Asymmetric Syntheses of Fused Bicyclic Lactams

Sung H. Lim, Sunghoon Ma, and Peter Beak*

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

beak@scs.uiuc.edu

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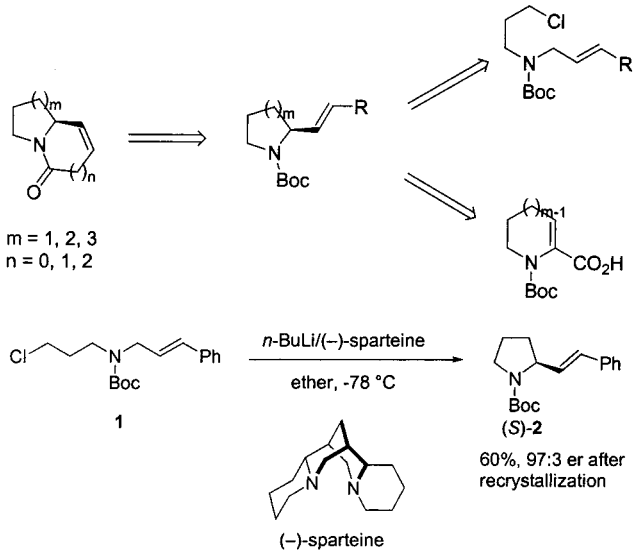
Azabicyclic compounds bearing nitrogen at the fusion of five- and six-membered rings are key structures in many multistep alkaloid and drug syntheses.[1,2] Strategies for asymmetric syntheses of these compounds generally have utilized the chiral pool and/or a chiral auxiliary to provide the diastereoselectivity necessary for enantioenrichment.[2,3] We now report combinations of chiral ligand mediated lithiation/cyclization or asymmetric catalytic reduction technology with ring-closing metathesis (RCM) for asymmetric syntheses of fused bicyclic five-, six-, and seven-membered lactams. These compounds have the requisite structure and functional group locations for further elaborations to synthetic targets, particularly azabicyclic alkaloids.[4] The retrosynthetic analyses are illustrated in Scheme 1.

We have previously reported efficient methods to prepare highly enantioenriched *N*-Boc-2-styrylpyrrolidines from achiral *N*-Boc-*N*-(3-chloropropyl)cinnamylamines.[5] This compound can be efficiently used in a sequence terminating in a ring-closing metathesis to provide bicyclic lactams.[6]

Treatment of *N*-Boc-*N*-(2-chloropropyl)cinnamylamine **1** with *n*-BuLi/(−)-sparteine in Et_2O at −78 °C gives (*S*)-**2** in 85% yield with an enantiomeric ratio (er) of 90:10.[5] Recrystallization from hexane provides (*S*)-**2** in 60% yield with an er of 97:3. Removal of the Boc group with trifluoroacetic acid (TFA) affords **3** which upon treatment with either vinylacetic acid or pent-4-enoic acid in the presence of diethyl cyanophosphonate (DEPC) and triethylamine provides the corresponding dienes **4** and **5** in 85% and 78% yields, respectively (Scheme 2). Treatment of **4** or **5** with the second generation Grubbs catalyst **6** in refluxing methylene chloride affords the corresponding lactams **7** and **8** in 86% and 84% yields, respectively. With the first generation Grubbs catalyst **9**, the reaction times were much longer and the yields were significantly lower.[7] Alternatively, treatment of **3** with triethylamine and acryloyl chloride affords **10** in 81% yield. Attempts to cyclize **10** to prepare (*S*)-pyrrolam with either Grubbs catalyst **6** or **9** were unsuccessful. Nakagawa and coworkers have shown that (−)-coniceine **11**, a simple indolizidine alkaloid, can be synthesized from **7** via stepwise reduction.[3a] Their synthesis of **7** involved the transformation of L-proline to a diene which was cyclized by ring-closing metathesis.

We demonstrated previously that (*S*)-*N*-Boc-pipecolic acid (*S*)-**13** can be prepared by asymmetric hydrogenation of 2-carboxy-*N*-Boc-1,4,5,6-tetrahydropyridine **12** using the Noyori catalyst.[8,9] Using highly enantioenriched (*S*)-**13**, alcohol **14** may be prepared with BH_3·THF in 97% yield (Scheme 3). Swern oxidation of **14** provides the aldehyde **15**, which in a Wittig reaction affords *N*-Boc-2-vinylpiperidine **16** in 92% yield for two steps.[10] The Boc group is removed using 10 equiv of TFA in methylene chloride to afford **17**, and subsequent acylation with acryloyl chloride provides **18**. Attempts to cyclize **18** with the Grubbs catalyst **9** failed, however, using the more reactive catalyst **6**, bicyclic compound **21** is synthesized in 82% yield. Dienes **19** and **20** were prepared from **17** with the corresponding acids in the presence of DEPC

Scheme 1



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(2) For recent examples of asymmetric syntheses of azabicyclic compounds, see: (a) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem*. **2001**, *66*, 5438. (b) Comins, D. L.; Huang S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett.* **2001**, *3*, 469. (c) Voigtmann, U.; Blechert, S.; *Org. Lett*. **2000**, *2*, 3971. (d) Davis, F. A.; Chao, B. *Org. Lett*. **2000**, *2*, 2623. (e) Back, T. G.; Nakajima, K. *J. Org. Chem*. **2000**, *65*, 4543. (f) Gosselin, F.; Lubell, W. D. *J. Org. Chem*. **2000**, *65*, 2163. (g) Tang, X.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950. (h) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700.

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(4) For other uses of bicyclic lactams in asymmetric syntheses, see: Molander, G. A.; Nichols, J. *J. Org. Chem*. **1996**, *61*, 6040. Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem*. **2001**, *66*, 1413 and references therein.

(5) Serino, C.; Stehle, N.; Park Y−S.; Florio, S.; Beak, P. *J. Org. Chem*. **1999**, *64*, 1160.

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(7) Sanford, M. S.; Love, J. A.; Gurbbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

(8) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett*. **2000**, *2*, 155. Foti, C. J.; Comins, D. L. *J. Org. Chem*. **1995**, *60*, 2656.

(9) Both (*S*)- and (*R*)-*N*-Boc-pipecolic acids are commercially available from Aldrich.

(10) The alcohol was oxidized by the Katzenellenbogen-modified Swern oxidation to provide the aldehyde which was reacted immediately with the ylide to avoid epimerization. Our previous report indicated that no epimerization had occurred at the position α to nitrogen for the synthesis of *N*-Boc-2-propenyl piperidine from **14**.[8]

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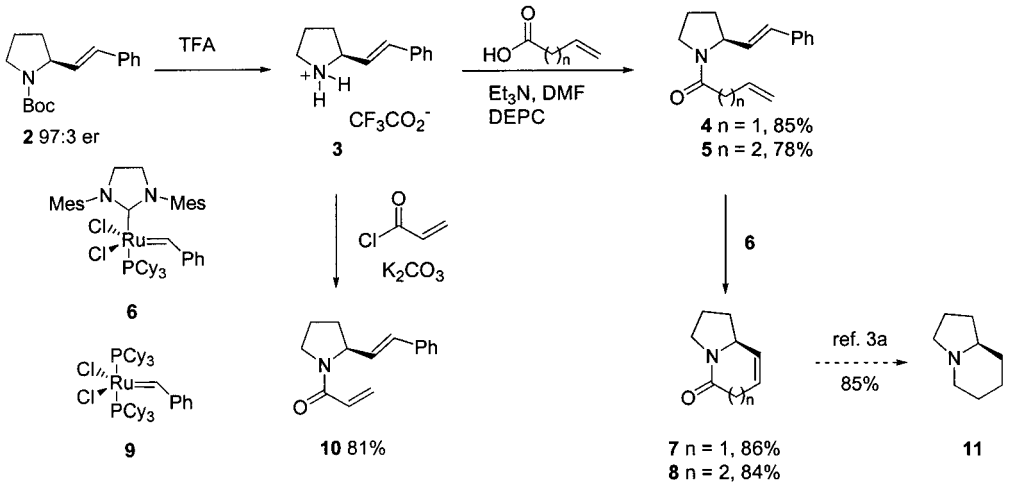
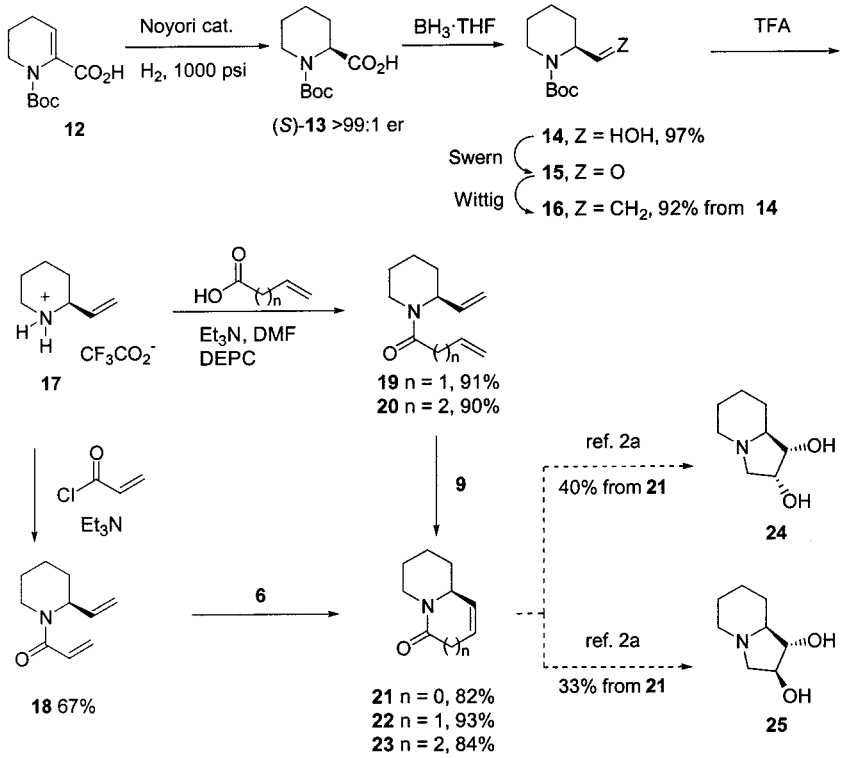
Scheme 2



Scheme 3

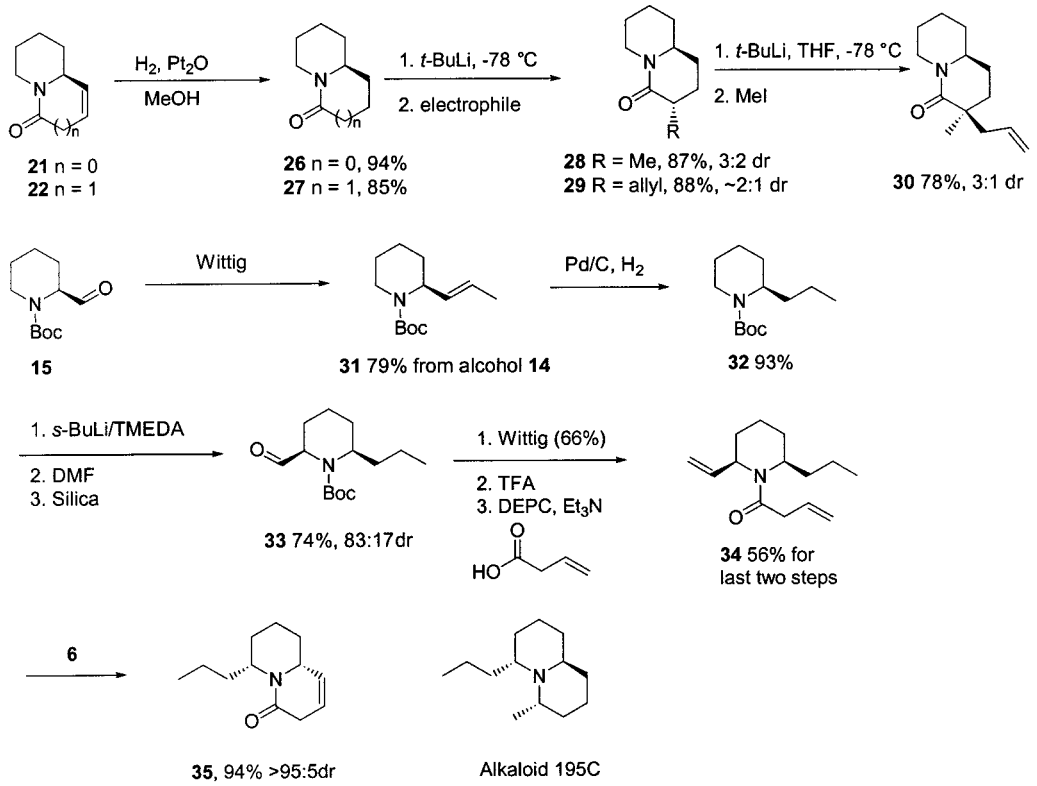


and triethylamine. Grubbs catalyst **9** is sufficient to carry out the ring-closing metathesis of **19** or **20** to provide the corresponding fused bicyclic lactams **22** and **23**. Greene and co-workers have recently demonstrated that the compound **21** can be transformed into (−)-2-epilentiginosine **24** and (−)-lentiginosine **25** in few steps.[2a] In their work, **21** was prepared from (*S*)-1-(triisopropylphenyl)-ethanol in 11 steps with 23% overall yield.

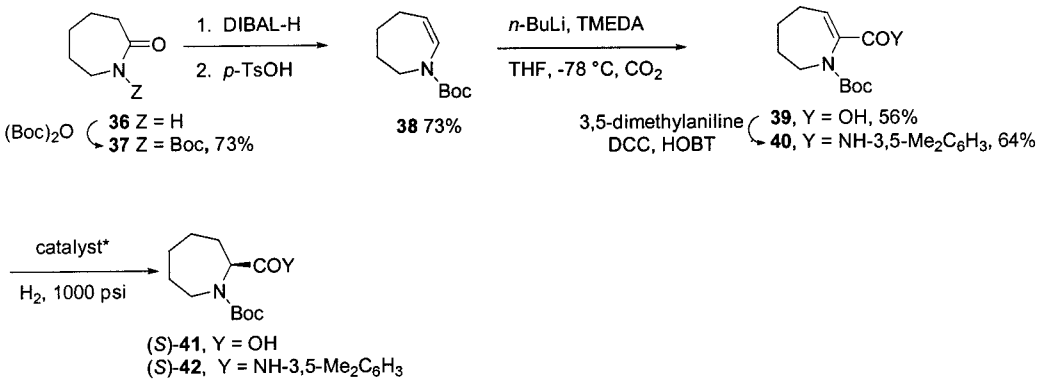
This methodology can be extended to diastereoselective syntheses of 3-substituted octahydro-quinolizin-4-ones. Hydrogenation of **21** or **22** with PtO_2 provides the corresponding products **26** and **27** in 94% and 85% yields, respectively (Scheme 4). Treatment of **27** with *t*-BuLi at −78 °C followed by reaction with either methyl iodide or allyl bromide affords 3-substituted octahydro-quinolizin-4-ones **28** and **29** in 87% and 88% yields with low diastereoselectivities. The diastereomers of **28** can be separated by preparative HPLC, and the diastereomers of **29** can be separated by column chromatography. Further reaction of the single diastereomer of **29** with *t*-BuLi and methyl iodide affords **30** in 78% yield with a 3:1 dr for diastereomers which are separable by column chromatography.

Our previous work demonstrated access to both *cis* and *trans* 2,6-disubstituted piperidines with high diastereo- and enantioselectivity.[8] This high stereochemical control allows preparation of a single enantiomer of a 6-substituted hexahydroquinolizin-4-one. Reaction of aldehyde **15** with the ylide of ethyltriphenylphosphonium bromide affords **31**. Catalytic hydrogenation of **31** with 5% Pd/C provides **32** in 93% yield. Treatment of **32** with *s*-BuLi/TMEDA followed by reaction with DMF affords a 10:90 *cis*−*trans* mixture of **33**, which can be isomerized with silica gel to provide an 83:17 *cis*−*trans* mixture. The c*is* isomer is isolated in 74% yield as a single diastereomer after flash chromatography. Wittig olefination of alde-

Scheme 4



Scheme 5



hyde **33** affords the olefin in 66% yield.[11] Removal of the Boc group with TFA, and amidation with vinylacetic acid and DEPC provides the required diene **34**. The chiral diene is readily cyclized using catalyst **6** in 94% yield to afford the desired lactam **35** with a >95:5 dr. Since the *cis*−*trans* stereochemistry of **35** can be controlled, this strategy could be useful in the preparation of alkaloid 195C which is an alkaloid isolated from ants and frogs.[8,12]

Extension of this methodology to seven-membered ring would expand the approach to analogue syntheses. Synthesis of **39** was accomplished starting from ϵ-caprolactam **36** for the seven-membered ring. Protection of **36** with the Boc group and subsequent reduction of **37** with DIBAL-H to the corresponding lactamol, followed by dehydration with a catalytic amount of *p*-TsOH gives **38** as previously described by Kieter and Sharma (Scheme 5).[13] Reaction of **38** with *n*-BuLi/TMEDA, followed by reaction with CO_2 provides **39** in 56% yield.

Asymmetric hydrogenation of **39** with the Noyori catalyst generates (*S*)-**41** in 90% yield with a disappointing 67:33 er. However, with [Rh(COD)-(+)-(2*S*,5*S*)-Et-DuPHOS]OTf as the catalyst, **39** is reduced to provide (*S*)-**41** in 98% yield with a 95:5 er.[14] Table 1 also shows the results of asymmetric hydrogenation of *N*-(3,5-dimethylphenyl amide) with either (*S*)-BINAP−$RuCl_2$ or [Rh-(COD)-(+)-(2*S*,5*S*)-Et-DuPHOS]OTf. A multigram preparation of (*S*)-**41** can be accomplished in four steps from commercially available ϵ-caprolactam in 30% overall yield.

(11) ^{1}H NMR shows a small amount of impurity around 1.0−2.0 ppm which was not separated from the product, but was removed in the following step.

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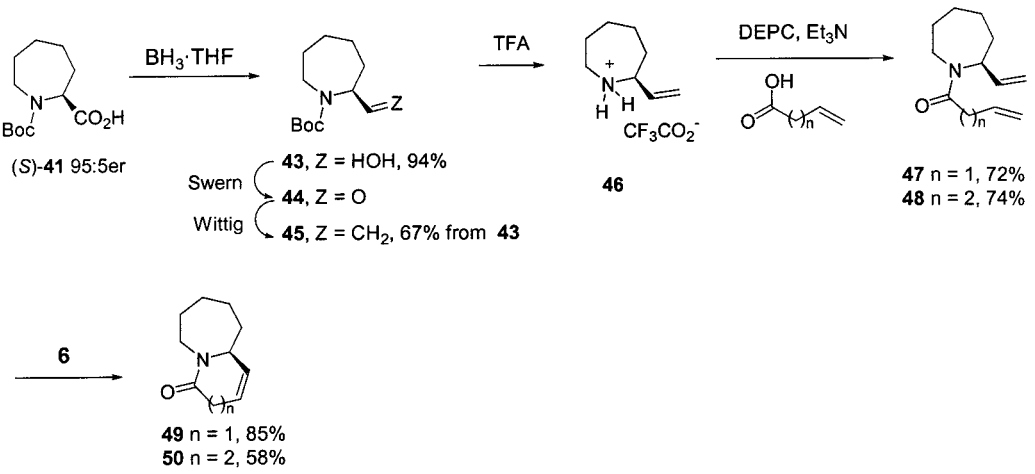
(13) Kieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180.

(14) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345.

Table 1. Reduction of 39 and Derivatives with the Catalyst

Y	catalyst*	product	yield, %	er
OH	(*S*)-BINAP−$RuCl_2$	(*S*)-**41**	90	67:33
OH	[Rh(COD)-(+)-(2*S*,5*S*)-Et-DuPHOS]OTf	(*S*)-**41**	98	95:5
NH-3,5-$Me_2C_6H_3$	(*S*)-BINAP−$RuCl_2$	(*S*)-**42**	88	67:33
NH-3,5-$Me_2C_6H_3$	[Rh(COD)-(+)-(2*S*,5*S*)-Et-DuPHOS]OTf	(*S*)-**42**	90	97:3

Scheme 6



The acid (*S*)-**41** is reduced with BH_3•THF to provide **43** in 94% yield (Scheme 6). Alcohol **43** is oxidized by a Swern oxidation to afford **44**, which is immediately reacted with the ylide of methyltriphenylphosphonium bromide to give **45** in 67% yield for two steps.[10] Deprotection of the Boc group, and amidation with either vinylacetic acid or pent-4-enoic acid, provided the corresponding dienes **47** and **48** in 72% and 74% yields, respectively. Ring-closing metathesis of the diene with the catalyst **6** provides bicyclic lactams in **49** and **50** in 85% and 58% yields, respectively.

In summary, asymmetric lithiation−substitution or asymmetric hydrogenation strategies can be combined with ring-closing metathesis to provide efficient syntheses of the highly enantioenriched bicyclic lactams **7**, **8**, **21**, **22**, **23**, **30**, **35**, **49**, and **50** with five-, six-, and seven-membered fused rings. The enantiomers of **21**, **22**, **23**, **30**, **35**, **49**, and **50** could be obtained by use of (*R*)-BINAP−$RuCl_2$ or [Rh(COD)-(−)-(2*R*,5*R*)-Et-DuPHOS]-OTf in the catalytic reduction. The enantioenriched compounds we have reported and the methodology provided should be useful for the syntheses of many synthetic targets, particularly the azabicyclic alkaloids.

Experimental Section

All air-sensitive reactions were performed in oven- or flame-dried glassware under nitrogen with freshly distilled solvents. Methylene chloride was distilled over CaH_2, and diethyl ether and tetrahydrofuran (THF) were distilled from sodium and benzophenone. Commercially available TMEDA was used to obtain racemic product and used without purification. *n*-BuLi solution in hexanes (1.6 M) was titrated prior to use against *N*-pivaloyl-*o*-toluidine. All other commercial reagents, including catalysts for RCM and hydrogenation, were used without further purification.

Purity of the sample is established to be >95% based on ^{13}C NMR spectra. Elemental analyses were carried out by the University of Illinois Microanalytical Service Laboratory. All numbered compounds were obtained as oils unless otherwise indicated. Diastereomeric purity was determined by ^1H NMR integration. "Standard workup" refers to dilution with diethyl ether, addition of H_2O, separation of phases, extraction of the aqueous layer with ether (3×), combination of the organic phases, drying with $MgSO_4$ and concentration by rotary evaporation.

Representative Diene Preparation: Synthesis of 1-(2-Styrylpyrrolidin-1-yl)but-3-en-1-one (4). To a stirring solution of (*S*)-*N*-Boc-2-styryl-pyrrolidine (220 mg, 0.80 mmol) in 20 mL of CH_2Cl_2 was added TFA (0.62 mL, 8.00 mmol), and the reaction mixture was stirred for 2 h. The solvent and excess TFA was removed under vacuum, and 50 mL of DMF was added. Triethylamine (0.67 mL, 4.80 mmol), diethyl cyanophosphonate (0.36 mL, 2.4 mmol), and vinylacetic acid (0.20 mL, 2.4 mmol) were added to the reaction mixture at 0 °C. After stirring overnight at room temperature, the reaction mixture was washed with aqueous 10% $NaHCO_3$. Standard workup and column chromatography (35% ethyl acetate in hexane) provided **4** (164 mg, 0.68 mmol, 85%) ^1H NMR ($CDCl_3$, 500 MHz, sample rotameric at room temperature) δ 1.90 (m, 2H), 2.01 (m, 1H), 2.19 (m, 1H), 3.15 (m, 2H), 3.61 (m, 2H), 4.57 (bt, J = 6.5 Hz, 0.7H), 4.86 (bt, J = 5.8 Hz, 0.3H), 5.13 (m, 2H), 6.02 (m, 1H), 6.16 (m, 1H), 6.43 (m, 1H), 7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.0, 22.0, 24.2, 31.0, 33.4, 39.9, 46.5, 58.3, 59.5, 117.9, 126.6, 126.7, 128.1, 128.6, 128.9, 129.9, 130.4, 170.7. HRMS: Calcd for $C_{16}H_{19}NO$: 241.1467; found: 241.1463.

Representative Ring-Closing Metathesis: Preparation of 2,3,6,8a-Tetrahydro-1*H*-indolizin-5-one (7). To a stirring solution of **4** (65 mg, 0.27 mmol) in 50 mL of CH_2Cl_2 was added the Grubbs catalyst **6** (11.5 mg, 0.014 mmol). The reaction mixture was refluxed for 28 h, and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography (25% MeOH in ethyl acetate) to afford **7** (32 mg, 0.23 mmol, 86%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.52 (qd, J = 11.9, 7.5 Hz, 1H), 1.86 (m, 1H), 2.02 (m, 1H), 2.16 (pent, J = 6.4 Hz, 1H), 2.95 (m, 2H), 3.44 (td, J = 11.2, 2.2 Hz, 1H), 3.74 (ddd, J = 17.9, 12.0, 9.0 Hz, 1H), 4.06 (bs, 1H), 5.81 (m, 1H), 5.89 (dm, J = 10.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.3, 32.3, 33.1, 44.3, 59.1, 123.2, 125.5, 166.78. HRMS: Calcd for $C_8H_{11}NO$: 137.0841; found: 137.0841.

1,2,3,6,7,9a-Hexahydro-pyrrolo[1,2-*a*]azepin-5-one (8). The general diene preparation was followed using **2** (277 mg, 1.01 mmol) to afford **5** (201 mg, 0.78 mmol, 78%). To a stirring solution of **5** (75.8 mg, 0.30 mmol) in 100 mL of CH_2Cl_2 was added **6** (13 mg, 0.015 mmol) and refluxed for 24 h. The solvent was removed under reduced pressure, and the resulting oil was purified by column chromatography (5% MeOH in ethyl acetate) to afford **8** (38 mg, 0.25 mmol, 84%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.7−1.9 (m, 3H), 2.29 (m, 2H), 2.44 (m, 2H), 2.92 (td, J = 14.1,

3.9 Hz, 1H), 3.46 (dt, J = 15.0, 7.7 Hz, 1H), 3.66 (ddd, J = 11.8, 7.6, 4.9 Hz, 1H), 4.55 (m, 1H), 5.53 (dq, J = 11.5, 2.2 Hz, 1H), 5.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.4, 25.0, 34.7, 35.2, 46.9, 55.3, 130.1, 130.4, 173.1. HRMS: Calcd for $C_9H_{13}NO$: 151.0997; found: 151.0997.

1-(2-Styryl-pyrrolidin-1-yl)-propenone (10). To a stirring solution of **2** (480 mg, 1.73 mmol) in 10 mL of CH_2Cl_2 was added TFA (1.33 mL, 17.3 mmol) and stirred for 2 h. The solvent and excess TFA was removed under vacuum. The resulting oil was dissolved in 10 mL of CH_2Cl_2 followed by triethylamine (2.46 mL, 17.3 mmol) and acryloyl chloride (1.40 mL, 17.3 mmol) treatment. Standard workup and column chromatography provided **10** (320 mg, 1.41 mmol, 81%). ^{1}H NMR ($CDCl_3$, 500 MHz, sample rotameric at room temperature) δ 1.92 (m, 2H), 2.05 (m, 1H), 2.20 (m, 1H), 3.64 (m, 1H), 3.72 (m, 1H), 4.66 (bt, J = 6.5 Hz, 0.8H), 4.94 (bt, J = 6.5 Hz, 0.2H), 5.16 (dd, J = 9.7, 3.0 Hz, 0.8H), 5.72 (dd, J = 10.0, 2.4 Hz, 0.2H), 6.19 (m, 1H), 6.47 (m, 3H), 7.31 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.0, 22.0, 31.0, 33.3, 46.6, 58.5, 59.3, 126.7, 127.7, 128.1, 128.6, 128.9, 129.2, 130.2, 130.6, 136.4, 137.4, 164.8, 165.6. HRMS: Calcd for $C_{15}H_{17}NO$: 227.1310; found: 227.1312.

6,7,8,8a-Tetrahydro-5*H*-indolizin-3-one (21). To a stirring solution of **16** (374 mg, 1.77 mmol) in 25 mL of CH_2Cl_2 was added TFA (1.35 mL, 17.7 mmol) and stirred for 2 h. The solvent and excess TFA was removed under vacuum. The resulting oil was dissolved in 50 mL of THF, and K_2CO_3 (2.45 g, 17.7 mmol) was added along with acryloyl chloride (1.43 mL, 17.7 mmol). The reaction mixture was diluted with 5% HCl (150 mL), after refluxing for 24 h. The aqueous layer was extracted with ether (3 × 50 mL), washed with saturated Na_2CO_3 (pH = 9.0), and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography (35% ethyl acetate in petroleum ether), providing 1-(2-vinylpiperidin-1-yl)propenone **18** (196 mg, 1.18 mmol, 67%). HRMS: Calcd for $C_{10}H_{15}NO$: 165.1154; found: 165.1156. General ring-closing metathesis procedure was followed using **18** (160 mg, 0.965 mmol) in 20 mL of CH_2Cl_2 and **6** (40 mg, 0.048 mmol) to afford **21** (109 mg, 0.80 mmol, 82%) after the purification by flash chromatography (75% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (qd, J = 12.9, 3.5 Hz, 1H), 1.29 (qdd, J = 13.0, 5.1, 3.6 Hz, 1H), 1.51 (qt, J = 13.2, 3.2 Hz, 1H), 1.75 (dm, J = 12.9 Hz, 1H), 1.92 (dm, J = 13.3 Hz, 1H), 2.10 (dm, J = 13.3 Hz, 1H), 2.83 (td, J = 12.9, 3.7 Hz, 1H), 3.86 (dm, J = 12.2 Hz, 1H), 4.28 (dd, J = 13.3, 5.0 Hz, 1H), 6.15 (dd, J = 5.9, 1.7 Hz, 1H), 7.02 (dd, J = 5.8, 1.3 hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.7, 25.5, 30.9, 39.4, 61.6, 127.6, 147.1, 169.1. HRMS: Calcd for $C_8H_{11}NO$: 137.0841; found: 137.0844.

3,6,7,8,9,9a-Hexahydro-quinolizin-4-one (22). General diene preparation procedure was followed using **16** (1.2 g, 5.68 mmol) to afford **19** (930 mg, 5.18 mmol, 91%). To a stirring solution of **19** (323 mg, 1.80 mmol) in 35 mL of CH_2Cl_2 the Grubbs catalyst **9** (74 mg, 0.09 mmol) was added, and the reaction mixture was refluxed for 24 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography (65% ethyl acetate in petroleum ether) to afford **22** (254 mg, 1.68 mmol, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12 (qd, J = 13.0, 3.1 Hz, 1H), 1.27 (qt, J = 13.0, 3.7 Hz, 1H), 1.39 (qt, J = 13.1, 3.7 Hz, 1H), 1.55 (bd, J = 12.4 Hz, 1H), 1.72 (m, 2H), 2.31 (td, J = 13.1, 2.6 Hz, 1H), 2.78 (bs, 2H), 3.68 (m, 1H), 4.71, (dm, J = 13.1 Hz, 1H), 5.45 (dm, J = 10.7 Hz, 1H), 5.53 (dm, J = 10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.8, 25.4, 31.8, 34.3, 42.3, 58.4, 121.1, 125.9, 165.8. HRMS: Calcd for $C_9H_{13}NO$: 151.0997; found: 151.0989.

1,3,4,7,8,10a-Hexahydro-2*H*-pyrido[1,2-*a*]azepin-6-one (23). General procedure for the diene preparation was followed using **16** (182 mg, 0.86 mmol) to afford **20** (150 mg, 0.78 mmol, 90%). To a stirring solution of **20** (140 mg, 0.726 mmol) in 15 mL of CH_2Cl_2 was added the Grubbs catalyst **9** (30 mg, 0.04 mmol), and the reaction mixture was refluxed for 24 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography (65% ethyl acetate in petroleum ether) to afford **23** (101 mg, 0.611 mmol, 84%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.62 (m, 5H), 1.79 (m, 1H), 2.38 (m, 2H), 2.42 (dt, J = 13.1, 4.6 Hz, 1H), 3.16 (ddd, J = 13.3, 10.5, 7.0 Hz, 1H), 3.33 (ddd, J = 13.6, 9.0, 4.2 Hz, 1H), 3.74 (td, J = 13.3, 4.9 Hz, 1H), 4.62 (m, 1H), 5.56, (dm, J = 11.1 Hz, 1H), 5.68 (dm, J = 11.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.6, 23.2, 25.5, 29.5, 35.5, 40.0, 52.4, 131.0, 131.1, 175.1. HRMS: Calcd for $C_{10}H_{15}NO$: 165.1154; found: 165.1153.

Hexahydro-indolizin-3-one (26). To a stirring solution of **21** (72 mg, 0.53 mmol) in 10 mL of MeOH was added PtO_2 (12 mg, 0.05 mmol). The heterogeneous mixture was hydrogenated for 8 h at room temperature using a balloon. The solvent was removed, and the crude product was purified by flash chromatography (20% MeOH in ethyl acetate) to afford **26** (69 mg, 0.495 mmol, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (m, 1H), 1.36 (m, 2H), 1.57 (m, 1H), 1.68 (m, 1H), 1.86 (m, 2H), 2.19 (m, 1H), 2.34 (m, 2H), 2.60 (td, J = 12.5, 3.4 Hz, 1H), 3.39 (md, J = 3.39 Hz, 1H), 4.10 (dm, J = 13.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 24.7, 25.6, 30.5, 33.8, 40.4, 57.5, 173.8. HRMS: Calcd for $C_8H_{13}NO$: 139.0997; found: 138.0921 (M − 1 calcd: 138.0919).

Octahydro-quinolizin-4-one (27). To a stirring solution of **22** (200 mg, 1.322 mmol) in 30 mL of MeOH was added PtO_2 (30 mg, 0.132 mmol) was added. The heterogeneous mixture was hydrogenated for 5 h at room temperature using a balloon. The solvent was removed, and the crude product was purified by flash chromatography (20% MeOH in ethyl acetate) to afford **27** (172 mg, 1.12 mmol, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (m, 4H), 1.66 (m, 3H), 1.79 (m, 2H), 1.94 (m, 1H), 2.34 (m, 3H), 3.19 (m, 1H), 4.74 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4, 24.7, 25.6, 30.7, 33.2, 34.2, 42.5, 57.1, 169.5. HRMS: Calcd for $C_9H_{15}NO$: 153.1154; found: 153.1151.

3-Methyl-octahydro-quinolizin-4-one (28). A solution of **27** (133 mg, 0.869 mmol) in 15 mL of THF was cooled to −78 °C, and *t*-BuLi (0.61 mL, 1.04 mmol) was added. After stirring for 10 min, methyl iodide (0.08 mL, 1.30 mmol) was added. After stirring for 2 h, the solution was warmed to room temperature. Standard workup and purification by column chromatography (50% ethyl acetate in hexane) afforded **28** (126 mg, 0.75 mmol, 87%, 3:2 dr; R_f = 0.30 and 0.25). The diastereomers were separated using preparative HPLC (30% ethyl acetate in hexane). **Major diastereomer:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (d, J = 7.2 Hz, 3H), 1.45 (m, 5H), 1.72 (m, 2H), 1.81 (m, 1H), 1.88 (m, 1H), 2.01 (m, 1H), 2.36 (m, 2H), 3.21 (m, 1H), 4.78 (dm, J = 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.7, 24.5, 25.6, 28.1, 30.2, 34.75, 37.3, 42.6, 57.6, 172.9. HRMS: Calcd for $C_{10}H_{17}NO$: 167.1310; found: 167.1308. **Minor diastereomer:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (d, J = 7.2 Hz, 3H), 1.45 (m, 5H), 1.72 (m, 2H), 1.87 (m, 2H), 2.01 (m, 1H), 2.42 (m, 2H), 3.25 (m, 1H), 4.76 (dm, J = 13.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.2, 24.9, 25.6, 26.5, 27.3, 34.0, 36.8, 43.2, 57.1, 172.9. HRMS: Calcd for $C_{10}H_{17}NO$: 167.1310; found: 167.1307.

3-Allyl-octahydro-quinolizin-4-one (29). A solution of **27** (73 mg, 0.48 mmol) in 15 mL of THF was cooled to −78 °C, and *t*-BuLi (0.34 mL, 0.58 mmol) was added. After stirring for 10 min, allyl bromide (0.06 mL, 0.72 mmol) was added. After stirring for 2 h, the solution was warmed to room temperature, providing **29** (81 mg, 88%, ∼2:1 dr). The diastereomers were separated by flash chromatography (65% ethyl acetate in petroleum ether). Major diastereomer: 53.4 mg, 0.28 mmol, 58%, R_f = 0.40; minor diastereomer: 28 mg, 0.15 mmol, 30%, R_f = 0.32). **Major diastereomer:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (m, 1H), 1.42 (m, 4H), 1.72 (m, 2H), 1.84 (m, 2H), 2.02 (m, 1H), 2.23 (m, 2H), 2.38 (td, J = 12.8, 2.8 Hz, 1H), 2.75 (m, 1H), 3.19 (m, 1H), 4.77 (dm, J = 13.2 Hz, 1H), 5.04 (m, 2H), 5.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 24.6, 25.6, 30.1, 34.8, 36.2, 41.9, 42.6, 57.4, 116.6, 137.2, 171.5. HRMS: Calcd for $C_{12}H_{19}NO$: 193.1467; found: 193.1461. **Minor diastereomer:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (m, 4H), 1.67 (m, 5H), 1.86 (m, 2H), 2.25 (m, 1H), 2.39 (m, 2H), 2.66 (m, 1H), 3.25 (m, 1H), 4.76 (dm, J = 13.4 Hz, 1H), 5.06 (m, 2H), 5.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 25.0, 25.7, 27.2, 34.0, 36.4, 41.5, 43.4, 57.2, 116.8, 137.0, 171.5. HRMS: Calcd for $C_{12}H_{19}NO$: 193.1467; found: 193.1462.

3-Allyl-3-methyl-octahydro-quinolizin-4-one (30). A solution of **29** (35 mg, 0.18 mmol) in 10 mL of THF was cooled to −78 °C, and *t*-BuLi (0.13 mL, 0.22 mmol) was added. After stirring for 10 min, methyl iodide (0.014 mL, 0.23 mmol) was added. After stirring for 2 h, the solution was warmed to room temperature, providing **30** (29 mg, 78%, 3:1 dr). The diastereomers were separated by flash chromatography (50% ethyl acetate in petroleum ether). Major diastereomer: 22 mg, 0.11 mmol, 59% R_f = 0.50; minor diastereomer: 7 mg, 0.03 mmol, 19%, R_f = 0.42. **Major diastereomer:** ^{1}H NMR ($CDCl_3$, 500

MHz) δ 1.18−1.5 (m, 6H), 1.67−1.89 (m, 5H), 2.02 (m, 1H), 2.25 (m, 2H), 2.39 (td, J = 13.1, 3.2 Hz, 1H), 2.76 (m, 1H), 3.20 (m, 1H), 4.78 (dm, J = 14.3 Hz, 1H), 5.05 (m, 2H), 5.80 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.5, 24.6, 25.6, 30.0, 34.7, 36.2, 41.9, 42.6, 57.4, 116.6, 137.2, 164.8. HRMS: Calcd for $C_{13}H_{21}NO$: 207.1623; found: 207.1621.

2-Propyl-6-vinylpiperidine-1-carboxylic Acid *tert*-Butyl Ester. A suspension of Ph_3PCH_3Br (1.39g, 3.9 mmol) in 50 mL of THF was cooled to −78 °C, and *n*-BuLi (2.06 mL, 3.3 mmol) was added. After stirring for 10 min, the reaction mixture was warmed to room temperature and stirred for addition 30 min. The aldehyde **33** (758 mg, 3.00 mmol) in 10 mL of THF was slowly added to the ylide at −78 °C. After the reaction mixture was stirred for 2 h, standard workup and flash chromatography (7% ethyl acetate in hexane) provided 2-propyl-6-vinylpiperidine-1-carboxylic acid *tert*-butyl ester (503 mg, 1.99 mmol, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz, sample rotameric at room temperature) Contains impurity, δ 0.8−1.8 (m, >10H), 4.08 (m, 1H), 4.65 (bs, 1H), 4.98 (dt, J = 10.5, 1.6 Hz, 1H), 5.07 (dt, J = 17.1, 1.9 Hz, 1H), 5.85 (ddd, J = 17.5, 10.7, 5.6 Hz, 1H).

1-(2-Propyl-6-vinylpiperidin-1-yl)but-3-en-1-one (34). The standard procedure for the diene synthesis was followed using 2-propyl-6-vinylpiperidine-1-carboxylic acid (400 mg, 1.58 mmol) to afford **34** (195 mg, 0.88 mmol, 56%) after flash chromatography (35% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$, 500 MHz, sample rotameric at room temperature) δ 0.86 (m, 3H), 1.2−1.7 (m, 10H), 1.9 (m, 1H), 3.01 (m, 1H), 3.18 (m, 1H), 3.80 (m, 0.33 H), 4.39 (m, 0.33H), 4.64 (m, 0.34H), 5.10 (m, 4H), 5.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 14.7, 14.8, 20.62, 27.1, 27.4, 28.2, 29.5, 36.2, 36.7, 39.2, 48.6, 48.9, 53.2, 54.1, 114.8, 115.8, 117.4, 132.5, 139.8, 170.6, 170.9. HRMS: Calcd for $C_{14}H_{23}NO$: 221.1780; found: 221.1781.

6-Propyl-3,6,7,8,9,9a-hexahydro-quinolizin-4-one (35). The standard procedure for the ring-closing metathesis was followed using **34** (139 mg, 0.628 mmol) and **6** (26.6 mg, 0.03 mmol) to afford **35** (114 mg, 0.59 mmol, 94%) after flash chromatography (50% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J = 7.4 Hz, 3H), 1.31 (m, 2H), 1.50 (m, 2H), 1.67 (m, 1H), 1.74 (m, 2H), 1.82 (m, 2H), 2.02 (m, 1H), 2.89 (m, 2H), 3.69 (m, 1H), 3.98 (m, 1H), 5.58 (dm, J = 10.2 Hz, 1H), 5.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.3, 19.5, 20.6, 24.8, 31.3, 33.8, 35.9, 55.7, 56.8, 122.4, 127.4, 168.3. HRMS: Calcd for $C_{12}H_{19}NO$: 193.1467; found: 193.1478. M − 1 calcd for 192.1388; found 192.1391.

4,5,6,7-Tetrahydro-azepine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester (39). To a solution of *N*-Boc-2,3,4,5-tetrahydroazepine **38** (12.43g, 63.05 mmol) and TMEDA (9.52g, 81.96 mmol) in anhydrous THF (125 mL, 0.5M) at −65 °C was added dropwise *n*-BuLi (53 mL, 81.96 mmol) in hexane. The resulting yellow mixture was slowly warmed to −30 °C over 3 h and then stirred additional 45 min at −30 °C. This reaction mixture was then cooled to −78 °C, and CO_2 was passed through the solution for 30 min. The reaction was allowed to reach to ambient temperature slowly. Saturated solution of NH_4Cl was poured into the mixture and extracted with ether. The organic layer was washed with 10% NaOH (pH = 8−10), and then the resulting aqueous layer was acidified with 3 M HCl. The aqueous layer was washed with ether, brine, dried over $MgSO_4$, filtered, and then concentrated in vacuo. The yellow mixture was purified by flash chromatography on silica gel to give **39** (8.58 g, 56%). Melting point 77−80 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 1.42 (s, 9H), 1.40−1.67 (m, 3H), 1.78−1.84 (m, 2H), 2.33−2.39 (m, 2H), 3.49 (bs, 1H), 6.78 (t, 1H). Elemental Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.38; H, 7.99; N, 5.75. HRMS (EI) *m*/*z* calcd for $C_{12}H_{19}NO_4$ 241.1314; found 241.1314.

7-(3,5-Dimethyl-phenylcarbamoyl)-2,3,4,5-tetrahydro-azepine-1-carboxylic Acid *tert*-Butyl Ester (40). To a solution of (*S*)-**39** (308 mg, 1.27 mmol), DCC(262 mg, 1.27 mmol), and HOBT(206 mg, 1.52 mmol) in methylene chloride (15 mL) was added 3,5-dimethylaniline (185 mg, 1.52 mmol) at room temperature. The resulting mixture was stirred for 24 h and filtered through a pad of Celite. The filtrate was concentrated in vacuo and was purified by flash chromatography on silica gel to give **40** (279 mg, 64%): Melting point: 139−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (bs, 9H), 1.44−1.48 (m, 4H), 1.82−1.89 (t, 2H), 2.26 (s, 6H), 3.50 (bs, 2H), 6.60−6.63 (t, 1H), 6.71 (s, 1H), 7.18 (s, 2H), 7.69 (bs, 1H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 21.17, 23.06, 27.01, 27.91, 28.59, 47.56, 81.06, 117.29, 125.67, 131.06, 137.48, 138.40, 139.21, 153.54, 162.83. LRMS(FAB) calcd for $C_{20}H_{28}N_2O_3$: 344.2; found 345.2 ($M^+ + H$)

Representative Catalytic Hydrogenation of Enecarbamates: Preparation of (*S*)-Azepane-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester (41). [Rh(COD)-(+)-(2*S*,5*S*)-Et-DuPHOS]OTf (100 mg, 0.138 mmol) was added to a solution of **39** (667 mg, 2.76 mmol) in 10 mL of MeOH. The tube was pressurized to 1000 psi of hydrogen for 20 h at room temperature. The solvent was evaporated, and the resulting oil was purified by flash chromatography to give **41** (659 mg, 98%). Melting point: 110−112 °C (lit.[15] 110−113 °C); $[\alpha]^{20} = -59.1°$ (c = 1.0, MeOH) (lit. $[\alpha]^{20} = -58°$, c = 1.0, MeOH, *S*-enantiomer); ^{1}H NMR (500 MHz;$CDCl_3$, sample rotameric at room temperature) δ 1.21−1.38 (m, 3H), 1.41, 1.46 (s, 9H), 1.85−2.07 (m, 4H), 2.25−2.38 (m, 1H), 2.88−3.04, 3.40−3.41 (bt, 1H), 3.77−3.82, 3.94−4.13 (bd, 1H), 4.38−4.36, 4.63−4.59 (m, 1H), 10.21 (bs, 1H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 14.0, 25.3, 26.1, 28.2, 28.3, 29.1, 29.2, 29.4, 29.5, 29.7, 30.3, 30.5, 43.3, 43.9, 58.0, 59.5, 60.4, 80.3, 155.3, 156.7, 177.8, 178.9. HRMS(EI) *m*/*z* calcd for $C_{12}H_{21}NO_4$ 241.1314, found 198.1497($M^+ - CO_2H$). The enantiomeric purity was determined to be 95:5 by CSP−HPLC analysis of the 3,5-dimethylaniline derivative obtained above on a Pirkle concept Whelk-O column with 5%(v/v) isopropyl alcohol/hexane mobile phase by a flow rate 1.5 mL/min. The major enantiomer had a retention time of 16.7 min, and the minor enantiomer had a retention time of 11.1 min.

(*S*)-2-(3,5-Dimethylphenylcarbamoyl)azepane-1-carboxylic Acid *tert*-Butyl Ester (42). The standard procedure for the catalytic hydrogenation was followed using **40** (42.5 mg, 0.12 mmol) in 5 mL of MeOH to afford **42** (38 mg, 0.11 mmol, 90%). ^{1}H NMR (500 MHz;$CDCl_3$), δ 1.35 (s, 9H), 1.72−2.20 (m, 8H), 2.28(bs, 6H), 2.92−2.97 (bt, 1H), 3.71−3.75 (bd, 1H), 4.57−4.62(m, 1H), 6.72(bs, 1H), 7.18(bs, 2H), 8.62(bs, 1H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 21.57, 28.63, 29.61, 58.97, 80.86, 117.55, 125.81, 138.85, 157.81, 170.63. LRMS(FAB) *m*/*z* calcd for $C_{20}H_{30}N_2O_3$ 346.4; found 347.2($M^+ + H$). The enantiomeric purity was determined to be 97:3 er by CSP−HPLC analysis of the product obtained above on a Pirkle concept Whelk-O column with 5% (v/v) isopropyl alcohol/hexane mobile phase by a flow rate 1.5 mL/min. The major enantiomer had a retention time of 16.91min, and the minor enantiomer had a retention time of 11.06 min.

2-Hydroxymethylazepane-1-carboxylic Acid *tert*-Butyl Ester (43). To a stirring solution of **41** (665 mg, 2.73 mmol) in 40 mL of THF cooled to 0 °C was added BH_3·THF (1.0 M in THF, 4.1 mL, 4.1 mmol). The reaction mixture was warmed to room temperature, and 1 mL of water was added. Potassium carbonate (700 mg) was added, and the mixture was stirred for 30 min. Standard workup and flash chromatography (50% ethyl acetate in petroleum ether) provided **43** (586 mg, 2.56 mmol, 94%). $[\alpha]^{20} = -58.4°$ (c = 0.01, $CHCl_3$) (lit.[16] $[\alpha] = -62.8°$, c = 0.31, $CHCl_3$, *S*-enantiomer); ^{1}H NMR ($CDCl_3$, 500 MHz, sample rotameric at room temperature) δ 1.16 (m, 3H), 1.37 (m, 9H), 1.39 (m, 1H), 1.59 (m, 1H), 1.72 (m, 2H), 1.92 (m, 1H), 2.69 (m, 0.8H), 3.01 (m, 0.2H), 3.40 (m, 2H), 3.56 (bd, J = 14.4 Hz, 0.7H), 3.71 (bd, J = 14.4 Hz, 0.3H), 3.88 (m, 0.2H), 4.03 (m, 0.8H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.3, 28.6, 28.6, 29.6, 29.6, 30.1, 42.5, 42.9, 57.5, 57.8, 65.1, 65.7, 79.7, 157.8. HRMS: Calcd for $C_{12}H_{23}NO_3$: 229.1678; found: 229.1680.

2-Vinylazepane-1-carboxylic Acid *tert*-Butyl Ester (45). A solution of oxalyl chloride (0.27 mL, 3.06 mmol) in 20 mL of CH_2Cl_2 under nitrogen was cooled to −78 °C and stirred for 15 min. A solution of DMSO (0.36 mL, 5.1 mmol) in 2 mL of CH_2Cl_2 was added, and the mixture was stirred for 10 min. A solution of **43** (586 mg, 2.55 mmol) in 5 mL of CH_2Cl_2 was added dropwise and stirred for 2 h. Diisopropylethylamine (1.78 mL, 10.2 mmol) was added slowly, and the solution was warmed to room temperature. The mixture was washed with 1 M HCl (10 mL), and standard workup provided 2-formyl-azepane-1-carboxylic acid *tert*-butyl ester **44** which was used immediately in the next step. *n*-BuLi (1.59 mL, 2.55 mmol) was added to a

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stirring suspension of Ph_3PCH_3Br (1.09 g, 3.06 mmol) in 20 mL of THF at −78 °C. After stirring for 15 min, the solution was warmed to room temperature for 30 min. The reaction mixture was cooled to −78 °C, and 2-formylazepane-1-carboxylic acid *tert*-butyl ester was added. After stirring for 1 h, the reaction mixture was warmed to room temperature. Standard workup and flash chromatography (10% ethyl acetate in petroleum ether) provided **45** (382 mg, 1.70 mmol, 67%). ^{1}H NMR ($CDCl_3$, 500 MHz, sample rotameric at room temperature) δ 1.0−1.5 (m, 11H), 1.68 (m, 4H), 2.03 (m, 2H), 2.64 (t, J = 14.4 Hz, 1H), 3.64 (bd, J = 14.2 Hz, 0.6H), 3.81 (bd, J = 13.9 Hz, 0.4H), 4.34 (m, 0.5H), 4.54 (m, 0.5H), 4.94 (m, 2H), 5.68 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.0, 25.4, 28.5, 28.6, 28.7, 29.3, 29.4, 29.8, 29.9, 33.7, 34.1, 41.9, 42.4, 56.7, 58.0, 112.9, 113.0, 138.4, 138.7, 156.0. HRMS: Calcd for $C_{13}H_{23}NO_2$: 225.1729; found: 225.1734.

1-(2-Vinylazepan-1-yl)but-3-en-1-one (47). The standard procedure for the diene preparation was followed using **45** (168 mg, 0.745 mmol) to afford **47** (104 mg, 0.53 mmol, 72%) after flash chromatography (35% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz, sample rotameric at room temperature) δ 1.16−2.10 (m, 7H), 2.13 (m, 1H), 2.60 (tm, J = 12.8 Hz, 1H), 2.95−3.30 (m, 2H), 3.60 (m, 0.5H), 4.20 (m, 1.5H), 5.00 (m, 2H), 5.13 (m, 2H), 5.73 (m, 1H), 5.98 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.8, 25.2, 28.7, 29.6, 29.9, 30.5, 32.9, 34.6, 38.8, 38.9, 41.3, 43.0, 55.4, 59.3, 113.6, 114.0, 117.6, 117.7, 132.4, 137.6, 137.7, 171.5 HRMS: Calcd for $C_{12}H_{19}NO$: 193.1467; found: 193.1467.

1-(2-Vinylazepan-1-yl)pent-4-en-1-one (48). The standard procedure for the diene preparation was followed using **45** (92 mg, 0.41 mmol) to afford **48** (63 mg, 0.30 mmol, 74%) after flash chromatography (35% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.19−1.98 (m, 7H), 2.14 (m, 1H), 2.30−2.60 (m, 5H), 2.98 (ddd, J = 15.6, 12.2, 1.1 Hz, 0.5H), 3.61 (dm, J = 15.2 Hz, 0.5H), 4.22 (m, 1H), 5.02 (m, 4H), 5.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.9, 25.3, 28.8, 29.6, 30.0, 30.4, 32.7, 32.8, 33.0, 34.7, 41.3, 43.0, 55.4, 59.3, 113.5, 113.9, 115.2, 115.3, 137.7, 137.8, 138.0, 138.02, 172.2. HRMS: Calcd for $C_{13}H_{21}NO$: 207.1623; found: 207.1618.

6,7,8,9,10,10a-Hexahydro-3*H*-pyrido[1,2-*a*]azepin-4-one (49). The standard procedure for the ring closing metathesis was following using **47** (78 mg, 0.40 mmol) and the Grubbs catalyst **6** (17 mg, 0.02 mmol) to afford **49** (56 mg, 0.34 mmol, 85%) after flash chromatography (65% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.53 (m, 3H), 1.63 (m, 3H), 1.95 (m, 2H), 2.79 (ddd, J = 14.2, 10.7, 4.0 Hz, 1H), 2.94 (m, 2H), 3.98 (m, 1H), 4.36 (td, J = 14.0, 4.7 Hz, 1H), 5.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.5, 26.4, 27.4, 32.3, 37.8, 46.1, 60.1, 121.9, 128.0, 167.9. HRMS: Calcd for $C_{10}H_{15}NO$: 165.1154; found: 165.1153.

3,4,7,8,9,10,11,11a-Octahydro-azepino[1,2-*a*]azepin-5-one (50). The standard procedure for the ring-closing metathesis was following using **48** (53 mg, 0.27 mmol) and the Grubbs catalyst **6** (12 mg, 0.014 mmol) to afford **50** (28 mg, 0.16 mmol, 58%) after flash chromatography (5% MeOH in ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22−1.56 (m, 4H), 1.86 (m, 2H), 1.96 (m, 2H), 2.16 (m, 2H), 2.73 (dd, J = 14.0, 12.1 Hz, 1H), 2.91 (m, 1H), 3.67 (dm, J = 17.6 Hz, 1H), 4.78 (m, 1H), 4.24 (dm, J = 13.8 Hz, 1H), 5.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.6, 29.7, 30.4, 34.8, 34.9, 36.5, 40.1, 56.7, 121.7, 129.1, 164.8. HRMS: Calcd for $C_{11}H_{17}NO$: 179.1310; found: 179.1308.

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