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An Enantioselective Biginelli Reaction Catalyzed by a Simple Chiral Secondary Amine and Achiral Brønsted Acid by a Dual-Activation Route

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Abstract: An enantioselective Biginelli reaction that proceeds by a dual-activation route has been developed by using a combined catalyst of a readily available *trans*-4-hydroxyproline-derived secondary amine and a Brønsted acid. Aromatic, heteroaromatic, and fused-ring aldehydes were found to be suitable substrates for this multicomponent reaction. The corresponding dihydropyrimidines were obtained in moderate-to-good yields with up to 98% *ee* under mild conditions. Based on the experimental results and the observed absolute configurations of the products, a plausible transition state has been proposed to explain the origin of the activation and the asymmetric induction.

Keywords: asymmetric catalysis · Biginelli reaction · dual activation · multicomponent reactions · pyrimidines · reaction mechanisms

Introduction

In recent years, optically active dihydropyrimidine (DHPM) derivatives have attracted considerable attention because of their important pharmacological and biological properties[1a–d] as well as their use in analytical chemistry.[1e] The Biginelli reaction,[2] one of the most useful multicomponent reactions,[3] allows straightforward access to multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones and related compounds.[4] Besides chemical resolution and auxiliary-assisted asymmetric synthesis,[5] only a few examples of the enantioselective synthesis of these heterocyclic compounds have been reported.[6] Despite the importance of preparing chiral dihydropyrimidines, to the best of our knowledge, just two chiral catalyst systems catalyze this reaction efficiently. The breakthrough in the catalytic asymmetric Biginelli reaction was realized by Zhu and co-workers with a chiral hydrogenated salen–ytterbium complex.[7] The other catalytic system was Gong and co-worker's BINOL-derived phosphoric acid, which was the first organocatalyst used in this multicomponent reaction.[4h,8] Although great success has been achieved in previous work, the design and synthesis of new catalysts remains an interesting challenge. Herein we report an organocatalytic asymmetric Biginelli reaction that involves the use of a simple chiral secondary amine and a Brønsted acid as a combined catalyst, a reaction that proceeds by a dual-activation route. The reactions afforded various DHPMs with good-to-excellent enantioselectivities, particularly those reactions involving aldehydes bearing electron-donating groups.

Chiral secondary amines have undoubtedly been the most successful catalysts in enamine-type reactions, and a number of asymmetric reactions catalyzed by chiral secondary amines have been reported.[9,10] In the light of these successes and with knowledge of the mechanism of the Biginelli reaction,[4a] we assumed that the combination of a secondary amine and a Brønsted acid could promote the asymmetric Biginelli reaction through a dual-activation pathway.[11,12] As shown in Scheme 1, *N*-acylimine **5** activated by a Brønsted acid would be attacked by chiral enamine **6** generated from amine **8** and 1,3-keto ester **3** to provide enantioenriched product **4** via the intermediate **9**.

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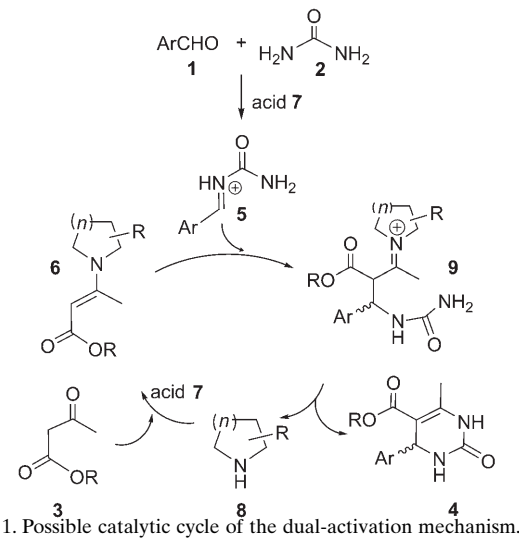


Scheme 1. Possible catalytic cycle of the dual-activation mechanism.

Results and Discussion

Initially, the catalytic asymmetric Biginelli reaction of benzaldehyde, urea, and ethyl acetoacetate was carried out with L-proline-derived amine **8a** and trifluoroacetic acid (TFA) at room temperature in THF. The reaction proceeded to give DHPM **4aa** in a yield of 32% with 9% *ee* (Table 1, entry 1). Although the enantioselectivity was low, this result encouraged us to further optimize the catalyst scaffold. The efficacy of a series of chiral secondary amines derived from various amino acids **8a–k** was evaluated in the presence of TFA. As shown in Table 1, both the amine and the amide moieties were important for the enantioselectivity of the reaction (Table 1, entries 1–10). Compared with L-proline and other amino acid derivatives, chiral amines derived from *trans*-4-hydroxyproline exhibited superior catalytic properties (Table 1, entries 1–3). With this backbone, bulkier amide-substituted amines gave higher enantioselectivities (Table 1, entries 4–10). In the presence of an amine with an adamantyl group (**8j**) and TFA, the reaction delivered **4aa** in a yield of 23% with 51% *ee* (Table 1, entry 10). When the hydroxy group on the pyrrole ring of **8j** was methylated, a low *ee* of **4aa** was observed, which further established the importance of the hydroxy group in the reaction (Table 1, entry 10 vs. 11). The amidic proton did not exert a significant influence on the enantioselectivity of the reaction (Table 1, entry 4 vs. 8). Therefore, on the basis of the results obtained from the reactions with amines **8a–k**, *trans*-4-hydroxyproline derivative **8j** was evidently the best choice for the present reaction system in terms of both enantioselectivity and reactivity. Furthermore, increasing the catalyst loading from 10 to 20 mol% did not affect the yield, but resulted in a lower *ee* (Table 1, entry 12). In contrast, the enantioselectivity (up to 71% *ee*) was greatly improved when the catalyst loading was decreased to 5 mol% (Table 1, entry 13).

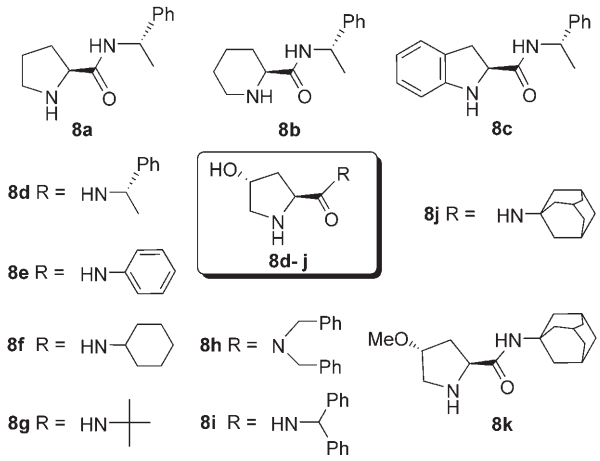
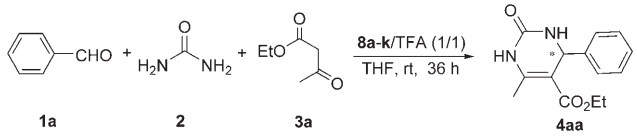


Table 1. Asymmetric Biginelli reaction catalyzed by the combined catalyst of a secondary amine and TFA.[a]

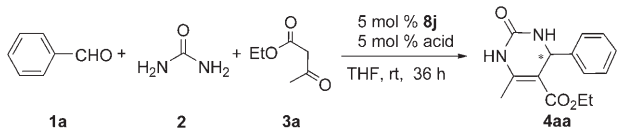


Entry	Amine	Loading [mol%]	Yield [%][b]	*ee* [%][c]
1	**8a**	10	32	9
2	**8b**	10	trace	<3
3	**8c**	10	trace	<3
4	**8d**	10	29	39
5	**8e**	10	37	13
6	**8f**	10	17	32
7	**8g**	10	20	36
8	**8h**	10	22	36
9	**8i**	10	25	23
10	**8j**	10	23	51
11	**8k**	10	25	9
12	**8j**	20	23	30
13	**8j**	5	22	71

[a] Reagents and conditions: After stirring a solution of amine **8** and TFA in THF (0.5 mL) at room temperature for 30 min, **2** (0.25 mmol), **1a** (0.25 mmol), **3a** (0.25 mmol), and THF (0.5 mL) were added sequentially. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralcel OD-H).

Various acids combined with **8j** were then employed to catalyze the reaction (Table 2). Compared with TFA and other sulfonic acids, 4-methylbenzenesulfonic acid (**7b**) provided the best results (Table 2, entries 1–4). Further experiments revealed that, under the same experimental conditions, the enantioselectivity of the reaction could be further improved to 81% by using 3,5-dinitrobenzoic acid, although the yield of **4aa** was poor (Table 2, entry 5). To our delight, screening of differently substituted benzoic acids indicated that 2-chloro-4-nitrobenzoic acid (**7g**) was favorable in terms of reactivity, and the enantioselectivity was maintained as well (Table 2, entries 5 and 7). The optimized results shown in Table 2 clearly demonstrate the advantage of electron-withdrawing-substituted benzoic acids over sulfonic

Table 2. Investigation of Brønsted acids.[a]



1a 2 3a 4aa

Entry[b]	Acid	Yield [%][c]	*ee* [%][d]
1	TFA (**7a**)	22	71
2	*p*-TSA (**7b**)	26	76
3	*D*-CSA (**7c**)	13	66
4	*p*-NH_2-benzenesulfonic acid (**7d**)	15	71
5	3,5-dinitrobenzoic acid (**7e**)	8	81
6	2-nitrobenzoic acid (**7f**)	11	80
7	2-chloro-4-nitrobenzoic acid (**7g**)	22	81
8	4-methoxybenzoic acid (**7h**)	n.r.	–

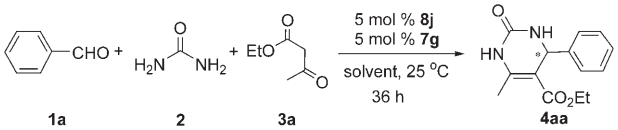
[a] Reagents and conditions: After stirring a solution of **8j** (5 mol%) and acid (5 mol%) in THF (0.5 mL) at room temperature for 30 min, **2** (0.25 mmol), **1a** (0.25 mmol), **3a** (0.25 mmol), and THF (0.5 mL) were added sequentially. [b] *p*-TSA = 4-methylbenzenesulfonic acid; D-CSA = D-camphorsulfonic acid. n.r. = no reaction. [c] Yield of isolated product. [d] Determined by HPLC analysis (Chiralcel OD-H).

acids and TFA in the control of enantioselectivity which probably results from the substituted benzoic acids in this reaction system having an appropriate acidity. Moreover, the acidity of the benzoic acids, adjusted by different substituents, could further affect the reaction yield (Table 2, entries 5–7). The fact that the reaction with 4-methoxybenzoic acid did not yield any of the corresponding product somewhat supported this hypothesis (Table 2, entry 8).

Optimization of other reaction parameters with the combined catalyst of **7g** and **8j** led to further improvement in enantioselectivity. Slightly better results were achieved by adjusting the experimental procedure; compound **4aa** was obtained in a yield of 27% with an 85% *ee* (Table 3, entry 1 vs. 2). In addition, solvent effects were studied. The use of polar solvents such as DMSO and 2-propanol almost prevented the reaction (Table 3, entries 3 and 4). In anisole and CH_2Cl_2, the reaction proceeded without any improvement in terms of both enantioselectivity and yield (Table 3, entries 5 and 6). Interestingly, the reaction in 1,4-dioxane gave the best *ee* (up to 90%), but the yield dropped dramatically (Table 3, entry 7). Therefore, mixed solvents were screened and revealed that the best results were obtained in 1,4-dioxane/THF (2:8, v/v) as compared with neat solvents or another mixed solvent (Table 2, entries 8 and 9).

To further improve the reactivity and enantioselectivity, the effect of additives was investigated. Although a significantly decreased *ee* was obtained by adding *p*-TSA, the yield was improved significantly (Table 4, entry 1). In contrast, addition of 1-adamantanamine favored the enantioselectivity but the yield was dramatically reduced (Table 4, entry 2). Inspired by these results, the effect of organic amine salts as additives was surveyed. To our delight, the combination of *p*-TSA and 1-adamantanamine indeed improved the yield of the reaction, although a little loss of enantioselectivity was observed (Table 4, entry 3). Similar results were obtained when other *p*-TSA salts, including primary, secondary, and tertiary amines, were investigated (Table 4, entries 4–6). Fortunately, after further screening the acidic component of the *t*$BuNH_2$ salt, it was found that employment of *t*$BuNH_2$·TFA gave superior results in terms of reactivity and enantioselectivity (45% yield, 86% *ee*, Table 4, entry 8). The yield could be improved to 60% by prolonging the reaction time and increasing the amount of urea and 1,3-keto ester, albeit with 80% *ee* (Table 4, entry 9). Accordingly, extensive screening has shown that the optimized catalytic reaction conditions are 0.25 mmol aldehyde, 1.2 equiv urea, 2.0 equiv 1,3-keto ester, 5 mol% **7g**,

Table 3. Optimization of conditions for the asymmetric Biginelli reaction.

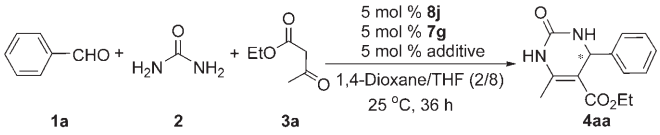


1a 2 3a 4aa

Entry	Solvent	Method[a]	Yield [%][b]	*ee* [%][c]
1	THF	A	22	81
2	THF	B	27	85
3	DMSO	B	trace	n.d.
4	2-propanol	B	trace	n.d.
5	anisole	B	14	63
6	CH_2Cl_2	B	26	80
7	1,4-dioxane	B	trace	90
8	CH_2Cl_2/THF (2:8)	B	25	82
9	1,4-dioxane/THF (2:8)	B	28	88

[a] Method A: After stirring a solution of **8j** (5 mol%) and **7g** (5 mol%) in THF (0.5 mL) at 25°C for 30 min, **2** (0.25 mmol), **1a** (0.25 mmol), **3a** (0.25 mmol), and THF (0.5 mL) were added sequentially. Method B: After stirring a solution of **1a** (0.25 mmol), **2** (0.25 mmol), and **7g** (5 mol%) in solvent (1.0 mL) at 25°C for 30 min, **8j** (5 mol%) and **3a** (0.25 mmol) were added sequentially. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralcel OD-H). n.d. = not determined.

Table 4. Screening additives for the reaction.[a]



1a 2 3a 4aa

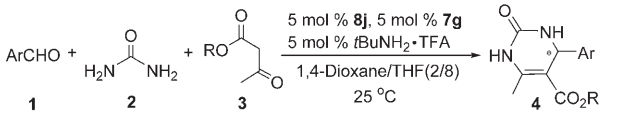
Entry	Additive	Yield [%][b]	*ee* [%][c]
1	*p*-TSA	49	60
2	1-adamantanamine	12	89
3	1-adamantyl-NH_2·*p*-TSA	43	83
4	piperidine·*p*-TSA	37	83
5	Et_3N·*p*-TSA	38	83
6	*t*$BuNH_2$·*p*-TSA	43	85
7	*t*$BuNH_2$·HCl	34	85
8	*t*$BuNH_2$·TFA	45	86
9[d]	*t*$BuNH_2$·TFA	60	80

[a] Reagents and conditions: After stirring a solution of **1a** (0.25 mmol), **2** (0.25 mmol), **7g** (5 mol%), and additive (5 mol%) in solvent (1.0 mL) at 25°C for 30 min, **8j** (5 mol%) and **3a** (0.25 mmol) were added sequentially. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralcel OD-H). [d] The reaction was carried out with a reaction time of 60 h and a **1a**/**2**/**3a** ratio of 1:1.2:2.

5 mol% **8j**, and 5 mol% *t*BuNH$_2$·TFA in 1.0 mL 1,4-dioxane/THF (2:8, v/v) at 25 °C.

With the optimized conditions, the substrate scope of the reaction was probed (Table 5). The corresponding DHPM derivatives were obtained in moderate-to-good yields with up to 98% *ee*. As shown in Table 5, both the electronic and

Table 5. Scope of the organocatalytic enantioselective Biginelli reaction.[a]



3a R = Et, **3b** R = iPr, **3c** R = Me

Entry	Ar	R	**4**	*t* [d]	Yield [%][b]	*ee* [%][c]
1	C_6H_5 (**1a**)	Et	**4aa**	2.5	60	80 (*R*)[d]
2[e]	3-ClC_6H_4 (**1b**)	Et	**4ba**	4	46	77 (*R*)
3[f]	3-MeC_6H_4 (**1c**)	Et	**4ca**	5.5	73	98 (*R*)
4	4-MeC_6H_4 (**1d**)	Et	**4da**	5.5	56	71 (*R*)
5[f]	3-MeOC_6H_4 (**1e**)	Et	**4ea**	6	68	98 (*R*)
6	3-HOC_6H_4 (**1f**)	Et	**4fa**	3.5	54	73 (*R*)[d]
7[f]	1-naphthyl (**1g**)	Et	**4ga**	6.5	60	97
8[f]	2-thiophene (**1h**)	Et	**4ha**	3	34	70
9	C_6H_5 (**1a**)	*i*Pr	**4ab**	3	61	77 (*R*)
10[f]	3-MeC_6H_4 (**1c**)	*i*Pr	**4cb**	6.5	60	83 (*R*)
11[f]	2-naphthyl (**1i**)	*i*Pr	**4ib**	5	62	72
12[f]	piperonal (**1j**)	*i*Pr	**4jb**	4.5	46	80 (*R*)
13[e]	4-BrC_6H_4 (**1k**)	*i*Pr	**4kb**	6.5	57	75 (*R*)
14[f]	3-MeOC_6H_4 (**1e**)	Me	**4ec**	6.5	50	97 (*R*)
15	3-MeC_6H_4 (**1c**)	Me	**4cc**	5.5	62	71 (*R*)

[a] Reagents and conditions: After stirring a solution of **7g** (5 mol%), *t*BuNH$_2$·TFA (5 mol%), **1** (0.25 mmol), and **2** (0.3 mmol) in 1,4-dioxane/THF (2:8, v/v, 1.0 mL) at 25 °C for 30 min, **8j** (5 mol%) and **3** (0.5 mmol) were added sequentially. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralcel OD-H or AD-H). The absolute configurations were assigned by comparing the Cotton effect of the CD spectra with that of **4aa**. [d] The absolute configuration was determined by comparison of the optical rotation with the literature.[7] [e] *t*BuNH$_2$·TFA was not used and the amount of **7g** and **8j** was 2.5 mol%. [f] The amount of **7g**, **8j**, and *t*BuNH$_2$·TFA used was 10 mol%.

steric effects of the aromatic ring have a significant influence on the enantioselectivity. In most cases, aromatic aldehydes with electron-donating groups at the *meta* position (Table 5, entries 3, 5, 10, and 14) afforded excellent enantioselectivities (83–98% *ee*).[13] In contrast, *p*-methylbenzaldehyde (**1d**) gave a moderate *ee* (Table 5, entry 4). Excellent enantioselectivity was obtained when fused-ring 1-naphthalenecarbaldehyde (**1g**) was employed (Table 5, entry 7). The reactions were also applied to hydroxy-substituted benzaldehyde **1f** and heteroaromatic aldehyde **1h**; enantioselectivities of 73 and 70%, respectively, were obtained, (Table 5, entries 6 and 8). For aromatic aldehydes bearing electron-withdrawing groups, moderate enantioselectivities were achieved by using 2.5 mol% catalyst in the absence of additive (Table 5, entries 2 and 13). Isopropyl (**3b**) and methyl 3-oxobutanoate (**3c**) gave similar results to 1,3-keto ester **3a** (Table 5, entries 9–15).

To determine the absolute configurations of the products, the CD spectra of **4aa–4fa, 4ab**, **4cb**, and **4jb–4cc** were measured in EtOH (see the Supporting Information). These compounds all exhibited a similar Cotton effect in their CD spectra. It can be deduced, therefore, that these compounds possess the same *R* configuration as (−)-**4aa**.[7]

The involvement of both a Brønsted acid and a secondary amine in this multicomponent reaction was quite crucial as neither **7g** nor **8j** alone could catalyze the formation of DHPM efficiently.[14] The achiral acid **7g** might not only favor the formation of the *N*-acylimine **5** and the enamine intermediate **6** in Scheme 1, but may also serve to activate the *N*-acylimine **5** and participate in the asymmetric induction of the reaction. Based on the observed absolute configurations of the products and the discussion above, we have proposed a possible transition state that requires dual activation in the asymmetric-induction step (Figure 1).[15] In this

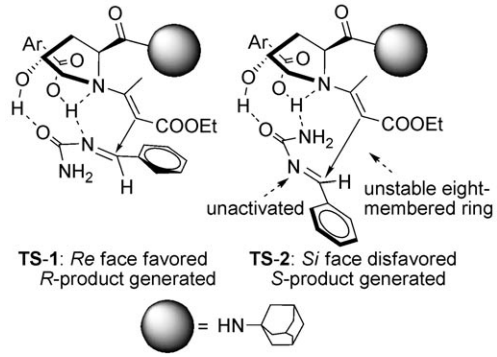


Figure 1. Proposed transition state in the asymmetric Biginelli condensation reaction.

transition state (**TS-1**), one face of the enamine was efficiently shielded by the steric hindrance of the bulky adamantyl amide moiety, whereas the other face was available to attack the imine. Favorable hydrogen-bonding interactions between the pyrrolic hydroxy group and the ureic carbonyl, and the nitrogen atom of the pyrrole, the proton of the Brønsted acid, and the *N*-acylimine moiety positioned the Brønsted acid activated imine moiety under the enamine, which allowed the enamine double bond to approach the *Re* face of the imine via a stable six-membered-ring transition state. Through this approach, the reaction resulted in the product with *R* configuration. We considered that for the strong interaction between the Brønsted acid and the nitrogen atom of pyrrole, a stronger acid was unfavorable for the formation of this hydrogen-bridged transition state. On the other hand, a weaker acid could not efficiently activate *N*-acylimine **5**. Hence, a Brønsted acid of suitable acidity is essential for this organocatalytic multicomponent reaction. In **TS-2**, when the *Si* face of the *N*-acylimine was directed towards the enamine an unstable eight-membered-ring transition state compared with **TS-1** was formed. In addition, unactivated *N*-acylimine might exhibit lower activity. Therefore, the generation of the *S* product was not favored.

Conclusion

In summary, we have developed an enantioselective multicomponent Biginelli reaction catalyzed by a *trans*-4-hydroxyproline-derived secondary amine and a Brønsted acid as the combined catalyst with an organic amino salt as additive, a reaction that proceeds through a dual-activation route. The reaction occurs with good-to-excellent *ee* values (up to 98%). Attractive features of the method include the ease of catalyst preparation, mild reaction conditions, and a broad substrate generality. A plausible transition state has been proposed to explain the origin of the activation and the asymmetric induction. Further studies focused on the design of more efficient catalysts for the enantioselective Biginelli reaction are underway.

Experimental Section

Typical procedure for the organocatalytic asymmetric Biginelli reaction: After stirring a solution of **7g** (2.6 mg, 5 mol%, 0.0125 mmol), *t*BuNH$_2$·TFA (2.4 mg, 5 mol%, 0.0125 mmol), benzaldehyde **1a** (25.0 μL, 0.25 mmol), and **2** (18.0 mg, 0.3 mmol, 1.2 equiv) in 1,4-dioxane/THF (2:8, v/v, 1.0 mL) at 25 °C for 30 min, **8j** (3.3 mg, 5 mol%, 0.0125 mmol) and **3a** (63.0 μL, 0.5 mmol, 2.0 equiv) were added sequentially. The reaction mixture was stirred at 25 °C for 2.5 days. Then, the crude product was purified by preparative TLC (petroleum ether/ethyl acetate, 2:3) to afford **4aa** (40 mg, 60% yield) as a white solid with 80% *ee*; $[\alpha]_D^{30} = -30.5$ ($c = 0.2$ in MeOH) {lit.:[7] 90% *ee*; $[\alpha]_D^{20} = -58$ ($c = 0.5$ in MeOH)}; m.p. 199–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.93$ (s, 1H), 7.33–7.28 (m, 5H), 5.65 (m, 1H), 5.41–5.40 (d, $J = 2.9$ Hz, 1H), 4.10–4.03 (m, 2H), 2.35 (s, 3H), 1.18–1.14 ppm (t, $J = 11.4$ Hz, 3H); HPLC (Chiralpak OD-H column, hexane/2-propanol 85:15, 1.0 mL min^{-1}): t_R (minor) = 7.860, t_R (major) = 9.634 min.

Acknowledgement

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[13] This phenomenon is very similar to Gong and co-worker's BINOL-derived phosphoric acid system, see ref. [8].

[14] The sole application of **7g** afforded trace amounts of **4aa**, whereas in the absence of **7g**, amine **8j** did not catalyze the reaction.

[15] For a previous report on the catalytic model involving *trans*-4-hydroxyprolinamide, see ref. [10m].

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