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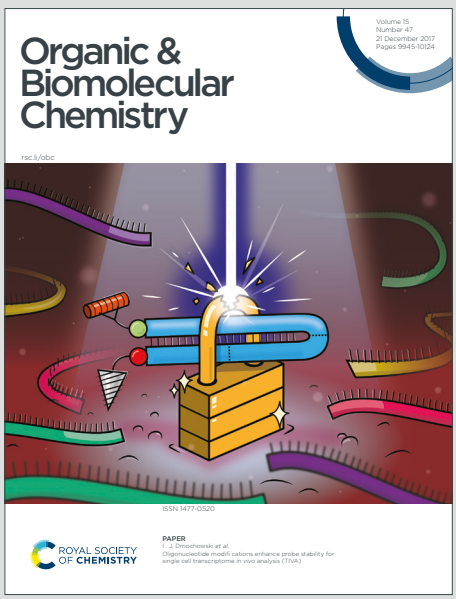

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ARTICLE

TetraPh-Tol-BITIOPO: a new atropisomeric 3,3'-bithiophene based phosphine oxide as organocatalyst in Lewis Base-catalyzed Lewis Acid mediated reactions.

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A new chiral phosphine oxide based on 3,3'-bithiophene scaffold (tetraPh-Tol-BITIOPO) was synthesized, fully characterized and separated into antipodes through chiral HPLC. This new compound was successfully employed as organocatalyst in Lewis base-catalyzed Lewis acid mediated reactions involving trichlorosilyl compounds. The new atropisomeric catalyst was able to promote the allylation of aldehydes with allyltrichlorosilane in up to 98% yield and up to 96% enantiomeric excess (ee), and the direct aldol reaction to afford β-hydroxy ketones and β-hydroxy thioesters, with good chemical yields and modest stereochemical efficiency. Computational studies helped to elucidate and to rationalize the stereochemical outcome of the reactions catalyzed by TetraPh-Tol-BITIOPO, that was found to favour the formation of the isomer with the opposite absolute configuration in comparison with the products obtained with the previously reported 3,3'-bithiophene-based catalyst.

Introduction

The development of new chiral catalysts able to perform stereoselective chemical transformation is a topic of great interest, since it represents one of the best opportunities to introduce stereogenic centers into organic molecules. In this field, Lewis bases represent one of the most investigated classes of compounds that has found application in a large number of chemical transformations thanks to their strong versatility and applicability.[1] Moreover, due to their unique properties, Lewis bases have found applications also in the so called Lewis base-catalyzed Lewis acid-mediated reactions, a class of reactions where the Lewis base acts as activator of a weak Lewis acid (generally a silicon-based compound), leading to the formation of a new hypervalent adduct[2] able to promote different chemical transformations.[3] A milestone in this field was reported by Kobayashi in 1993, describing for the first time a stereoselective allylation of aldehydes using allyltrichlorosilanes activated by dimethylformamide.[4] On the basis of this work, many examples of diastereo- and enantioselective transformations involving the use of chiral Lewis bases for the activation of trichlorosilane, allyltrichloro silane and silicon tetrachloride were developed.[5] In this sense, optically pure *N*-formyl derivatives, picolinamides, N-oxides and sulfoxides, sulfinamides[6] have found great application as chiral organocatalysts toward stereoselective C-N and C-O double bond reductions,[6-7] whereas phosphoramides[8] and phosphine oxides[9] have been employed mostly for stereoselective C-C bond formation reactions.[8k, 10]

Although several mono and bis phosphoramides with different geometries have been developed, examples of phosphine oxides were essentially related to the use of bis(diphenylphosphinoyl)-binaphthyl dioxide (BINAPO) and its modified versions.[9i, 11] In order to expand this field, our group reported for the first time the synthesis and the use of a more electron rich phosphine oxide, based on 3,3'-bithiophene scaffold[12] that showed improved performances compared to BINAPO catalyst.[13] Following our strategy, other different phosphine oxides were then reported, such as the spiro[4,4]-1,6-nonadiene-based diphosphine oxide,[9d] the atropoisomeric (*Z,Z*)-2,3-bis[1-(diphenylphosphinyl)ethylidene]tetralin,[14] and also bisphosphine oxides containing an allene backbone.[15] Phosphine oxides based on Taddol scaffold,[16] on aziridinyl moiety[17] or on bis(triazolyl) backbone[18] were also recently described. Unfortunately, some of these catalysts, despite their great stereochemical efficiency, required long preparations in terms of synthetic steps that limited their real applicability. As part of our continuing interest in the development of chiral phosphine oxide-catalyzed, Lewis acid-mediated reactions,[13, 19] we herein report the synthesis of enantiopure 2,2',5,5'-tetraphenyl-4,4'-bis-(di-(4-methyl)-phenylphosphino)-3,3'-bithiophene oxide (TetraPh-Tol-BITIOPO, **4**) and its use as organocatalyst, after the resolution of the racemate by semipreparative HPLC, in a few selected stereoselective organic reactions promoted by the activation of a silicon weak Lewis acidic species.

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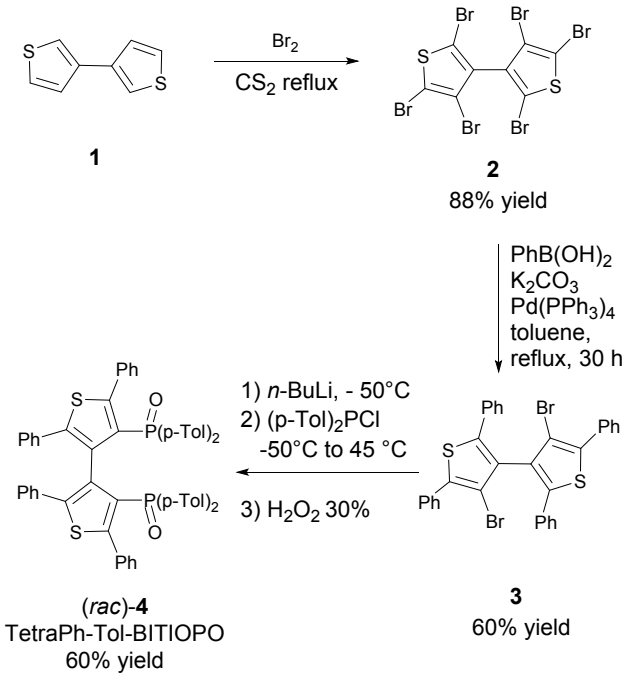
Result and Discussion

The synthesis of diphosphine oxide **4** was carried out starting from commercially available 3,3'-bithiophene **1**, having the preformed interanular bond, in order to skip the crucial, hindrance sensitive, coupling reaction of functionalized thiophene units (scheme 1). The bromination of the 3,3'-bithiophene in refluxing CS_2 afforded the hexabromoderivative **2** in good yields without any further purification need. Unfortunately, the use of CS_2 was found to be essential for the success of the reaction since when the reaction was performed both in other solvents, such as CCl_4, $CHCl_3$ and AcOH, or in the absence of solvent, only the 2,2',5,5'-tetrabromothiophene was formed.



Scheme 1. Synthesis of TetraPh-Tol-BITIOPO.

The tetraphenylderivative **3** was obtained in good yields by means of a regioselective Suzuki coupling reaction mediated by catalytic amounts of Tetrakis(triphenylphosphine)palladium.[20] Finally, the bis-anion, generated by reaction of **3** with *n*-BuLi at – 50 °C, was reacted with 2 equiv. of ditolylphosphinic chloride and the crude product was oxidized *in situ* with a 30% hydrogen peroxide solution to give, after chromatographic purification, TetraPh-Tol-BITIOPO **4** in 60% yield as racemic form.

The separation of the two enantiomers of TetraPh-Tol-BITIOPO **4** was initially attempted through the formation of diastereomeric adducts with enantiopure chiral acids, following a classical strategy successfully applied to the resolution of the racemates of electron-rich diphosphane oxides.[21] The reaction can be carried out either with stoichiometric amounts of the enantiopure acid, when the solubility of the two diastereomeric salts is quite different, or with half equiv. of resolving agent in order to induce the preferential crystallization of a single diastereoisomer. Both the strategies were investigated, employing different solvents and resolving agents (see Table 1) but, unfortunately, when the formation of a precipitate occurred, a racemic mixture was always obtained.

Table 1. Classical resolution attempts

Solvent[a]	Resolving Agent[a]	Moles	Precipitate formation	ee (%)
AcOEt	(-)-DBTA	1	yes	Rac
$CHCl_3$	(-)-DBTA	1	Yes	Rac
THF	(-)-DBTA	1	No	-
THF/Et_2O 1:1	(-)-DBTA	1	Yes	Rac
THF/Et_2O 1:1	(-)-DBTA	0.5	Yes	Rac
$CHCl_3$	(+)-Naproxen	0.5	No	-
$CHCl_3$	(+)-10-Camphorsulphonic acid	1	Yes	Rac
$CHCl_3$	(+)-Binaphthyl phosphoric acid	1	yes	rac

[a] DBTA = O,O'-Dibenzoyl-*L*-tartaric acid

The resolution of racemic **4** on a multimilligram scale was successfully performed by enantioselective HPLC on chiral stationary phase. Excellent separation of the enantiomers of **4** was achieved by HPLC using the Chiralpak IB column (250 mm x 4.6 mm; 5 μm particle size) under normal-phase chlorinated elution mode (i.e. mobile phase: *n*-hexane-dichloromethane-2-propanol-diethylamine 70:15:30:0.1 (v/v/v/v)).Typical HPLC UV and CD chromatograms pertinent to the analytical resolution of **4** are shown in Figure 1.

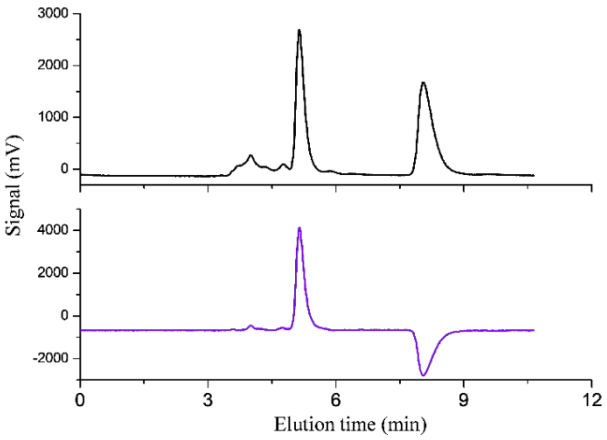


Figure 1: Analytical HPLC resolution of **4**. Column, Chiralpak IB (250 mm × 4.6 mm); mobile phase, *n*-hexane:methylene chloride:2-propanol:diethylamine 70:15:30:0.1; flow-rate, 1.0 ml/min; temperature, 40 °C; detection, UV (black) and CD (purple) at 280 nm.

The analytical separation was easily scaled up to a semipreparative scale using a 250 mm × 10 mm Chiralpak IB

column. At a flow-rate of 5.0 mL/min and a temperature of 40° C the chromatographic run was completed within 6 min. Therefore, considering that the maximum limit of sample injection onto the 1-cm i.d. Chiralpak IB column was 5 mg (dissolved in 0.5 ml of eluent) and the yields for enantiomeric separations were about 90%, a total of 22.5 mg for each enantiomer per hour could be produced. The enantiomeric excess (ee) value of both fractions collected on a multimilligram level was > 99.0%.

Electronic circular dichroism (ECD) and optical rotation dispersion (ORD) spectra of (**4**)-antipodes were recorded in order to attribute their absolute configuration (AC). Afterwards, both spectra were compared to the relevant ones simulated by means of Density Function Theory (DFT) calculations (see SI for further details), starting from the (*S*)-TetraPh-Tol-BITIOPO enantiomer (Figure 2).

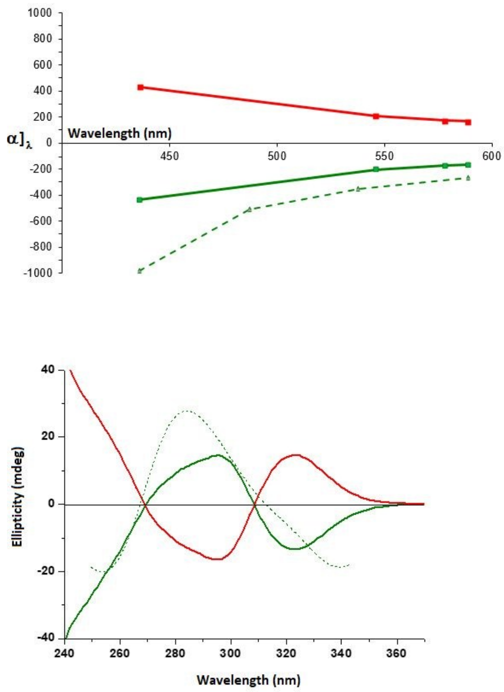


Figure 2: Experimental (full lines) and calculated (dashed lines) ORD and ECD spectra of TetraPh-Tol-BITIOPO enantiomers in chloroform. First eluted (-)-**4** is shown as green line; (+)-**4** as red line. Dashed traces refer to calculated ORD or ECD spectra of (*S*)-TetraPh-Tol-BITIOPO enantiomer.

By these analysis, it is possible to attribute the (*S*) configuration to the first eluted enantiomer (-)-TetraPh-Tol-BITIOPO.

Optically pure TetraPh-Tol-BITIOPO was then tested as catalyst in a few selected stereoselective Lewis base-catalyzed Lewis acid-mediated reactions (Table 2). We initially focused our attention on the stereoselective allylation of aromatic aldehydes: a typical experiment involved the reaction of 1 mol equiv of aldehyde **5a-g** with 1.2 mol equiv. of allyltrichloro silane in the presence of 0.1 mol equiv. of catalyst and 3 mol equiv. of *i*-Pr_2NEt in acetonitrile for 40 h at 0 °C.[12b] Isolated yields and enantiomeric excesses of alcohols **6a-g** were determined by HPLC on a chiral stationary phase and the absolute configuration was assigned by comparison with literature data (see supporting information). Preliminary experiments with benzaldehyde (**5a**) under standard conditions afforded homoallyl alcohol (**6a**) in 87% yield and 70% ee (entry 1). These result are comparable with those reported in literature for analogous bitiophene-based catalyst.[12b] However, in order to further improve the TetraPh-Tol-BITIOPO solubility, the use of dichloromethane was also investigated. In this case, the desired product **5a** was obtained with 94 % ee, even if yield decrease to 50% (entry 2). Since **4** exhibited improved chemical efficiency when operating in CH_2Cl_2, we decided to extend the substrate scope by performing in CH_2Cl_2 the reaction with diversely substituted aromatic aldehydes, bearing electron donating and electron withdrawing substituents on the aromatic ring (entries 3-5). In all cases, products were obtained in modest yields but with high enantioselectivities, up to 96% ee, demonstrating that the catalyst is able to effectively control the stereoselection of the process. More interesting, catalyst **4** showed high chemical efficiency in the allylation of cinnamaldehyde **5e** allowing to the formation of product **6e** in complete conversion and with 70 % ee (entry 6).

(-)-TetraPh-Tol-BITIOPO confirmed its activity also at low temperatures, since the reaction of **5e** performed at – 20 °C afforded the product 6e in 96% yield and 69% ee (entry 7). The **4**-catalyzed allylation of heteroaromatic aldehydes, such as 2-thiophenyl carboxaldehyde **5f**, was also investigated and product **6f** was obtained in 60% yield and 76% ee (entry 8).

Encouraged by these results, we extended the use of catalyst **4** to other Lewis base-catalyzed Lewis acid mediated reactions such as the direct aldol reaction between aromatic aldehydes with both ketones and thioesters (Scheme 2a and b) as well as the direct double aldol reaction between aryl methyl ketones with aromatic aldehydes in the presence of tetrachlorosilane (Scheme 2c). The reaction between cyclohexanone and benzaldehyde was investigated in the presence of stoichiometric amounts of $SiCl_4$ and a catalytic amount of enantiomerically pure (-)-TetraPh-Tol-BITIOPO at -25 °C for 36 hours.[19b] β-Hydroxy-etone **8a** was obtained in 70% yield very high *anti* selectivity (95:5 *anti:syn* ratio) and in 51% enantiomeric excess for the (1'*S*,2*R*)-**8a**-*anti* enantiomer.

The performances of tetraPh-Tol-BITIOPO were also investigated in the organocatalytic stereoselective direct aldol reaction of trifluoroethyl thioester **9** performed according to literature procedure.[13] The corresponding β-hydroxy thioester **10a** was obtained in 74% yield with 76:24 *syn:anti* ratio, although a decrement in terms of enantioselectivity was observed. However, these results are remarkable considering that TetraPh-Tol-BITIOPO showed an increased reactivity compared to the use of BINAPO (which is not able to effectively promote this type of transformation).

Finally, the direct double aldol reaction between acetophenone (**11**) and benzaldehyde mediated by the presence of $SiCl_4$ was also explored. Double aldol product was isolated as diacetate form in good yield and 86:14 ratio between the chiral isomer **12**-*chiro* and the achiral **12**-*meso* stereoisomers, with 60% ee for the chiral one (it must be noted that **12**-*meso* is an achiral molecule that may exist in two diastereoisomers, however in this case only one form was observed by ^{1}H-NMR.

These results represent only the starting point for further investigation to expand the application of this new class of phosphine oxides in other Lewis base-catalyzed Lewis acid-mediated transformations.

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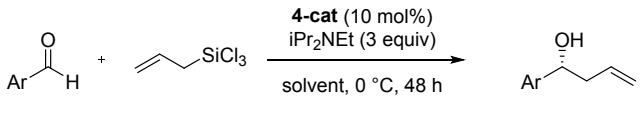
Table 2. Substrate scope of the enantioselective addition of allyltrichorosilane to aldehydes

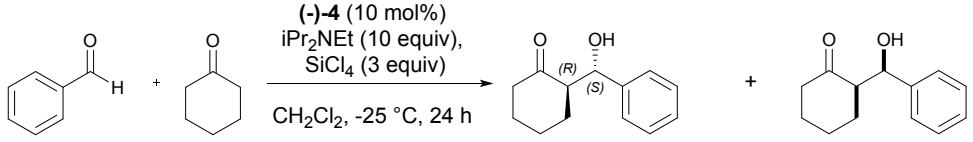


5a-g **6a-g**

Entry	Aldehyde	Ar	Catalyst	Solvent	Product	Yield (%)	ee (%)[a]
1	**5a**	C_6H_5	(-)-(*S*)-TetraPh-Tol-BITIOPO	CH_3CN	**6a**	87	70 (*S*)
2	**5a**	C_6H_5	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_2Cl_2	**6a**	50	94 (*R*)
3	**5b**	4-OCH_3-C_6H_4	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_3CN:CH_2Cl_2 (1:1)	**6b**	49	94 (*R*)
4	**5c**	4-Cl-C_6H_4	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_2Cl_2	**6c**	46	96 (*R*)
5	**5d**	4-NO_2-C_6H_4	(-)-(*S*)-TetraPh-Tol-BITIOPO	CH_3CN	**6d**	50	90 (S)
6	**5e**	Ph-CH=CH-	(-)-(*S*)-TetraPh-Tol-BITIOPO	CH_3CN	**6e**	98	70 (S)
7[b]	**5e**	Ph-CH=CH-	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_3CN	**6e**	96	69 (R)
8	**5f**	2-Thiophenyl	(-)-(*S*)-TetraPh-Tol-BITIOPO	CH_2Cl_2	**6f**	60	76 (*S*)
9	**5g**	Ph-CH_2CH_2	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_2Cl_2	**6g**	43	rac

[a]determined using HPLC on a chiral stationary phase. [b] stereogenic center configuration was assigned based on comparison with literature data. [c] reaction conducted at – 20 °C.

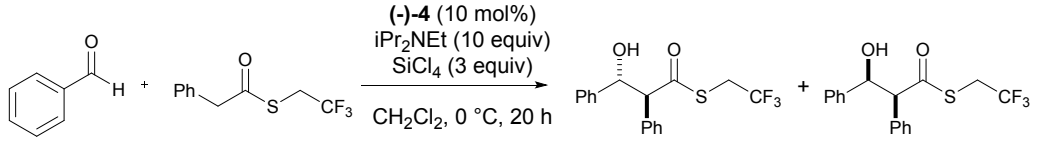
a) Direct aldol addition between benzaldehyde and cicloexanone



5a **7** **8a-*anti*** **8a-*syn***

yield = 70% *anti:syn* 95:5, 51% ee (*anti*)

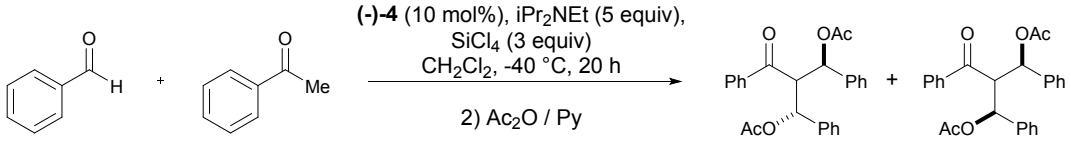
b) Direct aldol addition of activated thioester to benzaldehyde



5a **9** **10a-*anti*** **10a-*syn***

yield = 74%, *anti:syn* 24:76, 60% ee (*anti*), 36% ee (*syn*)

c) Direct double aldol addition between benzaldehyde and acetophenone



5a **11** **12-*chiro*** **12-*meso***

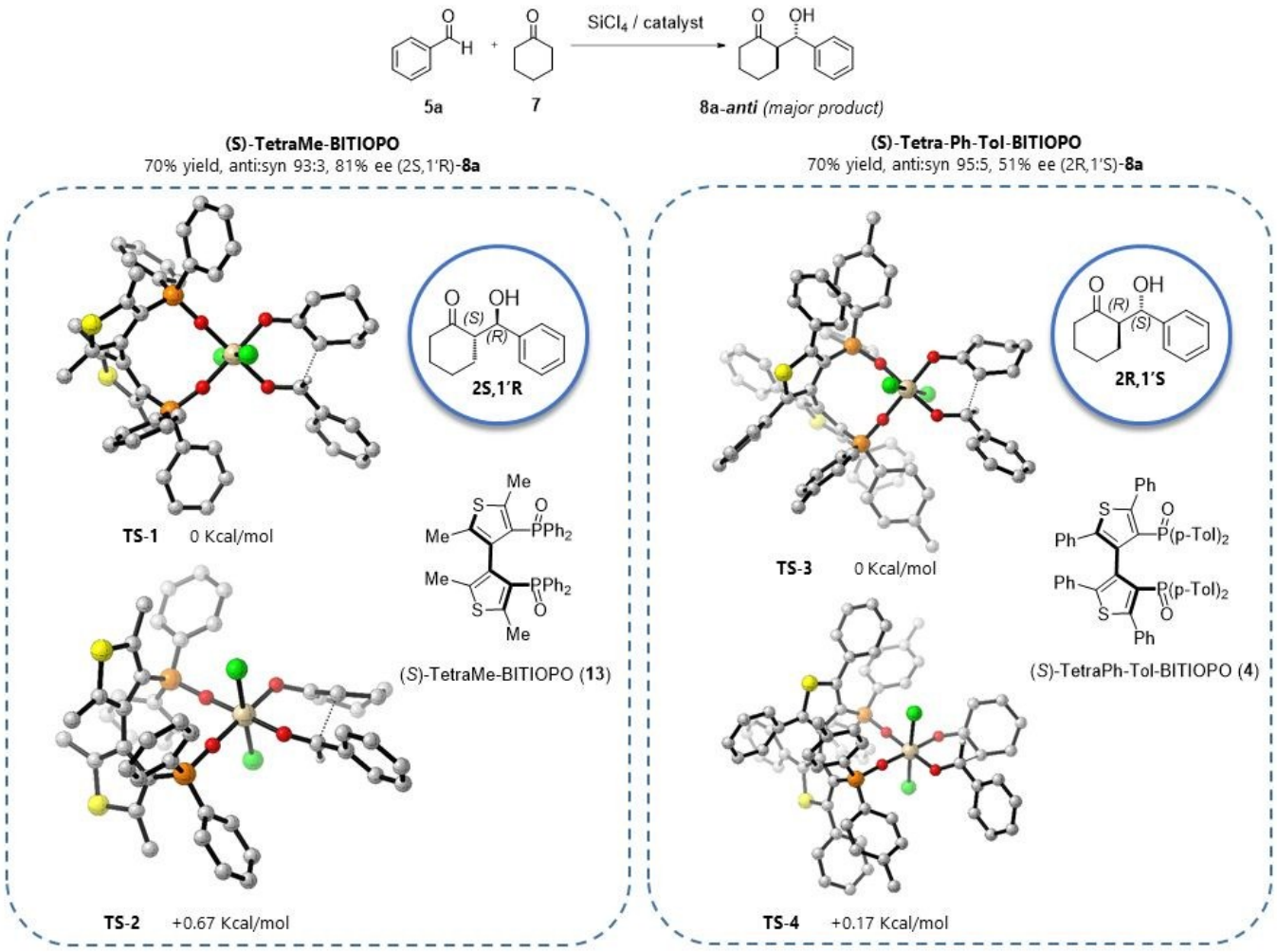
yield = 64%, *chiro:meso* 86:14, 60% ee (*chiro*)

Scheme 2. Direct (Double) aldol reaction of benzaldehyde with activated nucleophiles.

A comparison in terms of chemical and stereochemical efficiency between the new synthetized catalyst TetraPh-Tol-BITIOPO (**4**) and the previously reported TetraMe-BITIOPO (**13**)[12b] shows that both two compounds are able to promote the

allylation of aldehydes with good yields and high levels of stereoselectivities. However, a lower level of enantioselection was observed when the direct aldol reaction between benzaldehyde and cyclohexanone was performed in the presence of catalyst **4**. Surprisingly, the two catalysts, featuring the same 3,3'-bithiophene chiral scaffold afforded, in all the investigated reactions, enantiomers with opposite configuration while retaining, in the case of direct aldol reaction, the same diastereoselectivity.[19b]

In order to elucidate the origin of this behavior, the direct aldol reaction promoted by both TetraMe-BITIOPO (**13**) and TetraPh-Tol-BITIOPO was studied by semiempirical calculations (scheme 3). Initially, a conformational analysis with Monte Carlo technique was performed using the OPLS_2005 force field[22] with Macromodel Schrodinger suite package[23] on a model of the TSs, in order to obtain the best geometrical arrangement for the different substituents. Then, the two structures leading to the formation of the two experimentally observed *anti* products, were fully optimized to the relative genuine TSs with AM1 methods (both with only one imaginary frequency).[25]



Scheme 3. ΔΔG in kcal/mol at the B3LYP/6-31G(p,d) level of theory of TSs related to the aldol addition reaction mediated by $SiCl_4$ and promoted by BITIOPOs catalysts (hydrogen were omitted for clarity, cream = silicon, yellow = sulfur, green = chlorine, red = oxygen, orange = phosphorous, grey = carbon).

The calculations, performed using (*S*)-TetraMe-BITIOPO (**13**) as catalyst, showed that **TS-1**, responsible of the formation of the experimentally observed *anti*-(2S,1'R)-diastereoisomer, was more stable by 0.67 kcal/mol than **TS-2**. The same calculations using (*S*)-TetraPh-tol-BITIOPO (**4**) showed instead an opposite trend: **TS-3**, which leads to the formation of *anti*-(2R,1'S)-(**8a**)-diastereoisomer is more stable of 0.17 kcal/mol than **TS-4**. The energy differences between the TSs determined by computational studies are in good agreement with the experimentally observed lower enantioselectivity obtained with catalyst (*S*)-**4** compared to the (*S*)-TetraMe-BITIOPO derivative (**13**).

This unexpected behavior could be explained with the presence in catalyst **4** of a π- π interaction between a phenyl group of the 3,3'-bithienyl scaffold with the tolyl group connected to the phosphorous atom. Such interaction cause a different local atom rearrangement in the chiral pocket generated by the hypervalent silicon species $SiCl_4$-catalyst(**4**), compared to those generated when (*S*)-TetraMe-BITIOPO was employed.

Conclusion

A new atropisomeric diphosphine oxide based on the 3,3'-bithiophene scaffold was synthesized and resolved into antipodes through semipreparative chiral HPLC. Their absolute configuration was assigned on the basis of the comparison between experimental and DFT calculated ECD and ORD spectra. The enantiomers were tested as organocatalysts to promote the enantioselective allylation of aldehydes, in up to 96% e.e., and aldol type reactions, with lower stereoselectivities.

Although the stereocontrol induced by the new atropisomeric catalyst was not completely satisfactory, a simple replacement of a methyl group with a phenyl ring on the 3,3'-atropisomeric bithiophene scaffold produces a strong modification on the stereochemical outcome of the reactions.

Since further studies are clearly needed to investigate this new class of chiral catalysts, the present work opens the pathway towards the design of new, highly tunable biheterocyclic phosphine derivatives, to be employed as chiral promoters in stereoselective transformations.

Experimental

General: All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen unless otherwise stated. Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical TLC using silica gel 60 F254 precoated glass plates (0.25 mm thickness) and visualized by using UV light. Flash chromatography was carried out on silica gel (230–400 mesh). ^{1}H NMR spectra were recorded with a Bruker Fourier or Bruker Advanced spectrometer operating at 300 or 500 MHz. ^{1}H chemical shifts are reported in ppm (δ) with the solvent as reference relative to tetramethylsilane (TMS) employed as internal standard ($CDCl_3$: δ = 7.26 ppm). ^{13}C NMR spectra were recorded with the same spectrometer at 125 MHz with complete proton decoupling. ^{13}C chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as internal standard ($CDCl_3$: δ = 77.0 ppm). ^{31}P spectra were recorded at 121.4 MHz and were referenced to phosphoric acid (H_3PO_4) at 0.0 ppm. Enantiomeric excesses were determined by HPLC with Agilent 1100 and 1200 series HPLC systems. CD spectra were recorded by using a Jasco Model J-700 spectropolarimeter. DFT calculations where performed by using the Gaussian 09 package. Hexabromo-3,3'-bithiophene (**2**) and 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,'-bithiophene (**3**) were prepared according to the procedures reported in ref. 25.

2,2',5,5'-Tetraphenyl-4,4'-bis-(di-(4-methyl)-phenylphosphino)-3,3'-bithiophene oxide (TetraPh-Tol-BITIOPO, 4). 1.6M *n*-BuLi solution (6 mL) was added dropwise under stirring into a solution of **3** (2.5 g, 3.97 mmol) in dry THF (20 mL) under Argon atmosphere at – 50 °C. After 45 min the temperature was allowed to warm up to -40 °C and ditolylphosphinic acid was added dropwise (2.0 g 8.1 mmol). The reaction mixture was refluxed for 8 h and the solvent evaporated under reduced pressure. The residue was dilute with CH_2Cl_2 (20 mL) and a 30% H_2O_2 solution (10.4 mL 2.4 mmol) was added at RT. The reaction mixture was stirred for 1 h, then treated with a 1N HCl solution (30 mL). The organic layer was washed with a saturated $NaHCO_3$ solution (30 mL); the aqueous phase was extracted with CH_2Cl_2 (3x 30 mL) and the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with a CH_2Cl_2/ethyl acetate/ Et_3N mixture (7:3:0.1). The last fractions eluted was combined and evaporated to dryness to give **4** as a white solid (60 % yield); m.p. 134 °C (uncorrected). ^{1}H NMR (300MHz, $CDCl_3$): δ = 7.30-6.90 (m, 16H), 6.81 (dd, *J* = 2.4 Hz, 2H), 6.71 (dd, *J* = 2.4 Hz., 2H), 2.22(s, 3H), 2.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.15, 150.97, 142.14, 141.97, 140.29, 135.67, 135.50, 134.09, 133.40, 132.31, 132.17, 132.04, 131.90, 131.37, 131.23, 130.67, 129.92, 129.83, 129.36, 128.98, 128.65, 128.54, 128.24, 128.05, 127.86, 127.47, 127.29, 126.95, 21.48, 21.41. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 21.82. MS (EI) 926 (M+).

General procedure for the enantioselective allylation of aldehydes 5a-g with allyltrichlorosilane: Allyltrichlorosilane (40,49 mg, 0.214 mmol, 1.2 equiv) was added dropwise to a mixture of TetraPh-Tol-BITIOPO (**4**) (0.017 mg, 0.018 mmol, 0.1 mol%), freshly distilled aldehyde (**5**) (0.178 mmol, 1 equiv), and diisopropylethylamine (0.093 mL, 0.534 mmol, 3 equiv) dissolved in the desired solvent (1.2 mL, 0.15 M) under nitrogen at 0 °C. The reaction mixture was stirred at this temperature for 48 h, then it was quenched with a saturated $NaHCO_3$ aqueous solution (1 mL). The mixture was allowed to warm up to room temperature, then the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layer was washed with aqueous sodium chloride, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with a *n*-hexane/ethyl acetate mixture (9:1). The yields and enantioselectivities are given in Table 2. Analytical and spectral data are available in the Supporting Information.

General procedure of enantioselective direct aldol-type reaction between ketones or thioesters and aldehydes: To a stirred solution of enantiopure TetraPh-Tol-BITIOPO **4** (0.017 mg, 0.018 mmol, 0.1 mol%), in dichloromethane (1.2 mL), diisopropylethylamine (0.310 mL, 1.78 mmol, 10 equiv) and cyclohexanone (0.035g, 0.356 mmol, 2 equiv) or thioester **9** (0.099, 0.356 mmol, 2 equiv) were added. The mixture was then cooled at 0 °C and freshly distilled tetrachlorosilane (0.031 mL, 0.267 mmol, 1.5 equiv) was added dropwise via syringe. After 15 min, freshly distilled aldehyde (0.018 mL, 0.178 mmol, 1 equiv) was added. The mixture was stirred for 5/12 hours (5 h for thioesters, 12 h for ketones), then the same amount of tetrachlorosilane (1.5 equiv) was added. After further 12/15 hours (15 h for thioesters, 12 h for ketones), the reaction was quenched by the addition of a saturated $NaHCO_3$ aqueous solution (3 mL). The mixture was allowed to warm up to room temperature and stirred for 30 min, then water (2.5 mL) and ethyl acetate (8 mL) were added. The two-layers mixture was separated and the aqueous layer was extracted with ethyl acetate (8 mL). The combined organic layers were washed with 10% HCl (10 mL), sat $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum at room temperature. The crude product was purified by column chromatography with *n*-hexane/ethyl acetate 9:1 mixture as eluent

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to afford the pure aldol adducts (see scheme 2). The *syn*/*anti* ratio was evaluated by ^{1}H NMR spectroscopy of the crude mixture; the enantiomeric excesses were determined by HPLC. Catalyst **4** was quantitatively recovered by further elution with 10% MeOH in CH_2Cl_2 without any loss of optical purity (for example: recovered (+)-**4** catalyst $[\alpha]^D_{25}$ = +138.8, c=0.78 in $CHCl_3$).

General procedure of enantioselective direct double aldol-type reaction: To a stirred solution of enantiopure TetraPh-Tol-BITIOPO **4** (0.017 mg, 0.018 mmol, 0.1 mol%) in dichloromethane (1.2 mL), diisopropylethylamine (0.155 mL, 0.89 mmol, 5 equiv) and acetophenone (0.021g, 0.178 mmol, 1 equiv) were added. The mixture was then cooled at -40 °C and freshly distilled tetrachlorosilane (0.081 mL, 0.712 mmol, 4 equiv) was added dropwise via syringe. After 15 min, freshly distilled aldehyde (0.044 mL, 0.391 mmol, 2.2 equiv) was added. The mixture was stirred for 20 h. After this time, the reaction was quenched by the addition of a saturated NH_4Cl aqueous solution (2 mL). The mixture was allowed to warm to room temperature and stirred for 30 min, then CH_2Cl_2 (10 mL) was added. The two-layer mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum at room temperature to give the crude 1,3-diols, as confirmed by ^{1}H-NMR. The crude products were then treated with acetic anhydride (0.185 mL, 1.95 mmol, 11 equiv) in 2mL of pyridine at RT. After stirring for 20 h, the mixture was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 8 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum at RT. The crude product was purified by column chromatography with *n*-hexane/ethyl acetate 9:1 mixture as eluent to afford the pure aldol adducts (see scheme 2).

Conflicts of interest

There are no conflicts to declare.

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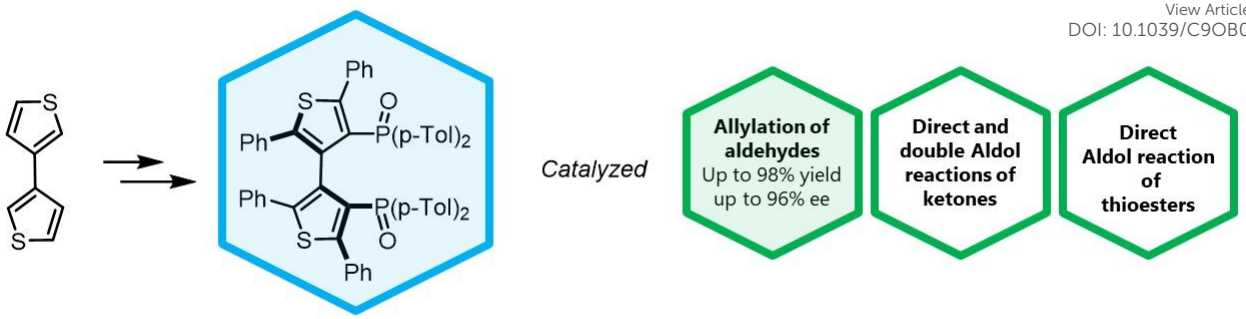

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