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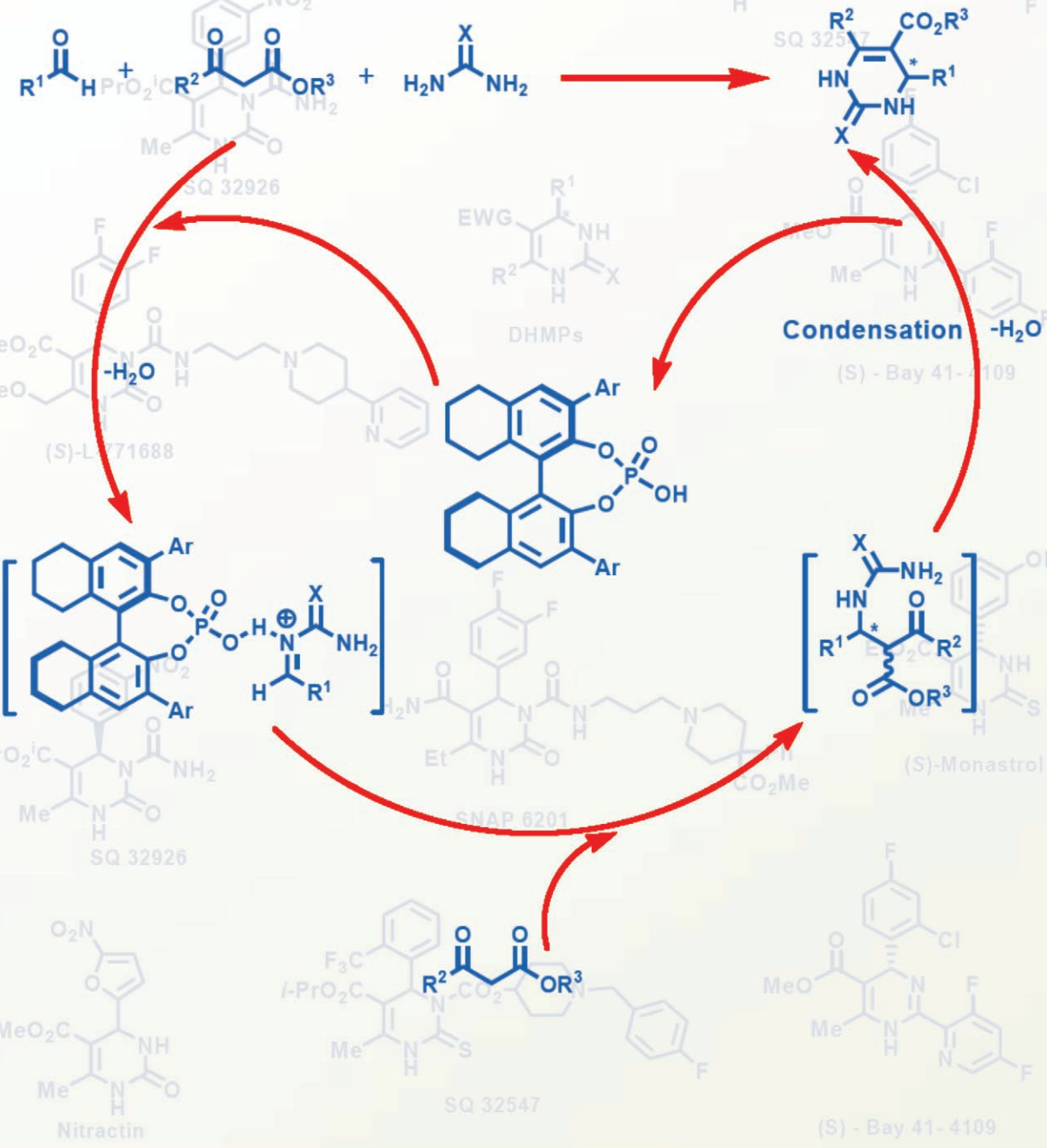
Asymmetric Organocatalytic Biginelli Reactions



Asymmetric Organocatalytic Biginelli Reactions: A New Approach To Quickly Access Optically Active 3,4-Dihydropyrimidin-2-(1*H*)-ones

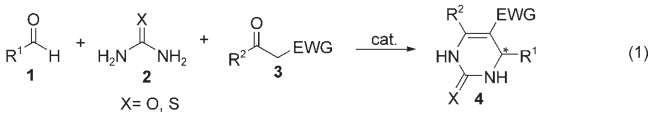
Liu-Zhu Gong,*[a, b] Xiao-Hua Chen,[b] and Xiao-Ying Xu[b]

Abstract: The Biginelli reaction, known for over 100 years, is an important multicomponent reaction for accessing dihydropyrimidinones (DHPMs). The individual enantiomers of DHPMs exhibit different or even opposite pharmaceutical activities, which require synthetic methods to easily access the optically pure DHPMs. In recent decades, many efforts have focused on developing procedures for the preparation of optically active Biginelli products. In this article, we will summarize the developments in the synthetic methods to access optically active DHPMs with an emphasis on the recent advances in the asymmetric catalytic Biginelli reactions, along with concepts to design the organocatalytic asymmetric variants.

Keywords: asymmetric catalysis · Biginelli reaction · multicomponent reactions · organocatalysis

Introduction

The Biginelli reaction [Eq. (1)], a three-component condensation reaction between an aldehyde (**1**), a urea or thiourea (**2**), and an easily enolizable carbonyl compound (**3**), was originally described by Italian chemist Pietro Biginelli in 1893.[1] This reaction offers a straightforward approach to multifunctionalized 3,4-dihydropyrimidin-2-(1*H*)-ones (Figure 1, DHPMs, **4**) and related heterocyclic compounds.[2]



(1)

The medicinal importance of DHPM compounds has long been recognized, as illustrated by the antiviral activity of Nitractin (**5**) against the trachoma group of viruses, first described in the 1960s.[3] The DHPMs and their derivatives have shown a wide scope of important pharmacological properties, including calcium channel modulation, α_{1a}-adrenergic receptor antagonism, and mitotic kinesin inhibition.[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. The individual enantiomers exhibit different or even opposite pharmaceutical activities.[4] For example, the *R* enantiomer of SQ 32926 (**6**), a calcium channel blocker, exhibits >400-fold more potent antihypertensive activity in vitro than the other enantiomer.[5] (*S*)-Monastrol (**7**) is 15-fold more potent in the inhib-

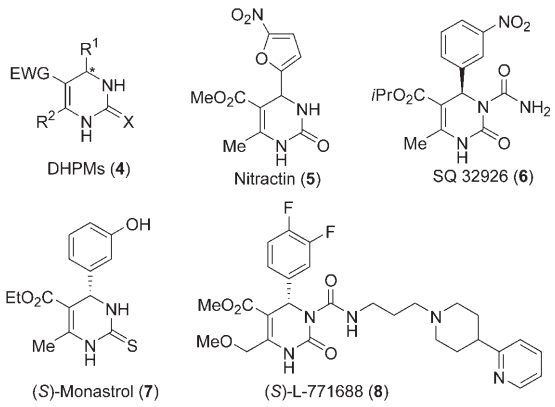


Figure 1. Medicinally relevant optically pure dihydropyrimidinones.

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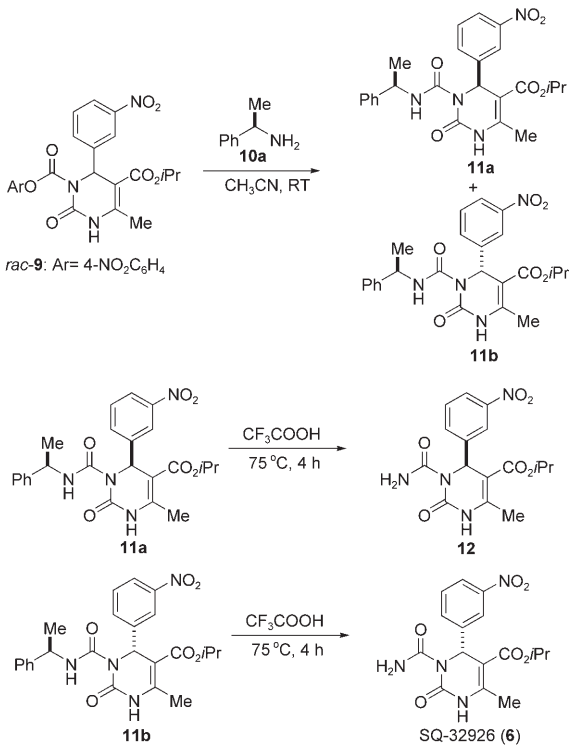
ition of Eg5 ATPase than (*R*)-monastrol.[6] (*S*)-L-771688 (**8**) is a more potent and selective α_{1a} receptor antagonist for the treatment of benign prostatic hyperplasia (BPH) than the *R* enantiomer.[7]

Therefore, an efficient method for the preparation of optically pure DHPMs is highly desirable. Currently, the preparation of optically pure DHPMs in the pharmaceutical research laboratory mainly relies on resolution and chiral auxiliary-assisted asymmetric synthesis. In contrast, the asymmetric catalytic Biginelli reactions yield optically active DHPMs in a straightforward manner with greater synthetic efficiency. On the other hand, advances in the catalytic asymmetric Biginelli reaction have proceeded slowly, with no significant refinements occurring since the first description over a century ago. Recent research interests in the asymmetric Biginelli reaction have focused on finding new catalysts for the production of enantioenriched DHPMs, with particular emphasis of the rare earth metal-based chiral complexes.[8,9] The most significant achievements[9] have dealt with the enantioselective and catalytic Biginelli reactions that point toward the design of new chiral catalysts for asymmetric Biginelli reactions or that disclose new procedures for the preparation of enantioenriched DHPMs. In this article, we will summarize some representative methods to approach optically active DHPMs which have a single stereogenic center at C4 and have been applied to the synthesis of pharmaceutical lead compounds. In particular, we will emphasize on the concept of employing organic molecules to promote the enantioselective Biginelli reaction. We will exclude the asymmetric Biginelli reactions that start with optically pure reagents to afford the DHPMs with multiple stereogenic centers, as these procedures have been recently featured in excellent review articles.[2]

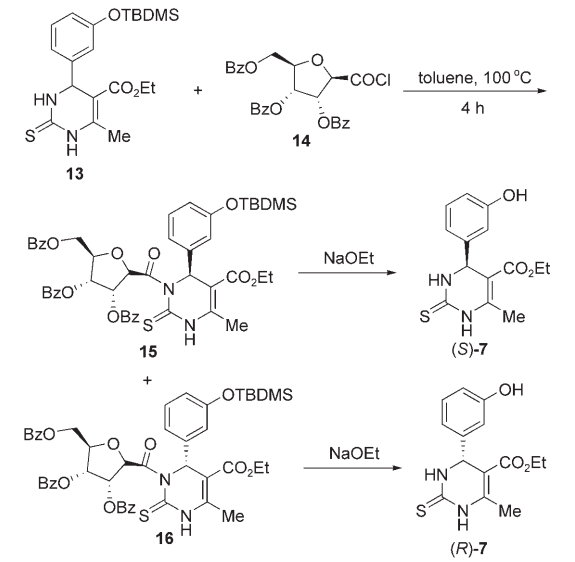
Chiral Resolution of Racemic DHPMs

Chemical resolution: Chemical resolution by conversion of racemic compounds into their diastereomers is the most reliable approach to optically pure enantiomers, although this methodology lacks synthetic efficiency. Optically pure SQ-32926 (**6**) was initially prepared by chemical resolution following a procedure shown in Scheme 1.

Racemic compound **9** reacted with optically pure (*R*)-(α)-benzylmethylamine (**10a**) to generate a pair of diastereomers **11a** and **11b**, which could be separated by recrystallization. The treatment of **11a** and **11b** with trifluoroacetic acid at 75 °C, respectively, afforded optically pure **12** and SQ-32926 (**6**).[10]

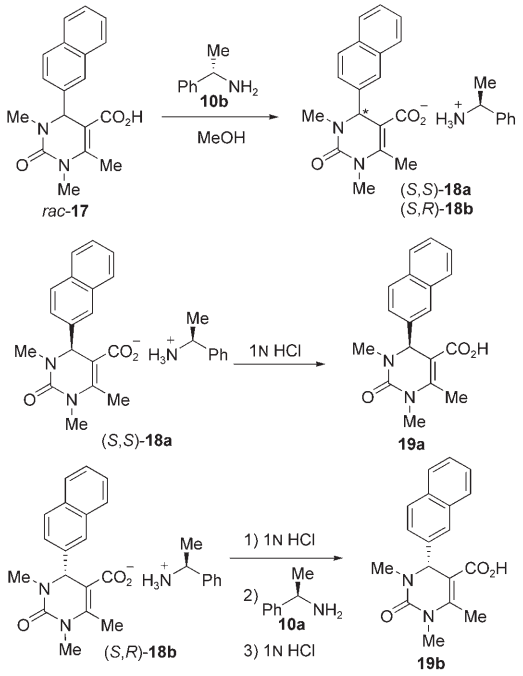


Scheme 1. Preparation of SQ-32926 through chemical resolution.



Scheme 2. Chemical resolution of racemic monastrol.

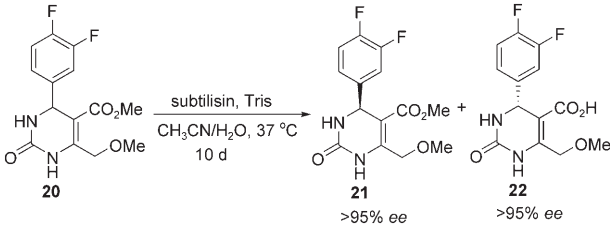
An alternative chemical resolution of monastrol racemate was described by Dondoni (Scheme 2).[11] This method consisted of the conversion of racemic monastrol into the diastereomeric *N*-glycosyl amides **15** and **16** by the reaction of β-linked C-glycosyl carbonyl chloride (**14**) with O-TBDMS protected monastrol (**13**). The separation of the two diastereomers **15** and **16** by flash chromatography followed by removal of the chiral auxiliary in the presence of sodium ethoxide gave the optically pure enantiomers. Resolution of racemic 5-dihydropyrimidinonecarboxylic acids by the treatment with optically pure amine is an alternative chemical resolution to access optically pure DHPMs. The racemic 4-(2-naphthyl)-5-dihydropyrimidinonecarboxylic acid (**17**) was treated with (*S*)-(α)-benzylmethylamine (**10b**) to give, after a single recrystallization, the diastereomerically pure (*S*,*S*)-**18a** (Scheme 3). The diastereoenriched **18b** obtained from



Scheme 3. Resolution of the racemic 4-(2-naphthyl)-5-dihydro-pyrimidinonecarboxylic acid by forming diastereomeric salts.

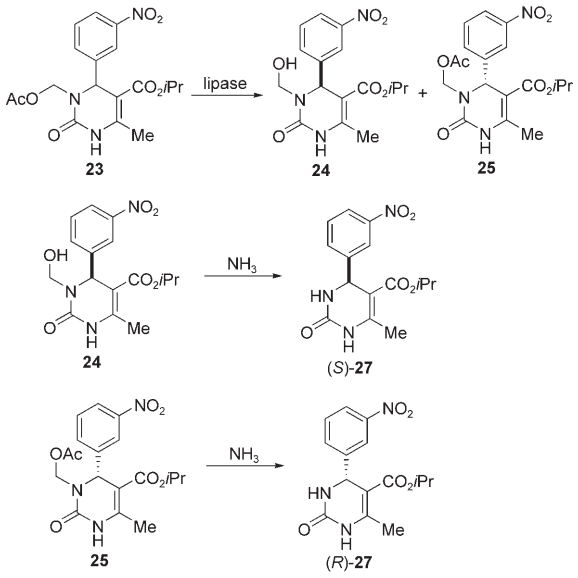
the mother liquor was treated with 1N HCl to release the enantioenriched acid **19b**, which was treated with (*R*)-(α)-benzylmethylamine (**10a**) to give a diastereomerically pure salt (*R*,*R*)-**18c**. The diastereomeric salts **18a** and **18c** were subjected to 1N HCl, respectively, yielding the optically pure **19a** and **19b**.[12]

Enzymatic kinetic resolution: The enzymatic hydrolysis of the ester moiety of dihydropyrimidinones was first introduced by Ikemoto to resolve the racemic DHPMs.[13] The protocol was extended to the resolution of **20**, giving corresponding acid **22** with >95% *ee* (Scheme 4). The remaining ester **21** with >95% *ee* is a key synthetic intermediate for the preparation of optically pure (*S*)-L771688 (**8**).[14]



Scheme 4. Enzymatic kinetic resolution of **20**.

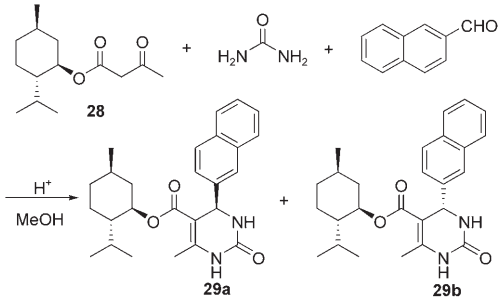
Optically pure (*R*)-**27**, a key precursor for the preparation of SQ-32926 (**6**), can be synthesized from the enzymatic resolution of racemic-**23** (Scheme 5). The racemic-**23** was subjected to kinetic hydrolysis in the presence of lipase, giving enantiomerically pure compound **24** and leaving unreacted **25**. The degradation of compounds **24** and **25** with aqueous ammonia gave (*S*)- and (*R*)-**27**, respectively.[15]



Scheme 5. Enzymatic approach to the precursor of SQ-32926 (**6**).

Attempted Synthesis of Optically Active DHPMs by Asymmetric Induction

Asymmetric induction is another well-recognized synthetic method to approach enantiomerically pure organic molecules. While asymmetric Biginelli reactions involving chiral aldehydes have been well established,[2a] similar strategies applicable to the synthesis of enantioenriched 4-aryl DHPMs are less well recognized. The Biginelli reaction involving a chiral acetoacetate, derived from (−)-menthol, was attempted to prepare optically active 4-(2-naphthyl)-dihydropyridine. The reaction led to a mixture of diastereomers **29a** and **29b** in 1:1 dr (Scheme 6). Unfortunately, **29a**

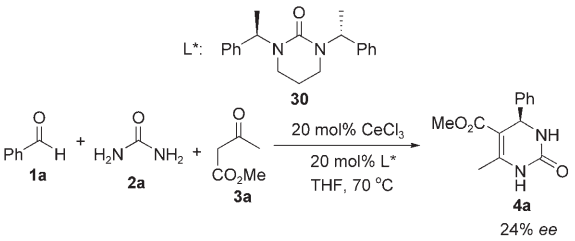


Scheme 6. Synthesis of optically active DHPMs via asymmetric induction.

and **29b** could not be separated by either recrystallization or chromatographic techniques. This effort by Kappe and colleagues is the only reported attempt to synthesize optically active 4-aryl dihydropyridinones by asymmetric induction.[12]

Asymmetric Catalytic Biginelli Reactions with Chiral Metal Complexes

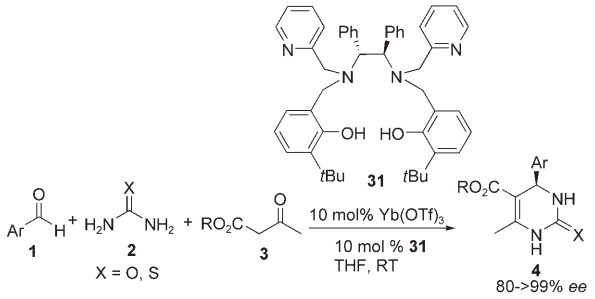
Compared with resolution and chiral auxiliary-assisted asymmetric synthesis, the catalytic asymmetric Biginelli reaction is definitely the most straightforward approach to access optically active DHPMs. Efforts to develop the asymmetric catalytic Biginelli reaction started in 2003. Juaristi and Muñoz-Muñiz reported the use of a chiral amide **30**, in combination with $CeCl_3$ (Scheme 7), to catalyze the Biginelli



Scheme 7. Asymmetric Biginelli reaction catalyzed by a complex of $CeCl_3$ and chiral amide **30**.

reaction of benzaldehyde (**1a**), urea (**2a**), and methyl acetoacetate (**3a**) with 24% *ee*.[8] Modification of the reaction conditions improved slightly the enantioselectivity up to 40% *ee*, but the yield was sacrificed dramatically.[8]

Zhu and co-workers recently described a breakthrough in the asymmetric catalytic Biginelli reactions.[9] Catalysis by 10 mol% of $Yb(OTf)_3$ (Scheme 8) and chiral ligand **31** pro-

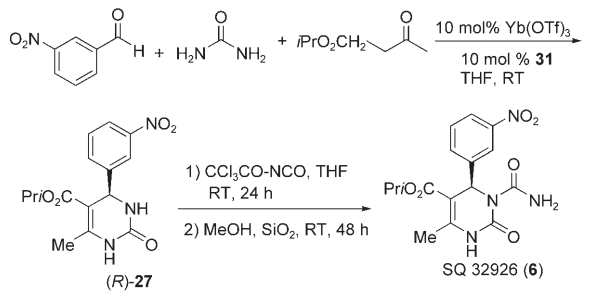


Scheme 8. Asymmetric catalytic Biginelli reaction by a complex of $Yb(OTf)_3$ and chiral ligand **31**.

ceeded efficiently, providing DHPMs **4** in high yields with excellent enantioselectivities ranging from 80 to >99% *ee* (Scheme 8). Importantly, the optically pure pharmaceutical compound SQ-32926 (**6**) could be obtained in an overall 58% yield starting with the Biginelli reaction of *meta*-nitrobenzaldehyde, urea, and isopropyl acetoacetate (Scheme 9).

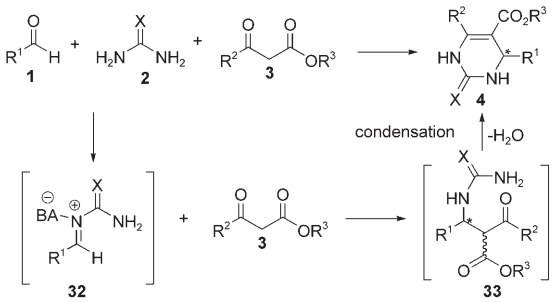
Asymmetric Organocatalytic Biginelli Reaction

Mechanistic studies revealed that the Biginelli reaction is initiated by the condensation of an aldehyde with urea or thi-



Scheme 9. Synthesis of SQ 32926 starting with asymmetric catalytic Biginelli reaction.

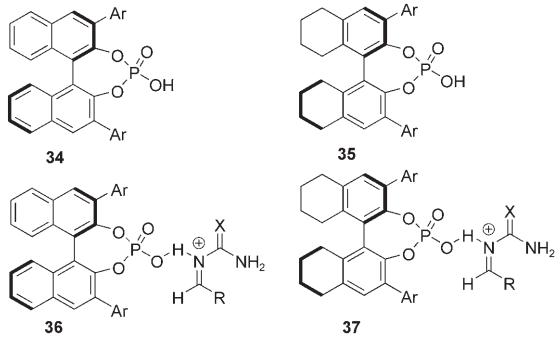
ourea in the presence of either a Brønsted (Scheme 10) or a Lewis acid, generating an activated *N*-acyliminium **32**, which is subsequently attacked by acetoacetate via the Mannich reaction to generate the reactive intermediate **33**. Under acidic conditions, intermediate **33** cyclizes to afford the DHPMs, with the concomitant release of a molecule of water.[16]



Scheme 10. Mechanism of Brønsted acid-catalyzed Biginelli reaction.

There are two possible pathways to realize the catalytic asymmetric Biginelli reaction: 1) Discovery of new chiral Lewis acids, which should efficiently activate imine functionalities; these Lewis acids must be water-compatible because two molecules of water are generated during the reaction; 2) development of a chiral Brønsted acid-catalyzed procedure. As most Lewis acids are sensitive to water, very few chiral Lewis acids can catalyze asymmetric Biginelli reactions[8,9] although many chiral Lewis acids can efficiently catalyze other asymmetric reactions. Since the first Biginelli reaction was carried out by heating a solution of benzaldehyde, urea, and ethyl acetoacetate in ethanol with catalytic amounts of HCl at reflux temperature,[1] Brønsted acids such as trifluoroacetic acid[17] and *p*-toluenesulfonic acid[18] have been often exploited to catalyze the Biginelli reaction. The Brønsted acid-catalyzed Biginelli reaction proceeded through a mechanism shown in Scheme 10. The Mannich reaction of the iminium with acetoacetate generates stereogenic centers. Actually, the chiral Brønsted acid catalyzed asymmetric Biginelli reaction was attempted earlier. In 1992, Kappe and co-workers tried to use (*R*,*R*)-tartaric acid as a chiral acidic catalyst in an asymmetric Biginelli reac-

tion, but with no enantioselectivity.[12] In recent years, important advances have been made in chiral Brønsted acid-catalyzed asymmetric reactions.[19] In particular, chiral phosphoric acids have frequently used as the catalysts of choice for transformations related to enantioselective activation of imines.[20] These results provided an entry into the organic catalytic asymmetric Biginelli reaction. Thus, we envisioned that chiral phosphoric acids **34** and **35** (Scheme 11) would



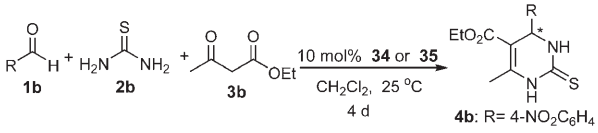
Scheme 11. Chiral phosphoric acids and the possible iminium intermediates.

catalyze the asymmetric Biginelli reaction by forming chiral *N*-acyliminium–phosphate ion pairs **36** and **37**, which should undergo enantioselective addition of β-keto esters **3** to generate optically active **4**.[21]

Asymmetric Biginelli reaction catalyzed by chiral phosphoric acids 34 and 35: The Biginelli reaction of 4-nitrobenzaldehyde (**1b**), thiourea (**2b**), and ethyl acetoacetate (**3b**) proceeded in the presence of 10 mol% chiral phosphoric acids to afford the desired optically active product **4b**. As shown in Table 1, the 3,3′-substituents on the phosphoric acids had considerable impact on the reaction behavior. Of the phosphoric acids **34** and **35**, **35a** gave the highest enantioselectivity of 85% *ee* (entry 9). The water, generated from the condensation steps of forming *N*-acyliminium intermediate **37** and the final product **4b**, has little effect on the reaction since the addition of 5 Å MS did not enhance the yield (entry 8). The yield could be improved by prolonging the reaction time without sacrificing the stereochemistry (entry 9). However, increasing the reaction temperature slightly eroded the enantioselectivity with 93% yield.

The phosphoric acid-catalyzed asymmetric Biginelli reaction tolerates a wide scope of the aldehyde components, which reacted with thiourea (**2b**) and ethyl acetoacetate, giving the Biginelli products **4c–o** with high enantioselectivities ranging from 88% to 97% *ee* (entries 1–13). The reaction conversion and enantiochemical outcome depend, to some degree, on the substituent on the aldehydes. Importantly, an aliphatic aldehyde was reacted with thiourea (**2b**) and ethyl acetoacetate, affording high enantioselectivity of 92% *ee* (entry 11). The electron-rich 3-anisaldehyde and cinnamaldehyde provided 90 and 88% *ee*, respectively (entries 13 and 12). The investigation of the scope of acetoacetate revealed that variation of the R^2 substituent of β-keto esters **3** could be tolerated and generally high enantioselectivities (91–96% *ee*, entries 14–17) were achieved for the reactions related to these substrates. Biginelli reactions of urea (**2a**) with various aldehydes and β-keto esters were carried out to give corresponding DHPMs with up to 97% *ee* (entries 18 and 19).

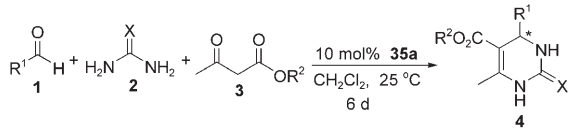
Table 1. Screening catalysts and optimization of reaction conditions.[a]



Entry	Catalyst	Ar	Yield [%][b]	*ee* [%][c]
1	**34a**	Ph	67	80
2	**34b**	4-FC_6H_4	41	53
3	**34c**	3,5-$(CF_3)_2C_6H_3$	25	52[d]
4	**34d**	2-naphthyl	<10%	ND
5	**35a**	Ph	84	85
6	**35b**	4-FC_6H_4	45	70
7	**35c**	4-ClC_6H_4	24	68
8	**35a**	Ph	75	82[e]
9	**35a**	Ph	94	85[f]
10	**35a**	Ph	93	82[g]

[a] The reaction was carried out on a 0.2 mmol scale, the ratio of **1b**/**2b**/**3b** 1:1.2:3. [b] Isolated yield based on the aldehyde. [c] Determined by HPLC. [d] An enantiomer opposite to that observed with another catalysts. [e] Addition of 5 Å MS. [f] Reaction time: 6 d. [g] At 35 °C.

Table 2. Biginelli reactions catalyzed by 10 mol% of **35a**.[a]



Entry	Product	R^1	X	R^2	Yield [%][b]	*ee* [%][c]
1	**4c**	3-FC_6H_4	S	Et	86	91
2	**4d**	3-$NO_2C_6H_4$	S	Et	80	88
3	**4e**	2-ClC_6H_4	S	Et	77	91
4	**4f**	3-ClC_6H_4	S	Et	73	90
5	**4g**	2-$NO_2C_6H_4$	S	Et	52	90
6	**4h**	3-BrC_6H_4	S	Et	85	91
7	**4i**	3,5-$Br_2C_6H_3$	S	Et	66	96
8	**4j**	3,5-$(CF_3)_2C_6H_3$	S	Et	56	97
9	**4k**	4-$MeO_2CC_6H_3$	S	Et	67	90
10	**4L**	1-$BrC_{10}H_6$	S	Et	64	91
11	**4m**	*c*-C_6H_{11}	S	Et	40	92
12	**4n**	PhCH=CH	S	Et	44	88
13	**4o**	3-$MeOC_6H_4$	S	Et	83	90
14	**4p**	3-BrC_6H_4	S	Me	85	91
15	**4q**	3,5-$Br_2C_6H_3$	S	Me	51	96
16	**4r**	3-BrC_6H_4	S	*i*Pr	65	92
17	**4s**	3-BrC_6H_4	S	*t*Bu	64	92
18	**4t**	3-$NO_2C_6H_4$	O	*i*Pr	75	90[d]
19	**4u**	3,5-$Br_2C_6H_3$	O	Et	51	97[d]

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

Conclusion

With the finding that individual enantiomers of dihydropyrimidines (DHPMs) exhibited different pharmaceutical properties, the asymmetric synthetic approaches to access optically pure DHPMs have been a target for organic and medicinal chemists. As a result, the chemical and enzymatic resolutions of medicinally relevant DHPMs into optically pure enantiomers have emerged and play an important role in drug discovery. The asymmetric catalytic Biginelli reaction with chiral Lewis acids was achieved and led to the design of new chiral ligands. Our concept of using chiral Brønsted acids to catalyze asymmetric Biginelli reaction opens a window for the development of new procedures to synthesize optically active DHPMs. Despite these recent successes in catalytic asymmetric Biginelli reactions, the design of new efficient chiral catalysts still remains an important challenge.

Acknowledgements

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