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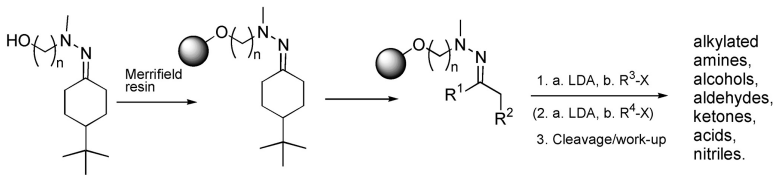

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Strategy for the Synthesis of Polymeric Supports with Hydrazone Linkers for Solid-Phase Alkylation of Ketones and Aldehydes

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A new approach to polymeric supports useful for the immobilization of aldehydes and ketones via hydrazone linkers is reported. The new strategy gives supports with better properties and is effective for the synthesis of all supports previously used for the alkylation of ketones anchored as hydrazones. In contrast to other approaches, the new strategy also provided a polymer with an economical C_2 spacer linker. The supports were used for immobilization of ketones 3-pentanone, acetone, *N*-benzylpiperidone, and aldehydes hexanal and 3-phenylpropanal in the form of their hydrazones. The polymer-supported hydrazones were subjected to α-alkylation (LDA/RX) followed by acidic, reductive, or oxidative cleavage/workup procedures to provide α-alkylated aldehydes or ketones as well as corresponding primary amines, alcohols, nitriles or acids.

Solid-phase synthesis of small molecules is one of the most important tools of combinatorial chemistry.[1] Methodologies that allow for construction of C−C bonds on solid phase are especially important for creation of diversified carbon frameworks of small molecules.[2] Alkylation of metalated hydrazones constitutes a proven and powerful methodology to build up carbon skeletons.[3] Recently, we reported alkylation of ketones on a polymeric support,[4] followed by reductive cleavage,[5] which provides a viable strategy for the preparation of libraries of α-branched ketones and *β*-branched primary amines. Although the anchoring of ketones and aldehydes to solid support has been realized with the help of various anchors,[6] including hydrazone linkers,[7,8] we are pursuing possible applications of spacer-modified *N*,*N*-dimethylhydrazone analogues and piperazine-derived hydrazones. Because we previously did not succeed in the preparation of a polymer (**4**) with the simplest two-carbon atom spacer (for binding ketones via so-called "C_2 hydrazone linker", Scheme 1),[5] we have been looking for a new method that would allow preparation of this class of supports. Such a general method could allow for preparation of supports with chiral, α-amino acid-derived, "C_2 hydrazone linker" analogues for use in solid-phase asymmetric synthesis (SPAS).[9]

In this paper, we present a new strategy for an efficient preparation of a series of polymeric supports with protected hydrazine anchors and application of such supports for immobilization of ketones as well as aldehydes on solid phase in the form of their hydrazones (via hydrazone linker). The new strategy differs from previously used approaches[4,5,8] through preparation of the whole hydrazone linker−spacer construct in solution instead of on solid support (Scheme 1). Judging from our experience, this approach should give better control over chemical homogenity of the linker construct (i.e., analysis and purification by orthodox solution chemistry methods) as well as give polymers with better reproducibility and higher loadings, since the supports would be prepared in only one synthetic operation starting from Merrifield gel.

Moreover, we wanted to demonstrate that the alkylated supported hydrazones could be manipulated to a variety of different classes of organic compounds, such as nitriles, amines, alcohols, or acids, though simple variation of cleavage and postcleavage workup protocols.

Results and Discussion

Syntheses of Polymeric Supports. For the successful implementation of the planned strategy, a judicious choice of a suitable protection for the hydrazine group is decisive. After considering several options, we planned to protect the hydrazine in a form of a ketone hydrazone. 4-*tert*-Butylcyclohexanone was chosen as the ketone because of its availability, relatively high molecular mass, and relatively low volatility. The last two properties would allow for direct gravimetric measurement of hydrazine/hydrazone loadings of the synthesized polymers (vide infra).

Thus, the inexpensive, commercially available 2-(*N*-methylamino)ethanol was nitrosated with *tert*-butyl nitrite (99% crude yield, Scheme 2)[5], and the crude product **7a** was reduced with lithium aluminum hydride to give the hydrazine **8a**. The hydrazine was hard to recover in a good yield from the reaction mixture; therefore, it was converted in a one-pot procedure to the hydrazone **9a**. The hydrazone was obtained in a very good overall yield (81%, Scheme 2) and satisfactory purity solely by extraction and distillation. Hydrazones **9b**, **9c**, and **14** were prepared in an analogous fashion (Scheme 2). Anchoring of the protected hydrazines **9** and **14** to the polymeric gel was tested in solution in a reaction with benzyl chloride. Previously used conditions[5] gave unsatisfactory yields. The reaction suffered from low conversion, even with excess of bases (NaH, KH), extended reaction times, and crown ether additives. It was observed

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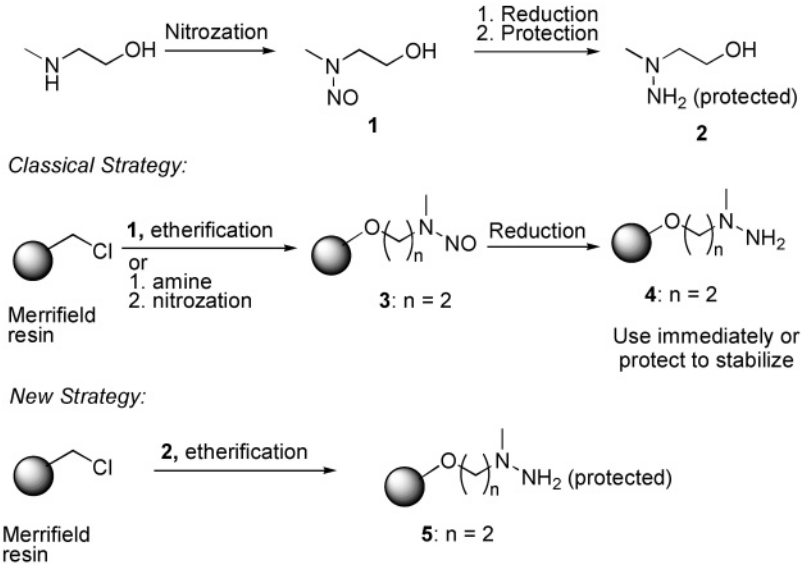
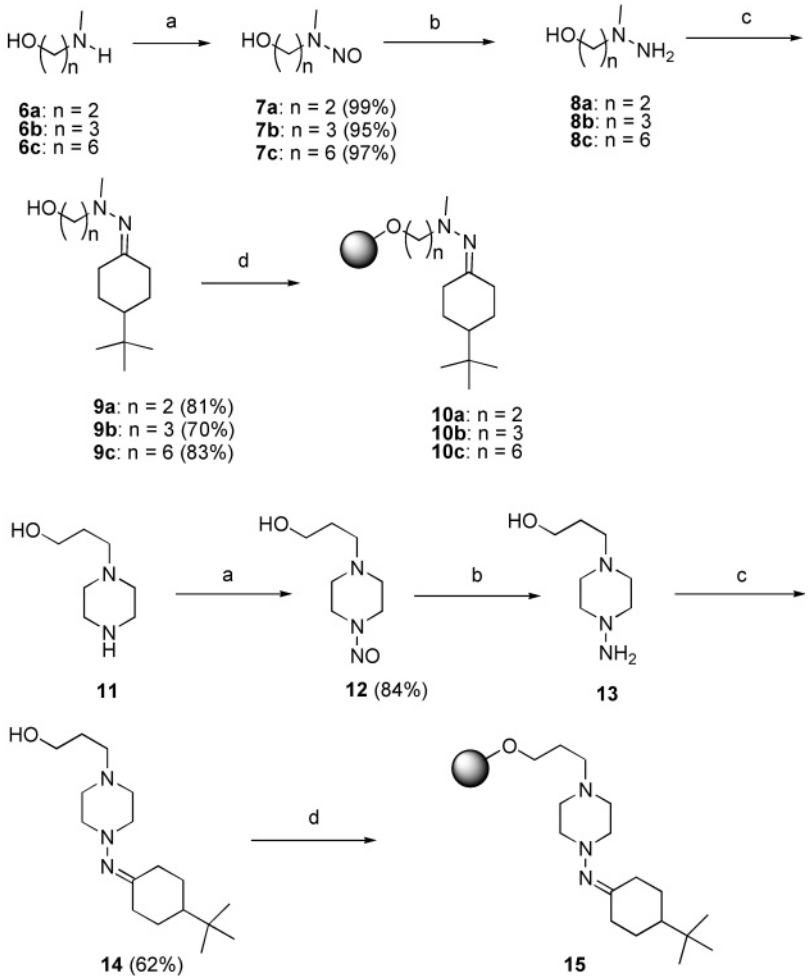
Scheme 1. Comparison of the New and the Classical Strategy for Preparation of the Protected Hydrazine Supports with "C_2 Hydrazone Linker".



Scheme 2



Reagents: (a) *tert*-Butyl nitrite, THF; (b) $LiAlH_4$, THF; (c) 4-*tert*-butylcyclohexanone; (d) Merrifield polymer, *t*-BuOK, THF.

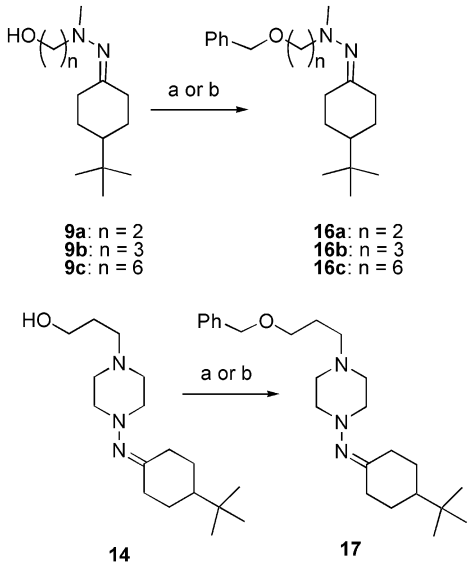
that for some reasons, part of the hydride used did not react, and the reaction stopped before reaching satisfactory conversion. Therefore, we opted for a THF-soluble, moderately strong base, that is, potassium *tert*-butoxide, which gave excellent conversion and high crude product purity (Scheme 3). The benzyl ethers **16** and **17** were isolated in very good yields (90−96%). The only byproduct observed was the benzyl *tert*-butyl ether. Thus, these conditions, when applied to Merrifield gel, should result in a polymer-bound hydrazone and cupping of the remaining unreacted, chloromethyl groups

Table 1. Loadings of 4-*tert*-Butylcyclohexanone on the Supports **10** and **15** Synthesized by the Classical and the New Strategy

entry	polymeric support	theoretical loading (mmol/g)	practical loading (mmol/g) (yield as percent of the theoretical loading)		
			classical strategy[a,b]	new strategy[b]	new strategy[c]
1	C_2 (**10a**)	0.91	0.064 (7%)	0.65 (71%)	0.88 (97%)
2	C_3 (**10b**)	0.90	0.50 (56%)	0.69 (77%)	0.84 (93%)
3	C_6 (**10c**)	0.87	0.50 (58%)	0.66 (76%)	0.84 (96%)
4	$PipC_3$ (**15**)	0.86	0.48 (57%)	0.79 (92%)	0.89 (103%)

[a] Ref 5. [b] The loadings of hydrazone groups determined from mass of the released ketone. [c] Loading based on nitrogen content from elemental analysis.

Scheme 3

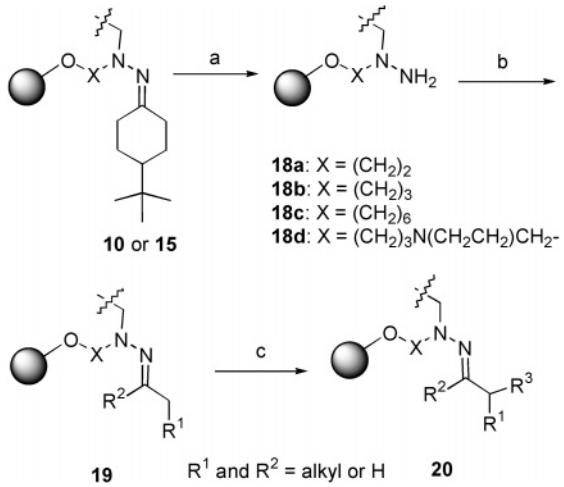


Reagents: (a) BnCl, KH in oil, THF (36−75%); (b) BnCl, *t*-BuOK, THF (90−96%).

in the form of *tert*-butyl ethers. According to the modified method of the Williamson-type etherification, the hydrazone **9a** was attached to the Merrifield polymer to give a support **10a** with a much higher hydrazone loading than previously obtained (Table 1, entry 1). The three other supports, **10b**, **10c**, and **15**, previously synthesized by the classical approach were prepared by the new strategy with high efficiency and with loadings of hydrazone (i.e., protected hydrazine) measurably higher than by previous methods (Scheme 2, Table 1). The loadings were inferred both from elemental analysis and from direct gravimetric analysis of the mass of 4-*tert*-butylcyclohexanone released from the polymers during deprotective activation with TFA solution (Scheme 4, reaction a). Interestingly, the loadings determined by elemental analysis were consistently higher than loadings from the mass of released *tert*-butylcyclohexanone. This could be due to an unavoidable loss of some of the relatively volatile ketone during the evaporation of solvents. On the other hand, the obtained loading for the support with the piperazine-derived linker and 3-carbon atom spacer, so-called $PipC_3$ (**15**, Table 1, entry 4), was higher than the theoretical value and seemed to indicate occurrence of a systematic error in the microanalysis. Therefore, the loadings based on elemental analysis should be approached with caution.

In general, the new strategy gave polymers with better loadings. Moreover, only the new approach was effective

Scheme 4



Reagents: (a) (i) 10% TFA, THF; (ii) Et_3N; (b) ketone or aldehyde, MS 4A, THF; (c) (i) LDA, THF, 0 °C; (ii) R^3-X, −78 °C; ((iii) LDA, THF, 0 °C; (iv) R^4-X, −78 °C).

for preparation of the least expensive of all the supports tested, that is, C_2-spacer support **10a**.

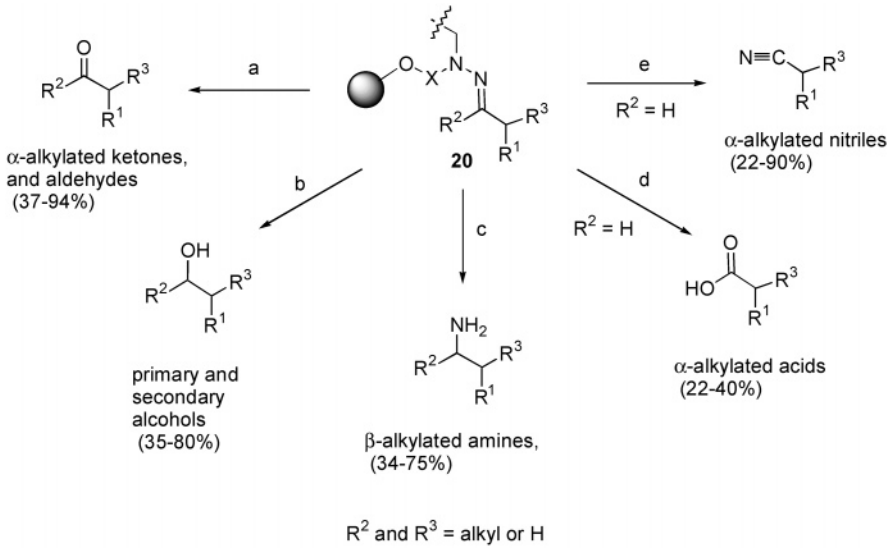
Solid-Phase Alkylation, Cleavage and Cleavage/Work-up Manipulation. The 4-*tert*-butylcyclohexanone hydrazone-protected hydrazine polymers **10** and **15** prepared by the new approach were tested as supports for a few typical solid-phase alkylations of aldehydes and ketones. The supports were activated, that is, the hydrazine groups of the supports were freed, by washing the polymers with TFA solution (10% TFA in wet THF), followed by washing with triethylamine (Scheme 4). Then ketone or aldehyde substrates were attached to the free hydrazine resin **18** in the form of their hydrazones under previously established conditions[4] (excess of carbonyl compound, THF, reflux, molecular sieves 4 Å). Then the hydrazones **19** were lithiated (excess of LDA in THF, typically 4 h at 0 °C) and the resulting lithiated hydrazones were alkylated with representative alkyl halides (typically, propyl iodide or benzyl bromide at −78 °C for 12 h, Scheme 4). Repetition of the deprotonation/alkylation procedure was used for a second alkylation at the α′ position. Such iterative alkylation of acetone could be used to prepare unsymmetrical ketones, as demonstrated in Table 2 (entry 8, 13, 17). Now the alkylated ketone or aldehyde hydrazones could be either cleaved with trifluoroacetic acid to provide carbonyl compounds or subjected to specific cleavage/workup manipulations. Thus, oxidative protocols applied to aldehyde hydrazones provide nitriles (m-CPBA)[10] and carboxylic acids (e.g., hydrogen peroxide) while reductive

Table 2. Representative Products Synthesized from the Supported Hydrazones

				yield of product[a] (%) (purity[b])				
entry	resin	substrate	R^3X, R^4X	aldehyde or ketone	amine	alcohol	nitrile	acid
1	C_2 **10a**	3-Ph-propanal	PrI	57 (70%)	36 (90%)	35 (88%)	53 (92%)	33 (90%)
2	C_2 **10a**	3-Ph-propanal	BnBr	79 (69%)	38 (90%)	50 (80%)	22 (70%)	30 (93%)
3	C_2 **10a**	3-Ph-propanal		67 (70%)	50 (80%)	59 (82%)	90 (95%)	40 (90%)
4	C_2 **10a**	hexanal	BnBr	37 (59%)	48 (88%)	40 (80%)	45 (63%)	22 (85%)
5	C_2 **10a**	3-pentanone	PrI	90 (88%)	40 (79%)	75 (85%)		
6	C_2 **10a**	3-pentanone	BnBr	70 (55%)	58 (90%)	67 (85%)		
7	C_2 **10a**	acetone	BnBr	74 (86%)	55 (90%)	70 (88%)		
8	C_2 **10a**	acetone	PrI, BnBr	47 (95%)	36 (88%)	45 (80%)		
9	C_3 **10b**	*N*-Bn-piperidone	PrI	72 (90%)	75 (88%)	75 (85%)		
10	C_3 **10b**	3-pentanone	PrI	90 (85%)	39 (77%)	70 (82%)		
11	C_3 **10b**	3-pentanone	BnBr	75 (75%)	48 (96%)	69 (87%)		
12	C_3 **10b**	acetone	BnBr	74 (86%)	55 (90%)	71 (88%)		
13	C_3 **10b**	acetone	PrI, BnBr	47 (95%)	34 (90%)	46 (81%)		
14	C_6 **10c**	3-pentanone	PrI	94 (85%)	39 (77%)	71 (86%)		
15	C_6 **10c**	3-pentanone	BnBr	88 (91%)	54 (89%)	77 (86%)		
16	C_6 **10c**	acetone	BnBr	70 (90%)	55 (90%)	66 (85%)		
17	C_6 **10c**	acetone	PrI BnBr	57 (85%)	38 (90%)	40 (77%)		
18	C_6 **10c**	*N*-Bn-piperidone	PrI	49 (91%)	72 (75%)	45 (88%)		
19	$PipC_3$ **15**	cyclohexanone	PrI	90 (85%)	52 (80%)	80 (91%)		
20	$PipC_3$ **15**	cyclohexanone	BnBr	89 (86%)	48 (85%)	82 (90%)		
21	$PipC_3$ **15**	3-pentanone	PrI	90 (88%)	44 (87%)	77 (85%)		
22	$PipC_3$ **15**	3-pentanone	BnBr	89 (83%)	54 (87%)	80 (88%)		

[a] Yields based on loadings of the used supports. [b] Purities of the products were measured by GC/MS or NMR analysis.

Scheme 5



Reagents: (a) 10% TFA, THF; (b) 10% TFA, THF, $NaBH_4$, EtOH; (c) BH_3·THF, reflux; (d) 10% TFA, THF, H_2O_2; (e) m-CPBA.

cleavage[11] with borane−THF or reductive postcleavage workup (e.g., sodium borohydride) gave primary amines and alcohols, respectively (Scheme 5).

In terms of yields based on the loadings of substrates and purities of products (Table 2), all the tested alkylations on polymers prepared by the new strategy were equally or even more effective than reactions on supports prepared by reduction of nitrosoamines on solid phase. In general, the polymers **10** gave reasonable yields of the synthesized products; however, aldehydes usually gave lower yields and purities of cleaved-off products.

Conclusions

We have demonstrated that the new strategy for the synthesis of polymeric supports for immobilization of ketones and aldehydes via hydrazone linkers based on preparation of the 4-*tert*-butylcyclohexanone hydrazone-protected hydrazines in solution is more effective than previously reported approaches.[4,5] The synthesized polymeric supports could be used for the synthesis of amines, alcohols, aldehydes, ketones, acids, and nitriles through solid-phase alkylation of aldehydes or ketones. The whole methodology constitutes a useful tool for the solid-phase synthesis of diverse classes of small molecules and, as such, may find use in combinatorial chemistry.

Experimental Section

(A) General Methods. All air-sensitive reactions were carried out under argon atmosphere. Tetrahydrofuran was distilled under argon from sodium/benzophenone. Dichloromethane (DCM) was distilled before use. Chromatographic purifications were achieved by dry-column flash chroma-

tography (DFC).[12] Thin-layer chromatography (TLC) was performed on precoated plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm), and phosphomolybdic acid followed by charring. Mass spectra were recorded with an AMD-604 spectrometer and are reported as *m*/*z* ratio (relative intensity). Electron impact (EI) ionization was accomplished at 70 eV. GC/MS analyses were obtained with a Perkin-Elmer AutoSystem XL TurboMass mass spectrometer on an Elite Series PE5HT column (30 m × 0.25 mm) using EI ionization at 70 or 30 eV. Infrared (IR) spectra were recorded on a Nicolet Magna-IR 550 FTIR Series II spectrometer as $CHCl_3$ solutions or, in the case of polymers, as pressed dicks with KBr. Only diagnostic peaks are reported (cm^{-1}). Magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Bruker 200 spectrometer from $CDCl_3$ unless indicated otherwise. The gel phase ^{13}C NMR spectra of polymers were recorded after at least 1 h of swelling in $CDCl_3$. Chemical shifts are reported in parts per million downfield of tetramethylsilane.

(B) Starting Materials. The hydroxy nitrosoamines,[13] *N*-nitroso-*N*-methyl-2-hydroxyethylamine[14,15] (**7a**), *N*-nitroso-*N*-methyl-3-hydroxypropylamine[15] (**7b**), and *N*-methyl-6-hydroxyhexylamine,[17,18] (**7c**) were prepared as previously described.[5] Merrifield gel was purchased from Novabiochem (Catalog No. 01-64-0002, batch no. A19409).

1-(3-Hydroxypropyl)piperazine (11).[19,20]. 3-Chloro-1-propanol (5.67 g, 60 mmol) was added to a solution of piperazine (20.67 g, 240 mmol) in ethanol, and the resulting mixture was heated under reflux condenser for 12 h. Then the solvent and excess of piperazine were removed under vacuum, and the residue was treated with a solution of KOH (13.44 g, 240 mmol) in methanol (50 mL). Then the solvent and remaining piperazine were removed from the mixture under vacuum, and the residue was taken up in dichloromethane (30 mL) and filtered through a pad of Celite. The filtrate was concentrated under vacuum, and the residue was distilled on a Kugelrohr apparatus (140 °C /0.1 Torr) to give a white solid (6.22 g, 68%). R_f 0.40 (20% MeOH/DCM saturated NH_3 aq). mp 38−41 °C; lit mp 47−48 °C.[19] ν_{max} ($CHCl_3$): 3215 (N−H) cm^{-1}, 1070 cm^{-1} (C−O). δ_H (200 MHz, $CDCl_3$): 3.82−3.72 (m, 2H), 2.86 (t, J = 5 Hz, 2H), 2.62−2.28 (m, 10H), 1.77−1.61 (m, 2H). δ_C (50.3 MHz, $CDCl_3$): 64.1, 59.0, 54.4, 45.9, 26.9. MS (EI 70 eV): *m*/*z* 144 (M^+, 7), 102 (28), 99 (81), 58 (100), 56 (62), 44 (36), 43 (42), 42 (37).

1-(3-Hydroxypropyl)-4-nitrosopiperazine (12).[20] To a solution of hydroxylamine **11** (4.25 g, 29.5 mmol) in ethanol (55 mL) was added *tert*-butyl nitrite (5.8 mL, 4.56 g, 44.3 mmol, 1.5 equiv), and the mixture was stirred for 2 h at room temperature (rt) and then heated to 40−42 °C for 14 h. The solvent and the excess of the nitrite were removed under vacuum, and the residue was taken up in dichloromethane and filtered through a pad of silica. Removal of the solvent gave a yellow solid (4.29 g, 84%). R_f 0.40 (10% MeOH/DCM). mp 41−43 °C; lit mp 44 °C.[19] ν_{max} ($CHCl_3$): 3343 cm^{-1} (OH), 1457 cm^{-1} (N═O). δ_H (200 MHz, $CDCl_3$): 4.35−4.23 (m, 2H), 3.98−3.75 (m, 4H), 2.85−2.60 (m, 4H), 2.58−2.43 (m, 2H), 1.90−1.70 (m, 2H). δ_C (50.3 MHz, $CDCl_3$): 62.8, 56.8, 53.0, 51.6, 49.2, 39.1, 27.8. MS (EI 70 eV): *m*/*z* 173 (M^+, 0.06), 143 (38), 99 (34), 70 (38), 58 (38), 56 (100), 43 (26), 42 (57).

General Procedure for the Preparation of Hydroxyhydrazones 9 and 14. To a stirred, heated suspension of $LiAlH_4$ (2.28 g, 60 mmol, 2 equiv) in dry THF (60 mL) was added a solution of the nitrosoamine **7** or **12** (30 mmol) in dry THF (15 mL). The reaction mixture was heated under reflux for 16−20 h until TLC showed no remaining nitrosoamine. Then the excess of $LiAlH_4$ was decomposed by careful addition of water (no more than necessary to turn the precipitate white). To the resulting suspension was added 4-*tert*-butylcyclohexanone (6.92 g, 45 mmol, 1.5 equiv), and the mixture was heated under reflux for 2−24 h (TLC should show no hydrazine). Then the precipitate was filtered off, washed with THF (90 mL), and extracted two times with hot THF (120 mL). The combined filtrates and extracts were concentrated under vacuum, taken up in DCM (100 mL), dried with $MgSO_4$, and distilled under vacuum to remove solvent and excess 4-*tert*-butylcyclohexanone. The residue was distilled on a Kugelrohr apparatus to give the hydrazone **9** or **14**.

2-[2-(4-*tert*-Butylcyclohexylidene)-1-methylhydrazino]-ethan-1-ol (9a). Kugelrohr distillation (ot 100−110 °C/0.07 Torr) gave a colorless oil (5.49 g, 81%). R_f 0.30 (40% AcOEt/Hex + 5% Et_2NH). HRMS (EI): M^+, found 226.2053. $C_{13}H_{26}N_2O$ requires 226.2045. ν_{max} ($CHCl_3$): 3150 cm^{-1} (O−H), 1640 cm^{-1} (C═N). δ_H (200 MHz, $CDCl_3$): (major isomer) 4.00−3.78 (m, 3H), 2.50−2.30 (m, 2H), 2.37 (s, 3H), 1.65−1.15 (m, 9H), 0.86 (s, 9H). δ_C (50.3 MHz, $CDCl_3$): (major isomer) 172.2, 85.9, 84.6, 59.6, 57.9, 47.3, 32.1, 27.5, 23.5, 22.0. MS (EI 70 eV): *m*/*z* 226 (M^+, 17), 195 (65), 96 (22), 59 (31), 57 (100), 55 (17), 44 (34), 41 (36).

3-[2-(4-*tert*-Butylcyclohexylidene)-1-methylhydrazino]-propan-1-ol (9b). Kugelrohr distillation (ot 114−117 °C/0.04 Torr) gave a colorless oil (5.04 g, 70%). R_f 0.33 (40% AcOEt/Hex + 5% Et_2NH). HRMS (EI): M^+, found 240.2206. $C_{14}H_{28}N_2O$ requires 240.2202. ν_{max} ($CHCl_3$): 3295 cm^{-1} (O−H), 1641 cm^{-1} (C═N). δ_H (200 MHz, $CDCl_3$): 3.73 (s, J = 5.5, 2H), 2.94−2.88 (m, 2H), 2.52−2.40 (m, 2H), 2.34 (s, 3H), 2.20−1.88 (m, 4H), 1.78−1.66 (m, 4H), 1.30−1.15 (m, 4H), 0.86 (s, 9H). δ_C (50.3 MHz, $CDCl_3$): 172.0, 63.1, 59.6, 47.5, 45.0, 35.5, 32.3, 29.2, 28.4, 28.0, 27.4, 27.1. MS (EI 70 eV): *m*/*z* 241 (M^+ + 1, 6), 195 (31), 85 (37), 57 (100), 44 (27), 43 (20), 41 (18), 41 (24).

6-[2-(4-*tert*-Butylcyclohexylidene)-1-methylhydrazino]-hexan-1-ol (9c). Kugelrohr distillation (ot 155−170 °C/0.03 Torr) gave a colorless oil (7.02 g, 83%). R_f 0.56 (40% AcOEt/Hex + 5%Et_2N). HRMS (EI): M^+, found 285.2678. $C_{17}H_{34}N_2O$ requires 285.2671. ν_{max} ($CHCl_3$): 3354 cm^{-1} (O−H), 1640 cm^{-1} (C═N). δ_H (200 MHz, $CDCl_3$): 4.62 (t, J = 6 Hz, 2H), 2.65−2.40 (m, 4H), 2.33 (s, 3H), 2.20−1.84 (m, 4H), 1.76−1.08 (m, 12H), 0.87 (s, 9H). δ_C (50.3 MHz, $CDCl_3$): 172.0, 62.2, 60.0, 47.5, 45.2, 35.3, 32.6, 32.2, 28.2, 28.1, 28.0, 27.4, 27.2, 26.9, 25.6. MS (EI 70 eV): *m*/*z* 282 (M^+, 16), 196 (14), 195 (100), 96 (21), 57 (90), 55 (17), 44 (23), 41 (24).

3-{4-[(4-*tert*-Butylcyclohexylidene)amino]piperazin-1-yl}-propan-1-ol (14). Kugelrohr distillation (ot 176 °C/0.04 Torr) gave a colorless oil (5.487 g, 62%). R_f 0.27 (AcOEt +

5%Et_2N). HRMS (EI): M^+, found 295.2633. $C_{17}H_{33}N_3O$ requires 295.2624. ν_{max} ($CHCl_3$): 3448 cm^{-1} (O−H), 1636 cm^{-1} (C═N), 1046 cm^{-1} (C−O). δ_H (200 MHz, $CDCl_3$): 4.80 (t, J = 5, 2H), 2.80−2.40 (m, 10 H), 2.20−1.95 (m, 4H), 1.92−1.85 (m, 4H), 1.25−1.10 (m, 4H), 0.87 (s, 9H). δ_C (50.3 MHz, $CDCl_3$): 170.9, 64.2, 58.3, 54.7, 52.4, 47.4, 35.5, 32.3, 28.3, 28.2, 27.4, 27.2. MS (EI 70 eV): *m*/*z* 295 (M^+, 5), 181 (37), 142 (71), 100 (48), 97 (100), 70 (47), 57 (46), 56 (50).

General Procedure for Model Reaction of Anchoring of Protected Hydroxyhydrazines on Merrifield Gel: Reaction of Hydroxyhydrazone 9 and 14 with Benzyl Chloride. To a stirred solution of the hydrazone **9** or **14** (1.46 mmol) in dry THF (2 mL) was added potassium *tert*-butyl alcoholate (0.231 g, 2.06 mmol, 1.4 equiv). After 5 min, benzyl chloride (0.22 mL, 1.91 mmol, 1.3 equiv) was added, and the mixture was heated under reflux for 20 h. Then the solvent was removed under vacuum, and the residue was taken up in ether (20 mL) and washed with water (20 mL). The aqueous layer was back-extracted with ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum to give a crude product that was analyzed by NMR. Analytically pure product was obtained through chromatographic purification (DFC).

1-[2-(Benzyloxy)ethyl]-1-methyl-2-(4-*tert*-butylcyclohexylidene)hydrazine (16a). Yellow oil (96%); DFC (0−30% AcOEt/Hex + 5% Et_2NH). R_f 0.55 (40% AcOEt/Hex + 5%Et_2NH). HRMS (EI): M^+, found 316.2512. $C_{20}H_{32}N_2O$ requires 316.2515. ν_{max} ($CHCl_3$): 1641 cm^{-1} (C═N), 1100 cm^{-1} (C−O). δ_H (200 MHz, $CDCl_3$): 7.35−7.30 (m, 5H), 4.53 (s, 2H), 3.55−3.45 (m, 2H), 2.93−2.84 (m, 2H), 2.40 (s, 3H), 2.20−1.90 (m, 4H), 1.80−1.64 (m, 2H), 1.35−1.10 (m, 2H), 0.95−0.85 (m, 10H). δ_C (50.3 MHz, $CDCl_3$): 172.1, 138.3, 128.0, 127.4, 127.2, 72.8, 68.1, 59.6, 47.4, 45.6, 35.3, 32.2, 28.2, 28.0, 27.3, 27.1. MS (EI 70 eV): *m*/*z* (EI 70 eV) 316 (M^+, 10), 195 (92), 182 (38), 96 (26), 91 (54), 57 (100), 44 (13), 41 (22).

1-[3-(Benzyloxy)propyl]-1-methyl-2-(4-*tert*-butylcyclohexylidene)hydrazine (16b). Yellow oil (95%); DFC (0−30% AcOEt/Hex + 5% Et_2NH). R_f 0.61 (10% AcOEt/Hex + 5% Et_2NH), 0.86 (40% AcOEt/Hex + 5% Et_2NH). HRMS (EI): M^+, found 330.2677. $C_{21}H_{34}N_2O$ requires 330.2671. ν_{max} ($CHCl_3$): 1640 cm^{-1} (C═N), 1098 cm^{-1} (C−O). δ_H (200 MHz, $CDCl_3$): 7.40−7.25 (m, 5H), 4.51 (s, 2H), 3.53 (t, 3H), 2.71 (t, 2H), 2.50−2.40 (m, 2H), 2.34 (s, 3H), 2.15−1.60 (m, 6H), 1.30−1.05 (m, 3H), 0.90 (s, 9H). δ_C (50.3 MHz, $CDCl_3$): 171.8, 138.5, 128.1, 127.4, 127.3, 72.7, 68.3, 56.8, 47.6, 45.2, 35.5, 32.3, 28.4, 28.1, 27.4, 27.2. MS (EI 70 eV): *m*/*z* (EI 70 eV) 330 (M^+, 8), 239 (26), 195 (83), 96 (24), 91 (60), 57 (100), 44 (36), 41 (30).

1-[6-(Benzyloxy)hexyl]-1-methyl-2-(4-*tert*-butylcyclohexylidene)hydrazine (16c). Yellow oil (90%); DFC (1−5% Et_2NH/Hex). R_f 0.59 (40% AcOEt/Hex + 5%Et_2NH). HRMS (EI): M^+, found 372.3145. $C_{24}H_{40}N_2O$ requires 372.3141. ν_{max} ($CHCl_3$): 1645 cm^{-1} (C═N), 1095 cm^{-1} (C−O). δ_H (200 MHz, $CDCl_3$): 7.38−7.25 (m, 5H), 4.50 (s, 2H), 3.46 (t, 2H), 2.64−2.35 (m, 4H), 2.34 (s, 3H), 2.25−1.00 (m, 15H), 0.88 (s, 9H). δ_C (50.3 MHz, $CDCl_3$): 171.3, 138.4, 128.0, 127.3, 127.1, 72.5, 70.2, 60.0, 47.4, 46.4, 45.1, 41.0, 35.4, 32.1, 29.5, 28.0, 27.3, 27.1, 26.9, 26.0. MS (EI 70 eV): *m*/*z* 373 (M^+ + 1, 14), 281 (19), 195 (100), 96 (24), 91 (64), 69 (17), 57 (96), 44 (34).

4-(3-Benzyloxypropyl)-1-[(4-*tert*-butylcyclohexylidene)-amino]piperazine (17). Yellow oil (95%); DFC (1−6% Et_2-NH/AcOEt). R_f 0.38 (40% AcOEt/Hex + 5%Et_2N). HRMS (EI): M^+, found 385.3093. $C_{24}H_{39}N_3O$ requires 385.3093. ν_{max} ($CHCl_3$): 1638 cm^{-1} (C═N), 1100 cm^{-1} (C−O). δ_H (200 MHz, $CDCl_3$): 7.40−7.25 (m, 5H), 4.51 (s, 2H), 3.53 (t, 2H), 2.80−2.40 (m, 10 H), 2.20−1.85 (m, 7H), 1.30−1.10 (m, 4H), 0.88 (s, 9H). δ_C (50.3 MHz, $CDCl_3$): 170.5, 138.3, 128.1, 127.4, 127.3, 72.7, 68.4, 55.0, 54.8, 52.3, 47.4, 35.4, 32.2, 28.2, 27.9, 27.4, 27.1. MS (EI 70 eV): *m*/*z* 386 (M^+ + 1, 3), 125 (56), 99 (100), 97 (63), 91 (96), 84 (66), 57 (51), 56 (51).

General Procedure for Anchoring of Protected Hydrazines on Merrifield Gel. To a stirred solution of the hydrazone **9** or **14** (11.2 mmol, 5 equiv) in dry THF (20 mL) was added potassium *tert*-butyl alcoholate (1.258 g, 11.2 mmol, 5 equiv). After the solids dissolved, Merrifield gel (2.042 g, 2.25 mmol, Novabiochem, 1% PS-DVB, 200−400 mesh, 1.1 mmol/g) was added. The resulting suspension was intermittently stirred at room temperature for 6 h, followed by heating at 60 °C for 30 h. Then the polymer was washed under argon with THF (2 × 15 mL), MeOH (2 × 15 mL), THF (2 × 5 mL), MeOH (3 × 5 mL),), H_2O/DMF mixture (2 × 2 mL + 8 mL), H_2O (2 × 10 mL), H_2O/DMF mixture (2 × 2 mL + 8 mL), MeOH (2 × 5 mL), THF (2 × 5 mL), MeOH (3 × 5 mL), DCM (3 × 5 mL), MeOH (2 × 5 mL), DCM (2 × 5 mL), and MeOH (2 × 5 mL). The residual solvent was evaporated under vacuum, and the gel was dried to a constant mass under high vacuum to give a yellowish powder. Solutions from the first four washings were combined and used for recovery of the unreacted hydrazones (recovery 46−55%).

2-[2-(4-*tert*-Butylcyclohexylidene)-1-methylhydrazino]-ethoxymethylpolystyrene (10a). 0.88 mmol/g (by elemental analysis of nitrogen), 0.65 mmol/g (based on mass of 4-*tert*-butylcyclohexanone). Anal. found: C, 81.37; H, 7.90; N, 2.25. ν_{max} (KBr): 1638 cm^{-1} (C═N), 1100 cm^{-1} (C−O). δ_C (50.3 MHz, $CDCl_3$): 172.1, 68.3, 59.8, 47.6, 45.8, 35.6, 32.4, 28.2, 27.6.

3-[2-(4-*tert*-Butylcyclohexylidene)-1-methylhydrazino]-propoxymethylpolystyrene (10b). 0.84 mmol/g (by elemental analysis of nitrogen), 0.69 mmol/g (based on mass of 4-*tert*-butylcyclohexanone). Anal. found: C, 83.47; H, 8.10; N, 2.11. ν_{max} (KBr) 1640 cm^{-1} (C═N), 1100 cm^{-1} (C−O). δ_C (50.3 MHz, $CDCl_3$): 171.5, 68.0, 57.2, 46.7, 41.3, 34.5, 32.5, 27.6, 27.0.

6-[2-(4-*tert*-Butylcyclohexylidene)-1-methylhydrazino]-hexyloxymethylpolystyrene (10c). 0.84 mmol/g (by elemental analysis of nitrogen), 0.66 mmol/g (based on mass of 4-*tert*-butylcyclohexanone). Anal. found: C, 84.22; H, 8.46; N, 2.04. ν_{max} (KBr) 1640 cm^{-1} (C═N), 1095 cm^{-1} (C−O). δ_C (50.3 MHz, $CDCl_3$): 170.0, 68.0, 60.5, 47.7, 45.5, 41.3, 35.7, 32.5, 28.4, 28.3, 27.7, 27.6, 27.2.

3-{4-[(4-*tert*-Butylcyclohexylidene)amino]piperazin-1-yl}propoxymethylopolystyrene (15). 0.89 mmol/g (by

elemental analysis of nitrogen), 0.79 mmol/g (based on mass of 4-*tert*-butylcyclohexanone). Anal. found: C, 83.16; H, 8.32; N, 3.22. ν_{max} (KBr): 1639 cm^{-1} (C═N), 1099 cm^{-1} (C−O). δ_C (50.3 MHz, $CDCl_3$): 160.7, 72.0, 68.0, 54.5, 52.0, 47.0, 40.5, 38.0, 32.0, 28.0, 27.0.

General Procedure for Gravimetric Quantification of Loadings of Hydrazone Polymers 10 and 15. The hydrazone gel (0.500 g) was washed with a mixture of TFA/H_2O/THF (1:1:8, 3 × 15 min), followed by THF, MeOH, THF, MeOH, DCM, and MeOH. The combined acidic solutions were washed with a 20% solution of K_2CO_3. The aqueous phase was back-washed three times with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under moderate vacuum in temperature lower than 40 °C to give 4-*tert*-butylcyclohexanone in the form of an off-white solid. δ_H (200 MHz, $CDCl_3$): 2.40−2.25 (m, 4H), 2.15−2.00 (m, 2H), 1.55−1.40 (m, 3H), 0.92 (s, 9H). Loading of the hydrazone gel was calculated from the following formula:

$$\text{loading [mmol/g]} = \frac{m_{\text{ketone}}[\text{g}] \times 1000}{M_{\text{ketone}}[\text{g/mol}] \times m_{\text{gel}}[\text{g}]}$$

General Procedure for Anchoring of an Aldehyde or Ketone on Polymers 10 and 15. The polymer **10** or **15** (1 g, 0.65−0.79 mmol of protected hydrazine) was washed under argon with a mixture of TFA/H_2O/THF (1:1:8, 3 × 10 min), followed by THF (2 × 5 mL), MeOH (2 × 5 mL), THF (2 × 5 mL), MeOH (2 × 5 mL), DCM (2 × 5 mL), MeOH (2 × 5 mL), 10% Et_3N in DCM, (3 × 5 mL), MeOH (2 × 5 mL), DCM (3 × 5 mL), and dry THF (4 × 2 mL), then a solution of a carbonyl compound (6−10 mmol, 9−12 equiv) in dry THF (2.5 mL) was added. The suspension was heated under reflux for 48 h in the presence of molecular sieves 4 Å. Then the molecular sieves were removed with tweezers, and the gel was washed with THF (2 × 5 mL), MeOH (2 × 5 mL), THF (2 × 5 mL), MeOH (2 × 5 mL), DCM (2 × 5 mL), and MeOH (2 × 5 mL). The resulting gel was dried to a constant mass under high vacuum and used for alkylation.

General Procedure for Deprotonation/Alkylation of Aldehydes or Ketones Bound in the Form of Hydrazones on Polymers 18. The resin **19** (0.5 g) was washed with dry THF (3 × 3 mL) and was cooled to 0 °C. Then a cooled solution of LDA (3.60 mL, 0.98 M, 13 equiv) in THF was added, and the suspension was agitated for 4 h at 0 °C. Then the mixture was cooled to −78 °C, the solution of LDA was removed by a positive pressure of argon, and a solution of an alkylating agent (10 equiv) in THF (3 mL) was subsequently added. The resulting mixture was agitated and warmed slowly from −78 °C to rt over 12 h. The gel was washed successively with THF (2 × 5 mL), Et_2O (2 × 5 mL), THF (2 × 5 mL), Et_2O (2 × 5 mL), DCM (2 × 5 mL), Et_2O (2 × 5 mL), DCM (2 × 5 mL), and Et_2O (2 × 5 mL). The resulting alkylated product was subjected to cleavage from the gel or after washing with dry THF subjected to the second lithiation/alkylation.

General Procedure for Acidic Hydrazone Cleavage. A polymeric support with a carbonyl compound immobilized via the hydrazone linker was washed with a mixture of TFA/H_2O/THF (1:1:8, 3 × 15 min), followed by THF, MeOH, THF, MeOH, DCM, and MeOH. The combined acidic solutions were washed with a 20% solution of K_2CO_3. The aqueous phase was back-washed three times with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under low vacuum to give the alkylated aldehyde or ketone.

General Procedure for Reductive Hydrazone Cleavage. A polymeric support with a carbonyl compound immobilized via the hydrazone linker was washed twice with anhydrous THF (2 × 3 mL). The polymer was swollen in borane THF solution (1 M, 5 mL, 15−20 equiv), and the suspension was heated to 60−65 °C under argon over 12 h. Then the mixture was cooled and treated carefully with 6 M HCl (2 mL). After stirring the mixture for 2 h, the polymer was washed with MeOH (2 × 3 mL), 2 M HCl (5 mL), THF (2 × 3 mL), MeOH (2 × 3 mL), and THF (2 × 3 mL). The collected washings were partially concentrated in vacuo, washed with hexane (2 × 8 mL), basified with aq KOH, and extracted with DCM (4 × 8 mL). The organic extract was dried ($MgSO_4$) and concentrated to give a β-alkylated primary amine.

General Procedure for Acidic Cleavage/Reductive Workup. A polymeric support with a carbonyl compound immobilized via the hydrazone linker was washed with a mixture of TFA/H_2O/THF (1:1:8, 3 × 15 min), followed by THF, MeOH, THF, and MeOH. To the combined acidic washings was added $NaBH_4$ (20 equiv), and the mixture was left for 3 h, diluted with water (4 × volume of the mixture), and extracted three times with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under low vacuum to give the β-alkylated alcohol.

General Procedure for Acidic Cleavage/Oxidative Workup. A polymeric support with an aldehyde immobilized via the hydrazone linker was washed with a mixture of TFA/H_2O/THF (1:1:8, 3 × 15 min), followed by THF, MeOH, THF, and MeOH. To the combined acidic washings was added aqueous hydrogen peroxide (30% 1 mL/2 mL of acidic washings), and the mixture was left for 5 h, then extracted three times with DCM. The combined organic extracts were washed with aqueous sodium sulfite solution, washed with water, dried ($MgSO_4$), and concentrated under moderate vacuum to give the α-alkylated acid.

General Procedure for Oxidative Cleavage. A polymeric support with an aldehyde immobilized via the hydrazone linker was treated with m-CPBA (50 mg, 2.2 equiv) in DCM (2 mL) for 3 h. Then the gel was washed with DCM 4 × 2 mL). The combined organic washings were extracted with 10% Na_2SO_3 solution and 2 M KOH solution (1 mL of each solution/2 mL of the organic washings), and the aqueous washings were back-extracted three times with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under low vacuum (or without vacuum in the case of more volatile products) to give the α-alkylated nitrile.

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