by flash chromatography on silica gel eluting with

25% ethyl acetate in hexanes afforded **3g** (21.2 g, 49% over two steps) as a white foam: mp 108-110 °C; 93% ee; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (d, *J* = 7.6 Hz, 1H), 7.95 (t, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.73-7.63 (m, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.47-7.34 (m, 3H), 4.38 (quintet, *J* = 7.3 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d6) δ 160.3, 158.1 (d, *J* = 256.6 Hz), 157.5 (d, *J* = 248.7 Hz), 156.2, 154.4, 146.5, 135.6, 132.3 (t, *J* = 10.3 Hz), 127.8, 127.5, 126.6, 119.7, 113.2-112.3 (m), 78.1, 48.0, 28.1, 18.6. Anal. Calcd for $C_{21}H_{21}F_2N_3O_3$ 0.15 EtOAc: C, 62.57; H, 5.40; N, 10.13; F, 9.16. Found: C, 62.28; H, 5.19; N, 10.30; F, 9.23.

Synthesis of *tert*-butyl (*S*)-1-(3-(2,6-difluorophenyl)-5-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3h).



3h

Solid KHMDS (10.6 g, 53.0 mmol) was added to a solution of **9h** (15.5 g, 53.0 mmol) in THF (200 mL) at 0 ºC. The reaction mixture was stirred for 10 min at 0 °C, after which time Boc-*L*-Ala-OSu (15.2 g, 53.0 mmol) was added. After stirring for an additional 15 min at the same temperature, the reaction mixture was concentrated, and the residue was dissolved in ethyl acetate (300 mL) and washed with water (3 × 100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to afford the crude imide, which was used without purification in the subsequent step. The crude material was dissolved in acetic acid (65 mL) and treated with zinc powder (11.2 g, 172 mmol) in three portions. After stirring for 2 h, the procedure for the preparation of **3a** was followed. Final purification by flash chromatography on silica gel, eluting with 30% ethyl acetate in hexanes, afforded **3h** (4.35 g, 20%) as a white solid: mp 123-125 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.46 (m, 3H), 7.28 (br s, 1H), 7.28-7.25 (m, 1H, partially overlaps with $CHCl_3$ signal), 7.16-7.11 (m, 2H), 5.80 (br d, *J* = 8.4 Hz, 1 H), 4.49 (m, 1H), 2.82 (s, 3H), 1.42 (s, 9H), 1.33 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.8, 161.3, 158.9 (dd, *J* = 252.6, 3.8 Hz), 158.5 (dd, *J* = 248.7, 3.8 Hz), 156.8, 155.2, 148.8, 141.4, 135.1, 132.8 (t, *J* = 10.0 Hz), 130.6, 126.3, 118.9, 113.8 (t, *J* = 17.2 Hz), 114.1-113.0 (m), 78.8, 55.5, 48.6, 28.8, 23.1, 19.3. Anal. Calcd for $C_{22}H_{23}F_2N_3O_3$: C, 63.60; H, 5.58; N, 10.12. Found: C, 63.23; H, 5.60; N, 9.99.

References

[1] Agwada, V. C. *J. Chem. Eng. Data* **1984**, *29*, 231.
[2] Gruszecki, W.; Gruszecka, M.; Bradaczek, H. *Lieb. Ann. Chem.* **1988**, 331.