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Biheteroaromatic diphosphine oxides-catalyzed stereoselective direct aldol reactions

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ABSTRACT

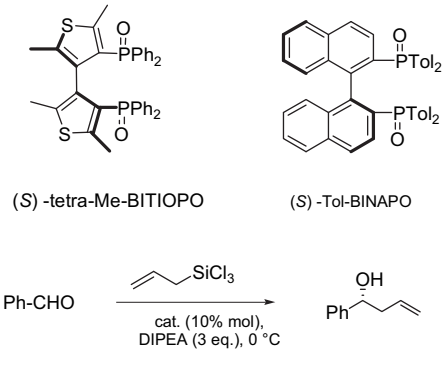
A highly stereoselective direct aldol condensation of ketones to aromatic aldehydes was realized; the trichlorosilyl enolether generated in situ in the presence of tetrachlorosilane is activated by catalytic amounts of an enantiomerically pure biheteroaromatic phosphine oxide to react with aldehydes, coordinated as well as activated by the chiral cationic hypervalent silicon species. This Lewis acid-mediated Lewis base-catalyzed transformation allowed, starting from two carbonyl compounds, to directly synthesize β-hydroxy ketones generally with high *anti* stereoselectivity and up to 93% ee for the *anti* isomer.

1. Introduction

Small organic Lewis bases are protagonists in an incredibly rich amount of chemistry and are efficient catalysts for a wide variety of synthetic transformations.[1] They include different classes of compounds, such as naturally-occurring alkaloids and aminoacids, synthetic amines-based catalysts and phosphines. While *N*-oxides derived from both heteroaromatic systems[2] and aliphatic amines[3] have found widespread application in organocatalysis, quite surprisingly phosphine oxides have been scarcely used.[4]

The first truly organocatalyzed reaction with chiral phosphine oxides was reported by Nakajima, who employed substoichiometric amounts of bis-(diphenylphosphanyl)-binaphthyl dioxide (BINAPO) to promote the enantioselective addition of allyltrichlorosilane to aldehydes.[5] Based on the pioneering work by Denmark,[6] later it was shown that chiral phosphine oxides could also catalyze other nucleophilic additions to carbonyl compounds,[7] including the reaction of trichlorosilyl enolethers[8] and silyl keteneacetals[9] with aldehydes. However relatively few classes of phosphine oxides have been investigated and only bis-(diphenylphosphanyl)-binaphthyl dioxide (BINAPO) has been used with some success.

Our group has recently started to explore the activity of biheteroaryldiphosphine oxides, which may offer the possibility to develop a series of catalysts displaying different electronic properties, where the influence of both the electronic availability of the heterocyclic system and of the position of the phosphorus atoms on the latter may be investigated[10] (Scheme 1).



Scheme 1. Organocatalytic enantioselective allylation of aromatic aldehydes.

It was found that electron-rich compounds, like (*S*)-tetramethylbithiophene phosphine oxide, (*S*)-tetra-Me-BITIOPO, showed significant catalytic activity, promoting the addition of allyltrichlorosilane

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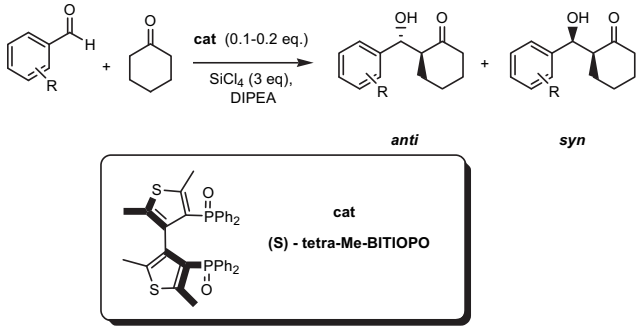
to benzaldehyde at 0 °C in higher yield (85%) and enantioselectivity (93%) than the less electron-rich diphosphine oxide Tol-BINAPO.

Based on these promising results we decided to extend the use of (*S*)-tetra-Me-BITIOPO to other reactions. In this field a real breakthrough was achieved by Denmark, who developed phosphoroamide-catalyzed and $SiCl_4$-mediated stereoselective reactions.[11] The coordination of a Lewis base to silicon tetrachloride makes the new hypervalent trichlorosilyl cationic species more electrophilic; this new adduct of increased Lewis acidity was shown to be able to promote the addition of different nucleophiles to carbonyl compounds.[1] However, until last year, basically only chiral phosphoroamide-based catalysts have been successfully used.

2. Results and discussion

The possibility to promote reactions through a chiral Lewis acid generated by coordination to $SiCl_4$ of catalytic amounts of a chiral phosphine oxide was obviously very attractive. The direct aldol reaction[12] of a ketone to aromatic aldehydes was selected for a preliminary study in view of its importance in synthetic organic chemistry and of its simple procedure that does not involve the preparation of enolethers or keteneacetals. The trichlorosilyl enolether is generated in situ in the presence of tetrachlorosilane and it is activated by phosphine oxide to react with an aldehyde, that is, also coordinated by the chiral cationic hypervalent silicon species. Prompted by a recent work in the field by Nakajima where BINAPO was employed as organocatalyst,[13] we wish to report here our studies on a direct aldol condensation of a ketone to aromatic aldehydes promoted by the chiral biheteroaryldiphosphine oxide tetra-Me-BITIOPO.

First the reaction between cyclohexanone and benzaldehyde was investigated in the presence of stoichiometric amounts of $SiCl_4$ and a catalytic amount of enantiomerically pure tetra-Me-BITIOPO (Scheme 2).



Scheme 2. Enantioselective direct aldol condensation of cyclohexanone with aromatic aldehydes.

Different experimental conditions of solvent, temperature and additives were screened in order to optimize the performance of the Lewis base; a few selected results are shown in Table 1. The direct condensation of 1 mol equiv of cyclohexanone with 1 mol equiv of benzaldehyde in the presence of 3 mol equiv of silicon tetrachloride and 10 mol equiv of DIPEA afforded the corresponding β-hydroxy ketone **1** (Scheme 2, R=H), after 15 h at 0 °C in CH_3CN in 53% yield, as mixture of *anti*/*syn* isomers (92/8) and 60% enantioselectivity for the major *anti* isomer (entry 1, Table 1). By looking for best experimental conditions the reaction was found to proceed better in dichloromethane, by employing 2 mol equiv of ketone for 1 mol equiv of aldehyde; in that case the *anti* diastereoisomer was isolated as major product (88/12 *anti*/*syn*) in 75% ee (entry 4, Table 1).

The use of other solvents was detrimental to the enantioselectivity of the process, even if an interesting switch of the sense of the diastereoselectivity was observed when the reaction was conducted in the non-coordinating solvent toluene, where a *syn* selectivity was observed (entry 5). Shorter reaction times did not bring appreciable variations of the stereochemical outcome of the reaction (entries 8–9).

Table 1
Tetra-Me-BITIOPO-catalyzed condensation of cyclohexanone with benzaldehyde at 0 °C

Entry	Solvent	*R.* time (h)	Yield[a] (%)	*anti*/*syn* Ratio[b]	ee *anti*-(ee *syn*)[c] (%)
1[d]	CH_3CN	15	53	92/8	**60** (33)
2[e]	CH_3CN	15	67	92/8	**67** (15)
3	CH_3CN	15	91	90/10	**69** (37)
4	DCM	15	63	88/12	**75** (42)
5	Toluene	15	50	25/75	**31** (7)
6	THF	15	70	84/16	**61** (17)
7	$CHCl_3$	15	40	88/12	**67** (41)
8	DCM	2	51	89/11	**70** (31)
9	CH_3CN	2	65	90/10	**53** (15)

[a] Reactions were run with 3 mol equiv of $SiCl_4$, 2 mol equiv of ketone, 1 mol equiv of aldehyde and 10 mol % amount of catalyst; yields were determined after chromatographic purification.
[b] Diastereoisomeric ratio was determined by ^1H NMR and confirmed by HPLC.
[c] Enantiomeric excess was determined by HPLC on chiral column (see Supplementary data).
[d] Ketone (1 mol equiv) was used.
[e] $SiCl_4$ (1 mol equiv) was used.

Lowering the reaction temperature generally had a positive effect on the stereocontrol of the aldol reaction, but it was detrimental for the chemical efficiency (Table 2). When the reaction temperature was decreased to −45 °C longer reaction times and 20 mol % of tetra-Me-BITIOPO catalyst were necessary in order to obtain satisfactory chemical yields. Once again DCM secured better performances than acetonitrile: after 36 h at −25 °C in DCM, the product was obtained in 70% yield, 93/7 *anti*/*syn* ratio and 83% enantioselectivity for the *anti* isomer. Enantioselectivity was further improved by running the reaction at −45 °C, when the major diastereoisomer was produced with 86% ee (entries 2–3).

Bases other than DIPEA were investigated in the attempt of further increasing the chemical yield; however DABCO or NMM did not bring any significant change. A comparison between the performances of BITIOPO and BINAPO was made; by performing the reaction in the reported literature conditions[13] (CHCN, 0 °C, 2 h) in our hands BINAPO promoted the reaction in 64% yield, 89/11 *anti*/*syn* ratio and 40% ee for the *anti* isomer, lower than enantioselection observed with BITIOPO (53% ee, entry 6 Table 2 vs entry 9 Table 1). At lower temperature bithiophene-based phosphine oxide confirmed to perform better than binaphthyl-derived diphenylphosphine, affording the aldol adduct in 93/7 *anti*/*syn* ratio and 80% ee, while

Table 2
Stereoselective aldol condensation of cyclohexanone with benzaldehyde

Entry	Solvent	Temp (°C)	CAT	Yield[a] (%)	*anti*/*syn* ratio[b]	ee *anti*-(ee *syn*)[c] (%)
1	CH_3CN	−25	BITIOPO	30	81/19	**65** (27)
2	DCM	−25	BITIOPO	70	93/7	**83** (49)
3[d]	DCM	−45	BITIOPO	44	79/21	**86** (11)
4[e]	DCM	−25	BITIOPO	42	76/24	**57** (10)
5[f]	DCM	−25	BITIOPO	40	91/9	**65** (18)
6[g]	CH_3CN	0	BINAPO	64	89/11	**40** (5)
7	DCM	−25	BINAPO	40	79/21	**60** (3)

[a] Reactions were run for 30 h with 3 mol equiv of $SiCl_4$, 2 mol equiv of ketone, 1 mol equiv of aldehyde and 10 mol % amount of catalyst in the presence of DIPEA; yields were determined after chromatographic purification.
[b] Diastereoisomeric ratio was determined by ^1H NMR and confirmed by HPLC.
[c] Enantiomeric excess was determined by HPLC on chiral column (see Supplementary data).
[d] Reaction run in the presence of 20 mol % cat.
[e] Reaction run in the presence of DABCO.
[f] Reaction run in the presence of *N*-methylmorpholine.
[g] Reaction time 2 h.

BINAPO led to the *anti* isomer in the same conditions with 60% enantioselectivity and lower *anti* selectivity (entries 2 and 7 Table 2).

The general applicability of such a methodology to different aldehydes was then investigated; when cyclohexanone was reacted at −25 °C with 4-nitrobenzaldehyde in the presence of a catalytic amount of Lewis base the product was isolated in 87/13 diastereoisomeric ratio and 93% ee for the major isomer (entry 3, Table 3). A further decrease of the reaction temperature did not improve the stereoselectivity (92% ee for *anti* isomer entry 5, Table 3).

Table 3
Tetra-Me-BITIOPO-catalyzed aldol condensation of cyclohexanone with different aldehydes

Entry	R	Temp (°C)	Product	Yield[a] (%)	*anti*/*syn* ratio[b]	ee *anti*- (ee *syn*)[c] (%)
1	Ph	−25	**1**	70	93/7	**81** (49)
2	Ph	−45	**1**	34	79/21	**86** (11)
3	4-$NO_2C_6H_4$	−25	**2**	71	87/13	**93** (65)
4[d]	4-$NO_2C_6H_4$	−25	**2**	51	90/10	**85** (71)
5[e]	4-$NO_2C_6H_4$	−45	**2**	50	86/14	**92** (67)
6[e]	4-ClC_6H_4	−45	**3**	41	81/19	**88** (11)
7	4-ClC_6H_4	−25	**3**	56	98/2	**71** (n.d.)
8	2-ClC_6H_4	−25	**4**	55	90/10	**87** (27)
9	4-$CF_3C_6H_4$	−25	**5**	57	92/8	**77** (33)
10	3,5$CF_3C_6H_3$	−25	**6**	65	94/6	**83** (n.d.)
11	2-MeC_6H_4	−25	**7**	56	94/6	**73** (31.)
12	4-MeC_6H_4	−25	**8**	55	98/2	**77** (n.d.)
13[e]	4-$OMeC_6H_4$	−45	**9**	42	92/8	**87** (22)
14	1-Naph	−25	**10**	40	93/7	**77** (n.d.)
15	2-Thioph	−25	**11**	55	98/2	**53** (n.d.)
16	2-Furyl	−25	**12**	36	98/2	**51** (n.d.)
17	PhCH=CH	−25	**13**	41	90/10	**37** (n.d.)
18	$Ph(CH_2)_2$	0	**14**	—	—	—
19	$C(CH_3)_3$	0	**15**	—	—	—

[a] Reactions were run with 3 mol equiv of SiCl4, 2 mol equiv of ketone, 1 mol equiv of aldehyde and 10 mol % amount of catalyst; yields were determined after chromatographic purification.
[b] Diastereoisomeric ratio was determined by ^1H NMR and confirmed by HPLC.
[c] Enantiomeric excess was determined by HPLC on chiral column (see Supplementary data).
[d] Reaction was run in CH_3CN.
[e] With 20 mol % of BITIOPO.

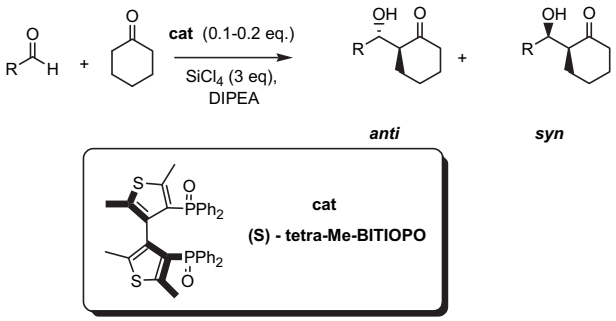
Generally aromatic aldehydes bearing electron-withdrawing groups reacted at −25 °C with high *anti* selectivity in fair yields and enantioselectivity often higher than 80% (entries 6–10 in Table 3) (see Scheme 3).

The same high level of stereoselectivity was maintained also with other aromatic aldehydes with electron-donating residues. For example, the reaction of cyclohexanone with 4-methoxybenzaldehyde led to the corresponding hydroxy ketone **9** in comparable 87% enantioselectivity for the *anti* isomer (entry 13, Table 3) Also *ortho*-substituted aromatic aldehydes may be suitable substrates for the reaction, as shown by the case of 2-chlorobenzaldehyde, where the product **4** was formed in 90/10 *anti*/*syn* ratio and 87% ee for the major isomer. The condensation of 2-methyl-benzaldehyde afforded the corresponding aldol **7** in high diastereoselectivity (94/6) but lower enantioselectivity (73% ee, entry 11, Table 3).

Heteroaromatic aldehydes were also investigated and proofed to be suitable substrates for the present methodology; satisfactory levels of *anti* selectivity were reached, while only modest enantioselectivity was observed both with 2-thiophene carboxyaldehyde and 2-furfurol (entries 15–16).

Finally the aldol condensation was attempted with non aromatic aldehydes; as expected aliphatic aldehydes did not react, even at 0 °C,[14] while cinnamic aldehyde reacted with cyclohexanone in 41% yield 90/10 *anti*/*syn* ratio but only gave 37% enantioselectivity of the major isomer.

The reaction of different ketones with aromatic aldehydes was then investigated (Scheme 4).



Scheme 3. Reaction of cyclohexanone with different aldehydes.

Also in the aldol condensation of cyclopentanone with benzaldehyde tetra-Me-BITIOPO catalyzed the transformation with higher stereoselectivity than BINAPO (83% ee vs 53% ee[13]) and with very high *anti* selectivity (94%). Lower selectivity was observed in the reaction of cycloheptanone, where no diastereoselectivity and a modest enantioselectivity were observed.

Also heterocyclic ketones as well as 4,4-disubstituted cyclohexanone may be employed as aldol donors in this Lewis base-catalyzed $SiCl_4$-mediated direct aldol condensation (see Scheme 4). The products were generally obtained in high *anti*/*syn* ratios (>80% dr) and enantioselectivity up to 86% ee Best result was obtained with ketone **21** that afforded after condensation with benzaldehyde the *anti* isomer of compound **22** in 93/7 dr and 86% ee.

The methodology could be applied to ketones containing oxygen, nitrogen or sulfur atoms. Usually a good *anti* selectivity was obtained with all substrates. For example ketone **24** was employed in the condensation with benzaldehyde and afforded the aldol product with good *anti* selectivity and 83% ee for the major isomer.

A tentative model of the stereoselectivity observed in the reactions promoted by tetra-Me-BITIOPO must take in account mechanistic considerations. It is well known that the coordination of a Lewis base to a Lewis acid makes it more electrophilic;[1] the chiral cationic hypervalent silicon species[15] coordinates and activate the aldehyde towards the attack of the in situ generated trichlorosilyl enolether.[13]

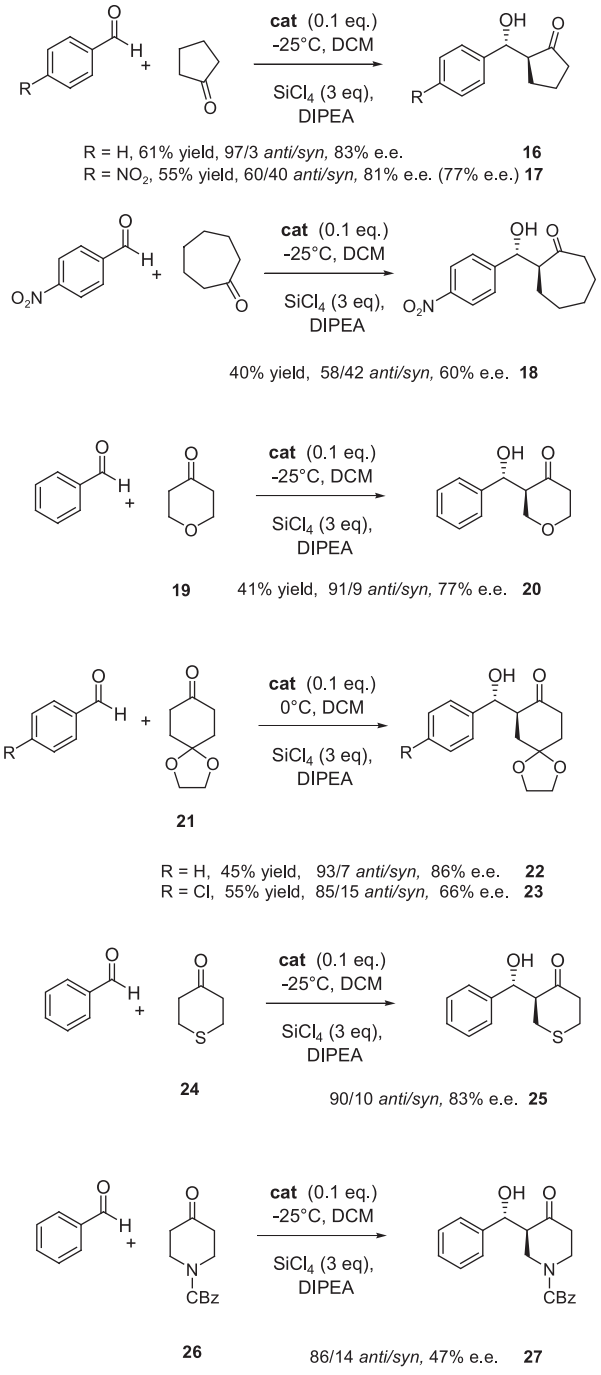
A chairlike six-membered cyclic transition state may be hypothesized and would explain the *anti* selectivity generally observed for these reactions[16] (Fig. 1).

The steric hindrance of the diphenyl-phosphinoyl group of the Lewis base with cyclohexanone-derived enolether would be responsible for the favourable attack of the enolether onto the *Re* face of the aldehyde, to afford the experimentally observed major (2*S*,1′*R*)-*anti* stereoisomer.

Confirmation of the proposed cyclic transition state comes from an additional experiment, where the aldol condensation between benzaldehyde and cyclohexanone has been performed at −25 °C in the presence of a stoichiometric amount of BF_3, a Lewis acid able to coordinate the aldehyde. In that case the product was isolated in 65% yield as 60/40 *syn*/*anti* selectivity, both isomers basically as racemic compounds, clearly suggesting the importance of the aldehydes coordination to the chiral cationic silicon species.

Preliminary NMR investigations[17] seem to support the proposed mechanism: ^{31}P NMR analysis shows that the coordination of tetra-Me-BITIOPO with $SiCl_4$ at 0 °C in $CDCl_3$ caused a shift of the *P* signal from 24.3 to 34.8 ppm (neutral $SiCl_4$/phosphine oxide complex) and, after addition of DIPEA, to 27.7 ppm. The same cationic silicon species was observed when the ketone was treated with DIPEA in the presence of $SiCl_4$ and tetra-Me-BITIOPO (*P* signal at 28.0 ppm).[18]

Finally we decided to test our methodology in the cross-aldol condensation between two aldehydes.[19]



Scheme 4. Tetra-Me-BITIOPO-catalyzed aldol reaction of different ketones with aromatic aldehydes.

In very early studies the reaction of isobutyraldehyde with benzaldehyde was attempted in DCM in the presence of 3 equiv of $SiCl_4$ and 0.1 equiv of tetra-Me-BITIOPO, followed by reduction of the carbonyl group by treatment with $NaBH_4$. By working at 0 °C 1-phenyl, 2,2-dimethyl propanediol **28** was isolated in 55% yield and 48% ee, that was increased up to 70% by running the reaction at −45 °C.

The cross condensation between benzaldehyde and cyclohexane carboxyaldehyde afforded the 1,3-diol **29** with lower enantioselectivity. By exploring the use of other aromatic aldehydes in the reaction with isobutyraldehyde different results were observed; while 4-chloro benzaldehyde afforded the product **30** in 48% ee only, 4-nitrobenzaldehyde led to the formation of **31** in 93% ee at

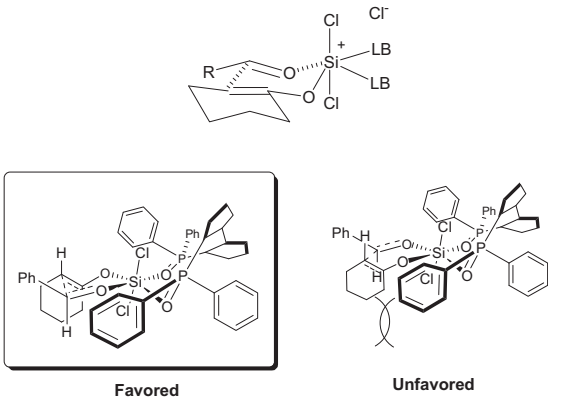
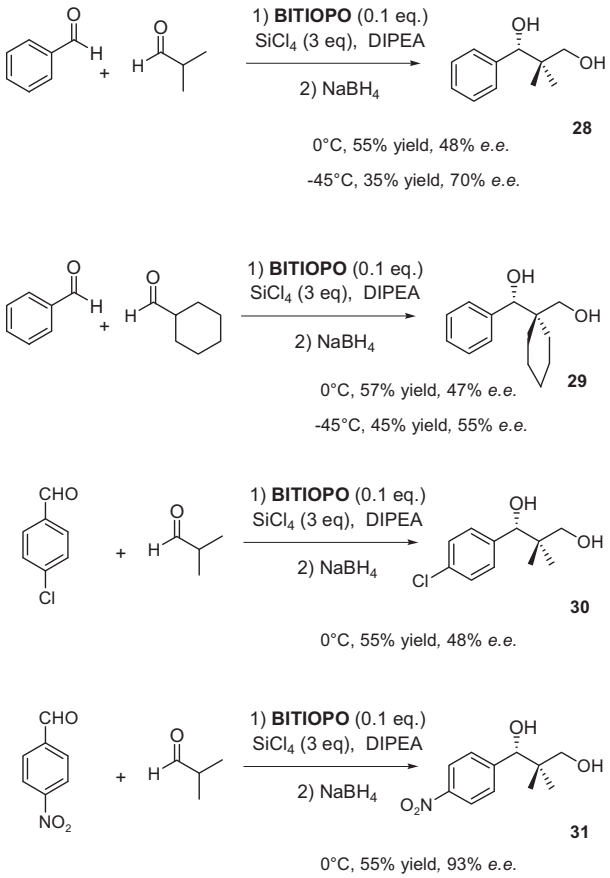


Fig. 1. A proposed model of stereoselectivity.

0 °C. More studies are needed in order to fully investigate the scope of the methodology but the feasibility of the synthetic approach was surely demonstrated (Scheme 5).



Scheme 5. Lewis base-catalyzed cross-aldol reaction.

3. Conclusion

In conclusion, we have realized a direct aldol condensation catalyzed by tetra-Me-BITIOPO, a chiral bithiophene-based phosphine oxide. This Lewis base was shown to perform better than carboxylic aromatic derivatives, such as BINAPO, affording β-hydroxy ketones with good *anti* stereoselectivity, and enantioselectivity often higher than 85% and up to 95%. The methodology was successfully extended to structurally different ketones, including compounds containing

heteroatoms, such as nitrogen, oxygen and sulfur. Finally the methodology was showed to be feasible for the development of cross-aldol condensation between an aromatic and an aliphatic aldehyde.

The major drawback of the proposed catalytic system is the sometimes low chemical efficiency. However, even if many issues still need to be tackled, the results clearly show that a still unexplored novel class of chiral biheteroaryl-based phosphine oxides are now available as suitable catalysts, whose electronic and steric properties could be modulated by a proper choice of substituents.

4. Experimental

4.1. General methods

All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown cap). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light or phosphomolibdic acid. Proton NMR spectra were recorded on spectrometers operating at 200, 300 or 500 MHz, respectively. Proton chemical shifts are reported in parts per million (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ=7.26 ppm). ^{13}C NMR spectra were recorded on 300 or 500 MHz spectrometers operating at 75 and 125 MHz, respectively, with complete proton decoupling. Carbon chemical shifts are reported in parts per million (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ=77.0 ppm). Optical rotations were obtained on a polarimeter at 589 nm using a 5 mL cell with a length of 1 dm. HPLC for enantiomeric excess determination was performed under the conditions reported below. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with Mass Spectrometer APEX II & Xmass software (Bruker Daltonics).

Starting materials: 2,2′,5,5′-Tetramethyl-4,4′-bis-(diphenyl-phoshino)-3,3′-bithiophene oxide (tetra-Me-BITIOPO) was prepared by literature method;[1] ketones (cyclohexanone, cyclopentanone, 1,4-cycloexandion-monoethylenacetal, tetra-hydro-4*H*-pyran-4-one, dihydro-2*H*-thiopyran-4(3*H*)-one, 1-*Z*-4-piperidone,) and aldehydes (benzaldehyde, *p*-Cl-benzaldehyde, *o*-Cl-benzaldehyde, *p*-NO_2-benzaldehyde, *p*-OMe-benzaldehyde, *p*-Me-benzaldehyde, *o*-Me-benzaldehyde, thiophene-2-carbaldehyde, furan-2-carbaldehyde, *p*-CF_3-benzaldehyde, 1-naphthaldehyde 3,5-bis(trifluoromethyl)-benzaldehyde, cyclohexane carboxyaldehyde, isobutyraldehyde) were obtained commercially and used after immediately distillation. $SiCl_4$ was also freshly distilled before use.

4.2. Typical procedure of enantioselective direct aldol-type reactions between ketones and aldehydes

To a stirred solution of (*S*)-tetra-Me-BITIOPO (0.1 or 0.2 equiv) in the chosen solvent (2 mL), the ketone (2 equiv) and diisopropylethylanime (10 equiv) were added. The mixture was then cooled to the chosen temperature and freshly distilled tetrachlorosilane (1.5 equiv) was added dropwise via syringe. After 15 min, freshly distilled aldehyde (1 equiv) was added. The mixture was stirred for 5 h (if the operating temperature is 0 °C) or 12 h (if the operating temperature is −25 °C), then the same amount of tetrachlorosilane (1.5 equiv) was added.

For example, in Table 3, entry 1 (typical procedure), the quantities are: (*S*)-tetra-Me-BITIOPO (0.1, 0.03 mmol, 18.7 mg); cyclohexanone (2 equiv, 0.60 mmol, 62 μl); DIPEA (10 equiv, 3 mmol, 513 μl) tetrachlorosilane (1.5 equiv, 0.45 mmol, 52 μl); benzaldehyde (1 equiv, 0.30 mmol, 30 μl).

After a proper time (see tables) the reaction was quenched by the addition of a satd aqueous solution of $NaHCO_3$ (3 mL). The mixture was allowed to warm up to room temperature and stirred for 30 min, then water (5 mL) and ethyl acetate (15 mL) were added. The two-layers mixture was separated and the aqueous layer was extracted with ethyl acetate (15 mL). The combined organic layers were washed with 10% HCl (20 mL), sat $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum at room temperature. The crude product was purified by column chromatography with different hexane/ethyl acetate mixture as eluent (see below) to afford the pure aldol adducts. Yields and enantiomeric excess for each reaction are indicated in the tables. The *syn*/*anti* ratio was calculated by ^1H NMR spectroscopy; the enantiomeric excess was determined by HPLC (*S*)-tetra-Me-BITIOPO was quantitatively recovered by further elution with 10% MeOH in CH_2Cl_2 without any loss of optical purity (as determined by HPLC analysis on chiral column, recovered catalyst $[\alpha]_D^{25}$ −65.3 (*c* 0.2, C_6H_6), known value $[\alpha]_D^{25}$ −68 (*c* 0.5, C_6H_6)[10]).

*4.2.1. Characterization of products 2-(hydroxyphenylmethyl)cyclohexan-1-one (**1**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^1H NMR data were in agreement with those reported in the literature.[20,21]

Data for anti: R_f=0.21 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid) ^1H NMR (200 MHz, $CDCl_3$): δ 7.31–7.24 (m, 5H), 4.79 (d, 1H, *J*=8.6 Hz), 3.95 (br s, 1H), 2.72–2.35 (m, 3H), 2.12–2.05 (m, 1H), 1.71–1.52 (m, 4H), 1.31–1.26 (m, 1H).

Data for syn: R_f=0.32 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid) ^1H NMR (200 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 5.39 (d, 1H), 2.60 (m, 1H), 2.60–2.32 (m, 2H), 2.08–2.01 (m, 1H), 1.87–1.29 (m, 5H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak OD-H column [eluent: 98:2 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; t_R 19.7 min (*syn*-minor), t_R 21.8 min (*syn*-major), t_R 27.8 min (*anti*-major (1′*R*, 2*S*)), t_R 44.9 min (*anti*-minor (1′*S*, 2*R*)). The absolute configuration of aldol products was determined by comparison of the literature data].

*4.2.2. 2-(Hydroxy-(4-nitrophenyl)methyl)cyclohexan-1-one (**2**).* This product was purified by flash column chromatography on silica gel with a 7:3 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^1H NMR data were in agreement with those reported in the literature.[21]

Data for anti: R_f=0.11 (Hex/EtOAc 7:3, stained blue with phosphomolibdic acid) $[\alpha]_D^{25}$ +12.3 (*c* 0.26, $CHCl_3$), 95% ee, $[\alpha]_{Dmax}^{25}$ +12.8 (*c* 0.26, $CHCl_3$), >99% ee.[21] ^1H NMR (200 MHz, $CDCl_3$): δ 8.20 (d, 2H, *J*=8.5 Hz), 7.51 (d, 2H, *J*=8.5 Hz), 4.90 (d, 1H), 2.65–2.55 (m, 1H), 2.55–2.25 (m, 1H), 2.20–1.95 (m, 1H), 1.95–1.70 (m, 1H), 1.65–1.15 (m, 5H).

Data for syn: R_f=0.15 (Hex/EtOAc 7:3, stained blue with phosphomolibdic acid) ^1H NMR (200 MHz, $CDCl_3$): δ 8.23 (d, 2H, *J*=8.8 Hz), 7.51 (d, 2H, *J*=8.8 Hz), 5.48 (s, 1H), 2.70–2.65 (m, 1H), 2.65–2.30 (m, 2H), 2.20–2.05 (m, 1H), 1.95–1.35 (m, 4H), 1.30–1.20 (m, 1H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak OJ-H column [eluent: 7:3 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; t_R 14.3 min (*syn*-major), t_R 23.4 min (*syn*-minor), t_R 12.9 min (*anti*-major (1′*R*, 2*S*)), t_R 15.6 min (*anti*-minor (1′*S*, 2*R*)). The absolute configuration of aldol products was confirmed by comparison of the optical rotation values.

*4.2.3. 2-(Hydroxy-(4-chlorophenyl)methyl)cyclohexan-1-one (**3**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[3,7]

Data of a mixture *syn*/*anti*: R_f=0.25 (Hex/EtOAc 9:1, stained blue with phosphomolibdic acid). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33–7.22 (m, 4H), 5.35 (s, 1H *syn*), 4.78 (d, 1H, J=8.7 Hz, *anti*), 3.04–2.20 (m, 3H), 2.20–1.95 (m, 1H), 1.95–1.40 (m, 3H), 1.40–1.05 (m, 1H), 1.05–0.85 (m, 1H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD column [eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; t_R 11.06 min (*syn*-major), t_R 11.82 min (*syn*-minor), t_R 15.7 min (*anti*-major), t_R 25.5 min (*anti*-minor)].

*4.2.4. 2-(Hydroxy-(2-chlorophenyl)methyl)cyclohexan-1-one (**4**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[7]

Data of a mixture syn/*anti*: R_f=0.10 (Hex/EtOAc=9:1, stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, 1H, J=8.4 Hz), 7.35–7.20 (m, 3H), 5.75 (s, 1H *syn*), 5.35 (d, 1H, J=8.0 Hz, *anti*), 4.10–3.85 (br s, 1H), 2.71–2.65 (m, 1H), 2.59–2.46 (m, 1H), 2.45–2.25 (m, 1H), 2.15–2.00 (m, 1H), 1.90–1.50 (m, 5H).The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column [eluent: 8:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; t_R: 6.4 min (*syn*-major), t_R: 6.9 (*syn*-minor), t_R: 9.0 min (*anti*-major), t_R: 10.2 min (*anti*-minor)].

*4.2.5. 2-(Hydroxy-(4-trifluoromethylphenyl)methyl)-cyclohexan-1-one (**5**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[9]

Data of a mixture syn/*anti*: R_f=0.13 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70–7.60 (m, 2H), 7.57–7.33 (m, 2H), 5.44 (m, 1H, *syn*), 4.86–4.88 (d, 1H, J=8.55 Hz, *anti*), 4.04 (s, 1H), 2.70–2.20 (m, 3H), 2.15–2.05 (m, 1H), 1.85–1.25 (m, 5H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell IB column [eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 213 nm; t_R 13.5 min (*syn*-major), t_R 14.5 min (*syn*-minor), t_R 18.7 min (*anti*-major), t_R 21.2 min (*anti*-minor).

*4.2.6. 2-(Hydroxy-(3,5–bis(trifluoromethyl)phenyl)methyl)-cyclohexan-1-one (**6**).* This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent afforded a mixture of *anti* and *syn* aldol adducts.

Data of a mixture *syn*/*anti*: R_f=0.14 (Hex/EtOAc 95:5, stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (m, 3H), 5.50 (s, 1H, *syn*), 4.92 (d, 1H, J=8.4 Hz, *anti*,), 4.16 (s, 1H), 2.75–2.25 (m, 2H), 2.25–2.00 (m, 1H), 2.00–1.80 (m, 1H), 1.75–1.40 (m, 3H), 1.40–1.05 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 214.53 (s), 143.79 (s), 131.56 (q), 127.24 (s), 123.14 (q), 73.97 (s), 42.64 (s), 30.67 (s), 27.58 (s), 24.66 (s). Mass (ESI$^+$): m/z=[M+Na]$^+$ calcd for $C_{15}H_{14}O_2F_6Na$ 363.07902, found 363.07858 [M+Na]$^+$. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD-H column [eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate, detection: 254 nm; t_R 9.0 min (*anti*-major), t_R 10.2 min (*anti*-minor)].

*4.2.7. 2-(Hydroxy-(2-methylphenyl)methyl)-cyclohexan-1-one (**7**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[10]

Data of a mixture syn/*anti*: R_f=0.22 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.15 (m, 4H), 5.60 (m, 1H, *syn*) 5.15 (d, J=8.6 Hz, *anti*), 3.93 (br s, 1H), 2.60–2.55 (m, 1H), 2.55–1.95 (m, 3H), 1.90–1.00 (m, 8H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell IB column [eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; t_R 11.4 min (*syn*-minor), t_R 12.5 min (*syn*-major), t_R 18.1 min (*anti*-major), t_R 20.6 min (*anti*-minor).

*4.2.8. 2-(Hydroxy-(4-methylphenyl)methyl)-cyclohexan-1-one (**8**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[10]

Data of a mixture syn/*anti*: R_f=0.18 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13–7.21 (m, 4H), 5.38 (m, 1H, *syn*) 4.73–4.75 (d, J=8.6 Hz, *anti*), 3.87 (br s, 1H), 2.59–2.48 (m, 1H), 2.44–2.20 (m, 2H), 2.18–2.09 (m, 1H), 1.78–1.42 (m, 4H), 1.30–1.12 (m, 4H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell IB column [eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 213 nm; t_R 19.0 min (*anti*-major), t_R 21.2 min (*anti*-minor).

*4.2.9. 2-(Hydroxy-(4-nitrophenyl)methyl)cyclohexan-1-one (**9**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[3]

Data of a mixture syn/*anti* R_f=0.10 (Hex/EtOAc 9:1, stained blue with phosphomolibdic acid). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (dd, 2H, J=8.4 Hz, J=14.6 Hz), 6.89 (d, 2H, J=8.4 Hz, J=14.6 Hz), 5.30 (s, 1H, *syn*), 4.76 (d, 1H, J=8.8 Hz, *anti*), 3.82 (s, 3H), 2.65–2.45 (m, 1H), 2.45–2.25 (m, 2H), 2.20–2.00 (m, 1H), 1.85–1.65 (m, 2H), 1.65–1.45 (m, 2H), 1.35–1.10 (m, 1H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column [eluent: 97:3 Hex/IPA; 0.8 mL/min flow rate, detection: 225 nm; t_R 37.9 min (*syn*-major), t_R 46.4 min (*syn*-minor), t_R 74.0 min (*anti*-minor), t_R 80.1 min (*anti*-major)].

*4.2.10. 2-(Hydroxyl-1-napthylmethyl)cyclohexan-1-one (**10**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[8]

Data of a mixture syn/*anti*: R_f=0.18 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.24–8.27 (m, 1H), 7.80–7.89 (m, 2H), 7.45–7.56 (m, 4H), 6.25 (br s, 1H, *syn*), 5.60 (d, J=9.0 Hz, *anti*), 4.16 (br, 1H), 3.05 (m, 1H), 2.35–2.51 (m, 2H), 2.06–2.12 (m, 2H), 1.65–1.75 (m, 2H), 1.36–1.52 (m, 2H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column [eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; t_R 23.9 min (*anti*-minor), t_R 28.8 min (*anti*-major).

*4.2.11. 2-(Hydroxyl-(thiophen-2-yl)methyl)cyclohexan-1-one (**11**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature9.

Data of a mixture syn/*anti*: R_f=0.16 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (m,

1H), 6.93–6.95 (m, 2H), 5.52 (m, 1H, *syn*), 5.05–5.08 (d, *J*=8.37 Hz, *anti*), 4.05 (br, 1H), 2.80–2.60 (m, 1H), 2.60–2.20 (m, 2H), 2.20–2.05 (m, 1H), 1.90–1.50 (m, 4H), 1.40–1.20 (m, 1H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD-H column [eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm; tR 8.93 min (*anti*-major), tR 12.7 min (*anti*-minor).

*4.2.12. 2-(Hydroxyl-(furan-2-yl)methyl)cyclohexan-1-one (**12**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* aldol adduct. Its ^{1}H NMR data were in agreement with those reported in the literature.[9]

Data of anti: R_f=0.21 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40 (s, 1H), 6.27–6.33 (m, 2H), 4.81–4.84 (dd, *J*=8.22 Hz), 3.85 (d, 1H, *J*=3.68 Hz), 2.97–2.83 (m, 1H), 2.50–2.30 (m, 2H), 2.20–2.05 (m, 1H), 1.95–1.45 (m, 4H), 1.40–1.25 (m, 1H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell IB column [eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 213 nm; tR 23.2 min (*anti*-major), tR 26.3 min (*anti*-minor).

*4.2.13. 2-(1-Hydroxy-3-phenyl-2-propenyl)cyclohexanone (**13**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[11]

TLC: R_f 0.27 (Hex/EtOAc=9:1, stained blue with phosphomolybdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.10 (m, 10H), 6.70–6.50 (m, 2H), 4.77 (br, 1H, *syn*), 4.43 (t, 1H, *anti*), 3.60 (br, 1H), 2.60–2.30 (m, 6H), 2.20–2.00 (m, 2H), 1.90–1.80 (m, 2H), 1.80–1.30 (m, 8H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column [eluent 97:3 Hex/IPA; flow rate: 0.5 mL/min; detection: 254 nm; t_R: 47.7 min (*syn*-major), t_R: 52.2 min (*syn*-minor), t_R: 56.7 min (*anti*-major), t_R: 66.9 min (*anti*-minor)].

*4.2.14. 2-(Hydroxyphenylmethyl)cyclopentan-1-one (**16**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. ^{1}H NMR data were in agreement with those reported in the literature.[2,4–6]

Data of a mixture syn/anti: R_f=0.27 (Hex/EtOAc 8:2, stained blue with phosphomolibdic acid). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25–7.35 (m, 5H), 5.29 (br s, 1H *syn*), 4.72 (d, 1H, *J*=9.1 Hz, *anti*), 2.49–2.25 (m, 3H), 2.25–1.85 (m, 1H), 1.85–1.30 (m, 3H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD-H column [eluent: 9:1 Hex/IPA; 0.5 mL/min flow rate, detection: 210 nm; t_R 14.1 min (*syn*-minor), t_R 16.6 min (*syn*-major) t_R 21.1 (*anti*-major (2*S*, 1′*R*)), t_R 25.7 min (*anti*-minor (2*R*, 1′*S*)). The absolute configuration of aldol products was determined by comparison of the literature data].

*4.2.15. 2-(Hydroxyl-(4-nitrophenyl)methyl)cyclopentan-1-one (**17**).* This product was purified by flash column chromatography on silica gel with a 9:1 then 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[3]

Data of a mixture syn/anti: R_f=0.12 (Hex/EtOAc 9:1 then 8:2, stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, 2H, *J*=8.6), 7.54 (d, 2H, *J*=8.6), 5.41 (d, 1H, *J*=2.8, *syn*), 4.86 (d, 1H, *J*=9 Hz, *anti*), 2.50–2.10 (m, 2H), 2.10–1.85 (m, 2H), 1.85–1.60 (m, 2H), 1.60–1.40 (m, 1H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column [eluent: 95:5 Hex/IPA; 0.8 flow rate, detection: 254 nm; t_R 24.6 min (*syn*-minor), t_R 31.5 min (*syn*-major) t_R 160.8 min (*anti*-minor (1′*R*, 2*S*)), t_R 171.3 min (*anti*-major (1′*S*, 2*R*))].

*4.2.16. Tetrahydro-3-(hydroxyphenylmethyl)-4H-pyran-4-one (**20**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[2]

Data of a mixture syn/anti: R_f=0.12 (Hex/EtOAc=9:1, stained stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.47 (m, 5H), 5.75 (s, 1H, *syn*), 4.91 (m, 1H, *J*=8.2 Hz, *anti*), 4.20–3.75 (m, 4H), 3.05 (m, 1H), 2.70–2.45 (m, 2H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column [eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 270 nm; t_R: 19.5 min (*anti*-major), t_R 23.5 min (*anti*-minor)].

*4.2.17. 4,4-(Ethylenedioxy)-2-(hydroxyphenylmethyl)cyclohexan-1-one (**22**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[2]

Data of a mixture syn/anti: R_f=0.10 (Hex/EtOAc=8:2, stained stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.26 (m, 5H), 5.43 (m, 1H, *syn*), 4.83 (d, 1H, *J*=8.5 Hz, *anti*), 3.88–3.82 (m, 5H), 3.05–2.95 (m, 1H), 2.80–2.65 (m, 1H), 2.55–2.40 (m, 1H), 2.10–1.90 (m, 2H), 1.60–1.45 (m, 2H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD-H column [eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate; detection: 210 nm; t_R: 20.8 min (*anti*-major), t_R 29.0 min (*anti*-minor)].

*4.2.18. Tetrahydro-3-(hydroxyphenylmethyl)-4H-thiopyran-4-one (**25**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[2]

R_f=0.21 (Hex/EtOAc 9:1 stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5H), 5.38 (s, 1H *syn*), 4.97 (dd, 1H, *J*=3.2, 8.7 Hz, *anti*), 3.37 (d, 1H, *J*=3.2 Hz), 3.01–2.85 (m, 3H), 2.85–2.65 (m, 2H), 2.65–2.55 (m, 2H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD column [eluent: 97:3 hex/IPA; 1 mL/min flow rate, detection: 210 nm; t_R: 28.3 min (*anti*-major), t_R: 39.5 min (*anti*-minor)].

*4.2.19. 3-(Hydroxy(phenyl)methyl)-4-oxopiperidine-1-benzylcarboxylate (**27**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent afforded a mixture of *anti* and *syn* aldol adducts.

Data of a mixture syn/anti: R_f=0.14 (Hex/EtOAc 9:1, stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 10H), 5.35 (m, 1H, *syn*), 5.20–5.00 (m, 2H), 4.85 (d, 1H, *J*=4 Hz, *anti*), 4.25–4.15 (m, 1H, *anti*), 4.05–3.95 (m, 1H, *syn*), 3.85–3.65 (m, 2H), 3.60–3.30 (m, 2H), 3.10–2.40 (m, 1H), 2.60–2.40 (m, 2H), 1.75–1.50 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 213.2 (s), 155.0 (s), 141.4 (s), 128.6 (m), 126.8 (s), 72.7 (s), 67.6 (s), 56.6 (s), 45.9 (s), 43.8 (s), 41.3 (s), 40.8 (s). Mass (ESI$^+$): *m*/*z*=[M+Na]$^+$ calcd for $C_{20}H_{21}O_4NNa$ 362.13628, found 362.13599 [M+Na]$^+$. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak OD column [eluent: 97:3 Hex/IPA; 1 mL/min flow rate, detection: 210 nm; t_R 37.4 min (*anti*-minor), t_R 41.0 min (*anti*-major)].

4.3. Typical procedure of enantioselective direct aldol-type reactions between aldehydes

Tetrachlorosilane (1.5 equiv, 0.45 mmol, 52 μl) was added to a solution of isobutyraldehyde (1.5 equiv, 0.45 mmol, 42 μl), benzaldehyde (1.0 equiv, 0.30 mmol, 30 μl), diisopropylethylamine (5 equiv, 1.50 mmol, 185 μl) and (*S*)-tetra-Me-BITIOPO (0.1 equiv) in CH_2Cl_2 (2 mL) at the chosen temperature. After being stirred for 12 h, the reaction was quenched with satd $NaHCO_3$ (3 mL) and the slurry was

stirred for 0.5 h at room temperature. The mixture was extracted with EtOAc (15 mL). The combined organic layers were washed with brine (2×15 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was used for the next step without further purification. Tetrachlorosilane (1.5 equiv) was added to a solution of isobutyraldehyde (1.5 equiv), benzaldehyde (1.0 equiv), diisopropylethylamine (10 equiv) and (*S*)-tetra-Me-BITIOPO (0.1 equiv) in CH_2Cl_2 (2 mL) at the chosen temperature. After being stirred for 12 h, the reaction was quenched with satd $NaHCO_3$ (3 mL) and the slurry was stirred for 0.5 h at room temperature. The mixture was extracted with EtOAc (15 mL). The combined organic layers were washed with brine (2×15 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was used for the next step without further purification.

$NaBH_4$ (1.5 equiv, 0.45 mmol, 38 mg) was added to the solution of the obtained crude product in MeOH (5 mL), and the reaction mixture was stirred for 30 min at room temperature. The reaction was quenched with satd NH_4Cl (5 mL) and extracted by CH_2Cl_2 (3×10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent furnished the crude product, which was purified by column chromatography (Hex/EtOAc=8:2) to give the desired diol.

(*S*)-Tetra-Me-BITIOPO was quantitatively recovered by further elution with 10% EtOH in CH_2Cl_2 without any loss of optical purity.

*4.3.1. 2,2-Dimethyl-1-phenyl-1,3-propanediol (**28**).* This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *anti* and *syn* aldol adducts. Its ^{1}H NMR data were in agreement with those reported in the literature.[21]

TLC: R_f 0.25 (Hex/EtOAc=2:1, stained blue with phosphomolybdic acid/EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.31 (m, 5H), 4.66 (m, 1H), 3.56 (d, 1H, J=10.5 Hz), 3.48 (d, 1H, J=10.5 Hz), 2.70 (s, 2H), 0.88 (s, 3H), 0.84 (s, 3H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD column [eluent 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 220 nm; t_R: 54.6 min (*S*-major), t_R: 60.0 min (*R*-minor)].

*4.3.2. 2-Cyclohexyl-1-(4-phenyl)-1,3-propanediol (**29**).* This product was purified by flash column chromatography on silica gel with a 7:3 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[14]

TLC: R_f 0.22 (Hex/EtOAc=7:3, stained blue with phosphomolybdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 4.73 (s, 1H), 3.80–3.60 (dd, 2H), 2.80 (br, 1H), 1.95–1.80 (m, 1H), 1.65–1.50 (m, 5H), 1.40–1.00 (m, 4H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column [eluent 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; t_R: 61.6 min (minor), t_R: 80.2 min (major)].

4.3.3. 2,2-Dimethyl-1-(4-chlorophenyl)-1,3-propanediol (30). This product was purified by flash column chromatography on silica gel with a 7:3 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[13]

TLC: R_f 0.25 (Hex/EtOAc=7:3 stained blue with phosphomolybdic acid/EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 4H), 4.60 (s, 1H), 3.45 (q, 2H), 0.85 (s, 3H), 0.80 (s, 3H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column [eluent 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; t_R: 46.2 min (minor), t_R: 48.2 min (major)].

*4.3.4. 2,2-Dimethyl-1-(4-chlorophenyl)-1,3-propanediol (**30**).* This product was purified by flash column chromatography on silica gel with a 7:3 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[23]

TLC: R_f 0.25 (Hex/EtOAc=7:3 stained blue with phosphomolybdic acid/EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 4H), 4.60 (s, 1H), 3.45 (q, 2H), 0.85 (s, 3H), 0.80 (s, 3H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD column [eluent 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; t_R: 46.2 min (minor), t_R: 48.2 min (major)].

*4.3.5. 2,2-Dimethyl-1-(4-nitrophenyl)-1,3-propanediol (**31**).* This product was purified by flash column chromatography on silica gel with a 7:3 hexane/ethyl acetate mixture as eluent. Its ^{1}H NMR data were in agreement with those reported in the literature.[22]

TLC: R_f 0.19 (Hex/EtOAc=7:3, stained blue with phosphomolybdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, 2H), 7.55 (d, 2H), 4.78 (m, 1H), 3.59 (br, 1H), 3.57 (d, 2H), 2.40 (br, 1H), 0.86 (s, 6H). The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD column [eluent 98:2 Hex/IPA; flow rate: 0.8 mL/min; detection: 270 nm; t_R: 53.1 min (MINOR), t_R: 70.3 min (major)].

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Supplementary data

Experimental details of the direct aldol condensation. Characterization details for reaction products. ^{1}H NMR spectra and HPLC chromatograms on chiral stationary phase. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.11.009. These data include MOL files and InChIKeys of the most important compounds described in this article.

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