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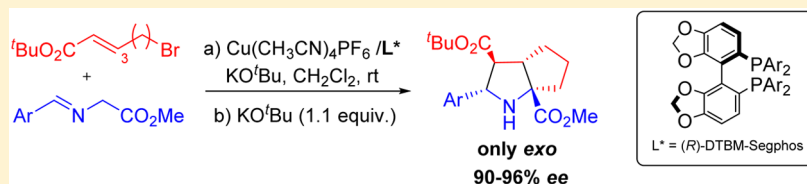
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Catalytic Asymmetric Synthesis of Bicycloprolines by a 1,3-Dipolar Cycloaddition/Intramolecular Alkylation Strategy

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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 peptidomimetics⁵ and natural products such as kopsihainanine B⁶ 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 procedures¹⁰ 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 Grigg¹¹ and Overman¹² have elegantly applied this methodology to the preparation of azabicyclooctanes and azatricyclo-decanes. 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-hexenoate¹⁷ (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^tBu in CH₂Cl₂ (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 adduct¹⁹ was 74

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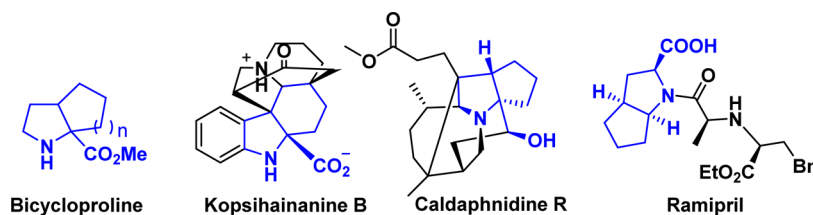


Figure 1. Selected compounds containing a bicycloproline motif.

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

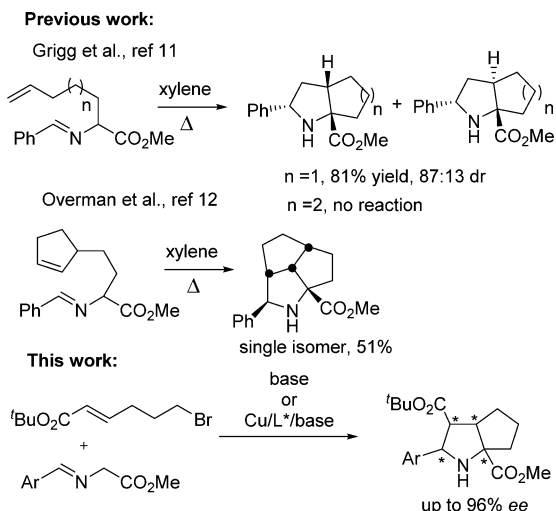
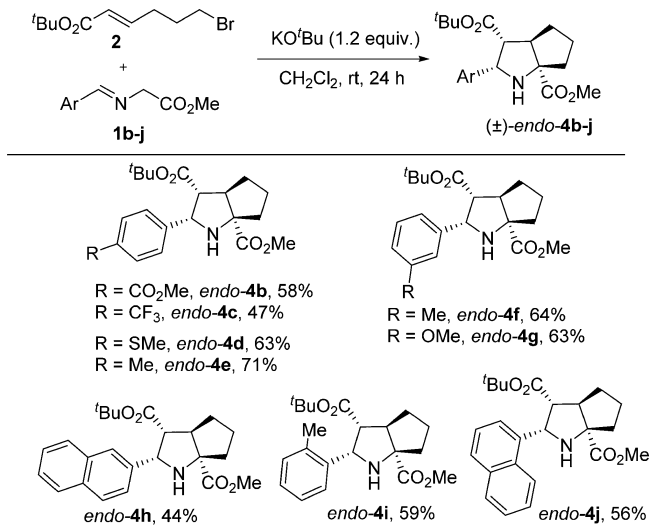


Table 1. Optimization Experiments for the Model Reaction

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 ₂ Cl ₂	>98	71
5	KHMDS ^c	CH ₂ Cl ₂	70	60
6	LiHMDS ^d	CH ₂ Cl ₂	>98	16
7	4-DMAP ^e	CH ₂ Cl ₂	0	
8	DBU ^f	CH ₂ Cl ₂	0	
9	Et ₃ N	CH ₂ Cl ₂	0	
10	Cs ₂ CO ₃	CH ₂ Cl ₂	28	

^aIsolated yield. ^bLithium diisopropylamide. ^cPotassium bis(trimethylsilyl)amide. ^dLithium bis(trimethylsilyl)amide. ^e4-Dimethylaminopyridine. ^f1,8-Diazabicycloundec-7-ene.

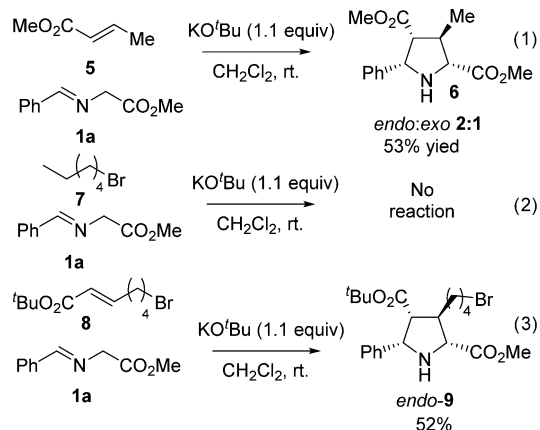
Scheme 2. Scope of the Base-Mediated Process



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^tBu in CH₂Cl₂) 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

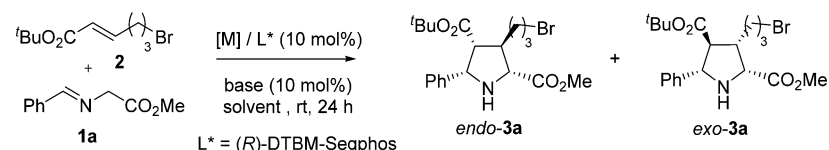
Scheme 3. Related Studies of the Base-Mediated Reaction



75 detected in the ¹H NMR of the crude mixtures. In contrast, 76 very low or no reactivity was observed using weaker bases, such 77 as DBU, Et₃N, and Cs₂CO₃ (entries 7–10).

78 Since this approach constitutes a straightforward and 79 powerful diastereoselective one-pot procedure for the prepara- 80 tion of bicycloproline analogues, involving the formation of 81 three C–C bonds in a single operation, we undertook the study 82 of the scope of the process. As summarized in Scheme 2, under 83 the optimized reaction conditions, the reaction took place with

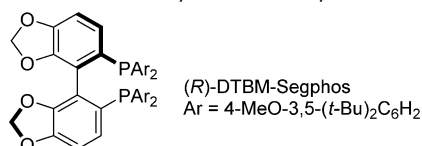
Table 2. Optimization Experiments for Catalytic Asymmetric 1,3-Dipolar Cycloaddition with (R)-DTBM-Segphos as Ligand



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 ₂ Cl ₂	<2/>98	89	73
3	AgOAc	KO ^t Bu	toluene	14/86	90	51
4	AgOAc	KHMDS	CH ₂ Cl ₂	27:/	28	77
5	CuPF ₆ ^d	KO ^t Bu	CH ₂ Cl ₂	<2/>98	93	95
6 ^e	CuPF ₆ ^d	KO ^t Bu	CH ₂ Cl ₂	<2/>98	70 ^f	n.d. ^g

^aDetermined by ¹H NMR from the crude reaction mixture. ^bIsolated yield of adducts 3a. ^cEnantiomeric excess of *exo*-3a determined by HPLC.

^dCuPF₆ = Cu(CH₃CN)₄PF₆. ^e5 mol % of catalyst. ^f70% conversion yield after 5 days of reaction. ^gNot determined.



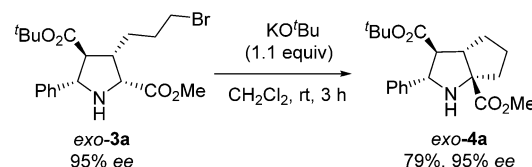
ester **1a** with 1-bromohexane (**7**) in the presence of KO^tBu (eq 2), showing that the intermolecular alkylation process is not facile. Interestingly, the reaction of (*E*)-*tert*-butyl 7-bromo-2-heptenoate (**8**; homologous substrate of the model bromoalkene **2**) with the imino ester **1a** in the presence of 1.1 equiv of KO^tBu 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 bicycprolines **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^tBu (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^tBu (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 CH₂Cl₂ 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^tBu in CH₂Cl₂ 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^tBu 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 (\pm)-*exo*-**4a**.²³ As exemplified in the case of the bicycproline *exo*-**4d**, the selective deprotection of the *tert*-butyl ester can be readily achieved by straightforward treatment with TFA (product *exo*-**4d**-CO₂H, 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^tBuO) provided selectively the *endo* bicycprolines 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

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

entry	1	Pyrrolidine 3 ^{a,b}	Bicyclopoline 4 ^{a,b}
1	1b	 exo-3b, 78%, 94% ee	 exo-4b, 55%, 93% ee
2	1d	 exo-3d, 95%, 96% ee	 TFA → R = tBu, exo-4d, 51%, 96% ee R = H, exo-4d CO ₂ H, 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

^aIsolated yield after chromatographic purification. ^bee determined by HPLC. ^cIsolated as ammonium trifluoroacetate.

169 substituted bicycloprolines with high enantiopurity (90–96%
170 ee).

171 ■ EXPERIMENTAL SECTION

172 **General Procedures.** All air- and moisture-sensitive manipulations
173 were carried out in anhydrous solvents and under a nitrogen
174 atmosphere. Dichloromethane, toluene, tetrahydrofuran, and acetonitrile
175 were dried over the PureSolv MD purification system. Reactions
176 were monitored by thin-layer chromatography carried out on 0.25 mm
177 silica gel plates (230–400 mesh). Flash column chromatography was
178 performed using silica gel (230–400 mesh). When it was required,
179 silica gel was deactivated with a stirred solution of triethylamine in
180 cyclohexane (10% v/v) overnight and then filtered, washed with
181 cyclohexane, and evaporated under reduced pressure. NMR spectra
182 were recorded on 300 and 500 MHz spectrometers and calibrated
183 using residual undeuterated solvent (CDCl₃) as the internal reference
184 (δ_H 7.26 ppm, δ_C 77.16 ppm). HRMS spectra were measured on a
185 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: (2S*,3R*,3aR*,6aR*)-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. ¹H NMR (300 MHz, CDCl₃): 7.30–7.28 (m, 4H), 7.23–7.18 (m, 1H), 4.56 (d, 203 J = 6.3 Hz, 1H), 3.77 (s, 3H), 3.11 (t, J = 8.8 Hz, 1H), 2.90 (dd, J = 204

205 6.3, 1.9 Hz, 1H), 2.22–2.19 (m, 2H), 1.83–1.74 (m, 3H), 1.61–1.49
206 (m, 1H), 1.02 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): 176.8, 172.1,
207 138.6, 128.2, 127.1, 126.8, 80.6, 76.8, 64.2, 58.2, 53.7, 52.5, 41.0, 33.6,
208 27.7, 26.7. HRMS (EI-QTOF): calcd for C₂₀H₂₈NO₄, 346.2013;
209 found, 346.2023 ([M + H]⁺, 100%).

210 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(4-
211 (Methoxycarbonyl)phenyl)octahydrocyclopenta[b]pyrrole-3,6a-di-
212 carboxylate (endo-4b). Following the typical procedure, the reaction
213 of α-imino ester 1b (56.7 mg, 0.241 mmol), bromoalkene 2 (50 mg,
214 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution
215 in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-
216 4b (47.0 mg, 58%, yellow oil). ¹H NMR (300 MHz, CDCl₃): 7.98 (d,
217 J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 4.59 (d, J = 6.2 Hz, 1H),
218 3.90 (s, 3H), 3.78 (s, 3H), 3.14–3.09 (m, 1H), 2.94 (dd, J = 6.2, 1.5
219 Hz, 1H), 2.26–2.20 (m, 2H), 1.85–1.73 (m, 3H), 1.56–1.50 (m, 2H),
220 1.02 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): 176.6, 171.8, 167.0, 144.0,
221 129.6, 129.0, 126.9, 81.0, 76.8, 64.1, 58.0, 53.7, 52.6, 52.2, 41.0, 33.7,
222 27.8, 26.7. HRMS (EI-QTOF): calcd for C₂₂H₃₀NO₆, 404.2068;
223 found, 404.2080 ([M + H]⁺, 86.5%).

224 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(4-
225 (Trifluoromethyl)phenyl)octahydrocyclopenta[b]pyrrole-3,6a-dicar-
226 boxylate (endo-4c). Following the typical procedure, the reaction of
227 α-imino ester 1c (59.1 mg, 0.241 mmol), bromoalkene 2 (50 mg,
228 0.201 mmol), and potassium *tert*-butoxide (241 μL of a 1 M solution
229 in THF, 0.241 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-
230 4c (39.1 mg, 47%, yellow oil). ¹H NMR (500 MHz, CDCl₃): 7.57 (d, J
231 = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.60 (d, J = 6.1 Hz, 1H), 3.78
232 (s, 3H), 3.12 (t, J = 8.0 Hz, 1H), 2.93 (d, J = 5.5 Hz, 1H), 2.27–2.21
233 (m, 2H), 1.75–1.71 (m, 3H), 1.65–1.49 (m, 1H), 1.02 (s, 9H). ¹³C
234 NMR (125 MHz, CDCl₃): 176.6, 171.8, 142.9 (q, J = 1.3 Hz), 129.6
235 (q, J = 32.4 Hz), 127.3, 125.2 (q, J = 3.8 Hz), 124.3 (q, J = 271.8 Hz),
236 81.1, 76.8, 63.9, 56.0, 53.6, 52.6, 41.0, 33.6, 27.8, 26.7. ¹⁹F NMR (470
237 MHz, CDCl₃): –62.50. HRMS (EI-QTOF): calcd for C₂₁H₂₇F₃NO₄,
238 414.1887; found, 414.1896 ([M + H]⁺, 100%).

239 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(4-(Methylthio)-
240 phenyl)octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-
241 4d). Following the typical procedure, the reaction of α-imino ester
242 1d (53.8 mg, 0.241 mmol), bromoalkene 2 (50 mg, 0.201 mmol), and
243 potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241
244 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-4d (49.6 mg,
245 63%, yellow oil). ¹H NMR (300 MHz, CDCl₃): 7.22–7.18 (m, 4H),
246 4.51 (d, J = 6.2 Hz, 1H), 3.77 (s, 3H), 3.12–3.07 (m, 1H), 2.88 (dd, J
247 = 6.2, 1.5 Hz, 1H), 2.44 (s, 3H), 2.23–2.18 (m, 2H), 1.83–1.73 (m,
248 3H), 1.54–1.52 (m, 1H), 1.05 (s, 9H). ¹³C NMR (75 MHz, CDCl₃):
249 176.7, 172.0, 137.1, 135.7, 127.3, 126.8, 80.8, 76.8, 63.8, 58.1, 53.6,
250 52.5, 41.0, 33.6, 27.7, 26.7, 16.3. HRMS (EI-QTOF): calcd for
251 C₂₁H₃₀NO₄S, 392.1891; found, 392.1886 ([M + H]⁺, 100%).

252 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(*p*-Tolyl)-
253 octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-4e). Fol-
254 lowing the typical procedure, the reaction of α-imino ester 1e (4.1 mg,
255 0.241 mmol), bromoalkene 2 (50 mg, 0.201 mmol), and potassium
256 *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry
257 dichloromethane (2.5 mL) afforded *endo*-4e (51.3 mg, 71%, yellow
258 oil). ¹H NMR (300 MHz, CDCl₃): 7.18 (d, J = 8.0 Hz, 2H), 7.09 (d, J
259 = 8.0 Hz, 2H), 4.51 (d, J = 6.2 Hz, 1H), 3.76 (s, 3H), 3.10 (t, J = 8.0
260 Hz, 1H), 2.87 (dd, J = 6.2, 1.6 Hz, 1H), 2.29 (s, 3H), 2.21–2.18 (m,
261 2H), 1.83–1.76 (m, 3H), 1.61–1.48 (m, 1H), 1.04 (s, 9H). ¹³C NMR
262 (75 MHz, CDCl₃): 176.8, 172.2, 136.7, 135.4, 128.8, 126.6, 80.6, 76.8,
263 64.0, 58.3, 53.6, 52.5, 41.1, 33.6, 27.7, 26.7, 21.1. HRMS (EI-QTOF):
264 calcd for C₂₁H₃₀NO₄, 360.2170; found, 360.2158 ([M + H]⁺, 100%).

265 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-methyl 2-(*m*-Tolyl)-
266 octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-4f). Fol-
267 lowing the typical procedure, the reaction of α-imino ester 1f (4.1 mg,
268 0.241 mmol), bromoalkene 2 (50 mg, 0.201 mmol), and potassium
269 *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry
270 dichloromethane (2.5 mL) afforded *endo*-4f (46.2 mg, 64%, yellow
271 oil). ¹H NMR (300 MHz, CDCl₃): 7.20–7.08 (m, 3H), 7.04–7.01 (m,
272 2H), 4.53 (d, J = 6.2 Hz, 1H), 3.78 (s, 3H), 3.09 (t, J = 7.4 Hz, 1H),
273 2.88 (dd, J = 6.2, 1.5 Hz, 1H), 2.31 (s, 3H), 2.22–2.15 (m, 2H), 1.84–
274 1.71 (m, 3H), 1.54–1.51 (m, 1H), 1.04 (s, 9H). ¹³C NMR (75 MHz,
275 CDCl₃): 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-
276 QTOF): calcd for C₂₁H₃₀NO₄, 360.2170; found, 360.2180 ([M + H]⁺,
277 100%).

278 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(3-
279 Methoxyphenyl)octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate
280 (endo-4g). Following the typical procedure, the reaction of α-imino
281 ester 1g (49.9 mg, 0.241 mmol), bromoalkene 2 (50 mg, 0.201 mmol),
282 and potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241
283 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-4g (38.5 mg,
284 63%, yellow oil). ¹H NMR (300 MHz, CDCl₃): 7.23–7.18 (m, 1H),
285 6.91–6.88 (m, 2H), 6.78 (dd, J = 8.0, 2.2 Hz, 1H), 4.58 (d, J = 6.3 Hz,
286 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.16–3.10 (m, 1H), 2.92 (dd, J = 6.3,
287 2.0 Hz, 1H), 2.23–2.17 (m, 2H), 1.86–1.80 (m, 3H), 1.57–1.51 (m,
288 1H), 1.07 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): 176.5, 172.0, 159.7,
289 140.0, 129.3, 119.1, 113.1, 112.4, 80.8, 76.9, 64.1, 57.9, 55.4, 53.5, 52.6,
290 40.8, 33.7, 27.7, 26.7. HRMS (EI-QTOF): calcd for C₂₁H₃₀NO₅,
291 376.2119; found, 376.2107 ([M + H]⁺, 100%).

292 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(Naphthalen-2-yl)-
293 octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-4h). Fol-
294 lowing the typical procedure, the reaction of α-imino ester 1h (54.8
295 mg, 0.241 mmol), bromoalkene 2 (50 mg, 0.201 mmol), and
296 potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241
297 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-4h (35.0 mg,
298 44%, yellow oil). ¹H NMR (300 MHz, CDCl₃): 7.80–7.80 (m, 4H),
299 7.50–7.40 (m, 3H), 4.75 (d, J = 6.1 Hz, 1H), 3.80 (s, 3H), 3.19–3.14
300 (m, 1H), 3.02 (d, J = 6.2 Hz, 1H), 2.30–2.20 (m, 2H), 1.88–1.80 (m,
301 3H), 1.61–1.55 (m, 1H), 0.92 (s, 9H). ¹³C NMR (75 MHz, CDCl₃):
302 176.8, 172.1, 136.0, 133.4, 132.7, 128.0, 127.7, 127.6, 126.2, 125.8,
303 125.7, 124.9, 80.8, 76.9, 64.3, 58.1, 53.8, 52.6, 41.1, 33.7, 27.7, 26.8.
304 HRMS (EI-QTOF): calcd for C₂₄H₂₉NO₄Na, 418.1989; found,
305 418.2003 ([M + Na]⁺, 81.1%).

306 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(*o*-Tolyl)-
307 octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-4i). Fol-
308 lowing the typical procedure, the reaction of α-imino ester 1i (4.1 mg,
309 0.241 mmol), bromoalkene 2 (50 mg, 0.201 mmol), and potassium
310 *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241 mmol) in dry
311 dichloromethane (2.5 mL) afforded *endo*-4i (42.6 mg, 59%, yellow
312 oil). ¹H NMR (300 MHz, CDCl₃): 7.32–7.30 (m, 1H), 7.16–7.13 (m,
313 3H), 4.64 (d, J = 6.4 Hz, 1H), 3.80 (s, 3H), 3.14 (t, J = 7.8 Hz, 1H),
314 2.98 (d, J = 6.4 Hz, 1H), 2.36 (s, 3H), 2.29–2.18 (m, 2H), 1.86–1.72
315 (m, 3H), 1.51–1.57 (m, 1H), 0.99 (s, 9H). ¹³C NMR (75 MHz,
316 CDCl₃): 176.8, 171.9, 136.0, 135.9, 130.1, 127.2, 125.9, 125.2, 80.5,
317 76.0, 61.7, 56.0, 53.5, 52.5, 40.9, 33.8, 27.7, 26.8, 19.9. HRMS (EI-
318 QTOF): calcd for C₂₁H₃₀NO₄, 360.2170; found, 360.2175 ([M + H]⁺,
319 100%).

320 (2S*,3R*,3aR*,6aR*)-3-tert-Butyl 6a-Methyl 2-(Naphthalen-1-yl)-
321 octahydrocyclopenta[b]pyrrole-3,6a-dicarboxylate (endo-4j). Fol-
322 lowing the typical procedure, the reaction of α-imino ester 1j (54.8
323 mg, 0.241 mmol), bromoalkene 2 (50 mg, 0.201 mmol), and
324 potassium *tert*-butoxide (241 μL of a 1 M solution in THF, 0.241
325 mmol) in dry dichloromethane (2.5 mL) afforded *endo*-4j (44.5 mg,
326 56%, yellow oil). ¹H NMR (300 MHz, CDCl₃): 7.99 (d, J = 8.2 Hz,
327 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.55–7.39 (m,
328 4H), 5.26 (d, J = 6.2 Hz, 1H), 3.80 (s, 3H), 3.20–3.24 (m, 2H), 2.33–
329 3.21 (m, 2H), 1.98–1.87 (m, 3H), 1.84–1.70 (m, 1H), 0.75 (s,
330 9H). ¹³C NMR (75 MHz, CDCl₃): 176.8, 171.7, 133.7, 133.7, 131.6,
331 128.9, 128.1, 126.1, 125.5, 125.3, 123.3, 122.7, 80.1, 75.9, 61.0, 57.4,
332 53.3, 52.5, 41.0, 33.9, 27.4, 26.9. HRMS (EI-QTOF): calcd for
333 C₂₄H₂₉NO₄Na, 418.1989; found, 418.1982 ([M + Na]⁺, 71.9%).

334 (2S*,3R*,4R*,5S*)-4-tert-Butyl 2-Methyl 3-(4-Bromobutyl)-5-*phe*-
335 nylpyrrolidine-2,4-dicarboxylate (endo-9). Following the typical
336 procedure, the reaction of α-imino ester 1a (54.8 mg, 0.241 mmol),
337 bromoalkene 8 (50 mg, 0.201 mmol), and potassium *tert*-butoxide
338 (241 μL of a 1 M solution in THF, 0.241 mmol) in dry
339 dichloromethane (2.5 mL) afforded *endo*-9 (55.2 mg, 52%, yellow
340 oil). ¹H NMR (300 MHz, CDCl₃): 7.45–7.18 (m, 5H), 4.51 (d, J =
341 8.0 Hz, 1H), 3.81 (s, 3H), 3.56 (d, J = 7.9 Hz, 1H), 3.42 (t, J = 6.7 Hz,
342 2H), 3.04–2.89 (m, 2H), 2.67–2.53 (m, 1H), 1.96–1.82 (m, 2H),
343 1.81–1.68 (m, 1H), 1.62–1.40 (m, 3H), 1.02 (s, 9H). ¹³C NMR (75
344 MHz, CDCl₃): 173.1, 171.8, 138.7, 128.1, 127.4, 127.1, 80.7, 66.3, 345

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: (2R,3S,4S,5S)-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 μ L 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 immediately used in the next cyclization step or stored at $-20^\circ C$. $[\alpha]_D^{20} = -11.4$ ($c = 1.0$, $CHCl_3$), 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 ((2S,3R,4R,5R)-**3a**) and 37.3 min ((2R,3S,4S,5S)-**3a**). 1H 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-methoxycarbonylphenyl)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 μ L 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 ((2S,3R,4R,5R)-**3b**) and 19.9 min ((2R,3S,4S,5S)-**3b**). 1H 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-methylthiophenyl)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 μ L 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 ((2R,3S,4S,5S)-**3d**) and 40.4 min ((2S,3R,4R,5R)-**3d**). 1H 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 μ L 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 ((2S,3R,4R,5R)-**3e**) and 33.1 min ((2R,3S,4S,5S)-**3e**). 1H 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 μ L 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 ((2S,3R,4R,5R)-**3f**) and 27.3 min ((2R,3S,4S,5S)-**3f**). 1H 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 μ L 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 ((2S,3R,4R,5R)-**3k**) and 28.6 min ((2R,3S,4S,5S)-**3k**). 1H 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 μ L 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 ((2S,3R,4R,5R)-**3i**) and 19.8 min ((2R,3S,4S,5S)-**3i**). 1H 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: (2S,3S,3aS,6aS)-3-tert-Butyl 6a-Methyl 2-

Phenyl-octahydrocyclopenta[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 μ L 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, bicyclopiperidines *exo*-4, once isolated, were stored at $-20\text{ }^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} = +9.4$ ($c = 9.3$, CHCl_3), 96% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 95/5, flow rate 0.5 mL min^{-1} (λ 211 nm), $t_{\text{r}} = 11.1$ min ((2*R*,3*R*,3*aR*,6*aR*)-4a) and 12.9 min ((2*S*,3*S*,3*aS*,6*aS*)-4a). ^1H 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 $\text{C}_{20}\text{H}_{28}\text{NO}_4$, 346.2013; found, 346.2020 ($[\text{M} + \text{H}]^+$, 100%).

(2*S*,3*S*,3*aS*,6*aS*)-3-*tert*-Butyl 6*a*-Methyl 2-(4-(Methoxycarbonyl)phenyl)octahydrocyclopenta[b]pyrrole-3,6*a*-dicarboxylate (exo-4b). Following the typical procedure, the reaction of pyrrolidine *exo*-3b (50 mg, 0.103 mmol) and potassium *tert*-butoxide (113 μ L 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). $[\alpha]_{\text{D}}^{20} = -17.9$ ($c = 4.7$, CHCl_3), 93% ee. HPLC: Daicel Chiralpak IA, hexane/isopropyl alcohol 98/2, flow rate 0.7 mL min^{-1} (λ 254 nm), $t_{\text{r}} = 14.6$ min ((2*R*,3*R*,3*aR*,6*aR*)-4b) and 20.8 min ((2*S*,3*S*,3*aS*,6*aS*)-4b). ^1H 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 $\text{C}_{22}\text{H}_{30}\text{NO}_6$, 404.2068; found, 404.2080 ($[\text{M} + \text{H}]^+$, 100%).

(2*S*,3*S*,3*aS*,6*aS*)-3-*tert*-Butyl 6*a*-Methyl 2-(4-(Methylthio)phenyl)octahydrocyclopenta[b]pyrrole-3,6*a*-dicarboxylate (exo-4d). Following the typical procedure, the reaction of pyrrolidine *exo*-3d (50 mg, 0.106 mmol) and potassium *tert*-butoxide (116 μ L 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). $[\alpha]_{\text{D}}^{20} = -1.7$ ($c = 1.1$, CHCl_3), 96% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 95/5, flow rate 0.7 mL min^{-1} (λ 254 nm), $t_{\text{r}} = 12.2$ min ((2*R*,3*R*,3*aR*,6*aR*)-4d) and 16.2 min ((2*S*,3*S*,3*aS*,6*aS*)-4d). ^1H 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 $\text{C}_{21}\text{H}_{30}\text{NO}_4\text{S}$, 392.1891; found, 392.1855 ($[\text{M} + \text{H}]^+$, 100%).

(2*S*,3*S*,3*aS*,6*aS*)-3-*tert*-Butyl 6*a*-Methyl 2-(4-Methylphenyl)octahydrocyclopenta[b]pyrrole-3,6*a*-dicarboxylate (exo-4e). Following the typical procedure, the reaction of pyrrolidine *exo*-3e (50 mg, 0.114 mmol) and potassium *tert*-butoxide (125 μ L 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). $[\alpha]_{\text{D}}^{20} = -17.6$ ($c = 10.7$, CHCl_3), 93% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 95/5, flow rate 0.7 mL min^{-1} (λ 211 nm), $t_{\text{r}} = 10.2$ min ((2*R*,3*R*,3*aR*,6*aR*)-4e) and 13.4 min ((2*S*,3*S*,3*aS*,6*aS*)-4e). ^1H 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 $\text{C}_{21}\text{H}_{30}\text{NO}_4$, 360.2170; found, 360.2169 ($[\text{M} + \text{H}]^+$, 100%).

(2*S*,3*S*,3*aS*,6*aS*)-3-*tert*-Butyl 6*a*-Methyl 2-(4-Chlorophenyl)octahydrocyclopenta[b]pyrrole-3,6*a*-dicarboxylate (exo-4k). Following the typical procedure, the reaction of pyrrolidine *exo*-3k (50 mg, 0.109 mmol) and potassium *tert*-butoxide (125 μ L 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). $[\alpha]_{\text{D}}^{20} = -13.0$ ($c = 10.4$, CHCl_3), 90% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 99/1, flow rate 0.7 mL min^{-1} (λ 211 nm), $t_{\text{r}} = 13.3$ min ((2*R*,3*R*,3*aR*,6*aR*)-4k) and 18.1 min ((2*S*,3*S*,3*aS*,6*aS*)-4k). ^1H 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 $\text{C}_{20}\text{H}_{27}\text{ClNO}_4$, 380.1624; found, 380.1638 ($[\text{M} + \text{H}]^+$, 100%).

(2*S*,3*S*,3*aS*,6*aS*)-3-*tert*-Butyl 6*a*-Methyl 2-(3-Methylphenyl)octahydrocyclopenta[b]pyrrole-3,6*a*-dicarboxylate (exo-4f). Following the typical procedure, the reaction of pyrrolidine *exo*-3f (50 mg, 0.114 mmol) and potassium *tert*-butoxide (125 μ L 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). $[\alpha]_{\text{D}}^{20} = -12.5$ ($c = 9.5$, CHCl_3), 92% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 98/2, flow rate 0.7 mL min^{-1} (λ 211 nm), $t_{\text{r}} = 12.5$ min ((2*R*,3*R*,3*aR*,6*aR*)-4f) and 16.1 min ((2*S*,3*S*,3*aS*,6*aS*)-4f). ^1H 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 $\text{C}_{21}\text{H}_{30}\text{NO}_4$, 360.2170; found, 360.2161 ($[\text{M} + \text{H}]^+$, 100%).

(2*S*,3*S*,3*aS*,6*aS*)-3-*tert*-Butyl 6*a*-Methyl 2-(2-Methylphenyl)octahydrocyclopenta[b]pyrrole-3,6*a*-dicarboxylate (exo-4i). Following the typical procedure, the reaction of pyrrolidine *exo*-3i (50 mg, 0.114 mmol) and potassium *tert*-butoxide (125 μ L 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). $[\alpha]_{\text{D}}^{20} = -9.9$ ($c = 7.4$, CHCl_3), 96% ee. HPLC: Daicel Chiralpak IC, hexane/isopropyl alcohol 98/2, flow rate 0.7 mL min^{-1} (λ 211 nm), $t_{\text{r}} = 9.8$ min ((2*R*,3*R*,3*aR*,6*aR*)-4i) and 13.3 min ((2*S*,3*S*,3*aS*,6*aS*)-4i). ^1H 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 $\text{C}_{21}\text{H}_{30}\text{NO}_4$, 360.2170; found, 360.2182 ($[\text{M} + \text{H}]^+$, 100%).

(2*S*,3*S*,3*aS*,6*aS*)-6*a*-(Methoxycarbonyl)-2-(4-(methylthio)phenyl)octahydrocyclopenta[b]pyrrole-3-carboxylic Acid (exo-4d-CO₂H). The azabicyclic *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-CO₂H (13.2 mg, 87%, yellow oil). $[\alpha]_{\text{D}}^{20} = -15.8$ ($c = 10.2$, CHCl_3). ^1H 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 $\text{C}_{17}\text{H}_{22}\text{NO}_4\text{S}$, 336.1264; found, 336.1279 ($[\text{M} + \text{H}]^+$, 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.

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

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621 **Notes**

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(21) Both bromopropyl pyrrolidines **3** and bicycprolines **4** are
relatively labile compounds. Once isolated, they were stored in the
freezer at -20 °C. In solution at room temperature, they slowly
decompose.
(22) See the [Supporting Information](#) for details.
(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*,3*aS*,6*aS* for *exo-4*)
on the basis of previously reported results in the highly
enantioselective Cu/(*R*)-DTBM-Segphos catalyzed 1,3-dipolar cyclo-
addition 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.