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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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Abstract

Several chiral primary amines, mainly those derived from the cinchona alkaloids, were evaluated as the organocatalysts for the asymmetric Biginelli reaction. With the 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.

Keywords

Biginelli reaction; Catalysis; Enantioselective; Dihydropyrimidinone; Multi-component reaction

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 the HIV.[1] Biginelli reaction,[2] which uses 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 these DHPM derivatives in recent years.[4] For examples, Zhu and co-workers reported the first highly enantioselective synthesis of DHPMs 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 using a BINOL-derived Brønsted acid.[5c,d] Besides Lewis acids[5a,b] and Brønsted acid,[5c,d] asymmetric induction in this reaction may also be achieved by using secondary amines as the catalyst and a suitable acid as the cocatalyst.[5e–i] The reported catalysts are mainly proline derivatives.[5e–h] In contrast, although primary amines are also known to participate as a catalyst in reactions that involve the enamine intermediate,[6] to our knowledge, there is no report on using primary amines as the catalyst for the enantioselective synthesis of DHPMs, except for the bifunctional primary amine thioureas reported most recently by Chen and co-workers[5i] during the progress of our current work. Herein we wish to disclose our study of using primary amines, mainly those derived from

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Supporting Information: ¹H NMR data and spectra of the products; HPLC conditions and chromatograms.

the cinchona alkaloids, as the catalyst for the asymmetric synthesis of DHPMs using a three-component Biginelli reaction.

Results and Discussion

According to the 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 the enamine activation mechanism.[5e–h] Since primary amines, especially those derived from the cinchona alkaloids, are also highly efficient catalysts for organic reactions involving the 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 the DHPM derivative **11a**. The results of the screening are summarized in Table 1.

As shown by the results in Table 1, when the 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 the desired product **11a** in 64% yield and 66% ee after 3 days at room temperature (entry 1). The absolute configuration of the major enantiomer was determined to be *R* by comparing the measured optical rotation with those reported data.[5] The demethylated catalyst **2** yielded this product in a similar yield after a reaction of 5 days at room temperature, and the ee value obtained was slightly lower (entry 2). The quinidine-derived amine **3**, which is a pseudo-enantiomer of **1**, gave the opposite enantiomer as the major product in 57% ee (entry 3). When a similarly demethylated catalyst **4** was used, the reaction became very sluggish and the ee value obtained was much lower (40%, entry 4). These results indicate that both the reaction rate and enantioselectivity are highly sensitive towards the subtle changes in the catalyst structure. While 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 (entries 5–7).

This screening identified the 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 values of 61% was obtained with 1,4-dioxane (entry 8). When chloroform and dichloromethane were used as the solvent, the ee values obtained were also inferior (59% and 50%, respectively, entries 9 and 10). The reaction is also slower in these three solvents (entries 8–10). Other common organic solvents, such as toluene (entry 11), 2,2,2-trifluoroethanol (entry 12), CH₃CN (entry 13), DMSO (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 (entry 16) and 2-nitrobenzoic acid (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 (entry 18), *p*-toluenesulfonic acid (entry 19), and trifluoromethanesulfonic acid (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. In order to obtain better yield and enantioselectivity in this reaction, the catalyst loading and ratio of the three substrates were further studied. Dropping the catalyst loading to 5 mol % led to lower yields and ee value of the product (entry 21). On the other hand, increasing the catalyst loading to 20 mol % only resulted in slightly better product yield (entry 22). Nevertheless, we found that 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 (entry 23). The yield was further improved to 97% if this ratio was 1:2:5 (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% (entry 25). Further dropping the reaction temperature is impractical since 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, 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 (entry 26).

The scope of this reaction was then evaluated 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. As shown in Table 2, besides benzaldehyde (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 (entries 2–4 vs. 1). In contrast, electron-withdrawing groups on the phenyl ring have no influence on the enantioselectivities (entries 5–10). For example, similar ee values of 72% and 74% were obtained for the strong electron-withdrawing *para*- and *meta*-nitro-substituted benzaldehydes, respectively (entries 9 and 10 vs. 1). Nonetheless, while weak electron-withdrawing groups only reduce the reaction yields slightly (entries 5–7), strong electron-withdrawing groups, such as cyano and nitro groups, diminish the yield dramatically (entries 8–10). Although aromatic aldehydes are often studied in the asymmetric synthesis of DHPMs,^[5] aliphatic aldehydes are seldom used as the substrates. [5b,c] To 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%, entry 11).

On the basis of the mechanism proposed for the secondary-amine-catalyzed synthesis of DHPMs,^[5e–h] we believe the present reaction also works through a dual activation mechanism realized by the 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 a nucleophilic attack, but also helps bring the imine closer to the reaction center and limit 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 the observed *R*-configured product **11a**.

Conclusions

We have demonstrated that chiral primary amines, such as the amine derived from quinine, may be used the catalyst 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

¹H NMR spectra were obtained on a Varian INOVA 500 MHz or a GE 300 MHz spectrometers using residual solvent as the standard. TLC was performed with silica gel GF₂₅₄ 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 on 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, CH₂Cl₂, CHCl₃, and CH₃CN were distilled from CaH₂. THF was freshly distilled from benzophenone and sodium metal. DMSO was dried over molecular sieves. Catalysts **1**,^[8] **2**,^[9] **3**,^[8] **4**,^[9] **6**,^[10] and **7**^[11] were synthesized according to the 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 days at this temperature. Then the reaction mixture was directly transferred to a silica gel column and purified by column chromatography (1:1 hexane/ethyl acetate) to afford the DHPM products. All the products are known compounds and have identical spectroscopic data as those reported.^[5b,c]

Catalyst recovering—Once the DHMP product was separated, the column was flushed with 1:2:4 Et₃N/CH₃OH/EtOAc 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 CH₂Cl₂ (10 mL), washed with aq. NaHCO₃ (5 mL), and dried over Na₂SO₄. 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(1H)-one (11k)^[7,12]—Yield 28.8 mg, 43%, white solid, m.p. 126–128 °C. [α]_D²³ = +40.0 (c 1.02, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 8.04 (s, br, 1H), 5.75 (s, br, 1H), 4.29–4.32 (m, 1H), 4.14–4.24 (m, 2H), 2.29 (s, 3H), 1.49–1.60 (m, 2H), 1.23–1.43 (m, 1H), 0.87–0.92 (m, 3H) ppm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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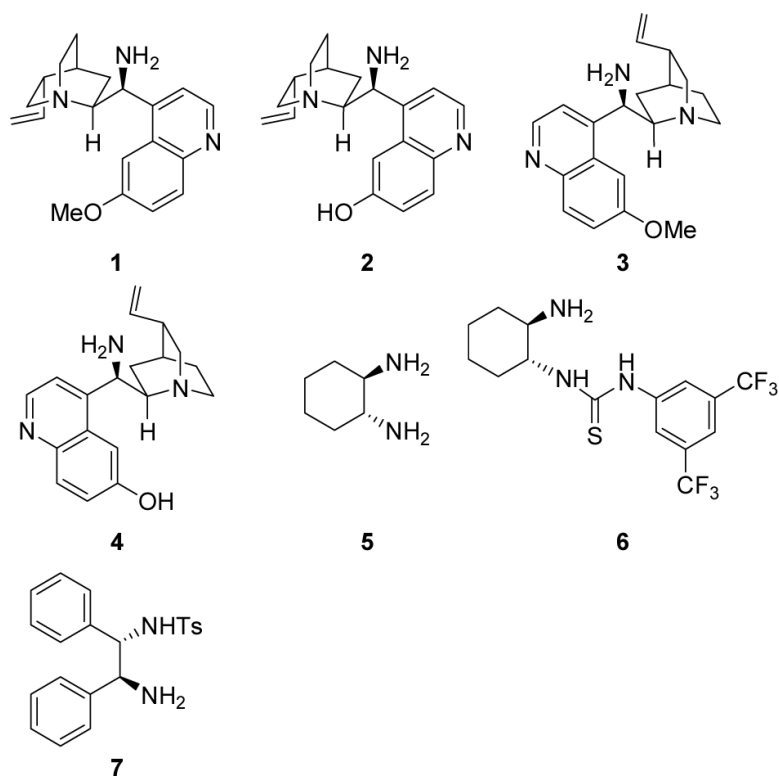
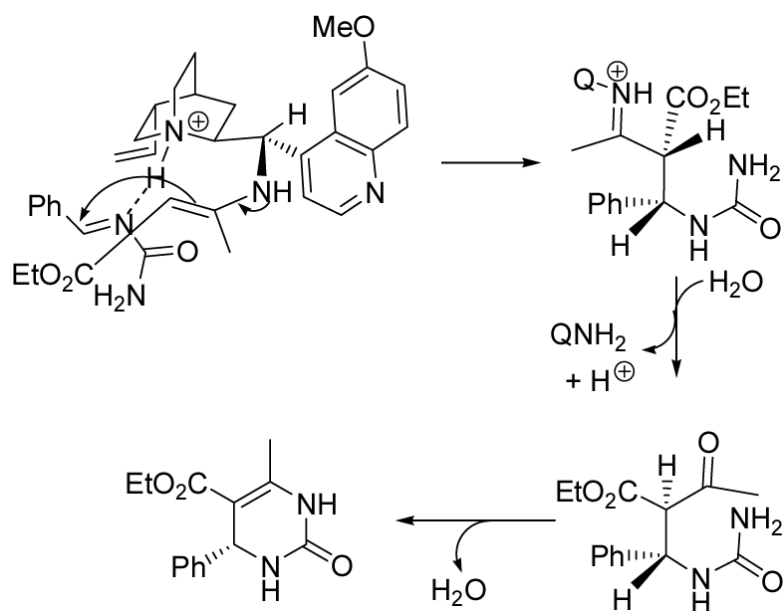


Figure 1.
Catalysts screened for the three-component synthesis of DHPM 11a

**Scheme 1.**

Plausible transition state for the formation of the *R*-configured enantiomer (QNH₂ = catalyst **1**).

Table 1

Screening of the catalysts and optimization of the reaction conditions^[a]

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 ₂ Cl ₂	5	62	50
11	1	HCl	toluene	9	12	37
12	1	HCl	TFE ^[f]	5	trace	nd ^[e]
13	1	HCl	CH ₃ CN	5	85	40
14	1	HCl	DMSO	5	83	17
15	1	HCl	acetone	5	43	46
16	1	PhCO ₂ H	THF	15	<5	nd
17	1	2-NBA ^[g]	THF	15	13	0
18	1	TFA	THF	5	60	44
19	1	<i>p</i> -TSA	THF	8	75	55
20	1	CF ₃ SO ₃ H	THF	6	71	20
21 ^[h]	1	HCl	THF	7	51	52
22 ^[i]	1	HCl	THF	5	73	61

Entry	Catalyst	Acid	Solvent	Time [d]	Yield [%] ^[b]	ee [%] ^[c]
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 compounds **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 ChiralCel 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 compounds **8a** (0.25 mmol), **9** (0.375 mmol), and **10** (0.75 mmol).

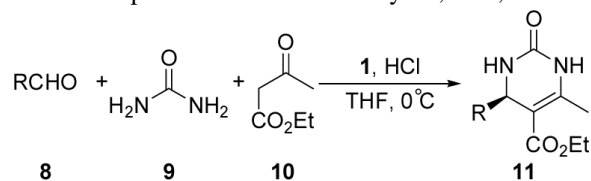
^[k] Conducted with compounds **8a** (0.25 mmol), **9** (0.50 mmol), and **10** (1.25 mmol).

^[l] The reaction temperature was 0 °C.

^[m] Catalyst **1** was recovered in 93% yield after the reaction.

^[n] Carried out with the recovered catalyst **1**.

^[o] Catalyst **1** was recovered in 98% yield after the reaction.

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

Entry	R	Product	Yield [%] ^[b]	ee [%] ^[c]
1	Ph	11a	81	73
2	4-MeC ₆ H ₄	11b	53	69
3	4-MeOC ₆ H ₄	11c	71	51
4	2-MeC ₆ H ₄	11d	53	53 ^[d]
5	4-FC ₆ H ₄	11e	61	73
6	4-ClC ₆ H ₄	11f	63	76
7	4-BrC ₆ H ₄	11g	68	78
8	4-CNC ₆ H ₄	11h	20	76
9	4-NO ₂ C ₆ H ₄	11i	14	72
10	3-NO ₂ C ₆ H ₄	11j	21	74
11	<i>n</i> -C ₆ H ₁₃	11k	43	72

^[a] All reactions were conducted with compounds **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 days.

^[b] Yield of the isolated product after column chromatography.

^[c] Unless otherwise noted, ee values were determined by the HPLC analysis on a ChiralCel OD-H column.

^[d] Determined by the HPLC analysis on a ChiralPak AD-H column.