Brønsted Acid–Thiourea Co-catalysis: Asymmetric Synthesis of Functionalized 1,4-Dihydropyridines from β-Enamino Esters and α,β-Unsaturated Aldehydes

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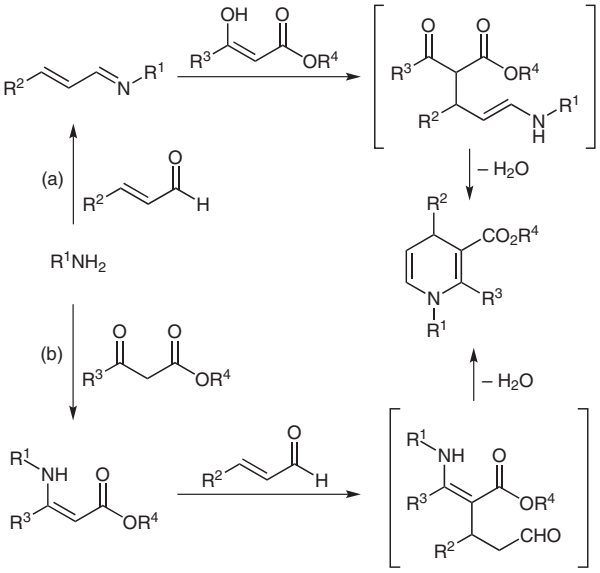
Abstract: A Brønsted acid and a novel thiourea derivative co-catalyze the addition of β-enamino esters to α,β-unsaturated aldehydes leading to functionalized 1,4-dihydropyridines with moderate to good enantioselectivity. A regioselective synthesis of 1,2-dihydropyridines from α,β-unsaturated aldehydes is also described.

Key words: asymmetric organocatalysis, Brønsted acid, thiourea, 1,4-dihydropyridines, β-enamino esters, α,β-unsaturated aldehydes

1,4-Dihydropyridines (1,4-DHP) and their derivatives are important bioactive molecules in the field of drugs and pharmaceuticals. These compounds are well-known calcium channel blockers that are used for the treatment of hypertension[1] and have a broad range of other pharmacological activities such as HIV protease inhibition,[2] noncompetitive inhibition of topoisomerase I,[3] MDR reversal,[4] and radioprotection.[5] These examples clearly indicate the noteworthy potential of novel dihydropyridine derivatives as seeds for valuable drug candidates. In addition, 1,4-DHP can be used as effective hydrogen sources in the field of synthetic chemistry.[6]

Due to the importance of 1,4-DHP derivatives from pharmaceutical and synthetic points of view, various methods have been reported for their preparation.[7] The best known procedure for the preparation of symmetrical 1,4-DHP is the classical Hantzsch method,[8] but N-substituted DHP that do not bear substituents on the 5- and/or 6-positions cannot be synthesized with this protocol. Recently, synthetic methods leading to such unsymmetrical DHP have been reported.[9] However, there have been only a few reports on the catalytic enantioselective synthesis of 1,4-DHP.[10,11] These methods can be classified into two synthetic pathways, as shown in Scheme 1.

Gong et al. reported the highly enantioselective three-component cyclization of cinnamaldehydes, arylamines, and 1,3-dicarbonyl compounds catalyzed by a chiral phosphoric acid via pathway a.[10] However, the substituent (R^3) of 1,3-dicarbonyl compounds is limited to methyl or ethyl. So far, only a single asymmetric example that used the β-enamino esters (route b) has been reported by Renaud et al., who used a chiral phosphoric acid catalyst to obtain the product in 50% ee.[11] This preliminary result has not been elaborated further. Herein, we describe Brønsted acid–thiourea co-catalyzed asymmetric cycloadditions of β-enamino esters and α,β-unsaturated aldehydes, which afford functionalized 5,6-unsubstituted 1,4-DHP with enantioselectivities of up to 80% ee.



Scheme 1 Possible synthetic routes to 1,4-DHP

The key to success for this strategy is how to activate β-enamino esters as nucleophiles by aminothiourea **1**, which efficiently deprotonated β-keto esters in the asymmetric reaction reported previously.[12] Our working hypothesis is shown in Scheme 2. When thiourea **1** and a Brønsted acid are mixed in a 1:1 ratio, an ammonium salt complex **A**[13] would be formed, in which the conjugate base is anchored to the thiourea moiety by hydrogen bonds.[14] This complex can be considered as a new bifunctional catalyst; α,β-unsaturated aldehyde **3** and enamino ester **2** should be activated by the ammonium proton and the conjugate base (X^-), respectively. As a result, 1,4-conjugated addition would be promoted in a chiral environment to furnish the desired 1,4-DHP **4**, after subsequent intramolecular cyclization and dehydration. The merit of this strategy is that the acidity and basicity of complex **A** can be tuned by appropriate selection of the acid (HX).

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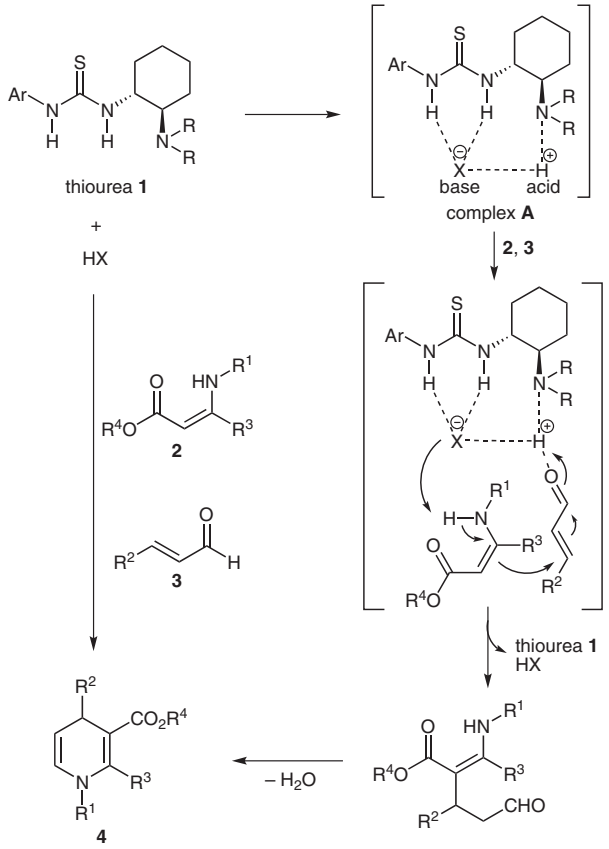


Scheme 2 A mechanistic proposal for the reaction of β-enamino

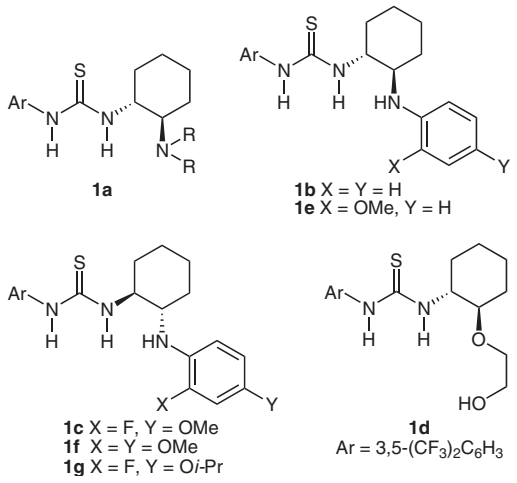
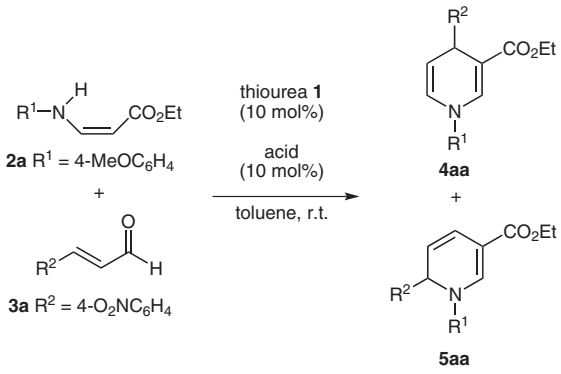


Figure 1 Structures of thiourea catalysts employed

The reaction of β-enamino ester **2a** (*E*/*Z* = <5:95)[15] and aldehyde **3a** was carried out with various ratios of HX and thioureas **1a**–**d**[16] (Figure 1, Table 1). We first investigated the reaction in the presence of **1a** alone, but only recovered the starting material (entry 1). Although the presence of 10 mol% difluoroacetic acid (DFA) effectively promoted the reaction even at ambient temperature to give 1,4-DHP **4aa** and 1,2-DHP **5aa** in a ratio of 35:65, the same reaction with a 1:1 mixture of **1a** and DFA gave none of the desired products (entries 2 and 3). This means that the conjugate acid of **1a** is too weak to activate the electrophile. We then examined *N*-arylthioureas **1b** and **1c**, whose aniline moieties are weaker bases than the *N*,*N*-dimethylamine moiety of **1a**, in the presence of several carboxylic acids. As expected, the use of **1b** or **1c** with DFA in a 1:1 ratio provided 1,4-DHP **4aa** in 59% or 72% yield together with 1,2-DHP **5aa** as a minor product (entries 4 and 5). In both cases, moderate enantioselectivities were observed for **4aa** (28% and 39% ee). The use of TFA instead of DFA with **1c** decreased the enantioselectivity to 28% ee, while 78% ee was obtained with AcOH, albeit with very low yield (entries 6 and 7). Unfortunately, we could not improve both the chemical yield and enantioselectivity despite screening a variety of conditions (solvent, temperature, and additives).[17] Finally, we found that the slow addition of β-enamino ester **2a** to a mixture of **3a**, DFA, and **1c** improved the chemo- (**4aa**/**5aa**) and enantioselectivity (86%, 50% ee; entry 8). Notably, **1d**, which has a hydroxy group in place of the amine, exclusively gave **5aa** in 51% yield with low enantioselectivity (12% ee) un-

Table 1 Initial Screening of Reaction Conditions[a]



Entry	Brønsted Acid–Thiourea	Time (h)	Yield of **4aa** (%)[b]	ee of **4aa** (%)[c]	Yield of **5aa** (%)[b]	ee of **5aa** (%)[c]
1	(*R*,*R*)-**1a**	48	0		0	
2	DFA	24	(35)[d]		(65)[d]	
3	DFA–(*R*,*R*)-**1a**	48	0		0	
4	DFA–(*R*,*R*)-**1b**	24	59	28 (*S*)	28	2
5	DFA–(*S*,*S*)-**1c**	24	72	39 (*R*)	17	0
6	TFA–(*S*,*S*)-**1c**	24	71	28 (*R*)	18	1
7	AcOH–(*S*,*S*)-**1c**	48	11	78 (*R*)	trace	
8[e]	DFA–(*S*,*S*)-**1c**	12[f]	86	50 (*R*)	0	
9[e]	DFA–(*R*,*R*)-**1d**[g]	12[f]	0		51	12

[a] The reactions were carried out with **2a** (0.1 mmol, *E*/*Z* = <5:95), **3a** (0.1 mmol), thiourea (10 mol%), and Brønsted acid (10 mol%) in toluene (1 mL) at r.t.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Conversion as determined by ^{1}H NMR.
[e] Slow addition of **2a** (0.01 mmol/30 min).
[f] Stirred for 12 h after completion of the addition of **2a**.
[g] Conditions: 20 mol% thiourea **1d** was used.

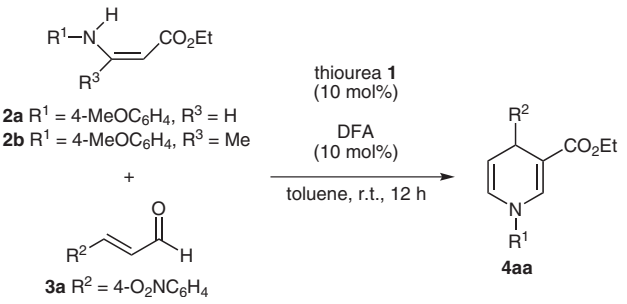
der otherwise the same conditions (entry 9). This is the first example of a catalytic asymmetric synthesis of a 1,2-DHP.

Next, we screened the substituent of the aniline moiety of the thiourea (Table 2). When **2a** was slowly added to a reaction mixture of **3a**, **1b**, and DFA at room temperature, both the chemical yield and enantioselectivity were predictably improved but lower than when **1c** was used (entry 1). The use of β-enamino ester **2b** resulted in a slight increase in enantioselectivity (61% ee; entry 2).

Therefore, we evaluated thioureas **1e–g** with both **2a** and **2b**, respectively. We found that thiourea **1g** gave the best results in terms of ee among the synthesized thiourea catalysts (66% ee; entries 3–7). With this result, we established that, optimally, the reaction should be carried out in the presence of DFA and **1g** and with the slow addition of β-enamino esters.

With the optimized conditions in hand we examined several substrates (**2c–k** and **3a–f**, Table 3).[18] No great difference was found between the use of *tert*-butyl ester and ethyl ester (entry 1), but the use of enaminone **2d** derived from diketone led to low enantioselectivity (entry 2). A phenyl group at the β-position (**2e**, R^3 = Ph) also gave **4ea** with similarly good enantioselectivity, as was observed for **2b** (R^3 = Me, entry 3). Moderate enantioselectivities were observed in the reaction of **2f** with various α,β-unsaturated aldehydes **3a–f** with both electron-rich and -poor aromatic groups (entry 4–9). In these cases, the removal of an electron-withdrawing substituent or introduction of an electron-donating group led to a decrease in enantioselectivity (entries 5 and 6). In addition, we examined the reaction of **3a** with β-enamino esters **2g–k** with different N-substituents (entries 10–14). β-Enamino ester **2g** and **2h** with a *para*-chlorophenyl group on nitrogen led to a decrease in enantioselectivity (entries 10 and 11). On the other hand, the reaction of β-enamino esters with a benzyl group at the nitrogen and a methyl group at the β-position afforded the corresponding 1,4-DHP with good enantioselectivities (entries 13 and 14). These results indicate that the substituents on nitrogen and at the β-position of the β-enamino ester might be the most important factors in this reaction. The absolute configuration of the products **4** was determined by comparison of the specific rotation of **4ba** to that described in the literature.[10]

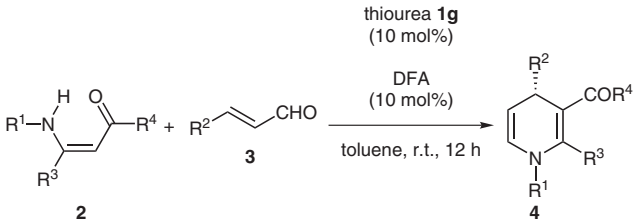
Table 2 Catalyst Screening[a]



Entry	Thiourea	Enamino Ester	Product	Yield (%)[b]	ee (%)[c]
1	(*R*,*R*)-**1b**	**2a**	**4aa**	86	42 (*S*)
2	(*S*,*S*)-**1c**	**2b**	**4ba**	84	61 (*R*)
3	(*R*,*R*)-**1e**	**2a**	**4aa**	47	41 (*S*)
4	(*S*,*S*)-**1f**	**2a**	**4aa**	91	55 (*R*)
5	(*S*,*S*)-**1f**	**2b**	**4ba**	65	56 (*R*)
6	(*S*,*S*)-**1g**	**2a**	**4aa**	92	50 (*R*)
7	(*S*,*S*)-**1g**	**2b**	**4ba**	93	66 (*R*)

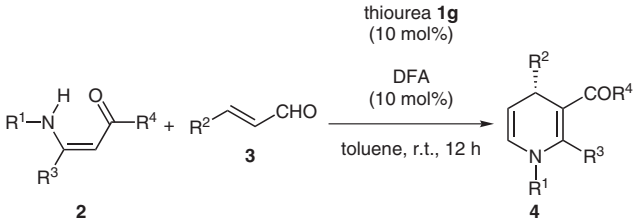
[a] Reaction conditions: slow addition (0.01 mmol/30 min) of **2a** (0.1 mmol, *E*/*Z* = <5:95) or **2b** (0.1 mmol, *E*/*Z* = <5:95) to a mixture of **3a** (0.1 mmol), thiourea (10 mol%), and DFA (10 mol%) in toluene (1 mL) at r.t. The mixture was stirred for an additional 12 h after completion of the addition.
[b] Isolated yield.
[c] Determined by HPLC.

Table 3 Substrate Scope[a]



Entry	Emanino Esters				α,β-Unsaturated Aldehydes		Product	Yield (%)[b]	ee (%)[c]
	2	R^1	R^3	R^4	**3**	R^2	**4**		
1	**2c**	4-$MeOC_6H_4$	Me	O*t*-Bu	**3a**	4-$O_2NC_6H_4$	**4ca**	81	51
2	**2d**	4-$MeOC_6H_4$	H	Ph	**3a**	4-$O_2NC_6H_4$	**4da**	76	18
3	**2e**	4-$MeOC_6H_4$	Ph	OEt	**3a**	4-$O_2NC_6H_4$	**4ea**	85	61
4	**2f**	3,4-$(MeO)_2C_6H_3$	Me	OEt	**3a**	4-$O_2NC_6H_4$	**4fa**	96	66

Table 3 Substrate Scope[a] (continued)



Entry	Emanino Esters				α,β-Unsaturated Aldehydes		Product	Yield (%)[b]	ee (%)[c]
	2	R^1	R^3	R^4	**3**	R^2	**4**		
5	**2f**	3,4-$(MeO)_2C_6H_3$	Me	OEt	**3b**	Ph	**4fb**	61	44
6	**2f**	3,4-$(MeO)_2C_6H_3$	Me	OEt	**3c**	4-$MeOC_6H_4$	**4fc**	56	38
7	**2f**	3,4-$(MeO)_2C_6H_3$	Me	OEt	**3d**	4-FC_6H_4	**4fd**	62	53
8	**2f**	3,4-$(MeO)_2C_6H_3$	Me	OEt	**3e**	3-FC_6H_4	**4fe**	55	58
9	**2f**	3,4-$(MeO)_2C_6H_3$	Me	OEt	**3f**	2-FC_6H_4	**4ff**	70	44
10	**2g**	4-ClC_6H_4	H	OEt	**3a**	4-$O_2NC_6H_4$	**4ga**	78	49
11	**2h**	4-ClC_6H_4	Me	OEt	**3a**	4-$O_2NC_6H_4$	**4ha**	78	38
12	**2i**[d]	Bn	H	OEt	**3a**	4-$O_2NC_6H_4$	**4ia**	83	45
13	**2j**	Bn	Me	OEt	**3a**	4-$O_2NC_6H_4$	**4ja**	81	80
14	**2k**	4-$MeOC_6H_4CH_2$	Me	OEt	**3a**	4-$O_2NC_6H_4$	**4ka**	65	77

[a] Reaction conditions: slow addition (0.01 mmol/30 min) of enamino esters **2** (0.1 mmol, *E*/*Z* = <5:95) to a mixture of α,β-unsaturated aldehydes **3** (0.1 mmol), thiourea (*S*,*S*)-**1g** (10 mol%), and DFA (10 mol%) in toluene (1 mL) at r.t The mixture was stirred for an additional 12 h after completion of the addition.
[b] Isolated yield.
[c] Determined by HPLC.
[d] The ratio of *E*/*Z* of **2i** was 33:67.

In conclusion, we have developed a Brønsted acid–thiourea co-catalyzed asymmetric cycloaddition of β-enamino esters and α,β-unsaturated aldehydes to afford 1,3,4-trisubstituted and 1,2,3,4-tetrasubstituted 1,4-DHP, using novel thiourea catalyst **1g** as a source of chirality.

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(15) When **2a** (*E*/*Z* = 25:75) was reacted with **3a** in the presence of DFA-(*S*,*S*)-**1c**, **4aa** was obtained in 50% ee (compared to entry 8 in Table 1). Therefore we concluded that the stereochemistry of the enamino esters would not effect to the enantioselectivities.

(16) The absolute configuration of the thiourea catalysts described has been assigned based on the known configuration of the starting 1,2-diaminocyclohexane or has been established by X-ray-analysis (CCDC768496).

(17) In addition to toluene, we tested a chlorinated solvent (CH_2Cl_2) and ethers (THF, Et_2O). Lower temperature (0 °C) led to a decrease in yield (<5%), while higher temperatures (50 °C) and catalyst loading (20 mol%) led to an increased yield but lower ee (28%, 55% ee). The addition of molecular sieves (3 Å, 4 Å) inhibited the reaction, while other additives ($NaSO_4$, $MgSO_4$) led to a decrease in enantioselectivity without improving the yield.

(18) **Typical Procedure for the Reaction of 2j and 3a Catalyzed by Thiourea 1g – DFA**

To a solution of cinnamaldehyde (**3a**, 17.7 mg, 0.10 mmol) in toluene (0.40 mL) were added thiourea **1f** (5.4 mg, 0.010 mmol) and 0.1 M difluoroacetic acid in toluene solution (100 μL, 0.010 mmol) at r.t. To this mixture was added dropwise (50 μL/30 min) a solution of **2j** (22.0 mg, 0.10 mmol) in toluene (0.50 mL) at r.t. 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–EtOAc = 5:1) to give **4ja** (30.8 mg, 81%) as a yellow oil.

(*R*)-Ethyl 1-Benzyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (4ja)

IR (ATR): 2979, 2925, 1684, 1516 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.8 Hz, 2 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.38–7.31 (m, 3 H), 7.22–7.20 (m, 2 H), 6.02 (d, *J* = 7.6 Hz, 1 H), 4.93 (dd, *J* = 7.6, 5.5 Hz, 1 H), 4.78 (d, *J* = 5.5 Hz, 1 H), 4.69 (d, *J* = 16.8 Hz, 1 H), 4.59 (d, *J* = 16.8 Hz, 1 H), 3.99 (q, *J* = 7.1 Hz, 2 H), 2.46 (s, 3 H), 1.09 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 155.9, 149.8, 146.3, 137.6, 130.3, 129.0, 128.1, 127.7, 126.2, 123.6, 106.6, 99.3, 59.5, 53.8, 40.5, 16.0, 14.2. MS (FAB$^+$): *m*/*z* (%) = 378 (100) [M$^+$]. HRMS (FAB$^+$): *m*/*z* calcd for $C_{22}H_{22}N_2O_4$ [M$^+$]: 378.1580; found: 378.1578. HPLC (CHIRALCEL AD-H, hexane–2-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm): t_r(minor) = 12.0 min, t_r(major) = 15.3 min. A sample with 80% ee gave $[\alpha]_D^{23}$ +309.8 (*c* 1.36, $CHCl_3$).