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Highly stereoselective direct aldol reactions catalyzed by (*S*)-NOBIN-L-prolinamide

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Abstract—(*S*)-NOBIN-L-prolinamide was employed as organocatalyst in the direct aldol reactions of different ketones and aromatic aldehydes using dioxane as solvent and in the presence of water as additive. Acetone led to the aldol products in up to 93% ee, while cyclic ketones furnished the *anti*-aldols in moderate to high yield, excellent diastereoselectivity (up to >99/<1 *anti*/*syn* ratio) and high ee (up to 95%).

1. Introduction

The stereoselective aldol reaction plays a fundamental role among the carbon–carbon bond forming transformations as a key step in natural product synthesis and for the rapid access to polyoxygenated compounds.[1] After the discovery by List and co-workers that L-proline catalyzes the enantioselective intermolecular direct aldol reaction,[2] a significant amount of work has been undertaken to improve the efficiency and increase the scope of the organocatalyzed aldol reaction. Thus, a rapid development of asymmetric methodologies employing cyclic and linear unmodified ketones with different aldehydes has been observed.[3] Several organocatalysts have been synthesized mainly by modifying the acidic moiety of L-proline and the most efficient derivatives are those having groups, which can be involved in hydrogen bonding interactions.[4] According to the mechanism proposed for this reaction, the enamine derived from the condensation of acetone with proline[4a] (**TS-1**) or proline-based organocatalysts as amides[4c,e] (**TS-2**) forms rigid transition states where the stereochemistry of the novel carbon–carbon bond is regulated through hydrogen bonding interactions with the carbonyl group of the approaching aldehyde (Fig. 1). Hence, the presence of acidic protons in the organocatalyst is an important structural feature for the development of more efficient proline-derived promoters.

Axial chirality in proline-based compounds has been introduced as BINAM mono- and bis-prolinamides, which were successfully employed under different conditions in direct aldol reactions.[5] We have recently reported the employment

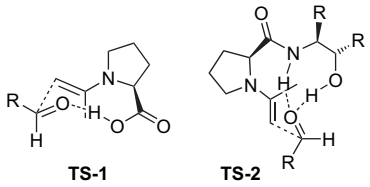

Figure 1. Transition states for proline and prolinamides catalyzed aldol reactions.

of prolinamides having (*S*)- and (*R*)-NOBIN ligands as the amide portion in the direct aldol reaction (Fig. 2).[6] These compounds, easily obtained from *N*-benzyloxy-L-proline,[6] were designed with the intention of synthesizing more reactive promoters with the presence of better H-bond donors in the phenolic OH and amidic NH groups, and to enhance the stereocontrol due to the axial element of chirality.

Diastereoisomer **2** proved to be a better catalyst than **1** in the reaction of acetone and different aldehydes, showing the

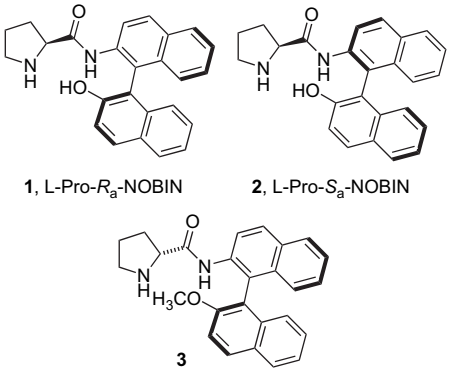

Figure 2. NOBIN-based prolinamides.

Keywords: Organocatalysis; Aldol reactions; NOBIN; Prolinamides.
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matching combination of L-proline with axial (*S*)-configured NOBIN. Unexpectedly high reactivity of **2** was observed when carrying out the reaction in the unusual hexane and this enabled reactions with a low loading of **2** (5 mol %) and of acetone (3 equiv) with respect to the aldehyde. Although the products were isolated in good to high yields, the enantioselectivity ranged from 53 to 77% ee. The presence of an OH group in catalyst **2** was important, which is likely to be involved as a H-bond donor. In fact, the reaction performed using **3**, the O-methylated enantiomer of **2**, furnished the product in high yield, but with a significantly lower ee.

Herein, we report a more in-depth investigation on the aldol reactions catalyzed by compound **2**. An improvement of the enantioselectivity was achieved for acetone as donor under different conditions and the scope of the reaction was extended to different ketones achieving excellent levels of diastereo- and enantioselectivity.[7]

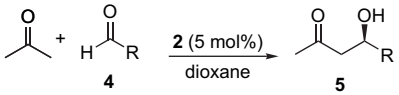
2. Results and discussion

It has been shown that the presence of acid and basic additives affected the outcome of organocatalyzed direct aldol reactions.[8] Depending on the amount, addition of water to the reaction solvent improved the activity and asymmetric induction of L-proline[9] and other derivatives[5e] as catalysts. We therefore investigated the effect of different equivalents of water in the model reaction of acetone and *p*-nitrobenzaldehyde at room temperature catalyzed by 5 mol % of compound **2** (Table 1). Amongst the solvents to be examined, dioxane was chosen for this investigation.[10] Anhydrous conditions furnished the product in low yield and 65% ee (entry 1). The addition of 0.5 equiv of water to the reaction mixture doubled the conversion and the aldol product was isolated in 78% ee (entry 2). Higher conversion was observed when adding 1.1 equiv of water (entry 3), while 4.5 or 9 equiv afforded a maximum of 41% yield, but the enantioselectivity slightly decreased (entries 4 and 5). These experiments showed that the presence of water is beneficial for both the activity and the asymmetric induction in a more restricted molar range when compared to L-proline.[9a,d] It is likely that the amount of water added, in order to regulate the activity, is related to the structure of the proline-based organocatalysts. This is similar to what happens to reactions catalyzed by enzymes in organic solvents, where the water content is known to modulate their activity and stereoselectivity.[11] With the optimum amount of water additive (1.1 equiv), THF and DME were examined as alternative ethereal solvents, but they gave unsatisfactory results when compared to dioxane (entries 6 and 7). It must be noted that the reaction performed in the polar protic methanol and in the absence of water furnished racemic aldol product in moderate yield (entry 8). Predictably, methanol was highly competitive with the catalyst as a H-bond donor in activating the aldehyde through an unselective pathway. Carrying out the reaction using 5 mol % of TFA as acid additive and 10 mol % of **2** in dioxane (entry 9) had a detrimental effect on the reaction (compare with entry 1) even in the presence of water (entry 10).

Using 1.1 equiv of water and working at 4 °C in dioxane, some representative aldol products were obtained in good yield using 5 mol % of catalyst, but in higher ee with respect to the use of hexane as the solvent[6] (entries 11–13).

Under the same conditions cyclic ketones were studied as donors employing 10 mol % of catalyst **2** (Table 2).

Table 1. Direct aldol reaction of acetone and aromatic aldehydes catalyzed by **2** in different conditions using water as an additive[a]

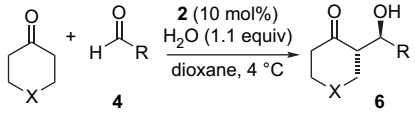


4 5

Entry	R	H_2O (equiv)	*T* (°C)	*t* (h)	Yield[b] (%)	ee[c] (%)
1	*p*-$NO_2C_6H_4$	—	rt	24	11	65
2	*p*-$NO_2C_6H_4$	0.55	rt	27	30	78
3	*p*-$NO_2C_6H_4$	1.1	rt	20	37	78
4	*p*-$NO_2C_6H_4$	4.5	rt	24	41	76
5	*p*-$NO_2C_6H_4$	9.0	rt	23	41	72
6[d]	*p*-$NO_2C_6H_4$	1.1	rt	21	13	75
7[e]	*p*-$NO_2C_6H_4$	1.1	rt	23	27	54
8[f]	*p*-$NO_2C_6H_4$	—	rt	46	46	3
9[g]	*p*-$NO_2C_6H_4$	—	rt	25	13	47
10[g]	*p*-$NO_2C_6H_4$	1.1	rt	28	<5	—
11[h]	*p*-$NO_2C_6H_4$	1.1	4	70	77	80 (70)[i]
12[h]	*o*-$NO_2C_6H_4$	1.1	4	88	74	79 (71)[i]
13[h]	2,6-$Cl_2C_6H_3$	1.1	4	129	88	93 (77)[i]

[a] Reaction conditions: **4** (0.2 mmol), acetone (0.6 mmol), solvent (400 μL).
[b] Yield of isolated product after flash chromatography.
[c] Determined by HPLC on Chiralpak AS-H column. Absolute configuration was determined by comparison of the HPLC retention times with those in the literature.
[d] The reaction was carried out in THF.
[e] The reaction was carried out in dimethoxyethane (DME).
[f] The reaction was carried out in methanol.
[g] The reaction was carried out with 10 mol % of **2** and 5 mol % of TFA.
[h] The reaction was carried out using 200 μL of solvent.
[i] ee in parenthesis was achieved in hexane as reported in Ref. 6.

Table 2. Direct aldol reaction of cyclic ketones and aromatic aldehydes catalyzed by **2** at 4 °C in dioxane and in the presence of 1.1 equiv of water[a]



4 6

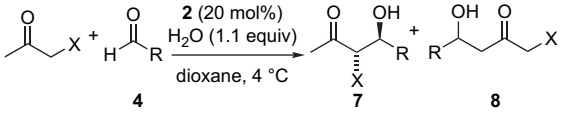
Entry	R	X	*T* (h)	Yield[b] (%)	dr[c] (%, *anti*/*syn*)	ee[d] (%)
1	*p*-$NO_2C_6H_4$	CH_2	65	86	98/2	92
2[e]	*p*-$NO_2C_6H_4$	CH_2	96	42	87/13	71[f]
3	*o*-$NO_2C_6H_4$	CH_2	63	50	95/5	90
4	2,6-$Cl_2C_6H_3$	CH_2	72	78	>99/<1	95
5	*p*-CNC_6H_4	CH_2	94	61	98/2	93
6	*p*-$CF_3C_6H_4$	CH_2	113	71	99/1	91
7	*p*-ClC_6H_4	CH_2	166	26	98/2	93
8	*o*-ClC_6H_4	CH_2	120	60	95/5	90
9	5-Nitrofuran-2-yl	CH_2	24	99	96/4	79
10	*p*-$NO_2C_6H_4$	—	48	98	35/65	92(62)
11	*o*-$NO_2C_6H_4$	—	75	82	44/56	90(56)
12	*p*-$NO_2C_6H_4$	O	48	90	>99/<1	70
13	*p*-$NO_2C_6H_4$	S	96	40	>99/<1	94
14	*o*-$NO_2C_6H_4$	S	192	31	97/3	93
15	*p*-CNC_6H_4	S	160	64	97/3	90
16	*p*-$CF_3C_6H_4$	S	160	50	>99/<1	90

[a] Reaction conditions: **4** (0.2 mmol), acetone (0.6 mmol), H_2O (0.22 mmol), solvent (200 μL).
[b] Yield of isolated aldol products (*anti*/*syn*) after flash chromatography.
[c] The *anti*/*syn* ratio was determined by ^1H NMR analysis on the crude reaction mixture.
[d] Determined by HPLC on chiral columns. ee in parenthesis for *syn*-isomer.
[e] Catalyst **3** was used.
[f] The opposite enantiomer of the *anti*-**6** was obtained.

The aldol product obtained from the reaction of *p*-nitrobenzaldehyde and cyclohexanone was recovered in excellent diastereoisomeric ratio and high ee for the *anti* adduct (entry 1).

In order to check if under these modified conditions the phenolic OH group of catalyst **2** was involved in the process, the reaction was performed using catalyst **3** (entry 2). The conversion to the aldol product was remarkably reduced and both the diastereo- and the enantioselectivity were significantly lowered, which confirmed[6] the importance of the OH group in promoting the reaction and controlling the stereoselectivity. Excellent *anti*/*syn* ratio and ee higher than 90% for the *anti*-isomer were generally achieved (entries 4–9). The *anti*/*syn* ratio was marginally decreased to 95/5 when reacting *ortho* substituted aromatic aldehydes (entries 3 and 8), but the asymmetric induction was maintained at high levels. Heteroaromatic aldehydes are also suitable substrates (entry 9). When reacting cyclopentanone the conversion to the products improved and a slight preference for the *syn*-isomer was observed (entries 10 and 11). Nevertheless, the *anti*-aldol was recovered in high ee. Tetrahydropyran-4-one reacted much faster than tetrahydro-4*H*-thiopyran-4-one with *p*-nitrobenzaldehyde (entries 12 and 13).[12] In both cases the *anti*-isomer was exclusively obtained, but only the thio-derivative showed appreciable ee. Although being a relatively unreactive ketone, tetrahydro-4*H*-thiopyran-4-one furnished different aldol products in satisfactory yields, excellent diastereoselectivity and high enantioselectivity (entries 14–16). These products are synthetically useful building blocks[13] since they can be converted to 3-pentanone derivatives, which are difficult to prepare by direct aldol reaction of the linear ketone with high stereocontrol.[14] Finally, two more challenging linear ketones[15] were reacted to ascertain the degree of regio- and stereocontrol with model *p*-nitrobenzaldehyde (Table 3). In the case of α-methoxyacetone (entry 1) reasonable regioselectivity in favor of isomers **7** as well as comparable *anti*-diastereoselectivity were observed. *anti*-**7** was recovered in 84% ee. Unreactive α-chloroacetone[16] furnished the aldols in modest yield, but with excellent regio- and diastereoselectivity and a*nti*-**7** was obtained in 85% ee (entry 2). These results showed that linear ketones, although more flexible donors, can be successfully converted in high regio- and

Table 3. Direct aldol reaction of linear ketones and *p*-nitrobenzaldehyde catalyzed by **2** at 4 °C in dioxane and in the presence of 1.1 equiv of water[a]



Entry	X	Regioselectivity[e] (**7**/**8**)	*t* (h)	Yield[b] of **7** (%)	dr[c] of **7** (%, *anti*/*syn*)	ee[d] of **7** (%)
1	OCH_3	85/15	168	62	84/16	84
2[e]	Cl	95/5	182	41	95/5	85

[a] Reaction conditions: **4** (0.2 mmol), acetone (0.6 mmol), H_2O (0.22 mmol), solvent (200 μL).
[b] Yield of isolated aldol products (**7** and **8**) after flash chromatography.
[c] The *anti*/*syn* ratio was determined by ^{1}H NMR analysis on the crude reaction mixture.
[d] Determined by HPLC on chiral columns.
[e] The regioisomeric ratio was determined by ^{1}H NMR analysis on the crude reaction mixture.

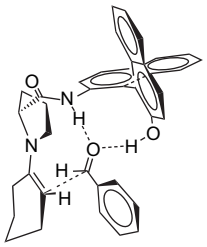


Figure 3. Plausible transition state for the direct aldol reaction catalyzed by **2**.

diastereoselective control to *anti*-isomers with fairly good level of enantioselectivity.

On the basis of experimental results, the high stereocontrol observed when using catalyst **2** can be rationalized by invoking the transition state depicted in Figure 3, which is similar to transition state **TS-2** previously suggested by Gong et al.[4c] (Fig. 1). Both NH and OH groups take part in the activation of the aldehyde as H-bond donors and the new C–C bond is formed by the attack of enamine from its *Re* face onto the *Re* face of aldehyde.

3. Conclusion

Under optimized conditions, which required the presence of water as additive,[17] (*S*)-NOBIN-L-prolinamide **2** was shown to be a highly stereoselective catalyst in direct aldol reactions of linear and cyclic ketones with aromatic aldehydes. *anti*-Aldols were generally isolated in excellent diastereoselectivity and high ee. Although the activity of catalyst **2** decreased when using non-activated aromatic aldehydes, it can be used at 5–10 mol % loading and only a slight excess of the ketone with respect to the aldehyde is required. From a practical and economic point of view these reaction conditions are convenient with respect to most of the organocatalyzed protocols where a large excess of ketones is used.

4. Experimental

4.1. General

All reactions requiring dry or inert conditions were conducted in flame dried glassware under a positive pressure of nitrogen. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by a 10% H_2SO_4/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 400 and Bruker DRX 300 spectrometers at room temperature in $CDCl_3$ as solvent. Chemical shifts are reported relative to the residual solvent peaks ($CHCl_3$: δ_H=7.26 and δ_C=77.0). Optical rotations were performed on a Jasco Dip-1000 digital polarimeter using the Na lamp. All commercially available reagents were purchased from Aldrich. Petrol ether (PE) refers to light petroleum ether (bp 40–60 °C). The absolute configurations were determined by comparison with optical rotations and/or HPLC retention times using Daicel Chiralcel OD and Daicel Chiralpak AD and AS-H columns, as reported in the

literature. Synthesis and spectral data of organocatalysts **1**–**3** were previously reported.[6]

4.2. General procedure for the aldol reaction

In a capped vial, catalyst **2** (7.6 mg, 0.02 mmol), aldehyde (0.2 mmol), dry dioxane (200 μL), and H_2O (4.0 μL) were added at room temperature. The reaction was cooled to +4 °C, then the ketone (0.6 mmol) was added and the mixture was stirred at +4 °C. After monitoring by TLC, the mixture was directly purified by flash chromatography eluting with PE/AcOEt 9/1 to 7/3 mixtures to provide the aldol adduct. Spectral data of aldols were identical to those previously reported.[4c–e,g,9d,15,18] The enantiomeric excess of aldols was determined by chiral HPLC analysis using Daicel Chiralcel OD and Daicel Chiralpak AD and AS-H columns according to the literature.[4c,e,g,9d,18]

4.2.1. (*R*)-4-Hydroxy-4-(*p*-nitrophenyl)-butan-2-one (Table 1, entry 11).[4e] $[\alpha]_D^{29}$ +25.6 (*c* 0.38, $CHCl_3$), 80% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H, C*H*$_3$CO), 2.86–2.90 (m, 2H, C*H*$_2$CO), 3.56 (d, *J*=3.2 Hz, 1H, O*H*), 5.22–5.26 (m, 1H, C*H*OH), 7.52 (d, *J*=7.0 Hz, 2H, Ar*H*), 8.20 (d, *J*=7.0 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralpak AS-H column (70/30 hexane/2-propanol), 254 nm, 1.0 mL/min, t_r=13.0 min (major), t_r=16.3 min (minor).

4.2.2. (*R*)-4-Hydroxy-4-(*o*-nitrophenyl)-butan-2-one (Table 1, entry 12).[4e] $[\alpha]_D^{31}$ +14.0 (*c* 0.95, $CHCl_3$), 79% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H, C*H*$_3$CO), 2.85–2.90 (m, 2H, C*H*$_2$CO), 3.71 (br s, 1H, O*H*), 5.26 (dd, *J*=3.6, 7.2 Hz, 1H, C*H*OH), 7.52 (t, *J*=7.8 Hz, 1H, Ar*H*), 7.70 (d, *J*=7.8 Hz, 1H, Ar*H*), 8.10–8.14 (m, 1H, Ar*H*), 8.24 (m, 1H, Ar*H*). The ee was determined by HPLC with Chiralpak AS-H column (70/30 hexane/2-propanol), 254 nm, 1.0 mL/min, t_r=10.92 min (major), t_r=9.98 min (minor).

4.2.3. (*R*)-4-Hydroxy-4-(2,6-dichlorophenyl)-butan-2-one (Table 1, entry 13).[4e] $[\alpha]_D^{22}$ −47.4 (*c* 0.58, $CHCl_3$)]; 93% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, C*H*$_3$CO), 2.73–3.44 (m, 2H, C*H*$_2$CO), 3.22 (br s, 1H, O*H*), 5.96–6.03 (m, 1H, C*H*OH), 7.13–7.33 (m, 3H, Ar*H*). The ee was determined by HPLC with Chiralpak AS-H column (70/30 hexane/2-propanol), 220 nm, 1.0 mL/min, t_r= 5.3 min (major), t_r=5.8 min (minor).

4.2.4. (2*S*,1′*R*)-2-(Hydroxy-(*p*-nitrophenyl)methyl)cyclohexan-1-one (Table 2, entry 1).[3q,v,w] $[\alpha]_D^{22}$ +18.3 (*c* 0.58, $CHCl_3$), 92% ee. *anti*-Isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 1.31–1.45 (m, 1H, one proton of CH_2), 1.51–1.67 (m, 3H, C*H*$_2$ and one proton of CH_2), 1.78–1.87 (m, 1H, one proton of CH_2), 2.06–2.17 (m, 1H, one proton of C*H*$_2$), 2.36 (td, *J*=13.2, 5.7 Hz, 1H, C*H*), 2.45–2.65 (m, 2H, C*H*$_2$), 4.09 (d, *J*=3.0 Hz, 1H, O*H*), 4.90 (dd, *J*=8.4, 3.0 Hz, 1H, C*H*OH), 7.51 (d, *J*=8.7 Hz, 2H, Ar*H*), 8.21 (d, *J*=8.7 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralpak AD column (80/20 hexane/2-propanol), 254 nm, 0.5 mL/min, t_r=52.7 min (major), t_r=41.7 min (minor).

4.2.5. (2*S*,1′*R*)-2-(Hydroxy-(*o*-nitrophenyl)methyl)cyclohexan-1-one (Table 2, entry 3).[3v,w] $[\alpha]_D^{24}$ +7.6 (*c* 0.99, $CHCl_3$), 90% ee. *anti*-Isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 1.55–1.90 (m, 4 H, 2 C*H*$_2$), 2.06–2.15 (m, 1H, one proton of CH_2), 2.34 (td, *J*=12.3, 5.7 Hz, 1H, C*H*), 2.40–2.50 (m, 1H, C*H*), 2.70–2.82 (m, 1H, C*H*), 3.90 (br s, 1H, O*H*), 5.45 (d, *J*=6.6 Hz, 1H, C*H*OH), 7.43 (t, *J*=7.8 Hz, 1H, Ar*H*), 7.63 (t, *J*=7.5 Hz, 1H, Ar*H*), 7.77 (d, *J*=7.8 Hz, 1H, Ar*H*), 7.84 (d, *J*=8.1 Hz, 1H, Ar*H*). The ee was determined by HPLC with Chiralpak AD column (90/10 hexane/2-propanol), 254 nm, 0.5 mL/min, t_r=59.4 min (major), t_r=63.0 min (minor).

4.2.6. (2*S*,1′*R*)-2-(Hydroxy-(2,6-dichlorophenyl)methyl)-cyclohexan-1-one (Table 2, entry 4).[4i] $[\alpha]_D^{22}$ −24.7 (*c*=2.12, $CHCl_3$), 95% ee. *anti*-Isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.68 (m, 4H, 2 C*H*$_2$), 1.71–1.77 (m, 1H, one proton of CH_2), 2.03–2.08 (m, 1H, one proton of CH_2), 2.38–2.49 (m, 2H, C*H*$_2$), 3.42–3.49 (m, 1H, C*H*), 3.65 (d, *J*=4.2 Hz, 1H, O*H*), 5.80 (dd, *J*=4.2 Hz, 1H, C*H*OH), 7.11–7.31 (m, 3 H, Ar*H*). The ee was determined by HPLC with Chiralpak AS-H column (95/5 hexane/2-propanol), 220 nm, 0.5 mL/min; t_r=29.1 min (major), t_r=23.3 min (minor).

4.2.7. (2*S*,1′*R*)-2-(Hydroxy-(*p*-cyanophenyl)methyl)-cyclohexan-1-one (Table 2, entry 5).[3v,w] $[\alpha]_D^{25}$ +9.7 (*c* 1.28, $CHCl_3$), 93% ee. *anti*-Isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 1.31–1.44 (m, 1H, one proton of CH_2), 1.47–1.72 (m, 3H, C*H*$_2$ and one proton of CH_2), 1.77–1.88 (m, 1H, one proton of CH_2), 2.06–2.17 (m, 1H, one proton of CH_2), 2.37 (td, *J*=12.9, 6.0 Hz, 1H, C*H*), 2.44–2.65 (m, 2H, C*H*$_2$), 4.11 (d, *J*=3.0 Hz, 1H, O*H*), 4.85 (dd, *J*=8.1, 3.0 Hz, 1H, C*H*OH), 7.45 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.65 (d, *J*=8.1 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralpak AD column (80/20 hexane/2-propanol), 254 nm, 0.5 mL/min, t_r=46.6 min (major), t_r=37.9 min (minor).

4.2.8. (2*S*,1′*R*)-2-(Hydroxy-(*p*-(trifluoromethyl)phenyl)-methyl)cyclohexan-1-one (Table 2, entry 6).[3w] $[\alpha]_D^{27}$ +10.1 (*c* 1.33, $CHCl_3$), 91% ee. *anti*-Isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 1.24–1.37 (m, 1H, one proton of CH_2), 1.48–1.70 (m, 3H, C*H*$_2$ and one proton of CH_2), 1.77–1.82 (m, 1H, one proton of CH_2), 2.09 (ddd, *J*=12.8, 6.0, 3.2 Hz, 1H, C*H*), 2.34 (ddt, *J*=13.6, 6.0, 0.8 Hz, 1H, C*H*), 2.44–2.50 (m, 1H, C*H*), 2.54–2.61 (m, 1H, C*H*), 3.99 (br s, 1H, O*H*), 4.83 (d, *J*=8.8 Hz, 1H, C*H*OH), 7.42 (d, *J*=8.0 Hz, 2H, Ar*H*), 7.59 (d, *J*=8.0 Hz, 2H, Ar*H*). The ee was determined by HPLC with a Chiralpak AD column (90/10 hexane/2-propanol), 220 nm, 0.5 mL/min, t_r=33.0 min (major), t_r=35.3 min (minor).

4.2.9. (2*S*,1′*R*)-2-(Hydroxy-(*p*-chlorophenyl)methyl)-cyclohexan-1-one (Table 2, entry 7).[3v,w] $[\alpha]_D^{25}$ +13.7 (*c* 0.33, $CHCl_3$), 93% ee. *anti*-Isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 1.20–1.37 (m, 1H, one proton of CH_2), 1.50–1.70 (m, 3H, C*H*$_2$ and one proton of CH_2), 1.75–1.85 (m, 1H, one proton of CH_2), 2.05–2.15 (m, 1H, one proton of CH_2), 2.35 (td, *J*=12.9, 5.4 Hz, 1H, C*H*), 2.44–2.61 (m, 2H, C*H*$_2$), 3.99 (d, *J*=3.0 Hz, 1H, O*H*), 4.76 (dd, *J*=8.7, 2.7 Hz, 1H, C*H*OH), 7.23 (d, *J*=8.4 Hz, 2H, Ar*H*), 7.30 (d, *J*=8.4 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralpak AD column (90/10 hexane/2-propanol), 220 nm, 0.5 mL/min, t_r=31.8 min (major), t_r=26.6 min (minor).

4.2.10. (2*S*,1′*R*)-2-(Hydroxy-(*o*-chlorophenyl)methyl)-cyclohexan-1-one (Table 2, entry 8).[4f] $[\alpha]_D^{22}$ +10.2 (*c* 1.01, $CHCl_3$), 90% ee. *anti*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51–2.09 (m, 6H, 3 CH_2), 2.28–2.46 (m, 2H, CH_2), 2.63–2.70 (m, 1H, C*H*), 3.92 (s, 1H, O*H*), 5.34 (d, *J*=8.0 Hz, 1H, C*H*OH), 7.19 (t, *J*=7.6 Hz, 1H, Ar*H*), 7.28 (d, *J*=7.6 Hz, 1H, Ar*H*), 7.31 (d, *J*=8.0 Hz, 1H, Ar*H*), 7.53 (d, *J*=7.6 Hz, 1H, Ar*H*). The ee was determined by HPLC with a Chiralcel OD column (95/5 hexane/2-propanol), 220 nm, 0.8 mL/min; t_r=11.5 min (major), t_r=13.3 min (minor).

4.2.11. (2*S*,1′*R*)-2-[Hydroxy-(5-nitrofuran-2-yl)methyl]-cyclohexan-1-one (Table 2, entry 9).[18] $[\alpha]_D^{24}$ +14.0 (*c* 2.15, $CHCl_3$), 79% ee. *anti*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59–1.79 (m, 3H, CH_2 and one proton of CH_2), 1.89–1.95 (m, 2H, CH_2), 2.14–2.18 (m, 1H, one proton of CH_2), 2.37–2.50 (m, 2H, CH_2), 2.95–3.00 (m, 1H, C*H*), 4.02 (br s, 1H, O*H*), 4.82 (d, *J*=6.5 Hz, 1H, C*H*OH), 6.59 (d, *J*=3.6 Hz, 1H, Ar*H*), 7.28 (d, *J*=3.6 Hz, 1H, Ar*H*); ^{13}C NMR (100.1 MHz, $CDCl_3$): 24.6, 27.7, 30.8, 42.6, 54.3, 68.8, 110.5, 112.4, 151.6, 158.4, 214.2. The ee was determined by HPLC with Chiralpak AD column (95/5 hexane/2-propanol), 254 nm, 1.0 mL/min, t_r=36.5 min (major), t_r=43.3 min (minor).

4.2.12. 2-(Hydroxy-(*p*-nitrophenyl)methyl)cyclopentan-1-one (Table 2, entry 10).[4e] *anti*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50–2.03 (m, 4H, 2 CH_2), 2.25–2.48 (m, 3H, CH_2 and C*H*), 4.78 (s, 1H, O*H*), 4.84 (d, *J*=4.6 Hz, 1H, C*H*OH), 7.54 (d, *J*=4.3 Hz, 2H, Ar*H*), 8.21(d, *J*=4.3 Hz, 2H, Ar*H*). *syn*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60–2.20 (m, 4H, 2 CH_2), 2.30–2.50 (m, 2H, CH_2), 2.65 (d, *J*=2.4 Hz, 1H, C*H*), 5.42 (s, 1H, C*H*OH), 7.52 (d, *J*=4.4 Hz, 2H, Ar*H*), 8.20 (d, *J*=4.4 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralpak AS-H column (70/30 hexane/2-propanol), 254 nm, 1.0 mL/min, *syn*-isomer: t_r=20.8 min (major), t_r=7.6 min (minor); *anti*-isomer: t_r=17.3 min (major), t_r=13.8 min (minor).

4.2.13. 2-(Hydroxy-(*o*-nitrophenyl)methyl)cyclopentan-1-one (Table 2, entry 11).[4h] *anti*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70–2.03 (m, 4H, 2 CH_2), 2.19–2.38 (m, 2H, CH_2), 2.68 (d, *J*=7.6 Hz, 1H, C*H*), 2.90 (br s, 1H, O*H*), 5.21 (d, *J*=7.2 Hz, 1H, C*H*OH), 7.44 (t, *J*=8.0 Hz, 1H, Ar*H*), 7.66 (t, *J*=8.0 Hz, 1H, Ar*H*), 7.89 (d, *J*=8.0 Hz, 1H, Ar*H*), 8.00 (dd, *J*=8.0, 0.8 Hz, 1H, Ar*H*). *syn*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70–1.78 (m, 2H, CH_2), 2.03–2.19 (m, 3H, CH_2 and C*H*), 2.37 (dd, *J*=8.0, 1.6 Hz, 1H, C*H*), 2.60 (br s, 1H, O*H*), 2.74 (m, 1H, C*H*,), 5.92 (d, *J*=2.4 Hz, 1H, C*H*OH), 7.44 (td, *J*=8.0, 0.8 Hz, 1H, Ar*H*), 7.66 (t, *J*=8.0 Hz, 1H, Ar*H*), 7.89 (d, *J*=8.0 Hz, 1H, Ar*H*), 8.02 (d, *J*=8.0 Hz, 1H, Ar*H*). The ee was determined by HPLC with Chiralpak AS-H column (95/5 hexane/2-propanol), 254 nm, 1.0 mL/min; *syn*-isomer: t_r=35.1 min (major), t_r=25.8 min (minor); *anti*-isomer: t_r=43.3 min (major), t_r=36.9 min (minor).

4.2.14. (3*S*,1′*R*)-3-(Hydroxy-(*p*-nitrophenyl)methyl)-tetrahydropyran-4-one (Table 2, entry 12).[4g] $[\alpha]_D^{26}$ +1.0 (*c* 1.86, $CHCl_3$), 70% ee. *anti*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50–2.54 (m, 1H, one proton of CH_2), 2.66–2.69 (m, 1H, one proton of CH_2), 2.88–2.90 (m, 1H, C*H*), 3.46 (t, *J*=9.9 Hz, 1H, C*H*), 3.70–3.83 (m, 3H, CH_2 and O*H*), 4.18–4.23 (m, 1H, C*H*), 4.96 (dd, *J*=3.3, 8.1 Hz, 1H, C*H*OH), 7.50 (d, *J*=8.7 Hz, 2H, Ar*H*), 8.21 (d, *J*=8.7 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralpak AD column (80/20 hexane/2-propanol), 254 nm, 1.0 mL/min, t_r=25.0 min (major), t_r=21.9 min (minor).

4.2.15. (3*S*,1′*R*)-3-(Hydroxy-(*p*-nitrophenyl)methyl)-tetrahydrothiopyran-4-one (Table 2, entry 13).[4g,9d] $[\alpha]_D^{30}$ +3.0 (*c* 0.7, $CHCl_3$), 94% ee. *anti*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51–2.55 (m, 1H, C*H*), 2.64–2.70 (m, 1H, C*H*), 2.74–2.88 (m, 2H, CH_2), 2.97–3.05 (m, 3H, CH_2 and C*H*), 3.68 (br s, 1H, O*H*), 5.06 (d, *J*=8.0 Hz, 1H, C*H*OH), 7.55 (d, *J*=8.8 Hz, 2H, Ar*H*), 8.23 (d, *J*=8.8 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralpak AD column (90/10 hexane/2-propanol), 254 nm, 1 mL/min; t_r=75.6 min (major), t_r=42.4 min (minor).

4.2.16. (3*S*,1′*R*)-3-(Hydroxy-(*o*-nitrophenyl)methyl)-tetrahydrothiopyran-4-one (Table 2, entry 14).[4g] $[\alpha]_D^{25}$ +7.2 (*c* 0.74, $CHCl_3$), 93% ee. *anti*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (dt, *J*=13.6, 3.2 Hz, 1H, C*H*), 2.72–3.06 (m, 5H, 2 CH_2 and C*H*), 3.14–3.20 (m, 1H, C*H*), 3.83 (br s, 1H, O*H*), 5.56 (d, *J*=7.2 Hz, 1H, C*H*OH), 7.46 (t, *J*=8.0 Hz, 1H, Ar*H*), 7.67 (t, *J*=7.6 Hz, 1H, Ar*H*), 7.77 (d, *J*=7.6 Hz, 1H, Ar*H*), 7.89 (d, *J*=8.4 Hz, 1H, Ar*H*). The ee was determined by HPLC with Chiralpak AD column (90/10 hexane/2-propanol), 254 nm, 1 mL/min, t_r=41.4 min (major), t_r=33.7 min (minor).

4.2.17. (3*S*,1′*R*)-3-(Hydroxy-(*p*-cyanophenyl)methyl)-tetrahydrothiopyran-4-one (Table 2, entry 15).[4g] $[\alpha]_D^{24}$ +8.0 (*c* 0.78, $CHCl_3$), 90% ee. *anti*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (ddd, *J*=13.6, 4.8, 2.0 Hz, 1H, C*H*), 2.63 (dd, *J*=13.6, 10.4 Hz, 1H, C*H*), 2.73–3.03 (m, 5H, 2 CH_2 and C*H*), 3.69 (br s, 1H, O*H*), 5.02 (d, *J*=8.0 Hz, 1H, C*H*OH), 7.48 (d, *J*=8.0 Hz, 2H, Ar*H*), 7.67 (d, *J*=8.4 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralcel OD column (92/8 hexane/2-propanol), 254 nm, 1 mL/min; t_r=43.6 min (major), t_r=61.1 min (minor).

4.2.18. (3*S*,1′*R*)-3-(Hydroxy-(*p*-(trifluoromethyl)phenyl)-methyl)-tetrahydrothiopyran-4-one (Table 2, entry 16).[9d] $[\alpha]_D^{25}$ +4.4 (*c* 0.77, $CHCl_3$), 90% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (ddd, *J*=13.7, 4.9, 2.2 Hz, 1H, C*H*), 2.63 (dd, *J*=13.7, 10.6 Hz, 1H, C*H*), 2.77 (ddd, *J*=13.5, 10.2, 5.8 Hz, 1H, C*H*), 2.84 (dt, *J*=13.5, 4.2 Hz, 1H, C*H*), 2.93–3.04 (m, 3H, CH_2 and C*H*), 3.54 (d, *J*=3.7 Hz, 1H, O*H*), 5.04 (dd, *J*=8.4, 3.7 Hz, 1H, C*H*OH), 7.48 (d, *J*=8.3 Hz, 2H, Ar*H*), 7.63 (d, *J*=8.3 Hz, 2H, Ar*H*). The ee was determined by HPLC with a Chiralpak OD column (90/10 hexane/2-propanol), 220 nm, 0.7 mL/min; t_r=21.8 min (major), t_r=34.4 min (minor).

4.2.19. (3*S*,4*S*)-3-Methoxy-4-(*p*-nitrophenyl)-butan-2-one (Table 3, entry 1).[8d,15] $[\alpha]_D^{25}$ −8.4 (*c* 0.21, $CHCl_3$), 84% ee. *anti*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H, CH_3CO), 3.14 (d, *J*=3.7 Hz, 1H, O*H*), 3.33 (s, 3H, OCH_3), 3.71 (d, *J*=6.2 Hz, 1H, C*H*), 5.03 (dd, *J*=6.2, 3.7 Hz, 1H, C*H*OH), 7.57 (d, *J*=8.7 Hz, 2H, Ar*H*), 8.23 (d, *J*=8.7 Hz, 2H, Ar*H*). The ee was determined by HPLC with a Chiralpak OD column (90/10 hexane/2-propanol), 254 nm, 0.8 mL/min; t_r=15.8 min (major), t_r=18.8 min (minor).

4.2.20. (3*S*,4*S*)-3-Chloro-4-(*p*-nitrophenyl)-butan-2-one (Table 3, entry 2).[15,16] ee, 85%. *anti*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3CO), 3.86 (d, J=4.2 Hz, 1H, O*H*), 4.26 (d, J=8.1 Hz, 1H, C*H*), 5.12 (dd, J=8.1, 4.2 Hz, 1H, C*H*OH), 7.57 (d, J=8.7 Hz, 2H, Ar*H*), 8.19 (d, J=8.7 Hz, 2H, Ar*H*). The ee was determined by HPLC with Chiralpak AS-H column (85/15 hexane/2-propanol), 254 nm, 1.0 mL/min; t_r=13.5 min (major), t_r=12.3 min (minor).

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