Preparation of polysubstituted piperidines *via* radical cyclization

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Polysubstituted piperidines were prepared *via* radical cyclization of α-aminoalkyl radicals onto unactivated double bonds. [1,2]-aza-Wittig rearrangements were observed when an aryl group was attached to the α-aminoalkyl radical center.

Introduction

Radical cyclizations are frequently utilized for ring construction, especially for five-membered rings,[1a–e] such as cyclopentanes, tetrahydrofurans and pyrrolidines.[2a–f] However, radical cyclizations leading to six-membered rings are less common than those leading to five-membered rings due to (i) slower cyclization rates, (ii) lower regioselectivity of 6-*exo* radical cyclization compared with 5-*exo* cyclization and (iii) competitive 1,5-hydrogen transfer.[1a–d,3a,b]

Mariano *et al*. reported that photo-induced radical cyclizations of α-silylaminoenones and α-silylynones furnished functionalized piperidines and piperidine derivatives,[4a,b] and used SET-photo-induced α-aminoalkyl radical cyclizations to prepare indolizidines and quinolizidines.[5] Aurrecoechea *et al*. synthesized six-membered rings by cyclization of α-aminoalkyl radicals.[2d] However, these previous 6-*exo* radical cyclization reactions require an activating electron-withdrawing group on the alkene terminus.

Molander *et al*. prepared six-membered carbocyclic and some heterocyclic rings by radical cyclization of phenyl or ketyl-olefin radicals to unactivated double bonds promoted by samarium diiodide.[6a–c] However, no nitrogen six-membered heterocycles were reported by this method. Parsons and Pettifer demonstrated that substituted pyrrolidines and piperidines could be formed using tin hydride-mediated cyclization of a variety of α- and β-homoallylamino aldehydes.[7] Pandey *et al*. reported that photo-induced electron transfer promoted intramolecular cyclizations of α-silylmethyl amines to unactivated double bonds could afford nitrogen-containing six-membered rings.[8a,b] Jones *et al*. effected aryl-radical cyclizations to unactivated double bonds to prepare quinolines, isoquinolones and 1-benzazepin-2-ones by treatment of appropriate *o*-substituted aryl halides with tri-*n*-butyltin hydride.[9] We previously achieved regioselective additions of α-aminoalkyl radicals to unactivated double bonds to give pyrrolidines,[2b] and have now extended this approach to 6-*exo*-α-aminoalkyl radical cycloadditions affording polysubstituted piperidines.

Results and discussion

The preparation of benzotriazole derivatives 3a–e

Starting materials **3a**–**e** were prepared by the condensation of a secondary amine **1**,[10] aldehydes **2a**–**e** and benzotriazole (BtH) in the presence of molecular sieves in Et_2O at room temperature. Compounds **3a**–**e** decompose easily on contact with water and this decomposition is accelerated by silica gel. Compound **3e** is crystalline and was purified by recrystallization from dry diethyl ether. Benzotriazole derivatives **3a**–**d** could not be purified, but can be used in a crude form for preparative purposes. These crude products, **3a**–**d**, contained *ca*. 3% of secondary amine **1** as a contaminant as demonstrated by a singlet around 3.8 ppm which was assigned to the methylene $PhCH_2N$ of **1** in the crude ^{1}H NMR spectra. Structures **3a**–**d** were supported by AB systems around 3.0–4.5 ppm in their ^{1}H NMR spectra for the $PhCH_2N$ methylene and by the correct integration ratio of this signal to that characteristic of the benzotriazole ring protons.[2d]

Cyclization reactions of 3a–e

Initial cyclization studies were conducted on benzotriazole derivative **3a**. Treatment of **3a** with samarium diiodide in THF–HMPA under argon at 0 °C, followed by a water quench gave piperidine derivative **7a** as a mixture of *cis* and *trans* isomers in 56% yield. This reaction is thought to proceed *via* radical intermediates **4a** and **5a**, and organic samarium derivative **6a** (Scheme 1).[2b] The *cis* and *trans* ratios of **7a** (Table 1) were determined by GC/MS results.

When a ketone (pentan-3-one, butan-2-one or pentan-2-one) was added as electrophile to the reaction mixture of **3a** and SmI_2, intermediate **6a** was trapped to form piperidines **8a**–**c** in 41–51% yields, together with the protonated product **7a**, in 30–34% yield, as a by-product. Changing the solvent from THF to THP, or extending the reaction time to four days before quenching the reaction with water when compound **3a** was used as starting material and pentan-3-one was used as electrophile did not decrease the yield of protonated product **7a**.

When benzaldehyde, acetaldehyde or isopropyl isocyanate were used as electrophiles, **7a** was obtained as the major product in 47–50% yield, along with compounds **8d**–**f** formed by trapping **6a** with the corresponding electrophile in 17–25% yield. Compounds *cis*-**8b**–**e**, which possess an additional extracyclic asymmetric center, were isolated as mixtures of diastereomers. The NMR spectra of the diastereomers of *cis*-**8b**–**e** show only small differences.

The structural integrity and the stereochemistry of compound *cis*-**8d** were investigated by NMR. The proton spectrum of *cis*-**8d** at room temperature displayed broad lines, indicative of slowed exchange between conformations (see Fig. 1). At 55 °C the exchange was fast and sharp lines allowed the measurement of the coupling constants. The complete assignments of the ^{1}H and ^{13}C chemical shifts were made using DQCOSY and the gradient HMQC spectra. The coupling constants of the two protons in position 6 (2.75 ppm, ddd, 12.9, 9.1, 3.3 Hz and 2.23 ppm, dt, 12.9, 4.7 Hz) indicated that in the preferred

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Table 1 The preparation of piperidine derivatives **7** and **8**

Starting material	Electrophile	Product **8** No.	R	E	Yield	Ratio[a]	Product **7** No.	R	Yield	Ratio[a]
3a	H_2O	[b]					**a**	Pr	56	1:8.9
3a	EtCOEt	**a**	Pr	EtC(OH)Et	51	1:4.3	**a**	Pr	34	1:1.1
3a	MeCOEt	**b**	Pr	MeC(OH)Et	43	1:7.5	**a**	Pr	30	1:1.2
3a	MeCOPr	**c**	Pr	MeC(OH)Pr	41	1:4.8	**a**	Pr	33	1:1.1
3a	PhCHO	**d**	Pr	PhCHOH	17	1:3.2	**a**	Pr	47	1:1.2
3a	MeCHO	**e**	Pr	MeCHOH	21	1:6.4	**a**	Pr	49	1:1.1
3a	i-PrNCO	**f**	Pr	i-PrNHCO	25	1:2.5	**a**	Pr	50	1:1.3
3b	H_2O	[b]					**b**	i-Pr	53	1:1.4
3c	H_2O	[b]					**c**	t-Bu	52	1:1.1

[a] This is the *trans*:*cis* ratio and was determined by GC/MS. All the yields are isolated yields. [b] In these runs no electrophile other than water was added.

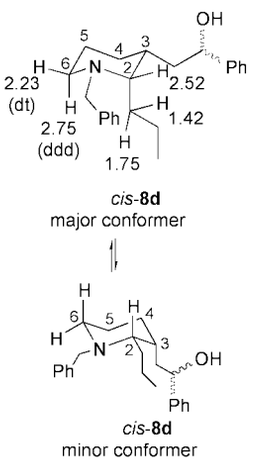
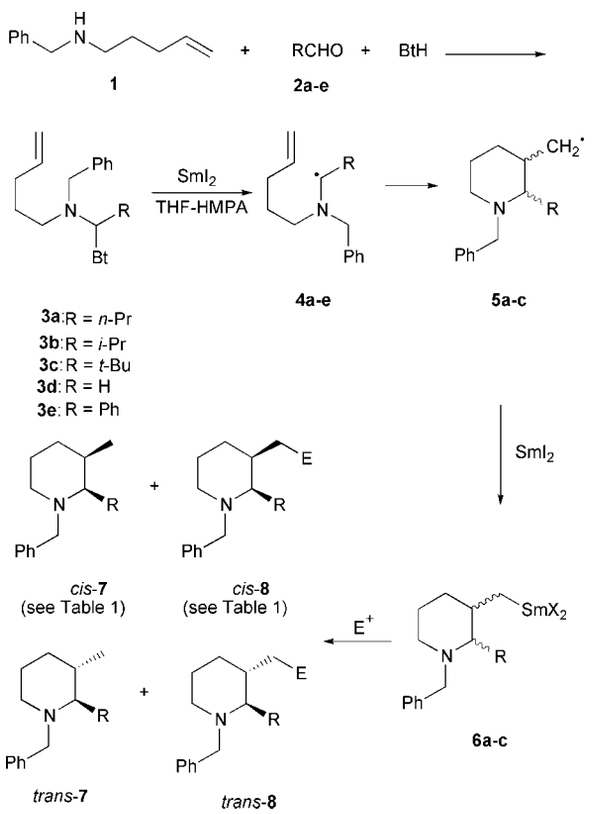


Fig. 1 Conformers of **8d**.

conformation the proton at 2.75 is axial. The NOESY spectrum contained two sets of cross-peaks: (i) between the protons at 2.23 and 2.52 and (ii) between those at 2.75 and 1.75. We believe cross-peaks (i) arise from the minor conformer of *cis*-**8d** (see Fig. 1), whereas cross-peaks (ii) arise from the major conformer of *cis*-**8d**. In the preferred conformation, the propyl group in position 2 is axial, because it is *cis* to the axial proton in position 6. We assign the substituent in position 3 of *cis*-**8d** as *cis* to the 2-propyl group because if positions 2 and 3 were mutually *trans*, they would both be axial in their most stable conformation, which is highly unlikely. By analogy, we assigned all the major products **7a** and **8a**–**f** as *cis* isomers. We also examined the ^{1}H-spectra of *cis*-**8d** at low temperature. Coalescence occurred at *ca.* −20 °C and the spectra were sharp again at −80 °C. The easiest pattern to interpret was the benzyl $-CH_2$ signal which changed from an AB system at high temperature to an AX system at low temperature. A detailed interpretation of the spectra was not possible because of their complexity.

We next utilized compounds **3b** and **3c** which cyclized to produce **7b** and **7c** with the larger isopropyl and *tert*-butyl groups at the C-2 position. After quenching by water, cyclization product **7b** was obtained in 51% yield. Compound **7c** (yield estimated as 52% by GC/MS) was isolated only as a mixture with an acyclic product arising from the protonation of intermediate **4c**.

Attempted use of **3d** (*i.e.* R = H) as starting material failed. Reaction of **3d** with SmI_2 and quenching by water gave a complex mixture in which no cyclic product was detected. The primary radical **4a** is presumably too short-lived to cyclize. The yields of compounds **8** and **7** in Table 1 are all based on the amount of starting amine **1** used, and are, therefore, overall yields for a two-pot, three-step reaction process. The total yields

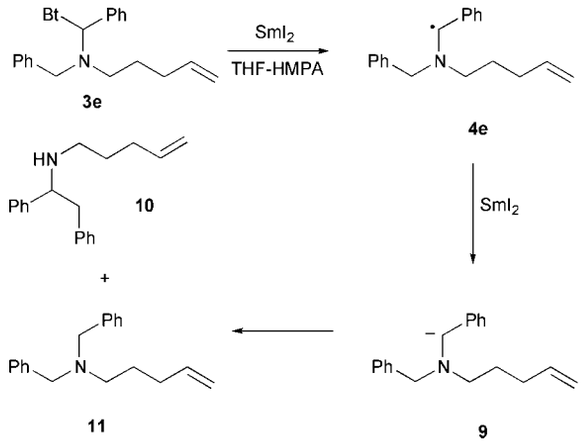


Scheme 1

for **8a**–**f** were more than 70% when the amount of **7a** was taken into account, which indicates that the radical cyclization proceeds smoothly.

The [1,2]-aza-Wittig rearrangement reaction of 11a–f

When compound **3e** was reacted with SmI_2 and the reaction mixture quenched by water, no cyclic products of type **7** and **8** were found, instead compounds **10** and **11** were obtained (Scheme 2). We believe that the major product **10** is formed by a [1,2]-aza-Wittig rearrangement of α-aminocarbanion **9**, and that another portion of **9** undergoes protonation to **11**. The structures of compounds **10** and **11** were supported by their ^{1}H NMR spectra. The double doublets around 4.8 ppm with J = 10.6 and 1.5 Hz and the multiplets around 5.7 ppm showed the existence of a terminal double bond in compounds **10** and **11**. The singlet at 3.56 ppm with four protons in the ^{1}H NMR spectrum of compound **11** which was assigned to the two $PhCH_2N$ methylenes demonstrated that these two $PhCH_2$ groups were attached to N respectively. However, this singlet was not found in the ^{1}H NMR spectrum of compound **10**. Instead, one doublet around 2.9 ppm with two protons and one



Scheme 2

triplet around 3.8 ppm with one proton were found. These supported the structure of compound **10** and showed that the rearrangement had occurred. The different reaction course is probably due to radical **4e** being more stable (and less reactive) so that it is reduced further to carbanion **9** before cyclization occurs.

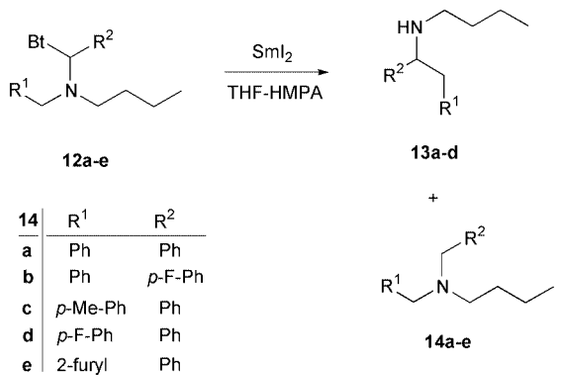
We further explored this rearrangement reaction using **12a**–**e** (Scheme 3) as starting materials to ascertain its scope and limitations. Benzotriazole derivatives **12a**–**e** were prepared using the same method as for the preparation of compounds **3a**–**e**. Compounds **12a**–**e** are crystalline. They were purified by recrystallization from diethyl ether and their structures were supported by NMR spectra and microanalysis or HRMS. Treatment of **12a**–**d** with samarium diiodide in THF–HMPA under argon at 0 °C, followed by a water quench, gave mixtures of the corresponding rearrangement products **13a**–**d** and reduction products **14a**–**d** in which **13a**–**d** predominated (Table 2). When **12e** was used as starting material to perform this reaction, only the reduction product **14e** and no migration product **13e** was found. The results show that this type of rearrangement occurs for R^1 = phenyl and phenyl substituted by both electron-withdrawing and electron-donating groups.

[2,3]- and, to a much lesser extent, [1,2]-aza-Wittig rearrangements have been studied mechanistically and for synthetic application by several groups during the last three decades.[11] A detailed study of the [1,2]-anionic rearrangement by Eisch and Kovacs in 1971 reported the rearrangement tendencies of the benzylic anions obtained from benzyldiphenylamine and *N*-benzylcarbazole.[12] In 1972, Durst *et al.* reported the base-induced ring enlargements of 1-benzyl- and 1-allyl-2-azetidinones *via* [1,2]- or [2,3]-aza-Wittig rearrangement.[13] Reetz *et al.* found (9-lithio-9-fluorenyl)allylmethylamine underwent an aza-Wittig rearrangement when refluxed in THF, but it is not clear whether this is a [1,2]- or [2,3]-shift.[14] Reductive lithiation of *N*-allyl-*N*-heptyl-*N*-[(phenylsulfanyl)methyl]amine yielded a homoallylic amine, claimed as a [2,3]-sigmatropic rearrangement.[15] However, Nakai *et al.* found later that a similar reductive desulfurization did not afford a [2,3]-shifted product, instead it gave a 4:1 mixture of the reduction product and the [1,2]-shifted product.[16] Gawley *et al.* demonstrated that a [2,3]-aza-Wittig rearrangement proceeds with inversion of configuration at the lithium-bearing carbon, which was itself formed through tin–lithium exchange.[17] Somfai *et al.* studied the mechanism, scope and limitations of the [2,3]-aza-Wittig rearrangements of vinylaziridines.[18a,b] Coldham and his co-workers demonstrated that the [1,2]-aza-Wittig rearrangement occurred in certain *N*-benzylaminomethylstannanes,[19] whereas the [2,3]-route was adopted for 2-benzoylaziridines[20a,b] and *N*-alkyl-*N*-allyl amino esters.[21] This previous work concentrated on the [2,3]-aza-Wittig rearrangement, with much less comment on the alternative [1,2]-mechanism. To our best knowledge, SmI_2 has not previously been used as a reductive

Table 2 The yields (%) of compounds **13a**–**d** and **14a**–**e**[a]

Entry	R^1	R^2	**13**	**14**
a	Ph	Ph	40	27
b	Ph	*p*-F-Ph	60	23
c	*p*-Me-Ph	Ph	60	29
d	*p*-F-Ph	Ph	57	35
e	2-furyl	Ph		100

[a] All the yields are from GC/MS results.



Scheme 3

agent to induce the [1,2]-aza-Wittig rearrangement and no report was found of benzyl and/or substituted benzyl as a migrating group.

Conclusion

In conclusion, we have demonstrated the capacity of 6-*exo*-α-aminoalkyl radical cyclizations to form a variety of piperidine derivatives. Syntheses of piperidines are well documented[4a,22a–g] due to their presence in numerous natural products and their biological properties.[23a–e] To the best of our knowledge, no previous procedures have been reported using the cycloaddition of unstable α-aminoalkyl radicals to unactivated double bonds as a means to prepare piperidine derivatives. In compound **3e** (R = Ph), [1,2]-aza-Wittig rearrangement occurred instead of cyclization and further [1,2]-aza-Wittig rearrangements were studied using **12a**–**e** as starting materials. This work significantly extends the scope of the previously little studied [1,2]-aza-Wittig rearrangement.

Experimental

General comments

Melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ with TMS or $CHCl_3$ as internal reference. The spectra of compound **8d** were taken on a Varian Inova instrument at 500 MHz for ^{1}H, in $CDCl_3$. Elemental analyses were performed on a Carlo Erba-1106 instrument. High resolution mass spectra were measured on a Kratos/AE1-MS 30 mass spectrometer. GC–MS analyses were run on a Hewlett Packard 5890 Series II Gas Chromatograph HP-5 (30 m × 0.32 mm × 0.25 μm) capillary column with an HP 5972 Series Mass Selective Detector. THF and ether were distilled from sodium–benzophenone under nitrogen immediately prior to use. HMPA was dried over molecular sieves. All reactions with air-sensitive compounds were carried out under an argon atmosphere.

General procedure for the preparation of benzotriazole derivatives 3a–e and 12a–e

N-Benzylpent-4-enylamine **1** (for **3a**–**e**, 2.0 mmol) or *N*-benzylbutylamine (for **12a**–**e**, 2.0 mmol), the corresponding aldehyde

(2.0 mmol) and benzotriazole (2.1 mmol) were mixed in 25 mL dry ether with 4 Å molecular sieves and stirred for 12 h before the resulting solution was filtered through celite and washed using a small amount of dry diethyl ether. The solvent was removed under vacuum to yield **3a**–**d** as an oil. They were used in a crude form for preparative purposes. For **3e** and **12a**–**e**, the solids were obtained after solvent was removed. Recrystallization from dry diethyl ether yielded a white crystalline solid as the desired product.

***N*-[Benzotriazol-1-yl(phenyl)methyl]-*N*-benzylpent-4-en-1-amine (3e).** mp 112–114 °C. Yield: 60%. ^{1}H NMR δ 1.62–1.68 (m, 2H), 1.90–1.97 (m, 1H), 2.03–2.13 (m, 1H), 2.50–2.59 (m, 1H), 2.94–3.07 (m, 1H), 3.41 (d, J = 4.3 Hz, 1H), 4.18 (d, J = 4.3 Hz, 1H), 4.87 (d, J = 1.4 Hz, 1H), 4.94 (d, J = 9.3 Hz, 1H), 5.64–5.75 (m, 1H), 6.90 (s, 1H), 7.04–7.12 (m, 2H), 7.20–7.46 (m, 10H), 7.96–7.99 (m, 1H), 8.12–8.15 (m, 1H); ^{13}C NMR δ 27.6, 31.2, 49.4, 54.2, 85.0, 110.7, 114.7, 118.6, 120.0, 123.9, 126.3, 127.1, 127.4, 128.4, 128.5, 128.6, 128.7, 136.9, 138.2, 138.8, 145.6. HRMS (CI) *m*/*z* calcd. for $C_{25}H_{27}N_4$ (M + 1): 383.2236. Found (M + 1): 383.2252.

***N*-[Benzotriazol-1-yl(phenyl)methyl]-*N*-benzylbutan-1-amine (12a).** mp 100–102 °C. Yield: 69%. ^{1}H NMR δ 0.82 (t, J = 7.2 Hz, 3H), 1.18–1.45 (m, 2H), 1.52–1.61 (m, 2H), 2.46–2.60 (m, 1H), 2.95–3.06 (m, 1H), 3.41 (d, J = 14.3 Hz, 1H), 4.19 (d, J = 14.3 Hz, 1H), 6.92 (s, 1H), 7.05–7.42 (m, 12H), 7.82–7.98 (m, 1H), 8.13–8.16 (m, 1H); ^{13}C NMR δ 13.9, 20.2, 30.4, 49.5, 54.1, 77.5, 110.7, 120.0, 123.8, 127.0, 127.3, 127.4, 128.3, 128.4, 128.5, 128.6, 134.0, 136.9, 138.9, 145.6. Anal. Calcd. for $C_{24}H_{26}N_4$: C, 77.80; H, 7.07; N, 15.12. Found: C, 77.47; H, 7.22; N, 15.49%.

***N*-[Benzotriazol-1-yl(4-fluorophenyl)methyl]-*N*-benzylbutan-1-amine (12b).** mp 77–79 °C. Yield: 80%. ^{1}H NMR δ 0.83 (t, J = 7.2 Hz, 3H), 1.22–1.24 (m, 2H), 1.53–1.60 (m, 2H), 2.48–2.52 (m, 1H), 2.95–3.18 (m, 1H), 3.39 (d, J = 14.3 Hz, 1H), 4.17 (d, J = 14.3 Hz, 1H), 6.87 (s, 1H), 6.99–7.47 (m, 11H), 7.81–7.97 (m, 1H), 8.15–8.18 (m, 1H); ^{13}C NMR δ 13.9, 20.2, 30.4, 49.4, 54.0, 77.2, 110.5, 115.4 (d, J = 22.5 Hz), 120.0, 124.0, 127.2, 128.2, 128.5 (d, J = 7.5 Hz), 129.1, 132.2, 132.7, 134.0, 138.7, 145.5, 162.5 (d, J = 247.5 Hz). Anal. Calcd. for $C_{24}H_{25}FN_4$: C, 74.20; H, 6.49; N, 14.42. Found: C, 74.30; H, 6.63; N, 14.75%.

***N*-[Benzotriazol-1-yl(phenyl)methyl]-*N*-(4-methylbenzyl)-butan-1-amine (12c).** mp 83–85 °C. Yield: 51%. ^{1}H NMR δ 0.84 (t, J = 7.2 Hz, 3H), 1.23–1.54 (m, 2H), 1.57–1.68 (m, 2H), 2.37 (s, 3H), 2.46–2.55 (m, 1H), 2.96–3.05 (m, 1H), 3.36 (d, J = 14.2, 1H), 4.16 (d, J = 14.2 Hz, 1H), 6.91 (s, 1H), 7.06–7.45 (m, 11H), 7.93–8.05 (m, 1H), 8.15–8.17 (m, 1H); ^{13}C NMR δ 13.9, 20.2, 21.1, 30.4, 49.4, 53.7, 77.0, 110.8, 115.1, 119.9, 123.9, 127.3, 128.3, 128.6, 129.0, 129.1, 129.2, 129.7, 134.4, 135.7, 137.0. HRMS (CI) *m*/*z* calcd. for $C_{25}H_{29}N_4$ (M + 1): 385.2392. Found (M + 1): 385.2408.

***N*-[Benzotriazol-1-yl(phenyl)methyl]-*N*-(4-fluorobenzyl)-butan-1-amine (12d).** mp 84–86 °C. Yield: 44%. ^{1}H NMR δ 0.81 (t, J = 7.3 Hz, 3H), 1.10–1.40 (m, 2H), 1.42–1.61 (m, 2H), 2.38–2.50 (m, 1H), 2.83–3.00 (m, 2H), 3.42 (d, J = 14.3 Hz, 1H), 4.13 (d, J = 14.3 Hz, 1H), 6.89 (s, 1H), 6.99–7.45 (m, 10H), 7.91–7.97 (m, 1H), 8.08–8.18 (m, 1H); ^{13}C NMR δ 13.9, 20.2, 30.4, 49.5, 53.3, 76.9, 110.6, 115.3 (d, J = 22.5 Hz), 118.5, 120.0, 123.9, 126.3, 127.0, 127.1, 127.3, 128.4, 128.6, 130.2 (d, J = 7.5 Hz), 136.8, 145.6, 162.8 (d, J = 248.5 Hz). Anal. Calcd. for $C_{24}H_{25}FN_4$: C, 74.20; H, 6.49; N, 14.42. Found: C, 73.88; H, 6.54; N, 14.76%.

***N*-[Benzotriazol-1-yl(phenyl)methyl]-*N*-butyl-2-furylmethylamine (12e).** mp 77–79 °C. Yield: 65%. ^{1}H NMR δ 0.81 (t, J = 7.1 Hz, 3H), 1.20–1.37 (m, 2H), 1.47–1.56 (m, 2H), 2.50–2.56 (m, 1H), 2.83–2.90 (m, 1H), 3.51 (d, J = 14.8 Hz, 1H), 4.13 (d, J = 14.8 Hz, 1H), 6.18 (d, J = 3.0 Hz, 1H), 6.30 (d, J = 3.0 Hz, 1H), 7.00 (s, 1H), 7.23–7.39 (m, 8H), 7.85–9.00 (m, 1H), 8.12–8.14 (m, 1H); ^{13}C NMR δ 13.8, 20.0, 30.0, 47.0, 49.3, 78.3, 108.6, 110.1, 110.8, 119.9, 123.8, 127.1, 127.5, 128.4, 128.6, 133.7, 136.6, 142.2, 145.7, 152.3. Anal. Calcd. for $C_{22}H_{24}N_4O$: N, 15.54. Found: N, 15.84%.

General procedure for the preparation of piperidine derivatives 7a–c and 8a–f

Compound **3a**–**c** (2 mmol) in THF (20 mL) was added dropwise to the solution of SmI_2 in THF (60 mL, 0.1 M) and HMPA (6 mL) at 0 °C. After the addition was finished, the mixture was stirred for a further 10 min and electrophile (2.5 mmol) was added. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was extracted with ether (3 × 40 mL). The combined organic layer was dried over Na_2SO_4. After evaporation under vacuum, the residue was purified by flash chromatography (silica gel saturated with Et_3N) using hexanes–EtOAc = 100 : 0.5 as eluent to afford desired product **7a**–**c** or **8a**–**f**. (For compounds **7a**–**c**, no electrophile was used.)

1-Benzyl-3-methyl-2-propylpiperidine (7a). Oil. Yield: 56%. (single isomer) ^{1}H NMR δ 0.87 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H), 1.21–1.76 (m, 8H), 1.85–2.18 (m, 1H), 2.21–2.36 (m, 1H), 2.37–2.60 (m, 2H), 3.68, 3.75 (AB, J = 13.8 Hz, 2H), 7.13–7.47 (m, 5H); ^{13}C NMR δ 14.5, 17.5, 21.8, 22.9, 27.0, 29.1, 31.8, 47.1, 58.3, 63.1, 126.5, 128.0, 128.6, 140.9. HRMS (CI) *m*/*z* calcd. for $C_{16}H_{26}N$ (M + 1): 232.2065. Found (M + 1): 232.2042.

1-Benzyl-2-isopropyl-3-methylpiperidine (7b). Oil. Yield: 51%. (single isomer) ^{1}H NMR δ 0.96 (d, J = 6.7 Hz, 3H), 1.00–1.12 (m, 6H), 1.12–1.30 (m, 1H), 1.52–1.80 (m, 3H), 1.92–2.15 (m, 2H), 2.20–2.35 (m, 2H), 2.81 (dd, J = 13.0, 3.6 Hz, 1H), 3.53, 3.94 (AB, J = 14.0, 2H), 7.16–7.42 (m, 5H); ^{13}C NMR δ 16.1, 17.4, 20.0, 20.7, 27.7, 29.5, 33.1, 51.2, 54.1, 69.1, 126.3, 128.1, 141.6. HRMS (CI) *m*/*z* calcd. for $C_{16}H_{26}N$ (M + 1): 232.2065. Found (M + 1): 232.2099.

3-[(1-Benzyl-2-propylpiperidin-3-yl)methyl]pentan-3-ol (8a). Oil. Yield: 51%. (single isomer) ^{1}H NMR δ 0.68–0.93 (m, 9H), 1.10–1.30 (m, 5H), 1.30–1.40 (m, 2H), 1.40–1.55 (m, 4H), 1.55–1.75 (m, 4H), 1.97–2.12 (m, 1H), 2.35–2.49 (m, 1H), 2.50–2.70 (m, 2H), 3.70, 3.80 (AB, J = 13.5 Hz, 2H), 7.13–7.39 (m, 5H); ^{13}C NMR δ 7.9, 8.0, 14.5, 22.1, 22.9, 26.5, 28.2, 31.2, 31.4, 32.0, 41.1, 44.9, 58.4, 63.0, 75.5, 126.5, 128.0, 128.6, 140.7. Anal. Calcd. for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.02; H, 11.55; N, 4.87%.

2-[(1-Benzyl-2-propylpiperidin-3-yl)methyl]butan-2-ol (8b). Oil. Yield: 43%. (mixture of two isomers) ^{1}H NMR δ 0.89 (t, J = 7.4 Hz, 6H), 1.16 (s, 3H), 1.02–1.42 (m, 7H), 1.43–1.73 (m, 6H), 1.97–2.11 (m, 1H), 2.35–2.48 (m, 1H), 2.50–2.68 (m, 2H), 3.70, 3.80 (AB, J = 13.6 Hz, 2H), 7.15–7.45 (m, 5H); ^{13}C NMR δ 8.3, 8.4, 14.5, 22.1, 22.2, 22.8, 22.9, 26.6, 26.7, 26.8, 28.2, 28.3, 29.7, 32.6, 32.8, 34.8, 35.2, 43.8, 43.9, 44.0, 44.8, 45.0, 58.4, 63.0, 63.1, 73.6, 126.5, 128.0, 128.5, 140.7. Anal. Calcd. for $C_{20}H_{33}NO$: C, 79.15; H, 10.96; N, 4.62. Found: C, 79.30; H, 11.19; N, 4.81%.

2-[(1-Benzyl-2-propylpiperidin-3-yl)methyl]pentan-2-ol (8c). Oil. Yield: 41%. (mixture of two isomers) ^{1}H NMR δ 0.77–0.98 (m, 6H), 1.05–1.20 (m, 4H), 1.20–1.52 (m, 12H), 1.56–1.74 (m, 2H), 1.96–2.12 (m, 1H), 2.36–2.48 (m, 1H), 2.49–2.70 (m, 2H), 3.70, 3.80 (AB, J = 13.4 Hz, 2H), 7.16–7.40 (m, 5H); ^{13}C NMR δ 14.5, 14.6, 17.2, 17.3, 22.1, 22.2, 22.8, 22.9, 26.5, 26.6, 27.1,

27.4, 28.2, 28.3, 29.7, 32.5, 32.8, 44.5, 44.9, 45.1, 45.2, 58.4, 62.9, 63.0, 73.5, 126.6, 128.0, 128.6, 140.6. Anal. Calcd. for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.45; H, 11.38; N, 4.54%.

2-(1-Benzyl-2-propylpiperidin-3-yl)-1-phenylethanol (8d). Oil. Yield: 17%. (single isomer) ^{1}H NMR δ 0.90 (t, J = 7.2 Hz, 3H), 1.25–1.43 (m, 4H), 1.50–1.65 (m, 4H), 1.72–1.83 (m, 2H), 2.04–2.12 (m, 1H), 2.15–2.25 (m, 1H), 2.46–2.59 (m, 1H), 2.67–2.80 (m, 1H), 3.42, 3.92 (AB, J = 11.2 Hz, 2H), 4.78 (dd, J = 9.0, 4.4 Hz, 1H), 7.20–7.40 (m, 10H); ^{13}C NMR δ 14.5, 21.0, 22.4, 22.9, 27.6, 29.7, 33.5, 41.7, 58.0, 62.4, 71.7, 125.9, 126.9, 127.3, 128.2, 128.4, 129.0, 139.2, 145.6. HRMS (CI) *m*/*z* calcd. for $C_{23}H_{32}NO$ (M + 1): 338.2484. Found (M + 1): 338.2480.

1-(1-Benzyl-2-propylpiperidin-3-yl)propan-2-ol (8e). Oil. Yield: 21%. (single isomer) ^{1}H NMR δ 0.93 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.1 Hz, 3H), 1.10–1.30 (m, 5H), 1.20–1.50 (m, 2H), 1.50–1.90 (m, 5H), 2.30–2.47 (m, 2H), 2.48–2.60 (m, 1H), 3.50–3.65 (m, 2H), 3.86–4.00 (m, 1H), 7.16–7.45 (m, 5H); ^{13}C NMR δ 14.4, 20.8, 22.7, 24.1, 26.1, 29.7, 33.5, 45.2, 45.7, 59.1, 63.0, 65.2, 126.9, 128.2, 129.1, 138.9. HRMS (CI) *m*/*z* calcd. for $C_{18}H_{30}NO$ (M + 1): 276.2327. Found (M + 1): 276.2330.

2-(1-Benzyl-2-propylpiperidin-3-yl)-*N*-isopropylacetamide (8f). Oil. Yield: 25%. (single isomer) ^{1}H NMR δ 0.88 (t, J = 7.2 Hz, 3H), 1.13 (d, J = 6.6 Hz, 6H), 1.18–1.30 (m, 1H), 1.30–1.48 (m, 4H), 1.50–1.88 (m, 5H), 1.90–2.68 (m, 4H), 3.62, 3.78 (AB, J = 13.7 Hz, 2H), 3.92–4.17 (m, 1H), 5.18–5.33 (m, 1H), 7.15–7.45 (m, 5H); ^{13}C NMR δ 14.5, 21.1, 21.2, 22.8, 22.9, 26.6, 27.8, 29.7, 34.2, 39.5, 41.2, 58.1, 61.8, 126.6, 128.1, 128.6, 140.6, 171.5. HRMS (CI) *m*/*z* calcd. for $C_{20}H_{33}N_2O$ (M + 1): 317.2593. Found (M + 1): 317.2594.

General procedure for [1,2]-aza-Wittig rearrangement

The solution of compound **3e** or **12a**–**e** (2 mmol) in THF (20 mL) was added dropwise to the mixed solution of 0.1 M SmI_2 in THF (60 mL) and HMPA (6 mL) at 0 °C within 20 min. After an additional 20 min, the reaction mixture was warmed to room temperature and stirred overnight. A saturated K_2CO_3 aqueous solution was added to quench the reaction. Ethyl acetate (150 mL) was added and the aqueous solution was removed. The organic solution was dried over anhydrous Na_2SO_4 and solvent was removed *in vacuo*. The residue was subjected to silicon gel chromatography to yield the rearrangement and reductive product, respectively.

***N*-(1,2-Diphenylethyl)pent-4-en-1-amine (10).** Oil. Yield: 20%. ^{1}H NMR δ 1.43–1.50 (m, 2H), 1.89–1.95 (m, 2H), 2.36–2.42 (m, 2H), 2.91 (d, J = 6.9 Hz, 2H), 3.83 (t, J = 6.9 Hz, 1H), 4.85 (d, J = 10.7 Hz, 1H), 4.88 (d, J = 1.5 Hz, 1H), 5.60–5.76 (m, 1H), 7.09–7.35 (m, 10H); ^{13}C NMR δ 29.1, 31.3, 45.3, 47.0, 64.7, 114.5, 126.3, 127.0, 127.3, 128.3, 128.4, 129.3, 138.4, 139.0, 144.0. HRMS (CI) *m*/*z* calcd. for $C_{19}H_{24}N$ (M + 1): 266.1909. Found (M + 1): 266.1909.

***N*,*N*-Dibenzylpent-4-en-1-amine (11).** Oil. Yield: 18%. ^{1}H NMR δ 1.55–1.64 (m, 2H), 2.01–2.07 (m, 2H), 2.44 (t, J = 7.4 Hz, 2H), 3.56 (s, 4H), 4.89 (d, J = 10.6 Hz, 1H), 4.97 (d, J = 1.4 Hz, 1H), 5.68–5.82 (m, 1H), 7.21–7.39 (m, 10H); ^{13}C NMR δ 26.5, 31.5, 53.0, 58.4, 114.3, 126.7, 128.1, 128.8, 138.8, 140.0. Anal. Calcd. for $C_{19}H_{23}N$: N, 5.28. Found: N, 5.55%.

***N*-(1,2-Diphenylethyl)butan-1-amine (13a).** Oil. Yield: 40%. ^{1}H NMR δ 0.82 (t, J = 7.2 Hz, 3H), 1.15–1.30 (m, 2H), 1.30–1.42 (m, 2H), 2.30–2.50 (m, 2H), 2.95 (d, J = 6.9 Hz, 2H), 3.87 (t, J = 6.9 Hz, 1H), 7.13 (d, J = 7.4 Hz, 2H), 7.21–7.49 (m, 8H); ^{13}C NMR δ 13.9, 20.3, 32.1, 45.2, 47.5, 64.9, 126.3, 127.0, 127.3, 128.3, 128.4, 129.3, 138.9, 143.9. HRMS (CI) *m*/*z* calcd. for $C_{18}H_{24}N$ (M + 1): 254.1909. Found (M + 1): 254.1925.

***N*-[1-(4-Fluorophenyl)-2-phenylethyl]butan-1-amine (13b).** Oil. Yield: 60%. ^{1}H NMR δ 0.81 (t, J = 7.2 Hz, 3H), 1.18–1.26 (m, 2H), 1.31–1.39 (m, 2H), 2.33–2.38 (m, 2H), 2.87 (d, J = 7.2 Hz, 2H), 3.82 (t, J = 7.2 Hz, 1H), 7.00 (t, J = 8.2 Hz, 2H), 7.14 (d, J = 9.0 Hz, 2H), 7.22–7.33 (m, 5H); ^{13}C NMR δ 13.9, 20.3, 32.1, 45.4, 47.4, 64.2, 115.0 (d, J = 22.5 Hz), 126.3, 128.4, 128.7 (d, J = 7.5 Hz), 129.2, 138.7, 139.6, 161.8 (d, J = 240.0 Hz). Anal. Calcd. for $C_{18}H_{22}FN$: C, 79.67; H, 8.17; N, 5.16. Found: C, 79.42; H, 8.36; N, 5.21%.

***N*-[2-(4-Methylphenyl)-1-phenylethyl]butan-1-amine (13c).** Oil. Yield: 60%. ^{1}H NMR δ 0.83 (t, J = 7.2 Hz, 3H), 1.17–1.25 (m, 2H), 1.29–1.40 (m, 2H), 2.34 (s, 3H), 2.35–2.43 (m, 2H), 2.80–2.95 (m, 2H), 3.83 (t, J = 7.4 Hz, 1H), 6.98–7.12 (m, 4H), 7.26–7.34 (m, 5H); ^{13}C NMR δ 13.9, 20.3, 21.0, 32.2, 44.9, 47.5, 64.9, 126.9, 127.3, 128.2, 129.0, 129.1, 135.8, 142.9, 144.2. HRMS (CI) *m*/*z* calcd. for $C_{19}H_{26}N$ (M + 1): 268.2065. Found (M + 1): 268.2065.

***N*-[2-(4-Fluorophenyl)-1-phenylethyl]butan-1-amine (13d).** Oil. Yield: 57%. ^{1}H NMR δ 0.83 (t, J = 7.2 Hz, 3H), 1.18–1.31 (m, 2H), 1.32–1.54 (m, 2H), 2.30–2.50 (m, 2H), 2.88 (d, J = 7.1 Hz, 2H), 3.78 (t, J = 7.1 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.99–7.06 (m 2H), 7.23–7.32 (m, 5H); ^{13}C NMR δ 13.9, 20.3, 32.2, 44.4, 47.5, 65.0, 115.1 (d, J = 22.5 Hz), 127.0, 127.2, 128.3, 130.7, 134.6 (d, J = 7.5 Hz), 143.7, 161.6 (d, J = 247.5 Hz). HRMS (CI) *m*/*z* calcd. for $C_{18}H_{23}N$ (M + 1): 272.1815. Found (M + 1): 272.1818.

***N*,*N*-Dibenzylbutan-1-amine (14a).** Oil. Yield: 27%. ^{1}H NMR δ 0.83 (t, J = 7.2 Hz, 3H), 1.25–1.30 (m, 2H), 1.35–1.42 (m, 2H), 2.41 (t, J = 7.2 Hz, 2H), 3.55 (s, 4H), 7.21–7.38 (m, 10H); ^{13}C NMR δ 14.0, 20.4, 29.2, 53.1, 58.2, 126.7, 128.1, 128.7, 140.0. HRMS (CI) *m*/*z* calcd. for $C_{18}H_{24}N$ (M + 1): 254.1909. Found (M + 1): 254.1862.

***N*-Benzyl-*N*-(4-fluorobenzyl)butan-1-amine (14b).** Oil. Yield: 23%. ^{1}H NMR δ 0.84 (t, J = 7.1 Hz, 3H), 1.20–1.38 (m, 2H), 1.45–1.58 (m, 2H), 2.40 (t, J = 7.1 Hz, 2H), 3.51 (s, 2H), 3.54 (s, 2H), 6.99 (t, J = 8.6 Hz, 2H), 7.24–7.40 (m, 7H); ^{13}C NMR δ 14.0, 20.4, 29.1, 53.0, 57.5, 58.2, 114.9 (d, J = 22.5 Hz), 126.8, 128.2, 128.8, 130.2 (d, J = 7.5 Hz), 131.5, 161.8 (d, J = 240.0 Hz). Anal. Calcd. for $C_{18}H_{22}FN$: C, 79.67; H, 8.17; N, 5.16. Found: C, 79.78; H, 8.41; N, 5.22%.

***N*-Benzyl-*N*-(4-methylbenzyl)butan-1-amine (14c).** Oil. Yield: 29%. ^{1}H NMR δ 0.86 (t, J = 7.1 Hz, 3H), 1.20–1.35 (m, 2H), 1.42–1.55 (m, 2H), 2.35 (s, 3H), 2.42 (t, J = 7.4 Hz, 2H), 3.54 (s, 2H), 3.56 (s, 2H), 7.28 (d, J = 6.6 Hz, 2H), 7.32–7.46 (m, 7H); ^{13}C NMR δ 14.0, 20.4, 21.1, 29.7, 52.8, 57.7, 57.9, 126.9, 128.2, 128.6, 128.9, 129.0, 129.7, 129.8, 136.5. HRMS (CI) *m*/*z* calcd. for $C_{19}H_{26}N$ (M + 1): 268.2065. Found (M + 1): 268.2066.

***N*-Benzyl-*N*-(2-furylmethyl)butan-1-amine (14e).** Oil. Yield: 100%. ^{1}H NMR δ 0.88 (t, J = 7.2 Hz, 3H), 1.29–1.36 (m, 2H), 1.48–1.57 (m, 2H), 2.46 (t, J = 7.2 Hz, 2H), 3.61 (s, 2H), 3.64 (s, 2H), 6.19 (d, J = 3.0 Hz, 1H), 6.34 (d, J = 3.0 Hz, 1H), 7.23–7.42 (m, 6H); ^{13}C NMR δ 13.9, 20.4, 29.2, 49.3, 52.9, 57.9, 108.3, 109.9, 126.7, 128.1, 128.8, 139.4, 141.7, 152.7. Anal. Calcd. for $C_{16}H_{21}NO$: N, 5.76. Found: N, 6.01%.

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