Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4467

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PAPER

Highly enantioselective Biginelli reaction catalyzed by SPINOL-phosphoric acids†

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Received 12th January 2012, Accepted 4th April 2012
DOI: 10.1039/c2ob25663k

A highly enantioselective Biginelli reaction promoted by chiral spirocyclic SPINOL-phosphoric acids has been developed. Under the optimized conditions with 5 mol% catalyst loading, a wide range of optically active dihydropyrimidinethiones (DHPMs) were obtained in high yields (up to 98%) with good to excellent enantioselectivities (up to 99% ee). The synthetic utility of this method was demonstrated by the synthesis of chiral precursors of three drugs, including (*S*)-Monastrol, (*S*)-L-771688 and (*S*)-SQ 32926.

Introduction

Enantioselective organocatalysis has been recognized as an environmentally benign and practical methodology for asymmetric synthesis.[1] Chiral cyclic phosphoric acids, which contain both a Brønsted acidic site and Lewis basic site, represent an important and widely applicable class of organocatalysts for a variety of enantioselective transformations.[2] Since the pioneering works of BINOL-phosphoric acids reported independently by the groups of Akiyama and Terada in 2004,[2a,b] a number of chiral diol-based phosphoric acids have been developed for widespread applications as metal-free chiral catalysts.[2c–f] Recently, we reported the chiral spirocyclic SPINOL-phosphoric acids as a novel skeleton of Brønsted acids, which effectively promoted the asymmetric Friedel–Crafts reaction of various indoles with imines[3a] and the highly enantioselective Pictet–Spengler reaction of N_b-α-naphthylmethyl tryptamines with aldehydes.[3b] The groups of List, Hu and Zhou also independently reported SPINOL-phosphoric acid-promoted enantioselective transformations.[4]

The Biginelli reaction is one of the most useful multicomponent reactions, it allows straightforward access to the functionalized 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones (DHPMs) *via* a one-pot condensation of an aldehyde, urea or thiourea, and acetoacetate.[5] Chiral DHPMs have exhibited a wide range of important pharmaceutical activities and have become the key structural units in many drugs,[6,7] such as (*S*)-Monastrol,[7a,b] (*S*)-L-771688,[7c] SNAP-7941[7d] and SQ 32926[7e] (Fig. 1), as well as in some natural alkaloids.[8] Consequently, the approach to access optically active DHPMs *via* asymmetric catalytic Biginelli reactions has received much attention.[9,10] Zhu and co-workers described the first highly enantioselective synthesis of DHPMs by using a chiral ytterbium Lewis acid catalyst.[10a] Gong and co-workers reported the first organocatalytic Biginelli reaction using BINOL-phosphoric acids with excellent enantiocontrol.[10b] The asymmetric synthesis of DHPMs *via* the chiral secondary amines,[10c–g] primary amines,[10h] bifunctional primary amine-thioureas,[10i] and $NbCl_5$/primary amines[10j] catalyzed enantioselective Biginelli reactions were also reported. Despite these elegant examples, the development of new organocatalysis with high enantiocontrol for this important reaction remains highly valuable. As a continuation of our work on SPINOL catalysts,[3] we herein report the first chiral SPINOL-phosphoric acid-catalyzed enantioselective Biginelli reaction.

Results and discussion

Initially, a series of SPINOL-phosphoric acids (*S*)-**1a–f** bearing different 6,6′-substituents were evaluated for their capacity to catalyze the model reaction of 4-nitrobenzaldehyde (**2a**), thiourea (**3a**), and ethyl acetoacetate (**4a**) (Table 1). The reaction was performed at 50 °C in the presence of 10 mol% catalyst in toluene. **1a** and **1b** showed much lower catalytic activity (Table 1, entries 1 and 2), while **1c–e** could promote the reaction in 64–88% yields with an ee of 64–84% (Table 1, entries 3–5). Interestingly,

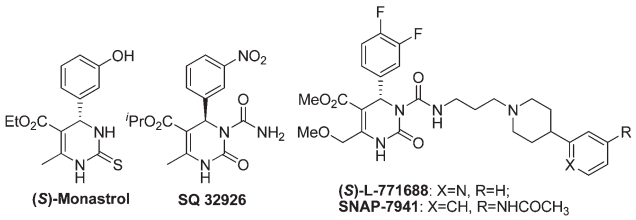

Fig. 1 Examples of biologically active DHPMs.

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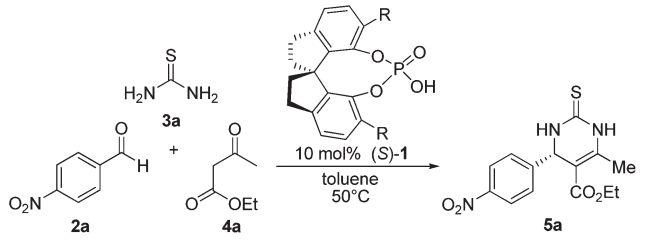
†Electronic supplementary information (ESI) available: Experimental procedure, ^1H, ^{13}C NMR and HPLC spectra for all compounds. See DOI: 10.1039/c2ob25663k

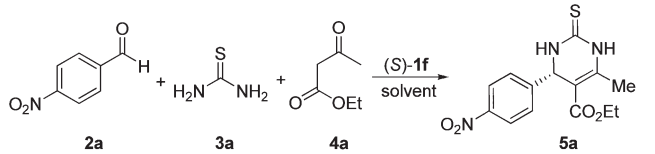
Table 1 Screening of the catalysts for the enantioselective Biginelli reaction[a]



Entry	Catalyst, R	Time (d)	Yield[b] (%)	ee[c] (%)
1	**1a**, Ph	6	47	38
2	**1b**, 4-PhC_6H_4	6	30	34
3	**1c**, 4-ClC_6H_4	3	64	70
4	**1d**, 3,5-$(CH_3)_2C_6H_3$	3	80	64
5	**1e**, 3,5-$(CF_3)_2C_6H_3$	3	88	84
6	**1f**, 1-Naphthyl	2	91	90

[a] Reactions were carried out with **2a** (0.10 mmol), **3a** (0.12 mmol), **4a** (0.30 mmol) and 10 mol% of catalyst in toluene (1 mL) at 50 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Table 2 Optimization of the reaction conditions with catalyst **1f**[a]



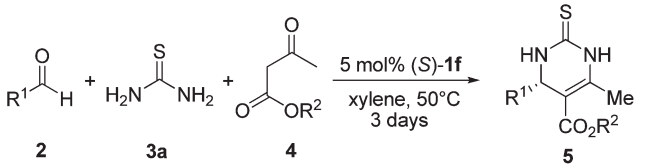
Entry	**1f** (mol%)	Solvent	*T*(°C)	Time (d)	Yield[b] (%)	ee[c] (%)
1	10	Benzene	50	3	90	92
2	10	Toluene	50	2	91	90
3	10	Xylene	50	1.5	96	93
4	10	1,4-Dioxane	50	6	48	87
5	10	CH_3CN	50	6	55	76
6	10	$ClCH_2CH_2Cl$	50	3	82	91
7	10	CH_2Cl_2	rt	6	63	93
8	10	Xylene	rt	6	56	90
9	5	Xylene	50	3	92	94
10	5	Xylene	70	1.5	85	91
11	2	Xylene	70	3	71	91

[a] Reactions were carried out with **2a** (0.10 mmol), **3a** (0.12 mmol), **4a** (0.30 mmol) and catalyst **1f** in solvent (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

catalyst **1f**, which provided excellent enantioselectivity in our previous reports,[3] was also the best catalyst for the present reaction, affording the desired DHPM **5a** in 91% yield with 90% ee (Table 1, entry 6).

Encouraged by these results, we further optimized the reaction conditions by using **1f** as catalyst. With 10 mol% catalyst loading, a brief survey of solvent effect was carried out, and ee values of 76–93% were obtained in all cases (Table 2, entries 1–7). Accordingly, xylene was chosen to be the most favorable solvent, in terms of both yield (96%) and enantioselectivity (93%). Subsequent temperature and catalyst loading survey

Table 3 Substrates scope of the enantioselective Biginelli reaction[a]



Entry	R^1 (**2**)	R^2 (**4**)	**5**	Yield[b] (%)	ee[c] (%)
1	4-$NO_2C_6H_4$ (**2a**)	Et (**4a**)	**5a**	92	94
2	3-$NO_2C_6H_4$ (**2b**)	Et (**4a**)	**5b**	86	97
3	2-$NO_2C_6H_4$ (**2c**)	Et (**4a**)	**5c**	81	99
4	4-BrC_6H_4 (**2d**)	Et (**4a**)	**5d**	92	90
5	3-BrC_6H_4 (**2e**)	Et (**4a**)	**5e**	82	92
6	3-FC_6H_4 (**2f**)	Et (**4a**)	**5f**	89	94
7	2-ClC_6H_4 (**2g**)	Et (**4a**)	**5g**	88	97
8	4-MeC_6H_4 (**2h**)	Et (**4a**)	**5h**	96	91
9	3-$MeOC_6H_4$ (**2i**)	Et (**4a**)	**5i**	90	94
10	Piperonyl (**2j**)	Et (**4a**)	**5j**	84	94
11	1-Naphthyl (**2k**)	Et (**4a**)	**5k**	98	99
12	2-Furyl (**2l**)	Et (**4a**)	**5l**	80	90
13	Cyclohexyl (**2m**)	Et (**4a**)	**5m**	40	84
14	3-$NO_2C_6H_4$ (**2b**)	Me (**4b**)	**5n**	94	91
15	3-$NO_2C_6H_4$ (**2b**)	*i*-Pr (**4c**)	**5o**	94	95
16	3,4-$F_2C_6H_3$ (**2o**)	Me (**4b**)	**5p**	90	93

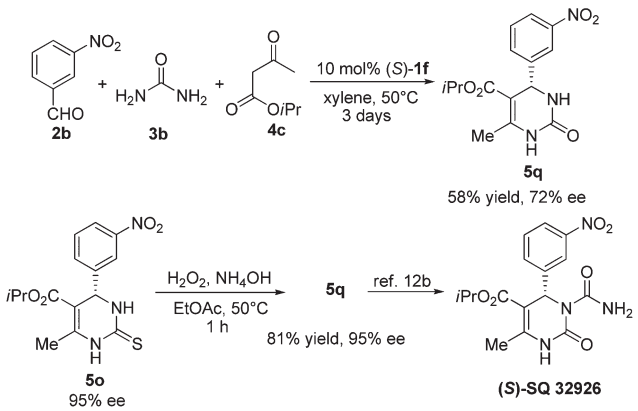
[a] Reactions were carried out with **2** (0.10 mmol), **3** (0.12 mmol), **4** (0.30 mmol) and 5 mol% of **1f** in xylene (1 mL) at 50 °C for 3 days. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

revealed that the operation with 5 mol% of **1f** at 50 °C was optimal for the synthesis of **5a** with the highest 94% ee (Table 2, entries 8–11).

With the optimal conditions in hand, the enantioselective Biginelli reactions of a variety of aldehydes with thiourea and ethyl acetoacetate were then investigated. As shown in Table 3, a variety of substituted benzaldehydes **2a–j** could undergo the reactions to afford DHPMs in high yields with excellent enantioselectivities ranging from 90% ee to 99% ee (Table 3, entries 1–10). In general, the electronic effect slightly influences the results, whereas the steric effect plays an important role on controlling the enantioselectivity, as demonstrated by that the *ortho*-substituted benzaldehydes afforded higher enantio-selectivities (Table 3, entries 3 and 7). Excellent yield (98%) and enantioselectivity (99% ee) was obtained when sterically hindered 1-naphthaldehyde **2k** was employed (Table 3, entry 11). Heteroaromatic aldehyde **2l** also underwent the reaction with 80% yield and 90% ee (Table 3, entry 12). However, aliphatic aldehydes were much less reactive. For example, cyclohexyl aldehyde (**2m**) afforded poor yield (40%) and lower enantioselectivity (84% ee) (Table 3, entry 13). For alkyl acetoacetates **4**, both methyl and iso-propyl gave similar yields and enantioselectivity (Table 3, entries 14–16).

It is a remarkable fact that DHPMs **5i** and **5p** may be the chiral precursors of two drugs, including (*S*)-Monastrol and (*S*)-L-771688,[10k,11] respectively. The absolute configurations of DHPMs **5** were correlated to the absolute configuration of **5a**, which was confirmed to be *S* by comparison of the optical rotation with the literature.[10k]

The Biginelli reaction involving urea instead of thiourea was revealed to be much less reactive even with 10 mol% of **1f**,



Scheme 1 Highly enantioselective synthesis of dihydropyrimidinone **5q**.

affording dihydropyrimidinone **5q** with a significant drop of both yield and enantioselectivity (Scheme 1). Alternatively, treatment of the corresponding dihydropyrimidinethione **5o** (Table 3, entry 15) with hydrogen peroxide afforded **5q** in 81% yield with a maintained enantioselectivity of 95% ee (Scheme 1). Further conversion of **5q** will lead to (*S*)-SQ 32926, whose enantiomer has been identified as potent orally active antihypertensive agent.[12]

Conclusions

In summary, we have identified SPINOL-phosphoric acids as highly efficient organocatalysts for the enantioselective Biginelli reaction, providing a variety of optically active DHPMs in good yields with excellent ee values. The synthetic utility of this method was demonstrated by the synthesis of chiral precursors of three drugs, including (*S*)-Monastrol, (*S*)-L-771688 and (*S*)-SQ 32926. Further applications of the novel chiral spirocyclic SPINOL-phosphoric acids in asymmetric catalysis are currently underway.

Experimental section

General information

Unless otherwise noted, all reagents were purchased from commercial supplies and used without further purification. Solvents were used without dryness. ^{1}H NMR spectra were recorded on 400 MHz spectrometer. The chemical shifts were reported relative to internal standard TMS (0) in $CDCl_3$ or 2.5 in DMSO-d_6. The following abbreviations were used to describe peak patterns where appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants were reported in Hertz (Hz). ^{13}C NMR spectra were recorded on 100 MHz spectrometer, referred to the internal solvent signals (77.0 for $CDCl_3$ or 40.0 for DMSO-d_6). Optical rotations were determined using a Perkin Elmer Model 341 polarimeter at 20 °C. The enantiomeric excess (ee) values were determined by chiral HPLC analysis on Daicel Chiralpak AS-H or AD-H columns.

General procedure for the enantioselective Biginelli reaction

Under nitrogen atmosphere, aldehyde **2** (0.1 mmol), thiourea **3a** (0.12 mmol) and catalyst (*S*)-**1f** (0.005 mmol) were dissolved in 1 mL xylene. After being stirred at room temperature for 2 hours, acetoacetate **4** (0.3 mmol) was added, and the resulting mixture was stirred at 50 °C for 3 days as monitored by TLC. Then the reaction was cooled to room temperature, diluted with ethyl acetate and added some silica gel. The organic solvents were removed under vacuum and the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4–1/2) to afford the corresponding DHPM product **5**.

(*S*)-Ethyl-6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5a). This product was obtained in 92% yield after chromatography and 94% ee as determined by HPLC [Daicel Chiralpak AS-H, *n*-hexane/*i*-propanol = 70/30, 1.0 mL min^{-1}, λ = 254 nm, *t* (minor) = 17.84 min, *t* (major) = 22.50 min]. $[\alpha]_D^{20}$ = +223.6° (*c* = 0.6, EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (t, *J* = 6.8 Hz, 3H), 2.33 (s, 3H), 4.03 (q, *J* = 6.8 Hz, 2H), 5.33 (d, *J* = 3.6 Hz, 1H), 7.51 (d, *J* = 9.2 Hz, 2H), 8.25 (d, *J* = 8.8 Hz, 2H), 9.76 (s, 1H), 10.49 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.4, 17.7, 54.1, 60.2, 100.2, 124.4, 128.3, 146.4, 147.4, 150.8, 165.3, 175.0; MS (ESI) *m*/*z* 320.1 ([M − H]$^-$).

Synthesis of dihydropyrimidinone 5q

To a solution of **5o** (28.9 mg, 0.086 mmol) in ethyl acetate (1.6 mL) was added ammonia (0.7 mL) and 30% aqueous H_2O_2 (0.7 mL). After stirring at 50 °C for 1 hour in open air, the reaction mixture was quenched with 1 mL water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 2/1).

(*S*)-Isopropyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5q). This product was obtained in 81% yield and 95% ee as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol = 80/20, 1.0 mL min^{-1}, λ = 254 nm, *t* (minor) = 9.30 min, *t* (major) = 13.19 min]. $[\alpha]_D^{20}$ = +90.8° (*c* = 0.6, EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 2.30 (s, 3H), 4.81–4.88 (m, 1H), 5.32 (s, 1H), 7.66–7.74 (m, 2H), 7.91 (s, 1H), 8.11–8.16 (m, 2H), 9.37 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.3, 21.9, 22.2, 54.2, 67.1, 99.1, 121.6, 122.7, 130.6, 133.5, 147.6, 148.2, 149.7, 152.3, 165.0; MS (ESI) *m*/*z* 317.9 ([M − H]$^-$).

Acknowledgements

We thank the National Natural Science Foundation of China (no. 21032005) and the Fundamental Research Funds for the Central Universities for financial support of this research.

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