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A Base-Catalyzed Domino-Isomerization–Hydroamination Reaction—A New Synthetic Route to Amphetamines

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Abstract—An efficient synthesis of pharmaceutically interesting amphetamines by a base-catalyzed domino-isomerization–hydroamination reaction is presented. Starting from allylbenzene and various primary or secondary amines, the basic structural pattern of amphetamines is synthesized directly in yields of up to 91% in the presence of catalytic amounts of *n*-butyllithium.

Introduction

New amination reactions are of general interest in synthetic organic and industrial chemistry because of the importance of amines and their derivatives as natural products, pharmacological agents, fine chemicals and dyes. The direct addition of *N*-nucleophiles to alkenes—the hydroamination reaction—is the most atom economic and elegant way to synthesize amines, since in principle no by-products are formed.[1] The low prices and ubiquitous availability of the substrates are further advantages of the hydroamination in contrast to classical amination reactions. Although transition metal complexes,[1] lanthanide catalysts[2] and traditional acids[3] as well as bases[4] have been used as catalysts for the hydroamination of olefins, so far no efficient general methodology has been developed. Therefore, a general hydroamination reaction is still one of the major goals in catalysis research.[5]

Derivatives of 2-amino-1-phenylpropane (amphetamines) belong to the psychopharmacologically active class of sympathomimetic drugs and are of pharmacological interest not only because of the stimulating and inhibiting effect on the central nervous system, but also due to their anti-inflammatory activity and ability to inhibit several enzymes.[6] In general, classical methods for synthesizing the C–N bond in amphetamines are the reductive amination reactions of the appropriate ketones,[7] reactions of aryl aldehydes with nitroalkanes and subsequent reduction,[8] amidomercuration–demercuration of olefins[9] or *N*-alkylation of ammonia, primary and secondary amines using alkylating agents.[10] Most of these reactions have disadvantages because they require complicated substrates as starting materials in combination with a hydrogen donor, they use stoichiometric amounts of toxic mercury salts or they produce at least one equivalent of a salt as a by-product.

Results and Discussion

In 1998, Seijas and Vázquez-Tato et al. demonstrated that the synthesis of 2-phenylethylamines can be performed by the addition of lithium amides to styrene derivatives.[11] In the first step the lithium amide was prepared in a stoichiometric reaction of the amine with *n*-butyllithium. The subsequent addition to the styrene derivative is performed with a 2.5-fold excess of the lithium amide. For instance, the conversion of β-methylstyrene and different amines leads to amphetamine derivatives in yields of 33–58%. In earlier work we showed that styrene derivatives are hydroaminated with amines, even in the presence of only catalytic amounts of bases, in excellent yields of up to 99%.[12] Consequently, we were interested in developing an efficient method for preparing amphetamines in a *catalytic* hydroamination reaction.

In view of our earlier work,[12] the base-catalyzed conversion of alkenes and amines with *n*-butyllithium seemed to be a promising approach to this goal. Due to the considerably lower price of allylbenzene compared to β-methylstyrene (ca. 5-fold)[13] we were interested in the direct synthesis of amphetamines via base-catalyzed domino-reaction[14] of allylbenzenes. Preliminary studies revealed that under the reaction conditions required for base-catalyzed hydroamination, it should be possible to isomerize allylbenzene to yield β-methylstyrene.[15] Thus, as a model reaction to generate amphetamine derivatives we studied the reaction

Keywords: domino-isomerization–amination reaction; base-catalysis; hydroamination; amphetamines.
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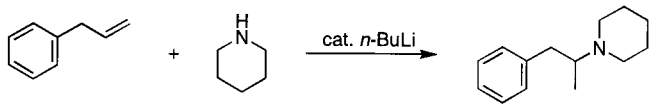
Table 1. *n*-Butyllithium-catalyzed hydroamination of allylbenzene (**1**) with piperidine (**2**) (allylbenzene–piperidine ratio 2:1; 20 mol% *n*-BuLi refers to piperidine)



1 2 3

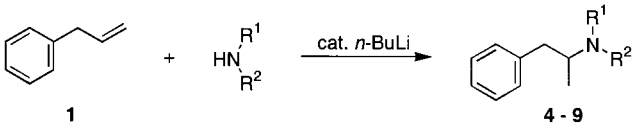
Entry	Temperature (°C)	Solvent	Additive (mol%)	Yield of 3 (%)[a]
1	Room temperature	THF	–	89
2	−78 to room temperature	THF	–	91
3	50	THF	–	85
4	100	THF	–	60
5	Room temperature	THF	TMEDA[b] (20)	88
6[c]	Room temperature	THF	–	68
7	Room temperature	Toluene	–	20
8	Room temperature	Toluene	TMEDA[b] (20)	88
9	Room temperature	Pentane	TMEDA[b] (20)	60

[a] Yields refer to piperidine and were determined by GC with internal standard (hexadecane).
[b] TMEDA: tetramethylethylenediamine.
[c] Allylbenzene–piperidine ratio 1:1.

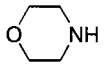
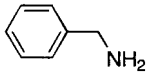
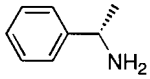
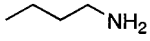
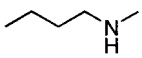
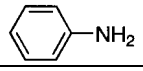
of allylbenzene (**1**) and piperidine (**2**) (Table 1). Indeed, in the presence of catalytic amounts of *n*-butyllithium (0.2 equiv.) a fast isomerization of allylbenzene to the thermodynamically more stable isomer β-methylstyrene is observed at room temperature. The subsequent hydroamination of β-methylstyrene proceeds regioselectively (>99%) to yield *N*-2-(1-phenyl)propyl-piperidine **3**. As shown in Table 1 the reaction gave the best yields of product **3** (89–91%) using an allylbenzene–piperidine ratio of 2:1 in tetrahydrofuran as the solvent at room temperature. Oligomers of β-methylstyrene are obtained as side-products by an anionic polymerization reaction. The amount of oligomers increases at higher reaction temperature. Using an equimolar amount of allylbenzene and piperidine, product **3** is obtained in 68% yield (entry 6). In general, the hydroamination of allylbenzene can also be performed in nonpolar solvents such as toluene or pentane in the presence of tetramethylethylenediamine (TMEDA) as the co-catalyst. TMEDA is needed for the solvation and deaggregation of *n*-butyllithium and the resulting lithium amides (entries 7, 8, 9). Remarkably, no oligomers of β-methylstyrene were detected applying these nonpolar solvents.

The scope of the new domino-isomerization–hydroamination reaction is demonstrated in the reaction of allylbenzene and 4-phenyl-1-butene with various primary and secondary amines (Table 2 and Scheme 1).

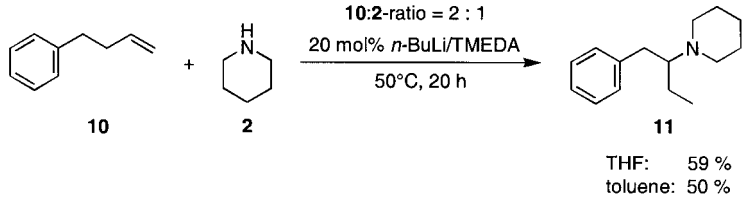
Table 2. *n*-Butyllithium-catalyzed hydroamination of allylbenzene (**1**) with primary and secondary amines (allylbenzene–amine ratio 2:1; 20 mol% *n*-BuLi refers to the amine)



1 4 - 9

Entry	Amine	Product	Temperature (°C)	Solvent	Additive (mol%)	Yield of amphetamine (%)[a]
1		**4**	Room temperature	THF	–	44
2			50	THF	–	88
3			100	Toluene	TMEDA[b] (20)	38
4		**5**	50	THF	–	65
5			50	Toluene	TMEDA[b] (20)	22
6		**6**	50	THF	TMEDA[b] (20)	32 (*de* 8%)
7			100	Toluene	TMEDA[b] (20)	36 (*de* 0%)
8		**7**	50	THF	–	62
9			100	Toluene	TMEDA[b] (20)	41
10		**8**	Room temperature	THF	–	66
11			50	Toluene	TMEDA[b] (20)	36
12[c]		**9**	120	THF	KO^{t}Bu (30)	54

[a] Yields refer to the amine and were determined by GC with internal standard (hexadecane).
[b] TMEDA: tetramethylethylenediamine.
[c] Allylbenzene–aniline ratio 1:1; mixture of 30 mol% *n*-BuLi and 30 mol% KO^{t}Bu.



Scheme 1.

As shown in Table 2 most of the applied amines give improved yields of hydroamination products at higher reaction temperatures compared to piperidine. As an example morpholine reacts with allylbenzene at 50°C to give the corresponding amphetamine in 88% yield, while the reaction at room temperature leads to only a 44% yield (Table 2, entries 1, 2). With toluene as the solvent, in general higher temperatures are required, however, the yields are lower compared to tetrahydrofuran (22–41% yield, entries 3, 5, 9, 11); but advantageously no oligomers of the alkene are formed. Apart from cyclic and acyclic secondary amines primary amines such as benzylamine or *n*-butylamine produce the corresponding products in tetrahydrofuran as the solvent in yields of 65 and 62%, respectively. (Table 2, entries 4, 8). The catalytic hydroamination reaction with the chiral amine *S*-(−)-α-methylbenzylamine only resulted in the formation of diastereomeric mixtures (diastereomeric excess <10%) in yields of 32 and 36% (Table 2, entries 6, 7). Interestingly, anilines may be used successfully in this new domino-amination reaction. Due to the lower nucleophilicity of lithium anilides compared to aliphatic amides the addition of KO^{t}Bu as the second base is needed to generate the more ionic and therefore more reactive potassium anilides in situ in low concentrations.[12a] Hence, in the presence of a mixture of 0.3 equiv. *n*-butyllithium and 0.3 equiv. KO^{t}Bu, aniline reacts with allylbenzene to give the amphetamine derivative in 54% yield (Table 2, entry 12).

We would like to emphasize that tertiary (double alkylated) amines were produced in yields <1% in the reactions of allylbenzene with primary amines. This makes the method especially attractive for the selective synthesis of 'secondary amphetamines' because typical nucleophilic substitution procedures with primary amines gave mixtures of secondary, tertiary and even quaternary amines. Furthermore, the reaction of benzylamine is noteworthy, since the benzyl group is easily removed by hydrogenation with H_2/Pd/C to give 1-phenyl-2-aminopropane in 65% overall yield by GC analysis.

The presented domino-isomerization–hydroamination reaction has also been expanded to aryl olefins whereby the double bond is separated from the aryl group by two CH_2-units. In the reaction of 4-phenyl-1-butene **10** with piperidine **2**, the 2-amino-1-phenylbutane derivative **11** is produced in 59% yield in tetrahydrofuran as the solvent at 50°C (Scheme 1). In toluene **11** can be obtained in 50% yield without any formation of oligomers.

In conclusion, we have found that amphetamine derivatives can be produced atom-efficiently by a new base-catalyzed domino-isomerization–hydroamination reaction of allylbenzenes. The reaction is easily performed and does not require expensive reagents. Further investigations on stereoselective variants of this method are currently under investigation.

Experimental

Chemicals were obtained from Aldrich and Fluka and used without further purification. All operations were carried out under an argon atmosphere. Solvents and amines were dried according to standard procedures. NMR spectra (^{1}H, ^{13}C) were recorded with a 400 MHz Bruker ARX 400 instrument (^{1}H: 400.1 MHz, ^{13}C: 100.6 MHz). ^{1}H and ^{13}C NMR chemical shift were referenced to tetramethylsilane (0 ppm) and $CDCl_3$ (77.0 ppm), respectively. Coupling constants are reported in Hertz. Elemental analyses were performed by the Microanalytical Laboratory at IfOK Rostock. GC–MS spectra were measured with a Hewlett–Packard gas chromatograph GC 5890 equipped with a mass-selective detector MS 5989 A. Quantitative analyses were performed with a Hewlett–Packard GC 6890 instrument using a HP-5 capillary column in conjunction with a flame ionization detector (GC/FID). Column chromatography was carried out using silica gel 60 (0.063–0.2 mm Fluka). The hydroamination reactions were performed in Aldrich Ace-pressure tubes (30 ml). *(Caution: The required safety measures should be taken when performing reactions under pressure.)*

General procedure

The amine (2.5 mmol) and 100 μl hexadecane (internal standard) were dissolved in 5 ml dry tetrahydrofuran in an Ace-pressure tube under an argon atmosphere. 20 mol% *n*-butyllithium (1.6 M *n*-BuLi solution in hexane) was added slowly at room temperature. The solution was stirred for 10 min and then allylbenzene (5 mmol) was added. The intensive coloured solutions were reacted for 20 h at the defined temperature. After cooling to room temperature, the solution was quenched with 2 ml water, whereby a discolouration of the solution was observed. The products were isolated by acidification of the mixture with 5 ml of 1 M HCl followed by addition of 5 ml dichloromethane. The resulting aqueous phase was collected and the organic phase was extracted three times with 5 ml of 1 M HCl. The combined aqueous phases were neutralized with solid Na_2CO_3 and were extracted five times with 5 ml dichloromethane. The organic phases were washed with water and dried over $MgSO_4$. After removal of the solvent in vacuo the products were isolated by column chromatography.

***N*-2-(1-Phenyl)propyl-piperidine (3).** According to the general procedure piperidine (2.5 mmol; 247 μl) and allyl-

benzene (5 mmol; 662 μl) were reacted in the presence of 20 mol% *n*-BuLi solution (0.5 mmol; 313 μl) at room temperature. The residue was purified by column chromatography (*n*-hexane/ethyl acetate=3:1) to afford **3** as a colourless oil.—Yield: 89% (GC); 84% (isolated).—^{1}H NMR ($CDCl_3$, 25°C, δ=ppm): 7.24 (m, 2H, phenyl); 7.15 (m, 3H, phenyl); 3.00 (dd, ^2J(H,H)=12.9 Hz, ^3J(H,H)=3.8 Hz, 1H, Ph–CH_2); 2.76 (ddq, ^3J(H,H)=10.1 Hz, ^3J(H,H)= 6.5 Hz, ^3J(H,H)=3.8 Hz, 1H, Ph–CH_2–C*H*); 2.54 (m, 4H, N–CH_2); 2.36 (dd, ^2J(H,H)=12.9 Hz, ^3J(H,H)=10.1 Hz, 1H, Ph–CH_2); 1.59 (m, 4H, N–CH_2–CH_2); 1.43 (m, 2H, N–CH_2–CH_2–CH_2); 0.91 (d, ^3J(H,H)=6.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25°C, δ=ppm): 141.0, 129.2, 128.1, 125.7, 62.1, 49.6, 39.1, 26.4, 24.9, 14.2. GC–MS: *m*/*z*=203 [M^+], 112 [$M^+-C_6H_5-CH_2$], 91, 69. MS (CI, isobutane): 204 [M^++H], 112 [$M^+-C_6H_5-CH_2$], 86. Anal. Calcd for $C_{14}H_{21}N$: C 82.70, H 10.41, N 6.89. Found: C 82.68, H 10.42, N 6.85.

***N*-2-(1-Phenyl)propyl-morpholine (4).** According to the general procedure morpholine (2.5 mmol; 218 μl) and allylbenzene (5 mmol; 662 μl) were reacted in the presence of 20 mol% *n*-BuLi solution (0.5 mmol; 313 μl) at 50°C. The residue was purified by column chromatography (*n*-hexane/ethyl acetate=1:1) to afford **4** as a colourless oil.—Yield: 88% (GC); 80% (isolated).—^{1}H NMR ($CDCl_3$, 25°C, δ=ppm): 7.26 (m, 2H, phenyl); 7.16 (m, 3H, phenyl); 3.72 (m, 4H, O–CH_2); 2.99 (dd, ^2J(H,H)=13.1 Hz, ^3J(H,H)=4.4 Hz, 1H, Ph–CH_2); 2.75 (ddq, ^3J(H,H)= 9.7 Hz, ^3J(H,H)=6.5 Hz, ^3J(H,H)=4.4 Hz, 1H, Ph–CH_2–C*H*); 2.60 (m, 4H, N–CH_2); 2.39 (dd, ^2J(H,H)=13.1 Hz, ^3J(H,H)=9.7 Hz, 1H, Ph–CH_2); 0.94 (d, ^3J(H,H)=6.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25°C, δ=ppm): 140.3, 129.2, 128.2, 125.8, 67.3, 61.6, 49.0, 39.1, 14.2. GC–MS: *m*/*z*=114 [$M^+-C_6H_5-CH_2$], 91, 70. MS (CI, isobutane): 206 [M^++H], 114 [$M^+-C_6H_5-CH_2$]. Anal. Calcd for $C_{13}H_{19}NO$: C 76.06, H 9.33, N 6.82. Found: C 76.06, H 9.19, N 6.88.

***N*-2-(1-Phenyl)propyl-*N*-benzylamine (5).** According to the general procedure benzylamine (2.5 mmol; 273 μl) and allylbenzene (5 mmol; 662 μl) were reacted in the presence of 20 mol% *n*-BuLi solution (0.5 mmol; 313 μl) at 50°C. The residue was purified by column chromatography (*n*-hexane/ethyl acetate=4:1) to afford **5** as a colourless oil.—Yield: 65% (GC); 60% (isolated).—^{1}H NMR ($CDCl_3$, 25°C, δ=ppm): 7.29–7.12 (m, 10H, phenyl); 3.83 (d, ^2J(H,H)=13.3 Hz, 1H, Ph–CH_2–N); 3.72 (d, ^2J(H,H)=13.3 Hz, 1H, Ph–CH_2–N); 2.92 (sext, 1H, ^3J(H,H)=^3J(H,H)=6.3 Hz, 1H, Ph–CH_2–C*H*); 2.76 (dd, ^2J(H,H)=13.3 Hz, ^3J(H,H)=6.3 Hz, 1H, Ph–CH_2–CH); 2.62 (dd, ^2J(H,H)=13.3 Hz, ^3J(H,H)=6.3 Hz, 1H, Ph–CH_2–CH); 1.54 (s, 1H, N*H*); 1.08 (d, ^3J(H,H)=6.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25°C, δ=ppm): 140.4, 139.4, 129.3, 128.3, 128.3, 127.9, 126.8, 126.1, 53.7, 51.2, 43.5, 20.1. GC–MS: *m*/*z*=134 [$M^+-C_6H_5-CH_2$], 91, 65. MS (CI, isobutane): 226 [M^++H], 134 [$M^+-C_6H_5-CH_2$]. Anal. Calcd for $C_{16}H_{19}N$: C 85.28, H 8.50, N 6.22. Found: C 85.19, H 8.51, N 6.19.

***N*-(*S*)-1-Phenylethyl-*N*-2-(1-phenyl)propyl-amine (6).** According to the general procedure *S*-(−)-α-methylbenzylamine (2.5 mmol; 318 μl) and allylbenzene (5 mmol; 662 μl) were reacted in the presence of 20 mol% *n*-BuLi solution (0.5 mmol; 313 μl) and 20 mol% tetramethylethylenediamine (0.5 mmol, 75 μl) at 50°C. The residue was purified by column chromatography (*n*-hexane/ethyl acetate=2:1) to afford the diastereomeric mixture of **6** as a colourless oil.—Yield: 32% (GC); 30% (isolated).—^{1}H NMR ($CDCl_3$, 25°C, δ=ppm): 7.36–6.94 (m, 2×10H, phenyl); 3.93, 3.88 (2×q, ^3J(H,H)=6.6 Hz, 2×1H, Ph–C*H*Me–N); 2.88, 2.66 (2×dd, ^2J(H,H)=12.9 Hz, ^3J(H,H)= 5.0 Hz, 2×1H, Ph–CH_2); 2.77, 2.65 (2×m, 2×1H, Ph–CH_2–C*H*); 2.59, 2.50 (2×dd, ^2J(H,H)=12.9 Hz, ^3J(H,H)=7.5 Hz, 2×1H, Ph–CH_2); 1.46 (2×s, 2×1H, N*H*); 1.31, 1.27 (2×d, ^3J(H,H)=6.7 Hz, 2×3H, Ph–CH(CH_3)–N); 1.05, 0.92 (2×d, ^3J(H,H)=6.3 Hz, 2×3H, Ph–CH_2–CH–CH_3). ^{13}C NMR ($CDCl_3$, 25°C, δ=ppm): 146.1, 145.4, 139.5, 139.3, 129.4, 129.2, 128.4, 128.3, 128.3, 128.2, 126.8, 126.6, 126.5, 126.3, 126.1, 125.9, 55.3, 54.8, 51.9, 50.8, 44.2, 42.5, 25.0, 24.5, 21.1, 19.9. GC–MS: *m*/*z*=239 [M^+], 148 [$M^+-C_6H_5-CH_2$], 105 [C_6H_5–CH–CH_3], 91, 79. Anal. Calcd for $C_{17}H_{21}N$: C 85.30, H 8.84, N 5.85. Found: C 85.20, H 8.88, N 5.86.

***N*-*n*-Butyl-*N*-2-(1-phenyl)propyl-amine (7).** According to the general procedure *n*-butylamine (2.5 mmol; 247 μl) and allylbenzene (5 mmol; 662 μl) were reacted in the presence of 20 mol% *n*-BuLi solution (0.5 mmol; 313 μl) at 50°C. The residue was purified by column chromatography (*n*-hexane/ethyl acetate=1:2) to afford **7** as a colourless oil.—Yield: 62% (GC); 54% (isolated).—^{1}H NMR ($CDCl_3$, 25°C, δ=ppm): 7.27 (m, 2H, phenyl); 7.17 (m, 3H, phenyl); 2.87 (sext, ^3J(H,H)=^3J(H,H)=6.5 Hz, 1H, Ph–CH_2–C*H*); 2.73 (dd, ^2J(H,H)=13.3 Hz, ^3J(H,H)= 6.5 Hz, 1H, Ph–CH_2); 2.65 (ddd, ^2J(H,H)=11.1 Hz, ^3J(H,H)=8.1 Hz, ^3J(H,H)=6.5 Hz, 1H, N–CH_2); 2.58 (dd, ^2J(H,H)=13.3 Hz, ^3J(H,H)=6.5 Hz, 1H, Ph–CH_2); 2.51 (ddd, ^2J(H,H)=11.1 Hz, ^3J(H,H)=7.6 Hz, ^3J(H,H)= 6.7 Hz, 1H, N–CH_2); 1.40 (m, 2H, N–CH_2–CH_2); 1.37 (s, 1H, N*H*); 1.25 (sext, ^3J(H,H)=^3J(H,H)=7.4 Hz, 2H, CH_2–CH_2–CH_3); 1.04 (d, ^3J(H,H)=6.5 Hz, 3H, CH–CH_3); 0.85 (t, ^3J(H,H)=7.4 Hz, 3H, CH_2–CH_3). ^{13}C NMR ($CDCl_3$, 25°C, δ=ppm): 139.5, 129.2, 128.3, 126.1, 54.7, 47.0, 43.6, 32.3, 20.4, 20.2, 13.9. GC–MS: *m*/*z*=191 [M^+], 176 [M^+-CH_3], 100 [$M^+-C_6H_5-CH_2$], 91, 77. Anal. Calcd for $C_{13}H_{21}N$: C 81.61, H 11.06, N 7.32. Found: C 81.44, H 10.99, N 7.20.

***N*-*n*-Butyl-*N*-methyl-*N*-2-(1-phenyl)propyl-amine (8).** According to the general procedure *n*-butylmethylamine (2.5 mmol; 296 μl) and allylbenzene (5 mmol; 662 μl) were reacted in the presence of 20 mol% *n*-BuLi solution (0.5 mmol; 313 μl) at room temperature. The residue was purified by column chromatography (*n*-hexane/ethyl acetate=3:1) to afford **8** as a colourless oil.—Yield: 66% (GC); 61% (isolated).—^{1}H NMR ($CDCl_3$, 25°C, δ=ppm): 7.26 (m, 2H, phenyl); 7.17 (m, 3H, phenyl); 2.94 (dd, ^2J(H,H)=12.5 Hz, ^3J(H,H)=4.0 Hz, 1H, Ph–CH_2); 2.89 (m, 1H, Ph–CH_2–C*H*); 2.44 (m, 2H, N–CH_2); 2.38 (dd, ^2J(H,H)=12.5 Hz, ^3J(H,H)=9.5 Hz, 1H, Ph–CH_2); 2.28 (s, 3H, N–CH_3); 1.46 (m, 2H, N–CH_2–CH_2); 1.31 (m, 2H, CH_2–CH_2–CH_3); 0.91 (t, ^3J(H,H)=7.3 Hz, 3H, CH_2–CH_3); 0.90 (d, ^3J(H,H)=6.9 Hz, 3H, CH–CH_3). ^{13}C NMR ($CDCl_3$, 25°C, δ=ppm): 140.8, 129.2, 128.2, 125.7, 60.3, 53.2, 39.0, 37.1, 30.4, 20.7, 14.1, 13.9. GC–MS: *m*/*z*=205

[M^+], 190 [M^+-CH_3], 162 [$M^+-CH_2CH_2CH_3$], 114 [$M^+-C_6H_5-CH_2$], 91, 72, 58. Anal. Calcd for $C_{14}H_{23}N$: C 81.89, H 11.29, N 6.82. Found: C 81.31, H 11.19, N 6.76.

***N*-2-(1-Phenyl)propyl-aniline (9).** According to the general procedure aniline (2.5 mmol; 228 μl) and allylbenzene (2.5 mmol; 331 μl) were reacted in the presence of 30 mol% *n*-BuLi solution (0.75 mmol; 469 μl) and 30 mol% KO^{t}Bu (0.75 mmol, 84 mg) at 120°C. The residue was purified by column chromatography (*n*-hexane/ethyl acetate=15:1) to afford **9** as a colourless oil.—Yield: 54% (GC); 50% (isolated).—^{1}H NMR ($CDCl_3$, 25°C, δ=ppm): 7.28 (m, 2H, phenyl); 7.18 (m, 3H, phenyl); 7.16 (m, 2H, phenyl); 6.68 (m, 1H, phenyl); 6.62 (m, 2H, phenyl); 3.75 (m, 1H, Ph–CH_2–C*H*); 3.61 (s, 1H, N*H*); 2.93 (dd, ^2J(H,H)=13.4 Hz, ^3J(H,H)=4.8 Hz, 1H, Ph–CH_2); 2.68 (dd, ^2J(H,H)=13.4 Hz, ^3J(H,H)=7.3 Hz, 1H, Ph–CH_2); 1.13 (d, ^3J(H,H)=6.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25°C, δ=ppm): 147.1, 138.5, 129.5, 129.3, 128.3, 126.2, 117.2, 113.4, 49.4, 42.2, 20.1. GC–MS: *m*/*z*=211 [M^+], 120 [$M^+-C_6H_5-CH_2$], 91, 77. Anal. Calcd for $C_{15}H_{17}N$: C 85.26, H 8.11, N 6.63. Found: C 85.41, H 8.10, N 6.64.

***N*-2-(1-Phenyl)butyl-piperidine (10).** According to the general procedure piperidine (2.5 mmol; 247 μl) and 4-phenyl-1-butene (5 mmol; 746 μl) were reacted in the presence of 20 mol% *n*-BuLi solution (0.5 mmol; 313 μl) at 50°C. The residue was purified by column chromatography (*n*-hexane/ethyl acetate=4:1) to afford **10** as a colourless oil.—Yield: 59% (GC); 57% (isolated).—^{1}H NMR ($CDCl_3$, 25°C, δ=ppm): 7.25 (m, 2H, phenyl); 7.16 (m, 3H, phenyl); 2.94 (dd, ^2J(H,H)=12.9 Hz, ^3J(H,H)=4.0 Hz, 1H, Ph–CH_2); 2.66–2.40 (m, 5H, N–CH_2, Ph–CH_2–C*H*); 2.33 (dd, ^2J(H,H)=12.9 Hz, ^3J(H,H)=9.0 Hz, 1H, Ph–CH_2); 1.54 (m, 4H, N–CH_2–CH_2); 1.49–1.38 (m, 3H, N–CH_2–CH_2–CH_2, Ph–CH_2–CH–CH_2); 1.32 (m, 1H, Ph–CH_2–CH–CH_2); 0.81 (t, ^3J(H,H)=7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25°C, δ=ppm): 141.7, 129.2, 128.1, 125.4, 68.6, 49.6, 35.5, 26.6, 25.1, 23.3, 11.7. GC–MS: *m*/*z*=217 [M^+], 188 [$M^+-CH_2CH_3$], 126 [$M^+-C_6H_5-CH_2$], 91, 69. Anal. Calcd for $C_{15}H_{23}N$: C 82.89, H 10.67, N 6.44. Found: C 82.80, H 10.62, N 6.33.

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