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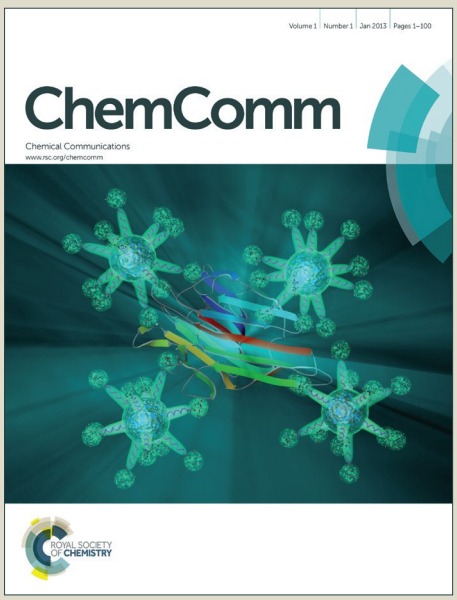

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Highly enantioselective Biginelli reaction using self-assembled methanoproline-thiourea organocatalysts: Asymmetric synthesis of 6-isopropyl-3,4-dihydropyrimidines

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An efficient self-assembled methanoproline-thiourea organocatalyst for the synthesis of optically active 6-isopropyl-3,4-dihydropyrimidines via asymmetric Biginelli reaction was developed, which is much more superior to the individual precatalyst. A wide range of optically active 6-isopropyl-3,4-dihydropyrimidines with remarkable pharmacological interest was obtained in high yields with excellent enantioselectivities (up to 99% ee). A plausible transition state has been proposed to explain the origin of the activation and the asymmetric induction.

Chiral dihydropyrimidines (DHPMs) have been found increasing applications to the synthesis of pharmaceutically relevant substances exhibiting a wide range of important pharmacological properties,[1] including calcium channel modulation,[2] α_{1a}-adrenergic receptor antagonism,[3] and mitotic kinesin inhibition.[4] It has been recognized that the individual enantiomers exhibit different or in some cases even opposite biological activities.[1] (Fig. 1 shows several representative examples). Currently, the preparation of optically pure DHPMs in the pharmaceutical research laboratory mainly relies on resolution and chiral auxiliary-assisted asymmetric synthesis. Due to these important properties and applications, an efficient met for the preparation of optically pure DHPMs is highly desirable. Recent developments in this area have focused on asymmetric Biginelli reactions, which provides an important method for the straightforward synthesis of optically active 3,4-dihydro-pyrimidin-2-(1*H*)-ones and -thiones (DHPMs). In 2005, the breakthrough in the catalytic asymmetric Biginelli reaction was realized by Zhu and co workers with a chiral ytterbium catalyst providing DHPMs in h yields with excellent enantioselectivities.[5] One year late, Gong and co-workers developed an organocatalytic Biginelli reaction usin chiral BINOL-derived phosphoric acid catalyzed, giving DHPMs with up to 97% ee.[6] In 2008, Feng and Juaristi independently described a organocatalytic asymmetric Biginelli reaction using a combined catalyst system consisting of chiral secondary amine and Brønste acid.[7] Subsequently, a variety of chiral DHPMs were obtained in goo yields with excellent enantioselectivities via asymmetric Biginel reaction,[8] including those primary amines,[8b-f] proline derivatives,[7, pyrrolidinyl tetrazole,[8h] and ionic liquids.[8i] Although great success has been achieved in previous work, the development of more-effec asymmetric catalysts and a substrate scope remains an interesting challenge.

Most recently, there was considerable interest in applying self-assembled organocatalysts in catalytic reactions.[9,10] For exampl Zhao[11] had reported the first example of self-assembl organocatalysts from proline and quinidine thioureas are high efficient catalysts for enantioselective direct nitro-Michael additio of ketones and aldehydes to nitroalkenes better than proline Subsequently, Demir,[9e, 9f] Hirose,[9j] Ramachary,[9m] and Zhao[2] respectively reported the similar self-assembled organocatalysts from proline and chiral or achiral thioureas, which could be used s efficient catalysts for Michael addition reactions, direct enantioselective aldol reactions, Mannich reactions and hetero-Diels-Alder reaction. Since self-assembled organocatalysts have undoubtedly been the efficient catalysts in enamine-type reactions, and in light of the mechanism of the Biginelli reaction,[13] herein, we wish to disclose an self-assembled of methanoproline-thiourea organocatalyzed asymmetric Biginelli reaction, directly providing the chiral 6-isopropyl-3,4-dihydropyrimidines compounds in high yields and with excellent enantioselectivities, which is the very important intermediate of Statin drugs and highly enantioselective synthesized via asymmetric Biginelli reaction are yet to be reported.

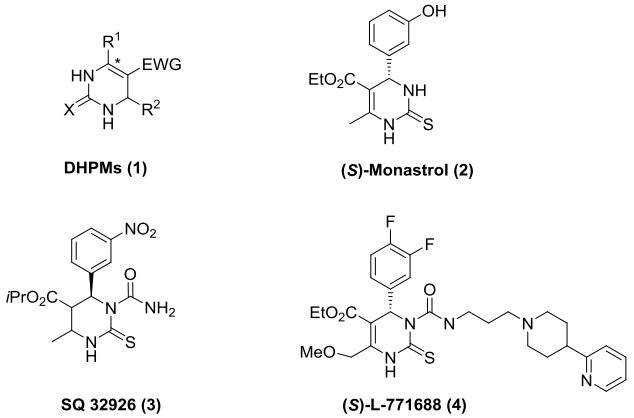

Fig. 1 Biologically active DHPMs

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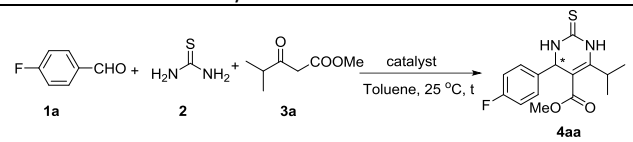
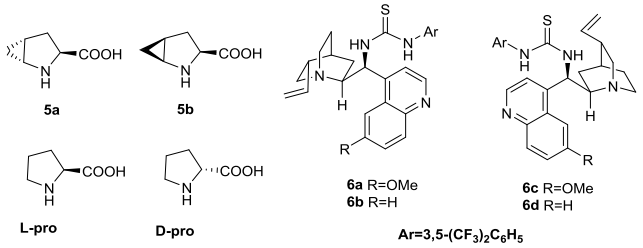
Results and discussion

Initially, the asymmetric Biginelli reaction of 4-fluorobenzaldehyde **1a** with thiourea **2** and methyl isobutyrylacetate **3a** were adopted as the model reaction for optimizing reaction conditions. As can see in Table 1, when *trans*-4,5-methano-L-proline **5a**[14] and quinidine thiourea **6a** (10 mol % loading each) were used as the catalyst in toluene at 25 °C, the desired product was obtained in excellent yield (91%) and high enantioselectivity (95% ee) (Table 1, entry 1). In contrast, when *trans*-4,5-methano-L-proline **5a**, L-proline or quinidine thiourea **6a** were used alone, low yield and enantioselectivity was observed (Table 1, entries 2-4). These results clearly demonstrate that the self-assembled organocatalysts are much more superior to the individual precatalyst. When the catalyst combination is shuffled to be L-proline or D-proline and quinidine thiourea **6a**, there was a slightly mismatching of catalyst observed to deliver the product in 89% ee and 83% ee respectively (Table 1, entries 5 and 6). Replacing the quinidine thiourea **6a** with hydro quinidine thiourea **6b** in catalyst combination of **5a/6b** for asymmetric Biginelli reaction was not found to give superior results (Table 1, entry 7). Instead of *trans*-4,5-methano-L-proline, when *cis*-4,5-methano-L-proline **5b** as used, the product was obtained with a similar yield and a slightly lower enantioselectivity (Table 1, entry 8). The reaction catalyzed by the organocatalyst assembly of *cis*-4,5-methano-L-proline **5b** and quinidine thiourea **6c** yields the opposite enantiomer in 93% ee at 25 °C in toulene. Similar results were obtained for the assembly of *cis*-4,5-methano-L-proline **5b** and quinidine thiourea **6d** (Table 1, entries 9 and 10).

Table 1 Influence of catalyst for the model reaction [a]



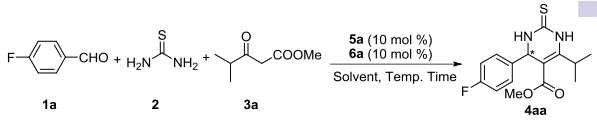


Entry	Cat. (mol %)	t	Yield (%)[b]	Ee (%)[c]
1	**5a/6a** (10:10)	15 h	91	95
2	**5a** (10)	5 d	25	<10
3	**6a** (10)	5 d	17	<10
4	**L-pro** (10)	5 d	18	<10
5	**L-pro/6a** (10:10)	22 h	90	89
6	**D-pro/6a** (10:10)	27 h	89	83
7	**5a/6b** (10:10)	18 h	90	93
8	**5b/6a** (10:10)	20 h	89	92
9[d]	**5b/6c** (10:10)	21 h	87	93
10[d]	**5b/6d** (10:10)	22 h	85	91

[a] Unless stated otherwise, all reactions were carried out with 4-fluorobenzaldehyde (**1a**; 0.4 mmol, 1.0 equiv.), thiourea (**2**; 0.48 mmol, 1.2 equiv.), methyl isobutyrylacetate (**3a**; 0.6 mmol, 1.5 equiv.), **5** and **6** (10 mol % each) in toluene(3 mL) at 25 °C. [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis by using a chiral column, and the configuration was assigned as *S* by comparison with the literature data.[9d] [d] The opposite configuration enantiomer value were obtained.

Having identified assembly of *trans*-4,5-methano-L-proline **5a** and quinidine thiourea **6a** as the optimal catalyst, we studied the solvent and temperature effects on this reaction. As summarized in Table 2, normal organic solvents were found to have only minimal influences on the enantioselectivity vaule, except that poor results were obtained with a very polar solvent DMF (Table 2, entry 6). When the reaction was carried out at 50 °C, the reaction proceed much faster, and while there was a slightly increased in the product ee value (Table 2, entry 7). When the temperature increase from 50 to 60 °C, the reaction yielded the product in 93% yield with a little compromise in enantioselectivity of 96% ee (Table 2, entry 8). In addition, catalyst loading were also surveyed. It was found that reducing the precatalyst loading to 5 mol % each did not affect the yield and enantioselectivity. However, further dropping the loading to 3 mol % each slowed down the desired reaction, and found a drop in both the yield and enantioselectivity. Increasing the catalyst loading did not show a clear improvement in the catalytic performance (Table 2, entries 9-11). By screening a series of reaction conditions, operating with self-assembled of **5a/6a** (5 mol % loading each) in toulene at 50 °C was found to be the most favorable.

Table 2 Influence of solvents, temperature and catalyst loading for the reaction [a]



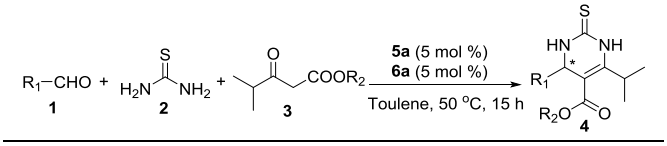
Entry	Solvent	T(°C)	t (h)	Yield (%)[b]	Ee (%)[c]
1	CH_2Cl_2	25	15	83	93
2	toluene	25	15	91	95
3	THF	25	21	62	92
4	CH_3CN	25	17	65	94
5	1,4-dioxane	25	20	57	91
6	DMF	25	48	trace	n.d
7	toluene	50	15	92	98
8	toluene	60	15	93	96
9[d]	toluene	50	15	92	99
10[e]	toluene	50	24	89	94
11[f]	toluene	50	15	93	

[a] Unless stated otherwise, all reactions were carried out with 4-fluorobenzaldehyde (**1a**; 0.4 mmol, 1.0 equiv.), thiourea (**2**; 0.48 mmol, 1.2 equiv.), methyl isobutyrylacetate (**3a**; 0.6 mmol, 1.5 equiv.), **5a** and **6a** (10 mol % each), solvent (3 mL). [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis by using a chiral column, and the configuration was assigned as *S* by comparison with the literature data.[9d] [d] The catalyst loading is 5 mol %. [e] The catalyst loading is 3 mol %. [f] The catalyst loading is 20 mol %.

With the optimal reaction conditions in hand, we explored the generality of the self-assembled of **5a/6a** catalyzed asymmetric Biginelli reaction (Table 3). The scope of the aldehyde component was first investigated by reaction with thiourea (**2**) and methyl isobutyrylacetate (**3a**) (Table 3, entries 1-10). A variety of aromatic aldehydes bearing various types of substituents underwent the reaction to afford DHPMs in high yields (90-95%) with excellent enantioselectivities (92-99% *ee*). It appears that the electronic properties of the substituents on the aromatic aldehyde have a significant influence on the enantioselectivity of the reaction. All the reactions of *para*-substituted benzaldehydes with electron withdrawing groups proceeded in excellent yields and higher enantioselectivities (Table 3, entries 1-4, 99% ee). Excellent enantioselectivity was obtained when no-substituents benzaldehyde was employed (Table 3, entry 5). For aromatic aldehydes bearing

electron-donating groups underwent the reaction also afforded high enantioselectivities ranging from 92 to 96% ee. In particular, the 2,4,6-trimethylbenzaldehyde delivered a comparably lower yield and enantioselectivities may be attributed to the effect of steric hindrance (Table 3, entries 10 and 20). Furthermore, the scope of *β*-keto ester components in the organocatalytic asymm-etric Biginelli reaction was examined next. Replacement the R_2 of *β*-keto ester with ethyl group with various aldehydes in the Biginelli reaction were carried out to give corresponding 6-isopropyl DHPMs with up to 96% yield (Table 3, entries 11-20). The experimental results indicated that variation of the R_2 substituent of *β*-keto esters **3** could be tolerated and generally high enantioselectivities (91-99% ee) were provided for the reactions related to these substrates. For the aliphatic aldehydes, such as n-butyraldehyde was also reacted with *β*-keto esters **3** to generate the 6-isopropyl-3,4-dihydropyrimi-dines product with extremely high enantioselectivities (Table 3, entries 21 and 22, ee up to 94% and 95%, respectively).

Table 3 Scope of the organocatalytic enantioselective Biginelli reaction [a]

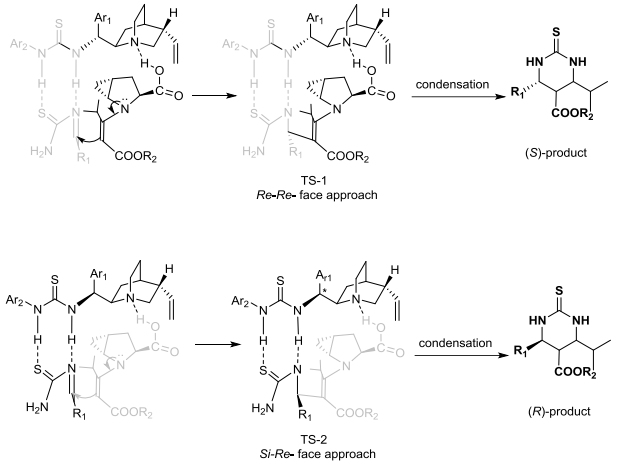


Entry	R_1	R_2	4	Yield (%)[b]	Ee (%)[c]
1	4-FPh	Me	**4aa**	92	99
2	4-ClPh	Me	**4ba**	93	99
3	4-CF_3Ph	Me	**4ca**	94	99
4	4-NO_2Ph	Me	**4da**	95	99
5	Ph	Me	**4ea**	90	97
6	4-OHPh	Me	**4fa**	93	95
7	4-MePh	Me	**4ga**	92	96
8	4-OMePh	Me	**4ha**	92	95
9	4-$CH(CH_3)_2$Ph	Me	**4ia**	91	94
10	2,4,6-$(CH_3)_3$Ph	Me	**4ja**	90	92
11	4-FPh	Et	**4ab**	92	99
12	4-ClPh	Et	**4bb**	93	99
13	4-CF_3Ph	Et	**4cb**	93	99
14	4-(NO_2)Ph	Et	**4db**	96	99
15	Ph	Et	**4eb**	92	98
16	4-OHPh	Et	**4fb**	94	95
17	4-MePh	Et	**4gb**	92	96
18	4-OMePh	Et	**4hb**	93	96
19	4-$CH(CH_3)_2$Ph	Et	**4ib**	92	93
20	2,4,6-$(CH_3)_3$Ph	Et	**4jb**	90	91
21	n-Pr	Me	**4ka**	93	94
22	n-Pr	Et	**4kb**	91	95

[a] Unless stated otherwise, all reactions were carried out with aldehyde (**1**; 0.4 mmol, 1.0 equiv.), thiourea (**2**; 0.48 mmol, 1.2 equiv.), *β*-keto ester (**3**; 0.6 mmol, 1.5 equiv.), **5a** and **6a** (10 mol% each) in toluene (3 mL) at 50 °C. [b] Isolated yield after flash chromatography, and the configuration was assigned as *S* by comparison with the literature data.[9d] [c] Determined by HPLC analysis by using a chiral column.

Biginelli reactions of urea with aromatic aldehydes and isobutyrylacetate were also tested on the basis of the optimal conditions and with adjusted reaction conditions (solvent, temperature and feed ratio), but no corresponding products were obtained.

The opposite senses of enantioselectivity for the assemblies of **5a** with **6a** and **6c** may be rationalized by the proposed transition states, as shown in Scheme 1. Base on relevant reports[9m, 12c], there are three important interactions among the substrates and the catalysts: 1) Carboxylic group of *trans*-4,5-methano-L-proline **5** undergoes proton exchange with quinoline moiety of quinidine thiourea **6a**, thus bringing the electronic and steric environment closer to the reaction center; 2) Two *NH* groups of quinidine thiourea engage themselves in hydrogen bonding with imine by condensation of the aldehyde and thiourea to activate the electrophilic nature and the benzylideneurea is restricted by the quinidine thiourea scaffold of the catalyst; 3) Secondary amine group of **5a** forms enamine intermediate with *β*-keto esters **3** to activate the nucleophilic nature. In the case of quinidine thiourea **6a** (TS-1), in which the *Re*-face of the imine is predominantly approached by the enamine intermediate, the *Re*, *Re*-attack of the hydrogen-bonded imine on the enamine intermediate leads to the major *S*-configured product. In contrast, in the case of quinidine thiourea **6c** (TS-2), and the *Re*, *Si*-attack of the hydrogen-bonded imine on the enamine intermediate leads to the major *R*-configured product.



Scheme 1. Plausible reaction mechanism for the Biginelli reaction

Conclusions

In summary, we have designed a new and efficient self-assembled methanoproline-thiourea organocatalysts for the asymmetric Biginelli reaction, which is much more superior to the individual precatalyst. Under the optimal reaction conditions, a wide range of optically active 6-isopropyl-3,4-dihydropyrimi-dines with remarkable pharmacological interest was obtained in high yields with excellent enantioselectivities (up to 99% ee) using this practical method under mild conditions. A plausible transition state has been proposed to explain the origin of the activation and the asymmetric induction. Further exploration of the catalytic mechanism and applications of the novel self-assembled methanoproline-thiourea organocatalysts in asymmetric catalysis are in progress in our laboratory.

Acknowledgements

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