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# Probing the Mode of Asymmetric Induction of Biginelli Reaction Using Proline Ester Salts

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**Keywords:** Asymmetric Biginelli reaction / Organocatalysis / Proline / Multicomponent reactions

Described are the studies on the mechanism of the asymmetric Biginelli reaction using proline ester salt catalyst to explain the enantioselectivity of the 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) formation. Of the three possible activation methods by the catalyst that could provide asymmetric induction we revealed that the steric environment of the chiral enamine formed by the condensation of β-keto ester with the catalyst is most responsible for the enantioselectivity. This assumption is supported by experiments with the *N*-methylated catalyst, and the combination sets of L- or D-proline ester catalyst with racemic or chiral BINOL-derived phosphoric acid as counter acid.


## Introduction

Multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivatives are of great importance in the field of medicinal chemistry ever since compounds possessing this DHPM privileged structure were identified as drug candidates or lead scaffolds. The DHPM derivatives have been found to possess antihypertensive, antiviral, antitumor, antibacterial, and antiinflammatory properties.[1] These compounds have also emerged as calcium channel blockers,[1a] Rho kinase inhibitors,[2] inhibitors of the fatty acid transporter,[3] $\alpha_{1a}$ receptor antagonists,[4] antioxidant,[5] and neuropeptide Y (NPY) antagonists.[1] Due to the chirality of these compounds, pharmacological studies concerning the absolute configuration at the C(4) stereogenic center are well documented and, in some cases, individual enantiomers show more different biological properties. For instance, only the enantiomer, (*R*)-SQ 32,926 exhibits an antihypertensive effect,[6] and only (*S*)-Monastrol[7] and (*R*)-Mon-97[8] present potential anticancer activity.

The Biginelli reaction,[9] one of the most useful and well known multicomponent reactions, allows straightforward access to multifunctionalized DHPM compounds.[10] Recently, several examples of enantioselective Biginelli reactions in which asymmetric catalysis with either chiral metal complexes, BINOL-derived phosphoric acids, or chiral secondary amines was employed, have been described.[11,12] Although success has been achieved in these works, the design and synthesis of new catalysts remains an interesting challenge mostly due to ambiguity of the exact mechanism of the Biginelli reaction and the mode of chiral induction. During the development of enantioselective Biginelli reactions with organocatalysts, we realized that the understanding of the mode of chirality transfer is essential. To reach this goal, well designed experiments that offer pivotal evidence for characterizing the reaction mechanism are required.[13] Herein, we report on the asymmetric induction of the Biginelli reaction catalyzed by chiral secondary amine salts. Such salts have been applied to many asymmetric reactions as organocatalysts, and these applications have resulted in a number of successful asymmetric reactions through the formation of enamine-type intermediates.[14,15] However, in the Biginelli reactions for the synthesis of racemic mixture of DHPMs, Brønstead- or Lewis acids have been employed as catalysts to activate either the aldehyde or acylimine intermediate.[16] Furthermore, a recent report on the asymmetric Biginelli reaction suggested that proline-derived secondary amine and a Brønsted acid as the combined catalyst made the reaction proceed through a dual-activation route.[11e]

In the case of the asymmetric Biginelli reaction catalyzed by chiral secondary amine salts, there are three possible modes of activation methods which allow for asymmetric induction. These pathways are outlined in Figure 1: 1) the catalyst acts as chiral Brønstead acid to activate the acylimine generated by the condensation of aldehyde and urea (**A**);[17] 2) chiral enamine, which is produced by the reaction between the catalyst and β-keto ester, attacks stereoselectively onto the acylimine (**B**);[18] or 3) dual activation property

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(**C**).[11e] In order to get deeper insight into the mode of stereoinduction of the enantioselective reaction we employed a proline ester salt as organocatalyst.

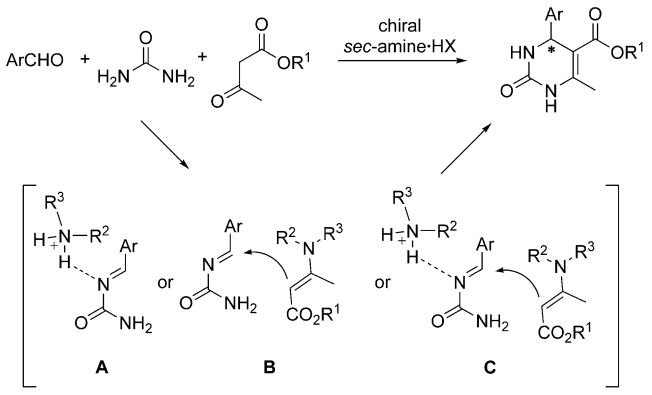


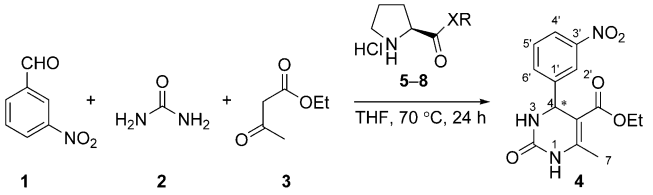

Figure 1. Three possible activation protocols leading to enantioselectivity with chiral secondary amine salt catalyst.

## Results and Discussion

Since the proline ester or its salt, to the best of our knowledge, has not been reported to be used in the enantioselective Biginelli reaction, we needed to investigate the eligibility of the proline ester or its salt for our purpose. The Biginelli reaction is not at all successful with proline ester catalyst but proceeds well with its hydrochloride salt. We carried out the reaction using HCl salts of methyl, isopropyl, and *tert*-butyl L-proline esters. The reaction mixture of *m*-nitrobenzaldehyde (**1**), urea (**2**), β-keto ester (**3**) and each catalyst in THF was allowed to stir at 70 °C for 24 h to afford an enantiomeric mixture of DHPM **4**.

While we were setting up the reaction protocol, we found out that the solubilities of the pure enantiomers and racemic mixtures of the products in organic solvents were dramatically different. For example, when the resulting reaction mixture was filtered and washed with diethyl ether after addition of water, the isolated product was a racemate (e.r. = 53:47) whereas the product solution in the diethyl ether filtrate was highly enantiomerically pure (e.r. = 99:1). When the extraction of products with organic solvents like diethyl ether or ethyl acetate was performed after the addition of water, low product yields with relatively high enantiomeric ratio (>90:10) were observed. Afterwards, it was confirmed that the racemic mixture was nearly insoluble in diethyl ether or ethyl acetate but the pure enantiomer was soluble in such solvents.[19] This finding is very important for the determination of enantiomeric ratios since the solubility differences among enantiomers, racemates, and mixtures of enantiomers can lead to false conclusions. The correct e.r. value without loss of either enantiomer was measured by dilution of the resulting reaction mixture with *i*PrOH, which converted the heterogeneous mixture to a homogeneous solution. The reaction yield was obtained by removal of the solvent from the diluted reaction mixture followed by the column chromatographic purification of the residue. Table 1 exhibits the final results of the Biginelli reaction using three ester salts. The enantioselectivity depends on the bulkiness of the ester group in the catalyst (entries 1–3). The enantiomeric ratio for *tert*-butyl ester **7** was 70:30 which is higher than either for methyl ester **5** (58:42) or isopropyl ester **6** (61:39), and the loading amount of catalyst insignificantly affected the enatioselectivity (entries 3–5). The *N*-*tert*-butyl amide **8** afforded lower enantioselectivity (e.r. = 58:42, entry 6). This result was quite unexpected but indicates that, along with the result from isopropylamide (e.r. ≈ 1:1), amides that are more rigid than esters, could not influence the enantioselectivity as much as esters. The enantiomeric ratio (70:30), generated by the *tert*-butyl ester salt **7**, is thought to provide a good starting point for mechanistic studies on the mode of asymmetric activation.

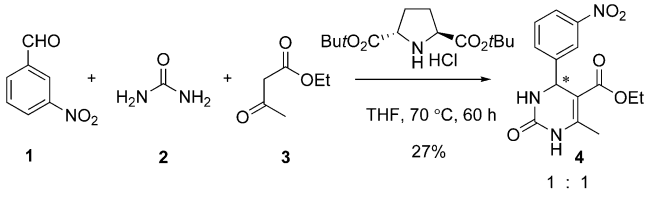
Table 1. Biginelli reaction catalyzed by the L-proline ester·HCl.




| Entry | XR | % Loading[a] | Ratio (*R*/*S*)[b] | % Yield[c] |
|---|---|---|---|---|
| 1 | MeO (**5**) | 10 | 58:42 | 82 |
| 2 | *i*PrO (**6**) | 10 | 61:39 | 85 |
| 3 | *t*BuO (**7**) | 10 | 70:30 | 87 |
| 4 | *t*BuO (**7**) | 20 | 71:29 | 83 |
| 5 | *t*BuO (**7**) | 30 | 70:30 | 83 |
| 6 | *t*BuNH (**8**) | 10 | 58:42 | 80 |

[a] mol-% of catalyst. [b] Ratio of crude product. Absolute configuration was determined by the comparison of the characteristic CD spectrum with DHPMs of known absolute configuration.[21] [c] Isolated yield.

At first, we carried out the Biginelli reaction with a $C_2$-symmetric proline derivative to provide the symmetric environment around the chiral amine catalyst.[20] To our surprise, the reaction did not proceed well and there was no enantioselectivity observed (Scheme 1). This result could mean that the 1,5-disubstituted pyrrolidine is not able to bind to the substrate effectively and thus did not provide any enantioinduction.



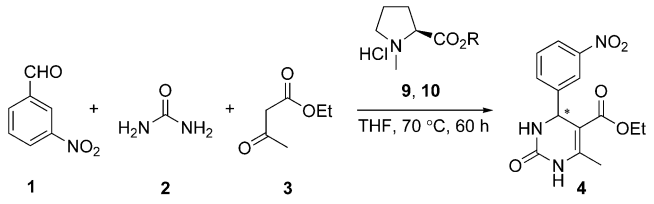

Scheme 1. Biginelli reaction catalyzed by proline derivative with $C_2$ symmetry.

To further probe the asymmetric induction, the *N*-methylated catalysts **9** and **10** were employed. If the proline ester salt catalysts act as Brønstead acids for the asymmetric induction with the activation of the acylimine, it was expected

that their *N*-methylated forms could give e.r. values ranging from racemic mixture to higher than that for catalyst **7**. On the other hand, if the enantioselectivity is generated due to the steric environment of chiral enamine species which attacks stereoselectively onto the acylimine, the reaction product should be racemic mixture since *tert*-amine cannot produce an enamine or iminium ion. The catalysts were each prepared by reductive amination of methyl or *tert*-butyl proline ester using NaOAc, paraformaldehyde and Pd/C under $H_2$ in MeOH, followed by formation of the hydrochloride salt.[22] When the mixture of *m*-nitrobenzaldehyde (**1**), urea (**2**), β-keto ester (**3**) was treated with catalyst **9** or **10** (10 mol-%) in THF and allowed to stir at 70 °C for 60 h, the DHPM obtained from the reaction was completely racemic in each case (Table 2). These results indicate that, for the asymmetric induction, the formation of an enamine species might be crucial; methylated proline derivatives cannot form enamine intermediates. Another observation from the reactions using *N*-methylated catalysts was that the reaction proceeded even without making enamine intermediates though slower than those using the corresponding secondary amine salts and could not provide the environment for asymmetric induction. This result also supports the findings for the $C_2$-symmetric catalyst which is not able to form an enamine species with **3**.

Table 2. The Biginelli reaction catalyzed by *N*-methylated proline ester salt.




| Entry | R | % Loading[a] | Ratio (*R*/*S*)[b] | % Yield[c] |
|---|---|---|---|---|
| 1 | Me (**9**) | 10 | 49.8:50.2 | n.d.[d] |
| 2 | *t*Bu (**10**) | 10 | 49.3:50.7 | 63% |

[a] mol-% of catalyst. [b] Ratio of crude product. [c] Isolated yield, reactions incomplete. [d] n.d.: not determined.

We next investigated the effect of the counter acid of the proline ester to confirm the asymmetric induction through the formation of enamine species. At first, the effect of various acid salts of proline was investigated. It turned out that acids with p$K_a$ values ranging from 0 to –8 ($CF_3CO_2H$ to HCl) show similar enantioselelctivities. The reaction did not proceed at all with weak acids like AcOH. These results support the enamine-mediated asymmetric induction since salts of weak acids would react too sluggish and salts of strong acids could compete with an acid-catalyzed reaction. Since chiral BINOL-derived phosphoric acids were reported to afford high enantioselectivity in Biginelli reaction,[11c] we employed this acid as the counter acid of proline derivatives. We designed experiments that would accomplish with catalysts consisting of combinations of L- or D-proline ester (**11** or **12**) and racemic or chiral BINOL phosphoric acid **13**.[11c] If only the enamine species are responsible for the asymmetric induction, the Biginelli reactions would afford e.r. values comparable to 70:30 for all cases of the combinations. If the Brønstead acid affects the asymmetric induction or the dual activation operates the reaction would result in unpredictable e.r. values (Figure 2).

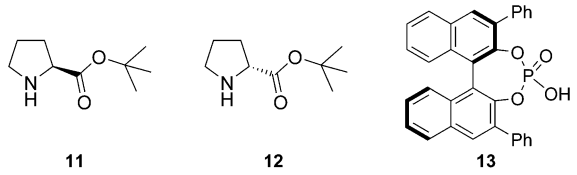
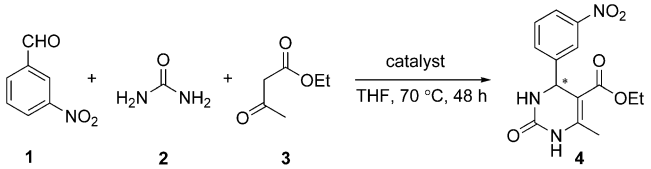



Figure 2. L,D-proline ester and BINOL-phosphoric acid for combined catalysts.

With the necessary elements for the combined catalysts in hand, we made five combination sets of proline derivatives and BINOL-phosphoric acids, and carried out the Biginelli reaction. The reaction mixture of *m*-nitrobenzaldehyde (**1**), urea (**2**), β-keto ester (**3**) was treated with catalyst (10 mol-%) in THF and allowed to stir at 70 °C for 48 h to afford DHPM **4** in good yield (≥ 80%). Table 3 displays the results. BINOL-phosphoric acid **13** alone gave e.r. = 58:42, and this lower value, compared to those reported, is presumably caused by the higher reaction temperature (entry 1). As anticipated, the hydrochloride of D-proline ester, **12**·HCl, afforded an e.r. opposite to that produced by its enantiomer (entry 2). The results, showing that catalysts **11**·*rac*-**13** or **11**·**13** provided a similar e.r. to catalyst **7** (e.r. = 7:3), obviously indicate that the enantioselectivity in the Biginelli reaction stems from the steric environment of the chiral enamine species, while also ruling out the role of the catalyst as chiral Brønstead acid or the dual activation pathway (entries 3 and 4). This fact was confirmed by another experiment using the D-proline-based catalyst **12**·**13**, which gave the e.r. value that is the same value but opposite sign to that for catalysts **7** or **11**·**13**.

Table 3. Biginelli reaction using catalysts consisting of L- or D-proline ester and BINOL-phosphoric acid.




| Entry | Combination | % Loading[a] | Ratio (*R*/*S*)[b] | % Yield[c] |
|---|---|---|---|---|
| 1 | **13** | 10 | 58:42 | > 80 |
| 2 | **12**·HCl | 10 | 32:68 | > 80 |
| 3 | **11**·*rac*-**13** | 10 | 67:33 | 80 |
| 4 | **11**·**13** | 10 | 69:31 | > 80 |
| 5 | **12**·**13** | 10 | 32:68 | > 80 |

[a] mol-% of catalyst. [b] Ratio of crude product. [c] Isolated yield.

Based on the results exhibited in Tables 2 and 3, we assume that the reaction promoted by the proline ester salt that act as Brønstead acids is a rather slow background

reaction (slower than the enamine formation) and results in deterioration of the enantioselectivity.

## Conclusions

Studies on the mechanism of the asymmetric Biginelli reaction using different proline ester salts as catalysts reveal that the steric environment of the chiral enamine formed by the condensation of β-keto ester with the catalyst is most responsible for the observed enantioselectivity (path B in Figure 1).

## Experimental Section

**General Procedure for the Biginelli Reaction:** A microreactor was charged with a mixture of aldehyde **1** (0.2 mmol), urea **2** (1.2 equiv.), acetoacetate **3** (1.0 equiv.) and L-proline-based catalyst (10 mol-%) in THF (0.5 mL), and sealed. After stirring for 24 h at 70 °C, the resulting suspension was diluted with *i*PrOH until it turned to homogeneous solution. The e.r. value was determined by HPLC (Daicel Chirapak AD-H, *n*-hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min): $t_R$ = 10.26 {*R* form, $[\alpha]_D^{25}$ = –154.0 (*c* = 0.105, MeOH)}, $t_R$ = 13.46 (*S* form). The mixture was concentrated under reduced pressure and purified by silica gel column chromatography to afford DHPM **4**. $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.35 (s, 1 H, 1-H), 8.13 (dd, *J* = 1.4, 7.8 Hz, 1 H, 4′-H), 8.07 (s, 1 H, 2′-H), 7.88 (s, 1 H, 3-H), 7.70–7.62 (m, 2 H, 5′-H and 6′-H), 5.29 (d, *J* = 3.3 Hz, 2 H, 4-H), 3.99 (m, 2 H, OC*H*$_2$Me), 2.26 (s, 3 H, 7-H), 1.08 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$) ppm. $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 165.0, 151.8, 149.4, 147.7, 147.0, 133.0, 130.2, 122.3, 121.0, 98.3, 59.4, 53.5, 17.8, 14.0 ppm.

**Supporting Information** (see also the footnote on the first page of this article): $^1$H NMR, $^{13}$C NMR, and CD spectra of DHPM **4**.

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