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Enantioselective Organocatalytic Michael Additions of *N*,*N*'-Dialkylbarbituric Acids to Enones

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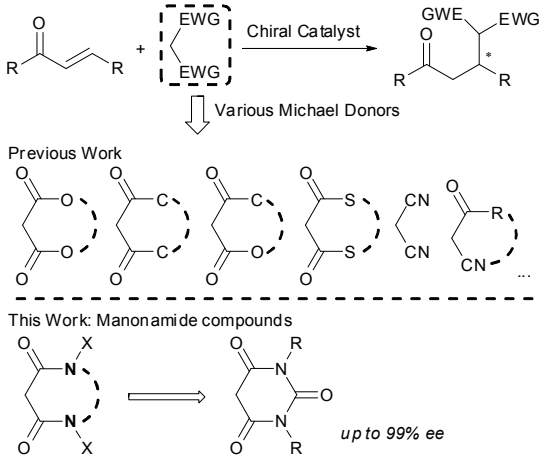
Ying Liu, Yongna Zhang,* Hui-Xin Duan, Dong-Yan Wanyan and You-Qing Wang*

N,*N*'-Dialkylbarbituric acids as cyclic malonamide donors were successfully used in the enantioselective Michael addition reaction of enones. Using cinchona alkaloid-based bifunctional squaramide as an organocatalyst, this Michael reaction of *N*,*N*'-di-*tert*-butylbarbituric acid with various enones features a highly enantioselective (91-99% ee) production of the corresponding optically active 5-substituted barbituric acid derivatives. The transformations of Michael product for the barbituric acid structural unit were realized in two ways, deprotection to remove N-*tert*-butyl group and alkylation to produce 5,5-disubstituted barbituric acid derivatives.

Introduction

Michael addition reaction is characterized as a nucleophilic addition reaction to electron-deficient olefins. In recent years, the catalytic asymmetric Michael addition has made remarkable progress that has been demonstrated by a number of examples with excellent enantioselectivity.[1] However, there still exist some challenging, such as unexplored substrate species to be remaining to be studied, and it is the desire to broaden the substrate scope, especially towards the target- and diversity-oriented synthesis of the drug-like chiral small molecules.[2] Typically, active methylene compounds are being used as the carbon nucleophiles for the addition to α,β-unsaturated carbonyl compounds in the formation of C-C bonds producing a chiral carbon stereocenter. As shown in Scheme 1 (EWG = Electron-Withdrawing Group), active methylene compounds used as Michael donors reported in the literature are mostly 1,3-dicarbonyl derivatives including malonates,[3] 1,3-diketone,[4] β-keto esters,[3g,4a,5] dithiomalonates,[6] malononitrile,[4b,7] other electron-deficient nitriles,[8] and nitro esters[9] etc. Meanwhile, exploring other new Michael donors from simple, yet readily available reagents remains a critical scientific goal. Among others, malonamide compounds have received considerably less attention in the literature to be used as precursors in the Michael reaction. A few examples of precursors for the catalytic Michael addition using malonamide compounds as substrates were previously only accessible in a racemic manner.[10-11] However, from a synthetic point of view, the application of malonamide compounds in catalytic enantioselective Michael reactions of enones remains an interesting topic in synthetic organic chemistry.



Scheme 1 Catalytic asymmetric Michael reaction using various active methylene compounds as Michael donors.

Barbituric acids, a class of organic compound based on a cyclic malonamide skeleton, are widely distributed in varous biologically relevant molecules.[12] As a pharmacologically and physiologically active structural unit, the development of asymmetric synthesis to diversify chiral barbituric acid derivatives allows for the production of large chemical libraries of potentially bioactive molecules. In spite of the high demand for the asymmetric synthesis of chiral barbituric acid derivatives, only a few examples have been described recently in the literature detailing the catalytic asymmetric reaction of barbituric acid derivatives to achieve high enantioselectivities (Scheme 2). Guo's group[13] as well as Zhao's group[14] have developed the highly enantioselective annulation reactions of barbiturate-derived alkenes to construct chiral spirobarbiturate scaffolds through the separate use of chiral phosphines and cinchona-based thioureas as organocatalysts. In their works,[13-14] the barbituric acid scaffold was incorporated into an electron-deficient alkene used as an electrophilic acceptor

[a] Provincial Key Laboratory of Polyoxometalate Chemistry, Provincial Key Laboratory of Natural Medicine and Immuno-Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng, Henan 475004, P. R. China. E-mail: wyouqing@hotmail.com, zhangyongna@henu.edu.cn

† Footnotes relating to the title and/or authors should appear here.

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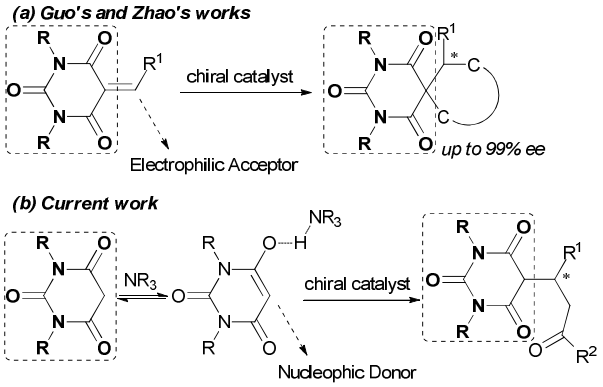
subjected to nucleophilic attack by a dipolar compound for initiation of the reaction and eventually acting as a C_2 synthon leading to a corresponding [2+4] or [2+3] annulation (Scheme 2a). If *N*,*N*′-disubstituted barbituric acid could be directly used as the substrate for the asymmetric catalytic reaction, the reaction outcome is worth looking forward to the research. *N*,*N*′-disubstituted barbituric acids as nucleophiles have been employed in palladium-catalyzed allylation reactions, but with lower enantioselectivity for most substrates and limited substrate scope in the early stages.[15] Considering that cyclic malonamide may undergo a 1,3-prototropy process to afford a cyclic enol, we speculated that the *N*,*N*′-disubstituted barbituric acids may represent suitable Michael donors through organic tertiary amine catalysis (Scheme 2b).[16] In continuation of our interest in the catalytic asymmetric addition reactions of cyclic imines to construct chiral *N*-heterocycles,[17] we now disclose that a highly enantioselective Michael addition of *N*,*N*′-dialkylbarbituric acids as the *N*-heterocycle substrates to enones[18] catalyzed by cinchona alkaloid squaramide.[19]



Scheme 2 Highly enantioselective catalytic reactions for the synthesis of chiral barbituric acid derivatives.

Results and discussion

The Michael addition between *N*,*N*′-dimethylbarbituric acid **1a** and chalcone **2a** was selected as a model reaction to optimize the reaction conditions (Table 1). Initial experiments were conducted using commercially available quinine and quinidine as catalysts.[7c,19b] Although the expected compound **3a** was obtained in a good product yield, enantioselectivity was found to be much lower (entries 1-2). The subsequent screening of various catalysts focused on different amine species, including modified cinchona alkaloids and 1,2-cyclohexanediamine derivatives (Figure 1). The quinine-derived bifunctional squaramide catalyst **C-3** afforded good activity and the best enantioselectivity with 78% *ee* (entry 5). Bifunctional thiourea or squaramide catalysts containing double hydrogen bond donors were found to be superior over hydroxyl or sulfonamide catalysts bearing a single hydrogen bond donor (entries 4-8 *vs.* 1-3). Chiral 1,2-cyclohexanediamine derived squaramide **C-7** and thiourea **C-8** were both found to be efficient catalysts, providing almost equal moderate enantioselectivities (entries 9-10). Upon lowering the temperature to 0°C, the reaction progress required more time for completion ensuring full conversion to produce better *ee* values (entry 11). Further solvent screening was performed and *o*-xylene was found to be the best solvent for achieving highest levels of asymmetric induction (entry 17).

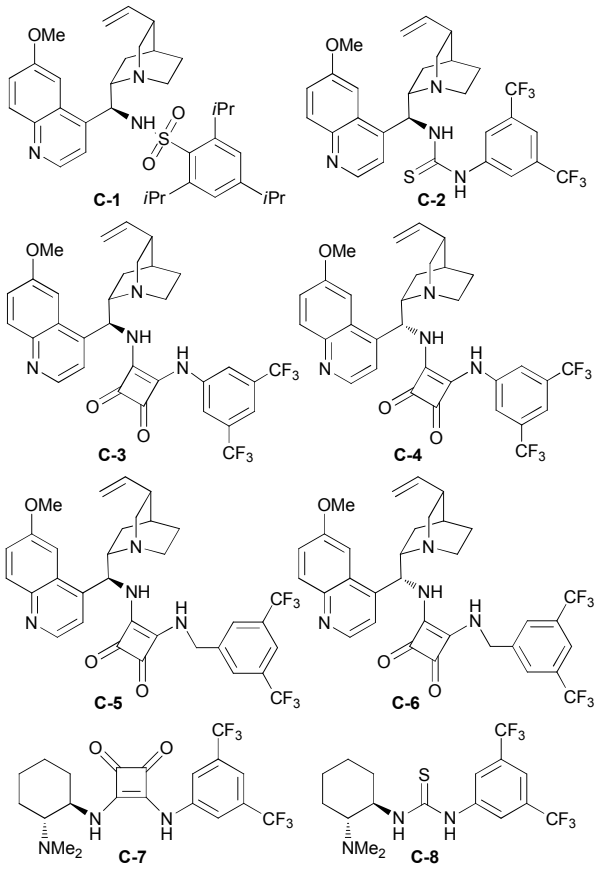
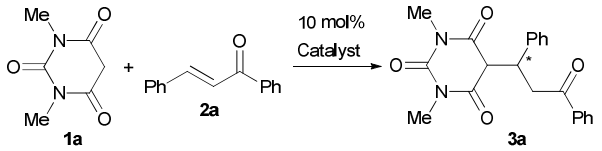


Figure 1 Several chiral catalysts screened.

Table 1 Optimization of the reaction conditions.[a]



entry	catalyst	solvent	*T* (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1	quinine	toluene	25	1	68	15
2	quinidine	toluene	25	1	81	<5
3	**C-1**	toluene	25	24	57	<5
4	**C-2**	toluene	25	1	95	55
5	**C-3**	toluene	25	1.5	88	78
6	**C-4**	toluene	25	5	93	-63[d]
7	**C-5**	toluene	25	1.5	81	47
8	**C-6**	toluene	25	5.5	83	-32[d]
9	**C-7**	toluene	25	5.5	63	55
10	**C-8**	toluene	25	1	95	58
11	**C-3**	toluene	0	36	78	81

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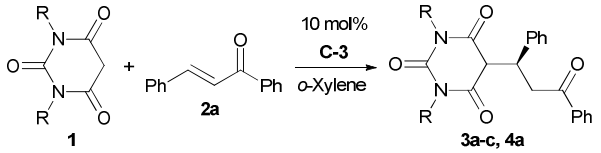
12	**C-3**	DCM	0	23.5	57	71
13	**C-3**	THF	0	24.5	70	63
14	**C-3**	CH_3CN	0	29	70	72
15	**C-3**	DCE	0	24.5	71	78
16	**C-3**	$PhCF_3$	0	23	80	58
17	**C-3**	*o*-xylene	0	42	72	88
18	**C-3**	*m*-xylene	0	25.5	36	58
19	**C-3**	*p*-xylene	0	15	82	62
20	**C-3**	benzene	0	25	70	63

[a] The reactions were conducted with **1a** (0.05 mmol), **2a** (0.075 mmol) and catalyst (0.005 mmol) in 0.25 mL of solvent. [b] Isolated yield. [c] Determined by HPLC using a chiral column. [d] The minus *ee* value indicates that the opposite enantiomer was obtained as the major form.

The effect of different *N*-substituents on the barbituric acids **1** for the asymmetric Michael reaction was investigated in *o*-xylene using **C-3** as an organocatalyst at a temperature of 10°C. As shown in Table 2, the obtained results suggest that *N*-substituents exhibit a remarkable effect on the enantioselectivity. Among the representative *N*-substituents screened, barbituric acid **1d** carrying a sterically demanding *tert*-butyl group, resulted in a good reactivity and the best enantioselectivity (95% *ee*) for this Michael reaction, probably due to the steric factor (entry 4). The reaction was found to also proceed efficiently at room temperature (entry 5). Interestingly, the different substrate ratios between **1d** and enone **2a** did not appear to alter the reaction results (entry 6). The purification of product **4a** from the excess of barbituric acid **1d** was quite tedious by column chromatography, because both compounds have a similar R_f values on silica gel. Due to this reason, we chose an excess of enone (1.5 equiv) as the optimized reaction conditions.

Table 2. Effects of different *N*-substituents of barbituric acids.[a]



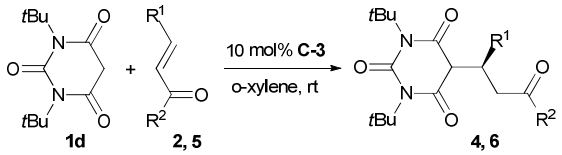
1 2a 3a-c, 4a

entry	R (**1**)	product	*T* (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1	Me (**1a**)	**3a**	10	12	78	88
2	cC_6H_{11} (**1b**)	**3b**	10	20.5	95	94
3	Ph (**1c**)	**3c**	10	33	72	74
4	*t*Bu (**1d**)	**4a**	10	10	90	95
5	*t*Bu (**1d**)	**4a**	25	6	94	96
6[d]	*t*Bu (**1d**)	**4a**	25	17	99	96

[a] Reaction conditions: barbituric acid **1** (0.05 mmol), **2a** (0.075 mmol) and **C-3** (0.005 mmol) in *o*-xylene (0.25 mL) at 10°C. [b] Isolated yield. [c] Determined by HPLC using a chiral column. [d] Barbituric acid **1** (0.075 mmol) and **2a** (0.05 mmol) were used.

With the optimal reaction conditions established,[20] the Michael reaction of a series of aromatic enones **2** with *tert*-butyl substituted barbituric acid **1d** was carried out (Table 3). Various substitutions bearing both electron-donating as well as electron-withdrawing groups on the aromatic ring in different positions of R^1, and in β-position of enones **2** were shown to be compatible and furnished the corresponding barbituric acid derivatives **4a–4m** with excellent enantioselectivities (95-98% *ee*) (entries 1-13). The characteristics of R^2 substituent on the carbonyl functionality of the enones were vastly different and included *para*-methyl, fluoro, bromophenyl (entries 14-16), and β-naphthyl (entry 17). Interestingly, for an unsaturated ketone **2r** with a phenyl ring bearing a hydroxyl group as an active functional group, the Michael addition proceeded smoothly to afford the corresponding product **4r** in 91% yield with a slightly lower *ee* of 91% (entry 18). Fortunately, the heteroaryl enone was also found to tolerate the reaction conditions, affording the desired pyridinyl Michael products **4s** with excellent 99% *ee* (entry 19). Enones, both bearing a variety of substituent groups on two aromatic rings (R^1 and R^2), have also been shown to be suitable Michael acceptors for this reaction (entries 20-26). These species could be easily transformend into the corresponding barbituric acid derivatives **4t–4z** in high yields and with excellent enantioselectivities (96-98% *ee*).

Table 3. Substrate scope using different aromatic enones.[a]



1d 2, 5 4, 6

Entry	R^1/R^2 (**2**)	Time (h)	**4**	Yield (%)[b]	*ee* (%)[c]
1	C_6H_5/C_6H_5 (**2a**)	7	**4a**	99	96
2	4-MeC_6H_4/C_6H_5 (**2b**)	12	**4b**	75	96
3	4-$MeOC_6H_4/C_6H_5$ (**2c**)	23	**4c**	96	96
4	3,4-$(MeO)_2C_6H_3/C_6H_5$ (**2d**)	23	**4d**	95	98
5	4-FC_6H_4/C_6H_5 (**2e**)	5	**4e**	86	97
6	4-ClC_6H_4/C_6H_5 (**2f**)	5	**4f**	93	96
7	3-ClC_6H_4/C_6H_5 (**2g**)	12	**4g**	92	96
8	2-ClC_6H_4/C_6H_5 (**2h**)	30	**4h**	83	95
9	4-CNC_6H_4/C_6H_5 (**2i**)	12	**4i**	83	97
10	4-$NO_2C_6H_4/C_6H_5$ (**2j**)	24	**4j**	88	97
11	2-$NO_2C_6H_4/C_6H_5$ (**2k**)	10	**4k**	44	96
12	4-$CF_3C_6H_4/C_6H_5$ (**2l**)	12	**4l**	92	97
13	2-Naphthyl/C_6H_5 (**2m**)	12	**4m**	85	98
14	C_6H_5/4-MeC_6H_4 (**2n**)	12	**4n**	89	98
15	C_6H_5/4-FC_6H_4 (**2o**)	7	**4o**	86	96
16	C_6H_5/4-BrC_6H_4 (**2p**)	24	**4p**	55	95
17	C_6H_5/2-Naphthyl (**2q**)	24	**4q**	96	96
18	C_6H_5/2-OHC_6H_4 (**2r**)	24	**4r**	91	91
19	C_6H_5/2-Pyridinyl (**2s**)	21	**4s**	80	99
20	4-MeC_6H_4/4-MeC_6H_4 (**2t**)	24	**4t**	98	98
21	4-ClC_6H_4/4-ClC_6H_4 (**2u**)	24	**4u**	91	96
22	4-MeC_6H_4/4-$MeOC_6H_4$ (**2v**)	24	**4v**	89	98
23	4-ClC_6H_4/4-MeC_6H_4 (**2w**)	24	**4w**	98	97
24	4-$MeOC_6H_4$/4-ClC_6H_4 (**2x**)	24	**4x**	84	96
25	4-FC_6H_4/4-$MeOC_6H_4$ (**2y**)	25	**4y**	89	97
26	4-FC_6H_4/4-ClC_6H_4 (**2y**)	24	**4z**	80	96
27	*n*-Pr/Ph (**5a**)	27	**6a**	88	92
28	Cyclohexyl/Ph (**5b**)	72	**6b**	83	94

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29	CH_2CH_2Ph/Ph (**5c**)	35	**6c**	93	93
30	Ph/Me (**5d**)	24	-	0	-
31	*n*-Pr/Me (**5e**)	24	-	0	-

[a] Reaction conditions: 1,3-di-*tert*-butylbarbituric acid **1** (0.12 mmol), **2** (0.1 mmol), and catalyst **C-3** (0.001 mmol) in *o*-xylene (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC using a chiral column.

The substrate scope of this reaction type could be extended to β-alkyl substituted enones (Table 3, entries 27-29). Generally high enantioselectivities were obtained (92-94% *ee*), albeit a slight *ee* reduction could be observed in comparison to aromatic enones. Three examples have been studied under optimized conditions, providing liner *n*-propyl substituted **6a** with 92% *ee*, branched cyclohexyl substituted **6b** with 94% *ee*, and an aryl-containing phenylethyl substituted species **6c** with 93% *ee*. Unfortunately, 2-phenylvinyl methyl ketone **5d** and dialkyl substituted enone **5e** were ineffective substrates for the Michael additions (Table 3, entries 30-31).

On the basis of a single-crystal X-ray structure, the absolute configuration of product **4w** was determined to be *S* (Figure 2).[21] The cinchona alkaloid derivative **C-3** that combine a tertiary amine group with Brønsted base and squaramide with hydrogen-bond donor may act as a bifunctional organocatalyst. A proposed transition-state model for the Michael reaction is shown in Figure 3, and *Re*-face attack of barbituric acid **1d** in β-position of the acyclic enones was found to be favored. Provided the same reaction behaviour of this catalytic system takes place in all substrate species, by analogy the configuration of all other Michael products **4** and **6** could be assigned.

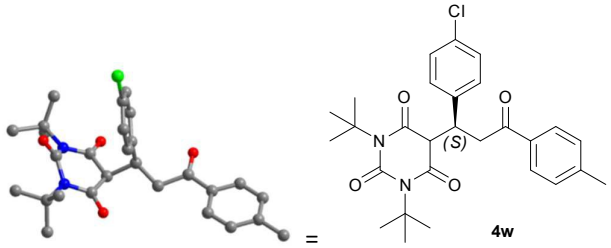


Figure 2 X-ray structure of product **4w**.

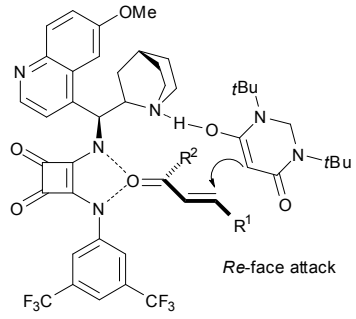
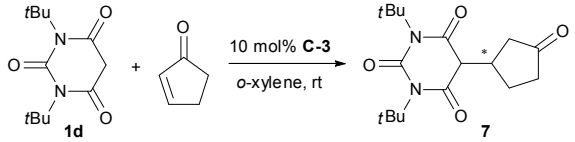


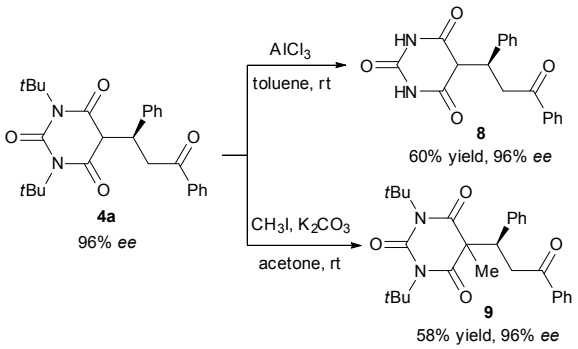
Figure 3 Proposed transition state for the Michael reaction.

In addition, cyclic enones may also be used in the Michael addition using the *N*,*N*′-dialkylbarbituric acid, albeit with a much lower enantioselectivity. As shown in Scheme 3, the reaction of **1d** with 2-cyclopentenone afforded product **7** in 84% yield with 29% *ee* under standard conditions. However, six-member ring 2-cyclohexen-1-one resulted no reaction.



Scheme 3 Further substrate scope using cyclic enone as a Michael acceptor.

Barbituric acid derivatives possessed pharmacologically active qualities to attract the chemist's attention to synthesize them. The transformations centred around the barbituric acid structural unit have been realized in two ways, deprotection to remove *N*-*tert*-butyl group and alkylation to produce 5,5-disubstituted barbituric acid derivatives (Scheme 4). For example, with Michael product **4a**, the *tert*-butyl group can be removed in the presence of $AlCl_3$ in toluene to give chiral barbituric acid derivative **8**, a known compound in racemate.[11c-e] Compared with obtained chiral *N*,*N*′-dimethylbarbituric acid or *N*,*N*′-diphenylbarbituric acid derivatives that was not cleaved its nitrogen protective group in the literatures,[13-14,16] the removal of *tert*-butyl group from nitrogen is easier than methyl or phenyl group.[22] The Michael product **4a** also could be transformed to methylation 5,5-disubstituted barbituric acid derivative **9**. These transformations can completely retain their optical purity, and provides an efficient pathway to the synthesis of some optically active barbituric acid derivatives with molecular diversity.



Scheme 4 Transformation of Michael product **4a**.

Conclusions

In conclusion, we have developed a highly enantioselective Michael addition of 1,3-di-*tert*-butyl barbituric acid to various enones by using a bifunctional cinchona alkaloid-squaramide organocatalyst. A variety of enones bearing different substituents, including aryl, heteroaryl and alkyl groups, were found to be suitable. This study extends the scope of the catalytic asymmetric Michael addition with interesting biologically active molecules, providing novel and efficient access to a series of optically active 5-substituted barbituric acid derivatives.

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Experimental

General.

^{1}H NMR, and ^{13}C NMR spectra were recorded on 300 MHz Bruker spectrometers. Chemical shifts were recorded in ppm (δ), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Flash column chromatography was performed on silica gel (200-300 mesh). TLC analysis was performed using glass-backed plates coated with 0.2 mm silica. After elution, plate was visualized under at 254 nm UV illumination. The following abbreviations were used for elution solvents: PE = petroleum ether, EA = ethyl acetate. All commercially available compounds were used as provided without further purification. The solvents were distilled from appropriate drying agents prior to use, unless otherwise noted. Copies of ^{1}H, ^{13}C NMR spectra and HPLC chromatograms are available in the Supplementary information.

Preparation of barbituric acids derivatives.

Barbituric acid **1b** was synthesized from DCC and malonic acid according to the procedures reported in the literature.[23] Barbituric acids **1c** and **1d** were synthesized from malonyl chloride and corresponding substituted urea according to the following procedures.

1,3-Diphenyl-pyrimidine-2,4,6-trione (1c). To a mixture of *N*,*N*'-diphenylurea (2 mmol, 424.5 mg) in $CHCl_3$ (6 mL) was added the malonyl chloride (2.4 mmol, 338.3 mg). This reaction mixture stirred was refluxed for 4 hours. This reaction mixture was extracted with DCM then the organic layer was dried over Na_2SO_4. After filtration to collect filtrate and concentration under reduced pressure, further purification by column chromatography on a silica gel (PE/EA) gave the desired product **1c** as yellow solid, 343.1 mg, 62% yield; known compound,[24] R_f = 0.5 (PE:EA/2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50-7.48 (m, 6H), 7.25 (d, *J* = 6.8 Hz, 4H), 3.97 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =164.5, 151.2, 133.9, 129.5, 129.4, 128.4, 40.4.

1,3-Di-*tert*-butyl-pyrimidine-2,4,6-trione (1d). To a mixture of *N*,*N*'-di(*tert*-butyl)urea (8.0 mmol, 1.3782 g) in $CHCl_3$ (30 mL) was added the malonyl chloride (9.6 mmol, 0.93 ml). This reaction mixture stirred was refluxed for 4 hours. HCl (1 M) were added to reaction mixture. This reaction mixture was extracted with DCM then the organic layer was dried over Na_2SO_4. After filtration to collect filtrate and concentration under reduced pressure, further purification by column chromatography on a silica gel (PE/EA) gave the desired product **1d** as white solid, 984.1 mg, 51% yield; known compound,[25] R_f = 0.6 (PE:EA/5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.46 (s, 2H), 1.59 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =164.5, 153.6, 62.0, 43.8, 29.2.

Typical procedure for catalytic asymmetric Mannich reaction. To a mixture of **C-3** (0.01 mmol, 10 mol%) and barbituric acid derivative **1** (0.1 mmol) in *o*-xylene (0.5 mL) was added enone **2** or **5** (0.075 mmol). The reaction mixture was stirred at room temperature. Direct purification reaction mixture by column chromatography on a silica gel (PE, EA or DCM) to afford the desired products. The enantiomeric excess was determined by HPLC. Racemic samples were prepared from *N*,*N*'-dialkylbarbituric acids and enones catalyzed by Et_2NH.[11b]

(S)-1,3-dimethyl-5-(3-oxo-1,3-diphenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (3a). Known compound in racemate;[11b] R_f = 0.6 (PE:EA/2:1); 87% *ee*, $[\alpha]^{23}_D$ = 13.9 (c 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.4 Hz, 2H), 7.58-7.45 (m, 3H), 7.26 (s, 3H), 7.10 (s, 2H), 4.36 (s, 1H), 4.13-3.99 (m, 2H), 3.57-3.49 (m, 1H), 3.11 (s, 3H), 3.05 (s, 3H); HPLC (Lux Amylose-2 column, CH_3CN/H_2O/TFA = 50/50/0.1, 1.0 mL/min, 254 nm): t_1 = 11.8 min (minor), t_2 = 13.4 min (major, *S*).

(S)-1,3-dicyclohexyl-5-(3-oxo-1,3-diphenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (3b). Colorless oil, 27.0 mg, 99% yield; R_f = 0.6 (PE:EA/5:1); 94% *ee*, $[\alpha]^{13}_D$ = 8.69 (c 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.4 Hz, 2H), 7.66-7.35 (m, 3H), 7.34-7.26 (m, 5H), 4.63-4.46 (m, 3H), 4.22-4.14 (m, 1H), 3.99 (s, 1H), 3.67-3.59 (m, 1H), 2.26-1.24 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8, 168.5, 168.1, 150.5, 138.3, 136.8, 133.3, 128.8, 128.6, 128.1, 55.1, 55.0, 52.9, 44.3, 41.0, 29.1, 28.9, 28.7, 28.6, 26.4, 26.3, 26.2, 26.1, 25.2; HRMS (ESI): m/z calcd for $C_{31}H_{37}N_2O_4^+$ $[M+H]^+$ 501.2748, found: 501.2749; HPLC (Chiralpak AD-H column, hexane/iPrOH = 95/5, 0.7 mL/min, 254 nm): t_1 = 34.1 min (minor), t_2 = 35.4 min (major, S).

5-(3-oxo-1,3-diphenylpropyl)-1,3-diphenylpyrimidine-2,4,6(1H,3H,5H)-trione (3c). Known compound in racemate;[26] R_f = 0.7 (PE:EA/2:1); 74% *ee*, $[\alpha]^{13}_D$ = 8.35 (c 1.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.6 Hz, 2H), 7.56-7.39 (m, 14H), 7.12 (d, *J* = 6.9 Hz, 2H), 6.91 (m, 2H), 4.57 (s, 1H), 4.39 (s, 1H), 4.22-3.13 (m, 1H), 3.62-3.56 (m, 1H); 13C NMR (75 MHz, CDCl3): δ = 198.0, 167.8, 167.7, 150.4, 138.9, 136.7, 133.9, 133.4, 129.4, 129.3, 129.2, 129.0, 128.7, 128.3, 128.2, 128.1, 52.9, 44.3, 40.7; HPLC (Chiralpak AD-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 46.2 min (minor), t_2 = 70.5 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-oxo-1,3-diphenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4a). Colorless oil, 44.4 mg, 99% yield; R_f = 0.7 (DCM); 96% *ee*, $[\alpha]^{13}_D$ = 8.35 (c 1.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.7 Hz, 2H), 7.52-7.37 (m, 3H), 7.20-7.14 (m, 5H), 4.23 (s, 1H), 4.06-3.97 (m, 1H), 3.66-3.48 (m, 2H), 1.40 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7, 167.7, 167.1, 152.5, 138.4, 136.9, 133.2, 128.8, 128.6, 128.3, 128.1, 62.0, 61.9, 55.5, 43.6, 41.3, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{27}H_{33}N_2O_4^+$ $[M+H]^+$ 449.2435, found: 449.2434; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 8.7 min (minor), t_2 = 12.6 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-oxo-3-phenyl-1-(p-tolyl)propyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4b). Yellow oil, 34.7 mg, 75% yield; R_f = 0.8 (DCM); 96% *ee*, $[\alpha]^{13}_D$ = 37.3 (c 1.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (t, *J* = 7.7 Hz, 2H), 7.47-7.42 (m, 3H), 7.06 (s, 1H), 4.24 (s, 1H), 4.08-3.99 (m, 1H), 3.69 (s, 1H), 3.58-3.50 (m, 1H), 2.30 (s, 3H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8, 167.9, 167.3, 152.4, 137.7, 137.0, 135.4, 133.1, 129.4, 128.6, 128.1, 61.9, 55.7, 43.2, 41.5, 29.1, 29.0, 21.2; HRMS (ESI): m/z calcd for $C_{28}H_{35}N_2O_4^+$ $[M+H]^+$ 463.2590,

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found: 463.2590; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 8.3 min (minor), t_2 = 12.2 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4c). Colorless oil, 46.0 mg, 96% yield; R_f = 0.7 (DCM); 96% *ee*, $[\alpha]^{13}_D$ = 35.0 (c 1.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.5 Hz, 2H), 7.57-7.42 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.24 (s, 1H), 4.06-3.97 (m, 1H), 3.76 (s, 3H), 3.67 (d, *J* = 3.75 Hz, 1H), 3.59-3.51 (m, 1H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8, 167.8, 167.2, 159.4, 152.3, 136.9, 133.1, 130.3, 129.4, 128.6, 128.1, 114.1, 61.9, 61.8, 55.9, 55.3, 42.9, 41.6, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{28}H_{35}N_2O_5^+$ $[M+H]^+$ 479.2541, found: 479.2541; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 9.7 min (minor), t_2 = 19.8 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(3,4-dimethoxyphenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4d). Colorless oil, 48.3 mg, 98% yield; R_f = 0.5 (DCM); 98% *ee*, $[\alpha]^{22}_D$ = 16.9 (c 0.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.6 Hz, 2H), 7.57-7.42 (m, 3H), 6.72 (d, *J* = 7.0 Hz, 3H), 4.24 (s, 1H), 4.01-3.97 (m, 1H), 3.82 (d, *J* = 5.5 Hz, 6H), 3.69 (d, *J* = 2.9 Hz, 1H), 3.60-3.52 (m, 1H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 167.8, 167.3, 152.3, 148.8, 136.9, 133.2, 131.1, 128.6, 128.1, 120.2, 111.9, 111.4, 61.8, 61.7, 56.0, 55.9, 55.8, 43.1, 41.8, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{29}H_{37}N_2O_6^+$ $[M+H]^+$ 509.2646, found: 509.2646. HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 13.1 min (minor), t_2 = 42.9 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(4-fluorophenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4e). Colorless oil, 40.0 mg, 86% yield; R_f = 0.8 (DCM); 97% *ee*, $[\alpha]^{22}_D$ = 25.4 (c 0.37, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.7 Hz, 2H), 7.58-7.43 (m, 3H), 7.16 (t, *J* = 6.1 Hz, 2H), 6.94 (t, *J* = 8.0 Hz, 2H), 4.30 (s, 1H), 4.06-3.97 (m, 1H), 3.67-3.54 (m, 2H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5, 167.5, 167.0, 162.5 (d, $^1J_{C\text{-}F}$ = 246.9 Hz), 152.4, 134.3 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 130.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 128.6, 128.1, 115.7 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 62.0, 61.9, 55.6, 42.8, 41.5, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{29}H_{37}N_2O_6^+$ $[M+H]^+$ 509.2646, found: 509.2646; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 5.9 min (minor), t_2 = 9.3 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4f). Colorless oil, 45.0 mg, 93% yield; R_f = 0.6 (DCM); 96% *ee*, $[\alpha]^{23}_D$ = 26.5 (c 0.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.5 Hz, 2H), 7.58-7.43 (m, 3H), 7.24-7.13 (m, 4H); 4.28 (s, 1H), 4.05-3.96 (m, 1H), 3.67-3.54 (m, 2H), 1.48 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5, 167.4, 167.9, 152.3, 137.2, 136.7, 133.3, 129.7, 128.9, 128.6, 128.1, 62.1, 62.0, 55.5, 42.7, 41.4, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{27}H_{32}ClN_2O_4^+$ $[M+H]^+$ 483.2045, found: 483.2046; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 5.4 min (minor), t_2 = 8.0 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(3-chlorophenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4g). Colorless oil, 44.3 mg, 92% yield; R_f = 0.7 (DCM); 96% *ee*, $[\alpha]^{22}_D$ = 25.2 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 6.2 Hz, 2H), 7.57-7.47 (m, 3H), 7.26-7.09 (m, 4H), 4.30 (s, 1H), 4.09-4.01 (m, 1H), 3.69-3.59 (m, 2H), 1.49 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 167.3, 166.6, 152.5, 140.4, 136.7, 134.7, 133.3, 130.2, 126.6, 62.2, 55.1, 43.3, 41.0, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{27}H_{32}ClN_2O_4^+$ $[M+H]^+$ 483.2045, found: 483.2044; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 6.3 min (minor), t_2 = 9.8 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(2-chlorophenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4h). Colorless oil, 40.2 mg, 83% yield; R_f = 0.7 (DCM); 95% *ee*, $[\alpha]^{22}_D$ = 18.2 (c 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.6 Hz, 2H), 7.54-7.34 (m, 5H), 7.20 (s, 2H); 4.82 (d, *J* = 6.1 Hz, 1H), 3.92-3.78 (m, 2H), 3.58-3.50 (m, 2H), 1.52 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 167.5, 167.1, 152.9, 137.5, 136.5, 133.3, 130.2, 129.1, 128.8, 128.6, 128.1, 127.2, 62.2, 62.1, 55.8, 41.9, 38.7, 29.2, 29.1; HRMS (ESI): m/z calcd for $C_{27}H_{32}ClN_2O_4^+$ $[M+H]^+$ 483.2045, found: 483.2044; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 6.7 min (minor), t_2 = 11.7 min (major, *S*).

(S)-4-(1-(1,3-di-*tert*-butyl-2,4,6-trioxohexahydropyrimidin-5-yl)-3-oxo-3-phenylpropyl) benzoin-trile (4i). Colorless oil, 39.4 mg, 83% yield; R_f = 0.7 (DCM); 97% *ee*, $[\alpha]^{13}_D$ = 31.5 (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.5 Hz, 2H), 7.49-7.36 (m, 5H), 7.25 (s, 1H), 7.18 (s, 1H); 4.32-4.20 (m, 1H), 3.97-3.88 (m, 1H), 3.65-3.56 (m, 2H), 1.39 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1, 166.9, 166.6, 152.3, 144.4, 136.4, 133.5, 132.5, 128.7, 128.1, 118.6, 111.9, 62.3, 62.2, 55.2, 43.0, 41.1, 29.0, 28.9; HRMS (ESI): m/z calcd for $C_{28}H_{32}N_3O_4^+$ $[M+H]^+$ 474.2387, found: 474.2386; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 11.5 min (minor), t_2 = 16.1 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4j). White solid, 43.5 mg, 96% yield; R_f = 0.7 (DCM); mp: 151-152 °C; 97% *ee*, $[\alpha]^{13}_D$ = 32.0 (c 3.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 14.3 Hz, 1H), 7.48-7.40 (m, 4H), 4.44 (d, *J* = 2.34 Hz, 1H), 4.06-3.98 (m, 1H), 3.77-3.70 (m, 2H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1, 166.8, 166.5, 152.3, 147.5, 146.5, 136.4, 133.5, 128.1, 123.9, 62.3, 62.3, 55.2, 42.8, 41.2, 29.0, 28.9; HRMS (ESI): m/z calcd for $C_{27}H_{32}N_3O_6^+$ $[M+H]^+$ 494.2286, found: 494.2284; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 7.7 min (minor), t_2 = 9.7 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(2-nitrophenyl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4k). Colorless oil, 21.5 mg, 44% yield; R_f = 0.8 (DCM); 96% *ee*, $[\alpha]^{13}_D$ = 35.0 (c 1.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16-7.99 (m, 4H), 7.58-7.45 (m, 5H), 4.50-4.42 (m,1H), 4.11-4.03 (m, 1H), 3.76-3.68 (m, 2H), 1.44 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1, 166.9, 166.3, 152.5, 148.4, 140.9, 133.5, 128.1, 123.1,123.0 62.4, 55.2, 42.8, 41.2, 29.0, 28.9; HRMS (ESI): m/z calcd for $C_{27}H_{32}N_3O_6^+$ $[M+H]^+$ 494.2286, found: 494.2285; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 7.1 min (minor), t_2 = 9.2 min (major, *S*).

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(S)-1,3-di-*tert*-butyl-5-(3-oxo-3-phenyl-1-(4-(trifluoromethyl)phenyl)propyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4l). Colorless oil, 47.5 mg, 92% yield; R_f = 0.7 (DCM); 97% *ee*, $[\alpha]^{25}_D$ = 37.8 (c 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.5 Hz, 2H), 7.59-7.33 (m, 7H), 4.38 (s, 1H), 4.08-4.00 (m, 1H), 3.70-3.62 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 167.2, 166.8, 152.2, 142.9, 136.6, 133.4, 130.0, 128.1, 125.7, 125.6, 122.2, 65.6, 62.2, 62.1, 55.4, 42.9, 41.3, 30.6, 29.0, 28.9, 19.2, 13.7; HRMS (ESI): m/z calcd for $C_{28}H_{32}F_3N_2O_4^+$ $[M+H]^+$ 517.2309, found: 517.2305; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 4.3 min (minor), t_2 = 6.3 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(naphthalen-2-yl)-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4m). Colorless oil, 42.3 mg, 85% yield; R_f = 0.8 (DCM); 98% *ee*, $[\alpha]^{16}_D$ = 59.6 (c 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.5 Hz, 2H), 7.78-7.31 (m, 10H), 4.48 (s, 1H), 4.22-4.13 (m, 1H), 3.79-3.67 (m, 2H), 1.42 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7, 167.7, 167.1, 152.3, 136.9, 136.0, 133.2, 133.1, 133.0, 128.7, 128.6, 128.2, 127.7, 127.3, 126.3, 126.1, 61.9, 61.8, 55.7, 43.7, 41.5, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{31}H_{35}N_2O_4^+$ $[M+H]^+$ 499.2591, found: 499.2590; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 10.0 min (minor), t_2 = 19.0 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-oxo-1-phenyl-3-(p-tolyl)propyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4n). Colorless oil, 41.1 mg, 89% yield; R_f = 0.8 (DCM); 98% *ee*, $[\alpha]^{13}_D$ = 46.7 (c 2.37, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.0 Hz, 2H), 7.26-7.20 (m, 7H), 4.29 (s, 1H), 4.08-3.99 (m, 1H), 3.71 (d, *J* = 3.5 Hz, 1H), 3.61-3.52 (m, 1H), 2.40 (s, 3H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 167.7, 167.1, 152.5, 143.9, 138.5, 134.5, 129.3, 128.8, 128.3, 128.2, 128.0 , 62.0, 61.9, 55.6, 43.7, 41.1, 29.1, 29.0, 21.7; HRMS (ESI): m/z calcd for $C_{28}H_{35}N_2O_4^+$ $[M+H]^+$ 463.2591, found: 463.2590; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 11.6 min (minor), t_2 = 19.6 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-(4-fluorophenyl)-3-oxo-1-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4o). Colorless oil, 38.4 mg, 86% yield; R_f = 0.6 (DCM); 96% *ee*, $[\alpha]^{13}_D$ = 24.5 (c 0.69, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (t, *J* = 6.4 Hz, 2H), 7.26-7.09 (m, 7H), 4.27 (s, 1H), 4.10-4.00 (m, 1H), 3.69 (s, 1H), 3.57-3.45 (m, 1H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.2, 167.6, 167.1, 159.87 (d, $^1J_{C\text{-}F}$ = 260.3 Hz), 152.5, 138.3, 133.4 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 130.8 (d, $^3J_{C\text{-}F}$ = 9.3 Hz), 128.9, 128.3, 128.2, 115.7 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 62.0, 61.9, 55.4, 43.6, 41.2, 29.01, 29.0; HRMS (ESI): m/z calcd for $C_{27}H_{32}FN_2O_4^+$ $[M+H]^+$ 467.2341, found: 467.2341; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 7.3 min (minor), t_2 = 9.7 min (major, *S*).

(S)-5-(3-(4-bromophenyl)-3-oxo-1-phenylpropyl)-1,3-di-*tert*-butylpyrimidine-2,4,6(1H,3H,5H)-trione (4p). Colorless oil, 29.2 mg, 55% yield; R_f = 0.7 (DCM); 95% *ee*, $[\alpha]^{23}_D$ = 39.0 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.30-7.16 (m, 5H), 4.26 (s, 1H), 4.08-4.00 (m, 1H), 3.68 (s, 1H), 3.56-3.48 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.8, 167.5, 167.0, 152.5, 138.1, 135.6, 131.9, 129.7, 128.9, 128.4, 128.3, 128.2, 62.0, 61.9, 55.3, 43.6, 41.2, 29.1, 28.0; HRMS (ESI): m/z calcd for $C_{27}H_{32}BrN_2O_4^+$ $[M+H]^+$ 527.1540, found: 527.1540; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 9.1 min (minor), t_2 = 14.1 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-(naphthalen-2-yl)-3-oxo-1-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4q). Colorless oil, 48.0 mg, 96% yield; R_f = 0.7 (DCM); 96% *ee*, $[\alpha]^{13}_D$ = 68.5 (c 2.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1H), 8.07-7.86 (m, 4H), 7.62-7.52 (m, 2H), 7.26 (s, 5H), 4.36 (s, 1H), 4.25-4.16 (m, 1H), 3.78-3.70 (m, 2H), 1.48 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 167.7, 167.1, 152.5, 138.4, 135.7, 134.3, 132.5, 129.8, 129.6, 128.8, 128.4, 128.1, 127.8, 126.7, 123.9, 62.0, 61.9, 55.6, 43.8, 41.4, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{31}H_{35}N_2O_4^+$ $[M+H]^+$ 499.2591, found: 499.2590; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 13.3 min (minor), t_2 = 22.0 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-(2-hydroxyphenyl)-3-oxo-1-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4r). Colorless oil, 42.2 mg, 91% yield; R_f = 0.8 (DCM); 91% *ee*, $[\alpha]^{13}_D$ = 11.3 (c 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.14 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), δ = 7.46 (t, *J* = 7.7 Hz, 1H), 7.28-7.16 (m, 5H), 6.97-6.89 (m, 2H), 4.28-4.14 (m, 2H), 3.70-3.36 (m, 2H), 1.45 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 167.6, 166.9, 162.4, 152.4, 137.9, 136.5, 129.9, 128.9, 128.3, 128.2, 119.5, 119.0, 118.5, 62.1, 62.0, 55.2, 43.2, 40.6, 29.2, 29.0, 28.9; HRMS (ESI): m/z calcd for $C_{27}H_{33}N_2O_5^+$ $[M+H]^+$ 465.2384, found: 465.2384; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 5.2 min (minor), t_2 = 23.5 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-oxo-1-phenyl-3-(pyridin-2-yl)propyl)pyrimidine-2,4,6(1H,3H,5H)-(trione (4s). Colorless oil, 35.8 mg, 80% yield; R_f = 0.3 (DCM); 99% *ee*; $[\alpha]^{25}_D$ = 13.4 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (d, *J* = 3.5 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.47-7.43 (m, 1H), 7.26-7.22 (m, 5H), 4.29-4.20 (m, 2H), 3.97-3.87 (m, 1H), 3.77 (s, 1H), 1.45 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5, 167.8, 166.7, 153.2, 152.6, 149.0, 138.4, 136.8, 128.7, 128.5, 128.0, 121.8, 61.9, 61.9, 55.7, 43.7, 40.6, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{26}H_{32}N_3O_4^+$ $[M+H]^+$ 450.2387, found: 450.2385; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 11.4 min (minor), t_2 = 23.6 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-oxo-1,3-di-p-tolylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4t). white solid, 46.7 mg, 98% yield; R_f = 0.6 (DCM); mp: 145.6-145.8 °C; 98% *ee*, $[\alpha]^{13}_D$ = 9.3 (c 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.26 (s, 3H), 4.24-4.16 (m, 1H), 3.88 (s, 1H), 3.77-3.69 (m, 1H), 2.60 (s, 3H), 2.51 (s, 3H), 1.67 (s, 9H), 1.65 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 167.8, 166.3, 152.4, 143.9, 137.7, 135.5, 134.5, 129.4, 129.2, 128.2, 128.1, 61.9, 61.8, 55.8, 43.3, 41.4, 29.1, 29.0, 21.7, 21.2; HRMS (ESI): m/z calcd for $C_{29}H_{37}N_2O_4^+$ $[M+H]^+$ 477.2748, found: 477.2746; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 12.4 min (minor), t_2 = 27.2 min (major, *S*).

(S)-5-(1,3-bis(4-chlorophenyl)-3-oxopropyl)-1,3-di-*tert*-butylpyrimidine-2,4,6(1H,3H,5H)-trione (4u). Colorless oil, 47.1 mg,

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91% yield; R_f = 0.6 (DCM); 96% *ee*, $[\alpha]^{13}_D$ = 43.2 (c 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.39-7.26 (m, 4H), 4.41 (s, 1H), 4.18-4.09 (m, 1H), 3.80-3.63 (m, 2H), 1.62 (s, 9H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.3, 167.3, 166.9, 152.3, 139.8, 136.9, 135.0, 134.0, 129.6, 129.5, 129.0, 62.1, 62.0, 55.3, 42.7, 41.4, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{27}H_{31}Cl_2N_2O_4^+$ $[M+H]^+$ 517.1655, found: 517.1655; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 5.6 min (minor), t_2 = 10.5 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-(4-methoxyphenyl)-3-oxo-1-(p-tolyl)propyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4v). white solid, 43.8 mg, 89% yield; R_f = 0.7 (DCM); mp: 145.3-145.5 °C; 95% *ee*, $[\alpha]^{13}_D$ = 45.7 (c 0.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.3 Hz, 2H), 7.05 (s, 4H), 6.91 (d, *J* = 7.3 Hz, 2H), 4.23 (s, 1H), 4.01-3.92 (m, 1H), 3.86 (s, 3H), 3.67 (s, 1H), 3.53-3.45 (m, 1H), 2.30 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.3, 167.8, 167.3, 163.5, 152.4, 137.6, 136.5, 130.4, 130.1, 129.4, 128.1, 113.7, 61.9, 61.8, 55.8, 55.5, 43.4, 41.1, 29.1, 29.0, 21.2; HRMS (ESI): m/z calcd for $C_{29}H_{37}N_2O_5^+$ $[M+H]^+$ 493.2697, found: 493.2695; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 18.3 min (minor), t_2 = 44.1 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(4-chlorophenyl)-3-oxo-3-(p-tolyl)propyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4w). white solid, 48.8 mg, 98% yield; R_f = 0.7 (DCM); mp: 140.6-145.8 °C; 97% *ee*, $[\alpha]^{13}_D$ = 51.7 (c 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.5 Hz, 2H), 7.26-7.12 (m, 6H), 4.28-4.27 (m, 1H), 4.00-3.92 (m, 1H), 3.67-3.53 (m, 2H), 2.40 (s, 3H), 1.48 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0, 167.4, 167.0, 152.4, 144.1, 137.2, 134.3, 133.8, 129.7, 129.3, 128.9, 128.2, 62.1, 62.0, 55.6, 42.8, 41.3, 29.1, 29.0, 21.7; HRMS (ESI): m/z calcd for $C_{28}H_{34}ClN_2O_4^+$ $[M+H]^+$ 497.2202, found: 497.2202; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 7.8 min (minor), t_2 = 15.6 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-oxopropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4x). Colorless oil, 43.1 mg, 84% yield; R_f = 0.7 (DCM); 96% *ee*, $[\alpha]^{13}_D$ = 53.2 (c 1.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), δ = 6.77 (d, *J* = 8.07 Hz, 2H), 4.22 (s, 1H), 4.03-3.95 (m, 1H), 3.78 (s, 3H), 3.65 (d, *J* = 3.0 Hz, 1H), 3.53-3.45 (m, 1H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =196.7, 167.7, 167.2, 159.4, 152.3, 139.6, 136.3, 130.2, 129.6, 129.3, 128.9, 114.2, 61.9, 61.8, 55.7, 55.3, 42.9, 41.6, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{28}H_{34}ClN_2O_5^+$ $[M+H]^+$ 513.2151, found: 513.2149; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 8.7 min (minor), t_2 = 21.6 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-(4-fluorophenyl)-3-(4-methoxyphenyl)-3-oxopropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4y). Colorless oil, 41.2 mg, 89% yield; R_f = 0.5 (DCM); 97% *ee*, $[\alpha]^{24}_D$ = 33.1 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.56-7.43 (m, 3H), 7.16 (d, *J* = 5.7 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 4.29 (s, 1H), 4.06-3.97 (m, 1H), 3.67-3.54 (m, 2H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.0, 167.5, 167.0, 163.6, 152.4, 134.4 (d, $^4J_{C\text{-}F}$ = 3.1 Hz) 130.4, 130.0, 129.9 (d, $^3J_{C\text{-}F}$ = 8.0 Hz) 115.8, 115.5 (d, $^1J_{C\text{-}F}$ = 212.0 Hz) 113.7, 62.0, 61.9, 55.5, 42.9, 41.1, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{28}H_{34}FN_2O_5^+$ $[M+H]^+$ 497.2446, found: 497.2444; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 11.0 min (minor), t_2 = 26.8 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(3-(4-chlorophenyl)-1-(4-fluorophenyl)-3-oxopropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (4z). Colorless oil, 40.1 mg, 80% yield; R_f = 0.7 (DCM); 96% *ee*, $[\alpha]^{24}_D$ = 52.3 (c 2.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.15 (t, *J* = 6.5 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 4.27 (s, 1H), 4.04-3.95 (m, 1H), 3.65-3.48 (m, 2H), 1.47 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.4, 167.3, 166.9, 162.5 (d, $^1J_{C\text{-}F}$ = 247.2 Hz), 152.3, 139.7, 135.1, 134.1 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 129.9 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.5, 128.9, 115.7 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 62.1, 62.0, 55.4, 42.7, 41.5, 29.1, 29.0; HRMS (ESI): m/z calcd for $C_{27}H_{31}ClFN_2O_4^+$ $[M+H]^+$ 501.1951, found: 501.1948; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 5.8 min (minor), t_2 = 11.0 min (major, *S*).

(S)-1,3-di-*tert*-butyl-5-(1-oxo-1-phenylhexan-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (6a). white solid, 36.5 mg, 88% yield; R_f = 0.6 (DCM); mp: 73.5-73.7 °C; 92% *ee*, $[\alpha]^{23}_D$ = -54.2 (c 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.7 Hz, 2H), 7.58-7.42 (m, 3H), 3.49-3.40 (m, 2H), 3.07-3.02 (m, 2H), 1.59 (s, 9H), 1.55 (s, 9H), 1.44-1.25 (m, 4H), 0.92-0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.0, 169.0, 168.2, 152.8, 136.9, 133.1, 128.6, 128.1, 61.9, 61.7, 55.1, 40.1, 36.3, 34.3, 29.3, 29.2, 20.4, 14.0; HRMS (ESI): m/z calcd for $C_{24}H_{35}N_2O_4^+$ $[M+H]^+$ 415.2591, found: 415.2591; HPLC (Chiralpak AD-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 5.0 min (minor), t_2 = 5.7 min (major *S*).

(R)-1,3-di-*tert*-butyl-5-(1-cyclohexyl-3-oxo-3-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (6b). white solid, 40.0 mg, 88% yield; R_f = 0.8 (DCM); mp: 104.2-104.5 °C; 92% *ee*, $[\alpha]^{23}_D$ = -62.2 (c 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.7 Hz, 2H), 7.57-7.41 (m, 3H), 3.51-3.35 (m, 2H), 3.08-2.93 (m, 2H), 1.83-0.85 (m, 29H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =199.1, 170.0, 167.8, 153.1, 136.9, 133.1, 128.6, 128.1, 61.7, 61.5, 54.4, 41.0, 40.1, 37.4, 31.8, 29.3, 29.1, 26.6, 26.4, 26.3; HRMS (ESI): m/z calcd for $C_{27}H_{39}N_2O_4^+$ $[M+H]^+$ 455.2904, found: 455.2904; HPLC (Chiralpak AD-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 4.2 min (minor), t_2 = 7.3 min (major *R*).

(S)-1,3-di-*tert*-butyl-5-(1-oxo-1,5-diphenylpentan-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (6c). Colorless oil, 36.6 mg, 93% yield; R_f = 0.7 (DCM); 93% *ee*, $[\alpha]^{25}_D$ = -14.1 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 2H), 7.56-7.14 (m, 8H), 3.53-3.45 (m, 2H), 3.13 (d, *J* = 3.5 Hz, 2H), 2.70-2.62 (m, 2H), 1.90-1.77 (m, 2H), 1.58 (s, 9H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.8, 168.8, 167.9, 152.8, 141.4, 136.8, 133.2, 128.6, 128.5, 128.3, 128.1, 126.1, 61.9, 61.8, 55.1, 40.1, 36.3, 34.2, 33.7, 29.3, 29.2; HRMS (ESI): m/z calcd for $C_{29}H_{37}N_2O_4^+$ $[M+H]^+$ 477.2748, found: 477.2746; HPLC (Chiralpak AD-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 5.9 min (minor), t_2 = 9.2 min (major *S*).

1,3-di-*tert*-butyl-5-(3-oxocyclopentyl)pyrimidine-2,4,6(1H,3H,5H)-trione (7). white solid, 26.9 mg, 84% yield; R_f = 0.5 (PE:EA/5:1); mp: 94.7-94.9 °C; 29% *ee*, $[\alpha]^{23}_D$ = 23.9 (c 0.43, $CHCl_3$); ^{1}H NMR (300

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MHz, $CDCl_3$): δ = 3.21 (d, *J* = 6.8 Hz, 1H), 3.22-3.20 (m, 1H), 3.51-3.35 (m, 2H), 2.42-2.09 (m, 5H), 1.96-1.78 (m, 1H), 1.57 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.0, 167.6, 167.3, 153.2, 62.2, 56.8, 42.1, 39.6, 38.3, 29.2, 27.0; HRMS (ESI): m/z calcd for $C_{17}H_{27}N_2O_4^+$ $[M+H]^+$ 323.1965, found: 323.1965; HPLC (Chiralcel OD-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 5.3 min (major), t_2 = 7.1 min (minor).

Transformation of Michael product 4a.

(S)-5-(3-oxo-1,3-diphenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (8). To a stirred solution of **4a** (44.9 mg, 0.1 mmol) in toluene (0.5 ml) at room temperature was added $AlCl_3$ (40.2 mg, 0.3 mmol) under a N_2 atmosphere. The reaction mixture was stirred for 1-2 hours and monitored by TLC. Then the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic phase was washed with brine, and concentrated in vacuo. The residue was further purified by rapid column chromatography to give the desired product **8** (20.2 mg, 60% yield). A slower column chromatography could result in a few oxidation byproducts. Known compound in racemate;[11c-e] R_f = 0.3 (EA:MeOH/20:1); 96% *ee*, $[\alpha]^{20}_D$ = 15.2 (c 0.85, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ = 11.05 (d, *J* = 14.6 Hz, 2H), δ = 7.99 (d, *J* = 7.2 Hz, 2H), 7.68-7.52 (m, 3H), 7.31-7.16 (m, 5H), 4.18-4.00 (m, 2H), 3.82 (d, *J* = 3.7 Hz, 1H), 3.67-3.59 (m, 1H); HPLC (Chiralpak AS-H column, hexane/iPrOH/TEA= 85/15/0.1, 1.0 mL/min, 254 nm): t_1 = 43.6 min (minor), t_2 = 48.2 min (major, *S*).

(R)-1,3-di-*tert*-butyl-5-methyl-5-(3-oxo-1,3-diphenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione (9). A round-bottomed flask was charged with **4a** (44.9 mg , 0.1 mmol), K_2CO_3 (27.6 mg, 0.2 mmol) and acetone (0.5 mL). Iodomethane (6.2 uL, 0.1 mmol) was added to the reaction mixture by a microsyringe at room temperature. The reaction mixture was stirred for 12h and monitored by TLC. Then the reaction mixture was quenched with water and extracted with ethyl acetate. After usual work-up, further purification by column chromatography on a silica gel (PE/EA) gave the desired product **9** as a white solid (26.8 mg, 58% yield). R_f = 0.6 (PE:EA/10:1); mp: 105.0-105.2 °C; 96% *ee*, $[\alpha]^{20}_D$ = 60.9 (c 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 9.3 Hz, 2H), 7.55-7.39 (m, 3H), 7.20-7.17 (m, 5H), 4.17-4.12 (m, 1H), 3.90-3.69 (m, 2H), 1.60 (s, 3H), 1.53 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =197.9, 171.4, 170.9, 151.6, 139.0, 137.0, 133.0, 128.9, 128.6, 128.5, 128.1, 127.7, 61.9, 56.4, 48.2, 39.1, 29.0, 28.9, 23.5; HRMS (ESI): m/z calcd for $C_{28}H_{34}N_2O_4^+$ $[M+H]^+$ 462.2591, found: 462.2593; HPLC (Chiralpak IC-H column, hexane/iPrOH = 70/30, 1.0 mL/min, 254 nm): t_1 = 4.7 min (major, *R*), t_2 = 8.2 min (minor).

Conflicts of interest

There are no conflicts to declare.

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