


 Cite this: *RSC Adv.*, 2021, 11, 23825

# Synthesis of optically active 2-substituted azetidine-2-carbonitriles from chiral 1-arylethylamine via $\alpha$ -alkylation of *N*-borane complexes†

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The base-promoted  $\alpha$ -alkylation of *N*-((*S*)-1-arylethyl)azetidine-2-carbonitriles **3** via formation of their *N*-borane complexes **4** was investigated. For example, treatment of diastereomerically pure borane *N*-((*S*)-1'-(4''-methoxyphenyl)ethyl)azetidine-2-carbonitrile complex (1*S*,2*S*,1'*S*)-**4b** with 1.2 equivalents of LDA at  $-78$  °C followed by 1.3 equivalents of benzyl bromide at  $-78$  °C and warming to room temperature produced  $\alpha$ -benzylated (2*S*,1'*S*)-**5ba** in 72% yield and (2*R*,1'*S*)-**5ba** in 2% yield. A mechanism for this diastereoselective  $\alpha$ -alkylation was proposed. Our method enables the production of optically active 2-substituted azetidine-2-carbonitriles, such as  $\alpha$ -benzylated (*S*)-**10a** and (*R*)-**10a**, starting from commercially available (*S*)-1-(4-methoxyphenyl)ethylamine.

 Received 14th June 2021  
 Accepted 30th June 2021

DOI: 10.1039/d1ra04585g

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## Introduction

Azetidines, four-membered N-heterocycles, are valuable compounds because they act as building blocks for the synthesis of nitrogen-containing compounds such as amino acids, alkaloids, biologically active drugs, chiral ligands and organocatalysts.<sup>1,2</sup> The four-membered ring is relatively rigid compared with five- and six-membered rings, which enables stereoselective functionalization on the ring by using steric effects of substituents already present. The ring-strained four-membered N-heterocycles are stable without any additives; however, upon electrophilic activation of the nitrogen atom with Lewis/Brønsted acids<sup>3</sup> or *N*-quaternization,<sup>4,5</sup> nucleophilic ring-opening or successive ring-expansion reactions proceed to give highly functionalized nitrogen-containing compounds. Therefore, the development of synthetic methods to produce substituted azetidines attracts much interest in synthetic organic chemistry.

Recently, our group reported the diastereoselective  $\alpha$ -alkylation of (2*S*,1'*S*)-*N*-(1'-phenylethyl)azetidine-2-carboxylic acid *tert*-butyl ester via formation of its *N*-borane (BH<sub>3</sub>) complex (Scheme 1, eqn (1)).<sup>6,7</sup> This protocol enabled the synthesis of various types of  $\alpha$ -substituted azetidine-2-carboxylic acid esters from (*S*)-1-phenylethylamine, which is one of the least expensive chiral sources. However, the same reaction with other (2*R*,1'*S*)-isomers

resulted in lower yields and diastereoselectivities (eqn (2)). These results in hand, we attempted the same transformations to convert nitrile derivatives **3** into  $\alpha$ -substituted azetidine-2-carbonitriles **5** to clarify that both diastereomers of *N*-BH<sub>3</sub> complexes (2*S*,1'*S*)- and (2*R*,1'*S*)-**4** provide the corresponding  $\alpha$ -alkylated diastereomers, respectively (eqn (3) and (4)). In addition, previous reports on *N*-BH<sub>3</sub> complexes derived from  $\alpha$ -amino nitriles are quite limited and their chemical properties are unclear.<sup>8</sup> Thus, we started to investigate the preparation of *N*-BH<sub>3</sub> complexes **4**, diastereoselective  $\alpha$ -alkylation of **4**, and further synthetic transformation of the resulting products **5**.

## Results and discussion

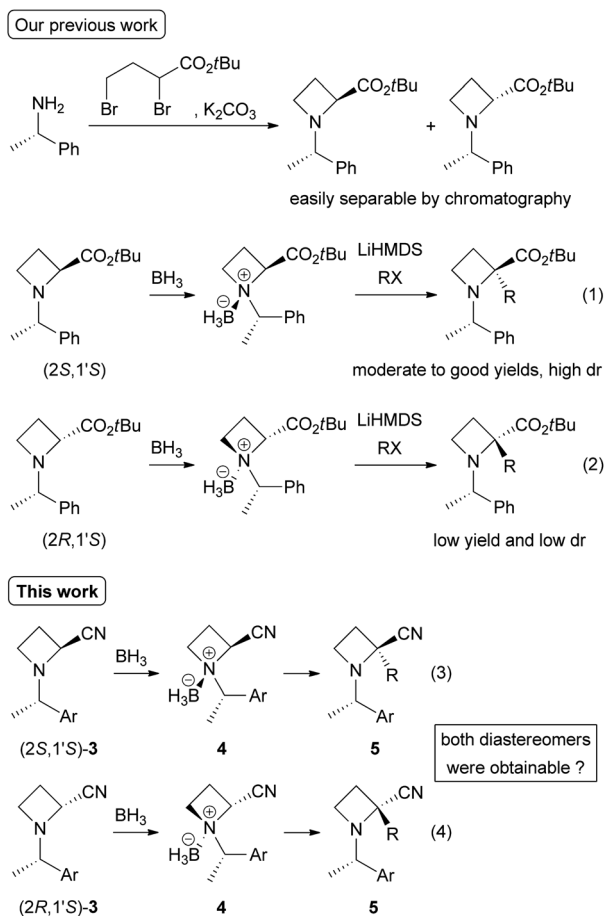
### Preparation of *N*-benzylic azetidine-2-carbonitriles (**3**)

First, we investigated preparative routes to *N*-((*S*)-1-phenylethyl)azetidine-2-carbonitriles (**3a**)<sup>9</sup> from easily obtainable methyl esters **1a**<sup>10</sup> (Scheme 2). Amidation of **1a** with aqueous NH<sub>3</sub> (25–28%) gave **2a** in moderate yields [(2*S*,1'*S*)-**2a**: 71%, (2*R*,1'*S*)-**2a**: 60%]. We found that the use of trifluoroacetic anhydride with pyridine<sup>11</sup> was quite effective in dehydration of the resulting amides **2a** to nitriles **3a** [(2*S*,1'*S*)-**3a**: 90%, (2*R*,1'*S*)-**3a**: 94%]. Analogous *N*-((*S*)-1-(4-methoxyphenyl)ethyl) derivatives **3b** were also prepared. Amidation of **1b**<sup>12</sup> was carried out with methanolic NH<sub>3</sub> (7 N) in the presence of NaCN in 1,4-dioxane because the use of aqueous NH<sub>3</sub> resulted in lower conversion. The desired amides **2b** were obtained in excellent yields [(2*S*,1'*S*)-**2b**: 99%, (2*R*,1'*S*)-**2b**: 100%]. Dehydration of **2b** with trifluoroacetic anhydride gave **3b** [(2*S*,1'*S*)-**3b**: 80%, (2*R*,1'*S*)-**3b**: 74%]. The lower yields of this dehydration were due to undesired substitution at the benzylic carbon with trifluoroacetate anion.<sup>13</sup>

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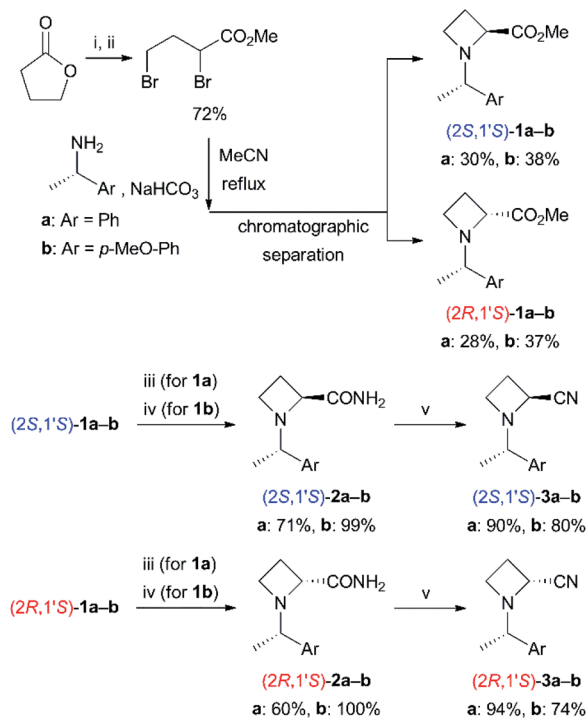
† Electronic supplementary information (ESI) available: Copies of <sup>1</sup>H, <sup>13</sup>C and <sup>11</sup>B NMR spectra. See DOI: 10.1039/d1ra04585g

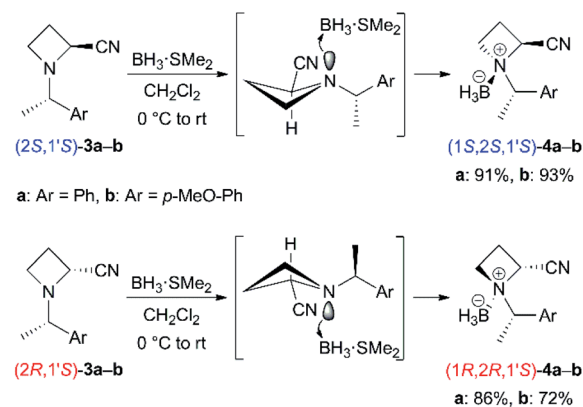
Scheme 1 Diastereoselective *N*-boration and  $\alpha$ -alkylation of azetidine-2-carbonitriles.

### Preparation of *N*-BH<sub>3</sub> complexes (4)

Next, we attempted to prepare *N*-BH<sub>3</sub> complexes **4** as substrates for base-promoted  $\alpha$ -alkylation (Scheme 3). Treatment of *N*-(1-phenylethyl) derivatives **3a** with a BH<sub>3</sub> dimethyl sulfide complex in CH<sub>2</sub>Cl<sub>2</sub> proceeded smoothly with high stereoselectivities at the nitrogen atom, as in **3a** (>9 : 1 dr). Silica-gel chromatographic purification (*n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> as the eluent) to isolate the major diastereomer observed by TLC analysis afforded **4a** in good yields [(1*S*,2*S*,1'*S*)-**4a**: 91%, (1*R*,2*R*,1'*S*)-**4a**: 86%]. In contrast, the yields of *N*-(1-(4-methoxyphenyl)ethyl) derivatives **4b** were slightly decreased [(1*S*,2*S*,1'*S*)-**4b**: 93%, (1*R*,2*R*,1'*S*)-**4b**: 72%]. The exact reason is unclear at present, and the coordinating ability of the methoxy substituent might cause undesirable complexation. Isolated *N*-BH<sub>3</sub> complexes **4a** and **4b** were obtained as solid and were stable for several days without decomposition. However, they epimerized to the other isomer and/or decomposed slowly in coordinating solvents such as THF.<sup>14</sup> The stereochemistries of **4a** and **4b** were determined analogically by comparison with previous examples of *N*-boration of 2-substituted azetidine derivatives.<sup>6,15</sup> The adjacent 2- and *N*-substituents are equatorial, and the axial lone pair of the nitrogen atom coordinates to BH<sub>3</sub>.



Scheme 2 Preparation of azetidine-2-carbonitriles **3**. (i) Br<sub>2</sub>, PBr<sub>3</sub>, 100 °C. (ii) MeOH, rt. (iii) NH<sub>3</sub> aq. rt. (iv) NH<sub>3</sub>, NaCN, MeOH, rt. (v) (CF<sub>3</sub>CO)<sub>2</sub>O, pyridine, 1,4-dioxane, ca. 10 °C to rt.

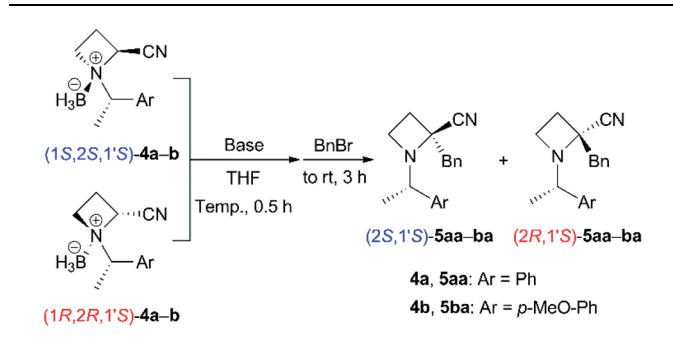


Scheme 3 Preparation of *N*-BH<sub>3</sub> complexes **4**.

### Base-promoted $\alpha$ -benzylation of *N*-BH<sub>3</sub> complexes (4)

We started to investigate the base-promoted  $\alpha$ -alkylation of **4** with benzyl bromide as an electrophile (Table 1). According to our previous work,<sup>6</sup> the reaction of *N*-((*S*)-1-phenylethyl) derivative (1*S*,2*S*,1'*S*)-**4a** in THF was examined with 2.4 equivalents of LiHMDS at 0 °C for 30 min followed by 2.6 equivalents of benzyl bromide at room temperature for 3 h (entry 1). The desired  $\alpha$ -benzylated (2*S*,1'*S*)-**5aa** was obtained in only 14% as a single diastereomer. The *N*-BH<sub>3</sub> complex derived from product (2*S*,1'*S*)-**5aa** was not obtained. The use of 1.2 equivalents of LDA and 1.3 equivalents of benzyl bromide did not give **5aa** (entry 2). To minimize the epimerization and/or decomposition of



Table 1 Optimization of reaction conditions in  $\alpha$ -benzylation of **4**

Entry	<b>4</b>	Base (eq.), temp.	BnBr (eq.)	Yield of <b>5<sup>a</sup></b> (%)	
				2 <i>S</i> ,1' <i>S</i>	2 <i>R</i> ,1' <i>S</i>
1	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i> - <b>4a</b>	LiHMDS, 2.4, 0 °C	2.6	14	0
2	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i> - <b>4a</b>	LDA, 1.2, 0 °C	1.3	0	0
3	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i> - <b>4a</b>	LiHMDS, 2.4, -78 °C	2.6	64	8
4	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i> - <b>4a</b>	LDA, 1.2, -78 °C	1.3	70	0
5	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i> - <b>4a</b>	LiHMDS, 2.4, 0 °C	2.6	4	48
6	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i> - <b>4a</b>	LiHMDS, 2.4, -78 °C	2.6	8	74
7	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i> - <b>4a</b>	LDA, 1.2, -78 °C	1.3	0	59
8	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i> - <b>4b</b>	LiHMDS, 2.4, -78 °C	2.6	49	5
9	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i> - <b>4b</b>	LDA, 1.2, -78 °C	1.3	72	2
10	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i> - <b>4b</b>	LiHMDS, 2.4, -78 °C	2.6	9	56
11	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i> - <b>4b</b>	LDA, 1.2, -78 °C	1.3	0	83

<sup>a</sup> Yield of isolated product.

(1*S*,2*S*,1'*S*)-**4a** in THF,<sup>14</sup> the mixture was cooled at -78 °C as soon as possible after the addition of THF to (1*S*,2*S*,1'*S*)-**4a**. Then, the mixture was treated with base at -78 °C (entries 3 and 4). These procedures and conditions improved the yields to approximately 70%. Each diastereomeric product, (2*S*,1'*S*)- and (2*R*,1'*S*)-**5aa** was easily separable with silica gel chromatography. The corresponding amounts of BH<sub>3</sub> were also recovered as BH<sub>3</sub>-diisopropylamine complexes after chromatographic purification. The use of 1.2 equivalents of LDA seemed to be preferred for achieving excellent diastereoselectivity (entry 4). We attempted the reactions of the other diastereomer (1*R*,2*R*,1'*S*)-**4a** under the conditions described above to produce the corresponding  $\alpha$ -alkylated (2*R*,1'*S*)-**5aa** (entries 5–7). Similar yields (52–82% combined yields) and diastereoselectivities were observed. Next, we prepared *N*-((*S*)-1-(4-methoxyphenyl)ethyl) derivatives **4b** and carried out their reactions because the *N*-substituent, as in product **5ba**, could be removed without hydrogenolysis, which may reduce the nitrile substituent. The reactions of (1*S*,2*S*,1'*S*)-**4b** also gave (2*S*,1'*S*)-**5ba** preferentially in moderate yields (entries 8 and 9, 54% and 74% combined yields). The diastereomeric products, (2*S*,1'*S*)- and (2*R*,1'*S*)-**5ba**, were easily separable with silica gel chromatography. The reactions of the other diastereomer (1*R*,2*R*,1'*S*)-**4b** to (2*R*,1'*S*)-**5ba** also showed similar results (entries 10 and 11, 65% and 83% combined yields). Both  $\alpha$ -alkylated diastereomers (2*S*,1'*S*)- and (2*R*,1'*S*)-**5ba** were successfully obtained with high diastereoselectivities from the corresponding *N*-BH<sub>3</sub> complexes **4b**.<sup>16</sup>

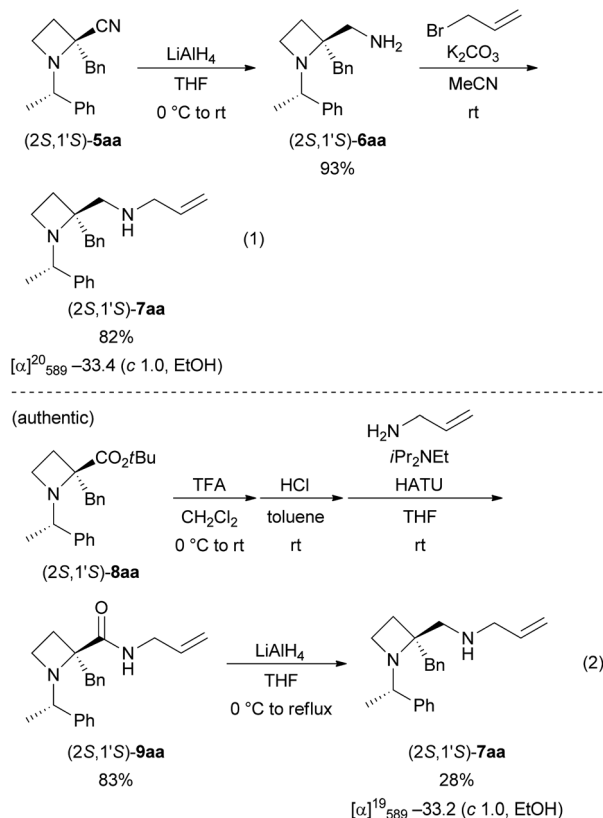
To define the scope and limitations of this diastereoselective  $\alpha$ -alkylation, we attempted the reactions of **4b** with various electrophiles (Table 2).<sup>17</sup> The reactions with allyl bromide gave **5bb** in moderate to good yields and with excellent diastereoselectivities (entries 1 and 7, 56% and 85% combined yields). Simple alkyl halides, such as methyl-, ethyl-, and *n*-butyl iodides, were applicable (entries 2–4 and 8–10). The corresponding products **5bc–be** were obtained in moderate yields (66–77% combined yields) with good diastereoselectivities. Previously, we reported that ethyl chloroformate could be used as an electrophile in the reaction of the *N*-BH<sub>3</sub> complex of a *tert*-butyl ester derivative.<sup>6</sup> Therefore, the reactions of nitrile derivatives **4b** with ethyl chloroformate were examined under the same conditions (entries 5 and 11). The yields of the corresponding products **5bf** were low to moderate (29% and 57% combined yields). We attempted to use di-*tert*-butyl dicarbonate as an electrophile (entries 6 and 12)<sup>18</sup> instead of ethyl chloroformate; however, the yields of **5bg** were not so improved (58% and 43% combined yields).

The stereochemistry of (2*S*,1'*S*)-**5aa** was assigned by conversion into the *N*-allylamine derivative (2*S*,1'*S*)-**7aa** (Scheme 4).

Table 2 Diastereoselective  $\alpha$ -substitution of **4b** with various electrophiles

Entry	<b>4b</b>	RX	<b>5</b>	Yield of <b>5<sup>a</sup></b> (%)	
				2 <i>S</i> ,1' <i>S</i>	2 <i>R</i> ,1' <i>S</i>
1	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i>	BrCH <sub>2</sub> CH=CH <sub>2</sub>	<b>5bb</b>	56	0
2	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i>	MeI	<b>5bc</b>	73	4
3	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i>	EtI	<b>5bd</b>	61	5
4	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i>	<i>n</i> BuI	<b>5be</b>	67	2
5	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i>	ClCO <sub>2</sub> Et	<b>5bf</b>	29	0
6	1 <i>S</i> ,2 <i>S</i> ,1' <i>S</i>	( <i>t</i> BuOCO) <sub>2</sub> O	<b>5bg</b>	58	0
7	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i>	BrCH <sub>2</sub> CH=CH <sub>2</sub>	<b>5bb</b>	1	84
8	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i>	MeI	<b>5bc</b>	7	65
9	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i>	EtI	<b>5bd</b>	10	62
10	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i>	<i>n</i> BuI	<b>5be</b>	5	61
11	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i>	ClCO <sub>2</sub> Et	<b>5bf</b>	4	53
12	1 <i>R</i> ,2 <i>R</i> ,1' <i>S</i>	( <i>t</i> BuOCO) <sub>2</sub> O	<b>5bg</b>	0	43

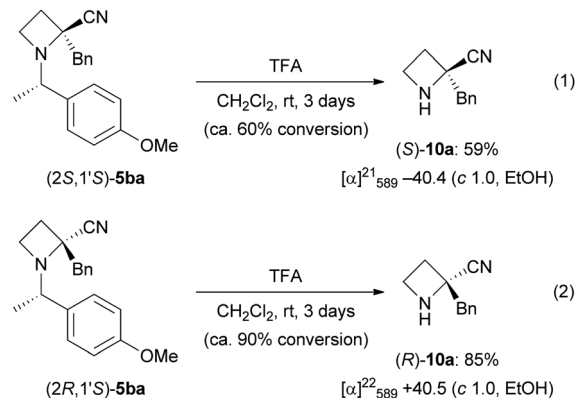
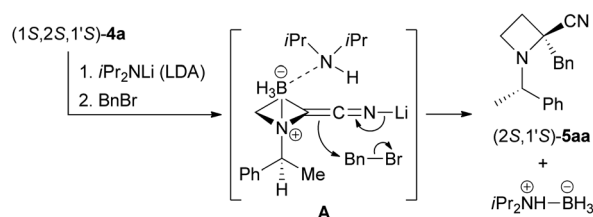
<sup>a</sup> Yield of isolated product.



Scheme 4 Determination of the stereochemistry of 5aa.

Reduction of nitrile derivative (2*S*,1'*S*)-5aa with LiAlH<sub>4</sub> provided primary amine (2*S*,1'*S*)-6aa in 93% yield. *N*-Alkylation with allyl bromide gave mono-*N*-alkylated (2*S*,1'*S*)-7aa in 82% yield because of steric hindrance (eqn (1)). The authentic sample of (2*S*,1'*S*)-7aa was prepared from the *tert*-butyl ester derivative (2*S*,1'*S*)-8aa, for which the absolute stereochemistry was determined in our previous work<sup>6</sup> (eqn (2)). First, *tert*-butyl ester, as in (2*S*,1'*S*)-8aa, was cleaved with TFA and amidation with allylamine using HATU followed to give *N*-allyl amide (2*S*,1'*S*)-9aa in 83% yield.<sup>19</sup> Reduction of sterically hindered amide (2*S*,1'*S*)-9aa into (2*S*,1'*S*)-7aa with LiAlH<sub>4</sub> proceeded very slowly. To prevent the formation of side products, we quenched the reaction without good conversion of (2*S*,1'*S*)-9aa. The desired (2*S*,1'*S*)-7aa was obtained in 28% yield with the recovery of (2*S*,1'*S*)-9aa (59% recovery). The absolute stereochemistry of 5aa was determined by comparison of the specific rotation values of 7aa thus obtained. The stereochemistry of 5ba–bg was assigned by analogy.

The *N*-((*S*)-1-(4-methoxyphenyl)ethyl) substituent, as in 5ba, could be removed by treatment with TFA in CH<sub>2</sub>Cl<sub>2</sub> (1 : 1) at room temperature (Scheme 5).<sup>20</sup> After 3 days, (*S*)-10a was obtained in 59% yield from (2*S*,1'*S*)-5ba (eqn (1)); in contrast, (*R*)-10a was obtained in 85% yield from (2*R*,1'*S*)-5ba (eqn (2)). The removal from (2*S*,1'*S*)-5ba proceeded more slowly than that from (2*R*,1'*S*)-5ba, but the details are unclear at present. The corresponding amounts of unremoved 5ba were observed by <sup>1</sup>H NMR analysis of the crude products. Specific rotation values of (*S*)- and (*R*)-10a showed good agreement for each enantiomer.

Scheme 5 Removal of the *N*-((*S*)-1-(4-methoxyphenyl)ethyl) substituent, as in 5ba.

Scheme 6 Proposed reaction mechanism.

With these results in hand, we proposed a reaction mechanism in this diastereoselective  $\alpha$ -alkylation (Scheme 6). The alkylation proceeds from the side of the *N*-benzylic substituent as in (1*S*,2*S*,1'*S*)-4a to afford (2*S*,1'*S*)-5aa, not the side of the smaller *N*-BH<sub>3</sub> group. With chromatographic purification of the products, the corresponding amounts of BH<sub>3</sub>–diisopropylamine complex could be isolated. Decomposition of BH<sub>3</sub> by aqueous workup of the reaction did not proceed to completion. Thus, we propose formation of nitrile enolate A derived from (1*S*,2*S*,1'*S*)-4a. Diisopropylamine generated from LDA after deprotonation might interact with *N*-BH<sub>3</sub>. The side of the *N*-BH<sub>3</sub> group was blocked by diisopropylamine. Benzyl bromide reacts from the side of the *N*-benzylic substituent to provide (2*S*,1'*S*)-5aa. After  $\alpha$ -alkylation, BH<sub>3</sub> moves to the sterically less hindered diisopropylamine. The resulting BH<sub>3</sub>–diisopropylamine complex was isolated after aqueous workup and chromatographic purification. The reaction of (1*R*,2*R*,1'*S*)-4a also proceeded *via* the same mechanism.

In our previous work using a *tert*-butyl ester derivative as a substrate and LiHMDS as a base,<sup>6</sup> we proposed different mechanisms. That reaction of the *tert*-butyl ester derivative might also proceed *via* the simple mechanism described above.

## Conclusions

In conclusion, we have demonstrated preparative routes to *N*-((*S*)-1-arylethyl)azetidine-2-carbonitriles 3, stereoselective preparation of their *N*-BH<sub>3</sub> complexes 4, and LDA-promoted diastereoselective  $\alpha$ -alkylation to produce  $\alpha$ -alkylated azetidine-2-carbonitriles 5. The scope and limitations of this reaction



towards various electrophiles were described. The *N*-((*S*)-1-(4-methoxyphenyl)ethyl) substituent, as in  $\alpha$ -alkylated products (*2S,1'S*)- and (*2R,1'S*)-**5ba**, could be removed by TFA treatment. The corresponding enantiomers, 2-benzylazetidine-2-carbonitriles (*S*)-**10a** and (*R*)-**10a**, were successfully synthesized.

Our protocol enables the production of optically active nitrogen-containing fine chemicals starting from commercially available chiral 1-arylethylamines, which are inexpensive chiral compounds.

## Experimental

### General

Specific rotations were recorded on a JASCO polarimeter P-1010. Infrared spectra (IR) were recorded on a JASCO FT/IR-4600 spectrometer.  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{11}\text{B}$  NMR spectra were measured on a Varian ( $^1\text{H}$ : 400 MHz,  $^{13}\text{C}$ : 100 MHz) or a Bruker ( $^1\text{H}$ : 400 MHz,  $^{13}\text{C}$ : 100 MHz,  $^{11}\text{B}$ : 128 MHz) spectrometer. As an internal standard in  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$  ( $\delta$  0 ppm) for  $^1\text{H}$  NMR and  $\text{CDCl}_3$  ( $\delta$  77.00 ppm) for  $^{13}\text{C}$  NMR were used. In  $^{11}\text{B}$  NMR, boron trifluoride diethyl etherate ( $\text{BF}_3 \cdot \text{OEt}_2$ ) was used as an external standard ( $\delta$  0 ppm). The splitting patterns are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad peak. High-resolution mass spectra (ESI) were measured on a Thermo Fisher Scientific LC/FT-MS spectrometer. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate round-bottomed flasks with a magnetic stirring bar under an argon (Ar) atmosphere. Reactions at  $-78^\circ\text{C}$  were carried out using a constant temperature bath with a magnetic stirrer (PSL-1800, EYELA, Japan) and an ultracooling reactor (UCR-150, Techno-Sigma Co., Ltd., Japan). Borane dimethyl sulfide complex was purchased from KANTO Chemical Co., Inc. (Japan). A 1.0 M lithium bis(trimethylsilyl) amide (LiHMDS) solution in THF was purchased from Sigma-Aldrich. Anhydrous tetrahydrofuran (THF) was purchased from KANTO Chemical Co., Inc. Dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) was purchased from FUJIFILM Wako Chemical Corporation (Japan) and dried over 4 Å molecular sieves. For the thin layer chromatography (TLC) analysis throughout this work, Silicagel 70 TLC Plate-Wako purchased from FUJIFILM Wako Chemical Corporation was used. The products were purified by preparative column chromatography on silica gel (Wakosil 60, 64–210  $\mu\text{m}$ ) purchased from FUJIFILM Wako Chemical Corporation. For strong basic compound such as (*2S,1'S*)-**6aa**, NH TLC plates and amino-functionalized silica gel (Chromatorex NH-DM1020) purchased from Fuji Silysia Chemical Ltd. (Japan) were used.

### Representative procedure for preparation of methyl 1-((*S*)-1'-phenylethyl)azetidine-2-carboxylate [(*2S,1'S*)-**1a** and (*2R,1'S*)-**1a**]

(Step 1)  $\gamma$ -Butyrolactone (6.0 mL, 78 mmol) and  $\text{PBr}_3$  (0.2 mL, 2.0 mmol) was stirred at  $100^\circ\text{C}$  under an Ar atmosphere.  $\text{Br}_2$  (4.4 mL, 86 mmol) was added dropwise for 1 h to the mixture with stirring. After stirring for 5 min at  $100^\circ\text{C}$ , the resulting mixture was cooled to room temperature and the excess  $\text{Br}_2$  was removed by flow of  $\text{N}_2$ . The residue was dissolved in MeOH (30

mL) and stirred for 20 h at room temperature. The resulting mixture was treated with saturated aqueous  $\text{Na}_2\text{SO}_3$  and extracted with *n*-hexane. The combined extracts were washed with saturated aqueous  $\text{NaHCO}_3$  followed by water. The solution was dried over  $\text{Na}_2\text{SO}_4$  and evaporated. The residue was purified by chromatography on silica gel (*n*-hexane/EtOAc = 20/1 to 10/1 as the eluent) to afford methyl 2,4-dibromobutanoate with impurities (14.54 g, 72% yield) as a colourless oil. (Step 2) A mixture of methyl 2,4-dibromobutanoate (747 mg, 2.87 mmol), (*S*)-1-phenylethylamine (0.37 mL, 2.9 mmol), and  $\text{NaHCO}_3$  (1.21 g, 14.4 mmol) in MeCN (14 mL) was refluxed for 13 h. The resulting mixture was cooled to room temperature followed by filtered. The filtrate was evaporated and the residue was purified by chromatography on silica gel [*n*-hexane/EtOAc = 4/1 to 2/1 as the eluent,  $R_f$ : (*2S,1'S*) > (*2R,1'S*)] to obtain (*2S,1'S*)-**1a** (190 mg, 30% yield) as a colourless oil and (*2R,1'S*)-**1a** (178 mg, 28% yield) as a colourless oil. (*2S,1'S*)-**1a**:  $[\alpha]_{589}^{24} -118.9$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$  3084, 3061, 3025, 3004, 2966, 2930, 2841, 2781, 1749, 1728, 1493, 1451, 1435, 1371, 1319, 1280, 1229, 1193, 1170, 1095, 1071, 1038, 980, 955, 936, 911, 831, 813, 763, 699;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.20 (5H, m, Ph), 3.76 (1H, dd,  $J = 8.8, 8.2$  Hz, 2-H), 3.75 (3H, s,  $\text{OCH}_3$ ), 3.45 (1H, q,  $J = 6.6$  Hz, 1'-H), 3.11 (1H, dddd,  $J = 8.2, 7.2, 2.8, 0.8$  Hz, 4-H), 2.80 (1H, ddd,  $J = 8.8, 8.2, 7.2$  Hz, 4-H), 2.27 (1H, dddd,  $J = 10.5, 8.8, 8.8, 8.2$  Hz, 3-H), 2.18 (1H, dddd,  $J = 10.5, 8.2, 8.2, 2.8$  Hz, 3-H), 1.22 (3H, d,  $J = 6.6$  Hz, 1'- $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.6, 142.4, 128.2, 127.4, 127.2, 67.2, 63.9, 51.9, 49.6, 20.9, 20.8; HRMS (ESI): calcd for  $\text{C}_{13}\text{H}_{18}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$  220.1332, found 220.1328. (*2R,1'S*)-**1a**:  $[\alpha]_{589}^{24} +59.8$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$  3085, 3061, 3026, 3005, 2966, 2929, 2869, 2828, 2785, 1731, 1494, 1452, 1435, 1372, 1353, 1308, 1277, 1230, 1194, 1169, 1112, 1082, 1056, 1031, 977, 912, 818, 763, 742, 698;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.18 (5H, m, Ph), 3.62–3.54 (2H, m, 2-H and 4-H), 3.36 (1H, q,  $J = 6.4$  Hz, 1'-H), 3.30 (3H, s,  $\text{OCH}_3$ ), 3.01 (1H, ddd,  $J = 9.2, 8.0, 6.8$  Hz, 4-H), 2.30 (1H, dddd,  $J = 10.2, 9.2, 8.8, 8.8$  Hz, 3-H), 2.14 (1H, dddd,  $J = 10.2, 8.2, 8.0, 2.2$  Hz, 3-H), 1.29 (3H, d,  $J = 6.4$  Hz, 1'- $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.6, 141.6, 128.0, 127.9, 127.5, 68.1, 64.4, 51.5, 50.8, 20.8, 19.7; HRMS (ESI): calcd for  $\text{C}_{13}\text{H}_{18}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$  220.1332, found 220.1329.

### Methyl 1-((*S*)-1'-(4'-methoxyphenyl)ethyl)azetidine-2-carboxylate [(*2S,1'S*)-**1b** and (*2R,1'S*)-**1b**]

Prepared by the same procedure with **1a** using (*S*)-1-(4-methoxyphenyl)ethylamine (1.48 mL, 10.0 mmol) instead of (*S*)-1-phenylethylamine. The reaction time was 18 h. Purification by chromatography on silica gel [*n*-hexane/EtOAc = 2/1 to 1/2 as the eluent,  $R_f$ : (*2S,1'S*) > (*2R,1'S*)] gave (*2S,1'S*)-**1b** (953 mg, 38% yield) as a colourless oil and (*2R,1'S*)-**1b** (910 mg, 37% yield) as a colourless oil. (*2S,1'S*)-**1b**:  $[\alpha]_{589}^{24} -110.7$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$  3000, 2963, 2932, 2835, 1748, 1727, 1610, 1584, 1509, 1437, 1370, 1320, 1281, 1242, 1194, 1168, 1097, 1033, 982, 955, 935, 910, 831, 733;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (2H, ddd,  $J = 8.4, 2.6, 2.6$  Hz, ArH), 6.84 (2H, ddd,  $J = 8.4, 2.6, 2.6$  Hz, ArH), 3.79 (3H, s,  $\text{OCH}_3$ ), 3.75 (3H, s,  $\text{OCH}_3$ ), 3.73 (1H, dd,  $J = 8.6, 8.4$  Hz, 2-H), 3.40 (1H, q,  $J = 6.6$  Hz, 1'-H), 3.08 (1H, dddd,  $J =$



= 8.3, 7.1, 2.6, 0.8 Hz, 4-H), 2.79 (1H, ddd,  $J = 8.9, 8.2, 7.1$  Hz, 4-H), 2.26 (1H, dddd,  $J = 10.5, 8.9, 8.6, 8.3$  Hz, 3-H), 2.16 (1H, dddd,  $J = 10.5, 8.4, 8.2, 2.6$  Hz, 3-H), 1.20 (3H, d,  $J = 6.6$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.7, 158.7, 134.5, 128.5, 113.6, 66.5, 63.9, 55.2, 51.9, 49.4, 20.9, 20.8; HRMS (ESI): calcd for C<sub>14</sub>H<sub>20</sub>NO<sub>3</sub> [M + H]<sup>+</sup> 250.1438, found 250.1435. (2*R*,1'*S*)-**1b**: [ $\alpha$ ]<sub>589</sub><sup>24</sup> +43.8 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3000, 2963, 2931, 2868, 2835, 1730, 1611, 1585, 1510, 1436, 1372, 1350, 1293, 1279, 1241, 1194, 1169, 1104, 1058, 1032, 980, 956, 935, 911, 832, 808, 738; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.21 (2H, ddd,  $J = 8.8, 3.0, 3.0$  Hz, ArH), 6.80 (2H, ddd,  $J = 8.8, 3.0, 3.0$  Hz, ArH), 3.77 (3H, s, OCH<sub>3</sub>), 3.61–3.52 (2H, m, 2-H and 4-H), 3.37 (3H, s, OCH<sub>3</sub>), 3.31 (1H, q,  $J = 6.4$  Hz, 1'-H), 2.98 (1H, ddd,  $J = 9.2, 8.0, 7.2$  Hz, 4-H), 2.34–2.22 (1H, m, 3-H), 2.13 (1H, dddd,  $J = 10.4, 8.0, 8.0, 2.4$  Hz, 3-H), 1.26 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.7, 158.9, 133.7, 129.0, 113.4, 67.4, 64.3, 55.2, 51.5, 50.7, 20.8, 19.8; HRMS (ESI): calcd for C<sub>14</sub>H<sub>20</sub>NO<sub>3</sub> [M + H]<sup>+</sup> 250.1438, found 250.1434.

#### Representative procedure for preparation of (S)-1-((S)-1'-phenylethyl)azetidide-2-carboxamide [(2*S*,1'*S*)-**2a**]

A mixture of (2*S*,1'*S*)-**1a** (151 mg, 0.689 mmol) and 25% NH<sub>3</sub>·H<sub>2</sub>O solution (2.8 mL) was stirred for 1 day at room temperature. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined extracts were washed with brine. The solution was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 20/1 to 10/1 as the eluent) to afford (2*S*,1'*S*)-**2a** (99.3 mg, 71% yield) as a colourless gum. [ $\alpha$ ]<sub>589</sub><sup>24</sup> -109.2 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3429, 3262, 3195, 3060, 3027, 3004, 2964, 2930, 2849, 2788, 1671, 1573, 1494, 1450, 1396, 1372, 1354, 1331, 1298, 1282, 1226, 1168, 1141, 1099, 1071, 1031, 998, 972, 939, 914, 761, 734, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.42–7.22 (6H, m, NH<sub>2</sub> and Ph), 6.03 (1H, br s, NH<sub>2</sub>), 3.67 (1H, dd,  $J = 8.8, 8.6$  Hz, 2-H), 3.47 (1H, q,  $J = 6.6$  Hz, 1'-H), 3.13 (1H, ddd,  $J = 8.2, 8.2, 2.6$  Hz, 4-H), 2.81 (1H, ddd,  $J = 8.8, 8.6, 8.2$  Hz, 4-H), 2.37 (1H, dddd,  $J = 11.0, 8.6, 8.6, 2.6$  Hz, 3-H), 2.11 (1H, dddd,  $J = 11.0, 8.8, 8.8, 8.2$  Hz, 3-H), 1.19 (3H, d,  $J = 6.6$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  177.2, 142.7, 128.4, 127.2, 126.9, 67.5, 65.1, 49.8, 21.8, 21.2; HRMS (ESI): calcd for C<sub>12</sub>H<sub>17</sub>N<sub>2</sub>O [M + H]<sup>+</sup> 205.1335, found 205.1333.

#### (*R*)-1-((S)-1'-Phenylethyl)azetidide-2-carboxamide [(2*R*,1'*S*)-**2a**]

Prepared from (2*R*,1'*S*)-**1a** (433 mg, 1.97 mmol) by the same procedure with (2*S*,1'*S*)-**2a**. Purification by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 20/1 to 10/1 as the eluent) afforded (2*R*,1'*S*)-**2a** (243 mg, 60% yield) as colourless crystals, mp 116–119 °C. [ $\alpha$ ]<sub>589</sub><sup>24</sup> +44.4 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3388, 3151, 3029, 3006, 2979, 2965, 2928, 2891, 2850, 2800, 1683, 1653, 1620, 1496, 1483, 1442, 1409, 1374, 1363, 1336, 1303, 1281, 1240, 1227, 1213, 1194, 1158, 1147, 1117, 1085, 1049, 1016, 967, 941, 917, 815, 761, 702; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32–7.20 (5H, m, Ph), 6.42 (1H, br s, NH<sub>2</sub>), 5.23 (1H, br s, NH<sub>2</sub>), 3.57 (1H, dd,  $J = 8.8, 8.5$  Hz, 2-H), 3.50–3.43 (1H, m, 4-H), 3.39 (1H, q,  $J = 6.4$  Hz, 1'-H), 3.08 (1H, ddd,  $J = 8.8, 8.8, 7.2$  Hz, 4-H), 2.33 (1H, dddd,  $J = 10.9, 8.8, 8.5, 2.6$  Hz, 3-H), 2.06 (1H,

dddd,  $J = 10.9, 8.8, 8.8, 8.8$  Hz, 3-H), 1.31 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.9, 141.3, 128.5, 127.85, 127.79, 66.8, 65.2, 49.6, 22.0, 18.3; HRMS (ESI): calcd for C<sub>12</sub>H<sub>17</sub>N<sub>2</sub>O [M + H]<sup>+</sup> 205.1335, found 205.1333.

#### Representative procedure for preparation of (S)-1-((S)-1'-(4'-methoxyphenyl)ethyl)azetidide-2-carboxamide [(2*S*,1'*S*)-**2b**]

A mixture of (2*S*,1'*S*)-**1b** (427 mg, 1.71 mmol) and NaCN (17 mg, 0.35 mmol) in 7 N NH<sub>3</sub> MeOH solution (2.4 mL) was stirred for 6 days at room temperature. The resulting mixture was evaporated and the residue was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 40/1 to 20/1 as the eluent) to obtain (2*S*,1'*S*)-**2b** (396 mg, 99% yield) as a colourless gum. [ $\alpha$ ]<sub>589</sub><sup>23</sup> -103.7 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3427, 3193, 3000, 2961, 2931, 2835, 1671, 1609, 1582, 1509, 1453, 1419, 1396, 1372, 1350, 1332, 1300, 1286, 1241, 1172, 1141, 1092, 1031, 973, 937, 831, 731; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35 (1H, br s, NH<sub>2</sub>), 7.22 (2H, ddd,  $J = 8.8, 2.4, 2.4$  Hz, ArH), 6.86 (2H, ddd,  $J = 8.8, 2.4, 2.4$  Hz, ArH), 6.35 (1H, br s, NH<sub>2</sub>), 3.80 (3H, s, OCH<sub>3</sub>), 3.64 (1H, dd,  $J = 8.8, 8.8$  Hz, 2-H), 3.42 (1H, q,  $J = 6.4$  Hz, 1'-H), 3.09 (1H, ddd,  $J = 8.2, 8.0, 2.8$  Hz, 4-H), 2.79 (1H, ddd,  $J = 8.8, 8.8, 8.0$  Hz, 4-H), 2.35 (1H, dddd,  $J = 11.0, 8.8, 8.8, 2.8$  Hz, 3-H), 2.09 (1H, dddd,  $J = 11.0, 8.8, 8.8, 8.2$  Hz, 3-H), 1.16 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  177.3, 158.7, 134.7, 127.9, 113.7, 66.7, 65.2, 55.1, 49.6, 21.8, 21.2; HRMS (ESI): calcd for C<sub>13</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup> 235.1441, found 235.1438.

#### (*R*)-1-((S)-1'-(4'-Methoxyphenyl)ethyl)azetidide-2-carboxamide [(2*R*,1'*S*)-**2b**]

Prepared from (2*R*,1'*S*)-**1b** (910 mg, 3.65 mmol) by the same procedure with (2*S*,1'*S*)-**2b**. The reaction time was 13 days. Purification by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 40/1 to 20/1 as the eluent) gave (2*R*,1'*S*)-**2b** (861 mg, 100% yield) as colourless crystals, mp 105–107 °C. [ $\alpha$ ]<sub>589</sub><sup>23</sup> +11.8 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3398, 3180, 2998, 2964, 2947, 2923, 2838, 1632, 1612, 1582, 1509, 1451, 1439, 1418, 1370, 1351, 1338, 1301, 1277, 1243, 1166, 1103, 1057, 1030, 970, 944, 922, 828, 810, 720; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.17 (2H, ddd,  $J = 8.8, 2.6, 2.6$  Hz, ArH), 6.81 (2H, ddd,  $J = 8.8, 2.6, 2.6$  Hz, ArH), 6.44 (1H, br s, NH<sub>2</sub>), 5.22 (1H, br s, NH<sub>2</sub>), 3.76 (3H, s, OCH<sub>3</sub>), 3.54 (1H, dd,  $J = 8.8, 8.4$  Hz, 2-H), 3.44 (1H, ddd,  $J = 8.3, 7.4, 2.4$  Hz, 4-H), 3.34 (1H, q,  $J = 6.8$  Hz, 1'-H), 3.05 (1H, ddd,  $J = 9.0, 8.8, 7.4$  Hz, 4-H), 2.32 (1H, dddd,  $J = 11.0, 8.8, 8.4, 2.4$  Hz, 3-H), 2.05 (1H, dddd,  $J = 11.0, 9.0, 8.8, 8.3$  Hz, 3-H), 1.28 (3H, d,  $J = 6.8$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  176.0, 159.1, 133.3, 128.8, 113.8, 66.2, 65.1, 55.1, 49.6, 21.9, 18.4; HRMS (ESI): calcd for C<sub>13</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup> 235.1441, found 235.1434.

#### Representative procedure for preparation of (S)-1-((S)-1'-phenylethyl)azetidide-2-carbonitrile [(2*S*,1'*S*)-**3a**]

A solution of (2*S*,1'*S*)-**2a** (645 mg, 3.16 mmol) and pyridine (0.31 mL, 3.8 mmol) in 1,4-dioxane (16 mL) was cooled at ca. 10 °C and treated with trifluoroacetic anhydride (0.53 mL, 3.8 mmol) under an Ar atmosphere. After stirring for 2 h at room temperature, the resulting mixture was quenched with H<sub>2</sub>O and extracted with EtOAc. The combined extracts were washed with



saturated aqueous NaHCO<sub>3</sub> followed by brine. The organic solution was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. Purification of the residue by chromatography on silica gel (*n*-hexane/EtOAc = 6/1 to 5/1 as the eluent) gave (2*S*,1'*S*)-**3a** (530 mg, 90% yield) as colourless crystals, mp 36–38 °C. [ $\alpha$ ]<sub>589</sub><sup>24</sup> –153.1 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3069, 3028, 2973, 2959, 2923, 2863, 2828, 2800, 2235, 1489, 1455, 1442, 1371, 1358, 1335, 1316, 1301, 1281, 1223, 1177, 1141, 1099, 1081, 1070, 1028, 972, 939, 926, 907, 820, 798, 756, 694; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.34–7.21 (5H, m, Ph), 3.84 (1H, dd, *J* = 7.2, 7.2 Hz, 2-H), 3.53 (1H, q, *J* = 6.6 Hz, 1'-H), 3.22 (1H, dddd, *J* = 7.7, 7.1, 5.5, 0.6 Hz, 4-H), 3.04 (1H, ddd, *J* = 7.2, 7.2, 7.1 Hz, 4-H), 2.43–2.30 (2H, m, 3-H), 1.31 (3H, d, *J* = 6.6 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  141.7, 128.5, 127.5, 127.2, 119.5, 66.1, 51.1, 50.8, 21.9, 20.7; HRMS (ESI): calcd for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub> [M + H]<sup>+</sup> 187.1230, found 187.1232.

#### (*R*)-1-((*S*)-1'-Phenylethyl)azetidione-2-carbonitrile [(2*R*,1'*S*)-**3a**]

Prepared from (2*R*,1'*S*)-**2a** (578 mg, 2.83 mmol) by the same procedure with (2*S*,1'*S*)-**3a**. Purification by chromatography on silica gel (*n*-hexane/EtOAc = 5/1 to 4/1 as the eluent) gave (2*R*,1'*S*)-**3a** (497 mg, 94% yield) as colourless crystals, mp 40–41 °C. [ $\alpha$ ]<sub>589</sub><sup>24</sup> +7.4 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3031, 2968, 2930, 2890, 2857, 2809, 2235, 1494, 1455, 1375, 1362, 1319, 1280, 1249, 1227, 1212, 1163, 1140, 1109, 1079, 1059, 1028, 1013, 1001, 977, 945, 920, 827, 801, 778, 756, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.38–7.25 (5H, m, Ph), 3.84 (1H, dd, *J* = 7.2, 7.2 Hz, 2-H), 3.46 (1H, q, *J* = 6.4 Hz, 1'-H), 3.42 (1H, dddd, *J* = 7.7, 7.1, 5.8, 0.8 Hz, 4-H), 3.03 (1H, ddd, *J* = 7.2, 7.2, 7.1 Hz, 4-H), 2.43–2.30 (2H, m, 3-H), 1.25 (3H, d, *J* = 6.4 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  140.8, 128.5, 127.9, 127.6, 118.7, 66.5, 51.4, 50.6, 21.8, 20.4; HRMS (ESI): calcd for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub> [M + H]<sup>+</sup> 187.1230, found 187.1232.

#### (*S*)-1-((*S*)-1'-(4''-Methoxyphenyl)ethyl)azetidione-2-carbonitrile [(2*S*,1'*S*)-**3b**]

Prepared from (2*S*,1'*S*)-**2b** (396 mg, 1.69 mmol) by the same procedure with (2*S*,1'*S*)-**3a**. Purification by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc = 100/1 to 50/1 as the eluent) gave (2*S*,1'*S*)-**3b** (294 mg, 80% yield) as colourless crystals, mp 94–95 °C. [ $\alpha$ ]<sub>589</sub><sup>23</sup> –140.1 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3043, 3006, 2968, 2925, 2861, 2838, 2816, 2235, 1608, 1581, 1509, 1460, 1439, 1367, 1335, 1319, 1300, 1290, 1246, 1224, 1179, 1169, 1143, 1109, 1094, 1078, 1032, 975, 942, 928, 832, 812, 788, 728; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.24 (2H, ddd, *J* = 8.6, 2.6, 2.6 Hz, ArH), 6.85 (2H, ddd, *J* = 8.6, 2.6, 2.6 Hz, ArH), 3.81 (1H, dd, *J* = 7.2, 7.2 Hz, 2-H), 3.79 (3H, s, OCH<sub>3</sub>), 3.49 (1H, q, *J* = 6.4 Hz, 1'-H), 3.19 (1H, ddd, *J* = 7.6, 7.2, 5.8 Hz, 4-H), 3.04 (1H, ddd, *J* = 7.2, 7.2, 7.2 Hz, 4-H), 2.42–2.28 (2H, m, 3-H), 1.28 (3H, d, *J* = 6.4 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.9, 133.7, 128.3, 119.5, 113.8, 65.4, 55.2, 51.0, 50.8, 21.8, 20.7; HRMS (ESI): calcd for C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O [M + H]<sup>+</sup> 217.1335, found 217.1335.

#### (*R*)-1-((*S*)-1'-(4''-Methoxyphenyl)ethyl)azetidione-2-carbonitrile [(2*R*,1'*S*)-**3b**]

Prepared from (2*R*,1'*S*)-**2b** (805 mg, 3.44 mmol) by the same procedure with (2*S*,1'*S*)-**3a**. Purification by chromatography on

silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/1 to 50/1 as the eluent) gave (2*R*,1'*S*)-**3b** (547 mg, 74% yield) as colourless crystals, mp 39–42 °C. [ $\alpha$ ]<sub>589</sub><sup>24</sup> +5.3 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3043, 3006, 2968, 2925, 2861, 2838, 2816, 2235, 1608, 1581, 1509, 1460, 1439, 1367, 1335, 1319, 1300, 1290, 1246, 1179, 1169, 1143, 1109, 1094, 1078, 1032, 975, 942, 928, 832, 812, 788, 728; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.26 (2H, ddd, *J* = 8.8, 2.5, 2.5 Hz, ArH), 6.88 (2H, ddd, *J* = 8.8, 2.5, 2.5 Hz, ArH), 3.86–3.77 (1H, m, 2-H), 3.80 (3H, s, OCH<sub>3</sub>), 3.46–3.36 (2H, m, 4-H), 3.01 (1H, q, *J* = 6.8 Hz, 1'-H), 2.43–2.29 (2H, m, 3-H), 1.22 (3H, d, *J* = 6.8 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.3, 132.8, 128.6, 118.8, 113.9, 65.9, 55.2, 51.4, 50.5, 21.7, 20.4; HRMS (ESI): calcd for C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O [M + H]<sup>+</sup> 217.1335, found 217.1334.

#### Representative procedure for preparation of ((1*S*,2*S*)-2-cyano-1-((*S*)-1'-phenylethyl)azetidione-1-ium-1-yl)trihydroborate [(1*S*,2*S*,1'*S*)-**4a**]

Borane dimethyl sulfide complex (*ca.* 10 M, 0.31 mL, 3.1 mmol) was added to a solution of (2*S*,1'*S*)-**3a** (530 mg, 2.85 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (14 mL) at 0 °C under an Ar atmosphere and the mixture was stirred for 30 h at room temperature. The resulting mixture was purified by chromatography on silica gel (*n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/2 to 0/1 as the eluent) to obtain (1*S*,2*S*,1'*S*)-**4a** (519 mg, 91% yield) as colourless crystals, mp 126–128 °C. [ $\alpha$ ]<sub>589</sub><sup>24</sup> –152.2 (*c* 1.0 in CHCl<sub>3</sub>); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3030, 2978, 2945, 2361, 2340, 2297, 2244, 1496, 1456, 1444, 1386, 1337, 1315, 1288, 1252, 1242, 1210, 1194, 1173, 1155, 1128, 1102, 1079, 1061, 1030, 1014, 945, 923, 890, 840, 779, 761, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.48–7.37 (5H, m, Ph), 4.30 (1H, dd, *J* = 9.2, 8.8 Hz, 2-H), 4.18 (1H, q, *J* = 7.0 Hz, 1'-H), 3.83 (1H, ddd, *J* = 9.4, 8.8, 8.8 Hz, 4-H), 3.32 (1H, ddd, *J* = 9.2, 8.8, 3.2 Hz, 4-H), 3.04 (1H, dddd, *J* = 10.9, 9.4, 9.2, 9.2 Hz, 3-H), 2.50–1.50 (3H, br, BH<sub>3</sub>), 2.21 (1H, dddd, *J* = 10.9, 8.8, 8.8, 3.2 Hz, 3-H), 1.68 (3H, d, *J* = 7.0 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  135.3, 130.0, 129.8, 129.0, 114.7, 70.3, 54.55, 54.48, 20.8, 15.3; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  –13.3 (br); HRMS (ESI): calcd for C<sub>12</sub>H<sub>18</sub>BN<sub>2</sub> [M + H]<sup>+</sup> 201.1558, found 201.1559.

#### ((1*R*,2*R*)-2-Cyano-1-((*S*)-1'-phenylethyl)azetidione-1-ium-1-yl) trihydroborate [(1*R*,2*R*,1'*S*)-**4a**]

Prepared from (2*R*,1'*S*)-**3a** (496 mg, 2.66 mmol) by the same procedure with (1*S*,2*S*,1'*S*)-**4a**. Purification by chromatography on silica gel (*n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/2 to 0/1 as the eluent) to obtain (1*R*,2*R*,1'*S*)-**4a** (458 mg, 86% yield) as colourless crystals, mp 126–128 °C. [ $\alpha$ ]<sub>589</sub><sup>25</sup> +120.4 (*c* 1.0 in CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3026, 2978, 2937, 2429, 2364, 2337, 2293, 2247, 1491, 1455, 1383, 1328, 1313, 1283, 1254, 1213, 1193, 1171, 1149, 1103, 1082, 1064, 1042, 1029, 1017, 988, 951, 923, 876, 838, 766, 702; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.49–7.37 (5H, m, Ph), 4.62 (1H, dd, *J* = 9.2, 8.8 Hz, 2-H), 4.11 (1H, q, *J* = 7.0 Hz, 1'-H), 3.58 (1H, dddd, *J* = 9.6, 9.2, 3.4, 0.6 Hz, 4-H), 3.52 (1H, ddd, *J* = 9.4, 9.2, 8.9 Hz, 4-H), 3.02 (1H, dddd, *J* = 11.1, 9.6, 9.4, 9.2 Hz, 3-H), 2.50–1.50 (3H, br, BH<sub>3</sub>), 2.22 (1H, dddd, *J* = 11.1, 8.9, 8.8, 3.4 Hz, 3-H), 1.68 (3H, d, *J* = 7.0 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  134.8, 130.0, 129.9, 129.0, 114.5, 71.1, 58.6, 51.6, 20.7, 15.6; <sup>11</sup>B



NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  -13.6 (br); HRMS (ESI): calcd for C<sub>12</sub>H<sub>18</sub>BN<sub>2</sub> [M + H]<sup>+</sup> 201.1558, found 201.1557.

**((1*S*,2*S*)-2-Cyano-1-((*S*)-1'-(4''-methoxyphenyl)ethyl)azetidino-1-ium-1-yl)trihydroborate [(1*S*,2*S*,1'*S*)-4*b*]**

Prepared from (2*S*,1'*S*)-3*b* (173 mg, 0.800 mmol) by the same procedure with (1*S*,2*S*,1'*S*)-4*a*. Purification by chromatography on silica gel (*n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/2 to 0/1 as the eluent) gave (1*S*,2*S*,1'*S*)-4*b* (171 mg, 93% yield) as colourless crystals, mp 108–110 °C. [ $\alpha$ ]<sub>589</sub><sup>24</sup> -150.3 (*c* 1.0 in CHCl<sub>3</sub>); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  2963, 2935, 2841, 2363, 2339, 2298, 2245, 2157, 1609, 1581, 1514, 1463, 1449, 1389, 1335, 1295, 1250, 1211, 1178, 1171, 1099, 1070, 1022, 996, 941, 882, 824, 739, 726; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32 (2H, ddd, *J* = 8.8, 2.6, 2.6 Hz, ArH), 6.96 (2H, ddd, *J* = 8.8, 2.6, 2.6 Hz, ArH), 4.32 (1H, dd, *J* = 9.2, 9.2 Hz, 2-H), 4.13 (1H, q, *J* = 6.8 Hz, 1'-H), 3.84 (3H, s, OCH<sub>3</sub>), 3.79 (1H, ddd, *J* = 9.2, 9.2, 8.8 Hz, 4-H), 3.27 (1H, ddd, *J* = 9.2, 9.2, 3.0 Hz, 4-H), 3.02 (1H, dddd, *J* = 10.8, 9.2, 9.2, 9.2 Hz, 3-H), 2.50–1.50 (3H, br, BH<sub>3</sub>), 2.22 (1H, dddd, *J* = 10.8, 9.2, 8.8, 3.0 Hz, 3-H), 1.64 (3H, d, *J* = 6.8 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  160.5, 131.2, 127.2, 114.8, 114.2, 69.8, 55.3, 54.4 (2C), 20.7, 15.4; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  -13.6 (br); HRMS (ESI): calcd for C<sub>13</sub>H<sub>20</sub>BN<sub>2</sub>O [M + H]<sup>+</sup> 231.1663, found 231.1665.

**((1*R*,2*R*)-2-Cyano-1-((*S*)-1'-(4''-methoxyphenyl)ethyl)azetidino-1-ium-1-yl)trihydroborate [(1*R*,2*R*,1'*S*)-4*b*]**

Prepared from (2*R*,1'*S*)-3*b* (461 mg, 2.13 mmol) by the same procedure with (1*S*,2*S*,1'*S*)-4*a*. Purification by chromatography on silica gel (*n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/2 to 0/1 as the eluent) to obtain (1*R*,2*R*,1'*S*)-4*b* (351 mg, 72% yield) as colourless crystals, mp 108–110 °C. [ $\alpha$ ]<sub>589</sub><sup>24</sup> +102.1 (*c* 1.0 in CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3062, 3027, 2996, 2979, 2961, 2938, 2838, 2431, 2361, 2341, 2298, 2245, 1698, 1608, 1582, 1514, 1445, 1386, 1298, 1288, 1244, 1217, 1180, 1151, 1099, 1071, 1028, 994, 949, 877, 833, 825, 740, 729; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35 (2H, ddd, *J* = 8.6, 2.5, 2.5 Hz, ArH), 6.94 (2H, ddd, *J* = 8.6, 2.5, 2.5 Hz, ArH), 4.60 (1H, dd, *J* = 9.2, 9.2 Hz, 2-H), 4.05 (1H, q, *J* = 6.8 Hz, 1'-H), 3.83 (3H, s, OCH<sub>3</sub>), 3.61–3.49 (2H, m, 4-H), 2.99 (1H, dddd, *J* = 11.0, 9.6, 9.2, 9.2 Hz, 3-H), 2.50–1.50 (3H, br, BH<sub>3</sub>), 2.25 (1H, dddd, *J* = 11.0, 9.2, 7.4, 4.2 Hz, 3-H), 1.63 (3H, d, *J* = 6.8 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  160.5, 131.3, 126.7, 114.7, 114.1, 70.7, 58.6, 55.3, 51.8, 20.6, 15.7; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  -14.0 (br); HRMS (ESI): calcd for C<sub>13</sub>H<sub>20</sub>BN<sub>2</sub>O [M + H]<sup>+</sup> 231.1663, found 231.1663.

**Preparation of ca. 0.7 M LDA solution in THF/*n*-hexane**

A dried 100 mL storage flask with stopcock-equipped septum-inlet was charged with diisopropylamine (3.0 mL, 21 mmol) and THF (13.4 mL) under an Ar atmosphere. A 1.6 M *n*BuLi *n*-hexane solution (12.8 mL, 20.4 mmol) was added to the solution at -78 °C. The mixture was stirred for 20 min at the same temperature and allowed to warm to 0 °C. The resulting pale yellow solution was stored in a refrigerator.

**Representative procedure for  $\alpha$ -alkylation of (1*S*,2*S*,1'*S*)-4*a* with LDA (Table 1, entry 4)**

THF (8.0 mL) was added to (1*S*,2*S*,1'*S*)-4*a* (200 mg, 1.00 mmol) in a flask under an Ar atmosphere and the mixture was cooled at -78 °C as soon as possible. The mixture was treated with a ca. 0.7 M LDA solution in THF/*n*-hexane (1.7 mL, 1.2 mmol) and stirred for 0.5 h at -78 °C. The mixture was treated with benzyl bromide (154  $\mu$ L, 1.29 mmol) and allowed to warm at room temperature. After stirring for 3 h, the resulting mixture was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> followed by brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The volatiles were removed by evaporation and the residue was purified by chromatography on silica gel [*n*-hexane/EtOAc = 10/1 as the eluent] to obtain (*S*)-2-benzyl-1-((*S*)-1'-phenylethyl)azetidino-2-carbonitrile [(2*S*,1'*S*)-5*aa*] (193 mg, 70% yield) as colourless crystals, mp 73–75 °C. [ $\alpha$ ]<sub>589</sub><sup>26</sup> -163.6 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3026, 2968, 2936, 2870, 2826, 2798, 1492, 1453, 1371, 1355, 1332, 1305, 1277, 1253, 1240, 1210, 1189, 1160, 1137, 1108, 1089, 1075, 1058, 1027, 1003, 988, 910, 866, 768, 752, 699; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.52–7.48 (2H, m, ArH), 7.39–7.33 (2H, m, ArH), 7.28 (1H, tt, *J* = 7.2, 1.4 Hz, ArH), 7.25–7.16 (3H, m, ArH), 7.03–6.98 (2H, m, ArH), 3.79 (1H, q, *J* = 6.6 Hz, 1'-H), 3.47 (1H, ddd, *J* = 8.2, 6.6, 1.6 Hz, 4-H), 3.18 (1H, ddd, *J* = 9.6, 7.6, 6.6 Hz, 4-H), 2.54 (1H, d, *J* = 13.6 Hz, CH<sub>2</sub>Ph), 2.32 (1H, ddd, *J* = 10.6, 9.6, 8.2 Hz, 3-H), 2.05–1.97 (1H, m, 3-H), 2.02 (1H, d, *J* = 13.6 Hz, CH<sub>2</sub>Ph), 1.31 (3H, d, *J* = 6.6 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  142.5, 134.2, 129.6, 128.5, 128.37, 128.36, 127.9, 127.1, 119.3, 66.5, 62.9, 48.7, 45.1, 28.3, 20.0; HRMS (ESI): calcd for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub> [M + H]<sup>+</sup> 277.1699, found 277.1700.

**Representative procedure for  $\alpha$ -alkylation of (1*R*,2*R*,1'*S*)-4*a* with LiHMDS (Table 1, entry 6)**

THF (1.2 mL) was added to (1*R*,2*R*,1'*S*)-4*a* (42 mg, 0.21 mmol) in a flask under an Ar atmosphere and the mixture was cooled at -78 °C as soon as possible. The mixture was treated with a 1 M LiHMDS solution in THF (0.50 mL, 0.50 mmol) and stirred for 0.5 h at -78 °C. The mixture was treated with benzyl bromide (65  $\mu$ L, 0.55 mmol) and allowed to warm at room temperature. After stirring for 3 h, the resulting mixture was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> followed by brine. The solution was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated by evaporation. Purification of the residue by chromatography on silica gel [*n*-hexane/EtOAc = 10/1 as the eluent, *R*<sub>F</sub>: (2*R*,1'*S*) > (2*S*,1'*S*)] afforded (2*R*,1'*S*)-5*aa* (42.9 mg, 74% yield) as colourless crystals and (2*S*,1'*S*)-5*aa* (4.8 mg, 8% yield) as colourless crystals. (2*R*,1'*S*)-5*aa*: colourless crystals, mp 72–74 °C. [ $\alpha$ ]<sub>589</sub><sup>25</sup> -91.3 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3085, 3061, 3029, 2970, 2932, 2837, 2222, 1604, 1494, 1453, 1371, 1356, 1330, 1305, 1282, 1236, 1219, 1188, 1155, 1137, 1092, 1075, 1056, 1029, 1011, 982, 949, 912, 864, 766, 751, 697; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.39–7.22 (10H, m, ArH), 3.76 (1H, q, *J* = 6.4 Hz, 1'-H), 3.24 (1H, d, *J* = 13.8 Hz, CH<sub>2</sub>Ph), 3.20 (1H, d, *J* = 13.8 Hz, CH<sub>2</sub>Ph), 2.91 (1H, ddd, *J* = 8.4, 7.1, 2.4 Hz, 4-H), 2.84



(1H, ddd,  $J = 9.5, 7.9, 7.1$  Hz, 4-H), 2.26 (1H, ddd,  $J = 10.8, 9.5, 8.4$  Hz, 3-H), 2.03 (1H, ddd,  $J = 10.8, 7.9, 2.4$  Hz, 3-H), 1.39 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  142.3, 134.2, 130.0, 128.52, 128.46, 127.42, 127.38, 127.36, 119.2, 65.1, 64.2, 48.5, 46.5, 27.2, 22.6; HRMS (ESI): calcd for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub> [M + H]<sup>+</sup> 277.1699, found 277.1699.

### Representative procedure for $\alpha$ -alkylation of (1*S*,2*S*,1'*S*)-4b with LDA (Table 1, entry 9)

THF (4.0 mL) was added to (1*S*,2*S*,1'*S*)-4b (115 mg, 0.500 mmol) in a flask under an Ar atmosphere and the mixture was cooled at  $-78$  °C as soon as possible. The mixture was treated with a *ca.* 0.7 M LDA solution in THF/*n*-hexane (0.86 mL, 0.60 mmol) at  $-78$  °C. The mixture was stirred for 0.5 h at  $-78$  °C and treated with benzyl bromide (77  $\mu$ L, 0.65 mmol). The mixture was allowed to warm at room temperature and stirred for 3 h. The resulting mixture was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> followed by brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The volatiles were removed by evaporation and the residue was purified by chromatography on silica gel [*n*-hexane/EtOAc = 7/1 as the eluent,  $R_f$ : (2*R*,1'*S*) > (2*S*,1'*S*)] to obtain (*S*)-2-benzyl-1-((*S*)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carbonitrile [(2*S*,1'*S*)-5ba] (110.6 mg, 72% yield) as colourless crystals and (*R*)-2-benzyl-1-((*S*)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carbonitrile [(2*R*,1'*S*)-5ba] (2.6 mg, 2% yield) as a colourless oil. (2*S*,1'*S*)-5ba: colourless crystals, mp 93–95 °C. [ $\alpha$ ]<sub>589</sub><sup>24</sup>  $-205.5$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3061, 3029, 2961, 2931, 2833, 2221, 1611, 1584, 1510, 1454, 1372, 1352, 1331, 1303, 1294, 1279, 1242, 1173, 1134, 1116, 1099, 1030, 993, 936, 909, 830, 785, 754, 736, 700; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.41 (2H, ddd,  $J = 8.8, 2.4, 2.4$  Hz, ArH), 7.26–7.16 (3H, m, ArH), 7.05–7.00 (2H, m, ArH), 6.90 (2H, ddd,  $J = 8.8, 2.4, 2.4$  Hz, ArH), 3.80 (3H, s, OCH<sub>3</sub>), 3.74 (1H, q,  $J = 6.4$  Hz, 1'-H), 3.45 (1H, ddd,  $J = 8.2, 6.6, 1.8$  Hz, 4-H), 3.15 (1H, ddd,  $J = 9.9, 7.6, 6.6$  Hz, 4-H), 2.54 (1H, d,  $J = 13.6$  Hz, CH<sub>2</sub>Ph), 2.30 (1H, ddd,  $J = 10.7, 9.9, 8.2$  Hz, 3-H), 2.07 (1H, d,  $J = 13.6$  Hz, CH<sub>2</sub>Ph), 1.99 (1H, ddd,  $J = 10.7, 7.6, 1.8$  Hz, 3-H), 1.28 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.2, 134.4, 134.2, 129.65, 129.57, 128.3, 127.1, 119.4, 113.7, 66.3, 62.2, 55.2, 48.7, 45.1, 28.1, 20.0; HRMS (ESI): calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O [M + H]<sup>+</sup> 307.1805, found 307.1804. (2*R*,1'*S*)-5ba: colourless oil. [ $\alpha$ ]<sub>589</sub><sup>24</sup>  $-95.3$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3061, 3030, 2968, 2933, 2835, 2221, 1610, 1584, 1510, 1454, 1371, 1350, 1329, 1302, 1289, 1242, 1173, 1138, 1092, 1059, 1032, 983, 949, 910, 832, 784, 753, 699; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.39–7.28 (5H, m, ArH), 7.27 (2H, ddd,  $J = 8.8, 2.4, 2.4$  Hz, ArH), 6.86 (2H, ddd,  $J = 8.8, 2.4, 2.4$  Hz, ArH), 3.80 (3H, s, OCH<sub>3</sub>), 3.70 (1H, q,  $J = 6.4$  Hz, 1'-H), 3.24 (1H, d,  $J = 13.6$  Hz, CH<sub>2</sub>Ph), 3.19 (1H, d,  $J = 13.6$  Hz, CH<sub>2</sub>Ph), 2.89 (1H, ddd,  $J = 8.4, 7.1, 2.4$  Hz, 4-H), 2.83 (1H, ddd,  $J = 9.4, 7.9, 7.1$  Hz, 4-H), 2.25 (1H, ddd,  $J = 11.0, 9.4, 8.4$  Hz, 3-H), 2.03 (1H, ddd,  $J = 11.0, 7.9, 2.4$  Hz, 3-H), 1.36 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.9, 134.4, 134.3, 130.0, 128.5, 128.4, 127.4, 119.3, 113.8, 65.1, 63.5, 55.2, 48.5, 46.5, 27.1, 22.6; HRMS (ESI): calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>Na</sub> [M + Na]<sup>+</sup> 329.1624, found 329.1624.

### (*S*)-2-Allyl-1-((*S*)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carbonitrile [(2*S*,1'*S*)-5bb] (Table 2, entry 1)

Purified by chromatography on silica gel (*n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/5 as the eluent). 37.0 mg, 56% yield, colourless oil. [ $\alpha$ ]<sub>589</sub><sup>20</sup>  $-145.2$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3078, 3004, 2967, 2933, 2834, 2222, 1642, 1612, 1585, 1511, 1455, 1442, 1372, 1353, 1333, 1296, 1242, 1216, 1173, 1116, 1099, 1031, 990, 922, 833, 817, 797, 767, 737, 701; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32 (2H, ddd,  $J = 8.8, 2.4, 2.4$  Hz, ArH), 6.85 (2H, ddd,  $J = 8.8, 2.4, 2.4$  Hz, ArH), 5.56 (1H, dddd,  $J = 17.1, 10.2, 7.2, 7.2$  Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.07 (1H, dddd,  $J = 10.2, 1.2, 1.2, 1.2$  Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.96 (1H, dddd,  $J = 17.1, 1.2, 1.2, 1.2$  Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 3.80 (3H, s, OCH<sub>3</sub>), 3.68 (1H, q,  $J = 6.4$  Hz, 1'-H), 3.42 (1H, ddd,  $J = 7.9, 6.6, 2.0$  Hz, 4-H), 3.18 (1H, ddd,  $J = 9.7, 7.9, 6.6$  Hz, 4-H), 2.23 (1H, ddd,  $J = 10.7, 9.7, 7.9$  Hz, 3-H), 2.14 (1H, ddd,  $J = 10.7, 7.9, 2.0$  Hz, 3-H), 1.92 (1H, dddd,  $J = 14.0, 7.2, 1.2, 1.2$  Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 1.67 (1H, dddd,  $J = 14.0, 7.2, 1.2, 1.2$  Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 1.24 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.1, 134.4, 130.6, 129.4, 119.7, 119.5, 113.6, 64.8, 62.3, 55.2, 48.9, 42.9, 27.3, 20.2; HRMS (ESI): calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>Na</sub> [M + Na]<sup>+</sup> 279.1468, found 279.1470.

### (*R*)-2-Allyl-1-((*S*)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carbonitrile [(2*R*,1'*S*)-5bb] (Table 2, entry 7)

Purified by chromatography on silica gel (*n*-hexane/EtOAc = 7/1 as the eluent). 53.3 mg, 84% yield, colourless oil. [ $\alpha$ ]<sub>589</sub><sup>20</sup>  $-94.5$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3078, 3005, 2969, 2933, 2835, 2221, 1642, 1611, 1585, 1511, 1457, 1442, 1371, 1352, 1329, 1290, 1242, 1172, 1132, 1110, 1060, 1034, 993, 983, 923, 832, 792, 735, 702; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 (2H, ddd,  $J = 8.8, 2.5, 2.5$  Hz, ArH), 6.85 (2H, ddd,  $J = 8.8, 2.5, 2.5$  Hz, ArH), 5.94–5.82 (1H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.28–5.25 (1H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.25–5.21 (1H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 3.79 (3H, s, OCH<sub>3</sub>), 3.65 (1H, q,  $J = 6.4$  Hz, 1'-H), 2.94–2.83 (2H, m, 4-H), 2.66 (2H, ddd,  $J = 7.6, 1.1, 1.1$  Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 2.26–2.14 (2H, m, 3-H), 1.26 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.8, 134.4, 130.5, 128.4, 120.0, 119.4, 113.8, 63.7, 63.2, 55.2, 48.5, 44.6, 26.9, 22.4; HRMS (ESI): calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>Na</sub> [M + Na]<sup>+</sup> 279.1468, found 279.1469.

### (*S*)-1-((*S*)-1'-(4''-Methoxyphenyl)ethyl)-2-methylazetidene-2-carbonitrile [(2*S*,1'*S*)-5bc] (Table 2, entry 2)

Purified by chromatography on silica gel (*n*-hexane/EtOAc = 7/1 as the eluent). 45.0 mg, 73% yield, colourless crystals, mp 73–75 °C. [ $\alpha$ ]<sub>589</sub><sup>22</sup>  $-205.7$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3009, 2967, 2931, 2852, 2836, 2819, 2219, 1612, 1583, 1508, 1462, 1451, 1439, 1373, 1352, 1334, 1302, 1240, 1220, 1197, 1183, 1166, 1116, 1103, 1026, 949, 838, 816, 763, 736; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32 (2H, ddd,  $J = 8.6, 2.5, 2.5$  Hz, ArH), 6.84 (2H, ddd,  $J = 8.6, 2.5, 2.5$  Hz, ArH), 3.79 (3H, s, OCH<sub>3</sub>), 3.64 (1H, q,  $J = 6.4$  Hz, 1'-H), 3.43 (1H, ddd,  $J = 8.0, 6.8, 2.2$  Hz, 4-H), 3.17 (1H, ddd,  $J = 9.9, 7.8, 6.8$  Hz, 4-H), 2.28 (1H, ddd,  $J = 10.4, 7.8, 2.2$  Hz, 3-H), 2.15 (1H, ddd,  $J = 10.4, 9.9, 8.0$  Hz, 3-H), 1.24 (3H, d,  $J = 6.4$  Hz, 1'-CH<sub>3</sub>), 0.94 (3H, s, 2-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.0, 134.2, 129.3, 120.4, 113.5, 62.3, 61.1, 55.1, 49.0, 30.1,



26.1, 20.2; HRMS (ESI): calcd for  $C_{14}H_{19}N_2O$   $[M + H]^+$  231.1492, found 231.1490.

**(R)-1-((S)-1'-(4''-Methoxyphenyl)ethyl)-2-methylazetidene-2-carbonitrile [(2R,1'S)-5bc] (Table 2, entry 8)**

Purified by chromatography on silica gel (*n*-hexane/ $CH_2Cl_2$  = 1/5 as the eluent). 47.7 mg, 65% yield, colourless crystals, mp 93–95 °C.  $[\alpha]_{589}^{24}$  –86.8 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  3031, 2998, 2968, 2932, 2864, 2834, 2811, 2217, 1609, 1578, 1512, 1462, 1439, 1367, 1344, 1321, 1301, 1285, 1243, 1194, 1183, 1169, 1130, 1106, 1062, 1030, 987, 956, 902, 866, 834, 817, 769, 736, 722;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.25 (2H, ddd, *J* = 8.4, 2.5, 2.5 Hz, ArH), 6.85 (2H, ddd, *J* = 8.4, 2.5, 2.5 Hz, ArH), 3.80 (3H, s, OCH<sub>3</sub>), 3.62 (1H, q, *J* = 6.2 Hz, 1'-H), 2.92 (1H, ddd, *J* = 8.4, 7.0, 3.0 Hz, 4-H), 2.88 (1H, ddd, *J* = 9.2, 7.6, 7.0 Hz, 4-H), 2.32 (1H, ddd, *J* = 10.7, 7.6, 3.0 Hz, 3-H), 2.12 (1H, ddd, *J* = 10.7, 9.2, 8.4 Hz, 3-H), 1.66 (3H, s, 2-CH<sub>3</sub>), 1.25 (3H, d, *J* = 6.2 Hz, 1'-CH<sub>3</sub>);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  158.8, 134.4, 128.4, 120.2, 113.7, 63.2, 60.1, 55.2, 48.5, 29.7, 27.5, 21.9; HRMS (ESI): calcd for  $C_{14}H_{19}N_2O$   $[M + H]^+$  231.1492, found 231.1489.

**(S)-2-Ethyl-1-((S)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carbonitrile [(2S,1'S)-5bd] (Table 2, entry 3)**

Purified by chromatography on silica gel (*n*-hexane/ $CH_2Cl_2$  = 1/5 as the eluent). 30.5 mg, 61% yield, colourless oil.  $[\alpha]_{589}^{21}$  –187.6 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  2967, 2935, 2876, 2834, 2222, 1612, 1585, 1512, 1461, 1442, 1372, 1354, 1321, 1294, 1242, 1218, 1192, 1171, 1116, 1098, 1032, 987, 965, 882, 833, 816, 787, 738;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.31 (2H, ddd, *J* = 8.4, 2.5, 2.5 Hz, ArH), 6.83 (2H, ddd, *J* = 8.4, 2.5, 2.5 Hz, ArH), 3.80 (3H, s, OCH<sub>3</sub>), 3.67 (1H, q, *J* = 6.6 Hz, 1'-H), 3.42 (1H, ddd, *J* = 7.6, 6.8, 2.4 Hz, 4-H), 3.16 (1H, ddd, *J* = 9.6, 8.0, 6.8 Hz, 4-H), 2.19 (1H, ddd, *J* = 10.7, 8.0, 2.4 Hz, 3-H), 2.14 (1H, ddd, *J* = 10.7, 9.6, 7.6 Hz, 3-H), 1.23 (1H, dq, *J* = 14.0, 7.4 Hz,  $CH_2CH_3$ ), 1.23 (3H, d, *J* = 6.6 Hz, 1'-CH<sub>3</sub>), 0.94 (1H, dq, *J* = 14.0, 7.4 Hz,  $CH_2CH_3$ ), 0.72 (3H, dd, *J* = 7.4, 7.4 Hz,  $CH_2CH_3$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  159.0, 134.7, 129.3, 119.9, 113.5, 66.7, 62.3, 55.2, 48.7, 31.8, 27.5, 20.3, 7.6; HRMS (ESI): calcd for  $C_{15}H_{20}N_2ONa$   $[M + Na]^+$  267.1468, found 267.1469.

**(R)-2-Ethyl-1-((S)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carbonitrile [(2R,1'S)-5bd] (Table 2, entry 9)**

Purified by chromatography on silica gel (*n*-hexane/EtOAc = 7/1 as the eluent). 30.5 mg, 62% yield, colourless oil.  $[\alpha]_{589}^{23}$  –96.1 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  2969, 2936, 2876, 2835, 2221, 1611, 1585, 1510, 1459, 1371, 1351, 1328, 1292, 1242, 1171, 1130, 1111, 1097, 1059, 1034, 962, 883, 831, 783, 734;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.25 (2H, ddd, *J* = 8.8, 2.5, 2.5 Hz, ArH), 6.85 (2H, ddd, *J* = 8.8, 2.5, 2.5 Hz, ArH), 3.79 (3H, s, OCH<sub>3</sub>), 3.64 (1H, q, *J* = 6.6 Hz, 1'-H), 2.90 (1H, ddd, *J* = 8.2, 7.1, 2.6 Hz, 4-H), 2.85 (1H, ddd, *J* = 9.3, 7.8, 7.1 Hz, 4-H), 2.22 (1H, ddd, *J* = 10.8, 7.8, 2.6 Hz, 3-H), 2.12 (1H, ddd, *J* = 10.8, 9.3, 8.2 Hz, 3-H), 1.97 (1H, dq, *J* = 13.7, 7.6 Hz,  $CH_2CH_3$ ), 1.90 (1H, dq, *J* = 13.7, 7.6 Hz,  $CH_2CH_3$ ), 1.24 (3H, d, *J* = 6.6 Hz, 1'-CH<sub>3</sub>), 1.05 (3H, dd, *J* = 7.6, 7.6 Hz,  $CH_2CH_3$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  158.8, 134.6, 128.4, 119.7, 113.7, 65.6, 63.3, 55.2, 48.4, 33.4, 27.0, 22.4, 7.9;

HRMS (ESI): calcd for  $C_{15}H_{20}N_2ONa$   $[M + Na]^+$  267.1468, found 267.1468.

**(S)-2-Butyl-1-((S)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carbonitrile [(2S,1'S)-5be] (Table 2, entry 4)**

Purified by chromatography on silica gel (*n*-hexane/ $CH_2Cl_2$  = 1/5 as the eluent). 54.5 mg, 67% yield, colourless oil.  $[\alpha]_{589}^{17}$  –149.7 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  2958, 2932, 2861, 2834, 2221, 1612, 1585, 1511, 1465, 1457, 1371, 1354, 1329, 1294, 1278, 1242, 1171, 1115, 1097, 1030, 982, 962, 938, 896, 878, 832, 817, 790, 738;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.31 (2H, ddd, *J* = 8.8, 2.4, 2.4 Hz, ArH), 6.83 (2H, ddd, *J* = 8.8, 2.4, 2.4 Hz, ArH), 3.79 (3H, s, OCH<sub>3</sub>), 3.67 (1H, q, *J* = 6.3 Hz, 1'-H), 3.42 (1H, ddd, *J* = 6.7, 6.7, 3.0 Hz, 4-H), 3.16 (1H, ddd, *J* = 9.2, 8.2, 6.7 Hz, 4-H), 2.24–2.12 (2H, m, 3-H), 1.22 (3H, d, *J* = 6.3 Hz, 1'-CH<sub>3</sub>), 1.20–1.03 (5H, m,  $(CH_2)_3CH_3$ ), 1.00–0.87 (1H, m,  $(CH_2)_3CH_3$ ), 0.76 (3H, t, *J* = 7.0 Hz,  $(CH_2)_3CH_3$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  159.0, 134.6, 129.3, 120.0, 113.5, 65.9, 62.3, 55.2, 48.9, 38.3, 28.1, 25.5, 22.2, 20.2, 13.8; HRMS (ESI): calcd for  $C_{17}H_{25}N_2O$   $[M + H]^+$  273.1961, found 273.1957.

**(R)-2-Butyl-1-((S)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carbonitrile [(2R,1'S)-5be] (Table 2, entry 10)**

Purified by chromatography on silica gel (*n*-hexane/ $CH_2Cl_2$  = 1/5 as the eluent). 46.3 mg, 61% yield, colourless oil.  $[\alpha]_{589}^{25}$  –78.9 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  2958, 2932, 2861, 2835, 2221, 1611, 1585, 1511, 1458, 1371, 1329, 1301, 1289, 1243, 1171, 1131, 1111, 1060, 1035, 979, 831, 784, 733;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.24 (2H, ddd, *J* = 8.6, 2.5, 2.5 Hz, ArH), 6.85 (2H, ddd, *J* = 8.6, 2.5, 2.5 Hz, ArH), 3.79 (3H, s, OCH<sub>3</sub>), 3.63 (1H, q, *J* = 6.4 Hz, 1'-H), 2.90 (1H, ddd, *J* = 8.1, 7.2, 2.6 Hz, 4-H), 2.85 (1H, ddd, *J* = 9.6, 7.8, 7.2 Hz, 4-H), 2.23 (1H, ddd, *J* = 10.7, 7.8, 2.6 Hz, 3-H), 2.14 (1H, ddd, *J* = 10.7, 9.6, 8.1 Hz, 3-H), 2.00–1.82 (2H, m,  $(CH_2)_3CH_3$ ), 1.55–1.33 (4H, m,  $(CH_2)_3CH_3$ ), 1.25 (3H, d, *J* = 6.4 Hz, 1'-CH<sub>3</sub>), 0.95 (3H, t, *J* = 7.0 Hz,  $(CH_2)_3CH_3$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  158.8, 134.5, 128.4, 119.8, 113.7, 64.8, 63.3, 55.2, 48.6, 40.3, 27.7, 25.8, 22.5, 22.4, 13.9; HRMS (ESI): calcd for  $C_{17}H_{25}N_2O$   $[M + H]^+$  273.1961, found 273.1960.

**(S)-Ethyl 2-cyano-1-((S)-1'-(4''-methoxyphenyl)ethyl)azetidene-2-carboxylate [(2S,1'S)-5bf] (Table 2, entry 5)**

Purified by chromatography on silica gel (*n*-hexane/ $CH_2Cl_2$  = 1/5 as the eluent). 21.0 mg, 29% yield, colourless crystals, mp 72–74 °C.  $[\alpha]_{589}^{22}$  –112.9 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  3009, 2976, 2939, 2902, 2848, 1756, 1611, 1581, 1508, 1474, 1454, 1442, 1391, 1379, 1353, 1334, 1303, 1272, 1240, 1173, 1124, 1106, 1087, 1028, 864, 842, 820, 805, 737, 715, 701;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.27 (2H, ddd, *J* = 8.8, 2.5, 2.5 Hz, ArH), 6.81 (2H, ddd, *J* = 8.8, 2.5, 2.5 Hz, ArH), 3.92 (2H, dq, *J* = 10.8, 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.82 (2H, dq, *J* = 10.8, 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.77 (3H, s, OCH<sub>3</sub>), 3.75 (1H, q, *J* = 6.6 Hz, 1'-H), 3.58 (1H, ddd, *J* = 8.2, 6.4, 2.6 Hz, 4-H), 3.33 (1H, ddd, *J* = 9.1, 7.8, 6.4 Hz, 4-H), 2.75 (1H, ddd, *J* = 10.6, 9.1, 8.2 Hz, 3-H), 2.37 (1H, ddd, *J* = 10.6, 7.8, 2.6 Hz, 3-H), 1.28 (3H, d, *J* = 6.6 Hz, 1'-CH<sub>3</sub>), 1.03 (3H, dd, *J* = 7.2, 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  166.5, 159.2, 132.3, 129.6, 116.1, 113.6, 64.9, 62.6, 62.3, 55.2, 49.3, 27.5,



19.7, 13.6; HRMS (ESI): calcd for  $C_{16}H_{20}N_2O_3Na$   $[M + Na]^+$  311.1366, found 311.1366.

**(R)-Ethyl 2-cyano-1-((S)-1'-(4''-methoxyphenyl)ethyl)azetidine-2-carboxylate [(2R,1'S)-5bf] (Table 2, entry 11)**

Purified by chromatography on silica gel (*n*-hexane/EtOAc = 7/1 as the eluent). 38.1 mg, 53% yield, colourless oil.  $[\alpha]_{589}^{23} -76.6$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  2974, 2936, 2907, 2838, 1756, 1734, 1611, 1585, 1512, 1457, 1444, 1369, 1329, 1243, 1173, 1123, 1108, 1084, 1061, 1033, 1015, 979, 942, 919, 856, 833, 770, 751, 736, 719;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.29 (2H, ddd, *J* = 8.8, 2.4, 2.4 Hz, ArH), 6.86 (2H, ddd, *J* = 8.8, 2.4, 2.4 Hz, ArH), 4.31 (2H, q, *J* = 7.0 Hz,  $OCH_2CH_3$ ), 3.80 (3H, s,  $OCH_3$ ), 3.71 (1H, q, *J* = 6.4 Hz, 1'-H), 3.14–3.05 (2H, m, 4-H), 2.68 (1H, ddd, *J* = 10.9, 8.4, 8.4 Hz, 3-H), 2.45 (1H, ddd, *J* = 10.9, 6.7, 4.4 Hz, 3-H), 1.34 (3H, t, *J* = 7.0 Hz,  $OCH_2CH_3$ ), 1.19 (3H, d, *J* = 6.4 Hz, 1'- $CH_3$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  167.1, 159.1, 132.8, 128.7, 115.8, 113.8, 64.1, 62.8, 62.6, 55.2, 48.9, 27.5, 20.9, 13.9; HRMS (ESI): calcd for  $C_{16}H_{20}N_2O_3Na$   $[M + Na]^+$  311.1366, found 311.1366.

**(S)-tert-Butyl 2-cyano-1-((S)-1'-(4''-methoxyphenyl)ethyl)azetidine-2-carboxylate [(2S,1'S)-5bg] (Table 2, entry 6)**

Purified by chromatography on silica gel (*n*-hexane/EtOAc = 7/1 as the eluent). 67.6 mg, 58% yield, colourless crystals, mp 88–90 °C.  $[\alpha]_{589}^{21} -103.2$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  2975, 2934, 2871, 2837, 1732, 1612, 1585, 1512, 1457, 1394, 1369, 1282, 1243, 1172, 1153, 1117, 1083, 1033, 993, 963, 943, 919, 834, 746, 733, 720;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.30 (2H, ddd, *J* = 8.8, 2.4, 2.4 Hz, ArH), 6.81 (2H, ddd, *J* = 8.8, 2.4, 2.4 Hz, ArH), 3.77 (3H, s,  $OCH_3$ ), 3.75 (1H, q, *J* = 6.8 Hz, 1'-H), 3.53 (1H, ddd, *J* = 8.0, 6.4, 2.8 Hz, 4-H), 3.28 (1H, ddd, *J* = 8.8, 7.9, 6.4 Hz, 4-H), 2.66 (1H, ddd, *J* = 10.9, 8.8, 8.0 Hz, 3-H), 2.37 (1H, ddd, *J* = 10.9, 7.9, 2.8 Hz, 3-H), 1.28 (3H, d, *J* = 6.8 Hz, 1'- $CH_3$ ), 1.23 (9H, s, *t*Bu);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  165.2, 159.1, 132.6, 129.6, 116.6, 113.7, 83.5, 65.5, 62.2, 55.2, 49.2, 27.6, 27.4, 19.8; HRMS (ESI): calcd for  $C_{18}H_{24}N_2O_3Na$   $[M + Na]^+$  339.1679, found 339.1681.

**(R)-tert-Butyl 2-cyano-1-((S)-1'-(4''-methoxyphenyl)ethyl)azetidine-2-carboxylate [(2R,1'S)-5bg] (Table 2, entry 12)**

Purified by chromatography on silica gel (*n*-hexane/ $CH_2Cl_2$  = 1/5 as the eluent). 35.2 mg, 43% yield, colourless oil.  $[\alpha]_{589}^{20} -75.1$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  2975, 2934, 2837, 1731, 1611, 1585, 1512, 1458, 1394, 1370, 1280, 1244, 1152, 1124, 1110, 1061, 1034, 979, 942, 918, 833, 733, 719;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.29 (2H, ddd, *J* = 8.4, 2.4, 2.4 Hz, ArH), 6.86 (2H, ddd, *J* = 8.4, 2.4, 2.4 Hz, ArH), 3.80 (3H, s,  $OCH_3$ ), 3.70 (1H, q, *J* = 6.6 Hz, 1'-H), 3.06 (1H, ddd, *J* = 8.3, 6.8, 3.2 Hz, 4-H), 3.02 (1H, ddd, *J* = 8.7, 7.5, 6.8 Hz, 4-H), 2.64 (1H, ddd, *J* = 10.9, 8.7, 8.3 Hz, 3-H), 2.39 (1H, ddd, *J* = 10.9, 7.5, 3.2 Hz, 3-H), 1.54 (9H, s, *t*Bu), 1.20 (3H, d, *J* = 6.6 Hz, 1'- $CH_3$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  166.0, 159.1, 133.2, 128.7, 116.1, 113.8, 83.9, 64.9, 62.6, 55.2, 48.8, 27.7, 27.3, 21.2; HRMS (ESI): calcd for  $C_{18}H_{25}N_2O_3$   $[M + H]^+$  317.1860, found 317.1858.

**Determination of stereochemistry of (2S,1'S)-5aa (Scheme 4, eqn (1))**

A solution of (2S,1'S)-5aa (83 mg, 0.30 mmol) in THF (1.5 mL) was added to a suspension of  $LiAlH_4$  (34 mg, 0.90 mmol) in THF (1.5 mL) at 0 °C under an Ar atmosphere. After stirring for 2 h at room temperature, the resulting mixture was cooled at 0 °C and diluted with  $Et_2O$  (3 mL). The mixture was quenched at 0 °C by addition of  $H_2O$  (34  $\mu$ L), 15 wt% NaOH solution in  $H_2O$  (34  $\mu$ L), and  $H_2O$  (102  $\mu$ L). The suspension was diluted with EtOAc (3 mL) and stirred for 12 h at room temperature. The resulting mixture was filtered through a pad of Celite and the filtrate mixture was concentrated by evaporation. The residue was purified by chromatography on amino-functionalized silica gel (Chromatorex NH-DM1020, *n*-hexane/EtOAc = 7/1 to 4/1 as the eluent) to obtain ((S)-2-benzyl-1-((S)-1'-phenylethyl)azetidin-2-yl)methanamine [(2S,1'S)-6aa] (78.0 mg, 93% yield) as colourless crystals, mp 65–69 °C.  $[\alpha]_{589}^{20} -5.6$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  3357, 3281, 3083, 3058, 3028, 3001, 2966, 2926, 2853, 2825, 1602, 1492, 1452, 1440, 1366, 1309, 1278, 1268, 1217, 1173, 1128, 1100, 1074, 1050, 1026, 1011, 974, 951, 897, 864, 768, 751, 716, 696;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.42–7.16 (10H, m, ArH), 3.85 (1H, q, *J* = 6.4 Hz, 1'-H), 3.29 (1H, d, *J* = 12.8 Hz,  $CH_2NH_2$ ), 2.99–2.81 (2H, m, 4-H), 2.85 (1H, d, *J* = 13.6 Hz,  $CH_2Ph$ ), 1.92 (1H, ddd, *J* = 10.5, 8.6, 8.6 Hz, 3-H), 1.79 (1H, ddd, *J* = 10.5, 7.9, 3.2 Hz, 3-H), 1.67 (2H, br,  $NH_2$ ), 1.28 (3H, d, *J* = 6.4 Hz, 1'-H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  144.4, 138.0, 130.2, 128.2, 128.1, 127.5, 127.0, 126.1, 69.9, 59.5, 47.6, 47.0, 37.6, 23.6, 21.2; HRMS (ESI): calcd for  $C_{19}H_{25}N_2$   $[M + H]^+$  281.2012, found 281.2007. A mixture of (2S,1'S)-6aa (32 mg, 0.11 mmol), allyl bromide (9.8  $\mu$ L, 0.11 mmol) and  $K_2CO_3$  (47 mg, 0.34 mmol) in MeCN (1.1 mL) was stirred for 3 h at room temperature. The resulting mixture was filtered and the filtrate was concentrated by evaporation. The residue was purified by chromatography on silica gel ( $CH_2Cl_2$ /MeOH = 20/1 to 10/1 as the eluent) to obtain *N*-(((S)-2-benzyl-1-((S)-1'-phenylethyl)azetidin-2-yl)methyl)prop-2-en-1-amine [(2S,1'S)-7aa] (29.0 mg, 82% yield) as a colourless oil.  $[\alpha]_{589}^{20} -33.4$  (*c* 1.0 in EtOH); IR (ATR)  $\nu_{max}/cm^{-1}$  3300, 3083, 3061, 3027, 2968, 2924, 2823, 1643, 1603, 1493, 1451, 1370, 1311, 1278, 1218, 1181, 1123, 1092, 1075, 1049, 1029, 993, 948, 914, 880, 764, 725, 698;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.40–7.16 (10H, m, ArH), 5.95 (1H, dddd, *J* = 17.0, 10.2, 6.4, 6.4 Hz,  $CH_2CH=CH_2$ ), 5.22 (1H, dddd, *J* = 17.0, 1.6, 1.6, 1.4 Hz,  $CH_2CH=CH_2$ ), 5.12 (1H, dd, *J* = 10.2, 1.4 Hz,  $CH_2CH=CH_2$ ), 3.87 (1H, q, *J* = 6.2 Hz, 1'-H), 3.38–3.23 (2H, m, 4-H), 3.27 (1H, d, *J* = 13.0 Hz, 2- $CH_2NH$ ), 3.20–2.70 (1H, br, NH), 3.00–2.80 (2H, m, 3-H), 2.88 (1H, d, *J* = 13.0 Hz, 2- $CH_2NH$ ), 2.60 (1H, d, *J* = 12.0 Hz,  $CH_2Ph$ ), 2.56 (1H, d, *J* = 12.0 Hz,  $CH_2Ph$ ), 2.22–2.10 (1H, m,  $CH_2CH=CH_2$ ), 1.92–1.80 (1H, m,  $CH_2CH=CH_2$ ), 1.27 (3H, d, *J* = 6.2 Hz, 1'- $CH_3$ );  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  144.2, 137.8, 136.8, 130.2, 128.3, 128.1, 127.5, 127.0, 126.2, 116.0, 68.8, 59.5, 55.0, 52.6, 47.1, 38.0, 23.6, 22.7; HRMS (ESI): calcd for  $C_{22}H_{29}N_2$   $[M + H]^+$  321.2325, found 321.2320.

**Preparation of authentic sample (2S,1'S)-7aa from (2S,1'S)-8aa (Scheme 4, eqn (2))**

A solution of (S)-tert-butyl 2-benzyl-1-((S)-1'-phenylethyl)azetidine-2-carboxylate [(2S,1'S)-8aa]<sup>6</sup> (150 mg, 0.427 mmol) in



CH<sub>2</sub>Cl<sub>2</sub> (0.85 mL) was treated with trifluoroacetic acid (TFA) (0.85 mL) at 0 °C and the solution was stirred for 16 h at room temperature. The resulting solution was concentrated by evaporation and the residue was treated with toluene (4 mL). The mixture was concentrated by evaporation to remove excess amounts of TFA. The residual TFA salt was treated with toluene (4 mL) followed by a *ca.* 4 M HCl solution in cyclopentyl methyl ether (0.16 mL, 0.64 mmol). After stirring for 10 min at room temperature, the mixture was concentrated by evaporation to remove TFA. Toluene (4 mL) was added to the residue and the mixture was concentrated by evaporation again to remove TFA completely. THF (4.3 mL) was added to the residue at room temperature and diisopropylethylamine (0.28 mL, 1.6 mmol) followed by allylamine (38 μL, 0.51 mmol) were added. 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (194 mg, 0.51 mmol) was added to the solution at room temperature and the mixture was stirred for 22 h. The resulting mixture was concentrated by evaporation and the residue was purified by chromatography on silica gel (*n*-hexane/EtOAc = 5/1 to 3/1 as the eluent) to give (*S*)-*N*-allyl-2-benzyl-1-((*S*)-1'-phenylethyl)azetid-2-carboxamide [(2*S*,1'*S*)-**9aa**] (118 mg, 83% yield) as a colourless oil. [ $\alpha$ ]<sub>589</sub><sup>22</sup> -92.0 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3355, 3084, 3060, 3026, 2966, 2926, 2841, 1664, 1603, 1506, 1494, 1452, 1419, 1373, 1338, 1279, 1265, 1217, 1175, 1131, 1096, 1075, 1057, 1029, 999, 988, 913, 764, 733, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 (1H, br, NH-CHH-CH=CHH), 7.54–7.48 (2H, m, ArH), 7.36–7.22 (7H, m, ArH), 7.20 (1H, tt, *J* = 7.2, 1.2 Hz, ArH), 5.90 (1H, dddd, <sup>3</sup>*J*<sub>trans</sub> = 17.2, <sup>3</sup>*J*<sub>cis</sub> = 10.2, <sup>3</sup>*J* = 5.6, <sup>3</sup>*J* = 5.6 Hz, NH-CHH-CH=CHH), 5.24 (1H, dddd, <sup>3</sup>*J*<sub>trans</sub> = 17.2, <sup>2</sup>*J* = 1.6, <sup>4</sup>*J* = 1.6, <sup>4</sup>*J* = 1.6 Hz, NH-CHH-CH=CHH<sub>trans</sub>), 5.16 (1H, dddd, <sup>3</sup>*J*<sub>cis</sub> = 10.2, <sup>2</sup>*J* = 1.6, <sup>4</sup>*J* = 1.6, <sup>4</sup>*J* = 1.6 Hz, NH-CHH-CH=CHH<sub>cis</sub>), 4.07 (1H, dddd, <sup>2</sup>*J* = 15.7, <sup>3</sup>*J* = 6.6, <sup>3</sup>*J* = 5.6, <sup>4</sup>*J*<sub>trans</sub> = 1.6, <sup>4</sup>*J*<sub>cis</sub> = 1.6 Hz, NH-CHH-CH=CHH), 4.00 (1H, q, *J* = 6.4 Hz, 1'-H), 3.91 (1H, dddd, <sup>2</sup>*J* = 15.7, <sup>3</sup>*J* = 5.6, <sup>3</sup>*J* = 5.6, <sup>4</sup>*J*<sub>trans</sub> = 1.6, <sup>4</sup>*J*<sub>cis</sub> = 1.6 Hz, NH-CHH-CH=CHH), 3.48 (1H, d, *J* = 14.4 Hz, CH<sub>2</sub>Ph), 3.43 (1H, d, *J* = 14.4 Hz, CH<sub>2</sub>Ph), 2.92–2.80 (2H, m, 4-H), 2.13 (1H, ddd, <sup>2</sup>*J* = 11.1, <sup>3</sup>*J* = 8.4, <sup>3</sup>*J* = 8.4 Hz, 3-H), 1.98 (1H, ddd, <sup>2</sup>*J* = 11.1, <sup>3</sup>*J* = 7.9, <sup>3</sup>*J* = 2.8 Hz, 3-H), 0.92 (3H, d, *J* = 6.4 Hz, 1'-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.5, 142.9, 138.5, 134.4, 130.8, 128.4, 128.1, 127.4, 127.3, 126.2, 116.1, 71.2, 60.4, 47.5, 41.6, 35.3, 28.6, 22.6; HRMS (ESI): calcd for C<sub>22</sub>H<sub>27</sub>N<sub>2</sub>O [M + H]<sup>+</sup> 335.2118, found 335.2110. A solution of (2*S*,1'*S*)-**9aa** (118 mg, 0.353 mmol) in THF (1.8 mL) was added to a suspension of LiAlH<sub>4</sub> (42 mg, 1.1 mmol) in THF (1.8 mL) at 0 °C under an Ar atmosphere. The mixture was refluxed for 4 h. The resulting mixture was cooled at 0 °C and diluted with Et<sub>2</sub>O (4 mL). The mixture was quenched by addition of H<sub>2</sub>O (42 μL), 15 wt% NaOH solution in H<sub>2</sub>O (42 μL), and H<sub>2</sub>O (126 μL). The suspension was diluted with EtOAc (4 mL) and stirred for 12 h at room temperature. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated by evaporation. Purification of the residue by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 20/1 to 10/1 as the eluent) gave (2*S*,1'*S*)-**7aa** (32.1 mg, 28% yield) as a colourless oil and recovered (2*S*,1'*S*)-**9aa** (69.5 mg, 59% recovery) as a colourless oil. (2*S*,1'*S*)-**7aa**: [ $\alpha$ ]<sub>589</sub><sup>19</sup> -33.2 (*c* 1.0 in EtOH).

### Representative procedure for preparation of (*R*)-**10a** (Scheme 5, eqn (2))

TFA (2.2 mL) was added to a solution of (2*R*,1'*S*)-**5ba** (135 mg, 0.441 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.2 mL) at room temperature and the solution was stirred for 3 days. The resulting solution was concentrated by evaporation and the residue was treated with a 1 M NaOH solution in H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combine extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated by evaporation. <sup>1</sup>H NMR analysis of this crude product in CDCl<sub>3</sub> showed a mixture of (2*R*,1'*S*)-**5ba**/(*R*)-**10a** = 1/9 (*ca.* 90% conversion). The CDCl<sub>3</sub> solution was concentrated by evaporation and residue was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 60/1 to 30/1 as the eluent) to obtain (*R*)-2-benzylazetid-2-carbonitrile [(*R*)-**10a**] (64.4 mg, 85% yield) as a pale yellow oil. [ $\alpha$ ]<sub>589</sub><sup>22</sup> +40.5 (*c* 1.0 in EtOH); IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$  3326, 3245, 3086, 3062, 3030, 3006, 2960, 2921, 2879, 2224, 1604, 1495, 1454, 1439, 1346, 1283, 1240, 1174, 1134, 1093, 1031, 993, 951, 930, 850, 764, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.38–7.25 (5H, m, Ph), 3.82 (1H, ddd, *J* = 8.4, 8.4, 7.4 Hz, 4-H), 3.37 (1H, ddd, *J* = 7.8, 7.4, 4.6 Hz, 4-H), 3.11 (1H, d, *J* = 13.6 Hz, CH<sub>2</sub>Ph), 3.06 (1H, d, *J* = 13.6 Hz, CH<sub>2</sub>Ph), 2.58 (1H, ddd, *J* = 11.2, 8.4, 4.6 Hz, 3-H), 2.55 (1H, ddd, *J* = 11.2, 8.4, 7.8 Hz, 3-H), 2.21 (1H, br, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  134.2, 129.7, 128.5, 127.4, 122.6, 59.7, 46.0, 42.7, 31.8; HRMS (ESI): calcd for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub> [M + H]<sup>+</sup> 173.1073, found 173.1072.

### (*S*)-2-Benzylazetid-2-carbonitrile [(*S*)-**10a**] (Scheme 5, eqn (1))

The reaction was performed using (2*S*,1'*S*)-**5ba** (103 mg, 0.336 mmol) by the same procedure with (2*R*,1'*S*)-**5ba**. <sup>1</sup>H NMR analysis of the crude product in CDCl<sub>3</sub> showed a mixture of (2*S*,1'*S*)-**5ba**/(*S*)-**10a** = 4/6 (*ca.* 60% conversion). Purification by chromatography on silica gel gave (*S*)-**10a** (33.9 mg, 59% yield) as a pale yellow oil. [ $\alpha$ ]<sub>589</sub><sup>21</sup> -40.4 (*c* 1.0 in EtOH).

## Author contributions

E. T. was supervisor of this project and conducted all area of this work, idea, development of methodology, a part of experiments and writing the manuscript. N. N. performed the main experiments and compound analyses.

## Conflicts of interest

There are no conflicts to declare.

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- 14 Chromatographic purification of **4** must be performed using *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> as the eluent to avoid epimerization. When (1*S*,2*S*,1'*S*)-**4b** was stirred in THF for 30 min at room temperature, approximately 20 mol% of (1*S*,2*S*,1'*S*)-**4b** was epimerized to the other isomer, as observed by <sup>1</sup>H NMR analysis.
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