

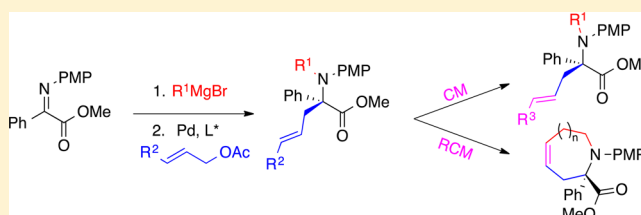
α -Allyl- α -aryl α -Amino Esters in the Asymmetric Synthesis of Acyclic and Cyclic Amino Acid Derivatives by Alkene Metathesis

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S Supporting Information

ABSTRACT: Allylating agents were explored for the asymmetric synthesis of α -allyl- α -aryl α -amino acids by tandem *N*-alkylation/ π -allylation. Cross-metathesis of the tandem product was developed to provide allylic diversity not afforded in the parent reaction; the synthesis of homotyrosine and homoglutamate analogues was completed. Cyclic α -amino acid derivatives could be accessed by ring-closing metathesis presenting a viable strategy to higher ring homologue of enantioenriched α -substituted proline. The eight-membered proline analogue was successfully converted to the pyrrolizidine natural product backbone.



The α,α -disubstituted α -amino acid structure, found in many natural products,¹ has been employed in antibiotics² and is important in peptidomimetics.³ Synthesis of α,α -disubstituted α -amino acids is difficult, with congeners beyond the α -Me, α -Et, and α -Bn becoming even more difficult.⁴ Furthermore, the construction of enantioenriched α -allyl- α -aryl α -amino acids is extremely challenging. Kinetic resolutions were first reported by Tourwe in 1997.⁵ Diastereoselective processes were reported by Tayama^{6a} and Barrett.^{6b} Maruoka and Ooi in 2000 established the use of phase-transfer catalyst to generate α,α -disubstituted α -amino acids.^{7a,b} Yet, in the asymmetric synthesis of α -allyl- α -aryl α -amino acids, only the parent α -allyl- α -phenylglycine α -amino acid has been made efficiently.^{7a-d}

Asymmetric allylic alkylation (AAA) to generate α,α -disubstituted α -amino acids was pioneered in 1997 by Trost utilizing azlactones.⁸ α -Aryl α -amino acids pose a challenge to AAA because of the large steric bulk of the aryl ring near the nucleophilic carbon of the α -amino acids. Recently, we developed an asymmetric method for synthesizing α -allyl- α -aryl α -amino acids,⁹ which relies on the formation of a chelated magnesium enolate¹⁰ that is generated in situ. This work was the first example of an asymmetric tandem *N*-alkylation/ π -allylation of α -iminoesters (Scheme 1). The α -iminoester undergoes an umpolung *N*-alkylation with the Grignard reagent, generating an enolate in situ that can be used in AAA.¹¹ This example was the first utilization of phenylglycine amino acid in AAA and enables the synthesis of previously inaccessible enantioenriched α -allyl- α -aryl α -amino acids. In this paper, the use of cross-metathesis is described to overcome challenges incurred when other allylating agents were employed. Capitalizing on the *N*-alkyl group introduced in the α -iminoester addition, the construction of cyclic α -amino acids by ring-closing metathesis is also reported.

Scheme 2 displays representative examples of the three-component coupling by *N*-alkylation/ π -allylation of α -imi-

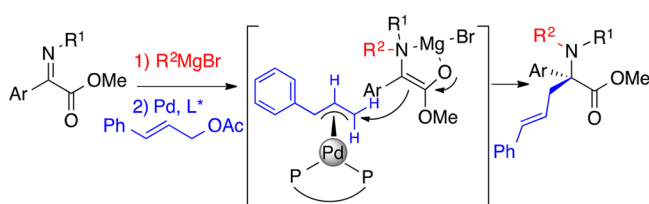
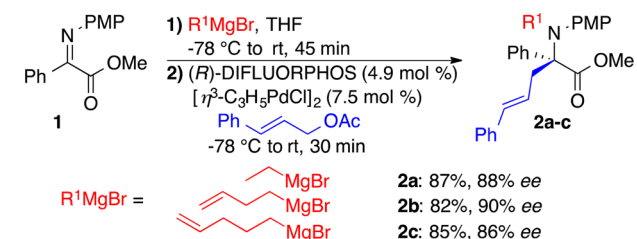
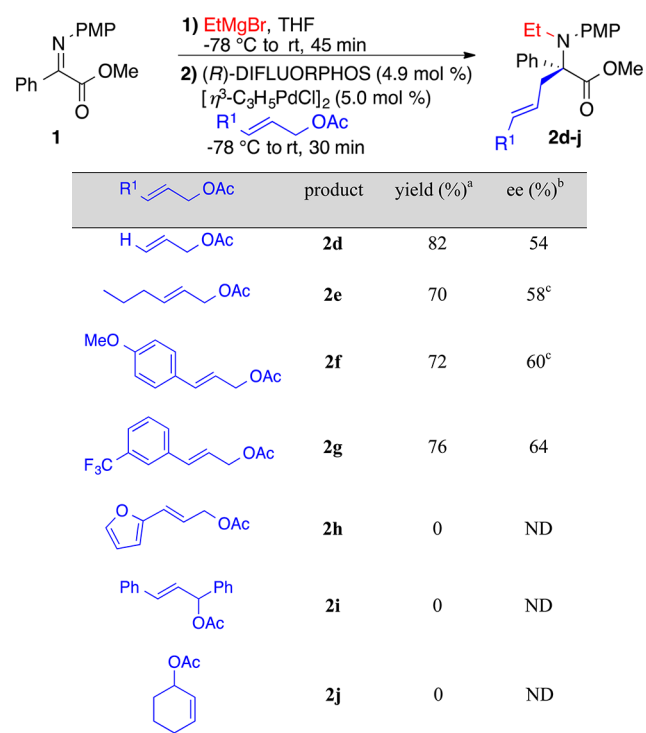
noesters.⁹ The phenyl substituent on **1** could be substituted with electron-donating or -withdrawing groups, representing the first asymmetric synthesis of α -allyl- α -aryl α -amino acids where the aryl is other than phenyl.⁷ Further variation of the phenyl group on **2** to the 2-naphthalene or 2-thiophene also proceeded well.⁹ The *p*-methoxyphenyl (PMP) was the best activating group for preferential *N*-alkylation; the methyl ester could be modified (ethyl, *tert*-butyl, benzyl), but enantioselectivity was reduced.⁹

Table 1 describes the further exploration of the substrate scope by looking at allylating agents beyond cinnamyl acetate. Replacing the phenyl ring of cinnamyl acetate with hydrogen reduced selectivity (Table 1, **2d**). This result is in line with the phenyl differentiating the termini of the allylpalladium complex (Scheme 1), which is expected to increase selectivity.¹² However, modification of the phenyl group in cinnamyl acetate with either electron-donating or -withdrawing groups did not increase selectivity (Table 1, **2f** and **2g**). Driven by a desire to generate aspartic/glutamic acid analogues, the corresponding furyl allyl acetate was surveyed, but no product was observed (Table 1, **2h**). Lastly, 1,3-disubstituted allylating agents generated no tandem product (Table 1, **2i** and **2j**).

α -Aryl homologues of tyrosine and glutamate have been shown to be biologically active.¹³ Yet, the challenges described above (Table 1) with various allylating agents prevented access to such compounds by this technology. In an alternate approach, cross-metathesis was studied to enable generation of a broad range of different allyl adducts from a single intermediate **2a** (Table 2). Notably, cross-metathesis between type 1 and type 2 olefins has proven difficult.¹⁴ Cross-metathesis of α,α -disubstituted α -amino acids has been limited

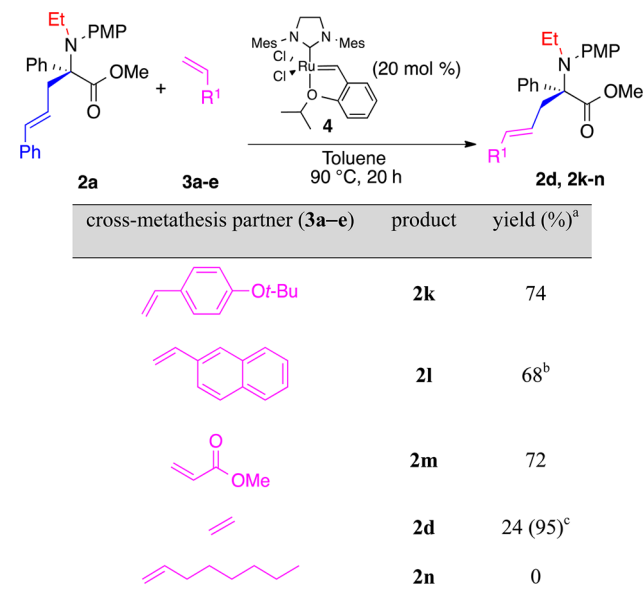
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Scheme 1. Tandem *N*-Alkylation/ π -Allylation of α -IminoestersScheme 2. Our Previous Work on the Tandem *N*-Alkylation/ π -Allylation of α -IminoestersTable 1. Exploration of Allylating Agent in the Tandem *N*-Alkylation/ π -Allylation of α -Iminoesters

^aIsolated yield. ^bDetermined by chiral stationary phase (CSP) HPLC. ^c(*R*)-BINAP was substituted for (*R*)-DIFLUORPHOS.

to α -allyl- α -methyl- and α -allylproline with the nitrogen protected as a carbamate to prevent coordination to the ruthenium catalyst.¹⁵ Indeed, amines are notoriously poor in metathesis due to deactivation of the ruthenium. However, we envisioned that the enantioenriched tandem product **2a** could be an acceptable type 2 olefin for cross-metathesis because the tertiary amine does not behave as expected. For example, the hydrochloride salts of **2** could not be formed. Apparently, the *N*-substitution and the sterics at the α -carbon contribute to this unique profile.

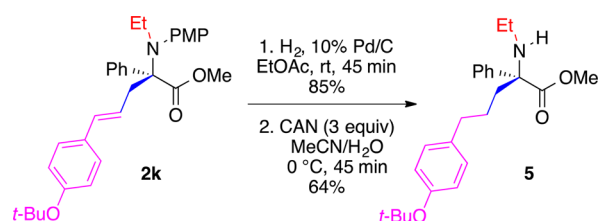
Table 2. Cross-Metathesis of the Tandem Product **2a**

^aIsolated yield. ^b1,2-Dichloroethane substituted for toluene at 70 °C. ^cYield based on recovered starting material.

Table 2 showcases that **2a** does indeed undergo cross-metathesis with various type 1 olefins, accessing previously unknown α -amino acid analogues in good yields with retention of enantiopurity. Importantly, *p*-*tert*-butoxystyrene and methyl acrylate could be employed. Microwave conditions did not accelerate the cross-metathesis, and other catalysts were inferior to the second-generation Hoveyda–Grubbs catalyst.¹⁶ Ethylene proved recalcitrant but did afford product **2d** with high enantioselectivity, in contrast to direct allylation (see Table 1, entry 1) and low conversion (with high yield based on recovered starting material).

To further our objective of generating α -amino acid homologues, hydrogenation and PMP removal was performed on **2k** to provide the α -aryl tyrosine homologue **5** (Scheme 3). Notably, *N*-ethylamino acids can be difficult to generate due to the difficulty of reductive amination with acetaldehyde. We have shown previously that the primary amines can be generated by using but-3-enyl Grignard in the *N*-alkylation/ π -allylation,⁹ where the *N*-butenyl is ultimately removed by an isomerization/hydrolysis using the Grotjahn catalyst.¹⁷

There is much great synthetic and pharmaceutical interest in cyclic α -amino acid derivatives.¹⁸ Further, α -substituted prolines have been shown to be important as organocatalysts and privileged ligands. Seebach pioneered the asymmetric synthesis of α -substituted prolines in 1983,¹⁹ yet the development of asymmetric methodology for the synthesis of higher ring homologues of proline has received little attention.²⁰ The *N*-

Scheme 3. Generation of α -Aryl Tyrosine Homologue

substituents and the α -alkene functionality present in the α -iminoester addition products **2b** and **2c** described above provide an effective entry to cyclic analogues via ring-closing metathesis (Scheme 4). Microwave irradiation allowed for the formation of **6** to occur in 1 h vs 20–24 h under thermal conditions.

Hydrogenation of RCM product **6** provided crystalline **7** (Scheme 5), which was triturated with dichloromethane to provide >95% ee material. The absolute configurations of products **2a–n** were inferred by the X-ray crystal structure of **7**.

The corresponding 8-membered ring analogue **8** could be formed by ring-closing metathesis of **2c** (Scheme 6). Microwave irradiation not only expedited the reaction but also increased its efficiency compared to thermal conditions. Furthermore, azocine **8** presents an expeditious entry to substituted pyrrolizidines via transannular cyclization.

The naturally occurring pyrrolizidine structural motif exists in over 370 natural products and has been shown to have toxicity against livestock, wildlife, and humans.²¹ The PMP group was removed from azocine **8** to provide **9**. Secondary amine **9** is poised to undergo an iodine-induced transannular cyclization.²² Treatment of **9** with NIS led exclusively to *cis*-iodide **10**, consistent with a formal syn-addition across the olefin.²³ Since most naturally occurring pyrrolizidines are substituted at C1, this route offers a labile functional group for further manipulation.²¹ The relative configuration of **10** was assigned by comparing the MM2* calculated bond distances and coupling constants of the four potential diastereomers with the NOESY and coupling constant data of **10**.¹⁶

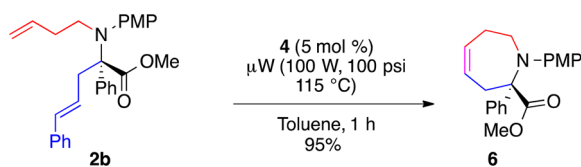
In summary, this paper outlines an entry to enantioenriched acyclic and cyclic α,α -disubstituted amino acid derivatives by means of cross-metathesis or ring-closing metathesis of the previously disclosed products from asymmetric tandem *N*-alkylation/ π -allylation of α -iminoesters. This approach provided rapid entry to homologues of tyrosine and glutamate as well as to higher ring homologues of proline. The eight-membered cyclic α -amino acid was further transformed to the pyrrolizidine natural product backbone in three steps.

EXPERIMENTAL SECTION

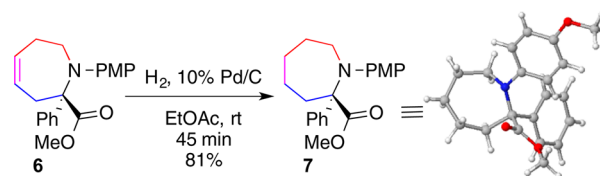
Starting material compounds **1** and **2a–c** were made following our previous report.⁹

(S,E)-Methyl 2-(N-Ethyl-N-(4-methoxyphenyl)amino)-2-phenylpent-4-enoate (2d). General Procedure A. Compound **1** (25 mg, 0.093 mmol) was added to a flamed dried Schlenk flask that had been charged with a stir bar and was then vacuum-purged three times under argon. THF (0.5 mL) was added, the reaction was cooled to -78 °C, and EtMgBr (3.0 M in Et₂O, 50 μ L, 0.15 mmol) was added. The mixture was slowly warmed to room temperature, allowed to stir for an additional 30 min and then cooled to -78 °C. A flame-dried round-bottom flask equipped with a stir bar was charged with $[\eta^3\text{-C}_3\text{H}_5\text{PdCl}]_2$ (0.85 mg, 0.0023 mmol) and (*R*)-DIFLUORPHOS (3.1 mg, 0.0045 mmol) and vacuum-purged three times under argon. THF (0.5 mL) and allyl acetate (11 μ L, 0.10 mmol) were added. The

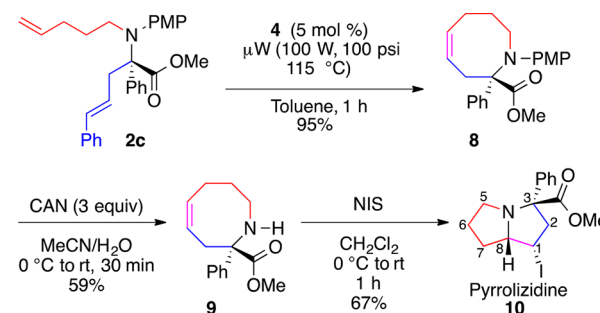
Scheme 4. Synthesis of Higher Ring Homologue of α -Substituted Proline



Scheme 5. Establishing the Absolute Configuration of Products **2a–n**



Scheme 6. Ring-Closing Metathesis To Generate Cyclic Pyrrolizidine Analogue



solution was stirred for 5 min at ambient temperature under argon, cooled to -78 °C, and added to the cooled first solution via syringe. The combined mixture warmed to room temperature and stirred for 45 min. The resultant reaction mixture was quenched with satd NH₄Cl (5 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification via column chromatography (prewash SiO₂ with 5% NEt₃/hexanes, eluent 3% EtOAc/hexanes) provided product **2d** (26 mg) in 82% yield as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28–7.25 (m, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.43–5.35 (m, 1H), 4.72 (d, *J* = 10.3 Hz, 1H), 4.59 (d, *J* = 17.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.02–2.88 (m, 2H), 2.48 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.28 (dd, *J* = 13.9, 7.3 Hz, 1H), 0.79 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 157.9, 141.5, 139.2, 134.2, 131.2, 128.0, 127.8, 127.3, 117.7, 113.8, 74.8, 55.5, 51.4, 46.6, 45.3, 14.7; IR (film) 2962, 2929, 1726, 1605, 1507, 1243 cm⁻¹; HRMS (ESI) calcd for C₂₁H₂₆NO₃ [*M* + *H*]⁺ *m/z* = 340.1913, found 340.1900; [α]_D²⁵ = +58.6 (*c* 0.08, 54% ee, CH₂Cl₂); chiral HPLC (IA, 97.5:2.5 hexanes/*i*-PrOH, 1 mL/min, 254 nm): *t*_R of **2d**: 4.8 min (major) and 5.2 min (minor).

(S,E)-Methyl 2-(N-Ethyl-N-(4-methoxyphenyl)amino)-2-phenyloct-4-enoate (2e). General procedure A was followed using **1** (50 mg, 0.19 mmol) in THF (1.0 mL), 3.0 M EtMgBr (100 μ L, 0.30 mmol), $[\eta^3\text{-C}_3\text{H}_5\text{PdCl}]_2$ (1.7 mg, 0.0047 mmol), *R*-BINAP (5.7 mg, 0.0091 mmol), and hex-2-enyl acetate (31 μ L, 0.20 mmol) in THF (1.0 mL). Purification by column chromatography (8% EtOAc/hexanes) provided product **2e** (49 mg) in 70% yield as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.27–7.22 (m, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 9 Hz, 2H), 5.03–4.88 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.03–2.86 (m, 2H), 2.42 (dd, *J* = 14, 6.3 Hz, 1H), 2.19 (dd, *J* = 14, 7.0 Hz, 1H), 1.71 (dt, *J* = 7.6, 6.9 Hz, 2H), 1.16–1.09 (m, 2H), 0.79 (t, *J* = 7.0 Hz, 3H), 0.71 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.2, 157.8, 141.7, 139.2, 134.1, 131.2, 128.1, 127.6, 127.0, 125.2, 113.7; IR (film) 2959, 1726, 1508, 1244 cm⁻¹; HRMS (ESI) calcd for C₂₄H₃₂NO₃ [*M* + *H*]⁺ *m/z* = 382.2382, found 382.2388; [α]_D²⁵ = +128.75 (*c* 0.32, 58% ee, CH₂Cl₂); chiral HPLC (IA, 97.5:2.5 hexanes/*i*-PrOH, 1 mL/min, 254 nm): *t*_R of **2e**: 4.8 min (major) and 6.8 min (minor).

(S,E)-Methyl 2-(N-Ethyl-N-(4-methoxyphenyl)amino)-5-(4-methoxyphenyl)-2-phenylpent-4-enoate (2f). General procedure A was followed using **1** (40 mg, 0.15 mmol) in THF (1.0 mL), 3.0 M EtMgBr (80 μ L, 0.24 mmol), $[\eta^3\text{-C}_3\text{H}_5\text{PdCl}]_2$ (1.36 mg, 0.0037

mmol), *R*-BINAP (4.6 mg, 0.0073 mmol) and (4-methoxy)cinnamyl acetate (32 mg, 0.16 mmol) in THF (1.0 mL). Purification by column chromatography (prewash SiO₂ with 5% NEt₃/hexanes, eluent 8% EtOAc/hexanes) provided **2f** (48 mg) in 72% yield as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.28–7.27 (m, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.01 (m, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 5.82 (d, *J* = 15.8 Hz, 1H), 5.26 (dt, *J* = 15.8, 7.4 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.06–2.99 (m, 1H), 2.97–2.90 (m, 1H), 2.59 (ddd, *J* = 13.7, 7.0, 1.3 Hz, 1H), 2.39 (ddd, *J* = 13.8, 7.5, 1.1 Hz, 1H), 0.81 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 158.7, 157.8, 141.7, 139.2, 132.4, 131.3, 130.9, 127.9, 127.8, 127.3, 127.1, 123.8, 113.9, 113.8, 75.2, 55.5, 55.4, 51.4, 46.6, 44.3, 14.7; IR (film) 2960, 2931, 1724, 1607, 1509, 1246 cm⁻¹; HRMS (ESI) calcd for C₂₈H₃₂NO₄ [M + H]⁺ *m/z* = 446.2331, found 446.2322; [α]_D²⁵ = +95.3 (c 0.21, 60% ee, CH₂Cl₂); chiral HPLC (IA, 97.5:2.5 hexanes/*i*-PrOH, 1 mL/min, 254 nm): *t*_R of **2f**: 9.9 min (major) and 11.8 min (minor).

(*S,E*)-Methyl 2-(*N*-Ethyl-*N*-(4-methoxyphenyl)amino)-5-(3-(3-trifluoromethyl)phenyl)-2-phenylpent-4-enoate (2g**).** General procedure A was followed using **1** (40 mg, 0.149 mmol) in THF (1.0 mL), 3.0 M EtMgBr (80 μL, 0.240 mmol), [η³-C₃H₅PdCl]₂ (1.36 mg, 0.0037 mmol), *R*-DIFLUORPHOS (4.98 mg, 0.0073 mmol), and (3-trifluoromethyl)cinnamyl acetate (38 mg, 0.156 mmol) in THF (1.0 mL). Purification by column chromatography (prewash SiO₂ with 5% NEt₃/hexanes, eluent 8% EtOAc/hexanes) provided **2g** (55 mg) in 76% yield as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, *J* = 7.9 Hz, 2H), 7.38–7.34 (m, 3H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.87 (d, *J* = 15.8 Hz, 1H), 5.80–5.74 (dt, *J* = 15.6, 7.0 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.08–3.01 (m, 1H), 2.98–2.92 (m, 1H), 2.63 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.43 (dd, *J* = 13.7, 7.3 Hz, 1H), 0.82 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 158.0, 141.5, 139.1, 138.7, 131.6, 131.3, 130.8 (q, *J* = 32 Hz), 129.0, 128.8, 128.4, 128.0, 127.7, 127.5, 124.4 (q, *J* = 254 Hz), 123.5–123.4 (m), 122.8–122.7 (m), 113.9, 75.1, 55.5, 51.6, 46.8, 44.5, 14.7; IR (film) 3036, 2837, 1725, 1606, 1508, 1328, 1245, 1124 cm⁻¹; HRMS (ESI) calcd for C₂₈H₂₉F₃NO₃ [M + H]⁺ *m/z* = 484.2100, found 484.2099; [α]_D²⁵ = +99.5 (c 0.26, 64% ee, CH₂Cl₂); chiral HPLC (IA, 97.5:2.5 hexanes/*i*-PrOH, 1 mL/min, 254 nm): *t*_R of **2g**: 6.0 min (major) and 5.6 min (minor).

(3-Trifluoromethyl)cinnamyl Acetate. Following the modified procedure previously reported.²⁴ Reaction conditions: 3-iodobenzotrifluoride (577 μL, 4.0 mmol), allyl acetate (1.6 g, 16.0 mmol), Pd(OAc)₂ (45 mg, 0.20 mmol), Ag₂CO₃ (662 mg, 2.4 mmol), toluene (24 mL). (3-Trifluoromethyl)cinnamyl acetate (315 mg) was obtained in 32% yield as a colorless liquid. Spectral data agreed with those reported previously.²⁵

(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-5-(4-(*tert*-butoxy)phenyl)-2-phenylpent-4-enoate (2k**).** General Procedure B. Compound **4** (6.0 mg, 0.0096 mmol) was added to a flame-dried 8 mL microwave vial equipped with stir bar in the glovebox. Compound **3a** (85 mg, 0.48 mmol) was added followed by **2a** (20 mg, 0.048 mmol) in toluene (482 μL). The vial was sealed with a Teflon cap, taken out of the glovebox, placed in a 90 °C oil bath, and stirred for 20 h. The mixture was cooled, passed through SiO₂ with 30% EtOAc in hexanes, and concentrated in vacuo. Purification by column chromatography (prewash SiO₂ with 5% NEt₃ in hexanes, eluent 3% acetone in hexanes) provided **2k** (17 mg) in 74% yield as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.1 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.86 (d, *J* = 15.7 Hz, 1H), 5.58 (dt, *J* = 15.9, 7.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.06–2.99 (m, 1H), 2.96–2.91 (m, 1H), 2.60 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.41 (dd, *J* = 13.9, 7.4 Hz, 1H), 1.31 (s, 9H), 0.81 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.2, 157.8, 154.5, 141.6, 139.1, 133.2, 132.4, 131.3, 127.9, 127.8, 127.3, 126.5, 124.7, 124.1, 113.8, 78.6, 75.1, 55.5, 51.5, 46.6, 44.3, 29.0, 14.7; IR (film) 2975, 2855, 1725, 1604, 1507, 1241, 1162 cm⁻¹; HRMS (ESI)

calcd for C₃₁H₃₈NO₄ [M + H]⁺ *m/z* = 488.2801, found 488.2811; [α]_D²⁵ = +170.1 (c 0.13, 88% ee, CH₂Cl₂).

(*S,E*)-Methyl 2-(*N*-Ethyl-*N*-(4-methoxyphenyl)amino)-5-(naphthalene-2-yl)-2-phenylpent-4-enoate (2l**).** General procedure B was followed using **2a** (20 mg, 0.048 mmol, 81% ee), **3b** (22 mg, 0.15 mmol), and **4** (6.0 mg, 0.0096 mmol) in dichloroethane (482 μL) at 70 °C for 20 h. Purification by column chromatography (prewash SiO₂ with 5% NEt₃ in hexanes, eluent 7% EtOAc in hexanes) provided **2l** (15 mg) in 68% yield as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.72 (dd, *J* = 12.0, 4.0 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.42–7.33 (m, 5H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.02 (d, *J* = 16.0 Hz, 1H), 5.84 (dt, *J* = 16.0, 7.1 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.08–3.01 (m, 1H), 2.98–2.92 (m, 1H), 2.66 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.47 (dd, *J* = 13.6, 7.5 Hz, 1H), 0.82 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.4, 157.9, 141.6, 139.2, 135.4, 133.7, 133.1, 132.7, 131.3, 128.0, 127.9 (3), 127.7, 127.4, 126.6, 126.2, 125.6, 125.5, 123.7, 113.9, 75.2, 55.5, 51.5, 46.7, 44.6, 14.7; IR (film) 2924, 2853, 1725, 1507 cm⁻¹; HRMS (ESI) calcd for C₃₁H₃₂NO₄ [M + H]⁺ *m/z* = 466.2382, found 466.2399; [α]_D²⁵ = +125.5 (c 0.21, 81% ee, CH₂Cl₂).

(*S,E*)-Dimethyl 5-(*N*-Ethyl-*N*-(4-methoxyphenyl)amino)-5-phenylhex-2-enedioate (2m**).** General procedure B was followed using **2a** (20 mg, 0.048 mmol), **3c** (42 mg, 0.48 mmol), and **4** (6.0 mg, 0.0096 mmol) in toluene (482 μL). Purification by column chromatography (prewash SiO₂ with 5% NEt₃ in hexanes, eluent 3% acetone in hexanes) provided **2m** (14 mg) in 72% yield as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.61–6.55 (m, 1H), 5.32 (d, *J* = 16.5 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H), 3.05–2.98 (m, 1H), 2.95–2.88 (m, 1H), 2.57 (ddd, *J* = 14.5, 7.3, 0.6 Hz, 1H), 2.43 (ddd, *J* = 14.4, 7.6, 0.6 Hz, 1H), 0.79 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.2, 166.8, 158.1, 145.1, 140.9, 138.9, 131.2, 128.2, 127.7, 127.4, 123.2, 114.0, 74.5, 55.5, 51.7, 51.4, 46.8, 43.7, 14.7; IR (film) 2951, 2855, 1724, 1655, 1508, 1245, 1035 cm⁻¹; HRMS (ESI) calcd for C₂₃H₂₈NO₅ [M + H]⁺ *m/z* = 398.1967, found 398.1963; [α]_D²⁰ = +107.2 (c 0.13, 88% ee, CH₂Cl₂).

2d. General procedure B was followed using **2a** (20 mg, 0.0482 mmol) and **4** (8.2 mg, 0.0096 mmol) in dichloroethane (482 μL) and the following modification: ethylene gas **3d** was sparged through the flask for 10 min and then subjected to microwave (100 W, 100 psi, 90 °C) conditions for 30 min. The mixture was cooled, ethyl vinyl ether (50 μL, 0.523 mmol) was added, and the mixture was stirred for 30 min. The mixture was passed through SiO₂ with 30% EtOAc in hexanes and concentrated in vacuo. Purification by column chromatography (prewash SiO₂ with 5% NEt₃ in hexanes, eluent 5% EtOAc in hexanes) provided **2d** (3.9 mg) in 24% yield (characterization the same as **2d** above) with unreacted **2a** (15 mg, 0.036 mmol) recovered.

(*S*)-Methyl 2-(*N*-Ethyl-*N*-(4-methoxyphenyl)amino)-5-(4-*tert*-butoxyphenyl)-2-phenylpentanoate (2k_{sat}**).** General Procedure C. Compound **2k** (17 mg, 0.035 mmol), 10% Pd/C (3.7 mg, 0.0035 mmol), and EtOAc (1.1 mL) were added to a flame-dried 10 mL round-bottom flask equipped with a stir bar. At ambient temperature, the flask was purged with one hydrogen balloon and then subjected to a hydrogen atmosphere with a new hydrogen balloon for 45 min. The flask was opened to air, passed through SiO₂ with 30% EtOAc/hexanes, and concentrated in vacuo. Purification by column chromatography (10% EtOAc in hexanes) provided **2k_{sat}** (14.4 mg) in 85% yield as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.77 (b, 4H), 3.83 (s, 3H), 3.01–2.83 (m, 2H), 2.25–2.19 (m, 1H), 2.15–2.09 (m, 1H), 1.72–1.66 (m, 1H), 1.56–1.50 (m, 1H), 1.29 (s, 9H), 1.28–1.25 (b, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 157.8, 153.1, 141.9, 139.3, 137.3, 131.1, 128.6, 127.9, 127.8, 127.1, 124.0, 113.8, 78.1, 74.5, 55.5, 51.3, 46.6, 40.1, 35.5, 29.0, 26.6, 14.7; IR (film) 3337, 2974, 2930, 1724, 1507, 1241, 1162 cm⁻¹; HRMS (ESI) calcd for C₃₁H₄₀NO₄ [M + H]⁺ *m/z* = 490.2957, found 490.2947; [α]_D²⁵ = +67.9 (c 0.11, 88% ee, CH₂Cl₂).

(S)-Methyl 2-(Ethylamino)-5-(4-*tert*-butoxyphenyl)-2-phenylpentanoate (5). General Procedure D. A solution of **2k_{sat}** (15 mg, 0.031 mmol) in MeCN (618 μ L) was cooled to 0 °C and put under N₂ in an 8 mL microwave vial equipped with stir bar. A solution of ceric ammonium nitrate (51 mg, 0.092 mmol) in H₂O (309 μ L) was added dropwise. The mixture was allowed to warm to ambient temperature, stirred for 45 min, cooled to 0 °C, and quenched with 5% NaHCO₃ until a pH of 9 was obtained (~1 mL). The mixture was diluted with 20% Na₂SO₃ (20 mL) and extracted with EtOAc (3 \times 20 mL). The combined organic phases were washed with brine (2 \times), dried over Na₂SO₄, and concentrated in vacuo. Purification by column chromatography (5% to 30% EtOAc/hexanes) provided **5** (7.5 mg) in 64% yield as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.27–7.25 (m, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.66 (s, 3H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.32–2.24 (m, 2H), 2.18–2.12 (m, 1H), 2.06–1.97 (m, 1H), 1.54–1.39 (m, 2H), 1.31 (s, 9H), 1.09 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 175.8, 153.2, 142.0 (b), 137.3, 128.8, 128.4, 127.4, 126.2, 124.2, 78.2, 68.4, 52.4, 37.6, 35.3, 34.4, 29.0, 25.0, 15.8; IR (film) 2965, 2928, 1733, 1607, 1505, 1234 cm⁻¹; HRMS (ESI) calcd for C₂₄H₃₄NO₃ [M + H]⁺ *m/z* = 384.2539, found 384.2547; [α]_D²⁴ = -1.5 (c 0.36, 88% ee, CH₂Cl₂).

(S)-Methyl 1-(4-Methoxyphenyl)-2-phenyl-2,3,6,7-tetrahydro-1*H*-azepine-2-carboxylate (6). General procedure B was followed using **2b** (29 mg, 0.066 mmol, 81% ee) and **4** (2.8 mg, 0.003 mmol) in toluene (6 mL). The reaction was subjected to microwave (100 W, 100 psi, 115 °C) conditions for 1 h. The mixture cooled to ambient temperature, ethyl vinyl ether (75 μ L, 0.78 mmol) was added, and the mixture was allowed to stir for 30 min. The mixture was passed through SiO₂ with 30% EtOAc in hexanes and concentrated in vacuo. Purification by column chromatography (prewash SiO₂ with 5% NEt₃ in hexanes, eluent 5% EtOAc in hexanes) provided **6** (23 mg) in >98% yield as a light yellow oil. Spectral data agreed with our previous report.⁹

(S)-Methyl 1-(4-Methoxyphenyl)-2-phenylazepane-2-carboxylate (7). General procedure C was followed using **6** (0.033 M ethyl acetate solution, 0.20 mmol) and 10% Pd/C (22 mg, 0.020 mmol). Purification by column chromatography (prewash SiO₂ with 3% NEt₃ in hexanes, eluent 6% EtOAc/hexanes) provided **7** (55 mg) in 81% yield as a white solid. Trituration of **7** in CH₂Cl₂ provided undissolved white solid that was close to racemic and liquid that had enhanced ee to 98%. The liquid was concentrated and recrystallized from Et₂O via slow evaporation over 24 h: mp (98% ee material) = 113–110 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.29–7.26 (m, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.65–6.63 (m, 2H), 6.54–6.52 (m, 2H), 3.75–3.70 (m, 4H), 3.59 (s, 3H), 3.53 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.61 (dd, *J* = 15.4, 8.9 Hz, 1H), 2.08 (dd, *J* = 15.1, 10 Hz, 1H), 1.96–1.93 (b, 1H), 1.88–1.84 (b, 2H), 1.72–1.69 (b, 1H), 1.63–1.60 (b, 1H), 1.50–1.41 (b, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 175.4, 151.8, 145.1, 141.1, 128.8, 127.9, 126.9, 117.0, 113.8, 72.2, 55.7, 52.4, 51.6, 44.8, 31.0, 29.7, 23.6; IR (film) 2929, 2855, 1731, 1511, 1246, 1222, 1036, 823 cm⁻¹; HRMS (ESI) calcd for C₂₁H₂₆NO₃ [M + H]⁺ *m/z* = 340.1913, found 340.1926; [α]_D²⁵ = -7.1 (c 0.34, 98% ee, CH₂Cl₂).

(S,Z)-Methyl 1-(4-Methoxyphenyl)-2-phenyl-1,2,3,6,7,8-hexahydroazocine-2-carboxylate (8). General procedure B was followed using **2c** (30 mg, 0.066 mmol) and **4** (2.82 mg, 0.003 mmol) in toluene (6 mL). The reaction was subjected to microwave (100 W, 100 psi, 115 °C) conditions for 1 h. The mixture was cooled to ambient temperature, and ethyl vinyl ether (75 μ L, 0.784 mmol) was added and stirred for 30 min. The mixture was passed through SiO₂ with 30% EtOAc in hexanes, concentrated in vacuo, and chromatographed (prewash SiO₂ with 5% NEt₃ in hexanes, eluent 5% EtOAc in hexanes) to provide **8** (22 mg) in 95% yield as a light yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, *J* = 8.34 Hz, 2H), 7.29–7.26 (m, 2H), 7.20 (t, *J* = 7.0 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 5.92–5.87 (m, 1H), 5.72–5.67 (m, 1H), 3.72 (s, 3H), 3.60–3.50 (m, 1H), 3.43 (s, 3H), 3.35–3.30 (m, 2H), 3.27–3.15 (b, 1H), 2.11–2.03 (m, 1H), 2.03–1.93 (b, 1H), 1.92–1.77 (b, 1H), 1.58–1.44 (b, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 174.2, 152.7,

142.5, 140.7, 132.9, 128.8, 128.0, 127.5, 127.4, 121.1 (b), 113.7, 75.4, 55.5, 52.4, 48.3, 33.6, 29.1, 24.1; IR (film) 3021, 2860, 1728, 1511, 1244, 1038 cm⁻¹; HRMS (ESI) calcd for C₂₂H₂₆NO₃ [M + H]⁺ *m/z* = 352.1913, found 352.1923; [α]_D²⁴ = -1.03 (c 0.33, 83% ee, CH₂Cl₂).

(S,Z)-Methyl 2-Phenyl-1,2,3,6,7,8-hexahydroazocine-2-carboxylate (9). General procedure D was followed using **8** (10 mg, 0.029 mmol), CAN (50 mg, 0.086 mmol), MeCN (3.2 mL), and H₂O (1.6 mL). The mixture was allowed to stir at ambient temperature for 15 min instead of 45 min then cooled to 0 °C and quenched with 10% NaHCO₃ until a pH of 7 was obtained (~0.5 mL). Purification by column chromatography (prewash SiO₂ with 3% NEt₃ in hexanes, eluent 5% to 30% EtOAc in hexanes) provided **9** (4 mg) in 59% yield as a yellow oil. The reaction did not scale up well so it was more effective to run multiple reactions with the scale indicated above side-by-side and then combine the material for purification: ¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.28–7.27 (m, 1H), 5.98–5.93 (m, 1H), 5.55–5.50 (m, 1H), 3.67 (s, 3H), 3.06–3.01 (m, 1H), 2.87–2.78 (b, 1H), 2.76–2.72 (m, 1H), 2.69–2.57 (b, 1H), 2.22–2.15 (m, 2H), 1.69–1.63 (m, 1H), 1.60–1.51 (m, 1H), 1.3 (b, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 175.0, 142.3, 134.3, 128.5, 127.6, 126.8, 126.3, 70.0, 52.6, 44.5, 35.0, 32.2, 26.0; IR (film) 3419, 2924, 1731, 1645, 1220, 1032 cm⁻¹; HRMS (ESI) calcd for C₁₅H₂₀NO₂ [M + H]⁺ *m/z* = 246.1494, found 246.1497; [α]_D²⁵ = -4.8 (c 0.09, 90% ee, CH₂Cl₂).

(S,S,S)-Methyl 1-Iodo-3-phenyloctahydro-1*H*-pyrrolizine-3-carboxylate (10). A solution of **9** (23 mg, 0.094 mmol) in CH₂Cl₂ (1 mL) open to air was cooled to 0 °C in a flame-dried 5 mL round-bottom flask equipped with stirbar. NIS (freshly recrystallized from dichloromethane, 42 mg, 0.19 mmol) was added. The mixture was warmed to ambient temperature and stirred for 1.5 h. At 0 °C, the mixture was quenched with 500 μ L of 10% aq Na₂S₂O₃. The mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 \times 10 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by column chromatography (prewash SiO₂ with 5% NEt₃ in hexanes, gradient eluent 5% to 30% EtOAc in hexanes) provided **10** (23 mg) in 67% yield as a light yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.44 (d, *J* = 7.0 Hz, 2H), 7.36–7.30 (m, 3H), 4.27 (ddd, *J* = 14, 7.5, 6.5 Hz, 1H, C1–H), 3.65 (s, 3H), 3.60–3.52 (b, 1H, C8–H), 3.16 (dd, *J* = 12.3, 6.1 Hz, 1H, C2–H_a), 2.88–2.80 (b, 1H, C5–H_a), 2.58 (t, *J* = 12.0 Hz, 1H, C2–H_b), 2.14–2.09 (m, 2H, C7–H_a, C5–H_b), 1.87–1.71 (m, 3H, C7–H_b, C6–H_a, C6–H_b); ¹³C NMR (125 MHz, CDCl₃) δ 173.8, 137.4, 128.6, 128.2, 127.6, 77.2, 66.2, 58.1, 53.2, 52.2, 42.1, 36.7, 25.5; IR (film) 2949, 2868, 1741, 1725, 1448, 1251 cm⁻¹; HRMS (ESI) calcd for C₁₅H₁₉NO₂I [M + H]⁺ *m/z* = 372.0461, found 372.0450; [α]_D²⁵ = +8.2 (c 0.58, 90% ee, CH₂Cl₂).

■ ASSOCIATED CONTENT

📄 Supporting Information

Figures giving spectroscopic data for the products as well as computational studies on **10** and the CIF for **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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