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Meritxell Guin, Emilie Brul, and Yolanda R. de Miguel

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Recycling and Reuse of a Polymer-Supported Scavenger for Amine Sequestration

Meritxell Guinó, Emilie Brulé, and Yolanda R. de Miguel*

Department of Chemistry, King's College London, Strand, London U.K. WC2R 2LS

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The regeneration and reuse of a supported scavenger **1** for amine sequestration has been achieved up to three times without significant loss of activity. The scavenging process between the aldehyde resin **1** and a range of amines has been investigated in detail to determine the scope of this scavenger. Its application for the rapid purification of a small library of secondary amines **7a–j** has also been demonstrated, and it has been shown that the large excess of scavenger resin used can be recovered and recycled, making this a more cost-effective process.

The use of polymer supported catalysts, reagents, and scavengers to facilitate purification in solution-phase, parallel synthesis and combinatorial chemistry has become widespread and has been the subject of many recent reviews.^{1–3} The main advantage of using the polymer-assisted solution-phase synthesis approach is the simplicity of the process (relative to solid-phase organic synthesis) and the ease of product purification by simple filtration of the insoluble polymer. However, the main drawbacks of this approach are the high cost of the supports coupled with the need to use them in large quantities, even for small-scale reactions. The preferred strategy is to employ soluble reagents and then use supported scavengers to remove any remaining reagents at the end of the reaction. In particular, several resins have been developed to scavenge excess amines⁴ from solution-phase reaction mixtures, and many of them have become commercially available. This is due to the fact that there is a wide diversity of amines commercially available and that they are used in a broad range of synthetic reactions and in the synthesis of many nitrogen-containing pharmaceutical and agricultural products. In 1996, Kaldor et al.⁵ demonstrated the use of an aldehyde resin as a scavenger for primary amines. This was exploited in the parallel solution-phase synthesis of a library of secondary amines, which were prepared by reductive amination. The use of aldehyde resins to capture and separate the product from the reaction mixture has been reported in the parallel solution-phase synthesis of libraries of several compounds.⁶

Wang aldehyde resin^{5,6a,6d} is a commonly employed amine scavenger; however, this resin is often used in stoichiometric or larger amounts, which is not cost-effective. Here, we report a detailed study of the scavenging process and the successful recycling of the aldehyde scavenger resin without significant loss of activity.

Scheme 1

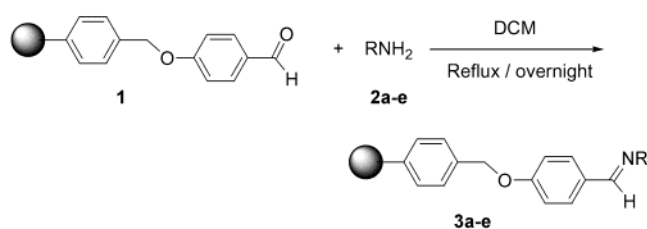


Table 1. Yields of Polymer-Supported Imines **3a–e** Prepared from a Variety of Amines **2a–e**

	Amines	Yield ^a
2a		78%
2b		66% 69% ^b
2c		64%
2d		59%
2e		82%

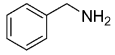
^a Determined from percent nitrogen microanalysis, ^b Determined by percent chlorine microanalysis.

Results and Discussion

Part 1. Solid-Phase Synthesis of Imines. The synthesis of supported imines has been previously studied and used in the solid-phase synthesis of *N*-alkyl-*N*-(β -keto)amides⁷ and 2,3-dihydro-4-pyridones.⁸ Initially, a more detailed study was carried out to better understand imine formation on solid phase. It involved investigating the reaction between Wang aldehyde resin **1** and a series of amines, **2a–e** (Scheme 1). The formation of supported imines **3a–e** was carried out in dichloromethane⁹ using an excess of amine in order to drive the reaction to completion. Several amines, **2a–e** (Table 1),

* Phone: +44(0)207 8481180. Fax: +44(0)207 8482810. E-mail: yolanda.demiguel@kcl.ac.uk.

Table 2. Imine Yields Obtained from Consecutive Treatments on the Same Resin after Its Regeneration

Amines	Yield	Yield after 1st regeneration	Yield after 2nd regeneration
2a 	78%	76%	76%

were chosen for this investigation in order to determine the scope of the scavenger.

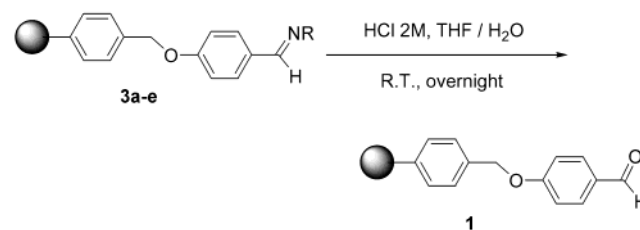
These solid-phase reactions were monitored by single bead FT-IR spectroscopy.¹⁰ In all cases, it was found that the peak for carbonyl stretching (for **1**) at 1695 cm⁻¹ disappeared gradually, and a new band for the imine stretch appeared in the range 1638–1645 cm⁻¹.

Amines **2a–e** and Wang-aldehyde resin **1** were reacted overnight in order to ensure complete conversion of the supported aldehyde to the corresponding imine. The yields of **3a–e** (determined by percent nitrogen microanalysis) were good in all cases (59–82%) [Yields were based on the amount of aldehyde functionality available on the resin (as reported by the manufacturer). It is not yet clear why the yields of supported imines are not closer to 100%. In some cases, traces of unreacted aldehyde functionality could be detected by IR or NMR.]. In the case of *m*-chlorobenzylamine **2b**, the derivatization was also monitored by percent chlorine microanalysis. The yields determined by nitrogen (66% ± 2%) and chlorine (69% ± 2%) microanalysis were both in agreement.

These initial studies confirmed that the aldehyde resin **1** would be useful as a scavenger of a wide range of primary amines.

Part 2. Regeneration and Recycling. The regeneration of the scavenger aldehyde resin **1** by cleavage of the imine bond of **3a–e** to release the aldehyde was carried out with HCl, 2 M, in H₂O/THF mixture (1:2) shaking at room temperature overnight. Initially, the imine resins **3a–e** were treated in this manner to give the regenerated resin **1**. It was found by single bead FT-IR that the peak corresponding to the imine stretching was completely replaced by a new peak corresponding to the aldehyde stretching. The complete removal of the imine was further confirmed by nitrogen microanalysis. Moreover, the gel-phase HR-MAS ¹H NMR¹¹ spectra for these recycled resins and the commercial resin were identical. The peak at 8.3 ppm from the imine proton had completely disappeared from the spectrum of the recycled beads, which showed only the aldehyde peak at 9.8 ppm. The regeneration of the scavenger from the imine **3b** was also investigated. In this case, the complete removal of the amine was also proved by chlorine microanalysis.

The recycled resins were treated with an excess of amine **2a** to demonstrate that the activity of the scavenger had been retained after the regeneration process. The yields for these reactions (Table 2) were found to be identical (within experimental error) (the error for the nitrogen microanalysis results is ± 0.5%, so the error in the yields estimated is ± 2%) to those obtained for the commercial resin. The reused beads were then regenerated for the second time and treated as before. The yield after the second regeneration was also identical (the error for the nitrogen microanalysis results is

Scheme 2

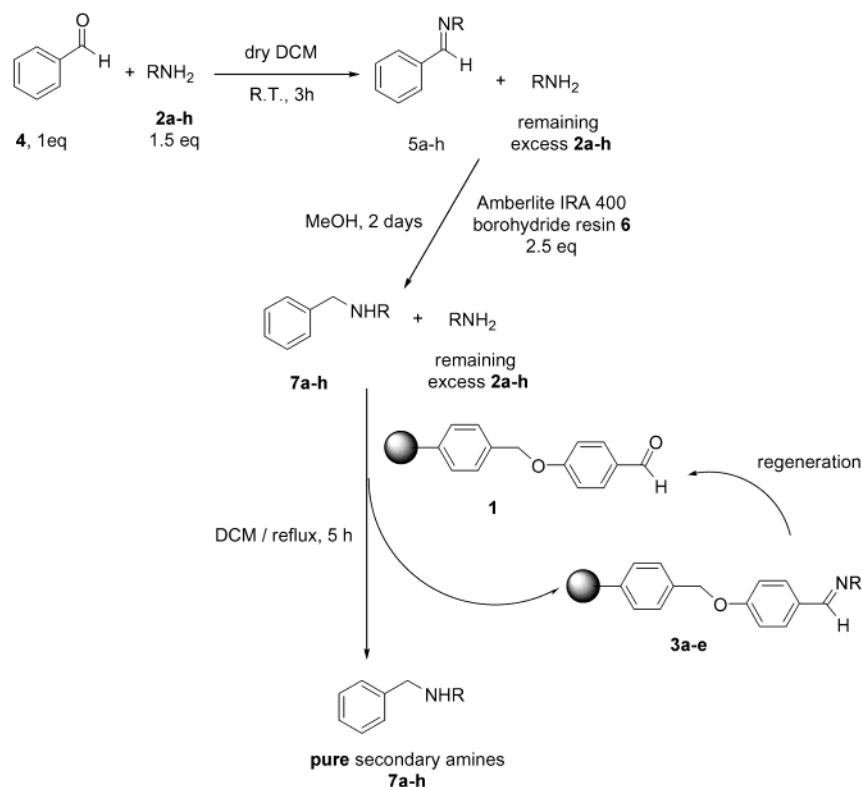
± 0.5%, so the error in the yields estimated is ± 2%) to that obtained when using fresh resin.

Part 3. Parallel Synthesis of a Library of Secondary Amines (7a–j). The most common application of the Wang aldehyde resin **1** as a scavenger is for selective purification of secondary amines in the presence of primary amines after reductive amination.⁵ Thus, the parallel synthesis of a library of secondary amines (**7a–h**) was carried out as shown in Scheme 3. First, the parallel solution-phase synthesis of imines **5a–h** was performed by the previously described procedure^{6a} but without using trimethylorthoformate, because it had been demonstrated that the reaction did not require orthoformate. The ¹H NMR spectra of the resulting mixtures of imine (**5a–h**) and excess amine (**2a–h**) were recorded. The reduction of the imines to secondary amines (**7a–h**) was then carried out in parallel using Amberlite IRA-400 borohydride resin **6**. Bradley et al.¹² reported that the reduction was solvent-dependent for the polymer-supported borohydride resin **6**. Thus, it was found that the reduction was successful in a mixture of MeOH and dichloromethane (whereas pure MeOH led to poor results). (In methanol, the polymer-supported borohydride resin failed to reduce the imines to the secondary amines.) The reduction was therefore carried out using these new conditions: a mixture of MeOH and DCM (1:1) during 24 h. The reaction was successful this time, but some imine was still remaining. After the reaction time was increased to 48 h, the reduction was finally successful. Because we were interested in the regeneration and reuse of the aldehyde resin **1**, the polymer-supported borohydride resin **6** was filtered off before the addition of DCM and the aldehyde resin **1**. Before the scavenging step, the ¹H NMR spectra of these mixtures of secondary amine (**7a–h**) and primary amine (**2a–h**) were again recorded. Finally, the scavenging of the remaining excess of primary amine was performed by stirring the mixture in refluxing DCM for 5 h with Wang aldehyde resin **1**. The pure secondary amines (**7a–h**) were obtained in good yields (63–92%) and high purities (~98%), as observed by ¹H NMR (Table 3).

During these experiments, the scavenging resin was regenerated and reused twice without loss of activity. The regenerated beads were used in the scavenging of a different primary amine to prove that there was no cross-contamination.

It should be noted that commercial beads were used in the preparation of **7a** and **7c**. The resins obtained after these reactions were regenerated and reused in the synthesis of amines **7b** and **7d**, respectively. The ¹H NMR spectra of these amines (**7b** and **7d**) did not show traces of **2a** or **2c**. The beads used to synthesize **7b** and **7d** were then regenerated once more and used during the preparation of **7e** and

Scheme 3



7f, respectively. The spectra of these amines again did not detect the presence of any unwanted amines **2b** or **2d**.

This small library was always created by reacting benzaldehyde **4** and different amines **2a-h**.

To establish the usefulness of the method presented herein, two more examples derived from aliphatic aldehydes were included. Thus, octanal **8** and decanal **9** were reacted with benzylamine **2a** in order to synthesize two new secondary amines **7i** and **7j** by following exactly the same procedure shown in Scheme 3. It was proved that the procedure was also successful for aliphatic aldehydes (Table 3).

In summary, the Wang aldehyde resin **1** has been used several times as a scavenger for a variety of amines **2a-h**, thanks to the successful regeneration of these beads. A simple recycling procedure has been developed and has led to the reuse of the scavenging resin up to three times without significant loss of activity. Its use has also been demonstrated in the parallel synthesis of a library of secondary amines **7a-j**, which were obtained in good yields (63–92%) and high purities (~98%). We have therefore developed a cost-effective procedure that allows recycling of the large amounts of scavenger resin **1** required for the secondary amine library synthesis.

Experimental Section

General. Wang-aldehyde polystyrene resin **1** was obtained from Novabiochem (2.81 mmol/g, 200–400 mesh, 2% DVB, batch A25322); Amberlite IRA 400 borohydride resin **6** (2.5 mmol/g) was obtained from Aldrich Chemical Co. ¹³C and ¹H NMR spectra were recorded on a Bruker AV 360. Gel-phase HR-MAS NMR spectra (in the gel phase, CDCl₃) were obtained on a Bruker AV-400 equipped with a special probe. The samples were packed into a 4-mm HR-MAS rotor, and CDCl₃ was added to the resin directly inside the rotor.

Chemical shifts are given in ppm. Single-bead FT-IR spectra (transmittance) were recorded on a Perkin-Elmer Spectrum One spectrometer with a beam-condensing accessory (BCA), using a diamond compression cell to flatten the bead. Mass spectra (MS) were carried out on a JEOL AX505W spectrometer. Electron impact (EI) was used as the method of ionization. Nitrogen microanalysis was carried out at North London University and chlorine microanalysis was carried out by the UCL Analytical Service.

Synthesis of the Supported Imines (3a–e). 4-Benzyl-oxybenzaldehyde polystyrene or Wang benzaldehyde resin **1** (100 mg, 2.81 mmol/g), amines **2a–e** (5 equiv) and dichloromethane (3 mL) were placed in a flask equipped with a flea (small magnetic stirrer bar) and condenser. The mixture was refluxed and stirred overnight. After cooling to room temperature, the beads were transferred to a sintered Alltech tube and washed with dichloromethane and HPLC-grade pentane. The beads **3a–e** were dried under vacuum at 50 °C for 2 h. For supported benzylimine **3a**: IR (beam condenser FT-IR) 3026, 2922, 2038, 1942, 1904, 1803, 1645 (s), 1601 (vs), 1577, 1514, 1453, 1422, 1380, 1224, 1167, 1109, 1028, 876, 835, 734 cm⁻¹. Gel-phase HR-MAS ¹H NMR (CDCl₃, 400 Hz) δ 8.28 (s, 1H, imine proton), 6.20–7.85 (br, PS + solvent + Ar–H), 4.71 (s, 2H, CH₂O), 3.63 (s, 2H, CH₂N) ppm.

General Procedure for the Regeneration of Wang Aldehyde Resin 1. Used scavenger resin (50 mg, 2.81 mmol/g) was placed in a flask open to air. An aqueous solution of hydrochloric acid (2 M, 0.25 mL), a 1:2 water/THF mixture (2.5 mL, 5 mL) and 10 drops of methanol were added. The flask was placed in the shaker at room temperature overnight. The beads were transferred to a sintered Alltech tube and washed using our standard protocol: methanol, acetone, water, methanol/acetone 50:50, ethyl acetate, dichlo-

Table 3. Yields of Secondary Amines **7a–j** Synthesized by the Procedure Shown in Scheme 3^d

Primary amines	Secondary amines synthesised	Yield
2a 	7a 	92%
2b 	7b 	83%
2c 	7c 	69%
2d 	7d 	89%
2e 	7e 	92%
2f 	7f 	90%
2g 	7g 	80% ^a
2h 	7h 	63% ^a
2a ^b 	7i 	78%
2a ^c 	7j 	73%

^a No need for scavenging of **2g** and **2h** due to their low bp. ^b ^cUse of octanal **8** and decanal **9** instead of benzaldehyde **4**. ^d ~98% purity obtained by ¹H NMR.

romethane, and HPLC-grade pentane. The Wang aldehyde beads were dried under vacuum at 50 °C; IR (beam condenser FT-IR): 3026, 2923, 2734 (w), 1683 (s), 1598 (s), 1510, 1453, 1314, 1214, 1110, 1004, 832 cm⁻¹. Gel-phase HR-MAS ¹H NMR (CDCl₃, 400 Hz): δ 9.84 (s, 1H, aldehyde proton), 7.78 (s br, 2H, Ar-H), 7.31 (s, solvent), 6.99 (s br, PS), 6.56 (s br, PS), 4.92 (s br, CH₂O), 1.60 (s br, PS), 1.35 (s br, PS). Anal. Found: C, 83.1; H, 5.9; N, 0 (gave a calculated yield of 100% N displacement).

Parallel Solution-Phase Synthesis of a Library of Secondary Amines (7a–j). Benzaldehyde **4**, octanal **8** or decanal **9** (1 equiv, 1 mmol), the amine **2a–h** (1.5 equiv, 1.5 mmol), and dry DCM (2.5 mL) were placed in a flask equipped with a magnetic stirrer bar. The mixture was stirred under nitrogen for 3 h at room temperature. Methanol (2.5 mL) and Amberlite IRA 400 borohydride resin **6** (2.5, 2.5 mmol/g, 1 g) were added to the reaction mixture. It was stirred at room temperature for 2 days. All of these reactions were carried out in parallel, using the carousel obtained from Radleys Discovery Technologies. After the filtration of the

resin, the NMR spectra of the crude mixtures of excess primary amine **2a–h** and secondary amine **7a–j** were recorded. An excess of Wang aldehyde resin **1** (~2.5 wrt. excess amine, 2.81 mmol/g, 450 mg) was added, as well as DCM (25 mL). The mixture was refluxed for 5 h. After cooling to room temperature, the beads were transferred to a sintered Alltech tube, and the solution was collected in a flask and then concentrated to give the pure secondary amine **7a–j**.

Dibenzylamine 7a. ¹H NMR (CDCl₃, 360 MHz) δ 7.33–7.16 (m, 10H, H_{ar} + solvent), 3.74 (s, 4H, 2 CH₂), 1.69 (s br, NH) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 53.57 (CH₂), 127.35 (CH), 128.56 (CH), 128.81 (CH), 140.74 (C) ppm; MS (EI) 197 ([M⁺], 100%).

N-(3-Chlorobenzyl)-benzylamine 7b. ¹H NMR (CDCl₃, 360 MHz) δ 7.36–7.13 (m, 9H, H_{ar} + solvent), 3.73 (s, 2H, CH₂), 3.72 (s, 2H, CH₂), 1.59 (s br, NH) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 53.64 (CH₂), 54.25 (CH₂), 126.28 (CH), 127.32 (CH), 127.85 (CH), 128.01 (CH), 128.17 (CH), 129.23 (CH), 129.30 (CH), 129.55 (CH), 130.72 (CH), 135.36 (C), 141.17 (C), 143.58 (C) ppm; MS (EI) 231 ([M⁺], 41%), 91 ([M⁺ - C₇H₇NCl], 100%).

N-Dodecylbenzylamine 7c. ¹H NMR (CDCl₃, 360 MHz) δ 7.30–7.15 (m, 5H, H_{ar} + solvent), 3.72 (s, 2H, Ph-CH₂-NH), 2.55 (t, 2H, CH₂-NH), 1.43 (m, 2H, CH₂-CH₃), 1.21–1.04 (m, 18H, 9 CH₂), 0.81 (t, 3H, CH₃) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 13.11 (CH₃), 21.67 (CH₂), 26.33 (CH₂), 28.33 (CH₂), 28.54 (CH₂), 28.59 (CH₂), 28.62 (CH₂), 28.64 (CH₂), 28.96 (CH₂), 30.90 (CH₂), 48.41 (CH₂), 52.97 (CH₂), 125.91 (CH), 127.17 (CH), 127.37 (CH), 139.21 (C) ppm; MS (EI) 288 ([M⁺], 43%), 120 ([M⁺ - C₁₂H₂₅], 100%).

N-(3-Methylbenzyl)-benzylamine 7d. ¹H NMR (CDCl₃, 360 MHz) δ 7.33–6.99 (m, 9H, H_{ar} + solvent), 3.74 (s, 2H, CH₂), 3.71 (s, 2H, CH₂), 2.28 (s, 3H, CH₃), 1.61 (s br, NH) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 21.83 (CH₃), 53.58 (CH₂), 53.64 (CH₂), 125.60 (CH), 127.34 (CH), 128.09 (CH), 128.57 (CH), 128.70 (CH), 128.81 (CH), 129.33 (CH), 138.43 (C), 140.65 (C), 140.75 (C) ppm; MS (EI) 211 ([M⁺], 8%), 106 ([M⁺ - C₇H₇N], 100%).

N-(4-Methoxybenzyl)-benzylamine 7e. ¹H NMR (CDCl₃, 360 MHz) δ 7.27–7.16 (m, 7H, H_{ar} + solvent), 6.80 (dd, 2H, H_{ar}), 3.73 (s, 5H, CH₂ + CH₃), 3.68 (s, 2H, CH₂), 1.87 (s br, NH) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 52.97 (CH₂), 53.48 (CH₂), 55.67 (CH₃), 114.18 (CH), 114.32 (CH), 127.33 (CH), 128.57 (CH), 128.68 (CH), 128.81 (CH), 129.38 (CH), 129.75 (CH), 132.89 (C), 140.81 (C), 159.01 (C) ppm; MS (EI) 227 ([M⁺], 77%), 91 ([M⁺ - C₈H₁₀ON], 100%).

N-Naphthalenemethylbenzylamine 7f. ¹H NMR (CDCl₃, 360 MHz) δ 8.01 (dd, 1H, H_{ar}), 7.76 (dd, 1H, H_{ar}), 7.69 (dd, 1H, H_{ar}), 7.45–7.16 (m, 9H, H_{ar} + solvent), 4.16 (s, 2H, CH₂), 3.84 (s, 2H, CH₂), 1.76 (s br, NH) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 51.28 (CH₂), 54.15 (CH₂), 124.16 (CH), 125.77 (CH), 126.01 (CH), 126.45 (CH), 126.50 (CH), 127.41 (CH), 128.17 (CH), 128.65 (CH), 128.83 (CH), 129.09 (CH), 132.25 (C), 134.29 (C), 136.28 (C), 140.76 (C) ppm; MS (EI) 247 ([M⁺], 75%), 141 ([M⁺ - C₇H₈N], 100%).

N-Cyclopentylbenzylamine 7g. ¹H NMR (CDCl₃, 360 MHz) δ 7.30–7.13 (m, 5H, H_{ar} + solvent), 3.69 (s, 2H, CH₂-NH), 3.03 (m, 1H, CH), 1.82–1.70 (m, 2H, CH₂), 1.68–1.55 (m, 2H, CH₂), 1.48–1.41 (m, 2H, CH₂), 1.39–

1.25 (m, 2H, CH₂) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 25.42 (CH₂), 34.49 (CH₂), 54.07 (CH₂), 60.44 (CH₂), 128.20 (CH), 129.49 (CH), 129.72 (CH), 142.06 (C) ppm; MS (EI) 175 ([M⁺], 36%), 91 ([M⁺ - C₅H₁₀N], 100%).

N-Butylbenzylamine 7h. ¹H NMR (CDCl₃, 360 MHz) δ 7.31–7.15 (m, 5H, H_{ar} + solvent), 3.72 (s, 2H, CH₂-NH), 2.56 (t, 2H, NH-CH₂-CH₂), 1.42 (m, 2H, CH₂), 1.28 (m, 2H, CH₂), 0.84 (t, 3H, CH₃) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 14.43 (CH₃), 20.89 (CH₂), 32.66 (CH₂), 49.61 (CH₂), 54.52 (CH₂), 127.28 (CH), 128.50 (CH), 128.76 (CH), 141.00 (C) ppm; MS (EI) 163 ([M⁺], 3%), 91 ([M⁺ - C₄H₁₀N], 100%).

N-Octylbenzylamine 7i. ¹H NMR (CDCl₃, 360 MHz) δ 7.31–7.14 (m, 5H, H_{ar} + solvent), 3.71 (s, 2H, CH₂-NH), 2.55 (t, 2H, NH-CH₂-CH₂), 1.42 (m, 2H, CH₂), 1.19 (m, 10H, 5CH₂), 0.80 (t, 3H, CH₃) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 14.52 (CH₃), 23.08 (CH₂), 27.42 (CH₂), 29.78 (CH₂), 30.10 (CH₂), 30.53 (CH₂), 32.20 (CH₂), 49.95 (CH₂), 54.22 (CH₂), 127.24 (CH), 128.42 (CH), 128.76 (CH), 141.53 (C) ppm; MS (EI) 219 ([M⁺], 8%), 120 ([M⁺ - C₇H₁₅], 100%).

N-Decylbenzylamine 7j. ¹H NMR (CDCl₃, 360 MHz) δ 7.30–7.16 (m, 5H, H_{ar} + solvent), 3.72 (s, 2H, CH₂-NH), 2.55 (t, 2H, NH-CH₂-CH₂), 1.42 (m, 2H, CH₂), 1.18 (m, 14H, 7CH₂), 0.81 (t, 3H, CH₃) ppm; ¹³C NMR (CDCl₃, 90 MHz) δ 14.55 (CH₃), 23.11 (CH₂), 26.26 (CH₂), 27.79 (CH₂), 29.76 (CH₂), 30.04 (CH₂), 30.23 (CH₂), 30.54 (CH₂), 33.25 (CH₂), 49.96 (CH₂), 54.23 (CH₂), 127.18 (CH), 128.60 (CH), 128.76 (CH), 140.98 (C) ppm; MS (EI) 247 ([M⁺], 6%), 120 ([M⁺ - C₉H₁₉N], 100%).

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Supporting Information Available. ¹H NMR spectra of secondary amines **7a–7j** and gel-phase HR-MAS ¹H NMR and single-bead FT-IR spectra of the commercial, recycled Wang aldehyde resin **1** and the supported benzylimine **3a**.

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