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Proline dipeptides containing fluorine moieties as oganocatalysts for the asymmetric aldol reaction

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ABSTRACT

A series of dipeptide analogues consisting of proline, phenylalanine and aniline- or phenol-fluorine derivatives were synthesized. Their catalytic ability was evaluated in the intermolecular asymmetric aldol reaction, both in organic and aqueous media. Aniline-fluorine derivatives proved to be superior and the best results were obtained, when 2-CF_3 aniline was employed. A diverse substrate scope consisting of both aromatic and aliphatic aldehydes, as well as different ketones was demonstrated, where aromatic aldehydes afforded products in high yields (up to 100%) with excellent diastereo- (up to 95:5) and enantioselectivities (up to 97%), whereas the aliphatic aldehydes afforded also excellent selectivities, but relatively low yield. A simple addition of fluorine to a dipeptide analogue affords organocatalysts with new interesting properties that can catalyze the aldol reaction more efficiently.

1. Introduction

Since the beginning of the millennium, small organic molecules have been utilized as organocatalysts to promote asymmetric organic transformations; this new and exciting field of Catalysis is referred as Organocatalysis [1,2]. List, Barbas and Lerner were among the first to reintroduce Organocatalysis, by employing proline as the catalyst in the intermolecular aldol reaction between acetone and 4-nitrobenzaldehyde (Scheme 1, **A**) [3], while MacMillan and his coworkers employed imidazolidinones as catalysts for cycloadditions and in Diels-Alder reaction more precisely (Scheme 1, **B**) [4]. Organocatalysis went blooming and is now considered to be among the traditional tools of Asymmetric Synthesis. One of the most common reactions used in modern Asymmetric Catalysis, in order to form a C–C bond, is the enantioselective aldol reaction (Scheme 1, **C**) [5]. Since Organocatalysis' first days, proline and proline derivatives containing different bioisosteric groups have undoubtedly been the most efficient catalysts in organocatalytic transformations [6]. It is widely accepted that prolinamides that contain functionalities able to act as hydrogen bond donors are among the most effective catalysts employed in the aldol reaction. Different types of organocatalysts have been developed through time, with each and every one of them contributing something different in order to fully understand all the parameters that affect the efficiency of the asymmetric aldol reaction. Representative examples are shown in Fig. 1 (compounds **1**–**9**) [7]. The driving force behind the catalytic potency of these prolinamides is the secondary amine of the five-membered pyrrolidine ring, which can activate carbonyl compounds via enamine formation, as well as the functional groups that allow the formation of hydrogen bonds and enhance the selectivities observed. Among the first examples of prolinamides able to participate in multiple hydrogen bonding networks were compounds **1** and **2**, which required cryogenic conditions to induce high levels of selectivities. Catalyst **4** was an improved version of catalyst **3**, while that study also highlighted the importance of the chiral centers in the diamine moiety for the adopted conformation of the catalyst in the assumed transition state. Peptides have been explored for many years as organocatalysts [8], but the selectivities that were obtained are anything but satisfactory in most cases [9,10]. In addition, the low solubility that peptides display in organic media is a limiting factor, while when aqueous solvents are

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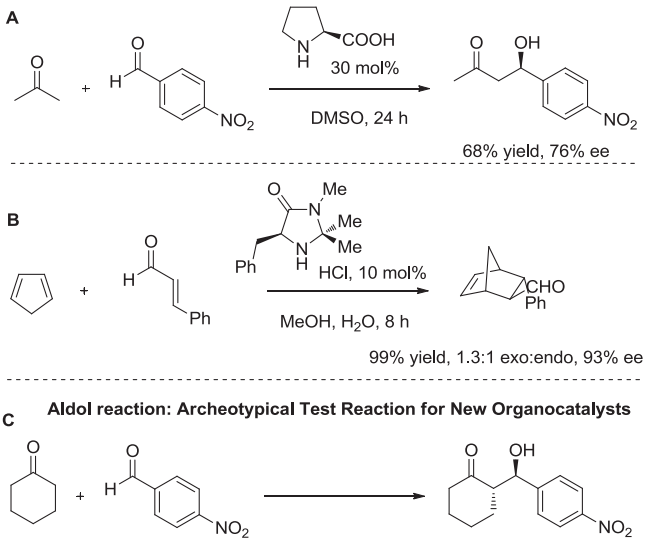

Scheme 1. Rebirth of Organocatalysis.

used, the selectivity drops significantly. Lately, more attention was drawn towards reactions that are conducted in aqueous media, which are considered to be in agreement with the principles of Green Chemistry, as water is a safe, environmentally friendly and abundant medium to carry out reactions. A milestone, for the use of proline [7e,11] and many other aminoacids derivatives [12] in aqueous media as catalysts for the aldol reaction, has been the work from the groups of Hayashi and Barbas [13].

Recently, we have demonstrated that proline dipeptides with *tert*-butyl esters of amino acids can be used as organocatalysts in the aldol reaction [14]. A series of simple dipeptide and tripeptide catalysts was introduced, where catalysts **6** and **7** proved to be the most efficient ones, while providing a green alternative, since the reaction could be performed in aqueous media. Very recently, we have developed prolinamide derivatives bearing 2-pyrrolidinone, like **8** and **9**, which can also catalyze the aldol reaction. Carbon materials in combination with amines have also been used to promote aldol reactions. Taking into account all our previous endeavors in Organocatalysis [15], and in an effort to provide a catalyst that is not only easy and cheap to synthesize, but also may exhibit more interactions with the carbonyl compounds, we questioned whether simple Pro-Phe dipeptides containing fluorine moieties could be employed as organocatalysts in the aldol reaction.

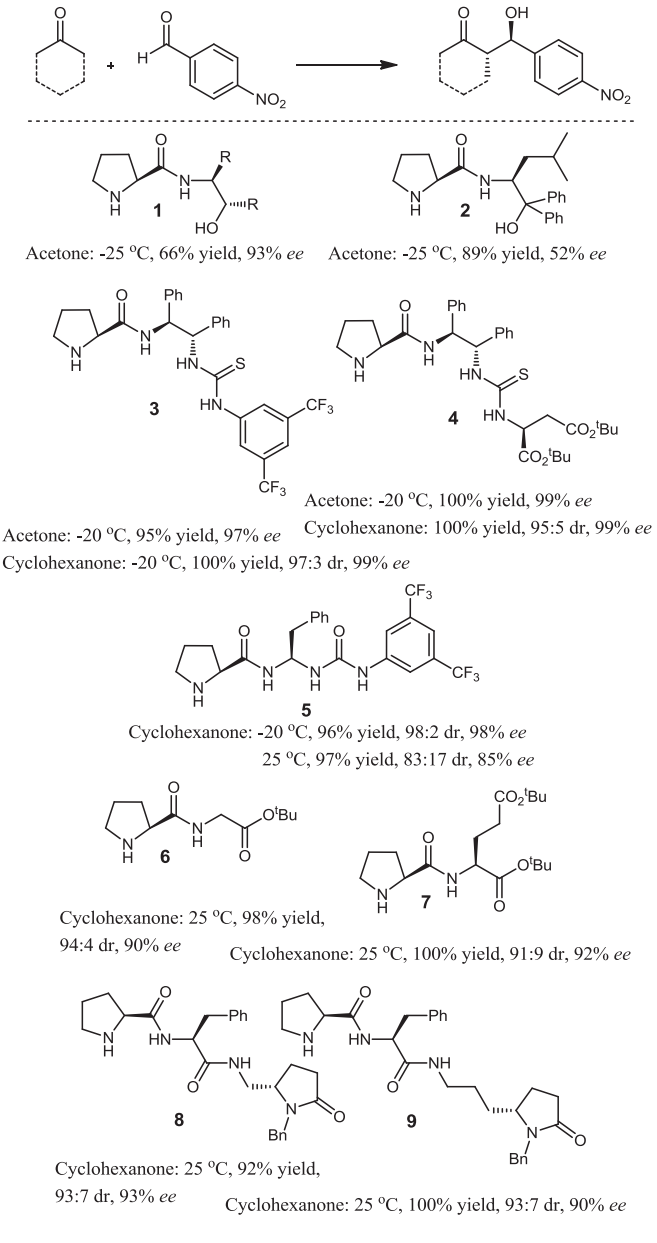

Fig. 1. Known prolinamide organocatalysts.

2. Results and discussion

Proline, although it is a powerful and archeotypical organocatalyst, is mostly insoluble in organic solvents (high catalyst loading) and provides moderate enantioselectivities (<90% *ee*). Also, it cannot be used in aqueous media. Prolinamides, like compounds **1**–**9**, are considered an improvement because they provide multiple recognition sites, via hydrogen bonding interactions, with the electrophile (aldehyde, see Fig. 2, top left). Thus, they provide a more compact transition state, leading from moderate to high enantioselectivities. Our hypothesis was to introduce fluorine moieties on the organocatalyst backbone, in order to create more and better hydrogen bonding interactions on the organocatalyst and/or change the adopted conformation of the catalyst, due to the fluorine, in the transition state (Fig. 2, top right and bottom). This idea would lead to enhanced enantioselectivities, which could also work in aqueous media.

(*S*)-Benzyloxycarbonyl-protected proline (**10**) was coupled with (*S*)-methyl phenylalaninate using *N*-(3-Dimethyl-aminopropyl)-*N*′-ethylcarbodiimide hydro-chloride (WSCI) as the condensing agent, in the presence of 1-hydroxybenzotriazole (HOBt) (Scheme 2). Saponification, under Schotten-Baumann conditions, afforded dipeptide **11**. To the resulting dipeptide, under conventional peptide coupling conditions, aniline or 2-fluoro-aniline were added, leading to peptide analogues **12a** and **12b**. Catalysts **13a** and **13b** were obtained via catalytic hydrogenation (Scheme 2) [16]. Following a similar procedure, but utilizing pentafluorophenol, catalyst **13c** was also prepared (Scheme 3). Unfortunately compounds **12d** and **12e** were not possible to synthesize under those conditions and a different synthetic pathway was followed, using triethyl amine (Et_3N) and ethyl chloroformate via the mixed anhydride intermediate (Scheme 4). Finally, deprotection via catalytic hydrogenation, afforded organocatalysts **13d** and **13e**.

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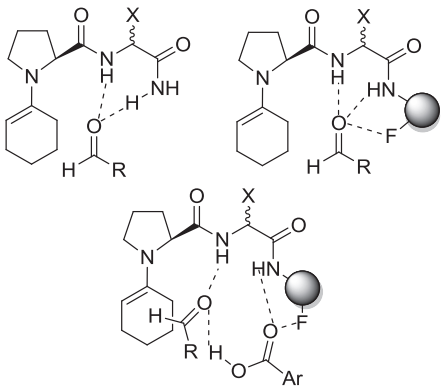
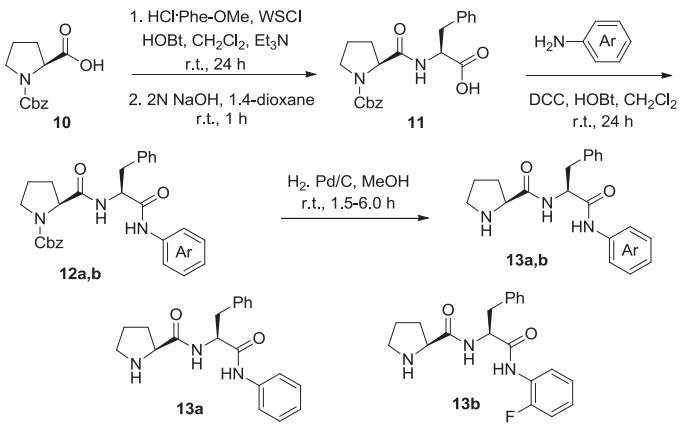


Fig. 2. Possible transition states in the absence or presence of fluorine moieties.

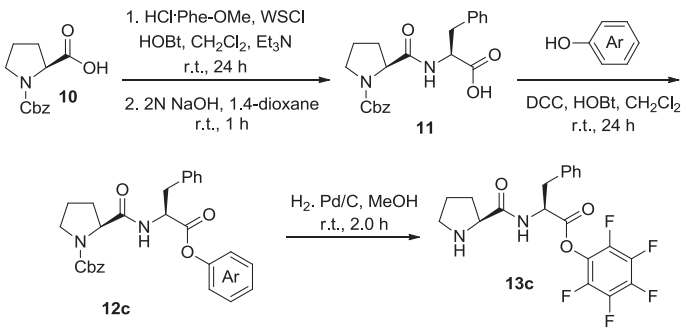
The synthesized catalysts were then evaluated in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde, both in organic and aqueous media (Table 1). Initially, compound **13a**, non-containing fluorine moiety was tested, leading to an excellent yield with good diastereoselectivity and 89% enantioselectivity in organic medium, but in aqueous medium, no reaction was observed (entries 1 and 2, Table 1). The addition of one fluorine substituent led to dipeptide **13b**, which was based on 2-fluoroaniline. When **13b** was used, not only the yield and enantioselectivity improved in organic medium, but also the reaction in brine resulted in excellent yield and 91% enantioselectivity (entries 3 and 4, Table 1). In an attempt to determine whether both the amide and fluorine moieties are essential, the pentafluorophenol derivative **13c** was tested. Unfortunately, no product was obtained neither in organic, nor in aqueous medium (entries 5 and 6, Table 1). These results highlight the importance of both moieties, as only their combination yielded improved results. Furthermore catalyst **13d**, based on 2-trifluoromethyl-aniline, was employed and afforded the best selectivity, reaching 96% *ee* (entries 7 and 8, Table 1). Considering all the above, these catalysts proved to be a cheap alternative to proline, since the combination of two aminoacids with fluorine-substituted aniline yields a potent organocatalyst for the aldol reaction in different media, in which the solubility of proline is limited. Trying to further improve the organocatalytic properties, we surmised that the addition of another fluorine substituent would limit the conformers and augment the acidity of the amide, which could amplify the interactions with the substrates, as well as improve the catalytic results in aqueous media. Catalyst **13e** was tested, and as postulated, excellent selectivity was observed, but the yield dramatically dropped (entries 9 and 10, Table 1). These results verify the hypothesis that if the catalyst has potent hydrogen bonding sites, the interactions that occur during the transition state with the electrophile are reinforced, leading to higher levels of stereocontrol.

Once **13d** was identified as the best catalyst, optimization of the reaction conditions was carried out (Table 2). Wet petroleum ether, CH_2Cl_2 and ether (Et_2O) proved to be the best solvents, leading to improved yield and selectivities of the product (entries 1–7, Table 2). Brine was the only aqueous medium that was used, affording the product in slightly lower enantioselectivity (entry 8, Table 2). It is known that the asymmetric aldol reaction is susceptible to the acid counterparts and thus, fine tuning is required, so different acid additives were employed (entries 9 and 10, Table 2). From the carboxylic acids tested, 4-nitrobenzoic acid yielded the best selectivity. Other strong acids were not employed, since it is known to promote salt formation with the catalyst, leading to its deactivation.

Our attention was then turned to the exploration of the substrate scope of the enantioselective aldol reaction employing catalyst **13d** (Table 3). Numerous substituted aromatic aldehydes can be employed with cyclohexanone, affording products from moderate to excellent yields and selectivities (entries 1–14, Table 3). Electron-withdrawing groups at any position of the aryl moiety led to moderate to excellent results (entries 1–5, Table 3), while the use of halogen substituted aromatic aldehydes resulted in high to excellent yields and selectivities (entries 6–11, Table 3). In all cases, higher selectivities were observed with the *ortho*-substituted aldehydes. However, the position of the substitution on the aromatic ring did not alter the reaction outcome. Heteroaromatic-substituted aldehydes and benzaldehyde, which are notoriously known as difficult substrates, either leading to lower yields or selectivities and/or requiring longer reaction times, proved to be more challenging (entries 12–14, Table 3). Benzaldehyde and 3-thiophenyl carboxaldehyde led to excellent yields and moderate to high selectivities, while 4-pyridinyl carboxaldehyde proved to have a better yield, but moderate selectivity. Trying to broaden the scope of substrates, different ketones were also employed. Tetrahydropyran-4-one and tetrahydrothiopyran-4-one, as expected from previous studies, required longer reaction time (entries 15 and 16, Table 3). The desymmetrization of ketones is a known process that can be achieved via organocatalytic aldol reactions and herein constitutes a possibility, since 4-methylcyclohexanone delivered excellent yield, but low selectivity (entry 17, Table 3). Cyclopentanone, which is known to provide reversed *anti:syn* selectivity, was also utilized, despite the yield being excellent, the diastereoselectivity was moderate and the enantioselectivity low (entry 18, Table 3). Moreover, in order to



Scheme 2. Synthesis of catalysts **13a** and **13b**.



Scheme 3. Synthesis of catalyst **13c**.

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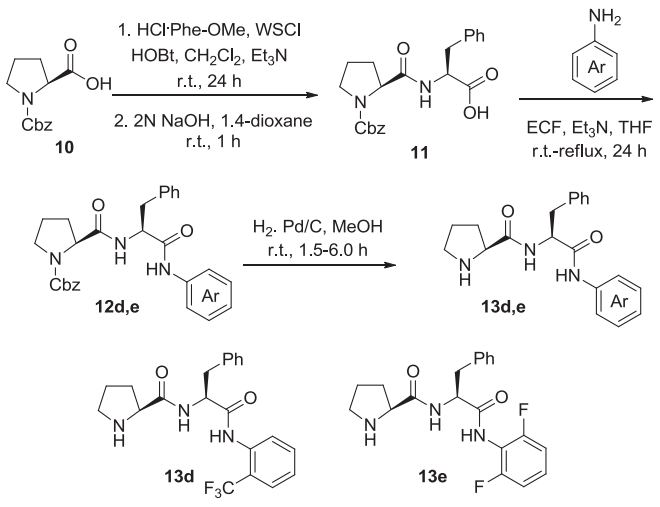
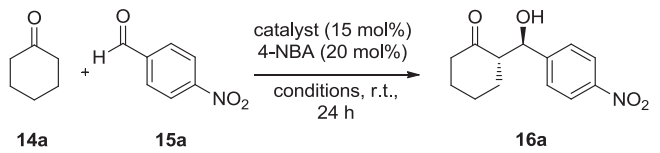


Scheme 4. Synthesis of catalysts **13d** and **13e**.

Table 1
Enantioselective reaction of cyclohexanone with 4-nitrobenzaldehyde using catalysts **13a-e**.[a]



Entry	Catalyst	Conditions	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	**13a**	PE/H_2O	96	91:9	89
2	**13a**	Brine	n.r.	–	–
3	**13b**	PE/H_2O	100	85:15	91
4	**13b**	Brine	100	86:14	91
5	**13c**	PE/H_2O	n.r.	–	–
6	**13c**	Brine	n.r.	–	–
7	**13d**	PE/H_2O	100	85:15	96
8	**13d**	Brine	100	86:14	91
9	**13e**	PE/H_2O	24	85:15	96
10	**13e**	Brine	50	88:12	93

4-NBA: 4-nitrobenzoic acid. PE: Petroleum ether.
[a] Catalyst (0.015 mmol) in solvent (1.0 mL), additive (0.02 mmol), H_2O (0.1 mL), aldehyde (0.10 mmol) and cyclohexanone (1.00 mmol).
[b] Isolated yield.
[c] The diastereomeric ratio (dr) *anti:syn* was determined by ^1H NMR of the crude reaction mixture.
[d] The enantiomeric excess (*ee*) for the major isomer was determined by chiral HPLC.

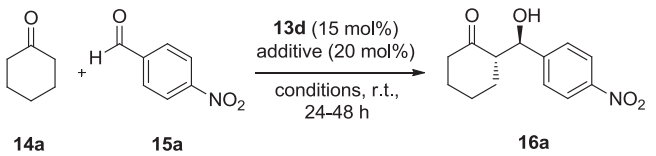
broaden the scope of this methodology, we investigated the reaction of acetone with 4-nitrobenzaldehyde. Unfortunately, this reaction led to excellent yield, but moderate enantioselectivity (entry 19, Table 3).

Finally, the reaction between isobutyraldehyde and cyclohexanone was investigated (Scheme 5). Unfortunately, the desired product was delivered in excellent selectivity, but in low yield.

3. Conclusion

In conclusion, the synthesis of dipeptides containing fluorine moieties was carried out. Previously, we had shown that the addition of the hydrogen bonding sites provided excellent catalysts for the aldol reaction. In this study, we have shown that dipeptide

Table 2
Enantioselective aldol reaction of cyclohexanone with 4-nitrobenzaldehyde using catalyst **13d**.[a]



Entry	Conditions	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	PE/H_2O, 4-NBA	100	85:15	96
2	MeCN, 4-NBA	88	71:29	96
3	THF, 4-NBA	100	65:35	96
4	CH_2Cl_2, 4-NBA	100	85:15	96
5	AcOEt, 4-NBA	100	66:34	95
6	Et_2O, 4-NBA	100	85:15	96
7	toluene, 4-NBA	100	70:30	94
8	brine, 4-NBA	100	86:14	91
9	PE/H_2O, $PhCO_2H$	91	81:19	95
10	PE/H_2O, AcOH	84	85:15	92

4-NBA: 4-nitrobenzoic acid. PE: Petroleum ether.
[a] Catalyst (0.015 mmol) in solvent (1.0 mL), additive (0.02 mmol), H_2O (0.1 mL), aldehyde (0.10 mmol) and cyclohexanone (1.00 mmol).
[b] Isolated yield.
[c] The diastereomeric ratio (dr) *anti:syn* was determined by ^1H NMR of the crude reaction mixture.
[d] The enantiomeric excess (*ee*) for the major isomer was determined by chiral HPLC.

Pro-Phe, which is easy to prepare, combined with fluorine-substituted aniline is a more powerful catalyst for the aldol reaction. A fluorine substituent can instill new properties to the catalyst, like increased acidity and can also interact with the substrate and as a result the selectivity is improved. An alternative scenario could be that it may also affect the adopted conformation of the catalyst. The catalyst was evaluated both in organic and aqueous media. When **13d** was utilized, high to excellent yields and moderate to excellent selectivities in wet petroleum ether were obtained, even when the substrates were problematic. It is worth mentioning that the catalyst works at room temperature and has distinct advantages compared to proline, as it can bypass the low solubility that proline displays in organic solvents and the low selectivity it affords in aqueous media. Furthermore, expensive chiral moieties are not required to be incorporated in the catalyst's structure, since the chirality source is the Pro-Phe dipeptide, coupled with commercially available 4-trifluoromethyl aniline.

4. Experimental section

4.1. General information

Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Chromatographic purification of products was accomplished using column chromatography on Merck Kieselgel 60 F_{254} 230–400 mesh. Thin-Layer chromatography (TLC) was performed on aluminium backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using PMA stain. Melting points were determined on a Buchi 530 hot stage apparatus. ^1H, ^{19}F and ^{13}C NMR spectra were recorded on Varian Mercury 200 MHz and are internally referenced to residual solvent signals ($CDCl_3$ or CD_3OD). Data for ^1H NMR spectroscopy are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal), integration, coupling constant, and assignment. Wherever rotamers exist, are cited. ^{19}F NMR

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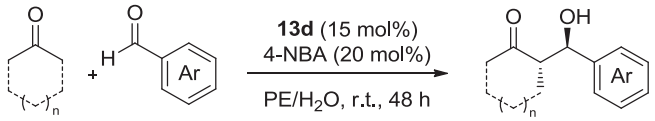
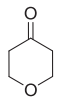
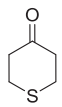
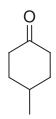
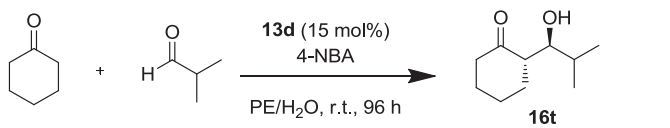
Table 3
Enantioselective aldol reaction between ketones and aldehydes using catalyst **13d**.



14 **15** **16**

Entry	Ketone	Aldehyde	Yield (%)[a]	dr[b]	*ee* (%)[c]
1		4-$NO_2C_6H_4$	100 (**16a**)	85:15	96
2[d]		3-$NO_2C_6H_4$	100 (**16b**)	88:12	93
3[d]		2-$NO_2C_6H_4$	100 (**16c**)	91:9	97
4[f]		4-$CF_3C_6H_4$	100 (**16d**)	80:20	87
5[e]		3-CNC_6H_4	100 (**16e**)	79:21	56
6[f]		4-FC_6H_4	88 (**16f**)	88:12	90
7[e]		2-FC_6H_4	100 (**16g**)	95:5	97
8[f]		4-BrC_6H_4	90 (**16h**)	89:11	87
9[e]		2-BrC_6H_4	100 (**16i**)	89:11	93
10[f]		4-ClC_6H_4	84 (**16j**)	83:17	89
11[e]		2-ClC_6H_4	100 (**16k**)	89:11	95
12[f]		C_6H_5	84 (**16l**)	83:17	89
13[d]		4-pyridinyl	100 (**16m**)	67:33	84
14[f]		3-thiophenyl	77 (**16n**)	74:26	76
15[f]		4-$NO_2C_6H_4$	100 (**16o**)	74:26	88
16[e]		4-$NO_2C_6H_4$	100 (**16p**)	68:32	97
17[d]		4-$NO_2C_6H_4$	100 (**16q**)	(30:29):41	24 (*syn*) 24 (*anti*)
18[d]		4-$NO_2C_6H_4$	100 (**16r**)	24:76	4
19		4-$NO_2C_6H_4$	100 (**16s**)	–	52

[a] Isolated yield.
[b] The diastereomeric ratio (dr) *anti:syn* was determined by ^{1}H NMR of the crude reaction mixture.
[c] The enantiomeric excess (*ee*) for the major isomer was determined by chiral HPLC.
[d] Reaction time 72 h.
[e] Reaction time 96 h.
[f] Reaction time 120 h.



Scheme 5. Study of catalytic activity of **13d** in the reaction of cyclohexanone with isobutyraldehyde.

spectra were recorded on Varian Mercury (188 MHz). Mass spectra were recorded on a Finnigan Surveyor MSQ Plus, with only molecular ions and major peaks being reported with intensities quoted as percentages of the base peak. High Performance Liquid Chromatography (HPLC) was used to determine enantiomeric excesses and was performed on an Agilent 1100 Series apparatus using Chiralpak® AD-H, OD-H and AS-H columns. Optical rotations were measured on a Perkin Elmer 343 polarimeter. The *syn*:*anti* ratio of the crude reaction mixture was assigned by comparison to literature data [7h,7n]. The configuration of the products has been assigned by comparison to literature data [7h,7n]. Data for known compounds matched literature data. All new compounds were assigned by analogy.

4.2. General procedure for the synthesis of the organocatalysts

4.2.1. General procedure for the synthesis of ((benzyloxy)carbonyl)-L-prolyl-L-phenylalanine

To a stirring solution of Cbz-Pro-OH (1.20 g, 4.81 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, HCl. H-Phe-OMe (1.10 g, 5.10 mmol), 1-ethyl-3-(3-dimethylamino) carbodiimide (0.83 g, 5.35 mmol), 1-hydroxybenzotriazole (HOBt) (0.74 g, 4.83 mmol) and Et_3N (2 mL, 15.51 mmol) were added consecutively. The reaction mixture was left stirring at 0 °C for 30 min and then warmed to room temperature and left stirring overnight. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with aq. HCl 1 N (2 × 25 mL), brine (25 mL), aq. NaOH 1 N (2 × 25 mL) and brine (25 mL). The organic layer was then dried over $CaCl_2$, filtered and concentrated under reduced pressure. The crude Cbz-Pro-Phe-OMe (1.60 g, 3.90 mmol) was dissolved in dioxane (8 mL) and then an aqueous solution of NaOH 2 N (2.4 mL, 4.80 mmol) was added. The reaction was left stirring at room temperature, for approximately 1 h, until the reaction was completed (determined by TLC). Dioxane was evaporated under reduced pressure, and the residue was diluted with water (40 mL) and extracted with Et_2O (25 mL). The aqueous layer was washed with aq. H_2SO_4 5% (30 mL) and was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over $CaCl_2$, filtered and concentrated under reduced pressure to afford the free acid. The ^{1}H and ^{13}C NMR data were in full agreement with literature [7h].

4.2.2. General procedure for the synthesis of catalysts (*13a-c*)

To a stirring solution of Cbz-Pro-Phe-OH (100 mg, 0.25 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C, dicyclohexyl carbodiimide (62 mg, 0.30 mmol), 1-hydroxybenzotriazole (HOBt) (38 mg, 0.25 mmol) and aniline or phenol (0.35 mmol) were added consecutively. The reaction mixture was left stirring at 0 °C for 30 min and then warmed to room temperature and left stirring overnight. The reaction mixture was filtered and the filtrate was concentrated and then diluted with EtOAc (1 mL) left at 0 °C for 10 min and then filtered once again. The filtrate was diluted with EtOAc (10 mL) and washed with aq. H_2SO_4 5% (2 × 10 mL), H_2O (10 mL), aq. $NaHCO_3$ 5% (2 × 10 mL) and brine (10 mL). The organic layer was dried over $CaCl_2$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with EtOAc/PE (1:1). The crude product was dissolved in absolute MeOH (10 mL) and 10% Pd/C (10 w/w%) was added and the reaction mixture was left stirring at room temperature for 2–24 h under hydrogen atmosphere. After filtration through Celite, the solvent was evaporated under vacuum to yield the desired product.

4.2.3. General procedure for the synthesis of catalysts (*13d,e*)

To a flame dried two-neck round bottom flask, Cbz-Pro-Phe-OH (1.00 g, 2.54 mmol) was dissolved in dry THF (10 mL) at 0 °C under argon atmosphere. To the stirring solution, Et_3N (0.4 mL, 2.92 mmol) and ethyl chloroformate (0.25 mL, 2.64 mmol) were added and the reaction mixture was left stirring for 1 h at 0 °C. Finally, substituted aniline (0.67 mmol) was introduced to the reaction mixture dropwise. The reaction mixture was stirred at 0 °C

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for 1 h, then warmed to room temperature for 2 h and finally heated to reflux for 16 h. Then, the reaction mixture was filtered and concentrated. The crude product was purified by column chromatography eluting with EtOAc/PE (3:7). The deprotection of the amino moiety of proline was performed similarly to the general procedure that was followed for the synthesis of catalysts **13a-c**.

4.2.4. (S)-N-((S)-1-Oxo-3-phenyl-1-(pheynylamino)propan-2-yl) pyrrolidine-2-carboxamide (**13a**) [17]

The product was obtained as a white solid. Yield: 91%; mp 151–153 °C; R_f (EtOAc/MeOH 80:20) 0.32; $[\alpha]_D^{25}$ −52.8 (c 0.8, $CHCl_3$); ^{1}H NMR (200 MHz, CD_3OD) δ 8.81 (1H, d, J = 6.3 Hz, NH), 7.50–7.05 (11H, m, ArH and NH), 4.84–4.73 (1H, m, NCH), 4.32–4.24 (1H, m, NCH), 3.50–3.32 (2H, m, NCH_2), 3.21 (1H, dd, J = 14.0 and 6.7 Hz, C*H*HPh), 3.04 (1H, dd, J = 14.0 and 8.4 Hz, C*H*HPh), 2.51–2.37 (1H, m, C*H*H), 2.08–1.69 (4H, m, 3 × C*H*H and NH); ^{13}C NMR (50 MHz, CD_3OD) δ 171.4, 169.5, 139.3, 137.9, 130.3, 129.8, 129.5, 127.9, 125.4, 121.3, 60.9, 57.3, 47.5, 39.1, 31.1, 26.0; HRMS exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}N_3O_2$) requires m/z 338.1869, found m/z 338.1875.

4.2.5. (S)-N-((S)-1-((Fluorophenyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**13b**)

The product was obtained as a white solid. Yield: 89%; mp 117–119 °C; R_f ($CHCl_3$/MeOH 90:10) 0.36; $[\alpha]_D^{25}$ −15.6 (c 0.5, DMF); ^{1}H NMR (200 MHz, CD_3OD) δ 7.77–7.68 (1H, m, ArH), 7.23–6.99 (8H, m, ArH), 4.80–4.76 (1H, m, NCH), 3.67–3.57 (1H, m, NCH), 3.23–3.11 (1H, m, NC*H*H), 2.99–2.74 (3H, m, NC*H*H and 2 × C*H*HPh), 2.04–1.90 (1H, m, C*H*H), 1.65–1.42 (3H, m, 3 × C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ 176.3, 172.2, 155.8 (d, J = 246.1 Hz), 138.0, 130.4, 129.5, 127.9, 127.3 (d, J = 7.7 Hz), 126.6 (d, J = 11.8 Hz), 125.7 (d, J = 1.0 Hz), 125.3 (d, J = 3.7 Hz), 116.4 (d, J = 19.7 Hz), 61.3, 55.9, 47.9, 39.2, 31.7, 26.6; ^{19}F NMR (188 MHz, CD_3OD) δ −81.3 (s); MS (ESI) 356.22 ($[M+H]^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}FN_3O_2$) requires m/z 356.1774, found m/z 356.1780.

4.2.6. Perfluorophenyl L-prolyl-L-phenylalaninate (**13c**)

The product was obtained as a colourless oil. Yield: 41%; R_f ($CHCl_3$/MeOH 95:5) 0.50; $[\alpha]_D^{25}$ −61.0 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, mixture of rotamers) δ 7.82 (1H, br s, NH), 7.38–7.15 (5H, m, ArH), 6.08 (1H, s, NH), 4.36–4.33 (1H, m, NCH), 4.18–4.08 (1H, m, NCH), 3.77–3.44 (2H, m, NCH_2), 3.25–3.02 (1H, m, C*H*HPh), 2.85 (1H, dd, J = 14.0 and 10.0 Hz, C*H*HPh), 2.44–2.27 (1H, m, C*H*H), 2.05–1.70 (3H, m, 3 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8, 172.1, 167.7, 167.6, 156.5, 143.6–127.5 (m), 60.8–60.1 (m), 53.1–52.6 (m), 49.5–47.0 (m), 37.5–37.2 (m), 33.8–30.7 (m), 27.9–23.3 (m); ^{19}F NMR (188 MHz, $CDCl_3$) δ −120.9 (dd, J = 18.0 and 5.7 Hz), −122.6 to −122.8 (m), −128.0 (tt, J = 22.1 and 5.8 Hz); HRMS exact mass calculated for $[M+H]^+$ ($C_{20}H_{18}F_5N_2O_3$) requires m/z 429.1238, found m/z 429.1244.

4.2.7. (S)-N-((S)-1-Oxo-3-phenyl-1-((2-(trifluoromethyl)phenyl) amino)propan-2-yl)pyrrolidine-2-carboxamide (**13d**)

The product was obtained as a white solid. Yield: 49%; mp 49–51 °C; R_f ($CHCl_3$/MeOH 90:10) 0.38; $[\alpha]_D^{25}$ −37.8 (c 0.8, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 7.74–7.20 (9H, m, ArH), 4.89–4.84 (1H, m, NCH), 3.79–3.67 (1H, m, NCH), 3.36–3.26 (1H, m, NCH*H*), 3.05–2.81 (3H, m, NCH*H* and 2 × CH*H*Ph), 2.12–1.97 (1H, m, C*H*H), 1.71–1.50 (3H, m, 3 × C*H*H); ^{13}C (50 MHz, CD_3OD) δ 176.5, 173.1, 138.2 (q, J = 8.5 Hz), 138.1, 135.8 (q, J = 1.8 Hz), 134.0, 130.5 (q, J = 3.9 Hz), 130.4, 129.5, 128.1 (q, J = 12.3 Hz), 127.5 (q, J = 5.2 Hz), 126.6 (q, J = 29.9 Hz), 125.4 (q, J = 272.8 Hz), 61.3, 55.7, 47.9, 38.8, 31.7, 26.6; ^{19}F NMR (188 MHz, CD_3OD) δ −16.1 (s); MS (ESI) 406.25 ($[M+H]^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{20}H_{22}F_3N_3O_2$) requires m/z 406.1742, found m/z 406.1747.

4.2.8. (S)-N-((S)-1-((2,6-Difluorophenyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**13e**)

The product was obtained as a yellow oil. Yield: 52%; Rf ($CHCl_3$/MeOH 90:10) 0.33; $[\alpha]_D^{25}$ −44.0 (c 0.25, $CHCl_3$); ^{1}H NMR (200 MHz, CD_3OD, mixture of rotamers) δ 7.70–7.63 (1H, m, NH), 7.38–7.16 (6H, m, ArH), 7.09–6.98 (2H, m, ArH), 5.17–4.99 (1H, m, NH), 4.58–4.50 (1H, m, NCH), 4.35–4.25 (1H, m, NCH), 3.55–3.39 (2H, m, 2 × NC*H*H), 3.14–2.98 (2H, m, 2 × C*H*HPh), 2.29–1.85 (4H, m, 4 × C*H*H); ^{13}C (50 MHz, CD_3OD) δ 174.6, 174.3, 159.7 (d, J = 250.4 Hz), 159.6 (d, J = 250.6 Hz), 155.5, 138.4, 138.1–137.9 (m), 132.4, 130.5–127.8 (m), 113.0–112.8 (m), 112.5 (dd, J = 5.8 Hz and 2.5 Hz), 62.2–60.6 (m), 57.4–52.7 (m), 47.4, 41.2–38.1 (m), 34.7–30.1 (m), 27.6–23.3 (m); ^{19}F NMR (188 MHz, CD_3OD) δ −73.8 (s); HRMS exact mass calculated for $[M+H]^+$ ($C_{20}H_{22}F_2N_3O_2$) requires m/z 374.1680, found m/z 374.1687.

4.3. General procedure for the aldol reaction

To a round-bottom flask, catalyst (0.015 mmol), 4-NBA (3 mg, 0.02 mmol) and aldehyde (0.10 mmol) were added. After the addition of Petroleum Ether (PE) (1 mL) and H_2O (0.1 mL), ketone (1.00 mmol) was added and the reaction mixture was stirred at room temperature for 24–120 h. The solvent was evaporated and the crude product was purified by column chromatography. The diastereomeric ratio was calculated by ^{1}H NMR of the crude reaction mixture and the enantiomeric excess was determined by chiral HPLC. All known products from the asymmetric aldol reaction were in full agreement with the literature [7i,7k].

4.3.1. (S)-2-[(R)-Hydroxy-(4-nitrophenyl)methyl]-cyclohexanone (**16a**) [7i]

Colorless oil. Yield: 100%; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.20 (2H, d, J = 8.8 Hz, ArH), 7.51 (2H, d, J = 8.8 Hz, ArH), 4.87 (1H, d, J = 8.4 Hz, OCH), 4.09 (1H, br s, OH), 2.64–2.26 (3H, m, COCH and 2 × C*H*H), 2.17–1.29 (6H, m, 6 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6, 148.4, 127.9, 127.8, 123.4, 73.8, 57.0, 42.5, 30.6, 27.5, 24.5; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 1.0 mL/min, retention time: 32.79 (minor) and 38.87 (major), 96% *ee*.

4.3.2. (S)-2-[(R)-Hydroxy-(3-nitrophenyl)methyl]-cyclohexanone (**16b**) [7i]

Colorless oil. Yield: 100%; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.23–8.14 (2H, m, ArH), 7.67 (1H, d, J = 7.3 Hz, ArH), 7.55 (1H, d, J = 7.6 Hz, ArH), 4.90 (1H, d, J = 8.4 Hz, OCH), 4.11 (1H, br s, OH), 2.68–2.31 (3H, m, COCH and 2 × C*H*H), 2.17–1.32 (6H, m, 6 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6, 148.2, 143.1, 133.1, 129.2, 122.7, 121.9, 74.0, 57.0, 42.6, 30.6, 27.6, 24.6; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 66.49 (major) and 87.69 (minor), 93% *ee*.

4.3.3. (S)-2-[(R)-Hydroxy-(2-nitrophenyl)methyl]-cyclohexanone (**16c**) [7i]

Yellow solid. Yield: 100%; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.91–7.72 (2H, m, ArH), 7.63 (1H, t, J = 6.6 Hz, ArH), 7.42 (1H, t, J = 6.6 Hz, ArH), 5.43 (1H, d, J = 7.1 Hz, OCH), 4.16 (1H, br s, OH), 2.85–2.61 (1H, m, COCH), 2.55–2.08 (2H, m, 2 × C*H*H), 1.90–1.52 (6H, m, 6 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.9, 136.5, 133.0, 128.9, 128.3, 124.0, 69.7, 57.2, 42.8, 31.1, 27.7, 24.9; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 95:5, flow rate 0.8 mL/min, retention time: 61.80 (major) and 66.83 (minor), 97% *ee*.

4.3.4. (S)-2-[(R)-Hydroxy-(4-(trifluoromethyl)phenyl)methyl]-cyclohexanone (**16d**) [7i]

White solid. Yield: 100%; mp 73–75 °C; ^{1}H NMR (200 MHz,

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$CDCl_3$) *anti* δ 7.61 (2H, d, $J = 8.2$ Hz, ArH), 7.44 (2H, d, $J = 8.2$ Hz, ArH), 4.84 (1H, d, $J = 8.6$ Hz, OCH), 4.03 (1H, br s, OH), 2.69–2.02 (4H, m, COCH and 3 × C*H*H), 1.90–1.39 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.1, 144.9, 129.6 (q, $J = 31.2$ Hz), 127.3, 125.3 (q, $J = 8.1$ Hz), 123.9 (q, $J = 271.4$ Hz), 74.2, 57.2, 42.6, 30.7, 27.6, 24.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ −7.50 (s); HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 25.83 (minor) and 31.87 (major), 87% *ee*.

4.3.5. (R)-3-[Hydroxy-(2-(S)-oxocyclohexyl)methyl]-benzonitrile (**16e**) [7i]

Colorless oil. Yield: 100%; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.68–7.38 (4H, m, ArH), 4.81 (1H, d, $J = 8.5$ Hz, OCH), 4.01 (1H, br s, OH), 2.65–2.03 (4H, m, COCH and 3 × C*H*H), 1.87–1.22 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHZ, $CDCl_3$) δ 214.6, 142.6, 131.5, 130.6, 129.1, 118.7, 112.4, 73.9, 57.1, 42.6, 30.6, 27.6, 24.6; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 95:5, flow rate 1.0 mL/minm retention time: 40.98 (minor) and 62.07 (major), 56% *ee*.

4.3.6. (S)-2-[(R)-Hydroxy-(4-(fluorophenyl)methyl]-cyclohexanone (**16f**) [7i]

White solid. Yield: 88%; mp 84–86 °C; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.33–7.27 (2H, m, ArH), 7.03 (2H, d, $J = 8.7$ Hz, ArH), 4.77 (1H, d, $J = 8.4$ Hz, OCH), 4.03 (1H, br s, OH), 2.65–2.31 (3H, m, COCH and C*H*H), 2.08–1.22 (6H, m 6 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.4, 162.3 (d, $J = 246.2$ Hz), 136.6, 128.5 (d, $J = 5.1$ Hz), 115.2 (d, $J = 20.0$ Hz), 74.1, 57.4, 42.6, 30.7, 27.7, 24.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ −59.49 HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 36.52 (minor), 40.21 (major), 90% *ee*.

4.3.7. (S)-2-[(R)-Hydroxy-(2-(fluorophenyl)methyl]-cyclohexanone (**16g**) [7i]

Colorless oil. Yield: 100%; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.48 (1H, td, $J = 7.4$ and 1.9 Hz, ArH), 7.36–7.14 (2H, m, ArH), 7.02 (1H, ddd, $J = 10.2$, 8.0 and 1.6 Hz, ArH), 5.18 (1H, d, $J = 8.7$ Hz, OCH), 4.00 (1H, br s, OH), 2.74–2.62 (1H, m, COCH), 2.52–2.28 (2H, m, 2 × COC*H*H), 2.19–2.03 (1H, m, C*H*H), 1.89–1.38 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.2, 159.9 (d, $J = 245.8$ Hz), 129.1 (d, $J = 8.3$ Hz), 128.2 (d, $J = 4.3$ Hz), 128.0, 124.3 (d, $J = 3.4$ Hz), 115.0 (d, $J = 22.3$ Hz), 67.8, 57.0, 42.5, 30.1, 27.6, 24.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ −62.92 (s); HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 95:5, flow rate 0.5 mL/min, retention time: 40.98 (major) and 54.35 (minor), 97% *ee*.

4.3.8. (S)-2-[(R)-Hydroxy-(4-(bromophenyl)methyl]-cyclohexanone (**16h**) [7i]

White solid. Yield: 90%; mp 89–91 °C; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.47 (2H, d, $J = 8.5$ Hz, ArH), 7.20 (2H, d, $J = 8.5$ Hz, ArH), 4.75 (1H, d, $J = 8.6$ Hz, OCH), 3.94 (1H, br s, OH), 2.61–2.13 (3H, m, COCH and 2 × C*H*H), 2.11–2.01 (1H, m, C*H*H), 1.88–1.24 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.2, 140.0, 131.5, 128.7, 121.7, 74.2, 27.3, 42.6, 30.7, 27.7, 24.7; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 37.83 (minor) and 44.00 (major), 87% *ee*.

4.3.9. (S)-2-[(R)-Hydroxy-(2-(bromophenyl)methyl]-cyclohexanone (**16i**) [7i]

White solid. Yield: 100%; mp 103–105 °C; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.56–7.46 (2H, m, ArH), 7.34 (1H, t, $J = 7.4$ Hz, ArH), 7.18–7.06 (1H, m, ArH), 5.30 (1H, d, $J = 7.9$ Hz, OCH), 4.02 (1H, br s, OH), 2.78–2.61 (1H, m, COCH), 2.52–2.25 (2H, m, 2 × COC*H*H), 2.18–2.01 (1H, m, C*H*H), 1.88–1.36 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.2, 140.7, 132.5, 129.1, 128.5, 127.9, 123.4, 72.9, 57.6, 42.7, 30.6, 27.8, 25.0; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 98:2, flow rate 1.0 mL/min, retention time: 15.58 (major) and 18.51 (minor), 93% *ee*.

4.3.10. (S)-2-[(R)-Hydroxy-(4-(chlorophenyl)methyl]-cyclohexanone (**16j**) [7i]

White solid. Yield: 84%; mp 96–98 °C; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.32 (2H, d, $J = 8.5$ Hz, ArH), 7.24 (2H, d, $J = 8.5$ Hz, ArH), 4.76 (1H, d, $J = 8.7$ Hz, OCH), 3.98 (1H, br s, OH), 2.63–2.28 (3H, m, COCH and 2 × C*H*H), 2.19–2.01 (1H, m, C*H*H), 1.88–1.42 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.3, 139.5, 133.6, 128.5, 128.4, 74.2, 57.4, 42.7, 30.7, 27.7, 24.7; HPLC analysis: Diacel Chiralpak OD-H, hexane/^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 19.30 (major) and 25.59 (minor), 89% *ee*.

4.3.11. (S)-2-[(R)-Hydroxy-(2-(chlorophenyl)methyl]-cyclohexanone (**16k**) [7i]

Pale yellow solid. Yield: 100%; mp 88–90 °C; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.54 (1H, dd, $J = 7.8$ and 1.9 Hz, ArH), 7.36–7.16 (3H, m, ArH), 5.34 (1H, d, $J = 8.2$ Hz, OCH), 3.86 (1H, br s, OH), 2.77–2.61 (1H, m, COCH), 2.54–2.22 (2H, m, 2 × COC*H*H), 2.17–2.02 (1H, m, C*H*H), 1.86–1.42 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.3, 139.1, 132.9, 129.2, 128.7, 128.3, 127.3, 70.5, 57.6, 42.7, 30.4, 27.8, 24.9; HPLC analysis: Diacel Chiralpak OD-H, hexane/^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 20.68 (major) and 23.63 (minor), 95% *ee*.

4.3.12. (S)-2-[(R)-Hydroxy-(phenyl)methyl]-cyclohexanone (**16l**) [7i]

Colorless oil. Yield: 84%; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.51–7.21 (5H, m, ArH), 4.78 (1H, d, $J = 8.8$ Hz, OCH), 3.84 (1H, br s, OH), 2.70–2.31 (3H, m, COCH and 2 × C*H*H), 2.15–1.24 (6H, m, 6 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.5, 140.8, 128.3, 127.8, 125.7, 74.7, 57.4, 42.6, 30.8, 27.8, 24.7; HPLC analysis: Diacel Chiralpak OD-H, hexane/^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 20.32 (major) and 26.21 (minor), 89% *ee*.

4.3.13. (S)-2-[(R)-Hydroxy-(pyridine-4-yl)methyl]-cyclohexanone (**16m**) [7i]

White solid. Yield: 100%; mp 107–109 °C; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.58–8.52 (2H, m, ArH), 7.27–7.21 (2H, m, ArH), 4.78 (1H, d, $J = 8.1$ Hz, OCH), 3.19 (1H, br s, OH), 2.67–2.225 (3H, m, COCH and 2 × C*H*H), 2.18–2.01 (1H, m, C*H*H), 1.87–1.35 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.5, 150.1, 149.7, 122.1, 73.3, 57.0, 42.6, 30.8, 27.7, 24.7; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 92:8, flow rate 1.0 mL/min, retention time: 28.47 (minor) and 38.70 (major), 84% *ee*.

4.3.14. (S)-2-[(R)-Hydroxy-(thiophen-3-yl)methyl]-cyclohexanone (**16n**) [7i]

Pale yellow oil. Yield: 77%; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.36–7.26 (1H, m, ArH), 7.19 (1H, d, $J = 2.4$ Hz, ArH), 7.08 (1H, d, $J = 5.0$ Hz, ArH), 4.92 (1H, d, $J = 8.4$ Hz, OCH), 3.90 (1H, br s, OH), 2.74–2.22 (3H, m, COCH and 2 × C*H*H), 2.17–2.04 (1H, m, C*H*H), 1.86–1.44 (5H, m, 5 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.3, 142.3, 126.0, 125.9, 122.2, 70.6, 57.1, 42.6, 30.8, 27.8, 24.7; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 1.0 mL/min, retention time: 14.01 (minor) and 19.43 (major), 76% *ee*.

4.3.15. (S)-3-[(R)-Hydroxy-[4-(nitrophenyl)methyl]dihydro-2H-pyran-4(3H)-one (**16o**) [7i]

Pale yellow solid. Yield: 100%; mp 116–118 °C; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.21 (2H, d, $J = 8.8$ Hz, ArH), 7.50 (2H, d, $J = 8.8$ Hz, ArH), 4.97 (1H, d, $J = 8.2$ Hz, OCH), 4.28–4.09 (1H, m, OC*H*H), 3.90–3.64 (3H, m, 2 × OC*H*H and OH), 3.44 (1H, dd, $J = 11.4$

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and 9.8 Hz, OC*H*H), 3.02–2.41 (3H, m, 3 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.2, 147.7, 147.4, 127.4, 123.8, 71.2, 69.7, 68.2, 57.5, 42.7; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 80:20, flow rate 1.0 mL/min, retention time: 18.86 (minor) and 27.00 (major), 88% *ee*.

4.3.16. (S)-3-[(R)-Hydroxy-[4-(nitrophenyl)methyl]dihydro-2H-thiopyran-4(3H)-one (**16p**) [7i]

Yellow solid. Yield: 100%; mp 137–139 °C; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.23 (2H, d, *J* = 8.3 Hz, ArH), 7.53 (2H, d, *J* = 8.3 Hz, ArH), 5.04 (1H, d, *J* = 7.9 Hz, OCH), 3.63 (1H, br s, OH), 3.07–2.91 (3H, m, COCH and 2 × C*H*H), 2.87–2.70 (2H, m, 2 × C*H*H), 2.68–2.42 (2H, m, 2 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.2, 147.7, 147.6, 127.7, 123.8, 73.1, 59.4, 44.7, 32.8, 30.7; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 1.0 mL/min, retention time: 51.83 (minor) and 73.77 (major), 97% *ee*.

4.3.17. (2S,4S)-2-[(R)-Hydroxy-(4-(nitrophenyl)methyl]-4-methylcyclohexanone (**16q**) [7l,7m]

White solid. Yield: 100%; mp 109–111 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23–8.18 (2H, m, ArH), 7.52–7.47 (2H, m, ArH), 5.48 (1H, br s, *syn* OCH), 4.92 (1H, d, *J* = 8.6 Hz, *anti*, OCH), 3.89–3.82 (1H, br s, OH), 2.78–2.72 (1H, m, *anti*, COCH), 2.72–2.66 (1H, m, *syn*, COCH), 2.50–2.48 (1H, m, C*H*H), 2.43–2.36 (1H, m, C*H*H), 2.09–2.07 (1H, m, C*H*H), 1.93 (1H, m, CH), 1.81–1.78 (1H, m, C*H*H) 1.60–1.54 (1H, m, C*H*H), 1.33 (1H, m, C*H*H) 1.05 (3H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.9, 148.4, 147.6, 127.8, 123.6, 74.1, 52.8, 38.1, 36.0, 32.9, 26.6, 18.1; HPLC analysis: Diacel Chiralpak OD-H, hexane/^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 27.42 (*syn* minor), 32.70 (*syn* major), 45.19 (*anti* major) and 54.59 (*anti* minor), 24% (*anti*) and 24% (*syn*) *ee*.

4.3.18. (R)-2-[(R)-Hydroxy-(4-(nitrophenyl)methyl]-cyclopentanone (**16r**) [7n]

Colourless oil. Yield: 100%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.21 (2H, d, *J* = 8.7 Hz, ArH), 7.52 (2H, d, *J* = 8.7 Hz, ArH), 5.42 (1H, s, *syn*, OCH), 4.84 (1H, d, *J* = 9.1 Hz, *anti*, OCH), 4.77 (1H, s, *anti*, COCH), 2.95 (1H, s, *syn*, COCH), 2.55–1.90 (5H, m, OH and 4 × C*H*H), 1.75–1.72 (2H, m. 2 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ *syn* 219.6, 150.2, 147.0, 126.3, 123.6, 70.3, 56.0, 38.8, 22.2, 20.2. *anti* 222.8, 148.5, 147.2, 127.3, 123.5, 74.3, 55.0, 38.5, 26.7, 20.2; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 29.99 (*syn* minor), 41.76 (*syn* major), 54.57 (*anti* minor) and 55.83 (*anti* major), 4% *ee*.

4.3.19. (R)-4-Hydroxy-4-(4-nitrophenyl)-butan-2-one (**16s**) [7i]

Colourless oil. Yield: 100%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 7.0 Hz, ArH), 7.52 (2H, d, *J* = 7.0 Hz, ArH), 5.25 (1H, m, OCH), 3.56 (1H, br s, OH), 3.01–2.71 (2H, m, 2 × C*H*HCO), 2.21 (3H, s, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.6, 149.9, 147.4, 126.4, 123.8, 68.9, 51.5, 30.7; HPLC analysis: Diacel Chiralpak AS-H, hexane/^{i}PrOH 85:15, flow rate 1.0 mL/min, retention time: 31.93 (major) and 42.52 (minor), 52% *ee*.

4.3.20. (S)-2-((S)-1-Hydroxy-2-methylpropyl)cyclohexan-1-one (**16t**) [7k]

Colorless oil. Yield: 17%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.52 (1H, m, OCH), 3.27 (1H, d, *J* = 4.8 Hz, COCH), 2.42–2.34 (3H, m, 3 × COC*H*H and CH), 2.35–2.25 (2H, m, 2 × C*H*H), 2.04–1.62(5H, m, 4 × C*H*H and OH), 0.98 (3H, d, *J* = 6.8 Hz, CH_3), 0.88 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 216.1, 75.6, 53.7, 42.9, 30.6, 29.2, 27.8, 25.0, 20.1, 15.2; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 97:3, flow rate 0.5 mL/min, retention time: 25.08 (minor) and 37.77 (major), 91% *ee*.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.08.038.

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