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Enantioselective Synthesis of 3,3-Disubstituted Oxindoles Bearing Two Different Heteroatoms at the C3 Position by Organocatalyzed Sulfenylation and Selenenylation of 3-Pyrrolyl-oxindoles

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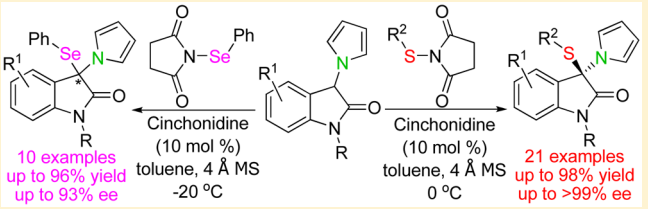
Supporting Information

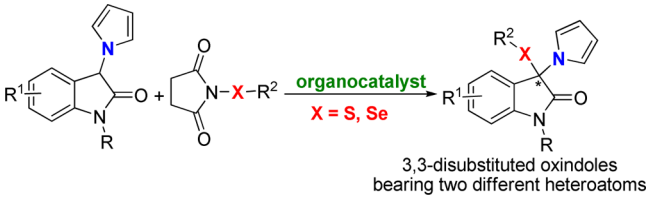
ABSTRACT: Catalytic asymmetric sulfenylation and selenenylation of 3-pyrrolyl-oxindoles for the synthesis of 3,3-disubstituted oxindoles bearing two different heteroatoms at the C3 position have been achieved with commercially available cinchonidine as catalyst. A wide range of optically active 3-thio-3-pyrrolyl-oxindoles and 3-seleno-3-pyrrolyl-oxindoles could be smoothly obtained under mild conditions with satisfactory results. The promising applicability of the protocol was also demonstrated by large-scale production.



3,3-Disubstituted oxindoles are common structural features of numerous pharmaceuticals and biologically active compounds.[1] Enormous synthetic efforts have been invested in the development of various catalytic asymmetric methods for the construction of diverse 3,3-disubstituted oxindole skeletons in the past few years.[2] To the best of our knowledge, most of the published studies mainly focused on the synthesis of 3,3-disubstituted oxindoles bearing an all-carbon quaternary stereocenter at the C3 positions.[3] Recently, some strategies for the preparation of 3,3-disubstituted oxindoles containing an oxygen or a nitrogen atom at the C3 positions are also reported.[4] However, in contrast, the relevant research on enantioselective synthesis of 3,3-disubstituted oxindoles featuring two different heteroatoms at the C3 position remains underdeveloped,[5] despite an increasing number of studies that suggest that these structural motifs have promising potential for the research and development of new biopharmaceutics.[2a,b,h,k] In particular, 3,3-disubstituted oxindoles containing both nitrogen and sulfur at the C3 position are useful and have been paid much more attention by synthetic organic chemists.[6] However, only a few studies involved the catalytic enantioselective synthesis of them.[7] Accordingly, the development of efficient methods for the generation of 3,3-disubstituted oxindoles bearing two different heteroatoms at the C3 position is still highly desirable and also a challenge.

Recently, we disclosed that 3-pyrrolyl-oxindoles, directly connecting the nitrogen atom at the C3 positions, could serve as highly reactive nucleophiles reacting with diverse electrophiles.[8] On the other hand, *N*-(arylsulfanyl)succinimides and *N*-(alkylsulfanyl)succinimides have been proven to be a type of potent sulfenylation reagents for the formation of a C−S bond in organic synthesis.[9] Meanwhile, a variety of methods for the construction of sulfur-containing tetrasubstituted stereocenters with these reagents have been developed.[10] On the basis of these considerations, and as part of our research program aimed at establishing new methods for enantioselective synthesis of chiral oxindole compounds,[11] we are interested in the generation of 3,3-disubstituted oxindoles bearing two different heteroatoms (*N*,*S*- and *N*,*Se*-) at the C3 position with 3-pyrrolyl-oxindoles as starting materials by asymmetric organocatalysis (Scheme 1). Herein, we hope to report our research results on this subject. *Notably, this work will represent the first example of the organocatalytic enantioselective synthesis of selenium-containing oxindoles.*[12]

Scheme 1. Approaches for the Synthesis of 3,3-Disubstituted Oxindoles Bearing *N*,*S*- and *N*,*Se*-Heteroatoms with 3-Pyrrolyl-oxindoles as Starting Materials



At the outset, we selected the reaction of 3-pyrrolyl-oxindole **1a**[13] and *N*-(phenylsulfanyl)succinimide **2a** in dichloromethane to determine the catalytic activity and enantioselectivity of

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organocatalysts **A**–**F** (Figure 1). With the commercially available cinchona alkaloids **A**–**D** as catalysts, the reactions

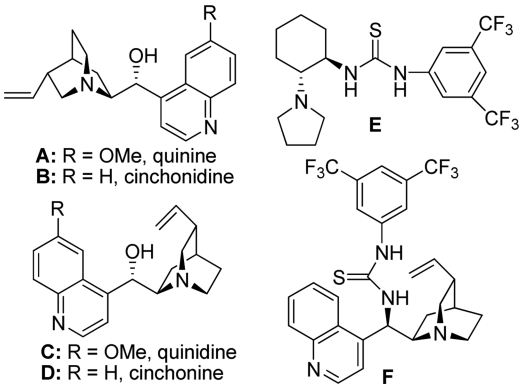
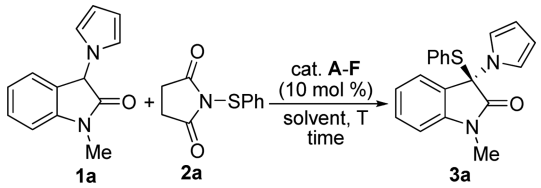


Figure 1. Catalysts tested in the sulfenylation of 3-pyrrolyl-oxindole.

proceeded smoothly at room temperature and furnished the desired 3-thio-3-pyrrolyl-oxindole **3a** in excellent yields but with moderate to good enantioselectivies (Table 1, entries 1–4).[14] Chiral bifunctional thiourea-tertiary amine catalysts **E** and **F** showed marked inferior catalytic activity and asymmetric induction capability (Table 1, entries 5 and 6). By comparison, cinchonidine **B** was identified as the optimal catalyst. Afterward, the effect of solvent on the sulfenylation of 3-pyrrolyl-oxindole was examined (Table 1, entries 7–11). It was found that the use of toluene as a reaction medium was superior to other solvents, such as chloroform, 1,2-dichloroethane, THF, and hexane (Table 1, entry 9 vs entries 7–8, 10–11). In toluene, the reaction was carried out at 0 °C, and **3a** could be obtained in 97% yield with 91% ee within 14 h (Table 1, entry 12). Further decreasing the temperature to −20 °C, the reaction afforded **3a** in 93% yield also with 91% ee, but a longer reaction period of 48 h was needed (Table 1, entry 13). When the catalyst loading was reduced from 10 to 5 mol %, there were no changes in the reactivity and enantioselectivity, but 30 h was also needed (Table 1, entry 14). Ultimately, using 4 Å molecular sieves (MS) as additive, the reaction proceeded well at 0 °C with 10 mol % **B**, giving **3a** in 95% yield with 93% ee after 18 h (Table 1, entry 15).

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	cat.	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	DCM	**A**	25	24	96	50
2	DCM	**B**	25	13	98	78
3	DCM	**C**	25	14	94	49(−)
4	DCM	**D**	25	14	95	67(−)
5	DCM	**E**	25	50	75	6(−)
6	DCM	**F**	25	14	trace	
7	$CHCl_3$	**B**	25	10	95	82
8	DCE	**B**	25	7	93	77
9	toluene	**B**	25	5	98	85
10	THF	**B**	25	12	92	35
11	hexane	**B**	25	15	96	66
12	toluene	**B**	0	14	97	91
13	toluene	**B**	−20	48	93	91
14	toluene	**B**	0	30	92	91[d]
15	toluene	**B**	0	18	95	93[e]

[a]Unless specified, the reactions were carried out using **1a** (0.1 mmol), **2a** (0.12 mmol), and catalyst (10 mol %) in 2.0 mL of solvent for the indicated time. [b]Isolated yield. [c]Determined by Chiral HPLC analysis. [d]5 mol % **B** was used. [e]50 mg 4 Å MS was used. DCM = dichloromethane. DCE = 1,2-dichloroethane.

Under the optimal reaction conditions, we then focused on the variation of 3-pyrrolyl-oxindoles and sulfur reagents. As shown in Scheme 2, a survey of 3-pyrrolyl-oxindole substrates was first conducted (see **3b**–**i**). The steric size of the *N*-protecting group does not seem to be important to the reactivity and enantioselectivity because ethyl (**3b**), phenyl (**3c**), and benzyl (**3d**) gave very similar results as methyl (**3a**). Afterward, introducing different substituent groups on the phenyl ring of oxindole, it was observed that the reactions with *N*-(phenylsulfanyl)succinimide **2a** proceeded smoothly to furnish the corresponding products in 87–97% yield with 89–92% ee regardless of the electron nature and position of the substituents on the phenyl rings (see **3e**–**i**). These results suggest that the structure characteristic of 3-pyrrolyl-oxindole substrates has less effect on the reactivity and the enantioselectivity. Then, we turned our attention to test the *N*-thiosuccinimide component by reacting with **1a**. For *N*-(arylsulfanyl)succinimides bearing electron-withdrawing substituents, such as Cl and Br, the reactions provided **3j**–**l** in excellent yields with very high ee values. Meanwhile, similar results could also be obtained for the electron-donating groups incorporating to *N*-(arylsulfanyl)succinimide substrates (see **3n**–**p**). However, when *ortho*-methyl-substituted *N*-(phenylsulfanyl)succinimide was used as precursor, the reactivity was dramatically reduced and the selectivity was clearly diminished (see **3m**), probably due to the high steric hindrance of *ortho*-substitution. In the case of *N*-(2-naphthylsulfanyl)succinimide as substrate, the reaction proceeded well under the standard conditions and delivered **3q** with excellent results. The use of *N*-(arylsulfanyl)succinimide with a heteroaromatic group, such as thienyl, also afforded the desired product **3r** in 72% yield with >99% ee, but a 6 day long reaction time was needed. Replacing *N*-(arylsulfanyl)succinimides with *N*-(alkylsulfanyl)-succinimides for the reaction with **1a**, the reactions not only furnished moderate enantioselectivity but also showed very low reactivity (see **3s**–**t**), which may be due to the electronic nature of alkyl substituents on the S atom. These two cases revealed that the *N*-(arylsulfanyl)succinimide was crucial to the reactivity. Ultimately, using the *N*-unprotected 3-pyrrolyl-oxindole as nucleophile in a reaction with **2a**, the product **3u** could be obtained after 10 h in 78% yield with only 50% ee for the influence of the electronic nature and the steric hindrance of the substituents on the N atom.

To evaluate the applicability of our method, the preparation of compound **3a** was attempted on a gram scale. As shown in Scheme 3, the reaction between 3.5 mmol of **1a** and 4.2 mmol of **2a** in toluene with 10 mol % cinchonidine at 0 °C for 22 h, which is 35 times larger than the scale of the original reaction shown in Table 1, entry 15, proceeded smoothly to afford product **3a** in 1.09 g and without loss in the reactivity and enantioselectivity. This experiment suggests that the protocol is amenable to large-scale production. The absolute R-configuration of **3a** was determined by X-ray analysis.[14] The

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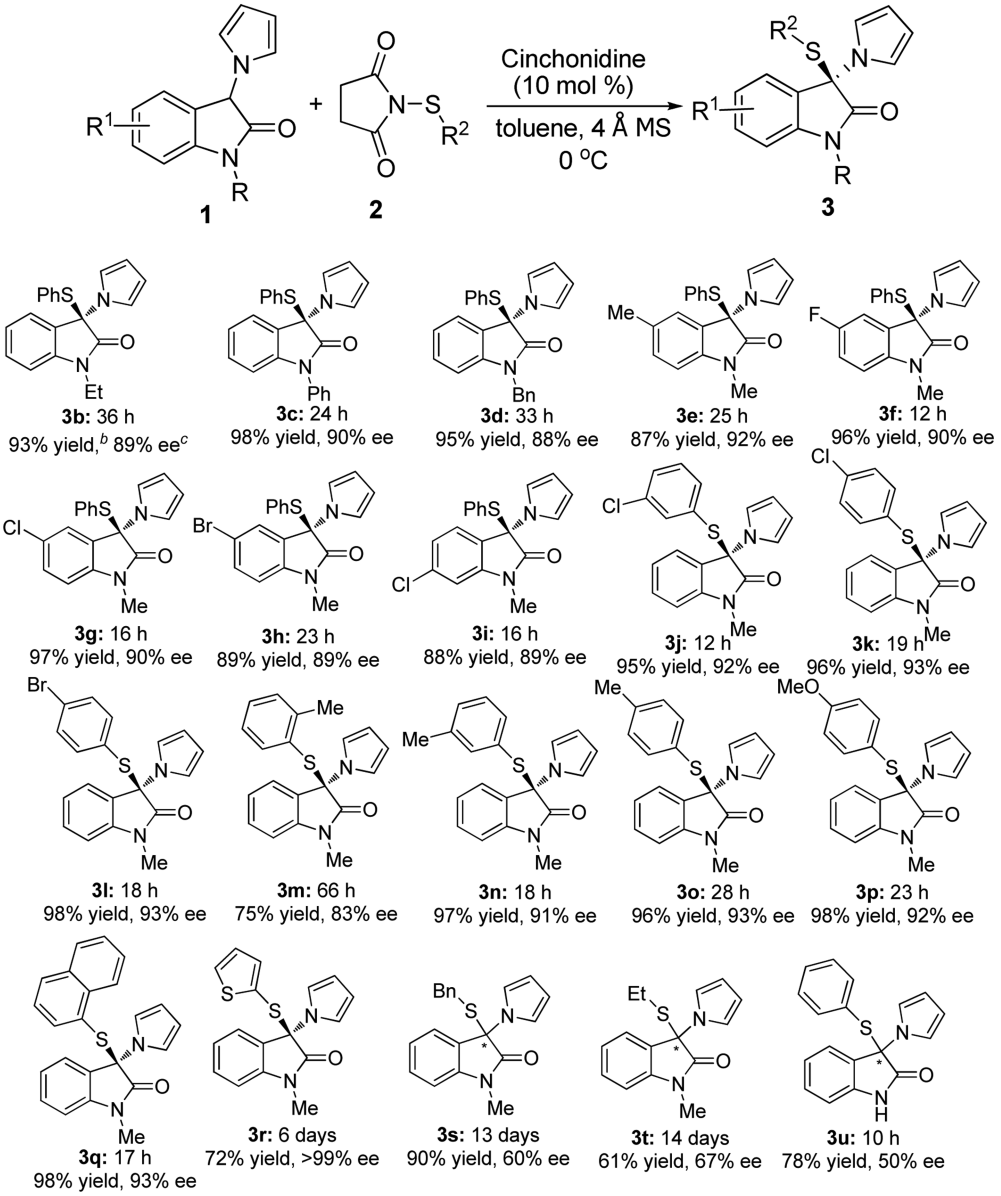
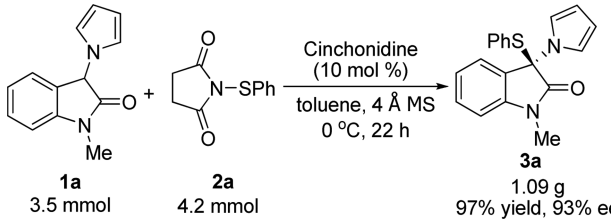
Scheme 2. Substrate Scope for the Asymmetric Sulfenylation of 3-Pyrrolyl-oxindoles[a]



[a]Unless specified, the reactions were carried out using **1** (0.1 mmol), **2** (0.12 mmol), and cinchonidine (10 mol %) in 2.0 mL of toluene with 50 mg of 4 Å MS at 0 °C for the indicated time. [b]Isolated yield. [c]Determined by Chiral HPLC analysis.

Scheme 3. Synthesis of 3a on a Gram Scale



configurations of the other products **3b–r** in Scheme 2 were assigned on the assumption of a uniform mechanistic pathway.

Following these promising results, we attempted to further extend the methodology to the enantioselective selenenylation of 3-pyrrolyl-oxindoles for the construction of *N*,*Se*-containing oxindoles. As shown in Scheme 4, with *N*-(phenylseleno)-succinimide **4** as the electrophilic selenium source, a series of 3-seleno-3-pyrrolyl-oxindole derivatives could be smoothly generated in the presence of 10 mol % cinchonidine under mild reaction conditions. The reaction is insensitive to the electronic nature and the steric hindrance of the *N*-protecting group of 3-pyrrolyl-oxindoles (see **5a–d**), but the existence of the *N*–*H* moiety in oxindole seems to display an impact on the asymmetric induction (see **5e**). In addition, electron-withdrawing substitution on the oxindole aromatic ring does not affect the reactivity and enantioselectivity, regardless of its electronic property and position on the phenyl ring (see **5f–i**). Installing an electron-donating group on the oxindole aromatic ring is not detrimental to the asymmetric process, giving product **5j** in 88% yield with 82% ee.

In conclusion, we have developed an organocatalytic asymmetric sulfenylation and selenenylation of 3-pyrrolyl-oxindoles under mild reaction conditions. With commercially available cinchonidine as a catalyst, a wide range of 3,3-

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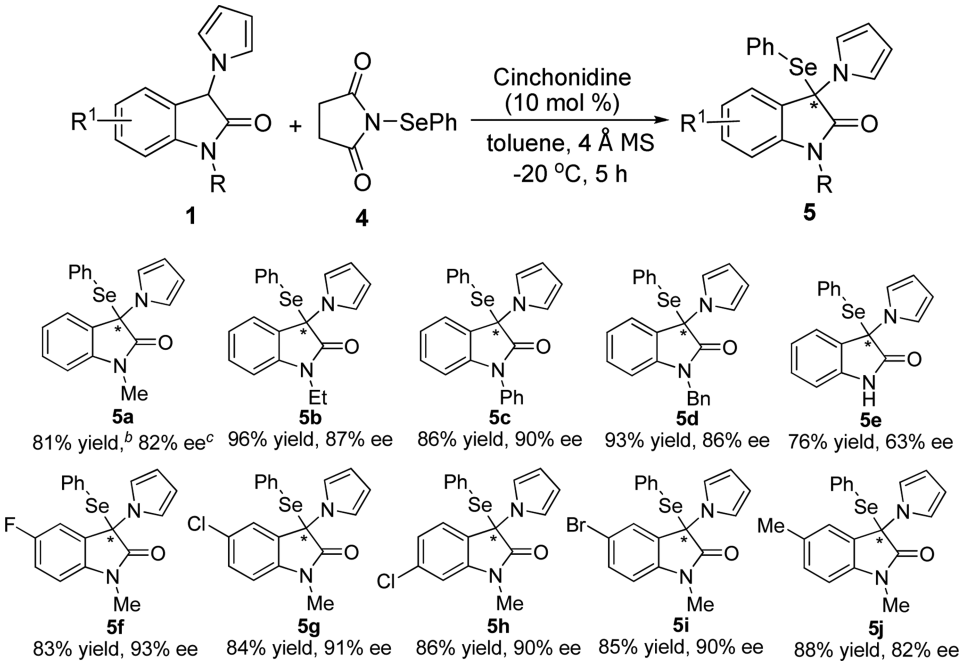
Scheme 4. Asymmetric Selenenylation of 3-Pyrrolyl-oxindoles with Cinchonidine[a]



[a]Unless specified, the reactions were carried out using **1** (0.1 mmol), **4** (0.3 mmol), and cinchonidine (10 mol %) in 2.0 mL of toluene with 50 mg of 4 Å MS at −20 °C for 5 h. [b]Isolated yield. [c]Determined by Chiral HPLC analysis.

disubstituted oxindoles bearing two different heteroatoms at the C3 position could be obtained with satisfactory results. The promising applicability of the protocol was also demonstrated by large-scale production. In particular, this work should be the first example of the organocatalytic enantioselective synthesis of selenium-containing oxindoles. Moreover, the developed protocol will open up a new and straightforward way to access optically active 3-thio-3-pyrrolyl-oxindoles and 3-seleno-3-pyrrolyl-oxindoles.

EXPERIMENTAL SECTION

General Methods. Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$. ^{1}H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm). Melting points were recorded on a Büchi Melting Point B-545. *N*-(Phenylseleno)succinimide was prepared according to the method reported.[15]

General Procedure for the Synthesis of Racemic Compounds 3. In an ordinary vial equipped with a magnetic stirring bar, the oxindoles **1** (0.1 mmol, 1.0 equiv), *N*-thiosuccinimides **2** (0.12 mmol, 1.2 equiv), and DABCO (20 mol %) were dissolved in 2.0 mL of DCM, and then the mixture was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was purified directly with flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 4/1) to afford racemic compound **3**.

General Procedure for the Synthesis of Compounds 3a−u. In an ordinary vial equipped with a magnetic stirring bar, the oxindoles **1** (0.1 mmol, 1.0 equiv), *N*-thiosuccinimides **2** (0.12 mmol, 1.2 equiv), and cinchonidine (10 mol %) were dissolved in 2.0 mL of toluene with 50 mg of 4 Å MS, and then the mixture was stirred at 0 °C for the indicated time. After completion of the reaction, as indicated by TLC, the reaction mixture was purified directly with flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 4/1) to afford compound **3**.

(R)-1-Methyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one ***(3a)***. White solid; 30.4 mg, 95% yield; 93% ee; $[\alpha]_D^{20}$ = −274.1 (*c* 1.52, $CHCl_3$); mp 100.9−102.3 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.6 min, t_{major} = 8.5 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.08 (s, 3H), 6.24 (t, *J* = 2.1 Hz, 2H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 7.06−7.09 (m, 2H), 7.16−7.22 (m, 4H), 7.30−7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 71.3, 108.7, 109.5, 120.6, 122.5, 125.7, 125.8, 128.6, 128.8, 129.9, 130.2, 136.5, 142.3, 170.8; HRMS (ESI-TOF) calcd. for $C_{19}H_{16}N_2NaOS$ $[M + Na]^+$ 343.0876; found: 343.0877.

(R)-1-Ethyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one ***(3b)***. White solid; 31.0 mg, 93% yield; 89% ee; $[\alpha]_D^{20}$ = −224.7 (*c* 1.55, $CHCl_3$); mp 110.8−112.7 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 5.1 min, t_{major} = 5.6 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (t, *J* = 7.2 Hz, 3H), 3.49−3.73 (m, 2H), 6.24 (t, *J* = 2.1 Hz, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.97−7.05 (m, 2H), 7.07−7.11 (m, 2H), 7.15−7.21 (m, 4H), 7.30−7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2, 35.0, 71.2, 108.7, 109.5, 120.5, 122.4, 126.0, 126.3, 128.6, 128.8, 129.9, 130.2, 136.6, 141.6, 170.4; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}N_2NaOS$ $[M + Na]^+$ 357.1032; found: 357.1024.

(R)-1-Phenyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one ***(3c)***. White solid; 37.5 mg, 98% yield; 90% ee; $[\alpha]_D^{20}$ = −185.1 (*c* 1.88, $CHCl_3$); mp 145.4−146.8 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.9 min, t_{major} = 6.0 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.29 (t, *J* = 2.1 Hz, 2H), 6.68 (d, *J* = 7.8 Hz, 1H), 7.07−7.14 (m, 3H), 7.16−7.28 (m, 8H), 7.35−7.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.4, 109.7, 109.9, 120.6, 123.1, 125.9, 126.3, 126.4, 128.4, 128.6, 128.8, 129.5, 130.1, 130.2, 133.4, 136.8, 142.6, 170.2; HRMS (ESI-TOF) calcd. for $C_{24}H_{18}N_2NaOS$ $[M + Na]^+$ 405.1032; found: 405.1032.

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(R)-1-Benzyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one (**3d**). White solid; 37.6 mg, 95% yield; 88% ee; $[\alpha]_D^{20}$ = −93.5 (*c* 1.88, $CHCl_3$); mp 116.4−118.1 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 14.6 min, t_{major} = 7.5 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74 (d, *J* = 15.9 Hz, 1H), 4.89 (d, *J* = 15.9 Hz, 1H), 6.27 (t, *J* = 2.1 Hz, 2H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.90−7.00 (m, 2H), 7.11−7.15 (m, 4H), 7.18−7.29 (m, 8H), 7.33−7.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.1, 71.3, 109.6, 109.8, 120.6, 122.6, 125.7, 126.0, 127.0, 127.7, 128.7, 128.8, 130.0, 130.2, 134.9, 136.6, 141.4, 170.9; HRMS (ESI-TOF) calcd. for $C_{25}H_{20}N_2NaOS$ $[M + Na]^+$ 419.1189; found: 419.1177.

(R)-1,5-Dimethyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one (**3e**). White solid; 28.9 mg, 87% yield; 92% ee; $[\alpha]_D^{20}$ = −203.1 (*c* 1.44, $CHCl_3$); mp 144.5−146.3 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.4 min, t_{major} = 6.9 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.07 (s, 3H), 6.24 (t, *J* = 2.1 Hz, 2H), 6.53 (s, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.11−7.24 (m, 5H), 7.33−7.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 26.4, 71.5, 108.4, 109.4, 120.6, 125.7, 126.4, 128.5, 129.0, 129.9, 130.4, 132.0, 136.6, 139.8, 170.7; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}N_2NaOS$ $[M + Na]^+$ 357.1032; found: 357.1034.

(R)-5-Fluoro-1-methyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one (**3f**). White solid; 32.4 mg, 96% yield; 90% ee; $[\alpha]_D^{20}$ = −230.0 (*c* 1.62, $CHCl_3$); mp 106.8−108.3 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 8.3 min, t_{major} = 8.8 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.08 (s, 3H), 6.25 (t, *J* = 2.1 Hz, 2H), 6.49 (dd, *J* = 2.4 Hz, 8.1 Hz, 1H), 6.70 (dd, *J* = 3.9 Hz, 8.4 Hz, 1H), 7.01−7.09 (m, 3H), 7.14 (t, *J* = 2.1 Hz, 2H), 7.20−7.26 (m, 2H), 7.35−7.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 71.3, 109.3 (d, *J* = 8.0 Hz, 1C), 109.8, 113.6 (d, *J* = 25.8 Hz, 1C), 116.6 (d, *J* = 23.5 Hz, 1C), 120.5, 127.1 (d, *J* = 8.0 Hz, 1C), 128.4, 128.8, 130.3, 136.4, 138.2, 158.6 (d, *J* = 240.7 Hz, 1C), 170.6; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}FN_2NaOS$ $[M + Na]^+$ 361.0781; found: 361.0778.

(R)-5-Chloro-1-methyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one (**3g**). White solid; 34.3 mg, 97% yield; 90% ee; $[\alpha]_D^{20}$ = −152.7 (*c* 1.72, $CHCl_3$); mp 144.2−145.8 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 1/99, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 14.9 min, t_{major} = 15.7 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (s, 3H), 6.26 (t, *J* = 2.1 Hz, 2H), 6.64 (d, *J* = 2.1 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 7.06−7.09 (m, 2H), 7.13 (t, *J* = 2.1 Hz, 2H), 7.22−7.27 (m, 2H), 7.29−7.33 (m, 1H), 7.36−7.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5, 71.2, 109.6, 109.8, 120.5, 125.9, 127.2, 127.9, 128.4, 128.8, 130.0, 130.3, 136.5, 140.7, 170.4; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}ClN_2NaOS$ $[M + Na]^+$ 377.0486; found: 377.0473.

(R)-5-Bromo-1-methyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one (**3h**). White solid; 35.6 mg, 89% yield; 89% ee; $[\alpha]_D^{20}$ = −118.3 (*c* 1.78, $CHCl_3$); mp 145.9−147.4 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 9.2 min, t_{major} = 9.8 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (s, 3H), 6.25 (t, *J* = 2.1 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 1.8 Hz, 1H), 7.05−7.09 (m, 2H), 7.12 (t, *J* = 2.1 Hz, 2H), 7.22−7.28 (m, 2H), 7.36−7.42 (m, 1H), 7.44−7.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5, 71.2, 109.9, 110.1, 115.0, 120.5, 127.5, 128.4, 128.7, 128.8, 130.3, 132.9, 136.6, 141.2, 170.3; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}BrN_2NaOS$ $[M + Na]^+$ 420.9981; found: 420.9978.

(R)-6-Chloro-1-methyl-3-(phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one (**3i**). White solid; 31.2 mg, 88% yield; 89% ee; $[\alpha]_D^{20}$ = −208.5 (*c* 0.78, $CHCl_3$); mp 100.3−101.9 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.5 min, t_{major} = 8.2 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.08 (s, 3H), 6.24 (t, *J* = 2.1 Hz, 2H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.94−6.97 (m, 1H), 7.05−7.09 (m, 2H), 7.12 (t, *J* = 2.1 Hz, 2H), 7.19−7.25 (m, 2H), 7.34−7.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 70.9, 109.4, 109.8, 120.5, 122.4, 124.1, 126.5, 128.5, 128.8, 130.2, 136.2, 136.5, 143.4, 170.7; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}ClN_2NaOS$ $[M + Na]^+$ 377.0486; found: 377.0483.

(R)-3-((3-Chlorophenyl)thio)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (**3j**). White solid; 33.7 mg, 95% yield; 92% ee; $[\alpha]_D^{20}$ = −221.7 (*c* 1.68, $CHCl_3$); mp 105.6−107.4 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.5 min, t_{major} = 9.1 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (s, 3H), 6.25 (t, *J* = 2.1 Hz, 2H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.94−7.00 (m, 3H), 7.03−7.06 (m, 1H), 7.11−7.18 (m, 3H), 7.29−7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 71.1, 108.8, 109.8, 120.5, 122.7, 125.5, 125.6, 129.5, 130.0, 130.6, 134.1, 134.4, 135.9, 142.2, 170.5; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}ClN_2NaOS$ $[M + Na]^+$ 377.0486; found: 377.0482.

(R)-3-((4-Chlorophenyl)thio)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (**3k**). White solid; 34.0 mg, 96% yield; 93% ee; $[\alpha]_D^{20}$ = −209.3 (*c* 1.70, $CHCl_3$); mp 143.1−145.0 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 9.3 min, t_{major} = 11.3 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.11 (s, 3H), 6.23 (t, *J* = 2.1 Hz, 2H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.93−7.01 (m, 3H), 7.02−7.07 (m, 1H), 7.15−7.20 (m, 4H), 7.33−7.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 71.0, 108.8, 109.7, 120.5, 122.7, 125.5, 125.7, 127.2, 128.9, 130.5, 136.5, 137.6, 142.2, 170.5; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}ClN_2NaOS$ $[M + Na]^+$ 377.0486; found: 377.0484.

(R)-3-((4-Bromophenyl)thio)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (**3l**). White solid; 39.1 mg, 98% yield; 93% ee; $[\alpha]_D^{20}$ = −202.5 (*c* 1.95, $CHCl_3$); mp 146.5−148.3 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 9.8 min, t_{major} = 12.9 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.12 (s, 3H), 6.23 (t, *J* = 2.1 Hz, 2H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.90−6.95 (m, 3H), 7.05 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 2.1 Hz, 2H), 7.32−7.39 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5, 70.9, 108.9, 109.7, 120.5, 122.7, 124.9, 125.5, 125.7, 127.9, 130.5, 131.8, 137.8, 142.2, 170.4; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}BrN_2NaOS$ $[M + Na]^+$ 420.9981; found: 420.9978.

(R)-1-Methyl-3-(1H-pyrrol-1-yl)-3-(o-tolylthio)indolin-2-one (**3m**). White solid; 25.0 mg, 75% yield; 83% ee; $[\alpha]_D^{20}$ = −227.8 (*c* 1.25, $CHCl_3$); mp 129.6−131.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 8.3 min, t_{major} = 9.0 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (s, 3H), 3.18 (s, 3H), 6.23 (t, *J* = 1.8 Hz, 2H), 6.45 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.14−7.17 (m, 3H), 7.24−7.29 (m, 1H), 7.35 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 26.5, 71.4, 108.6, 109.4, 120.8, 122.3, 125.2, 125.4, 126.2, 128.6, 130.1, 130.2, 130.3, 137.2, 142.1, 144.5, 170.7; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}N_2NaOS$ $[M + Na]^+$ 357.1032; found: 357.1035.

(R)-1-Methyl-3-(1H-pyrrol-1-yl)-3-(m-tolylthio)indolin-2-one (**3n**). White solid; 32.4 mg, 97% yield; 91% ee; $[\alpha]_D^{20}$ = −248.3 (*c* 1.62, $CHCl_3$); mp 94.9−96.5 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.5 min, t_{major} = 7.2 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.07 (s, 3H), 6.24 (t, *J* = 2.1 Hz, 2H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.80−6.85 (m, 2H), 6.90 (d, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.13−7.18 (m, 3H), 7.30−7.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 26.4, 71.2, 108.6, 109.4, 120.6, 122.4, 125.8, 128.3, 128.4, 130.2, 130.6, 133.4, 137.0, 138.5, 142.3, 170.8; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}N_2NaOS$ $[M + Na]^+$ 357.1032; found: 357.1028.

(R)-1-Methyl-3-(1H-pyrrol-1-yl)-3-(p-tolylthio)indolin-2-one (**3o**). White solid; 32.1 mg, 96% yield; 93% ee; $[\alpha]_D^{20}$ = −246.5 (*c* 0.80, $CHCl_3$); mp 121.9−123.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 8.8 min, t_{major} = 10.7 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.10 (s, 3H), 6.23 (t, *J* = 2.1 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.94−7.03 (m, 5H), 7.17 (t, *J* = 2.1 Hz, 2H), 7.30−7.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 26.4, 71.2, 108.6, 109.4, 120.6, 122.4, 125.2, 125.6, 125.9, 129.4,

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130.1, 136.4, 140.3, 142.2, 170.8; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}N_2NaOS$ $[M + Na]^+$ 357.1032; found: 357.1035.

*(R)-3-((4-Methoxyphenyl)thio)-1-methyl-3-(1H-pyrrol-1-yl)-indolin-2-one (**3p**).* White solid; 34.3 mg, 98% yield; 92% ee; $[\alpha]_D^{20}$ = −244.6 (*c* 1.71, $CHCl_3$); mp 131.2−133.1 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 13.9 min, t_{major} = 16.2 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (s, 3H), 3.78 (s, 3H), 6.22 (t, *J* = 2.1 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.98−7.04 (m, 3H), 7.16 (t, *J* = 2.1 Hz, 2H), 7.30−7.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 55.3, 71.3, 108.6, 109.4, 114.1, 119.4, 120.6, 122.5, 125.8, 125.9, 130.1, 138.2, 142.3, 161.1, 170.9; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}N_2NaO_2S$ $[M + Na]^+$ 373.0981; found: 373.0986.

*(R)-1-Methyl-3-(naphthalen-2-ylthio)-3-(1H-pyrrol-1-yl)indolin-2-one (**3q**).* White solid; 36.3 mg, 98% yield; 93% ee; $[\alpha]_D^{20}$ = −227.1 (*c* 1.82, $CHCl_3$); mp 102.5−104.3 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.3 min, t_{major} = 8.3 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.05 (s, 3H), 6.28 (t, *J* = 2.1 Hz, 2H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 1.5 Hz, 8.4 Hz, 1H), 7.22 (t, *J* = 2.1 Hz, 2H), 7.27−7.33 (m, 1H), 7.44−7.56 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 71.3, 108.7, 109.6, 120.6, 122.5, 125.7, 125.8, 126.1, 126.4, 127.3, 127.5, 128.0, 128.1, 130.2, 132.2, 133.1, 133.4, 136.8, 142.2, 170.7; HRMS (ESI-TOF) calcd. for $C_{23}H_{18}N_2NaOS$ $[M + Na]^+$ 393.1032; found: 393.1030.

*(R)-1-Methyl-3-(1H-pyrrol-1-yl)-3-(thiophen-2-ylthio)indolin-2-one (**3r**).* Orange solid; 23.5 mg, 72% yield; >99% ee; $[\alpha]_D^{20}$ = −198.1 (*c* 0.78, $CHCl_3$); mp 127.4−129.1 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 9.4 min, t_{major} = 8.5 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.13 (s, 3H), 6.24−6.25 (m, 2H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 3.3 Hz, 1H), 6.90−6.97 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.15−7.16 (m, 2H), 7.34−7.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5, 72.3, 108.8, 109.7, 120.5, 122.8, 125.4, 125.7, 126.6, 127.5, 130.5, 132.8, 138.0, 142.5, 170.5; HRMS (ESI-TOF) calcd. for $C_{17}H_{14}N_2NaOS_2$ $[M + Na]^+$ 349.0440; found: 349.0444.

*(R)-3-(Benzylthio)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (**3s**).* White solid; 30.1 mg, 90% yield; 60% ee; $[\alpha]_D^{20}$ = +35.6 (*c* 1.50, $CHCl_3$); mp 134.8−136.3 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.7 min, t_{major} = 7.6 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.32 (s, 3H), 3.77 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 6.27 (t, *J* = 2.1 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 2.1 Hz, 2H), 7.21−7.29 (m, 5H), 7.33−7.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7, 33.5, 68.0, 108.8, 109.8, 119.9, 123.3, 124.2, 127.2, 127.3, 128.6, 129.3, 130.4, 135.6, 141.4, 171.4; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}N_2NaOS$ $[M + Na]^+$ 357.1032; found: 357.1046.

*(R)-3-(Ethylthio)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (**3t**).* White solid; 16.5 mg, 61% yield; 67% ee; $[\alpha]_D^{20}$ = +53.5 (*c* 0.82, $CHCl_3$); mp 85.3−86.9 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 5.9 min, t_{major} = 6.5 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.5 Hz, 3H), 2.61−2.73 (m, 1H), 2.89−3.01 (m, 1H), 3.31 (s, 3H), 6.23 (t, *J* = 2.1 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 1H), 7.05−7.12 (m, 3H), 7.32−7.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 23.0, 26.7, 67.6, 108.7, 109.5, 119.9, 123.2, 124.1, 127.7, 130.2, 141.4, 171.6; HRMS (ESI-TOF) calcd. for $C_{15}H_{16}N_2NaOS$ $[M + Na]^+$ 295.0876; found: 295.0879.

*(R)-3-(Phenylthio)-3-(1H-pyrrol-1-yl)indolin-2-one (**3u**).* White solid; 24 mg, 78% yield; 50% ee; $[\alpha]_D^{20}$ = −121.1 (*c* 1.20, $CHCl_3$); mp 164.4−166.0 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 15/85, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 8.0 min, t_{major} = 5.3 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24−6.28 (m, 2H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.92−6.98 (m, 1H), 7.10−7.23 (m, 6H), 7.24−7.35 (m, 2H), 8.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.8, 109.7, 110.9, 120.6, 122.5, 125.8, 126.4, 128.6, 128.8, 130.1, 130.3, 136.5, 139.4, 173.0; HRMS (ESI-TOF) calcd. for $C_{18}H_{14}N_2NaOS$ $[M + Na]^+$ 329.0719; found: 329.0724.

General Procedure for the Synthesis of Racemic Compounds 5. In an ordinary vial equipped with a magnetic stirring bar, the oxindoles **1** (0.1 mmol, 1.0 equiv), *N*-(phenylseleno)succinimides **4** (0.12 mmol, 1.2 equiv), and DABCO (20 mol %) were dissolved in 2.0 mL of DCM, and then the mixture was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was purified directly with flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 4/1) to afford compound **5**.

General Procedure for the Synthesis of Compounds 5a−j. In an ordinary vial equipped with a magnetic stirring bar, the oxindoles **1** (0.1 mmol, 1.0 equiv), *N*-(phenylseleno)succinimides **4** (0.3 mmol, 3.0 equiv), and cinchonidine (10 mol %) were dissolved in 2.0 mL of toluene with 50 mg of 4 Å MS, and then the mixture was stirred at −20 °C for 5 h. The reaction mixture was purified directly with flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 4/1) to afford racemic compound **5**.

*1-Methyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5a**).* White solid; 29.6 mg, 81% yield; 82% ee; $[\alpha]_D^{20}$ = −150.1 (*c* 0.86, $CHCl_3$); mp 116.4−118.0 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.7 min, t_{major} = 8.2 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99 (s, 3H), 6.25 (t, *J* = 2.1 Hz, 2H), 6.66 (d, *J* = 7.8 Hz, 1H), 7.01−7.03 (m, 2H), 7.13−7.17 (m, 4H), 7.19 (t, *J* = 2.1 Hz, 2H), 7.26−7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 65.7, 108.5, 109.3, 109.6, 120.9, 122.6, 125.7, 126.3, 126.4, 128.6, 129.7, 129.9, 137.4, 141.7, 171.4; HRMS (ESI-TOF) calcd. for $C_{19}H_{16}N_2NaOSe$ $[M + Na]^+$ 391.0321; found: 391.0316.

*1-Ethyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5b**).* White solid; 38.1 mg, 96% yield; 87% ee; $[\alpha]_D^{20}$ = −154.2 (*c* 1.27, $CHCl_3$); mp 88.7−90.3 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 5.5 min, t_{major} = 6.5 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, *J* = 7.2 Hz, 3H), 3.56 (q, *J* = 7.2 Hz, 2H), 6.25 (t, *J* = 2.1 Hz, 2H), 6.71 (d, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 4.5 Hz, 4H), 7.21 (t, *J* = 2.1 Hz, 2H), 7.26−7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2, 34.9, 65.6, 108.7, 109.6, 120.9, 122.4, 125.9, 126.3, 126.7, 128.7, 129.7, 129.9, 137.4, 141.0, 171.0; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}N_2NaOSe$ $[M + Na]^+$ 405.0477; found: 405.0476.

*1-Phenyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5c**).* White solid; 33.6 mg, 86% yield; 90% ee; $[\alpha]_D^{20}$ = −171.9 (*c* 1.12, $CHCl_3$); mp 118.8−120.4 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.1 min, t_{major} = 7.0 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (t, *J* = 2.1 Hz, 2H), 6.64 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.16−7.26 (m, 5H), 7.28−7.31 (m, 3H), 7.35−7.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.6, 109.7, 109.8, 120.9, 123.1, 126.2, 126.3, 126.4, 128.3, 128.8, 129.4, 129.8, 129.9, 133.4, 137.6, 142.0, 170.7; HRMS (ESI-TOF) calcd. for $C_{24}H_{19}N_2OSe$ $[M + H]^+$ 431.0658; found: 431.0655.

*1-Benzyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5d**).* White solid; 41.2 mg, 93% yield; 86% ee; $[\alpha]_D^{20}$ = −129.7 (*c* 1.37, $CHCl_3$); mp 100.3−102.0 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 16.7 min, t_{major} = 13.0 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77 (s, 2H), 6.28 (t, *J* = 2.1 Hz, 2H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.93−7.00 (m, 2H), 7.15−7.22 (m, 7H), 7.24 (t, *J* = 2.1 Hz, 2H), 7.25−7.32 (m, 3H), 7.35−7.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.0, 65.8, 109.7, 121.0, 122.6, 125.5, 126.3, 126.4, 127.1, 127.7, 128.7, 128.8, 129.8, 129.9, 135.1, 137.4, 140.7, 171.5; HRMS (ESI-TOF) calcd. for $C_{25}H_{20}N_2NaOSe$ $[M + Na]^+$ 467.0634; found: 467.0629.

*3-(Phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5e**).* White solid; 26.8 mg, 76% yield; 63% ee; $[\alpha]_D^{20}$ = −164.1 (*c* 1.06, $CHCl_3$); mp 147.3−149.0 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 12.2 min, t_{major} = 7.1 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.25−

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6.29 (m, 2H), 6.82 (d, J = 7.8 Hz, 1H), 6.86−6.89 (m, 1H), 6.94−6.99 (m, 1H), 7.11−7.27 (m, 7H), 7.32−7.35 (m, 1H), 8.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.3, 109.7, 110.7, 121.0, 122.6, 125.6, 126.3, 126.8, 128.8, 129.8, 129.9, 137.3, 137.4, 138.8, 173.7; HRMS (ESI-TOF) calcd. for $C_{18}H_{14}N_2NaOSe$ $[M + Na]^+$ 377.0164; found: 377.0158.

*5-Fluoro-1-methyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5f**).* White solid; 26.1 mg, 83% yield; 93% ee; $[\alpha]_D^{20}$ = −223.8 (c 0.87, $CHCl_3$); mp 85.5−87.3 °C; the ee was determined by HPLC (Chiralpak OD-H, i-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.4 min, t_{major} = 8.7 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 3H), 6.27 (t, J = 2.1 Hz, 2H), 6.60 (dd, J = 4.2 Hz, 8.7 Hz, 1H), 6.66 (dd, J = 2.4 Hz, 8.1 Hz, 1H), 6.97−7.03 (m, 1H), 7.15−7.23 (m, 6H), 7.34−7.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 65.7, 109.1 (d, J = 8.0 Hz, 1C), 109.9, 113.4 (d, J = 25.8 Hz, 1C), 116.3 (d, J = 23.5 Hz, 1C), 120.8, 126.1, 127.8 (d, J = 8.6 Hz, 1C), 128.8, 130.0, 137.3, 137.6, 158.7 (d, J = 240.3 Hz, 1C), 171.2; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}FN_2NaOSe$ $[M + Na]^+$ 409.0227; found: 409.0230.

*5-Chloro-1-methyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5g**).* White solid; 29.8 mg, 84% yield; 91% ee; $[\alpha]_D^{20}$ = −142.4 (c 0.99, $CHCl_3$); mp 122.4−124.0 °C; the ee was determined by HPLC (Chiralpak OD-H, i-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.2 min, t_{major} = 8.0 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01 (s, 3H), 6.27 (t, J = 2.1 Hz, 2H), 6.62 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 2.1 Hz, 1H), 7.14−7.18 (m, 4H), 7.19−7.28 (m, 3H), 7.35−7.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 65.6, 109.5, 109.9, 120.9, 125.7, 126.1, 127.7, 127.8, 127.9, 128.8, 129.4, 129.7, 130.1, 137.4, 140.0, 171.0; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}ClN_2NaOSe$ $[M + Na]^+$ 424.9928; found: 424.9931.

*6-Chloro-1-methyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5h**).* White solid; 34.5 mg, 86% yield; 90% ee; $[\alpha]_D^{20}$ = −194.0 (c 1.09, $CHCl_3$); mp 101.2−103.1 °C; the ee was determined by HPLC (Chiralpak OD-H, i-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.5 min, t_{major} = 9.5 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99 (s, 3H), 6.25 (t, J = 2.1 Hz, 2H), 6.68 (d, J = 1.8 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.96−7.00 (m, 1H), 7.13−7.23 (m, 6H), 7.33−7.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 65.3, 109.2, 109.9, 119.2, 120.9, 122.4, 124.8, 126.1, 126.4, 128.8, 130.0, 135.8, 137.4, 142.8, 171.4; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}ClN_2$-$NaOSe$ $[M + Na]^+$ 424.9928; found: 424.9934.

*5-Bromo-1-methyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5i**).* White solid; 33.4 mg, 85% yield; 90% ee; $[\alpha]_D^{20}$ = −103.8 (c 1.11, $CHCl_3$); mp 105.6−107.5 °C; the ee was determined by HPLC (Chiralpak OD-H, i-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.7 min, t_{major} = 8.4 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.02 (s, 3H), 6.27 (t, J = 2.1 Hz, 2H), 6.58 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 7.13−7.17 (m, 4H), 7.20−7.26 (m, 2H), 7.36−7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 65.6, 109.7, 109.9, 115.1, 119.1, 120.9, 126.1, 128.1, 128.4, 128.9, 130.1, 132.5, 137.5, 140.5, 170.9; HRMS (ESI-TOF) calcd. for $C_{19}H_{15}BrN_2$-$NaOSe$ $[M + Na]^+$ 468.9423; found: 468.9428.

*1,5-Dimethyl-3-(phenylselanyl)-3-(1H-pyrrol-1-yl)indolin-2-one (**5j**).* White solid; 33.5 mg, 88% yield; 82% ee; $[\alpha]_D^{20}$ = −138.8 (c 1.12, $CHCl_3$); mp 100.3−102.1 °C; the ee was determined by HPLC (Chiralpak OD-H, i-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.0 min, t_{major} = 6.8 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.00 (s, 3H), 6.25 (t, J = 2.1 Hz, 2H), 6.58 (d, J = 7.8 Hz, 1H), 6.67 (s, 1H), 7.07−7.10 (m, 1H), 7.12−7.22 (m, 6H), 7.32−7.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 26.3, 66.0, 108.3, 109.5, 121.0, 126.1, 126.2, 126.5, 128.6, 129.7, 130.1, 132.1, 137.4, 137.5, 139.2, 171.3; HRMS (ESI-TOF) calcd. for $C_{20}H_{18}$-N_2NaOSe $[M + Na]^+$ 405.0477; found: 405.0475.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01491.

Copies of ^{1}H, ^{13}C NMR, and HPLC spectra for new products (PDF)

Single-crystal X-ray crystallography data for product **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273. (b) Jensen, B. S. *CNS Drug Rev.* **2002**, *8*, 353. (c) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (d) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *2003*, 2209. (e) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (f) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758.

(2) For selected reviews, see: (a) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *2009*, 3003. (b) Zhou, J.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (c) Alba, A.-N. R.; Rios, R. *Chem. - Asian J.* **2011**, *6*, 720. (d) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327. (e) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (f) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (g) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (h) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (i) Chauhan, P.; Chimni, S. S. *Tetrahedron: Asymmetry* **2013**, *24*, 343. (j) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (k) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F., III *ACS Catal.* **2014**, *4*, 743.

(3) For selected recent examples, see: (a) Ohmatsu, K.; Ando, Y.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 18706. (b) Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869. (c) Afewerki, S.; Ma, G.-N.; Ibrahem, I.; Liu, L.-F.; Sun, J.-L.; Córdova, A. *ACS Catal.* **2015**, *5*, 1266. (d) Du, T.-P.; Du, F.; Ning, Y.-Q.; Peng, Y.-G. *Org. Lett.* **2015**, *17*, 1308. (e) Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 1685. (f) Shimizu, S.; Tsubogo, T.; Xu, P.-Y.; Kobayashi, S. *Org. Lett.* **2015**, *17*, 2006. (g) Xie, D.-B.; Yang, L.-M.; Lin, Y.-Q.; Zhang, Z.-M.; Chen, D.-D.; Zeng, X.-F.; Zhong, G.-F. *Org. Lett.* **2015**, *17*, 2318.

(4) For selected examples, see: (a) Murata, Y.; Takahashi, M.; Yagishita, F.; Sakamoto, M.; Sengoku, T.; Yoda, H. *Org. Lett.* **2013**, *15*, 6182. (b) Li, C.; Guo, F.-F.; Xu, K.; Zhang, S.; Hu, Y.-B.; Zha, Z.-G.; Wang, Z.-Y. *Org. Lett.* **2014**, *16*, 3192. (c) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *J. Org. Chem.* **2014**, *79*, 4332. (d) Chen, D.; Xu, M.-H. *J. Org. Chem.* **2014**, *79*, 7746. (e) Jayakumar, S.; Kumarswamyreddy, N.; Prakash, M.; Kesavan, V. *Org. Lett.* **2015**, *17*, 1066. (f) Murru, S.; Lott, C. S.; Fronczek, F. R.; Srivastava, R. S. *Org. Lett.* **2015**, *17*, 2122.

(5) (a) Liu, Z.; Feng, X.; Du, H. *Org. Lett.* **2012**, *14*, 3154. (b) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *Tetrahedron* **2013**, *69*, 7314. (c) Arai, T.; Tsuchiya, K.; Matsumura, E. *Org. Lett.* **2015**, *17*, 2416. (d) Nakamura, S.; Takahashi, S. *Org. Lett.* **2015**, *17*, 2590.

(6) (a) Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hübel, K.; Rauh, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5902. (b) Gomez-Monterrey, I.; Bertamino, A.; Porta, A.; Carotenuto, A.; Musella, S.; Aquino, C.; Granata, I.; Sala, M.; Brancaccio, D.; Picone, D.; Ercole, C.; Stiuso, P.; Campiglia, P.; Grieco, P.; Ianelli, P.; Maresca, B.; Novellino, E. *J. Med. Chem.* **2010**, *53*, 8319. (c) Sakhuja, R.; Panda,

DOI: 10.1021/acs.joc.5b01491
J. Org. Chem. 2015, 80, 8470−8477

S. S.; Khanna, L.; Khurana, S.; Jain, S. C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5465. (d) Vintonyak, V. V.; Warburg, K.; Over, B.; Hübel, K.; Rauh, D.; Waldmann, H. *Tetrahedron* **2011**, *67*, 6713. (e) Bertamino, A.; Soprano, M.; Musella, S.; Rusciano, M. R.; Sala, M.; Vernieri, E.; Di Sarno, V.; Limatola, A.; Carotenuto, A.; Cosconati, S.; Grieco, P.; Novellino, E.; Illario, M.; Campiglia, P.; Gomez-Monterrey, I. *J. Med. Chem.* **2013**, *56*, 5407. (f) Arya, K.; Tomar, P.; Singh, J. *RSC Adv.* **2014**, *4*, 3060.

(7) (a) Zhou, F.; Zeng, X.-P.; Wang, C.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2013**, *49*, 2022. (b) Nakamura, S.; Takahashi, S.; Nakane, D.; Masuda, H. *Org. Lett.* **2015**, *17*, 106. (c) Beceño, C.; Chauhan, P.; Rembiak, A.; Wang, A.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 672.

(8) (a) Cui, B.-D.; You, Y.; Zhao, J.-Q.; Zuo, J.; Wu, Z.-J.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51*, 757. (b) You, Y.; Cui, B.-D.; Zhou, M.-Q.; Zuo, J.; Zhao, J.-Q.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 5951.

(9) For reviews, see: (a) Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis* **2007**, *2007*, 959. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Postigo, A. *RSC Adv.* **2011**, *1*, 14. (d) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590. (e) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (f) Liu, W.; Zhao, X. *Synthesis* **2013**, *45*, 2051. (g) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807.

(10) For selected examples, see: (a) Cai, Y.; Li, J.; Chen, W.; Xie, M.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2012**, *14*, 2726. (b) Li, X.; Liu, C.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2012**, *14*, 4374. (c) Han, Z.; Chen, W.; Dong, S.; Yang, C.; Liu, H.; Pan, Y.; Yan, L.; Jiang, Z. *Org. Lett.* **2012**, *14*, 4670. (d) Wang, C.; Yang, X.; Loh, C. C. J.; Raabe, G.; Enders, D. *Chem. - Eur. J.* **2012**, *18*, 11531. (e) Shirakawa, S.; Tokuda, T.; Kasai, A.; Maruoka, K. *Org. Lett.* **2013**, *15*, 3350. (f) Qiao, B.; Liu, X.; Duan, S.; Yan, L.; Jiang, Z. *Org. Lett.* **2014**, *16*, 672.

(11) For selected examples from our group, see: (a) Han, Y.-Y.; Chen, W.-B.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 490. (b) Liu, X.-L.; Han, W.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2013**, *15*, 1246. (c) Cui, B.-D.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2013**, *78*, 8833. (d) Zuo, J.; Wu, Z.-J.; Zhao, J.-Q.; Zhou, M.-Q.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 634. (e) Zhao, J.-Q.; Zhou, M.-Q.; Wu, Z.-J.; Wang, Z.-H.; Yue, D.-F.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2015**, *17*, 2238.

(12) For selected examples of the asymmetric synthesis of chiral selenium-containing compounds, see: (a) Tiecco, M.; Carlone, A.; Sternativo, S.; Marini, F.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6882. (b) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2011**, *13*, 1040. (c) Marcos, V.; Alemán, J.; Ruano, J. L. G.; Marini, F.; Tiecco, M. *Org. Lett.* **2011**, *13*, 3052.

(13) For the details of the synthesis of 3-pyrrolyl-oxindoles, see: Banik, B. K.; Garcia, I.; Morales, F. R.; Aguilar, C. *Heterocycl. Commun.* **2007**, *13*, 109.

(14) CCDC-1402689 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4208.

DOI: 10.1021/acs.joc.5b01491
J. Org. Chem. 2015, 80, 8470−8477