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Note

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Asymmetric Synthesis of 2-Substituted Azetidin-3-ones via Metalated SAMP/RAMP Hydrazones

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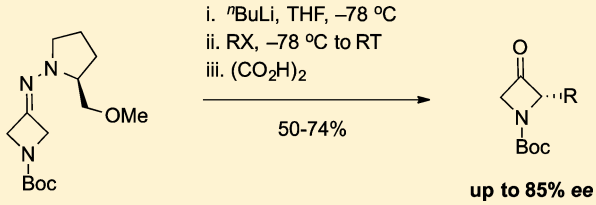
Supporting Information

ABSTRACT: 2-Substituted azetidin-3-ones can be prepared in good yields and enantioselectivities (up to 85% ee) by a one-pot procedure involving the metalation of the SAMP/RAMP hydrazones of *N*-Boc-azetidin-3-one, reaction with a wide range of electrophiles, including alkyl, allyl, and benzyl halides and carbonyl compounds, followed by hydrolysis using oxalic acid.



Azetidines are an important class of azaheterocycle that has attracted considerable interest in recent years as a structural motif within drug discovery. They possess a broad range of biological activities[1] and provide a means of introducing molecular rigidity, novelty, and improved pharmacological profiles in lead optimization programs.[2] Substituted azetidines are present in several natural products and compounds patented for pharmaceutical applications, including the marketed drug Azelnidipine,[3] Penaresidin A,[1b,4] antithrombotics,[5] and GLPG1690 (Figure 1).[6] While a number of methods have been developed for the preparation of azetidines,[7] only limited methods exist for the stereocontrolled synthesis of chiral derivatives. These include rhodium- or copper-catalyzed N−H insertion reactions of diazoketones derived from α-amino acids,[8] gold-catalyzed oxidative cyclization of chiral *N*-propagylsulfonamides,[9] nickel-catalyzed cross-coupling of organozinc reagents with chiral aziridines,[10] lithiation−electrophilic substitution of *tert*-butoxythiocarbonyl (Botc)-protected azetidine in the presence of a chiral ligand,[11] through imino-aldol reactions of ester enolates with chiral aldimines[12] and via the organocatalyzed synthesis of α-chloroaldehydes.[13] These approaches either have limited scope, involve multiple steps with low overall yield, or introduce the azetidine substituent early on in the synthesis, thereby reducing the efficiency by which structure−activity relationships (SAR) can be explored. In particular, the asymmetric routes do not provide sufficiently general methods to 2-substituted azetidin-3-ones.

To provide both a general and short asymmetric synthesis of 2-substituted azetidin-3-ones, and thus increase the diversity of chiral azetidine building blocks available, we decided to explore the SAMP/RAMP hydrazone methodology developed by Enders,[14] which we recently applied to the asymmetric synthesis of 2-substituted oxetan-3-ones.[15] This could allow a rather direct and efficient access to a broad range of 2,3-disubstituted azetidines[16] and other pharmaceutically relevant nitrogen heterocycles.[17]

Our proposed strategy from commercial *N*-Boc-azetidin-3-one is depicted in Scheme 1. The α-lithiation and alkylation of selected N-protected azetidines are well-documented, providing further encouragement for this study.[18] In this Note, we demonstrate how a variety of chiral 2-substituted azetidin-3-ones can be prepared in high enantioselectivity in one pot by the metalation/alkylation of the SAMP/RAMP hydrazones derived from *N*-Boc-azetidin-3-one, offering a procedurally straightforward route to these pharmaceutically relevant building blocks.

The SAMP hydrazone (*S*)-**1** was prepared in quantitative yield by treatment of SAMP with an excess of commercially available *N*-Boc-azetidin-3-one at 55 °C without solvent (Table 1). The corresponding *R*-enantiomer was made using RAMP in an identical fashion. In order to optimize the metalation of (*S*)-**1**, a screen of different lithium bases, metalation times, solvents, and concentrations was performed, where the lithiated intermediate was quenched with deuterated methanol. The conversion of **1** to **2** was estimated by mass spectrometry, and deuterated product **2** was isolated by chromatography (Table 1). Initial reactions using 1.1 equiv of either ^{t}BuLi or LDA in THF indicated a higher yield of **2** using ^{t}BuLi (entries 1 and 2, Table 1). A decrease in the metalation time to 1 h led to an increase to 73% yield (entry 4). This finding perhaps suggests that the lithiated heterocycle has moderate stability under these reaction conditions. By reducing the reaction concentration to 0.1 M and reverting to a 2 h metalation time, a further improvement in yield to 77% was achieved (entry 6). No improvement in yield was observed when a mixture of THF and pentane was used as solvent (entry 7). With a highest yield of 77% for **2** using ^{t}BuLi as the base (THF, metalation time 2 h, concentration 0.1 M, entry 6), we decided to explore use of easier to handle ^{n}BuLi under the same reaction conditions. Satisfyingly, this led to a further small improvement in yield (entry 8).

Having identified practical conditions for the lithiation of **1**, we turned our attention to the optimization of the yield and

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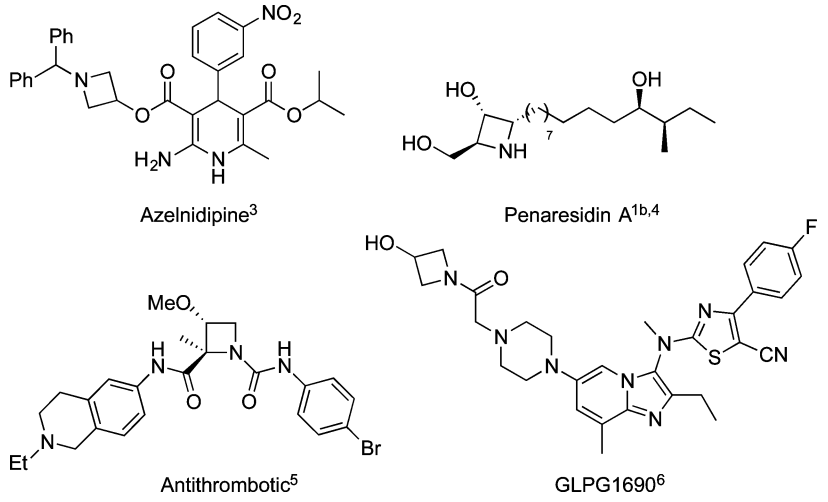


Figure 1. Examples of biologically active 3-oxygenated azetidines.

Scheme 1. Proposed Route to Chiral 2-Substituted Azetidin-3-ones

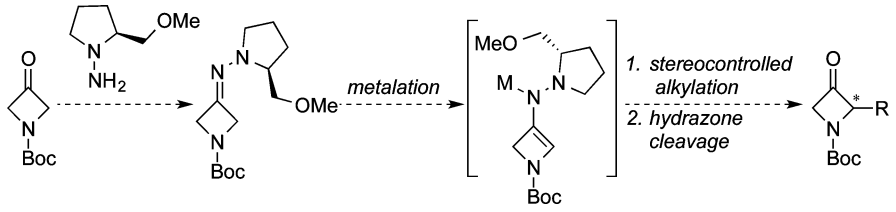
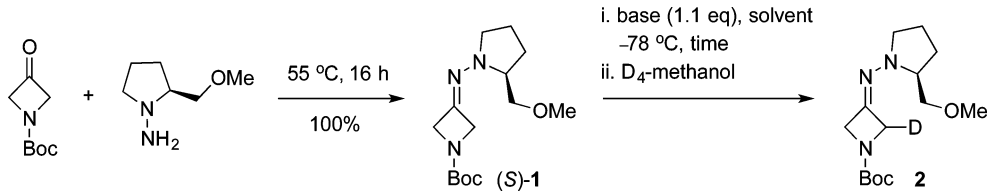


Table 1. Optimization of Conditions for Lithiation of SAMP Hydrazone (*S*)-1



entry	base	solvent	time (h)	concn (M)	yield of **2** (%)[a]	conversion (%)[b]
1	^{t}BuLi	THF	2	0.3	55	84
2	LDA	THF	2	0.3	49	72
3	^{t}BuLi	THF	3	0.3	45	83
4	^{t}BuLi	THF	1	0.3	73	83
5	^{t}BuLi	THF	1	0.1	69	85
6	^{t}BuLi	THF	2	0.1	77	86
7	^{t}BuLi	1:1 THF/pentane	2	0.1	67	86
8	^{n}BuLi	THF	2	0.1	81	84

[a]Isolated yield after chromatography. [b]Determined by mass spectrometry.

stereoselectivity for the subsequent alkylation step with allyl bromide. An initial reaction using the best lithiation conditions and 1.2 equiv of allyl bromide gave hydrazone **3** in 66% yield after chromatography (Scheme 2). Hydrolysis of **3** using aqueous oxalic acid provided ketone (*S*)-**4** in 75% yield (50% over two steps) and 81% ee (as determined by chiral GC). The racemic ketone **4** was prepared from achiral hydrazone **5** using the same general approach.[19,20]

We briefly examined the use of alternative nitrogen-protecting groups in this chemistry. The alternative SAMP hydrazone **6** derived from *N*-benzhydrylazetidin-3-one produced **7** in low 20% yield after hydrolysis, indicating that the Boc group is a better N-protecting group for this chemistry (Scheme 3).

By performing the two-step sequence from **1** to (*S*)-**4** in one pot, omitting isolation of the hydrazone intermediate **3**, ketone (*S*)-**4** was prepared in comparable overall yield (48%) with no erosion of stereoselectivity (81% ee) (entry 1, Table 2). For convenience, all subsequent reactions to optimize the yield and enantioselectivity were performed using this one-pot method. A switch to diethyl ether as solvent proved detrimental to the yield (entry 2), and introduction of the additive TMEDA led to a drop in enantioselectivity (entry 3). Performing the lithiation at a higher temperature of −40 °C gave no product (entry 4), and a change in solvent to 1:1 THF/pentane led to an improvement in selectivity but a slight decrease in yield (entry 5). Finally, a much improved 67% yield and high enantioselectivity was achieved by maintaining the reaction

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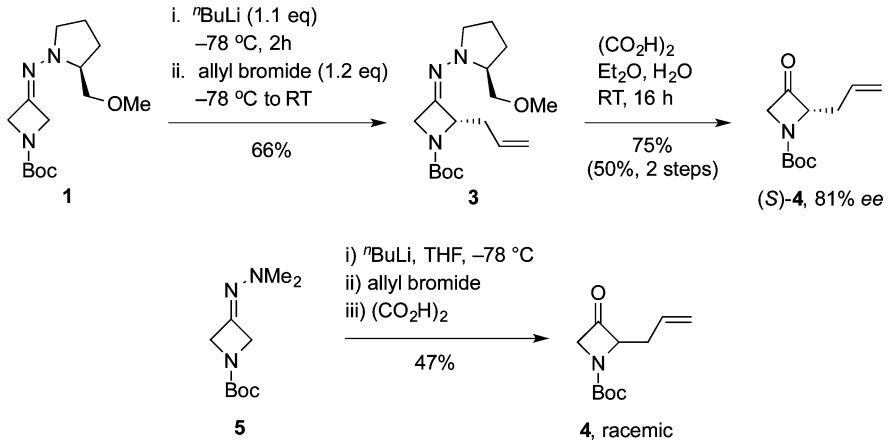
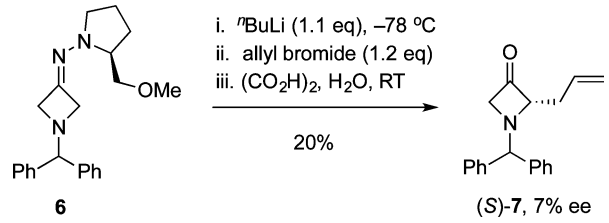
Scheme 2. Synthesis of Enantiomerically Enriched and Racemic *N*-Boc-2-Allylazetidin-3-one (4)



Scheme 3. Synthesis of (*S*)-*N*-Benzhydryl-2-allylazetidin-3-one (7)



temperature at −78 °C for 2 h after addition of the electrophile prior to warming to room temperature (entry 6). Using RAMP-derived (*R*)-**1**, the opposite enantiomer (*R*)-**4** was produced in an identical 81% ee (see Experimental Section).

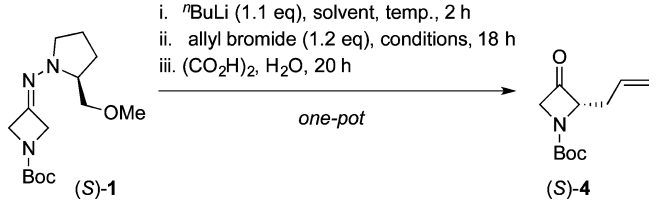
Having established conditions for the one-pot preparation of (*S*)-**4** from (*S*)-**1** in good yield and high enantioselectivity, we sought to establish the scope of the alkylation step (Table 3). A representative range of electrophiles including alkyl, allyl, and benzyl halides, benzaldehyde, and acetone were screened. Satisfyingly, additional allyl bromides were found to react in good yield and high selectivity (entries 3 and 4) as did both primary and secondary alkyl iodides (entries 5 and 6). The stereoselectivity for each iodide was found to reflect its steric demand, with the most hindered, $(CH_3)_2CHI$, giving the highest enantioselectivity of 85% (entry 6). A much lower enantioselectivity was observed with benzyl bromide, which suggests a different mechanism is operating with this electrophile, possibly involving electron transfer (entry 7). Reaction of the lithiated intermediate with acetone gave alcohol **14** in good yield and high enantioselectivity (entry 9), although low selectivity was seen with benzaldehyde (entry 8). Preliminary attempts to make 2,2-disubstituted derivatives by repetition of the deprotonation/alkylation sequence have not been fruitful.

The absolute configuration of the major enantiomer of **14** was established by performing a Pictet−Spengler reaction on ketone **14** with L-tryptophan methyl ester, using reaction conditions developed previously.[21] The major ester **15** was separated from the reaction mixture in 81% yield and was converted to amide **16**. X-ray crystal structure analysis of **16** unambiguously determined the *S*-configuration of the azetidine C2 stereocenter of **14** (Scheme 4 and Supporting Information).

The stereochemical outcome of the alkylation of SAMP hydrazone (*S*)-**1** is in accordance with previous studies by Enders et al. and can be explained by preferential attack of a conformationally rigid and chelated $E_{C=C}Z_{C-N}$ azaenolate by the electrophile from the less sterically hindered *Si* face (Scheme 5).[22] The sense of asymmetric induction in the other alkylations reported herein was made by analogy.

In conclusion, we have developed a practical and efficient asymmetric synthesis of 2-substituted azetidin-3-ones in high

Table 2. Optimization of Yield and Enantioselectivity for the Formation of (*S*)-4



entry	solvent	temp (°C)	conditions	yield (%)	ee (%)[a]
1	THF	−78	EA, −78 °C to rt	48	81
2	Et_2O	−78	EA, −78 °C to rt	26	79
3	THF, TMEDA[b]	−78	EA, −78 °C to rt	44	74
4	THF	−78 to −40	−78 °C, EA, to rt	0	
5	1:1 THF/pentane	−78	EA, −78 °C to rt	42	85
6	THF	−78	EA, −78 °C, 2 h, to rt	67	80

[a]Enantioselectivity determined by chiral GC analysis (see Supporting Information). [b]1.1 equiv of TMEDA was used. EA = electrophile added.

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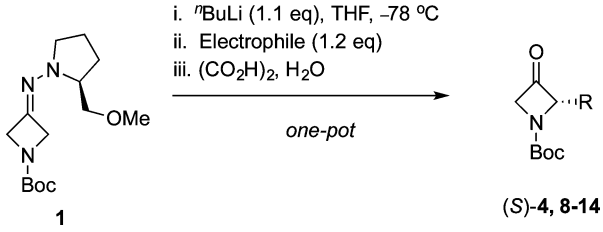
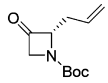
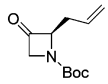
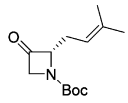
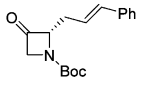
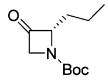
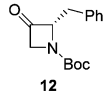
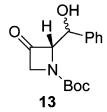
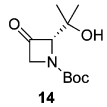
Table 3. Stereoselective Synthesis of 2-Substituted *N*-Boc-azetidin-3-ones 4 and 8−13



1 (*S*)-**4, 8-14**

entry	electrophile	product	yield (%)	*ee* (%)
1	CH_2=$CHCH_2Br$	 **4**	67	81[a]
2	CH_2=$CHCH_2Br$[c]	 **4**	55	81[a]
3	$(CH_3)_2C$=$CHCH_2Br$	 **8**	53	81[a]
4	PhCH=$CHCH_2Br$	 **9**	74	77[b]
5	$CH_3CH_2CH_2I$	 **10**	50	79[a]
6	$(CH_3)_2CHI$	 **11**	52	85[a]
7	$PhCH_2Br$	 **12**	57	33[b]
8	PhCHO	 **13**	71	31, 17[b,d]
9	$(CH_3)_2CO$	 **14**	59	78[b]

[a]Enantioselectivity determined by chiral GC analysis. [b]Enantioselectivity determined by chiral HPLC analysis. [c](*R*)-**1** was reacted. [d]Obtained as an inseparable 3:2 mixture of diastereomers. In all cases, racemic samples were prepared from achiral hydrazone **5** for comparison purposes. See Supporting Information for GC and HPLC conditions and chromatograms.

enantiomeric excesses via a one-pot procedure involving the alkylation of the lithiated SAMP hydrazone of *N*-Boc-azetidin-3-one. Reactions with allyl bromides, alkyl iodides, and carbonyl compounds were found to be high yielding (50−74% over two steps) and stereoselective (up to 85% ee). These products are expected to be useful in the preparation of novel 2,3-disubstituted azetidine-containing scaffolds and other heterocycles used in drug discovery programs.

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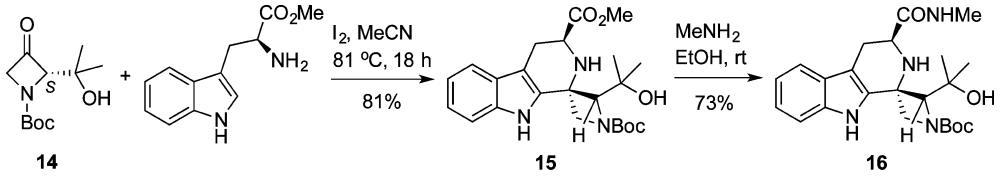
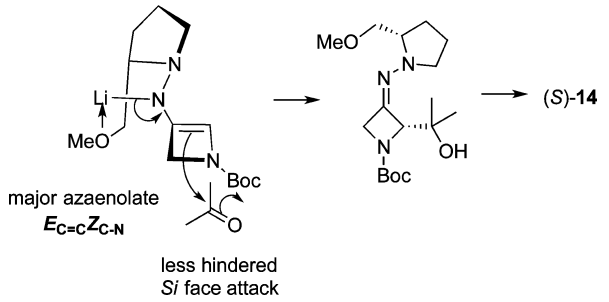
Scheme 4. Determination of Absolute Configuration of the Major Enantiomer of 14



Scheme 5. Proposed Mechanism of Formation of the Major Enantiomer of 14



EXPERIMENTAL SECTION

NMR assignments were deduced using 2D experiments (COSY, HMBC, and HMQC).

(S)-3-(2-(Methoxymethyl)-N-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-tert-butylcarboxylate (1). (*S*)-(−)-1-Amino-2-(methoxymethyl)pyrrolidine (537 μL, 4.00 mmol) was added dropwise to *N*-Boc-azetidin-3-one (822 mg, 4.80 mmol). The mixture was heated to 55 °C for 16 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3:1 hexane/ethyl acetate) to give (*S*)-**1** (1.13 g, 100%) as a pale yellow oil: R_f (3:1 hexane/ethyl acetate) 0.31; $[\alpha]_D^{26}$ +23.4 (*c* 0.12, $CHCl_3$); ν_{max} (film)/cm^{-1} 2929, 2867, 1703, 1457, 1365, 1087, 940, 859, 767; δ_H (400 MHz, $CDCl_3$) 4.76−4.68 (1H, m, NC*H*H), 4.64−4.52 (3H, m, NCH*H*, NCH_2), 3.50 (1H, dd, *J* = 8.0, 4.0 Hz, C*H*HOCH$_3$), 3.44−3.39 (2H, m, CH*H*OCH$_3$, NCH), 3.38 (3H, s, CH_2OCH_3), 3.33−3.26 (1H, m, NC*H*H), 2.79 (1H, q, *J* = 8.0 Hz, NCH*H*), 1.98−1.84 (3H, m, C*H*H, CH_2), 1.78−1.69 (1H, m, CH*H*), 1.46 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 156.2 (C═O), 135.9 (C═N), 80.1 ($C(CH_3)_3$), 74.9 (CH_2OCH_3), 65.2 (NCH), 61.4 (NCH_2), 60.4 (NCH_2), 59.3 (CH_2OCH_3), 52.5 (NCH_2), 28.4 ($C(CH_3)_3$), 25.9 (CH_2), 22.7 (CH_2); MS (ES^+) *m*/*z* 284 (MH^+); HRMS (ESI/TOF-Q) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{26}N_3O_3$ 284.1969; found 284.1972.

(R)-3-(2-(Methoxymethyl)-N-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-tert-butylcarboxylate (1). (*R*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine (269 μL, 2.00 mmol) was added dropwise to *N*-Boc-azetidin-3-one (411 mg, 2.40 mmol). The mixture was heated to 55 °C for 16 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3:1 hexane/ethyl acetate) to give (*R*)-**1** (540 mg, 95%) as a pale yellow oil: R_f (3:1 hexane/ethyl acetate) 0.24; $[\alpha]_D^{29}$ −21.2 (*c* 0.11, $CHCl_3$); ν_{max} (film)/cm^{-1} 2979, 2930, 2888, 2835, 1687, 1460, 1364, 1146, 1105, 941, 858, 767; δ_H (400 MHz, $CDCl_3$) 4.77−4.68 (1H, m, NC*H*H), 4.65−4.53 (3H, m, NCH*H*, NCH_2), 3.54−3.46 (1H, m, C*H*HOCH$_3$), 3.45−3.35 (2H, m, CH*H*OCH$_3$, NC*H*CH$_2$OCH$_3$), 3.38 (3H, s, CH_2OCH_3), 3.34−3.26 (1H, m, NC*H*HCH$_2$), 2.79 (1H, q, *J* = 8.1 Hz, NCH*H*CH$_2$), 1.98−1.83 (3H, m, C*H*H, CH_2), 1.79−1.69 (1H, m, CH*H*), 1.46 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 156.2 (C═O), 135.9 (C═N), 80.1 ($C(CH_3)_3$), 74.9 (CH_2OCH_3), 65.1 (NCH), 61.4 (NCH_2), 59.3 (CH_2OCH_3), 52.5 (NCH_2CH_2), 28.3 ($C(CH_3)_3$), 25.9 (CH_2), 22.7 (CH_2); MS (ES^+) *m*/*z* 284 (MH^+); HRMS (ESI/TOF-Q) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{26}N_3O_3$ 284.1969; found 284.1964.

N,N-Dimethyl-N′-azetidine-3-ylidinehydrazine-1-tert-butylcarboxylate (5). *N*,*N*-Dimethyl hydrazine (304 μL, 4.00 mmol) was added dropwise to *N*-Boc-azetidin-3-one (822 mg, 4.80 mmol). The mixture was heated to 65 °C for 16 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 1:1 hexane/ethyl acetate) to give **5** (784 mg, 92%) as a pale yellow oil: R_f (1:1 hexane/ethyl acetate) 0.53; ν_{max} (film)/cm^{-1} 2974, 2864, 1700, 1452, 1388, 1365, 1124, 1016, 940, 859, 765; δ_H (400 MHz, $CDCl_3$) 4.71 (2H, t, *J* = 2.7 Hz, NCH_2), 4.57 (2H, t, *J* = 2.7 Hz, NCH_2), 2.70 (6H, s, $N(CH_3)_2$), 1.46 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 156.1 (C═O), 138.4 (C═N), 80.2 ($C(CH_3)_3$), 61.6 (NCH_2), 61.0 (NCH_2), 45.8 ($N(CH_3)_2$), 28.3 ($C(CH_3)_3$); MS (ES^+) *m*/*z* 236 (MNa^+); HRMS (ESI/TOF-Q) *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{19}N_3O_2Na$ 236.1369; found 236.1365.

(S)-3-(2-(Methoxymethyl)-N-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-benzhydryl (6). (*S*)-(−)-1-Amino-2-(methoxymethyl)-pyrrolidine (671 μL, 5.00 mmol) was added dropwise to 1-benzhydrylazetidin-3-one (1.42 g, 6.00 mmol). The mixture was heated to 90 °C for 16 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3:1 hexane/ethyl acetate) to give **6** (1.76 g, 100%) as an orange oil: R_f (3:1 hexane/ethyl acetate) 0.37; $[\alpha]_D^{25}$ +33.5 (*c* 0.106, $CHCl_3$); ν_{max} (film)/cm^{-1} 2926, 2875, 2825, 1686, 1599, 1451, 1115, 1091, 950, 742, 700; δ_H (400 MHz, $CDCl_3$) 7.44 (4H, d, *J* = 7.6 Hz, ArH), 7.31−7.24 (4H, m, ArH), 7.23−7.16 (2H, m, ArH), 4.53 (1H, s, NCH), 4.00 (2H, s, NCH_2), 3.92 (2H, s, NCH_2), 3.54−3.48 (1H, m, C*H*HOCH$_3$), 3.41−3.28 (2H, m, CH*H*OCH$_3$, NC*H*CH$_2$), 3.36 (3H, s, CH_2OCH_3), 3.23−3.15 (1H, m, NC*H*HCH$_2$), 2.68 (1H, q, *J* = 8.3 Hz, NCH*H*CH$_2$), 1.96−1.85 (1H, m, C*H*H), 1.85−1.75 (2H, m, CH_2), 1.73−1.62 (1H, m, NCH*H*); δ_C (125 MHz, $CDCl_3$) 142.53 (C═N), 142.51 (C, Ar), 128.6 (CH, Ar), 127.4 (CH, Ar), 127.32 (CH, Ar), 127.28 (CH, Ar), 127.25 (CH, Ar), 77.4 (NCH), 75.1 (CH_2OCH_3), 65.3 ($NCHCH_2$), 64.9 (NCH_2), 64.5 (NCH_2), 59.3 (CH_2OCH_3), 53.0 (NCH_2CH_2), 26.0 (CH_2), 22.6 (CH_2); MS (ES^+) *m*/*z* 350 (MH^+); HRMS (ESI/TOF-Q) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{28}N_3O$ 350.2227; found 350.2221.

(S)-2-Allyl-1-benzyhydrylazetidin-3-one (7). *n*-Butyllithium (2.35 M solution in hexanes, 187 μL, 0.44 mmol) was added dropwise to a stirred solution of **6** (140 mg, 0.40 mmol) in anhydrous THF (4 mL) at −78 °C under nitrogen. After 2 h at −78 °C, allyl bromide (42 μL, 0.48 mmol) was added by syringe, and the solution was maintained at this temperature for 2 h before being warmed slowly to rt over 18 h. Saturated aqueous oxalic acid solution (4 mL) was added and the solution stirred vigorously at rt for 20 h. The reaction mixture was diluted with diethyl ether (50 mL), and the layers were separated. The organic layer was washed with brine (25 mL) and saturated aqueous sodium bicarbonate (25 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave **7** (22 mg, 20%) as a pale yellow oil: R_f (7:1 hexane/ethyl acetate) 0.53; $[\alpha]_D^{24}$ +6.50 (*c* 0.100, $CHCl_3$); ν_{max} (film)/cm^{-1} 3063, 2932, 2819, 1804, 1599, 1453, 1429, 920, 743, 698; δ_H (400 MHz, $CDCl_3$) 7.90−6.95 (10H, m, ArH), 5.74−5.52 (1H, m, $CH_2CH{=}CH_2$), 5.01−4.75 (2H, m, $CH_2CH{=}CH_2$), 4.53 (1H, s, NCH), 4.18−3.90 (2H, m, NC*H*H, NC*H*CH$_2$), 3.61 (1H, d, *J* = 16.2 Hz, NCH*H*), 1.96−1.80 (2H, m, NCHC*H*$_2$); δ_C (125 MHz, $CDCl_3$) 204.4 (C═O), 142.5 (C, Ar), 142.3 (C, Ar), 133.3 ($CH_2CH{=}CH_2$), 128.7 (CH, Ar), 128.5 (CH, Ar), 128.3 (CH, Ar), 127.8 (CH, Ar), 127.4 (CH, Ar), 127.3 (CH, Ar), 117.5 ($CH_2CH{=}CH_2$), 84.7 ($NCHCH_2$), 77.3 (NCH), 72.9 (NCH_2), 35.0 ($NCHCH_2$); MS (ES^+) *m*/*z* 278 (MH^+); HRMS (ESI/TOF-Q) *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{20}NO$ 278.1539; found 278.1541; 7% ee (determined by chiral HPLC on a Chiralpak AD-H column (0.46 cm ø × 25 cm), 99:1

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hexane/propan-2-ol, 0.5 mL/min, T = 25 °C, detection wavelength = 224 nm; see Supporting Information).

Two-Step Synthesis of (*S*)-4. *(2S)-2-(Methoxymethyl)-N-[2-(S)-allylazetidine-3-ylidine-1-tert-butylcarboxylate]-1-pyrrolidinamine (**3**).* *n*-Butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol) was added dropwise to a stirred solution of (*S*)-**1** (113 mg, 0.40 mmol) in anhydrous THF (4 mL) at −78 °C under nitrogen. After 2 h at −78 °C, allyl bromide (42 μL, 0.48 mmol) was added by syringe, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with ether (40 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3:1 hexane/ethyl acetate) to give **3** (85 mg, 66%) as a pale yellow oil: R_f (3:1 hexane/ethyl acetate) 0.34; ν_{max} (film)/cm^{-1} 2925, 2870, 1703, 1477, 1457, 1390, 1365, 1129, 1030, 913, 768; δ_H (400 MHz, $CDCl_3$) major isomer, 5.73−5.86 (1H, m, CH_2CH═CH_2), 5.19−5.07 (2H, m, CH_2CH═CH_2), 5.01−4.91 (1H, m, NC*H*CH_2CH═CH_2), 4.48−4.40 (1H, m, NC*H*H), 4.37 (1H, dd, J = 13.6, 3.4 Hz, NCH*H*), 3.52 (1H, dd, J = 9.1, 4.1 Hz, C*H*HOCH_3), 3.46−3.25 (3H, m, CH*H*OCH_3, NC*H*CH_2, NC*H*HCH_2), 3.37 (3H, s, CH_2OCH_3), 2.81−2.60 (1H, m, NCH*H*CH_2), 2.66 (1H, q, J = 8.3 Hz, C*H*HCH═CH_2), 2.55−2.46 (1H, m, CH*H*CH═CH_2), 2.06−1.83 (3H, m, NC*H*H, NCH_2), 1.71−1.63 (1H, m, NCH*H*), 1.47 (9H, s, $C(CH_3)_3$); δ_C (176 MHz, $CDCl_3$) 155.2 (C═O), 141.8 (C═N), 132.2 (CH_2CH═CH_2), 118.0 (CH_2CH═CH_2), 79.2 ($C(CH_3)_3$), 75.1 (CH_2OCH_3), 72.4 (NCHCH_2CH═CH_2), 65.3 (NCHCH_2OCH_3), 58.5 (CH_2OCH_3), 53.0 (NCH_2CH_2), 33.0 (CH_2CH═CH_2), 27.7 ($C(CH_3)_3$), 26.0 (CH_2), 22.3 (CH_2), azetidine CH_2 not observed; MS (ES$^+$) m/z 346 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{17}H_{29}N_3O_3Na$ 346.2101; found 346.2101.

*(S)-2-(Allyl-3-oxoazetidine)-1-tert-butyl carboxylate (**4**).* To (*S*)-**3** (61 mg, 0.19 mmol) were added saturated aqueous oxalic acid (1.5 mL) and diethyl ether (2.5 mL), and the reaction was stirred vigorously at room temperature for 18 h. The reaction mixture was diluted with diethyl ether (50 mL), and the layers were separated. The organic layer was washed with brine (25 mL) and saturated aqueous sodium bicarbonate (25 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave (*S*)-**4** (30 mg, 75%) as a pale yellow oil: R_f (7:1 hexane/ethyl acetate) 0.32; $[\alpha]_D^{25}$ +55.4 (*c* 0.106, $CHCl_3$); ν_{max} (film)/cm^{-1} 3082, 2979, 2928, 1822, 1704, 1479, 1458, 1392, 1365, 1177, 1124, 923, 772; δ_H (400 MHz, $CDCl_3$) 5.91−5.73 (1H, m, CH_2CH═CH_2), 5.24−5.12 (2H, m, CH_2CH═CH_2), 5.01−4.87 (1H, m, NC*H*CH_2), 4.67 (1H, d, J = 16.6 Hz, NC*H*H), 4.47 (1H, dd, J = 16.6, 2.2 Hz, NCH*H*), 2.72−2.61 (1H, m, NCHC*H*H), 2.61−2.51 (1H, m, NCHCH*H*), 1.49 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 199.9 (C═O), 155.9 (C═O), 131.6 (CH_2CH═CH_2), 119.3 (CH_2CH═CH_2), 82.2 (NCHCH_2), 80.8 ($C(CH_3)_3$), 69.1 (NCH_2), 34.1 (NCHCH_2), 28.3 ($C(CH_3)_3$); MS (ES$^+$) m/z 234 (MNa^+); HRMS (ESI/TOF-Q) [M + Na]$^+$ calcd for $C_{11}H_{17}NO_3Na$ 234.1101; found 234.1093; 81% ee (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50 m × 0.25 mm × 0.25 μm column, T = 110 °C, P = 15 psi, H_2 carrier gas; see Supporting Information).

One-Pot Synthesis of (*S*)-4 and 8−13: General Procedure. *n*-Butyllithium (2.5 M solution in hexanes, 1.1 equiv) was added dropwise to a stirred solution of (*S*)-**1** or (*R*)-**1** (0.40 mmol) in anhydrous THF (4 mL) at −78 °C under nitrogen. After 2 h at −78 °C, the electrophile (1.2 equiv) was added by syringe, and the solution was stirred at −78 °C for 2 h before being warmed slowly to room temperature over 18 h. Saturated aqueous oxalic acid solution (4 mL) was added and the solution stirred vigorously at room temperature for 20 h. The reaction mixture was diluted with diethyl ether (50 mL), and the layers were separated. The organic layer was washed with brine (25 mL) and saturated aqueous sodium bicarbonate (25 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo. Purification by flash column chromatography gave the 2-substituted azetidin-3-ones as detailed below.

*(S)-2-(Allyl-3-oxoazetidine)-1-tert-butyl Carboxylate (**4**).* (*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol), anhydrous THF (4 mL), and allyl bromide (42 μL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave (*S*)-**4** (57 mg, 67%) as a pale yellow oil: R_f (7:1 hexane/ethyl acetate) 0.32; $[\alpha]_D^{25}$ +52.7 (*c* 0.112, $CHCl_3$); ν_{max} (film)/cm^{-1} 3082, 2979, 2928, 1822, 1704, 1479, 1458, 1392, 1365, 1177, 1124, 923, 772; δ_H (400 MHz, $CDCl_3$) 5.91−5.73 (1H, m, CH_2CH═CH_2), 5.24−5.12 (2H, m, CH_2CH═CH_2), 5.01−4.87 (1H, m, NC*H*CH_2), 4.67 (1H, d, J = 16.6 Hz, NC*H*H), 4.47 (1H, dd, J = 16.6, 2.2 Hz, NCH*H*), 2.72−2.61 (1H, m, NCHC*H*H), 2.61−2.51 (1H, m, NCHCH*H*), 1.49 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 199.9 (C═O), 155.9 (C═O), 131.6 (CH_2CH═CH_2), 119.3 (CH_2CH═CH_2), 82.2 (NCHCH_2), 80.8 ($C(CH_3)_3$), 69.1 (NCH_2), 34.1 (NCHCH_2), 28.3 ($C(CH_3)_3$); MS (ES$^+$) m/z 234 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{11}H_{17}NO_3Na$ 234.1101; found 234.1093; 81% ee (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50 m × 0.25 mm × 0.25 μm column, T = 110 °C, P = 15 psi, H_2 carrier gas; see Supporting Information).

*(R)-2-(Allyl-3-oxoazetidine)-1-tert-butyl Carboxylate (**4**).* (*R*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.35 M solution in hexanes, 187 μL, 0.44 mmol), anhydrous THF (4 mL), and allyl bromide (42 μL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave (*R*)-**4** (46 mg, 55%) as a pale yellow oil; $[\alpha]_D^{30}$ −47.4 (*c* 0.116, $CHCl_3$); 81% ee (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50 m × 0.25 mm × 0.25 μm column, T = 110 °C, P = 15 psi, H_2 carrier gas; see Supporting Information).

*(S)-2-((3-Methylbut-2-en-1-yl)-3-oxoazetidine)-1-tert-butyl Carboxylate (**8**).* (*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.35 M solution in hexanes, 187 μL, 0.44 mmol), anhydrous THF (4 mL), and 3,3-dimethylallyl bromide (56 μL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave (*S*)-**8** (51 mg, 53%) as a pale yellow oil: R_f (7:1 hexane/ethyl acetate) 0.39; $[\alpha]_D^{25}$ +30.3 (*c* 0.125, $CHCl_3$); ν_{max} (film)/cm^{-1} 2977, 2927, 1821, 1701, 1365, 1176, 1129, 856, 772; δ_H (400 MHz, $CDCl_3$) 5.18 (1H, t, J = 7.2 Hz, CH_2CH═$C(CH_3)_2$), 4.94−4.86 (1H, m, NC*H*CH_2), 4.64 (1H, d, J = 16.5 Hz, NC*H*H), 4.45 (1H, dd, J = 16.6, 4.1 Hz, NCH*H*), 2.61−2.51 (2H, m, NCHCH_2), 1.72 (3H, s, CH_2CH═$C(CH_3)(CH_3)$), 1.63 (3H, s, CH_2CH═$C(CH_3)(CH_3)$), 1.49 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 200.6 (C═O), 155.9 (C═O), 136.3 (CH═$C(CH_3)_2$), 116.9 (*C*H═$C(CH_3)_2$), 82.8 (NCHCH$_2$), 80.6 ($C(CH_3)_3$), 68.9 (NCH$_2$), 28.6 (NCHCH_2), 28.3 ($C(CH_3)_3$), 25.9 (CH═$C(CH_3)(CH_3)$), 17.9 (CH═$C(CH_3)(CH_3)$); MS (ES$^+$) m/z 262 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{13}H_{21}NO_3Na$ 262.1414; found 262.1415; 81% ee (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m × 0.25 mm × 0.25 μm column, T = 140 °C, P = 15 psi, He carrier gas; see Supporting Information).

*(S)-2-(Phenylallyl-3-oxoazetidine)-1-tert-butyl Carboxylate (**9**).* (*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol), anhydrous THF (4 mL), and 3-bromo-1-phenyl-1-propene (95 mg, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave (*S*)-**9** (85 mg, 74%) as a pale yellow oil: R_f (7:1 hexane/ethyl acetate) 0.36; $[\alpha]_D^{19}$ +71.3 (*c* 0.122, $CHCl_3$); ν_{max} (film)/cm^{-1} 2976, 2929, 1822, 1699, 1494, 1391, 1365, 1129, 966, 743, 693; δ_H (400 MHz, $CDCl_3$) 7.40−7.19 (5H, m, ArH), 6.51 (1H, d, J = 15.8 Hz, CH_2CH═C*H*Ar), 6.24−6.13 (1H, m, CH_2CH═CH), 5.04−4.97 (1H, m, NC*H*CH_2), 4.67 (1H, d, J = 16.6 Hz, NC*H*H), 4.48 (1H, dd, J = 16.6, 4.3 Hz, NCH*H*), 2.88−2.77 (1H, m, NCHC*H*H), 2.76−2.64 (1H, m, NCHCH*H*), 1.48 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 199.9 (C═O), 155.9 (C═O), 136.9 (C, Ar), 134.4 (CH_2CH═CH), 128.6 (CH, Ar), 127.5 (CH, Ar), 126.3 (CH, Ar), 122.8 (CH_2CH═CH), 82.4 (NCHCH$_2$), 80.9 ($C(CH_3)_3$), 69.2 (NCH$_2$), 33.4 (NCHCH$_2$), 28.3 ($C(CH_3)_3$); MS (ES$^+$) m/z 310 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd

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for $C_{17}H_{21}NO_3Na$ 310.1414; found 310.1412; 77% ee (determined by chiral HPLC on a Chiralcel OJ column (0.46 cm ø × 25 cm), 97:3 hexane/propan-2-ol, 0.5 mL/min, T = 25 °C, detection wavelength = 254 nm; see Supporting Information).

*(S)-2-(Propyl-3-oxoazetidine)-1-tert-butyl Carboxylate (**10**).* (*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol), anhydrous THF (4 mL), and 1-iodopropane (47 μL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave (*S*)-**10** (43 mg, 50%) as a pale yellow oil: R_f (7:1 hexane/ethyl acetate) 0.41; $[\alpha]_D^{19}$ +54.8 (*c* 0.104, $CHCl_3$); ν_{max} (film)/cm^{-1} 2964, 2934, 2875, 1819, 1701, 1478, 1458, 1389, 1365, 1138, 1119, 774; δ_H (400 MHz, $CDCl_3$) 4.93−4.86 (1H, m, NC*H*CH_2), 4.68 (1H, d, J = 16.7 Hz, NC*H*H), 4.51 (1H, dd, J = 16.7, 4.3 Hz, NCH*H*), 1.87−1.77 (2H, m, NCHCH_2), 1.60−1.37 (2H, m, $CH_2CH_2CH_3$), 1.49 (9H, s, $C(CH_3)_3$), 0.95 (3H, t, J = 7.3 Hz, $CH_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 201.1 (C═O), 156.3 (C═O), 82.9 (NCHCH_2), 80.7 ($C(CH_3)_3$), 68.9 (NCH_2), 32.4 (NCHCH_2), 28.3 ($C(CH_3)_3$), 18.1 ($CH_2CH_2CH_3$), 13.9 ($CH_2CH_2CH_3$); MS (ES^+) m/z 236 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{11}H_{19}NO_3Na$ 236.1257; found 236.1254; 79% ee (determined by chiral GC analysis on a CP-ChiraSil-DEX CB 25m × 0.25 mm × 0.25 μm column, T = 130 °C, P = 18 psi, He carrier gas; see Supporting Information).

*(S)-2-(Isopropyl-3-oxoazetidine)-1-tert-butyl Carboxylate (**11**).* (*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol), anhydrous THF (4 mL), and 2-iodopropane (48 μL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave (*S*)-**11** (44 mg, 52%) as a colorless yellow oil: R_f (7:1 hexane/ethyl acetate) 0.40; $[\alpha]_D^{28}$ +85.2 (*c* 0.260, $CHCl_3$); ν_{max} (film)/cm^{-1} 2966, 2931, 2875, 1818, 1704, 1460, 1387, 1366, 1174, 1120, 776; δ_H (500 MHz, $CDCl_3$) 4.76−4.71 (1H, m, NC*H*$CH(CH_3)_2$), 4.65 (1H, d, J = 16.7 Hz, NC*H*H), 4.44 (1H, dd, J = 16.7, 4.3 Hz, NCH*H*), 2.17 (1H, octet, J = 6.7 Hz, NCHC*H*$(CH_3)_2$), 1.49 (9H, s, $C(CH_3)_3$), 1.04 (3H, d, J = 6.9 Hz, NCHCH(CH_3CH$_3$)), 1.03 (3H, d, J = 6.9 Hz, NCHCH(CH_3CH$_3$)); δ_C (125 MHz, $CDCl_3$) 201.0 (C═O), 156.7 (C═O), 88.4 (NCHCH$(CH_3)_2$), 80.8 ($C(CH_3)_3$), 69.4 (NCH_2), 30.0 (NCHCH-$(CH_3)_2$), 28.3 ($C(CH_3)_3$), 18.2 (CH(CH_3)CH$_3$)), 17.7 (CH(CH_3)CH$_3$)); MS (ES^+) m/z 236 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{11}H_{19}NO_3Na$ 236.1257; found 236.1255; 85% ee (determined by chiral GC analysis on a CP-ChiraSil-DEX CB 25m × 0.25 mm × 0.25 μm column, T = 130 °C, P = 18 psi, He carrier gas; see Supporting Information).

*(S)-2-(Benzyl-3-oxoazetidine)-1-tert-butyl Carboxylate (**12**).* (*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol), anhydrous THF (4 mL), and benzyl bromide (57 μL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 7:1 hexane/ethyl acetate) gave (*S*)-**12** (60 mg, 57%) as a pale yellow oil: R_f (7:1 hexane/ethyl acetate) 0.31; $[\alpha]_D^{19}$ +65.5 (*c* 0.103, $CHCl_3$); ν_{max} (film)/cm^{-1} 2955, 2915, 2850, 1820, 1695, 1498, 1392, 1367, 1176, 1125, 776, 717, 703; δ_H (400 MHz, $CDCl_3$) 7.33−7.17 (5H, m, ArH), 5.15−5.09 (1H, m, NC*H*CH_2), 4.54 (1H, d, J = 16.6 Hz, NC*H*H), 4.05 (1H, dd, J = 16.6, 4.3 Hz, NCH*H*), 3.20 (1H, dd, J = 14.2, 6.4 Hz, NCHC*H*H), 3.11 (1H, dd, J = 14.2, 4.1 Hz, NCHCH*H*), 1.48 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 199.8 (C═O), 155.6 (C═O), 135.5 (C, Ar), 129.8 (CH, Ar), 128.5 (CH, Ar), 127.0 (CH, Ar), 83.2 (NCHCH_2), 80.8 ($C(CH_3)_3$), 69.0 (NCH_2), 35.8 (NCHCH_2), 28.3 ($C(CH_3)_3$); MS (ES^+) m/z 284 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{15}H_{19}NO_3Na$ 284.1257; found 284.1266; 33% ee (determined by chiral HPLC on a Chiralcel OD column (0.46 cm ø × 25 cm), 99:1 hexane/propan-2-ol, 0.5 mL/min, T = 23 °C, detection wavelength = 254 nm; see Supporting Information).

*(S,R)- and (S,S)-2-(-Hydroxy(phenyl)methyl-3-oxoazetidine)-1-tert-butyl Carboxylate (**13**).* (*S*)-**1** (113 mg, 0.4 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol), anhydrous THF (4 mL), and benzaldehyde (49 μL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 4:1 hexane/ethyl acetate) gave (*S*)-**13** (79 mg, 71%) as a yellow oil and inseparable 1.5:1 mixture of diastereomers: R_f (4:1 hexane/ethyl acetate) 0.29; ν_{max} (film)/cm^{-1} 3414, 2978, 2927, 1824, 1678, 1455, 1393, 1367, 1171, 1145, 1119, 768, 733; δ_H (500 MHz, $CDCl_3$) 7.38−7.29 (12.5H, m, ArH,), 5.27−5.18 (1H, m, NC*H*CH), 5.17−5.12 (1.5H, m, NCHC*H*), 5.10−5.03 (2.5H, m, NC*H*CH, NCHC*H*), 4.65 (2H, d, J = 16.5 Hz, NC*H*H, NC*H*H), 4.52 (1H, br s, COH), 4.47 (3H, dd, J = 16.5, 3.5 Hz, NCH*H*, NCH*H*), 1.50 (9H, s, $C(CH_3)_3$), 1.44 (13.5H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 195.8 (CO), 195.6 (CO), 156.9 (COO), 156.3 (COO), 138.8 (C, Ar), 138.6 (C, Ar), 128.5 (CH, Ar), 128.42 (CH, Ar), 128.40 (CH, Ar), 128.1 (CH, Ar), 126.8 (CH, Ar), 126.5 (CH, Ar), 87.8 (NCHCH), 87.7 (NCHCH), 82.0 ($C(CH_3)_3$), 81.8 ($C(CH_3)_3$), 73.4 (NCHCH), 72.6 (NCHCH), 70.0 (NCH_2), 69.8 (NCH_2), 28.3 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$); MS (ES^+) m/z 300 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{15}H_{19}NO_4Na$ 300.1206; found 300.1204; 31% (major diastereomer), 17% (minor diastereomer) ee (determined by chiral HPLC on a Chiralpak IA column (0.46 cm ø × 25 cm), 95:5 hexane/propan-2-ol, 0.5 mL/min, T = 25 °C, detection wavelength = 254 nm; see Supporting Information).

*(S)-2-((2-Hydroxypropan-2-yl)-3-oxoazetidine)-1-tert-butyl Carboxylate (**14**).* (*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.35 M solution in hexanes, 187 μL, 0.44 mmol), anhydrous THF (4 mL), and acetone (36 μL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO_2, 3:1 hexane/ethyl acetate) gave (*S*)-**14** (54 mg, 59%) as a colorless oil: R_f (3:1 hexane/ethyl acetate) 0.34; $[\alpha]_D^{27}$ +38.2 (*c* 0.114, $CHCl_3$); ν_{max} (film)/cm^{-1} 3459, 2955, 2912, 2872, 2850, 1826, 1472, 1391, 1371, 1114, 1095, 717; δ_H (400 MHz, $CDCl_3$) 4.90−4.84 (1H, m, NC*H*COH), 4.70 (1H, d, J = 16.6 Hz, NC*H*H), 4.56−4.47 (1H, m, NCH*H*), 1.51 (9H, s, $C(CH_3)_3$), 1.33 (3H, s, $C(CH_3)(CH_3)OH$), 1.30 (3H, s, $C(CH_3)(CH_3)OH$); δ_C (125 MHz, $CDCl_3$) 197.2 (C═O), 156.9 (C═O), 91.2 (NCHCOH), 82.0 ($C(CH_3)_3$), 71.2 ($C(CH_3)_2OH$), 70.0 (NCH_2), 28.2 ($C(CH_3)_3$), 26.1 $C(CH_3)(CH_3)OH$), 24.3 ($C(CH_3)(CH_3)OH$); MS (ES^+) m/z 252 (MNa^+); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{11}H_{19}NO_4Na$ 252.1206; found 252.1204; 78% ee (determined by chiral HPLC on a Chiralcel OJ column (0.46 cm ø × 25 cm), 9:1 hexane/propan-2-ol, 0.5 mL/min, T = 25 °C, detection wavelength = 254 nm; see Supporting Information).

*(2R,3S,3′S)-2-(2-Hydroxypropan-2-yl)-2′,3′,4′,9′-tetrahydrospiro-[azetidine-3,1′-pyrido[3,4-b]indole]-1-tert-butyl-3′-methyl Dicarboxylate (**15**).* To a stirred solution of **14** (123 mg, 0.54 mmol) in dry CH_3CN (6 mL) was added L-tryptophan methyl ester (142 mg, 0.65 mmol) and I_2 (6.8 mg, 0.027 mmol), and the mixture was stirred at reflux for 18 h. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with saturated $Na_2S_2O_3$ solution (10 mL), saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 7:3, petroleum ether/ethyl acetate) gave **15** (188 mg, 81%) as a cream solid: mp 118−120 °C; R_f (7:3, petroleum ether/ethyl acetate) 0.46; $[\alpha]_D^{26}$ −44.0 (*c* 0.100, $CHCl_3$); ν_{max} (film)/cm^{-1} 3347, 2975, 2939, 2848, 1734, 1677, 1500, 1456, 1380, 1366, 1144, 1133, 747, 736; δ_H (300 MHz, $CDCl_3$) 8.40−8.25 (1H, br s, NH), 7.49 (1H, d, J = 7.7 Hz, ArH), 7.36 (1H, d, J = 8.0 Hz, ArH), 7.21 (1H, td, J = 7.6, 1.2 Hz, ArH), 7.15−7.10 (1H, m, ArH), 4.56 (1H, s, NC*H*C$(CH_3)_2OH$), 4.09 (1H, d, J = 8.6, NC*H*H), 3.98 (1H, d, J = 8.7, NCH*H*), 3.84 (3H, s, CO_2CH_3), 3.70 (1H, dd, J = 11.2, 4.1 Hz, NHC*H*CH_2), 3.11 (1H, dd, J = 15.2, 4.1 Hz, NHCHC*H*H), 2.82 (1H, dd, J = 15.2, 11.2 Hz, NHCHCH*H*), 1.52 (9H, s, $C(CH_3)_3$), 1.49 (3H, s, $C(CH_3)(CH_3)OH$), 1.25 (3H, s, $C(CH_3)(CH_3)OH$), piperidine NH and OH not observed; δ_C (125 MHz, $CDCl_3$) 172.9 (C═O), 158.0 (C═O), 136.4 (C, Ar), 134.2 (C, Ar), 126.7 (C, Ar), 122.6 (CH, Ar), 120.1 (CH, Ar), 118.4 (CH, Ar), 111.2 (CH, Ar), 109.3 (C, Ar), 81.2 ($C(CH_3)_3$), 77.6 (NCHC$(CH_3)_2OH$), 72.1 (NC$(CH_3)_2OH$), 63.9 (NCH_2), 56.4 (NHC), 53.6 (CO_2CH_3), 52.4 (NHCHCH_2), 28.4 ($C(CH_3)_3$), 26.4 ($C(CH_3)(CH_3)OH$), 26.3 ($C(CH_3)(CH_3)OH$), 25.2 (NHCHCH_2); MS (ES^+) m/z 430

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(MH$^+$); HRMS (ESI/TOF-Q) m/z [M + H]$^+$ calcd for $C_{23}H_{32}N_3O_5$ 430.2336; found 430.2333.

*(2R,3S,3′S)-2-(2-Hydroxypropan-2-yl)-2′,3′,4′,9′-tetrahydrospiro-[azetidine-3,1′-pyrido[3,4-b]indole]-1-tert-butyl Carboxylate-3′-N-methyl Carboxamide (**16**).* A solution of **15** (40 mg, 0.0931 mmol) and 33% methylamine in ethanol (10 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (SiO_2, ethyl acetate) to give **16** (29 mg, 73%) as a cream solid; mp 247−248 °C; R_f (ethyl acetate) 0.30; $[\alpha]_D^{22}$ −91.3 (*c* 0.260, $CHCl_3$); ν_{max} (film)/cm^{-1} 3291, 2972, 1657, 1393, 1366, 1133, 741; δ_H (500 MHz, $CDCl_3$) 8.14 (1H, br s, NH), 7.49 (1H, d, *J* = 7.9 Hz, ArH), 7.35 (1H, d, *J* = 8.1 Hz, ArH), 7.22 (1H, t, *J* = 7.5 Hz, ArH), 7.14 (1H, t, *J* = 7.4 Hz, ArH), 6.63−6.58 (1H, br m, NH), 4.53 (1H, s, C*H*C(CH$_3$)$_2$OH), 4.02 (1H, d, *J* = 8.7 Hz, C*H*HN), 3.97 (1H, d, *J* = 8.7 Hz, CH*H*N), 3.55−3.50 (1H, m, NCHCO), 3.21 (1H, dd, *J* = 15.6, 4.4 Hz, C*H*HCHCO), 2.92 (3H, d, *J* = 4.9 Hz, NCH$_3$), 2.74 (1H, dd, *J* = 15.6, 11.3 Hz, CH*H*CHCO), 2.69−2.50 (1H, br s, OH), 1.51 (12H, br s, C(CH$_3$)$_3$ and C(C*H*$_3$)(CH$_3$)OH), 1.26 (3H, s, C(CH$_3$)(C*H*$_3$)OH), piperidine NH not observed; δ_C (125 MHz, $CDCl_3$) 173.1 (C═O), 158.0 (C═O), 136.4 (C, Ar), 134.1 (C, Ar), 126.8 (C, Ar), 122.8 (CH, Ar), 120.2 (CH, Ar), 118.6 (CH, Ar), 111.2 (CH, Ar), 109.6 (C, Ar), 81.4 (*C*(CH$_3$)$_3$), 77.0 (CHCMe$_2$OH), 72.0 (*C*Me$_2$OH), 63.2 (CH$_2$N), 56.4 (CH$_2$CNH), 55.1 (CHCO), 28.3 (C(*C*H$_3$)$_3$), 26.8 (CH$_3$), 26.6 (CH$_3$), 26.2 (CH$_3$), 25.6 (CH$_2$CHCO); MS (ES$^+$) m/z 252 (MNa$^+$); HRMS (ESI/TOF-Q) m/z [M + Na]$^+$ calcd for $C_{23}H_{32}N_4O_4Na$ 451.2316; found 451.2315.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01284.

X-ray crystal structure of compound **16** (CIF)

Copies of ^{1}H and ^{13}C NMR spectra of compounds **1** and **3**−**16** and copies of chiral GC and HPLC chromatograms of racemic and enantiomerically enriched **4** and **7**−**14** (PDF)

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Notes

The authors declare no competing financial interest.

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(20) Attempts to form racemic **4** by direct formation of the enolate of *N*-Boc-azetidin-3-one with ^{t}BuLi at −78 °C, with subsequent trapping with allyl bromide, gave the carbinol as a result of direct addition of the organolithium to the ketone.
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■ NOTE ADDED AFTER ASAP PUBLICATION

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