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# Highly Enantioselective Organocatalytic Biginelli and Biginelli-Like Condensations: Reversal of the Stereochemistry by Tuning the 3,3′-Disubstituents of Phosphoric Acids

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***Abstract:*** Organocatalytic enantioselective Biginelli and Biginelli-like reactions by chiral phosphoric acids derived from 3,3′-disubstituted binaphthols have been investigated. The size of 3,3′-substituents of the catalysts is able to control the stereochemistry of the Biginelli reaction. By tuning the 3,3′-disubstituents of the phosphoric acids, the stereochemistry of the Biginelli reaction can be reversed. This organocatalytic Biginelli reaction by Brønsted acids **12b** and **13** is applicable to a wide range of aldehydes and various $\beta$-keto esters, providing a highly enantioselective method to access DHPMs. 3,3′-Di(triphenylsilyl) binaphthol-derived phosphoric acid afforded Biginelli-like reactions of a broad scope of aldehydes and enolizable ketones with benzylthiourea, giving structurally diverse dihydropyrimidinethiones with excellent optical purity. Theoretical calculations with the ONIOM method on the transition states of the stereogenic center forming step showed that the imine and enol were simultaneously activated by the bifunctional chiral phosphoric acid through formation of hydrogen bonds. The effect of the 3,3′-substituents in phosphoric acids on the stereochemistry of the Biginelli reaction was also theoretically rationalized. The current protocol has been applied to the synthesis of some pharmaceutically interesting compounds and intermediates, such as chiral thioureas, dihydropyrimidines, guanidines, and the precursor of (*S*)-L-771688.

## Introduction

Chiral dihydropyrimidinethiones (DHPMs) have found increasing applications to the synthesis of pharmaceutically relevant substances exhibiting a wide range of important pharmacological properties,[1] including calcium channel modulation,[2] $\alpha_{1a}$-adrenergicreceptor antagonism,[3] and mitotic kinesin inhibition.[4] It has been reported that the individual enantiomers have been found to exhibit different or even opposite pharmaceutical activities.[1] For example, the (*R*)-enantiomer of SQ 32926 (**1**), a calcium channel blocker, exhibits >400-fold more potent antihypertensive activity in vitro than the other enantiomer.[5] (*S*)-Monastrol (**2**) is 15-fold more potent in the inhibition of Eg 5 ATPase than (*R*)-monastrol.[6] (*S*)-L-771688 (**3**) is a more potent and selective $\alpha_{1a}$ receptor antagonist for the treatment of benign prostatic hyperplasia (BPH) than the (*R*)-enantiomer.[7] In addition, chiral thioureas readily available from the reduction of dihydropyrimidinethiones have been widely employed in asymmetric catalysis as ligands.[8] Moreover, dihydropyrimidinethiones can be converted into either 1,3-diamines or guanidines, which are core structural elements commonly present in natural products exemplified by the batzelladine family of polycyclic

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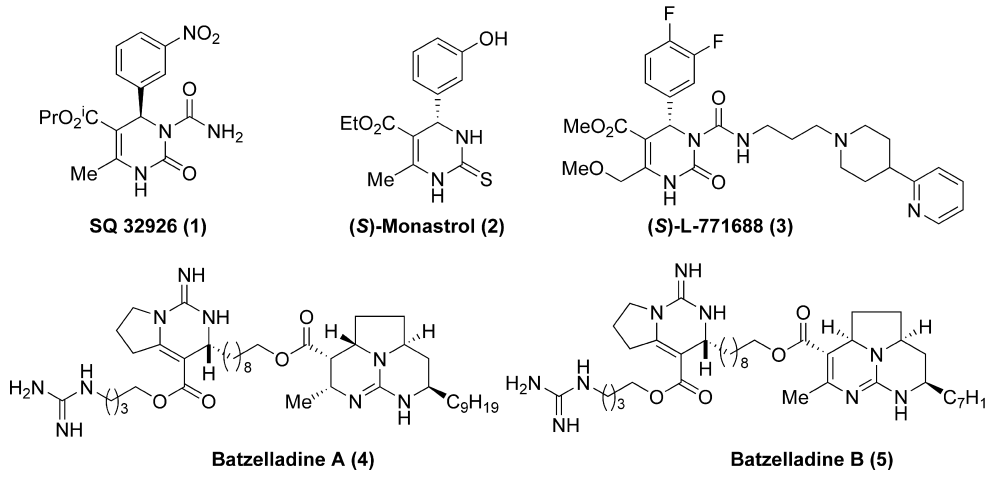


***Figure 1.*** Biologically significant compounds containing DHPM and related structural motifs.

marine alkaloids,[9] of which batzelladine A and B (**4** and **5**) were reported to inhabit the binding of HIV-gp120 to the CD4 cell surface receptor protein on T-cells to be potentially useful in the treatment of AIDS.[10] Therefore, an efficient method for the preparation of optically pure DHPMs is in a great demand.

Biginelli and Biginelli-like reactions that assemble aldehydes, urea/thiourea, and enolizable carbonyls into dihydropyrimidinethiones provide robust tools for the creation of these structural motifs.[1a,11] Since the first description of the Biginelli reaction over a century ago,[11a] the research interest has long been focused on seeking new catalysts for efficiently producing racemic DHPMs.[1a] In contrast, the asymmetric catalytic Biginelli reactions, although they provide access to optically active DHPMs in a straightforward manner, have been a long-standing challenge. As such, the preparation of optically pure DHPMs in the pharmaceutical research laboratory mainly relies on resolution and chiral auxiliary-assisted asymmetric synthesis.[12] Juaristi and Muñoz-Muñiz reported the use of a chiral amide, in combination with $CeCl_3$, to catalyze the Biginelli reaction of benzaldehyde, urea, and methyl acetoacetate with up to 40% *ee*.[13] Zhu and co-workers described an asymmetric catalytic Biginelli reaction with a chiral ytterbium catalyst providing DHPMs in high yields with excellent enantioselectivities ranging from 80 to >99% ee.[14] Schaus and co-workers introduced an elegant asymmetric access to DHPMs starting with the organocatalytic Mannich reaction.[15] Recently, we reported the first organocatalytic Biginelli reaction using Brønsted acids as catalysts, giving DHPMs with up to 97% ee.[16] Subsequent to our reports, Feng and Juaristi independently described an organocatalytic asymmetric Biginelli reaction using a combined catalyst system consisting of chiral secondary amine and Brønsted acid.[17] Despite these elegant examples, a catalytic enantioselective protocol that tolerates a broad scope of $\beta$-keto esters for Biginelli reactions and enolizable ketones for Biginelli-like reactions has remains unknown. In this paper, we report the full results of our studies on the Brønsted acid-catalyzed enantioselective Biginelli and Biginelli-like reactions, which provided a highly efficient method to access DHPMs with structural diversity and excellent levels of enantioselectivity (>99% ee).

## General Consideration of the Brønsted Acid Catalyzed Enantioselective Biginelli and Biginelli-like Reactions

Either a Biginelli or Biginelli-like reaction is initiated with the condensation of an aldehyde with urea or thiourea in the presence of a Brønsted acid, generating an activated *N*-acyliminium, which is subsequently attacked by enolizable carbonyls, including acetoacetates (Biginelli reaction) and ketones (Biginelli-like reaction), to undergo a Mannich reaction, and ultimately followed by cyclization and dehydration reactions to afford the DHPMs.[18] The nucleophilic addition of the enolizable carbonyls to *N*-acyliminium is the stereogenic center forming step (Scheme 1). Consequently, an optically active Brønsted acid would afford an enantioselective Biginelli or Biginelli-like reaction.

## Results and Discussion

**Summary of Previous Studies on the Evaluation of Chiral Brønsted Acids.** Chiral phosphoric acids provide sufficient

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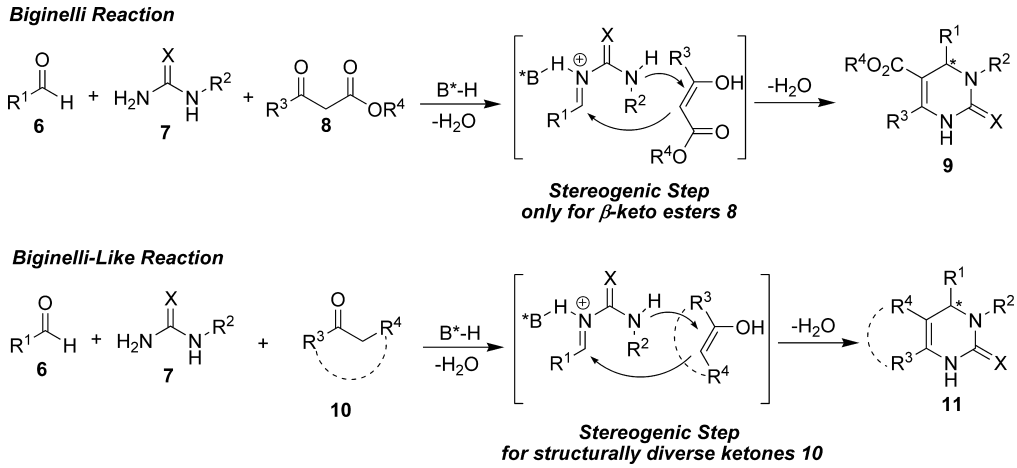
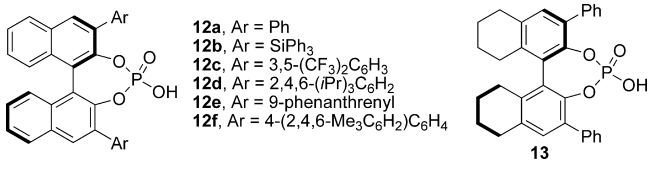
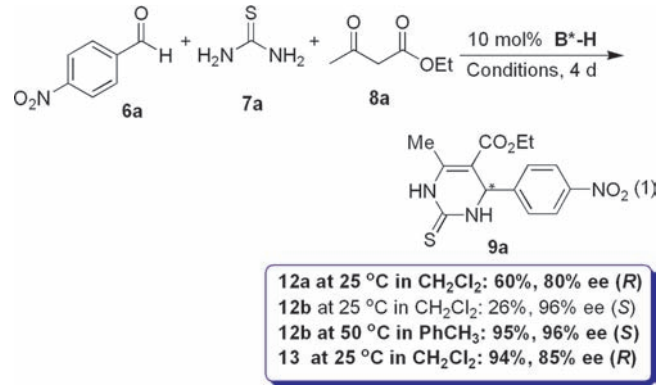
***Scheme 1.*** Biginelli and Biginelli-Like Reactions




acidity required for the activation of imines leading to many new asymmetric procedures.[19] In particular, they afforded Mannich reactions with high enantioselectivities.[19d,e] In the light of these successes as well as the mechanism of the Biginelli reaction, we believed that chiral phosphoric acids **12** and **13** and their structural analogues would effectively catalyze the asymmetric Biginelli reaction.




Our previous evaluation of the BINOL- and $H_8$−BINOL-based phosphoric acids **12** and **13** and their derivatives to catalyze the Biginelli reaction of 4-nitrobenzaldehyde (**6a**), thiourea (**7a**), and ethyl acetoacetate (**8a**) revealed that the 3,3′-substituents on the phosphoric acids considerably impacted the reaction performance.[16] Both reaction conversion and stereochemistry were considerably dependent on the size of the substituents on the catalysts. Increasing the size of 3,3′-substituents usually diminished the yield and enantioselectivity as shown in the reactions catalyzed by phosphoric acids.[16] Interestingly, the stereochemistry of the Biginelli reaction can be reversed by tuning the 3,3′-disubstituents of the phosphoric acids. For example, using the phosphoric acid **12b**,[20] which has highly bulky 3,3′-substituents, as the catalyst gave (*S*)-**9a** with the highest enantioselectivity (96% ee), whereas the structurally similar phosphoric acid **12a** bearing less sterically hindered substituents favored the formation of (*R*)-**9a** with 80% ee (eq 1). The enantioselectivity of (*R*)-**9a** could be improved to 85% ee by the replacement of **12a** with H8-BINOL based phosphoric acid **13**.[16]




**Scope of the Organocatalytic Asymmetric Biginelli Reaction by 12b and 13.** The generality of the asymmetric Biginelli reaction catalyzed by **13** has been investigated and reported previously.[16] This protocol is applicable to a wide range of aldehydes and provided a highly enantioselective method to access DHPMs with 88 to 96% ee. The variation of the $R^3$ substituent of $\beta$-keto esters **8** could be tolerated, and generally, high enantioselectivities were achieved for the reactions related to the substrates.[16]

Basically, the asymmetric Biginelli reaction using **12b** as the catalyst always generated DHPMs with stereochemistry opposite to those obtained with **13**,[16] regardless of the substrate used (Table 1). Notably, **12b** provided generally higher levels of

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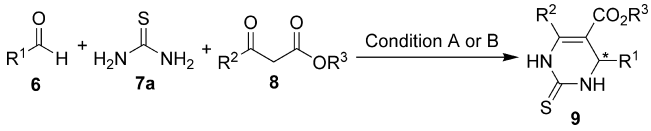
***Table 1.*** Organocatalytic Enantioselective Biginelli Reaction with Phosphoric Acid **12b** and **13**[a]




**6** **7a** **8** **9**

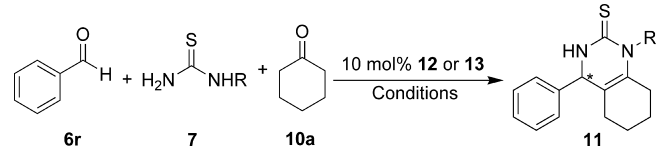
| entry | $R^1$ (**6**) | $R^2$, $R^3$ (**8**) | DHMPs (**9**) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | 3-$FC_6H_4$ (**6b**) | Me, Et (**8a**) | **9b** | 82 | 95 |
| 2 | 3-$NO_2C_6H_4$ (**6c**) | Me, Et (**8a**) | **9c** | 95 | 96 |
| 3 | 2-$ClC_6H_4$ (**6d**) | Me, Et (**8a**) | **9d** | 91 | 96 |
| 4 | 3-$ClC_6H_4$ (**6e**) | Me, Et (**8a**) | **9e** | 94 | 95 |
| 5 | 2-$NO_2C_6H_4$ (**6f**) | Me, Et (**8a**) | **9f** | 72 | 98 |
| 6 | 3-$BrC_6H_4$ (**6g**) | Me, Et (**8a**) | **9g** | 95 | 96 |
| 7 | 4-$MeO_2CC_6H_3$ (**6h**) | Me, Et (**8a**) | **9h** | 97 | 94 |
| 8 | 3-$MeOC_6H_4$ (**6i**) | Me, Et (**8a**) | **9i** | 94 | 92 |
| 9 | 2-$MeC_6H_4$ (**6j**) | Me, Et (**8a**) | **9j** | 87 (81) | 91 (88) |
| 10 | 4-$MeC_6H_4$ (**6k**) | Me, Et (**8a**) | **9k** | 98 (84) | 90 (75) |
| 11 | 4-$^t$Bu$C_6H_4$ (**6l**) | Me, Et (**8a**) | **9l** | 96 (88) | 93 (76) |
| 12 | 3,5-$Br_2C_6H_3$ (**6m**) | Me, Et (**8a**) | **9m** | 54[d] | 91 |
| 13 | 1-$BrC_{10}H_6$ (**6n**) | Me, Et (**8a**) | **9n** | 92 | 94 |
| 14 | *c*-$C_6H_{11}$ (**6o**) | Me, Et (**8a**) | **9o** | 54[e] | 90 |
| 15 | $PhCH{=}CH_2$ (**6p**) | Me, Et (**8a**) | **9p** | 44 | 30 |
| 16 | 3-$BrC_6H_4$ (**6g**) | Me, Me (**8b**) | **9q** | 83 | 96 |
| 17 | 3-$BrC_6H_4$ (**6g**) | Me, *i*-Pr (**8c**) | **9r** | 82 | 96 |
| 18 | 3-$BrC_6H_4$ (**6g**) | Me, *t*-Bu (**8d**) | **9s** | 80 | 97 |
| 19 | 3-$FC_6H_4$ (**6b**) | Et, Me (**8e**) | **9t** | 53[g] (67)[f] | 87 (85) |
| 20 | 3,5-$F_2C_6H_3$ (**6q**) | Et, Me (**8e**) | **9u** | 26[g] (51)[f] | 69 (92) |
| 21 | 3-$BrC_6H_4$ (**6g**) | Et, Me (**8e**) | **9v** | 58[g] (56)[f] | 90 (85) |

[a] Condition A: the reaction was carried out on a 0.2 mmol scale in toluene at 50 °C catalyzed by 10 mol % of **12b** for 60 h and the ratio of **6/7a/8** was 1/1.2/3. Condition B: the reaction was carried out on a 0.2 mmol scale in $CH_2Cl_2$ at room temperature catalyzed by 10 mol % of **13** for 6 days and the ratio of **6/7a/8** was 1/1.2/3. [b] Isolated yield based on aldehyde, and the data in parentheses was obtained under condition B. [c] Determined by HPLC, and ee of the opposite enantiomer in parentheses was obtained under condition B. [d] Reaction time was 96 h. [e] Ratio of **6/7a/8** was 2/1/3. [f] Ratio of **6/7a/8** was 1/1.2/5 and the reaction time was 8 days. [g] Ratio of **6/7a/8** was 1/1.2/5 and the reaction time was 96 h.

enantioselectivity than **13** in most cases[16] with the exception of reactions involving either 3,5-dibromobenzaldehyde, aliphatic, or unsaturated aldehydes (entries 12, and 14−15). Moreover, **12b** delivered excellent enantioselectivity ranging from 90 to 93% ee for electronically rich benzaldehydes **6j**−**l** whereas **13** afforded much lower enantioselectivity ranging from 75 to 88% ee (entries 9−11). In addition, the phosphoric acid **12b** exhibited higher enantioselectvity than **13** for the Biginelli reactions of propionylacetate (entries 19 and 21) except for the reaction with 3,5-difluorobenzaldehyde (entry 20).

**Optimization of the Biginelli-Like Reaction.** In contrast to numerous protocols available for Biginelli reactions, Biginelli-like reactions using enolizable ketones have been explored less even in a racemic manner.[21] To the best of our knowledge, there have been no reports describing the asymmetric catalytic version of Biginelli-like reactions. The inferior reactivity of ketones, compared to that of $\beta$-keto esters, appears to be a key factor hindering the Biginelli-like reaction from successfully proceeding under the catalysis of relatively mild Lewis or Brønsted acids. Most commonly, stronger Lewis or Brønsted acids were exploited to afford a racemic reaction at the elevated temperature. This was also indicated by our initial studies on the Biginelli-like reaction of cyclohexanone with thiourea and benzaldehyde using phosphoric acid catalyst **13** or **12a**, which failed to proceed under conditions that were used for either the Biginelli reaction[16] or the Mannich reaction (Table 2, entries 1 and 2).[22] To our delight, the use of benzylthiourea to replace thiourea as a reaction component gave 75% yield and 40% ee by employing **12a** as the catalyst (entry 3). Encouraged by this primarily promising result, we performed the optimization studies to improve the stereoselectivity by varying catalysts and solvents. A series of BINOL-based phosphoric acids were screened by conducting the reaction in toluene at 50 °C (entries 4−9), of which the catalyst **12b** gave the highest levels of enantioselectivity (99% ee, entry 5). The investigation of the solvent effect concluded that the nonpolar solvents were suitable media for controlling the enantioselectivity (entries 10−13). Accordingly, considerably higher enantiomeric excesses were obtained using either toluene or *m*-xylene as a solvent (entries 9, 11 and 13).

***Table 2.*** Asymmetric Biginelli-Like Condensation of Benzaldehyde, Thiourea, and Cyclohexanone Catalyzed by **12** and **13**[a]




**6r** **7** **10a** **11**

| entry | catalyst, Ar | **7** (R) | temp. (°C) | solvent | **11** | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **13** | H | 25 | $CH_2Cl_2$ | **11a** | <5% | ND |
| 2 | **12a**, Ph | H | 25 | $CH_2Cl_2$ | **11a** | <5% | ND |
| 3 | **12a**, Ph | Bn | 50 | toluene | **11b** | 75 | 40 |
| 4 | **13** | Bn | 50 | toluene | **11b** | 53 | 24 |
| 5 | **12b**, $SiPh_3$ | Bn | 50 | toluene | **11b** | 66 | 99 |
| 6 | **12c**, 3,5-$(CF_3)_2C_6H_3$ | Bn | 50 | toluene | **11b** | 21 | 74 |
| 7 | **12d**, 2,4,6-($i$Pr)$_3C_6H_2$ | Bn | 50 | toluene | **11b** | 82 | 1 |
| 8 | **12e**, 9-phenanthrenyl | Bn | 50 | toluene | **11b** | 34 | 64 |
| 9 | **12f**, 4-(2,4,6-$Me_3C_6H_2$)$C_6H_4$ | Bn | 50 | toluene | **11b** | 50 | 87 |
| 10 | **12b**, $SiPh_3$ | Bn | 50 | $CHCl_3$ | **11b** | 94 | 93 |
| 11 | **12b**, $SiPh_3$ | Bn | 50 | m-xylene | **11b** | 63 | 97 |
| 12 | **12b**, $SiPh_3$ | Bn | 50 | $Cl(CH_2)_2Cl$ | **11b** | 61 | 59 |
| 13 | **12b**, $SiPh_3$ | Bn | 50 | toluene | **11b** | 69 | 99[d] |

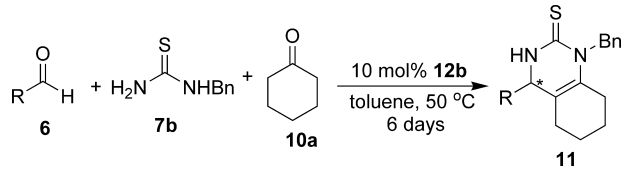
[a] Reaction was carried out on a 0.1 mmol scale, the ratio of **6r/7/10a** was 1.5/1.0/5.0 and the reaction time was 5 days. [b] Isolated yield. [c] ee was determined by HPLC. [d] Reaction time was 6 days.

After establishing the optimal conditions, we examined the scope of the aldehyde component by reactions with cyclohexanone (Table 3). A wide spectrum of aromatic aldehydes could be tolerated and underwent smooth Biginelli-like condensations. Significantly, unlike most phosphoric acid-catalyzed nucleophilic additions to imines wherein the stereoselectivity is highly dependent on the electron density of the imines,[19] the Biginelli-like reaction afforded excellent levels of enantioselectivity for electronically poor, neutral, and rich benzaldehydes (92−99% ee). Moreover, the position of the substituent on the benzaldehydes had little effect on the stereoselectivity as demonstrated by reactions involving bromo- (entries 1−3), cyano- (entries 6 and 8), and methylbenzaldehydes (entries 10 and 12). The number of the substituent on the benzaldehydes also had little influence on the stereoselection (96−99% ee, entries 1−16), with the exception of 3,4,5-trifluorobenzaldehyde, which delivered a comparably lower enantioselectivity (92% ee, entry

(21) (a) Abelman, M. M.; Smith, S. C.; James, D. R. *Tetrahedron Lett.* **2003**, *44*, 4559. (b) Wang, Z.-T.; Xu, L.-W.; Xia, C.-G.; Wang, H.-Q. *Tetrahedron Lett.* **2004**, *45*, 7951. (c) Sabitha, G.; Reddy, K. B.; Srinivas, R.; Yadav, J. *Helv. Chim. Acta* **2005**, *88*, 2996. (d) Zhu, Y.-L.; Huang, S.-L.; Pan, Y.-J. *Eur. J. Org. Chem.* **2005**, 2354.

(22) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790.

***Table 3.*** Scope of Aldehydes in the Biginelli-Like Reaction[a]




| entry | 11 | R | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | **11c** | 2-$BrC_6H_4$ | 86 | 98 |
| 2 | **11d** | 3-$BrC_6H_4$ | 76 | 98 |
| 3 | **11e** | 4-$BrC_6H_4$ | 65 | 98 |
| 4 | **11f** | 4-$NO_2C_6H_4$ | 55 | 97 |
| 5 | **11g** | 4-$MeO_2CC_6H_4$ | 61 | 97 |
| 6 | **11h** | 4-$CNC_6H_4$ | 74 | 98 |
| 7 | **11i** | 4-$CF_3C_6H_4$ | 67 | 98 |
| 8 | **11j** | 3-$CNC_6H_4$ | 76 | 98 |
| 9 | **11k** | 4-$^tBuC_6H_4$ | 56 | 98 |
| 10 | **11l** | 4-$MeC_6H_4$ | 63 | 98 |
| 11 | **11m** | 4-$MeOC_6H_4$ | 60 | 98 |
| 12 | **11n** | 2-$MeC_6H_4$ | 64 | 98 |
| 13 | **11o** | 4-Cl,3-$FC_6H_3$ | 72 | 97 |
| 14 | **11p** | 2,3-$Cl_2C_6H_3$ | 68 | 99 |
| 15 | **11q** | 3,5-$Br_2C_6H_3$ | 58 | 96 |
| 16 | **11r** | 3,4-$(MeO)_2C_6H_3$ | 86 | 96 |
| 17 | **11s** | 3,4,5-$F_3C_6H_2$ | 55 | 92 |
| 18 | **11t** | 2-naphthyl | 51 | 98 |
| 19 | **11u** | 2-furanyl | 65 | 98 |
| 20 | **11v** | 4-$NO_2C_6H_4$ | 75 | 90[d] |

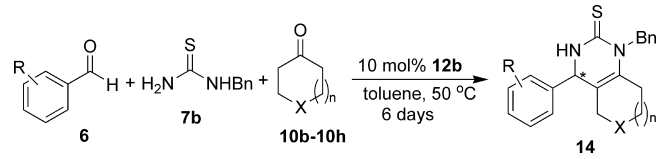
[a] Reaction was carried out on a 0.1 mmol scale, the ratio of **6/7b/10a** was 1.5/1.0/5.0. [b] Isolated yield. [c] ee was determined by HPLC. [d] Methylthiourea (**7c**) was used as reaction component.

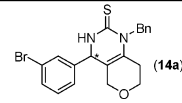
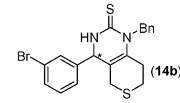
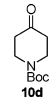
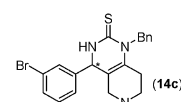
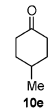
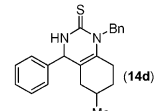
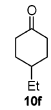
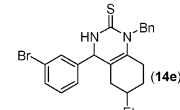
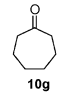
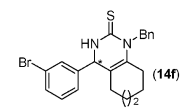
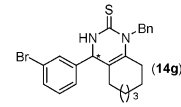
17). 2-Naphthaldehyde and furanylaldehyde both furnished the Biginelli-like products with excellent enantioselectivities (98% ee, entries 18 and 19). The absolute configuration of product **11u** was accessed by X-ray analysis (see Supporting Information). Moreover, the replacement of benzylthiourea with methylthiourea (**7c**) also gave high levels of enantioselectivity (90% ee, entry 20).

We next studied the generality of cyclic enolizable ketones in the Biginelli-like reaction (Table 4). Tetrahydropyran- and tetrahydrothiopyran-4-one were both good reaction partners, undergoing clean Biginelli-like reactions with 3-bromobenzaldehyde with excellent levels of enantioselectivity (97 and 98% ee, respectively, entries 1 and 2). *N*-Boc-protected piperidin-4-one was seemly less reactive, and thus gave the product in only 39% yield, but with 98% ee (entry 3). Enantioselective desymmetrization could be partially realized in the Biginelli-like reactions with prochiral 4-alkylcyclohexanones. Although the diastereoselectivity was moderate, perfect enantiomeric excess was obtained for each individual diastereomer (>99% ee, entries 4 and 5). Interestingly, the ring size of the cyclic ketone had considerable impact on the reaction. Cycloheptanone and cyclooctanone were both suitable substrates, affording corresponding Biginelli-like products in good yields with 91 and 90% ee, respectively (entries 6 and 7). In contrast, cyclopentanone showed low reactivity under the same conditions.[23]

Most significantly, the extension of the reaction conditions to acyclic ketones was also successful (Table 5).[24] The Biginelli-like condensation took place at the thermodynamically stable

***Table 4.*** Scope of Cyclic Ketones in the Biginelli-Like Reaction[a]




| entry | ketone | product (**14**) | yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 |  |  | 75 | -- | 97 |
| 2 |  |  | 86 | -- | 98 |
| 3 |  |  | 39 | -- | 98 |
| 4 |  |  | 60 | 80/20 | >99[e] (>99) |
| 5 |  |  | 50 | 75/25 | >99[e] (>99) |
| 6 |  |  | 64 | -- | 91[e,f] |
| 7 |  |  | 62 | -- | 90[e,f] |

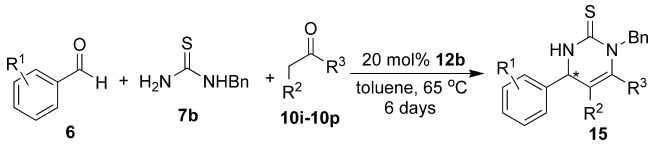
[a] Reaction was carried out on a 0.1 mmol scale, the ratio of **6/7b/10** was 1.5/1.0/5.0. [b] Isolated yield. [c] Determined by $^1H$ NMR. [d] ee was determined by HPLC and the ee in parentheses represents the minor diastereomer. [e] Using 20 mol % **12b**. [f] At 65 °C.

enolizable site of the unsymmetrical ketones, and interestingly, the steric factor of the ketone had little influence on the regiocontrol (entries 1−6). For the linear aliphatic ketones, high yields and regioselection were obtained with enantioselectivity ranging from 92 to 96% ee for the major regiomer (entries 1−4). Notably, α-branched aliphatic ketones such as 3-methyl-2-pentanone and 3-methylbutanone could also participate in the Biginelli-like reaction, which favorably took place at the more substituted carbon with complete regioselective control and provided greater than 96% ee (entries 5 and 6). These observations indicated that the regioselectivity might be thermodynamically controlled. 3-Pentanone participated in a slower reaction, but the stereochemical outcome remained excellent (entry 7). Aromatic ketones such as 1-*p*-tolylethanone could undergo a smooth Biginelli-like reaction but with only moderate enantioselectivity (61% ee, entry 8). The absolute configuration of product **15f** was assigned by X-ray analysis (see Supporting Information).

(23) Less than 5% yield was isolated with no determination of enantiomeric excess.

(24) Notably, enolizable acyclic ketones gave poor stereoselectivity in the phosphoric acid-catalyzed direct Mannich reaction, see ref 22.

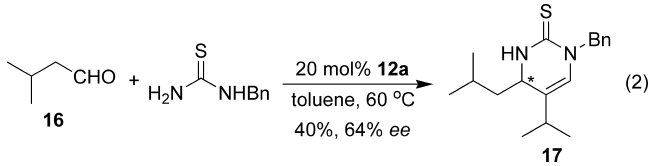
***Table 5.*** Scope of Acyclic Ketones in the Biginelli-Like Reaction[a]




| entry | ketone | product (**15**) | yield (%)[b] | rr[c] | ee(%)[d] |
|---|---|---|---|---|---|
| 1 | **10i** | (**15a**) | 78 | 98/2 | 95[e,h] |
| 2 | **10j** | (**15b**) | 83 | 82/18 | 95(90) |
| 3 | **10k** | (**15c**) | 82 | 88/12 | 96(92) |
| 4 | **10l** | (**15d**) | 75 | 91/9 | 92(85) |
| 5 | **10m** | (**15e**) | 57 | >99/1 | 97[f,g,i] |
| 6 | **10n** | (**15f**) | 77 | >99/1 | 96[f] |
| 7 | **10o** | (**15g**) | 33 | --- | 96[h] |
| 8 | **10p** | (**15h**) | 49 | --- | 61[h,j] |

[a] Reaction was carried out on a 0.1 mmol scale, the ratio of **6**/ **7b**/ **10** was 1.5/ 1.0/ 5.0. [b] Isolated yield. [c] rr refers to regiomeric ratio and was determined by $^1$H NMR of the crude product. [d] ee was determined by HPLC and the ee in parentheses is the minor regiomer. [e] Ratio of **6**/ **7b**/ **10** was 1.5/ 1.0/ 20.0. [f] Ratio of **6**/ **7b**/ **10** was 1.5/ 1.0/ 10.0. [g] Diastereomeric ratio was 63/37. [h] At 50 °C. [i] Scale: 0.2 mmol. [j] Using **12e** as a catalyst.

Interestingly, enolizable aliphatic aldehydes could not participate in the cross Biginelli-like reaction with ketones but could more easily undergo a self-Biginelli-like reaction. For example, the self-reaction of 3-methylbutanal (**16**) catalyzed by **12a** furnished **17** in a moderate yield and enantiomeric purity (eq 2).




(2)

**Theoretical Explanation of the Stereochemistry.** To understand the origin of enantioselectivity and how the 3,3′-substituents of BINOL-phosphoric acids control the stereochemistry, theoretical calculations were performed on the nucleophilic addition of enol to imine, the stereogenic center forming step. For this Mannich-type reaction catalyzed by chiral BINOL-phosphoric acid derivatives, a general mechanism has been proposed that the catalyst may simultaneously activate both nucleophile and electrophile by hydrogen bonds between catalyst and substrates, and the stereochemistry was controlled by different steric interactions within the competing diastereomeric transition states.[25] We investigated the transition states with the similar model by theoretical calculations to identify key factors that control the enantioselectivity, particularly, the influence of the size of 3,3′-substituents of the BINOL-phosphoric acid on the stereochemistry. We observed that the use of *N*-methylthiourea as a reaction component afforded the desired product with excellent enantioselectivity with configuration similar to that observed for *N*-benzylthiourea (Table 3, entries 4 and 20). To simplify the calculation, we employed the reaction involving *N*-methylthiourea as a chemical model. The full DFT calculation was performed on the key intermediates of imine using B3LYP functional and 6-31+G* basis set,[26] while the location of transition state structures was established with the ONIOM[27] method implemented in Gaussian03 program.[28]

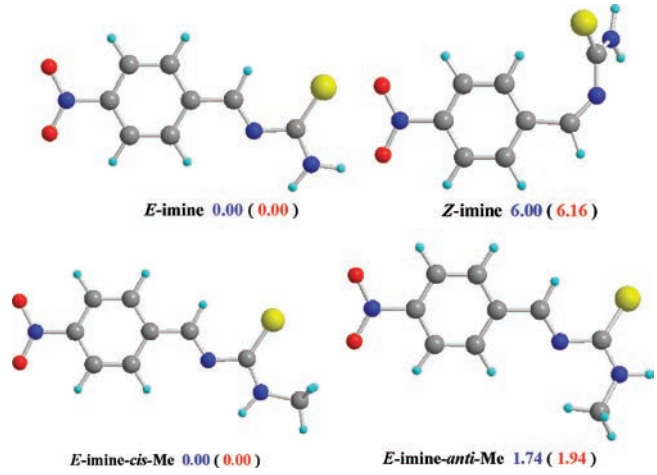



***Figure 2.*** Computed structures of imine intermediates and relative energies in enthalpy and free energy in parentheses.

The full optimized structures of the imine intermediates formed by condensation of 4-nitrobenzaldehyde with thiourea or *N*-methylthiourea, respectively, were shown in Figure 2. This calculation indicated that *E*-imine was more stable by 6 kcal/mol than *Z*-imine, arising from the steric repulsion between the phenyl ring and sulfur atom, which makes the thiourea twist to the phenyl ring and thereby partially destroys the conjugation interaction in *Z*-imine. When a methyl group replaced the H atom in the thiourea, the formed *E*-imine preferred the orientation of methyl group *cis* to sulfur atom. Thus, for both kinds of imine intermediates, the calculations implied that the imine was stabilized by the conjugated system formed with phenyl ring and thiourea and preferentially generated a conformer with the H atom of NH cis to the N atom of imine. Such an orientation of the intermediate led to two possible pathways in the

(25) (a) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756. (b) Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741. (c) Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 4070. (d) Yamanaka, M.; Hirata, T. *J. Org. Chem.* **2009**, *74*, 3266.
(26) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Gill, P. M. W.; Johnson, B. G.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1992**, *197*, 499. (c) Krishnan, R.; Binkley, J. S.; Seeger, R; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.
(27) (a) Svensson, M.; Humbel, S.; Morokuma, K. *J. Chem. Phys.* **1996**, *105*, 3654. (b) Vreven, T.; Morokuma, K. *J. Comput. Chem.* **2000**, *21*, 1419. (c) Dapprich, S.; Komáromi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. J. *J. Mol. Struct. (Theochem)* **1999**, 461.
(28) Frisch, M. J.; et al. *Gaussian 03, revision C.02*; Gaussian, Inc.: Wallingford, CT, 2004.

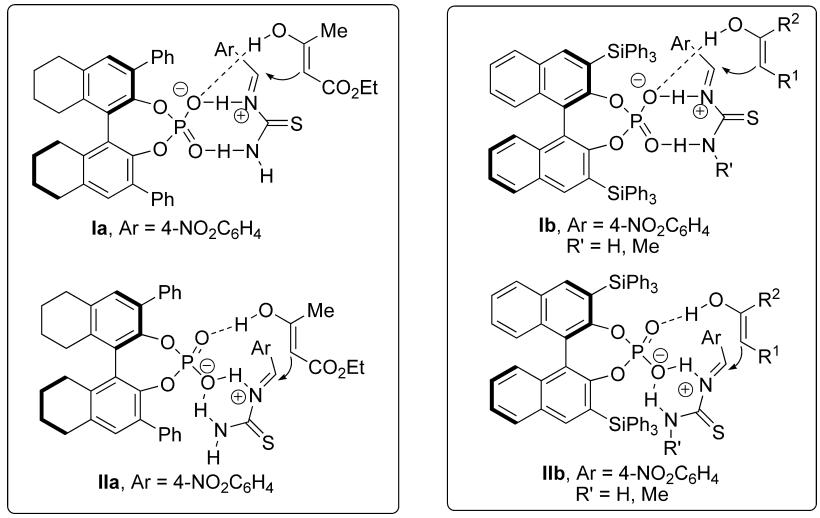



***Figure 3.*** Activation models and possible reaction pathways of the stereogenic step in the phosphoric acid-catalyzed Biginelli reaction.

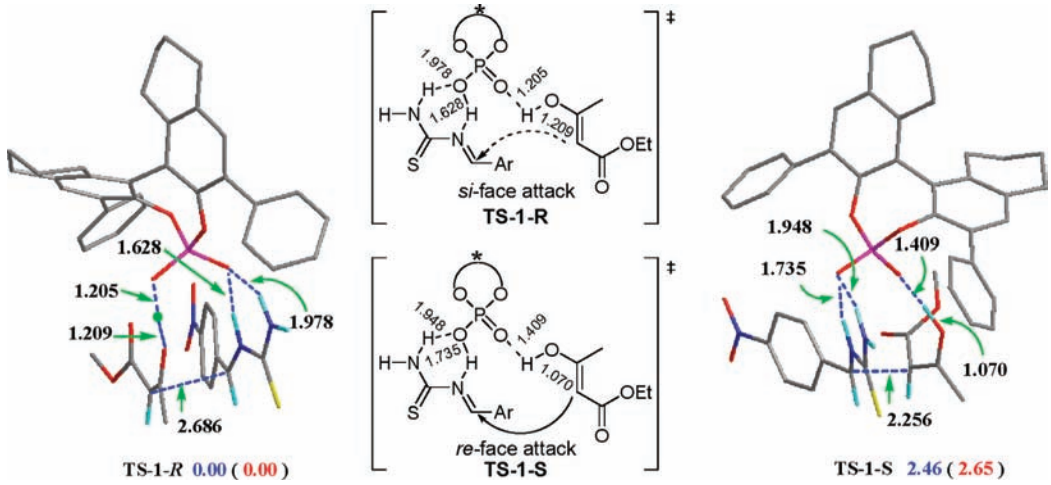



***Figure 4.*** Located transition state structures with distance parameters in angstroms and relative energies in enthalpy and free energy in parentheses.

nucleophilic addition step, respectively, as shown in **I** and **II** (Figure 3). In pathways **Ia** and **Ib**, the imine was activated by the proton of phosphoric acid OH to generate a zwitterionic iminium salt, accompanying an additional hydrogen bond formed between the enol proton and oxygen atom on the phosphoric acid OH.[25d] In pathways **IIa** and **IIb**, the bifunctional phosphoric acid allows the activation of the imine with the proton of OH and the enol by Lewis basic phosphoryl oxygen. Both kinds of zwitterionic iminium salts might adapt the nucleophilic addition of enol to either the Re- or *Si*-face of imine with different steric interactions within the competing diastereomeric transition states. Thus, further theoretical calculations were performed on the transition states to identify the preferred attacking pathway on the basis of these two pathways.

Goodman and Simons has shown that the ONIOM method could be successfully used to calculate the large catalyst system like BINOL-based phosphoric acids, leading to the discovery of reasonable mechanism and the explanation of enantioselectivity in transfer hydrogenation and Strecker reaction.[25b,c] Inspired by these successes, we also performed DFT calculation of the stereogenic step of Biginelli reaction using ONIOM method. All atoms in the catalyst were included in the lower-level layer except the phosphoric acid moiety, which was included in the higher-level layer, together with the imine and nucleophilic enol involved in reaction pathways **I** and **II** (Figure 3), according to a typical ONIOM scheme in Gaussian03. The DFT functional of B3LYP combined with 6-31G* basis set was used in the higher-level layer, and the UFF molecular mechanics force field was used in the lower-level layer.

TS-1-*R* and TS-1-*S* were the located transition state structures, as shown in Figure 4, illustrating the addition reaction of the enol of acetacetate to the imine of (*E*)-(4-nitrobenzylidene)thiourea activated by 3,3′-diphenyl-$H_8$−BINOL phosphoric acid to offer Mannich-like reaction intermediates. Both structures showed that the 3,3′-diphenyl groups of the catalyst created a cave, large enough to allow the phosphoric acid activating the enol nucleophile and the imine electrophile simultaneously by triple hydrogen bonding interactions as indicated in model **IIa** (Figure 3). In both cases, the TSs were stabilized by forming HBs as indicated by the relatively shorter distance of HBs (O--H distance: ca. 2 Å in the TSs). TS-1-*R* was predicted to be more favored by about 2.5 kcal/mol than TS-1-*S*, because of: (1) The earlier transfer of the OH proton of enol to phosphoryl oxygen in TS-1-*R* causes the enol more nucleophilic than that in TS-1-*S* and the longer distance of the forming C−C bond in TS-1-*R* means an early transition state for TS-1-*R* rather than TS-

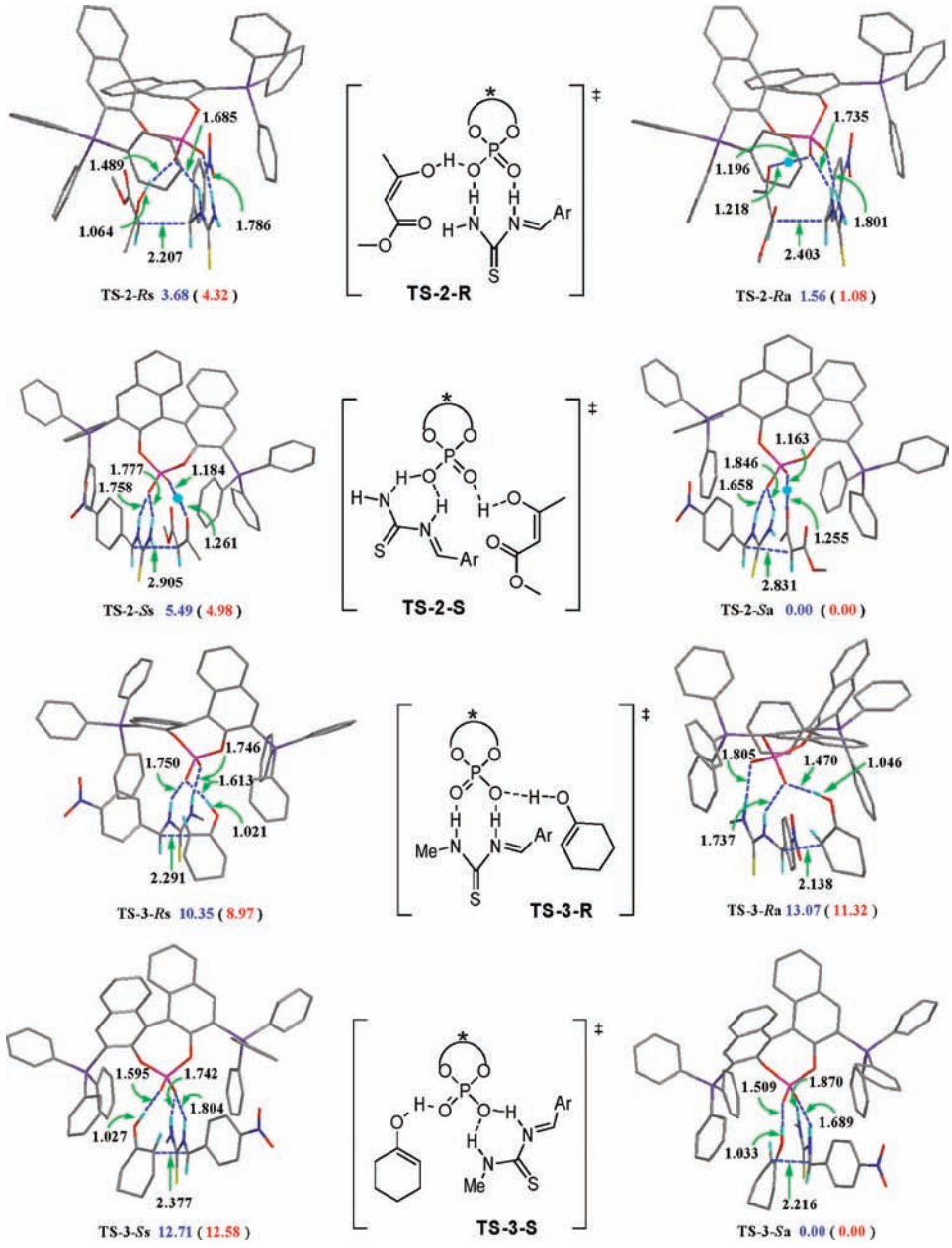
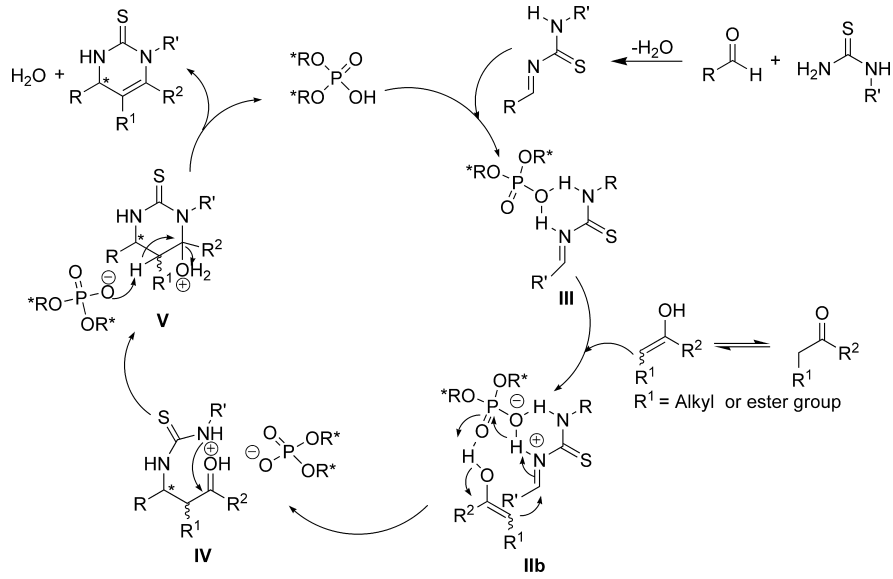



***Figure 5.*** Located transition state structures with distant parameters in angstroms and relative energies in enthalpy and free energy in parentheses.

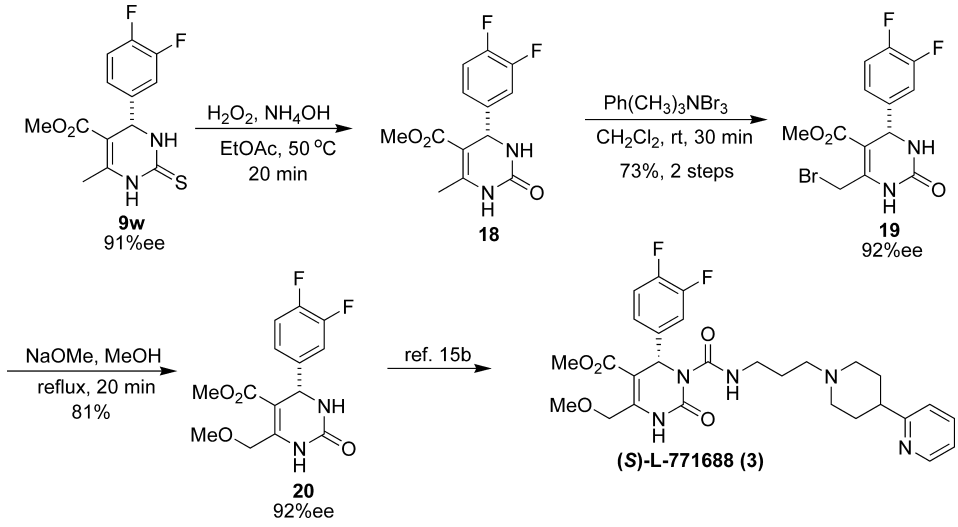
1-*S* as indicated by the computed distance parameters (2.686 vs 2.256 Å) in Figure 4; (2) the *Si*-face of the imine seems less obstructive than *Re*-face and thereby the nucleouphilic attacking on the *Si*-face of imine is easier than *Re*-face with respect to steric consideration. After the formation of C−C bond through TS-1-*R* and followed by an addition of N atom of the thiourea to the carbonyl of acetacetate and a subsequent dehydration, the experimentally observed major product with *R*-configuration would be furnished. However, the TS located from the model **Ia** (Figure 3) failed to be obtained.

Computed transition state structures of Biginelli and Biginelli-like reactions catalyzed by 3,3′-di(triphenylsilyl) BINOL-phosphoric acid (**12b**) were shown in Figure 5. The imines formed from the condensation of 4-nitrobenzaldehyde with either thiourea or *N*-methyl thiourea and the enol nucleophile formed from the tautomerization of acetacetate or cyclohexanone. The lowest energy transition state was obtained for each case when the *Re*-face of imine was attacked by the *Si*-face of enol with a OH of enol *anti* to the thiourea moiety of imine via the pathways **IIb**, wherein the imine and enol were simultaneously activated by the proton of phosphoric acid OH and the Lewis basic site as shown in TS-2-*S*a and TS-3-*S*a, which correspond to the major product with (*S*)-configuration observed experimentally. In contrast, the TS structures that correspond to (*R*)-products were located from reaction pathway **Ib** rather than **IIb** as displayed in TS-2-*R*a/*R*s and TS-3-*R*a/*R*s. Moreover, the HB interactions between catalyst and enol in the TS-*R*s were weaker than those in the TS-*S*s as indicated by a longer hydrogen bond distance between the oxygen of phosphoric acid OH and enol (1.489 Å in TS-2-*R*s vs 1.184 Å in TS-2-*S*s, and 1.613 Å in TS-3-*R*s vs 1.595 Å in TS-3-*S*s, respectively). As a result, the enol in TS-*R*s was less activated than that in TS-*S*s, leading to a kinetically less favored nucloephilic addition to the activated imines. This finding suggested that even if the energy deference between TS-2-*S*a and TS-2-*R*a is small in the Biginelli reaction (ca. 1.08 kcal/mol), the high enantioselectivity (96% ee) was

***Scheme 2.*** Plausible Reaction Mechanism of the Biginelli and Biginelli-Like Reactions Catalyzed by Chiral Phosphoric Acid




***Scheme 3.*** Asymmetric Synthesis of Chiral Precursor of (S)-L-771688

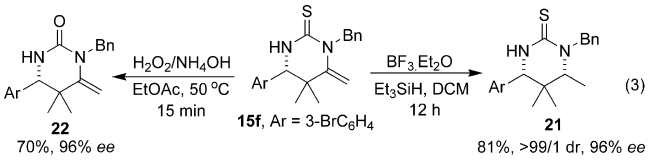



still obtained. On the basis of these theoretical calculations, the calculated energy differences in the transition states of the stereogenic center forming step confirmed that the Biginelli and Biginelli-like reactions catalyzed by the 3,3′-di(triphenylsilyl) BINOL-phosphoric acid (**12b**) proceeded via reaction pathway **IIb** through simultaneously activating the imine by forming 6-membered cyclic hydrogen bonding structure with the OH of phosphoric acid and the enol by Lewis basic phosphoryl oxygen, giving (*S*)-product in agreement with that observed experimentally.

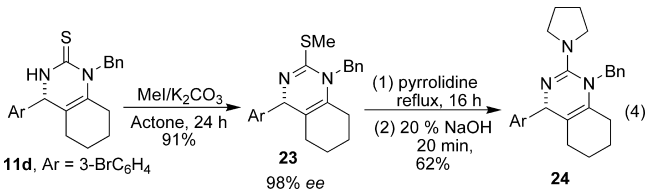
**Reaction Mechanism.** A reaction mechanism was proposed on the basis of the DFT calculation and relevant studies by others[18,25] (Scheme 2). The Biginelli reaction started with a condensation of the aldehyde with thiourea/urea, accelerated by Brønsted acid, to give an imine. The chiral phosphoric acid catalyst activated the imine through forming a chiral iminium species **III**, which was attacked by the $\beta$-keto ester or the enolizable ketone to undergo an enantioselective Mannich reaction via the intermediate **IIb**, as suggested by DFT calculation. The subsequent cyclization and dehydration reactions gave the Bignelli product and released the phosphoric acid catalyst.

**Synthetic Applications of Biginelli and Biginelli-Like Reactions.** The practical utility of the asymmetric catalytic Biginelli reaction has been demonstrated in the synthesis of a chiral precursor of (*S*)-L-771688 (**3**), selective $\alpha_{1a}$ receptor antagonist (Scheme 3). The dihydropyrimidinethione **9w** (84% yield, 91% ee), obtained from Biginelli condensation involving 3,4-difluorobenzaldehyde catalyzed by **12b**, was subjected to an oxidation with hydrogen peroxide and followed by a bromination with $PhMe_3N^+Br_3^-$, producing **19** in 73% yield with a maintained enantiomeric excess. Methoxylation of **19** using sodium methoxide under the refluxing condition rapidly afforded **20** in 81% yield. This compound has been readily transformed into (*S*)-L-771688 (**3**) by following a procedure developed by Schaus and co-workers.[15b]

Diastereoselective reduction of dihydropyrimidinethione **15f** with triethylsilane in the presence of trifluoroborane generated chiral thiourea **21** in 81% yield with >99/1 dr and 96% ee. Oxidation of the **15f** with hydrogen peroxide afforded chiral dihydropyrimidinone **22** with maintained enantiomeric excess (eq 3).




The treatment of **11d** with methyl iodide in the presence of $K_2CO_3$ furnished a 2-methylthio dihydropyrimidine **23** in 91% yield (eq 4). The structural analogues of **23** have been found to show antifilarial activity.[29] In addition, the transformation of compounds of type **23** into chiral guanidine compounds could be achieved by reaction with amines. For example, treatment of **23** with pyrrolidine under refluxing conditions furnished guanidine **24** in good yield (eq 4). Thus, this method also provides a facile access to chiral guanidine containing heterocycles, which constitute a large family of biologically active compounds.[30]




## Conclusion

In summary we have developed highly enantioselective Biginelli and Biginelli-like reactions using chiral phosphoric acids derived from 3,3′-disubstituted binaphthols as catalysts. The size of 3,3′-substituents of the catalysts was found to be able to control the stereochemistry of Biginelli reaction. This organocatalytic Biginelli reaction by Brønsted acids **12b** and **13** is applicable to a wide range of aldehydes and various $\beta$-keto esters, providing a highly enantioselective method to access DHPMs. Biginelli-like reactions catalyzed by 3,3′-di(triphenylsilyl) binaphthol derived phosphoric acid tolerated a broad scope of aldehydes and enolizable ketones. Theoretical calculations with the ONIOM method on the transition states of the stereogenic step showed that the imine and enol were both activated by the bifunctional chiral phosphoric acid through the formation of hydrogen bonds. In the case catalyzed by 3,3′-diphenyl binaphthol-derived phosphoric acid, the dual activation model existed in both *Si*-facial and *Re*-facial attacking TSs while the *Si*-facial attacking TS was more favored and thereby gave (*R*)-enantiomer in major. In contrast, in the reaction catalyzed by 3,3′-di(triphenylsilyl) phosphoric acid, the dual activation model stably existed in *Re*-facial attacking TS, whereas in the *Si*-facial attacking TS the phosphoric acid forms an 8-membered cyclic hydrogen bonding structure with imine and a weaker hydrogen bond with the enol to thereby cause the enol less reactive than that in the *Re*-facial attacking TSs, therefore the (*S*)-enantiomer was preferentially produced. These procedures provide new accesses to a wide spectrum of structurally diverse dihydropyrimidinethiones and their pharmaceutically relevant derivatives with high enantiomeric purity.

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**Supporting Information Available:** Experimental details, characterization of new compounds, selected NMR and HPLC spectra, and complete refs 2c,3a−d,4b, 7 and 28. This material is available free of charge via the Internet at http://pubs.acs.org.

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