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Cooperative Thiourea–Brønsted Acid Organocatalysis: Enantioselective Cyanosilylation of Aldehydes with TMSCN

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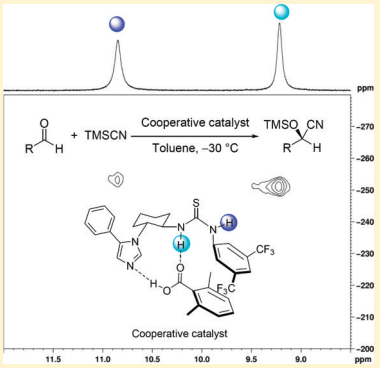
Supporting Information

ABSTRACT: We report a new thiourea–Brønsted acid cooperative catalytic system for the enantioselective cyanosilylation of aldehydes with yields up to 90% and enantioselectivities up to 88%. The addition of an achiral acid was found to be crucial for high asymmetric induction. Mechanistic investigations using a combination of NMR, ESI-MS, and density functional theory computations (including solvent corrections) at the M06/6-31G(d,p) level of theory suggest that the key catalytic species results from the cooperative interaction of bifunctional thioureas and an achiral acid that form well-defined chiral hydrogen-bonding environments.



INTRODUCTION

Optically active cyanohydrins are of high synthetic utility, as they can be converted into a number of key functional groups, including α-hydroxy acids, β-hydroxy alcohols, and other valuable building blocks.[1] The asymmetric addition of a cyanide source to carbonyl compounds with a chiral catalyst represents one of the most appealing approaches to enantiomerically enriched cyanohydrins. Among others, trimethylsilyl cyanide (TMSCN) has been the most widely used cyanide source[2] since the first reports by the groups of Evans[3] and Lidy,[4] allowing the desired cyanohydrin to be prepared directly as the corresponding trimethylsilyl ether.[5] As a consequence, a multitude of catalysts have been reported for the enantioselective addition of TMSCN to aldehydes and ketones, including Lewis acids, Lewis bases, peptides, and enzymes;[6] however, there are only a few organocatalytic approaches to this asymmetric transformation.[7]

The past decade has seen an explosion of interest in the use of thiourea derivatives as catalysts in asymmetric synthesis, in large part due to their hydrogen-bonding interactions with partially developing negatively charged atoms in the substrates.[8,9] In this context, the development of bifunctional catalysts by incorporating a Lewis basic functionality and a thiourea moiety in one chiral scaffold is the most active research area and has found widespread applications.[10−13] Recently, in contrast to asymmetric counteranion-directed catalysis (ACDC) developed by the List group,[14] we[15] as well as others[16,17] advanced a novel mechanistic feature in which the cooperative interaction of a hydrogen-bonding catalyst with a Brønsted acid gives rise to improvement in terms of reactivity and enantioselectivity. Herein, we report that this interaction mode can be applied advantageously to the enantioselective cyanosilylation of various aldehydes.

RESULTS AND DISCUSSION

Early on, we demonstrated that low-molecular-weight hydrogen-bonding catalysts such as **1** are highly active for a variety of organic transformations;[18,19] indeed, the 3,5-bis(trifluoromethyl)phenyl motif can now be found in the majority of (thio)urea-derived organocatalysts.[20] Our initial experiments showed that **1** catalyzes the addition of TMSCN to aldehydes under solvent-free conditions, and our catalyst design principle builds on the bifunctional concept by combining the privileged 3,5-bis(trifluoromethyl)phenyl thiourea motif with an additional Lewis basic functionality. On the basis of these considerations, we synthesized chiral thiourea derivatives **2a–g**, **3a**, and **4a,b** and several known thiourea catalysts **3b,c**, **5**, and **6** (Figure 1).

In a first set of experiments, the catalytic efficacy of the prepared thiourea derivatives was tested for the direct addition of TMSCN to benzaldehyde **7a** (Table 1). While **1** catalyzes this transformation with low conversion, the oxazoline thioureas **2a–g** display—unfortunately—*no* catalytic activity in the test reaction.[21] Schiff base–thiourea derivatives **3a,b** and the pyrrole thiourea derivative **3c** also do not promote this transformation. Thiourea derivatives **4a,b**, **5**, and **6** give the product in moderate to high conversion but with poor enantioselectivities (Table 1, entries 1, 3, 5, and 7).

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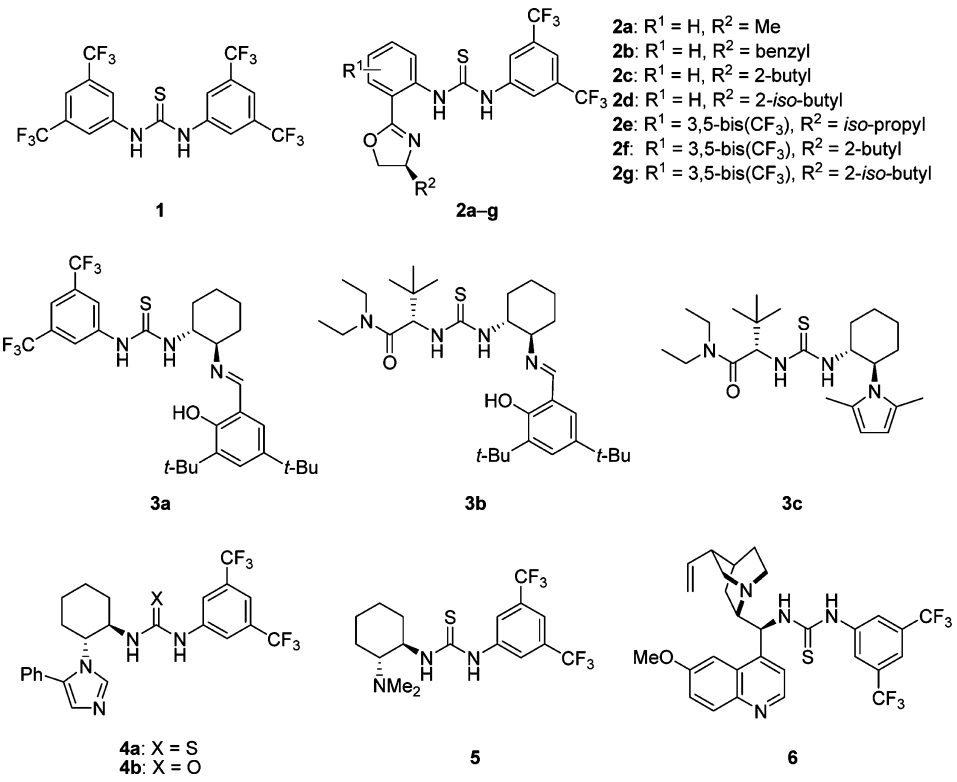
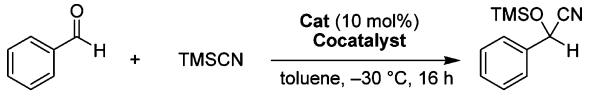


Figure 1. The 15 compounds prepared as potential catalysts for the title reaction.

Indeed, we recently documented a case where catalytic activity of thiourea (the parent compound) itself was ascribed in the reductive amination of aldehydes. After careful examination, we found that thiourea is ineffective and that catalysis was achieved through small amounts of benzoic acid derivatives from oxidation.[22] At the same time, it is clear that two Brønsted acids indeed can operate cooperatively, so that these effects need to be examined very carefully.[15] Inspired by the recent developments on anion recognition with (thio)urea derivatives[9,23] and cooperative Brønsted acid catalysis,[15,17,24] we added 10 mol % of benzoic acid to the reaction mixture. To our delight, our novel imidazole-derived thiourea **4a** in combination with benzoic acid drastically improves the enantioselectivity (Table 1, entry 2). Unexpectedly, *urea* catalyst **4b** with or without benzoic acid **9** gives high conversion but virtually no ee (Table 1, entries 3 and 4), presumably owing to the propensity for self-assembly of ureas in solution.[19] The addition of benzoic acid has little influence on the efficiency of Takemoto's catalyst **5** and quinine-derived catalyst **6** (Table 1, entries 5–8). As a consequence, we envisaged that the cooperative species formed by thiourea **4a** and benzoic acid is the active catalyst for the asymmetric addition of TMSCN to benzaldehyde.

Table 1. Catalyst Screening in the Asymmetric Addition of TMSCN to Freshly Distilled Benzaldehyde[a]



7a 8a

entry	cat.	cocat. (amt (mol %))	conversn[b] (%)	ee[c] (%)
1	**4a**		92	0
2	**4a**	benzoic acid (10)	98	74
3	**4b**		96	0
4	**4b**	benzoic acid (10)	97	3
5	**5**		81	30
6	**5**	benzoic acid (10)	89	30
7	**6**		47	−32[d]
8	**6**	benzoic acid (10)	54	−33[d]

[a]Under an argon atmosphere, the reaction was carried out on 0.2 mmol scale with 10 mol % catalyst in 1 mL of anhydrous toluene and with 1.5 equiv of TMSCN. [b]Determined by GC using *n*-dodecane as internal standard. [c]Determined by chiral GC analysis. [d]The minus indicates opposite enantioselectivity relative to that of the product with catalyst **4a**.

The finding that the enantioselectivity increases with the addition of substoichiometric amounts of benzoic acid **9** encouraged us to investigate the effect of a number of acids and alcohols on the catalytic efficiency of **4a** (Table 2). In the absence of an additive, the cyanosilylation product with freshly distilled benzaldehyde **7a** forms in high conversion but gives no ee in the presence of 10 mol % of **4a**, implying the key role of Brønsted acid additives in the stereocontrolled cyanosilylation addition step (Table 2, entry 1). HCN generated in situ from TMSCN with CF_3CH_2OH, utilized in Jacobsen's tertiary amine–thiourea promoted cyanosilylation of ketones, gives rise to comparable conversion but a nearly racemic product (Table 2, entry 3).[12]

Substituted benzoic acid derivatives give the cyanosilylation products with comparable conversions but slightly inferior enantioselectivities (Table 2, entries 5–9 and 12), with the exception of *p*-methoxybenzoic acid and 3,5-dichlorobenzoic acid, owing to their poor solubility in toluene (Table 2, entries 10 and 11). Some other Brønsted acids led to significant decreases in enantioselectivities, suggesting that aqueous acidity (pK_a) may be limited to a specific range (in this case around 4), which agrees with our previous observations (Table 2, entries 13–18).[15] Chiral acids as cocatalysts do not improve the ee

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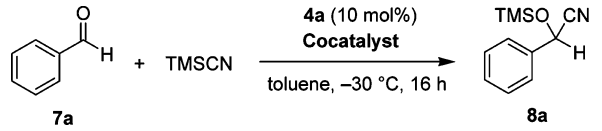
Table 2. Acid Screening in the Asymmetric Addition of TMSCN to Benzaldehyde with 4a[a]



7a 8a

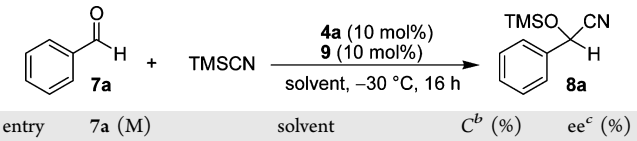
entry	cocat. (10 mol %)	pK_a	C^b (%)	ee (%)[c]
1			92	0
2	PhCOOH	4.2	98	74
3	CF_3CH_2OH	11.4	85	−9
4	MeOH	15.5	76	−4
5	*p*-*t*-Bu-PhCOOH	n.a.	95	71
6	*m*-Cl-PhCOOH	3.8	87	69
7	*p*-Me-PhCOOH	n.a.	93	68
8	*p*-*n*-octyl-PhCOOH	n.a.	90	71
9	*m*-Br-PhCOOH	4.0	96	72
10	*p*-OMe-PhCOOH	4.5	84	22
11	3,5-Cl_2PhCOOH	n.a.	86	54
12	2,6-Me_2PhCOOH	3.25	90	62
13	*p*-NO_2-PhOH	7.1	96	52
14	PhCOCOOH	4.2	56	57
15	$PhCH_2COOH$	4.3	94	15
16	CH_3COOH	4.8	94	36
17	$(CH_3)_3COOH$	n.a.	96	38
18	CF_3COOH	−0.3	54	−6
19	aspirin	3.5	100	49
20	vitamin C	4.2	100	73
21	Boc-L-Pro-OH	n.a.	84	67
22	Boc-L-Phe-OH	n.a.	93	68
23	Boc-L-Val-OH	n.a.	100	73
24	Boc-L-Cha-OH	n.a.	100	2
25	Boc-D-Asp(OBzl)-OH	n.a.	100	64
26	(*R*)-Mosher's acid	n.a.	89	73
27	(*S*)-Mosher's acid	n.a.	62	53
28	(*R*)-mandelic acid	3.4	84	46
29	(*S*)-mandelic acid	3.4	91	74
30	*O*-methyl-D-mandelic acid	3.1	83	30
31	*O*-methyl-L-mandelic acid	3.1	95	71

[a]Under an argon atmosphere, the reactions were carried out on a 0.2 mmol scale with 10 mol % of catalyst **4a** and cocatalyst (10 mol %) in 1 mL of anhydrous toluene, with 1.5 equiv of TMSCN. [b]Determined by GC using *n*-dodecane as internal standard. [c]Determined by chiral GC analysis.

values (Table 2, entries 21−31), but there are noticeable matching and mismatching effects: the addition of (*R*)-Mosher's acid, (*S*)-mandelic acid, and *O*-methyl-L-mandelic acid exhibited results superior to those of their enantiomers for the **4a**-catalyzed cyanosilylation product in terms of reactivities and enantioselectivities (Table 2, entries 26−31). Interestingly, vitamin C is also a good cocatalyst, giving the product with quantitative conversion and good enantioselectivity (Table 2, entry 20). These studies established the necessity of adding a Brønsted acid for obtaining significant enantioselectivity. In view of the efficiency, cost, and adaptability of the Brønsted acids, we chose benzoic acid as the ideal cocatalyst.

We next examined the influence of solvents, temperature, concentrations, and catalyst loadings on the reaction in the presence of **4a** as the catalyst and benzoic acid **9** as the cocatalyst (Table 3). The reaction in toluene gives the best result in terms of conversion and ee (Table 3, entry 1); as expected, the reaction in xylenes is similar (Table 3, entry 8).

Table 3. Solvent, Concentration, Temperature and Catalyst Loading Effects for the Test Reaction[a]



7a 8a

entry	7a (M)	solvent	C^b (%)	ee[c] (%)
1	0.2	toluene	98	74
2[d]	0.2	toluene	87	43
3[e]	0.2	toluene	93	54
4	0.2	CH_2Cl_2	30	0
5	0.2	$CHCl_3$	36	0
6	0.2	THF	90	0
7	0.2	Et_2O	87	57
8	0.2	xylenes	96	65
9	0.2	chlorobenzene	92	0
10	0.2	cyclopentyl methyl ether	73	6
11	0.1	toluene	90	71
12	0.04	toluene	89	72
13	0.4	toluene	91	57
14	1.0	toluene	98	23

[a]Under an Ar atmosphere on a 0.2 mmol scale with 10 mol % of **4a**, 10 mol % of **9**, and 1.5 equiv of TMSCN. [b]Determined by GC using *n*-dodecane as internal standard. [c]Determined by chiral GC analysis. [d]At −50 °C. [e]With 5 mol % of **4a** and benzoic acid **9**.

Performing the reaction in THF led to racemic product, suggesting that nonpolar solvents are critical for the formation of hydrogen-bonded complexes (Table 3, entry 6). Chlorinated solvents generally give lower conversions and no enantioselectivities, in agreement with the observation of ion pair formation via thiourea−chloride anion binding observed by the Jacobsen group (Table 3, entries 4, 5, and 9).[25] The potential binding with partially negatively charged chloride in chlorinated solvents might compete with the formation of a thiourea−benzoic acid complex, leading to poor results. Lowering the temperature reduces the reaction rate but does not increase the ee (Table 3, entry 2). A reduction of the catalyst loadings results in a decrease of ee values (Table 3, entry 3). While reactions run at lower concentrations give comparable conversions and enantioselectivities, higher concentrations lead to inferior results (Table 3, entries 11−14).

Using 10 mol % of **4a** and 10 mol % of benzoic acid **9** as the cooperative catalyst pair, a wide range of aldehydes was investigated in toluene at −30 °C (Table 4). Benzaldehydes bearing either electron-donating or -withdrawing substituents at *ortho*, *meta*, and *para* positions are well tolerated, giving the corresponding cyanohydrin acetates in moderate to good yields. Benzaldehydes with electron-donating substituents at the *para* position react much more slowly than benzaldehydes bearing electron-withdrawing groups (Table 4, entries 6 and 13). Generally, substituents at the *para* position of benzaldehyde give higher enantioselectivities (Table 4, entries 3, 6, 8, 10, and 13) than substituents at *ortho* and *meta* positions of benzaldehyde, probably due to steric hindrance (Table 4, entries 2, 4, 5, 7, and 9). The substrate scope was further extended to α,β-unsaturated aldehyde and aliphatic aldehydes, affording the corresponding products in good yields (Table 4, entries 14−16). However, aliphatic aldehydes give poor enantioselectivities, which strongly suggests that $\pi-\pi$ stacking interactions between the aromatic aldehydes and **4a** are important in the enantiodifferentiating step (Table 4, entries 15 and 16).

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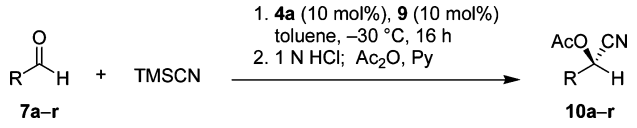
Table 4. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Thiourea 4a[a]



entry	aldehyde	yield[b] (%)	ee (%)[c]
1	benzaldehyde (**7a**)	73	73
2	3-methylbenzaldehyde (**7b**)	74	46
3	4-methylbenzadehyde (**7c**)	80	84
4	2-methoxybenzaldehyde (**7d**)	69	8
5	3-methoxybenzaldehyde (**7e**)	72	58
6[d]	4-methoxybenzaldehyde (**7f**)	57	68
7	2-fluorobenzaldehyde (**7g**)	83	42
8	4-fluorobenzaldehyde (**7h**)	79	82
9	3-chlorobenzaldehyde (**7i**)	66	65
10	4-bromobenzaldehyde (**7j**)	78	85
11	4-(trifluoromethyl)benzaldehyde (**7k**)	87	82
12	4-acetoxybenzaldehyde (**7l**)	80	77
13[e]	4-(allyloxy)benzaldehyde (**7m**)	88	83
14[f]	*trans*-cinnamaldehyde (**7n**)	67	88
15	cyclohexanecarboxaldehyde (**7o**)	90	18
16	octanal (**7p**)	72	51

[a]Under an argon atmosphere, the reactions were carried out on a 0.2 mmol scale in the presence of 10 mol % of **4a** and 10 mol % of benzoic acid with 1.5 equiv of TMSCN in anhydrous toluene at −30 °C for 16 h, unless otherwise stated. [b]Yield of isolated product after the conversion to cyanohydrin acetate. [c]Determined by chiral GC or chiral HPLC analysis for the corresponding acetate. [d]Reaction time 60 h. [e]Reaction time 60 h. [f]Reaction time 48 h.

Mechanistic Considerations. Jacobsen et al. has proposed a pathway for tertiary amine−thiourea promoted cyanosilylation of ketones and aldehydes, in which the tertiary amine activates in situ generated HCN toward the addition of thiourea-bound ketones or aldehydes.[26] In our reaction system, the addition of CF_3CH_2OH gives rise to comparable conversion but a nearly racemic product, suggesting the different roles that **9** and CF_3CH_2OH play in thiourea-catalyzed cyanosilylations (Table 2, entry 3). To devise a plausible mechanism, we then focused on mechanistic investigations by means of NMR and ESI-MS, as well as computations.

NMR Studies of the Binary Bifunctional Thiourea Catalyst/Benzoic Acid Complex. To establish the presence of a hydrogen-bonded complex of catalyst **4a** and benzoic acid, ^{1}H NMR, 2D NMR, NOESY, ROESY, and ^{1}H DOSY spectra were measured. Initial NMR studies in d_6-benzene on the association of catalyst **4a** and benzoic acid **9** through hydrogen bonding did not provide insights into the structure of the complex, as the ^{1}H NMR spectra are rather crowded in the aromatic region and no unique interpretation was possible. Therefore, 2,6-dimethylbenzoic acid (**11**) was chosen as an alternative acid, providing the methyl group signal as a unique reporter.[27] The low-field shifts of the NH protons by the addition of **11** clearly show the presence of the H-bonding complexation of **4a** with **11**. Further evidence for the interaction of **4a** with **11** was provided by ^{1}H NMR titration studies, in which various ratios of **4a** to **11** in d_6-benzene resulted in interpretable chemical shift changes for the two different NH signals (shown in Figure 2 as dark and light blue at $\Delta\delta$ 0.48 and 0.95 ppm, respectively). Additionally, the *ortho* proton (gray) of the catalyst and one of the imidazole's methine protons (red) shift downfield, while the second imidazole methine proton (light green) shifts upfield. The strong dependence of the chemical shifts on increasing the amount of acid confirms the strong interaction of **11** and **4a**.

To elucidate the detailed geometric arrangement of the components in the complex, we next measured NOE effects with 2D NMR NOESY and ROESY experiments in d_6-benzene. Unfortunately, all cross signals have the same sign as the diagonal signals, and negative NOEs indicate slowly tumbling molecules (see the Supporting Information). To avoid undesirable overlaps in the aromatic region arising from d_6-benzene, CD_2Cl_2 was chosen as the solvent. To our delight, all the proton signals of **4a** and **11** were sufficiently well separated so that all ROESY cross-peaks could be assigned unambiguously and an intermolecular NOE contact from the methyl group at 2.23 ppm can be seen for the aromatic *ortho* H's at 8.14 ppm (Figure 3). This is further corroborated by the NOE

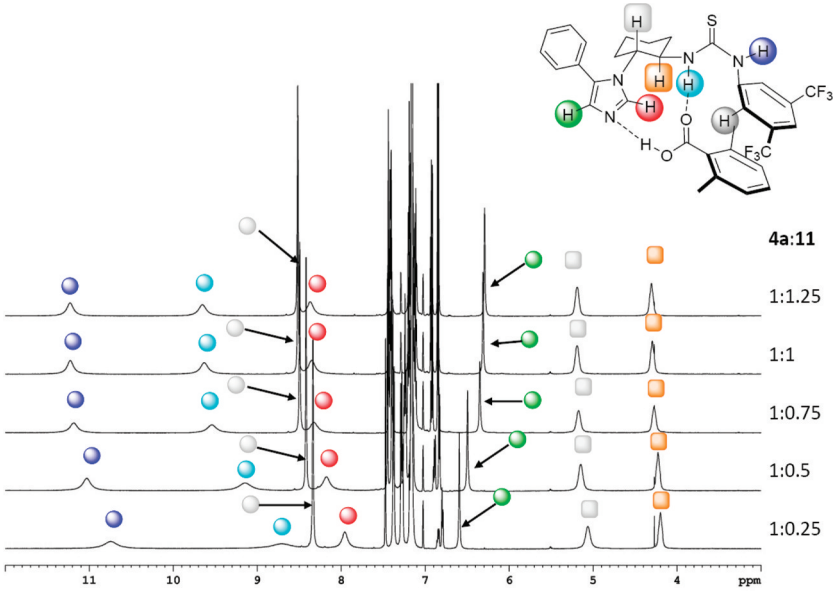


Figure 2. ^{1}H NMR spectra of thiourea catalyst **4a** and 2,6-dimethylbenzoic acid **11** in various ratios.

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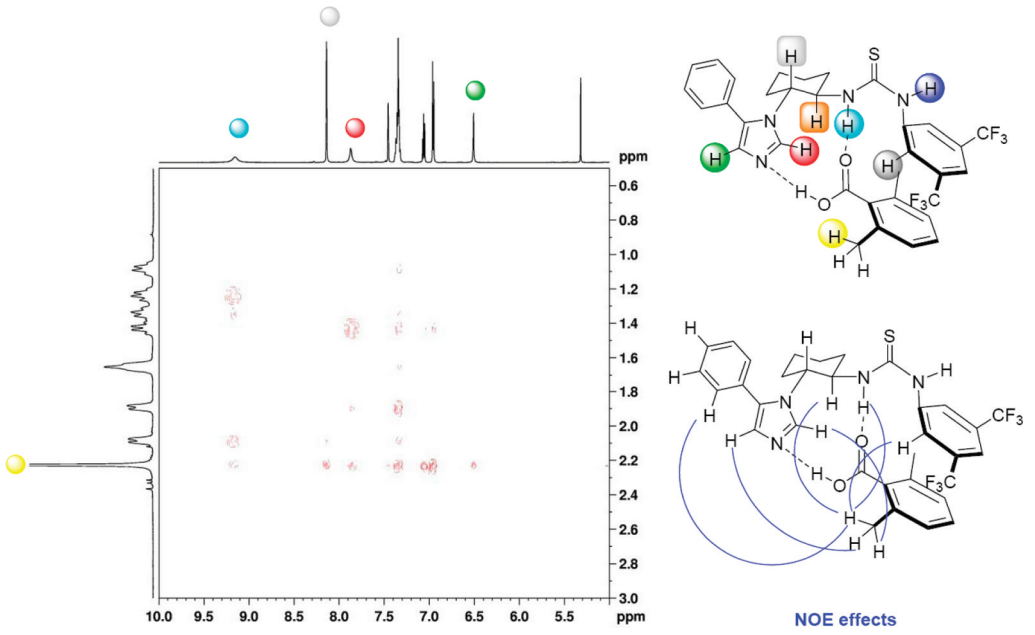

Figure 3. Section of the ^{1}H 2D ROESY spectrum for **4a** and 2,6-dimethylbenzoic acid (1:1 mixture of **4a** (0.01 mmol) and **11** (0.01 mmol) in CD_2Cl_2), showing the cross peaks arising from the interactions between the CH_3 groups of **11** with the catalyst.

of the methyl group with the NH (light blue) at 9.16 ppm and the imidazole protons at 7.87 and 6.51 ppm. Since the signal of the methyl group further displays an NOE contact to the aromatic phenyl ring protons at 7.34 ppm, the phenyl ring of **4a** and **11** must be also in close proximity.

To explore the roles of the two thiourea NH protons in the complex, a ^{1}H, ^{15}N HSQC experiment in CD_2Cl_2 was carried out (Figure 4). The NH signal at $\delta(^{15}N)$ −253.5 ppm (dark blue) appears as a weak cross peak in the correlation spectrum, due to the broad NH proton signal. The NH signal at $\delta(^{15}N)$ −251.0 ppm (light blue) appears as an intense peak, indicating that the exchange of this NH proton slowed down due to an intermolecular hydrogen bond with the carbonyl oxygen of **11**, and the proposed complex structure is depicted in Figure 4. There is no signal for a third NH function, confirming that **11** is not deprotonated.

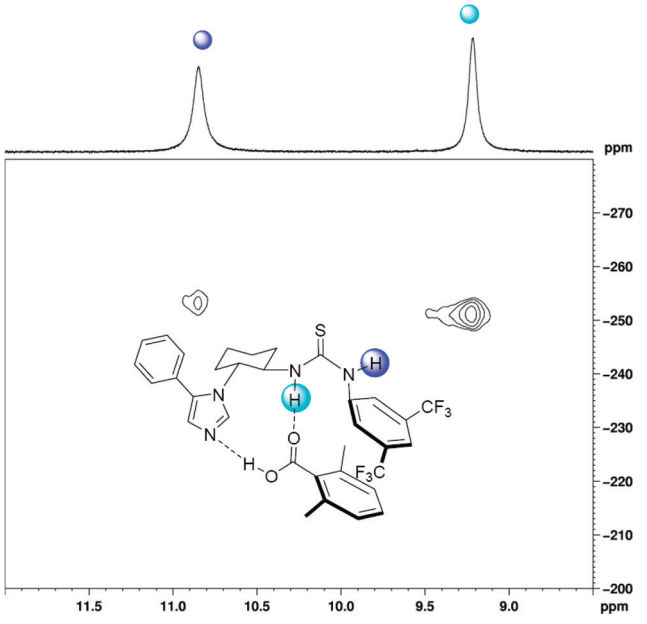

Figure 4. Section of the ^{1}H, ^{15}N HSQC spectrum in CD_2Cl_2 for **4a** and **11** (1:1 at 0.01 mmol), showing the NH signals, especially the one NH signal arising from the interaction between the NH protons and of **11**.

The NH proton adjacent to the cyclohexyl ring is a singlet through the coupling with ^{14}N, which has a spin of 1. The relative amount of ^{15}N is too low (<0.4%) to split the NH signal (light blue). For further support of our proposed complex structure in Figure 4 through a hydrogen-bonded complex with the acid-protonated function, we measured 1D and 2D NOESY NMR and ^{1}H, ^{15}N HSQC spectra of *N*-methylimidazole with an excess of **11**. The secondary nitrogen of the *N*-methylimidazole ring is not protonated (see the Supporting Information).

The interaction between **4a** and **11** can also be derived from the ^{1}H DOSY spectrum (Figure 5). The presence of the hydrogen-bonded complex was followed by concomitant changes observed in the diffusion coefficient D of **11** as it changes from $D = 4.92 \times 10^{-10}$ m^2 s^{-1} in the free state to $D = 4.32 \times 10^{-10}$ m^2 s^{-1} after the addition of the bifunctional catalyst. The changes of D are affected through the complexation of the **4a** with **11** through hydrogen bonding. Structure **11** diffuses more slowly, owing to its effectively larger solvated radius upon complexation with **4a**.

ESI/MS-Studies of the Binary Bifunctional Thiourea Catalyst/Benzoic Acid Complex. The proposed chiral structure ensuing from complexation of **4a** and **9** was further confirmed by means of mass spectrometry (MS). The ESI-MS spectrum in negative mode shows the presence of [**4a** + PhCOO]$^-$ at m/z 633.18, which is consistent with its isotopic pattern (for details see the Supporting Information).

Computational Studies of the Binary Bifunctional Thiourea Catalyst/Benzoic Acid Complex. First we searched for the energetically favored conformers of **4a**; the results are summarized in the Supporting Information. When ΔG_{298} values are compared, **4a_4** is favored in the gas phase but the energy differences are small. The PCM model[28] computations in benzene differ somewhat from those in the gas phase: while

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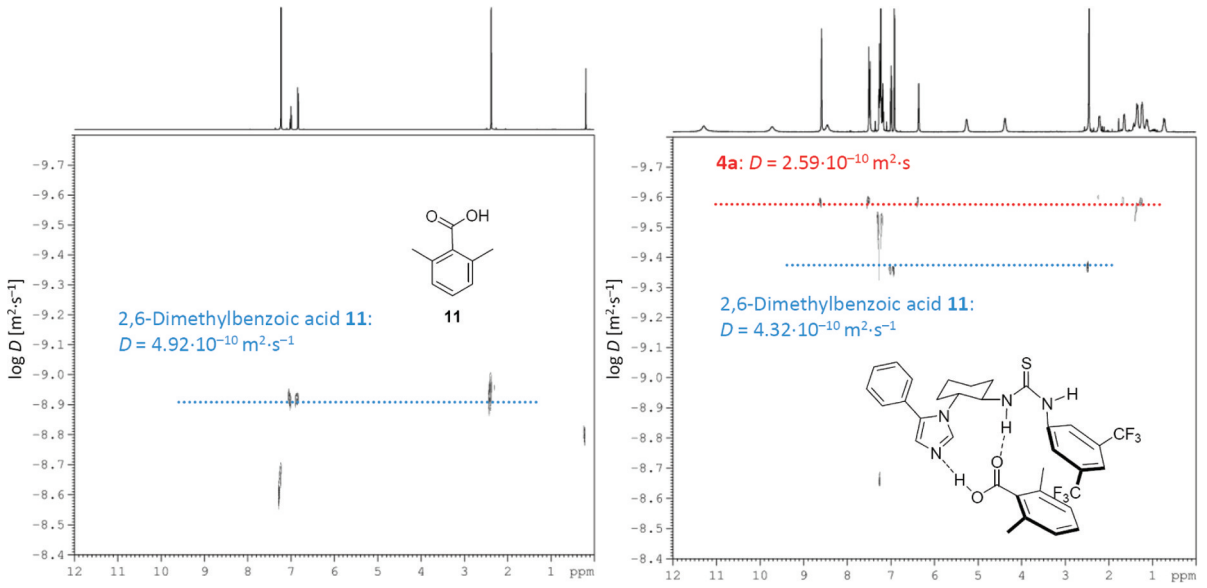

Figure 5. ^{1}H DOSY NMR of (left) **11** (0.01 mmol in d_6-benzene) and (right) **11** + **4a** (equimolar mixture of 0.01 mmol of each component in d_6-benzene).

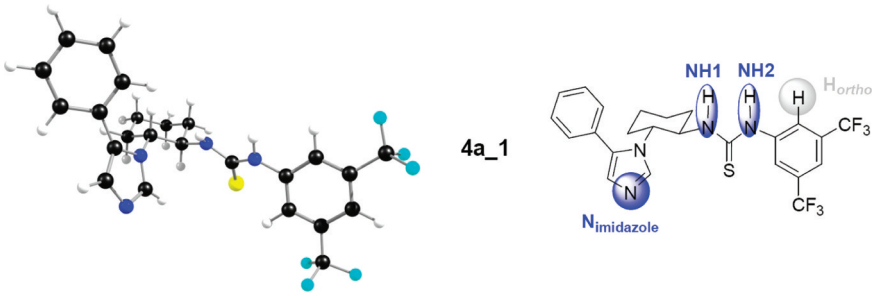

Figure 6. Lowest lying conformer of **4a** at the M06/6-31G(d,p) level, including solvent inclusion via SCRF (benzene) according to relative ΔG_{298}.

4a_4 is the lowest-lying structure at 0 K, inclusion of entropy and thermal effects at higher temperatures eventually favor **4a_1** (Figure 6). However, the relative energy differences are only within ca. 1.0 kcal mol^{-1}. It is clear that no single structure can be identified as the most favorable minimum structure and the uncomplexed thiourea catalyst is conformationally flexible. Equally it is currently entirely unfeasible to optimize transition structures for such a large and highly flexible system. A simplified model system would not take into account the fine yet important details of the manifold weak interactions.

Figure 7 shows a selection of two low-lying complexes of **4a** with **9**. Both complexes include hydrogen bonding due to a N−H···O═C interaction of the thiourea with the acid and an additional interaction of the benzoic acid proton with the nitrogen of the imidazole ring. The conformation of **4a** in complex **4a·9_7** displays a *Z,Z* orientation of the thiourea NH bond and offers double hydrogen bonding. Additionally, the acidified *ortho* protons of the 3,5-bis(trifluoromethyl)phenyl groups coordinate to the acid. The presence of three complexation sites should favor this complex. Structure **4a·9_8** prefers an *E,Z* orientation of the NH protons but offers only one N−H···O═C hydrogen bond. When the relative energies are compared at room temperature (ΔG_{298}) and at 0 K (ΔH_0), the energetically preferred complex in the gas phase and in solution is **4a·9_8** (Table 5). The dissociation

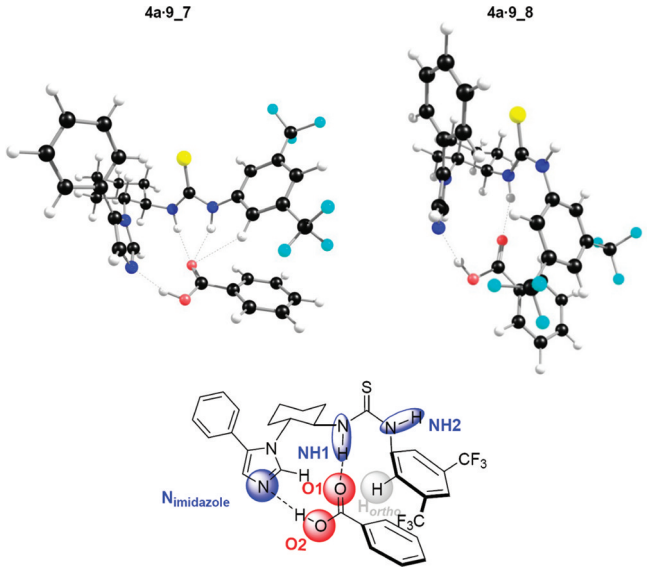

Figure 7. Lowest lying complex of **4a** with **9** at M06/6-31G(d,p), including solvent modeling at SCRF (benzene). Distances of **4a·9_7**: NH1···O1 d = 2.111 Å (2.368 Å), NH2···O1 d = 2.000 Å (2.052 Å), H_{ortho}···O1 d = 3.379 Å (3.459 Å), $N_{imidazole}$···OH2 d = 1.725 Å (1.744 Å). Distances of **4a·9_8**: NH1···O1 d = 2.021 Å (2.220 Å), $N_{imidazole}$···OH2 d = 1.712 Å (1.746 Å).

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Table 5. Overview of the Lowest Lying Conformers of 4a and Complexes 4a·9, Computed at the M06/6-31G(d,p) level in the Gas Phase and in Solution (SCRF for Benzene)

	ΔH_0 (kcal mol^{-1})	D_0 (kcal mol^{-1})	ΔG_{298} (kcal mol^{-1})	D_{298} (kcal mol^{-1})
4a_1	2.4 (0.7)		−1.5 (−3.5)	
4a _4	0.3 (−0.5)		−0.8 (−2.2)	
4a·9_7	−12.8 (−4.4)	22.2 (12.7)	−10.7 (−2.2)	8.6 (−1.6)
4a·9_8	−14.8 (−9.3)	24.2 (17.6)	−9.3 (−4.4)	7.2 (0.6)

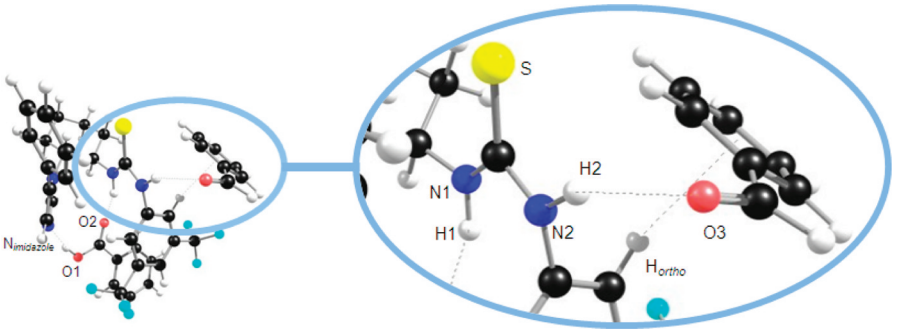
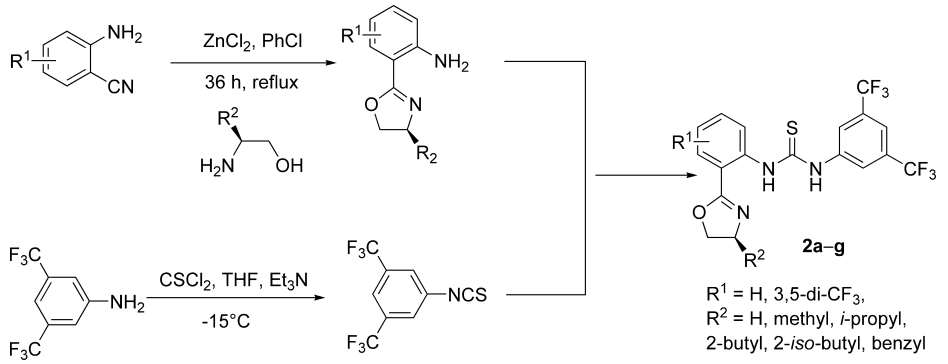


Figure 8. Lowest lying complex of catalyst **4a·9·7a_7** at the M06/6-31G(d,p) level and solvent model SCRF (benzene) according to relative D_0 and ΔG_{298}. Distances: NH1···O1 d = 2.044 Å (2.420 Å), NH2···O3═C d = 2.080 Å (2.167 Å), $N_{imidazole}$···H−O2 d = 1.708 Å (1.743 Å), H_{ortho}···phenyl ring d = 2.626 Å (2.585 Å).



energies (D_{298}) underline the stabilities of **4a·9_7** in the gas phase and **4a·9_8** in solution. Both NMR and computational studies favor the presence of **4a·9_8** in solution at room temperature. Analogous computations were performed with 2,6-dimethylbenzoic acid **11** (see the Supporting Information); the results are comparable.

Computational Studies of the Ternary Bifunctional Thiourea Catalyst/Benzoic Acid/Benzaldehyde Complex. The computations for the ternary bifunctional thiourea−benzoic acid−benzaldehyde complex **4a·9·7a_7** show a clear preference for the *E,Z* orientation of the NH protons and for the association depicted in Figure 8, whereby the free second thiourea NH proton coordinates the C═O bond of the benzaldehyde. This interaction is additionally aided by a T-shaped $\pi-\pi$ interaction of the thiourea's *ortho* proton to the phenyl ring of benzaldehyde;[29] this interaction increases with π electron donors such as Cl substituents. The *Si* face is shielded by the thiourea's phenyl ring, and the *Re* face of this complex is therefore preferentially attacked by TMSCN. This is consistent with our cyanosilylation protocol, because *S* enantiomers are preferred. The T-shaped stabilizing interaction is strong when π-electron-withdrawing substituents are involved. The enantioselectivities for aliphatic aldehydes are low (Table 4, entries 17 and 18), because these $\pi-\pi$ interactions are absent.[30]

CONCLUSIONS

We have developed the enantioselective addition of TMSCN to aldehydes promoted by a cooperative catalyst system comprised of the novel chiral bifunctional imidazole−thiourea catalyst **4a** and benzoic acid as the cocatalyst. A range of optically active cyanohydrin acetates were obtained in good yields. Aromatic aldehydes generally gave good enantioselectivities with this protocol. Mechanistic investigations using a combination of NMR and ESI-MS techniques reveal the presence of a hydrogen-bonded complex of thiourea **4a** with benzoic acid, which is consistent with our computational studies.

The new mechanistic feature is that the key catalytic species results from the synergistic interplay of a bifunctional thiourea catalyst and an achiral acid that forms a well-defined chiral hydrogen-bonding environment. The addition of an achiral acid is critical for the conformational fixation of the flexible "free" catalyst. The computations of the ternary complex of the catalysts with the substrate show that one of the thiourea NH protons interacts with the C═O group of the acid while the other binds to the C═O function of benzaldehyde. Additionally, there is a strong fixation of the aromatic aldehyde via a T-shaped $\pi-\pi$ stacking interactions of the acidified *ortho* proton of the 3,5-bis(trifluoromethyl)phenyl moiety with the phenyl ring. This interplay of hydrogen-bonding and $\pi-\pi$-stacking

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interactions supports the formation of a chiral complex preferring *Re* facial nucleophilic attack of TMSCN.

EXPERIMENTAL SECTION

General Procedures for the Synthesis of Thiourea Derivatives 2a–g. *2-(4,5-Dihydro-1,3-oxazol-2-yl)aniline.* An oven-dried 50 mL two-neck round-bottom flask was fitted with a magnetic stirring bar and a reflux condenser. Under an argon atmosphere, the flask was charged with anthranilonitrile (2.95 g, 25 mmol) and 2-aminoethanol (75 mmol), in anhydrous PhCl (40 mL), using $ZnCl_2$ (0.51 g, 3.75 mmol) as a catalyst. The mixture was refluxed about 36 h to give a red solution. The solvent was removed, and the crude product was dissolved in CH_2Cl_2. After washing with H_2O, the organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (19/1) as eluent to yield the corresponding oxazoline.

2-[(4S)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]aniline. This compound was prepared from anthranilonitrile (3.0 g, 25.0 mmol) and L-phenylalanol (11.2 g, 74.1 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (10/1) as eluent to yield the corresponding oxazoline (1.5 g, 23.8%) as a white solid. IR (KBr): 3395, 3273, 2909, 1630, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J = 7.9, 1.7, 1 H), 7.17–7.32 (m, 6 H), 6.61–6.69 (m, 2 H), 6.08 (br, 2 H, NH), 4.57–4.64 (m, 1 H), 4.25–4.30 (m, 1 H), 4.01–4.04 (m, 1 H), 3.12 (dd, J = 13.7, 6.2, 1 H), 2.75 (dd, J = 13.7, 7.9, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 148.9, 138.6, 132.3, 129.8, 129.4, 128.7, 126.6, 116.2, 115.9, 109.2, 70.4, 68.3, 42.4. HRMS: m/z calcd for $C_{16}H_{16}N_2O$ 252.1257, found 252.1226. Anal. Calcd for $C_{16}H_{16}N_2O$ (252.32): C, 76.16; H, 6.39; N, 11.10. Found: C, 76.16; H, 6.32; N, 11.07.

2-[(4S)-4-Isobutyl-4,5-dihydro-1,3-oxazol-2-yl]aniline. This compound was prepared from anthranilonitrile (2.95 g, 25.0 mmol) and L-isoleucinol (8.78 g, 75.0 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9/1) as eluent to yield the corresponding oxazoline (0.9 g, 16.5%) as a white solid. IR (KBr): 3416, 3278, 2953, 1640, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, J = 7.9, 1.6, 1 H), 7.17–7.21 (m, 1 H), 6.63–6.70 (m, 2 H), 6.10 (br s, 2 H, NH), 4.33–4.42 (m, 2 H), 3.82–3.89 (m, 1 H), 1.80–1.91 (m, 1 H), 1.61–1.68 (m, 1 H), 1.35–1.42 (m, 1 H), 0.98 (t, J = 4.7, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 148.5, 131.8, 129.5, 116.0, 115.6, 109.3, 71.4, 65.2, 45.8, 25.7, 22.9, 22.6. HRMS: m/z calcd for $C_{13}H_{18}N_2O$ 218.1414, found 218.1421. Anal. Calcd for $C_{13}H_{18}N_2O$ (218.30): C, 71.53; H, 8.31; N, 12.83. Found: C, 71.65; H, 8.29; N, 12.75.

2-[(4S)-4-(sec-Butyl)-4,5-dihydro-1,3-oxazol-2-yl]aniline. This compound was prepared from anthranilonitrile (2.95 g, 25.0 mmol) and L-leucinol (8.78 g, 75.0 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9/1) as eluent to yield the corresponding oxazoline (2.3 g, 42.1%) as a white solid. IR (KBr): 3464, 3287, 2962, 1638, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, J = 7.8, 1.5, 1 H), 7.15–7.19 (m, 1 H), 6.61–6.67 (m, 2 H), 6.10 (br, 2 H, NH), 4.26–4.30 (m, 2 H), 4.17–4.23 (m, 1 H), 3.96–4.00 (m, 1 H), 1.57–1.70 (m, 2 H), 1.17–1.28 (m, 1 H), 0.93 (t, J = 7.4, 3 H), 0.86 (d, J = 6.7, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 148.5, 131.8, 129.5, 115.9, 115.5, 109.1, 71.5, 68.3, 39.5, 26.0, 14.7, 11.4. HRMS: m/z calcd for $C_{13}H_{18}N_2O$ 218.1414, found 218.1421. Anal. Calcd for $C_{13}H_{18}N_2O$ (218.30): C, 71.53; H, 8.31; N, 12.83. Found: C, 71.07; H, 8.31; N, 12.83.

2-[(4S)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)aniline. This compound was prepared from 2-amino-4,6-bis(trifluoromethyl)benzonitrile (2.54 g, 10.0 mmol) and L-valinol (3.09 g, 30.0 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9/1) as eluent to yield the corresponding oxazoline (1.5 g, 44.2%) as a white solid. IR (KBr): 3452, 3324, 3203, 2974, 1667, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (s, 1 H), 7.10 (s, 1 H), 5.57 (br, 2 H, NH), 4.41 (dd, J = 9.1, 7.6, 1 H), 4.10–4.21 (m, 2 H), 1.83–1.91 (m, 1 H), 1.04 (d, J = 6.7, 3 H), 0.97 (d, J = 6.9, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 148.3, 133.2, 132.9, 132.6, 132.3, 132.2, 131.9, 131.6, 131.2, 127.2, 124.5, 121.8, 115.7, 112.0, 72.8, 70.0, 32.7, 18.8, 18.4. HRMS: m/z calcd for $C_{14}H_{14}N_2OF_6$ 340.1010, found 340.1004. Anal. Calcd for $C_{14}H_{14}F_6N_2O$ (340.26): C, 49.42; H, 4.15; N, 8.23. Found: C, 49.38; H, 4.03; N, 8.56.

2-[(4S)-4-Methyl-4,5-dihydro-1,3-oxazol-2-yl]aniline. This compound was prepared from anthranilonitrile (2.96 g, 25.0 mmol) and L-alaninol (5.6 g, 74.5 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9/1) as eluent to yield the corresponding oxazoline (2.4 g, 54.5%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, J = 7.9, 1.5, 1 H), 7.15–7.20 (m, 1 H), 6.61–6.66 (m, 2 H), 6.06 (br, 2 H, NH), 4.33–4.43 (m, 2 H), 3.78–3.82 (m, 1 H), 1.31 (d, J = 6.4, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 148.4, 131.8, 129.5, 115.9, 115.5, 109.0, 72.1, 62.0, 21.6.

2-[(4S)-4-(sec-Butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)aniline. This compound was prepared from 2-amino-4,6-bis(trifluoromethyl)benzonitrile (2.0 g, 7.87 mmol) and L-leucinol (2.76 g, 23.61 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to yield the corresponding oxazoline (1.34 g, 48.0%) as a white solid. IR (KBr): 3432, 3321, 3199, 2979, 1668, 874 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 1 H), 7.07 (s, 1 H), 5.54 (br, 2 H, NH), 4.37–4.41 (m, 1 H), 4.26–4.32 (m, 1 H), 4.10–4.14 (m, 1 H), 1.67–1.75 (m, 1 H), 1.56–1.65 (m, 1 H), 1.20–1.30 (m, 1 H), 0.94 (t, J = 7.5, 3 H), 0.88 (d, J = 6.8, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 148.3, 133.2, 132.9, 132.6, 132.23, 132.19, 131.9, 131.5, 131.2, 127.2, 127.1, 124.5, 124.4, 121.8, 121.7, 119.0, 115.7, 112.0, 111.7, 71.3, 69.5, 39.0, 26.1, 14.5, 11.4. HRMS: m/z calcd for $C_{15}H_{16}F_6N_2O$ 354.1161, found 354.1165. Anal. Calcd for $C_{15}H_{16}F_6N_2O$ (354.30): C, 50.85; H, 4.55; N, 7.91. Found: C, 50.90; H, 4.44; N, 7.62.

2-[(4S)-4-Isobutyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)aniline. This compound was prepared from 2-amino-4,6-bis(trifluoromethyl)benzonitrile (2.0 g, 7.87 mmol) and L-isoleucinol (2.76 g, 23.61 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9/1) as eluent to yield the corresponding oxazoline (1.8 g, 64.5%) as a white solid. IR (KBr): 3440, 3325, 3201, 2967, 1668, 1642, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 1 H), 7.08 (s, 1 H), 5.46 (br, 2 H, NH), 4.46 (dd, J = 9.4, 7.9, 1 H), 4.36–4.39 (m, 1 H), 3.96 (t, J = 7.9, 1 H), 1.78–1.88 (m, 1 H), 1.66–1.72 (m, 1 H), 1.39–1.46 (m, 1 H), 0.96 (t, J = 6.9, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 148.2, 132.9, 132.6, 131.9, 131.5, 124.5, 124.4, 121.8, 121.7, 115.74, 115.71, 112.1, 112.0, 111.9, 72.8, 65.1, 45.4, 25.6, 22.8, 22.6. HRMS: m/z calcd for $C_{15}H_{16}F_6N_2O$ 354.1161, found 354.1165. Anal. Calcd for $C_{15}H_{16}F_6N_2O$ (354.30): C, 50.85; H, 4.55; N, 7.91. Found: C, 51.03; H, 4.48; N, 7.65.

General Procedure for Oxazoline Thiourea Formation. An oven-dried two-neck round-bottom flask was fitted with a magnetic stirring bar and an additional funnel. Under an argon atmosphere, the flask was charged with 3,5-bis(trifluoromethyl)phenylisothiocyanate (1.08 g, 4.0 mmol) and anhydrous THF (5 mL), followed by dropwise addition of a solution of oxazoline (1.0 equiv) in anhydrous THF (15 mL) under 0 °C. The resulting mixture was stirred overnight at room temperature. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography on silica gel using hexane/EtOAc (5/1) as eluent to yield the corresponding product.

*3,5-Bis(trifluoromethyl)anilino-2-[(4S)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]anilinomethanethione (**2a**).* This compound was prepared from 2-[(4S)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (1.76 g, 10.0 mmol) and 3,5-bis(trifluoromethyl)phenylisothiocyanate (1.0 equiv) by the general procedure described above. The crude product was purified by column chromatography on silica gel using

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hexane/EtOAc (5/1) as eluent to yield **2a** (2.08 g, 46.5%) as a white solid. IR (KBr): 3198, 3042, 2976, 2898, 1639, 1618, 891, 683 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 12.96 (br, 1 H, NH), 8.94 (d, J = 8.3, 1 H), 8.69 (br, 1 H, NH), 7.86 (s, 2 H), 7.80 (dd, J = 7.9, 1.5, 1 H), 7.72 (s, 1 H), 7.49−7.52 (m, 1 H), 7.14−7.17 (m, 1 H), 4.36 (t, J = 8.8, 1 H), 3.96−4.02 (m, 1 H), 3.79 (t, J = 8.0, 1 H), 0.90 (d, J = 6.7, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.0, 163.1, 139.6, 139.1, 133.1, 132.9, 132.7, 132.5, 131.7, 124.7, 123.8, 121.8, 119.4, 115.3, 72.9, 61.4, 20.9. HRMS: m/z calcd for $C_{19}H_{15}F_6N_3OS$ 447.0834, found 447.0816. Anal. Calcd for $C_{19}H_{15}F_6N_3OS$ (447.40): C, 51.01; H, 3.38; N, 9.39. Found: C, 50.80; H, 3.23; N, 9.62.

*2-[(4S)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]anilino-3,5-bis-(trifluoromethyl)anilinomethanethione (**2b**).* This compound was prepared from 2-[(4*S*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (1.16 g, 4.6 mmol) and 3,5-bis(trifluoromethyl)phenylisothiocyanate (1.0 equiv) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5/1) as eluent to yield **2b** (0.9 g, 43.0%) as a white solid. IR (KBr): 3345, 2909, 2791, 1634, 1276, 1120, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 13.03 (s, 1 H, NH), 9.06 (d, J = 8.5, 1 H, NH), 7.83−7.87 (m, 2 H), 7.71 (s, 1 H), 7.50−7.55 (m, 1 H), 7.10−7.32 (m, 8 H), 4.45−4.53 (m, 1 H), 4.38−4.44 (m, 1 H), 4.07−4.13 (m, 1 H), 2.75−2.81 (m, 1 H), 2.63−2.70 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 164.0, 140.1, 137.8, 132.0, 129.4, 129.0, 128.6, 126.8, 124.6, 123.4, 121.0, 114.5, 71.1, 67.4, 41.9. HRMS: m/z calcd for $C_{25}H_{19}F_6N_3OS$ 523.1148, found 523.1122. Anal. Calcd for $C_{25}H_{19}F_6N_3OS$ (523.49): C, 57.36; H, 3.66; N, 8.03. Found: C, 57.47; H, 3.53; N, 7.98.

*3,5-Bis(trifluoromethyl)anilino-2-[(4S)-4-(sec-butyl)-4,5-dihydro-1,3-oxazol-2-yl]anilinomethanethione (**2c**).* This compound was prepared from 2-[(4*S*)-4-(*sec*-butyl)-4,5-dihydro-1,3-oxazol-2-yl]-aniline (0.87 g, 4.0 mmol) and 3,5-bis(trifluoromethyl)-phenylisothiocyanate (1.0 equiv) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5/1) as eluent to yield **2c** (1.08 g, 55.6%) as a white solid. IR (KBr): 3169, 2966, 1637, 1377, 1277, 682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 13.10 (s, 1 H, NH), 8.89 (d, J = 8.3, 1 H, NH), 8.12 (s, 1 H), 7.80−7.82 (m, 3 H), 7.66 (s, 1 H), 7.50−7.54 (m, 1 H), 7.15−7.19 (m, 1 H), 4.24−4.29 (m, 1 H), 3.98−4.02 (t, J = 8.3, 1 H), 3.87−3.93 (m, 1 H), 1.15−1.28 (m, 2 H), 0.84−0.97 (m, 1 H), 0.78−0.82 (m, 3 H), 0.62−0.64 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 163.1, 139.7, 139.4, 133.0, 132.7, 131.7, 129.3, 123.7, 123.4, 121.5, 118.8, 115.2, 70.8, 68.6, 38.8, 25.7, 14.0, 11.2. HRMS: m/z calcd for $C_{22}H_{21}F_6N_3OS$ 489.1304, found 489.1315. Anal. Calcd for $C_{22}H_{21}F_6N_3OS$ (489.48): C, 53.98; H, 4.32; N, 8.58. Found: C, 54.00; H, 4.25; N, 8.59.

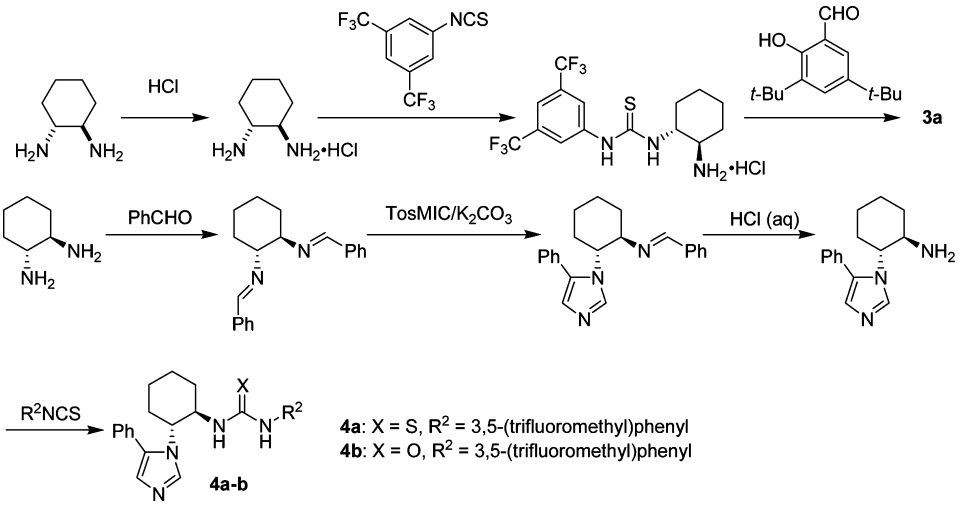
*3,5-Bis(trifluoromethyl)anilino-2-[(4S)-4-isobutyl-4,5-dihydro-1,3-oxazol-2-yl]anilinomethanethione (**2d**).* This compound was prepared from 2-[(4*S*)-4-isobutyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (0.87 g, 4.0 mmol) and 3,5-bis(trifluoromethyl)phenylisothiocyanate (1.0 equiv) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5/1) as eluent to yield **2d** (0.6 g, 30.6%) as a white solid. IR (KBr): 3190, 2965, 2929, 1640, 1275, 682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 13.16 (s, 1 H, NH), 8.94 (d, J = 8.4, 1 H, NH), 8.07 (s, 1 H), 7.83−7.85 (m, 3 H), 7.64−7.68 (m, 1 H), 7.50−7.54 (m, 1 H), 7.15−7.19 (m, 1 H), 4.36−4.40 (m, 1 H), 3.99−4.07 (m, 1 H), 3.83−3.87 (m, 1 H), 1.32−1.42 (m, 1 H), 1.04−1.17 (m, 2 H), 0.78−0.81 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8, 163.0, 139.7, 139.3, 133.0, 131.7, 129.3, 123.7, 123.2, 121.4, 118.8, 118.76, 118.7, 115.2, 71.8, 64.6, 45.0, 25.3, 22.5, 22.3. HRMS: m/z calcd for $C_{22}H_{21}F_6N_3OS$ 489.1304, found 489.1327. Anal. Calcd for $C_{22}H_{21}F_6N_3OS$ (489.48): C, 53.98; H, 4.32; N, 8.58. Found: C, 54.15; H, 4.29; N, 8.54.

*3,5-Bis(trifluoromethyl)anilino-2-[(4S)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)anilinomethanethione (**2e**).* This compound was prepared from 2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)aniline (1.02 g, 3.0 mmol) and 3,5-bis(trifluoromethyl)phenylisothiocyanate (1.0 equiv) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5/1) as eluent to yield **2e** (0.22 g, 14.8%) as a white solid. IR (KBr): 3418, 2971, 1377, 1279, 1131, 683 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ 10.79 (s, 1 H, NH), 10.05 (s, 1 H, NH), 8.41 (s, 1 H), 8.26 (s, 2 H), 8.08 (s, 1 H), 7.89 (s, 1 H), 4.46−4.50 (m, 1 H), 4.14−4.18 (m, 1 H), 4.06−4.12 (m, 1 H), 1.71−1.80 (m, 1 H), 0.90 (t, J = 6.6, 3 H), 0.86 (d, J = 6.8, 3 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 180.7, 157.3, 140.9, 140.1, 130.6, 130.5, 130.3, 130.2, 130.0, 129.8, 129.7, 127.3, 124.4, 123.7, 121.7, 120.8, 117.8, 72.7, 70.6, 31.8, 18.4, 18.1. HRMS: m/z calcd for $C_{23}H_{17}F_{12}N_3OS$ 611.0895, found 611.0936. Anal. Calcd for $C_{23}H_{17}F_{12}N_3OS$ (611.45): C, 45.18; H, 2.80; N, 7.07. Found: C, 45.33; H, 2.67; N, 6.75.

*3,5-Bis(trifluoromethyl)anilino-2-[(4S)-4-(sec-butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)anilinomethanethione (**2f**).* This compound was prepared from 2-[(4*S*)-4-(*sec*-butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)aniline (0.77 g, 2.17 mmol) and 3,5-bis(trifluoromethyl)phenylisothiocyanate (1.1 equiv) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5/1) as eluent to yield **2f** (0.69 g, 51.0%) as a white solid. IR (KBr): 3427, 3179, 2972, 1375, 1279, 683 cm^{-1}. ^1H NMR (600 MHz, d_6-DMSO): δ 10.84 (br, 1 H, NH), 10.12 (br, 1 H, NH), 8.44 (s, 1 H), 8.26 (s, 2 H), 8.10 (s, 1 H), 7.91 (s, 1 H), 4.47−4.50 (m, 1 H), 4.16−4.23 (m, 1 H), 1.52−1.59 (m, 2 H), 1.10−1.15 (m, 1 H), 0.79−0.81 (m, 6 H). ^{13}C NMR (150 MHz, d_6-DMSO): δ 180.7, 157.3, 140.9, 140.1, 130.7, 130.6, 130.4, 130.2, 130.0, 129.9, 129.7, 127.1, 125.8, 124.0, 123.6, 123.4, 122.2, 121.8, 121.5, 120.9, 120.4, 117.8, 71.3, 70.2, 38.2, 25.2, 14.2, 11.1. HRMS: m/z calcd for $C_{24}H_{19}F_{12}N_3OS$ 625.1054, found 625.1018. Anal. Calcd for $C_{24}H_{19}F_{12}N_3OS$ (625.47): C, 46.09; H, 3.06; N, 6.72. Found: C, 46.08; H, 2.82; N, 6.70.

*3,5-Bis(trifluoromethyl)anilino-2-[(4S)-4-isobutyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)anilinomethanethione (**2g**).* This compound was prepared from **2**-[(4*S*)-4-isobutyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-bis(trifluoromethyl)aniline (1.06 g, 3.0 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.1 equiv) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5/1) as eluent to yield **2g** (0.93 g, 42.1%) as a white solid. IR (KBr): 3428, 3177, 2972, 1375, 683 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ 10.71 (s, 1 H, NH), 10.03 (br, 1 H, NH), 8.35 (s, 1 H), 8.27 (s, 2 H), 8.03 (s, 1 H), 7.83 (s, 1 H), 4.50 (t, J = 8.8, 1 H), 4.30−4.38 (m, 1 H), 3.99 (t, J = 7.9, 1 H), 1.70−1.81 (m, 1 H), 1.51−1.58 (m, 1 H), 1.33−1.40 (m, 1 H), 0.83 (d, J = 6.5, 3 H), 0.86 (d, J = 6.6, 3 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 177.3, 159.1, 158.6, 156.2, 150.4, 150.2, 149.3, 141.5, 140.6, 131.3, 131.0, 130.6, 130.3, 124.9, 124.5, 124.0, 122.2, 121.8, 118.6, 118.0, 116.4, 115.2, 112.8, 107.0, 72.4, 64.8, 62.2, 60.9, 25.0, 22.7. HRMS: m/z calcd for $C_{24}H_{19}F_{12}N_3OS$ 625.1054, found 625.1024. Anal. Calcd for $C_{24}H_{19}F_{12}N_3OS$ (625.47): C, 46.09; H, 3.06; N, 6.72. Found: C, 46.16; H, 2.86; N, 6.78.

Synthesis of 2-Amino-4,6-bis(trifluoromethyl)benzonitrile.[31] Under an argon atmosphere, in a three-neck round-bottom flask equipped with a magnetic stirbar and thermometer were added 1-nitro-3,5-bistrifluoromethylbenzene (10.36 g, 0.04 mol), ethyl cyanoacetate (13.84 g, 0.12 mol, 98%), anhydrous powdered KOH (2.60 g, 0.04 mol), and dry DMF (120 mL). The resulting mixture was stirred vigorously at room temperature and then was cooled to 0 °C and stirred for 60 min. The solvent was removed *in vacuo*. The residue was mixed with 80 mL of 5% NaOH solution and refluxed for 60 min. The reaction mixture was cooled to room temperature, and chloroform (180 mL) was added. After separation of the organic phase, the aqueous phase was extracted with chloroform (2 × 100 mL). The combined organic phase was dried over Na_2SO_4, filtered, and evaporated to afford the crude product as a brown solid, which was purified by column chromatography on silica gel using chloroform as eluent, yielding the product (4.89 g, 48.1%) as a yellow solid. IR (KBr): 3509, 3359, 3247, 2234, 1647, 1584 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1 H), 7.21 (s, 1 H), 5.02 (br, 2 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 136.0, 135.7, 135.4, 135.0, 134.8, 134.4, 134.1, 133.8, 126.5, 126.0, 115.3, 113.3, 111.6, 94.6.



Synthesis of Schiff Base Thiourea 3a. *Preparation of Monoammonium Salts of (R,R)-1,2-Diaminocyclohexane.*[32] (*R*,*R*)-1,2-Diaminocyclohexane (810 mg, 7.1 mmol) was dissolved in ether (25 mL). The solution was stirred vigorously while anhydrous HCl in ether (2.35 mL, 2.9 M, 7.1 mmol, 1.0 equiv) was added dropwise over 15 min. An exothermic reaction was observed upon the addition of the acid, and a precipitate was formed. After complete addition of the acid, the mixture was stirred at room temperature for 10 h. The precipitation was collected by vacuum filtration, washed with excess ether, and dried in vacuo to give the product (900 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ 2.29 (br, 2 H), 1.67 (d, J = 10.4, 2 H), 1.40 (br, 2 H), 0.96 (m, 4 H). ^{13}C NMR (100 MHz, D_2O): δ 54.5, 32.2, 24.2.

1-((1R,2R)-2-Aminocyclohexyl)-3-(3,5-bis(trifluoromethyl)-phenyl)thiourea Hydrochloride. (*R*,*R*)-1,2-Diaminohexane hydrogen chloride (453 mg, 3.0 mmol) was dissolved in a mixture of methanol and ethanol (50/50, v/v, 25 mL). 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (814 mg, 3.0 mmol, 1.0 equiv) was added to the reaction mixture, and it was stirred at room temperature for 40 h. The solvents were evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH 10/1−4/1) to give the corresponding product (739 mg, 71%) as a white solid. IR (KBr): 3247, 3051, 2948, 2869, 1553, 1277, 681. ^{1}H NMR (200 MHz, d_6-DMSO): δ 8.93 (br, 1 H), 8.41 (s, 2 H), 7.78 (s, 1 H), 4.38 (br, 1 H), 3.06−3.18 (m, 1 H), 2.54−2.58 (m, 1 H), 1.96−2.15 (m, 2 H), 1.75−1.78 (m, 2 H), 1.15−1.59 (m, 4 H). ^{13}C NMR (50 MHz, d_6-DMSO): δ 180.8, 142.1, 131.0, 130.3, 130.0, 129.7, 129.0, 125.9, 121.7, 120.5, 115.9, 54.8, 53.0, 30.4, 29.3, 23.8, 23.1.

*(1R,2R)-2-(E)-1-[3,5-Di-tert-butyl-2-hydroxyphenyl]-methylideneaminocyclohexylamino-3,5-bis(trifluoromethyl)-anilinomethanethione (**3a**).* A 50 mL two-necked flask equipped with a reflux condenser and an addition funnel was charged with (*R*,*R*)-1,2-diaminohexane hydrogen chloride thiourea (168.7 mg, 0.4 mmol), K_2CO_3 (55.2 mg, 0.4 mmol), and distilled water (8.0 mL). The mixture was stirred until dissolution was achieved, and then ethanol (8.0 mL) was added. The resulting colorless solution was heated to reflux (75−80 °C), and a solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde in ethanol (4.0 mL) was added dropwise over 15 min. The yellow solution was stirred at reflux 2.5 h before heating was discontinued. Distilled water (8.0 mL) was added, and the stirred mixture was cooled to less than 5 °C under an ice bath and maintained at that temperature overnight. The product was collected by vacuum filtration and dried under vacuum to give **3a** (168 mg, 70%) as a yellow solid. Mp: 153 °C. IR (KBr): 3274, 2968, 2865, 1628, 1539, 1279, 1138 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.04 (br, 1 H, OH), 8.45 (s, 1 H), 7.69 (s, 1 H), 7.61 (s, 1 H), 7.52 (s, 2 H), 7.39 (d, J = 2.4, 1 H), 7.13 (d, J = 2.4, 1 H), 6.23 (br, 1 H), 3.96 (br, 1 H), 3.09−3.12 (m, 1 H), 2.26−2.28 (m, 1 H), 1.73−1.95 (m, 4 H), 1.22−1.59 (m, 22 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.4, 167.2, 157.5, 141.0, 139.6, 136.7, 132.3, 128.2, 126.9, 126.4, 125.5, 124.1, 121.4, 119.7, 117.4, 59.1, 34.8, 34.2, 33.5, 31.7, 31.4, 29.4, 29.3, 29.1, 24.6, 23.8. HRMS: m/z calcd for $C_{30}H_{37}F_6N_3OS$ 601.2561, found 601.2550. Anal. Calcd for $C_{30}H_{37}F_6N_3OS$ (601.69): C, 59.88; H, 6.20; N, 6.98. Found: C, 59.87; H, 6.18; N, 7.18.

The synthesis of catalysts **3b,c** was carried out according to known protocols.[33]

Synthesis of Thiourea Derivatives 4a,b. *N,N′-Bis-(benzylidiene)-(R,R)-1,2-diaminocyclohexane. Method 1.*[34] (*R*,*R*)-1,2-Diaminocyclohexane (786 mg, 6.88 mmol) and benzaldehyde (1.40 mL, 13.76 mmol) were dissolved in anhydrous methanol (20 mL) and stirred under reflux for 5 h to produce a precipitate. The reaction mixture was cooled to room temperature and the Schiff base isolated by filtration and purified by recrystallization from a solvent mixture of dichloromethane and hexane to give the product as white platelike crystals (1.0 g, 50%).

Method 2 (Modified from Literature Procedure).[35] A 500 mL, three-necked flask equipped with a magnetic stirring bar, a reflux condenser, and an addition funnel was charged with (*R*,*R*)-1,2-diammoniumcyclohexane (+)-tartrate salt (7.9 g, 30.0 mmol), K_2CO_3 (8.3 g, 60.0 mmol), and distilled water (60 mL). The mixture was stirred until dissolution was achieved, and then ethanol (150 mL) was added. The resulting mixture was heated to reflux (70−80 °C), and a solution of benzaldehyde (6.09 mL, 60 mmol) was added in a steady stream over 30 min. The yellow mixture was stirred at reflux for 2 h before heating was discontinued. The solution was rotary evaporated, and the residue was suspended in dichloromethane (200 mL) and washed with water (60 mL) and brine (60 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated to give the crude product as a yellow solid, which was further purified by recrystallization from a solvent mixture of dichloromethane and hexane to yield the product as yellow crystals (8.0 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 2H), 7.60−7.57 (m, 4H), 7.33−7.28 (m, 6H), 3.45−3.39 (m, 2H), 1.88−1.80 (m, 6H), (m, 2H), 1.52−1.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 136.4, 130.2, 128.4, 127.9, 73.9, 33.0, 24.6.

1-[(1R,2R)-2-(Benzylideneamino)cyclohexyl]-4-phenylimidazole.[36] Under an argon atmosphere, anhydrous potassium carbonate (2.7 g, 17.0 mmol), TosMIC (1.7 g, 8.7 mmol), and (1*R*,2*R*)-diaminocyclohexane-*N*,*N*′-dibenzylidene (2.5 g, 8.6 mmol), activated molecular sieves 4 Å (5.0 g), and anhydrous acetonitrile (25 mL) were mixed, and the mixture was stirred at 70 °C for 72 h. The brown mixture was filtered, and the solvent was removed from the filtrate under reduced pressure to afford a brown oil (3.1 g), which was extracted with diethyl ether (200 mL), and the solution was then concentrated to 20 mL and added dropwise to pentane (200 mL); a pale yellow solid and brown oil appeared. The organic solvent was decanted, and the crude brown oil (730 mg, 26%) was confirmed as the corresponding product and was used without further purification for the next step.

(1R,2R)-2-(5-Phenyl-1H-imidazol-1-yl)cyclohexanamine.[37] A mixture of 1*R*-(benzylideneamino)-2*R*-(5-phenylimidazolyl)-cyclohexane (730 mg, 2.2 mmol) and hydrochloric acid (15 mL,

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1 M) was stirred at 25 °C for 2 h and filtered, and the filtrate was washed with dichloromethane (2 × 15 mL). The aqueous solution was cooled to 5 °C, and an aqueous solution of sodium hydroxide (17 mL, 1 M) was added dropwise to pH 9−11. The resulting cloudy precipitate was extracted with diethyl ether (2 × 15 mL), and the combined ether layers were washed with water (15 mL), dried over $MgSO_4$, and filtered. Removal of the volatiles under reduced pressure gave (1*R*,2*R*)-2-(5-phenyl-1*H*-imidazol-1-yl)cyclohexanamine (224 mg, 42%) as a yellow oil.

*1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1R,2R)-2-(5-phenyl-1H-imidazol-1-yl)cyclohexyl)thiourea (**4a**).* In a 50 mL round-bottom flask, (1*R*,2*R*)-2-(5-phenyl-1*H*-imidazol-1-yl)cyclohexanamine (217 mg, 0.9 mmol) was dissolved in dry THF (5.0 mL) and 3,5-bis-(trifluoromethyl)phenyl isothiocyanate (243.9 mg, 0.9 mmol) was added dropwise. After the reaction mixture was stirred for 48 h at room temperature, it was concentrated and purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate (1/2)), yielding the product as a yellow solid (316 mg, 68%). Mp: 177−178 °C.

IR (KBr): 3313, 3052, 2945, 2865, 1542, 1474, 1386, 1277, 1178, 1133 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ + d_6-DMSO): δ 9.76 (s, 1H, NH), 8.20 (s, 2H), 8.04 (s, 1H), 7.83 (d, 1H, J = 8.6), 7.43−7.52 (m, 5H), 7.03 (s, 1H, ^{imidazole}NC*H*C), 5.04 (s, 1H, NH), 4.09−4.17 (m, 2H, $^{c\text{-}hex}$C*H*N), 2.32 (d, 1H, J = 12.6, $^{c\text{-}hex}C\mathit{H}_2$), 2.07 (d, 1H, J = 12.6, $^{c\text{-}hex}C\mathit{H}_2$), 1.81 (br, 2H, $^{c\text{-}hex}C\mathit{H}_2$), 1.61−1.71 (m, 1H, $^{c\text{-}hex}C\mathit{H}_2$), 1.44−1.55 (m, 1H, $^{c\text{-}hex}C\mathit{H}_2$), 1.21−1.35 (m, 2H, $^{c\text{-}hex}C\mathit{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$ + d_6-DMSO): δ 180.1, 140.9, 135.5, 132.6, 130.6 (q, $^2J_{CF}$ = 33.3), 129.1, 128.8, 128.4, 127.9, 126.1, 122.7 (q, $^1J_{CF}$ = 272.9), 121.8, 116.2, 58.2, 55.0, 34.6, 32.1, 24.4, 24.0. Anal. Calcd for $C_{24}H_{22}F_6N_4S$ (512.15): C, 56.24; H, 4.33; N, 10.93. Found: C, 56.58; H, 4.41; N, 10.72.

*1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,2R)-2-(5-phenyl-1H-imidazol-1-yl)cyclohexyl)urea (**4b**).* In a 25 mL round-bottom flask, (1*R*,2*R*)-2-(5-phenyl-1*H*-imidazol-1-yl)cyclohexanamine (154.0 mg, 0.64 mmol) was dissolved in dry THF (5.0 mL) and 3,5-bis(trifluoromethyl)phenyl isocyanate (179.5 mg, 0.70 mmol) was added dropwise. After the reaction mixture was stirred overnight, it was concentrated and purified by flash column chromatography on silica gel (ethyl acetate as eluent), yielding the product as a pale yellow solid (195 mg, 61%). Mp: 133−134 °C.

IR (KBr): 3357, 3082, 2942, 2864, 1708, 1564, 1475, 1389, 1278, 1130 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1H, NH), 7.75 (s, 2H), 7.67 (s, 1H), 7.41−7.30 (m, 6H), 6.86 (s, 1H, ^{imidazole}NC*H*C), 6.45 (d, J = 7.1, 1H), 4.24−4.29 (m, 1H, $^{c\text{-}hex}$C*H*N), 3.71−3.73 (m, 1H, $^{c\text{-}hex}$C*H*N), 3.06 (br, 2H), 2.15−2.04 (m, 2H, $^{c\text{-}hex}C\mathit{H}_2$), 1.74−1.76 (m, 3H, $^{c\text{-}hex}C\mathit{H}_2$), 1.49−1.58 (m, 1H, $^{c\text{-}hex}C\mathit{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 154.7, 141.4, 135.7, 134.6, 131.8 (q, $^2J_{CF}$ = 33.0), 129.7, 129.0, 128.9, 128.8, 125.6, 123.2 (q, $^1J_{CF}$ = 272.9), 117.7, 114.8, 77.3, 54.8, 34.4, 32.5, 25.0, 24.9. HRMS: m/z calcd for $C_{24}H_{22}F_6N_4O$ 496.1692, found 496.1719. Anal. Calcd for $C_{24}H_{22}F_6N_4O$ (496.17): C, 58.06; H, 4.47; N, 11.28. Found: C, 57.94; H, 4.39; N, 11.69.

Catalysts **5**[10,38] and **6**[13] were prepared according to published protocols.

General Procedures for Enantioselective Aldehyde Cyanosilylations. Under anargon atmosphere, an oven-dried 10 mL Schlenk flask equipped with a magnetic stir bar was charged with the aldehyde (0.2 mmol), catalyst **4a** (10 mol %), acid cocatalyst **9** (10 mol %), and anhydrous toluene (1.0 mL). The flask was sealed with a rubber septum and cooled to −30 °C. TMSCN (40.2 μL, 0.3 mmol) was added dropwise, and the reaction progress was monitored with GC/MS. After the indication of a complete conversion (some substrates cannot be completely converted), the respective TMS-protected cyanohydrins were converted in situ to the corresponding cyanohydrin acetate products by the following procedure, which allows convenient determination of ee values by chiral GC. The reaction mixture was quenched with 1 M HCl (2.0 mL) and ethyl acetate (5.0 mL). After the mixture was stirred for 3 h at room temperature, the organic phase was separated and the aqueous layer was extracted with ethyl acetate (2 × 5.0 mL). The organic extracts were combined, washed with brine (5.0 mL), and dried over Na_2SO_4. The evaporation of the solvent afforded the corresponding crude cyanohydrin, which was dissolved in CH_2Cl_2 (1.0 mL) and converted to the acetate by reaction with pyridine (2 equiv) and Ac_2O (2 equiv) from −30 °C to room temperature for 30 min and diluted with 1 M HCl (5.0 mL) and ethyl acetate (10.0 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10.0 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (5.0 mL) and brine (5.0 mL), dried over Na_2SO_4, and evaporated to give the crude cyanohydrin acetate, which was purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate (10/1)), affording the desired product.

*Cyano(3-methylphenyl)methyl Acetate (**10b**).*[39,40] ^1H NMR (400 MHz, $CDCl_3$): δ 7.29−7.18 (m, 4H), 6.30 (s, 1H), 2.32 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 139.3, 131.6, 131.2, 129.2, 128.5, 125.0, 116.2, 62.9, 21.3, 20.5. The enantiomeric excess was determined to be 46% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 24.92 min, t_R(major) = 26.96 min.

*Cyano(p-tolyl)methyl Acetate (**10c**).*[39] ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.0, 2H), 7.26 (d, J = 8.0, 2H), 6.38 (s, 1H), 2.21 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 140.7, 129.9, 128.9, 127.9, 116.3, 62.8, 21.3, 20.5. The enantiomeric excess was determined to be 84% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 26.37 min, t_R(major) = 29.34 min.

*Cyano(2-methoxyphenyl)methyl Acetate (**10d**).*[39] ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, J = 7.6, 1.6, 1H), 7.43 (td, J = 8.0, 1.6, 1H), 7.04 (td, J = 7.6, 0.9, 1H), 6.94 (d, J = 8.3, 1H), 6.71 (s, 1H), 3.88 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 156.7, 131.8, 128.8, 121.0, 119.9, 116.3, 111.1, 58.2, 55.8, 20.5. The enantiomeric excess was determined to be 8% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 32.62 min, t_R(major) = 33.40 min.

*Cyano(3-methoxyphenyl)methyl Acetate (**10e**).*[39,40] ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, J = 8.0, 1H), 7.09 (d, J = 7.8, 1H), 7.02−7.04 (m, 1H), 7.00−6.97 (m, 1H), 6.38 (s, 1H), 3.84 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 160.1, 133.0, 130.4, 120.0, 116.1, 116.0, 113.2, 62.7, 55.4, 20.5. The enantiomeric excess was determined to be 58% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 32.85 min, t_R(major) = 34.35 min.

*Cyano(4-methoxyphenyl)methyl Acetate (**10f**).*[39,41] ^1H NMR (400 MHz, $CDCl_3$): δ 7.53−7.56 (m, 2H), 7.17−7.20 (m, 2H), 6.35 (s, 1H), 3.76 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 161.2, 129.7, 123.8, 116.4, 114.6, 62.6, 55.4, 20.6. The enantiomeric excess was determined to be 68% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 35.75 min, t_R(major) = 38.05 min.

*Cyano(2-fluorophenyl)methyl Acetate (**10g**).*[42] ^1H NMR (400 MHz, $CDCl_3$): δ 7.62−7.66 (m, 2H), 7.50−7.45 (m, 1H), 7.28−7.24 (m, 1H), 7.18−7.13 (m, 1H), 6.63 (s, 1H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 160.1 (d, J = 252.1), 132.6 (d. J = 8.7), 129.6 (d, J = 2.2), 124.9 (d, J = 3.7), 119.3 (d, J = 13.3), 116.2 (d, J = 20.6), 115.3, 57.4, 20.3. HRMS: m/z calcd for $C_{10}H_8FNO_2$ 193.053 36, found 193.055 05. The enantiomeric excess was determined to be 42% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 23.23 min, t_R(major) = 24.88 min.

*Cyano(4-fluorophenyl)methyl Acetate (**10h**).*[43] ^1H NMR (400 MHz, $CDCl_3$): δ 7.54−7.50 (m, 2H), 7.16−7.12 (m, 2H), 6.38 (s, 1H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 163.8 (d, J = 252.2), 130.1 (d. J = 9.0), 127.8 (d, J = 3.0), 116.4 (d, J = 22.0), 116.0, 62.2, 20.5. The enantiomeric excess was determined to be 82% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 21.97 min, t_R(major) = 26.22 min.

*(3-Chlorophenyl)(cyano)methyl Acetate (**10i**).*[39,40] ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.53 (m, 1H), 7.46−7.38 (m, 3H), 6.39 (s, 1H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 135.3, 133.5, 130.7, 130.6, 128.0, 126.0, 115.6, 62.1, 20.4. The enantiomeric excess was determined to be 65% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 29.88 min, t_R(major) = 32.56 min.

*Cyano(4-bromophenyl)methyl Acetate (**10j**).*[40] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.61 (m, 2H), 7.38−7.39 (m, 2H), 6.36 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 132.5, 130.8, 129.5, 124.9, 115.6, 62.2, 20.4. The enantiomeric excess was determined to be 85% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 36.44 min, t_R(major) = 39.66 min.

*Cyano[4-(trifluoromethyl)phenyl]methyl Acetate (**10k**).*[40] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.2, 2H), 7.66 (d, J = 8.2, 2H), 6.46 (s, 1H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 135.5, 132.6 (q, J = 32.8), 128.3, 126.3 (q, J = 3.6), 123.5 (q, J = 272.2), 115.5, 62.1, 20.4. The enantiomeric excess was determined to be 82% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 22.73 min, t_R(major) = 29.08 min.

*Cyano(4-acetyloxyphenyl)methyl Acetate (**10l**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02−8.04 (m, 2H), 7.61−7.63 (m, 2H), 6.41 (s, 1H), 2.63 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 168.9, 152.1, 129.4, 129.3, 122.6, 116.0, 62.2, 21.1, 20.5. Anal. Calcd for $C_{12}H_{11}NO_4$ (233.22): C, 61.80; H, 4.75; N, 6.00. Found: C, 61.45; H, 4.64; N, 6.10. The enantiomeric excess was determined to be 77% by chiral GC analysis (Hydrodex-β-6-TBDM, 100−250 °C, 2 °C/min, 11.5 psi): t_R(minor) = 44.76 min, t_R(major) = 46.63 min.

*Cyano(4-allyloxyphenyl)methyl Acetate (**10m**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.46 (m, 2H), 6.94−6.98 (m, 2H), 6.35 (s, 1H), 6.09−5.99 (m, 1H), 5.45−5.39 (m, 1H), 5.33−5.30 (m, 1H), 4.56 (m, 2H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 160.2, 132.6, 129.7, 124.0, 118.1, 116.3, 115.3, 68.9, 62.6, 20.6. Anal. Calcd for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.61; H, 5.61; N, 5.61. The enantiomeric excess was determined to be 83% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 43.71 min, t_R(major) = 46.22 min.

*(E)-1-Cyano-3-phenylallyl Acetate (**10n**).*[44,45] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.32 (m, 5H), 6.98 (d, J = 15.7, 1H), 6.20 (dd, J = 15.7, 6.7, 1H), 6.03 (d, J = 6.7, 1H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 137.9, 134.4, 129.5, 128.9, 127.2, 118.3, 115.5, 61.5, 20.5. The enantiomeric excess was determined to be 88% by chiral HPLC analysis with a Chiralpak IA (hexane/i-PrOH 98/2, 254 nm, 0.7 mL/min): t_R(minor) = 15.42 min, t_R(major) = 17.50 min.

*Cyano(cyclohexyl)methyl Acetate (**10o**).*[44,46] ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.17 (d, J = 6.1, 1H), 2.14 (s, 3H), 1.92−1.96 (m, 6H), 1.33−1.07 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 116.2, 65.6, 40.0, 28.1, 27.9, 25.7, 25.34, 25.27, 20.4. The enantiomeric excess was determined to be 18% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 21.04 min, t_R(major) = 25.17 min.

*1-Cyanooctyl Acetate (**10p**).*[46] ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30 (t, J = 6.8, 1H), 2.13 (s, 3H), 1.91−1.85 (m, 2H), 1.52−1.44 (m, 2H), 1.40−1.20 (m, 8H), 0.87 (t, J = 6.9, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 117.0, 61.1, 32.3, 31.6, 28.9, 28.8, 24.5, 22.6, 20.4, 14.0. The enantiomeric excess was determined to be 51% by chiral GC analysis (Chiraldex γ-TA, 100−180 °C, 2 °C/min, 11.5 psi): t_R(minor) = 22.98 min, t_R(major) = 26.88 min.

Computational Studies. We computed various conformers of catalyst **4a** in combination with and without benzoic acid and in combination with benzoic acid and benzaldehyde to investigate the active catalyst system in solution. All computations were done with the Gaussian09 program suite. The M06 density functional theory method was used in conjunction with a 6-31G(d,p) basis set in the gas phase.[47] The computations were also performed with a self-consistent reaction field (SCRF) model to determine the solvent effects in benzene.[48] The bulk solvent was described with the united atom topological model (UAHF) applied on radii optimized for the HF/6-31G(d) level of theory. All given energies (ΔH_0) include ZPVE corrections.

■ ASSOCIATED CONTENT

Supporting Information

Text, tables, and figures giving general information on materials and analyses, NMR and ESI-MS studies, computational data including all computational results on conformational analysis of the catalyst and complexes with benzoic acid and benzaldehyde, respectively, Cartesian coordinates, and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This is apparently due to the strong hydrogen-bonding interactions between the thiourea N−H hydrogen and the electron lone pair of the nitrogen of the oxazoline ring as evident from the very different chemical shifts of the NH protons. The two broad signals for the NH protons appear at 13.3−10.1 ppm and 10.1−8.7 ppm ($CDCl_3$). Computations on **2a−g** support the notion of a strong intramolecular hydrogen bond. As a consequence, the binding ability of **2a−g** is drastically reduced.
(22) When working with aldehydes as substrates, particular care is called for, as they are often readily oxidized to their corresponding acids. See, for instance: Zhang, Z.; Schreiner, P. R. *Synlett* **2007**, 1455−1457.
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(27) As shown in Table 2, substituted benzoic acids behave similarly to the parent system.
(28) We found shifts of the stretching vibrations of the cyclohexyl methine C−H bonds of about ∼400 cm^{-1}; at this time the reasons for these unphysical shifts are unclear but only occur when using the UAHF model in solvent computations.
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