Supporting Information

Catalytic and Diastereoselective Cascade Reaction for the Preparation of cis-1,3-Disubstituted Isoindoline-Aminal Hybrid Compounds.

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1. General methods and materials

**General.** Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 FT-IR spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a JEOL JNM-ECZ500R (500 MHz for $^1$H and 126 MHz for $^{13}$C) spectrometer. Chemical shifts ($\delta$) are reported in ppm referenced to tetramethylsilane as internal standard (CDCl$_3$: $\delta = 0$ ppm for $^1$H) and residual solvent signal (CDCl$_3$: $\delta = 77.0$ ppm for $^{13}$C). J-values are given in Hz. For the correct assignment of both $^1$H and $^{13}$C NMR spectra of 3aa, $^1$H–$^1$H COSY HMQC, HMBC, and NOESY experiments were performed. The high-resolution mass spectra (HRMS) were obtained with a Shimadzu LCMS-IT-TOF mass spectrometer. All melting points were determined on a BÜCHI melting apparatus B-540 and are uncorrected. All manipulations were carried out with standard Schlenk technique under an argon atmosphere. Reactions were monitored by TLC (silica gel 60 F$_{254}$, 0.25 mm) analysis. Flash column chromatography was performed on flash silica gel 60N (spherical neutral, particle size 40–50 $\mu$m).

**Materials.** Anhydrous toluene, THF, 1,4-dioxane, DME, MeCN, DMF, and CH$_2$Cl$_2$ were purchased and used without any purification. (E)-S$_1$ and Imines 1a-1k were prepared according to the procedure described in the literature.

2. Experimental procedures

**General procedure for aminalization/IMAMR Cascade reaction of 1.**

![Reaction Diagram]

To a solution of 1 (0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere was added a solution of MTBD (1.5 $\mu$L, 0.010 mmol, 20 mol %) and aniline 2 (0.055 mmol, 1.1 equiv.) in dry MeCN (1.0 mL) at 30 °C. The mixture was stirred at 30 °C for 30 min. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (hexane/CHCl$_3$/EtOAc = 6/6/1 to 3/3/1) to afford 3.

S2
(1S*,3S*)-Methyl 2-{3-(4-methylphenlamino)-2-tosylisoindolin-1-yl}acetate (3aa).

According to the general procedure, 1a (17.2 mg, 0.050 mmol) and p-toluidine 2a (6.0 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3aa was obtained in 89% yield (20.0 mg, 0.0444 mmol) as pale yellow foam.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.32 (s, 3H), 2.35 (s, 3H), 2.43 (dd, $J$ = 7.7, 16.8 Hz, 1H), 2.93 (dd, $J$ = 3.7, 16.8 Hz, 1H), 3.64 (s, 3H), 4.65 (brs, 1H, NH), 5.11 (dd, $J$ = 3.6, 7.7 Hz, 1H), 6.31 (s, 1H), 6.57 (d, $J$ = 8.4 Hz, 2H), 6.93 (d, $J$ = 8.0 Hz, 2H), 7.11–7.13 (m, 1H), 7.22 (d, $J$ = 8.0 Hz, 2H), 7.28–7.32 (m, 2H), 7.39–7.41 (m, 1H), 7.72 (d, $J$ = 8.2 Hz, 2H).

$^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 20.5 (CH$_3$), 21.5 (CH$_3$), 41.4 (CH$_2$), 51.7 (CH$_3$), 60.0 (CH), 78.1 (CH), 119.1 (CH), 122.6 (CH), 124.2 (CH), 127.4 (CH), 128.5 (CH), 129.3 (CH), 129.4 (CH), 129.8 (CH), 130.4 (C), 135.3 (C), 137.8 (C), 139.1 (C), 141.9 (C), 143.7 (C), 171.5 (C).

IR (KBr) v: 3385, 3028, 2951, 2917, 2867, 1735, 1520, 1344, 1300, 1163, 1011, 814 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{25}$H$_{26}$NaO$_4$S 473.1505; Found 473.1508.

(1S*,3S*)-Methyl 2-(3-phenlamino-2-tosylisoindolin-1-yl)acetate (3ab).

According to the general procedure, 1a (17.2 mg, 0.050 mmol) and aniline 2b (5.0 µL, 0.055 mmol) were used. After a reaction time of 30 min, cis-3ab was obtained in 83% yield (18.2 mg, 0.0417 mmol) as colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.36 (s, 3H), 2.56 (dd, $J$ = 7.4, 16.8 Hz, 1H), 2.95 (dd, $J$ = 3.6, 16.8 Hz, 1H), 3.63 (s, 3H), 4.75 (brs, 1H, NH), 5.15 (dd, $J$ = 3.6, 7.4 Hz, 1H), 6.39 (s, 1H), 6.66 (d, $J$ = 8.3 Hz, 2H), 6.85 (t, $J$ = 7.3 Hz, 1H), 7.12–7.15 (m, 3H), 7.21 (d, $J$ = 8.1 Hz, 2H), 7.30–7.33 (m, 2H), 7.38–7.40 (m, 1H), 7.71 (d, $J$ = 8.2 Hz, 2H).

$^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 21.5 (CH$_3$), 41.2 (CH$_2$), 51.6 (CH$_3$), 60.0 (CH), 77.4 (CH), 118.0 (CH), 120.6 (CH), 122.5 (CH), 124.1 (CH), 127.4 (CH), 128.6 (CH), 128.9 (CH), 129.3 (CH), 129.8 (CH), 135.5 (C), 137.9 (C), 139.0 (C), 143.7 (C), 144.7 (C), 171.4 (C).

IR (KBr) v: 3388, 3032, 2952, 2927, 2850, 1735, 1601, 1510, 1340, 1161, 1092, 909, 814 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{24}$N$_2$NaO$_4$S 459.1349; Found 459.1351.
(1S*,3S*)-Methyl 2-[3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl]acetate (3ac).

According to the general procedure, 1a (17.2 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3ac was obtained in 91% yield (21.2 mg, 0.0454 mmol) as pale yellow oil.

1H NMR (500 MHz, CDCl3): δ 2.09 (dd, J = 8.2, 16.8 Hz, 1H), 2.36 (s, 3H), 2.82 (dd, J = 3.8, 16.8 Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 4.52 (brs, 1H, NH), 5.03 (dd, J = 3.8, 8.2 Hz, 1H), 6.19 (s, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.29 (dd, J = 7.6, 7.6 Hz, 1H), 7.34 (dd, J = 7.4, 7.4 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H).

13C{1H} NMR (126 MHz, CDCl3): δ 21.5 (CH3), 41.8 (CH2), 51.6 (CH3), 55.5 (CH3), 60.0 (CH), 79.3 (CH), 114.1 (CH), 122.7 (CH), 123.0 (CH), 124.5 (CH), 127.3 (CH), 128.4 (CH), 129.3 (CH), 129.9 (CH), 135.1 (C), 137.2 (C), 137.3 (C), 139.6 (C), 143.8 (C), 155.2 (C), 171.6 (C).

IR (KBr) v: 3371, 3029, 2952, 2927, 2835, 1735, 1511, 1340, 1236, 1160, 1035, 818 cm⁻¹.

HRMS (ESI-TOF) m/z: [M+Na]⁺ Calcd for C25H26N2NaO4S 489.1455; Found 489.1458.

(1S*,3S*)-Methyl 2-[3-(4-chlorophenylamino)-2-tosylisoindolin-1-yl]acetate (3ad).

According to the general procedure, 1a (17.2 mg, 0.050 mmol) and p-chloroaniline 2d (7.2 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3ad was obtained in 86% yield (20.3 mg, 0.0431 mmol) as pale yellow oil.

1H NMR (500 MHz, CDCl3): δ 2.36 (s, 3H), 2.69 (dd, J = 7.0, 16.9 Hz, 1H), 3.00 (dd, J = 3.5, 16.9 Hz, 1H), 3.63 (s, 3H), 4.83 (brd, J = 6.2 Hz, 1H, NH), 5.15 (dd, J = 3.5, 7.0 Hz, 1H), 6.36 (d, J = 5.3 Hz, 1H), 6.60 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 7.13–7.15 (m, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.31–7.37 (m, 3H), 7.70 (d, J = 8.3 Hz, 2H).

13C{1H} NMR (126 MHz, CDCl3): δ 21.5 (CH3), 41.0 (CH2), 51.7 (CH3), 60.0 (CH), 77.1 (CH), 118.7 (CH), 122.5 (CH), 123.9 (CH), 125.1 (C), 127.4 (CH), 128.7 (CH), 128.8 (CH), 129.4 (CH), 129.8 (CH), 135.3 (C), 137.6 (C), 138.8 (C), 143.5 (C), 143.9 (C), 171.3 (C).

IR (KBr) v: 3383, 3029, 2952, 2923, 2853, 1737, 1598, 1510, 1339, 1159, 1093, 814 cm⁻¹.

HRMS (ESI-TOF) m/z: [M+Na]⁺ Calcd for C24H23ClIN2NaO4S 493.0959; Found 493.0961.
(1S*,3S*)-Methyl 2-{3-(4-bromophenylamino)-2-tosylisodolin-1-yl}acetate (3ae).

According to the general procedure, 1a (17.2 mg, 0.050 mmol) and 4-bromoaniline 2e (9.6 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3ae was obtained in 82% yield (21.1 mg, 0.0409 mmol) as pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.37 (s, 3H), 2.74 (dd, $J = 6.9, 16.9$ Hz, 1H), 3.01 (dd, $J = 3.5, 16.9$ Hz, 1H), 3.63 (s, 3H), 4.85 (brd, $J = 6.9$ Hz, 1H, NH), 5.17 (dd, $J = 3.5, 6.9$ Hz, 1H), 6.38 (d, $J = 5.9$ Hz, 1H), 6.55 (d, $J = 8.4$ Hz, 2H), 7.14–7.15 (m, 1H), 7.21–7.23 (m, 4H), 7.31–7.35 (m, 3H), 7.69 (d, $J = 8.2$ Hz, 2H).

$^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 21.5 (CH$_3$), 40.9 (CH$_2$), 51.7 (CH$_3$), 60.1 (CH), 76.8 (CH), 112.2 (C), 118.7 (CH), 122.5 (CH), 123.9 (CH), 127.4 (CH), 128.7 (CH), 129.5 (CH), 129.8 (CH), 131.7 (CH), 135.4 (C), 137.7 (C), 138.7 (C), 143.9 (C), 144.1 (C), 171.3 (C).

IR (KBr) v: 3384, 3033, 2952, 2923, 2850, 1737, 1594, 1510, 1460, 1338, 1159, 812 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{23}$N$_2$NaO$_4$S 537.0454; Found 537.0455.

m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{23}$N$_2$NaO$_4$S 539.0436; Found 539.0450.

(1S*,3S*)-Methyl 2-{3-(4-nitrophenylamino)-2-tosylisodolin-1-yl}acetate (3af).

According to the general procedure, 1a (17.2 mg, 0.050 mmol) and p-nitroaniline 2f (7.7 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3af was obtained in 63% yield (15.2 mg, 0.0316 mmol) as dark yellow amorphous solid.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.36 (s, 3H), 3.08 (dd, $J = 3.2, 17.3$ Hz, 1H), 3.20 (dd, $J = 5.4, 17.3$ Hz, 1H), 3.57 (s, 3H), 5.22 (dd, $J = 3.2, 5.1$ Hz, 1H), 5.86 (brd, $J = 9.7$ Hz, 1H, NH), 6.66 (d, $J = 9.7$ Hz, 1H), 6.73 (d, $J = 9.2$ Hz, 2H), 7.17 (d, $J = 7.7$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 7.5$ Hz, 1H), 7.33 (dd, $J = 7.1, 7.1$ Hz, 1H), 7.37 (dd, $J = 1.2, 7.4, 7.4$ Hz, 1H), 7.68 (d, $J = 8.2$ Hz, 2H), 8.09 (d, $J = 9.2$ Hz, 2H).

$^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 21.5 (CH$_3$), 39.5 (CH$_2$), 51.7 (CH$_3$), 60.2 (CH), 74.1 (CH), 112.6 (CH), 122.1 (CH), 123.5 (CH), 126.1 (CH), 127.4 (CH), 128.9 (CH), 129.7 (CH), 129.8 (CH), 135.6 (C), 137.4 (C), 138.1 (C), 139.1 (C), 144.2 (C), 151.0 (C), 171.1 (C).

IR (KBr) v: 3366, 3078, 3012, 2952, 2923, 2855, 1738, 1599, 1503, 1343, 1320, 1163, 1112, 816 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{23}$N$_3$NaO$_6$S 504.1200; Found 504.1202.
(1S*,3S*)-Ethyl 2-{3-(4-methoxyphenylamino)-2-tosylisodolin-1-yl}acetate (3bc).

According to the general procedure, 1b (17.9 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3bc was obtained in 90% yield (21.6 mg, 0.0450 mmol) as pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 1.23 (t, J = 7.1 Hz, 3H), 2.12 (dd, J = 8.2, 16.8 Hz, 1H), 2.36 (s, 3H), 2.83 (dd, J = 3.8, 16.8 Hz, 1H), 3.73 (s, 3H), 4.10 (qd, J = 7.1, 10.8 Hz, 1H), 4.13 (qd, J = 7.2, 10.8 Hz, 1H), 4.59 (brs, 1H, NH), 5.05 (dd, J = 3.7, 8.1 Hz, 1H), 6.20 (s, 1H), 6.62 (d, J = 9.0 Hz, 2H), 6.69 (d, J = 9.0 Hz, 2H), 7.11 (d, J = 7.7 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.29 (ddd, J = 1.0, 7.5, 7.5 Hz, 1H), 7.33 (dd, J = 7.2, 7.2 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H).

$^{13}$C$^{1}$H NMR (126 MHz, CDCl$_3$): δ 14.11 (CH$_3$), 21.5 (CH$_3$), 41.9 (CH$_2$), 55.5 (CH$_3$), 60.0 (CH), 60.6 (CH$_2$), 79.2 (CH), 114.1 (CH), 122.66 (CH), 122.72 (CH), 124.4 (CH), 127.3 (CH), 128.3 (CH), 129.3 (CH), 129.8 (CH), 135.2 (C), 137.3 (C), 137.4 (C), 139.7 (C), 143.7 (C), 155.1 (C), 171.1 (C).

IR (KBr) v: 3367, 3033, 2983, 2930, 2835, 1730, 1598, 1511, 1461, 1340, 1236, 1160, 1034, 819 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^{+}$ Calcd for C$_{26}$H$_{32}$N$_{2}$NaO$_{5}$S 503.1611; Found 503.1615.

(1S*,3S*)-tert-Butyl 2-{3-(4-methoxyphenylamino)-2-tosylisodolin-1-yl}acetate (3cc).

According to the general procedure, 1c (19.3 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3cc was obtained in 44% yield (11.3 mg, 0.0222 mmol) as pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 1.42 (s, 9H), 2.02 (dd, J = 8.5, 16.6 Hz, 1H), 2.36 (s, 3H), 2.84 (dd, J = 3.5, 16.5 Hz, 1H), 3.73 (s, 3H), 4.53 (brs, 1H, NH), 5.04 (dd, J = 3.4, 8.5 Hz, 1H), 6.21 (s, 1H), 6.61 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 7.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.29 (dd, J = 7.4, 7.4 Hz, 1H), 7.32 (dd, J = 7.3, 7.3 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H).

$^{13}$C$^{1}$H NMR (126 MHz, CDCl$_3$): δ 21.5 (CH$_3$), 28.0 (CH$_3$), 43.0 (CH$_2$), 55.5 (CH$_3$), 60.2 (CH), 79.0 (CH), 80.9 (C), 114.1 (CH), 122.3 (CH), 122.7 (CH), 124.4 (CH), 127.4 (CH), 128.3 (CH), 129.2 (CH), 129.8 (CH), 135.3 (C), 137.4 (C), 137.5 (C), 139.9 (C), 143.7 (C), 155.0 (C), 170.4 (C).

IR (KBr) v: 3367, 2978, 2933, 2833, 1719, 1598, 1510, 1460, 1340, 1236, 1158, 819 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^{+}$ Calcd for C$_{28}$H$_{32}$N$_{2}$NaO$_{5}$S 531.1924; Found 531.1926.
(1S*,3S*)-Benzy1 2-{3-(4-methoxyphenylamino)-2-tosyloindolin-1-yl}acetate (3dc).

According to the general procedure, 1d (21.0 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3dc was obtained in 92% yield (25.0 mg, 0.0461 mmol) as dark orange foam.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.15 (dd, $J = 7.9, 16.5$ Hz, 1H), 2.35 (s, 3H), 2.82 (dd, $J = 4.0, 16.6$ Hz, 1H), 3.68 (s, 3H), 4.53 (brs, 1H, NH), 5.05 (dd, $J = 4.0, 7.9$ Hz, 1H), 5.10 (s, 2H), 6.20 (s, 1H), 6.59 (d, $J = 8.6$ Hz, 2H), 6.65 (d, $J = 8.6$ Hz, 2H), 7.02 (d, $J = 7.7$ Hz, 1H), 7.20–7.26 (m, 3H), 7.31–7.38 (m, 6H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 2H).

$^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 21.5 (CH$_3$), 42.0 (CH$_2$), 55.4 (CH$_3$), 60.0 (CH), 66.4 (CH$_2$), 79.3 (CH), 114.1 (CH), 122.7 (CH), 122.9 (CH), 124.5 (CH), 127.3 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.3 (CH), 129.8 (CH), 135.1 (C), 135.6 (C), 137.2 (C), 137.4 (C), 139.5 (C), 143.7 (C), 155.2 (C), 170.9 (C). One aromatic carbon (CH) was not observed due to overlap.

IR (KBr) v: 3379, 3033, 2932, 2833, 1731, 1512, 1343, 1296, 1238, 1163, 1095, 818 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{31}$H$_{30}$N$_2$NaO$_5$S 565.1768; Found 565.1770.

(1S*,3S*)-[3-(4-methoxyphenylamino)-2-tosyloindolin-1-yl]acetonitrile (3ec).

According to the general procedure, 1e (15.5 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3ec was obtained in 93% yield (20.2 mg, 0.0466 mmol) as pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.86 (dd, $J = 8.9, 16.8$ Hz, 1H), 2.38 (s, 3H), 2.92 (dd, $J = 2.9, 16.8$ Hz, 1H), 3.73 (s, 3H), 4.43 (brs, 1H, NH), 4.83 (dd, $J = 3.2, 9.0$ Hz, 1H), 6.25 (s, 1H), 6.63 (d, $J = 8.7$ Hz, 2H), 6.68 (d, $J = 8.7$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.39–7.44 (m, 3H), 7.52 (d, $J = 7.4$ Hz, 1H), 7.70 (d, $J = 8.2$ Hz, 2H).

$^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 21.5 (CH$_3$), 25.7 (CH$_2$), 55.4 (CH$_3$), 59.2 (CH), 79.3 (CH), 114.1 (CH), 117.5 (C), 122.9 (CH), 123.0 (CH), 124.8 (CH), 127.1 (CH), 129.3 (CH), 129.7 (CH), 130.1 (CH), 135.0 (C), 136.9 (C), 137.1 (C), 137.6 (C), 144.3 (C), 155.4 (C).

IR (KBr) v: 3379, 3021, 2929, 2854, 2833, 2250, 1510, 1339, 1234, 1160, 1033, 820 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{23}$N$_3$NaO$_5$S 456.1352; Found 456.1355.
(1S*,3S*)-Methyl 2-{6-methoxy-3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl}acetate (3fc).

According to the general procedure, 1f (18.7 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3fc was obtained in 84% yield (20.9 mg, 0.0421 mmol) as pale orange oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.00 (dd, $J = 8.4, 16.9$ Hz, 1H), 2.37 (s, 3H), 2.78 (dd, $J = 3.8, 16.9$ Hz, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 4.56 (brs, 1H, NH), 4.96 (dd, $J = 3.8, 8.3$ Hz, 1H), 6.10 (s, 1H), 6.60 (d, $J = 2.2$ Hz, 1H), 6.62 (d, $J = 8.9$ Hz, 2H), 6.69 (d, $J = 8.9$ Hz, 2H), 6.88 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.26 (d, $J = 8.1$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.73 (d, $J = 8.2$ Hz, 2H).

$^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 21.5 (CH$_3$), 41.8 (CH$_2$), 51.7 (CH$_3$), 55.4 (CH$_3$), 55.5 (CH$_3$), 59.9 (CH), 79.1 (CH), 107.2 (CH), 114.0 (CH), 115.1 (CH), 123.5 (CH), 125.4 (CH), 127.3 (CH), 129.1 (C), 129.9 (CH), 135.0 (C), 137.0 (C), 141.3 (C), 143.8 (C), 155.3 (C), 160.7 (C), 171.8 (C).

IR (KBr): $\nu$: 3381, 3000, 2950, 2924, 2836, 1734, 1512, 1340, 1240, 1162, 1034, 818 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Caled for C$_{26}$H$_{28}$N$_2$NaO$_6$S 519.1560; Found 519.1554.

(1S*,3S*)-Methyl 2-{5-chloro-3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl}acetate (3gc).

According to the general procedure, 1g (18.9 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3gc was obtained in 90% yield (22.6 mg, 0.0451 mmol) as pale yellow foam.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.04 (dd, $J = 8.3, 17.0$ Hz, 1H), 2.38 (s, 3H), 2.82 (dd, $J = 3.7, 17.0$ Hz, 1H), 3.65 (s, 3H), 3.74 (s, 3H), 4.57 (brs, 1H, NH), 4.97 (dd, $J = 3.5, 8.3$ Hz, 1H), 6.13 (s, 1H), 6.64 (d, $J = 8.9$ Hz, 2H), 6.71 (d, $J = 8.9$ Hz, 2H), 7.04 (d, $J = 8.2$ Hz, 1H), 7.24–7.27 (m, 3H), 7.45 (d, $J = 1.9$ Hz, 1H), 7.71 (d, $J = 8.3$ Hz, 2H).

$^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 21.5 (CH$_3$), 41.5 (CH$_2$), 51.7 (CH$_3$), 55.5 (CH$_3$), 59.6 (CH), 78.8 (CH), 114.1 (CH), 123.2 (CH), 124.1 (CH), 124.6 (CH), 127.2 (CH), 129.7 (CH), 130.0 (CH), 134.4 (C), 134.8 (C), 136.8 (C), 138.0 (C), 139.3 (C), 144.0 (C), 155.4 (C), 171.5 (C).

IR (KBr): $\nu$: 3375, 3000, 2952, 2925, 2835, 1734, 1512, 1344, 1238, 1163, 1087, 1036, 822 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Caled for C$_{25}$H$_{25}$ClN$_2$NaO$_5$S 523.1065; Found 523.1061.
(1S*,3S*)-Methyl 2-[3-(4-methoxyphenylamino)-2-benzenesulfonylisooindolin-1-yl]acetate (3ic).

According to the general procedure, 1i (16.5 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3ic was obtained in 87% yield (19.7 mg, 0.0435 mmol) as pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.11 (dd, $J = 8.1, 16.8$ Hz, 1H), 2.82 (dd, $J = 3.8, 16.8$ Hz, 1H), 3.65 (s, 3H), 3.73 (s, 3H), 4.58 (brs, 1H, NH), 5.06 (dd, $J = 3.8, 8.0$ Hz, 1H), 6.23 (s, 1H), 6.63 (d, $J = 8.8$ Hz, 2H), 6.69 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 7.6$ Hz, 1H), 7.29 (dd, $J = 7.2, 7.2$ Hz, 1H), 7.34 (dd, $J = 7.2, 7.2$ Hz, 1H), 7.45–7.48 (m, 3H), 7.53 (dd, $J = 7.4, 7.4$ Hz, 1H), 7.84–7.86 (m, 2H).

$^{13}$C$[^1$H$]$ NMR (126 MHz, CDCl$_3$): $\delta$ 41.7 (CH$_2$), 51.7 (CH$_3$), 55.5 (CH$_3$), 60.0 (CH), 79.4 (CH), 114.1 (CH), 122.7 (CH), 122.9 (CH), 124.5 (CH), 127.3 (CH), 128.4 (CH), 129.2 (CH), 129.4 (CH), 132.9 (CH), 137.2 (C), 137.3 (C), 138.2 (C), 139.5 (C), 155.2 (C), 171.5 (C).

IR (KBr) v: 3367, 3029, 2952, 2836, 1745, 1510, 1460, 1338, 1233, 1160, 1032, 828 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{24}$N$_2$NaO$_5$S 475.1298; Found 475.1302.

(1S*,3S*)-Methyl 2-[3-(4-methoxyphenylamino)-2-(4-methoxybenzenesulfonyl)isooindolin-1-yl]acetate (3jc).

According to the general procedure, 1j (18.0 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3jc was obtained in 91% yield (21.9 mg, 0.0454 mmol) as pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.12 (dd, $J = 8.1, 16.8$ Hz, 1H), 2.82 (dd, $J = 3.9, 16.8$ Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 4.51 (brs, 1H, NH), 5.03 (dd, $J = 3.8, 8.1$ Hz, 1H), 6.18 (s, 1H), 6.61 (d, $J = 8.9$ Hz, 2H), 6.68 (d, $J = 8.7$ Hz, 2H), 6.91 (d, $J = 9.0$ Hz, 2H), 7.09 (d, $J = 7.5$ Hz, 1H), 7.29 (dd, $J = 7.2, 7.2$ Hz, 1H), 7.34 (dd, $J = 7.4, 7.4$ Hz, 1H), 7.46 (d, $J = 7.5$ Hz, 1H), 7.78 (d, $J = 9.0$ Hz, 2H).

$^{13}$C$[^1$H$]$ NMR (126 MHz, CDCl$_3$): $\delta$ 41.7 (CH$_2$), 51.7 (CH$_3$), 55.51 (CH$_3$), 55.53 (CH$_3$), 60.0 (CH), 79.2 (CH), 114.1 (CH), 114.4 (CH), 122.7 (CH), 122.8 (CH), 124.5 (CH), 128.4 (CH), 129.3 (CH), 129.4 (CH), 129.8 (C), 137.3 (C), 137.4 (C), 139.6 (C), 155.2 (C), 163.1 (C), 171.7 (C).

IR (KBr) v: 3369, 3013, 2952, 2838, 1737, 1596, 1510, 1340, 1236, 1157, 1029, 833 cm$^{-1}$.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{25}$H$_{26}$N$_2$NaO$_6$S 505.1404; Found 505.1408.
(1S*,3S*)-Methyl 2-[3-(4-methoxyphenylamino)-2-(4-chlorobenzenesulfonyl)isoindolin-1-yl]acetate (3kc).

According to the general procedure, 1k (18.2 mg, 0.050 mmol) and p-anisidine 2c (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, cis-3kc was obtained in 52% yield (12.7 mg, 0.0261 mmol) as yellow oil.

^1H NMR (500 MHz, CDCl3): δ 2.19 (dd, J = 7.7, 16.8 Hz, 1H), 2.79 (dd, J = 3.9, 16.8 Hz, 1H), 3.64 (s, 3H), 3.74 (s, 3H), 4.56 (brs, 1H, NH), 5.07 (dd, J = 3.9, 7.6 Hz, 1H), 6.25 (s, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 7.11 (d, J = 7.5 Hz, 1H), 7.30–7.37 (m, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 7.3 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H).

^13C{^1H} NMR (126 MHz, CDCl3): δ 41.4 (CH2), 51.7 (CH3), 55.5 (CH3), 60.0 (CH), 79.4 (CH), 114.2 (CH), 122.4 (CH), 122.6 (CH), 124.4 (CH), 128.6 (CH), 128.7 (CH), 129.5 (2CH), 137.0 (C), 137.20 (C), 137.23 (C), 139.2 (C), 139.4 (C), 155.2 (C), 171.4 (C).

IR (KBr) v: 3368, 3028, 3006, 2950, 2927, 2852, 1737, 1511, 1340, 1235, 1162, 1033, 828 cm⁻¹.

HRMS (ESI-TOF) m/z: [M+Na]^+ Calcd for C₂₄H₂₃ClN₂NaO₅S 509.0908; Found 509.0909.

Aminalization/IMAMR cascade reaction of 1a on a 0.50 mmol scale (Table 2, entry 7).

To a solution of 1a (0.50 mmol, 171.7 mg) in dry MeCN (5.0 mL) under an argon atmosphere was added a solution of MTBD (15.2 µL, 0.10 mmol, 20 mol %) and p-anisidine 2c (68.4 mg, 0.55 mmol, 1.1 equiv.) in dry MeCN (7.0 mL) at 30 °C. The mixture was stirred at 30 °C for 30 min. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (hexane/CHCl₃/EtOAc = 4/4/1) to afford cis-3ac (207.2 mg, 0.444 mmol, 89%). The data of NMR, HRMS, IR, and HRMS were matched with the case of the reaction on a 0.050 mmol scale.
General procedure for the preparation of imine 4a, 4c, and 4d.

According to the reported procedure for preparation of imines, imines (E)-4a, (E)-4c, and (E)-4d were prepared. To a mixture of (E)-S1 (38.0 mg, 0.20 mmol), 2 (1.1 equiv.), and MgSO₄ (80 mg) was added dry CH₂Cl₂ (1.0 mL) at rt under Ar atmosphere. After being stirred the mixture at rt for 18 h, the reaction mixture was filtered. The filtrate was evaporated to dryness and the residue was purified by recrystallization from hexane and CH₂Cl₂ at rt to –10 °C. In the case of (E)-4a, the purification was carried out by flash column chromatography on silica gel (hexane/EtOAc = 10/1).

(E)-Methyl 3-(2-[[4-methylphenyl]iminomethyl]phenyl)prop-2-enoate (E)-4a.

According to the general procedure, (E)-S1 (38.0 mg, 0.20 mmol) and p-toluidine 2a (23.8 mg, 0.22 mmol) were used. (E)-4a was obtained in 75% yield (42.1 mg, 0.151 mmol) as dark yellow amorphous solid.

¹H NMR (500 MHz, CDCl₃): δ 2.38 (s, 3H), 3.82 (s, 3H), 6.38 (d, J = 15.8 Hz, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.46–7.50 (m, 2H), 7.59–7.61 (m, 1H), 8.08–8.10 (m, 1H), 8.41 (d, J = 15.8 Hz, 1H), 8.83 (s, 1H).

¹³C{¹H} NMR (126 MHz, CDCl₃): δ 21.0 (CH₃), 51.8 (CH₃), 120.9 (CH), 121.2 (CH), 127.5 (CH), 128.9 (CH), 129.8 (CH), 130.0 (CH), 130.9 (CH), 134.6 (C), 135.2 (C), 136.3 (C), 141.8 (CH), 149.2 (C), 156.8 (CH), 167.0 (C).

IR (KBr) ν: 3023, 2983, 2944, 2911, 1721, 1631, 1505, 1319, 1277, 1196, 1171, 982, 820 cm⁻¹.

HRMS (ESI-TOF) m/z: [M+Na]^+ Calcd for C₁₈H₁₇NNaO₂ 302.1152; Found 302.1148.
(E)-Methyl 3-(2-[[4-methoxyphenyl]imino)methyl]phenyl)prop-2-enoate (E)-4c.

According to the general procedure, (E)-S1 (38.0 mg, 0.20 mmol) and p-anisidine 2c (27.4 mg, 0.22 mmol) were used. (E)-4c was obtained in 87% yield (51.4 mg, 0.174 mmol) as yellow solid.

Mp: 72.8–73.7 °C

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 3.82 (s, 3H), 3.85 (s, 3H), 6.39 (d, \(J = 15.8\) Hz, 1H), 6.95 (d, \(J = 8.4\) Hz, 2H), 7.27 (d, \(J = 8.4\) Hz, 2H), 7.45–7.50 (m, 2H), 7.59–7.61 (m, 1H), 8.07–8.09 (m, 1H), 8.43 (d, \(J = 15.8\) Hz, 1H), 8.84 (s, 1H).

\(^{13}\)C\{\(^1\)H\} NMR (126 MHz, CDCl\(_3\)): \(\delta\) 51.8 (CH\(_3\)), 55.5 (CH\(_3\)), 114.4 (CH), 121.1 (CH), 122.4 (CH), 127.5 (CH), 128.8 (CH), 130.0 (CH), 130.7 (CH), 134.8 (C), 135.0 (C), 142.0 (CH), 144.7 (C), 155.5 (CH), 158.6 (C), 167.1 (C).

IR (KBr) \(\nu\): 2985, 2946, 2900, 2839, 1720, 1627, 1505, 1318, 1248, 1195, 1166, 1031, 986, 830 cm\(^{-1}\).

HRMS (ESI-TOF) m/z: [M+Na]\(^+\) Calcd for C\(_{18}\)H\(_{17}\)NNaO\(_3\) 318.1101; Found 318.1098.

(E)-Methyl 3-(2-[[4-chlorophenyl]imino)methyl]phenyl)prop-2-enoate (E)-4d.

According to the general procedure, (E)-S1 (38.0 mg, 0.20 mmol) and p-chloroaniline 2d (28.6 mg, 0.22 mmol) were used. (E)-4d was obtained in 68% yield (40.8 mg, 0.136 mmol) as pale yellow solid.

Mp: 88.4–88.8 °C

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 3.82 (s, 3H), 6.39 (d, \(J = 15.8\) Hz, 1H), 7.18 (d, \(J = 8.4\) Hz, 2H), 7.37 (d, \(J = 8.4\) Hz, 2H), 7.48–7.52 (m, 2H), 7.60–7.63 (m, 1H), 8.06–8.09 (m, 1H), 8.41 (d, \(J = 15.8\) Hz, 1H), 8.79 (s, 1H).

\(^{13}\)C\{\(^1\)H\} NMR (126 MHz, CDCl\(_3\)): \(\delta\) 51.9 (CH\(_3\)), 121.5 (CH), 122.3 (CH), 127.6 (CH), 129.1 (CH), 129.3 (CH), 130.0 (CH), 131.3 (CH), 131.9 (C), 134.2 (C), 135.4 (C), 141.7 (CH), 150.2 (C), 158.1 (CH), 167.0 (C).

IR (KBr) \(\nu\): 2998, 2952, 2917, 2867, 1714, 1631, 1486, 1432, 1320, 1284, 1198, 1174, 1089, 827 cm\(^{-1}\).

HRMS (ESI-TOF) m/z: [M+H]\(^+\) Calcd for C\(_{17}\)H\(_{15}\)ClNO\(_2\) 300.0786; Found 300.0787.
Mechanistic Study

The Cascade Reaction of 1a in the absence of MTBD (Scheme 2a).

To a solution of 1a (17.2 mg, 0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere was added a solution of p-toluidine 2 (6.0 mg, 0.055 mmol, 1.1 equiv.) in dry MeCN (1.0 mL) at 30 °C. The mixture was stirred at 30 °C for 1 h. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in vacuo. The yield of cis-3aa and 4a were determined by NMR spectroscopy on the basis of benzyl 4-hydroxybenzoate as an internal standard.

The Cascade Reaction of 4 with p-Toluenesulfonamide (Scheme 2b).

To a solution of 4 (0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere was added a solution of p-toluenesulfonamide (9.6 mg, 0.055 mmol, 1.1 equiv.) and MTBD (1.5 μL, 0.010 mmol, 20 mol %) in dry MeCN (1.0 mL) at 30 °C. The mixture was stirred at 30 °C for 24 h. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in vacuo. The yields of cis-3aa, cis-3ac, and cis-3ad were determined by NMR spectroscopy on the basis of benzyl 4-hydroxybenzoate as an internal standard, respectively.
The Aminal Exchange of cis-3aa with p-Anisidine 2c (Scheme 2c).

To a solution of cis-3aa (11.3 mg, 0.025 mmol) and p-anisidine (3.4 mg, 0.028 mmol, 1.1 equiv.) in dry MeCN (0.50 mL) under an argon atmosphere was added a solution of MTBD (0.80 μL, 0.0050 mmol, 20 mol %) in dry MeCN (0.50 mL) at 30 °C. The mixture was stirred at 30 °C for 24 h and filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in vacuo. The yield of cis-3aa and cis-3ac were determined by NMR spectroscopy on the basis of benzyl 4-hydroxybenzoate as an internal standard.
3. Plausible Reaction Mechanisms of the Aminal Exchange of Cascade Reaction Product 3

The aminal exchanges of cis-3 might have proceeded through a retro-Michael reaction or the formation of an N-sulfonyliminium cation as shown in Scheme S1.

Scheme S1. Plausible reaction mechanisms of aminal exchange of product 3 through (a) a retro-Michael reaction or (b) the formation of an N-sulfonyliminium cation.

4. The effects of reaction temperature and the reaction of cis-3ac under reflux conditions.

To gain some insight into the selective formation of cis-3ac, which is thermodynamic products or kinetic products, the effects of reaction temperature were examined (Scheme S2a). In all case, cis-3ac was formed as the main product, and trans-3ac was not observed at all. Furthermore, the isomerization of cis-3ac to trans-3ac was not observed under reflux conditions in MeCN (Scheme S2b).

Scheme S2. (a) the effect of reaction temperature and (b) the reaction of cis-3ac under reflux conditions.
5. References


6. Copy of $^1$H and $^{13}$C NMR spectra

cis-1,3-disubstituted isoindolines 3

$^1$H NMR

(500 MHz, CDCl$_3$)

$^{13}$C NMR

(126 MHz, CDCl$_3$)
$^{1}H$ NMR

(500 MHz, CDCl$_3$)

$^{13}$C NMR

(126 MHz, CDCl$_3$)
$^{1}H$ NMR
(500 MHz, CDCl$_3$)

$^{13}C$ NMR
(126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
Inmes 4

$^1$H NMR
(500 MHz, CDCl$_3$)

$^{13}$C NMR
(126 MHz, CDCl$_3$)
$^{1}$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$4d$

$^1$H NMR
(500 MHz, CDCl$_3$)

$^{13}$C NMR
(126 MHz, CDCl$_3$)

S34
7. Copy of 2D NMR spectra