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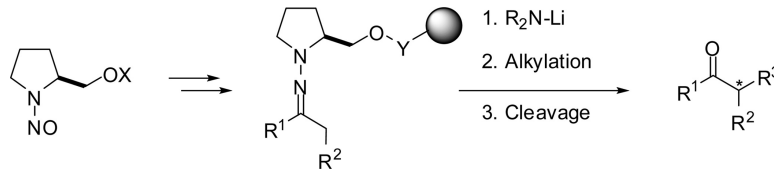

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Asymmetric Solid-Phase Alkylation of Ketones Immobilized via SAMP Hydrazone Analogue Linkers

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The preparation and application of new solid supports with chiral linkers, analogues of SAMP hydrazine on solid-phase, are described. The supports were used for immobilization of ketones (diethylketone, cyclohexanone, 4-*tert*-butylcyclohexanone), and diastereoselective alkylation of formed chiral ketone hydrazones. The enantiomeric purities of cleaved α-alkylated chiral ketones ranged from 10 to 73%. The use of chiral lithium amides for metalation of hydrazones of *t*-butylcyclohexanone increased the enantiomeric excess of the alkylated product by 25−47%.

Introduction

Alkylation of aldehydes, ketones, or their *N*,*N*-dialkylhydrazone derivatives is one of the most common, classical reactions for C−C bond construction in organic synthesis.[1] Because of the variety of known synthetic applications[2,3] and many, diverse methods for hydrazone cleavage,[4] hydrazone structural units are well suited for multifunctional linkers.[5,6] Hydrazones, including alkylhydrazones,[7] dialkylhydrazones,[8,9] sulfonylhydrazones,[10] and acylhydrazones[11−15] have been used in SPOS[16] for binding (immobilization) and transformations of aldehydes,[17,18] ketones,[10,16,19,20] amino acid-derived carbonyl compounds[11,14,15] and for polymer-supported synthesis of α-substituted ketones, aldehydes, nitriles, acids, alcohols,[20] and ketone- and aldehyde C-terminal peptides.[12,13] Enders' chiral hydrazines, SAMP and its enantiomer RAMP, are possibly[21] the most successful chiral auxiliaries used in asymmetric alkylations and many other electrophilic transformations of ketones and aldehydes in solution synthesis[2,22,23] Enders' group have prepared and used supported chiral hydrazines, SAMP and RAML analogues, for diastereoselective 1,2-addition of alkyllithiums to hydrazone C=N bonds resulting, after cleavage, in synthesis of enantiomerically enriched (50−86% ee) primary amines.[17]

Previously, we have shown that alkylation of *N*,*N*-dialkylhydrazones on solid-phase supports can give products in good yields and high purities.[8,9,19,20] In principle it should be possible to achieve asymmetric alkylation of ketones through diastereoselective alkylation of lithiated chiral hydrazones acting as linkers and chiral auxiliaries at the same time.

There are very few reports describing asymmetric alkylations of carbonyl compounds and analogues,[24] such as imines[25−27]on solid-support. Carboxylic acids are the only other carbonyl compounds, which were alkylated on solid phase, but in the form of synthetically equivalent, oxazolidinones[28−30] and oxazolines.[31] To the best of our knowledge, there are no literature reports[32] on asymmetric alkylation of ketones through alkylation of hydrazones on solid support.[33,34] In this paper, we wish to disclose our first results on asymmetric alkylation of ketones immobilized on solid phase via chiral hydrazone linkers and the first observations of an effect of metalation with a chiral lithium amide on such asymmetric alkylations.

Results and Discussion

In order to reduce the concept of chiral hydrazone linker to practice, we embarked on synthesis of Merrifield-type polymers with chiral hydrazine functionality analogous to SAMP hydrazine. We deemed the most economical approach to a chiral auxiliary-linker construct was from the chiral pool privileged structure of proline. For the sake of simplicity, the attachment of prolinol through the oxygen atom and an ether linkage to the polymer matrix was a valid option. Thus (*S*)-nitrosoprolinol (**2**) was prepared in a manner similar to that previously described for nitrosoamines.[8,9,20] The commercially available (*S*)-prolinol (**1**) was nitrosated with *tert*-butyl nitrite in THF. Because of the good performance of the nitrosation reaction and to minimize manipulation of a potentially carcinogenic (**Caution!**) substance, the resulting *N*-nitroso amino alcohol **2** was used in the next step without purification and in the same vessel (Scheme 1).

Synthesis of Chiral Hydrazone Linkers with and without Spacers in Solution. We were aware of the possible deleterious effect of the polymer matrix on the performance and selectivity of reactions involving low temperatures and lithiated reagents and decided to test the effect of a spacer between the polymer matrix and chiral auxiliary. To prepare the chiral auxiliary with a 3- or 6-carbon atom spacer, (*S*)-nitrosoprolinol (**2**) was subjected to the Williamson etherification with THP-protected 3-bromo- or 3-iodopropan-1-ol and with THP protected 6-iodohexan-1-ol (**3**). The Williamson reaction was attempted with NaH or potassium *tert*-butoxide as a base in THF, DMF, and *N*-methylpyrrolidone (NMP) with or without crown ethers. In general, the reactions

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Scheme 1

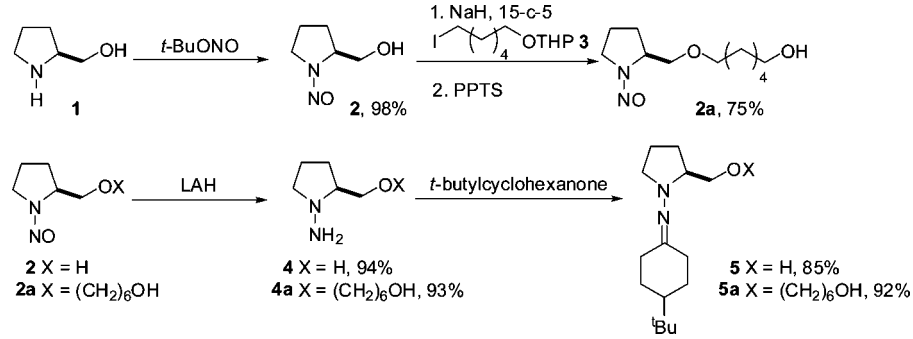


Table 1. Loadings of Ketones on Hydrazone Polymeric Supports

polymeric support (ketone)	theoretical loading of ketone [mmol/g]	practical loading of ketone[a] [mmol/g]	yield based on loading (%)
6 (4-*tert*-butylcyclohexanone)	0.95	0.59	62
6a (4-*tert*-butylcyclohexanone)	0.87	0.86	99
8 (cyclohexanone)	1.01	0.52	51
8a (cyclohexanone)	0.91	0.74	81
9 (3-pentanone)	1.02	0.54	53
9a (3-pentanone)	0.92	0.73	79

[a] Loading determined from mass of the released ketone.

of iodides with sodium hydride and the crown ether (15-crown-5) in *N*-methyl-2-pyrrolidone[35] gave better results. The best isolated yield of the ether product **2a** was obtained for 6-iodo-1-hexanol (75%). The yield of the reaction of (*S*)-nitrosoprolinol (**2**) with 3-iodo-1-propanol was poor (10%), even with the crown ether as the additive and NMP as the solvent. In light of these results, we opted for the linker with a 6-carbon atom spacer only (Scheme 1).

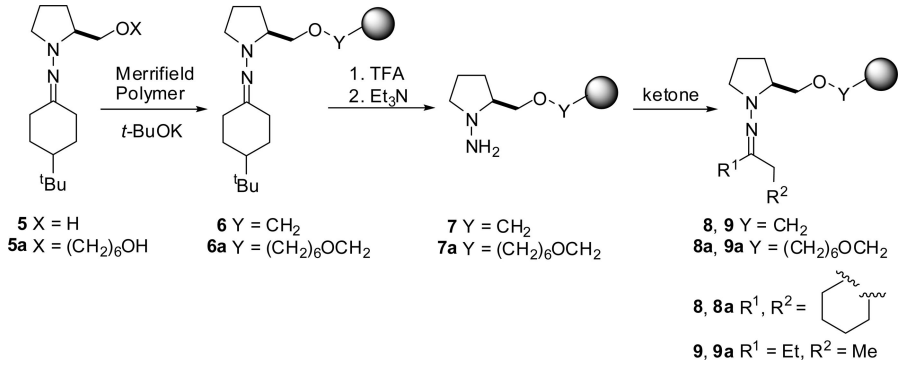
Two prolinol-derived hydrazones with and without spacer were prepared in solution. (*S*)-Nitrosoprolinol (**2**) and its spacer modified counterpart, (*S*)-6-(1-nitrosopyrrolidin-2-ylmethoxy)hexan-1-ol (**2a**), were reduced with lithium aluminum hydride in THF (Scheme 1) to give corresponding hydrazines **4** and **4a** in good isolated yields (93% and 94%). The crude isolated hydrazines were reacted with 4-*tert*-butylcyclohexanone in dry THF. Evaporation of volatiles and distillation on a Kugelrohr apparatus furnished hydrazones **5** and **5a** in 85% and 92% yields, respectively.

Reactions on Polymeric Support. The chiral hydrazones **5** and **5a** were anchored to the Merrifield resin under previously described conditions[20] (*t*-BuOK, THF, 80 °C) giving 4-*tert*-butylcyclohexanone hydrazone-protected hydrazine supports **6** and **6a**. The loadings of hydrazine groups on these polymers (determined from mass of the released 4-*tert*-butylcyclohexanone, Table 1) proved that this strategy of attachment of protected chiral hydrazines on solid-support was very effective. To immobilize other ketone substrates for solid-phase alkylations, the 4-*tert*-butylcyclohexanone immobilized on resins **6** and **6a** was exchanged for 3-pentanone or cyclohexanone. This was done by activation of the linkers (cleavage of hydrazone) with wet 10% trifluoroacetic acid solution in THF (release of 4-*tert*-butylcyclohexanone), washing with triethylamine (neutralization), and formation of hydrazones with new ketones (Scheme 2).

Asymmetric Alkylation. The resulting immobilized chiral hydrazones (**6**, **8**, **9**, **6a**, **8a**, **9a**) were alkylated in the standard way:[20] deprotonated/lithiated with LDA (4 h, 0 °C) and reacted with benzyl bromide or propyl iodide (−78 °C to rt overnight, Scheme 3). Cleavage of the α-alkylated ketones from the chiral polymeric auxiliary gave products with overall moderate enantiomeric excesses (10−73%, Table 2), and good overall yields (50−80%) after 3 reaction steps: (i) loading by ketone exchange (except for 4-*tert*-butylcyclohexanone), (ii) alkylation, and (iii) cleavage followed by workup (yields based on gravimetric loading[20] of 4-*tert*-butylcyclohexanone on resins **6** or **6a**). A measurable effect of the 6-carbon atom spacer on the enantioselectivities of these reactions was observed. Enantiomeric excesses (Table 2) were higher for ketones immobilized on solid support via the linker separated from the polymer matrix with the spacer (18−73%) than for ketones immobilized via the same linker without a spacer (10−63%). The highest enantioselectivity obtained for alkylation of 3-pentanone with propyl iodide was 73% ee and for alkylation of cyclohexanone with propyl iodide was 67% ee. The selectivities obtained on solid phase were, nevertheless, lower compared to results obtained with SAMP in solution. Enders using SAMP hydrazine as the chiral auxiliary in solution, reported higher enantioselectivities for these alkylations, 99.5% ee[22] and 86% ee[36] respectively. The lowering of the ee values compared to analogous reactions in solution was in accord with other reports[33] and most likely stems from the effect of the polymer support because possible racemization during workup was experimentally excluded. Potential detrimental effects of remaining, unreacted halogens of the Merrifield resin (benzylic chloride) should not be problematic because our hydrazone immobilization procedure (prolonged reaction with *t*-BuOK and primary alcohol) was specifically designed and tested (chlorine could not be detected in so prepared polymers) for quantitative reaction and capping of unreacted benzylic chloride with *tert*-butyl ether.[20]

Effect of Chiral Lithium Amides on Solid-Phase Reaction. To the best of our knowledge, chiral hydrazone auxiliaries have been deprotonated (metalated) with achiral bases such as LDA, *n*-BuLi, or KDA,[2,3] and one attempt has been made to use chiral base, lithium bis-(1-phenylethyl)-amide, to deprotonate and alkylate chiral hydrazone in toluene solution,[37] albeit with decrease of diastereoselectivity with either enantiomer of the chiral base used. We felt that the theoretically possible influence of a chiral metalating reagent on diastereoselectivity of alkylation and, as a result,

Scheme 2



Scheme 3

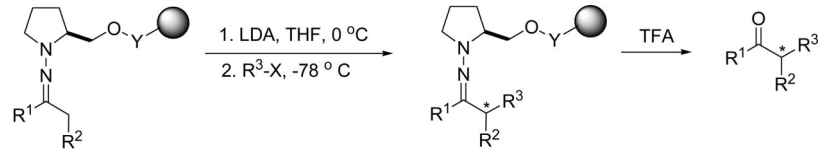
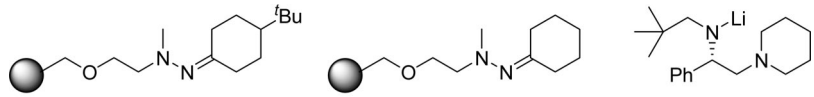


Table 2. Enantiomeric Excesses of Cleaved Alkylated Ketones

polymeric support without spacer (ketone)	R_3X	ee[a] (%)	yield (%)	polymeric support with spacer (ketone)	R_3X	ee[a] (%)	yield (%)
6 (4-*t*-Bu-cyclohexanone)	PrI	14[b]	53	**6a** (4-*t*-Bu-cyclohexanone)	PrI	33[b]	80
6 (4-*t*-Bu-cyclohexanone)	BnBr	10[b]	51	**6a** (4-*t*-Bu-cyclohexanone)	BnBr	18[b]	80
8 (cyclohexanone)	PrI	63	50	**8a** (cyclohexanone)	PrI	67	71
8 (cyclohexanone)	BnBr	60	57	**8a** (cyclohexanone)	BnBr	62	79
9 (3-pentanone)	PrI	53	59	**9a** (3-pentanone)	PrI	**73**	71
9 (3-pentanone)	BnBr	55	51	**9a** (3-pentanone)	BnBr	67	77

[a] ee determined by GC with chiral phase column. [b] ee of the major diastereoisomer (dr = from 80:20 to 87.5:12.5).

Table 3. Enantiomeric Excesses of Cleaved Alkylated Ketones **11** Obtained by Deprotonation with Koga's Chiral Lithium Amide **14** and Alkylation with Benzyl Bromide



12 **13** **14**

polymeric support (loaded ketone)	ee[a] (%)	dr[c] (%)	yield (%)
12 (4-*t*-Bu-cyclohexanone)	<1[b]	79:21	66
13 (cyclohexanone)	<1		60
8 (cyclohexanone)	65		51
6 (4-*t*-Bu-cyclohexanone)	56[b]	82:18	67
6a (4-*t*-Bu-cyclohexanone)	55[b]	77:23	78

[a] ee determined by GC with chiral phase column. [b] ee of the major diastereoisomer. [c] dr = diastereomeric ratio determined by GC.

on the enantiomeric purity of the alkylated ketone products is worth probing and could, potentially, be useful for solid-phase asymmetric synthesis (SPAS).[24,38] The effect of chiral deprotonating base could be easily probed in a reaction on solid phase. During the metalation(deprotonation)/alkylation sequence on an immobilized hydrazone, the deprotonating reagent can be washed out before the alkylating reagent is added thus eliminating the necessary separation of the chiral reagent (in this case the chiral amine) from the alkylation product. The use of the chiral base introduces new potential stereocontrolling elements (in addition to chiral hydrazone auxiliary) and could influence the diastereoselective alkylation. On the basis of the above reasoning, the influence of chiral lithium amides on enantioselectivity of deprotonation/lithiation of achiral (**12** and **13**) and chiral hydrazones (**6** and **6a**) was shortly investigated.

The deprotonation of achiral hydrazone of cyclohexanone **13** and 4-*tert*-butylcyclohexanone **12** with chiral lithium amide **14** (Koga's lithium amide made from phenyl glycine and piperidine[39]), followed by washing with THF and alkylation with BnBr, gave virtually racemic (within experimental error) products 0.5−1% ee (Table 3). The use of the same chiral reagents and same reactions sequence on chiral cyclohexanone hydrazones **8** gave products with enantiomeric purity changed by 4−5% compared to the results with LDA. These results, in principle, are in agreement with the known rationalization for diastereoselectivity (precisely the diastereotopic face selectivity) of prolinol derived hydrazone

azaenolate (e.g., SAMP) alkylations where the chiral auxiliary (in this case the chiral linker) controls the face selectivity of this reaction. On the other hand, the products of alkylation of 4-*tert*-butylcyclohexanone hydrazone had measurably increased ee's by 25−27% for the hydrazone **6a** with C_6 spacer and by 30−47% for the hydrazone **6** with no spacer. For the C_s symmetrical ketone such as 4-*tert*-butylcyclohexanone where the whole ketone alkylation process is an enantiotopic group selective substitution (enantiotopic hydrogen atoms are selectively exchanged for alkyl groups), one would expect combined effects of the chiral hydrazone linker and the chiral deprotonating reagent. Indeed, the observed increase in the stereoselection for the solid-phase alkylation could be rationalized on the basis of the diastereoselective deprotonation/lithiation of the chiral hydrazones with the chiral lithium amide. SAMP-type hydrazones of 4-*tert*-butylcyclohexanone has two elements of chirality: axis of chirality and the prolinol center of chirality and, as such, form two equilibrating diastereomers (via configuration change on nitrogen atom of the hydrazone C═N bond). Diastereoselective lithiation of the diastereomers by the chiral lithium amide may be invoked to rationalize the observed effect. However any rationalizations of the newly observed effects are very speculative (e.g., the specific bidentate structure of the Koga's lithium amide can also play a role) and therefore wider research of this type of reactions will be necessary.

Conclusions

In summary, two novel chiral hydrazine resins, analogues of SAMP hydrazine on solid-phase, have been developed and used as chiral auxiliaries in alkylation of ketones immobilized on polymer supports. The formed chiral hydrazones acting as chiral linkers allowed for enantioselective alkylation of ketones on solid-phase supports. The obtained chiral α-alkylated ketones had moderate enantiomeric excesses: 18−73% ee for the chiral polymer with the 6-carbon atom spacer and 10−63% for the analogous resin without a spacer. This may indicate a necessity for separation of the reacting lithiated hydrazones from the polymer matrix. The application of chiral deprotonating agents and chiral hydrazones may improve stereoselectivity of hydrazone reactions and may be conveniently achieved on solid support, which allows for easy recovery of the chiral agents.

A significant increase of stereoselectivity of alkylation was observed for the C_s symmetrical ketone, that is, 4-*tert*-butylcyclohexanone hydrazone only. This approach to stereoselective deprotonations and performing synthesis of enantiomerically enriched compounds will be further studied in our laboratories.

Experimental Section

General. All air-sensitive reactions were carried out under argon. Tetrahydrofuran was distilled under argon from sodium/benzophenone. Chromatographic purifications were achieved by dry-column flash chromatography[40] (DFC). 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. Infrared (IR) spectra were recorded on a Nicolet Magna-IR 550 FTIR Series II spectrometer as $CHCl_3$ solutions or, in case of polymers, as pressed disks with KBr. Only diagnostic peaks are reported (cm^{-1}). Magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on a Bruker 200 MHz spectrometer in $CDCl_3$, unless otherwise stated. The gel-phase ^{13}C NMR spectra of polymers were recorded after at least 1 h swelling in $CDCl_3$. Chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane. The enantiomeric purities of alkylated ketones were determined by GC analysis on chiral stationary phase column (CP-Chirasil-Dex CB 25m, 0.25 mm). **CAUTION***: Any exposure to the* N*-nitroso and hydrazine derivatives must be avoided because of their potential high toxicity*.

(*S*)-(1-Nitroso-pyrrolidin-2-yl)-methanol (2).[41] To a solution of (*S*)-(+)-pyrrolidin-2-ylmethanol (**1**, 1.01 g, 10 mmol) in THF (8 mL) was added *tert*-butyl nitrite (2.38 mL, 2.06 g, 20 mmol), and the mixture was refluxed for 18 h without admission of light. The solvent and the excess of *tert*-butyl nitrite were removed in vacuo to give a crude product as a yellow oil (1.27 g, 98%): R_f (10% MeOH/DCM) 0.65; δ_H 4.60−4.40 (m, 1H), 4.12−3.90 (m, 2H), 3.82−3.45 (m, 2H), 2.70 (s, 1H), 2.30−1.80 (m, 4H).

Preparation of 2a. (A). (2*S*)-1-Nitroso-2-((6-(tetrahydro-2H-pyran-2-yloxy)hexyloxy)methyl)pyrrolidine. To a solution of (*S*)-(1-nitrosopyrrolidin-2-yl)methanol (**2**, 0.130 g, 1 mmol) in NMP (1 mL), under argon, was added sodium hydride (0.050 g, 1.2 mmol, 60% dispersion in oil) and the crown ether 15-C-5 (0.037 g, 0.03 mL 0.17 mmol). The mixture was stirred for 30 min and cooled to 0 °C. Then 2-(6-iodohexyloxy)tetrahydro-2*H*pyran (**3**, 0.624 g, 2 mmol) was added, and the mixture was allowed to warm up to room temperature. After 16 h, the reaction mixture was dissolved in water and extracted with DCM (3 × 10 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo to give a crude product. Purification through DFC (0−50% AcOEt/Hex) gave the title compound as a yellow oil (0.238 g, 75%): R_f (50% AcOEt/Hex) 0.50 and 0.55 (two diastereoisomers); HRMS (EI) M^+, found 314.2201; $C_{16}H_{30}N_2O_4$ requires 314.2206; δ_H 4.71−4.35 (m, 2H), 4.20−3.31 (m, 10H), 2.25−1.67 (m, 6H), 1.65−1.23 (m, 12H); δ_C 98.4, 71.9, 71.2, 67.0, 61.9, 60.2, 45.4, 30.4, 29.3, 29.1, 27.0, 25.7, 25.6, 25.5, 20.6, 19.3; (NMR signals are reported for the major diastereomer) $\nu_{max}(CHCl_3)$ 1312 (N═O), 1025 (C−O) cm^{-1}; *m*/*z* (EI) 314 (M^+, 2), 85 (100), 55 (77), 70 (75), 41 (63), 83 (36), 84 (26), 55 (25).

(B). (*S*)-6-((1-Nitrosopyrrolidin-2-yl)methoxy)hexan-1-ol (2a). To a solution of PPTS (0.180 g, 0.75 mmol) in 95% ethanol (10 mL) was added a solution of (2*S*)-1-nitroso-2-((6-(tetrahydro-2*H*-pyran-2-yloxy)hexyloxy)methyl)-pyrrolidine (1.260 g, 4.00 mmol) in EtOH (10 mL). The reaction mixture was heated to 55 °C for 10 h and then was concentrated in vacuo. The crude product was purified by DFC (20−80% AcOEt/Hex) to give a yellow oil (0.775 g, 84%): R_f (50% AcOEt/Hex) 0.20; HRMS (EI) M^+, found 230.1636; $C_{11}H_{22}N_2O_3$ requires 230.1630; δ_H 4.65−4.33 (m,

1H), 4.17−3.30 (m, 8H), 2.28−1.82 (m, 4H), 1.80−1.26 (m, 9H); δ_C 72.0, 71.0, 62.5, 60.5, 45.8, 32.4, 29.2, 27.1, 25.7, 25.3, 20.8; (NMR signals are reported for the major isomer) $\nu_{max}(CHCl_3)$: 3453 (OH), 1311 (N═O), 1126 (C−O) cm^{-1}; *m/z* (EI) 230 (M^+, 2), 55 (100), 83 (50), 70 (39), 41 (38), 99 (19), 42 (18), 84 (14).

(*S*)-6-((1-Aminopyrrolidin-2-yl)methoxy)hexan-1-ol (4a). To a heated suspension of $LiAlH_4$ (0.379 g, 10 mmol) in dry THF (10 mL) was added a solution of nitrosoamine **2a** (1.15 g, 5 mmol) in THF (10 mL), and the resulting mixture was refluxed for 7 h. Then the excess of $LiAlH_4$ was quenched with aq NH_3 and aq 2 M KOH. The solids were filtered off and washed with hot THF (3 × 10 mL). The combined filtrates were evaporated in vacuo, and the residue was dissolved in DCM (10 mL), dried ($MgSO_4$), and again evaporated in vacuo to give the crude product as a yellow oil (1.00 g, 93%): R_f (10%MeOH/DCM) 0.10; HRMS (EI) M^+, found 216.1842; $C_{11}H_{24}N_2O_2$ requires 216.1838; δ_H 3.67−3.38 (m, 7H), 3.30−3.20 (m, 1H), 2.52−2.25 (m, 2H), 2.03−1.30 (m, 14H); δ_C 74.2, 71.2, 68.3, 61.9, 59.4, 32.5, 29.3, 26.2, 25.7, 25.4, 20.7; $\nu_{max}(CHCl_3)$: 3666, 3630 (NH_2), 3340 (OH), 1108 (C−O) cm^{-1}; *m/z* (EI) 216 (M^+, 3), 85 (100), 41 (15), 68 (8), 55 (7), 43 (6), 86 (5), 57 (4).

General Procedure for Preparation of Chiral Hydroxyhydrazones 5 and 5a. To a solution of 4-*tert*-butylcyclohexanone (1.16 g, 7.5 mmol) in dry THF (20 mL) was added the hydrazine **4** or **4a** (5 mmol), and the mixture was refluxed for 12−14 h. Then the solvent was removed under vacuum, and the residue was distilled on a Kugelrohr apparatus to give the hydrazone **5** or **5a**.

(*S*)-(1-(4-*tert*-Butylcyclohexylideneamino)pyrrolidin-2-yl)methanol (5). Kugelrohr distillation (130−150 °C/0.17 mmHg) gave a yellow oil (1.36 g, 85%): R_f (10%MeOH/DCM) 0.55; HRMS (EI) M^+, found 252.2198; $C_{15}H_{28}N_2O$ requires 252.2202; δ_H 3.73−3.45 (m, 2H), 3.30−2.98 (m, 3H), 2.50−2.33 (m, 1H), 2.20−1.57 (m, 9H), 1.35−1.05 (m, 4H), 0.87 (s, 9H); δ_C 168.8, 67.1, 64.2, 54.3, 47.4, 35.6, 32.4, 29.1, 27.9, 27.5, 27.1, 25.0, 22.2 (NMR signals are reported for the major isomer); $\nu_{max}(CHCl_3)$: 1638 (C═N) cm^{-1}; *m/z* (EI) 240 (M^+, 2), 57 (100), 221 (79), 41 (40), 70 (25), 55 (19), 96 (17), 69 (15).

(*S*)-6-((1-(4-*tert*-Butylcyclohexylideneamino)pyrrolidin-2-yl)methoxy)hexan-1-ol (5a). Kugelrohr distillation (200−218 °C/0.3 mmHg) gave a yellow oil (1.72 g, 92%): R_f (10%MeOH/DCM) 0.50; HRMS (EI) M^+, found 352.3099; $C_{21}H_{40}N_2O_2$ requires 352.3090; δ_H 3.63 (t, J = 7,5 Hz, 2H), 3.56−3.38 (m, 2H), 3.35−3.18 (m, 2H), 3.10−3.00 (m, 1H), 2.65−2.26 (m, 2H), 2.20−1.52 (m, 13 H), 1.43−1.02 (m, 9H), 0.90 (s, 9H); δ_C 169.0, 73.6, 71.2, 65.8, 62.4, 54.5, 47.3, 35.2, 32.6, 32.2, 29.5, 29.3, 28.8, 27.9, 27.4, 26.9, 25.8, 25.5, 21.9 (NMR signals are reported for the major isomer); $\nu_{max}(CHCl_3)$: 1637 (C═N) cm^{-1}; *m/z* (EI) 352 (M^+, 3), 221 (100), 57 (65), 41 (38), 55 (28), 22 (15), 69 (13), 70 (12).

General Procedure for Anchoring of Chiral Hydroxyhydrazones 5 and 5a on Merrifield Resin. To a solution of chiral hydroxyhydrazones **5** or **5a** (4 mmol) in dry THF (6 mL) was added potassium *tert*-butoxide (0.448 g, 4 mmol), and the mixture was stirred under argon for 30 min. Then Merrifield gel (1.110 g, Novabiochem, 1% PS-DVB, 200−400 mesh, 1.2 mmol/g) was added, and the suspension was heated to 80 °C for 48 h with intermittent stirring. The polymer was washed successively with THF (2 × 6 mL), MeOH (2 × 4 mL), THF (2 × 6 mL), MeOH (2 × 4 mL), DCM (2 × 6 mL), MeOH (2 × 4 mL), DCM (2 × 6 mL), MeOH (2 × 4 mL), H_2O/DMF (v/v = 2:8, 2 × 4 mL), H_2O (1 × 4 mL), MeOH (2 × 4 mL), H_2O/DMF (v/v = 2:8, 2 × 4 mL), THF (2 × 6 mL), MeOH (2 × 4 mL), THF (2 × 6 mL), MeOH (2 × 4 mL), DCM (2 × 6 mL), MeOH (2 × 4 mL), DCM (2 × 6 mL), and MeOH (2 × 4 mL). The residual solvent was removed from the gel in vacuo, and the gel was dried to a constant mass (ca. 2 h) under high vacuum.

(*S*)-(1-(4-*tert*-Butylcyclohexylideneamino)pyrrolidin-2-yl)methyloxymethylpolystyrene (6): yellow powder (1.239 g, 89%, loading 0.59 mmol/g, theoretical loading 0.95 mmol/g); ν_{max}(KBr) 1639 (C═N) cm^{-1}; δ_C 168.3, 67.2, 64.4, 54.5, 47.7, 35.8, 32.6, 29.3, 28.5, 28.2, 27.7, 25.7, 22.8.

(*S*)-6-((1-(4-*tert*-Butylcyclohexylideneamino)pyrrolidin-2-yl)methoxy)hexyloxymethylpolystyrene (6a): orange powder (1.490 g, 97%, loading 0.86 mmol of 4-*tert*-butylcyclohexanone/g, theoretical loading 0.87 mmol/g); ν_{max}(KBr) 1637 (C═N) cm^{-1}; δ_C 168.5, 73.7, 71.4, 70.5, 66.2, 54.7, 47.5, 35.6, 32.5, 32.4, 29.7, 29.4, 28.9, 28.5, 28.0, 27.6, 27.1, 26.1, 22.1.

General Procedure for Anchoring of a Ketone, Alkylation, and Cleavage on Polymers Type 6 and 6a. The polymer **6** or **6a** (0.3 g) was washed under argon with a mixture of TFA/H_2O/THF (1: 1: 8, 3 × 10 min), followed by THF (2 × 5 mL), Et_2O (2 × 5 mL), THF (2 × 5 mL), Et_2O (2 × 5 mL), 10% Et_3N in DCM, (2 × 5 mL), MeOH (2 × 5 mL), DCM (2 × 5 mL), and dry THF (6 × 2 mL). Then a solution of a ketone (9−12 equiv) in dry THF (2.5 mL) was added. The suspention was heated under reflux for 48 h in the presence of molecular sieves 4 A. Then the molecular sieves were removed with tweezers, and the gel was washed with THF (2 × 5 mL), Et_2O (2 × 5 mL), THF (2 × 5 mL), and Et_2O (2 × 5 mL). The resulting gel, **8**, **8a**, **9**, or **9a**, was washed with dry THF (3 × 3 mL) and was cooled to 0 °C. Then a cooled solution of lithium amide (3.0 mL, 10 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 the lithium amide was removed, and the gel was washed with dry THF (2−3 × 3 mL) by a positive pressure of argon. A solution of an alkylating agent (10 equiv) in THF (3 mL) was subsequently added. The resulting mixture was agitated and warmed up 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), and DCM (2 × 5 mL). The polymeric support was then subjected to hydrazone linker cleavage by washing with a mixture of TFA/H_2O/THF (1: 1: 8, 3 × 10 min), followed by THF, MeOH, DCM, MeOH, DCM, MeOH. The combined acidic solutions were washed with a saturated aqueous solution of $NaHCO_3$. 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 ketone products.

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