Titanium Tetrachloride-Mediated Approach to Access 2-Chloro-2-Substituted Isoindolin-1-ones through the Addition of Alkynes to Acyliminium ions

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An asymmetric approach to access 2-substituted isoindolin-1-ones **9**–**11** was developed through $TiCl_4$-mediated addition-chlorination of *N*,*O*-acetals **7a**–**7c** with terminal alkynes **8**. A range of substrates were amenable to this transformation, and the desired substituted isoindolin-1-ones were obtained in moderate to good yields with moderate diastereoselectivities.

Introduction

The enantioselective construction of a stereogenic center at the α-position of nitrogen-containing heterocycles (*N*-heterocycles) is one of the most challenging tasks in synthetic heterocyclic chemistry.[1] Chiral isoindolinone skeleton (**1**) (Figure 1), which is prevalent in many natural products[2] and serves as a sub-structure for numerous biologically pharmaceutical agents,[3,4] has attracted significant interest in synthetic and medicinal chemistry. Typical examples include Lennoxamine (**2**), which was isolated from the plants of Chilean *Berberis species*,[2d] (*R*)-JM1232 (**3**), Pazinaclone (**4**), Pagoclone (**5**) and (*S*)-PD-172938 (**6**). In particular, (*S*)-PD 172938 (**6**) shows potent affinity for dopamine D_4 receptor,[5] and Pazinaclone (**4**) is currently used as sedative and anxiolytic drug.[6] Meanwhile, tremendous efforts have been devoted to the construction of a chiral functionalized isoindolinone scaffold (**1**) and several asymmetric syntheses have been reported.[7]

Two general approaches were applied to construct such a chiral functionalized isoindolinone scaffold. One approach was to use powerful catalytic enantioselective syntheses including Mannich-lactamization,[8] *aza*-Michael addition,[9] enantioselective *aza*-Wacker-type cyclization,[10] and tandem Mannich-lactamization.[11] The other approach was to use a chiral auxiliary group in the reaction substrates. For examples, Allin *et al* established a new approach to the synthesis of 2-allyl substituted isoindolin-1-one through the application of a cyclic *N*,*O*-acetal chiral substrate as a *N*-acylhninium ion precursor in 1999 (Figure 2a).[12] Huang *et al* established a diastereoselective approach to chiral substituted isoindolinones through the successive addition-reduction process from chiral 2-(2-hydroxy-1-phenylethyl)isoindoline-1,3-dione in 2005 (Figure 2b).[13] In 2019, Allin's group used the cyclic *N*,*O*-acetal chiral substrate to synthesize 2-alkyl/aryl substituted- isoindolin-1-ones (Figure 2c).[14]

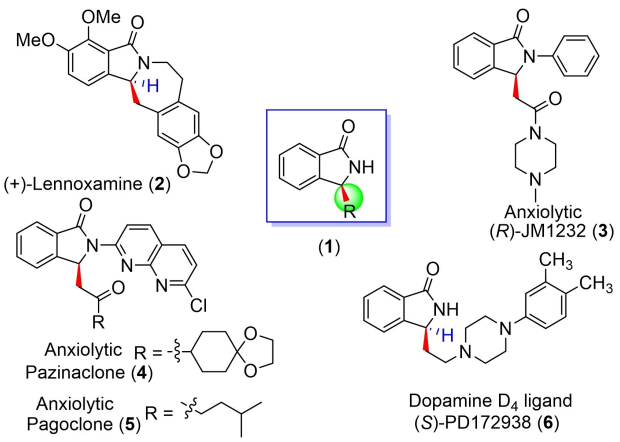

Figure 1. Structures of several natural products.

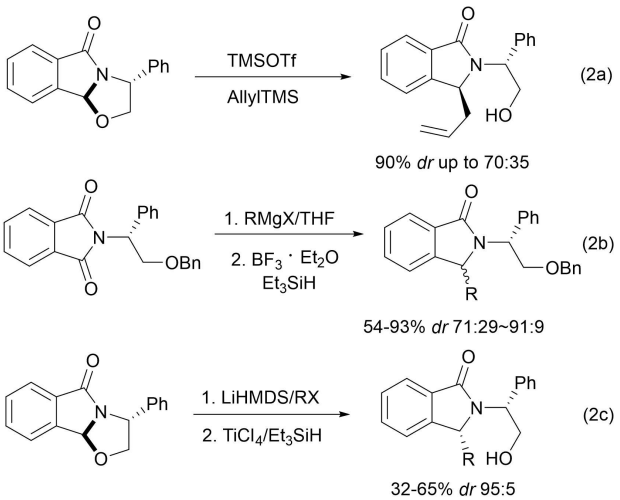

Figure 2. The asymmetric methods based on chiral substrates.

N-Acyliminium ions, acting as important organic synthetic intermediates, are widely used in the formation of C–C and

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202100368

C–heteroatom bonds,[15] mostly through intermolecular addition[16] and intramolecular cyclization[17] with various nucleophilic reagents. In this field, alkyne could serve as a nucleophile to react with *N*-acyliminium ions affording important organic intermediates. For example, $SnCl_4$[18a] or TMSX[18b] could lead to intramolecular cyclization of alkyne group with the *in situ* generated iminium ion (Figure 3a and Figure 3b). Our group also established a stereoselective approach to pyrido and pyrrolo[1,2-c][1,3]oxazin-1-ones skeletons through the intermolecular addition cyclization of triple bond to *N*-acyliminium ions process (Figure 3c).[19] Interestingly, two different kinds of nucleophilic reagents, ynamides and alkynes, could afford the desired products with different configurations in this process. Encouraged by these results, we envisioned that similar chiral *N*-acyliminium ions with styrene acrylic framework could potentially produce chiral isoindolinones. Herein we report our results of $TiCl_4$-mediated reactions of *N,O*-acetals **7a**–**7c**, in which the chiral phenyl glycine alcohol unit could control the stereochemistry of addition-chlorination process with terminal alkynes **8** (Figure 3d).

Results and Discussion

Our investigation started with the reaction of *N,O*-acetal **7a**, which was readily prepared according to the known method,[13,20] with phenylacetylene. The reaction could not take place in the absence of Lewis acid (Table 1, entry 1). When TMSOTf was examined, the reaction was complicated (Table 1, entry 2). When $AuCl_3$, TMSCl, $ZnCl_2$ and $AlCl_3$ were examined, no product was observed (Table 1, entries 3–6). $SnCl_4$ could afford the desired product **9a** in 62% yield, albeit with low diastereoselectivity (*dr* = 62:38, Table 1, entry 7). When $TiCl_4$ was examined, the desired product **9a** was isolated in 68% yield with 85:15 diastereoselectivity (Table 1, entry 8). Conducting the reaction at lower temperature of −78 °C not only failed to improve the diastereoselectivity, but also led to a significant decrease in yield (Table 1, entry 9). Delightfully, when 1.5 equiv. $TiCl_4$ was used, the desired **9a** was isolated in 72% yield with 91:9 diastereoselectivity (Table 1, entry 10). Further dropping the loading of $TiCl_4$ to 1.0 equiv. resulted in lower yield (Table 1, entry 11). Other solvents (MeCN, THF) were also screened, which turned out to be incompatible for this transformation (Table 1, entries 12–13).

With the above identified optimized reaction conditions, *N,O*-acetal **7a** with different substituted terminal alkynes **8a**–**8t** were examined and the results were summarized in Scheme 1. First, *para* substituted phenylacetylenes **8a**–**8i** could afford the desired products **9a**–**9i** in moderate yields, with the diastereoselectivities going up to 95:5. Regarding different substitutions at the *para* position of phenylacetylenes, halogen or electron withdrawing groups (such as CF_3) offered better yields of the desired products **9b**–**9e** than alkyl and methoxy groups (products **9f**–**9i**, Scheme 1). *Ortho* substituted phenylacetylenes **8j**–**8l** could afford the desired products **9j**–**9l** in 64–75% yields with good diastereoselectivities. Several *meta* substituted phenylacetylenes **8m**–**8p** were also examined, and the substitutions (methyl, methoxy and halogen) did not affect the yields and diastereoselectivities of the products **9m**–**9p**. *β*-

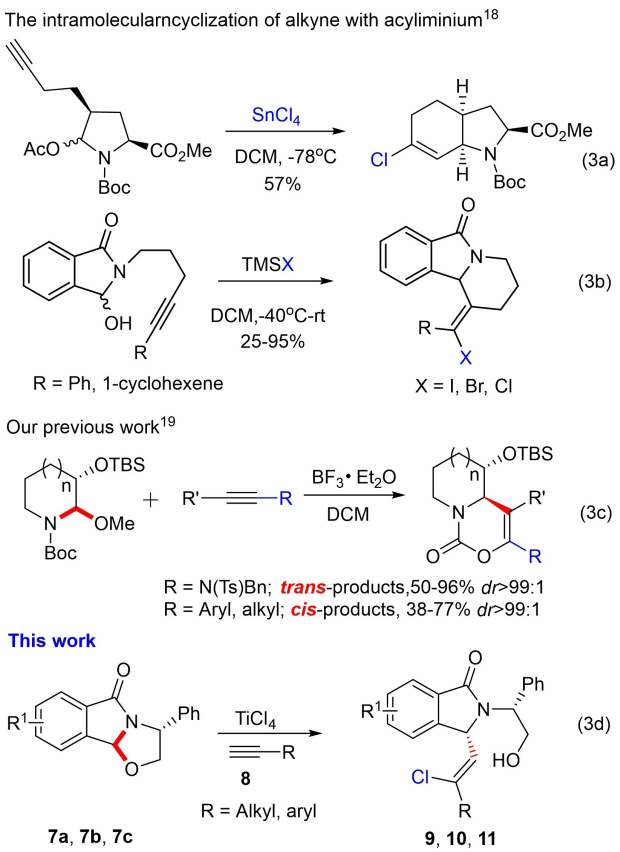
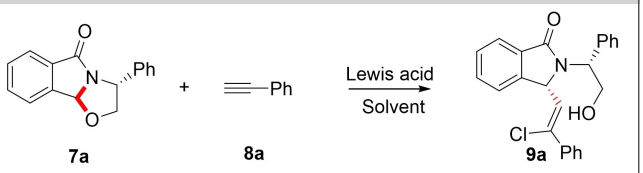


Figure 3. The reaction of alkynes with *N*-acyliminium ions.

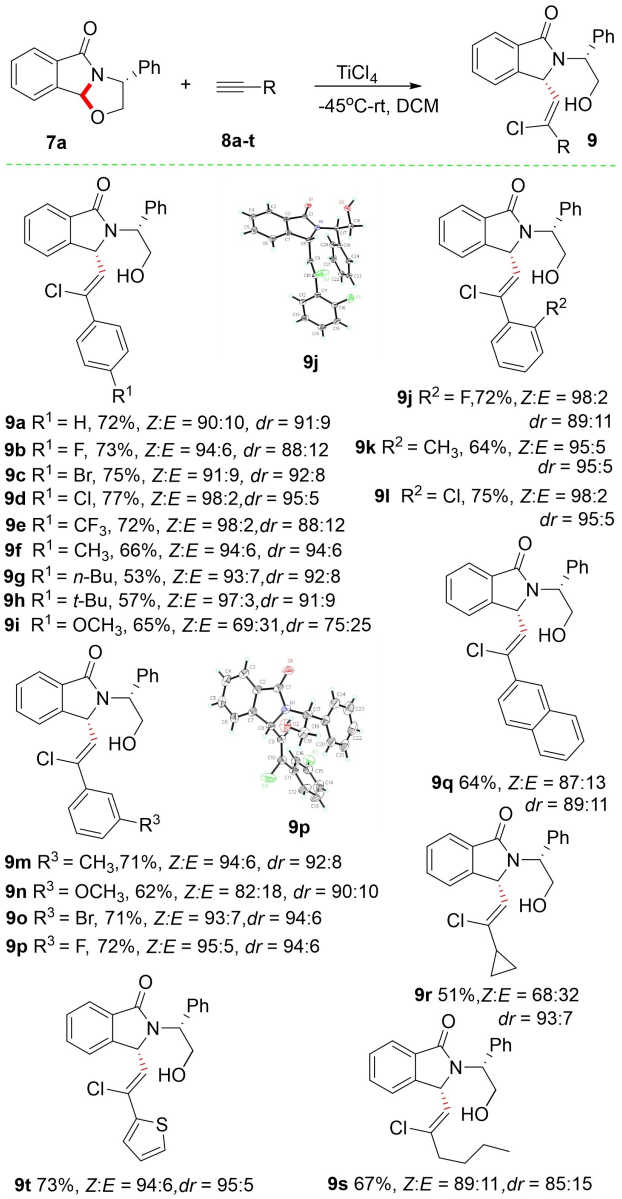
Table 1. Optimization of reaction conditions.



7a 8a 9a

Entries[a]	Lewis acid(eq)	Solvent	Y%[c]	*Z*:*E*[d]	*Dr*[e]
1	–	DCM	NR	–	–
2	TMSOTf(2.0)	DCM	Complex	–	–
3	$AuCl_3$(0.1)	DCM	NR	–	–
4	TMSCl(2.0)	DCM	NR	–	–
5	$ZnCl_2$(2.0)	DCM	NR	–	–
6	$AlCl_3$(2.0)	DCM	NR	–	–
7	$SnCl_4$(2.0)	DCM	62	58:42	62:38
8	$TiCl_4$(2.0)	DCM	68	76:24	85:15
9[b]	$TiCl_4$(2.0)	DCM	33	81:19	86:14
10	$TiCl_4$(1.5)	DCM	72	90:10	91:9
11	$TiCl_4$(1.0)	DCM	53	88:12	91:9
12	$TiCl_4$(1.5)	MeCN	trace	–	–
13	$TiCl_4$(1.5)	THF	trace	–	–

[a] The reactions were performed with Lewis acid, *N,O*-acetal (0.79 mmol) and alkyne (1.19 mmol) in dry DCM (5 mL) at −45 °C to room temperature for 4 h; [b] The mixture was treated at −78 °C for 12 h; [c] Isolated yield; [d] *Z*:*E* ratio was determined by HPLC of crude products; [e] *dr* was determined by HPLC of crude products.

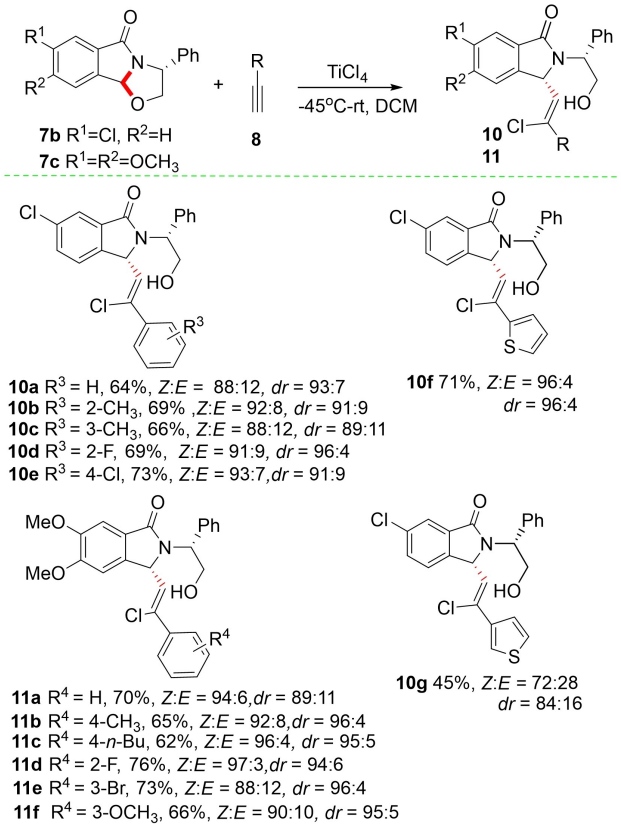


Scheme 1. The reactions of *N,O*-acetal **7a** with different terminal alkynes. [a] The reactions were performed with $TiCl_4$ (1.19 mmol), *N,O*-acetal (0.79 mmol) and alkyne (1.19 mmol) in dry DCM (5 mL) at −45 °C-room temperature for 4 h; [b] Isolated yield; [c] *Z*:*E* was determined by HPLC of crude products; [d] *dr* was determined by HPLC of crude products. [e] **9p** (1.30 g, 67% yield) was obtained with **7a** (4.74 mmol), **8p** (7.14 mmol), and $TiCl_4$ (7.14 mmol) in dry DCM (15 mL) at −45 °C to rt for 4 h.

Naphthalene acetylene **8q** also worked well, leading to the desired product **9q** in moderate yield and diastereoselectivity. It was worth mentioning that alkyl substituted acetylenes (cyclopropylacetylene **8r** and 1-heptyne **8s**) could also produce the desired **9r**–**9s** in moderate yields and diastereoselectivities. In addition, heterocycle substituted acetylene, 2-thiophene acetylene **8t**, could react with *N,O*-acetal **7a** to afford the desired **9t** in 73% yield with good diastereoselectivity (*dr* = 95:5). Unfortunately, the heterocycle 3-ethynylpyridine cannot react. The chemical structures and relative stereochemistry of **9a**–**9t** were unambiguously confirmed based on the X-ray crystallographic analysis of compounds **9j** and **9p** (The supplementary crystallographic data of **9j** and **9p** can be obtained in the Supporting Information). The absolute configuration of (*R,E,R*)-**9p** was determined by ECD experiments (see supporting information). The absolute configurations of (*S,Z,R*)-**9p** and (*S,E,R*)-**9p** were elucidated by quantum chemical calculations (see supporting information).[21]

Next, we turned our attention to investigate the scope and limitation for the reactions of different substituted *N,O*-acetals **7b**–**7c** with different substituted alkynes **8** (Scheme 2). First, the reaction of chlorinated *N,O*-acetal **7b** with different substituted alkynes were examined. The results showed that the substitution of chlorine atoms on *N,O*-acetals has a little effect on the yield and diastereoselectivity of the product. The desired **10a**–**10f** were obtained in moderate yields and good diastereoselectivities. It is worth mentioning that 3-ethynylthiophene could also react with **7b** to give the desired **10g** in 45% yield, but the diastereoselectivity of **10g** was slightly lower (*dr* = 84:16). Other 5,6-dimethoxy substituted *N,O*-acetal **7c** could also react with different substituted alkynes, affording the desired **11a**–**11f**, respectively, in moderate yields and good diastereoselectivities.

On the basis of our experimental results, a possible mechanism was illustrated in Figure 4. First, $TiCl_4$ coordinated



Scheme 2. The reactions of *N,O*-acetal **7a** with different terminal alkynes. [a] The reactions were performed with $TiCl_4$ (1.19 mmol), *N,O*-acetal (0.79 mmol) and alkyne (1.19 mmol) in dry DCM (5 mL) at −45 °C-room temperature for 4 h; [b] Isolated yield; [c] *Z*:*E* was determined by HPLC of crude products; [d] *dr* was determined by HPLC of crude products.

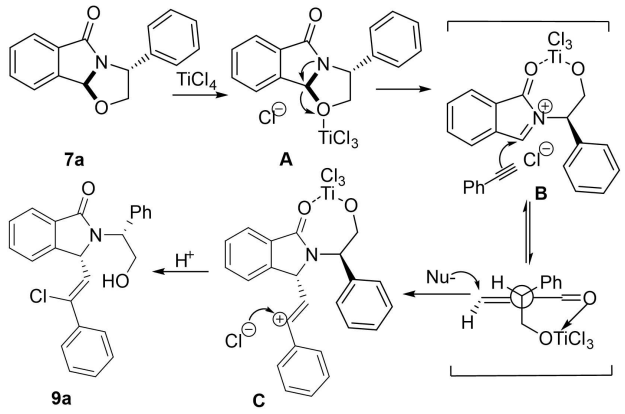


Figure 4. Proposed mechanism for the formation of 2-chloro-2-substituted isoindolin-1-ones.

with the oxygen of *N*,*O*-acetal **7a** to form an intermediate **A**, which readily underwent ring-opening to generate a *N*-acyliminium ion **B**. Subsequently, the formation of alternative ring, due to the coordination of the carbonyl group with titanium, resulted in nucleophilic attack of the phenylacetylene substrate predominantly from the less hindered face, and the resultant cationic intermediate **C** further reacted with chloride to give intermediate, which ultimately led to the desired (*R*)-3-((*Z*)-2- chloro-2-phenylvinyl)-2-((*R*) −2-hydroxy-1- phenylethyl) isoindolin −1-one **9a** under acidic conditions.

Conclusion

In summary, we established a diastereoselective approach for the synthesis of 2-substituted isoindolin-1-ones skeleton. The reaction of *N*,*O*-acetals **7a**–**7c** with terminal alkynes **8** went through a $TiCl_4$ mediated successive addition-chlorination process. As a result, a series of 2-substituted isoindolin-1-ones **9**–**11** were obtained in moderate to good yields and diastereoselectivities under mild reaction conditions.

Experimental Section

General: Reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with a fluorescent indicator. Flash chromatography was performed on silica gel (300–400) with petroleum/EtOAc as the eluent. Optical rotations were measured on a polarimeter with a sodium lamp. HRMS was conducted on Thermo Scientific LTQ Orbitrap XL apparatus. IR spectra were record using a film on a Fourier transform infrared spectrometer. NMR spectra were recorded at 400 MHz, and chemical shifts are reported in (ppm) referenced to an internal TMS standard for H NMR and $CDCl_3$ (77.16 ppm) for $^{13}C\{^1H\}$ NMR. The *N*,*O*-acetals were synthesized according to the known method.[13,20]

General Procedure for Synthesis of 9–11. To a solution of *N*,*O*-acetal **7** (0.79 mmol) and **8** (1.19 mmol) in anhydrous DCM (5 mL) was treated with $TiCl_4$ (1.19 mmol) at −45 °C under an argon atmosphere. The rection mixture was slowly warmed to room temperature and stirred for 4 h. The mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc for three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel (PE/EA = 2:1) to give the desired product **9–11**.

(*R*)-3-((*Z*)-2-Chloro-2-phenylvinyl)-2-((*R*)-2-hydroxy-1-phenylethyl) isoindolin-1-one (9a). White solid (222 mg, 72%), mp 173–175 °C; $[\alpha]_D^{26} = -109.8$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3055, 2926, 1669, 1467, 1394, 1220, 1071, 749, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.84 (m, 1H), 7.55–7.45 (m, 4H), 7.43–7.39 (m, 1H), 7.37–7.25 (m, 8H), 5.78 (d, *J* = 9.2 Hz, 1H), 5.66 (d, *J* = 8.8 Hz, 1H), 4.95–4.88 (m, 1H), 4.57–4.47 (m, 1H), 4.34 (brs, 1H), 4.20–4.13 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 144.1, 138.7, 138.1, 136.6, 132.5, 132.3, 129.8, 129.1, 129.0, 128.7, 128.2, 128.0, 126.8, 124.1, 123.9, 123.3, 64.0, 62.0, 60.8 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{20}ClNO_2Na^+$, 412.1075, found 412.1073.

(*R*)-3-((*Z*)-2-Chloro-2-(4-fluorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9b). White solid (235 mg, 73%), mp 161–163 °C; $[\alpha]_D^{25} = -79.8$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3059, 2920, 1671, 1598, 1502, 1395, 1230, 1159, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.78 (m, 1H), 7.51–7.33 (m, 7H), 7.31–7.20 (m, 3H), 7.05–6.93 (m, 2H), 5.75–5.68 (m, 1H), 5.66–5.60 (m, 1H), 5.13–5.03 (m, 1H), 4.56–4.49 (m, 1H), 4.23–4.15 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 163.4 (d, *J* = 248.8 Hz), 143.8, 137.8, 137.4, 132.6 (d, *J* = 3.4 Hz), 132.3, 132.0, 129.0, 128.8, 128.6, 128.5, 128.1, 127.7, 124.0, 123.7 (d, *J* = 1.2 Hz), 123.0, 115.4 (d, *J* = 21.8 Hz), 63.8, 61.8, 60.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.1 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{19}FClNO_2Na^+$, 430.0981, found 430.0979.

(*R*)-3-((*Z*)-2-(4-Bromophenyl)-2-chlorovinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9c). White solid (277 mg, 75%), mp 169–171 °C; $[\alpha]_D^{24} = -91.9$ (*c* 0.57, $CHCl_3$); IR (film): ν_{max} 3057, 2924, 1669, 1482, 1465, 1392, 1349, 1071, 749, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (m, 1H), 7.54–7.46 (m, 4H), 7.41–7.38 (m, 1H), 7.35–7.26 (m, 7H), 5.76 (d, *J* = 8.8 Hz, 1H), 5.65 (d, *J* = 9.2 Hz, 1H), 4.93 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.51 (dd, *J* = 12.0, 9.6 Hz, 1H), 4.24–4.04 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 143.6, 137.8, 137.2, 135.3, 132.3, 132.0, 131.6, 129.0, 128.8, 128.1 (2 C), 127.7, 124.5, 124.0, 123.9, 123.0, 63.7, 61.6, 60.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{19}ClBrNO_2Na^+$, 490.0180, found 490.0181.

(*R*)-3-((*Z*)-2-Chloro-2-(4-chlorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9d). White solid (258 mg, 77%), mp 150–152 °C; $[\alpha]_D^{24} = -89.1$ (*c* 0.32, $CHCl_3$); IR (film): ν_{max} 3061, 2920, 1673, 1491, 1470, 1395, 1349, 1088, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.81 (m, 1H), 7.55–7.46 (m, 2H), 7.40–7.35 (m, 3H), 7.33–7.24 (m, 7H), 5.77–5.69 (m, 1H), 5.66–5.59 (m, 1H), 4.97–4.88 (m, 1H), 4.56–4.43 (m, 1H), 4.257–4.18 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 143.6, 137.8, 137.2, 135.3, 132.3, 132.0, 131.6, 129.0, 128.8, 128.1, 127.7, 124.5, 124.0, 123.9, 123.0, 63.6, 61.5, 60.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{19}Cl_2NO_2Na^+$, 468.1701, found 468.1705.

(*R*)-3-((*Z*)-2-Chloro-2-(4-(trifluoromethyl)phenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9e). Colorless oil (260 mg, 72%); $[\alpha]_D^{24} = -79.2$ (*c* 0.38, $CHCl_3$); IR (film): ν_{max} 2920, 2849, 1669, 1465, 1406, 1322, 1170, 1131, 1066, 749, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.86 (m, 1H), 7.61–7.49 (m, 6H), 7.42–7.39 (m, 1H), 7.37–7.27 (m, 5H), 5.84 (d, *J* = 8.8 Hz, 1H), 5.70 (d, *J* = 9.2 Hz, 1H), 4.99 (d, *J* = 8.8, 4.4 Hz, 1H), 4.59–4.47 (m, 1H), 4.22–4.14 (m, 1H), 4.07 (brs, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 143.4, 139.7, 137.7, 136.7, 132.4, 132.0, 129.1, 128.9, 128.2, 127.7, 127.0, 126.2, 125.5, 125.4, 124.1, 123.0, 63.7, 61.1, 60.3 ppm; ^{19}F NMR

(376 MHz, $CDCl_3$) δ −63.2 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{19}ClF_3NO_2Na^+$, 480.0949, found 480.0950.

(*R*)-3-((*Z*)-2-Chloro-2-(p-tolyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9f). White solid (210 mg, 66%), mp 148–150 °C; $[\alpha]_D^{24} = -85.7$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3059, 2920, 1669, 1598, 1467, 1392, 1350, 1071, 747, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.86 (m, 1H), 7.56–7.47 (m, 2H), 7.42–7.37 (m, 3H), 7.34–7.25 (m, 5H), 7.19–7.13 (m, 2H), 5.75 (d, *J* = 8.8 Hz, 1H), 5.63 (d, *J* = 9.2 Hz, 1H), 4.91–4.82 (m, 1H), 4.50 (dd, *J* = 11.6, 8.4 Hz, 1H), 4.33 (brs, 1H), 4.15 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.37 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 144.0, 139.9, 138.8, 137.9, 133.7, 132.3, 132.1, 129.2, 128.9, 128.8, 128.0, 127.7, 126.5, 123.9, 123.1, 122.5, 64.0, 62.1, 60.7, 21.2 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}ClNO_2Na^+$, 426.1231, found 426.1230.

(*R*)-3-((*Z*)-2-(4-Butylphenyl)-2-chlorovinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9g). Colorless oil (186 mg, 53%); $[\alpha]_D^{23} = -76.0$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3057, 2953, 2927, 1676, 1467, 1395, 1355,1071, 752, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89–7.83 (m, 1H), 7.52–7.43 (m, 2H), 7.40–7.23 (m, 8H), 7.17–7.12 (m, 2H), 5.74 (d, *J* = 9.2 Hz, 1H), 5.67 (d, *J* = 9.2 Hz, 1H), 4.93 (dd, *J* = 8.4, 4.0 Hz, 1H), 4.51 (dd, *J* = 12.0, 8.8 Hz, 1H), 4.16 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.63–2.57 (m, 2H), 1.62–1.54 (m, 2H), 1.37–1.31 (m, 2H), 0.94–0.90 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 144.9, 144.0, 138.7, 138.0, 133.8, 132.2, 132.0, 128.8, 128.7, 128.0, 127.7, 126.5, 123.9, 123.0, 122.6, 63.8, 61.8, 60.7, 35.3, 33.4, 22.3, 13.9 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{28}ClNO_2Na^+$, 468.1701, found 468.1704.

(*R*)-3-((*Z*)-2-(4-(*tert*-Butyl)phenyl)-2-chlorovinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9h). Colorless oil (200 mg, 57%); $[\alpha]_D^{24} = -83.4$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2963, 2865, 1673, 1467, 1398, 1349,1076, 751, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.83 (m, 1H), 7.52–7.44 (m, 4H), 7.40–7.30 (m, 8H), 5.78 (d, *J* = 9.2 Hz, 1H), 5.61 (d, *J* = 9.2 Hz, 1H), 4.87–4.77 (m, 1H), 4.53–4.44 (m, 1H), 4.44–4.39 (m, 1H), 4.17–4.09 (m, 1H), 1.31 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 153.2, 144.0, 138.8, 137.8, 133.5, 132.3, 132.1, 128.9, 128.8, 128.0, 127.7, 126.3, 125.5, 123.9, 123.1, 122.5, 64.1, 62.3, 60.8, 34.7, 31.2 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{28}ClNO_2Na^+$, 468.1701, found 468.1705.

(*R*)-3-((*Z*)-2-Chloro-2-(4-methoxyphenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9i). White solid (215 mg, 65%), mp 147–149 °C; $[\alpha]_D^{23} = -109.2$ (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3055, 2918, 1669, 1604, 1507, 1255, 1178, 1029, 747, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.87 (m, 1H), 7.57–7.49 (m, 2H), 7.47–7.39 (m, 3H), 7.36–7.27 (m, 5H), 6.89–6.84 (m, 2H), 5.69 (d, *J* = 9.2 Hz, 1H), 5.64 (d, *J* = 8.8 Hz, 1H), 4.86 (dd, *J* = 8.4, 4.0 Hz, 1H), 4.50 (dd, *J* = 12.0, 8.4 Hz, 1H), 4.15 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.83 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 160.7, 144.2, 138.5, 137.9, 132.3, 132.1, 129.0 (2 C), 128.8, 128.7, 128.0, 127.7, 123.9, 123.1, 121.5, 113.8, 64.0, 62.1, 60.8, 55.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}ClNO_3Na^+$, 442.1180, found 442.1179.

(*R*)-3-((*Z*)-2-Chloro-2-(2-fluorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9j). White solid (232 mg, 72%), mp 148–150 °C; $[\alpha]_D^{24} = -54.3$ (*c* 0.40, $CHCl_3$); IR (film): ν_{max} 3059, 2922, 1671, 1486, 1449, 1397, 1237, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.83 (m, 1H), 7.57–7.43 (m, 4H), 7.38–7.26 (m, 6H), 7.19–7.13 (m, 1H), 7.12–7.05 (m, 1H), 5.80 (d, *J* = 9.2 Hz, 1H), 5.61 (d, *J* = 9.2 Hz, 1H), 4.90–4.82 (m, 1H), 4.58–4.44 (m, 2H), 4.21–4.12 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 159.3 (d, *J* = 250.5 Hz), 143.6, 137.8, 132.3, 132.1, 132.0 (d, *J* = 2.1 Hz), 131.1 (d, *J* = 8.6 Hz), 130.2 (d, *J* = 1.7 Hz), 129.0, 128.8, 128.0, 127.8, 125.3, 125.2, 124.2 (d, *J* = 3.7 Hz), 123.9, 123.0, 116.2 (d, *J* = 22.2 Hz), 64.0, 62.5, 60.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.2 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{19}FClNO_2Na^+$, 430.0981, found 430.0978.

(*R*)-3-((*Z*)-2-Chloro-2-(o-tolyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9k). Colorless oil (204 mg, 64%); $[\alpha]_D^{23} = -25.4$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3057, 2924, 1671, 1467, 1395, 1348, 1239, 1076, 749, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.85 (m, 1H), 7.61–7.56 (m, 1H), 7.53–7.47 (m, 1H), 7.39–7.25 (m, 6H), 7.22–7.14 (m, 3H), 5.58 (d, *J* = 8.0 Hz, 1H), 5.44 (d, *J* = 8.0 Hz, 1H), 4.88–4.82 (m, 1H), 4.59–4.51 (m, 1H), 4.44 (brs, 1H), 4.19–4.12 (m, 1H), 2.41 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 143.9, 138.6, 137.9, 135.7, 132.4, 132.1, 130.6, 129.4, 129.1, 128.9 (2 C), 128.1, 127.7, 126.9, 125.9, 124.0, 122.8, 64.1, 62.7, 60.5, 20.0 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}ClNO_2Na^+$, 426.1231, found 426.1230.

(*R*)-3-((*Z*)-2-Chloro-2-(2-chlorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9l). Colorless oil (251 mg, 75%); $[\alpha]_D^{21} = -18.5$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3059, 2922, 1671, 1467, 1449, 1397, 1237, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.89 (m, 1H), 7.59–7.49 (m, 4H), 7.44–7.41 (m, 1H), 7.39–7.29 (m, 7H), 5.80 (d, *J* = 9.2 Hz, 1H), 5.66 (d, *J* = 9.2 Hz, 1H), 4.84 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.59–4.50 (m, 1H), 4.19 (dd, *J* = 12.0, 3.6 Hz, 1H), 4.08 (brs, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 143.5, 137.9, 136.9, 135.5, 132.6, 132.4, 132.1, 130.6 (2 C), 130.1, 129.0, 128.8, 128.6, 128.1, 127.8, 126.9, 123.9, 123.1, 64.1, 62.6, 60.3 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}ClNO_2Na^+$, 446.0685, found 446.0682.

(*R*)-3-((*Z*)-2-Chloro-2-(m-tolyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9m). White solid (226 mg, 71%), mp 163–165 °C; $[\alpha]_D^{24} = -93.3$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3057, 2920, 1669, 1467, 1392, 1349, 1071, 747, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (m, 1H), 7.55–7.46 (m, 2H), 7.42–7.38 (m, 1H), 7.37–7.23 (m, 8H), 7.19–7.14 (m, 1H), 5.76 (d, *J* = 9.2 Hz, 1H), 5.66 (d, *J* = 9.2 Hz, 1H), 4.96–4.88 (m, 1H), 4.55–4.45 (m, 1H), 4.34 (brs, 1H), 4.23–4.11 (m, 1H), 2.36 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 144.0, 138.7, 138.2, 137.9, 136.4, 132.3, 132.0, 130.4, 128.9, 128.8, 128.4, 128.0, 127.7, 127.2, 123.9, 123.8, 123.4, 123.0, 63.8, 61.8, 60.6, 21.3 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}ClNO_2Na^+$, 426.1231, found 426.1230.

(*R*)-3-((*Z*)-2-Chloro-2-(3-methoxyphenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9n). White solid (205 mg, 62%), mp 139–141 °C; $[\alpha]_D^{21} = -88.6$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3061, 2928, 1596, 1470, 1394, 1265, 1048, 779, 747, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (m, 1H), 7.55–7.47 (m, 2H), 7.43–7.39 (m, 1H), 7.36–7.23 (m, 6H), 7.09–7.02 (m, 2H), 6.93–6.88 (m, 1H), 5.79 (d, *J* = 9.2 Hz, 1H), 5.65 (d, *J* = 9.2 Hz, 1H), 4.90 (dd, *J* = 8.4, 4.0 Hz, 1H), 4.55–4.46 (m, 1H), 4.34 (brs, 1H), 4.16 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.81 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 159.4, 143.6, 138.0, 137.6 (2 C), 132.0, 131.8, 129.3, 128.7, 128.5, 127.8, 127.5, 123.7, 122.8, 118.8, 114.9, 112.2, 63.5, 61.6, 60.3, 55.2 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}ClNO_3Na^+$, 442.1180, found 442.1181.

(*R*)-3-((*Z*)-2-(3-Bromophenyl)-2-chlorovinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9o). Yellow oil (261 mg, 71%); $[\alpha]_D^{24} = -304.0$ (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3059, 2922, 1669, 1472, 1397, 1349, 1215, 1068, 749, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.83 (m, 1H), 7.55–7.45 (m, 4H), 7.43–7.39 (m, 1H), 7.38–7.25 (m, 8H), 5.78 (d, *J* = 9.2 Hz, 1H), 5.66 (d, *J* = 8.8 Hz, 1H), 4.92 (dd, *J* = 8.0, 3.6 Hz, 1H), 4.56–4.47 (m, 1H), 4.34 (brs, 1H), 4.20–4.12 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 144.0, 138.5, 137.9, 136.4, 132.3, 132.1, 129.6, 128.9, 128.8, 128.5, 128.0, 127.7, 126.6, 123.9, 123.7, 123.1, 63.8, 61.8, 60.6 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}ClNO_3Na^+$, 490.0180, found 490.0181.

(*R*)-3-((*Z*)-2-Chloro-2-(3-fluorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9p). White solid (232 mg, 72%), mp 157–159 °C; $[\alpha]_D^{24} = -97.4$ (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3061, 2922, 1669, 1582, 1392, 1263, 1155, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.82 (m, 1H), 7.56–7.47 (m, 2H), 7.42–7.37 (m, 1H), 7.36–7.22 (m, 7H), 7.21–7.13 (m, 1H), 7.10–7.01 (m, 1H), 5.79 (d, J = 8.8 Hz, 1H), 5.66 (d, J = 8.8 Hz, 1H), 4.94 (dd, J = 8.8, 4.4 Hz, 1H), 4.58–4.47 (m, 1H), 4.20–4.14 (m, 1H), 4.13–4.06 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 162.6 (d, J = 245.2 Hz), 143.6, 138.6 (d, J = 7.9 Hz), 137.8, 136.8 (d, J = 2.7 Hz), 132.3, 132.0, 130.0 (d, J = 8.3 Hz), 129.0, 128.8, 128.1, 127.7, 125.1, 124.0, 123.0, 122.2 (d, J = 2.7 Hz), 116.5 (d, J = 21.2 Hz), 113.9 (d, J = 23.7 Hz), 63.6, 61.6, 60.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.8 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{19}FClNO_2Na^+$, 430.0981, found 430.0980.

(*S*)-3-((*Z*)-2-Chloro-2-(3-fluorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one ((*S*,*Z*,*R*)-**9p**). $[\alpha]_D^{23} = -125.2$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3061, 2922, 1669, 1582, 1392, 1263, 1155, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.86 (m, 1H), 7.62–751 (m, 2H), 7.37–7.33 (m, 1H), 7.24–7.14 (m, 4H), 7.12–7.05 (m, 2H), 7.04–6.92 (m, 3H), 5.70 (d, J = 10.4 Hz, 1H), 4.94 (d, J = 10.4 Hz, 1H), 4.70 (dd, J = 8.0, 3.6 Hz, 1H), 4.58–4.48 (m, 1H), 4.44–4.34 (m, 1H), 4.16–4.07 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 162.4 (d, J = 247.1 Hz), 143.3, 137.43 (d, J = 7.7 Hz), 137.42, 137.1 (d, J = 2.2 Hz), 132.4, 132.1, 130.2 (d, J = 8.4 Hz), 129.2, 128.7, 128.0, 127.1, 126.6, 124.1, 124.0 (d, J = 3.0 Hz), 122.9, 116.6 (d, J = 21.0 Hz, 1H), 115.7 (d, J = 22.7 Hz), 64.4, 63.1, 60.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.2 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{19}ClFNO_2Na^+$ 430.0981, found 430.0988.

(*S*)-3-((*E*)-2-Chloro-2-(3-fluorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one ((*S*,*E*,*R*)-**9p**). $[\alpha]_D^{23} = +159.0$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3061, 2922, 1669, 1582, 1392, 1263, 1155, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.84 (m, 1H), 7.55–7.46 (m, 2H), 7.41–7.26 (m, 6H), 7.25–7.20 (m, 1H), 7.05–7.00 (m, 2H), 6.96–6.90 (m, 1H), 5.74 (d, J = 6.0 Hz, 1H), 5.71 (d, J = 6.0 Hz, 1H), 5.16 (dd, J = 5.6, 3.2 Hz, 1H), 4.40 (dd, J = 8.0, 5.6 Hz, 1H), 4.20 (dd, J = 8.0, 3.2 Hz, 1H), 3.79 (brs, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 162.5 (d, J = 245.1 Hz), 143.5, 138.7 (d, J = 7.8 Hz), 138.0, 135.4, 132.3, 131.9, 129.9 (d, J = 8.3 Hz), 129.0, 128.9, 128.0, 127.9, 125.7, 123.9, 122.9, 122.1 (d, J = 2.4 Hz), 116.3 (d, J = 21.1 Hz), 113.8 (d, J = 23.6 Hz), 63.9, 61.9, 61.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.5 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{19}ClFNO_2Na^+$ 430.0981, found 430.0981.

(*R*)-3-((*E*)-2-Chloro-2-(3-fluorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one ((*R*,*E*,*R*)-**9p**). $[\alpha]_D^{23} = +232.0$ (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3061, 2922, 1669, 1582, 1392, 1263, 1155, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89–7.85 (m, 1H), 7.61–756 (m, 1H), 7.54–7.49 (m, 1H), 7.40–7.37 (m, 1H), 7.35–7.31 (m, 1H), 7.26–7.20 (m, 5H), 7.14–7.04 (m, 3H), 5.57 (d, J = 6.8 Hz, 1H), 5.11 (dd, J = 6.0 Hz, 3.6 Hz, 1H), 5.08 (d, J = 7.2 Hz, 1H), 4.36 (dd, J = 8.0, 6.0 Hz, 1H), 4.20 (dd, J = 8.0, 3.6 Hz, 1H), 3.17 (brs, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.6, 162.5 (d, J = 246.8 Hz), 143.3, 137.6 (d, J = 7.9 Hz), 137.2, 135.0, 132.3, 131.8, 130.4 (d, J = 8.4 Hz), 129.1, 128.8, 128.0, 127.6, 124.1, 122.8, 116.7 (d, J = 20.9 Hz), 115.7 (d, J = 22.5 Hz), 63.5, 60.2, 60.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.0 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{19}ClFNO_2Na^+$ 30.0981, found 430.0988.

(*R*)-3-((*Z*)-2-Chloro-2-(naphthalen-2-yl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9q). Colorless oil (222 mg, 64%); $[\alpha]_D^{21} = -143.8$ (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3059, 2922, 1671, 1604, 1499, 1424, 1298, 1220, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04–7.98 (m, 1H), 7.92–7.78 (m, 4H), 7.57–7.44 (m, 6H), 7.40–7.26 (m, 5H), 5.93 (d, J = 9.2 Hz, 1H), 5.71 (d, J = 9.2 Hz, 1H), 4.90–4.90 (m, 1H), 4.59–4.48 (m, 1H), 4.29–4.07 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 143.9, 138.6, 137.9, 133.6, 133.5, 132.9, 132.3, 132.1, 128.9, 128.8, 128.6, 128.2, 128.1, 127.8, 127.6, 127.2, 126.9, 126.7, 124.0 (2 C), 123.5, 123.1, 63.9, 62.0, 60.7 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{22}ClNO_2Na^+$, 462.1231, found 462.1231.

(*R*)-3-((*Z*)-2-Chloro-2-cyclopropylvinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9r). White solid (142 mg, 51%), mp 169–171 °C; $[\alpha]_D^{24} = -60.1$ (*c* 0.40, $CHCl_3$); IR (film): ν_{max} 3059, 2922, 1671, 1467, 1397, 1348, 1208, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.83 (m, 1H), 7.54–7.46 (m, 2H), 7.34–7.27 (m, 6H), 5.42 (d, J = 9.2 Hz, 1H), 5.24 (d, J = 9.2 Hz, 1H), 4.76 (dd, J = 7.6, 3.6 Hz, 1H), 4.52–4.38 (m, 2H), 4.17–4.10 (m, 1H), 1.74–1.67 (m, 1H), 0.83–0.73 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 144.4, 143.2, 137.9, 132.1, 132.0, 128.7 (2 C), 127.9, 127.7, 123.7, 123.0, 120.3, 64.1, 62.0, 60.2, 18.7, 6.4, 6.1 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{20}ClNO_2Na^+$, 376.1075, found 376.1075.

(*R*)-3-((*Z*)-2-Chlorohept-1-en-1-yl)-2-((*R*)-2-hydroxy-1-phenylethyl) isoindolin-1-one (9s). Colorless oil (195 mg, 67%); $[\alpha]_D^{24} = -27.5$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3059, 2922, 1671, 1469, 1395, 1352, 1130, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.87 (m, 1H), 7.58–7.50 (m, 2H), 7.37–7.28 (m, 4H), 7.25–7.23 (m, 2H), 5.31 (d, J = 10.4 Hz, 1H), 4.97 (d, J = 10.0 Hz, 1H), 4.80 (s, 1H), 4.68 (dd, J = 7.6, 3.2 Hz, 1H), 4.43–4.35 (m, 1H), 4.17–4.10 (m, 1H), 2.22–2.14 (m, 2H), 1.59–1.51 (m, 2H), 1.27–1.23 (m, 2H), 0.90–0.84 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 144.0, 142.4, 138.0, 132.5, 132.2, 129.1, 129.0, 128.2, 127.5, 124.1, 123.8, 123.0, 64.7, 63.2, 60.0, 34.2, 31.2, 27.8, 22.4, 14.0 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{26}ClNO_2Na^+$, 406.1544, found 406.1543.

(*R*)-3-((*Z*)-2-Chloro-2-(thiophen-3-yl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (9t). White solid (228 mg, 73%), mp 165–167 °C; $[\alpha]_D^{24} = -107.1$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3030, 2922, 1671, 1624, 1469, 1397, 1352, 1073, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.86 (m, 1H), 7.56–7.48 (m, 2H), 7.41–7.37 (m, 1H), 7.35–7.26 (m, 7H), 7.03–6.99 (m, 1H), 5.75 (d, J = 9.2 Hz, 1H), 5.57 (d, J = 9.2 Hz, 1H), 4.86 (dd, J = 8.0, 3.6 Hz, 1H), 4.52–4.43 (m, 1H), 4.33 (brs, 1H), 4.19–4.12 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 143.7, 140.2, 137.8, 132.3, 132.0, 131.8, 128.9, 128.8, 128.0, 127.7, 127.6, 127.2, 127.1, 123.9, 123.1, 121.4, 64.0, 62.1, 60.4 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{18}ClNO_2SNa^+$, 418.0639, found 418.0638.

(*R*)-6-Chloro-3-((*Z*)-2-chloro-2-phenylvinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (10a). Colorless oil (214 mg, 64%); $[\alpha]_D^{21} = -52.4$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3059, 2927, 1678, 1614, 1422, 1352, 1118, 1061, 762, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (m, 1H), 7.52–7.46 (m, 3H), 7.42–7.30 (m, 9H), 5.80–5.75 (m, 1H), 5.72–5.66 (m, 1H), 5.01–4.92 (m, 1H), 4.60–4.48 (m, 1H), 4.30–4.03 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 145.5, 138.9, 138.7, 137.7, 136.2, 130.5, 129.8, 129.5, 128.8, 128.5, 128.1, 127.7, 126.6, 125.1, 123.4, 123.0, 63.4, 61.5, 60.0 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{21}Cl_2NO2Na^+$, 446.0685, found 446.0686.

(*R*)-6-Chloro-3-((*Z*)-2-chloro-2-(o-tolyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (10b). Colorless oil (238 mg, 69%); $[\alpha]_D^{21} = -47.3$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3059, 2920, 1681, 1611, 1420, 1389, 1352, 1297, 1063, 769, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.75 (m, 1H), 7.49–7.44 (m, 1H), 7.40–7.23 (m, 7H), 7.22–7.13 (m, 3H), 5.56 (d, J = 8.8 Hz, 1H), 5.43 (d, J = 9.2 Hz, 1H), 4.84 (dd, J = 9.2, 4.0 Hz, 1H), 4.59–4.51 (m, 1H), 4.22–4.11 (m, 2H), 2.42 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 145.5, 139.1, 138.7, 137.6, 135.6, 130.6, 129.5, 129.1, 128.9, 128.2, 127.6, 126.2, 126.0, 125.2, 123.2, 63.8, 62.5, 60.0, 20.0 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{21}Cl_2NO_2Na^+$, 460.0842, found 460.0844.

(*R*)-6-Chloro-3-((*Z*)-2-chloro-2-(m-tolyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (10 c). Colorless oil (228 mg, 66 %); $[\alpha]_D^{21} = -40.8$ (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3059, 2928, 1676, 1609, 1425, 1392, 1352, 1065, 781, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.76 (m, 1H), 7.47–7.44 (m, 1H), 7.39–7.37 (m, 1H), 7.34–7.24 (m, 8H), 7.20–7.17 (m, 1H), 5.73 (d, $J = 9.2$ Hz, 1H), 5.64 (d, $J = 9.2$ Hz, 1H), 4.92 (dd, $J = 8.8$, 4.0 Hz, 1H), 4.56–4.45 (m, 1H), 4.21–4.01 (m, 2H), 2.36 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 145.5, 139.2, 138.7, 138.3, 137.7, 136.2, 130.6, 130.5, 129.5, 128.9, 128.4, 128.1, 127.7, 127.2, 125.1, 123.9, 123.4, 122.6, 63.6, 61.6, 60.1, 21.3 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{21}Cl_2NO_2Na^+$, 460.0842, found 460.0840.

(*R*)-6-Chloro-3-((*Z*)-2-chloro-2-(2-fluorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (10 d). Colorless oil (241 mg, 69 %); $[\alpha]_D^{22} = -47.8$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3061, 2926, 2851, 1679, 1487, 1434, 1344, 1196, 762, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.74 (m, 1H), 7.51–7.26 (m, 9H), 7.18–7.05 (m, 2H), 5.77 (d, $J = 9.2$ Hz, 1H), 5.62 (d, $J = 9.2$ Hz, 1H), 4.94–4.86 (m, 1H), 4.60–4.48 (m, 1H), 4.34 (brs, 1H), 4.19–4.11 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.4, 159.3 (d, $J = 250.5$ Hz), 141.8, 137.6, 135.2, 133.8, 132.5, 132.2, 131.2 (d, $J = 8.5$ Hz), 130.2, 128.8, 128.3 (d, $J = 6.7$ Hz), 128.2, 127.8, 125.0 (d, $J = 11.7$ Hz), 124.3, 124.0, 124.2 (d, $J = 3.6$ Hz), 116.2 (d, $J = 22.3$ Hz), 63.6, 62.2, 60.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.1 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{18}Cl_2FNO_2Na^+$, 464.0591, found 464.0594.

(*R*)-6-Chloro-3-((*Z*)-2-chloro-2-(4-chlorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (10 e). Colorless oil (264 mg, 73 %); $[\alpha]_D^{21} = -55.1$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3060, 2925, 1681, 1611, 1492, 1395, 1352, 1088, 826, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.74 (m, 1H), 7.47–7.42 (m, 1H), 7.40–7.42 (m, 1H), 7.40–7.37 (m, 1H), 7.37–7.32 (m, 7H), 7.32–7.25 (m, 2H), 5.72 (d, $J = 9.2$ Hz, 1H), 5.69 (d, $J = 9.2$ Hz, 1H), 5.05 (dd, $J = 8.8$, 3.6 Hz, 1H), 4.61–4.47 (m, 1H), 4.21 (dd, $J = 12.0$, 4.0 Hz, 1H), 4.13 (brs, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 145.3, 138.7, 137.7, 137.3, 135.8, 134.7, 130.4, 129.5, 128.8, 128.6, 128.1, 127.9, 127.7, 125.1, 123.8, 123.4, 63.1, 60.8, 59.7 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{18}Cl_3NO_2Na^+$, 480.0295, found 480.0298.

(*R*)-6-Chloro-3-((*Z*)-2-chloro-2-(thiophen-2-yl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (10 f). Colorless oil (241 mg, 71 %); $[\alpha]_D^{22} = -52.7$ (*c* 0.3, $CHCl_3$); IR (film): ν_{max} 3061, 2926, 2851, 1679, 1487, 1434, 1344, 1196, 762, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.77 (m, 1H), 7.57–7.53 (m, 1H), 7.49–7.45 (m, 1H), 7.41–7.38 (m, 1H), 7.36–7.28 (m, 6H), 7.11–7.07 (m, 1H), 5.72 (d, $J = 9.2$ Hz, 1H), 5.65 (d, $J = 9.2$ Hz, 1H), 4.95 (dd, $J = 9.2$, 3.6 Hz, 1H), 4.53 (dd, $J = 11.6$, 7.2 Hz, 1H), 4.31–4.05 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 145.5, 138.7, 138.1, 137.7, 133.6, 130.5, 129.5, 128.8, 128.1, 127.7, 126.8, 125.1, 124.8, 123.5, 121.4, 63.4, 61.5, 59.8 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{17}Cl_2NO_2SNa^+$, 452.0249, found 452.0248.

(*R*)-6-Chloro-3-((*Z*)-2-chloro-2-(thiophen-3-yl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one (10 g). Colorless oil (153 mg, 45 %); $[\alpha]_D^{24} = -22.7$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2928, 1666, 1606, 1501, 1467, 1300, 1223, 1120, 1073, 828, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.77 (m, 1H), 7.56–7.51 (m, 1H), 7.48–7.44 (m, 1H), 7.38–7.36 (m, 1H), 7.35–7.27 (m, 6H), 7.11–7.06 (m, 1H), 5.71 (d, $J = 9.2$ Hz, 1H), 5.60 (d, $J = 9.2$ Hz, 1H), 4.88 (dd, $J = 8.4$, 3.2 Hz, 1H), 4.55–4.45 (m, 1H), 4.15 (dd, $J = 12.4$, 3.6 Hz, 1H), 4.16 (brs, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 145.5, 138.7, 138.0, 137.6, 133.8, 130.5, 129.5, 128.8, 128.2, 127.7, 126.9, 125.1 (2 C), 124.8, 123.5, 121.3, 63.6, 61.8, 59.8 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{17}Cl_2NO_2SNa^+$, 452.0249, found 452.0252.

(*R*)-3-((*Z*)-2-Chloro-2-phenylvinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)-5,6-dimethoxyisoindolin-1-one (11 a). White solid (248 mg, 70 %), mp 143–145 °C; $[\alpha]_D^{21} = -75.9$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3059, 2935, 1663, 1624, 1499, 1424, 1298, 1217, 759, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (m, 1H), 7.40–7.28 (m, 9H), 6.82–6.78 (m, 1H), 5.80 (d, $J = 9.2$ Hz, 1H), 5.56 (d, $J = 9.2$, 1H), 4.86 (dd, $J = 8.0$, 3.6 Hz, 1H), 4.47 (dd, $J = 12.4$, 9.2 Hz, 1H), 4.16 (dd, $J = 12.0$, 3.6 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1, 153.3, 150.3, 138.4, 138.1, 137.6, 136.3, 129.7, 128.8, 128.5, 128.3, 127.9, 127.6, 126.6, 124.2, 124.0, 105.3, 104.8, 64.0, 61.9, 60.2, 56.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{24}ClNO_4Na^+$, 450.1468, found 450.1468.

(*R*)-3-((*Z*)-2-Chloro-2-(p–tolyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)-5,6-dimethoxyisoindolin-1-one (11 b). White solid (238 mg, 65 %), mp 108–110 °C; $[\alpha]_D^{21} = -57.1$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3026, 2925, 1663, 1502, 1465, 1302, 1220, 1081, 757, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.34–7.28 (m, 5H), 7.20–7.14 (m, 2H), 6.82–6.78 (m, 1H), 5.75 (d, $J = 9.2$ Hz, 1H), 5.54 (d, $J = 9.2$ Hz, 1H), 4.86 (dd, $J = 8.0$, 4.0 Hz, 1H), 4.55 (brs, 1H), 4.44 (dd, $J = 12.0$, 8.8 Hz, 1H), 4.15 (dd, $J = 11.6$, 3.6 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.37 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 153.3, 150.3, 139.9, 138.5, 138.1, 137.8, 133.6, 129.2, 128.7, 127.9, 127.6, 126.5, 124.2, 122.8, 105.3, 104.8, 64.0, 62.0, 60.3, 56.3, 21.2 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{26}ClNO_4Na^+$, 486.1443, found 486.1444.

(*R*)-3-((*Z*)-2-(4-Butylphenyl)-2-chlorovinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)-5,6-dimethoxyisoindolin-1-one (11 c). Colorless oil (247 mg, 62 %); $[\alpha]_D^{20} = -22.4$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2922, 2851, 1669, 1599, 1494, 1390, 1300, 1217, 769, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2H), 7.35–7.27 (m, 6H), 7.20–7.16 (m, 2H), 6.82–6.78 (m, 1H), 5.77 (d, $J = 9.2$ Hz, 1H), 5.53 (d, $J = 9.2$ Hz, 1H), 4.87–4.76 (m, 1H), 4.63–4.37 (m, 2H), 4.17–4.10 (m, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 2.60–2.61 (m, 2H), 1.62–1.56 (m, 2H), 1.37–1.32 (m, 2H), 0.94–0.90 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 153.3, 150.3, 145.0, 138.6, 138.1, 137.8, 133.7, 128.7, 128.6, 127.9, 127.6, 126.5, 124.2, 122.8, 105.3, 104.8, 64.1, 62.1, 60.4, 56.3, 35.3, 33.5, 22.3, 13.9 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{32}ClNO_4Na^+$, 506.2096, found 506.2097.

(*R*)-3-((*Z*)-2-Chloro-2-(2-fluorophenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)-5,6-dimethoxyisoindolin-1-one (11 d). Colorless oil (280 mg, 76 %); $[\alpha]_D^{21} = -57.7$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2926, 1667, 1498, 1348, 1298, 1219, 1075, 1031, 761, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.43 (m, 1H), 7.38–7.24 (m, 7H), 7.20–7.15 (m, 1H), 7.13–7.05 (m, 1H), 6.89–6.83 (m, 1H), 5.79 (d, $J = 9.2$ Hz, 1H), 5.52 (d, $J = 9.2$ Hz, 1H), 4.89–4.79 (m, 1H), 4.61 (brs, 1H), 4.52–4.39 (m, 1H), 4.20–4.14 (m, 1H), 3.95 (s, 3H), 3.92 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1, 159.3 (d, $J = 250.3$ Hz), 153.4, 150.4, 138.0, 137.3, 131.7, 131.1 (d, $J = 8.6$ Hz), 130.2, 129.2 (d, $J = 6.6$ Hz), 128.7, 128.0, 127.7, 125.2 (d, $J = 11.7$ Hz), 124.3, 124.2 (d, $J = 3.5$ Hz), 116.2 (d, $J = 22.3$ Hz), 105.3, 104.8, 64.2, 62.4, 60.2, 56.4, 56.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.6 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{23}ClFNO_4Na^+$, 490.1192, found 490.1193.

(*R*)-3-((*Z*)-2-(3-Bromophenyl)-2-chlorovinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)-5,6-dimethoxyisoindolin-1-one (11 e). Colorless oil (304 mg, 73 %); $[\alpha]_D^{20} = -89.0$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2930, 1666, 1501, 1424, 1382, 1300, 1217, 1078, 759, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.42 (m, 1H), 7.35–7.30 (m, 6H), 7.27–7.23 (m, 1H), 7.18–7.12 (m, 6H), 7.17–7.13 (m, 1H), 7.10–7.03 (m, 1H), 6.85–6.81 (m, 1H), 5.78 (d, $J = 9.2$ Hz, 1H), 5.48 (d, $J = 8.8$ Hz, 1H), 4.84–4.81 (m, 1H), 4.64–4.56 (m, 1H), 4.51–4.35 (m, 1H), 4.17–4.10 (m, 1H), 3.93 (s, 3H), 3.89 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 153.4, 150,5, 138.3, 137.9, 137.3, 136.5, 132.5, 130.0, 129.6, 128.8, 128.1, 127.6, 125.5, 125.2, 124.3, 122.7, 105.4, 104.8, 63.9, 61.7, 59.9, 56.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{23}ClBrNO_4Na^+$, 550.0391, found 550.0394.

(*R*)-3-((*Z*)-2-Chloro-2-(3-methoxyphenyl)vinyl)-2-((*R*)-2-hydroxy-1-phenylethyl)-5,6-dimethoxyisoindolin-1-one (11 f). Colorless oil (250 mg, 66%); $[\alpha]_D^{25} = -66.7$ (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2924, 2851, 1665, 1597, 1500, 1467, 1295, 1216, 777, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 7H), 712–7.05 (m, 2H), 6.96–6.87 (m, 1H), 6.83–6.74 (m, 1H), 5.81 (d, $J = 9.2$ Hz, 1H), 5.50 (d, $J = 8.8$ Hz, 1H), 4.80–4.76 (m, 1H), 4.49–4.42 (m, 2H), 4.17–4.09 (m, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 159.6, 153.4, 150.4, 138.2, 138.0, 137.7, 137.6, 129.5, 128.7, 128.0, 127.6, 124.3, 124.1, 119.0, 115.1, 112.5, 105.3, 104.9, 64.1, 62.1, 60.3, 56.4, 56.3, 55.5 ppm; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{26}ClNO_5Na^+$, 502.1392, found 502.1393.

Deposition Numbers 2055347 (for **9 j**), and 2055348 (for **9 p**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

We thank the National Natural Science Foundation of China (21772027) for financial support. We also thank Dr Han-Qing Dong (Arvinas, Inc.) for helpful suggestions.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Chiral isoindolinone scaffolds · Diastereoselectivity · Lewis acids · *N,O*-acetal · Terminal alkynes

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Manuscript received: March 24, 2021
Revised manuscript received: April 18, 2021