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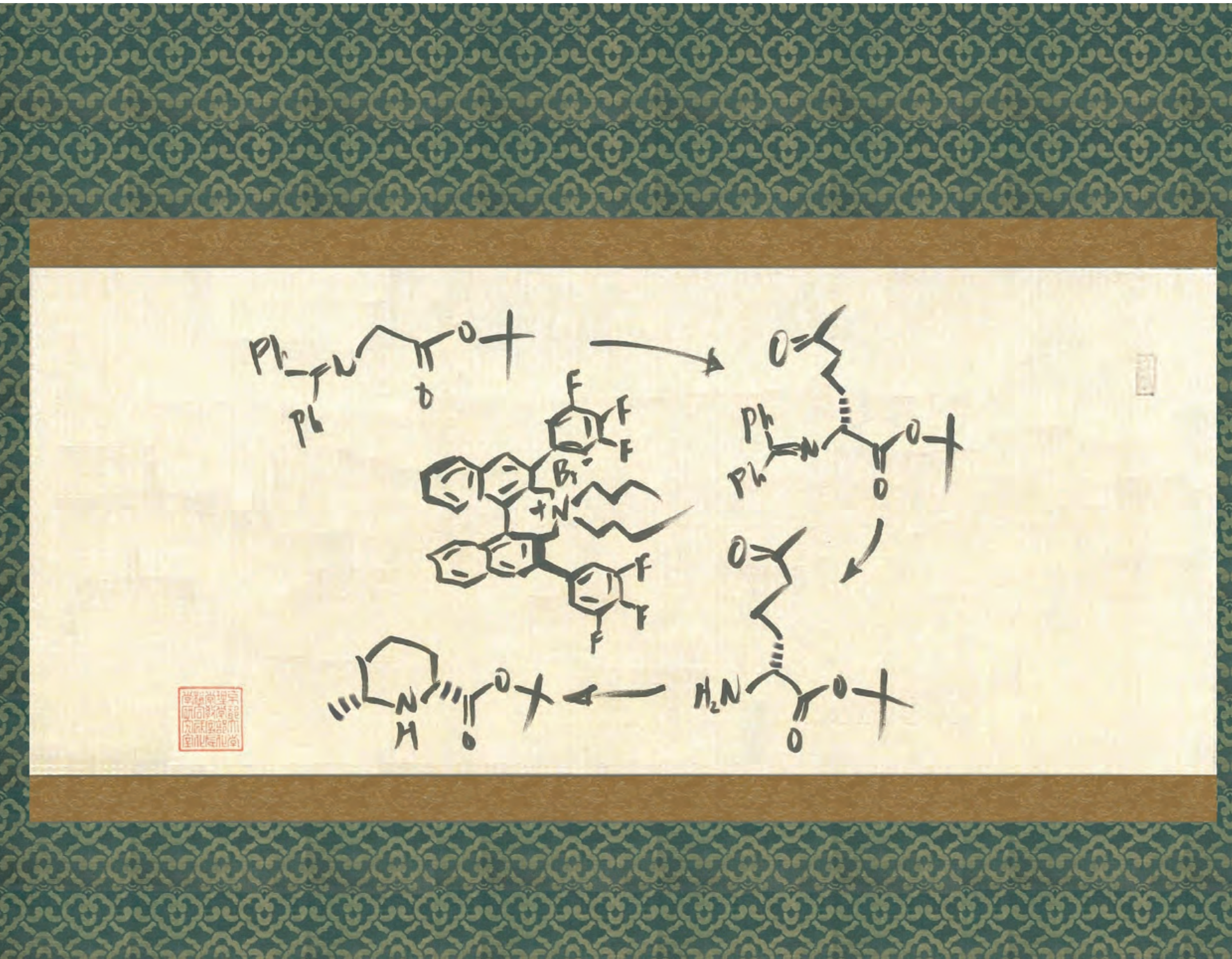

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PAPER
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Stereoselective synthesis of cyclic amino acids *via* asymmetric phase-transfer catalytic alkylation†

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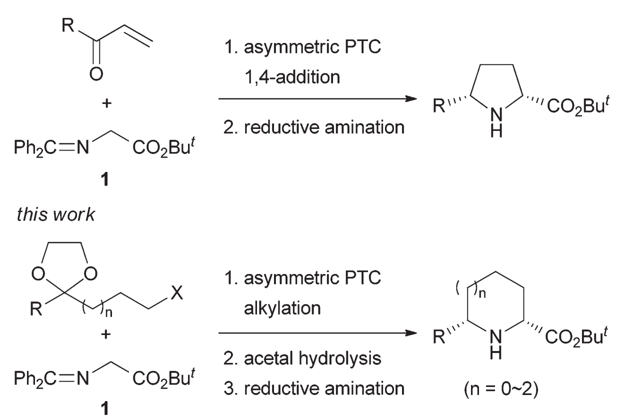
An asymmetric synthesis of cyclic amino acids having piperidine and azepane core structures was realized starting from readily available glycine and alanine esters by combination of phase-transfer catalyzed asymmetric alkylation and subsequent reductive amination.

Introduction

Organocatalysis is well-recognized as a powerful tool for the preparation of optically active compounds including natural products and biologically active compounds.[1] An important benefit of organocatalysis is the lack of toxic metal byproducts that often accompany metal-catalyzed reactions. In this area, chiral quaternary ammonium salts are frequently utilized as a phase-transfer catalyst for the asymmetric synthesis of non-proteinogenic amino acids.[2] Recently, we have developed an organocatalytic approach to asymmetric one-pot synthesis of proline derivatives with a five-membered ring through the phase-transfer catalyzed asymmetric 1,4-addition of a readily available glycine ester **1** to α,β-unsaturated ketones and subsequent reductive amination (Scheme 1).[3] With this method, however, other cyclic amino acid derivatives with a larger ring size could not be accessible in spite of their synthetic and pharmacological importance.[4] Accordingly, we have been interested in applying the powerful phase-transfer catalyzed asymmetric alkylation as the initial C–C bond forming reaction to prepare cyclic amino acids with several different ring sizes (Scheme 1).[5] Here we wish to report a catalytic asymmetric synthesis of a wide variety of cyclic amino acid derivatives starting from glycine ester **1** in combination with phase-transfer catalyzed asymmetric alkylation and subsequent diastereoselective reductive amination.



Scheme 1 Asymmetric synthesis of cyclic amino acids.

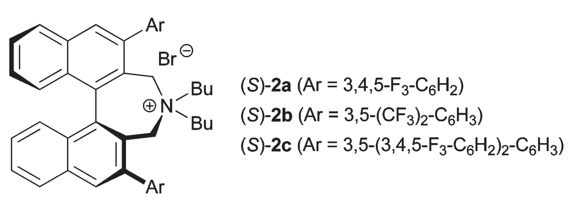


Fig. 1

Results and discussion

We first examined asymmetric alkylation of *N*-(diphenylmethylene)glycine ester **1** and alkyl bromide **3a** with an acetal moiety by using a chiral phase transfer catalyst of type (*S*)-**2**[6] Fig. 1 (Table 1).[5] Attempted reaction of **1** and **3a** with CsOH in the presence of 1 mol% of catalyst (*S*)-**2a** in toluene at −20 °C gave alkylation product **4a** in 46% yield with 88% ee (entry 1).[7] While use of (*S*)-**2b** improved the yield (entry 2), a sterically more hindered catalyst (*S*)-**2c** was not as effective as (*S*)-**2a** (entry 3). Lowering reaction temperature improved the enantioselectivity (entry 4). Using a decreased amount of CsOH and an increased amount of **3a**, the desired **4a** was obtained in a satisfactory yield with virtually complete enantioselectivity (entries 6 and 7).

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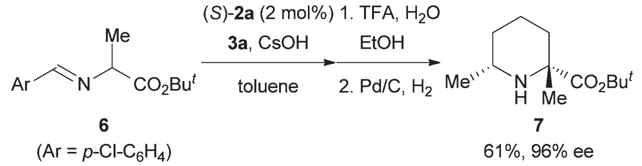
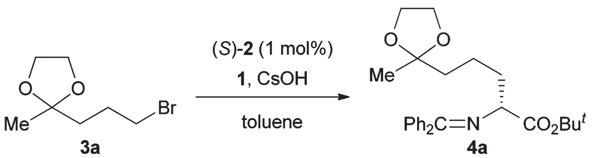
With the optimal reaction condition for asymmetric alkylation at hand, we then examined the reactions of various alkyl bromides **3** (n = 0–2, R = H or Me) and subsequent reductive amination (Table 2). The reaction between **1** and **3b** (n = 0, R = H) gave the corresponding alkylation product **4b** (n = 0, R = H) in good yield, and subsequent one-pot acetal hydrolysis with CF_3CO_2H (3 equiv.) in aqueous EtOH at room temperature and intramolecular reductive amination with Pd on carbon under a H_2 atmosphere at 45 °C proceeded to furnish proline ester **5b** (n = 0, R = H) in good yield and enantioselectivity (entry 1). Unfortunately, however, the reaction using the sterically more hindered alkyl bromide **3c** (n = 0, R = Me) gave only a trace amount of the alkylation product (entry 2). Under similar conditions, the reactions of alkyl bromides **3** (n = 1–2, R = H or Me) with a longer alkyl chain were examined. The reaction of **3** (n = 1–2, R = H) with an acetal moiety proceeded to afford the corresponding alkylated products in good yield, and the following cyclization gave cyclic amino esters **5** (n = 1–2, R = H) in excellent enantioselectivity (entries 3 and 5). The reaction of **3** (n = 1–2, R = Me) with a ketal moiety also gave the corresponding cyclic amino esters **5** (n = 1–2, R = Me) in excellent diastereo- and enantioselectivity (entries 4 and 6).[8] In all the cases examined, the minor diastereomers were not detected. When *N*-(4-chlorophenylmethylene)alanine ester **6** was used instead of glycine ester **1**, cyclic amino ester **7** having a tetrasubstituted carbon was obtained with excellent diastereo- and enantioselectivity (Scheme 2).[5]

We then turned our attention to the stereoselective synthesis of cyclic amino esters **10** with a different substitution pattern (Table 3).[9] Using racemic branched alkyl bromides **8** (n = 1, R^1 = H, R^2 = Me or Ph) with an acetal moiety, 4-substituted pipecolic acid esters were obtained as an almost 1 : 1 diastereomixture (entries 2 and 3). On the other hand, the reaction of branched alkyl bromide **8d** (n = 1, R^1 = Me, R^2 = Me) with a ketal moiety gave the all-*cis* 4,5-dimethylpipecolic acid ester as a major diastereomer, albeit with low diastereoselectivity (entry 4). In the case of alkyl bromide **8** (n = 1, R^1, R^2 = $(CH_2)_3$ or $(CH_2)_4$) with a 5 or 6-membered ring, further improvement of diastereoselectivity was observed (entries 5 and 6). The



Scheme 2 Synthesis of cyclic amino ester **7**.

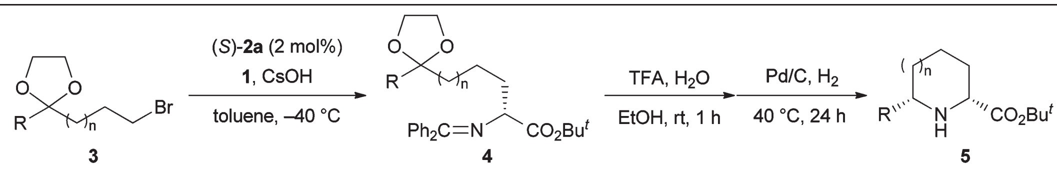
Table 1 Asymmetric alkylation of glycine ester **1** with (*S*)-**2a–c** under phase transfer conditions[a]



Entry	Cat	Conditions (°C, h)	Yield[b] (%)	ee[c] (%)
1	(*S*)-**2a**	−20, 6	46	88
2	(*S*)-**2b**	−20, 6	58	85
3	(*S*)-**2c**	−20, 6	36	39
4	(*S*)-**2a**	−40, 18	31	98
5[d]	(*S*)-**2a**	−40, 20	50	97
6[d,e]	(*S*)-**2a**	−40, 20	79	99
7[d,e,f]	(*S*)-**2a**	−40, 16	85	99

[a] Unless otherwise specified, the reaction was carried out with glycine derivative **1** and 5 equiv. of alkyl bromide **3a** in the presence of 1 mol% of (*S*)-**2a–c**, and 5 equiv. of CsOH under the given reaction conditions. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd). [d] 2.5 equiv. of CsOH. [e] 10 equiv. of **3**. [f] 2 mol% of (*S*)-**2a**.

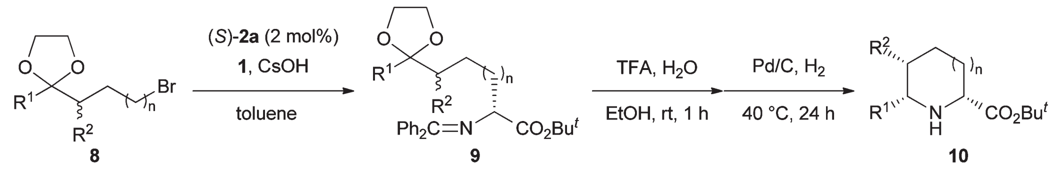
Table 2 Asymmetric alkylation of glycine ester **1** with various alkyl bromides **3** under phase transfer conditions and reductive amination[a]



Entry	**3** (n, R)	Time (h)	Yield of **4**[b] (%)	Yield of **5**[b] (%)	ee[c] (%)
1[d]	**3b** (0, H)	14	78 (**4b**)	71 (**5b**)	90
2	**3c** (0, Me)	12	<5	—	—
3	**3d** (1, H)	16	87 (**4d**)	75 (**5d**)	99
4	**3a** (1, Me)	16	85 (**4a**)	88 (**5a**)	99
5	**3e** (2, H)	16	76 (**4e**)	77 (**5e**)	99
6	**3f** (2, Me)	20	81 (**4f**)	79 (**5f**)	98

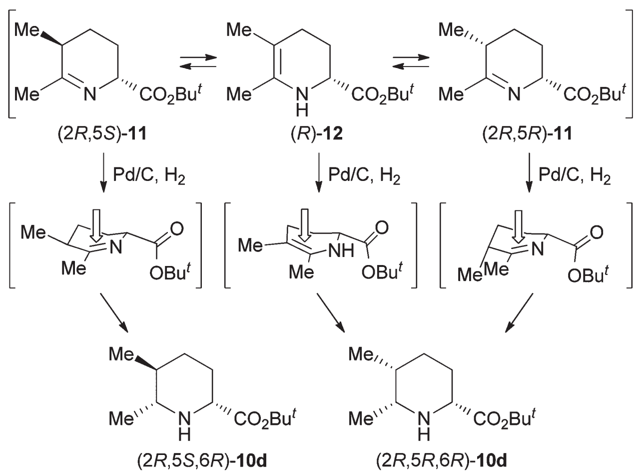
[a] Unless otherwise specified, the reaction was carried out with glycine derivative **1** and 5 equiv. of alkyl bromide **3** in the presence of 2 mol% of (*S*)-**2a**, and 5 equiv. of CsOH under the given reaction conditions. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] Hydrogenation was performed at 45 °C.

Table 3 Asymmetric alkylation of glycine ester **1** with various alkyl bromides **8** under phase transfer conditions and reductive amination[a]

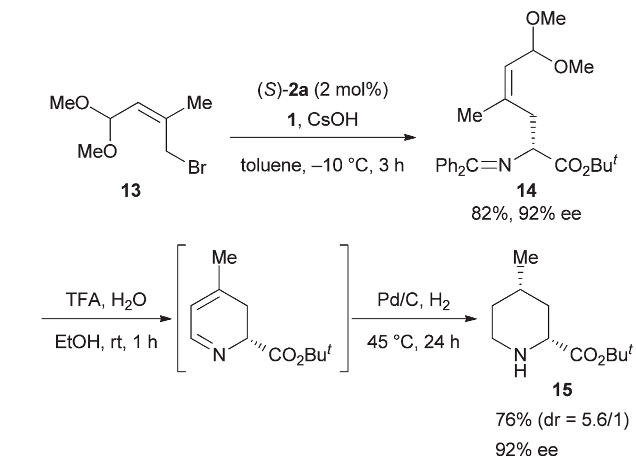


Entry	8 (n, R[1], R[2])	Conditions (°C, h)	Yield of 9[b] (%)	Yield of 10[b] (%)	dr[c]	ee[d] (%)
1[e]	**8a** (0, $(CH_2)_3$)	0, 6	n.d.	—	—	—
2[f]	**8b** (1, H, Me)	−40, 28	73 (**9b**)	75 (**10b**)	1.2/1	98/96
3[f]	**8c** (1, H, Ph)	−30, 16	71 (**9c**)	79 (**10c**)	1.0/1	92/89
4	**8d** (1, Me, Me)	−40, 16	84 (**9d**)	82 (**10d**)	2.5/1	98
5	**8e** (1, $(CH_2)_3$)	−40, 14	87 (**9e**)	82 (**10e**)	13/1	99
6	**8f** (1, $(CH_2)_4$)	−40, 30	71 (**9f**)	72 (**10f**)	6.0/1	99
7[g]	**8g** (2, $(CH_2)_3$)	−40, 20	84 (**9g**)	73 (**10g**)	5.7/1	90

[a] Unless otherwise specified, the reaction was carried out with glycine derivative **1** and 5 equiv. of alkyl bromide **8** in the presence of 2 mol% of (*S*)-**2a**, and 5 equiv. of CsOH under the given reaction conditions. [b] Isolated yield. [c] Determined by ^{1}H-NMR analysis. [d] Determined by HPLC analysis using a chiral column. [e] User of TBAB (20 mol%) instead of (*S*)-**2a**. [f] Hydrogenation was performed at 45 °C. [g] Hydrogenation was performed for 35 h.



Scheme 3 Postulated origins of stereocontrol in the reaction cascade.



Scheme 4 Synthesis of 4-methylpipecolic acid ester **15**.

reaction of alkyl bromide **8g** (n = 2, R[1], R[2] = $(CH_2)_3$) with a longer alkyl chain also gave the all-*cis* isomer as a major diastereomer (entry 7).

In the reaction using racemic branched alkyl bromide **8d** (n = 1, R[1] = Me, R[2] = Me), dimethylpipecolic acid ester (2*R*,5*S*,6*R*)-**10d** was also obtained as a minor diastereomer along with the all-*cis* isomer (2*R*,5*R*,6*R*)-**10d** (Table 3, entry 4 and Scheme 3). Since (2*R*,5*R*,6*R*)-**10d** was obtained in more than 50% yield, imine intermediate (2*R*,5*S*)-**11** would be partially epimerized to (2*R*,5*R*)-**11** *via* the enamine tautomer (*R*)-**12**, giving (2*R*,5*R*,6*R*)-**10d** after reduction of (2*R*,5*R*)-**11** and/or (*R*)-**12**, as shown in Scheme 3. Based on the fact that reduction proceeded through imine (2*R*,5*S*)-**11**, 6-methylpipecolic acid ester **5a** (n = 1, R = Me) seemed to be obtained *via* facile reduction of the corresponding sterically less hindered imine intermediate than (2*R*,5*S*)-**11**.

With the present asymmetric alkylation/reductive amination protocol, stereoselective synthesis of 4-methylpipecolic acid ester **15**[10] has also been realized by using 2-substituted allyl bromide **13**, and the stereochemistry at the 4-position of the piperidine ring was found to be controllable (Scheme 4). Indeed, treatment of the alkylation products with CF_3CO_2H in aqueous EtOH and then the catalytic hydrogenation with Pd on carbon under a H_2 atmosphere produced 4-methylpipecolic acid ester **15** stereoselectively.[5]

Conclusions

In summary, we were successfully able to develop an asymmetric synthesis of piperidine and azepane core structures starting from a readily available glycine ester by combination of phase-transfer catalyzed asymmetric alkylation and subsequent diastereoselective reductive amination.

Experimental

General information

Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane (in the case of $CDCl_3$) as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, br = broad, and app = apparent), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-FX400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using Daicel CHIRALPAK AD-H, AS-H and CHIRALCEL OD-H 4.6 mm × 25 cm columns. The high-resolution mass spectra (HRMS) were performed on an Applied Biosystems Mariner 8295 API-TOF and a Bruker micro-TOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230–400 mesh). Glycine *t*-butyl ester-benzophenoneimine Schiff base **1**,[11] alanine *t*-butyl ester-*p*-chlorobenzaldimine Schiff base **6**,[12] chiral phase transfer catalysts (*S*)-**2a**, (*S*)-**2b** and (*S*)-**2c** were prepared according to the literature procedure.[6b] Alkyl halides **3**,[13–15] **8**[13] and **13**[16] were prepared according to the literature procedure. Cyclic amino esters **5b**,[17] **5d**,[18] **5a**,[8a] **10e**[9] and **10f**[9] are known compounds. Other simple chemicals were purchased and used as such.

General procedure for asymmetric alkylation under phase-transfer conditions

To a mixture of **1** (30 mg, 0.10 mmol), **3a** (209 mg, 1.0 mmol) and (*S*)-**2a** (1.5 mg, 0.002 mmol) in toluene (1 mL) was added CsOH (42 mg, 0.25 mmol) at −40 °C, and the reaction mixture was vigorously stirred for 16 h. After the consumption of the starting material, the mixture was diluted with H_2O and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as an eluent) to afford **4a** (36 mg, 0.085 mmol, 85% yield) as an oil. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 6.3 min (major) and 10.0 min (minor)). $[\alpha]_D^{25}$ = 81.1 (*c* 1.0, $CHCl_3$, 99% ee); ^{1}H NMR δ 7.66–7.63 (2H, m), 7.45–7.29 (6H, m), 7.19–7.17 (2H, m), 3.93–3.84 (5H, m), 1.93–1.87 (2H, m), 1.60–1.55 (2H, m), 1.44 (9H, s), 1.40–1.30 (2H, m), 1.27 (3H, s); ^{13}C NMR δ 171.5, 169.9, 139.7, 136.7, 130.1, 128.8, 128.5, 128.4, 127.94, 127.88, 111.0, 80.8, 66.0, 64.6, 38.9, 33.8, 28.1, 23.8, 20.6; IR (neat) 2951, 1732, 1622, 1447, 1368, 1148, 1069 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{26}H_{34}NO_4$: 424.2482 ($[M + H]^+$), Found: 424.2491 ($[M + H]^+$).

(*R*)-*tert*-Butyl 4-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)butanoate (4b). Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 9.7 min (major) and 12.9 min (minor); $[\alpha]_D^{21}$ = 74.3 (*c* 1.0, $CHCl_3$, 90% ee); ^{1}H NMR δ 7.66–7.63 (2H, m), 7.46–7.28 (6H, m), 7.19–7.17 (2H, m), 4.82 (1H, t, *J* = 4.8 Hz), 3.97–3.87 (3H, m), 3.84–3.75 (2H, m), 2.07–1.98 (2H, m), 1.76–1.67 (1H, m), 1.63–1.55 (1H, m), 1.44 (9H, s); ^{13}C NMR δ 171.1, 170.1, 139.6, 136.6, 130.1, 128.7, 128.4, 128.3, 127.9, 127.8, 104.2, 80.8, 65.5, 64.8, 64.7, 30.4, 28.02, 27.98; IR (neat) 2976, 2355, 1732, 1368, 1146 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{24}H_{30}NO_4$: 396.2169 ($[M + H]^+$), Found: 396.2181 ($[M + H]^+$).

(*R*)-*tert*-Butyl 5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)pentanoate (4d). Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 7.7 min (major) and 9.9 min (minor); $[\alpha]_D^{23}$ = 20.1 (*c* 1.0, $CHCl_3$, 99% ee); ^{1}H NMR δ 7.66–7.63 (2H, m), 7.46–7.29 (6H, m), 7.20–7.15 (2H, m), 4.81 (1H, t, *J* = 4.8 Hz), 3.96–3.88 (3H, m), 3.85–3.77 (2H, m), 1.97–1.91 (2H, m), 1.63–1.58 (2H, m), 1.44 (9H, s), 1.42–1.26 (2H, m); ^{13}C NMR δ 171.4, 170.0, 139.7, 136.7, 130.1, 128.7, 128.43, 128.36, 127.9, 127.8, 104.4, 80.8, 65.9, 64.8, 33.7, 33.5, 28.0, 20.6; IR (neat) 2949, 1732, 1622, 1368, 1146 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{25}H_{32}NO_4$: 410.2326 ($[M + H]^+$), Found: 410.2334 ($[M + H]^+$).

(*R*)-*tert*-Butyl 6-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)hexanoate (4e). Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 8.1 min (major) and 10.8 min (minor); $[\alpha]_D^{28}$ = 7.4 (*c* 1.0, $CHCl_3$, 99% ee); ^{1}H NMR δ 7.66–7.63 (2H, m), 7.46–7.29 (6H, m), 7.18–7.16 (2H, m), 4.80 (1H, t, *J* = 4.8 Hz), 3.97–3.88 (3H, m), 3.85–3.77 (2H, m), 1.92–1.87 (2H, m), 1.65–1.60 (2H, m), 1.44 (9H, s), 1.41–1.20 (4H, m); ^{13}C NMR δ 171.4, 169.8, 139.7, 136.7, 130.0, 128.7, 128.4, 128.3, 127.9, 127.8, 104.4, 80.7, 65.9, 64.7, 33.7, 33.5, 28.0, 25.9, 23.8; IR (neat) 2976, 1732, 1622, 1144, 1030 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{26}H_{34}NO_4$: 424.2482 ($[M + H]^+$), Found: 424.2488 ($[M + H]^+$).

(*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-6-(2-methyl-1,3-dioxolan-2-yl)hexanoate (4f). Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 12.0 min (major) and 15.7 min (minor). $[\alpha]_D^{20}$ = 83.6 (*c* 0.5, $CHCl_3$, 98% ee); ^{1}H NMR δ 7.65–7.63 (2H, m), 7.56–7.30 (6H, m), 7.18–7.15 (2H, m), 3.94–3.85 (5H, m), 1.88 (2H, q, *J* = 7.6 Hz), 1.61–1.57 (2H, m), 1.44 (9H, s), 1.37–1.20 (7H, m); ^{13}C NMR δ 171.6, 169.8, 136.8, 135.3, 130.1, 128.8, 128.42, 128.37, 128.0, 127.9, 110.0, 80.8, 66.0, 64.6, 39.1, 34.7, 33.6, 28.1, 26.3, 23.9, 23.7; IR (neat) 2978, 2359, 1732, 1622, 1368, 1152 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{27}H_{36}NO_4$: 438.2639 ($[M + H]^+$), Found: 438.2646 ($[M + H]^+$).

General procedure for diastereoselective reductive amination

To a mixture of **4a** (67 mg, 0.16 mmol), EtOH (3 mL) and H_2O (1.5 mL) was added TFA (36 μL, 0.48 mmol). After stirring for 1 h, to the mixture was added 10% Pd/C (34 mg) and the mixture was stirred at 40 °C for 24 h under a hydrogen atmosphere. After filtration through celite, the filtrate was basified with aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and purified by chromatography on silica gel (dichloromethane/methanol = 50/1 as an eluent) to afford **5a** (28 mg, 0.14 mmol, 88% yield) as an oil. $[\alpha]_D^{21}$ = 7.1 (*c* 0.7, $CHCl_3$, 99% ee); ^{1}H NMR δ 3.22 (1H, dd, *J* = 11.5, 2.7 Hz), 2.64 (1H, dqd, *J* = 11.0, 6.4, 2.7 Hz), 1.99–1.94 (1H, m), 1.89–1.83 (1H, m), 1.77 (1H, br), 1.62–1.57 (1H, m), 1.46 (9H, s), 1.44–1.25 (2H, m), 1.12 (3H, d, *J* = 6.4 Hz), 1.08–0.98 (1H, m); ^{13}C NMR δ 172.6, 80.8, 59.8, 51.8, 33.8, 29.0, 28.0, 24.6, 22.8; IR (neat) 2357, 2930, 2357, 1730, 1368, 1153 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{11}H_{22}NO_2$: 200.1645 ([M + H]$^+$), Found: 200.1644 ([M + H]$^+$).

(*R*)-*tert*-Butyl azepane-2-carboxylate (5e). $[\alpha]_D^{23}$ = −6.3 (*c* 1.2, $CHCl_3$, 99% ee); ^{1}H NMR δ 3.42 (1H, dd, *J* = 8.8, 5.2 Hz), 3.10–3.04 (1H, m), 2.75–2.68 (1H, m), 2.57 (1H, br), 2.09–2.02 (1H, m), 1.76–1.54 (7H, m), 1.46 (9H, s); ^{13}C NMR δ 172.0, 82.1, 59.9, 45.8, 31.3, 29.5, 28.0, 27.4, 25.0; IR (neat) 2928, 1728, 1368, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{11}H_{22}NO_2$: 200.1645 ([M + H]$^+$), Found: 200.1648 ([M + H]$^+$).

(2*R*,7*R*)-*tert*-Butyl 7-methylazepane-2-carboxylate (5f). $[\alpha]_D^{22}$ = 15.0 (*c* 0.5, $CHCl_3$, 98% ee); ^{1}H NMR δ 3.39 (1H, dd, *J* = 9.8, 5.1 Hz), 2.79–2.71 (1H, m), 2.07–1.98 (1H, m), 1.88 (1H, br), 1.61–1.76 (5H, m), 1.46 (9H, s), 1.44–1.40 (1H, m), 1.34–1.26 (1H, m), 1.12 (3H, d, *J* = 6.6 Hz); ^{13}C NMR δ 174.1, 80.9, 61.0, 54.5, 39.6, 33.6, 28.0, 25.3, 25.0, 23.9; IR (neat) 2926, 2359, 1726, 1368, 1157 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{12}H_{24}NO_2$: 214.1802 ([M + H]$^+$), Found: 214.1799 ([M + H]$^+$).

(2*R*,6*R*)-*tert*-Butyl 2,6-dimethylpiperidine-2-carboxylate (7). To a mixture of **6** (161 mg, 0.60 mmol), **3a** (1.25 g, 6.0 mmol) and (*S*)-**2a** (9 mg, 0.012 mmol) in toluene (6 mL) was added CsOH (280 mg, 1.5 mmol) at −20 °C, and the reaction mixture was vigorously stirred for 20 h. After the consumption of the starting material, the mixture was concentrated under reduced pressure, and to the residue were added EtOH (3 mL), H_2O (3 mL), and TFA (245 μL, 3.3 mmol). After stirring for 1 h, to the mixture was added 10% Pd/C (80 mg) and the mixture was stirred at 40 °C for 36 h under a hydrogen atmosphere. After filtration through celite, the result solution was basified with aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and purified by chromatography on silica gel (dichloromethane/methanol = 30/1 as an eluent) to afford **7** (79 mg, 0.37 mmol, 61% yield) as an oil. $[\alpha]_D^{21}$ = 18.3 (*c* 1.0, $CHCl_3$, 96% ee); ^{1}H NMR δ 2.91–2.86 (1H, m), 1.73–1.49 (6H, m), 1.46 (9H, s), 1.35 (3H, s), 1.07 (3H, d, *J* = 6.4 Hz), 1.02–0.91 (1H, m); ^{13}C NMR δ 175.7, 80.4, 58.1, 45.5, 34.0, 32.8, 27.8, 22.9, 20.6, 20.1; IR (neat) 2932, 1724, 1454, 1368, 1284, 1145 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{12}H_{24}NO_2$: 214.1802 ([M + H]$^+$), Found: 214.1794 ([M + H]$^+$).

Determination of the enantiomeric excess of (*R*)-*tert*-butyl 2-amino-2-methyl-5-(2-methyl-1,3-dioxolan-2-yl)pentanoate

To a mixture of **6** (54 mg, 0.20 mmol), **3a** (418 mg, 2.0 mmol) and (*S*)-**2a** (3 mg, 0.004 mmol) in toluene (2 mL) was added CsOH (93 mg, 0.50 mmol) at −20 °C, and the reaction mixture was vigorously stirred for 24 h. After the consumption of the starting material, the mixture was concentrated under reduced pressure, and to the residue were added MeOH (1 mL), H_2O (1 mL), and TFA (53 μL, 0.7 mmol). After stirring for 0.5 h, the solution was basified with aqueous $NaHCO_3$, extracted with dichloromethane, dried over Na_2SO_4 and concentrated. To a solution of the residue and triethylamine (56 μL, 0.40 mmol) in dichloromethane (2 mL) was added benzoyl chloride (34 μL, 0.24 mmol) at 0 °C. After stirring for 3 h at 0 °C, the mixture was quenched with H_2O and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and purified by chromatography on silica gel (hexane/ethylacetate = 5/1 as an eluent) to afford the *N*-benzoylated derivative of the title compound (41 mg, 0.11 mmol, 51% yield) as an oil. $[\alpha]_D^{19}$ = −12.6 (*c* 0.9, $CHCl_3$, 96% ee); ^{1}H NMR δ 7.81–7.78 (2H, m), 7.51–7.41 (3H, m), 3.92–3.83 (4H, m), 2.60–2.52 (1H, m), 1.86–1.78 (1H, m), 1.71 (3H, s), 1.69–1.55 (2H, m), 1.51 (9H, s), 1.48–1.38 (2H, m), 1.26 (3H, s); ^{13}C NMR δ 174.2, 166.0, 135.2, 131.3, 128.5, 126.8, 109.8, 82.3, 64.6, 64.5, 61.2, 38.8, 36.0, 27.9, 23.7, 23.4, 19.1; IR (neat) 3408, 2980, 1728, 1663, 1152 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{21}H_{32}NO_5$: 378.2275 ([M + H]$^+$), Found: 378.2271 ([M + H]$^+$).

(*R*)-*tert*-Butyl 5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)hexanoate (9b). $[\alpha]_D^{23}$ = 82.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 7.66–7.63 (2H, m), 7.46–7.30 (6H, m), 7.19–7.16 (2H, m), 4.65 (1H, d, *J* = 5.0 Hz), 3.95–3.87 (3H, m), 3.86–3.78 (2H, m), 2.04–1.85 (2H, m), 1.60–1.67 (2H, m), 1.44 (9H, s), 1.22–1.13 (1H, m), 0.91 (3H, d, *J* = 6.8 Hz); ^{13}C NMR δ 171.5, 170.0, 139.7, 136.8, 130.1, 128.8, 128.42, 128.35, 127.94, 127.87, 107.5, 80.8, 66.2, 64.97, 64.95, 36.8, 31.3, 28.0, 27.9, 13.7; IR (neat) 2974, 1732, 1622, 1447, 1368, 1150 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{26}H_{34}NO_4$: 424.2482 ([M + H]$^+$), Found: 424.2469 ([M + H]$^+$).

Diastereo-mixture of (*R*)-*tert*-butyl 5-methylpiperidine-2-carboxylate (10b). (2*R*,5*R*)/(2*R*,5*S*) = 1.2/1. ^{1}H NMR δ 3.45–3.42 (0.55H, m), 3.11 (0.45H, dd, *J* = 11.6, 2.8 Hz), 3.08–3.04 (0.45H, m), 2.80 (0.55H, dd, *J* = 11.6, 3.6 Hz), 2.52 (0.55H, dd, *J* = 11.6, 9.2 Hz), 2.30 (1H, br), 2.22 (0.45H, app t), 2.04–1.96 (1H, m), 1.86–1.62 (3H, m), 1.48 (4.95H, s), 1.46 (4.05H, s), 1.15–1.01 (1H, m), 0.88 (1.65H, d, *J* = 6.4 Hz), 0.82 (1.35H, d, *J* = 6.8 Hz); ^{13}C NMR δ 173.2, 172.6, 80.7, 63.4, 59.2, 56.5, 53.5, 50.3, 33.2, 31.5, 30.1, 30.0, 29.7, 28.0, 27.9, 26.0, 19.2, 18.8; IR (neat) 2930, 1728, 1456, 1368, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{11}H_{22}NO_2$: 200.1645 ([M + H]$^+$), Found: 200.1654 ([M + H]$^+$).

Determination of the enantiomeric excess of (*R*)-*tert*-butyl 5-methylpiperidine-2-carboxylate (10b). The enantiomeric excess of **10b** was determined by HPLC analysis after conversion to the corresponding benzamide. (2*R*,5*R*)/(2*R*,5*S*) = 1.2 (98% ee)/1(96% ee). Daicel Chiralpak OD-H, hexane/2-propanol = 200/1, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: (2*R*,5*R*: 56.2 min (major) and 102.7 min (minor)), (2*R*,5*S*: 62.5 min (major) and 78.9 min (minor)); ^{1}H NMR (toluene-d$_8$, 80 °C) δ 7.48–7.46 (2H, m), 7.15–7.05 (3H, m), 5.07 (0.45H, br), 3.60 (0.55H, br), 3.35 (0.45H, d, *J* = 13.2 Hz), 2.85 (0.55H, br), 2.22–2.17 (1.55H, m), 2.01–1.98 (0.45H, m), 1.83–1.80 (0.55H, m), 1.69–1.48 (2.45H, m), 1.43 (4.05H, s), 1.41 (4.95H, s), 1.24–1.21 (0.45H, m), 1.14–1.04 (0.55H, m), 0.87 (1.35H, d, J = 6.8 Hz), 0.65 (1.65H, br); ^{13}C NMR δ 174.6, 173.6, 173.2, 173.1, 140.40, 140.35, 132.3, 132.1, 131.3, 130.4, 130.3, 130.0, 84.2, 83.8, 61.2, 55.4, 55.2, 49.7, 34.5, 33.7, 33.2, 30.8, 30.3, 29.9, 24.4, 22.2, 21.8, 19.2; IR (neat) 2930, 1728, 1638, 1420, 1225, 1142 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{18}H_{26}NO_3$: 304.1907 ([M + H]$^+$), Found: 304.1915 ([M + H]$^+$).

(*R*)-*tert*-Butyl 5-(1,3-dioxolan-2-yl)-2-(diphenylmethylene-amino)-5-phenylpentanoate (9c). $[\alpha]_D^{24}$ = 41.5 (c 1.3, $CHCl_3$); ^{1}H NMR δ 7.64–7.61 (2H, m), 7.43–7.10 (13H, m), 4.96 (0.5H, d, J = 4.8 Hz), 4.94 (0.5H, d, J = 4.4 Hz), 3.88–3.87 (1H, m), 3.80–3.74 (4H, m), 2.80–2.76 (1H, m), 1.89–1.70 (4H, m), 1.41 (4.5H, s), 1.39 (4.5H, s); ^{13}C NMR δ 171.4, 171.2, 169.8, 169.7, 140.0, 139.9, 139.74, 139.69, 136.69, 136.65, 130.08, 130.06, 128.9, 128.78, 128.75, 128.44, 128.41, 128.38, 128.36, 128.3, 128.20, 128.17, 128.0, 127.93, 127.87, 127.85, 126.7, 126.6, 111.6, 106.8, 80.8, 80.7, 66.2, 65.9, 65.10, 65.07, 65.0, 49.9, 49.7, 33.9, 31.5, 28.02, 28.01, 26.3, 26.2, 20.9; IR (neat) 2976, 1732, 1368, 1146 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{31}H_{36}NO_4$: 486.2639 ([M + H]$^+$), Found: 486.1632 ([M + H]$^+$).

(2*R*,5*S*)-*tert*-Butyl 5-phenylpiperidine-2-carboxylate ((2*R*,5*S*)-10c). Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 25.1 min (major) and 28.9 min (minor); $[\alpha]_D^{25}$ = 1.0 (c 0.4, $CHCl_3$, 92% ee); ^{1}H NMR δ 7.31–7.27 (2H, m), 7.21–7.18 (3H, m), 3.58 (1H, dd, J = 5.2, 3.2 Hz), 3.01–2.92 (2H, m), 2.80–2.73 (1H, m), 2.28–2.23 (1H, m), 1.93–1.81 (3H, m), 1.52 (9H, m), 1.48–1.41 (1H, m); ^{13}C NMR δ 173.4, 144.6, 128.4, 127.2, 126.3, 81.0, 55.9, 49.6, 42.5, 28.8, 28.2, 26.8; IR (neat) 2932, 1724, 1368, 1150 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{16}H_{24}NO_2$: 262.1802 ([M + H]$^+$), Found: 262.1794 ([M + H]$^+$).

(2*R*,5*R*)-*tert*-Butyl 5-phenylpiperidine-2-carboxylate ((2*R*,5*R*)-10c). Daicel Chiralpak AS-H, hexane/2-propanol = 50/1, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 18.2 min (major) and 20.2 min (minor); $[\alpha]_D^{22}$ = −6.3 (c 0.8, $CHCl_3$, 89% ee); ^{1}H NMR δ 7.32–7.28 (2H, m), 7.22–7.19 (3H, m), 3.30–3.25 (2H, m), 2.74–2.63 (2H, m), 2.17–2.06 (3H, m), 1.75–1.54 (2H, m), 1.48 (9H, s); ^{13}C NMR δ 172.4, 144.1, 128.4, 127.0, 126.4, 81.0, 59.2, 53.0, 43.4, 31.6, 29.9, 28.0; IR (neat) 2932, 1730, 1368, 1153 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{16}H_{24}NO_2$: 262.1802 ([M + H]$^+$), Found: 262.1799 ([M + H]$^+$).

Diastereo-mixture of (2*R*)-*tert*-butyl 2-(diphenylmethylene-amino)-5-(2-methyl-1,3-dioxolan-2-yl)hexanoate (9d). (2*R*,5*R*)/(2*R*,5*S*) = 1/1. ^{1}H NMR δ 7.16–7.19 (2H, m) 7.65–7.63 (2H, m), 7.46–7.30 (6H, m), 3.93–3.79 (5H, m), 2.10–1.97 (1H, m), 1.88–1.69 (1H, m), 1.65–1.51 (2H, m), 1.45 (4.5H, s), 1.44 (4.5H, s), 1.19 (3H, s), 1.11–0.99 (1H, m), 0.93 (1.5H, d, J = 7.1 Hz), 0.91 (1.5H, d, J = 6.8 Hz); ^{13}C NMR δ 14.5, 14.6, 20.2, 20.3, 28.06, 28.12, 31.4, 31.8, 32.0, 32.1, 41.3, 41.4, 47.5, 47.6, 48.8, 48.9, 64.49, 65.54, 66.3, 66.6, 80.76, 80.81, 112.29, 112.34, 127.89, 127.90, 127.94, 128.35, 128.37, 128.43, 128.77, 128.82, 129.9, 130.1, 136.78, 136.82, 139.80, 139.83, 169.7, 169.9, 171.5, 171.6, 171.5, 169.9, 169.7, 139.83, 139.80, 136.82, 136.78, 130.1, 129.9, 128.82, 128.77, 128.43, 128.37, 128.35, 127.94, 127.90, 127.89, 112.34, 112.29, 80.81, 80.76, 66.6, 66.3, 65.54, 64.49, 48.9, 48.8, 47.6, 47.5, 41.4, 41.3, 32.1, 32.0, 31.8, 31.4, 28.12, 28.06, 20.3, 20.2, 14.6, 14.5; IR (neat) 2976, 1732, 1368, 1150 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{27}H_{36}NO_4$: 438.2639 ([M + H]$^+$), Found: 438.2622 ([M + H]$^+$).

Diastereo-mixture of (2*R*,6*R*)-*tert*-butyl 5,6-dimethyl-piperidine-2-carboxylate (10d). (2*R*,5*R*,6*R*)/(2*R*,5*S*,6*R*) = 2.5/1. ^{1}H NMR (toluene-d$_8$, 80 °C) δ 3.26–3.21 (1H, m), 2.85 (0.71H, dq, J = 2.9, 6.6 Hz), 2.24 (0.29H, dq, J = 8.8, 6.4 Hz), 2.00–1.95 (0.29H, m), 1.81–1.78 (0.29H, m), 1.71–1.47 (5.42H, m), 1.46 (9H, s), 1.11 (0.86H, d, J = 6.4 Hz), 1.03 (2.14H, d, J = 6.6 Hz), 0.89 (2.14H, d, J = 7.1 Hz), 0.85 (0.86H, d, J = 6.1 Hz); ^{13}C NMR δ (2*R*,5*R*,6*R*/2*R*,5*S*,6*R*) 172.9/172.6, 80.7/80.6, 60.2/59.7, 57.9/53.6, 33.8/37.7, 31.5/32.0, 28.01/28.00, 23.6/29.9, 20.0/20.3, 10.9/18.4; IR (neat) 1730, 1368, 1233, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{12}H_{24}NO_2$: 214.1802 ([M + H]$^+$), Found: 214.1807 ([M + H]$^+$).

Determination of the enantiomeric excess of 10d

The enantiomeric excess of **10d** was determined by HPLC analysis after conversion to the corresponding benzamide. (2*R*,5*R*,6*R*)/(2*R*,5*S*,6*R*) = 2.5 (99% ee)/1(99% ee). Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: (2*R*,5*S*,6*R*: 9.8 min (minor), 10.9 min (major)), (2*R*,5*R*,6*R*: 12.1 min (major), 20.7 min (minor)). ^{1}H NMR (toluene-d$_8$, 80 °C) δ 7.19–7.13 (2H, m), 6.90–6.82 (3H, m), 4.69–3.76 (2H, m), 1.96 (0.71H, d, J = 13.2 Hz), 1.88–1.85 (0.71H, m), 1.80–1.74 (0.29H, m), 0.81 (2.14H, d, J = 7.1 Hz), 1.64–1.55 (0.29H, m), 1.49–1.09 (11H, m), 0.95 (0.86H, d, J = 7.6 Hz), 0.93 (0.71H, m), 0.79–0.77 (0.29H, m), 0.61 (0.86H, d, J = 7.1 Hz), 0.38 (2.14H, d, J = 6.6 Hz); ^{13}C NMR δ (2*R*,5*R*,6*R*/2*R*,5*S*,6*R*) 174.8/175.5, 174.1/174.4, 141.4/141.5, 140.4/140.7, 131.2/131.9, 130.0/129.9, 84.0/83.8, 56.9/55.4, 56.1/55.1, 37.8/37.7, 36.17/36.15, 30.9/29.3, 27.3/26.1, 21.5/21.4, 15.6/23.1; IR (neat) 2976, 2361, 1726, 1641, 1412, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{19}H_{28}NO_3$: 318.2064 ([M + H]$^+$), Found: 318.2048 ([M + H]$^+$).

6-(2-Bromoethyl)-1,4-dioxaspiro[4.4]nonane (8e). The title compound was prepared by a similar method described in the literature.[4] ^{1}H NMR δ 3.95–3.87 (4H, m), 3.52–3.42 (1H, m), 3.40–3.35 (1H, m), 2.12–2.05 (2H, m), 1.95–1.91 (1H, m), 1.84–1.63 (5H, m), 1.36–1.31 (1H, m); ^{13}C NMR δ 117.8, 64.5, 64.4, 44.6, 35.5, 32.8, 32.6, 28.9, 20.6; IR (neat) 2876, 2957, 2876, 1738, 1315, 1260, 1206, 1139, 1026 cm^{-1}.

Diastereo-mixture of (2*R*)-*tert*-butyl 2-(diphenylmethylene-amino)-4-(1,4-dioxaspiro[4.4]nonan-6-yl) butanoate (9e). $[\alpha]_D^{24}$ = 91.6 (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.65–7.63 (2H, m), 7.44–7.29 (6H, m), 7.19–7.17 (2H, m), 3.91–3.81 (5H, m), 1.94–1.81 (4H, m), 1.74–1.57 (4H, m), 1.44 (9H, s), 1.42–1.21 (3H, m); ^{13}C NMR δ 171.6, 169.8, 139.8, 136.8, 130.1, 128.8, 128.4, 128.3, 127.9, 118.2, 80.7, 66.3, 64.6, 64.4, 46.0, 35.8, 32.5, 31.6, 29.4, 28.1, 25.4, 20.6; IR (neat) 2953, 1732, 1148, 1030 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{28}H_{36}NO_4$: 450.2639 ([M + H]$^+$), Found: 450.2619 ([M + H]$^+$).

Determination of the enantiomeric excess of 10e

The enantiomeric excess of **10e** was determined by HPLC analysis after conversion to the corresponding benzamide.

Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 16.4 min (major) and 22.3 min (minor). $[\alpha]_D^{20}$ = 41.6 (*c* 0.7, $CHCl_3$, 99% ee); ^{1}H NMR (toluene-d_8, 80 °C) δ 7.15–7.13 (2H, m), 6.89–6.86 (3H, m), 4.68 (1H, br), 4.04 (1H, br), 1.88–1.84 (1H, m), 1.73–1.65 (2H, m), 1.57–1.51 (1H, m), 1.27 (3H, br), 1.12 (9H, s), 1.06–0.92 (4H, m); ^{13}C NMR δ 174.6, 174.4, 141.6, 140.4, 131.2, 129.9, 83.8, 60.2, 57.2, 39.6, 33.1, 31.8, 30.9, 28.1, 27.7, 24.4; IR (neat) 1726, 2972, 1726, 1603, 1414, 1368, 1153 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{20}H_{28}NO_3$: 330.2064 ([M + H]$^+$), Found: 330.2069 ([M + H]$^+$).

6-(2-Bromoethyl)-1,4-dioxaspiro[4.5]decane (8f). The title compound was prepared by a similar method described in the literature.[4] ^{1}H NMR δ 3.99–3.91 (4H, m), 3.55–3.49 (1H, m), 3.45–3.38 (1H, m), 2.28–2.15 (1H, m), 1.81–1.76 (3H, m), 1.72–1.59 (3H, m), 1.49–1.43 (1H, m), 1.39–1.25 (3H, m); ^{13}C NMR δ 110.4, 64.7, 64.5, 43.2, 34.5, 32.9, 32.3, 29.1, 24.5, 23.6; IR (neat) 2978, 3335, 2978, 1713, 1524, 1221, 1117 cm^{-1}.

Diastereo-mixture of (2*R*)-*tert*-butyl 2-(diphenylmethyleneamino)-4-(1,4-dioxaspiro[4.5]decan-6-yl) butanoate (9f). (2*R*,4*R*)/(2*R*,4*S*) = 1/1. $[\alpha]_D^{22}$ = 87.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.66–7.63 (2H, m), 7.44–7.29 (6H, m), 7.20–7.16 (2H, m), 3.93–3.81 (5H, m), 2.00–1.97 (1H, m), 1.81–1.65 (3H, m), 1.62–1.59 (2H, m), 1.50–1.47 (1H, m), 1.45 (4.5H, s), 1.44 (4.5H, s), 1.44–1.41 (2H, m), 1.34–1.18 (4H, m); ^{13}C NMR δ 171.7, 171.6, 169.8, 169.5, 139.9, 139.8, 136.9, 136.8, 130.03, 130.01, 128.77, 128.75, 128.42, 128.36, 128.28, 128.26, 128.0, 127.93, 127.91, 127.98, 110.83, 110.80, 82.0, 80.7, 66.7, 66.3, 64.8, 64.7, 64.64, 64.61, 44.43, 44.39, 34.9, 34.8, 31.9, 31.8, 29.2, 29.0, 28.1, 24.7, 24.6, 24.52, 24.49, 23.9, 23.8, 21.8; IR (neat) 2932, 1732, 1368, 1150 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{29}H_{38}NO_4$: 464.2795 ([M + H]$^+$), Found: 464.2785 ([M + H]$^+$).

Determination of the enantiomeric excess of 10f

The enantiomeric excess of **10f** was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 13.6 min (major) and 16.5 min (minor). $[\alpha]_D^{19}$ = 67.1 (*c* 1.0, $CHCl_3$, 99% ee); ^{1}H NMR (toluene-d_8, 80 °C) δ 7.59–7.57 (1H, m), 7.30–7.23 (3H, m), 7.17–7.15 (1H, m), 5.05 (1H, br), 4.45 (1H, br), 2.46 (1H, d, *J* = 12.4 Hz), 2.28–2.27 (1H, m), 2.12–2.01 (2H, m), 1.88–1.73 (3H, m), 1.67–1.54 (2H, m), 1.51 (9H, s), 1.33–1.23 (4H, m); ^{13}C NMR δ 174.2, 174.1, 141.4, 140.4, 131.2, 129.9, 83.9, 58.0, 55.9, 39.3, 38.0, 35.8, 34.9, 30.9, 30.1, 29.3, 24.7; IR (neat) 2930, 1724, 1638, 1411, 1368, 1325, 1153 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{21}H_{29}NNaO_3$: 366.2040 ([M + H]$^+$), Found: 366.2033 ([M + H]$^+$).

6-(3-Bromopropyl)-1,4-dioxaspiro[4.4]nonane (8g). The title compound was prepared by a similar method described in the literature.[1] ^{1}H NMR δ 3.94–3.86 (4H, m), 3.45–3.36 (2H, m), 1.95–1.82 (4H, m), 1.80–1.54 (5H, m), 1.40–1.30 (2H, m); ^{13}C NMR δ 118.0, 64.5, 64.4, 45.4, 35.7, 34.1, 31.6, 29.5, 27.7, 20.6; IR (neat) 2876, 2953, 2876, 1450, 1209, 1142, 1110, 1028 cm^{-1}.

(*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-5-(1,4-dioxaspiro[4.4]nonan-6-yl)pentanoate (9g). $[\alpha]_D^{23}$ = 70.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.65–7.63 (2H, m), 7.46–7.29 (6H, m), 7.18–7.16 (2H, m), 3.92–3.79 (5H, m), 1.94–1.80 (4H, m), 1.74–1.58 (4H, m), 1.44 (9H, s), 1.42–1.40 (1H, m), 1.30–1.15 (4H, m); ^{13}C NMR δ 171.57, 171.56, 169.68, 169.66, 139.73, 139.71, 136.78, 136.75, 130.1, 130.0, 128.7, 128.37, 128.35, 128.32, 127.90, 127.85, 127.83, 127.82, 118.17, 118.15, 80.8, 66.1, 66.0, 64.52, 64.47, 64.4, 46.04, 45.96, 35.7, 34.0, 33.9, 29.4, 29.3, 28.7, 28.5, 28.0, 24.71, 24.67, 20.6; IR (neat) 2947, 1732, 1622, 1368, 1287, 1150 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{29}H_{38}NO_4$: 464.2795 ([M + H]$^+$), Found: 464.2796 ([M + H]$^+$).

(2*R*,5*aR*,8*aR*)-*tert*-Butyl decahydrocyclopenta[*b*]azepine-2-carboxylate (10g). $[\alpha]_D^{23}$ = −6.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 3.59 (1H, app t), 2.75–2.70 (1H, m), 2.44–2.42 (1H, m), 2.04–1.51 (11H, m), 1.45 (9H, s), 1.26–1.15 (1H, m), 1.12–1.02 (1H, m); ^{13}C NMR δ 174.3, 80.9, 63.2, 60.5, 50.2, 34.3, 33.2, 32.6, 32.4, 28.0, 23.7, 21.6; IR (neat) 2930, 1724, 1368, 1225, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{14}H_{26}NO_2$: 240.1952 ([M + H]$^+$), Found: 240.1958 ([M + H]$^+$).

Determination of the enantiomeric excess of (2*R*,5*aR*,8*aR*)-*tert*-butyl decahydrocyclopenta[*b*]azepine-2-carboxylate (10g). The enantiomeric excess of **10g** was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 13.8 min (minor) and 16.8 min (major); $[\alpha]_D^{23}$ = −5.6 (*c* 1.1, $CHCl_3$, 90% ee); ^{1}H NMR (toluene-d_8, 80 °C) δ 7.51–7.48 (2H, m), 7.19–7.12 (2H, m), 7.08–7.06 (1H, m), 5.04 (1H, br), 4.06–3.99 (1H, m), 2.79 (1H, br), 2.30–1.92 (3H, m), 1.85–1.81 (1H, m), 1.76–1.42 (6H, m), 1.42 (9H, s), 1.29–1.09 (2H, m); ^{13}C NMR δ 175.0, 174.1, 142.1, 140.4, 132.1, 130.0, 84.0, 69.2, 64.1, 46.3, 36.6, 35.5, 35.3, 35.2, 31.0, 27.5, 24.4; IR (neat) 2930, 1728, 1639, 1404, 1327, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{21}H_{30}NO_3$: 344.2220 ([M + H]$^+$), Found: 344.2211 ([M + H]$^+$).

(*R*,*Z*)-*tert*-Butyl 2-(diphenylmethyleneamino)-6,6-dimethoxy-4-methylhex-4-enoate (14). Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 17.2 min (minor) and 23.4 min (major). $[\alpha]_D^{19}$ = 82.2 (*c* 0.9, $CHCl_3$; 92% ee); ^{1}H NMR δ 7.65–7.62 (2H, m), 7.46–7.28 (6H, m), 7.18–7.14 (2H, m), 5.30 (1H, dd, *J* = 6.4, 0.8 Hz), 4.95 (1H, d, *J* = 6.4 Hz), 4.07 (1H, dd, *J* = 8.3, 5.1 Hz), 3.26 (3H, s), 3.15 (3H, s), 2.68–2.56 (2H, m), 1.52 (3H, d, *J* = 1.2 Hz), 1.45 (9H, s); ^{13}C NMR δ 171.0, 170.0, 139.6, 138.1, 136.4, 130.1, 128.8, 128.5, 128.3, 127.94, 127.91, 124.9, 100.1, 81.2, 64.7, 52.6, 51.5, 43.4, 28.0, 17.1; IR (neat) 2367, 1734, 1150, 1053 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{26}H_{34}NO_4$: 424.2482 ([M + H]$^+$), Found: 424.2465 ([M + H]$^+$).

(2*R*,4*S*)-*tert*-Butyl 4-methylpiperidine-2-carboxylate (15). $[\alpha]_D^{21}$ = 8.8 (*c* 0.4, $CHCl_3$; 92% ee); ^{1}H NMR δ 3.18 (1H, dd, *J* = 11.7, 2.7 Hz), 3.16–3.11 (1H, m), 2.60 (1H, td, *J* = 12.5, 2.7 Hz), 1.99–1.93 (1H, m), 1.63–1.48 (2H, m), 1.46 (9H, s), 1.05–0.95 (2H, m), 0.94 (3H, d, *J* = 6.4 Hz); ^{13}C NMR δ 172.6, 80.8, 59.6, 45.8, 38.1, 34.7, 31.3, 28.0, 22.4; IR (neat) 2949, 2924, 1732, 1368, 1269, 1161 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{11}H_{22}NO_2$: 200.1645 ([M + H]$^+$), Found: 200.1641 ([M + H]$^+$).

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