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Organocatalytic Stereoselective Direct Aldol Reaction of Trifluoroethyl Thioesters

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Dedicated to Professor Piero Dalla Croce on the occasion of his 73rd birthday.

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Abstract: The first organocatalytic, stereoselective and direct aldol reaction of activated thioesters with aldehydes has been accomplished. The trichlorosilyl ketene thioacetal generated *in situ* by adding a tertiary amine to a trifluoroethyl thioester in the presence of tetrachlorosilane is activated by catalytic amounts of an enantiomerically pure biheteroaromatic phosphine oxide to react with different aldehydes, coordinated to as well as activated by the chiral cationic hypervalent silicon species. Starting from a variety of readily available thioesters, this Lewis acid-mediated Lewis base-catalyzed transformation allows the direct synthesis of *syn*-β-hydroxy thioesters in up to 95% *ee*.

Keywords: aldol reaction; organocatalysis; phosphine oxides; tetrachlorosilane; thioesters

The development of a direct diastereo- and enantioselective, catalytic aldol reaction of esters with carbonyl derivatives remains one of the unsolved challenges in organocatalysis.[1] The difficulty of successfully realizing such a transformation arises from the lower acidity of the α protons of carboxylic esters compared to those of a ketone or an aldehyde. Indeed, the pK_a value for ester derivatives (*ca.* 19)[2] is significantly higher than that (*ca.* 16–17) necessary to activate a nucleophilic substrate *via* amine catalysis.[3] Since reactions with donors in the ester oxidation state *via* an enamine-based organocatalytic approach are not feasible,[4] and thioesters may react with a secondary amine to afford the corresponding amide, activation of the ester nucleophile is necessary. Taking inspiration from Nature, a few groups have recently studied the possibility to perform catalytic stereoselective transformations with malonic acid hemithioesters, exploiting either organometallic or metal-free catalysis. For the organometallic approach Shair's group and ours[5a,b] have investigated the use of chiral copper(II) complexes in the malonic acid hemithioester addition to aldehydes. Studying the metal-free methodology Ricci's group has realized a decarboxylative addition to imines catalyzed by a readily available *Cinchona*-based compound to afford β-amino thioesters in up to 79% *ee*[6] At the same time, Wennemers showed that a bifunctional thiourea derivative of a *Cinchona* alkaloid could efficiently promote the enantioselective 1,4-addition of malonic acid hemithioesters to nitroolefins under mild conditions and in up to 90% *ee*[7] More recently, Ricci and Bernardi reported an efficient stereoselective Mannich reaction of sulfonylacetates with *N*-carbamoylimines under phase-transfer catalysis conditions in the presence of a quinine-derived chiral ammonium salt;[8] in this case, further synthetic elaboration was necessary to convert the reaction products into β-amino esters.

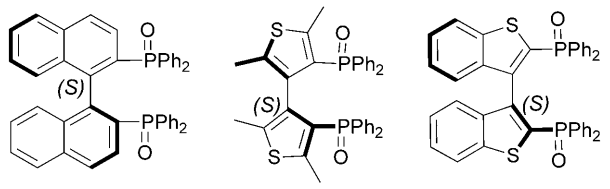
An alternative approach has been recently investigated by Barbas who introduced the use of trifluoroethyl thioesters as activated nucleophilic substrates suitable for organocatalytic amine activation.[9] In the attempt to have access to a set of reacting substrates wider than malonic acid derivatives, a fine tuning of the electronic properties of trifluoroethyl thioesters was performed to identify proper substrates suitable for organocatalytic amine activation. A steoreoselective Michael reaction was successfully accomplished by using catalytic amounts of an α,α-diphenyl prolinol ether. Later, catalytic Mannich reactions were also reported to be feasible, although only with a modest

level of enantioselection.[10] In both cases, however, trifluoroethyl thioesters required the presence of a group in the α position such as an aryl residue or an halogen atom, as a further activating element necessary to guarantee the low p*K* value required for α deprotonation by a chiral amine.

The very limited number of examples reported for the stereoselective catalytic reaction of ester derivatives clearly testified for the difficulty of the challenge of performing a direct aldol process and called for new studies in the field. We decided to tackle this problem by exploring an alternative metal-free approach. It is well known that the coordination of a Lewis base to silicon tetrachloride generates a new hypervalent trichlorosilyl cationic species of enhanced electrophilicity; this new adduct of increased Lewis acidity was shown to be able to promote the addition of different nucleophiles to carbonyl compounds.[11] A significant breakthrough in the field was achieved by Denmark who reported a highly efficient enantioselective aldol reaction of silyl ketene acetals catalyzed by a binaphthyldiamino-based phosphoramide (1 mol%) in the presence of stoichiometric amount of tetrachlorosilane.[12] Over the last few years it was demonstrated that an *in situ* generated chiral phosphoroamide-bound trichlorosilyl cation was an active catalyst for different transformations,[13] according to a general mechanism that can be properly defined as a phosphoroamide-catalyzed and $SiCl_4$-mediated process.[11]

In the context of thioester addition to aldehydes, the possibility of promoting reactions through a chiral Lewis acid generated by coordination of catalytic amounts of a chiral phosphine oxide to $SiCl_4$ was obviously very attractive.[14] Prompted by a recent work by Nakajima, where BINAPO was employed as organocatalyst in aldol reactions,[15] we have recently reported our studies on a direct aldol condensation of ketones to aromatic aldehydes promoted by the chiral biheteroaryl-diphosphine oxide tetra-Me-BITIOPO.[16] Based on these promising results we decided to extend the use of this synthetic methodology to the addition of activated thioesters to carbonyl compounds and we here report the successful results of this study. To the best of our knowledge, this procedure represents the first stereoselective, organocatalytic and direct aldol addition of thioesters to aldehydes.

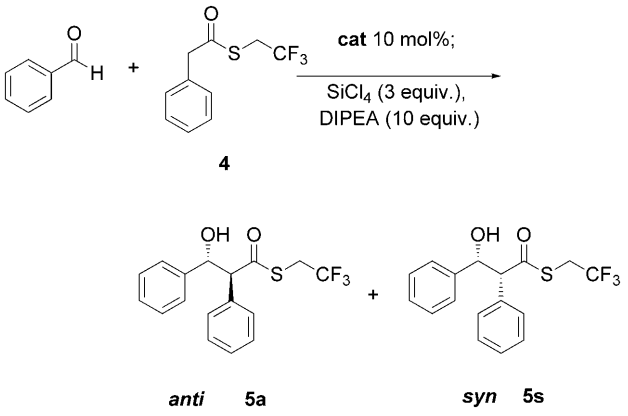
Different enantiomerically pure phosphine oxides were tested as possible catalysts: along with the popular bis-(diphenylphosphanyl)-binaphthyl dioxide, (*S*)-BINAPO **1**, its heteroaromatic countertparts (*S*)-tetramethyl-bithiophene phosphine oxide, (*S*)-tetraMe-BITIOPO **2**, and dibenzothiophene phosphine oxide, (*S*)-BITIANPO **3**, were employed (Scheme 1). Since compounds **2** and **3** have been shown to feature phosphine oxide residues that are electron richer and electron poorer than those of **1**, respectively, a series of catalysts endowed with different electronic properties was available.[13]



Scheme 1. Chiral phosphine oxides.

The addition of trifluoroethyl phenylthioacetate **4** to benzaldehyde was investigated as model reaction in the presence of an excess of both $SiCl_4$ and a base, and of a catalytic amount of enantiomerically pure phosphine oxide (Scheme 2). The use of different solvents, temperatures and additives was screened in order to optimize the reaction; a few selected results are shown in Table 1. The direct condensation of 1 mol equiv. of thioester with 1 mol equiv. of benzaldehyde in the presence of 3 mol equiv. of silicon tetrachloride, 10 mol equiv. of DIPEA and a 10 mol% amount of (*S*)-tetramethyl BITIOPO (DCM, 18 h, 0 °C) afforded the corresponding trifluoroethyl β-hydroxythioester **5** in 40% yield (entry 1, Table 1). This was isolated almost as single diastereoisomer (*dr* 98/2) having 80% *ee* The relative and absolute configuration of the product was shown to be *syn*-(*2R,3R*) by chemical correlation.[17]

By optimization of the experimental conditions, it was found that the reaction proceeded better in dichloromethane than in other solvents and by employing 2 mol equiv. of ester for 1 mol equiv. of aldehyde; under these conditions, the *syn* diastereoisomer was isolated as the major product (98/2 *syn/anti*) in 89% *ee* (entry 3, Table 1). As for the use of different bases,



Scheme 2. Stereoselective addition of thioester **4** to benzaldehyde.

Table 1. Phosphine oxides-catalyzed condensation of thioester **4** with benzaldehyde at 0 °C.

Entry	Solvent	Time [h]	Temperature [°C]	Yield [%][a]	Catalyst	*syn/anti* ratio[b]	***ee syn*** (*ee anti*)[c] [%]
1[d]	DCM	15	0	40	**2**	98/2	**80** (–)
2[e]	DCM	15	0	35	**2**	96/4	**70** (–)
3	DCM	15	0	80	**2**	98/2	**89** (–)
4	CH_3CN	15	0	49	**2**	82/18	**65** (16)
5	THF	15	0	53	**2**	98/2	**81** (–)
6[f]	DCM	15	0	41	**2**	98/2	**83** (–)
7	DCM	40	−40	55	**2**	88/12	**83** (55)
8	DCM	15	0	35	**1**	97/3	**81** (–)
9	DCM	15	0	9	**3**	96/4	**79** (–)

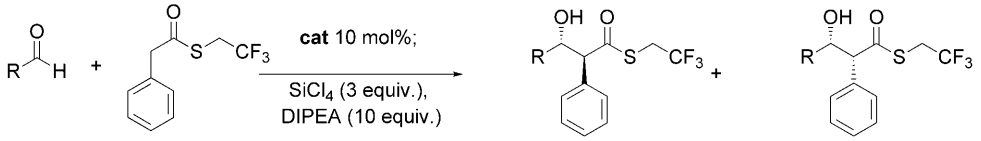
[a] Reactions were run with 3 mol equiv. of $SiCl_4$, 2 mol equiv. of thioester, 1 mol equiv. of aldehyde and 0.1 mol equiv. of catalyst; yields were determined after chromatographic purification.
[b] Diastereoisomeric ratio was determined by ^1H NMR on the crude reaction product and confirmed by HPLC.
[c] The *ee* value was determined by HPLC on a chiral column (see Supporting Information).
[d] 1 mol equiv. of thioester was used.
[e] 2 mol equiv. of aldehydes for 1 equiv. of thioester.
[f] *N*-Methylmorpholine was used as base.

it was found that while *N*-methylmorpholine led to the β-hydroxythioester in comparable stereoselectivity but in lower chemical yield, other bases (such as triethylamine, diethylamine, DABCO, DBU) led to a significant decrease in the enantioselectivity. Furthermore, lowering the reaction temperature to −40 °C turned out to be detrimental because the chemical yields were depressed (to the point that longer reaction times were required to obtain the product in fair yields), and virtually no improvement in the enantioselectivity of the process was observed.

The performances of catalysts **1–3** were also compared. With respect to BITIOPO **2**, BINAPO **1** catalyzed the reaction under standard conditions (entries 3 and 8, Table 1) in lower chemical yield (35% *vs.* 80%), comparable *syn/anti* ratio (97/3 *vs.* 98/2), and marginally lower enantioselectivity (81% *vs.* 89% *ee*). Noteworthy, a more electron poor chiral phosphine oxide, such as BITIANPO **3**, promoted the reaction in very low yield (9%), although with good diastereo- and enantioselectivity (96/4 *syn/anti*, 79% *ee*). These results confirm a trend already observed in the chiral Lewis base-promoted enantioselective addition of allyltrichlorosilane to aldehydes[20] and pointed to the importance of the electronic properties of the chiral phosphine oxide in fine-tuning the catalyst's performance.

The general applicability of this methodology to different aldehydes was then investigated (Scheme 3). When trifluoroethyl thioester **4** was reacted at 0 °C with 4-methoxybenzaldehyde in the presence of a catalytic amount of (*S*)-tetramethyl-BITIOPO **2** the product was isolated essentially as a single isomer with 83% *ee* (entry 2, Table 2). A further decrease of the reaction temperature did not improve the enantioselection (81% *ee* for major isomer, entry 3 of Table 2) and caused a decrease in the diastereoselectivity.

Constantly good levels of stereoselectivity were observed when other aromatic aldehydes, either bearing



R = Ph	**5**
R = 4-$OMeC_6H_4$	**6**
R = 4-ClC_6H_4	**7**
R = 4-$NO_2C_6H_4$	**8**
R = 4-MeC_6H_4	**9**
R = 2-naphthyl	**10**
R = 2-thienyl	**11**
R = 2-furyl	**12**
R = Ph-CH=CH-	**13**

Scheme 3. Stereoselective addition of thioester **4** to different aldehydes.

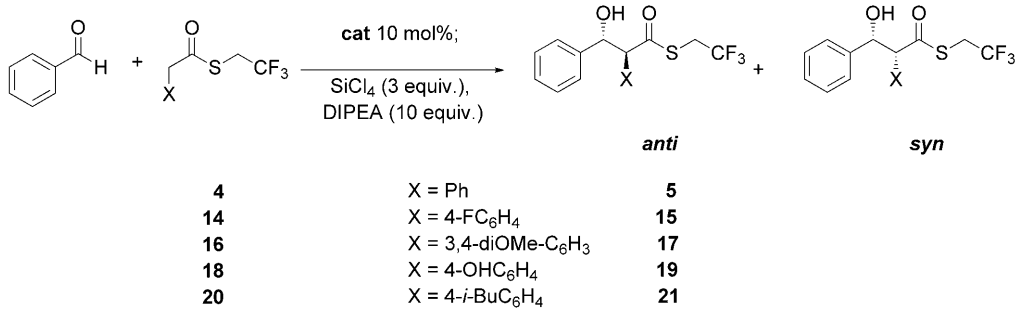
Table 2. Tetra-Me-BITIOPO-catalyzed condensation of thioester **4** with different aldehydes.

Entry	Solvent	Time [h]	Temperature [°C]	Yield [%][a]	R	*syn/anti* ratio[b]	***ee syn*** (*ee anti*)[c] [%]
1	DCM	15	0	80	Ph	98/2	**89** (–)
2	DCM	40	0	51	4-MeO-C_6H_4	>98/2	**83** (–)
3	DCM	15	−40	35	4-MeO-C_6H_4	70/30	**80** (<5)
4	DCM	40	−40	40	4-Cl-C_6H_4	88/12	**81** (33)
5	DCM	15	0	33	4-NO_2-C_6H_4	80/20	**55** (<5)
6	DCM	15	0	51	4-Me-C_6H_4	>98/2	**85** (–)
7	DCM	15	0	41	1-naphthyl	66/34	**63** (35)
8	DCM	15	0	25	2-thienyl	>98/2	**93** (–)
9	DCM	15	0	37	2-furyl	>98/2	**91** (–)
10	DCM	15	0	63	Ph-CH=CH-	>98/2	**83** (–)
11	DCM	15	0	n.r.	$(CH_3)_2$CH-	–	**–**

[a] Reactions were run with 3 mol equiv. of $SiCl_4$, 2 mol equiv. of thioester,1 mol equiv. of aldehyde and 0.1 mol equiv. of catalyst; yields were determined after chromatographic purification.

[b] Diastereoisomeric ratio was determined on the crude reaction product by ^{1}H NMR and confirmed by HPLC; the *syn* configuration of the major isomer was assigned based on the reasonable assumption that all the substrates reacted according to the same proposed mechanism.

[c] The *ee* value was determined by HPLC on a chiral column (see Supporting Information).



Scheme 4. Stereoselective addition of activated thioesters to benzaldehyde.

electron-withdrawing or electron-donating groups, were employed. For instance, by reacting thioester **4** with 4-chloro- and 4-methylbenzaldehydes, the enantioselectivities remained higher than 80%. Quite inexplicably, however, when the condensation was carried out on 4-nitrobenzaldehyde or 1-naphthaldehyde the product was isolated in lower *ee*

The methodology was successfully extended also to heteroaromatic aldehydes (entries 8 and 9, Table 2). The reaction of **4** with 2-furyl- and 2-thienylcarboxyaldehyde in dichloromethane at 0 °C led to the corresponding β-hydroxythioesters as single diastereoisomers in 91% and 93% *ee*, respectively, albeit in low yields. Interestingly, also cinnamic aldehyde reacted under the present experimental conditions, affording the condensation product in good yield, complete *syn* diastereocontrol, and 80% *ee* As expected on the basis of previous investigations, aliphatic aldehydes did not react under these conditions.[16]

The scope of this reaction was further investigated by varying the aryl residue of the trifluoroethyl thioester (Scheme 4). Generally, substrates with electron-donating substituents on the aromatic ring showed a better reactivity and afforded the condensation products in higher enantioselectivity. This is the case, for example, of thioester **16** derived from 3,4-dimethoxyphenylacetic acid, that in the reaction with benzaldehyde gave the corresponding β-hydroxythioester **17** with 95% *ee* for the major isomer (entry 3, Table 3). Interestingly also thioester **18** bearing a free OH group reacted smoothly, leading to product **19** as a single stereoisomer with 85% enantioselectivity.

In a further attempt to expand the scope of this reaction, this methodology was extended to a trifluoroethyl thioester featuring an α-activating group different from an aryl and whose condensation would lead to the creation of a quaternary stereocenter. Thus, trifluoroethyl thioester **22**, derived from 2-bromohexanoic acid, was reacted with benzaldehyde to afford under the usual conditions adduct **23** in good yield (68%) as a single diastereoisomer of unknown configuration having 88% *ee* (Scheme 5).

In order to understand the origin of the stereoselectivity of this reaction, preliminary NMR studies were

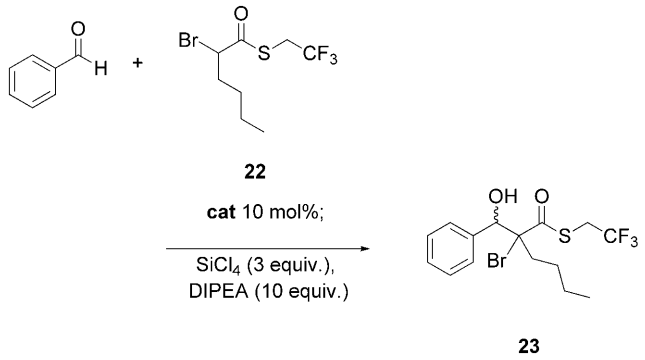
Table 3. Tetra-Me-BITIOPO-catalyzed condensation of different thioesters with benzaldehyde.

Entry	Yield [%][a]	X	*syn/anti* ratio[b]	***ee syn*** (*ee anti*)[c] [%]
1	80	Ph	98/2	**89** (–)
2	37	4-F-C_6H_4	88/12	**71** (23)
3	57	3,4-$(MeO)_2$-C_6H_3	80/20	**95** (75)
4	65	4-HO-C_6H_4	>98/2	**85** (–)
5	51	4-*i*-Bu-C_6H_4	96/4	**80** (37)

[a] Reactions were run at 0 °C for 15 h in DCM with 3 mol equiv. of $SiCl_4$, 2 mol equiv. of thioester, 1 mol equiv. of aldehyde and 0.1 mol equiv. of catalyst; yields were determined after chromatographic purification.

[b] Diastereoisomeric ratio was determined on the crude reaction product by ^1H NMR and confirmed by HPLC.

[c] The *ee* value was determined by HPLC on a chiral column (see Supporting Information).



Scheme 5. Stereoselective addition of thioester **22** to benzaldehyde.

carried out. On the basis of Denmark's work[22] the formation of a cationic hypervalent silicon species may be postulated; NMR investigations seem to support this hypothesis. Indeed, ^{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 ppm to 34.8 ppm (neutral $SiCl_4$/phosphine oxide complex). This was further shifted by addition of DIPEA to 27.7 ppm, a value consistent with the formation of a cationic silicon species. The same species was observed when the thioester was treated with DIPEA in the presence of $SiCl_4$ and tetra-Me-BITIOPO (^{31}P signal at 28.1 ppm).[23]

In attempting a rationalization of the stereochemical outcome of this reaction, the understanding of the enolization step of thioester **4** is of crucial importance. On the basis of steric considerations, the adduct formed by co-ordination of **4** with the chlorosilane species can be expected to adopt the so-called "pinwheel" conformation **A**[24] (Figure 1) to minimize repulsion between the bulky peripheral groups.

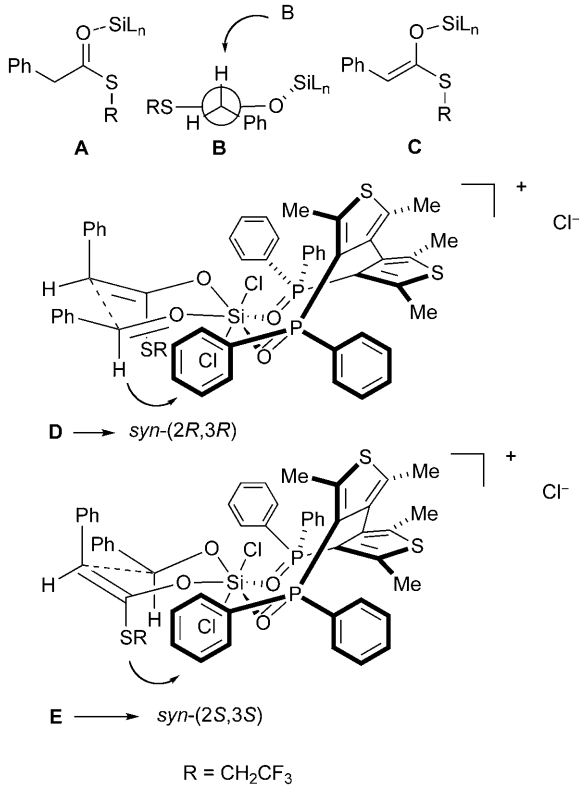


Figure 1. Model of stereoselection in the enolization of thioester **4** and in the aldol addition.

Deprotonation with a bulky base such as DIPEA should occur as in **B**[25] to afford *O*-silylenolate **C** possessing the *E*-configuration according to the Cahn, Ingold, Prelog rules and the *Z*-configuration in the conventional enolate nomenclature (substituent at C-α *cis* to the carbonyl oxygen). From this "*Z*" enolate the formation of *syn* aldol is expected to occur *via* a chair-like transition structure in which the Lewis acidic silicon atom coordinates and activates the aldehyde towards the attack of the nucleophile. Of the two competing transition structures that lead to the *syn* aldols, model **D**, affording the experimentally obtained (2*R*,3*R*)-product can tentatively be considered favoured over model **E** because the latter features a destabilizing steric interaction between a phenyl residue of the catalyst and the bulky trifluoroethylthio group of the thioester (see arrows in Figure 1).

In conclusion, the first stereoselective organocatalytic addition of activated thioesters to aldehydes has been developed; the addition of trifluoroethylthio phenylacetate to aldehydes in the presence of stoichiometric amount of tetrachlorosilane and catalytic amounts of a chiral phosphine oxide led to the formation of β-hydroxy thioesters in high *syn* stereoselectivity and in up to 95% *ee* The reaction is supposed to be catalyzed by a chiral cationic hypervalent silicon species that acts as chiral Lewis acid in promoting the

reaction. Further studies and applications of the methodology to other transformations are currently underway.

Experimental Section

General Remarks

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 under nitrogen over molecular sieves (bottles with crown caps). 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 phosphomolybdic acid. Proton NMR spectra were recorded on spectrometers operating at 200, 300 or 500 MHz, respectively. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ $\delta = 7.26$ 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 ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta =$ 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 *ee* determinations 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).

Typical Procedure of Enantioselective Direct Aldol Reactions between Thioesters and Aldehydes

To a stirred solution of (*S*)-tetra-Me-BITIOPO (0.1 or 0.2 equiv.) in the chosen solvent (2 mL), the thioester (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 the example reported in Table 3, entry 1, the quantities are: (*S*)-tetra-Me-BITIOPO (0.1 equiv, 0.03 mmol, 18.7 mg); thioester **4** (2 equiv., 0.60 mmol, 140.5 mg); 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 the indicated reaction time the reaction was quenched by the addition of a saturated 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 organic layer was separated and the aqueous layer was extracted with ethyl acetate (15 mL). The combined organic layers were washed with saturated NH_4Cl solution (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 different hexane:ethyl acetate mixture as eluant (see below) to afford the pure aldol adducts. Yields and *ee* for each reaction are indicated in the Tables. The *syn:anti* ratio was determined by ^1H NMR spectroscopy on the crude product; the enantiomeric excess was determined by HPLC on a chiral stationary phase. (*S*)-tetra-Me-BITIOPO was quantitatively recovered by further elution with 10% MeOH in CH_2Cl_2.

Supporting Information

^1H NMR spectra and HPLC chromatograms of chiral products, synthesis of activated thioesters, and experimental details of the direct aldol condensation are available in the Supporting Information.

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[23] It must be noted that on simply mixing tetra-Me-BITIOPO with HCl a shift in the P signal to 31.7 ppm (instead of 34.8) was detected and that no change was observed after addition of DIPEA. Under the present analysis conditions the *in situ* formation of a silyl ketene thioacetal in solution was not clearly observed.
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