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Tunable Bifunctional Phosphine–Squaramide Promoted Morita–Baylis–Hillman Reaction of *N*-Alkyl Isatins with Acrylates

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Abstract: A series of highly tunable bifunctional phosphine-squaramide H-bond donor organocatalysts **6** has been synthesized from inexpensive and commercially available β-amino alcohols in moderate yields. Catalyst **6f** can efficiently promote the asymmetric Morita–Baylis–Hillman (MBH) reaction of *N*-alkyl isatins with acrylate esters providing the chiral 3-substituted 3-hydroxy-2-oxindoles in good yields and enantioselectivities (up to 93% yield and 95% *ee*), in which the challenging substrate *tert*-butyl acrylate **9d**, provided the best *ee* value to date. Moreover, this methodology was applied successfully in the synthesis of chiral cyclic spiropyrrolizidineoxindole and γ-butyrolactone derivatives without enantioselectivity deterioration. The possible mechanism of this MBH reaction was also investigated by ^{31}P NMR, ESI-MS and KIE studies. The KIE experiments show that the electrophilic addition of *N*-methyl isatin to the complex of acrylate ester and phophine-squaramide is the rate-determing step of the asymmetric MBH reaction.

Keywords: Morita–Baylis–Hillman reaction; mechanistic study; phosphine-squaramide

Introduction

The Morita–Baylis–Hillman (MBH) reaction is one of the most valuable C–C bond forming reactions in organic synthesis owing to its high efficiency in construction of densely functionalized products in an atom-economic manner.[1] In the last few years, the asymmetric version of MBH reaction has been extensively investigated by employing several different catalytic systems, such as cinchonine derivatives and chiral phosphines as well (Figure 1).[2]

Among these, the enantioselective MBH reaction of isatins was particularly attractive since the MBH adducts,[3] 3-substituted 3-hydroxy-2-oxindoles, constitute the core building blocks of many valuable drug candidates.[4–5] In 2010, Zhou and coworkers reported the first MBH reaction of isatin with acrolein catalyzed by β-isocupreidine **1a** (β-ICD) providing the oxindole derivatives in excellent enantioselectivity (Figure 1).[6] Shi et al. reported the β-ICD-catalyzed asymmetric MBH reaction of 1-naphthyl acrylate with isatins to generate the oxindoles in good *ee* values (up to 94%).[7] Lu's group also applied β-ICD to promote the asymmetric MBH reaction of benzyl acrylate with isatins.[8] As is well known, chiral phosphine organocatalysts have attracted considerable attention in asymmetric catalytic synthesis;[9] particularly, amino acid based bifunctional phosphine organocatalysts have been widely explored in various reactions.[10] In 2011, Wu et al. employed the phosphino-thiourea organocatalyst to catalyze the reaction of isatin and acrylate.[11] Following their previous work,[12] more re-

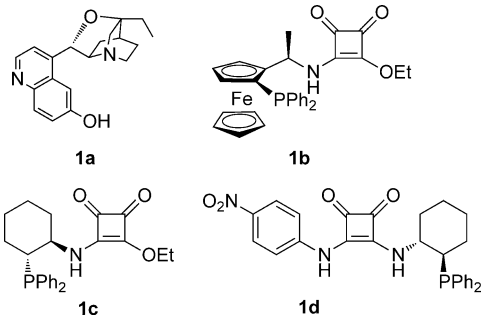


Figure 1. Reported chiral organocatalysts for the asymmetric MBH reaction

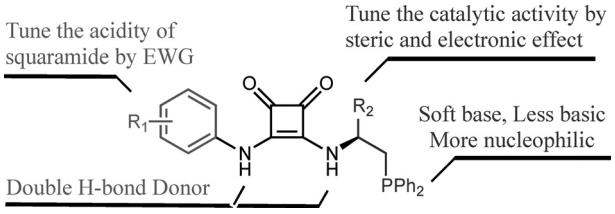


Figure 2. Design of novel chiral phosphine squaramides

cently, Wu[13] and another group[14] developed several chiral bifunctional phosphine–squaramide organocatalysts, which were efficient for the asymmetric MBH reaction. Despite important progress in this area, there is still room for improvement. For example, these phosphine organocatalysts cannot be effectively tuned.

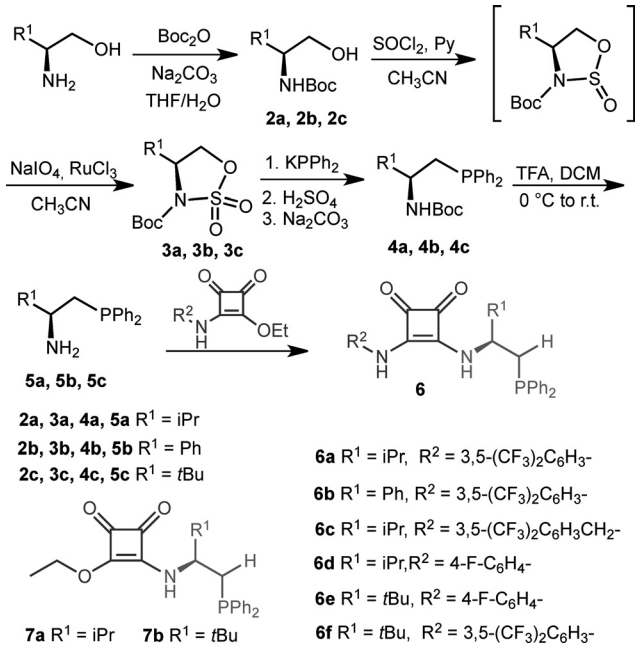
As part of our projects in development of hydrogen bond donor chiral squaramide organocatalysts,[15–16] we are interested in exploring the potential of chiral squaramide organocatalyst[17] in the asymmetric MBH transformation. We envisioned that having the squaramide motif and the highly tunable phosphine moiety within one molecule could synergistically activate the substrates in stereocontrolled manner, which might lead to high enantioselectivity. As shown in Figure 2, simple incorporation of various substituents into phenyl ring could alter the acidity of the squaramide.[18] Meanwhile, the diversity of β-aminophosphines could tune the catalytic activity by steric and electronic effect as well.

Herein, we report a series of highly tunable bifunctional phosphine–squaramides from inexpensive, easily obtained, commercially available β-amino alcohols and their application in the asymmetric catalyzed MBH reactions of isatin with acrylates, providing the MBH adducts in good yields and up to 95% *ee*. The possible mechanism of this MBH reaction was also investigated by ^{31}P NMR, ESI-MS and KIE studies.

Results and Discussion

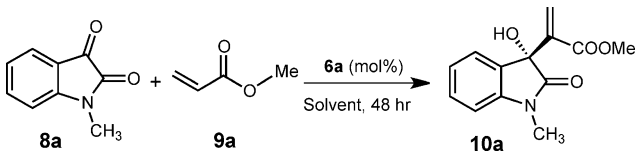
The highly tunable phosphine–squaramides **6a–f** were prepared in 43-56% yields by the condensation of ethyl squarate with the corresponding β-aminophosphines derived from β-aminoalcohols (Scheme 1).[19]

Firstly, the optimal reaction conditions of the enantioselective MBH reaction were investigated by employing *N*-methyl isatin **8a** with methyl acrylate **9a** in the presence of catalyst **6a**, the results were illustrated in Table 1. To our delight, in the presence of 7.5 mol% of **6a**, the reaction in THF at 10 °C for 2 days gave **10a** in 96% yield and 82% *ee* (entry 1). Lowering the catalyst loading to 1 mol% led to a significant decrease in yield albeit with a slight increase in enantioselectivity (entry 4). Then Various solvents



Scheme 1. General synthetic route of phosphine-squaramide organocatalysts

Table 1. Optimization of reaction conditions for catalyst **6a**[a]

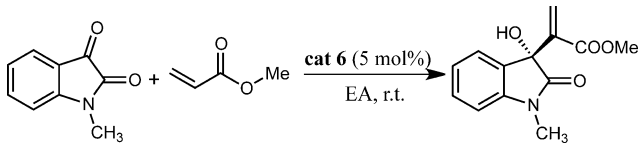


Entry	Cat. [mol%]	Solvent	Yield [%][b]	ee [%][c]
1	7.5	THF	96	82
2	5.0	THF	87	82
3	2.5	THF	54	84
4	1.0	THF	18	86
5	5.0	CH_2Cl_2	51	81
6	5.0	toluene	18	85
7	5.0	CH_3CN	60	80
8	5.0	acrylate	30	79
9	5.0	EA	77	85
10[d]	5.0	EA	87	87
11[d,e]	5.0	EA	90	84
12[d,g]	5.0	EA	13	92
13[d,f,g]	5.0	EA	17	82

[a] Condition: **8a** (0.2 mmol), **9a** (0.4 mmol), solvent (1 mL), **6a**, the mixture was stirred at r.t. for 48 hrs.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] 1.0 mmol **9a** was used.
[e] r.t.
[f] 100 uL EA/THF (1:1).
[g] 0 °C.

were examined (entries 2 and 5-9). Ethyl acetate (EA) was proved to be the best solvent in terms of

Table 2. Screening of catalysts[a]



8a 9a 10a

Entry	Cat.	Yield [%][b]	ee [%][c]
1	**6a**	90	84
2	**6b**	86	83
3	**6c**	78	69
4	**6d**	90	84
5	**6e**	90	90
6	**6f**	90	94
7	**7a**	89	62
8	**7b**	79	32

[a] Condition: **8a** (0.2 mmol), **9a** (1.0 mmol), EA (1 mL), **Cat. 6** (0.01 mmol), the mixture was stirred at r.t. for 48 hrs.
[b] Isolated yield.
[c] Determined by HPLC analysis.

catalytic reactivity and enantioselectivity (entry 10). As expected, the lower reaction temperature did improve the *ee* value (entries 12 and 13). Finally, we chose a 5 mol% catalyst loading and EA as the most suitable solvent to do further screening.

Following the optimized reaction conditions, efficiency of other bifunctional phosphine squaramides **6b–f** were evaluated, the results were shown in Table 2.

Catalyst **6f**, derived from L-*tert*-leucinol, was found to promote the MBH reaction of **8a** with methyl acrylate **9a** to give the product **10a** in 90% yield and 94% *ee* (entry 6). The L-valinol derived phosphine-squaramide catalysts **6a**, **6c**, **6d** and L-phenylglycinol derived **6b** exhibit inferior enantioselectivities (entries 1–4). In contrast, when the single hydrogen bond donor catalyst **7a** was used in the reaction, **10a** was formed in 89% yield and 62% *ee* (entry 7). Unfortunately, **7b** showed even lower catalytic activity for the MBH reaction (entry 8). These results implied that the assembly of bulkier *tert*-butyl group and more electron-deficient phenyl amine benefits the enantioselectivity (comparion of catalyst **6f** with others).

With the optimized reaction conditions in hand, we next carried out the MBH reaction of acrylate ester **9** with various *N*-alkyl isatins **8** catalyzed by the bifunctional phosphine-squaramide organocatalyst **6f**. The results were summarized in Table 3. As shown in Table 3, the reactions worked very well with isatins bearing either electron-withdrawing or electron-donating substituents on the phenyl ring and the desired products can be obtained in good yields and enantioselectivities (89–95% *ee*) (entry 1, entries 3–15). **8b** with the substituent at the 4-position retard the reactive process possibly due to the steric effect, affording the product in 86% *ee* (entry 2). Lowering the reaction temperature could slightly enhance enantioselectivity (entries 3, 4 and 9 in parenthesis). Moreover, other acrylate esters were also employed in this reaction affording the corresponding products **10p–r** in excellent ees (entries 16-18). It is worth noting that the challenging substrate *t*-butyl acrylate **9d**, which was reported to give moderate *ee* presumably due to the bulky *t*-butyl group, gave 95% *ee* in our catalytic system (entry 18).[13a] Furthermore, the MBH transformation of *N*-methyl isatin **8c** with methyl acrylate **9a** on 0.8 mmol scale was conducted to explore the reaction practicality; to our delight, even in the presence of 2.5 mol% of **6f**, **10c** was isolated in 90% yield and 92% *ee* (entry 22).

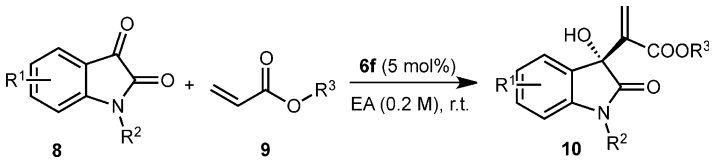
To further illustrate the synthetic potential of this methodology, the synthesis of a chiral polycyclic oxindole and a γ-butyrolactone were performed. As shown in Figure 3, the asymmetric MBH adduct **10c** was treated with L-proline and isatin in methanol to generate polycyclic compound **12** in 84% yield and 94% *ee*. This type of polycyclic compound has served as a potential synthon for the preparation of drug intermediates and clinical pharmaceuticals.[20] Furthermore, the product **10c** can be easily reduced with sodium borohydride in THF to provide the γ-butyrolactone **11** in 62% yield and 92% *ee*, which have potential activity in the inhibition of various bacteria and fungi species.[21]

The mechanism of the asymmetric catalytic MBH reaction of *N*-alkyl isatin with acrylate ester by chiral phosphine squaramide was not entirely clear. During our manuscript prepararion, Wu reported the aza-MBH reaction of isatin and acrylate ester and a plausible TS was also proposed.[13b] To gain insight into this type of asymmetric transformation, several experiments were performed. First, the key intermediate detected by ^{31}P NMR experiment (Support Information **S1**) is consistent with the intermediate formed by Michael reaction of the chiral tertiary phosphine in catalyst **6f** with butyl acrylate.

Furthermore, the suspension of catalyst **6f** with butyl acrylate in EA was stirred about 10 min till the reaction system became clear, the key zwitterionic intermediate of *m*/*z* 721 was detected by ESI-MS, which correlated to the authentic active species **I** in the MBH reaction. Then, the *N*-methyl isatin was added, after 10 min, another intermediate *m*/*z* 882 was intercepted as well, which was potentially the triple adduct **II**.

To understand the possible pathway of this asymmetric MBH reaction better, we performed the KIE experiments to discern the rate-limiting step of the MBH reaction catalyzed by tunable bifunctional phosphine–squaramide catalyst **6f**. The carbon isotopic effect on both the reactants was investigated by em-

Table 3. Substrate scope of the enantioselective MBH reactions catalyzed by **6f**[a]



Entry	Substrate **8**	R^1	R^2	R^3	Products **10**, Yield [%][b]	ee [%][c]
1	**8a**	H	Me	Me	**10a**, 92	94
2	**8b**	4-Br	Me	Me	**10b**, 75	86[e]
3	**8c**	5-Br	Me	Me	**10c**, 92 (62)	93 (95)[d]
4	**8d**	6-Br	Me	Me	**10d**, 93 (49)	94 (95)[d]
5	**8e**	7-Br	Me	Me	**10e**, 84	92
6	**8f**	5-Me	Me	Me	**10f**, 90	92
7	**8g**	5-MeO	Me	Me	**10g**, 76	94
8	**8h**	5-F	Me	Me	**10h**, 92	93
9	**8i**	5-Cl	Me	Me	**10i**, 92 (43)	93 (94)[d]
10	**8j**	7-Cl	Me	Me	**10j**, 92	93
11	**8k**	H	Et	Me	**10k**, 89	92
12	**8l**	H	allyl	Me	**10l**, 86	93
13	**8m**	H	Bn	Me	**10m**, 84	90
14	**8n**	H	iPr	Me	**10n**, 80	92
15	**8o**	H	*n*-pentyl	Me	**10o**, 82	89
16	**8a**	H	Me	Et	**10p**, 93	90
17	**8a**	H	Me	Bu	**10q**, 83	92
18	**8a**	H	Me	*t*Bu	**10r**, 74	95
19	**8l**	H	allyl	Me	**10l**, 88	90[e]
20	**8m**	H	Bn	Me	**10m**, 86	87[e]
21	**8a**	H	Me	Me	**10a**, 87	87[e]
22	**8c**	5-Br	Me	Me	**10c**, 90	92[f]

[a] Condition: **8** (0.1 mmol), **9** (0.5 mmol), EA (0.5 mL), **6f** (0.005 mmol), the mixture was stirred at r.t. for 48 hrs.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral columns, (*R*)-configuration was assigned by the sign of specific rotation with that reported in the literature.[13a]
[d] The results in parenthesis were obtained at 10 °C.
[e] **Cat. 6d** was used.
[f] The reaction was conducted in 0.8 mmol scale.

ploying Singleton's NMR technique[22] at natural abundance (Figure 4). When the reaction proceeded at 62% conversion of *N*-methyl isatin, the two remaining reactants *N*-methyl isatin and butyl acrylate were recovered and then the kinetic isotope effect experiments were performed for butyl acrylate and *N*-methyl isatin, respectively. A pronounced carbon isotope effect was observed on the 3-carbon when the ^{13}C ratio of recovered *N*-methyl isatin was compared to that of the original sample (^{13}C(recovered)/^{13}C(original) at $C_3 = 1.021$). This kinetic isotope effect indicates the nucleophilic addition of active species I to *N*-methyl isatin is the rate-limiting step of the asymmetric MBH reaction.

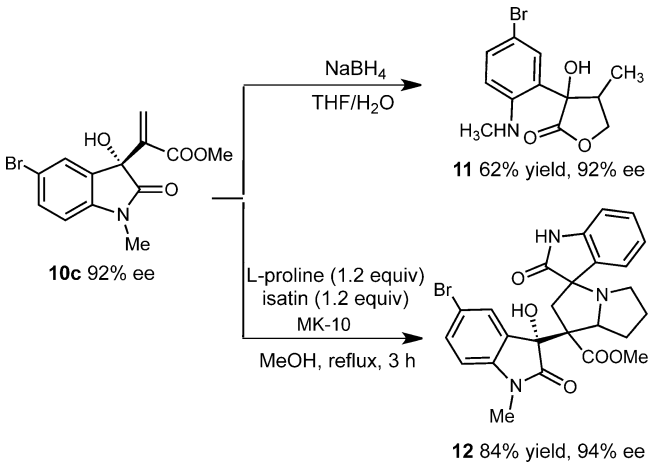


Figure 3. Synthetic applications of the MBH adduct

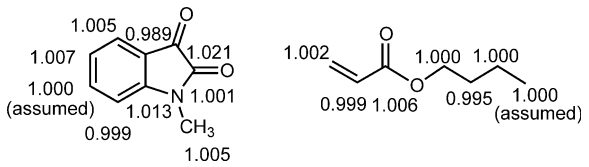


Figure 4. KIEs of two reactants

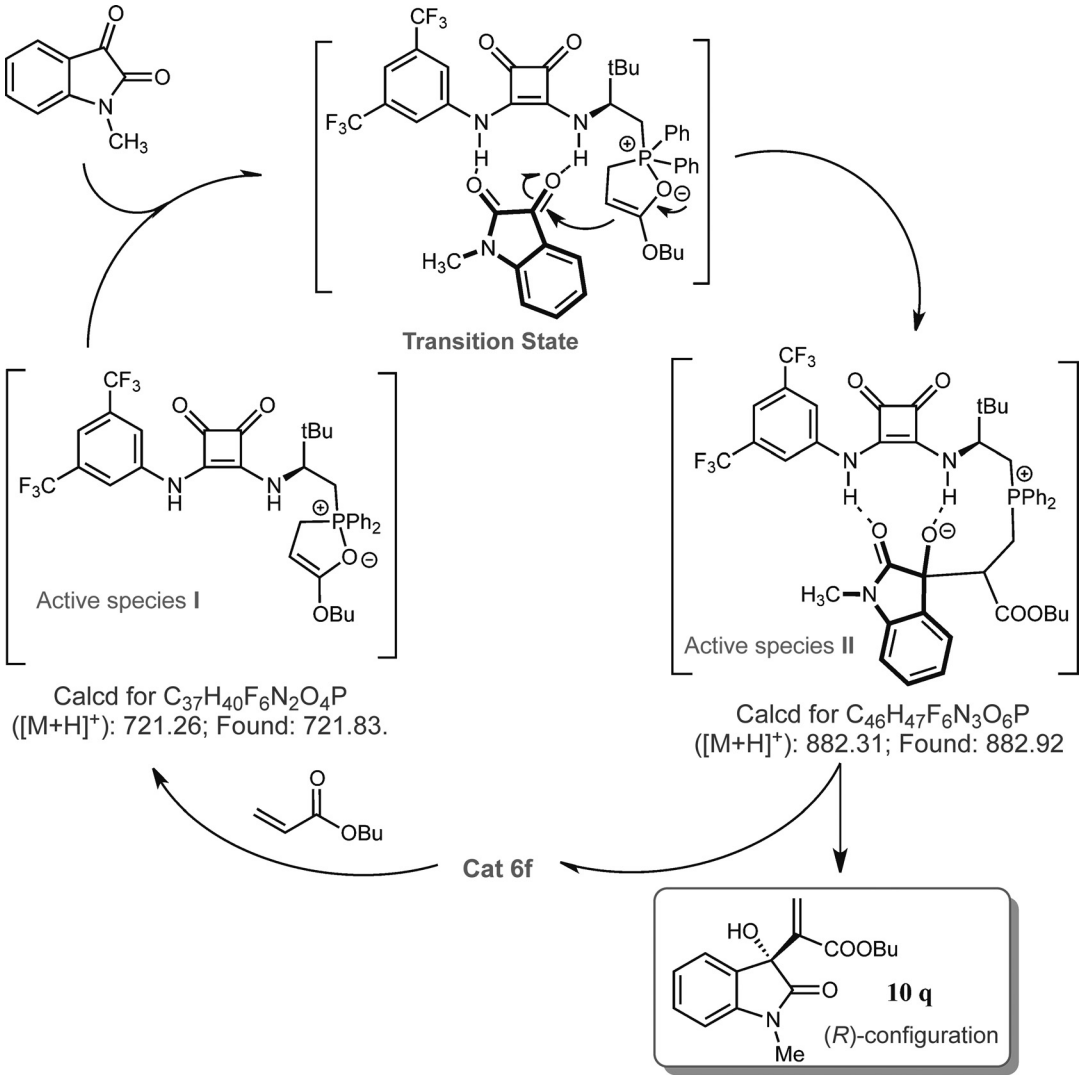


Figure 5. Proposed transition state of the MBH reaction

Based on these results, a proposed mechanism is shown in Figure 5. The chiral tertiary phosphine first add to butyl acrylate, generating reactive intermediate **I**, which then interacts with isatin through hydrogen bonding leading to the key intermediate **TS** which possibly exists as cyclic phosphinoyl associated enolate.[13b,23] Then the nucleophilic attack of the enolate to the isatin carbonyl affords species **II**. In the following elimination of the catalyst, the desired product is formed, completing the catalytic cycle.

Conclusions

In conclusion, we have prepared a series of novel bifunctional phosphine–squaramide organocatalysts from commercially available β-amino alcohols. These chiral catalysts exhibited excellent enantioselectivity in the asymmetric MBH reaction of *N*-alkyl isatins with acrylate esters. This methodology was applied successfully in the further synthesis of chiral polycyclic oxindole and γ-butyrolactone derivatives. To gain further mechanistic insight, we have intercepted two critical catalytic active intermediates with the aid of the ESI-MS and determined the authentic catalytic active species by tracing the catalytic cycle through ^{31}P NMR. In combination with the KIE study, we have identified the rate-limiting step of the asymmetric MBH reaction catalyzed by bifunctional phosphine–squaramide catalyst. Investigation of further application of this kind of organocatalyst to the construction of other pharmaceutically active substances is in progress and will be reported in a due course.

Experimental Section

General Information

Analytical-grade solvents and amino alcohols were purchased and used as received. Catalyst **6** was obtained in multiple steps synthesis from commercially available amino alcohols and squaric acid as described below. Column chromatography purifications were performed using 230–400 mesh silica gel. Enantiomeric excesses (ees) were determined by HPLC analysis with AD-H chiral column (250 cm × 4.6 mm), AS-H chiral column (250 cm × 4.6 mm), OJ-H chiral column (250 cm × 4.6 mm) or Chiralcel OD-H chiral column (250 cm × 4.6 mm), as indicated. Optical rotation was reported as follows: [α] (c g/100 mL, solvents). NMR spectra were measured at 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C spectra by Bruker NMR instrument (Biospin 2.1) and calibrated from residual solvent signal. HRMS was also acquired with the indicated source. IR spectra were obtained by FT-IR.

General procedure for the synthesis of carbamates 2

To a stirred solution of β-amino alcohol (10 mmol) and Na_2CO_3 (20 mmol) in THF (20 mL) and water (15 mL) was added Boc_2O (11 mmol) in THF (25 mL) in the ice-water bath. After the consumption of β-amino alcohol, the resulting suspension was poured into water (80 mL) and extracted with CH_2Cl_2 (80 mL × 3), then dried over anhydrous Na_2SO_4. Filtration followed by solvent evaporation afforded Boc-protected amino alcohols, which are pure enough without further purification.

(*S*)-*tert*-Butyl (1-hydroxy-3-methylbutan-2-yl)-carbamate (2a): colorless oil, (1.87 g, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 1H), 3.64 (m, 2H), 3.42 (s, 1H), 3.09 (s, 1H), 1.86 (m, 1H), 1.45 (s, 9H), 0.98–0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 79.5, 63.9, 57.9, 28.4, 27.4, 19.5, 18.5.

(*S*)-*tert*-Butyl (2-hydroxy-1-phenylethyl)carbamate (2b): white solid, (2.21 g, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.38 (s, 1H), 4.76 (s, 1H), 3.78 (s, 2H), 2.87 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 139.5, 128.7, 127.7, 126.6, 80.0, 66.6, 56.9, 28.5.

(*S*)-*tert*-Butyl (1-hydroxy-3,3-dimethylbutan-2-yl)- carbamate (2c): white solid (2.02 g, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (s, 1H), 3.82 (m, 1H), 3.48 (m, 2H), 2.55 (m, 1H), 1.46 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 79.5, 63.0, 61.0, 33.7, 28.4, 26.8.

General procedure for the synthesis of cyclic sulfamidates 3

A solution of Boc-protected amino alcohol **2** (3.0 mmol) in CH_3CN (10 mL) was added slowly to the mixture of $SOCl_2$ (7.5 mmol) in CH_3CN (30 mL) at −40 °C under Argon atmosphere. Subsequently pyridine (15 mmol) was added at this temperature. Then the reaction system was allowed to warm to room temperature and stirred for another 3 h. The reaction was concentrated and then water (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed to give the crude cyclic sulfamidite as orange oil.

Crude cyclic sulfamidite (3.0 mmol) (prepared above) was dissolved in CH_3CN (6.0 mL) and cooled to 0 °C. Then a catalytic amount of $RuCl_3{\cdot}nH_2O$ (9.0 mg) was added and $NaIO_4$ (4.5 mmol) was added in portions at this temperature,followed by water (6.0 mL). The resulting mixture was allowed to warm to room temperature for another 1 h stirring. The reaction endpoint was the change of color from black to orange. The reactive mixture was poured into water and the aqueous phase was extracted with diethyl ether; the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent afforded the cyclic sulfamidate as a solid.

(*S*)-*tert*-Butyl 4-isopropyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (3a): white solid, (517 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (m, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 2.27 (m, 1H), 1.56 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 85.4, 67.0, 62.0, 30.0, 27.9, 18.0, 16.5.

(*S*)-*tert*-Butyl 4-phenyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (3b): white solid, (565 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 5H), 5.29 (m, 1H), 4.88 (m, 1H), 4.41 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.29, 136.9, 129.2, 126.2, 85.6, 71.8, 60.8, 27.8.

(*S*)-*tert*-Butyl 4-(*tert*-butyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (3c): white solid, (597 mg, 71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (m, 1H), 4.49 (d, J = 9.6 Hz, 1H), 4.18 (d, J = 6.0 Hz, 1H), 1.56 (s, 9H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 85.4, 67.7, 65.1, 35.5, 27.8, 25.7.

General procedure for the synthesis of phosphino carbamates 4

A solution of $KPPh_2$ (0.5 M in THF, 1.65 mmol) was added drop wise to a solution of **3** (1.5 mmol) in THF (15 mL), which had been cooled to −78 °C. After addition, the mixture was stirred at −60 °C for 0.5 h, then slowly warmed to room temperature and stirred overnight. H_2SO_4 (10 mL, 2N) and brine (20%, 30 mL) were added to the mixture, which was stirred at room temperature for 1 h. Saturated sodium carbonate was added to neutralize the mixture and make the solution basic. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The filtrate was evaporated to almost dryness, and then purification was carried out by flash chromatography on silica gel (petroleum ether to petroleum ether/EA 20:1 (v/v)).

(*S*)-*tert*-Butyl (1-(diphenylphosphino)-3-methylbutan-2-yl)carbamate (4a):[10o] colorless oil, (390 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.26 (m, 10H), 4.39 (d, J = 7.2 Hz, 1H), 3.60 (m, 1H), 2.33–2.10 (m, 2H), 1.90 (m, 1H), 1.41 (s, 9H), 0.86 (m, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −22.94.

(*S*)-*tert*-Butyl (2-(diphenylphosphino)-1-phenylethyl)carbamate (4b):[24] white solid, (395 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.23 (m, 15H), 5.01 (s, 1H), 4.70 (s, 1H), 2.53 (m, 2H), 1.39 (s, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −23.46.

(*S*)-*tert*-Butyl (1-(diphenylphosphino)-3,3-dimethylbutan-2-yl)carbamate (4c):[24] white solid, (414 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 10H), 4.24 (d, J = 10.4 Hz, 1H), 3.52–3.35 (m, 1H), 2.33–2.24 (m, 1H), 1.86

(m, 1H), 1.34 (s, 9H), 0.77 (s, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −20.83.

General procedure for the synthesis of phosphino amines 5

CF_3CO_2H (7.5 mmol) was added to a solution of **4** (0.3 mmol) in CH_2Cl_2 (10 mL) slowly at 0 °C and the mixture was stirred for 1 h, then allowed to warm to room temperature and stirred for 4 h. All the volatiles were removed under vacuum. Saturated Na_2CO_3 solution was added in the ice-water bath to neutralize the mixture and make it basic. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration and removal of solvent gave the crude product as colorless oil, which was then isolated by flash chromatography on silica gel (petroleum ether/EA, 2:1 to 1:1 (v/v)).

(*S*)-1-(Diphenylphosphino)-3-methylbutan-2-amine (5a):[19] colorless oil, (72 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.13 (m, 10H), 2.64–2.47 (m, 1H), 2.25 (m, 1H), 1.93–1.81 (m, 1H), 1.69–1.56 (m, 1H), 1.38 (s, 2H), 0.80 (m, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −21.50.

(*S*)-2-(Diphenylphosphino)-1-phenylethanamine (5b):[25] colorless oil, (82 mg, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.23 (m, 15H), 3.97 (m, 1H), 2.52 (m, 1H), 2.41 (m, 1H), 1.92 (s, 2H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −21.91.

(*S*)-1-(Diphenylphosphino)-3,3-dimethylbutan-2-amine (5c):[19] colorless oil, (81 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.10 (m, 10H), 2.46–2.27 (m, 2H), 1.75–1.62 (m, 1H), 1.47 (s, 2H), 0.77 (s, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −19.56 (s, 1H).

General procedure for the synthesis of bifunctional phosphine-squaramide catalysts 6

Under an argon atmosphere, to a solution of squaramide ester (0.6 mmol) in CH_2Cl_2 (5 mL) was added the solution of corresponding β-amino phosphine (0.6 mmol) in CH_2Cl_2 (2 mL). After stirring for five days at room temperature, the solid was filtered and washed by CH_2Cl_2 three times to afford phosphine-squaramide catalyst as a white solid.

Catalyst (6a): white solid, (180 mg, 52% yield); m.p. 230–232 °C; $[\alpha]_D^{20} = +11.7$ (*c* 0.10, DMSO); ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ 9.90 (s, 1H), 8.00 (s, 2H), 7.68 (s, 1H), 7.65(s, 1H), 7.51–7.17 (m, 10H), 4.05 (m, 1H), 2.48–2.31 (m, 1H), 1.99–1.88 (m, 1H), 1.20 (m, 1H), 0.91 (m, 6H); ^{31}P NMR (162 MHz, [D$_6$]DMSO) δ −21.66; ^{13}C NMR (100 MHz, [D$_6$]DMSO) δ 184.6, 180.7, 170.2, 162.2, 141.4, 138.4, 138.3, 138.2, 137.9, 133.3, 133.14, 133.07, 132.95, 132.0, 131.7, 129.3, 129.1, 129.0, 128.9, 125.2, 122.3, 118.4, 115.1, 58.4 (d, J = 15.2), 33.9 (d, J = 7.4), 32.3 (d, J = 12.3), 19.4, 17.2; HRMS (MALDI/DHB) Calcd for $C_{29}H_{26}F_6N_2O_2P$ ([M+H]$^+$): 579.1636; found: 579.1630; FTIR (KBr) ν_{max} (cm^{-1}): 3443, 3194, 3070, 2962, 1799, 1657, 1581.

Catalyst (6b): white solid, (158 mg, 43% yield); m.p. 240–242 °C; $[\alpha]_D^{20} = +14.5$ (*c* 0.12, DMSO); ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ 10.03 (s, 1H), 8.28 (m, 1H), 7.99 (s, 2H), 7.68 (s, 1H), 7.52–7.27 (m, 15H), 5.27 (s, 1H), 3.04–2.91 (m, 1H), 2.83 (m, 1H); ^{31}P NMR (162 MHz, [D$_6$]DMSO) δ −22.85; ^{13}C NMR (100 MHz, [D$_6$]DMSO) δ 184.5, 180.9, 169.0, 162.8, 142.3 (d, J = 6.1 Hz), 141.3, 138.2, 138.0, 137.9, 137.8, 133.3, 133.1, 132.9, 131.9, 131.6, 131.4, 129.3, 129.2, 129.04, 129.02, 128.95, 128.2, 127.7, 126.9, 124.9, 122.2, 118.5, 115.3, 56.5 (d, J = 19.1 Hz), 35.9 (d, J = 13.5 Hz); HRMS (MALDI/DHB) Calcd for $C_{32}H_{24}F_6N_2O_2P$ ([M+H]$^+$): 613.1480; found: 613.1474; FTIR (KBr) ν_{max} (cm^{-1}): 3418, 3140, 3070, 2925, 1795, 1670, 1562.

Catalyst (6c): white solid, (199 mg, 56% yield); m.p. 243–245 °C; $[\alpha]_D^{20} = +44.2$ (*c* 0.16, DMSO); ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ 8.07 (m, 3H), 7.31 (m, 12H), 4.87 (s, 2H), 3.96 (s, 1H), 2.45 (m, 1H), 2.36–2.21 (m, 1H), 1.87 (s, 1H), 0.83 (m, 6H); ^{31}P NMR (162 MHz, [D$_6$]DMSO) δ-22.14; ^{13}C NMR (100 MHz, [D$_6$]DMSO) δ 182.8, 182.7, 168.6, 167.1, 143.1, 138.7 138.6, 138.4, 138.3, 133.1, 133.0, 132.9, 132.8, 131.1, 130.8, 129.2, 129.0, 128.91, 128.85, 128.78, 127.8, 125.1, 122.4, 121.7, 57.3 (d, J = 13.7 Hz), 46.1, 34.0 (d, J = 11.5), 32.3 (d, J = 12.6), 19.3, 17.2; HRMS (MALDI/DHB) Calcd for $C_{30}H_{28}F_6N_2O_2P$ ([M+H]$^+$): 593.1793; found: 593.1787; FTIR (KBr) ν_{max} (cm^{-1}): 3167, 3070, 2965, 1793, 1644, 1562.

Catalyst (6d): white solid, (138 mg, 50% yield); m.p. 251–252 °C. $[\alpha]_D^{20} = +36.8$ (*c* 0.11, DMSO); ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ 9.38 (s, 1H), 7.57–7.14 (m, 15H), 4.17–3.95 (m, 1H), 2.35 (m, 1H), 1.93 (m, 1H), 0.90 (t, J = 6.6 Hz, 6H); ^{31}P NMR (162 MHz, [D$_6$]DMSO) δ −21.89. ^{13}C NMR (100 MHz, [D$_6$]DMSO) δ 183.6, 180.5, 169.4, 169.2, 159.6, 157.2, 138.5, 138.41, 138.36, 138.3, 135.9 (d, J = 2.2 Hz), 133.2, 133.1, 133.0, 132.9, 129.2, 129.1, 129.0, 128.9, 120.0 (d, J = 8.0 Hz), 116.5, 116.3, 58.0 (d, J = 18.3 Hz), 34.0 (d, J = 8.0 Hz), 32.4 (d, J = 13.0 Hz), 19.4, 17.2; HRMS (MALDI/DHB) Calcd for $C_{27}H_{27}FN_2O_2P$ ([M+H]$^+$): 461.1794; found: 461.1788; FTIR (KBr) ν_{max} (cm^{-1}): 3419, 3180, 3053, 2924, 1794, 1657, 1569.

Catalyst (6e): white solid, (128 mg, 45% yield); m.p. 282–284 °C. $[\alpha]_D^{20} = +49.1$ (*c* 0.11, DMSO); ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ 9.30 (s, 1H), 7.48–7.17 (m, 15H), 4.03–3.87 (m, 1H), 2.58 (m, 1H), 2.15 (m, 1H), 0.91 (s, 9H); ^{31}P NMR (162 MHz, [D$_6$]DMSO) δ −20.16; ^{13}C NMR (100 MHz, [D$_6$]DMSO) δ 183.5, 180.5, 169.6, 162.9, 159.6, 157.2, 138.7, 138.6, 138.3, 138.1, 135.9 (d, J = 2.3 Hz), 133.3, 133.2, 133.1, 133.0, 129.3, 129.01, 128.99, 128.9, 128.8, 120.0 (d, J = 8.0 Hz), 116.6, 116.3, 61.4 (d, J = 15.7 Hz), 36.1 (d, J = 7.3 Hz), 30.0 (d, J = 12.1 Hz), 26.0; HRMS (MALDI/DHB) Calcd for $C_{28}H_{29}FN_2O_2P$ ([M+H]$^+$): 475.1951; found: 475.1945; FTIR (KBr) ν_{max} (cm^{-1}): 3425, 3192, 3054, 2962, 1793, 1657, 1563.

Catalyst (6f): white solid, (163 mg, 46% yield); m.p. 267–269 °C; $[\alpha]_D^{20} = +28.0$ (*c* 0.16, DMSO); ^{1}H NMR (400 MHz, [D$_6$]DMSO) δ 9.84 (s, 1H), 8.01 (s, 2H), 7.68 (s, 1H), 7.64 (d, J = 10.4 Hz), 7.49–7.10 (m, 10H), 3.95 (m, 1H), 2.60 (d, J = 14.5 Hz, 1H), 2.19 (t, J = 12.2 Hz, 1H), 0.92 (s, 9H); ^{31}P NMR (162 MHz, [D$_6$]DMSO) δ −20.28; ^{13}C NMR (100 MHz, [D$_6$]DMSO) δ 189.3, 185.5, 175.1, 166.7, 146.3, 143.4, 143.3, 142.9, 142.8, 138.1, 138.0, 137.9, 137.8, 136.8, 136.4, 134.2, 133.8, 133.7, 129.8, 127.0, 123.1, 119.9, 66.5 (d, J = 15.9 Hz), 40.8 (d, J = 7.2 Hz), 34.7 (d, J = 11.9 Hz), 30.8; HRMS (MALDI/DHB) Calcd for $C_{30}H_{27}F_6N_2O_2P$ ([M+H]$^+$): 593.1793; found: 593.1787; FTIR (KBr) ν_{max} (cm^{-1}): 3403, 3144, 3070, 1965, 1798, 1657, 1580.

General procedure for the synthesis of bifunctional phosphine-squaramide catalysts 7

Under argon atmosphere, to a solution of diethyl squarate (1.0 mmol) in EtOH (5 mL) was added the solution of corresponding β-amino phosphine (1.0 mmol) in EtOH (5 mL), after stirring for 2 days at room temperature, the desired product was isolated by flash chromatography on silica gel (petroleum ether/EA, 6:1 to 4:1 (v/v)).

Catalyst (7a): colorless oil, (352 mg, yield 89%); $[\alpha]_D^{20} = -10.0$ (*c* 0.22, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.23 (m, 10H), 6.87 (m, 1H), 4.62 (m, 2H), 3.55 (m, 1H), 2.50–2.28 (m, 2H), 1.96–1.91 (m, 1H), 1.30 (t, J=7.2 Hz, 3H), 0.92 (m, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −21.84, −23.35; ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 182.5, 176.9, 172.0, 137.9 (d, J=2.5 Hz), 137.3 (d, J=2.5 Hz), 133.2, 133.0, 132.7, 132.5, 129.1, 128.9, 128.7, 128.63, 128.61, 128.57, 69.5, 59.1 (d, J=13.9 Hz), 34.1 (d, J=7.1 Hz), 32.4 (d, J=14.5 Hz), 19.1, 17.2, 15.7; HRMS (MALDI/DHB) Calcd for $C_{23}H_{27}NO_3P$ ($[M+H]^+$): 396.1729; found: 396.1723; FTIR (KBr) ν_{max} (cm^{-1}): 3250, 3028, 2960, 1804, 1703, 1607.

Catalyst (7b): colorless oil, (326 mg, 80% yield); $[\alpha]_D^{20} = +18.5$ (*c* 0.18, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.27 (m, 10H), 6.83 (d, J=10.4 Hz, 1H), 4.67 (m, 1H), 4.53 (m, 1H), 3.42 (m, 1H), 2.49 (m, 1H), 2.29–2.16 (m, 1H), 1.29 (t, J=7.1 Hz, 3H), 0.91 (s, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −20.18, −21.13; ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 182.5, 176.8, 172.4, 138.3, 136.9, 133.6, 133.4, 132.5, 132.2, 129.2, 128.8, 128.7, 128.61, 128.59, 128.5, 69.4, 62.3 (d, J=13.5 Hz), 36.1 (d, J=6.2 Hz), 29.9 (d, J=13.5 Hz), 25.9, 15.7; HRMS (MALDI/DHB) Calcd for $C_{24}H_{29}NO_3P$ ($[M+H]^+$): 410.1885; found: 410.1890; FTIR (KBr) ν_{max} (cm^{-1}): 3254, 3066, 2925, 1801, 1693, 1602.

General procedure of the asymmetric MBH reaction

To a solution of catalyst (3.0 mg, 5 mol%) in ethyl acetate (0.5 mL) at room temperature was added acrylate ester (0.5 mmol); after 10 min, when the solution became clear, *N*-alkyl isatin (0.1 mmol) was added. The reaction was monitored by TLC until the *N*-alkyl isatin disappeared. Then the resulting mixture was condensed on a rotary evaporator and the target compounds were purified by flash chromatography on silica gel (petroleum ether/EA, 4:1 (v/v)). The *ee* values were determined by HPLC with chiral column.

(*R*)-Methyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10a):[11] yellow solid, (22.7 mg, 92% yield); HPLC (Chiralpak OD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major}=11.958 min, t_{minor}=19.848 min, ee=94%; $[\alpha]_D^{20} = -49.6$ (*c* 0.10, CH_2Cl_2); m.p. 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J=8.4 Hz, 1H), 7.16 (d, J=7.2 Hz, 1H), 7.04 (5, J=7.5 Hz, 1H), 6.85 (d, J=7.8 Hz, 1H), 6.55 (s, 1H), 6.46 (s, 1H), 4.37 (s, 1H), 3.61 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 165.1, 144.5, 139.2, 130.2, 129.5, 127.9, 123.8, 123.0, 108.7, 76.2, 52.1, 26.4; FTIR (KBr) ν_{max} (cm^{-1}): 3377, 3067, 2924, 2853, 1700, 1615, 1495.

(*R*)-Methyl 2-(4-bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10b): yellow solid, (24.4 mg, 75% yield); HPLC (Chiralpak OD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major}=27.384 min, t_{minor}=18.037 min, ee=86%; $[\alpha]_D^{20} = -24.3$ (c 0.10, CH_2Cl_2); m.p. 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.03 (m, 2H), 6.74 (d, J=7.5 Hz, 1H), 6.67 (s, 1H), 6.50 (s, 1H), 3.90 (s, 1H), 3.55 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 165.0, 146.6, 136.8, 131.4, 130.7, 127.3, 119.5, 107.6, 77.3, 52.1, 26.7; HRMS (MALDI/DHB) Calcd for $C_{13}H_{13}BrNO_4$ ($[M+H]^+$): 326.0028; found: 326.0022; FTIR (KBr) ν_{max} (cm^{-1}): 3394, 3058, 2923, 2853, 1704, 1605, 1458.

(*R*)-Methyl 2-(5-bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10c): yellow oil, (30.0 mg, 92% yield); HPLC (Chiralpak AD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major}=22.482 min, t_{minor}=15.680 min, ee=93%; $[\alpha]_D^{20} = -42.6$ (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 1H), 7.26 (m, 1H), 6.74 (d, J=8.3 Hz, 1H), 6.58 (s, 1H), 6.49 (s, 1H), 4.30 (s, 1H), 3.63 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 164.8, 143.5, 138.7, 132.9, 131.4, 128.4, 127.1, 115.6, 110.2, 76.0, 52.2, 26.6; HRMS (ESI Positive) Calcd for $C_{13}H_{12}BrNNaO_4$ ($[M+Na]^+$): 347.9847; found: 347.9842; FTIR (KBr) ν_{max} (cm^{-1}): 3367, 3068, 2924, 2853, 1716, 1610.

(*R*)-Methyl 2-(6-bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10d): light yellow solid, (30.2 mg, 93% yield); HPLC (Chiralpak OD-H column, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major}=10.940 min, t_{minor}=21.407 min, ee=94%; $[\alpha]_D^{20} = -61.7$ (*c* 0.10, CH_2Cl_2); m.p. 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 1H), 7.01 (m, 2H), 6.56 (s, 1H), 6.46 (s, 1H), 4.42 (s, 1H), 3.62 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 164.9, 145.8, 138.8, 128.4, 128.2, 125.8, 125.1, 123.9, 112.3, 75.7, 52.1, 26.6: HRMS (ESI Positive) Calcd for $C_{13}H_{12}BrNNaO_4$ ($[M+Na]^+$): 347.9847; found: 347.9842; FTIR (KBr) ν_{max} (cm^{-1}): 3380, 3035, 2923, 2852, 1710, 1606.

(*R*)-Methyl 2-(7-bromo-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10e): yellow oil, (27.4 mg, 84% yield); HPLC (Chiralpak AD-H, 90:10 *n*hexane:*i*PrOH, 1 mL min^{-1}, 254 nm): t_{major}=22.670 min, t_{minor}=15.670 min, ee=92%; $[\alpha]_D^{20} = -63.8$ (*c* 0.21, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J=8.2, 1.0 Hz, 1H), 7.06 (dd, J=7.3, 1.0 Hz, 1H), 6.87 (t, J=7.7 Hz, 1H), 6.56 (s, 1H), 6.48 (s, 1H), 4.49 (s, 1H), 3.63 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 164.9, 141.8, 139.0, 135.7, 132.5, 128.2, 124.2, 122.9, 102.9, 75.4, 52.1, 30.1; HRMS (ESI Positive) Calcd for $C_{13}H_{12}BrNNaO_4$ ($[M+Na]^+$): 347.9847; found: 347.9842; FTIR (KBr) ν_{max} (cm^{-1}): 3348, 2994, 2952, 2852, 1715, 1608.

(*R*)-Methyl 2-(3-hydroxy-1,5-dimethyl-2-oxoindolin-3-yl)acrylate (10f):[11] yellow oil, (23.5 mg, 90% yield); HPLC (Chiralpak AD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major}=22.670 min, t_{minor}=15.670 min, ee=92%; $[\alpha]_D^{20} = -40.0$ (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J=7.8 Hz, 1H), 6.98 (s, 1H), 6.74 (d, J=7.9 Hz, 1H), 6.55 (s, 1H), 6.46 (s, 1H), 4.33 (s, 1H), 3.62 (s, 3H), 3.20 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 165.1, 142.1, 139.3, 132.6, 130.3, 129.4, 127.8, 124.6, 108.4, 76.3, 52.0, 26.5, 21.0; FTIR (KBr) ν_{max} (cm^{-1}): 3363, 3118, 2923, 2853, 1705, 1624.

(*R*)-Methyl 2-(3-hydroxy-5-methoxy-1-methyl-2-oxoindolin-3-yl)acrylate (10g): yellow oil, (21.7 mg, 76% yield); HPLC (Chiralpak AD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major}=31.612 min, t_{minor}=25.908 min, ee=94%; $[\alpha]_D^{20} = -31.8$ (*c* 0.13, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78–6.68 (m, 1H), 6.72–6.68 (m, 2H), 6.48 (s, 1H), 6.39 (s, 1H), 4.43 (s, 1H), 3.68 (s, 3H), 3.55 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4,

165.0, 156.3, 139.2, 137.8, 130.7, 128.0, 114.5, 111.1, 109.1, 76.6, 55.8, 52.1, 29.7, 26.5; HRMS (MALDI/DHB) Calcd for $C_{14}H_{16}NO_5$ ($[M+H]^+$): 278.1028; found: 278.1023; FTIR (KBr) ν_{max} (cm^{-1}): 3315, 2997, 2924, 2852, 1709, 1605.

(*R*)-Methyl 2-(5-fluoro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10h): yellow oil, (24.4 mg, 92% yield); HPLC (Chiralpak AD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 21.943 min, t_{minor} = 15.282 min, ee = 93%; $[\alpha]_D^{20} = -47.5$ (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (m, 1H), 6.92 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.78 (m, 1H), 6.57 (s, 1H), 6.48 (s, 1H), 4.52 (s, 1H), 3.63 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 164.9, 160.6, 158.2, 140.4, 138.9, 131.1, 128.2, 116.3, 116.1, 112.2, 112.0, 109.2, 76.2, 52.1, 26.6; HRMS (MALDI/DHB) Calcd for $C_{13}H_{13}FNO_4$ ($[M+H]^+$): 266.0829; found: 266.0823; FTIR (KBr) ν_{max} (cm^{-1}): 3353, 2955, 2924, 2853, 1711, 1620.

(*R*)-Methyl 2-(5-chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10i):[11] yellow oil, (25.9 mg, 92% yield); HPLC (Chiralpak AD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 20.000 min, t_{minor} = 14.042 min, ee = 93%; $[\alpha]_D^{20} = -44.7$ (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 4.0, 4.0 Hz, 1H), 7.06 (d, *J* = 4.0 Hz, 1H), 6.71 (d, *J* = 12.0 Hz, 1H),6.50 (s, 1H), 6.41 (s, 1H), 4.46 (s, 1H), 3.56 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 164.9, 143.0, 138.8, 131.2, 130.0, 128.3, 128.3, 124.4, 109.7, 76.0, 52.1, 26.6; FTIR (KBr) ν_{max} (cm^{-1}): 3316, 3075, 2952, 2914, 2853, 1707, 1611.

(*R*)-Methyl 2-(7-chloro-3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10j): yellow oil, (25.9 mg, 92% yield); HPLC (Chiralpak AD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 14.862 min, t_{minor} = 11.283 min, ee = 93%; $[\alpha]_D^{20} = -68.9$ (*c* 0.14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.03 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.98–6.87 (m, 1H), 6.58 (s, 1H), 6.48 (s, 1H), 4.47 (s, 1H), 3.63 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 164.9, 140.3, 139.0, 132.4, 132.3, 128.2, 123.8, 122.3, 116.0, 75.5, 52.1, 29.9; HRMS (MALDI/DHB) Calcd for $C_{13}H_{13}ClNO_4$ ($[M+H]^+$): 282.0533; found: 282.0528; FTIR (KBr) ν_{max} (cm^{-1}): 3355, 2997, 2953, 2924, 2853, 1716, 1609.

(*R*)-Methyl 2-(1-ethyl-3-hydroxy-2-oxoindolin-3-yl)acrylate (10k):[11] light yellow solid, (23.3 mg, 89% yield); HPLC (Chiralpak OD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 9.233 min, t_{minor} = 12.063 min, ee = 92%; $[\alpha]_D^{20} = -55.3$ (*c* 0.10, CH_2Cl_2); m.p. 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 1H), 7.20–7.11 (m, 1H), 7.01 (m, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.56 (s, 1H), 6.46 (s, 1H), 4.37 (s, 1H), 3.82 (m, 1H), 3.70 (m, 1H), 3.59 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 165.0, 143.6, 139.3, 130.1, 129.8, 128.0, 123.9, 122.8, 108.7, 76.1, 51.9, 34.9, 12.2; FTIR (KBr) ν_{max} (cm^{-1}): 3327, 3055, 2981, 1950, 2852, 1698, 1612.

(*R*)-Methyl 2-(1-allyl-3-hydroxy-2-oxoindolin-3-yl)acrylate (10l): light yellow solid, (23.5 mg, 80% yield); HPLC (Chiralpak OD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 8.380 min, t_{minor} = 12.428 min, ee = 93%; $[\alpha]_D^{20} = -48.0$ (*c* 0.10, CH_2Cl_2); m.p. 127–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 1H), 7.21–7.11 (m, 1H), 7.02 (m, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.56 (s, 1H), 6.46 (s, 1H), 5.87 (m, 1H), 5.37 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.24 (dd, *J* = 10.3, 1.1 Hz, 1H), 4.40 (m, 1H), 4.29 (m, 1H), 4.24 (s, 1H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 165.0, 143.7, 139.2, 131.2, 130.0, 129.5, 128.0, 123.8, 123.0, 117.9, 109.6, 76.1, 52.0, 42.7; HRMS (ESI Positive) Calcd for $C_{15}H_{15}NO_4Na$ ($[M+Na]^+$): 296.0899; found: 296.0893; FTIR (KBr) ν_{max} (cm^{-1}): 3321, 3120, 2947, 2925, 2851, 1700, 1612.

(*R*)-Methyl 2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)acrylate (10m):[11] yellow solid, (27.2 mg, 84% yield); HPLC (Chiralpak OD-H column, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 11.150 min, t_{minor} = 15.542 min, ee = 90%; $[\alpha]_D^{20} = -35.3$ (*c* 0.10, CH_2Cl_2); m.p. 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.1 Hz, 2H), 7.34–7.23 (m, 3H), 7.21–7.12 (m, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.59 (s, 1H), 6.48 (s, 1H), 4.91 (m, 2H), 4.25 (s, 1H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 165.1, 143.7, 139.1, 135.5, 130.1, 129.6, 128.8, 128.2, 127.6, 123.8, 123.1, 109.8, 76.2, 52.0, 44.2; FTIR (KBr) ν_{max} (cm^{-1}): 3414, 3060, 2955, 2924, 2853, 1708, 1611.

(*R*)-Methyl 2-(3-hydroxy-1-isopropyl-2-oxoindolin-3-yl)-acrylate (10n): light yellow solid, (22.0 mg, 80% yield); HPLC (Chiralpak AD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 15.788 min, t_{minor} = 13.372 min, ee = 92%; $[\alpha]_D^{20} = -10.7$ (*c* 0.10, CH_2Cl_2). m.p. 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.99–6.85 (m, 2H), 6.48 (s, 1H), 6.39 (s, 1H), 4.59–4.40 (m, 1H), 4.21 (s, 1H), 3.51 (s, 3H), 1.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 164.9, 143.2, 139.4, 130.0, 129.8, 127.9, 124.1, 122.4, 110.2, 75.9, 51.9, 44.2, 19.1, 19.0; HRMS (ESI Positive) Calcd for $C_{15}H_{17}NO_4Na$ ($[M+Na]^+$): 298.1055; found: 298.1050; FTIR (KBr) ν_{max} (cm^{-1}): 3461, 3329, 3054, 2983, 2941, 2852, 1716, 1610.

(*R*)-Methyl 2-(3-hydroxy-2-oxo-1-pentylindolin-3-yl)acrylate (10o): light yellow solid, (24.8 mg, 82% yield); HPLC (Chiralpak OD-H column, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 10.672 min, t_{minor} = 6.512 min, ee = 89%; $[\alpha]_D^{20} = -40.0$ (*c* 0.10, CH_2Cl_2); m.p. 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 1H), 7.21–7.12 (m, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.54 (s, 1H), 6.44 (s, 1H), 4.35 (s, 1H), 3.77–3.63 (m, 2H), 3.60 (s, 3H), 1.79–1.64 (m, 2H), 1.37 (m,4H), 0.95–0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 165.0, 144.0, 139.3, 130.0, 129.8, 127.9, 123.9, 122.7, 108.9, 76.1, 51.9, 40.3, 29.1, 26.8, 22.4, 14.0; HRMS (ESI Positive) Calcd for $C_{12}H_{10}NO_4Na$ ($[M+Na]^+$): 255.0508; found: 255.0504; FTIR (KBr) ν_{max} (cm^{-1}): 3345, 3265, 3059, 2955, 2926, 2857, 1715, 1612.

(*R*)-Ethyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10p):[13a] yellow oil, (24.3 mg, 93% yield); HPLC (Chiralpak OD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 10.970 min, t_{minor} = 17.285 min, ee = 90%; $[\alpha]_D^{20} = -39.9$ (*c* 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.50 (s, 1H), 6.36 (s, 1H), 4.35–4.21 (m, 1H), 4.03–3.85 (m, 2H), 3.15 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 164.6, 144.5, 139.4, 130.1, 129.6, 127.8, 123.8, 123.0, 108.6, 76.2, 61.0, 26.4, 13.8; FTIR (KBr) ν_{max} (cm^{-1}): 3356, 2924, 2853, 1708, 1613.

(*R*)-Butyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate (10q):[13a] yellow oil, (24.0 mg, 83% yield); HPLC (Chiralpak OD-H, 90:10 *n*hexane/iPrOH, 1 mL min^{-1}, 254 nm): t_{major} = 18.030 min, t_{minor} = 25.602 min, ee = 92%; $[\alpha]_D^{20} = -30.0$ (*c* 0.08, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.50 (s, 1H), 6.36 (s, 1H), 4.30 (s, 1H), 3.99–3.80 (m, 2H), 3.14 (s, 3H), 1.45–1.34 (m, 2H), 1.13 (m,

2H), 0.83–0.76 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 164.7, 144.5, 139.4, 130.1, 129.6, 127.9, 123.8, 123.0, 108.6, 76.2, 64.9, 30.4, 26.4, 19.0, 13.7; FTIR (KBr) ν_{max} (cm^{-1}): 3342, 3058, 2958, 2926, 2854, 1709, 1613.

(*R*)-*tert*-Butyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-acrylate (10r):[13a] yellow oil, (21.4 mg, 74% yield); HPLC (Chiralpak AS-H, 90:10 *n*hexane/iPrOH, 0.8 mL min^{-1}, 254 nm): t_{major} = 13.903 min, t_{minor} = 9.243 min, ee = 95%; $[\alpha]_D^{20} = -8.8$ (*c* 0.09, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 0.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.51 (s, 1H), 6.28 (s, 1H), 3.90 (s, 1H), 3.22 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 164.0, 144.4, 140.3, 130.1, 129.8, 127.2, 123.9, 123.0, 108.4, 81.8, 76.2, 27.7, 26.4; FTIR (KBr) ν_{max} (cm^{-1}): 3339, 3058, 2954, 2924, 2853, 1711, 1613.

Synthesis of γ-butyrolactone 11[26]

To a solution of MBH adduct **10c** (0.2 mmol) in 4 mL cosolvent of THF/water (9:1 v/v) was added $NaBH_4$ in an ice-water bath. After the consumption of MBH adduct **10c**, which was monitored by TLC, the reaction was quenched by a saturated NH_4Cl solution. The aqueous phase was extracted by CH_2Cl_2 (5 mL × 3), then the combined organic phase was dried with anhydrous Na_2SO_4, followed by filtration. The filtrate was concentrated and the residue was purified by silica gel column chromatography (petroleum ether/EA, 6:1 (v/v)). The product was isolated as yellow oil, (18.6 mg, 62% yield); HPLC (Chiralpak OJ-H, 90:10 *n*hexane:*i*PrOH, 1.0 mL min^{-1}, 254 nm): t_{major} = 15. 207 min; t_{minor} = 9.587 min, ee = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 6.29 (d, *J* = 8.9 Hz, 1H), 5.25 (s, 1H), 4.08–3.95 (m, 1H), 3.16 (m, 1H), 2.86 (s, 3H), 2.70–2.59 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 133.0, 128.7, 128.4, 108.4, 107.0, 106.4, 89.1, 73.1, 45.6, 31.4, 11.3.

Synthesis of polycyclic compound 12

A mixture of MBH adduct **10c** (0.1 mol), isatin (0.12 mol), L-proline (0.12 mol) and MK-10 (1.0 equiv for MBH adduct) in methanol was heated to reflux for 3 h until the MBH adduct **10c** was disappeared. The reactive system was filtered through a pad of Celite, concentrated, purified by silica gel column chromatography (petroleum ether/EA, 1:2 (v/v)). The product was isolated as yellow solid, (49.5 mg, 84% yield); HPLC (Chiralpak OD-H, 85:15 *n*hexane/iPrOH, 1.0 mL min^{-1}, 254 nm): t_{major} = 13.877 min, t_{minor} = 24.843 min, ee = 94%; m.p. 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.40 (m, 1H), 7.34 (s, 1H), 7.27–7.22 (m, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.98 (s, 1H), 4.93–4.89 (m, 1H), 3.53 (s, 1H), 3.49 (s, 3H), 3.26 (m, 1H), 3.19 (s, 3H), 2.63 (m, 1H), 2.34 (m, 1H), 2.19 (m, 1H), 1.94 (m, 2H), 1.44–1.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 176.3, 172.2, 143.5, 140.9, 132.7, 131.2, 129.4, 129.3, 127.5, 125.3, 123.2, 115.2, 110.5, 109.4, 68.2, 66.0, 60.5, 52.2, 42.8, 26.8, 26.2, 26.0, 21.1, 14.2; HRMS (ESI Positive) Calcd for $C_{25}H_{25}BrN_3O_5$ ($[M+H]^+$): 526.0978; found: 526.0938.

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