An efficient synthesis of chiral phosphinyl oxide pyrrolidines and their application to asymmetric direct aldol reactions†

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Chiral pyrrolidine-based phosphinyl oxides were synthesized and their performance as organocatalysts for asymmetric direct aldol reactions was evaluated. High enantioselectivities and diastereoselectivies were achieved for a range of cyclic ketones and aromatic aldehydes.

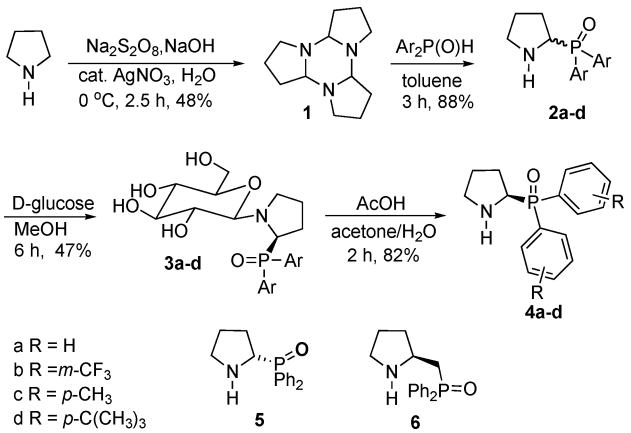
Introduction

The aldol reaction is recognized as one of the most important carbon–carbon bond-forming reactions in modern organic synthesis.[1] Although highly enantioselective transition-metal catalysts for asymmetric aldol reactions have been developed,[2] more attention has been directed toward developing organocatalysts for direct aldol reactions in recent years. Since the pioneering discovery, by List and Barbas in 2000,[3] that L-proline may be used as a catalyst in the enantioselective direct aldol reaction, several proline derivatives, for example amides and tetrazoles,[4] have been synthesized and applied in highly enantioselective direct aldol reactions.

Cyclic aminophosphonates, to the best of our knowledge, were the first chiral pyrrolidines bearing phosphorous substituents to catalyze the asymmetric direct aldol reaction.[5] High enantioselectivities were obtained and the use of organic bases as co-catalysts favored *syn*-selectivity. Herein, we describe the synthesis of chiral phosphinyl oxide pyrrolidines, with the replacement of the dihydroxy/diethoxy groups in pyrrolidine-based aminophosphonates by diphenyl groups. Herein, we wish to report the preliminary results for direct aldol reactions catalyzed by these phosphinyl oxide compounds.

Results and discussion

The chiral pyrrolidine derivatives **4a–d** bearing phosphinyl substituents were synthesized from pyrrolidine. Reaction of pyrrolidine with sodium peroxodisulfate and sodium hydroxide in the presence of silver nitrate catalyst afforded triazine compound **1** in 48% yield.[6] The triazine was then reacted with different phosphine oxides to give racemic mixtures **2a–d** of phosphinylpyrrolidines.[7] We were able to separate the two enantiomers by glycosylation.[8] Treatment of the racemic mixture with D-glucose in methanol led to the formation of two diastereomeric *N*-glucosylation products that could be separated by column chromatography; their absolute configuration was assigned by X-ray crystallography. Chiral phosphinyl oxide pyrrolidines **4a–d** and **5** were obtained by the removal of glucose in the presence of acetic acid[9] (Scheme 1). Compound **4a** has an *R* configuration, and **5** has an *S* configuration. Homo-analogue **6** was also prepared according to the literature method.[10,11]



Scheme 1 Synthesis of phosphinyl oxide pyrrolidines.

The catalytic activity of **4a–d**, **5** and **6** for the asymmetric direct aldol reaction was investigated by performing a model reaction of cyclohexanone **7** and *p*-nitrobenzaldehyde **8**. In our initial experiment, the reaction was performed in DMSO using catalytic amounts (20 mol%) of phosphinyl oxide pyrrolidines. The results are summarized in Table 1.

In most cases, the desired aldol product **9** was obtained as a mixture of diastereomers, with the *anti*-(1*R*,2*S*) isomer being predominant. Since the *syn* diastereomers were always the minor products, the ee values of the *anti* diastereomers were primarily considered. Compound **4a**, **4c** and **5** mediated the asymmetric aldol reactions with good yield (80–90%) and good enantioselectivities (79–85%) although only modest diasteroselectivities (69 : 31) were obtained (entries 1, 3 and 5). A better diastereoselectivity (*anti*:*syn* = 80 : 20) was obtained in the reaction using **4d** as catalyst (entry 4). In contrast, compound **4b** and **6** catalyzed the formation of nearly 1 : 1 mixture of *anti*:*syn* products with moderate enantioselectivity (entry 2 and 6).

Compound **4a** was chosen for further studies on the basis of good enantioselectivity and ease of preparation on a large scale. The solvents, catalyst loading, temperature and the additives in the reaction were extensively studied for this catalyst. Results

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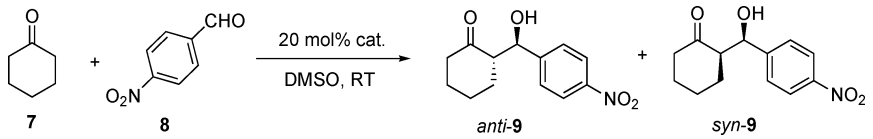
Table 1 Screening of catalysts for the model asymmetric aldol reaction of *p*-nitrobenzaldehyde with cyclohexanone



Entry	Catalyst	Time/h	Yield (%)[a]	dr (*anti*:*syn*)[b]	% ee (*anti*)[b]
1	**4a**	120	90	69 : 31	85
2	**4b**	102	33	52 : 48	63
3	**4c**	96	86	67 : 33	79
4	**4d**	124	79	80 : 20	84
5	**5**	120	79	69 : 31	81
6	**6**	96	55	55 : 45	35

[a] Isolated yield after silica gel chromatography. [b] Determined by chiral HPLC; the *anti*-isomer is the major product.

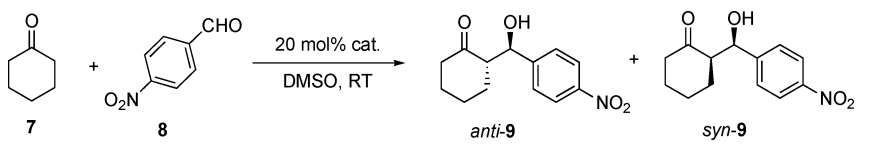
show that the reaction in DMSO afforded the *anti* product with the highest yield and enantioselectivity; reactions in DCM and chloroform gave slightly better *anti*:*syn* ratios but with lower yields and enantioselectivities (Table 2, entries 1–5). Furthermore, reduction in catalyst loading to 5–10% resulted in sluggish reactions with poor yields (entry 6 and 7). Therefore, 20 mol% was the preferred catalyst loading.

The effect of additives on the asymmetric aldol reactions was examined. The addition of acids and bases has been reported to accelerate the reaction rate by promoting enamine formation.[5,12] Unsatisfactory results were observed with the addition of strong acid of HCOOH and TsOH (entries 10 and 11), but the reaction rate was enhanced and good enantioselectivities were observed when weaker acids, AcOH and PhCOOH, were used as the additives (entries 8 and 9).

To further improve the diastereoselectivity, we investigated the effect of temperature on the reaction. To our disappointment, the reaction proceeded very slowly at 0 °C. At 50 °C, the ee dropped significantly (entries 12–14). Based on our extensive screening results, we concluded that the optimal reaction conditions were to utilize **4a** as a catalyst, AcOH as an additive, and DMSO as solvent at room temperature.

Under our optimized reaction conditions, the application of catalyst **4a** in the direct asymmetric intermolecular aldol reaction between different aromatic aldehyde acceptors and ketone donors was further explored (Table 3). The best enantioselectivity of 93% was obtained in the reaction between thiopyranone and *p*-nitrobenzaldehyde with an *anti*:*syn* ratio of 85 : 15 (entry 2). Aldol reactions of 3,4-dihydro-2*H*-thiopyranone with *m*-nitrobenzaldehyde or *o*-nitrobenzaldehyde gave a slightly lower *anti*:*syn* ratio of 83 : 17 and an ee of 82–87% (entries 6 and 8). The highest *anti*:*syn* ratio of 86 : 14 was observed between the reaction of *p*-nitrobenzaldehyde and 3,4-dihydro-2*H*-pyranone (entry 3). 4-Methylcyclohexanone and *N*-Boc-piperidin-4-one were also employed in the aldol reactions but showed lower enantioselectivities compared to cyclohexanone in our catalytic system (entries 4

Table 2 Enantioselective direct aldol reaction of *p*-nitrobenzaldehyde with cyclohexanone catalyzed by **4a** under various conditions



Entry	Additive	Solvent	Time/h	Yield (%)[a]	dr (*anti*:*syn*)[b]	% ee (*anti*)[b]
1	—	DCM	96	77	77 : 23	72
2	—	$CHCl_3$	96	88	74 : 26	60
3	—	DMF	96	48	66 : 24	71
4	—	THF	96	56	57 : 43	70
5	—	DMSO	96	90	69 : 31	85
6	—	DMSO[c]	192	55	68 : 32	82
7	—	DMSO[d]	144	61	74 : 26	83
8	AcOH	DMSO	48	73	69 : 31	85
9	$PhCO_2H$	DMSO	48	58	70 : 30	80
10	HCO_2H	DMSO	48	64	64 : 26	74
11	TsOH	DMSO	48	Trace	—	—
12	AcOH	DMSO[e]	48	Trace	—	—
13	AcOH	DMSO[f]	29	73	62 : 38	60
14	PhOH	DMSO[f]	29	78	69 : 31	64

[a] Isolated yield after silica gel chromatography. [b] Determined by chiral HPLC; the *anti*-isomer is the major product. [c] Only 5% catalyst was used. [d] Only 10% catalyst was used. [e] Reaction carried out at 0 °C. [f] Reaction carried out at 50 °C.

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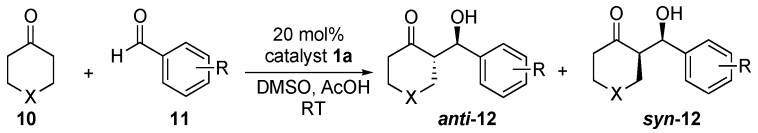
Table 3 The direct aldol reaction catalyzed by catalyst **4a** with different aldehydes and ketones



Entry	R	X	Time/h	Yield (%)[a]	dr (*anti*:*syn*)[b]	% ee (*anti*)[b]
1	*p*-NO_2	CH_2	48	73 (**9**)	69 : 31	85
2	*p*-NO_2	S	41	44 (**12a**)	85 : 15	93
3	*p*-NO_2	O	60	60 (**12b**)	86 : 14	82
4	*p*-NO_2	CHMe	48	61 (**12c**)	64 : 26	85
5	*p*-NO_2	NBoc	60	43 (**12d**)	69 : 31	80
6	*m*-NO_2	S	48	76 (**12e**)	83 : 17	87
7	*m*-NO_2	O	48	73 (**12f**)	74 : 26	82
8	*o*-NO_2	S	48	66 (**12g**)	83 : 17	82
9	*o*-NO_2	O	48	75 (**12h**)	83 : 17	89

[a] Isolated yield after silica gel chromatography. [b] Determined by chiral HPLC; the *anti*-isomer is the major product.

and 5). The current method has its limitations since we can not extend it to simple acyclic ketones and non-aromatic aldehydes.

Theoretical calculations have been performed to understand the mechanism of our catalytic system. It is well known that the key step in amine-catalyzed aldol reactions is the formation of the carbon–carbon single bond in the reaction of the enamine intermediate and aldehyde or acetone.[13] Unlike proline-catalyzed aldol reactions, there is no H-bonding involved in the transition state for carbon–carbon bond formation. Fig. 1a shows one of many possible transition state geometries without an acid additive in the gas phase. *p*-Nitrobenzaldehyde approaches the enamine intermediate preferentially from the side opposite to the bulky phosphine oxide group. The transition state has a C–C bond length of 1.6847 Å and a C=N bond length of 1.3182 Å. This zwitterionic structure leads to an oxetane intermediate. The reaction barrier is 32.82 kcal mol^{-1} after zero-point energy correction at B3LYP/6-31G(d) calculation, and the free energy of activation is 44.74 kcal mol^{-1}, a relatively high value.

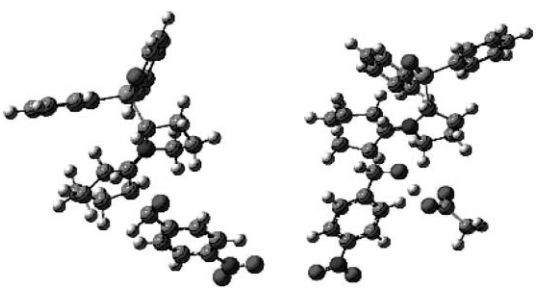


Fig. 1 The calculated transition state of aldol reaction of **7** and **8** catalyzed by **4a**. a) without acid additive, left; b) with acetic acid additive, right.

Fig. 1b shows a possible transition state geometry with AcOH as acid additive in the gas phase. The forming C–C bond length is 1.6529 Å and C=N bond length is 1.3073 Å. In this transition state, the hydrogen ion from acetic acid has been partially transferred to the oxygen atom of the carboxyl group in *p*-nitrobenzaldehyde, as the calculated two O–H bond lengths are 1.1634 Å and 1.2596 Å and the O–H–O angle is 172.4°. The bond length of C–O in *p*-nitrobenzaldehyde is elongated to 1.3515 Å. Bahmanyar and Houk have predicted that for such reactions, there is almost no reaction barrier.[13] In our calculation, the reaction barrier is about 4.33 kcal mol^{-1} after zero-point energy correction, which is in agreement with their calculations. However, at room temperature, the free energy of activation is about 28.05 kcal mol^{-1}, due to the entropy penalty.

Table 4 The reaction barrier ($E_a^{\ddagger}$) and free energy ($\Delta G^{\circ\ddagger}$) of activation at room temperature for reaction without acid additive

	Gas phase	$CHCl_3$	DCM	DMSO	THF
$E_a^{\ddagger}$ (kcal mol^{-1})	32.82	29.81	29.30	29.12	29.62
$\Delta G^{\circ\ddagger}$ (kcal mol^{-1})	44.74	45.31	46.69	44.05	43.30

The reaction barrier ($E_a^{\ddagger}$) and free energy of activation ($\Delta G^{\circ\ddagger}$) at room temperature for the gas phase and for different solvents are reported in Table 4 for reactions without acid additive. The results show that different solvents do not change the reaction barrier and free energy of activation very much and the reactions are slow, in agreement with observation. With AcOH as the acid additive, the reaction barrier is 8.72 kcal mol^{-1} and the free energy of activation at room temperature is about 35.71 kcal mol^{-1} in DMSO solution, so whether in gas phase or in solution, the acid additive can promote the direct aldol reactions.

In summary, we have demonstrated the direct aldol reaction of cyclic ketones with different aromatic aldehydes catalyzed by phosphinyl oxide pyrrolidines with good yields, moderate diastereoselectivities, and up to 93% ee. The catalytic transition state was rationalized by the DFT calculations. Further exploration of this catalyst in other asymmetric reactions is under way.

Experimental

General

Unless otherwise noted, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen, and distilled solvents were transferred by syringe. Solvents and reagents were purified according to standard procedures prior to use. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). NMR spectra were recorded

at room temperature on a 300 MHz Bruker ACF 300 or a 400 MHz Bruker DPX 400 instrument. The residual solvent signals were taken as the reference (7.26 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad signal. Infrared spectra were recorded on a Bio-RAD FTS 165 FT-IR spectrometer and are reported in cm^{-1}. Samples were prepared using the thin film technique. HR-MS (ESI) spectra were recorded on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. X-Ray crystallographic data was collected by using a Bruker X8 Apex diffractometer with MoKα radiation (graphite monochromator). The ee values were determined by HPLC using a Daicel AD-H, or OD-H column, $\lambda = 254$ nm.

General procedure for racemic compounds 2a–d

A solution of triazine **1**[6] (2.07 g, 10 mmol) and diphenylphosphine oxide (6.06 g, 30 mmol) in toluene (100 ml) was refluxed for 3 h. Toluene was removed under vacuum and the residue was purified by silica gel chromatography (DCM–MeOH, 40 : 1) to obtain the racemic 2-diphenylphosphinylpyrrolidine **2**.

2-(Diphenylphosphoryl)pyrrolidine, 2a. Yield 88%. IR (Nujol, cm^{-1}): 3419 (NH), 1618, 1456, 1436 (phenyl), 1180 (P=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77–7.90 (m, 4H), 7.43–7.53 (m, 6H), 3.88–3.93 (m, 1H), 2.98–3.03 (m, 1H), 2.88–2.94 (m, 1H), 1.92–2.0 (m, 3H), 1.71–1.78 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 131.8, 131.7, 131.5, 130.9, 128.4, 56.9, 48.3, 26.5, 26.4. ^{31}P NMR ($CDCl_3$) δ: 32.0. HRMS, calc. for $C_{16}H_{18}NOP$: 271.1126, found: 271.1121.

2-(Bis(3-(trifluoromethyl)phenyl)phosphoryl)pyrrolidine, 2b. Yield 83%. IR (Nujol, cm^{-1}): 3296.4 (NH), 1604.8, 1479.4, 1421.5 (phenyl), 1168.9 (P=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, J = 10.6, 1H), 8.20–8.17 (m, 2H), 8.03–7.98 (m, 1H), 7.77–7.73 (m, 2H), 7.59-7.56 (m, 2H), 3.97–3.92 (m, 1H), 2.97-2.91 (m, 1H), 2.82-2.79 (m, 1H), 2.11-2.04 (m, 1H), 1.94–1.835 (m, 2H), 1.66–1.64 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.1, 134.2, 133.2, 132.3, 131.4, 131.0, 129.1, 128.9, 128.5, 127.9, 124.8, 122.1, 56.7, 48.0, 26.5, 26.4. ^{31}P NMR ($CDCl_3$) δ: 28.21. HRMS, calc. for $C_{18}H_{16}F_6NOP$: 407.0874, found: 407.0826.

2-(Di-*p*-tolylphosphoryl)pyrrolidine, 2c. Yield 79%. IR (Nujol, cm^{-1}): 3280 (NH), 1600, 1452 (phenyl), 1168 (P=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76–7.71 (m, 2H), 7.63–7.58 (m, 2H), 7.18–7.16 (m, 4H), 3.77–3.74 (m, 1H), 2.92-2.89 (m, 1H), 2.82-2.79 (m, 1H), 2.42 (brs, 1H), 2.28 (s, 3H), 1.90–1.83 (m, 2H), 1.67–1.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.8, 131.5, 130.8, 129.6, 129.0, 128.8, 128.5, 127.5, 56.7, 48.0, 26.3, 26.1, 21.2. ^{31}P NMR ($CDCl_3$) δ: 31.7. HRMS, calc. for $C_{18}H_{22}NOP$: 299.1439, found: 299.1433.

2-(Bis(4-*tert*-butylphenyl)phosphoryl)pyrrolidine, 2d. Yield 89%. IR (Nujol, cm^{-1}): 3421 (NH), 1599, 1460 (phenyl), 1176 (P=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84–7.79 (m, 2H), 7.71–7.67 (m, 2H), 7.44–7.41 (m, 4H), 3.84–3.80 (m, 1H), 3.13 (brs, 1H), 3.00-2.98 (m, 1H), 2.87-2.85 (m, 1H), 1.97–1.95 (m, 2H), 1.67–1.62 (m, 2H), 1.26(s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.9, 154.8, 131.4, 130.8, 129.6, 128.6, 127.6, 125.4, 56.8, 48.1, 34.7, 30.9, 26.4, 26.2. ^{31}P NMR ($CDCl_3$) δ: 31.3. HRMS, calc. for $C_{24}H_{34}NOP$: 383.2378, found: 383.2364.

General procedure for compounds 3a–d

The racemic 2-diphenylphosphinylpyrrolidine **2a–d** (14 mmol), α-D-glucose (42 mmol) and $(NH_4)_2SO_4$ (55 mg, 0.42 mmol) were refluxed in MeOH (40 mL) for 26 h. The solvent was removed under vacuum and the residue was purified by silica gel chromatography (DCM–MeOH, 8 : 1) to obtain the intermediate **3a–3d**.

(2*R*,3*S*,4*R*,5*S*)-2-((*R*)-2-(Diphenylphosphoryl)pyrrolidin-1-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, 3a. Yield 47%. $[\alpha]^{25}_D = -11.83$ (c = 1.0, CH_2Cl_2). IR (Nujol, cm^{-1}): 3446 (OH), 1589, 1487, 1440 (phenyl), 1215 (P=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99–7.96 (m, 2H), 7.89–7.86 (m, 2H), 7.61–7.52 (m, 6H), 4.53–4.47 (m, 1H), 3.86–3.83 (m, 1H), 3.58–3.54 (m, 1H), 3.39–3.30 (m, 3H), 3.24 (t, J = 8.9, 1H), 3.12–3.04 (m, 2H), 2.99-2.97 (m, 1H), 2.88-2.82 (m, 2H), 2.22-2.13 (m, 1H), 2.00-1.95 (m, 1H), 1.76-1.71 (m, 1H), 1.65-1.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.04, 131.7, 131.5, 131.0, 130.6, 129.2, 128.5, 128.4, 91.3, 78.0, 77.6, 71.8, 70.5, 61.9, 58.1, 45.4, 27.2, 24.7. ^{31}P NMR ($CDCl_3$) δ: 31.7. HRMS, calculated for $C_{22}H_{28}NO_6P$: 433.1654, found: 433.1716.

*Crystal data for **3a**·2H$_2$O.* $C_{22}H_{32}NO_8P$, $M = 469.46$, prism, $a = 8.0227(3)$ Å, $b = 8.8488(4)$ Å, $c = 31.8469(13)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2260.85(16)$ Å^3, space group $P2_12_12_1$, $T = 173(2)$ K, $Z = 4$, $F(000) = 1000$, $D_{calc} = 1.739$ Mg m^{-3}, 6889 total reflections collected, 2937 Friedel pairs used. X-Ray crystallographic data was collected by using a Bruker X8 Apex diffractometer with graphite-monochromated MoKa radiation.

(2*R*,3*S*,4*R*,5*S*)-2-((*R*)-2-(Bis(3-(trifluoromethyl)phenyl)phosphoryl)pyrrolidin-1-yl)-6-(hydroxylmethyl)tetrahydro-2*H*-pyran-3,4,5-triol, 3b. Yield 33%. $[\alpha]^{25}_D = -12.36$ (c = 1.0, CH_2Cl_2). IR (Nujol, cm^{-1}): 3369 (OH), 1604, 1421 (phenyl), 1215 (P=O).^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39-8.31 (m, 2H), 8.27-8.21 (m, 2H), 7.92 (d, J = 7.78, 2H), 7.80–7.75 (m, 2H), 4.69–4.60 (m, 1H), 3.90–3.86 (m, 1H), 3.61–3.55 (m, 1H), 3.41 (d, J = 8.99, 1H), 3.34–3.28 (m, 3H), 3.17–3.07 (m, 2H), 3.00-2.87 (m, 3H), 2.27–2.16 (m, 1H), 1.98–1.95 (m, 1H), 1.78–1.75 (m, 1H), 1.61–1.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.3, 134.7, 133.6, 132.3, 131.2, 130.9, 129.6, 128.8, 128.6, 127.7, 125.5, 122.9, 92.0, 78.0, 77.7, 71.7, 70.4, 61.8, 58.4, 45.4, 27.0, 24.0. ^{31}P NMR ($CDCl_3$) δ: 30.9. HRMS, calc. for $C_{30}H_{44}NO_6P$: 545.2906, found: 545.2916.

(2*R*,3*S*,4*R*,5*S*)-2-((*R*)-2-(Di-*p*-tolylphosphoryl)pyrrolidin-1-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, 3c. Yield 46%. $[\alpha]^{25}_D = -16.08$ (c = 1.0, CH_2Cl_2). IR (Nujol, cm^{-1}): 3412 (OH), 1600, 1437, 1419 (phenyl), 1222 (P=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85–7.81 (m, 2H), 7.75–7.70 (m, 2H), 7.36–7.30 (m, 4H), 4.45–4.41 (m, 1H), 3.86–3.83 (m, 1H), 3.59–3.54 (m, 1H), 3.43–3.41 (m, 1H), 3.34–3.30 (m, 2H), 3.23 (t, J = 8.9, 1H), 3.11–3.04 (m, 2H), 2.98–2.95 (m, 1H), 2.90–2.83 (m, 2H), 2.39 (s, 6H), 2.17–2.09 (m, 1H), 1.99–1.93 (m, 1H), 1.73–1.70 (m, 1H), 1.63–1.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.7, 131.6, 130.9, 129.0, 128.7, 127.6, 127.4, 126.4, 91.2, 77.9, 77.6, 71.7, 70.4, 61.8, 58.0, 45.3, 27.1, 24.6, 20.1, 20.1. ^{31}P NMR

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($CDCl_3$) δ: 33.7. HRMS, calc. for $C_{24}H_{32}NO_6P$: 461.1967, found: 461.1920.

(2*R*,3*S*,4*R*,5*S*)-2-((*R*)-2-(Bis(4-*tert*-butylphenyl)phosphoryl)-pyrrolidin-1-yl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, 3d. Yield 42%. $[\alpha]_D^{25} = -11.57$ ($c = 1.0$, CH_2Cl_2). IR (Nujol, cm^{-1}): 3402 (OH), 1599, 1458, 1442 (phenyl), 1215 (P=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.90–7.85 (m, 2H), 7.79–7.76 (m, 2H), 7.59–7.57 (m, 4H), 4.46–4.40 (m, 1H), 3.86–3.82 (m, 1H), 3.58–3.54 (m, 1H), 3.43–3.41 (m, 1H), 3.34–3.30 (m, 2H), 3.22 (t, $J = 8.9$, 1H), 3.13–3.04 (m, 2H), 2.99–2.95 (m, 1H), 2.88–2.77 (m, 2H), 2.19–2.11 (m, 1H), 2.02–1.93 (m, 1H), 1.75–1.71 (m, 1H), 1.64–1.58 (m, 1H), 1.33 (d, $J = 3.7$, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.7, 132.4, 131.5, 127.5, 126.3, 126.1, 125.6, 125.1, 91.1, 77.8, 77.7, 71.7, 70.4, 61.8, 58.0, 45.3, 34.4, 30.0, 27.1, 24.6. ^{31}P NMR ($CDCl_3$) δ: 33.7. HRMS, calc. for $C_{30}H_{44}NO_6P$: 545.2906, found: 545.2916.

Synthesis of the enantiopure 2-diphenylphosphinylpyrrolidines 4a–d and 5

A mixture of the intermediate **3a–d** (0.5 g, 1.15 mmol), acetone (5 mL), water (1 mL), and acetic acid (0.2 mL) was heated under reflux for 2 h and then concentrated. The residue was purified by silica gel chromatography (DCM–MeOH, 8 : 1) to obtain the enantiopure 2-diphenylphosphinylpyrrolidine **4a–d** and **5**.

(*R*)-2-(Diphenylphosphoryl)pyrrolidine, 4a. Yield 49%. $[\alpha]_D^{25} = -9.6$ ($c = 1.0$, CH_2Cl_2). Retention time: 22.60 min (HPLC chiral AD-H column, hexane–*i*-PrOH = 90 : 10, 1 mL min^{-1}).

(*R*)-2-(Bis(3-(trifluoromethyl)phenyl)phosphoryl)pyrrolidine 4b. Yield 39%. $[\alpha]_D^{25} = -5.2$ ($c = 1.0$, CH_2Cl_2).

(*R*)-2-(Di-*p*-tolylphosphoryl)pyrrolidine, 4c. Yield 60%. $[\alpha]_D^{25} = -6.7$ ($c = 1.0$, CH_2Cl_2).

(*R*)-2-(Bis(4-*tert*-butylphenyl)phosphoryl)pyrrolidine, 4d. Yield 42%. $[\alpha]_D^{25} = -3.4$ ($c = 1.0$, CH_2Cl_2).

(*S*)-2-(Diphenylphosphoryl)pyrrolidine, 5. Yield 45%. $[\alpha]_D^{25} = +9.7$ ($c = 1.0$, CH_2Cl_2). Retention time: 15.32 min (HPLC chiral AD-H column, hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}).

(*S*)-2-((Diphenylphosphoryl)methyl)pyrrolidine 6

To a solution of (*S*)-2-((diphenylphosphino)methyl)pyrrolidine[10] (500 mg, 1.85 mmol) in chloroform (20 mL) was added slowly at room temperature 25 mL of a 10% aqueous solution of H_2O_2. After being stirred for 2 h and hydrolytic workup, the residue was purified by silica gel chromatography (DCM–MeOH, 40 : 1) to obtain compound **6** as a white solid (474 mg, 90%). IR (Nujol, cm^{-1}): 3419 (NH), 1618, 1456, 1436 (phenyl), 1180 (P=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75–7.69 (m, 4H), 7.45–7.25 (m, 6H), 3.39–3.34 (m, 1H), 3.00–2.96 (m, 1H), 2.82–2.75 (m, 1H), 2.61–2.41 (m, 2H), 1.93–1.62 (m, 3H), 1.42–1.37(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.1, 133.0, 131.7, 130.8, 130.7, 130.6, 128.7, 128.6, 53.2, 45.5, 35.8, 33.0, 24.2. ^{31}P NMR ($CDCl_3$) δ: 30.8. HRMS, calc. for $C_{16}H_{18}NOP$: 285.1283, found: 285.1221.

General procedure for the aldol reaction

A mixture of phosphorylpyrrolidine catalyst (0.1 mmol), ketone (2.5 mmol) and the additive (0.1 mmol) were stirred in 1 mL DMSO for 15 min at rt. The aldehyde (0.5 mmol) was added and the mixture was stirred for several hours. The mixture was treated with 1 mL of saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and concentrated to give crude aldol adduct. The *anti*-isomer was purified by flash column chromatography on silica gel (hexane–ethyl acetate, 4 : 1).

(*S*)-2-((*R*)-Hydroxy-(4-nitrophenyl)methyl)cyclohexanone, 9-*anti*. Yield 73%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, $J = 8.6$ Hz, 2H), 7.50 (d, $J = 8.6$ Hz, 2H), 4.89 (dd, $J = 8.3$ Hz, 2.8 Hz, 1H), 4.08 (d, $J = 3.0$ Hz, 1H), 2.62–2.55 (m, 1H), 2.50–2.47 (m, 1H), 2.38–2.31 (m, 1H), 2.13–2.08 (m, 1H), 1.65–1.53 (m, 3H), 1.41–1.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.7, 148.3, 147.5, 127.8, 123.5, 73.9, 57.1, 42.6, 30.7, 27.6, 24.6. HPLC: Chiralpak AD-H column, hexane–*i*-PrOH 90 : 10, flow rate 1 mL min^{-1}; t_R (*anti*-minor) = 22.5 min; t_R (*anti*-major) = 29.8 min.

(*S*)-3-((*R*)-Hydroxy-(4-nitrophenyl)methyl)dihydro-2*H*-thiopyran4(3*H*)-one, 12a-*anti*. Yield 44%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.7$ Hz, 2H), 5.05 (dd, $J = 8.0$, 3.6 Hz, 1H), 3.66 (br s, 1H), 3.02–2.96 (m, 3H), 2.85–2.76 (m, 2H), 2.79–2.63 (m, 1H), 2.54–2.49 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.2, 147.7, 147.6, 127.7, 123.8, 73.1, 59.4, 44.7, 32.8, 30.8. HPLC: Chiralpak AD-H column, hexane–*i*-PrOH 90 : 10, flow rate 1 mL min^{-1}; t_R (*anti*-minor) = 47.1 min; t_R (*anti*-major) = 56.5 min.

(*S*)-3-((*R*)-Hydroxy-(4-nitrophenyl)methyl)dihydro-2*H*-pyran-4(3*H*)-one, 12b-*anti*. Yield 60%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, $J = 8.7$ Hz, 2H), 7.50 (d, $J = 8.7$ Hz, 2H), 4.96 (dd, $J = 8.1$, 3.3 Hz, 1H), 4.23–4.18 (m, 1H), 3.83–3.70 (m, 3H), 3.46 (t, $J = 9.9$ Hz, 1H), 2.90–2.88 (m, 1H), 2.69–2.66 (m, 1H), 2.54–2.50 (m, 1H). HPLC: Chiralpak AD-H column, hexane–*i*-PrOH 90 : 10, flow rate 1 mL min^{-1}; t_R (*anti*-minor) = 37.2 min; t_R (*anti*-major) = 45.0 min.

(2*S*)-2-((*R*)-Hydroxy-(4-nitrophenyl)methyl)-4-methylcyclohexanone, 12c-*anti*. Yield 61%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, $J = 8.6$ Hz, 2H), 7.49 (d, $J = 8.6$ Hz, 2H), 4.91 (d, $J = 8.4$ Hz, 1H), 3.91 (d, $J = 2.4$ Hz, 1H), 2.77–2.71 (m, 1H), 2.57–2.49 (m, 1H), 2.42–2.35 (m, 1H), 2.10–2.06 (m, 1H), 1.97–1.89 (m, 1H), 1.82–1.76 (m, 1H), 1.63–1.55 (m, 1H), 1.34–1.27 (m, 1H), 1.05 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.9, 148.3, 147.6, 127.7, 123.6, 74.1, 52.8, 38.1, 36.0, 32.8, 26.5, 18.1. HPLC: Chiralpak OD-H column, hexane–*i*-PrOH 95 : 5, flow rate 1 mL min^{-1}; t_R (*anti*-major) = 70.6 min; t_R (*anti*-minor) = 86.3 min.

(*S*)-*tert*-Butyl-3-((*R*)-hydroxy-(4-nitrophenyl)methyl)-4-oxopiperidine-1-carboxylate, 12d-*anti*. Yield 43%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, $J = 8.9$ Hz, 2H), 7.56 (d, $J = 8.9$ Hz, 2H), 4.99 (dd, $J = 8.0$, 2.7 Hz, 1H), 4.17–4.11 (m, 1H), 3.88 (d, $J = 3.6$ Hz, 1H), 3.88–3.70 (m, 1H), 3.27 (br, 1H), 2.93 (t, $J = 11.3$ Hz, 1H), 2.76 (br, 1H), 2.59–2.48 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.0, 154.2, 147.6, 147.1, 127.7, 123.6, 81.0, 71.7, 56.4, 43.7, 42.8, 41.5, 28.3. HPLC: HPLC: Chiralpak OD-H column, hexane–*i*-PrOH 97 : 3, flow rate 1 mL min^{-1}; t_R (*anti*-major) = 63.0 min; t_R (*anti*-minor) = 71.9 min.

(*S*)-3-((*R*)-Hydroxy(3-nitrophenyl)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one, 12e-*anti*. Yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24-8.16 (m, 2H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 5.04 (dd, $J = 8.2$, 4.0 Hz, 1H), 3.69 (d, $J = 4.0$ Hz, 1H), 3.07–2.95 (m, 3H), 2.85–2.76 (m, 2H), 2.68 (dd, $J = 13.7$, 11.0 Hz, 1H), 2.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.4, 148.4, 142.6, 133.0, 129.6, 123.2, 122.0, 73.2, 59.4, 44.8, 32.8, 30.8. HPLC: Chiralpak AD-H column, hexane–*i*-PrOH 90 : 10, flow rate 1 mL min^{-1}; t_R (*anti*-major) = 63.2 min; t_R (*anti*-minor) = 89.1 min.

(*S*)-3-((*R*)-Hydroxy(3-nitrophenyl)methyl)dihydro-2*H*-pyran-4-(3*H*)-one, 12f-*anti*. Yield 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, $J = 8.1$ Hz, 1H), 7.77 (d, $J = 7.7$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 1H), 5.55 (d, $J = 6.9$ Hz, 1H), 3.83 (br, 1H), 3.18–3.13 (m, 1H), 3.01–2.95 (m, 3H), 2.80–2.74 (m, 2H), 2.62–2.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.4, 148.5, 135.9, 133.4, 128.9, 128.8, 124.3, 69.3, 59.4, 45.1, 33.2, 30.7. HPLC: Chiralpak AD-H column, hexane–*i*-PrOH 90 : 10, flow rate 1 mL min^{-1}; t_R (*anti*-minor) = 24.3 min; t_R (*anti*-major) = 30.1 min.

(*S*)-3-((*R*)-Hydroxy(2-nitrophenyl)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one, 12g-*anti*. Yield 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21-8.17 (m, 2H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.57 (t, $J = 8.0$ Hz, 1H), 4.97 (d, $J = 8.2$ Hz, 1H), 4.24–4.19 (m, 1H), 3.89 (brs, 1H), 3.79–3.70 (m, 2H), 3.45 (t, $J = 11.3$ Hz, 1H), 2.96–2.89 (m, 1H), 2.73–2.65 (m, 1H), 2.56–2.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.4, 148.4, 142.3, 132.7, 129.7, 123.3, 121.6, 71.3, 69.8, 68.3, 57.5, 42.9. HPLC: Chiralpak OD-H column, hexane–*i*-PrOH 95 : 5, flow rate 1 mL min^{-1}; t_R (*anti*-major) = 93.8 min; t_R (*anti*-minor) = 128.4 min.

(*S*)-3-((*R*)-Hydroxy(2-nitrophenyl)methyl)dihydro-2*H*-pyran-4-(3*H*)-one, 12h-*anti*. Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.80 (dd, $J = 8.4$, 1.2 Hz, 1H) 7.68–7.63 (m, 1H), 7.48–7.42 (m, 1H), 5.46 (d, $J = 6.6$ Hz, 1H), 4.23–4.16 (m, 1H), 4.03 (br, 1H), 3.93–3.87 (m, 1H), 3.82–3.71 (m, 2H), 3.08–3.00 (m, 1H), 2.71–2.61 (m, 1H), 2.53–2.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.5, 148.0, 136.0, 133.5, 128.8, 128.7, 124.3, 70.4, 68.3, 67.3, 57.8, 43.2. HPLC: Chiralpak OD-H column, hexane–*i*-PrOH 97 : 3, flow rate 1 mL min^{-1}; t_R (*anti*-major) = 89.9 min; t_R (*anti*-minor) = 99.1 min.

Computational details

DFT calculations were carried out with the Gaussian 03 package.[14] The equilibrium and transition structures were fully optimized by the B3LYP[15] method using the 6-31G(d) basis set.[16] All stationary structures obtained were confirmed to be a true minimum or saddle point by harmonic frequency calculations at the same level of theory. Transition states were further confirmed by intrinsic reaction coordinate (IRC) calculations,[17] whereby they were shown to connect the relevant reactants and products.

Solvation energies were estimated using solvation model CPCM[18] as implemented in Gaussian 03, for chloroform, dichloromethane, dimethyl sulfoxide, and tetrahydrofuran without acid additive, and for dimethyl sulfoxide with AcOH. Gas-phase stationary geometries were used for single-point calculations in the various solvents.

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