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General Entry to Asymmetric One-Pot [*N* + 2 + *n*] Cyclization for the Synthesis of Three- to Seven-Membered Azacycloalkanes

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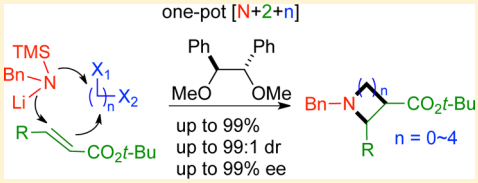
Supporting Information

ABSTRACT: Enantio- and diastereoselective one-pot synthesis of three- to seven-membered *cis*-azaheterocycles was achieved using a triggered asymmetric conjugate addition reaction of lithium amide with an enoate, followed by alkylation of the resulting lithium enolate with α,ω-dihaloalkane and N-alkylation. Isomerization of *cis*-azaheterocycles with a base yielded the *trans*-product, constituting a one-pot synthesis of *cis*-azacycles and a two-step synthesis of *trans*-azacycles. The four-step asymmetric synthesis of nemonapride highlights the general utility of the method.



INTRODUCTION

Azacycloalkane is a fundamental component of structures often occurring in biologically active natural products, pharmaceuticals, organocatalysts, and ligands. Preparation methodologies of chiral azacycloalkanes are therefore studied extensively, especially the five-membered pyrrolidines[1] and the six-membered piperidines,[2,3] by intramolecular hydroamination of olefins,[4] cycloaddition,[5,6] and N-alkylation of chiral amines.[7] Chiral piperidines are also available by asymmetric hydrogenation of *N*-iminopyridinium[8] and desymmetrization of *N*-Boc-piperidine by asymmetric deprotonation.[9] In contrast, synthesis of chiral azacycloalkanes of other ring sizes has been less explored. For example, a three-membered chiral aziridine, a useful building block and substructure of some biologically significant compounds,[10] was constructed from chiral 1,2-aminoalcohol[11] or by a transition-metal-catalyzed reaction of nitrenoid with alkene[12] or carbenoid with imine.[13] A chiral Lewis[14] or Brønsted[15] acid-catalyzed reaction of diazoacetic acid derivatives with imines has been also reported. Although *cis*-aziridines are obtained with high enantioselectivity by the above-mentioned methods,[14b] the *trans*-selective asymmetric aziridination reported so far suffered from moderate diastereoselectivity and/or yield.[12−16] Chiral azacyclobutane, an important azetidine class of azacyclic compounds endowed with remarkable bioactivity,[17,18] is prepared from chiral amines[19] or chiral diols[20] through a multistep synthesis and by enzymatic kinetic resolution of racemic azetidines.[21] A chiral seven-membered azepane, often found in natural products[22] and extensively developed as pharmacophores,[23] is usually synthesized by cyclization of chiral amines through a multistep sequence,[24] although asymmetric synthesis of 4,5,6- and 3,4,5,6-substituted azepanes by a diastereo- and enantioselective lithiation−conjugate addition sequence has been reported.[25] Thus, different methods are needed for the synthesis of azacycloalkanes with different ring sizes.

Enantioselective construction of three- to six-membered cyclic α-amino acid derivatives was recently reported by Maruoka,[26] who utilized a three-step sequence, including chiral ammonium-catalyzed asymmetric α-alkylation of α-amino acid derivatives. To the best of our knowledge, this is the only method that is generally applicable for the construction of chiral azacycloalkanes with different ring sizes starting from easily available reagents. The formation of a four-membered ring, which involves challenging alkylation with 1,2-dihaloethane as an ethylene dication equivalent, however, has been reported, albeit in low yield.[27,28]

Azacyclic β-amino acid derivatives are not only potential intermediates for azacyclic bioactive compounds, such as azirinomycin (**1**),[29] piperazine surrogate **2**,[18] β-proline (**3**),[30,31] antipsychotic nemonapride (**4**),[32] substance P antagonist CP-99,994 (**5**),[33] and croomine (**6**),[34] but also interesting building blocks for artificial peptides[35,36] (Figure 1). We recently reported the asymmetric total synthesis of

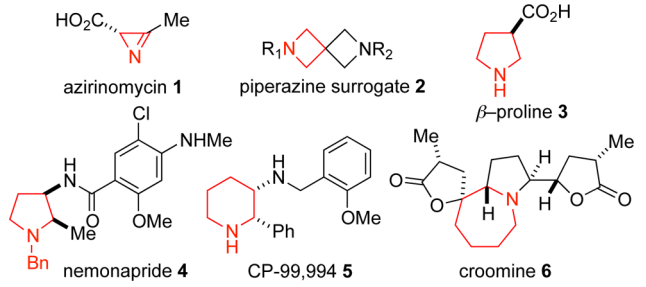


Figure 1. Pharmaceuticals and bioactive compounds with three- to seven-membered azacycloalkane moieties.

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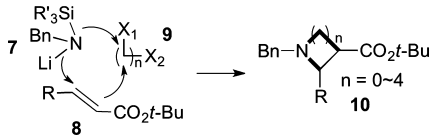
(−)-kopsinine based on one-pot [*N* + 2 + 3] cyclization strategy (Scheme 1, *n* = 3),[37] that is, chiral diether-controlled

Scheme 1. Asymmetric One-Pot [*N* + 2 + *n*] Cyclization Strategy for Three- to Seven-Membered Azacycloalkanes

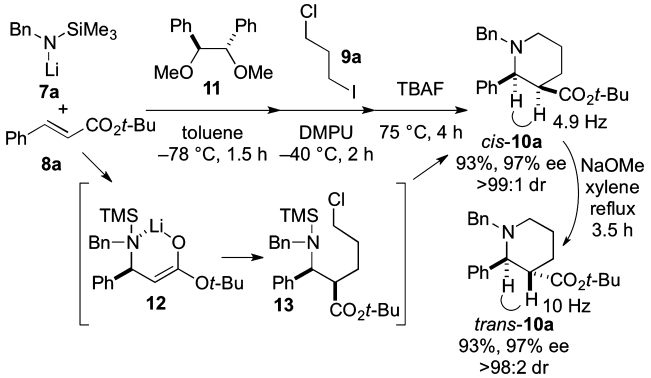


asymmetric conjugate addition of lithium *N*-benzyltrimethylsilylamide (**7a**: R′ = Me) to indolepropenoate (**8c**: R = *N*-Boc-indol-3-yl)[38,39] followed by C,N-dual alkylation with 1-chloro-3-iodopropane (**9a**: *n* = 3, X_1 = Cl, X_2 = I).[40,41] Herein, we describe an extension of this methodology to realize general entry to enantio- and diastereoselective one-pot [*N* + 2 + *n*] cyclization for azacyclic *β*-amino acid derivatives (Scheme 1, *n* = 0−4). The present study also addresses the above-mentioned ethylene dication equivalent problem in the synthesis of pyrrolidines. This methodology provides the first general entry to a one-pot synthesis of three- to seven-membered chiral azacycloalkanes from readily available starting materials.

RESULTS AND DISCUSSION

One-Pot Asymmetric Construction of Piperidine-3-carboxylate. Asymmetric one-pot [*N* + 2 + 3] cyclization giving piperidine **10a** was started with the chiral diether **11**-controlled conjugate addition of 3 equiv of lithium amide **7a** with *tert*-butyl cinnamate (**8a**) in toluene at −78 °C for 1.5 h,[38a] followed by successive treatment with 1-chloro-3-iodopropane (**9a**)[42] in DMPU at −40 °C for 2 h and then tetrabutylammonium fluoride (TBAF) at 75 °C for 4 h, affording *cis*-**10a** with 97% ee as a single diastereomer in 93% yield (Scheme 2 and Table 1, entry 1). Chiral ligand **11** was

Scheme 2. [*N* + 2 + 3] Cyclization Giving Piperidine *cis*-10a and Epimerization to *trans*-10a



quantitatively recovered and reused. Since both enantiomers of **11** are available, each enantiomer of the azacycloalkane can be synthesized. Notably, the amount of lithium amide could be reduced to 1.5 equiv, giving *cis*-**10a** with the same level of selectivity in 83% yield (entry 2).

The *S*-absolute configuration at the chiral center-attached nitrogen of **10a** was constructed at the stage of the conjugate addition of lithium amide, as reported previously.[38] The *cis*-configuration of **10a** was apparent from the 4.9 Hz coupling constant of the two adjacent methine protons and was further confirmed by epimerization to the thermodynamically more stable *trans*-**10a** in a >98:2 ratio through sodium methoxide treatment for 3.5 h in refluxing xylene (Scheme 2).[43] Thus, one-pot cyclization allowed for the preparation of both *cis*- and *trans*-azacycloalkanes with high enantio- and diastereoselectivity.

Chiral ligand **11** was not responsible for the alkylation diastereoselectivity because no enantioselectivity was observed in the reaction of *tert*-butyl acrylate, in place of cinnamate, to give the corresponding racemic piperidinecarboxylate in 42% yield. The observed diastereoselectivity was predictable based on the preferred axial alkylation[44] in conformer **A**, giving *cis*-**10a** (Scheme 3).[45] The conformer **B** should be less stable because of steric repulsion caused by the phenyl and the trimethylsilyl group on the nitrogen.

Piperidine functionalized with an exomethylene was available using dibromoisobutene **9b** instead of **9a** to give isomer-free *cis*-**10b** with 97% ee in 86% yield (entry 3). The asymmetric one-pot piperidine formation was generally applicable to enoates other than cinnamate **8a** (Table 1, entries 4−8). The reaction of naphthalene-2-propenoate **8b** with **9a** afforded the corresponding piperidine **10c** with 94% ee and 99:1 dr in 73% yield (entry 4). Indolepropenoate **8c** gave cyclization product **10d** with 98% ee and >99:1 dr in 85% yield (entry 5).[37] Crotonate **8d** was also converted to column chromatographically separable *cis*-**10e** with 97% ee and 72:28 dr in 93% yield (entry 6). Heptenoate **8e** quantitatively gave *cis*-**10f** with 95% ee in 86:14 dr (entry 7). In the reaction of **8f**, isomer-free *trans*-fused bicyclic **10g** having a quaternary asymmetric center with 87% ee was obtained in 90% yield (entry 8).

Isopropyldimethylsilyl Group to Improve Diastereoselectivity. Although sufficiently high >99:1 diastereoselectivity was observed in most of the cyclization, an unsatisfactory poor 72:28 diastereoselectivity was observed in the reaction of crotonate **8d** (Table 1, entry 6). On the basis of the assumption of lesser steric repulsion between the methyl group, in place of the phenyl, and the trimethylsilyl group (or benzyl group) on the nitrogen of the chelate **B** (Scheme 3), a more bulky trialkylsilyl group of **7** was screened in the reaction of crotonate **8d** (Table 2, entries 1−4). As expected, the reaction with TBS-amide **7b** gave the product with the highest dr (95:5), whereas the yield of **10e** decreased unexpectedly to 32% due to the *γ*-deprotonation of **8d** (entry 2). TES-amide **7c** did not improve the selectivity, giving **10e** with 63:37 dr (entry 3). The most reliable diastereomeric ratio, 86:14, was obtained with isopropyldimethylsilylamide **7d**, giving chromatographically separable *cis*-**10e** with 98% ee in 92% yield (entry 4). The trialkylsilyl group on the nitrogen did not affect the sense of enantioselectivity, giving *cis*-**10e** with the same absolute configuration.

Competitive Alkylation, Halogenation, and Protonation in the Construction of Five-Membered Pyrrolidine. To construct the five-membered pyrrolidines using the [*N* + 2 + 2] cyclization strategy, we first addressed the ethylene dication problem. Competitive halogenation[27a] and protonation[27b] are both observed when 1,2-dihaloethane **9** is used as a C2 source (Scheme 4).[27] Indeed, the reaction of **7a** and **8a** followed by an alkylative cyclization process with 1-chloro-2-iodoethane (**9c**) afforded column chromatographically separable three-membered *trans*-aziridine **10i**[46] with 97% ee and 87:13 dr in 92% yield, without the formation of pyrrolidine **10h** (Table 3, entry 1). The relative configuration of *trans*-**10i** was determined based on the 2.2 Hz coupling constant of the

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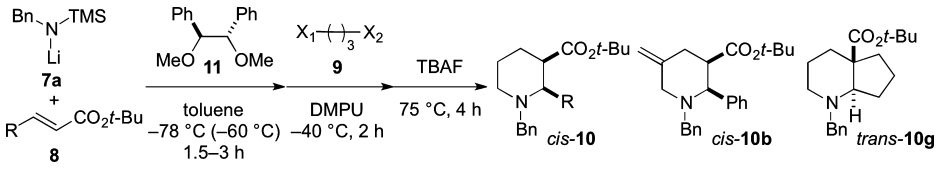
Table 1. One-Pot Asymmetric [*N* + 2 + 3] Construction of Piperidines[a]



entry	8	R	9	$X_1(CH_2)_3X_2$	10	yield %	ee %[b]	*cis*:*trans*
1	**8a**	Ph	**9a**	$Cl(CH_2)_3I$	*cis*-**10a**	93	97	99:1
2[c]	**8a**	Ph	**9a**	$Cl(CH_2)_3I$	*cis*-**10a**	83	94	99:1
3	**8a**	Ph	**9b**	Br Br	*cis*-**10b**	86	97	99:1
4	**8b**	2-naphthyl	**9a**	$Cl(CH_2)_3I$	*cis*-**10c**	73	94	99:1
5[d]	**8c**	*N*-Boc-indol-3-yl	**9a**	$Cl(CH_2)_3I$	*cis*-**10d**	85	98	99:1
6	**8d**	Me	**9a**	$Cl(CH_2)_3I$	*cis*-**10e**	93	97	72:28
7	**8e**	Bu	**9a**	$Cl(CH_2)_3I$	*cis*-**10f**	99	95	86:14
8	**8f**	CO2t-Bu	**9a**	$Cl(CH_2)_3I$	*trans*-**10g**	90	87	1:99

[a]Conditions: *N*-trimethylsilylbenzylamine (1.5 mmol), BuLi (1.5 mmol), **11** (1.8 mmol), **8** (0.5 mmol), and **9** (5 mmol). [b]The % ee of the major diastereomer. [c]Conditions: *N*-trimethylsilylbenzylamine (0.75 mmol), BuLi (0.75 mmol), **11** (0.9 mmol), **8** (0.5 mmol), and **9** (2.5 mmol). [d]Quoted from ref 37.

Scheme 3. Diastereoselective Alkylation via Conformation A

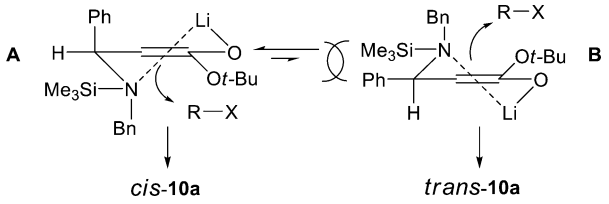
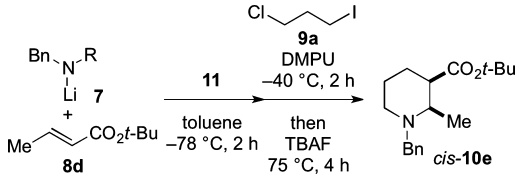


Table 2. Diastereoselectivity Dependency on Trialkylsilylamide 7[a]



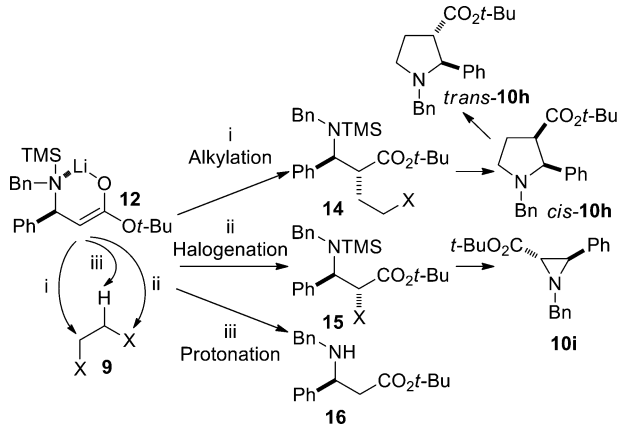
entry	7	R	yield %	ee %[a]	*cis*:*trans*
1[b]	**7a**	Me_3Si	93	97	72:28
2	**7b**	*t*-BuMe_2Si	32	97	95:5
3	**7c**	Et_3Si	85	95	63:37
4	**7d**	*i*-PrMe_2Si	92	98	86:14

[a]The % ee of *cis*-**10e**. [b]Quoted from Table 1, entry 6.

adjacent methine protons.[46] The 2*S*,3*R*-absolute configuration was apparent from the conjugate amination chemistry and further confirmed by conversion to (*S*)-phenylalanine *tert*-butyl ester (vide infra).

The intermediacy of α-iodide **15** (X = I) by diastereoselective iodination with **9c** was further confirmed by treatment of the resulting lithium enolate **12** with iodine to afford *trans*-**10i** with 76:24 dr in 38% yield (entry 2). With 1-bromo-2-chloroethane (**9d**)[27b] in place of iodide **9c**, the expected pyrrolidine *cis*-**10h** with 96% ee was obtained in 27% yield, along with protonated **16**[38a] with 97% ee in 62% yield (entry 3). The relative configuration of *cis*-**10h** was confirmed by

Scheme 4. Competitive Alkylation, Halogenation, and Protonation of 12 with Dihaloethane 9 Giving Pyrrolidine 10h, Aziridine 10i, and β-Amino Ester 16



epimerization with sodium methoxide in refluxing xylene for 5 h to a separable 8:92 mixture of *cis*-**10h** and thermodynamically more stable *trans*-**10h**.

Protonation of **12** with **9d** was confirmed by successive workup with tetradeuteriomethanol to give **16** in 69% yield without any incorporation of deuterium, whereas direct treatment of **12** with tetradeuteriomethanol gave a 4:1 diastereomeric mixture of **16** with 94% deuterium incorporation at the α-position in 97% yield (entry 4). When 2-chloroethyl tosylate (**9f**) was used, no alkylation proceeded at all and **16** was produced in 70% yield (entry 6). The use of dibromoethane (**9e**) or 2-bromoethyl triflate (**9g**) also gave **16** as a major product along with a small amount of **10h** (entries 5 and 7). Vinyl sulfonium salt **9h**[47] was a nonprotonating C2 source that unfortunately afforded **16** in 81% yield at −40 °C (entry 8). Finally, ethylene sulfate (**9i**)[48] was found to be a satisfactory C2 source, giving separable *cis*-**10h** with 97% ee and 9:1 dr quantitatively with no production of **10i** and **16** (entry 9).

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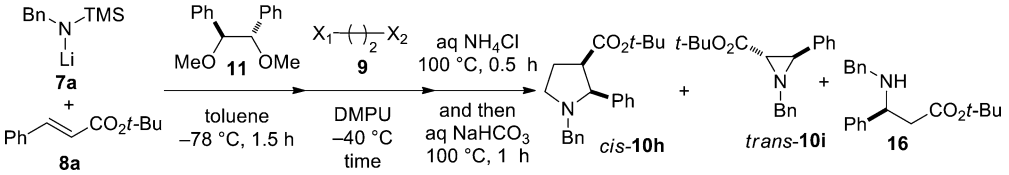
Table 3. [*N* + 2 + *n*] Cyclization to Pyrrolidine 10h, Aziridine 10i, and β-Amino Ester 16 by the Reaction of 7a, 8a, and Ethylene Dication Source 9c–i

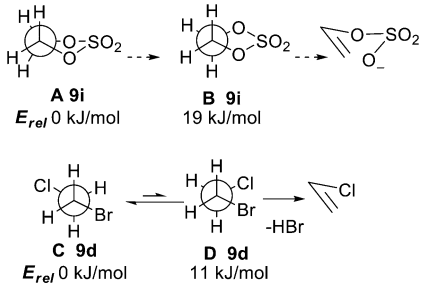


entry	9	X_1–X_2	time h	**10h** yield %	*cis*:*trans*	ee %[a]	**10i** yield %	*trans*:*cis*	ee %[a]	**16** yield %
1	**9c**	$Cl(CH_2)_2I$	2	0			92	87:13	97	0
2		I_2	2	0			38	76:24	97	0
3	**9d**	$Br(CH_2)_2Cl$	22	27	99:1	96	0			62
4	**9d**	$Br(CH_2)_2Cl$; CD_3OD	2	21	99:1	97	0			69 (0%D)[b]
5	**9e**	$Br(CH_2)_2Br$	2	17	nd[c]	nd[c]	0			68
6	**9f**	$TsO(CH_2)_2Cl$	2	0			0			70
7	**9g**	$TfO(CH_2)_2Br$	2	5	nd[c]	nd[c]	0			40
8	**9h**	CH_2=CHSPh$_2$OTf	2	0			0			81
9	**9i**	$(CH_2)_2SO_4$	2	99	90:10	97	0			0

[a]The % ee of the major diastereomer. [b]No deuterium incorporation at the α-position upon workup with CD_3OD, whereas 94% deuterium incorporation upon direct CD_3OD quench of lithium enolate **12**. [c]Not determined.

Successful block of the protonation with **9i** is rationalized based on the unfavorable and not local minimum conformation **B**, where H–C and the adjacent C–O bonds are *anti*-periplanar to proceed to elimination (Scheme 5, HF/6-31G* level of calculations). In the stable conformation **A**, the dihedral angle of these two bonds is around 150° and does not proceed easily to elimination. In contrast, conformation **D** of **9d** is a local minimum that proceeds to E2 elimination; that is, protonation occurs on enolate **12** (Table 3, entry 3).

Scheme 5. Conformations A–D in Ethylene Sulfate (9i) and 1-Bromo-2-chloroethane (9d) for E2 Elimination (HF/6-31G*)



One-Pot Asymmetric [*N* + 2 + *n*] Construction of Three-, Four-, Five-, and Seven-Membered Azacycles. Having established the conditions for asymmetric and diastereoselective one-pot [*N* + 2 + *n*] construction of azacycloalkanes using **7d** as an initiating lithium amide and **9i** as a C2 source, cinnamate **8a** and crotonate **8d** were incorporated into the corresponding azacycloalkanes, as summarized in Table 4. The reaction of **7d**, **8a**, and **9i** provided *cis*-pyrrolidine **10h** with 97% ee and 97:3 dr in 97% yield (Table 4, entry 5). The reaction of **7d**, crotonate **8d**, and **9d** proceeded relatively smoothly to give chromatographically separable *cis*-**10m** with 99% ee and 93:7 dr in 73% yield along with **16** in 24% yield, indicating that a steric environment affects the competitive alkylation–protonation step (Table 4 entry 6 vs Table 3 entry 3). Interestingly, pyrrolidine *trans*-**10m** was obtained as a 90:10 major isomer with 96% ee when **9i** was used as the C2 source (Table 4, entry 7). Epimerization of a 1:1 diastereomixture of **10m** to 83:17 *trans*-major **10m** quantitatively by sodium methoxide in refluxing xylene for 5 h clearly confirmed the relative configuration of both isomers. The relative and absolute configuration of *cis*-**10m** was further confirmed by a short-step conversion to the dopamine D2 and D3 receptor antagonist nemonapride **4** (Scheme 6). Production of *trans*-major **10m** by alkylation with **9i** likely occurs through *syn*-alkylation of the enolate **12** and not through epimerization. Although the reason for this reversal of diastereoselectivity is not clear, coordination of the sulfonate moiety to the lithium of a chelate **A** could be responsible (Scheme 3).

An [*N* + 2 + 0] cyclization of **7d** and **8a**/**8d** with **9c** as a halogen source proceeded smoothly to afford *trans*-aziridine **10i** with 98% ee and >99:1 dr in 86% yield and **10j** with 98% ee and 81:19 dr in 93% yield (Table 4, entries 1 and 2). The relative and absolute configuration of *trans*-**10j** was confirmed by its conversion to the azirinomycin intermediate **18**.[29e] An [*N* + 2 + 1] cyclization was possible using bromoiodomethane (**9j**) as the C1 source to give *cis*-azetidine **10k** and **10l** with high enantio- and diastereoselectivity (entries 3 and 4). The [*N* + 2 + 4] cyclization used C4 sources, 1,4-diiodobutane (**9k**) and 1,2-bis(bromomethyl)benzene (**9l**), to afford diastereomer-free *cis*-azepane **10n** and benzazepane **10o** enantioselectively (entries 8 and 9). The relative configuration of *cis*-**10k**, *cis*-**10l**, *cis*-**10n**, and *cis*-**10o** was assigned by analogy. The absolute configuration assignment of **10k–o** was based on the stereochemistry of the conjugate addition.[38a]

Short-Step Asymmetric Synthesis of Phenylalanine, Azirinomycin Ester, and Nemonapride. Aziridine *trans*-**10i** was hydrogenated under hydrogen atmosphere (1 atm) in

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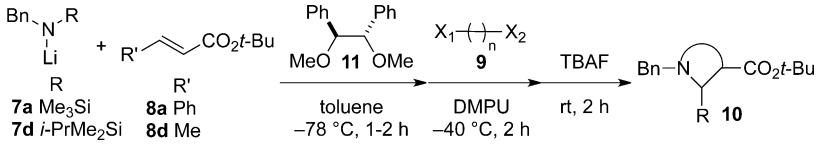
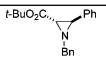
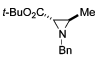
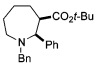
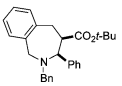
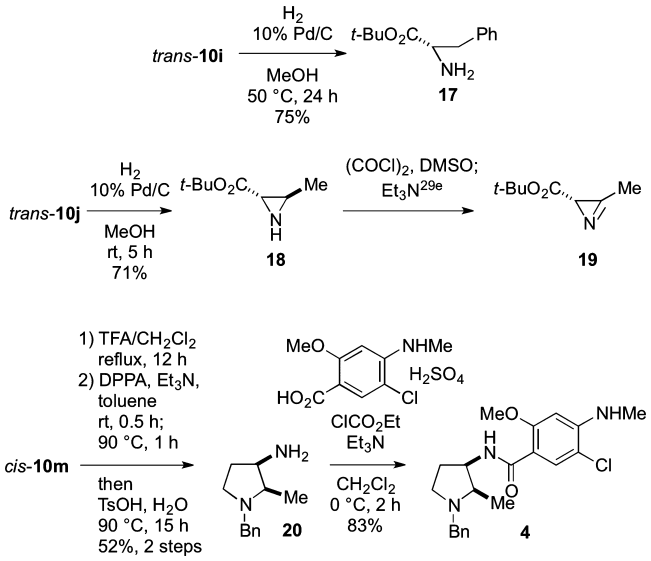
Table 4. One-Pot Asymmetric [*N* + 2 + *n*] Cyclization to Aziridine, Azetidine, Pyrrolidine, and Azepane



entry	7	R	8	R'	9	$X_1(\ )_nX_2$	10		yield %	ee %[a]	*cis*:*trans*
1	**7d**	*i*-PrMe$_2$Si	**8a**	Ph	**9c**	Cl(CH$_2$)$_2$I	*trans*-**10i**		86	98	1:99
2	**7d**	*i*-PrMe$_2$Si	**8d**	Me	**9c**	Cl(CH$_2$)$_2$I	*trans*-**10j**		93	98 (97)[b]	19:81
3[c]	**7a**	Me$_3$Si	**8a**	Ph	**9j**	BrCH$_2$I	*cis*-**10k**		82	97	99:1
4[c]	**7d**	*i*-PrMe$_2$Si	**8d**	Me	**9j**	BrCH$_2$I	*cis*-**10l**		57	98	80:20
5[c]	**7d**	*i*-PrMe$_2$Si	**8a**	Ph	**9i**	(CH$_2$)$_2$SO$_4$	*cis*-**10h**		97	97	97:3
6[c]	**7d**	*i*-PrMe$_2$Si	**8d**	Me	**9d**	Br(CH$_2$)$_2$Cl	*cis*-**10m**		73	99	93:7
7[c]	**7a**	Me$_3$Si	**8d**	Me	**9i**	(CH$_2$)$_2$SO$_4$	*trans*-**10m**		97	96	10:90
8[d]	**7a**	Me$_3$Si	**8a**	Ph	**9k**	I(CH$_2$)$_4$I	*cis*-**10n**		71	97	99:1
9[d]	**7a**	Me$_3$Si	**8a**	Ph	**9l**		*cis*-**10o**		57	98	99:1

[a]The ee % of the major diastereomer. [b]The ee % of the minor diastereomer is in the parentheses. [c]With aqueous HCl at 0 °C for 0.5 h and then aqueous NaHCO$_3$ at 100 °C for 1 h instead of TBAF treatment for cyclization. [d]With aqueous HCl at 0 °C for 0.5 h and then aqueous NaHCO$_3$ at 100 °C for 24 h instead of TBAF treatment for cyclization.

Scheme 6. Asymmetric Synthesis of (*S*)-Phenylalanine, Azirinomycin Ester, and Nemonapride



methanol at 50 °C for 24 h into (*S*)-phenylalanine *tert*-butyl ester (**17**)[49] in 75% yield (Scheme 6).[50] Hydrogenolysis of *trans*-**10j** under hydrogen atmosphere (1 atm) at room temperature for 5 h cleaved off the *N*-benzyl group to give **18**, a known intermediate of azirinomycin *tert*-butyl ester (**19**), in 71% yield.[29e]

Conversion of *cis*-**10m** with TFA to carboxylic acid, Curtius rearrangement with DPPA,[51] and hydrolysis in the presence of *p*-toluenesulfonic acid afforded the known intermediate **20** in 52% overall yield (Scheme 6). Amidation gave antipsychotic nemonapride (**4**) in 83% yield. Similarly, piperidine *cis*-**10a** is likely convertible into an NK1 antagonist, CP-99,994 (**5**)[33] (Figure 1), in an analogous reaction sequence.

■ CONCLUSIONS

A highly enantio- and diastereoselective one-pot [*N* + 2 + *n*] synthesis of azacycles was developed using a chiral diether-controlled asymmetric aza-Michael addition–alkylation–cyclization sequence. Two stereogenic centers in *cis* and three covalent bonds were constructed in one pot, and three- to seven-membered chiral azacyclic esters were generally accessible. The high applicability of the developed methodology was clearly demonstrated by the shortest synthesis of nemonapride and azirinomycin ester.

■ EXPERIMENTAL SECTION

General. All melting points are uncorrected. Silica gel was used for column chromatography. NMR (500 MHz for ^{1}H and 125 MHz for

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^{13}C) was measured in $CDCl_3$ unless otherwise mentioned. Chemical shifts and coupling constants (J) are presented in parts per million relative to tetramethylsilane and hertz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C peak multiplicity assignments were made based on DEPT data. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. A double-focusing magnetic sector mass spectrometer was used for low- and high-resolution FABMS and high-resolution EIMS, while low-resolution EIMS was measured with a quadrupole mass spectrometer.

$BnNH_2$ and DMPU were distilled from CaH_2 prior to use. Dehydrated solvents and anhydrous Et_3N were purchased for the reactions and used without further desiccation. *N*-Benzyl-*N*-trimethylsilylamine,[52] *N*-benzyl-*N*-*tert*-butyldimethylsilylamine,[53] *N*-benzyl-*N*-triethylsilylamine,[53] enoates **8b**[38a] and **8e**,[54] vinyl sulfonium salt **9h**,[47] (1*S*,2*S*)-1,2-dimethoxy-1,2-diphenylethane (**11**),[55] and 4-carboxy-2-chloro-5-methoxy-*N*-methylammonium hydrogen sulfate[56] were prepared according to reported procedures. Other reagents were purchased and used as received.

***N*-Benzyl-*N*-(isopropyldimethylsilyl)amine.** To a solution of $BnNH_2$ (15.4 mL, 141 mmol), Et_3N (25.3 mL, 183 mmol), and DMAP (172 mg, 1.41 mmol) in Et_2O (140 mL) was added dimethylisopropylchlorosilane (25.0 mL, 162 mmol) over 20 min at 0 °C, and the mixture was stirred for 16 h at rt, and generated precipitate was removed by filtration. Concentration of the filtrate and distillation (70 °C/0.1 mmHg) gave title compound (24.2 g, 83%) as a colorless oil: ^1H NMR δ 0.02 (6H, s), 0.71 (1H, br s), 0.79 (1H, m), 0.97 (6H, d, J = 7.5), 3.94 (2H, d, J = 8.0), 7.21 (1H, m), 7.29−7.31 (4H, m); ^{13}C NMR δ −4.0 (CH_3), 14.9 (CH), 17.4 (CH_3), 46.1 (CH_2), 126.3 (CH), 126.9 (CH), 128.2 (CH), 144.4 (C); IR 3402, 2947, 1250; EIMS m/z 207 (M^+), 164 (M − *i*-Pr), 106 (M − Me_2*i*-PrSi); HRMS−EI (m/z) $[M]^+$ calcd for $C_{12}H_{21}NSi$ 207.1443, found 207.1449.

***tert*-Butyl Cyclopentene-1-carboxylate (8f).** To a stirred solution of cyclopentene-1-carboxylic acid (10 g, 89 mmol) in THF (18 mL) was added $SOCl_2$ (8.4 mL, 116 mmol) at rt, and the mixture was heated under reflux for 1 h. After being cooled to rt, the mixture was concentrated in vacuo, and the residue was dissolved in THF (21 mL). To the solution was added a solution of *t*-BuOLi (11 g, 133 mmol) in THF (24 mL) at 0 °C, and the mixture was stirred at rt. After 2 h, saturated NH_4Cl (50 mL) was added to the mixture, and the whole was extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine and then dried over Na_2SO_4. Concentration followed by distillation (80−81 °C/13 mmHg) gave the title compound as a colorless oil (13 g, 61%). The ^1H and ^{13}C NMR, IR, and MS were identical to those reported.[57]

One-Pot Asymmetric [*N* + 2 + *n*] Construction of Three- to Seven-Membered Azacycloalkanes. *Typical Procedure A: (−)-tert-Butyl (2S,3R)-1-Benzyl-2-phenylpiperidine-3-carboxylate (cis-**10a**):* To a solution of *N*-benzyl-*N*-trimethylsilylamine (0.29 mL, 1.5 mmol) in toluene (4 mL) was added a 1.61 M hexane solution of BuLi (0.93 mL, 1.5 mmol) at −78 °C over 4 min, and the mixture was stirred for 30 min at −78 °C. A solution of chiral diether **11** (436 mg, 1.8 mmol) in toluene (2 mL) was added over 5 min, and after 30 min, a solution of enoate **8a** (102 mg, 0.5 mmol) in toluene (2 mL) was added over 8 min. The mixture was stirred for 1.5 h at −78 °C, and a solution of 1-chloro-3-iodopropane **9a** (0.54 mL, 5 mmol) in DMPU (8 mL) was added over 30 min at −78 °C. The mixture was stirred for 2 h at −40 °C, and a 1.0 M THF solution of TBAF (7.5 mL, 7.5 mmol) was added. The whole was stirred for 4 h at 75 °C, then cooled to rt, and diluted with water and toluene. The organic layer was washed with water three times and brine and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt = 100/1 to 10/1) gave the title compound (164 mg, 93%, >99:1 dr) as a colorless oil: R_f = 0.7 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −13.2 (c 1.13, $CHCl_3$); ^1H NMR δ 1.16 (9H, s), 1.59 (1H, m), 1.79 (1H, m), 1.99−2.09 (2H, m), 2.25 (1H, m), 2.84−2.94 (2H, m), 3.26 (1H, d, J = 14.0), 3.56 (1H, d, J = 14.0), 3.89 (1H, d, J = 4.9), 7.19−7.41 (10H, m); ^{13}C NMR δ 22.8 (CH_2), 24.3 (CH_2), 27.7 (CH_3), 46.8 (CH), 48.7 (CH_2), 59.3 (CH_2), 66.0 (CH), 79.7 (C), 126.6 (CH), 127.0 (CH), 127.8 (CH), 128.0 (CH), 128.4 (CH), 129.4 (CH), 139.4 (C), 139.9 (C), 172.2 (C); IR 2932, 1728, 1149; EIMS m/z 351 (M^+), 294 (M − *t*-Bu), 260 (M − Bn). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.31; H, 8.38; N, 3.99. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 200/1, 1 mL/min, major 7.0 min and minor 7.5 min). The chiral diether ligand **11** (436 mg, quant) was recovered as colorless plates.

*(+)-tert-Butyl (2S,3R)-1-Benzyl-5-methylene-2-phenylpiperidine-3-carboxylate (cis-**10b**).* The typical procedure A with **9b** in place of **9a** and column chromatography (hexane/AcOEt = 50/1) gave the title compound (86%, >99:1 dr, 97% ee) as a colorless oil: R_f = 0.5 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ +25.5 (c 0.90, $CHCl_3$); ^1H NMR δ 1.20 (9H, s), 2.55 (1H, dd, J = 5.2, 14.6), 2.82 (1H, m), 2.85 (1H, d, J = 13.8), 3.10 (1H, ddd, J = 5.2, 5.7, 10.9), 3.33 (1H, d, J = 13.8), 3.50 (1H, d, J = 13.8), 3.63 (1H, d, J = 13.8), 4.12 (1H, d, J = 5.7), 4.75 (1H, s), 4.86 (1H, s), 7.22−7.43 (10H, m); ^{13}C NMR δ 27.7 (CH_3), 31.8 (CH_2), 45.0 (CH), 53.2 (CH_2), 58.5 (CH_2), 63.9 (CH), 80.3 (C), 110.2 (CH_2), 126.9 (CH), 127.1 (CH), 128.0 (CH), 128.2 (CH), 128.8 (CH), 129.3 (CH), 139.0 (C), 139.5 (C), 142.3 (C), 172.1 (C); IR 2977, 1728, 1149; EIMS m/z 363 (M^+), 306 (M − *t*-Bu), 272 (M − Bn); HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{24}H_{30}NO_2$ 364.2277, found 364.2278. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 1000/1, 1 mL/min, minor 14.1 min and major 17.1 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

*(−)-tert-Butyl (2S,3R)-1-Benzyl-2-(naphthalen-2-yl)piperidine-3-carboxylate (cis-**10c**).* The typical procedure A with **8b** in place of **8a** and column chromatography (hexane/AcOEt = 50/1) gave the title compound (73%, >99:1 dr, 94% ee) as a colorless oil: R_f = 0.5 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −10.0 (c 0.99, $CHCl_3$); ^1H NMR δ 1.09 (9H, s), 1.63 (1H, m), 1.85 (1H, m), 2.06−2.16 (2H, m), 2.28 (1H, m), 2.94−3.01 (2H, m), 3.30 (1H, d, J = 14.0), 3.66 (1H, d, J = 14.0), 4.02 (1H, d, J = 5.2), 7.20−7.33 (5H, m), 7.42−7.46 (2H, m), 7.59 (1H, m), 7.76−7.81 (3H, m), 7.85 (1H, s); ^{13}C NMR δ 22.6 (CH_2), 24.7 (CH_2), 27.7 (CH_3), 46.8 (CH), 49.2 (CH_2), 59.5 (CH_2), 66.2 (CH), 79.8 (C), 125.5 (CH), 125.8 (CH), 126.7 (CH), 127.4 (CH), 127.5 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.6 (CH), 132.7 (C), 133.1 (C), 138.0 (C), 139.3 (C), 174.2 (C); IR 2970, 1728, 1149; EIMS m/z 401 (M^+), 344 (M − *t*-Bu), 310 (M − Bn). Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.67; H, 7.84; N, 3.51. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-3, 254 nm, hexane/*i*-PrOH = 100/1, 1 mL/min, major 5.7 min and minor 6.3 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

*(−)-tert-Butyl (2R,3R)- and (2S,3R)-1-Benzyl-2-methylpiperidine-3-carboxylate (cis- and trans-**10e**).* The typical procedure A with **8d** in place of **8a** and column chromatography (hexane/AcOEt = 100/1 to 19/1) gave *cis*-**10e** (67%, 97% ee) as a colorless powder of mp 57−58 °C, *trans*-**10e** (26%, 97% ee) as a colorless oil, and chiral diether ligand **11** (quantitative recovery) as colorless plates. The enantiomeric excess of *cis*- and *trans*-**10e** was determined by HPLC analysis (*cis*-**10e**: Daicel Chiralcel OJ-H × 2, 254 nm, hexane/*i*-PrOH = 1000/1, 2 mL/min, major 13.4 min and minor 16.5 min; *trans*-**10e**: Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 1500/1, 2 mL/min, major 9.0 min and minor 10.2 min).

cis-**10e**: R_f = 0.5 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −6.55 (c 1.47, $CHCl_3$); ^1H NMR δ 0.94 (3H, d, J = 6.6), 1.43 (9H, s), 1.46−1.73 (4H, m), 2.34−2.42 (2H, m), 2.74 (1H, ddd, J = 12.3, 4.3, 4.0), 3.40 (1H, dq, J = 4.3, 6.6), 3.52 (1H, d, J = 17.2), 3.67 (1H, d, J = 17.2), 7.21−7.35 (5H, m); ^{13}C NMR δ 6.0 (CH_3), 20.5 (CH_2), 24.4 (CH_2), 28.0 (CH_3), 44.2 (CH_2), 46.8 (CH), 54.6 (CH), 59.2 (CH_2), 79.9 (C), 126.7 (CH), 128.1 (CH), 128.5 (CH), 139.8 (C), 173.4 (C); IR 2939, 1720, 1134; EIMS m/z 289 (M^+), 274 (M − Me), 232 (M − *t*-Bu); HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{18}H_{28}NO_2$ 290.2120, found 290.2127.

trans-**10e**: R_f = 0.5 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −24.5 (c 0.89, $CHCl_3$); ^1H NMR δ 1.20 (3H, d, J = 5.7), 1.45 (9H, s), 1.48−1.52 (3H, m), 1.84 (1H, m), 2.05 (1H, m), 2.23 (1H, m), 2.64−2.74 (2H, m), 3.25 (1H, d, J = 13.2), 3.97 (1H, d, J = 13.2), 7.21−7.31 (5H, m);

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^{13}C NMR δ 17.4 (CH_3), 23.9 (CH_2), 27.5 (CH_2), 28.1 (CH_3), 50.4 (CH), 51.3 (CH_2), 57.4 (CH_2), 57.6 (CH), 80.1 (C), 127.0 (CH), 128.1 (CH), 128.9 (CH), 139.5 (C), 174.5 (C); IR 2978, 1728, 1157; EIMS m/z 289 (M^+), 274 (M − Me), 232 (M − t-Bu). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.81; H, 9.25; N, 4.82.

*(−)-tert-Butyl (2S,3R)-1-Benzyl-2-butylpiperidine-3-carboxylate (cis-**10f**).* The typical procedure A with **8e** in place of **8a** and column chromatography (hexane/AcOEt = 100/1 to 50/1) gave a 79:21 mixture of *cis*- and *trans*-**10f** (66%) as a colorless oil, *cis*-**10f** (33%, 95% ee) as a colorless oil, and chiral diether ligand **11** (quantitative recovery) as colorless plates. The enantiomeric excess of *cis*-**10f** was determined by HPLC analysis (Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 600/1, 1 mL/min, minor 7.3 min and major 8.3 min).

cis-**10f**: R_f = 0.2 (hexane/AcOEt = 9/1); $[\alpha]_D^{25}$ −6.58 (c 1.11, $CHCl_3$); ^{1}H NMR δ 0.87 (3H, d, J = 7.2), 1.09 (1H, m), 1.23−1.76 (9H, m), 1.42 (9H, s), 2.48 (1H, m), 2.67 (1H, m), 2.80 (1H, m), 3.06 (1H, m), 3.70 (1H, d, J = 13.5), 3.85 (1H, d, J = 13.5), 7.21−7.35 (5H, m); ^{13}C NMR δ 14.1 (CH_3), 21.0 (CH_2), 21.6 (CH_2), 22.7 (CH_2), 25.1 (CH_2), 28.1 (CH_3), 30.1 (CH_2), 42.8 (CH), 43.7 (CH_2), 58.2 (CH_2), 59.8 (CH), 79.9 (C), 127.6 (CH), 128.1 (CH), 128.6 (CH), 140.3 (C), 174.0 (C); IR 2932, 1728, 1142; EIMS m/z 331 (M^+), 274 (M − Bu); HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{21}H_{34}NO_2$ 332.2590, found 332.2585.

*(−)-tert-Butyl (4R,7R)-1-Benzyloctahydro-1H-cyclopentapyridine-4-carboxylate (trans-**10g**).* The typical procedure A with **8f** in place of **8a** and column chromatography (hexane/AcOEt = 100/1 to 50/1) gave the title compound (90%, >99:1 dr, 87% ee) as a colorless oil: R_f = 0.4 (hexane/AcOEt = 8/2); $[\alpha]_D^{25}$ −36.3 (c 1.20, $CHCl_3$); ^{1}H NMR δ 1.02 (1H, m), 1.42−1.49 (2H, m), 1.49 (9H, s), 1.67−1.93 (6H, m), 2.11−2.19 (2H, m), 2.37 (1H, m), 2.82 (1H, m), 3.70 (1H, d, J = 13.5), 3.97 (1H, d, J = 13.5), 7.19−7.36 (5H, m); ^{13}C NMR δ 20.3 (CH_2), 23.8 (CH_2), 27.5 (CH_2), 28.2 (CH_3), 35.0 (CH_2), 35.6 (CH_2), 53.7 (C), 54.9 (CH_2), 60.2 (CH_2), 73.7 (CH), 79.6 (C), 126.5 (CH), 127.9 (CH), 128.6 (CH), 140.1 (C), 174.6 (C); IR 2955, 1713, 1150; EIMS m/z 315 (M^+), 258 (M − t-Bu); HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{20}H_{30}NO_2$, 316.2277; found, 316.2281. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 600/1, 1 mL/min, major 7.2 min and minor 7.8 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

*Typical Procedure B: (−)-tert-Butyl (2S,3R)-1-Benzyl-2-phenylpyrrolidine-3-carboxylate (cis-**10h**).* To a solution of *N*-benzyl-*N*-(isopropyldimethylsilyl)amine (311 mg, 1.5 mmol) in toluene (4 mL) was added a 1.61 M hexane solution of BuLi (0.93 mL, 1.5 mmol) at −78 °C over 4 min, and the mixture was stirred for 30 min at −78 °C. A solution of chiral diether **11** (436 mg, 1.8 mmol) in toluene (2 mL) was added over 5 min, and after 30 min, a solution of enoate **8a** (102 mg, 0.5 mmol) in toluene (2 mL) was added over 8 min. The mixture was stirred for 1.5 h at −78 °C, and a solution of ethylene sulfate **9i** (620 mg, 5 mmol) in DMPU (8 mL) was added over 30 min at −78 °C. The mixture was stirred for 2 h at −40 °C, and 10% HCl (3 mL) was added. The whole was stirred for 0.5 h at 0 °C, and then saturated $NaHCO_3$ (12 mL) was added. The whole was stirred for another 1 h at 100 °C, then cooled to rt, and diluted with water and toluene. The organic layer was washed with water three times and brine and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt = 97/3 to 9/1) gave the title compound (164 mg, 97%, 97% ee) as a colorless oil: R_f = 0.7 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −13.2 (c 1.13, $CHCl_3$); ^{1}H NMR δ 0.98 (9H, s), 1.92 (1H, m), 2.22−2.37 (2H, m), 3.11 (1H, d, J = 13.5), 3.14−3.26 (2H, m), 3.80 (1H, d, J = 12.0), 3.83 (1H, d, J = 13.5), 7.19−7.31 (8H, m), 7.45−7.46 (2H, m); ^{13}C NMR δ 26.8 (CH_2), 27.4 (CH_3), 49.8 (CH), 52.3 (CH_2), 57.5 (CH_2), 70.4 (CH), 79.8 (C), 126.7 (CH), 127.3 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 129.1 (CH), 139.2 (C), 140.0 (C), 172.0 (C); IR 2970, 1720, 1149; EIMS m/z 337 (M^+), 264 (M − t-BuO), 246 (M − Bn). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.23; H, 8.11; N, 4.10. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-3, 254 nm, hexane/*i*-PrOH = 100/1, 1 mL/min, major 4.6 min and minor 5.3 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

*(−)-tert-Butyl (2S,3R)-1-Benzyl-3-phenylaziridine-2-carboxylate (trans-**10i**).* The typical procedure A with *N*-benzyl-*N*-(isopropyldimethylsilyl)amine and **9c** in place of *N*-benzyl-*N*-trimethylsilylamine and **9a**, respectively, and column chromatography (hexane/AcOEt = 150/1) gave the title compound (94%, >99:1 dr, 98% ee) as a colorless powder of mp 51−52 °C: R_f = 0.5 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −8.55 (c 1.07, $CHCl_3$). ^{1}H and ^{13}C NMR, and MS were identical to those reported.[58] The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-3, 254 nm, hexane/*i*-PrOH = 100/1, 1 mL/min, major 6.5 min and minor 7.3 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

*(−)-tert-Butyl (2S,3R)- and (2R,3R)-1-Benzyl-3-methylaziridine-2-carboxylate (trans- and cis-**10j**).* The typical procedure A with *N*-benzyl-*N*-(isopropyldimethylsilyl)amine, **8d**, and **9c** in place of *N*-benzyl-*N*-trimethylsilylamine, **8a**, and **9a**, respectively, and column chromatography (hexane/AcOEt = 98/2 to 85/15) gave *trans*-**10j** (75%, 98% ee) as a colorless oil, *cis*-**10j** (18%, 97% ee) as colorless needles of mp 62−63 °C, and chiral diether ligand **11** (quantitative recovery) as colorless plates. The enantiomeric excess of *trans*- and *cis*-**10j** was determined by HPLC analysis (*trans*-**10j**: Daicel Chiralpak AD-3, 254 nm, hexane/*i*-PrOH = 100/1, 1 mL/min, major 18.2 min and minor 34.3 min; *cis*-**10j**: Daicel Chiralpak AD-3, 254 nm, hexane/*i*-PrOH = 100/1, 1 mL/min, major 22.1 min and minor 23.2 min).

trans-**10j**: R_f = 0.4 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −70.8 (c 0.97, $CHCl_3$). Two isomers, probably invertomers of the nitrogen atom,[59] were observed in 7:3 ratio by NMR: ^{1}H NMR δ 1.24 (2.1H, d, J = 5.4), 1.35 (0.9H, d, J = 6.0), 1.38 (6.3H, s), 1.45 (2.7H, s), 1.89 (0.3H, d, J = 2.6), 2.27 (0.7H, dq, J = 2.8, 5.4), 2.38 (0.7H, d, J = 2.8), 2.55 (0.3H, dq, J = 2.6, 6.0), 3.70 (0.3H, d, J = 14.5), 3.82 (0.3H, d, J = 14.5), 3.88 (0.7H, d, J = 14.0), 4.05 (0.7H, d, J = 14.0), 7.21−7.39 (5H, m). Major isomer of *trans*-**10j**: ^{13}C NMR δ 17.8 (CH_3), 27.9 (CH_3), 42.1 (CH), 42.5 (CH), 54.7 (CH_2), 81.3 (C), 126.7 (CH), 127.9 (CH), 128.2 (CH), 139.6 (C), 168.7 (C). Minor isomer of *trans*-**10j**: ^{13}C NMR δ 10.7 (CH_3), 28.0 (CH_3), 39.4 (CH), 45.2 (CH), 54.5 (CH_2), 81.0 (C), 126.7 (CH), 127.4 (CH), 128.4 (CH), 139.2 (C), 170.3 (C); IR 2978, 1720, 1157; EIMS m/z 247 (M^+), 232 (M − Me), 190 (M − t-Bu), 146 (M − CO_2t-Bu); HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{15}H_{22}NO_2$ 248.1651, found 248.1661.

cis-**10j**: R_f = 0.3 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ +76.1 (c 1.04, $CHCl_3$); ^{1}H NMR δ 1.28 (3H, d, J = 5.7), 1.47 (9H, s), 1.92 (1H, dq, J = 6.8, 5.7), 2.11 (1H, d, J = 6.8), 3.54 (1H, d, J = 14.0), 3.63 (1H, d, J = 14.0), 7.23−7.37 (5H, m); ^{13}C NMR δ 13.0 (CH_3), 28.1 (CH_3), 41.3 (CH), 43.6 (CH), 63.4 (CH_2), 81.6 (C), 126.9 (CH), 127.6 (CH), 128.2 (CH), 138.4 (C), 168.9 (C); IR 2970, 1728, 1157; EIMS m/z 247 (M^+), 232 (M − Me), 190 (M − t-Bu), 146 (M − CO_2t-Bu). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.59; H, 8.34; N, 5.66.

*(−)-tert-Butyl (2S,3R)-1-Benzyl-2-phenylazetidine-3-carboxylate (cis-**10k**).* The typical procedure B with *N*-benzyl-*N*-trimethylsilylamine and **9j** in place of *N*-benzyl-*N*-(isopropyldimethylsilyl)amine and **9i**, respectively, and column chromatography (hexane/AcOEt = 100/1 to 50/1) gave the title compound (82%, >99:1 dr, 97% ee) as a colorless powder of mp 83−84 °C: R_f = 0.3 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −118.4 (c 1.16, $CHCl_3$); ^{1}H NMR δ 1.00 (9H, s), 2.93 (1H, dd, J = 7.2, 7.2), 3.34 (1H, ddd, J = 9.2, 7.2, 2.6), 3.45 (1H, d, J = 13.5), 3.69 (1H, dd, J = 7.2, 2.6), 3.86 (1H, d, J = 13.5), 4.55 (1H, d, J = 9.2), 7.21−7.49 (10H, m); ^{13}C NMR δ 27.5 (CH_3), 42.0 (CH), 51.1 (CH_2), 60.8 (CH_2), 69.1 (CH), 80.1 (C), 126.8 (CH), 127.3 (CH), 127.4 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 137.9 (C), 139.0 (C), 170.4 (C); IR 2978, 1728, 1157; EIMS m/z 323 (M^+), 266 (M − t-Bu), 232 (M − Bn); HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{21}H_{25}NO_2$ 324.1964, found 324.1951. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-3, 254 nm, hexane/*i*-PrOH = 100/1, 1 mL/min, major 6.5 min and minor 7.6 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

(−)-tert-Butyl (2R,3R)-1-Benzyl-2-methylazetidine-3-carboxylate (cis-10l). The typical procedure B with **8d** and **9j** in place of **8a** and **9i**, respectively, and column chromatography (hexane/AcOEt = 24/1 to 10/1) gave a 7:3 mixture of *trans*- and *cis*-**10l** (16%) as a colorless oil, *cis*-**10l** (41%, 98% ee) as a colorless oil, and chiral diether ligand **11** (quantitative recovery) as colorless plates. The enantiomeric excess of *cis*-**10l** was determined by HPLC analysis (Daicel Chiralpak AD-3, 254 nm, hexane/*i*-PrOH = 100/1, 1 mL/min, minor 6.3 min and major 19.9 min).

cis-**10l**: R_f = 0.3 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −1.54 (*c* 1.10, $CHCl_3$); ^{1}H NMR δ 1.05 (3H, d, *J* = 6.3), 1.47 (9H, s), 2.91 (1H, dd, *J* = 7.8, 7.5), 3.09 (1H, m), 3.56 (1H, d, *J* = 13.0), 3.57 (1H, m), 3.65 (1H, m), 3.66 (1H, d, *J* = 13.0), 7.21−7.32 (5H, m); ^{13}C NMR δ 17.2 (CH_3), 28.2 (CH_3), 39.6 (CH), 52.3 (CH_2), 61.6 (CH_2), 62.8 (CH), 80.6 (C), 126.9 (CH), 128.1 (CH), 128.8 (CH), 138.0 (C), 171.7 (C); IR 2970, 1728, 1150; EIMS *m*/*z* 261 (M^+), 204 (M − *t*-Bu), 170 (M − Bn); HRMS−FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{24}NO_2$ 262.1807, found 262.1792.

(−)-tert-Butyl (2R,3S)-1-Benzyl-2-methylpyrrolidine-3-carboxylate (trans-10m). The typical procedure B with *N*-benzyl-*N*-(trimethylsilyl)amine and **8d** in place of *N*-benzyl-*N*-(isopropyldimethylsilyl)amine and **8a**, respectively, and column chromatography (hexane/AcOEt = 50/1 to 9/1) gave a 9:1 mixture of *trans*- and *cis*-**10m** (97%, 96% ee for *trans*-isomer) as a colorless oil and chiral diether ligand **11** (quantitative recovery) as colorless plates. The enantiomeric excess of *trans*-**10m** was determined by HPLC analysis (Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 1000/1, 1 mL/min, major 13.7 min and minor 18.0 min).

trans-**10m**: R_f = 0.4 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −60.1 (*c* 1.15, $CHCl_3$); ^{1}H NMR δ 1.29 (3H, d, *J* = 5.2), 1.46 (9H, s), 1.91−1.97 (2H, m), 2.21 (1H, m), 2.49−2.55 (2H, m), 2.88 (1H, m), 3.12 (1H, d, *J* = 13.3), 4.01 (1H, d, *J* = 13.3), 7.22−7.30 (5H, m); ^{13}C NMR δ 18.7 (CH_3), 25.9 (CH_2), 28.1 (CH_3), 51.5 (CH), 53.2 (CH_2), 58.0 (CH_2), 63.6 (CH), 80.3 (C), 126.9 (CH), 128.2 (CH), 129.0 (CH), 139.2 (C), 174.3 (C); IR 2970, 1728, 1157; EIMS *m*/*z* 275 (M^+), 260 (M − Me), 218 (M − *t*-Bu), 204 (M − Me − *t*-Bu), 184 (M − Bn). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.17; H, 9.27; N, 5.10.

(−)-tert-Butyl (2R,3R)-1-benzyl-2-methylpyrrolidine-3-carboxylate (cis-10m). The typical procedure B with **8d** and **9d** in place of **8a** and **9i**, respectively, and column chromatography (hexane/AcOEt = 19/1) gave a 93:7 mixture of *cis*- and *trans*-**10m** (73%, 99% ee for *cis*-isomer) as a colorless oil and chiral diether ligand **11** (quantitative recovery) as colorless plates. The enantiomeric excess of *cis*-**10m** was determined by HPLC analysis (Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 400/1, 1 mL/min, minor 10.2 min and major 10.9 min).

cis-**10m**: R_f = 0.4 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ −41.7 (*c* 1.53, $CHCl_3$); ^{1}H NMR δ 1.07 (3H, d, *J* = 6.2), 1.46 (9H, s), 1.83 (1H, m), 2.13 (1H, m), 2.28 (1H, m), 2.89−2.97 (3H, m), 3.38 (1H, d, *J* = 13.3), 3.89 (1H, d, *J* = 13.3), 7.21−7.34 (5H, m); ^{13}C NMR δ 14.6 (CH_3), 25.7 (CH_2), 28.1 (CH_3), 48.1 (CH), 52.1 (CH_2), 57.4 (CH_2), 59.9 (CH), 80.2 (C), 126.7 (CH), 128.1 (CH), 128.7 (CH), 139.3 (C), 172.9 (C); IR 2970, 1728, 1150; EIMS *m*/*z* 275 (M^+), 260 (M − Me), 218 (M − *t*-Bu), 204 (M − Me − *t*-Bu), 184 (M − Bn); HRMS−FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{26}NO_2$ 276.1964, found 276.1971.

(+)-tert-Butyl (2S,3R)-1-Benzyl-2-phenylazepane-3-carboxylate (cis-10n). The typical procedure B with *N*-benzyl-*N*-trimethylsilylamine and **9k** in place of *N*-benzyl-*N*-(isopropyldimethylsilyl)amine and **9i**, respectively, and column chromatography (hexane/AcOEt = 100/1 to 9/1) gave the title compound (71%, >99:1 dr, 97% ee) as a colorless powder of mp 116−118 °C: R_f = 0.5 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ +79.7 (*c* 1.01, $CHCl_3$); ^{1}H NMR δ 1.25 (9H, s), 1.31 (1H, m), 1.55 (1H, m), 1.63 (1H, m), 1.85−1.93 (2H, m), 2.10 (1H, m), 2.64 (1H, m), 2.75 (1H, m), 2.99 (1H, m), 3.25 (1H, d, *J* = 14.0), 3.67 (1H, d, *J* = 14.0), 4.11 (1H, d, *J* = 6.3), 7.17−7.30 (10H, m); ^{13}C NMR δ 24.1 (CH_2), 27.9 (CH_3), 28.1 (CH_2), 30.7 (CH_2), 49.5 (CH_2), 51.6 (CH), 59.9 (CH_2), 69.2 (CH), 80.2 (C), 126.6 (CH), 127.3 (CH), 127.8 (CH), 128.0 (CH), 128.4 (CH), 129.1 (CH), 140.5 (C), 141.7 (C), 172.9 (C); IR 2924, 1728, 1149; EIMS *m*/*z* 365 (M^+), 308 (M − *t*-Bu), 274 (M − Bn); HRMS−FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{24}H_{32}NO_2$ 366.2433, found 366.2431. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 400/1, 1 mL/min, major 8.4 min and minor 8.9 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

(+)-tert-Butyl (2S,3R)-1-Benzyl-3-phenyl-2,3,4,5-tetrahydro-1H-benzoazepine-4-carboxylate (cis-10o). The typical procedure B with *N*-benzyl-*N*-trimethylsilylamine and **9l** in place of *N*-benzyl-*N*-(isopropyldimethylsilyl)amine and **9i**, respectively, and column chromatography (hexane/AcOEt = 50/1) gave the title compound (57%, >99:1 dr, 98% ee) as a colorless oil: R_f = 0.6 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ +59.3 (*c* 1.14, $CHCl_3$); ^{1}H NMR δ 1.30 (9H, s), 3.22 (1H, m), 3.29 (1H, d, *J* = 15.5), 3.50−3.65 (4H, m), 4.02 (1H, d, *J* = 15.5), 4.57 (1H, d, *J* = 3.7), 6.87 (1H, d, *J* = 7.5), 7.08 (1H, dd, *J* = 7.3, 0.7), 7.16 (1H, dd, *J* = 7.5, 1.2), 7.22−7.37 (9H, m), 7.60−7.62 (2H, m); ^{13}C NMR δ 27.8 (CH_3), 31.2 (CH_2), 42.8 (CH), 53.0 (CH_2), 56.9 (CH_2), 66.0 (CH), 80.8 (C), 125.9 (CH), 126.8 (CH), 126.9 (CH), 127.1 (CH), 128.1 (CH), 128.2 (CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 129.7 (CH), 138.6 (C), 139.3 (C), 140.3 (C), 140.7 (C), 173.7 (C); IR 2977, 1720, 1149; EIMS *m*/*z* 413 (M^+), 356 (M − *t*-Bu), 322 (M − Bn); HRMS−FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{28}H_{32}NO_2$ 414.2433, found 414.2448. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OZ-H, 254 nm, hexane/*i*-PrOH = 600/1, 1 mL/min, major 8.9 min and minor 16.8 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

(±)-tert-Butyl 1-Benzylpiperidine-3-carboxylate. The typical procedure A with *N*-benzyl-*N*-(isopropyldimethylsilyl)amine and *tert*-butyl acrylate in place of *N*-benzyl-*N*-trimethylsilylamine and **8a**, respectively, and column chromatography (hexane/AcOEt = 19/1) gave the title compound (42%, 0% ee) as a colorless oil: R_f = 0.4 (hexane/AcOEt = 4/1); ^{1}H NMR δ 1.41 (9H, s), 1.42 (1H, m), 1.54 (1H, m), 1.69 (1H, m), 1.86−2.17 (3H, m), 2.47 (1H, m), 2.70 (1H, m), 2.92 (1H, m), 3.46 (1H, d, *J* = 13.2), 3.53 (1H, d, *J* = 13.2), 7.22−7.39 (5H, m); ^{13}C NMR δ 24.5 (CH_2), 27.0 (CH_2), 28.0 (CH_3), 42.7 (CH), 53.6 (CH_2), 55.7 (CH_2), 63.3 (CH_2), 80.0 (C), 126.9 (CH), 128.1 (CH), 129.0 (CH), 138.5 (C), 173.7 (C); IR 2939, 1728, 1150; FABMS *m*/*z* 276 (M + H)$^+$, 218 (M − *t*-Bu); HRMS−FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{26}NO_2$ 276.1964, found 276.1965. The enantiomeric excess of the title compound was determined by HPLC analysis (Daicel Chiralcel OD-3, 254 nm, hexane/*i*-PrOH = 400/1, 1 mL/min, 13.0 and 15.9 min). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

Epimerization of *cis*-10a (Scheme 2). *(+)-tert-Butyl (2S,3S)-1-Benzyl-2-phenylpiperidine-3-carboxylate (trans-10a).* A suspension of *cis*-**10a** (50 mg, 0.14 mmol) and NaOMe (31 m, 0.57 mmol) in xylene (1 mL) was stirred under reflux. After 3.5 h, saturated $NaHCO_3$ (2 mL) was added, and the organic layer was separated. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with brine and then dried over Na_2SO_4. The diastereomer ratio was determined to be >98:2 by ^{1}H NMR of the crude material. Concentration and column chromatography (hexane/AcOEt = 50/1) gave the title compound (93%, >99:1 dr, 97% ee) as a colorless oil: R_f = 0.7 (hexane/AcOEt = 4/1); $[\alpha]_D^{25}$ +37.1 (*c* 1.28, $CHCl_3$); ^{1}H NMR δ 1.13 (9H, s), 1.60−1.71 (3H, m), 1.96−2.03 (2H, m), 2.61 (1H, m), 2.79 (1H, d, *J* = 13.5), 2.95 (1H, m), 3.30 (1H, d, *J* = 10.0), 3.70 (1H, d, *J* = 13.5), 7.16−7.45 (10H, m); ^{13}C NMR δ 24.7 (CH_2), 27.7 (CH_3), 28.7 (CH_2), 52.6 (CH_2), 52.7 (CH), 59.1 (CH_2), 70.3 (CH), 79.8 (C), 126.6 (CH), 127.4 (CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 140.0 (C), 141.7 (C), 173.4 (C); IR 2939, 1728, 1149; EIMS *m*/*z* 351 (M^+), 294 (M − *t*-Bu), 260 (M − Bn); HRMS−FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{23}H_{30}NO_2$ 352.2277, found 352.2272. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-3, 254 nm, hexane/*i*-PrOH = 200/1, 1 mL/min, major 5.8 min and minor 6.4 min).

A Control Experiment for Table 3, entry 4. *(R)-tert-Butyl 3-(Benzylamino)-2-deuterio-3-phenylpropanoate (16d).* To a solution of *N*-benzyl-*N*-trimethylsilylamine (0.29 mL, 1.5 mmol) in toluene (4

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mL) was added a 1.61 M hexane solution of BuLi (0.93 mL, 1.5 mmol) at −78 °C over 4 min, and the mixture was stirred for 30 min at −78 °C. A solution of chiral diether **11** (436 mg, 1.8 mmol) in toluene (2 mL) was added over 5 min, and after 30 min, a solution of enoate **8a** (102 mg, 0.5 mmol) in toluene (2 mL) was added over 8 min. The mixture was stirred for 15 h at −78 °C, and CD_3OD (0.75 mL) was added at −78 °C. The mixture was warmed up to rt and stirred for 20 min, and aqueous NH_4Cl (2 mL) and saturated $NaHCO_3$ (12 mL) were added. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt = 97/3 to 92/8) gave the title compound (151 mg, 97%, 80:20 dr, 94%-deuteration) as a colorless oil: R_f = 0.5 (hexane/AcOEt = 4/1); ^{1}H NMR δ 1.37 (9H, s), 2.05 (1H, br s), 2.51 (0.2H, d, J = 5.2), 2.62 (0.8H, d, J = 8.9), 3.54 (1H, d, J = 13.0), 3.62 (1H, d, J = 13.0), 4.06 (1H, d, J = 6.4), 7.22−7.37 (10H, m); ^{13}C NMR δ 28.0 (CH_3), 43.9 (CH), 51.4 (CH_2), 59.1 (CH), 80.6 (C), 126.8 (CH), 127.2 (CH), 127.3 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 140.3 (C), 142.6 (C), 171.1 (C); IR 2978, 1721, 1153; EIMS m/z 312 (M^+), 255 (M − t-BuO), 221 (M − Bn); HRMS−FAB (m/z) [M + H]$^+$ calcd for $C_{20}H_{24}DNO_2$ 313.2026, found 313.2030. The diastereomer ratio was determined by the integration area of the ^{1}H NMR signals at 2.51 and 2.62 ppm. The percent deuterium incorporation was determined by the integration area of the ^{1}H NMR signals at 2.54 and 2.63 ppm (the two diastereomeric α-protons of **16**). The chiral diether ligand **11** was quantitatively recovered as colorless plates.

Short Step Asymmetric Synthesis of Phenylalanine, Azinomycin Ester, and Nemonapride. *(+)-L-Phenylalanine tert-Butyl Ester (17).* A suspension of *trans*-**10i** (15 mg, 0.046 mmol) and 10% Pd/C (4.9 mg, 4.6 μmol) in MeOH (1 mL) was stirred under H_2 (1 atm) for 24 h at 50 °C and filtrated through Celite pad, which was then washed with $CHCl_3$. The filtrate was washed with saturated $NaHCO_3$ (5 mL), and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt = 4/1 to 1/1) gave the title compound (8.0 mg, 75%) as a colorless oil: R_f = 0.1 (hexane/AcOEt = 3/2); $[\alpha]_D^{25}$ +14.5 (c 0.80, $CHCl_3$). ^{1}H and ^{13}C NMR, IR, and MS were identical to those reported.[60]

(+)-tert-Butyl (2S,3R)-3-Methylaziridine-2-carboxylate (18). A suspension of *trans*-**10j** (165 mg, 0.67 mmol) and 10% Pd/C (71 mg, 0.067 mmol) in MeOH (5 mL) was stirred under H_2 (1 atm) for 5 h at rt and filtrated through Celite pad, which was then washed with $CHCl_3$. Concentration and column chromatography (pentane/Et_2O = 85/15) gave the title compound (75 mg, 71%) as a colorless oil: R_f = 0.2 (pentane/Et_2O = 85/15); $[\alpha]_D^{25}$ +63.0 (c 1.03, $CHCl_3$). ^{1}H and ^{13}C NMR, IR, and MS were identical to those reported.[61]

(−)-(2R,3R)-1-Benzyl-2-methylpyrrolidin-3-amine (20). A solution of *cis*-**10m** (70 mg, 0.254 mmol) in TFA (0.5 mL) and CH_2Cl_2 (2.5 mL) was stirred under reflux 12 h and then concentrated to give a black oil.

To the black oil were added toluene (5 mL), Et_3N (0.14 mL, 1.0 mmol), and then diphenylphosphoryl azide (0.071 mL, 0.33 mmol). The mixture was stirred at rt for 30 min and then at 90 °C for 1 h. To the solution were added TsOH·H_2O (483 mg, 2.54 mmol) and H_2O (1 mL), and the mixture was stirred at 90 °C. After 15 h, 10% NaOH (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography (CH_2Cl_2/MeOH = 4/1 to 1/1) to give the title compound (25 mg, 52%) as a colorless oil: R_f = 0.1 (CH_2Cl_2/ MeOH = 7/3); $[\alpha]_D^{25}$ −83.1 (c 1.25, $CHCl_3$). ^{1}H and ^{13}C NMR, IR, and MS were identical to those reported.[62]

Nemonapride (4). To a solution of 4-carboxy-2-chloro-5-methoxy-*N*-methylammonium hydrogen sulfate (70 mg, 0.16 mmol) and Et_3N (0.12 mL, 0.84 mmol) in CH_2Cl_2 (1 mL) was added $ClCO_2Et$ (0.015 mL, 16 mmol) at 0 °C, and the whole was stirred for 0.5 h at 0 °C. To the solution was added **20** (20 mg, 0.105 mmol) in CH_2Cl_2 (1 mL), the mixture was stirred for 2 h at 0 °C, and then saturated $NaHCO_3$ (3 mL) was added. The aqueous layer was extracted with AcOEt, and the combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt = 1/4) gave the title compound (34 mg, 83%) as a colorless powder: R_f = 0.5 (AcOEt); $[\alpha]_D^{19}$ −1.42 (c 0.60, $CHCl_3$). ^{1}H and ^{13}C NMR, IR, and MS were identical to those reported.[62]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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