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Highly Enantioselective Organocatalytic Biginelli Reaction

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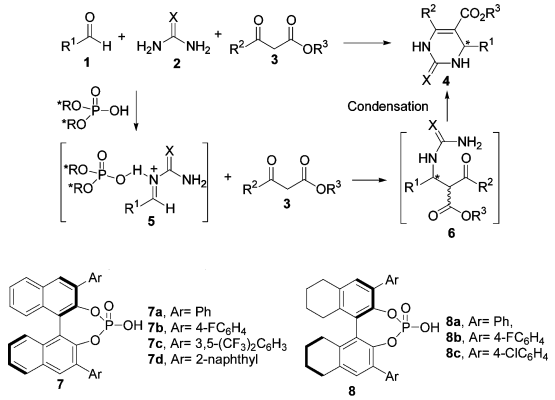
Multicomponent reactions in which three or more reactants are combined in a single vessel to generate new molecules that contain portions of each reactant undoubtedly maintain great importance in organic and medicinal chemistry due to the synthetic efficiency and molecular diversity required in the discovery of new lead compounds.[1] The Biginelli reaction,[2] one of the most useful multicomponent reactions, offers an efficient way to access multifunctionalized 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and related heterocyclic compounds. Such heterocycles show a wide scope of important pharmacological properties and make up a large family of medicinally relevant compounds.[3] Asymmetric Biginelli reactions have therefore received renewed attention.[4] Compounds containing the DHPM moiety have an inherent stereogenic center, and the influence of the absolute configuration of the stereogenic center on the biological activity has been extensively investigated.[3] The individual enantiomers have been found to exhibit different or opposite pharmaceutical activities.[5] The procedure most often used for manufacturing optically pure 3,4-dihydropyrimidin-2-(1*H*)-ones relies on resolution and chiral auxiliary-assisted asymmetric synthesis.[6] Despite its importance for preparing enantioenriched DHPMs, the catalytic asymmetric Biginelli reaction has rarely been studied.[7,8] To date, only one asymmetric variant with a chiral ytterbium catalyst provided synthetically useful enantioselectivity.[8] There has been no report of organocatalytic asymmetric Biginelli dihydropyrimidine synthesis, which essentially avoids the metal contamination in the preparation of these medicinally relevant compounds.[9] Herein, we will report the first organocatalytic highly enantioselective Biginelli reaction.

Traditionally, Brønsted acids are primarily used for promoting the Biginelli reaction.[2,4] Recently, chiral Brønsted acids have appeared to be efficient organocatalysts for asymmetric additions of nucleophiles to imines.[10] Among them, chiral phosphoric acids have received increasing attention since their first application in the asymmetric catalysis[11]and have frequently been the catalyst of choice for transformations related to enantioselective activation of imines.[12] In light of these successes as well as the mechanism of the Biginelli reaction,[13] we envisioned that chiral phosphoric acids would effectively catalyze the asymmetric Biginelli reaction by forming chiral *N*-acyliminium phosphate ion pairs **5**, to which enantioselective addition of β-keto esters **3** should occur to generate optically active **4** via the enantioenriched intermediate **6** (Scheme 1).

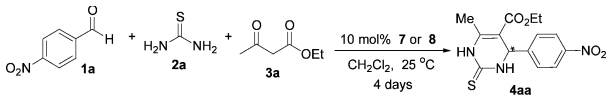
Validation of the hypothesis started by evaluating the ability of binol- and H_8-binol-based phosphoric acids **7** and **8** to catalyze the Biginelli reaction of 4-nitrobenzaldehyde (**1a**), thiourea (**2a**), and ethyl acetoacetate (**3a**). Indeed, the reaction proceeded in the presence of 10 mol % of chiral phosphoric acids to afford the desired optically active product **4aa**. As shown in Table 1, the 3,3′-

Scheme 1. Proposed Chiral Phosphoric Acid-Catalyzed Biginelli Reaction



substituents on the phosphoric acids considerably impacted the reaction behavior. In general, increasing the size of 3,3′-substituents on the catalyst resulted in decreased yields and enantioselectivities (entries 1−4 and 5−7), which is in contrast to the substituent effect of the other phosphoric acid-catalyzed reactions.[12] For instance, the catalyst **7c**, which is highly efficient in catalyzing the hydrophosphonylation of imines,[12b] afforded only 25% yield and 52% ee (entry 3). Trace amounts of the product were obtained with **7d**, which bears two 2-naphthyl substituents at the 3,3′-positions (entry 4). Surprisingly, the configuration of the product was inverted using the highly hindered Brønsted acid **7c** (entry 3). Of binol-derived phosphoric acids **7**, **7a** turned out to be the most enantioselective (80% ee), albeit affording only a moderate yield (entry 1). To our delight, the yield and enantioselectivity were both improved from 67 to 84% and 80 to 85% ee, respectively, when the H_8-binol-

Table 1. Screening Catalysts and Optimization of Reaction Conditions[a]



entry	catalyst	yield (%)[b]	ee (%)[c]
1	**7a**	67	80
2	**7b**	41	53
3	**7c**	25	−52
4	**7d**	<10	
5	**8a**	84	85
6	**8b**	45	70
7	**8c**	24	68
8	**8a**	75	82[d]
9	**8a**	94	85[e]
10	**8a**	93	82[f]

[a] The reaction was carried out on a 0.2 mmol scale, and the ratio of **1a**/**2a**/**3a** is 1/1.2/3. [b] Isolated yield based on the aldehyde. [c] Determined by HPLC. [d] Addition of 5 Å MS. [e] The reaction time is 6 days. [f] At 35 °C.

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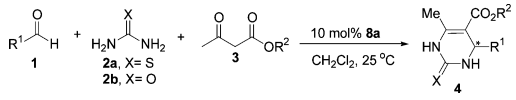
Table 2. Organocatalytic Enantioselective Biginelli Reaction with Phosphoric Acid **8a**[a]



entry	4	R^1	2	R^2	yield (%)[b]	ee (%)[c]
1	**4ba**	3-FC_6H_4	**2a**	Et	86	91
2	**4ca**	3-$NO_2C_6H_4$	**2a**	Et	80	88
3	**4da**	2-ClC_6H_4	**2a**	Et	77	91
4	**4ea**	3-ClC_6H_4	**2a**	Et	73	90
5	**4fa**	2-$NO_2C_6H_4$	**2a**	Et	52	90
6	**4ga**	3-BrC_6H_4	**2a**	Et	85	91
7	**4ha**	3,5-$Br_2C_6H_3$	**2a**	Et	66	96
8	**4ia**	3,5-$(CF_3)_2C_6H_3$	**2a**	Et	56	97
9	**4ja**	4-$MeO_2CC_6H_4$	**2a**	Et	67	90
10	**4ka**	1-$BrC_{10}H_6$	**2a**	Et	64	91
11	**4la**	*c*-C_6H_{11}	**2a**	Et	40	92
12	**4ma**	PhCH═CH	**2a**	Et	44	88
13	**4na**	3-$MeOC_6H_4$	**2a**	Et	83	90
14	**4gb**	3-BrC_6H_4	**2a**	Me	85	91
15	**4hb**	3,5-$Br_2C_6H_3$	**2a**	Me	51	96
16	**4gc**	3-BrC_6H_4	**2a**	i-Pr	65	92
17	**4bc**	3-FC_6H_4	**2a**	i-Pr	70	94
18	**4jd**	3-BrC_6H_4	**2a**	t-Bu	64	92
19	**4bd**	3-FC_6H_4	**2a**	t-Bu	65	94
20	**4oc**	2-FC_6H_4	**2a**	i-Pr	86	91
21	**4od**	2-FC_6H_4	**2a**	t-Bu	84	92
22	**4cb**	3-$NO_2C_6H_4$	**2b**	*i*-Pr	75	90[d]
23	**4hc**	3,5-$Br_2C_6H_3$	**2b**	Et	51	97[d]
24	**4pb**	3,5-$F_2C_6H_3$	**2b**	Me	84	93[d]

[a] The reaction was carried out on a 0.2 mmol scale, and the ratio of **1**/**2**/**3** is 1/1.2/3. [b] Isolated yield based on aldehyde. [c] Determined by HPLC. [d] The ratio of **1**/**2**/**3** is 1/1.2/5.

based phosphoric acid **8a** replaced **7a** as a catalyst (entries 1 and 5). A survey of solvents revealed that dichloromethane is a better solvent than the others examined (see Supporting Information). Importantly, the water generated from the condensation steps of forming *N*-acyliminium intermediate **5** and the final product **4aa** (Scheme 1) has little effect on the reaction since the addition of 5 Å molecular sieves did not enhance the yield (entry 8). Further improvement in the yield without sacrificing the stereochemistry could be achieved by prolonging the reaction time (entry 9). However, increasing reaction temperature slightly eroded the enantioselectivity, albeit with 93% yield (entry 10).

After we established the optimal conditions, we explored the generality of the phosphoric acid-catalyzed asymmetric Biginelli reaction (Table 2). The scope of the aldehyde component was first investigated by reaction with thiourea (**2a**) and ethyl acetoacetate (**3a**) (entries 1−13). A variety of aromatic aldehydes bearing various types of substituents underwent the reaction to afford high enantioselectivities ranging from 88 to 97% ee. The reaction conversion and enantiochemical outcome depend, to some degree, on the substituent on the aldehydes (entries 1−10). The reaction of *meta*-substituted benzaldehydes and *ortho*-chlorobenzaldehyde proceeded in high yields (entries 1−4 and 6). *meta*-Disubstituted benzaldehydes resulted in excellent enantioselectivities (96−97% ee), albeit with a slight decrease in the yields (entries 7 and 8). An aliphatic aldehyde was less reactive but afforded high enantioselectivity of 92% ee (entry 11). The electron-rich 3-anisaldehyde and cinnamaldehyde provided 90 and 88% ee, respectively (entries 12 and 13).

The scope of β-keto ester components in the organocatalytic asymmetric Biginelli reaction was examined next (Table 2, entries 14−21). Primary experimental results indicated that variation of the R_2 substituent of β-keto esters **3** could be tolerated, and generally high enantioselectivities (91−96% ee) were provided for the reactions related to these substrates (entries 14−21). Biginelli reactions of urea (**2b**) with various aldehydes and β-keto esters were carried out to give corresponding DHPMs with up to 97% ee (entries 22−24).

Individual enantiomers of monastrol show distinct pharmaceutical properties.[5b] The enantioenriched monastrol could be readily prepared in high optical purity (91% ee), commencing with the Biginelli reaction of *meta*-TBSO-benzaldehyde (**1q**) with thiourea (**2a**) and ethyl acetoacetate (**3a**) (See Supporting Information).

In summary, we have discovered the first organocatalytic asymmetric Biginelli reaction. The optimal chiral phosphoric acid, derived from H_8-binol, afforded the reaction in high yields with excellent enantioselectivities of up to 97% ee. A wide variety of substrates, including aldehydes and β-keto esters, could be tolerated. This reaction has an advantage of avoiding the contamination of transition metals in the manufacture of the medicinally relevant chiral 3,4-dihydropyrimidin-2-(1*H*)-ones.

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Supporting Information Available: Experimental details and characterization of new compounds and complete ref 5c. This material is available free of charge via the Internet at http://pubs.acs.org.

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