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Regioselective hydroaminomethylation of 1,1-diaryl-allyl-alcohols: a new access to 4,4-diarylbutylamines

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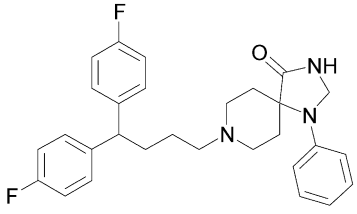
Abstract—Pharmacologically active 4,4-diarylbutylamines like Fluspirilene and 4-amino-1,1-diarylbutan-1-ols like Difenidol were prepared in high yields via rhodium catalysed hydroaminomethylation of 1,1-diaryl-allylalcohols. Conversion of these olefins with carbon monoxide, hydrogen and secondary amines proceeds with complete regioselectivity. This group can easily be removed under acidic and hydrogenating conditions, enabling the transformation of 4-amino-1,1-diarylbutan-1-ols to 4,4-diarylbutylamines in high yields. Thus Fluspirilene was synthesised in 88% yield in four steps starting from commercially available materials.

1. Introduction

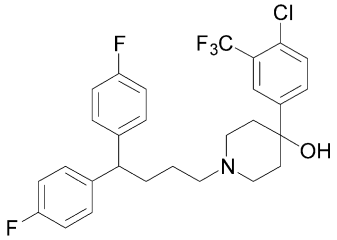
Numerous tertiary 4,4-diarylbutylamines possess therapeutical activity and are commercially obtainable therapeutic agents. Especially amines with the 4,4-bis(*p*-fluorophenyl)butyl group have been synthesised and successfully tested for pharmacological activity, among them some older neuroleptics such as Fluspirilene (**1**)[1] and Penfluridol (**2**)[2] (Fig. 1).

Most synthetic strategies leading to these 4,4-diarylbutylamines proceed via connection of a 4,4-diarylbutylhalide with the amino group.[3] The synthesis of these halides requires several steps with low overall yields, but recently one of us presented a new approach to 4,4-bis(*p*-fluorophenyl)butylbromide via hydroformylation of 1,1-bis(*p*-fluorophenyl)prop-3-en-1-ol.[4] The oxo-aldehyde obtained was transformed to the desired halide in only few steps. An earlier published route towards the halide starting from 3,3-diaryl-1-propene required several steps for the synthesis of the olefin and the hydroformylation of this olefin proceeded with poor regioselectivities.[5]

On the other hand we have presented a very short and efficient synthesis of the homologues 3,3-diarylpropylamines, which are normally prepared similarly to the 4,4-diarybutylamines.[6] In this route the amines are formed via hydroaminomethylation of 1,1-diarylethenes.[7] This tandem reaction[8] enables the synthesis of the desired 3,3-diarylpropylamines in one step with high yields by a direct reductive amination of the oxo-aldehyde formed without isolation of any intermediates. Here now we report a new synthetic route to 4,4-diarylbutylamines via direct hydroaminomethylation of 1,1-diaryl-2-propen-1-ols.



Fluspirilene
1



Penfluridol
2

Figure 1. Pharmacologically active 4,4-diarylbutylamines.

Keywords: Hydroformylation; Hydroaminomethylation; Rhodium; Homogeneous catalysis.
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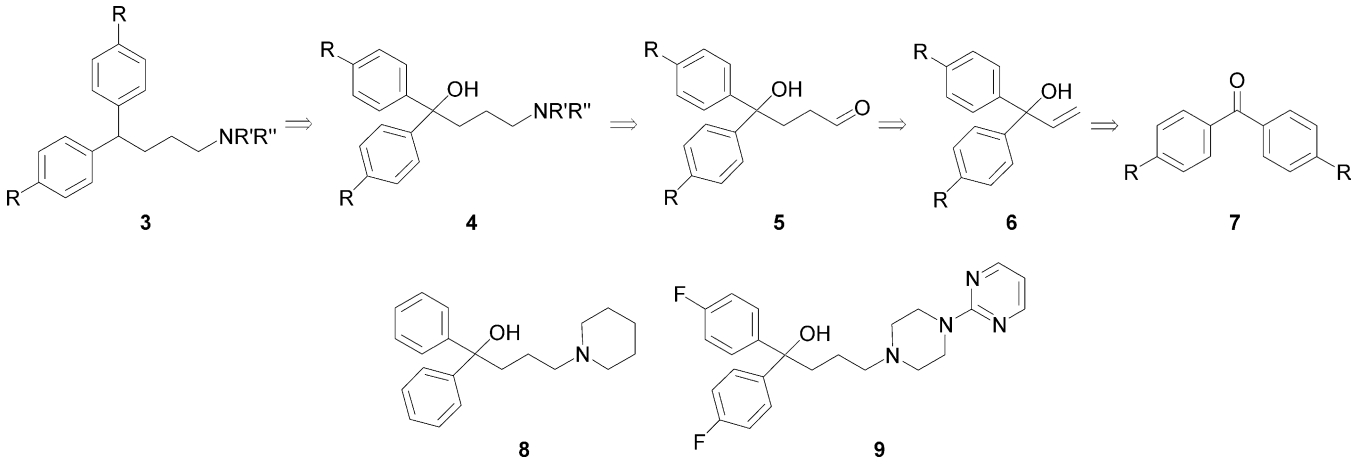


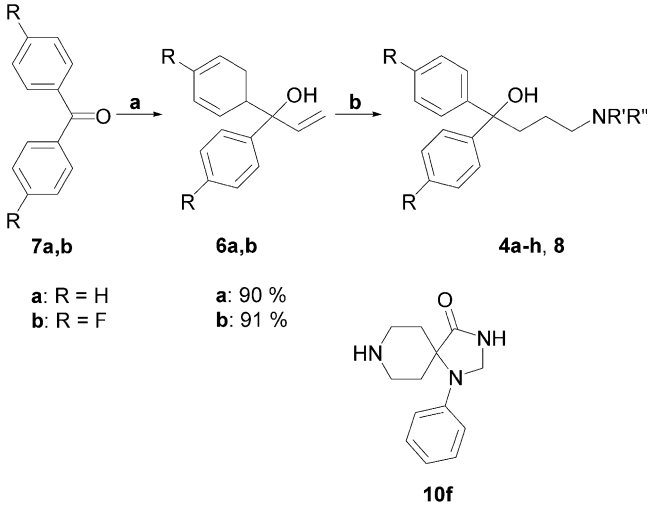
Scheme 1. Retrosynthetical analysis of 4,4-diarylbutylamines **3** and 4-amino-1,1-diaryl-1-butanols **4**.

2. Results and discussion

Based on the previously described stepwise synthesis of Fluspirilene (**1**)[4] we developed a new synthetic strategy to obtain the 4,4-diarylbutylamines **3** via the 4-amino-1,1-diarylbutan-1-ols **4**, which can be formed by reductive amination of the aldehyde **5**. This aldehyde is prepared by hydroformylation of the corresponding allylic alcohol **6**, which is obtained from the commercially available diarylketones **7** (Scheme 1).

Under hydroaminomethylation conditions[8] the aldehyde **5** is not isolated but directly converted to the amines **4**. These intermediates of our synthetic route are also interesting targets, since various 4-amino-1,1-diarylbutan-1-ols are known for pharmacological activity, like the antihistaminic agent Difenidol (**8**)[9] or the piperazine derivative **9**.[10] These aminoalcohols are normally prepared similarly to the 4,4-diarylbutylamines by reacting the heterocyclic amine with the corresponding butyl chloride.[11]

For model investigations we used both the unsubstituted benzophenone (**7a**) and *p*,*p*′-difluorobenzophenone (**7b**).



Scheme 2. Synthesis of 4-amino-1,1-diaryl-1-butanols. Reagents and reaction conditions: (a) vinyl magnesium chloride, THF, reflux; (b) amine **10a–f**, $[Rh(cod)Cl]_2$, 50 bar CO/H_2 (3:2), 120 °C, 1,4-dioxane, 45–65 h.

Both ketones were converted to the allylic alcohols **6a** resp. **6b** by reaction with the vinyl magnesium chloride solution in THF in 90% resp. 91% yield (Scheme 2). The alcohols were subjected to rhodium catalysed hydroaminomethylation with various secondary amines **10** at 120 °C and 50 bar syngas ($CO/H_2=3:2$) using the $[Rh(cod)Cl]_2$ catalyst precursor. Under these conditions all hydroaminomethylation reactions proceed with quantitative yields, giving exclusively the linear products **4**.

The high regioselectivity of the oxo-reaction[12] can be explained by the catalyst directing effect of the bulky trisubstituted carbon in the starting olefin **6**, as it was observed with similar tertiary and secondary allylic alcohols.[13] Also the high reaction tem-perature generally causes a higher *n*-selectivity of the hydroformylation with unmodified rhodium catalysts.[14] Thus small amounts of branched oxo-aldehydes or decomposition products derived thereof were observed if using unmodified rhodium catalysts at lower reaction temperatures during the hydroformylation process.[4] Phosphorous ligands are not necessary for a regioselective hydroaminomethylation reaction, probably due to the presence of the amines, which can support the catalyst directing effect of the starting olefin.

Both cyclic (**10a–10c**, **10f**) and acyclic amines (**10d**, **10e**) are tolerated (Table 1). If using 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (**10f**), only the amino functionality at N-8 reacts as a nucleophile, the amide functionality at N-3 undergoes neither any condensation with the oxo-aldehyde nor any hydrogenation. Also the aminal functionality, formed by N-1 and N-3 is stable under hydroformylation conditions. Thus the aminoalcohol **4h**, a precursor of Fluspirilene (**1**) is obtained in 99% yield.

If using piperidine (**10c**) as amine, Difenidol (**8**) is formed in 99% yield. Starting from benzophenone (**6a**), Difenidol is accessible in two steps with an overall yield of 89% using only commercially available and inexpensive chemicals. This novel synthesis of Difenidol (**8**) demonstrates the applicability of the hydroaminomethylation for the synthesis of 4-amino-1,1-diarylbutan-1-ols.

For the defunctionalisation of the aminoalcohols **4** to the amines **3** several methods are described, like refluxing with

Table 1. Hydroaminomethylation of allyl alcohols **6a**,**b**[a]

Olefin		Secondary amine			Time (h)	Product	Yield, %
	R		R′	R″			
6a	H	**10a**	$-(CH_2)_2-O-(CH_2)_2-$		65	**4a**	100
6a	H	**10b**	$-(CH_2)_6-$		45	**4b**	99
6a	H	**10c**	$-(CH_2)_5-$		65	**8**	99
6a	H	**10d**	Me	Me	65	**4d**	100
6a	H	**10e**	Bzl	Bzl	65	**4e**	100
6a	H	**10f**	cf. Scheme 2		65	**4f**	100
6b	F	**10a**	$-(CH_2)_2-O-(CH_2)_2-$		45	**4g**	99
6b	F	**10f**	cf. Scheme 2		65	**4h**	99

[a] Reaction conditions: 120 °C, 50 bar syngas ($CO/H_2=3:2$), 1 equiv olefin **6**, 1–1.3 equiv amine **10**, 0.5 mol% $[Rh(cod)Cl]_2$, 10 mL 1,4-dioxane.

hydroiodic acid in the presence of red phosphorous[15] or hydrogenation with palladium on charcoal in ethanol.[4,16] Furthermore it is possible to perform the transformation in two steps by isolating the dehydration product, which can be hydrogenated by homogeneous and heterogeneous catalysts.

We decided to investigate the defunctionalisation of the model morpholine derivative **4a** under acidic and hydrogenation conditions, since this reaction can be performed at room temperature in neutral or weakly acidic media. Using ethanol as the solvent no reaction occurred, but addition of hydrochloric acid enables a selective defunctionalisation in high yields (Scheme 3). In summary, 4-(4,4-diphenyl)morpholin (**11**) is available starting from benzophenone (**7a**) in three steps with an overall yield of 87%.

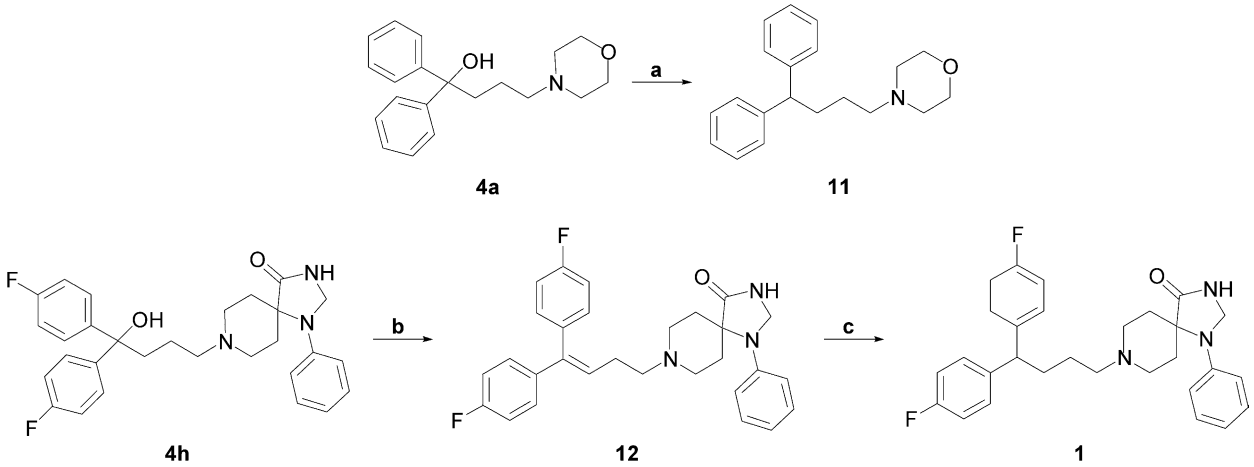
For the preparation of Fluspirilene (**1**) we tried to apply the same reaction conditions for the defunctionalisation of the intermediate **4h**. Surprisingly no conversion was observed, further optimisation also failed, but the dehydration to the olefin **12** was easily achieved. Thus we executed the reaction in two steps by dehydration of the alcohol **4h** with catalytic amounts of hydrochlorid acid in refluxing ethanol to obtain **12** in quantitative yields, followed by hydrogenation in ethanol at room temperature. This protocol enables to synthesise Fluspirilene (**1**) in a new four step reaction sequence starting from *p*,*p*′-difluorobenzo-phenone (**7b**) with an overall yield of 88%.

3. Conclusions

We have developed a convenient method for the synthesis of 4,4-diarylbutylamines via a hydroaminomethylation sequence. The use of easily obtainable 1,1-diaryl allyl alcohols allows the regioselective formation of the desired linear hydroaminomethylation products. Both the 4-amino-1,1-diarylbutan-1-ols and the 4,4-diarylbutylamines, which can be formed by dehydration of the aminoalcohol and hydrogenation of the unsaturated amine, are interesting classes of compounds. As demonstrated for the synthesis of Difenidol (**8**) and Fluspirilene (**1**) this synthetic route enables the preparation of pharmaceutical agents in excellent yields, in which both the aromatic substituents and the substituents of the amino groups can be varied. Thus our new method represents an interesting alternative to the hitherto applied methods. Upon upscaling further optimisations of catalyst effectivity (reaction times, catalyst amounts, TOF) can be achieved by use of appropriate ligands.[14,22]

4. Experimental

All chemicals were purchased from commercial sources, all solvents were dried by standard methods if necessary. The catalyst precursor $[Rh(cod)Cl]_2$ was prepared as previously described.[17] Unless otherwise noted ^1H and ^{13}C NMR spectra were recorded at room temperature with Bruker DRX 400 and DRX 500 spectrometer using $CDCl_3$ as



Scheme 3. Defunctionalisation reactions. Reagents and conditions: (a) H_2, Pd–C, ethanol/HCl, 97%; (b) HCl, ethanol, reflux, 100%; (c) H_2, Pd–C, ethanol, 98%.

solvent and TMS as internal standard. The signals were assigned using DEPT techniques. Infrared spectra were recorded with a Nicolet Impact 400 D spectrometer using neat compounds as films between NaCl plates or as disks with KBr. Mass spectra were recorded with a Finnigan CA 5 spectrometer (Electron Impact, 70 eV) and with a Finnigan ThermoQuest TSQ (ESI). Elemental analyses were performed. Analytical gas chromatography was performed with a Fisons 8130 gas chromatograph with 30-m CP sil-5 capillaries.

Pressure reactions were carried out in autoclaves (250 mL, PTFE insert) from Berghof, Eningen. After charging the autoclave with the starting material, the catalyst precursor, and the solvent, the reactor was flushed with argon, then pressurised with hydrogen and carbon monoxide at room temperature, and heated to the required reaction temperature.

4.1. Synthesis of 1,1-diphenylprop-2-en-1-ol (6a)

A solution of vinyl magnesium chloride (25 mL, 15 wt%, 40 mmol) in THF was added to a solution of benzophenone (**7a**; 3.62 g, 20 mmol) in 20 mL dry THF. After refluxing for 3 h the solution was stirred overnight at room temperature. 25 g ice were added and the mixture was diluted with a saturated solution of NH_4Cl. The phases were separated, the aqueous phase was extracted with ether. The combined etheral solution was dried over $MgSO_4$ and evaporated at reduced pressure. 3.77 g (18 mmol; 90% yield) of alcohol **6a** were obtained.[18]

4.2. Synthesis of 1,1-bis(*p*-fluorophenyl)prop-2-en-1-ol (6b)

A solution of vinyl magnesium chloride (19 mL, 15 wt%, 30 mmol) in THF was added to a solution of 4,4′-difluorobenzophenone (**7b**; 3.62 g, 20 mmol) in 20 mL dry THF. After refluxing for 3 h the solution was stirred overnight at room temperature. 25 g ice were added and the mixture was diluted with a saturated solution of NH_4Cl. The phases were separated, the aqueous phase was extracted with ether. The combined etheral solution was dried over $MgSO_4$ and evaporated at reduced pressure. 3.35 g (14 mmol; 91% yield) of alcohol **6b** were obtained as a yellow oil.[4]

4.3. General procedure for the hydroaminomethylation of allylic alcohols 6

A mixture of the olefin **6**, the corresponding amine **10** and $[Rh(cod)Cl]_2$ (6 mg, 12 μmol) in 10 mL anhydrous 1,4-dioxane was heated at 120 °C for the reaction time given below in an autoclave under 30 bar carbon monoxide and 20 bar hydrogen. Following the reaction, the catalyst was filtered off by passage through a small pad of basic alumina (activity II–III) and the solvent was removed by rotary evaporation. The crude product was crystallised from ethanol.

4.3.1. 4-Morpholin-4-yl-1,1-diphenylbutan-1-ol (4a). Hydroaminomethylation of olefin **6a** (421 mg, 2.0 mmol) with morpholin (**10a**; 0.2 mL, 2.3 mmol) gave 620 mg (2.0 mmol, 100% yield) of aminoalcohol **4a**.[19] ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.63 (quint, 2H, ^3J=5.5 Hz), 2.27 (br s, 4H), 2.39 (dd, 2H, ^3J=5.5, 5.5 Hz), 2.48 (dd, 2H, ^3J=5.5, 5.5 Hz), 3.70 (t, 4H, ^3J=4.8 Hz), 7.16 (m, 2H), 7.27 (m, 4H), 7.49 (d, 4H, ^3J=7.3 Hz), 8.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.1, 42.5, 53.1, 59.5, 66.3, 76.6, 126.1, 126.2, 127.9, 148.1.

4.3.2. 4-Azepan-1-yl-1,1-diphenylbutan-1-ol (4b). Hydroaminomethylation of olefin **6a** (315 mg, 1.5 mmol) with hexamethylenimine (**10b**; 0.23 mL, 2.0 mmol) gave 482 mg (1.5 mmol, 99% yield) of aminoalcohol **4b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.54–1.75 (m, 12H), 2.42–2.48 (m, 6H), 7.15 (t, 2H, ^3J=7.3 Hz), 7.26 (m, 4H), 7.50 (d, 4H, ^3J=8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.9, 26.4, 26.7, 42.7, 55.7, 59.1, 76.4, 126.0, 126.2, 127.7, 148.6. MS (ESI): *m/z* (%)=324 (100, M^++1).

4.3.3. 1,1-Diphenyl-4-piperidin-1-ylbutan-1-ol (Difenidol, 8). Hydroaminomethylation of olefin **6a** (315 mg, 1.5 mmol) with piperidin (**10c**; 0.2 mL, 2.0 mmol) gave 460 mg (1.5 mmol, 99% yield) of aminoalcohol **8**[20] as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.43–1.62 (m, 8H), 2.22 (br s, 4H), 2.31 (dd, 2H, ^3J=5.5, 5.5 Hz), 2.47 (dd, 2H, ^3J=5.5, 5.5 Hz), 7.13–7.38 (m, 6H), 7.50 (dd, 4H, ^3J=8.6 Hz, ^4J=1.3 Hz), 7.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.7, 24.1, 25.2, 42.7, 54.1, 59.8, 76.4, 126.0, 126.2, 127.8, 148.5. MS (ESI): *m/z* (%)=310 (100, M^++1).

4.3.4. 4-Dimethylamino-1,1-diphenylbutan-1-ol (4d). Hydroaminomethylation of olefin **6a** (430 mg, 2.0 mmol) with a solution of dimethylamine (**10d**) in ethanol (1 mL, *c*=5 mol/L, 2.0 mmol) gave 550 mg (2.0 mmol, 100% yield) of aminoalcohol **4d**[21] as a white solid. Mp 102 °C. IR (disk): ν [cm^{-1}]=3423, 3058, 2954, 2942, 2785, 2638, 1658, 1597, 1487, 1447, 1252, 1179, 1065, 1017, 777, 744, 707. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.56 (quint, 2H, ^3J=5.8 Hz), 2.09 (s, 6H), 2.32 (dd, 2H, ^3J=5.8, 5.8 Hz), 2.48 (dd, 2H, ^3J=5.8, 5.8 Hz), 5.81 (s, 1H), 7.13–7.38 (m, 6H), 7.49 (d, 4H, ^3J=7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.5, 42.2, 44.7, 59.9, 76.2, 126.0, 126.1, 127.8, 128.4. MS (ESI): *m/z* (%)=310 (100, M^++1).

4.3.5. 4-Dibenzylamino-1,1-diphenylbutan-1-ol (4e). Hydroaminomethylation of olefin **6a** (315 mg, 1.5 mmol) with dibenzylamine (**10e**; 0.38 mL, 2.0 mmol) gave 630 mg (1.5 mmol, 100% yield) of aminoalcohol **4e** as a yellow solid. Mp 90 °C. IR (disk): ν [cm^{-1}]=3435, 3060, 3028, 2936, 2817, 1599, 1495, 1450, 1383, 1376, 1247, 1168, 1103, 1055, 1027, 990, 734, 698. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.60 (quint, 2H, ^3J=6.3 Hz), 2.25 (t, 2H, ^3J=6.3 Hz), 2.42 (t, 2H, ^3J=6.3 Hz), 3.48 (s, 4H), 7.15–7.44 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.6, 41.4, 53.1, 58.0, 77.3, 126.3, 126.9, 127.1, 127.9, 128.4, 129.6, 140.2, 147.9. MS (EI, 70 eV): *m/z* (%)=421 (10, M^+), 287 (8), 210 (100), 196 (9), 183 (12), 161 (3), 148 (7), 118 (3), 105 (20), 91 (87), 77 (8). $C_{30}H_{31}NO$ (421.6): calcd. C 85.5, H 7.4, N 3.8; found C 84.9, H 7.5, N 3.8.

4.3.6. 8-(4-Hydroxy-4,4-diphenylbutyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (4f). Hydroaminomethylation of olefin **6a** (315 mg, 1.5 mmol) with 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (**10f**; 0.38 mL, 2.0 mmol)

gave 680 mg (1.5 mmol, 100% yield) of aminoalcohol **4f** as a white solid. Mp 80 °C. IR (disk): ν [cm^{-1}]=3391, 3204, 3958, 2926, 2848, 1705, 1600, 1502, 1371, 1308, 1264, 1189, 748, 698. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.60–1.77 (m, 4H), 2.48 (dd, 2H, ^3J=5.1, 5.2 Hz), 2.54 (dd, 2H, ^3J=5.2, 5.3 Hz), 2.64–2.91 (m, 6H), 3.70 (s, 1H), 4.72 (s, 2H), 6.87–7.60 (m, 15 H), 9.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.1, 28.3, 42.4, 49.3, 58.8, 58.9, 59.2, 76.2, 114.3, 118.5, 125.9, 126.0, 127.9, 129.4, 142.9, 148.8, 177.9. MS (ESI): *m/z* (%)=456 (100, M^+).

4.3.7. 1,1-Bis-(*p*-fluorophenyl)-4-morpholin-4-yl-butan-1-ol (4g). Hydroaminomethylation of olefin **6b** (407 mg, 1.7 mmol) with morpholine (**10a**; 0.15 mL, 1.7 mmol) gave 585 mg (1.7 mmol, 99% yield) of aminoalcohol **4g**. IR (film): ν [cm^{-1}]=3410, 3068, 2956, 2921, 2856, 2818, 1662, 1601, 1506, 1457, 1446, 1305, 1268, 1223, 1158, 1117, 1013, 837. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.62 (quint, 2H, ^3J=5.5 Hz), 2.29 (br s, 4H), 2.40 (dd, 2H, ^3J=5.5, 5.5 Hz), 2.43 (dd, 2H, ^3J=5.5, 5.5 Hz), 3.69 (t, 4H, ^3J=4.8 Hz), 6.97 (td, 4H, ^3J=2.0, 8.8 Hz), 7.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.1, 42.8, 53.0, 59.4, 66.2, 76.0, 114.7 ($J_{C,F}$=21 Hz), 127.7 ($J_{C,F}$=8 Hz), 143.8 ($J_{C,F}$=3 Hz), 161.4 ($J_{C,F}$=243 Hz). MS (ESI): *m/z* (%)=348 (100, M^++1).

4.3.8. 8-[4,4-Bis(-*p*-fluorophenyl)-4-hydroxybutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (4h). Hydroaminomethylation of olefin **6b** (369 mg, 1.5 mmol) with 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (**10f**; 400 mg, 1.7 mmol) gave 730 mg (1.5 mmol, 99% yield) of aminoalcohol **4h** as a white solid. Mp 203 °C. IR (disk): ν [cm^{-1}]=3381, 3118, 3072, 2973, 2952, 2930, 2857, 1707, 1599, 1502, 1369, 1223, 1155, 822, 748, 558. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.63–1.69 (m, 4H), 2.48 (m, 4H), 2.65–2.85 (m, 6H), 3.71 (s, 1H), 4.74 (s, 2H), 6.88–7.06 (m, 7H), 7.36–7.39 (m, 3H), 7.50–7.52 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=22.1, 28.3, 42.7, 49.3, 58.8, 58.8, 59.2, 75.6, 114.5, 114.7 ($J_{C,F}$=20 Hz), 118.7, 127.5 ($J_{C,F}$=9 Hz), 129.4, 142.9, 144.5, 161.3 ($J_{C,F}$=233 Hz), 177.9. MS (ESI): *m/z* (%)=492 (100, M^+). $C_{29}H_{31}F_2N_3O_2$ (491.6): calcd. C 70.9, H 6.4, N 8.6; found C 70.4, H 6.6, N 8.4.

4.4. Direct synthesis of 4-(4,4-diphenylbutyl)-morpholin (11) from 4a

A suspension of aminoalcohol **4a** (65 mg, 0.21 mmol) and palladium on charcoal (200 mg, 10 wt%) in 50 mL ethanol and 1 mL concentrated hydrochlorid acid was stirred for 3 days under a hydrogen atmosphere (1.5 bar). The catalyst was removed by suction, the filtrate was neutralised with a diluted solution of $NaHCO_3$ and extracted with ether. The etheral solution was dried over $MgSO_4$ and evaporated at reduced pressure to obtain 60 mg (0.20 mmol, 97% yield) of amine **11**. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.47 (quint, 2H, ^3J=7.8 Hz), 2.07 (q, 2H, ^3J=7.8 Hz), 2.35–2.41 (m, 6H), 3.69 (t, 4H, ^3J=4.5 Hz), 3.89 (t, 1H, ^3J=7.8 Hz), 7.14–7.29 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.9, 33.4, 51.3, 53.6, 58.8, 66.8, 126.1, 127.8, 128.4, 144.9.

4.5. Synthesis of Fluspirilene (1)

A solution of **4h** (305 mg, 0.62 mmol) and 1 mL concentrated hydrochlorid acid in 50 mL ethanol was refluxed for 4 h. The solution was neutralised with a diluted solution of NaOH and extracted with dichloromethane. The extraction was dried over $MgSO_4$ and evaporated at reduced pressure to obtain 293 mg (0.62 mmol, 100% yield) of 8-[4,4-bis-(4-fluorophenyl)-but-3-enyl]-1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one (**12**).

The olefin **12** (280 mg, 0.59 mmol) was dissolved in 50 mL ethanol, palladium on charcoal (150 mg, 10 wt%) was added and the suspension was stirred for 3 days at room temperature under a hydrogen atmosphere (1.5 bar). The catalyst was removed by suction and the filtrate was evaporated at reduced pressure to obtain 275 mg (0.58 mmol, 98% yield) of Fluspirilene (**1**).[4]

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