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

Eiji Tayama (iD *a and Nobuhiro Nakanome ${ }^{\text {b }}$


#### Abstract

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 $N-\left((S)-1^{\prime}-\right.$ ( $4^{\prime \prime}$-methoxyphenyl)ethyl)azetidine-2-carbonitrile complex ( $15,2 S, 1^{\prime} S$ )-4b with 1.2 equivalents of LDA at $-78{ }^{\circ} \mathrm{C}$ followed by 1.3 equivalents of benzyl bromide at $-78^{\circ} \mathrm{C}$ and warming to room temperature produced $\alpha$-benzylated ( $2 S, 1^{\prime} S$ )-5ba in $72 \%$ yield and ( $2 R, 1^{\prime} S$ )-5ba in $2 \%$ yield. A mechanism for this diastereoselective $\alpha$-alkylation was proposed. Our method enables the production of optically active 2substituted azetidine-2-carbonitriles, such as $\alpha$-benzylated (S)-10a and (R)-10a, starting from commercially available (S)-(1-(4-methoxyphenyl)ethyl)amine.


## 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. ${ }^{1,2}$ 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 fourmembered N -heterocycles are stable without any additives; however, upon electrophilic activation of the nitrogen atom with Lewis/Brønsted acids ${ }^{3}$ or $N$-quaternization, ${ }^{4,5}$ 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 $\left(2 S, 1^{\prime} S\right)$-N-( $1^{\prime}$-phenylethyl)azetidine-2-carboxylic acid tertbutyl ester via formation of its $N$-borane $\left(\mathrm{BH}_{3}\right)$ complex (Scheme 1 , eqn (1)). ${ }^{6,7}$ This protocol enabled the synthesis of various types of $\alpha$-substituted azetidine-2-carboxylic acid esters from ( $S$ )-1phenylethylamine, which is one of the least expensive chiral sources. However, the same reaction with other $\left(2 R, 1^{\prime} S\right)$-isomers

[^0]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-2carbonitriles 5 to clarify that both diastereomers of $N-\mathrm{BH}_{3}$ complexes $\left(2 S, 1^{\prime} S\right)$ - and $\left(2 R, 1^{\prime} S\right)-4$ provide the corresponding $\alpha$ alkylated diastereomers, respectively (eqn (3) and (4)). In addition, previous reports on $N$ - $\mathrm{BH}_{3}$ complexes derived from $\alpha$-amino nitriles are quite limited and their chemical properties are unclear. ${ }^{8}$ Thus, we started to investigate the preparation of $\mathrm{N}-\mathrm{BH}_{3}$ complexes $\mathbf{4}$, diastereoselective $\alpha$-alkylation of $\mathbf{4}$, and further synthetic transformation of the resulting products 5.

## Results and discussion

Preparation of $\boldsymbol{N}$-benzylic azetidine-2-carbonitriles (3)
First, we investigated preparative routes to $N-((S)-1-$ phenylethyl $)$ azetidine-2-carbonitriles (3a) from easily obtainable methyl esters $\mathbf{1 a}^{\mathbf{1 0}}$ (Scheme 2). Amidation of $\mathbf{1 a}$ with aqueous $\mathrm{NH}_{3}(25-$ $28 \%)$ gave $\mathbf{2 a}$ in moderate yields $\left[\left(2 S, 1^{\prime} S\right)\right.$-2a: $71 \%,\left(2 R, 1^{\prime} S\right)$-2a: $60 \%]$. We found that the use of trifluoroacetic anhydride with pyridine ${ }^{11}$ was quite effective in dehydration of the resulting amides $2 \mathbf{a}$ to nitriles $3 \mathbf{a}\left[\left(2 S, 1^{\prime} S\right)\right.$-3a: $90 \%$, $\left.\left(2 R, 1^{\prime} S\right)-3 \mathbf{a}: 94 \%\right]$. Analogous $N$-((S)-1-(4-methoxyphenyl)ethyl) derivatives 3b were also prepared. Amidation of $\mathbf{1 b}^{\mathbf{1 2}}$ was carried out with methanolic $\mathrm{NH}_{3}(7 \mathrm{~N})$ in the presence of NaCN in 1,4-dioxane because the use of aqueous $\mathrm{NH}_{3}$ resulted in lower conversion. The desired amides $\mathbf{2 b}$ were obtained in excellent yields $\left[\left(2 S, 1^{\prime} S\right)-\mathbf{2 b}\right.$ : $\left.99 \%,\left(2 R, 1^{\prime} S\right)-2 \mathbf{b}: 100 \%\right]$. Dehydration of $2 \mathbf{b}$ with trifluoroacetic anhydride gave 3b [(2S, $\left.1^{\prime} S\right)$-3b: $\left.80 \%,\left(2 R, 1^{\prime} S\right)-\mathbf{3 b}: 74 \%\right]$. The lower yields of this dehydration were due to undesired substitution at the benzylic carbon with trifluoroacetate anion. ${ }^{13}$
Our previous work

$(2 S, 1$ 'S) moderate to good yields, high dr

low yield and low dr


Scheme 1 Diastereoselective $N$-boration and $\alpha$-alkylation of azeti-dine-2-carbonitriles.

## Preparation of $\mathrm{N}-\mathrm{BH}_{3}$ complexes (4)

Next, we attempted to prepare $N-\mathrm{BH}_{3}$ complexes 4 as substrates for base-promoted $\alpha$-alkylation (Scheme 3). Treatment of $N$-(1phenylethyl) derivatives 3a with a $\mathrm{BH}_{3}$ dimethyl sulfide complex in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ proceeded smoothly with high stereoselectivities at the nitrogen atom, as in 3 a ( $>9: 1 \mathrm{dr}$ ). Silica-gel chromatographic purification ( $n$-hexane $/ \mathrm{CH}_{2} \mathrm{Cl}_{2}$ as the eluent) to isolate the major diastereomer observed by TLC analysis afforded 4a in good yields [(1S,2S, $\left.\left.1^{\prime} S\right)-4 \mathrm{a}: ~ 91 \%,\left(1 R, 2 R, 1^{\prime} S\right)-4 a: 86 \%\right]$. In contrast, the yields of $N$-(1-(4-methoxyphenyl)ethyl) derivatives $\mathbf{4 b}$ were slightly decreased $\left[\left(1 S, 2 S, 1^{\prime} S\right)-\mathbf{4 b}: 93 \%,\left(1 R, 2 R, 1^{\prime} S\right)-\mathbf{4 b}\right.$ : $72 \%$ ]. The exact reason is unclear at present, and the coordinating ability of the methoxy substituent might cause undesirable complexation. Isolated $N-\mathrm{BH}_{3}$ complexes $\mathbf{4 a}$ and $\mathbf{4 b}$ 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. ${ }^{14}$ The stereochemistries of $\mathbf{4 a}$ and $\mathbf{4 b}$ were determined analogically by comparison with previous examples of $N$-boration of 2 -substituted azetidine derivatives. ${ }^{6,15}$ The adjacent 2and N -substituents are equatorial, and the axial lone pair of the nitrogen atom coordinates to $\mathrm{BH}_{3}$.


Scheme 2 Preparation of azetidine-2-carbonitriles 3. (i) $\mathrm{Br}_{2}, \mathrm{PBr}_{3}$, $100{ }^{\circ} \mathrm{C}$. (ii) MeOH , rt. (iii) $\mathrm{NH}_{3}$ aq. rt. (iv) $\mathrm{NH}_{3}, \mathrm{NaCN}, \mathrm{MeOH}$, rt. (v) $\left(\mathrm{CF}_{3} \mathrm{CO}\right)_{2} \mathrm{O}$, pyridine, 1,4-dioxane, ca. $10^{\circ} \mathrm{C}$ to rt .



Scheme 3 Preparation of $\mathrm{N}-\mathrm{BH}_{3}$ complexes 4.

## Base-promoted $\alpha$-benzylation of $\boldsymbol{N}$ - $\mathrm{BH}_{3}$ 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, ${ }^{6}$ the reaction of $N-((S)$-1-phenylethyl) derivative $\left(1 S, 2 S, 1^{\prime} S\right)$-4a in THF was examined with 2.4 equivalents of LiHMDS at $0^{\circ} \mathrm{C}$ for 30 min followed by 2.6 equivalents of benzyl bromide at room temperature for 3 h (entry 1 ). The desired $\alpha$ benzylated $\left(2 S, 1 S^{\prime}\right)$-5aa was obtained in only $14 \%$ as a single diastereomer. The $N-\mathrm{BH}_{3}$ complex derived from product $\left(2 S, 1 S^{\prime}\right)$-5aa was not obtained. The use of 1.2 equivalents of LDA and 1.3 equivalents of benzyl bromide did not give $\mathbf{5 a a}$ (entry 2 ). To minimize the epimerization and/or decomposition of

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


4a, 5aa: $\mathrm{Ar}=\mathrm{Ph}$
(1R,2R,1'S)-4a-b
4b, 5ba: $\mathrm{Ar}=p-\mathrm{MeO}-\mathrm{Ph}$

| Entry | 4 | Base (eq.), temp. | BnBr (eq.) | Yield of $5^{a}$ (\%) |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | $2 S, 1^{\prime} S$ | $2 R, 1^{\prime} S$ |
| 1 | $1 S, 2 S, 1^{\prime} S-\mathbf{4 a}$ | LiHMDS, $2.4,0^{\circ} \mathrm{C}$ | 2.6 | 14 | 0 |
| 2 | $1 S, 2 S, 1^{\prime} S$-4a | LDA, 1.2, $0{ }^{\circ} \mathrm{C}$ | 1.3 | 0 | 0 |
| 3 | $1 S, 2 S, 1^{\prime} S$-4a | LiHMDS, 2.4, $-78{ }^{\circ} \mathrm{C}$ | 2.6 | 64 | 8 |
| 4 | $1 S, 2 S, 1^{\prime} S$-4a | LDA, $1.2,-78{ }^{\circ} \mathrm{C}$ | 1.3 | 70 | 0 |
| 5 | $1 R, 2 R, 1^{\prime} S$-4a | LiHMDS, $2.4,0^{\circ} \mathrm{C}$ | 2.6 | 4 | 48 |
| 6 | $1 R, 2 R, 1^{\prime} S-4 \mathbf{a}$ | LiHMDS, $2.4,-78{ }^{\circ} \mathrm{C}$ | 2.6 | 8 | 74 |
| 7 | $1 R, 2 R, 1^{\prime} S-4 \mathbf{a}$ | LDA, $1.2,-78{ }^{\circ} \mathrm{C}$ | 1.3 | 0 | 59 |
| 8 | $1 S, 2 S, 1^{\prime} S-4 \mathbf{b}$ | LiHMDS, 2.4, $-78{ }^{\circ} \mathrm{C}$ | 2.6 | 49 | 5 |
| 9 | $1 S, 2 S, 1^{\prime} S-4 \mathbf{b}$ | LDA, 1.2, $-78{ }^{\circ} \mathrm{C}$ | 1.3 | 72 | 2 |
| 10 | $1 R, 2 R, 1^{\prime} S-4 \mathbf{b}$ | LiHMDS, $2.4,-78{ }^{\circ} \mathrm{C}$ | 2.6 | 9 | 56 |
| 11 | $1 R, 2 R, 1^{\prime} S-4 \mathbf{b}$ | LDA, 1.2, $-78{ }^{\circ} \mathrm{C}$ | 1.3 | 0 | 83 |

${ }^{a}$ Yield of isolated product.
$\left(1 S, 2 S, 1^{\prime} S\right)-\mathbf{4 a}$ in THF,,$^{14}$ the mixture was cooled at $-78{ }^{\circ} \mathrm{C}$ as soon as possible after the addition of THF to $\left(1 S, 2 S, 1^{\prime} S\right)$-4a. Then, the mixture was treated with base at $-78{ }^{\circ} \mathrm{C}$ (entries 3 and 4). These procedures and conditions improved the yields to approximately $70 \%$. Each diastereomeric product, $\left(2 S, 1^{\prime} S\right)$ - and $\left(2 R, 1^{\prime} S\right)$-5aa was easily separable with silica gel chromatography. The corresponding amounts of $\mathrm{BH}_{3}$ were also recovered as $\mathrm{BH}_{3}$-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 $\left(1 R, 2 R, 1^{\prime} S\right)$-4a under the conditions described above to produce the corresponding $\alpha$-alkylated ( $2 R, 1 S^{\prime}$ )-5aa (entries 5-7). Similar yields ( $52-82 \%$ combined yields) and diastereoselectivities were observed. Next, we prepared $N$-((S)-1-(4-methoxyphenyl)ethyl) derivatives $\mathbf{4 b}$ 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 $\left(1 S, 2 S, 1^{\prime} S\right)$ - $\mathbf{4 b}$ also gave $\left(2 S, 1 S^{\prime}\right)$-5ba preferentially in moderate yields (entries 8 and $9,54 \%$ and $74 \%$ combined yields). The diastereomeric products, $\left(2 S, 1^{\prime} S\right)$ - and $\left(2 R, 1^{\prime} S\right)$-5ba, were easily separable with silica gel chromatography. The reactions of the other diastereomer $\left(1 R, 2 R, 1^{\prime} S\right)-\mathbf{4 b}$ to $\left(2 R, 1 S^{\prime}\right)$ 5ba also showed similar results (entries 10 and 11, 65\% and $83 \%$ combined yields). Both $\alpha$-alkylated diastereomers ( $2 S, 1 S^{\prime}$ )and $\left(2 R, 1 S^{\prime}\right)$-5ba were successfully obtained with high diastereoselectivities from the corresponding $N-\mathrm{BH}_{3}$ complexes $\mathbf{4 b} .{ }^{16}$

To define the scope and limitations of this diastereoselective $\alpha$-alkylation, we attempted the reactions of $\mathbf{4 b}$ with various electrophiles (Table 2). ${ }^{17}$ 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 $\mathbf{5 b c}$-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 $\mathrm{N}-\mathrm{BH}_{3}$ complex of a tertbutyl ester derivative. ${ }^{6}$ Therefore, the reactions of nitrile derivatives $\mathbf{4 b}$ with ethyl chloroformate were examined under the same conditions (entries 5 and 11). The yields of the corresponding products $\mathbf{5 b}$ were low to moderate ( $29 \%$ and $57 \%$ combined yields). We attempted to use di-tert-butyl dicarbonate as an electrophile (entries 6 and 12$)^{18}$ instead of ethyl chloroformate; however, the yields of $\mathbf{5} \mathbf{b g}$ were not so improved ( $58 \%$ and $43 \%$ combined yields).

The stereochemistry of $\left(2 S, 1^{\prime} S\right)$-5aa was assigned by conversion into the $N$-allylamine derivative ( $2 S, 1^{\prime} S$ )-7aa (Scheme 4).

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


| Entry | 4b | RX | 5 | Yield of $5^{a}$ (\%) |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | $2 S, 1^{\prime} S$ | $2 R, 1^{\prime} S$ |
| 1 | $1 S, 2 S, 1^{\prime} S$ | $\mathrm{BrCH}_{2} \mathrm{CH}=\mathrm{CH}_{2}$ | 5bb | 56 | 0 |
| 2 | $1 S, 2 S, 1^{\prime} S$ | MeI | 5bc | 73 | 4 |
| 3 | $1 S, 2 S, 1^{\prime} S$ | EtI | 5bd | 61 | 5 |
| 4 | $1 S, 2 S, 1^{\prime} S$ | $n \mathrm{BuI}$ | 5be | 67 | 2 |
| 5 | $1 S, 2 S, 1^{\prime} S$ | $\mathrm{ClCO}_{2} \mathrm{Et}$ | 5bf | 29 | 0 |
| 6 | $1 S, 2 S, 1^{\prime} S$ | $(t \mathrm{BuOCO})_{2} \mathrm{O}$ | 5bg | 58 | 0 |
| 7 | $1 R, 2 R, 1^{\prime} S$ | $\mathrm{BrCH}_{2} \mathrm{CH}=\mathrm{CH}_{2}$ | 5bb | 1 | 84 |
| 8 | $1 R, 2 R, 1^{\prime} S$ | MeI | 5bc | 7 | 65 |
| 9 | $1 R, 2 R, 1^{\prime} S$ | EtI | 5bd | 10 | 62 |
| 10 | $1 R, 2 R, 1^{\prime} S$ | $n \mathrm{BuI}$ | 5be | 5 | 61 |
| 11 | $1 R, 2 R, 1^{\prime} S$ | $\mathrm{ClCO}_{2} \mathrm{Et}$ | 5bf | 4 | 53 |
| 12 | $1 R, 2 R, 1^{\prime} S$ | $(t \mathrm{BuOCO})_{2} \mathrm{O}$ | 5bg | 0 | 43 |

[^1]

Scheme 4 Determination of the stereochemistry of 5aa.

Reduction of nitrile derivative ( $2 S, 1^{\prime} S$ )-5aa with $\mathrm{LiAlH}_{4}$ provided primary amine $\left(2 S, 1^{\prime} S\right)$-6aa in $93 \%$ yield. $N$-Alkylation with allyl bromide gave mono- $N$-alkylated ( $2 S, 1^{\prime} S$ )-7aa in $82 \%$ yield because of steric hindrance (eqn (1)). The authentic sample of ( $2 S, 1^{\prime} S$ )-7aa was prepared from the tert-butyl ester derivative ( $2 S, 1^{\prime} S$ )-8aa, for which the absolute stereochemistry was determined in our previous work ${ }^{6}$ (eqn (2)). First, tert-butyl ester, as in $\left(2 S, 1^{\prime} S\right)$-8aa, was cleaved with TFA and amidation with allylamine using HATU followed to give $N$-allyl amide ( $2 S, 1^{\prime} S$ )-9aa in $83 \%$ yield. ${ }^{19}$ Reduction of sterically hindered amide ( $2 S, 1^{\prime} S$ )-9aa into $\left(2 S, 1^{\prime} S\right)$-7aa with $\mathrm{LiAlH}_{4}$ proceeded very slowly. To prevent the formation of side products, we quenched the reaction without good conversion of $\left(2 S, 1^{\prime} S\right)$-9aa. The desired $\left(2 S, 1^{\prime} S\right)$ 7 aa was obtained in $28 \%$ yield with the recovery of $\left(2 S, 1^{\prime} S\right)-9 a a$ ( $59 \%$ recovery). The absolute stereochemistry of 5 aa 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}(1: 1)$ at room temperature (Scheme 5). ${ }^{\mathbf{2 0}}$ After 3 days, ( $S$ ) $\mathbf{- 1 0 a}$ was obtained in $59 \%$ yield from $\left(2 S, 1^{\prime} S\right)$-5ba (eqn (1)); in contrast, $(R)$ 10 a was obtained in $85 \%$ yield from $\left(2 R, 1^{\prime} S\right)$-5ba (eqn (2)). The removal from $\left(2 S, 1^{\prime} S\right)$-5ba proceeded more slowly than that from $\left(2 R, 1^{\prime} S\right)-5 b \mathbf{b a}$, but the details are unclear at present. The corresponding amounts of unremoved 5ba were observed by ${ }^{1} \mathrm{H}$ NMR analysis of the crude products. Specific rotation values of $(S)$ - and $(R)-\mathbf{1 0 a}$ showed good agreement for each enantiomer.


(2S,1'S)-5ba

(2R,1'S)-5ba

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 $\left(1 S, 2 S, 1^{\prime} S\right)$-4a to afford $\left(2 S, 1^{\prime} S\right)$-5aa, not the side of the smaller $\mathrm{N}-\mathrm{BH}_{3}$ group. With chromatographic purification of the products, the corresponding amounts of $\mathrm{BH}_{3}$-diisopropylamine complex could be isolated. Decomposition of $\mathrm{BH}_{3}$ by aqueous workup of the reaction did not proceed to completion. Thus, we propose formation of nitrile enolate A derived from $\left(1 S, 2 S, 1^{\prime} S\right)$ 4a. Diisopropylamine generated from LDA after deprotonation might interact with $\mathrm{N}-\mathrm{BH}_{3}$. The side of the $\mathrm{N}-\mathrm{BH}_{3}$ group was blocked by diisopropylamine. Benzyl bromide reacts from the side of the $N$-benzylic substituent to provide $\left(2 S, 1^{\prime} S\right)$-5aa. After $\alpha$-alkylation, $\mathrm{BH}_{3}$ moves to the sterically less hindered diisopropylamine. The resulting $\mathrm{BH}_{3}$-diisopropylamine complex was isolated after aqueous workup and chromatographic purification. The reaction of $\left(1 R, 2 R, 1^{\prime} S\right)$-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, ${ }^{6}$ 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 $N-\mathrm{BH}_{3}$ complexes 4, and LDA-promoted diastereoselective $\alpha$-alkylation to produce $\alpha$-alkylated azetidine-2carbonitriles 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 $\left(2 S, 1^{\prime} S\right)$ - and $\left(2 R, 1^{\prime} S\right)$-5ba, could be removed by TFA treatment. The corresponding enantiomers, 2-benzylazetidine-2carbonitriles $(S)$-10a and $(R) \mathbf{- 1 0 a}$, 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. ${ }^{1} \mathrm{H},{ }^{13} \mathrm{C}$ and ${ }^{11} \mathrm{~B}$ NMR spectra were measured on a Varian ( ${ }^{1} \mathrm{H}: 400 \mathrm{MHz},{ }^{13} \mathrm{C}: 100 \mathrm{MHz}$ ) or a Bruker ( ${ }^{1} \mathrm{H}: 400 \mathrm{MHz}$, ${ }^{13} \mathrm{C}$ : $100 \mathrm{MHz},{ }^{11} \mathrm{~B}: 128 \mathrm{MHz}$ ) spectrometer. As an internal standard in $\mathrm{CDCl}_{3}, \mathrm{Me}_{4} \mathrm{Si}(\delta 0 \mathrm{ppm})$ for ${ }^{1} \mathrm{H}$ NMR and $\mathrm{CDCl}_{3}(\delta$ 77.00 ppm ) for ${ }^{13} \mathrm{C}$ NMR were used. In ${ }^{11} \mathrm{~B}$ NMR, boron trifluoride diethyl etherate $\left(\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}\right)$ was used as an external standard ( $\delta 0 \mathrm{ppm}$ ). 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 $-78{ }^{\circ} \mathrm{C}$ 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 SigmaAldrich. Anhydrous tetrahydrofuran (THF) was purchased from KANTO Chemical Co., Inc. Dichloromethane $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2}\right)$ was purchased from FUJIFILM Wako Chemical Corporation (Japan) and dried over $4 \AA$ 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 $\mu \mathrm{m})$ purchased from FUJIFILM Wako Chemical Corporation. For strong basic compound such as $\left(2 S, 1^{\prime} S\right)$-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-( $(S)-1^{\prime}-$ phenylethyl)azetidine-2-carboxylate $\left[\left(2 S, 1^{\prime} S\right)\right.$-1a and $\left(2 R, 1^{\prime} S\right)$ 1a]

(Step 1) $\gamma$-Butyrolactone $(6.0 \mathrm{~mL}, 78 \mathrm{mmol})$ and $\mathrm{PBr}_{3}(0.2 \mathrm{~mL}$, 2.0 mmol ) was stirred at $100{ }^{\circ} \mathrm{C}$ under an Ar atmosphere. $\mathrm{Br}_{2}$ ( $4.4 \mathrm{~mL}, 86 \mathrm{mmol}$ ) was added dropwise for 1 h to the mixture with stirring. After stirring for 5 min at $100{ }^{\circ} \mathrm{C}$, the resulting mixture was cooled to room temperature and the excess $\mathrm{Br}_{2}$ was removed by flow of $\mathrm{N}_{2}$. The residue was dissolved in MeOH (30
mL ) and stirred for 20 h at room temperature. The resulting mixture was treated with saturated aqueous $\mathrm{Na}_{2} \mathrm{SO}_{3}$ and extracted with $n$-hexane. The combined extracts were washed with saturated aqueous $\mathrm{NaHCO}_{3}$ followed by water. The solution was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ 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 ( $14.54 \mathrm{~g}, 72 \%$ yield) as a colourless oil. (Step 2) A mixture of methyl 2,4-dibromobutanoate ( $747 \mathrm{mg}, 2.87 \mathrm{mmol}$ ), ( $S$ )-1-phenylethylamine ( $0.37 \mathrm{~mL}, 2.9 \mathrm{mmol}$ ), and $\mathrm{NaHCO}_{3}$ ( $1.21 \mathrm{~g}, 14.4 \mathrm{mmol}$ ) 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, $\left.R_{\mathrm{f}}:\left(2 S, 1^{\prime} S\right)>\left(2 R, 1^{\prime} S\right)\right]$ to obtain $\left(2 S, 1^{\prime} S\right)-1 \mathrm{a}(190 \mathrm{mg}$, $30 \%$ yield) as a colourless oil and $\left(2 R, 1^{\prime} S\right)-\mathbf{1 a}(178 \mathrm{mg}, 28 \%$ yield $)$ as a colourless oil. $\left(2 S, 1^{\prime} S\right)-1 \mathrm{a}:[\alpha]_{589}^{24}-118.9$ (c 1.0 in EtOH); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3084,3061,3025,3004,2966,2930,2841,2781$, 1749, 1728, 1493, 1451, 1435, 1371, 1319, 1280, 1229, 1193, 1170, 1095, 1071, 1038, 980, 955, 936, 911, 831, 813, 763, 699; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.36-7.20(5 \mathrm{H}, \mathrm{m}, \mathrm{Ph}), 3.76(1 \mathrm{H}, \mathrm{dd}, J$ $=8.8,8.2 \mathrm{~Hz}, 2-\mathrm{H}), 3.75\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.45\left(1 \mathrm{H}, \mathrm{q}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\right.$ H), $3.11(1 \mathrm{H}, \mathrm{dddd}, J=8.2,7.2,2.8,0.8 \mathrm{~Hz}, 4-\mathrm{H}), 2.80(1 \mathrm{H}, \mathrm{ddd}, J$ $=8.8,8.2,7.2 \mathrm{~Hz}, 4-\mathrm{H}), 2.27(1 \mathrm{H}$, dddd, $J=10.5,8.8,8.8,8.2 \mathrm{~Hz}$, $3-\mathrm{H}), 2.18$ ( 1 H, dddd, $J=10.5,8.2,8.2,2.8 \mathrm{~Hz}, 3-\mathrm{H}), 1.22(3 \mathrm{H}, \mathrm{d}, J$ $\left.=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.6,142.4$, 128.2, 127.4, 127.2, 67.2, 63.9, 51.9, 49.6, 20.9, 20.8; HRMS (ESI): calcd for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{NO}_{2}[\mathrm{M}+\mathrm{H}]^{+}$220.1332, found 220.1328. $\left(2 R, 1^{\prime} S\right)-1 \mathrm{a}:[\alpha]_{589}^{24}+59.8\left(c 1.0\right.$ in EtOH); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3085$, 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; ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.32-7.18(5 \mathrm{H}, \mathrm{m}, \mathrm{Ph}), 3.62-3.54(2 \mathrm{H}, \mathrm{m}, 2-\mathrm{H}$ and $4-\mathrm{H}), 3.36\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, \mathrm{1}^{\prime}-\mathrm{H}\right), 3.30\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.01(1 \mathrm{H}$, ddd, $J=9.2,8.0,6.8 \mathrm{~Hz}, 4-\mathrm{H}), 2.30(1 \mathrm{H}$, dddd, $J=10.2,9.2,8.8$, $8.8 \mathrm{~Hz}, 3-\mathrm{H}), 2.14(1 \mathrm{H}, \mathrm{dddd}, J=10.2,8.2,8.0,2.2 \mathrm{~Hz}, 3-\mathrm{H}), 1.29$ $\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 172.6$, 141.6, 128.0, 127.9, 127.5, 68.1, 64.4, 51.5, 50.8, 20.8, 19.7; HRMS (ESI): calcd for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{NO}_{2}[\mathrm{M}+\mathrm{H}]^{+}$220.1332, found 220.1329.

## Methyl 1-((S)-1'-(4' $4^{\prime \prime}$ methoxyphenyl)ethyl)azetidine-2carboxylate $\left[\left(2 S, 1^{\prime} S\right)-1 \mathrm{bb}\right.$ and $\left.\left(2 R, 1^{\prime} S\right)-1 \mathrm{~b}\right]$

Prepared by the same procedure with 1a using (S)-1-(4methoxyphenyl)ethylamine ( $1.48 \mathrm{~mL}, 10.0 \mathrm{mmol}$ ) 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, $R_{\mathrm{f}}$ : $\left.\left(2 S, 1^{\prime} S\right)>\left(2 R, 1^{\prime} S\right)\right]$ gave $\left(2 S, 1^{\prime} S\right)-\mathbf{1 b}(953 \mathrm{mg}, 38 \%$ yield) as a colourless oil and $\left(2 R, 1^{\prime} S\right)-\mathbf{1 b}(910 \mathrm{mg}, 37 \%$ yield) as a colourless oil. $\left(2 S, 1^{\prime} S\right)$-1b: $[\alpha]_{589}^{24}-110.7$ (c 1.0 in EtOH); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3000,2963,2932,2835,1748,1727,1610,1584$, 1509, 1437, 1370, 1320, 1281, 1242, 1194, 1168, 1097, 1033, 982, 955, 935, 910, 831, 733 ; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.25(2 \mathrm{H}$, ddd, $J=8.4,2.6,2.6 \mathrm{~Hz}, \mathrm{ArH}), 6.84(2 \mathrm{H}, \mathrm{ddd}, J=8.4,2.6,2.6 \mathrm{~Hz}$, $\mathrm{ArH}), 3.79\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.75\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.73(1 \mathrm{H}, \mathrm{dd}, J=$ $8.6,8.4 \mathrm{~Hz}, 2-\mathrm{H}), 3.40\left(1 \mathrm{H}, \mathrm{q}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.08(1 \mathrm{H}$, dddd, $J$
$=8.3,7.1,2.6,0.8 \mathrm{~Hz}, 4-\mathrm{H}), 2.79(1 \mathrm{H}, \mathrm{ddd}, J=8.9,8.2,7.1 \mathrm{~Hz}, 4-$ H), $2.26(1 \mathrm{H}$, dddd, $J=10.5,8.9,8.6,8.3 \mathrm{~Hz}, 3-\mathrm{H}), 2.16(1 \mathrm{H}$, dddd, $J=10.5,8.4,8.2,2.6 \mathrm{~Hz}, 3-\mathrm{H}), 1.20\left(3 \mathrm{H}, \mathrm{d}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\right.$ $\left.\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 173.7,158.7,134.5,128.5$, 113.6, 66.5, 63.9, 55.2, 51.9, 49.4, 20.9, 20.8; HRMS (ESI): calcd for $\mathrm{C}_{14} \mathrm{H}_{20} \mathrm{NO}_{3}[\mathrm{M}+\mathrm{H}]^{+}$250.1438, found 250.1435. $\left(2 R, 1^{\prime} S\right)-1 \mathrm{~b}$ : $[\alpha]_{589}^{24}+43.8(c 1.0$ in EtOH $)$; IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3000,2963,2931$, 2868, 2835, 1730, 1611, 1585, 1510, 1436, 1372, 1350, 1293, 1279, 1241, 1194, 1169, 1104, 1058, 1032, 980, 956, 935, 911, 832, 808, 738; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.21$ ( $2 \mathrm{H}, \mathrm{ddd}, J=$ $8.8,3.0,3.0 \mathrm{~Hz}, \mathrm{ArH}), 6.80(2 \mathrm{H}, \mathrm{ddd}, J=8.8,3.0,3.0 \mathrm{~Hz}, \mathrm{ArH})$, $3.77\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.61-3.52(2 \mathrm{H}, \mathrm{m}, 2-\mathrm{H}$ and $4-\mathrm{H}), 3.37(3 \mathrm{H}, \mathrm{s}$, $\left.\mathrm{OCH}_{3}\right), 3.31\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 2.98(1 \mathrm{H}, \mathrm{ddd}, J=9.2,8.0$, $7.2 \mathrm{~Hz}, 4-\mathrm{H}), 2.34-2.22(1 \mathrm{H}, \mathrm{m}, 3-\mathrm{H}), 2.13(1 \mathrm{H}$, dddd, $J=10.4$, 8.0, $8.0,2.4 \mathrm{~Hz}, 3-\mathrm{H}), 1.26\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 172.7,158.9,133.7,129.0,113.4,67.4,64.3$, $55.2,51.5,50.7,20.8,19.8 ;$ HRMS (ESI): calcd for $\mathrm{C}_{14} \mathrm{H}_{20} \mathrm{NO}_{3}[\mathrm{M}$ $+\mathrm{H}]^{+} 250.1438$, found 250.1434 .

## Representative procedure for preparation of $(S)-1-\left((S)-1^{\prime}-\right.$ phenylethyl)azetidine-2-carboxamide [(2S,1'S)-2a]

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

## ( $R$ )-1-((S)-1'-Phenylethyl)azetidine-2-carboxamide [( $\left.2 R, 1^{\prime} S\right)$-2a]

Prepared from $\left(2 R, 1^{\prime} S\right)-1 \mathrm{a}(433 \mathrm{mg}, 1.97 \mathrm{mmol})$ by the same procedure with $\left(2 S, 1^{\prime} S\right)$-2a. Purification by chromatography on silica gel $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}=20 / 1\right.$ to $10 / 1$ as the eluent) afforded ( $2 R, 1^{\prime} S$ )-2a ( $243 \mathrm{mg}, 60 \%$ yield) as colourless crystals, $\mathrm{mp} 116-$ $119{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{24}+44.4$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3388$, 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; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.32-7.20(5 \mathrm{H}, \mathrm{m}, \mathrm{Ph}), 6.42\left(1 \mathrm{H}, \mathrm{br} \mathrm{s}, \mathrm{NH}_{2}\right), 5.23(1 \mathrm{H}, \mathrm{br} \mathrm{s}$, $\left.\mathrm{NH}_{2}\right), 3.57(1 \mathrm{H}, \mathrm{dd}, J=8.8,8.5 \mathrm{~Hz}, 2-\mathrm{H}), 3.50-3.43(1 \mathrm{H}, \mathrm{m}, 4-\mathrm{H})$, $3.39\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.08(1 \mathrm{H}, \mathrm{ddd}, J=8.8,8.8,7.2 \mathrm{~Hz}$, $4-\mathrm{H}), 2.33(1 \mathrm{H}, \mathrm{dddd}, J=10.9,8.8,8.5,2.6 \mathrm{~Hz}, 3-\mathrm{H}), 2.06(1 \mathrm{H}$,
dddd, $J=10.9,8.8,8.8,8.8 \mathrm{~Hz}, 3-\mathrm{H}), 1.31\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\right.$ $\left.\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 175.9,141.3,128.5,127.85$, 127.79, 66.8, 65.2, 49.6, 22.0, 18.3; HRMS (ESI): calcd for $\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$205.1335, found 205.1333.

Representative procedure for preparation of $(S)-1-\left((S)-1^{\prime}-\left(4^{\prime \prime}-\right.\right.$ methoxyphenyl)ethyl)azetidine-2-carboxamide [(2S,1'S)-2b]
A mixture of $\left(2 S, 1^{\prime} S\right)-\mathbf{1 b}(427 \mathrm{mg}, 1.71 \mathrm{mmol})$ and $\mathrm{NaCN}(17 \mathrm{mg}$, 0.35 mmol ) in $7 \mathrm{~N} \mathrm{NH}_{3} \mathrm{MeOH}$ 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 $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}=40 / 1\right.$ to $20 / 1$ as the eluent $)$ to obtain $\left(2 S, 1^{\prime} S\right)-2 \mathbf{b} \quad(396 \mathrm{mg}, 99 \%$ yield) as a colourless gum. $[\alpha]_{589}^{23}-103.7$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3427,3193$, 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; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.35(1 \mathrm{H}$, br s, $\mathrm{NH}_{2}$ ), $7.22(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 6.86(2 \mathrm{H}$, ddd, $J=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 6.35\left(1 \mathrm{H}, \mathrm{br} \mathrm{s}, \mathrm{NH}_{2}\right), 3.80(3 \mathrm{H}, \mathrm{s}$, $\left.\mathrm{OCH}_{3}\right), 3.64(1 \mathrm{H}, \mathrm{dd}, J=8.8,8.8 \mathrm{~Hz}, 2-\mathrm{H}), 3.42(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}$, $\left.1^{\prime}-\mathrm{H}\right), 3.09(1 \mathrm{H}, \mathrm{ddd}, J=8.2,8.0,2.8 \mathrm{~Hz}, 4-\mathrm{H}), 2.79(1 \mathrm{H}, \mathrm{ddd}, J=$ $8.8,8.8,8.0 \mathrm{~Hz}, 4-\mathrm{H}), 2.35(1 \mathrm{H}, \mathrm{dddd}, J=11.0,8.8,8.8,2.8 \mathrm{~Hz}, 3-$ H), $2.09(1 \mathrm{H}$, dddd, $J=11.0,8.8,8.8,8.2 \mathrm{~Hz}, 3-\mathrm{H}), 1.16(3 \mathrm{H}, \mathrm{d}, J$ $\left.=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 177.3,158.7$, 134.7, 127.9, 113.7, 66.7, 65.2, 55.1, 49.6, 21.8, 21.2; HRMS (ESI): calcd for $\mathrm{C}_{13} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{2}[\mathrm{M}+\mathrm{H}]^{+}$235.1441, found 235.1438.

## (R)-1-((S)-1'-(4"-Methoxyphenyl)ethyl)azetidine-2-carboxamide [(2R, $\left.\left.\mathbf{1}^{\prime} S\right)-2 \mathrm{~b}\right]$

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

Representative procedure for preparation of $(S)-1-\left((S)-1^{\prime}-\right.$ phenylethyl)azetidine-2-carbonitrile [(2S, $\left.\mathbf{1}^{\prime} S\right)$-3a]
A solution of $\left(2 S, 1^{\prime} S\right)$-2a ( $645 \mathrm{mg}, 3.16 \mathrm{mmol}$ ) and pyridine $(0.31$ $\mathrm{mL}, 3.8 \mathrm{mmol}$ ) in 1,4-dioxane ( 16 mL ) was cooled at ca. $10{ }^{\circ} \mathrm{C}$ and treated with trifluoroacetic anhydride ( $0.53 \mathrm{~mL}, 3.8 \mathrm{mmol}$ ) under an Ar atmosphere. After stirring for 2 h at room temperature, the resulting mixture was quenched with $\mathrm{H}_{2} \mathrm{O}$ and extracted with EtOAc. The combined extracts were washed with
saturated aqueous $\mathrm{NaHCO}_{3}$ followed by brine. The organic solution was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. Purification of the residue by chromatography on silica gel ( $n$-hexane/EtOAc $=$ $6 / 1$ to $5 / 1$ as the eluent) gave ( $2 S, 1^{\prime} S$ )-3a ( $530 \mathrm{mg}, 90 \%$ yield) as colourless crystals, $\mathrm{mp} 36-38{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{24}-153.1$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3069,3028,2973,2959,2923,2863,2828$, 2800, 2235, 1489, 1455, 1442, 1371, 1358, 1335, 1316, 1301, 1281, 1223, 1177, 1141, 1099, 1081, 1070, 1028, 972, 939, 926, $907,820,798,756,694 ;{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.34-7.21$ $(5 \mathrm{H}, \mathrm{m}, \mathrm{Ph}), 3.84(1 \mathrm{H}, \mathrm{dd}, J=7.2,7.2 \mathrm{~Hz}, 2-\mathrm{H}), 3.53(1 \mathrm{H}, \mathrm{q}, J=$ $\left.6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.22(1 \mathrm{H}, \mathrm{dddd}, J=7.7,7.1,5.5,0.6 \mathrm{~Hz}, 4-\mathrm{H}), 3.04$ $(1 \mathrm{H}, \mathrm{ddd}, J=7.2,7.2,7.1 \mathrm{~Hz}, 4-\mathrm{H}), 2.43-2.30(2 \mathrm{H}, \mathrm{m}, 3-\mathrm{H}), 1.31$ $\left(3 \mathrm{H}, \mathrm{d}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 141.7$, 128.5, 127.5, 127.2, 119.5, 66.1, 51.1, 50.8, 21.9, 20.7; HRMS (ESI): calcd for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}$187.1230, found 187.1232.

## $(R)-1-\left((S)-1^{\prime}\right.$-Phenylethyl)azetidine-2-carbonitrile [(2R,1'S)-3a]

Prepared from $\left(2 R, 1^{\prime} S\right)$-2a $(578 \mathrm{mg}, 2.83 \mathrm{mmol})$ by the same procedure with $\left(2 S, 1^{\prime} S\right)$-3a. Purification by chromatography on silica gel ( $n$-hexane/EtOAc $=5 / 1$ to $4 / 1$ as the eluent) gave ( $2 R, 1^{\prime} S$ )-3a ( $497 \mathrm{mg}, 94 \%$ yield) as colourless crystals, $\mathrm{mp} 40-$ $41^{\circ} \mathrm{C}$. $[\alpha]_{589}^{24}+7.4\left(c 1.0\right.$ in EtOH); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3031,2968$, 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; ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.38-7.25(5 \mathrm{H}, \mathrm{m}, \mathrm{Ph}), 3.84(1 \mathrm{H}, \mathrm{dd}, J=7.2$, $7.2 \mathrm{~Hz}, 2-\mathrm{H}), 3.46\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.42(1 \mathrm{H}$, dddd, $J=$ $7.7,7.1,5.8,0.8 \mathrm{~Hz}, 4-\mathrm{H}), 3.03(1 \mathrm{H}, \mathrm{ddd}, J=7.2,7.2,7.1 \mathrm{~Hz}, 4-\mathrm{H})$, $2.43-2.30(2 \mathrm{H}, \mathrm{m}, 3-\mathrm{H}), 1.25\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 140.8,128.5,127.9,127.6,118.7,66.5,51.4$, 50.6, 21.8, 20.4; HRMS (ESI): calcd for $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}$ 187.1230, found 187.1232.

## (S)-1-((S)-1'-( $\mathbf{4}^{\prime \prime}$-Methoxyphenyl)ethyl)azetidine-2-carbonitrile [(2S,1'S)-3b]

Prepared from $\left(2 S, 1^{\prime} S\right)-2 \mathbf{b}(396 \mathrm{mg}, 1.69 \mathrm{mmol})$ by the same procedure with $\left(2 S, 1^{\prime} S\right)$-3a. Purification by chromatography on silica gel $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{EtOAc}=100 / 1\right.$ to $50 / 1$ as the eluent $)$ gave ( $2 S, 1^{\prime} S$ )-3b ( $294 \mathrm{mg}, 80 \%$ yield) as colourless crystals, mp 94$95{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{23}-140.1$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3043$, 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, $728 ;{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.24(2 \mathrm{H}, \mathrm{ddd}, J=8.6,2.6$, $2.6 \mathrm{~Hz}, \mathrm{ArH}), 6.85(2 \mathrm{H}, \mathrm{ddd}, J=8.6,2.6,2.6 \mathrm{~Hz}, \mathrm{ArH}), 3.81(1 \mathrm{H}$, $\mathrm{dd}, J=7.2,7.2 \mathrm{~Hz}, 2-\mathrm{H}), 3.79\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.49(1 \mathrm{H}, \mathrm{q}, J=$ $\left.6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.19(1 \mathrm{H}$, ddd, $J=7.6,7.2,5.8 \mathrm{~Hz}, 4-\mathrm{H}), 3.04(1 \mathrm{H}$, ddd, $J=7.2,7.2,7.2 \mathrm{~Hz}, 4-\mathrm{H}), 2.42-2.28(2 \mathrm{H}, \mathrm{m}, 3-\mathrm{H}), 1.28(3 \mathrm{H}$, $\left.\mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 158.9,133.7$, 128.3, 119.5, 113.8, 65.4, 55.2, 51.0, 50.8, 21.8, 20.7; HRMS (ESI): calcd for $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$217.1335, found 217.1335.

## $(R)-1-\left((S)-1^{\prime}-\left(4^{\prime \prime}-\right.\right.$ Methoxyphenyl)ethyl)azetidine-2-carbonitrile [( $\left.\left.2 R, \mathbf{1}^{\prime} S\right)-3 \mathrm{~b}\right]$

Prepared from $\left(2 R, 1^{\prime} S\right)-2 b(805 \mathrm{mg}, 3.44 \mathrm{mmol})$ by the same procedure with $\left(2 S, 1^{\prime} S\right)$-3a. Purification by chromatography on
silica gel $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}=100 / 1\right.$ to $50 / 1$ as the eluent $)$ gave ( $2 R, 1^{\prime} S$ ) $\mathbf{3} \mathbf{3 b}$ ( $547 \mathrm{mg}, 74 \%$ yield) as colourless crystals, $\mathrm{mp} 39-$ $42^{\circ} \mathrm{C}$. $[\alpha]_{589}^{24}+5.3\left(c 1.0\right.$ in EtOH); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3043,3006$, 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; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.26(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.5,2.5 \mathrm{~Hz}$, ArH), $6.88(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 3.86-3.77(1 \mathrm{H}, \mathrm{m}$, $2-\mathrm{H}), 3.80\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.46-3.36(2 \mathrm{H}, \mathrm{m}, 4-\mathrm{H}), 3.01(1 \mathrm{H}, \mathrm{q}, J=$ $\left.6.8 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 2.43-2.29(2 \mathrm{H}, \mathrm{m}, 3-\mathrm{H}), 1.22\left(3 \mathrm{H}, \mathrm{d}, J=6.8 \mathrm{~Hz}, 1^{\prime}-\right.$ $\mathrm{CH}_{3}$ ); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 159.3,132.8,128.6,118.8$, 113.9, 65.9, 55.2, 51.4, 50.5, 21.7, 20.4; HRMS (ESI): calcd for $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$217.1335, found 217.1334.

## Representative procedure for preparation of ((1S,2S)-2-cyano-1-((S)-1'-phenylethyl)azetidin-1-ium-1-yl)trihydroborate [(1S,2S, $\left.\left.\mathbf{1}^{\prime} S\right)-\mathbf{4 a}\right]$

Borane dimethyl sulfide complex (ca. $10 \mathrm{M}, 0.31 \mathrm{~mL}, 3.1 \mathrm{mmol}$ ) was added to a solution of $\left(2 S, 1^{\prime} S\right)$-3a ( $530 \mathrm{mg}, 2.85 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(14 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ 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 $/ \mathrm{CH}_{2} \mathrm{Cl}_{2}$ $=1 / 2$ to $0 / 1$ as the eluent) to obtain $\left(1 S, 2 S, 1^{\prime} S\right)-\mathbf{4 a}(519 \mathrm{mg}, 91 \%$ yield) as colourless crystals, mp 126-128 ${ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{24}-152.2$ (c 1.0 in $\mathrm{CHCl}_{3}$ ); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3030,2978,2945,2361,2340$, 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; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 7.48-7.37(5 \mathrm{H}, \mathrm{m}, \mathrm{Ph}), 4.30(1 \mathrm{H}, \mathrm{dd}, J=9.2,8.8 \mathrm{~Hz}, 2-$ H), $4.18\left(1 \mathrm{H}, \mathrm{q}, J=7.0 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.83(1 \mathrm{H}, \mathrm{ddd}, J=9.4,8.8$, $8.8 \mathrm{~Hz}, 4-\mathrm{H}), 3.32(1 \mathrm{H}, \mathrm{ddd}, J=9.2,8.8,3.2 \mathrm{~Hz}, 4-\mathrm{H}), 3.04(1 \mathrm{H}$, dddd, $J=10.9,9.4,9.2,9.2 \mathrm{~Hz}, 3-\mathrm{H}), 2.50-1.50\left(3 \mathrm{H}, \mathrm{br}, \mathrm{BH}_{3}\right)$, $2.21(1 \mathrm{H}, \mathrm{dddd}, J=10.9,8.8,8.8,3.2 \mathrm{~Hz}, 3-\mathrm{H}), 1.68(3 \mathrm{H}, \mathrm{d}, J=$ $\left.7.0 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 135.3,130.0,129.8$, 129.0, 114.7, 70.3, 54.55, 54.48, 20.8, 15.3; ${ }^{11}$ B NMR ( 128 MHz , $\mathrm{CDCl}_{3}$ ) $\delta-13.3$ (br); HRMS (ESI): calcd for $\mathrm{C}_{12} \mathrm{H}_{18} \mathrm{BN}_{2}[\mathrm{M}+\mathrm{H}]^{+}$ 201.1558, found 201.1559.

## ((1R,2R)-2-Cyano-1-((S)-1'-phenylethyl)azetidin-1-ium-1-yl) trihydroborate $\left[\left(1 R, 2 R, 1^{\prime} S\right)-4 a\right]$

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

NMR ( $128 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-13.6$ (br); HRMS (ESI): calcd for $\mathrm{C}_{12} \mathrm{H}_{18} \mathrm{BN}_{2}[\mathrm{M}+\mathrm{H}]^{+}$201.1558, found 201.1557.

## ((1S,2S)-2-Cyano-1-((S)-1'-(4"-methoxyphenyl)ethyl)azetidin-1-ium-1-yl)trihydroborate [(1S,2S,1'S)-4b]

Prepared from $\left(2 S, 1^{\prime} S\right)-\mathbf{3 b}(173 \mathrm{mg}, 0.800 \mathrm{mmol})$ by the same procedure with $\left(1 S, 2 S, 1^{\prime} S\right)-4 a$. Purification by chromatography on silica gel ( $n$-hexane/ $\mathrm{CH}_{2} \mathrm{Cl}_{2}=1 / 2$ to $0 / 1$ as the eluent) gave $\left(1 S, 2 S, 1^{\prime} S\right)$-4b ( $171 \mathrm{mg}, 93 \%$ yield) as colourless crystals, mp $108-110^{\circ} \mathrm{C}$. $[\alpha]_{589}^{24}-150.3\left(c 1.0\right.$ in $\mathrm{CHCl}_{3}$ ); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1}$ 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; ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.32(2 \mathrm{H}$, ddd, $J=8.8,2.6,2.6 \mathrm{~Hz}, \mathrm{ArH}), 6.96$ $(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.6,2.6 \mathrm{~Hz}, \mathrm{ArH}), 4.32(1 \mathrm{H}, \mathrm{dd}, J=9.2,9.2 \mathrm{~Hz}$, $2-\mathrm{H}), 4.13\left(1 \mathrm{H}, \mathrm{q}, J=6.8 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.84\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.79(1 \mathrm{H}$, ddd, $J=9.2,9.2,8.8 \mathrm{~Hz}, 4-\mathrm{H}), 3.27(1 \mathrm{H}, \mathrm{ddd}, J=9.2,9.2$, $3.0 \mathrm{~Hz}, 4-\mathrm{H}), 3.02(1 \mathrm{H}$, dddd, $J=10.8,9.2,9.2,9.2 \mathrm{~Hz}, 3-\mathrm{H})$, $2.50-1.50\left(3 \mathrm{H}, \mathrm{br}, \mathrm{BH}_{3}\right), 2.22(1 \mathrm{H}$, dddd, $J=10.8,9.2$, 8.8 , $3.0 \mathrm{~Hz}, 3-\mathrm{H}), 1.64\left(3 \mathrm{H}, \mathrm{d}, J=6.8 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( 100 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 160.5,131.2,127.2,114.8,114.2,69.8,55.3,54.4$ (2C), 20.7, 15.4; ${ }^{11}$ B NMR ( $128 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-13.6$ (br); HRMS (ESI): calcd for $\mathrm{C}_{13} \mathrm{H}_{20} \mathrm{BN}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$231.1663, found 231.1665.

## ((1R,2R)-2-Cyano-1-((S)-1'-(4"-methoxyphenyl)ethyl)azetidin-1-ium-1-yl)trihydroborate [(1R,2R,1'S)-4b]

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

## Preparation of $\boldsymbol{c a} \boldsymbol{0} \mathbf{0 . 7}$ M LDA solution in THF/ $\boldsymbol{n}$-hexane

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

## Representative procedure for $\alpha$-alkylation of $\left(1 S, 2 S, 1^{\prime} S\right)$-4a with LDA (Table 1, entry 4)

THF ( 8.0 mL ) was added to $\left(1 S, 2 S, 1^{\prime} S\right)-\mathbf{4 a}(200 \mathrm{mg}, 1.00 \mathrm{mmol})$ in a flask under an Ar atmosphere and the mixture was cooled at $-78{ }^{\circ} \mathrm{C}$ as soon as possible. The mixture was treated with a $c a$. 0.7 M LDA solution in THF $/ n$-hexane ( $1.7 \mathrm{~mL}, 1.2 \mathrm{mmol}$ ) and stirred for 0.5 h at $-78^{\circ} \mathrm{C}$. The mixture was treated with benzyl bromide ( $154 \mu \mathrm{~L}, 1.29 \mathrm{mmol}$ ) and allowed to warm at room temperature. After stirring for 3 h , the resulting mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $\mathrm{NaHCO}_{3}$ followed by brine, and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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)azetidine-2-carbonitrile $\left[\left(2 S, 1^{\prime} S\right)\right.$-5aa] (193 mg, 70\% yield) as colourless crystals, $\mathrm{mp} 73-75{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{26}-163.6$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3026,2968,2936,2870,2826,2798$, 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; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.52-7.48(2 \mathrm{H}$, $\mathrm{m}, \mathrm{ArH}), 7.39-7.33(2 \mathrm{H}, \mathrm{m}, \mathrm{ArH}), 7.28(1 \mathrm{H}, \mathrm{tt}, J=7.2,1.4 \mathrm{~Hz}$, ArH), 7.25-7.16 (3H, m, ArH), 7.03-6.98 (2H, m, ArH), 3.79 ( 1 H , $\left.\mathrm{q}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.47(1 \mathrm{H}, \mathrm{ddd}, J=8.2,6.6,1.6 \mathrm{~Hz}, 4-\mathrm{H}), 3.18$ $(1 \mathrm{H}, \mathrm{ddd}, J=9.6,7.6,6.6 \mathrm{~Hz}, 4-\mathrm{H}), 2.54(1 \mathrm{H}, \mathrm{d}, J=13.6 \mathrm{~Hz}$, $\left.\mathrm{CH}_{2} \mathrm{Ph}\right), 2.32(1 \mathrm{H}, \mathrm{ddd}, J=10.6,9.6,8.2 \mathrm{~Hz}, 3-\mathrm{H}), 2.05-1.97(1 \mathrm{H}$, $\mathrm{m}, 3-\mathrm{H}), 2.02\left(1 \mathrm{H}, \mathrm{d}, J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 1.31(3 \mathrm{H}, \mathrm{d}, J=6.6 \mathrm{~Hz}$, $\left.1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 142.5,134.2,129.6,128.5$, 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 $\mathrm{C}_{19} \mathrm{H}_{21} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+} 277.1699$, found 277.1700.

## Representative procedure for $\alpha$-alkylation of $\left(1 R, 2 R, 1^{\prime} S\right)-4 a$ with LiHMDS (Table 1, entry 6)

THF ( 1.2 mL ) was added to $\left(1 R, 2 R, 1^{\prime} S\right)$ - $\mathbf{4 a}(42 \mathrm{mg}, 0.21 \mathrm{mmol})$ in a flask under an Ar atmosphere and the mixture was cooled at $-78{ }^{\circ} \mathrm{C}$ as soon as possible. The mixture was treated with a 1 M LiHMDS solution in THF ( $0.50 \mathrm{~mL}, 0.50 \mathrm{mmol}$ ) and stirred for 0.5 h at $-78{ }^{\circ} \mathrm{C}$. The mixture was treated with benzyl bromide ( $65 \mu \mathrm{~L}, 0.55 \mathrm{mmol}$ ) and allowed to warm at room temperature. After stirring for 3 h , the resulting mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $\mathrm{NaHCO}_{3}$ followed by brine. The solution was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated by evaporation. Purification of the residue by chromatography on silica gel [ $n$-hexane/EtOAc $=10 / 1$ as the eluent, $\left.R_{\mathrm{f}}:\left(2 R, 1^{\prime} S\right)>\left(2 S, 1^{\prime} S\right)\right]$ afforded $\left(2 R, 1^{\prime} S\right)$-5aa ( 42.9 mg , $74 \%$ yield) as colourless crystals and ( $2 S, 1^{\prime} S$ )-5aa ( $4.8 \mathrm{mg}, 8 \%$ yield) as colourless crystals. $\left(2 R, 1^{\prime} S\right)$-5aa: colourless crystals, mp $72-74{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{25}-91.3$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3085$, 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; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.39-7.22(10 \mathrm{H}, \mathrm{m}, \mathrm{ArH}), 3.76(1 \mathrm{H}, \mathrm{q}, J$ $\left.=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.24\left(1 \mathrm{H}, \mathrm{d}, J=13.8 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 3.20(1 \mathrm{H}, \mathrm{d}, J=$ $13.8 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}$ ), $2.91(1 \mathrm{H}, \mathrm{ddd}, J=8.4,7.1,2.4 \mathrm{~Hz}, 4-\mathrm{H}), 2.84$
(1H, ddd, $J=9.5,7.9,7.1 \mathrm{~Hz}, 4-\mathrm{H}), 2.26(1 \mathrm{H}, \mathrm{ddd}, J=10.8,9.5$, $8.4 \mathrm{~Hz}, 3-\mathrm{H}), 2.03(1 \mathrm{H}, \mathrm{ddd}, J=10.8,7.9,2.4 \mathrm{~Hz}, 3-\mathrm{H}), 1.39(3 \mathrm{H}$, $\left.\mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 142.3,134.2$, 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 $\mathrm{C}_{19} \mathrm{H}_{21} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}$ 277.1699, found 277.1699.

## Representative procedure for $\alpha$-alkylation of $\left(1 S, 2 S, \mathbf{1}^{\prime} S\right)$-4b with LDA (Table 1, entry 9)

THF ( 4.0 mL ) was added to $\left(1 S, 2 S, 1^{\prime} S\right)-\mathbf{4 b}(115 \mathrm{mg}, 0.500 \mathrm{mmol})$ in a flask under an Ar atmosphere and the mixture was cooled at $-78{ }^{\circ} \mathrm{C}$ as soon as possible. The mixture was treated with a $c a$. 0.7 M LDA solution in $\mathrm{THF} / n$-hexane ( $0.86 \mathrm{~mL}, 0.60 \mathrm{mmol}$ ) at $-78{ }^{\circ} \mathrm{C}$. The mixture was stirred for 0.5 h at $-78^{\circ} \mathrm{C}$ and treated with benzyl bromide ( $77 \mu \mathrm{~L}, 0.65 \mathrm{mmol}$ ). The mixture was allowed to warm at room temperature and stirred for 3 h . The resulting mixture was quenched with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $\mathrm{NaHCO}_{3}$ followed by brine, and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The volatiles were removed by evaporation and the residue was purified by chromatography on silica gel $[n-$ hexane/EtOAc $=7 / 1$ as the eluent, $\left.R_{f}:\left(2 R, 1^{\prime} S\right)>\left(2 S, 1^{\prime} S\right)\right]$ to obtain ( $S$ )-2-benzyl-1-((S)-1'-(4'-methoxyphenyl)ethyl)azetidine2 -carbonitrile $\left[\left(2 S, 1^{\prime} S\right)-5 b a\right](110.6 \mathrm{mg}, 72 \%$ yield) as colourless crystals and (R)-2-benzyl-1-((S)-1'-(4'"-methoxyphenyl)ethyl) azetidine-2-carbonitrile $\left[\left(2 R, 1^{\prime} S\right)-5 \mathbf{b a}\right](2.6 \mathrm{mg}, 2 \%$ yield) as a colourless oil. $\left(2 S, 1^{\prime} S\right)$-5ba: colourless crystals, mp 93-95 ${ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{24}-205.5$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3061,3029$, 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; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.41(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 7.26-7.16(3 \mathrm{H}, \mathrm{m}$, ArH), $7.05-7.00(2 \mathrm{H}, \mathrm{m}, \mathrm{ArH}), 6.90(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4,2.4 \mathrm{~Hz}$, $\mathrm{ArH}), 3.80\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.74\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.45(1 \mathrm{H}$, ddd, $J=8.2,6.6,1.8 \mathrm{~Hz}, 4-\mathrm{H}), 3.15(1 \mathrm{H}, \mathrm{ddd}, J=9.9,7.6,6.6 \mathrm{~Hz}$, $4-\mathrm{H}), 2.54\left(1 \mathrm{H}, \mathrm{d}, J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 2.30(1 \mathrm{H}, \mathrm{ddd}, J=10.7$, 9.9, $8.2 \mathrm{~Hz}, 3-\mathrm{H}), 2.07\left(1 \mathrm{H}, \mathrm{d}, J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 1.99(1 \mathrm{H}, \mathrm{ddd}$, $J=10.7,7.6,1.8 \mathrm{~Hz}, 3-\mathrm{H}), 1.28\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 159.2,134.4,134.2,129.65,129.57$, 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 $\mathrm{C}_{20} \mathrm{H}_{23} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+} 307.1805$, found 307.1804. ( $2 R, 1^{\prime} S$ )-5ba: colourless oil. $[\alpha]_{589}^{24}-95.3$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3061,3030,2968,2933,2835,2221$, 1610, 1584, 1510, 1454, 1371, 1350, 1329, 1302, 1289, 1242, 1173, 1138, 1092, 1059, 1032, 983, 949, 910, 832, 784, 753, 699; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.39-7.28(5 \mathrm{H}, \mathrm{m}, \mathrm{ArH}), 7.27(2 \mathrm{H}$, ddd, $J=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 6.86(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4,2.4 \mathrm{~Hz}$, $\mathrm{ArH}), 3.80\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.70\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.24(1 \mathrm{H}$, d, $\left.J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 3.19\left(1 \mathrm{H}, \mathrm{d}, J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 2.89$ ( $1 \mathrm{H}, \mathrm{ddd}, J=8.4,7.1,2.4 \mathrm{~Hz}, 4-\mathrm{H}$ ), $2.83(1 \mathrm{H}, \mathrm{ddd}, J=9.4,7.9$, $7.1 \mathrm{~Hz}, 4-\mathrm{H}), 2.25(1 \mathrm{H}, \mathrm{ddd}, J=11.0,9.4,8.4 \mathrm{~Hz}, 3-\mathrm{H}), 2.03(1 \mathrm{H}$, ddd, $J=11.0,7.9,2.4 \mathrm{~Hz}, 3-\mathrm{H}), 1.36\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right)$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 158.9,134.4,134.3,130.0,128.5$, 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 $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{ONa}[\mathrm{M}+\mathrm{Na}]^{+} 329.1624$, found 329.1624.
(S)-2-Allyl-1-((S)-1'-(4'"-methoxyphenyl)ethyl)azetidine-2carbonitrile $\left[\left(2 S, 1^{\prime} S\right)-5 b b\right]$ (Table 2, entry 1)
Purified by chromatography on silica gel ( $n$-hexane/ $\mathrm{CH}_{2} \mathrm{Cl}_{2}=1 /$ 5 as the eluent). $37.0 \mathrm{mg}, 56 \%$ yield, colourless oil. $[\alpha]_{589}^{20}-145.2$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3078,3004,2967,2933,2834$, 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; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.32$ ( $2 \mathrm{H}, \mathrm{ddd}, J$ $=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 6.85(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH})$, $5.56\left(1 \mathrm{H}\right.$, dddd, $\left.J=17.1,10.2,7.2,7.2 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 5.07$ ( 1 H , dddd, $\left.J=10.2,1.2,1.2,1.2 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 4.96(1 \mathrm{H}$, dddd, $\left.J=17.1,1.2,1.2,1.2 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 3.80(3 \mathrm{H}, \mathrm{s}$, $\left.\mathrm{OCH}_{3}\right), 3.68\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.42(1 \mathrm{H}, \mathrm{ddd}, J=7.9,6.6$, $2.0 \mathrm{~Hz}, 4-\mathrm{H}), 3.18(1 \mathrm{H}, \mathrm{ddd}, J=9.7,7.9,6.6 \mathrm{~Hz}, 4-\mathrm{H}), 2.23(1 \mathrm{H}$, ddd, $J=10.7,9.7,7.9 \mathrm{~Hz}, 3-\mathrm{H}), 2.14(1 \mathrm{H}, \mathrm{ddd}, J=10.7,7.9$, $2.0 \mathrm{~Hz}, 3-\mathrm{H}), 1.92\left(1 \mathrm{H}\right.$, dddd, $J=14.0,7.2,1.2,1.2 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=$ $\mathrm{CH}_{2}$ ), $1.67\left(1 \mathrm{H}\right.$, dddd, $J=14.0,7.2,1.2,1.2 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}$ ), $1.24\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 159.1,134.4,130.6,129.4,119.7,119.5,113.6,64.8,62.3,55.2$, 48.9, 42.9, 27.3, 20.2; HRMS (ESI): calcd for $\mathrm{C}_{16} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{ONa}[\mathrm{M}+$ $\mathrm{Na}]^{+} 279.1468$, found 279.1470 .

## (R)-2-Allyl-1-((S)-1'-(4"-methoxyphenyl)ethyl)azetidine-2carbonitrile [( $\left.\left.2 R, 1^{\prime} S\right)-5 b b\right]$ (Table 2, entry 7)

Purified by chromatography on silica gel ( $n$-hexane $/$ EtOAc $=7 / 1$ as the eluent). $53.3 \mathrm{mg}, 84 \%$ yield, colourless oil. $[\alpha]_{589}^{20}-94.5$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3078,3005,2969,2933,2835$, 2221, 1642, 1611, 1585, 1511, 1457, 1442, 1371, 1352, 1329, 1290, 1242, 1172, 1132, 1110, 1060, 1034, 993, 983, 923, 832, 792, 735, 702; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.25$ ( $2 \mathrm{H}, \mathrm{ddd}, J=$ $8.8,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 6.85(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH})$, 5.94-5.82 (1H, m, CH $\left.{ }_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 5.28-5.25\left(1 \mathrm{H}, \mathrm{m}, \mathrm{CH}_{2} \mathrm{CH}=\right.$ $\left.\mathrm{CH})_{2}\right), 5.25-5.21\left(1 \mathrm{H}, \mathrm{m}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 3.79\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.65$ $\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 2.94-2.83(2 \mathrm{H}, \mathrm{m}, 4-\mathrm{H}), 2.66(2 \mathrm{H}, \mathrm{ddd}, J$ $\left.=7.6,1.1,1.1 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 2.26-2.14(2 \mathrm{H}, \mathrm{m}, 3-\mathrm{H}), 1.26$ $\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 158.8$, 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 $\mathrm{C}_{16} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{ONa}[\mathrm{M}+\mathrm{Na}]^{+}$ 279.1468, found 279.1469.

## (S)-1-((S)-1'-(4'-Methoxyphenyl)ethyl)-2-methylazetidine-2-

carbonitrile $\left[\left(2 S, 1^{\prime} S\right)-5 b c\right]$ (Table 2, entry 2)
Purified by chromatography on silica gel ( $n$-hexane/EtOAc $=7 / 1$ as the eluent). $45.0 \mathrm{mg}, 73 \%$ yield, colourless crystals, $\mathrm{mp} 73-$ $75{ }^{\circ} \mathrm{C} .[\alpha]_{589}^{22}-205.7$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3009$, 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; ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.32(2 \mathrm{H}, \mathrm{ddd}, J=8.6,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 6.84(2 \mathrm{H}$, ddd, $J=8.6,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 3.79\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.64(1 \mathrm{H}, \mathrm{q}, J$ $\left.=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.43(1 \mathrm{H}, \mathrm{ddd}, J=8.0,6.8,2.2 \mathrm{~Hz}, 4-\mathrm{H}), 3.17(1 \mathrm{H}$, ddd, $J=9.9,7.8,6.8 \mathrm{~Hz}, 4-\mathrm{H}), 2.28(1 \mathrm{H}, \mathrm{ddd}, J=10.4,7.8,2.2 \mathrm{~Hz}$, $3-\mathrm{H}), 2.15(1 \mathrm{H}, \mathrm{ddd}, J=10.4,9.9,8.0 \mathrm{~Hz}, 3-\mathrm{H}), 1.24(3 \mathrm{H}, \mathrm{d}, J=$ $\left.6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right), 0.94\left(3 \mathrm{H}, \mathrm{s}, 2-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 159.0,134.2,129.3,120.4,113.5,62.3,61.1,55.1,49.0,30.1$,
26.1, 20.2; HRMS (ESI): calcd for $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$231.1492, found 231.1490.
(R)-1-((S)-1'-(4'-Methoxyphenyl)ethyl)-2-methylazetidine-2carbonitrile $\left[\left(2 R, 1^{\prime} S\right)-5 b c\right]$ (Table 2, entry 8)
Purified by chromatography on silica gel ( $n$-hexane/ $\mathrm{CH}_{2} \mathrm{Cl}_{2}=1$ / 5 as the eluent). $47.7 \mathrm{mg}, 65 \%$ yield, colourless crystals, $\mathrm{mp} 93-$ $95{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{24}-86.8$ (c 1.0 in EtOH); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3031$, 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,$722 ;{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.25(2 \mathrm{H}, \mathrm{ddd}, J=8.4,2.5$, $2.5 \mathrm{~Hz}, \mathrm{ArH}), 6.85(2 \mathrm{H}, \mathrm{ddd}, J=8.4,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 3.80(3 \mathrm{H}, \mathrm{s}$, $\left.\mathrm{OCH}_{3}\right), 3.62\left(1 \mathrm{H}, \mathrm{q}, J=6.2 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 2.92(1 \mathrm{H}, \mathrm{ddd}, J=8.4,7.0$, $3.0 \mathrm{~Hz}, 4-\mathrm{H}), 2.88(1 \mathrm{H}, \mathrm{ddd}, J=9.2,7.6,7.0 \mathrm{~Hz}, 4-\mathrm{H}), 2.32(1 \mathrm{H}$, ddd, $J=10.7,7.6,3.0 \mathrm{~Hz}, 3-\mathrm{H}), 2.12(1 \mathrm{H}, \mathrm{ddd}, J=10.7,9.2$, $8.4 \mathrm{~Hz}, 3-\mathrm{H}), 1.66\left(3 \mathrm{H}, \mathrm{s}, 2-\mathrm{CH}_{3}\right), 1.25\left(3 \mathrm{H}, \mathrm{d}, J=6.2 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right)$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 158.8,134.4,128.4,120.2,113.7$, 63.2, 60.1, 55.2, 48.5, 29.7, 27.5, 21.9; HRMS (ESI): calcd for $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$231.1492, found 231.1489.

## (S)-2-Ethyl-1-((S)-1'-(4"-methoxyphenyl)ethyl)azetidine-2carbonitrile [(2S, $\left.\mathbf{1}^{\prime} S\right)$-5bd] (Table 2, entry 3)

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

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

Purified by chromatography on silica gel ( $n$-hexane/EtOAc $=7 / 1$ as the eluent). $30.5 \mathrm{mg}, 62 \%$ yield, colourless oil. $[\alpha]_{589}^{23}-96.1$ ( $c$ 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 2969,2936,2876,2835,2221$, 1611, 1585, 1510, 1459, 1371, 1351, 1328, 1292, 1242, 1171, 1130, 1111, 1097, 1059, 1034, 962, 883, 831, 783, 734; ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.25(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 6.85$ $(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 3.79\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.64(1 \mathrm{H}$, $\left.\mathrm{q}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 2.90(1 \mathrm{H}, \mathrm{ddd}, J=8.2,7.1,2.6 \mathrm{~Hz}, 4-\mathrm{H}), 2.85$ ( $1 \mathrm{H}, \mathrm{ddd}, J=9.3,7.8,7.1 \mathrm{~Hz}, 4-\mathrm{H}$ ), $2.22(1 \mathrm{H}, \mathrm{ddd}, J=10.8,7.8$, $2.6 \mathrm{~Hz}, 3-\mathrm{H}), 2.12(1 \mathrm{H}, \mathrm{ddd}, J=10.8,9.3,8.2 \mathrm{~Hz}, 3-\mathrm{H}), 1.97(1 \mathrm{H}$, $\left.\mathrm{dq}, J=13.7,7.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}_{3}\right), 1.90(1 \mathrm{H}, \mathrm{dq}, J=13.7,7.6 \mathrm{~Hz}$, $\left.\mathrm{CH}_{2} \mathrm{CH}_{3}\right), 1.24\left(3 \mathrm{H}, \mathrm{d}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right), 1.05(3 \mathrm{H}, \mathrm{dd}, J=7.6$, $7.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}_{3}$ ); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 158.8,134.6$, 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 $\mathrm{C}_{15} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{ONa}[\mathrm{M}+\mathrm{Na}]^{+}$267.1468, found 267.1468.

## (S)-2-Butyl-1-((S)-1'-(4"-methoxyphenyl)ethyl)azetidine-2carbonitrile [( $\left.\left.2 S, 1^{\prime} S\right)-5 b e\right]$ (Table 2, entry 4)

Purified by chromatography on silica gel ( $n$-hexane/ $\mathrm{CH}_{2} \mathrm{Cl}_{2}=1$ / 5 as the eluent). $54.5 \mathrm{mg}, 67 \%$ yield, colourless oil. $[\alpha]_{589}^{17}-149.7$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 2958,2932,2861,2834,2221$, 1612, 1585, 1511, 1465, 1457, 1371, 1354, 1329, 1294, 1278, 1242, 1171, 1115, 1097, 1030, 982, 962, 938, 896, 878, 832, 817, 790,$738 ;{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.31(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4$, $2.4 \mathrm{~Hz}, \mathrm{ArH}), 6.83(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 3.79(3 \mathrm{H}, \mathrm{s}$, $\left.\mathrm{OCH}_{3}\right), 3.67\left(1 \mathrm{H}, \mathrm{q}, J=6.3 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.42(1 \mathrm{H}, \mathrm{ddd}, J=6.7,6.7$, $3.0 \mathrm{~Hz}, 4-\mathrm{H}), 3.16(1 \mathrm{H}, \mathrm{ddd}, J=9.2,8.2,6.7 \mathrm{~Hz}, 4-\mathrm{H}), 2.24-2.12$ $(2 \mathrm{H}, \mathrm{m}, 3-\mathrm{H}), 1.22\left(3 \mathrm{H}, \mathrm{d}, J=6.3 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right), 1.20-1.03(5 \mathrm{H}, \mathrm{m}$, $\left.\left(\mathrm{CH}_{2}\right)_{3} \mathrm{CH}_{3}\right), 1.00-0.87\left(1 \mathrm{H}, \mathrm{m},\left(\mathrm{CH}_{2}\right)_{3} \mathrm{CH}_{3}\right), 0.76(3 \mathrm{H}, \mathrm{t}, J=$ $\left.7.0 \mathrm{~Hz},\left(\mathrm{CH}_{2}\right)_{3} \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 159.0,134.6$, 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 $\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$273.1961, found 273.1957.

## (R)-2-Butyl-1-((S)-1'-(4"-methoxyphenyl)ethyl)azetidine-2carbonitrile [( $\left.2 R, 1^{\prime} S\right)$-5be] (Table 2, entry 10)

Purified by chromatography on silica gel ( $n$-hexane/ $\mathrm{CH}_{2} \mathrm{Cl}_{2}=1 /$ 5 as the eluent). $46.3 \mathrm{mg}, 61 \%$ yield, colourless oil. $[\alpha]_{589}^{25}-78.9$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 2958,2932,2861,2835,2221$, 1611, 1585, 1511, 1458, 1371, 1329, 1301, 1289, 1243, 1171, 1131, 1111, 1060, 1035, 979, 831, 784, 733; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 7.24(2 \mathrm{H}, \mathrm{ddd}, J=8.6,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 6.85(2 \mathrm{H}, \mathrm{ddd}, J$ $=8.6,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 3.79\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.63(1 \mathrm{H}, \mathrm{q}, J=$ $\left.6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 2.90(1 \mathrm{H}, \mathrm{ddd}, J=8.1,7.2,2.6 \mathrm{~Hz}, 4-\mathrm{H}), 2.85(1 \mathrm{H}$, ddd, $J=9.6,7.8,7.2 \mathrm{~Hz}, 4-\mathrm{H}), 2.23(1 \mathrm{H}, \mathrm{ddd}, J=10.7,7.8,2.6 \mathrm{~Hz}$, $3-\mathrm{H}), 2.14(1 \mathrm{H}, \mathrm{ddd}, J=10.7,9.6,8.1 \mathrm{~Hz}, 3-\mathrm{H}), 2.00-1.82(2 \mathrm{H}, \mathrm{m}$, $\left.\left(\mathrm{CH}_{2}\right)_{3} \mathrm{CH}_{3}\right), 1.55-1.33\left(4 \mathrm{H}, \mathrm{m},\left(\mathrm{CH}_{2}\right)_{3} \mathrm{CH}_{3}\right), 1.25(3 \mathrm{H}, \mathrm{d}, J=$ $\left.6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right), 0.95\left(3 \mathrm{H}, \mathrm{t}, J=7.0 \mathrm{~Hz},\left(\mathrm{CH}_{2}\right)_{3} \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 158.8,134.5,128.4,119.8,113.7,64.8,63.3$, 55.2, 48.6, 40.3, 27.7, 25.8, 22.5, 22.4, 13.9; HRMS (ESI): calcd for $\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$273.1961, found 273.1960.

## (S)-Ethyl 2-cyano-1-((S)-1'-( $4^{\prime \prime}$-methoxyphenyl)ethyl)azetidine-2-carboxylate [(2S, $\left.\mathbf{1}^{\prime} S\right)$-5bf] (Table 2, entry 5)

Purified by chromatography on silica gel ( $n$-hexane/ $\mathrm{CH}_{2} \mathrm{Cl}_{2}=1$ / 5 as the eluent). $21.0 \mathrm{mg}, 29 \%$ yield, colourless crystals, $\mathrm{mp} 72-$ $74{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{22}-112.9$ (c 1.0 in EtOH); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 3009$, 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; ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.27(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 6.81(2 \mathrm{H}$, ddd, $J=8.8,2.5,2.5 \mathrm{~Hz}, \mathrm{ArH}), 3.92(2 \mathrm{H}, \mathrm{dq}, J=10.8,7.2 \mathrm{~Hz}$, $\left.\mathrm{OCH}_{2} \mathrm{CH}_{3}\right), 3.82\left(2 \mathrm{H}, \mathrm{dq}, J=10.8,7.2 \mathrm{~Hz}, \mathrm{OCH}_{2} \mathrm{CH}_{3}\right), 3.77(3 \mathrm{H}, \mathrm{s}$, $\left.\mathrm{OCH}_{3}\right), 3.75\left(1 \mathrm{H}, \mathrm{q}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.58(1 \mathrm{H}, \mathrm{ddd}, J=8.2,6.4$, $2.6 \mathrm{~Hz}, 4-\mathrm{H}), 3.33(1 \mathrm{H}, \mathrm{ddd}, J=9.1,7.8,6.4 \mathrm{~Hz}, 4-\mathrm{H}), 2.75(1 \mathrm{H}$, ddd, $J=10.6,9.1,8.2 \mathrm{~Hz}, 3-\mathrm{H}), 2.37(1 \mathrm{H}, \mathrm{ddd}, J=10.6,7.8$, $2.6 \mathrm{~Hz}, 3-\mathrm{H}), 1.28\left(3 \mathrm{H}, \mathrm{d}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right), 1.03(3 \mathrm{H}, \mathrm{dd}, J=$ $\left.7.2,7.2 \mathrm{~Hz}, \mathrm{OCH}_{2} \mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 166.5$, $159.2,132.3,129.6,116.1,113.6,64.9,62.6,62.3,55.2,49.3,27.5$,
19.7, 13.6; HRMS (ESI): calcd for $\mathrm{C}_{16} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}$ 311.1366, found 311.1366.

## (R)-Ethyl 2-cyano-1-((S)-1'-( $4^{\prime \prime}$-methoxyphenyl)ethyl)azetidine-2-carboxylate $\left[\left(2 R, 1^{\prime} S\right)-5 b f\right]$ (Table 2, entry 11)

Purified by chromatography on silica gel ( $n$-hexane/EtOAc $=7 / 1$ as the eluent). $38.1 \mathrm{mg}, 53 \%$ yield, colourless oil. $[\alpha]_{589}^{23}-76.6$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 2974,2936,2907,2838,1756$, 1734, 1611, 1585, 1512, 1457, 1444, 1369, 1329, 1243, 1173, 1123, 1108, 1084, 1061, 1033, 1015, 979, 942, 919, 856, 833, 770, $751,736,719 ;{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.29(2 \mathrm{H}, \mathrm{ddd}, J=$ $8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 6.86(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH})$, $4.31\left(2 \mathrm{H}, \mathrm{q}, J=7.0 \mathrm{~Hz}, \mathrm{OCH}_{2} \mathrm{CH}_{3}\right), 3.80\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.71(1 \mathrm{H}$, $\left.\mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.14-3.05(2 \mathrm{H}, \mathrm{m}, 4-\mathrm{H}), 2.68(1 \mathrm{H}, \mathrm{ddd}, J=$ $10.9,8.4,8.4 \mathrm{~Hz}, 3-\mathrm{H}), 2.45(1 \mathrm{H}, \mathrm{ddd}, J=10.9,6.7,4.4 \mathrm{~Hz}, 3-\mathrm{H})$, $1.34\left(3 \mathrm{H}, \mathrm{t}, J=7.0 \mathrm{~Hz}, \mathrm{OCH}_{2} \mathrm{CH}_{3}\right), 1.19\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\right.$ $\left.\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 167.1,159.1,132.8,128.7$, 115.8, 113.8, 64.1, 62.8, 62.6, 55.2, 48.9, 27.5, 20.9, 13.9; HRMS (ESI): calcd for $\mathrm{C}_{16} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}$311.1366, found 311.1366.

## (S)-tert-Butyl 2-cyano-1-((S)-1'-(4"-methoxyphenyl)ethyl) azetidine-2-carboxylate $\left[\left(2 S, 1^{\prime} S\right)-5 b g\right]$ (Table 2 , entry 6)

Purified by chromatography on silica gel ( $n$-hexane/EtOAc $=7 / 1$ as the eluent). $67.6 \mathrm{mg}, 58 \%$ yield, colourless crystals, $\mathrm{mp} 88-$ $90{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{21}-103.2\left(c 1.0\right.$ in EtOH); IR (ATR) $\nu_{\max } / \mathrm{cm}^{-1} 2975$, 2934, 2871, 2837, 1732, 1612, 1585, 1512, 1457, 1394, 1369, 1282, 1243, 1172, 1153, 1117, 1083, 1033, 993, 963, 943, 919, 834, 746, 733, $720 ;{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.30(2 \mathrm{H}, \mathrm{ddd}, J$ $=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 6.81(2 \mathrm{H}, \mathrm{ddd}, J=8.8,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH})$, $3.77\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.75\left(1 \mathrm{H}, \mathrm{q}, J=6.8 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.53(1 \mathrm{H}, \mathrm{ddd}, J$ $=8.0,6.4,2.8 \mathrm{~Hz}, 4-\mathrm{H}), 3.28(1 \mathrm{H}, \mathrm{ddd}, J=8.8,7.9,6.4 \mathrm{~Hz}, 4-\mathrm{H})$, $2.66(1 \mathrm{H}$, ddd, $J=10.9,8.8,8.0 \mathrm{~Hz}, 3-\mathrm{H}), 2.37(1 \mathrm{H}, \mathrm{ddd}, J=10.9$, $7.9,2.8 \mathrm{~Hz}, 3-\mathrm{H}), 1.28\left(3 \mathrm{H}, \mathrm{d}, J=6.8 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right), 1.23(9 \mathrm{H}, \mathrm{s}$, $t \mathrm{Bu}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 165.2,159.1,132.6,129.6$, 116.6, 113.7, 83.5, 65.5, 62.2, 55.2, 49.2, 27.6, 27.4, 19.8; HRMS (ESI): calcd for $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}$339.1679, found 339.1681.

## (R)-tert-Butyl 2-cyano-1-((S)-1'-(4"-methoxyphenyl)ethyl) azetidine-2-carboxylate $\left[\left(2 R, 1^{\prime} S\right)-5 b g\right]$ (Table 2 , entry 12)

Purified by chromatography on silica gel ( $n$-hexane/ $\mathrm{CH}_{2} \mathrm{Cl}_{2}=1$ / 5 as the eluent). 35.2 mg , $43 \%$ yield, colourless oil. $[\alpha]_{589}^{20}-75.1$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 2975,2934,2837,1731,1611$, 1585, 1512, 1458, 1394, 1370, 1280, 1244, 1152, 1124, 1110, 1061, 1034, 979, 942, 918, 833, 733, 719; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 7.29(2 \mathrm{H}, \mathrm{ddd}, J=8.4,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 6.86(2 \mathrm{H}, \mathrm{ddd}, J$ $=8.4,2.4,2.4 \mathrm{~Hz}, \mathrm{ArH}), 3.80\left(3 \mathrm{H}, \mathrm{s}, \mathrm{OCH}_{3}\right), 3.70(1 \mathrm{H}, \mathrm{q}, J=$ $\left.6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.06(1 \mathrm{H}, \mathrm{ddd}, J=8.3,6.8,3.2 \mathrm{~Hz}, 4-\mathrm{H}), 3.02(1 \mathrm{H}$, ddd, $J=8.7,7.5,6.8 \mathrm{~Hz}, 4-\mathrm{H}), 2.64(1 \mathrm{H}, \mathrm{ddd}, J=10.9,8.7,8.3 \mathrm{~Hz}$, $3-\mathrm{H}), 2.39(1 \mathrm{H}, \mathrm{ddd}, J=10.9,7.5,3.2 \mathrm{~Hz}, 3-\mathrm{H}), 1.54(9 \mathrm{H}, \mathrm{s}, t \mathrm{Bu})$, $1.20\left(3 \mathrm{H}, \mathrm{d}, J=6.6 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right)$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 166.0,159.1,133.2,128.7,116.1,113.8,83.9,64.9,62.6,55.2$, 48.8, 27.7, 27.3, 21.2; HRMS (ESI): calcd for $\mathrm{C}_{18} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}_{3}[\mathrm{M}+\mathrm{H}]^{+}$ 317.1860, found 317.1858.

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

A solution of $\left(2 S, 1^{\prime} S\right)-5 a a(83 \mathrm{mg}, 0.30 \mathrm{mmol})$ in THF $(1.5 \mathrm{~mL})$ was added to a suspension of $\mathrm{LiAlH}_{4}(34 \mathrm{mg}, 0.90 \mathrm{mmol})$ in THF $(1.5$ mL ) at $0^{\circ} \mathrm{C}$ under an Ar atmosphere. After stirring for 2 h at room temperature, the resulting mixture was cooled at $0^{\circ} \mathrm{C}$ and diluted with $\mathrm{Et}_{2} \mathrm{O}(3 \mathrm{~mL})$. The mixture was quenched at $0^{\circ} \mathrm{C}$ by addition of $\mathrm{H}_{2} \mathrm{O}(34 \mu \mathrm{~L}), 15 \mathrm{wt} \% \mathrm{NaOH}$ solution in $\mathrm{H}_{2} \mathrm{O}(34 \mu \mathrm{~L})$, and $\mathrm{H}_{2} \mathrm{O}(102$ $\mu \mathrm{L})$. 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 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] ( $78.0 \mathrm{mg}, 93 \%$ yield) as colourless crystals, mp $65-69{ }^{\circ} \mathrm{C}$. $[\alpha]_{589}^{20}-5.6$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3357,3281,3083$, 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; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 7.42-7.16(10 \mathrm{H}, \mathrm{m}, \mathrm{ArH}), 3.85\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right)$, $3.29\left(1 \mathrm{H}, \mathrm{d}, J=12.8 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{NH}_{2}\right), 2.99-2.81(2 \mathrm{H}, \mathrm{m}, 4-\mathrm{H}), 2.85(1 \mathrm{H}$, $\left.\mathrm{d}, J=12.8 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{NH}_{2}\right), 2.72\left(1 \mathrm{H}, \mathrm{d}, J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 2.53(1 \mathrm{H}$, $\left.\mathrm{d}, J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 1.92(1 \mathrm{H}, \mathrm{ddd}, J=10.5,8.6,8.6 \mathrm{~Hz}, 3-\mathrm{H})$, $1.79(1 \mathrm{H}$, ddd, $J=10.5,7.9,3.2 \mathrm{~Hz}, 3-\mathrm{H}), 1.67\left(2 \mathrm{H}, \mathrm{br}, \mathrm{NH}_{2}\right), 1.28$ $\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 144.4,138.0$, 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 $\mathrm{C}_{19} \mathrm{H}_{25} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}$281.2012, found 281.2007. A mixture of $\left(2 S, 1^{\prime} S\right)$-6aa ( $32 \mathrm{mg}, 0.11 \mathrm{mmol}$ ), allyl bromide ( $9.8 \mu \mathrm{~L}, 0.11 \mathrm{mmol}$ ) and $\mathrm{K}_{2} \mathrm{CO}_{3}(47 \mathrm{mg}, 0.34 \mathrm{mmol})$ 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 $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}=20 / 1\right.$ 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 $\left[\left(2 S, 1^{\prime} S\right)-7 \mathrm{aa}\right](29.0 \mathrm{mg}, 82 \%$ yield) as a colourless oil. $[\alpha]_{589}^{20}-33.4$ ( $c 1.0$ in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3300,3083,3061$, 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; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.40-7.16(10 \mathrm{H}, \mathrm{m}, \mathrm{ArH})$, $5.95\left(1 \mathrm{H}\right.$, dddd, $\left.J=17.0,10.2,6.4,6.4 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 5.22(1 \mathrm{H}$, dddd, $\left.J=17.0,1.6,1.6,1.4 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 5.12(1 \mathrm{H}, \mathrm{dd}, J=$ $\left.10.2,1.4 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}\right), 3.87\left(1 \mathrm{H}, \mathrm{q}, J=6.2 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.38-3.23$ $(2 \mathrm{H}, \mathrm{m}, 4-\mathrm{H}), 3.27\left(1 \mathrm{H}, \mathrm{d}, J=13.0 \mathrm{~Hz}, 2-\mathrm{CH}_{2} \mathrm{NH}\right), 3.20-2.70(1 \mathrm{H}, \mathrm{br}$, NH), $3.00-2.80(2 \mathrm{H}, \mathrm{m}, 3-\mathrm{H}), 2.88\left(1 \mathrm{H}, \mathrm{d}, J=13.0 \mathrm{~Hz}, 2-\mathrm{CH}_{2} \mathrm{NH}\right)$, $2.60\left(1 \mathrm{H}, \mathrm{d}, J=12.0 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 2.56\left(1 \mathrm{H}, \mathrm{d}, J=12.0 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right)$, 2.22-2.10 ( $1 \mathrm{H}, \mathrm{m}, \mathrm{CH}_{2} \mathrm{CH}=\mathrm{CH}_{2}$ ), 1.92-1.80 $\left(1 \mathrm{H}, \mathrm{m}, \mathrm{CH}_{2} \mathrm{CH}=\right.$ $\left.\mathrm{CH}_{2}\right), 1.27\left(3 \mathrm{H}, \mathrm{d}, J=6.2 \mathrm{~Hz}, \mathrm{1}^{\prime}-\mathrm{CH}_{3}\right) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 144.2,137.8,136.8,130.2,128.3,128.1,127.5,127.0,126.2,116.0$, 68.8, 59.5, 55.0, 52.6, 47.1, 38.0, 23.6, 22.7; HRMS (ESI): calcd for $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}$321.2325, found 321.2320.

Preparation of authentic sample ( $2 S, 1^{\prime} S$ )-7aa from ( $2 S, 1^{\prime} S$ )-8aa (Scheme 4, eqn (2))

A solution of (S)-tert-butyl 2-benzyl-1-((S)-1'-phenylethyl) azetidine-2-carboxylate $\left[\left(2 S, 1^{\prime} S\right)-8 a a\right]^{6}(150 \mathrm{mg}, 0.427 \mathrm{mmol})$ in
$\mathrm{CH}_{2} \mathrm{Cl}_{2}(0.85 \mathrm{~mL})$ was treated with trifluoroacetic acid (TFA) $(0.85 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ 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 $(4 \mathrm{~mL})$ followed by a ca. 4 M HCl solution in cyclopentyl methyl ether ( $0.16 \mathrm{~mL}, 0.64 \mathrm{mmol}$ ). 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 ( $0.28 \mathrm{~mL}, 1.6 \mathrm{mmol}$ ) followed by allylamine ( $38 \mu \mathrm{~L}, 0.51 \mathrm{mmol}$ ) were added. 1-[bis(-dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) ( $194 \mathrm{mg}, 0.51 \mathrm{mmol}$ ) 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)azetidine-2-carboxamide $\left[\left(2 S, 1^{\prime} S\right)-9 a a\right]\left(118 \mathrm{mg}, 83 \%\right.$ yield) as a colourless oil. $[\alpha]_{589}^{22}-92.0$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3355,3084,3060,3026,2966$, 2926, 2841, 1664, 1603, 1506, 1494, 1452, 1419, 1373, 1338, 1279, 1265, 1217, 1175, 1131, 1096, 1075, 1057, 1029, 999, 988, 913, $764,733,698 ;{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.93(1 \mathrm{H}, \mathrm{br}, \mathrm{NH}-$ CHH-CH=CHH), 7.54-7.48 ( $2 \mathrm{H}, \mathrm{m}, \mathrm{ArH}$ ), 7.36-7.22 ( $7 \mathrm{H}, \mathrm{m}$, ArH), $7.20(1 \mathrm{H}, \mathrm{tt}, J=7.2,1.2 \mathrm{~Hz}, \mathrm{ArH}), 5.90\left(1 \mathrm{H}\right.$, dddd, ${ }^{3} J_{\text {trans }}=$ $17.2,{ }^{3} J_{\text {cis }}=10.2,{ }^{3} J=5.6,{ }^{3} J=5.6 \mathrm{~Hz}$, NH-CHH-CH=CHH), 5.24 $\left(1 \mathrm{H}\right.$, dddd, ${ }^{3} \mathrm{Jtrans}=17.2,{ }^{2} J=1.6,{ }^{4} J=1.6,{ }^{4} J=1.6 \mathrm{~Hz}$, NH-CHH$\left.\mathrm{CH}=\mathrm{CH} H_{\text {trans }}\right), 5.16\left(1 \mathrm{H}\right.$, dddd, ${ }^{3} J_{\text {cis }}=10.2,{ }^{2} J=1.6,{ }^{4} J=1.6,{ }^{4} J$ $=1.6 \mathrm{~Hz}, \mathrm{NH}-\mathrm{CHH}-\mathrm{CH}=\mathrm{CH} H_{c i s}$, $4.07\left(1 \mathrm{H}\right.$, ddddd, ${ }^{2} J=15.7,{ }^{3} J$ $\left.=6.6,{ }^{3} J=5.6,{ }^{4} J_{\text {trans }}=1.6,{ }^{4} J_{c i s}=1.6 \mathrm{~Hz}, \mathrm{NH}-\mathrm{C} H \mathrm{H}-\mathrm{CH}=\mathrm{CHH}\right)$, $4.00\left(1 \mathrm{H}, \mathrm{q}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{H}\right), 3.91\left(1 \mathrm{H}\right.$, ddddd, ${ }^{2} J=15.7,{ }^{3} J=5.6$, $\left.{ }^{3} J=5.6,{ }^{4} J_{\text {trans }}=1.6,{ }^{4} J_{\text {cis }}=1.6 \mathrm{~Hz}, \mathrm{NH}-\mathrm{CH} H-\mathrm{CH}=\mathrm{CHH}\right), 3.48$ $\left(1 \mathrm{H}, \mathrm{d}, J=14.4 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 3.43\left(1 \mathrm{H}, \mathrm{d}, J=14.4 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right)$, $2.92-2.80(2 \mathrm{H}, \mathrm{m}, 4-\mathrm{H}), 2.13\left(1 \mathrm{H}, \mathrm{ddd},{ }^{2} J=11.1,{ }^{3} J=8.4,{ }^{3} J=\right.$ $8.4 \mathrm{~Hz}, 3-\mathrm{H}), 1.98\left(1 \mathrm{H}, \mathrm{ddd},{ }^{2} J=11.1,{ }^{3} J=7.9,{ }^{3} J=2.8 \mathrm{~Hz}, 3-\mathrm{H}\right)$, $0.92\left(3 \mathrm{H}, \mathrm{d}, J=6.4 \mathrm{~Hz}, 1^{\prime}-\mathrm{CH}_{3}\right)$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 175.5,142.9,138.5,134.4,130.8,128.4,128.1,127.4,127.3$, 126.2, 116.1, 71.2, 60.4, 47.5, 41.6, 35.3, 28.6, 22.6; HRMS (ESI): calcd for $\mathrm{C}_{22} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$335.2118, found 335.2110. A solution of $\left(2 S, 1^{\prime} S\right)$-9aa ( $118 \mathrm{mg}, 0.353 \mathrm{mmol}$ ) in THF ( 1.8 mL ) was added to a suspension of $\mathrm{LiAlH}_{4}(42 \mathrm{mg}, 1.1 \mathrm{mmol})$ in THF $(1.8 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ under an Ar atmosphere. The mixture was refluxed for 4 h . The resulting mixture was cooled at $0{ }^{\circ} \mathrm{C}$ and diluted with $\mathrm{Et}_{2} \mathrm{O}(4 \mathrm{~mL})$. The mixture was quenched by addition of $\mathrm{H}_{2} \mathrm{O}(42 \mu \mathrm{~L}), 15 \mathrm{wt} \% \mathrm{NaOH}$ solution in $\mathrm{H}_{2} \mathrm{O}(42 \mu \mathrm{~L})$, and $\mathrm{H}_{2} \mathrm{O}(126 \mu \mathrm{~L})$. 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 $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}=20 / 1\right.$ to $10 / 1$ as the eluent) gave ( $2 S, 1^{\prime} S$ )-7aa ( $32.1 \mathrm{mg}, 28 \%$ yield) as a colourless oil and recovered ( $2 S, 1^{\prime} S$ )-9aa ( $69.5 \mathrm{mg}, 59 \%$ recovery) as a colourless oil. $\left(2 S, 1^{\prime} S\right)$-7aa: $[\alpha]_{589}^{19}-33.2$ (c 1.0 in EtOH).

## Representative procedure for preparation of ( $R$ )-10a (Scheme

 5, eqn (2))TFA $(2.2 \mathrm{~mL})$ was added to a solution of $\left(2 R, 1^{\prime} S\right)-5 \mathbf{b a}(135 \mathrm{mg}$, $0.441 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2.2 \mathrm{~mL})$ 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 $\mathrm{H}_{2} \mathrm{O}$ and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The combine extracts were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated by evaporation. ${ }^{1} \mathrm{H}$ NMR analysis of this crude product in $\mathrm{CDCl}_{3}$ showed a mixture of $\left(2 R, 1^{\prime} S\right)-\mathbf{5 b a} /(R)-\mathbf{1 0 a}=1 / 9$ (ca. $90 \%$ conversion). The $\mathrm{CDCl}_{3}$ solution was concentrated by evaporation and residue was purified by chromatography on silica gel $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}=60 / 1\right.$ to $30 / 1$ as the eluent) to obtain (R)-2-benzylazetidine-2-carbonitrile $[(R)-10 a](64.4 \mathrm{mg}, 85 \%$ yield) as a pale yellow oil. $[\alpha]_{589}^{22}+40.5$ (c 1.0 in EtOH); IR (ATR) $\nu_{\text {max }} / \mathrm{cm}^{-1} 3326,3245,3086,3062$, 3030, 3006, 2960, 2921, 2879, 2224, 1604, 1495, 1454, 1439, 1346, 1283, 1240, 1174, 1134, 1093, 1031, 993, 951, 930, 850, 764, 698; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 7.38-7.25(5 \mathrm{H}, \mathrm{m}, \mathrm{Ph}), 3.82(1 \mathrm{H}, \mathrm{ddd}, J=8.4,8.4$, $7.4 \mathrm{~Hz}, 4-\mathrm{H}), 3.37(1 \mathrm{H}, \mathrm{ddd}, J=7.8,7.4,4.6 \mathrm{~Hz}, 4-\mathrm{H}), 3.11(1 \mathrm{H}, \mathrm{d}$, $\left.J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 3.06\left(1 \mathrm{H}, \mathrm{d}, J=13.6 \mathrm{~Hz}, \mathrm{CH}_{2} \mathrm{Ph}\right), 2.58(1 \mathrm{H}$, ddd, $J=11.2,8.4,4.6 \mathrm{~Hz}, 3-\mathrm{H}), 2.55(1 \mathrm{H}, \mathrm{ddd}, J=11.2,8.4$, $7.8 \mathrm{~Hz}, 3-\mathrm{H}), 2.21(1 \mathrm{H}, \mathrm{br}, \mathrm{NH}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 134.2,129.7,128.5,127.4,122.6,59.7,46.0,42.7,31.8$; HRMS (ESI): calcd for $\mathrm{C}_{11} \mathrm{H}_{13} \mathrm{~N}_{2}[\mathrm{M}+\mathrm{H}]^{+}$173.1073, found 173.1072.

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

The reaction was performed using $\left(2 S, 1^{\prime} S\right)$-5ba ( $103 \mathrm{mg}, 0.336$ mmol ) by the same procedure with ( $2 R, 1^{\prime} S$ )-5ba. ${ }^{1} \mathrm{H}$ NMR analysis of the crude product in $\mathrm{CDCl}_{3}$ showed a mixture of $\left(2 S, 1^{\prime} S\right)-5 b \mathbf{b a} /(S)-\mathbf{1 0 a}=4 / 6$ (ca. $60 \%$ conversion). Purification by chromatography on silica gel gave ( $S$ )-10a ( $33.9 \mathrm{mg}, 59 \%$ yield) as a pale yellow oil. $[\alpha]_{589}^{21}-40.4$ (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 $\mathbf{4}$ must be performed using $n$-hexane $/ \mathrm{CH}_{2} \mathrm{Cl}_{2}$ as the eluent to avoid epimerization. When $\left(1 S, 2 S, 1^{\prime} S\right)-\mathbf{4 b}$ was stirred in THF for 30 min at room temperature, approximately $20 \mathrm{~mol} \%$ of $\left(1 S, 2 S, 1^{\prime} S\right)-\mathbf{4 b}$ was epimerized to the other isomer, as observed by ${ }^{1} \mathrm{H}$ NMR analysis.
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17 Each diastereomer was separable by silica gel chromatography. In some cases, the yields of the minor diastereomer were not exact due to the difficulty of isolating the pure product.
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[^0]:    ${ }^{a}$ Department of Chemistry, Faculty of Science, Niigata University, Niigata, 950-2181, Japan. E-mail: tayama@chem.sc.niigata-u.ac.jp
    ${ }^{b}$ Graduate School of Science and Technology, Niigata University, Niigata, 950-2181, Japan
    $\dagger$ Electronic supplementary information (ESI) available: Copies of ${ }^{1} \mathrm{H},{ }^{13} \mathrm{C}$ and ${ }^{11} \mathrm{~B}$ NMR spectra. See DOI: 10.1039/d1ra04585g

[^1]:    ${ }^{a}$ Yield of isolated product.

