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Catalytic Asymmetric Synthesis of Bicycloprolines by a 1,3-Dipolar Cycloaddition/Intramolecular Alkylation Strategy

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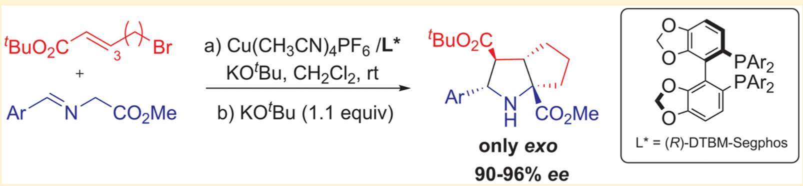
Supporting Information



ABSTRACT: The diastereoselective one-pot synthesis of hexahydrocyclopenta[*b*]pyrrole derivatives (bicycloprolines) has been achieved by base-mediated reactions of (*E*)-*tert*-butyl 6-bromo-2-hexenoate with α-imino esters. The catalytic asymmetric version of this process has been efficiently achieved using the Cu^{I}/(*R*)-DTBM-Segphos complex as a catalyst following a two-step 1,3-dipolar cycloaddition/intramolecular alkylation sequence.

The pyrrolidine ring is present in a myriad of natural products and has been broadly used as a chemical core to synthesize molecules with interesting pharmaceutical properties.[1] In peptidomimetic chemistry α-quaternary proline analogues have generated special interest due to their ability to restrict the conformation and limit torsional angles of the peptide backbone.[2] Furthermore, proline derivatives have been intensely used as ligands and organocatalysts in asymmetric synthesis.[3]

Hexahydrocyclopenta[*b*]pyrrole derivatives (bicycloprolines) are a significant subclass of pyrrolidines, which represent an important synthetic target due to their utility as amino acid surrogates in biologically active peptides and their presence in the structure of natural products.[4] Representative examples include hexahydrocyclopenta[*b*]pyrrole-6a-carboxylate, which has been used as a building block in the synthesis of peptidomimetics[5] and natural products such as kopsihainanine B[6] and caldaphnidine R.[7] Furthermore, Ramipril,[8] a marketed drug used to treat hypertension, presents a bicycloproline motif in its structure (Figure 1).

Despite the interest in these kinds of compounds, most of the methods reported for their asymmetric preparation are based on multistep sequences starting from enantioenriched starting materials.[9] Among the nonenantioselective procedures[10] for the synthesis of hexahydrocyclopenta[*b*]pyrrole derivatives, the 1,3-dipolar cycloaddition of azomethine ylides has emerged as one of the most efficient. Thus, the groups of Grigg[11] and Overman[12] have elegantly applied this methodology to the preparation of azabicyclooctanes and azatricyclodecanes. Both procedures were conducted under thermal activation in refluxing xylene, providing racemic products (Scheme 1).

One of the most direct methods for the preparation of enantioenriched pyrrolidines is the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with activated olefins. Since the first examples reported in 2002,[13] numerous highly efficient protocols using chiral metal catalysts as well as organocatalysts have been described. These new catalyst systems have allowed expanding the structural scope of the dipolarophiles and azomethine ylide precursors suitable for the intermolecular version of this reaction, providing enantioselective access to pyrrolidines with a variety of substitution patterns.[14] In contrast, only a few examples of the intramolecular version of this reaction have been reported.[15]

Herein, in connection with our interest in metal-catalyzed asymmetric [3 + 2] cycloadditions of azomethine ylides,[16] we report the first procedure for the catalytic enantioselective synthesis of bicycloproline derivatives using a 1,3-dipolar cycloaddition/intramolecular alkylation sequence. This approach affords straightforward access to highly enantioenriched bicycloproline derivatives from readily available starting materials.

We began our study by examining the reaction of *N*-benzylidene glycine methyl ester (**1a**) with (*E*)-*tert*-butyl 6-bromo-2-hexenoate[17] (**2**) in the presence of a base such as NaH, conditions previously described for the preparation of α-alkylated iminoglycinates.[18] We found that, using NaH in THF, the expected alkylated product was not observed, the bicyclic product **4a** being the only product detected (Table 1, entry 1). In a survey of a set of bases and solvents we obtained the best result using KO^{t}Bu in CH_2Cl_2 (Table 1, entry 4), which proved to be more efficient than other strong bases such as LDA (entry 2), KHMDS, and LiHMDS (entries 5 and 6). Remarkably, under all the conditions studied only the endo adduct[19] was

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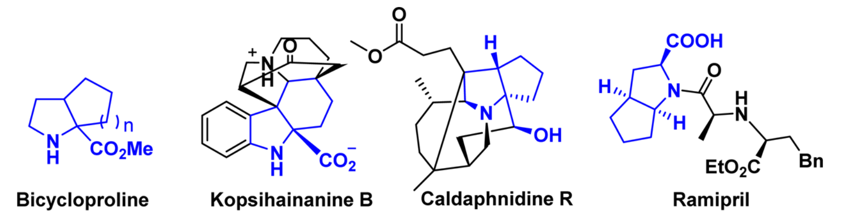


Figure 1. Selected compounds containing a bicycloproline motif.

Scheme 1. Synthesis of Bicycloprolines and Related Derivatives by 1,3-Dipolar Cycloaddition of Azomethine Ylides

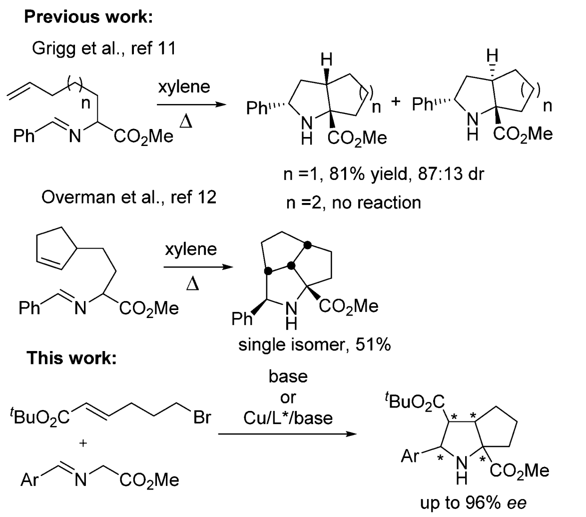
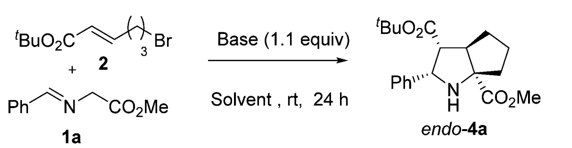


Table 1. Optimization Experiments for the Model Reaction



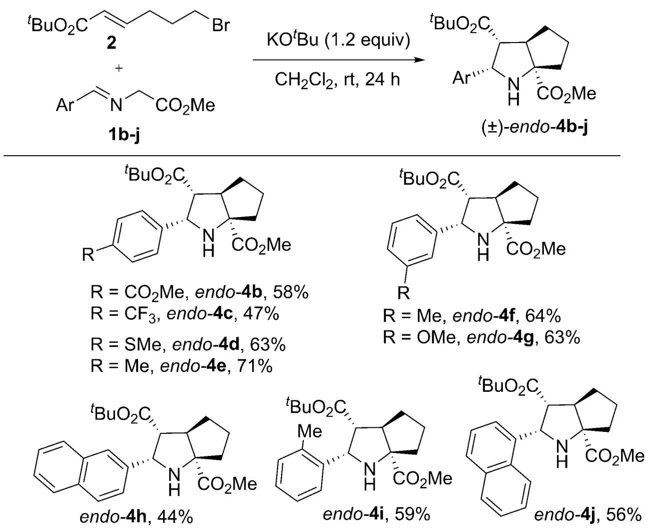
entry	base	solvent	conversion (%)	yield (%)[a]
1	NaH	THF	>98	49
2	LDA[b]	THF	>98	43
3	KO^{t}Bu	THF	>98	57
4	KO^{t}Bu	CH_2Cl_2	>98	71
5	KHMDS[c]	CH_2Cl_2	70	60
6	LiHMDS[d]	CH_2Cl_2	>98	16
7	4-DMAP[e]	CH_2Cl_2	0	
8	DBU[f]	CH_2Cl_2	0	
9	Et_3N	CH_2Cl_2	0	
10	Cs_2CO_3	CH_2Cl_2	28	

[a]Isolated yield. [b]Lithium diisopropylamide. [c]Potassium bis(trimethylsilyl)amide. [d]Lithium bis(trimethylsilyl)amide. [e]4-Dimethylaminopyridine. [f]1,8-Diazabicycloundec-7-ene.

detected in the ^{1}H NMR of the crude mixtures. In contrast, very low or no reactivity was observed using weaker bases, such as DBU, Et_3N, and Cs_2CO_3 (entries 7–10).

Since this approach constitutes a straightforward and powerful diastereoselective one-pot procedure for the preparation of bicycloproline analogues, involving the formation of three C–C bonds in a single operation, we undertook the study of the scope of the process. As summarized in Scheme 2, under the optimized reaction conditions, the reaction took place with

Scheme 2. Scope of the Base-Mediated Process



moderate to good yields (compounds **4b–j**, 44–71% yield) and excellent diastereoselectivity (only the endo bicycloproline was isolated) with an array of aryl-substituted imino esters, regardless of the electronic and steric nature of the substituents, including the sterically demanding ortho-substituted aryl derivatives (products **4i,j**).

To gain some insight into the mechanism of this tandem reaction, a series of control experiments were carried out (Scheme 3). First, we studied the feasibility of the cycloaddition between *N*-benzylidene glycine methyl ester (**1a**) with a *β*-substituted dipolarophile such as methyl crotonate (**5**). Under the base-mediated optimized conditions (1.1 equiv of KO^{t}Bu in CH_2Cl_2) the 1,3-dipolar cycloaddition afforded a 2:1 mixture of endo/exo adducts **6** in 53% yield (Scheme 3, eq 1). On the other hand, no reaction was observed after treatment of imino

Scheme 3. Related Studies of the Base-Mediated Reaction

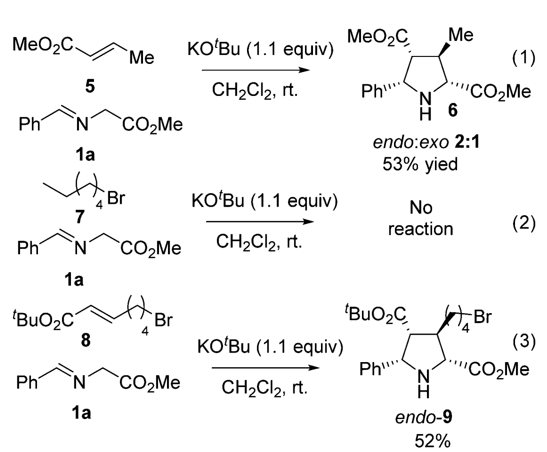


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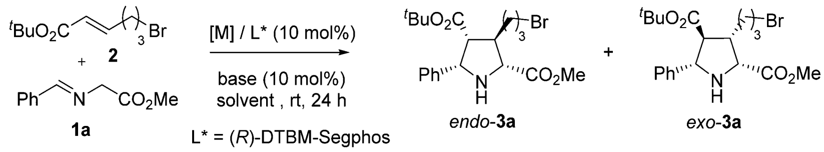
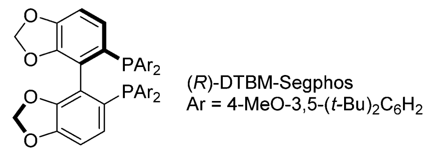
Table 2. Optimization Experiments for Catalytic Asymmetric 1,3-Dipolar Cycloaddition with (*R*)-DTBM-Segphos as Ligand



entry	[M]	base	solvent	endo/exo[a]	yield (%)[b]	ee (%)[c]
1	AgOAc	KO^{t}Bu	THF	8/92	94	54
2	AgOAc	KO^{t}Bu	CH_2Cl_2	<2/>98	89	73
3	AgOAc	KO^{t}Bu	toluene	14/86	90	51
4	AgOAc	KHMDS	CH_2Cl_2	27:/	28	77
5	$CuPF_6$[d]	KO^{t}Bu	CH_2Cl_2	<2/>98	93	95
6[e]	$CuPF_6$[d]	KO^{t}Bu	CH_2Cl_2	<2/>98	70[f]	n.d.[g]

[a]Determined by ^{1}H NMR from the crude reaction mixture. [b]Isolated yield of adducts **3a**. [c]Enantiomeric excess of *exo*-**3a** determined by HPLC. [d]$CuPF_6$ = $Cu(CH_3CN)_4PF_6$. [e]5 mol % of catalyst. [f]70% conversion yield after 5 days of reaction. [g]Not determined.

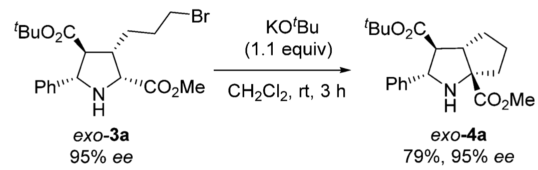


ester **1a** with 1-bromohexane (**7**) in the presence of KO^{t}Bu (eq 2), showing that the intermolecular alkylation process is not facile. Interestingly, the reaction of (*E*)-*tert*-butyl 7-bromo-2-heptenoate (**8**; homologous substrate of the model bromoalkene **2**) with the imino ester **1a** in the presence of 1.1 equiv of KO^{t}Bu led selectively to the pyrrolidine *endo*-**9**, the corresponding azabicycle not being detected by NMR (Scheme 3, eq 3). All of these test reactions strongly suggest that the direct synthesis of bicycloprolines **4** by base-promoted reaction of α-imino esters **1** with the 6-bromohexenoate **2** occurs by a starting intermolecular 1,3-dipolar cycloaddition followed by intramolecular alkylation.

Next, we turned our attention toward the development of the metal-mediated asymmetric version of the reaction in the presence of a catalytic amount of the metal salt, chiral ligand, and base. Taking into account the excellent enantioselectivities described by several research groups,[20] including ours,[16] using the chiral biphenyl DTBM-Segphos ligand, we focused our attention on this ligand under silver- and copper-catalyzed reaction conditions in the presence of a catalytic amount of KO^{t}Bu (Table 2). In agreement with the typically highly exo diastereoselective behavior of this very bulky ligand in the 1,3-dipolar cycloaddition with α,β-unsaturated esters,[20b,16e] the reaction catalyzed by AgOAc provided the expected pyrrolidine **3a** with high exo selectivity, albeit with moderate enantioselectivity regardless of the solvent (entries 1–3, 51–73% ee). A similar outcome was obtained using KHMDS instead of KO^{t}Bu (entry 4). Pleasingly, further optimization of the reaction conditions revealed that the Cu-catalyzed process was much more enantioselective. Thus, the use of Cu^I/(*R*)-DTBM-Segphos as the catalyst system in CH_2Cl_2 afforded excellent levels of efficiency and stereoselectivity (93% yield for *exo*-**3a**, 95% ee, entry 5). This cycloaddition can be also performed with a lower catalyst loading (5 mol %), albeit with a very important drop in the reactivity (70% conversion after 5 days, entry 6).

At this stage we next studied the subsequent ring closure by intramolecular S_N2 alkylation of *exo*-**3a**. After a survey of reaction conditions, we found that the treatment of the isolated pyrrolidine *exo*-**3a** with KO^{t}Bu in CH_2Cl_2 gave rise to the desired bicyclic product **4a** in good yield (79%, Scheme 4), preserving the enantiopurity of the starting pyrrolidine.

Scheme 4. Intramolecular S_N2 Alkylation of *exo*-3a



Since this straightforward 1,3-dipolar cycloaddition/alkylation process worked efficiently, we next studied the scope of the procedure with regard to the substitution at the azomethine ylide (Table 3). Thus, imino esters **1** with different aryl groups were investigated. The cycloaddition step proceeded nicely to afford the desired pyrrolidines *exo*-**3b–k** as the only detectable isomers with excellent yield and enantioselectivity regardless of the steric and electronic nature of the substituents (78–95% yield, 90–96% ee).[21] Further intramolecular alkylation by reaction with KO^{t}Bu took place with reasonable yield (51–65% yield), providing the desired highly enantioenriched diester azabicycles *exo*-**4**. The relative configuration of the adducts *exo*-**3** was established by NOE studies,[22] while the *exo* configuration of products **4** was unequivocally established by an X-ray diffraction analysis of (±)-*exo*-**4a.**[23] As exemplified in the case of the bicycloproline *exo*-**4d,** the selective deprotection of the *tert*-butyl ester can be readily achieved by straightforward treatment with TFA (product *exo*-**4d**-CO_2H, 75% yield).

In conclusion, *tert*-butyl 6-bromo-2-hexenoate has been studied as a novel dipolarophile in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. The reaction in the presence of a stoichiometric amount of base (K^{t}BuO) provided selectively the endo bicycloprolines in high yield by means of a tandem 1,3-dipolar cycloaddition/alkylation process. The enantioselective version of this reaction was achieved using Cu^I/(*R*)-DTBM-Segphos as the catalyst system for the starting highly exo selective cycloaddition step. The further base-promoted intramolecular alkylation afforded the corresponding

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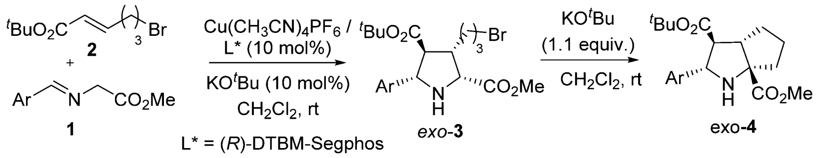
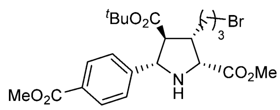
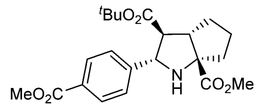
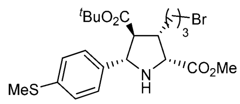
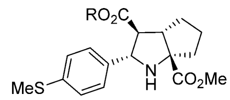
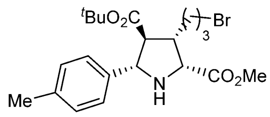
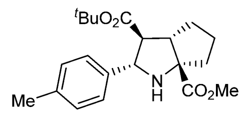
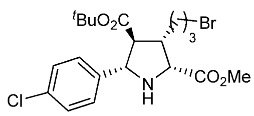
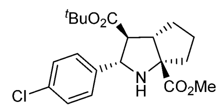
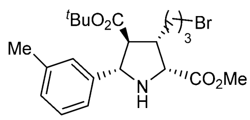
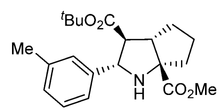
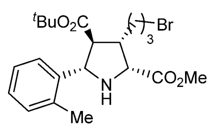
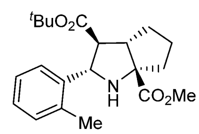
Table 3. Substrate Scope of the Cu^{I}-DTBM-Segphos-Catalyzed Cycloaddition/Alkylation Sequence



entry	1	Pyrrolidine 3[a,b]	Bicycloproline 4[a,b]
1	**1b**	 *exo*-**3b**, 78%, 94% *ee*	 *exo*-**4b**, 55%, 93% *ee*
2	**1d**	 *exo*-**3d**, 95%, 96% *ee*	 TFA: R = ^{t}Bu, *exo*-**4d**, 51%, 96% *ee*; R = H, *exo*-**4d** CO_2H, 75% [c]
3	**1e**	 *exo*-**3e**, 93%, 92% *ee*	 *exo*-**4e**, 65%, 93% *ee*
4	**1k**	 *exo*-**3k**, 78%, 90% *ee*	 *exo*-**4k**, 64%, 90% *ee*
5	**1f**	 *exo*-**3f**, 83%, 93% *ee*	 *exo*-**4f**, 62%, 92% *ee*
6	**1i**	 *exo*-**3i**, 78%, 95% *ee*	 *exo*-**4i**, 60%, 95% *ee*

[a]Isolated yield after chromatographic purification. [b]ee determined by HPLC. [c]Isolated as ammonium trifluoroacetate.

substituted bicycloprolines with high enantiopurity (90−96% ee).

■ EXPERIMENTAL SECTION

General Procedures. All air- and moisture-sensitive manipulations were carried out in anhydrous solvents and under a nitrogen atmosphere. Dichloromethane, toluene, tetrahydrofuran, and acetonitrile were dried over the PureSolv MD purification system. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (230−400 mesh). Flash column chromatography was performed using silica gel (230−400 mesh). When it was required, silica gel was deactivated with a stirred solution of triethylamine in cyclohexane (10% v/v) overnight and then filtered, washed with cyclohexane, and evaporated under reduced pressure. NMR spectra were recorded on 300 and 500 MHz spectrometers and calibrated using residual undeuterated solvent ($CDCl_3$) as the internal reference (δ_H 7.26 ppm, δ_C 77.16 ppm). HRMS spectra were measured on a TOF mass spectrometer with electrospray ionization (ESI) as the ionization source. α-Imino esters **1a**−**k** were prepared by condensation of methyl glycinate hydrochloride and the corresponding aldehydes.[16] Due to their lability, all α-imino esters, once isolated, were immediately used in the 1,3-dipolar cycloaddition without further purification.

Typical Procedure for the Base Mediated Synthesis of Azabicycles: (2*S,3*R**,3a*R**,6a*R**)-3-*tert*-Butyl 6a-Methyl 2-Phenyloctahydrocyclopenta[*b*]pyrrole-3,6a-dicarboxylate (*endo*-4a).** To a solution of α-imino ester **1a** (42.7 mg, 0.241 mmol) and bromoalkene **2** (50 mg, 0.201 mmol) in dry dichloromethane (2.5 mL) was added potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) dropwise. After 24 h at room temperature the reaction mixture was quenched with methanol (0.3 mL) and the solvent evaporated under reduced pressure. The residue was purified by deactivated silica gel flash chromatography (hexane/AcOEt 6/1) to afford *endo*-**4a** (49.3 mg, 71%, yellow oil). Due to their relative lability, bicycloprolines *endo*-**4**, once isolated. were stored at −20 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.30−7.28 (m, 4H), 7.23−7.18 (m, 1H), 4.56 (d, *J* = 6.3 Hz, 1H), 3.77 (s, 3H), 3.11 (t, *J* = 8.8 Hz, 1H), 2.90 (dd, *J* =

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6.3, 1.9 Hz, 1H), 2.22−2.19 (m, 2H), 1.83−1.74 (m, 3H), 1.61−1.49 (m, 1H), 1.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.8, 172.1, 138.6, 128.2, 127.1, 126.8, 80.6, 76.8, 64.2, 58.2, 53.7, 52.5, 41.0, 33.6, 27.7, 26.7. HRMS (EI-QTOF): calcd for $C_{20}H_{28}NO_4$, 346.2013; found, 346.2023 ([M + H]$^+$, 100%).

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(4-(Methoxycarbonyl)phenyl)octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4b**).* Following the typical procedure, the reaction of α-imino ester **1b** (56.7 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4b** (47.0 mg, 58%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.98 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 4.59 (d, J = 6.2 Hz, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.14−3.09 (m, 1H), 2.94 (dd, J = 6.2, 1.5 Hz, 1H), 2.26−2.20 (m, 2H), 1.85−1.73 (m, 3H), 1.56−1.50 (m, 2H), 1.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.6, 171.8, 167.0, 144.0, 129.6, 129.0, 126.9, 81.0, 76.8, 64.1, 58.0, 53.7, 52.6, 52.2, 41.0, 33.7, 27.8, 26.7. HRMS (EI-QTOF): calcd for $C_{22}H_{30}NO_6$, 404.2068; found, 404.2080 ([M + H]$^+$, 86.5%).

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(4-(Trifluoromethyl)phenyl)octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4c**).* Following the typical procedure, the reaction of α-imino ester **1c** (59.1 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4c** (39.1 mg, 47%, yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$): 7.57 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.60 (d, J = 6.1 Hz, 1H), 3.78 (s, 3H), 3.12 (t, J = 8.0 Hz, 1H), 2.93 (d, J = 5.5 Hz, 1H), 2.27−2.21 (m, 2H), 1.75−1.71 (m, 3H), 1.65−1.49 (m, 1H), 1.02 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): 176.6, 171.8, 142.9 (q, J = 1.3 Hz), 129.6 (q, J = 32.4 Hz), 127.3, 125.2 (q, J = 3.8 Hz), 124.3 (q, J = 271.8 Hz), 81.1, 76.8, 63.9, 56.0, 53.6, 52.6, 41.0, 33.6, 27.8, 26.7. ^{19}F NMR (470 MHz, $CDCl_3$): −62.50. HRMS (EI-QTOF): calcd for $C_{21}H_{27}F_3NO_4$, 414.1887; found, 414.1896 ([M + H]$^+$, 100%)

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(4-(Methylthio)-phenyl)octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4d**).* Following the typical procedure, the reaction of α-imino ester **1d** (53.8 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4d** (49.6 mg, 63%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.22−7.18 (m, 4H), 4.51 (d, J = 6.2 Hz, 1H), 3.77 (s, 3H), 3.12−3.07 (m, 1H), 2.88 (dd, J = 6.2, 1.5 Hz, 1H), 2.44 (s, 3H), 2.23−2.18 (m, 2H), 1.83−1.73 (m, 3H), 1.54−1.52 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.7, 172.0, 137.1, 135.7, 127.3, 126.8, 80.8, 76.8, 63.8, 58.1, 53.6, 52.5, 41.0, 33.6, 27.7, 26.7, 16.3. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_4S$, 392.1891; found, 392.1886 ([M + H]$^+$, 100%).

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(p-Tolyl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4e**).* Following the typical procedure, the reaction of α-imino ester **1e** (4.1 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4e** (51.3 mg, 71%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.18 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 4.51 (d, J = 6.2 Hz, 1H), 3.76 (s, 3H), 3.10 (t, J = 8.0 Hz, 1H), 2.87 (dd, J = 6.2, 1.6 Hz, 1H), 2.29 (s, 3H), 2.21−2.18 (m, 2H), 1.83−1.76 (m, 3H), 1.61−1.48 (m, 1H), 1.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.8, 172.2, 136.7, 135.4, 128.8, 126.6, 80.6, 76.8, 64.0, 58.3, 53.6, 52.5, 41.1, 33.6, 27.7, 26.7, 21.1. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_4$, 360.2170; found, 360.2158 ([M + H]$^+$, 100%).

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-methyl 2-(m-Tolyl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4f**).* Following the typical procedure, the reaction of α-imino ester **1f** (4.1 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4f** (46.2 mg, 64%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.20−7.08 (m, 3H), 7.04−7.01 (m, 2H), 4.53 (d, J = 6.2 Hz, 1H), 3.78 (s, 3H), 3.09 (t, J = 7.4 Hz, 1H), 2.88 (dd, J = 6.2, 1.5 Hz, 1H), 2.31 (s, 3H), 2.22−2.15 (m, 2H), 1.84−1.71 (m, 3H), 1.54−1.51 (m, 1H), 1.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.8, 172.2, 138.3, 137.8, 128.1, 127.8, 127.4, 123.9, 80.6, 76.8, 64.1, 58.1, 53.7, 52.5, 41.0, 33.6, 27.8, 26.7, 21.5. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_4$, 360.2170; found, 360.2180 ([M + H]$^+$, 100%).

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(3-Methoxyphenyl)octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4g**).* Following the typical procedure, the reaction of α-imino ester **1g** (49.9 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4g** (38.5 mg, 63%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.23−7.18 (m, 1H), 6.91−6.88 (m, 2H), 6.78 (dd, J = 8.0, 2.2 Hz, 1H), 4.58 (d, J = 6.3 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.16−3.10 (m, 1H), 2.92 (dd, J = 6.3, 2.0 Hz, 1H), 2.23−2.17 (m, 2H), 1.86−1.80 (m, 3H), 1.57−1.51 (m, 1H), 1.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.5, 172.0, 159.7, 140.0, 129.3, 119.1, 113.1, 112.4, 80.8, 76.9, 64.1, 57.9, 55.4, 53.5, 52.6, 40.8, 33.7, 27.7, 26.7. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_5$, 376.2119; found, 376.2107 ([M + H]$^+$, 100%).

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(Naphthalen-2-yl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4h**).* Following the typical procedure, the reaction of α-imino ester **1h** (54.8 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4h** (35.0 mg, 44%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.80−7.80 (m, 4H), 7.50−7.40 (m, 3H), 4.75 (d, J = 6.1 Hz, 1H), 3.80 (s, 3H), 3.19−3.14 (m, 1H), 3.02 (d, J = 6.2 Hz, 1H), 2.30−2.20 (m, 2H), 1.88−1.80 (m, 3H), 1.61−1.55 (m, 1H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.8, 172.1, 136.0, 133.4, 132.7, 128.0, 127.7, 127.6, 126.2, 125.8, 125.7, 124.9, 80.8, 76.9, 64.3, 58.1, 53.8, 52.6, 41.1, 33.7, 27.7, 26.8. HRMS (EI-QTOF): calcd for $C_{24}H_{29}NO_4Na$, 418.1989; found, 418.2003 ([M + Na]$^+$, 81.1%).

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(o-Tolyl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4i**).* Following the typical procedure, the reaction of α-imino ester **1i** (4.1 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4i** (42.6 mg, 59%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.32−7.30 (m, 1H), 7.16−7.13 (m, 3H), 4.64 (d, J = 6.4 Hz, 1H), 3.80 (s, 3H), 3.14 (t, J = 7.8 Hz, 1H), 2.98 (d, J = 6.4 Hz, 1H), 2.36 (s, 3H), 2.29−2.18 (m, 2H), 1.86−1.72 (m, 3H), 1.51−1.57 (m, 1H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.8, 171.9, 136.0, 135.9, 130.1, 127.2, 125.9, 125.2, 80.5, 76.0, 61.7, 56.0, 53.5, 52.5, 40.9, 33.8, 27.7, 26.8, 19.9. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_4$, 360.2170; found, 360.2175 ([M + H]$^+$, 100%).

(2S,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(Naphthalen-1-yl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-**4j**).* Following the typical procedure, the reaction of α-imino ester **1j** (54.8 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**4j** (44.5 mg, 56%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.99 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.55−7.39 (m, 4H), 5.26 (d, J = 6.2 Hz, 1H), 3.80 (s, 3H), 3.20−3.24 (m, 2H), 2.33−3.21 (m, 2H), 1.98−1.87 (m, 3H), 1.84−1.70 (m, 1H), 0.75 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$): 176.8, 171.7, 133.7, 133.7, 131.6, 128.9, 128.1, 126.1, 125.5, 125.3, 123.3, 122.7, 80.1, 75.9, 61.0, 57.4, 53.3, 52.5, 41.0, 33.9, 27.4, 26.9. HRMS (EI-QTOF): calcd for $C_{24}H_{29}NO_4Na$, 418.1989; found, 418.1982 ([M + Na]$^+$, 71.9%).

(2S,3R*,4R*,5S*)-4-tert-Butyl 2-Methyl 3-(4-Bromobutyl)-5-phenylpyrrolidine-2,4-dicarboxylate (endo-**9**).* Following the typical procedure, the reaction of α-imino ester **1a** (54.8 mg, 0.241 mmol), bromoalkene **8** (50 mg, 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-**9** (55.2 mg, 52%, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): 7.45−7.18 (m, 5H), 4.51 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 3.56 (d, J = 7.9 Hz, 1H), 3.42 (t, J = 6.7 Hz, 2H), 3.04−2.89 (m, 2H), 2.67−2.53 (m, 1H), 1.96−1.82 (m, 2H), 1.81−1.68 (m, 1H), 1.62−1.40 (m, 3H), 1.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 173.1, 171.8, 138.7, 128.1, 127.4, 127.1, 80.7, 66.3,

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64.6, 56.9, 52.3, 48.5, 33.5, 33.1, 32.5, 27.4, 26.3. MS (ESI-QTOF): calcd for $C_{21}H_{31}BrNO_4$, 440.1431; found, 440.1425 ([M + H]$^+$, 100%).

Typical Procedure for the Asymmetric [3 + 2] Cycloaddition: (2*R*,3*S*,4*S*,5*S*)-4-*tert*-Butyl 2-Methyl 3-(3-Bromopropyl)-5-phenylpyrrolidine-2,4-dicarboxylate (*exo*-3a). To a stirred suspension of (*R*)-DTBM-Segphos (26.0 mg, 0.022 mmol) and [Cu(MeCN)$_4$]PF$_6$ (7.5 mg, 0.020 mmol) in dry dichloromethane were successively added α-imino ester **1a** (42.7 mg, 0.241 mmol in 0.5 mL of dry dichloromethane), potassium *tert*-butoxide (20 μL of a 1 M solution in THF, 0.020 mmol), and bromoalkene **2** (50 mg, 0.201 mmol in 0.5 mL of dry dichloromethane), After 24 h at room temperature the reaction mixture was filtered over Celite and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/AcOEt 5/1) to afford *exo*-**3a** (79.1 mg, 93%, yellow oil). All of the 3-bromopropyl-substituted pyrrolidines **3** are relatively labile compounds. After isolation by chromatography they were inmediatelly used in the next cyclization step or stored at −20 °C. $[\alpha]_D^{20}$ = −11.4 (*c* = 1.0, CHCl$_3$), 95% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 95/5, flow rate 0.7 mL min^{-1} (λ 211 nm), t_R = 29.0 min ((2*S*,3*R*,4*R*,5*R*)-**3a**) and 37.3 min ((2*R*,3*S*,4*S*,5*S*)-**3a**). ^{1}H NMR (300 MHz, CDCl$_3$): 7.48−7.46 (m, 2H), 7.35−7.28 (m, 3H), 4.34−4.31 (m, 1H), 4.11−4.08 (m, 1H), 3.77 (s, 3H), 3.37 (t, *J* = 6.5 Hz, 2H), 2.78−2.74 (m, 1H), 2.64−2.58 (m, 1H), 2.51 (bs, 1H), 1.94−1.89 (m, 2H), 1.59−1.52 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): 174.0, 172.4, 140.9, 128.6, 127.9, 127.2, 81.2, 67.0, 63.1, 58.4, 52.0, 46.8, 33.3, 30.8, 28.9, 28.0. HRMS (EI-QTOF): calcd for $C_{20}H_{29}BrNO_4$, 426.1275; found, 426.1288 ([M + H]$^+$, 100%).

*(2R,3S,4S,5S)-4-tert-Butyl 2-Methyl 3-(3-Bromopropyl)-5-(4-(methoxycarbonyl)phenyl)pyrrolidine-2,4-dicarboxylate (exo-**3b**).* Following the typical procedure, the reaction of α-imino ester **1b** (56.7 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), potassium *tert*-butoxide (20 μL of a 1 M solution in THF, 0.020 mmol), [Cu(MeCN)$_4$]PF$_6$ (7.5 mg, 0.020 mmol), and (*R*)-DTBM-Segphos (26.0 mg, 0.022 mmol) in dry dichloromethane (2.5 mL) afforded *exo*-**3b** (75.8 mg, 78%, yellow oil). $[\alpha]_D^{20}$ = + 5.1 (*c* = 0.7, CHCl$_3$), 94% ee. HPLC: Daicel Chiralpak IB, hexane/isopropyl alcohol 90/10, flow rate 0.7 mL min^{-1} (λ 254 nm), t_r = 16.4 min ((2*S*,3*R*,4*R*,5*R*)-**3b**) and 19.9 min ((2*R*,3*S*,4*S*,5*S*)-**3b**). ^{1}H NMR (300 MHz, CDCl$_3$): 8.01 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.9 Hz, 2H), 4.45−4.41 (m, 1H), 4.17−4.13 (m, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.38 (t, *J* = 6.5 Hz, 2H), 2.79−2.77 (m, 1H), 2.64−2.62 (m, 1H), 1.95−1.86 (m, 2H), 1.59−1.55 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): 174.0, 172.2, 167.1, 146.9, 130.0, 129.8, 127.2, 81.6, 66.6, 63.2, 58.3, 52.2, 52.1, 47.0, 33.3, 30.9, 28.8, 28.1. HRMS (EI-QTOF): calcd for $C_{22}H_{31}BrNO_6$, 484.1330; found, 484.1332 ([M + H]$^+$, 100%).

*(2R,3S,4S,5S)-4-tert-Butyl 2-Methyl 3-(3-Bromopropyl)-5-(4-(methylthio)phenyl)pyrrolidine-2,4-dicarboxylate (exo-**3d**).* Following the typical procedure, the reaction of α-imino ester **1d** (53.8 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), potassium *tert*-butoxide (20 μL of a 1 M solution in THF, 0.020 mmol), [Cu(MeCN)$_4$]PF$_6$ (7.5 mg, 0.020 mmol), and (*R*)-DTBM-Segphos (26.0 mg, 0.022 mmol) in dry dichloromethane (2.5 mL) afforded *exo*-**3d** (83.3 mg, 95%, yellow oil). $[\alpha]_D^{20}$ = −0.4 (*c* = 10.2, CHCl$_3$), 96% ee. HPLC: Daicel Chiralpak IA, hexane/isopropyl alcohol 95/5, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 33.9 min ((2*R*,3*S*,4*S*,5*S*)-**3d**) and 40.1 min ((2*S*,3*R*,4*R*,5*R*)-**3d**). ^{1}H NMR (300 MHz, CDCl$_3$): 7.40 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 4.33−4.31 (m, 1H), 4.11−4.09 (m, 1H), 3.78 (s, 3H), 3.38 (t, *J* = 6.5 Hz, 2H), 2.78−2.77 (m, 1H), 2.62−2.59 (m, 2H), 2.47 (s, 3H), 1.95−1.89 (m, 2H), 1.56−1.54 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): 174.0, 172.3, 138.0, 137.9, 127.7, 126.9, 81.4, 66.6, 63.1, 58.2, 52.1, 46.9, 33.4, 30.9, 29.8, 28.1, 16.1. HRMS (EI-QTOF): calcd for $C_{21}H_{31}BrNO_4S$, 472.1152; found, 472.1139 ([M + H]$^+$, 93.3%).

*(2R,3S,4S,5S)-4-tert-Butyl 2-Methyl 3-(3-Bromopropyl)-5-(4-methylphenyl)pyrrolidine-2,4-dicarboxylate (exo-**3e**).* Following the typical procedure, the reaction of α-imino ester **1e** (46.1 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), potassium *tert*-butoxide (20 μL of a 1 M solution in THF, 0.020 mmol), [Cu(MeCN)$_4$]PF$_6$ (7.5 mg, 0.020 mmol), and (*R*)-DTBM-Segphos (26.0 mg, 0.022 mmol) in dry dichloromethane (2.5 mL) afforded *exo*-**3e** (82.3 mg, 93%, yellow oil). $[\alpha]_D^{20}$ = −12.1 (*c* = 0.7, CHCl$_3$), 92% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 90/10, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 24.5 min ((2*S*,3*R*,4*R*,5*R*)-**3e**) and 33.1 min ((2*R*,3*S*,4*S*,5*S*)-**3e**). ^{1}H NMR (300 MHz, CDCl$_3$): 7.35 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.33−4.30 (m, 1H), 4.12−4.09 (m, 1H), 3.78 (s, 3H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.81−2.75 (m, 1H), 2.63−2.56 (m, 2H), 2.33 (s, 3H), 1.97−1.88 (m, 2H), 1.62−1.48 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): 173.9, 172.4, 137.7, 137.5, 129.3, 127.0, 81.2, 66.8, 63.2, 58.3, 52.0, 46.9, 33.3, 30.8, 29.0, 28.1, 21.2. HRMS (EI-QTOF): calcd for $C_{21}H_{31}BrNO_4$, 440.1431; found, 440.1428 ([M + H]$^+$, 100%).

*(2R,3S,4S,5S)-4-tert-Butyl 2-Methyl 3-(3-Bromopropyl)-5-(3-methylphenyl)pyrrolidine-2,4-dicarboxylate (exo-**3f**).* Following the typical procedure, the reaction of α-imino ester **1f** (46.1 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), potassium *tert*-butoxide (20 μL of a 1 M solution in THF, 0.020 mmol), [Cu(MeCN)$_4$]PF$_6$ (7.5 mg, 0.020 mmol), and (*R*)-DTBM-Segphos (26.0 mg, 0.022 mmol) in dry dichloromethane (2.5 mL) afforded *exo*-**3f** (73.5 mg, 83%, yellow oil). $[\alpha]_D^{20}$ = −5.4 (*c* = 1.0, CHCl$_3$), 93% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 90/10, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 19.6 min ((2*S*,3*R*,4*R*,5*R*)-**3f**) and 27.3 min ((2*R*,3*S*,4*S*,5*S*)-**3f**). ^{1}H NMR (300 MHz, CDCl$_3$): 7.26−7.18 (m, 3H), 7.09−7.07 (m, 1H), 4.30 (d, *J* = 9.4 Hz, 1H), 4.10 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H), 3.37 (t, *J* = 6.6 Hz, 2H), 2.80−2.75 (m, 2H), 2.59 (t, *J* = 9.4 Hz, 1H), 2.34 (s, 3H), 1.96−1.87 (m, 2H), 1.63−1.47 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): 173.9, 172.5, 140.8, 138.2, 128.9, 128.5, 127.9, 124.2, 81.3, 67.1, 63.3, 58.4, 52.1, 46.9, 33.4, 30.9, 29.1, 28.1, 21.6. HRMS (EI-QTOF): calcd for $C_{21}H_{31}BrNO_4$, 440.1431; found, 440.1436 ([M + H]$^+$, 99.4%).

*(2R,3S,4S,5S)-4-tert-Butyl 2-Methyl 3-(3-Bromopropyl)-5-(4-chlorophenyl)pyrrolidine-2,4-dicarboxylate (exo-**3k**).* Following the typical procedure, the reaction of α-imino ester **1k** (51.0 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), potassium *tert*-butoxide (20 μL of a 1 M solution in THF, 0.020 mmol), [Cu(MeCN)$_4$]PF$_6$ (7.5 mg, 0.020 mmol), and (*R*)-DTBM-Segphos (26.0 mg, 0.022 mmol) in dry dichloromethane (2.5 mL) afforded *exo*-**3k** (89.8 mg, 78%, yellow oil). $[\alpha]_D^{20}$ = −4.9 (*c* = 10.0, CHCl$_3$), 90% ee. HPLC: Daicel Chiralpak AS-H, hexane/isopropyl alcohol 98/2, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 22.9 min ((2*S*,3*R*,4*R*,5*R*)-**3k**) and 28.6 min ((2*R*,3*S*,4*S*,5*S*)-**3k**). ^{1}H NMR (300 MHz, CDCl$_3$): 7.42 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 4.33−4.31 (m, 1H), 4.09−4.07 (m, 1H), 3.76 (s, 3H), 3.36 (t, *J* = 6.6 Hz, 2H), 2.78−2.72 (m, 1H), 2.61−2.54 (m, 1H), 2.34 (bs, 1H), 1.91−1.87 (m, 2H), 1.57−1.50 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): 174.1, 172.2, 140.1, 133.5, 128.7, 128.6, 81.4, 66.2, 63.0, 58.3, 52.0, 46.8, 33.3, 30.8, 28.8, 28.1. HRMS (EI-QTOF): calcd for $C_{20}H_{28}BrClNO_4$, 460.0885; found, 460.0897 ([M + H]$^+$, 67.7%).

*(2R,3S,4S,5S)-4-tert-Butyl 2-Methyl 3-(3-Bromopropyl)-5-(2-methylphenyl)pyrrolidine-2,4-dicarboxylate (exo-**3i**).* Following the typical procedure, the reaction of α-imino ester **1i** (46.1 mg, 0.241 mmol), bromoalkene **2** (50 mg, 0.201 mmol), potassium *tert*-butoxide (20 μL of a 1 M solution in THF, 0.020 mmol), [Cu(MeCN)$_4$]PF$_6$ (7.5 mg, 0.020 mmol), and (*R*)-DTBM-Segphos (26.0 mg, 0.022 mmol) in dry dichloromethane (2.5 mL) afforded *exo*-**3i** (69.0 mg, 78%, yellow oil). $[\alpha]_D^{20}$ = −18.1 (*c* = 12.7, CHCl$_3$), 95% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 90/10, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 13.9 min ((2*S*,3*R*,4*R*,5*R*)-**3i**) and 19.8 min ((2*R*,3*S*,4*S*,5*S*)-**3i**). ^{1}H NMR (300 MHz, CDCl$_3$): 7.66 (d, *J* = 7.6 Hz, 1H), 7.23−7.10 (m, 3H), 4.62 (d, *J* = 8.9 Hz, 1H), 4.10 (d, *J* = 8.1 Hz, 1H), 3.77 (s, 3H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.82−2.70 (m, 3H), 2.36 (s, 3H), 1.98−1.88 (m, 2H), 1.62−1.52 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$): 174.1, 172.7, 138.6, 136.6, 130.4, 127.6, 126.6, 126.4, 81.2, 63.4, 62.5, 57.5, 52.1, 47.1, 33.4, 30.9, 29.1, 28.0, 19.6. HRMS (EI-QTOF): calcd for $C_{21}H_{31}BrNO_4$, 440.1431; found, 440.1444 ([M + H]$^+$, 100%).

Typical Procedure for the Cyclization of (3-Bromopropyl)-pyrrolidines: (2*S*,3*S*,3a*S*,6a*S*)-3-*tert*-Butyl 6a-Methyl 2-

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Phenyloctahydrocyclopenta[*b*]pyrrole-3,6a-dicarboxylate (*exo*-4a). To a stirred solution of pyrrolidine *exo*-**3a** (50 mg, 0.117 mmol) in dry dichloromethane (2.0 mL) was added potassium *tert*-butoxide (129 μL of a 1 M solution in THF, 0.129 mmol) dropwise. After 3 h at room temperature the reaction mixture was quenched with methanol (0.3 mL) and evaporated under reduced pressure. The residue was purified by deactivated silica gel flash chromatography (hexane/AcOEt 6/1) to afford *exo*-**4a** (31.9 mg, 79%, yellow oil). Due to their relative lability, bicycloprolines *exo*-**4**, once isolated, were stored at −20 °C. $[\alpha]_D^{20}$ = + 9.4 (*c* = 9.3, $CHCl_3$), 95% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 95/5, flow rate 0.5 mL min^{-1} (λ 211 nm), t_r = 11.1 min ((2*R*,3*R*,3a*R*,6a*R*)-**4a**) and 12.9 min ((2*S*,3*S*,3a*S*,6a*S*)-**4a**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.43 (d, *J* = 7.0 Hz, 2H), 7.27 (m, 3H), 4.20 (d, *J* = 10.0 Hz, 1H), 3.77 (s, 3H), 3.06 (t, *J* = 7.0 Hz, 1H), 2.36 (t, *J* = 9.4 Hz, 1H), 1.86 (m, 6H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 178.4, 172.5, 141.6, 128.3, 127.7, 127.3, 80.8, 74.5, 65.7, 60.5, 52.8, 52.6, 40.5, 33.3, 28.2, 25.3. HRMS (EI-QTOF): calcd for $C_{20}H_{28}NO_4$, 346.2013; found, 346.2020 ([M + H]$^+$, 100%).

*(2S,3S,3aS,6aS)-3-tert-Butyl 6a-Methyl 2-(4-(Methoxycarbonyl)-phenyl)octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (exo-**4b**).* Following the typical procedure, the reaction of pyrrolidine *exo*-**3b** (50 mg, 0.103 mmol) and potassium *tert*-butoxide (113 μL of a 1 M solution in THF, 0.113 mmol) in dry dichloromethane (2.0 mL) afforded *exo*-**4b** (22.9 mg, 55%, yellow oil). $[\alpha]_D^{20}$ = −17.9 (*c* = 4.7, $CHCl_3$), 93% ee. HPLC: Daicel Chiralpak IA, hexane/isopropyl alcohol 98/2, flow rate 0.7 mL min^{-1} (λ 254 nm), t_r = 14.6 min ((2*R*,3*R*,3a*R*,6a*R*)-**4b**) and 20.8 min ((2*S*,3*S*,3a*S*,6a*S*)-**4b**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.97 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 4.27 (d, *J* = 9.8 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.06 (m, 1H), 2.34 (t, *J* = 9.3 Hz, 1H), 1.87 (m, 6H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 178.2, 172.2, 167.2, 147.2, 129.7, 129.5, 127.3, 81.0, 74.6, 65.2, 60.5, 52.9, 52.6, 52.2, 40.5, 33.2, 28.2, 25.2. HRMS (EI-QTOF): calcd for $C_{22}H_{30}NO_6$, 404.2068; found, 404.2080 ([M + H]$^+$, 100%).

*(2S,3S,3aS,6aS)-3-tert-Butyl 6a-Methyl 2-(4-(Methylthio)phenyl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (exo-**4d**).* Following the typical procedure, the reaction of pyrrolidine *exo*-**3d** (50 mg, 0.106 mmol) and potassium *tert*-butoxide (116 μL of a 1 M solution in THF, 0.116 mmol) in dry dichloromethane (2.0 mL) afforded *exo*-**4d** (21.2 mg, 51%, yellow oil). $[\alpha]_D^{20}$ = −1.7 (*c* = 1.1, $CHCl_3$), 96% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 95/5, flow rate 0.7 mL min^{-1} (λ 254 nm), t_r = 12.2 min ((2*R*,3*R*,3a*R*,6a*R*)-**4d**) and 16.2 min ((2*S*,3*S*,3a*S*,6a*S*)-**4d**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.36 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 4.17 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 3H), 3.03 (t, *J* = 7.3, 1H), 2.81 (bs, 1H), 2.46 (s, 3H), 2.31 (t, *J* = 9.4 Hz, 1H), 1.86 (m, 6H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 178.3, 172.4, 128.8, 137.4, 127.8, 126.8, 80.8, 74.4, 65.1, 60.4, 52.8, 52.5, 40.9, 33.2, 28.2, 25.2, 16.3. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_4S$, 392.1891; found, 392.1855 ([M + H]$^+$, 100%).

*(2S,3S,3aS,6aS)-3-tert-Butyl 6a-Methyl 2-(4-Methylphenyl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (exo-**4e**).* Following the typical procedure, the reaction of pyrrolidine *exo*-**3e** (50 mg, 0.114 mmol) and potassium *tert*-butoxide (125 μL of a 1 M solution in THF, 0.125 mmol) in dry dichloromethane (2.0 mL) afforded *exo*-**4e** (26.6 mg, 65%, yellow oil). $[\alpha]_D^{20}$ = −17.6 (*c* = 10.7, $CHCl_3$), 93% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 95/5, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 10.2 min ((2*R*,3*R*,3a*R*,6a*R*)-**4e**) and 13.4 min ((2*S*,3*S*,3a*S*,6a*S*)-**4e**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.31 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.17 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 3H), 3.04 (t, *J* = 7.4, 1H), 2.33 (m, 4H), 1.83 (m, 6H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 178.4, 172.6, 138.6, 137.2, 128.9, 127.1, 80.7, 74.5, 65.4, 60.4, 52.9, 52.5, 40.5, 33.3, 28.2, 25.2, 21.3. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_4$, 360.2170; found, 360.2169 ([M + H]$^+$, 100%).

*(2S,3S,3aS,6aS)-3-tert-Butyl 6a-Methyl 2-(4-Chlorophenyl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (exo-**4k**).* Following the typical procedure, the reaction of pyrrolidine *exo*-**3k** (50 mg, 0.109 mmol) and potassium *tert*-butoxide (125 μL of a 1 M solution in THF, 0.119 mmol) in dry dichloromethane (2.0 mL) afforded *exo*-**4k** (26.5 mg, 64%, yellow oil). $[\alpha]_D^{20}$ = −13.0 (*c* = 10.4, $CHCl_3$), 90% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 99/1, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 13.3 min ((2*R*,3*R*,3a*R*,6a*R*)-**4k**) and 18.1 min ((2*S*,3*S*,3a*S*,6a*S*)-**4k**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.38 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 4.18 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 3H), 3.03 (t, *J* = 7.1, 1H), 2.28 (t, *J* = 9.4 Hz, 1H), 1.84 (m, 6H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 178.2, 172.3, 140.3, 133.2, 128.6, 128.4, 81.0, 74.5, 64.8, 60.5, 52.8, 52.6, 40.5, 33.2, 28.2, 25.2. HRMS (EI-QTOF): calcd for $C_{20}H_{27}ClNO_4$, 380.1624; found, 380.1638 ([M + H]$^+$, 100%).

*(2S,3S,3aS,6aS)-3-tert-Butyl 6a-Methyl 2-(3-Methylphenyl octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (exo-**4f**).* Following the typical procedure, the reaction of pyrrolidine *exo*-**3f** (50 mg, 0.114 mmol) and potassium *tert*-butoxide (125 μL of a 1 M solution in THF, 0.125 mmol) in dry dichloromethane (2.0 mL) afforded *exo*-**4f** (25.4 mg, 62%, yellow oil). $[\alpha]_D^{20}$ = −12.5 (*c* = 9.5, $CHCl_3$), 92% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 98/2, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 12.5 min ((2*R*,3*R*,3a*R*,6a*R*)-**4f**) and 16.1 min ((2*S*,3*S*,3a*S*,6a*S*)-**4f**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.19 (m, 3H), 7.05 (d, *J* = 6.8 Hz, 1H), 4.16 (d, *J* = 10.1 Hz, 1H), 3.76 (s, 3H), 3.05 (t, *J* = 7.2, 1H), 2.33 (m, 5H), 1.85 (m, 6H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 178.4, 172.6, 141.5, 137.8, 128.4, 128.2, 127.8, 124.3, 80.7, 74.5, 65.7, 60.4, 52.9, 52.5, 40.5, 33.2, 28.1, 25.2, 21.6. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_4$, 360.2170; found, 360.2161 ([M + H]$^+$, 100%).

*(2S,3S,3aS,6aS)-3-tert-Butyl 6a-Methyl 2-(2-Methylphenyl)-octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (exo-**4i**).* Following the typical procedure, the reaction of pyrrolidine *exo*-**3i** (50 mg, 0.114 mmol) and potassium *tert*-butoxide (125 μL of a 1 M solution in THF, 0.125 mmol) in dry dichloromethane (2.0 mL) afforded *exo*-**4i** (24.6 mg, 60%, yellow oil). $[\alpha]_D^{20}$ = −9.9 (*c* = 7.4, $CHCl_3$), 95% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 98/2, flow rate 0.7 mL min^{-1} (λ 211 nm), t_r = 9.8 min ((2*R*,3*R*,3a*R*,6a*R*)-**4i**) and 13.3 min ((2*S*,3*S*,3a*S*,6a*S*)-**4i**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (d, *J* = 7.1 Hz, 1H), 7.13 (m, 3H), 4.45 (d, *J* = 10.1 Hz, 1H), 3.78 (s, 3H), 3.06 (t, *J* = 7.4, 1H), 2.79 (bs, 1H), 2.54 (t, *J* = 9.3 Hz, 1H), 2.39 (s, 3H), 1.84 (m, 6H), 1.28 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 178.4, 172.7, 138.8, 136.6, 130.7, 127.3, 126.8, 126.1, 80.7, 74.5, 61.3, 59.1, 53.0, 52.5, 40.2, 33.2, 28.1, 25.4, 19.6. HRMS (EI-QTOF): calcd for $C_{21}H_{30}NO_4$ 360.2170; found, 360.2182 ([M + H]$^+$, 100%).

(2*S*,3*S*,3a*S*,6a*S*)-6a-(Methoxycarbonyl)-2-(4-(methylthio)-phenyl)octahydrocyclopenta[*b*]pyrrole-3-carboxylic Acid (*exo*-4d-CO_2H). The azabicycle *exo*-**4d** (17.6 mg, 0.045 mmol) was dissolved in trifluoroacetic acid (1 mL), and the resulting solution was stirred at room temperature for 1 h. The acid was removed in vacuo to provide *exo*-**4d-CO_2H** (11.2 mg, 75%, yellow oil). $[\alpha]_D^{20}$ = −15.8 (*c* = 10.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 9.97 (bs), 7.33−7.30 (m, 2H), 7.17−7.15 (m, 2H), 4.70 (d, *J* = 11.6 Hz, 1H), 3.92 (s, 3H), 3.38−3.23 (m, 2H), 2.62−2.32 (m, 4H), 2.15−2.09 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 173.1, 171.7, 142.8, 128.6, 126.3, 124.8, 77.2, 77.0, 66.7, 54.9, 53.7, 52.3, 35.7, 31.7, 25.0, 15.0. HRMS (ESI-QTOF): calcd for $C_{17}H_{22}NO_4S$, 336.1264; found, 336.1279 ([M + H]$^+$, 100%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01100.

^{1}H and ^{13}C NMR spectra for all new compounds, HPLC traces used to determine enantiomeric purity, and X-ray crystallographic data of compound (±) *exo*-**4a** (PDF)

X-ray crystallographic data of (±) *exo*-**4a**(CIF)

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Notes

The authors declare no competing financial interest.

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(23) The absolute configuration of adducts *exo*-**3** was tentatively assigned as 2*R*,3*S*,4*S*,5*S* (and consequently as 2*S*,3*S*,3a*S*,6a*S* for *exo*-**4**) on the basis of previously reported results in the highly enantioselective Cu/(*R*)-DTBM-Segphos catalyzed 1,3-dipolar cycloaddition of azomethine ylides with diverse dipolarophiles. In all examples hitherto described, the pyrrolidines with a 2*R*,5*S* configuration were always obtained as the major enantiomers regardless of the dipolarophile. See refs 16 and 20.

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