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Primary Amine Catalyzed Biginelli Reaction for the Enantioselective Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

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Several chiral primary amines, mainly those derived from cinchona alkaloids, were evaluated as organocatalysts for the asymmetric Biginelli reaction. With quinine-derived amine catalyst **1** and after extensive optimization of the reaction conditions, 3,4-dihydropyrimidin-2(1*H*)-ones were obtained in moderate to good yields and 51–78 % *ee* from a three-component reaction of aryl and aliphatic aldehydes, urea, and acetoacetate.

Introduction

3,4-Dihydropyrimidin-2(1*H*)-one derivatives (DHPMs) are very important pharmacologically active molecules and have found applications as calcium channel modulators, α_{1a} adrenoceptor-selective antagonists, and inhibitors of the kinesin motor protein and HIV.[1] The Biginelli reaction,[2] which is a three-component reaction of an aromatic aldehyde, urea, and acetoacetate, is the most efficient method for the assembly of these biologically significant heterocyclic compounds. Because it has been found that individual enantiomers of a given DHPM may exhibit totally different or even opposite pharmaceutical activities,[3] there has been a lot of interest in developing highly enantioselective syntheses of DHPM derivatives in recent years.[4] For example, Zhu and co-workers reported the first highly enantioselective synthesis of DHPMs by using a chiral ytterbium Lewis acid catalyst in 2005.[5b] Soon afterwards, Gong and co-workers successfully developed an asymmetric synthesis of these compounds with excellent enantiocontrol by using a BINOL-derived Brønsted acid.[5c,5d] Besides Lewis acids[5a,5b] and Brønsted acids,[5c,5d] asymmetric induction in this reaction may also be achieved by using secondary amines as the catalyst and a suitable acid as the cocatalyst.[5e–5i] The reported catalysts are mainly proline derivatives.[5e–5h] In contrast, although primary amines are also known to participate as catalysts in reactions that involve enamine intermediates,[6] to the best of our knowledge, there is no report on the use of primary amines as catalysts in the enantioselective synthesis of DHPMs, except for the use of bifunctional primary amine thioureas reported recently by Chen and co-workers[5i] during the progress of our current work. Herein we wish to disclose our study on the use of primary amines, mainly those derived from cinchona alkaloids, as catalysts in the asymmetric synthesis of DHPMs using the Biginelli reaction.

Results and Discussion

According to previous reports by Feng,[5e] Juaristi,[5f] Wang,[5g] and Lee,[5h] the observed stereoselectivities in the asymmetric synthesis of DHPMs catalyzed by secondary amine catalysts were explained by an enamine activation mechanism.[5e–5h] Because primary amines, especially those derived from cinchona alkaloids, are also highly efficient catalysts for organic reactions involving enamine intermediates,[6] we reasoned that these compounds should also be good catalysts for the asymmetric synthesis of DHPMs. Thus, we screened some readily available chiral primary amine catalysts (**1**–**7**, Figure 1) in the three-component reaction of benzaldehyde (**8a**), urea (**9**), and ethyl acetoacetate (**10**) for the asymmetric synthesis of DHPM derivative **11a**. The results of the screening are summarized in Table 1.

As shown by the results in Table 1, when quinine-derived amine **1** was used as the catalyst and HCl as the acid cocatalyst (10 mol-% each), the reaction of benzaldehyde (**8a**), urea (**9**), and ethyl acetoacetate (**10**) in THF led to desired product **11a** in 64% yield and 66%*ee* after 3 d at room temperature (Table 1, Entry 1). The absolute configuration of the major enantiomer was determined to be *R* by comparing the measured optical rotation with reported data.[5] Demethylated catalyst **2** yielded this product in a similar yield after a reaction time of 5 d at room temperature, and the *ee* value obtained was slightly lower (Table 1, Entry 2). Quinidine-derived amine **3**, which is a pseudoenantiomer of **1**, gave the opposite enantiomer as the major product in 57%*ee* (Table 1, Entry 3). When similarly demethylated catalyst **4** was used, the reaction became very sluggish and the *ee* value obtained was much lower (40%; Table 1, Entry 4).

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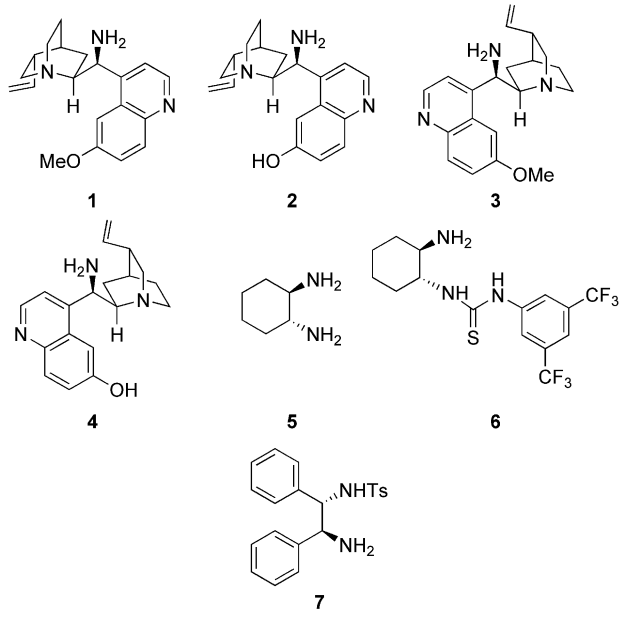
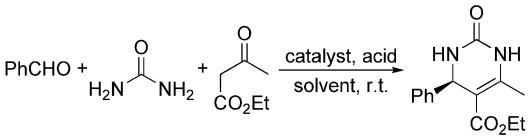


Figure 1. Catalysts screened for the three-component synthesis of DHPM **11a**.

These results indicate that both the reaction rate and the enantioselectivity are highly sensitive towards subtle changes in the structure of the catalyst. Although these catalysts generate only mediocre *ee* values of the product, 1,2-cyclohexanediamine (**5**) and its thiourea derivative **6** and sulfonamide derivative **7** proved to be even poorer catalysts for this reaction, because low yields and/or poor *ee* values of the product were obtained (Table 1, Entries 5–7).

This screening identified quinine-derived amine **1** as the best catalyst for this reaction. Then, we studied the solvent effects on this reaction by using **1** as the catalyst. As revealed in Table 1, a slightly lower *ee* value of 61% was obtained with 1,4-dioxane (Table 1, Entry 8). When chloroform and dichloromethane were used as solvents, the *ee* values obtained were also inferior (59 and 50%, respectively; Table 1, Entries 9 and 10). The reaction is also slower in these three solvents (Table 1, Entries 8–10). Other common organic solvents, such as toluene (Table 1, Entry 11), 2,2,2-trifluoroethanol (Table 1, Entry 12), CH_3CN (Table 1, Entry 13), DMSO (Table 1, Entry 14), and acetone (Entry 15), all led to poorer *ee* values of the product. Next, different acid cocatalysts were evaluated. Weak acids such as benzoic acid (Table 1, Entry 16) and 2-nitrobenzoic acid (Table 1, Entry 17) are not effective in promoting the reactivity and the enantioselectivity of this reaction at all. In contrast, good yields of the product were obtained with a stronger acid, such as TFA (Table 1, Entry 18), *p*-toluenesulfonic acid (Table 1, Entry 19), and trifluoromethanesulfonic acid (Table 1, Entry 20), albeit the *ee* values obtained were slightly lower with these acid cocatalysts. Thus, THF was identified as the best solvent and HCl was identified as the best acid cocatalyst for this reaction. To obtain better yields and enantioselectivities in this reaction, the catalyst loading and ratio of the three substrates were further studied. Dropping the catalyst loading to 5 mol-% led to a lower yield and *ee* value of the product (Table 1, Entry 21). On the other hand, increasing the catalyst loading to 20 mol-% only resulted in a slightly better product yield (Table 1, Entry 22). Nevertheless, we found that a much better product yield could be achieved if an excess amount of urea and acetoacetate was used together with a 20 mol-% loading of the catalyst. For example, the yield improved to 91% when the molar ratio of **8a**/**9**/**10** was changed to 1:1.5:3 (Table 1, Entry 23). The yield was further improved to 97% if this

Table 1. Screening of the catalysts and optimization of the reaction conditions.[a]



8a **9** **10** **11a**

Entry	Catalyst	Acid	Solvent	Time [d]	Yield [%][b]	*ee* [%][c]
1	**1**	HCl	THF	5	64	66
2	**2**	HCl	THF	5	63	50
3	**3**	HCl	THF	5	51	57[d]
4	**4**	HCl	THF	8	21	40[d]
5	**5**	HCl	THF	9	trace	nd[e]
6	**6**	HCl	THF	5	21	5
7	**7**	HCl	THF	6	56	3
8	**1**	HCl	dioxane	7	80	61
9	**1**	HCl	$CHCl_3$	5	60	59
10	**1**	HCl	CH_2Cl_2	5	62	50
11	**1**	HCl	toluene	9	12	37
12	**1**	HCl	TFE[f]	5	trace	nd[e]
13	**1**	HCl	CH_3CN	5	85	40
14	**1**	HCl	DMSO	5	83	17
15	**1**	HCl	acetone	5	43	46
16	**1**	$PhCO_2H$	THF	15	<5	nd
17	**1**	2-NBA[g]	THF	15	13	0
18	**1**	TFA	THF	5	60	44
19	**1**	*p*-TSA	THF	8	75	55
20	**1**	CF_3SO_3H	THF	6	71	20
21[h]	**1**	HCl	THF	7	51	52
22[i]	**1**	HCl	THF	5	73	61
23[i,j]	**1**	HCl	THF	5	91	62
24[i,k]	**1**	HCl	THF	5	97	64
25[i,k,l]	**1**[m]	HCl	THF	6	81	73
26[i,k,l]	**1**[n,o]	HCl	THF	6	76	72

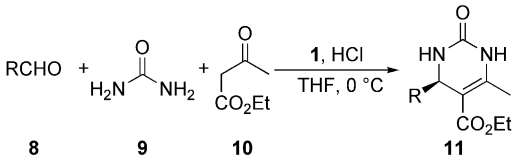
[a] Unless otherwise noted, all reactions were conducted with **8a** (0.25 mmol), **9** (0.25 mmol), and **10** (0.25 mmol) in the presence of the catalyst (0.025 mmol, 10 mol-%) and the acid cocatalyst (0.025 mmol, 10 mol-%) in the specified solvent (1.5 mL) at room temperature. [b] Yield of the isolated product after column chromatography. [c] Determined by the HPLC analysis on a Chiral-Cel OD-H column. [d] The *S* enantiomer was obtained as the major product. [e] Not determined. [f] 2,2,2-Trifluoroethanol. [g] 2-Nitrobenzoic acid. [h] Conducted with 5 mol-% of the catalyst and 5 mol-% of the acid cocatalyst. [i] Conducted with 20 mol-% of the catalyst and 20 mol-% of the acid cocatalyst. [j] Conducted with **8a** (0.25 mmol), **9** (0.375 mmol), and **10** (0.75 mmol). [k] Conducted with **8a** (0.25 mmol), **9** (0.50 mmol), and **10** (1.25 mmol). [l] The reaction temperature was 0 °C. [m] Catalyst **1** was recovered in 93% yield after the reaction. [n] Carried out with recovered catalyst **1**. [o] Catalyst **1** was recovered in 98% yield after the reaction.

ratio was 1:2:5 (Table 1, Entry 24). Moreover, the *ee* values obtained for the product remained almost steady in these two cases. Finally, the temperature effects were studied, and it was found that lowering the reaction temperature to 0 °C can improve the *ee* value to 73% (Table 1, Entry 25). Further dropping the reaction temperature is impractical, as the reaction becomes very sluggish. Although 10 mol-% of catalyst **1** has to be used to achieve a good yield of the product, it is possible to recover the catalyst in high yields (93 to 98% yield; Table 1, Entries 25 and 26) during the chromatographic purification of the product. Furthermore, the recycled catalyst shows almost the same reactivity and selectivity as the original catalyst (Table 1, Entry 26).

The scope of this reaction was then evaluated by using compound **1** as the catalyst and HCl as the cocatalyst under the optimized conditions (Table 1, Entry 25). The results are collected in Table 2. Besides benzaldehyde (Table 2, Entry 1), substituted benzaldehydes may also be applied as the substrates in this reaction. The electronic nature of the substituent on the benzene ring was found to have influences on both the reactivity and the enantioselectivity of this reaction. Electron-donating groups, such as methyl or methoxy groups, diminish slightly the reaction yield and the *ee* values of this reaction as compared to the unsubstituted phenyl group (Table 2, Entries 2–4 vs. Entry 1). In contrast, electron-withdrawing groups on the phenyl ring have no influence on the enantioselectivities (Table 2, Entries 5–10). For example, similar *ee* values of 72 and 74% were obtained for the strongly electron-withdrawing *para*- and *meta*-nitro-substituted benzaldehydes, respectively (Table 2, Entries 9 and 10 vs. Entry 1). Nonetheless, whereas weak electron-withdrawing groups only reduce the reaction yields slightly (Table 2, Entries 5–7), strong electron-withdrawing groups, such as cyano and nitro groups, diminish the yield dramatically (Table 2, Entries 8–10). Although aromatic aldehydes are often studied in the asymmetric synthesis of DHPMs,[5] aliphatic aldehydes are seldom used as substrates.[5b,5c] To the best of our knowledge, aliphatic aldehydes have never been studied in an enamine-mediated asymmetric Biginelli reaction. To test the scope our catalyst, we studied heptanal in our reaction, and found the reaction gave comparable enantioselectivity of the product (72%*ee*) as aromatic substrate, although the yield of the product is much lower (43%; Table 2, Entry 11).

On the basis of the mechanism proposed for the secondary-amine-catalyzed synthesis of DHPMs,[5e–5h] we believe the present reaction also works through a dual activation mechanism realized by quinine amine catalyst **1**. The formation of the *R*-configured product may be interpreted by the proposed transition state in Scheme 1. As shown in Scheme 1, the imine formed between benzaldehyde and urea is hydrogen bonded to the protonated quinuclidine backbone of catalyst **1**. Such a hydrogen bond not only activates the imine for nucleophilic attack, but also helps bring the imine closer to the reaction center and limits its possible orientations. The primary amine group on the side chain of the catalyst activates acetoacetate through the formation of an enamine. Attack of this enamine onto the *Si* face of the imine gives an intermediate, which, after hydrolysis, intramolecular cyclization, and dehydration reaction, yields observed *R*-configured product **11a**.

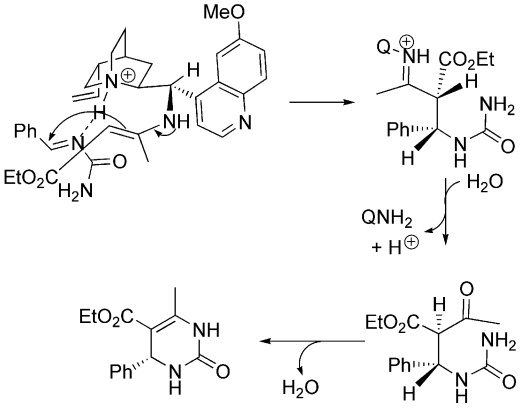
Table 2. Three-component reaction of aldehydes, urea, and acetoacetate for the asymmetric synthesis of DHPMs.[a]



8 **9** **10** **11**

Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**11a**	81	73
2	4-MeC_6H_4	**11b**	53	69
3	4-$MeOC_6H_4$	**11c**	71	51
4	2-MeC_6H_4	**11d**	53	53[d]
5	4-FC_6H_4	**11e**	61	73
6	4-ClC_6H_4	**11f**	63	76
7	4-BrC_6H_4	**11g**	68	78
8	4-NCC_6H_4	**11h**	20	76
9	4-$O_2NC_6H_4$	**11i**	14	72
10	3-$O_2NC_6H_4$	**11j**	21	74
11	*n*-C_6H_{13}	**11k**	43	72

[a] All reactions were conducted with **8** (0.25 mmol), **9** (0.5 mmol), and **10** (1.25 mmol) in the presence of catalyst **1** (0.05 mmol, 20 mol-%) and HCl (0.05 mmol, 20 mol-%) in THF (1.5 mL) at 0 °C for 6 d. [b] Yield of the isolated product after column chromatography. [c] Unless otherwise noted, *ee* values were determined by HPLC analysis on a ChiralCel OD-H column. [d] Determined by the HPLC analysis on a ChiralPak AD-H column.



Scheme 1. Plausible transition state for the formation of the *R*-configured enantiomer (QNH_2 = catalyst **1**).

Conclusions

We have demonstrated that chiral primary amines, such as the amine derived from quinine, may be used as catalysts for the three-component reaction of aldehydes, urea, and acetoacetate in the enantioselective synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs). Under the optimized conditions, the corresponding DHPMs may be obtained in moderate to good yields and good *ee* values (up to 78%*ee*).

Experimental Section

General: ^{1}H NMR spectra were obtained with a Varian INOVA 500 MHz or a GE 300 MHz spectrometers by using residual solvent as the standard. TLC was performed with silica gel GF_{254} precoated on aluminum plates, and spots were visualized with UV and/or iodine vapor. Flash column chromatography was performed on silica gel. HPLC analysis was performed with a Shimadzu instrument with LC-20AT pump and SPD-20AV UV/Vis detector. ChiralCel and ChiralPak HPLC columns were purchased from Daicel Chemical Industry, Ltd. Compounds used in this study were purchased from Aldrich, Alfa-Aesar, Acros, TCI, or Strem and were used as received. Toluene, CH_2Cl_2, $CHCl_3$, and CH_3CN were distilled from CaH_2. THF was freshly distilled from benzophenone and sodium metal. DMSO was dried with molecular sieves. Catalysts **1**,[8] **2**,[9] **3**,[8] **4**,[9] **6**,[10] and **7**[11] were synthesized according to reported procedures. Unless otherwise specified, all reactions were carried out at ambient temperature in oven-dried glassware.

General Procedure for the Three-Component Reaction of Aldehyde, Urea, and Acetoacetate: To a mixture of the aldehyde (0.25 mmol) and urea (30.0 mg, 0.5 mmol) in THF (1.5 mL) at 0 °C was added ethyl acetoacetate (162.7 mg, 1.25 mmol), catalyst **1** (16.2 mg, 0.05 mmol), and HCl (4.0 M in dioxane, 13 μL, 0.05 mmol). The mixture was further stirred for 6 d at this temperature. Then the reaction mixture was directly transferred to a silica gel column and purified by column chromatography (hexane/ethyl acetate, 1:1) to afford the DHPM products. All the products are known compounds and have identical spectroscopic data as those reported.[5b,5c]

Catalyst Recovering: Once the DHMP product was separated, the column was flushed with $Et_3N/CH_3OH/EtOAc$ (1:2:4) as the eluent to isolate catalyst **1** (as its HCl salt, R_f = 0.62). The fractions were combined and the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), washed with aqueous $NaHCO_3$ (5 mL), and dried with Na_2SO_4. The solvent was removed to afford the catalyst (15.0 mg, 93% recovery).

(*R*)-5-Ethoxycarbonyl-4-(*n*-hexyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (11k):[7,12] Yield: 28.8 mg, 43%, white solid, m.p. 126–128 °C. $[\alpha]_D^{23}$ = +40.0 (*c* = 1.02, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (br. s, 1 H), 5.75 (br. s, 1 H), 4.29–4.32 (m, 1 H), 4.14–4.24 (m, 2 H), 2.29 (s, 3 H), 1.49–1.60 (m, 2 H), 1.23–1.43 (m, 1 H), 0.87–0.92 (m, 3 H) ppm.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR spectroscopic data and spectra of the products; HPLC conditions and chromatograms.

Acknowledgments

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