JOC The Journal of Organic Chemistry

Note

Synergistic Catalysis for Asymmetric [3+2] Cycloadditions of 2-Indolylmethanols with #,#-Unsaturated Aldehydes

Jia Mao, Hao Zhang, Xiang-Feng Ding, Xiaoyan Luo, and Wei-Ping Deng

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b01234 • Publication Date (Web): 31 Jul 2019

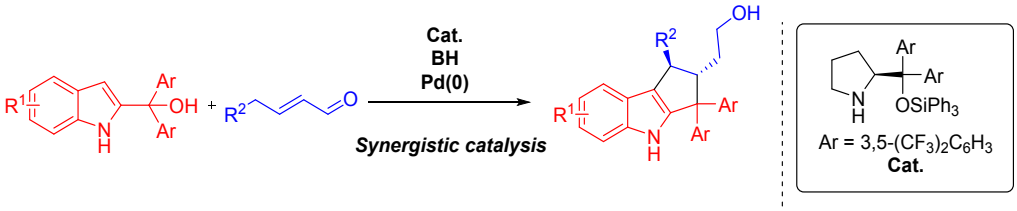
Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synergistic Catalysis for Asymmetric [3+2] Cycloadditions of 2-Indolylmethanols with *α,β*-Unsaturated Aldehydes

Jia Mao, Hao Zhang, Xiang-Feng Ding, Xiaoyan Luo* and Wei-Ping Deng*

School of Pharmacy and Shanghai Key Laboratory of New Drug Design, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, People's Republic of China



Abstract: A catalytic asymmetric [3+2] cycloaddition of 2-indolylmethanols with *α,β*-unsaturated aldehydes was developed for the first time. This transformation was achieved by a synergistic catalytic system consisting of a palladium complex, a Brønsted acid, and a chiral secondary amine to synthesize biologically active cyclopenta[*b*]indole derivatives with excellent diastereo- and enantioselectivities (up to >20:1 dr, up to 99% ee).

Chiral cyclopenta[*b*]indole has been recognized as an important heterocyclic skeleton which can be widely found in various natural products and pharmaceutically active molecules (Figure 1).[1] Therefore, the method of asymmetrically synthesizing this skeleton has attracted considerable attention of the synthetic scientific community. [2]

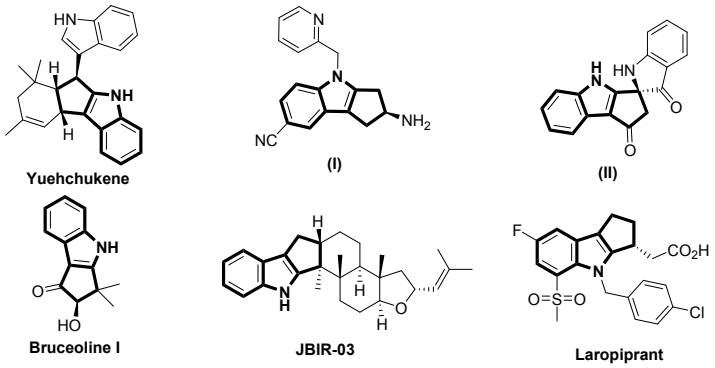
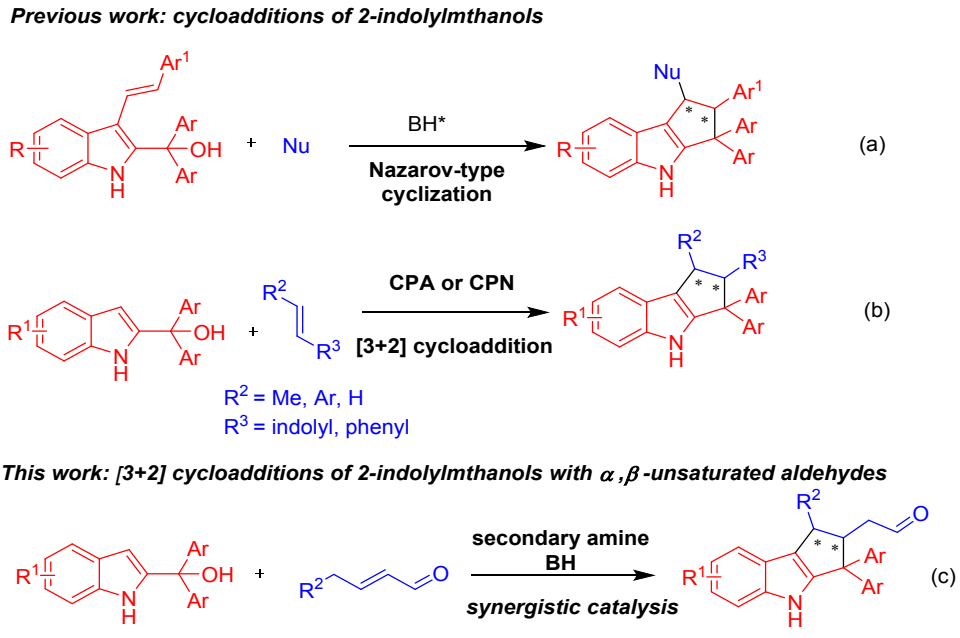


Figure 1. Representative biologically active molecules containing cyclopenta[*b*]indole scaffold.

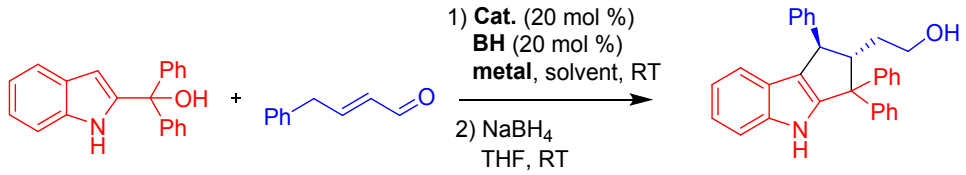
Among numerous approaches, catalytic asymmetric reactions involving indolylmethanols have been employed as an important strategy for the construction of cyclopenta[*b*]indole scaffolds.[3] In particular, 2-indolylmethanols have exhibited their great potential in catalytic enantioselective cycloadditions. For instance, the asymmetric interrupted Nazarov-type cyclization of C3-alkenyl-substituted 2-indolylmethanols has been achieved by the Shi group, affording chiral cyclopenta[*b*]indole derivatives (Scheme 1a).[4] In addition, the Shi group reported an asymmetric [3+2] cycloaddition of 2-indolymethanols with alkenes in the presence of a chiral phosphoric acid (CPA) or a chiral phosphoramide (CPN) to synthesize cyclopenta[*b*]indole derivatives (Scheme 1b).[5] On the other hand, the Shi group has described a cooperative catalysis-enabled asymmetric *α*-arylation of aldehydes employing 2-indolylmethanols as arylation reagents.[6] Based on the superiority of cooperative catalysis[7] and our continuing efforts in using chiral diarylprolinol silyl ethers as an effective promoter for activation of 2-enals,[8] we design the asymmetric [3+2] cycloaddition of 2-indolylmethanols and *α,β*-unsaturated aldehydes, which was catalyzed by a synergistic catalytic system consisting of Brønsted acids (BH) and secondary amines, providing rapid access to various cyclopenta[*b*]indole derivatives (Scheme 1c).



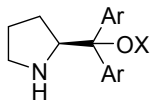
Scheme 1. Catalytic asymmetric cycloadditions of 2-indolylmethanols.

To testify our hypothesis, we started our investigations with the model reaction shown in Table 1. 2-Indolylmethanol **1a** was treated with Brønsted acid in chloroform at room temperature, and then *α,β*-unsaturated aldehyde **2a** and 20 mol% chiral secondary amine (**Cat-1**) was slowly added. To our delight, the reaction proceeded smoothly to generate the corresponding cyclopenta[*b*]indole derivative **3aa** in good yield (85%) and with high enantioselectivity (75%). Encouraged by this promising result, several chiral amine catalysts (**Cat-2-6**) were screened (entries 2-6), **Cat-6** was found to deliver the reaction in the highest enantioselectivity (90% ee) and diastereoselectivity (>20:1 dr). Then, screening of solvents (entries 7-12) revealed that $(i\text{-Pr})_2O$ was the optimal reaction medium on the part of enantioselectivities, affording corresponding product **3aa** in 94% ee. Subsequently, a series of Brønsted acids (BH) were screened, which demonstrated that $TsOH\cdot H_2O$ was the best additive in terms of both yields and enantioselectivities (entries 13-15).

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3aa**



Cat-1: X = TMS, Ar = Ph
Cat-2: X = TBS, Ar = Ph
Cat-3: X = TMS, Ar = 3,5-$(CF_3)_2C_6H_3$
Cat-4: X = TMS, Ar = 3,5-$(t\text{-Bu})_2C_6H_3$
Cat-5: X = TBS, Ar = 3,5-$(CF_3)_2C_6H_3$
Cat-6: X = $SiPh_3$, Ar = 3,5-$(CF_3)_2C_6H_3$

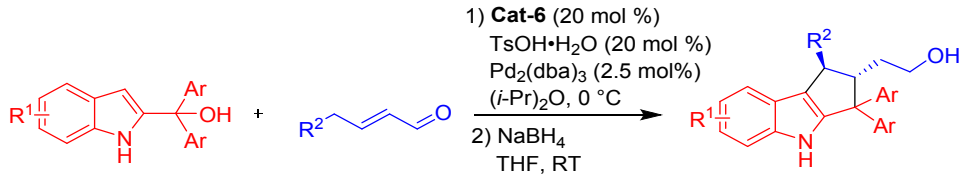
entry	**cat.**	solvent	BH	metal [mol%]	yield [%][b]	ee [%][c]	dr[d]
1	**Cat-1**	$CHCl_3$	$TsOH\cdot H_2O$	none	85	75	10:1
2	**Cat-2**	$CHCl_3$	$TsOH\cdot H_2O$	none	30	68	>20:1
3	**Cat-3**	$CHCl_3$	$TsOH\cdot H_2O$	none	90	81	>20:1
4	**Cat-4**	$CHCl_3$	$TsOH\cdot H_2O$	none	50	50	>20:1
5	**Cat-5**	$CHCl_3$	$TsOH\cdot H_2O$	none	81	52	>20:1
6	**Cat-6**	$CHCl_3$	$TsOH\cdot H_2O$	none	55	90	>20:1

7	**Cat-6**	THF	$TsOH·H_2O$	none	71	90	>20:1
8	**Cat-6**	acetone	$TsOH·H_2O$	none	37	90	>20:1
9	**Cat-6**	CH_2Cl_2	$TsOH·H_2O$	none	61	75	>20:1
10	**Cat-6**	toluene	$TsOH·H_2O$	none	40	89	>20:1
11	**Cat-6**	MeCN	$TsOH·H_2O$	none	70	70	>20:1
12	**Cat-6**	$(i\text{-Pr})_2O$	$TsOH·H_2O$	none	70	94	>20:1
13	**Cat-6**	$(i\text{-Pr})_2O$	CF_3COOH	none	51	84	>20:1
14	**Cat-6**	$(i\text{-Pr})_2O$	$p\text{-NO}_2$BA[g]	none	N.P.[h]		>20:1
15	**Cat-6**	$(i\text{-Pr})_2O$	CH_3COOH	none	N.P.		>20:1
16	**Cat-6**	$(i\text{-Pr})_2O$	$TsOH·H_2O$	$Pd_2(dba)_3$ (2.5)	90	93	>20:1
17	**Cat-6**	$(i\text{-Pr})_2O$	$TsOH·H_2O$	PPh_3AuCl (5)	37	92	>20:1
18	**Cat-6**	$(i\text{-Pr})_2O$	$TsOH·H_2O$	PPh_3RhCl (5)	65	93	>20:1
19[e]	**Cat-6**	$(i\text{-Pr})_2O$	$TsOH·H_2O$	$Pd_2(dba)_3$ (2.5)	80	96	>20:1
20[f]	**Cat-6**	$(i\text{-Pr})_2O$	$TsOH·H_2O$	$Pd_2(dba)_3$ (2.5)	47	97	>20:1

[a] General conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), BH (20 mol%), metal (5 mol%) and **Cat.** (20 mol%) in solvent (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by crude ^{1}H NMR spectroscopy. [e] Reaction was conducted at 0 °C. [f] Reaction was conducted at -20 °C. [g] BA is benzoic acid. [h] N.P. is no product.

It was reported that the addition of some transition metals could stabilize the delocalized cation generated from 2-indolylmethanols,[9] which was beneficial for the yield of the reaction. Therefore, various transition metals were screened in this reaction to further improve the yield of the reaction (entries 16-18) and a palladium complex was found to greatly improve the yield to 90% with a retained enantioselectivity. The effect of temperature on the reaction activity was also investigated. Lowering the temperature could improve the enantioselectivity, but the yield dropped significantly (entries 19-20). Thus, the optimal reaction conditions were finally set as what entry 19 illustrated.

Table 2. Screening of substrate scope.[a]

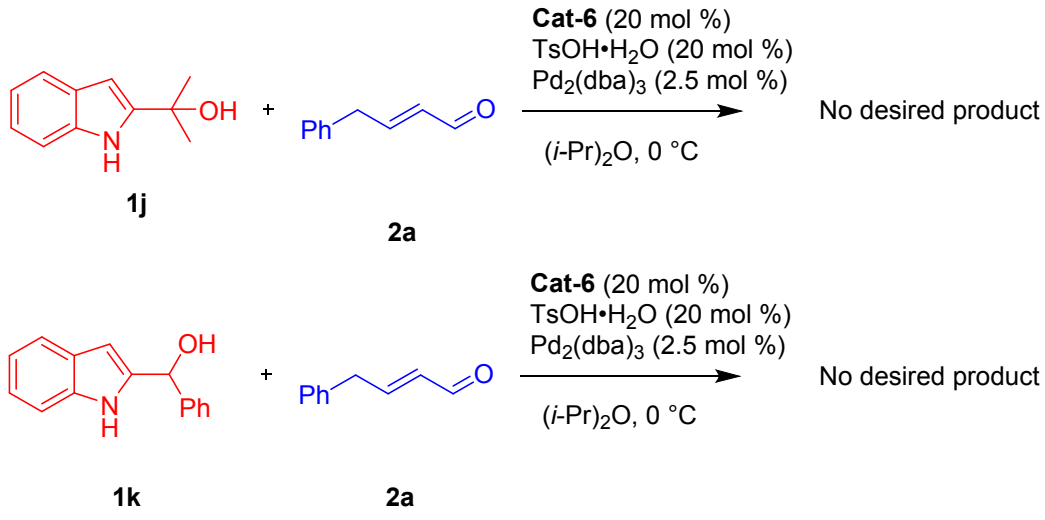


1 **2** **3**

entry	**3**	R^1/Ar	R^2	yield [%][b]	ee [%][c]	dr[d]
1	**3aa**	H/Ph (**1a**)	Ph (**2a**)	80	96	>20:1
2	**3ba**	5-Br/Ph (**1b**)	Ph (**2a**)	60	91	>20:1
3	**3ca**	5-Cl/Ph (**1c**)	Ph (**2a**)	50	90	>20:1
4	**3da**	5-Me/Ph (**1d**)	Ph (**2a**)	83	97	>20:1
5	**3ea**	5-OMe/Ph (**1e**)	Ph (**2a**)	56	83	>20:1
6	**3fa**	6-Br/Ph (**1f**)	Ph (**2a**)	71	95	>20:1
7	**3ga**	6-OMe/Ph (**1g**)	Ph (**2a**)	86	85	>20:1
8	**3ha**	H/*m*-$MeOC_6H_4$ (**1h**)	Ph (**2a**)	55	96	>20:1
9	**3ia**	H/*p*-$MeOC_6H_4$ (**1i**)	Ph (**2a**)	65	97	>20:1
10	**3ab**	H/Ph (**1a**)	4-$MeOC_6H_4$ (**2b**)	89	96	>20:1
11	**3ac**	H/Ph (**1a**)	3-$MeOC_6H_4$ (**2c**)	88	96	>20:1
12	**3ad**	H/Ph (**1a**)	2-$MeOC_6H_4$ (**2d**)	99	94	>20:1
13	**3ae**	H/Ph (**1a**)	4-MeC_6H_4 (**2e**)	80	95	>20:1
14	**3af**	H/Ph (**1a**)	3-MeC_6H_4 (**2f**)	60	96	>20:1
15	**3ag**	H/Ph (**1a**)	4-ClC_6H_4 (**2g**)	81	91	>20:1
16	**3ah**	H/Ph (**1a**)	3-ClC_6H_4 (**2h**)	45	89	>20:1
17	**3ai**	H/Ph (**1a**)	5-piperonyl (**2i**)	84	95	>20:1
18	**3aj**	H/Ph (**1a**)	1-naphthyl (**2j**)	50	89	>20:1
19	**3ak**	H/Ph (**1a**)	2-thienyl (**2k**)	70	90	>20:1
20	**3al**	H/Ph (**1a**)	Et (**2l**)	32/30	99/94	1.1:1

[a] General conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), TsOH·H_2O (20 mol%), $Pd_2(dba)_3$ (2.5 mol%) and **Cat-6** (20 mol%) in $(i\text{-}Pr)_2O$ (1.0 mL) at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by crude ^1H NMR spectroscopy.

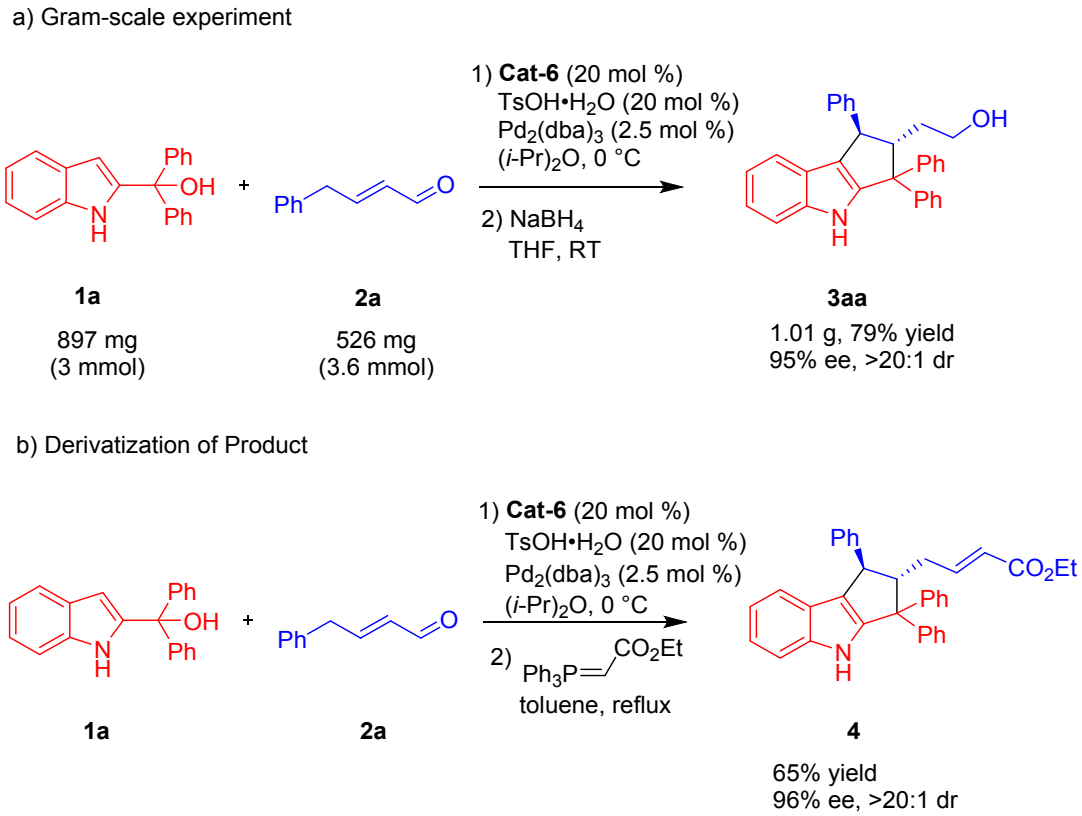
With the optimized reaction conditions in hand, the generality and substrate scope of this process was investigated (Table 2). Firstly, various 2-indolylmethanols **1a-1i** were employed with *α,β*-unsaturated aldehyde **2a** (entries 1-7), providing products **3** in moderate to high yields (50-86%), with excellent diastereoselectivities (>20:1 dr) and high to excellent enantioselectivities (83-97% ee). In addition, the two Ar groups in **1** could be changed from phenyl groups to methoxy substituted phenyl groups, which generated the corresponding products **3ha** and **3ia** in moderate yields, with excellent enantioselectivities (entries 8-9). In addition, a wide range of *α,β*-unsaturated aldehydes (**2b-2j**) containing electron-rich (entries 10-14), electron-deficient (entries 15-16), and electron-neutral (entries 17-18) substituents on any position of the phenyl ring were employed, and the transformation worked efficiently, affording the corresponding cycloadducts in moderate to excellent yields (45−99%), with high to excellent enantioselectivities (89-96% ee). Furthermore, the outstanding outcome was still obtained for heteroaromatic 2- thienyl derived *α,β*-unsaturated aldehyde **2k** (entry 19). Noteworthily, aliphatic substituted *α,β*-unsaturated aldehyde was also suitable to this system, affording the corresponding product **3al** in excellent enantioselectivity, however with poor diastereoselectivity (entry 20).



Scheme 2. Further Substrate Expansion.

In order to further explore the scope of the reaction, dimethyl (**1j**) and monophenyl (**1k**) instead of diphenyl on the indole alcohol were employed as substrate to react with *α,β*-unsaturated aldehyde **2a** under the optimal condition. Unfortunately, no desired

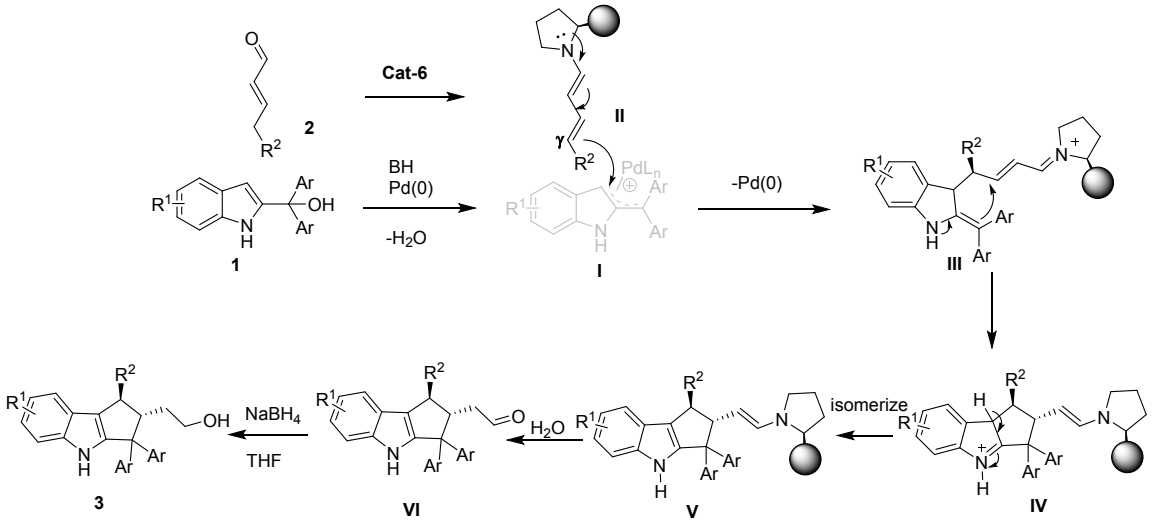
product were observed and only dimerization of 2-indolylmethanol occurred (Scheme 2**)**. We also did a further screen of various Brønsted acids (TsOH•H_2O, phosphoric acid, PhCOOH), reaction temperature (30 °C, 0 °C), and aldehyde (methoxy substituted phenyl group), however still no target product was observed. According to the previously reports,[10] the in-situ derived carbocation species from **1j** or **1k** is supposed to be more easily attacked by nucleophiles at this benzylic position, which may account for the above dimerization.



Scheme 3. Demonstration of synthetic utility.

As a further demonstration of the utility of this process, the asymmetric cycloaddition between 2-indolylmethanol **1a** and *α,β*-unsaturated aldehyde **2a** was carried out on a gram scale with a lower aldehyde equivalent (1.2 equiv), and **3aa** was obtained in 79% yield with 95% ee and >20:1 dr (Scheme 3a). On the other hand, the cycloadduct of 2-indolylmethanol **1a** and *α,β*-unsaturated aldehyde **2a** could undergo a Wittig reaction to generate product **4** in 65% yield with 96% ee (Scheme 3b). And the absolute stereochemistry of compound **4** was determined by single-crystal X-ray

diffraction analysis as (*1R,2S*) (see the Supporting Information). The absolute configurations of other products were assigned by analogy to **4**.



Scheme 4 Proposed mechanism.

Based on the observed absolute configuration and previously reports,[6] a hypothetical activation model is depicted in Scheme 4. Firstly, the dehydration of 2-indolylmethanols **1** were promoted by the Pd(0)/BH to form the delocalized carbocation **I**.[11] Meanwhile, enamine intermediate **II** were formed through the reaction between **2** and **Cat-6**. Then, the *γ*- position of the enamine intermediate **II** attacked the carbon cation of the intermediate **I** to give rise to a transient intermediate **III**, which underwent intramolecular cyclization to form intermediate **IV**. Subsequently, the intermediate **IV** rapidly isomerized into intermediate **V**, and hydrolysis of intermediate **V** generated **VI** by releasing **Cat-6**. Finally, the product **3** were obtained after $NaBH_4$ reduction (Scheme 4).

In conclusion, we have developed an efficient catalytic asymmetric [3+2] cycloaddition of 2-indolylmethanols with *α,β*-unsaturated aldehydes via synergistic catalysis in the presence of palladium complex, Brønsted acid, and chiral secondary amine, affording potential biologically active and synthetically challenging polysubstituted fused cyclopenta[*b*]indole derivatives containing two stereocenters in high yields (up to 99%) with excellent stereoselectivities (up to >20:1 dr, up to 99% ee). The present strategy is obviously complementary to previous methods for the

synthesis of biologically important enantioenriched cyclopenta[*b*]indole with high efficiency.

EXPERIMENTAL SECTION

General Information

^{1}H NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The spectra are interpreted as: s = singlet, d = doublet, t= triplet, m = multiplet, dd = doublet of doublets, brs = broad singlet, coupling constant(s) *J* are reported in Hz and relative integrations are reported. ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm with the internal chloroform signal at 77.06 ppm as a standard. Optical rotations were measured on an AUTOPOL V instrument. Diastereomeric ratios were determined from crude ^{1}H NMR spectroscopy interpretation or by analysis of HPLC traces. Enantiomer ratios were determined by analysis of HPLC traces, obtained by using Chiralpak AD-H column with *n*-hexane and *i*-propanol as solvents. (Chiralpak AD-H column was purchased from Daicel Chemical Industries, LTD.) Melting points were obtained in open capillary tubes using SGW X-4 micro melting point apparatus which were uncorrected. Mass spectra were recorded on TOF mass spectrometer. Solvents were dried and distilled following usual protocols. 2-Indolylmethanols **1** were prepared according to the literature procedures,[10a, 12], *α,β*-unsaturated aldehydes **2** were prepared by reference to the literature procedures.[13]

General procedure for the synthesis of 2-indolylmethanols 1.

Substrates **1** were synthesized by modification of the literature method.[10a] In a flame-dried Schlenk bottle under argon, phenylmagnesium bromide (40 mL, 1.0 mmol/mL) was added to the Schlenk bottle. Then, in a ice-water bath, the solution of ethyl 1H-indole-2-carboxylate (1.89 g, 10 mmol) in anhydrous THF (10 mL) was added to the Schlenk bottle. Subsequently, the reaction mixture was moved to a oil bath, which was refluxed at 80 °C overnight. After the completion of the reaction indicated by TLC, the reaction mixture was quenched by saturated ammonium chloride solution and was

extracted by ethyl acetate for three times. The combined organic layer was dried by anhydrous sodium sulfate, which was concentrated under the reduced pressure. The resulted residue was purified through flash chromatography on silica gel (petroleum ether/ethyl acetate = 20/1) to afford the pure 2-indolylmethanol **1a** in 80% yield.

(1*H*-indol-2-yl)diphenylmethanol (1a): 2.4g; 80% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.26 (m, 11H), 7.20 – 7.13 (m, 1H), 7.11 – 7.05 (m, 1H), 6.18 – 6.00 (m, 1H), 2.94 (s, 1H). (The ^{1}H NMR data was consistent with the literature[10a] data)

(5-bromo-1*H*-indol-2-yl)diphenylmethanol (1b): 2.3g; 62% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.36 – 7.30 (m, 10H), 7.26 – 7.22 (m, 1H), 7.19 – 7.12 (m, 1H), 6.14 – 6.03 (m, 1H), 2.95 (s, 1H).

(5-chloro-1*H*-indol-2-yl)diphenylmethanol (1c): 2.0g; 60% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (s, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.42 – 7.24 (m, 10H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.11 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.11 – 6.04 (m, 1H), 2.96 (s, 1H).

(5-methyl-1*H*-indol-2-yl)diphenylmethanol (1d): 2.4g; 78% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 7.39 – 7.25 (m, 11H), 7.17 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.07 – 6.02 (m, 1H), 3.01 – 2.91 (m, 1H), 2.41 (s, 3H).

(5-methoxy-1*H*-indol-2-yl)diphenylmethanol (1e): 2.5g; 75% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.41 – 7.26 (m, 10H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.10 – 6.04 (m, 1H), 3.81 (s, 3H), 2.95 (s, 1H).

(6-bromo-1*H*-indol-2-yl)diphenylmethanol (1f): 2.3g; 61% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.36 (s, 1H), 7.48 – 7.43 (m, 1H), 7.41 – 7.29 (m, 11H), 7.18 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.24 – 5.99 (m, 1H), 2.94 (s, 1H).

(6-methoxy-1*H*-indol-2-yl)diphenylmethanol (1g): 1.8g; 55% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.45 – 7.24 (m, 11H), 6.80 – 6.67 (m, 2H), 6.13 – 5.92 (m, 1H), 3.79 (s, 3H), 3.03 (s, 1H).

(1*H*-indol-2-yl)bis(3-methoxyphenyl)methanol (1h): 2.1g; 58% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 (s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.28

– 7.22 (m, 2H), 7.21 – 7.12 (m, 1H), 7.12 – 7.04 (m, 1H), 7.00 – 6.95 (m, 2H), 6.96 – 6.88 (m, 2H), 6.88 – 6.80 (m, 2H), 6.28 – 6.15 (m, 1H), 3.75 (s, 6H), 2.91 (s, 1H).

(1*H*-indol-2-yl)bis(4-methoxyphenyl)methanol (1i): 2.2g; 60% yield; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.20 (m, 5H), 7.20 – 7.11 (m, 1H), 7.12 – 7.03 (m, 1H), 6.88 – 6.80 (m, 4H), 6.16 – 6.06 (m, 1H), 3.79 (s, 6H), 2.86 (s, 1H).

General procedure for the preparation of cyclopenta[*b*]indole (3aa-3an).

Under a nitrogen atmosphere, 2-indolylmethanol **1** (0.1 mmol), $Pd_2(dba)_3$ (0.0025 mmol) and $TsOH\cdot H_2O$ (0.02 mmol) were dissolved in 1.0 mL dry $(i\text{-Pr})_2O$, and stirred at room temperature for about 10 minutes. Then, chiral amine catalyst **Cat-6** (0.02 mmol) was added, subsequently *α,β*-unsaturated aldehydes **2** (0.15 mmol) were added, and the mixture was stirred at 0 °C until the reaction was completed monitored by TLC. Then the crude product was purified by column chromatography using petroleum ether and EtOAc (10:1) to get crude aldehyde compound. The aldehyde compound was dissolved in THF, and $NaBH_4$ (0.2 mmol) was added. The mixture was then stirred at room temperature. After the reaction was completed (indicated by TLC), the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=4:1) to afford product **3**.

2-((*1R,2S*)-1,3,3-Triphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3aa): white solid, 34.1 mg, 80% yield, m.p: 252–253 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.85 (s, 1H), 7.63 – 7.53 (m, 2H), 7.47 – 7.36 (m, 4H), 7.36 – 7.30 (m, 3H), 7.30 – 7.23 (m, 2H), 7.22 – 7.16 (m, 3H), 7.11 – 7.04 (m, 1H), 6.97 – 6.86 (m, 2H), 6.80 – 6.70 (m, 2H), 4.06 (d, *J* = 8.4 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.45 – 3.30 (m, 2H), 1.87 – 1.74 (m, 1H), 1.42 – 1.30 (m, 1H), 0.89 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 146.5, 144.8, 143.9, 143.3, 140.7, 129.0 (2C), 128.9 (2C), 128.7 (2C), 128.4 (2C), 128.0 (2C), 127.6 (2C), 126.9, 126.8, 126.7, 123.8, 121.8, 121.5, 119.9, 118.9, 111.9, 60.9, 59.9, 58.4, 50.2, 34.5. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{31}H_{27}NO]^+$: 429.2087; found: 429.2090; $[\alpha]_D^{20}$= +31.6 (CH_2Cl_2, c=1.00); HPLC

(Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=7.83 min, 20.95 min.

2-((*1R,2S*)-7-Bromo-1,3,3-triphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3ba): white solid, 30.3 mg, 60% yield, m.p: 229–230 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.88 (s, 1H), 7.62 – 7.52 (m, 2H), 7.49 – 7.41 (m, 2H), 7.40 – 7.34 (m, 4H), 7.34 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 7.21 – 7.09 (m, 2H), 7.04 – 6.98 (m, 1H), 6.78 – 6.65 (m, 2H), 4.01 (d, *J* = 8.4 Hz, 1H), 3.96 – 3.84 (m, 1H), 3.49 – 3.25 (m, 2H), 1.86 – 1.72 (m, 1H), 1.41 – 1.30 (m, 1H), 0.86 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 147.9, 144.5, 143.4, 143.0, 139.3, 129.1 (2C), 128.9 (2C), 128.8 (2C), 128.2 (2C), 128.1 (2C), 127.6 (2C), 127.1, 127.1, 126.9, 125.4, 124.4, 121.4 (2C), 113.3, 113.2, 60.9, 59.9, 58.3, 50.0, 34.4. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{31}H_{26}{}^{79}BrNO]^+$: 507.1192; found: 507.1197; calcd for $[C_{31}H_{26}{}^{81}BrNO]^+$: 509.1172; found: 509.1187 $[\alpha]_D{}^{20}$= +53.2 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=9.49 min, 16.34 min.

2-((*1R,2S*)-7-Chloro-1,3,3-triphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3ca): white solid, 23 mg, 50% yield, m.p: 235–236 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87 (s, 1H), 7.61 – 7.52 (m, 2H), 7.49 – 7.41 (m, 2H), 7.39 – 7.34 (m, 4H), 7.34 – 7.26 (m, 2H), 7.25 – 7.16 (m, 4H), 7.07 – 7.01 (m, 1H), 6.90 – 6.83 (m, 1H), 6.76 – 6.66 (m, 2H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.97 – 3.87 (m, 1H), 3.45 – 3.27 (m, 2H), 1.86 – 1.73 (m, 1H), 1.41 – 1.29 (m, 1H), 0.88 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 148.1, 144.5, 143.4, 143.0, 139.0, 129.1 (2C), 128.9 (2C), 128.8 (2C), 128.3 (2C), 128.1 (2C), 127.6 (2C), 127.1, 127.1, 126.9, 125.5, 124.8, 121.8, 121.5, 118.4, 112.8, 60.9, 59.9, 58.3, 50.0, 34.4. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{31}H_{26}ClNO]^+$: 463.1697; found: 463.1702; $[\alpha]_D{}^{20}$= +48.1 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=9.62min, 17.78 min.

2-((*1R,2S*)-7-Methyl-1,3,3-triphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3da): white solid, 36.8 mg, 83% yield, m.p: 230–232 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.73 (s, 1H), 7.60 – 7.51 (m, 2H), 7.47 – 7.36 (m, 4H), 7.36 – 7.22 (m, 4H), 7.22 – 7.14 (m, 4H), 6.93 – 6.87 (m, 1H), 6.78 – 6.66 (m, 3H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.94 – 3.83 (m, 1H), 3.45 – 3.27 (m, 2H), 2.27 (s, 3H), 1.85 – 1.74 (m, 1H), 1.39 – 1.30 (m, 1H), 0.86 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 146.7, 144.9, 144.1, 143.4, 139.0, 129.2, 129.0 (2C), 128.9 (2C), 128.7 (2C), 128.4 (2C), 128.0 (2C), 127.7 (2C), 126.9, 126.8, 126.7, 124.0, 123.0, 121.3, 118.6, 111.6, 61.0, 59.9, 58.4, 50.2, 34.5, 21.4. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{29}NO]^+$: 443.2244; found: 443.2252; $[\alpha]_D^{20}$= +37.0 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=7.54 min, 13.95 min.

2-((*1R,2S*)-7-Methoxy-1,3,3-triphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3ea): white solid, 25.7 mg, 56% yield, m.p: 110–111 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.71 (s, 1H), 7.60 – 7.50 (m, 2H), 7.47 – 7.34 (m, 4H), 7.37 – 7.22 (m, 4H), 7.25 – 7.11 (m, 4H), 6.80 – 6.69 (m, 3H), 6.40 – 6.30 (m, 1H), 4.03 (d, *J* = 8.4 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.63 (s, 3H), 3.45 – 3.31 (m, 2H), 1.87 – 1.74 (m, 1H), 1.42 – 1.30 (m, 1H), 0.88 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 154.1, 147.5, 144.8, 143.8, 143.4, 135.8, 128.9 (4C), 128.7 (2C), 128.3 (2C), 128.0 (2C), 127.6 (2C), 126.9, 126.9, 126.7, 124.3, 121.6, 112.4, 110.8, 101.6, 61.0, 59.9, 58.3, 55.8, 50.1, 34.5. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{29}NO_2]^+$: 459.2193; found: 459.2200; $[\alpha]_D^{20}$= +53.4 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=9.21 min, 14.30 min.

2-((*1R,2S*)-6-Bromo-1,3,3-triphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3fa): white solid, 35.9 mg, 71% yield, m.p: 118–119 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.85 (s, 1H), 7.61 – 7.50 (m, 2H), 7.49 – 7.40 (m, 3H), 7.38 – 7.34 (m, 3H), 7.34 – 7.25 (m, 3H), 7.25 – 7.17 (m, 3H), 7.06 – 7.00 (m, 1H), 6.80 – 6.67 (m, 3H), 4.03 (d, *J* = 8.4 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.45 – 3.29 (m, 2H), 1.87 – 1.72 (m, 1H), 1.41 – 1.30 (m, 1H), 0.86 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz,

Chloroform-*d*) δ 147.2, 144.5, 143.6, 143.0, 141.3, 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.3 (2C), 128.1 (2C), 127.6 (2C), 127.1, 127.0, 126.9, 123.2, 122.6, 121.9, 120.0, 114.9, 114.8, 60.9, 60.0, 58.4, 50.1, 34.4. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{31}H_{26}{}^{79}BrNO]^+$: 507.1192; found: 507.1196; calcd for $[C_{31}H_{26}{}^{81}BrNO]^+$: 507.1172; found: 507.1186; $[\alpha]_D{}^{20}$= +25.8 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=9.13 min, 20.34 min.

2-((*1R,2S*)-6-Methoxy-1,3,3-triphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3ga): white solid, 39.5 mg, 86% yield, m.p: 122–123 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (s, 1H), 7.59 – 7.52 (m, 2H), 7.47 – 7.34 (m, 4H), 7.37 – 7.22 (m, 4H), 7.24 – 7.16 (m, 3H), 6.84 – 6.70 (m, 4H), 6.63 – 6.56 (m, 1H), 4.02 (d, *J* = 8.3 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.76 (s, 3H), 3.45 – 3.30 (m, 2H), 1.86 – 1.73 (m, 1H), 1.40 – 1.29 (m, 1H), 0.88 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 156.0, 145.1, 145.0, 144.1, 143.5, 141.5, 129.0 (2C), 128.9 (2C), 128.7 (2C), 128.3 (2C), 128.0 (2C), 127.6 (2C), 126.9, 126.8, 126.7, 121.7, 119.4, 118.2, 109.2, 96.1, 61.0, 60.0, 58.3, 55.7, 50.3, 34.5. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{29}NO_2]^+$: 459.2193; found: 459.2199; $[\alpha]_D{}^{20}$= +13.2 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=13.33 min, 37.82 min.

2-((*1R,2S*)-3,3-Bis(3-methoxyphenyl)-1-phenyl-1,2,3,4-tetrahydrocyclopenta-[*b*]indol-2-yl)ethan-1-ol (3ha): white solid, 26.9 mg, 55% yield, m.p: 105–106 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87 (s, 1H), 7.40 – 7.36 (m, 2H), 7.35 – 7.29 (m, 3H), 7.28 – 7.22 (m, 2H), 7.20 – 7.14 (m, 1H), 7.16 – 7.02 (m, 3H), 6.95 – 6.82 (m, 3H), 6.77 – 6.70 (m, 1H), 6.40 – 6.32 (m, 2H), 4.07 (d, *J* = 8.3 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.45 – 3.30 (m, 2H), 1.88 – 1.75 (m, 1H), 1.48 – 1.37 (m, 1H), 0.88 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 160.0, 159.3, 146.4, 146.3, 144.9, 143.9, 140.7, 129.9, 128.8, 128.7 (2C), 128.4 (2C), 126.8, 123.8, 121.8, 121.5, 121.5, 120.2, 119.8, 118.9, 115.8, 114.5, 111.9, 111.2, 111.0, 61.0, 60.0, 58.6, 55.4, 55.1, 50.3, 34.4. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{33}H_{31}NO_3]^+$: 489.2298;

found: 489.2300; $[\alpha]_D^{20}$= +22.7 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=15.31 min, 46.47 min.

2-((*1R,2S*)-3,3-Bis(4-methoxyphenyl)-1-phenyl-1,2,3,4-tetrahydrocyclopenta-[*b*]indol-2-yl)ethan-1-ol (3ia): white solid, 31.8 mg, 65% yield, m.p: 141– 142°C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.79 (s, 1H), 7.55 – 7.44 (m, 2H), 7.42 – 7.34 (m, 2H), 7.37 – 7.22 (m, 4H), 7.12 – 7.03 (m, 1H), 7.00 – 6.84 (m, 4H), 6.78 – 6.69 (m, 2H), 6.71 – 6.62 (m, 2H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.90 – 3.77 (m, 4H), 3.76 (s, 3H), 3.46 – 3.31 (m, 2H), 1.86 – 1.71 (m, 1H), 1.45 – 1.31 (m, 1H), 0.86 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 158.3, 158.3, 147.2, 144.0, 140.7, 137.0, 135.4, 130.0 (2C), 128.7 (2C), 128.6 (2C), 128.4 (2C), 126.8, 123.9, 121.4, 121.4, 119.8, 118.9, 114.2 (2C), 113.3 (2C), 111.9, 61.0, 58.8, 58.6, 55.4, 55.2, 50.3, 34.4. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{33}H_{31}NO_3]^+$: 489.2298; found: 489.2299; $[\alpha]_D^{20}$= +37.8 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=18.40 min, 69.86 min.

2-((*1R,2S*)-1-(4-Methoxyphenyl)-3,3-diphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]-indol-2-yl)ethan-1-ol (3ab): white solid, 40.7 mg, 89% yield, m.p: 139–140 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.63 – 7.53 (m, 2H), 7.47 – 7.38 (m, 2H), 7.38 – 7.23 (m, 4H), 7.24 – 7.14 (m, 3H), 7.13 – 7.02 (m, 1H), 6.97 – 6.89 (m, 2H), 6.91 – 6.82 (m, 2H), 6.79 – 6.69 (m, 2H), 4.01 (d, *J* = 8.4 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.80 (s, 3H), 3.47 – 3.32 (m, 2H), 1.87 – 1.72 (m, 1H), 1.40 – 1.29 (m, 1H), 0.91 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 158.4, 146.4, 144.9, 143.3, 140.7, 135.8, 129.2 (2C), 129.0 (2C), 128.9 (2C), 128.0 (2C), 127.7 (2C), 126.9, 126.7, 123.8, 122.0, 121.5, 119.8, 118.9, 114.1 (2C), 111.9, 61.0, 59.9, 58.4, 55.3, 49.3, 34.5. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{29}NO_2]^+$: 459.2193; found: 459.2196; $[\alpha]_D^{20}$= +43.7 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=11.09 min, 42.01 min.

2-((*1R,2S*)-1-(3-Methoxyphenyl)-3,3-diphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]-indol-2-yl)ethan-1-ol (3ac) : white solid, 40.5 mg, 88% yield, m.p: 245–246 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.61 – 7.54 (m, 2H), 7.48 – 7.40 (m, 2H), 7.37 – 7.26 (m, 2H), 7.26 – 7.18 (m, 4H), 7.11 – 7.06 (m, 1H), 7.02 – 6.91 (m, 4H), 6.83 – 6.80 (m, 1H), 6.77 – 6.70 (m, 2H), 4.03 (d, *J* = 8.4 Hz, 1H), 3.97 – 3.88 (m, 1H), 3.75 (s, 3H), 3.46 – 3.35 (m, 2H), 1.88 – 1.75 (m, 1H), 1.42 – 1.30 (m, 1H), 0.94 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 159.9, 146.5, 145.7, 144.9, 143.3, 140.7, 129.7, 129.0 (4C), 128.0 (2C), 127.7 (2C), 126.9, 126.7, 123.8, 121.7, 121.5, 120.7, 119.9, 119.0, 114.2, 112.0, 111.9, 61.0, 59.9, 58.2, 55.2, 50.3, 34.6. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{29}NO_2]^+$: 459.2193; found: 459.2196; $[\alpha]_D^{20}$= +19.9 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=10.75 min, 25.94 min.

2-((*1S,2S*)-1-(2-Methoxyphenyl)-3,3-diphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]-indol-2-yl)ethan-1-ol (3ad) : white solid, 45.5 mg, 99% yield, m.p: 120–121 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.61 – 7.50 (m, 2H), 7.46 – 7.38 (m, 2H), 7.35 – 7.27 (m, 2H), 7.25 – 7.15 (m, 5H), 7.12 – 7.04 (m, 1H), 7.00 – 6.90 (m, 3H), 6.89 – 6.83 (m, 1H), 6.82 – 6.72 (m, 2H), 4.70 (d, *J* = 8.1 Hz, 1H), 3.95 – 3.88 (m, 1H), 3.86 (s, 3H), 3.46 – 3.34 (m, 2H), 1.87 – 1.72 (m, 1H), 1.44 – 1.32 (m, 1H), 0.98 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 157.1, 146.5, 145.2, 143.6, 140.7, 132.1, 129.1 (3C), 128.8 (2C), 127.9 (2C), 127.7 (2C), 127.6, 126.8, 126.6, 123.8, 122.0, 121.3, 121.2, 119.7, 119.0, 111.8, 110.8, 61.0, 60.0, 58.5, 55.6, 35.0, 18.5. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{29}NO_2]^+$: 459.2193; found: 459.2202; $[\alpha]_D^{20}$= +29.9 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=10.63 min, 23.13 min.

2-((*1R,2S*)-3,3-Diphenyl-1-(*p*-tolyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3ae): white solid, 35.4 mg, 80% yield, m.p: 124–125 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 (s, 1H), 7.62 – 7.50 (m, 2H), 7.48 – 7.39 (m, 2H), 7.37 – 7.22 (m, 4H), 7.24 – 7.15 (m, 3H), 7.16 – 7.02 (m, 3H), 6.97 – 6.88 (m, 2H), 6.79 –

6.69 (m, 2H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.95 – 3.84 (m, 1H), 3.46 – 3.32 (m, 2H), 2.35 (s, 3H), 1.87 – 1.74 (m, 1H), 1.40 – 1.30 (m, 1H), 0.88 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 146.4, 144.9, 143.4, 140.8, 140.7, 136.3, 129.5 (2C), 129.0 (2C), 128.9 (2C), 128.2 (2C), 128.0 (2C), 127.7 (2C), 126.9, 126.7, 123.9, 122.0, 121.4, 119.8, 119.0, 111.9, 61.0, 59.9, 58.4, 49.7, 34.5, 21.2. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{29}NO]^+$: 443.2244; found: 443.2247; $[\alpha]_D^{20}$= +46.9 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=7.93 min, 29.64 min.

2-((*1R,2S*)-3,3-Diphenyl-1-(*m*-tolyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3af): white solid, 25.0 mg, 60% yield, m.p: 181–182 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.62 – 7.54 (m, 2H), 7.47 – 7.41 (m, 2H), 7.38 – 7.26 (m, 2H), 7.24 – 7.15 (m, 6H), 7.14 – 7.03 (m, 2H), 6.98 – 6.90 (m, 2H), 6.78 – 6.69 (m, 2H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.45 – 3.33 (m, 2H), 2.32 (s, 3H), 1.87 – 1.74 (m, 1H), 1.42 – 1.28 (m, 1H), 0.88 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 146.4, 144.9, 143.8, 143.3, 140.7, 138.2, 129.0, 129.0 (2C), 128.9 (2C), 128.6, 128.0 (2C), 127.7 (2C), 127.6, 126.9, 126.7, 125.4, 123.9, 121.9, 121.5, 119.8, 119.0, 111.9, 61.0, 59.9, 58.2, 50.1, 34.5, 21.6. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{29}NO]^+$: 443.2244; found: 443.2247; $[\alpha]_D^{20}$= +18.7 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=7.05 min, 16.58 min.

2-((*1R,2S*)-1-(4-Chlorophenyl)-3,3-diphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]-indol-2-yl)ethan-1-ol (3ag): white solid, 37.4 mg, 81% yield, m.p: 133–134 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.60 – 7.52 (m, 2H), 7.48 – 7.39 (m, 2H), 7.37 – 7.32 (m, 1H), 7.32 – 7.26 (m, 5H), 7.24 – 7.16 (m, 3H), 7.14 – 7.05 (m, 1H), 7.00 – 6.88 (m, 2H), 6.79 – 6.69 (m, 2H), 4.03 (d, *J* = 8.3 Hz, 1H), 3.89 – 3.81 (m, 1H), 3.46 – 3.30 (m, 2H), 1.85 – 1.71 (m, 1H), 1.44 – 1.31 (m, 1H), 0.98 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 146.7, 144.7, 143.1, 142.6, 140.7, 132.4, 129.7 (2C), 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.0 (2C), 127.6 (2C), 127.0, 126.8, 123.6,

121.6, 121.2, 120.0, 118.8, 112.0, 60.9, 60.0, 58.5, 49.7, 34.4. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{31}H_{26}ClNO]^+$: 463.1697; found: 463.1704; $[\alpha]_D^{20}$= +42.1(CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=8.29 min, 22.14 min.

2-((*1R,2S*)-1-(3-Chlorophenyl)-3,3-diphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]-indol-2-yl)ethan-1-ol (3ah): white solid, 20.6 mg, 45% yield, m.p: 139–140 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.65 – 7.52 (m, 2H), 7.49 – 7.40 (m, 2H), 7.40 – 7.29 (m, 3H), 7.28 – 7.23 (m, 3H), 7.24 – 7.15 (m, 3H), 7.15 – 7.05 (m, 1H), 7.00 – 6.89 (m, 2H), 6.81 – 6.67 (m, 2H), 4.03 (d, *J* = 8.3 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.48 – 3.29 (m, 2H), 1.85 – 1.72 (m, 1H), 1.49 – 1.34 (m, 1H), 0.95 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 146.7, 146.3, 144.6, 143.1, 140.7, 134.5, 130.0, 129.0 (2C), 128.9 (2C), 128.5, 128.1 (2C), 127.6 (2C), 127.1, 127.0, 126.8, 126.6, 123.6, 121.7, 121.1, 120.0, 118.9, 112.0, 61.0, 60.0, 58.4, 50.1, 34.4. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{31}H_{26}ClNO]^+$: 463.1697; found: 463.1700; $[\alpha]_D^{20}$= +24.5 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=9.12 min, 17.98 min.

2-((*1R,2S*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-3,3-diphenyl-1,2,3,4-tetrahydrocyclo-penta[*b*]indol-2-yl)ethan-1-ol (3ai): white solid, 39.5 mg, 84% yield, m.p: 125–126 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.60 – 7.50 (m, 2H), 7.48 – 7.38 (m, 2H), 7.37 – 7.24 (m, 2H), 7.23 – 7.15 (m, 3H), 7.13 – 7.03 (m, 1H), 7.04 – 6.91 (m, 2H), 6.91 – 6.81 (m, 2H), 6.80 – 6.67 (m, 3H), 6.01 – 5.84 (m, 2H), 3.99 (d, *J* = 8.4 Hz, 1H), 3.88 – 3.75 (m, 1H), 3.50 – 3.34 (m, 2H), 1.86 – 1.71 (m, 1H), 1.45 – 1.31 (m, 1H), 0.99 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 148.0, 146.4, 146.4, 144.8, 143.3, 140.7, 137.9, 128.9 (2C), 128.9 (2C), 128.0 (2C), 127.6 (2C), 126.9, 126.7, 123.8, 121.8, 121.5, 121.4, 119.9, 119.0, 111.9, 108.4, 108.3, 101.0, 61.1, 59.9, 58.5, 50.1, 34.5. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{32}H_{27}NO_3]^+$: 473.1985; found: 473.1993; $[\alpha]_D^{20}$= +35.9 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=14.05 min, 53.58 min.

2-((*1R,2S*)-1-(Naphthalen-1-yl)-3,3-diphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]-indol-2-yl)ethan-1-ol (3aj): white solid, 24.1 mg, 50% yield, m.p: 141–142 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.91 – 7.75 (m, 5H), 7.64 – 7.57 (m, 2H), 7.52 – 7.41 (m, 5H), 7.39 – 7.26 (m, 2H), 7.27 – 7.18 (m, 3H), 7.13 – 7.01 (m, 1H), 6.90 – 6.73 (m, 4H), 4.24 (d, *J* = 8.3 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.43 – 3.28 (m, 2H), 1.90 – 1.76 (m, 1H), 1.48 – 1.36 (m, 1H), 0.88 (brs, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 146.7, 144.8, 143.3, 141.5, 140.7, 133.6, 132.7, 129.0 (4C), 128.6, 128.0 (2C), 127.8, 127.8, 127.7 (2C), 127.0, 127.0, 126.8, 126.4, 126.1, 125.6, 123.8, 121.7, 121.5, 119.9, 119.0, 111.9, 61.0, 60.0, 58.1, 50.5, 34.5. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{35}H_{29}NO]^+$: 479.2244; found: 479.2248; $[\alpha]_D^{20}$= -4.7 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=11.13 min, 36.59 min.

2-((*1S,2S*)-3,3-Diphenyl-1-(thiophen-2-yl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (3ak): white solid, 30.6 mg, 70% yield, m.p: 221–222 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 (s, 1H), 7.61 – 7.53 (m, 2H), 7.48 – 7.40 (m, 2H), 7.38 – 7.27 (m, 2H), 7.24 – 7.16 (m, 4H), 7.14 – 7.05 (m, 3H), 7.03 – 6.95 (m, 2H), 6.76 – 6.69 (m, 2H), 4.42 (d, *J* = 8.3 Hz, 1H), 4.03 – 3.93 (m, 1H), 3.59 – 3.43 (m, 2H), 1.88 – 1.75 (m, 1H), 1.47 – 1.37 (m, 1H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 148.6, 146.0, 144.5, 143.1, 140.6, 129.0 (2C), 128.9 (2C), 128.0 (2C), 127.6 (2C), 127.0, 126.8, 126.8, 124.8, 124.1, 123.7, 121.7, 121.4, 120.0, 118.9, 112.0, 61.0, 59.8, 59.2, 45.2, 34.6. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{29}H_{25}NOS]^+$: 435.1651; found: 435.1656; $[\alpha]_D^{20}$= +39.3 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=11.47 min, 26.01 min.

2-((*1S,2S*)-1-ethyl-3,3-diphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (*trans*-3al): white solid, 13 mg, 32% yield, m.p: 89–90 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.78 (s, 1H), 7.65 – 7.55 (m, 1H), 7.48 – 7.39 (m, 2H), 7.39 – 7.21

(m, 4H), 7.21 – 7.06 (m, 5H), 6.89 – 6.76 (m, 2H), 4.08 – 3.96 (m, 1H), 3.95 – 3.74 (m, 2H), 3.35 – 3.15 (m, 1H), 2.11 – 1.94 (m, 1H), 1.53 – 1.34 (m, 3H), 1.17 – 1.09 (m, 4H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) (for *trans*-**3al**) δ 146.0, 145.9, 145.7, 140.1, 130.0 (2C), 128.8 (2C), 127.7 (2C), 127.3 (2C), 126.6, 126.5, 125.6, 122.5, 121.1, 120.2, 119.9, 111.8, 61.6, 58.5, 51.0, 42.3, 31.4, 23.6, 14.1. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{27}H_{27}NO]^+$: 381.2087; found: 381.2097; $[\alpha]_D^{20}$= +133.4 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=12.15 min, 43.61 min.

2-((*1S,2R*)-1-ethyl-3,3-diphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)ethan-1-ol (*cis*-3al): white solid, 11 mg, 30% yield, m.p: 95–96 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (s, 1H), 7.63 – 7.50 (m, 3H), 7.44 – 7.33 (m, 2H), 7.34 – 7.26 (m, 2H), 7.21 – 7.07 (m, 5H), 6.80 – 6.70 (m, 2H), 3.75 – 3.62 (m, 2H), 3.61 – 3.52 (m, 1H), 3.12 – 3.02 (m, 1H), 2.16 – 2.01 (m, 1H), 1.85 – 1.68 (m, 1H), 1.61 – 1.53 (m, 1H), 1.52 – 1.40 (m, 1H), 1.18 (brs, 1H), 1.09 – 0.97 (m, 3H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) (for *cis*-**3al**) δ 146.3, 145.7, 143.8, 140.9, 129.1 (2C), 128.7 (2C), 127.9 (2C), 127.8 (2C), 126.7, 126.5, 124.4, 121.6, 121.3, 119.8, 119.3, 111.9, 61.6, 60.2, 53.5, 45.5, 35.6, 26.1, 11.2. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{27}H_{27}NO]^+$: 381.2087; found: 381.2097; $[\alpha]_D^{20}$= +17.7 (CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=16.27 min, 17.30 min.

Gram-Scale Procedure for the synthesis 3aa

Under a nitrogen atmosphere, 2-indolylmethanol **1a** (897 mg, 3.0 mmol), $Pd_2(dba)_3$ (68.7 mg, 0.075 mmol) and $TsOH\cdot H_2O$ (114 mg, 0.6 mmol) were dissolved in 30 mL dry $(i\text{-Pr})_2O$, and stirred at room temperature for about 10 minutes. Then, chiral amine catalyst **Cat-6** (470 mg, 0.6 mmol) was added, subsequently *α,β*-unsaturated aldehydes **2a** (526 mg, 3.6 mmol) were added, and the mixture was stirred at 0 °C until the reaction was completed monitored by TLC. Then the crude product was purified by column chromatography using petroleum ether and EtOAc (10:1) to get crude aldehyde

compound. The aldehyde compound was dissolved in THF, and $NaBH_4$ (227 mg, 6.0 mmol) was added. The mixture was then stirred at room temperature. After the reaction was completed (indicated by TLC), the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=4:1) to afford product **3aa**.

General procedure for the synthesis of 4

Under a nitrogen atmosphere, 2-indolylmethanol **1a** (59.8 mg, 0.20 mmol), $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) and $TsOH{\cdot}H_2O$ (7.6 mg, 0.04 mmol) were dissolved in 2.0 mL dry $(i\text{-Pr})_2O$, and stirred at room temperature for about 10 min. Then, chiral amine catalyst **Cat-6** (31.4 mg, 0.04 mmol) were added, subsequently add *α,β*-unsaturated aldehydes **2a** (44.0 mg, 0.30 mmol), and the mixture was stirred at 0 °C until the reaction was completed monitored by TLC. Then the crude product was purified by column chromatography using petroleum ether and EtOAc (10:1) to get crude aldehyde compound. The aldehyde compound was dissolved in toluene, and ethyl (triphenylphosphoranylidene) acetate (104.5 mg, 0.30 mmol) was added. The reaction mixture was refluxed at 120 °C overnight. After the reaction was completed (indicated by TLC), the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether/DCM=1:1) to afford product **4**.

Ethyl (*E*)-4-((*1R,2S*)-1,3,3-triphenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl)but-2-enoate (4): white solid, 64.7 mg, 65% yield, m.p: 197–198 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.84 (s, 1H), 7.53 – 7.46 (m, 2H), 7.47 – 7.39 (m, 2H), 7.38 – 7.18 (m, 10H), 7.15 – 7.07 (m, 1H), 7.02 – 6.90 (m, 2H), 6.83 – 6.70 (m, 2H), 6.54 – 6.44 (m, 1H), 5.54 (d, *J* = 15.5 Hz, 1H), 4.18 – 3.98 (m, 3H), 3.85 – 3.72 (m, 1H), 2.43 – 2.29 (m, 1H), 2.21 – 2.05 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C {^{1}H} NMR** (100 MHz, Chloroform-*d*) δ 166.1, 147.4, 146.3, 144.4, 142.8, 142.8, 140.7, 129.0 (2C), 129.0 (2C), 128.8 (2C), 128.5 (2C), 128.1 (2C), 127.6 (2C), 127.0, 127.0, 126.8, 123.8, 122.3, 121.6, 121.2, 120.0, 119.2, 111.9, 61.7, 60.1, 60.0, 49.8, 33.7, 14.3. **HRMS** (EI-TOF) m/z: $[M]^+$ calcd for $[C_{35}H_{31}NO_2]^+$: 497.2349; found: 497.2356; $[\alpha]_D^{20}$= +15.5

(CH_2Cl_2, c=1.00); HPLC (Chiralpak AD-H, *n*-hexane/*i*-propanol=90/10, 1.0 mL/min, 220 nm) t_R=5.83 min, 6.75 min.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website http://pubs.acs.org.

Crystallographic data (CIF)

Crystallographic data and NMR and HPLC spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-Mail: xyluo@ecust.edu.cn.

*E-Mail: weiping_deng@ecust.edu.cn.

ORCID

Wei-Ping Deng: 0000-0002-4232-1318

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work is supported by the National Natural Science Foundation of China (No. 21572053) and the Fundamental Research Funds for the Central Universities.

REFERENCES

1 (a) Kong, Y. C.; Ng, K. H.; Wat, K. H.; Wong, A.; Saxena, I. F.; Cheng, K. F.; But, P. P.; Chang, H. T. Yuehchukene, a Novel Anti-Implantation Indole Alkaloid from Murraya paniculata. *Planta Med.* **1985**, *51*, 304-307. (b) Ishikura, M.; Imaizumi, K.; Katagiri, N. Total Synthesis of Yuehchukene. *Heterocycles* **2000**, *53*, 553-553. (c) Lai E.; Lepeleire I. De; Crumley T. M.; Liu F.; Wenning L. A.; Michiels N.; Vets E.; O'Neill G.; Wagner J. A.; Gottesdiener K. Suppression of Niacin-Induced Vasodilation with an

Antagonist to Prostaglandin D_2 Receptor Subtype 1. *Clin. Pharmacol. Ther.* **2007**, *81*, 849-857. (d) Talaz, O.; Gülçin, I.; Göksu, S.; Saracoglu, N. Antioxidant Activity of 5, 10-Dihydroindeno[1,2-*b*]indoles Containing Substituents on Dihydroindeno Part. *Bioorg. Med. Chem.* **2009**, *17*, 6583-6589. (e) Chen, H.; Bai, J.; Fang, Z.-F.; Yu, S.-S.; Ma, S.-G.; Xu, S.; Li, Y.; Qu, J.; Ren, J.-H.; Li, L. Indole Alkaloids and Quassinoids from the Stems of Brucea Mollis. *J. Nat. Prod.* **2011**, *74*, 2438-2445. (f) Yi, P.; Rehmel, J.-F.; Cassidy, K.; Hadden, C.; Campanale, K.; Patel, N.; Johnson, J. Disposition and Metabolism of LY2452473, a Selective Androgen Receptor Modulator, in Humans. *Drug Metab. Dispos.* **2012**, *40*, 2354-2364.

2 For selected examples, see: (a) Trost, B. M.; Quancard, J. Palladium-Catalyzed Enantioselective C-3 Allylation of 3-Substituted-1*H*-Indoles Using Trialkylboranes. *J. Am. Chem. Soc.* **2006**, *128*, 6314-6315. (b) Müller, S.; Webber, M. J.; List, B. The Catalytic Asymmetric Fischer Indolization. *J. Am. Chem. Soc.* **2011**, *133*, 18534-18537. (c) Xu, B.; Guo, Z.-L.; Jin, W.-Y.; Wang, Z.-P.; Peng, Y.-G.; Guo, Q.-X. Multistep One-Pot Synthesis of Enantioenriched Polysubstituted Cyclopenta[*b*]indoles. *Angew. Chem. Int. Ed.* **2012**, *51*, 1059-1062. (d) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. Copper-Catalyzed Highly Enantioselective Cyclopentannulation of Indoles with Donor-Acceptor Cyclopropanes. *J. Am. Chem. Soc.* **2013**, *135*, 7851-7854. (e) Zi, W.; Wu, H.; Toste, F. D. Gold (I)-Catalyzed Dearomative Rautenstrauch Rearrangement: Enantioselective Access to Cyclopenta[*b*]indoles. *J. Am. Chem. Soc.* **2015**, *137*, 3225-3228. (f). Zhao, X.; Liu, X.; Mei, H.; Guo, J.; Lin, L.; Feng, X. Asymmetric Dearomatization of Indoles through a Michael/Friedel-Crafts-Type Cascade to Construct Polycyclic Spiroindolines. *Angew. Chem. Int. Ed.* **2015**, *54*, 4032-4035.

3 For selected examples, see: (a) Han, B.; Xiao, Y.-C.; Yao, Y.; Chen, Y.-C. Lewis Acid Catalyzed Intramolecular Direct Ene Reaction of Indoles. *Angew. Chem. Int. Ed.* **2010**, *49*, 10189-10191. (b) Tan, W.; Li, X.; Gong, Y.-X.; Ge, M.-D.; Shi, F. Highly Diastereo- and Enantioselective Construction of a Spiro[cyclopenta[*b*]indole-1,3′-oxindole] Scaffold via Catalytic Asymmetric Formal [3+2] Cycloadditions. *Chem. Commun*. **2014**, *50*, 15901-15904. (c) Shi, F.; Zhang, H.-H.; Sun, X.-X.; Liang, J.; Fan, T.; Tu, S.-J. Organocatalytic Asymmetric Cascade Reactions of 7-Vinylindoles:

Diastereo- and Enantioselective Synthesis of C7-Functionalized Indoles. *Chem. Eur. J.* **2015**, *21*, 3465-3471. (d) Lebée, C.; O. Kataja, A.; Blanchard, F.; Masson, G. Formal Asymmetric Organocatalytic [3+2] Cyclization between Enecarbamates and 3-Indolylmethanols: Rapid Access to 3-Aminocyclopenta[*b*]indoles. *Chem. Eur. J.* **2015**, *21*, 8399-8402. (e) Fan, T.; Zhang, H.-H.; Li, C.; Shen, Y.; Shi, F. The Application of N‐Protected 3-Vinylindoles in Chiral Phosphoric Acid-Catalyzed [3+2] Cyclization with 3-Indolylmethanols: Monoactivation of the Catalyst to Vinyliminium. *Adv. Synth. Catal.* **2016**, *358*, 2017-2031.

4 (a) Wang, C.-S.; Wu, J.-L.; Li, C.; Li, L.-Z.; Mei, G.-J.; Shi, F. Design of C3-Alkenyl−Substituted 2-Indolylmethanols for Catalytic Asymmetric Interrupted Nazarov-Type Cyclization. *Adv. Synth. Catal.* **2018**, *360*, 846-851. (b) Wu, J.-L.; Wang, J.-Y.; Wu, P.; Wang, J.-R.; Mei, G.-J.; Shi, F. Diastereo- and Enantioselective Construction of Chiral Cyclopenta[*b*]indole Framework via a Catalytic Asymmetric Tandem Cyclization of 2-Indolymethanols with 2-Naphthols. *Org. Chem. Front.* **2018**, *5*, 1436-1445. (c) Wang, J.-Y.; Wu, P.; Wu, J.-L.; Mei, G.-J.; Shi, F. Chemo-Divergent Tandem Cyclizations of 2-Indolylmethanols with Tryptophols: C-N Versus C-C Bond Formation. *J. Org. Chem.* **2018**, *83*, 5931-5946. (d) Wu, J.-L.; Wang, C.-S.; Wang, J.-R.; Mei, G.-J.; Shi, F. A Catalytic Asymmetric Interrupted Nazarov-Type Cyclization of 2-Indolylmethanols with Cyclic Enaminones. *Org. Biomol. Chem.* **2018**, *16*, 5457-5464.

5 (a) Zhu, Z.-Q.; Shen, Y.; Sun, X.-X.; Tao, J.-Y.; Liu, J.-X.; Shi, F. Catalytic Asymmetric [3+2] Cycloadditions of C-3 Unsubstituted 2-Indolylmethanols: Region-, Diastereo- and Enantioselective Construction of the Cyclo-penta[*b*]indole Framework. *Adv. Synth. Catal.* **2016**, *358*, 3797-3808. (b) Xu, M.-M.; Wang, H.-Q.; Wan, Y.; Wang, S.-L.; Shi, F. Enantioselective Construction of Cyclopenta[*b*]indole Scaffolds via the Catalytic Asymmetric [3 + 2] Cycloaddition of 2-Indolylmethanols with *p*-Hydroxystyrenes. *J. Org. Chem*. **2017**, *82*, 10226-10233.

6 Xu, M.-M.; Wang, H.-Q.; Mao, Y.-J.; Mei, G.-J.; Wang, S.-L.; Shi, F. Cooperative Catalysis-Enabled Asymmetric *α*-Arylation of Aldehydes Using 2-Indolylmethanols as Arylation Reagents. *J. Org. Chem.* **2018**, *83*, 5027-5034.

7 For selected examples, see: (a) Ibrahem I.; Córdova A. Direct Catalytic Intermolecular *α*-Allylic Alkylation of Aldehydes by Combination of Transition-Metal and Organocatalysis. *Angew. Chem. Int. Ed.* **2006**, *45*, 1952-1956. (b) Leth L.A.; Glaus F.; Meazza M.; Fu L.; Thøgersen M.K.; Bitsch E.A.; Jørgensen K.A. Decarboxylative [4+2] Cycloaddition by Synergistic Palladium and Organocatalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 15272-15276. (c) Meazza M.; Polo V.; Merino P.; Rios R. Synergistic Catalysis: Enantioselective Cyclopropanation of Alkylidene Benzoxazoles by Pd(II) and Secondary Amine Catalysis. Scope, Limitations and Mechanistic Insight. *Org. Chem. Front.* **2018**, *5*, 806-812.

8 (a) Gu, B.-Q.; Zhang, H.; Deng, W.-P. Organocatalytic Asymmetric Synthesis of Dihydro-Carbazoles via a Formal [4+2] Cycloaddition of in Situ Generated *o*-Quinodimethanes with Enals. *Tetrahedron* **2016**, *72*, 6595-6602. (b) Su, R.-H.; Ding, X.-F.; Wu, S.-X.; Zhao, J.-H.; Deng, W.-P. Secondary Amine-Catalyzed Asymmetric Formal Aza [3 + 3] Cycloaddition to Construct Enantio-Enriched Piperidines Derivatives. *Tetrahedron* **2017**, *73*, 6031-6038. (c) Ding, X.-F.; Su, R.-H.; Yang, W.-L.; Deng, W.-P. Organocatalytic Asymmetric Formal Aza-[3+3]Cyclo-Additions of 3-Aminobenzofuran with *α, β*-Unsaturated Aldehydes. *Adv. Synth. Catal.* **2018**, *360*, 4168-4177. (d) Gu, B.-Q.; Yang, W.-L.; Wu, S.-X.; Wang, Y.-B.; Deng, W.-P. Organocatalytic Asymmetric Synthesis of Tetrahydro-Carbazoles via an Inverse-Electron-Demand Diels-Alder Reaction of 2,3-Indole-Dienes with Enals. *Org. Chem. Front.* **2018**, *5*, 3430-3434.

9 Zhu, Z.-Q.; Shen, Y.; Liu J.-X.; Tao J.-Y.; Shi, F. Enantioselective Direct *α*-Arylation of Pyrazol-5-Ones with 2-Indolylmethanols via Organo-Metal Cooperative Catalysis. *Org. Lett.* **2017**, *19*, 1542-1545.

10 (a) He, Y.-Y.; Sun, X.-X.; Li, G.-H.; Mei, G.-J.; Shi, F. Substrate-Controlled Regioselective Arylations of 2-Indolylmethanols with Indoles: Synthesis of Bis(indolyl)methane and 3,3′-Bisindole Derivatives. *J. Org. Chem.* **2017**, *82*, 2462-2471. (b) Wang J.-Y.; Wu P.; Wu J.-L.; Mei G.-J.; Shi F. Chemodivergent Tandem Cyclizations of 2-Indolylmethanols with Tryptophols: C–N versus C–C Bond Formation. *J. Org. Chem.* **2018**, *83*, 5931−5946.

11 (a) Li M-L; Datta S; Barber D. M.; Dixon D. J. Dual Amine and Palladium Catalysis in Diastereo- and Enantioselective Allene Carbocyclization Reactions. *Org. Lett.* **2012**, *14*, 6350-6353. (b) Meazza M.; Ceban V.; Pitak M. B.; Coles S.J.; Rios R. Synergistic Catalysis: Enantioselective Addition of Alkylbenzoxazoles to Enals. *Chem. Eur. J.* **2014**, *20*, 16853-16857. (c) Laugeois M.; Ponra S.; Ratovelomanana-Vidal V.; Michelet V.; Vitale M. R. Asymmetric Preparation of Polysubstituted Cyclopentanes by Synergistic Pd(0)/Amine Catalyzed Formal [3+2] Cycloadditions of Vinyl Cyclopropanes with Enals. *Chem. Commun*. **2016**, *52*, 5332-5335. (d) Su Y.-L.; Han Z.-Y.; Li Y.-H.; Gong L.-Z. Asymmetric Allylation of Furfural Derivatives: Synergistic Effect of Chiral Ligand and Organocatalyst on Stereochemical Control. *ACS Catal.* **2017**, *7*, 7917-7922.

12 Xu J.; H. Rawal V.; Total Synthesis of (−)-Ambiguine P. *J. Am. Chem. Soc.* **2019**, *141*, 4820-4823.

13 Albrecht, Ł.; Dickmeiss, G.; Acosta, F. -C.; Rodríguez-Escrich, C.; L. Davis, R.; Jørgensen, K. A. Asymmetric Organocatalytic Formal [2 + 2]-Cycloadditions via Bifunctional H-Bond Directing Dienamine Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 2543-2546.