DOI: 10.1002/adsc.201700203
Advanced Synthesis & Catalysis

Catalytic Asymmetric [3+3] Cycloaddition of Azomethine Ylides with C3-Substituted 2-Indolylmethanols

Xiao-Xue Sun,[a] Can Li,[a] Ying-Ying He,[a] Zi-Qi Zhu,[a] Guang-Jian Mei,[a] and Feng Shi[a,*]

[a] School of Chemistry & Material Science, Jiangsu Normal University, Xuzhou, 221116, People's Republic of China
E-mail: fshi@jsnu.edu.cn

Received: February 17, 2017; Revised: April 27, 2017; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201700203

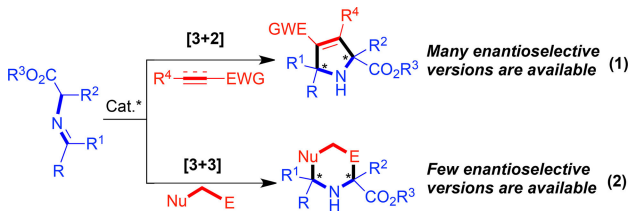
Abstract: The first catalytic asymmetric [3+3] cycloaddition of azomethine ylides with C3-substituted 2-indolylmethanols has been established, leading to diastereo- and enantioselective construction of a tetrahydropyrimido[1,6-a]indole framework (up to 91% yield, >95:5 dr, 98:2 er). This reaction also represents a new type of catalytic enantioselective [3+3] cycloaddition using azomethine ylides.

Keywords: azomethine ylide; chiral phosphoric acid; enantioselectivity; [3+3] cycloaddition; organic catalysis

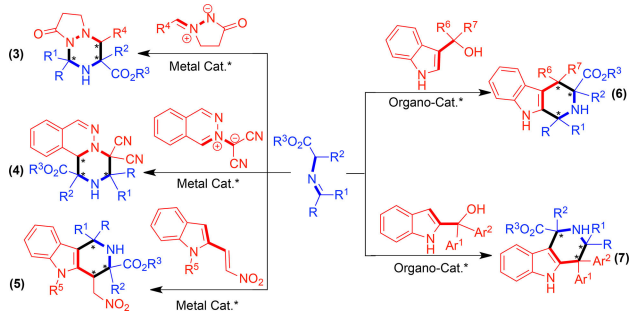
Introduction

Catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylide is one of the most powerful methods for constructing enantioenriched heterocyclic frameworks and the technique has been well-developed over the past two decades.[1–6] As illustrated in Scheme 1, most enantioselective transformations of azomethine ylides have utilized electronically poor alkenes or alkynes as dipolarophiles to perform [3+2] cycloaddition reaction (eq. 1). This results in the construction of chiral, five-membered heterocyclic skeletons, such as pyrrolidine or 2,5-dihydropyrrole.[1–3] In contrast, the enantioselective [3+3] cycloaddition of azomethine ylides using three-atom unconventional dipolarophiles has been only sporadically reported in the literature (eq. 2).[4–5] Nevertheless, this transformation is an efficient means of creating chiral, six-membered heterocyclic scaffolds.

Until recently, a limited number of examples of catalytic asymmetric [3+3] cycloaddition of azomethine ylides have been provided (Scheme 2).[4–5] Using chiral metal catalysis, the enantioselective cross-[3+3] cycloaddition of azomethine ylides with other 1,3-dipoles was realized by Wang and Guo (eq. 3–4).[4a–c] The Deng group has recently reported tandem [3+3] cycloaddition of azomethine ylide and 2-indolylnitroethylenes (eq. 5).[4d] Employing an organocatalytic strategy, the Gong group and our group have developed asymmetric [3+3] cycloaddition of azomethine ylides with 3-indolylmethanols (eq. 6).[5a–c] Very recently, we demonstrated the use of C3-unsubstituted 2-indolylmethanols as 3C building blocks to carry out an enantioselective and regioselective [3+3] cycloaddition with azomethine ylide (eq. 7).[5d] In spite of this recent progress, the catalytic asymmetric [3+3] cycloaddition of azomethine ylides remains under-



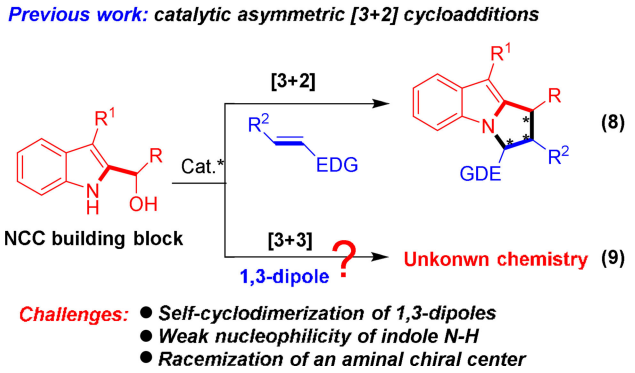
Scheme 1. Profile of catalytic asymmetric cycloadditions of azomethine ylides.



Scheme 2. Limited examples of catalytic asymmetric [3+3] cycloaddition of azomethine ylides.

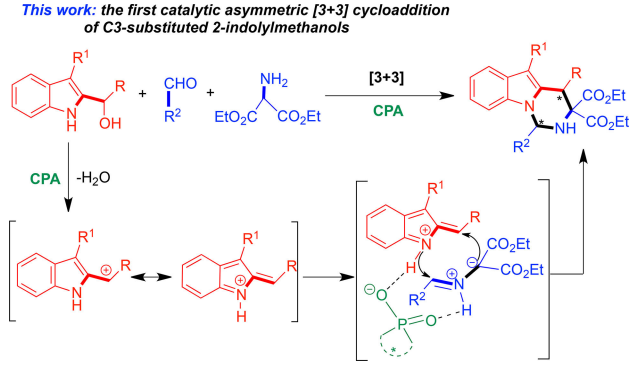
developed. Thus, the development of new enantioselective [3+3] cycloadditions of azomethine ylides using other three-atom dipolarophiles is highly desired.

C3-substituted 2-indolylmethanols can act as NCC (Nitrogen-Carbon-Carbon) building blocks in cycloaddition reactions (Scheme 3).[7] Using this class of reactants with electron-rich alkenes (vinylindoles and enamides), the Schneider group demonstrated [3+2] cycloadditions with excellent enantioselectivities (eq. 8).[7] However, this class of NCC building block has never been employed in [3+3] cycloadditions with 1,3-dipoles, nor in analogous catalytic asymmetric syntheses (eq. 9). There are three inherent challenges in this type of transformation. The first is the self-cyclodimerization of 1,3-dipoles, which will compete with the [3+3] cycloaddition of 1,3-dipoles and C3-substituted 2-indolylmethanols. The second is the relatively weak nucleophilicity of the indole N-H in tandem cycloaddition. The third is the tendency for racemization at the aminal chiral center contained in the [3+3] cycloaddition products. So, it has become an urgent task to explore the unknown chemistry and settle the great challenges in catalytic asymmetric [3+3] cycloadditions of C3-substituted 2-indolylmethanols with 1,3-dipoles.



Scheme 3. Profile of C3-substituted 2-indolylmethanol-involved catalytic asymmetric cycloadditions.

To address these challenges and develop new enantioselective [3+3] cycloaddition reactions with azomethine ylides, we designed a chiral phosphoric acid (CPA)[8]-catalyzed asymmetric [3+3] cycloaddition of azomethine ylides with C3-substituted 2-indolylmethanols (Scheme 4). In this design, the vinyliminium ion, derived from 2-indolylmethanol and the azomethine ylide, generated *in situ* from a reaction between the aldehyde and amino-ester, is activated by CPA anion via hydrogen-bonding and/or ion pair interactions. This facilitates the stereoselective tandem [3+3] cycloaddition of azomethine ylide with C3-substituted 2-indolylmethanol, resulting in a diastereo- and enantioselective tetrahydropyrimido[1,6-a]indole framework.



Scheme 4. Design of catalytic asymmetric [3+3] cycloaddition reactions of azomethine ylides with C3-substituted 2-indolylmethanols.

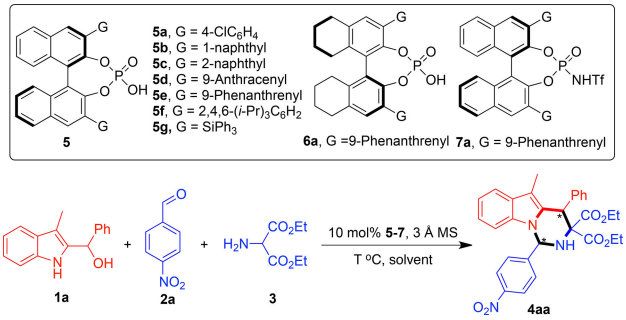
Herein, we report the first catalytic asymmetric [3+3] cycloaddition of azomethine ylides with C3-substituted 2-indolylmethanols, resulting in the diastereo- and enantioselective construction of a tetrahydropyrimido[1,6-*a*]indole framework (up to 91% yield, >95:5 dr, 98:2 er). This reaction is not only the first catalytic asymmetric [3+3] cycloaddition of C3-substituted 2-indolylmethanols, but also represents a new type of catalytic enantioselective [3+3] cycloaddition reaction using azomethine ylides.

Results and Discussion

As shown in Table 1, a model three-component reaction of C3-substituted 2-indolylmethanol **1a**, *p*-nitrobenzaldehyde **2a**, and amino-ester **3** was employed to test our hypothesized synthesis. Initially, in the presence of CPA **5a**, the designed [3+3] cycloaddition occurred, affording the desired product **4aa**, albeit with a moderate yield of 45% and a low enantioselectivity of 65:35 er (entry 1). A series of BINOL-derived CPAs, **5b**–**5g**, were then screened through the same reaction (entries 2–7), revealing that CPA **5e**, which bears two 3,3'-(9-phenanthrenyl) groups, delivered the highest enantioselectivity of 84:16 er (entry 5). To further improve enantioselectivity while keeping the 3,3'-(9-phenanthrenyl) groups unchanged, H_8-BINOL-derived CPA **6a** and phosphoramide **7a** were also evaluated as catalysts (entries 8–9). Catalyst **6a** facilitated an enantioselectivity of 95:5 er with a moderate yield of 54% (entry 8).

Therefore, different solvents (entries 8 and 10–13) were evaluated in the presence of the optimal catalyst **6a**. Toluene was the most effective solvent for controlling enantioselectivity (entries 10–13 vs. 8) and was therefore chosen as the most suitable solvent for

Table 1. Screening of catalysts and optimization of reaction conditions[a]



entry	Cat.	solvent	T (°C)	yield (%)[b]	er[c]
1	**5a**	toluene	50	45	65:35
2	**5b**	toluene	50	33	78:22
3	**5c**	toluene	50	34	65:35
4	**5d**	toluene	50	38	77:23
5	**5e**	toluene	50	20	84:16
6	**5f**	toluene	50	trace	–
7	**5g**	toluene	50	16	75:25
8	**6a**	toluene	50	54	95:5
9	**7a**	toluene	50	47	57:43
10	**6a**	acetone	50	trace	–
11	**6a**	EtOAc	50	23	92:8
12	**6a**	DCE	50	67	78:22
13	**6a**	1,4-dioxane	50	trace	–
14[d]	**6a**	toluene	50	17	92:8
15[e]	**6a**	toluene	50	45	95:5
16[f]	**6a**	toluene	50	54	93:7
17	**6a**	toluene	0	22	90:10
18	**6a**	toluene	25	31	95:5
19	**6a**	toluene	70	59	86:14
20	**6a**	toluene	90	60	67:33
21[g]	**6a**	toluene	50	54	95:5
22[h]	**6a**	toluene	50	51	95:5
23[i]	**6a**	toluene	50	64	95:5
24[j]	**6a**	toluene	50	63	93:7
25[k]	**6a**	toluene	50	66	92:8
26[i,l]	**6a**	toluene	50	64	95:5

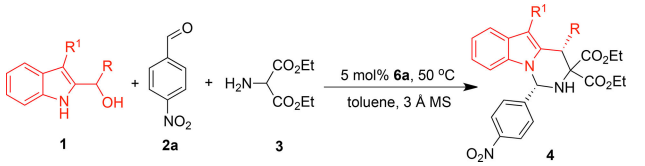
[a] Unless otherwise indicated, the reaction was carried out at the 0.1 mmol scale in the presence of 10 mol% **5–7** for 15 h in a solvent (2 mL) with 3 Å MS (100 mg), and at a molar ratio of **1a**:**2a**:**3** = 1:1.2:1.1.
[b] Isolated yield and only one diastereomer was observed.
[c] The *er* value was determined by HPLC.
[d] In the absence of additives.
[e] In the presence of 4 Å MS (100 mg).
[f] In the presence of 5 Å MS (100 mg).
[g] The molar ratio of **1a**:**2a**:**3** was 1:2.4:2.2.
[h] The molar ratio of **1a**:**2a**:**3** was 1:3.6:3.3.
[i] The molar ratio of **1a**:**2a**:**3** was 2:1.2:1.
[j] The molar ratio of **1a**:**2a**:**3** was 3:1.2:1.
[k] The molar ratio of **1a**:**2a**:**3** was 4:1.2:1.
[l] In the presence of 5 mol% **6a**.

these syntheses. Running the reactions in the absence of additives (entry 14) or in the presence of molecular sieves (MS) (entries 8 and 15–16) revealed that 3 Å MS was the best additive, absorbing water generated from the reaction and modulating both enantioselectivity and yield (entry 8 vs. 14).

Reaction temperature was also evaluated for its effect on enantioselectivity (entries 17–20). However, no improvements were observed upon lowering or elevating the reaction temperature (entries 17–20 vs. 8). Altering the reagent ratio (entries 21–25), however, had a strong effect. A yield of 64% and an enantioselectivity of 95:5 er were observed at **1a**:**2a**:**3** = 2:1.2:1 (entry 23 vs. 8). Lowering the catalyst load to 5 mol% still afforded product **4aa** while maintaining both yield and enantioselectivity (entry 26 vs. 23). The above set of optimal conditions was therefore used in subsequent experiments. It should be noted that only one diastereomer of **4aa** was observed during condition optimization, and the yield of product **4aa** could hardly be improved due to the self-cyclodimerization of azomethine ylide.[9]

With this set of optimal conditions, we then investigated the substrate scope of catalytic asymmetric [3+3] cycloaddition. First, the applicability of C3-substituted 2-indolylmethanols **1** was evaluated by reactions with *p*-nitrobenzaldehyde **2a** and amino-ester **3**. As shown in Table 2, this reaction was indeed

Table 2. Applicability of C3-substituted 2-indolylmethanols **1** in catalytic asymmetric [3+3] cycloadditions[a]



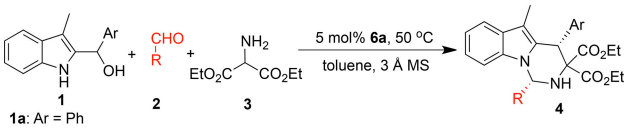
entry	4	R/R^1(**1**)	yield (%)[b]	dr[c]	er[d]
1	**4aa**	Ph/Me (**1a**)	65	>95:5	95:5
2	**4ba**	2-MeC$_6$H$_4$/Me (**1b**)	77	>95:5	95:5
3	**4ca**	3-MeC$_6$H$_4$/Me (**1c**)	49	>95:5	93:7
4	**4da**	4-MeC$_6$H$_4$/Me (**1d**)	60	>95:5	98:2
5	**4ea**	4-MeOC$_6$H$_4$/Me (**1e**)	61	>95:5	98:2
6	**4fa**	4-FC$_6$H$_4$/Me (**1f**)	60	>95:5	94:6
7	**4ga**	4-ClC$_6$H$_4$/Me (**1g**)	47	>95:5	93:7
8	**4ha**	2-thiophenyl/Me (**1h**)	58	>95:5	95:5
9	**4ia**	4-MeOC$_6$H$_4$/4-ClC$_6$H$_4$ (**1i**)	57	77:23	98:2 (91:9)[e]

[a] Unless otherwise indicated, the reaction was carried out at the 0.1 mmol scale and catalyzed by 5 mol% **6a** in toluene (2 mL) with 3 Å MS (100 mg) for 15 h, and the molar ratio of **1**:**2a**:**3** was 2:1.2:1.
[b] Isolated yield.
[c] The *dr* value was determined by ^{1}H NMR.
[d] The *er* value was determined by HPLC.
[e] The *er* value of minor diastereomer.

applicable to a series of C3-substituted 2-indolylmethanols **1** bearing different R/R^1 groups, which participated in [3+3] cycloadditions to give the products **4** in generally high enantioselectivities (93:7 to 98:2 er) and excellent diastereoselectivities (most >95:5 dr). In general, both electronically rich (entries 2–5) and electronically poor (entries 6–7) phenyl groups served as suitable R substituents. The position of the substituents may have exerted some effect on enantioselectivity, as evidenced by the *para*-methyl-substituted substrate **1d** delivering a higher enantioselectivity than its *ortho*- or *meta*-substituted counterparts **1b**–**1c** (entry 4. vs 2–3). The electronic nature of the substituents also had some influence on enantioselectivity, since *para*-methyl or *para*-methoxy-substituted substrates **1d**–**1e** yielded higher enantioselectivity than *para*-fluoro or *para*-chloro-substituted analogues **1f**–**1g** (entries 4–5 vs. 6–7). Notably, a 2-thiophenyl group as a heteroaromatic substituent was also a suitable R group of substrate **1h**, which successfully took part in the [3+3] cycloaddition to generate product **4ha** in an acceptable yield of 58%, a high enantioselectivity of 95:5 er and an excellent diastereoselectivity of >95:5 dr (entry 8). In addition, the R^1 group could be changed from a methyl group to a *para*-chlorobenzyl group, which also underwent [3+3] cycloaddition (entry 9). Although the diastereoselectivity was not very satisfying (77:23 dr), both of the diastereomers of product **4ia** were produced with good enantioselectivity (98:2 and 91:9 er).

Second, the substrate scope of aldehydes **2** was investigated. As listed in Table 3, entries 1–7, this reaction was not only amenable to electronically poor benzaldehydes **2a**–**2e** (entries 1–5), but also to electronically rich benzaldehydes **2f**–**2g** (entries 6–7), which often display low reactivity and poor enantioselective control in 1,3-dipolar cycloadditions of azomethine ylides.[9–10] The position of the substituents linked to the phenyl ring seemed to have some effect on both the yield and stereoselectivity of the reaction. For instance, *ortho*-bromobenzaldehyde **2e** showed much higher reactivity than *para*- and *meta*-bromobenzaldehydes **2c**–**2d** (entry 5 vs. 3–4), while the latter demonstrated higher diastereo- and enantioselective control of the reaction than the former (entries 3–4 vs. 5). 1-Naphthaldehyde **2h** was also suitable for [3+3] cycloaddition and resulted in a moderate yield of 50%, a good enantioselectivity of 94:6 er and an excellent diastereoselectivity of >95:5 dr (entry 8). Moreover, heteroaromatic aldehydes, as exemplified by thiophene-3-carbaldehyde **2i**, were also suitable substrates, generating the corresponding product **4ei** in moderate yield and good enantioselectivity (entry 9). As listed in entry 10, cinnamaldehyde **2j**, an unsaturated aliphatic aldehyde, also took part in the [3+3] cycloaddition with an acceptable yield and a moderate enantioselectivity. It is worth noting that aliphatic aldehydes, such as cyclohexanecarbaldehyde **2k** and 2-phenylacetaldehyde **2l**, which often failed to participate in 1,3-dipolar cycloadditions of azomethine ylides,[5a–b,9–10] were amenable to [3+3] cycloaddition (entries 11–12). Although yields were unsatisfying and the degree of enantioselectivity only moderate, the inclusion of aliphatic aldehydes **2k**–**2l** in catalytic asymmetric [3+3] cycloadditions greatly enhanced the applicability of the reaction.

Table 3. Substrate scope of aldehydes **2**.[a]



1a: Ar = Ph
1b: Ar = 2-MeC$_6$H$_4$
1d: Ar = 4-MeC$_6$H$_4$
1e: Ar = 4-MeOC$_6$H$_4$

entry	4	1	R (2)	yield (%)[b]	dr[c]	er[d]
1	**4aa**	**1a**	4-$NO_2C_6H_4$ (**2a**)	65	>95:5	95:5
2	**4bb**	**1b**	4-CNC_6H_4 (**2b**)	63	>95:5	92:8
3	**4dc**	**1d**	4-BrC_6H_4 (**2c**)	57	>95:5	92:8
4	**4ed**	**1e**	3-BrC_6H_4 (**2d**)	53	>95:5	92:8
5[e]	***ent*-4ee**	**1e**	2-BrC_6H_4 (**2e**)	91	67:33	88:12 (98:2)[f]
6[g]	**4df**	**1d**	3-$MeOC_6H_4$ (**2f**)	47	>95:5	92:8
7[g]	**4eg**	**1e**	2-MeC_6H_4 (**2g**)	52	>95:5	87:13
8[g]	**4eh**	**1e**	1-naphthyl (**2h**)	50	>95:5	94:6
9[h]	***ent*-4ei**	**1e**	3-thiophenyl (**2i**)	53	>95:5	89:11
10[i,j]	**4ej**	**1e**	styryl (**2j**)	41	>95:5	80:20
11[i]	**4ek**	**1e**	cyclohexyl (**2k**)	33	>95:5	89:11
12	**4bl**	**1b**	Bn (**2l**)	47	>95:5	82:18

[a] Unless otherwise indicated, the reaction was carried out at the 0.1 mmol scale and catalyzed by 5 mol% **6a** in toluene (2 mL) with 3 Å MS (100 mg) for 15 h, and the molar ratio of **1**:**2**:**3** was 2:1.2:1.
[b] Isolated yield.
[c] The *dr* value was determined by ^{1}H NMR.
[d] The *er* value was determined by HPLC.
[e] Catalyzed by 5 mol% ***ent*-6a**.
[f] The *er* value of minor diastereomer.
[g] The volume of toluene is 5 mL.
[h] Catalyzed by 5 mol% ***ent*-6a** in acetal acetate (14 mL).
[i] Catalyzed by 5 mol% ***ent*-5f**.
[j] The volume of toluene was 8 mL.

The relative and absolute configuration of product **4fa** (99:1 er after recrystallization) was unambiguously determined to be *cis* and (1*S*, 4*R*) by single crystal X-ray diffraction analysis (Figure 1).[11] The relative and absolute configurations of other products **4** were assigned by analogy.

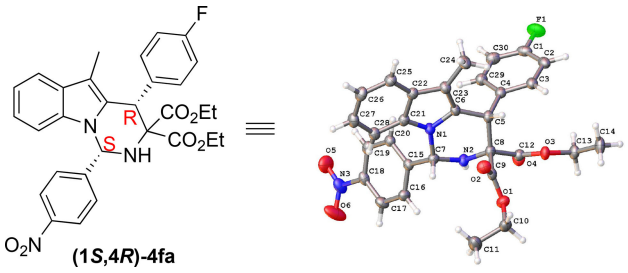
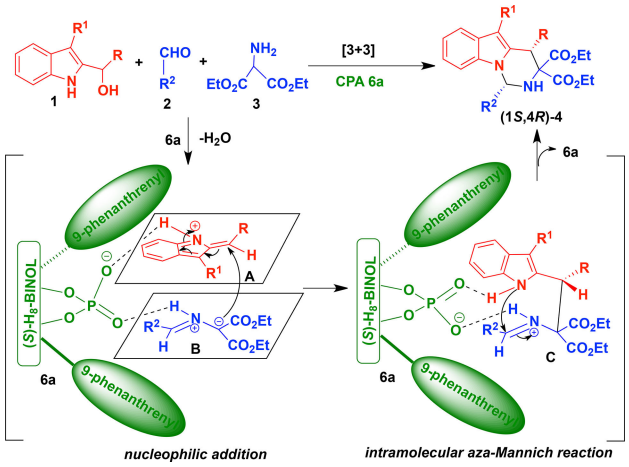


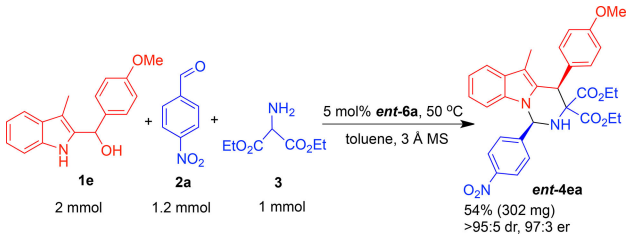
Figure 1. Single crystal structure of **4fa**.

Based on the experimental results, we propose a reaction pathway, shown in Scheme 5, to explain the chemistry and stereochemistry of this [3+3] cycloaddition via stepwise tandem cyclization. In the presence of CPA **6a**, C3-substituted 2-indolylmethanols **1** transformed into vinyliminium **A** via dehydration, and azomethine ylide **B** was generated *in situ* by the condensation of aldehydes **2** with amino-ester **3**. The two intermediates were simultaneously activated by CPA **6a** via hydrogen-bonding and ion pair interactions, which facilitated the enantioselective nucleophilic addition of azomethine ylide **B** to vinyliminium **A** to generate another intermediate **C**. This intermediate **C** could be activated again by catalyst **6a** to perform an intramolecular aza-Mannich reaction, leading to the formation of final products **4** with (1*S*, 4*R*)-configurations.



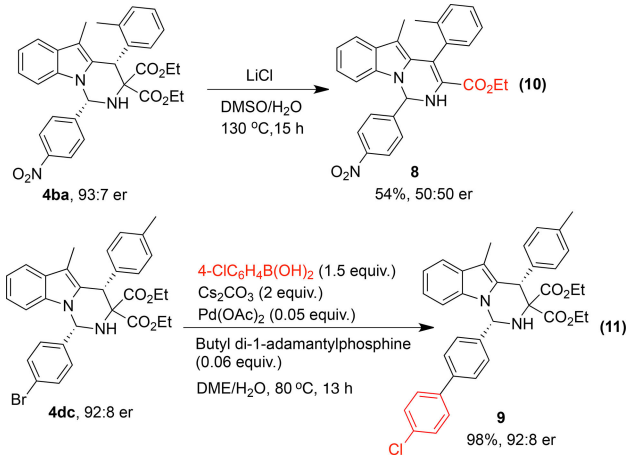
Scheme 5. Suggested reaction pathway.

To show the utility of this reaction, a preparative scale synthesis of ***ent*-4ea** was carried out in 1 mmol scale under standard conditions (Scheme 6). The resulting [3+3] cycloaddition generated the product ***ent*-4ea** in a moderate yield of 54%, while largely maintaining the high degree of stereoselectivity (> 95:5 dr, 97:3 er) observed in the small-scale reaction (Table 2, entry 5).



Scheme 6. Preparative scale synthesis of ***ent*-4ea**.

We also performed preliminary synthetic transformations of products **4** (Scheme 7). First, we performed a Krapcho decarboxylation of compound **4ba**, which gave the decarboxylative product **8** in a moderate yield (eq. 10). However, due to the high reaction temperature of 130 °C, product **8** was racemized. We next performed a Suzuki coupling of compound **4dc** with 4-chlorophenylboronic acid at a lower temperature of 80 °C, which afforded the desired product **9** with a high yield of 98% and a retained enantioselectivity of 92:8 er.



Scheme 7. Preliminary synthetic transformations.

Conclusions

We have established the first catalytic asymmetric [3+3] cycloaddition of azomethine ylides with C3-substituted 2-indolylmethanols, which resulted in tetrahy-

dropyrimido[1,6-a]indole frameworks in high diastereo- and enantioselectivities (up to 91% yield, >95:5 dr, 98:2 er). This reaction was not only the first catalytic asymmetric [3+3] cycloaddition of C3-substituted 2-indolylmethanols, but also represents a new type of catalytic enantioselective [3+3] cycloaddition of azomethine ylides. This approach has provided valuable insight into the chemistry of, and resolved several of the challenges associated with, catalytic asymmetric [3+3] cycloadditions of C3-substituted 2-indolylmethanols with 1,3-dipoles. In addition, this protocol also provides a useful means of enantioselectively constructing tetrahydropyrimido[1,6-a]indole skeletons.

Experimental Section

General

^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS (ESI) was determined by a HRMS/MS instrument. Enantiomeric ratios (*er*) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of enantiomeric ratio by chiral HPLC were Chiralpak AD-H, OD-H, AD-H and IA columns. Optical rotation values were measured with instruments operating at λ=589 nm, corresponding to the sodium D line at the temperatures indicated. The X-ray source used for the single crystal X-ray diffraction analysis of compound **4fa** was CuKα (λ=1.54178), and the thermal ellipsoid was drawn at the 30% probability level. Analytical grade solvents for the preparative thin layer chromatography were distilled before use. All starting materials commercially available were used directly. Substrates **1** were synthesized according to the literature method.[7a]

General Procedure for the Catalytic Asymmetric Synthesis of Products 4

Toluene (0.5 mL) was added to the mixture of aldehydes **2** (0.12 mmol), 3Å MS (100 mg), and the catalyst **6a** (0.005 mmol). Then, amino-ester **3** (0.1 mmol) and another potion of toluene (0.5 mL) were sequentially added to the reaction mixture, which was stirred at room temperature for 30 min. Next, C3-substituted 2-indolylmethanols **1** (0.2 mmol) and another potion of toluene (1 mL) were sequentially added to the reaction mixture, which was stirred at 50 °C for 15 h. After the completion of the reaction indicated by TLC, the reaction mixture was filtered to remove the molecular sieves. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through preparative thin layer chromatography to afford pure products **4**.

(1*S*,4*R*)-Diethyl5-methyl-1-(4-nitrophenyl)-4-phenyl-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4aa): Flash column chromatography eluent, petroleum ether/ethyl acetate=8/1; Reaction time=15 h; yield: 65% (34.4 mg); yellowish solid, m.p 78–80 °C; $[\alpha]_D^{20}=+122.8$ (c 0.37, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J*=8.6 Hz, 2H), 7.80 (d, *J*=8.6 Hz, 2H), 7.49 (t, *J*=6.8 Hz, 3H), 7.29 (d, *J*=6.5 Hz, 2H), 7.25–7.21 (m, 1H), 7.06 (t, *J*=7.5 Hz, 1H), 6.87 (t, *J*=7.7 Hz, 1H), 6.26 (d, *J*=8.3 Hz, 1H), 5.96 (d, *J*=5.6 Hz, 1H), 5.27 (s, 1H), 4.28 (q, *J*=7.1 Hz, 2H), 4.10–4.01 (m, 1H), 4.00–3.91 (m, 1H), 3.09 (d, *J*=5.6 Hz, 1H), 2.15 (s, 3H), 1.28 (t, *J*=7.1 Hz, 3H), 1.11 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.9, 148.7, 146.2, 138.2, 134.6, 133.1, 130.1, 129.3, 128.9, 128.4, 127.6, 124.5, 121.1, 120.0, 118.6, 111.3, 109.1, 69.9, 69.4, 62.7, 62.5, 43.2, 14.2, 13.8, 7.9; IR (KBr): 3342, 2980, 2921, 2854, 1741, 1526, 1459, 1348, 1017, 856, 744, 702 cm^{-1}; ESI FTMS exact mass calcd for $(C_{30}H_{29}N_3O_6\text{-}H)^-$ requires m/z 526.1972, found m/z 526.1965; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 95:5, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol=70/30, flow rate 1.0 mL/min, T=30 °C, 254 nm): t_R=5.58 min (minor), t_R=6.74 min (major).

(1*S*,4*R*)-Diethyl5-methyl-1-(4-nitrophenyl)-4-(o-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ba): Preparative thin layer chromatography: petroleum ether/ toluene/ethyl acetate=10:10:1; Reaction time=15 h; yield: 77% (41.7 mg); yellow solid; m.p. 43–45 °C; $[\alpha]_D^{20}=+149.3$ (c 0.66, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J*=8.5 Hz, 2H), 7.82 (d, *J*=8.5 Hz, 2H), 7.67 (d, *J*=7.5 Hz, 1H), 7.50 (d, *J*=7.9 Hz, 1H), 7.19 (d, *J*=7.2 Hz, 1H), 7.14 (d, *J*=7.0 Hz, 1H), 7.09 (s, 1H), 7.08–7.03 (m, 1H), 6.87 (t, *J*=7.7 Hz, 1H), 6.25 (d, *J*=8.3 Hz, 1H), 5.99 (d, *J*=5.7 Hz, 1H), 5.66 (s, 1H), 4.35–4.27 (m, 2H), 3.88–3.78 (m, 1H), 3.88–3.77 (m, 1H), 3.20 (d, *J*=5.7 Hz, 1H), 2.68 (s, 3H), 2.12 (s, 3H), 1.32 (t, *J*=7.1 Hz, 3H), 1.01 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.0, 148.7, 146.1, 136.5, 135.8, 134.5, 134.1, 130.6, 130.0, 129.5, 128.9, 127.4, 126.3, 124.6, 120.9, 119.9, 118.5, 111.4, 108.8, 69.7, 69.2, 62.7, 62.4, 37.5, 20.2, 14.2, 13.6, 8.0; IR (KBr): 3358, 2971, 2923, 1735, 1524, 1459, 1343, 1258, 1100, 1023, 858, 748 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{31}N_3O_6\text{-}H)^-$ requires m/z 540.2129, found m/z 540.2130; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 95:5, determined by HPLC (Daicel Chiralpak OD-H, hexane/ isopropanol=80/20, flow rate 1.0 mL/min, T=30 °C, 254 nm): t_R=5.47 min (minor), t_R=7.52 min (major).

(1*S*,4*R*)-Diethyl5-methyl-1-(4-nitrophenyl)-4-(m-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ca): Preparative thin layer chromatography: petroleum ether/ toluene/ethyl acetate=10:10:1; Reaction time=15 h; yield: 49% (26.5 mg); yellow solid; m.p. 45–47 °C; $[\alpha]_D^{20}=+141.5$ (c 0.42, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J*=8.5 Hz, 2H), 7.83 (d, *J*=8.5 Hz, 2H), 7.53 (d, *J*=7.8 Hz, 1H), 7.30–7.26 (m, 2H), 7.17 (t, *J*=7.6 Hz, 1H), 7.11–7.03 (m, 2H), 6.89 (t, *J*=7.7 Hz, 1H), 6.31 (d, *J*=8.3 Hz, 1H), 6.00 (d, *J*=6.3 Hz, 1H), 5.26 (s, 1H), 4.33–4.24 (m, 2H), 4.13–4.04 (m, 1H), 4.04–3.94 (m, 1H), 3.07 (d, *J*=6.3 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 1.27 (t, *J*=7.0 Hz, 3H), 1.15 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.9, 148.7, 146.2, 138.0, 137.8, 134.7, 133.2, 130.2, 130.1, 128.9, 128.4, 128.3, 126.3, 124.5, 121.1, 120.0, 118.6, 111.3, 109.0, 69.9, 69.4, 62.6, 62.4, 43.2, 21.5, 14.2, 13.8, 7.9; IR (KBr): 3418, 2971, 2923,

1743, 1527, 1458, 1347, 1256, 1101, 1018, 856, 744 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{31}N_3O_6\text{-}H)^-$ requires m/z 540.2129, found m/z 540.2133; Diastereomeric ratio: >95:5, determined by ^1H NMR; Enantiomeric ratio: 93:7, determined by HPLC (Daicel Chiralpak OD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 4.91 min (minor), t_R = 5.91 min (major).

(1*S*,4*R*)-Diethyl5-methyl-1-(4-nitrophenyl)-4-(p-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4da): Preparative thin layer chromatography: petroleum ether/ toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 60% (32.6 mg); yellow solid; m.p. 41–43 °C; $[\alpha]_D^{20}$ = +162.1 (c 0.69, Acetone); ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.6 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.13–7.04 (m, 3H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.28 (d, *J* = 8.3 Hz, 1H), 5.98 (d, *J* = 6.0 Hz, 1H), 5.26 (s, 1H), 4.35–4.24 (m, 2H), 4.15–4.05 (m, 1H), 4.05–3.93 (m, 1H), 3.08 (d, *J* = 5.9 Hz, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.0, 148.7, 146.2, 137.3, 135.1, 134.7, 133.4, 130.2, 129.1, 129.1, 128.9, 124.5, 121.0, 120.0, 118.6, 111.3, 108.9, 69.9, 69.4, 62.6, 62.5, 42.9, 21.1, 14.2, 13.8, 7.9; IR (KBr): 3434, 2975, 2924, 1743, 1525, 1457, 1347, 1257, 1104, 1019, 824, 745 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{31}N_3O_6\text{-}H)^-$ requires m/z 540.2129, found m/z 540.2129; Diastereomeric ratio: >95:5, determined by ^1H NMR; Enantiomeric ratio: 98:2, determined by HPLC (Daicel Chiralpak OD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 4.90 min (minor), t_R = 6.11 min (major).

(1*S*,4*R*)-Diethyl4-(4-methoxyphenyl)-5-methyl-1-(4-nitrophenyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ea): Preparative thin layer chromatography: petroleum ether/toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 61% (33.9 mg); yellow solid; m.p. 58–60 °C; $[\alpha]_D^{20}$ = +122.3 (c 0.71, Acetone); ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.27 (d, *J* = 8.3 Hz, 1H), 5.96 (d, *J* = 5.5 Hz, 1H), 5.23 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.14–4.05 (m, 1H), 4.03–3.93 (m, 1H), 3.76 (s, 3H), 3.09 (d, *J* = 5.5 Hz, 1H), 2.16 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 167.0, 159.0, 148.7, 146.2, 134.6, 133.5, 130.4, 130.2, 128.9, 124.5, 121.0, 120.0, 118.6, 113.7, 111.3, 108.8, 70.0, 69.4, 62.6, 62.5, 55.2, 42.5, 14.2, 13.9, 7.9; IR (KBr): 3422, 2978, 1743, 1610, 1521, 1458, 1347, 1251, 1104, 1029, 830, 743 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{31}N_3O_7\text{-}H)^-$ requires m/z 556.2078, found m/z 556.2073; Diastereomeric ratio: >95:5, determined by ^1H NMR; Enantiomeric ratio: 98:2, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.47 min (major), t_R = 12.92 min (minor).

(1*S*,4*R*)-Diethyl4-(4-fluorophenyl)-5-methyl-1-(4-nitrophenyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4fa): Preparative thin layer chromatography: petroleum ether/toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 60% (32.6 mg); yellow solid; m.p. 62–64 °C; $[\alpha]_D^{20}$ = + 123.2 (c 0.47, Acetone); ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.57–7.47 (m, 3H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 8.5 Hz, 2H), 6.88 (t, *J* = 7.7 Hz, 1H), 6.26 (d, *J* = 8.3 Hz, 1H), 5.96 (d, *J* = 4.5 Hz, 1H), 5.27 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.14–4.04 (m, 1H), 4.03–3.94 (m, 1H), 3.13 (d, *J* = 4.3 Hz, 1H), 2.16 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.8, 162.1 (*J* = 246.0 Hz), 148.7, 146.1, 134.6, 134.2, 134.2, 132.9, 131.0, 130.1 (*J* = 8.0 Hz), 128.9, 124.6, 121.2, 120.1, 118.6, 115.2 (*J* = 21.0 Hz), 111.3, 109.1, 69.8, 69.5, 62.7, 62.6, 42.4, 14.2, 13.8, 7.9; IR (KBr): 2981, 2925, 1743, 1606, 1526, 1457, 1347, 1217, 1102, 1017, 833, 739 cm^{-1}; ESI FTMS exact mass calcd for $(C_{30}H_{28}FN_3O_6\text{-}H)^-$ requires m/z 544.1878, found m/z 544.1877; Diastereomeric ratio: >95:5, determined by ^1H NMR; Enantiomeric ratio: 94:6, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 5.97 min (minor), t_R = 7.51 min (major).

(1*S*,4*R*)-Diethyl4-(4-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ga): Preparative thin layer chromatography: petroleum ether/toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 47% (26.5 mg); yellow solid; m.p. 52–54 °C; $[\alpha]_D^{20}$ = + 114.9 (c 0.48, Acetone); ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.49 (t, *J* = 8.3 Hz, 3H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.25 (d, *J* = 8.3 Hz, 1H), 5.95 (d, *J* = 4.4 Hz, 1H), 5.25 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.14–4.05 (m, 1H), 4.03–3.94 (m, 1H), 3.12 (d, *J* = 4.4 Hz, 1H), 2.15 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 166.8, 148.7, 146.1, 136.9, 134.7, 133.5, 132.6, 130.7, 130.1, 128.8, 128.5, 124.6, 121.3, 120.1, 118.7, 111.3, 109.3, 69.7, 69.5, 62.7, 62.6, 42.6, 14.2, 13.8, 8.0; IR (KBr): 2970, 2925, 1743, 1527, 1459, 1346, 1259, 1098, 1018, 824, 746, 668 cm^{-1}; ESI FTMS exact mass calcd for $(C_{30}H_{28}ClN_3O_6\text{-}H)^-$ requires m/z 560.1583, found m/z 560.1575; Diastereomeric ratio: >95:5, determined by ^1H NMR; Enantiomeric ratio: 93:7, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 5.98 min (minor), t_R = 7.36 min (major).

(1*S*,4*R*)-Diethyl5-methyl-1-(4-nitrophenyl)-4-(thiophen-2-yl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ha): Preparative thin layer chromatography: petroleum ether/toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 58% (31.0 mg); yellow solid; m.p. 64–66 °C; $[\alpha]_D^{20}$ = + 105.1 (c 0.52, Acetone); ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 5.3 Hz, 1H), 7.12 (d, *J* = 3.3 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.95–6.91 (m, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.27 (d, *J* = 8.3 Hz, 1H), 6.00 (d, *J* = 4.7 Hz, 1H), 5.63 (s, 1H), 4.30–4.21 (m, 2H), 4.19–4.12 (m, 1H), 4.12–4.05 (m, 1H), 3.31 (d, *J* = 4.6 Hz, 1H), 2.27 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 166.6, 148.7, 146.3, 140.6, 134.7, 132.7, 130.0, 129.2, 126.6, 126.0, 125.7, 124.4, 121.4, 120.1, 118.7, 111.2, 109.2, 69.6, 62.7, 39.5, 14.1, 13.8, 7.9; IR (KBr): 3436, 2978, 2925, 1744, 1527, 1459, 1346, 1231, 1103, 1018, 855, 739 cm^{-1}; ESI FTMS exact mass calcd for $(C_{28}H_{27}N_3O_6S\text{-}H)^-$ requires m/z 532.1537, found m/z 532.1526; Diastereomeric ratio: >95:5,

determined by ^{1}H NMR; Enantiomeric ratio: 95:5, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.50 min (minor), t_R = 10.12 min (major).

(1*S*,4*R*)-Diethyl5-(4-chlorophenyl)-4-(4-methoxyphenyl)-1-(4-nitrophenyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ia): Preparative thin layer chromatography: petroleum ether/ethyl acetate = 4/1; Reaction time = 15 h; yield: 57% (37.4 mg) (inseparable diastereomers); yellow solid; m.p. 83–85 °C; $[\alpha]_D^{20}$ = +17.3 (c 0.50, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.4 Hz, 2.6H), 7.88 (t, *J* = 7.5 Hz, 2.6H), 7.61 (d, *J* = 8.0 Hz, 0.3H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.40–7.30 (m, 3H), 7.28 (s, 0.9H), 7.24 (s, 1.9H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.13–7.07 (m, 1.3H), 6.96 (t, *J* = 7.7 Hz, 1.3H), 6.82–6.76 (m, 2.6H), 6.40 (d, *J* = 8.3 Hz, 1.3H), 6.13–6.02 (m, 1.3H), 5.25 (s, 0.3H), 5.18 (s, 1H), 4.31–4.16 (m, 2.6H), 4.14–4.05 (m, 1.3H), 4.02–3.93 (m, 1.3H), 3.77 (s, 3.9H), 3.09 (d, *J* = 6.4 Hz, 1.3H), 1.22–1.16 (m, 3.9H), 1.13 (q, *J* = 7.3 Hz, 3.9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 166.8, 166.7, 159.0, 158.9, 148.7, 145.9, 145.7, 134.9, 134.3, 134.1, 132.5, 132.3, 131.3, 131.1, 130.3, 129.8, 129.1, 128.9, 128.8, 128.6, 128.4, 126.5, 124.6, 121.9, 121.7, 121.1, 121.0, 119.6, 119.3, 115.1, 113.9, 113.8, 111.7, 111.6, 69.9, 69.8, 62.6, 62.6, 55.2, 42.8, 14.2, 13.9; IR (KBr): 3348, 2973, 1742, 1608, 1521, 1456, 1348, 1246, 1097, 1030, 836, 742 cm^{-1}; ESI FTMS exact mass calcd for ($C_{36}H_{32}ClN_3O_7$-H)$^-$ requires m/z 652.1845, found m/z 652.1838; Diastereomeric ratio: 77:23, determined by ^{1}H NMR; Enantiomeric ratio of major diastereomer: 98:2, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.27 min (minor), t_R = 21.18 min (major); Enantiomeric ratio of minor diastereomer: 91:9, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 6.37min (minor), t_R = 16.28 min (major).

(1*S*,4*R*)-Diethyl1-(4-cyanophenyl)-5-methyl-4-(o-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4bb): Preparative thin layer chromatography: petroleum ether/ toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 63% (32.9 mg); yellow solid; m.p. 81–83 °C; $[\alpha]_D^{20}$ = +160.7 (c 0.52, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 7.7 Hz, 1H), 6.22 (d, *J* = 8.3 Hz, 1H), 5.90 (d, *J* = 5.7 Hz, 1H), 5.63 (s, 1H), 4.33–4.24 (m, 2H), 4.04–3.93 (m, 1H), 3.85–3.72 (m, 1H), 3.16 (d, *J* = 5.7 Hz, 1H), 2.66 (s, 3H), 2.09 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.0, 144.3, 136.6, 135.7, 134.5, 134.1, 133.1, 130.5, 129.9, 129.5, 128.7, 127.4, 126.3, 120.9, 119.9, 118.4, 118.3, 113.6, 111.4, 108.7, 69.6, 69.5, 62.6, 62.4, 37.5, 20.2, 14.2, 13.5, 7.9; IR (KBr): 3439, 2980, 1741, 1460, 1256, 1209, 1103, 1052, 842, 745, 675 cm^{-1}; ESI FTMS exact mass calcd for ($C_{32}H_{31}N_3O_4$-H)$^-$ requires m/z 520.2231, found m/z 520.2234; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 92:8, determined by HPLC (Daicel Chiralpak OD-H, hexane/ isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.03 min (minor), t_R = 7.79 min (major).

(1*S*,4*R*)-Diethyl1-(4-bromophenyl)-5-methyl-4-(p-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4dc): Preparative thin layer chromatography: petroleum ether/ ethyl acetate = 6/1; Reaction time = 15 h; yield: 57% (32.9 mg); yellow solid; m.p. 75–77 °C; $[\alpha]_D^{20}$ = +131.1 (c 0.64, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.53–7.46 (m, 3H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.10–7.02 (m, 3H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.37 (d, *J* = 8.3 Hz, 1H), 5.81 (d, *J* = 6.1 Hz, 1H), 5.22 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.13–4.03 (m, 1H), 4.02–3.91 (m, 1H), 3.03 (d, *J* = 6.1 Hz, 1H), 2.29 (s, 3H), 2.14 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 167.1, 138.4, 137.1, 135.3, 134.8, 133.6, 132.4, 130.1, 129.5, 129.2, 129.0, 123.5, 120.8, 119.7, 118.3, 111.7, 108.5, 70.0, 69.7, 62.4, 62.3, 42.9, 21.1, 14.2, 13.8, 7.9; IR (KBr): 3366, 2976, 1743, 1458, 1256, 1207, 1103, 1061, 1014, 816, 742, 674 cm^{-1}; ESI FTMS exact mass calcd for ($C_{31}H_{31}BrN_2O_4$-H)$^-$ requires m/z 573.1383, found m/z 573.1366; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 92:8, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 4.93 min (minor), t_R = 6.66 min (major).

(1*S*,4*R*)-Diethyl1-(3-bromophenyl)-4-(4-methoxyphenyl)-5-methyl-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ed): Preparative thin layer chromatography: petroleum ether/toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 53% (31.1 mg); yellow oil; $[\alpha]_D^{20}$ = +124.4 (c 0.59, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.88 (t, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.37 (d, *J* = 8.3 Hz, 1H), 5.77 (d, *J* = 5.6 Hz, 1H), 5.21 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.14–4.04 (m, 1H), 4.03–3.93 (m, 1H), 3.76 (s, 3H), 3.07 (d, *J* = 5.7 Hz, 1H), 2.15 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.1, 158.9, 141.7, 134.9, 133.7, 132.7, 131.0, 130.8, 130.5, 130.4, 130.1, 126.4, 123.1, 120.9, 119.7, 118.3, 113.7, 111.7, 108.5, 70.0, 69.8, 62.5, 62.3, 55.2, 42.4, 14.2, 13.9, 7.9; IR (KBr): 3831, 3735, 3440, 1746, 1646, 1513, 1465, 1249, 1106, 676 cm^{-1}; ESI FTMS exact mass calcd for ($C_{31}H_{31}BrN_2O_5$-H)$^-$ requires m/z 589.1333, found m/z 589.1323; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 92:8, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 4.45 min (major), t_R = 5.75 min (minor).

(1*R*,4*S*)-Diethyl1-(2-bromophenyl)-4-(4-methoxyphenyl)-5-methyl-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (*ent*-4ee): Preparative thin layer chromatography: petroleum ether/ethyl acetate = 10/1; Reaction time = 15 h; yield: 91% (53.5 mg) (inseparable diastereomers); yellow solid; m.p. 60–62 °C; $[\alpha]_D^{20}$ = -57.7 (c 1.08, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 0.5H), 7.53 (d, *J* = 7.4 Hz, 1.5H), 7.49 (d, *J* = 8.3 Hz, 3H), 7.40–7.30 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.11–7.02 (m, 2H), 7.02–6.96 (m, 1H), 6.93 (t, *J* = 7.6 Hz, 0.5H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.75 (t, *J* = 8.1 Hz, 1.5H), 6.33 (d, *J* = 4.1 Hz, 1H), 6.30 (d, *J* = 8.3 Hz, 1H), 5.70 (d, *J* = 7.7 Hz, 0.5H), 5.23 (s, 0.5H), 5.20 (s, 1H), 4.35–4.19 (m, 2H), 4.15–4.02 (m, 2H), 4.02–3.93 (m, 1H), 3.91–3.83 (m,

0.5H), 3.76 (s, 3H), 3.75 (s, 1.5H), 3.65–3.56 (m, 0.5H), 3.30 (d, J = 4.0 Hz, 1H), 2.85–2.72 (m, 0.5H), 2.17 (s, 3H), 2.13 (s, 1.5H), 1.29 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 6.8 Hz, 3H), 1.12 (d, J = 7.1 Hz, 1.5H), 0.87 (t, J = 7.1 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 168.5, 167.9, 167.3, 158.8, 158.7, 136.5, 136.1, 134.6, 134.0, 133.9, 133.2, 132.9, 132.6, 131.5, 130.7, 130.6, 130.4, 130.3, 130.1, 130.0, 129.5, 129.3, 129.2, 128.7, 127.9, 126.3, 121.0, 120.7, 119.6, 119.6, 118.4, 118.3, 113.5, 113.4, 111.5, 110.4, 108.3, 107.6, 69.9, 66.8, 66.4, 65.6, 62.5, 62.2, 62.0, 61.6, 55.2, 55.1, 42.5, 41.1, 14.2, 13.9, 13.9, 13.4, 8.1, 8.0; IR (KBr): 3370, 2928, 1742, 1611, 1511, 1460, 1249, 1103, 1041, 832, 737, 675 cm^{-1}; ESI FTMS exact mass calcd for ($C_{31}H_{31}BrN_2O_5$-H)$^-$ requires m/z 589.1333, found m/z 589.1330; Diastereomeric ratio: 67:33, determined by ^{1}H NMR; Enantiomeric ratio of major diastereomer: 88:12, determined by HPLC (Daicel Chiralpak OD-H, hexane/ isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 5.93 min (minor), t_R = 8.17 min (major); Enantiomeric ratio of minor diastereomer: 98:2, determined by HPLC (Daicel Chiralpak OD-H, hexane/ isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 6.71min (minor), t_R = 10.28 min (major).

(1*S*,4*R*)-Diethyl1-(3-methoxyphenyl)-5-methyl-4-(p-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4df): Preparative thin layer chromatography: petroleum ether/ethyl acetate = 6/1; Reaction time = 15 h; yield: 47% (24.8 mg); yellow solid; m.p. 53–55 °C; $[\alpha]_D^{20}$ = +138.9 (c 0.53, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.8 Hz, 1H), 7.43–7.35 (m, 3H), 7.20 (d, J = 7.7 Hz, 1H), 7.16 (s, 1H), 7.07 (d, J = 7.9 Hz, 2H), 7.05–7.00 (m, 2H), 6.85 (t, J = 7.7 Hz, 1H), 6.42 (d, J = 8.3 Hz, 1H), 5.76 (d, J = 6.0 Hz, 1H), 5.21 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.12–4.02 (m, 1H), 4.00–3.91 (m, 1H), 3.83 (s, 3H), 3.09 (d, J = 6.1 Hz, 1H), 2.28 (s, 3H), 2.14 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.2, 160.2, 141.0, 137.0, 135.5, 135.1, 133.7, 130.2, 130.0, 129.2, 128.9, 120.6, 120.0, 119.5, 118.1, 115.1, 113.2, 111.9, 108.2, 70.3, 70.0, 62.4, 62.2, 55.4, 42.9, 21.1, 14.2, 13.8, 7.9; IR (KBr): 2926, 1741, 1601, 1458, 1257, 1207, 1153, 1102, 1043, 814, 744, 678 cm^{-1}; ESI FTMS exact mass calcd for ($C_{32}H_{34}N_2O_5$-H)$^-$ requires m/z 525.2384, found m/z 525.2376; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 92:8, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 4.93 min (minor), t_R = 5.61 min (major).

(1*S*,4*R*)-Diethyl4-(4-methoxyphenyl)-5-methyl-1-(o-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4eg): Preparative thin layer chromatography: petroleum ether/toluene/dichloromethane = 1:1:1; Reaction time = 15 h; yield: 52% (27.5 mg); yellow solid; m.p. 73–75 °C; $[\alpha]_D^{20}$ = + 143.8 (c 0.59, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 6.2 Hz, 2H), 7.31 (d, J = 5.9 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.91–6.79 (m, 3H), 6.34 (d, J = 8.2 Hz, 1H), 6.08 (d, J = 7.1 Hz, 1H), 5.27 (s, 1H), 4.28 (q, J = 6.9 Hz, 2H), 4.16–4.05 (m, 1H), 4.04–3.94 (m, 1H), 3.77 (s, 3H), 3.03 (d, J = 7.1 Hz, 1H), 2.62 (s, 3H), 2.19 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 167.2, 158.8, 137.0, 136.2, 135.1, 134.3, 132.0, 131.1, 130.8, 130.4, 130.1, 129.0, 127.2, 126.9, 120.6, 119.5, 118.2, 114.4, 113.7, 112.0, 108.3, 70.0, 66.3, 62.4, 62.2, 55.2, 42.6, 18.8, 14.2, 13.9, 7.9; IR (KBr): 3371, 2979, 2926, 1742, 1511, 1458, 1250, 1104, 1036, 830, 739, 672 cm^{-1}; ESI FTMS exact mass calcd for ($C_{32}H_{34}N_2O_5$-H)$^-$ requires m/z 525.2384, found m/z 525.2375; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 87:13, determined by HPLC (Daicel Chiralpak IA, hexane/ isopropanol = 98/2, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.80 min (minor), t_R = 12.94 min (major).

(1*S*,4*R*)-Diethyl4-(4-methoxyphenyl)-5-methyl-1-(naphthalen-1-yl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4eh): Preparative thin layer chromatography: petroleum ether/ethyl acetate = 6/1; Reaction time = 15 h; yield: 50% (28.2 mg); yellow solid; m.p. 70–72 °C; $[\alpha]_D^{20}$ = +190.8 (c 0.66, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.2 Hz, 1H), 7.99 (t, J = 9.0 Hz, 2H), 7.70 (d, J = 7.1 Hz, 1H), 7.66–7.56 (m, 2H), 7.52 (t, J = 7.2 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.04 (t, J = 7.4 Hz, 1H), 6.84–6.73 (m, 4H), 6.30 (d, J = 8.3 Hz, 1H), 5.31 (s, 1H), 4.44–4.26 (m, 2H), 4.13–4.02 (m, 1H), 4.00–3.89 (m, 1H), 3.74 (s, 3H), 3.23 (d, J = 7.2 Hz, 1H), 2.21 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.0, 158.8, 135.0, 134.2, 134.1, 134.0, 131.0, 130.5, 130.4, 130.1, 129.5, 129.0, 127.0, 126.1, 125.5, 125.2, 123.0, 120.5, 119.5, 118.2, 113.7, 112.4, 108.4, 70.0, 65.9, 62.5, 62.2, 55.2, 43.0, 14.2, 13.9, 7.9; IR (KBr): 3439 2971, 1742, 1610, 1511, 1458, 1303, 1251, 1208, 1039, 742, 674 cm^{-1}; ESI FTMS exact mass calcd for ($C_{35}H_{34}N_2O_5$-H)$^-$ requires m/z 561.2384, found m/z 561.2377; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 94:6, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 4.14 min (major), t_R = 6.43 min (minor).

(1*R*,4*S*)-Diethyl 4-(4-methoxyphenyl)-5-methyl-1-(thiophen-3-yl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (*ent*-4ei): Flash column chromatography eluent, petroleum ether/toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 53% (27.6 mg); yellowish solid, m.p 53–55 °C; $[\alpha]_D^{20}$ =-158.8 (c 0.54, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.49–7.45 (m, 1H), 7.44–7.39 (m, 2H), 7.36 (d, J = 4.9 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 6.87–6.77 (m, 2H), 6.53 (d, J = 8.3 Hz, 1H), 6.02 (d, J = 6.2 Hz, 1H), 5.24 (s, 1H), 4.35–4.24 (m, 2H), 4.18–4.08 (m, 1H), 4.07–3.96 (m, 1H), 3.78 (d, J = 1.7 Hz, 3H), 3.15 (d, J = 6.2 Hz, 1H), 2.17 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.3, 158. 9, 141.2, 135.1, 133.7, 130.7, 130.5, 130.0, 127.3, 126.8, 124.8, 120.8, 119.6, 118.2, 113.7, 111.6, 108.0, 70.0, 65.9, 62.4, 62.3, 55.2, 42.5, 14.2, 14.0, 7.9; IR (KBr): 2980, 1740, 1610, 1511, 1460, 1300, 1253, 1177, 1036, 833, 743, 662 cm^{-1}; ESI FTMS exact mass calcd for ($C_{29}H_{30}N_2O_5S$-Na)$^-$ requires m/z 495.1977, found m/z 495.1974; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 89:11, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 9.59 min (major), t_R = 10.27 min (minor).

(1*S*,4*R*)-Diethyl 4-(4-methoxyphenyl)-5-methyl-1-((*E*)-styryl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ej): Flash column chromatography eluent, petroleum

ether/toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 41% (22.1 mg); yellowish solid, m.p 38–40 °C; $[\alpha]_D^{20}$ = -56.5 (c 0.40, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.51 (m, 2H), 7.49 (d, J = 7.1 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.43–7.37 (m, 2H), 7.37–7.32 (m, 1H), 7.30–7.26 (m, 2H), 7.11–6.99 (m, 3H), 6.84–6.75 (m, 2H), 6.70–6.63 (m, 1H), 5.65–5.53 (m, 1H), 5.15 (s, 1H), 4.30–4.18 (m, 2H), 4.16–4.06 (m, 1H), 4.06–3.95 (m, 1H), 3.75 (s, 3H), 3.00 (d, J = 5.5 Hz, 1H), 2.09 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.3, 158.8, 135.6, 135.4, 134.9, 132.7, 130.5, 129.8, 128.8, 128. 7, 128.7, 127.1, 120.7, 119.5, 118.3, 113.6, 111.4, 107.4, 69.6, 68.6, 62.4, 62.3, 55.2, 42.5, 14.1, 13.9, 7.8; IR (KBr): 2980, 2915, 1741, 1611, 1511, 1460, 1250, 1177, 1108, 1035, 823, 744, 695 cm^{-1}; ESI FTMS exact mass calcd for ($C_{33}H_{34}N_2O_5$-Na)$^-$ requires m/z 515.2570, found m/z 515.2567; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 80:20, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.42 min (minor), t_R = 13.10 min (major).

(1*S*,4*R*)-Diethyl 1-cyclohexyl-4-(4-methoxyphenyl)-5-methyl-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4ek): Flash column chromatography eluent, petroleum ether/dichlormethane = 1/1; Reaction time = 15 h; yield: 33% (17.2 mg); yellowish solid, m.p 44–46 °C; $[\alpha]_D^{20}$ = -195.9 (c 0.39, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.43 (m, 2H), 7.30–7.26 (m, 2H), 7.16–7.06 (m, 2H), 6.80–6.74 (m, 2H), 5.09 (s, 1H), 5.01–4.91 (m, 1H), 4.21–4.07 (m, 3H), 4.05–3.93 (m, 1H), 3.76 (s, 3H), 2.95 (d, J = 5.9 Hz, 1H), 2.03 (s, 3H), 1.99–1.92 (m, 1H), 1.90–1.75 (m, 3H), 1.67–1.53 (m, 3H), 1.52–1.39 (m, 2H), 1.35–1.27 (m, 2H), 1.21 (t, J = 6.3 Hz, 3H), 1.17 (t, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.8, 158.7, 134.3, 134.1, 130.8, 130.7, 130.1, 120.5, 119.1, 118.3, 113.4, 111.2, 107.6, 70.9, 69.3, 62.1, 62.1, 55.1, 43.0, 41.1, 29.2, 27.0, 26.5, 26.4, 25.0, 14.1, 13.9, 7.8; IR (KBr): 3381, 2932, 2853, 1742, 1611, 1512, 1459, 1258, 1096, 1035, 826, 738 cm^{-1}; ESI FTMS exact mass calcd for ($C_{31}H_{38}N_2O_5$-H)$^-$ requires m/z 517.2703, found m/z 517.2700; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 89:11, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 3.86 min (minor), t_R = 4.49 min (major).

(1*S*,4*R*)-Diethyl1-benzyl-5-methyl-4-(o-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (4bl): Preparative thin layer chromatography: petroleum ether/toluene/ethyl acetate = 10:10:1; Reaction time = 15 h; yield: 47% (24.1 mg); yellow solid; m.p. 41–42 °C; $[\alpha]_D^{20}$ = +20.0 (c 0.42, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.49 (m, 2H), 7.30–7.25 (m, 3H), 7.23–7.19 (m, 1H), 7.17–7.09 (m, 5H), 7.09–7.02 (m, 2H), 5.44–5.34 (m, 1H), 4.61 (d, J = 6.0 Hz, 1H), 4.33 (d, J = 5.9 Hz, 1H), 4.16–4.02 (m, 4H), 3.65 (t, J = 5.6 Hz, 1H), 3.22 (t, J = 6.9 Hz, 1H), 2.02 (s, 3H), 1.95 (s, 3H), 1.18 (t, J = 4.9 Hz, 3H), 1.15 (t, J = 4.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.3, 141.2, 141.1, 139.7, 136.0, 133.9, 132.7, 130.4, 128.9, 127.6, 127.4, 127.3, 126.8, 126.5, 120.9, 119.4, 118.6, 110.3, 103.1, 65.4, 62.2, 62.0, 60.5, 47.1, 19.8, 14.0, 13.9, 8.3; IR (KBr): 3436, 2924, 2857, 1741, 1458, 1227, 1157, 1103, 1027, 806, 745, 676 cm^{-1}; ESI FTMS exact mass calcd for ($C_{32}H_{34}N_2O_4$-H)$^-$ requires m/z 509.2435, found m/z 509.2437; Diastereomeric ratio: >95:5, determined by ^{1}H NMR; Enantiomeric ratio: 82:18, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 5.69 min (major), t_R = 6.53 min (minor).

Procedure for the Synthesis of Product 8

Under argon atmosphere, compound **4ba** (0.05 mmol) and lithium chloride (6 equiv.) were added to a dried tube. After adding DMSO (2 mL) and water (0.5 mL) to the reaction system, the reaction mixture was stirred at 130 °C for 15 h. After the completion of the reaction which was indicated by TLC, the reaction mixture was subjected to preparative thin layer chromatography on silicon gel to give pure product **8**.

Ethyl 5-methyl-1-(4-nitrophenyl)-4-(o-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3-carboxylate (8): Flash column chromatography eluent, petroleum ether/ethyl acetate = 6/1; Reaction time = 15 h; yield: 54% (12.5 mg); red solid, m.p 27–29 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.2 Hz, 2H), 7.96 (s, 2H), 7.73 (d, J = 8.1 Hz, 1H), 7.43–7.37 (m, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.4 Hz, 1H), 7.27 (s, 1H), 7.25–7.21 (m, 1H), 7.14–7.08 (m, 1H), 6.64 (d, J = 8.7 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 2.22 (s, 3H), 1.76 (s, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 149.1, 147.6, 141.3, 137.1, 135.0, 132.1, 130.9, 130.0, 129.9, 129.6, 129.0, 128.7, 128.6, 125.7, 124.5, 124.1, 122.8, 119.4, 114.7, 109.2, 61.2, 19.8, 13.6, 8.5; IR (KBr): 2965, 2918, 1721, 1523, 1446, 1380, 1346, 1263, 1151, 1018, 853, 802, 733 cm^{-1}; ESI FTMS exact mass calcd for ($C_{28}H_{25}N_3O_4$-H)$^-$ requires m/z 466.1767, found m/z 466.1762; Enantiomeric ratio: 50:50, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 29.46 min, t_R = 34.39 min.

Procedure for the Synthesis of Product 9

Under argon atmosphere, compound **4dc** (0.06 mmol), 4-chlorophenylboronic acid (1.5 equiv.), $CsCO_3$ (2 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and butyl di-1-adamantylphosphine (0.06 equiv.) were added to a dried tube. After adding DME (4 mL) and water (1 mL) to the reaction system, the reaction mixture was stirred at 80 °C for 13 h. After the completion of the reaction which was indicated by TLC, the reaction mixture was subjected to preparative thin layer chromatography on silicon gel to give pure product **9**.

(1*S*,4*R*)-Diethyl 1-(4′-chloro-[1,1′-biphenyl]-4-yl)-5-methyl-4-(p-tolyl)-1,2-dihydropyrimido[1,6-a]indole-3,3(4H)-dicarboxylate (9): Flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; Reaction time = 13 h; yield: 98% (35.5 mg); yellowish solid, m.p 37–39 °C; $[\alpha]_D^{20}$ = +75.2 (c 0.67, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 4H), 7.62–7.57 (m, 2H), 7.52–7.43 (m, 3H), 7.38 (d, J = 8.1 Hz, 2H), 7.11–7.00 (m, 3H), 6.91–6.81 (m, 1H), 6.45 (d, J = 8.3 Hz, 1H), 5.87 (d, J = 6.4 Hz, 1H), 5.24 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.15–4.03 (m, 1H), 4.02–3.89 (m, 1H), 3.09 (d, J = 6.4 Hz, 1H), 2.29 (s, 3H), 2.16 (s, 3H), 1.29 (d, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.2, 141.0, 138.9, 138.7, 137.0, 135.5, 135.0, 133.8, 133.7, 130.1, 129.2, 129.1, 129.0, 128.5, 128.4, 127.7, 120.6,

119.6, 118.3, 111.9, 108.3, 70.0, 70.0, 62.4, 62.3, 42.9, 21.1, 14.2, 13.8, 7.9; IR (KBr): 2980, 2919, 2858, 1741, 1459, 1299, 1257, 1207, 1094, 1017, 817, 741 cm^{-1}; ESI FTMS exact mass calcd for $(C_{37}H_{35}ClN_2O_4\text{-}H)^-$ requires m/z 605.2207, found m/z 605.2204; Enantiomeric ratio: 92:8, determined by HPLC (Daicel Chiralpak AD-H, hexane/ isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.67 min (minor), t_R = 10.83 min (major).

Acknowledgements

We are grateful for financial supports from NSFC (21372002 and 21232007), PAPD, Natural Science Foundation of Jiangsu Province (BK20160003).

References

[1] For some recent reviews: a) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784; b) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296; c) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366.

[2] For early reports on metal-catalyzed asymmetric [3+2] cycloadditions of azomethine ylide: a) J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400; b) A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4236.

[3] For early reports on organocatalytic asymmetric [3+2] cycloadditions of azomethine ylide: a) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem. Int. Ed.* **2007**, *46*, 5168; b) I. Ibrahem, R. Rios, J. Vesely, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 6252; c) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691; d) Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873; e) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652.

[4] For metal-catalyzed asymmetric [3+3] cycloadditions of azomethine ylide: a) M.-C. Tong, X. Chen, H.-Y. Tao, C.-J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 12377; b) H. Guo, H. Liu, F.-L. Zhu, R. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Y. Xiao, X.-P. Hu, M. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 12641; c) C. Yuan, H. Liu, Z. Gao, L. Zhou, Y. Feng, Y. Xiao, H. Guo, *Org. Lett.* **2015**, *17*, 26; d) W.-L. Yang, C.-Y. Li, W.-J. Qin, F.-F. Tang, X. Yu, W.-P. Deng, *ACS Catal.* **2016**, *6*, 5685.

[5] For organocatalytic asymmetric [3+3] cycloadditions of azomethine ylide: a) J. Huang, S. Luo, L. Gong, *Acta Chim. Sin.* **2013**, *71*, 879; b) F. Shi, R.-Y. Zhu, W. Dai, C.-S. Wang, S.-J. Tu, *Chem. Eur. J.* **2014**, *20*, 2597; c) W. Dai, H. Lu, X. Li, F. Shi, S.-J. Tu, *Chem. Eur. J.* **2014**, *20*, 11382; d) X.-X. Sun, H.-H. Zhang, G.-H. Li, Y.-Y. He, F. Shi, *Chem. Eur. J.* **2016**, *22*, 17526.

[6] For catalytic asymmetric [6+3] cycloadditions of azomethine ylide: a) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2012**, *51*, 9512; b) Z.-L. He, H.-L. Teng, C.-J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2934; c) H.-L. Teng, L. Yao, C.-J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 4075; d) Q.-H. Li, L. Wei, C.-J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 8685; e) Z.-L. He, F. K. Sheong, Q.-H. Li, Z. Lin, C.-J. Wang, *Org. Lett.* **2015**, *17*, 1365.

[7] a) K. Bera, C. Schneider, *Chem. Eur. J.* **2016**, *22*, 7074; b) K. Bera, C. Schneider, *Org. Lett.* **2016**, *18*, 5660.

[8] For some reviews: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; b) M. Terada, *Chem. Commun.* **2008**, *35*, 4097; c) M. Terada, *Synthesis* **2010**, 1929; d) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156; e) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047; f) H. Wu, Y.-P. He, F. Shi, *Synthesis*, **2015**, *47*, 1990; For some recent prominent examples: g) W. Zhao, Z. Wang, B. Chu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 1910; h) Z. B. Wang, F. J. Ai, Z. Wang, W. X. Zhao, G. Y. Zhu, Z. Y. Lin, J. W. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 383; For some representative examples in our group: i) F. Shi, G.-J. Xing, R.-Y. Zhu, W. Tan, S. Tu, *Org. Lett.* **2013**, *15*, 128; j) Y.-C. Zhang, J.-J. Zhao, F. Jiang, S.-B. Sun, F. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 13912.

[9] R.-Y. Zhu, C.-S. Wang, F. Jiang, F. Shi, S.-J. Tu, *Tetrahedron*: *Asymmetry* **2014**, *25*, 617.

[10] a) W.-J. Liu, X.-H. Chen, L.-Z. Gong, *Org. Lett.* **2008**, *10*, 5357; b) F. Shi, G.-J. Xing, W. Tan, R.-Y. Zhu, S. Tu, *Org. Biomol. Chem.* **2013**, *11*, 1482.

[11] CCDC 1524703 (**4fa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.

Catalytic Asymmetric [3+3] Cycloaddition of Azomethine Ylides with C3-Substituted 2-Indolylmethanols

Adv. Synth. Catal. **2017**, *359*, 1–12

X.-X. Sun, C. Li, Y.-Y. He, Z.-Q. Zhu, G.-J. Mei, F. Shi*