Rhodium-catalysed conjugate addition of arylboronic acids to enantiopure dehydroamino acid derivatives†

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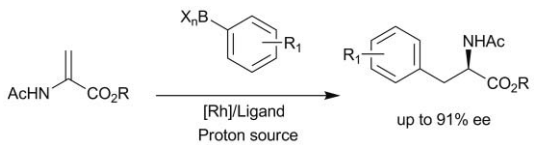
The rhodium-catalysed conjugate addition of arylboronic acids to an enantiopure acceptor derived from (*R*)-S-methylcysteine proceeds under substrate control to provide a range of functionalised phenylalanine derivatives with excellent stereocontrol *via* a highly diastereoselective protonation.

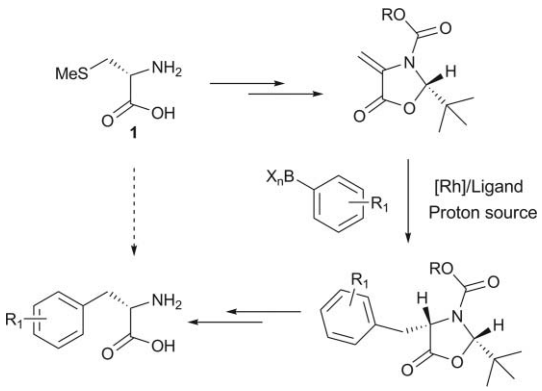
Introduction

The transition-metal catalysed conjugate addition of organometallics to activated alkenes is regarded as fundamental methodology for organic synthesis.[1] In particular, the rhodium catalysed conjugate addition of organometallics to activated alkenes is a powerful synthetic tool for establishing new carbon–carbon bonds, often with high stereoselectivity.[2,3] The introduction of a practical, efficient method for introducing functionalised aryl and alkenyl fragments with predictable stereocontrol has caught the attention of synthetic chemists and emerging examples are growing in number and complexity.[4] In the large majority of reported additions to prochiral acceptors, a single stereocentre is established by an asymmetric carbometalation under control of an enantiopure rhodium complex. A variation on the standard rhodium catalysed addition process is the asymmetric arylation of activated alkenes or allenes *via* enantioselective protonation.[5] An important example of this methodology is the enantioselective rhodium catalysed additions of boronic acids to α,β-dehydroamino acid derivatives allowing access to a range of α-amino acid derivatives with differing enantioselectivities depending on enantiopure ligand and proton source (Scheme 1).[6]



Scheme 1 The synthesis of amino acid derivatives by enantioselective protonation.

Whilst this methodology offers an expeditious route to certain amino acid derivatives there are limitations when high levels of enantioselectivity are required. The growing number of examples of rhodium catalysed conjugate additions to enantiopure acceptors inspired us to explore a solution based on substrate control.[7] The functionalisation of enantiopure templates to prepare enantioenriched amino acids has long been a cornerstone of organic synthesis.[8] In this context, enantiopure oxazolidinone scaffolds have proved particularly useful due to their simple synthesis and high stereoselectivity across a variety of reactions.[9] In this paper we describe the substrate controlled stereoselective synthesis of amino acid derivatives employing the rhodium catalysed addition of arylboronic acids to an enantiopure oxazolidinone scaffold. The strategy shown in Scheme 2 provides a straightforward method to convert (*R*)-S-methylcysteine **1** into a range of functionalised phenylalanine derivatives with perfect stereocontrol *via* a highly diastereoselective protonation.[10]



Scheme 2 The catalytic synthesis of functionalised phenylalanine derivatives by diastereoselective protonation.

Results and discussion

The desired methyleneoxazolidinone **4** was prepared as described in the literature (Scheme 3).[11] The reaction of (*R*)-S-methylcysteine **1** with pivaldehyde under Dean–Stark conditions, followed by treatment with benzyl chloroformate and purification of the major diastereomer **2** by flash chromatography. The methylthiomethyloxazolidinone **2** was converted to the corresponding sulfone **3** employing *m*-CPBA. The stereochemistry of the single diastereomer **3** was assigned as (2*R*,4*R*) by analogy of ^{1}H NMR and NOE spectra with literature data.[9,11] Treatment of **3** with DBU afforded the methyleneoxazolidinone **4** in excellent yield with high enantioselectivity (>99% ee determined by chiral HPLC analysis).

An initial investigation of the rhodium-catalysed conjugate addition of phenylboronic acid to **4** employing a variety of reaction conditions revealed a high-yielding and stereoselective route to the desired phenylalanine derivative **5** (Table 1). After testing

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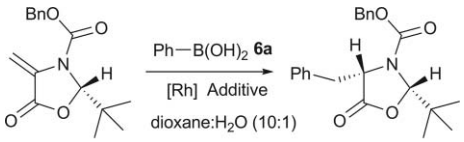
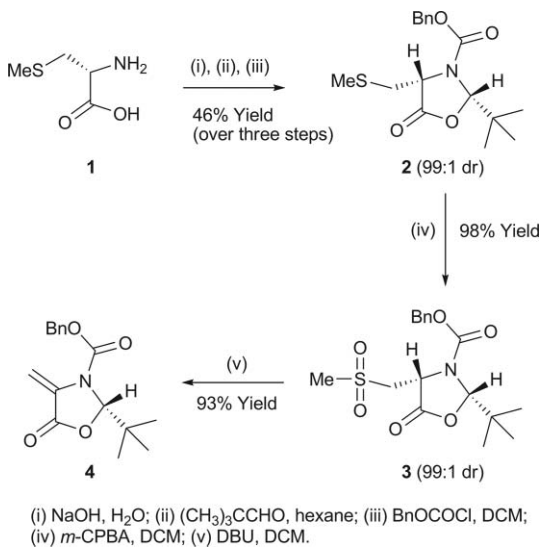
† Electronic supplementary information (ESI) available: General experimental procedures and NMR spectra. CCDC reference number 776776. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00158a

Table 1 Optimisation of reaction parameters



Entry	Rh loading	Catalyst	Additive	Yield[c] (%)
1[a]	1 mol%	$[Rh(cod)_2]BF_4$	—	41
2	1 mol%	$[Rh(cod)_2]BF_4$	—	60
3	1 mol%	$[Rh(cod)_2]BF_4$	NaF	44
4[b]	5 mol%	$[Rh(cod)_2]BF_4$	—	0
5	5 mol%	$[Rh(acac)(C_2H_4)_2]_2$	—	0
6	5 mol%	$[RhCl(C_2H_4)_2]_2$	—	0
7	5 mol%	$[Rh(cod)_2]BF_4$	—	69
8	**5 mol%**	**$[Rh(cod)_2]BF_4$**	**NaF**	**81**
9	5 mol%	$[Rh(cod)_2]BF_4$	KOH	72
10	5 mol%	$[Rh(cod)_2]BF_4$	TBAF	50
11	5 mol%	$[Rh(cod)_2]BF_4$	cod	70
12	5 mol%	$[Rh(cod)(MeCN)]BF_4$	—	15
13	5 mol%	$[Rh(cod)_2]BF_4$	phenol	0

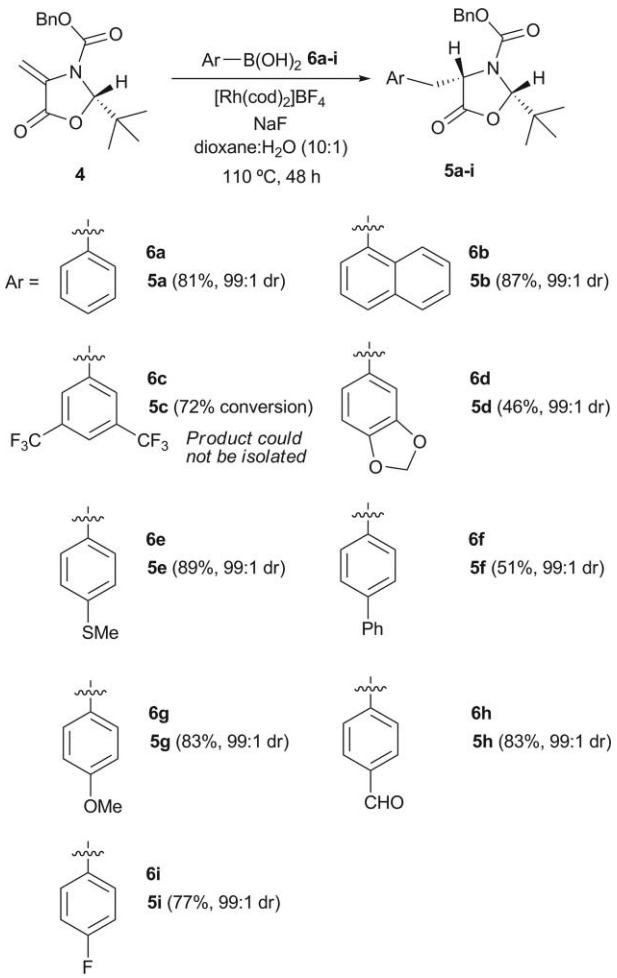
All reactions were performed at 110 °C for 48 h, in a dioxane : H_2O solution (10 : 1) unless otherwise stated.[a] 24 h. [b] Room temperature. [c] Determined to be a single diastereomer from the crude ^1H NMR spectroscopy and chiral HPLC analysis (Chiralpak AD or Chiracel OD column).



Scheme 3 The synthesis of enantiopure methyleneoxazolidinone.

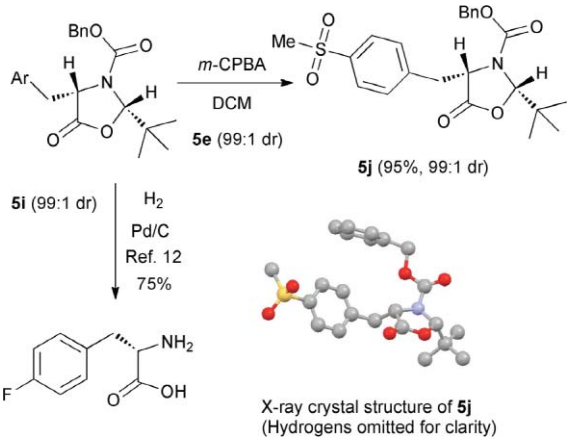
a variety of rhodium complexes, solvents and proton sources it emerged that the application of cationic rhodium complex $[Rh(cod)_2]BF_4$ in a dioxane/water mix (10 : 1) resulted in the highest yield. Interestingly elevated temperatures were crucial for effective conversion and catalyst loadings of 5 mol% were required for higher isolated yields. The effect of additives was also studied with NaF proving beneficial, presumably aiding transmetallation of $PhB(OH)_2$ with rhodium, *via* fluoride anion coordination. Due to the nature of the system involved and the presence of the carbamate group, reaction times of 48 h were needed. Once key reaction parameters had been established, our attention turned towards the versatility of the reaction. It should be noted that poor reaction yields were observed when changing the protecting group from a Cbz to an acetyl moiety and no reactivity at all took place with *N*-phenylacetyl derivatives.

With the optimised set of reaction conditions, we next explored the scope of the process with respect to the boronic acid; in all cases the enantiopure acceptor **4** was employed as substrate. A diverse range of arylboronic acids (**6a–i**) was shown to successfully participate in the conjugate addition to **4** (Scheme 4). It is useful to note that both electron-donating and electron-withdrawing substituents are tolerated alongside a range of substitution patterns. The products were obtained as single diastereomers in good to excellent yields. The high yield obtained using 4-formylphenylboronic acid **6h** was noteworthy, illustrating the preference for 1,4-conjugate addition over 1,2-addition under the presented conditions. The high diastereoselectivity was confirmed *via* 2D COSY NMR spectroscopic analysis, by the appearance of only one set of diastereotopic coupling signals in all environments and *via* chiral HPLC analysis. In order to establish the resulting stereochemistry of the arylated oxazolidinones, 2D ^1H–^1H NOESY experiments were employed. A NOE interaction was observed between the two diastereotopic protons, indicating a likely *syn* facial configuration to one another. Through-space couplings were observed between the ^{t}Bu group and the newly formed benzylic protons, providing further evidence for this conformation. The resulting *syn* conformation from



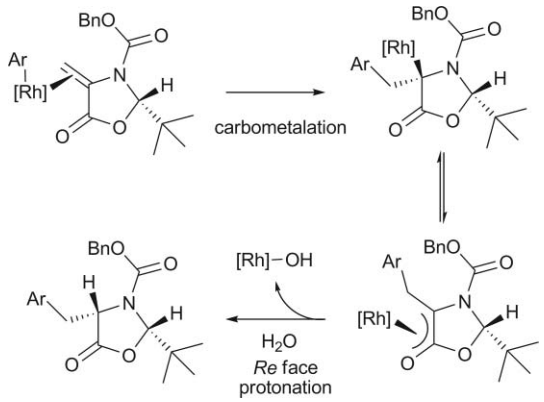
Scheme 4 Exploring the scope of the addition.

these experiments was further supported by X-ray analysis of oxazolidinone **5j** derived from the oxidation of addition product **5e** (Scheme 5). The conversion of the oxazolidinone moiety into the α-amino acid can be performed by a variety of methods, depending on the choice of nitrogen protecting group. In the presented case, *N*-Cbz oxazolidinones can be cleaved by direct hydrogenolysis. Thus, treatment of **5i** with palladium on activated carbon under one atmosphere of hydrogen gave the unnatural amino acid in accordance with the literature protocol.[12]



Scheme 5 Modification of oxazolidinones and X-ray structure. Structure deposited with the CCDC; entry number 776776.†

A mechanism for the diastereoselective protonation that is consistent with the presented experimental observations is shown in Scheme 6.[13] Following transmetalation of the arylboronic acid to the active rhodium complex, the substrate is proposed to associate on the least hindered face of the oxazolidinone ring *anti* to the bulky ^{t}Bu group. This is followed by carbometalation of the activated alkene to reveal a η^1-C rhodium species which is anticipated to be in equilibrium with an oxa-π-allyl species, both lying on the *Re* face of the ring. Protonation must occur, *anti* to the ^{t}Bu group *via* pre-coordination of the proton source to rhodium to afford the *syn* product as a single diastereomer.[14]



Scheme 6 Mode of diastereoselective protonation.

In conclusion, the rhodium catalysed conjugate addition of arylboronic acids to an enantiopure oxazolidinone template proceeds under substrate control to provide a range of functionalised phenylalanine derivatives with excellent stereocontrol *via* a highly diastereoselective protonation.

Experimental

IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrophotometer, using NaCl discs. ^{1}H NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 300 MHz, unless otherwise noted, with tetramethylsilane as an internal standard. *J* values are given in Hz. ^{13}C NMR spectra were obtained on a Bruker Advance 300 spectrometer operating at 75 MHz, unless otherwise noted. All dry solvents were freshly distilled under nitrogen prior to use. Mass spectra were obtained on a Bruker Time-of-Flight mass spectrometer (ESI-TOF). Enantiomeric excesses were determined using HPLC (see data see individual compounds details) with a UV detector at 254 nm. Tetrahydrofuran was distilled over alumina column. Petroleum ether refers to that fraction obtained between 40–60 °C. All other reagents were obtained from commercial suppliers and used as received. All glassware used under anhydrous conditions was dried in an oven and allowed to cool under nitrogen prior to use. All reactions were carried out under argon unless otherwise stated. Flash chromatography was conducted under medium pressure, using matrix 60 silica.

Procedure for the synthesis of (2*R*,4*R*)-benzyl-2-*tert*-butyl-4-(methylthiomethyl)-5-oxooxazolidine-3- carboxylate (2)

(*R*)-S-Methylcysteine **1** (6.75 g, 0.05 mmol) was treated with a solution of sodium hydroxide (1.99 g, 0.05 mmol) in water (200 mL) for 5 min and then evaporated to dryness under reduced pressure to leave a white solid. A solution of pivaldehyde (4.30 mL, 0.05 mmol) in hexane (150 mL) was added to the solid, and the suspension was stirred and heated to reflux in the presence of a Dean–Stark water separator for 24 h. The reaction mixture was then cooled and evaporated to dryness. The resulting pale yellow gum was suspended in anhydrous dichloromethane (150 mL) and treated with benzyl chloroformate (12.43 mL, 0.087 mmol) at 0 °C for 3 h and then a further 36 h at room temperature. A solution of 10% sodium bicarbonate (200 mL) was then added and stirring was continued for a further 3 h. The layers were then separated and the organic portion dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was then purified by silica chromatography (4 : 1, petroleum ether : ethyl acetate) to obtain the major diastereomer as a clear oil (7.81 g, 46%); R_f (4 : 1, petroleum ether : ethyl acetate) 0.45; IR (film, cm^{-1}) ν 3434, 2921, 1663, 1430, 1380, 1235, 1197, 1163, 1072, 1007, 871, 802, 654, 607; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42–7.39 (5H, m, Ar), 5.59 (1H, s, C*H*), 5.21 (2H, s, CH_2), 4.55 (1H, dd, J = 6.0, 7.8 Hz, C*H*), 3.03 (1H, dd, J = 7.8, 13.9 Hz, CH_2), 2.88 (1H, dd, J = 6.0, 13.9 Hz, CH_2), 2.13 (3H, s, SCH_3), 0.99 (9H, s, (CH_2)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.7, 156.2, 135.3, 129.2, 129.1, 129.1, 96.6, 69.0, 57.4, 37.3, 37.0, 25.2, 16.4; HRMS (ESI) calcd for $C_{17}H_{23}NO_4S$ [MH^+]: m/z 338.1421; found m/z 338.1422.

Procedure for the synthesis of (2*R*,4*R*)-benzyl 2-*tert*-butyl-4-(methylsulfonylmethyl)-5-oxooxazolidine-3-carboxylate (3)

To a solution of (2*R*,4*R*)-benzyl 2-*tert*-butyl-4-(methylthiomethyl)-5-oxooxazolidine-3-carboxylate **2** (1 g, 2.96 mmol) in

DCM (50 mL) was added a solution of 3-chloroperoxybenzoic acid (1.66 g, 7.41 mmol) in DCM (25 mL). The resulting solution was stirred at room temperature for 24 h and then water (50 mL) was added to the reaction mixture. The two layers were separated and the organics were dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica chromatography (4 : 1, petroleum ether: ethyl acetate), and recrystalised in ethanol to give the title compound as a white solid, as a single diastereomer (1.08 g, 98%); R_f (4 : 1, petroleum ether : ethyl acetate) 0.25; mp 89 °C (ethanol); $[\alpha]_D^{24}$ +11 (*c* 1.0, EtOH); IR (film, cm^{-1}) ν 3059, 2923, 2848, 1941, 1867, 1800, 1600, 1582, 1492, 1452, 1372, 1328, 1181, 1154, 1068, 1028, 965; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.2 (5H, m, Ar), 5.52 (1H, s, C*H*), 5.18 (1H, d, *J* = 11.8 Hz, CH_2), 5.08 (1H, d, *J* = 11.8 Hz, CH_2), 4.88 (1H, dd, *J* = 3.7, 7.5 Hz, C*H*), 3.55–3.45 (1H, m, CH_2), 3.28 (1H, dd, *J* = 3.7, 14.3 Hz, CH_2), 2.96 (3H, s, SCH_3), 0.85 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 155.7, 135.3, 129.1, 129.0, 97.2, 69.1, 57.4, 53.8, 42.6, 37.1, 25.0; HRMS (ESI) calcd for $C_{17}H_{23}NO_6S$ [*M*+NH_4^+]: *m*/*z* 387.1584; found *m*/*z* 387.1583.

Procedure for the synthesis of (*R*)-benzyl 2-*tert*-butyl-4-methylene-5-oxooxazolidine-3-carboxylate (4)

To a solution of (2*R*,4*R*)-benzyl 2-*tert*-butyl-4-(methylsulfonyl-methyl)-5-oxooxazolidine-3-carboxylate **3** (509 mg, 1.37 mmol) in dichloromethane (15 mL) at 0 °C was added DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (228 µl, 1.51 mmol) dropwise. The solution was stirred for 30 min at 0 °C and then treated with water (10 mL). The layers were separated and the organic phase was further washed with water (2 × 10 mL), dried over $MgSO_4$ and evaporated to dryness to give the crude product which was filtered through a short column of silica gel (eluent petroleum ether : ethyl acetate, 1 : 1) to give the product as a colourless oil (370 mg, 93%); R_f (1 : 1, petroleum ether : ethyl acetate) 0.5; $[\alpha]_D^{24}$ −20.0. (*c* 0.8, $CHCl_3$); IR (film, cm^{-1}) ν 2971, 1795, 1727, 1656, 1480, 1398, 1362, 1327, 1270, 1208, 1181, 1118, 1091, 1038, 1011, 914; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.29 (5H, m, Ar), 5.63 (1H, s, C*H*), 5.60 (2H, app. s, C*H*, C*H*), 5.17 (2H, s, CH_2), 0.84 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.9, 152.7, 135.0, 130.5, 129.2, 129.1, 129.0, 104.7, 94.3, 69.1, 39.0, 24.7; HRMS (ESI) calcd for $C_{16}H_{19}NO_4$ [*M*+NH_4^+]: *m*/*z* 307.1652; found *m*/*z* 307.1651. HPLC Diacel Chiralcel OD–H, hexane : propan-2-ol (95 : 5), 1.0 mL min^{-1}, t_R = 6.1 min.

General procedure for the rhodium-catalysed conjugate addition of arylboronic acids to (*R*)-benzyl 2-*tert*-butyl-4-methylene-5-oxooxazolidine-3-carboxylate

A suspension of (*R*)-benzyl-2-*tert*-butyl-4-methylene-5-oxooxazolidine-3-carboxylate **4** (100 mg, 0.34 mmol), arylboronic acid (1.38 mmol, 4 equiv.) **6a–i**, sodium fluoride (58 mg, 1.38 mmol) and [Rh(cod)$_2$][BF_4] (7 mg, 0.017 mmol, 5 mol%), in dioxane (3.0 mL) and water (0.3 mL) was refluxed at 110 °C for 48 h under an atmosphere of nitrogen. The resulting solution was cooled to room temperature and evaporated under reduced pressure. The resulting residue was re-dissolved in ethyl acetate (20 mL) and washed with water (2 × 20 mL). The organic layer was further washed with brine (2 × 20 mL), dried over $MgSO_4$, and concentrated in *vacuo*. The crude material was purified by flash chromatography on silica gel (ethyl acetate : petrol, 1 : 4 by volume) to afford the desired product.

(2*S*,4*R*)-benzyl-4-benzyl-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate (5a)

Title compound was isolated as a colourless oil (99 mg, 60%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.19; $[\alpha]_D^{24}$ −33.3 (*c* 0.35,CH_3Cl) IR (film, cm^{-1}) ν 3346, 3089, 3065, 3032, 2951, 2360, 2250, 1717, 1631, 1586, 1531, 1498, 1454, 1440, 1407, 1368, 1305, 1252, 1217, 1157, 1062, 1026, 952; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (4H, m, Ar), 7.22–7.10 (6H, m, Ar), 5.49 (1H, s, C*H*), 5.07 (1H, d, *J* = 11.8 Hz, CH_2), 4.85 (1H, d, *J* = 11.8 Hz, CH_2), 4.41 (1H, dd, *J* = 5.6, 7.4 Hz, C*H*), 3.13 (1H, dd, *J* = 5.6, 13.9 Hz, CH_2), 3.04 (1H, dd, *J* = 5.6, 13.9 Hz, CH_2), 0.91 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.3, 155.1, 136.1, 134.4, 134.3, 128.8, 128.0, 127.9, 127.8, 126.3, 95.6, 67.6, 58.3, 38.6, 36.4, 24.2; HRMS (ESI) calcd for $C_{22}H_{25}NNaO_4$ [*M*+Na^+]: *m*/*z* 390.1709; found 390.1681.

(2*S*,4*R*)-benzyl-2-*tert*-butyl-4-(naphthalen-1-ylmethyl)-5-oxo-oxazolidine-3-carboxylate (5b)

Title compound was isolated as a colourless oil (62 mg, 87%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.1; $[\alpha]_D^{24}$ −15 (*c* 0.2, CH_2Cl_2); IR (film, cm^{-1}) ν 3673, 2960, 2360, 1792, 1718, 1456, 1395, 1334, 1305, 1229, 1197, 1118, 1034, 977; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, d, *J* = 8.2 Hz, Ar), 7.78 (1H, d, *J* = 8.2 Hz, Ar), 7.71–7.69 (1H, m, Ar), 7.36–7.12 (7H, m, Ar), 6.91 (2H, br. s, Ar), 5.49 (1H, s, CH_2), 4.94 (1H, d, *J* = 12.0, CH_2), 4.64 (1H, app. t, *J* = 7.2 Hz, CH_2), 4.38 (1H, br. s, C*H*), 3.65 (1H, dd, *J* = 7.3, 14.0 Hz, CH_2), 3.48 (1H, dd, *J* = 7.3, 14.0 Hz, CH_2), 0.98 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.9, 156.3, 135.4, 134.1, 132.8, 132.3, 129.3, 128.9, 128.9, 128.7, 128.4, 126.6, 126.0, 125.7, 123.7, 96.8, 68.5, 57.9, 37.4, 36.9, 25.5; HRMS (ESI) calcd for $C_{26}H_{27}NO_4$ [*M*+NH_4^+]: *m*/*z* 435.2278; found 435.2277. HPLC Diacel Chiralcel OD–H, hexane : propan-2-ol (95 : 5), 1.0 mL min^{-1}, t_R = 43.5 min.

(2*S*,4*R*)-benzyl-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate (5d)

Title compound was isolated as a colourless oil (65 mg, 46%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.28; $[\alpha]_D^{24}$ −16.5 (*c* 1.1, CH_2Cl_2); IR (film, cm^{-1}) ν 3410, 2970, 2360, 2132, 1792, 1720, 1651, 1503, 1491, 1445, 1394, 1369, 1336, 1307, 1271, 1248, 1232, 1191, 1176, 1121, 1038, 1019, 933; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32–7.26 (3H, m, Ar), 7.24–7.18 (2H, m, Ar), 6.64 (1H, s, Ar), 6.57 (2H, br. s, Ar), 5.82 (2H, s, OCH_2), 5.48 (1H, s, C*H*), 5.08 (1H, d, *J* = 12.0 Hz, CH_2), 4.94 (1H, d, *J* = 12.0 Hz, CH_2), 4.34 (1H, dd, *J* = 5.6, 7.5 Hz, C*H*), 3.04 (1H, dd, *J* = 7.5, 14.2 Hz, CH_2), 2.95 (1H, dd, *J* = 5.6, 14.2 Hz, CH_2), 0.91 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.3, 156.2, 148.0, 146.9, 135.5, 130.8, 129.0, 128.9, 122.9, 110.2, 108.6, 101.2, 96.6, 68.8, 59.4, 39.4, 37.4, 25.3; HRMS (ESI) calcd for $C_{23}H_{25}N_1NaO_6$ [*M*+Na^+]: *m*/*z* 434.1579; found *m*/*z* 434.1567. HPLC Diacel Chiralcel OD–H, hexane : propan-2-ol (95 : 5), 1.0 mL min^{-1}, t_R = 25.4 min.

(2*S*,4*R*)-benzyl-4-(4-(methylthio)benzyl)-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate (5e)

Title compound was isolated as a colourless oil (105 mg, 89%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.13; $[\alpha]_D^{24}$ −9.2 (*c* 1.4, CH_2Cl_2); IR (film, cm^{-1}) *ν* 3435, 2360, 2101, 1792, 1644, 1496, 1481, 1393, 1347, 1310, 1283, 1232, 1199, 1175, 1121, 1036, 931; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.33–7.26 (3H, m, Ar), 7.22–7.16 (2H, m, Ar), 7.03 (4H, br. s, Ar), 5.47 (1H, s, C*H*), 5.06 (1H, d, *J* = 11.8, CH_2), 4.87 (1H, d, *J* = 11.8, CH_2), 4.36 (1H, dd, *J* = 5.8, 7.6 Hz, C*H*), 3.07 (1H, dd, *J* = 7.6, 13.9 Hz, CH_2), 2.99 (1H, dd, *J* = 5.8, 13.9 Hz, CH_2), 2.37 (3H, s, SCH_3), 0.92 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) *δ* 172.4, 156.2, 137.3, 135.4, 134.0, 130.3, 129.0, 129.0, 127.2, 127.1, 96.6, 68.8, 59.3, 39.1, 37.5, 25.3, 16.3; HRMS (ESI) calcd for $C_{23}H_{27}NO_4S$ [*M*+NH_4^+]: *m*/*z* 431.1999; found 431.1999.

(2*S*,4*R*)-benzyl 4-biphenyl-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate (5f)

Title compound was isolated as a colourless oil (67 mg, 51%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.20; $[\alpha]_D^{24}$ −6.6 (*c* 0.3, CH_2Cl_2); IR (film, cm^{-1}) *ν* 3430, 2963, 2350, 2340, 2100, 1792, 1716, 1644, 1520, 1486, 1456, 1394, 1347, 1264, 1232, 1199, 1172, 1036; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.50–7.46 (2H, m, Ar), 5.40–7.32 (4H, m, Ar), 7.28–7.22 (4H, m, Ar), 7.22–7.14 (4H, m, Ar), 5.49 (1H, s, C*H*), 5.06 (1H, d, *J* = 11.6 Hz, CH_2), 4.86 (1H, d, *J* = 11.6 Hz, CH_2), 4.43 (1H, dd, *J* = 5.6, 7.7 Hz, C*H*), 3.16 (1H, dd, *J* = 7.7, 13.9 Hz, CH_2), 3.07 (1H, dd, *J* = 5.6, 13.9 Hz, CH_2), 0.94 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) *δ* 172.4, 156.2, 141.2, 140.2, 136.2, 135.5, 130.3, 129.1, 129.0, 128.7, 127.9, 127.8, 127.6, 127.4, 96.7, 68.8, 59.3, 39.3, 37.5, 25.3; HRMS (ESI) calcd for $C_{28}H_{29}N_1NaO_4$ [*M*+ Na^+]: *m*/*z* 466.1989; found 466.1992. HPLC Diacel Chiralcel OD–H, hexane : propan-2-ol (90 : 10), 1.0 mL min^{-1}, t_R = 10.5.

(2*S*,4*R*)-benzyl-4-(4-methoxybenzyl)-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate (5g)

Title compound was isolated as a colourless oil (112 mg, 83%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.19; IR (film, cm^{-1}) *ν* 3019, 2971, 2400, 1790, 1720, 1599, 1570, 1478, 1394, 1310, 1269, 1215, 1121, 1036, 756; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.32–7.27 (3H, m, *Ar*), 7.22–7.18 (2H, m, *Ar*), 7.02 (2H, d, *J* = 8.6 Hz, *Ar*), 6.68 (2H, d, *J* = 8.6 Hz, *Ar*), 5.47 (1H, s, C*H*), 5.07 (1H, d, *J* = 12.0 Hz, CH_2), 4.90 (1H, d, *J* = 12.0 Hz, CH_2), 4.36 (1H, dd, *J* = 5.4, 7.5 Hz, C*H*), 3.69 (3H, s, CH_3), 3.07 (1H, dd, *J* = 7.5, 13.9 Hz, CH_2), 2.98 (1H, dd, *J* = 5.4, 13.9 Hz, CH_2), 0.92 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) *δ* 172.4, 158.9, 156.2, 135.5, 130.8, 129.2, 129.0, 128.9, 114.2, 96.5, 68.7, 59.4, 55.6, 38.8, 37.4, 25.3; HRMS (ESI) calcd for $C_{23}H_{27}NO_5Na$ [*M*+Na^+]: *m*/*z* 420.1786; found 420.1789. HPLC Diacel Chiralcel OD–H, hexane : propan-2-ol (95 : 5), 1.0 mL min^{-1}, t_R = 12.1 min.

(2*S*,4*R*)-benzyl-4-(4-formylbenzyl)-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate (5h)

Title compound was isolated as a colourless oil (112 mg, 83%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.08; $[\alpha]_D^{24}$ −18.3 (*c* 3, CH_2Cl_2); IR (film, cm^{-1}) *ν* 3621, 3211, 3066, 2971, 2360, 1792, 1721, 1607, 1578, 1481, 1456, 1393, 1346, 1305, 1277, 1232, 1199, 1170, 1121, 1036, 1018, 979, 731; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.86 (1H, s, C*H*O), 7.63 (2H, d, *J* = 8.2 Hz, Ar), 7.32–7.24 (5H, m, Ar), 7.19–7.14 (2H, m, Ar), 5.51 (1H, s, C*H*), 5.02 (1H, d, *J* = 12.0 Hz, CH_2), 4.88 (1H, d, *J* = 12.0 Hz, CH_2), 4.42 (1H, dd, *J* = 5.6, 7.3 Hz, C*H*), 3.20 (1H, dd, *J* = 7.3, 13.9 Hz, CH_2), 3.09 (1H, dd, *J* = 5.6, 13.9 Hz, CH_2), 0.94 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) *δ* 192.2, 172.0, 156.1, 144.2, 135.6, 135.2, 130.5, 130.2, 129.2, 129.1, 129.0, 96.8, 68.9, 59.0, 39.8, 37.5, 25.3; HRMS (ESI) calcd for $C_{23}H_{25}N_1NaO_5$ [*M*+Na^+]: *m*/*z* 418.1630; found *m*/*z* 418.1622. HPLC Diacel Chiralcel OD–H, hexane : propan-2-ol (90 : 10), 1.0 mL min^{-1}, t_R = 27.4 min.

(2*S*,4*R*)-benzyl 4-(4-fluorobenzyl)-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate (5i)

Title compound was isolated as a colourless oil (102 mg, 77%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.26; $[\alpha]_D^{24}$ 10.0 (*c* 0.5, CH_2Cl_2); IR (film, cm^{-1}) *ν* 3323, 2983, 2939, 2880, 2360, 2253, 2082, 1773, 1720, 1511, 1468, 1386, 1376, 1305, 1238, 1181, 1109, 1047; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.34–7.28 (3H, m, Ar), 7.21–7.17 (2H, m, Ar), 7.09–7.04 (2H, m, Ar), 6.84–6.76 (2H, m, Ar), 5.48 (1H, s, C*H*), 5.05 (1H, d, *J* = 11.6 Hz, CH_2), 4.91 (1H, d, *J* = 11.6 Hz, CH_2), 4.35 (1H, dd, *J* = 5.4, 7.3 Hz, C*H*), 3.10 (1H, dd, *J* = 7.3, 13.9 Hz, CH_2), 2.99 (1H, dd, *J* = 5.4, 13.9 Hz, CH_2), 0.92 (9H, s, (CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) *δ* 172.3, 162.1 (d, J_{C-F} = 279 Hz), 156.2, 135.9, 132,9, 131.4, 131.3, 129.1, 129.0, 115.6 (d, J_{C-F} = 21.7 Hz), 96.6, 68.9, 59.4, 38.8, 37.5, 25.2; ^{19}F NMR (376 MHz, $CDCl_3$) *δ* −115.8 ppm; HRMS (ESI) calcd for $C_{22}H_{24}FNNaO_4$ [*M*+Na^+]: *m*/*z* 408.1587; found 408.1529. HPLC Diacel Chiralcel OD–H, hexane : propan-2-ol (95 : 5), 1.0 mL min^{-1}, t_R = 11.9 min.

Procedure for synthesis of (2*S*,4*R*)-benzyl-4-(4-(methylsulfonyl)benzyl)-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate (5j)

To a solution of (2*S*,4*R*)-benzyl 4-(4-(methylthio)benzyl)-2-*tert*-butyl-5-oxooxazolidine-3-carboxylate **5e** (41 mg, 0.09 mmol) in DCM (10 ml) at 0 °C was added 3-chloroperoxybenzoic acid (55.5 mg, 0.24 mmol) portion-wise. The solution was stirred at room temperature for 5 h, quenched with dilute acetic acid (5 ml), and washed with water (20 ml). The organic layer was dried over $MgSO_4$ and the crude material was recrystalised in ethanol to give the title compound as a white solid (41 mg, 95%); R_f (9 : 1, petroleum ether : ethyl acetate) 0.09; mp 145 °C (ethanol); IR (film, cm^{-1}) *ν* 3447, 3035, 2973, 2876, 2256, 1792, 1721, 1644, 1497, 1482, 1456, 1399, 1308, 1228, 1201, 1180, 1229, 1082, 1041, 1017, 969, 912, 885, 821, 780; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.71 (2H, d, *J* = 8.2 Hz, Ar), 7.36–7.19 (7H, m, Ar), 5.51 (1H, s, C*H*), 5.08 (1H, d, *J* = 11.8, CH_2), 4.95 (1H, d, *J* = 11.8 Hz, CH_2), 4.38 (1H, dd, *J* = 5.1, 7.6 Hz, CH_2), 3.24–3.08 (2H, m, CH_2), 2.94 (3H, s, SCH_3), 0.93 (9H, s, (CH_3)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 171.6, 155.6, 143.2, 139.2, 134.8, 130.5, 128.9, 128.8, 128.7, 127.5, 96.3, 68.7, 58.5, 44.5, 39.2, 37.1, 24.8; HRMS (ESI) calcd for $C_{23}H_{27}NO_6S$ [*M*+NH_4^+]: *m*/*z* 463.1897; found *m*/*z* 463.1898. Diacel Chiralcel OD–H, hexane : propan-2-ol (90 : 10), 1.0 mL min^{-1}, t_R = 10.4 min.

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References

1 T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2009, **38**, 1039; A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, *Chem. Rev.*, 2008, **108**, 2796; J. Christoffers, G. Koripelly, A. Rosiak and M. Rössle, *Synthesis*, 2007, 1279; T. Hayashi, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 13.

2 M. Sakai, H. Hayashi and N. Miyaura, *Organometallics*, 1997, **16**, 4229.

3 Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai and N. Miyaura, *J. Am. Chem. Soc.*, 1998, **120**, 5579.

4 For reviews see: T. Hayashi, *Synlett*, 2001, 879; T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829; K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169; S. Darses and J.–P. Genêt, *Eur. J. Org. Chem.*, 2003, 4313; J. D. Hargrave, J. C. Allen and C. G. Frost, *Chem.–Asian J.*, 2010, **5**, 386; H. J. Edwards, J. D. Hargrave, S. D. Penrose and C. G. Frost, *Chem. Soc. Rev.*, 2010, **39**, 2093.

5 J. T. Mohr, A. Y. Hong and B. M. Stoltz, *Nat. Chem.*, 2009, **1**, 359.

6 M. T. Reetz, D. Moulin and A. Gosberg, *Org. Lett.*, 2001, **3**, 4083; C. J. Chapman, K. J. Wadsworth and C. G. Frost, *J. Organomet. Chem.*, 2003, **680**, 206; L. Navarre, S. Darses and J.–P. Genêt, *Angew. Chem., Int. Ed.*, 2004, **43**, 719; J. D. Hargrave, J. Herbert, G. Bish and C. G. Frost, *Org. Biomol. Chem.*, 2006, **4**, 3235; L. Navarre, R. Martinez, J.-P. Genêt and S. Darses, *J. Am. Chem. Soc.*, 2008, **130**, 6159.

7 G. de la Herran, M. Mba, M. C. Murcia, J. Plumet and A. G. Csákÿ, *Org. Lett.*, 2005, **7**, 1669; A. Segura and A. G. Csákÿ, *Org. Lett.*, 2007, **9**, 3667; C. J. Chapman, A. Matsuno, C. G. Frost and M. C. Willis, *Chem. Commun.*, 2007, 3903; C. S. Burgey, D. V. Paone, A. W. Shaw, J. Z. Deng, D. N. Nguyen, C. M. Potteiger, S. L. Graham, J. P. Vacca and T. M. Williams, *Org. Lett.*, 2008, **10**, 3235; C. J. Chapman, J. D. Hargrave, G. Bish and C. G. Frost, *Tetrahedron*, 2008, **64**, 9528; G. Kumaraswamy, G. Ramakrishna, P. Naresh, B. Jagadeesh and B. Sridhar, *J. Org. Chem.*, 2009, **74**, 8298; C. Navarro, A. Moreno and A. G. Csákÿ, *J. Org. Chem.*, 2009, **74**, 466; L. Zoute, G. Kociok-Köhn and C. G. Frost, *Org. Lett.*, 2009, **11**, 2491.

8 U. Schöllkopf, *Pure Appl. Chem.*, 1983, **55**, 1799; D. Seebach, T. Gees and F. Schuler, *Liebigs Ann. Chem.*, 1994, **785**; R. M. Williams and M. N. Im, *J. Am. Chem. Soc.*, 1991, **113**, 9276.

9 D. Seebach and A. Fadel, *Helv. Chim. Acta*, 1985, **68**, 1243; D. Blaser, S. Y. Ko and D. Seebach, *J. Org. Chem.*, 1991, **56**, 6230; J. R. Axon and A. L. J. Beckwith, *J. Chem. Soc., Chem. Commun.*, 1995, 549; F. Alonso, S. G. Davies, A. S. Elend and J. L. Haggitt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 257.

10 For related conjugate additions of organocuprates to dehydroalanine derivatives followed by diastereoselective protonation, see: S. D. Bull, S. G. Davies, S. W. Epstein and J. V. A. Ouzman, *Chem. Commun.*, 1998, 659; S. D. Bull, S. G. Davies, S. W. Epstein, M. A. Leech and J. V. A. Ouzman, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2321; S. D. Bull, S. G. Davies and M. D. O'Shea, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3657; S. D. Bull, S. G. Davies, A. C. Garner and N. Mujtaba, *Synlett*, 2001, 781; S. D. Bull, S. G. Davies, A. C. Garner and M. D. O'Shea, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3281.

11 A. L. J. Beckwith, S. G. Pyne, B. Dikic, C. L. L. Chai, P. A. Gordon, B. W. Skelton, M. J. Tozer and A. H. White, *Aus. J. Chem.*, 1993, **46**, 1425. For access to the opposite enantiomer of methyleneoxazolidinone, see: A. Sutherland and J. C. Vederas, *Chem. Commun.*, 2002, 224.

12 R. M. Suarez, J. P. Sestelo and L. A. Sarandeses, *Org. Biomol. Chem.*, 2004, **2**, 3584.

13 T. Hayashi, M. Takahashi, Y. Takaya and M. Ogasawara, *J. Am. Chem. Soc.*, 2002, **124**, 5052; P. J. Zhao, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 1876.

14 J. D. Hargrave, J. C. Allen, G. Kociok-Köhn, G. Bish and C. G. Frost, *Angew. Chem., Int. Ed.*, 2010, **49**, 1825.