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Cooperative and Enantioselective $NbCl_5$/Primary Amine Catalyzed Biginelli Reaction

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A series of chiral organocatalysts and Lewis acids have been evaluated in the Lewis acid/organocatalysts-based cooperative catalytic Biginelli reaction, which resulted in the determination of a novel cooperative Lewis acid/primary amine catalyst system, $NbCl_5$/QN-NH_2. The synergistic effect of $NbCl_5$ and the quinine-derived primary amine is pronounced and gave dihydropyrimidiones (DHPMs) in moderate to good enantioselectivities (up to 84 % *ee*) and good to excellent yields (up to 99 % yield) under mild conditions.

Introduction

The Biginelli reaction, a well-known three-component one-pot condensation reaction of urea or thiourea, aldehyde, and β-oxo ester, was originally described by Pietro Biginelli over a century ago.[1] This reaction played an important role in organic and medicinal chemistry, because it offers a straightforward approach to multifunctional dihydropyrimidiones (DHPMs) and related heterocyclic compounds.[2] It is well recognized that the DHPMs and their derivatives are pharmaceutically important as calcium channel blockers, α_1-1-a-antagonists, antihypertensive agents, inhibitors of the fatty acid transporter, and mitotic kinesin inhibition.[3] These compounds have also been found to possess antiviral, antitumor, and antibacterial properties.[4] Furthermore, the biological activity of some isolated marine natural products and alkaloids has been attributed to the dihydropyrimidinone moiety.[5] Thus, the development of new methods for the Biginelli reaction, Biginelli-like reactions, or the synthesis of DHPMs and its derivatives has received renewed interest. In the last decades, many improved procedures with new catalysts have been reported.[6] However, most of the reported methods only resulted in racemic DHPMs, and the asymmetric catalytic Biginelli reactions have been a long-standing challenge. In contrast, compounds containing the DHPM moiety have an inherent stereogenic center, which is very important, and the influence of the absolute configuration of the chiral center on the biological activity has been extensively investigated. In most cases only one enantiomer was found to be biologically active.[7] Therefore, an efficient method for the preparation of optically pure DHPMs is highly desirable.

Currently, besides chemical resolution and auxiliary-assisted asymmetric synthesis,[8] several revolutionary examples of the enantioselective synthesis of these DHPMs through asymmetric Biginelli or Mannich reaction have been reported.[9] The breakthrough in the catalytic asymmetric Biginelli reaction was realized by Zhu and coworkers in 2006 with a chiral ytterbium complex with a hexadenate ligand.[10] Another important improvement was developed by Gong et al. who established an organocatalytic, chiral BINOL-derived phosphoric acid catalyzed Biginelli reaction.[11] Very recently, bifunctional and combined organocatalytic systems consisting of chiral secondary/primary amines and Brønsted acids have been reported to promote the Biginelli reaction with moderate to good enantioselectivities.[12] Despite these elegant examples, it is still desirable to develop novel strategies for this important transformation. As a part of our continued interest in the studies of combined Lewis acids and organocatalysts for organic transformations,[13] we assumed that the combination of a primary amine and Lewis acid could promote the asymmetric Biginelli reaction through a dual-activation pathway.[14] As shown in Scheme 1, the chiral enamine intermediate **4**, activated by a metal-based Lewis acid, would react with *N*-acylimine **6** in situ, generated from aldehyde and urea, to provide enantioenriched DHPM product **8**.

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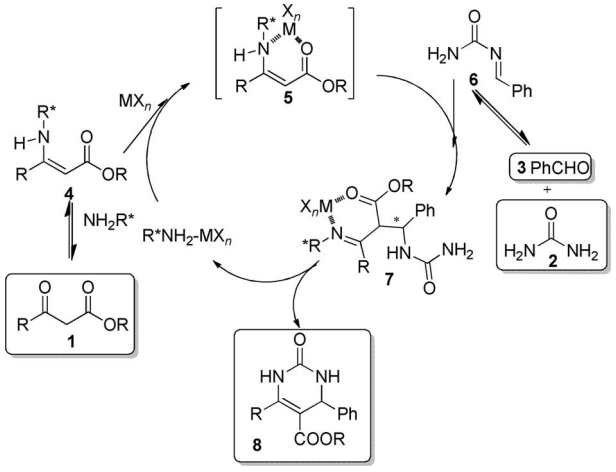


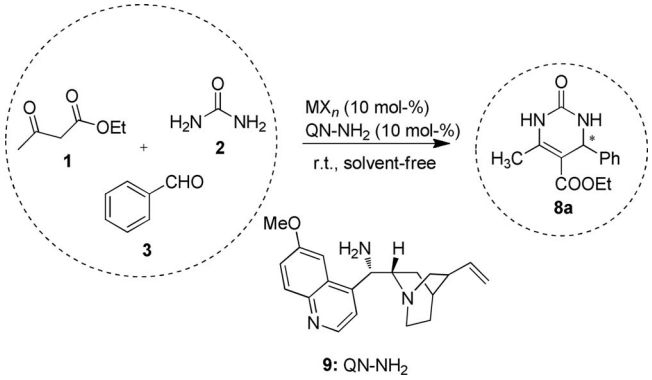
Scheme 1. Possible catalytic cycle of the dual-activation mechanism in the combined metal salt based Lewis acid and primary amine catalyzed Biginelli reaction.

Results and Discussion

Chiral primary amines and derivatives have proven to be extraordinarily useful organocatalysts in asymmetric synthesis.[15] Being interested in the effort to enhance the catalytic activities of the simultaneous use of Lewis acid and chiral primary amines, we started to investigate the development of a novel combined catalyst system for the Biginelli reaction. Our study began with a preliminary screening of several different commercially available metal salts with strong Lewis acid activity. By using the Biginelli reaction of benzaldehyde, ethyl acetoacetate, and urea, as a model reaction with a quinine-derived primary amine (QN-NH_2) and metal salts as co-catalyst, the asymmetric transformation was performed under solvent-free conditions at room temperature. As shown in Table 1, significant variations in the stereoselectivity (2–41% *ee*) were observed depending on the nature of the metal salts. The salts of Fe^{III}, Nb^{III}, Sb^{III} gave promising enantioselectivities (>10% *ee*). When the salts of In^{III}, Li^{I}, Mg^{II}, Zn^{II}, Ce^{III}, Ni^{II}, Ag^{I} were used, no product or only a trace amount of the Biginelli adduct was detected (<20% yield). It is worthy to note that QN-NH_2 only resulted in poor conversion under solvent-free conditions. Therefore, the $NbCl_5$ was found to be the best Lewis acid in the primary amine based cooperative catalyst system.

To improve the enantioselectivity based on this strategy, dozens of known cinchona alkaloids and derivatives, and some chiral primary amines derived from (*R*,*R*)-1,2-diphenylethylenediamine (DPEN), were screened as cooperative organocatalysts in the $NbCl_5$-catalyzed Biginelli reaction (see Supporting Information); however, no organocatalyst evaluated in this work could replace the cinchona alkaloid derived primary amine. These results show that both the quinine-derived primary amine plays a privileged role in the enantiomeric induction. In addition, solvent effects were evaluated after finding the cooperative Nb/primary amine catalyst system (Table 2, Entries 1–8). In terms of both yield and enantioselectivity, 1,4-dioxane as the solvent gave the

Table 1. Screening metal salt based Lewis acids for the asymmetric Biginelli reaction.



9: QN-NH_2

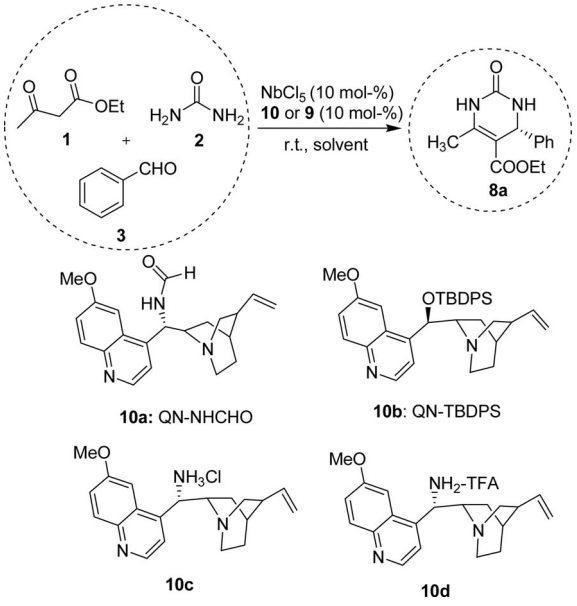
Entry[a]	MX_n	% *ee*[b]	Entry	MX_n	% *ee*
1	$InCl_3$	–[c]	7	$NbCl_5$	41[d]
2	$FeCl_3$	19[d]	8	$SbCl_3$	25[d]
3	$LiClO_4$	–[c]	9	$ZnCl_2$	–[c]
4	$Mg(ClO_4)_2$	–[c]	10	$Ni(OAc)_2$	–[c]
5	$Bi(OTf)_3$	9[d]	11	$CeCl_3{\cdot}7H_2O$	–[c]
6	$Cu(OTf)_2$	2[d]	12	AgF	–[c]

[a] The reaction was carried out on a 1 mmol scale at room temperature for 72 h, and the ratio of **1/2/3** was 5:1.2:1. [b] The enantiomer excess was determined by HPLC (chiral OD-H). [c] The yield was poor (<20%), and therefore the enantiomer excess was not determined. [d] The conversion was complete, and the yield was >95%.

best result (Table 2, Entry 8). Encouragingly, we found that the combination of QN-NH_2 and $NbCl_5$ could promote this reaction effectively to provide product **8a** in 76% yield and 69% *ee* at room temperature. The absolute configuration of the major enantiomer was determined to be (*R*) by comparing the reported data.[11,12] Furthermore, we screened some representative structurally modified quinine derivatives in this reaction under the optimal conditions. Surprisingly, with the same backbone, the primary amine moiety was proven to be a crucial group in the activation of oxo ester (Table 2, Entries 9, 10). In the presence of a catalytic amount of HCl and TFA, the yield or enantioselectivity is poor (Table 2, Entries 11, 12). Therefore, on the basis of the results obtained from the reactions with $NbCl_5$ and organocatalysts screened, QN-NH_2 was evidently the best choice for the present reaction system.

With the optimized conditions, the scope of this reaction was then investigated by using the cooperative catalyst system ($NbCl_5$/QN-NH_2). The corresponding DHPMs were obtained in good to excellent yields (up to 99%) and moderate to good enantioselectivities (up to 84% *ee*) at room temperature. As shown in Scheme 2, both the electronic and steric effects of the aromatic ring have a significant influence on the enantioselectivity and conversion. In most cases, aromatic aldehydes with electron-donating groups in the *para* position afforded moderate enantioselectivities, and halogen-substituted aromatic aldehydes resulted in better enantioselectivities. For aromatic aldehydes bearing electron-donating groups in the *meta* position, good enantioselectivities (84% *ee*) were achieved. In addition, the cata-

Table 2. Screening of organocatalysts and solvents for the $NbCl_5$-catalyzed asymmetric Biginelli reaction.[a]

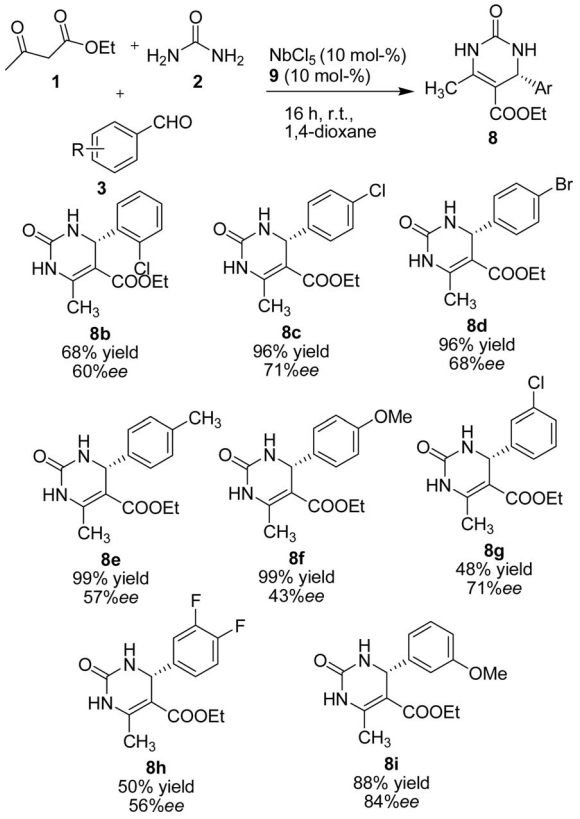


Entry	Catalyst	Solvent	t [h]	Yield [%][b]	% *ee*[c]
1	**9**	EtOH	48	43	40
2	**9**	THF	48	59	64
3	**9**	toluene	48	56	12
4	**9**	DCM	48	42	41
5	**9**	CH_3CN	48	84	41
6	**9**	CH_3NO_2	48	73	38
7	**9**	acetone	48	74	54
8	**9**	1,4-dioxane	48	76	69
9	**10a**	1,4-dioxane	48	<10	35
10	**10b**	1,4-dioxane	48	<10	3
11	**10c**	1,4-dioxane	48	65	36
12	**10d**	1,4-dioxane	48	13	4

[a] The reaction was carried out on a 1 mmol scale in the presence of 10 mol-% of $NbCl_5$ and 10 mol-% of organocatalyst **10** or **9** at room temperature, and the ratio of **1/2/3** was 5:1.2:1. [b] Isolated yields. [c] The enantiomer excess was determined by HPLC (chiral OD-H).

lytic system required a markedly shorter reaction time (16 h) compared with previous organocatalytic systems (36–72 h).[12] Notably, although the enantioselectivities are not very satisfying, the catalytic system described in this work was proven to be a novel cooperative strategy, in which the application of metal complexes or Lewis acids in tuning the reactivity of reactions promoted by organic molecules would be a simple, efficient, privileged, and highly enantioselective biomimetic catalytic process in asymmetric catalysis.

In the meantime, our efforts to improve the enantiomeric excess of DHPMs commenced with crystallization. Interestingly, when **8a** (65% *ee*) was used as model substrate, ethanol (EtOH) was found to be an excellent solvent in the crystallization, and an excellent enantiomeric excess (>99% *ee*) was obtained easily with one simple operation. Very importantly, under the same reaction conditions, we also found that an excellent enantiomeric excess (99% *ee*) could



Scheme 2. $NbCl_5$/QN-NH_2-catalyzed Biginelli reaction.

be obtained directly without column chromatography as the workup was modified: Different from the general procedure, after the reaction was completed, most of the solvent was removed under reduced pressure. Then the crude product was precipitated with small amounts of ethanol and water, and then the product was filtered by suction and washed twice with cold ethanol to yield a pure product with high enantiomeric excess. These results show that one should be very careful in evaluating the catalytic activity and stereoselectivity of a catalyst in the Biginelli reaction. For the Biginelly reaction, high enantioselectivities were observed for the DHPMs obtained directly by simple precipitation with the solvent or water; thus, it was revealed that column chromatography is necessary to determine the enantiomeric excess values of the DHPMs accurately.

Conclusions

We have developed a novel strategy for the asymmetric Biginelli reaction by using a combined cooperative catalyst system of Lewis acid and primary amine. The screening and optimization of catalyst structures and metal-based Lewis acids, including transition metal salts and organocatalysts, resulted in the determination of a novel and effective cooperative catalyst system, $NbCl_5$/QN-NH_2, which provided the corresponding 3,4-dihydropyrimidine-2(1*H*)-one (DHPM) derivatives in good to excellent yields and

enantioselectivities under mild reaction conditions. It is an ideal cooperative catalyst system in which $NbCl_5$ is responsible for the reactivity, and the chiral primary amine, QN-NH_2, introduces the stereoselectivity to this reaction. These studies allow further adjustments to both organocatalysts and Lewis acids for further design and optimization for the enantioselective Biginelli reaction and expand the application of this novel cooperative catalyst system in asymmetric catalysis.

Experimental Section

General Remarks: All reagents and solvents were used directly without purification. Flash column chromatography was performed on silica (200–300 mesh). ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively with a Bruker Avance 400 MHz NMR spectromer, and were referenced to the internal solvent signals. Thin layer chromatography was performed by using silica gel F254 TLC plates and visualized with ultraviolet light. HPLC was carried out with a Waters 2695 Millennium system equipped with a photodiode array detector. EI and CI mass spectra were performed with a Trace DSQ GC/MS spectrometer. Data are reported in the form of *m*/*z* values. The organocatalysts were commercially available and used directly. The Biginelli reaction products were known and confirmed by GC–MS and usual spectral methods (^1H, ^{13}C NMR). The ESI-MS analysis of the samples was carried out with an LCQ advantage mass spectrometer (ThermoFisher Company, USA), equipped with an ESI ion source in the positive ionization mode, with data acquisition using the Xcalibur software (version 1.4). Organocatalysts were synthesized according to reported procedures.[16]

General Procedure for the Biginelli Reaction: A catalytic amount of QN-NH_2 (10 mol-%) and $NbCl_5$ (10 mol-%) were added to a vial containing aldehyde (1 mmol), urea (1.2 mmol), and ethyl acetoacetate (5 mmol) in 1,4-dioxane (2 mL). After vigorous stirring at room temperature for the times shown in the tables or schemes, the reaction mixture was poured into an extraction funnel containing brine, diluted with distilled water, and EtOAc. The aqueous phase was extracted with EtOAc. The combined organic phases were dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to furnish the desired known DHPMs, which were confirmed by GC–MS and NMR analysis; the *ee*s of the DHPMs were determined by chiral-phase HPLC analysis using a chiral column and the indicated eluent systems (see Supporting Information).

Supporting Information (see footnote on the first page of this article): General remarks, spectral data and HPLC diagrams for the Biginelli adducts.

Acknowledgments

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