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New Proline–Oxazoline Ligands and Their Application in the Asymmetric Nozaki–Hiyama–Kishi Reaction

Gráinne C. Hargaden,[a] Helge Müller-Bunz,[a][‡] and and Patrick J. Guiry*[a]

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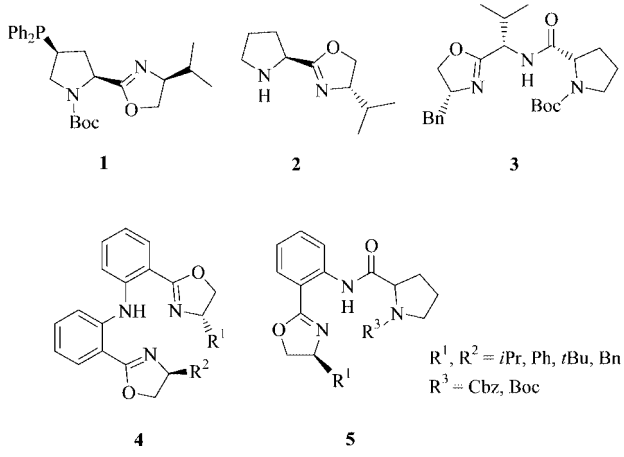
Sixteen members of a new ligand class incorporating an oxazoline ring linked by an amide bond to a chiral protected proline unit were prepared in a high-yielding four-step synthesis from readily available chiral amino alcohols and *N*-protected proline. The ligands were applied in the enantioselective Nozaki–Hiyama–Kishi allylation of benzaldehyde and gave enantioselectivities of up to 57%. Diastereomeric ligand pairs were prepared to determine the role of each chiral centre in enantioselection.

Introduction

Because of their ready availability, modular nature and applicability in a wide range of metal-catalysed transformations, compounds containing a chiral oxazoline ring have become one of the most successful, versatile and commonly used classes of ligands for asymmetric catalysis.[1] The majority of these ligands are synthesised from readily available chiral amino alcohols in a few high-yielding steps. Similarly, ligands derived from proline have been widely reported to induce high enantioselectivities in a range of organocatalytic processes.[2] Ligands that combine chiral oxazoline and proline units have resulted in good enantioselectivities, for example ligand **1**,[3] which has been applied in the asymmetric Heck reaction and allylic alkylation (Figure 1). We reported the application of ligand class **2** in the transfer hydrogenation of ketones and obtained enantioselectivities of up to 61%.[4] More recently, Sigman applied proline–oxazoline ligand **3** in the chromium-catalysed Nozaki–Hiyama–Kishi allylation of aldehydes, achieving an enantioselectivity of 94%.[5] This study was extended to the allylation of ketones with analogues of ligand **3** affording enantioselectivities up to 92%.[6]

We previously reported the synthesis of tridentate bis(oxazoline) ligands **4** and their application in the enantioselective Nozaki–Hiyama–Kishi (NHK) allylation, crotylation and methallylation of a range of aromatic and aliphatic aldehydes.[7–9] The ligands were prepared by means of a palladium-catalysed aryl amination between the corresponding anilino–oxazoline and bromo–oxazoline. This convergent synthesis allowed the synthesis of both symmetric and nonsymmetric ligands. The optimum enantioselectivity in all three NHK processes was obtained utilising the non C_2-symmetric ligand with *t*Bu/Bn-substituted oxazolines, affording excellent enantioselectivities, for example, 99.5% in the methallylation of benzaldehyde. We wished to further investigate non C_2-symmetric ligands and therefore designed ligand class **5**, which incorporates the anilino–oxazoline unit used in the preparation of **4** linked by an amide bond to the structurally rigid proline unit.



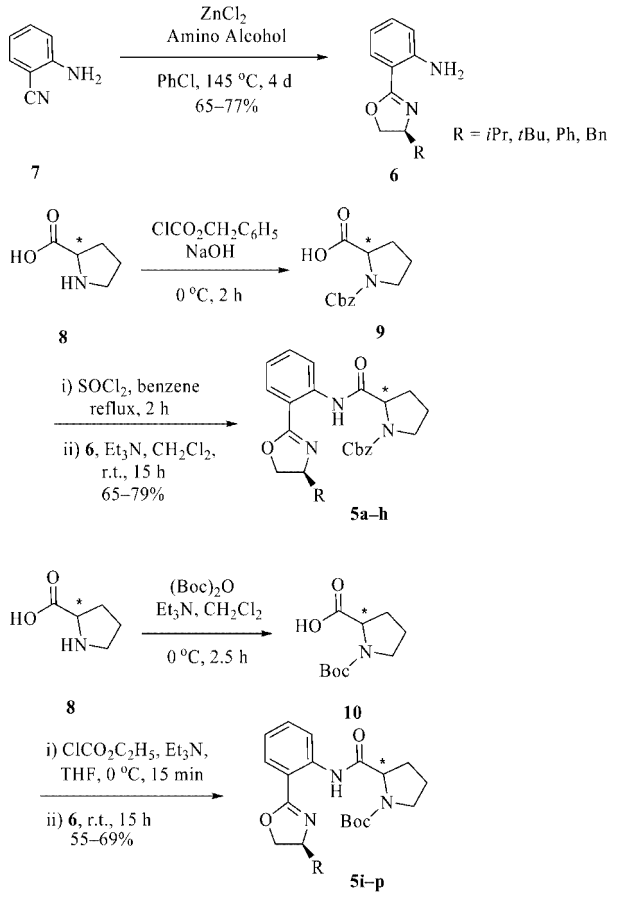
1 **2** **3** **4** **5**

Figure 1. Selected examples of oxazoline ligands.

Results and Discussion

We envisaged that ligands **5** could be prepared by means of a four-step synthesis from readily available chiral amino alcohols and proline (Scheme 1).

[a] Centre for Synthesis and Chemical Biology, Conway Institute of Biomolecular and Biomedical Research, School of Chemistry and Chemical Biology, University College
Dublin, Belfield, Dublin 4, Ireland
Fax: +353-1-7162501
E-mail: p.guiry@ucd.ie
[‡] Correspondence concerning single-crystal X-ray analyses should be directed to this author E-mail: helge.muellerbunz-@ucd.ie).



Scheme 1.

Proline was protected as either the *N*-carbobenzyloxy (Cbz) or *tert*-butoxycarbonyl (Boc) under standard conditions in excellent yields (86–96%).[10,11] Anilino–oxazoline **6** was prepared by the reaction of anthranilonitrile (**7**) with the corresponding chiral amino alcohol in the presence of $ZnCl_2$ in yields of 65–77%.[12] This is a shorter and higher yielding synthesis of **6** than our previous approach, which involved ring-opening of isatoic anhydride followed by DAST-promoted cyclisation.[7]

The protected proline was activated towards nucleophilic attack using either thionyl chloride or ethyl chloroformate and then reacted without purification with anilino–oxazoline **6** in the presence of Et_3N to provide desired ligands **5** in good-to-high yields (55–79%). Due to the presence of two chiral centres in the ligands, we prepared diastereomers to examine the effect of matched and mismatched chiral centres on enantioselection. Sixteen ligands were prepared in total, eight from (*S*)-proline and (*S*)-oxazoline (**5a**–**d**, **5i**–**l**) and eight from (*S*)-proline and (*S*)-oxazoline (**5e**–**h**, **5m**–**p**) (Figure 2).

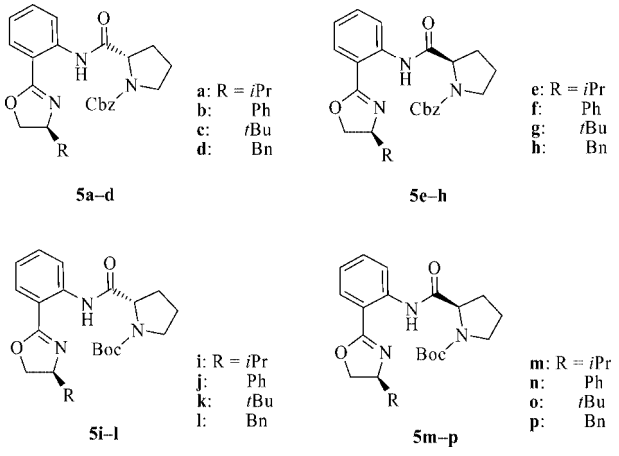


Figure 2. Ligands prepared and applied in the present study.

NMR Analysis

The ^1H and ^{13}C NMR spectra of ligands **5** confirmed that these ligands exist as rotamers, caused by hindered rotation of the proline protecting group. For example, the ^1H NMR ($CDCl_3$) spectrum of **5a** (Figure 3) shows a 2:1 mixture at –20 °C with the N-H peaks appearing as two distinct peaks at δ = 12.66 ppm and 12.62 ppm, respectively. On warming by 10 °C intervals, these peaks fully coalesced at 30 °C with a single resonance at δ = 12.44 ppm. The free energies of activation for rotation ($\Delta G^{\ddagger}$) calculated for ligands **5a**–**d** are: **5a** 60.58 kJ/mol, **5b** 62.78 kJ/mol, **5c** 65.47 kJ/mol, and **5d** 67.05 kJ/mol.[13] A similar coalescence was observed in the ^{13}C NMR spectrum where heating to 50 °C resulted in a single set of peaks.

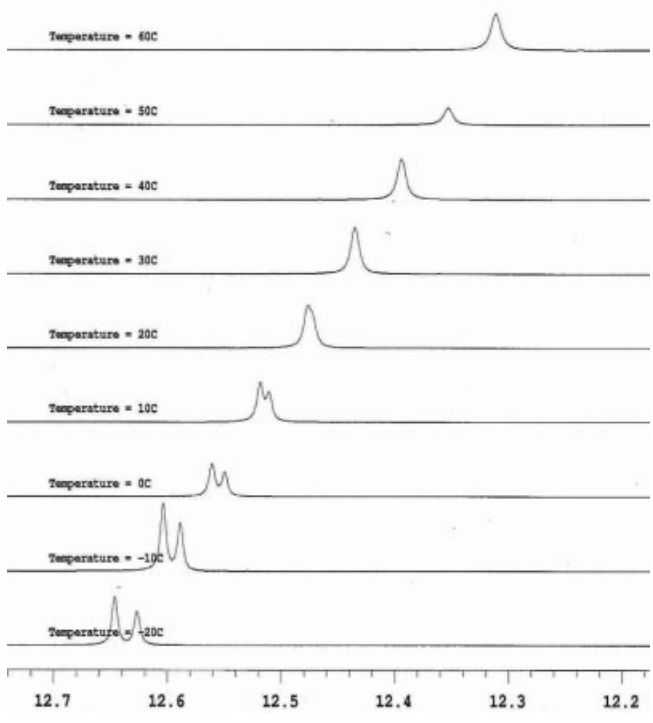


Figure 3. Chemical shift (ppm) of NH resonance in the ^1H NMR spectrum (600 MHz, $CDCl_3$) of **5a** at –20 °C to +60 °C.

X-ray Analysis

Ligands **5b** and **5g** were amenable to structure characterisation by X-ray crystallography as they were isolated as white needles from Et_2O (Figure 4).

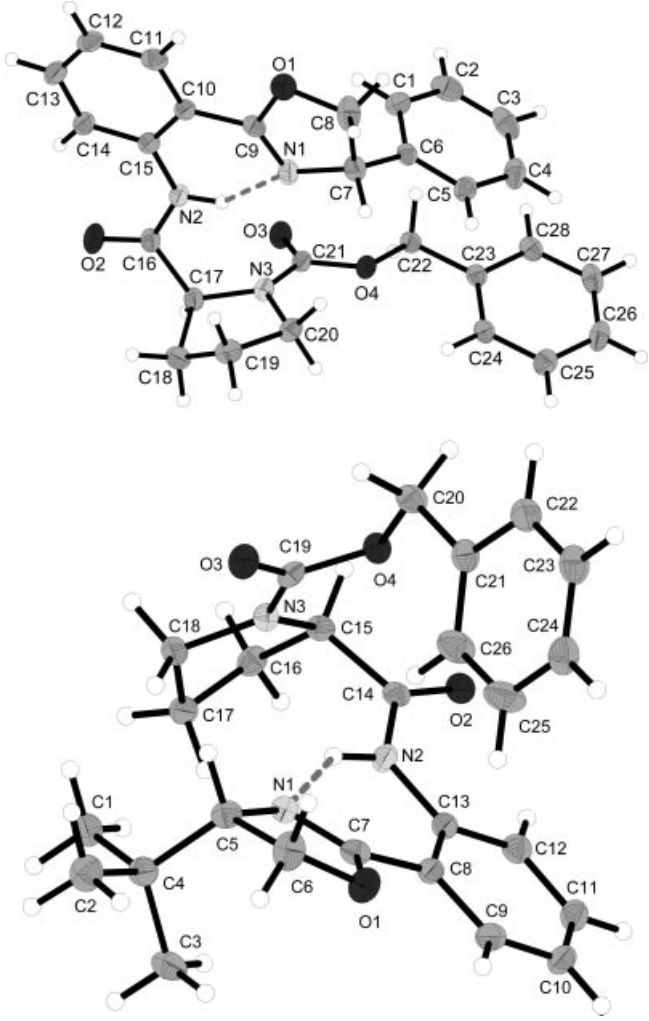


Figure 4. X-ray structures of **5b** (top) and **5g** (bottom).

In ligand **5b**, the H···N distance is 1.92 Å and the N(H)···N distance is 2.691(2) Å. The N(H)···N angle is 142(2)°. In contrast, for ligand **5g**, the H···N distance is 2.05 Å and the N(H)···N distance is 2.767(2) Å. The N(H)···N angle is 137(2)°.

Application in Catalysis: The Nozaki–Hiyama–Kishi Reaction

The Nozaki–Hiyama–Kishi reaction was first reported in the late 1970s and has proven to be a highly versatile procedure for the formation of C–C bonds involving the nucleophilic addition to carbonyl compounds of intermediate organochromium(III) reagents. These reagents are typically generated in situ from the insertion of chromium(II) species into allyl, alkenyl, alkynyl, propargyl and aryl halides or sulfonates.[14] A number of unique and important features, including pronounced chemoselectivity for reactions with aldehydes in the presence of ketones and an unprecedented compatibility with numerous functional groups in both reaction partners, has led to the reaction being utilised in the synthesis of many complex natural products. Two such examples are the total synthesis of palytoxin and halichondrin B, which both involve extensive use of chromium additions.[15]

To date there has been a limited range of ligand classes applied to the enantioselective process, with the most promising examples emerging from the groups of Sigman (**3**),[5] Cozzi and Umani-Ronchi (**11**),[16] Nakada (**12**, **13**),[17] Berkessel (**14**),[18] Kishi (**15**)[19] and ourselves (**4**)[8,9] (Figure 5). Our new ligand class **5** was applied in the chromium-catalysed reaction of allyl bromide with benzaldehyde (Table 1).

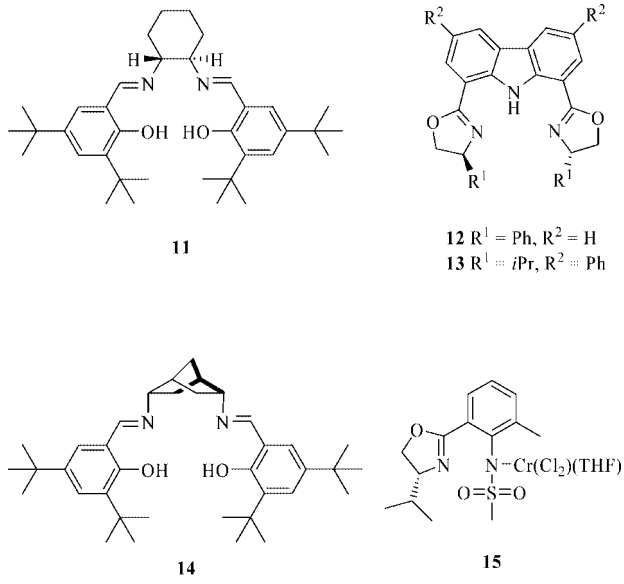


Figure 5. Selected examples of ligands applied in NHK to date.

Our previous studies showed that the optimal reaction conditions for allylation require THF/acetonitrile (7:1) as the solvent and *N*,*N*-diisopropylethylamine as the base. The reactions proceeded cleanly under these conditions with high conversions after 16 h at room temperature (Table 1).

Of Cbz-protected ligands **5a**–**h**, the highest enantioselectivity of 57% (*S*) was obtained with complete conversions and high isolated yield using ligand **5f**, derived from (*R*)-proline and the phenyl-substituted oxazoline. Diastereomeric ligand **5b** led to both a reversal and a lowering of the enantioselectivity to 32% (*R*). For ligands derived from both (*R*)- and (*S*)-proline, benzyl-substituted oxazoline ligands **5d** and **5h** provided the lowest enantioselectivity of 22% (*R*) and 18% (*S*), respectively.

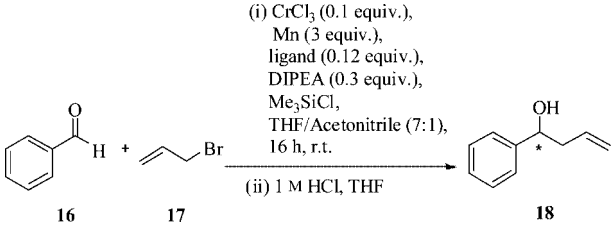
Boc-protected ligands **5i**–**p** generally displayed lower enantioselectivities and conversions, with the exception of **5l** and **5p** (Scheme 2). The optimum enantioselectivity of 54% (*R*) was obtained for ligand **5p** derived from (*R*)-proline, with benzyl-substituted oxazolines. Its diastereomeric ligand **5l** resulted in an enantioselectivity of 44% (*R*). In contrast to the results we obtained with ligand **2**, where the dominant element was the oxazoline chiral centre, it is more

Table 1. Results obtained in the enantioselective NHK reaction using ligands **5a**–**p**.

Entry	Ligand	Conversion[a] [%]	Yield[b] [%]	*ee*[c] (Configuration[d]) [%]
1	**5a**	100	93	38 (*S*)
2	**5b**	100	91	32 (*R*)
3	**5c**	85	80	23 (*R*)
4	**5d**	80	70	22 (*R*)
5	**5e**	100	91	36 (*R*)
6	**5f**	100	88	57 (*S*)
7	**5g**	100	87	30 (*R*)
8	**5h**	70	62	18 (*S*)
9	**5i**	65	60	10 (*S*)
10	**5j**	70	55	7 (*R*)
11	**5k**	75	69	16 (*S*)
12	**5l**	95	87	44 (*R*)
13	**5m**	70	60	11 (*R*)
14	**5n**	100	91	4 (*R*)
15	**5o**	90	83	10 (*R*)
16	**5p**	68	54	54 (*R*)

[a] Determined from the 300 MHz ^{1}H NMR spectrum of the crude silylated product. [b] Isolated yields of allylic alcohol **18**. [c] Determined by chiral HPLC analysis of alcohol product **18** using a Daicel Chiralcel OD column. [d] Determined by comparison of the chiral HPLC retention times with literature values.[20]

difficult to determine the key controlling factor in this new class of ligands. However, the highest enantioselectivity are those that follow the trend: (*R*)-proline gives the (*S*) product and (*S*)-proline gives the (*R*) product although the oxazoline substituent does also play a role, particularly when it is aromatic.



Scheme 2.Chromium-catalysed enantioselective allylation of benzaldehyde using ligands **5a**–**p**.

A potential model may be the binding of chromium to the oxazoline nitrogen atom, the carbonyl of the *N*-protecting group and the linking amide nitrogen atom. We believe that the carbonyl of the linking amide group does not orient itself in a conformation that allows it to bind, the presence of the hydrogen bond from the oxazoline to the amide appears to agree with this hypothesis. Subsequent binding of the aldehyde oxygen to chromium, and reaction in a head-to-tail fashion as proposed by Cozzi and Umani-Ronchi,[16] requires *si* face attack of the allyl fragment to afford the (*S*) product. We believe that the size of the *N*-protecting group is important, such that the phenyl unit of the aldehyde prefers to be orientated over the oxazoline ring when the group is large. When the 4-substituent on the oxazoline ring is phenyl-containing, as in **5f**, **5l** and **5p** the potential for π-stacking exists. This may explain the enhanced enantioselectivities observed in these cases.

Conclusions

We have prepared a new class of ligands **5** comprising chiral oxazoline and proline rings linked by an amide bond. These ligands were prepared in a high-yielding four-step synthesis from chiral proline and amino alcohols, and this route allows the preparation of a modular series of these ligands. Ligands **5** were used in the asymmetric allylation of benzaldehyde with **5f** resulting in complete conversion and enantioselectivity of 57% (*S*). This work adds to the limited number of ligand classes used in the NHK reaction, and the good enantioselectivities compare favourably to other reported results. Our ligand class **5** is currently being applied in other catalytic asymmetric processes, the results of which will be reported in due course.

Experimental Section

General Remarks: ^{1}H NMR (300, 400 and 600 MHz) and ^{13}C (100 and 150 MHz) spectra were recorded with Varian Oxford 300, 400 or 600 spectrometers at r.t. in $CDCl_3$ using tetramethylsilane as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. NMR spectra are reported for a mixture of two rotamers. Where two peaks are observed in the ^{13}C NMR spectra, * denotes the major peak when this can be assigned. HRMS were obtained using a Micromass/Waters LCT instrument. Elemental analyses were performed by Ms Anne Connolly, School of Chemistry and Chemical Biology, University College Dublin. Crystal data were collected with a Bruker SMART APEX CCD area detector diffractometer. A full sphere of the reciprocal space was scanned by ϕ–ω scans. Pseudoempirical absorption correction based on redundant reflections was performed by the program SADABS (X-1). The structures were solved by direct methods using SHELXS-97 (X-2) and refined by full-matrix least-squares on F^2 for all data using SHELXL-97 (X-3). Hydrogen atoms attached to nitrogen were located in the difference fourier map and allowed to refine freely. All other hydrogen atoms were added at calculated positions and refined using a riding model. Their isotropic temperature factors were fixed to 1.2 × (1.5 × for methyl groups) the equivalent isotropic displacement parameters of the carbon atom the H-atom is attached to. Anisotropic temperature factors were used for all non-hydrogen atoms. Friedel opposites were merged in the refinement.[21] Infrared spectra were recorded with a Perkin–Elmer Infrared FT spectrometer. Optical rotation values were measured with a Perkin–Elmer 343 polarimeter. All optical rotations were obtained at r.t. Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out on plastic sheets precoated with silica gel 60 F254 (Merck). Column chromatography separations were performed using Merck Kieselgel 60 (0.040–0.063 mm). HPLC analysis was performed with a LC 2010A machine equipped with a UV/Vis detector employing a Chiracel OD column from Daicel Chemical Industries. All reagents were purchased from Sigma–Aldrich and used as received. Solvents were dried immediately before use by distillation from standard drying agents. Anhydrous chlorobenzene was purchased from Sigma–Aldrich and used without further purification.

General Procedure for the Synthesis of 2-(*o*-Aminophenyl)oxazolines (6a–d): Anthranilonitrile **7** (1.29 g, 11 mmol) and the appropriate amino alcohol (11 mmol) was stirred at 60 °C in anhydrous chloro-

benzene (20 mL) for 15 min under an atmosphere of N_2. $ZnCl_2$ (1 M solution in Et_2O, 2.2 mmol, 2.2 mL) was added slowly, and the resulting mixture was heated at 145 °C for 4 d. The reaction mixture was allowed to cool, the solvent was removed in vacuo and the product was purified by flash column chromatography on silica gel (pentane/ethyl acetate, 3:1). All physical data was identical to that previously reported.[7]

General Procedure for the Synthesis of Cbz-Protected Ligands (5a–h): Cbz-protected proline **9** (0.80 g, 3.21 mmol) was dissolved in anhydrous benzene (7 mL) under an atmosphere of N_2. Thionyl chloride (0.43 mL, 1.8 equiv.) was added dropwise, and the resulting solution was heated at reflux for 2 h. The solvent was removed in vacuo to give the acid chloride as a yellow oil (yield: 99%). This was immediately dissolved in anhydrous dichloromethane (25 mL) under an atmosphere of N_2 and subsequently added dropwise to a solution of anilino–oxazoline **6** (1.1 equiv.) and Et_3N (1.1 equiv.) in anhydrous dichloromethane (10 mL) at 0 °C. The resulting cloudy solution was stirred at r.t. overnight. NH_4Cl (2 × 10 mL) was then added and the separated aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was removed in vacuo to give a thick yellow oil that was purified by flash chromatography on silica gel (pentane/ethyl acetate, 2:1) to yield the desired title compounds.

Benzyl (2*S*)-{2-[(4*S*)-Isopropyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5a): Yield: 0.97 g, 75%, colourless oil; R_f = 0.35 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = –9.7 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.66 [d, *J* = 6.7 Hz, 2 H, CH(CH_3)$_2$], 0.75 [d, *J* = 6.7 Hz, 1 H, CH(CH_3)$_2$], 0.84 [m, 3 H, CH(CH_3)$_2$], 1.76–1.80 and 1.88–1.97 [2 × m, 3 H, C*H*(CH$_3$)$_2$, pyr-H_2C(4)], 2.01–2.05 [m, 1 H, pyr-H_2C(3)], 2.11–2.19 [m, 1 H, pyr-H_2C(3)], 3.44 and 3.50 [2 × q, *J* = 8.3 Hz, 1 H, pyr-H_2C(5)], 3.62 [m, 1 H, pyr-H_2C(5)], 3.96 (q, *J* = 7.4 Hz, 1 H, CH_2O), 4.06 (m, 1 H, C*H*N), 4.14 and 4.19 (2 × t, *J* = 8.8 Hz, 1 H, CH_2O), 4.30 [m, 1 H, pyr-*H*C(2)], 4.94 and 5.03 [2 × d, *J* = 12.7 Hz, 1 H, CH_2Ph(Cbz)], 5.14 [s, 1 H, CH_2Ph(Cbz)], 6.93–7.02 [Ar-*H*C(3)], 7.08–7.27 [m, 5 H, Ar-*H*C(Cbz)], 7.33 [qn, *J* = 7.6 Hz, 1 H, Ar-*H*C(2)], 7.73 [t, *J* = 8.4 Hz, 1 H, Ar-*H*C(4)], 8.68 [d, *J* = 8.3 Hz, Ar-*H*C(1)], 12.43 [br. s, 1 H, N*H*] ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = [15.8*, 16.6] [CH(*C*H$_3$)$_2$], [17.7, 17.9*] [CH(*C*H$_3$)$_2$], [22.6*, 23.3] [*C*H(CH$_3$)$_2$], 29.7 [pyr-H_2*C*(3)], [30.5, 30.7] [pyr-H_2*C*(3), pyr-H_2*C*(4)], 31.3 [pyr-H_2*C*(4)], [46.0, 46.4*] [pyr-H_2*C*(5)], 52.4 [*C*H$_2$Ph(Cbz)], [61.2*, 61.4] [pyr-H*C*(2)], [65.8*, 66.0] [*C*H$_2$Ph(Cbz)], [66.7*, 67.3] [*C*H$_2$O], [71.2*, 71.3] (*C*HN), [112.4, 112.5*] [Ar-*C*(5)], [118.6*, 118.9] [Ar-H*C*(1)], [121.3, 121.4*] [Ar-H*C*(3)], [{126.4*, 126.5}, {126.7*, 126.8}, {127.1*, 127.4}] [Ar-H*C*(Cbz)], [128.0, 128.1*] [Ar-H*C*(4)], 131.3 [Ar-H*C*(2)], [135.4*, 135.6] [Ar-*C*(6)], [138.6*, 138.7] [*ipso*-Ph(Cbz)], [153.5*, 154.1] [*C*=O(Cbz)], [162.1*, 162.3] [*C*=N], [170.4, 170.9*] [*C*=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2960, 1710, 1637, 1533, 1448 cm^{-1}. HRMS (ES+): calcd. for $C_{25}H_{30}N_3O_4$ [M + H]$^+$ 436.2238; found 436.2233. $C_{25}H_{29}N_3O_4$ (436.22): calcd. C 68.95, H 6.71, N 9.65; found C 68.64, H 6.75, N 9.68.

Benzyl (2*S*)-{4,5-Dihydro-2-[(4*S*)-phenyloxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5b): Yield: 0.93g, 67%, white solid; m.p. 124–126 °C; R_f = 0.29 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +71.2 (*c* = 0.67, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.72–1.80 [m, 1 H, pyr-H_2C(4)], 1.82–1.97 [m, 1 H, pyr-H_2C(4)], 2.02–2.11 [m, 2 H, pyr-H_2C(3)], 3.29–3.36 and 3.38–3.47 [2 × m, 2 H, pyr-H_2C(5)], 4.09 (t, *J* = 7.9 Hz, 1 H, CH_2O), 4.25 [t, *J* = 6.0 Hz, 1 H, pyr-*H*C(2)], 4.30–4.98 [3 × m, 3 H, CH_2O, CH_2Ph(Cbz)], 5.29 and 5.39 (2 × t, *J* = 8.8 Hz, 1 H, C*H*N), 6.99–7.07 [m, 1 H, Ar-*H*C(3)], 7.10–7.29 [m, 10 H, Ar-*H*C(Ph), Ar-*H*C(Cbz)], 7.37–7.44 [m, 1 H, Ar-*H*C(2)], 7.83–7.86 [t, *J* = 8.6 Hz, 1 H, Ar-*H*C(4)], 8.71–8.74 [t, *J* = 7.05 Hz, 1 H, Ar-*H*C(1)], 12.35 and 12.38 (2 × br. s, 1 H, N*H*, ratio 1.3:1) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = [23.4*, 24.2] [pyr-H_2*C*(4)], [30.5, 31.4*] [pyr-H_2*C*(3)], [46.8, 47.2*] [pyr-H_2*C*(5)], [62.1*, 62.4] [pyr-H*C*(2)], [66.5, 66.6*] [*C*H$_2$Ph(Cbz)], [69.9, 70.0*] (*C*HN), 73.6 (*C*H$_2$O), 113.2 [Ar-*C*(5)], [119.7*, 120.1] [Ar-H*C*(1)], 122.5 [Ar-H*C*(3)], [{126.3, 126.5*}, {127.5*,127.6}, {127.7}, {128.0*,128.2}, {128.7}] [Ar-H*C*(Ph), Ar-H*C*(Cbz)], [129.3, 129.4*] [Ar-H*C*(4)], 132.7 [Ar-H*C*(2)], [136.6*, 136.8] [Ar-*C*(6)], [139.7*, 139.8] [*ipso*-Ph(Cbz)], [141.7*, 142.0] (*ipso*-Ph), [154.3*, 155.2] [*C*=O(Cbz)], [164.6, 164.9] (*C*=N), [171.7, 172.1*] [*C*=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3470, 1720, 1635, 1533, 1448 cm^{-1}. HRMS (ES+): calcd. for $C_{28}H_{27}N_3O_4$ [M + H]$^+$ 470.2082; found 470.2090. $C_{28}H_{27}N_3O_4$ (470.20): calcd. C 71.62, H 5.80, N 8.95; found C 71.52, H 5.82, N 8.98.

Benzyl (2*S*)-{2-[(4*S*)-*tert*-Butyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5c): Yield: 1.06 g, 78%, white solid; m.p. 76–78 °C; R_f = 0.44 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = –4.0 (*c* = 0.65, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.85 [2 × s, 9 H, C(CH_3)$_3$], 1.81–1.83 [m, 1 H, pyr-H_2C(4)], 1.96–2.06 [m, 2 H, pyr-H_2C(3), pyr-H_2C(4)], 2.12–2.21 [m, 1 H, pyr-H_2C(3)], 3.44–3.51 and 3.52–3.55 [2 × m, 1 H, pyr-H_2C(5)], 3.64–3.68 [m, 1 H, pyr-H_2C(5)], 3.90–4.16 (m, 3 H, C*H*N, CH_2O), 4.20–4.37 [m, 1 H, pyr-*H*C(2)], 4.97 [d, *J* = 12.3 Hz, 1 H, CH_2Ph(Cbz)], 5.07 and 5.15 [2 × d, *J* = 12.33 Hz, 1 H, CH_2Ph(Cbz)], 6.99–7.02 [m, 1 H, Ar-*H*C(3)], 7.06–7.30 [m, 5 H, Ar-*H*C(Cbz)], 7.35–7.39 [m, 1 H, Ar-*H*C(2)], 7.74 [d, *J* = 7.9 Hz, 1 H, Ar-*H*C(4)], 8.06 [dd, *J* = 35.5, 8.22 Hz, 1 H, Ar-*H*C(1)], 12.31 and 12.47 (2 × br. s, 1 H, N*H*, ratio 1.1:1) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = [23.7*, 24.3] [pyr-H_2*C*(4)], 23.85 [C(*C*H$_3$)$_3$], [30.8, 31.7*] [pyr-H_2*C*(3)], 33.7 [*C*(CH$_3$)$_3$], [46.8, 47.4*] [pyr-H_2*C*(5)], [61.9*, 62.0] [pyr-H*C*(2)], 67.3 [*C*H$_2$Ph(Cbz)], 67.0 (*C*H$_2$O), 76.0 (*C*HN), [113.3, 113.4*] [Ar-*C*(5)], [119.8*, 120.0] [Ar-H*C*(1)], [122.3, 122.4*] [Ar-H*C*(3)], [127.5, {127.8. 127.9}, {128.0, 128.4}] [Ar-H*C*(Cbz)], [129.0, 129.1*] [Ar-H*C*(4)], 132.0 [Ar-H*C*(2)], [136.5*, 136.8] [Ar-*C*(6)], [139.6*, 139.8] [*ipso*-Ph(Cbz)], [154.5*, 155.0] [*C*=O(Cbz)], [163.3*, 163.4] (*C*=N), [171.2, 171.6*] [*C*=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2962, 1710, 1637, 1536, 1448, 1415 cm^{-1}. HRMS (ES+): calcd. for $C_{26}H_{31}N_3O_4$ [M + H]$^+$ 450.2395; found 450.2408. $C_{26}H_{31}N_3O_4$ (450.23): calcd. C 69.47, H 6.95, N 9.35; found C 69.51, H 6.99, N 9.50.

Benzyl (2*S*)-{2-[(4*S*)-Benzyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5d): Yield: 1.03 g, 71%, white solid; m.p. 55–60 °C; R_f = 0.23 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +10.9 (*c* = 0.69, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.81–2.01 [m, 2 H, pyr-H_2C(4)], 2.05–2.22 [m, 2 H, pyr-H_2C(3)], 2.39 and 2.62 (2 × dd, *J* = 13.8, 9 Hz and *J* = 13.8, 8.5 Hz, 1 H, *CH*$_2$Ph, ratio 2.6:1), 3.07 and 3.17 (2 × dd, *J* = 13.8, 4.7 Hz and *J* = 14.0, 4.5 Hz, 1 H, *CH*$_2$Ph, ratio 2.6:1), 3.50–3.69 [m, 2 H, pyr-H_2C(5)], 3.95–4.21 (m, 2 H, CH_2O), 4.27 and 4.33 [dd, *J* = 8.5, 3.2 Hz and m, 1 H, pyr-*H*C(2), ratio 2.6:1], 4.42 and 4.57 (2 × m, 1 H, C*H*N, ratio 2.6:1), 4.93 and 4.96 [s and d, *J* = 12.3 Hz, 1 H, CH_2Ph(Cbz), ratio 2.6:1], 5.09 and 5.16 [2 × d, *J* = 12.5 Hz and *J* = 12.3 Hz, 1 H, CH_2Ph(Cbz), ratio 2.6:1], 6.97–7.03 [m, 1 H, Ar-*H*C(3)], 7.05–7.21 [m, 10 H, Ar-*H*C(Bn), Ar-HC(Cbz)], 7.36–7.41 [m, 1 H, Ar-*H*C(2)], 7.74 [d, *J* = 7.28, 1 H, Ar-*H*C(4)], 8.76 and 8.74 [2 × d, *J* = 8.5 Hz and *J* = 8.5 Hz, 1 H, Ar-*H*C(1), ratio 2.6:1], 12.41 and 12.55 (2 × br. s, 1 H, N*H*, ratio 1:3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = [22.6*, 23.4] [pyr-H_2*C*(4)], [29.7*, 30.7] [pyr-H_2*C*(3)], [40.0*, 40.5] (*C*H$_2$Ph), [46.1, 46.5*] [pyr-H_2*C*(5)], [61.3*, 61.6] [pyr-H*C*(2)], [65.9*, 66.2] [*C*H$_2$Ph(Cbz)], [66.5, 66.7*]

(*C*HN), 69.3 (*C*H$_2$O), 112.4 [Ar-*C*(5)], [118.5*, 118.9] [Ar-H*C*(1)], [121.4, 121.5*] [Ar-H*C*(3)], [{125.4*, 125.5}, {126.6, 126.7*}, {126.9, 127.0*}, {127.1*, 127.4}, {127.5*, 127.6}] [Ar-H*C*(Bn), Ar-H*C*(Cbz)], [128.0, 128.1*] [Ar-H*C*(4)], 131.6 [Ar-H*C*(2)], 135.6 [Ar-*C*(6)], [136.4, 136.9*] [*ipso*-Ph(Cbz)], [138.6*, 138.7] (*ipso*-Ph), 153.7 [*C*=O(Cbz)], 162.7 (*C*=N), [170.7, 171, 2*] [*C*=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3411, 1706, 1633, 1533, 1448 cm^{-1}. HRMS (ES+): calcd. for $C_{29}H_{29}N_3O_4$ [M + H]$^+$ 484.2238; found 484.2259. $C_{29}H_{29}N_3O_4$ (484.22): calcd. C 72.03, H 6.04, N 8.69; found C 71.74, H 6.05, N 8.46.

Benzyl (2*R*)-{2-[(4*S*)-Isopropyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5e): Yield: 1.02 g, 79%, white solid; m.p. 69–70 °C; R_f = 0.35 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +103.4 (*c* = 0.79, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.70 [d, *J* = 6.7 Hz, 3 H, CH(CH_3)$_2$], 0.83 [d, *J* = 6.8 Hz, 3 H, CH(CH_3)$_2$], 1.67–1.90 [m, 3 H, CH(CH_3)$_2$, pyr-H_2C(4)], 2.16–2.33 [m, 2 H, pyr-H_2C(3)], 3.44–3.62 [m, 2 H, pyr-H_2C(5)], 3.93–4.13 (m, 3 H, C*H*N, CH$_2$O), 4.30–4.41 [m, 1 H, pyr-H*C*(2)], 4.83 [d, *J* = 12.5 Hz, 2 H, CH_2Ph(Cbz)], 5.11 [t, *J* = 9.9 Hz, 2 H, CH_2Ph(Cbz)], 6.91–7.03 [m, 4 H, Ar-H*C*(3), Ar-H*C*(Cbz)], 7.18–7.73 [m, 3 H, Ar-H*C*(2), Ar-H*C*(Cbz)], 7.72 [d, *J* = 7.3 Hz, 1 H, Ar-H*C*(4)], 8.73 [dd, *J* = 14.9, 8.7 Hz, 1 H, Ar-H*C*(1)], 12.42 and 12.49 (2 × br. s, 1 H, N*H*, ratio 1:2.2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [15.6*, 15.8] [CH(*C*H$_3$)$_2$], 18.0 [CH(*C*H$_3$)$_2$], [22.6*, 23.3] [*C*H(CH$_3$)$_2$], 29.7 [pyr-H$_2$*C*(3)], 30.5 [pyr-H$_2$*C*(3)], 30.7 [pyr-H$_2$*C*(4)], [46.0, 46.5*] [pyr-H$_2$*C*(5)], [61.2*, 61.4] [pyr-H*C*(2)], [65.8*, 66.1] [*C*H$_2$Ph(Cbz)], [66.4*, 66.6] (*C*H$_2$O), [70.6*, 71.0] (*C*HN), [112.4, 112.8*] [Ar-*C*(5)], [118.6*, 118.7] [Ar-H*C*(1)], [121.3, 121.4*], [Ar-H*C*(3)], [{126.6*, 127.0}, {127.4, 128.0*}, {127.1*, 127.4}], [Ar-H*C*(Cbz)], [131.2*, 131.3] [Ar-H*C*(4)], [133.4*, 133.6] [Ar-*C*(6)], [138.3*, 138.6] [*ipso*-Ph(Cbz)], [153.6*, 154.2] [*C*=O(Cbz)], [161.8*, 162.3] (*C*=N), [170.5, 171.9*] [*C*=O-(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2962, 2704, 1637, 1585, 1448, 1407 cm^{-1}. HRMS (ES+): calcd. for $C_{25}H_{29}N_3O_4$ [M + H]$^+$ 436.2238; found 436.2221. $C_{25}H_{29}N_3O_4$ (436.22): calcd. C 68.95, H 6.71, N 9.65; found C 68.93, H 6.74, N 9.55.

Benzyl (2*R*)-{4,5-Dihydro-2-[(4*S*)-Phenyloxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5f): Yield: 0.91 g, 65%, white solid; m.p. 58–60 °C; R_f = 0.29 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +134.6 (*c* = 0.79, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.44–1.59 [m, 1 H, pyr-H_2C(4)], 1.96–2.17 [m, 2 H, pyr-H_2C(3)], 2.80–3.08 [m, 2 H, pyr-H_2C(5)], 4.03 (m, 1 H, CH_2O), 4.23–4.45 [m, 2 H, CH_2O, pyr-H*C*(2)], 4.80 [m, 1 H, CH_2Ph(Cbz)], 4.97–5.21 [m, 2 H, C*H*N, CH_2Ph(Cbz)], 6.92–7.46 [m, 11 H, Ar-H*C*(2), Ar-H*C*(3), Ar-H*C*(Ph), Ar-H*C*(Cbz)], 7.82 [m, 1 H, Ar-H*C*(4)], 8.78 [dd, *J* = 29.9, 8.4 Hz, 1 H, Ar-H*C*(1)], 12.57 and 12.71 (2 × br. s, 1 H, N*H*, ratio 3:1) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [22.3*, 23.0] [pyr-H$_2$*C*(4)], [29.6, 30.6*] [pyr-H$_2$*C*(3)], [45.5, 45.8*] [pyr-H$_2$*C*(5)], [61.3*, 61.6] [pyr-H*C*(2)], [65.7*, 65.9] [*C*H$_2$Ph(Cbz)], [68.5*, 68.8] (*C*HN), [72.4*, 72.5] (*C*H$_2$O), [112.0, 112.3*] [Ar-C(5)], [118.5*, 118.7] [Ar-HC(1)], 121.5 [Ar-HC(3)], {125.6, 125.9*}, {126.6}, {126.7, 126.8*}, {126.9, 127.1*}, {127.3}, {127.4, 127.5*} [Ar-HC(Ph), Ar-HC(CBZ)], [128.2*, 128.3] [Ar-HC(4)], [131.7*, 131.8] [Ar-HC(2)], 135.6 [Ar-C(6)], [138.6*, 138.9] [*ipso*-Ph(Cbz)], [141.0, 141.1*] (*ipso*-Ph), [153.4*, 154.3] [C=O(Cbz)], 163.0 (C=N), [171.0, 171.5*] [C=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3401, 1637, 1533, 1448, 1403 cm^{-1}. HRMS (ES+): calcd. for $C_{28}H_{27}N_3O_4$ [M + H]$^+$ 470.2082; found 470.2061. $C_{28}H_{27}N_3O_4$ (470.20): calcd. C 71.62, H 5.80, N 8.95; found C 70.42, H 5.86, N 8.61.

Benzyl (2*R*)-{2-[(4*S*)-*tert*-Butyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5g): Yield: 1.03 g, 76%, white solid; m.p. 84–85 °C; R_f = 0.44 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +96.4 (*c* = 0.78, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.77 [2 × s, 9 H, C(CH_3)$_3$], 1.73–1.92 [m, 2 H, pyr-H_2C(4)], 2.05–2.21 [m, 2 H, pyr-H_2C(3)], 3.46–3.60 [m, 2 H, pyr-H_2C(5)], 3.88–4.05 [m, 3 H, pyr-H*C*(2), CH_2O], 4.18–4.22 (m, 1 H, C*H*N), 4.80–5.04 [m, 1 H, CH_2Ph(Cbz)], 5.07 and 5.15 [2 × d, *J* = 12.3 Hz, 1 H, CH_2Ph(Cbz)], 6.83–7.33 [m, 7 H, Ar-H*C*(2), Ar-H*C*(3), Ar-H*C*(Cbz)], 7.66 [d, *J* = 7.3 Hz, 1 H, Ar-H*C*(4)], 8.59 [d, *J* = 8.4 Hz, 1 H, Ar-H*C*(1)], 12.18 and 12.26 (2 × br. s, 1 H, N*H*, ratio 1.1:1) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [24.0*, 24.7] [pyr-H$_2$*C*(4)], [25.9*, 26.0] [C(*C*H$_3$)$_3$], [31.2, 32.0*] [pyr-H$_2$*C*(3)], 34.2 [*C*(CH$_3$)$_3$], [46.5, 47.8*] [pyr-H$_2$*C*(5)], 62.4 [pyr-H*C*(2)], [67.1, 67.6*] [*C*H$_2$Ph(Cbz)], 67.0 (*C*H$_2$O), 75.9 (*C*HN), [111.8, 112.0*] [Ar-*C*(5)], 120.2 [Ar-H*C*(1)], 122.7 [Ar-H*C*(3)], [127.5, {127.8. 127.9}, {128.0, 128.4}] [Ar-H*C*(Cbz)], [129.0, 129.1*] [Ar-H5(4)], 132.0 [Ar-H*C*(2)], [136.5*, 136.8] [Ar-*C*(6)], [139.6*, 139.8] [*ipso*-Ph(Cbz)], [154.5*, 155.0] [*C*=O(Cbz)], [163.3*, 163.4] (*C*=N), [171.2, 171.6*] [*C*=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 2967, 1639, 1535, 1448, 1411 cm^{-1}. HRMS (ES+): calcd. for $C_{26}H_{31}N_3O_4$ [M + H]$^+$ 450.2395; found 450.2380. $C_{26}H_{31}N_3O_4$ (450.23): calcd. C 69.47, H 6.95, N 9.35; found C 69.79, H 7.01, N 9.48.

Benzyl (2*R*)-{2-[(4*S*)-Benzyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5h): Yield: 1.05 g, 73%, white solid; m.p. 73–75 °C; R_f = 0.23 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +112.8 (*c* = 0.78, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.19–1.25 [m, 2 H, pyr-H_2C(4)], 2.13–2.30 [m, 2 H, pyr-H_2C(3)], 2.59 and 2.69 [dd, *J* = 13.3, 8.8 Hz and app t, *J* = 6.69 Hz, 1 H, C(5)Ph, ratio 2:1], 2.97 and 3.13 (2 × dd, *J* = 14.0, 8.1 Hz and *J* = 13.1, 5.0 Hz, 1 H, CH_2Ph, ratio 2:1), 3.58 [m, 2 H, pyr-H_2C(5)], 3.89–4.04 (m, 2 H, CH_2O), 4.25–4.37 [m, 2 H, C*H*N, pyr-H*C*(2)], 4.96 and 5.23 [2 × d, *J* = 12.4 Hz and *J* = 12.3 Hz, 2 H, CH_2Ph(Cbz), ratio 3:1], 6.98–7.50 [m, 12 H, Ar-H*C*(3), Ar-H*C*(2), Ar-H*C*(Bn), Ar-H*C*(Cbz)], 7.79 [d, *J* = 7.8 Hz, Ar-H*C*(4)], 8.83 [dd, *J* = 14.0, 8.6 Hz, 1 H, Ar-H*C*(1)], 12.47 and 12.67 (2 × br. s, 1 H, N*H*, ratio 1:2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [22.6*, 23.4] [pyr-H$_2$*C*(4)], [29.6*, 30.7] [pyr-H$_2$*C*(3)], [40.5*, 40.8] (*C*H$_2$Ph), [46.0, 46.4*] [pyr-H$_2$*C*(5)], [61.2*, 61.5] [pyr-H$_2$*C*(2)], [65.8*, 66.1] [*C*H$_2$Ph(Cbz)], [66.4*, 66.6] (*C*HN), [69.3, 69.4*] (*C*H$_2$O), [112.3, 112.6*] [Ar-*C*(5)], [118.5*, 118.6] [Ar-H*C*(1)], [121.4, 121.5*] [Ar-H*C*(3)], [{125.4*, 125.5}, {126.6, 126.7*},{127.0*, 127.1},{127.5*, 127.6}, {128.0*, 128.1}] [Ar-H*C*(Bn), Ar-H*C*(Cbz)], 128.2 [Ar-H*C*(4)], [131.4*, 131.6] [Ar-H*C*(2)], [135.5*, 135.6] [Ar-*C*(6)], [136.5, 136.8*] [*ipso*-Ph(Cbz)], [138.3*, 138.6] (*ipso*-Ph), [153.7*, 154.3] [*C*=O(Cbz)], [162.3*, 162.9] (*C*=N), [170.7, 171, 2*] [*C*=O-(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3027, 1693, 1635, 1535, 1448, 1407 cm^{-1}. HRMS (ES+): calcd. for $C_{29}H_{29}N_3O_4$ [M + H]$^+$ 484.2238; found 484.2229. $C_{29}H_{29}N_3O_4$ (484.22): calcd. C 72.03, H 6.04, N 8.69; found C 71.85, H 6.07, N 8.58.

General Procedure for the Synthesis of Boc-Protected Ligands (5i–p): A solution of Boc-protected proline **10** (215mg, 1 mmol) in THF (2.5 mL) and Et$_3$N (1 mmol) was cooled to 0 °C. Ethyl chloroformate (0.75 mmol) was added dropwise over 15 min, and the resulting white mixture was stirred at 0 °C for 30 min. A solution of anilino–oxazoline **6** (1 mmol) in THF (0.5 mL) was added over 10 min at 0 °C. The reaction was stirred at r.t. overnight, after which time the mixture was filtered and the white residue was washed with ethyl acetate. The solvent was removed in vacuo. The resulting oil was purified by column chromatography on silica gel (pentane/ethyl acetate, 2:1) to afford the title compounds.

***tert*-Butyl (2*S*)-{2-[(4*S*)-Isopropyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5i):** Yield: 0.25g, 62%, white solid; m.p. 109–111 °C; R_f = 0.54 (pentane/ethyl acetate, 2:1). $[\alpha]_D$

= –2.0 (c = 0.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.78 [d, J = 6.3 Hz, 2 H, $CH(CH_3)_2$], 0.86 [d, J = 6.3 Hz, 1 H, $CH(CH_3)_2$], 0.93 [d, J = 6.5 Hz, 3 H, $CH(CH_3)_2$], 1.18, 1.28, 1.40 and 1.50 [4 × s, 9 H, $C(CH_3)_3$], 1.82–2.25 [m, 5 H, $CH(CH_3)_2$, pyr-H_2C(3),pyr-H_2C(4)], 1.35 and 1.40 [2 × s, 9 H, $C(CH_3)_3$], 1.80–2.24 [m, 4 H, pyr-H_2C(3),pyr-H_2C(4)], 3.39–3.59 [m, 2 H, pyr-H_2C(5)], 4.03–4.34 [m, 4 H, pyr-HC(2), OCH_2, CHN], 7.01 [t, J = 7.5 Hz, 1 H, Ar-HC(3)], 7.40 [q, J = 7.5 Hz, 1 H, Ar-HC(2)], 7.78 [d, J = 8.0 Hz, 1 H, Ar-HC(4)], 8.70 [app t, J = 12.0 Hz, Ar-HC(1)], 12.34 and 12.40 (2 × br. s, 1 H, NH, ratio 1:2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [15.8*, 17.0] [$CH(CH_3)_2$], [17.8, 18.0*] [$CH(CH_3)_2$], [21.6, 22.8*] [$CH(CH_3)_2$], [27.2*, 27.4] [pyr-H_2C(4), pyr-H_2C(3)], [28.6, 29.8*] [$C(CH_3)_3$], [30.6*, 30.8] [pyr-H_2C(4)], [pyr-H_2C(3)], [45.8*, 46.2] [pyr-H_2C(5)], [60.9, 61.6*] [pyr-HC(2)], [66.7*, 67.4] (CH_2O), 75.7 (CHN), [78.7, 78.9*] [$C(CH_3)_3$], 112.3 [Ar-C(5)], [118.5*, 119.1] [Ar-C(1)], [121.2, 121.3*] [Ar-C(3)], [127.9, 128.2*] [Ar-C(4)], [131.3, 131.4*] [Ar-C(2)], [138.7*, 138.8] [Ar-C(6)], [153.0*, 153.7] [C=O(Boc)], [162.1*, 162.3] (C=N), 171.6 [C=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3436, 3321, 2968, 1680, 1644, 1586, 1518, 1449, 1391 cm^{-1}. HRMS (ES+): calcd. for $C_{22}H_{31}N_3O_4$ [M + H]$^+$ 402.2395; found 402.2376. $C_{22}H_{31}N_3O_4$ (402.23): calcd. C 65.81, H 7.78, N 10.47; found C 65.70, H 7.75, N 10.26.

***tert*-Butyl (2*S*)-{4,5-Dihydro-2-[(4*S*)-phenyloxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5j):** Yield: 0.28 g, 64%, white solid; m.p. 126–130 °C; R_f = 0.42 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +105.5 (c = 0.62, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.22 [s, 9 H, $CH(CH_3)_2$], 1.69–2.07 [m, 4 H, pyr-H_2C(4), pyr-H_2C(3)], 3.25–3.39 [m, 2 H, pyr-H_2C(5)], 4.11–4.25 [m, 2 H, CH_2O, pyr-HC(2)], 4.67 (t, J = 9.1 Hz, 1 H, CH_2O), 5.39 (t, J = 8.9 Hz, 1 H, CHN), 7.05 [t, J = 7.3 Hz, 1 H, Ar-HC(3)], 7.18–7.39 [m, 5 H, Ar-HC(Ph)], 7.44 [t, J = 7.5 Hz, 1 H, Ar-HC(2)], 7.87 [d, J = 7.72 Hz, 1 H, Ar-HC(4)], 8.65 and 8.7 [2 × d, J = 7.0 Hz and J = 8.4 Hz, 1 H, Ar-HC(1), ratio 1:2], 12.15 and 12.22 (2 × br. s, 1 H, NH, ratio 1:2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [23.9*, 24.2] [pyr-H_2C(4), pyr-H_2C(3)], 28.4 [$C(CH_3)_3$], [31.4, 31.6*] [pyr-H_2C(4), pyr-H_2C(3)], [46.8*, 46.9] [pyr-H_2C(5)], [62.0, 62.8*] [pyr-HC(2)], 70.3 (CHN), 73.8 (CH_2O), 80.0 [$C(CH_3)_3$], 113.4 [Ar-C(5)], [120.0*, 120.2] [Ar-HC(1)], 122.69 [Ar-HC(3)], [126.7, 128.0, 129.1, 129.6] [Ar-HC(4), Ar-HC(Ph)], 133.1 [Ar-HC(2)], 140.1 [Ar-C(6)], [141.7*, 142.2] (*ipso*-Ph), [154.0*, 154.4] [C=O(Boc)], 164.8 (C=N), [172.5, 173.0*] [C=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3428, 1689, 1634, 1532, 1448, 1388 cm^{-1}. HRMS (ES+): calcd. for $C_{25}H_{29}N_3O_4$ [M + H]$^+$ 436.2238; found 436.2220. $C_{25}H_{29}N_3O_4$ (436.22): calcd. C 68.95, H 6.71, N 9.65; found C 68.63, H 6.68, N 9.40.

***tert*-Butyl (2*S*)-{2-[(4*S*)-*tert*-Butyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5k):** Yield: 0.28 g, 67%, white solid; m.p. 92–93 °C; R_f = 0.52 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = –16.6 (c = 1.04, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.89 [s, 9 H, $C(CH_3)_2$], 1.27 [s, 6 H, $C(CH_3)_2$(Boc)], 1.39 [s, 3 H, $C(CH_3)_2$(Boc)], 1.80–1.93 [m, 1 H, pyr-H_2C(4)], 1.97–2.15 [m, 2 H, pyr-H_2C(4), pyr-H_2C(3)] 2.18–2.20 [m, 1 H, pyr-H_2C(3)], 3.37–3.57 [m, 2 H, pyr-CH_2(5)], 4.03–4.33 [m, 4 H, pyr-HC(2), CHN, CH_2O], 7.01 [t, J = 7.4 Hz, 1 H, Ar-HC(3)], 7.20–7.41 [m, 1 H, Ar-HC(2)], 7.74 [t, J = 18.5 Hz, 1 H, Ar-HC(4)], 8.66 [d, J = 8.4 Hz, 1 H, Ar-HC(1)], 12.22 and 12.36 (2 × br. s, 1 H, NH, ratio 1:1) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [24.0*, 24.2] [pyr-H_2C(4)], 26.0 [$C(CH_3)_3$], [29.0*, 29.1] [$C(CH_3)_3$(Boc)], [31.0, 32.0*] [pyr-H_2C(3)], 34.1 [$C(CH_3)_3$], 47.1 [pyr-H_2C(5)], [62.0, 63.1*] [pyr-HC(2)], [67.7*, 68.3] (CH_2O), 75.9 (CHN), 80.0 [$C(CH_3)_3$(Boc)], 114.0 [Ar-C(5)], 120.0 [Ar-HC(1)], 122.5 [Ar-HC(3)], 129.9 [Ar-HC(4)], 132.4 [Ar-HC(2)], 140.0 [Ar-C(6)], 154.1 [C=O(Boc)], 162.4 (C=N), 172.1 [C=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3406, 2096, 1637, 1543, 1393 cm^{-1}. HRMS (ES+): calcd. for $C_{23}H_{33}N_3O_4$ [M + H]$^+$ 416.2551; found 416.2542. $C_{23}H_{33}N_3O_4$ (416.25): calcd. C 66.48, H 8.00, N 10.11; found C 66.81, H 8.20, N 10.45.

***tert*-Butyl (2*S*)-{2-[(4*S*)-Benzyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5l):** Yield: 0.27g, 60%, white solid; m.p. 106–109 °C; R_f = 0.55 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +9.9 (c = 0.72, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.24 [s, 9 H, $C(CH_3)_3$], 1.71–1.86 [m, 2 H, pyr-H_2C(4)], 1.95–2.08 [m, 1 H, pyr-H_2C(3)], 2.13–2.23 [m, 1 H, pyr-H_2C(3)], 2.67 (dd, J = 8.5, 13.4 Hz, 1 H, CH_2Ph), 3.16 (dd, J = 5.6, 12.4 Hz, 1 H, CH_2Ph), 3.35–3.47 [m, 2 H, pyr-H_2C(5)], 3.99–4.24 [m, 3 H, pyr-HC(2), CH_2O], 4.66 (qn, J = 7.1 Hz, 1 H, CHN), 6.99 [dd, J = 15.2, 7.4 Hz, 1 H, Ar-HC(3)], 7.12–7.24 [m, 5 H, Ar-HC(Ph)], 7.35–7.41 [m, 1 H, Ar-HC(2)], 7.74 [dd, J = 1.5, 7.9 Hz, 1 H, Ar-HC(2)], 8.75 [t, J = 10.6 Hz, 1 H, Ar-HC(1)], 12.26 and 12.50 (2 × br. s, 1 H, NH, ratio 1:3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [22.8*, 23.5] [pyr-H_2C(4)], 27.3 [$C(CH_3)_3$], [29.7, 30.7*] [pyr-H_2C(3)], [40.5*, 41.0] (CH_2Ph), [45.9*, 46.3] [pyr-H_2C(5)], [61.1, 61.6*] [pyr-HC(2)], 67.0 (CHN), [69.3, 69.5*] (CH_2O), 79.0 [$C(CH_3)_3$], 112.1 [Ar-C(5)], [118.3*, 119.0] [Ar-HC(1)], 121.3 [Ar-HC(3)], {125.5*, 125.6}, {127.5*, 127.6}, {127.8, 128.0*}, {128.1*, 128.2} [Ar-HC(4), Ar-HC(Ph)], 131.6 [Ar-HC(2)], 136.9 [Ar-C(6)], 138.7 (*ipso*-Ph), 153.1 [C=O(Boc)], 162.7 (C=N), [171.1, 171.8*] [C=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3471, 2977, 1688, 1638, 1584, 1534, 1448 cm^{-1}. HRMS (ES+): calcd. for $C_{26}H_{31}N_3O_4$ [M + H]$^+$ 450.2395; found 450.2388. $C_{26}H_{31}N_3O_4$ (450.23): calcd. C 69.47, H 6.95, N 9.35; found C 69.20, H 6.99, N 9.24.

***tert*-Butyl (2*R*)-{2-[(4*S*)-Isopropyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5m):** Yield: 0.24 g, 59%, white solid; m.p.76–78 °C; R_f = 0.44 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +128.7 (c = 0.67, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.81 [d, J = 6.5 Hz, 3 H, $CH(CH_3)_2$], 0.93 [d, J = 6.4 Hz, 3 H, $CH(CH_3)_2$], 1.23 [s, 6 H, $C(CH_3)_3$], 1.38 [d, J = 7.3 Hz, 3 H, $C(CH_3)_3$], 1.79–2.30 [m, 5 H, $CH(CH_3)_2$, pyr-H_2C(4),pyr-H_2C(3)], 3.38–3.63 [m, 1 H, pyr-H_2C(5)], 4.03–4.34 [m, 4 H, pyr-HC(2), CH_2O, CHN], 7.01 [t, J = 7.6 Hz, 1 H, Ar-HC(3)], 7.34 [dd, J = 7.9, 15.8 Hz, 1 H, Ar-HC(2)], 7.76 [d, J = 7.6 Hz, 1 H, Ar-HC(3)], 8.72 [d, J = 8.3 Hz, 1 H, Ar-HC(1)], 12.30 and 12.40 (2 × br. s, 1 H, NH, ratio 1:2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 [$CH(CH_3)_2$], [18.1, 18.2*] [$CH(CH_3)_2$], [22.7*, 23.3] [$CH(CH_3)_2$], [27.2*, 27.5] [pyr-H_2C(4), pyr-H_2C(3)], [28.3*, 28.6] [$C(CH_3)_3$], [29.4, 30.5*] [pyr-H_2C(4), pyr-H_2C(3)], [45.5*, 45.7] [pyr-H_2C(5)], 54.2 [pyr-HC(2)], [60.5, 61.5*] (CH_2O), 71.1 (CHN), 79.1 [$C(CH_3)_3$], 112.3 [Ar-C(5)], [119.2, 120.0*] [Ar-C(1)], 121.9 [Ar-C(3)], 125.4[Ar-C(4)],[131.6,131.8*][Ar-C(2)],138.4,[Ar-C(6)],153.5[C=O(Boc)], 167.3 (C=N), 171.3 [C=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3450, 2947, 1685, 1637, 1334, 1448, 1386 cm^{-1}. HRMS (ES+): calcd. for $C_{22}H_{31}N_3O_4$ [M + H]$^+$ 402.2395; found 402.2399. $C_{22}H_{31}N_3O_4$ (402.23): calcd. C 65.81, H 7.78, N 10.47; found C 65.73, H 7.74, N 10.29.

***tert*-Butyl (2*R*)-{4,5-Dihydro-2-[(4*S*)-Phenyloxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5n):** Yield: 0.30g, 69%, white solid; m.p. 99–102 °C; R_f = 0.52 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +134.3 (c = 0.82, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.23 [s, 9 H, $CH(CH_3)_2$], 1.88–1.95 [m, 2 H, pyr-H_2C(4)], 2.09 [qn, J = 7.3 Hz, 1 H, pyr-H_2C(3)], 2.84 [qn, J = 5.5 Hz, 1 H, pyr-H_2C(3)], 3.03 [q, J = 8.4 Hz, 1 H, pyr-H_2C(5)], 4.00–4.21 [m, 2 H, OCH_2, pyr-HC(2)], 4.51 (dd, J = 9.1, 18.8 Hz, 1 H, CH_2O), 5.43 (dd, J = 9.6, 17.7 Hz, 1 H, CHN), 7.04 [t, J = 7.5 Hz, 1 H, Ar-HC(3)], 7.19–7.29 [m, 5 H, Ar-HC(Ph)], 7.42 [t, J = 7.5 Hz, 1 H, Ar-HC(2)], 7.86 [d, J = 7.7 Hz, 1 H, Ar-HC(4)], 8.76 [t, J =

9.2 Hz, Ar-*H*C(1)], 12.41 and 12.66 (2 × br. s, 1 H, N*H*, ratio 1:2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [23.7*, 24.0] [pyr-H_2C(4)], 28.3 [C(*C*H_3)$_3$], [31.5, 31.7*] [pyr-H_2C(3)], [46.5*, 46.7] [pyr-H_2C(5)], [62.2, 62.9*] [pyr-H*C*(2)], [70.1*, 70.9] (*C*HN), 73.9 (*C*H_2O), 79.9 [*C*(CH$_3$)$_3$], 113.3 [Ar-*C*(5)], [119.7*, 120.0] [Ar-H*C*(1)], 122.6 [Ar-H*C*(3)], [127.2, 128.0, 128.9, 129.5] [Ar-H*C*(4), Ar-H*C*(Ph)], 133.0 [Ar-H*C*(2)], 140.0 [Ar-*C*(6)], 142.3 (*ipso*-Ph), 154.0 [*C*=O(Boc)], 164.0 (*C*=N), [171.8, 173.3*] [*C*=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3406, 2385, 1636, 1535, 1449, 1387 cm^{-1}. HRMS (ES+): calcd. for $C_{25}H_{29}N_3O_4$ [M + H]$^+$ 436.2238; found 436.2244. $C_{25}H_{29}N_3O_4$ (436.22): calcd. C 68.95, H 6.71, N 9.65; found C 68.71, H 6.71, N 9.57.

***tert*-Butyl (2*R*)-{2-[(4*S*)-*tert*-Butyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5o):** Yield: 0.23 g, 55%, white solid; m.p 78–80 °C; R_f = 0.64 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +122.1 (*c* = 0.75, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.88 [s, 9 H, C(C*H*$_3$)$_2$], 1.22 [s, 9 H, C(C*H*$_3$)$_2$(Boc)], 1.76–1.87 [m, 1 H, pyr-H_2C(4)], 1.92 [qn, *J* = 6.5 Hz, 1 H, pyr-H_2C(4)], 2.02–2.14 [m, 1 H, pyr-H_2C(3)], 2.22–2.31 [m, 1 H, pyr-H_2C(3)], 3.37–3.49 [m, 1 H, pyr-H_2C(5)], 3.59–3.83 [m, 1 H, pyr-H_2C(5)], 4.08–4.30 [m, 4 H, pyr-*H*C(2), C*H*N, CH_2O], 7.00 [t, *J* = 7.5 Hz, 1 H, Ar-*H*C(3)], 7.20–7.46 [m, 1 H, Ar-*H*C(2)], 7.74 [d, *J* = 7.6 Hz, 1 H, Ar-*H*C(4)], 8.68 [d, *J* = 8.3 Hz, 1 H, Ar-*H*C(1)], 12.19 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [24.1*, 24.3] [pyr-H_2C(4)], 26.0 [C(*C*H_3)$_3$], [28.3*, 28.5] [C(*C*H_3)$_3$-(Boc)], [28.7, 31.9*] [pyr-H_2C(3)], 34.4 [C(*C*H_3)$_3$], 47.1 [pyr-H_2C(5)], [62.0, 62.8*] [pyr-H*C*(2)], 67.8 (*C*H_2O), 76.0 (*C*HN), 80.0 [*C*(CH$_3$)$_3$(Boc)], [113.9*, 114.4] [Ar-*C*(5)], 120.0 [Ar-H*C*(1)], 122.6 [Ar-H*C*(3)], 129.2 [Ar-H*C*(4)], 132.5 [Ar-H*C*(2)], 139.6 [Ar-*C*(6)], 154.3 [*C*=O(Boc)], 163.4 (*C*=N), [172.0, 172.7*] [*C*=O(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3428, 2972, 1637, 1539, 1449 cm^{-1}. HRMS (ES+): calcd. for $C_{23}H_{33}N_3O_4$ [M + H]$^+$ 416.2551; found 416.2529. $C_{23}H_{33}N_3O_4$ (416.25): calcd. C 66.48, H 8.00, N 10.11; found C 66.82, H 8.36, N 10.43.

***tert*-Butyl (2*R*)-{2-[(4*S*)-Benzyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (5p):** Yield: 0.26 g, 58%, white solid; m.p. 90–92 °C; R_f = 0.55 (pentane/ethyl acetate, 2:1). $[\alpha]_D$ = +71.2 (*c* = 0.66, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.25 [s, 9 H, C(C*H*$_3$)$_3$], 1.73–1.86 [m, 2 H, pyr-H_2C(4)], 2.02–2.19 [m, 1 H, pyr-H_2C(3)], 2.20–2.23 [m, 1 H, pyr-H_2C(3)], 2.68 (dd, *J* = 8.3, 13.3 Hz, 1 H, CH_2Ph), 3.18 (dd, *J* = 5.7, 13.3 Hz, 1 H, CH_2Ph), 3.36–3.47 [m, 2 H, pyr-H_2C(5)], 4.00–4.23 [m, 3 H, pyr-*H*C(2), CH_2O], 4.70 (qn, *J* = 7.9 Hz, 1 H, CHN), 7.01 [dd, *J* = 7.5, 15.0 Hz, 1 H, Ar-*H*C(3)], 7.14–7.25 [m, 5 H, Ar-*H*C(Ph)], 7.39 [dd, *J* = 8, 15 Hz, 1 H, Ar-*H*C(2)], 7.75 [d, *J* = 7.8 Hz, 1 H, Ar-HC(4)], 8.75 [dd, *J* = 9.0, 16.4 Hz, 1 H, Ar-*H*C(4)], 12.25 and 12.49 (2 × br. s, 1 H, N*H*, ratio 1:3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [24.1*, 25.0] [pyr-H_2C(4)], 28.4 [C(*C*H_3)$_3$], [31.4, 31.8*] [pyr-H_2C(3)], 42.1 (*C*H_2Ph), [47.0*, 47.5] [pyr-H_2C(5)], [62.5, 62.8*] [pyr-H*C*(2)], 68.0 (*C*HN), [70.7, 70.9*] (*C*H_2O), 80.0 [*C*(CH$_3$)$_3$], 113.6 [Ar-*C*(5)], 119.7 [Ar-H*C*(1)], 122.6 [Ar-H*C*(3)], (126.8, 129.3, 129.5) [Ar-H*C*(4), Ar-H*C*(Ph)], 132.8 [Ar-H*C*(2)], 138.0 [Ar-*C*(6)], 139.7 (*ipso*-Ph), 154.0 [*C*=O(Boc)], 163.8 (*C*=N), 173.1 [*C*=O-(amide)] ppm. IR ($CHCl_3$ film): $\tilde{\nu}$ = 3437, 3006, 2997, 1686, 1636, 1584, 1534, 1449 cm^{-1}. HRMS (ES+): calcd. for $C_{26}H_{31}N_3O_4$ [M + H]$^+$ 450.2395; found 450.2388. $C_{26}H_{31}N_3O_4$ (459.23): calcd. C 69.47, H 6.95, N 9.35; found C 69.18, H 6.99, N 9.25.

General Procedure for NHK Allylation of Benzaldehyde: A flame-dried Schlenk tube was charged with dry THF (1 mL) and dry acetonitrile (150 μL). Anhydrous chromium(III) chloride (4.0 mg, 25.3 μmol) and manganese (41.7 mg, 0.76 mmol) were added simultaneously to the solvent mixture. The resulting suspension was allowed to stand at r.t. for approximately 30 min until the characteristic purple colour of the chromium(III) salt disappeared. The mixture was stirred vigorously under an atmosphere of nitrogen for 1 h, resulting in a green reaction mixture. DIPEA (13 μL, 75.9 μmol) was added followed by ligand **5** (30.4 μmol), resulting in an immediate green catalyst mixture. This was stirred at r.t. for 1 h prior to the addition of allyl bromide (0.51 mmol) with the resulting chromium(III) allyl solution being stirred for a further 1 h. The reaction was initiated by the addition of aldehyde (0.25 mmol) and chlorotrimethylsilane (64 μL, 0.51 mmol) and stirred under an atmosphere of nitrogen at r.t. for 16 h. The resulting green–brown suspension was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with Et_2O (3 × 1 mL). The combined organic layers were concentrated in vacuo to give a green residue. This was flushed through a small silica gel column (1.5 × 5 cm, pentane/AcOEt, 9:1) to remove the catalyst, and after evaporation of the solvent, the reaction products were isolated as a yellow oil. The% conversion of the reaction was determined at this stage from the ^{1}H NMR spectrum of the crude product (generally a mixture of silylated and free alcohol) by measuring the ratio of aldehyde to product and assuming that all aldehyde consumed went to product. The yellow oil was dissolved in THF (1 mL), a few drops of aqueous 1 M HCl were added, and the resulting solution was stirred for 10 min when TLC (pentane/AcOEt, 9:1) showed complete desilylation. The solvent was removed in vacuo, and the resulting aqueous phase was extracted with Et_2O (3 × 2 mL). The organic layers were combined, dried with anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow oil. This was purified by flash column chromatography on silica gel (1 × 15 cm, cyclohexane/AcOEt, 5:1) to give the required product as a pale yellow oil. Enantioselectivity was determined by HPLC: Chiralcel OD; hexane/2-propanol, 98:2; flow rate 0.3 mL/min; (*R*) 35.1 min, (*S*) 41.7 min.

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