Tetrahedron: *Asymmetry* xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of a novel sterically hindered chiral cyclic phosphoric acid derived from L-tartaric acid and application to the asymmetric catalytic Biginelli reaction

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ARTICLE INFO

Article history:
Received 10 September 2016
Revised 11 November 2016
Accepted 20 November 2016
Available online xxxx

ABSTRACT

A novel sterically hindered chiral cyclic phosphoric acid derived from L-tartaric acid was designed and synthesized based on highly regioselective cyclosulfitation of chiral 1,1,4,4-tetraphenylbutanetetraol. The asymmetric Biginelli reaction catalyzed by this newly synthesized chiral phosphoric acid was examined, and enantioselectivities up to 99% ee was obtained.

1. Introduction

Chiral cyclic phosphoric acids are considered to be powerful Brønsted acid catalysts in asymmetric catalytic reactions.[1] In 2004, both Akiyama et al. and Terada et al. independently reported asymmetric Mannich reaction catalyzed by chiral BINOL-derived phosphoric acids.[2] Since then, novel chiral cyclic phosphoric acid catalysts have been continuously developed and have achieved great success in asymmetric selective C—H activations,[3] Friedel-Crafts reactions[4] hetero-Diels-Alder reactions,[5] Biginelli and Biginelli-like condensations,[6] transfer hydrogenations,[7] and so on.[8]

So far most of the studies have focused on the synthesis and application of chiral phosphoric acids derived from enantiomerically pure 1,1′-bi-2-naphthol and its derivatives; however, the introduction of a substituent at the 3,3′-position of 1,1′-bi-2-naphthols, which is usually considered as a chiral control group, plays a crucial role for their chiral induction ability.[9] The cost of the synthesis of 1,1′-bi-2-naphthols and their derivatives is high because of complicated preparative procedures (Scheme 1),[10] although some of them have been marketed. In 2011, an improved synthesis route,[11] in which the protection and deprotection procedure of the hydroxyl groups was simplified, was reported, although an organolithium reagent and Suzuki coupling reaction are still required.

Enantiomerically pure tartaric acid is an inexpensive chiral starting material, and its derivatization is generally easy to carry out. Chiral tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs), a class of important derivatives of tartaric acid, have been utilized as versatile chiral ligands in various syntheses and as chiral hosts in supramolecular chemistry.[12] However, asymmetric transformations catalyzed by chiral phosphoric acids derived from TADDOLs have seldom been reported to date.[13] Considering that (2*R*,3*R*)-1,1,4,4-tetrasubstituted butanetetraols could be readily prepared via a one step reaction of enantiomerically pure diethyl tartrate with a Grignard reagent[14] and our previous work,[15] a novel sterically hindered chiral cyclic phosphoric acid was designed and synthesized based on regioselective cyclosulfitation reaction of (2*R*,3*R*)-1,1,4,4-tetraphenylbutanetetraol **1** (Scheme 2). We observed that the newly synthesized chiral cyclic phosphoric acid showed an excellent chiral induction ability for asymmetric Biginelli reactions. Herein we report the first application of chiral cyclic phosphoric acids derived from (2*R*,3*R*)-1,1,4,4-tetraphenylbutanetetraol to asymmetric catalyzed Biginelli reactions.

2. Results and discussion

2.1. Design and synthesis of novel chiral phosphoric acid 4

During our continuing study of the chemistry of chiral 1,1,4,4-tetrasubstituted butanetetraol,[14,15] which can be readily prepared via one-step arylation reaction of L-diethyl tartrate with a Grignard reagent, we found that (2*R*,3*R*)-**1** could undergo highly selective 2,3-cyclosulfitation reaction with $SOCl_2$ to give cyclic sulfite ester (4*R*,5*R*)-**2** in excellent yield.[16] Further studies found that (4*R*,5*R*)-**2** was stable toward acidic solutions and organic bases, such as pyridine and triethyl amine, but the sulfite group can easily undergo hydrolysis in NaOH solution to give (2*R*,3*R*)-**1**. Compared with the deprotection of TADDOL, which is usually involved with

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http://dx.doi.org/10.1016/j.tetasy.2016.11.014
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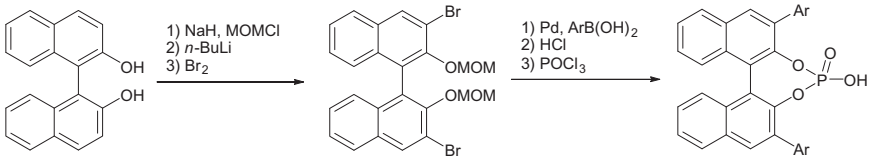
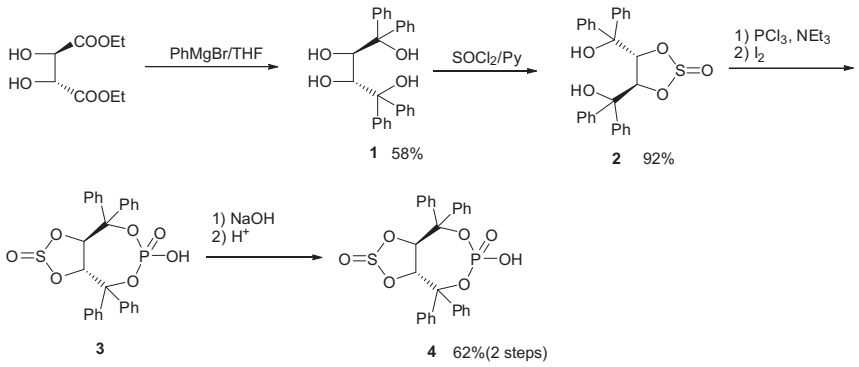


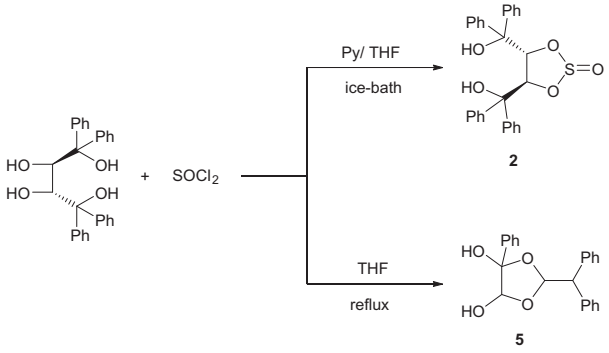
Scheme 1. General procedure for the synthesis of BINOL-derived phosphoric acids.



Scheme 2. Synthesis of chiral phosphoric acid **4** based on the regioselective sulfitation of (2*R*,3*R*)-**1**.

the oxidation and reduction procedure with DDQ and $LiALH_4$,[17] selective 2,3-protection and deprotection of (2*R*,3*R*)-**1** can be readily realized. Based on the selective 2,3-cyclosulfitation of (2*R*,3*R*)-**1**, we designed and synthesized chiral phosphoric acid **4**.

As shown in Scheme 3, selective 2,3-cyclosulfitation of (2*R*,3*R*)-**1** with an equivalent of thionyl chloride was carried out in an ice-bath, and stoichiometric organic bases such as triethylamine or pyridine were used to promote this reaction. If the reaction was carried out at high temperature and in the absence of organic bases, the HCl generated in situ would break the C—C bond to afford 5,5-diphenyl-2-diphenylmethyl-4-hydroxy-1,3-dioxolane **5**, whose structure has been confirmed in our previous work.[15a]



Scheme 3. Selective 2,3-cyclosulfitation of (2*R*,3*R*)-**1** with $SOCl_2$.

Direct phosphorylation of cyclosulfite **2** to cyclic phosphate **3** using $POCl_3$, which is effective for the preparation of chiral BINOL-phosphoric acids, was unsuccessful. Therefore, an alternative synthetic route[18] was adopted, namely, cyclosulfite **2** was treated with PCl_3, subsequently oxidized into **3** by I_2, and finally **3** was hydrolyzed by NaOH solution to give chiral phosphoric acid **4** in good yield. As seen in Figure 1, recrystallization from ethanol afforded a solvate of **4** with an ethanol molecule, which has a C_2 symmetric axis.

2.2. Asymmetric Biginelli reaction catalyzed by chiral phosphoric acid 4

A chiral inducer with a C_2-symmetry axis usually provides high levels of absolute stereo chemical control. The newly synthesized C_2 chiral phosphoric acid **4** was employed to catalyze the asymmetric Biginelli reaction. The Biginelli reaction of benzaldehyde, thiourea and ethyl acetoacetate catalyzed by chiral phosphoric acid **4** was set as a model reaction. As shown in Table 1, the one-pot Biginelli reaction catalyzed by chiral phosphoric acid **4** was examined under different conditions.

From Table 1, it can be seen that the reaction medium plays a crucial role in promoting the reaction yield and enantioselectivity. Using THF as the reaction solvent is favorable for the reaction yield, but only gave moderate enantioselectivity (entry 1). Only trace amounts of the product were afforded when CH_2Cl_2 was used as the solvent, although displayed excellent enantioselectivity (entry 3). Lewis acid or protonic acid was added as an additive, it increased the reaction yield, but decreased the enantioselectivity (entries 6, 7). An improvement in the yield could be achieved by elevating the reaction temperature, but the stereoselectivity decreased (entry 9).

With the optimal conditions in hand, we explored the generality of the phosphoric acid-catalyzed asymmetric Biginelli reaction. Table 2 indicates that enantiomeric excess for the asymmetric Biginelli reaction catalyzed by chiral phosphoric acid **4** is in a close relationship with the composition of aromatic aldehydes. It was observed that the reaction with unsubstituted aromatic aldehyde and the electron-rich aromatic aldehydes (3- or 4-MeO and 4-Me_2N-substituted aromatic aldehydes) generally gave excellent asymmetric induction (entries 1–4, 6), except for 2-$MeOC_6H_4CHO$ (entry 5). For the electron-deficient aromatic aldehydes (entries 7–9), poor reaction yields and the enantioselectivities were obtained, while the reaction for 3-$NO_2C_6H_4CHO$ showed no enantioselectivity.

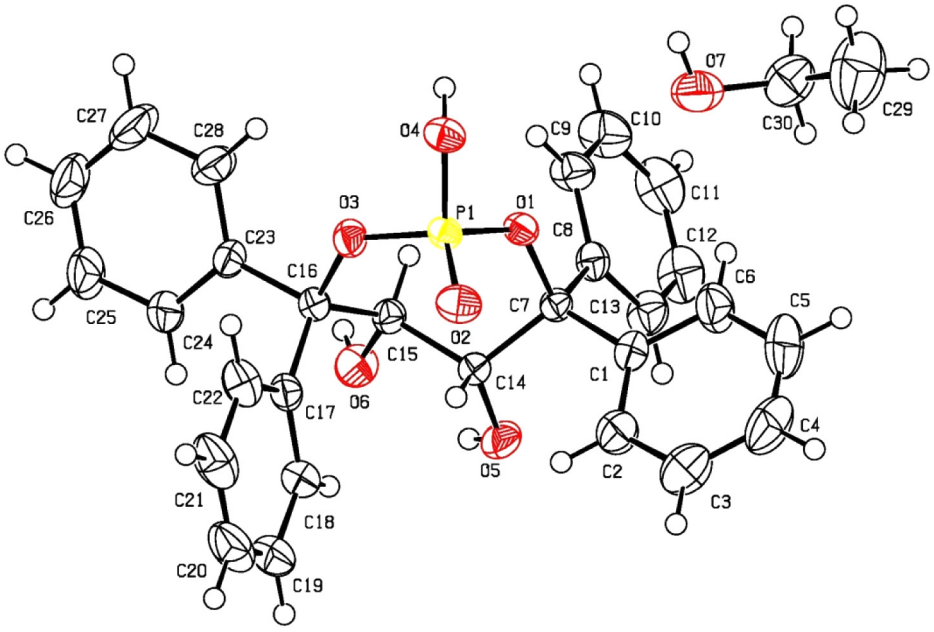
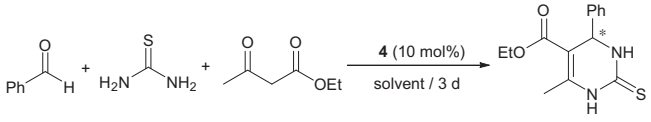


Figure 1. ORTEP of chiral phosphoric acid **4** bearing one ethanol molecule.

Table 1
Influence of experimental conditions on the asymmetric Biginelli reaction catalyzed by chiral phosphoric acid **4**[a]



Entry	Solvent	Reaction temperature	Additive	Yield, %[b]	ee, %[c]
1	THF	rt	–	62	47
2	PhMe	rt	–	36	29
3	CH_2Cl_2	rt	–	Trace	>99
4	CH_3COCH_3	rt	–	58	>99
5	MeOH	rt	–	Trace	8
6	CH_3COCH_3	rt	HOAc	72	42
7	CH_3COCH_3	rt	$B(OH)_3$	69	42
8	CH_3COCH_3	0 °C	–	Trace	>99
9	CH_3COCH_3	50 °C	–	66	47

[a] Reaction conditions: benzaldehyde (0.2 mmol), thiourea (0.24 mmol), ethyl acetoacetate (0.6 mmol) and chiral phosphoric acid **4** (10 mol%) in 1 mL of solvent were stirred vigorously for 3 days at room temperature.
[b] Isolated yield based on aldehyde.
[c] Determined by HPLC.

3. Conclusion

A novel sterically hindered C_2 chiral phosphoric acid **4** has been synthesized by a convenient procedure based on the highly regioselective 2,3-cyclosulfitation of (2*R*,3*R*)-**1** derived from L-tartaric acid with thionyl chloride, and its asymmetric catalytic activity to Biginelli reaction was preliminary examined. Chiral phosphoric acid **4** showed excellent enantioselectivities of up to 99% ee for unsubstituted and electron-rich aromatic aldehydes, while for the electron-deficient nitro-substituted aromatic aldehydes, the reaction gave very low yield and enantioselectivity. Further investigations on the type and the size of the substituent on the asymmetric Biginelli reaction, as well as the asymmetric catalytic activity of this novel chiral phosphoric acid in other asymmetric reactions are currently underway in our laboratory.

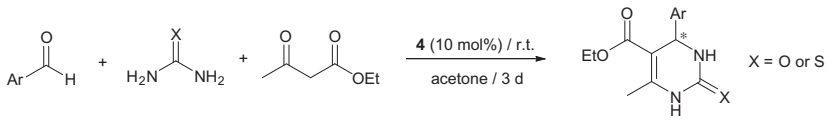
4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were performed on a Varian Mercury VS 300 or Bruker Avance III 400. MS was recorded on a VG ZAB-HF-3F spectrometer. Optical rotations were measured on a PE-341 Mc polarimeter. Melting points were determined on a VEB Wagetechnik Rapio PHMK05 instrument, and are uncorrected. Ee values were analyzed by HPLC on a Chiralcel AD-H column at room temperature with *n*-hexane/*i*-propanol as eluent. Diethyl L-tartrate was prepared from L-tartaric acid and ethanol. THF was freshly distilled after refluxing with Na, while $SOCl_2$, Py, PCl_3 and I_2 were purchased and used directly. Commercially available starting materials were used without further purification if not specified.

Please cite this article in press as: Hu, X.; et al. *Tetrahedron: Asymmetry* (2016), http://dx.doi.org/10.1016/j.tetasy.2016.11.014

Table 2
Preliminary examination of asymmetric catalytic ability of chiral phosphoric acid **4**[a]



Entry	Ar	X	Yield (%)[b]	ee (%)[c]
1	Ph	O	56	>99
2	Ph	S	58	>99
3	4-$MeOC_6H_4$	S	65	97
4	3-$MeOC_6H_4$	S	61	>99
5	2-$MeOC_6H_4$	S	63	7
6	4-$NMe_2C_6H_4$	S	66	97
7	2-$NO_2C_6H_4$	S	23	17
8	3-$NO_2C_6H_4$	S	20	0
9	4-$NO_2C_6H_4$	S	21	17

[a] Reaction conditions: aromatic aldehydes (0.2 mmol), urea or thiourea (0.24 mmol), ethyl acetoacetate (0.6 mmol) and chiral phosphoric acid **4** (10 mol%) in 1 mL of acetone were stirred vigorously for 3 days at room temperature.
[b] Isolated yield based on aldehyde.
[c] Determined by HPLC.

4.2. Preparation of (2*R*,3*R*)-1

PhMgBr was prepared via a conventional Grignard reaction procedure, followed by the careful dropwise addition of a solution of (2*R*,3*R*)-diethyl tartrate (4.1 g, 20 mmol) in 20 mL of freshly distilled THF. After the addition, the mixture was allowed to stir for an additional 0.5 h, and then refluxed for 1 h. After cooling to rt, 100 mL of saturated aqueous NH_4Cl were added and stirred until a two-phase solution was obtained. The solution was extracted with Et_2O (20 mL × 3), dried over Na_2SO_4, followed by removal of most of the solvent, then steam distillation was carried out, and the residue was recrystallized with 80% ethanol to give 4.9 g of (2*R*,3*R*)-**1** as white needle crystals, yield: 58%, mp: 148–151 °C, $[\alpha]_D^{25}$ = +154.2 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.13 (m, 20H, Ar-H), 4.65 (d, *J* = 7.2 Hz, 2H, OH), 4.41 (d, *J* = 4.7 Hz, 2H, CH), 3.77 (d, *J* = 5.3 Hz, 2H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.8, 142.7, 134.6, 131.5, 129.3, 128.3, 128.2, 127.9, 127.5, 126.7, 125.5, 81.3, 69.7.

4.3. Preparation of (4*R*,5*R*)-2

A 50 mL dried round-bottomed flask was charged with (2*R*,3*R*)-**1** (4.26 g, 10 mmol), pyridine (2 mL, 25 mmol) and freshly distilled THF (20 mL). The flask was sealed with a rubber septum and stirred in an ice-bath for 10 min, after which thionyl chloride (0.8 mL, 11 mmol) was added slowly with a syringe. After complete addition, the mixture was allowed to stir for an additional 1 h in an ice-bath. The mixture was treated with H_2O, and the organic phase was separated, and the aqueous phase extracted with Et_2O (10 mL × 3). The organic solutions were combined, dried and concentrated; 4.3 g of colorless crystals were obtained from THF and Et_2O solution in 94% yield, mp:165–167 °C, $[\alpha]_D^{20}$ = +65.8 (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.42 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.34–7.19 (m, 8H, Ar-H), 7.03 (s, 8H, Ar-H), 5.97 (d, *J* = 2.1 Hz, 1H, CH), 5.90 (d, *J* = 2.1 Hz, 1H, CH), 4.49 (s, 1H, OH, disappeared after adding D_2O), 3.70 (t, *J* = 6.0 Hz, 4H), 2.37 (s, 1H, OH, disappeared after adding D_2O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.1, 143.3, 141.5, 141.0, 128.7, 128.5, 128.4, 128.0, 127.4, 127.1, 126.9, 125.9, 89.7, 89.6, 87.2, 87.1, 78.8, 77.7. LC–MS(EI): 471 (40, [M^+−1]), 408 (100, [M^+−64 (SO_2)]).

4.4. Preparation of (5*R*,6*R*)-4

Under Ar, a freshly dried three-necked round bottomed 150 mL flask equipped with a magnetic bar, 100 mL pressure-equalizing dropping funnel and reflux condenser with oil seal was charged with 10 mL dry of THF and 2.1 mL of NEt_3 (15 mmol). The flask was cooled in an ice-bath for 15 min, after which 1 mL of PCl_3 was added. The mixture was then stirred in an ice-bath for another 15 min. The pressure-equalizing dropping funnel was charged with a solution of (4*R*,5*R*)-**2** (4.3 g, 9 mmol) in dry THF (80 mL) and then added dropwise into the flask. After the complete addition, the mixture was stirred in an ice-bath for 1 h, and then warmed to room temperature and stirred for an additional 0.5 h. Next, 1.0 mL of H_2O was added, followed by 7.3 g of I_2 and 4.7 mL of Py and stirred for another 1 h. The mixture was poured into saturated $NaHSO_3$ solution and stirred so as to remove the excess I_2.

The organic phase containing intermediate **3** was not further purified and directly mixed with 2 M NaOH solution, stirred at room temperature for 2 h, after which 2 M HCl was added to adjust the pH to 2–3. The solution was then extracted with Et_2O (20 mL × 3), dried and concentrated. The residue was recrystallized with 80% ethanol to afford 2.7 g of colorless bulk crystal **4**, 62%yield over 2 steps. Mp: 100–105 °C, $[\alpha]_D^{25}$ = −76 (*c* 0.3, MeOH). ^1H NMR (400 MHz, DMSO): δ 7.54–7.52 (q, 8H, Ar-H), 7.37–7.22 (m, 12H, Ar-H), 5.69 (s, 2H, OH), 4.78 (s, 2H, CH). ^{13}C NMR (100 MHz, DMSO): δ 145.44, 141.25, 128.73, 127.80, 86.63, 71.63.

A single crystal suitable for X-ray structural analysis was obtained by slowly cooling a hot methanol solution of (5*R*,6*R*)-**4** to room temperature. A colorless crystal was mounted on a glass fibre. X-ray diffraction intensity data collection and cell refinement were performed on Bruker P4 four-circle diffractometer equipped with a graphite monochromator. A total of 7579 unique reflections were collected using Mokα (λ = 0.71073 Å) radiation by fine-focus sealed tube at 298(2) K, of which 6945 reflections had I > 2σ (*I*) and were used in the structure solution and refinements. The corrections for Lp factors and empirical absorption were applied to the intensity data. All calculations were performed on Enraf-Nonius Molen/VAX Software using the program SHELXL-97. The structure was solved by direct methods and refined on F^2 using a full-matrix least-squares technique. The non-hydrogen atoms were also refined by a full-matrix least-squares technique, anisotropically, and hydrogen atoms were included but not refined. Cell dimensions were obtained by the least-squares refinement of well centered 350 reflections in the range of 1.77 < θ < 29.99°.

Crystal data for (4*R*,5*R*)-**4**: empirical formula, $C_{30}H_{31}O_7P$; formula weight, 534.52; calculated density, 1.299 g/cm^3; volume (*V*), 1366.1(3) Å^3; crystal system, Monoclinic; space group, *P*2(1); *Z* = 2; unit cell dimensions, *a* = 12.5539 (18), *b* = 9.4686 (14), *c* = 12.5539 (18), α = 90° β = 113.73°, γ = 90°; absorption coefficient

(μ), 0.147 mm^{-1}; independent reflections:7579[R(int) = 0.0972; index ranges $-15 \leqslant h \leqslant 17$, $-13 \leqslant k \leqslant 12$, $-17 \leqslant l \leqslant 17$; F(000), 564; GOF, 1.030.

4.5. Typical procedure for asymmetric catalyzed Biginelli reactions

After a solution of aromatic aldehyde (0.2 mmol), thiourea (0.24 mmol) and chiral phosphoric acid **4** (0.02 mmol) in acetone (1 mL) was stirred vigorously at room temperature for 2 h, ethyl acetoacetate (0.6 mmol) was added. The resulting reaction mixture was stirred vigorously at room temperature for 3 days and then EtOAc (10 mL) and some silica gel were added. After removal of the solvent, the residue was purified via the column chromatography using petroleum ether:ethyl acetate (6:1).

4.5.1. Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Yield: 56%, $[\alpha]_D^{20} = -63$ (c 0.25, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H, NH), 7.72 (s, 1H, NH), 7.37–7.07 (m, 5H, Ar-H), 5.12 (d, J = 2.8 Hz, 1H, CH), 3.95 (q, J = 7.1 Hz, 2H, OCH_2), 2.22 (s, 3H, CH_3), 1.06 (t, J = 7.1 Hz, 3H, CH_3). Enantiomeric excess: >99%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 9.298 -min(major), t_R = 10.507 min(minor).

4.5.2. 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione

Yield: 58%, $[\alpha]_D^{20} = -68$ (c 0.25, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.32 (s, 1H, NH), 9.63 (s, 1H, NH), 7.38–7.16 (m, 5H, Ar-H), 5.16 (d, J = 3.6 Hz, 1H, CH), 3.98 (q, J = 7.1 Hz, 2H, OCH_2), 2.25 (d, J = 17.4 Hz, 3H, CH_3), 1.11–0.97 (m, 3H, CH_3). Enantiomeric excess: >99%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 9.255 min(minor), t_R = 10.923 min(major).

4.5.3. 5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione

Yield: 65%, $[\alpha]_D^{20} = -18.3$ (c 0.24, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H, NH), 9.58 (s, 1H, NH), 7.10 (d, J = 8.6 Hz, 2H, Ar-H), 6.87 (d, J = 8.6 Hz, 2H, Ar-H), 5.09 (d, J = 3.4 Hz, 1H, CH), 3.97 (q, J = 7.1 Hz, 2H, OCH_2), 3.69 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.13–0.99 (m, 3H, CH_3). Enantiomeric excess: 97.5%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 95:5, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 6.780 min(minor), t_R = 7.840 min(major).

4.5.4. 5-Ethoxycarbonyl-6-methyl-4-(3-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione

Yield 61%, $[\alpha]_D^{20} = -113.7$ (c 0.31, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H, NH), 7.87 (s, 1H, NH), 7.22 (t, J = 7.6 Hz, 1H, Ar-H), 6.87 (d, J = 7.6 Hz, 1H, Ar-H), 6.82–6.79 (m, 2H, CH), 5.36 (d, J = 3.2 Hz, 1H, CH), 4.14–4.06 (m, 2H, OCH_2), 3.77 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 1.17 (t, J = 6.8 Hz, 3H, CH_3). Enantiomeric excess: >99%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 12.982 min(minor), t_R = 13.960 min(major).

4.5.5. 5-Ethoxycarbonyl-6-methyl-4-(2-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione

Yield: 63%, $[\alpha]_D^{20} = -114.5$ (c 0.2, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H, NH), 9.21 (s, 1H, NH), 7.23 (t, J = 7.7 Hz, 1H, Ar-H), 7.00 (dd, J = 20.2, 7.8 Hz, 2H, Ar-H, Ar-H), 6.87 (t, J = 7.5 Hz, 1H, Ar-H), 5.48 (d, J = 3.4 Hz, 1H, CH), 3.91 (dd, J = 13.8, 6.7 Hz, 2H, OCH_2), 3.76 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.01 (t, J = 7.1 Hz, 3H, CH_3). Enantiomeric excess: 7%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 10.047 min(major), t_R = 11.872 min(minor).

4.5.6. 5-Ethoxycarbonyl-6-methyl-4-(4-dimethylaminophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione

Yield: 66%, $[\alpha]_D^{20} = -41.7$ (c 0.25, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H, NH), 9.51 (s, 1H, NH), 6.99 (d, J = 8.7 Hz, 2H, Ar-H), 6.63 (d, J = 8.7 Hz, 2H, Ar-H), 5.03 (d, J = 3.6 Hz, 1H, CH), 3.97 (q, J = 7.0 Hz, 2H, OCH_2), 2.84 (d, J = 16.6 Hz, 6H, CH_3), 2.25 (s, 3H, CH_3), 1.06 (dt, J = 22.1, 7.1 Hz, 3H, CH_3). Enantiomeric excess: 96.8%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 95:5, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 12.967 min(major), t_R = 14.940 min(minor).

4.5.7. 5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione

Yield: 23%, $[\alpha]_D^{20} = -32.6$ (c 0.12, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H, NH), 9.76 (s, 1H, NH), 8.25 (d, J = 8.8 Hz, 2H, Ar-H), 7.51 (d, J = 9.2 Hz, 2H, Ar-H), 5.33 (s, J = 3.6 Hz, 1H, CH), 4.03 (q, J = 6.8 Hz, 2H, OCH_2), 2.33 (s, 3H, CH_3), 1.12 (t, J = 6.8 Hz, 3H, CH_3). Enantiomeric excess: 16.9%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 15.347 min(major), t_R = 19.545 min(minor).

4.5.8. 5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione

Yield: 20%, $[\alpha]_D^{20} = 0$ (c 0.10, EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H, NH), 9.77 (d, J = 1.6 Hz, 1H, NH), 8.19–8.16 (m, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 7.72–7.69 (m, 2H, Ar-H), 5.36 (d, J = 3.6 Hz, 1H, CH), 4.08–4.00 (m, 2H, OCH_2), 2.34 (s, 3H, CH_3), 1.12 (t, J = 6.4 Hz, 3H, CH_3). Enantiomeric excess: 0.16%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90:10, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 16.557 min(major), t_R = 19.342 min(minor).

4.5.9. 5-Ethoxycarbonyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione

Yield: 21%, $[\alpha]_D^{20} = -52.0$ (c 0.1,2 EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ10.46 (s, 1H, NH), 9.58 (s, 1H, NH), 7.94 (d, J = 8.0 Hz, 1H, Ar-H), 7.76 (t, J = 7.6 Hz, 1H, Ar-H), 7.57–7.52 (m, 2H, Ar-H), 5.97 (d, J = 2.4 Hz, 1H, CH), 3.92–3.84 (m, 2H, OCH_2), 2.32 (s, 3H, CH_3), 0.94 (t, J = 6.8 Hz, 3H, CH_3). Enantiomeric excess: 16.6%, determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 80:20, flow rate = 0.8 mL/min, λ = 220 nm): t_R = 13.728 min(minor), t_R = 15.340 min(major).

Acknowledgments

The Project was supported by the Nature Science Foundation of Hubei Province of China (No. 2012FFB07410) and the National Nature Science Foundation of China (No. 21302233) for financial support.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.11.014.

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Please cite this article in press as: Hu, X.; et al. *Tetrahedron: Asymmetry* (2016), http://dx.doi.org/10.1016/j.tetasy.2016.11.014