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Synthesis of novel chiral bithiophene-based phosphine oxides as Lewis bases in organocatalytic stereoselective reactions

Abstract: Novel enantiomerically pure tetramethyl-bithiophene diphosphine oxides (tetraMe-BITIOPO) featuring differently substituted aromatic rings at the phosphorous atoms were synthesized, fully characterized and isolated in enantiomerically pure form. The new Lewis bases were tested as organocatalysts in two different reactions involving trichlorosilyl compounds. The introduction of electron donating substituents on the aromatic rings connected to the phosphine oxide groups positively affected the chemical and stereochemical catalytic efficiency of these ligands. The new catalysts were able to promote the allylation of aldehydes with allyltrichlorosilane in up to 76% yield and up to 86% enantiomeric excess (ee), and the direct aldol reaction to afford β-hydroxy ketones in high diastereoselectivity (up to 88:12 *anti:syn* ratio) and up to 72% ee.

Keywords: organocatalysis, biheteroaromatic diphosphine oxides, chiral Lewis bases, allylation, direct aldol addition

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1 Introduction

In the last few years, enantiomerically pure Lewis bases have attracted increasing attention as chiral organocatalysts promoting stereoselective reactions. Among the different classes of Lewis bases, phosphine oxides are especially interesting because of the availability of several compounds in enantiomerically pure form [1,2]. Phosphine oxides have been employed as organocatalysts in several chemical transformations including enantioselective addition of allyltrichlorosilanes to aldehydes [3-5], ring opening of meso-epoxides [3,6-8], the Abramov-type phosphonylation of carbonyl compounds [8,9] and for the synthesis of γ-amino alcohols [10] and oxazines [11]. Furthermore, phosphine oxides are excellent catalysts for aldol reactions involving trichlorosilyl enolethers [12] and silyl ketene acetals, [13] and also for direct, cross, intermolecular, [14] and double aldol-type reactions involving aldehydes, ketones [15-24] or thioesters [25,26]. More recently, this class of compounds have found application in reductive aldol reactions in the presence of tertiary amines, [27,28] and in the Morita–Baylis–Hillman reaction [29].

In all these examples, catalytic amounts of phosphine oxides act as potentiating-Lewis-acidity agents for chlorosilanes derivatives, leading to an *in situ* formation of a new hypervalent silicate species having increased Lewis acidity at the silicon center [2]. It is well known that Lewis base donor ligands can enhance the activity of a Lewis acidic acceptor, resulting in a net increase in electron density on the donor atom and a net decrease of electron density on the acceptor atom. In this way, the central atom of a Lewis acid becomes more electrophilic causing a transfer of electron density on the peripheral ligands. This transfer of electron density results in an ionization of one of the ligands from the Lewis acid, which increases the Lewis acidity of the central atom generating a new species with enhanced activity (Scheme 1) [30]. In this manner, a poorly Lewis acidic species, although itself unable to promote a chemical transformation, may be activated upon binding of a chiral phosphine oxide, thus generating a hypervalent cationic species with enhanced activity.

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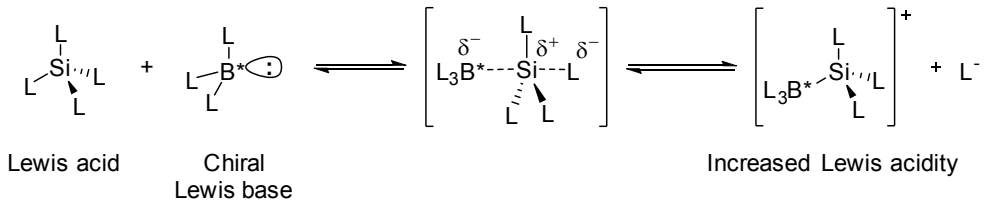


Scheme 1: Hypervalent silicon complexes generated by coordination of a Lewis base to a silicon-based Lewis acid.

Due to the nature of this mode of activation, it is clear that the greater the Lewis base character of the phosphine oxide, the greater the Lewis acidity of the resulting Lewis acid, due to the greater transfer of electron density on the silicon peripheral ligands.

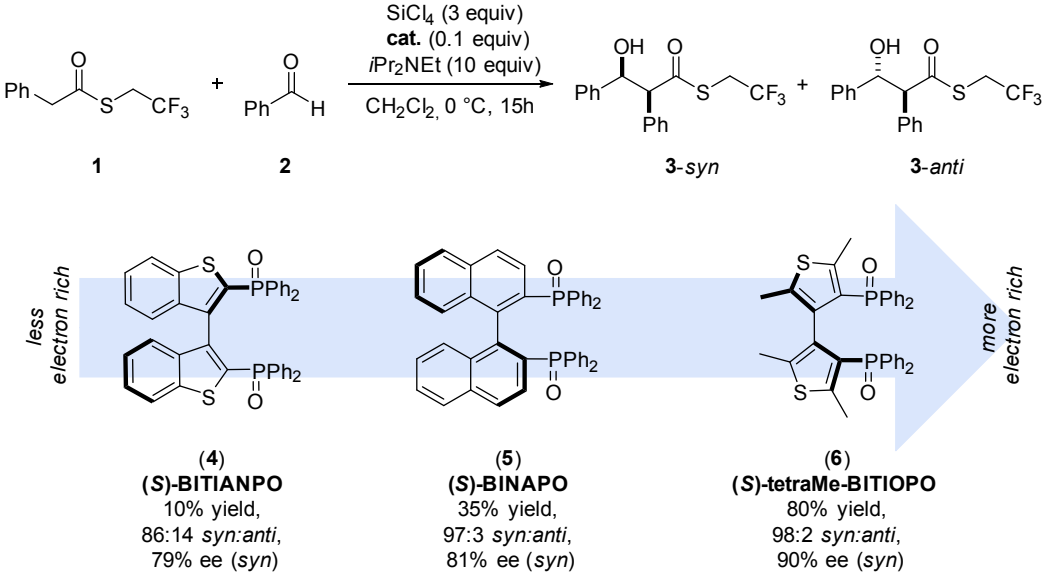
2 Results and discussion

In continuation of our investigations in the use of chiral phosphine oxides as organocatalysts, we wish here to report the synthesis and the use of new bithiophene-based phosphine oxides of increased Lewis basicity based on 2,2',5,5'-tetramethyl-4,4'-bis-(diphenylphosphino)-3,3'-bithiophene oxide (tetraMe-BITIOPO) scaffold.[31]

As previously reported, tetraMe-BITIOPO (**6**) can be employed as an efficient metal-free catalyst in many organic reactions giving often better results than when the corresponding binaphtyl analogue (*S*)-BINAPO (**5**) is employed.[15, 16, 25, 26] The ability of tetraMe-BITIOPO to promote a reaction is related to its electronic properties; tetraMe-BITIOPO is indeed more electron rich than BINAPO because of the presence of two thiophene rings in place of the binaphthyl scaffold. This electronic difference is responsible for difference in chemical efficiency, as seen in the direct aldol addition of activated thioesters to benzaldehyde promoted by $SiCl_4$ (Scheme 2). [25]

β-Hydroxy thioester (**3**) was obtained in low yields and 86:14 *syn*:*anti* ratio using the less electron rich BITIANPO and in 35% yield and 97:3 *syn*:*anti* ratio when BINAPO was employed. Only by using tetraMe-BITIOPO was it possible to obtain the desired aldol product in high yield and increased diastereoselectivity. Gratifyingly, the enantioselectivity was also improved up to 90%, indicating that the final geometry of the hypervalent silicon species generated *in situ* by coordination of the phosphine oxide to $SiCl_4$ had a controlling influence on the stereochemical outcome of the addition process.

On the basis of these preliminary results, we investigated the synthesis of new bithiophene-based phosphine oxides bearing modified aryl groups connected to the phosphorus atoms, with the aim of modulating the electronic characteristics of the two P=O double bonds,



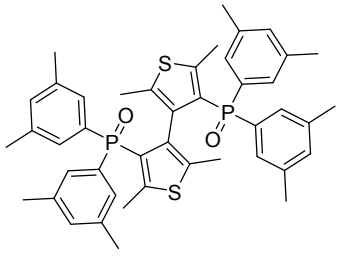
Scheme 2: Direct aldol addition of activated thioester to benzaldehyde catalyzed by different phosphine oxides.

and consequently, of positively influencing the activation by the silicon species. Following this approach, we decided to synthesize three new phosphine oxides, reported in Scheme 3a. The synthesis of racemic MPP-tetraMe-BITIOPO (**16**), PMP-tetraMe-BITIOPO (**17**) and the most electron rich MMP-tetraMe-BITIOPO (**18**) was planned according to the synthetic approach reported for the tetraMe-BITIOPO,[31] starting from the inexpensive and commercially available precursor, 2,5-dimethylthiophene (**12**).

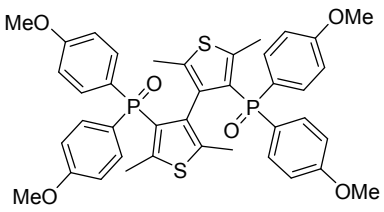
The retrosynthetic strategy is shown in Scheme 3b. The synthesis of new tetraMe-BITIOPO based phosphine oxides was achieved *via* lithium-halogen exchange reaction between the dibromo-bithiophene (**8**) and diarylphosphinic chlorides **9**-**11** which were synthesized from the corresponding arylhalides **13**-**15**.

Compound **8** was obtained in three steps from 2,5-dimethylthiophene (**12**). Bromination of **12** with *N*-bromosuccinimide (NBS) in a 1:1 mixture of $CHCl_3$ and CH_3COOH as solvent gives **19**. Oxidative coupling with $CuCl_2$ of 2,5-dimethyl-3-thienyllithium, obtained by transmetallation of 3-bromo-2,5-dimethylthiophene with *tert*-butyllithium, gives the 2,2',5,5'-tetramethyl-3,3'-bithiophene (**20**) in 77% yield. Bisbromination of the latter with NBS in the presence of hydroquinone affords the known dibromo-bithiophene (**8**) in 85% yield.[31]

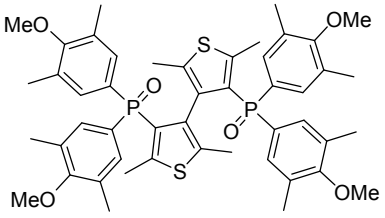
a) Novel TetraMe-BITIOPO derivates



(**16**)
MPP-tetraMe-BITIOPO
2,2',5,5'-TetraMethyl-4,4'-bis
(3,5-di**M**ethyl**P**henyl**P**hosphino)
-3,3'-bithiophene *P*-Oxide

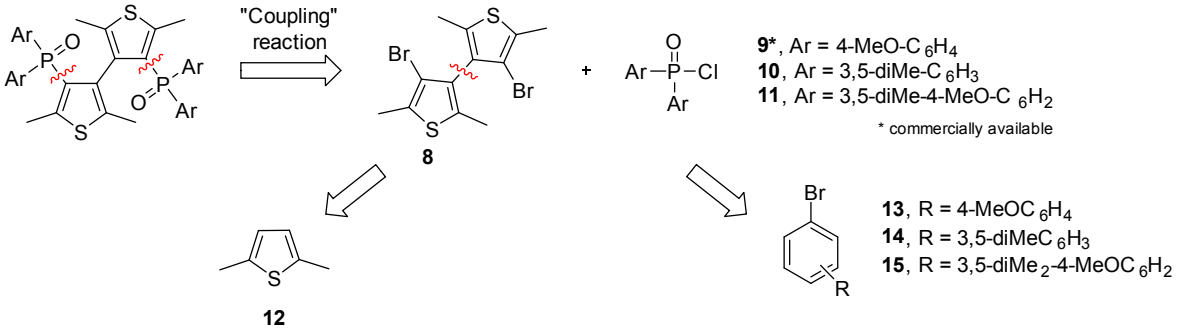


(**17**)
PMP-tetraMe-BITIOPO
2,2',5,5'-TetraMethyl-4,4'-bis
(***p*-M**ethoxy **P**henylPhosphino)
-3,3'-bithiophene *P*-Oxide

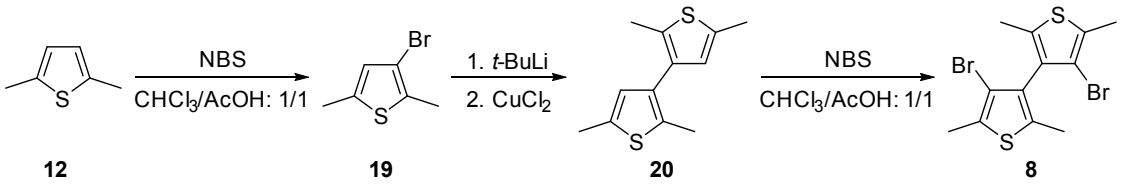


(**18**)
MMP-tetraMe-BITIOPO
2,2',5,5'-TetraMethyl-4,4'-bis
(4-**M**ethoxy-3,5-di**M**ethyl**P**henylPhoshino)
-3,3'-bithiophene *P*-Oxide

b) Retrosynthetic approach



Scheme 3: Synthesis of different tetraMe-BITIOPO based new phosphine oxides



Scheme 4: Preparation of dibromo-bithiophene (**8**).

The preparation of diarylphosphinic chlorides **9**-**11** through the direct introduction of lithiated arylhalides to $POCl_3$ is problematic,[32] but they can be synthesized according to a Takaya procedure that involves the use of phosphorodiamidic chloride.[33] However, this procedure is also troublesome, due to the harsh conditions required for the hydrolysis of the amide group. For this reason, we optimized the synthesis of diarylphosphinic chlorides **10** and **11** from their corresponding phosphinic esters **22** and **23** (Scheme 5). Treatment of aryl lithium compounds prepared by a lithium-halogen exchange from arylbromo derivatives **14** and **15** in the presence of ethyl dichlorophosphate (**21**) leads to the formation of the corresponding stable phosphinic esters **22** and **23** in high yields. Subsequent reaction with $SOCl_2$ gives the desired diarylphosphinic chlorides **10** and **11**. These compounds were not isolated and were directly used in the synthesis of tetraMe-BITIOPO derivatives.

Reaction of **8** with *n*BuLi at -55 °C in THF generates the corresponding bislithium intermediate which in the presence of phosphoric chloride **10** gives the desired racemic MPP-tetraMe-BITIOPO in 60% yield after chromatographic purification (Scheme 6). PMP-tetraMe-BITIOPO and MMP-tetraMe-BITIOPO were similarly synthesized albeit in lower yields.[34]

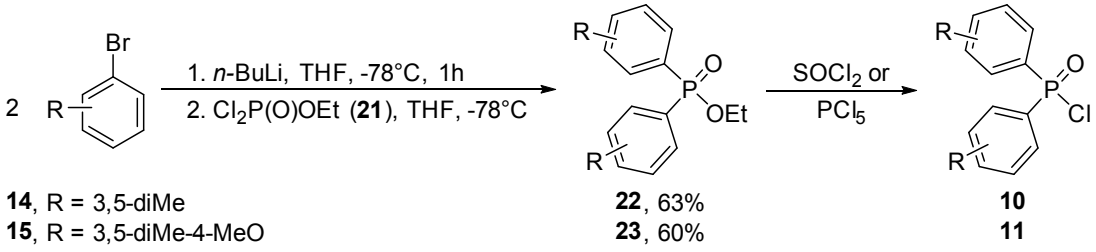
Optically pure phosphine oxides were then isolated by HPLC on chiral stationary phase and tested as catalysts in a few selected stereoselective organic reactions characterized by the activation of a Lewis acidic species by a Lewis base.[35] We initially focused our attention on the stereoselective allylation of benzaldehyde in the presence of allyl trichlorosilane with CH_2Cl_2 as solvent and 3 equiv of iPr_2NEt (Table 1).

As reported, after 40 hours at 0 °C, MPP-tetraMe-BITIOPO (**16**) exhibited improved chemical efficiency than (*S*)-tetraMe-BITIOPO (**6**), giving an increased yield of the allylic alcohol [95% vs 85% (entry 1 vs 2)]. When the reactions were performed at -20 °C, catalyst **6** was not able to promote the reaction, but as expected, all new tetraMe-BITIOPO derivatives gave the desired product in modest to good yields. Catalysts **16** and **18** showed modest chemical and stereochemical efficiency (entries 4 and 6), while better results were obtained when PMP-tetraMe-BITIOPO (**17**) was employed (entry 5), affording **26** in 76% yield and 86% ee.

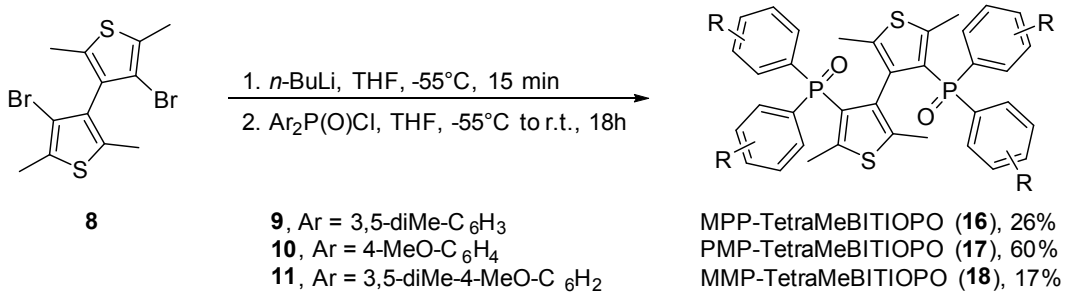
Furthermore, the *S* configuration was assigned to the (-)-BITIOPO derivatives **16**-**18**, by comparison of the absolute configuration of product **26** obtained using known *S*-(-)-tetraMe-BITIOPO (**6**) with those of the allylation products obtained with **16-18**.

Encouraged by these promising results, we investigated another class of reaction suitable to a Lewis base catalysis; direct aldol condensation between benzaldehyde and cyclohexanone performed in the presence of $SiCl_4$ (Table 2).

MPP-tetraMe-BITIOPO (**18**) promotes the reaction with comparable chemical and stereochemical efficiency as tetraMe-BITIOPO (**6**), leading to the aldol product **29** in 67% yield, 88:12 *anti:syn* ratio and 72% ee for the

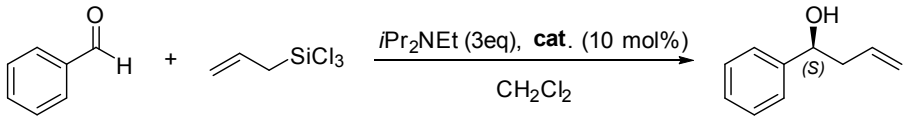


Scheme 5: Synthesis of diarylphosphoric chlorides.



Scheme 6: Synthesis of tetraMe-BITIOPO derivatives.

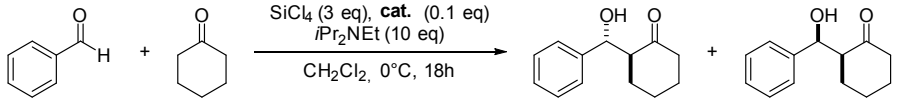
Table 1: Allylation of benzaldehyde using tetraMe-BITIOPO derivatives.



24 **25** **26**

entry	catalyst	temp (°C)	time (h)	yield (%)	ee (%)
1	**(*S*)-(-)-6**	0	40	85	93 (*R*)
2	**(rac)-16**	0	40	95	-
3	**(*S*)-(-)-6**	-20	72	<5	n.d.
4	**(*S*)-(+)-16**	-20	72	55	38 (*S*)
5	**(*S*)-(+)-17**	-20	72	76	86 (*S*)
6	**(*S*)-(+)-18**	-20	72	52	27(*S*)

Table 2: Direct aldol addition promoted by $SiCl_4$ and catalyzed by phosphine oxides.



24 **28** **29**-*anti* **29**-*syn*

entry	catalyst	yield (%)	anti:syn	ee (anti) (%)
1	**(*S*)-(-)-6**	63	88:12	75 (2*S*,*R*)
2	**(R)-(-)-16**	77	88:12	57 (2*R*,*S*)
3	**(R)-(-)-17**	70	77:23	34 (2*R*,*S*)
4	**(R)-(-)-18**	67	88:12	72(2*R*,*S*)

anti diastereoisomer (entry 1 vs 4, Table 2). The more electron rich phosphine oxide PMP-tetraMe-BITIOPO (**17**) gave the aldol adduct in 70% yield, but with a lower enantioselectivity (entry 3). As before, catalyst **16** exhibits intermediate properties of the three phosphine oxides.

3 Conclusions

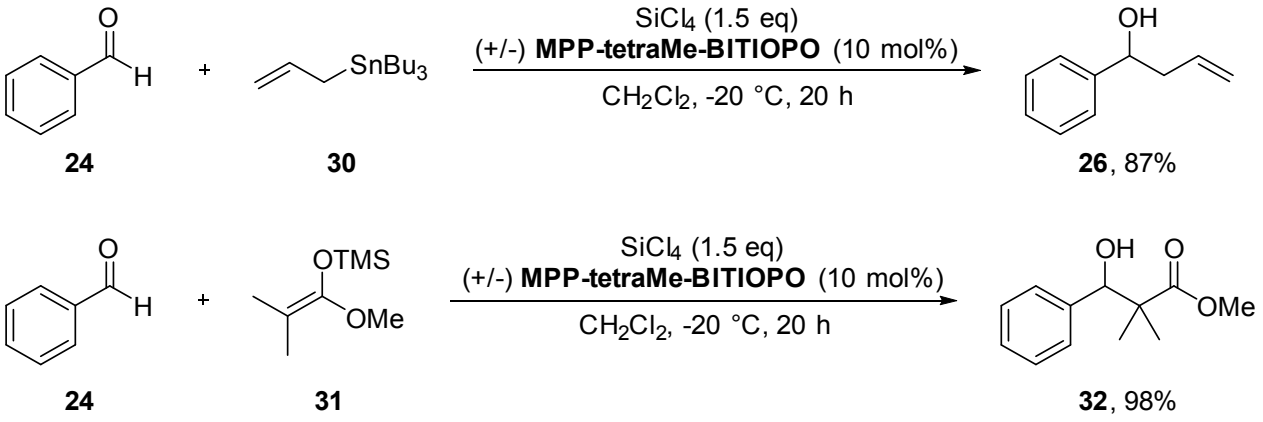
We have reported the synthesis of three different novel chiral phosphine oxides, enantiopure tetraMe-BITIOPO derivatives bearing electron donating substituents on the aromatic rings connected to the phosphorous atoms. All these phosphine oxides exhibit enhanced reactivity compared to the known tetraMe-BITIOPO and can act as Lewis base catalysts for allylation of aldehydes and for the direct aldol reaction promoted by $SiCl_4$. Preliminary studies showed that the same novel biheteroaromatic phosphine oxides were able to promote the addition of allyltributylstannane and silyl ketene acetals in high yields (Scheme 7).

These results will encourage further investigation to expand the application of tetraMe-BITIOPO derivatives as catalysts of increased efficiency in known transformations or as catalytic systems in hitherto unexplored Lewis base-catalyzed Lewis acid-mediated activation strategies.

4 Experimental Section

4.1 General Considerations

All reactions were carried out in oven-dried glassware with magnetic stirring under a nitrogen atmosphere, unless otherwise stated. Dry solvents were purchased and stored



Scheme 7: Application of novel chiral phosphine oxides in stereoselective transformations

under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated glass plates (0.25 mm thickness) and visualized using UV light or with phosphomolybdic acid. ^{1}H-NMR spectra were recorded on spectrometers operating at 300 and 200 MHz (Bruker AC200 or AMX 300). Proton chemical shifts are reported in ppm (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 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ^{31}P spectra were recorded at 121.4 or 202.4 MHz and were referenced to phosphoric acid (H_3PO_4) at 0.0 ppm. Optical rotations were obtained on a polarimeter at 589 nm using a 5-mL cell with a length of 1 dm. HPLC for ee determinations was performed under the conditions reported below using Agilent 1100 or 1200 series.

3-Bromo-2,5-dimethylthiophene (19): 2,5-dimethylthiophene **12** (1 equiv, 18 mmol) was dissolved in a 1:1 mixture of $CHCl_3$:AcOH (35 mL) and cooled to 0°C, then hydroquinone (0.002 equiv, 0.036 mmol) and freshly crystallized NBS (1 equiv, 18 mmol) were added. The mixture was stirred at 0 °C for 1 h, then was warmed to room temperature and stirred for 2 h. After this time, water (10 mL) and CH_2Cl_2 (15 mL) were added. The organic layer was separated, washed with saturated solution of $NaHCO_3$ (10 mL) and water (10 mL), dried over Na_2SO_4 and the solvent was removed under vacuum. The title compound was obtained as brown oil in 96% yield. R_f = 0.65 (9:1 hexane/ethyl acetate). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.53 (s, 1H), 2.40 (s, 3H), 2.29 (s, 3H).

2,2',5,5'-Tetramethyl-3,3'-bithiophene (20): A solution of **19** (1 equiv, 10 mmol) in dry Et_2O (10 ml) was added dropwise to a 15 ml of 1.5 M solution of *t*-butyl lithium cooled to -30°C. After 30 min, the mixture was cooled to -60°C and $CuCl_2$ (1 equiv, 10 mmol) was added. The mixture was stirred for 4 h at -60 °C then it was allowed to warm to RT. After this time, 20 ml of HCl 5% was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were then washed with H_2O (10 mL), a saturated solution of $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by flash chromatography on silica gel using hexane as eluent, affording the title compound in 77% yield. R_f = 0.73 (hexane). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.52 (s, 2H), 2.41 (s, 6H), 2.27 (s, 6H).

4,4'-Dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene (8): has been prepared by similar procedure reported for **19**. Obtained as grey solid in 85% yield. mp = 93-95°C ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 6H), 2.15 (s, 6H).

Ethyl bis(3,5-dimethylphenyl)phosphinate (22): A solution of 1-bromo-3,5-dimethylbenzene (2 equiv, 14 mmol) in dry THF (20 ml) was cooled to -78°C under nitrogen atmosphere, then 10 mL of 1.6 M solution of *n*-BuLi was added dropwise over 10 min. The mixture was stirred for 40 min at -78°C, then $Cl_2P(O)OEt$ (neat) was added. Subsequently, the mixture was stirred for 6 h at -78°C and then warmed to room temperature and stirred for an additional 12 h. After this time, 10 ml of water and 10 mL of ethyl acetate were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were then dried over Na_2SO_4 and the solvent was removed under vacuum to give a crude oil that was purified by flash chromatography

on silica gel using a mixture of 8:2 hexane/ethyl acetate as eluent affording the title compound in 63% yield. R_f = 0.14. (8:2 hexane/ethyl acetate). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.42 (d, *J* = 13.0 Hz, 2H), 7.27 (d, *J* = 13.0 Hz, 2H), 7.14 (m, 2H), 4.10 (m, 2H), 2.32 (d, *J* = 4.1 Hz, 12H), 1.35 (m, 3H). ^{31}P-NMR (121.4 MHz, $CDCl_3$) δ 30.48.

Ethyl bis(4-methoxy-3,5-dimethylphenyl) phosphinate (23): has been prepared by similar procedure reported for (**22**) starting from 4-bromo-2,6-dimethylanisole. Yield 60%. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.45 (d, *J* = 12.14 Hz, 4H), 4.05 (m, 2H), 3.72 (s, 6H), 2.28 (s, 12H), 1.35 (m, 3H). ^{31}P-NMR (121.4 MHz, $CDCl_3$): 33.18.

General procedure for the synthesis of bisarylphosphinic chlorides: The desired ethyl bisarylphosphinate **22**) or **23** [or the commercial available bis(4-methoxyphenyl)phosphinic acid **9**] was gently refluxed in thionyl chloride (2 mL/mmol substrate) for 5 h. Excess thionyl chloride was removed under nitrogen flux and gentle heating. The crude product was dried under high vacuum for 1 h, and used directly in the next step.

General procedure for the synthesis of tetraMe-BITIOPO derivatives: A solution of *n*-BuLi (2.2 equiv, 4.81 mmol) was added to a solution of compound **8** (1 equiv, 2.19 mmol) in dry THF (20 mL) at -55 °C under nitrogen atmosphere. After 15 min of stirring at this temperature, a solution of phosphinic chloride (2.5 equiv, 5.47 mmol) in THF (5 mL) was added dropwise *via* syringe. The reaction mixture was stirred at -55°C for 12 h, warmed to room temperature and stirred for an additional 12 h. After this time, a solution of 5% HCl (15 mL) and ethyl acetate (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic layers were then dried over Na_2SO_4 filtered and concentrated under vacuum to give the crude product that was purified by column chromatography on silica gel.

MPP-tetraMe-BITIOPO (16): [35] A purification through silica gel using a mixture of 98:2 CH_2Cl_2:MeOH as eluent (R*f* = 0.18) gave the title compound in 26% yield. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35 (d, *J* = 12.8 Hz, 4H), 7.08 (t, *J* = 15.3 Hz, 8H), 2.30 (s, 12H), 2.13 (s, 18H), 1.69 (s, 6H). ^{31}P-NMR (121.4 MHz, $CDCl_3$): δ 25.06. Mass (ESI+): *m/z* = 735.7 $[M+H]^+$ and 757.7 $[M+Na]^+$. HPLC: Chiralcel OD column (250 mm × 4.6 mm I.D.); [eluent: Hexane:iPrOH:Et_2NH 95:5:0.1, flow rate: 0.8 ml/min, detection: 280 nm; t_1= 8.4 min (-)-*enantiomer*) t_2= 10.8 min (+)-*enantiomer*). First eluted enantiomer: $[\alpha]_D^{25}$ = - 56 (c 0.1, EtOH); ee > 99%. Second eluted enantiomer: $[\alpha]_D^{25}$ = + 54 (c 0.1, EtOH); ee > 99%.

PMP-tetraMe-BITIOPO (17): [35] A purification through silica gel using a mixture of 98:2 CH_2Cl_2:MeOH as eluent (R*f* = 0.23) gave the title compound in 60% yield. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.44 (dt, *J* = 11.0 Hz, *J* = 24 Hz, 8H), 6.83 (dd, *J* = 18 Hz, *J* = 8.4 Hz, 8H), 3.81 (s, 6H), 3.78 (s, 6H), 2.03 (s, 6H), 1.67 (s, 6H). ^{31}P-NMR (121.4 MHz, $CDCl_3$): δ 21.69. HPLC: Chiralcel OD-H column (250 mm × 4.6 mm I.D.); eluent: Hex:*i*PA 8:2, flow rate = 0.8 ml/min detection: 230 nm; t_1= 8.7 min (-)-*enantiomer*) t_2= 27.8 min (+)-*enantiomer*). First eluted enantiomer $[\alpha]_D^{25}$ = - 12.87 (c 0.22, C_6H_6); ee > 99%. Second eluted enantiomer $[\alpha]_D^{25}$ = + 15.45 (c 0.28, C_6H_6); ee > 99%.

MPP-tetraMe-BITIOPO (18): [35] A purification through silica gel using a mixture of 98:2 CH_2Cl_2:MeOH as eluent (R_f = 0.20) gave the title compound in 17% yield. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.77-7.46 (m, 4H), 6.86 (dd, *J* = 15.0 Hz, *J* = 7.4 Hz, 4H), 3.81 (s, 6H), 3.78 (s, 6H), 2.30 (s, 12H), 2.02 (s, 18H), 1.57 (s, 6H). ^{31}P-NMR (121.4 MHz, $CDCl_3$): δ 22.94. HPLC: Chiralcel OD column (250 mm × 4.6 mm I.D.); eluent: Hex:*i*PA 7:3, flow rate =0.8 ml/min detection: 230 nm; t_1= 10.7 min (-)-*enantiomer*), t_2= 17.0 min (+)-*enantiomer*).

General procedure for allylation of benzaldehyde with allyl trichlorosilane (25): To a stirred solution of catalyst (0.1 equiv, 0.03 mmol) in CH_2Cl_2 (2 mL), freshly distilled benzaldehyde (1 equiv, 0.3 mmol) and *i*Pr_2NEt (3 equiv, 0.154 mL, 0.9 mmol) were added. The mixture was then cooled to the chosen temperature and allyl trichlorosilane (1.2 eq, 0.054 mL, 0.36 mmol) was added dropwise *via* a syringe. After the desired time, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The mixture was allowed to warm to room temperature and water (2 mL) and ethyl acetate (5 mL) were added. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated under vacuum at room temperature to afford the crude product that was purified by flash chromatography on silica gel using a mixture of 9:1 hexane/ethyl acetate as eluent (R_f = 0.31)

General procedure for allylation of benzaldehyde with allyltributylstannane (30): To a stirred solution of catalyst (0.1 equiv, 0.05 mmol) in CH_2Cl_2 (1 mL), allyltributylstannane (1 equiv, 0.5 mmol) was added. The mixture was then cooled to -20 °C and after 20 min, freshly distilled $SiCl_4$ (2 eq, 1 mmol) and benzaldehyde (1 equiv, 0.5 mmol) were added dropwise *via* a syringe. After 16 h, the cold reaction mixture was poured into a rapidly stirring solution of 1/1 sat. aq. KF/1M KH_2PO_4 (5 mL). This biphasic mixture was stirred vigorously for 2 h after which the mixture was filtered and the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product was purified by flash chromatography on silica gel using

a mixture of 9:1 hexane/ethyl acetate as eluent (R_f = 0.31)

1-Phenylbut-3-en-1-ol (26): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.29-7.17 (m, 5H), 5.79-5.68 (m, 1H), 5.12-5.06 (m, 2H), 4.65 (dd, *J* = 7.6 Hz, *J* = 5.6 Hz, 1H), 2.47-2.39 (m, 2H), 1.93 (br s, 1H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 143.8, 134.4, 128.3, 127.5, 125.7, 118.4, 73.2, 43.8. HPLC: Chiralcel OD-H column [eluent: 95:5 Hex/IPA; 0.5 mL/min flow rate, detection: 210 nm; t_R 14.4 min, t_R 17.2 min].

General procedure for the direct aldol condensation of cyclohexanone with benzaldehyde: To a stirred solution of phosphine oxide (0.1 equiv, 0.03 mmol) in CH_2Cl_2 (2 mL), cyclohexanone (2 equiv, 0.60 mmol) and *i*PrNEt (10 equiv, 3 mmol) were added. The mixture was then cooled to the chosen temperature and freshly distilled tetrachlorosilane (3 equiv, 0.45 mmol) was added dropwise *via* a syringe. After 15 min, freshly distilled benzaldehyde (1 equiv, 0.30 mmol) was added. The mixture was stirred for 18 h, then the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (3 mL). The mixture was allowed to warm to room temperature and stirred for 30 min, then water (5 ml) and ethyl acetate (15 mL) were added. The biphasic 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), saturated $NaHCO_3$ (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 on silica gel using a mixture of 9:1 hexane/ethyl acetate as eluent (R_f = 0.32 *syn* isomer, R_f = 0.21 *anti* isomer stained blue with phosphomolybdic acid).

2-(Hydroxyphenylmethyl)cyclohexan-1-one (29): (*anti*) ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.31-7.24 (m, 5H), 4.79 (d, *J* = 8.6 Hz, 1H), 3.95 (br, 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). (*syn*) ^{1}H-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). HPLC: Chiralcel OD-H column (250 mm × 4.6 mm I.D.); eluent: 98:2 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; t_R 19.7 min (*syn*), t_R 21.8 min (*syn*), t_R 27.8 min (*anti*), t_R 44.9 min (*anti*).

Procedure for the addition of silyl ketene acetal (31) to benzaldehyde: A solution of phosphine oxide (0.1 equiv, 0.05 mmol) in CH_2Cl_2 (2 mL) was cooled to -20 °C, then freshly distilled benzaldehyde (1 equiv, 0.5 mmol) and freshly distilled $SiCl_4$ (1.1 equiv, 0.55 mmol) were added. After 15 min, silyl ketene acetal **31** (1.2 equiv, 0.6 mmol) was added dropwise (over 5 min) to the reaction mixture. After 20 h, the cold reaction mixture was poured into a rapidly stirring solution of 1/1 sat. aq. KF/1M KH_2PO_4 (5 mL). This biphasic mixture was stirred vigorously for 2 h after which the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The residue was then purified by silica gel column chromatography, 8:2 hexane:ethyl acetate as eluent (R_f = 0.46).

Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (32): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.28 (s, 5H), 4.87 (s, 1H), 3.69 (s, 3H), 1.10 (s, 6H).

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