Magnesium-mediated *ortho*-Specific Formylation and Formaldoximation of Phenols

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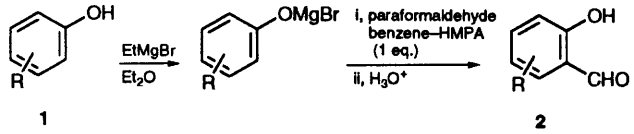
Deprotonation of phenols using magnesium methoxide, followed by distillative removal of free methanol and addition of paraformaldehyde results in *ortho*-specific magnesium-mediated formylation to give the corresponding salicylaldehyde magnesium salts, from which the salicylaldehydes can be isolated by acidic work-up. Addition of aq. hydroxylamine sulfate to the salicylaldehyde magnesium salts, in place of the acid work-up, gives the corresponding salicylaldoximes.

Significant industrial demand exists for *ortho*-formylated phenols and their derivatives (including the corresponding oximes), for example as intermediates for the synthesis of various pharmaceuticals, agrochemicals, fragrance chemicals,[1] mining chemical ligands[2] and other products. Whilst conventional aromatic formylation procedures (*e.g.* Duff,[3] Reimer–Tiemann,[4] Vilsmeier[5] or Gatterman[6] reactions) can be effective when the phenol hydroxyl is derivatised (for example, as an ether[7]), attempted formylation of the free phenol by these procedures frequently gives rise to poor yields and/or poor regioselectivity, or a predominance of *para*-formylation. α,α-Dichloromethyl methyl ether can be used for efficient formylation of phenols,[8] but use of this material on a large scale is unattractive owing to toxicity and cost. Phenols can be *ortho*-formylated by formaldehyde in the presence of one of a variety of metal salt catalysts (*e.g.* use of Sn,[9] Ti,[10,11] Fe,[11,12] Cr[13] and Zr[10] salts) but such reactions generally require high pressure and can give rise to unattractive process-effluent implications. Formylation of aryloxymagnesium bromides by formaldehyde has been reported by Casiraghi, Casnati and co-workers.[14] These authors, however, prepared their phenol magnesium salts by the reaction of the parent phenols with alkyl Grignard reagents (Scheme 1) and carried out formylation in the pres-



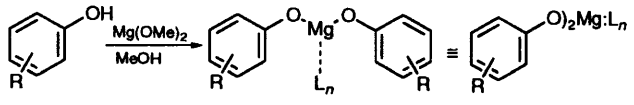
1 2

Scheme 1

ence of stoichiometric amounts of hexamethylphosphoramide (HMPA). They subsequently dismissed this chemistry as having limited large-scale applicability due to the need for the considerable amount of toxic HMPA and for the troublesome preparation of the magnesium phenolates.[15] Mindful of the potential environmental advantages associated with catalysis by magnesium salts, compared with use of many other formylation catalysts (magnesium already being distributed in its various salts as the 6th most abundant element on the earth's surface[16]), we undertook investigation of alternative conditions for the synthesis and reaction of phenol magnesium salts with the aim of avoiding the disadvantages of the conditions involving Grignard reagents and HMPA reported by Casiraghi and Casnati.[14] We now report the successful *ortho*-formylation[17] by paraformaldehyde of magnesium bis(phenoxides) prepared from phenols and magnesium methoxide, using methanol as the cosolvent instead of HMPA. We also report oximation of the derived formylated products by hydroxylamine sulfate, again catalysed by the magnesium cation.[18]

Results

Reaction of phenols **1** with magnesium methoxide in methanol (or a methanol–toluene azeotropic distillate recovered from a subsequent step of the reaction sequence) gives the corresponding phenol magnesium salts[19] **3** (Scheme 2). These magnesium

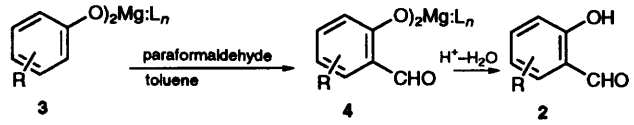


1 L = solvating ligand, *e.g.* MeOH 3

a R = H
b R = *o*-Me
c R = *m*-Me
d R = *p*-Me
e R = *o*-F
f R = *m*-F
g R = *p*-F
h R = *o*-Me and *p*-Me
i R = *o*-OMe
j R = *p*-OMe
k R = *p*-Cl
l R = *p*-NO_2
m R = *o*-Bu^s
n R = *m*-Bu^t
o R = *p*-C_9H_{19} (mixed isomers)
p R = *p*-$C_{12}H_{25}$ (mixed isomers)

Scheme 2

salts in methanol are not efficiently formylated by formaldehyde, however, removal of the free methanol by distillation with the addition of toluene (or xylene) as a replacement solvent, followed by the addition of paraformaldehyde at around 95 °C (with removal of volatile reaction by-products by distillation) gives the corresponding salicylaldehyde magnesium salts **4** as a result of formylation at the position *ortho* to the parent phenol hydroxyl (Scheme 3). The *ortho*-formylated phenols **2** are



3 4 2

Scheme 3

obtained from their magnesium salts by acidic work-up. Formylation yields are summarised in Table 1.

Methanol is produced as a formylation reaction by-product and, if it is not removed by distillation during the course of the reaction, the progress of formylation is inhibited, resulting in poorer conversion of starting material to products. The major by-products from the reaction (as seen by GCMS, size exclusion

Table 1 Formylation of phenols **1** to give salicylaldehydes **2**

Starting phenol **1**, substituent R	Salicylaldehyde product **2**	Yield of salicylaldehyde (%)	Unchanged starting phenol **1** (%)
H	**a**	83	<2
3-Me	**c**	74[a]	<1
2-F[b]	**e**	5[b]	*ca.* 72
3-F[b]	**f**	72[b,c]	<1
4-F[b]	**g**	46[b]	*ca.* 36
2-OMe	**i**	None detected	>95
4-OMe	**j**	94	<1
4-Cl	**k**	33	*ca.* 38
4-NO_2	**l**	None detected	>95
4-Nonyl (mixed isomers)	**o**	78[d]	<1
4-Nonyl (mixed isomers)[b]	**o**	85[b]	<1
4-Nonyl (mixed isomers)[b,e]	**o**	81[b,e]	<2

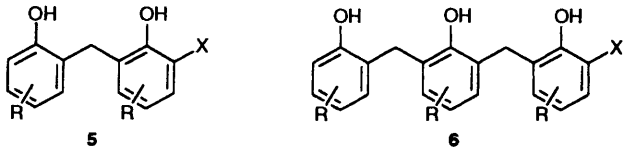
[a] 80:20 Ratio of 2-hydroxy-4-methylbenzaldehyde:2-hydroxy-6-methylbenzaldehyde isomers by ^{13}C NMR. [b] Formylation carried out under reduced pressure (other examples carried out at atmospheric pressure). [c] 86:14 Ratio of 4-fluoro-2-hydroxybenzaldehyde:2-fluoro-6-hydroxybenzaldehyde isomers by ^1H NMR and GC. [d] Size exclusion chromatography and mass spec. indicate presence of 9.4% diarylmethanes **5** and 2.9% trinuclear products **6**. [e] Xylene as reaction solvent (other examples carried out in toluene).

Table 2 Formaldoximation of phenols **1** to give salicylaldoximes **7**

Starting phenol **1** substituent R	Salicylaldoxime product **7**	Yield of salicylaldoxime (%)	Yield of diarylmethane by-product **5** (%)	Unchanged starting phenol **1** (%)	Intermediate aldehyde **2** (%)
H	**a**	88	2–4	1–2	*ca.* 2
2-Me	**b**	56	*ca.* 29	<0.1	*ca.* 1.5
3-Me	**c**	72[a]	*ca.* 5	<0.1	*ca.* 3[b]
4-Me	**d**	74	*ca.* 1.5	1	*ca.* 4[b]
2-Me and 4-Me	**h**	33	*ca.* 65	<0.1	<1
2-Me and 4-Me[c]	**h**	58[c]	*ca.* 35	<0.1	<1
4-OMe	**j**	84	*ca.* 3	4.5	<1
2-Bu[s]	**m**	14	*ca.* 58	<1	<2
3-Bu[t]	**n**	63	*ca.* 5	<0.5	<1.5
4-Nonyl (mixed isomers)	**o**	83	*ca.* 10[d]	<1.5	<1
4-Dodecyl (mixed isomers)	**p**	87.3	Not determined	<1	<2

[a] *ca.* 80:20 Ratio of 2-hydroxy-4-methylbenzaldoxime:2-hydroxy-6-methylbenzaldoxime isomers, estimated by NMR. [b] Aldehyde due mainly to oxime hydrolysis on protracted acid work-up. [c] Formylation step carried out under reduced pressure (all other examples at atmospheric pressure). [d] *ca.* 3% Yield of trinuclear by-products **6** also identified by size exclusion chromatography/mass spec.

chromatography and mass spectroscopy) are the 2,2′-dihydroxydiarylmethanes **5** and, to a lesser extent, the trinuclear compounds **6** (in common with the formylation products reported by Casiraghi and Casnati).[14] The reaction selectivity in favour of formylation (as opposed to formation of by-products **5** and **6**) is enhanced in many cases by carrying out the

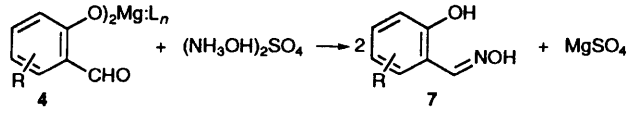


5 **6**

X = H, CHO, CH_2OMe, HC=NOH

reaction at temperatures around 70–90 °C (*i.e.* below the atmospheric reflux temperature of *ca.* 95 °C) using reduced pressure (200–400 mmHg) so as to maintain removal of the methanol by distillation (*cf.* Table 1, formation of the aldehyde **2o** and Table 2, formation of the oxime **7h** at atmospheric and at reduced pressures). When (unsubstituted) phenol **1** (R = H) is formylated, the *o*-hydroxybenzaldehyde product **2** (R = H) is obtained containing less than 0.05% (w/w) *p*-hydroxybenzaldehyde detectable by GC analysis of the crude reaction product.

Addition of aq. hydroxylamine sulfate to the product of the formylation reaction, present as its magnesium salt **4** (without acidic work-up), results in efficient oximation (Scheme 4). In the case of the 5-nonylsalicylaldehyde magnesium salt **4** (R = *p*-C_9H_{19}), oximation (to ⩾95% conversion of salicylaldehyde into salicylaldoxime) was achieved in about one-fifth of the time required for oximation of 2-hydroxy-5-nonylbenzaldehyde **2** (R = *p*-C_9H_{19}) by hydroxylamine sulfate solution in the presence of sodium carbonate (1 equiv. on hydroxylamine sulfate) but in the absence of the magnesium cation, under otherwise identical reaction conditions. Formaldoximation yields are summarised in Table 2. It should be noted that HCN can be generated on acidification and heating of the aqueous phase after oximation.



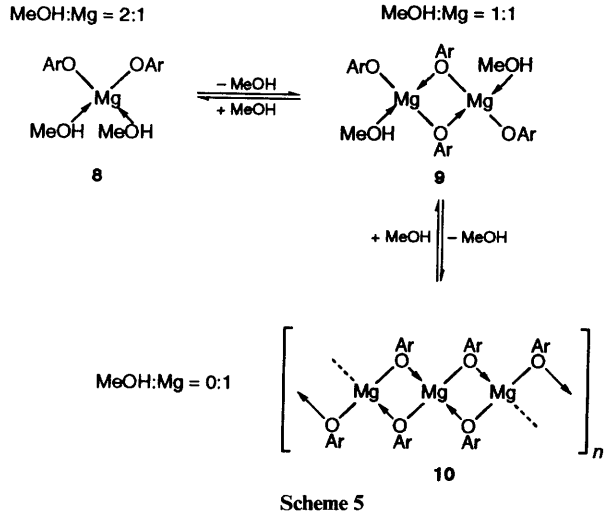
4 **7**

Scheme 4

Discussion

It is likely that formylation is preceded by depolymerisation[20] of paraformaldehyde to liberate monomeric formaldehyde (CH_2O), under the basic conditions of the formylation reaction. In the absence of the magnesium counter-ion, phenols with formaldehyde give phenol–formaldehyde resin polymerisation products under either acidic or basic conditions.[21] The high selectivity for phenol *ortho*-formylation in the presence of the magnesium counter-ion indicates coordination of phenoxide and formaldehyde to the magnesium counter-ion under the reaction conditions described in this paper.

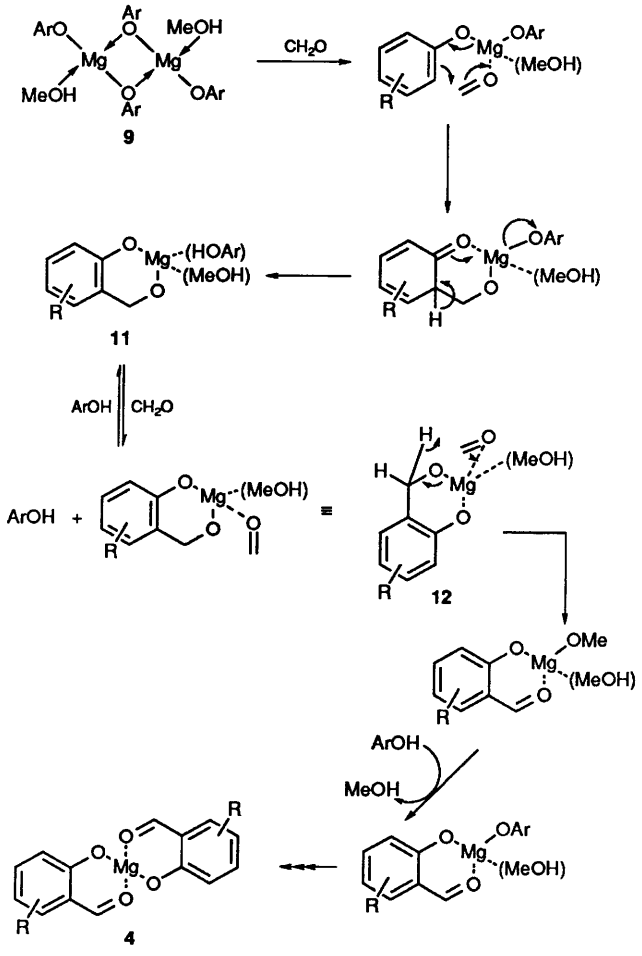
The lack of formylation on addition of paraformaldehyde to phenol magnesium salts in methanol is presumably due to competitive inhibition by methanol of the coordination of formaldehyde to the magnesium counter-ion. Methanol is, accordingly, removed by distillation and replaced by toluene prior to addition of paraformaldehyde; however, as the methanol–magnesium salt ratio is reduced below 2:1, the phenol magnesium salt must presumably undergo first dimerisation and then polymerisation to maintain magnesium tetracoordination (Scheme 5). This is supported by the marked



Scheme 5

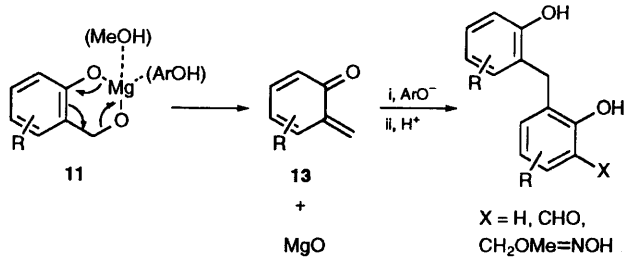
increase in reaction mixture viscosity observed on removing methanol below *ca.* 2 mol per mol magnesium bis(phenoxide), by distillation from the toluene-soluble magnesium bis(phenoxide) **8** (ArOH = *p*-nonylphenol) prepared from *p*-nonylphenol. Reactivity to formylation is enhanced with a methanol–magnesium salt ratio of between 1 and 2 mol per mol such that the magnesium cation is at least partially in the form of the dimeric species **9**, due to methanol ligand depletion. Under these conditions, added formaldehyde is presumably coordinated to magnesium in the ligand-depleted dimer **9** to give the better solvated monomeric salt **8**, but with a formaldehyde in place of one of the methanol molecules.

A suggested mechanism for the formylation is outlined in Scheme 6 whereby formaldehyde (coordinated to the magnesium cation acting as Lewis Acid) undergoes addition of phenoxide to give the hydroxymethylated phenol magnesium salt **11**. Coordination of a second formaldehyde then results in redox conversion of the hydroxymethyl anion to formyl with reduction of formaldehyde to methoxide by hydride transfer through a chair-like 6-membered transition state (*cf.* **12**). Proton transfer from phenol to the more basic methoxide then completes the reaction to give the formylated phenol magnesium salt along with an equivalent of methanol (from formaldehyde reduction) as a volatile by-product. Methyl formate is also produced as a volatile by-product, presumably as a result of Tischenko reaction[22] of formaldehyde catalysed by the magnesium cation.



Scheme 6

Varying amounts of the diarylmethane by-products **5** (and lesser amounts of the trinuclear species **6**) are also produced during the course of the reaction, presumably as a result of elimination of magnesium oxide from intermediate **11**, followed by coupling of the quinone methide intermediate **13** with phenoxide (Scheme 7).

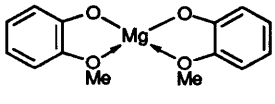


Scheme 7

Casiraghi and Casnati[14] report a predominance of this latter pathway in the absence of stabilising ligand, and suppression of this elimination pathway in the presence of stoichiometric quantities of HMPA (which reduces Mg^{2+} Lewis-acidity) during reaction of formaldehyde with their Grignard-derived aryloxymagnesium bromide system. Our results indicate the equivalent suppression of the unwanted elimination pathway in the presence of 1–2 equiv. of methanol as stabilising ligand in place of HMPA, thereby avoiding the cost and toxicity of HMPA and with the additional advantage that use of magnesium methoxide as base both introduces the methanol ligand into the reaction system by default and allows use of half the molar quantity of diacidic and cheap magnesium methoxide, as compared with use of the mono-acidic and costly Grignard reagent.

In the same way that methanol must be removed prior to formylation, the methanol by-product of formylation is also removed by distillation during the course of the reaction so as to avoid yield penalties due to inhibition by methanol of coordination of formaldehyde to magnesium. The increased reaction selectivity observed on reducing the reaction temperature (whilst maintaining removal of volatile reaction by-products by distillation under reduced pressure) indicates greater differentiation of the formylation and elimination reaction pathways at the lower reaction temperature. There is no substantial build-up of hydroxymethylated intermediate evident during the course of the reaction. ACSL[23] modelling of the reaction profile generated on addition of 2 equiv. of paraformaldehyde as a single charge to 4-nonylphenol magnesium salt in toluene at 95 °C suggests approximate values for the rate constants for the addition step and the redox step of *ca.* 0.035 and 0.10 $dm^3\ mol^{-1}\ s^{-1}$ respectively, *i.e.* a redox-step rate constant approximately 3 times that for the addition to formaldehyde. Use of less tightly coordinating cations (*e.g.* Li^+, Na^+ or K^+) in place of the small highly charged Mg^{2+}, does result in the first (addition) step (albeit without the *ortho*-specificity observed with Mg^{2+}) but this is followed by elimination of hydroxyl and formation of phenol–formaldehyde resins *via* quinone methides (*cf.* **13**; Scheme 7) in preference to the redox step (*cf.* **12**; Scheme 6) giving salicylaldehydes, which predominates in the presence of the methanol solvated Mg^{2+} counter-ion. If the methanol–magnesium salt ratio is decreased much below 1:1, then formylation efficiency deteriorates as reaction mixture viscosity becomes increasingly unmanageable and (as reported by Casiraghi and Casnati with decreasing HMPA usage[14]) the generation of diarylmethane by-products (*e.g.* **5**) increases.

para-Electron withdrawing substituents on the starting material phenols (*e.g.* **1**, R = *p*-F, *p*-Cl or *p*-NO_2; Table 1) give rise to reduced reactivity and poorer formylation yield whilst the converse is true for electron-donating substituents (*e.g.* **1**, R = *p*-OMe; Tables 1 and 2). Bulky substituents in the *ortho*-position (*e.g.* **1**, R = *o*-Bu^s; Table 2) give rise to increased formation of by-products **5** and **6** due, presumably, to steric hindrance inhibiting coordination of formaldehyde to magnesium (necessary for formylation) resulting in increased base-catalysed (but not magnesium mediated) by-product generation (Scheme 7). Bulky substituents *meta* to the starting material phenol hydroxyl (*e.g.* **1**, R = *m*-Bu^t; Table 2) direct formylation to the position *ortho* to the hydroxyl and opposite the *meta* substituent. Smaller *meta* substituents (*e.g.* **1**, R = *m*-F or *m*-Me; Tables 1 and 2) direct formylation to the less hindered position *ortho* to oxygen, but give rise to a mixture of products formylated in either the 2 or the 6 positions. Substituents in the *ortho* position able to coordinate to the magnesium cation (*e.g.* **1**, R = *o*-F or *o*-OMe; Table 1) result in partial or complete inhibition of formylation, presumably due to chelation of magnesium (*e.g.* in 2-methoxyphenol magnesium salt **14**) which precludes the coordination of formaldehyde necessary for formylation. Formylation of 3-fluorophenol gives a higher yield of salicylaldehydes **2f** than does formylation of either 2-fluorophenol or 4-fluorophenol, due presumably to π-electron donation by the fluoro substituent in 3-fluorophenol, (i) serving to activate the positions *ortho* and *para* to fluorine and *ortho* to oxygen, to electrophilic attack, and (ii) offsetting to some extent the deactivating inductive electron withdrawal by the electronegative fluorine substituent.



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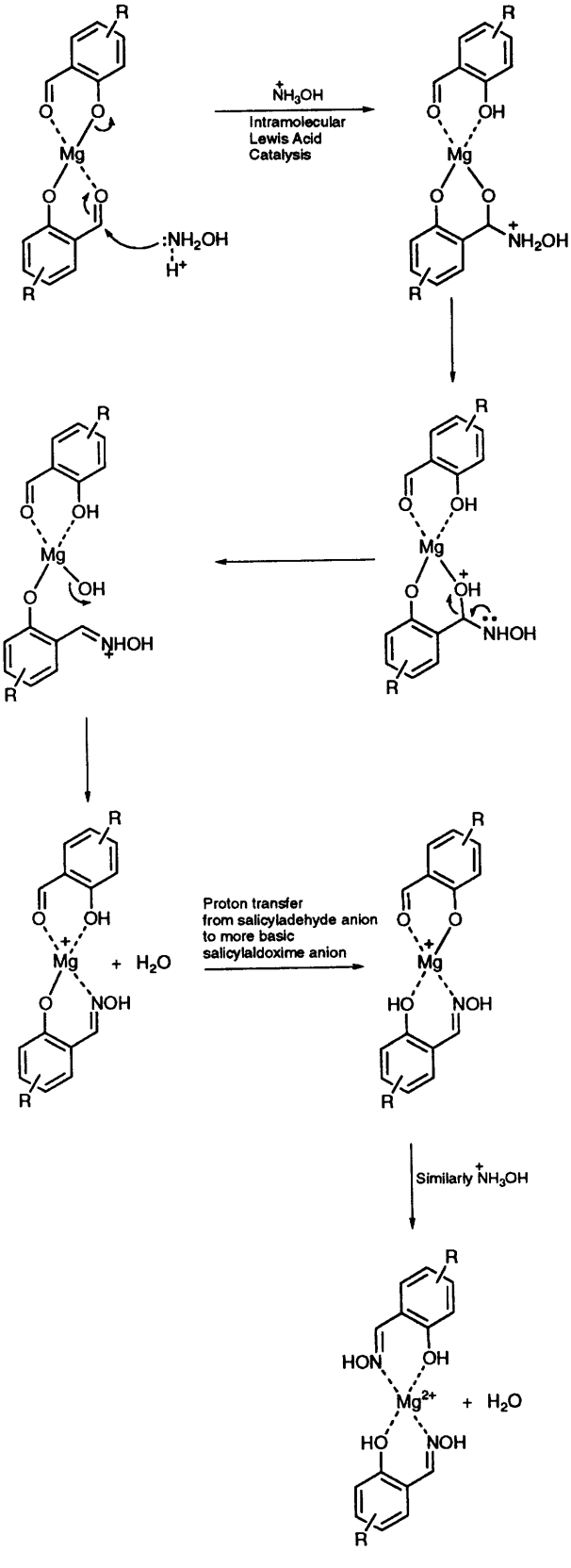

Scheme 8

It is likely that the faster oximation observed on addition of hydroxylamine sulfate to the formylated phenol magnesium salt **4** (R = *p*-C_9H_{19}) in toluene (compared with use of sodium cation in place of magnesium) is due to intramolecular Lewis acid catalysis of oximation by Mg^{2+} (Scheme 8) whereby the

magnesium counter-ion enhances the reactivity of the co-ordinated formyl group carbonyl to nucleophilic attack by hydroxylamine. Catalysis by the Mg^{2+} counter-ion throughout oximation (despite the liberation of H_2SO_4 on reaction of hydroxylamine) can be explained by protonation of the more basic salicylaldoxime magnesium salt, in preference to protonation of salicylaldehyde magnesium salt, during the course of the oximation reaction (Scheme 8).

It is possible that the greater rate of oximation of magnesium salt **4** (R = *p*-C_9H_{19}) (compared with sodium salt) could also be influenced by different surfactant effects of the amphipathic nonylsalicylaldehyde magnesium salt (compared with sodium salt) at the aqueous–organic interface during the heterogeneous oximation.

It should be noted that although a catalytic role is ascribed to the magnesium cation in the chemistry described above (in that the magnesium cation facilitates both the formylation and oximation steps whilst itself remaining essentially chemically unchanged), it is used in a 'stoichiometric' amount ($\geq$0.5 mol used per mol of phenol) and not in the much smaller amounts that are conventionally associated with use of the word 'catalytic'.

Unchanged formaldehyde left over after the formylation step is likely to be converted into formaldoxime during the oximation;[24] this formaldoxime can then be dehydrated to give HCN in the presence of strong acid and/or when heated. Care should, therefore, be taken both to minimise the amount of formaldehyde used and to avoid strong acidic treatment of the aqueous phase after oximation in conversion of phenols **1** into salicylaldoximes **7**.

Conclusions

Reaction of magnesium bis(aryl oxides) (prepared from hydroxyaromatics and magnesium methoxide) with paraformaldehyde gives rise to *ortho*-formylation, without the need for HMPA or use of Grignard reagents for aryloxymagnesium salt preparation. Reaction of the salicylaldehyde magnesium salt products of formylation with hydroxylamine sulfate allows efficient conversion into the corresponding salicylaldoximes without the need for work-up and isolation of the intermediate salicylaldehydes.

Experimental

NMR coupling constants (*J*) are given in Hz. GC conditions comprise use of Chrompack UK Ltd CPSil 5CB 25m capillary column (injector temperature: 250 °C, column temperature: 100 °C for 2 min, then 10 °C min^{-1} to 250 °C). HPLC conditions comprise use of Whatman 10 cm C-18 ODS reverse phase column, with an eluent gradient of MeOH–buffer of 75:25 to 90:10 over 10 min; held at 90:10 for 10 min and then increased to 100% MeOH over 10 min [the buffer comprised NaOAc (0.56 g), AcOH (7 cm^3) and HPLC grade water (1 dm^3)].

2-Hydroxybenzaldehyde **2a**.—Phenol (37.6 g, 0.4 mol) was added to magnesium methoxide (259 g of 8 wt.% solution in methanol; 20.7 g, 0.24 mol) and the mixture was heated to reflux. Approximately half the methanol was distilled off and toluene (300 g) was added to the residue. The azeotropic mixture of toluene and methanol was removed by fractional distillation, until the temperature of the reaction mixture rose to 95 °C. A slurry of paraformaldehyde powder (43.2 g, 1.44 mol) in toluene (75 g) was added in small portions over 1 h to the reaction mixture at 95 °C with concurrent removal of volatile materials by distillation. Stirring was continued at 95 °C for 1 h, after which mixture was cooled to 25 °C and added slowly to 10% sulfuric acid (450 g). The resulting mixture was stirred at 30–40 °C for 2 h, after which the aqueous layer was separated and extracted with toluene (2 × 100 g). The combined organic layers and extracts were washed with 10% sulfuric acid (50 g) and water (50 g) and evaporated under reduced pressure to give the aldehyde **2a** as a pale yellow oil (48.35 g, 84% w/w by GC and ^1H NMR comparison against a reference standard and against a commercial sample[25] of known purity; 83% yield); δ_H(400 MHz; $CDCl_3$; Me_4Si) 6.99 (1 H, dd, *J* 1 and 7.5, 3-H), 7.02 (1 H, dt, *J* 1 and 7.5, 5-H), 7.52 (1 H, dt, *J* 1.7 and 7.5, 4-H), 7.55 (1 H, dd, *J* 1.7 and 7.5, 6-H), 9.9 (1 H, s, CHO) and 11.05 (1 H, s, OH); δ_C(100.6 MHz; $CDCl_3$; Me_4Si) 117.45 (3-C), 119.74 (5-C), 120.53 (1-C), 133.64 (6-C), 136.88 (4-C), 161.45 (2-C) and 196.53 (CHO).

2-Hydroxy-4-methylbenzaldehyde **2c** *and 2-Hydroxy-6-methylbenzaldehyde* **2c**.—In a similar way to that described above, 3-methylphenol (27.0 g, 0.25 mol), magnesium methoxide (0.15 mol) and paraformaldehyde powder (23.2 g, 0.77 mol) gave a pale yellow oil which solidified with time (31.5 g) and comprised 2-hydroxy-4-methylbenzaldehyde[14] (64%, w/w, by ^1H NMR using 1,2-diphenylethane as internal standard; 59% yield); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.35 (3 H, s, Me), 6.76 (1 H, s, 3-H), 6.80 (1 H, d, *J* 7.8, 5-H), 7.39 (1 H, d, *J* 7.8, 6-H), 9.76 (1 H, s, CHO) and 11.1 (1 H, s, OH); δ_C(75.4 MHz; $CDCl_3$; Me_4Si; broad band proton decoupled) 22.4 (Me), 118 (3-C), 119 (1-C), 121.5 (5-C), 134 (6-C), 149 (4-C), 162 (2-C) and 196 (CHO), ^{13}C NMR data consistent with ^{13}C reference spectral data for the expected product,[26] and 2-hydroxy-6-methylbenzaldehyde[14] (15.9%, w/w; 15% yield); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.57 (3 H, s, Me), 6.68 (1 H, d, *J* 7.8, 3-H), 6.75–6.88 (1 H, obscured by major isomer peaks, 5-H), 7.34 (1 H, t, *J* 7.8, 4-H), 10.26 (1 H, s, CHO) and 11.9 (1 H, s, OH); δ_C(75.4 MHz; $CDCl_3$; Me_4Si; broad band proton decoupled) 18.3 (Me), 116.5 (3-C), 119 (1-C), 122 (5-C), 137.5 (4-C), 142.5 (6-C), 163.5 (2-C) and 195.5 (CHO). The substitution pattern of the products obtained was confirmed by comparison of ^{13}C NMR chemical shift data for the ring carbons against values predicted[27] for the possible product isomers.

3-Fluoro-2-hydroxybenzaldehyde **2e**.—Magnesium raspings (5.85 g, 0.24 mol), methanol (120 g) and magnesium methoxide (4 g of 8% solution in methanol) were heated under reflux until the magnesium had dissolved and hydrogen evolution had ceased. 2-Fluorophenol (44.8 g, 0.40 mol) was added to the solution, followed by toluene (260 g) to maintain fluidity of the resulting slurry. The azeotropic mixture of methanol and toluene were distilled off under reduced pressure (380 mmHg) until the temperature of the reaction mixture rose to 75 °C. A slurry of paraformaldehyde powder (36.0 g, 1.2 mol) in toluene (70 g) was added to the mixture over 1 h at 75 °C with concurrent removal of volatile materials by distillation under reduced pressure (380–280 mmHg). Stirring was continued at 75 °C (280 mmHg) for 2 h, after which 10% sulfuric acid (250 g) was added to the mixture. After the mixture had been stirred for a further 10 min, the organic layer was separated, washed with water (2 × 150 g) and evaporated under reduced pressure to give a brown oil (35.7 g); δ_H(400 MHz; $CDCl_3$; Me_4Si) 6.15 (1 H, br s, OH), 6.7–7.3 (m, 2-fluorophenol and 3-fluoro-2-hydroxybenzaldehyde aromatic protons) and 9.75 (1 H, s, CHO). The oil comprised the aldehyde **2e**[28,29] (8.5%, w/w, by ^1H NMR against internal standard; 5.1% yield); GCMS *m/z* 140 (100%, M^+), 139 (95, M − H), 122 (15), 111 (17, M − CHO), 94 (21, M − CHO and OH) and 83 (25) along with unchanged 2-fluorophenol (90%, w/w, by GC; 72% yield).

4-Fluoro-2-hydroxybenzaldehyde **2f** *and 2-Fluoro-6-hydroxybenzaldehyde* **2f**.—In a similar way to that described above,

3-fluorophenol (44.8 g, 0.40 mol), magnesium methoxide (0.24 mol) and paraformaldehyde powder (36 g, 1.2 mol) gave a partially crystalline pale brown gum (53.1 g) comprising 4-fluoro-2-hydroxybenzaldehyde[30] (70.3% w/w by ^{1}H NMR against 2,3,4,5-tetrachloronitrobenzene internal standard; 62.6% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 6.62 (1 H, dd, *J* 3 and 11, 3-H), 6.69 (1 H. ddd, *J* 3, 8 and 11, 5-H), 7.52 (1 H, dd, *J* 7 and 8, 6-H), 9.78 (1 H, s, CHO) and 11.38 (1 H, s, OH); GCMS m/*z* 140 (85%, M^+), 139 (100, M − H), 122 (7), 94 (15, M − CHO and OH) and 83 (28); and 2-fluoro-6-hydroxybenzaldehyde[31] (11%, w/w, by ^{1}H NMR and GC; 9.8% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 6.6 (2 H, obscured m, 3-H and 5-H), 7.43 (1 H, m, 4-H), 10.2 (1 H, s, CHO) and 11.48 (1 H, s, OH); GCMS *m*/*z* 140 (96%, M^+), 139 (100, M − H), 122 (13), 94 (18, M − CHO and OH) and 83 (25).

3-*Fluoro*-6-*hydroxybenzaldehyde* **2g**.—In a similar way to that described above, 4-fluorophenol (44.8 g, 0.40 mol), magnesium methoxide (0.24 mol) and paraformaldehyde powder (36 g, 1.2 mol) gave a brown gum (42.9 g) comprising the aldehyde **2g**[28,32] (63.4% w/w by ^{1}H NMR against 2,3,4,5-tetrachlorobenzene internal standard; 45.6% yield); δ_H(250 MHz; [$^2H_6$]DMSO; Me_4Si) 7.13 (1 H, dd, *J* 4.3 and 9, 5-H), 7.37 (1 H, dd, *J* 3.3 and 8.6, 2-H), 7.4 (1 H, ddd, *J* 3.3, 8.3 and 8.9, 4-H), 9.78 (1 H, s, CHO) and 10.8 (1 H, s, OH); with unchanged 4-fluorophenol (38% w/w; 36% yield).

2-*Hydroxy*-5-*methoxybenzaldehyde* **2j**.—In a similar way to that for the aldehyde **2c**, 4-methoxyphenol (31.0 g, 0.25 mol), magnesium methoxide (0.15 mol) and paraformaldehyde powder (23.2 g, 0.77 mol) gave the aldehyde **2j**[14] as a pale yellow oil (36.0 g; 97% w/w measured by GC and HPLC; 92% yield); GCMS *m*/*z* 152 (100%, M^+), 137 (86, M − Me), 123 (6, M − CHO), 109 (32), 81 (34) and 53 (49).

3-*Chloro*-6-*hydroxybenzaldehyde* **2k**.—In a similar way to that described above, 4-chlorophenol (32.2 g, 0.25 mol), magnesium methoxide (0.15 mol) and paraformaldehyde powder (23.2 g, 0.77 mol) gave the aldehyde **2k**[14] as a dark brown oil (32.3 g; 40%, w/w, measured by ^{1}H NMR against 1,2-diphenylethane internal standard; 33% yield); δ_H(300 MHz; $CDCl_3$; Me_4Si) 6.5–7.6 (m, aromatic protons unresolved from impurities), 9.75 (1 H, s, CHO) and 10.93 (1 H, s, OH); GCMS *m*/*z* 158 (32%, $^{37}M^+$), 157 (39, ^{37}M − H), 156 (98, $^{35}M^+$), 155 (100, ^{35}M − H), 140 (5, $^{37}M - H_2O$), 138 (16, $^{35}M - H_2O$), 129 (6.5, ^{37}M − CHO), 127 (19, ^{35}M − CHO), 112 (8), 110 (23), 101 (7), 99 (27), 75 (14), 73 (15), 65 (22), 63 (27), 38 (26) and 36 (48).

2-*Hydroxy*-5-*nonylbenzaldehyde* (*Mixed Side-chain Isomers*) **2o**.—*Prepared with toluene as solvent at atmospheric pressure.* Magnesium raspings (7.3 g, 0.3 mol), methanol (112 g), toluene (48.5 g) and magnesium methoxide (1.6 g of 8% w/w solution in methanol; 1.5 mmol) were heated under reflux for 2 h until the magnesium had dissolved and hydrogen evolution had ceased. 4-Nonylphenol (mixed side-chain isomers, prepared by alkylation of phenol by propylene trimer) (112 g, 0.5 mol), was added to the mixture which was then heated under reflux for a further hour. Toluene (104 g) was then added to the mixture and the methanol–toluene azeotrope removed by fractional distillation until the temperature of the reaction mixture rose to 94 °C. A slurry of paraformaldehyde powder (45 g, 1.5 mol) in toluene (65 g) was added over 50 min to the reaction mixture at 97–104 °C with concurrent removal of volatile products of reaction by distillation. Stirring was continued at 100 °C for 2 h after which the mixture was cooled to 25 °C and added slowly to cold 20% sulfuric acid (625 g, 1.28 mol). The resulting mixture was stirred at 50 °C for 2 h, after which the lower (aqueous) layer was separated and extracted with toluene (2 × 100 g). The combined organic layer and extracts were washed with 10% sulfuric acid (50 g) and water (50 g) and then evaporated under reduced pressure to give the aldehyde **2o**[33] as a pale yellow oil (122.7 g; 78.8%, w/w, measured by GC comparison against an authentic standard sample of known purity; 78.0% yield). The product was purified by short-path vacuum distillation; b.p. 150–160 °C at 5 mmHg; ν_{max}/cm^{-1} 3200 (OH), 3000–2800 (aliphatic CH), 2720 (*CH*O) and 1665 (C=O); δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.6–1.8 (19 H, m, C_9H_{19}), 6.92 (1 H, d, *J* 9, 3-H), 7.35–7.6 (2 H, m, 4-H and 6-H), 9.9 (1 H, s, CHO) and 10.85 (1 H, s, OH); GCMS *m*/*z* 248 (7%, M^+), 233 (3, M − Me), 219 (7, M − CHO and M − Et), 205 (9, M − C_3H_7), 191 (20, M − C_4H_9), 177 (38, M − C_5H_{11}), 163 (100, M − C_6H_{13}), 149 (29, M − C_7H_{15}), 135 (35, M − C_8H_{17}). The crude aldehyde **2o** was analysed by preparative size exclusion chromatography [0.5 × 30 cm PL Gel 5μ (2 × 500 Å, 2 × 100 Å, 1 × 50 Å); eluent: THF; flow rate 1 cm^3 min^{-1}; wavelength 225 mm], mass spec. analysis of SEC product peaks indicated presence of 2,2′-methylene bis(4-nonylphenols) (*ca.* 9.4% w/w) molecular ions at *m*/*z* 452 (**5**; X = H), 480 (**5**; X = CHO) and 482 (**5**; X = CH_2OH) and the trinuclear species **6** (*ca.* 2.9% w/w) molecular ions at *m*/*z* 684 (**6**, X = H), 712 (**6**; X = CHO) and 714 (**6**; X = CH_2OH).

Prepared with toluene as solvent under reduced pressure. Magnesium raspings (14.6 g, 0.6 mol) were added in portions over 1.5 h to a mixture of methanol (225 g), toluene (108 g) and magnesium bis(4-nonylphenoxide) (*ca.* 4 g) at reflux temperature. Dissolution of the magnesium occurred with evolution of hydrogen. After the mixture had been heated under reflux for a further hour to complete the dissolution, 4-nonylphenol (mixed side-chain isomers) (224 g, 1 mol) was added to it followed by toluene (208 g). The azeotropic mixture of methanol and toluene was removed by fractional distillation under reduced pressure (380 mmHg) until an increase in viscosity was noted and the temperature of the reaction mixture had risen to 75 °C. A slurry of paraformaldehyde powder (90 g, 3 mol) in toluene (130 g) was then added to the reaction mixture at 75 °C over 2 h, under reduced pressure (380–270 mmHg) so as to maintain removal of volatile materials by distillation. The mixture was stirred at 75 °C under reduced pressure (260 mmHg) for a further 1 h after which it was cooled to 35 °C and added slowly to cold 14% sulfuric acid (872.5 g, 1.25 mol). The resulting mixture was stirred for 2 h at 40 °C after which the organic layer was separated with water (2 × 250 g) and evaporated under reduced pressure to give the aldehyde **2o** as a pale-yellow oil (253 g; 83.3%, w/w, measured by GC comparison against an authentic sample of known purity; 85% yield); characterization as above.

Prepared with xylene as solvent under reduced pressure. A mixture of magnesium raspings (7.3 g, 0.3 mol), methanol (112 g) and magnesium methoxide (8%, w/w, solution in methanol; 1.6 g, 1.5 mmol) were heated under reflux until the magnesium had dissolved and hydrogen evolution had ceased (2 h). 4-Nonylphenol (112 g, 0.5 mol) was added to the solution followed by xylenes (mixed isomers) (129 g). Methanol was removed by fractional distillation under reduced pressure (210 mmHg) until the temperature of the reaction mixture rose to 75 °C and the viscosity of the mixture began to significantly increase. A slurry of paraformaldehyde powder (45 g, 1.5 mol) in xylene (65 g) was added over 2 h to the reaction mixture at 75 °C under reduced pressure (210–90 mmHg) so as to maintain removal of volatile materials by distillation. Stirring was continued at 75 °C under reduced pressure (90 mmHg) for 1 h after which the mixture was cooled to 35 °C and then added slowly to cold 20% sulfuric acid (625 g). The resulting mixture was stirred at 40 °C for 2 h after which the organic layer was separated, washed with water (2 × 250 g) and evaporated

under reduced pressure to give the aldehyde **2o** as a pale yellow oil (126.25 g, 79.4% w/w measured by GC comparison against an authentic sample of known purity; 81% yield); characterization as above.

2-Hydroxybenzaldehyde Oxime **7a**.—Magnesium raspings (5.85 g, 0.24 mol), methanol (119 g), toluene (43.5 g) and magnesium methoxide (8% w/w solution in methanol; 4.08 g, 3.8 mmol) were heated under reflux until the magnesium had dissolved and evolution of hydrogen had ceased. Phenol (37.6 g, 0.4 mol) was added to the mixture which was then heated under reflux for 1 h. After this it was diluted with toluene (208 g) and the methanol–toluene azeotropic was removed by fractional distillation until the temperature of the reaction mixture rose to 95 °C. Toluene (43 g) was added to mobilise the resulting slurry and a slurry of paraformaldehyde powder (37.6 g, 1.25 mol) in toluene (70 g) was added over 1.5 h to the mixture at 95 °C with removal of volatiles from the reaction mixture by distillation. Stirring was continued at 95 °C for 30 min after which the mixture was cooled to 55 °C and treated with a solution of hydroxylamine sulfate (39.4 g, 0.24 mol) in water (120 g), added at 50–55 °C over 30 min with vigorous stirring. Stirring was continued at 55 °C for 1 h after which the reaction mixture was cooled to 20 °C and the organic layer separated, washed at 10 °C with 7% sulfuric acid (195 g) and water (2 × 150 g) and evaporated under reduced pressure to give the oxime **7a**[34] as a white crystalline solid (52.3 g; 92.2%, w/w, by ^{1}H NMR against benzyl acetate internal standard and by GC against an authentic commercial sample[34] of known purity; 88% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 6.87 (1 H, dt, *J* 1 and 7.5, 5-H), 6.97 (1 H, dd, *J* 7.5 and 1, 3-H), 7.11 (1 H, dd, *J* 7.5 and 1.6, 6-H), 7.24 (1 H, dt, *J* 1.6 and 7.5, 4-H), 7.85 (1 H, br s, ArOH), 8.2 (1 H, s, CH=N) and 10.0 (1 H, s, NOH).

2-Hydroxy-3-methylbenzaldehyde Oxime **7b**.—Magnesium raspings (5.85 g, 0.24 mol), methanol (119 g), toluene (43.5 g) and magnesium methoxide (4.08 g of 8%, w/w, solution in methanol, 3.8 mmol) were heated under reflux until the magnesium had dissolved and hydrogen evolution had ceased. 2-Methylphenol (43.2 g, 0.4 mol) was added to the mixture which was then heated under reflux for 1 h. After this, toluene (208 g) was added to the mixture and the methanol–toluene azeotrope was removed by fractional distillation until the temperature of the reaction mixture rose to 97 °C. A slurry of paraformaldehyde powder (36 g, 1.2 mol) in toluene (70 g) was added over 1 h at 95 °C with concurrent removal of volatile materials by distillation. Stirring was continued at 95 °C for 1.25 h after which the mixture was cooled to 55 °C and treated with a solution of hydroxylamine sulfate (39.4 g, 0.24 mol) in water (120 g), added over 30 min at 50–55 °C with vigorous stirring. Stirring was continued at 55 °C for 1 h after which the mixture was cooled to 10 °C and 1.5%, w/w, sulfuric acid (254 g) was added with stirring. The organic layer was separated, washed with cold 10% sulfuric acid (280 g) and then water (2 × 250 g) and evaporated under reduced pressure to give the oxime **7b**[35] as a pale yellow crystalline solid (61.1 g, 55.1%, w/w, by ^{1}H NMR against benzyl acetate internal standard; 56% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.3 (3 H, s, Me), 6.85 (1 H, t, *J* 7.5, 5-H), 7.0 (1 H, dd, *J* 7.5 and 1.4, 4-H), 7.14 (1 H, obscured, 6-H), 8.15 (1 H, s, ArOH), 8.2 (1 H, s, CH=N) and 10.35 (1 H, s, NOH); GCMS indicates the crude reaction product contains 2-hydroxy-3-methylbenzaldehyde oxime (GC area 64.4%), GCMS *m/z* 151 (56%, M^+), 135 (52), 133 (100, M − H_2O) and 104 (98) and 6,6′-Methylene bis(2-methylphenol) (GC area 25.2%), GCMS *m/z* 228 (43%, M^+), 121 (100, M − C_7H_7O) and 108 (52, M − C_8H_8O).

2-Hydroxy-4-methylbenzaldehyde Oxime **7c** *and 2-Hydroxy-6-methylbenzaldehyde Oxime* **7c**.—In a similar way to that described above, 3-methylphenol (43.2 g, 0.4 mol), magnesium methoxide (0.24 mol) and paraformaldehyde powder (36 g, 1.2 mol), followed by hydroxylamine sulfate (39.4 g, 0.24 mol) gave a pale yellow crystalline solid (60.1 g) comprising 2-hydroxy-4-methylbenzaldehyde oxime[36] (61.3%, w/w, by ^{1}H NMR against benzyl acetate internal standard; 61% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.3 (3 H, s, Me), 6.72 (1 H, dd, *J* 7.5 and 1.5, 5-H), 6.81 (1 H, d, *J* 1.5, 3-H), 7.03 (1 H, d, *J* 7.5, 6-H), 8.16 (2 H, br s, CH=N and ArOH) and 10.05 (1 H, s, NOH); GCMS *m/z* 151 (53%, M^+), 135 (39), 133 (76, M − H_2O) and 104 (100) and 2-hydroxy-6-methylbenzaldehyde oxime (10.95%, w/w, by GC peak area ratio to major product; 10.9% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.3 (3 H, s, Me), 6.71 (1 H, dd, *J* 7.5 and 1.5, 5-H), 6.77–6.87 (2 H, obscured, 3-H and 4-H), 8.15 (2 H, br s, ArOH and CH=N) and 10.1 (1 H, s, NOH); GCMS *m/z* 151 (36%, M^+), 135 (29), 134 (35), 133 (92) and 104 (100).

2-Hydroxy-5-methylbenzaldehyde Oxime **7d**.—In a similar way to that described above, 4-methylphenol (43.2 g, 0.4 mol), magnesium methoxide (0.24 mol) and paraformaldehyde powder (36 g, 1.2 mol), followed by hydroxylamine sulfate (39.4 g, 0.24 mol) gave a pale yellow crystalline solid (57.65 g) comprising the oxime **7d**[36] (77.3%, w/w, by ^{1}H NMR against benzyl acetate internal standard; 73.8% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.3 (3 H, s, Me), 6.9 (1 H, d, *J* 9, 3-H), 6.96 (1 H, d, *J* 1.8, 6-H), 7.09 (1 H, dd, *J* 9 and 1.8, 4-H), 8.0 (1 H, s, ArOH), 8.19 (1 H, s, CH=N) and 9.9 (1 H, s, NOH); GCMS *m/z* 151 (86%, M^+), 135 (38), 134 (44), 133 (91, M − H_2O), 132 (98, M − H and H_2O), 104 (100), 78 (74) and 77 (73) and 2-hydroxy-4-methylbenzaldehyde (*ca.* 4% yield by GC) (formed by partial hydrolysis of oxime during protracted acid washing overnight) GCMS *m/z* 136 (100%, M^+), 135 (95, M − H), 118 (12), 107 (34, M − CHO) and 77 (32).

2-Hydroxy-3,5-dimethylbenzaldehyde Oxime **7h**.—*Prepared at atmospheric pressure.* In a similar way to that described above, 2,4-dimethylphenol (48.8 g, 0.4 mol), magnesium methoxide (0.24 mol) and paraformaldehyde powder (36 g, 1.2 mol), followed by hydroxylamine sulfate (39.4 g, 0.24 mol) gave a pale yellow crystalline solid (65.8 g) comprising the oxime **7h**[37] (32.9%, w/w, by ^{1}H NMR against benzyl acetate internal standard; 32.8% yield) and 6,6′-methylene bis(2,4-dimethylphenol) (*ca.* 65% yield by GC). Crude product GCMS: oxime **7h** *m/z* 165 (60%, M^+), 149 (35), 148 (39), 147 (63, M − H_2O), 146 (49), 132 (100, M − H_2O and Me), 118 (35, M − CHO and H_2O), 91 (54) and 77 (32) and diarylmethane **5** (R = *ortho* and *para* Me_2); *m/z* 256 (51%, M^+), 135 (96, M − $C_6H_2Me_2OH$), 122 (100), 107 (24) and 91 (34). The crude product was recrystallised from toluene to give a white crystalline solid (47.8 g) comprising the oxime **7h** (36.9%, w/w, by ^{1}H NMR against benzyl acetate) and the diarylmethane **5** (R = *ortho* and *para* Me_2) (57% w/w by GC); δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.15–2.45 (4 × s, Me groups in both products), 3.85 (2 H, s, ArCH_2Ar). 6.2 (2 H, s, *H*OArCH$_2$ArO*H*), 6.78 (2 H, d, *J* 2, diarylmethane aromatic MeCC*H*CMe), 6.80 (1 H, d, *J* 2, oxime 4-H), 6.92 (2 H, d, *J* 2, diarylmethane aromatic CH_2C*H*CMe), 6.97 (1 H, d, *J* 2, oxime 6-H), 7.8 (1 H, s, oxime ArOH), 8.17 (1 H, s, oxime CH=N) and 10.0 (1 H, s, NOH).

Prepared under reduced pressure. Magnesium raspings (5.85 g, 0.24 mol), methanol (120 g) and magnesium methoxide (8% solution in methanol, 4 g) were heated under reflux until the magnesium had dissolved and hydrogen evolution had ceased. 2,4-Dimethylphenol (48.8 g, 0.4 mol) was added to the mixture followed by toluene (44 g) and the methanol–toluene azeotrope was removed by fractional distillation under reduced pressure (380 mmHg) until the temperature of the reaction mixture rose to 75 °C. A slurry of paraformaldehyde powder (36 g, 1.2 mol)

in toluene (70 g) was then added over 1.5 h to the reaction mixture at 75 °C under reduced pressure (380–250 mmHg) so as to maintain removal of volatile materials by distillation. Stirring was continued at 75 °C for 30 min, after which the mixture was cooled to 50 °C and treated with a solution of hydroxylamine sulfate (39.4 g, 0.24 mol) in water (120 g), added over 30 min with vigorous stirring at 50–55 °C. The mixture was stirred for a further 3 h at 55 °C, after which 0.5% sulfuric acid (200 g) was added to dissolve solids. The organic layer was separated, washed with cold 10% sulfuric acid (260 g) and water (2 × 200 g) and evaporated under reduced pressure to give the oxime **7h** as a white crystalline solid (68.4 g; 55%, w/w, by ^{1}H NMR and by GC against internal standards; 57.5% yield); characterization as above.

2-Hydroxy-5-methoxybenzaldehyde Oxime **7j**.—Magnesium raspings (5.85 g, 0.24 mol), methanol (120 g), toluene (44 g) and magnesium methoxide (8% w/w solution in methanol; 4.1 g, 3.8 mmol) were heated under reflux until the magnesium had dissolved and hydrogen evolution had ceased. 4-Methoxyphenol (49.6 g, 0.4 mol) and toluene (26 g) were added to the mixture and the methanol–toluene azeotrope was removed by fractional distillation until the temperature of the reaction mixture rose to 93 °C to give a white slurry of the 4-methoxyphenol magnesium salt. A slurry of paraformaldehyde powder (36 g, 1.2 mol) in toluene (63 g) was added to the mixture at 93–95 °C over 1 h with concurrent removal of volatile materials by distillation. Stirring was continued at 93 °C for 1 h after which the mixture was cooled to 55 °C and a solution of hydroxylamine sulfate (39.4 g, 0.24 mol) in water (120 g) was added to it over 30 min at 55 °C with vigorous stirring. Stirring was continued at 55 °C for 3 h, after which the resulting slurry was cooled to 10 °C, treated with cold 5% sulfuric acid (200 g) and extracted with dichloromethane (3 × 250 g). The combined extracts were washed with water (2 × 100 g) and evaporated under reduced pressure to give the oxime **7j**[38] as a pale yellow crystalline solid (57.9 g; 88%, w/w, by ^{1}H NMR against benzyl acetate internal standard; 84.3% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 3.78 (3 H, s, OMe), 6.72 (1 H, d, *J* 2.6, 6-H), 6.88 (1 H, dd, *J* 2.6 and 9, 4-H), 6.93 (1 H, d, *J* 9, 3-H), 7.85 (1 H, s, ArOH), 8.19 (1 H, s, CH=N) and 9.55 (1 H, s, NOH); GCMS *m/z* 167 (8%, M^+), 149 (76, M − H_2O), 134 (100, M − H_2O and Me), 106 (37, M − CHNOH and OH) and 79 (24).

3-sec-*Butyl-2-hydroxybenzaldehyde Oxime* **7m**.—In a similar way to that described for the oxime **7a**, 2-*sec*-butylphenol (30 g, 0.2 mol), magnesium methoxide (0.12 mol), paraformaldehyde powder (18 g, 0.6 mol) and then hydroxylamine sulfate (19.7 g, 0.12 mol) gave the crude oxime **7m** as an orange oil (38.6 g); δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.9 (3 H, overlapped, CH_2Me), 1.2 (3 H, overlapped, CH*Me*), 1.65 (2 H, overlapped, $MeCH_2CH$), 3.1 (1 H, overlapped, $MeCHCH_2$), 6.15 (1 H, s, ArO*H*), 6.8 (1 H, m, 5-H), 7.0 (1 H, m, 4-H), 7.1 (1 H, m, 6-H), 8.2 (1 H, s, CH=N) and 10.1 (1 H, s, NOH). Analysis of this crude product indicated the presence of the oxime **7m** (14.4%, w/w, by ^{1}H NMR against benzyl acetate internal standard; 14.4% yield), GCMS *m/z* 193 (29%, M^+), 175 (22, M − H_2O), 164 (96, M − CHO), 146 (100), 132 (24), 118 (23), 103 (14) and 91 (47), with 6,6′-methylene bis(2-*sec*-butylphenol) **5** (R = *ortho*-Bu^s) (58% yield by GCMS), GCMS *m/z* 194 (23%, M^+), 162 (31, M − Me and OH), 147 (100), 133 (69), 120 (32), 105 (43), 91 (35) and 77 (33).

4-tert-*Butyl-2-hydroxybenzaldehyde Oxime* **7n**.—In a similar way to that described above, 3-*tert*-butylphenol (15 g, 0.1 mol), magnesium methoxide (0.06 mol), paraformaldehyde powder (9.0 g, 0.3 mol) and then hydroxylamine sulfate (9.85 g, 0.06 mol) gave a pale yellow crystalline solid (16.7 g) comprising the oxime **7n** (73%, w/w, by ^{1}H NMR against benzyl acetate internal standard; 63.2% yield); δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.3 (9 H, s, Bu^t), 6.95 (1 H, dd, *J* 9 and 1.5, 5-H), 7.0 (1 H, d, *J* 1.5, 3-H), 7.1 (1 H, d, *J* 9, 6-H), 8.15 (1 H, br s, ArOH), 8.2 (1 H, s, CH=N) and 10.05 (1 H, br s, NOH), GCMS *m/z* 193 (31%, M^+), 178 (78, M − Me), 175 (28, M − H_2O), 160 (100, M − H_2O and Me), 132 (60) and 120 (28). Negligible product regioisomer was evident by GC or NMR.

2-Hydroxy-5-nonylbenzaldehyde Oxime.—Mixed side-chain isomers **7o**. Magnesium raspings (29.2 g, 1.2 mol) were added over 2 h to methanol (450 g), toluene (195 g) and magnesium methoxide (20 g of 8%, w/w, solution in methanol) under reflux. The mixture was heated under reflux for 1.5 h until the magnesium had dissolved and evolution of hydrogen had ceased after which 4-nonylphenol (mixed side-chain isomers) (440 g, 2.0 mol) was added to it. The methanol–toluene azeotrope was then removed by fractionation distillation further toluene (408 g) being added, until the temperature of the reaction mixture rose to 95 °C. A slurry of paraformaldehyde powder (170 g, 5.65 mol) in toluene (250 g) was added to the mixture over 1.5 h at 95 °C with concurrent removal of volatile materials by distillation. Stirring was continued at 95–100 °C for 1 h, after which the mixture was cooled to 45 °C and treated with a solution of hydroxylamine sulfate (197 g, 1.2 mol) in water (600 g), added over 1 h at 45–50 °C with vigorous stirring. Stirring was continued at 50 °C for 2 h, after which the lower (aqueous) layer was separated and extracted with toluene (170 g). The combined organic layer and extracts were washed with 7% sulfuric acid (537 g) and water (2 × 250 g) and then evaporated under reduced pressure to give the oxime **7o**[2] as a yellow oil (528 g, 82.5%, w/w, measured by GC with internal standard against an authentic sample of known purity; 83% yield); b.p. 185 °C 0.4 mmHg (thermally unstable); δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.4–1.8 (19 H, m, C_9H_{19}), 6.95 (1 H, d, *J* 9, 3-H), 7.1 (1 H, d, *J* 1, 6-H), 7.25 (1 H, dd, *J* 9 and 1, 4-H), 8.25 (1 H, s, CH=N), 8.6 (1 H, br s, ArOH) and 10.1 (1 H, br s, NOH); δ_C(100.6 MHz; $CDCl_3$; Me_4Si) 8.6–51.7 (C_9H_{19}), 115 (1-C), 116 (3-C), 129 (4-C and 6-C), 140 (5-C) and 153–154 (CH=N and COH).

3-*Dodecyl-6-hydroxybenzaldehyde Oxime.—Mixed side-chain isomers* **7p**. In a similar way to that described above, 4-dodecylphenol (mixed isomers) (46.8 g, 0.179 mol), magnesium methoxide (0.121 mol), paraformaldehyde powder (18 g, 0.6 mol) and then hydroxylamine sulfate (19.7 g, 0.12 mol) gave the oxime **7p**[39] as a pale yellow oil (53.25 g; 89.3%, w/w, by ^{1}H NMR and GC; 87.3% yield); b.p. 232 °C 2 mmHg; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.4–1.8 (25 H, m, $C_{12}H_{25}$), 6.9 (1 H, d, *J* 9, 5-H), 7.05 (1 H, dd, *J* 9 and 1, 4-H), 7.2 (1 H, d, *J* 1, 3-H), 7.3 (1 H, br s, ArOH), 8.2 (1 H, s, CH=N) and 9.7 (1 H, s, NOH).

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