Catalytic Asymmetric Synthesis of Both Enantiomers of 4-Substituted 1,4-Dihydropyridines with the Use of Bifunctional Thiourea-Ammonium Salts Bearing Different Counterions

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Abstract: Organoammonium salts composed of a Brønsted acid and an anilinothiourea promoted the Michael addition of β-keto esters and α,β-unsaturated aldehydes in the presence of primary amines to give functionalized 1,4-dihydropyridines enantioselectively. With the use of the different Bronsted acids such as DFA and HBF₄ with the same bifunctional thiourea, both enantiomers of 4-substituted 1,4-dihydropyridine were synthesized from the same starting materials.

Keywords: bifunctional thiourea-ammonium salt; aminothiourea; Brønsted acid; 1,4-dihydropyridines; Michael addition; α,β-unsaturated aldehydes, β-keto esters

1. Introduction

Asymmetric catalysis using bifunctional catalysts has attracted considerable attention in synthetic organic chemistry. Various types of bifunctional metal- [1-4] and organo-catalysts [5,6] have been developed and used for catalytic enantioselective reactions over the past decade. Generally, bifunctional acid-base catalysts concurrently activate both nucleophiles and electrophiles to promote addition reactions with high catalytic activity and excellent stereoselectivity via a dual activation mechanism [7,8]. We have previously reported that bifunctional aminothiourea 1 could be used for the asymmetric 1,2- and 1,4-addition of various active methylene compounds to imines and nitroolefins [see (a) in
A different approach to asymmetric organocatalysis has been realized through the use of conjugated acid systems, such as in Diels-Alder and aldol reactions [12-15]. By combining these two concepts, we recently realized Brønsted acid-bifunctional thiourea co-catalysis, in which bifunctional thiourea not only activates an achiral Brønsted acid, but also changes its reaction mode to give the alternative regioisomer as a major product, albeit with moderate enantioselectivity [16]. Our working hypothesis is shown in Figure 1, (b) and (c). When thiourea 1 and a Brønsted acid (HX) are mixed in a 1:1 ratio, ammonium salt complexes A and B are equilibrated with the starting materials 1 and HX, depending on the acidity of HX and the hydrogen-bonding (H-bonding) ability of the conjugate base (X⁻). If the conjugate base is a strong H-bonding acceptor, H-bonding complex A, in which X⁻ is anchored to the thiourea moiety by H-bonds, would be predominant. Otherwise, ion-pair complex B might prevail. The difference between the original bifunctional thiourea 1 and ammonium salt A is that the conjugate base (X⁻) acts not as a nucleophile, but as a base, which activates a co-existing nucleophile (Nu-H) such as enamino ester or β-keto ester. To explore this hypothesis, a wide range of Brønsted acid-bifunctional thiourea co-catalysts were synthesized and examined. In this article, we describe the details of the versatility of various Brønsted acid-bifunctional thiourea co-catalysts [17,18] together with their application to the asymmetric synthesis of functionalized 1,4-dihydropyridines.

**Figure 1.** Proposed dual activation mode of aminothiourea.
2. Results and Discussion

1,4-Dihydropyridines (1,4-DHPs) and their derivatives are important bioactive compounds and versatile synthetic intermediates in the pharmaceutical industry and in process chemistry. Due to the need for 1,4-DHP derivatives, various synthetic methods have been developed [19-22]. Although symmetrical 1,4-DHP can be easily prepared by the well-known Hantzsch method [23], new methods for the synthesis of unsymmetrical DHPs are still needed. Furthermore, there have been only a few reports on the organocatalytic enantioselective synthesis of 1,4-DHP [24-26]. These routes are shown in Scheme 1. The highly enantioselective synthesis of 1,4-DHP via route a from cinnamaldehyde, arylamine, and a 1,3-dicarbonyl compound with a chiral phosphoric acid was achieved by Gong’s group [24]. Similarly, Renaud et al. reported that another chiral phosphoric acid catalyzed three-component cyclization to afford the product with moderate selectivity (50% ee) via route b [25]. Therefore, we examined three-component cyclization via both routes a and b in the presence of the Brønsted acid-bifunctional thiourea co-catalysts to test their abilities in asymmetric reactions.

Scheme 1. Synthetic routes to 1,4-DHPs.

2.1. Synthesis of chiral bifunctional thioureas 1a-h for Brønsted acid-thiourea co-catalysts

To investigate the catalytic potential of various Brønsted acid-thiourea co-catalysts, we first synthesized several bifunctional thioureas 1a-h bearing a functional group, such as a hydroxy or N-arylamino group, which have different Brønsted basicities (Figure 2). By changing the basicity of the second functional group of the thiourea catalyst as well as the acidity of Brønsted acid, we can tune both the acidity of the oxonium or ammonium proton and the basicity of the counterion (X\(^{-}\)).

To synthesize N-arylaminothioureas 1d-h, we examined two synthetic routes. In the first Buchwald-type amination of (R,R)-1,2-cyclohexyldiamine with appropriate aryl iodides was used as a key step (Scheme 2). However, the key reaction gave the desired products 1d and 1e in low yields. We then used the second route to synthesize more functionalized catalysts 1f-h, which involved the diastereoselective ring-opening of chiral aziridine 2 [27] with functionalized anilines, as shown in Scheme 3. The ring-opening of 2 with the corresponding anilines produced the two diastereomers 3f-h and 4f-h. The absolute configurations of 3f and 4f were determined to be (1S,2S,1'S) and (1R,2R,1'S'), respectively, based on the results of an X-ray single crystallographic analysis of 4f. The stereochemistries of other products 3g-h and 4g-h were deduced from this result for 4f (Scheme 3). The hydrogenation and thiocarbamoylation of 3f-h provided the desired thioureas 1f-h in good yields.
Figure 2. Structures of thiourea catalysts employed.

1a

1b

1c

1d: X = Y = H  
1e: X = OMe, Y = H 
1f: X = F, Y = OMe 
1g: X = Y = OMe 
1h: X = F, Y = O'Pr 

(Ar = 3,5-(CF3)2-C6H3)

Scheme 2. Synthesis of thiourea (R, R)-1d and 1e.

NPh

R2

R1

cat. B(C6F5)3

MeCN, 65 ºC, 36 h

R1

R2

(1S,2S,1'S)-3f-h

(1R,2R,1'S)-4f-h

R1 = F, R2 = MeO (3f: 43%, 4f: 17%) 
R1 = F, R2 = MeO (3g: 52%, 4g: 25%) 
R1 = F, R2 = i-PrO (3h: 57%, 4h: 11%)

Scheme 3. Synthesis of thiourea (R, R)-1f-h.

NPh

Ph

R1

R2

R1

R2

Pd/C

HCO2NH4

MeOH, 50 ºC, 12 h

DCM, rt, 3 h

(1S,2S,1'S)-3f-h

(1R,2R,1'S)-4f-h

Pd/C

HCO2NH4

MeOH, 50 ºC, 12 h

DCM, rt, 3 h

(S, S)-1f (84%) 
(S, S)-1g (72%) 
(S, S)-1h (81%)
2.2. Brønsted acid-bifunctional thiourea co-catalysts for the synthesis of 3,4-disubstituted 1,4-DHPs

We initially investigated the reaction of enamino ester 5a and α,β-unsaturated aldehyde 6a in toluene with Brønsted acid-bifunctional thiourea co-catalysts as well as achiral Brønsted acids. Representative results are summarized in Table 1. Notably, strong Brønsted acids such as HBF₄ and TfOH provided the desired 1,4-DHP 7aa as a major product, while the same reactions with TFA (trifluoroacetic acid) and DFA (difluoroacetic acid) afforded mixtures of 1,4-DHP 7aa and 1,2-DHP 8aa in ratios of 2:1 and 1:2, respectively. In contrast, a weak Brønsted acid such as AcOH did not give any products, and only the starting materials were recovered. These results indicate that the acidity of the catalyst significantly affected the yield and regioselectivity of the products. On the other hand, neither aminothiourea 1a nor DFA-1a co-catalyst furnished any of the desired DHP's in the same reaction. In an attempt to decrease the Brønsted basicity of bifunctional thiourea, we used hydroxythioureas 1b and 1c with DFA, but this only had marginal effects on the chemical yield and stereoselectivity. However, the desired product 7aa was obtained in 74% yield with better regio- and enantioselectivities (7aa/8aa = 72/17 and 39% ee) with the use of 10 mol% of DFA-chiral N-arylaminothiourea 1f as a co-catalyst.

Table 1. Initial screening of various catalysts for the synthesis of 1,4-DHP 7aa.

| Entry | Thiourea | BA  | Time (h) | Conversion (%)b | 7aa | 8aa | Yield (%)c | Ee (%)d | Yield (%)c | Ee (%)d |
|-------|----------|-----|----------|-----------------|-----|-----|------------|---------|------------|---------|
| 1     | None     | HBF₄| 24       | 40              | 6   | -   | -          | -       | -          | -       |
| 2     | None     | TfOH| 24       | 40              | 1   | -   | -          | -       | -          | -       |
| 3     | None     | TFA | 24       | 64              | 35  | -   | -          | -       | -          | -       |
| 4     | None     | DFA | 24       | 35              | 64  | -   | -          | -       | -          | -       |
| 5     | None     | AcOH| 24       | 0               | 0   | -   | -          | -       | -          | -       |
| 6     | (R, R)-1a| None| 48       | 0               | 0   | -   | -          | -       | -          | -       |
| 7     | (R, R)-1a| DFA | 48       | 0               | 0   | -   | -          | -       | -          | -       |
| 8     | (R, R)-1b| DFA | 36       | 46              | 47  | 33  | 1          | 41      | 1          | 1       |
| 9     | (R, R)-1c| DFA | 36       | 29              | 56  | 24  | 1          | 48      | 1          | 1       |
| 10    | (S, S)-1f| DFA | 24       | 79              | 19  | 72  | 39 (R)    | 17      | 0          |         |

a The reactions were carried out with 5a (0.1 mmol), 6a (0.1 mmol), thiourea (10 mol%) and Brønsted acid (10 mol%) in toluene (1 mL) at room temperature; b Conversion as determined by ¹H-NMR; c Isolated yield; d Determined by HPLC.

Since the co-catalysts DFA and N-arylaminothiourea 1f gave good results, a wide range of Bronsted acids were next examined in the presence of 1f (Table 2). As a result, while the addition of acids [HBF₄, TfOH, TFA, TCA, perfluorobenzoic acid (PFB)] stronger than DFA (entries 2–6) led to a decrease in enantioselectivity, the concurrent use of 1f and a weak acid such as AcOH or BzOH significantly improved the enantioselectivity to give the same enantiomer (R)-7aa with more than 70% ee, albeit in
low yield (entries 7 and 8). Since the reaction did not occur with either AcOH or bifunctional thiourea 1f, we can surmise that bifunctional thiourea 1f would activate AcOH by forming H-bond complex A or ion-pair complex B. Since AcO\(^-\) is well-known to be a good H-bond acceptor, in contrast to BF\(_4^-\) and OTf\(^-\), the H-bond complex A could be the actual catalyst. Unfortunately, despite many trials with AcOH and BzOH under various conditions, the chemical yield could not be enhanced without a decrease in ee.

Table 2. Effect of Brønsted acids in the presence of 1f for the synthesis of 1,4-DHP 7aa.

| Entry | Brønsted acid | Time (h) | Yield (%) \(^b\) | Ee (%) \(^c\) |
|-------|---------------|----------|------------------|----------|
| 1     | HBF\(_4\)     | 48       | 68               | 16       |
| 2     | TfOH          | 48       | 78               | 19       |
| 3     | TFA           | 46       | 64               | 29       |
| 4     | TCA           | 46       | 83               | 34       |
| 5     | DFA           | 48       | 72               | 39       |
| 6     | C\(_6\)F\(_5\)CO\(_2\)H | 24       | 61               | 37       |
| 7     | AcOH          | 48       | 11               | 78       |
| 8     | BzOH          | 48       | 17               | 75       |

\(^a\) The reactions were carried out with 5a (0.1 mmol), 6a (0.1 mmol), thiourea (S,S)-1f (10 mol%) and Brønsted acid (10 mol%) in toluene (1 mL) at room temperature; \(^b\) Isolated yield. \(^c\) Determined by HPLC.

Therefore, we selected DFA as an optimized Brønsted acid and turned our attention to \(N\)-aryl-aminothioureas 1d-h to improve the stereoselectivity (Table 3). Due to the instability of enamo ester 5a under the reaction conditions, the slow addition of 5a to the reaction mixture of 6a and co-catalyst 1f-DFA in toluene was examined, which resulted in the exclusive formation of 4aa in 86% yield with 50% ee (entry 1). Thus, DFA-catalyzed reactions with several bifunctional thioureas 1e-h were carried out under slow-addition conditions. The use of phenyl- and mono-substituted anilines 1d and 1e as catalysts led to a slight decrease in ee (entries 2 and 3). In contrast, the catalysts 1g bearing a 2,4-dimethoxypyphenyl group gave the same product with a slightly enhanced enantioselectivity, while a similar result was obtained with more bulky catalyst 1h bearing a 2-fluoro-4-isopropoxyaniline group (entries 4 and 5). Furthermore, other enamo esters 5b and 5c, prepared from different primary amines, also underwent cyclization to afford the corresponding products 7ba and 7ca with moderate ee's (entries 6 and 7). Despite several trials, we could not improve the enantioselectivity of 3,4-disubstituted 1,4-DHP's 7aa-7ca.
Table 3. Effect of N-arylaminothioureas in the presence of DFA for the synthesis of 1,4-DHP's.

\[
\begin{align*}
R^1\text{-NH} & \quad \text{CO}_2\text{Et} \quad + \quad R^2\text{CHO} \\
5\text{a} (R^1 = 4-\text{MeO-C}_6\text{H}_4) & \quad 6\text{a} (R^2 = 4-\text{NO}_2\text{-C}_6\text{H}_4) \\
5\text{b} (R^1 = 4-\text{Cl-C}_6\text{H}_4) & \\
5\text{c} (R^1 = \text{C}_6\text{H}_5\text{CH}_2) & \\
\end{align*}
\]

| Entry | Thiourea 1 | β-Enamino ester 5 | Product 7 | Yield (%) \text{b} | Ee (%) \text{c} |
|-------|------------|------------------|-----------|---------------------|-----------------|
| 1     | (S, S)-1f  | 5\text{a}       | 7\text{aa} | 86                  | 50 (R)          |
| 2     | (R, R)-1d  | 5\text{a}       | 7\text{aa} | 86                  | 42 (S)          |
| 3     | (R, R)-1e  | 5\text{a}       | 7\text{aa} | 47                  | 41 (S)          |
| 4     | (S, S)-1g  | 5\text{a}       | 7\text{aa} | 91                  | 55 (R)          |
| 5     | (S, S)-1h  | 5\text{a}       | 7\text{aa} | 92                  | 50 (R)          |
| 6     | (S, S)-1h  | 5\text{b}       | 7\text{ba} | 78                  | 49 (R)          |
| 7     | (S, S)-1h  | 5\text{c}       | 7\text{ca} | 83                  | 45 (R)          |

\text{a} Reaction conditions: Slow addition (0.01 mmol/30 min) of β-enamino esters 5a-c (0.1 mmol) to a mixture of α,β-unsaturated aldehydes 6a (0.1 mmol), thiourea 1 (10 mol%) and DFA (10 mol%) in toluene (1 mL) at room temperature. The mixture was stirred for an additional 12 h after completion of the addition; \text{b} Isolated yield; \text{c} Determined by HPLC.

2.3. Application of new thiourea-ammonium salts to the synthesis of 2,3,4-trisubstituted 1,4-DHP's

Having succeeded in the catalytic asymmetric synthesis of 3,4-disubstituted 1,4-DHP's, we next applied this method to the asymmetric synthesis of 2,3,4-trisubstituted 1,4-DHP's (Table 4). For this purpose, we first studied the reaction of enamino ester 5\text{d}, derived from ethyl acetoacetate and 4-methoxyaniline, and 3-(4-nitrophenyl)acrylaldehyde 6\text{a} under the optimized conditions using co-catalysts DFA-1f-h. In fact, all of the reactions provided the desired product 7\text{da} in 65–93% yields and the highest ee was achieved with DFA-1h complex (entries 1-3). Further experiments with β-enamino esters 5e-j and α,β-unsaturated aldehydes 6a-f were performed with DFA-1h (entries 4-14). With regard to the enamino esters, tert-butyl ester 5e and β-phenyl-substituted analogue 5f could be used as nucleophiles without a significant decrease in ee (entries 4 and 5). In addition, both electron-rich aryl and arylmethyl groups of 5g-j could also be tolerated as the substituent (R\text{1}) on the nitrogen (entries 6 and 12-14). Moreover, the reactions of several unsaturated aldehydes 6b-f bearing different aryl groups with 5g provided the corresponding 1,4-DHP's in reasonable yields, but electron-deficient substrates 6d-f generally led to better enantioselectivity than electron-rich substrates 6b and 6c (entries 7–11). The reaction of β-enamino esters with a benzyl group at the nitrogen (R\text{1}) and a methyl group at the β-position (R\text{3}) afforded the corresponding 1,4-DHP's 7\text{ia} and 7\text{ja} with good enantioselectivities (entries 13 and 14).
Table 4. Scope of the substrates 5 and 6 for the synthesis of 2,3,4-trisubstituted 1,4-DHP's.\(^a\)

| Entry | Thiourea | 5 R\(^1\) | R\(^2\) | 6 R\(^3\) | 7 R\(^4\) | Yield (%) | Ee (%) |
|-------|----------|-----------|--------|-----------|----------|-----------|--------|
| 1     | (S, S)-1f| 5d        | Me     | 6a        | 7da      | 84        | 61     |
| 2     | (S, S)-1g| 5d        | Me     | 6a        | 7da      | 65        | 56     |
| 3     | (S, S)-1h| 5d        | Me     | 6a        | 7da      | 93        | 66     |
| 4     | (S, S)-1h| 5e        | Me     | 6a        | 7ea      | 81        | 51     |
| 5     | (S, S)-1h| 5f        | Ph     | 6a        | 7fa      | 85        | 61     |
| 6     | (S, S)-1h| 5g        | Me     | 6a        | 7ga      | 96        | 66     |
| 7     | (S, S)-1h| 5g        | Me     | 6b        | 7gb      | 61        | 44     |
| 8     | (S, S)-1h| 5g        | Me     | 6c        | 7gc      | 56        | 38     |
| 9     | (S, S)-1h| 5g        | Me     | 6d        | 7gd      | 62        | 53     |
| 10    | (S, S)-1h| 5g        | Me     | 6e        | 7ge      | 55        | 58     |
| 11    | (S, S)-1h| 5g        | Me     | 6f        | 7gf      | 70        | 44     |
| 12    | (S, S)-1h| 5h        | Me     | 6a        | 7ha      | 78        | 38     |
| 13    | (S, S)-1h| 5i        | Me     | 6a        | 7ia      | 81        | 80     |
| 14    | (S, S)-1h| 5j        | Me     | 6a        | 7ja      | 65        | 77     |

\(^a\) Reaction conditions: Slow addition (0.01 mmol/30 min) of \(\beta\)-enaminoesters 5d-j (0.1 mmol) to a mixture of \(\alpha,\beta\)-unsaturated aldehydes 6a-f (0.1 mmol), thiourea 1 (10 mol\%) and DFA (10 mol\%) in toluene (1 mL) at room temperature. The mixture was stirred for an additional 12 h after completion of the addition. \(^b\) Isolated yield. \(^c\) Determined by HPLC.

2.4. Utility of thiourea-ammonium salts derived from strong Brønsted acids and anilinothioureas

We have demonstrated that H-bonding complexes A, prepared from anilinothiourea and DFA, efficiently catalyzed the three-component coupling via route b to give the functionalized 1,4-DHP's with moderate to good enantioselectivity. We next examined the alternative reaction path via route a with the Brønsted acid-anilinothiourea co-catalysts. The reaction was performed as follow. \(\beta\)-Keto ester 10 was added to the preformed imines, prepared from \(\alpha,\beta\)-unsaturated aldehyde 6a and \(p\)-anisidine 9, in the presence of various co-catalysts composed of bifunctional thioureas 1d-h and Brønsted acids such as DFA, TFA, TfOH, and HBF\(_4\) (Table 5). Initially we examined the best co-catalyst DFA•(S,S)-1h for route b, which gave the same product (R)-7da in 64% yield with a slightly low ee (entry 1). Although the same treatment of imine and 10 with co-catalyst TFA•(S,S)-1h led to a similar result, an enantiomer of the product (S)-7da was obtained, albeit with poor enantioselectivity, with the use of strong Brønsted acids (TfOH, and HBF\(_4\)) as co-catalysts (entries 2–4). The same trend was observed with other bifunctional thioureas (S,S)-1f, g and (R,R)-1d, e (entries 5–14). Among the various co-catalysts prepared from 1d-h, HBF\(_4\)•(R,R)-1e gave (R)-7da with the highest ee (69% ee) (entry 14). Consequently, we have established a method for the synthesis of both enantiomers of highly functionalized 1,4-DHP's by simply switching the Brønsted acids (DFA and HBF\(_4\)) used as the co-catalysts, starting from the same substrates.
Table 5. Three-component cyclization catalyzed by Brønsted acid-anilinothiourea co-catalysts.a

| Entry | Thiourea | Bronsted acid | Time | Yield (%) b | Ee (%) c |
|-------|----------|---------------|------|-------------|---------|
| 1     | (S, S)-1h | DFA           | 48   | 64          | 50 (R)  |
| 2     | (S, S)-1h | TFA           | 24   | 73          | 49 (R)  |
| 3     | (S, S)-1h | TfOH          | 60   | 82          | 20 (S)  |
| 4     | (S, S)-1h | HBF4          | 72   | 69          | 28 (S)  |
| 5     | (S, S)-1f | DFA           | 48   | 53          | 43 (R)  |
| 6     | (S, S)-1f | TFA           | 24   | 76          | 25 (R)  |
| 7     | (S, S)-1f | TfOH          | 48   | 82          | 50 (S)  |
| 8     | (S, S)-1f | HBF4          | 72   | 61          | 37 (S)  |
| 9     | (S, S)-1g | DFA           | 48   | 49          | 39 (R)  |
| 10    | (S, S)-1g | TFA           | 24   | 82          | 1 (R)   |
| 11    | (S, S)-1g | TfOH          | 60   | 77          | 33 (S)  |
| 12    | (R, R)-1d | TfOH          | 96   | 56          | 39 (R)  |
| 13    | (R, R)-1e | TfOH          | 96   | 69          | 61 (R)  |
| 14    | (R, R)-1e | HBF4          | 72   | 52          | 69 (R)  |

a Reaction conditions: The mixture of 6a (0.15 mmol), p-anisidine 9 (0.1 mmol), thiourea 1 (10 mol%) and Bronsted acid (10 mol%) in toluene (1 mL) was stirred at room temperature for 30 min. After keto ester 10 (0.2 mmol) was added, the resulting mixture was stirred at rt; b Isolated yield. c Determined by HPLC.

2.5. Proposed reaction mechanism of Brønsted acid-anilinothiourea co-catalysis

In a former reaction with carboxylic acid-thiourea co-catalysts, H-bonded ammonium complex A would be equilibrated with free acid (HX) and uncomplexed thiourea 1 due to the weak acidity of HX (Figure 1). If the free acid can promote the reaction, both the catalyzed and uncatalyzed reactions would proceed, to give the product in low enantioselectivity. This is why DFA, which has medium acidity, gave better results than strong acids such as TFA and TCA. In contrast, high enantioselectivity was achieved with the AcOH•(S,S)-1f co-catalyst, since free AcOH has no catalytic activity for the cyclization. This result obviously indicates that an appropriate bifunctional thiourea can activate weak acids to catalyze three-component cyclization, even though the co-catalysts must be weaker acids than the free acids. To explain this result, we speculate that the conjugate base (X-) should play an important role for acceleration of the reaction. Based on this assumption, a proposed reaction mechanism is shown in Figure 3. Initially, the ammonium carboxylate complex A, in which each of two ammonium protons interacts with the carboxylate anion or ortho-substituent of the aniline via H-bond, would be formed from the catalyst 1 and HX. The aldehyde would then interact with one of the ammonium protons of the co-catalyst from the less-hindered side. The protonated aldehyde would be attacked from the bottom face (Si-face) by the enamino ester, which is concurrently deprotonated by the conjugate base. In this transition-state TS-(a), which is energetically more stable than TS-(b), both nucleophile 5 and electrophile 6 are activated simultaneously by HX complexed with the bifunctional anilinothiourea, to generate the desired (S)-product, when (R,R)-thiourea is used.
Similarly, the reaction of \(\alpha,\beta\)-unsaturated imine and \(\beta\)-keto ester with DFA-(\(R,R\))-thiourea 1 can be explained by TS-(c) in Figure 3. In this case, (\(Z\))-imine [28] should coordinate to the ammonium proton of the same co-catalyst and the nucleophile approaches from the same Si-face to predominantly give the (S)-isomer. On the other hand, the ion-pair complex B would be exclusively generated when strong acids such as TfOH, and HBF\(_4\) are reacted with bifunctional thiourea 1. As shown in Figure 3, in TS-(d), the (\(Z\))-imine coordinates to the ammonium proton of the ion-pair complex B in the same way as in TS-(c), but the nucleophile is considered to approach from the less-hindered upper side (Re-face) without any assistance of the conjugate base, since the ammonium proton of the ion-pair complex B should be more acidic than that of the H-bonding complex A, to predominantly give the (R)-isomer.

**Figure 3.** Proposed TS models for the co-catalyzed three-component reaction.

3. Experimental

3.1. General

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. All melting points were determined on a Yamamoto micro melting point apparatus and are uncorrected. \(^1\)H- and \(^13\)C-NMR spectra were recorded in CDCl\(_3\) at 500 or 400 MHz, and at 125 or 100 MHz, respectively; Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a JASCO FT/IR-410 Fourier-transfer infrared spectrometer. Low and High resolution mass spectra were obtained by EI or FAB method. Optical rotations were recorded on a JASCO DIP-360
polarimeter with a path length of 1 cm; concentrations are quoted in mg (2 mL). \([\alpha]^{D}\) values are measured in \(10^{-1}\) deg cm\(^2\) g\(^{-1}\). Enantiomeric excess was determined by high performance liquid chromatography (HPLC) analysis.

3.2. Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,2R)-2-(2-methoxyphenylamino)cyclohexyl)thiourea [(R, R)-1e]

To a solution of (1R,2R)-1,2-diaminocyclohexane (251 mg, 2.20 mmol) in toluene (10 mL) was added 2-bromoanisole (374 mg, 2.00 mmol), rac-BINAP (124 mg, 0.20 mmol), sodium t-butoxide (577 mg, 6.00 mmol) and Pd(OAc)\(_2\) (22.5 mg, 0.10 mmol). After the mixture was stirred at 80 °C for 12 h and cooled at ambient temperature, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo. The resulting residue was passed through silica gel pad (hexane-ethyl acetate = 1:1 to CHCl\(_3\)-CH\(_3\)OH-aq.NH\(_3\) = 100:10:1) to give crude (1R,2R)-N\(_1\)-(2-methoxyphenyl)cyclohexane-1,2-diamine, which was used in next reactions without further purification. This crude material was dissolved with CH\(_2\)Cl\(_2\) (5 mL), and added 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (81.5 mg, 0.30 mmol). After the mixture was stirred at ambient temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (hexane:ethyl acetate = 5:1) to give thiourea (R, R)-1e (95.1 mg, 0.193 mmol, 10%) as a colorless amorphous solid; IR (ATR) 3326, 2925, 1507, 1091 cm\(^{-1}\); 1H-NMR (500 MHz, DMSO-\(d_6\) at 100 °C) \(\delta\) (ppm) 9.68 (s, 1H), 8.17 (s, \(2H\)), 7.94 (br, 1H), 7.61 (s, 1H), 6.76 (d, \(J = 8.0\) Hz, \(1H\)), 6.75 (dd, \(J = 8.0\) and 8.0 Hz, \(1H\)), 6.65 (d, \(J = 8.1\) Hz, \(1H\)), 6.51 (dd, \(J = 8.1\) and 8.0 Hz, \(1H\)), 4.72 (br, \(1H\)), 4.41-4.38 (m, \(1H\)), 3.71 (s, 3H), 3.33-3.30 (m, 1H), 2.16-2.06 (m, \(2H\)), 1.78-1.64 (m, \(2H\)), 1.49-1.18 (m, \(4H\)); 13C-NMR (125 MHz, DMSO-\(d_6\) at 100 °C) \(\delta\) (ppm) 180.4, 146.4, 141.7, 137.3, 129.8 (q, \(2J(C,F) = 33.8\) Hz), 122.8 (q, \(1J(C,F) = 271\) Hz), 121.8, 120.7, 115.4, 115.1, 110.4, 109.5, 56.3, 55.9, 55.2, 31.6, 30.7, 23.8, 23.4; MS (FAB\(^{+}\)) \(m/z\): 492 (M + H\(^+\), 100); HRMS (FAB+) \(m/z\): calcd for C\(_{22}\)H\(_{24}\)F\(_6\)N\(_3\)OS (M + H\(^+\)): 492.1544. Found: 492.1537; \([\alpha]^{D}_{25}\) = -6.1 (c 1.07, CHCl\(_3\)).

3.3. Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,2R)-2-(phenylamino)cyclohexyl)thiourea [(R, R)-1d]

A procedure similar to that described for the preparation of 1e afforded 1d (15%). Colorless amorphous solid; IR (ATR) 3327, 2925, 2858, 1536, 1091 cm\(^{-1}\); 1H-NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) (ppm) 9.95 (s, 1H), 8.19 (br, \(1H\)), 8.18 (s, \(2H\)), 7.69 (s, \(1H\)), 7.04 (dd, \(J = 8.1\) and 7.5 Hz, \(2H\)), 6.63 (d, \(J = 8.1\) Hz, \(2H\)), 6.50 (t, \(J = 7.5\) Hz, \(1H\)), 5.36 (d, \(J = 8.6\) Hz, \(1H\)), 4.27-4.21 (m, \(1H\)), 3.42-3.29 (m, \(1H\)), 2.33-2.01 (m, \(2H\)), 1.78-1.63 (m, \(2H\)), 1.41-1.13 (m, \(4H\)); 13C-NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) (ppm) 179.9, 148.1, 141.8, 130.1 (q, \(2J(C,F) = 33.4\) Hz), 122.8, 121.2 (q, \(1J(C,F) = 272\) Hz), 121.8, 115.9, 115.6, 112.5, 56.5, 55.1, 31.5, 30.7, 24.1, 23.8; MS (FAB\(^{+}\)) \(m/z\): 462 (M + H\(^+\), 100); HRMS (FAB+) \(m/z\): calcd for C\(_{21}\)H\(_{22}\)F\(_6\)N\(_3\)S (M + H\(^+\)): 462.1439. Found: 462.1429; \([\alpha]^{D}_{23}\) = 34.9 (c 1.02, CHCl\(_3\)).

3.4. Synthesis of (1S,2S,1’S)-3f and (1R,2R,1’S)-4f

To a solution of aziridine 2 (603 mg, 3.00 mmol) in CH\(_3\)CN (15 mL) was added 2-fluoro-4-methoxyaniline (430 mg, 3.05 mmol) and tris(perfluorophenyl)borane (154 mg, 0.300 mmol). After the
mixture was stirred at 65 °C for 36 h and cooled at ambient temperature, the reaction mixture was added 0.3 g of Amberlyst A-21 resin and 5 mL of dichloromethane. The mixture was stirred for 1 h then the resin was removed by filtration through a cotton plug. The solvent was removed in vacuo and the residue was purified by flash amino silica gel chromatography (hexane-ethyl acetate = 5:1) to give (1S,2S,1′S)-3f (440 mg, 1.28 mmol, 43%) as a clear oil and (1R,2R,1′S)-4f (175 mg, 0.51 mmol, 17%) as a clear oil that solidified to a white solid after standing.

(1S,2S)-N1-(2-Fluoro-4-methoxyphenyl)-N2-((S)-1-phenylethyl)cyclohexane-1,2-diamine [(1S,2S,1′S)-3f]: Colorless oil; IR (ATR) 3330, 2979, 2921 cm\(^{-1}\); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.34-7.19 (m, 5H), 6.75 (dd, \(J = 9.5\) and 9.5 Hz, 1H), 6.65 (dd, \(J = 12.5\) and 2.5 Hz, 1H), 6.57 (dd, \(J = 9.5\) and 2.5 Hz, 1H), 3.89 (q, \(J = 7.5\) Hz, 1H), 3.74 (s, 3H), 3.67 (br, 1H), 2.93 (dt, \(J = 3.5\) and 9.5 Hz, 1H), 2.48 (dt, \(J = 3.5\) and 9.9 Hz, 1H), 2.14-2.09 (m, 1H), 1.89-1.83 (m, 1H), 1.68-1.57 (m, 2H), 1.32 (d, \(J = 7.5\) Hz, 3H), 1.29-1.00 (m, 4H); \(^13\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) (ppm) 152.8 (d, \(^1J_{(C,F)} = 242\) Hz), 151.9 (d, \(^3J_{(C,F)} = 6.0\) Hz), 147.3, 130.5 (d, \(^2J_{(C,F)} = 12.0\) Hz), 128.3, 126.6, 126.5, 115.2 (d, \(^3J_{(C,F)} = 3.6\) Hz), 109.4 (d, \(^4J_{(C,F)} = 3.5\) Hz), 102.3 (d, \(^2J_{(C,F)} = 22.8\) Hz), 60.5, 59.0, 56.2, 55.9, 32.72, 32.66, 24.79, 24.76, 24.1; MS (FAB\(^+\)) \(m/z\): 342 (M\(^+\), 100); HRMS (FAB\(^+\)) \(m/z\): calcd for C\(_{21}\)H\(_{27}\)FN\(_2\)O (M\(^+\)): 342.2107. Found: 342.2110; \([\alpha]_D^{26} = 34.5\) (c 1.16, CHCl\(_3\)).

(1R,2R)-N1-(2-Fluoro-4-methoxyphenyl)-N2-((S)-1-phenylethyl)cyclohexane-1,2-diamine [(1R,2R,1′S)-4f]: White solid; Mp. 57–58 °C (hexane); IR (ATR) 3359, 2973, 2924 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.38-7.24 (m, 5H), 6.71 (dd, \(J = 9.2\) and 9.2 Hz, 1H), 6.64 (dd, \(J = 13.1\) and 2.9 Hz, 1H), 6.58 (dd, \(J = 9.2\) and 2.9 Hz, 1H), 3.90 (q, \(J = 7.5\) Hz, 1H), 3.74 (s, 3H), 3.25 (br, 1H), 2.98-2.96 (m, 1H), 2.18-2.14 (m, 1H), 2.08-2.02 (m, 2H), 1.70-1.59 (m, 2H), 1.33 (d, \(J = 7.5\) Hz, 3H), 1.29-1.05 (m, 3H), 0.94-0.85 (m, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) (ppm) 152.7 (d, \(^1J_{(C,F)} = 238\) Hz), 151.8 (d, \(^3J_{(C,F)} = 9.5\) Hz), 145.8, 130.2 (d, \(^2J_{(C,F)} = 11.9\) Hz), 128.3, 126.6, 126.4, 114.8 (d, \(^3J_{(C,F)} = 3.6\) Hz), 109.4 (d, \(^4J_{(C,F)} = 3.6\) Hz), 102.4 (d, \(^2J_{(C,F)} = 22.7\) Hz), 58.4, 57.9, 55.9, 54.3, 32.3, 31.3, 25.3, 24.9, 24.4; MS (FAB\(^+\)) \(m/z\): 342 (M\(^+\), 100); HRMS (FAB\(^+\)) \(m/z\): calcd for C\(_{21}\)H\(_{27}\)FN\(_2\)O (M\(^+\)): 342.2107. Found: 342.2109; \([\alpha]_D^{26} = 50.7\) (c 1.03, CHCl\(_3\)). Single crystals suitable for X-ray diffraction were grown by cooling a solution of (1R,2R,1′S)-4f in hexane in a closed tube to -20 °C. The crystal data of (1R,2R,1′S)-4f are as follows: space group, P\(_21\); a = 8.5306(19) Å, b = 14.839(4) Å, c = 14.805(4) Å, \(V = 1874.1(8) \text{ Å}^3\), Z = 4, \(D_{calc} = 1.214 \text{ g/cm}^3\), \(R = 0.0568\), \(R_w = 0.1334\), GOF = 0.930. CCDC 768496 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3.5. Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1S,2S)-2-(2-fluoro-4-methoxyphenylamino)cyclohexyl)thiourea [(S, S)-1f]

To a solution of (1S,2S,1′S)-3f (350 mg, 1.02 mmol) in CH\(_3\)OH (15 mL) was added 10% Pd/C (100 mg) and ammonium formate (1.50 g). After the mixture was stirred at 60 °C for 12 h and cooled at ambient temperature, the mixture was filtered through through a pad of celite. The filtrate was concentrated in vacuo, The resulting material was dissolved with CH\(_2\)Cl\(_2\) (5 mL), and added 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (280 mg, 1.00 mmol). After the mixture was stirred at ambient temperature for 3 h, the reaction mixture was concentrated in vacuo. The residue was purified
by silica gel chromatography (hexane-ethyl acetate = 5:1) to give (S, S)-1f (436 mg, 0.856 mmol, 84%) as a colorless amorphous solid; IR (ATR) 3275, 2937, 1514, 1278, 1090 cm⁻¹; ¹H-NMR (500 MHz, DMSO-d₆) δ (ppm) 9.98 (s, 1H), 8.27 (br, 1H), 8.17 (s, 2H), 7.69 (s, 1H), 6.78 (dd, J = 9.2 and 8.6 Hz, 1H), 6.72 (dd, J = 13.2 and 2.3 Hz, 1H), 6.61 (dd, J = 8.6 and 2.3 Hz, 1H), 4.69-4.66 (m, 1H), 4.39 (br, 1H), 3.65 (s, 3H), 3.32-3.26 (m, 1H), 2.21-2.02 (m, 2H), 1.74-1.67 (m, 2H), 1.41-1.20 (m, 4H); ¹³C-NMR (125 MHz, DMSO-d₆) δ (ppm) 180.2, 150.4 (d, 3J(C,F) = 9.5 Hz), 151.3 (d, 1J(C,F) = 237 Hz), 141.9, 130.2 (q, 2J(C,F) = 11.9 Hz), 123.2 (q, 1J(C,F) = 272 Hz), 121.8, 115.8, 113.5, 109.6, 102.1 (d, 2J(C,F) = 22.6 Hz), 79.2, 56.7, 55.5, 31.9, 31.1, 24.4, 24.0; MS (FAB⁺) m/z: 438 (M + H⁺, 100); HRMS (FAB⁺) m/z: calecd for C₂₂H₂₃F₇N₃OS (M + H⁺): 510.1450. Found: 510.1438; [α]D²⁴ = -49.0 (c 1.02, CHCl₃).

3.6. Synthesis of (1S,2S,1' S)-3g and (1R,2R,1' S)-4g

By a similar procedure described for the preparation of (1S,2S,1' S)-3f and (1R,2R,1' S)-4f, (1S,2S,1' S)-3g (550 mg, 1.55 mmol, 52%) and (1R,2R,1' S)-4g (270 mg, 0.76 mmol, 25%) were obtained from 2 (603 mg, 3.00 mmol) and 2,4-dimethoxyaniline (470 mg, 3.07 mmol).

(1S,2S)-N¹-(2,4-Dimethoxyphenyl)-N²-(S)-1-phenylethyl)cyclohexane-1,2-diamine [(1S,2S,1' S)-3g]: Colorless oil; IR (ATR) 3330, 2978, 2922 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) δ (ppm) 7.34-7.18 (m, 5H), 6.64 (d, J = 8.6 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 6.40 (dd, J = 8.6 and 2.3 Hz, 1H), 3.89 (q, J = 6.9 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 2.96 (dt, J = 3.6 and 9.9 Hz, 1H), 2.49 (dt, J = 3.8 and 9.7 Hz, 1H), 2.15-2.11 (m, 1H), 1.84-1.80 (m, 1H), 1.66-1.60 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H), 1.28-1.00 (m, 4H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 152.0, 148.7, 147.5, 132.5, 128.24, 128.23, 126.6, 112.1, 104.0, 99.3, 60.7, 58.7, 56.4, 55.8, 55.5, 32.8, 32.6, 24.9, 24.8, 24.2; MS (FAB⁺) m/z: 354 (M⁺, 100); HRMS (FAB⁺) m/z: calecd for C₂₂H₂₃F₇N₃OS (M⁺): 354.2307. Found: 354.2292; [α]D²⁶ = 41.0 (c 0.98, CHCl₃).

(1R,2R)-N¹-(2,4-Dimethoxyphenyl)-N²-(S)-1-phenylethyl)cyclohexane-1,2-diamine [(1R,2R,1' S)-4g]: Colorless oil; IR (ATR) 3335, 2974, 2926 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) δ (ppm) 7.37-7.24 (m, 5H), 6.61 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 2.9 Hz, 1H), 6.40 (dd, J = 8.6 and 2.9 Hz, 1H), 3.91 (q, J = 6.9 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.05-2.98 (m, 1H), 2.18-2.04 (m, 3H), 1.69-1.58 (m, 2H), 1.33 (d, J = 6.9 Hz, 3H), 1.24-1.05 (m, 3H), 0.91-0.82 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 151.9, 148.60, 148.59, 132.1, 128.5, 126.7, 126.5, 111.8, 104.1, 99.3, 60.4, 58.1, 57.9, 55.8, 55.8, 32.2, 31.3, 25.4, 25.0, 24.5; MS (FAB⁺) m/z: 354 (M⁺, 100); HRMS (FAB⁺) m/z: calecd for C₂₂H₂₃N₂O₂ (M⁺): 354.2307. Found: 354.2291; [α]D²⁶ = 20.8 (c 1.18, CHCl₃).

3.7. Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-(((1S,2S)-2-(2,4-dimethoxyphenylamino)cyclohexyl)thioureia [(S, S)-1g]

By a similar procedure described for the preparation of (S, S)-1f, (S, S)-1g (502 mg, 0.96 mmol, 72%) was obtained from (1S,2S,1' S)-3g (470 mg, 1.33 mmol); Colorless amorphous Solid; IR (ATR) 3331, 2935, 1510, 1277, 1091 cm⁻¹; ¹H-NMR (500 MHz, DMSO-d₆) δ (ppm) 9.94 (s, 1H), 8.25 (br, 1H), 8.18 (s, 2H), 7.70 (s, 1H), 6.55 (d, J = 8.6 Hz, 1H), 6.47 (d, J = 2.9 Hz, 1H), 6.37 (dd, J = 8.6 and 2.9 Hz, 1H), 6.27 (t, J = 9.2 Hz, 1H).
1H), 4.47-4.31 (m, 2H), 3.71 (s, 3H), 3.65 (s, 3H), 3.31-3.14 (m, 1H), 2.20-2.01 (m, 2H), 1.77-1.61 (m, 2H), 1.46-1.06 (m, 4H); 13C-NMR (125 MHz, DMSO-d6) δ (ppm) 180.2, 150.9, 147.4, 141.9, 130.1 (q, J(C,F) = 31.0 Hz), 123.2 (q, J(C,F) = 272 Hz), 121.8, 115.8, 109.9, 104.3, 99.2, 56.6, 56.5, 55.4, 55.3, 31.9, 31.1, 31.2, 24.4, 24.0; MS (FAB+) m/z: 438 (M + H+, 100); HRMS (FAB+) m/z: calcd for C23H26FeN3O2S (M + H+): 522.1650. Found: 522.1633; [α]D−25 = −14.5 (c 1.25, CHCl3).

3.8. Synthesis of (1S,2S,1’S)-3h and (1R,2R,1’S)-4h

By a similar procedure described for the preparation of (1S,2S,1’S)-3f and (1R,2R,1’S)-4f, (1S,2S, 1’S)-3h (425 mg, 1.14 mmol, 57%) and (1R,2R,1’S)-4h (85 mg, 0.22 mmol, 11%) were obtained from 2 (403 mg, 2.00 mmol) and 2-fluoro-4-isopropoxyaniline (340 mg, 2.00 mmol).

(1S,2S)-N1-(2-Fluoro-4-isopropoxyphenyl)-N2-(1-phenylethyl)cyclohexane-1,2-diamine [(1S, 2S, 1’S)-3h]: Colorless oil; IR (ATR) 3335, 2974, 2926 cm−1; 1H-NMR (500 MHz, CDCl3) δ (ppm) 7.34-7.19 (m, 5H), 6.74 (dd, J = 9.1 and 8.6 Hz, 1H), 6.65 (dd, J = 13.2 and 2.9 Hz, 1H), 6.57 (dd, J = 8.6 and 2.9 Hz, 1H), 4.35 (seq, J = 6.3 Hz, 1H), 3.89 (q, J = 6.9 Hz, 1H), 3.69 (br, 1H), 2.93 (dt, J = 3.5 and 9.9 Hz, 1H), 2.47 (dt, J = 4.0 and 9.8 Hz, 1H), 2.14-2.10 (m, 1H), 1.87-1.83 (m, 1H), 1.67-1.61 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 6.3 Hz, 6H), 1.28-1.00 (m, 4H); 13C-NMR (125 MHz, CDCl3) δ (ppm) 125.7 (d, J(C, F) = 237 Hz), 149.8 (d, J(C, F) = 9.5 Hz), 147.2, 130.5 (d, J(C, F) = 12.1 Hz), 128.3, 126.6, 126.5, 114.9 (d, J(C, F) = 4.8 Hz), 112.3 (d, J(C, F) = 3.6 Hz), 104.7 (d, J(C, F) = 20.7 Hz), 71.2, 60.5, 58.9, 56.2, 32.71, 32.66, 24.77, 24.74, 24.1, 22.1; MS (FAB+) m/z: 370 (M +, 100); HRMS (FAB+) m/z: calcd for C23H31FN2O (M+ 370.2420. Found: 370.2411; [α]D−25 = 30.0 (c 1.22, CHCl3).

(1R,2R)-N1-(2-Fluoro-4-isopropoxyphenyl)-N2-(1-phenylethyl)cyclohexane-1,2-diamine [(1R,2R, 1’S)-4h]: Colorless oil; IR (ATR) 3361, 2977, 2923 cm−1; 1H-NMR (500 MHz, CDCl3) δ (ppm) 7.38-7.24 (m, 5H), 6.69 (dd, J = 9.8 and 8.6 Hz, 1H), 6.63 (dd, J = 12.6 and 2.9 Hz, 1H), 6.57 (dd, J = 9.8 and 2.9 Hz, 1H), 4.36 (seq, J = 6.3 Hz, 1H), 3.90 (q, J = 6.9 Hz, 1H), 3.29 (br, 1H), 2.99-2.95 (m, 1H), 2.18-2.02 (m, 3H), 1.69-1.60 (m, 2H), 1.33 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 6.3 Hz, 6H), 1.28-1.08 (m, 3H), 0.92-0.87 (m, 1H); 13C NMR (125 MHz, CDCl3) δ (ppm) 153.0 (d, J(C, F) = 237 Hz), 149.7 (d, J(C, F) = 9.5 Hz), 145.8, 130.4 (d, J(C, F) = 11.9 Hz), 128.6, 126.9, 126.4, 114.7 (d, J(C, F) = 4.8 Hz), 112.4 (d, J(C, F) = 2.4 Hz), 104.8 (d, J(C, F) = 22.7 Hz), 71.3, 58.4, 58.0, 54.3, 32.3, 31.3, 25.3, 24.9, 24.5, 22.1; HRMS (FAB+) m/z: calcd for C23H31FN2O (M+): 370.2420. Found: 370.2411; [α]D−25 = 43.7 (c 1.18, CHCl3).

3.9. Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-(1H,S,2S)-2-(2-fluoro-4-isopropoxyphenylaminolino cyclohexyl)thiourea [(S, S)-1h]

By a similar procedure described for the preparation of (S,S)-1f, (S,S)-1h (410 mg, 0.762 mmol, 81%) was obtained from (1S,2S,1’S)-3h (350 mg, 0.944 mmol); Colorless amorphous Solid; IR (ATR) 3276, 2923, 1512, 1090 cm−1; 1H-NMR (500 MHz, DMSO-d6 at 100 °C) δ (ppm) 9.67 (s, 1H), 8.15 (s, 2H), 7.94 (br, 1H), 7.61 (s, 1H), 6.74 (dd, J = 9.2 and 9.2 Hz, 1H), 6.61 (d, J = 13.8 Hz, 1H), 6.55 (d, J = 9.2 Hz, 1H), 4.42-4.35 (m, 1H), 4.32 (seq, J = 5.8 Hz, 1H), 4.30 (br, 1H), 3.31-3.24 (m, 1H), 2.11-2.06 (m, 2H), 1.73-1.68 (m, 2H), 1.45-1.20 (m, 4H), 1.18 (d, J = 5.8 Hz, 6H); 13C-NMR (125 MHz,
DMSO-d$_6$ at 100 °C $\delta$ (ppm) 180.3, 150.9 (d, $^1J_{(C,F)} = 237$ Hz), 148.4 (d, $^3J_{(C,F)} = 9.5$ Hz), 141.6, 129.8 (q, $^2J_{(C,F)} = 33.4$ Hz), 129.6 (d, $^2J_{(C,F)} = 11.9$ Hz), 122.7 (q, $^1J_{(C,F)} = 271$ Hz), 121.8, 115.4, 113.6 (d, $^3J_{(C,F)} = 3.6$ Hz), 112.2 (d, $^4J_{(C,F)} = 3.6$ Hz), 104.3 (d, $^2J_{(C,F)} = 21.5$ Hz), 70.4, 56.7, 56.6, 31.7, 30.7, 23.8, 23.5, 21.3; MS (FAB$^+$) $m/z$: 438 (M + H$^+$, 100); HRMS (FAB$^+$) $m/z$: calcd for C$_{24}$H$_{27}$F$_7$N$_3$OS (M + H$^+$): 538.1763. Found: 538.1760; $[\alpha]_D^{25} = -48.3$ (c 1.15, CHCl$_3$).

3.10. Preparation of (Z)-ethyl 3-(4-methoxyphenylamino)acrylate (5a)

To a solution of ethyl 3-oxopropanoate (1.16 g, 10.0 mmol) in CH$_2$Cl$_2$ (20 mL) was added $p$-anisidine (1.23 g, 10.0 mmol) at ambient temperature. After the mixture was stirred at the same temperature overnight, the reaction mixture was concentrated. The resulting residue was passed through silica gel pad (hexane-ethyl acetate = 4:1) to afford the desired material as a Z/E mixture, which was recrystallized from hexane-ethyl acetate to give the title material 5a (352 mg, 1.59 mmol, 16%, predominantly Z form) as a pale yellow solid; Mp. 48–49 °C (ethyl acetate-hexane); IR (ATR) 3276, 2981, 2918, 1699 cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ (ppm) 9.81 (brd, $^1J = 12.6$ Hz, 1H), 7.15 (dd, $^1J = 12.6$, 8.0 Hz, 1H), 6.91 (d, $^1J = 8.6$ Hz, 2H), 6.85 (d, $^1J = 8.6$ Hz, 2H), 4.77 (d, $^1J = 8.0$ Hz, 1H), 4.17 (q, $^2J = 7.4$ Hz, 2H), 3.78 (s, 3H), 1.30 (t, $^3J = 7.4$ Hz, 3H); 13C-NMR (125 MHz, CDCl$_3$) $\delta$ (ppm) 170.5, 155.5, 144.1, 134.5, 117.0, 114.9, 86.1, 59.1, 55.6, 14.5; MS (FAB$^+$) $m/z$: 221 (M$^+$, 100); HRMS (FAB$^+$) $m/z$: calcd for C$_{12}$H$_{15}$NO$_3$ (M$^+$): 221.1052. Found: 221.1069.

3.11. Preparation of enaminio esters 5b-k

Enaminooesters 5b-k were prepared using literature procedures [29]. Enaminioesters 5b-k was used in the reactions without further purification.

3.12. General Procedure for the reaction of enaminoester 5a with 4-nitrocinnamaldehyde (6a) catalyzed by thiourea 1 – Brønsted acid (Tables 1 and 2).

To a solution of thiourea 1 (0.010 mmol) and Brønsted acid (0.010 mmol) in toluene (1.0 mL) were added 5a (0.10 mmol) and 6a (0.10 mmol) at ambient temperature. After being stirred at the same temperature, the reaction mixture was concentrated in vacuo. The resulting residue was purified by silica gel chromatography (hexane-ethyl acetate = 5:1) to give 7aa and 8aa.

**Ethyl 1-(4-methoxyphenyl)-6-(4-nitrophenyl)-1,6-dihydropyridine-3-carboxylate (8aa):** An orange oil; IR (ATR) 2979, 2919, 1685, 1513 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.20 (d, $^1J = 8.7$ Hz, 2H), 7.80 (s, 1H), 7.49 (d, $^1J = 7.4$ Hz, 2H), 7.49 (d, $^1J = 8.7$ Hz, 2H), 6.96 (d, $^1J = 8.8$ Hz, 2H), 6.82 (d, $^1J = 8.8$ Hz, 2H), 6.58 (d, $^1J = 9.8$ Hz, 1H), 5.66 (d, $^1J = 5.4$ Hz, 1H), 5.37 (dd, $^1J = 9.8$ and 5.4 Hz, 1H), 4.22 (q, $^1J = 7.1$ Hz, 2H), 3.77 (s, 3H), 1.30 (t, $^1J = 7.4$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ (ppm) 166.2, 157.5, 149.5, 141.8, 138.1, 129.0, 126.4, 124.4, 122.2, 121.2, 114.7, 113.7, 102.3, 62.7, 59.8, 55.5, 14.5; MS (FAB$^+$) $m/z$: 380 (M$^+$, 100); HRMS (FAB$^+$) $m/z$: calcd for C$_{21}$H$_{20}$N$_2$O$_5$ (M$^+$): 380.1372. Found: 380.1359.
3.13. Typical Procedure for the reaction of enaminoester 5a with 4-nitrocinnamaldehyde 6a catalyzed by thiourea (S, S)-1h – difluoro acid (Tables 3 and 4)

To a solution of 3a (17.7 mg, 0.10 mmol) in toluene (0.40 mL) were added thiourea (S, S)-1h (5.4 mg, 0.010 mmol) and 0.1 M difluoroacetic acid in toluene solution (100 μL, 0.010 mmol) at ambient temperature. To this mixture was added dropwise (50 μL/30 min) a solution of 2a (22.1 mg, 0.10 mmol) in toluene (0.50 mL) at ambient temperature. After being stirred at the same temperature for 12 h, the reaction mixture was concentrated in vacuo. The resulting residue was purified by silica gel chromatography (hexane-ethyl acetate = 5:1) to give 7aa (32.7 mg, 86%) as a yellow oil.

(R)-Ethyl 1-(4-methoxyphenyl)-4-(4-nitrophophenyl)-1,4-dihydropyridine-3-carboxylate (7aa): A yellow oil; IR (ATR) 2978, 2836, 1689, 1511 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.18 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 1.7 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.39 (dd, J = 8.0 and 1.7 Hz, 1H), 4.99 (dd, J = 8.0 and 4.6 Hz, 1H), 4.74 (d, J = 4.6 Hz, 1H), 4.14-4.00 (m, 2H), 3.83 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 167.4, 157.6, 154.6, 146.6, 138.7, 137.2, 128.7, 127.1, 123.7, 122.0, 114.9, 108.1, 103.4, 59.9, 55.6, 38.9, 14.3; MS (FAB⁺) m/z: 380 (M⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₁H₂₀N₂O₅ (M⁺): 380.1372. Found: 380.1367; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 80:20, flow rate 1.0 mL/min, 254 nm), t₀(minor) = 18.1 min, t₀(major) = 22.2 min. A sample with 50% ee by HPLC analysis gave [α]D²² = 125.2 (c 1.33, CHCl₃).

(R)-Ethyl 1-(4-chlorophenyl)-4-(4-nitrophophenyl)-1,4-dihydropyridine-3-carboxylate (7ba): By a similar procedure described for the preparation of 7aa, 7ba was obtained from 5b and 6a as a yellow oil (78%); IR (ATR) 2980, 2907, 1692, 1518 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.18 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 1.9 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.46 (dd, J = 7.8 and 1.9 Hz, 1H), 5.06 (dd, J = 7.8 and 4.6 Hz, 1H), 4.74 (d, J = 4.6 Hz, 1H), 4.15-4.05 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 167.1, 154.0, 146.6, 130.8, 129.9, 128.7, 126.0, 123.8, 121.0, 109.1, 105.0, 60.1, 38.8, 14.2; MS (FAB⁺) m/z: 384 (M⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₀H₁₇ClN₂O₄ (M⁺): 384.0877. Found: 384.0887; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 80:20, flow rate 1.0 mL/min, 254 nm), t₀(minor) = 14.4 min, t₀(major) = 19.5 min. A sample with 49% ee by HPLC analysis gave [α]D²⁵ = 91.8 (c 1.09, CHCl₃).

(R)-Ethyl 1-benzyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7ca): By a similar procedure described for the preparation of 7aa, 7ca was obtained from 5c and 6a as a yellow oil (83%); IR (ATR) 2980, 2907, 1692, 1518 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.13 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.41-7.35 (m, 5H), 7.28 (s, 1H), 5.97 (d, J = 7.8 Hz, 1H), 4.86 (dd, J = 7.8 and 4.6 Hz, 1H), 4.68 (d, J = 4.6 Hz, 1H), 4.47 (s, 2H), 4.03 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 167.5, 154.9, 146.4, 140.8, 136.7, 129.0, 128.6, 128.2, 127.7, 127.1, 123.6, 107.5, 101.3, 59.7, 57.9, 38.7, 14.3; MS (FAB⁺) m/z: 365 (M⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₁H₂₁N₂O₄ (M⁺): 365.1501. Found: 365.1528; HPLC (CHIRALCEL AD-H, hexane/2-propanol = 85/15, flow rate 1.0 mL/min, 254 nm), t₀(minor) = 14.9 min, t₀(major) = 17.8 min. A sample with 45% ee by HPLC analysis gave [α]D²² = 117.6 (c 1.14, CHCl₃).
(R)-Ethyl 1-(4-methoxyphenyl)-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7da): By a similar procedure described for the preparation of 7aa, 7da was obtained from 5d and 6a as a yellow oil (93%); IR (ATR) 2979, 2918, 1685, 1512 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.18 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.13 (d, J = 7.6 Hz, 1H), 2.16 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 168.2 155.8, 149.6, 146.3, 136.1, 130.6, 128.8, 128.2, 123.7, 114.8, 105.7, 99.7, 59.6, 55.5, 40.5, 18.5, 14.3; MS (FAB⁺) m/z: 395 (M + H⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₂H₂₃N₂O₆ (M + H⁺): 395.1607; Found: 395.1607; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 90:10, flow rate 0.5 mL/min, 254 nm), tₘ(minor) = 7.2 min, tₘ(major) = 16.7 min. A sample with 66% ee by HPLC analysis gave [α]D²³ = 277.0 (c 1.20, CHCl₃).

(R)-tert-Butyl 1-(4-methoxyphenyl)-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7ea): By a similar procedure described for the preparation of 7aa, 7ea was obtained from 5e and 6a as a yellow oil (81%); IR (ATR) 2976, 2917, 1686, 1510 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.19 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.09 (d, J = 7.6 Hz, 1H), 2.16 (s, 3H), 1.30 (s, 9H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 167.7, 158.8, 156.1, 148.6, 146.3, 136.3, 130.5, 128.8, 128.1, 123.7, 114.7, 101.1, 79.5, 55.5, 41.0, 28.2, 18.4; MS (FAB⁺) m/z: 422 (M⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₄H₂₆N₂O₅ (M⁺): 422.1842. Found: 422.1852; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 90:10, flow rate 0.5 mL/min, 254 nm), tₘ(minor) = 13.9 min, tₘ(major) = 18.5 min. A sample with 51% ee by HPLC analysis gave [α]D²³ = 208.3 (c 1.30, CHCl₃).

(R)-Ethyl 1-(4-methoxyphenyl)-4-(4-nitrophenyl)-2-phenyl-1,4-dihydropyridine-3-carboxylate (7fa): By a similar procedure described for the preparation of 7aa, 7fa was obtained from 5f and 6a as a yellow amorphous solid (85%); IR (ATR) 2980, 2917, 1674, 1511 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.23 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.13-6.91 (m, 5H), 6.86 (d, J = 9.0 Hz, 2H), 6.64 (d, J = 9.0 Hz, 2H), 6.42 (d, J = 7.6 Hz, 1H), 5.08 (dd, J = 7.6 and 5.6 Hz, 1H), 4.88 (d, J = 5.6 Hz, 1H), 3.75-3.68 (m, 2H), 3.70 (s, 3H), 0.70 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 167.7, 157.7, 155.3, 150.9, 146.5, 136.1, 135.9, 131.2, 128.6, 128.3, 127.8, 127.41, 127.40, 123.9, 114.0, 106.1, 101.4, 59.5, 55.3, 40.3, 13.5; MS (FAB⁺) m/z: 457 (M + H⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₇H₂₅N₂O₅ (M + H⁺): 457.1763. Found: 457.1784; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 93:7, flow rate 0.5 mL/min, 254 nm), tₘ(major) = 31.4 min, tₘ(minor) = 34.9 min. A sample with 61% ee by HPLC analysis gave [α]D²³ = 237.0 (c 1.12, CHCl₃).

(R)-Ethyl 1-(3,4-dimethoxyphenyl)-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7ga): By a similar procedure described for the preparation of 7aa, 7ga was obtained from 5g and 6a as a yellow oil (96%); IR (ATR) 2977, 2933, 1687, 1511 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.19 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.6 Hz, 1H), 6.76 (dd, J = 8.6 and 2.4 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.15 (d, J = 7.6 Hz, 1H), 4.93 (dd, J = 7.6 and 5.4 Hz, 1H), 4.83 (d, J = 5.4 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 2.18 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 168.2 155.8, 149.6, 149.5, 148.6, 146.3, 136.2, 130.5, 128.2, 123.7, 111.3,
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105.6, 99.7, 59.6, 56.11, 56.07, 40.5, 18.5, 14.2; MS (FAB⁻) m/z: 425 (M + H⁻, 100); HRMS (FAB⁻) m/z: calcd for C_{23}H_{25}N_{2}O_{6} (M + H⁻): 425.1713. Found: 425.1725; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 80:20, flow rate 1.0 mL/min, 254 nm), t_r(minor) = 10.2 min, t_r(major) = 38.8 min. A sample with 66% ee by HPLC analysis gave [α]_D^{22} = 239.5 (c 1.18, CHCl₃).

(R)-Ethyl 1-(3,4-dimethoxyphenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (7gb): By a similar procedure described for the preparation of 7aa, 7gb was obtained from 5g and 6b as a pale yellow oil (61%); IR (ATR) 2977, 2929, 1686, 1510 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.38-7.29 (m, 5H), 7.21-7.16 (m, 1H), 6.87 (d, J = 8.6 Hz, 1H), 6.77 (dd, J = 8.6 and 2.4 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.12 (d, J = 7.8 Hz, 1H), 4.98 (dd, d = 7.8 and 5.4 Hz, 1H), 4.69 (d, J = 5.4 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 2.16 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); 13C-NMR (125 MHz, CDCl₃) δ (ppm) 168.8, 149.5, 148.6, 148.35, 148.32, 136.7, 129.6, 128.3, 127.5, 126.1, 119.9, 111.3, 111.1 107.1, 101.1, 59.3, 56.06, 56.05, 40.2, 18.4, 14.2; MS (FAB⁻) m/z: 380 (M + H⁺, 100); HRMS (FAB⁻) m/z: calcd for C_{23}H_{26}NO_{5} (M + H⁺): 380.1862. Found: 380.1862; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 80:20, flow rate 1.0 mL/min, 254 nm), t_r(minor) = 6.1 min, t_r(major) = 14.5 min. A sample with 44% ee by HPLC analysis gave [α]_D^{25} = 154.0 (c 1.23, CHCl₃).

(R)-Ethyl 1-(3,4-dimethoxyphenyl)-4-(4-methoxypyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (7gc): By a similar procedure described for the preparation of 7aa, 7gc was obtained from 5g and 6c as a pale yellow oil (56%); IR (ATR) 2977, 2929, 1686, 1508 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.28 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 8.6 and 2.4 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.12 (d, J = 7.6 Hz, 1H), 4.96 (dd, d = 7.6 and 5.4 Hz, 1H), 4.63 (d, J = 5.4 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.79 (s, 3H), 2.14 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); 13C-NMR (125 MHz, CDCl₃) δ (ppm) 168.9, 149.5, 148.6, 148.32, 136.7, 129.6, 128.3, 127.5, 126.1, 119.9, 111.3, 111.1 107.1, 101.1, 59.3, 56.06, 56.05, 40.2, 18.4, 14.2; MS (FAB⁻) m/z: 409 (M +, 100); HRMS (FAB⁻) m/z: calcd for C_{24}H_{27}NO_{5} (M +): 409.1889. Found: 409.1883; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 80:20, flow rate 1.0 mL/min, 254 nm), t_r(minor) = 7.6 min, t_r(major) = 21.0 min. A sample with 38% ee by HPLC analysis gave [α]_D^{25} = 136.1 (c 1.21, CHCl₃).

(R)-Ethyl 1-(3,4-dimethoxyphenyl)-4-(4-fluorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (7gd): By a similar procedure described for the preparation of 7aa, 7gd was obtained from 5g and 6d as a pale yellow oil (62%); IR (ATR) 2981, 2935, 1685, 1507 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.31 (dd, J = 8.8 and 5.9 Hz, 2H), 6.99 (dd, J = 8.8 and 8.8 Hz, 2H), 6.87 (d, J = 8.3 Hz, 1H), 6.76 (dd, J = 8.3 and 2.4 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.12 (d, J = 7.8 Hz, 1H), 4.95 (dd, d = 7.8 and 5.4 Hz, 1H), 4.63 (d, J = 5.4 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 2.15 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 168.7, 161.4 (d, J(C,F) = 242 Hz), 149.5, 148.4, 148.3, 144.5 (d, J(C,F) = 3.6 Hz), 136.6, 129.7, 128.9 (d, J(C,F) = 8.4 Hz), 119.9, 114.9 (d, J(C,F) = 21.4 Hz), 111.3, 111.0, 106.9, 101.1, 59.4, 56.09, 56.07, 39.5, 18.4, 14.2; MS (FAB⁻) m/z: 398 (M + H⁺, 100); HRMS (FAB⁻) m/z: calcd for C_{23}H_{25}FNO_{4} (M + H⁺): 398.1889. Found: 398.1883; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 80:20, flow rate 1.0 mL/min, 254 nm), t_r(minor) = 6.0 min, t_r(major) = 13.1 min. A sample with 53% ee by HPLC analysis gave [α]_D^{27} = 148.7 (c 1.73, CHCl₃).
(R)-Ethyl 1-(3,4-dimethoxyphenyl)-4-(3-fluorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (7ge): By a similar procedure described for the preparation of 7aa, 7ge was obtained from 5g and 6e as a pale yellow oil (55%); IR (ATR) 2977, 2934, 1686, 1510 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.28-7.23 (m, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.08-7.04 (m, 1H), 6.92-6.83 (m, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.76 (dd, J = 8.4 and 2.4 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 7.6 Hz, 1H), 4.96 (dd, J = 7.6 and 5.4 Hz, 1H), 4.70 (d, J = 5.4 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 2.16 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 168.6, 163.2 (d, 1J(C,F) = 243 Hz), 151.3 (d, 3J(C,F) = 6.0 Hz), 149.6, 148.7, 148.4, 136.5, 130.0, 129.5 (d, 3J(C,F) = 8.4 Hz), 122.9 (d, 4J(C,F) = 2.4 Hz), 119.9, 114.3 (d, 2J(C,F) = 21.4 Hz), 112.9 (d, 2J(C,F) = 21.4 Hz), 111.3, 111.0, 106.5, 100.6, 59.4, 56.08, 56.07, 40.0, 18.4, 14.2; MS (FAB⁺) m/z: 398 (M + H⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₃H₂₅FNO₄ (M + H⁺): 398.1768. Found: 398.1748; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 85:15, flow rate 1.0 mL/min, 254 nm), tₘin = 7.2 min, tₘajor = 13.0 min. A sample with 58% ee by HPLC analysis gave [α]D = 189.7 (c 1.35, CHCl₃).

(R)-Ethyl 1-(3,4-dimethoxyphenyl)-4-(2-fluorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (7gf): By a similar procedure described for the preparation of 7aa, 7gf was obtained from 5g and 6f as a pale yellow oil (70%); IR (ATR) 2976, 2931, 1687, 1510 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 7.39-7.34 (m, 1H), 7.19-7.09 (m, 2H), 7.02-6.97 (m, 1H), 6.87 (d, J = 8.6 Hz, 1H), 6.77 (dd, J = 8.6 and 2.4 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.05 (d, J = 7.6 Hz, 1H), 5.03 (d, J = 5.4 Hz, 1H), 4.97 (dd, J = 7.6 and 5.4 Hz, 1H), 3.99 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 2.20 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 168.6, 159.6 (d, 1J(C,F) = 244 Hz), 149.7, 149.5, 148.4, 136.6, 135.3 (d, 2J(C,F) = 14.3 Hz), 130.0, 129.76, 129.71, 127.4 (d, 3J(C,F) = 7.2 Hz), 124.1 (d, 4J(C,F) = 3.6 Hz), 120.0, 115.0 (d, 2J(C,F) = 22.6 Hz), 111.2 (d, 3J(C,F) = 10.7 Hz), 105.7, 98.8, 95.3, 56.06, 56.04, 33.8, 18.3, 14.2; MS (FAB⁺) m/z: 398 (M + H⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₃H₂₅FNO₄ (M + H⁺): 398.1768. Found: 398.1761; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 80:20, flow rate 1.0 mL/min, 254 nm), tₘin = 6.0 min, tₘajor = 11.4 min. A sample with 44% ee by HPLC analysis gave [α]D = 175.8 (c 0.985, CHCl₃).

(R)-Ethyl 1-(4-chlorophenyl)-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7ha): By a similar procedure described for the preparation of 7aa, 7ha was obtained from 5h and 6a as a yellow oil (78%); IR (ATR) 2980, 2901, 1691, 1517 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.18 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.15 (d, J = 7.6 Hz, 1H), 4.97 (dd, J = 7.6 and 5.4 Hz, 1H), 4.82 (d, J = 5.4 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 2.16 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ (ppm) 168.0, 155.3, 148.4, 146.4, 141.8, 133.5, 130.0, 129.9, 128.8, 128.2, 123.8, 106.3, 101.1, 59.7, 40.4, 18.6, 14.2; MS (FAB⁺) m/z: 398 (M⁺, 100); HRMS (FAB⁺) m/z: calcd for C₂₁H₁₉ClN₂O₄ (M⁺): 398.1033. Found: 398.1052; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 90:10, flow rate 1.0 mL/min, 254 nm), tₘin = 10.4 min, tₘajor = 23.9 min. A sample with 38% ee by HPLC analysis gave [α]D = 158.0 (c 1.22, CHCl₃).

(R)-Ethyl 1-benzyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7ia): By a similar procedure described for the preparation of 7aa, 7ia was obtained from 5i and 6a as a yellow oil (81%); IR (ATR) 2979, 2925, 1684, 1516 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 8.13 (d, J = 8.8 Hz, 2H),
7.39 (d, \(J = 8.8\) Hz, 2H), 7.38-7.31 (m, 3H), 7.22-7.20 (m, 2H), 6.02 (d, \(J = 7.6\) Hz, 1H), 4.93 (dd, \(J = 7.6\) and 5.5 Hz, 1H), 4.78 (d, \(J = 5.5\) Hz, 1H), 4.69 (d, \(J = 16.8\) Hz, 1H), 4.59 (d, \(J = 16.8\) Hz, 1H), 3.99 (q, \(J = 7.1\) Hz, 2H), 2.46 (s, 3H), 1.09 (t, \(J = 7.1\) Hz, 3H); 13C-NMR (125 MHz, CDCl3) δ (ppm) 168.3, 155.9, 149.8, 146.3, 137.6, 130.3, 129.0, 128.1, 127.7, 126.2, 106.6, 99.3, 59.5, 53.8, 40.5, 16.0, 14.2; MS (FAB+) m/z: 378 (M+, 100); HRMS (FAB+) m/z: calcd for C\(_{22}\)H\(_{22}\)N\(_2\)O\(_4\) (M+) 378.1580. Found: 378.1578; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 90:10, flow rate 1.0 mL/min, 254 nm), \(t_{(\text{minor})} = 12.0\) min, \(t_{(\text{major})} = 15.3\) min. A sample with 80% ee by HPLC analysis gave \([\alpha]_{D}^{23} = 309.8\) (c 1.36, CHCl3).

**(R)-Ethyl 1-(4-methoxybenzyl)-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7ja):** By a similar procedure described for the preparation of 7aa, 7ja was obtained from 5j and 6a as a yellow oil (65%); IR (ATR) 2978, 2922, 1683, 1513 cm\(^{-1}\); ^1H-NMR (400 MHz, CDCl3) δ (ppm) 8.12 (d, \(J = 8.1\) Hz, 2H), 7.37 (d, \(J = 8.1\) Hz, 2H), 7.13 (d, \(J = 8.6\) Hz, 2H), 6.90 (d, \(J = 8.6\) Hz, 2H), 6.01 (d, \(J = 7.5\) Hz, 1H), 4.92 (dd, \(J = 7.5\) and 5.7 Hz, 1H), 4.77 (d, \(J = 5.7\) Hz, 1H), 4.62 (d, \(J = 16.6\) Hz, 1H), 4.51 (d, \(J = 16.6\) Hz, 1H), 3.99 (q, \(J = 7.1\) Hz, 2H), 3.82 (s, 3H), 2.46 (s, 3H), 1.09 (t, \(J = 7.1\) Hz, 3H); 13C-NMR (125 MHz, CDCl3) δ (ppm) 168.3, 159.2, 155.9, 149.9, 146.2, 130.3, 129.5, 128.1, 123.6, 114.3, 106.5, 99.2, 59.5, 55.3, 53.3, 40.5, 16.0, 14.2; MS (FAB+) m/z: 408 (M+, 100); HRMS (FAB+) m/z: calcd for C\(_{23}\)H\(_{24}\)N\(_2\)O\(_5\) (M+) 408.1685. Found: 408.1701; HPLC (CHIRALCEL AD-H, hexane-2-propanol = 90:10, flow rate 1.0 mL/min, 254 nm), \(t_{(\text{minor})} = 16.2\) min, \(t_{(\text{major})} = 19.3\) min. A sample with 77% ee by HPLC analysis gave \([\alpha]_{D}^{26} = 286.6\) (c 1.20, CHCl3).

### 3.14. General Procedure for the reaction of 4-nitro cinnamaldehyde 6a and 4-methoxyaniline (9) with ethyl acetoacetate (10) catalyzed by thiourea 1—Brønsted acid (Table 5)

To a mixture of thiourea 1 (0.010 mmol) and Brønsted acid (0.010 mmol) in toluene (1.0 mL) were added 6 (0.15 mmol) and 9 (0.10 mmol) at ambient temperature. After being stirred at the same temperature for 30 min, 10 (0.20 mmol) was then added, and the resulting mixture was stirred at the same temperature. The reaction mixture was concentrated in vacuo, and the resulting residue was purified by silica gel chromatography (hexane-ethyl acetate = 5:1) to give 7da.

### 4. Conclusions

We have developed a Brønsted acid–bifunctional thiourea co-catalyzed asymmetric cycloaddition of \(\beta\)-enamino esters and \(\alpha,\beta\)-unsaturated aldehydes to afford 1,3,4-trisubstituted and 1,2,3,4-tetrasubstituted 1,4-DHPs, which uses novel thiourea catalysts 1f and 1h as a source of chirality. With the use of different Brønsted acids such as DFA and HBF\(_4\) with the same bifunctional thiourea, both enantiomers of 4-substituted 1,4-dihydropyridine can be synthesized from the same starting materials. Both the Brønsted acid and bifunctional thiourea co-catalysts are important for determining the enantioselectivity and sense of chirality.

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Sample Availability: Contact the authors.

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