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Solid Phase Synthesis of Tertiary Amines on Amide REM Resins: Grignard and Metal Hydride Compatible Resins

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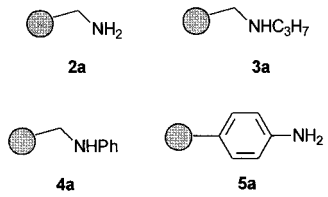
Four new amide REM resins (AM REM **2**−**5**) are described, and their use is illustrated for the synthesis of tertiary amines **6**−**9** and **13**−**16**. Amide REM resins **4** and **5**, which have a phenyl ring attached to the amide nitrogen, are found to give superior product yields and purities, and the resins are stable to a wider range of reagents and conditions compared to REM resin **1**.

The solid phase synthesis of small quantities of individual compounds and combinatorial libraries of pharmaceutically interesting molecules is accelerating the process of drug discovery.[1] Advances in molecular biology leading to the isolation of drug receptor targets has facilitated the screening of many therapeutic compounds which can now be routinely screened using 1 mg of sample or less. Traceless linkers[2−4] for tethering compounds to polymer supports are of interest particularly for the discovery of drugs active in the central nervous system because polar functional groups such as alcohols and carboxylic acids can restrict penetration of the blood brain barrier. The REM resin **1**, based on an acrylic ester Michael acceptor, is a traceless linker useful for the synthesis of tertiary amine libraries via initial Michael addition of the amine, quaternization, followed by Hofmann elimination.[5,6] (Scheme 1). Strategies for the synthesis of libraries of tertiary amines are of considerable interest to the medicinal chemist, since over a quarter of all registered drugs contain this functionality.[6]

The REM resin **1** is useful for the synthesis of tertiary amine libraries, but the ester linkage limits the choice of reactions that can be performed on solid phase. For example, the ester linkage is not compatible with Grignard reagents, metal hydride reducing agents, or transesterification conditions. It was therefore of interest to investigate the corresponding amide REM resins (AM REM) that were expected to show enhanced chemical stability and compatibility with a wider choice of reagents. In this context we cite previously published results showing that the ester group of REM resin can be replaced with a sulfone group to confer enhanced stability, e.g., to Grignard and metal hydride reducing agents while still demonstrating the characteristic reaction sequence of Michael addition, quaternization, and Hofmann elimination.[7] The sulfone REM resin does, however, require a multistep synthesis for its preparation, making it less readily available.

Amide REM resins **2**, **3**, **4**, and **5** were conveniently prepared by the treatment of aminomethyl **2a**, *N*-(*n*-propyl)-aminomethyl **3a**, *N*-phenylaminomethyl **4a,** and aminopolystyrene **5a** resins, respectively, with acryloyl chloride, in the



2a **3a** **4a** **5a**

presence of diisopropylethylamine (DIPEA), in an analogous manner to the preparation of REM resin **1**. *N*-(*n*-Propyl)-aminomethyl and *N*-phenylaminomethyl functionalized polystyrene resins were prepared by heating chloromethyl polystyrene resin with *n*-propylamine and aniline, respectively. Aminopolystyrene was prepared by reduction of nitrated polystyrene with stannous chloride. Michael addition of the amines listed in Table 1 with resins **2** and **3** was accomplished by heating with 10 equiv of the amine in DMF at 60 °C for 18 h (Scheme 1). No addition occurred at room temperature. However, the amines added smoothly to resins **4** and **5** under ambient conditions in a manner analogous to the addition of amines to REM resin. The IR spectra of the AM REM resins show an amide stretch at 1650−1660 cm^{-1}. After Michael addition of an amine, the resultant resins show a downward shift of the amide carbonyl group of about 20 cm^{-1} to 1640 cm^{-1}, owing to the loss of conjugation to the alkene. This contrasts with the ester analogue in which deconjugation leads to an upfield shift of the carbonyl group stretch.[6,8]

Quaternization of all four resins was accomplished under ambient conditions by treatment with *p*-nitrobenzylbromide for 18 h. The quaternized resins showed little change to the amide stretch but have a characteristic stretch at 1490 cm^{-1} owing to the nitro group which assists monitoring both the quaternization reaction and the subsequent Hofmann cleavage from the resin. Tertiary amines **6**, **7**, **8**, and **9** were cleaved from the resin by treatment with DIPEA at room temperature in dichloromethane for 18 h (Table 1). Superior yields and high purity products were obtained from the *N*-arylamino

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Scheme 1

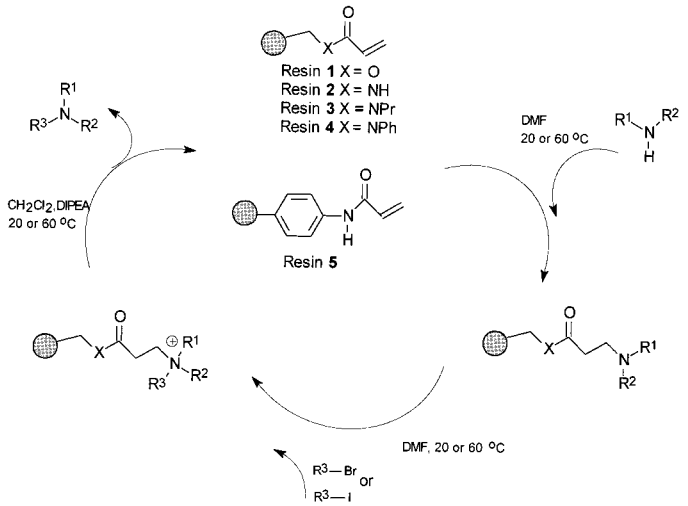
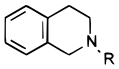
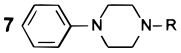
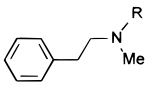
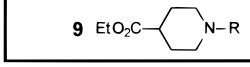


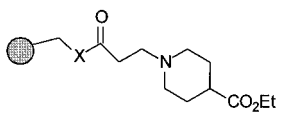
Table 1. Yields of Tertiary Amines Obtained from Amide REM Resins [% (mg)]

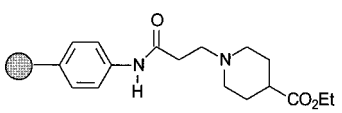
Compound[a]	Resin **2**[b]	Resin **2**[c]	Resin **3**	Resin **4**	Resin **5**[d]
6 	23 (7)	32 (16)	35 (17)	48 (24)	40 (16)
7 	10 (4)	15 (8)	——	30 (17)	34 (15)
8 	12 (4)	17 (6)	——	29 (10)	47 (13)
9 	10 (3)	22 (12)	——	31 (16)	28 (12)

[a] All compounds gave satisfactory 250 or 400 MHz ^{1}H NMR spectra and correct *m*/*z* molecular ions by mass spectrometry, R = *p*-nitrobenzylbromide. Typically 150 mg of resin gave 10−20 mg of product. The products were purified by filtration through an isolute silica column. Product purity was shown to be >98% by GC-MS. [b] Cleavage at 20 °C. [c] Cleavage at 60 °C. [d] Capacity of 1 mmol g^{-1} determined by the Fmoc quantitation method. For resins **2**, **3**, and **4**, the yields for four steps are based on the manufacturers quoted resin capacity.

resins **4** (29−48%) and **5** (28−47%), compared to the yield and purity of products obtained from resins **2** (10−32%) and **3** (35%). IR analysis of resins **4** and **5** after Hofmann elimination showed no characteristic stretch for the nitro group, indicating that all of the quaternized product had been eliminated. However, the recovered resins **2** and **3** still showed a stretch owing to the nitro groups, indicating that the reaction had not gone to completion. Higher yields of products for resin **2** were obtained by heating the resin with DIPEA at 60 °C in THF for 18 h. Amide REM resins **2** and **3** are poorer Michael acceptors than REM resin **1**, probably owing to poorer stabilization of the enolate which is formed upon addition of the amine. Likewise slower Hofmann elimination of the quaternized amine can be attributed to the lower acidity of the methylene protons α to the amide carbonyl group. These characteristic properties might have been desirable, giving a resin which would be compatible with less reactive alkylating reagents (which require heating to effect quaternization) without excessive premature cleavage from the resin. However, the inferior yields and lower purity of products, as evidenced by NMR spectroscopy, render resins **2** and **3** of less practical use. In comparison, resins **4** and **5** are better Michael acceptors. Conjugation of the amide nitrogen to the aryl ring was expected to enhance the Michael acceptor properties. Likewise, the elimination reaction proceeds smoothly, probably owing to the enhanced acidity of the hydrogens α to the carbonyl group compared to resins **2** and **3**.

To investigate whether AM REM resins **2**, **4**, and **5** were more chemically stable than REM resin **1**, which would allow a more diverse range of reagents and conditions to be employed for library synthesis, a comparison of the chemical stability of the ethyl isonipecotate derivatized resins **10**, **11**, and **12** was made (Table 2). Reactions and conditions were


10 X = NH
11 X = NPh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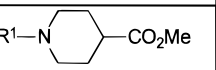
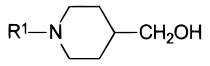
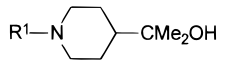
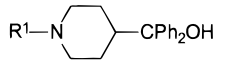
selected that are of interest for library synthesis such as *trans*-esterification, borohydride reduction, and treatment with Grignard reagents.

Table 2. Stability Studies on Ethyl Isonipecotate Derivatized Amide REM Resins **10**−**12**[a]

Reagents and conditions	R^1	Products	Resin **10**	Resin **11**	Resin **12**
NaOMe (0.1 eq) MeOH-THF (1:4) Δ 18h	benzyl	 **13**	16 (8)	32 (23)	29 (17)
$LiBH_4$ (10 eq) MeOH-THF (1:1) Δ18 h	benzyl	 **14**	6 (3)	23 (15)	29 (15)
MeMgBr (5 eq) THF 0 ^{0}C to rt	Me	 **15**	10 (3)	20 (9)	45 (18)
PhMgBr (5 eq) THF 0 ^{0}C to rt	Me	 **16**	12 (7)	19 (17)	39 (27)

[a] After treatment with the reagents shown, the resins were quaternized and cleaved with DIPEA to give products **13**−**16**. No products were obtained from resin **1** under these conditions [% (mg)].

The conditions shown in Table 2 are incompatible with the ester linker **1**. For example, treatment of REM resin **1** with NaOMe (0.1 equiv) in MeOH−THF (1:4) solution under reflux causes complete cleavage of the ester group linker as evidenced by the absence of an ester IR stretch in the recovered polymer. This result was not unexpected because it has been demonstrated that other resin bound esters can be cleaved under comparable conditions.[9,10] Treatment of REM resin **1** with 95% TFA at 80 °C for 18 h, or $LiBH_4$, or MeMgBr or PhMgBr caused cleavage of the linker as shown by the complete absence of an ester IR stretch. However, the AM REM resins **10**, **11,** and **12**, after treatment with NaOMe under identical conditions, showed no loss of the amide bands. After quaternization with benzylbromide and cleavage, the expected *trans*-esterified methyl ester product **13** was obtained in 16, 32, and 29% yield, respectively. The AM REM resins **10** and **12** have improved acid stability compared to REM resin **1** because, after treatment with 95% TFA at 80 °C for 18 h, no loss of amide or ester bands was apparent in the IR spectra. However, AM REM resin **11** was not stable under these conditions and decomposed. The AM REM resins **10**, **11**, and **12** showed loss of the ester group after treatment with $LiBH_4$ but retention of the amide band at 1654 cm^{-1}. Quaternization with benzyl bromide and cleavage gave the expected primary alcohol substituted piperidine **14**.

Treatment of the AM REM resins **10**, **11**, or **12** with either MeMgBr or PhMgBr caused the disappearance of the ester IR stretch but retention of the amide stretch, indicating the stability of the linkers to Grignard reagents. Quaternization with methyl iodide followed by Hofmann elimination gave the desired tertiary alcohol products **15** and **16** (Table 2). The yield of Grignard addition products from the tertiary arylamine resin **11** are low (19−32%), probably because the Grignard reagent slowly attacks the amide linker and causes cleavage. As expected, the amide bond is more robust and less electrophilic than the ester group of **1** under these conditions. The yields of Grignard addition products from resin **12**, which contains a secondary amide group, are higher (29−45%) probably because the Grignard reagent deprotonates the amide group which is then inert to further nucleophilic attack.

In summary, the synthesis of the amide resins **2**−**5** are described. Resins **4** and **5** are shown to be suitable for the solid phase synthesis of tertiary amines in good purity from secondary amine starting materials. In comparison with the previously reported ester analogue **1**, the amide resins **4** and **5** exhibit increased stability to acidic, to Grignard, and to metal hydride reducing reagents. These resins are currently under evaluation for the automated preparation of chemical drug libraries.

Experimental Section

Melting point determinations were carried out using a Kofler hot-stage microscope and are uncorrected. IR spectra were obtained as KBr disks on an ATI Mattson Genesis series or a Perkin-Elmer 16PC FTIR instrument. ^{1}H and ^{13}C solution NMR spectra were recorded on either a Bruker AC 250 MHz or a Varian Unity 400 MHz instrument using tetramethylsilane ($\delta = 0.0$) as the internal standard. Chemical shifts are given in ppm relative to $SiMe_4$. Coupling constants in ^{1}H NMR spectra are given in hertz, and assignments in ^{13}C NMR spectra are made on the basis of correlated experiments. Low resolution mass spectra were obtained on a Finnigan Masslab Navigator running in CI or EI mode. GC-MS samples were run on a Hewlett-Packard GCD system with an electron ionization detector. Hydroxymethyl polystyrene resin, aminomethyl polystyrene resin, chloromethyl polystyrene resin, and nitropolystyrene resin were purchased from Bachem.

General Procedure for Resins 1−5: REM Resin 1.[6] Hydroxymethyl polystyrene resin (1 g, 0.85 mmol/g) was added to a 10 mL Biorad polypropylene tube. The resin was swollen in DCM (7 mL) and then treated with DIPEA (1.49 mL, 8.5 mmol) and acryloyl chloride (0.69 mL, 8.5 mmol). The reaction vessel was then placed on a Stuart Scientific SB1 tube rotator and agitated for 4 h at 20 °C. The tube was then placed on a VacMaster sample processing station or a Buchner flask, drained, washed with DCM (3 × 3 mL)

and MeOH (3 × 3 mL), and dried under vacuum (1 g). ν_{max}-(KBr)/cm^{-1} 1718 (CO).

Amide REM Resin 2. Starting from aminomethyl polystyrene resin **2a** (1 g, 0.8 mmol/g), resin **2** (1 g) was obtained. ν_{max}(KBr)/cm^{-1} 1675−1650 br (CO).

***N*-(*n*-Propyl)aminomethyl Polystyrene Resin 3a.** Chloromethyl polystyrene resin (0.75 g, 1.25 mmol/g) was suspended in neat *n*-propylamine (7 mL, 85 mmol). The reaction mixture was heated in a sealed PTFE stainless steel bomb for 4 days and agitated periodically. The resin was then drained, washed with DMF and DCM followed by MeOH, and dried under vacuum (0.75 g). Found Cl, <0.3; N, 2.1. Calcd Cl, 0; N, 2.4%.

***N*-(*n*-Propyl)aminomethyl REM Resin 3.** Starting from *N*-propylaminomethyl polystyrene resin **3a** (0.25 g, 1.25 mmol/g), resin **3** (0.25 g) was obtained. A chloranil test for secondary amines was negative, indicating that all the secondary amine sites had reacted. ν_{max}(KBr)/cm^{-1} 1646s (CO).

***N*-Phenylaminomethyl Resin 4a.** Chloromethyl polystyrene resin (1 g, 1.25 mmol/g) was suspended in neat aniline (10 mL, 110 mmol). The reaction mixture was heated in a sealed PTFE stainless steel bomb for 4 days and agitated periodically. The resin was then drained, washed with DMF and DCM followed by MeOH, and dried under vacuum (1 g). Found Cl, <0.3; N, 0.8. Calcd Cl, 0; N, 0.8%.

***N*-Phenylaminomethyl REM Resin 4.** Starting from *N*-phenylaminomethyl polystyrene resin **4a** (250 mg, 1.25 mmol/g), resin **4** (250 mg) was obtained. ν_{max}(KBr)/cm^{-1} 1654 (CO).

Aminopolystyrene Resin 5a. Nitropolystyrene (250 mg, 1 mmol/g) was swollen in a solution of $SnCl_2 \cdot 2H_2O$ in DMF [2.0 M] (4 mL, 8 mmol). The suspension was stirred slowly under nitrogen overnight then drained. It was washed with DMF−H_2O (50:50) then with DMF, DCM, and MeOH and then dried under vacuum at 45 °C (250 mg). Found N, 2.9. Calcd N, 2.8%. The IR spectrum showed no evidence of nitro groups.

Aminopolystyrene REM Resin 5. Starting from aminopolystyrene resin **5a** (250 mg, 1 mmol/g), resin **5** (250 mg) was obtained. ν_{max}(KBr)/cm^{-1} 1637 (CO).

General Procedures for Solid Phase Synthesis. Michael Addition. A total of 150 mg of resin (**2**, **3**, **4**, or **5**) was swollen in DMF (4 mL) and treated with an amine (10 equiv). For resins **3**, **4**, and **5**, the mixture was agitated in a polypropylene tube at room temperature. Resin **2** was heated at 60 °C in a quickfit test tube for 18 h. The resin was drained, washed with DMF, DCM, then MeOH, and dried under vacuum.

Quaternization. A total of 150 mg of resin was swollen in DMF (4 mL) and then treated with *p*-nitrobenzylbromide (10 equiv). The mixture was agitated in a polypropylene tube on a tube-rotator at room temperature for 18 h. The resin was drained, washed with DMF, DCM, then MeOH, and dried under vacuum.

Cleavage from Resin. A total of 150 mg of resin was swollen in a solution of DIPEA (2 equiv) in DCM (REM resin) or THF (AM REM resin) and agitated at room temperature for 18 h. The resin was then drained and washed with DCM, and the filtrate was concentrated under reduced pressure. The residue in DCM (2 mL) was washed with K_2CO_3 (1 mL, 20% aqueous solution), dried over K_2CO_3 (0.3 g), filtered, and evaporated. Trace amounts of "plasticizer" and DIPEA were removed using an isolute-XL solid phase extraction column containing 500 mg of silica. The crude material was loaded in DCM (0.5 mL) and eluted with heptane (3 mL) then ethyl acetate (3 mL) to give the final product.

Amide REM Resin Products. The yield of product from each resin is given in Table 1.

2-(4-Nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline 6.[11] ^{1}H NMR ($CDCl_3$) δ 8.16 (d, J = 8.55 Hz, 2H), 7.55 (d, J = 8.89 Hz, 2H), 7.09 (m, ArH, 4H), 3.74 (s, ArCH_2N, 2H), 3.61 (s, NCH_2-ring, 2H), 2.89 (t, J = 5.81 Hz, NCH_2CH_2, 2H), 2.73 (t, J = 5.98 Hz, NCH_2CH_2, 2H). ^{13}C NMR ($CDCl_3$) δ 148.3, 147.6 (q), 135.4 (q), 135.1 (q), 130.4, 129.8, 127.6, 127.4, 126.8, 124.6, 62.9, 57.2, 51.9, 30.2. GC-MS *m*/*z* 268 (M^+, 31%), 267 (66%), 104 (100%). GC ramp 15°/min, 60−300 °C. Purity = 99%.

1-(4-Nitrobenzyl)-4-phenylpiperazine 7. ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 8.85 Hz, ArH, C*H*CNO_2C*H*, 2H) 7.54 (d, J = 8.85 Hz, C*H*CCH_2C*H*, 2H), 7.21−7.17 (m, ArH, 2H), 6.88 (d, J = 8.21 Hz, ArH, 2H), 6.79 (t, J = 7.35, ArH, 1H), 3.65 (s, ArCH_2N, 2H), 3.21 (t, J = 5.04 Hz, CH_2NCH_2, 4H), 2.62 (t, J = 5.04 Hz, CH_2NCH_2, 4H).^{13}C NMR ($CDCl_3$) δ 152.3 (q), 148.3 (q), 147.2 (q), 129.5, 129.2, 123.6, 119.9, 116.1, 62.2, 53.3, 49.2. GC-MS *m*/*z* 297 (M^+, 45%), 106 (100%). GC ramp 25°/min, 100−300 °C. Purity >99%.

***N*,*N*,*N*-Methyl(4-nitrobenzyl)phenethylamine 8.** ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 8.62 Hz, ArH, C*H*NO_2C*H*, 2H), 7.38 (d, J = 8.89 Hz, ArH, C*H*CCH_2C*H*, 2H), 7.27−7.22 (m, ArH, 2H), 7.19−7.12 (m, ArH, 2H), 3.59 (s, NCH_2Ar, 2H), 2.78 (t, J = 7.53 Hz, NCH_2CH_2Ar, 2H), 2.62 (t, J = 7.53 Hz, NCH_2CH_2Ar, 2H), 2.26 (s, NCH_3, 3H). ^{13}C NMR ($CDCl_3$) δ 148.4, 148.1, 130.3, 129.8, 129.4, 127.1, 124.5, 62.6, 60.2, 43.3, 35.0. GC-MS *m*/*z* 179 (100%). GC ramp 25°/min, 60−300 °C. Purity >99%.

1-(4-Nitrobenzyl)isonipecotic Acid Ethyl Ester 9. ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 8.90 Hz, ArH, C*H*CNO_2C*H*, 2H), 7.46 (d, J = 8.20 Hz, ArH, C*H*CCH_2C*H*, 2H), 4.10 (q, J = 7.18 Hz, CH_2CH_3, 2H), 3.53 (s, ArCH_2N, 2H), 2.79−2.75 (m, 2H of NCH_2CH_2), 2.29−2.22 (m, C*H*CO, 1H), 2.04 (dt, J = 2.40, 11.30 Hz, 2H of NCH_2CH_2), 1.87−1.83 (m, 2H of NCH_2CH_2), 1.75 (dt, J = 3.80, 12.10 Hz, 2H of NCH_2CH_2), 1.21 (s, CH_3, 3H). ^{13}C NMR ($CDCl_3$) δ 176.1, 147.8 (q), 130.3, 125.8 (q), 124.5, 63.4, 61.4, 54.1, 42.0, 29.3, 15.3. GC-MS *m*/*z* 292 (M^+, 6%), 156 (100%). GC ramp 25°/min, 100−300 °C. Purity = 99.7%.

General Procedure for Stability Studies on the Ethyl Isonipecotate Derivatized Resins 10−12. The yield of product from each resin is given in Table 2.

***N*-Benzylisonipecotate Methyl Ester 13.**[12] The derivatized resin **10**, **11**, or **12** (250 mg) was swollen in a solution of MeOH (1 mL) and THF (4 mL) in a quickfit test tube. After addition of sodium methoxide (28 μL, 0.028 mmol, 1.0 M solution in MeOH), the resulting suspension was stirred and heated under reflux overnight. When cooled, the resin was drained and washed with DCM (3 × 3 mL) then

MeOH (2 × 3 mL), and dried under vacuum at 45 °C. The resin was quaternized with benzylbromide and cleaved with DIPEA by standard procedures to give compound **13**. ^{1}H NMR ($CDCl_3$) δ 7.31−7.23 (m, ArH, 5H), 3.66 (s, OCH_3, 3H), 3.48 (s, ArCH_2N, 2H), 2.86−2.81 (m, 2H of NCH_2CH_2), 2.33−2.22 (m, C*H*CO, 1H), 2.05−1.96 (m, 2H of NCH_2CH_2), 1.88−1.71 (m, 4H of NCH_2CH_2). ^{13}C NMR ($CDCl_3$) δ 176.3, 138.3 (q), 130.1, 129.2, 128.0, 64.3, 61.3, 53.9, 52.6, 30.7, 29.3, 15.3. GC-MS *m*/*z* 233 (M^+ 9%), 91 (100%). GC ramp 15°/min, 40−250 °C. Purity > 99%.

1-Benzyl-4-(1-hydroxymethyl)piperidine 14.[13] The derivatized resin **10**, **11**, or **12** (250 mg) was swollen in a solution of MeOH (0.11 mL, 2.83 mmol) in THF (4 mL). Lithium borohydride in THF (2M, 1.4 mL, 2.83 mmol) was added dropwise under nitrogen, and the resulting suspension stirred and heated under reflux overnight. The resin was drained and washed with DMF (3 × 3 mL), DCM (3 × 3 mL), and MeOH (2 × 3 mL) and dried under vacuum at 45 °C. The resin was quaternized with benzylbromide and cleaved with DIPEA by standard procedures to give compound **14**. ^{1}H NMR ($CDCl_3$) δ 7.48−7.20 (m, ArH, 5H), 3.50 (s, ArCH_2N, 2H), 3.46 (d, J = 6.50 Hz, CH_2OH, 2H), 2.92−2.90 (m, 2H), 2.00−1.94 (m, 2H of NCH_2CH_2), 1.70−1.67 (m, 2H of NCH_2CH_2), 1.54−1.10 (m, 2H of NCH_2CH_2 and C*H*CH_2, 3H).

2-(1-Methylpiperidin-4-yl)propan-2-ol 15.[14] The derivatized resin **10**, **11**, or **12** (250 mg) was swollen in THF (4 mL). MeMgBr (0.47 mL, 1.4 mmol, 3 M solution in ether) was added dropwise under nitrogen at 0 °C. The suspension was allowed to reach room temperature and then stirred overnight. The reaction was quenched with ammonium chloride (0.5 mL, saturated aqueous solution) and the resin drained. The resin was then washed with DMF (3 × 3 mL), DCM (3 × 3 mL), and then MeOH (2 × 3 mL) and dried under vacuum at 45 °C. The resin was quaternized with methyl iodide and cleaved with DIPEA by standard procedures to give compound **15**. ^{1}H NMR ($CDCl_3$) δ 3.64 (br, OH, 1H), 3.05−2.99 (m, 2H of CH_2NCH_2), 2.32 (s, NCH_3, 3H), 2.05−1.12 (m, 2H of CH_2NCH_2 and 5H of CH_2-$CHCH_2$), 1.24 (s, CH_3, 6H). GC ramp 25°/min, 60−300 °C. Purity = 95%. GC-MS *m*/*z* 157 (M^+, 24%), 98 (100%).

1-Methyl-(4-piperidyl)diphenylmethanol 16.[15,16] ^{1}H NMR ($CDCl_3$) δ 7.48−7.43 (m, ArH, 4H), 7.27−7.22 (m, ArH, 4H), 7.16−7.12 (m, ArH, 3H), 2.84 (m, 2H), 2.37 (m, 1H), 2.21 (s, NCH_3, 3H), 1.95−1.90 (m, 2H). 1.67−1.46 (m, 4H).^{13}C NMR ($CDCl_3$) δ 146.9, 129.2, 127.6, 126.8, 80.5, 57.2, 47.3, 44.6, 27.5. GC-MS *m*/*z* 281 (M^+, 18%). GC ramp 15°/min 40−250 °C. Purity = 75%.

TFA/H_2O Hydrolysis. A suspension of the resins **10**, **11**, or **12** (0.25 g) in 95% TFA/5% H_2O solution (4 mL) was heated under reflux for 18 h. When cooled, the resin was drained and washed with DCM (3 × 3 mL), 20% DIPEA/DCM (3 × 3 mL), and MeOH (2 × 3 mL) and dried under vacuum at 45 °C. The resin was then analyzed by IR spectroscopy.

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