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BIFUNCTIONAL ORGANOCATALYST TO PROMOTE THE BIGINELLI REACTION UNDER MILD CONDITIONS

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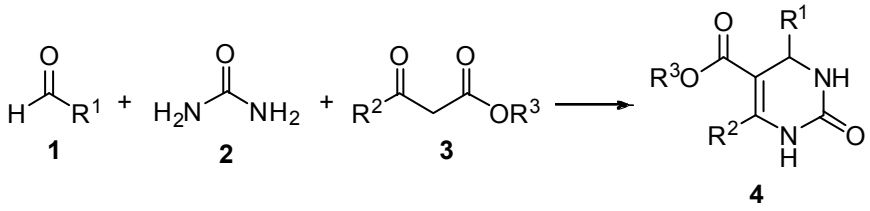
Abstract – Binaphthyl compounds, which include a pyridinium ion moiety as an acid and pyridine moiety as a base, have been synthesized and evaluated as bifunctional organocatalysts for the three-component Biginelli reaction. 3,3'-(2,2'-Dimethoxy-1,1'-binaphthyl-3,3'-diyl)dipyridine in the presence of equimolar amount of methanesulfonic acid catalyzed the Biginelli reaction to give the desired product in up to 79% yield even at 25 °C.

INTRODUCTION

Dihydropyrimidinone derivatives (DHPMs) have garnered considerable attention over the years because of their wide-ranging biological activities as calcium channel blockers and antihypertensive agents. The simple and direct method for the synthesis of DHPMs named as the Biginelli reaction[1] involves the one-pot three-component condensation of an aldehyde **1**, urea **2**, and β-ketoester **3** under strong acidic conditions (Scheme 1). In the 1990's this multicomponent reaction was considered a practical approach for the preparation of bioactive compounds. Therefore, numerous Brønsted and Lewis acids were employed to perform the Biginelli reaction.[2,3] However, strongly acidic conditions, high temperature, long reaction time, expensive reagents, and unsatisfactory yields were present in several of these procedures. With the explosion of interest in green chemistry in the 21st century, organocatalysis has grown rapidly as a new category of catalyst for organic transformations.[4] Recently, organocatalysts such as H8-binol-based phosphoric acid, chiral tetrazole, and prolineamide/Brønsted acid promoted the Biginelli reaction with excellent chemical yields and stereoselectivities.[5] As detailed in this report, we investigated a new bifunctional organocatalyst containing both Brønsted acid and Lewis base units in the single catalyst molecule to promote the Biginelli reaction.



Scheme 1. The Biginelli reaction

The positioning of the acid and base functionalities on the catalyst molecule should work synergistically to furnish the product. As shown in Figure 1, the acid moiety independently activates an acceptor; meanwhile, the base moiety activates a donor to form carbon-carbon bond. To activate two molecules simultaneously in a transition state, a specific distance is required between the acid and base functionalities; therefore, a biphenyl backbone was selected to fix conformation. In order to form single catalyst species, two identical pyridyl groups attached to the biphenyl backbone were designed as a pre-bifunctional organocatalyst (e.g. compound **9**). Addition of an equimolar amount of strong acid to the pre-organocatalyst forms the bifunctional organocatalyst which includes a pyridinium ion moiety (pKa = 3.4) as an acid and pyridine moiety as a base.

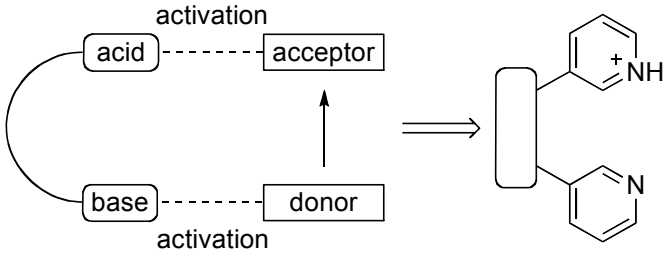
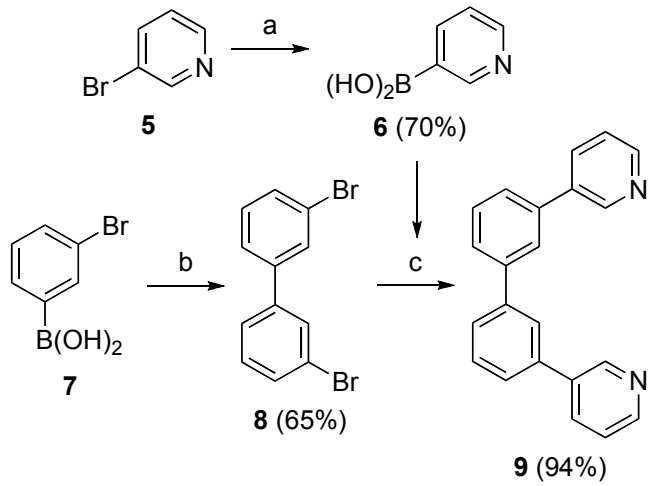


Figure 1. Catalyst design and double activation

RESULTS AND DISCUSSION

The preparation of 3,3'-di(pyridin-3-yl)biphenyl (**9**) is shown in Scheme 2. Pyridin-3-ylboronic acid (**6**) was obtained from 3-bromopyridine (**5**) in 70% yield according to Cai's procedure.[6] Oxidative dimerization of 3-bromophenylboronic acid (**7**) in the presence of copper(II) acetate as a catalyst furnished the symmetrical 3,3'-dibromobiphenyl (**8**).[7] Suzuki-Miyaura coupling of the bromide **8** with the boronic acid **6** afforded the desired compound **9** in 94% yield.[8]

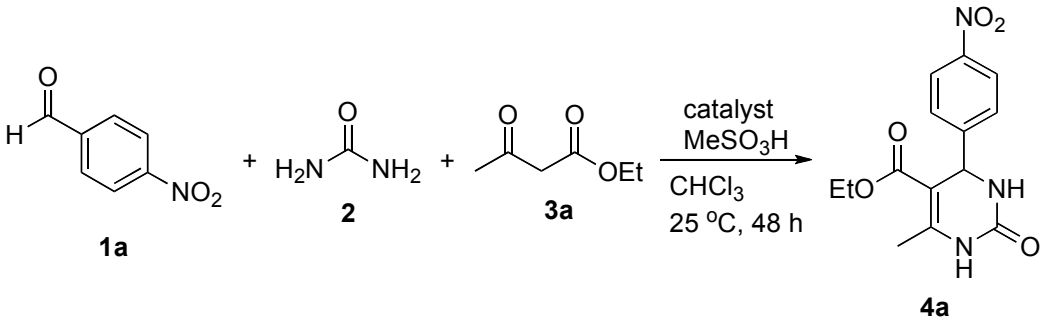
4-Nitrobenzaldehyde (**1a**), urea (**2**), and ethyl acetoacetate (**3a**) were used as model substrates in the Biginelli reaction. The reactions were performed in $CHCl_3$ and results are summarized in Table 1. Methanesulfonic acid was used as a co-catalyst. This co-catalyst is usually an efficient catalyst in the Biginelli reaction under reflux conditions;[9] however, at 25 °C, the desired product **4a** was obtained in only 15% yield (entry 1). The catalyst **9** in the presence of equimolar methanesulfonic acid afforded the Biginelli product **4a** in slightly better yield (entry 2), whereas, catalyst complex (**9**/$MeSO_3H$ = 1:2) gave



Scheme 2. Reagents and conditions: (a) (i) *n*-BuLi, toluene, -60 °C, 2 h, (ii) triisopropyl borate, toluene/THF, -60 to -15 °C, 4 h, (iii) 2.7N HCl aq, rt, 15 min; (b) $Cu(OAc)_2$, DMF, 100 °C, 1 h; (c) **6**, $Pd(PPh_3)_4$, $Ba(OH)_2 \cdot 8H_2O$, 1,4-dioxane / H_2O, reflux, 24 h.

the product **4a** in 5% yield (entry 3). To confirm the beneficial effects of the bipyridyl moiety of catalyst **9**, pyridine was used for catalysis of the Biginelli reaction. Pyridine (0.3 eq)/sulfonic acid (0.3 eq) catalyst showed very low reactivity to give the product **4a** in 4% yield (entry 4). The same result was observed when pyridine (0.6 eq)/sulfonic acid (0.3 eq) catalyst was used (entry 5). These results suggested that a pyridinium cation as acid moiety and pyridine as base moiety in the catalyst **9** cooperatively catalyzed the Biginelli reaction. However, reactivity was very low, unreacted imine derived from the aldehyde **1a** and urea **2** were the main products recovered.

Table 1. Biginelli reactions using the bipyridyl catalyst **9**[a]



Entry	Catalyst	Equiv.	Yield (%)[b]
1	none	-	15
2	**9**	0.3	18
3[c]	**9**	0.3	5
4	pyridine	0.3	4
5	pyridine	0.6	4

[a] Reactions were carried out using the aldehyde (**1a**, 0.2 mmol), urea (**2**, 0.3 mmol), and ethyl acetoacetate (**3a**, 0.2 mmol) in the presence of a catalyst (0.06 mmol) and methanesulfonic acid (0.06 mmol) in $CHCl_3$ (0.2 mL) at 25 °C for 48 h, otherwise noted. [b] Isolated yield. [c] Methanesulfonic acid (0.12 mmol) was used.

Low reactivity was presumed to be caused by free rotation around phenyl-phenyl bond. Cis-conformation of **9** activates both the donor and acceptor; on the other hand, the trans-conformer **9** does not activate them in a transition state (Figure 2). To restrict free rotation around phenyl-phenyl bond we designed a modified catalyst **10**, in which two pyridyl groups are attached to the binaphthyl backbone.

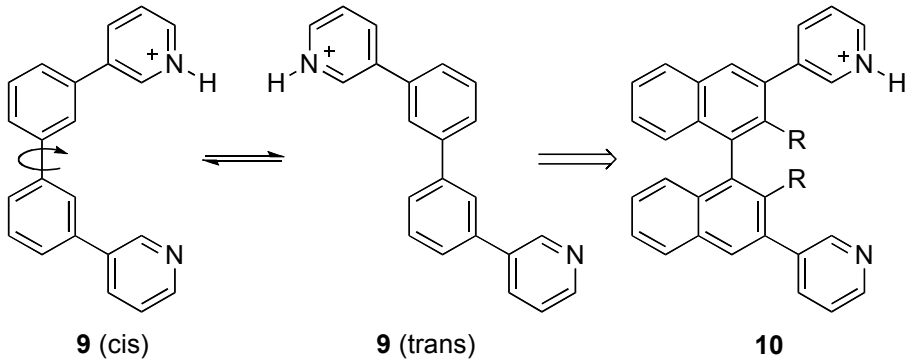
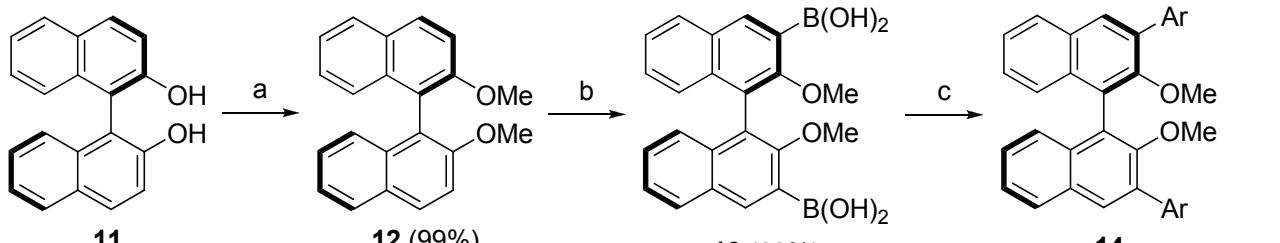


Figure 2. Free rotation around phenyl-phenyl bond and modified catalyst design

Synthesis of 2,2'-dimethoxy-3,3'-diaryl-1,1'-binaphthyl derivatives **14** is shown in Scheme 3.[8b] Methylation of binaphthol **11** gave the ether **12** in 99% yield. The boronic acid **13** was synthesized from the ether **12** in 63% yield under standard reaction conditions. Suzuki-Miyaura coupling of aryl bromide with the boronic acid **13** catalyzed by $Pd(PPh_3)_4$ under reflux in 1,4-dioxane / H_2O afforded the desired pre-catalysts **14** in more than 80% yields except **14d** in 51% yield.

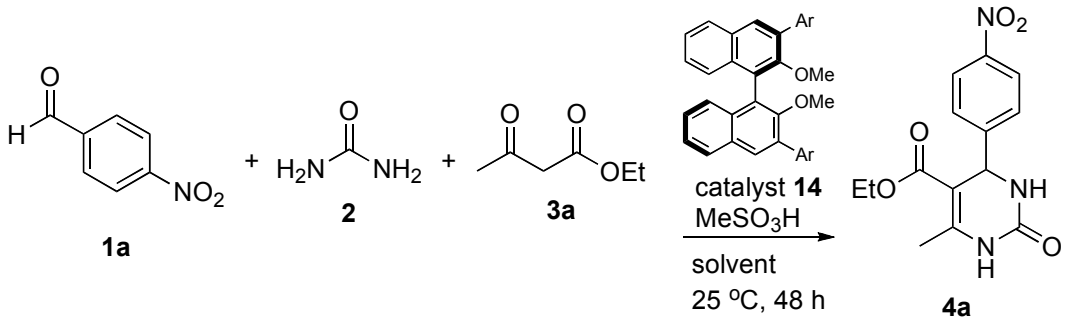


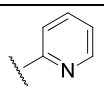
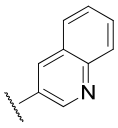
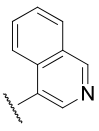
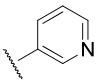
Scheme 3. Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 17 h; (b) (i) *n*-BuLi, TMEDA, Et_2O, rt, 5 h, (ii) $(EtO)_3B$, −78 °C - rt, 17 h; (iii) HCl aq, rt, 2 h; (c) ArBr, $Pd(PPh_3)_4$, $Ba(OH)_2$, 1,4-dioxane / H_2O, reflux, 24 h.

Biginelli reactions using these modified organocatalysts **14** were subsequently examined (Table 2). 2-Pyridyl derivative **14a**/$MeSO_3H$ catalyzed the reaction to give the Biginelli product **4a** in 26% yield (entry 1). As expected, the binaphthyl backbone is superior to a biphenyl backbone (catalyst **14** vs. **9**). Chemical yield was slightly improved by using 3-pyridyl derivative **14b**/$MeSO_3H$ as a catalyst (entry

2).[10, 11] Interestingly, 4-pyridyl derivative **14c**/$MeSO_3H$ did not provide the Biginelli product **4a** at all (entry 3). The position of the pyridine ring is very important to catalyze the reaction. 3-Quinolinyl group **14d** and 4-isoquinolinyl group **14e** were also effective in catalyzing the reaction, affording the product **4a** in 38% and 27% yield, respectively (entries 4 and 5). Using **14b** as the primary catalyst, a series of different solvent systems were evaluated. Acetonitrile and tetrahydrofuran were inferior solvents in terms of product yield (entries 6 and 7). Alcohol solvents such as MeOH and EtOH showed similar reactivity to $CHCl_3$ (entries 8 and 9).

Table 2. Biginelli reactions using binaphthyl catalysts **14**[a]



Entry	Catalyst **14**	Ar	Solvent	Yield (%)[b]
1	**14a**		$CHCl_3$	26
2	**14b**		$CHCl_3$	29
3	**14c**		$CHCl_3$	<1
4	**14d**		$CHCl_3$	38
5	**14e**		$CHCl_3$	27
6	**14b**		MeCN	1
7	**14b**		THF	6
8	**14b**		MeOH	27
9	**14b**		EtOH	20

[a,b] See Table 1.

All of the reactions were carried out as a suspension due to low solubility of urea **2** and the imine **15** derived from the aldehyde **1a**, this is probably a reason for low reactivity. However, our bifunctional catalyst proved more effective than previously reported conventional catalysts. For example, Brønsted

acid and Lewis acid such as NH_4Cl,[12] LiBr,[13] and $CeCl_3 \cdot 7H_2O$[14] are known as a good catalysts for the Biginelli reaction at reflux conditions, but at 25 °C low chemical yields (0-5%) were observed.

The mechanism of the three-component Biginelli reaction was reinvestigated by Kappe,[15] in which an *N*-acyliminium ion is the key intermediate, formed by acid-catalyzed condensation of aryl aldehyde and urea. Interception of this iminium ion by ethyl acetoacetate produces open-chain ureides which subsequently cyclize to the dihydropyrimidinones. In our system, the imine intermediate **15** derived from aldehyde **1** and urea **2** is activated by the pyridinium acid moiety to form *N*-acyliminium ion, and acetoacetate is activated by pyridine base moiety to form the ammonium enolate. Using 3-pyridyl derivative **14b**/$MeSO_3H$ as a bifunctional organocatalyst, these active species effectively make a carbon-carbon bond (Figure 3, left). On the other hand, distance between acyliminium ion and ammonium enolate in 4-pyridyl derivative **14c**/$MeSO_3H$ catalysis is too far away to undergo catalysis (Figure 3, right), therefore, no formation of Biginelli product is observed (Table 2, entry 3).

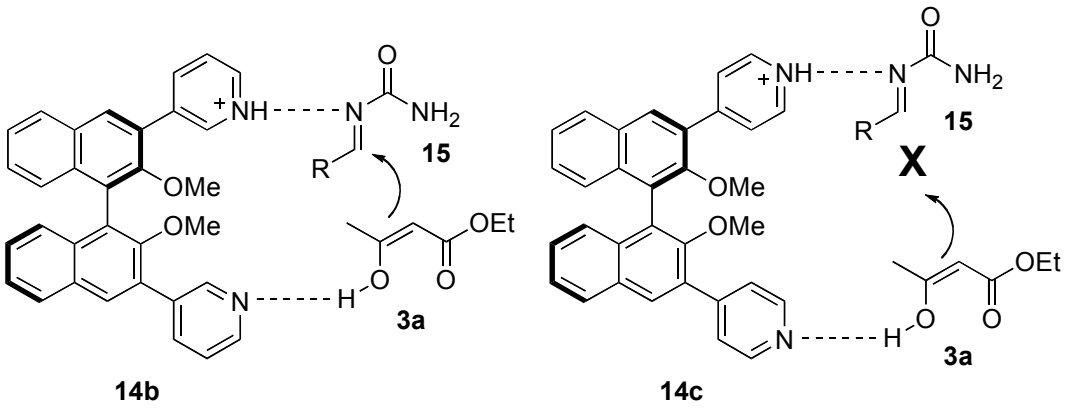
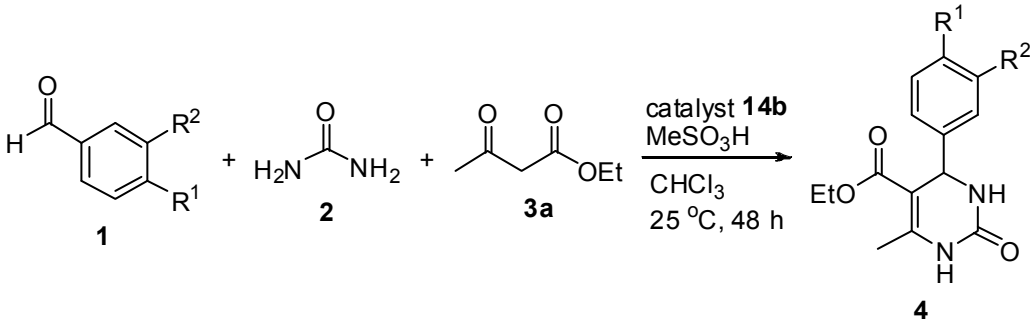


Figure 3. Proposed transition state

Encouraged by these results, we further examined the scope of this class of Biginelli reactions by utilizing a series of aldehydes **1** with 3-pyridyl derivative **14b**/$MeSO_3H$ catalyst under the same reaction conditions (Table 3). Benzaldehyde (**1b**) was a good substrate: the reaction provided the Biginelli product **4b** in 79% yield (entry 2). The reactions of *p*-hydroxybenzaldehyde (**1c**), *p*-methoxybenzaldehyde (**1d**), and piperonal (**1e**) afforded the corresponding product **4** in moderate to good yield (entries 3-5). Electron withdrawing groups including nitro and chloro decreased reactivity furnishing the Biginelli product **4** in low chemical yields (entries 1 and 6).

In summary, we have developed an improved bifunctional organocatalyst for the three-component Biginelli reaction. Chemical yields of the desired products are not as high as desired, however; our double activation strategy presents wide-ranging biological active products under mild reaction conditions, including 25 °C. Correct positioning of the acid-base functionalities on the catalyst molecule is crucial for promoting the reaction.

Table 3. Biginelli reactions using binaphthyl catalyst **14b**[a]



Entry	R^1	R^2	Product	Yield (%)[b]	Entry	R^1	R^2	Product	Yield (%)[b]
1	NO_2	H	**4a**	29	4	OMe	H	**4d**	45
2	H	H	**4b**	79	5	-OCH_2O-		**4e**	61
3	OH	H	**4c**	67	6	Cl	H	**4f**	21

[a,b] See Table 1.

EXPERIMENTAL

General. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates (Merck 60 F_{254}) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash column chromatography was performed using KANTO silica gel 60N (particle size 63-210 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-AL spectrometer at ambient temperature. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at ambient temperature. TMS served as internal standard (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ was used as internal standard (δ = 77.0) for ^{13}C NMR. Infrared spectra were recorded on a SHIMADZU FTIR-8200A spectrometer. Mass spectra were recorded on a SHIMADZU GCMS-QP5050 spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-T100LP. HPLC was carried out using a JASCO PU-2089 Plus intelligent pump, JASCO UV-2075 Plus detector, and JASCO BORWIN Chromatography Software.

Pyridin-3-ylboronic acid (6).[6] Toluene (1.1 mL) in a 30 mL flask was cooled down to −60 °C. *n*-BuLi (1.6 M in hexane, 0.71 mL, 1.1 mmol) was mixed with the toluene. After the internal temperature reached −60 °C, a solution of 3-bromopyridine (**5**, 0.1 mL, 1.0 mmol) in toluene (0.5 mL) was added. The internal temperature was maintained under −50 °C by controlling the rate of addition. A yellow solid precipitated. The resulting slurry was aged for 40 min, then THF (0.4 mL) was added slowly, keeping the internal temperature under −50 °C. The mixture was aged for 30 min, then triisopropyl

borate (0.28 mL, 1.2 mmol) was added over 3 min. The solids dissolved and a brown homogeneous solution was obtained. The reaction solution was warmed to −15 °C and quenched with 2.7N HCl (1.0 mL). The phases were separated and organic layer was washed with water (3×1 mL). The aqueous layers were combined, neutralized with 10N NaOH (1.9 mL) to pH 7, and extracted with THF (3×1 mL). The organic layers were combined and concentrated to dryness. The resulting solid was dissolved with THF (5 mL) and methanol (5 mL). This mixture was filtered to remove inorganic salts and the solids were washed with THF/MeOH (1:1; 5 mL). The combined filtrate and wash was concentrated. The solvent composition was switched to acetonitrile (5 mL) by distillation whereupon the product crystallized. The solids was filtered and dried to give the desired product (**6**, 86 mg, y. 70%) as a pale brown solid: Registry number: 1692-25-7; R_f = 0.05 (methanol); ^{1}H NMR (300 MHz, CD_3OD) δ = 8.64 (s, 1H, H-2), 8.58 (d, J = 3.9 Hz, 1H, H-6), 8.34 (d, J = 7.2 Hz, 1H, H-4), 7.64 (dd, J = 3.9, 7.2 Hz, 1H, H-5).

3,3'-Dibromobiphenyl (8).[7] To a mixture of $Cu(OAc)_2$ (45 mg, 0.25 mmol) in DMF (1 mL) was added 3-bromophenylboronic acid (**7**, 100 mg, 0.5 mmol), and the resulting mixture was stirred at 100 °C for 1 h. After completion of the reaction (formation of the products was monitored by TLC), the mixture was filtered through a pad of silica (SiO_2 6 g) using hexane (90 mL) as eluent. Concentration in *vacuo* furnished the desired product (**8**, 51 mg, y. 65%) as a colourless solid: Registry number: 16400-51-4; R_f = 0.88 (hexane : AcOEt = 60 : 40); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.68 (dd, J = 1.8, 1.8 Hz, 2H, H-4), 7.54-7.41 (m, 4H, H-2, H-5), 7.31 (d, J = 7.8 Hz, 2H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.87 (C), 130.88 (CH), 130.44 (CH), 130.23 (CH), 125.78 (CH), 123.06 (C); GC (GL Science TC-17, T_{inj} =120 °C, T_{det} = 250 °C, N_2 = 0.5 kg/cm^2, H_2 = 0.5 kg/cm^2, Air = 0.5 kg/cm^2, T_i = 120 °C (10 min), T_f = 250 °C (15 °C /min, 30 min): t_R = 18.76 min.

3,3'-Di(pyridin-3-yl)biphenyl (9).[8] To a solution of the bromide **8** (156 mg, 0.5 mmol) in degassed 1,4-dioxane (2.9 mL) and water (0.96 mL) were added the boronic acid (**7**, 184 mg, 1.5 mmol), $Ba(OH)_2 \cdot 8H_2O$ (473 mg, 1.5 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The reaction mixture was heated at reflux for 24 h and cooled to room temperature. 1,4-Dioxane was removed, and the resulting residue was redissolved in CH_2Cl_2 (5 mL), washed with water (3×1 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo* to give crude yellow coupling products. Chromatography (SiO_2 10 g, hexanes/ AcOEt = 70:30) gave the desired product (**9**, 146 mg, y. 94%) as a colourless solid: R_f = 0.58 (AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.92 (d, J = 2.2 Hz, 2H, H-2), 8.62 (dd, J = 4.8, 1.5 Hz, 2H, H-6), 7.94 (ddd, J = 2.2, 1.5, 7.9 Hz, 2H, H-4), 7.83 (dd, J = 0.6, 2.1 Hz, 2H, H-2'), 7.71-7.64 (m, 2H), 7.62-7.56 (m, 4H), 7.39 (ddd, J = 7.9, 4.8, 0.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.76 (CH), 148.46 (CH), 141.79 (C), 138.63 (C), 136.53 (C), 134.49 (CH), 129.67 (CH), 127.02 (CH), 126.44 (CH), 126.17 (CH), 123.60 (CH); ESI-TOFMS: calcd for $C_{22}H_{17}N_2$ (MH^+) 309.1, found 309.1; HPLC (Daicel Mightysil, Hexane/2-PrOH = 80 : 20, flow rate 0.5 mL/min, λ = 254 nm); t_R = 52.808 min.

(*R*)-2,2'-Dimethoxy-1,1'-binaphthyl (12).[8] A suspension of (*R*)-1,1'-bi-2-naphthol (**11**, 4.3 g, 15 mmol) was heated in acetone (15 mL) to give a homogeneous solution. To this solution were added potassium carbonate (7.0 g, 51 mmol) and methyl iodide (3.69 mL, 59 mmol), and the mixture was heated at reflux for 18 h. The solvent was evaporated, which was treated with 40 mL of water. The mixture was stirred for 18 h, and the resulting solid was washed with water and dried to afford the desired product (**12**, 4.68 g, y. 99%) as a colourless solid: Registry number: (*R*)-35294-28-1, (*S*)-2960-93-2; R_f = 0.49 (hexane : AcOEt = 70 : 30); $[\alpha]^{26}_D$ +54.5° (*c* 0.99, $CHCl_3$), lit (Aldrich). $[\alpha]^{20}_D$ +52 ° (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 9.0 Hz, 2H, H-8, H-8'), 7.85 (d, *J* = 8.1 Hz, 2H, H-5, H-5'), 7.44 (d, *J* = 9.0 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.0 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 6H, 2 x -OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.09 (C), 134.10 (C), 129.45 (CH), 129.30 (C), 127.98 (CH), 126.35 (CH), 125.32 (CH), 123.56 (CH), 119.68 (C), 114.32 (CH), 56.85 (CH_3).

(*R*)-2,2'-Dimethoxy-1,1'-binaphthyl-3,3'-diyldiboronic acid (13).[8] To a solution of TMEDA (1.29 mL, 8.4 mmol) in Et_2O (40 mL) was added at room temperature 1.59 M *n*-BuLi in hexane (5.38 mL, 8.4 mmol). The solution was stirred for 30 min, solid binaphthyl (**12**, 880 mg, 2.8 mmol) was added in one portion, and the reaction mixture was stirred for 3 h. The resulting light brown suspension was cooled to −78 °C, and ethyl borate (3.44 mL, 20 mmol) was added over a period of 10 min. The solution was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was cooled to 0 °C, 1 M HCl solution (20 mL) was added, and the resulting solution was stirred for 2 h at room temperature. The organic layer was washed with 1 M HCl solution (3 x 5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The resulting pale yellow solid was recrystallized from toluene to give the desired product (**13**, 712 mg, y. 63%) as a colourless solid: Registry number: rac-220204-00-2, (*R*)- 215433-49-1, (*S*)-428874-68-4; R_f = 0.49 (hexane : AcOEt = 30 : 70); $[\alpha]^{27}_D$ -151.1 ° (*c* 0.10, $CHCl_3$), lit.[8b] $[\alpha]_D$ -159.0 ° (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3COCD_3) δ = 8.59 (s, 2H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.43 (dt, *J* = 7.4, 1.0 Hz, 2H), 7.43 (s, 4H, 4 x -OH),7.30 (dt, *J* = 1.3, 7.6 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 3.42 (s, 6H, 2 x -OCH_3); ^{13}C NMR (75 MHz, CD_3COCD_3) δ = 162.38 (C), 140.21 (CH), 137.67 (C), 132.49 (C), 130.76 (CH), 129.28 (CH), 127.39 (CH), 126.77 (CH), 125.26 (C), 62.78 (CH_3).

(*R*)-2,2'-(2,2'-Dimethoxy-1,1'-binaphthyl-3,3'-diyl)dipyridine (14a).[8] To a solution of the boronic acid ((*R*)-**13**, 40.2 mg, 0.1 mmol)) in degassed 1,4-dioxane/water (0.77 mL, 3:1) were added 2-bromopyridine (30 μL, 0.3 mmol), $Ba(OH)_2 \cdot 8H_2O$ (96.6 mg, 0.3 mmol), and $Pd(PPh_3)_4$ (4.7 mg, 0.01 mmol). The reaction mixture was heated at reflux for 24 h and cooled to room temperature. 1,4-Dioxane was removed, and the resulting residue was redissolved in CH_2Cl_2 (3 mL), washed with 1 N HCl solution (2 x 2 mL) and brine (2 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo* to give crude coupling products. Chromatography (SiO_2 3 g, hexanes/ AcOEt, 80:20) gave the desired product (**14a**, 12 mg, y. 88%) as a pale brown solid: R_f = 0.49 (hexane : AcOEt = 30 : 70); $[\alpha]^{27}_D$ -14.7 ° (*c* 0.29, $CHCl_3$); ^{1}H

NMR (300 MHz, $CDCl_3$) δ = 8.87-8.77 (m, 2H), 8.44 (s, 2H), 8.00 (t, J = 7.5 Hz, 4H), 7.74 (dt, J = 7.8, 1.8 Hz, 2H), 7.45-7.37 (m, 2H), 7.31-7.19 (m, 6H), 3.24 (s, 6H, 2 x $-OCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.52 (C), 154.07 (C), 149.81 (CH), 136.16 (C), 134.35 (C), 133.43 (C), 131.64 (CH), 130.86 (CH), 128.78 (CH), 126.89 (CH), 125.90 (C), 125.73 (CH), 125.13 (CH), 124.93 (CH), 122.17 (CH), 61.02 (CH_3); ESI-TOFMS: calcd for $C_{32}H_{24}N_2O_2Na$ (MNa^+) 491.1735, found 491.1743.

(*R*)-3,3'-(2,2'-Dimethoxy-1,1'-binaphthyl-3,3'-diyl)dipyridine (14b). The reaction was carried out as described in the Experimental Section using 3-bromopyridine (150 μL, 1.5 mmol) to give the desired product (**14b**, 192 mg, y. 82%) as a pale brown solid: R_f = 0.27 (hexane : AcOEt = 30 : 70); $[\alpha]^{26}_D$ -26.4 ° (*c* 0.92, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.02 (d, J = 1.4 Hz, 2H), 8.64 (d, J = 3.9 Hz, 2H), 8.12 (d, J = 7.9 Hz, 2H), 8.01 (s, 2H), 7.95 (d, J = 8.1 Hz, 2H), 7.49-7.34 (m, 4H), 7.34-7.20 (m, 4H), 3.19 (s, 6H, 2 x $-OCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.90 (C), 149.90 (CH), 148.59 (CH), 136.72 (CH), 134.45 (C), 133.97 (C), 131.55 (C), 130.76 (CH), 128.23 (CH), 126.88 (CH), 125.87 (C), 125.71 (CH), 125.40 (CH), 123.15 (CH), 60.59 (CH_3); ESI-TOFMS: calcd for $C_{32}H_{24}N_2O_2Na$ (MNa^+) 491.1735, found 491.1528.

(*R*)-4,4'-(2,2'-Dimethoxy-1,1'-binaphthyl-3,3'-diyl)dipyridine (14c). The reaction was carried out as described in the Experimental Section using 4-bromopyridine hydrochloride (241 mg, 1.2 mmol) to give the desired product (**14c**, 160 mg, y. 85%) as a pale yellow solid: R_f = 0.36 (hexane : AcOEt = 30 : 70); $[\alpha]^{26}_D$ -26.8 ° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.03 (d, J = 1.4 Hz, 2H), 8.64 (d, J = 3.6 Hz, 2H), 8.12 (d, J = 7.9 Hz, 2H), 8.01 (s, 2H), 7.94 (d, J = 8.1 Hz, 2H), 7.54-7.21 (m, 10H), 3.19 (s, 6H, 2 x $-OCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.60 (C), 149.92 (CH), 146.49 (C), 134.06 (C), 132.11 (C), 130.86 (CH), 130.57 (C), 128.32 (CH), 127.12 (CH), 125.84 (C), 125.57 (CH), 125.43 (CH), 123.90 (CH), 60.73 (CH_3); ESI-TOFMS: calcd for $C_{32}H_{24}N_2O_2Na$ (MNa^+) 491.1735, found 491.1630.

(*R*)-3,3'-(2,2'-Dimethoxy-1,1'-binaphthyl-3,3'-diyl)diquinoline (14d). The reaction was carried out as described in the Experimental Section using 3-bromoquinoline (64 mg, 0.3 mmol) to give the desired product (**14d**, 29 mg, y. 51%) as a pale yellow solid: R_f = 0.65 (hexane : AcOEt = 30 : 70); $[\alpha]^{27}_D$ +78.8 ° (*c* 0.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.36 (d, J = 1.6 Hz, 2H), 8.60 (s, 2H), 8.20 (d, J = 8.4 Hz, 2H), 8.14 (s, 2H), 7.99 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H), 7.76 (t, J = 7.6 Hz, 2H), 7.60 (t, J = 7.4 Hz, 2H), 7.54-7.41 (m, 2H), 7.40-7.22 (m, 4H), 3.24 (s, 6H, 2 x $-OCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.12 (C), 151.49 (CH), 147.26 (C), 135.69 (CH), 134.06 (C), 131.75 (C), 131.65 (C), 131.24 (CH), 130.92 (C), 129.63 (CH), 129.27 (CH), 128.34 (CH), 128.12 (CH), 128.02 (C), 127.04 (CH), 126.96 (CH), 126.02 (C), 125.82 (CH), 125.54 (CH), 60.81 (CH_3); ESI-TOFMS: calcd for $C_{40}H_{29}N_2O_2Na$ (MH^+) 569.2229, found 569.2168.

(*R*)-4,4'-(2,2'-Dimethoxy-1,1'-binaphthyl-3,3'-diyl)diisoquinoline (14e). The reaction was carried out as described in the Experimental Section using 4-bromoisoquinoline (318 mg, 1.5 mmol) to give the

desired product (**14e**, 236 mg, y. 83% including four atropisomers) as a pale yellow solid: R_f = 0.41 (hexane : AcOEt = 30 : 70); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.32 (s, 2H), 8.85-8.65 (m, 2H), 8.16-7.77 (m, 8H), 7.78-7.21 (m, 10H), 3.57-2.63 (m, 6H); ESI-TOFMS: calcd for $C_{40}H_{29}N_2O_2Na$ (MH^+) 569.2229, found 569.2253.

Typical procedure for the Biginelli reaction (Table 3, entry 1): To a solution of the catalyst (**14b**, 0.06 mmol) in $CHCl_3$ (0.2 mL) methanesulfonic acid (0.06 mmol) was added. After stirring for 5 min at 25 °C, urea (**2**, 0.3 mmol), *p*-nitrobenzaldehyde (**1a**, 0.2 mmol), and ethyl acetoacetate (**3a**, 0.2 mmol) were added. The reaction mixture was stirred for 48 h at 25 °C, and then diluted with AcOEt (3 mL). Organic layer was washed with iced water (3 x 1 mL), dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography (silica gel, hexane/AcOEt = 50/50) to give the Biginelli product **4a** (29% yield) as a yellow solid. Low enantioselectivity (2% ee) was observed from chiral HPLC analysis

Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a). Registry number: (*S*)-390763-45-8, (*R*)-211613-31-9, rac-161374-08-9, isomer-321687-53-0; R_f = 0.26 (hexane : AcOEt = 30 : 70); ^{1}H NMR (300 MHz, DMSO) δ = 9.39 (s, 1H, -NH), 8.23 (dd, J = 8.6, 2.7 Hz, 2H, Ar), 7.93 (s, 1H, -NH), 7.53 (dd, J = 8.6, 2.6 Hz, 2H, Ar), 5.30 (s, 1H, -CHN-), 4.00 (dq, J = 2.7, 7.0 Hz, 2H, -CH_2O-), 2.29 (d, J = 2.4 Hz, 3H, -CH_3), 1.11 (dt, J = 6.9, 2.8 Hz, 3H, -CH_3); ^{13}C NMR (75 MHz, DMSO) δ = 165.19 (C=O), 152.12 (C=O), 151.90 (C), 149.50 (C), 146.81 (C), 127.74 (CH), 123.87 (CH), 98.22 (C), 59.35 (CH_2), 53.66 (CH), 17.76 (CH_3), 13.92 (CH_3); HPLC (Daicel CHIRALPAK AS-H, hexane/2-PrOH = 40:60, flow rate 0.5 mL/min, λ = 254 nm); t_R = 21.97 (*R*-isomer), 32.40 (*S*-isomer) min.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b). Registry number: (*S*)-390763-29-8, (*R*)-211613-29-5, rac-5395-36-8; R_f = 0.31 (hexane : AcOEt = 30 : 70); ^{1}H NMR (300 MHz, DMSO) δ = 9.19 (s, 1H, -NH), 7.73 (s, 1H, -NH), 7.50-7.08 (m, 5H, Ar), 5.14 (d, J = 2.8 Hz, 1H, -CHAr), 3.98 (q, J = 7.1 Hz, 2H, -CH_2-), 2.25 (s, 3H, -CH_3), 1.09 (t, J = 7.1 Hz, 3H, -$CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, DMSO) δ = 165.43 (C), 152.20 (C), 148.40 (C), 144.93 (C), 128.41 (CH), 127.28 (CH), 126.27 (CH), 99.26 (C), 59.10 (CH_2), 53.88 (CH), 17.63 (CH_3), 13.92 (CH_3); HPLC (Daicel CHIRALPAK AS-H, hexane/2-PrOH = 40:60, flow rate 0.5 mL/min, λ = 254 nm); t_R = 22.25 (*R*-isomer), 42.56 (*S*-isomer) min.

Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c). Registry number: rac-123629-41-4; R_f = 0. 27 (hexane : AcOEt = 30 : 70); ^{1}H NMR (300 MHz, DMSO) δ = 9.28 (s, 1H, -OH), 9.03 (s, 1H, -NH), 7.54 (s, 1H, -NH), 6.96 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 4.97 (d, J = 3.1 Hz, 1H, -CHAr), 3.90 (q, J = 7.1 Hz, 2H, -CH_2-), 2.16 (s, 3H, -CH_3), 1.02 (t, J = 7.1 Hz, 3H, -$CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, DMSO) δ = 165.63 (C), 156.75 (C), 152.43 (C), 147.92 (C), 135.58 (C), 127.56 (CH), 115.12 (CH), 99.86 (C), 59.16 (CH_2), 53.47 (CH), 17.71 (CH_3), 14.05 (CH_3); HPLC (Daicel CHIRALPAK AD-H, hexane/2-PrOH = 80:20, flow rate 0.5 mL/min, λ = 254 nm); t_R =

24.87, 47.77 min.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d). Registry number: rac-161374-07-8; R_f = 0. 38 (hexane : AcOEt = 30 : 70); ^{1}H NMR (300 MHz, DMSO) δ = 8.61 (s, 1H, -NH), 7.22 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.10 (s, 1H, -NH), 5.33 (d, J = 2.6 Hz, 1H, -CHAr), 4.07 (q, J = 7.1 Hz, 2H, -CH_2-), 3.77 (s, 3H, -OCH_3), 2.31 (s, 3H, -CH_3), 1.16 (t, J = 7.1 Hz, 3H, -$CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, DMSO) δ = 165.84 (C), 159.30 (C), 153.84 (C), 146.20 (C), 136.25 (C), 127.83 (CH), 113.99 (CH), 101.55 (C), 59.88 (CH_2), 55.17 (CH_3), 54.98 (CH), 18.39 (CH_3), 14.03 (CH_3); HPLC (Daicel CHIRALPAK AD-H, hexane/2-PrOH = 80:20, flow rate 0.5 mL/min, λ = 254 nm); t_R = 18.21, 26.06 min.

Ethyl 4-(benzo[*d*][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e). Registry number: rac-161374-09-0; R_f = 0.36 (hexane : AcOEt = 30 : 70); ^{1}H NMR (300 MHz, DMSO) δ = 8.79 (s, 1H, -NH), 6.67-6.83 (m, 3H), 6.39 (s, 1H, -NH), 5.92 (s, 2H, -OCH_2O-), 5.29 (d, J = 2.5 Hz, 1H, -CHAr), 4.08 (q, J = 7.2 Hz, 2H, -CH_2-), 2.31 (s, 3H, -CH_3), 1.18 (t, J = 7.1 Hz, 3H, -$CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, DMSO) δ = 165.46 (C), 152.19 (C), 148.40 (C), 147.35 (C), 146.45 (C), 138.96 (C), 119.38 (CH), 108.04 (CH), 106.69 (CH), 100.96 (CH_2), 99.32 (C), 59.15 (CH_2), 53.61 (CH), 17.66 (CH_3), 13.99 (CH_3); HPLC (Daicel CHIRALPAK AD-H, hexane/2-PrOH = 80:20, flow rate 0.5 mL/min, λ = 254 nm); t_R = 26.48, 31.53 min.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f). Registry number: rac-5948-71-0; R_f = 0.36 (hexane : AcOEt = 30 : 70); ^{1}H NMR (300 MHz, DMSO) δ = 8.27 (s, 1H, -NH), 7.42-7.11 (m, 4H), 5.97 (s, 1H, -NH), 5.37 (d, J = 2.8 Hz, 1H, -CHAr), 4.08 (q, J = 7.0 Hz, 2H, -CH_2-), 2.33 (s, 3H, -CH_3), 1.17 (t, J = 7.1 Hz, 3H, -$CH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, DMSO) δ = 165.35 (C), 152.09 (C), 148.82 (C), 143.89 (C), 131.89 (C), 128.46 (CH), 128.27 (CH), 98.89 (C), 59.23 (CH_2), 53.41 (CH), 17.71 (CH_3), 13.95 (CH_3); HPLC (Daicel CHIRALPAK AD-H, hexane/2-PrOH = 80:20, flow rate 0.5 mL/min, λ = 254 nm); t_R = 14.51, 17.78 min.

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10. In our system, strong acid was essential. In the absence of acid additive and/or in the presence of weak acid such as acetic acid, catalyst **14b** did not give the desired product **4b**. Although mineral acid additives were similarly a good co-catalyst, we chose $MeSO_3H$ for further study because of easy operation. Furthermore, we examined that chiral acid additives such as (+)-camphor-10-sulfonic acid (CSA), (-)-CSA, (*R*)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (+)-tartaric acid, and (-)-tartaric acid as a co-catalyst resulted in lower chemical yields (7-22%) and enantioselectivities (0-3% ee) compared with $MeSO_3H$ co-catalyst.
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