SEQUENTIAL Pd-CATALYZED ASYMMETRIC ALLENE DIBORATION/\(\alpha\)-AMINOALLYLLATION

Joshua D. Sieber and James P. Morken*

Department of Chemistry, Venable and Kenan Laboratories
University of North Carolina, Chapel Hill, NC, 27599-3290

Supplementary Material

General. Melting points were determined using a Mel-Temp II melting point apparatus and are uncorrected. \(^1\)H NMR spectra were recorded on Bruker DRX 300 or 400 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl\(_3\): 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hexet, br = broad, m = multiplet), coupling constants (Hz) and assignment. \(^13\)C NMR was recorded on a Bruker 400 MHz (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl\(_3\): 77.0 ppm). Low-resolution mass spectrometry was performed by the University of North Carolina, Department of Chemistry Mass Spectrometry Facility. Infrared (IR) spectra were obtained on a Nicolet 560 Magna-FTIR.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO\(_2\), 230 X 450 mesh) purchased from Sorbent Technologies. Thin layer chromatography was performed on 250 \(\mu\)m silica gel plates from EMD Chemicals Inc. Visualization was achieved using UV light, phosphomolybdic acid in ethanol, potassium permanganate in water, or cerium sulfate and ammonium molybdate in sulfuric acid, each followed by heating.

Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard Series 1100 liquid chromatograph equipped with a UV detector and a Daicel Chiralcel OD-H column. Analytical supercritical fluid chromatography (SFC) was performed on a Berger Instruments supercritical chromatograph equipped with an Alcott autosampler and a Knauer UV detector.

All reactions were conducted in oven or flame dried glassware under an inert atmosphere of nitrogen or argon. Toluene was distilled over CaH\(_2\) and degassed by freeze-pump-thaw cycles prior to use. Pd\(_2\)(dba)\(_3\) and tricyclohexylphosphine were purchased from Strem Chemical Company. Aldehydes were purchased from Aldrich Chemical Company and distilled prior to use. \(N\)-(trimethylsilyl)aldimines were synthesized via the known literature procedure (Colvin, E. W.; McGarry, D.; Nugent, M. J. Tetrahedron 1988, 44, 4157.) and distilled prior to use. Bis(pinacolato)diboron was purchased from BASF. [(\(R, R\))-xylylTADDOL]PNMe\(_2\) was synthesized according to the literature (Woodward, A. R.; Burks, H. E.; Chan, L., K., M.; Morken, J. P. Org. Lett. 2005, ASAP.). Allenes were synthesized according to the literature (Vermeer, P.; Meijer, J.; Brandsma, L. Recl. Trav. Chim. Pays-Bas 1975, 94, 112.). Acetic anhydride was purchased from Fisher Chemical and distilled under N\(_2\). All other reagents were purchased from either Fisher or Aldrich Chemical Companies and used directly.

Representative procedure for the preparation of \(\beta\)-amidoketones from allenes (Table 1).

Method A: An oven-dried 2-dram vial equipped with a magnetic stir-bar was charged with 9.9 mg (0.011 mmol) of tris(dibenzylideneacetone)dipalladium(0), 16.8 mg (0.0258 mmol) [(\(R, R\))-xylylTADDOL]PNMe\(_2\), and 0.86 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and stirred for 45 minutes and then 131 mg (0.516 mmol) of bis(pinacolato)diboron was added followed by 50.0
mg (0.430 mmol) of phenyl allene. The vial was capped, taped with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 14 h. After this time period, the vial was taken back into the dry-box, and 114 mg (0.645 mmol) of N-(trimethylsilyl)benzaldimine was weighed in. Next 28.7 µL (0.710 mmol) of MeOH was added dropwise while stirring the reaction. The vial was capped, removed from the dry-box, and stirred at ambient temperature for 1 h. Next, 0.12 mL (1.3 mmol) of acetic anhydride was added, followed by 0.5 mL of CHCl₃. The vial was purged with N₂, sealed with a cap, and stirred for an additional 1 h. Volatiles were then removed under reduced pressure, and the resulting residue was diluted with 1.6 mL of THF and 1.3 mL of pH 7 buffer. To this solution was added 0.48 mL of 30% H₂O₂(aq), and the mixture was stirred for 13 h at ambient temperature under N₂. The final mixture was then transferred to a separatory funnel with 25 mL of CH₂Cl₂ and 10 mL of pH 7 buffer. 2 mL of saturated Na₂S₂O₃ solution was added, and the organic layer was collected. The aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL), and the combined organics were washed with 15 ml of brine, dried with anhydrous Na₂SO₄, filtered, and concentrated using reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the crude mixture afforded 80.7 mg (67 %) of (R)-N-(3-oxo-1,4-diphenylbutyl)acetamide as a cream-colored solid.

**Method B:** An oven-dried 2-dram vial equipped with a magnetic stir-bar was charged with 9.9 mg (0.011 mmol) of tris(dibenzylideneacetone)dipalladium(0), 16.8 mg (0.0258 mmol) [(R,R)-xylylTADDOL]PNMe₂, and 0.86 mL of toluene in a dry-box under an argon atmosphere. The vial was capped and stirred for 45 minutes. After complexation was complete, 131 mg (0.516 mmol) of bis(pinacolato)diboron was added, followed by 50.0 mg (0.430 mmol) of phenyl allene. The vial was capped, taped with electrical tape, removed from the dry-box, and allowed to stir at ambient temperature for 14 h. After this time period, the mixture was taken up in a syringe and added to a solution of benzaldehyde and NH₄OAc in anhydrous MeOH with activated 4 Å molecular sieves that had been stirring under N₂ at room temperature for 2 h (see below for the preparation of this solution). The residue in the vial was then rinsed into the aldehyde solution using 0.5 mL of MeOH. This mixture was then stirred for 1 h. Next, 0.41 mL (4.3 mmol) of acetic anhydride was added by syringe, and the reaction was stirred for an additional 1 h. The crude reaction was then poured into 20 mL of Et₂O, and filtered over celite until a homogeneous solution was obtained. Volatiles were removed under reduced pressure, and the resulting mixture was then diluted with 1.2 mL of THF and 1.1 mL of pH 7 buffer. To this solution was added 0.37 mL of 30% H₂O₂(aq), and it was then allowed to stir at ambient temperature under N₂ for 13 h. The final mixture was then transferred to a separatory funnel with 25 mL of CH₂Cl₂ and 10 mL of pH 7 buffer. 2 mL of saturated Na₂S₂O₃ solution was added, and the organic layer was collected. The aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL), and the combined organics were washed with 15 ml of brine, dried with anhydrous Na₂SO₄, filtered, and concentrated using reduced pressure. Silica gel chromatography (hexanes/EtOAc) of the crude mixture afforded 74.5 mg (62 %) of (R)-N-(3-oxo-1,4-diphenylbutyl)acetamide as a cream-colored solid.

Preparation of the aldehyde solution: To a 5-mL RBF with a magnetic stir-bar and activated 4 Å molecular sieves, in a dry-box under an argon atmosphere, was added 249 mg (3.23 mmol) of NH₄OAc. Next, 0.81 mL of anhydrous MeOH was added, followed by 65.5 µL (0.645 mmol) of benzaldehyde. The flask was capped with a septum, removed from the dry-box, and allowed to stir, under N₂, for 2 h before addition of the crude diboration mixture.

**Representative procedure for the preparation of vinylboronate ester intermediates (Scheme 1).**

The diboration-allylation sequence was carried out as described in method A using phenyl allene and N-(trimethylsilyl)benzaldimine. After this was complete, 3.0 eq of the appropriate anhydride was added, followed by 0.5 mL of CHCl₃. After stirring the mixture for 1 h at ambient temperature, volatiles were removed under reduced pressure, and the product was isolated from the crude mixture using silica gel chromatography.
Procedure for the protonation of the vinylboronate ester intermediate in Scheme 1.

To 85.2 mg (0.210 mmol) of \((R,Z)-N-(1,4\text{-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl})\)propionamide, in a 20-mL scintillation vial with a magnetic stir-bar, was added 2.1 mL of propionic acid. The vial was purged with N\(_2\), sealed with a polypropylene cap, taped with electrical tape, and heated at 140°C for 28 h. After this time period, the reaction was transferred to a separatory funnel with 20 mL of Et\(_2\)O and extracted with saturated aqueous NaHCO\(_3\) (3 x 15 mL). The combined aqueous layers were then extracted with Et\(_2\)O (1 x 20 mL). The combined organics were washed with 10 mL of brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated using reduced pressure to afford a brown solid. Purification by silica gel chromatography (20:1 CH\(_2\)Cl\(_2\):Et\(_2\)O) afforded 54.2 mg (92 %) of \((R,Z)-N-(1,4\text{-diphenylbut-3-enyl})\)propionamide as a white solid.

Procedure for the Suzuki cross-coupling reaction in Scheme 1.

To 66.9 mg (0.149 mmol) of \((R,Z)-\text{tert-butyl-1,4-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enylcarbamate}\), in a 20-mL scintillation vial with a magnetic stir-bar, was weighed 6.1 mg (0.0075 mmol) of \([1,1\text{-bis(diphenylphosphino)ferrocene}]\)dichloropalladium(II) dichloromethane complex. The vial was capped with a septum and put under N\(_2\). To the vial was added 1.06 mL of dioxane, followed by 25.1 µL (0.224 mmol) of iodobenzene, and lastly 0.11 mL of 4 M KOH (aq). The septum was then quickly replaced with a propylene cap; the cap was taped on with electrical tape, and then the vial was heated at 80°C for 14 h. After this time period, the reaction was transferred to a separatory funnel with 20 mL of CH\(_2\)Cl\(_2\) and 10 mL of H\(_2\)O. The organic layer was collected, and the aqueous layer was washed with CH\(_2\)Cl\(_2\) (1 x 20 mL). The combined organics were washed with 15 mL of H\(_2\)O, 10 mL of brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated using reduced pressure. Purification by silica gel chromatography (9:1 hexanes:EtOAc) afforded 37.2 mg (63 %) of \((R,E)-\text{tert-butyl-1,3,4-triphenylbut-3-enylcarbamate}\) as a waxy solid.

Procedure for the preparation of the compound shown in Figure 2.

The diboration to phenyl allene was performed as described in Method A, with tricyclohexylphosphine in place of the chiral ligand and at 0.16 M concentration of toluene relative to the allene. After 14h at room temperature, 1.0 eq of \(N\)-(trimethylsilyl)benzaldimine was added in the dry-box, followed by 1.1 eq of MeOH. A white precipitate formed after stirring for 1h at ambient temperature, and after this time period, the reaction was poured into 15 mL of hexanes. The mixture was filtered using vacuum filtration, and an off-white solid was collected. Recrystallization from a mixture of hexanes and EtOAc afforded X-ray quality crystals.

Representative procedure for absolute stereochemistry determinations using X-ray analysis.

The same procedure described in Method A was employed using cyclohexyl allene and \((1E, 2E)-N\)-(trimethylsilyl)hex-2-en-1-imine with one modification. After the allylation step was complete, 0.24 mL (1.2 mmol) of \((S)-(+)-2\text{-methylbutyric anhydride (>98% ee and commercially available from Aldrich Chemical Co.)}\) was added in place of Ac\(_2\)O. After oxidation and the aqueous workup, silica gel column chromatography (30:1 DCM:Et\(_2\)O) afforded 81.7 mg (62 %) of \((S)-N-((R, E)-1\text{-cyclohexyl-2-oxonon-5-en-4-yl})-2\text{-methylbutanamide}\) as a white solid. Recrystallization using a mixture of hexanes and EtOAc afforded X-ray quality crystals.
**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was determined by X-ray analysis of (S)-2-methyl-N-((R)-3-oxo-1,4-diphenylbutyl)butanamide (characterization data shown below), which was prepared as described above using phenyl allene and N-(trimethylsilyl)benzaldimine.

Chiral SFC (AD-H, Chiralpak, 150 psi, 50° C, flow = 5.0 mL/min, 5.0 % MeOH) analysis of β-amidoketone product:
(S)-2-methyl-N-((R)-3-oxo-1,4-diphenylbutyl)butanamide. A white solid. mp 115-118°C. \( R_f = 0.19 \) (2:1 hexanes:EtOAc); IR (KBr): 3328 (br, m), 3029 (br, m), 2928 (br, m), 1945 (w), 1871 (w), 1706 (s), 1639 (s), 1526 (s), 1491 (s), 1449 (s), 1238 (s), 1172 (s) cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 7.20-7.32 (6H, m, ArH), 7.16 (2H, d, \( J = 7.2 \) Hz, ArH), 7.04 (2H, d, \( J = 6.8 \) Hz, ArH), 6.57 (1H, d, \( J = 7.6 \) Hz, NH), 5.40 (1H, m, ArCHN), 3.62 (1H, d, \( J = 16 \) Hz, ArCH\(_2\)H\(_6\)C(O)), 3.56 (1H, d, \( J = 16 \) Hz, ArCH\(_2\)H\(_6\)C(O)), 3.10 (1H, dd, \( J = 6.6 \) Hz, \( J = 6.0 \) Hz, C(O)CH\(_2\)H\(_6\)CN), 2.89 (1H, dd, \( J = 6.0 \) Hz, \( J = 6.0 \) Hz, C(O)CH\(_2\)H\(_6\)CN), 2.09 (1H, h, \( J = 7.2 \) Hz, NC(O)C\(_\text{H}_3\)), 1.63 (1H, m, NC(O)CH\(_2\)H\(_6\)H\(_3\)C\(_3\)), 1.40 (1H, m, NC(O)CH\(_2\)H\(_6\)H\(_3\)C\(_3\)), 1.08 (3H, d, \( J = 6.8 \) Hz, CHCH\(_3\)), 0.86 (3H, t, \( J = 7.6 \) Hz, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR: \( \delta \) 207.2, 175.7, 140.9, 133.3, 129.4, 128.7, 128.6, 127.3, 127.1, 126.1, 50.69, 49.13, 46.47, 43.07, 27.18, 17.30, 11.82. LRMS (ES+) Calc’d for C\(_{21}\)H\(_{25}\)NO\(_2\) (M + Na): 346.2. Found (M + Na): 346.3.
**(R)-N-(1-(furan-2-yl)-3-oxo-4-phenylbutyl)acetamide.** A cream-colored solid. mp 125-127°C. \( R_f \) = 0.20 (4:1 CH₂Cl₂:Et₂O); IR (KBr): 3293 (br, s), 3064 (br, m), 2901 (m), 2803 (w), 1953 (w), 1712 (s), 1631 (s), 1542 (s), 1363 (s), 1289 (s) cm⁻¹; \(^1^H\) NMR: δ 7.20-7.45 (4H, m, ArH), 7.15 (2H, d, \( J = 9.6 \) Hz, ArH), 6.49 (1H, d, \( J = 11 \) Hz, NH), 6.28 (1H, m, ArH), 6.09 (1H, m, ArH), 5.49 (1H, m, ArCH₂N), 3.69 (2H, s, ArCH₂C(O)), 3.16 (1H, dd, \( J = 22 \) Hz, \( J = 6.4 \) Hz, C(O)CH₃H₅CN), 2.90 (1H, dd, \( J = 22 \) Hz, \( J = 8.0 \) Hz, C(O)CH₃H₅CN), 1.97 (3H, s, NC(O)CH₃); \(^{13}\)C NMR: δ 206.7, 169.2, 153.1, 141.7, 133.3, 129.4, 128.8, 127.2, 110.4, 106.2, 50.49, 43.98, 43.83, 23.26. LRMS (APCI+) Calc’d for C₁₆H₁₇NO₃ (M + Na)⁺: 294.3. Found (M + Na)⁺: 294.3.

**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (R)-N-(3-oxo-1,4-diphenylbutyl)acetamide.

*Chiral SFC (AD-H, Chiralpak, 150 psi, 50°C, flow = 5.0 mL/min, 5.0 % MeOH) analysis of β-amidoketone product:*
**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (R)-N-(3-oxo-1,4-diphenylbutyl)acetamide.

*Chiral SFC (AD-H, Chiralpak, 150 psi, 50°C, flow = 5.0 mL/min, 4.0 % MeOH) analysis of β-amidoketone product:*
**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was determined by comparison to authentic material prepared by the following sequence. First, the \( \beta \)-amido methyl ester, \((R)\)-methyl 3-acetamido-3-phenyl-propanoate, was prepared using asymmetric hydrogenation as described in the literature (Zhou, Y. G.; Tang, W.; Wang, W. B.; Li, W.; Zhang, X. J. Am. Chem. Soc. 2002, 124, 4952). This compound was then converted to the Weinreb’s amide using a procedure employed by Toyooka and Nemoto (Toyooka, N.; Okumura, M.; Nemoto, H. J. Org. Chem. 2002, 67, 6078). Lastly, the amide was converted to the ketone by the addition of (3-phenylpropyl)magnesium bromide using Weinreb’s conditions (Nahm, S.; Weinreb, S., M. Tetrahedron Lett. 1981, 22, 3815).

Chiral SFC (AS-H, Chiralpak, 150 psi, 50°C, flow = 5.0 mL/min, 4.0 % MeOH) analysis of \( \beta \)-amidoketone product:
**R**-N-(1-(furan-2-yl)-3-oxo-6-phenylhexyl)acetamide. A cream-colored solid. mp 86-90°C. R_f = 0.22 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3304 (br, s), 3025 (br, m), 2932 (br, m), 1950 (w), 1872 (w), 1713 (s), 1646 (s), 1522 (s), 1405 (s), 1367 (s), 1297 (s) cm^{-1}; \(^1\)H NMR: \(\delta\) 7.05-7.30 (6H, m, ArH), 6.54 (1H, d, \(J = 8.4\) Hz, NH), 6.27 (1H, m, ArH), 6.12 (1H, m ArH), 5.44 (1H, m ArCHN), 3.06 (1H, dd, \(J = 17\) Hz, \(J = 4.8\) Hz, C(O)CH\(_2\)CH\(_3\)), 2.81 (1H, dd, \(J = 17\) Hz, \(J = 6.0\) Hz, C(O)CH\(_2\)CH\(_3\)), 2.56 (2H, t, \(J = 7.6\) Hz, ArCH\(_2\)), 2.38 (2H, m, -CH\(_2\)CH\(_2\)C(O)), 1.97 (3H, s, NC(O)CH\(_2\)), 1.85 (2H, p, \(J = 6.8\) Hz, ArCH\(_2\)CH\(_2\)); \(^{13}\)C NMR: \(\delta\) 209.0, 169.2, 153.3, 141.6, 141.3, 128.34, 128.30, 125.9, 110.4, 106.2, 44.78, 43.76, 42.24, 34.78, 24.76, 23.18. LRMS (APCI+) Calc’d for C\(_{18}\)H\(_{21}\)NO\(_3\) (M + Na): 322.1. Found (M + Na): 322.3.

**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (R)-N-(3-oxo-1,6-diphenylhexyl)acetamide.

**Chiral SFC (AD-H, Chiralpak, 150 psi, 50°C, flow = 5.0 mL/min, 5.0 % MeOH) analysis of \(\beta\)-amidoketone product:**

- Diboration-allylation-oxidation product
- Racemic
- Diboration-allylation-oxidation product + racemic coinjection
R,E)-N-(4-oxo-1-phenylundec-7-en-6-yl)acetamide. A white solid. mp 62-64°C.  Rf = 0.25 (4:1 CH₂Cl₂:Et₂O); IR (KBr): 3293 (br, m), 2947 (br, m), 1708 (s), 1650 (s), 1530 (s), 1370 (s) cm⁻¹; ¹H NMR: δ 7.10-7.30 (5H, m, ArH), 6.28 (1H, d, J = 8.4 Hz, NH), 5.54 (1H, dt, J = 15 Hz, J = 6.8 Hz, vinyl), 5.42 (1H, dd, J = 15 Hz, J = 6.4 Hz, vinyl), 4.69 (1H, m, CH=CHCH₃N); 2.71 (1H, dd, J = 17 Hz, J = 4.8 Hz, C(O)CH₃H₆CN), 2.62 (1H, dd, J = 17 Hz, J = 5.6 Hz, C(O)CH₆H₆CN), 2.58 (2H, t, J = 7.6 Hz, ArCH₂), 2.39 (2H, m, -CH₂CH₂C(O)), 1.80-2.0 (7H, m, allylic CH₂ + ArCH₂CH₂ + NC(O)CH₃), 1.32 (2H, h, J = 7.2 Hz, CH₂CH₃), 0.85 (3H, t, J = 7.6 Hz, CH₂CH₃); ¹³C NMR: δ 210.2, 169.3, 141.5, 133.6, 128.7, 128.6, 128.5, 126.1, 47.78, 433.6, 128.6, 128.5, 126.1, 47.78, 46.86, 42.73, 35.09, 34.32, 25.03, 23.62, 22.30, 13.74. LHRMS (APCI+) Calc’d for C₁₉H₂₇NO₂ (M + Na)+: 324.2. Found (M + Na)+: 324.4.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (R)-N-(3-oxo-1,6-diphenylhexyl)acetamide.

Chiral SFC (AD-H, Chiralpak, 150 psi, 50°C, flow = 4.0 mL/min, 4.0 % MeOH) analysis of β-amidoketone product:

![Chiral SFC analysis](image_url)
(R)-N-(4-cyclohexyl-3-oxo-1-phenylbutyl)acetamide. A white solid. mp 90-94°C. 

Rf = 0.26 (4:1 CH2Cl2:Et2O); IR (KBr): 3324 (br, s), 3064 (br, m), 2912 (br, s), 2949 (w), 1704 (s), 1642 (s), 1537 (s), 1413 (m), 1378 (m) cm⁻¹; ¹H NMR: δ 7.15-7.40 (5H, m, ArH), 6.74 (1H, d, J = 7.6 Hz, NH), 5.36 (1H, m, CHN), 3.04 (1H, dd, J = 16 Hz, J = 5.2 Hz, C(O)CH₂H₅CN), 2.82 (1H, dd, J = 16 Hz, J = 6.0 Hz, C(O)CH₂H₂CN), 2.16 (2H, m, CyCH₂C(O)), 1.97 (3H, s, NC(O)CH₃), 1.42-1.75 (6H, m, C₆H₁₁), 1.0-1.35 (3H, m, C₆H₁₁), 0.70-0.90 (2H, m, C₆H₁₁); ¹³C NMR: δ 209.9, 169.3, 140.9, 128.6, 127.4, 126.3, 51.28, 49.59, 47.63, 33.52, 33.04, 32.94, 26.04, 25.98, 23.37. LRMS (APCI+) Calc’d for C₁₈H₂₅NO₂ (M + Na)+: 310.2. Found (M + Na)+: 310.4.

Proof of stereochemistry. Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was determined by comparison to authentic material prepared by the following sequence. First, the β-amido methyl ester, (R)-methyl 3-acetamido-3-phenyl-propanoate, was prepared using asymmetric hydrogenation as described in the literature (Zhou, Y. G.; Tang, W.; Wang, W. B.; Li, W.; Zhang, X. J. Am. Chem. Soc. 2002, 124, 1952.). This compound was then converted to the Weinreb’s amide using a procedure employed by Toyooka and Nemoto (Toyooka, N.; Okumura, M.; Nemoto, H. J. Org. Chem. 2002, 67, 6078.). Lastly, the amide was converted to the ketone by the addition of (cyclohexylmethyl)magnesium bromide using Weinreb’s conditions (Nahm, S.; Weinreb, S., M. Tetrahedron Lett. 1981, 22, 3815.).

Chiral SFC (AD-H, Chiralpak, 150 psi, 50°C, flow = 5.0 mL/min, 3.0 % MeOH) analysis of β-amidoketone product:
(R)-N-(4-cyclohexyl-1-(furan-2-yl)-3-oxobutyl)acetamide. A white solid. mp 118-120°C. R_f = 0.26 (4:1 CH_2Cl_2:Et_2O); IR (KBr): 3304 (br, s), 3064 (br, m), 2912 (br, s), 1693 (s), 1642 (s), 1537 (s), 1370 (s), 1285 (s) cm^{-1}; ^1H NMR: δ 7.25 (1H, s, ArH), 6.68 (1H, d, J = 8.4 Hz, NH), 6.27 (1H, dd, J = 4.0 Hz, J = 2.6 Hz, ArH), 6.12 (1H, dd, J = 4.0 Hz, ArH), 5.44 (1H, m, CHN), 3.06 (1H, dd, J = 17 Hz, J = 4.0 Hz, C(O)C_Ha_HbCN), 2.80 (1H, dd, J = 17 Hz, J = 6.0 Hz, C(O)CH_2H_6CN), 2.23 (2H, d, J = 6.9 Hz, CyCH_2C(O)), 1.96 (3H, s, NC(O)CH_3), 1.50-1.85 (6H, m, C_6H_11), 1.0-1.35 (3H, m, C_6H_11), 0.75-1.0 (2H, m, C_6H_11); ^13C NMR: δ 209.3, 169.2, 153.4, 141.5, 110.4, 106.2, 50.95, 45.12, 43.83, 33.57, 33.02, 32.95, 26.04, 25.97, 23.22. LRMS (APCI+) Calc’d for C_{16}H_{23}NO_3 (M + Na)^+: 300.2. Found (M + Na)^+: 300.3.

**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was assumed to be analogous to that obtained for (R)-N-(4-cyclohexyl-3-oxo-1-phenylbutyl)acetamide and (R,E)-N-(1-cyclohexyl-2-oxonon-5-en-4-yl)acetamide.

*Chiral SFC (AS-H, Chiralpak, 150 psi, 50°C, flow = 3.0 mL/min, 3.0 % MeOH) analysis of β-amidoketone product:*

![Chiral SFC analysis](image-url)
(R,E)-N-(1-cyclohexyl-2-oxonon-5-en-4-yl)acetamide. A cream-colored solid. mp 61-63°C. \( R_f = 0.19 \) (4:1 CH\(_2\)Cl\(_2\):Et\(_2\)O); IR (KBr): 3324 (br, m), 2920 (br, m), 1704 (s), 1627 (s), 1546 (s), 1370 (s), 1293 (s) cm\(^{-1}\); \(^1\)H NMR: 6.32 (1H, d, \( J = 8.4 \) Hz, NH), 5.53 (1H, dt, \( J = 16 \) Hz, \( J = 6.4 \) Hz, vinyl), 5.42 (1H, dd, \( J = 16 \) Hz, \( J = 6.4 \) Hz, vinyl), 4.68 (1H, m, CH=CHC\(_{\text{H}}\)N), 2.72 (1H, dd, \( J = 17 \) Hz, \( J = 4.8 \) Hz, C(O)CH\(_3\)H\(_2\)CN), 2.64 (1H, dd, \( J = 17 \) Hz, \( J = 5.2 \) Hz, C(O)CH\(_3\)H\(_2\)CN), 2.23 (2H, d, \( J = 6.8 \) Hz, CyCH\(_2\)C(O)), 1.85-1.97 (5H, m, allylic CH\(_2\) + NC(O)CH\(_3\)), 1.76 (1H, m, C\(_6\)H\(_{11}\)), 1.53-1.69 (5H, m, C\(_6\)H\(_{11}\)), 1.32 (2H, h, \( J = 7.2 \) Hz, CH\(_2\)CH\(_3\)) 1.02-1.26 (3H, m, C\(_6\)H\(_{11}\)), 0.82 (3H, t, \( J = 7.2 \) Hz, CH\(_2\)CH\(_3\)), 0.75-0.97 (2H, m, C\(_6\)H\(_{11}\)); \(^{13}\)C NMR: 210.3, 169.1, 132.3, 128.6, 51.17, 47.63, 47.12, 34.14, 33.74, 33.15, 33.04, 26.08, 25.99, 23.45, 22.11, 13.56. LRMS (APCI+) Calc’d for C\(_{17}\)H\(_{29}\)NO\(_2\) (M + Na): 302.2. Found (M + Na): 302.4.

**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material prepared using Method A with tricyclohexylphosphine as the achiral ligand in the diboration step. Absolute stereochemistry was determined by X-ray analysis of (S)-N-((R)-1-(furan-2-yl)-3-oxo-6-phenylhexyl)-2-methylbutanamide (characterization data shown below), which was prepared as described above.

*Chiral HPLC (Chiralcel-OD-H, Daicel, 3.0 % iPrOH in hexanes, 0.9 mL/min) analysis of β-amidoketone product:*
(S)-N-((R, E)-1-cyclohexyl-2-oxonon-5-en-4-yl)-2-methylbutanamide. A white solid. mp 92-96°C. \( R_f = 0.19 \) (30:1 CH\(_2\)Cl\(_2\):Et\(_2\)O); IR (KBr): 3393 (br, s), 2916 (br, s), 1709 (s), 1631 (s), 1538 (s), 1383 (m), 1281 (m) cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 6.26 (1H, d, \( J = 8.4 \) Hz, NH), 5.52 (1H, dt, \( J = 16 \) Hz, \( J = 6.4 \) Hz, vinyl), 5.43 (1H, dd, \( J = 16 \) Hz, \( J = 6.0 \) Hz, vinyl), 4.70 (1H, m, CH=CHCH\(_2\)), 2.73 (1H, dd, \( J = 17 \) Hz, \( J = 17 \) Hz, \( J = 4.8 \) Hz, C(O)CH\(_2\)H\(_2\)CN), 2.63 (1H, dd, \( J = 17 \) Hz, \( J = 5.6 \) Hz, C(O)CH\(_3\)H\(_6\)CN), 2.23 (2H, d, \( J = 6.8 \) Hz, CyCH\(_2\)C(O)), 2.04 (1H, h, \( J = 6.8 \) Hz, NC(O)CH(CH\(_3\))CH\(_2\)-), 1.93 (2H, q, \( J = 7.2 \) Hz, allylic CH\(_2\)), 1.54-1.86 (7H, m, aliphatic), 1.03-1.45 (7H, m, aliphatic), 1.07 (3H, d, \( J = 6.8 \) Hz, NC(O)CH(CH\(_3\))(CH\(_3\))CH\(_2\)-), 0.77-0.96 (7H, m, aliphatic); \(^{13}\)C NMR: \( \delta \) 210.3, 175.4, 132.2, 128.8, 51.15, 47.30, 47.26, 43.19, 34.16, 33.78, 33.15, 33.06, 27.25, 26.10, 26.00, 21.15, 17.35, 13.54, 11.81. LRMS (ES+) Calc’d for C\(_{20}\)H\(_{35}\)NO\(_2\) (M + Na): 344.3. Found (M + Na): 344.2.
(R,Z)-N-(1,4-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl)propionamide. A waxy solid. Rf = 0.27 (10:1 CH2Cl2:Et2O); IR (KBr): 3293 (br, s), 3060 (br, m), 2970 (br, m), 1949 (w), 1642 (s), 1600 (s), 1355 (s), 1142 (s) cm⁻¹; ¹H NMR: δ 7.10-7.48 (11H, m, ArH + vinyl CH), 6.36 (1H, d, J = 6.8 Hz, NH), 5.05 (1H, m, ArCHN), 2.82 (1H, m, C(B)CH₃CN), 2.73 (1H, m, C(B)CH₂CN), 2.12 (2H, q, J = 7.6 Hz, NC(O)CH₂CH₃), 1.32 (6H, s, C(CH₃)₂), 1.30 (6H, s, C(CH₃)₂), 1.08 (3H, t, J = 7.6 Hz, NC(O)CH₂CH₃); ¹³C NMR: δ 172.9, 145.9, 143.2, 137.3, 128.9, 128.33, 128.31, 127.5, 126.8, 126.0, 83.94, 54.33, 35.87, 29.63, 25.18, 24.51, 9.78. LRMS (APCI+) Calc’d for C₂₅H₃₂BNO₃ (M + Na)⁺: 428.2. Found (M + Na)⁺: 428.5.

(R,Z)-tert-butyl-1,4-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enylcarbamate. A white foam. Rf = 0.24 (CH₂Cl₂); IR (KBr): 3390 (br, m), 2975 (br, m), 1950 (w), 1717 (s), 1611 (m), 1514 (s), 1344 (s), 1262 (s), 1165 (s) cm⁻¹; ¹H NMR: δ 7.41 (1H, s, vinyl CH), 7.12-7.38 (10H, m, ArH), 5.81 (1H, br d, J = 5.2 Hz, NH), 4.71 (1H, br m, ArCHN), 2.77 (1H, m, C(CH₃)₂CN), 2.54 (1H, m, C(CH₃)₂CN), 1.37 (9H, s, OC(CH₃)₃), 1.35 (6H, s, C(CH₃)₂), 1.33 (6H, s, C(CH₃)₂); ¹³C NMR: δ 155.3, 145.7, 144.2, 137.3, 128.9, 128.3, 128.2, 127.5, 126.7, 125.8, 84.01, 78.86, 56.33, 36.48, 28.40, 24.98, 24.68. LRMS (ES+) Calc’d for C₂₇H₃₆BNO₄ (M + Na)⁺: 472.3. Found (M + Na)⁺: 472.3.
**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material, which was prepared using racemic starting material that had been synthesized as described above with tricyclohexylphosphine in place of the chiral ligand in the diboration step. Absolute stereochemistry was determined by comparison to that obtained for (R)-N-(3-oxo-1,4-diphenylbutyl)acetamide.

*Chiral SFC (AD-H, Chiralpak, 150 psi, 50° C, flow = 0.5 mL/min, 5.0 % MeOH) analysis of the Suzuki-coupling product:*
\( (R,Z)-N-(1,4\text{-diphenylbut-3-enyl})\text{propionamide}. \) A white solid. \( R_f = 0.22 \) (20:1 CH\(_2\)Cl\(_2\):Et\(_2\)O); IR (KBr): 3328 (br, m), 3017 (br, m), 2940 (br, m), 1953 (w), 1884 (w), 1802 (w), 1642 (s), 1530 (s), 1452 (s), 1383 (s), 1274 (s), 1102 (s) cm\(^{-1}\); \( ^1\)H NMR: \( \delta \) 7.15-7.39 (10H, m, ArH), 6.51 (1H, d, \( J = 11.6 \) Hz, ArCH=CH), 5.71 (1H, d, \( J = 8.0 \) Hz, NH), 5.58 (1H, m, ArCH=CHCH\(_2\)), 5.13 (1H, q, \( J = 7.6 \) Hz, ArCHN), 2.84 (2H, t, \( J = 6.8 \) Hz, ArCH=CHCH\(_2\)), 2.15 (2H, q, \( J = 7.6 \) Hz, CH\(_2\)CH\(_3\)), 1.10 (3H, t, \( J = 7.6 \) Hz, CH\(_2\)CH\(_3\)); \( ^{13}\)C NMR: 173.0, 141.63, 137.0, 131.5, 128.7, 128.6, 128.3, 127.7, 127.4, 126.9, 126.5, 52.97, 34.93, 29.69, 9.76. LRMS (ES+) Calc’d for C\(_{19}\)H\(_{21}\)NO (M + Na): 302.2. Found (M + Na): 302.3.

**Proof of stereochemistry.** Stereochemical ratios were determined in comparison with authentic racemic material, which was prepared using racemic starting material that had been synthesized as described above with tricyclohexylphosphine in place of the chiral ligand in the diboration step. Absolute stereochemistry was determined by comparison to that obtained for \((R)-N-(3\text{-oxo-1,4-diphenylbutyl})\text{acetamide}.\)

*Chiral SFC (AD-H, Chiralpak, 150 psi, 50ºC, flow = 4.0 mL/min, 3.0 % MeOH) analysis of the protonation product:*

![Chiral SFC analysis](image)
**(Z)-1,4-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-amine.** A white solid. mp 170-173°C. IR (KBr): 3309 (br, m), 3196 (br, m), 3067 (br, s), 2971 (br, s), 1945 (w), 1884 (w), 1806 (w), 1596 (s), 1495 (s), 1460 (s), 1383 (s), 1212 (s), 1150 (s) cm⁻¹; ¹H NMR: δ 7.24-7.50 (5H, m, ArH), 7.11 (5H, s, ArCH), 6.85 (1H, s, vinyl CH), 3.5-5.0 (2H, br s, NH₂), 4.09 (1H, m, ArCHN), 2.93 (1H, m, ArCH(N)CH₆H₆), 2.83 (1H, m, ArCH(N)CH₆H₆), 1.20 (6H, s, C(CH₃)₂); ¹³C NMR: δ 140.9, 139.3, 131.6, 128.7, 128.6, 128.1, 127.9, 126.9, 125.9, 80.25, 57.26, 38.84, 25.49. LRMS (ES⁺) Calc’d for C₂₂H₂₈BNO₂ (M + H)⁺: 350.2. Found (M + H)⁺: 350.4.

**(R)-3-acetamido-N-methoxy-N-methyl-3-phenylpropanamide.** An off-white solid. Rₚ = 0.19 (5% MeOH in EtOAc); IR (KBr): 3352 (br, s), 3033 (br, m), 2940 (br, m), 1957 (w), 1876 (w), 1670 (s), 1631 (s), 1534 (s), 1460 (s), 1367 (s), 1293 (s), 1204 (s) cm⁻¹; ¹H NMR: δ 7.41 (1H, d, J = 6.8 Hz, NH), 7.15-7.40 (5H, m, ArH), 5.39 (1H, m, ArCHN), 3.44 (3H, s, CH₃), 3.12 (1H, dd, J = 16 Hz, J = 5.0 Hz, ArCH(N)CH₆H₆), 3.06 (3H, s, CH₃), 2.77 (1H, dd, J = 16 Hz, J = 5.0 Hz, ArCH(N)CH₆H₆), 1.99 (3H, s, NC(O)CH₃); ¹³C NMR: δ 171.9, 169.3, 141.3, 128.5, 127.2, 126.2, 61.16, 49.66, 36.65, 31.73, 23.36. LRMS (ES⁺) Calc’d for C₁₃H₁₈N₂O₅ (M + Na)⁺: 273.1. Found (M + Na)⁺: 273.2.