Accelerated syntheses of amine-bis(phenol) ligands in polyethylene glycol or 'on water' under microwave irradiation

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Abstract

Pure amine-bis(phenol) ligands are readily accessible in high yield, often >90%, when the Mannich condensation reactions are performed ‘on water’ or in poly(ethyleneglycol) (PEG). Microwave-assisted synthesis dramatically reduces the time and energy required to prepare these molecules, typically from 24 h to 5 min. The approach seems to be widely applicable (7 amines and 5 phenols were tested to yield a diverse set of bis(phenol) ligands). Significant improvements in yield were observed for ligands derived from di-*tert*-amyl and di-*tert*-butyl phenols, possibly resulting from a hydrophobic effect. Single crystal X-ray diffraction data for the ligand derived from *p*-cresol and N,N'-dimethylethylenediamine is reported.

Keywords: amine-phenol, Mannich condensation, on water, microwave, ligand, high-throughput

Introduction

Over the last twenty years, researchers have been exploring a wide range of ligand systems for use in combination with metals as new homogeneous catalysts. N-heterocyclic carbenes have emerged as versatile alternatives to phosphine ligands in late-transition metal catalysed reactions.(1-3) Anionic ligands containing ‘hard’ nitrogen and oxygen donor atoms form a diverse set of ligands which are used as alternatives to cyclopentadienyl ligands, particularly, in early transition metal and lanthanide based catalysts.(4-9) Of these ligands, amine-bis(phenol) molecules have emerged as versatile, modular and easily accessible materials, Fig. 1.

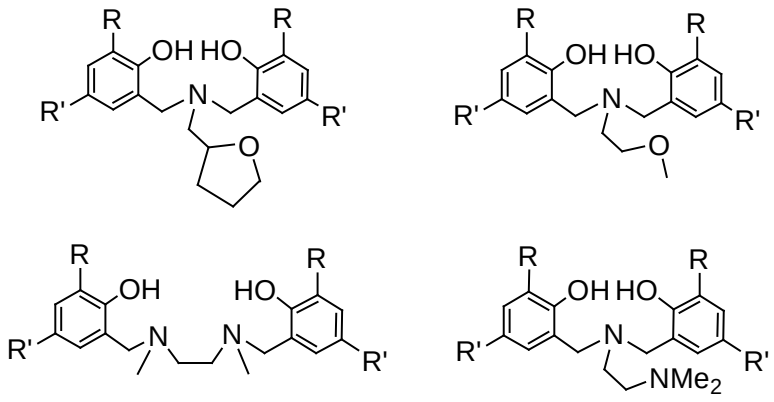


Fig. 1. Chelating amine-bis(phenol) ligands

Primarily, these ligands in combination with metals from throughout the periodic table are active catalysts for alkene polymerization, (10-17) and initiators in the ring opening polymerization of lactones.(18-30)

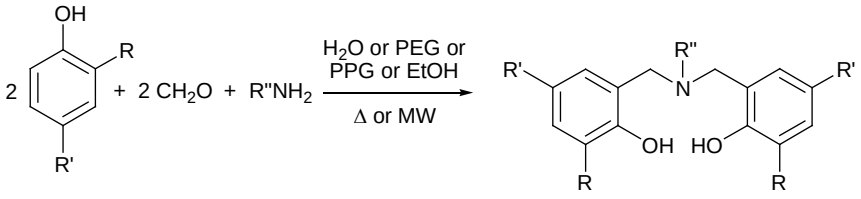
Liquid polymers are emerging as a useful class of non-volatile solvents and possess valuable, facile separation characteristics. The two most widely used polymers in this area are PEG (polyethylene glycol) and PPG (polypropylene glycol). (31,32) They have a very low toxicity ranking

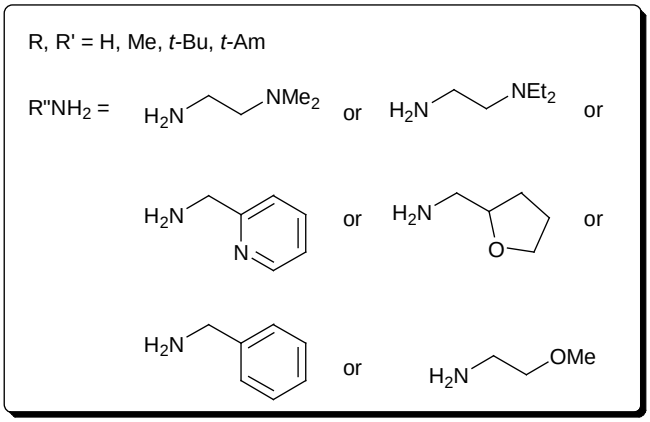
and have been approved by the US FDA for internal consumption.(31) The high stability and low toxicity of PEG and PPG allow these molecules to be used in a large number of products and industries. PEGs and PPGs are very similar in structure to glymes which are used as solvents due to their high chemical and thermal stability, broad pH range, and ability to dissolve polar compounds, such as water and acids, as well as non-polar compounds, such as hydrocarbons. The polarity of PEG can be compared with the commonly used laboratory solvents CH_2Cl_2 and MeCN, whereas PPG is slightly less polar.(32) In terms of laboratory safety, whereas glymes readily form explosive peroxides, PEGs and PPGS do not. The biodegradability of liquid polymers has recently been summarized,(32) for example PEG 400-1500 is >95% biodegraded in 14 days. This makes PEGs and PPGs much safer to use and dispose of than their corresponding class of volatile solvents – the glymes, and many other common laboratory solvents.

Recently, cleaner, more benign routes to bis-imine Schiff base ligands have been reported.(33) These reactions yielded high purity ligand under neat reaction conditions or by using polypropylene glycol (PPG) solvent. Inspired by this research, we sought to reduce the amount of solvent used in the preparation of our chosen ligand set and also the time involved. We report herein the rapid, high yielding synthesis of amine-bis(phenol) ligands on water under microwave irradiation and our journey en-route to these results via reactions in PEG solvents.

Results and discussion

In following the work of van den Ancker and co-workers,(33) the first modified procedure we attempted was the synthesis of amine-bis(phenol)s in PEG and PPG. The phenol reagents dissolved in the warm polymers to form solutions, however, the *tert*-amyl and *tert*-butyl substituted phenols were insoluble at room temperature. Vials were loaded with phenol, polymer, solvent, aqueous formaldehyde and finally, the amine was added to the stirred mixture. The reaction of primary amines with formaldehyde and paraformaldehye is exothermic and therefore, care should be taken when adding the amine. The reaction mixtures immediately warmed to around 40 ^{o}C, and were then heated to 75 ^{o}C overnight. Three polymer solvents were studied in this first series of reactions: PEG 400, PPG 400 and PPG 1000. Two concentrations were tested: 1mmol amine per gram polymer solvent and 2 mmol amine per gram solvent. The amine used was N,N-dimethylethylenediamine, the phenols were di-*tert*-butyl phenol and di-*tert*-amyl phenol.





Scheme 1. Synthetic route to modular amine-bis(phenol) ligands

Control reactions using ethanol as the solvent were also performed and gave similar yields of products for the same reaction temperatures and times. In this series of reactions, Table 1, yields were similar for all reactions irrespective of the substituted phenol used but yields were lower at the more dilute concentrations. PEG 400 gave slightly increased yields compared to the other solvents and was therefore used in subsequent experiments. Crystals of the ligand were sometimes obtained upon cooling the PEG and PPG containing reaction mixtures. However, larger crystals of the amine-bis(phenol)s were more readily obtained from saturated ethanol or methanol solutions. As in the work of van den Ancker,(33) the polymer solvent could be re-used in subsequent experiments.

Over the past decade, tremendous advances in organic synthesis (*e.g.* rate accelerations, enhanced selectivities) have been achieved through the use of microwave irradiation.(34-36) A wide variety of microwave assisted condensation reactions have been studied and therefore, we attempted amine-bis(phenol) syntheses in a household microwave oven. Although, there are concerns about the safety and reproducibility of results obtained using these ovens, as long as precautions are taken with safety and interpretation of the data, these ovens act as a good entry point into microwave chemistry.(37-39) PEG 400 was used as the solvent in these initial studies. Vials containing the reaction mixtures were prepared as in the conventionally heated experiments. Each vial was heated individually in the microwave at the desired power and for varying lengths of time. Each reaction was then triturated using ethanol, cooled to 0 ^{o}C and the crystalline precipitate collected by filtration. Initial experiments were performed using 60 s microwave pulses at low power settings; 50 % power (600 W) or 10 % power (120 W). However, as expected, the yields increased with increased reaction time and microwave power setting. Therefore, after preliminary experiments, all amine-bis(phenol) syntheses performed in the household microwave were conducted using ten 60 s full power (1200 W) pulses, Table 2. Reaction temperatures were monitored between pulses and were between 80 and 100 ^{o}C. Some reactions were also performed using catalytic amounts of aqueous acid, this did not increase the yield or rate of reactions.

To confirm the results obtained using a household microwave, selected reactions were repeated using a research grade instrument (Biotage Initiator System, 20 mL reaction volume sealed vessels), Table 2. In addition to reactions in PEG 400, reactions were performed using ethanol and water. Yields using ethanol (Table 2, Entries 15 – 18) were comparable with those using PEG 400 but interestingly, excellent yields were obtained using water, Table 2, Entries 19 and 20. These reactions can be reproduced using conventional heating, however, significantly longer reaction times are needed.

A wide range of reactions using water as the reaction medium have been studied because of their *green* potential.(40-42) These include Mannich-type reactions using surfactants to facilitate the acid catalyzed process.(43) Therefore, we decided to prepare a wide range of amine-bis(phenol) ligands in water. Recently, it has been discovered that in some cases, when reactants and products are insoluble in water, the reactions occur in a suspension or 'on water.'(44,45) Although, we did not see the rate enhancements observed by Sharpless and co-workers,(44) as can be seen in Table 3, the yields of these Mannich condensation reactions improve with an increase in hydrophobicity of the phenol. For example, yields using di-*tert*-butyl and di-*tert*-amyl phenol are always significantly higher that those using *para*-cresol or dimethyl phenol as the reagent, Table 3. We tentatively propose that the preferred reaction mechanism for the ligand syntheses is via formation of the iminium ion intermediates from the water-soluble amines and formaldehyde in homogeneous aqueous solution. This is followed by step-wise reactions of these species with two equivalents of phenol via a heterogenous process on the surface of the suspended droplets of liquid phenol. This prevents any alternative reaction pathways occuring such as reaction of the amine directly with the phenol in homogeneous solution, thus increasing the yields when hydrophobic phenols are used. As phenols can be regarded as enols, when the phenol is water-soluble, some of the amine reagent can react directly with the keto tautomer of the phenol. This reduces the amount of amine available for the desired reaction with formaldehyde and this decreases the yield of amine-bis(phenol) when less sterically demanding reagents such as *p*-cresol are used.

We have also performed this class of reaction on a large scale (50 mL aqueous formaldehyde) using a Morton flask, equipped with a condenser, a mechanical stirrer and a heating mantle. Reactions were performed using 2,4-di-*tert*-butyl phenol or 2,4-di-*tert*-amyl phenol, and N,N-dimethylethylenediamine, yields were over 90%. However, care should be taken given the large amount of precipitate that forms which can affect the stirring mechanism.

During the course of this research, crystals of one ligand suitable for single crystal X-ray diffraction studies were isolated.[†] The molecular structure of **1**, Fig. 2, is significantly different from the previously reported more sterically congested analogue derived from di-*tert*-amyl phenol, although important bond lengths and hydrogen-bond distances are similar.(29) The structure of **1** exhibits a twist along the back bone of the ligand resulting in the phenol OH groups residing on opposite sides of the molecule in the solid state. In contrast, the di-tert-amyl derived ligand contains both OH groups on the same side of the molecule.(29) The differences in the solid state molecular structures of these two molecules are presumably due to packing constraints in the solid state, as no significant differences in their solution state structures are observed by ^{1}H NMR spectroscopy.

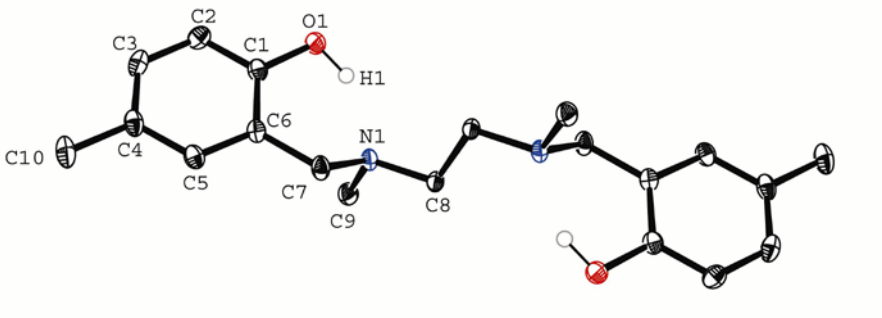


Fig. 2. Molecular structure of **1**. H atoms omitted for clarity. Thermal ellipsoids are drawn at the 20% probability level. Selected bond lengths (Å) and angles (°): C1-O1 1.3686(14), C7-N1 1.4758(14), C8-N1 1.4693(14), C9-N1 1.4687(15), C8-C8_2 1.520(2), O1-H1 0.91(2), C7-N1-C8 110.75(9), C7-N1-C9 110.79(9), C8-N1-C9 111.28(9)

[†] CCDC 658822 contains the supplementary crystallographic data for this paper. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk)

Conclusions

In summary, we have reported the synthesis of related amine-bis(phenol) ligands in ethanol, PEG, PPG or water as the solvent. Yields for these compounds are improved compared to conventional routes and reaction times are dramatically reduced when microwave heating and water are used. Therefore, microwave assisted synthesis could aid in the synthesis of libraries of these ligands for use in high-throughput catalytic studies and this approach could potentially be extended to other related ligand syntheses.(46-50) Also, even in the absence of a microwave synthesizer, the preferred method of synthesis for the di-*tert*-butyl and di-*tert*-amyl derived ligands, and perhaps other sterically demanding analogues, should be using water as the reaction medium. During the initial submission period for this article, a communication regarding the syntheses of related amine-phenol ligands using water as the reaction medium has been accepted for publication.(51) Therein, data on the relative solubilities of alkyl substituted phenols is reported. However, further studies are ongoing into the reasons for the increased yields of these ligands when hydrophobic phenol reagents are used during their preparation in aqueous media.

Experimental

General procedures and instrumentation

Amines, phenols and aqueous formaldehye were purchased from Aldrich and Alfa Aesar. Ethanol was purchased from Fisher Scientific. PEG 400, PPG 400 and PPG 1000 were purchased from Alfa Aesar. Microwave heating was achieved using either an unmodified household MW oven (Panasonic NN-S740WA-1200W) or a research grade microwave reactor (Biotage Initiator 2.0). NMR spectra were recorded on a Jeol EX 270, a Tecmag APOLLO 300 or a Bruker Avance 500 instrument, Table 5. ^{1}H NMR spectra were referenced to residual protons in the deuterated solvent and ^{13}C NMR spectra to the ^{13}C atoms therein. EI Mass spectra were recorded on a Fisons Instruments VG Analytical Autospec Mass Spectrometer and MALDI-TOF spectra (anthracene matrix) were obtained on an Applied Biosystems DE-RP instrument. Selected data are presented in Table 5. Elemental analyses were performed on several samples to provide additional confirmation of their synthesis at Elemental Microanalysis Ltd., Devon, UK and at Canadian Microanalytical Service Ltd., Delta, BC, Canada. For example, for $Me_2NCH_2CH_2N\{CH_2\text{-}3,5\text{-}Bu_2\text{-}C_6H_2OH\text{-}_2\}_2$ Found: C 77.32, H 10.94, N 5.41. $C_{34}H_{56}N_2O_2$ requires: 77.81, H 10.76, N 5.34. However, not all samples were analysed in this way, as full characterisation data was obtained on these ligands during their original preparation by Kol and co-workers.(10-14) Diffraction data were collected at 100K on a Bruker Smart Apex diffractometer with Mo-Kα radiation (λ = 0.71073 Å) using a SMART CCD camera. Diffractometer control, data collection and initial unit cell determination was performed using SMART.(52) Frame integration and unit cell refinement software was carried out with SAINT+.(53) Absorption corrections were applied by SADABS.(54) Structures were solved by direct methods (SHELXS-97) and refined by full-matrix least squares based on $|F|^2$ using SHELXL-97.(55,56)

General procedure for amine-(bis)phenol ligand synthesis in PEG under conventional heating

A capped 10-20 mL vial was loaded with PEG 400 (2.0 g), 37% aqueous formaldehyde (0.70 mL) and phenol (8.0 mmol). The mixture was stirred and N,N-dimethylethylenediamine (0.35 g, 4.0 mmol) was added dropwise. Vials were stirred in a heated block (Chemglass OptiChem™) at 75 ^{o}C for 18

h. The vial was cooled in an ice-bath and filtered. If required, the solid was washed with a minimum amount of ethanol and dried under vacuum to yield the amine-bis(phenol) as a colourless, crystalline solid.

General procedure for amine-(bis)phenol ligand synthesis in PEG under microwave heating

(a) Household microwave oven

A loosely capped 10-20 mL vial was loaded with PEG 400 (2.0 g), 37% aqueous formaldehyde (0.70 mL) and phenol (8.0 mmol). Substituted amine (4.0 mmol) was added dropwise. Vials were heated on full power (1200 W) for ten 60 s pulses. The temperature of the reaction mixture in the vial was measured between pulses, temperatures were maintained below 100 ^{o}C. Caution: Occasionally, the reaction mixtures would become very hot and spill out of the container, reactions in a household microwave oven should not be left unattended and safety precautions should be taken. After heating, the vial was cooled in an ice-bath and filtered. If required, the solid was washed with a minimum amount of ethanol and dried under vacuum.

(b) Biotage Initiator

A 10-20 mL Biotage reaction tube was loaded with PEG 400 (8.0 g), 37% aqueous formaldehyde (3.0 mL), substituted phenol (37 mmol) and amine (18 mmol). The tube was sealed with a lid containing a septum and placed in the reaction cavity. The mixture was stirred and heated to the desired temperature for 5 min. During this time, the pressure in the tube was monitored by a pressure sensor on the tube's lid. The reaction tube was rapidly cooled under a nitrogen flow, once the pressure in the tube had reduced to near atmospheric, the septum was removed. The contents of the tube were filtered, washed with a minimum amount of ethanol and dried under vacuum.

General procedure for amine-(bis)phenol ligand synthesis in ethanol under conventional heating

Phenol (0.123 mol) was weighed into a 100 mL beaker and ethanol (around 30 mL) added to give a saturated solution. The phenol solution was transferred to a 200 mL round bottom flask and 37%

aqueous formaldehyde (10 mL) was added. The flask was equipped with a condenser and the amine (0.06 mol) was added. The reaction mixture was stirred and heated at 70 ^{o}C for 18 h. The reaction mixture was cooled in an ice-bath, filtered and the residue washed with cold ethanol (2 × 20 mL). The solid was dried under vacuum.

General procedure for amine-(bis)phenol ligand synthesis in ethanol or water under microwave heating

A 10-20 mL Biotage reaction tube was loaded with water or ethanol (5.0 mL), 37% aqueous formaldehyde (3.0 mL), substituted phenol (37 mmol) and amine (18 mmol). The tube was sealed with a lid containing a septum and placed in the microwave reaction cavity. The mixture was stirred and heated to the desired temperature for 5 min. During this time, the pressure in the tube was monitored by a pressure sensor on the tube's lid. The reaction tube was rapidly cooled under a nitrogen flow, once the pressure in the tube had reduced to near atmospheric, the septum was removed. The contents of the tube were filtered, washed with a minimum amount of ethanol and dried under vacuum.

General procedure for amine-(bis)phenol ligand synthesis in water under conventional heating

Phenol (0.123 mol) was weighed directly into a 200 mL round bottom flask, water (80 mL) and 37% aqueous formaldehyde (10 mL) were added. The flask was equipped with a condenser and the amine (0.06 mol) was added. The reaction mixture was stirred and heated at 100 ^{o}C for 18 h. Upon cooling to room temperature, the product formed a separate phase as either a solid or an oil that could be easily isolated. The product was dried under vacuum or if significant quantities of water were still present, it was dissolved in an organic solvent and dried over anhydrous magnesium sulfate.

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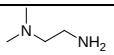
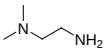
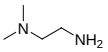
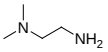
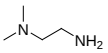
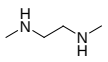
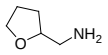
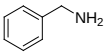
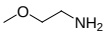
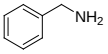
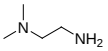
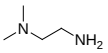
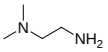
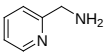
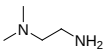
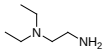
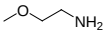
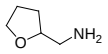
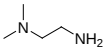
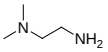
Tables

Table 1. Yields of amine-bis(phenol)s from reactions using PEG and PPG solvents

Entry	Phenol	Solvent [a]	Yield /% [b]
1	*t*-Bu, *t*-Bu	PPG 400 (dilute)	38
2	*t*-Bu, *t*-Bu	PPG 400	73
3	*t*-Bu, *t*-Bu	PEG 400(dilute)	48
4	*t*-Bu, *t*-Bu	PEG 400	81
5	*t*-Bu, *t*-Bu	PPG 1000 (dilute)	40
6	*t*-Bu, *t*-Bu	PPG 1000	73
7	*t*-Am, *t*-Am	PPG 400 (dilute)	52
8	*t*-Am, *t*-Am	PPG 400	74
9	*t*-Am, *t*-Am	PEG 400 (dilute)	43
10	*t*-Am, *t*-Am	PEG 400	96
11	*t*-Am, *t*-Am	PPG 1000 (dilute)	31
12	*t*-Am, *t*-Am	PPG 1000	76
13	*t*-Am, *t*-Am	Ethanol	72
14	*t*-Am, *t*-Am	Ethanol	79

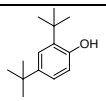
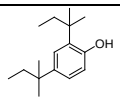
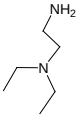
[a] All reactions were heated to 75 ^{o}C, 18 h. Reactions in polymers labelled dilute were performed using 1 mmol amine per gram of polymer, otherwise 2 mmol amine per gram of polymer was used. Reactions in ethanol were performed by starting with a saturated solution of the phenol. [b] Isolated yields, average of two identical reactions, compounds pure by ^{1}H NMR spectroscopy.

Table 2. Yields of amine-bis(phenol)s from reactions under microwave irradiation

Entry	Phenol	Amine	Conditions [a]	Yield /% [b]
1	*p*-cresol		Panasonic, 1200 W, 60 s × 10	43
2	Me, Me		Panasonic, 1200 W, 60 s × 10	67
3	*t*-Bu, Me		Panasonic, 1200 W, 60 s × 10	58
4	*t*-Bu, *t*-Bu		Panasonic, 1200 W, 60 s × 10	73
5	*t*-Am, *t*-Am		Panasonic, 1200 W, 60 s × 10	48
6	*t*-Am, *t*-Am		Panasonic, 1200 W, 60 s × 10	77
7	*t*-Am, *t*-Am		Panasonic, 1200 W, 60 s × 10	58
8	*t*-Am, *t*-Am		Panasonic, 1200 W, 60 s × 10	92
9	*t*-Am, *t*-Am		Panasonic, 1200 W, 60 s × 10	76
10	*t*-Am, *t*-Am		Panasonic, 1200 W, 60 s × 10	30
11	*t*-Bu, Me		Biotage, 140 °C, 8 g PEG 400	42
12	*t*-Bu, Me		Biotage, 160 °C, 8 g PEG 400	69
13	*t*-Bu, Me		Biotage, 180 °C, 8 g PEG 400	69
14	*t*-Bu, Me		Biotage, 160 °C, 8 g PEG 400	45
15	*t*-Bu, Me		Biotage, 160 °C, 5 mL EtOH	68
16	*t*-Bu, Me		Biotage, 160 °C, 5 mL EtOH	57
17	*t*-Bu, Me		Biotage, 160 °C, 5 mL EtOH	63
18	*t*-Bu, Me		Biotage, 160 °C, 5 mL EtOH	33
19	*t*-Bu, Me		Biotage, 160 °C, 5 mL H_2O	85
20	*t*-Bu, *t*-Bu		Biotage, 160 °C, 5 mL H_2O	92

[a] Panasonic = household microwave oven operated at constant power, 1200 W for 10 × 60 s, reaction scale of 2 g PEG 400 and 0.7 mL CH_2O(aq); Biotage = Biotage Initiator operated at constant temperature mode for 5 min at the temperature indicated, reaction scale of 3 mL CH_2O(aq) [b] Isolated yields, average of two identical reactions, compounds pure by ^{1}H NMR spectroscopy.

Table 3. Yields of amine-bis(phenol)s using water as the reaction medium[a]

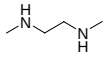
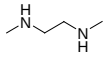
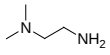
					
	23	66	76 (85)	94 (92)	98
	-	51	62	76	83
	25	28	55	72	98
	26	59	86	87	79
	-	94	88	92	89
	-	-	56	99	89
	23	46	33	54	98

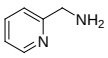
[a] Isolated yields, values in parentheses from microwave heated reactions using a Biotage Initiator system, compounds dried in a vacuum desiccator to constant mass and pure by ^{1}H NMR spectroscopy.

Table 4. Crystallographic data for compound **1**

	1
Empirical formula	$C_{20}H_{28}N_2O_2$
Formula weight	328.44
Temperature (K)	100(2)
Crystal system	Monoclinic
a (Å)	5.5722(8)
b (Å)	12.6340(19)
c (Å)	12.7270(19)
β (°)	92.380(3)
Space group	$P2_1/n$
Volume (Å3)	895.2(2)
Z	2
Density (calc.) (g/cm^3)	1.218
Absorption coefficient (mm^{-1})	0.079
θ Range for data collected (°)	2.27 to 28.33
Index ranges	$-7 \leq h \leq 7$, $-16 \leq k \leq 16$, $-16 \leq l \leq 16$
Reflections collected	9049
Independent reflections (R(int))	2224 (0.0300)
Max. and min. transmission	1.000 and 0.848
Data / restraints / parameters	2224 / 0 / 115
Goodness-of-fit on F^2	1.061
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0475$, $wR_2 = 0.1300$
Largest diff. peak and hole	0.444 and -0.192 $eÅ^{-3}$

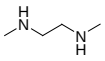
Table 5. Selected NMR and Mass Spectrometric Data of amine-bis(phenol) ligands

Amine and Phenol	Spectroscopic Data (^{1}H NMR, ^{13}C{^{1}H} NMR, Mass Spectra)
 2,4-dimethyl phenol	δ ^{1}H 10.69 (br, 2H, OH), 6.87 (d, $^{4}J_{HH}$ = 1.1 Hz, 2H ArH), 6.62 (d, $^{4}J_{HH}$ = 1.1 Hz, 2H ArH), 3.63 (s, 4H, $ArCH_2$), 2.65 (s, 4H, NC_2H_4N), 2.26 (s, 6H, NCH_3), 2.21 (s, 6H, $ArCH_3$), 2.20 (s, 6H, $ArCH_3$). δ ^{13}C{^{1}H} 153.3 (C), 130.5 (CH), 127.5 (C), 126.5 (CH), 124.6 (C), 120.5 (C), 61.7 (CH_2), 54.0 (CH_2), 20.4 (CH_3), 15.6 (CH_3). m/z 357 (100 %) $[MH]^+$, 223 (7 %) $[MH\text{-}C_9H_{10}O]^+$, 178 (26 %) $[C_{11}H_{16}ON]^+$, 135 (7 %) $[C_9H_{11}O]^+$.
 2,4-dimethyl phenol	δ ^{1}H 9.48 (br, 2H, OH), 6.88 (d, $^{4}J_{HH}$ = 1.9 Hz, 2H ArH), 6.68 (d, $^{4}J_{HH}$ = 1.9 Hz, 2H ArH), 3.57 (s, 4H, $ArCH_2$), 2.54 (s, 4H, NC_2H_4N), 2.34 (s, 6H, $N(CH_3)_2$), 2.20 (s, 12H, $ArCH_3$). δ ^{13}C{^{1}H} 152.5 (C), 131.1 (CH), 128.2 (CH), 127.2 (C), 125.3 (C), 121.4 (C), 55.9 (CH_2), 48.9 (CH_2), 44.7 (CH_2), 20.3 (CH_3), 16.1 (CH_3). m/z 357 (100 %) $[MH]^+$, 298 (30 %) $[MH\text{-}C_3H_9N]^+$, 223 (7 %) $[MH\text{-}C_9H_{10}O]^+$, 164 (7 %) $[C_{10}H_{14}NO]^+$, 135 (16 %) $[C_9H_{11}O]^+$, 58 (17 %) $[C_3H_8N]^+$.
 *p*-cresol	δ ^{1}H 9.06 (br, 2H, OH), 6.93 (d, $^{3}J_{HH}$ = 2.0 Hz, 2H, ArH), 6.83 (d, $^{3}J_{HH}$ = 2.0 Hz, 2H, ArH), 6.78 (s, 2H, ArH), 3.57 (s, 4H, $ArCH_2$), 2.57 (br, 4H, NC_2H_4N), 2.28 (s, 6H, $N(CH_3)_2$), 2.22 (s, 6H, $ArCH_3$). δ ^{13}C{^{1}H} 154.7 (C), 130.8 (CH), 129.9 (CH), 128.1 (CH), 122.2 (C), 116.6 (C), 55.3 (CH_2), 48.7 (CH_2), 44.4 (CH_2), 19.9 (CH_3), 19.9 (CH_3). m/z 329 (65 %) $[MH]^+$, 270 (29 %) $[MH\text{-}C_3H_9N]^+$, 221 (79%) $[MH\text{-}C_7H_8O]^+$, 209 (26 %) $[MH\text{-}C_8H_8O]^+$, 121 (12 %) $[C_8H_9O]^+$, 58 (100 %) $[C_3H_8N]^+$.



p-cresol

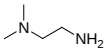
δ ^{1}H 9.50 (br, OH), 8.63 (dd, $^{3}J_{HH}$ = 5.1 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H, pyridine CH), 7.68 (dt, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H, pyridine CH), 7.25 (dd, $^{3}J_{HH}$ = 7.7 Hz, $^{3}J_{HH}$ = 5.1 Hz, 1H, pyridine CH), 7.11 (d, $^{3}J_{HH}$ = 7.7 Hz, 1H, pyridine CH), 6.95 (d, $^{3}J_{HH}$ = 2.0 Hz, 2H, ArCH), 6.84 (d, $^{3}J_{HH}$ = 2.0 Hz, 2H, ArCH), 6.78 (s, 1H, ArCH), 6.76 (s, 1H, ArCH), 3.86 (s, 2H, NCH_2), 3.75 (s, 4H, $ArCH_2$), 2.21 (s, 6H, $ArCH_3$). δ $^{13}C\{^{1}H\}$ 156.4 (C), 155.2 (C), 148.5 (CH), 137.9 (CH), 131.1 (CH), 130.1 (CH), 128.4 (CH), 123.7 (CH), 122.9 (CH), 121.4 (C), 116.9 (C), 58.2 (CH_2), 55.6 (CH_2), 20.1 (CH_3). m/z 349 (20 %) $[MH]^+$, 256 (10 %), $[MH\text{-}C_6H_7N]^+$, 241 (100 %) [MH-C_7H_8O]+, 121 (57 %) $[C_8H_9O]^+$, 108 (38 %) $[C_7H_8O]^+$, 93 (100 %) $[C_6H_7N]^+$.



p-cresol

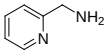
(**1**)

δ ^{1}H 9.95 (br, OH), 6.96 (d, $^{3}J_{HH}$ = 1.7 Hz, 2H, ArH), 6.75 (d, $^{3}J_{HH}$ = 1.7 Hz, 2H, ArH), 6.72 (s, 2H, ArH), 3.63 (s, 4H, $ArCH_2$), 2.63 (s, 4H, NC_2H_4N), 2.25 (s, 6H, NCH_3), 2.22 (s, 6H, $ArCH_3$). δ $^{13}C\{^{1}H\}$ 155.6 (C), 129.4 (CH), 129.3 (CH), 128.3 (C), 121.4 (C), 116.0 (CH), 61.6 (CH_2), 53.8 (CH_2), 41.4 (CH_3), 20.1 (CH_3). m/z 329 (100 %) $[MH]^+$, 209 (5 %) $[MH\text{-}C_8H_8O]^+$, 164 (19 %) $[C_{10}H_{14}NO]^+$, 121 (6 %) $[C_8H_9O]^+$.



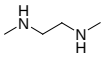
2,4-di-tert-amyl phenol

δ ^{1}H 9.62 (br, 2H, OH), 7.07 (d, $^{4}J_{HH}$ = 2.4 Hz, 2H, ArH), 6.83 (d, $^{4}J_{HH}$ = 2.4 Hz, 2H, ArH), 3.59 (s, 4H, $ArCH_2$), 2.54 (s, 4H, NC_2H_4N), 2.28 (s, 6H, $N(CH_3)_2$), 1.88 (m, 4H, CH_2), 1.56 (m, 4H, CH_2), 1.33 (s, 12H, CH_3), 1.23 (s, 12H, CH_3), 0.62 (m, 12H, CH_3). δ $^{13}C\{^{1}H\}$ 153.5 (C), 138.5 (C), 134.4 (C), 125.8 (CH), 121.7 (C), 56.4 (CH_2), 55.7 (CH_2), 48.7 (CH_2), 44.5 (CH), 38.3 (C), 36.9 (CH_2), 32.4 (CH_2), 28.3 (CH_3), 27.4 (CH_3), 9.23 (CH_3), 8.86 (CH_3). m/z 581 (100 %) $[MH]^+$, 522 (32 %) $[MH\text{-}C_3H_9N]^+$, 347 (14 %) $[MH\text{-}C_{16}H_{26}O]^+$, 247 (5 %) $[C_{17}H_{27}O]^+$, 72 (6 %) $[C_5H_{12}]^+$, 58 (16 %) $[C_3H_8N]^+$. Found: 78.15, H 11.36, N 4.92. $C_{38}H_{64}N_2O_2$ requires: C 78.57, H 11.10, N 4.82



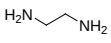
2,4-di-tert-amyl phenol

δ ^{1}H 10.39 (br, 2H, OH), 8.67 (dd, $^{3}J_{HH}$ = 5.0 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H, pyridine CH), 7.67 (dt, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.8 Hz, 1H, pyridine CH), 7.26 (dd, $^{3}J_{HH}$ = 7.4 Hz, $^{3}J_{HH}$ = 5.0 Hz, 1H, pyridine CH), 7.13 (d, $^{3}J_{HH}$ = 7.4 Hz, 1H, pyridine CH), 7.07 (d, $^{3}J_{HH}$ = 2.4 Hz, 2H, ArH), 6.85 (d, $^{3}J_{HH}$ = 2.4 Hz, 2H, ArH), 6.57 (s, 1H, ArH), 6.55 (s, 1H, ArH), 3.78 (s, 2H, NCH_2), 3.46 (s, 4H, $ArCH_2$), 1.85 (m, 4H, CH_2), 1.55 (m, 4H, CH_2), 1.32 (s, 12H, CH_3), 1.22 (s, 12H, CH_3), 0.64 (m, 12H, CH_3). δ $^{13}C\{^{1}H\}$ 153.9 (C), 152.1 (CH), 148.5 (C), 141.2 (C), 139.1 (C), 137.6 (CH), 137.6 (CH), 126.0 (CH), 126.0 (CH), 124.3 (CH), 122.7 (CH), 121.4 (C), 115.9 (CH), 56.4 (CH_2), 50.7 (CH_2), 38.4 (C), 37.0 (CH_2), 32.6 (C), 28.3 (CH_3), 27.3 (CH_3), 8.84 (CH_3). m/z 601 (15 %) $[MH]^+$, 508 (10 %) $[MH\text{-}C_6H_7N]^+$, 367 (24 %) $[MH\text{-}C_{16}H_{26}O]^+$, 205 (100 %) $[C_{14}H_{21}O]^+$, 93 (17 %) $[C_6H_7N]^+$.



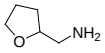
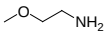
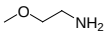
2,4-di-tert-amyl phenol

δ ^{1}H 10.60 (br, 2H, OH), 7.06 (d, $^{4}J_{HH}$ = 2.0 Hz, 2H, ArH), 6.73 (d, $^{4}J_{HH}$ = 2.0 Hz, 2H, ArH), 3.64 (s, 4H, $ArCH_2$), 2.60 (s, 4H, NC_2H_4N), 2.21 (s, 6H, NCH_3), 1.86 (m, 4H, CH_2), 1.55 (m, 4H, CH_2), 1.34 (s, 12H, CH_3), 1.22 (s, 12H, CH_3), 0.61 (m, 12H, CH_3). δ $^{13}C\{^{1}H\}$ 154.2 (C), 138.8 (C), 134.0 (C), 125.3 (CH), 124.2 (CH), 120.9 (C), 62.5 (CH_2), 53.4 (CH_2), 41.2 (CH_3), 38.3 (C), 36.9 (CH_2), 32.5 (CH_2), 28.2 (CH_3), 27.2 (CH_3), 9.18 (CH_3), 8.74 (CH_3). m/z 581 (100 %) $[MH]^+$, 347 (18 %) $[MH\text{-}C_{16}H_{26}O]^+$, 290 (40 %) $[C_{19}H_{32}NO]$+, 247 (11 %) $[C_{17}H_{27}O]^+$.



2,4-di-tert-amyl phenol

δ ^{1}H 10.57 (br, 2H, OH), 7.08 (d, $^{4}J_{HH}$ = 2.3 Hz, 2H, ArH), 6.75 (d, $^{4}J_{HH}$ = 2.3 Hz, 2H, ArH), 3.85 (s, 4H, $ArCH_2$), 3.15 (br, 2H, NH), 2.92 (s, 4H, NC_2H_4N), 1.84 (m, 4H, CH_2), 1.56 (m, 4H, CH_2), 1.35 (s, 12H, CH_3), 1.23 (s, 12H, CH_3), 0.64 (m, 12H, CH_3). δ $^{13}C\{^{1}H\}$ 154.2 (C), 139.2 (C), 134.2 (C), 126.3 (CH), 124.2 (CH), 120.9 (C), 59.0 (CH_2), 51.3 (CH_2), 38.1 (C), 37.0 (CH_2), 33.0 (CH_2), 28.3 (CH_3), 27.3 (CH_3), 9.10 (CH_3), 8.76 (CH_3). m/z = 319 (18 %) $[M\text{-}C_{16}H_{25}O]^+$, 234 (16 %) $[C_{16}H_{26}O]^+$, 219 (6 %) $[C_{15}H_{23}O]^+$, 205 (100 %) $[C_{14}H_{21}O]^+$.

 2,4-di-tert-butyl phenol	δ^1H 8.87 (br, 2H, OH), 7.20 (d, $^4J_{HH}$ = 2.0 Hz, 2H, ArH), 6.88 (d, $^4J_{HH}$ = 2.0 Hz, 2H, ArH), 4.27 (m, 1H, CHO), 3.89 (m, 2H, CH_2O), 3.77 (m, 4H, $ArCH_2NCH_2Ar$), 2.61(m, 4H, CH_2CH_2), 2.51(m, 2H, NCH_2Furf), 1.40 (s, 18H, $C(CH_3)_3$), 1.27 (s, 18H, $C(CH_3)_3$). δ $^{13}C\{^1H\}$ 153.02 (C), 140.63 (C), 136.05 (C), 124.95 (CH), 123.38 (CH), 121.43 (C), 77.54 (CH), 68.28 (CH_2), 57.52 (CH_2), 55.93 (CH_2), 34.99 (CMe_3), 34.10 (CMe_3), 31.67 (CH_3), 29.60 (CH_3), 29.60 (CH_2), 25.21 (CH_2). m/z = 537 (100 %) $[M]^+$, 466 (47 %) $[M\text{-}THF]^+$, 410 (9 %) $[M\text{-}THF\text{-}Bu]^+$, 332 (17 %) $[C_{21}H_{34}NO_2]^+$, 205 (100 %) $[C_{14}H_{21}O]^+$.
 2,4-di-tert-butyl phenol	δ ^{1}H NMR 8.39 (br, 2H, OH), 7.20 (d, $^4J_{HH}$ = 1.9 Hz, 2H, ArH), 6.87 (d, $^4J_{HH}$ = 1.9 Hz, 2H, ArH), 3.73 (s, 4H, $ArCH_2$), 3.55 (t, $^3J_{HH}$ = 5.0 Hz, NCH_2), 3.46 (s, 3H, OCH_3), 2.73 (t, $^3J_{HH}$= 5.0 Hz, 2H, CH_2O), 1.37 (s, 18H, $C(CH_3)_3$), 1.27 (s, 18H, $C(CH_3)_3$). δ $^{13}C\{^1H\}$ 152.8(C), 140.7(C), 136.0(C), 124.9(CH), 123.4(CH), 121.6(C), 71.4 ($ArCH_2$), 58.0 (OCH_3), 51.3 (CH_2), 35.0 ($C(CH_3)_3$), 34.1 ($C(CH_3)_3$), 31.6 ($C(CH_3)_3$), 30.1 ($C(CH_3)_3$). m/z = 512 (3 %) $[M]^+$, 454 (81 %) $[M\text{-}Bu]^+$, 306 (50 %) $[C_{19}H_{32}NO_2]^+$, 205 (100 %) $[C_{14}H_{21}O]^+$.
 2,4-di-methyl phenol	^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (s, 2H, OH), 6.85 (d, $^4J_{HH}$ = 1.8 Hz, 2H, ArH), 6.67 (d, $^4J_{HH}$ = 1.8 Hz, 2H, ArH), 3.72 (s, 4H, $ArCH_2N$), 3.58 (t, $^3J_{HH}$ = 5.0 Hz, 2H, CH_2O), 3.47 (s, 3H, OCH_3), 2.70 (t, $^3J_{HH}$ = 5.0 Hz, 2H, NCH_2), 2.20 (s, 12H, $ArCH_3$). δ $^{13}C\{^1H\}$ 152.84 (C), 131.37 (C), 121.24 (C), 127.68 (CH), 127.36 (CH), 125.15 (C), 70.89 (NCH_2CH_2O), 58.17 (OCH_3), 57.04 (NCH_2CH_2O), 50.77 (CH_2Ar), 20.24 (CH_3), 16.03 (CH_3). m/z = 343 (21 %) $[M]^+$, 320 (100 %) $[M\text{-}Me\text{-}H_2O]^+$, 222 (9 %) $[C_{13}H_{20}NO_2]^+$, 208 (87 %) $[C_{12}H_{18}NO_2]^+$.