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Graphical Abstract

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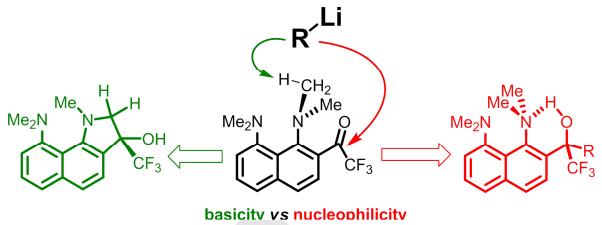

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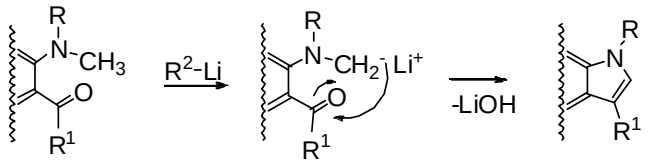
ABSTRACT

A novel approach to pyrrole ring closure in 2-trifluoroacetyl- and 2-ethoxycarbonyl-1,8-bis(dimethylamino)naphthalenes via treatment with 2-lithium-1,8-bis(dimethylamino)naphthalene producing the corresponding benzo[*g*]indole derivatives, was examined with different alkyl- and aryllithium compounds as well as with LDA. It was found that the highest yields of benzo[*g*]indoles (up to 70%) are obtained with aryllithium reagents when they contain NMe_2 group in *ortho*-position to the carbanionic center. In all other cases the formation of acyclic alcohol arising from ordinary intermolecular addition of the carbanion to the C=O group strongly prevails. The dramatic facilitation of deprotonation of the N-Me group in substrate followed by pyrrolic cyclization in the case of 2-lithium-N,N-dimethylanilines was explained through a specific structure of the reaction transition state.

1. Introduction

In view of the immense importance of indoles in Nature and in the different spheres of human activity[1] in conjunction with the rapid development of new synthetic procedures, the last 15 years have seen the elaboration of dozens of new methods for indole synthesis.[2] Most modern synthetic approaches to indoles are based on coupling various aniline and acetylene derivatives in the presence of appropriate transition metal catalysts. This usually provides atom- and step-economy protocol as well as nearly unlimited possibilities for indole functionalization. More surprising, quite simple and even obvious schemes remain unrealized. As an example, the pyrrole ring closure through intramolecular nucleophilic addition of α-aminomethyl carbanion **2** to *ortho*-carbonyl- or cyano- derivatives of *N*,*N*-dimethylanilines can be mentioned (Scheme 1). Two main reasons seem to be responsible for the difficulties of this method. The first one is a considerable destabilization of α-aminomethyl carbanions caused by electrostatic repulsion of neighbouring free electron pairs on nitrogen and carbon atoms (for a review on α-aminomethylcarbanions see ref. [3]). Indeed, there were registered no signs of their formation, for example, on treatment of *N*,*N*-dimethylaniline with *n*-butyl lithium.[4] The second reason, is a lack of the strong and highly selective (low nucleophilic) bases which are needed for lithiation of C-H bond in **1** in the presence of more active C=O (C≡N) group.

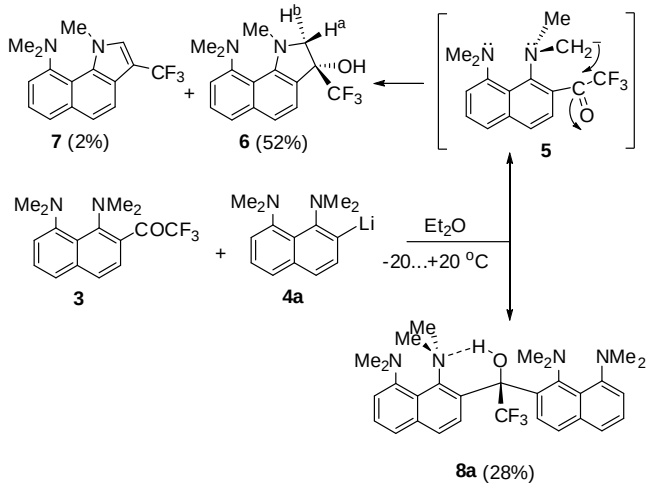


1 **2**

Scheme 1

Nevertheless, recently we have reported the first examples of indole synthesis based on Scheme 1.[5] In particular, we have found that treatment of 2-trifluoroacetyl-1,8-bis(dimethylamino)naphthalene **3** with 2-lithium-1,8-bis(dimethylamino)naphthalene **4a** in ether produces a mixture of benzo[*g*]indoles **6** and **7** along with 2,2'-binaphthyl alcohol **8a** (Scheme 2). Since **6** can be quantitatively dehydrated into **7** just by passing through a column with active SiO_2 (much worse with Al_2O_3) a total yield of benzoindole **7** is actually almost twice higher than **8a**. This means that lithium compound **4a** as a derivative of strong neutral base "proton sponge" possesses very high protophilicity and simultaneously quite moderate nucleophilicity. Our recent X-ray and solution studies of

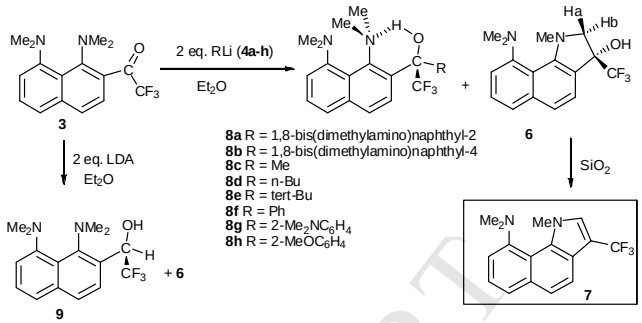
structure **4a** are in agreement with this view since **4a** exists in both media as a rather hindered dimer.[6] Following the above, the main purpose of this study consisted in using for this reaction instead of **4a** some other strong bases including alkyl- (**4c-e**) and aryllithiums (**4f-h**), as well as isomeric to **4a** 4-lithium-1,8-bis(dimethylamino)naphthalene **4b** and lithium diisopropylamide (LDA, **4i**). Thereby, we hoped to clarify factors influencing the formation of benzoindoles and to find out among these organometallic reagents even more selective protophilic reagent for the pyrrole ring closure in ketone **3**.



Scheme 2

2. Results and discussion

In a typical experiment, ketone **3** was reacted with two equivalents of organolithium reagent **4a-i** in dry ether at -20 °C for 42 hrs (Scheme 3). Thereafter, the reaction mixture was poured into water, extracted with Et_2O and subjected to column chromatography on Al_2O_3. Independently, the product ratio was determined by ^1H NMR method. For this, the ethereal extract was evaporated to dryness and ^1H NMR spectrum of the residue was recorded in $CDCl_3$. The results obtained are summarized in Table 1, which also includes the calculated gas-phase proton affinity values, PA, of the tested bases. It should be noted that in the latter case no visible amount of aromatized benzoindole **7** could be found in the spectra and mainly alcohols **6** and **8** were the detectable products. However, in two experiments where *n*-BuLi and LDA were used a considerable amount of alcohol **9** was also isolated (Runs 4 and 9). Evidently, this results from reduction of **3** by the above bases, whose reducing ability is well documented in literature.[7] Though ^1H NMR spectra of crude reaction mixtures were rather complicated, it was always possible to identify the main reaction products and estimate their ratio. The simplest way is to compare characteristic signal intensities for each type of compounds: OH singlet for **8** (δ = 12.3 – 13.4 *ppm*), geminal CH_2(b) doublet for **6** (3.93 *ppm*) and C<u>H</u>CF_3 quartet for **9** (5.46 *ppm*). This is illustrated for runs 2 and 8 in Figure 1.



Scheme 3. Interaction of Ketone **3** with Some Organolithium Compounds.

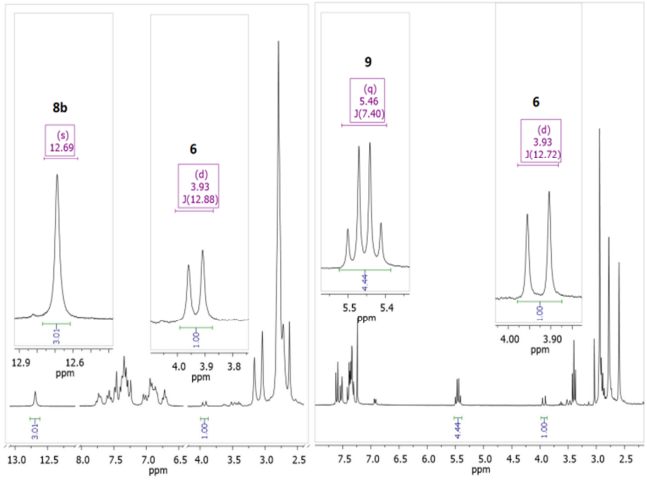


Figure 1. ^1H NMR spectra ($CDCl_3$, 250 MHz) of reaction mixtures for Run 2 (left) and Run 8 (right), compared signals are shown above.

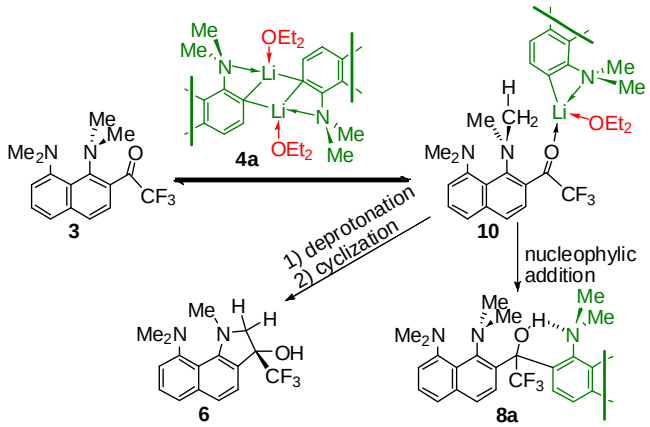
Analysis of the Table 1 data leads to two main conclusions: 1) ratio of benzo[*g*]indole **6** (or **7**) to acyclic alcohols **8** strongly depends on structure of the bases used but is little sensitive to PAs values; 2) all bases in regard to ratio **6**(**7**) : **8** are distinctly divided into two categories. The first one includes only aryllithium compounds **4a** and **4g**, both having NMe_2 group in *ortho*-position to carbanionic centre. They provide the largest yield of benzo[*g*]indole **7**, reaching 70% (after aromatization of **6**). All other bases constituting the second group give the benzoindole yield varying in a range 5-27%, while yields of **8** are increased to 63-95%, except *n*-BuLi and LDA where alcohol **9** prevails. We believe that these results can be interpreted in a favour of importance of the transition state structure (TSS) leading to the deprotonation of N-Me group in **3** and finally to the formation of benzoindole **6** (**7**).

Table 1. Results of Interaction of Ketone **3** with Some Organolithium Compounds

Run	Organolithiums	Aggregation in ethers	Yield (NMR), %			Gas-phase Proton Affinity Values of R^-, kcal/mol[b]	Yield (isolated), %		
			6	**8**	**9**		**7**	**8**	**9**
1	1,8-$(NMe_2)_2C_{10}H_5$-2-Li (**4a**)	Dimeric[6]	71	29	-	391.2	55	28	-
2	1,8-$(NMe_2)_2C_{10}H_5$-4-Li (**4b**)	-[a]	25	75	-	394.1	20	73	-
3	MeLi (**4c**)	Tetrameric[8a]	22	78	-	415.3	20	45	-
4	*n*-BuLi (**4d**)	Tetrameric[8b]	27	32	41	413.4	25	30	37
5	*tert*-BuLi (**4e**)	Dimeric[8c]	24	76	-	420.6	6	68	-
6	C_6H_5Li (**4f**)	Dimeric[8d]	5	95	-	399.2	4	85	-
7	2-$Me_2NC_6H_4$ (**4g**)	-[a]	69	31	-	395.1	60	23	-
8	2-$MeOC_6H_4$ (**4h**)	Tetrameric[8e]	27	63	-	389.7	21	64	-
9	LDA (**4i**)	Dimeric[8f]	18	-	82	385.3	13	-	51

[a] no data available. [b] B3LYP/6-311+G(d,p)(with ZPE)

Apparently, the presence of *ortho*-NMe_2 group in the bases **4a** and **4g** plays a key role. To support this we have performed DFT calculation of possible TSS with participation of **4g**. Recently, we have performed single crystal X-ray study for **4a** and found that it has dimeric structure with two molecules of Et_2O as additional ligands (Scheme 4). However, ^{13}C and ^{1}H NMR examination of **4a** in solution allows to conclude that under these conditions the dimer is relatively unstable (possibly due to sterics) and undergoes partial disaggregation. If so, the disaggregation of **4a** (or **4g**) in the presence of **3** might proceed with inclusion of the ketone in coordination sphere with realization of the structure close to **10** (Figure 2). The theoretical calculation demonstrated that such structure lies in the minimum on the potential energy curve and besides it provides close enough distance (2.56 Å) between a proton of the N-CH_3 group and carbanionic centre. Additionally the coordination of Li^+ ion with the C=O group should increase the N-CH_3 group acidity simultaneously preventing the nucleophilic addition to it by keeping carbanionic centre away from the carbonyl carbon atom.



Scheme 4. Proposed reaction mechanism for acidic ionization of N-Me group in **3**.

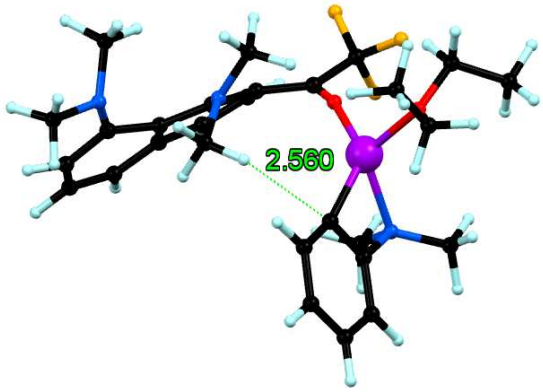
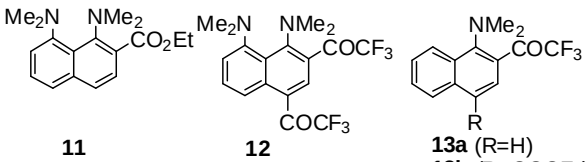
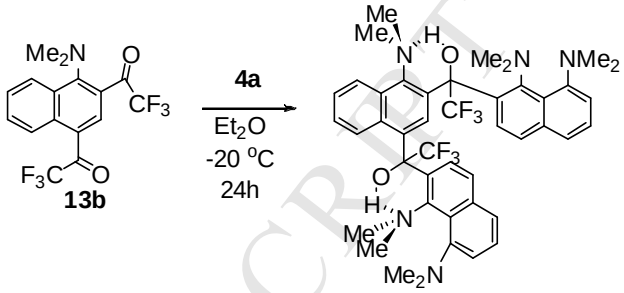


Figure 2. Theoretically calculated [B3LYP/6-311+G(d,p)] transition state structure for reaction of **3** with **4g**

Obviously, one of the central points of this study is how wide can be applicability of the method under consideration. Unfortunately, so far we were unable to extend it to other substrates, with the exception of ester **11** and diketone **12**.[5] The most attractive compounds of this type, 2-trifluoroacetyl-*N*,*N*-dimethylaniline and 2-trifluoroacetyl-*N*,*N*-dimethylnaphthalene **13a** turned out to be rather unavailable. The first of them is known to exist as a stable hydrate.[9] Synthesis of **13a** is described in the literature by 4-protodetrifluoroacetylation of diketone **13b** with CF_3CO_2H in CH_3CN/water mixture.[10] However we could not reproduce this procedure though similar preparation of **3** from **12** proceeded in our hands without any difficulties.[5] Since diketone**12** being treated with **4a** undergoes transformation into benzo[*g*]indole derivative we tried to repeat this cyclization with easily available **13b**[11]. However, after chromatographic separation on SiO_2 only alcohol **14** was isolated from the reaction mixture in 46% yield (Scheme 6).

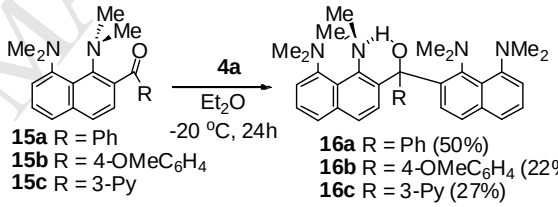


Scheme 5.



Scheme 6.

Finally, we also tested **4a** as base to obtain indoles from proton sponge ketones **15a-c**. But in all these cases the reaction proceeded with considerable tarring and only alcohols **16a-c** were isolated in moderate yields (scheme 7). We believe that this results from higher acidity of the ring C-H bonds in the substituent R as compared with that of 1-NMe_2 group.



Scheme 7

3. Conclusion

In summary, we have developed a very rare, if not absolutely novel, type of pyrrole ring closure in indole systems via deprotonation of the N-Me group. It was found that aryllithium reagents bearing NMe_2 group in *ortho*-position to carbanionic center provides the best yield of indole. It was shown that 2-lithium-1,8-bis(dimethylamino)naphthalene possesses extremely strong basicity (close to alkyllithium reagents) combined with remarkably low nucleophilicity. Such unprecedented for aryllithiums basicity inspiring great hopes to apply discovered cyclisation on the synthesis of hardly accessible indole derivatives.

4. Experimental section

4.1. General Methods.

CHN analysis was accomplished by combustion analysis (Dumas and Pregl method). Melting points were determined in glass capillaries on Stuart SMP30 device. Flash column chromatography was performed on SiO_2 and Al_2O_3. ^{1}H and ^{13}C NMR spectra were recorded on 250 and 600 MHz spectrometers. Chemical shifts are referred to TMS. The quantum-mechanical simulations were carried out using the Gaussian 09 suite of program.[12] The calculations were performed by the three-parameter functional of Becke[13] with correlation energy of Lee-

Yang-Parr,[14] denoted as B3LYP, and employing the 6-311+G(d,p) basis set[15]. Harmonic frequencies were calculated confirming that the obtained geometries correspond to potential energy surface (PES) minima.

4.1.1. Organolithium reagents.

Commercially available MeLi (1.6 M in Et_2O), *n*-BuLi (1.6 M in hexanes), *tert*-BuLi (1.7 M in pentane), PhLi (1.8 M in Bu_2O) were used; 2-lithio-1,8-bis(dimethylamino)naphthalene **4a** was prepared by previously reported teqnique[5].

*4.1.2. 4-Lithio-1,8-bis(dimethylamino)naphthalene (**4b**)*

To a solution of 4-bromo-1,8-bis(dimethylamino)naphthalene[16] (189 mg; 0.65 mmol) in 10 mL of dry Et_2O cooled to -20 °C a 1.6 M solution of *n*-BuLi in hexanes (0.4 mL; 0.65 mmol) was added; reaction mixture was kept at -20 °C under argon atmosphere for 30 min.

*4.1.3. 2-Lithio-N,N-dimethylaniline (**4g**)*

To a solution of 2-bromo-*N*,*N*-dimethylaniline (128 mg; 0.65mmol) in 10 mL of dry Et_2O cooled to -20 °C a 1.6 M solution of *n*-BuLi in hexanes (0.4 mL; 0.65 mmol) was added; reaction mixture was kept at -20 °C under argon atmosphere for 30 min.

*4.1.4. 2-Lithioanisole (**4h**)*

To a solution of 2-bromoanisole (122 mg; 0.65 mmol) in 10 mL of dry Et_2O cooled to -20 °C a 1.6 M solution of *n*-BuLi in hexanes (0.4 mL; 0.65 mmol) was added; reaction mixture was kept at -20 °C under argon atmosphere for 60 min.

*4.1.5. Lithium diisopropylamide (**4j**)*

To a solution of diisopropylamine (0.09 mL; 0.65 mmol) in 10 mL of dry Et_2O cooled to -20 °C a 1.6 M solution of *n*-BuLi in hexanes (0.4 mL; 0.65 mmol) was added; reaction mixture was kept at -20 °C under argon atmosphere for 10 min.

4.2. General method for interaction of organolithiums with 3

To oganolithium reagent (0.65 mmol; see above) in 10 mL dry Et_2O a solution of 2-trifluoroacetyl-1,8-bis(dimethylamino)naphthalene **1** (100 mg, 0.32 mmol) in 10 mL dry Et_2O was added dropwise at -20 °C under argon atmosphere and reaction mixture was stirred for 42 h. The resulting suspension was treated with water (20 mL). Organic layer was separated, water layer was extracted with Et_2O (5 x 5mL), organic fractions were combined, solvent was evaporated to dryness. Residue was chromatographed on SiO_2 with EtOAc/PET (1:15) as eluent, colorless fraction with R_f = 0.7 (blue after exposition to iodine vapor) containing pure benzo[*g*]indole **5**[17] was collected (isolated yields see in table **1**). Alcohols **6(7)** were washed out from sorbent with acetone and purified by chromatography on Al_2O_3.

*4.2.1. 1,1-Bis(1,8-bis(dimethylamino)naphthalen-2-yl)-2,2,2-trifluoroethanol (**8a**)*

R_f = 0.3 (Al_2O_3, CH_2Cl_2); colorless crystals; yield: 42 mg (28%); Characterization data were consistent with those reported in the literature.[5]

*4.2.2. 1-(4,5-Bis(dimethylamino)naphthalen-1-yl)-1-(1,8-bis(dimethylamino)naphthalen-2-yl)-2,2,2-trifluoroethanol (**8b**)*

R_f (Al_2O_3, EtOAc/PET 1:30) 0.6; colorless crystals; yield: 124 mg (73%), mp 160-163 °C (*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.61 (s, 1H), 7.76 – 7.71 (m, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.42 – 7.37 (m, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.91 – 6.85 (m, 2H), 6.72 (d, *J* = 7.2 Hz, 1H), 3.18 (s, 3H), 3.07 (s, 3H), 2.84 (s, 3H), 2.82 (s, 6H), 2.74 (brs, 6H), 2.65 (s, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ 152.38, 151.20, 151.05, 146.66, 137.38, 135.29, 134.93, 129.76 – 123.93 (m), 128.26, 128.22, 127.80, 127.43, 126.72, 126.39, 125.51 (d, *J* = 3.2 Hz), 124.24, 121.18, 120.03, 119.66, 111.59, 109.79, 85.29 (q, *J* = 26.6 Hz), 49.54, 47.05, 44.89, 44.50, 44.09, 43.80. ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.74 (brs) . EI MS: m/z (I,%). 58 (21), 227 (23), 524 (100) [M^+]. IR (ν/cm^{-1}) (CCl_4): 2783, 2828, 2857, 2932, 3062, 3084 (CH). Found: C, 68.83; H, 6.51; N, 10.91. Calc. for $C_{30}H_{35}F_3N_4O$: C, 68.68; H, 6.72; N, 10.68.

*4.2.3. 2-(1,8-bis(dimethylamino)naphthalen-2-yl)-1,1,1-trifluoropropan-2-ol (**8c**)*

R_f (Al_2O_3, Et_2O/PET 1:2) 0.7; colorless crystals; yield: 47 mg (45%), mp 53-54°C (MeCN). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.71 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 3.06 (s, 3H), 2.86 (s, 3H), 2.81 (s, 3H), 2.58 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.48, 146.87, 137.39, 133.45, 128.17, 127.78, 126.91 (q, *J* = 287.9 Hz), 126.76, 126.59, 126.38 (d, *J* = 1.9 Hz), 120.40, 78.26 (q, *J* = 28.0 Hz), 49.78, 46.79, 44.41, 26.18 (d, *J* = 0.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -81.71. EI MS: m/z (I,%) 15 (23), 31 (22), 42 (33), 43 (67), 44 (27), 58 (31), 127 (26), 154 (26), 168 (85), 169 (46), 170 (24), 197 (30), 198 (27), 212 (38), 213 (48), 257 (42), 282 (65), 326 (100) [M^+]. IR (ν/cm^{-1}) (CCl_4): 2785, 2811, 2840, 2914, 2935, 2971, 3047, 3069 (CH). Found: C, 62.69; H, 6.25; N, 8.74. Calc. for $C_{17}H_{21}F_3N_2O$: C, 62.56; H, 6.49; N, 8.58.

*4.2.4. 2-(1,8-bis(dimethylamino)naphthalen-2-yl)-1,1,1-trifluorohexan-2-ol (**8d**)*

R_f (Al_2O_3, EtOAc/PET 1:15) 0.96; pale-yellow crystals; yield: 36 mg (30%), mp 60-61 °C (MeCN). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.70 (s, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 1H), 3.03 (s, 3H), 2.87 (s, 3H), 2.80 (s, 3H), 2.61 (s, 3H), 2.24 (td, *J* = 12.9, 4.5 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.53 – 1.44 (m, 1H), 1.38 – 1.27 (m, 2H), 0.94 – 0.86 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.43, 148.05, 137.35, 131.49, 128.36, 127.78, 126.85 (m), 126.72, 126.72, 126.38 (q, *J* = 2.3 Hz), 81.24 (dd, *J* = 53.6, 27.0 Hz), 49.63, 47.23, 44.41, 44.30, 36.15, 25.07, 23.04, 14.12. ^{19}F NMR (282 MHz, $CDCl_3$) δ -81.10 (s). EI MS: m/z (I, %) 57 (30), 58 (100), 127 (22), 154 (21), 168 (45), 169 (23), 213 (22), 311 (40), 324 (23), 368 (26) [M^+]. IR (ν/cm^{-1}) (CCl_4): 2785, 2826, 2865, 2874, 2933, 2961, 3084 (CH). Found: C, 65.43; H, 7.18; N, 7.82. Calc. for $C_{20}H_{27}F_3N_2O$: C, 65.20; H, 7.39; N, 7.60.

*4.2.5. 2-(1,8-bis(dimethylamino)naphthalen-2-yl)-1,1,1-trifluoro-3,3-dimethylbutan-2-ol (**8e**)*

R_f (Al_2O_3, CH_2Cl_2) 0.4; pale-yellow crystals; yield: 81 mg (68%), mp 116-119°C (MeCN).^{1}H NMR (600 MHz, $CDCl_3$) δ 13.35 (s, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 3.08 (s, 3H), 2.79 (s, 3H), 2.78 (s, 3H), 2.60 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.29, 147.36, 137.03, 132.15, 128.21, 127.62 (q, *J* = 290.9 Hz), 126.70 (q, *J* = 3.7 Hz),126.57, 126.54, 126.41, 120.22, 86.02 (q, *J* = 24.7 Hz), 49.41, 47.07, 44.85, 44.29, 40.62, 27.65 (q, *J* = 2.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -69.33 (s). EI MS: m/z (I, %) 57 (21), 58 (53), 311 (100), 368 (21) [M^+]. IR (ν/cm^{-1}) (CCl_4): 2784, 2826, 2929, 2937, 2962, 3084 (CH). Found: C, 65.38; H, 7.15; N, 7.77. Calc. for $C_{20}H_{27}F_3N_2O$: C, 65.20; H, 7.39; N, 7.60.

*4.2.6. 1-(1,8-Bis(dimethylamino)naphthalen-2-yl)-2,2,2-trifluoro-1-phenylethanol (**8f**)*

R_f (Al_2O_3, EtOAc/PET 1:15) 0.8; colorless crystals; yield: 106 mg (85%), decomp. 187-188 °C (*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.29 (s, 1H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.61 – 7.56 (m, 3H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.35 – 7.28 (m, 3H), 2.84 (brs, 3H), 2.78 (s, 3H), 2.67 (brs, 3H), 2.45 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.17, 146.41, 142.62, 136.91, 134.18, 127.91 (d, *J* = 1.4 Hz), 127.89, 127.81, 127.77, 126.86, 126.54, 126.20 (q, *J* = 3.3 Hz), 125.94, 125.82 (q, *J* = 287.0 Hz), 119.18, 82.31 (q, *J* = 27.7 Hz), 49.31, 46.10. ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.09 (brs). ESI-HRMS: found 389.1833; calc. for $C_{22}H_{23}F_3N_2O$+H 389.1835.IR (ν/cm^{-1}) (CCl_4): 2785, 2826, 2859, 2862, 2899, 2902, 2937, 2940, 2980, 3029, 3063, 3065, 3084 (CH).

*4.2.7. 1-(1,8-bis(dimethylamino)naphthalen-2-yl)-1-(2-(dimethylamino)phenyl)-2,2,2-trifluoroethanol (**8g**)*

R_f (Al_2O_3, EtOAc/PET 1:20) 0.9; brown oil; yield: 32 mg (23%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.26 (s, 1H), 7.53 (m, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.38 – 7.33 (m, 3H), 7.32 – 7.26 (m, 2H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.07 (m, 1H), 3.10 (brs, 3H), 2.79 (s, 3H), 2.53 (s, 3H), 2.37 (brs, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.94, 152.77, 138.48, 137.34, 137.24, 128.96, 128.93, 128.13 (q, 2.1 Hz), 126.96 (q, *J* = 3.1 Hz), 126.85 (q, *J* = 288.8 Hz), 126.72, 126.00, 125.87, 125.66, 125.21, 124.89, 118.61, 83.99 (q, *J* = 26.2 Hz), 49.95, 45.98, 45.0-48.0 (very broad signal). ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.42 (brs) .EI MS: m/z (I,%) 148 (100), 168 (26), 213 (20), 297 (26), 431 (66) [M$^+$]. IR (ν/cm^{-1}) (CCl_4): 2783, 2824, 2858, 2932, 3061, 3084, 3436 (CH). Found: C, 67.06; H, 6.30; N, 9.99. Calc. for $C_{24}H_{28}F_3N_3O$: C, 66.80; H, 6.54; N, 9.74.

*4.2.8. 1-(1,8-bis(dimethylamino)naphthalen-2-yl)-2,2,2-trifluoro-1-(2-methoxyphenyl)ethanol (**8h**)*

R_f (Al_2O_3, EtOAc/PET 1:15) 0.6; colorless crystals; yield: 86 mg (64%), mp 147-148 °C (*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.62 (s, 1H), 7.79 – 7.74 (m, 1H), 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.31 (td, *J* = 8.8, 1.6 Hz, 1H), 7.11 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.02 (td, *J* = 7.8, 1.0 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.31 (s, 3H), 3.06 (s, 3H), 2.82 (s, 3H), 2.74 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.97, 152.30, 146.44, 136.99, 134.45, 131.34, 129.59, 127.88, 127.62 (q, *J* = 3.2 Hz), 127.10 (q, *J* = 2.3 Hz), 126.35 (q, *J* = 288.1 Hz), 126.46, 126.35, 126.18, 120.17, 119.48, 113.59, 82.54 (q, *J* = 27.4 Hz), 55.64, 48.80, 47.34, 44.24, 43.83. ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.02 (brs). EI MS: m/z (I,%) 58 (22), 121 (33), 168 (21), 297 (100), 418 (28) [M$^+$]. IR (ν/cm^{-1}) (CCl_4): 2784, 2826, 2835, 2860, 2938, 2980, 3062, 3083. Found: C, 66.31; H, 5.81; N, 6.93. Calc. for $C_{23}H_{25}F_3N_2O_2$: C, 66.02; H, 6.02; N, 6.69.

*4.2.9. 1-(1,8-bis(dimethylamino)naphthalen-2-yl)-2,2,2-trifluoroethanol (**9**)*

R_f (Al_2O_3, EtOAc/PET 1:15) 0.3; colourless waxy oil; yield: 38 mg (37%, from **4d**), 52 mg (51%, from **4i**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.6 Hz, 1H), 7.55 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.35 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.05 (brs, 1H), 5.48 (q, *J* = 7.2 Hz, 1H), 2.97 (s, 6H), 2.81 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.54, 148.31, 137.68, 129.62, 127.42, 126.86, 126.69, 126.34, 125.44 (q, *J* = 283.8 Hz), 125.36, 118.19, 72.71 (q, *J* = 31.2 Hz), 48.69, 46.26, 44.43. ^{19}F NMR (282 MHz, $CDCl_3$) δ -78.11 (s). EI MS: m/z (I,%) 32 (82), 42 (22), 58 (45), 168 (44), 169 (29), 198 (26), 266 (24), 267 (26), 268 (42), 312 (100) [M$^+$]. IR (ν/cm^{-1}) (CCl_4): 2785, 2826, 2856, 2928, 3060, 3084 (CH), 3617 (OH). Found: C, 61.77; H, 5.89; N, 9.12. Calc. for $C_{16}H_{19}F_3N_2O$: C, 61.53; H, 6.13; N, 8.97.

Alternatively **9** could be obtained by reduction of **3** with $NaBH_4$: to the solution of **3** (50 mg, 0.161 mmol) in 2 mL of EtOH $NaBH_4$ (2 mg, 0.05 mmol) was added. Reaction mixture was refluxed for 30 min. Solvent was evaporated to dryness. Residue was treated with water, product was extracted with Et_2O (6 x 6 mL). Solvent was removed in vacuum to yield 49 mg (98%) of **9**.

*4.3. Interaction of **4a** with ketone **13b***

To the solution of **4a** (0.72 mmol) in 10 mL dry Et_2O a solution of ketone **13b**[11] (100 mg, 0.24 mmol) in 10 mL dry Et_2O was added dropwise at -20 °C under argon atmosphere and reaction mixture was stirred for 42h. The resulting suspension was treated with water (20 mL). Organic layer was separated, water layer was extracted with Et_2O (5 x 5mL), organic fractions were combined, solvent was evaporated to dryness. Residue was chromatographed on SiO_2 with EtOAc/PET (1:2) as eluent, yellow fraction with R_f = 0.5 containing pure alcohol **14** was collected.

*4.3.1. 1,1'-(4-(dimethylamino)naphthalene-1,3-diyl)bis(1-(1,8-bis(dimethylamino)naphthalen-2-yl)-2,2,2-trifluoroethanol) (**14**)*

Yellow crystals; yield 100 mg (46%); decomp. 250-252 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.98 (s, 1H), 11.85 (s, 1H), 8.62 (s, 1H), 8.32 (d, *J* = 8.7 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.64 (q, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.45 – 7.39 (m, 2H), 7.39 – 7.32 (m, 2H), 7.30 – 7.23 (m, 1H), 7.16 – 7.08 (m, 2H), 3.18 (s, 1H), 3.01 (s, 3H), 2.86 (s, 3H), 2.80 (s, 3H), 2.75 (s, 3H), 2.70 (s, 3H), 2.67 (s, 3H), 2.50 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.25, 152.18, 148.53, 146.44, 145.11, 137.30, 137.20, 136.81, 136.50, 135.10, 134.23, 133.83, 133.06, 128.02, 127.71, 127.60, 127.59, 127.05, 126.54, 126.48, 126.66 (dd, *J* = 6.8, 4.0 Hz), 126.40 (q, *J* = 288.6 Hz), 126.22 (q, *J* = 287.3 Hz), 125.85, 125.55, 125.50, 125.33, 124.90, 124.53, 119.94, 118.16, 85.09 (q, *J* = 27.9 Hz), 82.18 (q, *J* = 27.0 Hz), 49.10, 48.96, 47.05, 45.96, 44.72, 44.41, 43.94, 43.83, 43.74. ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.16 (brs). EI MS: m/z (I,%) 58 (78), 154 (21), 167 (20), 168 (59), 169 (27), 170 (23), 182 (43), 183 (29), 184 (50), 196 (28), 197 (32), 198 (43), 212 (57), 213 (35), 227 (24), 264 (21), 266 (28), 281 (44), 297 (100), 311 (55), 791 (9) [M$^+$]. IR (ν/cm^{-1}) (CCl_4): 2785, 2827, 2861, 2932, 2979, 3057, 3060, 3084 (CH). Found: C, 66.99; H, 5.77; N, 9.02. Calc. for $C_{44}H_{47}F_6N_5O_2$: C, 66.74; H, 5.98; N, 8.84.

*4.4. General method for interaction of **4a** with ketones **15***

To the solution of **4a** (0.47 mmol) in 10 mL dry Et_2O a solution of ketone **15**[18] (0.24 mmol) in 10 mL dry Et_2O was added dropwise at -20 °C under argon atmosphere and reaction mixture was stirred for 42h. The resulting suspension was treated with water (20 mL). Organic layer was separated, water layer was extracted with Et_2O (5 x 5mL), organic fractions were combined, solvent was evaporated to dryness. The residue was recrystallized from *n*-hexane to yield pure alcohols **16.**

*4.4.1. Bis(1,8-bis(dimethylamino)naphthalen-2-yl)(phenyl)methanol (**16a**)*

Yellow crystals; yield 64 mg (50%); Characterization data were consistent with those reported in the literature.[19]

*4.4.2. Bis(1,8-bis(dimethylamino)naphthalen-2-yl)(4-methoxyphenyl)methanol (**16b**)*

Yellow crystals; yield 30 mg (22%); mp 179-180 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.69 (s, 1H), 7.47 – 7.15 (m, 10H), 6.88 – 6.74 (m, 4H), 3.81 (s, 3H), 2.72 (s, 6H), 2.54 (s, 12H), 2.51 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.11, 152.51, 146.34, 144.40, 142.57, 136.78, 129.79, 129.01, 127.88, 125.19, 124.31, 123.46, 116.07, 112.72, 84.83, 55.20, 48.47, 45.58, 44.35. EI MS: m/z (I,%) 43 (23), 149 (21), 227 (20), 335 (100), 336 (24), 349 (28), 562 (17) [M^+]. IR (ν/cm^{-1}) (KBr): 3052, 2930, 2856, 2823, 2779 (CH). Found: C, 77.03; H, 7.28; N, 10.17. Calc. for $C_{36}H_{42}N_4O_2$: C, 76.84; H, 7.52; N, 9.96.

*4.4.3. Bis(1,8-bis(dimethylamino)naphthalen-2-yl)(pyridin-3-yl)methanol (**16c**)*

Dark yellow crystals; yield 35 mg (27%); mp 144-145 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.64 (s, 1H), 8.47 (d, *J* = 4.0 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.50 – 7.15 (m, 9H), 6.77 (d, *J* = 8.6 Hz, 2H), 2.68 (s, 6H), 2.54 (s, 18H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 152.52, 150.05, 147.55, 146.64, 145.65, 143.28, 136.88, 135.92, 128.40, 127.99, 125.54, 124.45, 124.07, 122.47, 116.50, 83.98, 47.93, 46.22, 44.37. EI MS: m/z (I,%) 29 (30), 31 (30), 32 (49), 42 (23), 43 (72), 44 (60), 45 (40), 58 (70), 61 (59), 168 (59), 169 (21), 170 (20), 182 (36), 183 (30), 184 (22), 197 (24), 212 (25), 213 (24), 227 (82), 228 (27), 241 (29), 306 (100), 307 (22), 320 (57), 533 (23) [M^+]. IR (ν/cm^{-1}) (KBr): 3050, 2928, 2861, 2825, 2779 (CH). Found: C, 76.75; H, 7.14; N, 13.36. Calc. for $C_{34}H_{39}N_5O$: C, 76.51; H, 7.37; N, 13.12.

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Supplementary Material

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