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Preparation of aminals in water

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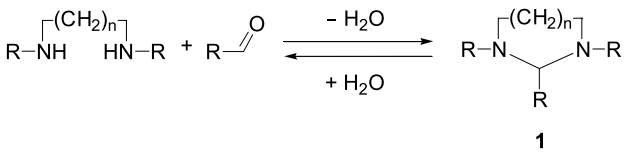
Abstract—Aminals, which are used as protecting groups in syntheses and are part of many biologically active compounds, are normally prepared from aldehydes and diamines under conditions that remove water in order to shift the equilibrium to the side of the aminal. Here we report for the first time that aminals can be prepared and isolated in pure water without a catalyst in high yield and purity.

1. Introduction

Aminals,[1] which are also known under the term *N*,*N*-acetals, are the aminated equivalents of acetals. The aminals can be either open chained or cyclic like aminal analogue **1**. Cyclic aminals can be used in synthesis as protecting groups for aldehydes.[2–6] In addition, five-membered ring aminals (imidazolidines) are important parts of biologically active compounds, for example, folic acid derivates.[7–9] Six-membered ring aminals (hexahydro-pyrimidines) are also often incorporated in biologically active molecules.[10,11]

Classical methods of preparing aminals involve the use of various drying agents, for example, potassium carbonate,[12] calcium sulfate,[13] boric anhydride[14] or removal of water by azeotropic distillation with benzene[15] in order to shift the equilibrium to the product side as shown in Scheme 1. If the aminals are crystallizing easily, reactions are performed in methanol or ethanol in the presence of a small amount of acetic acid.[2] If formaldehyde is used in the reaction, often an ethanol–water mixture is used as the solvent.[16]



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Scheme 1.

We noticed from the literature that imines can be conveniently prepared in pure water without the presence of a catalyst from corresponding amines and aldehydes.[17] Since we were interested in preparing imidazolidines in a fast and easy way, we wanted therefore to investigate, if it would be also possible to prepare aminals in a similar way. So far aminals have never been synthesized and isolated in pure water. There is only one example known in the literature where the equilibrium constants for the formation of a few imidazolidines were measured in water via UV absorbance, however, no products were isolated.[18] In addition an aminal was prepared in a biphasic system of water and dichloromethane from diamines and glyoxal.[19]

The preparation of aminals in water is desirable, since reaction procedures, where water is used as a solvent instead of an organic solvent have become in recent years more and more important due to environmental consideration.[20,21]

2. Results and discussion

In order to follow the procedure of Simion et al. for the preparation of imines in water,[17] *N*,*N*′-dibenzyl-ethane-1,2-diamine (**2**) was strongly stirred in water and benzaldehyde was added to the emulsion. During 3 h of stirring a white precipitate formed which was filtered of and washed with water. After drying under vacuum the desired product **3a** was obtained in 91% yield (Table 1, entry 1) in high purity according to NMR spectral data and CHN-analysis. In comparison, when **2** was refluxed with benzaldehyde and a catalytic amount of *p*-toluene sulfonic acid in benzene on a Dean–Stark apparatus, the reaction took 16 h and a flash column chromatography with deactivated silica gel had to be performed to get **3a** in proper purity. When the reaction was carried out in abs. ethanol the product had to be purified again via flash column chromatography or via recrystallisation, which gave the product in only 62% yield. Finally, benzaldehyde was added to neat diamine **2** and a strong exothermic reaction was observed, which was completed

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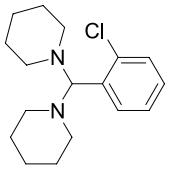
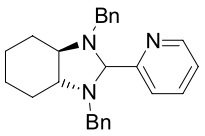
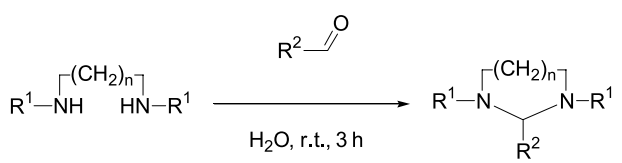
Table 1. Preparation of aminals

Entry		Diamine	Aldehyde		Aminal	Yield (%)
1	**2**	R^1=Bn, n=2	Benzaldehyde	**3a**	R^2=C_6H_5	91
2	**2**		2-Chlorobenzaldehyde	**3b**	R^2=1-(2-Cl–C_6H_4)	96
3	**2**		Pyridine-2-carbaldehyde	**3c**	R^2=2-(C_5H_4N)	99
4	**2**		Thiophene-2-carbaldehyde	**3d**	R^2=2-(C_4SH_3S)	99
5	**2**		2-Methoxybenzaldehyde	**3e**	R^2=1-(2-MeO–C_6H_4)	94
6[a]	**2**		2,4-Dichlorobenzaldehyde	**3f**	R^2=1-(2,4–Cl_2-C_6H_3)	96
7	**2**		Pentafluorobenzaldehyde	**3g**	R^2=1-(C_6F_5)	92
8[a]	**2**		4-Chlorobenzaldehyde	**3h**	R^2=1-(4-Cl–C_6H_4)	91
9[a]	**2**		2,6-Dichlorobenzaldhyde	**3i**	R^2=1-(2,6-Cl_2–C_6H_3)	88
10[b]	**2**		Propionaldehyde	**3j**	R^2=CH_2CH_3	85
11	**4**	R^1=Bn, n=3	Benzaldehyde	**5a**	R^2=C_6H_5	96
12	**4**		2-Chlorbenzaldehyde	**5b**	R^2=1-(2-Cl–C_6H_4)	88
13	**4**		Pyridine-2-carbaldehyde	**5c**	R^2=2-(C_5H_4N)	93
14	**6**	R^1=Bn, n=4	2-Chlorobenzaldehyde	**7a**	R^2=1-(2-Cl–C_6H_4)	99
15[b]	**8**	R^1=(*R*)-MeCHPh	2-Chlorobenzaldehyde	**9a**	R^2=1-(2-Cl–C_6H_4)	81
16[a,b]	**8**		4-Chlorobenzaldehyde	**9b**	R^2=1-(4-Cl–C_6H_4)	80
17[a]	**10**	R^1=Ph, n=2	2-Chlorobenzaldehyde	**11a**	R^2=1-(2-Cl–C_6H_4)	98
18[a]	**10**		Acetaldehyde	**11b**	R^2=CH_3	42
19	**12**	R^1=Me, n=2	Benzaldehyde	**13**	R^2=C_6H_5	67
20[c]	**14**	Piperidine	2-Chlorobenzaldehyde	**15**		99
21	**16**	(±)-*N*,*N*′-Dibenzyl-1,2-cyclohexanediamine	Pyridine-2-carbaldehyde	**17**		95

[a] Reaction temperature 80 °C.
[b] Reaction time 16 h.
[c] 2 equiv. piperidine.

after 15 min. However, due to the high temperature during the reaction many impurities next to **3a** were detected in the NMR spectra and again a flash column chromatography had to be carried out which gave the aminal **3a** in 60% yield. Given those results we concluded that for the preparation of aminal analogues of **3a** a reaction of diamines and benzaldehydes in water would be the most convenient and efficient procedure. The results are summarized in Table 1 Scheme 2.



Scheme 2.

First diamine **2** was reacted with different benzaldehydes to give the corresponding imidazolidines (entries 1–9). In all cases the obtained yields were very high (between 91 and 99%) and the products were pure according to NMR spectra and CHN-analysis. Electron deficient (entries 1–3, 6–9) and electron rich (entries 4, 5) benzaldehydes gave similar results. Even the hindered 2,6-dichloro-benzaldehyde gave the corresponding aminal **3i** in a good yield of 88% (entry 9). In cases where the melting points of the benzaldehydes where higher than room temperature, the mixtures were heated to 80 °C in order to melt the aldehydes and ensure the formation of an emulsion containing both reactants (entries 6, 8, 9, 16). When the benzaldehydes were not melted, yields where significantly lower.

In case of the polyfluorinated aminal **3g** (entry 7) the reaction was carried out in deoxygenated water under a nitrogen atmosphere. This was necessary to prevent the rapid oxidation of the aldehyde to the corresponding carboxylic acid before the formation of the desired aminal **3g** was finished. The product **3g** was isolated in a good yield of 92%. Since **3g** was a liquid, it was extracted from the reaction mixture with chloroform. To compare again methods, an attempt to prepare **3g** in benzene with a Dean–Stark apparatus under reflux was carried out, which gave no product at all. The same result was observed when abs. ethanol was chosen as a solvent for the reaction. When pentafluorobenzaldehyde was added to neat diamine **2** a strong exothermic reaction was observed, however no product was isolated, which may be due to the possible instability of either pentafluorobenzaldehyde or aminal **3g** at higher temperatures.

Aliphatic aldehydes can be applied in the described procedure also. Propionaldehyde gave with diamine **2** the expected aminal **3j** in 85% yield (entry 10). However, due to the lower reactivity of aliphatic aldehydes the reaction time had to be prolonged to 16 h. The scope of the reaction was extended with *N*,*N*′-dibenzyl-propane-1,3-diamine (**4**)[17,22] and *N*,*N*′-dibenzyl-butane-1,3-diamine (**6**)[22] which gave

with aldehydes cyclic aminals with a six- or a seven-membered ring in good yields between 88 and 99% (entries 11–14).

Furthermore *N*,*N*′-bis-((*R*)1-phenyl-ethyl)-ethane-1,2-diamine (**8**)[23] was used in the reaction with 2- and 4-chlorobenzaldehydes in order to have a more hindered system next to the nitrogen atoms. The reactions were complete after 16 h and the liquid products were isolated via extraction with chloroform giving the aminals **9a** and **9b** in 81 and 80% yield, respectively (entries 14, 15).

In addition *N*,*N*′-diphenyl-ethane-1,2-diamine (**10**) was forming with 2-chlorobenzaldehyde and acetaldehyde the aminals **11a** and **11b** in 98 and 42% yield, respectively (entries 17, 18). Since the melting point of the diamine **10** is 70 °C the reaction mixture was heated to 80 °C to melt the diamine. Aminal **13** was obtained in 67% yield from *N*,*N*′-dimethyl-ethane-1,2-diamine (**12**) and benzaldehyde (entry 19). Open aminals are also accessible as shown in entry 20, where 2 equiv. of piperidine (**14**) gave with 2-chlorobenzaldehyde the expected product in 99% yield (entry 20). Finally, the (±)-*trans*-cyclohexanediamine analogue **16** furnished with pyridine-2-carbaldehyde the aminal **17** in 95% yield (entry 21).

3. Conclusion

We were able to demonstrate a simple method to prepare cyclic aminals with various ring sizes in high yield and high purity in pure water without the presence of a catalyst. In addition it was possible to get access to aminals which could not be prepared via several different standard procedures.

4. Experimental

4.1. General experimental

N,*N*′-Dibenzyl-ethane-1,2-diamine (**2**), *N*,*N*′-diphenyl-ethane-1,2-diamine (**10**), *N*,*N*′-dimethyl-ethane-1,2-diamine (**12**), piperidine (**14**) and aldehydes were obtained from Aldrich and used without further purification. *N*,*N*′-Dibenzyl-propane-1,3-diamine (**4**),[17,22] *N*,*N*′-dibenzyl-butane-1,3-diamine (**6**),[22] *N*,*N*′-bis-((*R*)1-phenyl-ethyl)-ethane-1,2-diamine (**8**)[23] and (±)-*N*,*N*′-dibenzyl-1,2-cyclohexanediamine (**16**)[24] were prepared according to literature procedures. The reactions were carried out in dest. water.

Flash column chromatography[25] was performed on Sorbisil C-60. All reactions were monitored by TLC with Merck Silica gel 60 F_{254} plates. Elemental analyses were carried out by the Microanalytical Laboratory of the Institut für Pharmazeutische Chemie der Universität Braunschweig. Infrared spectra were recorded on a Perkin–Elmer 2000 FT-IR System FTIR instrument. NMR spectra were performed in $CDCl_3$ at ambient temperature on a Bruker AMX 400 and a Bruker AC 200F. Mass spectra were recorded on Hewlett–Packard 5898B (at 70 eV). Melting points were taken with an apparatus after Dr Tottoli and are uncorrected.

4.2. Preparation of aminals

General procedure. A diamine (1.00 mmol) was added to water (1.5 mL) and an aldehyde (1.00 mmol) was added. The mixture was vigorously stirred for 3 h at rt. For exceptions in temperature and reaction times see Table 1. The precipitate was isolated by filtration, washed with water (5 mL) and dried under vacuum to afford the desired product. In case the product was a liquid, the reaction mixture was extracted with $CHCl_3$ (3×5 mL) and the combined organic phases were dried (Na_2SO_4) and the solvent evaporated.

4.2.1. 1,3-Dibenzyl-2-phenyl-imidazolidine (3a). As a white solid (91%). Mp 97–98 °C (Lit.[26] 99 mp °C); MS (EI), *m*/*e* 328 (M^+, 25%), 327 (M^+-H, 25), 251 (M^+-Ph, 100), 91 (80); IR (KBr) 2780s, 1490s, 1450s, 1161s, 700s cm^{-1}; ^1H NMR (200 MHz) δ 7.67–7.16 (m, 15H), 3.84 (s, 1H), 3.79 (d, *J*=13.0 Hz, 2H), 3.22–3.13 (m, 2H), 3.20 (d, *J*=13.2 Hz, 2H), 2.53–2.45 (m, 2H); ^{13}C NMR (50 MHz) δ 140.3, 139.2, 129.5, 128.6, 128.2, 128.1, 126.8, 89.0, 56.9, 50.6. Anal. Calcd for $C_{23}H_{24}N_2$: C, 84.11; H, 7.36; N, 8.53, found: C, 83.80; H, 7.37; N, 8.48. The spectral data were consistent with literature values.[27,28]

4.2.2. 1,3-Dibenzyl-2-(2-chloro-phenyl)-imidazolidine (3b). As a white solid (96%). Mp 96 °C (Lit.[29] 96–97 °C); MS (EI), *m*/*e* 361 (M^++H, 25%), 251 (100), 91 (75); IR (KBr) 2793m, 1365m, 1151s, 757vs, 698vs cm^{-1}; ^1H NMR (400 MHz) δ 8.14 (d, *J*=7.8 Hz, 1H), 7.45–7.25 (m, 13H), 4.70 (s, 1H), 3.85 (d, *J*=13.2 Hz, 2H), 3.41 (d, *J*=13.2 Hz, 2H), 3.26–3.23 (m, 2H), 2.64–2.61 (m, 2H); ^{13}C NMR (100 MHz) δ 139.7, 138.2, 136.0, 131.8, 129.8, 129.3, 128.9, 128.6, 127.7, 127.3, 83.6, 57.3, 51.2. Anal. Calcd for $C_{23}H_{23}ClN_2$: C, 76.12; H, 6.39; N, 7.72, found: C, 75.82; H, 6.32; N, 7.55.

4.2.3. 2-(1,3-Dibenzyl-imidazolidin-2-yl)-pyridine (3c). As a white solid (99%). Mp 80–81 °C; MS (EI), *m*/*e* 329 (M^++H, 5%), 251 (100), 197 (10), 238 (10), 91 (80), 65 (10); IR (KBr) 2792m, 1493m, 1434s, 1360m, 1135m, 1148m, 781s, 749s, 696vs cm^{-1}; ^1H NMR (400 MHz) δ 8.56–8.55 (m, 1H), 8.01 (dt, *J*=8.0, 1.0 Hz, 1H), 7.79 (td, *J*=7.7, 1.8 Hz, 1H), 7.30–7.20 (m, 11H), 4.14 (s, 1H), 3.86 (d, *J*=13.4 Hz, 2H), 3.41 (d, *J*=13.4 Hz, 2H), 3.27–3.23 (m, 2H), 2.61–2.57 (m, 2H); ^{13}C NMR (100 MHz) δ 161.8, 148.6, 139.4, 137.3, 128.9, 128.5, 127.2, 123.7, 123.5, 89.9, 57.4, 51.3. Anal. Calcd for $C_{22}H_{23}N_3$: C, 80.21; H, 7.04; N, 12.76, found: C, 79.89; H, 7.12; N, 12.88.

4.2.4. 1,3-Dibenzyl-2-thiophen-2-yl-imidazolidine (3d). As a white solid (99%). Mp 122 °C; MS (EI), *m*/*e* 333 (M^++H, 1%), 124 (50), 97 (30), 91 (100); IR (KBr) 1307s, 1161s, 744s, 717s, 698s cm^{-1}; ^1H NMR (400 MHz) δ 7.42–6.99 (m, 13H), 4.82 (s, 1H), 3.96 (d, *J*=12.9 Hz, 2H), 3.29 (d, *J*=12.9 Hz, 2H), 3.20–3.17 (m, 2H), 2.56–2.52 (m, 2H); ^{13}C NMR (100 MHz) δ 146.4, 139.4, 129.0, 128.6, 128.0, 127.3, 127.1, 126.2, 84.0, 57.3, 50.7. Anal. Calcd for $C_{21}H_{22}N_2S$: C, 75.41; H, 6.63; N, 8.38, found: C, 75.41; H, 6.61; N, 8.77.

4.2.5. 1,3-Dibenzyl-2-(2-methoxy-phenyl)-imidazolidine (3e). As a white solid (94%). Mp 70 °C; MS (EI), *m*/*e* 357

(M^++H, 20%), 251 (100), 148 (15), 121 (20), 91 (100), 65 (20); IR (KBr) 2795s, 2492s, 1380s, 1239s, 1153s, 752s, 698s cm^{-1}; ^1H NMR (400 MHz) δ 8.00 (dd, J=7.6, 1.4 Hz, 1H), 7.32–7.03 (m, 12H), 6.87 (d, J=8.3 Hz, 1H), 3.59 (s, 1H), 3.84 (s, 3H), 3.80 (d, J=13.2 Hz, 2H), 3.29 (d, J=13.2 Hz, 2H), 3.17–3.14 (m, 2H), 2.56–2.52 (m, 2H); ^{13}C NMR (100 MHz) δ 159.5, 140.0, 130.3, 129.5, 128.4, 121.5, 110.6, 80.1, 55.9, 51.1. Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81, found: C, 80.3; H, 7.43; N, 7.71.

4.2.6. 1,3-Dibenzyl-2-(2,4-dichloro-phenyl)-imidazolidine (3f). As a yellow solid (96%). Mp 84 °C; MS (EI), *m/e* 395 (M^++H, 15%), 251 (100), 91 (80); IR (KBr) 2804s, 1337s, 1152s, 854s, 697vs cm^{-1}; ^1H NMR (400 MHz) δ 8.03 (d, J=8.3 Hz, 1H), 7.39–7.35 (m, 2H), 7.31–7.20 (m, 10H), 4.60 (s, 1H), 3.78 (d, J=13.1 Hz, 2H), 3.38 (d, J=13.1 Hz, 2H), 3.25–3.15 (m, 2H), 2.65–2.55 (m, 2H); ^{13}C NMR (100 MHz) δ 139.4, 137.2, 136.4, 134.7, 132.8, 128.9, 128.8, 128.6, 128.1, 127.3, 83.1, 57.2, 51.2. Anal. Calcd for $C_{23}H_{22}Cl_2N_2$: C, 69.52; H, 5.58; N, 7.05, found: C, 69.33; H, 5.46; N, 6.81.

4.2.7. 1,3-Dibenzyl-2-pentafluorophenyl-imidazolidine (3g). Reaction was carried out in deoxygenated water under a nitrogen atmosphere. The crude oily product was purified by flash chromatography (FCC) (eluant: 2.5% ethyl acetate −0.5% triethylamine–hexane) through a short pad of silica to afford the *title compound* **3g** as a clear oil (92%). MS (EI), *m/e* 418 (M^+, 10%), 251 (40), 91 (100); IR (KBr) 2795s, 1500s, 954s, 740s, 700s cm^{-1}; ^1H NMR (400 MHz) δ 7.22–7.18 (m, 10H), 4.61 (s, 1H), 3.75 (d, J=13.3 Hz, 2H), 3.66 (d, J=13.2 Hz, 2H), 3.32–3.29 (m, 2H), 2.72–2.69 (m, 2H); ^{13}C NMR (100 MHz) δ 138.8, 128.7, 128.5, 127.5, 79.8, 58.3, 52.0. Anal. Calcd for $C_{23}H_{19}N_2F_5$: C, 66.02; H, 4.58; N, 6.70, found: C, 65.67; H, 4.56; N, 6.55.

4.2.8. 1,3-Dibenzyl-2-(4-chloro-phenyl)-imidazolidine (3h). As a white solid (91%). Mp 106 °C (Lit.[29] 109 °C); MS (EI), *m/e* 361 (M^++H, 25%), 251 (75), 152 (20), 125 (20), 91 (100), 65 (20); IR (KBr) 2804m, 1493m, 1148m, 1186m, 822s, 698vs cm^{-1}; ^1H NMR (400 MHz) δ 7.64–7.61 (m, 2H), 7.44–7.38 (m, 2H), 7.33–7.22 (m, 10H), 4.01 (s, 1H), 3.79 (d, J=13.2 Hz, 2H), 3.28–3.20 (m, 4H), 2.57–2.53 (m, 2H); ^{13}C NMR (100 MHz) δ 139.6, 139.4, 134.6, 131.2, 128.9, 128.8, 128.6, 127.3, 88.6, 57.3, 51.1. Anal. Calcd for $C_{23}H_{23}ClN_2$: C, 76.12; H, 6.39; N, 7.72, found: C, 76.00; H, 6.39; N, 7.65.

4.2.9. 1,3-Dibenzyl-2-(2,6-dichloro-phenyl)-imidazolidine (3i). As a white solid (88%). Mp 145 °C; MS (EI), *m/e* 495 (M^++H, 5%), 251 (90), 91 (100); IR (KBr) 2792m, 1492m, 1436s, 1377m, 1337m, 1148m, 782m, 766m, 737vs, 698s cm^{-1}; ^1H NMR (400 MHz) δ 7.37–7.11 (m, 13H), 5.07 (s, 1H), 3.87 (d, J=13.6 Hz, 2H), 3.58 (d, J=13.6 Hz, 2H), 3.36–3.33 (m, 2H), 2.62–2.58 (m, 2H); ^{13}C NMR (100 MHz) δ 140.1, 137.7, 135.2, 129.5, 128.6, 128.5, 128.2, 127.1, 85.0, 58.2, 51.8. Anal. Calcd for $C_{23}H_{22}Cl_2N_2$: C, 69.52; H, 5.58; N, 7.06, found: C, 69.47; H, 5.59; N, 6.88.

4.2.10. 1,3-Dibenzyl-2-ethyl-imidazolidine (3j). The crude oil was purified by flash chromatography (FCC) (eluant: 2.5% ethyl acetate −0.5% triethylamine–hexane) to afford the title compound **3j** as a clear oil. (85%). MS (EI), *m/e* 280 (M^+, 5%), 251 (M^+−Et, 100); IR (neat) 2925s, 2785s, 1495s, 1455s, 1345s, 1028s, 700s cm^{-1}; ^1H NMR (200 MHz) δ 7.29–7.19 (m, 10H), 3.98 (d, J=13.1 Hz, 2H), 3.38 (d, J=13.3 Hz, 2H), 3.14 (t, J=3.8 Hz, 1H), 2.99–2.86 (m, 2H), 2.47–2.38 (m, 2H), 1.73–1.60 (m, 2H), 1.11–0.92 (m, 3H); ^{13}C NMR (50 MHz) δ 139.8, 128.6, 128.2, 126.8, 85.6, 58.5, 50.6, 24.4, 8.16. The spectral data were consistent with literature values.[27,28]

4.2.11. 1,3-Dibenzyl-2-phenyl-hexahydro-pyrimidine (5a). As a white solid (96%). Mp 113–114 °C (Lit.[30] 120 °C); MS (EI), *m/e* 341 (M^+−H, 10%), 265 (M^+−Ph, 100), 91 (95); IR (KBr) 2950s, 2795s, 1490s, 1450s, 1095s, 700s cm^{-1}; ^1H NMR (200 MHz) δ 7.69–7.13 (m, 15H), 3.612 (d, J=13.2 Hz, 2H), 3.608 (s, 1H), 3.02–2.95 (m, 2H), 2.85 (d, J=13.1 Hz, 2H), 2.11–1.41 (m, 4H); ^{13}C NMR (50 MHz) δ 141.9, 139.7, 129.6, 128.6, 128.3, 128.2, 128.0, 126.6, 89.0, 58.4, 51.8, 24.4. Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18, found: C, 84.20; H, 7.65; N, 8.13.

4.2.12. 1,3-Dibenzyl-2-(2-chloro-phenyl)-hexahydro-pyrimidine (5b). As a white solid (88%). Mp 94–96 °C; MS (EI), *m/e* 375 (M^++H, 5%), 365 (100), 91 (80); IR (KBr) 2923s, 1367s, 1098s, 756vs, 739vs, 698vs cm^{-1}; ^1H NMR (400 MHz) δ 8.19–8.16 (m, 1H), 7.41–7.19 (m, 13H), 4.34 (s, 1H), 3.58 (d, J=13.2 Hz, 2H,), 3.03–2.99 (m, 4H), 2.15–2.08 (m, 2H), 1.92–1.83 (m, 1H), 1.51–1.47 (m, 1H); ^{13}C NMR (100 MHz) δ 139.9, 136.1, 131.3, 129.5, 128.9, 128.7, 128.5, 128.0, 127.7, 127.1, 83.2, 58.1, 51.3, 25.1. Anal. Calcd for $C_{24}H_{25}ClN_2$: C, 76.48; H, 6.69; N, 7.43, found: C, 76.08; H, 6.69; N, 7.36.

4.2.13. 1,3-Dibenzyl-2-pyridin-2-yl-hexahydro-pyrimidine (5c). As a white solid (93%). Mp 80–81 °C; MS (EI), *m/e* 344 (M^++H, 25%), 265 (M^+−pyridinyl, 100), 91 (80); IR (KBr) 3060s, 2930s, 2790s, 1590s, 1490s, 1450s, 1440s, 1170s, 980s, 820s, 790s cm^{-1}; ^1H NMR (400 MHz) δ 8.58–8.56 (m, 1H), 8.07–8.04 (m, 1H), 7.77 (td, J=7.6, 1.7 Hz, 1H), 7.28–7.21 (m, 11H), 3.90 (s, 1H), 3.50 (d, J=13.6 Hz, 2H), 3.06 (d, J=13.6 Hz, 2H), 3.05–3.01 (m, 2H), 2.13 (td, J=11.8, 2.8 Hz, 2H), 1.94–1.85 (m, 1H), 1.56–1.52 (m, 1H); ^{13}C NMR (100 MHz) δ 163.1, 148.4, 139.7, 137.5, 129.0, 128.5, 127.1, 124.0, 123.6, 89.5, 58.7, 51.8, 25.0. Anal. Calcd for $C_{23}H_{25}N_3$: C, 80.43; H, 7.34; N, 12.23, found: C, 80.03; H, 7.28; N, 12.17.

4.2.14. 1,3-Dibenzyl-2-(2-chloro-phenyl)-[1,3]diazepane (7a). As a white solid (98%). Mp 67 °C; MS (EI), *m/e* 390 (M^++H, 1%), 160 (80), 91 (100); IR (KBr) 2791m, 1085s, 1070s, 762vs, 751vs, 697vs cm^{-1}; ^1H NMR (400 MHz) δ 8.10 (d, J=4 Hz, 1H), 7.45–7.19 (m, 13H), 5.04 (s, 1H), 3.90–3.84 (m, 2H) 3.70–3.66 (m, 2H) 3.02–2.97 (m, 2H), 2.88–2.82 (m, 2H), 1.71–1.55 (m, 4H); ^{13}C NMR (100 MHz) δ 140.6, 140.4, 135.6, 130.2, 129.2, 128.6, 128.6, 128.5, 127.0, 126.8, 82.6, 55.5, 48.9, 26.2. Anal. Calcd for $C_{22}H_{23}N_3$: C, 76.80; H, 6.96; N, 7.17, found: C, 76.42; H, 7.05; N, 6.99.

4.2.15. 2-Chlorophenyl-1,3-bis-((*R*)-1-phenyl-ethyl)-imidazoline (9a). The crude product was purified by Kugelrohr distillation (0.5 mbar, 200 °C) to afford the title compound **9a** as a clear yellow oil (81%). $[\alpha]_D^{25}$=−30 (c=1 in $CHCl_3$),

MS (EI), *m/e* 391 (M^++H, 15%), 279 (M^+−PhCl, 100), 105 (65); IR (neat) 2970s, 1490s, 1450s, 1370s, 1030s, 760s, 700s cm^{-1}; ^1H NMR (400 MHz) δ 7.98 (d, J=8.0 Hz, 1H), 7.38–7.14 (m, 13H), 4.97 (s, 1H), 3.81–3.71 (m, 2H), 3.20–3.14 (m, 1H), 2.90–2.85 (m, 1H), 2.74–2.63 (m, 2H), 1.42 (d, J=6.5 Hz, 3H), 1.15 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz) δ 145.0, 144.4, 141.9, 134.6, 132.3, 129.2, 128.9, 128.6, 128.2, 127.9, 127.7, 127.2, 127.1, 126.8, 78.5, 62.2, 55.4, 50.0, 49.1, 44.7, 23.4, 14.4. Anal. Calcd for $C_{25}H_{27}N_2Cl$: C, 76.81; H, 6.97; N, 7.17, found: C, 76.43; H, 6.95; N, 7.12.

4.2.16. 4-Chlorophenyl-1,3-bis-((*R*)-1-phenyl-ethyl)-imidazoline (9b). The crude product was purified by Kugelrohr distillation (0.5 T, 200 °C) to afford the title compound **9b** as a clear yellow oil (80%). $[\alpha]_D^{25}=-70$ (c=1 in $CHCl_3$), MS (EI), *m/e* 391 (M^++H, 25%), 279 (M^+−PhCl, 100), 105 (65); IR (neat) 2970s, 1490s, 1450s, 1090s, 700s cm^{-1}; ^1H NMR (400 MHz) δ 7.26–7.13 (m, 14H), 4.35 (s, 1H), 3.66 (q, J=6.5 Hz, 1H), 3.56 (q, J=6.5 Hz, 1H), 3.14–3.02 (m, 2H), 2.90–2.82 (m, 2H), 1.33 (d, J=6.5 Hz, 3H), 1.22 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz) δ 144.6, 144.3, 144.4, 133.1, 130.7, 128.5, 128.3, 128.09, 128.06, 127.99, 127.2, 127.1, 82.0, 60.3, 59.2, 48.3, 47.0, 23.7, 17.9. Anal. Calcd for $C_{25}H_{27}N_2Cl$: C, 76.81; H, 6.97; N, 7.17, found: C, 76.55; H, 7.02; N, 7.16.

4.2.17. 2-(2-Chloro-phenyl)-1,3-diphenyl-imidazolidine (11a). As a white solid (99%). Mp 128 °C (Lit.[31] 128–129 °C). The spectral data were consistent with literature values.[31]

4.2.18. Methyl-1,3-diphenyl-imidazolidine (11b). The crude product was filtered of and recrystallised from methanol to afford the title compound **11b** as a white solid. (42%). Mp 95–96 °C (Lit.[32] mp 97 °C). The spectral data were consistent with literature values.[33]

4.2.19. 1,3-Dimethyl-2-phenyl-imidazolidine (13). As a clear liquid (67%). The spectral data were consistent with literature values.[34]

4.2.20. 1,1′-(2-Chloro-phenylmethanediyl)-bis-piperidine (15). 2 equiv. piperidine were used in the reaction. The product was isolated as a yellow liquid (99%). (Lit.[35] 62 °C). MS (EI), *m/e* 292 (M^+, 5%), 208 (M^+, −piperidinyl, 95%), 125 (90), 84 (100); IR (neat) 2930s, 1470s, 1440s, 1270s, 1100s, 910s, 735s cm^{-1}; ^1H NMR (200 MHz) δ 7.44–7.12 (m, 4H), 4.39 (s, 1H), 2.84–2.28 (m, 8H), 1.56–1.34 (m, 12H); ^{13}C NMR (50 MHz) δ 134.8, 134.2, 130.0, 129.3, 127.7, 125.4, 83.1, 49.8, 26.2, 25.2.

4.2.21. (±)-1,3-Dibenzyl-2-(2-pyridinyl)-octahydrobenzoimidazole (17). As a white solid (95%). Mp 49–50 °C; MS (EI), *m/e* 383 (M^+, 5%), 305 (M^+, −pyridinyl, 50), 187 (25), 91 (100); IR (KBr) 2925s, 2800s, 1590s, 1450s, 1440s, 1145s, 700s cm^{-1}; ^1H NMR (400 MHz) δ 8.40–8.38 (m, 1H), 7.52 (td, J=7.6, 1.9 Hz, 1H), 7.38–7.35 (m, 1H), 7.20–7.05 (m, 11H), 4.74 (s, 1H), 3.84 (d, J=13.8 Hz, 1H), 3.79 (d, J=13.7 Hz, 1H), 3.53 (d, J=14.4 Hz, 1H), 3.47 (d, J=14.4 Hz, 1H), 2.99–2.94 (m, 1H), 2.55–2.49 (m, 1H), 1.83–1.70 (m, 2H), 1.31–1.13 (m, 2H); ^{13}C NMR (100 MHz) δ 162.0, 148.6, 141.3, 139.6, 135.8, 129.4, 128.4, 128.2, 128.1, 126.9, 126.7, 124.5, 122.5, 87.8, 69.3, 67.9, 56.9, 52.9, 30.6, 30.3, 25.0, 24.9. Anal. Calcd for $C_{26}H_{29}N_3$: C, 81.42; H, 7.62; N, 10.96, found: C, 81.22; H, 7.65; N, 10.90.

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