



Alkylation of Dianions Derived from 2-(1-Iminoalkyl) Phenols: Synthesis of Functionalized 2-Acyl Phenols.

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Abstract

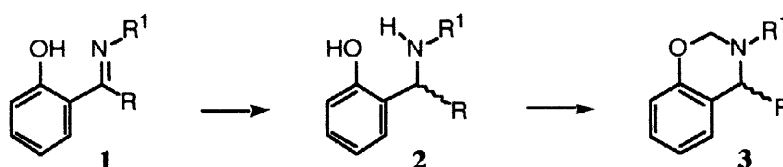
A method has been developed for the almost exclusive C-alkylation of the 2-(1-iminoalkyl) phenols **1**, important organic compounds with a range of employment, which allows the preparation of complex derivatives **4** with good yields starting from easily available materials. The operational simplicity of this method take advantages in providing a variety of alkylated 2-acyl phenols **5** by an easy hydrolysis of the 2-(1-iminoalkyl) phenols **4**.

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Key Words: alkylation; imines; phenols; lithium and compounds

The 2-(1-iminoalkyl) phenols **1** are important heterofunctionally substituted organic compounds with a range of uses. They serve as ligands in the preparation of rhodium(I) complexes, useful catalysts for the hydrosilylation of carbonyl compounds with Ph_2SiH_2 .¹ In addition, the 2-(1-iminoalkyl) phenols have interesting pharmacological activity as antifungal agents.² The 2-(1-aminoalkyl) phenols **2**, which can be prepared by simple reduction of 2-(1-iminoalkyl) phenols **1**,^{3,4} are very important intermediates in the synthesis of 3,4-dihydro-2H-1,3-benzoxazines **3** which show important biological and pharmacological activities.³ Enantiopure 2-(1-aminoalkyl) phenols **2**, prepared by stereoselective reduction of 2-(1-iminoalkyl) phenols **1**, serve as catalyst precursors for enantioselective addition of diethylzinc to aldehydes with chirality amplification⁵ and in other important stereoselective reactions⁶ with the use of organometallic reagents.

Scheme 1



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2-(1-iminoalkyl) phenols **1a-f** can be obtained by direct condensation of amines and 2-acyl phenol **5**,^{2,7} but the major problem of this synthetic route is the limited availability of the starting 2-acyl phenol **5**. An alternative strategy for introducing functionalized alkyl chains at the acyl group may be based on the reaction of their dimetalated species with carbon electrophiles.^{8,9} The reaction of enolate ion with carbon electrophile represents the most classical approach to C-C bond formation α to a CO group of aldehydes and ketones.¹⁰ More recently metallated imines, have been used extensively as advantageous reactive enolate equivalents.¹¹ This has solved many of the problems associated with the classical carbonyl chemistry, such as aldol type self condensation, di- and polyalkylation, control of regiochemistry, side reaction of products.¹²

Therefore, we undertook a study designed to explore the reaction conditions for the C-alkylation of 2-(1-iminoalkyl) phenol dianions. This extends one earlier research on the highly efficient regio- and stereoselective alkylation of β -enamino ketones.⁸ Lithium dianions of 2-(1-iminoalkyl) phenols (**Li₂1a-f**) can be easily generated by treatment with 2.5 eq. of LDA in THF at 0 °C (see Figure 1). Addition of the appropriate alkyl halide gives the desired 2-alkylated product **4aa-fd** in good to high yields (see Table 1). The entering electrophile alkyl halide attack the azaallylic system from the same side of the lithium atom.¹³ Different metallating agents and conditions tested gave less satisfactory results.

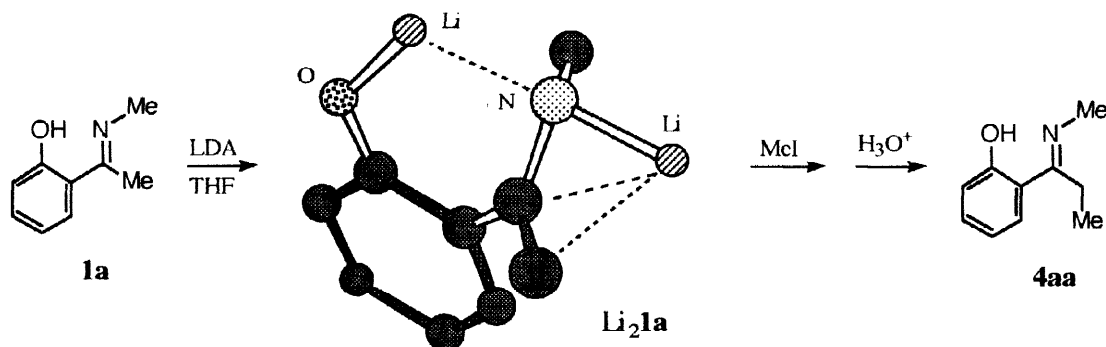


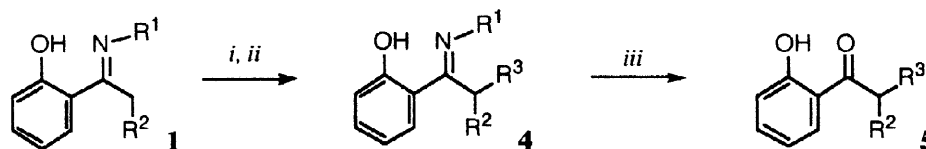
Figure 1. The PM3 calculated¹⁴ structure of 2-(1-methyliminoethyl) phenol lithium dianion (**Li₂1a**).

As showed in the Table 1, high yields have been obtained for the reaction of 2-(1-iminoalkyl) phenols **1a-f** with a large variety of functionalized alkyl halides. In the case of ethyl 3-bromopropionate the reaction take place with the exclusive replacement of the bromine atom. The reaction mixtures are generally pure enough and can be used for successive reaction without further purification. The purification of the 2-(1-iminoalkyl) phenol can be performed by fractional crystallization or by a short flash column chromatography. The lable imino phenol group hydrolyses on silica gel with a consequent lowering of yield. It is worth noting that using these conditions, N- or O-alkylation was negligible.

Several attempts were made to extend the reaction to the diastereoselective alkylation of dianions of 2-(1-iminoalkyl) phenols **1e** and **4fd** ($R^*NH_2 = (1R)$ -1-phenylethylamine), prepared stereoselectively with MeLi/HMPA/THF and treated respectively with ethyl- and methyl iodide.^{8b} Because the strongly sterically hindered lithium dianions intermediate, the reaction is not selective and sometimes predominant O-alkylation product are obtained.

Table 1

Alkylation of lithium dianions derived from 2-(1-iminoalkyl) phenols **1a-g** with alkyl halides; hydrolysis of functionalized 2-(1-iminoalkyl) phenols **4aa-fh** to 2-acyl phenols **5a-i**.



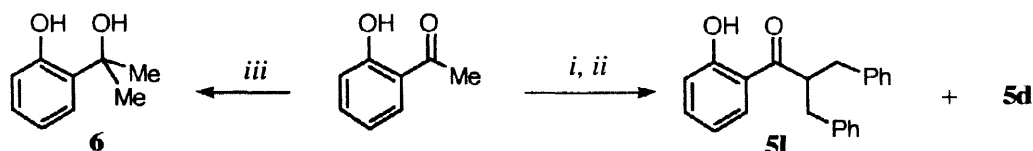
i: 2.5 eq. LDA/THF, 0 to 25 °C, 1 h; *ii*: 1.2 eq. R^3X /THF, -50 to 25 °C; *iii*: THF/H₂O/AcOH, 40 °C, 4h.

Entry	1	R ¹ ^a	R ²	R ³ -X	4	Yield (%) ^b	5	Yield (%) ^c
1	1a	Me	H	Me-I	4aa	62 (90)	5a	86 (72)
2	1a	Me	H	Et-I	4ab	58 (85)	5b	82 (62)
3	1a	Me	H	All-I	4ac	66 (90)	5c	79 (63)
4	1b	i-Pr	H	Me-I	4ba	56 (83)		
5	1b	i-Pr	H	Et-I	4bb	54 (79)		
6	1b	i-Pr	H	All-I	4bc	62 (77)		
7	1b	i-Pr	H	Bn-Cl	4bd	56 (81)	5d	89 (58)
8	1b	i-Pr	H	Br-(CH ₂) ₂ COOEt	4be	56 (73)	5e	76 (46)
9	1b	i-Pr	H	Cl-CH ₂ -CH=CH-Ph	4bf	53 (75)	5f	85 (57)
10	1c	Ph	H	Me-I	4ca	62 (85)		
11	1d	Bn	H	All-I	4dc	60 (86)		
12	1e	R*	Me	Me-I	4ea ^d	49 (72)	5i	77 (51)
13	1f	R*	H	Me-I	4fa	66 (91)		
14	1f	R*	H	Et-I	4fb	67 (87)		
15	1f	R*	H	All-I	4fc	56 (81)		
16	1f	R*	H	Bn-Cl	4fd	65 (90)		
17	1f	R*	H	i-Pr-I	4fg	65 (87)	5g	92 (73)
18	1f	R*	H	Bu-Br	4fh	63 (91)	5h	83 (65)

^a R*NH₂ = (1*R*)-1-phenylethylamine. ^b Yields of the pure compounds isolated by flash column chromatography; in parenthesis the gas chromatographic yields. ^c Yields of the pure isolated compounds; in parenthesis the yields of the pure isolated compounds prepared by one pot reaction without the isolation of the intermediate 2-(1-iminoalkyl) phenols. ^d The dianion was prepared by the use of 2.5 eq. MeLi/2.5 eq. HMPA/THF.^{8b}

It is worth noting that direct alkylation of the dianion of 2-hydroxyacetophenone in the same metallating conditions, using LDA in THF as base, affords a C,C-bisalkylation with formation of **5l** as well as **5d** (yields of 27 and 34 % respectively). Moreover treatment of *o*-hydroxyacetophenone with MeLi in HMPA/THF, the conditions that gave the best results for the diastereoselective alkylation of β -enamino ketones,^{8b} or again in the methylation of **1e** (Table 1, entry 12), results in the addition of the methyllithium reagent to the carbonyl group with the formation of the alcohol **6** (yields 64 %).

Scheme 2



i: 2.5 eq. LDA/THF, 0 to 25 °C, 1 h; *ii*: 1.2 eq. BnCl/THF, -50 to 25 °C;

iii: 2.5 eq. MeLi/2.5 eq. HMPA/THF, 0 to 25 °C, 1 h.

The alkylated 2-acyl phenols **5a-i** are easily obtained by hydrolysis of the corresponding 2-(1-iminoalkyl) phenols **4aa-fh** in THF/H₂O/AcOH mixture for 4 hours at 40 °C. The mild conditions used for the hydrolysis are compatible with the functional groups present in the 2-(1-iminoalkyl) phenols **4aa-fh**. The acyl phenols **5a-i** were recovered in high yields as reported in Table 1.

In conclusion, a method is now available for the almost exclusive C-alkylation of the 2-(1-iminoalkyl) phenols with good yields, which allows preparation of complex heterofunctional compounds starting from easily available materials. The operational simplicity of this method take advantages in providing a variety of alkylated 2-acyl phenols **5** by an easy hydrolysis of the 2-(1-iminoalkyl) phenol **4**.

EXPERIMENTAL SECTION

¹H and ¹³C-NMR spectra were recorded with a Varian VXR 300 instrument. Chemical shifts are given in ppm downfield from Me₄Si in CDCl₃ or D₂O solution. Coupling constants are given in Hertz. IR spectra were recorded with a Perkin-Elmer 257 spectrometer. GC-MS analyses were performed with an HP 59970 workstation formed by an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. All melting points are uncorrected. THF was dried by refluxing over sodium wires until the blue colour of benzophenone ketyl persisted and then distilled into a dry receiver under nitrogen atmosphere. All reagents and solvents were distilled prior to use or were of commercial quality from freshly opened containers. Commercial methyllithium and butyllithium solutions were employed under dry atmosphere.

Preparation of starting 2-(1-iminoalkyl) phenols 1a-f

The 2-(1-iminoalkyl)phenols **1a-f** were prepared by direct condensation of the appropriate *o*-acylphenol and the amine according to described procedure.^{2,7} The characterization of the 2-(1-iminoalkyl) phenols follows.

2-(1-Methyliminoethyl) phenol (1a): yellow needles, m.p. 68-70 °C (hexane); IR (nujol) 1715, 1621, 1309, 836 cm^{-1} ; $^1\text{H NMR } \delta$ 2.35 (s, 3 H), 3.36 (s, 3 H), 6.68-7.53 (m, 4 H), 16.67 (br s, 1 H); MS m/z 149 (M^+ , 76), 148 (74), 134 (100), 119 (24); Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{NO}$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.29; H, 7.51; N, 9.53.

2-(1-Isopropyliminoethyl) phenol (1b): yellow oil; IR (neat) 1615, 1448, 1303, 1162 cm^{-1} ; $^1\text{H NMR } \delta$ 1.30 (d, 6 H, $J = 6.3$ Hz), 2.34 (s, 3 H), 3.97 (septet, 1H, $J = 6.3$ Hz), 6.68-7.50 (m, 4 H), 16.97 (br s, 1 H); MS m/z 177 (M^+ , 72), 162 (26), 135 (24), 120 (100); Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.29; H, 8.61; N, 7.73.

2-(1-Phenyliminoethyl) phenol (1c): yellow needles, m.p. 79-80 °C (hexane); IR (neat) 1613, 1484, 1308, 1208 cm^{-1} ; $^1\text{H NMR } \delta$ 2.33 (s, 3 H), 6.80-7.68 (m, 9 H), 14.67 (br s, 1 H); MS m/z 211 (M^+ , 42), 196 (100), 120 (31), 77 (76); ; Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.43; H, 6.25; N, 6.49.

2-(1-Benzyliminoethyl) phenol (1d): yellow needles, mp 118-119 °C (hexane); IR (nujol) 1619, 1455, 1377, 744 cm^{-1} ; $^1\text{H NMR } \delta$ 2.43 (s, 3 H), 4.81 (s, 2 H), 6.70-7.65 (m, 9 H), 16.37 (br s, 1 H); m/z 225 (M^+ , 40), 208 (23), 134 (16), 91 (100); Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.82; H, 6.76; N, 6.03.

2-{1-[(1R)-1-Phenylethyl]iminopropyl} phenol (1e): yellow crystals, mp 79-81 (hexane); $[\alpha]_{\text{D}}^{20}$ -388.8 (c 2.1, CHCl_3); IR (nujol) 3350, 1595, 1440, 1295 cm^{-1} ; $^1\text{H NMR } \delta$ 1.16 (t, 3 H, $J = 7.7$ Hz), 1.66 (d, 3 H, $J = 6.7$ Hz), 2.81 (q, 2 H, $J = 7.7$ Hz), 4.98 (q, 1 H, $J = 6.7$ Hz), 6.73-7.46 (m, 9 H), 16.95 (br s, 1 H); Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.69; H, 7.59; N, 5.41.

2-{1-[(1R)-1-Phenylethyl]iminoethyl} phenol (1f): yellow oil; $[\alpha]_{\text{D}}^{20}$ -322.8 (c 2.5, CHCl_3); IR (neat) 1613, 1448, 1303, 1085 cm^{-1} ; $^1\text{H NMR } \delta$ 1.65 (d, 3 H, $J = 6.6$ Hz), 2.35 (s, 3 H), 4.96 (q, 1 H, $J = 6.6$ Hz), 6.74-7.55 (m, 9 H), 16.80 (br s, 1 H); Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.42; H, 7.09; N, 5.63.

General procedure for the alkylation of the 2-(1-iminoalkyl) phenols 1a-f.

Lithium dianion was prepared according to the following typical procedure. A solution of butyllithium (12.5 mmol) was dropped into a stirred solution of the 2-(1-iminoalkyl) phenols 1a-f (5.0 mmol) and diisopropylamine (12.5 mmol) in THF (5 mL) at 0 °C under nitrogen and then warmed to 25 °C for 1 h. When the evolution of butane ceased the complete formation of dianion was indicated. The mixture was cooled at -50 °C and then treated with alkyl halide (6.0 mmol) in THF (2 mL) for 30 min. The temperature was slowly allowed to rise to 25 °C (1-4 h) followed by quenching with water and extraction with dichloromethane. The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue obtained was submitted to a short flash column chromatographic purification (n-hexane/ethyl acetate).

2-(1-Methyliminopropyl) phenol (4aa): yellow oil; IR (neat) 1614, 1580, 1449, 1280 cm^{-1} ; $^1\text{H NMR } \delta$ 1.23 (t, 3 H, $J = 7.7$ Hz), 2.81 (q, 2 H, $J = 7.7$ Hz), 3.36 (s, 3 H), 6.65-7.53 (m, 4 H), 16.45 (br s, 1 H); $^{13}\text{C NMR } \delta$ 11.99, 20.80, 34.86, 116.72, 116.90, 120.38, 128.33, 133.37, 167.20, 178.45; MS m/z 163

(M⁺, 22), 174 (20), 160 (18), 134 (100); Anal. Calcd. for C₁₀H₁₃NO : C, 73.59; H, 8.03; N, 8.58. Found: C, 73.81; H, 7.91; N, 8.79.

2-(1-Methyliminobutyl) phenol (4ab): yellow oil; IR (neat) 1615, 1579, 1450, 1310 cm⁻¹; ¹H NMR δ 1.06 (t, 3 H, *J* = 7.3 Hz), 1.54–1.75 (m, 2 H), 2.69–2.80 (m, 2 H), 3.33 (s, 3 H), 6.60–7.50 (m, 4 H), 17.00 (br s, 1 H); ¹³C NMR δ 14.33, 20.88, 28.94, 34.63, 116.15, 117.46, 119.83, 127.98, 132.78, 166.61, 176.84; MS *m/z* 177 (M⁺, 67), 162 (74), 148 (33), 134 (100); Anal. Calcd. for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.66; H, 8.49; N, 7.71.

2-(1-Methylimino-3-pentenyl) phenol (4ac): yellow oil; IR (neat) 1615, 1579, 1449, 1311 cm⁻¹; ¹H NMR δ 2.20–2.43 (m, 2 H), 2.87 (t, 2 H, *J* = 7.7 Hz), 3.35 (s, 3 H), 5.03–5.20 (m, 2 H), 5.89 (ddt, 1 H, *J* = 17.0, 10.2, 6.5 Hz), 6.65–7.53 (m, 4 H), 16.80 (br s, 1 H); ¹³C NMR δ 26.37, 31.10, 34.97, 116.17, 116.46, 117.44, 119.67, 127.84, 132.76, 136.12, 166.06, 175.96; MS *m/z* 189 (M⁺, 22), 174 (20), 160 (18), 134 (100); Anal. Calcd. for C₁₂H₁₅NO : C, 76.16; H, 7.99; N, 7.40. Found: C, 75.88; H, 7.83; N, 7.62.

2-(1-Isopropyliminopropyl) phenol (4ba): yellow oil; IR (neat) 1611, 1450, 1306, 1161 cm⁻¹; ¹H NMR δ 1.26 (t, 3 H, *J* = 7.7 Hz), 1.32 (d, 6 H, *J* = 6.3 Hz), 2.79 (q, 2 H, *J* = 7.7 Hz), 4.00 (septet, 1 H, *J* = 6.3 Hz), 6.63–7.50 (m, 4 H), 17.15 (br s, 1 H); ¹³C NMR δ 13.38, 20.93, 24.11, 49.22, 116.81, 117.55, 120.18, 128.46, 133.04, 166.93, 174.35; MS *m/z* 191 (M⁺, 26), 176 (15), 120 (100); Anal. Calcd. for C₁₂H₁₇NO: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.24; H, 8.84; N, 7.14.

2-(1-Isopropyliminobutyl) phenol (4bb): yellow oil; IR (neat) 1611, 1449, 1305, 1160 cm⁻¹; ¹H NMR δ 1.02 (t, 3 H, *J* = 7.3 Hz), 1.26 (d, 6 H, *J* = 6.3 Hz), 1.50–1.80 (m, 2 H), 2.60–2.75 (m, 2 H), 3.95 (septet, 1 H, *J* = 6.3 Hz), 6.30–7.50 (m, 4 H), 17.20 (br s, 1 H); ¹³C NMR δ 14.33, 21.99, 24.02, 29.18, 48.81, 116.23, 118.47, 119.69, 128.09, 132.55, 166.45, 172.66; *m/z* 205 (M⁺, 31), 190 (22), 176 (23), 120 (100); Anal. Calcd. for C₁₃H₁₉NO: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.24; H, 9.39; N, 6.61.

2-(1-Isopropylimino-4-pentenyl) phenol (4bc): yellow oil; IR (neat) 1611, 1447, 1304, 1160, 917 cm⁻¹; ¹H NMR δ 1.32 (d, 6 H, *J* = 6.3 Hz), 2.28–2.47 (m, 2 H), 2.75–2.94 (m, 2 H), 3.99 (septet, 1 H, *J* = 6.3 Hz), 5.04–5.20 (m, 2 H), 5.89 (ddt, 1 H, *J* = 16.9, 10.2, 6.6 Hz), 6.65–7.54 (m, 4 H), 17.03 (br s, 1 H); ¹³C NMR δ 24.54, 27.04, 32.70, 49.55, 116.56, 117.01, 118.34, 120.09, 128.42, 133.05, 136.68, 166.46, 172.18; *m/z* 217 (M⁺, 17), 202 (14), 160 (28), 120 (100); Anal. Calcd. for C₁₄H₁₉NO: C, 77.38; H, 8.81; N, 6.45. Found: 77.12; H, 8.92; N, 6.25.

2-(1-Isopropylimino-3-phenylpropyl) phenol (4bd): yellow oil; IR (neat) 1611, 1448, 1303, 1158 cm⁻¹; ¹H NMR δ 1.20 (d, 6 H, *J* = 6.3 Hz), 2.88–3.14 (m, 4 H), 3.80 (septet, 1 H, *J* = 6.3 Hz), 6.70–8.00 (m, 9 H), 17.08 (br s, 1 H); ¹³C NMR δ 24.06, 29.28, 34.56, 49.34, 116.79, 118.76, 119.30, 119.93, 126.92, 128.11, 128.46, 128.97, 132.81, 166.28, 171.45; *m/z* 267 (M⁺, 19), 176 (74), 120 (100); Anal. Calcd. for C₁₈H₂₁NO: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.12; H, 7.83; N, 5.41.

Ethyl 5-(2-hydroxyphenyl)-5-(isopropylimino)pentanoate (4be): yellow oil; IR (neat) 1732, 1612, 1448, 1160 cm⁻¹; ¹H NMR δ 1.20–1.34 (m, 9 H), 1.80–2.10 (m, 2 H), 2.44 (t, 2 H, *J* = 6.7 Hz), 2.74–2.86 (m, 2 H), 4.00 (septet, 1 H, *J* = 6.2 Hz), 4.15 (q, 2 H, *J* = 7.1 Hz), 6.60–7.80 (m, 4 H), 16.95 (br s, 1 H); ¹³C NMR δ 14.24, 23.45, 24.08, 26.08, 33.67, 49.02, 60.64, 116.61, 119.47, 128.00, 132.56, 136.34, 165.83, 171.62, 172.66; MS *m/z* 277 (M⁺, 28), 232 (11), 190 (78), 176 (34), 120 (100); Anal. Calcd. for C₁₆H₂₃NO₃: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.43; H, 8.42; N, 5.19.

2-[(E)-1-Isopropylimino-5-phenyl-4-pentenyl] phenol (4bf): yellow oil; IR (neat) 1611, 1447, 1303, 1159 cm^{-1} ; $^1\text{H NMR } \delta$ 1.32 (d, 6 H, $J = 6.3$ Hz), 2.50–3.03 (m, 4 H), 4.04 (septet, 1 H, $J = 6.3$ Hz), 6.08–7.95 (m, 11 H), 17.10 (br s, 1 H); $^{13}\text{C NMR } \delta$ 24.54, 27.57, 32.13, 49.67, 117.06, 119.06, 120.24, 126.60, 127.96, 128.15, 128.50, 129.12, 131.95, 133.21, 137.04, 166.70, 172.12; MS m/z 293 (M^+ , 33), 250 (11), 176 (58), 160 (28), 120 (100); Anal. Calcd. for $\text{C}_{20}\text{H}_{23}\text{NO}$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.65; H, 7.96; N, 4.53.

2-(1-Phenyliminopropyl) phenol (4ca): yellow oil; IR (neat) 1605, 1573, 1463, 1377 cm^{-1} ; $^1\text{H NMR } \delta$ 1.22 (t, 3 H, $J = 7.6$ Hz), 2.72 (q, 2 H, $J = 7.6$ Hz), 6.80–7.68 (m, 9 H), 14.70 (br s, 1 H); $^{13}\text{C NMR } \delta$ 13.53, 23.00, 117.96, 118.10, 118.57, 120.81, 124.58, 128.96, 129.11, 133.00, 146.98, 162.70, 176.33; MS m/z 225 (M^+ , 43), 196 (100), 120 (28), 77 (78); Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.73; H, 6.87; N, 6.44.

2-(1-Benzylimino-4-pentenyl) phenol (4dc): yellow oil; IR (neat) 1611, 1449, 1304, 917 cm^{-1} ; $^1\text{H NMR } \delta$ 2.28–2.48 (m, 2 H), 2.96 (t, 2 H, $J = 7.8$ Hz), 4.84 (s, 2 H), 5.07–5.24 (m, 2 H), 5.93 (ddt, 1 H, $J = 17.0, 10.2, 6.5$ Hz), 6.65–7.60 (m, 9 H), 16.88 (br s, 1 H); $^{13}\text{C NMR } \delta$ 27.70, 31.95, 53.33, 116.73, 117.73, 118.52, 119.63, 127.81, 127.99, 128.62, 129.31, 133.21, 136.68, 138.98, 165.16, 175.55; MS m/z 265 (M^+ , 8), 236 (11), 174 (19), 120 (25), 91 (100); Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{NO}$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.32; H, 7.17; N, 5.42.

2-{2-Methyl-1-[(1R)-1-phenylethyl]iminopropyl} phenol (4ea): yellow oil; $[\alpha]_{\text{D}}^{20}$ -168.8 (c 1.6, CHCl_3); IR (neat) 1595, 1490, 1440, 1280 cm^{-1} ; $^1\text{H NMR } \delta$ 1.25 (d, 3 H, $J = 7.3$ Hz), 1.44 (d, 3 H, $J = 7.3$), 1.67 (d, 3 H, $J = 6.6$ Hz), 3.54 (sept, 1 H, $J = 7.3$ Hz), 5.12 (q, 1 H, $J = 6.6$ Hz), 6.65–7.72 (m, 9 H), 16.86 (br s, 1 H); $^{13}\text{C NMR } \delta$ 20.07, 20.55, 25.63, 29.52, 57.35, 115.80, 116.88, 119.98, 126.15, 127.22, 128.76, 128.81, 132.45, 144.21, 166.34, 178.27; MS m/z 267 (M^+ , 76), 252 (18), 162 (43), 120 (31), 105 (100); Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.99; H, 7.85; N, 5.04

2-{1-[(1R)-1-Phenylethyl]iminobutyl} phenol (4fb): yellow oil; $[\alpha]_{\text{D}}^{20}$ -275.3 (c 2.5, CHCl_3); IR (neat) 1609, 1575, 1449, 1305 cm^{-1} ; $^1\text{H NMR } \delta$ 0.70–2.15 (m, 8 H), 3.20–3.50 (m, 2 H), 5.16 (m, 1 H), 6.62–7.83 (m, 9 H), 16.86 (br s, 1 H); $^{13}\text{C NMR } \delta$ 14.44, 21.62, 25.53, 29.88, 57.96, 116.82, 119.08, 119.28, 126.27, 127.25, 128.19, 128.82, 132.64, 144.23, 165.33, 173.92, m/z 267 (M^+ , 38), 252 (10), 238 (19), 148 (36), 105 (100); Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.64; H, 7.86; N, 5.09.

2-{1-[(1R)-1-Phenylethyl]imino-4-pentenyl} phenol (4fc): yellow oil; $[\alpha]_{\text{D}}^{20}$ -194.2 (c 2.9, CHCl_3); IR (neat) 1600, 1440, 1300, 920 cm^{-1} ; $^1\text{H NMR } \delta$ 1.65 (d, 3 H, $J = 6.6$ Hz), 2.26 (m, 2 H), 2.88 (t, 2 H, $J = 8.2$ Hz), 4.90–5.14 (m, 3 H), 5.85 (ddt, 1 H, $J = 17.4, 9.7, 6.5$ Hz), 6.72–7.51 (m, 9 H), 16.37 (br s, 1 H); $^{13}\text{C NMR } \delta$ 26.07, 27.70, 32.25, 58.66, 116.49, 117.54, 118.32, 119.71, 126.80, 127.77, 128.57, 129.33, 133.17, 136.70, 144.73, 165.52, 173.60, m/z 279 (M^+ , 15), 278 (16), 238 (14), 174 (23), 160 (22), 105 (100); Anal. Calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.87; H, 7.66; N, 4.87.

2-{3-Phenyl-1-[(1R)-1-phenylethyl]iminopropyl} phenol (4fd): yellow oil; $[\alpha]_{\text{D}}^{20}$ -20.4 (c 2.2, CHCl_3); IR (neat) 1609, 1575, 1449, 1304 cm^{-1} ; $^1\text{H NMR } \delta$ 1.55 (d, 3 H, $J = 6.5$ Hz), 2.67–2.93 (m, 2 H), 3.00–3.15 (m, 2 H), 4.78 (q, 1 H, $J = 6.5$ Hz), 6.78–7.60 (m, 14 H), 16.90 (br s, 1 H); $^{13}\text{C NMR } \delta$ 25.68, 30.13, 34.11, 58.40, 117.33, 117.95, 119.56, 126.49, 126.91, 127.48, 128.27, 128.40, 128.99, 129.04,

132.95, 140.28, 144.47, 165.37, 173.04; MS m/z 329 (M^+ , 29), 238 (72), 224 (27), 120 (31), 105 (100);

Anal. Calcd. for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.61; H, 7.12; N, 4.11.

2-{3-Methyl-1-[(1*R*)-1-phenylethyl]iminobutyl} phenol (4fg): yellow crystals, m.p. 82–84 (hexane); $[\alpha]_D^{20}$ -311.5 (c 1.8, $CHCl_3$); IR (nujol) 1606, 1454, 1377, 1304 cm^{-1} ; 1H NMR δ 0.98 (d, 3 H, $J = 6.6$ Hz), 1.05 (d, 3 H, $J = 6.6$ Hz), 1.64 (d, 3 H, $J = 6.6$ Hz), 2.09 (nonet, 1 H, $J = 6.6$ Hz), 2.72 (d, 2 H, $J = 7.4$ Hz), 5.05 (q, 1 H, $J = 6.6$ Hz), 6.70–7.55 (m, 9 H), 16.91 (br s, 1 H); ^{13}C NMR δ 23.24, 23.35, 25.94, 29.04, 36.60, 58.51, 117.16, 118.81, 119.80, 126.77, 127.72, 129.12, 129.31, 133.08, 144.52, 165.76, 173.59; MS m/z 281 (M^+ , 23), 238 (34), 162 (39), 105 (100); Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.29; H, 8.15; N, 4.8.

2-{1-[(1*R*)-1-Phenylethyl]iminohexyl} phenol (4fh): yellow oil; $[\alpha]_D^{20}$ -193.4 (c 3.1, $CHCl_3$); IR (neat) 1610, 1576, 1449, 1303 cm^{-1} ; 1H NMR δ 0.89 (t, 3 H, $J = 6.8$ Hz), 1.20–1.63 (m, 6 H), 1.66 (d, 3 H, $J = 6.6$ Hz), 2.76 (t, 2 H, $J = 7.8$ Hz), 4.96 (q, 1 H, $J = 6.6$ Hz), 6.67–7.60 (m, 9 H), 17.10 (br s, 1 H); ^{13}C NMR δ 14.10, 22.51, 25.75, 27.97, 28.22, 32.32, 58.11, 116.99, 118.07, 119.53, 126.47, 127.45, 128.36, 129.01, 132.86, 144.47, 165.67, 174.42; MS m/z 295 (M^+ , 21), 238 (23), 148 (47), 105 (100); Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.53; H, 8.62; N, 4.56.

Hydrolysis of the 2-(1-iminoalkyl) phenols 4aa–fh; synthesis of 2-acyl phenols 5a–i. The 2-(1-iminoalkyl) phenol (3 mmol) dissolved in a mixture of THF (2 mL) and H_2O (2 mL) was treated with glacial AcOH (0.5 mL) and stirred at 40 °C for 4 h. The mixture was neutralized with sodium carbonate and extracted with dichloromethane. The organic layer was dried, evaporated under reduced pressure and the residue obtained, submitted to flash chromatographic purification (*n*-hexane/ethyl acetate, 95:5), furnished the pure 2-acyl phenol in almost quantitative yield.

1-(2-Hydroxyphenyl)-1-propanone (5a): colourless oil; IR (neat) 1642, 1448, 1281, 1206 cm^{-1} ; 1H NMR δ 1.25 (t, 3 H, $J = 7.3$ Hz), 3.05 (q, 2 H, $J = 7.3$ Hz), 6.80–7.83 (m, 4 H), 12.37 (s, 1 H); ^{13}C NMR δ 8.41, 31.75, 118.57, 118.94, 119.41, 130.00, 136.33, 162.54, 207.32; MS m/z 150 (M^+ , 37), 121 (100); Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.81; H, 6.66.

1-(2-Hydroxyphenyl)-1-butanone (5b): colourless oil; IR (neat) 1640, 1448, 1266, 1203 cm^{-1} ; 1H NMR δ 1.02 (t, 3 H, $J = 7.4$ Hz), 1.78 (sext, 2 H, $J = 7.4$ Hz), 2.96 (t, 2 H, $J = 7.4$ Hz), 6.80–7.82 (m, 4 H), 12.40 (s, 1 H); ^{13}C NMR δ 13.83, 17.90, 40.17, 118.48, 118.82, 119.36, 130.00, 136.17, 162.49, 206.79; MS m/z 164 (M^+ , 26), 121 (100); Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.02; H, 7.44.

1-(2-Hydroxyphenyl)-4-penten-1-one (5c): colourless oil; IR (neat) 1641, 1488, 1448, 1158 cm^{-1} ; 1H NMR δ 2.40–2.60 (m, 2 H), 3.10 (t, 2 H, $J = 7.1$ Hz), 4.95–5.20 (m, 2 H), 5.90 (ddt, 1 H, $J = 17.1, 10.2, 6.5$ Hz), 6.80–7.82 (m, 4 H), 12.30 (s, 1 H); ^{13}C NMR δ 28.59, 37.93, 116.16, 119.03, 119.40, 119.78, 130.37, 136.79, 137.28, 162.92, 206.14; MS m/z 176 (M^+ , 12), 158 (14), 121 (100); Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.15; H, 7.01.

1-(2-Hydroxyphenyl)-3-phenyl-1-propanone (5d): colourless oil; IR (neat) 1640, 1447, 1305, 1157 cm^{-1} ; 1H NMR δ 3.08 (t, 2 H, $J = 7.9$ Hz), 3.35 (t, 2 H, $J = 7.9$ Hz), 6.80–7.80 (m, 9 H), 12.37 (s, 1 H); ^{13}C NMR δ 30.0, 40.0, 118.5, 118.6, 118.9, 126.3, 128.4, 128.6, 129.8, 136.4, 140.7, 162.5, 205.4; MS

m/z 226 (M^+ , 22), 207 (16), 121 (100); Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.46; H, 6.31.

Etil 5-(2-hydroxyphenyl)-5-oxapentanoate (5e): colourless oil; IR (neat) 1732, 1641, 1448, 1203 cm^{-1} ; 1H NMR δ 1.26 (t, 3 H, $J = 7.1$ Hz), 2.08 (quint, 2 H, $J = 7.2$ Hz), 2.45 (t, 2 H, $J = 7.2$ Hz), 3.09 (t, 2 H, $J = 7.2$ Hz), 4.15 (q, 2 H, $J = 7.1$ Hz), 6.85–7.83 (m, 4 H), 12.28 (s, 1 H); ^{13}C NMR δ 14.2, 19.4, 33.3, 37.2, 60.5, 118.5, 118.6, 118.9, 129.9, 136.4, 162.4, 173.1, 205.7; MS m/z 236 (M^+ , 11), 191 (18), 162 (30), 121 (100); Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.24; H, 6.92.

(E)-1-(2-Hydroxyphenyl)-5-phenyl-4-penten-1-one (5f): colourless needles, mp 77–79 °C (MeOH); IR (nujol) 1640, 1378, 1251, 1198 cm^{-1} ; 1H NMR δ 2.20–2.55 (m, 2 H), 3.19 (t, 2 H, $J = 7.40$ Hz), 6.29 (dt, 1 H, $J = 15.8, 6.6$), 6.50 (d, 1 H, $J = 15.8$ Hz), 6.87–7.84 (m, 9 H), 12.36 (s, 1 H); ^{13}C NMR δ 27.46, 37.97, 118.48, 118.59, 118.95, 126.07, 127.22, 128.55, 129.89, 131.03, 131.16, 136.37, 137.31, 162.50, 205.55; MS m/z 252 (M^+ , 28), 234 (11), 121 (100), 117 (24); Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.76; H, 6.47.

1-(2-Hydroxyphenyl)-3-methyl-1-butanone (5g): colourless oil; IR (neat) 1639, 1488, 1447, 1158 cm^{-1} ; 1H NMR δ 1.02 (d, 6 H, $J = 6.6$ Hz), 1.78 (nonet, 1 H, $J = 6.7$ Hz), 2.85 (d, 2 H, $J = 6.9$ Hz), 6.82–7.81 (m, 4 H), 12.47 (s, 1 H); ^{13}C NMR δ 23.2, 26.0, 47.6, 119.0, 119.3, 120.1, 130.6, 136.7, 163.1, 207.2; MS m/z 178 (M^+ , 12), 163 (12), 145 (9), 121 (100); Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.02; H, 7.84.

1-(2-Hydroxyphenyl)-1-hexanone (5h): colourless oil; IR (neat) 1641, 1488, 1448, 1157 cm^{-1} ; 1H NMR δ 0.91 (t, 3 H, $J = 6.7$ Hz), 1.25–1.84 (m, 6 H), 2.98 (t, 2 H, $J = 7.6$ Hz), 6.80–7.82 (m, 4 H), 12.40 (s, 1 H); ^{13}C NMR δ 14.11, 22.67, 24.41, 31.64, 38.49, 118.70, 119.01, 119.53, 130.18, 136.36, 162.70, 207.18; MS m/z 192 (M^+ , 9), 149 (13), 136 (19), 121 (100); Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.44.

1-(2-Hydroxyphenyl)-2-methyl-1-propanone (5i): colourless oil; IR (neat) 1639, 1488, 1447, 1209 cm^{-1} ; 1H NMR δ 1.25 (d, 6 H, $J = 6.8$ Hz), 3.61 (sept, 1 H, $J = 6.8$ Hz), 6.85–7.85 (m, 4 H), 12.50 (s, 1 H); ^{13}C NMR δ 19.79, 35.41, 118.64, 119.22, 119.27, 130.32, 136.65, 163.62, 211.27; MS m/z 164 (M^+ , 19), 121 (100), 93 (18); Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.09; H, 7.24.

2-Benzyl-1-(2-hydroxyphenyl)-3-phenyl-1-propanone (5l): colourless oil; IR (neat) 1640, 1447, 1305, 1157 cm^{-1} ; 1H NMR δ 2.84 (dd, 2 H, $J = 13.7, 6.4$ Hz), 3.14 (dd, 2 H, $J = 13.7, 7.6$ Hz), 4.05 (quint, 1 H, $J = 7.0$ Hz), 6.70–7.60 (m, 14 H), 12.45 (s, 1 H); MS m/z 316 (M^+ , 2), 225 (100), 121 (96); Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.36; H, 6.27.

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