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Preparation of pyrrolidine–oxazoline containing ligands and their application in asymmetric transfer hydrogenation

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Abstract—Nine members of a new ligand class incorporating both an oxazoline ring and a pyrrolidine unit were prepared in an efficient four-step synthesis starting from readily available chiral amino alcohols and proline. A study of these ligands in the asymmetric transfer hydrogenation of acetophenone showed that the catalysts formed from $[Ir(cod)Cl]_2$ were the most active while those derived from $[Ru(p\text{-cymene})Cl_2]_2$ gave the highest enantioselectivities (up to 61% ee).

1. Introduction

The preparation of enantiopure secondary alcohols by the catalytic enantioselective reduction of prochiral ketones is an important transformation in organic synthesis.[1] In recent years, extensive research has been carried out in this area with the development of asymmetric transfer hydrogenation.[2] This process offers an attractive alternative and/or complement to the use of molecular hydrogen and hydride reduction due to its operational simplicity and use of a safe, inexpensive and easy to handle hydrogen source.

Rhodium,[3,4c] iridium[4] and ruthenium[5] are the most commonly used metals for transfer hydrogenation with 2-propanol being the hydrogen source of choice. Ruthenium(arene) complexes bearing chiral 1,2-amino alcohol,[6] monotosylated diamine[7] and 1,2-diamine ligands[8,7c] are some of the most effective catalysts for asymmetric transfer hydrogenation of aromatic ketones in terms of both enantioselectivity and catalytic activity. It is thought that the NH group in these ligands plays a crucial role in achieving high enantioselectivity via a six-membered cyclic transition state brought about by hydrogen bonding between it and the ketone substrate.[9]

Chiral oxazoline-containing ligands have also been successful in asymmetric transfer hydrogenation using 2-propanol as the hydrogen donor.[10] For example, Zhang's tridentate bis(oxazolinylmethyl)amine ligand **1** gives up to 97% ee for the ruthenium-catalysed reduction of a variety of aromatic ketones with excellent conversions.[11] The catalyst formed from $[Ru(p\text{-cymene})Cl_2]_2$ and the chiral 1,2,3,4-tetrahydroquinolinyl-oxazoline ligand **2** gave 83% ee for the reduction of acetophenone at −20 °C using 5 mol% ruthenium in moderate yield (46% after 21 h).[12]

α-Amino acids and their derivatives have also attracted attention as ligands for asymmetric transfer hydrogenation because they are relatively cheap and easily accessible.[13] Proline-derived ligands have recently been investigated and $[Ru(p\text{-cymene})Cl_2]_2$ complexes of prolinamide **3** with a 4 mol% catalyst loading gave enantioselectivities in the range of 60–93% ee at −24 °C for a variety of ketone substrates.[14] (*S*)-2-Anilinomethylpyrrolidine **4** and (*S*)-2-naphthylaminomethyl-pyrrolidine **5** form highly active complexes with $[Ru(p\text{-cymene})Cl_2]_2$ giving high enantioselectivities (74–96% ee) for the reduction of aromatic ketones in good to excellent yields (59–99%) with a catalyst loading of 0.2–0.5 mol% ruthenium.[15]

Encouraged by the results obtained by the use of both proline-derived and oxazoline-containing ligands, we have designed and prepared a new class of ligands **6a-i** for asymmetric transfer hydrogenation, which incorporate both of these structural units. These ligands contain the important NH moiety thought to be crucial for high enantioselectivities and the 1,2 arrangement of coordinating nitrogen atoms present in ligands **1** and **3-5**. In this paper, we describe the synthesis of nine members of this new class of ligands and discuss the results obtained in the reduction of acetophenone. As these ligands contain two chiral

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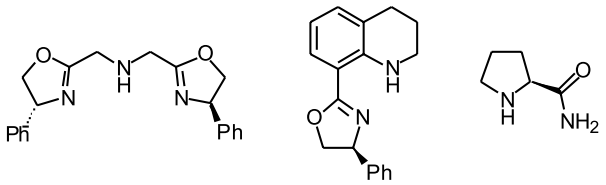
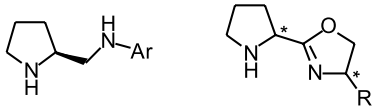


1 **2** **3**



4 Ar = phenyl
5 Ar = naphthyl

6

	pyr.[a]	R		pyr.[a]	R
6a	(*S*)	H	**6f**	(*S*)	(*S*)-^{t}Bu
6b	(*S*)	(*S*)-^{i}Pr	**6g**	(*R*)	(*S*)-^{t}Bu
6c	(*S*)	(*R*)-^{i}Pr	**6h**	(*S*)	(*S*)-Me
6d	(*S*)	(*S*)-Ph	**6i**	(*S*)	(*S*)- Bn
6e	(*S*)	(*R*)-Ph			

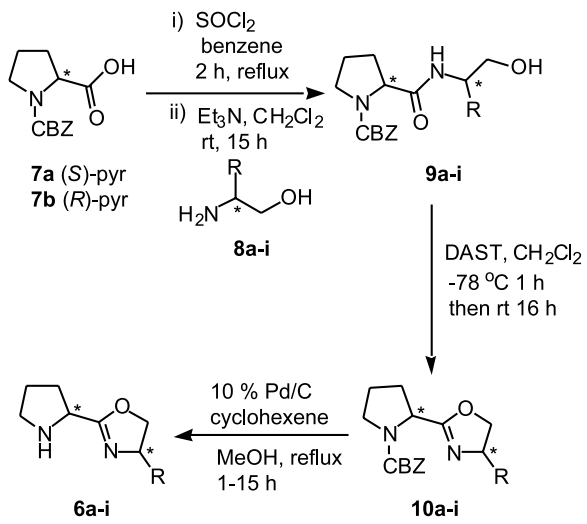
[a] Configuration of the pyrrolidine chiral centre

centres, diastereomeric ligand pairs (**6b** and **6c**, **6d** and **6e** and **6f** and **6g**) were investigated in order to determine the role of each chiral centre in enantioselection.

2. Results and discussion

2.1. Ligand synthesis

We envisaged that ligands **6a-i** could be prepared by means of a four-step synthesis starting from readily available chiral amino alcohols and proline (Scheme 1, Table 1). First, *N*-carbobenzyloxy(CBZ)-protected proline **7a-b** was chlorinated with thionyl chloride[16] and then reacted without purification with a chiral amino alcohol **8a-i** in the presence of triethylamine to give β-hydroxyamides **9a-i** in moderate to good yields (57–92%). We have recently reported that diethylaminosulfur triflouride (DAST) is a useful reagent for the cyclisation of β-hydroxyamides to oxazolines giving better results compared to the usual protocol of chlorination followed by base-induced cyclisation.[17] Cyclodehydration of **9a-i** by treatment with DAST afforded excellent yields (75–98%) of the CBZ-protected pyrrolidine–oxazolines **10a-i**, which were then deprotected in a transfer hydrogenolysis reaction using Pd/C and cyclohexene[18] yielding



Scheme 1. Synthesis of pyrrolidine–oxazoline ligands **6a-i**.

Table 1. Yields obtained for the reaction steps in the synthesis of ligands **6a-i**[a]

R	Hydroxyamide formation		Cyclisation		Deprotection	
	9	Yield (%)	**10**	Yield (%)	**6**	Yield (%)
H	**9a**	87	**10a**	86	**6a**	49
(*S*)-^{i}Pr	**9b**	92	**10b**	92	**6b**	89
(*R*)-^{i}Pr	**9c**	86	**10c**	87	**6c**	67
(*S*)-Ph	**9d**	57	**10d**	81	**6d**	46
(*R*)-Ph	**9e**	57	**10e**	94	**6e**	40
(*S*)-^{t}Bu	**9f**	81	**10f**	88	**6f**	48
(*S*)-^{t}Bu	**9g**[b]	82	**10g**[b]	75	**6g**[b]	55
(*S*)-Me	**9h**	60	**10h**	93	**6h**	55
(*S*)-Bn	**9i**	87	**10i**	98	**6i**	68

[a] (*S*)-Configuration of the pyrrolidine chiral centre.
[b] (*R*)-Configuration of the pyrrolidine chiral centre.

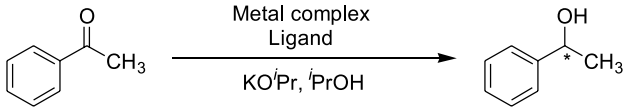
the required pyrrolidine–oxazoline ligands **6a-i** in moderate yields (40–89%). It was found that both **10a-i** and the final ligands were subject to ring-opening to the corresponding β-hydroxyamide after prolonged storage at room temperature. However, these compounds can be stored under nitrogen without significant decomposition at −6 °C.

Because the pyrrolidine–oxazoline ligands have two chiral centres, it was necessary to prepare diastereomers to examine the effect of match and mismatch chiral centres on enantioselection. Initially, five ligands **6b**,**d**,**f**,**h**,**i** were prepared from (*S*)-proline **7a** and the corresponding naturally occurring (*S*)-amino alcohol. Using (*R*)-amino alcohols, diastereomers **6c** and **6e** of the *iso*-propyl- and phenyl-substituted ligands **6b** and **6d**, respectively, were synthesised. Since (*R*)-*tert*-leucinol is more expensive than its enantiomer, a diastereomer **6g** of the *tert*-butyl substituted ligand **6f** was accessed using (*S*)-*tert*-leucinol and (*R*)-proline **7b**. In total, nine members of this new ligand class **6a-i**, including three diastereomeric pairs were prepared in good overall yield for application in asymmetric transfer hydrogenation.

2.2. Metal screening and reaction optimisation

Using Chemspeed® ASW 2000 equipment, ligands **6a-i** were evaluated in the asymmetric transfer hydrogenation of

Table 2. Optimisation of reaction conditions for transfer hydrogenation of acetophenone[a]



Entry	Metal complex	Ligand	Lig/Met	Conv. (%)[b]		ee (%)[b]		Conf.[c]
				1 h	10 h	1 h	10 h	
1	[Ru(*p*-cymene)Cl_2]$_2$	**6b**	2.0		2		62	*R*
2	[Ir(cod)Cl]$_2$	**6b**	1.2	10	79	36	43	*R*
3	[Ir(cod)Cl]$_2$	**6b**	2.0	13	80	44	43	*R*
4	[Ir(cod)Cl]$_2$	**6b**	3.0	13	78	43	42	*R*
5	[Ir(cod)Cl]$_2$	**6b**	4.0	17	84	41	42	*R*
6[d]	[Ir(cod)Cl]$_2$	**6b**	2.0		65		41	*R*
7	[Ir(cod)Cl]$_2$	**6c**	2.0	9	63	45	42	*S*
8[e]	[Ir(cod)Cl]$_2$	**6c**	2.0	5	19	45	49	*S*
9[f]	[Ir(cod)Cl]$_2$	**6c**	2.0	18	88	43	41	*S*

[a] Acetophenone:KO^{i}Pr:Metal=200:5:1.
[b] Determined by GC analysis on a CP-Chirasil-Dex CB column (25 m, 0.25 (diam.), 0.25 μm).
[c] Determined by reference to literature values.[20]
[d] Acetophenone:KO^{i}Pr:Metal=20:5:1, reaction conducted at 0 °C.
[e] Acetophenone:KO^{i}Pr:Metal=200:2.5:1.
[f] Acetophenone:KO^{i}Pr:Metal=100:5:1.

acetophenone (Table 2). Six metal complexes of rhodium, iridium and ruthenium were screened with ligand **6b** in an attempt to find the optimal metal for transfer hydrogenation. Ruthenium [$RuCl_2(PPh_3)_3$ and $RuCl_2(DMSO)_4$] and rhodium [$RhCl(PPh_3)_3$ and [Rh(cod)Cl]$_2$] complexes showed no catalytic activity when tested with ligand **6b**. [Ru(*p*-cymene)Cl_2]$_2$ gave a slight conversion (2%) accompanied by a moderate ee of 62% (entry 1). The best results were achieved with the catalyst formed from ligand **6b** and [Ir(cod)Cl]$_2$ which afforded moderate enantioselectivity (43% ee) and good conversion (79%) after 10 h at room temperature (entry 2). The reaction was optimised by varying the reaction temperature, catalyst loading of the [Ir(cod)Cl]$_2$ pre-catalyst and the equivalents of ligand and base used. Changing the number of equivalents of ligand **6b** used (up to 4 equiv. lig/metal) had very little effect on both conversion and enantioselectivity (entries 2–5). In an attempt to increase enantioselectivities, the reaction was carried out at 0 °C using the iridium source and ligand **6b**. At this temperature, the reaction was sluggish affording 65% conversion after 10 h with a ten-fold increase in catalyst loading (5 mol%) but the enenatioselectivity did not change (entry 6). With the diastereomeric (*S*)-proline-(*R*)-*iso*-propyl ligand **6c**, the enantioselectivity increased (49% vs. 42%) when the amount of base used was halved, however this was accompanied by a significant decrease in catalytic activity (19% vs. 63% conversion after 10 h) (entries 7–8). Not surprisingly, increasing the catalyst loading by a factor of 2–1 mol% iridium resulted in increased conversion but little change in enantioselectivity (entry 9).

2.3. Iridium catalysed asymmetric transfer hydrogenation

Having determined the optimal reaction conditions ([Ir(cod)Cl]$_2$ (0.25 mol%), 5 equiv. KO^{i}Pr/Ir, 2 equiv. lig/Ir, room temp.), isolated experiments were carried out to evaluate the pyrrolidine–oxazoline ligands **6a-i** in transfer hydrogenation (Table 3). Firstly, all catalysts formed from [Ir(cod)Cl]$_2$ and ligands **6a-i** demonstrated high catalytic activity in the reaction giving up to 94% conversion after 15 h. Of these the (*S*)-proline-(*S*)-*tert*-butyl-substituted ligand **6f** proved particularly active affording 96% conversion after just 1 h. However, the enantioselctivity obtained using this ligand was poor (20% ee after 1 h) (entry 6). Similar levels of enantioselectivity were afforded using the *tert*-butyl diastereomer **6g** and the methyl-substituted ligand **6h** (entries 7–8). The *iso*-propyl- (**6b** and **6c**), phenyl- (**6d** and **6e**) and benzyl- (**6i**) substituted ligands gave the best levels of enantioselection but these were modest at best (32–38% ee) (entries 2–5 and 9).

Table 3. Transfer hydrogenation of acetophenone using [Ir(cod)Cl]$_2$ and ligands **6a-i**[a]

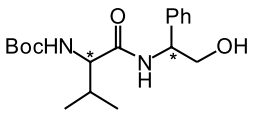
Entry	Ligand	R	Conv. (%)[b]		ee (%)[b]		Conf.[c]
			1 h	15 h	1 h	15 h	
1	**6a**	H	42	94	Rac.	Rac.	—
2	**6b**	^{i}Pr	30	91	38	37	*R*
3	**6c**	^{i}Pr	32	81	39	38	*S*
4	**6d**	Ph	40	79	33	32	*R*
5	**6e**	Ph	21	55	41	34	*S*
6	**6f**	^{i}Bu	96	97	20	17	*R*
7	**6g**	^{i}Bu	60	86	16	16	*R*
8	**6h**	Me	27	79	10	13	*S*
9	**6i**	Bn	19	74	29	32	*S*

[a] Acetophenone:KO^{i}Pr:ligand:Ir=200:5:2:1, reactions conducted at room temperature.
[b] Determined by GC analysis on a Supelco β-Dex 120 column (30 m, 0.25 mm (diam.), 0.25 μm).
[c] Determined by reference to literature values.[20]

Examining the results obtained using the three diastereomeric ligand pairs (**6b** and **6c**, **6d** and **6e** and **6f** and **6g**) reveals an interesting trend. In the case of the *iso*-propyl- and phenyl-substituted ligands, changing the configuration of the chiral centre at the oxazoline ring results in very similar levels of enantioselectivity but different enantiomers

of the 1-phenylethanol product (entries 2–5). The *tert*-butyl-substituted diastereomers (**6f** and **6g**) with the same chiral centre at the oxazoline ring but with opposite configurations of the pyrrolidine chiral centre both gave (*R*)-1-phenylethanol with almost identical enantioselectivities after 15 h (entries 6 and 7). These results suggest that only the chiral centre on the oxazoline ring is important in controlling the stereochemical outcome of the reaction. This was confirmed by the racemic product obtained when ligand **6a**, which comprises of an unsubstituted oxazoline ring, was used (entry 1).

Conversely, the chiral centre of the pyrrolidine ring, appears to play some part in determining catalyst activity. This is evident by examining the conversions obtained by the catalysts formed from the diastereomeric ligand pairs. In all three cases, the ligand derived from (*S*)-proline and the (*S*)-amino alcohol gave higher conversions than those obtained with their respective diastereomers. This is best seen with the *tert*-butyl-substituted ligands, where the (*S*)-pyrrolidine-(*S*)-*tert*-butyl ligand **6d** gives (*R*)-1-phenylethanol in 96% conversion after 1 h while its diastereomer **6g** afforded product in only 60% conversion (entries 6 vs 7). Also, ligand **6a** which contains only the pyrrolidine chiral centre gives high conversions (94% after 15 h). This effect where one chiral centre, of the two in the ligand, dictates the stereochemistry of the product has been previously reported by Adolfsson in his study of transfer hydrogenation employing ligands of type **11**.[19]



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2.4. Ruthenium-catalysed asymmetric transfer hydrogenation

As shown in Table 2 (entry 1), when ligand **6b** was screened with $[Ru(p\text{-cymene})Cl_2]_2$ (0.25 mol%), slight catalytic activity was observed. It has been reported in the literature, that quite high catalyst loadings (4–5 mol% Ru) were used for ruthenium-catalysed transfer hydrogenation with some oxazoline and pyrrolidine containing ligands.[12,14] Encouraged by this and in an attempt to increase the enantioselectivites obtained with this ligand class, we tested ligands **6a-i** in the transfer hydrogenation of acetophenone using a ten-fold increase in catalyst loading (2.5 mol% of $[Ru(p\text{-cymene})Cl_2]_2$). Gratifyingly, for the majority of ligands tested moderate catalytic activity was recorded accompanied by improved enantioselectivity in some cases (Table 4). The best results were obtained using the *iso*-propyl-substituted ligands **6b** and **6c**, giving much improved enantioselectivities (51 (*R*) and 61 (*S*)% ee, respectively) compared to those afforded by iridium catalysis (37 (*R*) and 38 (*S*)% ee, respectively). The catalysts formed from these ligands and $[Ru(p\text{-cymene})Cl_2]_2$ were also the most active giving 73–76% conversion after 15 h (entries 3 and 4). A much increased catalytic activity was obtained when the reaction was conducted at reflux temperature (98% conversion after 2 h) but the enantioselectivity decreased dramatically (16% ee) using **6b** as the ligand (entry 2). The remaining ligands afforded poor to moderate conversions (8–51% after 15 h) and enantioselectivites (4–25% ee) which were no better and in some cases lower than those obtained in the Ir-catalysed reaction. By comparing the results obtained with the diastereomeric ligand pairs (entries 3–8), it can be seen that the sense of asymmetric induction achieved was similar to that observed with iridium, i.e. the chiral centre on the oxazoline was dominant.

Table 4. Transfer hydrogenation of acetophenone using $[Ru(p\text{-cymene})Cl_2]_2$ and ligands **6-8**[a]

Entry	Ligand	R	Conv. (%)[b]		ee (%)[b]		
			1 h	15 h	1 h	15 h	Conf.[c]
1	**6a**	H	6	8	7	4	*R*
2	**6b**[d]	^{i}Pr	98[e]		16[e]		*R*
3	**6b**	^{i}Pr	8	76	52	51	*R*
4	**6c**	^{i}Pr	8	73	63	61	*S*
5	**6d**	Ph	3	30	14	15	*R*
6	**6e**	Ph	1	24	10	14	*S*
7	**6f**	^{t}Bu	5	43	25	20	*R*
8	**6g**	^{t}Bu	5	37	34	25	*R*
9	**6h**	Me	2	51	14	16	*R*
10	**6i**	Bn	5	40	18	17	*R*

[a] Acetophenone:KO^{i}Pr:ligand:Ru=20:5:2:1, reactions conducted at room temperature.
[b] Determined by GC ananlysis on a Supelco chiral β-dex column.
[c] Determined by reference to literature values.[20]
[d] Reaction carried out at 82 °C.
[e] Results after 2 h.

3. Conclusions

A new class of ligands **6a-i**, comprising chiral pyrrolidine and oxazoline rings, was prepared in four steps starting from readily available enantiopure proline and chiral amino alcohols. These were screened with a number of metal complexes and it was found that only those catalysts derived from $[Ir(cod)Cl]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ were successful. The catalysts formed from ligands **6a-i** and $[Ir(cod)Cl]_2$ (0.25 mol%) proved to be very active in this reaction (up to 96% conversion after 1 h at room temperature) but gave only modest enantioselectivities (up to 38% ee). Much improved enantioselectivities (61% ee with ligand **6c**) were achieved using $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol%) as the pre-catalyst. The results obtained using diastereomeric ligand pairs revealed that the stereochemical outcome of the reaction was controlled only by the oxazoline chiral centre.

4. Experimental

4.1. General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Oxford 300 spectrometer at room temperature in $CDCl_3$ or d^6-DMSO 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. Low resolution electron-impact MS spectra were measured at an ionization potential of 70 eV. Isomers were assumed to have the same response factors. Electro-spray mass spectrometric analysis was

performed on a Waters Micromass Quattro Ultima mass spectrometer. Elemental analyses were performed by Ms Anne Connolly, Department of Chemistry, University College Dublin. Infra-red spectra were recorded on a Perkin–Elmer Infra-red FT spectrometer. Optical rotation values were measured on a Perkin–Elmer 343 polarimeter. Melting points were determined in open capillary tubes in a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on plastic sheets pre-coated with silica gel 60 F_{254} (Merck). Column chromatography separations were performed using Merck Kieselgel 60 (0.040–0.063 mm). GC analysis was performed using (a) a Varian 3400 instrument equipped with a CP-Chirasil-Dex CB column (25 m, 0.25 mm (diam.), 0.25 μm) with nitrogen as a carrier gas at 15 psi and a flame-ionizing detector or (b) a Shimadzu GC-17A gas chromatograph equipped with a Shimadzu C-R3A chromatopac integrator and a Supelco β-Dex 120 chiral capillary column (30 m, 0.25 mm (diam.)×0.25 μm) with helium as a carrier gas at 1.0 mL/min and a flame-ionizing detector. Solvents were dried immediately before use by distillation from standard drying agents. Amino alcohols were prepared from their corresponding amino acids using a standard reduction procedure.[21] *N*-Carbobenzyloxy-(*S*)-proline and *N*-carbobenzyloxy-(*R*)-proline were prepared from the corresponding amino acids following the procedure reported by Corey.[22] It should be noted that for the majority of compounds prepared, the ^{1}H NMR and ^{13}C NMR spectra obtained showed two signals for most protons and carbons and such signals are given in square brackets.

4.2. Synthesis of hydroxyamides

Thionyl chloride (2.6 mL, 35.64 mmol) was added dropwise to a solution of carbobenzyloxy-(*S*)-proline (5.00 g, 20.06 mmol) in dry benzene (40 mL). The resulting clear solution was heated at reflux for 2 h. After cooling to room temperature, the yellow reaction mixture was concentrated in vacuo to give the acid chloride as a yellow oil. Yield: 99% (5.37 g), IR (neat): ν=1783 cm^{-1} (COCl) (lit.[16] 1780 cm^{-1}), 1709 cm^{-1} (CBZ).

The acid chloride (5.370 g, 20.05 mmol) was dissolved in dry CH_2Cl_2 (160 mL) in an oven-dried Schlenk tube and the resulting solution was cooled to 0 °C in an ice/water bath. To this was added dropwise a solution of the amino alcohol (22.06 mmol) and triethylamine (22.06 mmol) in dry CH_2Cl_2 (30 mL). A cloudy reaction mixture was obtained and this was allowed to stir at room temperature overnight (15 h) under an atmosphere of nitrogen. The reaction mixture was reduced in volume to approx. 50 mL, washed successively with aq. NH_4Cl (3×50 mL) and water (2×50 mL), dried over anhyd. sodium sulfate and concentrated in vacuo to give an off-white solid. The crude product was then purified by recrystallisation from CH_2Cl_2/pet. ether (40/60 °C).

4.2.1. (2*S*)-2-(2-Hydroxy-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9a). Yield: 5.11 g, 87%. White solid; mp: 106–108 °C; $[\alpha]_D$=−39.1 (*c* 0.45, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.80–1.92 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.05–2.24 (br m, 1H, pyr-H_2C(3)), 3.10–3.24 (br m, 2H, CH_2N), 3.43–3.51 (br m, 4H, pyr-H_2C(5), CH_2O, O*H*), 4.19–4.26 (m, 1H, pyr-*H*C(2)), 4.68 (app t, *J*=5.3 Hz, 1H, CH_2O), 5.01–5.18 (m, 2H, CH_2Ph(CBZ)), 7.36–7.44 (m, 5H, Ar-*H*C(CBZ)), 7.93–7.97 (m, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.8, 24.6] (pyr-H_2C(4)), [30.9, 32.0] (pyr-H_2C(3)), 42.1 (*C*H_2N), [47.2, 47.8] (pyr-H_2C(5)), [60.3, 60.8] (pyr-H*C*(2)), 60.5 (*C*H_2O), [66.4, 66.6] (*C*H_2Ph(CBZ)), [127.7, 128.5], [128.16, 128.23], [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), [154.6, 154.8] (*C*═O(CBZ)), [172.6, 172.9] (*C*ONH)); IR (KBr): ν 3428, 3292, 1689, 1646, 1548, 1431, 1363, 1138, 1093, 735 cm^{-1}; MS-ES$^+$ (CH_3CN): *m*/*z* 293 (M+H$^+$, 100%). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.61; H, 6.89; N, 9.62. Found: C, 61.25; H, 6.88; N, 9.50.

4.2.2. (2*S*)-2-((1*S*)-1-Hydroxymethyl-2-methyl-propyl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9b). Yield: 6.17 g, 92%. White solid; mp: 114–116 °C; $[\alpha]_D$=−61.0 (*c* 0.46, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ[0.73 (d, *J*=6.7 Hz), 0.77 (d, *J*=6.7 Hz) and 0.84 (app t, *J*=7.1 Hz)] (6H, CH(CH_3)$_2$, ratio 1.3:1.0), 1.73–1.90 (m, 4H, C*H*(CH$_3$)$_2$, pyr-H_2C(4), pyr-H_2C(3)), 2.07–2.15 (m, 1H, pyr-H_2C(3)), 3.37–3.46 (m, 3H, pyr-H_2C(5), CH_2O), 3.51–3.58 (m, 1H, C*H*N), [4.23 (dd, *J*=8.8, 2.7 Hz) and 4.29 (dd, *J*=8.8, 2.5 Hz)] (1H, pyr-*H*C(2), ratio 1.0:1.4), 4.47–4.54 (m, 1H, CH_2O), [4.95 (d, *J*=12.8 Hz), 5.04 (d, *J*=12.8 Hz) and 5.07 (d, *J*=10.3 Hz), 5.11 (d, *J*=10.3 Hz)] (2H, CH_2Ph(CBZ), ratio 1.3:1.0), 7.28–7.38 (m, 5H, Ar-*H*C(CBZ)), 7.52 (app t, *J*=9.0 Hz, 1H, CON*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [18.7, 18.8] (CH(*C*H$_3$)$_2$), [20.2, 20.4] (CH(*C*H$_3$)$_2$), [23.7, 24.6] (pyr-H_2C(4)), [28.8, 29.0] (*C*H(CH$_3$)$_2$), [30.8, 32.2] (pyr-H_2C(3)), [47.3, 47.9] (pyr-H_2C(5)), 56.3 (*C*HN), [60.0, 60.6] (pyr-H*C*(2)), [62.0, 62.1] (*C*H_2O), 66.4 (*C*H_2Ph(CBZ)), [127.8, 128.4], [128.15, 128.2], [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), [154.6, 154.7] (*C*═O(CBZ)), [172.4, 172.7] (*C*ONH); IR (KBr): ν 3455, 3299, 1666, 1656, 1544, 1441, 1357, 1171, 1119, 699, 668 cm^{-1}; MS-ES$^+$ (CH_3CN): *m*/*z* 335 (M+H$^+$, 100%). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.63; H, 7.83; N, 8.41. Found: C, 64.28; H, 7.83; N, 8.27.

4.2.3. (2*S*)-2-((1*R*)-1-Hydroxymethyl-2-methyl-propyl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9c). Yield: 5.84 g, 86%. White solid; mp: 118–122 °C; $[\alpha]_D$=−21.6 (*c* 0.61, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.77–0.86 (m, 6H, CH(CH_3)$_2$), 1.82–1.84 (br m, 4H, C*H*(CH$_3$)$_2$, pyr-H_2C(4), pyr-H_2C(3)), 2.09–2.22 (br m, 1H, pyr-H_2C(3)), 3.25–3.46 (m, 3H, pyr-H_2C(5), CH_2O), 3.57–3.59 (br m, 1H, C*H*N), 4.22–4.30 (m, 1H, pyr-*H*C(2)), 4.47–4.53 (m, 1H, CH_2O), 4.97–5.11 (m, 2H, CH_2-Ph(CBZ)), 7.29–7.37 (m, 5H, Ar-*H*C(CBZ)), [7.48 (d, *J*=9.2 Hz) and 7.52 (d, *J*=9.2 Hz)] (1H, CON*H*, ratio 1.0:1.2); ^{13}C NMR (75 MHz, DMSO-d_6): δ [18.4, 18.5] (CH(*C*H$_3$)$_2$), 20.4 (CH(*C*H$_3$)$_2$), [23.7, 24.6] (pyr-H_2C(4)), [26.7, 28.8] (*C*H(CH$_3$)$_2$), [31.1, 32.4] (pyr-H_2C(3)), [47.2, 47.8] (pyr-H_2C(5)), 55.9 (*C*HN), [60.2, 60.8] (pyr-H*C*(2)), 62.0 (*C*H_2O), 66.5 (*C*H_2(CBZ)), [127.8, 128.5], [128.1, 128.2], [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), 154.6 (*C*═O(CBZ)), [172.3 172.6] (*C*ONH); IR (KBr): ν 3455, 3303, 2970, 1673, 1655, 1551, 1441, 1353, 1178, 1129, 695, 624 cm^{-1}; MS-ES$^+$ (CH_3CN): *m*/*z* 335 (M+H$^+$, 100%). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.63; H, 7.83; N, 8.41. Found: C, 64.35; H, 7.76; N, 8.35.

4.2.4. (2*S*)-2-(2-Hydroxy-(1*S*)-1-phenyl-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9d). Yield: 4.21 g, 57%. White solid; mp: 151–154 °C; $[\alpha]_D$=+29.8 (*c* 0.58, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77–1.90 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.09–2.23 (m, 1H, pyr-H_2C(3)), 3.39–3.50 (m, 2H, pyr-H_2C(5)), 3.52–3.63 (m, 2H, CH_2O), [4.30–4.33 (m) and 4.36 (dd, *J*=8.0, 2.3 Hz)] (1H, pyr-*H*C(2)), 4.82–4.88 (m, 2H, C*H*N, CH_2Ph(CBZ)), [5.03 (d, *J*=12.9 Hz) and 5.09 (d, *J*=12.9 Hz)] (1H, CH_2Ph(CBZ)), 7.17–7.38 (m, 10H, Ar-*H*C(Ph), Ar-*H*C(CBZ)), [8.25 (d, *J*=8.2 Hz), and 8.33 (d, *J*=8.2 Hz)] (1H, N*H*, ratio 1.0:1.3); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.8, 24.7] (pyr-H$_2$*C*(4)), [30.9, 32.2] (pyr-H$_2$*C*(3)), [47.2, 47.9] (pyr-H$_2$*C*(5)), 55.6 (*C*HN), [60.1, 60.6] (pyr-H*C*(2)), [65.3, 65.4] (*C*H$_2$O), [66.4, 66.6] (*C*H$_2$-Ph(CBZ)), [127.3, 128.5], 127.6, 127.7, [128.1, 128.2], 128.6, [128.9, 129.1] (Ar-H*C*(Ph), Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), [141.7, 141.8] (*ipso*-Ph), [154.5, 154.8] (*C*=O (CBZ)), [172.3, 172.6] (*C*ONH); IR (KBr): ν 3405, 3318, 2891, 1665, 1542, 1456, 1361, 1259, 1174, 1126, 1078, 771, 698 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m*/*z* 369 (M+H$^+$, 100%). Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.44; H, 6.56; N, 7.63. Found: C, 68.11; H, 6.49; N, 7.58.

4.2.5. (2*S*)-2-(2-Hydroxy-(1*R*)-1-phenyl-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9e). Yield: 4.21 g, 57%. White solid; mp: 133–136 °C; $[\alpha]_D$=−108.7 (*c* 0.55, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77–1.80 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.09–2.18 (br m, 1H, pyr-H_2C(3)), 3.40–3.47 (m, 2H, pyr-H_2C(5)), 3.51–3.59 (m, 2H, CH_2O, O*H*), 4.28–4.34 (br m, 1H, pyr-*H*C(2)), 4.81–4.88 (m, 2H, C*H*N, CH_2O), 4.99–5.10 (m, 2H, CH_2Ph(CBZ)), 7.21–7.40 (m, 10H, Ar-*H*C(CBZ), Ar-*H*C(Ph)), 8.25–8.31 (m, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.7, 24.5] (pyr-H$_2$*C*(4)), [30.8, 31.9] (pyr-H$_2$*C*(3)), [47.3, 47.8] (pyr-H$_2$*C*(5)), 55.5 (*C*HN), [60.2, 60.7] (pyr-H*C*(2)), [65.1, 65.4] (*C*H$_2$O), 66.6 (*C*H$_2$Ph(CBZ)), 127.4, 127.5, [127.8, 128.5], [128.15, 128.25], 128.7, [129.0, 129.1] (Ar-H*C*(Ph), Ar-H*C*(CBZ)), [137.6, 137.8] (*ipso*-Ph(CBZ)), 142.0 (*ipso*-Ph), [154.7, 154.8] (*C*=O(CBZ)), [172.1, 172.3] (*C*ONH); IR (KBr): ν 3473, 3265, 3066, 1705, 1654, 1559, 1421, 1355, 1169, 1089, 699 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m*/*z* 369 (M+H$^+$, 100%). Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.44; H, 6.56; N, 7.63. Found: C, 68.00; H, 6.52; N, 7.59.

4.2.6. (2*S*)-2-((1*S*)-1-Hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9f). Yield: 5.50 g, 81%. White solid; mp: 136–138 °C; $[\alpha]_D$=−42.0 (*c* 0.49, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ [0.77 (s) and 0.85 (s)] (9H, C(CH_3)$_3$, ratio 1.2:1.0), 1.76–1.93 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.04–2.19 (br m, 1H, pyr-H_2C(3)), 3.24–3.33 (br m, 1H, CH_2O), 3.38–3.46 (br m, 2H, pyr-H_2C(5)), 3.54–3.58 (br m, 2H, C*H*N, O*H*), 4.25–4.38 (br m, 2H, pyr-*H*C(2), CH_2O), [4.90 (app d, *J*=13.1 Hz, 1H) and 5.04 (d, *J*=12.6 Hz), 5.10 (d, *J*=12.6 Hz)] (2H, CH_2Ph (CBZ)), 7.27–7.38 (m, 5H, Ar-*H*C(CBZ)), 7.44–7.49 (m, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.6, 24.6] (pyr-H$_2$*C*(4)), [27.5, 27.6] (C(*C*H$_3$)$_3$), [30.7, 32.2] (pyr-H$_2$*C*(3)), [34.2, 34.4] (*C*(CH$_3$)$_3$), [47.2, 47.9] (pyr-H$_2$*C*(5)), 59.3 (*C*HN), [60.1, 60.6] (pyr-H*C*(2)), 61.3 (*C*H$_2$O), 66.4 (*C*H$_2$-Ph(CBZ)), [127.9, 128.4], 128.2, [128.9, 129.1] (Ar-H*C*(CBZ)), [137.7, 137.8] (*ipso*-Ph(CBZ)), 154.6 (*C*=O(CBZ)), [172.6, 173.0] (*C*ONH)); IR (KBr): ν 3395, 3322, 2966, 1672, 1661, 1555, 1428, 1356, 1113 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m*/*z* 349 (M+H$^+$, 100%). Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.47; H, 8.10; N, 8.07. Found: C, 65.73; H, 8.00; N, 8.15.

4.2.7. (2*R*)-2-((1*S*)-1-Hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9g). Yield: 5.57 g, 82%. White solid; mp: 100–102 °C. $[\alpha]_D$=+47.4 (*c* 0.49, EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (s, 9H, C(CH_3)$_3$), 1.83–1.87 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.11–2.16 (br m, 1H, pyr-H_2C(3)), 3.39–3.59 (m, 4H, CH_2O, pyr-H_2C(5), O*H*), 3.62–3.66 (m, 1H, C*H*N), 4.21–4.35 (m, 2H, pyr-*H*C(2), CH_2O), 4.95–5.15 (m, 2H, CH_2Ph(CBZ)), 7.22–7.37 (m, 5H, Ar-*H*C(CBZ)), 7.44 (d, *J*=9.5 Hz, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.7, 24.6] (pyr-H$_2$*C*(4)), 27.6 (C(*C*H$_3$)$_3$), [31.0, 32.3] (pyr-H$_2$*C*(3)), 34.7 (*C*(CH$_3$)$_3$), [47.3, 47.8] (pyr-H$_2$*C*(5)), [58.8. 58.9] (*C*HN), [60.4, 60.9] (pyr-H*C*(2)), 61.5 (*C*H$_2$O), 66.5 (*C*H$_2$Ph(CBZ)), [128.0, 128.5], 128.2, [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), 154.8 (*C*=O(CBZ)), [172.3, 172.5] (*C*ONH)); IR (KBr): ν 3239, 3089, 2968, 1708, 1651, 1581, 1419, 1342, 1082, 697 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m*/*z* 349 (M+H$^+$, 100%). Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.47; H, 8.10; N, 8.07. Found: C, 65.24; H, 7.98; N, 7.98.

4.2.8. (2*S*)-2-((2-Hydroxy-(1*S*)-1-methyl-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9h). Yield: 3.69 g, 60%. White solid; mp: 116–118 °C. $[\alpha]_D$=−36.7 (*c* 0.46, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ [0.99 (d, *J*=6.6 Hz) and 1.08 (d, *J*=6.6 Hz)] (3H, CH_3, ratio 1.5:1.0), 1.84–1.96 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.09–2.22 (br m, 1H, pyr-H_2C(3)), 3.22–3.27 (m, 1H, CH_2O), 3.34–3.54 (m, 3H, pyr-H_2C(5), O*H*), 3.75–3.84 (m, 1H, C*H*N), [4.20 (d, *J*=6.0 Hz) and 4.24 (dd, *J*=8.4, 2.9 Hz)] (1H, pyr-*H*C(2)), 4.66–4.73 (m, 1H, CH_2O), [5.02 (d, *J*=12.9 Hz), 5.09 (d. *J*=12.9 Hz), 5.12 (d, *J*=12.8 Hz), 5.15 (d, *J*=12.8 Hz)] (2H, CH_2Ph(CBZ)), 7.32–7.43 (m, 5H, Ar-*H*C(CBZ)), [7.68 (d, *J*=8.1 Hz) and 7.73 (d, *J*=8.1 Hz)] (1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [17.7, 17.8) (pyr-H$_2$*C*(4)), [23.8, 24.6] (CH$_3$), [31.0, 32.1] (pyr-H$_2$*C*(3)), [47.1, 47.2] (pyr-H$_2$*C*(5)), 47.8 (CHN), [60.1, 60.6] (pyr-H*C*(2)), 65.1 (*C*H$_2$O), 66.4 (*C*H$_2$Ph(CBZ)), [127.7, 128.5], [128.1, 128.2], [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), 154.6 (*C*=O(CBZ)), [172.0, 172.3] (*C*ONH); IR (KBr): ν 3427, 3307, 2958, 2890, 1698, 1548, 1432, 1362, 769, 736 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m*/*z* 307 (M+H$^+$, 100%). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.70; H, 7.23; N, 9.18. Found: C, 62.52; H, 7.20; N, 8.93.

4.2.9. (2*S*)-2-((1*S*)-1-Benzyl-2-hydroxy-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9i). Yield: 6.68 g, 87%. White solid; mp: 138–140 °C; $[\alpha]_D$=−68.7 (*c* 0.52, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65–1.72 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 1.95–2.09 (m, 1H, pyr-H_2C(3)), 2.60–2.72 (m, 1H, CH_2Ph), 2.77–2.88 (m, 1H, CH_2Ph), 3.23–3.38 (m, 2H, pyr-H_2C(5)), 3.40–3.47 (m, 1H, CH_2O), 3.90–3.94 (m, 1H, C*H*N), 4.15–4.18 (m, 1H, CH_2O), 4.71–4.78 (m, 1H, pyr-*H*C(2)), [4.95 (d, *J*=13.0 Hz), 5.01 (d, *J*=13.0 Hz) and 5.07–5.15 (m)] (2H, CH_2Ph(CBZ), ratio 1.9:1.0), 7.12–7.40 (m, 10H,

Ar-*H*C(Bn), Ar-*H*C(CBZ)), [7.65 (d, *J*=8.2 Hz) and 7.73 (d, *J*=8.4 Hz)] (1H, N*H*, ratio 1.0:1.2); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.5, 24.4] (pyr-H_2C(4)), [30.6, 31.9] (pyr-H_2C(3)), 37.0 (CH_2Ph), [47.2, 47.8] (pyr-H_2C(5)), 52.9 (*C*HN), [60.4, 60.8] (pyr-H*C*(2)), 63.1 (CH_2O), [66.3, 66.6] (CH_2Ph(CBZ)), 126.5, 127.7, 128.2 (Ar-H*C*(Bn), Ar-H*C*(CBZ)), 128.5 (*ipso*-Ph(Bn), [128.7, 128.9], 129.1, [129.7, 129.9] (Ar-H*C*(Bn), Ar-H*C*(CBZ)), [137.8, 139.9] (*ipso*-Ph(CBZ)), [154.6, 154.9] (*C*=O(CBZ)), [172.1, 172.4] (*C*ONH); IR (KBr): ν 3367, 3321, 2875, 1679, 1643, 1541, 1430, 1364, 741, 698, 624 cm^{-1}; MS-ES$^+$ (CH_3CN): *m*/*z* 383 (M+H$^+$, 100%). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.07; H, 6.85; N, 7.35. Found: C, 68.88; H, 6.74; N, 7.28.

4.3. Synthesis of the oxazolines

The hydroxyamide (13.68 mmol) was dissolved in dry CH_2Cl_2 (120 mL) in an oven-dried Schlenk tube under an atmosphere of nitrogen and was cooled to −78 °C in a dry ice/acetone bath. DAST (15.05 mmol) was added dropwise via syringe and the resulting yellow solution was stirred at −78 °C for 1 h and then at room temperature overnight (16 h). The reaction mixture was poured slowly onto sat. aq. $NaHCO_3$ (150 mL), the two layers were separated and the organic layer was washed with water (2×50 mL). All the aqueous layers were then combined and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over anhyd. sodium sulfate and concentrated in vacuo to give a brown oil. This crude oil was then purified by flash column chromatography on silica gel (4×40 cm) using 10% MeOH/AcOEt as the eluent.

4.3.1. (2*S*)-2-(4,5-Dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10a). Yield: 3.22 g, 86%. Colourless oil; $[\alpha]_D$=−68.4 (*c* 0.54, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89–1.97 (br m, 1H, pyr-H_2C(4)), 2.01–2.09 (br m, 2H, pyr-H_2C(4), pyr-H_2C(3)), 2.12–2.23 (br m, 1H, pyr-H_2C(3)), 3.45–3.65 (m, 2H, pyr-H_2C(5)), 3.71 (app t, *J*=9.5 Hz, 1H, CH_2N/CH_2O), 3.86 (app t, *J*=9.5 Hz, 1H, CH_2N/CH_2O), 4.02 (app q, *J*=9.0 Hz, 0.5H, CH_2N/CH_2O), 4.14 (app q, *J*=9.0 Hz, 0.5H, CH_2N/CH_2O), 4.24–4.35 (m, 1H, CH_2N/CH_2O), 4.57 (br dd, *J*=13.2, 7.8 Hz, 1H, pyr-*H*C(2)), [5.00 (d, *J*=12.6 Hz), 5.08 (d, *J*=12.4 Hz), 5.21 (d, *J*=12.4 Hz), 5.28 (d, *J*=12.6 Hz)] (2H, CH_2Ph(CBZ)), 7.28–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [23.7, 24.4] (pyr-H_2C(4)), [30.4, 31.6] (pyr-H_2C(3)), [46.6, 47.1] (pyr-H_2C(5)), [54.5, 54.6] (CH_2N), [54.7, 55.1] (pyr-H*C*(2)), [66.9, 67.2] (CH_2-Ph(CBZ)), [68.0, 68.2] (CH_2O), 127.96, 128.04, 128.1, 128.4, 128.57, 128.64, 128.8 (Ar-H*C*(CBZ)) [137.0, 137.2] (*ipso*-Ph(CBZ)), [154.7, 155.0] (*C*=O(CBZ)), [168.3, 168.6] (*C*=N); IR (neat): ν 2964, 2882, 1709, 1673, 1416, 1358, 1160, 1118 cm^{-1}; MS-ES$^+$ (CH_3CN): *m*/*z* 275 (M+H$^+$, 100%). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.32; H, 6.54; N, 9.91.

4.3.2. (2*S*)-2-((4*S*)-4-Isopropyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10b). Yield: 3.98 g, 92%. Colourless oil; $[\alpha]_D$=−113.6 (*c* 0.39, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ [0.80 (d, *J*=6.8 Hz), 0.86 (d, *J*=6.8 Hz), 0.87 (d, *J*=6.8 Hz), 9.06 (d, *J*=6.8 Hz)] (6H, CH(CH_3)$_2$), [1.62–1.73 and 1.76–1.83] (m, 1H, C*H*(CH$_3$)$_2$), 1.86–1.95 (m, 1H, pyr-H_2C(4)), 1.98–2.05 (m, 2H, pyr-H_2C(4), pyr-H_2C(3)), 2.12–2.28 (m, 1H, pyr-H_2C(3)), 3.42–3.64 (m, 2H, pyr-H_2C(5)), 3.76–3.83 (m, 0.6H, C*H*N), 3.89 (app t, *J*=7.9 Hz, 0.6H, CH_2O), 3.95–4.05 (m, 1.4H, CH_2O(1H), C*H*N), 4.21 (app t, *J*=7.9 Hz, 0.4H, CH_2O), 4.54–4.60 (m, 1H, pyr-*H*C(2)), 5.04–5.23 (m, 2H, CH_2Ph(CBZ)), 7.27–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [17.5, 17.7) (CH(*C*H$_3$)$_2$), 18.4 (CH(*C*H$_3$)$_2$), [23.5, 24.3] (pyr-H_2C(4)), [30.6, 31.7] (pyr-H_2C(3)), 32.2 (*C*H(CH$_3$)$_2$),), [46.4, 47.0] (pyr-H_2C(5)), [54.7, 55.0] (pyr-H*C*(2)), [66.7, 66.8] (CH_2Ph(CBZ)), 70.1 (CH_2O), [71.6, 71.7] (*C*HN), 127.8, 128.3, 128.4 (Ar-H*C*(CBZ)), 136.9 (*ipso*-ph(CBZ)), [152.3, 154.5] (*C*=O(CBZ)), [166.9, 167.1] (*C*=N); IR (neat): ν 2960, 2878, 1709, 1673, 1413, 1357, 1171, 1117, 982, 770, 697 cm^{-1}; MS (70 eV, EI): *m*/*z*(%) 316 (M$^+$, 10), 225 (15), 199 (5), 164 (23), 140 (100), 127 (18). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 67.95; H, 7.62; N, 8.76.

4.3.3. (2*S*)-2-((4*R*)-4-Isopropyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10c). Yield: 3.77 g, 87%. Colourless oil; $[\alpha]_D$=−30.8 (*c* 0.37, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ [0.78 (d, *J*=6.7 Hz), 0.87 (app t, *J*=7.2 Hz), 0.93 (d, *J*=6.7 Hz)] (6H, CH(CH_3)$_2$), 1.51–1.62 (m, 0.5H, C*H*(CH$_3$)$_2$), 1.79–1.91 (m, 1.5H, pyr-H_2C(4)(1H), C*H*(CH$_3$)$_2$), 1.98–2.11 (m, 2H, pyr-H_2C(4), pyr-H_2C(3)), 2.14–2.28 (m, 1H, pyr-H_2C(3)), 3.42–3.65 (m, 2H, pyr-H_2C(5)), [3.75–3.84 and 3.93–4.02] (m, 2H, C*H*N, CH_2O), 4.11–4.29 (m, 1H, CH_2O), 4.56–4.59 (m, 1H, pyr-*H*C(2)), 5.06–5.21 (m, 2H, CH_2Ph(CBZ)), 7.28–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [17.8, 18.3] (CH(*C*H$_3$)$_2$), 19.1 (CH(*C*H$_3$)$_2$), [23.7, 24.4] (pyr-H_2C(4)), [30.8, 31.9] (pyr-H_2C(3)), [32.5, 32.7] (*C*H(CH$_3$)$_2$), [46.7, 47.2] (pyr-H_2C(5)), [54.8, 55.2] (pyr-H*C*(2)), [66.97, 67.08] (CH_2Ph(CBZ)), [70.3, 70.6] (CH_2O), [72.1, 72.4] (*C*HN), [128.0, 128.1], [128.4, 128.6], 128.8 (Ar-H*C*(CBZ)), 137.1 (*ipso*-Ph), 154.8 (*C*=O(CBZ)), [167.1, 167.5] (*C*=N); IR (neat): ν 2958, 2881, 1708, 1673, 1414, 1356, 1186, 1118, 980, 696 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 316 (M$^+$, 14), 225 (16), 199 (5), 164 (25), 140 (100), 127 (19). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 67.99; H, 7.52; N, 8.72.

4.3.4. (2*S*)-2-((4*S*)-4-Phenyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10d). Yield: 3.88 g, 81%. Yellow oil; $[\alpha]_D$=−85.1 (*c* 0.26, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92–2.05 (br m, 1H, pyr-H_2C(4)), 2.08–2.19 (br m, 2H, pyr-H_2C(4), pyr-H_2C(3)), 2.23–2.35 (br m, 1H, pyr-H_2C(3)), 3.45–3.62 (br m, 1H, pyr-H_2C(5)), 3.64–3.70 (m, 1H, pyr-H_2C(5)), [4.02 (app t, *J*=8.0 Hz,) and 4.12 (app t, *J*=8.0 Hz)] (1H, CH_2O/C*H*N, ratio 1.0:1.0), 4.40 (app t, *J*=9.1 Hz, 0.5H, CH_2O/C*H*N), 4.60–4.68 (m, 1.5H, pyr-*H*C(2), CH_2O/C*H*N(0.5H)), 5.05 (app t, *J*=9.1 Hz, 0.5H, CH_2O/C*H*N), 5.11–5.24 (m, 2.5H, CH_2Ph(CBZ), CH_2O/C*H*N (0.5H))), 7.12–7.27 (m, 1H, Ar-*H*C(Ph)), 7.30–7.39 (m, 9H, Ar-*H*C(Ph), Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [23.6, 24.4] (pyr-H_2C(4)), [30.6, 31.7] (pyr-H_2C(3)), [46.5, 47.0] (pyr-H_2C(5)), [54.7, 55.0] (pyr-H*C*(2)), [66.9, 67.0] (CH_2Ph(CBZ)), [69.4, 69.6] (*C*HN), [75.2, 75.5] (CH_2O), 126.5, 126.7, 127.4, 127.6, 127.85, 127.93, 128.5, 128.7 (Ar-H*C*(Ph), Ar-H*C*(CBZ)), 136.9 (*ipso*-Ph(CBZ)), 142.5 (*ipso*-Ph), 154.8 (*C*=O(CBZ)),

168.7 (*C*═N); IR (neat): ν 3031, 2957, 2893, 1703, 1668, 1416, 1358, 1170, 985, 761, 703 cm^{-1}; MS (70 eV, EI): *m/z* (%) 350 (M^+, 11), 259 (9), 215 (15), 198 (14), 174 (100), 161 (28), 132 (8), 104 (84). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.80; H, 6.34; N, 7.98.

4.3.5. (2*S*)-2-((4*R*)-4-Phenyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10e). Yield: 4.51 g, 94%. Yellow oil; $[\alpha]_D$=−16.9 (*c* 0.46, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91–2.01 (br m, 1H, pyr-H_2C(4)), 2.06–2.14 (br m, 2H, pyr-H_2C(4), pyr-H_2C(3)), 2.21–2.34 (br m, 1H, pyr-H_2C(3)), 3.48–3.58 (br m, 1H, pyr-H_2C(5)), 3.60–3.69 (br m, 1H, pyr-H_2C(5)), [3.94 (app t, *J*=8.3 Hz) and 4.08 (app t, *J*=7.9 Hz)] (1H, CH_2O/C*H*N, ratio 1.0:1.0), 4.54 (app t, *J*=8.8 Hz, 0.5H, CH_2O/C*H*N), 4.63–4.69 (m, 1.5H, pyr-*H*C(2), CH_2O/C*H*N(0.5H)), 5.05–5.24 (m, 3H, CH_2Ph(CBZ), CH_2O/C*H*N), 7.11–7.13 (br m, 1H, Ar-*H*C(Ph)), 7.24–7.36 (m, 9H, Ar-*H*C(Ph), Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [23.6, 24.4] (pyr-H_2C(4)), [30.6, 31.9] (pyr-H_2C(3)), [46.5, 47.1] (pyr-H_2C(5)), [54.6, 55.0] (pyr-H*C*(2)), [66.9, 67.0] (*C*H_2-Ph(CBZ)), [69.6, 69.7] (*C*HN), [75.1, 75.5] (*C*H_2O), 126.6, 126.7, 127.4, 127.6, 127.8, 127.9, 128.5, 128.7 (Ar-H*C*(Ph), Ar-H*C*(CBZ)), 136.9 (*ipso*-Ph(CBZ)), [142.1, 142.5] (*ipso*-Ph), 154.6 (*C*═O(CBZ)), [168.6, 168.9] (*C*═N); IR (neat): ν 3029, 2956, 2892, 1704, 1667, 1454, 1416, 1358, 1170, 1116, 984, 770, 699 cm^{-1}; MS (70 eV, EI): *m/z* (%) 350 (M^+, 16), 259 (13), 215 (15), 198 (58), 174 (100), 161 (29), 132 (9), 104 (76). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.72; H, 6.44; N, 7.81.

4.3.6. (2*S*)-2-((4*S*)-4-*tert*-Butyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10f). Yield: 3.98 g, 88%. Colourless oil; $[\alpha]_D$=−120.3 (*c* 0.30, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ [0.82 (s) and 0.87 (s)] (9H, C(CH_3)$_3$, ratio 1.5:1), 1.85–1.94 (br m, 1H, pyr-H_2C(4)), 1.96–2.04 (br m, 2H, pyr-H_2C(4), pyr-H_2C(3)), 2.10–2.26 (br m, 1H, Pyr-H_2C(3)), 3.42–3.62 (m, 2H, pyr-H_2C(5)), 3.70 (app t, *J*=7.7 Hz, 0.5H, CH_2O/C*H*N), 3.83–4.00 (m, 1.5H, CH_2O/C*H*N), 4.07–4.20 (m, 1H, CH_2O/C*H*N), 4.56–4.60 (m, 1H, pyr-*H*C(2)), 5.04–5.23 (m, 2H, CH_2Ph(CBZ)), 7.27–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [23.6, 24.3] (pyr-H_2C(4)), 25.7 (C(*C*H_3)$_3$), [30.7, 31.8] (pyr-H_2C(3)), 33.6 (*C*(CH$_3$)$_3$), [46.5, 47.0] (pyr-H_2C(5)), [54.7, 55.1] (pyr-H*C*(2)), 66.7 (*C*H_2Ph(CBZ)), [68.9, 69.1] (*C*H_2O), 75.7 (*C*HN), 127.4, 127.9, 128.4 (Ar-H*C*(CBZ)), 136.9 (*ipso*-Ph(CBZ)), 154.6 (*C*═O(CBZ)), [166.8, 167.1] (*C*═N); IR (neat): ν 2954, 2892, 1709, 1674, 1413, 1356, 1172, 1117, 982, 769 cm^{-1}; MS (70 eV, EI): *m/z* (%) 330 (M^+, 45), 273 (15), 229 (34), 195 (22), 154 (100), 141 (17), 114 (6). Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.69; H, 7.81; N, 8.26.

4.3.7. (2*R*)-2-((4*S*)-4-*tert*-Butyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10g). Yield: 3.39 g, 75%. Colourless oil; $[\alpha]_D$=+36.8 (*c* 0.13, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ [0.80(s) and 0.89 (s)] (9H, C(CH_3)$_3$, ratio 1.1:1), 1.87–1.93 (br m, 1H, pyr-H_2C(4)), 1.96–2.23 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 3.45–3.64 (m, 2H, pyr-H_2C(5)), [3.74–3.89 (m, 1.2H), 3.97 (app t, *J*=8.1 Hz, 0.5H), 4.04–4.22 (m, 1.2H)] (3H, C*H*N, CH_2O), 4.60 (br d, *J*=8.1 Hz, 1H, pyr-*H*C(2)), 5.06–5.19 (m, 2H, CH_2Ph(CBZ)), 7.27–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [23.7, 24.4] (pyr-H_2C(4)), [26.0, 27.0] (C(*C*H_3)$_3$) [30.8, 32.0] (pyr-H_2C(3)), [33.7, 34.0] (*C*(CH$_3$)$_3$), [46.6, 47.2] (pyr-H_2C(5)), [54.8. 55.2] (pyr-H*C*(2)), [63.1, 67.0] (*C*H_2Ph(CBZ)), 69.2 (*C*H_2O), 75.9 (*C*HN), 127.9, 128.0, 128.4, 128.6, 128.8 (Ar-H*C*(CBZ)), 137.1 (*ipso*-Ph), 154.9 (*C*═O(CBZ)), 167.4 (*C*═N)); IR (neat): ν 2956, 2879, 1709, 1675, 1414, 1358, 1194, 1116, 979, 789, 698 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 331 ($M+H^+$, 100%). Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.78; H, 7.99; N, 8.34.

4.3.8. (2*S*)-2-((4*S*)-4-Methyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10h). Yield: 3.67 g, 93%. Colourless oil; $[\alpha]_D$=−112.4 (*c* 1.09, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ [1.12 (d, *J*=6.2 Hz) and 1.23 (d, *J*=6.4 Hz)] (3H, CH_3, ratio 1.2:1), 1.87–1.93 (br m, 1H, pyr-H_2C(4)), 1.96–2.10 (br m, 2H, pyr-H_2C(4), pyr-H_2C(3)), 2.12–2.23 (br m, 1H, pyr-H_2C(3)), 3.42–3.53 (m, 1H, pyr-H_2C(5)), 3.55–3.65 (m, 1H, pyr-H_2C(5)), [3.69 (app t, *J*=6.6 Hz) and 3.82 (app t, *J*=7.4 Hz)] (1*H*, CH_2O, ratio 1.2:1), 3.98–4.22 (m, 1.5H, C*H*N, CH_2O), 4.33 (app t, *J*=8.3 Hz, 0.5H, CH_2O), 4.50–4.58 (m, 1H, pyr-*H*C(2)), 5.02 (d, *J*=12.6 Hz), 5.10 (d, *J*=12.6 Hz), 5.18 (d, *J*=12.6 Hz), 5.25 (d, *J*=12.6 Hz)] (2H, CH_2Ph(CBZ)), 7.30–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [21.6, 21.7] (*C*H_3), [23.7, 24.5] (pyr-H_2C(4)), [30.6, 31.6] (pyr-H_2C(3)), [46.7, 47.2] (pyr-H_2C(5)), [54.7 55.2] (pyr-H*C*(2)), 61.6 (*C*HN), [66.9, 67.1] (*C*H_2Ph(CBZ)), [74.5, 74.6] (*C*H_2O), 127.9, 128.0, 128.1, 128.55, 128.60 (Ar-H*C*(CBZ)), 137.1 (*ipso*-Ph(CBZ)), [154.7, 154.9] (C═O(CBZ)), [167.1, 167.3] (C═N); IR (neat): 2971, 2890, 1708, 1671, 1449, 1416, 1356, 1172, 1106, 977, 769, 701 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 289 ($M+H^+$, 100%). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.41; H, 6.86; N, 9.73.

4.3.9. (2*S*)-2-((4*S*)-4-Benzyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10i). Yield: 4.89 g, 98%. Colourless oil; $[\alpha]_D$=−101.7 (*c* 0.39, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83–2.01 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.07–2.25 (m, 1H, pyr-H_2C(3)), [2.46 (dd, *J*=13.8, 8.5 Hz) and 2.65 (dd, *J*=13.8, 8.5 Hz)] (1H, CH_2Ph, ratio 1.2:1.0), [2.96 (dd, *J*=13.8, 4.8 Hz) and 3.08 (dd, *J*=13.8, 4.8 Hz)] (1H, CH_2Ph, ratio 1.2:1.0), 3.41–3.62 (m, 2H, pyr-H_2C(5)), 3.81–3.96 (m, 1.5H, CH_2O), 4.03 (app t, *J*=7.9 Hz, 0.5H, CH_2O), [4.19–4.29 (m) and 4.36–4.46 (m)] (1H, C*H*N, ratio 1.2:1.0), 4.51–4.59 (m, 1H, pyr-*H*C(2)), [5.02 (d, *J*=12.6 Hz), 5.12 (d, *J*=12.6 Hz), 5.19 (d, *J*=12.6 Hz) and 5.26 (d, *J*=12.6 Hz)] (2H, CH_2Ph(CBZ)), 7.10–7.34 (m, 10H, Ar-*H*C(Ph), Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [23.7, 24.5] (pyr-H_2C(4)), [30.6, 31.6] (pyr-H_2C(3)), [41.6, 41.7] (*C*H_2Ph), [46.7, 47.2] (pyr-H_2C(5)), [54.8, 55.2] (pyr-H*C*(2)), [67.0, 67.1] (*C*H_2-Ph(CBZ)), [67.2, 67.3] (*C*HN), [72.1, 72.2] (*C*H_2O), 126.7, 128.1, 128.6, 128.7, 129.55, 129.64 (Ar-H*C*(Ph), Ar-H*C*(CBZ)), 137.1 (*ipso*-Ph(CBZ)), [137.9, 138.1] (*ipso*-Ph), 154.7 (*C*═O(CBZ)), 168.1 (*C*═N); IR (neat): ν 2959, 2896, 1709, 1670, 1415, 1357, 1168, 1117, 980, 699, 624 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 365 ($M+H^+$, 100%). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.40; H, 6.79; N, 7.52.

4.4. Deprotection of the CBZ-oxazolines

An oven-dried Schlenk tube was charged with 10% Pd/C (0.810 g) and to this was added cyclohexene (14.2 mL, 140 mmol). A solution of the protected oxazoline (10.13 mmol) in 10 mL of dry MeOH was added via syringe and the resulting black suspension was heated at reflux under a nitrogen atmosphere until TLC (10% MeOH in AcOEt) showed complete reaction (1–15 h). After cooling to room temperature, the reaction mixture was filtered through a pad of celite, washed thoroughly with MeOH and the filtrate was concentrated in vacuo to give product. The crude product was then purified by flash column chromatography on silica gel (3x30 cm) using 20% pet. ether(40–60 °C)/MeOH or 20% MeOH/AcOEt as the eluent.

4.4.1. 2-Pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6a). Yield: 0.70 g, 49%. Yellow oil; $[\alpha]_D=-5.2$ (*c* 1.8, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.72–1.95 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.00–2.13 (m, 1H, pyr-H_2C(3)), 2.43 (br s, 1H, N*H*), 2.88–2.95 (m, 1H, pyr-H_2C(5)), 3.05–3.13 (m, 1H, pyr-H_2C(5)), 3.80–3.87 (m, 3H, CH_2O/CH_2N, pyr-*H*C(2)), 4.29 (app t, *J*=9.3 Hz, 2H, CH_2N/CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6 (pyr-H_2C(4)), 30.1 (pyr-H_2C(3)), 46.9 (pyr-H_2C(5)), 54.1 (*C*H_2N), 55.3 (pyr-H*C*(2)), 67.9 (*C*H_2O), 170.4 (*C*=N); IR (neat): ν 3317, 2938, 1649, 1569, 1406, 1350, 1072 cm^{-1}; MS-ES$^+$ (MeOH): *m*/*z* 141 (M+H$^+$, 100%); HRMS (ES$^+$) calcd. for $C_7H_{12}N_2O$ [M+H]$^+$: 141.1028, found: 141.1023.

4.4.2. (4*S*)-4-Isopropyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6b). Yield: 1.64 g, 89%. Yellow oil; $[\alpha]_D=-91.0$ (*c* 0.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (app d, *J*=6.7 Hz, 3H, CH(CH_3)$_2$), [0.94 (d, *J*=6.9 Hz) and 0.95 (d, *J*=6.7 Hz)] (3H, CH(CH_3)$_3$), 1.69–1.93 (m, 4H, pyr-H_2C(4), pyr-H_2C(3), C*H*(CH$_3$)$_2$), 2.03–2.13 (m, 1H, pyr-H_2C(3)), 2.22 (br s, 1H, N*H*), 2.87–2.95(m, 1H, pyr-H_2C(5)), 3.08–3.14 (m, 1H, pyr-H_2C(5)), 3.82–3.94 (m, 2H, C*H*N, pyr-*H*C(2)), [3.99 (app t, *J*=7.8 Hz,) and 4.00 (app t, *J*=7.8 Hz)] (1H, CH_2O), 4.26 (dd, *J*=9.5, 8.2 Hz, 1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ [18.0, 18.1] (CH(*C*H$_3$)$_2$), 18.8 (CH(*C*H$_3$)$_2$), [25.6, 25.8] (pyr-H_2C(4)), 30.5 (pyr-H_2C(3)), [32.5, 32.6] (*C*H(CH$_3$)$_2$), [47.07, 47.10] (pyr-H_2C(5)), [55.46, 55.50] (pyr-H*C*(2)), [70.4, 70.5] (*C*H_2O), [71.7, 71.9] (*C*HN), [169.2, 169.3] (*C*=N); IR (neat): ν 3344, 2962, 2873, 1667, 1479, 1363, 1203, 1105, 985, 946 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 182 (M$^+$, 35), 153 (15), 140 (100), 127 (62), 111 (41), 84 (30), 70 (81); HRMS (ES$^+$) calcd. for $C_{10}H_{19}N_2O$ [M+H]$^+$: 183.1497, found: 183.1488.

4.4.3. (4*R*)-4-Isopropyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6c). Yield: 1.24 g, 67%. Yellow oil; $[\alpha]_D=+51.9$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, *J*=6.7 Hz, 3H, CH(CH_3)$_2$), [0.94 (d, *J*=6.7 Hz) and 0.95 (d, *J*=6.7 Hz)] (3H, CH(CH_3)$_2$), 1.71–1.99 (m, 4H, pyr-H_2C(4), Pyr-H_2C(3), C*H*(CH$_3$)$_2$), 2.01–2.13 (br m, 2H, N*H*, pyr-H_2C(3)), 2.86–2.95 (m, 1H, pyr-H_2C(5)), 3.08–3.15 (m, 1H, pyr-H_2C(5)), 3.82–3.88 (m, 1H, pyr-*H*C(2)), 3.88–3.95 (m, 1H, C*H*N), [3.99 (app t, *J*=7.8 Hz) and 4.00 (app t, *J*=7.8 Hz)] (1H, CH_2O), 4.26 (dd, *J*=9.4, 8.2 Hz, 1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 (CH(*C*H$_3$)$_2$), 18.9 (CH(*C*H$_3$)$_2$), 25.8 (pyr-H_2C(4)), 30.6 (pyr-H_2C(3)), 32.6 (*C*H(CH$_3$)$_2$), 47.2 (pyr-H_2C(5)), 55.6 (pyr-H*C*(2)), 70.5 (*C*H_2O), 71.8 (*C*HN), 169.4 (*C*=N); IR (neat): ν 3340, 2962, 2873, 1667, 1465, 1367, 1204, 1190, 1098, 988, 946, 789 cm^{-1}; MS-ES$^+$ (CH_3CN): *m*/*z* (183 (M+H$^+$, 80%); HRMS (ES$^+$) calcd. for $C_{10}H_{19}N_2O$ [M+H]$^+$: 183.1497, found: 183.1490.

4.4.4. (4*S*)-4-Phenyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6d). Yield: 1.01 g, 46%. Yellow oil; $[\alpha]_D=+37.6$ (*c* 0.25, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (br s, 1H, N*H*), 1.78–1.90 (m, 2H, pyr-H_2C(4)), 1.92–2.04 (m, 1H, pyr-H_2C(3)), 2.09–2.19 (m, 1H, pyr-H_2C(3)), 2.91–2.99 (m, 1H, pyr-H_2C(5)), 3.10–3.19 (m, 1H, pyr-H_2C(5)), 3.93–4.00 (m, 1H, pyr-*H*C(2)), [4.137 (app t, *J*=8.2 Hz) and 4.144 (app t, *J*=8.2 Hz)] (1H, CH_2O/C*H*N), [4.65 (dd, *J*=8.3, 1.3 Hz) and 4.68 (dd, *J*=8.3, 1.3 Hz)] (1H, CH_2O/C*H*N), 5.18 (app t, *J*=8.3 Hz, 1H, CH_2O/C*H*N), 7.21–7.38 (m, 5H, Ar-*H*C(Ph)); ^{13}C NMR (75 MHz, $CDCl_3$): 25.9 (pyr-H_2C(4)), [30.6, 30.8] (pyr-H_2C(3)), 47.2 (pyr-H_2C(5)), 55.6 (pyr-H*C*(2)), [69.46, 69.52] (*C*HN), 75.5 (*C*H_2O), [126.77, 126.80], 127.8, [128.96, 128.98] (Ar-HC(Ph)) [142.40, 142.48] (*ipso*-Ph), [171.01, 171.07] (*C*=N); IR (neat): ν 3324, 2959, 2874, 1661, 699 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 216 (M$^+$, 4), 174 (28), 161(4), 120 (76), 104 (100); HRMS (ES$^+$) calcd. for $C_{13}H_{17}N_2O$ [M+H]$^+$: 217.1341, found: 217.1347.

4.4.5. (4*R*)-4-Phenyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6e). Yield: 0.88 g, 40%. Yellow oil; $[\alpha]_D=+132.9$ (*c* 0.24, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (br s, 1H, N*H*), 1.79–1.90 (m, 2H, pyr-H_2C(4)), 1.93–2.04 (m, 1H, pyr-H_2C(3)), 2.09–2.21 (m, 1H, pyr-H_2C(3)), 2.91–2.99 (m, 1H, pyr-H_2C(5)), 3.10–3.19 (m, 1H, pyr-H_2C(5)), 3.93–4.00 (m, 1H, pyr-*H*C(2)), [4.137 (app t, *J*=8.2 Hz) and 4.144 (app t, *J*=8.2 Hz)] (1H, CH_2O/C*H*N), [4.65 (dd, *J*=8.5, 1.5 Hz) and 4.68 (dd, *J*=8.5, 1.6 Hz)] (1H, CH_2O/C*H*N), 5.18 (app t, *J*=8.5 Hz, 1H, CH_2O/C*H*N), 7.21–7.37 (m, 5H, Ar-*H*C(Ph)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 (pyr-H_2C(4)), [30.6, 30.7] (pyr-H_2C(3)), 47.2 (pyr-H_2C(5)), 55.6 (pyr-H*C*(2)), [69.46, 69.52] (*C*HN), 75.5 (*C*H_2O), [126.76, 126.80], 127.8, [128.96, 128.97] (Ar-H*C*(Ph)), [142.42, 142.49] (*ipso*-Ph), [171.02, 171.07] (*C*=N); IR (neat): ν 3321, 2969, 1661, 1174, 987, 700 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 216 (M$^+$, 11), 198 (21), 174 (45), 161 (50), 132 (6), 120 (96), 104 (100); HRMS (ES$^+$) calcd. for $C_{13}H_{17}N_2O$ [M+H]$^+$: 217.1341, found: 217.1338.

4.4.6. (4*S*)-4-*tert*-Butyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6f). Yield: 0.95 g, 48%. Yellow oil; $[\alpha]_D=-150.2$ (*c* 0.26, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (s, 9H, C(CH_3)$_3$), 1.69–1.92 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.01–2.12 (m, 1H, pyr-H_2C(3), 2.27 (br s, 1H, N*H*), 2.86–2.93 (m, 1H, pyr-H_2C(5)), 3.04–3.16 (m, 1H, pyr-H_2C(5)), 3.80–3.87 (m, 2H, pyr-*H*C(2), C*H*N), 4.09 (app t, *J*=8.6 Hz, 1H, CH_2O), 4.20 (dd, *J*=9.9, 8.6 Hz, 1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 (C(*C*H$_3$)$_3$), 26.0 (pyr-H_2C(4), 30.7 (pyr-H_2C(3)), 33.8 (*C*(CH$_3$)$_3$), 47.3 (pyr-H_2C(5)), 55.7 (pyr-H*C*(2)), 69.3 (*C*H_2O), 75.6 (*C*HN), 169.3 (*C*=N); IR (neat): ν 3378, 2960, 2871, 1668, 1364 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 196 (M$^+$, 18), 195 (22), 168 (25), 154 (100), 141 (100), 122 (23), 111 (96);

HRMS (ES^+) calcd. for $C_{11}H_{21}N_2O$ $[M+H]^+$: 197.1654, found: 197.1651.

4.4.7. (4*S*)-4-*tert*-Butyl-2-pyrrolidin-(2*R*)-2-yl-4,5-dihydro-oxazole (6g). Yield: 1.09 g, 55%. Yellow oil; $[\alpha]_D=-40.1$ (*c* 0.44, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (s, 9H, $(C(CH_3)_3)$, 1.73–1.90 (m, 3H, pyr-$H_2C(4)$, pyr-$H_2C(3)$), 1.99–2.10 (m, 1H, pyr-$H_2C(3)$), 2.38 (br s, 1H, N*H*), 2.87–2.94 (m, 1H, pyr-$H_2C(5)$), 3.09–3.16 (m, 1H, pyr-$H_2C(5)$), 3.80–3.86 (m, 2H, C*H*N, pyr-*H*C(2)), 4.09 (app t, *J*=8.6 Hz, 1H, CH_2O), 4.2 (dd, *J*=9.8, 8.6 Hz, 1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7 (pyr-$H_2C(4)$), 26.0 ($C(CH_3)_3$), 30.7 (pyr-$H_2C(3)$), 33.9 ($C(CH_3)_3$), 47.2 (pyr-$H_2C(5)$), 55.6 (pyr-H*C*(2)), 69.3 (CH_2O), 75.5 (*C*HN), 169.3 (*C*=N); IR (neat): ν 3312, 2959, 2908, 2860, 1669, 1478, 1364, 1207, 1176, 1105, 983, 943 cm^{-1}; MS-ES^+ (CH_3CN): *m*/*z* 197 ($M+H^+$, 88%); HRMS (ES^+) calcd. for $C_{11}H_{21}N_2O$ $[M+H]^+$: 197.1654, found: 197.1661.

4.4.8. (4*S*)-4-Methyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6h). Yield: 0.86 g, 55%. Yellow oil; $[\alpha]_D=-90.6$ (*c* 0.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ [1.25 (d, *J*=6.6 Hz) and 1.25 (d, *J*=6.6 Hz)] (3H, CH_3), 1.74–1.93 (m, 3H, pyr-$H_2C(4)$, pyr-$H_2C(3)$), 2.01–2.39 (m, 2H, N*H*, pyr-$H_2C(3)$), 2.87–2.95 (m, 1H, pyr-$H_2C(5)$), 3.06–3.14 (m, 1H, pyr-$H_2C(5)$), 3.78–3.85 (m, 2H, CH_2O, pyr-*H*C(2)), 4.12–4.19 (m, 1H, C*H*N), [4.371 (app t, *J*=9.2 Hz) and 4.374 (app t, *J*=9.2 Hz)] (1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ [21.57, 21.61] (CH_3), [25.80, 25.83] (pyr-$H_2C(4)$), 30.4 (pyr-$H_2C(3)$), 47.2 (pyr-$H_2C(5)$), 55.5 (pyr-H*C*(2)), 61.4 (*C*HN), [74.59, 74.63] (CH_2O), [169.4, 169.5] (*C*=N); IR (neat): ν 3318, 2971, 2889, 1664, 1450, 1363, 1287, 1203, 1178, 1106, 1068, 985, 949 cm^{-1}; MS-ES^+ (CH_3CN): *m*/*z* 155 ($M+H^+$, 100%); HRMS (ES^+) calcd. for $C_8H_{15}N_2O$ $[M+H]^+$: 155.1184, found: 155.1188.

4.4.9. (4*S*)-4-Benzyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6i). Yield: 1.58 g, 68%. Yellow oil; $[\alpha]_D=-37.4$ (*c* 0.77, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.71–1.90 (m, 3H, pyr-$H_2C(4)$, pyr-$H_2C(3)$), 2.00–2.11 (m, 1H, pyr-$H_2C(3)$), 2.17 (br s, 1H, N*H*), [2.64 (dd, *J*=8.5, 4.4 Hz) and 2.69 (dd, *J*=8.5, 4.4 Hz)] (1H, CH_2Ph), 2.87–2.95 (m, 1H, pyr-$H_2C(5)$), 3.05–3.14 (m, 2H, CH_2Ph, pyr-$H_2C(5)$), 3.80–3.84 (m, 1H, pyr-*H*C(2)), 4.01 (app t, *J*=7.5 Hz, 1H, CH_2O), 4.18–4.24 (m, 1H, CH_2O), 4.32–4.44 (m, 1H, C*H*N), 7.18–7.32 (m, 5H, Ar-*H*C(Ph)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [25.8, 25.9] (pyr-$H_2C(4)$), [30.3, 30.4] (pyr-$H_2C(3)$), [41.7, 41.9] (CH_2Ph), 47.2 (pyr-$H_2C(5)$), [55.4, 55.5] (pyr-H*C*(2)), [67.0, 67.2] (*C*HN), [72.3, 72.4] (CH_2O), 126.7, [128.68, 128.72], [129.52, 129.59] (Ar-H*C*(Ph), [137.9, 138.0] (*ipso*-Ph), 170.1 (*C*=N); IR (neat): ν 3326, 2964, 2881, 1664, 1496, 1463, 1365, 1203, 1777, 1105, 985, 949, 754, 700 cm^{-1}; MS-ES^+ (CH_3CN): *m*/*z* 231 ($M+H^+$, 30%); HRMS (ES^+) calcd. for $C_{14}H_{19}N_2O$ $[M+H]^+$: 231.1497, found: 231.1489.

4.5. General procedure for metal screening and optimisation:

All reactions were carried out using Chemspeed® ASW 2000 apparatus equipped with two reaction blocks under a nitrogen atmosphere. Reaction tubes containing the metal pre-catalyst (5.00 μmol metal) were placed in one reaction block and to these were added ligand (as a solution in ^{i}PrOH (approx. 300 μL) and dry ^{i}PrOH (approx. 2700 μL to bring the total volume to 3000 μL). The resulting mixtures were then heated at reflux for 30 min. After cooling to 25 °C, catalyst solution (1500 μL, 2.50 μmol) from each of the reaction vessels was transferred to the corresponding reaction tube in the second reaction block to which acetophenone (59 μL, 0.50 mmol) and dry ^{i}PrOH (3428 μL) had previously been added. The reactions were initiated by the addition of KO^{i}Pr (12.5 μL of a 1 M ^{i}PrOH solution, 12.5 μmol) to each reaction tube. The reactions were monitored by taking samples after 1 h and 10 h and were analysed by GC using a CP-Chirasil-Dex CB column (25 m, 0.25 mm (diam.), 25 μm). GC conditions: 100–130 °C (1.3 °C min^{-1}) then 130–180 °C (30 °C min^{-1}). Retention times: (*R*)-1-phenylethanol 12.34 min, (*S*)-1-phenylethanol 13.14 min.

4.6. General procedure for transfer hydrogenation using $[Ir(cod)Cl]_2$

An oven-dried schlenk tube was charged with $[Ir(cod)Cl]_2$ (1.7 mg, 2.53×10^{-3}mmol). To this was added a solution of the ligand (1.01×10^{-3}mmol, 2.0 equiv./Ir) in dry ^{i}PrOH (0.5 mL) and dry ^{i}PrOH (4.5 mL). The resulting suspension was heated at reflux under a nitrogen atmosphere for 30 min to give a yellow solution. After cooling to room temperature, dry ^{i}PrOH (5 mL) and acetophenone (117 μL, 1 mmol) were added and the reaction was started by the addition of KO^{i}Pr (25 μL of a 1 M solution in ^{i}PrOH). The reaction was allowed to stir at room temp. under an atmosphere of nitrogen and was monitored at time intervals by quenching aliquots of the reaction mixture with a 10% acetic acid/^{i}PrOH solution. The aliquots were filtered through a pad of silica and the conversion and enantioselectivity of the sample were determined by chiral GC analysis using a Supelco β-Dex 120 chiral capillary column (30 m, 0.25 mm (diam.), 0.25 μm). Retention times: 120 °C, (*R*)-1-phenylethanol 19.93 min, (*S*)-1-phenylethanol 21.15 min.

4.7. General procedure for transfer hydrogenation using $[Ru(p\text{-cymene})Cl_2]_2$

An oven-dried schlenk tube was charged with $[Ru(p\text{-cymene})Cl_2]_2$ (7.7 mg, 1.25×10^{-2} mmol). To this was added a solution of the ligand (0.05 mmol, 2.0 equiv./Ru) in dry ^{i}PrOH (0.5 mL) and dry ^{i}PrOH (2.0 mL). The resulting suspension was heated at reflux under a nitrogen atmosphere for 30 min to give an orange/brown solution. After cooling to room temperature, dry ^{i}PrOH (2.5 mL) and acetophenone (59 μL, 0.5 mmol) were added and the reaction was started by the addition of KO^{i}Pr (125 μL of a 1 M solution in ^{i}PrOH) which resulted in an instantaneous red reaction mixture. The reaction was allowed to stir at room temp. under an atmosphere of nitrogen and was monitored at time intervals by quenching aliquots of the reaction mixture with a 10% acetic acid/^{i}PrOH solution. The aliquots were filtered through a pad of silica and the conversion and enantioselectivity of the sample were determined by chiral GC analysis using a Supelco β-Dex 120 chiral capillary column (30 m, 0.25 mm (diam.),

0.25 μm). Retention times: 120 °C, (*R*)-1-phenylethanol 19.93 min, (*S*)-1-phenylethanol 21.15 min.

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