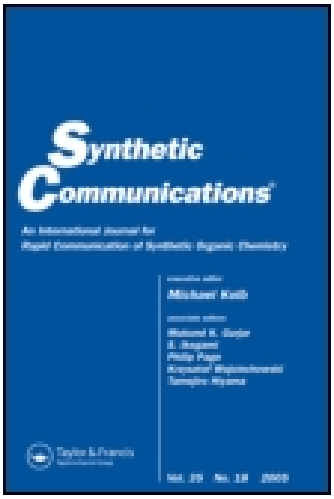

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Synthesis of New Chiral Schiff Bases Containing Bromo- and Iodo-Functionalized Hydroxynaphthalene Frameworks

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SYNTHESIS OF NEW CHIRAL SCHIFF BASES CONTAINING BROMO- AND IODO-FUNCTIONALIZED HYDROXYNAPHTHALENE FRAMEWORKS

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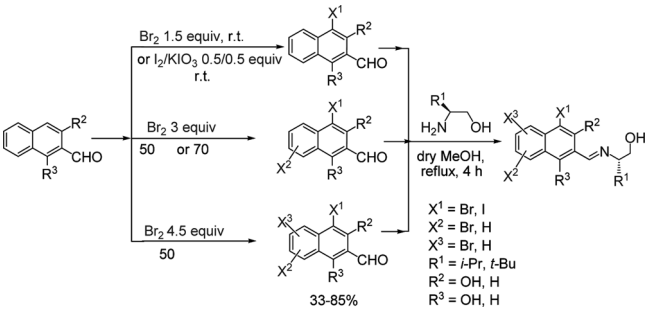
GRAPHICAL ABSTRACT



Abstract *Two series of chiral Schiff bases* ***3a–g*** *and* ***4a–g*** *containing bromo- and iodo-functionalized hydroxynaphthalene frameworks were conveniently prepared in acceptable to moderate yields by controlled halogenation of hydroxynaphthaldehyde and then condensation of the corresponding mono-, di-, and trihalohydroxynaphthaldehyde with the chiral amino alcohol. Except for* ***4d****, the Schiff bases* ***3a–g, 4a–c****, and* ***4e–g*** *prepared in the present work have not been reported in literature so far, and they might be used as effective chiral inducers in some asymmetrically synthetic reactions.*

Keywords Chiral schiff base; condensation; controlled halogenation; halohydroxynaphthaldehyde

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INTRODUCTION

Chiral Schiff bases play important roles in various asymmetric syntheses. Transition-metal complexes of chiral Schiff bases have been widely used as catalysts in asymmetric reactions, such as asymmetric Strecker reaction,[1] ring opening of epoxides,[2,3] epoxidation of olefins,[4–8] hetero-Diels–Alder reactions,[9–11] and sulfoxidations.[12–18] The structures of chiral Schiff base ligands can be easily modified to improve the activity and enantioselectivity of Schiff base–coordinate metal catalysts.

For chiral Schiff base ligands derived from salicylaldehyde and chiral amino alcohol, introduction of different substituents such as *tert*-butyl,[12,15] nitro,[12,16] bromo,[17] and iodo[18,19] to the 3- and/or 5-position of the salicylidenyl moiety of a Schiff base has an important influence on asymmetric catalytic reactions. It was found that the transition metal–based catalysts of 3,5-dibromo- and 3,5-diiodo-functionalized chiral Schiff bases displayed obviously better enantioselectivity in the asymmetric oxidation of sulfides as compared to other analogous Schiff bases. For example, in the case of the oxidation of thioanisole using the catalyst system of $VO(acac)_2$ and 3,5-diiodo (*S*)-**1** or (*R*)-**1** with H_2O_2 as oxidant at 0 °C,

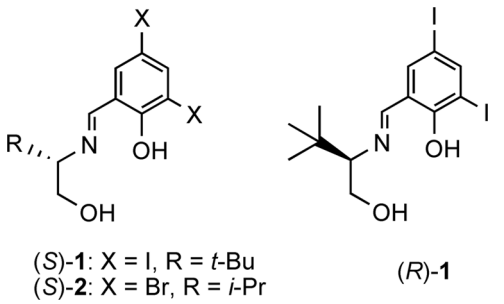
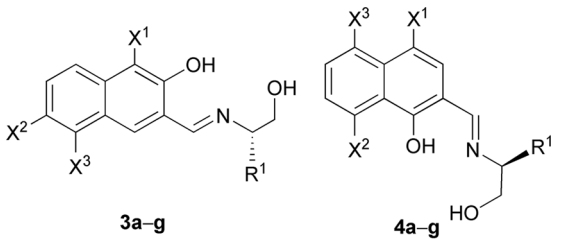


Figure 1. Structures of some effective chiral Schiff bases used for asymmetric oxidation of sulfides.



a: X^1 = Br X^2 = H X^3 = H R^1 = *i*-Pr
b: X^1 = Br X^2 = Br X^3 = H R^1 = *i*-Pr
c: X^1 = Br X^2 = Br X^3 = Br R^1 = *i*-Pr
d: X^1 = Br X^2 = H X^3 = H R^1 = *t*-Bu
e: X^1 = Br X^2 = Br X^3 = H R^1 = *t*-Bu
f: X^1 = I X^2 = H X^3 = H R^1 = *i*-Pr
g: X^1 = I X^2 = H X^3 = H R^1 = *t*-Bu

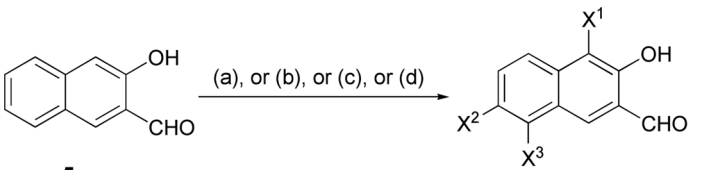
Figure 2. Structures of chiral Schiff bases **3a–g** and **4a–g** prepared in this work.

the enantioselectivities of the reaction were up to 90.0–96.7% ee with 70–81% yield of chiral methyl phenyl sulfoxide (Fig. 1).[15,17] In attempt to extend the scope of high-performance, low-cost, and conveniently prepared chiral Schiff base ligands, we prepared two series of chiral Schiff bases (**3a–g** and **4a–g)** containing bromo- and iodo-functionalized hydroxynaphthalene frameworks (Fig. 2) in acceptable to moderate yields by controlled halogenation of hydroxynaphthaldehyde and then condensation of the corresponding mono-, di-, and trihalohydroxynaphthaldehyde with the chiral amino alcohol.

RESULTS AND DISCUSSION

3-Hydroxy-2-naphthaldehyde (**5**) was conveniently prepared from 2-naphthol and dimethylformamide (DMF) according to the literature procedure.[20] The other starting compound, 1-hydroxy-2-naphthaldehyde (**7**), was synthesized by two steps: first, oxidation of 1-naphthaldehyde by *m*-chloroperbenzoic acid (MCPBA) and then by rearrangement of the formyl group from the oxygen atom to the 2-position of the naphthalene ring.[21,22]

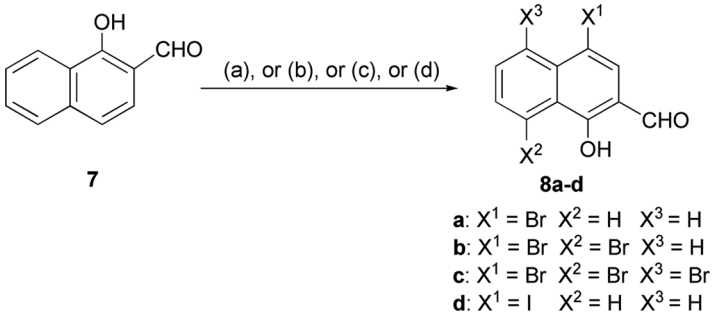
Mono-, di-, and tribromohydroxynaphthaldehydes were available by controlled bromination of 3-hydroxy-2-naphthaldehyde and 1-hydroxy-2-naphthaldehyde (Schemes 1 and 2). The number of the Br atom(s) introduced to the naphthalene ring depended on the reaction conditions, such as the ratio of Br_2 to hydroxynaphthaldehyde, reaction temperature, reaction period, solvents, and the absence or presence of iron powder as catalyst (Table 1). Bromination of 3-hydroxy-2-naphthaldehyde and 1-hydroxy-2-naphthaldehyde with 1.5 equiv of Br_2 at room temperature in $CHCl_3$ for 4 h gave the corresponding monobromohydroxynaphthaldehyde **6a** in 75–85% yields and **8a** in 45–50% yields,[23] respectively, as sole products. Compound **8a** was obtained in a lower yield than **6a** because it was more strongly adsorbed on silica gel when it was purified by chromatography. Introduction of the second Br atom to the naphthalene ring is more difficult. Dibromination of 3-hydroxy-2-naphthaldehyde was carried out with addition of 3.0 equiv of Br_2 in acetic acid at 70 °C for 24 h. Product **6b** was isolated in an acceptable yield (55%) by flash chromatography.



5 **6a-d**

a: X^1 = Br X^2 = H X^3 = H
b: X^1 = Br X^2 = Br X^3 = H
c: X^1 = Br X^2 = Br X^3 = Br
d: X^1 = I X^2 = H X^3 = H

Scheme 1. Bromination and iodination of 3-hydroxy-2-naphthaldehyde. Reagents and conditions: (a) Br_2 (1.5 equiv), $CHCl_3$, rt, 4 h; (b) Br_2 (3.0 equiv), AcOH, 70 °C, 24 h; (c) Br_2 (4.5 equiv), iron powder (0.54 equiv), $CHCl_3$, 50 °C, 24 h; (d) I_2 (0.5 equiv), KIO_3 (0.5 equiv), EtOH/AcOH/H_3PO_4 (1:1:1, v/v/v), rt, 6 h.



Scheme 2. Bromination and iodination of 1-hydroxy-2-naphthaldehyde. Reagents and conditions: (a) Br_2 (1.5 equiv), $CHCl_3$, rt, 4 h; (b) Br_2 (3.0 equiv), iron powder (0.36 equiv), $CHCl_3$, 50 °C, 24 h; (c) Br_2 (4.5 equiv), iron powder (0.54 equiv), $CHCl_3$, 50 °C, 24 h; (d) I_2 (0.5 equiv), KIO_3 (0.5 equiv), EtOH/AcOH/H_3PO_4 (1:1:1, v/v/v), rt, 6 h.

Compound **8b** was prepared by treating 1-hydroxy-2-naphthaldehyde with 3.0 equiv of Br_2 in the presence of iron powder in $CHCl_3$ at 50 °C for 24 h. Tribromonated hydroxynaphthaldehydes **6c** and **8c** were prepared with **5** and **7** as starting compounds, respectively, in a hydroxynaphthaldehyde/Br_2/Fe ratio of 1:4.5:0.54 in $CHCl_3$ at 50 °C for 24 h.

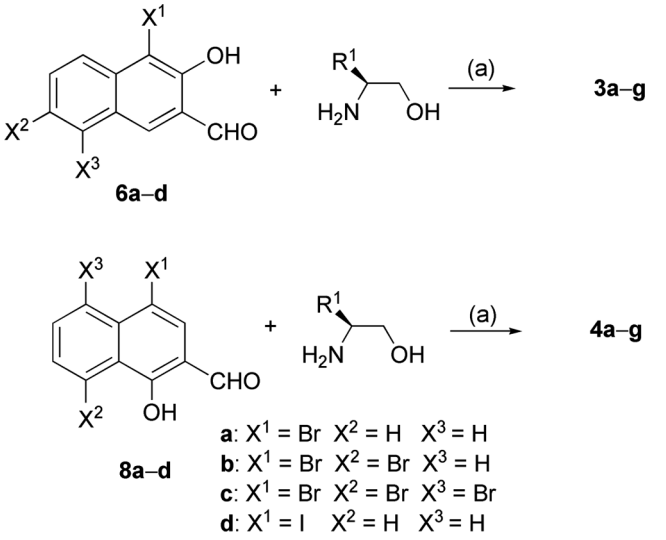
Introduction of an iodo group to *ortho*- and *para*-positions of the OH group of 3-hydroxy-2-naphthaldehyde and 1-hydroxy-2-naphthaldehyde was carried out, respectively, using I_2 and potassium iodate as iodating reagent in a mixed solvent of ethanol, acetic acid, and orthophosphoric acid in a ratio of 1:1:1 at room temperature for 6 h. Iodohydroxynaphthaldehydes **6d** and **8d** were obtained in 65–70% yields (Schemes 1 and 2). Both of them have not been previously reported in literature. Diiodination of naphthalene ring is more difficult. Our attempts to prepare diiodo-substituted hydroxynaphthaldehydes from **5** and **7** by a procedure similar to that for the preparation of **6d** and **8d** with a large excess of I_2 and potassium iodate were not successful.

Condensation of bromo- and iodo-functionalized hydroxynaphthaldehydes, **6a–d** and **8a–d**, with chiral amino alcohols, for example, (*S*)-*tert*-leucinol and (*S*)-valinol, gave two series of chiral Schiff bases, **3a–g** and **4a–g**. The condensation reactions were carried out with equivalent amounts of hydroxynaphthaldehydes and

Table 1. Reaction conditions for bromination of hydroxynaphthaldehydes **5** and **7**

Entry	Reactant	Product	Br_2 (equiv)	Temp. (°C)	Reaction time (h)	Solvent	Iron powder (equiv)	Yield (%)[a]
1	**5**	**6a**	1.5	rt	4	$CHCl_3$	—	75–85
2	**5**	**6b**	3.0	70	24	AcOH	—	55
3	**5**	**6c**	4.5	50	24	$CHCl_3$	0.54	71
4	**7**	**8a**	1.5	rt	4	$CHCl_3$	—	45–50
5	**7**	**8b**	3.0	50	24	$CHCl_3$	0.36	38
6	**7**	**8c**	4.5	50	24	$CHCl_3$	0.54	33

[a]Isolated yield.



Scheme 3. Condensation of bromo- and iodo-functionalized hydroxynaphthaldehydes and chiral amino alcohols. Reagents and conditions: (a) dry MeOH, reflux, 4 h.

chiral amino alcohols in anhydrous methanol solution at reflux for 4 h (Scheme 3). The desired Schiff base ligands were obtained in acceptable to moderate yields after flash chromatography and drying in vacuo or recrystallization from ethanol. Chiral Schiff bases were characterized by mass spectroscopy (MS), ^{1}H and ^{13}C NMR spectroscopy, and their optical rotations.

In summary, two series of mono-, di-, tribromo-, and monoiodohydroxy-naphthaldehydes, **6a–d** and **8a–d**, were prepared in 33–85% yields by controlled halogenation of 3-hydroxy-2-naphthaldehyde and 1-hydroxy-2-naphthaldehyde, respectively, under different reaction conditions. Fourteen chiral Schiff bases, **3a–g** and **4a–g**, were sequentially prepared from condensation of the corresponding bromo- and iodo-functionalized hydroxynaphthaldehydes with chiral amino alcohols. To our knowledge, except for **4d,**[19] the other 13 chiral Schiff bases have not been reported so far. These new chiral Schiff bases containing bromo- and iodo-functionalized hydroxynaphthalene frameworks may act as effective chiral inducers in some asymmetrically synthetic reactions.

EXPERIMENTAL

Chiral amino acids, (*S*)-*tert*-leucine and (*S*)-valine, were purchased from Aldrich and GL Biochem (Shanghai) Ltd., respectively. 2-Naphthol, 1-naphthaldehyde, and other starting compounds of reagent grade were obtained from local suppliers and used as received. 3-Hydroxy-2-naphthaldehyde (**5**) was prepared as yellow solid in 65% yield by formylation of 2-naphthol according to the literature procedure.[20] Chiral amino alcohols were prepared by reduction of corresponding amino acids.[24]

Melting points were measured on an XRc-1 melting-point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on an Unity Inova 400

NMR spectrometer with tetramethylsilane (TMS) as internal standard. Mass spectra were performed by electrospray ionization (ESI) on an HP 1100 MSD instrument. Elemental analyses were performed with a Thermoquest-Flash EA 1112 elemental analyzer. Optical rotations were measured at 589 nm with a Jasco P-1010 digital polarimeter.

1-Bromo-2-hydroxy-3-naphthaldehyde (6a)

Compound **6a** was prepared by monobromination of **5** according to the literature procedure.[23] Yellow solid; yield: 75–85%. ^{1}H NMR ($CDCl_3$): $\delta = 7.46$ (t, 1H, Ar*H*), 7.72 (t, 1H, Ar*H*), 7.9 (d, 1H, Ar*H*), 8.18 (s, 1H, Ar*H*), 8.23 (d, 1H, Ar*H*), 10.05 (s, 1H, *H*C=O), 11.06 (s, 1H, ArO*H*). API-ES: $m/z = 248.9$ $[M - H]^-$.

1,6-Dibromo-2-hydroxy-3-naphthaldehyde (6b)[23]

A solution of Br_2 (0.47 g, 3 mmol in 10 mL acetic acid) was added dropwise to the solution of 3-hydroxy-2-naphthaldehyde (0.17 g, 1.0 mmol) in 20 mL acetic acid for 30 min. After the mixture was stirred at 70 °C for 24 h, a $NaHSO_3$ saturated aqueous solution (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3×15 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the product was purified by flash chromatography on silica gel with petroleum ether/CH_2Cl_2 (1:1, v/v) as eluent. Yellow solid; yield: 55%. ^{1}H NMR ($CDCl_3$): $\delta = 7.76$ (d, 1H, Ar*H*), 8.07 (s, 1H, Ar*H*), 8.08 (s, 1H, Ar*H*), 8.11 (d, 1H, Ar*H*), 10.05 (s, 1H, *H*C=O), 11.06 (s, 1H, ArO*H*). API-ES: $m/z = 326.9$ $[M - H]^-$.

1,5,6-Tribromo-2-hydroxy-3-naphthaldehyde (6c)

Iron powder (30 mg) was added to the $CHCl_3$ solution (20 mL) of 3-hydroxy-2-naphthaldehyde (0.17 g, 1.0 mmol), followed by dropwise addition of Br_2 (0.71 g, 4.5 mmol in 10 mL $CHCl_3$) for 30 min. After the mixture was stirred at 50 °C for 24 h, a $NaHSO_3$ saturated aqueous solution (20 mL) was added. The following workup was essentially identical with that for **6b**. Yellow solid; yield: 71%. ^{1}H NMR ($CDCl_3$): $\delta = 7.83$ (d, 1H, Ar*H*), 8.11 (d, 1H, Ar*H*), 8.68 (s, 1H, Ar*H*), 10.12 (s, 1H, *H*C=O), 11.18 (s, 1H, ArO*H*). API-ES: $m/z = 405.0$ $[M - H]^-$.

1-Iodo-2-hydroxy-3-naphthaldehyde (6d)

Iodine (0.25 g, 1.0 mmol) and KIO_3 (0.21 g, 1.0 mmol) were added to the solution of 3-hydroxy-2-naphthaldehyde (0.34 g, 2.0 mmol) in a mixed solvent (1.5 mL) of ethanol, acetic acid, and orthophosphoric acid (1:1:1, v/v/v). After the mixture was stirred for 6 h at room temperature, a $NaHSO_3$ saturated aqueous solution (20 mL) was added. The following workup was essentially identical with that for **6b.** Yellow solid; yield: 70%. ^{1}H NMR ($CDCl_3$): $\delta = 7.44$ (t, 1H, Ar*H*), 7.69 (t, 1H, Ar*H*), 7.86 (d, 1H, Ar*H*), 8.16 (d, 1H, Ar*H*), 8.18 (s, 1H, Ar*H*), 9.98 (s, 1H, *H*C=O), 11.35 (s, 1H, ArO*H*). API-ES: $m/z = 296.9$ $[M - H]^-$.

1-Hydroxy-2-naphthaldehyde (7)

First, 1-naphthylformate was prepared by a modified procedure.[21] *m*-Chloroperbenzoic acid (0.19 g, 1.2 mmol) was added to the solution of 1-naphthaldehyde (0.16 g, 1.0 mmol) in dry CH_2Cl_2 (50 mL). The solution was stirred at room temperature under an N_2 atmosphere for 12 h until 1-naphthaldehyde could not be detected by thin-layer chromatographic (TLC) analysis. After filtration, a $NaHCO_3$ saturated aqueous solution (20 mL) was added. The following workup was essentially identical with that for **6b**. 1-Naphthylformate was isolated as a colorless oil in 75% yield and characterized by GC-MS ($m/z = 172.0$ $[M]^+$). Compound **7** was further prepared by rearrangement of the formyl group according to the literature procedure.[22] Yellow solid; yield: 42%. ^{1}H NMR ($CDCl_3$): $\delta = 7.37$ (d, 1H, Ar*H*), 7.50 (d, 1H, Ar*H*), 7.54 (t, 1H, Ar*H*), 7.65 (t, 1H, Ar*H*), 7.83 (d, 1H, Ar*H*), 8.44 (d, 1H, Ar*H*), 9.98 (s, 1H, *H*C=O), 12.67 (s, 1H, ArO*H*). API-ES: $m/z = 171.1$ $[M - H]^-$.

4-Bromo-1-hydroxy-2-naphthaldehyde (8a)

A solution of Br_2 (0.24 g, 1.5 mmol in 10 mL $CHCl_3$) was added dropwise to the solution of 1-hydroxy-2-naphthaldehyde (0.17 g, 1.0 mmol) in $CHCl_3$ (20 mL) for 30 min. After the mixture was stirred at room temperature for 4 h, a $NaHSO_3$ saturated aqueous solution (20 mL) was added. The following workup was essentially identical with that for **6b**. Yellow solid; yield: 45–50%. ^{1}H NMR ($CDCl_3$): $\delta = 7.64$ (t, 1H, Ar*H*), 7.79 (t, 1H, Ar*H*), 7.81 (s, 1H, Ar*H*), 8.18 (d, 1H, Ar*H*), 8.48 (d, 1H, Ar*H*), 9.92 (s, 1H, *H*C=O), 12.61 (s, 1H, ArO*H*). API-ES: $m/z = 248.9$ $[M - H]^-$.

4,8-Dibromo-1-hydroxy-2-naphthaldehyde (8b)

Iron powder (20 mg) was added to the $CHCl_3$ solution (20 mL) of 1-hydroxy-2-naphthaldehyde (0.17 g, 1.0 mmol), followed by dropwise addition of Br_2 (0.47 g, 3.0 mmol in 10 mL $CHCl_3$) for 30 min. After the mixture was stirred at 50 °C for 24 h, a $NaHSO_3$ saturated aqueous solution (20 mL) was added. The following workup was essentially identical with that for **6b**. Yellow solid; yield: 38%. API-ES: $m/z = 326.9$ $[M - H]^-$. The TLC analysis shows that product **8b** was contaminated with a small amount of unknown by-products of similar polarity, which are neither **8a** nor **8c**. The crude product **8b** was directly used for further preparation.

4,5,8-Tribromo-1-hydroxy-2-naphthaldehyde (8c)

Compound **8c** was prepared by a procedure similar to that for **6c**, using 1-hydroxy-2-naphthaldehyde in place of 3-hydroxy-2-naphthaldehyde. Yellow solid; yield: 33%. API-ES: $m/z = 404.8$ $[M - H]^-$. The TLC analysis shows that product **8c** was contaminated with a small amount of unknown by-products of similar polarity, which are neither **8a** nor **8b**. The crude product **8c** was directly used for further preparation.

4-Iodo-1-hydroxy-2-naphthaldehyde (8d)

Compound **8d** was prepared by a procedure similar to that for **6d**, using 1-hydroxy-2-naphthaldehyde in place of 3-hydroxy-2-naphthaldehyde. Yellow solid;

yield: 65%. ^{1}H NMR ($CDCl_3$): δ = 7.60 (t, 1H, Ar*H*), 7.75 (t, 1H, Ar*H*), 8.03 (d, 1H, Ar*H*), 8.07 (s, 1H, Ar*H*), 8.43 (d, 1H, Ar*H*), 9.91 (s, 1H, *H*C=O), 12.60 (s, 1H, ArO*H*). API-ES: $m/z = 297.0$ $[M - H]^-$.

General Procedure for the Preparation of Ligands 3a–g and 4a–g

A chiral amino alcohol (1.2 mmol) and bromo- or iodo-substituted hydroxynaphthylaldehyde (1.0 mmol) were dissolved in dry methanol (20–50 mL) under a nitrogen atmosphere. The solution was refluxed for 4 h, and then the solvent was removed under reduced pressure to give a crude product, which was purified by flash chromatography on silica gel with CH_2Cl_2/methanol (100:1, v/v) as eluent for **3a, 4a**–**g**, and with CH_2Cl_2 as eluent for **3d, 3f, 3g**, or by recrystallization from ethanol for **3b, 3c**, and **3e**.

3-((*E*)-((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)methyl)-1-bromonaphthalen-2-ol (3a)

Waxy red solid; yield: 50%; $[\alpha]_{589}^{21} = -19.1°$ ($c = 0.01$ mol/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.98 (d, 6H, HC(C*H*$_3$)$_2$), 1.56 (s br, 1H, CH_2O*H*), 1.98–2.03 [m, 1H, *H*C(CH$_3$)$_2$], 3.16–3.21 (m, 1H, C=N−C*H*), 3.78 (dd, 1H, C*H*$_2$OH), 3.89 (dd, 1H, C*H*$_2$OH), 7.35 (t, 1H, Ar*H*), 7.59 (t, 1H, Ar*H*), 7.77 (d, 1H, Ar*H*), 7.83 (s, 1H, Ar*H*), 8.17 (d, 1H, Ar*H*), 8.52 (s, 1H, *H*C=N), 14.14 (s br, 1H, ArO*H*). ^{13}C NMR ($CDCl_3$): δ = 165.23 (*C*H=N), 153.98 (*C*−OH), 133.85, 132.66, 129.42, 128.82, 127.62, 125.43, 124.04, 120.45, 106.27, 77.08 (*C*H−N), 64.31 (*C*H$_2$OH), 30.09 [*C*H(CH$_3$)$_2$], 19.84 and 18.52 [2C, CH(*C*H$_3$)$_2$]. API-ES: $m/z = 336.0$ and 338.0 $[M + H]^+$.

3-((*E*)-((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)methyl)-1,6-dibromonaphthalen-2-ol (3b)

Red solid; yield: 73%; mp: 190–193 °C; $[\alpha]_{589}^{21} = -17.2°$ ($c = 0.01$ mol/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 0.99 [d, 6H, HC(C*H*$_3$)$_2$], 1.55 (s br, 1H, CH_2O*H*), 1.97–2.03 (m, 1H, *H*C(CH$_3$)$_2$), 3.18–3.22 (m, 1H, C=N−C*H*), 3.78 (dd, 1H, C*H*$_2$OH), 3.90 (dd, 1H, C*H*$_2$OH), 7.63 (d, 1H, Ar*H*), 7.72 (s, 1H, Ar*H*), 7.94 (s, 1H, Ar*H*), 8.06 (d, 1H, Ar*H*), 8.51 (s, 1H, *H*C=N), 14.26 (s br, 1H, ArO*H*). API-ES: $m/z = 412.0$, 414.0, and 416.0 $[M - H]^-$.

3-((*E*)-((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)methyl)-1,5,6-tribromonaphthalen-2-ol (3c)

Red solid; yield: 71%; mp: 215–216 °C. ^{1}H NMR ($CDCl_3$): δ = 1.00 [d, 6H, HC(C*H*$_3$)$_2$], 1.55 (s br, 1H, CH_2O*H*), 1.99–2.03 [m, 1H, *H*C(CH$_3$)$_2$], 3.22–3.27 (m, 1H, C=N−C*H*), 3.78 (dd, 1H, C*H*$_2$OH), 3.92 (dd, 1H, C*H*$_2$OH), 7.67 (d, 1H, Ar*H*), 7.97 (d, 1H, Ar*H*), 8.30 (s, 1H, Ar*H*), 8.58 (s, 1H, *H*C=N), 14.60 (s br, 1H, ArO*H*). ^{13}C NMR ($CDCl_3$): δ = 165.58 (*C*H=N), 155.27 (*C*−OH), 132.93, 132.86, 126.94, 126.29, 125.28, 121.87, 121.15, 106.87, 77.59 (*C*H−N), 64.35 (*C*H$_2$OH),

31.06 [*C*H(CH_3)$_2$], 20.06 and 18.72 [2C, CH(*C*H_3)$_2$]. API-ES: $m/z = 490.0$, 492.0, 493.9, and 496.0 $[M - H]^-$.

3-((*E*)-((*S*)-1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl)-1-bromonaphthalen-2-ol (3d)

Waxy red solid; yield: 34%; $[\alpha]_{589}^{21} = -19.1°$ ($c = 0.01$ mol/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta = 1.01$ [s, 9H, C(C*H*$_3$)$_3$], 1.57 (s br, 1H, CH$_2$O*H*), 3.05–3.08 (m, 1H, C=N−C*H*), 3.74 (dd, 1H, C*H*$_2$OH), 3.97 (dd, 1H, C*H*$_2$OH), 7.32 (t, 1H, Ar*H*), 7.57 (t, 1H, Ar*H*), 7.73 (d, 1H, Ar*H*), 7.80 (s, 1H, Ar*H*), 8.13 (d, 1H, Ar*H*), 8.50 (s, 1H, *H*C=N), 14.24 (s br, 1H, ArO*H*). ^{13}C NMR ($CDCl_3$): $\delta = 165.31$ (*C*H=N), 154.14 (*C*−OH), 132.87, 131.82, 129.60, 128.98, 125.27, 124.23, 120.70, 106.41, 77.70 (*C*H−N), 62.31 (*C*H$_2$OH), 33.39 [*C*(CH$_3$)$_3$], 27.19 [3C, C(*C*H$_3$)$_3$]. API-ES: $m/z = 350.0$ and 352.0 $[M + H]^+$.

3-((*E*)-((*S*)-1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl)-1,6-dibromonaphthalen-2-ol (3e)

Orange solid; yield: 42%; mp: 254–255 °C; $[\alpha]_{589}^{21} = -24.7°$ ($c = 0.01$ mol/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ [s, 9H, C(C*H*$_3$)$_3$], 1.57 (s br, 1H, CH$_2$O*H*), 3.07–3.10 (m, 1H, C=N−C*H*), 3.74 (dd, 1H, C*H*$_2$OH), 4.00 (dd, 1H, C*H*$_2$OH), 7.62 (d, 1H, Ar*H*), 7.71 (s, 1H, Ar*H*), 7.90 (s, 1H, Ar*H*), 8.00 (d, 1H, Ar*H*), 8.49 (s, 1H, *H*C=N), 14.35 (s br, 1H, ArO*H*). ^{13}C NMR ($CDCl_3$): $\delta = 165.43$ (*C*H=N), 154.52 (*C*−OH), 132.54, 131.66, 130.60, 127.43, 125.64, 124.31, 121.11, 106.53, 77.68 (*C*H−N), 62.41 (*C*H$_2$OH), 33.37 [*C*(CH$_3$)$_3$], 27.21 [3C, C(*C*H$_3$)$_3$]. API-ES: $m/z = 426.0$, 428.0 and 430.0 $[M - H]^-$. Anal. calcd. for $C_{17}H_{19}Br_2NO_2$: C, 47.58; H, 4.46; N, 3.26. Found: C, 47.85; H, 4.40; N, 3.19.

3-((*E*)-((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)methyl)-1-iodonaphthalen-2-ol (3f)

Waxy red solid; yield: 35%. ^{1}H NMR ($CDCl_3$): $\delta = 0.98$ [d, 6H, HC(C*H*$_3$)$_2$], 1.60 (s br, 1H, CH$_2$O*H*), 1.97–2.02 [m, 1H, *H*C(CH$_3$)$_2$], 3.16–3.21 (m, 1H, C=N−C*H*), 3.78 (dd, 1H, C*H*$_2$OH), 3.89 (dd, 1H, C*H*$_2$OH), 7.34 (t, 1H, Ar*H*), 7.57 (t, 1H, Ar*H*), 7.74 (d, 1H, Ar*H*), 7.84 (s, 1H, Ar*H*), 8.10 (d, 1H, Ar*H*), 8.46 (s, 1H, *H*C=N), 14.32 (s br, 1H, ArO*H*). ^{13}C NMR ($CDCl_3$): $\delta = 165.09$ (*C*H=N), 156.97 (*C*−OH), 138.85, 136.53, 134.30, 130.62, 130.04, 129.19, 128.07, 124.28, 120.16, 77.70 (*C*H−N), 64.50 (*C*H$_2$OH), 30.24 [*C*H(CH$_3$)$_2$], 19.96 and 18.82 (2C, CH[*C*H$_3$)$_2$]. API-ES: $m/z = 382.0$ $[M - H]^-$.

3-((*E*)-((*S*)-1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl)-1-iodonaphthalen-2-ol (3g)

Waxy red solid; yield: 30%. ^{1}H NMR ($CDCl_3$): $\delta = 1.01$ [d, 9H, C(C*H*$_3$)$_3$], 1.59 (s br, 1H, CH$_2$O*H*), 3.06–3.09 (m, 1H, C=N−C*H*), 3.75 (dd, 1H, C*H*$_2$OH), 3.98 (dd, 1H, C*H*$_2$OH), 7.32 (t, 1H, Ar*H*), 7.55 (t, 1H, Ar*H*), 7.71 (d, 1H, Ar*H*), 7.82 (s, 1H, Ar*H*), 8.07 (d, 1H, Ar*H*), 8.44 (s, 1H, *H*C=N), 14.38 (s br, 1H, ArO*H*). ^{13}C NMR

($CDCl_3$): δ = 165.06 (*C*H=N), 156.92 (*C*−OH), 136.30, 134.28, 130.45, 129.88, 129.08, 127.90, 124.18, 120.01, 77.72 (*C*H−N), 62.28 (CH_2OH), 33.32 [$C(CH_3)_3$], 27.15 [3C, $C(CH_3)_3$]. API-ES: $m/z = 396.0$ $[M-H]^-$.

2-((*E*)-((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)methyl)-4-bromonaphthalen-1-ol (4a)

Yellow solid; yield: 65%; mp: 137–138 °C; $[\alpha]_{589}^{21} = -184.8°$ ($c = 0.01$ mol/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.01 [t, 6H, $HC(CH_3)_2$], 1.62 (s br, 1H, CH_2OH), 1.98–2.03 [m, 1H, $HC(CH_3)_2$], 3.23–3.24 (m, 1H, C=N−C*H*), 3.77 (dd, 1H, CH_2OH), 3.90 (dd, 1H, CH_2OH), 7.43 (t, 1H, Ar*H*), 7.54 (d, 1H, Ar*H*), 7.56 (s, 1H, Ar*H*), 7.65 (t, 1H, Ar*H*), 7.93 (d, 1H, Ar*H*), 8.32 (s, 1H, *H*C=N), 13.24 (s br, 1H, ArO*H*). ^{13}C NMR ($CDCl_3$): δ = 177.38 (*C*H=N), 161.70 (*C*−OH), 135.70, 131.30, 130.46, 127.55, 125.89, 125.26, 109.12, 106.58, 70.99 (*C*H−N), 64.17 (CH_2OH), 29.64 [$CH(CH_3)_2$], 19.87 and 18.31 [2C, $CH(CH_3)_2$]. API-ES: $m/z = 334.0$ and 336.0 $[M-H]^-$.

2-((*E*)-((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)methyl)-4,8-dibromonaphthalen-1-ol (4b)

Yellow solid; yield: 50%; mp: 159–160 °C; $[\alpha]_{589}^{21} = -148.6°$ ($c = 0.01$ mol/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.04 [d, 6H, $HC(CH_3)_2$], 1.58 (s br, 1H, CH_2OH), 2.02–2.07 [m, 1H, $HC(CH_3)_2$], 3.30–3.31 (m, 1H, C=N−C*H*), 3.78 (dd, 1H, CH_2OH), 3.94 (dd, 1H, CH_2OH), 7.00 (s, 1H, Ar*H*), 7.71 (t, 1H, Ar*H*), 7.73 (d, 1H, Ar*H*), 7.79 (d, 1H, Ar*H*), 8.50 (s, 1H, *H*C=N), 13.27 (s br, 1H, ArO*H*). ^{13}C NMR ($CDCl_3$): δ = 176.03 (*C*H=N), 161.83 (*C*−OH), 134.26, 134.17, 132.19, 130.98, 129.25, 128.09, 120.25, 109.51, 105.66, 70.95 (*C*H−N), 64.03 (CH_2OH), 29.65 [$CH(CH_3)_2$], 19.87 and 18.40 [2C, $CH(CH_3)_2$]. API-ES: $m/z = 411.9$, 413.9, and 415.9 $[M-H]^-$.

2-((*E*)-((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)methyl)-4,5,8-tribromonaphthalen-1-ol (4c)

Yellow solid; yield: 46%; mp: 190–193 °C; $[\alpha]_{589}^{21} = -117.4°$ ($c = 0.01$ mol/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.06 [d, 6H, $HC(CH_3)_2$], 1.55 (s br, 1H, CH_2OH), 2.04–2.11 [m, 1H, $HC(CH_3)_2$], 3.35–3.37 (m, 1H, C=N−C*H*), 3.81 (dd, 1H, CH_2OH), 3.94 (dd, 1H, CH_2OH), 7.69 (d, 1H, Ar*H*), 7.92 (d, 1H, Ar*H*), 8.48 (s, 1H, Ar*H*), 8.51 (s, 1H, *H*C=N), 13.71 (s br, 1H, ArO*H*). ^{13}C NMR ($CDCl_3$): δ = 176.44 (*C*H=N), 164.49 (*C*−OH), 135.11, 134.37, 131.74, 130.77, 128.52, 125.63, 121.30, 110.76, 109.20, 70.63 (*C*H−N), 63.92 (CH_2OH), 29.68 [$CH(CH_3)_2$], 19.83 and 18.50 [2C, $CH(CH_3)_2$]. API-ES: $m/z = 489.9$, 491.9, 493.9, and 495.9 $[M-H]^-$.

2-((*E*)-((*S*)-1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl)-4-bromonaphthalen-1-ol (4d)

Yellow solid; yield: 53%; mp: 190–192 °C. ^{1}H NMR ($CDCl_3$): δ = 1.07 [s, 9H, $C(CH_3)_3$], 1.62 (s br, 1H, CH_2OH), 3.16 (m, 1H, C=N−C*H*), 3.77 (dd, 1H, CH_2OH),

4.09 (dd, 1H, CH_2OH), 7.48 (t, 1H, ArH), 7.55 (d, 1H, ArH), 7.60–7.65 (m, 2H, ArH), 7.95 (d, 1H, ArH), 8.27 (s, 1H, HC=N), 13.28 (s br, 1H, ArOH). ^{13}C NMR ($CDCl_3$): $\delta = 177.12$ (CH=N), 162.02 (C–OH), 135.68, 131.27, 131.02, 130.40 127.62, 125.92, 125.25, 109.14, 106.69, 74.97 (CH–N), 62.11 (CH$_2$OH), 33.26 [C(CH$_3$)$_3$], 26.97 [3C, C(CH$_3$)$_3$]. API-ES: $m/z = 348.0$ and 350.0 $[M - H]^-$.

2-((*E*)-((*S*)-1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl)-4,8-dibromonaphthalen-1-ol (4e)

Yellow solid; yield: 66%; mp: 90–95 °C; $[\alpha]_{589}^{21} = -242.4°$ ($c = 0.01$ mol/L, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta = 1.07$ [s, 9H, C(CH_3)$_3$], 1.59 (s br, 1H, CH$_2$OH), 3.18 (m, 1H, C=N–CH), 3.73 (dd, 1H, CH_2OH), 4.08 (dd, 1H, CH_2OH), 6.82 (s, 1H, ArH), 7.66 (t, 1H, ArH), 7.71 (d, 1H, ArH), 7.79 (d, 1H, ArH), 8.48 (s, 1H, HC=N), 13.46 (s br, 1H, ArOH). ^{13}C NMR ($CDCl_3$): $\delta = 175.87$ (CH=N), 162.19 (C–OH), 134.22, 134.09, 132.07, 130.90, 129.30, 128.01, 120.16, 109.44, 105.60, 74.82 (CH–N), 61.94 (CH$_2$OH), 33.23 [C(CH$_3$)$_3$], 26.93 [3C, C(CH$_3$)$_3$]. API-ES: $m/z = 426.0$, 428.0, and 430.1 $[M - H]^-$.

2-((*E*)-((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)methyl)-4-iodonaphthalen-1-ol (4f)

Yellow solid; yield: 60%; mp: 127–129 °C. ^{1}H NMR ($CDCl_3$): $\delta = 1.03$ [d, 6H, HC(CH_3)$_2$], 2.01–2.05 [m, 1H, HC(CH$_3$)$_2$], 3.35 (s br, 1H, CH$_2$OH), 3.36 (m, 1H, C=N–CH), 3.78 (dd, 1H, CH_2OH), 3.95 (dd, 1H, CH_2OH), 7.29 (s, 1H, ArH), 7.47 (t, 1H, ArH), 7.63 (t, 1H, ArH), 7.78 (d, 1H, ArH), 7.79 (d, 1H, ArH), 8.39 (s, 1H, HC=N), 13.12 (s br, 1H, ArOH). ^{13}C NMR ($CDCl_3$): $\delta = 177.98$ (CH=N), 161.66 (C–OH), 138.26, 137.41, 132.54, 131.64, 130.99, 125.96, 125.28, 110.68, 71.01 (CH–N), 64.17 (CH$_2$OH), 29.67 [CH(CH$_3$)$_2$], 19.89 and 18.33 [2C, CH(CH$_3$)$_2$]. API-ES: $m/z = 382.0$ $[M - H]^-$.

2-((*E*)-((*S*)-1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl)-4-iodonaphthalen-1-ol (4g)

Yellow solid; yield: 79%; mp: 94–97 °C. ^{1}H NMR ($CDCl_3$): $\delta = 1.06$ [s, 9H, C(CH_3)$_3$], 3.15 (m, 1H, C=N–CH), 3.74 (dd, 1H, CH_2OH), 4.07 (dd, 1H, CH_2OH), 6.88 (s, 1H, ArH), 7.43 (t, 1H, ArH), 7.54 (d, 1H, ArH), 7.61 (t, 1H, ArH), 7.80 (d, 1H, ArH), 8.22 (s, 1H, HC=N), 13.35 (s br, 1H, ArOH). ^{13}C NMR ($CDCl_3$): $\delta = 177.76$ (CH=N), 161.98 (C–OH), 138.09, 137.38, 132.65, 131.59, 130.84, 125.92, 125.18, 110.57, 74.94 (CH–N), 62.06 (CH$_2$OH), 33.32 [C(CH$_3$)$_3$], 26.94 [3C, C(CH$_3$)$_3$]. API-ES: $m/z = 396.0$ $[M - H]^-$. Anal. calcd. for $C_{17}H_{20}INO_2$: C, 51.40; H, 5.07; N, 3.53. Found: C, 52.50; H, 5.51; N, 3.48.

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