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Practical preparation of chiral keto-imine type ONO Schiff base ligands

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ABSTRACT

A practical preparation of chiral keto-imine type ONO Schiff base ligands has been reported. Metal complexes of these Schiff bases work as efficient chiral catalysts in a variety of asymmetric reactions.

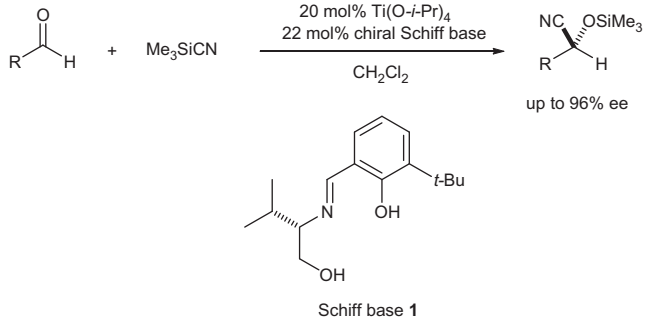
1. Introduction

Since our first report using a chiral ONO-type Schiff base–titanium alkoxide complex in the asymmetric silylcyanation of aldehydes (Scheme 1),[1] there have been many reports using this type of ONO tridentate chiral Schiff base in asymmetric reactions. Some representative examples include asymmetric Mukaiyama aldol reactions,[2] asymmetric oxidations of sulfides,[3,4] asymmetric oxidations of disulfides,[5] asymmetric hetero Diels–Alder reactions,[6,7] asymmetric pinacol couplings,[8] asymmetric allylations[9] and asymmetric hydrophosphonylations.[10] The general formula of these Schiff bases is shown in Figure 1. All the Schiff bases used in the above reactions[2–10] are of the aldo-imine type (R^3 = H in Fig. 1).

We also reported on the enantioselective addition of diketenes to aldehydes,[11] asymmetric alkylations using dialkylzincs[12] and asymmetric Reformatsky reactions.[13] In these reactions, the introduction of bulky substituents, such as a *t*-butyl group or an adamantyl group at the ortho-position of the phenolic hydroxyl group (see the R^1 substituent in the general formula of Fig. 1) is essential for obtaining highly enantioselective reactions. Furthermore, we have also reported that the introduction of an R^3 group, leads to the formation of keto-imine type Schiff bases with an increase in both the reactivity (chemical yield) and enantioselectivity when compared to those of the corresponding aldo-imine type Schiff bases. Some examples are shown in Schemes 2 and 3.

Despite its utility, there have only been a few reports using keto-imine type Shiff bases.[14] This is probably because of the difficulty of the introduction of the R^3 group. Previous methods for the synthesis of keto-imine type Schiff bases include an oxidation step as shown in Scheme 4.

Reagents, conditions and yields of the oxidation step were as follows (R^2 = *t*-Bu, R^3 = Ph): (1) CrO_3 in CH_2Cl_2, 31—35% yield.[11c] (2) Pd/C under $CH_2{=}CH_2$ in CH_3CN, 84% yield.[15] (3) Activated carbon under O_2 in xylene, 77% yield.[16]



Scheme 1.

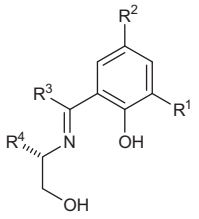


Figure 1.

2. Results and discussion

Herein we report a novel synthetic route for keto-imine Schiff bases without using an oxidation step. We used 3,5-di-*tert*-butyl-2-hydroxybenzoic acid as the starting material and treated this compound with benzotriazole to afford *o*-hydroxyarylacylbenzotriazole **5** in 88% yield (Scheme 5), which proved to be a crucial intermediate for the preparation of a variety of ketones using Grignard reagents (Table 1).[17]

Comparing the present method (Scheme 5 and Table 2) the conventional method (Scheme 4), it is clear that the present method is

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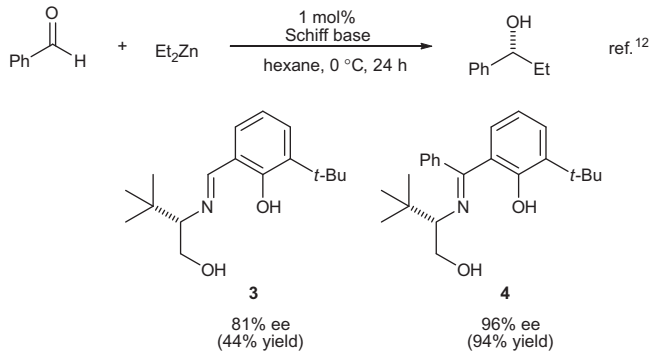
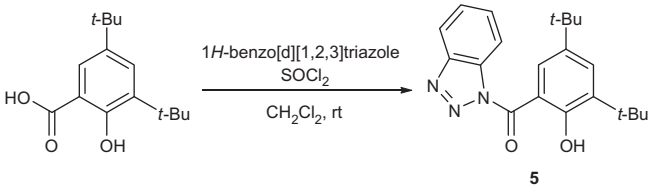


Scheme 2.

much more efficient. This is because in the previous method, in order to prepare a variety of keto-imines, a Grignard reaction followed by an oxidation step are necessary. However, in our present method, the common active amide intermediate, *o*-hydroxyarylacylbenzotriazole **5**, can be prepared on a large scale, and a variety of keto-imines can be obtained by changing only the Grignard reagents, while an oxidation step is not necessary. Thus, the obtained ketones were condensed with β-amino alcohols to give the desired keto-imine type Schiff bases (Table 2).

3. Conclusion

In conclusion, a practical method for the synthesis of keto-imine type Schiff bases using *o*-hydroxyarylacylbenzotriazole as a key intermediate has been reported. These chiral ligands exhibited a high performance in catalytic asymmetric reactions.

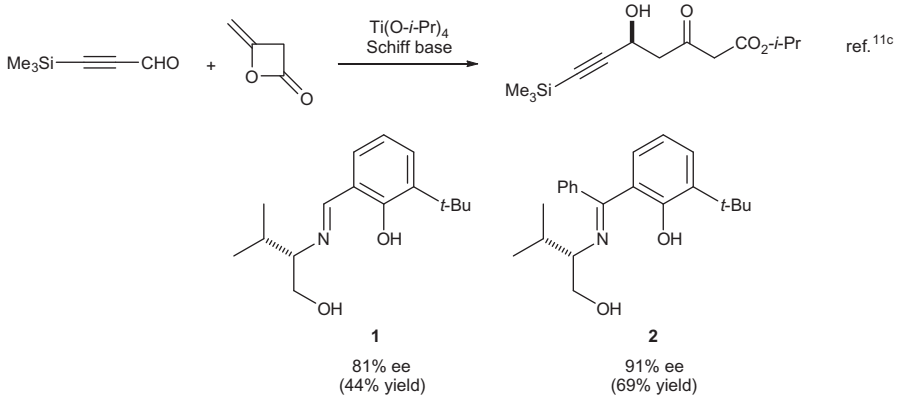


Scheme 5.

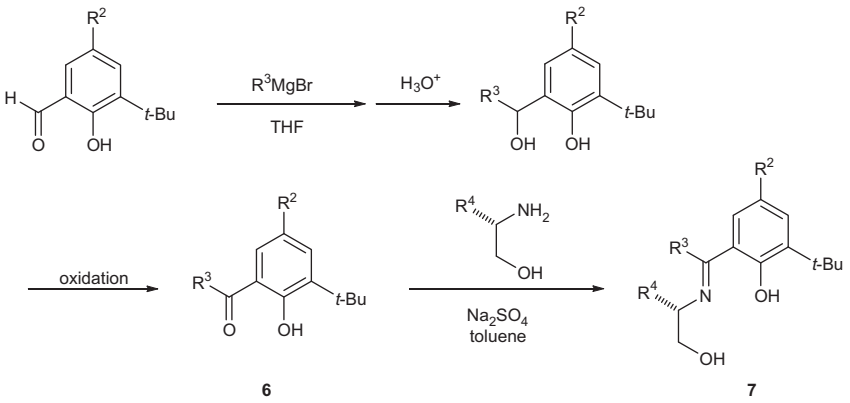
4. Experimental

4.1. General

All reactions were carried out in oven-dried glassware with magnetic stirring. Operations were performed under an atmosphere of dry argon using Schlenk and vacuum techniques. All starting materials were obtained from commercial sources and used without further purification unless otherwise stated. Melting points were measured by a Yanaco MP-500D and are not corrected. ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded on a JEOL JNM-LA 400 instrument using Me_4Si as an internal standard (0 ppm). The following abbreviations are used in connection with NMR; s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Mass spectra were measured using a Thermo Quest LCQ DECA plus. IR spectra were measured with a Thermo SCIENTIFIC NICOLET iS 5. Elemental analyses were carried out

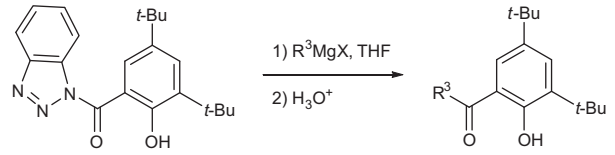


Scheme 3.



Scheme 4.

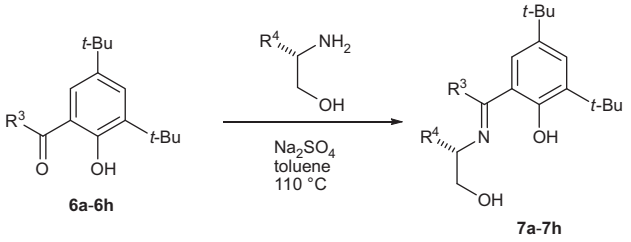
Table 1
Synthesis of diketones **6a–6h** from *o*-hydroxyarylacylbenzotriazoles **5**[a]



Entry	R^3	Temp (°C)	Time (h)	Yield[b] (%)
1	Me	25	15	**6a**; 60
2	*i*-Pr	23	18	**6b**; 76
3	Ph	23	17	**6c**; 79
4	4-MeC_6H_4	23	18	**6d**; 80
5	4-*t*-BuC_6H_4	25	20	**6e**; 94
6	3,5-$(CF_3)_2C_6H_3$	23	16	**6f**; 98
7	4-$CF_3C_6H_4$	24	14	**6g**; 59
8	3,4,5-$F_3C_6H_2$	24	17	**6h**; 51

[a] Reaction conditions: Substrate **5** (1.0 mmol), R^3MgX (2.5 mmol), THF, room temperature.
[b] Isolated yield after column chromatographic purification.

Table 2
Synthesis of keto-imine type (ONO) tridentate chiral Schiff base ligands **7a–7h**[a]



Entry	R^3	R^4	Time (h)	Yield[b] (%)
1	Me	*i*-Pr	48	**7a**; 66
2	Ph	*i*-Pr	46	**7c**; 72
3	Ph	*t*-Bu	52	**7c′**; 68
4	4-MeC_6H_4	*t*-Bu	48	**7d′**; 60
5	4-*t*-BuC_6H_4	*t*-Bu	51	**7e′**; 70
6	3,5-$(CF_3)_2C_6H_3$	*i*-Pr	47	**7f**; 48
7	3,5-$(CF_3)_2C_6H_3$	*t*-Bu	48	**7f′**; 50
8	4-$CF_3C_6H_4$	*i*-Pr	49	**7g**; 80
9	3,4,5-$F_3C_6H_2$	*i*-Pr	48	**7h**; 43

[a] Reaction conditions: Salicylketone **6a–6h** (1 mmol), (*S*)-(+)-valinol or (*S*)-(+)-*tert*-leucinol (1.2 mmol), Na_2SO_4 (1.0 g), toluene, 110 °C.
[b] Isolated yield after column chromatographic purification.

using a Yanako CHN recorder MT-5. Preparative column chromatography was carried out using Fuji Silysia BW-820MH silica gel or YMC-GEL Silica (6 nm I-40-63 μm). Thin layer chromatography (TLC) was carried out on Merck 25 TLC aluminium sheets silica gel 60 F_{254}. Optical rotations were measured on a HORIBA SEPA-300 polarimeter for solution in a 1 dm cuvette.

4.2. (1*H*-Benzo[*d*][1,2,3]triazol-1-yl)(3,5-di-*tert*-butyl-2-hydroxy phenyl)methanone 5

To a solution of benzotriazole (17.87 g, 150 mmol) in CH_2Cl_2 (60 mL), $SOCl_2$ (3.7 mL, 50 mmol) was added dropwise with stirring at room temperature. After 45 min, a solution of carboxylic acid (12.52 g, 50 mmol) in CH_2Cl_2 (60 mL) was added. After 24 h, the solid was filtered and washed with hexane. The solvent was removed under vacuum from the filtrate. To the residue, hexane was added and filtered. After removing the solvent under vacuum from the filtrate, it was recrystallized from methanol to give (1*H*-benzo[*d*][1,2,3]triazol-1-yl)(3,5-di-*tert*-butyl-2-hydroxy-phenyl) methanone **5** as a yellow solid.

Yield: 88%; mp 86.2–87.7 °C (methanol). IR (neat): ν 2960, 1656, 1589 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 11.19 (s, 1H), 8.28–8.25 (m, 2H), 8.17 (d, J = 8.0 Hz, 1H), 7.71–7.67 (m, 2H), 7.54 (t, J = 7.2 Hz, 1H), 1.49 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.5, 160.9, 145.5, 140.8, 137.7, 132.6, 132.3, 130.3, 127.9, 126.2, 120.2, 114.8, 112.7, 35.3, 34.5, 31.3, 29.4. MS (ESI) m/z: 352 ($M+H^+$). Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.87; H, 7.32; N, 11.85.

4.3. General procedure for synthesis of diaryl ketones 6a–6h

A solution of bromo compound (2.50 mmol) in dry THF (5 mL) was added (10 min) to a mixture of magnesium turnings (2.60 mmol) containing a catalytic amount of iodine (1 mg) in dry THF (10 mL) under an Ar atmosphere. After the addition of the bromo compound, the reaction mixture was stirred at room temperature for 6 h to ensure the completion of the Grignard formation. Next, this Grignard reagent was slowly added via an additional funnel to a solution of (1*H*-benzo[*d*][1,2,3]triazol-1-yl)(3,5-di-*tert*-butyl-2-hydroxy-phenyl)methanone **5** (1.0 mmol) in dry THF (3 mL) at room temperature. The reaction mixture was stirred at room temperature for the indicated reaction time (Table 1) and poured over ice-cold water (100 mL) containing ammonium chloride. It was then extracted with $CHCl_3$ (30 mL × 3) and dried (Na_2SO_4). Removal of the solvent followed by silica-gel column chromatography (eluent, hexane/ethyl acetate = 5:1) and recrystallization afforded the corresponding ketones **6a–6h**.

4.3.1. 1-(3,5-Di-*tert*-butyl-2-hydroxyphenyl)ethanone 6a

Yield: 60%; pale yellow solid; mp 50.5–51.4 °C (methanol) (lit.[18] mp 43.0–44.5 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 12.99 (s, 1H), 7.57–7.55 (m, 2H), 2.64 (s, 3H), 1.42 (s, 9H), 1.32 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 205.2, 160.1, 140.1, 138.0, 131.4, 124.3, 118.7, 35.1, 34.2, 31.4, 29.3, 27.0.

4.3.2. 1-(3,5-Di-*tert*-butyl-2-hydroxyphenyl)-2-methylpropan-1-one 6b

Yield: 76%; pale yellow solid; mp 34.8–35.6 °C (methanol) (lit.[18] mp 33.5–34.5 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 13.26 (s, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 3.71–3.61 (m, 1H), 1.43 (s, 9H), 1.32 (s, 9H), 1.26 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 211.4, 160.8, 139.8, 131.1, 123.5, 117.1, 35.2, 35.0, 34.2, 31.4, 29.3, 19.5.

4.3.3. Di-*tert*-butyl-2-hydroxyphenyl)phenylmethanone 6c

Yield: 79%; pale yellow solid; mp 59.3–61.5 °C (ethanol) (lit.[19] mp 60–62 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 12.71 (s, 1H), 7.67 (d, J = 6.8 Hz, 2H), 7.59–7.55 (m, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.43–7.42 (m, 1H), 1.47 (s, 9H), 1.24 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 202.5, 160.7, 139.8, 138.6, 137.8, 131.6, 131.2, 129.2, 128.1, 127.8, 118.2, 35.2, 34.2, 31.3, 29.4.

4.3.4. (3,5-Di-*tert*-butyl-2-hydroxyphenyl)*p*-tolylmethanone 6d

Yield: 80%; yellow solid; mp 70.5–72.9 °C (ethanol). IR (neat): ν 2955, 1614, 1239 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 12.68 (s, 1H), 7.60–7.56 (m, 3H), 7.45 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.47 (s, 9H), 1.24 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 202.2, 160.5, 142.3, 139.6, 137.8, 135.9, 130.9, 129.5, 128.8, 127.8, 118.3, 35.2, 34.2, 31.3, 29.4, 21.6. MS (ESI) m/z: 325 ($M+H^+$). Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.18; H, 8.78.

4.3.5. 4-*tert*-Butylphenyl(3,5-di-*tert*-butyl-2-hydroxyphenyl)methanone 6e

Yield: 94%; yellow thick liquid. IR (neat): ν 2958, 1615, 1241 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 12.66 (s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 2.4 Hz, 1H), 7.43–7.41 (m, 3H), 1.39 (s, 9H), 1.29 (s, 9H), 1.17 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 202.1, 160.5, 155.4, 139.6, 137.7, 135.8, 130.9, 129.4, 127.8, 125.1, 118.3, 35.2, 35.0, 34.2, 31.3, 31.2, 29.4. MS (ESI) m/z: 367 ($M+H^+$). Anal. Calcd for $C_{25}H_{34}O_2$: C, 81.92; H, 9.35. Found: C, 81.63; H, 9.46.

4.3.6. 3,5-Bis(trifluoromethyl)phenyl-(3,5-di-*tert*-butyl-2-hydroxyphenyl)methanone 6f

Yield: 98%; yellow thick liquid. IR (neat): ν 2960, 1628, 1275, 1132 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 12.36 (s, 1H), 8.16 (s, 2H), 8.09 (s, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 1.48 (s, 9H), 1.24 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 198.7, 161.2, 140.8, 140.2, 138.8, 132.5, 132.0 (q, J_{C-F} = 34.8 Hz), 129.6 (m), 127.1, 126.9, 125.0 (m), 124.3, 121.6, 118.9, 117.4, 35.4, 34.3, 31.2, 29.4. MS (ESI) m/z: 447 ($M+H^+$). Anal. Calcd for $C_{23}H_{24}F_6O_2$: C, 61.88; H, 5.42. Found: C, 61.63; H, 5.70.

4.3.7. 3,5-Di-*tert*-butyl-2-hydroxyphenyl-(4-trifluoromethylphenyl)methanone 6g

Yield: 59%; yellow solid; mp 96.4–97.2 °C (ethanol). IR (neat): ν 2960, 1613, 1322, 1137 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 12.60 (s, 1H), 7.77 (s, 4H), 7.64 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 1.48 (s, 9H), 1.24 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 201.1, 160.9, 141.9, 141.8, 140.3, 138.3, 133.1 (q, J_{C-F} = 33.1 Hz), 131.9, 129.3, 127.3, 125.2 (m), 125.0, 122.3, 117.8, 35.2, 34.2, 31.2, 29.4. MS (ESI) m/z: 379 ($M+H^+$). Anal. Calcd for $C_{22}H_{25}F_3O_2$: C, 69.82; H, 6.66. Found: C, 69.62; H, 6.80.

4.3.8. 3,5-Di-*tert*-butyl-2-hydroxyphenyl-(3,4,5-trifluorophenyl)methanone 6h

Yield: 51%; yellow solid; mp 103.8–104.5 °C (ethanol). IR (neat): ν 2960, 1613, 1359, 1048 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 12.26 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.37–7.32 (m, 3H), 1.46 (s, 9H), 1.26 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 198.2, 160.8, 152.1 (q, J_{C-F} = 3.3 Hz), 149.6 (q, J_{C-F} = 3.3 Hz), 143.4 (t, J_{C-F} = 14.9 Hz), 140.8 (t, J_{C-F} = 15.7 Hz), 140.4, 138.5, 134.1 (q, J_{C-F} = 6.6 Hz), 132.1, 126.8, 117.3, 114.0 (q, J_{C-F} = 5.8 Hz), 35.3, 34.3, 31.2, 29.3. MS (ESI) m/z: 365 ($M+H^+$). Anal. Calcd for $C_{21}H_{23}F_3O_2$: C, 69.22; H, 6.36. Found: C, 68.92; H, 6.51.

4.4. General procedure for the synthesis of keto-imine type chiral Schiff bases 7a–7h

A mixture of toluene (10 mL), (*S*)-valinol or (*S*)-*tert*-leucinol (1.20 mmol), salicylketone **6a–6h** (1.0 mmol) and anhydrous Na_2SO_4 (1.0 g) was refluxed at 115 °C for the indicated reaction time (Table 2). The mixture was filtered through a glass filter and the filtrate was evaporated. The residue was subjected to column chromatography on silica gel using hexane/ethyl acetate (5:1) as an eluent to afford the corresponding ONO-tridentate chiral Schiff base ligands **7a–7h**.

4.4.1. (*S*,*E*)-2,4-Di-*tert*-butyl-6-1-(1-hydroxy-3-methylbutan-2-ylimino)ethylphenol 7a

Yield: 66%; yellow solid; mp 32.1–33.5 °C. $[\alpha]_D^{28} = -30.4$ (c 1.0, $CHCl_3$) {lit.[11c] mp: 32–34 °C, $[\alpha]_D^{24} = -31.6$ (c 1.0, $CHCl_3$)}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 2.8 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 3.86–3.70 (m, 3H), 2.41 (s, 3H), 2.01–1.92 (m, 1H), 1.44 (s, 9H), 1.32 (s, 9H), 0.97–0.95 (m, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.9, 161.1, 137.9, 137.7, 127.1, 122.4, 118.1, 66.4, 64.9, 35.2, 34.2, 31.5, 30.6, 29.5, 19.6, 18.8, 15.1.

4.4.2. (*S*,*E*)-2,4-Di-*tert*-butyl-6-(1-hydroxy-3-methylbutan-2-ylimino)phenylmethylphenol 7c

Yield: 72%; yellow solid; mp: 65.8–68.5 °C. $[\alpha]_D^{28} = -30.5$ (c 1.0, $CHCl_3$) (lit.[11c] mp: 67–69 °C, $[\alpha]_D^{24} = -29.0$ (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.7.17 (m, 6H), 6.62 (t, J = 2.0 Hz, 1H), 3.79–3.70 (m, 2H), 3.30–3.26 (m, 1H), 1.93–1.85 (m, 1H), 1.48 (s, 9H), 1.09 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.9, 160.7, 160.6, 138.1, 137.1, 134.6, 128.5, 128.3, 128.0, 127.8, 127.1, 126.3, 118.7, 67.7, 64.9, 35.2, 33.9, 31.2, 30.4, 29.5, 19.6, 18.8.

4.4.3. (*S*,*E*)-2,4-Di-*tert*-butyl-6-(1-hydroxy-3,3-dimethylbutan-2-ylimino)phenyl-methylphenol 7c′

Yield: 68%; yellow solid; mp: 179.5–180.8 °C. $[\alpha]_D^{28} = -34.1$ (c 1.0, $CHCl_3$); (lit.[12b] mp: 180–181 °C, $[\alpha]_D^{25} = -25.9$ (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.37 (m, 5H), 7.17 (d, J = 4.8 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 3.85–3.77 (m, 2H), 3.29–3.23 (m, 1H), 1.49 (s, 9H), 1.09 (s, 9H), 0.91 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 176.0, 160.6, 138.0, 137.0, 134.5, 129.0, 128.5, 128.1, 127.8, 127.0, 126.5, 118.2, 70.8, 63.4, 35.2, 34.0, 33.8, 31.2, 29.5, 27.1.

4.4.4. (*S*,*E*)-2,4-Di-*tert*-butyl-6-(1-hydroxy-3,3-dimethylbutan-2-ylimino)*p*-tolyl-methylphenol 7d′

Yield: 60%; yellow solid; mp: 200.4–202.0 °C. $[\alpha]_D^{27} = -38.7$ (c 1.0, $CHCl_3$). IR (neat): ν 3422, 2955, 1580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 2.8 Hz, 1H), 7.25–7.22 (m, 3H), 7.05 (d, J = 7.2 Hz, 1H), 6.68 (d, J = 2.8 Hz, 1H), 3.81–3.77 (m, 2H), 3.31–3.24 (m, 1H), 2.42 (s, 3H), 1.48 (s, 9H), 1.10 (s, 9H), 0.90 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 176.4, 160.7, 138.2, 137.9, 137.0, 131.5, 128.8, 128.4, 128.1, 127.0 126.6, 118.9, 70.6, 63.4, 35.2, 34.0, 33.8, 31.3, 29.5, 27.1, 21.4. MS (ESI) m/z: 424 ($M+H^+$). Anal. Calcd for $C_{28}H_{41}NO_2$: C, 79.39; H, 9.76; N, 3.31. Found: C, 79.15; H, 9.50; N, 3.42.

4.4.5. (*S*,*E*)-2,4-Di-*tert*-butyl-6-(4-*tert*-butylphenyl)(1-hydroxy-3,3-dimethylbutan-2-ylimino)methylphenol 7e′

Yield: 70%; yellow thick liquid; $[\alpha]_D^{27} = -33.7$ (c 1.0, $CHCl_3$). IR (neat): ν 3393, 2956, 1583 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (t, J = 8.4 Hz, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 3.86–3.78 (m, 2H), 3.35–3.28 (m, 1H), 1.48 (s, 9H), 1.37 (s, 9H), 1.08 (s, 9H), 0.92 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.5, 160.7, 151.5, 137.9, 137.0, 131.5, 128.6, 127.9, 127.0, 126.5, 124.9, 124.6, 119.0, 70.7, 63.4, 35.2, 34.7, 33.9, 33.8, 31.3, 31.2, 29.5, 27.1, 22.6, 14.1. MS (ESI) m/z: 466 ($M+H^+$). Anal. Calcd for $C_{31}H_{47}NO_2$: C, 79.95; H, 10.17; N, 3.01. Found: C, 79.67; H, 10.49; N, 3.05.

4.4.6. (*S*,*E*)-2-3,5-Bis(trifluoromethyl)phenyl-(1-hydroxy-3-methylbutan-2-ylimino)methyl-4,6-di-*tert*-butylphenol 7f

Yield: 48%; yellow solid; mp: 131.8–132.8 °C. $[\alpha]_D^{27} = -7.3$ (c 1.0, $CHCl_3$). IR (neat): ν 3585, 2960, 1583, 1277, 1129 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.95 (s, 1H), 7.68 (s, 1H), 7.42 (d, J = 2.4 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 3.84–3.79 (m, 2H), 3.16–3.11 (m, 1H), 1.93–1.85 (m, 1H), 1.48 (s, 9H), 1.09 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.1, 160.2, 139.0, 137.7, 136.9, 131.7 (q, J_{C-F} = 18.2 Hz), 129.8, 128.4, 127.7, 125.5, 124.4, 122.4 (m), 121.7, 117.9, 68.7, 65.0, 35.3, 34.0, 31.1, 30.7, 29.5, 19.7, 18.7. MS (ESI) m/z: 532 ($M+H^+$). Anal. Calcd for $C_{28}H_{35}F_6NO_2$: C, 63.26; H, 6.64; N, 2.63. Found: C, 63.43; H, 6.74; N, 2.74.

4.4.7. (*S*,*E*)-2-3,5-Bis(trifluoromethyl)phenyl-(1-hydroxy-3,3-dimethylbutan-2-ylimino)methyl-4,6-di-*tert*-butylphenol 7f′

Yield: 50%; yellow solid; mp: 149.4–150.8 °C. $[\alpha]_D^{28} = -8.1$ (c 1.0, $CHCl_3$) (lit.[12b] mp: 149–150 °C, $[\alpha]_D^{29} = -7.6$ (c 1.0, $CHCl_3$). ^1H

NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.99 (s, 1H), 7.67 (s, 1H), 7.42 (d, J = 1.6 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 3.92–3.79 (m, 2H), 3.08–3.05 (m, 1H), 1.49 (s, 9H), 1.09 (s, 9H), 0.92 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.9, 160.2, 138.9, 137.6, 136.8, 131.5 (q, J_{C-F} = 25.6 Hz), 130.2, 128.6, 127.6, 125.5, 124.3, 122.3 (m), 121.6, 118.0, 71.8, 63.1, 35.3, 34.0, 33.9, 31.1, 29.5, 27.0.

4.4.8. (*S*,*E*)-2,4-Di-*tert*-butyl-6-(1-hydroxy-3-methylbutan-2-ylimino)(4-trifluoromethyl phenyl)methylphenol 7g

Yield: 80%; yellow solid; mp: 190.0–190.5 °C. $[\alpha]_D^{27} = -15.6$ (c 1.0, $CHCl_3$). IR (neat): ν 3465, 2960, 1584, 1322, 1121 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 3.80–3.75 (m, 2H), 3.20–3.15 (m, 1H), 1.92–1.82 (m, 1H), 1.48 (s, 9H), 1.09 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.3, 160.3, 138.7, 138.4, 137.4, 130.8 (q, J_{C-F} = 32.2 Hz), 129.3, 128.4, 127.4, 125.9, 125.3 (m), 122.5, 118.3, 68.2, 65.0, 35.2, 34.0, 31.2, 30.6, 29.5, 19.6, 18.8. MS (ESI) m/z: 464 (M+H$^+$). Anal. Calcd for $C_{27}H_{36}F_3NO_2$: C, 69.95; H, 7.83; N, 3.02. Found: C, 69.77; H, 7.95; N, 3.08.

4.4.9. (*S*,*E*)-2,4-Di-*tert*-butyl-6-(1-hydroxy-3-methylbutan-2-ylimino)(3,4,5-trifluorophenyl)methylphenol 7h

Yield: 43%; yellow solid; mp: 165.8–166.3 °C. $[\alpha]_D^{26} = -13.8$ (c 1.0, $CHCl_3$). IR (neat): ν 3592, 2955, 1585, 1366, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 2.4 Hz, 1H), 7.10 (s, 1H), 6.84 (s, 1H), 6.57 (d, J = 2.8 Hz, 1H), 3.78 (t, J = 5.2 Hz, 2H), 3.24–3.20 (m, 1H), 1.90–1.84 (m, 1H), 1.47 (s, 9H), 1.14 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.9, 160.1, 152.3, 149.8, 141.0 (t, J_{C-F} = 14.9 Hz), 138.8, 138.5 (t, J_{C-F} = 14.9 Hz), 137.5, 130.5 (q, J_{C-F} = 6.6 Hz), 127.6, 125.5, 117.8, 113.8 (d, J_{C-F} = 16.5 Hz), 112.5 (d, J_{C-F} = 19.9 Hz), 68.4, 64.9, 35.2, 34.0, 31.2, 30.6, 29.4, 19.6, 18.8. MS (ESI) m/z: 450 (M+H$^+$). Anal. Calcd for $C_{26}H_{34}F_3NO_2$: C, 69.46; H, 7.62; N, 3.12. Found: C, 69.39; H, 7.72; N, 3.11.

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