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Solid-phase synthesis of hydroxypiperazine derivatives using phenethylamine linker by oxidation–Cope elimination

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Abstract—A general method is reported for the parallel solid-phase synthesis of hydroxypiperazine derivatives based on the oxidation–Cope elimination of polymer-bound phenethylamine linker with *m*-CPBA. The key intermediate of phenethylamine *N*-oxide resins was separable on solid-phase for subsequent β-elimination, from which the desired hydroxypiperazine products could be obtained in high purities and yields without any significant contamination at 90 °C for 2 h. The utility of the methodology for solid-phase synthesis of general hydroxylamines was also investigated using the same linker. The progress of reactions could be monitored on polymer bound intermediates by ATR-FTIR spectroscopy on single bead. The desired products were obtained in good six-step overall yields upon cleavage from the resins and were characterized by LC/MS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

1. Introduction

Solid-phase synthesis has emerged as a powerful technique in generating combinatorial libraries of small organic molecules useful for drug discovery.[1] Hydroxylamines provide scaffold, on which pharmacophore can be arranged to yield potent and selective drugs.[2] Therefore, many hydroxylamine derivatives have been reported, since a variety of hydroxylamine derivatives possess drug-like characteristics and exhibit biological activities similar to their corresponding amines as a bioisostere.[3] Especially, hydroxypiperazine, a kind of hydroxylamine, showed good antimicrobial activity.[4] However, hydroxylamine derivatives have scarcely been reported in the research field of drug-like library construction by solid-phase synthesis, as compared with their tertiary amine analogues.[5] As only example, Kurth reported about solid-phase synthesis of hydroxylamines using REM (polymer-bound benzyl arylate) resin by β-elimination strategy, which is a good example of traceless linker.[6] The β-elimination strategy as a traceless cleavage method is very useful for construction of tertiary amine libraries and *N*,*N*-disubstituted hydroxylamines derivatives using REM resin. However, the synthesis of hydroxylamines on REM resin was accomplished through premature elimination reaction during the oxidation procedure with *meta*-chloroperbenzoic acid (*m*-CPBA) to generate *N*-oxide intermediate at room temperature. As the results of in situ β-elimination of *N*-oxide intermediate, were contaminated with *meta*-chlorobenzoic acid (*m*-CBA) and excess *m*-CPBA. Consequently further purification steps such as extraction and column chromatography were needed to obtain pure hydroxylamines after cleavage from the REM resins. To solve this problem, therefore, we tried to find more stable linker for the solid-phase synthesis of hydroxylamine derivatives under *m*-CPBA oxidation condition at room temperature because we needed to develop a facile and rapid solid-phase approach for construction of drug-like hydroxypiperazine derivatives as a part of our research on drug discovery program.[7]

Herein, we would like to report a solid-phase synthesis of hydroxypiperazine derivatives using phenethylamine linker. The polymer bound phenethylamine *N*-oxide, produced by oxidation reaction with *m*-CPBA on the phenethylamine resin, served as key intermediate. And further β-elimination reaction on this phenethylamine *N*-oxide resin under thermal condition, generated the desired various hydroxypiperazine derivatives with high purities. And we also attempted to develop the methodology of solid-phase synthesis of general hydroxylamine derivatives using the same linker.

Keywords: Solid-phase; Hydroxypiperazine; Phenethylamine linker; Oxidation–Cope.
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Our initial studies were concentrated to the design of thermally more stable linker than REM resin under *m*-CPBA oxidation condition. To this end, we decided to examine *N*-oxide formation from polymer bound phenethylamine under the same condition in hope that Cope elimination reaction would not occur at room temperature but take place at a higher temperature. The pK_a value of β-proton in REM resin **2** is about 25. On the other hand, the value of phenethylamine resin **1** is about 40, much higher than that of REM resin as shown in Figure 1.[8] That is to say, the phenethylamine *N*-oxide linker was expected to need much higher energy for β-elimination reaction, compared with REM resin. Fortunately we confirmed that the results of the experiment coincided with our expectation.

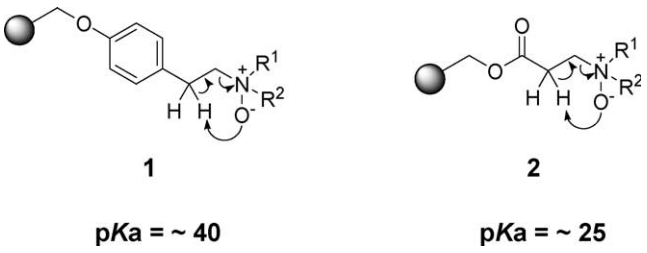


Figure 1. Comparision of stability toward β-elimination reaction.

As the first step, we selected Merrifield resin **3** as a polymer support for the preparation of phenethylamine, since the chloride group in the Merrifield resin **3** is suitable for the introduction of 4-hydroxyphenethyl alcohol through ether formation under the condition of sodium methoxide in *N*,*N*-dimethylacetamide (DMA) at 50 °C. The hydroxyl group of phenethyl alcohol resin **4** was changed to bromide in the presence of triphenylphosphine in carbon tetrabromide to give phenethylbromide resin, the formation, of which was confirmed by the disappearance of the hydroxyl group stretching frequency at 3350 cm^{-1} (Fig. 2, A and B). The phenethylbromide resin **5** was transformed to the polymer bound piperazine **6** by a nucleophilic substitution reaction with piperazine in the presence of triethylamine as a base in *N*,*N*-dimethylformamide (DMF) at 50 °C. To perform further derivatization on the piperazine resin **6**, we examined the reaction with various electrophiles, such as acid halides and sulfonyl halides, to introduce amide and sulfonamide functional groups on the nitrogen atom (N^a) of piperazine resin **6**. The completion of the reaction was confirmed by a negative chloranil test[9] with the substituted (N^a) phenethylpiperazine resins **7**. And we could successfully obtain the desired various phenethylpiperazine *N*-oxide resins **8** from the substituted (N^a) phenethylpiperazine resins **7** by oxidation reaction with *m*-CPBA at room temperature. Finally, to confirm formation of the final products **9**, we performed the β-elimination reaction of the polymer bound *N*-oxide resins **8** in toluene at 90 °C for 2 h, and we could obtain the desired various hydroxypiperazine derivatives in high purities and yields without any significant impurities from the key intermediate *N*-oxide resins **8**. The key intermediates, the phenethylpiperazine *N*-oxide resins **8**, were prepared in a six-step procedure starting from the Merrifield resin **3**, as shown in Scheme 1. As listed in Table 1, variously substituted (N^a) hydroxypiperazine derivatives were successfully synthesized in high six-step overall yields from Merrifield resin **3** with high purities by oxidation–Cope elimination of the phenethylpiperazine *N*-oxide resin **8**. The progress of these reactions could be monitored by ATR-FTIR spectroscopy on single beads (Fig. 2, C–E).

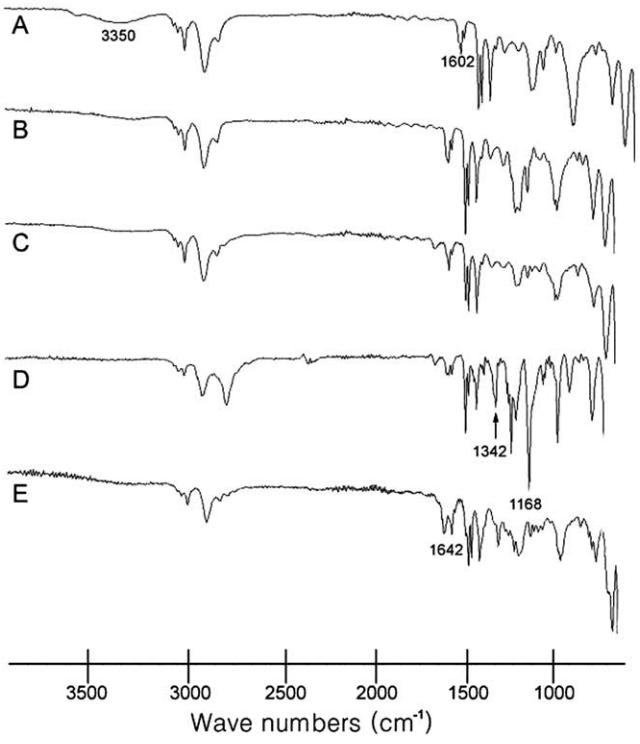
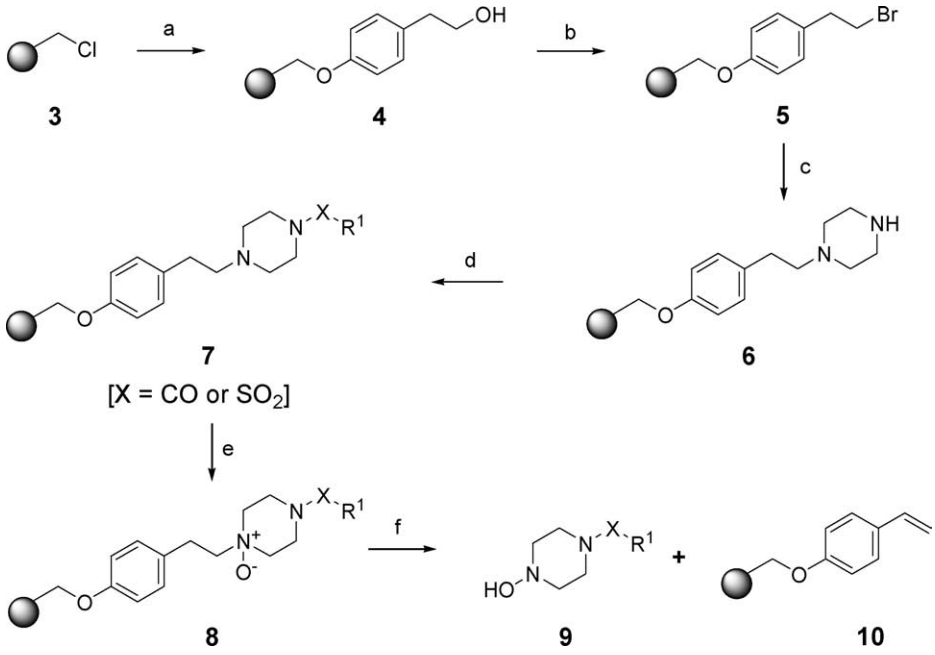


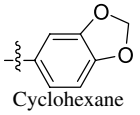
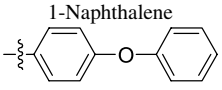
Figure 2. ATR-FTIR spectra on single bead of resin **4** (A), **5** (B), **6** (C), **7c** (D) and **7h** (E).

Further, we attempted to develop the methodology for solid-phase synthesis of general hydroxylamine derivatives using the same linker. The phenethylbromide resin **5** was transformed to the polymer bound secondary amines **11** by a nucelophilic substitution reaction with various primary aliphatic and aromatic amines in the presence of triethylamine as base in DMF at 50 °C. The secondary phenethylamine resins **11** were changed to the polymer bound tertiary amines **12** by reductive alkylation with various aldehyde and boran–pyridine complex. The completion of this step was also checked by a negative chloranil test. With the tertiary phenethylamine resins **12**, we examined the oxidation reaction with *m*-CPBA to obtain the desired phenethylamine *N*-oxide resins **13**. And we could successfully obtain the desired phenethylamine *N*-oxide resins **13** as the key intermediate. Finally, to confirm formation of the final products **14**, we carried out thermal reaction with the polymer bound *N*-oxide resins **13** for β-elimination reaction in toluene at 90 °C for 2 h, as shown in Scheme 2. By using this sequence of reactions, we could obtain the desired hydroxylamine derivatives **14** in relatively good six-step overall yields and purities from Merrifield resin **3**. However, the yields of most of the desired hydroxylamine derivatives **14** by this multistep synthetic method on solid phase were lower than those of hydroxypiperazines **9**. The reason was assumed that substituted hydroxyamines **14** were partly oxidized to the corresponding nitrone compounds **15** under the standard condition. In fact, we could identify



Scheme 1. Reagents and conditions: (a) 4-hydroxyphenethyl alcohol, NaOMe, DMA, 50 °C, 18 h; (b) CBr_4, PPh_3, CH_2Cl_2, rt, 12 h; (c) piperazine, TEA, DMF, 50 °C, 18 h; (d) acid halide or sulfonyl halide, TEA, DMF, rt, 18 h; (e) *m*-CPBA, CH_2Cl_2, rt, 2 h; (f) toluene, 90 °C, 2 h.

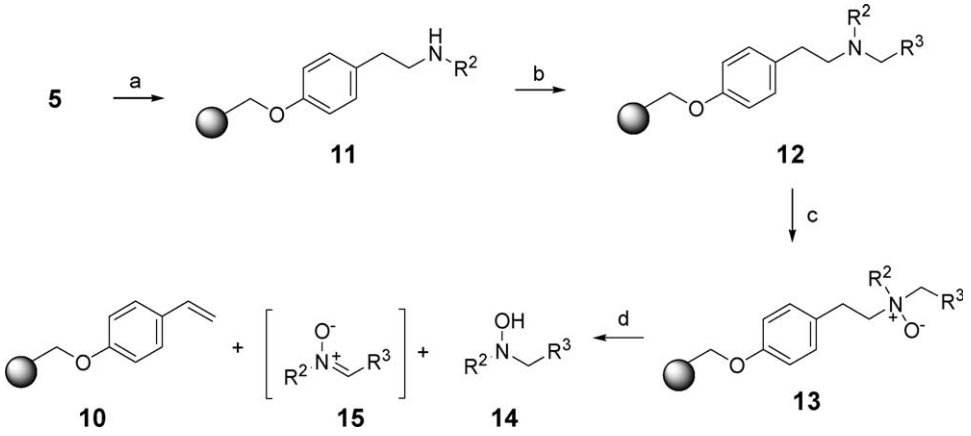
Table 1

Product	X	R^1	Purity[a] (%)	Yield[b] (%)	Product	X	R^1	Purity (%)	Yield (%)
9a	–SO_2–	4-MeO-Ph	99	50	**9g**	–CO–	4-MeO-Ph	98	39
9b	–SO_2–	4-NO_2-Ph	94	57	**9h**	–CO–	4-NO_2-Ph	99	49
9c	–SO_2–	4-Cl-Ph	97	45	**9i**	–CO–		97	24
9d	–SO_2–	2,4,6-Triisopropyl-Ph	95	33	**9j**	–CO–	Cyclohexane	97	55
9e	–SO_2–	1-Naphthalene	96	57	**9k**	–CO–	1-Naphthalene	99	29
9f	–SO_2–	4-*tert*-Bu-Ph	93	55	**9l**	–CO–		97	24

[a] Calculated from integrated peak areas recorded by LC/MS of the crude products.
[b] Six-step overall yields from Merrifield resin **3** (loading capacity of the resin **3** in 1.6 mmol/g).

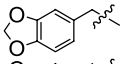
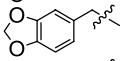
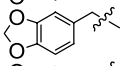
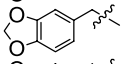
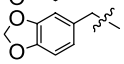
the nitrones **15** by LC/MS spectroscopy of the crude products (Table 2).

In summary, we succeeded in the solid-phase synthesis of hydroxypiperazines **9** and hydroxylamines **14** by using phenethylamine *N*-oxide resins **8**, **13** as the key intermediate. The key intermediates of *N*-oxide resins **8**, **13** were separable on solid phase for subsequent β-elimination



Scheme 2. Reagents and conditions: (a) amine, TEA, 50 °C, 18 h; (b) aldehyde, boran–pyridine complex, DMF/EtOH (4:1), rt, 3 days; (c) *m*-CPBA, CH_2Cl_2, rt, 2 h; (d) toluene, 90 °C, 2 h.

Table 2

Product	R^2	R^3	Purity (%)		Yield (%)[a]	Product	R^2	R^3	Purity (%)		Yield (%)
14a	Bn	Ph	82[b]	93[c]	40	**14f**		Ph	92	95	33
14b	Bn	4-F-Ph	81	97	38	**14g**		4-F-Ph	86	97	34
14c	Bn	4-NO_2-Ph	49	96	17	**14h**		4-MeO-Ph	88	88	23
14d	Bn	4-^{t}Bu-Ph	82	92	35	**14i**		4-^{t}Bu-Ph	74	93	24
14e[d]	Bn	Isopropyl	68	—	22	**14j**[d]		Isopropyl	55	—	20

[a] Six-step overall yields from Merrifield resin **3** after purification (loading capacity of the resin **3** in 1.6 mmol/g).
[b] Calculated from integrated peak areas recorded by LC/MS of the isolated products.
[c] Calculated from integrated peak areas recorded by LC/MS of the crude products.
[d] *Compounds*. **14e** and **14j** compounds could be not isolated from mixture of the hydroxylamine and nitrone.

reaction, from which the desired hydroxypiperazine and hydroxylamine products **9**, **14** could be obtained without any significant contamination at 90 °C. Especially, the hydroxypiperazine derivatives could be obtained in high six-step overall yields with high purities from Merrifield resin **3** without any purification step after the thermal cleavage step. With the high yields and purities, this method is the versatile approach to develop combinatorial libraries of hydroxypiperazine and hydroxylamine derivatives useful for the synthesis of biologically interesting compounds, which is a subject for our current research.

2. Experimental

2.1. Materials and methods

The polystyrene Merrifield resin (1.6 mmol/g, 1% cross-linking, 100–200 mesh) was obtained from NovaBiochem. Solvents were purchased from Merck and were anhydrous and HPLC grade. Reactions, filtrations, and washings were carried out on a MiniBlock (Bohdan). Solvent evaporation was performed on a GeneVac Atlas HT-4 centrifugal evaporator. Crude products were purified by parallel chromatography using QuadFlash silica-cartridges (Biotage Catalog no. QK0-1107-1504L). All of the intermediate resins were monitored by ATR-FTIR (SensIR Technology). The structures of final products were confirmed by ^{1}H NMR and ^{13}C NMR (Bruker AMX-500 FT NMR), and LC/MS spectroscopy. LC/MS data were recorded on a Waters ZQ electrospray mass spectrometer (EI) equipped with PDA (200–600 nm) detection using XTerraMS column (C_{18}, 5 μM, 4.6×100 mm) from Waters (UK). Typical gradient were 5–95% MeCN/H_2O containing 0.1% trifluoroacetic acid.

2.2. Procedure for the synthesis of the phenethyl alcohol resin 4

Sodium methoxide (1.30 g, 24.0 mmol) was added to a solution of 4-hydroxyphenethyl alcohol (3.32 g, 24.0 mmol) in cold DMA (80 mL) at 0 °C. The solution was stirred at room temperature for 2 h and Merrifield resin **3** (5 g, 8.0 mmol, loading 1.6 mmol/g: chloromethylated 1% vinylbenzene–styrene copolymer) was added. The resulting suspension was stirred for 18 h at 50 °C. The phenethyl alcohol resin **4** was filtered and washed with DMF (2× 100 mL), DCM (2×100 mL) and MeOH (2×100 mL), and dried under high vacuum.

2.3. Procedure for the synthesis of the phenethylbromide resin 5

To a suspension of phenethyl alcohol resin **4** (5 g, 8.0 mmol) in dry DCM (dichloromethane: 60 mL) was added triphenylphosphine (10.49 g, 40 mmol), followed by slow addition of carbon tetrabromide (13.27 g, 40 mmol) in dry DCM at 0 °C. The suspension was shaken for 12 h at room temperature under Ar gas. The phenethylbromide resin **5** was filtered and washed with DMF (2×100 mL), DCM (2×100 mL) and MeOH (2×100 mL), and dried under high vacuum.

2.4. Procedure for the synthesis of the polymer-bound piperazine resin 6

The phenethylbromide resin **5** (2.0 g, 3.2 mmol) was suspended in dry DMF (30 mL), and piperazine (1.4 g, 16.0 mmol) and TEA (2.23 mL, 16.0 mmol) were successively added. The mixture was shaken for 18 h at 50 °C. The polymer-bound piperazine resin **6** was filtered and washed with DMF (2×100 mL), DCM (2×100 mL) and MeOH (2×100 mL), and dried under high vacuum.

2.5. Procedure for the synthesis of the resin 7a

The polymer-bound piperazine resin **6** (100 mg, 0.16 mmol) was swollen in DMF (4 mL) and TEA (0.07 mL, 0.45 mmol) followed by addition of 4-methoxybenzene-sulfonyl chloride (92 mg, 0.45 mmol). After the reaction was shaken for 18 h at room temperature, the sulfonyl piperazine resin **7a** was filtered and washed with DMF (2×20 mL), DCM (2×20 mL) and MeOH (2×20 mL) and dried under high vacuum.

2.6. Representative procedure for the oxidation and Cope elimination steps 9a

To the pre-swollen sulfonyl piperazine resin **7a** (100 mg, 0.16 mmol) in DCM (4 mL) was added *m*-CPBA (158 mg, 0.64 mmol, ~70%) at 0 °C. The resin was agitated for 2 h at

room temperature and washed with 3% TEA/DMF (3×20 mL), DMF (3×20 mL), MeOH (3×20 mL), and then DCM (20 mL). After drying under high vacuum for 30 min, the resin **8a** was heated in 4 mL of toluene at 90 °C for the Cope elimination during 2 h. The resin was filtered off and washed with toluene (2×3 mL) and DCM (2×3 mL). The combined filtrate was concentrated under high vacuum and afforded the desired sulfonylpiperazine derivatives with high purities.

2.6.1. 4-(4-Methoxybenzenesulfonyl)piperazin-1-ol 9a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2H, J=7.0 Hz), 7.00 (d, 2H, J=7.0 Hz), 3.88 (s, 3H), 3.53 (m, 2H), 3.16 (m, 2H), 2.48–2.42 (m, 1H), 1.80 (br s, 2H), 1.70 (br s, 3H), 1.51 (m, 2H), 1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.23, 129.86, 127.14, 114.35, 56.36, 55.65, 44.09; LC/MS (ESI) m/z 273 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{16}N_2O_4S$, 272.0831; found, 272.0828.

The following compounds were synthesized using the above protocol.

2.6.2. 4-(4-Nitrobenzenesulfonyl)piperazin-1-ol 9b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, 2H, J=8.6 Hz), 7.96 (d, 2H, J=8.6 Hz), 3.57 (br, 2H), 3.21 (br, 2H), 2.85 (br, 4H); LC/MS (ESI) m/z 288 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{10}H_{13}N_3O_5S$, 287.0576; found, 287.0579.

2.6.3. 4-(4-Chlorobenzenesulfonyl)piperazin-1-ol 9c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, 2H, J=8.5 Hz), 7.52 (d, 2H, J=8.5 Hz), 3.52 (m, 2H), 3.18 (m, 2H), 2.84 (t, 2H, J=8.9 Hz), 2.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.71, 134.30, 129.53, 129.10, 56.21, 43.83; LC/MS (ESI) m/z 277 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{10}H_{13}ClN_2O_3S$, 276.0335; found, 276.0339.

2.6.4. 4-(2,4,6-Triisopropylbenzenesulfonyl)piperazin-1-ol 9d. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (m, 1H), 3.52 (m, 2H), 3.22 (m, 2H), 3.06 (t, 2H, J=10.8 Hz), 2.90 (m, 1H), 2.72 (t, 2H, J=10.1 Hz), 1.26 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.54, 151.89, 129.33, 124.00, 56.63, 42.58, 34.19, 29.34, 24.87, 23.54; LC/MS (ESI) m/z 369 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{19}H_{32}N_2O_3S$, 368.2134; found, 368.2135.

2.6.5. 4-(Naphthalene-1-sulfonyl)piperazin-1-ol 9e. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.99–7.92 (m, 3H), 7.75–7.63 (m, 3H), 3.61 (br, 2H), 2.16 (br, 2H), 2.80 (br, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.99, 132.82, 132.22, 129.39, 129.25, 129.12, 129.00, 127.97, 127.70, 122.84, 56.35, 44.06, 29.71; LC/MS (ESI) m/z 293 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{14}H_{16}N_2O_3S$, 292.0882; found, 292.0883.

2.6.6. 4-(4-*tert*-Butylbenzenesulfonyl)piperazin-1-ol 9f. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2H, J=8.4 Hz), 7.54 (d, 2H, J=8.4 Hz), 3.56 (br, 2H), 3.18 (br, 2H), 2.82 (br, 2H), 2.71 (br, 2H), 1.33 (s, 9H); LC/MS (ESI) m/z 299 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{22}N_2O_3S$, 298.4011; found, 298.4014.

2.6.7. (4-Hydroxypiperazin-1-yl)-(4-methoxyphenyl) methanone 9g. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, 2H, J=7.2 Hz), 6.92 (d, 2H, J=7.2 Hz), 3.84 (s, 3H), 3.22 (br, 4H), 2.67 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.36, 160.97, 129.15, 113.81, 57.50, 55.38; LC/MS (ESI) m/z 237 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{12}H_{16}N_2O_3$, 236.1161; found, 236.1163.

2.6.8. (4-Hydroxypiperazin-1-yl)-(4-nitrophenyl)methanone 9h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, 2H, J=8.0 Hz), 7.58 (d, 2H, J=8.0 Hz), 3.29 (br, 2H), 3.14 (br, 4H), 2.63 (br, 2H); LC/MS (ESI) m/z 252 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{13}N_3O_4$, 251.0906; found, 251.0906.

2.6.9. Benzo[1,3]dioxol-5-yl-(4-hydroxypiperazin-1-yl) methanone 9i. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, 1H, J=7.9, 1.6 Hz), 6.90 (d, 1H, J=1.6 Hz), 6.83 (d, 1H, J=7.9 Hz), 6.00 (s, 2H), 4.41–4.10 (m, 1H), 3.21 (m, 5H), 2.66 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.71, 134.30, 129.53, 129.10, 56.21, 43.83; LC/MS (ESI) m/z 251 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{12}H_{14}N_2O_4$, 250.0954; found, 250.0956.

2.6.10. Cyclohexyl-(4-hydroxypiperazin-1-yl)methanone 9j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (m, 1H), 3.86 (m, 1H), 3.29–3.21 (m, 3H), 2.93 (t, 1H, J=10.9 Hz), 2.60 (m, 2H), 2.48–2.42 (m, 1H), 1.80 (br s, 2H), 1.70 (br s, 3H), 1.51 (m, 2H), 1.25 (m, 3H); LC/MS (ESI) m/z 213 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{20}N_2O_2$, 212.2887; found, 212.2886.

2.6.11. (4-Hydroxypiperazin-1-yl)naphthalen-1-yl-methanone 9k. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.87 (m, 3H), 7.56–7.38 (m, 4H), 3.40 (br, 4H), 2.98 (br, 2H), 2.82 (br, 2H); LC/MS (ESI) m/z 257 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{15}H_{16}N_2O_2$, 256.1212; found, 256.1215.

2.6.12. (4-Hydroxypiperazin-1-yl)-(4-phenoxyphenyl) methanone 9l. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (m, 4H), 7.17 (m, 1H), 7.05 (d, 2H, J=7.7 Hz), 7.00 (d, 2H, J=8.6 Hz), 4.48–4.37 (m, 1H), 3.91–3.84 (m, 1H), 3.22 (m, 5H), 2.67 (m, 2H); LC/MS (ESI) m/z 299 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{17}H_{18}N_2O_3$, 298.1317; found, 298.1317.

2.7. Procedure for the synthesis of polymer-bound secondary amine resins 11a

The phenethylbromide resin **5** (2 g, 3.2 mmol) was suspended in dry DMF (30 mL), and benzyl amine (1.75 mL, 16.0 mmol) and triethyl amine (2.23 mL, 16.0 mmol) were successively added. The mixture was shaken for 18 h at 50 °C. Secondary amine resin **11a** was filtered and washed with DMF (2×100 mL), DCM (2×100 mL) and MeOH (2×100 mL), and dried under high vacuum.

2.8. Procedure for the reductive alkylation of polymer-bound secondary amine resin 12a

Secondary amine resin **11a** (100 mg, 0.16 mmol) was swollen in DMF/EtOH (4:1, 4 mL) and followed by addition of benzaldehyde (0.13 mL, 1.28 mmol) and

borane–pyridine complex (0.13 mL, 1.28 mmol). After the reaction was shaken for three days at room temperature, the tertiary amine resin **12a** was filtered and washed with DMF (2×20 mL), DCM (2×20 mL) and MeOH (2×20 mL) and dried under high vacuum.

2.9. Procedure for the oxidation and Cope elimination steps 14a

To pre-swollen tertiary amine resin **12a** (100 mg, 0.16 mmol) in DCM (4 mL) was added the *m*-CPBA (158 mg, 0.64 mmol, ~70%) at 0 °C. The resin was agitated for 3 h at room temperature and washed with 3% TEA(triethylamine)/DMF (3×20 mL), DMF (3×20 mL), MeOH (3×20 mL), and then DCM (20 mL). After drying under high vacuum for 30 min, the resin **13a** was heated in 4 mL of toluene at 90 °C for the Cope elimination during 2 h. The resin was filtered off and washed with toluene (2×3 mL) and DCM (2×3 mL).

The combined filtrate was evaporated and purified by silica gel column chromatography.

2.9.1. *N*,*N*-Dibenzylhydroxylamine 14a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 10H), 3.81 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.48, 129.52, 128.34, 127.42, 64.04; LC/MS (ESI) *m*/*z* 214 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{14}H_{15}NO$, 213.1154; found, 213.1155.

The following compounds were synthesized using the above protocol.

2.9.2. *N*-Benzyl-*N*-(4-fluorobenzyl)hydroxylamine 14b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 7H), 7.01 (t, 2H, J=8.7 Hz), 3.82 (s, 2H), 3.79 (s, 2H); LC/MS (ESI) *m*/*z* 232 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{14}H_{14}FNO$, 231.1059; found, 231.1062.

2.9.3. *N*-Benzyl-*N*-(4-nitrobenzyl)hydroxylamine 14c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, 2H, J=8.5 Hz), 7.55 (d, 2H, J=8.5 Hz), 7.39–7.33 (m, 5H), 3.98 (s, 4H); LC/MS (ESI) *m*/*z* 259 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{14}H_{14}N_2O_3$, 258.1004; found, 258.1003.

2.9.4. *N*-Benzyl-*N*-(4-*tert*-butylbenzyl)hydroxylamine 14d. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 6H), 7.27–7.25 (m, 3H), 3.79 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.33, 137.56, 134.38, 129.48, 129.26, 128.31, 127.37, 125.25, 64.00, 63.67, 34.50, 31.37; LC/MS (ESI) *m*/*z* 270 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{18}H_{23}NO$, 269.1780; found, 269.1781.

2.9.5. *N*-Benzyl-*N*-isopropylhydroxylamine 14e. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.33 (m, 5H), 3.79 (s, 2H), 2.50 (d, 2H, J=7.0 Hz), 1.93 (m,1H), 0.93 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 130.2, 129.1, 128.1, 68.4, 65.6, 26.3, 20.9; LC/MS (ESI) *m*/*z* 180 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{17}NO$, 179.1310; found, 179.1312.

2.9.6. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-benzylhydroxylamine 14f. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 6.87 (d, 1H, J=0.9 Hz), 6.79 (dd, 1H, J=7.9, 0.9 Hz), 6.76 (d, 1H, J=7.9 Hz), 5.93 (s, 2H), 3.83 (s, 2H), 3.76 (s, 2H); LC/MS (ESI) *m*/*z* 258 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{15}H_{15}NO_3$, 257.1052; found, 257.1050.

2.9.7. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-(4-fluorobenzyl) hydroxylamine 14g. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H), 7.01 (t, 2H, J=8.6 Hz), 6.85 (s, 1H), 6.78 (d, 1H, J=7.8 Hz), 6.75 (d, 1H, J=7.8 Hz), 5.93 (s, 2H), 3.77 (s, 2H), 3.74 (s, 2H); LC/MS (ESI) *m*/*z* 276 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{15}H_{14}FNO_3$, 275.0958; found, 275.0961.

2.9.8. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-(4-methoxybenzyl)hydroxylamine 14h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 6.87–6.86 (m, 3H), 6.78–6.75 (m, 2H), 5.92 (d, 2H, J=7.8 Hz), 3.79–3.78 (m, 5H), 3.75 (s, 2H); LC/MS (ESI) *m*/*z* 288 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{16}N_2O_4S$, 287.1158; found, 287.1159.

2.9.9. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-(4-*tert*-butylbenzyl)hydroxylamine 14i. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, 2H, J=8.2 Hz), 7.27 (d, 2H, J=8.2 Hz), 6.87 (d, 1H, J=0.8 Hz), 6.78 (dd, 1H, J=7.9, 0.8 Hz), 6.75 (d, 2H, J=7.9 Hz), 5.93 (s, 2H), 3.79 (s, 2H), 3.73 (s, 2H), 1.30 (s, 9H); LC/MS (ESI) *m*/*z* 314 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{19}H_{23}NO_3$, 313.1678; found 313.1676.

2.9.10. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-isopropylhydroxylamine 14j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, 1H, J=1.1 Hz), 6.79 (dd, 1H, J=7.9, 1.1 Hz), 6.76 (d, 1H, J=7.9 Hz), 5.94 (s, 2H), 3.71 (s, 2H), 2.48 (d, 2H, J=6.9 Hz), 1.96–1.89 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H); LC/MS (ESI) *m*/*z* 224 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{12}H_{17}NO_3$, 223.1208; found, 223.1207.

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