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Oxazoline-Substituted Prolinamide-Based Organocatalysts for the Direct Intermolecular Aldol Reaction between Cyclohexanone and Aromatic Aldehydes

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Oxazoline-substituted prolinamides catalyse the direct asymmetric aldol reaction between cyclohexanone and a range of aldehydes to give excellent conversions and enantioselectivities up to 84 % under optimum conditions. Reactions were highly substrate-specific with electron-deficient aldehydes giving the highest yields and *ee* values. The absolute configuration of the 4-chlorobenzaldehyde-derived product was unequivocally established as (2*S*,1′*R*) by single-crystal X-ray analysis, and the stereochemistry of the product was shown to be determined principally by the stereochemistry of the proline fragment.

Introduction

The direct asymmetric aldol reaction is an important carbon–carbon bond-forming reaction that results in the formation of either one or two adjacent stereocentres, and consequently, control of the absolute and relative stereochemistry of the resulting β-hydroxy ketone is important.[1] Even though a host of Lewis acid transition metal and main group element complexes catalyse this transformation,[1c,2] in some cases with exceptional levels of enantioselectivity and diastereoselectivity, there is an escalating interest in the development of new metal-free catalysts owing to their durability, operational simplicity, environmental compatibility and functional group tolerance.[1,2] List, Barbas III and coworkers first demonstrated that L-proline catalysed the asymmetric aldol reaction between acetone and an array of aldehydes to afford the corresponding β-hydroxy ketones in good yield and exceptional enantioselectivity (>99 %).[3,4] Following this discovery, a wide variety of small organic molecules have been successfully utilised as organocatalysts in the direct aldol reaction including simple naturally occurring amino acids,[5] small peptides,[5c,6] as well as a range of more complex primary and secondary amines, although L-proline remains one of the most efficient catalysts for this transformation. Despite this success, there are a number of serious drawbacks associated with the use of L-proline, including its limited solubility in organic solvents, the low enantioselectivities obtained for reactions involving aromatic aldehydes and the difficulty of tuning its reactivity by way of structural modification. As a result, a large number of proline derivatives, the majority of which are prolinamide-based, have been synthesised with the aim of identifying highly active and selective catalysts with broad substrate scope and tunable reactivity.[7] As the reactivity and selectivity of proline and its derivatives has been attributed to stabilisation of a cyclic transition state through hydrogen-bonding,[8] even subtle changes in catalyst structure or composition could affect the strength of these interactions and ultimately the catalyst efficiency. In this regard, Gong has recently reported that *N*-aryl prolinamide organocatalysts containing electron-withdrawing substituents give higher enantioselectivities and activities relative to their electron-donating counterparts.[7h] Intrigued by such a marked influence of the aryl substituent on catalyst performance, we prepared oxazoline-substituted *N*-aryl prolinamides **1a**–**c** (Figure 1). These ligands contain an electron-poor oxazoline ring, an additional stereocentre and the potential for hydrogen bond formation involving the oxazoline nitrogen,[9] each of which may influence their performance as organocatalysts for the direct intermolecular aldol reaction. We have now been prompted to disclose our preliminary studies in this area by a recent report describing the synthesis of *N*-Boc-protected versions of proline-oxazolines **1a**–**b** and their applications in the asymmetric chromium-catalysed Nozaki–Hiyama–Kishi allylation of aldehydes.[10]

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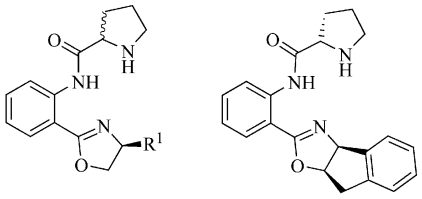


Figure 1. Prolinamide-oxazolines **1a**–**c**.

Results and Discussion

Proline-oxazolines **1a**–**c** are a particularly attractive class of organocatalyst, as they are relatively easy to prepare from inexpensive starting materials and the synthesis is modular in that it is relatively straightforward to modify the steric bulk and the number and type of stereocentres (Figure 2). The key intermediates in the synthesis of **1a**–**c** are the 2-(2′-aminophenyl)oxazolines **3a**–**c**, which were prepared in moderate yields (39–55%) by the zinc-catalysed coupling between anthranilonitrile and the corresponding amino alcohol, according to Scheme 1.[11] The desired Boc-protected oxazoline prolinamides **4a**–**c** were prepared in excellent yields (93–98%) by using the peptide-coupling protocol based on *N*,*N*′-dicyclohexylcarbodiimide (DCC) in the presence of 4-(dimethylamino)pyridine (DMAP).[12] In order to establish the relative importance of each stereocentre in the catalyst in controlling the enantioselectivity of the aldol reaction, both L- and D-Boc-proline were coupled with **3b** to afford diastereoisomers **4b** and **4b′**, respectively. Finally, the resulting prolinamides were deprotected by treatment with trifluoroacetic acid (TFA) to liberate **1a**–**c** in moderate-to-excellent yields (52–77%).

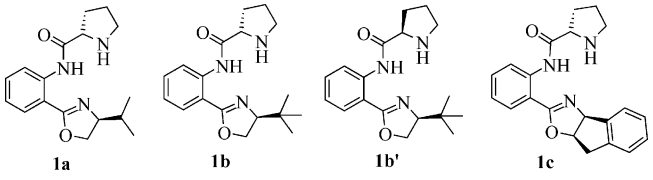
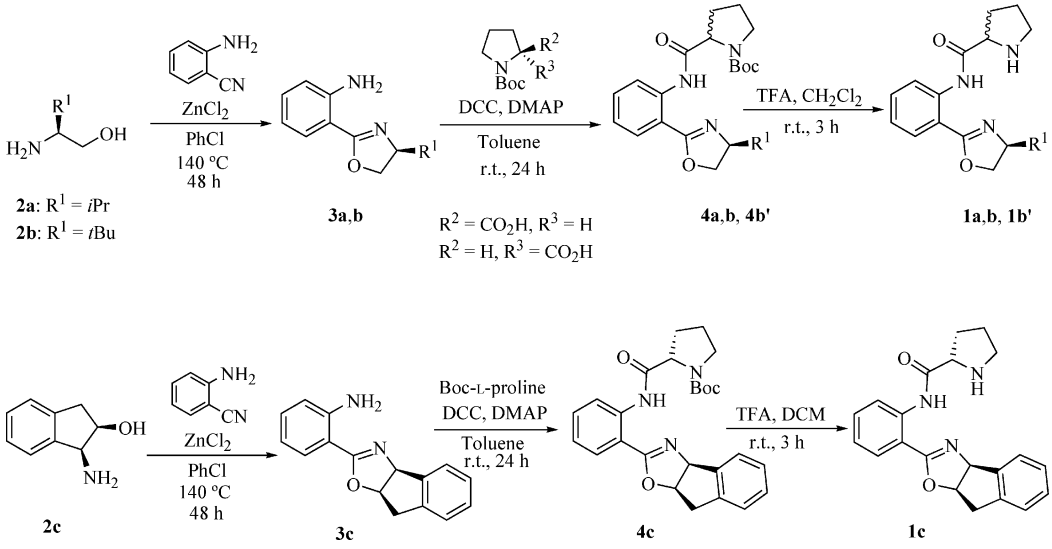


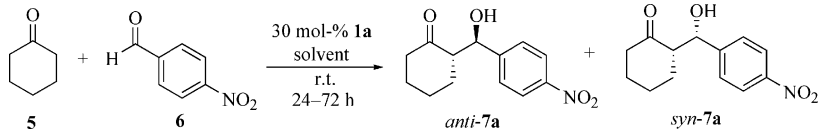
Figure 2. Organocatalysts **1a**–**c**.

The direct intermolecular aldol reaction between cyclohexanone **5** and 4-nitrobenzaldehyde **6** was chosen as the benchmark to identify the optimum conditions under catalysis by the valine-derived oxazoline prolinamide **1a**, the results of which are presented in Table 1. Preliminary screening revealed that both the yield and enantioselectivity showed a marked dependence on the solvent, and reactions in dimethyl sulfoxide (DMSO) gave the highest *ee* values, whereas the best yield was obtained in dichloromethane. For reactions conducted in DMSO, the addition of 10 equiv. of water to the reaction mixture resulted in a substantial increase in the yield with a marked improvement in enantioselectivity (Table 1, Entries 2 and 6). Similarly, the presence of water in reactions conducted in DMF resulted in significantly higher yields and a consistent enantioselectivity; the latter was irreproducible in the absence of water (Table 1, Entries 1 and 5). In contrast, the influence of water on reactions performed in methanol and dichloromethane was not as pronounced. In particular, the yields remained much the same, whereas the enantioselectivity decreased in methanol and increased in dichloromethane; both were significantly lower than those obtained in DMSO and DMF. However, attempts to further increase the catalytic activity by the addition of a larger volume of water, while maintaining a constant reaction volume and concentration, were unsuccessful; despite the reaction times being reduced to 48 h in both DMSO and DMF, the enantioselectivities decreased from 68 to 33% in the former and from 57 to 17% in the latter (Table 1, Entries 6, 10 and 5, 9). The concentration of the reaction mixture also proved to be critical: a reaction concentration of 0.67 mol dm^{-3} in



Scheme 1. Synthesis of oxazoline-substituted prolinamides **1a**–**c**.

Table 1. Optimisation of the direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalysed by **1a**.



5 6 *anti*-**7a** *syn*-**7a**

Entry	Solvent[a]	Time [h]	Yield[b] [%]	*dr*[c] *anti*/*syn*	*ee*[d] *anti* [%]
1	DMF	72	20	76:24	–[e]
2	DMSO	72	39	67:33	52
3	CH_2Cl_2	72	68	78:22	20
4	MeOH	72	57	81:19	41
5	DMF (10 equiv. H_2O)	72	77	81:19	57
6	DMSO (10 equiv. H_2O)	72	75	79:21	68
7	CH_2Cl_2 (10 equiv. H_2O)	72	66	80:20	33
8	MeOH (10 equiv. H_2O)	72	54	81:19	13
9	DMF/H_2O, 1:1	48	81	76:24	17
10	DMSO/H_2O, 1:1	48	87	68:32	33
11	DMSO (10 equiv. H_2O)[f]	72	81	88:12	72

[a] 1.5 mmol **5**, 0.5 mmol **6**, 2 mL of solvent, r.t., 30 mol-% catalyst. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC; the absolute configuration of the major *anti* enantiomer is (2*S*,1′*R*). [e] Inconsistent results obtained. [f] 0.5 mL of solvent.

aldehyde gave β-hydroxy ketone **7** in 81% yield and 72% *ee*, and a yield of 75% and an *ee* value of 68% was obtained at 0.22 mol dm^{-3} (Table 1, Entries 11 and 6).

The influence of acid additives was also studied in an attempt to improve the turnover frequency of the catalyst by accelerating the rate of formation of the intermediate enamine.[7m,13] A survey of several acids including trifluoroacetic acid, acetic acid and benzoic acid did not improve catalyst efficiency and in some cases both the yield and selectivity decreased. Whereas organocatalysis with proline and its derivatives can require high catalyst loadings, several recent studies have reported excellent enantioselectivities, diastereoselectivities and yields in reasonable reaction times with loadings as low as 0.5 mol-%.[7u] A corresponding study with **1a** revealed that conversions decreased as the catalyst loading was lowered from 30 to 1 mol-%, although the selectivities remained reasonably constant over this range (Table 2).

Table 2. Influence of catalyst loading on the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalysed by **1a**.

Entry	Catalyst loading[a] [mol-%]	Time [h]	Yield[b] [%]	*dr*[c] *anti*/*syn*	*ee*[d] *anti* [%]
1	30	72	81	88:12	72
2	20	72	72	86:14	66
3	10	72	67	87:13	68
4	5	72	40	86:14	72
5	1	72	22	91:9	63

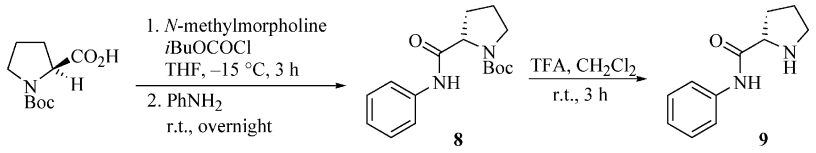
[a] 1.5 mmol **5**, 0.5 mmol **6**, 0.5 mL of DMSO, 10 equiv. H_2O, r.t. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC; the absolute configuration of the major *anti* enantiomer is (2*S*,1′*R*).

Within the narrow range of catalysts examined, the sterically bulky *tert*-butyl-based oxazoline out-performed its isopropyl-substituted counterpart and gave a markedly higher enantioselectivity with a comparable conversion after a much shorter reaction time (Table 3, Entries 1 and 2). In contrast, indanol-substituted **1c** gave a good conversion after an even shorter reaction time (24 h), although the enantioselectivity of 46% was significantly lower (Table 3, Entry 4). A comparison of L- and D-proline-based diastereoisomers **1b** and **1b′**, respectively, clearly shows that the absolute stereochemistry is determined by the proline fragment and that catalyst **1b** should be considered the matched combination and **1b′** the mismatched diastereoisomer. Furthermore, a comparison of the performance of prolinamides **1a**–**c** against their unsubstituted *N*-aryl counterpart **9**,[14,15] prepared according to the peptide coupling procedure in Scheme 2, strongly suggests that the oxazoline fragment influences both the conversion and enantioselectivity (Table 3, Entry 5) and could be used to fine-tune/optimise the catalyst. At this stage, the use of a stereochemical model to explain the influence of the oxazoline fragment on the enantioselectivity would be too speculative and a more detailed structure–selectivity study will be required to establish the role of this substituent in determining catalyst performance.

Table 3. Direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalysed by **1a**–**c** and **9**.

Entry	Catalyst[a]	Time [h]	Yield[b] [%]	*dr*[c] *anti*/*syn*	*ee*[d] *anti* [%]
1	**1a**	72	81	88:12	72 (2*S*,1′*R*)
2	**1b**	48	88	75:25	84 (2*S*,1′*R*)
3	**1b′**	48	81	82:18	74 (2*R*,1′*S*)
4	**1c**	24	90	83:17	46 (2*S*,1′*R*)
5	**9**	72	75	82:18	64 (2*S*,1′*R*)

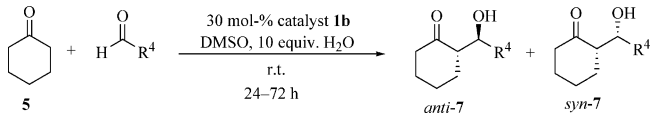
[a] 1.5 mmol **5**, 0.5 mmol **6**, 0.5 mL of DMSO, 10 equiv. H_2O, r.t., 30 mol-% catalyst. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC.



Scheme 2. Synthesis of unsubstituted proline **9**.

Having identified an optimum catalyst and conditions, the direct aldol reaction between cyclohexanone and a selection of aldehydes was investigated, the full details of which are presented in Table 4. In general, aromatic aldehydes bearing an electron-withdrawing group gave the best conversions and enantioselectivities, the latter of which increased with the electrophilicity of the substrate. Interestingly, 2-chlorobenzaldehyde gave excellent conversions after only 24 h, whereas its 4-chloro-substituted counterpart required 72 h to reach a moderate level of conversion, although the latter gave a significantly higher diastereoselectivity and *anti* enantioselectivity. In contrast, less electrophilic aldehydes such as benzaldehyde and 2-furaldehyde were poor substrates and gave the corresponding β-hydroxy ketone in low-to-moderate yields and *ee* values of 7 and 34%, respectively, whereas 4-methoxybenzaldehyde gave only a trace amount of product (Table 4, Entries 5–7).

Table 4. Direct aldol reaction between cyclohexanone and a range of aldehydes under optimum conditions.[a]



Entry	R^4	Time [h]	Yield[b] [%]	Product	*dr*[c] *anti*/*syn*	*ee*[d] *anti* [%]
1	4-$O_2NC_6H_4$	48	88	**7a**	75:25	84 (2*S*,1′*R*)
2	4-BrC_6H_4	72	84	**7b**	95:5	46 (2*S*,1′*R*)
3	4-ClC_6H_4	72	57	**7c**	97:3	55 (2*S*,1′*R*)
4	2-ClC_6H_4	24	95	**7d**	80:20	45 (2*S*,1′*R*)
5	Ph	72	59	**7e**	83:17	7 (2*S*,1′*R*)
6	2-furfuryl	72	19	**7f**	n.d.[e]	34 (2*S*,1′*R*)
7	4-$MeOC_6H_4$	72	trace	**7g**	n.d.[e]	n.d.[e]

[a] 1.5 mmol **5**, 0.5 mmol aldehyde, 0.5 mL of DMSO, 10 equiv. H_2O, r.t., 30 mol-% catalyst. [b] Isolated yield after column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC. [e] Not determined.

Despite the fact that these cyclohexanone-derived aldol products have been reported a number of times, we were unable to find unambiguous determination of the absolute stereochemistry of these compounds. We consequently determined the X-ray crystal structure of the 4-chlorobenzaldehyde-derived aldol product *anti*-**7c** (R^4 = 4-ClC_6H_4), which unequivocally establishes the absolute stereochemistry to be (2*S*,1′*R*). A view of the molecular structure of (2*S*,1′*R*)-**7c** is shown in Figure 3, and details of the structure determination are provided in the experimental section. A number of recent articles have either reported or implied that the absolute configuration of the major enantiomer of the *syn* diastereoisomer obtained from the prolinamide-catalysed aldol reaction between cyclohexanone and benzaldehyde and its derivatives is (2*R*,1′*R*), which we believe is unlikely.[7g] Houk and List[16a] have used a combination of quantum mechanical predictions and experimental tests together with a literature optical rotation value of the (2*S*,1′*S*) *syn* stereoisomer[16b] to unambiguously assign the absolute stereochemistry of the major enantiomer of the *syn* and *anti* aldol products from the proline-catalysed reaction between cyclohexanone and benzaldehyde. On the basis of this study, we are confident that prolinamide-based catalysts **1a**–**c** afford *syn*-**7c** with (2*S*,1′*S*) absolute configuration, and the stereochemistry of the other aldol products was assigned by analogy.

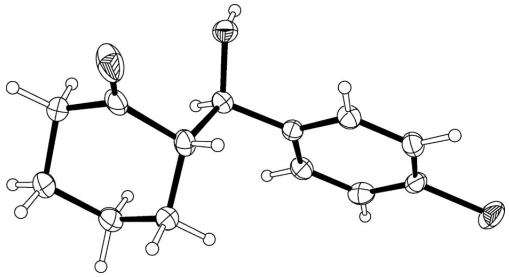


Figure 3. Molecular structure of 2-[hydroxy(4-chlorophenyl)-methyl]cyclohexanone (**7c**), unequivocally establishing the absolute stereochemistry as (2*S*,1′*R*).

Conclusions

Several prolinamide-based oxazolines were synthesised by using a straightforward peptide-coupling protocol and shown to catalyse the direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. The highest yields and enantioselectivities were obtained with the *tert*-butyl-substituted catalyst **1b** in a mixture of DMSO and 10 equiv. of water at 30 mol-% loading. A comparison with its D-proline-based diastereoisomeric counterpart **1b**′ revealed that the absolute configuration of the products is determined principally by the stereochemistry of the proline fragment. A single-crystal X-ray structure determination of the aldol product derived from 4-chlorobenzaldehyde and cyclohexanone confirmed the absolute configuration to be (2*S*,1′*R*), which is consistent with previous literature assignments. Reactions were found to be highly substrate-specific and electron-deficient aldehydes gave the highest yields and enantioselectivities, whereas their less electrophilic counterparts gave poor conversions and low *ee* values.

Experimental Section

General Remarks: ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded with a Bruker Ultrashield 300 instrument at ambient temperature. Data are reported as follows: chemical shifts (δ) are given in parts per million from the internal standard (tetramethylsilane), multiplicity (br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (J) are given in Hz, integration and assignment where possible. Elemental analyses were performed with a Carlo Erba 1108 Elemental Analyser with CE Eager 200 software. High-resolution mass spectra were obtained with a Micromass Autospec M instrument. Infrared spectra were recorded with a Nicolet Avatar 370DTGS spectrometer on a Smart-orbit diamond as a neat sample. Optical rotations were recorded with a PolAAr 2001 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{20}$: (c, g/100 mL, solvent). Melting points were determined with a hot stage and are uncorrected. HPLC analysis was performed by using a Varian ProStar 335 system with a variable-wavelength detector with the use of either a Chiralcel OD-H column or a Chiralpak AD-H column. Enantiomeric excesses were calculated from the HPLC profile. Thin-layer chromatography (TLC) was performed on EM reagent 0.25 mm silica gel 60F plates and flash-column chromatography was performed by using EM silica gel. All reactions involving air-sensitive materials were carried out by using standard Schlenk-line techniques under an atmosphere of nitrogen in flame-dried glassware. Where necessary, solvents were predried before distillation and subsequent use; toluene was distilled from sodium and stored over 4 Å molecular sieves. Dichloromethane was distilled from calcium hydride and THF was distilled from sodium/benzophenone under an atmosphere of nitrogen immediately prior to use. All reagents were purchased from commercial suppliers and used as received. Anhydrous chlorobenzene, DMSO and DMF were purchased from Sigma–Aldrich and used without further purification.

General Procedure for the Synthesis of Anilino-oxazolines (3a–c): Following the procedure reported by Sibi,[11] anilino-oxazolines were prepared from anthranilonitrile (1.0 equiv.) and the corresponding amino alcohol (1.5 equiv.) with a catalytic amount of $ZnCl_2$ (4 mol-%) in a minimum volume of dry chlorobenzene. All physical data were identical to those previously reported.

General Procedure for the Synthesis of *N*-Boc-Proline-oxazolines (4a–c):[12] To a solution of *N*-Boc-proline (1.6 equiv.) and anilino-oxazoline (1.0 equiv.) in toluene (5.0 mL/mmol aniline-oxazoline) was added DCC (1.6 equiv.) followed by DMAP (1.6 equiv.), and the reaction mixture was stirred at r.t. overnight. The solvent was removed in vacuo, and the resulting white residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) to afford the title compounds.

(*S*)-*tert*-Butyl 2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (4a):[10] This compound was prepared from 2-[(*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl]phenylamine (**3a**; 0.50 g, 2.45 mmol). Yield: 0.95 g, 97%; white solid; m.p. 108–110 °C. R_f = 0.24 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = +12.7 (c = 0.60, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, major rotamer): δ = 12.49 (br. s, 1 H, OCN*H*), 8.79 (m, J = 8.3 Hz, 1 H, Ar*H*), 7.85 (d, J = 7.9 Hz, 1 H, Ar*H*), 7.47 (m, J = 7.6 Hz, 1 H, Ar*H*), 7.09 (m, J = 7.6 Hz, 1 H, Ar*H*), 4.39–4.10 (m, 4 H, C*H*NBoc, CH_2O, C*H*N), 3.71–3.63 (m, 1 H), 3.59–3.48 (m, 1 H), 2.34–2.23 (m, 1 H), 2.16–2.03 (m, 2 H), 2.00–1.86 (m, 1 H), 1.80–1.66 [m, 1 H, C*H*(CH$_3$)$_2$], 1.35 [s, 9 H, C(CH_3)$_3$ (Boc)], 1.00 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 0.85 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, major rotamer): δ = 173.2, 163.8, 154.6, 140.3, 132.7, 129.5, 122.6, 120.2, 113.9, 80.2, 73.0, 68.6, 62.9, 47.4, 32.1, 28.8, 26.0, 24.9, 19.3, 17.7 ppm. In addition to these signals, the following resonances were assigned to the minor rotamer (major/minor rotamer, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$, minor rotamer): δ = 12.44 (br. s, 1 H, OCN*H*), 1.46 [s, 9 H, C(CH_3)$_3$ (Boc)], 0.93 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, minor rotamer): δ = 126.6, 60.5, 59.0, 47.8, 31.5, 28.7, 26.6, 24.3 ppm. IR: $\tilde{\nu}$ = 2929, 1694, 1636, 1606, 1584, 1522, 1450, 1383 cm^{-1}. MS (EI+): m/z (%) = 401 (2.2) [M]$^+$, 328 (23) [M – tBuO]$^+$, 231 (100) [M – BocNC$_4$H$_7$]$^+$, 70 (52), 57 (38) [tBu]$^+$. HRMS (EI+): calcd. for $C_{22}H_{31}N_3O_4$ [M$^+$] 401.2315; found 401.2320.

(*S*)-*tert*-Butyl 2-{2-[(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (4b):[10] This compound was prepared from 2-[(*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl]phenylamine (**3b**; 0.60 g, 2.75 mmol). Yield: 1.12 g, 98%; white solid; m.p. 68–70 °C. R_f = 0.28 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = +9.6 (c = 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, major rotamer): δ = 12.31 (br. s, 1 H, OCN*H*), 8.74 (d, J = 8.3 Hz, 1 H, Ar*H*), 7.84 (m, 1 H, Ar*H*), 7.52–7.38 (m, 1 H, Ar*H*), 7.09 (m, 1 H, Ar*H*), 4.35–4.29 (m, 1 H, C*H*NBoc), 4.26–4.09 (m, 3 H, CH_2O, C*H*N), 3.73–3.61 (m, 1 H), 3.57–3.45 (m, 1 H), 2.28–2.18 (m, 1 H), 2.14–2.00 (m, 2 H), 1.98–1.82 (m, 1 H), 1.36 [s, 9 H, C(CH_3)$_3$ (Boc)], 0.97 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, major rotamer): δ = 172.4, 162.8, 154.8, 140.3, 133.0, 129.6, 122.8, 120.0, 114.0, 80.2, 68.2, 62.5, 47.3, 34.1, 32.0, 31.5, 28.7, 26.0, 24.9 ppm. In addition to these signals, the following resonances were assigned to the minor rotamer (major/minor rotamer, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$, minor rotamer): δ = 12.45 (br. s, 1 H, OCN*H*), 1.45 [s, 9 H, C(CH_3)$_3$ (Boc)] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, minor rotamer): δ = 80.5, 47.8, 24.4 ppm. IR: $\tilde{\nu}$ = 2931, 1694, 1635, 1614, 1586, 1520, 1384, 1363 cm^{-1}. MS (EI+): m/z (%) = 416 (0.6) [M + H]$^+$, 342 (31) [M – tBuO]$^+$, 246 (100) [M – BocNC$_4$H$_7$]$^+$, 146 (65), 114 (38), 70 (21). HRMS (EI+): calcd. for $C_{23}H_{34}N_3O_4$ [M + H]$^+$ 416.2549; found 416.2563.

(*S*)-*tert*-Butyl 2-{2-[(3a*S*,8a*R*)-8,8a-Dihydro-3a*H*-indeno(1,2-*d*)oxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (4c): This compound was prepared from 2-[(3a*S*,8a*R*)-8,8a-dihydro-3a*H*-indeno(1,2-*d*)oxazo-2-yl]phenylamine (**3c**; 0.50 g, 2.00 mmol). Yield: 0.83 g, 93%; white solid; m.p. 78–80 °C. R_f = 0.27 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = +53.6 (c = 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, major rotamer): δ = 12.40 (br. s, 1 H, OCN*H*), 8.76 (d, J = 8.3 Hz, 1 H, Ar*H*), 7.86 (m, J = 7.9 Hz, 2 H, Ar*H*), 7.28 (m, 4 H, Ar*H* indanol), 7.07 (m, J = 7.9 Hz, 1 H, Ar*H*), 5.80 (d, J = 7.9 Hz, 1 H), 5.42 (t, 1 H), 4.39–4.35 (m, 1 H), 3.91–3.84 (m, 1 H), 3.74–3.66 (m, 1 H), 3.54–3.45 (m, 2 H), 2.41–2.28 (m, 1 H), 2.16–2.02 (m, 1 H), 2.02–1.91 (m, 1 H), 1.35 [s, 9 H, C(CH_3)$_3$ (Boc)] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, major rotamer): δ = 172.7, 164.3, 154.9, 141.8, 140.1, 139.6, 132.8, 129.7, 129.0, 128.0, 126.7, 125.4, 122.6, 120.4, 114.2, 82.6, 80.5, 63.0, 60.5, 47.5, 39.8, 28.8, 24.2, 21.1 ppm. In addition to these signals, the following resonances were assigned to the minor rotamer (major/minor rotamer, 10:1): ^{1}H NMR (300 MHz, $CDCl_3$, minor rotamer): δ = 12.22 (br. s, 1 H, OCN*H*), 1.53 [s, 9 H, C(CH_3)$_3$ (Boc)] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, minor rotamer): δ = 41.4, 29.0, 24.3, 21.2 ppm. IR: $\tilde{\nu}$ = 2974, 1682, 1628, 1607, 1584, 1526, 1447, 1383, 1365 cm^{-1}. MS (EI+): m/z (%) = 374 (6.4) [M – tBuO]$^+$, 277 (100) [M – BocNC$_4$H$_7$]$^+$, 146 (43), 115 (41), 70 (13), 57 (12) [tBu]$^+$. HRMS (EI+): calcd. for $C_{22}H_{20}N_3O_3$ [M – tBuO]$^+$ 374.1505; found 374.1495.

(*R*)-*tert*-Butyl 2-{2-[(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl]phenylcarbamoyl}pyrrolidine-1-carboxylate (4b′):[10] This compound was prepared from 2-[(*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl]phenyl-

amine (**3b**; 0.32 g, 1.47 mmol). Yield: 0.58 g, 95%; white solid; m.p. 58–60 °C. R_f = 0.30 (petroleum ether/ethyl acetate, 5:1). $[\alpha]_D$ = +89.5 (c = 0.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, major rotamer): δ = 12.13 (br. s, 1 H, OCN*H*), 8.68 (d, J = 8.3 Hz, 1 H, Ar*H*), 7.76 (m, J = 7.9 Hz, 1 H, Ar*H*), 7.40 (m, J = 8.3 Hz, 1 H, Ar*H*), 7.02 (m, J = 7.2 Hz, 1 H, Ar*H*), 4.23–4.08 (m, 4 H, C*H*NBoc, CH_2O, C*H*N), 3.67–3.54 (m, 1 H), 3.51–3.42 (m, 1 H), 2.31–2.22 (m, 1 H), 2.12–2.00 (m, 1 H), 1.97–1.69 (m, 2 H), 1.23 [s, 9 H, C(CH_3)$_3$ (Boc)], 0.88 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, major rotamer): δ = 172.5, 163.8, 154.6, 140.1, 132.6, 129.4, 122.5, 120.3, 114.1, 80.1, 76.5, 67.9, 62.9, 47.3, 34.4, 31.5, 28.6, 26.4, 24.9 ppm. In addition to these signals, the following resonances were assigned to the minor rotamer (major/minor rotamer, 3:1): ^1H NMR (300 MHz, $CDCl_3$, minor rotamer): δ = 1.35 [s, 9 H, C(CH_3)$_3$ (Boc)] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, minor rotamer): δ = 172.1, 155.4, 80.5, 47.8, 28.8, 24.3 ppm. IR: $\tilde{\nu}$ = 2985, 2931, 1696, 1636, 1586, 1526, 1448, 1390, 1365 cm^{-1}. MS (EI+): m/z (%) = 416 (0.1) $[M + H]^+$, 342 (9) $[M - t\text{BuO}]^+$, 245 (100) $[M - \text{BocNC}_4\text{H}_7]^+$, 146 (30), 114 (38), 70 (49), 57 (39) $[t\text{Bu}]^+$. HRMS (EI+): calcd. for $C_{23}H_{34}N_3O_4$ $[M + H]^+$ 416.2549; found 416.2555.

General Procedure for the Synthesis of Proline-Oxazolines (1a–c): To a solution of Boc-proline-oxazoline (1.0 equiv.) in CH_2Cl_2 (5.0 mL/mmol Boc-*N*-proline-oxazoline) was added trifluoroacetic acid (20 equiv.), and the reaction was stirred at r.t. for 3 h. The solvent was removed in vacuo, and the resulting residue was neutralised with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 2 mL). The organic layer was separated and dried with anhydrous $MgSO_4$ and then filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/methanol, 9:1) gave the pure title compounds.

(2*S*)-*N*-{2-[(*S*)-4,5-Dihydro-4-isopropyloxazol-2-yl]phenyl}pyrrolidine-2-carboxamide (1a): This compound was prepared from Boc-*N*-proline-oxazoline **4a** (0.95 g; 2.37 mmol). Yield: 0.55 g, 77%; white solid; m.p. 94–96 °C. R_f = 0.46 (CH_2Cl_2/methanol, 9:1). $[\alpha]_D$ = –67.6 (c = 0.88, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 12.59 (br. s, 1 H, OCN*H*), 8.71 (dd, J = 1.1, 8.3 Hz, 1 H, Ar*H*), 7.77 (dd, J = 1.5, 7.9 Hz, 1 H, Ar*H*), 7.38 (m, J = 1.5, 8.3 Hz, 1 H, Ar*H*), 7.00 (m, J = 1.1, 7.9 Hz, 1 H, Ar*H*), 4.31 (dd, J = 7.9, 9.4 Hz, 1 H, C*H*NH), 4.09 (m, 1 H, CH_2O), 3.98 (m, 1 H, CH_2O), 3.83 (dd, J = 5.7, 8.7 Hz, 1 H, C*H*N), 2.95 (m, 2 H), 2.16 (m, 3 H), 1.93 (m, 1 H), 1.73 [m, 1 H, C*H*(CH$_3$)$_2$], 1.00 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 0.91 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.6, 163.4, 140.0, 132.5, 129.6, 122.7, 120.5, 114.5, 73.5, 69.5, 62.6, 47.6, 33.4, 31.7, 26.2, 19.0, 18.9 ppm. IR: $\tilde{\nu}$ = 3390, 3050, 2960, 2870, 1672, 1640, 1579, 1513, 1447, 1287 cm^{-1}. MS (EI+): m/z (%) = 301 (2.5) $[M]^+$, 231 (100) $[M - C_4H_8N]^+$, 204 (49), 161 (61), 146 (66), 70 (71) $[C_4H_8N]^+$. HRMS (EI+): calcd. for $C_{17}H_{23}N_3O_2$ $[M]^+$ 301.1790; found 301.1797.

(2*S*)-*N*-{2-[(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl]phenyl}pyrrolidine-2-carboxamide (1b): This compound was prepared from Boc-*N*-proline-oxazoline **4b** (1.12 g, 2.70 mmol). Yield: 0.58 g, 68%; white solid; m.p. 110–112 °C. R_f = 0.47 (CH_2Cl_2/methanol, 9:1). $[\alpha]_D$ = –10.7 (c = 0.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 12.77 (br. s, 1 H, OCN*H*), 8.76 (dd, J = 1.1, 8.3 Hz, 1 H, Ar*H*), 7.88 (dd, J = 1.5, 7.9 Hz, 1 H, Ar*H*), 7.47 (m, J = 1.5, 8.3 Hz, 1 H, Ar*H*), 7.11 (m, J = 1.1, 7.9 Hz, 1 H, Ar*H*), 4.33 (m, 1 H, C*H*NH), 4.18 (m, 3 H, CH_2O, C*H*N), 3.90–3.70 (br. s, 1 H, CH$_2$N*H*), 3.22 (m, 2 H), 2.33 (m, 1 H), 2.10 (m, 1 H), 1.89 (m, 2 H), 0.99 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.0, 163.5, 140.0, 132.6, 129.5, 122.5, 120.5, 114.4, 67.7, 62.5, 53.6, 47.5, 34.1, 31.8, 26.3, 26.1 ppm. IR: $\tilde{\nu}$ = 3390, 2960, 2885, 1673, 1641, 1579, 1513, 1506, 1446, 1289 cm^{-1}. MS (EI+): m/z (%) = 315 (2.8) $[M]^+$, 245 (100) $[M - C_4H_8N]^+$, 218 (40), 161 (71), 146 (69), 70 (77) $[C_4H_8N]^+$. HRMS (EI+): calcd. for $C_{18}H_{25}N_3O_2$ $[M]^+$ 315.1947; found 315.1949. $C_{18}H_{25}N_3O_2$ (315.41): calcd. C 68.54, H 7.99, N 13.32; found C 68.34, H 8.10, N 13.22.

(2*S*)-*N*-{2-[(3a*S*,8a*R*)-8,8a-Dihydro-3a*H*-indeno(1,2-*d*)oxazol-2-yl]-phenyl}pyrrolidine-2-carboxamide (1c): This compound was prepared from Boc-*N*-proline-oxazoline **4c** (0.79 g, 1.77 mmol). Yield: 0.46 g, 75%; white solid; m.p. 203–205 °C. R_f = 0.47 (CH_2Cl_2/methanol, 9:1). $[\alpha]_D$ = –7.9 (c = 0.22, $CHCl_3$). ^1H NMR (300 MHz, [D$_4$]MeOH): δ = 12.96 (br. s, 1 H, OCN*H*), 8.57 (dd, J = 1.1, 8.3 Hz, 1 H, Ar*H*), 7.89 (dd, J = 1.5, 7.9 Hz, 1 H, Ar*H*), 7.53 (m, 1 H, Ar*H* indanol), 7.46 (m, J = 1.5, 8.3 Hz, 1 H, Ar*H*), 7.29 (m, 3 H, Ar*H* indanol), 7.15 (m, J = 1.1, 7.9 Hz, 1 H, Ar*H*), 5.86 (d, J = 7.9 Hz, 1 H), 5.53 (m, J = 1.9, 6.8, 7.9 Hz, 1 H), 4.30 (m, 1 H), 3.57 (dd, J = 6.8, 18.1 Hz, 1 H), 3.37 (m, 1 H), 3.32 (m, 2 H), 2.44 (m, 1 H), 2.00 (m, 3 H) ppm. ^{13}C NMR (75.5 MHz, [D$_4$]MeOH): δ = 172.2, 165.3, 143.3, 141.6, 140.2, 133.8, 130.9, 130.3, 128.8, 127.0, 126.7, 124.9, 121.6, 114.0, 84.3, 78.4, 63.4, 55.0, 40.9, 31.8, 26.2 ppm. IR: $\tilde{\nu}$ = 3365, 2971, 1681, 1627, 1588, 1538, 1520, 1505, 1447, 1353, 1289 cm^{-1}. MS (EI+): m/z (%) = 347 (0.6) $[M]^+$, 277 (100) $[M - C_4H_8N]^+$, 250 (34), 146 (28), 115 (30), 70 (21) $[C_4H_8N]^+$. HRMS (EI+): calcd. for $C_{21}H_{21}N_3O_2$ $[M]^+$ 347.1630; found 347.1634.

(2*R*)-*N*-{2-[(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl]phenyl}pyrrolidine-2-carboxamide (1b′): This compound was prepared from Boc-*N*-proline-oxazoline **4b′** (0.58 g, 1.40 mmol). Yield: 0.23 g, 52%; white solid; m.p. 100–102 °C. R_f = 0.50 (CH_2Cl_2/methanol, 9:1). $[\alpha]_D$ = +67.1 (c = 0.40, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 12.53 (br. s, 1 H, OCN*H*), 8.69 (dd, J = 1.1, 8.7 Hz, 1 H, Ar*H*), 7.77 (dd, J = 1.5, 7.9 Hz, 1 H, Ar*H*), 7.38 (m, J = 1.5, 8.7 Hz, 1 H, Ar*H*), 7.02 (m, J = 1.1, 7.9 Hz, 1 H, Ar*H*), 4.25 (m, J = 11.7, 13.2 Hz, 1 H, C*H*NH), 4.09 (m, 2 H, CH_2O), 3.91 (dd, J = 6.0, 8.7 Hz, 1 H, C*H*N), 3.39 (br. s, 1 H, CH$_2$N*H*), 3.04 (m, 2 H), 2.23 (m, 1 H), 1.99 (m, 1 H), 1.75 (m, 2 H), 0.91 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.4, 163.7, 140.0, 132.6, 129.6, 122.8, 120.5, 114.4, 67.8, 62.5, 47.4, 34.3, 34.2, 31.4, 26.3, 25.9 ppm. IR: $\tilde{\nu}$ = 3360, 2966, 2867, 1690, 1634, 1622, 1588, 1532, 1450, 1287 cm^{-1}. MS (EI+): m/z (%) = 245 (100) $[M - C_4H_8N]^+$, 218 (6), 161 (16), 146 (19), 70 (21) $[C_4H_8N]^+$. HRMS (EI+): calcd. for $C_{14}H_{17}N_2O_2$ $[M - C_4H_8N]^+$ 245.1290; found 245.1291. $C_{18}H_{25}N_3O_2$ (315.41): calcd. C 68.54, H 7.99, N 13.32; found C 68.02, H 8.35, N 13.08.

(*S*)-*tert*-Butyl-2-(phenylcarbamoyl)pyrrolidine-1-carboxylate (8):[15] *N*-methylmorpholine (0.91 mL, 8.25 mmol) and isobutylchloroformate (1.08 mL, 8.25 mmol) were added slowly to a solution of Boc-L-proline (1.62 g, 7.50 mmol) in THF (10 mL) at –15 °C and stirred for 3 h. After this time, aniline (0.70 g, 7.50 mmol) was added, and the reaction mixture was stirred overnight at r.t. The reaction mixture was then filtered through silica with ethyl acetate (200 mL), and the solvent was removed under reduced pressure to leave a white powder. The crude product was purified by recrystallisation from CH_2Cl_2/pentane to yield the title product as colourless crystals. Yield: 1.32 g, 61%; m.p. 185–188 °C. $[\alpha]_D$ = –138.3 (c = 0.24, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.50 (br. s, 1 H, OCN*H*), 7.52 (d, J = 7.6 Hz, 2 H, Ar*H*), 7.28 (m, J = 7.2, 7.6 Hz, 2 H, Ar*H*), 7.10 (m, 1 H, Ar*H*), 4.48 (m, 1 H, C*H*NBoc), 3.48 (m, 2 H, CH_2NBoc), 2.54 (m, 1 H), 1.96 (m, 3 H), 1.51 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.4, 156.4, 138.6, 129.2, 124.4, 120.2, 81.2, 61.5, 47.6, 29.0, 28.8, 24.8 ppm. IR: $\tilde{\nu}$ = 3271, 2967, 2876, 1667, 1548, 1398, 1154 cm^{-1}. MS (EI+):

m/*z* (%) = 290 (15) $[M]^+$, 170 (31) $[C_4H_7NBoc]^+$, 114 (82), 70 (100), 57 (65) $[t\text{Bu}]^+$. HRMS (EI+): calcd. for $C_{16}H_{22}N_2O_3$ $[M]^+$ 290.1620; found 290.1630. $C_{16}H_{22}N_2O_3$ (290.36): calcd. C 66.18, H 7.64, N 9.65; found C 66.13, H 9.67, N 7.76.

(*S*)-*N*-Phenylpyrrolidine-2-carboxamide (9):[14] This compound was prepared by the same procedure as that described above for **1a**–**c** from (*S*)-*tert*-butyl-2-(phenylcarbamoyl)pyrrolidine-1-carboxylate (**8**) (1.20 g, 4.13 mmol). Yield: 0.382 g, 49%. All physical data were identical to those previously reported.

Optimised Procedure for the Direct Aldol Reaction: To a mixture of aldehyde (0.50 mmol, 1.0 equiv.) in DMSO (0.5 mL) and H_2O (90 μL, 10 equiv.) was added cyclohexanone (0.16 mL, 1.50 mmol, 3.0 equiv.) followed by the catalyst (30 mol-%). The resulting mixture was stirred at r.t., and the reaction was monitored by TLC for disappearance of the aldehyde (up to a maximum of 72 h). The reaction mixture was then poured into brine (5 mL) and diluted with distilled water (5 mL) and ethyl acetate (15 mL). The organic layer was removed, and the aqueous phase was further extracted with ethyl acetate (2 × 15 mL). The combined organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate mixtures) to give the desired aldol product. The *ee* values of the aldol products were determined by chiral-phase HPLC analysis and the absolute configurations were determined by comparison to those previously reported in the literature.

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (7a):[5c,17] *anti* diastereoisomer. $[\alpha]_D$ = +9.6 (*c* = 1.1, $CHCl_3$; 95% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.45 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.84 (dd, *J* = 3.0, 8.3 Hz, 1 H, C*H*OH), 4.04 (d, *J* = 3.0 Hz, 1 H, O*H*), 2.53 (m, 1 H), 2.46–2.24 (m, 2 H), 2.11–1.47 (m, 6 H) ppm. HPLC (Daicel Chiralpak AD-H; hexane/2-propanol, 80:20; flow rate = 0.5 mL/min; λ = 254 nm): t_R = 27.6 [(2*R*,1′*S*) stereoisomer], 35.7 [(2*S*,1′*R*) stereoisomer] min.

2-[Hydroxy(4-bromophenyl)methyl]cyclohexanone (7b):[18] *anti* diastereoisomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.14 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.68 (d, *J* = 8.7 Hz, 1 H, C*H*OH), 3.20–2.80 (br. s, 1 H, O*H*), 2.53–2.23 (m, 3 H), 2.06–1.99 (m, 1 H), 1.74–1.15 (m, 5 H) ppm. HPLC (Daicel Chiralpak AD-H; hexane/2-propanol, 90:10; flow rate = 0.5 mL/min; λ = 220 nm): t_R = 26.9 [(2*R*,1′*S*) stereoisomer], 30.9 [(2*S*,1′*R*) stereoisomer] min.

2-[Hydroxy(4-chlorophenyl)methyl]cyclohexanone (7c):[17] *anti* diastereoisomer. $[\alpha]_D$ = +26.3 (*c* = 0.40, $CHCl_3$; >99% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 7.18 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.70 (d, *J* = 8.7 Hz, 1 H, C*H*OH), 3.93 (br. s, 1 H, O*H*), 2.54–2.23 (m, 2 H), 2.07–1.98 (m, 1 H), 1.76–1.41 (m, 5 H), 1.28–1.19 (m, 1 H) ppm. HPLC (Daicel Chiralpak AD-H; hexane/2-propanol, 90:10; flow rate = 0.5 mL/min; λ = 220 nm): t_R = 25.0 [(2*R*,1′*S*) stereoisomer], 28.3 [(2*S*,1′*R*) stereoisomer] min.

2-[Hydroxy(2-chlorophenyl)methyl]cyclohexanone (7d):[7f] *anti* diastereoisomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.26 (m, *J* = 1.5, 8.7 Hz, 2 H, Ar*H*), 7.17 (m, *J* = 1.5, 7.6 Hz, 1 H, Ar*H*), 5.28 (dd, *J* = 3.8, 8.3 Hz, 1 H, C*H*OH), 3.96 (d, *J* = 3.8 Hz, 1 H, O*H*), 2.63–2.57 (m, 1 H), 2.42–2.22 (m, 2 H), 2.05–1.51 (m, 6 H) ppm. HPLC (Daicel Chiralpak OD-H; hexane/2-propanol, 95:5; flow rate = 1.0 mL/min; λ = 220 nm): t_R = 11.7 [(2*S*,1′*R*) stereoisomer], 14.5 [(2*R*,1′*S*) stereoisomer] min.

2-[Hydroxyphenylmethyl]cyclohexanone (7e):[19] *anti* diastereoisomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 5 H, Ar*H*), 4.72 (d, *J* = 8.7 Hz, 1 H, C*H*OH), 4.80–4.50 (br. s, 1 H, O*H*), 2.61–2.24 (m, 3 H), 2.05–1.99 (m, 1 H), 1.74–1.18 (m, 5 H) ppm. HPLC (Daicel Chiralpak OD-H; hexane/2-propanol, 90:10; flow rate = 0.75 mL/min; λ = 220 nm): t_R = 14.1 [(2*S*,1′*R*) stereoisomer], 20.9 [(2*R*,1′*S*) stereoisomer] min.

2-(Furan-2-ylhydroxymethyl)cyclohexanone (7f):[20] *anti* diastereoisomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 1 H, Ar*H*), 6.26 (m, *J* = 3.0 Hz, 1 H, Ar*H*), 6.22 (d, *J* = 3.0 Hz, 1 H, Ar*H*), 4.76 (d, *J* = 8.7 Hz, 1 H, C*H*OH), 2.85 (m, 1 H), 2.46–2.25 (m, 2 H), 2.11–1.55 (m, 6 H) ppm. HPLC (Daicel Chiralpak AD-H; hexane/2-propanol, 95:5; flow rate = 1.0 mL/min; λ = 220 nm): t_R = 20.6 [(2*S*,1′*R*) stereoisomer], 22.7 [(2*R*,1′*S*) stereoisomer] min.

Crystal Structure Determination of 7c: $C_{13}H_{15}ClO_2$, *M* = 238.7, orthorhombic, space group $P2_12_12_1$, *a* = 5.8280(7) Å, *b* = 8.6342(10) Å, *c* = 23.867(2) Å, *V* = 1201.0(2) Å^3, *T* = 150 K, *Z* = 4; 33024 measured reflections (Nonius KappaCCD, Mo-K_α radiation, λ = 0.71073 Å), 2751 unique, R_{int} = 0.0487. 150 refined parameters, constrained H atoms (OH freely refined), *R* (*F*, $F^2 > 2\sigma$) = 0.0347, R_w (F^2, all data) = 0.0808, goodness-of-fit (F^2) = 1.17, absolute configuration parameter = –0.05(7), final difference map extremes +0.32 and –0.21 e Å^{-3}. Programs were standard Nonius control and integration, Bruker SHELXTL and local software. CCDC-661742 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] a) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; c) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, *33*, 65–75; d) B. List, *Chem. Commun.* **2006**, 819–824; e) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; f) G. Guillena, C. Nájera, D. J. Ramón, *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293.

[2] a) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137–1141; b) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651; c) M.-Y. Ngai, J.-R. Kong, M. J. Krische, *J. Org. Chem.* **2007**, *72*, 1063–1072; d) S. M. Lait, D. A. Rankic, B. A. Keay, *Chem. Rev.* **2007**, *107*, 767–796.

[3] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[4] a) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7336–7387; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; c) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575; d) B. List, *Synlett* **2001**, *11*, 1675–1686; e) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; f) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024–3025; g) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacM*ill*an, *Angew. Chem. Int. Ed.* **2004**, *43*, 2152–2154; h) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem. Int. Ed.* **2005**, *44*, 1343–1345; i) Y. Zhou, Z. Shan, *Tetrahedron: Asymmetry* **2006**, *17*, 1671–1677.

[5] a) A. Córdova, W. Zou, I. Ibrahem, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun.* **2005**, 3586–3588; b) M. Amedjkouh, *Tetrahedron: Asymmetry* **2005**, *16*, 1411–1414; c) A. Córdova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, *Chem. Eur. J.* **2006**, *12*, 5383–5397; d) P. Dziedzic, W. Zou, I. Ibrahem, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 6657–6661.

[6] a) W. Zou, I. Ibrahem, P. Dziedzic, H. Sundén, A. Córdova, *Chem. Commun.* **2005**, 4946–4948; b) P. Dziedzic, W. Zou, J. Háfren, A. Córdova, *Org. Biomol. Chem.* **2006**, *4*, 38–40.

[7] a) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; b) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5755–5760; c) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834; d) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570–579; e) P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, *7*, 1101–1103; f) J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan, W.-J. Xiao, *Org. Lett.* **2005**, *7*, 4543–4545; g) S. Samanta, J. Liu, R. Dodda, C.-G. Zhao, *Org. Lett.* **2005**, *7*, 5321–5323; h) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289; i) E. Bellis, G. Kokotos, *Tetrahedron* **2005**, *61*, 8669–8676; j) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96; k) G. Guillena, M. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 729–733; l) G. Guillena, M. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 1027–1031; m) G. Guillena, M. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 1493–1497; n) M. Raj, Vishnumaya, S. K. Ginotra, V. K. Singh, *Org. Lett.* **2006**, *8*, 4097–4099; o) N. Mase, Y. Naka, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735; p) D. Gryko, R. Lipinski, *Eur. J. Org. Chem.* **2006**, 3864–3876; q) J.-F. Zheng, Y.-X. Li, S.-Q. Zhang, S.-T. Yang, X.-M. Wang, Y.-Z. Wang, J. Bai, F.-A. Liu, *Tetrahedron Lett.* **2006**, *47*, 7793–7796; r) Q. Gu, X.-F. Wang, L. Wang, X.-Y. Wu, Q.-L. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 1537–1540; s) S. Guizzetti, M. Benaglia, L. Raimondi, G. Celentano, *Org. Lett.* **2007**, *9*, 1247–1250; t) J. Jiang, L. He, S.-W. Luo, L.-F. Cun, L.-Z. Gong, *Chem. Commun.* **2007**, 736–738; u) V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 2593–2595; v) M. Lei, L. Shi, G. Li, S. Chen, W. Fang, Z. Ge, T. Cheng, R. Li, *Tetrahedron* **2007**, *63*, 7892–7898; w) G. L. Puleo, M. Masi, A. Iuliano, *Tetrahedron: Asymmetry* **2007**, *18*, 1364–1375; x) G. Guillena, M. Hita, C. Nájera, S. F. Viózquez, *Tetrahedron: Asymmetry* **2007**, *18*, 2300–2304; y) F. Giacalone, M. Gruttadauria, A. Marculescu, R. Noto, *Tetrahedron Lett.* **2007**, *48*, 255–259; z) C. Wang, Y. Jiang, X.-X. Zhang, Y. Huang, B.-G. Li, G.-L. Zhang, *Tetrahedron Lett.* **2007**, *48*, 4281–4285; aa) M. Lombardo, F. Pasi, S. Easwar, C. Trombini, *Adv. Synth. Catal.* **2007**, *349*, 2061–2065; T. Kehat, M. Portnoy, *Chem. Commun.* **2007**, 2823–2825.

[8] a) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569; b) P. H.-Y. Cheong, K. N. Houk, *Synthesis* **2005**, 1533–1537.

[9] S. Rajaram, M. S. Sigman, *Org. Lett.* **2005**, *7*, 5473.

[10] G. C. Hargaden, H. Müller-Bunz, P. J. Guiry, *Eur. J. Org. Chem.* **2007**, 4235–4243.

[11] M. P. Sibi, J. B. Sausker, *J. Am. Chem. Soc.* **2002**, *124*, 984–991.

[12] S. H. Chen, D. M. Vyas, V. Farina, T. W. Doyle, *J. Org. Chem.* **1996**, *61*, 2065–2070.

[13] a) N. Mase, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2003**, *5*, 4369–4372; b) C. Ji, Y. Peng, C. Huang, N. Wang, Y. Jiang, *Synlett* **2005**, 986–990.

[14] M. Asami, H. Ohno, S. Kobayashi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869–1873.

[15] I. M. Pastor, P. Västilä, H. Adolfsson, *Chem. Eur. J.* **2003**, *9*, 4031–4045.

[16] a) S. Bahmanyer, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479; b) S. E. Danmark, R. A. Stavenger, K.-T. Wong, X. Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991.

[17] K. Banno, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2284–2291.

[18] Y.-Z. Huang, C. Chen, Y. Shen, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2855–2859.

[19] H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmstead, *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324.

[20] M. Kawai, M. Onaka, Y. Izumi, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1237–1245.

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