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Novel supramolecular organocatalysts of hydroxyprolinamide based on calix[4]arene scaffold for the enantioselective Biginelli reaction

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A series of novel supramolecular organocatalysts of hydroxyprolinamide based on the upper rim of calix[4]arene scaffold have been developed to catalyze enantioselective multi-component Biginelli reaction. Under the optimal conditions, the reactions occurred with moderate-to-excellent enantioselectivities (up to 98% *ee*). A plausible transition state constructed by the supramolecular interaction of hydrogen bond and cation–π between catalysts and substrates has been proposed.

supramolecular organocatalyst, calix[4]arene, hydroxyprolinamide, enantioselective Biginelli reaction

1 Introduction

The supramolecular catalysis of organic reactions is now a contemporary challenge that is just being taken up by chemists [1–7]. Especially supramolecular organocatalysis through the weak forces which offers attractive alternatives to metal (ion)-catalyzed reactions by combining supramolecular recognition with chemical transformations in an environmentally benign fashion has attracted considerable interest in recent years [8, 9]. Calix[4]arenes, as one of the most important supramolecular building blocks, can be useful in ion and metal complex because of their suitable scaffold for the development of new bulky and structurally well-defined ligands [10–15]. Combination of calixarene cavity with chiral catalytic centre or inherent chirality [16, 17] might lead to multifunctional supramolecular asymmetric catalyst [18]. Recently, we have demonstrated that proline based on calix[4]arene scaffold can catalyze the enantioselective direct aldol reactions with good-to-excellent enantioselectivities [19, 20]. As a part of our ongoing studies, we would like to report our preliminary results on hydroxyprolinamide based on calix[4]arene scaffold catalyzed the enantioselective Biginelli reactions of aromatic aldehydes, ethyl acetoacetate, and urea.

The multi-component Biginelli reaction [21] offers an efficient way to access 3,4-dihydropyrimidin-2-(1*H*)-ones and related heterocyclic compounds which have important pharmacological and biological properties [22–27] such as antiviral, antitumor, antibacterial, antihypertensive, and antiinflammatory properties. However, in the past decade, only the limited examples of the enantioselective Biginelli reaction have been reported [28–37]. Recently, Feng *et al*. [28] used hydroxyprolinamide based on diamantane **1** (Scheme 1) as organocatalyst assisted by a Brønsted acid to smoothly catalyze asymmetric Biginelli reaction with up to 98% *ee*. Herein, more bulky, rigid, and tunable hydroxyprolinamide organocatalysts based on calix[4]arene scaffold **2**

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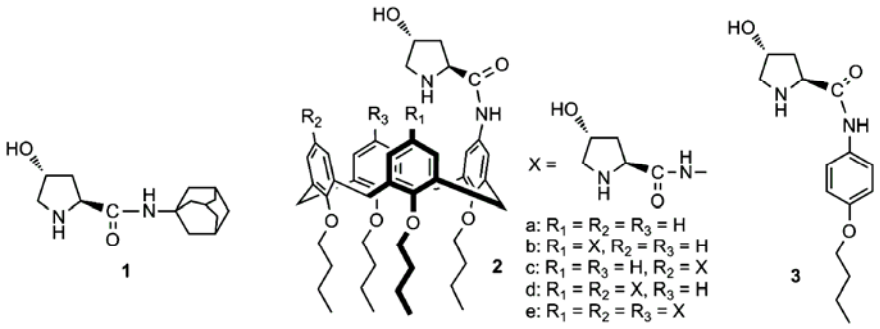


Scheme 1 Hydroxyprolinamide organocatalysts for enantioselective Biginelli reaction.

(Scheme 1) were designed for the enantioselective Biginelli reaction. Furthermore, cooperation of more hydroxyprolinamide moieties and the cativies derivated from calix[4] arenes might improve the enantioselectivity of the process.

2 Experimental

2.1 Materials and measurements

All reactions were performed in open atmosphere unless noted. The commercially available reagents and solvents were used without further purification unless otherwise noted. Column chromatography was performed with silica gel (200–300 mesh). All yields were given as isolated ones. NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Coupling constants (J values) are reported in Hertz. IR and ESI-MS data were measured on a Bruker Vector 22 as KBr pellets and a Finnigan Mat TSQ 7000 instruments, respectively. Microanalyses were obtained on a Perkin-Elmer 240 instrument, and melting points (mp) were determined with a digital electrothermal apparatus without further correction. HPLC was performed on Perkin Elmer LC equipped with a chiralcel OD-H or AD-H column. Aminocalix[4]arenes **5** [38] and racemic-**4** [39] were prepared according to literature procedures.

2.2 Representative synthetic procedure for catalyst 2a

To a solution of *trans*-4-hydroxy-L-*N*-Boc-proline (0.25 g, 1.1 mmol) in CH_2Cl_2 (30 mL) was added TEA (0.11 mL, 1.1 mmol) and ethyl chloroformate (0.14 mL, 1.1 mmol) at 0 °C under stirring. After 15 min, 5-amino-25,26,27,28-tetrabutoxycalix[4]arene **5a** (0.66 g, 1.0 mmol) was added. The reaction was allowed to warm to ambient temperature and stirred for 7 h. After reaction, the mixture was washed with $KHSO_4$ (1 M), saturated $NaHCO_3$, and brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the residue was purified by column chromatography with petroleum ether/ethyl acetate (2:1, *v*/*v*) as an eluent to give Boc-protected product (0.65 g) which was dissolved in $CHCl_3$ (30 mL). After addition of TFA (1 mL), the reaction mixture was stirred at 50 °C for 3 h. The solvent was removed, $CHCl_3$ (30 mL) and H_2O (30 mL) were added. The pH of the mixture was adjusted to 8–9 by the addition of aqueous NaOH (2 M), and the water layer was extracted with additional $CHCl_3$ (30 mL). The combined organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed to give pure yellow solid **2a** (0.58 g, 74%).

*Compound **2a***

Yellow solid, 74%, mp: 107–109 °C. $[\alpha]_D^{26}$–5.5 (c = 1.0, in THF). IR (KBr): 3413, 2959, 2929, 2868, 1677, 1605, 1533, 1460, 1382, 1290, 1245, 1205, 1134, 1085, 1029, 962, 763 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0.97 (t, J = 7.5 Hz, 12H, CH_3), 1.37–1.52 (m, 8H, CH_2), 1.67–2.03 (m, 10H, CH_2), 2.72–2.91 (m, 2H, NCH_2), 3.10 (d, J = 13.2 Hz, 2H, $ArCH_2Ar$), 3.16 (d, J = 13.2 Hz, 2H, $ArCH_2Ar$), 3.75–3.89 (m, 9H, NCHCO + $ArOCH_2$), 4.20 (m, 1H, HCOH), 4.31 (d, J = 13.2 Hz, 2H, $ArCH_2Ar$), 4.34 (d, J = 13.2 Hz, 2H, $ArCH_2Ar$), 4.76 (br s, 1H, OH), 6.45–6.62 (m, 7H, ArH), 6.68 (d, J = 7.5 Hz, 2H, ArH), 6.95 (d, J = 2.4 Hz, 1H, ArH), 6.97 (d, J = 2.4 Hz, 1H, ArH), 9.55 (s, 1H, CONH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 19.3, 19.4, 22.6, 29.6, 30.9, 31.3, 31.4, 31.9, 32.1, 32.2, 32.3, 39.6, 54.8, 59.7, 72.2, 74.8, 120.1, 121.6, 122.0, 128.0, 128.2, 131.3, 134.3, 134.5, 134.7, 135.5, 136.0, 153.9, 156.2, 156.9, 170.3. Anal. calcd for $C_{49}H_{64}N_2O_6$: C, 75.74; H, 8.30; N, 3.61. Found: C, 75.47; H, 8.59; N, 3.87. ESI-MS: m/z = 778 ($[M + 1]^+$, 9%), 800 ($[M + Na]^+$, 100%), 816 ($[M + K]^+$, 38%).

*Compound **2b***

Yellow solid, 55%, mp: 153–155 °C. $[\alpha]_D^{27}$–13.1 (c = 1.0, in THF). IR (KBr): 3426, 2957, 2928, 2869, 1661, 1604, 1533, 1465, 1210, 1073, 1028, 966, 869, 764 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 0.96 (t, J = 7.5 Hz, 12H, CH_3), 1.42 (m, 8H, CH_2), 1.62–2.00 (m, 12H, CH_2), 2.74–2.90 (m, 4H, NCH_2), 3.05 (d, J = 13.2 Hz, 1H, $ArCH_2Ar$), 3.11 (d, J = 13.2 Hz, 2H, $ArCH_2Ar$), 3.17 (d, J = 13.2 Hz, 1H, $ArCH_2Ar$), 3.76–3.82 (m, 10H, NCHCO + $ArOCH_2$), 4.19 (m, 2H, HCOH), 4.28 (d, J = 13.2 Hz, 1H, $ArCH_2Ar$), 4.31 (d, J =

13.2 Hz, 2H, $ArCH_2Ar$), 4.34 (d, J = 13.2 Hz, 1H, $ArCH_2Ar$), 4.75 (br s, 2H, OH), 6.49–6.62 (m, 6H, ArH), 6.80–6.90 (m, 3H, ArH), 6.99 (d, J = 2.1 Hz, 1H, ArH), 9.49 (s, 1H, CONH), 9.51 (s, 1H, CONH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 19.3, 30.9, 31.3, 31.4, 32.2, 39.8, 55.2, 60.0, 72.8, 74.7, 120.0, 121.7, 128.1, 131.4, 131.5, 134.7, 134.9, 135.1, 135.2, 135.4, 135.6, 135.8, 135.9, 153.4, 156.5, 156.6, 172.8, 173.0. Anal. calcd for $C_{54}H_{72}N_4O_8$: C, 71.65; H, 8.02; N, 6.19. Found: C, 71.84; H, 7.86; N, 6.35. ESI-MS: m/z = 906 ($[M + 1]^+$, 7%), 928 ($[M + Na]^+$, 100%), 944 ($[M + K]^+$, 20%).

Compound ***2c***

Yellow solid, 79%, mp: 171–173 °C. $[\alpha]_D^{27}$–6.5 (c = 1.0, in THF). IR (KBr): 3423, 2958, 2927, 2869, 1660, 1608, 1535, 1465, 1212, 1129, 1073, 1028, 965, 868, 765 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.96 (t, J = 7.2 Hz, 6H, CH_3), 0.98 (t, J = 7.2 Hz, 6H, CH_3), 1.28–1.36 (m, 4H, CH_2), 1.49–1.61 (m, 4H, CH_2), 1.85–2.06 (m, 12H, CH_2), 2.72–2.96 (m, 4H, NCH_2), 3.10 (d, J = 12.9 Hz, 4H, $ArCH_2Ar$), 3.69 (t, J = 6.6 Hz, 4H, $ArOCH_2$), 3.85–3.95 (m, 6H, NCHCO + $ArOCH_2$), 4.22 (m, 2H, HCOH), 4.31 (d, J = 12.9 Hz, 4H, $ArCH_2Ar$), 4.78 (br s, 2H, OH), 6.33 (s, 6H, ArH), 7.29 (s, 4H, ArH), 9.76 (s, 2H, CONH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0, 19.1, 19.4, 19.5, 22.6, 29.6, 31.0, 31.8, 32.0, 32.2, 32.4, 40.1, 55.0, 59.7, 72.7, 74.7, 74.9, 119.8, 122.0, 128.4, 128.7, 128.8, 131.4, 134.8, 135.3, 153.0, 156.8, 172.3. Anal. calcd for $C_{54}H_{72}N_4O_8$: C, 71.65; H, 8.02; N, 6.19. Found: C, 71.86; H, 8.24; N, 5.98. ESI-MS: m/z = 928 ($[M + Na]^+$, 100%), 944 ($[M + K]^+$, 30%).

Compound ***2d***

Yellow solid, 21%, mp > 280 °C. $[\alpha]_D^{26}$–27.7 (c = 1.0, in THF). IR (KBr): 3431, 2958, 2928, 2869, 1663, 1606, 1536, 1468, 1424, 1215, 1136, 1071, 1028, 966, 869, 765 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.93–0.99 (m, 12H, CH_3), 1.19–1.57 (m, 10H, CH_2), 1.75–2.00 (m, 12H, CH_2), 2.61–2.95 (m, 6H, NCH_2), 3.06 (d, J = 13.5 Hz, 2H, $ArCH_2Ar$), 3.14 (d, J = 13.5 Hz, 2H, $ArCH_2Ar$), 3.64–4.00 (m, 11H, NCHCO + $ArOCH_2$), 4.22 (m, 3H, HCOH), 4.29 (d, J = 13.5 Hz, 2H, $ArCH_2Ar$), 4.32 (d, J = 13.5 Hz, 2H, $ArCH_2Ar$), 4.79 (br s, 3H, OH), 6.08–7.38 (m, 9H, ArH), 9.39 (s, 1H, CONH), 9.75 (s, 2H, CONH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.3, 14.4, 19.2, 19.5, 30.9, 31.0, 32.0, 32.4, 55.5, 60.3, 71.9, 74.8, 74.9, 119.3, 119.9, 122.2, 128.0, 129.0, 129.6, 130.3, 132.9, 133.9, 135.6, 135.9, 152.0, 153.1, 155.8, 172.0, 172.7. Anal. calcd for $C_{59}H_{80}N_6O_{10}$: C, 68.58; H, 7.80; N, 8.13. Found: C, 68.81; H, 7.55; N, 8.34. ESI-MS: m/z = 1034 ($[M + 1]^+$, 37%), 1056 ($[M + Na]^+$, 100%).

Compound ***2e***

Yellow solid, 42%, mp > 280 °C. $[\alpha]_D^{26}$–189.8 (c = 0.5, in THF). IR (KBr): 3433, 2957, 2928, 2867, 1659, 1605, 1535, 1469, 1422, 1328, 1216, 1141, 1068, 1027, 966, 869 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.97 (t, J = 7.2 Hz, 12H, CH_3), 1.35–1.48 (m, 8H, CH_2), 1.66–1.98 (m, 16H, CH_2), 2.73–2.92 (m, 8H, NCH_2), 3.10 (d, J = 13.2 Hz, 4H, $ArCH_2Ar$), 3.61–3.65 (m, 4H, NCHCO), 3.77–3.84 (m, 8H, $ArOCH_2$), 4.19 (m, 4H, HCOH), 4.32 (d, J = 13.2 Hz, 4H, $ArCH_2Ar$), 4.73 (br s, 4H, OH), 6.99 (s, 4H, ArH), 7.04 (s, 4H, ArH), 9.55 (s, 4H, CONH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.3, 19.3, 29.5, 30.9, 31.2, 31.3, 31.8, 32.1, 32.5, 55.4, 60.2, 71.8, 75.0, 119.9, 133.0, 134.7, 152.5, 172.4. Anal. calcd for $C_{64}H_{88}N_8O_{12}$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.42; H, 7.38; N, 9.45. ESI-MS: m/z = 1162 ($[M + 1]^+$, 86%), 1184 ($[M + Na]^+$, 100%).

2.3 The procedure for the synthesis of model catalyst 3

Synthesis of ***7***

4-Nitrophenol **6** (1.39 g, 10 mmol), K_2CO_3 (1.52 g, 11 mmol) and *n*-bromobutane (1.44 g, 10.5 mmol) were refluxed in MeCN (50 mL) for 24 h under nitrogen gas. The solvent was evaporated and the residue was taken up in CH_2Cl_2 (50 mL), and then washed with HCl (1 N, 2 × 50 mL), H_2O (2 × 50 mL), and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$. The CH_2Cl_2 was removed to give 1.81 g **7** without further purification. Yellow solid, 93%, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.5 Hz, 3H, CH_3), 1.45–1.57 (m, 2H, CH_2), 1.76–1.86 (m, 2H, CH_2), 4.06 (t, J = 6.3 Hz, 2H, $ArOCH_2$), 6.94 (d, J = 9.0 Hz, 2H, ArH), 8.20 (d, J = 9.0 Hz, 2H, ArH).

Synthesis of ***8***

Hydrazine hydrate (30 mL) was added to a suspension of **7** (1.81 g, 9.27 mmol) and a catalytic amount of Raney nickel in methanol (50 mL). The mixture was refluxed for 4 h. After cooling to room temperature, the mixture was filtered. The filtrate was evaporated and the residue was taken up in CH_2Cl_2 (50 mL), washed with water twice, and dried over anhydrous $MgSO_4$. The CH_2Cl_2 was removed to afford **8** (1.53 g). Brown oil, > 99%, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.5 Hz, 3H, CH_3), 1.42–1.52 (m, 2H, CH_2), 1.71–1.81 (m, 2H, CH_2), 3.95 (t, J = 6.3 Hz, 2H, $ArOCH_2$), 6.91 (d, J = 8.7 Hz, 2H, ArH), 7.45 (d, J = 8.7 Hz, 2H, ArH), 10.42 (br s, 2H, $ArNH_2$).

Synthesis of ***3*** *from* ***8***

The procedure was similar to the synthesis of **2a**. White solid, 92%, mp 195–197 °C. IR (KBr): 3366, 3288, 2954, 2871, 1667, 1658, 1600, 1549, 1514, 1466, 1415, 1299, 1250, 1173, 1123, 1084, 1031, 970, 833 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.93 (t, J = 7.5 Hz, 3H, CH_3), 1.36–1.49 (m, 2H, CH_2), 1.63–1.73 (m, 2H, CH_2), 1.93–2.02 (m, 1H, CH_2), 2.36–2.43 (m, 1H, CH_2), 3.13 (d, J = 12.0 Hz, 1H, NCH_2), 3.39 (d, J = 12.0 Hz, 1H, NCH_2), 3.93 (t, J = 6.6 Hz, 2H, $ArOCH_2$), 4.47–4.53 (m, 2H, OCH + COCH), 5.62 (s, 1H, OH), 6.91 (d, J = 9.0 Hz, 2H, ArH),

7.53 (d, J = 9.0 Hz, 2H, ArH), 10.74 (s, 1H, CONH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1, 19.1, 31.1, 53.6, 58.8, 67.5, 69.4, 114.8, 121.2, 131.6, 155.5, 166.4. Anal. calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.96; H, 8.24; N, 9.83. ESI-MS: m/z = 279 ([M + 1]$^+$, 100%), 301 ([M + Na]$^+$, 8%).

2.4 General procedure for the asymmetric Biginelli reaction

A solution of catalyst **2a** (5 mol%), *p*-toluic acid (5 mol%), and piperidine·TFA (5 mol%) in THF (0.5 mL) was stirred at room temperature for 30 min, then urea (0.6 mmol), aldehyde (0.5 mmol), ethyl acetoacetate (1.0 mmol), and THF (0.5 mL) were added sequentially. The reaction mixture was stirred at room temperature for 3–4.5 d. Then, the crude product was purified by prepared TLC (petroleum ether/ethyl acetate, 2/3) to afford the corresponding products. The enantiomeric excesses were determined by HPLC (Daicel Chiralpak AD-H or OD-H column).

Product ***4a*** [28]

White solid; 69% *ee*, 41% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (s, 1H), 7.33–7.29 (m, 5H), 5.48 (s, 1H), 5.40 (d, J = 2.4 Hz, 1H), 4.11–4.04 (m, 2H), 2.36 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H); HPLC (OD-H, hexane/2-propanol 85/15, *v*/*v*, 1.0 mL, 254 nm), t_R (minor) = 8.42 min, t_R (major) = 10.78 min.

Product ***4b*** [28]

White solid; 91% *ee*, 32% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (s, 1H), 7.23–7.06 (m, 4H), 5.61 (s, 1H), 5.37 (d, J = 2.7 Hz, 1H), 4.13–4.02 (m, 2H), 2.35 (s, 3H), 2.33 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H); HPLC (OD-H, hexane/2-propanol 85/15, *v*/*v*, 1.0 mL, 254 nm), t_R (minor) = 7.83 min, t_R (major) = 10.26 min.

Product ***4c*** [28]

White solid; 98% *ee*, 32% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (s, 1H), 6.93–6.80 (m, 4H), 5.38 (d, J = 2.7 Hz, 1H), 5.35 (s, 1H), 4.13–4.06 (m, 2H), 3.79 (s, 3H), 2.36 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); HPLC (OD-H, hexane/2-propanol 85/15, *v*/*v*, 1.0 mL, 254 nm), t_R (minor) = 11.87 min, t_R (major) = 13.88 min.

Product ***4d*** [28]

White solid; 90% *ee*, 38% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (s, 1H), 7.30–7.21 (m, 4H), 5.76 (s, 1H), 5.38 (d, J = 2.7 Hz, 1H), 4.11–4.07 (m, 2H), 2.36 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); HPLC (OD-H, hexane/2-propanol 85/15, *v*/*v*, 1.0 mL, 254 nm), t_R (minor) = 8.14 min, t_R (major) = 9.12 min.

Product ***4e***

White solid; 80% *ee*, 48% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (s, 1H), 8.16 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.10 (s, 1H), 5.58 (s, 1H), 5.54 (d, J = 2.7 Hz, 1H), 4.13–4.09 (m, 2H), 2.39 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); HPLC (AD-H, hexane/2-propanol 85/15, *v*/*v*, 1.0 mL, 254 nm), t_R (major) = 13.11 min, t_R (minor) = 17.49 min.

Product ***4f*** [28]

White solid; 90% *ee*, 22% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.81–7.77 (m, 2H), 7.61–7.49 (m, 2H), 7.46–7.41 (m, 2H), 6.30 (s, 1H), 5.52 (s, 1H), 3.97–3.88 (m, 2H), 2.45 (s, 3H), 0.88 (t, J = 7.2 Hz, 3H); HPLC (AD-H, hexane/2-propanol 85/15, *v*/*v*, 1.0 mL, 254 nm), t_R (major) = 11.69 min, t_R (minor) = 17.48 min.

Product ***4g***

White solid; 39% *ee*, 44% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, J = 1.8 Hz, 1H), 7.04 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 2H), 6.89 (d, J = 7.8 Hz, 2H), 5.73 (s, 2H), 4.10–4.03 (m, 2H), 3.88 (s, 3H), 2.43 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); HPLC (OD-H, hexane/2-propanol 85/15, *v*/*v*, 1.0 mL, 254 nm), t_R (major) = 9.49 min, t_R (minor) = 13.29 min.

Product ***4h***

White solid; 67% *ee*, 32% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.42 (s, 1H), 5.38 (d, J = 2.4 Hz, 1H), 4.13–4.06 (m, 2H), 2.35 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); HPLC (OD-H, hexane/2-propanol 95/5, *v*/*v*, 1.0 mL, 254 nm), t_R (minor) = 14.85 min, t_R (major) = 17.07 min.

Product ***4i*** [35]

White solid; 34% *ee*, 36% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 5.78 (s, 1H); 5.36 (d, J = 2.7 Hz, 1H), 4.12–4.05 (m, 2H), 2.34 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); HPLC (AD-H, hexane/2-propanol 80/20, *v*/*v*, 0.8 mL, 254 nm), t_R (major) = 8.45 min, t_R (minor) = 10.99 min.

Product ***4j***

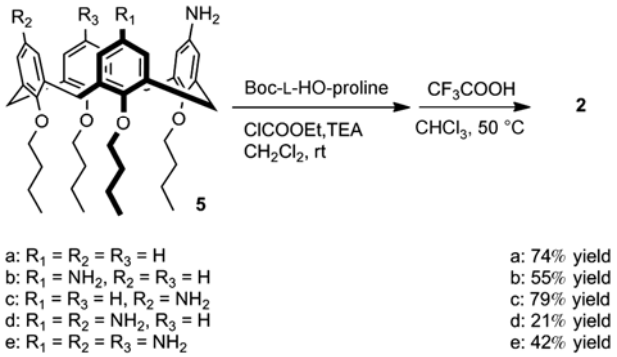
White solid; 20% *ee*, 26% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.32 (s, 1H), 5.63 (s, 1H), 5.53 (d, J = 2.7 Hz, 1H), 4.15–4.08 (m, 2H), 2.38 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); HPLC (AD-H, hexane/2-propanol 85/15, *v*/*v*, 1.0 mL, 254 nm), t_R (major) = 15.78 min, t_R (minor) = 18.98 min.

3 Results and discussion

3.1 Synthesis of catalysts 2 and 3

A series of novel organocatalysts of *trans*-4-hydroxy-

prolinamides based on calix[4]arenes **2** have been prepared conveniently within two steps which are depicted in Scheme 2. Starting from various aminocalix[4]arenes **5** [38], condensation with Boc-L-hydroxyproline by ClCOOEt in dried CH_2Cl_2 in the presence of a mild base triethylamine (TEA) gave Boc-protected products, and then hydrolysis in dried $CHCl_3$ in the presence of F_3CCO_2H (TFA) at 50 °C afforded target compounds **2**, respectively. As comparison, prolinamide derivate **3** as model catalyst was prepared by the similar procedure from *p*-butoxybenzenamine (Scheme 3).



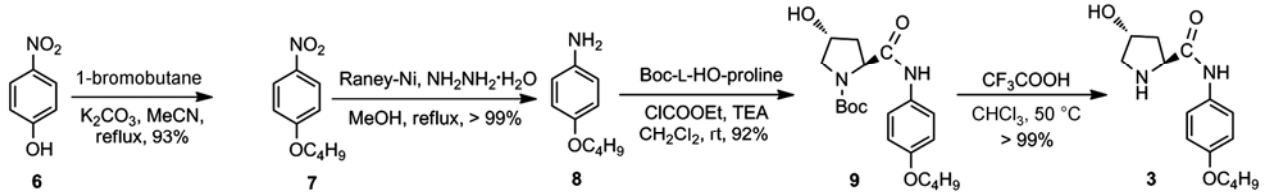
Scheme 2 Synthesis of hydroxyprolin-calix[4]arene-amides **2**.

3.2 Screening of catalysts for the Biginelli reaction

As a preliminary test, using the optimal conditions of catalyst **1** in Feng's work [28], organocatalysts based on calix[4]arene scaffold **2** were evaluated for their catalytic efficiencies in the enantioselective Biginelli reaction of benzaldehyde, ethyl acetoacetate, and urea. As shown in Table 1, compared to the results obtained from the reactions catalyzed by di-, tri- and tetra-hydroxyprolin-calix[4]arene-amides **2b–2e** with 10%–45% *ee*, mono-hydroxyprolinamide based on calix[4]arene **2a** with 54% *ee* was evidently the best choice for the present reaction system in terms of enantioselectivity. It might be ascribed to the effect of steric hindrance on the upper rim of calix[4]arene. More groups of hydroxyprolinamide conducted the cavity of calixarene binding toward the guest molecules difficultly.

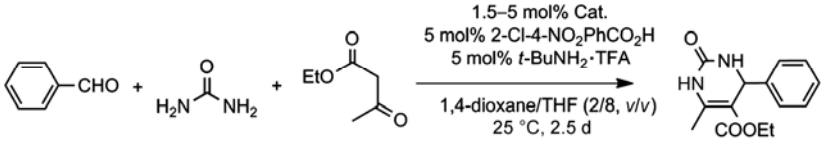
3.3 Optimization of reaction conditions

The new optimization of reaction conditions including acid, solvent, and additive for catalyst **2a** was then carried out, respectively, and the results are summarized in Table 2. Firstly, various substituted benzoic acids combined with **2a** were employed to catalyze the reaction in THF (entries 1–3). It is interesting that catalyst **1** assisted by aromatic acid bearing electron-donating groups such as 4-methoxybenzoic acid could not catalyze the Biginelli reaction [28], while **2a** with *p*-toluic acid was the best assembly than benzoic acid and 4-nitrobenzic acid. Secondly, in the presence of *p*-toluic acid, the solvent effects were then studied (Table 2, entries 3–6). It is obvious that THF is the best solvent compared with DMF, 1,4-dioxane, and $CHCl_3$. Finally, we surveyed the effects of the organic amine salts as additive in the



Scheme 3 Synthesis of model catalyst **3**.

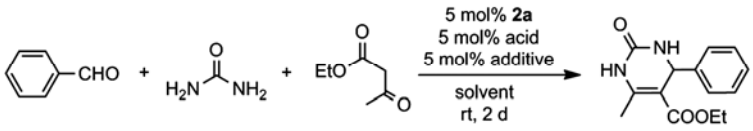
Table 1 Evaluation of the catalysts **2** in the asymmetric Biginelli reaction of benzaldehyde, ethyl acetoacetate, and urea[a)]



Entry	Catalyst	Loading (mol%)	Yield (%)[b)]	*ee* (%)[c)]
1	**2a**	5	44	54
2	**2b**	5	38	10
3	**2c**	3	46	45
4	**2d**	2	35	26
5	**2e**	1.5	65	22

a) A solution of 2-chloro-4-nitrobenzoic acid (5 mol%), *t*-$BuNH_2$·TFA (5 mol%), benzaldehyde (0.5 mmol), and urea (0.6 mmol) in 1,4-dioxane/THF (2:8, *v*/*v*, 1.0 mL) was stirred at 25 °C for 30 min, then catalyst (1.5–5 mol%) and ethyl acetoacetate (1.0 mmol) were added sequentially. The reactions were performed at 25 °C for 2.5 d; b) isolated yield; c) determined by HPLC analysis (Chiralcel OD-H).

Table 2 Screening of acids, solvents and additives for the Biginelli reaction catalyzed by **2a**[a)]



Entry	Acid	Solvent	Additive	Yield (%)[b)]	*ee* (%)[c)]
1	Benzoic acid	THF	–	15	55
2	*p*-Nitrobenzoic acid	THF	–	29	58
3	*p*-Toluic acid	THF	–	36	61
4	*p*-Toluic acid	DMF	–	16	46
5	*p*-Toluic acid	1,4-Dioxane	–	8	56
6	*p*-Toluic acid	$CHCl_3$	–	7	60
7	*p*-Toluic acid	THF	$tBuNH_2$·*p*-TSA	trace	n.d.
8	*p*-Toluic acid	THF	Piperidine·*p*-TSA	10	69
9	*p*-Toluic acid	THF	Pyridine·*p*-TSA	42	26
10	*p*-Toluic acid	THF	Piperidine·HCl	24	69
11	*p*-Toluic acid	THF	Piperidine·TFA	30	69
12[d)]	*p*-Toluic acid	THF	Piperidine·TFA	41	69
13[e)]	*p*-Toluic acid	THF	Piperidine·TFA	42	68
14[f)]	*p*-Toluic acid	THF	Piperidine·TFA	38	9

a) A solution of catalyst **2a** (5 mol%), acid (5 mol%) and additive (5 mol%) in solvent (1.0 mL) was stirred at room temperature for 30 min, then urea (0.5 mmol), benzaldehyde (0.5 mmol), and ethyl acetoacetate (0.5 mmol) were added sequentially. The reactions were performed at room temperature for 2 d; b) isolated yield; c) determined by HPLC analysis (Chiralcel OD-H); d) the ratio of benzaldehyde/urea/ethyl acetoacetate was 1:1.2:2, and the reaction time was prolonged to 3 d; e) 10 mol% of catalyst **2a** was used; f) model catalyst **3** (5 mol%) was used.

presence of *p*-toluic acid in THF, and the results are listed in Table 2, entries 7–11. Although the yield decreased from 36% to 30%, the enantioselectivity could be increased from 61% *ee* to 69% *ee* when piperidine·TFA was employed (Table 2, entry 11 *vs.* entry 3). Further elevation of yield without loss of enantioselectivity could be achieved by changing the ratio of benzaldehyde/urea/ethyl acetoacetate from 1:1:1 to 1:1.2:2 and prolonging the reaction time from 2 to 3 d (Table 2, entry 12). But more loading of catalyst **2a** (10 mol%) could not obviously influence the reaction (Table 2, entry 13). Accordingly, extensive screening has shown that the optimized reaction conditions are 1:1.2:2 of benzaldehyde/urea/ethyl acetoacetate, 5 mol% **2a**, 5 mol% *p*-toluic acid, and 5 mol% piperidine·TFA in THF at room temperature.

In order to display the importance of calix[4]arene skeleton in **2a**, *L*-prolinamide derivative **3** as model catalyst was further investigated in the Biginelli reaction of benzaldehyde, urea, and ethyl acetoacetate under the optimal reaction conditions described above. Without calix[4]arene scaffold, only 9% *ee* was obtained (Table 2, entry 14). It demonstrated that the calix[4]arene skeleton in **2a** played an important role in helping to enantiocontrol the Biginelli reaction.

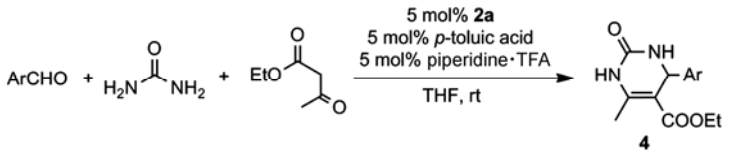
3.4 Scope of the enantioselective Biginelli reaction

With the optimized conditions in hand, the scope and limitations for the Biginelli reaction catalyzed by **2a** were examined. A range of aromatic aldehydes were employed to react with urea and ethyl acetoacetate, and the results were listed in Table 3. The location and electronic effect of substituent on the aromatic ring have a significant influence on the enantioselectivity of the process. The reactions of *meta*-substituted aromatic aldehydes afforded good-to-excellent enantioselectivities (80%–98% *ee*, Table 3, entries 2–5), while none- and *para*-substituted ones given lower *ee* values (20%–69% *ee*, Table 3, entries 1 and 7–10). Under the same location of substituents, aromatic aldehydes with electron-donating groups conducted higher enantioselectivities than electron-withdrawing ones. Furthermore, good enantioselectivity (90% *ee*, Table 3, entry 6) was also observed when fused-ring 1-naphthaldehyde was employed.

3.5 Mechanism studies

Based on the experimental results above, combining the structural characteristics of calix[4]arene [10–15] and hydroxyprolinamide [28], a possible transition state (TS) was proposed. As depicted in Figure 1, one face of the enamine was efficiently shielded by the steric hindrance of the bulky calix[4]arene skeleton, whereas the other face was available to attack the imine. Hence, a stable six-membered-ring TS afforded the products with *R* configuration in the favorable **TS-1**, while the unfavorable **TS-2** underwent an unstable eight-membered-ring and unactivated *N*-acylimine TS which conducted *S* products. Herein the piperidine·TFA, as a bridge between carbonyl of the enamine and the electron-rich cavity of calix[4]arene built by the supramolecular interaction of double hydrogen bond and cation-π [40, 41]

Table 3 Scope of the enantioselective Biginelli reaction catalyzed by **2a**[a)]



Entry	Ar	Product	Time (d)	Yield (%)[b)]	*ee* (%)[c)] (Configuration)[d)]
1	C_6H_5	**4a**	3	41	69 (*R*)
2	3-MeC_6H_4	**4b**	3	32	91 (*R*)
3	3-MeOC_6H_4	**4c**	3	32	98 (*R*)
4	3-ClC_6H_4	**4d**	3.5	38	90 (*R*)
5	3-$NO_2C_6H_4$	**4e**	4.5	48	80
6	1-Naphthyl	**4f**	3	22	90
7	4-MeOC_6H_4	**4g**	4	44	39
8	4-*t*BuC_6H_4	**4h**	4	32	67
9	4-BrC_6H_4	**4i**	4	36	34 (*R*)
10	4-$NO_2C_6H_4$	**4j**	4.5	26	20

a) Reagents and conditions: catalyst **2a** (5 mol%), *p*-toluic acid (5 mol%), piperidine·TFA (5 mol%), urea (0.6 mmol), aldehyde (0.5 mmol), ethyl acetoacetate (1.0 mmol), THF (1.0 mL), room temperature; b) isolated yield; c) determined by HPLC analysis (Chiralcel OD-H or AD-H); d) the absolute configuration was determined by comparison of the retention time with the ref. [28, 35].

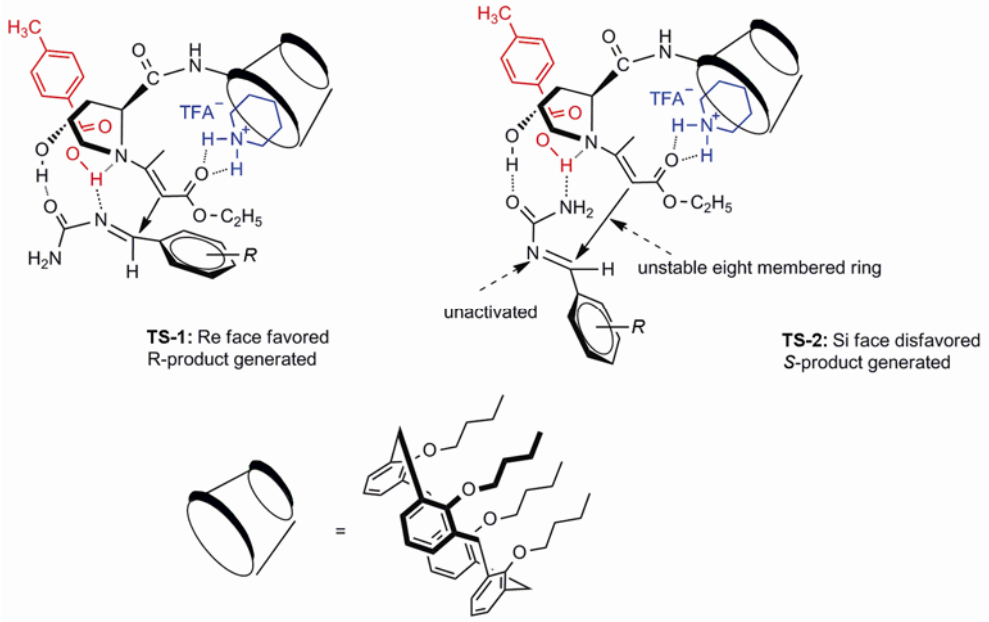


Figure 1 Plausible transition states in the asymmetric Biginelli reaction.

respectively, could further constrain the rotation of enamine, which leaded to the higher enantioselectivity of the process. The cation-π supramolecular interaction between piperidine·TFA and calix[4]arene cavity can be confirmed by ^{1}H NMR chemical shift change of the piperidine moiety in $CDCl_3$ induced by the ring current effect of calix[4]arene [40]. As shown in Figure 2, all the chemical shift of methylene protons (H_α, H_β and H_γ) on piperidine ring moved toward higher field ($\Delta\delta$ = 0.053, 0.069 and 0.090 ppm, respectively) because of the shield effect induced by calix[4]arene cavity. The degrees of the chemical shift changes of methylene protons ($\Delta\delta$: $H_\alpha < H_\beta < H_\gamma$) demonstrated the orientation of piperidine ring in the cavity (Distance between methylene and cavity: $D_\alpha < D_\beta < D_\gamma$) which was in agreement with the model in transition states (Figure 1). Furthermore, the achiral Brønsted acid (*p*-toluic acid) as the

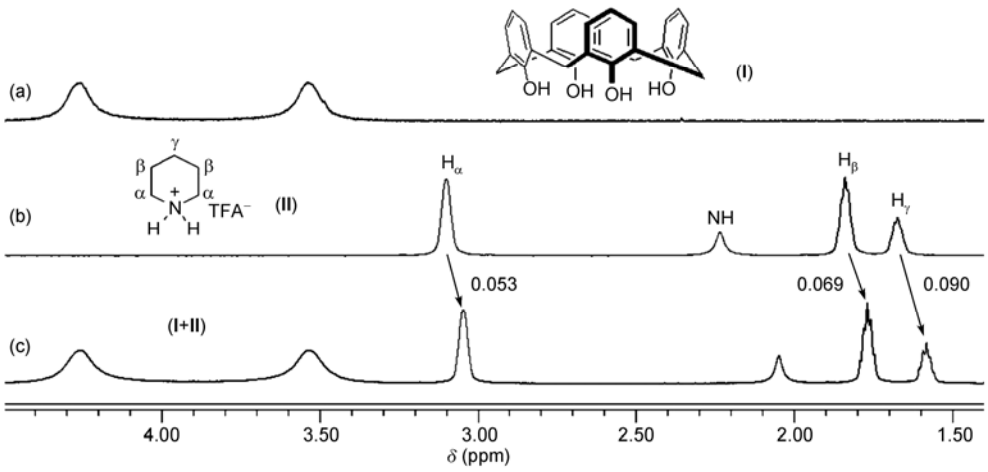


Figure 2 ^{1}H NMR chemical shift change of the piperidine moiety in $CDCl_3$ induced by the ring current effect of calix[4]arene. (a) Calix[4]arene (**I**) at 5 mM; (b) piperidine·TFA (**II**) at 5 mM; (c) complex (**I** + **II**) at 100 mM.

donor of double hydrogen bond was one of important components of six-membered-ring in **TS-1**. Therefore, the involvement of *p*-toluic acid, calix[4]arene scaffold, and piperidine·TFA in this reaction was quite crucial for the good enantioselectivities.

4 Conclusions

In conclusion, we have developed a series of novel supramolecular organocatalysts of hydroxyprolinamide based on the upper rim of calix[4]arene scaffold for the enantioselective Biginelli reaction. Under the optimal conditions, the reactions occurred with moderate-to-excellent *ee* values, especially the reactions of *meta*-substituted aromatic aldehydes with electron-donating groups and the fused-ring aldehyde afforded excellent enantioselectivities (90%–98% *ee*). A plausible transition state constructed by the supramolecular interactions including hydrogen bond and cation-π have been proposed to demonstrate the importance of calix[4]arene scaffold, *p*-toluic acid, and piperidine·TFA. This work has further extended the application of calixarene in asymmetric catalysis and presented an new way to prepare valuably optically active 3,4-dihydropyrimidin-2-(1*H*)-ones from enantioselective Biginelli reaction.

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