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Phosphine Oxide Catalyzed, Tetrachlorosilane-Mediated Enantioselective Direct Aldol Reactions of Thioesters

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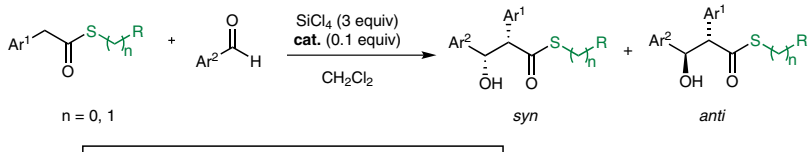

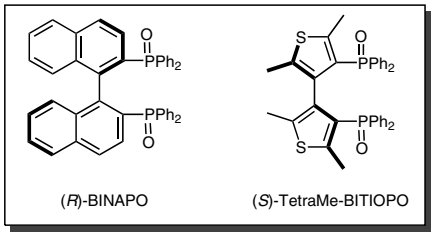

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Abstract The stereoselective direct aldol reaction of *S*-phenyl thioesters and aromatic aldehydes promoted by tetrachlorosilane was realized for the first time; the proposed mechanism involves the formation of a chiral cationic hypervalent silicon species and requires the presence of catalytic amounts of a Lewis base, like a chiral phosphine oxide. The reaction affords *syn* β-hydroxy thioesters as major isomers in good yields, high diastereoselectivity (up to 99:1), and up to 92% enantiomeric excess. The absolute configuration of the major isomer was established by converting the product into the corresponding β-hydroxy ester. The scope of the reaction was also investigated by employing differently substituted thioesters in combination with different aromatic aldehydes.

Key words asymmetric catalysis, direct aldol reaction, hypercoordinate silicon, phosphine oxides, thioesters

The use of tetrachlorosilane in combination with catalytic amounts of chiral Lewis bases to promote stereoselective reactions is nowadays a well-established method.[1] Generally, the coordination of a Lewis base to a Lewis acid leads to the formation of a stable and less reactive adduct. However, in some circumstances, this adduct presents enhanced reactivity, as in the case of the coordination of a chiral Lewis base to a molecule of $SiCl_4$, where a new silicon species with increased Lewis acidity is generated in situ.[2]

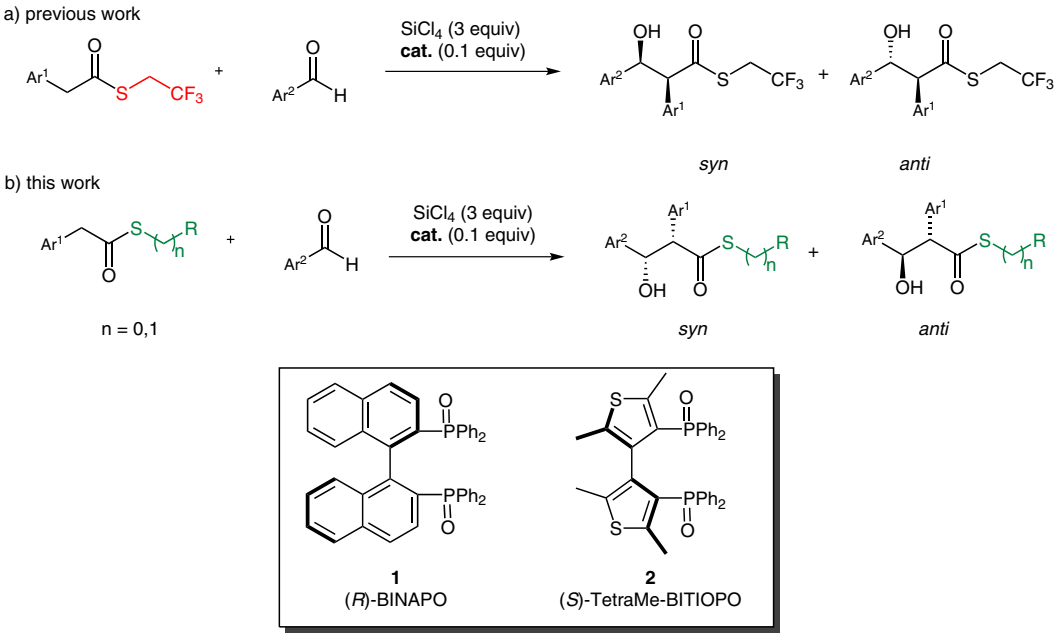
Due to its low cost and ready availability, the activation of tetrachlorosilane through the generation of hypervalent, highly reactive, silicate species can play an important role in the development of new, highly chemically and stereochemically efficient catalytic systems of low environmental impact.[3]

In this field, a real breakthrough was achieved by Denmark, who developed phosphoramide-catalyzed and $SiCl_4$-mediated stereoselective reactions.[1a] The coordination of the chiral Lewis base to $SiCl_4$ generates a new hypervalent[4] silicon species of increased acid character, responsible for the addition of different nucleophiles to carbonyl compounds with high chemical and stereochemical efficiency. These studies opened the way to the so-called 'Lewis base catalyzed Lewis acid mediated reactions' where chiral phosphoroamides,[1a,5] phosphine oxides,[1b,c,6] and sulfoxides[7] have found extensive application as Lewis bases for the activation of trichlorosilyl derivatives, including tetrachlorosilane.

In 2011, our group reported the first organocatalytic direct aldol addition of activated thioesters to aldehydes, catalyzed by phosphine oxides and mediated by the presence of $SiCl_4$.[8] Based on this method, activated fluorinated thioesters act as nucleophiles and react with aromatic aldehydes, leading to the formation of β-hydroxy thioesters in good yield and high diastereo- and enantioselectivity, up to 95% ee (Scheme 1, a).

Before our contribution, the use of activated fluorinated thioesters[9] or malonic acid half thioesters[10] as ester mimics was limited only to a few examples of nonstereoselective Mannich transformations and enantioselective Michael-type reactions, and no examples of direct aldol-type reaction were known. On the other hand, a few examples of organocatalytic, nonstereoselective, direct aldol reaction with carboxylic acid derivatives were known.[11] In 2013, List and Song[12] reported an organocatalytic enantioselective decarboxylative aldol reaction of malonic acid half thioesters with aldehydes using a cinchona-based sulfonamide, and very recently Wang[13] reported an enantioselective cascade reaction between α,β-unsaturated aldehydes and malonic half thioesters for the synthesis of chiral δ-lactones promoted by a prolinol-derived catalyst.

The use of activated fluorinated thioesters rather than malonic half thioesters offers the possibility to obtain highly functionalized products with more efficient atom econo-



Scheme 1 Direct aldol reaction of thioesters with aromatic aldehydes catalyzed by phosphine oxides

my through a straightforward procedure. Despite its potentiality, the direct aldol reaction of thioesters suffers mainly from two drawbacks: (1) trifluoroethanethiol used to synthetize the thioester is expensive and (2) the presence of an aryl group at the α-position is necessary to activate the substrate and make the organocatalytic approach feasible.

The possibility to use cheaper and more environmentally friendly starting materials for this fundamental transformation is of course very attractive; we now wish to report the results of our investigation on the use of simple, easily available thioester substrates in the organocatalytic direct aldol reaction (Scheme 1, b).

In order to extend the applicability of the direct aldol reaction of thioesters with aldehydes, the substitution of the activating trifluoroethylthio moiety with other substituents was performed, taking into consideration the reactivity scale depicted in Figure 1.[9b,14]

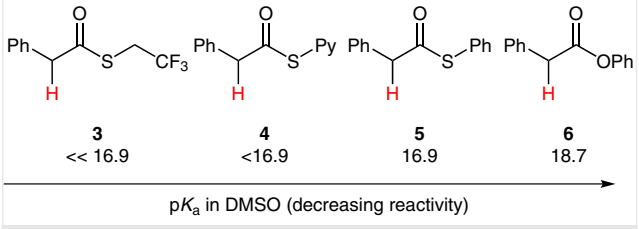
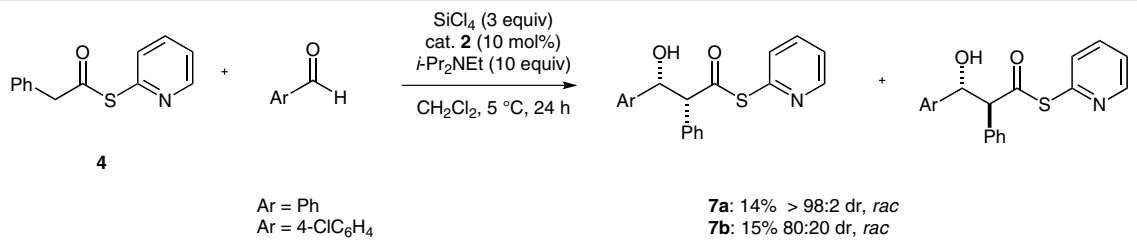


Figure 1 pK_a values of the α-protons of carboxylic acid derivatives in DMSO[9b,14]

It is known that esters are generally unreactive in organocatalysis due to the relatively low acidity of the proton at the α-position of the ester function (pK_a = 18.7 for compound **6**), and can be activated only by the presence of strong electron-withdrawing groups (as the SCH_2CF_3 group for compound **3**). However, no information is reported about the reactivity of compounds **4** and **5** as potential nucleophiles in direct aldol addition reaction catalyzed by Lewis bases and promoted by silicon tetrachloride.

Following this approach, the *S*-(3,3,3-trifluoro)ethyl group of **3** was initially replaced with an *S*-pyridin-2-yl moiety. Thioester **4** was synthesized and employed in the direct aldol reaction with aromatic aldehydes in the presence of 3 equivalents of $SiCl_4$, 10 equivalents of *i*-Pr_2NEt and 10 mol% of (*R*)-BINAPO at 5 °C in CH_2Cl_2 as solvent (Scheme 2).

Disappointingly, β-hydroxy thioesters **7a**,**b** were obtained with high diastereoselectivity, but in very low yields and no enantioselectivity. Hypothesizing that these unsatisfactory results could derive from the coordination of the pyridyl residue of the substrate to $SiCl_4$ (causing a competitive interference with the formation of the catalytic hypervalent species),[15] we envisioned that the replacement of the *S*-pyridin-2-yl moiety with the *S*-phenyl moiety could avoid this competitive coordination process. Thioester **5** was then synthesized in 80% yield by reaction of acyl chloride with thiophenol and reacted with benzaldehyde, in the presence of catalytic amounts of chiral phosphine oxide, under standard reaction conditions.[16] Selected results are reported in Table 1.



Scheme 2 Direct aldol reaction of pyridin-2-yl thioester with aromatic aldehydes

The reaction promoted by (*R*)-BINAPO (**1**) led to the formation of the β-hydroxy thioester **8a** in 70% yield, 66:34 *syn*/*anti* ratio, and 27% ee for the *syn*-enantiomer (Table 1, entry 1). Lowering the temperature decreased the yield, but improved the enantioselection (entries 1 vs 2 and 3 vs 4). In addition, these preliminary studies confirmed that catalyst, (*S*)-TetraMe-BITIOPO (**2**), catalyzes the reaction with better chemical and stereochemical efficiency than (*R*)-BINAPO (**1**), even if this difference could be observed only at lower temperature.[8a] Notably, at 0 °C, the electron-rich dithiophene phosphine oxide **2** was able to promote the addition of the readily available *S*-phenyl thioester of phenylacetic acid **5** to benzaldehyde with good *syn* selectivity and 74% enantioselectivity for the major isomer (entry 4). Considering the small difference in terms of reactivity of the two catalysts, we decided to employ phosphine oxide **2** in the survey of direct aldol addition of thioester **5** to substituted aromatic aldehydes.

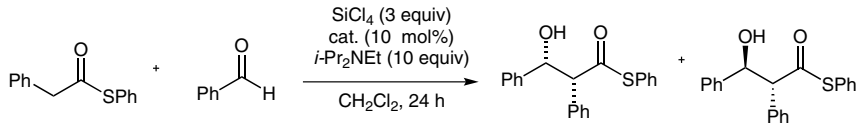
Aldehydes bearing electron-donating groups afforded products with higher levels of diastereo- and enantioselectivity than electron-poor aldehydes. In addition, diastereoselection seems to be influenced by steric characteristics of the substrates: *ortho*-substituted aldehydes lead to the formation of corresponding β-hydroxy thioesters with *syn*/*anti* ratio ranging from 91:9 to >99:1, even if in lower yields (Table 2, entries 6, 8, 9, 12).

The temperature plays an important role for the chemical and stereochemical outcome of the reaction: lowering the temperature increases the value of enantiomeric excess, but depresses the yield, and only with 20 mol% of catalyst **2** satisfactory results were obtained (Table 2, entry 3). Considering that yields are modest at 0 °C, no further attempts were performed in terms of temperature variation.

3-Methylbenzaldehyde afforded the hydroxy thioester **8e** in 80% yield, modest diastereoselectivity and 73% ee for the *syn*-diastereosiomer (Table 2, entry 7). 4-Trifluoromethylbenzaldehyde gave the product **8i** in 76% yield and 41% ee (entry 11), while the analogous 4-fluoro derivative **8h** was isolated in 59% yield and 68% ee (entry 10).

Heteroaromatic aldehydes were also investigated and proved to be suitable substrates for the present method; product **8n** derived by furfural was obtained in 76% yield, 84:16 *syn*/*anti* ratio and with 92% enantiomeric excess for the *syn*-distereoisomer. Finally, this method was applied to aliphatic aldehydes: as expected, no product was obtained with isobutyraldehyde (Table 2, entry 15), confirming that

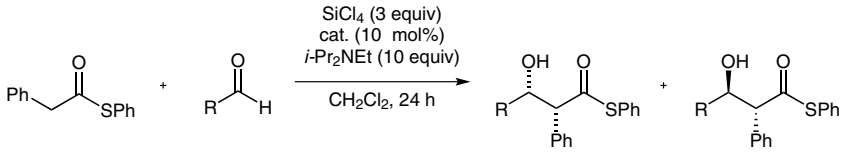
Table 1 Aldol Condensation between Thioester **5** and Benzaldehyde



Entry	Catalyst	Temp (°C)	Yield (%)[a]	*syn*/*anti*[b]	*syn* ee (%)[c]	*anti* ee (%)[c]
1	(*R*)-**1**	r.t.	70	66:34	27 (2*R*,3*R*)	60 (2*R*,3*S*)
2	(*R*)-**1**	0	33	69:31	30 (2*R*,3*R*)	68 (2*R*,3*S*)
3	(*S*)-**2**	r.t.	67	41:59	22 (2*S*,3*S*)	16 (2*S*,3*R*)
4	(*S*)-**2**	0	62	71:29	74 (2*S*,3*S*)	68 (2*S*,3*R*)
5[d]	(*S*)-**2**	0	47	74:26	50 (2*S*,3*S*)	73 (2*S*,3*R*)

[a] Yields were determined after chromatographic purification.
[b] Diastereoisomeric ratio was determined on the crude reaction product by ^{1}H NMR spectroscopy and confirmed by HPLC.
[c] The ee value was determined by HPLC on a chiral column.
[d] 1 equiv of thioester was used.

Table 2 Aldol Condensation between Thioester **5** and Different Aldehydes

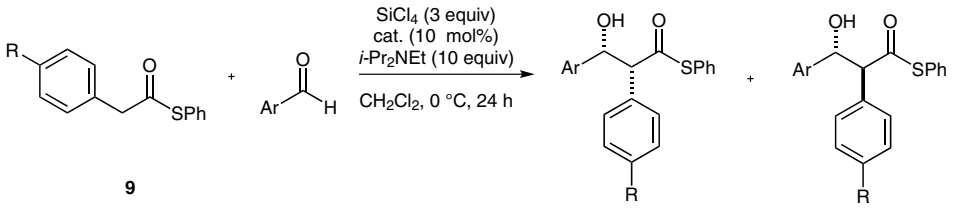


5 **8**-*syn* **8**-*anti*

Entry	R	Catalyst	Temp (°C)	Product	Yield (%)[a]	*syn*/*anti*[b]	*syn* ee (%)[c]	*anti* ee (%)[c]
1	4-MeOC$_6$H$_4$	(*R*)-**1**	r.t.	**8b**	41	62:38	7 (2*R*,3*R*)	17 (2*R*,3*S*)
2	4-MeOC$_6$H$_4$	(*R*)-**1**	0	**8b**	27	80:20	50 (2*R*,3*R*)	69 (2*R*,3*S*)
3[d]	4-MeOC$_6$H$_4$	(*S*)-**2**	0	**8b**	69	82:18	53 (2*S*,3*S*)	66 (2*S*,3*R*)
4	4-ClC$_6$H$_4$	(*R*)-**1**	r.t.	**8c**	66	65:35	6 (2*R*,3*R*)	11 (2*R*,3*S*)
5	4-ClC$_6$H$_4$	(*R*)-**1**	0	**8c**	45	58:42	6 (2*R*,3*R*)	35 (2*R*,3*S*)
6	2-MeC$_6$H$_4$	(*S*)-**2**	0	**8d**	35	92:8	69 (2*S*,3*S*)	75 (2*S*,3*R*)
7	3-MeC$_6$H$_4$	(*S*)-**2**	0	**8e**	80	67:33	73 (2*S*,3*S*)	66 (2*S*,3*R*)
8	2,4,6-Me$_3$C$_6$H$_2$	(*S*)-**2**	0	**8f**	58	>99:1	48 (2*S*,3*S*)	–
9	2,6-(MeO)$_2$ C$_6$H$_3$	(S)-**2**	0	**8g**	61	92:8	91 (2*S*,3*S*)	54 (2*S*,3*R*)
10	4-FC$_6$H$_4$	(*S*)-**2**	0	**8h**	59	69:31	68 (2*S*,3*S*)	65 (2*S*,3*R*)
11	4-CF$_3$C$_6$H$_4$	(*S*)-**2**	0	**8i**	76	75:25	41 (2*S*,3*S*)	15 (2*S*,3*R*)
12	2-NO$_2$C$_6$H$_4$	(*S*)-**2**	0	**8l**	67	91:9	29 (2*S*,3*S*)	nd
13	1-naphthyl	(*S*)-**2**	0	**8m**	44	69:31	51 (2*S*,3*S*)	82 (2*S*,3*R*)
14	2-furyl	(S)-**2**	0	**8n**	76	84:16	92 (2*S*,3*S*)	66 (2*S*,3*R*)
15	*i*-Pr	(*S*)-**2**	0	**8o**	–	–	–	–

[a] Yields were determined after chromatographic purification.
[b] Diastereoisomeric ratio was determined on the crude reaction product by ^{1}H NMR spectroscopy and confirmed by HPLC.
[c] The ee value was determined by HPLC on a chiral column.
[d] 1 equiv of thioester was used.

Table 3 Aldol Condensation between Substituted Thioester and Different Aldehydes



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9a R = 4-F
9b R = 4-*i*-Bu

10-*syn* **10**-*anti*

Entry	R	Ar	Catalyst	Product	Yield (%)[a]	*syn*/*anti*[b]	*syn* ee (%)[c]	*anti* ee (%)[c]
1	F	Ph	(*R*)-**1**	**10a**	44	66:34	70 (2*R*,3*R*)	13 (2*R*,3*S*)
2	F	Ph	(*S*)-**2**	**10a**	29	46:54	64 (2*S*,3*S*)	63 (2*S*,3*R*)
3	*i*-Bu	Ph	(*R*)-**1**	**10b**	46	73:27	22 (2*R*,3*R*)	50 (2*R*,3*S*)
4	*i*-Bu	Ph	(*S*)-**2**	**10b**	47	61:39	87 (2*S*,3*S*)	43 (2*S*,3*R*)
5	*i*-Bu	4-MeOC$_6$H$_4$	(*S*)-**2**	**10c**	43	83:17	85 (2*S*,3*S*)	71 (2*S*,3*R*)
6	*i*-Bu	4-ClC$_6$H$_4$	(*S*)-**2**	**10d**	59	87:13	65 (2*S*,3*S*)	39 (2*S*,3*R*)

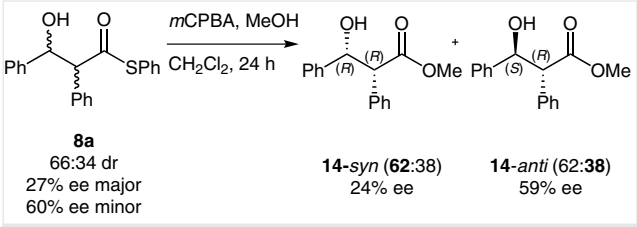
[a] Yields were determined after chromatographic purification.
[b] Diastereoisomeric ratio was determined on the crude reaction product by ^{1}H NMR spectroscopy and confirmed by HPLC.
[c] The ee value was determined by HPLC on a chiral column.

aliphatic aldehydes are less reactive in Lewis base catalyzed reactions.[17]

On the basis of these results we focused our attention on the use of substituted *S*-phenyl thioesters of arylacetic acids **9a**,**b** as substrates in the direct aldol reaction promoted by phosphine oxides (Table 3).

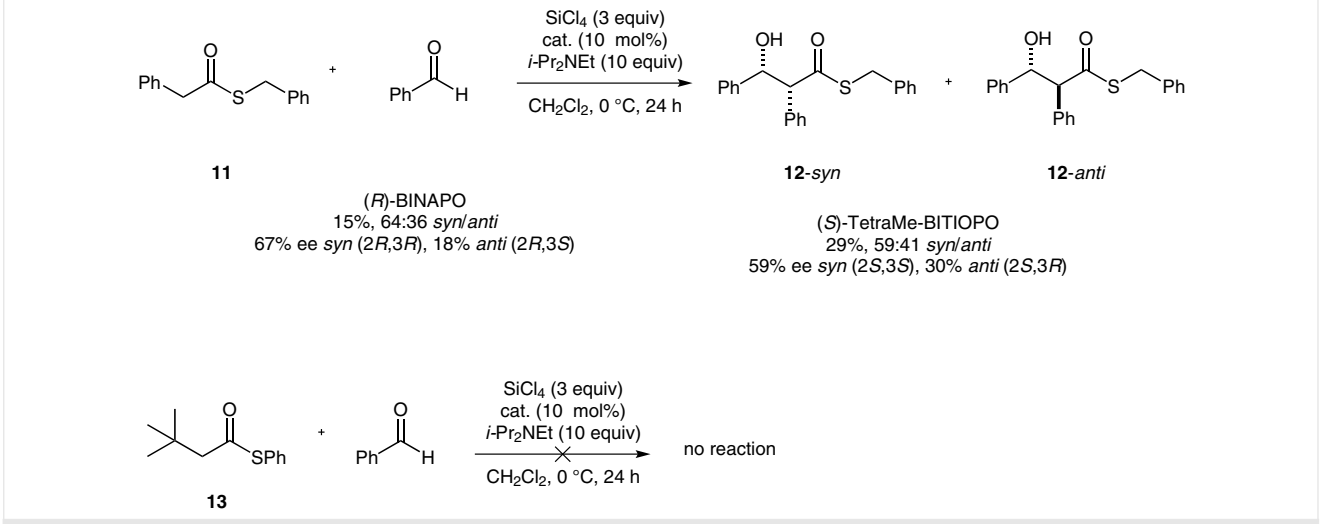
These results showed that starting from 4-fluorophenyl substituted thioester **9a**, β-hydroxy thioester **10a** was formed in 44% yield, 66:34 of *syn*/*anti* ratio, and 70% of enantiomeric excess for the *syn*-diastereoisomer using (*R*)-BINAPO (**1**) as catalyst (Table 3, entry 1). Comparable enantioselectivity was obtained using (*S*)-TetraMe-BITIOPO (**2**), even if with no diastereoselection (entry 2). Interestingly, thioester **9b** reacts with benzaldehyde to give **10b** in comparable yields in the presence of (*R*)-BINAPO (**1**) and (*S*)-TetraMe-BITIOPO (**2**). However, aldol products were obtained in higher enantioselectivity when phosphine oxide **2** was used (entry 3 vs 4); thus with **2** a remarkable level of enantioselectivity was reached (87% ee, entry 4,) The same high enantioselectivity was observed in the reaction with an electron-rich aldehyde (85% ee, entry 5), while the combination of thioesters **9b** with electron-poor aldehydes gave β-hydroxy thioesters in higher yield and diastereoselection, but lower enantiocontrol (entry 6). This method was further successfully extended to less reactive thioesters, such as *S*-benzyl 2-phenylethanethioate (**11**). In this case, the formation of the corresponding β-hydroxy thioesters **12** could be achieved in modest diastereo- and enantioselectivity and in low yields. No product was observed instead when *S*-phenyl 3,3-dimethylbutanethioate (**13**) was used. Therefore, the reaction was not further studied in detail (Scheme 3).

The relative configuration of β-hydroxy thioesters **8** was established by converting the *syn*/*anti* mixture of product **8a** (Table 1, entry 1) into the corresponding *syn*/*anti* mixture of the known β-hydroxy methyl ester **14** by reaction with *m*-CPBA and methanol in CH_2Cl_2 (Scheme 4).[18] The *syn*/*anti* ratio was assigned on the basis of the methoxy groups signals in the ^1H NMR spectrum of the crude mixture. The **14**-*syn* and **14**-*anti* compounds were then separated by chromatographic purification, and the absolute configuration was determined to be 2*R*,3*R* for the major *syn* enantiomer and 2*R*,3*S* for the major *anti* enantiomer by comparison of the optical rotation values with those reported in literature.[19] The configuration of the other compounds was assigned by analogy.

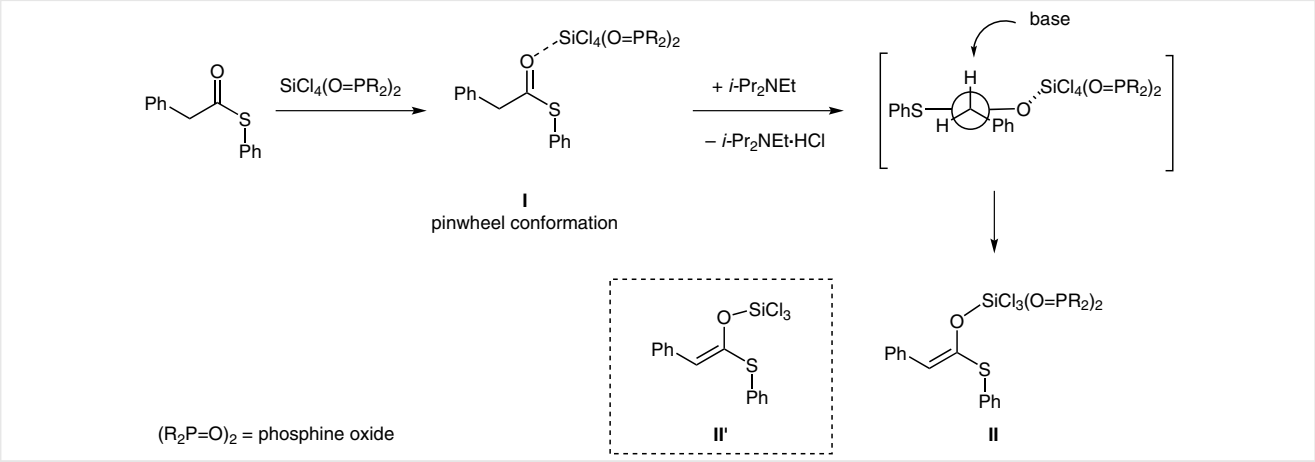


Scheme 4 Determination of relative and absolute configuration of β-hydroxy thioester **8**

After the absolute configuration was determined, simple computational calculations were performed in order to elucidate the origin of stereoselectivity. The reaction between thioester **5** and benzaldehyde in the presence of tetrachlorosilane promoted by catalyst **2** was computationally studied. On the basis of steric considerations, adduct **I**, formed upon coordination of thioester **5** with the chlorosilane species, will adopt a 'pinwheel' conformation to minimize the repulsion between bulky peripheral groups.[20]



Scheme 3 Aldol condensation of *S*-benzyl thioester

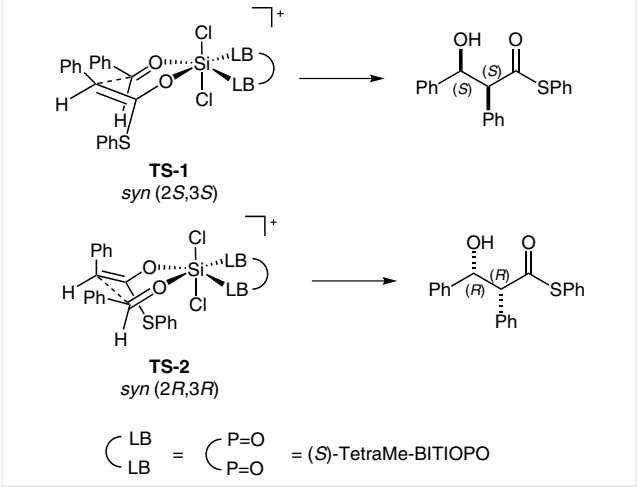


Scheme 5 Formation of the *O*-silyl ketene thioacelal derived from compound **5**

Deprotonation with a bulky base such as *i*-Pr_2NEt will afford the *O*-silyl ketene thioacetal **II**. In agreement with experimental observations, DFT calculations at B3LYP-631g level of theory confirmed that (*E*)-trichlorosilyl thioacetal **II′** (according to CIP rules) was more stable by 2.48 kcal/mol than the corresponding *Z*-isomer (Scheme 5).

From ketene thioacetal **II**, the formation of the aldol product is expected to occur via a Zimmerman–Traxler cationic chair-like transition structure[21] where the aldehyde is coordinated – and, thus, activated – by the positively charged silicon atom (Scheme 6). The two transition states (TSs) responsible of the formation of *syn*-β-hydroxy thioesters were located and depicted in Scheme 6. Computationally, a conformational analysis with Monte Carlo technique was performed using MMFFs as force field with Macromodel Schrodinger suite package[22] on a model of the TSs, obtained by constraining the two reacting atoms (the aldehyde electrophilic carbon and the *O*-silyl thioketene acetal nucleophilic α-carbon) at about 2.3 Å distance. In this way, the best arrangement for the different substituents around a model of the reaction moiety was obtained.

Subsequently, the two structures leading to the formation of the two *syn* products, were fully optimized to the relative genuine TSs with PM6 semiempirical methods (both with only one imaginary frequency).[23] The calculations, performed using (*S*)-TetraMe-BITIOPO as catalyst, showed that **TS-1**, responsible of the formation of *syn*-(2*S*,3*S*)-diastereoisomer, was more stable by 0.40 kcal/mol than **TS-2**. A possible explanation of these slight differences in energy could be ascribed to the steric repulsions, observed in **TS-2** between diphenylphosphinoyl group of the phosphine oxide **2** and the thiophenyl group of the *O*-silyl



Scheme 6 Transition states responsible for the *syn*-stereoselection

ketene thioacetal that would be responsible for the favorable attack of the thioacetal onto the *Si* face of the aldehyde (Figure 2).

In conclusion, a direct, organocatalytic addition of readily available thioesters to aldehydes catalyzed by a chiral cationic hypervalent silicon species has been developed. The reaction of *S*-phenyl α-arylthioesters with aromatic aldehydes in the presence of a catalytically amount of a chiral phosphine oxide and a stoichiometric amount of tetrachlorosilane led to the formation of the corresponding β-hydroxy thioesters in modest yields (up to 70%), good *syn*/*anti* ratio (up to 82:18), and in up to 87% enantiomeric excess. Further experiments are ongoing in our group to extend the applicability of this method, as well as to improve the chemical efficiency of this transformation.

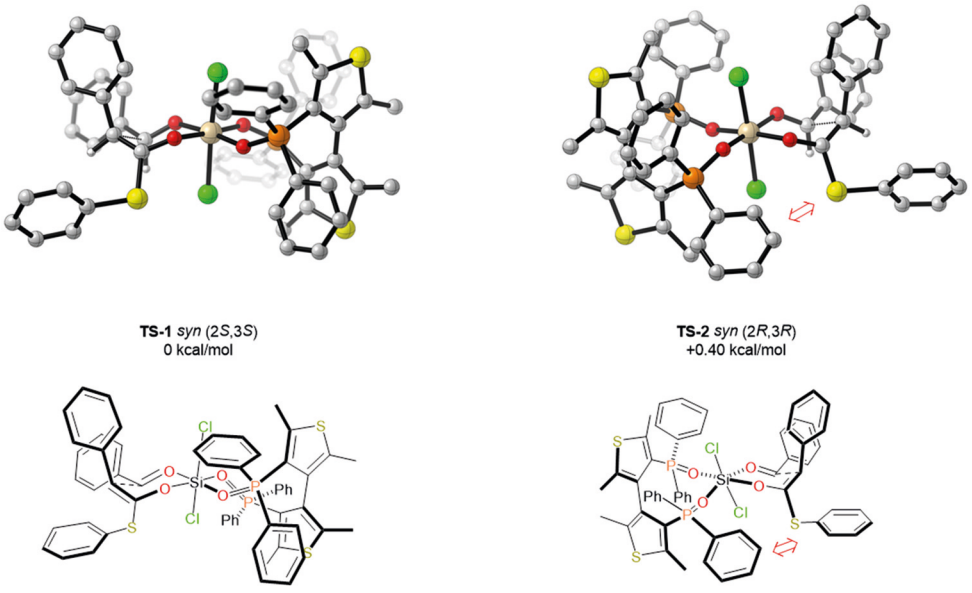


Figure 2 Calculated transition state geometries (hydrogens are omitted for clarity)

All reactions were carried out in oven-dried glassware with magnetic stirring under a nitrogen atmosphere, unless otherwise stated. Anhydrous 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 using UV light or with phosphomolybdic acid. ^{1}H NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300). The ^{1}H NMR chemical shifts are reported in ppm (δ) with the solvent reference relative to TMS as the internal standard ($CDCl_3$, δ = 7.26). ^{13}C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, with complete proton decoupling. ^{13}C NMR chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0). ^{19}F NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 282 MHz. ^{19}F NMR chemical shifts are reported in ppm (δ) relative to CF_3Cl. 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. All melting points are uncorrected and were obtained using an Electrothermal IA9100 digital melting point apparatus.

Thioester Condensation; General Procedure

The acid (1 equiv, 2.5 mmol) and thiophenol (1.1 equiv, 2.75 mmol) were dissolved in anhydrous THF (5 mL) and cooled to 0 °C; then *N*,*N*′-dicyclohexylcarbodiimide (DCC; 1 equiv, 2.5 mmol) was added. The reaction was monitored by TLC (eluent: using hexane–EtOAc, 95:5) and after 24 h, the crude mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography.

S-Phenyl 2-(4-Fluorophenyl)ethanethioate (9a)

2-(4-Fluorophenyl)acetic acid (385.3 mg, 2.5 mmol, 1 equiv), thiophenol (303.0 mg, 2.75 mmol, 1.1 equiv), DCC (515.8 mg, 2.5 mmol, 1 equiv), and anhydrous THF (5 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (96:4) as eluent; yield: 603.4 mg (98%); white solid; mp 35 °C; R_f = 0.35 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (s, 5 H), 7.28 (t, *J* = 9.0 Hz, 2 H), 7.06 (t, *J* = 9.0 Hz, 2 H), 3.89 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.2, 162.4 (d, *J* = 246.3 Hz), 134.5, 131.4, 131.3, 129.6, 129.3, 129.2, 127.7, 115.8, 115.5, 49.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –115.35.

MS (ESI+): *m*/*z* = 247.2 $[M + H]^+$.

S-Phenyl 2-(4-Isobutylphenyl)ethanethioate (9b)

2-(4-Isobutylphenyl)acetic acid (480.6 mg, 2.5 mmol, 1 equiv), thiophenol (303.0 mg, 2.75 mmol, 1.1 equiv), DCC (515.8 mg, 2.5 mmol, 1 equiv), and anhydrous THF (5 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (98:2) as eluent; yield: 604.4 mg (85%); pale-yellow solid; mp 30 °C; R_f = 0.51 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.38 (m, 5 H), 7.24 (d, *J* = 7.9 Hz, 2 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 3.89 (s, 2 H), 2.48 (d, *J* = 7.2 Hz, 2 H), 1.94–1.80 (m, 1 H), 0.91 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6, 141.1, 134.5, 130.6, 129.4, 129.5, 129.4, 129.2, 128.0, 49.8, 45.2, 30.3, 22.5.

MS (ESI+): *m*/*z* = 285.2 $[M + H]^+$ and 307.0 $[M + Na]^+$.

Enantioselective Direct Aldol Reaction between Thioesters and Aldehydes; General Procedure

To a stirred solution of catalyst **1** or **2** (0.1 equiv) in CH_2Cl_2 (2 mL) were added the thioester (0.6 mmol, 2 equiv) and *i*-Pr_2NEt (6 mmol, 10 equiv). The mixture was then cooled to 0 °C and freshly distilled

$SiCl_4$ (0.9 mmol, 3 equiv) was added dropwise via syringe. After 15 min, freshly purified aldehyde (0.3 mmol, 1 equiv) was added. The mixture was stirred for 24 h, then quenched by the addition of sat. aq $NaHCO_3$ (3 mL). The mixture was allowed to warm up to r.t., stirred for 30 min, and partitioned between H_2O (5 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were washed with sat. aq NH_4Cl (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum at r.t. The crude product was purified by column chromatography with 9:1 hexane–EtOAc mixture as eluent (see below) to afford the pure aldol adducts. Yields and ee for each reaction are indicated in Tables 1–3. The *syn*/*anti* ratio was determined by ^{1}H NMR spectroscopy of the crude product; the enantiomeric excess was determined by HPLC on a chiral stationary phase.

S-(Pyridin-2-yl) 3-Hydroxy-2,3-diphenylpropanethioate (7a)

Thioester **4** (137 mg, 0.6 mmol, 2 equiv), catalyst **2** (19 mg, 0.03 mmol, 0.1 equiv), benzaldehyde (32 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (7:3) as eluent. This purification furnished only one diastereoisomer; yield: 14.1 mg (14%); yellow solid; mp 38–40 °C; R_f = 0.48 (hexane–EtOAc, 6:4, stained with phosphomolybdic acid).

HPLC: Chiralcel OD-H; eluent: hexane–*i*-PrOH (85:15); flux: 0.8 mL/min; detection: 230 nm; t_R = 24.0 min, t_R = 30.6 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 4.4 Hz, 1 H) 7.72 (t, *J* = 7.7 Hz, 1 H), 7.60 (d, *J* = 7.7 Hz, 1 H), 7.35–7.08 (m, 11 H), 5.31 (d, *J* = 9.3 Hz, 1 H), 4.20 (d, *J* = 9.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 151.2, 150.3, 140.5, 137.5, 137.3, 134.2, 130.1, 129.0, 128.7, 128.1, 127.9, 126.6, 123.7, 77.2, 68.4.

MS (ESI+): *m*/*z* = 358.2 $[M + Na]^+$.

S-(Pyridin-2-yl) 3-(4-Chlorophenyl)-3-hydroxy-2-phenylpropanethioate (7b)

Thioester **4** (137 mg, 0.6 mmol, 2 equiv), catalyst **2** (19 mg, 0.03 mmol, 0.1 equiv), 4-chlorobenzaldehyde (42 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (7:3) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 16.7 mg (15%); pale-yellow solid; mp 40–43 °C; R_f = 0.21 (hexane–EtOAc, 6:4, stained with phosphomolybdic acid).

HPLC: The two diastereoisomers were separated on Supelco Ascentis Si column (3u) with hexane–*i*-PrOH (95:5) (t_R = 8.87 min, for minor diasteroisomer, t_R = 9.07 min, for major diastereoisomer). The enantiomeric excess of each separated diastereoisomer was determined on Chiralpak AD column; eluent: hexane–*i*-PrOH (7:3); flux: 0.8 mL/min; detection: 220 nm; t_R = 13.3 min, t_R = 18.2 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 4.4 Hz, 1 H, major), 8.45 (d, *J* = 3.1 Hz, 1 H, minor), 7.70 (t, *J* = 7.7 Hz, 1 H, minor), 7.59 (t, *J* = 6.8 Hz, 1 H, major), 7.31–6.94 (m, 11 H), 5.29 (d, *J* = 6.3 Hz, 1 H, major), 5.28 (d, *J* = 3.1 Hz, 1 H, minor), 4.13 (d, *J* = 5.2 Hz, 1 H, minor), 4.10 (d, *J* = 3.0 Hz, 1 H, major).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 150.3, 149.5, 139.0, 137.5, 133.9, 133.6, 130.2, 129.0, 128.9, 128.7, 128.3, 128.6, 128.0, 123.8, 121.2, 119.8, 76.0, 68.3.

MS (ESI+): *m*/*z* = 392.1 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-2,3-diphenylpropanethioate (8a)

Thioester **5** (137 mg, 0.6 mmol, 2 equiv), catalyst **1** (18 mg, 0.03 mmol, 0.1 equiv), benzaldehyde (32 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 70.2 mg (70%); white solid; mp 107–109 °C; R_f = 0.14 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Chiralcel OD-H; eluent: hexane–*i*-PrOH (93:7); flux: 0.8 mL/min; detection: 230 nm; (2*S*,3*R*)-*anti*-enantiomer, t_R = 19.7 min; (2*S*,3*S*)-*syn*-enantiomer, t_R = 22.8 min; (2*R*,3*S*)-*anti*-enantiomer, t_R = 27.1 min; (2*R*,3*R*)-*syn*-enantiomer, t_R = 29.8 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.08 (m, 15 H), 5.38 (d, *J* = 8.0 Hz, 1 H, *syn*), 5.31 (d, *J* = 9.0 Hz, 1 H, *anti*), 4.21 (d, *J* = 9.0 Hz, 1 H, *anti*), 4.16 (d, *J* = 8.0 Hz, 1 H, *syn*), 3.00 (br, 1 H, *syn*) 2.48 (br, 1 H, *syn*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1 (*anti*), 197.7 (*syn*), 140.6, 140.5, 134.5, 134.4, 134.3, 134.2, 129.6, 129.4, 129.2, 129.1, 128.9, 128.8, 128.7, 128.3, 128.1, 127.9, 126.8, 126.6, 75.4, 67.7.

MS (ESI+): *m*/*z* = 357.2 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-3-(4-methoxyphenyl)-2-phenylpropanethioate (8b)

Thioester **5** (137 mg, 0.6 mmol, 2 equiv), catalyst **2** (19 mg, 0.03 mmol, 0.1 equiv), 4-methoxybenzaldehyde (41 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 75.5 mg (69%); white solid, mp 36–39 °C; R_f = 0.07 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Chiralcel AS-3; eluent: hexane–*i*-PrOH (8:2); flux: 0.8 mL/min; detection: 230 nm; *anti*-enantiomer, t_R = 12.8 min; *syn*-enantiomer, t_R = 14.9 min; *anti*-enantiomer, t_R = 17.8 min; *syn*-enantiomer, t_R = 30.9 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.11 (m, 10 H), 7.26 (d, *J* = 7.5 Hz, 2 H, *syn*), 7.15 (d, *J* = 7.5 Hz, 2 H, *anti*), 6.87 (d, *J* = 7.5 Hz, 2 H, *syn*), 6.71 (d, *J* = 7.5 Hz, 2 H, *anti*), 5.29 (d, *J* = 8.0 Hz, 1 H, *syn*), 5.23 (d, *J* = 8.0 Hz, 1 H, *anti*), 4.15 (d, *J* = 9.0 Hz, 1 H, *anti*), 4.12 (d, *J* = 9.0 Hz, 1 H, *syn*), 3.81 (s, 3 H, *syn*), 3.73 (s, 3 H, *anti*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 159.4, 134.5, 134.4, 132.7, 129.6, 129.4, 129.2, 128.8, 128.7, 128.3, 128.1, 127.8, 127.2, 113.7, 113.5, 75.1, 67.8, 55.3.

MS (ESI+): *m*/*z* = 387.2 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-3-(4-chlorophenyl)-2-phenylpropanethioate (8c)

Thioester **5** (137 mg, 0.6 mmol, 2 equiv), catalyst **1** (18 mg, 0.03 mmol, 0.1 equiv), 4-chlorobenzaldehyde (42 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 73.1 mg (66%); white solid; mp 134–136 °C; R_f = 0.10 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Chiralcel AS-3; eluent: hexane–*i*-PrOH (8:2); flux: 0.8 mL/min; detection: 230 nm; *anti*-enantiomer, t_R = 9.1 min; *anti*-enantiomer, t_R = 9.8 min; *syn*-enantiomer, t_R = 10.4 min; *syn*-enantiomer, t_R = 16.4 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–6.99 (m, 14 H), 5.36 (d, *J* = 7.0 Hz, 1 H, *syn*), 5.27 (d, *J* = 9.1 Hz, 1 H, *anti*), 4.12 (d, *J* = 9.0 Hz, 1 H, *anti*), 4.10 (d, *J* = 7.0 Hz, 1 H, *syn*), 3.07 (d, *J* = 3.8 Hz, 1 H, *anti*), 2.57 (d, *J* = 2.3 Hz, 1 H, *syn*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1 (*anti*), 197.8 (*syn*), 139.2, 134.5, 134.4, 133.6, 129.7, 129.5, 129.3, 128.9, 128.8, 128.5, 128.3, 128.1, 128.0, 127.3, 76.1 (*anti*), 74.6 (*syn*), 67.7 (*anti*), 67.4 (*syn*).

MS (ESI+): *m*/*z* = 391.1 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-2-phenyl-3-(2-methylphenyl)propanethioate (8d)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), 2-methylbenzaldehyde (24 mg, 0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 24.7 mg (35%); pale-yellow solid; mp 30–32 °C; R_f = 0.14 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Chiralcel OD-H; eluent: hexane–*i*-PrOH (9:1); flux: 0.8 mL/min; detection: 254 nm; *syn*-enantiomer, t_R = 10.6 min; *anti*-enantiomer, t_R = 12.3; *syn*-enantiomer; t_R = 13.4 min; *anti*-enantiomer, t_R = 14.4 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.31 (m, 8 H), 7.31–7.00 (m, 7 H), 5.62 (d, *J* = 6.8 Hz, 1 H, *anti*), 5.55 (d, *J* = 8.8 Hz, 1 H, *syn*), 4.32 (d, *J* = 8.8 Hz, 1 H, *syn*), 4.26 (d, *J* = 6.8 Hz, 2 H, *anti*), 2.47 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7, 138.4, 135.0, 134.3, 130.4, 129.6, 129.1, 128.7, 128.2, 127.9, 127.2, 126.9, 126.1, 71.6, 65.9, 19.4.

MS (ESI+): *m*/*z* = 371.1 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-2-phenyl-3-(3-methylphenyl)propanethioate (8e)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), 3-methylbenzaldehyde (24 mg, 0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 56.0 mg (80%); pale-yellow solid; mp 33–35 °C; R_f = 0.13 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Phenomenex Lux-3u cellulose-2; eluent: hexane–*i*-PrOH (95:5); flux: 0.8 mL/min; detection: 210 nm; *syn*-enantiomer, t_R = 3.7 min; *syn*-enantiomer, t_R = 5.5 min; *anti*-enantiomer, t_R = 7.1 min; *anti*-enantiomer, t_R = 8.5 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–6.88 (m, 15 H, *syn* + *anti*), 5.34 (d, *J* = 7.6 Hz, 1 H, *syn*), 5.26 (d, *J* = 9.0 Hz, 1 H, *anti*), 4.21 (d, *J* = 9.0 Hz, 1 H, *syn*), 4.16 (d, *J* = 7.6 Hz, 1 H, *anti*), 2.38 (s, 3 H, *syn*), 2.27 (s, 3 H, *anti*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.0 (*anti*), 197.5 (*syn*), 140.5, 140.4, 137.9, 137.7, 134.5, 134.4, 134.2, 129.5, 129.4, 129.2, 129.1, 128.9, 128.8, 128.6, 128.2, 127.9, 127.8, 127.5, 127.2, 123.9, 123.7, 75.5, 67.7, 21.4.

MS (ESI+): *m*/*z* = 371.1 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-3-(mesityl)-2-phenylpropanethioate (8f)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), mesitaldehyde (30 mg, 0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished only the *syn*-diastereoisomer; yield: 44.0 mg (58%); pale-yellow solid; mp 57–60 °C; R_f = 0.16 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Phenomenex Lux-3u cellulose-1 equipped with security guard filter; eluent: hexane–*i*-PrOH (95:5); flux: 0.8 mL/min; detection: 210 nm; *syn*-minor enantiomer, t_R = 4.51 min; *syn*-major enantiomer, t_R = 0 6.1 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.1 Hz, 2 H), 7.50–7.21 (m, 6 H), 7.04 (d, *J* = 6.9 Hz, 2 H), 6.92 (s, 2 H), 5.72 (d, *J* = 9.3 Hz, 1 H), 4.68 (d, *J* = 9.4 Hz, 1 H), 2.55 (s, 6 H), 2.33 (s, 3 H), 1.88 (br, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.3, 137.5, 137.1, 135.6, 134.3, 132.8, 130.3, 129.4, 129.1, 129.0, 128.2, 127.4, 73.0, 64.5, 20.9.

MS (ESI+): *m*/*z* = 399.1 $[M + Na]^+$.

S-Phenyl 3-(2,6-Dimethoxyphenyl)-3-hydroxy-2-phenylpropanethioate (8g)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), 2,6-dimethoxybenzaldehyde (33 mg, 0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 48.4 mg (61%); pale-yellow solid; mp 77–80 °C; R_f = 0.10 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Phenomenex Lux-3u cellulose-2; eluent: hexane–EtOH (65:35); flux: 0.8 mL/min; detection: 230 nm; *syn*-enantiomer, t_R = 8.3 min; *syn*-enantiomer, t_R = 10.1 min; *anti*-enantiomer, t_R = 10.6 min; *anti*-enantiomer, t_R = 11.1 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 7.7 Hz, 2 H), 7.45–7.19 (m, 7 H), 7.10 (d, *J* = 7.4 Hz, 2 H), 6.62 (dd, *J* = 8.4, 2.6 Hz, 1 H), 5.90 (d, *J* = 7.9 Hz, 1 H), 4.56 (d, *J* = 8.2 Hz, 1 H), 3.83 (d, *J* = 2.4 Hz, 1 H), 2.07 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ =195.2, 158.2, 136.0, 134.4, 129.6, 129.4, 129.1, 128.9, 128.4, 127.6, 116.8, 104.4, 103.9, 69.3, 65.5, 55.9.

MS (ESI+): *m*/*z* = 417.1 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-3-(4-fluorophenyl)-2-phenylpropanethioate (8h)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), 4-fluorobenzaldehyde (25 mg, 0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 41.5 mg (59%); white solid; mp 92–95 °C; R_f = 0.11 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Chiralcel OD-H; eluent: hexane–*i*-PrOH (9:1); flux: 0.8 mL/min; detection: 210 nm; *anti*-enantiomer, t_R = 14.0 min; *syn*-enantiomer, t_R = 16.5 min; *anti*-enantiomer, t_R = 17.9 min; *syn*-enantiomer, t_R = 21.3 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.15 (m, 10 H), 7.15–7.03 (m, 2 H), 6.89 (t, *J* = 8.6 Hz, 1 H), 5.37 (d, *J* = 7.3 Hz, 1 H, *syn*), 5.29 (d, *J* = 9.2 Hz, 1 H, *anti*), 4.15 (d, *J* = 9.2 Hz, 1 H, *anti*), 4.11 (d, *J* = 7.3 Hz, 1 H, *syn*), 3.01 (br, 1 H, *anti*), 2.52 (br, 1 H, *syn*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1 (*anti*), 197.7 (*syn*), 162.7 (d, *J* = 228 Hz), 136.5, 136.3, 134.5, 134.4, 133.9, 129.7, 129.4, 129.2, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.0, 115.3, 115.1, 115.0, 114.8, 76.1, 74.7, 67.9, 67.7.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.5 (*syn*), –114.7 (*anti*).

MS (ESI+): *m*/*z* = 375.0 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-2-phenyl-3-[4-(trifluoromethyl)phenyl]propanethioate (8i)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), 4-(trifluoromethyl)benzaldehyde (35 mg, 0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 60.9 mg (76%); white solid; mp 110–112 °C; R_f = 0.11 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Phenomenex Lux-3u cellulose-1 equipped with securityguard filter; eluent: hexane–*i*-PrOH (95:5); flux: 0.8 mL/min; detection: 210 nm; *anti*-enantiomer, t_R = 9.4 min; *anti*-enantiomer, t_R = 12.1 min; *syn*-enantiomer, t_R = 14.8 min; *syn*-enantiomer, t_R = 27.8 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 2 H), 7.50–7.34 (m, 8 H), 7.22–7.13 (m, 3 H) 7.13–7.08 (m, 1 H), 5.46 (d, *J* = 6.8 Hz, 1 H, *syn*), 5.36 (d, *J* = 9.1 Hz, 1 H, *anti*), 4.13 (d, *J* = 9.1 Hz, 1 H, *anti*), 4.14 (d, *J* = 6.7 Hz, 1 H, *syn*), 3.17 (s, 1 H, *anti*), 2.68 (br, 1 H, *syn*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1 (*anti*), 197.9 (*syn*), 144.4, 134.5, 134.4, 134.1, 133.4, 130.4, 129.7, 129.5, 129.3, 128.9, 128.5, 128.2, 127.2, 126.9, 125.9, 125.0, 124 (q, *J* = 270 Hz), 76.1, 74.6, 67.5, 67.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.96 (*syn*), –62.98 (*anti*).

MS (ESI+): *m*/*z* = 425.1 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-3-(2-nitrophenyl)-2-phenylpropanethioate (8l)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), 2-nitrobenzaldehyde (30 mg, 0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 51.2 mg (67%); pale-yellow solid; mp 63–65 °C; R_f = 0.11 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Chiralcel OD-H; eluent: hexane–*i*-PrOH (9:1); flux: 0.8 mL/min; detection: 210 nm; minor enantiomer, t_R = 12.7 min; major enantiomer, t_R = 15.4 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*syn*) = 8.00 (dd, *J* = 6.0 Hz, 3.5 Hz, 1 H), 7.51–7.22 (m, 10 H), 7.10–7.13 (m, 3 H), 6.06 (d, *J* = 3.4 Hz, 1 H), 4.55 (d, *J* = 3.4 Hz, 1 H), 3.60 (br, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*syn*) = 200.3, 147.4, 135.5, 134.6, 132.9, 132.5, 130.3, 129.8, 129.3, 128.4, 128.4, 128.2, 126.9, 124.3, 69.7, 63.5.

MS (ESI+): *m*/*z* = 402.1 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-3-(naphthalen-1-yl)-2-phenylpropanethioate (8m)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), 1-naphthylaldehyde (0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 33.6 mg (44%); pale-yellow solid; mp 40–42 °C; R_f = 0.11 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Phenomenex Lux-3u cellulose-1 equipped with securityguard filter; eluent: hexane–EtOH (98:2); flux: 0.8 mL/min; detection: 210 nm; *syn*-enantiomer, t_R = 18.1 min; *syn*-enantiomer, t_R = 23.3 min; *anti*-enantiomer, t_R = 27.1 min; *anti*-enantiomer, t_R = 34.8 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.4 Hz, 1 H, *syn*), 8.18 (m, 1 H, *anti*), 7.94 (d, *J* = 7.7 Hz, 1 H, *syn*), 7.83–7.80 (m, 1 H, *syn* + *anti*), 7.76 (d, *J* = 7.7 Hz, 1 H), 7.68–7.20 (m, 12 H), 7.16–7.10 (m, 3 H), 6.23 (d, *J* = 5.6 Hz, 1 H, *syn*), 5.98 (d, *J* = 8.3 Hz, 1 H, *anti*), 4.68 (d, *J* = 8.3 Hz, 1 H, *anti*), 4.51 (d, *J* = 5.6 Hz, 1 H, *syn*), 3.31 (br, 1 H, *anti*), 2.91 (br, 1 H, *syn*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.4, 198.6, 135.6, 134.9, 134.5, 134.4, 133.8, 133.6, 129.8, 129.6, 129.2, 129.1, 128.8, 128.6, 128.5, 128.4, 128.1, 127.8, 126.3, 126.0, 125.5, 125.3, 125.2, 125.0, 123.5, 122.9, 75.0, 71.7, 65.8, 65.4.

MS (ESI+): *m*/*z* = 407.1 $[M + Na]^+$.

S-Phenyl 3-(Furan-2-yl)-3-hydroxy-2-phenylpropanethioate (8n)

Thioester **5** (91 mg, 0.4 mmol, 2 equiv), catalyst **2** (12 mg, 0.02 mmol, 0.1 equiv), furan-2-carbaldehyde (19 mg, 0.2 mmol, 1 equiv), *i*-Pr_2NEt (517 mg, 4 mmol, 10 equiv), $SiCl_4$ (102 mg, 0.6 mmol, 3 equiv), and anhydrous CH_2Cl_2 (1.3 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 49.1 mg (76%); pale-yellow solid; mp 77–79 °C; R_f = 0.10 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Phenomenex Lux-3u cellulose-1 equipped with securityguard filter; eluent: hexane–*i*-PrOH (95:5); flux: 0.8 mL/min; detection: 210 nm; *anti*-enantiomer, t_R = 7.0 min; *syn*-enantiomer, t_R = 8.7 min; *anti*-enantiomer; t_R = 11.3 min; *syn*-enantiomer, t_R = 14.2 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.33 (m, 9 H), 7.28 (s, 2 H), 6.35 (d, *J* = 15.0 Hz, 2 H), 6.14 (d, *J* = 40.6 Hz, 2 H, overlapping signals), 5.41 (d, *J* = 8.0 Hz, 1 H, *syn*), 5.32 (d, *J* = 8.8 Hz, 1 H, *anti*), 4.53 (d, *J* = 9.0 Hz, 1 H, *anti*), 4.46 (d, *J* = 8.1 Hz, 1 H, *syn*), 3.00 (br, 1 H), 2.34 (br, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0, 153.0, 142.4, 134.4, 134.1, 129.6, 129.3, 129.2, 129.0, 128.8, 128.6, 128.4, 128.0, 127.2, 110.4, 110.1, 108.1, 70.2, 69.1, 64.5.

MS (ESI+): *m*/*z* = 347.1 $[M + Na]^+$.

S-Phenyl 2-(4-Fluorophenyl)-3-hydroxy-3-phenylpropanethioate (10a)

Thioester **9a** (148 mg, 0.6 mmol, 2 equiv), catalyst **1** (18 mg, 0.03 mmol, 0.1 equiv), benzaldehyde (32 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 46.5 mg (44%); white solid; mp 106–108 °C; R_f = 0.13 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Phenomenex Lux-3u cellulose 4; eluent: hexane–EtOH (98:2); flux: 0.8 mL/min; detection: 210 nm; *syn*-enantiomer, t_R = 3.6 min; *syn*-enantiomer, t_R = 4.6 min; *anti*-enantiomer, t_R = 5.4 min; *anti*-enantiomer, t_R = 7.0 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.00 (m, 14 H), 5.35 (dd, *J* = 1.8, 6.7 Hz, 1 H, *syn*), 5.23 (dd, *J* = 2.3, 9.2 Hz, 1 H, *anti*), 4.17 (d, *J* = 9.2 Hz, 1 H, *anti*), 4.13 (d, *J* = 6.7 Hz, 1 H, *syn*), 2.89 (br, 1 H, *anti*), 2.51 (br, 1 H, *syn*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.89 (*anti*), 198.0 (*syn*), 162.7 (d, *J* = 247.2 Hz), 140.4, 134.5, 134.4, 131.2, 131.1, 130.5, 129.8, 129.7, 129.2, 128.3, 128.2, 128.1, 127.3, 127.0, 126.7, 126.6, 115.8, 115.5, 75.2, 66.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.37 (*syn*), –114.49 (*anti*).

MS (ESI+): *m*/*z* = 375.1 $[M + Na]^{+\cdot}$

S-Phenyl 3-Hydroxy-2-(4-isobutylphenyl)-3-phenylpropanethioate (10b)

Thioester **9b** (1.70 g, 0.6 mmol, 2 equiv), catalyst **2** (19 mg, 0.03 mmol, 0.1 equiv), benzaldehyde (32 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (95:5) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 55.0 mg (47%); white solid; mp 88–90 °C; R_f = 0.31 (*syn*), R_f = 0.23 (*anti*) (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: (*syn*-isomer) Chiralcel OD-H; eluent: hexane–*i*-PrOH (8:2); flux: 0.8 mL/min; detection: 210 nm; minor enantiomer, t_R = 9.7; major enantiomer, t_R = 11.5 min; (*anti*-isomer) Chiralcel OD-H; eluent: hexane–*i*-PrOH (8:2); flux: 0.8 mL/min; detection: 210 nm; major enantiomer, t_R = 11.8 min; minor enantiomer, t_R = 13.8 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*syn*) = 7.40–7.30 (m, 10 H), 7.28–7.15 (m, 4 H), 5.35 (d, *J* = 7.5 Hz, 1 H), 4.12 (d, *J* = 7.6 Hz, 1 H), 2.44 (d, *J* = 7.2 Hz, 2 H), 1.97–1.81 (m, 1 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H); δ (*anti*) = 7.42–7.38 (m, 5 H), 7.28–7.18 (m, 3 H), 7.15–7.08 (m, 2 H), 7.00 (s, 4 H) 5.28 (d, *J* = 7.5 Hz, 1 H), 4.15 (d, *J* = 7.5 Hz, 1 H), 2.42 (d, *J* = 7.2 Hz, 2 H), 1.97–1.81 (m, 1 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*syn*) = 199.3, 141.4, 140.8, 134.5, 131.9, 129.5, 129.4, 129.2, 128.6, 128.0, 127.7, 127.6, 126.5, 76.8, 67.5, 45.0, 30.1, 22.3.

MS (ESI+): *m*/*z* = 413.2 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-2-(4-isobutylphenyl)-3-(4-methoxyphenyl)propanethioate (10c)

Thioester **9b** (1.70 g, 0.6 mmol, 2 equiv), catalyst **2** (19 mg, 0.03 mmol, 0.1 equiv), 4-methoxybenzaldehyde (41 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (85:15) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 54.3 mg (43%); white solid; mp 81–83 °C; R_f = 0.10 (hexane–EtOAc, 97:3, stained with phosphomolybdic acid).

HPLC: Chiralcel OD-H; eluent: hexane–*i*-PrOH (9:1); flux: 0.8 mL/min; detection: 210 nm; *syn*-enantiomer, t_R = 12.6 min; *syn*-enantiomer, t_R = 14.3 min; *anti*-enantiomer, t_R = 16.2 min; *anti*-enantiomer, t_R = 18.5 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.38 (m, 7 H), 7.28–7.18 (m, 4 H), 6.90 (d, *J* = 8.7 Hz, 2 H, *syn*), 6.71 (d, *J* = 8.7 Hz, 2 H, *anti*), 5.30 (d, *J* = 7.8 Hz, 1 H, *syn*), 5.23 (d, *J* = 9.1 Hz, 1 H, *anti*), 4.12 (d, *J* = 9.1 Hz, 1 H, *anti*), 4.10 (d, *J* = 7.8 Hz, 1 H, *syn*), 3.84 (s, 3 H, *syn*), 2.50 (d, *J* = 7.8 Hz, 2H, *syn*), 2.40 (d, *J* = 7.8 Hz, 2 H, *anti*), 1.97–1.78 (m, 1 H), 0.94 (d, *J* = 6.60 Hz, 3 H, *syn* + *anti*), 0.93 (d, *J* = 6.60 Hz, 3 H, *syn* + *anti*), 0.88 (d, *J* = 6.60 Hz, 3 H, *syn* + *anti*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 159.4, 141.8, 134.4, 132.8, 131.5, 129.6, 129.4, 129.1, 129.0, 128.1, 127.3, 113.7, 75.1, 67.6, 55.3, 45.1, 30.1, 22.4.

MS (ESI+): *m*/*z* = 443.2 $[M + Na]^+$.

S-Phenyl 3-Hydroxy-2-(4-isobutylphenyl)-3-(4-chlorophenyl)propanethioate (10d)

Thioester **9b** (1.70 g, 0.6 mmol, 2 equiv), catalyst **2** (19 mg, 0.03 mmol, 0.1 equiv), 4-chlorobenzaldehyde (42 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc (97:3) as eluent. This purification furnished isolated *syn*- and *anti*-diastereoisomers; yield: 75.2 mg (59%); white solid; mp 103–105 °C; R_f = 0.22 (*syn*), R_f = 0.14 (*anti*) (hexane–EtOAc, 97:3, stained with phosphomolybdic acid).

HPLC: Chiralcel OD-H; eluent: hexane–*i*-PrOH (9:1); flux: 0.8 mL/min; detection: 210 nm; *syn*-enantiomer, t_R = 10.0 min; *syn*-enantiomer, t_R = 12.4 min; *anti*-enantiomer, t_R = 14.2 min; *anti*-enantiomer, t_R = 15.4 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*syn*) = 7.43–6.99 (m, 13 H), 5.31 (d, *J* = 7.2 Hz, 1 H), 4.03 (d, *J* = 7.2 Hz, 1 H), 2.48 (d, *J* = 7.1 Hz, 2 H), 1.88 (m, 1 H), 0.92 (d, *J* = 6.6 Hz, 6 H); δ (*anti*) = 7.45–7.34 (m, 4 H), 7.13 (d, *J* = 8.3 Hz, 2 H), 7.01–6.95 (m, 7 H), 5.23 (d, *J* = 9.1 Hz, 1 H), 4.06 (d, *J* = 9.1 Hz, 1 H), 3.03 (br, 1 H), 2.41 (d, *J* = 7.2 Hz, 2 H), 1.88–1.69 (m, 1 H), 8.86 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 141.8, 138.8, 134.4, 134.1, 133.4, 130.5, 129.3, 128.9, 128.1, 128.0, 126.8, 74.3, 66.9, 44.8, 29.8, 22.1.

MS (ESI+): *m*/*z* = 447.3 $[M + Na]^+$.

S-Benzyl 3-Hydroxy-2,3-diphenylpropanethioate (12)

Thioester **11** (145 mg, 2 equiv, 0.6 mmol), catalyst **2** (19 mg, 0.1 equiv, 0.03 mmol), benzaldehyde (32 mg, 0.3 mmol, 1 equiv), *i*-Pr_2NEt (775 mg, 6 mmol, 10 equiv), $SiCl_4$ (153 mg, 0.9 mmol, 3 equiv), and anhydrous CH_2Cl_2 (2 mL) were used. After workup, the product was purified by flash chromatography on silica gel with hexane–EtOAc–CH_2Cl_2 (9:0.5:0.5) as eluent. This purification furnished a mixture of *syn*- and *anti*-diastereoisomers; yield: 30.3 mg (29%); white solid; mp 81–83 °C; R_f = 0.18 (hexane–EtOAc, 9:1, stained with phosphomolybdic acid).

HPLC: Chiralcel OD-H; eluent: hexane–*i*-PrOH (9:1); flux: 0.8 mL/min; detection: 230 nm; *anti*-enantiomer, t_R = 14.4 min; *syn*-enantiomer, t_R = 16.6 min; *syn*-enantiomer, t_R = 20.4 min; *anti*-enantiomer, t_R = 30.8 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.06 (m, 15 H), 5.38 (d, *J* = 6.0 Hz, 1 H, *syn*), 5.30 (d, *J* = 6.0 Hz, 1 H, *anti*), 4.22 (d, *J* = 13.8 Hz, 1 H, *anti*), 4.13 (d, *J* = 13.8 Hz, 1 H, *syn*), 4.13–4.02 (m, 3 H), 3.87 (d, *J* = 14.0 Hz, 1 H, *anti*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1 (*anti*), 198.5 (*syn*), 140.5 (*syn*), 140.7 (*syn*), 140.5 (*anti*), 136.8, 134.9 (*anti*), 134.4 (*syn*), 129.3, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.3, 127.2, 126.8, 126.6, 75.2, 67.9 (*syn*), 67.8 (*anti*), 33.7 (*anti*), 33.3 (*syn*).

MS (ESI+): m/z = 371.2 $[M + Na]^+$.

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Supporting Information

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