HIGHLY REGIOSELECTIVE RING OPENING OF A COMMON N,N-DIALKYLAZIRIDINIUM ION BY CARBOXYLIC ACIDS

Ulises Hernández,1 Manuel Velasco,1 Jaime Vázquez,2 Joel L. Terán,1 Dino Gnecco,1 María L. Orea,1 David M. Aparicio,1 and Jorge R. Juárez1*

1Centro de Química, Instituto de Ciencias, Benemérita Universidad Autónoma de Puebla, Edif. IC8 Complejo de Ciencias, C.U., 72570 Puebla, México.  
2Universidad Politécnica Metropolitana de Puebla, Popocatépetl s/n, Tres Cerritos, 72480 Puebla, México. E-mail: jorge.juarez@correo.buap.mx

Abstract – A variety of optically active amino esters were synthesized via ring-opening reaction of (R)-1-phenyl-3-azaspiro[2.5]octan-3-ium ion derived from (R)-2-phenyl-2-(piperidin-1-yl)ethan-1-ol in a highly regioselective manner. Ring-opening reaction with carboxylates series generated in situ proceeded smoothly and with excellent yields (85-98%).

INTRODUCTION
Aziridinium ions have received considerable attention as reactive intermediates in the asymmetric synthesis of natural products,1-3 biologically active compounds4 and precursors in organic synthesis.5 Nucleophilic ring-opening of N,N-dialkylaziridinium ions have been recognized as efficient synthetic route to generate a variety of β-substituted amines including 1,2-diamines,6 1,2-amino alcohols,7 β-amino ethers,8 and β-haloamines.9 The N,N-dialkylaziridinium ions are usually produced in situ from β-amino alcohols.10 Compared with aziridine congeners, the N,N-dialkylaziridinium ions show a strong electrophilic character, whereas the unactivated aziridines require activation by a Lewis acid and, therefore, always becomes aziridinium prior to nucleophilic ring-opening reactions.11 Thus, N,N-dialkylaziridinium ions can be opened by a wide range of nucleophiles with or without rearrangement depending on the regioselectivity of the nucleophilic attack.10 Until now, opening reaction of aziridinium ions with carboxylate salts has been scarcely study.12 In this sense, we herein report a high regiospecific ring-opening reaction of a common N,N-dialkylaziridinium ion I with a variety of aliphatic, aromatic and α,β-unsaturated carboxylic acids (Scheme 1).
RESULTS AND DISCUSSION

Compound 1\(^{11}\) was allowed to react with MsCl and TEA as a base in order to trap the corresponding \(\beta\)-chloropiperidinium chloride 2. This intermediate was isolated as an air-stable white crystalline solid in 79% yield.\(^{14}\) The isolation of a single isomer, compound (S)-2, is consistent with the inclusion of an aziridinium ion intermediate II (Scheme 2). The structure was fully ascertained by an X-ray diffraction analysis (Figure 1).

As we anticipate, this result shows clearly the more nucleophilic character of chloride anion than mesylate. According to the literature, opening of aziridinium ions usually occurs with a more nucleophilic species and no participation of chloride anion are present, but what is the competitive effect when a softer nucleophilic specie, like a carboxylate, are present in the medium reaction. For this precedent, we turned our attention to the opening reaction of aziridinium ions with diverse carboxylic acids using a modified version of O’Brien’s method.\(^6\) We commence our investigation by the treatment of I with acetic acid.
After 30 min, we obtained the corresponding regioisomeric mixture of esters 3a + 4a in a 99:1 ratio, which are consistent with previous reports, where the nucleophiles attacks were performed at the more electrophilic benzylic carbon in the intermediate ion (Table 1, entry 1). Therefore, a series of carboxylic acids was tested in order to know the scope and limitation of this opening reaction. The use of aliphatic carboxylic acids afforded the desired amino ester 3 as a major regioisomer in excellent chemical yields (Table 1, entries 2-6). For aromatic carboxylic acids with electron-donating or electron-withdrawing groups on the phenyl ring compound 3 was obtained as a major regioisomer in good yields (Entries 7–14). Interestingly, carboxylic acids containing pyridine moiety was well tolerated and gave the desired product in good yield (Entry 15). In addition, aromatic olefinic acid gave good yield (Entry 16).

Table 1. Summary of regioselective synthesis of amino esters derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCO₂H</th>
<th>Product⁺</th>
<th>Regioselectivity 3:4</th>
<th>3 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>3a</td>
<td>99:1</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Br-(CH₂)₄-CO₂H</td>
<td>3b</td>
<td>98:2</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>Me-(CH₂)₃-CO₂H</td>
<td>3c</td>
<td>98:2</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Ph-CO₂H</td>
<td>3d</td>
<td>98:2</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>O-CO₂H</td>
<td>3e</td>
<td>97:3</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>O-CO₂H</td>
<td>3f</td>
<td>97:3</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>O-CO₂H</td>
<td>3g</td>
<td>97:3</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>O-CO₂H</td>
<td>3h</td>
<td>97:3</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>( \text{O}_2\text{N} - \text{CO}_2\text{H} )</td>
<td><strong>3i</strong></td>
<td>97:3</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>( \text{BocN} - \text{CO}_2\text{H} )</td>
<td><strong>3j</strong></td>
<td>97:3</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>( \text{Cl} \text{-CO}_2\text{H} )</td>
<td><strong>3k</strong></td>
<td>97:3</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>( \text{CO}_2\text{H} )</td>
<td><strong>3l</strong></td>
<td>97:3</td>
<td>85</td>
</tr>
<tr>
<td>13</td>
<td>( \text{CO}_2\text{H} )</td>
<td><strong>3m</strong></td>
<td>97:3</td>
<td>94</td>
</tr>
<tr>
<td>14</td>
<td>( \text{CO}_2\text{H} )</td>
<td><strong>3n</strong></td>
<td>97:3</td>
<td>93</td>
</tr>
<tr>
<td>15</td>
<td>( \text{N} \text{-CO}_2\text{H} )</td>
<td><strong>3o</strong></td>
<td>97:3</td>
<td>91</td>
</tr>
<tr>
<td>16</td>
<td>( \text{CO}_2\text{H} )</td>
<td><strong>3p</strong></td>
<td>98:2</td>
<td>92</td>
</tr>
</tbody>
</table>

*a* Enantiomeric purities were measurement by UHPLC normal phase; with an ULTRON ES-Pepsin Chiral column (all products show >99% ee). *b* Ratio of regioisomeric amino esters 3 and 4 in the crude product mixtures determined by \(^1\text{H} \)NMR spectroscopy. *c* Isolated yield after silica gel chromatography.

A single crystal of amino ester **3p** was obtained and X-ray crystallography analysis showed a (S) configuration for the new stereocenter and therefore a bimolecular nucleophilic ring opening reaction of aziridinium ion was proposed at this point (Figure 2).\(^{17}\)

![Figure 2. ORTEP of compound 3p](image-url)

In line with the model proposed by Anderson,\(^{16a}\) the stereochemical outcome of the reaction is consistent with the participation of an aziridinium ion where competition between bimolecular and monomolecular substitution is possible, for this reason chiral acids were allowed to react with 1 (Scheme 3). The
corresponding amino esters, derived from (S)-Naproxen® 3q and (S)-3-phenylbutyric acid 3r, were obtained in good to excellent chemical yield. For both cases, the $^1$H and $^{13}$C NMR spectra showed the presence of only one isomer, indicating a total stereoselectivity of the reaction, in consequence, no participation of carbocation intermediate was unambiguously confirmed. Finally, L-proline N-Boc protected was tested, affording the desired amino ester 3s in 96% yield as a single diastereoisomer which exist in rotameric form.

Scheme 3. Synthesis of amino esters coming from chiral acids

Finally, in order to examine reactions with more aziridinium ions derived from amino alcohols with different substituents at the ring nitrogen and/or other sites to show the scope and limitation of the present method, compounds 5, 8, 11 and 14 were subject to optimized reaction conditions using acetic acid as nucleophile. Compounds 5 and 8, derived from (R)-(−)-2-phenylglycinol, afforded the regioisomeric mixture 6:7 and 9:10 in a 99:1 ratio respectively, in favor of the benzylic opening amino ester compound (Scheme 4).

Scheme 4. Synthesis of amino esters coming from heterocycles derived from phenylglycinol

Interestingly, when piperidine 11, derived from (R)-(−)-2-amino-1-butanol, was allowed to react under the same conditions, the inseparable regioisomeric mixture 12:13 in 37:62 ratio in favor of the less substituted opening regioisomer 13 was obtained, while piperidine 14, derived from (S)-(−)-2-amino-3-methyl-1-butanol, afforded the inseparable regioisomeric mixture 15:16 in 50:50 ratio (Scheme 5).
Scheme 5. Synthesis of amino esters coming from piperidines derived from other chiral amino alcohols

Notably, the reactions exhibit high regioselectivity in the opening of aziridinium ion when a benzylic position is present on the aziridinium ion despite we use a soft nucleophile.

In conclusion, aliphatic and aromatic carboxylic acids react with 1 to afford, via an aziridinium intermediate, the corresponding amino ester in good to excellent yield and high regioselectivity. In addition, we demonstrated opening reaction occurs preferentially at benzylic position following possibly a $S_N2$ type mechanism despite the soft nucleophilic character of carboxylate specie; the developed method is clean and efficient.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources. $^1$H NMR and $^{13}$C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, in CDCl$_3$ using a Bruker Avance III Spectrometer. Chemical shifts are given in ppm and reported to the residual solvent peak (CHCl$_3$ 7.26 ppm and 77.16 ppm). Data are reported as follows: chemical shift ($\delta$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) ($J$, Hz), and integration. Analytical TLC was performed on silica gel 60 F$_{254}$ plates. Column chromatography was carried out on silica gel 60 (63-200 μm). IR spectra were obtained using an FT-IR spectrometer, Spectrum One, Perkin Elmer. Mass spectra were recorded on JEOL The MStation JMS-700 at a voltage of 70 eV. X-Ray diffraction analysis was performed on a diffractometer Agilent Gemini Atlas fitted with an Atlas CCD detector, using Cu-K$\alpha$ ($\lambda$ = 1.54184) radiation, and equipped with an Oxford Technologies Cryojet crystal cooling apparatus and a diffractometer STOE Stadivari using Ag-K$\alpha$ ($\lambda$ = 0.56083) and equipped with a Pilatus-100 K detector. Optical rotations were measured on the Perkin-Elmer 341 polarimeter at room temperature. Enantiomeric purity measurements were performed by chiral UHPLC analysis in normal phase with an Agilent 1260
Infinity Analytical SFC System equipped with an Agilent 6120 quadrupole LC/MS, using an ULTRON ES-Pepsin chiral column (Shinwa Chemical Industries LTD, 4.6 x 150 mm, 5 µm particle size).

**Experimental procedure for intermediate 2.**

To a stirred solution of β-amino alcohol 1 (0.5 g, 2.43 mmol) in CHCl₃ (10 mL) at 0 °C in presence of triethylamine (1.01 mL, 7.30 mmol). Then, methanesulfonyl chloride (0.41 mL, 5.35 mmol) was added dropwise at a rate to keep the reaction temperature bellow 5 °C. After 30 min, the reaction was monitored by TLC (CH₂Cl₂/MeOH, 95:5), indicating that the reactants were consumed. The reaction mixture was allowed to warm at room temperature for 16 h. Solvent was removed under vacuum, and the residue was dissolved in CH₂Cl₂ and washed with water and brine before drying over anhydrous sodium sulfate. Solvent was removed under vacuum and the crude product was purified by column chromatography (CH₂Cl₂/MeOH, 97:3) gave the desired β-chloropiperidinium chloride (S)-2.

**Intermediate: (S)-1-(2-chloro-2-phenylethyl)piperidin-1-ium chloride (2).** The desired pure product was obtained in 79% yield (500 mg) as white solid; mp 180 °C; [α]D²⁰ +23.6 (c 1.0, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 12.69 (br s, 1H), 7.49-7.26 (m, 5H), 5.85-5.83 (dd, J = 7.2, 4.5 Hz, 1H), 3.88-3.41 (d, J = 12.0 Hz, 1H), 3.50-3.41 (m, 2H), 3.18-3.16 (d, J = 12.1 Hz, 1H), 2.80-2.74 (m, 1H), 2.64-2.56 (m, 1H), 2.29-2.13 (m, 2H), 1.86-1.80 (m, 2H), 1.71-1.69 (m, 1H), 1.53 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 138.3, 129.4, 129.2, 127.0, 64.6, 55.5, 54.7, 53.8, 22.5, 21.8; HRMS (ESI): m/z [M+H]+ calcd for C₁₃H₂₀Cl₂N: 261.0973, found: 261.0970.

**General procedure and compound characterization data for products 3a-s.**

To a stirred solution of compound 1 (0.5 g, 2.43 mmol) in CHCl₃ (10 mL) at 0 °C in presence of triethylamine (1.01 mL, 7.30 mmol). Then, methanesulfonyl chloride (0.22 mL, 2.92 mmol) was added dropwise at a rate to keep the reaction temperature bellow 5 °C. After 30 min, the reaction was monitored by TLC (CH₂Cl₂/MeOH, 95:5), indicating the reactants were consumed. Triethylamine (0.50 mL, 3.65 mmol) was added. Finally, the corresponding carboxylic acid (1.2 equiv.) was added and the reaction mixture was allowed to warm to room temperature for 16 h. After completion of the reaction as indicated by TLC, the crude product was purified by column chromatography (CH₂Cl₂/MeOH, 97:3) provided the corresponding product 3.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl acetate (3a). The desired pure product was obtained in 93% yield (560 mg) as orange oil; [α]D²⁰ +52.9 (c 1.0, CH₂Cl₂); FT-IR νmax/cm⁻¹ 2932, 2858, 1736, 1230; ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.25 (m, 5H), 5.97-5.94 (dd, J = 9.0, 4.0 Hz, 1H), 2.85-2.80 (dd, J = 13.6, 9.0 Hz, 1H), 2.54-2.49 (m, 3H), 2.42-2.41 (m, 2H), 2.09 (s, 3H), 1.56-1.51 (m, 4H), 1.42-1.37 (m, 2H); ¹³C
NMR (125 MHz, CDCl₃) δ 170.2, 139.8, 128.3, 127.8, 126.4, 72.9, 64.4, 54.6, 26.0, 24.2, 21.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₅H₂₂NO₂: 248.1651, found: 248.1650.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 5-bromopentanoate (3b). The desired pure product was obtained in 94% yield (843 mg) as orange oil; [α]D²⁰ +41.5 (c 1.0, CH₂Cl₂); FT-IR νmax/cm⁻¹ 2933, 2853, 1732, 1257, 698; ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.26 (m, 5H), 6.00-5.97 (dd, J = 9.3, 3.7 Hz, 1H), 3.41-3.38 (m, 2H), 2.84-2.79 (dd, J = 13.6, 9.3 Hz, 1H), 2.55-2.49 (m, 3H), 2.43-2.37 (m, 4H), 1.93-1.87 (m, 2H), 1.82-1.77 (m, 2H), 1.55-1.52 (m, 4H), 1.42-1.39 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 139.5, 128.3, 127.8, 126.4, 72.7, 64.4, 54.6, 33.5, 33.1, 31.7, 25.9, 24.1, 23.5; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₂₇BrNO₂: 368.1225, found: 368.1222.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl hexacosanoate (3c). The desired pure product was obtained in 95% yield (1351 mg) as orange solid; mp 52 °C; [α]D²⁰ +10.4 (c 1.0, CH₂Cl₂); FT-IR νmax/cm⁻¹ 2920, 2851, 1736, 1466, 1263, 1162; ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.23 (m, 5H), 5.99-5.96 (dd, J = 9.1, 3.9 Hz, 1H), 2.83-2.78 (dd, J = 13.5, 9.1 Hz, 1H), 2.53-2.50 (dd, J = 13.5, 3.9 Hz, 1H), 2.51 (m, 2H), 2.45-2.39 (m, 2H), 2.35-2.28 (m, 2H), 1.65-1.59 (m, 2H), 1.55-1.50 (m, 4H), 1.41-1.37 (m, 2H), 1.29-1.25 (br, 44H), 0.89-0.86 (t, J = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.8, 139.8, 128.2, 127.6, 126.3, 72.5, 64.4, 54.6, 34.5, 31.8, 29.6, 29.6, 29.9, 29.5, 29.4, 29.3, 29.2, 29.0, 26.0, 24.9, 24.2, 22.6, 14.0; HRMS (ESI): m/z [M+H]⁺ calcd for C₃₉H₇₀NO₂: 584.5407, found: 584.5401.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-phenylacetate (3d). The desired pure product was obtained in 93% yield (732 mg) as orange oil; [α]D²⁰ +48.6 (c 1.0, CH₂Cl₂); FT-IR νmax/cm⁻¹ 2953, 2851, 1733, 1663, 1496, 1454; ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.23 (m, 10H), 5.98-5.96 (dd, J = 9.2, 3.6Hz, 1H), 3.70-3.67 (d, J = 15.0 Hz, 1H), 3.65-3.62 (d, J = 15.0 Hz, 1H), 2.80-2.75 (dd, J = 13.6, 9.2 Hz, 1H), 2.51-2.48 (dd, J = 13.6, 3.7 Hz, 1H), 2.46-2.45 (m, 2H), 2.34-2.33 (m, 2H), 1.50-1.45 (m, 4H), 1.38-1.35 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 170.6, 139.5, 134.1, 129.3, 128.4, 128.3, 127.7, 126.9, 126.3, 73.4, 64.4, 54.6, 41.7, 26.0, 24.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₂₆NO₂: 324.1964, found: 324.1951.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-(3,4-dimethoxyphenyl)acetate (3e). The desired pure product was obtained in 90% yield (840 mg) as orange oil; [α]D²⁰ +39.4 (c 1.0, CH₂Cl₂); FT-IR νmax/cm⁻¹ 2933, 2834, 1732, 1141, 1026; ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.25 (m, 5H), 6.83-6.77 (m, 3H), 5.98-5.95 (dd, J = 9.0, 3.8 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.63-3.60 (d, J = 14.8 Hz, 1H), 3.60-3.67 (d, J = 15.1 Hz, 1H), 2.81-2.77 (dd, J = 13.6, 9.0 Hz, 1H), 2.53-2.50 (dd, J = 13.6, 3.8 Hz, 1H), 2.47-2.45 (m, 2H), 2.36-2.34 (m, 2H), 1.50-1.46 (m, 4H), 1.38-1.34 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 148.7, 147.9, 139.5, 128.2, 127.7, 126.5, 126.3, 121.4, 112.2, 111.0, 73.4, 64.3, 55.8, 55.7, 54.5, 41.2, 25.9, 24.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₃H₃₀NO₄: 384.2175, found: 384.2188.
(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-(4-isobutylphenyl)propanoate (3f). The desired pure product was obtained as diastereomer mixture in 92% yield (881 mg, 3f = 1:1) as orange oil; FT-IR v_max/cm⁻¹ 2932, 2868, 1734, 1091, 1019; ¹H NMR (500 MHz, CDCl₃) δ 7.29-7.04 (m, 18 H), 5.95-5.92 (m, 2H), 3.77-3.71 (m, 2H), 2.78-2.69 (m, 2H), 2.51-2.48 (m, 4H), 2.45-2.43 (m, 4H), 2.39-2.35 (m, 4H), 2.24-2.22 (m, 2H), 1.86-1.81 (m, 2H), 1.52-1.45 (m, 8H), 1.40-1.37 (m, 6H), 1.30-1.26 (m, 2H), 0.90-0.89 (m, 12H); ¹³C NMR (125 MHz, CDCl₃) δ 173.6, 173.5, 140.3, 139.8, 139.6, 137.6, 137.6, 129.1, 128.3, 128.1, 127.7, 127.5, 127.3, 126.2, 126.0, 73.3, 73.0, 64.5, 64.2, 54.5, 54.2, 45.3, 45.2, 44.9, 44.9, 30.1, 30.1, 25.9, 25.8, 24.1, 24.0, 22.3, 22.3, 18.2, 18.2; HRMS (ESI): m/z [M+H]+ calcld for C₂₆H₃₆NO₂: 394.2746, found: 394.2736.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl benzoate (3g). The desired pure product was obtained in 91% yield (685 mg) as orange oil; [α]_D²⁰ -8.6 (c 1.0, CH₂Cl₂); FT-IR v_max/cm⁻¹ 2933, 2853, 1717, 1266, 1069; ¹H NMR (500 MHz, CDCl₃) δ 8.10-7.25 (m, 10H), 6.20-6.18 (dd, J = 8.5, 3.9 Hz, 1H), 3.03-2.98 (dd, J = 13.8, 8.5 Hz, 1H), 2.74-2.70 (dd, J = 13.8, 3.9 Hz, 1H), 2.59-2.56 (m, 2H), 2.52-2.49 (m, 2H), 1.54-1.49 (m, 4H), 1.40-1.37 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 165.7, 139.9, 132.8, 130.5, 129.6, 128.4, 128.3, 127.8, 126.3, 74.0, 64.5, 54.6, 26.0, 24.1; HRMS (ESI): m/z [M+H]+ calcld for C₂₀H₂₄NO₂: 310.1807, found: 310.1789.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 3-nitrobenzoate (3h). The desired pure product was obtained in 89% yield (768 mg) as yellow oil; [α]_D²⁰ -2.3 (c 1.0, CH₂Cl₂); FT-IR v_max/cm⁻¹ 2933, 2853, 1717, 1266, 1069; ¹H NMR (500 MHz, CDCl₃) δ 8.90-8.86 (m, 1H), 8.42-8.36 (m, 2H), 7.67-7.64 (m, 1H), 7.44-7.31 (m, 5H), 6.24-6.22 (dd, J = 8.9, 3.8 Hz, 1H), 3.03-2.98 (dd, J = 13.8, 8.9 Hz, 1H), 2.72-2.68 (dd, J = 13.8, 3.8 Hz, 1H), 2.60-2.58 (m, 2H), 2.49-2.44 (m, 2H), 1.52-1.48 (m, 4H), 1.40-1.36 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 163.6, 148.2, 139.0, 135.3, 129.5, 128.5, 128.1, 127.2, 126.4, 125.7, 124.5, 74.9, 64.3, 54.7, 26.0, 24.0; HRMS (ESI): m/z [M+H]+ calcld for C₂₀H₂₃N₂O₄: 355.1658, found: 355.1656.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 4-nitrobenzoate (3i). The desired pure product was obtained in 87% yield (751 mg) as yellow oil; [α]_D²⁰ -11.0 (c 1.0, CH₂Cl₂); FT-IR v_max/cm⁻¹ 2934, 2852, 1727, 1533, 1349; ¹H NMR (500 MHz, CDCl₃) δ 8.30-8.22 (m, 4H), 7.43-7.31 (m, 5H), 6.76 ( br, 1H), 6.24-6.22 (dd, J = 8.9, 3.8 Hz, 1H), 3.03-2.98 (dd, J = 13.8, 8.9 Hz, 1H), 2.72-2.68 (dd, J = 13.8, 3.8 Hz, 1H), 2.60-2.58 (m, 2H), 2.49-2.44 (m, 2H), 1.52-1.48 (m, 4H), 1.40-1.36 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 163.9, 150.4, 139.0, 136.0, 130.7, 128.5, 128.2, 126.4, 123.5, 74.9, 64.4, 54.7, 26.0, 24.1; HRMS (ESI): m/z [M+H]+ calcld for C₂₀H₂₃N₂O₄: 355.1658, found: 355.1656.

tert-Butyl 4-(((S)-1-phenyl-2-(piperidin-1-yl)ethoxy)carbonyl)phenylcarbamate (3j). The desired pure product was obtained in 91% yield (940 mg) as orange oil; [α]_D²⁰ -36.6 (c 1.0, CH₂Cl₂); FT-IR v_max/cm⁻¹ 2935, 2852, 1709, 1152, 1050; ¹H NMR (500 MHz, CDCl₃) δ 8.01-7.25 (m, 9H), 6.76 (br, 1H),
6.17-6.15 (dd, J = 8.4, 3.9 Hz, 1H), 3.01-2.96 (dd, J = 13.8, 8.5 Hz, 1H), 2.73-2.69 (dd, J = 13.8, 4.0 Hz, 1H), 2.56-2.48 (m, 4H), 1.52 (s, 9H), 1.50-1.48 (m, 4H), 1.38-1.35 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 165.3, 152.1, 142.6, 140.0, 130.9, 128.3, 127.7, 126.3, 124.7, 117.3, 81.1, 73.8, 64.5, 54.6, 28.2, 26.0, 24.1; HRMS (ESI): m/z [M+H]+ calcd for C25H33N2O4: 425.2440, found: 425.2428.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-(4-chlorobenzoyl)benzoate (3k). The desired pure product was obtained in 90% yield (981 mg) as orange oil; [α]D20 +20.0 (c 1.0, CH2Cl2); FT-IR νmax/cm−1 2934, 2853, 1717, 1674, 1454, 1267; 1H NMR (500 MHz, CDCl3) δ 8.15-7.12 (m, 13H), 5.98-5.96 (dd, J = 8.5, 4.2 Hz, 1H), 2.68-2.64 (dd, J = 13.6, 8.5 Hz, 1H), 2.46-2.43 (dd, J = 13.6, 4.2 Hz, 1H), 2.38-2.37 (m, 2H), 2.30-2.25 (m, 2H), 1.50-1.38 (m, 4H), 1.36-1.25 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 195.5, 164.6, 141.2, 139.4, 138.8, 135.5, 132.4, 130.7, 130.4, 129.5, 129.0, 128.7, 128.2, 127.9, 127.3, 126.5, 74.6, 63.8, 54.5, 25.9, 24.0; HRMS (ESI): m/z [M+H]+ calcd for C27H27ClNO3: 448.1679, found: 448.1681.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-methylbenzoate (3l). The desired pure product was obtained in 85% yield (669 mg) as yellow oil; [α]D20 +11.0 (c 1.0, CH2Cl2); FT-IR νmax/cm−1 2932, 2853, 1719, 1455, 1251, 1075; 1H NMR (500 MHz, CDCl3) δ 7.98-7.15 (m, 9H), 6.26-6.24 (dd, J = 9.2, 3.3 Hz, 1H), 3.13-3.08 (dd, J = 13.8, 9.2 Hz, 1H), 2.77-2.74 (dd, J = 13.8, 3.4 Hz, 1H), 2.70-2.64 (m, 2H), 2.60-2.56 (m, 2H), 2.57 (s, 3H), 1.62-1.58 (m, 4H), 1.45-1.40 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 166.6, 140.3, 139.6, 131.8, 131.5, 131.2, 130.5, 128.5, 128.0, 126.4, 125.6, 125.3, 73.0, 63.9, 54.3, 25.4, 23.9, 21.7; HRMS (ESI): m/z [M+H]+ calcd for C21H26NO2: 324.1964, found: 324.1961.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 3-methylbenzoate (3m). The desired pure product was obtained in 94% yield (740 mg) as yellow oil; [α]D20 -13.8 (c 1.0, CH2Cl2); FT-IR νmax/cm−1 2933, 2853, 1718, 1454, 1274, 1081; 1H NMR (500 MHz, CDCl3) δ 7.90-7.24 (m, 9H), 6.20-6.17 (dd, J = 8.4, 4.0 Hz, 1H), 3.01-2.98 (dd, J = 13.7, 8.4 Hz, 1H), 2.74-2.70 (dd, J = 13.7, 4.0 Hz, 1H), 2.57-2.48 (m, 4H), 2.39 (s, 3H), 1.53-1.49 (m, 4H), 1.40-1.35 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 165.8, 140.0, 138.0, 133.5, 130.1, 128.3, 128.1, 127.7, 126.7, 126.3, 73.9, 64.5, 54.6, 26.0, 24.1, 21.2; HRMS (ESI): m/z [M+H]+ calcd for C21H26NO2: 324.1964, found: 324.1962.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl 4-methylbenzoate (3n). The desired pure product was obtained in 93% yield (732 mg) as orange oil; [α]D20 -14.8 (c 1.0, CH2Cl2); FT-IR νmax/cm−1 2933, 2853, 1715, 1543, 1266, 1019; 1H NMR (500 MHz, CDCl3) δ 7.99-7.22 (m, 9H), 6.19-6.16 (dd, J = 8.4, 3.9 Hz, 1H), 3.01-2.96 (dd, J = 13.8, 8.5 Hz, 1H), 2.73-2.70 (dd, J = 13.8, 4.0 Hz, 1H), 2.57-2.49 (m, 4H), 2.39 (s, 3H), 1.53-1.48 (m, 4H), 1.39-1.34 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 165.7, 143.4, 140.0, 129.6, 129.0, 128.3, 127.8, 127.7, 126.3, 73.8, 64.5, 54.6, 26.0, 24.1, 21.6; HRMS (ESI): m/z [M+H]+ calcd for C21H26NO2: 324.1964, found: 324.1960.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl nicotinate (3o). The desired pure product was obtained in 91%
yield (687 mg) as orange oil; [α]D20 +3.4 (c 1.0, CH2Cl2); FT-IR νmax/cm⁻¹ 2931, 2853, 1721, 1590, 1419; ¹H NMR (500 MHz, CDCl3) δ 9.29-9.23 (m, 1H), 8.78-8.77 (m, 1H), 8.33-8.31 (m, 1H), 7.43, -7.28 (m, 6H), 6.22-6.20 (dd, J = 8.8, 3.8 Hz, 1H), 3.00-2.96 (dd, J = 13.8, 8.9 Hz, 1H), 2.71-2.68 (dd, J = 13.8, 3.8 Hz, 1H), 2.59-2.55 (m, 2H), 2.48-2.44 (m, 2H), 1.52-1.48 (m, 4H), 1.40-1.35 (m, 2H); ¹³C NMR (125 MHz, CDCl3) δ 164.4, 153.3, 150.9, 139.3, 137.1, 128.5, 128.1, 126.5, 126.4, 123.2, 74.5, 64.4, 54.7, 26.0, 24.1; HRMS (ESI): m/z [M+H]+ calcd for C19H23N2O2: 311.1760, found: 311.1754.

(S)-1-Phenyl-2-(piperidin-1-yl)ethyl cinnamate (3p). The desired pure product was obtained in 92% yield (783 mg) as white solid (recryst. from n-hexane/CH2Cl2); mp 82 °C; [α]D20 -35.1 (c 1.0, CH2Cl2); FT-IR νmax/cm⁻¹ 2933, 2853, 1709, 1636, 978; ¹H NMR (500 MHz, CDCl3) δ 7.70-7.67 (d, J = 16.0 Hz, 1H), 7.53-7.24 (m, 10H), 6.54-6.50 (d, J = 16.0 Hz, 1H), 6.11-6.08 (dd, J = 8.8, 3.9 Hz, 1H), 2.96-2.92 (dd, J = 13.7, 8.8 Hz, 1H), 2.64-2.60 (dd, J = 13.7, 4.0 Hz, 1H), 2.55-2.53 (m, 2H), 2.48-2.47 (m, 2H), 1.57-1.51 (m, 4H), 1.42-1.37 (m, 2H); ¹³C NMR (125 MHz, CDCl3) δ 166.1, 144.8, 139.9, 134.3, 130.2, 128.8, 128.3, 128.0, 127.8, 126.4, 118.3, 73.2, 64.3, 54.6, 25.9, 24.1; HRMS (ESI): m/z [M+H]+ calcd for C22H26NO2: 336.1964, found: 336.1951.

(2S)-(2S)-1-Phenyl-2-(piperidin-1-yl)ethyl 2-(2-methoxynaphthalen-6-y)propanoate (3q). The desired pure product was obtained in 98% yield (996 mg) as white solid; mp 71 °C; [α]D20 +17.3 (c 1.0, CH2Cl2); FT-IR νmax/cm⁻¹ 2934, 2852, 1730, 1605, 1154, 1031; ¹H NMR (500 MHz, CDCl3) δ 7.69-7.10 (m, 11H), 5.96-5.94 (dd, J = 9.0, 3.5 Hz, 1H), 3.90-3.87 (m, 1H), 3.89 (s, 3H), 2.71-2.66 (dd, J = 13.8, 9.0 Hz, 1H), 2.48-2.45 (dd, J = 13.8, 3.5 Hz, 1H), 2.30-2.28 (m, 2H), 2.16-2.14 (m, 2H), 1.55-1.54 (d, J = 7.2 Hz, 3H), 1.28-1.23 (m, 4H), 1.20-1.17 (m, 2H); ¹³C NMR (125 MHz, CDCl3) δ 173.5, 157.4, 139.7, 135.6, 133.5, 129.1, 128.8, 128.3, 127.7, 126.8, 126.4, 126.3, 126.0, 118.7, 105.4, 73.5, 64.2, 55.2, 54.3, 45.5, 25.8, 23.9, 18.3; HRMS (ESI): m/z [M+H]+ calcd for C27H32NO3: 418.2382, found: 418.2374.

(3S)-(3S)-1-Phenyl-2-(piperidin-1-yl)ethyl 3-phenylbutanoate (3r). The desired pure product was obtained in 94% yield (804 mg) as red oil; [α]D20 +62.5 (c 1.0, CH2Cl2); FT-IR νmax/cm⁻¹ 2933, 2802, 1747, 1698, 1157, 1087; (major rotamer) ¹H NMR (500 MHz, CDCl3) δ 7.22-7.11 (m, 10H), 5.87 (dd, J = 9.2, 3.5 Hz, 1H), 3.23-3.16 (m, 1H), 2.81-2.76 (dd, J = 13.7, 9.3 Hz, 1H), 2.64-2.60 (m, 1H), 2.53-2.49 (m, 1H), 2.48-2.41 (m, 3H), 2.40-2.35 (m, 2H), 1.44-1.41 (m, 4H), 1.32-1.29 (m, 2H), 1.19-1.17 (d, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl3) δ 171.4, 145.7, 139.4, 128.4, 128.3, 128.3, 127.9, 126.8, 126.7, 126.4, 126.3, 126.0, 72.4, 63.4, 54.0, 42.9, 36.3, 25.3, 23.8, 21.9; HRMS (ESI): m/z [M+H]+ calcd for C23H30NO2: 352.2277, found: 352.2274.

(2S)-tert-Butyl (S)-1-phenyl-2-(piperidin-1-yl)ethyl pyrrolidine-1,2-dicarboxylate (3s). The desired pure product was obtained as a rotamer mixture (ratio 67:33) in 96% yield (941 mg) as yellow oil; [α]D20 +32.5 (c 1.0, CH2Cl2); FT-IR νmax/cm⁻¹ 2933, 2853, 1721, 1590, 1419; ¹H NMR (500 MHz, CDCl3) δ 9.29-9.23 (m, 1H), 8.78-8.77 (m, 1H), 8.33-8.31 (m, 1H), 7.43, -7.28 (m, 6H), 6.22-6.20 (dd, J = 8.8, 3.8 Hz, 1H), 3.00-2.96 (dd, J = 13.8, 8.9 Hz, 1H), 2.71-2.68 (dd, J = 13.8, 3.8 Hz, 1H), 2.59-2.55 (m, 2H), 2.48-2.44 (m, 2H), 1.52-1.48 (m, 4H), 1.40-1.35 (m, 2H); ¹³C NMR (125 MHz, CDCl3) δ 164.4, 153.3, 150.9, 139.3, 137.1, 128.5, 128.1, 126.5, 126.4, 123.2, 74.5, 64.4, 54.7, 26.0, 24.1; HRMS (ESI): m/z [M+H]+ calcd for C19H23N2O2: 311.1760, found: 311.1754.
NMR (500 MHz, CDCl$_3$) δ 7.36-7.24 (m, 5H), 6.07-6.03 (m, 1H), 4.29-4.26 (dd, $J = 8.6$, 3.5 Hz, 1H), 3.63-3.54 (m, 1H), 3.44-3.34 (m, 1H), 2.80-2.76 (dd, $J = 13.4$, 9.7 Hz, 1H), 2.56-2.46 (m, 3H), 2.35-2.29 (m, 2H), 2.24-2.14 (m, 2H), 2.02-1.93 (m, 1H), 1.90-1.82 (m, 1H), 1.53-1.50 (m, 4H), 1.41-1.38 (m, 2H), 1.22 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.0, 153.7, 138.9, 128.1, 127.7, 126.4, 79.4, 72.3, 64.4, 58.9, 54.6, 46.1, 30.6, 28.2, 27.9, 24.0, 23.2; HRMS (ESI): $m/z$ [M+H]$^+$ calcd for C$_{23}$H$_{35}$N$_2$O$_4$: 403.2597, found: 403.2587.

Regioisomer: (R)-2-Phenyl-2-(piperidin-1-yl)ethyl acetate (4a). The desired pure product was obtained in 91% yield (548 mg) as yellow oil; [α]$_D^{20}$ -10.0 (c 1.0, CH$_2$Cl$_2$); FT-IR $\nu_{max}$/cm$^{-1}$ 2929, 2853, 1740, 1226; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.33-7.25 (m, 5H), 4.51-4.48 (dd, $J = 11.4$, 6.3 Hz, 1H), 4.36-4.32 (dd, $J = 11.4$, 6.5 Hz, 1H), 3.63-3.60 (t, $J = 6.4$ Hz, 1H), 2.40-2.36 (m, 4H), 1.97 (s, 3H), 1.55-1.51 (m, 4H), 1.39-1.34 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.9, 138.5, 128.4, 128.0, 127.3, 68.3, 64.9, 51.7, 26.2, 24.4, 20.9; HRMS (ESI): $m/z$ [M+H]$^+$ calcd for C$_{15}$H$_{22}$NO$_2$: 248.1651, found: 248.1648.

Regioisomer: (R)-2-Phenyl-2-(piperidin-1-yl)ethyl benzoate (4g). The desired pure product was obtained in 89% yield (670 mg) as orange oil; [α]$_D^{20}$ -8.1 (c 1.0, CH$_2$Cl$_2$); FT-IR $\nu_{max}$/cm$^{-1}$ 2933, 2853, 1733, 1262; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.97-7.25 (m, 10H), 4.79-4.76 (dd, $J = 11.4$, 6.2 Hz, 1H), 4.62-4.59 (dd, $J = 11.4$, 6.3 Hz, 1H), 3.83-3.81 (t, $J = 6.2$ Hz, 1H), 2.62-2.47 (m, 4H), 1.59-1.57 (m, 4H), 1.42-1.35 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.3, 132.8, 130.1, 129.5, 128.5, 128.2, 128.0, 127.5, 68.5, 65.5, 51.8, 25.9, 24.3; HRMS (ESI): $m/z$ [M+H]$^+$ calcd for C$_{20}$H$_{24}$NO$_2$: 310.1807, found: 310.1803.

(S)-2-((S)-3-Ethylpiperidin-1-yl)-1-phenylethyl acetate (5). The desired pure product was obtained in 91% yield (537 mg) as orange oil; [α]$_D^{20}$ +53.3 (c 1.0, CH$_2$Cl$_2$); FT-IR $\nu_{max}$/cm$^{-1}$ 2930, 2851, 1737, 1231, 1026; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.34-7.27 (m, 5H), 5.98-5.96 (dd, $J = 8.9$, 4.0 Hz, 1H), 2.91-2.82 (m, 2H), 2.88-2.84 (dd, $J = 13.6$, 9.0 Hz, 1H), 2.57-2.54 (dd, $J = 13.6$, 4.0 Hz, 1H), 2.12-2.03 (m, 1H), 2.09 (s, 3H), 1.74-1.68 (m, 2H), 1.64-1.50 (m, 2H), 1.43-1.35 (m, 1H), 1.25-1.17 (m, 2H), 0.88-0.85 (t, $J = 7.5$ Hz, 3H), 0.84-0.78 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.23, 139.67, 128.37, 127.86, 126.46, 73.00, 64.08, 59.90, 54.88, 37.62, 30.32, 27.10, 25.32, 21.37, 11.35. HRMS (ESI): $m/z$ [M+H]$^+$ calcd for C$_{17}$H$_{25}$NO$_2$: 276.1978, found: 276.1964.

(S)-2-Morpholino-1-phenylethyl acetate (8). The desired pure product was obtained in 93% yield (559 mg) as yellow oil; [α]$_D^{20}$ +70.1 (c 1.0, CH$_2$Cl$_2$); FT-IR $\nu_{max}$/cm$^{-1}$ 2958, 2854, 1733, 1229, 1115, 1026; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35-7.28 (m, 5H), 5.98-5.96 (dd, $J = 9.2$, 3.9 Hz, 1H), 3.71-3.64 (m, 4H), 2.86-2.82 (dd, $J = 13.4$, 9.3 Hz, 1H), 2.58-2.57 (m, 2H), 2.56-2.52 (dd, $J = 13.4$, 4.0 Hz, 1H), 2.48-2.47 (m, 2H), 2.10 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.23, 139.11, 128.41, 128.02, 126.44, 72.33, 66.94, 64.00, 53.71, 21.32; HRMS (ESI): $m/z$ [M+H]$^+$ calcd for C$_{14}$H$_{19}$NO$_3$: 250.1443, found: 250.1437.
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REFERENCES AND NOTES


14. Deposition number CCDC-1522551 for compound 2. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

15. The presence of the minority regioisomers 4a,g were confirmed by independent synthesis from 1.

\[
\begin{align*}
\text{N} & \quad \text{Ph} \quad \text{OH} & \quad \text{ROC} & \quad \text{Et}^3\text{N} & \quad 0 \degree \text{C to 25 \degree C} & \quad 1 \text{h} & \quad \text{N} & \quad \text{Ph} \quad \text{O} \quad \text{R} \\
1 & \quad & & & & & a : R = \text{Me} & & \text{g : R = Ph} \\
4
\end{align*}
\]


17. Deposition number CCDC-1551647 for compound 3p.