Solid-Phase Synthesis of Piperidines by N-Acyliminium Ion Chemistry

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An efficient solid-phase procedure for the synthesis of a number of 2-substituted piperidines is reported. Starting from solid-supported carbamate-tethered δ -amino acetals, 2-benzotriazolyl-substituted (Bt-substituted) piperidines were obtained by acid-induced ring-closure followed by trapping of the transient *N*-acyliminium ions with benzotriazole.

Introduction

Functionalised piperidines are frequently encountered structural motifs in bioactive compounds and in natural products.^[1] The piperidine ring is often present as a substructure in drug-like molecules.^[2] A well-known example is Ritalin (1, methyl α -phenyl-2-piperidinylacetate), used for the treatment of attention deficiency/hyperactivity disorder (ADHD) in children (Scheme 1).^[3] Some other piperidine-containing natural products that show interesting biological activity are febrifugine (2)^[4] and (-)-lobeline (3).^[5]

Consequently, a plethora of synthetic routes affording functionalised piperidines has been developed.^[6] In many groups, including ours, *N*-acyliminium ion pathways towards these scaffolds have been developed over the years.^[7] In conjunction with this work, a solid-phase approach that



Scheme 1. Bioactive piperidines

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These 2-Bt-substituted piperidines were then used as precursors for the successful introduction of several *C*-nucleophiles by *N*-acyliminium ion chemistry.

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would give facile access to libraries of piperidines by a similar type of method would be highly desirable.^[8,9] In a program to develop *N*-acyliminium ion chemistry on solid supports, we have previously described the solid-phase synthesis of several 2-substituted pyrrolidines, starting from immobilised γ -amino acetals.^[8e] These acetals were cyclised under Lewis acidic conditions and coupled with suitable Cnucleophiles in one-pot reactions, via *N*-acyliminium ion intermediates. Unfortunately, however, this one-pot procedure did not work satisfactory for the homologous piperidine analogues. Here we describe a modification of the initial procedure, which has resulted in the successful synthesis of a number of 2-substituted and 2,4-disubstituted piperidines. The general strategy is outlined in Scheme 2.



Scheme 2. Retrosynthetic approach

Rather than the one-pot cyclisation/coupling sequence, we anticipated that it would be more favourable to generate a stable intermediate aminal **6**, which upon suitable activation would provide the targeted *N*-acylimium ion intermediate **5**.^[10] In order to do this, we decided to apply the benzotriazole (Bt) group (**6**, LG = Bt) developed by Katritzky^[11] as a potentially good leaving group.

FULL PAPER

Results and Discussion

Our synthetic work commenced with the coupling of the amino acetals $9a-f^{[12]}$ to the sulfonylethoxycarbonyl-modified (SEC-modified) polystyrene resin 8 (Scheme 3).^[8c,8e]



Scheme 3. (a) DIPEA, THF, room temp.; (b) allyltrimethylsilane, $BF_3 \cdot OEt_2$, CH_2Cl_2 , 0 °C to room temp.; (c) 1 M NaOMe, THF/MeOH (2:1, v/v), room temp.; (d) Ac₂O, pyridine, DMAP (cat.), room temp.

Attempts to follow a one-pot procedure for the N-acyliminium ion mediated functionalisation (i.e., addition of a Lewis acid and allyltrimethylsilane as the nucleophile) produced mixtures of cyclic and linear products. This became apparent after sodium methoxide mediated cleavage and acetylation of the nitrogen atom to afford piperidines 11a (57%) and **11f** (47%) and the linear side products **12a** (4%)and 12f (6%). The linear products are the result of direct intermolecular attack of the allylsilane onto the oxycarbenium ion generated in situ, instead of intramolecular attack by the carbamate nitrogen atom. Interestingly, this side reaction was not observed in the pyrrolidine series, probably due to a faster rate of cyclisation. As would be expected, the ratio of cyclic to linear product is better for the 4-substituted piperidine 11a than for the unsubstituted analogue 11f. Sequential addition of the Lewis acid and the nucleophile did not improve the situation, resulting in low yields of the desired product. To suppress the side reaction the concentration of allylsilane was lowered fourfold, which should favour intramolecular attack of the carbamate moiety. Although this did indeed result in the exclusive formation of the cyclised product in both cases, the yields were significantly lower. More importantly, the high dilution factors render this approach unsuitable for possible application in automated procedures.

To optimise the *N*-acyliminium ion mediated functionalisation of piperidines at the 2-position from linear precursors, further studies in solution were conducted first. Consequently, amino acetal **9f** was protected with a benzyloxycarbonyl group (Cbz) to afford the solution-phase model system **13** (Scheme 4).

One-pot coupling of allyltrimethylsilane under identical conditions as for resin **10f** indeed afforded a 5:1 mixture of cyclic and linear products **14** and **15** in 95% yield. Alternatively, **13** was cyclised to the corresponding N,O-acetal **16** by catalytic *p*TSA in CH₂Cl₂ (conditions b), but partial formation of the undesired enamide **17** (1:2 ratio) could not be prevented.^[4] Use of slightly different conditions [CH₂Cl₂/EtOH, 2:1, v/v mixture; conditions c)] drastically



Scheme 4. (a) allyltrimethylsilane, BF₃·OEt₂, CH₂Cl₂, 0 °C to room temp.; (b) *p*TSA (cat.), CH₂Cl₂, room temp.; (c) *p*TSA (cat.), CH₂Cl₂/EtOH (2:1, v/v) room temp.; (d) *p*TSA (cat.), CH₂Cl₂, 15 min; then BtH, CH₂Cl₂, room temp.

improved this ratio to 6:1. However, compound **16** was found to be rather unstable, since subjection to column chromatography resulted largely in elimination to give enamide **17**. To provide a more stable precursor, the acetal **13** was treated with catalytic *p*TSA, followed by addition of an excess of 1*H*-benzotriazole, resulting in the 2-Bt-substituted piperidine **18** as the sole product in 88% isolated yield.^[13] Subsequent treatment of this intermediate under identical conditions as for **13** exclusively afforded the cyclic product **14** in an excellent yield of 93%.^[14] In contrast, sequential addition of *p*TSA and allyltrimethylsilane to compound **13** (not shown in Scheme 4) resulted in a low yield of product **14**, due to the facile formation of the enamide **17** under these conditions.^[15]

To determine the synthetic scope of the procedure, the resin-bound acetals 10a-f were cyclised to give the 2-Bt precursors 19a-f (Scheme 5). In all cases complete ringclosure was observed, as indicated by the disappearance of the NH signal in the IR spectra.



Scheme 5. (a) *p*TSA (cat.), CH₂Cl₂, 30 min; then 1*H*-Bt, CH₂Cl₂, room temp.; (b) nucleophile, BF₃·OEt₂, CH₂Cl₂, 0 °C to room temp.; (c) 1 M NaOMe, THF/MeOH (2:1, v/v), room temp.

Subsequently, a number of nucleophiles were coupled under these conditions and the products were cleaved from the resin (Table 1).

As expected, both allyl- and methallyltrimethylsilane could be coupled in high yield (Entries 1 and 2). Through the use of a stoichiometric amount of camphorsulfonic acid,^[16] a 2-furanyl substituent was coupled in reasonable yield (Entry 3). Finally, an ethyl chain was introduced, albeit in a low yield, by the use of diethylzinc as the nucleophile (not optimised, Entry 4).^[8b] Attempts to introduce a propargyl or an acetone moiety, with allenyltributyltin and isopropenyl acetate, respectively, as the nucleophiles, failed.^[17]

Entry	Substrate	Nucleophile	e Product		Yield (%) ^[a]
1	19a	SiMe	3 HN Ph	20a	80
2	19a	SiMe	3 HN Ph	21a	76
3	19a	$\langle 0 \rangle$	2-furanyl	22a	54 ^[b]
4	19a	Et ₂ Zn	HN	23a	14
5	19b	SiMe	3 HN	20b	71
6	19c	SiMe	$3 \qquad \qquad$	20c	85
7	19d	SiMe	3 HN 2-furanyl	20d	0
8	19e	SiMe	3 HN	20e	86 ^[c]
9	19f	///SiMe	3 HN	20f	78 ^[c]

^[a] Isolated yield over four steps from resin 8. ^[b] CSA (1 equiv.) was used. ^[c] Isolated as the HCl salt.

Next, the influence of the R substituent at the 4-position in the piperidine ring was determined, with allyltrimethylsilane as the nucleophile. In all cases, the product was obtained in excellent yield and diastereoselectivity (Entries 5-9), except in the presence of a 4-furanyl substituent (Entry 7), in which case an unidentifiable mixture of products was obtained.

Because of overlap of signals in the ¹H NMR spectrum it was not possible to assign the stereochemistry of the 2,4disubstituted piperidines directly. To effect splitting of the signals, the amine group of product **20a** was derivatised with a strongly electron-withdrawing tosyl group to give piperidine **24** in moderate yield (Scheme 6).



Scheme 6. Stereochemistry

Through the use of NOE difference measurements, a clear NOE contact between the CH₂ of the allyl group and 4-H of the piperidine ring was observed, indicating a cis relationship between 4-H and the allyl function. In addition, no NOE enhancement between 2-H and 4-H of the piperidine ring was observed, and the product was therefore assigned as the *trans* diastereoisomer. This stereochemistry can be explained by invoking the intermediate N-acyliminium ion 25. The phenyl group adopts a pseudoequatorial position, to minimise steric interactions. The nucleophile then comes in axially to minimise steric interaction with the axial proton at the C-3 position and to generate the product with the lowest-energy conformation. This then results in formation of the trans diastereoisomer. This stereochemistry is in good agreement with the results of Woerpel and co-workers, who investigated the additions of allyltrimethylsilane onto the analogous 4-alkyl-substituted oxycarbenium ions.^[18]

Conclusions

In conclusion, a good method for the synthesis of 2-substituted and 2,4-disubstituted piperidines has been developed. Formation of linear side products was eliminated by use of stable ring-closed 2-Bt-substituted piperidines derived from linear acetals, which were used as precursors for *N*-acyliminium ion chemistry. A small library of piperidines was synthesised by this methodology, demonstrating the potential for automated library synthesis.

Experimental Section

General Information: All reactions were carried out under dry nitrogen, unless stated otherwise. Standard syringe techniques were applied for transfer of air-sensitive reagents and dry solvents. $R_{\rm f}$ values were obtained by thin layer chromatography (TLC) on silica gel coated plastic sheets (Merck silica gel 60 F245) with the aforementioned solvent (mixture) unless noted otherwise. Chromatographic purification refers to flash chromatography^[19] with the indicated solvent (mixture) and ACROS silica gel (particle size 35-70 µm). Infrared spectra (IR) were recorded with a Bruker IFS 28 spectrophotometer, and wavelengths $[\tilde{v}]$ are reported in cm⁻¹. Infrared spectra of resins were measured in KBr using a DRIFT module. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were obtained with a Bruker ARX 400 (400 MHz and 100 MHz, respectively) unless indicated otherwise. Spectra are reported in ppm on the δ scale. HRMS measurements were performed with a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. The solid-phase reaction mixtures were either gently stirred with a magnetic stirring bar or agitated by rotation of the reaction vessel at an angle of 45° attached to a rotary evaporator engine. The resins were washed according to the indicated sequence. The resin was allowed to swell/shrink for 1 min before each filtration. "Drying" refers to drying in a vacuum oven at 50 °C. Dry THF and Et₂O were distilled from sodium benzophenone ketyl prior to use. Dry CH₂Cl₂ was distilled from CaH₂ and stored over MS (4 Å) under dry nitrogen. Diisopropylethylamine was dried and distilled from KOH pellets. Reagents were purchased at highest commercial quality and used without further purification unless stated otherwise. Fluka Merrifield resin (200-400 mesh, 1% DVB, 1.7 mmol Cl/g) was used. For an experimental procedure for the synthesis of 9a-e see the preceding article.^[12]

5,5-Diethoxy-3-phenylpentylamine (9a): ¹H NMR (400 MHz, CDCl₃): δ = 1.11 (t, J = 7.0 Hz, 3 H, CH₃), 1.19 (t, J = 7.0 Hz, 3 H, CH₃), 1.30 (br. s, 2 H, NH₂), 1.67–1.89 (m, 3 H), 1.93–2.00 (m, 1 H), 2.46–2.58 (m, 2 H, 1-H), 2.74–2.82 (m, 1 H, 3-H), 3.31–3.40 (m, 2 H, OCH₂), 3.41–3.52 (m, 1 H, OCH₂), 3.56–3.64 (m, 1 H, OCH₂), 4.16 (dd, J = 3.9, 8.0 Hz, 1 H, 5-H), 7.12–7.18 (m, 3 H, ArH), 7.20–7.30 (m, 2 H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 15.3 (CH₃), 39.5 (C-3), 40.2, 40.7, 40.9 (C-1), 60.7 (OCH₂), 61.4 (OCH₂), 101.2 (C-5), 126.2 (ArCH), 127.6 (ArCH), 128.5 (ArCH), 144.5 (ArC_q) ppm. IR (film): \tilde{v} = 3310 (NH₂), 1128, 1058. HRMS (C₁₅H₂₆NO₂ [MH⁺]; FAB): calcd. 252.1964; found 252.1965.

FULL PAPER

5,5-Diethoxy-3-(4-pyridyl)pentylamine (9b): ¹H NMR (400 MHz, CDCl₃): $\delta = 1.11$ (t, J = 7.0 Hz, 3 H, CH_3), 1.19 (t, J = 7.0 Hz, 3 H, CH_3), 0.85–1.25 (br. s, 2 H, NH_2), 1.68–1.89 (m, 3 H), 1.97–2.03 (m, 1 H), 2.30–2.57 (m, 2 H, 1-H), 2.80–2.87 (m, 1 H, 3-H), 3.32–3.40 (m, 2 H, OCH_2), 3.47–3.54 (m, 1 H, OCH_2), 3.56–3.65 (m, 1 H, OCH_2), 4.17 (dd, J = 4.1, 8.0 Hz, 1 H, 5-H), 7.11 (d, J = 6.0 Hz, 2 H, ArH), 8.51 (d, J = 6.1 Hz, 2 H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.2$ (CH_3), 39.0 (C-3), 39.8, 39.9, 40.0, 61.1 (OCH_2), 61.4 (OCH_2), 100.8 (C-5), 123.1 (ArCH), 149.9 (ArCH), 153.9 (ArC_q) ppm. IR (film): $\tilde{v} = 3340$ (NH_2), 1599, 1486, 1127, 1058. HRMS ($C_{14}H_{25}N_2O_2$ [MH^+]; FAB): calcd. 253.1916; found 253.1912.

3-(4-Bromophenyl)-5,5-diethoxypentylamine (9c): ¹H NMR (400 MHz, CDCl₃): $\delta = 1.11$ (t, J = 7.0 Hz, 3 H, CH_3), 1.18 (t, J = 7.0 Hz, 3 H, CH_3), 1.30 (br. s, 2 H, NH₂), 1.63–1.83 (m, 3 H), 1.93–1.99 (m, 1 H), 2.48–2.55 (m, 1 H, 1-H), 2.74–2.81 (m, 1 H, 3-H), 3.31–3.38 (m, 2 H, OCH₂), 3.48–3.53 (m, 1 H, OCH₂), 3.56–3.64 (m, 1 H, OCH₂), 4.15 (dd, J = 3.9, 8.0 Hz, 1 H, 5-H), 7.05 (d, J = 8.4 Hz, 2 H, ArH), 7.41 (d, J = 8.4 Hz, 2 H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.1$ (CH₃), 38.8 (C-3), 39.3, 39.7, 40.4, 60.7 (OCH₂), 61.1 (OCH₂), 100.8 (C-5), 119.7 (ArC_q), 129.1 (ArCH), 131.3 (ArCH), 143.5 (ArC_q) ppm. IR (film): $\tilde{\nu} = 3370$ (NH₂), 1589, 1128, 1058. HRMS (C₁₅H₂₅⁷⁹BrNO₂ [MH⁺]; FAB): calcd. 330.1069; found 330.1066.

5,5-Diethoxy-3-(2-furanyl)pentylamine (9d): ¹H NMR (400 MHz, CDCl₃): $\delta = 1.05 - 1.35$ [m, 8 H, (NH₂ + CH₃)], 1.70 - 1.79 (m, 2 H), 1.82 - 1.97 (m, 2 H), 2.56 - 2.61 (m, 2 H, 1-H), 2.90 - 2.98 (m, 1 H, 3-H), 3.38 - 3.45 (m, 2 H, OCH₂), 3.50 - 3.57 (m, 1 H, OCH₂), 3.58 - 3.67 (m, 1 H, OCH₂), 4.28 (dd, J = 5.0, 9.0 Hz, 1 H, 5-H), 6.01 [s, 1 H, CH-CH=CH(C)O], 6.25 (s, 1 H, OCH=CH), 7.29 (s, 1 H, OCH=CH) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.3$ (CH₃), 32.9 (C-3), 38.3, 38.5, 40.0 (C-1), 60.9 (OCH₂), 61.7 (OCH₂), 101.3 (C-5), 105.3 [CHCH=C(C)O], 109.9 (OCH=CH), 141.1 (OCH=CH), 157.6 (ArC_q) ppm. IR (film): $\tilde{\nu} = 3351$ (NH₂), 1576, 1127, 1059. HRMS (C₁₃H₂₄NO₃ [MH⁺]; FAB): calcd. 242.1756; found 242.1748.

5,5-Diethoxy-3-isopropylpentylamine (9e): ¹H NMR (400 MHz, CDCl₃): $\delta = 0.87$ (t, J = 11.0 Hz, 6 H, $iPr-CH_3$), 1.18 (t, J = 9.0 Hz, 6 H, OCH₂CH₃), 1.30–1.36 (m, 1 H), 1.37–1.49 (m, 2 H), 1.59–1.63 (m, 1 H), 1.68–1.73 (m, 1 H), 2.63–2.71 (m, 2 H, 1-H), 3.44–3.51 (m, 2 H, OCH₂), 3.57–3.70 (m, 2 H, OCH₂), 4.52 (t, J = 6.0 Hz, 1 H, 5-H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.1$ (OCH₂CH₃), 18.5 (*i*PrCH₃), 18.7 (*i*PrCH₃), 29.5 (*i*PrCH), 34.4, 34.8, 36.8 (C-3), 40.2 (C-1), 60.2 (OCH₂), 61.2 (OCH₂), 101.9 (C-5) ppm. IR (film): $\tilde{v} = 3296$ (NH₂), 1582, 1124, 1061. HRMS (C₁₂H₂₈NO₂ [MH⁺]; FAB): calcd. 218.2120; found 218.2117.

5,5-Diethoxypentylamine (9f):^[20] NaCN (2.7 g) and KI (1 mol %) were added to a solution of 4-chloro-1,1-diethoxybutane (10 g, 55 mmol) in dry DMSO (50 mL), and the mixture was stirred at 100 °C for 20 h. The reaction mixture was then poured into water (500 mL) and extracted with Et_2O (2×150 mL). The combined ether layers were washed with brine, dried with MgSO₄, concentrated and further purified by bulb-to-bulb distillation (100 °C, 1.5 mbar) to afford 6.68 g (39 mmol, 71%) of the corresponding cyanide as a clear oil. This oil (2.00 g, 11.7 mmol) was then dissolved in dry Et_2O (30 mL) and cooled to 0 °C, and LiAlH₄ (1.33 g, 35.1 mmol.) was added portionwise. After 15 min, the ice bath was removed and the mixture was stirred for 3 h. NaOH (2 M) was then added slowly at 0 °C until a white precipitate was formed. The reaction mixture was filtered through Celite, concentrated and further purified by bulb-to-bulb distillation (80 °C, 1.5 mbar) to afford

9f (1.1 g, 55%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃,): $\delta = 1.19$ (t, J = 7.0 Hz, 6 H, CH₃), 1.21 (br, 2 H, NH₂), 1.35–1.47 (m, 4 H), 1.59–1.64 (m, 2 H), 2.68 (t, J = 6.7 Hz, 2 H, 1-H), 3.44–3.51 (dq, J = 9.4, 7.0 Hz, 2 H, OCH₂), 3.59–3.67 (dq, J =9.4, 7.0 Hz, 2 H, OCH₂), 4.47 (t, J = 5.7 Hz, 1 H, 5-H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.1$ (CH₃), 21.8 (C-3), 33.0, 33.2, 41.7 (C-1), 60.8 (OCH₂), 102.7 (C-5) ppm. IR (film): $\tilde{v} = 3325$ (NH₂), 1573, 1127, 1062. HRMS (C₉H₂₂NO₂ [MH⁺]; FAB): calcd. 176.1651; found 176.1636.

General Procedure A for Coupling the Amino Acetals to the Resin: DIPEA (2 equiv.) and the appropriate amino acetal (2 equiv.) were added to a 0.05 g/mL suspension of resin in dry THF, and the suspension was swirled for 20 h. The resin was then filtered, washed with CH_2Cl_2 , MeOH, CH_2Cl_2 , MeOH, CH_2Cl_2 , Et_2O , CH_2Cl_2 , Et_2O and CH_2Cl_2 , and dried.

Resin 10a: IR: $\tilde{v} = 3356$, 1726, 1512, 1120.

Resin 10b: IR: $\tilde{v} = 3342, 3203, 1729, 1519, 1124.$

Resin 10c: IR: $\tilde{v} = 3340, 1732, 1513, 1124$.

Resin 10d: IR: $\tilde{v} = 3346, 1730, 1493, 1125.$

Resin 10e: IR: $\tilde{v} = 3344, 1731, 1511, 1121$.

Resin 10f: IR: $\tilde{v} = 3360, 1728, 1518, 1126.$

1-(2-Allyl-4-phenylpiperidin-1-yl)ethanone (11a) and N-(5-Ethoxy-3phenyloct-7-enyl)acetamide (12a): Allyltrimethylsilane (1.64 mL, 10.3 mmol) and BF₃·OEt₂ (0.39 mL, 3.08 mmol) were added at 0 °C to a suspension of resin 10a (1.00 g, 1.03 mmol) in dry CH₂Cl₂ (15 mL), and the reaction mixture was swirled for 20 h, thereby allowing it to warm to room temperature, after which the resin was filtered, washed with CH₂Cl₂, MeOH, CH₂Cl₂, MeOH, CH₂Cl₂, Et₂O, CH₂Cl₂, Et₂O and CH₂Cl₂, and dried. This resin (893 mg, 0.96 mmol) was suspended in 1 м NaOMe in THF/MeOH (9 mL, 2:1, v/v) and stirred gently for 1 h. The resin was then filtered and washed with CH2Cl2, MeOH, CH2Cl2, and MeOH, followed by addition of 1 M HCl in MeOH (20 mL) to the filtrate and evaporation of the solvent. The residue was taken up in pyridine (5 mL), and Ac₂O (0.18 mL, 1.9 mmol) and DMAP (cat.) were added. After stirring at room temperature for 20 h, the reaction mixture was concentrated to afford 11a (134 mg, 57%) as an oil after purification by chromatography (EtOAc). $R_f = 0.63$. ¹H NMR (400 MHz, CDCl₃, 1:1 mixture of rotamers): $\delta = 1.54 - 1.82$ (m, 2) H), 1.86–1.94 (m, 2 H), 2.12 (s, 1.5 H, CH₃), 2.13 (s, 1.5 H, CH₃), 2.35-2.53 (m, 1.5 H, CH₂CH=CH₂), 2.57-2.64 (m, 0.5 H, CH₂CH=CH₂), 2.75-2.82 (m, 0.5 H), 2.91-2.99 (m, 1 H), 3.28-3.38 (m, 0.5 H), 3.72-3.77 (m, 0.5 H), 4.05-4.10 (m, 0.5 H), 4.70-4.74 (m, 0.5 H), 4.99-5.18 (m, 2.5 H), 5.70-5.83 (m, 1 H), 7.17-7.23 (m, 3 H, ArCH), 7.29-7.33 (m, 2 H, ArCH) ppm. ¹³C NMR (100 MHz, CDCl₃, 1:1 mixture of rotamers): $\delta = 21.7$ (CH₃), 21.8, 32.6, 33.4, 34.5, 34.8, 35.0, 36.3, 36.4 (C-6), 36.5 (C-4), 36.6 (C-4), 41.8 (C-6), 47.3 (C-2), 53.8 (C-2), 116.7 (CH=CH₂), 118.1 (CH=CH₂), 126.4 (ArCH), 126.6 (ArCH), 128.5 (ArCH), 134.0 $(CH=CH_2)$, 135.1 $(CH=CH_2)$, 145.0 (ArC_a) , 145.1 (ArC_a) , 169.0 (C=O), 169.1 (C=O). IR (film): v = 1635 (C=O). HRMS (C16H22NO [MH+]; FAB): calcd. 244.1701; found 244.1684. Compound 12a (12 mg, 4%) was also obtained as an oil. $R_f = 0.45$. ¹H NMR (400 MHz, CDCl₃, 2:1 mixture, data of the major): $\delta = 1.09$ (t, J = 7.0 Hz, 3 H), 1.83 (s, 3 H), 1.69-1.99 (m, 4 H), 2.14-2.29(m, 2 H), 2.68–2.75 (m, 1 H), 2.96–3.06 (m, 1 H), 3.11–3.22 (m, 1 H), 3.26-3.34 (m, 1 H), 3.39-3.47 (m, 1 H), 5.01-5.06 (m, 2 H), 5.28 (br. s, 1 H), 5.72–5.83 (m, 1 H), 7.13–7.31 (m, 5 H) ppm. ¹³C NMR (100 MHz, CDCl₃, 2:1 mixture, data of the major): $\delta =$

15.5, 23.2, 36.0, 38.0, 38.3, 40.5, 41.0, 63.9, 75.9, 117.0, 126.4, 127.5, 128.6, 134.7, 144.7, 169.8 ppm. IR (film): $\tilde{\nu}$ = 3275, 1648. HRMS (C18H28NO2 [MH^+]; FAB): calcd. 290.2120; found 290.2134.

1-(2-Allylpiperidin-1-yl)ethanone (11f) and N-(5-Ethoxyoct-7-enyl)acetamide (12f): Treatment of resin 10f (0.98 g, 1.1 mmol) according to the procedure described above for resin 10a afforded 11f (85 mg, 47%) as an oil after purification by chromatography (EtOAc). $R_f =$ 0.52. ¹H NMR (400 MHz, CDCl₃, 1:1 mixture of rotamers): $\delta =$ 1.32-1.43 (m, 1 H), 1.54-1.66 (m, 5 H), 2.03 (s, 1.5 H, CH₃), 2.05 (s, 1.5 H, CH₃), 2.20–2.39 (m, 1.5 H, CH₂CH=CH₂), 2.43–2.50 (m, 0.5 H, CH₂CH=CH₂), 2.54-2.60 (m, 0.5 H), 3.04-3.11 (m, 0.5 H), 3.54-3.57 (m, 0.5 H), 3.89 (br. m, 0.5 H), 4.50-4.54 (0.5 H), 4.81-4.86 (m, 0.5 H), 4.96-5.10 (m, 2 H, $CH=CH_2$), 5.64-5.74 (m, 1 H, CH=CH₂) ppm. ¹³C NMR (100 MHz, CDCl₃, 1:1 mixture of rotamers): $\delta = 18.7, 18.8, 21.6$ (CH₃), 21.8 (CH₃), 25.2, 26.0, 27.1, 28.5, 34.1, 34.6, 36.3 (C-6), 41.8 (C-6), 47.1 (C-2), 53.7 (C-2), 116.5 (CH=CH₂), 117.8 (CH=CH₂), 134.3 (CH=CH₂), 135.3 (*C*H=CH₂), 169.1 (*C*=O), 169.2 (*C*=O) ppm. IR (film): \tilde{v} = 1641 (C=O), 1424. 12f (14 mg, 6%) was also obtained as an oil. $R_f = 0.33$. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.18$ (t, J = 7.0 Hz, 3 H), 1.32-1.37 (m, 1 H), 1.44-1.55 (m, 5 H), 1.97 (s, 3 H), 2.19-2.29 (m, 2 H), 3.21-3.29 (m, 3 H), 3.41-3.47 (m, 1 H), 3.52-3.59 (m, 1 H), 5.02-5.09 (m, 2 H), 5.55 (br. s, 1 H), 5.75-5.83 (m, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.5$, 22.8, 23.3, 29.5, 33.5, 38.4, 39.6, 64.3, 78.6, 116.8, 134.9, 170.1 ppm. IR (film): $\tilde{v} = 3294$, 1638. HRMS (C₁₂H₂₄NO₂ [MH⁺]; FAB): calcd. 214.1807; found 214.1816.

Benzyl 5,5-Diethoxypentylcarbamate (13): DIPEA (0.31 mL) and benzyl cyanoformate (0.23 mL) were added to a solution of 5,5diethoxypentylamine (9f, 286 mg, 1.63 mmol) in dry CH₂Cl₂ (5 mL), and the mixture was stirred at room temperature for 5 h. The reaction mixture was then poured into saturated aqueous NaHCO₃ (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined CH₂Cl₂ layers were washed with brine, dried with MgSO₄ and concentrated to afford 13 (440 mg, 87%) as a clear oil after purification by chromatography (pentane/Et₂O, 2:3). $R_f =$ 0.46. ¹H NMR (400 MHz, C_6D_6): $\delta = 1.12$ (t, J = 7.1 Hz, 6 H, CH₃), 1.15-1.21 (m, 4 H), 1.52-1.57 (m, 2 H), 2.93-2.96 (m, 2 H, 1-H), 3.30-3.38 (dq, J = 9.3, 7.1 Hz, 2 H, OCH₂CH₃), 3.48-3.55 (dq, J = 9.3, 7.1 Hz, 2 H, OCH₂CH₃), 4.10 (br. s, 1 H, NH), 4.36 (t, J = 5.6 Hz, 1 H, 5-H), 5.10 (s, 2 H, OCH₂Ph), 7.04–7.28 (m, 5 H, ArH) ppm. ¹³C NMR (100 MHz, C₆D₆): δ = 16.3 (CH₃), 22.8, 30.7, 34.2, 41.8 (C-1), 61.5, 67.2, 103.6 (C-5), 127.6 (ArCH), 128.0 (ArCH), 129.1 (ArCH), 129.3 (ArC_a), 156.9 (C=O) ppm. IR (film): $\tilde{v} = 3341, 1726, 1704.$

Benzyl 2-Allylpiperidine-1-carboxylate (14)^[21] and Benzyl (5-Ethoxyoct-7-enyl)carbamate (15): Allyltrimethylsilane (0.4 mL) and BF_3 ·OEt₂ (0.1 mL) were added at 0 °C to a solution of 13 (77 mg, 0.25 mmol) in dry CH₂Cl₂ (4 mL). After stirring for 1 h at 0 °C, the mixture was allowed to warm to room temperature and stirred for another 3 h. The reaction mixture was then poured into saturated aqueous NaHCO₃ (10 mL), the layers were separated, and the water layer was extracted with CH₂Cl₂ (5 mL). The combined CH₂Cl₂ layers were washed with brine, dried with MgSO₄ and concentrated to afford 14 (51 mg, 79%) as a clear oil after purification by chromatography (pentane/Et₂O, 2:1 \rightarrow 1:1). $R_f = 0.4$. ¹H NMR $(400 \text{ MHz}, \text{CDCl}_3): \delta = 1.35 - 1.45 \text{ (m, 1 H)}, 1.47 - 1.60 \text{ (m, 5 H)},$ 2.22-2.29 (m, 1 H), 2.39-2.46 (m, 1 H), 2.81-2.89 (m, 1 H), 4.04-4.07 (m, 1 H), 4.38 (br. m, 1 H), 4.98-5.07 (m, 2 H), 5.11 $(d, J = 12.5 \text{ Hz}, 1 \text{ H}), 5.14 (d, J = 12.5 \text{ Hz}, 1 \text{ H}), 5.65-5.73 (m, J = 12.5 \text{ Hz}), 5.65-5.73 (m, J = 12.5 \text{$ 1 H), 7.29–7.38 (m, 5 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta =$

18.7, 25.4, 27.6, 39.2, 50.4, 66.8, 116.8, 127.7, 127.8, 128.4, 135.2, 137.0, 155.5 ppm. IR (film): $\tilde{v} = 2932$, 1691, 1641, 1422, 1259. HRMS (C₁₆H₂₂NO₂, [MH⁺]; FAB): calcd. 260.1651; found 260.1660. **15** (12 mg, 16%) was also obtained as a clear oil. $R_f = 0.2$. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.17$ (t, J = 7.0 Hz, 3 H), 1.25–1.35 (m, 1 H), 1.41–1.52 (m, 5 H), 2.19–2.29 (m, 2 H), 3.17–3.28 (m, 3 H), 3.35–3.41 (m, 1 H), 3.43–3.58 (m, 1 H), 4.75 (br. s, 1 H), 5.02–5.09 (m, 4 H), 5.77–5.85 (m, 1 H), 7.26–7.37 (m, 5 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.6$, 22.6, 30.0, 33.6, 38.4, 41.0, 64.3, 66.6, 78.6, 116.8, 127.0, 128.1, 128.5, 135.0, 136.7, 156.4 ppm. IR (film): $\tilde{v} = 3417$, 3332, 1701, 1640, 1250. HRMS (C₁₈H₂₈NO₃, [MH⁺]; FAB): calcd. 306.2069; found 306.2057.

Benzyl 2-Benzotriazolylpiperidine-1-carboxylate (18): A catalytic amount of pTSA (10 mol%) was added to a solution of acetal 13 (93 mg, 0.3 mmol) in dry CH₂Cl₂ (6 mL). After 15 min, 1Hbenzotriazole (357 mg, 3 mmol) was added and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then poured into saturated aqueous K_2CO_3 (10 mL), the layers were separated, and the organic layer was washed with aqueous saturated K₂CO₃ (10 mL) and brine (10 mL), dried with MgSO₄ and concentrated to afford 18 (89 mg, 88%) as an oil after purification by chromatography (pentane/Et₂O, 5:6). $R_f = 0.5$. ¹H NMR (400 MHz, CDCl₃, 3:1 mixture, data of the major): $\delta = 1.49 - 1.72$ (m, 2 H), 1.75-1.86 (m, 2 H), 2.04-2.27 (m, 1 H), 2.38-2.59 (m, 2 H), 3.01-3.11 (m, 1 H), 4.00-4.15 (m, 1 H), 5.14 (d, J =12.2 Hz, 1 H), 5.19 (d, J = 12.2 Hz, 1 H), 6.85-6.98 (m, 1 H), 7.12-7.43, (m, 7 H), 8.04 (d, J = 8.7 Hz, 1 H) ppm. IR (film): $\tilde{v} = 1701$. HRMS (C₁₉H₂₁N₄O₂, [MH⁺]; FAB): calcd. 337.1665; found 337.1643.

Benzyl 2-Allylpiperidine-1-carboxylate (14) from 18: Allyltrimethylsilane (0.34 mL) and BF₃·OEt₂ (0.08 mL) were added at 0 °C to a solution of **18** (71 mg, 0.21 mmol) in dry CH₂Cl₂ (5 mL). After stirring for 1 h at 0 °C, the mixture was allowed to warm to room temperature and stirred for another 3 h. The reaction mixture was then poured into saturated aqueous K₂CO₃ (10 mL), the layers were separated, and the water layer was extracted with CH₂Cl₂ (5 mL). The combined CH₂Cl₂ layers were washed with brine, dried with MgSO₄ and concentrated to afford **14** (51 mg, 93%) as a clear oil after purification by chromatography.

General Procedure B for the Formation of the Bt Intermediates: A catalytic amount of pTSA (10 mol %) was added to a 0.05 g/mL suspension of resin in dry CH₂Cl₂, and the suspension was swirled for 30 min. 1*H*-Benzotriazole (10 equiv.) was then added, and the mixture was swirled for another 5 h. Subsequently, the resin was filtered, washed with CH₂Cl₂, MeOH, CH₂Cl₂, MeOH, CH₂Cl₂, Et₂O, CH₂Cl₂, Et₂O and CH₂Cl₂, and dried.

Resin 19a: IR: $\tilde{v} = 1713$, 1494, 1122. Resin 19b: IR: $\tilde{v} = 1722$, 1494, 1121. Resin 19c: IR: $\tilde{v} = 1713$, 1492, 1125. Resin 19d: IR: $\tilde{v} = 1701$, 1492, 1117. Resin 19e: IR: $\tilde{v} = 1722$, 1493, 1125. Resin 19f: IR: $\tilde{v} = 1714$, 1493, 1126.

General Procedure C for the *N*-Acyliminium Ion Reactions and Cleavage: The nucleophile (5 equiv.) and BF_3 ·OEt₂ (3 equiv.) were added at 0 °C to a suspension of 200 mg of resin in 5 mL of dry CH₂Cl₂, and the reaction mixture was swirled for 20 h, thereby allowing it to warm to room temperature, after which the resin was

FULL PAPER

filtered, washed with CH₂Cl₂, MeOH, CH₂Cl₂, MeOH, CH₂Cl₂, Et₂O, CH₂Cl₂, Et₂O and CH₂Cl₂, and dried. The resin was suspended in 1 M NaOMe in THF/MeOH (2 mL, 2:1, v/v) and gently stirred for 1 h, after which it was filtered and washed with CH₂Cl₂, MeOH, CH₂Cl₂ and MeOH. The filtrate was concentrated, and the residue was diluted with a 2 M solution of NaOH (5 mL) and a saturated NaCl solution (5 mL). The aqueous layer was extracted with EtOAc (2×5 mL), the combined organic layers were dried with MgSO₄ and filtered, and the solvent was removed.

General Procedure D for the *N*-Acyliminium Ion Reactions and Cleavage: This was identical to General Procedure C, except that, after cleavage, 1 M HCl in MeOH (4 mL) was added to the filtrate and the solvents were evaporated. The residue was extracted with *i*PrOH (2 mL), filtered and concentrated to afford the products as their HCl salts.

trans-2-Allyl-4-phenylpiperidine (20a): Treatment of resin 19a and allyltrimethylsilane according to General Procedure C afforded 20a (32 mg, 80%) as a yellow oil after purification by chromatography (CH₂Cl₂/3.5 M NH₃ in MeOH, 9:1). $R_f = 0.3$. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.74-1.91$ (m, 4 H), 1.96-2.01 (m, 1 H), 2.24-2.30 (m, 1 H, CH₂CH=CH₂), 2.44-2.50 (m, 1 H, CH₂CH=CH₂), 2.87-3.00 (m, 3 H, 6-H + 4-H), 3.07-3.12 (m, 1 H, 2-H), 5.09-5.15 (m, 2 H, CH=CH₂), 5.74-5.83 (m, 1 H, CH=CH₂), 7.18-7.21 (m, 2 H, ArH), 7.21-7.33 (m, 3 H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 33.0$ (C-3), 36.7 (C-4), 36.9, 37.0, 40.6 (C-6), 51.5 (C-2), 117.1 (CH=CH₂), 125.9 (ArCH), 127.1 (ArCH), 128.4 (ArCH), 136.0 (CH=CH₂), 146.0 (ArC_q) ppm. IR (film): $\tilde{v} = 3280$ (NH), 3030, 1440. HRMS (C₁₄H₂₀N [MH⁺]; FAB): calcd. 202.1596; found 202.1602.

trans-2-Methallyl-4-phenylpiperidine (21a): Treatment of resin 19a and 2-methallyltrimethylsilane according to General Procedure C afforded 21a (33 mg, 76%) as a yellow oil after purification by chromatography (CH₂Cl₂/3.5 M NH₃ in MeOH, 9:1). $R_f = 0.46$. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.74$ (s, 3 H, CH₃), 1.71–1.91 (m, 3 H), 1.97-2.04 (m, 1 H), 2.16 [dd, J = 14.0, 5.5 Hz, 1 H, $CH_2C(CH_3) = CH_2$], 2.52 (dd, J = 16.2, 9.2 Hz, 1 H, $CH_2C(CH_3) =$ CH_2), 2.86–3.03 (m, 3 H, 4-H + 6-H), 3.20–3.26 (m, 1 H, 2-H), 4.79 [d, J = 0.9 Hz, 1 H, CH₂C(CH₃)=CH₂], 4.86 [t, J = 1.7 Hz, 1 H, $CH_2C(CH_3)=CH_2$], 7.18–7.22 (m, 2 H, ArH), 7.25–7.33 (m, 3 H, Ar*H*) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 22.1$ (CH₃), 29.7 (C-3), 31.5 (C-5), 35.4 [CH₂C(CH₃)=CH₂], 35.9 (C-4), 40.1 (C-6), 49.6 (C-2), 113.6 [CH₂C(CH₃)=CH₂], 126.3 (ArCH), 127.0 (ArCH), 128.5 (ArCH), 142.0 [CH₂C(CH₃)=CH₂], 145.0 (ArC_q) ppm. IR (film): $\tilde{v} = 3330$ (NH), 2850, 1450. HRMS (C₁₅H₂₂N [MH⁺]; FAB): calcd. 216.1752; found 216.1759.

trans-2-(2-Furanyl)-4-phenylpiperidine (22a): CSA (1.1 equiv.) was added to a suspension of 200 mg of resin 19a in furan (5 mL). The reaction mixture was swirled for 20 h, filtered, washed with CH₂Cl₂, MeOH, CH₂Cl₂, MeOH, CH₂Cl₂, Et₂O, CH₂Cl₂, Et₂O and CH₂Cl₂, and dried. The product was then cleaved from the resin by General Procedure C to afford 22a (25 mg, 54%) as a yellow oil after purification by chromatography (CH₂Cl₂/3.5 M NH₃ in MeOH, 9:1). $R_f = 0.38$. ¹H NMR (400 MHz, CDCl₃): $\delta =$ 1.75-1.86 (m, 2 H, 5-H), 2.05 (br. s, 1 H, NH), 2.09-2.17 (m, 1 H, 3-H), 2.28-2.33 (m, 1 H, 3-H), 2.86-3.01 (m, 3 H, 4-H + 6-H), 4.37 (d, J = 3.4 Hz, 1 H, 2-H), 6.27 (dd, J = 2.0, 0.9 Hz, 1 H), 6.38 (dd, J = 3.1, 1.8 Hz, 1 H), 7.19–7.34 (m, 5 H, ArH), 7.41 (d, J = 0.9 Hz, 1 H, OCH=CH) ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 33.0$ (C-5), 34.2 (C-3), 37.6 (C-4), 41.5 (C-6), 50.5 (C-2), 106.8 (*C*H=C(CH)O), 110.2 (OCH=*C*H), 125.9 (Ar*C*H), 126.9 (Ar*C*H), 128.1 (ArCH), 141.5 (OCH=CH), 145.8 (Ar C_{qPh}), 155.7 (Ar C_{qFur})

ppm. IR (film): $\tilde{v} = 3296$ (NH), 2925, 1666, 1452. HRMS (C₁₅H₁₈NO [MH⁺]; FAB): calcd. 228.1388; found 228.1400.

trans-2-Ethyl-4-phenylpiperidine (23a): Treatment of resin 19a and diethylzinc according to General Procedure C afforded 23a (5 mg, 14%) as a yellow oil after purification by chromatography (CH₂Cl₂/ 3.5 m NH₃ in MeOH, 9:1). $R_f = 0.21$. ¹H NMR (400 MHz, CDCl₃): $\delta = 0.94$ (t, J = 7.5 Hz, 3 H, CH₂CH₃), 1.54–1.63 (m, 1 H), 1.65–1.81 (m, 3 H), 1.83–1.83 (m, 1 H), 1.93–2.00 (m, 2 H), 2.87–3.00 (m, 4 H), 7.18–7.19 (m, 1 H, Ar*H*), 7.21–7.33 (m, 4 H, Ar*H*) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 10.9$ (CH₃), 24.3 (CH₂CH₃), 32.2 (C-3), 35.4 (C-5), 36.0 (C-4), 40.3 (C-6), 53.9 (C-2), 126.2 (Ar*C*H), 127.0 (Ar*C*H), 128.5 (Ar*C*H), 145.3 (Ar*C*_q) ppm. IR (film): $\tilde{v} = 3304$ (NH), 2927, 1452. HRMS (C₁₃H₂₀N [MH⁺]; FAB): calcd. 190.1596; found 190.1594.

trans-2-Allyl-4-(4-pyridinyl)piperidine (20b): Treatment of resin 19b and allyltrimethylsilane according to General Procedure C afforded 20b (29 mg, 71%) as a yellow oil after purification by chromatography (CH₂Cl₂/3.5 M NH₃ in MeOH, 9:1). $R_f = 0.58$. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.72-1.78$ (m, 1 H), 1.80-1.92 (m, 2 H), 1.93-2.02 (m, 1 H), 2.20 (br, 1 H, NH), 2.23-2.29 (m, 1 H, $CH_2CH=CH_2$), 2.39-2.46 (m, 1 H, $CH_2-CH=CH_2$), 2.84-2.90 (m, 1 H, 4-H), 2.92-3.00 (m, 2 H, 6-H), 3.02-3.08 (m, 1 H, 2-H), 5.10-5.15 (m, 2 H, $CH=CH_2$), 5.71-5.82 (m, 1 H, $CH=CH_2$), 7.17 (d, J = 5.6 Hz, 2 H, ArH), 8.51 (d, J = 5.9 Hz, 2 H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 31.5$ (C-3), 35.6 (C-5), 35.9 (C-4), 37.1 ($CH_2CH=CH_2$), 40.4 (C-6), 51.3 (C-2), 117.7 ($CH=CH_2$), 122.6 (ArCH), 135.5 ($CH=CH_2$), 149.8 (ArCH), 154.4 (ArC_q) ppm. IR (film): $\tilde{v} = 3281$ (NH), 1598, 1413. HRMS ($C_{13}H_{19}N_2$ [MH⁺]; FAB): calcd. 203.1548; found 203.1549.

trans-2-Allyl-4-(4-bromophenyl)piperidine (20c): Treatment of resin 19c and allyltrimethylsilane according to General Procedure C afforded 20c (39 mg, 85%) as a yellow oil after purification by chromatography (CH₂Cl₂/3.5 M NH₃ in MeOH, 9:1). $R_f = 0.36$. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.71 - 1.82$ (m, 2 H, 5-H), 1.84-1.90 (m, 1 H, 3-H), 1.91-1.99 (m, 1 H, 3-H), 2.15 (br, 1 H, NH), 2.22-2.32 (m, 1 H, CH₂CH=CH₂), 2.41-2.50 (m, 1 H, CH_2 -CH=CH₂), 2.84-3.00 (m, 3 H, 6-H + 4-H), 3.08-3.13 (m, 1 H, 2-H), 5.07-5.13 (m, 2 H, CH=CH₂), 5.70-5.79 (m, 1 H, CH=CH₂), 7.12 (d, J = 1 0.0 Hz, 2 H, ArH), 7.39 (d, J = 1 0.0 Hz, 2 H, ArH) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 29.7$ (C-3), 31.9 (C-5), 35.8 (C-4), 36.2 (CH₂CH=CH₂), 40.1 (C-6), 51.4 (C-2), 117.8 (CH=CH₂), 119.8 (ArC_q), 128.8 (ArCH), 131.5 (ArCH), 135.0 (*C*H=CH₂), 144.3 (Ar C_q) ppm. IR (film): $\tilde{v} = 3356$ (NH), 2849, 1489. HRMS (C₁₃H₁₉⁷⁹BrN [MH⁺]; FAB): calcd. 280.0701; found 280.0698.

trans-2-AllyI-4-(2-propyI)piperidine HCl Salt (20e): Treatment of resin 19f and allyltrimethylsilane according to General Procedure D afforded 20e (37 mg, 86%) as its HCl salt. ¹H NMR (400 MHz, D₂O): $\delta = 0.90$ (d, J = 6.2 Hz, 6 H, CH_3), 1.53–1.69 (m, 3 H), 1.72–1.79 (m, 2 H), 1.83–1.89 (m, 1 H), 2.47–2.51 (m, 2 H, $CH_2CH=CH_2$), 3.17–3.20 (m, 2 H, 6-H), 3.53–3.56 (m, 1 H, 2-H), 5.25–5.30 (m, 2 H, CH= CH_2), 5.78–5.84 (m, 1 H, $CH=CH_2$) ppm. ¹³C NMR (125 MHz, D₂O): $\delta = 19.5$ (CH_3), 19.6 (CH_3), 25.1 (C-5), 29.7, 34.9, 35.2, 39.7 (C-6), 51.9 (C-2), 120.1 (CH= CH_2), 132.5 ($CH=CH_2$) ppm. HRMS ($C_{11}H_{21}N$ [M⁺]; EI): calcd. 167.1674; found 167.1640.

2-Allylpiperidine HCI Salt (20f):^[22] Treatment of resin **19f** and allyltrimethylsilane according to General Procedure **D** afforded **20f** (29 mg, 78%) as its HCl salt. ¹H NMR (400 MHz, D₂O): δ = 1.45–1.71 (m, 3 H), 1.89–1.93 (m, 2 H), 2.01–2.04 (m, 1 H), 2.36–2.52 (m, 2 H, CH₂CH=CH₂), 2.96–3.02 (m, 1 H, 6-H), 3.20–3.23 (m, 1 H, 6-H), 3.39–3.44 (m, 1 H, 2-H), 5.25–5.30 (m, 2 H, CH=CH₂), 5.80–5.90 (m, 1 H, CH=CH₂) ppm. ¹³C NMR (100 MHz, D₂O): δ = 23.6 (C-5), 23.8 (C-4), 30.2 (C-3), 39.7 (CH₂CH=CH₂), 46.8 (C-6), 58.1 (C-2), 122.1 (CH=CH₂), 123.9 (CH=CH₂). HRMS (C₈H₁₆N [MH⁺]; FAB): calcd. 126.1283; found 126.1245.

trans-2-Allyl-4-phenyl-1-(4-tolylsulfonyl)piperidine (24): p-Toluenesulfonyl chloride (72 mg, 0.38 mmol) was added to a solution of 20a (32 mg, 0.16 mmol) in pyridine (2 mL) and the mixture was stirred for 20 h. The reaction mixture was concentrated, and the residue was taken up in CH₂Cl₂ (10 mL) and extracted with saturated aqueous NaHCO₃ (10 mL), aqueous saturated CuSO₄ (10 mL) and brine (10 mL), dried with Na₂SO₄ and concentrated to afford 24 (37 mg, 65%) after purification by chromatography (PE/EtOAc, 7:1). $R_f = 0.21$. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.43 - 1.63$ (m, 2 H), 1.69-1.72 (m, 1 H), 1.76-1.80 (m, 1 H), 2.38-2.42 (m, 2 H, CH₂CH=CH₂), 2.44 (s, 3 H, CH₃), 2.77-2.85 (m, 1 H, 4-H), 3.14 (dt, J = 2.7, 13.5 Hz, 1 H, 6-H), 3.91-3.95 (m, 1 H, 6-H),4.24-4.29 (m, 1 H, 2-H), 5.03-5.11 (m, 2 H, CH=CH₂), 5.66-5.77 (m, 1 H, CH=CH₂), 7.02 (d, J = 8.4 Hz, 2 H, TsCH), 7.16-7.32 (m, 5 H, ArCH), 7.36 (d, J = 8.4 Hz, 2 H, TsCH) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 21.5$ (CH₃), 31.9, 34.3, 34.4, 36.0 (C-4), 40.9 (C-6), 52.8 (C-2), 117.4 (CH=CH₂), 126.5 (ArCH), 126.6 (ArCH), 127.1 (ArCH), 128.5 (ArCH), 129.7 (ArCH), 134.7 $(CH=CH_2)$, 138.6 (ArC_q) , 143.1 (ArC_q) , 145.1 (ArC_q) ppm. IR (film): $\tilde{v} = 1638$, 1307, 1155. HRMS ($C_{21}H_{26}NO_2S$ [MH⁺]; FAB: calcd. 356.1684; found 356.1687.

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