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Highly Enantioselective Biginelli Reaction Promoted by Chiral Bifunctional Primary Amine-Thiourea Catalysts: Asymmetric Synthesis of Dihydropyrimidines

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Dedicated to Prof. Ruyu Chen on the occasion of her 90th birthday.

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Abstract: The diastereospecific formation of dihydropyrimidines (DHPMs) has been achieved in moderate to high yields with up to 99% *ee* by a Biginelli reaction. The reaction was performed by using a combined catalyst consisting of a chiral bifunctional primary amine-thiourea **9f** and a Brønsted acid with *tert*-butylammonium trifluoroacetate (*t*-BuNH$_2$·TFA) as additive in dichloromethane at room temperature. The possible mechanism for the reaction has been proposed to explain the origin of the activation and the asymmetric induction.

Keywords: Biginelli reaction; enantioselectivity; organocatalysis; primary amino-thiourea catalyst

The synthesis of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) (**1**) *via* the Biginelli reaction, a three-component condensation reaction between an aldehyde, a urea or a thiourea, and an easily enolizable carbonyl compound which was originally described by the Italian chemist Pietro Biginelli in 1893.[1] The medicinal importance of DHPMs has been recognized for many decades and many compounds exhibit antiviral, antitumor, antibacterial, and anti-inflammatory properties.[2] Nitractin (**2**) was first reported in the 1960s as an agent against the trachoma group of viruses.[3] Monastrol (**3**) is currently known as a specific inhibitor of mitotic kinesis Eg5 and is considered as lead compound to develop new anticancer drugs.[4] Also, (*R*)-SQ32926 (**4**) has been identified as a potent orally active antihypertensive agent (Figure 1).[5] Furthermore, some marine natural products containing the dihydropyrimidine-5-carboxylate core have been isolated and exhibited interesting biological activities.[6]

Compounds containing the DHPM moiety are inherently asymmetric molecules, and the influence of the absolute configuration at the stereogenic center at C-4 on the biological activity has been extensively investigated. Different enantiomers exhibit different or even opposite biological activities.[7] The original Biginelli reaction does not have any enantiocontrol factor during formation of the new stereocenter. The procedures for manufacturing optically pure DHPMs mainly focus on resolution and chiral auxiliary-assisted asymmetric synthesis.[8] Compared with the two

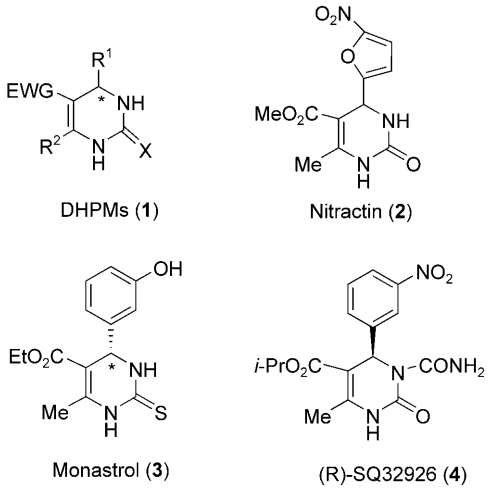


Figure 1. Examples of biologically active DHPMs.

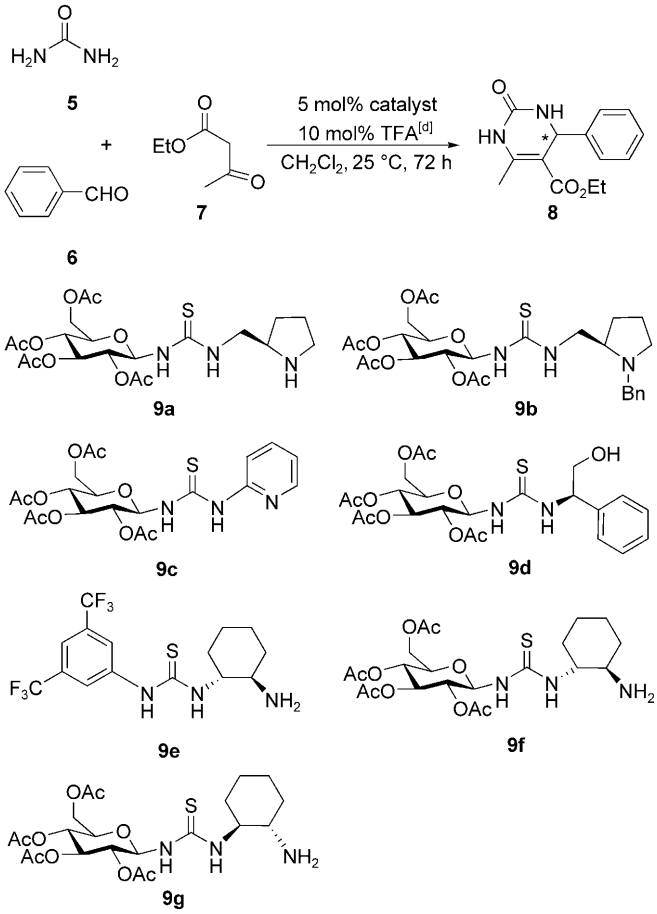
kinds of asymmetric synthesis methods, the catalytic asymmetric Biginelli reaction is definitely the most straightforward approach to access optically active DHPMs. Gong reported the first organocatalytic highly enantioselective Biginelli reaction using a H_8-Binol-based chiral phosphoric acids as catalyst.[9] Feng also reported an enantioselective Biginelli reaction catalyzed by a *trans*-4-hydroxyproline-derived secondary amine and a Brønsted acid as the combined catalyst.[10] Recently, Zhao and Wang reported the asymmetric Biginelli reaction catalyzed by substituted 5-(pyrrolidin-2-yl)tetrazoles.[11] Indeed, urea(thiourea)-based organocatalysts have been widely used in asymmetric catalysis.[12] Herein we wish to report the development of conditions for performing highly enantioselective Biginelli condensation reactions catalyzed by a chiral bifunctional primary amine-thiourea catalyst in the presence of a Brønsted acid as a combined catalyst.

Chiral urea and thiourea derivatives have proven to be extraordinarily useful as catalysts for the enantioselective activation of imine and carbonyl derivatives toward nucleophilic addition.[13] Carbohydrates are in general very attractive scaffolds because of their availability and well-defined stereocenters. Thus a novel saccharide scaffold was employed in asymmetric reactions. Ma has reported that thiourea catalysts possessing a neighboring primary amine function are essential for good reactivity and enantioselectivity of the Michael addition reaction of aromatic ketones to nitroolefins.[14] However, a bifunctional thiourea catalyst has never been employed in the Biginelli reaction.

We initially investigated the catalytic asymmetric Biginelli reaction of urea (**5**), benzaldehyde (**6**) and ethyl acetoacetate (**7**) with bifunctional thiourea catalyst (**9**) and trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature. Catalyst **9a** could catalyze this reaction to provide the desired product DHPM in 30% yield, but the enantioselectivity was rather poor (Table 1, entry 1). Moreover, the *N*-Bn-protected thiourea catalyst **9b**, the pyridine-substituted thiourea catalyst **9c**, and 2-phenylethanol-thiourea catalyst **9d**, all failed to catalyze the asymmetric Biginelli reaction (Table 1, entries 2–4). Next, we explored 3,5-bis(trifluoromethyl)phenylthiourea **9e** as catalyst and found that this reaction can work effectively to provide DHPM in 40% yield and 9% *ee*. This result suggested that a primary amine-thiourea structure is essential to effect the Biginelli reaction. Consequently, we found that gluco-2-aminocyclohexylthiourea **9f** could catalyze this reaction and produce the DHPM in 60% yield and 15% *ee*. Furthermore, increasing the loading amount of catalyst from 5 to 10% did not affect the yield, but resulted in a higher *ee* (Table 1, entry 7).

Several Lewis and Brønsted acids were reported to catalyze the Biginelli reaction such as HCl, H_2SO_4, TsOH, LiBr, $InBr_3$, $BF_3{\cdot}OEt_2$, $FeCl_3$, and so on.[15] In order to improve the efficiency, various acids combined with **9f** were then employed to catalyze this reaction. Compared with TFA, organic and inorganic acids can promote the reaction smoothly. For example HAc, HCOOH, HCl and H_3PO_4 combined with **9f** were employed to catalyze the reaction and get DHPMs in moderate *ee* (Table 2, entries 2–5). Recently, Feng reported that different substituted benzo-

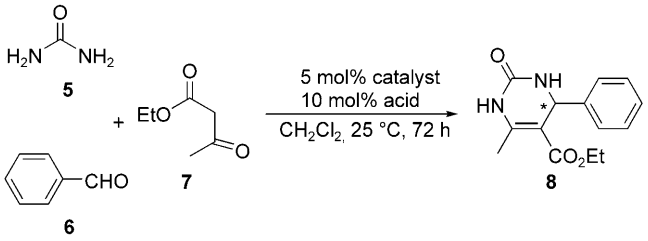
Table 1. Screening catalysts for the asymmetric Biginelli reaction.[a]



Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**9a**	30	<3
2	**9b**	13	<3
3	**9c**	19	<3
4	**9d**	27	<3
5	**9e**	40	9
6	**9f**	60	15
7[e]	**9f**	61	18

[a] The reaction was carried out on a 0.5 mmol scale and the ratio of **5**/**6**/**7** is 1/1.5/3.
[b] Isolated yield based on the urea.
[c] Determined by HPLC (Chiralcel OD-H).
[d] TFA = trifluoroacetic acid.
[e] 10 mol% of catalyst **9f** was used.

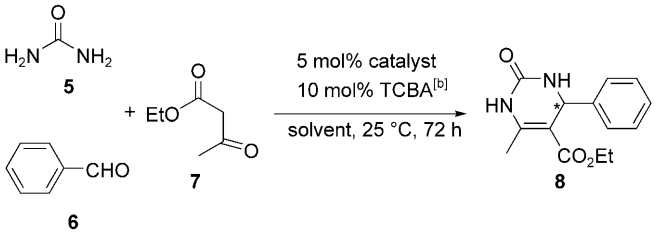
Table 2. Investigation of the Bønsted acid-catalyzed asymmetric Biginelli reaction.[a]



Entry	Acid	Yield [%][b]	*ee* [%][c]
1	TFA	60	15
2	HAc	20	60
3	HCOOH	25	63
4	HCl	10	80
5	H_3PO_4	15	60
6	Benzoic acid	26	53
7	*p*-TSA	30	53
8	2,4,6-Trichlorobenzoic acid	90	63
9[d]	2,4,6-Trichlorobenzoic acid	58	32

[a] The reaction was carried out on a 0.5 mmol scale and the ratio of **5**/**6**/**7** is 1/1.5/3.
[b] Isolated yield based on the urea.
[c] Determined by HPLC (Chiralcel OD-H).
[d] Catalyst **9e** was employed in the reaction.

Table 3. Optimization of solvent for the asymmetric Biginelli reaction.[a]



Entry	Solvent	Yield [%][c]	*ee* (%)[d]
1	CH_2Cl_2	90	63
2	THF	trace	n.d.[e]
3	DMF	35	2
4	1,4-Dioxane	65	2
5	$CHCl_3$	80	52
6	Toluene	70	49
7	Acetone	75	53
8	CH_3CN	65	40
9	Petroleum ether	60	50
10	CH_3OH	35	66
11[f]	CH_2Cl_2	93	94

[a] *Reagents and conditions:* after stirring a solution of acid (10 mol%), benzaldehyde (0.75 mmol), urea (0.5 mmol), in 2 mL of dry solvent at 25 °C for 1 h, catalyst **9f** (5 mol%) and ethyl acetoacetate (1.5 mmol) were added sequentially.
[b] TCBA = 2,4,6-trichlorobenzoic acid.
[c] Isolated yield based on urea.
[d] Determined by HPLC (Chiralcel OD-H).
[e] n.d. = not determined.
[f] 10 mol% *t*-$BuNH_2$·TFA was added as additive.

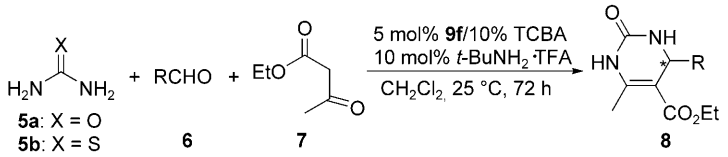
ic acids were favorable in terms of reactivity and enantioselectivity of the Biginelli reaction.[10] We screened benzoic acid, *p*-TSA and 2,4,6-trichlorobenzoic acid, the results indicated that the electron-withdrawing-substituted 2,4,6-trichlorobenzoic acid demonstrated the advantage of control of enantioselectivity in this reaction (Table 2, entries 6–8). When catalyst **9e** was employed in the presence of 2,4,6-trichlorobenzoic acid, the reaction achieved 58% yield with 32% *ee* (Table 2, entry 9).

To optimize the reaction conditions further, the solvent effect was investigated with thiourea catalyst **9f** combined with 2,4,6-trichlorobenzoic acid, and the best result was obtained in CH_2Cl_2 (Table 3, entry 1). The reaction cannot work in THF (Table 3, entry 2). When the reaction was performed in DMF or 1,4-dioxane, a very poor *ee* value was obtained even with increasing the catalyst loading from 5 to 10 mol% (Table 3, entries 3 and 4). Similar results were obtained when the reaction was performed in $CHCl_3$, toluene, acetone and CH_3CN (Table 3, entries 5–8). Interestingly, although the solubility of urea and catalyst was very low in petroleum ether, the reaction still worked very well and furnished the product in 60% yield with 50% *ee* (Table 3, entry 9). When using methanol as solvent a low yield was gained even with a prolonged reaction time, although the *ee* was comparable to that of CH_2Cl_2 (Table 3, entry 10).

To further improve the reactivity and enantioselectivity, the effect of additives was investigated. The organic amine salts were reported have the effect to improve the reactivity and enantioselectivity of the Biginelli reaction.[10] In our investigation, after screening the acidic component, it was found that *t*-$BuNH_2$·TFA combined with 2,4,6-trichlorbenzoic acid gave superior results in terms of reactivity and enantioselectivity (93% yield, 94% *ee*, Table 3, entry 11). There was no desired DHPM product obtained when only *t*-$BuNH_2$·TFA was employed in this reaction without 2,4,6-trichlorbenzoic acid. Thus, the optimal reaction conditions for this transformation were determined to be 0.5 mmol urea, 1.5 equivalents of aldehyde, 3 equivalents of ethyl acetoacetate, 5 mol% of **9f** combined with 10 mol% of 2,4,6-trichlorbenzoic acid containing 10 mol% of *t*-$BuNH_2$·TFA in CH_2Cl_2 as solvent at room temperature.

Based on the above optimization efforts, the substrate scope of this reaction was investigated (Table 4). In general, all the examined substrates could furnish the desired products in good yields and with moderate-to-good enantioselectivities. The scope of the aldehyde component was first investigated by reaction with urea (**5a**) and ethyl acetoacetate (**7**). A

Table 4. Enantioselective Biginelli reaction catalyzed by bifunctional primary amine-thiourea catalysts.[a]



Entry	8	R	X	Yield [%][b]	*ee* [%][c]	Configuration[d]
1	**8a**	C_6H_5	O	93	94	*S*
2	**8b**	4-F-C_6H_4	O	85	93	*S*
3	**8c**	4-Cl-C_6H_4	O	72	>99	*S*
4	**8d**	4-Br-C_6H_4	O	77	74	*S*
5	**8e**	4-Me-C_6H_4	O	83	89	*S*
6	**8f**	4-MeO-C_6H_4	O	81	67	*S*
7	**8g**	3-F-C_6H_4	O	88	80	*S*
8	**8h**	3-Me-C_6H_4	O	78	>99	*S*
9	**8i**	$CH_3CH_2CH_2$	O	51	15	*S*
10	**8j**		O	89	95	*R*
11	**8k**	C_6H_5	S	91	93	*S*
12	**8l**	3-F-C_6H_4	S	86	87	*S*
13[e]	**8m**	C_6H_5	O	90	92	*R*

[a] *Reagents and conditions:* after stirring a solution of TCBA (10 mol%), benzaldehyde (0.75 mmol), urea (0.5 mmol), and *t*-$BuNH_2$·TFA (10 mol%) in 2 mL of CH_2Cl_2 at 25 °C for 1 h, catalyst **9f** (5 mol%) and ethyl acetoacetate (1.5 mmol) were added sequentially.
[b] Isolated yield based on urea or thiourea.
[c] Determined by HPLC (Chiralcel OD-H or AD-H or AS-H).
[d] The absolute configuration was determined by comparison of the optical rotation with the literature.[16]
[e] Catalyst **9g** (5 mol%) was employed in the reaction.

variety of aromatic aldehydes bearing both electron-donating and electron-withdraw groups underwent the reaction to afford high enantioselectivities ranging from 67 to 99% *ee* (Table 4, entries1–8). Both the reactions of *meta*-substituted benzaldehydes and *para*-substituted benzaldehydes proceeded in high yields, *meta*-methylbenzaldehyde and *para*-chlorobenzaldehyde resulted in excellent enantioselectivities (>99% *ee*). An aliphatic aldehyde was found to be less reactive and afforded a low enantioselectivity of 15% *ee* (Table 4, entry 9). The existence of a hydrogen bond between a furan ring and the primary amine-thiourea structure is important: when furanaldehyde was employed in this reaction, the absolute configuration of the product changed to *R* (Table 4, entry 10). The Biginelli reactions of thiourea (**5b**) with various benzaldehydes and β-keto esters were carried out to give the corresponding DHPMs with up to 93% *ee* and 91% yield (Table 4, entry 11 and 12). Simultaneously, chiral catalyst **9g** exhibited a similar level of stereoselectivity with an opposite sense of asymmetric induction and up to 92% *ee* can be obtained. This result indicates that both the (*R,R*)- and the (*S,S*)-configuration of 1,2-diaminocyclohexane matched the β-D-glucopyranose to enhance the stereochemical control (Table 4, entry 13).

In order to determine the structure of the products, a single crystal X-ray diffraction study of **8a** was performed.[17] The molecular structure of **8a** is shown in

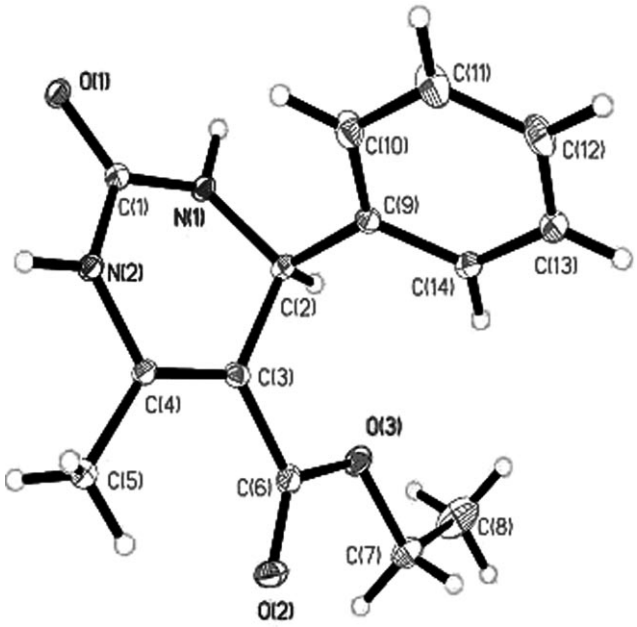


Figure 2. ORTEP presentation of the crystal structure of **8a**, with 20% probability displacement ellipsoids.

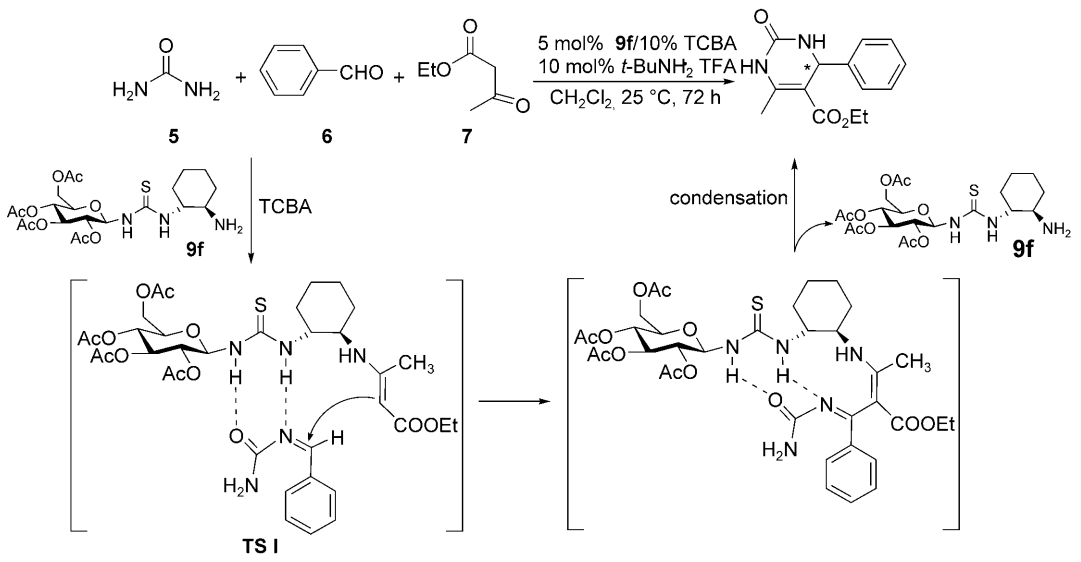


Figure 3. Plausible reaction mechanism.

Figure 2, and the structure showed that the absolute configuration of the DHPM main product was assigned as *S*.

The possible mechanism for the reaction is shown in Figure 3. In the transition state I (**TS I**), the thiourea moiety of bifunctional catalyst **9f** interacts through hydrogen bonding with the acyl group of benzylideneurea while the neighboring primary amine activates ethyl acetoacetate (**7**) involving an enamine intermediate. The obtained absolute configuration (*S*) of DHPMs was explained by the transition state I, in which the *Si*-face of the imine was predominantly approached by the enamine intermediate generated from ethyl acetoacetate (**7**) and the primary amine group of the bifunctional catalyst **9f**. The attack of the enamine to the *Re*-face of the benzylideneurea was restricted by the cyclohexyl scaffold of the catalyst. The mechanism indicates that the thiourea moiety and cyclohexyl scaffold of the bifunctional catalyst play a significant role in controlling the regio- and diastereoselectivity of the Biginelli reaction.

In conclusion, we have developed an enantioselective multicomponent Biginelli reaction catalyzed by a chiral bifunctional primary amine-thiourea **9f** and a Brønsted acid as the combined catalyst with *t*-$BuNH_2$·TFA as additive. A wide range of optically active dihydropyrimidines was obtained in high yields with good to excellent enantioselectivities (up to 99% *ee*). A plausible transition state has been proposed to explain the origin of the activation and the asymmetric induction. Further investigations on the diastereoselective Biginelli reaction and application of this novel catalyst in other asymmetric reactions are currently underway in our laboratory.

Experimental Section

Typical Procedure for the Preparation of 8

A solution of aldehyde **6** (0.75 mmol), urea/thiourea **5** (0.5 mmol), 2,4,6-trichlorobenzoic acid (0.0112 g, 0.05 mmol) and *t*-$BuNH_2$·TFA (0.009 g, 0.05 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h. Then the catalyst **9f** (0.013 g, 0.025 mmol) and ethyl acetoacetate **7** (0.195 g, 1.5 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 3 days, and the crude product was precipitated. The product was filtered by suction and washed twice with cold EtOAc to yield the DHPM as a white solid.

Acknowledgements

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[17] CCDC 729969 contains the supplementary crystallographic data of compound **8a** in 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 or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223–336033; E-mail: deposit@ccdc.cam.ac.uk.

