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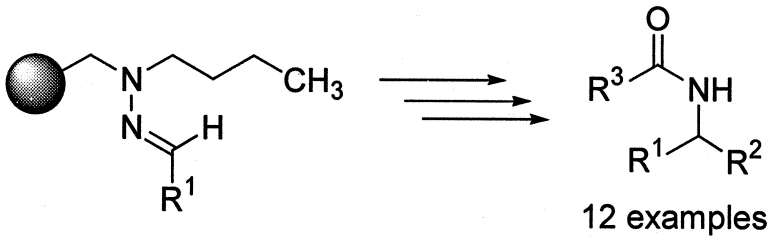

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A Novel Hydrazine Linker Resin and Its Application for the Solid-Phase Synthesis of α-Branched Primary Amines

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A novel hydrazine linker resin for solid-phase organic synthesis has been developed. Starting from Merrifield resin, the new *N*-butyl-*N*-methylpolystyrene-hydrazine linker is prepared in three steps. Polymer-supported hydrazones, readily prepared from aldehydes and the hydrazine resin, react with alkyl- and arylorganolithium reagents under 1,2-addition to the C−N double bond to afford the corresponding hydrazines. Release from solid support was achieved by reductive *N*−*N* bond cleavage using the borane-tetrahydrofuran complex. The resulting α-branched primary amines were protected as their amides or carbamates, respectively, and, after purification, were obtained in good overall yields and in high purity (12 examples).

Introduction

The solid-phase synthesis of primary amines is of great importance to various fields of organic and medicinal chemistry, since they are both valuable synthetic intermediates and often interesting target molecules. The generation of libraries of commercially unavailable amines has received considerable interest within combinatorial chemistry since a large number of primary amines show biological activity[2] and the primary amine moiety is incorporated into various molecules encountered in medicinal chemistry. Moreover, these amines can serve as building blocks in the preparation of further libraries.

The most common methods for the synthesis of amines on solid support include nucleophilic substitution, Michael-type additions, as well as the reduction of imines, amides, carbamates, nitro groups, and azides.[3] Nevertheless, only a few methods for the solid-phase synthesis of α-branched amines have been developed until now. These include the reduction of ketimines with metal hydride reagents[4] and the addition of carbon nucleophiles to the C−N bond of imines, employing C−H acidic compounds,[5] alkynes,[6] electron-rich heterocycles,[6] and organometallic compounds such as organolithium[7] and Grignard reagents[8] as nucleophiles. Support bound carbon nucleophiles such as *O*-silylthioketene acetals and alkynes have also been successfully added to imines.[6,9]

Most of these protocols have the disadvantage of leaving a "trace" of the polymer support on the nitrogen atom after cleavage. Some linker resins such as Rink and Sieber resins have been developed to circumvent this drawback;[8,10] however, rather long transformations are required for their preparation. Recently, Kobayashi et al.[11] described a novel *p*-benzyloxybenzylamine (BOBA) resin employing the addition of silyl enolates to polymer bound aldimines followed by oxidative cleavage with DDQ to release the α-branched amine.

The preparation of primary amines involving 1,2-addition of organometallic reagents to the C−N double bond of aldehyde hydrazones in solution are well documented.[12] Although hydrazones are frequently used as intermediates in organic synthesis,[13] they are rarely encountered in solid-phase organic synthesis (SPOS). Polymeric sulfonylhydrazines react readily with aldehydes and ketones to form hydrazones, which can release the corresponding alkenes, alkanes, and nitriles[14] or the carbonyl compound itself.[15] Polystyrene sulfonyl hydrazide is commercially available as scavenger resin.[16] For the preparation of peptide aldehydes and peptide trifluoromethyl ketones, some of which have been shown to be highly specific enzyme inhibitors, semicarbazide linker resins were successfully employed.[17] Solid support bound arylhydrazides have been used in the synthesis of peptide carboxylic acids, -amides, and -esters[18] as well as in the preparation of pyrazolone derivatives via $Sc(OTf)_3$ catalyzed reaction of ketene silyl acetals with polymer supported acylhydrazones.[19] Recently Waldmann et al.[20] described the use of arylhydrazides as "traceless linkers" and their application in cross coupling reactions.

In this paper, we report the synthesis and characterization of a novel dialkylhydrazine linker, which, in contrast to the linkers mentioned above, is stable toward organometallic reagents. Using this to our advantage, a series of α-branched primary amines were synthesized by attachment of various aldehydes, followed by 1,2-addition of organolithium reagents to the resulting hydrazones furnishing trisubstituted hydrazines and subsequent reductive cleavage from the solid support.

Results and Discussion

As outlined in Scheme 1, commercially available Merrifield resin **1** (1−2% divinylbenzene, 200−400 mesh, 0.75 mmol g^{-1}) was treated with an excess of *n*-butylamine in dry dimethylformamide (DMF) at 80 °C according to a literature procedure.[21] The yield of the reaction was determined to be quantitative by elemental analysis (see Experimental Section), and resin **2** was obtained as a tan colored product. The second step in the linker synthesis, the nitrosation of the secondary amine, was achieved by treat-

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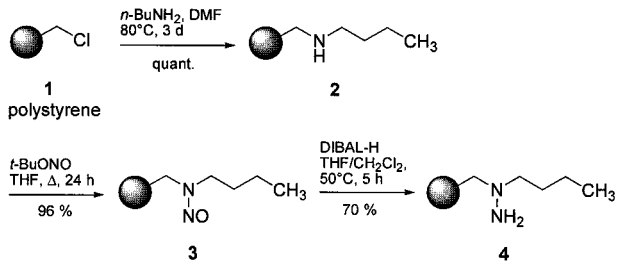
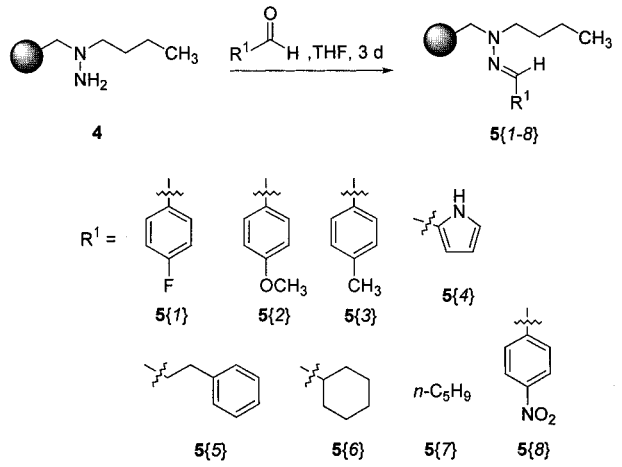
Scheme 1. Synthesis of the Hydrazine Linker **4**



Scheme 2. Attachment of Aldehydes to Hydrazine Resin **4**



ment of resin **2** with a 10-fold excess of *t*-BuONO in tetrahydrofuran under reflux for 24 h. Excess of reagent could be easily washed out to yield a yellowish resin **3** in 96% yield judged by elemental analysis (see Experimental Section). Qualitative IR analysis also indicated the successful formation of the nitrosamine moiety [appearance of the N−O stretch at 1450 cm^{-1}, literature: ν(N−O) 1430−1460 cm^{-1}].

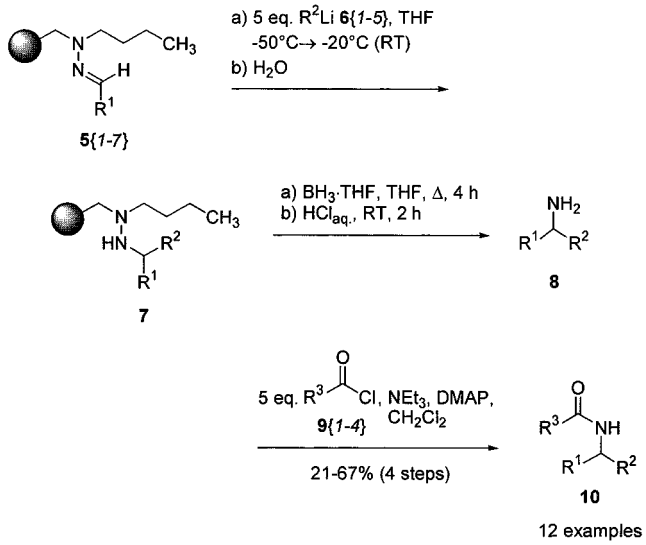
The reduction of the nitrosamine resin **3** with excess diisobutylaluminum hydride (DIBAL-H) in THF/CH_2Cl_2 at elevated temperature (50 °C) afforded the hydrazine linker **4** in good yield (70%). Crucial at this point was the complete hydrolysis of excess DIBAL-H and careful washing of the resin with THF/water mixtures. However, the resulting resin **4** still contained a considerable amount of aluminum salts, but still proved to be suitable for aldehyde attachment. The loading of the linker resin **4** was determined by condensation with nitrogen-containing aldehydes such as *p*-nitrobenzaldehyde or 2-pyrrolcarboxaldehyde and subsequent elemental analysis of the resulting hydrazone resins **5**{*8*} and **5**{*4*}. In both cases, the amount of nitrogen indicates a loading of 0.5 mmol g^{-1}.

Coupling of the resin **4** with various aliphatic and aromatic aldehydes (Scheme 2) at room temperature in dry THF led to the formation of a series of new hydrazone resins **5**{*1*−*8*}. An excess of the aldehydes was used to achieve a high conversion.

The hydrazone resins **5**{*1*−*8*} are stable at 0 °C for several months and have a slightly yellow to orange color. The swelling properties are comparable to those of the starting material.

Synthesis of α-Branched Amines via 1,2-Addition. For the addition of carbon nucleophiles to hydrazone resins **5**{*1*−*7*}, several organometallic reagents have been tested. It is well-known from solution-phase synthesis that organolithium, -cerium, -ytterbium, and Grignard reagents add to the C−N double bond of imino derivatives.[12,22] The application of organocerium and -ytterbium reagents to solid-phase synthesis appeared to be problematic, since the corresponding lanthanide oxides obtained after hydrolysis are insoluble and therefore cannot be separated from the product resin. We therefore investigated the reaction of Grignard-, organozinc, and organolithium reagents with resins **5**{*1*−*7*}. While Grignard and organozinc reagents did not add to the C−N double bond even at room temperature, organolithium compounds react very well even at mild temperatures (−50 °C). Optimized reaction conditions reflected the reactivity of the nucleophiles and usually involved the employment of 5 equiv of organolithium reagent at −50 °C in dry THF, warming to −20 °C after addition (3 h) and subsequent hydrolysis (Scheme 3). Very reactive nucleophiles such as *tert*-butyllithium were added at −78 °C.

Scheme 3. Synthesis of α-Branched Primary Amines (for details see Table 1)



The resulting lithium hydroxide could be easily washed out with THF/water mixtures, and the hydrazine resins **7** were obtained as slightly yellow products and with loadings ranging from 100 to 70% according to the nitrogen content determined by elemental analysis.

For the release of the α-branched amines via *N*−*N* bond cleavage of the trisubstituted hydrazines **7**, several methods are described for solution chemistry.[23] Protocols employing metal promoted hydrogenolysis or solvated electrons (alkalimetals, liquid ammonia) seemed unsuitable for solid-phase synthesis, owing to the nature of the solid support. *N*−*N* bond cleavage affording amines **8** was accomplished by using the borane-tetrahydrofuran complex (BH_3·THF) according to standard procedures developed in our group (Scheme 3). Thus, the hydrazine resins **7** were treated with excess BH_3·THF in THF under reflux for 4 h, followed by cooling to ambient temperature and hydrolysis with 3 M aqueous hydrochloric acid. After filtration and evaporation of solvents, the resulting residue was taken up in hydrochloric acid and extracted with pentane in order to remove nonpolar impurities. The crude amines **8** were obtained by basifying of the

aqueous phase and extraction with dichloromethane in yields of 30−80% based on resin **4** and initial purities of 50−70% estimated by NMR.

A series of α-branched amines were synthesized on solid support to study steric and electronic effects of both the hydrazone as well as the nucleophile during the C−C bond formation (Table 1).

Concerning the hydrazone resin **5**{*1*−*7*}, we found no significant electronic effects caused by electron-withdrawing or electron-donating groups on the aryl ring of the hydrazone (entries **1**, **2**, and **3**), though yields were variable. Both alkyl and aryl nucleophiles add to the C−N double bond of solid bound aromatic aldehyde hydrazones, although aryl nucleophiles require longer reaction times and higher temperatures (RT) (**4** and **5**, respectively). Even bulkier nucleophiles such as *s*-butyllithium gave good results (**3**), and substrates with acidic protons are tolerated (**6**). Also, the coupling of alkyl nucleophiles to aliphatic hydrazones works well. *n*-Hexyllithium, *n*-butyllithium, and even the sterically demanding *tert*-butyllithium add to linear (**7** and **8**) and α-branched hydrazones (**9** and **10**). The addition of phenyllithium to aliphatic hydrazones seems to proceed less efficiently, since in these cases the amides **10**{*7,4,4*} and **10**{*5,4,3*} were obtained in slightly lower yields than usual (entries **11** and **12**). However, we were not able to employ methyllithium in the reaction with aliphatic or aromatic hydrazones successfully. Even reaction at room temperature and use of additives such as HMPA or TMEDA did not give rise to the desired products after *N*−*N* bond cleavage. Surprisingly, treatment of hydrazone **5**{*3*} with methyllithium, followed by *N*−*N* bond cleavage and amine protection with benzoyl chloride, furnished not the expected α-branched amide but *N*-protected *p*-toluylamine **11** in 23% overall yield (Scheme 4). The same result was obtained by direct reduction of hydrazone **5**{*3*} with excess BH_3·THF.

A possible way to avoid this problem and to obtain the methyl-substituted amines could be addition of nucleophiles to acetaldehyde hydrazone resins.

The purification of the crude amines **8** was carried out by protection of the amine functionality as their corresponding amides and carbamates. Thus, the reaction of crude amines **8** with 3 equiv of acid chloride or chloroformate, 10 equiv NEt_3, and catalytic amounts of DMAP in dry dichloromethane, followed by chromatographic purification, afforded the acylated amines **10** in moderate to good yields and purities, which were determined by GC and HPLC to be consistently greater than 94%. While carbamates offer the possibility of convenient deprotection, amides are very important intermediates for peptide synthesis.

Conclusion

In summary, a new hydrazine linker has been developed and applied to the synthesis of α-branched amines. Although purification of the resulting amines is necessary, the methodology shows great flexibility regarding aliphatic and aromatic nucleophiles and aldehydes. In principle, the strategy should be applicable in the asymmetric synthesis of amines by using a chiral linker. Further investigations in this area are in progress in our laboratories and will be reported in due course.

Experimental Section

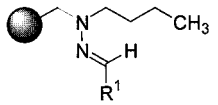
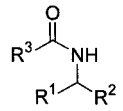
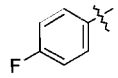
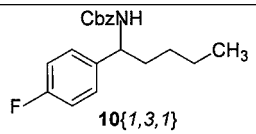
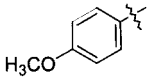
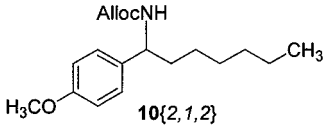
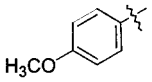
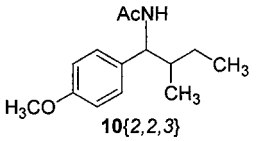
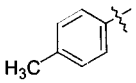
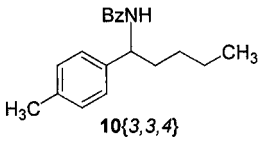
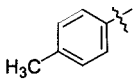
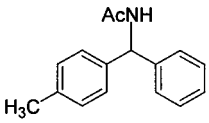
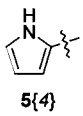
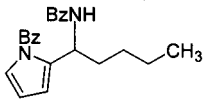
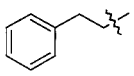
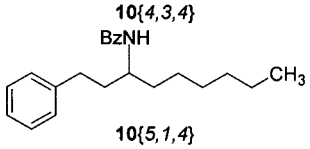
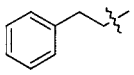
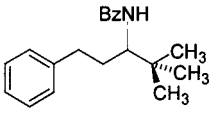
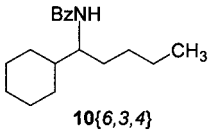
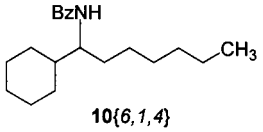
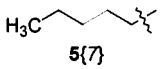
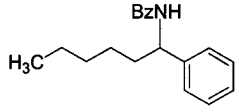
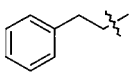
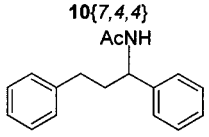
General. All chemicals were obtained from commercial suppliers and were of reagent grade. Merrifield resin (1−2% cross-linked, 200−400 mesh, 0.75 mmol g^{-1}) was purchased from NovaBioChem, *t*- and *n*-butyllithium were from Merck, *n*-hexyllithium was from Aldrich, phenyllithium was from Acros, and BH_3·THF solution (1 M) was from Aldrich. *t*-BuONO was synthesized according to a literature procedure.[24] Due to the toxicity of this compound, special precautions have to be taken during handling. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled from sodium/lead alloy under argon, and DMF was distilled from calcium hydride. Filtration devices with 20 μm pore size were purchased from International Sorbent Technology. Preparative column chromatography was carried out using Merck silica gel 60, particle size 0.040−0.063 mm (230−400 mesh), analytical TLC on silica gel 60 F254 plates, Merck, Darmstadt. Preparative HPLC chromatography was performed on Gilson Abimed, Lichrosorb-column, Si 60 (7 μm), UV detector. On-bead IR analysis was carried out using a Perkin-Elmer FT/IR 1750 spectrometer. Micro analyses were determined with a Heraeus CHN-O-Rapid element analyzer; mass spectra were obtained with a Varian MAT 212 (EI 70 eV). ^{1}H NMR analyses (300 and 400 MHz) were performed on Gemini 300 or Varian Inova 400 (solvent $CDCl_3$, TMS as internal standard.).

General Procedure for the Workup of the Resin (GP 1). The resin was washed on a glass or plastic frit alternately with THF and methanol (three times with each approximately 40 mL for each per 1.00 g of resin). Subsequently the resin was dried in vacuo.

Typical Experimental Procedure. *N*-Butyl-*N*-methylpolystyrene 2: In a dry 500 mL three-necked round-bottom flask, fitted with a mechanical stirrer, gas inlet, and a reflux condenser, Merrifield resin **1** (30.0 g, 22.5 mmol, loading 0.75 mmol g^{-1}) was swelled under argon in 300 mL of dry DMF, *n*-butylamine (16.43 g, 225 mmol, 10 equiv) was added, and the mixture was stirred for 3 days at 80 °C. After cooling to ambient temperature, the obtained resin was purified according to GP 1. IR (KBr): υ = 3436 (br m), 3081, 3059, 3024 (s), 2907, 2849 (s, CH_2), 1942 (m), 1870 (m), 1802 (m), 1745 (w), 1671 (m), 1600 (s), 1583 (s), 1543 (m), 1491 (s), 1447 (s), 1372 (s), 1328 (s), 1311 (s), 1274 (s), 1181 (s), 1153 (s), 1111 (m), 1026 (s), 964 (m), 905 (s), 840 (s), 748, 682 (vs), 531 (vs) cm^{-1}. $C_{104}H_{110}N$ (1372): calcd C 90.91, H 8.01, N 1.02; found C 89.1, H 8.52, N 1.02.

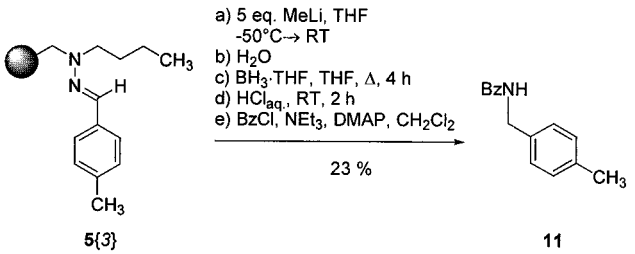
***N*-Butyl-*N*-nitroso-*N*-methylpolystyrene 3:** A 250 mL three-necked round-bottom flask, equipped with a mechanical stirrer and a reflux condenser, was charged with resin **2** (6.00 g, 4.37 mmol) and 100 mL of THF. *t*-BuONO (4.50 g, 43.7 mmol, 10 equiv) was added, and the reaction mixture was heated under reflux for 24 h. After cooling to ambient temperature, the resin was purified according to GP 1. IR (KBr): υ = 3476 (br m), 3081, 3059, 3024 (s), 2911, 2850

Table 1

Entry	 **5**{*1-7*}; R^1=	R^2Li **6**{*1-5*} R^2=	R^3COCl **9**{*1-4*} R^3CO=	 **10**	Yield[a] (%)
1	 **5**{*1*}	*n*-Bu **6**{*3*}	Cbz **9**{*1*}	 **10**{*1,3,1*}	47
2	 **5**{*2*}	*n*-Hex **6**{*1*}	Aloc **9**{*2*}	 **10**{*2,1,2*}	31
3[b]	 **5**{*2*}	*s*-Bu **6**{*2*}	Ac **9**{*3*}	 **10**{*2,2,3*}	36
4	 **5**{*3*}	*n*-Bu **6**{*3*}	Bz **9**{*4*}	 **10**{*3,3,4*}	48
5	 **5**{*3*}	Ph **6**{*4*}	Ac **9**{*3*}	 **10**{*3,4,3*}	38
6[c]	 **5**{*4*}	*n*-Bu **6**{*3*}	Bz **9**{*4*}	 **10**{*4,3,4*}	21
7	 **5**{*5*}	*n*-Hex **6**{*1*}	Bz **9**{*4*}	 **10**{*5,1,4*}	47
8	 **5**{*5*}	*t*-Bu **6**{*5*}	Bz **9**{*4*}	 **10**{*5,5,4*}	38
9	 **5**{*6*}	*n*-Bu **6**{*3*}	Bz **9**{*4*}	 **10**{*6,3,4*}	67
10	 **5**{*6*}	*n*-Hex **6**{*1*}	Bz **9**{*4*}	 **10**{*6,1,4*}	25
11	 **5**{*7*}	Ph **6**{*4*}	Bz **9**{*4*}	 **10**{*7,4,4*}	22
12	 **5**{*5*}	Ph **6**{*4*}	Ac **9**{*3*}	 **10**{*5,4,3*}	27

[a] Each compound was characterized by ^{1}H NMR and mass spectroscopic analysis. The yields are based on the amount of isolated acylated amines, considering an initial loading of hydrazine resin **4** of 0.5 mmol g^{-1}. The purity, according to HPLC and GC analysis, was always found to be greater than 94%. [b] *de* = 0%. [c] Product was obtained as bis-protected amide.

Scheme 4. Reductive Cleavage of Hydrazone **5**{*3*}



(s, CH_2), 2308 (w), 1943 (m), 1871 (m), 1802 (m), 1745 (w), 1721 (w), 1702 (w), 1677 (m), 1601 (s), 1584 (s), 1544 (m), 1492 (s), 1449 (s), 1342 (s), 1312 (s), 1276 (s), 1182 (s), 1151 (s), 1111 (m), 1026 (s), 964 (m), 905 (s), 841 (s), 749, 687 (vs), 533 (vs) cm^{-1}. $C_{104}H_{109}N_2O$ (1401): calcd C 88.96, H 7.90, N 2.00; found C 88.00, H 8.24, N 1.91.

***N*-Butyl-*N*-amino-*N*-methylpolystyrene 4:** A dry 250 mL three-necked round-bottom flask was fitted with a mechanical stirrer, gas inlet, and a reflux condenser. The apparatus was purged with argon and charged with 100 mL of dry THF and resin **3** (5.10 g, 3.64 mmol). Diisobutylaluminumhydride-solution (1 M in dichloromethane, 36.4 mL, 36.4 mmol, 10 equiv) was added carefully, and the mixture was stirred for 5 h at 50 °C. After cooling to ambient temperature, the resin was separated from the reaction solution by filtration, and excess diisobutylaluminumhydride was carefully destroyed with ethanol. The resin was washed with THF and a THF/water mixture (1:1) (hydrogen formation!). Subsequent workup was conducted according to GP 1. IR (KBr): υ = 3436 (vs), 3081, 3058, 3024 (s), 2915, 2849 (s, CH_2), 1943 (m), 1871 (m), 1802 (m), 1745 (w), 1669 (m), 1600 (s), 1583 (s), 1543 (m), 1510 (s), 1491 (s), 1450 (s), 1369 (s), 1181 (s), 1154 (s), 1068 (s), 1026 (s), 964 (m), 906 (s), 840 (s), 747, 690 (vs), 534 (vs) cm^{-1}. $C_{104}H_{111}N_2$ (1387): calcd C 89.93, H 8.05, N 2.02; found C 82.31, H 7.65, N 1.47.

General Procedure for the Preparation of Hydrazone Resins 5 (GP 2). In a glass or plastic frit *N*-butyl-*N*-amino-*N*-methylpolystyrene resin **4** was swelled in dry THF (15 mL/g resin), treated with aldehyde (30−40 equiv), and agitated for 3 d at room temperature. Subsequent workup was conducted according to GP 1.

General Procedure for the Preparation of Hydrazine Resins 7 via 1,2-Addition (GP 3). In a Schlenk flask, equipped with a stirring bar, resins **5** obtained from GP 2 were swelled under argon in dry THF (15 mL/g resin) and then cooled by means of a cold bath (ethanol/dry ice) to −50 °C or −78 °C, respectively. The organolithium solution (5 equiv) was added dropwise, and the reaction was allowed to warm to −20 °C or room temperature, respectively. Water (3 mL/g resin) was added, and the mixture was collected in a plastic frit, filtered, and washed with THF/water 10:1 (3 × 20 mL/g resin). The further transformations were conducted according to GP 1.

General Procedure for the Cleavage of the Resins 7 (GP 4). A Schlenk flask, equipped with a stirring bar and a reflux condenser, was purged with argon and charged with resins **7** obtained from GP 3. The resins were swelled in THF (15 mL/g resin), borane-tetrahydrofuran complex (1 M in THF, 20 equiv) was added, and the mixture was heated under reflux for 4 h. After cooling to ambient temperature, 3 M aqueous hydrochloric acid (4 mL/g resin) was added. The mixture was stirred for 2 h, then collected in a plastic frit, filtered, and washed alternately with THF and methanol (3 × 3 mL/g resin of each). The combined filtrates were concentrated in vacuo, 1 M HCl was added (10 mL/g resin), and the aqueous phase was extracted with pentane (2 × 1 mL/g resin). The aqueous phase was basified with saturated KOH solution and extracted with dichloromethane (6 × 10 mL/g resin). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo to yield the crude primary amines **8**.

General Procedure for the Protection of Primary Amines 8 (GP 5). The crude amines **8** obtained from GP 4 were dissolved in dry dichloromethane (10 mL/mmol), triethylamine (10 equiv) and catalytic amounts of DMAP were added, and the solution was cooled to 0 °C. The requisite acid chloride or chloroformate was added (3 equiv), and the reaction mixture was allowed to warm to room temperature and stirred for 3 days. The solvent was evaporated by a stream of argon, the residue taken up in ether and filtered through a glass pipet filled with a plug of glass wool and Florisil. The filtrate was concentrated in vacuo and the residue purified by preparative HPLC or flash chromatography (silica gel, pentane/ether mixtures, 1% triethylamine) to yield the protected amines **10**.

Analytical Data. *N*-(1-Pentyl-*para*-fluorophenyl)benzylcarbamate 10{*1,3,1*}, Table 1, entry 1: HPLC: 10.8 min (pentane/ether 3:2, 3% NEt_3, 18 mL/min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H, CH_3), 1.25−1.33 (m, 4H, CH_2), 1.66 (m, 2H, CH_2), 4.61 (m, 1H, CH), 4.98 (m, 1H, NH), 5.03 (d, J = 12.2 Hz, 1H, OCH_2), 5.10 (d, J = 12.2 Hz, 1H, OCH_2), 7.01 (m, 2H, H_{ar}), 7.17−7.40 (m, 7H, H_{ar}) ppm. MS (EI, 70 eV) *m*/*z* 258 (31.5, $M^+ - C_4H_9$); 224 (18.5, $M^+ - C_7H_7$); 109 (14.5, $C_7H_6F^+$); 91 (100, $C_7H_7^+$).

***N*-(1-Heptyl-*para*-methoxyphenyl)allylcarbamate 10{*2,1,2*}, Table 1, entry 2:** R_f: 0.84 (pentane/ether 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3H, CH_3), 1.20−1.32 (m, 8H, CH_2), 1.75 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.53 (m, 2H, OCH_2), 4.59 (m, 1H, CH), 4.91 (m, 1H, NH), 5.21 (d, J = 10.2 Hz, 1H, H_{allyl}), 5.26 (d, J = 10.2 Hz, 1H, H_{allyl}), 5.88 (m, 1H, H_2C═C*H*), 6.86 (d, J = 8.51 Hz, 2H, H_{ar}), 7.19 (d, J = 8.51 Hz, 2H, H_{ar}) ppm. MS (EI, 70 eV) *m*/*z* 305 (3.9, M^+); 264 (13.4, $M^+ - C_3H_5$); 220 (100, $M^+ - C_6H_{13}$).

***N*-(1-*sec*-Butyl-*para*-methoxybenzyl)acetamide 10{*2,2,3*}, Table 1, entry 3:** R_f: 0.24 (ether). ^{1}H NMR (400 MHz, $CDCl_3$) (2 diastereomers, *de* = 0%) δ 0.77−0.95 (m, 6H, CH_3), 1.10 (m, 1H, CH_2), 1.32 (m, 1H, CH_2), 1.78 (m, 1H, H_3CCH), 1.99/2.01 (s, 3H, H_3CCO), 3.79 (s, 3H, OCH_3), 4.76/4.86 (d/d, J = 8.79/8.51 Hz, 1H, CH), 5.66 (d, J = 8.51 Hz, 1H, NH), 6.87 (d, J = 8.7 Hz, 2H, H_{ar}), 7.15 (d, J = 8.7 Hz, 2H, H_{ar}) ppm. MS (EI, 70 eV) *m*/*z* 235 (4.3, M^+); 178 (78.7, $M^+ - C_4H_9$); 136 (100, $C_8H_{10}NO^+$).

***N*-(1-Pentyl-*para*-methylphenyl)benzylamide 10{*3,3,4*}, Table 1, entry 4:** R_f: 0.32 (pentane/ether 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.87 Hz, 3H, CH_3), 1.22−1.41

(m, 4H, CH_2), 1.90 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 5.13 (d/t, J = 7.70/7.42 Hz, 1H, CH), 6.36 (d, J = 7.70 Hz, 1H, NH), 7.17 (d, J = 7.96 Hz, 2H, H_{ar}), 7.25 (d, J = 7.96 Hz, 2H, H_{ar}), 7.36−7.50 (m, 3H, H_{ar}), 7.74 (m, 1H, H_{ar}), 7.76 (m, 1H, H_{ar}) ppm. MS (EI, 70 eV) *m/z* 281 (11.3, M^+); 224 (49.8, $M^+ - C_4H_9$); 105 (100, $C_7H_5O^+$).

***N*-(1-Benzyl-*para*-methylphenyl)acetamide 10{*3,4,3*}, Table 1, entry 5:** R_f: 0.49 (ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3H, H_3CCO), 2.33 (s, 3H, CH_3), 6.05 (d, J = 7.5 Hz, 1H, NH), 6.20 (d, J = 7.5 Hz, 1H, CH), 7.09−7.15 (m, 4H, H_{ar}), 7.20−7.34 (m, 5H, H_{ar}) ppm. MS (EI, 70 eV) *m/z* 239 (100, M^+); 196 (34.6, $M^+ - C_2H_3O$).

***N*-[1-Pentyl-(2-(*N*-benzoyl)pyrrol)]benzylamide 10{*4,3,4*}, Table 1, entry 6:** R_f: 0.19 (pentane/ether 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.0 Hz, 3H, CH_3), 1.23−1.35 (m, 4H, CH_2), 1.85 (m, 2H, CH_2), 5.61 (d/t, J = 9.34/7.96 Hz, 1H, CH), 6.15 (t, J = 3.30 Hz, 1H, NCHC*H*), 6.44 (d/d, J = 3.30/1.65 Hz, 1H, NCHCHC*H*), 6.81 (d/d, J = 3.30/1.65 Hz, 1H, NC*H*), 7.40−7.57 (m, 5H, H_{ar}), 7.65 (m, 1H, H_{ar}), 7.77 (m, 2H, H_{ar}), 7.89 (m, 2H, H_{ar}), 8.28 (d, J = 9.34 Hz, 1H, NH) ppm. MS (EI, 70 eV) *m/z* 360 (2.3, M^+); 303 (6.9, $M^+ - C_4H_9$); 255 (85.9, $M^+ - C_7H_5O$); 105 (100, $C_7H_5O^+$); 77 (33.9, $C_6H_5^+$).

***N*-[1-Hexyl-(3-phenylpropyl)]benzylamide 10{*5,1,4*}, Table 1, entry 7:** HPLC: 11.0 min (pentane/ether 3:2, 3% NEt_3, 18 mL/min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3H, CH_3), 1.20−1.43 (m, 8H, CH_2), 1.45−1.65 (m, 2H, CH_2), 1.82 (m, 1H, CH_2), 1.95 (m, 1H, CH_2), 2.72 (t, J = 8.1 Hz, 2H, CH_2), 4.25 (m, 1H, CH), 5.81 (d, J = 8.79 Hz, 1H, NH), 7.15−7.30 (m, 5H, H_{ar}), 7.40−7.52 (m, 3H, H_{ar}), 7.68 (m, 1H, H_{ar}), 7.71 (m, 1H, H_{ar}) ppm. MS (EI, 70 eV) *m/z* 323 (19.8, M^+); 219 (28.6, $M^+ - C_8H_8$); 105 (100, $C_7H_5O^+$).

***N*-[1-*tert*-Butyl-(3-phenylpropyl)]benzylamide 10{*5,5,4*}, Table 1, entry 8:** R_f: 0.34 (pentane/ether 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H, CH_3), 1.56 (m, 1H, CH_2), 2.06 (m, 1H, CH_2), 2.69 (m, 2H, CH_2), 4.09 (d/t, J = 10.72/2.48 Hz, 1H, CH), 5.83 (d, J = 10.72 Hz, 1H, NH), 7.13−7.20 (m, 3H, H_{ar}), 7.23−7.30 (m, 2H, H_{ar}), 7.42−7.56 (m, 3H, H_{ar}), 7.75 (m, 1H, H_{ar}), 7.78 (m, 1H, H_{ar}) ppm. MS (EI, 70 eV) *m/z* 295 (6.13, M^+); 238 (26.7, $M^+ - C_4H_9$); 105 (100, $C_7H_5O^+$).

***N*-(1-*cyclo*-Hexyl-pentyl)benzylamide 10{*6,3,4*}, Table 1, entry 9:** HPLC: 9.6 min (pentane/ether 3:2, 2% NEt_3, 18 mL/min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3H, CH_3), 1.02−1.40 (m, 13H, CH_2), 1.64 (m, 1H, CH_2), 1.75 (m, 2H, CH_2), 1.85 (m, 1H, CH_{c-hex}), 4.01 (m, 1H, CH), 5.79 (d, J = 8.79 Hz, 1H, NH), 7.41−7.53 (m, 3H, H_{ar}), 7.76 (m, 1H, H_{ar}), 7.79 (m, 1H, H_{ar}) ppm. MS (EI, 70 eV) *m/z* 273 (2.1, M^+); 216 (14.9, $M^+ - C_4H_9$); 190 (72.5, $M^+ - C_6H_{11}$); 105 (100, $C_7H_5O^+$).

***N*-(1-*cyclo*-Hexyl-heptyl)benzylamide 10{*6,1,4*}, Table 1, entry 10:** R_f: 0.39 (pentane/ether 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H, CH_3), 1.0−1.51 (m, 17H, CH_2), 1.65 (m, 1H, CH_2), 1.75 (m, 2H, CH_2), 1.85 (m, 1H, CH_{c-hex}), 4.02 (m, 1H, CH), 5.80 (d, J = 9.62 Hz, 1H, NH), 7.36−7.52 (m, 3H, H_{ar}), 7.76 (m, 1H, H_{ar}), 7.78 (m, 1H, H_{ar}) ppm. MS (EI, 70 eV) *m/z* 301 (3.0, M^+); 218 (80.8, M^+-C_6H_{11}); 105 (100, $C_7H_5O^+$).

***N*-(1-Hexyl-phenyl)benzylamide 10{*7,4,4*}, Table 1, entry 11:** R_f: 0.44 (pentane/ether 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.15 Hz, 3H, CH_3), 1.27−1.41 (m, 6H, CH_2), 1.91 (m, 2H, CH_2), 5.18 (m, 1H, CH), 6.26 (d, J = 8.7 Hz, 1H, NH), 7.25−7.51 (m, 8H, H_{ar}), 7.75 (m, 1H, H_{ar}), 7.78 (m, 1H, H_{ar}) ppm. MS (EI, 70 eV) *m/z* 281 (12.7, M^+); 210 (42.0, M^+-C_5H_{11}); 105 (100, $C_7H_5O^+$).

***N*-[1-Phenyl-(3-phenylpropyl)]acetamide 10{*5,4,3*}, Table 1, entry 12:** R_f: 0.56 (ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (s, 3H, H_3CCO), 2.14 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 5.03 (d/t, J = 8.79/7.69 Hz, 1H, CH), 5.62 (d, J = 8.79 Hz, 1H, NH), 7.15−7.38 (m, 10H, H_{ar}) ppm. MS (EI, 70 eV) *m/z* 253 (22.2, M^+); 149 (51.6, $M^+ - C_8H_8$); 106 (100, $C_7H_6N^+$).

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Supporting Information Available. ^{1}H NMR and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(2) (a) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707. (b) Kempf, D. J.; Norbeck, D. W.; Codacovi, L. M.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Paul, D. A.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Rosenbrook, W., Jr.; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, *33*, 2687. (c) Pirie, D. K.; Welch, W. M.; Weeks, P. D.; Volkmann, R. A. *Tetrahedron Lett.* **1986**, *27*, 1549.
(3) For a most recent, comprehensive overview see: Dörwald, F. Z.; Organic Synthesis on Solid-Support, Wiley-VCH: 2000; pp 229−249.
(4) (a) Matsueda, G. R.; Stewart, J. M. *Peptides* **1981**, *2*, 45. (b) Ley, S. V.; Mynett, D. M.; Koot, W. J. *Synlett* **1995**, 1017. (c) Bui, C. T.; Bray, A. M.; Ercole, F.; Pham, Y.; Rasoul, F. A.; Maeji, N. J. *Tetrahedron Lett.* **1999**, *40*, 3471.
(5) Jönsson, D.; Molin, H.; Undén, A. *Tetrahedron Lett.* **1998**, *39*, 1059.
(6) McNally, J. J.; Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1998**, *39*, 967.
(7) (a) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem* **1996**, *108*, 2111; *Angew. Chem., Int. Ed.* **1996**, *35*, 1979. (b) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999.
(8) Katritzky, A. R.; Xie, L.; Zhang, G.; Griffith, M.; Watson, K.; Kiely, J. S. *Tetrahedron Lett.* **1997**, *38*, 7011.
(9) (a) Kobayashi, S.; Moriwaki, M. *Tetrahedron Lett.* **1997**, *38*, 4251. (b) Dyatkin, A. B.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 3647.
(10) Boyd, E. A.; Chan, W. C.; Loh, Jr. V. M. *Tetrahedron Lett.* **1996**, *37*, 1647.
(11) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345.
(12) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

(13) Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 275.
(14) Kamogawa, H.; Kanzawa, A.; Kadoya, M.; Naito, T.; Nanasawa, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 762.
(15) Emerson, D. W.; Emerson, R. R.; Joshi, S. C.; Sorensen, E. M.; Turek, J. E. *J. Org. Chem.* **1979**, *44*, 4634.
(16) http://www.argotech.com.
(17) (a) Murphy, A. M.; Dagnino, R.; Vallar, P. L.; Trippe, A. J.; Sherman, S. L.; Lumpkin, R. H.; Tamura, S. Y.; Webb, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 3156. (b) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356.
(18) (a) Semenov, A. N.; Gordeev, K. Y.; *Int. J. Pept. Protein Res.* **1995**, *45*, 303. (b) Millington, C. R.; Quarrell, R.; Lowe, G. *Tetrahedron Lett.* **1998**, *39*, 7201.
(19) Kobayashi, S.; Furuta, T.; Sugita, K.; Okitsu, O.; Oyamada, H. *Tetrahedron Lett.* **1999**, *40*, 1341.
(20) Stieber, F.; Grether, U.; Waldmann, H. *Angew. Chem.* **1999**, *111*, 1142; *Angew. Chem., Int. Ed.* **1999**, *38*, 1073.
(21) Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. *Angew. Chem.* **1998**, *110*, 3614; *Angew. Chem., Int. Ed.* **1998**, *37*, 3413 and literature cited therein.
(22) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.
(23) Enders, D.; Lochtmann, R.; Meiers, M.; Müller, S.; Lazny, R. *Synlett* **1998**, 1182 and literature cited therein.
(24) Noyes, W. A. In *Organic Syntheses*; Wiley: New York, 1943; Vol. 2, p 108.

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