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Preparation of the MacMillan imidazolidinones

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ABSTRACT

A general method for the preparation of the MacMillan imidazolidinones is described. Treatment of an α-amino amide with a carbonyl compound in refluxing chloroform in the presence of $Yb(OTf)_3$ (1 mol %) provides convenient access to the corresponding imidazolidinones.

1. Introduction

Over the past decade imidazolidinones have been shown to provide an efficient platform for the acceleration of iminium ion, enamine and SOMO catalysed processes.[1,2] From this privileged structure seven principal imidazolidinone catalysts have been reported (**1**–**7**) (Fig. 1).

Catalyst **1** is used for cycloaddition[3] and closed transition state conjugate addition reactions[4] of α,β-unsaturated aldehydes along with several enamine catalysed processes.[5,6] Catalyst **2** is the most broad ranging scaffold and is effective for cycloaddition,[7] conjugate addition,[8] enamine[9] and SOMO[10,13a] catalysis. Catalyst **3** is efficient for reactions of α,β-unsaturated ketones that proceed via iminium ion intermediates, expanding the substrate scope of known transformations to encompass this important functionality.[11] Tryptophan based catalysts (e.g., **4** and **5**) provide a similar reactivity profile to the phenylalanine derived catalysts and in certain cases have resulted in higher levels of enantioselectivity.[12] More recently, the imidazolidinones **6** and **7** have been introduced for SOMO catalysed transformations.[13]

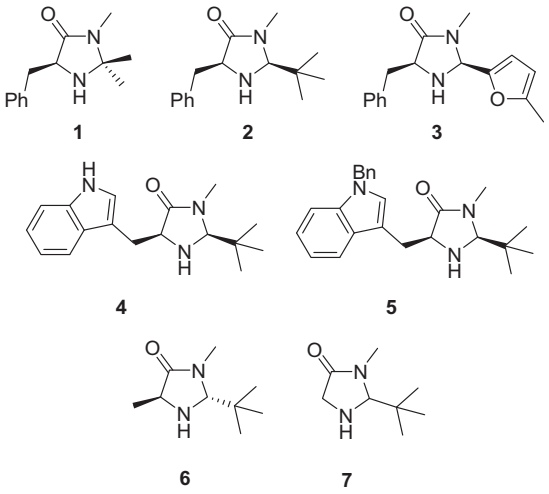
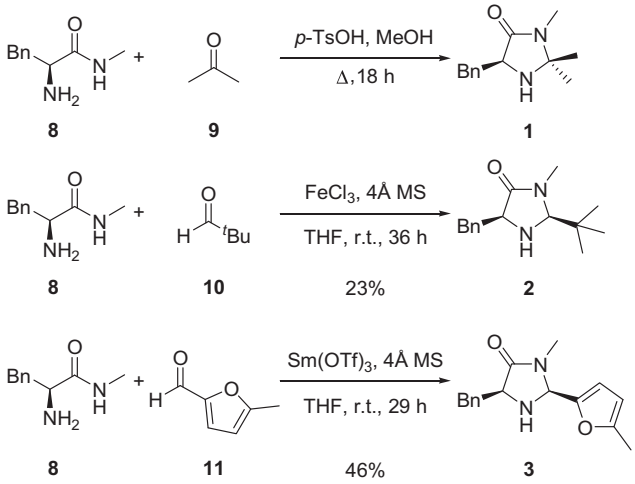


Fig. 1. Principal imidazolidinone catalysts for iminium ion, enamine and SOMO catalysed transformations.

Literature methods for the preparation of the imidazolidinones **1**–**3** are outlined in Scheme 1. Catalyst **1** is made by condensation of acetone (**9**) with amide **8** using *p*-toluene sulfonic acid as the catalyst.[3] It has been reported that with alternative ketone and aldehyde substrates, Brønsted acid catalysed methods and elevated temperatures lead to racemisation, limiting the applicability of this method.[14] For the alternative imidazolidinones it is necessary to use Lewis acid catalysis. The pivaldehyde derived catalyst **2** is



Scheme 1. Literature methods for the synthesis of **1**–**3**.

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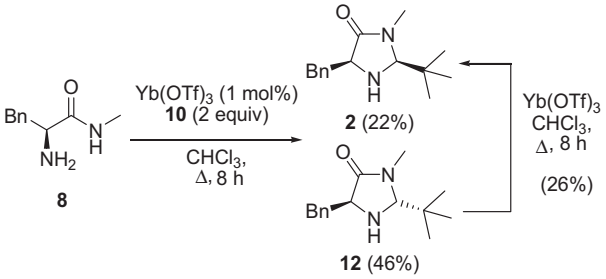
prepared from the same amide **8** using iron(III) chloride as the Lewis acid (23%).[8b] The furan containing catalyst **3** is far more challenging to prepare using air sensitive samarium(III) triflate, freshly distilled aldehyde **11** and glove box techniques.[11a] Alternative methods for the preparation of imidazolidinones are available, the most broad ranging being the two-step procedure developed by Seebach.[15]

Given the importance of **1**–**7** and the possibility that further structural modification may lead to innovation and discovery we sought to develop a standard, robust method for their preparation. Within this paper we describe a simple and scalable protocol for the preparation of the imidazolidinone architecture.

2. Results and discussion

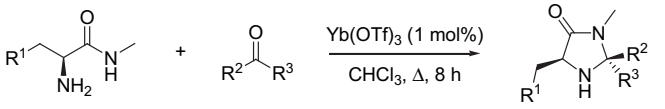
Our investigations began with a broad survey of both Lewis and Brønsted acid catalysts to promote the formation of imidazolidinone **2** using conductive and microwave heating. From these screens the optimal method emerged to be that shown in Scheme 2. Treatment of amide **8** with 2 equiv of pivaldehyde (**10**) in the presence of $Yb(OTf)_3$ (1 mol %) gave the diastereomeric imidazolidinones **2** and **12** in approximately a 1:2 ratio. These diastereoisomers could easily be separated by chromatography to give the desired catalyst **2** (22%, >99% ee). Recycling of the undesired diastereoisomer **12** was also possible (1 mol % $Yb(OTf)_3$, $CHCl_3$, Δ), providing **2** with a small loss of enantiopurity (26%, 98% ee).[16]

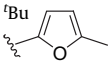


Scheme 2. Standard method for the synthesis of **2**.

Application of this standard method to alternative imidazolidinones architectures (**1** and **3**–**7**) is summarised in Table 1. The first generation catalyst **1** was effectively prepared by this method in 96% isolated yield (>99% ee). The synthetically more challenging furan containing catalyst **3** was also accessed by this method (32%; >99% ee). Although this yield is lower than the literature report, glove box techniques and distillation of aldehyde precursor were not required to access target material analytically pure. In addition to the phenylalanine based catalysts, tryptophan derived systems (e.g., **4**, 26%; **5**, 26%) were also accessible suggesting the method should be applicable to alternative amino acid scaffolds with equal efficiency. This was further exemplified by preparation of the alanine and glycine derived imidazolidinones **6** (77%) and **7** (55%), which have recently been used for SOMO catalysis.[10,13a]

Table 1
Application of imidazolidinone synthesis[a]

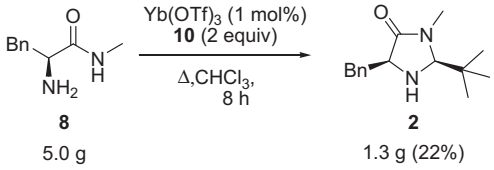


Imidazolidinone	R^1	R^2	R^3	% Yield	ee[c]
1	Ph	Me	Me	96	>99%
2	Ph	^{t}Bu	H	22	>99%
3	Ph		H	32	>99%
4	3-Indolyl	^{t}Bu	H	26	>99%
5	*N*-Bn-3-indolyl	^{t}Bu	H	26	>99%
6	H	H	^{t}Bu	77	>99%
7[b]	—	^{t}Bu	H	55	—

[a] Standard reaction conditions: $Yb(OTf)_3$ (1 mol %); $CHCl_3$ (0.5 M); Δ; 8 h.
[b] Catalyst **7** prepared under standard reaction conditions from glycine *N*-methylamide and pivaldehyde as a racemic mixture.
[c] Determined by HPLC on a chiral stationary phase. See Supplementary data for full details.

Confirmation of ee for the imidazolidinones **1**–**6** came from their preparation using racemic amino amide starting materials and comparison of HPLC traces (see Supplementary data for full details). In each case, the ee was found to be >99%, showing this to be a viable method for the preparation of imidazolidinones from a variety of amino acid and carbonyl substrates without racemisation.

Finally, to confirm the robust nature of this method the second generation catalyst **2** was prepared from 5 g of amide **8**. Thus, imidazolidinone **2** was prepared in 22% yield and >99% ee (together with the recyclable diastereoisomer **12**; 46%) suggesting the method should be scalable (Scheme 3).



Scheme 3. Scale up of imidazolidinone synthesis.

3. Conclusion

In summary, we have developed a standard method for synthesis of the principal MacMillan imidazolidinones **1**–**7** that have demonstrated widespread use in LUMO, HOMO and SOMO accelerated transformations. The reactions are scalable and proceed without loss of optical purity. In certain cases, the current method offers distinct operational advantages over literature procedures and importantly, provides a standard protocol to prepare the structures. The methodology should be applicable to alternative carbonyl substrates and provide opportunity to diversify the known scaffolds, providing the impetus for further development in this exciting and important area of contemporary research.

4. Experimental section

4.1. General

Commercially available solvents and reagents were used without further purification. Petroleum ether refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. Flash chromatography was carried out using Merck Kieselgel 60H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254} that were visualised under UV light (at 254 and/or 360 nm). Infra-red (IR) spectra were recorded in the range 4000–600 cm^{-1} using KBr disks for solid samples and thin films between NaCl plates for liquid samples or as a Nujol mull and are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ at 18 °C and were reported in parts per million; *J* values were recorded in Hertz and multiplicities were expressed by the usual conventions. Low-resolution mass spectra (MS) were determined using electrospray ionization (ES) unless otherwise stated. APCI refers to atmospheric pressure chemical ionization, CI refers to chemical ionization (ammonia) and EI refers to electron ionization. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University of Wales,

Swansea, U.K. using the ionization methods specified. In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

4.1.1. L-Phenylalanine N-methylamide[3]. L-Phenylalanine ethyl ester hydrochloride (100.8 g, 439 mmol) was stirred in a 33% w/w ethanolic solution of methylamine (300 mL, 74.8 g, 2.41 mol) for 95 h. The solution was evaporated and the residue dissolved in sodium hydrogen carbonate solution (saturated, 200 mL) then extracted with chloroform (4×100 mL). The combined extracts were dried over sodium carbonate and evaporated to give the crude product, a white solid (52.4 g, 294 mmol, 67%). This was recrystallised from ethyl acetate/hexanes (1:2, 600 mL) and dried in vacuo to give the product as white crystals (42.7 g, 240 mmol, 55%); mp 58–60 °C [lit.[17] mp 92–93 °C]; $[\alpha]_D^{34}$ +72.6 (*c* 0.1, CH_2Cl_2); ν_{max} (NaCl disk)/cm^{-1} 3358, 1651, 1573, 1496, 1454, 1412; δ_H (500 MHz, $CDCl_3$) 7.33–7.21 (6H, m, Ar*H* and N*H*), 3.61 (1H, dd, *J* 9.5 and 4.0, COC*H*), 3.28 (1H, dd, *J* 13.7 and 4.0, CH_2), 2.82 (3H, d, *J* 5.0, NCH_3), 2.68 (1H, dd, *J* 13.7 and 9.5, CH_2), 1.41 (2H, s, NH_2); δ_C (125 MHz, $CDCl_3$) 174.8 (C), 138.0 (C), 129.3 (CH), 128.7 (CH), 126.8 (CH), 56.5 (CH), 41.1 (CH_2), 25.8 (CH_3); *m*/*z* (ES^+): 179.1 ($M+H^+$); HRMS (ES^+): found $M+H^+$, 179.1181. $C_{10}H_{14}N_2O$ requires, 179.1184.

4.1.2. L-Tryptophan N-methylamide[18]. Thionyl chloride (10.0 mL, 16.3 g, 134 mmol) was added dropwise to ethanol (130 mL). The solution was cooled to room temperature before L-tryptophan (9.7 g, 47.6 mmol) was added and the mixture stirred for 24 h then evaporated. The residue was washed with ethyl acetate (1×300 mL, 1×100 mL) and petroleum ether (ca. 100 mL) then dried to yield a cream solid. The solid was stirred in an ethanolic solution of methylamine (70 mL, 560 mmol) for 120 h then evaporated, taken up in sodium bicarbonate (saturated, 100 mL) and extracted with chloroform (4×40 mL). The combined chloroform extract was dried over sodium carbonate and evaporated to yield the desired product, a yellow solid (6.1 g, 28 mmol, 59%); mp 123–125 °C; $[\alpha]_D^{34}$ +32.0 (*c* 0.1, CH_3OH); ν_{max} (NaCl disk)/cm^{-1} 3282, 1650, 1537, 1457, 1411, 1342, 1232, 1101; δ_H (500 MHz, DMSO-d_6) 10.89 (1H, br s, N*H*), 7.84–7.83 (1H, m, N*H*), 7.57 (1H, d, *J* 8.1, Ar*H*), 7.36 (1H, d, *J* 2.2, Ar*H*), 7.17 (1H, s, Ar*H*), 7.07 (1H, ddd, *J* 7.0, 7.0 and 0.9, Ar*H*), 6.98 (1H, ddd, *J* 7.0, 7.0 and 0.9, Ar*H*), 3.44 (1H, dd, *J* 8.1 and 4.9, COC*H*), 3.09 (1H, dd, *J* 14.1 and 4.9, CH_2), 2.77 (1H, dd, *J* 14.1 and 8.1, CH_2), 2.60 (3H, d, *J* 4.7, CH_3), 1.70 (1H, br s, NH_2); δ_C (125 MHz, DMSO-d_6) 175.7 (C), 136.7 (C), 128.0 (C), 124.2 (CH), 121.3 (CH), 119.0 (CH), 118.7 (CH), 111.8 (CH), 111.3 (C), 56.0 (CH), 31.7 (CH_2), 26.0 (CH_3); *m*/*z* (ES^+): 218.1 ($M+H^+$); HRMS (ES^+): found $M+H^+$, 218.1285. $C_{12}H_{16}N_3O_1$ requires, 218.1293.

4.1.3. 1-Benzyl-L-tryptophan ethyl ester hydrochloride[19]. Iron(III) nitrate nonahydrate (0.31 g, 0.78 mmol) was dissolved in liquid ammonia (500 mL). Sodium (3.95 g, 172 mmol) was dissolved and the ammonia was kept at reflux for 1 h before L-tryptophan (15.4 g, 75.4 mmol) was added, along with anhydrous diethyl ether (10 mL). The reaction was refluxed for 60 min and benzyl chloride was added dropwise (12.0 mL, 13.2 g, 104 mmol). The reaction mixture was then allowed to evaporate slowly overnight and quenched by the addition of water (600 mL) then heated to precipitate a solid, which was removed by filtration. The filtrate was treated with glacial acetic acid (65 mL), cooled to around 10 °C and the resultant white precipitate filtered, washed with water (500 mL), ethanol (200 mL) and 40–60 °C petroleum ether (200 mL) then dried in vacuo. It was then refluxed for 23 h in an ethanolic solution of hydrogen chloride formed by the cautious addition of thionyl chloride (30 mL) to ethanol (1.1 L). The solution was then evaporated and the residue washed with 1:1 ethyl acetate/diethyl ether (300 mL) and copious diethyl ether then dried to give the desired product, a fluffy white solid (17.7 g, 43.4 mmol, 58%); mp 192–195 °C; $[\alpha]_D^{25}$ +4.6 (*c* 0.1, CH_2Cl_2); ν_{max} (NaCl disk)/cm^{-1} 1736, 1507, 1238, 734, 699; δ_H (500 MHz, DMSO-d_6) 8.81 (3H, s, NH_{3+}), 7.62 (1H, d, *J* 7.8, Ar*H*), 7.42 (1H, d, *J* 7.1, Ar*H*), 7.39 (1H, s, Ar*H*), 7.31 (2H, t, *J* 7.5, Ar*H*), 7.25 (1H, t, *J* 7.3, Ar*H*), 7.21 (2H, d, *J* 7.0, Ar*H*), 7.12 (1H, t, *J* 7.0, Ar*H*), 7.05 (1H, t, *J* 7.0, Ar*H*), 5.39 (2H, t, *J* 16.5, PhCH_2), 4.15 (1H, dd, *J* 7.9 and 5.4, COC*H*), 4.08–3.95 (2H, m, CH_3CH_2), 3.41 (1H, dd, *J* 14.6 and 5.2, CHCH_2), 3.27 (1H, dd, *J* 14.6 and 7.9, CHCH_2), 1.00 (3H, t, *J* 7.1, CH_2CH_3); δ_C (125 MHz, DMSO-d_6) 169.8 (C), 138.6 (C), 136.5 (C), 128.9 (CH), 128.1 (C), 127.8 (CH), 127.5 (CH), 122.0 (CH), 119.4 (CH), 119.0 (CH), 110.7 (CH), 107.3 (C), 62.0 (CH_2), 53.3 (CH), 49.5 (CH_2), 26.7 (CH_2), 14.1 (CH_3); *m*/*z* (EI): 323.2 ($M+H^+$); HRMS (ES^+): found $M+H^+$, 323.1758. $C_{20}H_{23}N_2O_2$ requires, 323.1760.

4.1.4. 1-Benzyl-L-tryptophan N-methylamide[19]. 1-Benzyl-L-tryptophan ethyl ester hydrochloride (5.34 g, 14.9 mmol) was taken up in potassium carbonate (4 M, 100 mL) and extracted with chloroform (3×50 mL). The chloroform was evaporated and the residue was stirred in an ethanolic methylamine solution (25 mL, 201 mmol) for 62 h then evaporated and dried to yield the desired product, a cream solid (3.71 g, 12.1 mmol, 86%); mp 80–82 °C; $[\alpha]_D^{34}$ −51.8 (*c* 0.1, CH_2Cl_2); ν_{max} (NaCl disk)/cm^{-1} 3362, 3059, 2935, 1655, 1537, 1467, 1333, 1178; δ_H (500 MHz, $CDCl_3$) 7.55 (1H, d, *J* 7.9, Ar*H*), 7.17–6.93 (9H, m, Ar*H*), 6.83 (1H, s, Ar*H*), 5.07 (2H, s, PhCH_2), 3.54 (1H, dd, *J* 8.8 and 4.2, COC*H*), 3.22 (1H, dd, *J* 14.5 and 3.7, CHCH_2), 2.78 (1H, dd, *J* 14.5 and 8.8, CHCH_2), 2.62 (3H, d, *J* 5.0, CH_3), 1.33 (2H, br s, NH_2); δ_C (125 MHz, $CDCl_3$) 175.5 (C), 137.6 (C), 136.9 (C), 128.8 (CH), 128.4 (C), 127.7 (CH), 127.2 (CH), 126.9 (CH), 122.1 (CH), 119.4 (CH), 119.3 (CH), 111.1 (C), 109.9 (CH), 55.8 (CH), 49.9 (CH_2), 30.9 (CH_2), 25.9 (CH_3); *m*/*z* (ES^+): 308.2 ($M+H^+$); HRMS (ES^+): found $M+H^+$, 308.1756. $C_{19}H_{22}N_3O_1$ requires, 308.1763.

4.1.5. L-Alanine N-methylamide[20]. L-Alanine ethyl ester hydrochloride (8.1 g, 52.4 mmol) was stirred in an ethanolic methylamine solution (36 mL, 289 mmol) for 97 h then evaporated. The residue was taken up in potassium carbonate (4 M, 30 mL) and sodium bicarbonate (saturated, 20 mL) then extracted with chloroform (5×25 mL), which was dried over sodium carbonate and evaporated to yield crude L-Alanine *N*-methylamide, a red oil (3.62 g, 35.5 mmol, 68%). A solution of the free amine (1.9 g, 18.5 mmol) in diethyl ether (200 mL) was treated with hydrogen chloride gas for 10 min before the product was removed by filtration and washed with diethyl ether to yield the hydrochloride salt, a clear crystalline solid (2.2 g, 16.0 mmol, 86%). This was further purified by recrystallisation from ethanol and hexane; mp 213–215 °C; $[\alpha]_D^{25}$ 19.6 (*c* 0.1, CH_3OH); ν_{max} (NaCl disk)/cm^{-1} 3408, 1674, 1514, 1417, 1275, 1169; δ_H (400 MHz, D_2O) 3.85 (1H, q, *J* 7.1, C*H*), 2.60 (3H, s, NCH_3), 1.32 (3H, d, *J* 7.1, CCH_3); δ_C (100 MHz, D_2O) 174.1 (C), 51.2 (CH), 28.5 (CH_3), 19.2 (CH_3). L-Alanine *N*-methylamide hydrochloride (0.58 g, 4.17 mmol) and sodium carbonate (0.56 g, 5.30 mmol) were stirred in ethanol (40 mL) at 60 °C for 1 min, then cooled to room temperature, filtered and evaporated to yield the desired product; $[\alpha]_D^{34}$ +2.0 (*c* 0.1, CH_2Cl_2); ν_{max} (NaCl disk)/cm^{-1} 3364, 1646, 1575, 1456, 1413, 1375, 1318, 1272, 1160; δ_H (500 MHz, $CDCl_3$) 7.29 (1H, br s, N*H*), 3.34 (1H, q, *J* 7.0, C*H*), 2.66 (3H, d, *J* 5.0, NCH_3), 1.39 (2H, br s, NH_2), 1.17 (3H, d, *J* 7.0, CHCH_3); δ_C (125 MHz, $CDCl_3$) 176.5 (C), 50.7 (CH), 25.7 (CH_3), 21.6 (CH_3); *m*/*z* (EI^+): 102.1 (M^+); HRMS (EI^+): found M^+, 102.0788. $C_4H_{10}N_2O_1$ requires, 102.0793.

4.1.6. Glycine N-methylamide[21]. Glycine ethyl ester hydrochloride (5.23 g, 37.5 mmol) was stirred in a 33% w/w ethanolic solution of methylamine (25 mL, 6.24 g, 201 mmol) at 50 °C for 30 min before sodium hydroxide (1.61 g, 40.4 mmol) was added and stirring continued for 3 min. The mixture was evaporated to give a slurry then extracted with ethyl acetate (2×50 mL), which was filtered and removed in vacuo to yield the desired product, a clear oil (2.56 g,

29.1 mmol, 77%); ν_{max} (NaCl disk)/cm^{-1} 3353, 3101, 2947, 1659, 1564, 1414, 1312, 1161; δ_H (500 MHz, DMSO-d_6) 7.79 (1H, br s, CONH), 3.06 (2H, s, CH_2), 2.61 (3H, d, J 4.7, CH_3), 1.89 (2H, s, NH_2); δ_C (125 MHz, DMSO-d_6) 173.9 (C), 45.3 (CH_2), 25.7 (CH_3); m/z (EI$^+$): 88.1 (M$^+$); HRMS (EI$^+$): found M+H$^+$, 88.0634. $C_3H_8N_2O_1$ requires, 88.0637.

4.2. Standard procedure for imidazolidinone synthesis

Recrystallised amino amide (1 equiv), aldehyde/ketone (2 equiv) and ytterbium trifluromethane sulfonate (0.01 equiv) were refluxed in chloroform (10 mL/mmol amino amide) for 8 h after which time the mixture was allowed to cool and the solvent evaporated. The products were purified by column chromatography.

4.3. Standard method for the isomerisation of trans-isomers

(2*R*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (1.11 g, 4.51 mmol, 99% ee) and ytterbium trifluoromethanesulfonate (0.028 g, 0.045 mmol) were refluxed in chloroform for 24 h. The reaction mixture was evaporated, and the diastereoisomers separated via column chromatography to yield (2*R*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (0.62 g, 2.52 mmol, 56%, 98% ee) and (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (0.29 g, 1.18 mmol, 26%, 98% ee).

4.3.1. (S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one **1**[3]. Colourless oil; R_f=0.32 (ethyl acetate); $[\alpha]_D^{30}$ −57.8 (*c* 0.1, CH_3OH) [lit.[22] $[\alpha]_D^{25}$ −48.7 (*c* 2.92, EtOH)]; ν_{max} (NaCl disk)/cm^{-1} 3318, 2975, 1682, 1428, 1400, 1148, 1090, 748, 702; δ_H (500 MHz, $CDCl_3$) 7.24–7.14 (5H, m, Ar*H*), 3.72 (1H, dd, *J* 6.8 and 4.5, COC*H*), 3.07 (1H, dd, *J* 14.2 and 4.5, CH_2), 2.94 (1H, dd, *J* 14.2 and 6.8, CH_2), 2.68 (1H, s, NCH_3), 1.19 (3H, s, CCH_3), 1.09 (3H, s, CCH_3); δ_C (125 MHz, $CDCl_3$) 173.4 (C), 137.2 (C), 129.5 (CH), 128.6 (CH), 126.8 (CH), 75.5 (C), 59.3 (CH), 37.4 (CH_2), 27.3 (CH_3), 25.4 (CH_3), 25.2 (CH_3); m/z (ES$^+$): 219.1 (M+H$^+$); HRMS (ES$^+$): found M+H$^+$, 219.1492. $C_{13}H_{19}N_2O_1$ requires, 219.1497.

4.3.2. (2S,5S)-5-Benzyl-2-tert-butyl-3-methylimidazolidin-4-one **2**[8b]. White solid; R_f=0.22 (ethyl acetate/petroleum ether 3:1); mp 78–80 °C; $[\alpha]_D^{30}$ −48.6 (*c* 0.1, CH_3OH) [lit.[23] $[\alpha]_D^{25}$ +71.8 ($CHCl_3$)]; ν_{max} (NaCl disk)/cm^{-1} 3354, 2975, 1676, 1392, 1340, 1106; δ_H (400 MHz, $CDCl_3$) 7.24–7.14 (5H, m, Ar*H*), 3.99 (1H, s, CH_3NC*H*), 3.64 (1H, dd, *J* 7.1 and 3.8, COC*H*), 3.09 (1H, dd, *J* 13.7 and 4.0, CH_2), 2.89 (1H, dd, *J* 13.7 and 7.6, CH_2), 2.85 (3H, s, NCH_3), 1.64 (1H, s, N*H*), 0.77 (9H, s, CCH_3); δ_C (125 MHz, $CDCl_3$) 175.2 (C), 137.9 (C), 129.6 (CH), 128.5 (CH), 126.6 (CH), 82.5 (CH), 59.4 (CH), 38.3 (CH_2), 35.0 (C), 30.7 (CH_3), 25.3 (CH_3); m/z (ES$^+$): 247.2 (M+H$^+$); HRMS (ES$^+$): found M+H$^+$, 247.1810. $C_{15}H_{23}N_2O_1$ requires, 247.1810.

4.3.3. (2S,5S)-5-Benzyl-3-methyl-2-(5-methylfuran-2-yl)imidazolidin-4-one **3**[11a]. Colourless oil; R_f=0.22 (ethyl acetate); $[\alpha]_D^{30}$ −151.0 (*c* 0.1, CH_3OH); ν_{max} (NaCl disk)/cm^{-1} 3331, 2920, 1694, 1454, 791, 702; δ_H (500 MHz, $CDCl_3$) 7.20–7.11 (5H, m, Ph*H*), 6.02 (1H, d, *J* 3.1, OCC*H*), 5.80 (1H, d, *J* 3.1, OCC*H*), 5.09 (1H, s, ArC*H*), 3.68 (1H, dd, *J* 7.5 and 4.2, COC*H*), 3.15 (1H, dd, *J* 14.2 and 4.2, CH_2), 2.99 (1H, dd, *J* 14.2 and 7.7, CH_2), 2.54 (3H, s, NCH_3), 2.11 (1H, br s, N*H*), 2.11 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$) 173.7 (C), 153.3 (C), 148.7 (C), 137.2 (C), 129.4 (CH), 128.6 (CH), 126.7 (CH), 110.8 (CH), 106.4 (CH), 70.9 (CH), 60.1 (CH), 37.6 (CH_2), 27.0 (CH_3), 13.5 (CH_3); m/z (ES$^+$): 271.2 (M+H$^+$); HRMS (ES$^+$): found M+H$^+$, 271.1444. $C_{16}H_{19}N_2O_2$ requires, 271.1447.

4.3.4. (2S,5S)-5-((1H-Indol-3-yl)methyl)-2-tert-butyl-3-methylimidazolidin-4-one **4**. White solid; R_f=0.15 (ethyl acetate); mp 178–181 °C; $[\alpha]_D^{30}$ −85.8 (*c* 0.1, CH_3OH); ν_{max} (NaCl disk)/cm^{-1} 3299, 2960, 1682, 1481, 1432, 1400, 1103; δ_H (500 MHz, $CDCl_3$) 8.45 (1H, s, Ar*H*), 7.69 (1H, d, *J* 7.8, Ar*H*), 7.34 (1H, d, *J* 8.0, Ar*H*), 7.18 (1H, td, *J* 7.6 and 0.8, Ar*H*), 7.12 (1H, td, *J* 7.2 and 0.8, Ar*H*), 7.08 (1H, d, *J* 2.2, Ar*H*), 4.00 (1H, s, CH_3CC*H*), 3.75–3.65 (1H, m, COC*H*), 3.34 (1H, dd, *J* 14.7 and 4.2, CH_2), 3.15 (1H, dd, *J* 14.7 and 6.4, CH_2), 2.88 (3H, s, NCH_3), 1.81 (1H, br s, NH), 0.70 (9H, s, CCH_3); δ_C (125 MHz, $CDCl_3$) 176.2 (C), 136.3 (C), 128.1 (C), 123.2 (CH), 122.1 (CH), 119.6 (CH), 118.9 (CH), 111.2 (C), 111.2 (CH), 82.6 (CH), 59.5 (CH), 34.7 (C), 30.7 (CH_3), 27.1 (CH_2), 25.3 (CH_3); m/z (ES$^+$): 286.2 (M+H$^+$); HRMS (ES$^+$): found M+H$^+$, 286.1925. $C_{17}H_{24}N_3O_1$ requires, 286.1919.

4.3.5. (2S,5S)-5-((1-Benzyl-1H-indol-3-yl)methyl)-2-tert-butyl-3-methylimidazolidin-4-one **5**. Colourless oil; R_f=0.14 (ethyl acetate); $[\alpha]_D^{30}$ −11.4 (*c* 0.1, CH_3OH); ν_{max} (NaCl disk)/cm^{-1} 2962, 1720, 1468, 1397, 1262, 740; δ_H (500 MHz, $CDCl_3$) 7.63 (1H, d, *J* 7.7, Ar*H*), 7.21–7.14 (4H, m, Ar*H*), 7.09 (1H, td, *J* 8.2 and 1.0, Ar*H*), 7.05–7.02 (3H, m, Ar*H*), 6.97 (1H, s, Ar*H*), 5.17 (2H, s, PhCH_2), 3.91 (1H, s, CH_3CC*H*), 3.64 (1H, t, *J* 4.9, COC*H*), 3.25 (1H, dd, *J* 14.7 and 4.2, CH_2), 3.09 (1H, dd, *J* 14.7 and 6.3, CH_2), 2.79 (3H, s, NCH_3), 0.60 (9H, s, CCH_3); δ_C (125 MHz, $CDCl_3$) 176.2 (C), 137.6 (C), 136.6 (C), 128.8 (CH), 128.7 (C), 127.6 (CH), 127.3 (CH), 126.9 (CH), 121.9 (CH), 119.4 (CH), 119.2 (CH), 110.4 (C), 109.7 (CH), 82.6 (CH), 59.4 (CH), 50.0 (CH_2), 34.6 (C), 30.6 (CH_3), 26.9 (CH_2), 25.3 (CH_3); m/z (ES$^+$): 376.2 (M+H$^+$); HRMS (ES$^+$): found M+H$^+$, 376.2380. $C_{24}H_{30}N_3O_1$ requires, 376.2389.

4.3.6. (2R,5S)-5-Methyl-2-tert-butyl-3-methylimidazolidin-4-one **6**. Colourless oil; R_f=0.16 (ethyl acetate); $[\alpha]_D^{25}$ −1.8 (*c* 0.1, CH_3OH); ν_{max} (NaCl disk)/cm^{-1} 3419, 2981, 1664, 1479, 1404; δ_H (500 MHz, CD_3OD) 4.92 (1H, s, CH_3CC*H*), 4.29 (1H, q, *J* 7.1, COC*H*), 3.08 (3H, s, NCH_3), 1.58 (1H, d, *J* 7.1, CHCH_3), 1.18 (9H, s, CHCCH_3); δ_C (125 MHz, CD_3OD) 168.1 (C), 78.9 (CH), 51.9 (CH), 34.6 (C), 29.5 (CH_3), 22.4 (CH_3), 11.8 (CH_3); m/z (APCI): 171.2 (M+H$^+$); HRMS (ES$^+$): found M+H$^+$, 171.1492. $C_9H_{19}N_2O_1$ requires, 171.1497.

4.3.7. 2-tert-Butyl-3-methylimidazolidin-4-one **7**[24]. Colourless oil; R_f=0.30 (ethyl acetate/methanol 4:1); ν_{max} (NaCl disk)/cm^{-1} 3339, 2957, 1694, 1483, 1432, 1400, 1322, 1260; δ_H (500 MHz, DMSO-d_6) 4.05 (1H, s, C*H*), 3.35 (1H, br s, N*H*), 3.21 (2H, s, CH_2), 2.82 (3H, s, NCH_3), 0.89 (9H, s, CCH_3); δ_C (125 MHz, DMSO-d_6) 174.6 (C), 84.5 (CH), 49.2 (CH_2), 37.8 (C), 31.1 (CH_3), 25.9 (CH_3); m/z (ES$^+$): 157.1 (M+H$^+$); HRMS (ES$^+$): found M+H$^+$, 157.1334. $C_8H_{17}N_2O_1$ requires, 157.1341.

4.3.8. (2R,5S)-5-Benzyl-2-tert-butyl-3-methylimidazolidin-4-one **12**[8b]. White solid; R_f=0.36 (ethyl acetate/petroleum ether 3:1); mp 86–88 °C; $[\alpha]_D^{30}$ −51.2 (*c* 0.1, CH_3OH); ν_{max} (NaCl disk)/cm^{-1} 2956, 1691, 1454, 1397, 1104, 702; δ_H (500 MHz, $CDCl_3$) 7.31–7.22 (5H, m, Ar*H*), 3.86–3.84 (1H, m, COC*H*), 3.81 (1H, s, $(CH_3)_3$CC*H*), 3.11 (1H, dd, *J* 14.1 and 4.2, CH_2), 2.92–2.89 (1H, m, CH_2), 2.87 (3H, s, NCH_3), 1.91 (1H, br s, N*H*), 0.90 (9H, s, CCH_3); δ_C (125 MHz, $CDCl_3$) 175.3 (C), 137.5 (C), 129.5 (CH), 128.5 (CH), 126.7 (CH), 83.4 (CH), 59.5 (CH), 38.6 (CH_2), 37.7 (C), 31.3 (CH_3), 25.6 (CH_3); m/z (ES$^+$): 247.2 (M+H$^+$); HRMS (ES$^+$): found M+H$^+$, 247.1802. $C_{15}H_{23}N_2O_1$ requires, 247.1810.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.009.

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