Tetrahedron 66 (2010) 4900–4904

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Catalytic asymmetric synthesis of cyclic α-alkyl-amino acid derivatives by C,N-double alkylation

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ARTICLE INFO

Article history:
Received 14 January 2010
Received in revised form 27 January 2010
Accepted 27 January 2010
Available online 2 February 2010

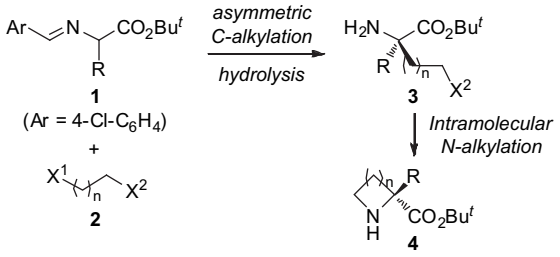
Keywords:
Asymmetric synthesis
Amino acid
Phase-transfer catalyst
Alkylation
Cyclization

ABSTRACT

Catalytic asymmetric synthesis of various cyclic α-alkyl-amino acid derivatives having a tetrasubstituted α-carbon, such as α-alkylprolines has been accomplished by asymmetric phase-transfer C-alkylation of α-alkyl-amino acid derivatives and subsequent intramolecular N-alkylation.

1. Introduction

Conformationally constrained α,α-dialkyl-α-amino acids serve as an important building block in designing a novel peptide.[1] Among them, cyclic α-alkyl-α-amino acids with the amine group inside the cyclic system, such as α-methylproline are applied not only to peptide chemistry but also to organocatalytic reactions as catalyst,[2] and there is a need to expand synthetic approaches for their preparation. While a number of asymmetric syntheses of such cyclic amino acids via construction of tetrasubstituted α-carbon have been reported to date,[3–9] general methods for their preparation based on the catalytic asymmetric construction of tetrasubstituted α-carbon are scarce.[7–9] In this context, we have been interested in utilization of asymmetric phase-transfer alkylation to prepare cyclic α-alkyl-α-amino acid derivatives.[8–10] The asymmetric C-alkylation of α-alkyl-α-amino acid derivatives **1** with dihaloalkane **2** would give optically enriched α,α-dialkyl-α-amino acid derivatives **3**, which could be readily converted to cyclic α-alkyl-α-amino acid derivatives **4** by the intramolecular N-alkylation (Scheme 1). Here we wish to report the efficient asymmetric synthesis of α-alkylproline, α-alkylpipecolic acid, α-alkylaziridine-2-carboxylic acid, and α-alkylazetidine-2-carboxylic acid derivatives based on the asymmetric phase-transfer alkylation.



Scheme 1. Asymmetric synthesis of cyclic α-alkyl-α-amino acid derivatives by C,N-double alkylation.

2. Results and discussion

We first examined the synthesis of α-alkylproline *tert*-butyl esters by C,N-double alkylation of C-alkyl-substituted-*N*-(4-chlorobenzylidene)glycine esters **1** using 1-chloro-3-iodopropane as an alkylating agent. The reaction of **1** (R=Me) with 1-chloro-3-iodopropane (2 equiv) in toluene in the presence of a chiral phase-transfer catalyst (*S*)-**5**[11] (1 mol %) and $CsOH \cdot H_2O$ (5 equiv) at 0 °C proceeded smoothly to afford the corresponding α-alkylated alanine derivative. Acidic hydrolysis with 1 N HCl and subsequent ring-closing N-alkylation with an excess amount of Na_2CO_3 gave α-methylproline *tert*-butyl ester **6** (R=Me) in 87% yield. The enantiomeric excess of **6** (R=Me) was determined to be 99% ee by chiral HPLC analysis of its *N*-benzoyl adduct (Table 1, entry 1). Other *C*-primary-alkyl-substituted glycine derivatives **1** (R=*i*-Bu, allyl,

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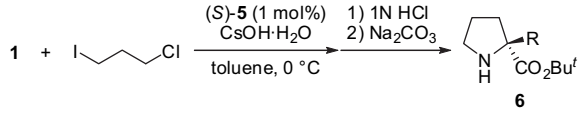
doi:10.1016/j.tet.2010.01.105

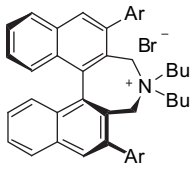
and Bn) were also applicable to this reaction sequence, and the corresponding α-alkylproline *tert*-butyl esters **6** (R=*i*-Bu, allyl, and Bn) were obtained in good yield with excellent enantioselectivity (entries 2–4). The catalyst loading could be reduced without significant loss of enantioselectivity, and moderate to good yields of **6** (R=Bn) were obtained with prolonged reaction time (entries 5 and 6). While the reaction of phenylglycine derivatives **1** (R=Ph) also gave the corresponding cyclic amino acid **6** (R=Ph) in good yield, a significant decrease in enantioselectivity was observed (entry 7). Sterically hindered valine derivative **1** (R=*i*-Pr) was found to be unreactive toward 1-chloro-3-iodopropane (entry 8).

Table 1
Asymmetric synthesis of α-alkylproline *tert*-butyl esters **6**



Entry	R	Time (h)	Yield[a] (%)	ee[b] (%) (config)
1[c]	Me	6	87	99[d] (*R*)
2	*i*-Bu	12	94	99[d]
3	Allyl	8	76	98[d]
4	Bn	6	91	99
5[e]	Bn	24	81	99
6[f]	Bn	40	75	98
7	Ph	8	88	64
8[e]	*i*-Pr	30	0	—

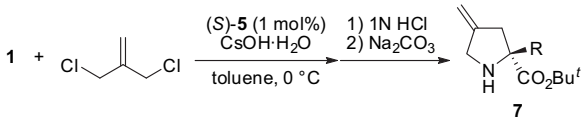
[a] Isolated yield.
[b] Determined by HPLC analysis using chiral column (Chiralpak AD-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd.).
[c] 2 equiv of 1-chloro-3-iodopropane was used.
[d] ee of the corresponding *N*-benzoyl adduct.
[e] 0.5 mol % of (*S*)-**5**.
[f] 0.1 mol % of (*S*)-**5**.



(*S*)-**5**
(Ar = 3,4,5-$F_3C_6H_2$)

In a similar manner, using 1,3-dichloro-2-methylenepropane instead of 1-chloro-3-iodopropane, a variety of α-alkyl-4-methyleneproline *tert*-butyl esters **7** could be synthesized in moderate yield with excellent enantioselectivity (Table 2).

Table 2
Asymmetric synthesis of α-alkyl-4-methyleneproline *tert*-butyl esters **7**

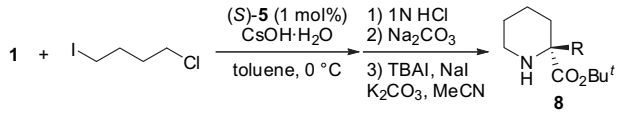


Entry	*R*	Time (h)	Yield[a] (%)	ee[b] (%)
1	Me	2	44	97[c]
2	*i*-Bu	1	48	96[c]
3	Allyl	0.7	64	96[c]
4	Bn	0.75	56	97

[a] Isolated yield.
[b] Determined by HPLC analysis using chiral column (Chiralpak AD-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd.).
[c] ee of the corresponding *N*-benzoyl adduct.

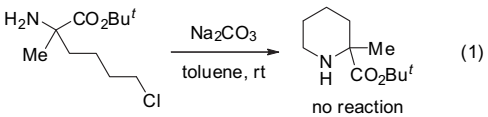
Based on the above results, we then examined the catalytic asymmetric synthesis of α-alkylpipecolic acid *tert*-butyl esters using 1-chloro-4-iodobutane. Unfortunately, however, it was found that the ring-closing N-alkylation did not proceed under similar conditions (Eq. 1). Thus the chloro group in the C-alkylation product was replaced by the better leaving group. When the cyclization was performed in the presence of TBAI (0.1 equiv), NaI (5.0 equiv), and K_2CO_3 (2.0 equiv) in MeCN under reflux overnight, the desired α-alkylpipecolic acid *tert*-butyl esters **8** (R=Me, allyl, and Bn) were obtained in good yield with excellent enantioselectivity (Table 3, entries 1–3).

Table 3
Asymmetric synthesis of α-alkyl-pipecolic acid *tert*-butyl esters **8**



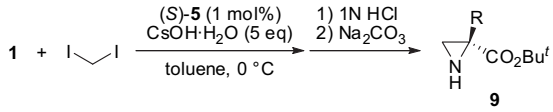
Entry	*R*	Time (h)	Yield[a] (%)	ee[b] (%)
1	Me	12	83	99[c]
2	allyl	8	81	98[c]
3	Bn	8	84	99

[a] Isolated yield.
[b] Determined by HPLC analysis using chiral column (Chiralpak AS-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd.).
[c] ee of the corresponding *N*-benzoyl adduct.



Using diiodomethane as an alkylating agent, α-alkylaziridine-2-carboxylic acid *tert*-butyl esters **9** were also effectively synthesized (Table 4). In the case of phenylalanine derivative **1** (R=Bn), the enantioselectivity was improved by lowering the reaction temperature from 0 °C to −20 °C (entry 2 vs 3).

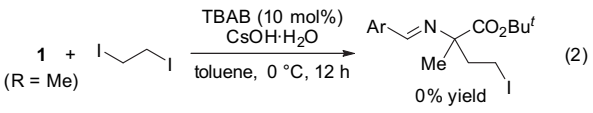
Table 4
Asymmetric synthesis of α-alkylaziridine-2-carboxylic acid *tert*-butyl esters **10**



Entry	R	Time (h)	Yield[a] (%)	ee[b] (%)
1	*i*-Bu	6	89	97[c]
2	Bn	6	91	83
3[d]	Bn	12	87	98

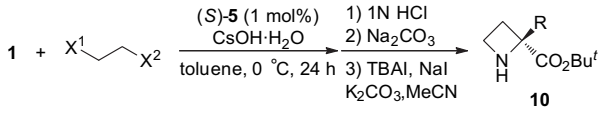
[a] Isolated yield.
[b] Determined by HPLC analysis using chiral column (Chiralcel OJ-H, Daicel Chemical Industries, Ltd.).
[c] ee of the corresponding *N*-benzoyl adduct.
[d] The reaction was performed at −20 °C.

The alkylation of **1** (R=Me) with 1,2-diiodoethane did not proceed in the presence of TBAB as catalyst, probably due to the decomposition of 1,2-diiodoethane under basic alkylation conditions, and the attempted synthesis of α-alkylazetidine-2-carboxylic acid derivative failed (Eq. 2).



We then examined various dihaloethanes using (*S*)-**5** as catalyst, and the results are summarized in Table 5. When an increased amount of 1,2-diiodoethane, or 1,2-dichloroethane was used as an alkylating agent, the desired C-alkylation did not proceed (entries 1 and 2). On the other hand, the reaction using 1-chloro-2-iodoethane or 1,2-dibromoethane gave α-benzylazetidine-2-carboxylic acid *tert*-butyl ester **10** (R=Bn), albeit in low yield (entries 3 and 4). In both cases, the ring-closing N-alkylation required the replacement of the leaving group (chloro or bromo group) with iodo group. In terms of enantioselectivity, 1,2-dibromoethane was then chosen for further investigation. The yield of **10** was improved by using an increased amount of (*S*)-**5** and/or 1,2-dibromomethane (entries 5–7), and the desired cyclic amino ester **10** was obtained in moderate yield with excellent enantioselectivity (entry 7).

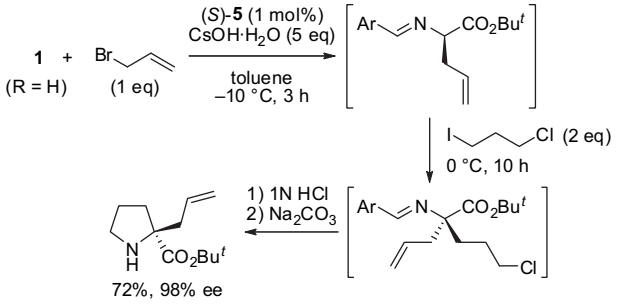
Table 5
Asymmetric synthesis of α-alkylazetidine-2-carboxylic acid *tert*-butyl ester **10**



Entry	R	X^1, X^2	Yield[a] (%)	ee[b] (%)
1	Me	I, I (5 equiv)	0[c]	—
2	Me	Cl, Cl	0[c]	—
3	Bn	I, Cl	17	59
4	Bn	Br, Br	15	98
5[d]	Bn	Br, Br	29	98
6	Bn	Br, Br (10 equiv)	33	98
7[d]	Bn	Br, Br (10 equiv)	39	98

[a] Isolated yield.
[b] Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).
[c] The C-alkylation did not proceed.
[d] 5 mol % of (*S*)-**5**.

To enhance the utility of this methodology we further examined the synthesis of an α-alkylproline derivative through the one-pot double C-alkylation of *N*-(4-chlorobenzylidene)glycine ester **1** (R=H) and the following intramolecular N-alkylation.[12] Using α-unsubstituted glycine derivative **1** (R=H), sequential C-alkylations were performed with allyl bromide (1.0 equiv) and 1-chloro-3-iodopropane (2.0 equiv) in one-pot, and the intramolecular N-alkylation of the resulting α,α-dialkylated product gave the α-allylproline *tert*-butyl ester in 72% yield with 98% ee (Scheme 2).



Scheme 2. Asymmetric synthesis of α-allylproline *tert*-butyl ester by C,C,N-triple alkylation.

3. Conclusion

In summary, we have demonstrated an efficient asymmetric synthesis of cyclic α-alkyl-amino acid derivatives, such as α-alkylproline, α-alkylpipecolic acid, α-alkylaziridine-2-carboxylic acid, and α-alkylazetidine-2-carboxylic acid derivatives by the highly enantioselective phase-transfer C-alkylation and the following ring-closing N-alkylation. Further investigations to expand the scope of this and related reactions are currently underway.

4. Experimental

4.1. General information

Infrared (IR) spectra were recorded on a Shimadzu IR Prestige-21 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-FX400 NMR instrument (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) at ambient temperature and calibrated using $SiMe_4$ (δ=0 ppm) and the central line of $CDCl_3$ triplet (δ=77 ppm) as internal references unless otherwise noted. The following abbreviations were used to express the multiplicities: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet; br=broad app=apparent. High performed liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using Daicel Chiralpak AD-H, AS-H, Chiralcel OD, OD-H, and OJ-H 4.6 mm×25 mm columns. High-resolution mass spectra (HRMS) were performed on BRUKER microTOF focus–KR. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. All reactions were monitored by thin-layer chromatography carried out on Merck silica gel plates (0.25 mm thick, 60F-254), visualization by using UV (254 nm), or dyes, such as $KMnO_4$, PMA, and $CeSO_4$. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230–400 mesh). In experiments requiring dry solvents, ether, and tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc. as 'Dehydrated'. Toluene was dried over sodium metal. Dichloromethane (CH_2Cl_2) was stored over 4 Å molecular sieves. Other simple chemicals were purchased and used as such.

4.2. Representative procedure for synthesis of α-substituted-proline ester

To a mixture of alanine *tert*-butyl ester aldimine Schiff base **1** (200 mg, 0.747 mmol), PTC (*S*)-**5** (4.3 mg, 1 mol %), and 1-chloro-3-iodopropane (0.079 mL, 0.747 mmol) in toluene (1.0 mL) was added $CsOH·H_2O$ (314 mg, 1.87 mmol) at 0 °C under an argon atmosphere. After being stirred vigorously for 6 h at 0 °C, the resulting mixture was poured into water and extracted with Et_2O twice. The combined extracts were dried over Na_2SO_4 and concentrated. To the residue dissolved in ethyl acetate (5 mL) was added 1 N HCl (5 mL). After being stirred at room temperature for 1 h, the aqueous phase was separated. The organic phase was washed with H_2O (3 mL) twice. The combined aqueous phase was adjusted to pH=9–10 by addition of Na_2CO_3. The mixture was stirred for 2 h at room temperature and extracted by CH_2Cl_2 for three times. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residual oil was purified by column chromatography on silica gel (ethyl acetate/hexane=1:6 as eluent) to give *tert*-butyl (*R*)-2-methylpyrrolidine-2-carboxylate (60 mg, 87%) as an oil.

4.2.1. tert-Butyl (R)-2-methylpyrrolidine-2-carboxylate. $[\alpha]_D^{28}$ 22.6 (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 3.03–2.92 (2H, m), 2.20–2.08 (2H, m), 1.88–1.58 (3H, m), 1.46 (9H, s), 1.34 (3H, s); ^{13}C NMR δ 176.5, 80.5, 65.9, 46.1, 36.5, 27.7, 25.7, 24.9; IR (neat) 2974, 2357, 2342, 1719, 1155, 1121 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{20}NO_2$: 186.1489 ($[M+H]^+$), found: 186.1489 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralpak AS-H, 254 nm, hexane/2-propanol=30:1, flow rate 0.5 mL/min, retention time: 14.6 min (*R*) and 15.6 min (*S*).

4.2.2. tert-Butyl (S)-2-isobutylpyrrolidine-2-carboxylate. $[\alpha]_D^{28}$ 52.2 (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 3.03–2.92 (2H, m), 2.47 (1H, br s), 2.18–2.07 (1H, m), 1.82–1.60 (5H, m), 1.51–1.47 (1H, m), 1.47 (9H, s), 0.93 (3H, d, *J*=6.5 Hz), 0.87 (3H, d, *J*=6.5 Hz); ^{13}C NMR δ 176.6, 80.6, 69.3,

48.2, 46.0, 37.3, 27.8, 25.4, 24.1, 24.0, 23.1; IR (neat) 2955, 2359, 1717, 1368, 1148 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{26}NO_2$: 228.1958 ($[M+H]^+$), found: 228.1953 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralpak AS-H, 254 nm, hexane/2-propanol=50:1, flow rate 0.5 mL/min, retention time: 12.6 min (*S*) and 19.4 min (*R*).

4.2.3. tert-Butyl (S)-2-allylpyrrolidine-2-carboxylate. $[\alpha]_D^{28}$ 64.6 (*c* 0.68, $CHCl_3$); ^1H NMR δ 5.84–5.70 (1H, m), 5.19–5.02 (2H, m), 3.05–2.90 (2H, m), 2.54 (1H, dd, *J*=13.7, 7.3 Hz), 2.30 (1H, dd, *J*=13.7, 7.3 Hz), 2.18–2.05 (2H, m), 1.85–1.62 (3H, m), 1.45 (9H, s); ^{13}C NMR δ 175.5, 133.9, 117.4, 80.6, 69.0, 46.1, 44.0, 35.2, 27.7, 24.6; IR (neat) 2976, 2342, 2330, 1721, 1148 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{22}NO_2$: 222.1645 ($[M+H]^+$), found: 222.1670 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol=20:1, flow rate 0.5 mL/min, retention time: 15.7 min (*R*) and 17.0 min (*S*).

4.2.4. tert-Butyl (S)-2-benzylpyrrolidine-2-carboxylate. $[\alpha]_D^{28}$ 29.6 (*c* 0.54, $CHCl_3$); ^1H NMR δ 7.28–7.16 (5H, m), 3.12 (1H, d, *J*=13.2 Hz), 3.04–2.92 (2H, m), 2.84 (1H, d, *J*=13.2 Hz), 2.33 (1H, br s), 2.25–2.12 (1H, m), 1.87–1.57 (3H, m), 1.37 (9H, s); ^{13}C NMR δ 175.3, 137.7, 129.8, 127.7, 126.3, 80.8, 70.4, 45.8, 45.1, 36.1, 27.8, 24.2; IR (neat) 2974, 1719, 1367, 1152 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{24}NO_2$: 262.1802 ($[M+H]^+$), found: 262.1802 ($[M+H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol=30:1, flow rate 0.5 mL/min, retention time: 8.0 min (*R*) and 9.5 min (*S*).

4.2.5. tert-Butyl (S)-2-phenyl-2-pyrrolidinecarboxylate. $[\alpha]_D^{28}$ 22.7 (*c* 0.97, $CHCl_3$); ^1H NMR δ 7.52 (2H, app d), 7.39–7.19 (3H, m), 3.07 (2H, app t), 2.78 (1H, br s), 2.74–2.66 (1H, m), 2.11–1.96 (1H, m), 1.93–1.70 (2H, m), 1.38 (9H, s); ^{13}C NMR δ 174.7, 143.1. 127.9, 126.8, 126.0, 81.3, 72.6, 45.5, 36.4, 27.7, 24.5; IR (neat) 2974, 1719, 1250, 1150 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{22}NO_2$: 248.1645 ($[M+H]^+$), found: 248.1647 ($[M+H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 210 nm, hexane/2-propanol=33:1, flow rate 0.5 mL/min, retention time: 9.5 min (*S*) and 10.7 min (*R*).

4.3. Determination of the absolute stereochemistry of (*R*)-α-methylproline

To a solution of *tert*-butyl (*R*)-2-methylproline-2-carboxylate (38 mg, 0.205 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.076 mL, 1.03 mmol). The resulting solution was stirred at room temperature for 3 h and concentrated. To the residue dissolved in EtOH (2 mL) was added propylene oxide (0.5 mL), and the resulting solution was heated at reflux for 2 h and concentrated. The residual solid was rinsed with ethyl acetate and acetone and dried up to give (*R*)-α-methylproline (20 mg, 76%) as a white solid: ^1H NMR δ 3.44–3.37 (1H, m), 3.31 (1H, s), 3.30–3.22 (1H, m), 2.44–2.38 (1H, m), 2.07–1.78 (3H, m), 1.56 (3H, s); HRMS (ESI-TOF) calcd for $C_6H_{12}NO_2$: 130.0863 ($[M+H]^+$), found: 130.0862 ($[M+H]^+$); $[\alpha]_D^{28}$ 80.1 (*c* 1.0, H_2O). The absolute configuration of the obtained α-methylproline was determined to be *R* by comparison of the sign of the optical rotation with the literature data.[5b]

4.3.1. tert-Butyl (R)-2-methyl-4-methylenepyrrolidine-2-carboxylate. $[\alpha]_D^{28}$ −19.2 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.93 (1H, app dd, *J*=2.0, 2.0 Hz), 4.88 (1H, app dd, *J*=2.0, 2.0 Hz), 3.63 (1H, d, *J*=16.8 Hz), 3.58 (1H, d, *J*=16.4 Hz), 2.82 (1H, d, *J*=16.0 Hz), 2.38 (1H, br), 2.37 (1H, d, *J*=16.0 Hz), 1.46 (9H, s), 1.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 147.8, 105.5, 81.1, 66.4, 50.5, 43.3, 27.9, 24.6; IR (neat) 2976, 1724, 1367, 1248, 1153 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{20}NO_2$: 198.1489 ($[M+H]^+$), found: 198.1480 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol=20:1, flow rate 0.5 mL/min, retention time: 17.9 min (*S*) and 21.4 min (*R*).

4.3.2. tert-Butyl (R)-2-allyl-4-methylenepyrrolidine-2-carboxylate. $[\alpha]_D^{28}$ −10.0 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.81–5.70 (1H, m), 5.13–5.07 (2H, m), 4.92 (1H, d, *J*=2.0 Hz), 4.88 (1H, d, *J*=2.0 Hz), 3.63 (1H, d, *J*=14.4 Hz), 3.57 (1H, d, *J*=14.4 Hz), 2.80 (1H, d, *J*=15.2 Hz), 2.55 (1H, dd, *J*=14.0, 6.8 Hz), 2.45 (1H, br), 2.45–2.32 (2H, m), 1.45 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 147.4, 133.4, 118.2, 105.5, 81.3, 69.4, 50.4, 43.1, 41.9, 28.0; IR (neat) 2976, 1722, 1367, 1248, 1227, 1149 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{22}NO_2$: 224.1645 ($[M+H]^+$), found: 224.1644 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol=20:1, flow rate 0.5 mL/min, retention time: 16.1 min (*S*) and 23.7 min (*R*).

4.3.3. tert-Butyl (R)-2-Benzyl-4-methylenepyrrolidine-2-carboxylate. $[\alpha]_D^{28}$ −29.3 (*c* 1.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.18 (5H, m, Ar-H), 4.93 (1H, d, *J*=2.0 Hz), 4.87 (1H, d, *J*=2.0 Hz), 3.60 (2H, s), 3.15 (1H, d, *J*=13.2 Hz), 2.88 (1H, d, *J*=13.2 Hz), 2.80 (1H, d, *J*=15.6 Hz), 2.52 (1H, d, *J*=15.6 Hz), 2.30 (1H, br), 1.37 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 147.2, 137.1, 129.9, 128.1, 126.7, 105.5, 81.3, 70.6, 50.3, 44.3, 42.9, 27.9; IR (neat) 2976, 1722, 1367, 1248, 1150 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{24}NO_2$: 274.1801 ($[M+H]^+$), Found: 274.1795 ($[M+H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol=100:1, flow rate 0.5 mL/min, retention time: 11.4 min (*R*) and 13.1 min (*S*).

4.3.4. tert-Butyl (R)-2-isobutyl-4-methylenepyrrolidine-2-carboxylate. $[\alpha]_D^{28}$ −13.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.91 (1H, s), 4.86 (1H, s), 3.61 (1H, d, *J*=14.8 Hz), 3.54 (1H, d, *J*=14.4 Hz), 2.80 (1H, d, *J*=16.4 Hz), 2.36 (1H, d, *J*=13.6 Hz), 2.35 (1H, br), 1.79–1.51 (3H, m), 1.45 (9H, s), 0.94 (3H, d, *J*=6.0 Hz), 0.89 (3H, d, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 147.6, 105.2, 81.1, 69.7, 50.4, 47.3, 44.0, 27.9, 25.3, 24.1, 23.3; IR (neat) 2955, 1721, 1368, 1234, 1150 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{26}NO_2$: 240.1958 ($[M+H]^+$), found: 240.1965 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol=19:1, flow rate 0.5 mL/min, retention time: 13.0 min (*S*) and 20.3 min (*R*).

4.4. Representative procedure for synthesis of *tert*-butyl 2-alkylpiperidine-2-carboxylate

To a mixture of alanine *tert*-butyl ester aldimine Schiff base **1** (80 mg, 0.30 mmol), PTC (*S*)-**5** (2.2 mg, 1 mol %), and 1-chloro-4-iodobutane (110 μL, 0.36 mmol) in toluene (1.5 mL) was added $CsOH\cdot H_2O$ (251 mg, 1.50 mmol) at 0 °C under an argon atmosphere. After being stirred vigorously for 8 h at 0 °C, the resulting mixture was poured into water and extracted with Et_2O twice. The combined extracts were dried over Na_2SO_4 and concentrated. To the residue dissolved in ethyl acetate (5 mL) was added 1 N HCl (5 mL). After being stirred at room temperature for 1 h, the aqueous phase was separated. The organic phase was washed with H_2O (3 mL) twice. The combined aqueous phase was adjusted to pH=9–10 by addition of Na_2CO_3 and extracted by CH_2Cl_2 for three times. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residual oil was used for the next reaction without further purification.

To a solution of the crude mixture obtained above in MeCN (5.0 mL) were added TBAI (11 mg, 0.03 mmol), NaI (224 mg, 1.49 mmol), and K_2CO_3 (83 mg, 0.60 mmol). The resulting mixture was refluxed overnight and cooled to room temperature. Then the reaction mixture was filtered through a pad of Celite with ethyl

acetate. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (ethyl acetate/hexane=1:5 as eluent) to give (*R*)-*tert*-butyl 2-methylpiperidine-2-carboxylate (45 mg, 76%) as an oil.

4.4.1. tert-Butyl (R)-2-methylpiperidine-2-carboxylate. $[\alpha]_D^{28}$ −28.1 (*c* 0.71, $CHCl_3$); ^1H NMR δ 2.91–2.83 (1H, m), 2.68 (1H, td, *J*=11.7, 3.2 Hz), 2.25 (1H, br s), 2.15–2.07 (1H, m), 1.72–1.60 (1H, m), 1.59–1.40 (2H, m), 1.48 (9H, s), 1.39–1.26 (2H, m), 1.21 (3H, s); ^{13}C NMR δ 175.7, 80.5, 59.6, 43.5, 34.0, 27.9, 27.8, 24.9, 22.1; IR (neat) 2932, 2361, 1720, 1368, 1242, 1126 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{22}NO_2$: 200.1645 ($[M+H]^+$), found: 200.1644 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralpak AS-H, 254 nm, hexane/2-propanol=20:1, flow rate 0.5 mL/min, retention time: 8.6 min (*R*) and 9.0 min (*S*).

4.4.2. tert-Butyl (S)-2-allylpiperidine-2-carboxylate. $[\alpha]_D^{28}$ −60.4 (*c* 1.4, $CHCl_3$); ^1H NMR δ 5.75–5.62 (1H, m), 5.15–5.05 (2H, m), 2.90–2.80 (1H, m), 2.73 (1H, td, *J*=11.7, 3.1 Hz), 2.36 (1H, dd, *J*=13.5, 6.5 Hz), 2.21 (1H, dd, *J*=13.7, 8.6 Hz), 2.16–2.08 (2H, m), 1.48 (9H, s), 1.71–1.62 (1H, m), 1.60–1.26 (4H, m); ^{13}C NMR δ 174.4, 132.3, 118.7, 80.8, 62.3, 45.9, 43.3, 33.2, 28.1, 25.3, 22.1; IR (neat) 2932, 1721, 1250, 1227, 1142 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{24}NO_2$: 226.1802 ($[M+H]^+$), found: 226.1804 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol=50:1, flow rate 0.5 mL/min, retention time: 15.7 min (*R*) and 16.9 min (*S*).

4.4.3. tert-Butyl (S)-2-benzylpiperidine-2-carboxylate. $[\alpha]_D^{28}$ −11.3 (*c* 0.8, $CHCl_3$); ^1H NMR δ 7.28–7.15 (5H, m), 2.92 (1H, d, *J*=13.2 Hz), 2.91–2.84 (1H, m), 2.77 (1H, d, *J*=13.2 Hz), 2.69 (1H, td, *J*=11.6, 3.2 Hz), 2.22–2.16 (1H, m), 2.09 (1H, br s), 1.72–1.65 (1H, m), 1.40 (9H, s), 1.60–1.22 (4H, m); ^{13}C NMR δ 174.0, 135.8, 130.2, 127.8, 126.6, 80.9, 63.3, 47.7, 43.2, 34.0, 27.9, 25.1, 22.0; IR (neat) 2930, 2359, 1717, 1366, 1246, 1150, 1123 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{26}NO_2$: 276.1958 ($[M+H]^+$), found: 276.1953 ($[M+H]^+$); HPLC analysis: Daicel Chiralpak AS-H, 254 nm, hexane/2-propanol=100:1, flow rate 0.5 mL/min, retention time: 8.8 min (*R*) and 9.1 min (*S*).

4.4.4. tert-Butyl (R)-2-benzylaziridine-2-carboxylate. $[\alpha]_D^{28}$ 59.8 (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.36–7.15 (5H, m), 3.26 (1H, d, *J*=14.5 Hz), 2.71 (1H, d, *J*=14.5 Hz), 2.06 (1H, s), 1.70 (1H, s), 1.54 (1H, br s), 1.33 (9H, s); ^{13}C NMR δ 172.3, 138.4, 129.2, 127.9, 126.2, 82.0, 39.3, 37.6, 32.6, 27.7; IR (neat) 2978, 2359, 2342, 1713, 1358, 1227, 1152 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{20}NO_2$: 234.1489 ($[M+H]^+$), found: 234.1485 ($[M+H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol=20:1, flow rate 0.5 mL/min, retention time: 9.2 min (*R*) and 11.1 min (*S*).

4.4.5. tert-Butyl (R)-2-isobutylaziridine-2-carboxylate. $[\alpha]_D^{28}$ 14.1 (*c* 0.65, $CHCl_3$); ^1H NMR δ 2.00–1.90 (3H, m), 1.58 (1H, br s), 1.47 (9H, s), 1.25–1.18 (1H, m), 0.95 (3H, d, *J*=5.6 Hz), 0.93 (3H, dd, *J*=13.7, 5.9 Hz); ^{13}C NMR δ 173.0, 81.6, 40.6, 37.9, 33.5, 27.8, 26.4, 22.9, 22.8; IR (neat) 2957, 1713, 1368, 1234, 1153 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{22}NO_2$: 200.1645 ($[M+H]^+$), found: 200.1636 ($[M+H]^+$); the enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct: Daicel Chiralcel OJ-H, 254 nm, hexane/2-propanol=50:1, flow rate 0.5 mL/min, retention time: 10.2 min (*S*) and 11.1 min (*R*).

4.4.6. tert-Butyl (R)-2-Benzylazetidine-2-carboxylate. $[\alpha]_D^{28}$ 84.9 (*c* 1.2, $CHCl_3$); ^1H NMR δ 7.30–7.15 (5H, m); 3.49 (1H, app q), 3.24–3.15 (1H, m), 3.09 (2H, dd, *J*=18.4, 13.5 Hz), 2.58 (1H, br), 2.53–2.43 (1H, m), 2.43–2.34 (1H, m), 1.39 (9H, s); ^{13}C NMR δ 175.2, 136.9, 129.5, 128.0, 126.5, 81.3, 68.8, 45.5, 41.5, 31.1, 27.9; IR (neat) 2976, 1722, 1368, 1271, 1155 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{22}NO_2$: 248.1645 ($[M+H]^+$), found: 248.1638 ($[M+H]$); HPLC analysis: Daicel Chiralpak AD-H, 210 nm, hexane/2-propanol=5:1, flow rate 0.5 mL/min, retention time: 9.4 min (*S*) and 9.8 min (*R*).

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformation of Carbon Resources' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. H.M. is grateful to the Japan Society for the Promotion of Science for Young Scientists for a research fellowship.

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