Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

© Wiley-VCH 2006

69451 Weinheim, Germany

General Preparation of Primary, Secondary and Tertiary Arylamines via the Oxidative Coupling of Polyfunctional Aryl and Heteroaryl Amidocuprates

Vicente del Amo, Srinivas Reddy Dubbaka, Arkady Krasovskiy and Paul Knochel*
Ludwig-Maximilians-Universität München,
Department Chemie und Biochemie
Butenandtstrasse 5-13, Haus F, 81377 München (Germany)
Fax: (+49) 089 2180 77680
e-mail: paul.knochel@cup.uni-muenchen.de

General All reactions were carried out under argon atmosphere in dried glassware. All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. $(i\text{-Pr})_2NH$ was distilled from CaH_2 under nitrogen atmosphere. Yields refer to isolated yields of compounds estimated to be > 95 % pure as determined by ^1H NMR and capillary GC.

Preparation of the reagent *i*-PrMgCl·LiCl:

Magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol) were placed in an argon-flushed flask, and THF (50 mL) was added. A solution of *i*-PrCl (100 mmol) in THF (50 mL) was slowly added at room temperature. The reaction starts within few minutes. After the addition was finished, the reaction mixture was stirred for 12 h at room temperature. The grey solution of *i*-PrMgCl·LiCl was cannulated to a different flask under argon and removed in this way from excess of magnesium. A yield of ca. 95-98% of *i*-PrMgCl·LiCl was obtained. The reagent was titrated prior to use by the method of Paquette,[1] or the method developed by our laboratory.[2]

Preparation of the reagent TMPMgCl·LiCl:

A dry and nitrogen-flushed 250 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated *i*-PrMgCl·LiCl (1.2 M in THF) (100 mL, 120 mmol). 2,2,6,6-Tetramethylpiperidine (TMPH) (19.8 g, 126 mmol, 1.05 equiv) was added dropwise at room temperature. The reaction mixture was stirred at room temperature until gas evolution was completed (ca. 24 h).[3]

Preparation of the reagent CuCl·2LiCl (1 M in THF):

A dry and argon-flushed 50 mL *Schlenk*-flask, equipped with a magnetic stirrer and a glass stopper, was charged with LiCl (1.7 g, 40 mmol) and heated up to 130 °C under high vacuum for 1 h. After cooling to room temperature under argon, CuCl (1.98 g, 20 mmol, 99.5% Cu) was added under inert atmosphere inside a glove-box. The *Schlenk*-flask was further heated to 130 °C for 5 h under high vacuum, cooled to room temperature, charged with freshly distilled THF (20 mL) under argon and wrapped in aluminium foil to protect it from light. The mixture was vigorously stirred until all solid goes in solution (ca. 6 h.). The reagent CuCl·2LiCl (1 M in THF) appears as a colourless or slightly yellow solution.

OPTIMIZATION OF THE REACTION CONDITIONS:

In preliminary experiments, we have reacted PhMgCl·LiCl with various copper(I) salts, followed by the addition of Et_2NLi (3 equiv) and any of the three representative quinones: 3,3',5, 5'-tetra-*tert*-butyldiphenoquinone (**A**), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and 2,3,5,6-tetrachloro-1,4-benzoquinone **1** (chloranil) (1.2 equiv, addition at -78 °C and 12 h at -40 °C); Table. The reaction was monitored by GC-analysis and the yield of $PhNEt_2$ was determined by the analysis of hydrolyzed reaction aliquots. 3,3',5,5'-Tetra-*tert*-butyldiphenoquinone (**A**) led to sluggish reactions especially by using CuCN·2LiCl (entry 1, Table 1). Better results were obtained with CuCl·2LiCl or $CuBr{\cdot}Me_2S$ (entries 2 and 3), but clearly a more reactive quinone had to be used. The addition of DDQ combined with CuCl·2LiCl led to a faster and more efficient reaction affording a GC-yield of 70% (entry 4). $CuBr{\cdot}Me_2S$ and CuI·LiCl led to lower yields (40-42%; entries 5 and 6). Finally, the best result was obtained with CuCl·2LiCl and chloranil (1.2 equiv) as oxidant leading to the formation of $PhNEt_2$ in 95% by GC-analysis.

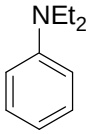
Table: Reaction of PhMgCl·LiCl (1 equiv) with various copper salts, addition of Et_2NLi (3 equiv) and oxidative amination with various quinones (1.2 equiv) leading to $PhNEt_2$.

Entry	Cu(I) salt	Quinone	Yield[%][a]
1	CuCN·2LiCl	**A**	9
2	CuCl·2LiCl	**A**	21
3	$CuBr{\cdot}Me_2S$	**A**	41

4	CuCl·2LiCl	DDQ	70
5	CuBr·Me_2S	DDQ	42
6	CuI·LiCl	DDQ	40
7	CuCl·2LiCl	**1**	95 [88][b] [84][c]

[a] GC-yields determined by the analysis of hydrolyzed reaction aliquots using tetradecane as an internal standard. Reaction conditions: Addition of the oxidant at -78 ^{o}C and then 12 h at -40 ^{o}C. [b] 10% vol. of NMP used as co-solvent. [c] isolated yield of analytical pure compound.

Synthesis of *N,N*-diethylaniline



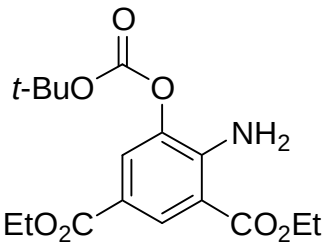
Prepared in preliminary experiments from PhMgCl·LiCl (1.22 M in THF; 0.82 mL, 1.0 mmol) and *N*-lithium-diethylamine (3.0 mmol, prepared by adding *n*-BuLi to diethylamine at -40 °C and stirring for 45 min). Flash chromatography (pentane/5 % CH_2Cl_2) afforded *N,N*-diethylamine (125 mg, 84 %) as a colourless oil. The ^{1}H NMR spectrum matches with that of the commercially available product.

^{1}H NMR (200 MHz, $CDCl_3$): *d* = 7.50-7.39 (m, 2 H, ArH), 6.92-6.84 (m, 3 H, ArH), 3.58-3.51 (m, 4 H, CH_2), 1.40-1.33 (m, 6 H, CH_3).

MS (EI^+): *m/z* (%) = 149 (100) $[M]^+$.

TYPICAL PROCEDURES:

Synthesis of 4-amino-5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester (7a) (TP1) (Scheme 1)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester **2a** (338 mg, 1.0 mmol) in dry THF (3 mL). After cooling to 0 °C, TMPMgCl·LiCl (1.20 M in THF; 0.92 mL, 1.1 mmol) was added dropwise and stirred for 1 h to afford the corresponding Grignard reagent (**3a**). This reagent was added dropwise to a solution of CuCl·2LiCl (1.0 M in THF; 1.2 mL, 1.2 mmol) and *bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (192 mg, 1.2 mmol) at -50 °C and the mixture was stirred for 45 min. To the resulting aryl cuprate (**5a**), LiHMDS (1.0 M in THF) (2.0 mL, 2.0 mmol) was added dropwise and the mixture was further stirred for 90 min at -50 °C. The reaction mixture was cooled to -78 °C, then chloranil (**1**) (295 mg, 1.2 mmol), in dry THF (7 mL), was added slowly over a period of 45 min. The reaction mixture was allowed to reach -50 °C and stirred for 12 h. Diethyl ether (10 mL) was poured to the crude reaction mixture and it was filtered through *Celite*, washed with Et_2O thoroughly (ca. 100 mL), and the liquors washed with 2 x 10 mL portions of NH_4OH (aq., 2.0 M) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. This crude material was redissolved in Et_2O (3 mL) before tetrabutylammonium fluoride (TBAF) (1.0 M in THF; 2 mL, 2 mmol) was added in one portion and the mixture was stirred at room temperature for 10 min, poured over EtOAc (10 mL) and washed with deionised water (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by flash chromatography (pentane/Et_2O; 4:1) afforded the title amine **7a** (254 mg, 72 %) as a white crystalline solid.

mp.: 87–88 °C.

IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) = 3260, 3070, 2981, 2936, 1715, 1680, 1538, 1451, 1394, 1366, 1331, 1318, 1288, 1218, 1187, 1154, 1111, 1063, 1021, 937, 891, 864, 795, 764, 700.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.58 (broad. s, 1H, N*H*), 9.95 (s, 1H, NH), 8.29 (d, ^4J(H,H) = 1.6 Hz, 1H, Ar*H*), 7.84 (d, ^4J(H,H) = 1.6 Hz, 1H, Ar*H*), 4.42 (q, ^3J(H,H) = 7.2 Hz,

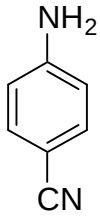
2H), 4.39 (q, ^3J(H,H) = 7.2 Hz, 4H, CH_2), 1.57 (s, 9H, C(CH_3)$_3$), 1.45 (t, ^3J(H,H) = 7.2 Hz, 3H, CH_3), 1.41 (t, ^3J(H,H) = 7.2 Hz, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = 168.1, 165.6, 156.1, 150.0, 133.1, 126.7, 129.9, 124.8, 119.0, 83.7, 62.2, 61.4, 28.4, 14.5, 14.4.

MS (70 eV, EI): *m/z* (%) = 353 (1), 297 (30), 279 (34), 253 (100), 233 (57), 207 (36), 179 (10), 150 (4), 59 (16), 57 (40), 41 (7).

HRMS (EI): *m/z* calc. for [$C_{17}H_{23}NO_7$] 353.1475, found: 353.1455.

Synthesis of 4-aminobenzonitrile (7b) (Table 1, entry 1) (TP2)

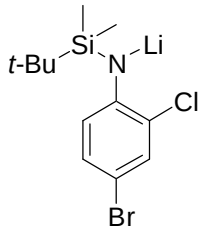


A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with *i*-PrMgCl·LiCl (1.39 M in THF; 0.79 mL, 1.1 mmol) and cooled to 0 ^oC. 4-Bromobenzonitrile (182 mg, 1.0 mmol) was added dropwise and the mixture was stirred at 0 °C for 2 h to afford the Grignard reagent **3b**. The I/Mg-exchange was completed after 2 h as determined by GC analysis of a reaction aliquot. This solution was cooled to -50 °C before CuCl·2LiCl (1.0 M in THF; 1.2 mL, 1.2 mmol) and *bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (192 mg, 1.2 mmol) were added dropwise and the mixture was stirred for 45 min. To the so formed aryl cuprate, LiHMDS (1.0 M in THF) (2.0 mL, 2.0 mmol) was added dropwise and the mixture was further stirred for 45 min at -50°C. The reaction mixture was cooled to -78 ^oC, then chloranil (**1**) (295 mg, 1.2 mmol), in dry THF (7 mL), was added slowly over a period of 45 min. The reaction mixture was allowed to reach -50 °C and stirred for 12 h. Diethyl ether (10 mL) was added to the crude reaction mixture and it was filtered through *Celite*, washed with Et_2O thoroughly, and the liquors washed with 2 x 10 mL portions of NH_4OH (aq., 2.0 M) and extracted with Et_2O. The organic solvent was evaporated and the crude material so obtained was redissolved in diethyl ether (3 mL) before HCl (5 mL, aq. 1.0 M) was added in one portion and the mixture was stirred for 15 min at room temperature. The mixture was neutralized with an aqueous NaOH solution, extracted with EtOAc (3 x 10 mL portions), the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated

under reduced pressure. Purification by flash chromatography (pentane/EtOAc; 7:3) afforded the title amine **3b** (102 mg, 86 %) as an off-white solid. The spectroscopic data matches with the literature.[4]

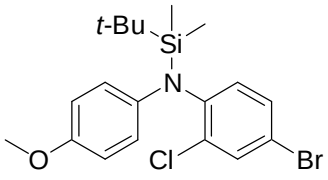
^{1}H NMR (200 MHz, $CDCl_3$): *d* = 7.42 (d, ^3J(H,H) = 8.8 Hz, 2H, Ar*H*), 6.65 (d, ^3J(H,H) = 8.8 Hz, 2H, Ar*H*), 4.12 (broad s, 2H, N*H*).

Preparation of the lithium silanamide 10a (TP3) (Scheme 2)



In a dry and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum, 2-chloro-4-bromoaniline **8a** (289 mg, 1.4 mmol) was dissolved in dry THF (1 mL) and cooled to -50 °C. MeLi (1.55 M in Et_2O; 1.0 mL, 1.55 mmol) was added dropwise and the mixture was stirred for 10 min. Then, TBDMSCl (274 mg, 1.82 mmol), dissolved in dry THF (1 mL), was added dropwise. The reaction mixture was allowed to reach room temperature and was further stirred for 30 min, then the solvent and volatiles were removed under high vacuum for 2 h. The residue was redissolved in dry THF (1 mL) and was again cooled to -50 °C. MeLi (1.55 M in Et_2O) (1.0 mL, 1.55 mmol) was added dropwise and the mixture was stirred for 10 min, affording the lithium silanamide **10a**.

Synthesis of the diaryl silanamine 12a (TP4) (Scheme 2)



A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum was charged with 4-iodoanisole **2d** (234 mg, 1.0 mmol). *i*-PrMgCl·LiCl (1.39 M in THF; 0.79 mL, 1.1 mmol) was added dropwise at room temperature and under argon atmosphere. The I/Mg-exchange was completed after 20 min as determined by GC analysis of a reaction aliquot. The

reaction mixture was then cooled to -50 °C before CuCl·2 LiCl (1.0 M in THF; 1.1 mL, 1.1 mmol) was added and the mixture was stirred for 30 min at -50 °C. The resulting cuprate **4d** was canulated under argon over a solution of the lithium silamide **10a** (1.4 mmol, prepared according to **TP3**) cooled to -50 °C. Freshly distilled and dried (*i*-Pr)$_2$NH (283 mg, 0.39 mL, 2.80 mmol) was added and the reaction mixture was stirred at -50 °C for 2 h. The reaction mixture was cooled to -78 °C, then chloranil (**1**) (295 mg, 1.2 mmol), in dry THF (7 mL), was added slowly over a period of 45 min. The reaction mixture was allowed to reach -50 °C and stirred for 12 h. Then it was allowed to reach room temperature and was further stirred for 10 min. Pentane (10 mL) was poured over the reaction crude which was vigorously stirred for 30 min before it was filtered through *Celite* and the liquors concentrated under reduced pressure. Flash chromatography (pentane/5 % CH_2Cl_2) afforded the title diaryl silanamide **12a** (308 mg, 72 %) as a colourless wax.

IR (neat): ?$_{max}$ (cm^{-1}) = 2928, 1504, 1464, 1235, 808.

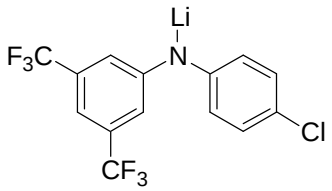
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.19 (s, 6 H, Si(C*H*$_3$)$_2$), 0.94 (s, 9 H, C(C*H*$_3$)$_3$), 3.76 (s, 3 H, OC*H*$_3$), 6.75 (dd, 2 H, *J* = 6.2, 2.6 Hz, Ar*H*), 6.94 (dd, 2 H, *J* = 7.0, 2.6 Hz, Ar*H*), 7.25 (d, 1 H, *J* = 8.8 Hz, Ar*H*), 7.38 (dd, 1 H, *J* = 8.8, 2.6 Hz, Ar*H*), 7.56 (d, 1 H, *J* = 1.8 Hz, Ar*H*).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = - 2.0 (Si(*C*H$_3$)$_2$), 20.3 (*C*(CH$_3$)$_3$), 27.8 (C(*C*H$_3$)$_3$), 55.7 (O*C*H$_3$), 114.2 (Ar*C*H), 119.2 (Ar*C*), 125.0 (Ar*C*H), 130.6 (Ar*C*H), 133.6 (Ar*C*H), 134.5 (Ar*C*H), 137.1 (Ar*C*), 141.9 (Ar*C*), 145.3 (Ar*C*), 155.0 (Ar*C*).

MS (EI$^+$): *m/z* (%) = 427 (25) [*M*]$^+$, 370 (51) [*M* – C(CH$_3$)$_3$]$^+$, 289 (100) [*M* – Br – C(CH$_3$)$_3$]$^+$, 274 (39) [*M* – Br – CH$_3$ – C(CH$_3$)$_3$]$^+$.

HRMS (EI)$^+$: *m/z* calcd. for [$C_{19}H_{25}Br(^{35}Cl)NOSi$] 425.0577, found 425.0601 (427.0572 found for [$C_{19}H_{25}Br(^{37}Cl)NOSi$]).

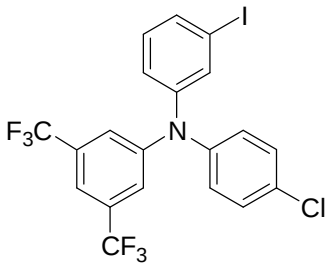
Preparation of the lithium diarylamide 14a (TP5) (Scheme 3)



A flame-dried and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum was charged with the diarylamine **13a** (340 mg, 1.0 mmol) dissolved in dry THF (1 mL). The solution was cooled to -40 °C. Then, LDA (freshly prepared from (*i*-Pr)$_2$NH, 202 mg, 0.28 mL, 2.0 mmol and 1.05 mmol of *n*-BuLi) was added dropwise under vigorous stirring. The

reaction mixture was stirred for 1 h at -40 °C to ensure quantitative formation of the lithium amide **14a**.

Synthesis of the triarylamine 16a, (TP6) (Scheme 3)



A dry and argon-flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum was charged with 1,3-diiodobenzene (**2n**; 462 mg, 1.4 mmol). *i*-PrMgCl·LiCl (1.39 M in THF; 1.11 mL, 1.54 mmol) was added dropwise at 0 °C and under argon. The I/Mg-exchange was completed after 15 min as determined by GC analysis of a reaction aliquot. The reaction mixture was then cooled to -40 °C before CuCl·2LiCl (1.0 M in THF; 1.55 mL, 1.55 mmol) was added and the mixture was stirred for 30 min at –40 °C. The resulting cuprate **4n** was canulated under argon to a solution of the lithium diarylamide **14a** (prepared according to **TP5**) (1.0 mmol) and cooled to -78 °C. The reaction mixture was stirred for 2 h at -78 °C before chloranil (**1**, 332 mg, 1.35 mmol), dissolved in dry THF (8 mL), was added dropwise over a period of 45 min. When the addition was completed the reaction mixture was allowed to reach -40 °C and was stirred for 12 h before it was allowed to reach room temperature and was further stirred for 10 min. Diethyl ether (10 mL) was poured over the reaction mixture before it was filtered trough *Celite*, washed abundantly with diethyl ether and the liquors were washed with 2 x 10 mL portions of 1M NH_4OH (aq.). The organic layer was concentrated under reduced pressure and was purified by flash chromatography (pentane/5 % CH_2Cl_2) affording the title compound **16a** (382 mg, 71 %) as a brownish wax.

IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) = 3056, 1580, 1489, 1466, 1374, 1274, 1128, 770, 682.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.05 (m, 2 H, Ar*H*), 7.12 (t, 2 H, *J* = 7.7 Hz, Ar*H*), 7.37 (s, 1 H, Ar*H*), 7.49 (d, 2 H, *J* = 7.9 Hz, Ar*H*), 7.70 (d, 2 H, *J* = 7.9 Hz, Ar*H*), 7.89 (t, 2 H, *J* = 1.5 Hz, Ar*H*).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 95.2, 115.8, 121.7, 124.3, 124.4, 126.7, 126.9, 130.6, 130.8, 131.0, 131.7, 133.1, 133.3, 134.0, 134.4, 136.4, 137.1, 142.2, 144.6, 147.5, 148.8.

MS (EI^+): *m/z* (%) = 541 (100) $[M]^+$, 413 (11) $[M - I]^+$, 379 (28) $[M - Cl - I]^+$.

HRMS (EI)$^+$: *m/z* calcd. for [$C_{20}H_{11}N(^{35}Cl)F_6I$] 540.9529, found 540.9533 (542.9499 found for [$C_{20}H_{11}N(^{37}Cl)F_6I$]).

Typical procedure for the preparation of tolylazo sulfones (TP7a)

A 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged with the corresponding aniline derivative (10.0 mmol) suspended in aq. HBF_4 solution (50 % w/w in water; 15 mL) . The suspension was cooled to 0 °C, then a solution of $NaNO_2$ (760 mg, 11.0 mmol) in water (5 mL) was added dropwise and under vigorous stirring. After 30 min of stirring the reaction mixture was warmed to room temperature and was stirred for an additional hour. The bulk precipitate formed was filtered off, washed thoroughly with aq. HBF_4 solution and suspended in CH_2Cl_2 (20 mL). Sodium *p*-toluenesulfinate (2.14 g, 12.0 mmol) was added solid in small portions and the reaction mixture was stirred overnight at room temperature before it was filtered and the liquors concentrated under reduced pressure to afford a dark orange solid. Crystallisation from EtOH yielded the desired arylazo sulfone.

Typical procedure for the preparation of tolylazo sulfones (TP7b)

A 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged with the corresponding aniline derivative (10.0 mmol) suspended in aq. HBF_4 solution (50 % w/w in water; 15 mL). The suspension was cooled to 0 °C, then a solution of $NaNO_2$ (760 mg, 11.0 mmol) in water (5 mL) was added dropwise and under vigorous stirring. After 30 min. of stirring the reaction mixture was warmed to room temperature and was stirred for an additional hour, before of CH_2Cl_2 (20 mL) was added. Sodium *p*-toluenesulfinate (2.14 g, 12.0 mmol) was added solid in small portions and the reaction mixture was stirred overnight at room temperature. The organic layer was washed with water (3 x 15 mL portions), dried ($MgSO_4$), filtered, and the solvent evacuated in vacuum to afford a dark orange solid. Crystallisation from EtOH yielded the desired arylazo sulfone.

Typical procedure for the preparation of diarylamines using arylazosulfones (TP8)

A dry and argon-flushed 25 mL round-bottomed flask equipped with a magnetic stirrer and a septum was charged with the corresponding bromo- or iodoarene (1.10 mmol), which was treated with *i*-PrMgCl·LiCl (1.15 mmol) for halogen/Mg-exchange. The exchange reaction

was checked by GC analysis of reaction aliquots until completion. Once the Grignard reagent was formed, the arylazo sulfone (1.0 mmol, prepared according to **TP7a** or **TP7b**), dissolved in dry THF (3 mL), was added dropwise to the Grignard reagent. After 1 h of stirring at -20 °C, the reaction mixture was treated with allyl iodide (504 mg, 0.27 mL, 3.0 mmol) and stirred for 12 h at room temperature. The solvents were removed under reduced pressure and the residue redissolved in glacial acetic acid (10 mL) and TFA (5 mL) before Zn powder (981 mg, 15 mmol) was added and the reaction mixture was heated to 75 °C for 10 h. The reaction mixture was allowed to cool to room temperature, was diluted in Et_2O (30 mL) and washed with 2M aq. NaOH until neutal pH and then with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. Flash chromatography on silica gel afforded the desired diarylamines.

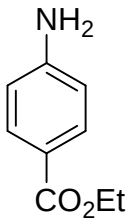
Typical procedure for the Boc-protection of polyfunctional phenols (TP9):[6]

A dry 100 mL-round-bottomed flask, equipped with a magnetic stirrer, was charged with a solution of the corresponding ArOH (15 mmol) in dry CH_2Cl_2 (50 mL). After cooling to 0 °C, DMAP (92 mg, 0.75 mmol) and Boc_2O (3.93 g, 18 mmol) were added and the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 (3 x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure. Purification by flash chromatography afforded the desired products.

EXPERIMENTAL SECTION

In this Experimental Section the compounds are ordered from top to bottom according to the entry number they received in Table 1 (manuscript). Then, compounds appearing in Scheme1 and Scheme 4 (manuscript) are listed and finally other compounds which were prepared as starting materials.

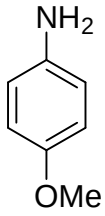
Synthesis of ethyl 4-aminobenzoate (7c) (Table 1, entry 2)



Prepared according to **TP2** from ethyl 4-iodobenzoate (276 mg, 1.0 mmol) [I/Mg-exchange conditions: *i*-PrMgCl·LiCl at T = -20 °C for 20 min] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/EtOAc; 6:4) yielded **7c** (139 mg, 84 %) as a white crystalline solid. The spectroscopic data matches with the literature.[5]

^{1}H NMR (200 MHz, $CDCl_3$): *d* = 7.86 (d, ^3J(H,H) = 8.5 Hz, 2 H, Ar*H*), 6.63 (d, ^3J(H,H) = 8.5 Hz, 2 H, Ar*H*), 4.29 (q, ^3J(H,H) = 7.0 Hz, 2 H, CH_2), 4.07 (broad s, 2 H, N*H*), 1.36 (t, ^3J(H,H) = 7.0 Hz, 3 H, CH_3).

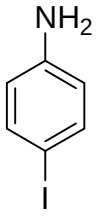
Synthesis of 4-methoxyphenylamine (7d) (Table 1, entry 3)



Prepared according to **TP2** from 4-iodoanisole (234 mg, 1.0 mmol) [I/Mg-exchange conditions: *i*-PrMgCl·LiCl at room temperature for 20 min] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/EtOAc; 7:3) yielded **7d** (108 mg, 88 %) as a dark solid. The spectroscopic data matches with the literature.[4,5]

^{1}H NMR (200 MHz, $CDCl_3$): *d* = 6.74 (d, ^3J(H,H) = 8.8 Hz, 2 H, Ar*H*), 6.66 (d, ^3J(H,H) = 8.8 Hz, 2 H, Ar*H*), 3.75 (s, 3H, CH_3), 3.42 (broad s, 2 H, N*H*).

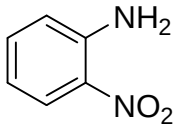
Synthesis of 4-iodophenylamine (7e) (Table 1, entry 4)



Prepared according to **TP2** from 1,4-diiodobenzene (330 mg, 1.0 mmol) [I/Mg-exchange conditions: *i*-PrMgCl·LiCl at T = 0 °C for 15 min] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/Et_2O; 1:1) yielded **7e** (131 mg, 60 %) as white needles. The ^{1}H NMR spectrum matches with that of the commercially available product.

^{1}H NMR (200 MHz, $CDCl_3$): *d* = 7.40 (d, ^3J(H,H) = 8.5 Hz, 2 H, Ar*H*), 6.45 (d, ^3J(H,H) = 8.5 Hz, 2 H, Ar*H*), 3.67 (broad s, 2 H, N*H*).

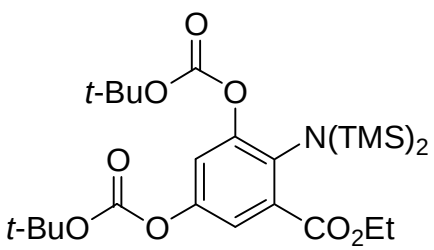
Synthesis of 2-nitrophenylamine (7f) (Table 1, entry 5)



Prepared according to **TP2** from 2-iodonitrobenzene (249 mg, 1.0 mmol) [I/Mg-exchange conditions: PhMgCl at T = -40 °C for 20 min] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/EtOAc; 7:3) yielded **7f** (84 mg, 61 %) as a brown crystalline solid. The ^{1}H NMR spectrum matches with that of the commercially available product.

^{1}H NMR (200 MHz, $CDCl_3$): *d* = 8.10 (dd, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 1.5 Hz, 1 H, Ar*H*), 7.36 (dt, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 1.5 Hz, 1 H, Ar*H*), 6.81 (dd, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 1.5 Hz, 1 H, Ar*H*), 6.71 (dt, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 1.5 Hz, 1 H, Ar*H*), 6.05 (broad s, 2 H, N*H*).

Synthesis of ethyl 3,5-bis-*tert*-butoxycarbonyloxy-2-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-benzoate (6b) (Table 1, entry 6)



Prepared according to **TP1** from ethyl 3,5-bis-*tert*-butoxycarbonyloxy-benzoate (382 mg, 1.0 mmol) [reaction conditions: deprotonation with TMPMgCl·LiCl at T = 0 °C for 3 h] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/Et_2O/Et_3N; 9:1:0.05) yielded the silyl-protected amine **6b** (423 mg, 78 %) as a colourless oil.

IR (neat): ?$_{max}$ (cm^{-1}) = 2980, 2950, 2904, 1758, 1732, 1458, 1395, 1458, 1395, 1370, 1318, 1242, 1228, 1150, 1125, 1060, 1030, 930, 906, 841, 825, 778, 757, 685, 622.

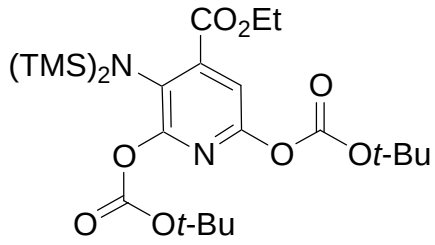
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 7.29 (d, ^4J(H,H) = 2.9 Hz, 1 H, Ar*H*), 7.23 (d, ^4J(H,H) = 2.9 Hz, 1 H, Ar*H*), 4.31 (q, ^3J(H,H) = 7.2 Hz, 2 H, CH_2), 1.53 (s, 9 H, C(CH_3)$_3$), 1.52 (s, 9 H, C(CH_3)$_3$), 1.34 (t, ^3J(H,H) = 7.2 Hz, 3 H, CH_2CH_3), 0.05 (s, 18 H, 2 x Si(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = 166.3, 151.2, 150.9, 149.6, 145.9, 137.8, 133.9, 119.1, 118.3, 83.7, 83.4, 60.9, 27.7, 14.3, 1.7.

MS (70 eV, EI) *m/z* (%) = 543 526 (5), 496 (34), 486 (1), 470 (100), 414 (23), 370 (40), 298 (10), 238 (7), 73 (10), 57 (12).

HRMS (ES): calc. for [$C_{25}H_{44}NO_8(^{28}Si)_2$] 542.2605 [M + H]$^+$, found 542.2587.

Synthesis of 4,6-bis-*tert*-butoxycarbonyloxy-3-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-pyridine-2-carboxylic acid ethyl ester (6c) (Table 1, entry 7)



Prepared according to **TP1** from 4,6-bis-*tert*-butoxycarbonyloxy-pyridine-2-carboxylic acid ethyl ester (383 mg, 1.0 mmol) [reaction conditions: deprotonation with TMPMgCl·LiCl at T = 0 °C for 1 h] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/Et_2O/Et_3N; 10:1:0.05) yielded **6c** (390 mg, 72 %) as a yellow oil.

IR (neat): ?$_{max}$ (cm^{-1}) = 2981, 1765, 1738, 1598, 1445, 1395, 1370, 1243, 1222, 1203, 1148, 1120, 1073, 1028, 904, 841, 824, 730, 686, 648.

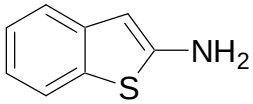
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 7.18 (s, 1 H, Ar*H*), 4.34 (q, ^3J(H,H) = 7.1 Hz, 2 H, CH_2), 1.53 (s, 18 H, 2 x C(CH_3)$_3$), 1.37 (t, ^3J(H,H) = 7.1 Hz, 3 H, CH_2CH_3), 0.08 (s, 18 H, 2 x Si(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = 165.2, 155.2, 150.9, 150.5, 149.5, 145.2, 132.9, 112.7, 84.2, 83.9, 61.7, 27.6 (2 x C(CH_3)$_2$), 14.2, 1.8.

MS (70 eV, EI) *m/z* (%) = 342 (25) [M – 2 x Boc]$^+$, 327 (93), 283 (10), 181 (8), 147 (8), 73 (60), 57 (100).

HRMS (EI): calcd. for [$C_{18}H_{26}N_2O_8$] [*M* – ($Si(CH_3)_3$)$_2$]$^+$ 398.1689, found 398.1653.

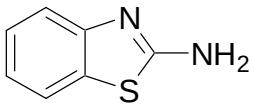
Synthesis of 2-amino benzo[b]thiophene (7g) (Table 1, entry 8)



Prepared according to **TP1** from benzo[b]thiophene (134 mg, 1.0 mmol) [reaction conditions: deprotonation with TMPMg·LiCl at T = 25 °C for 24 h][3] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/Et_2O; 8.5:1.5) yielded **7g** (103 mg, 69 %) as a white solid. The spectroscopic data matches with the literature.[6]

^{1}H NMR (200 MHz, $CDCl_3$): *d* = 7.57 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.4 Hz, 1 H, Ar*H*), 7.43 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.4 Hz, 1 H, Ar*H*), 7.23 (dt, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.4 Hz, 1 H, Ar*H*), 7.09 (dt, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.4 Hz, 1 H, Ar*H*), 6.28 (s, 1 H, Ar*H*), 4.05 (broad. s, 2 H, N*H*).

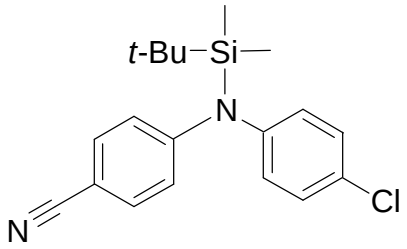
Synthesis of 2-aminobenzothiazole (7h) (Table 1, entry 9)



Prepared according to **TP1** from benzothiazole (135 mg, 1.0 mmol) [reaction conditions: deprotonation with TMPMgCl·LiCl at T = 0 ^{o}C for 0.1 h][3] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/EtOAc; 4:6) yielded **7h** as a pale brown solid (120 mg, 80 %). The spectroscopic data matches with that of the commercially available product.

^{1}H NMR (200 MHz, $CDCl_3$): *d* = 7.57 (td, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.4 Hz, 2 H, Ar*H*), 7.31 (td, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.4 Hz, 1 H, Ar*H*), 7.13 (td, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.4 Hz, 1 H, Ar*H*), 5.49 (broad s, 2 H, N*H*).

Synthesis of 4-[(*tert*-butyl-dimethyl-silanyl)-(4-chlorophenyl)-amino]-benzonitrile (12b) (Table 1, entry 10)



Prepared according to **TP4** from bromobenzonitrile (182 mg, 1.0 mmol) [Br/Mg-exchange conditions: *i*-PrMgCl·LiCl at T = 0 °C for 2h] and 4-chloroaniline (179 mg, 1.4 mmol). Flash chromatographical purification (pentane) afforded the title compound **12b** (222 mg, 65 %) as a pale yellow oil.

IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) = 2950, 2925, 2858, 2217, 1605, 1584, 1507, 1486, 1278, 1173, 1090, 1013, 956, 928, 835, 806, 778, 713.

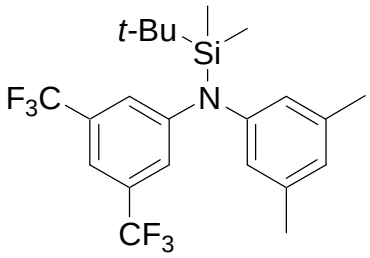
^{1}H NMR (600 MHz, $CDCl_3$): *d* = 7.36 (t, ^3J(H,H) = 8.5 Hz, 4 H, Ar*H*), 7.00 (d, ^3J(H,H) = 8.5 Hz, 2 H, Ar*H*), 6.71 (d, ^3J(H,H) = 8.5 Hz, 2 H, Ar*H*), 1.00 (s, 9 H, C(CH_3)$_3$), 0.20 (s, 6 H, 2 x CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): *d* = 154.7, 144.6, 132.8, 131.5, 129.9, 127.3, 119.7, 119.5, 101.6, 27.9, 20.6, -1.7.

MS (70 eV, EI): *m/z* (%) = 342 (9) $[M]^+$, 287 (38), 285 (100), 250 (36), 235 (5), 73 (6).

HRMS (EI): *m/z* calc. for [$C_{19}H_{23}N_2$(^{35}Cl)(^{28}Si)] 342.1319, found: 342.1291.

Synthesis of (3,5-bis-trifluoromethyl-phenyl)-(*tert*-butyl-dimethyl-silanyl)-(3,5-dimethyl-phenyl)-amine (12c) (Table 1, entry 11)



Prepared according to **TP4** from 1-bromo-3,5-bis-trifluoromethyl-benzene (293 mg, 1.0 mmol) [Br/Mg-exchange conditions: *i*-PrMgCl·LiCl at T = 0 °C for 15 min] and 3,5-dimethyl

aniline (169 mg, 1.4 mmol). Flash chromatographical purification (pentane) afforded the title compound **12c** (313 mg, 70 %) as a white solid.

mp.: 108.4-110.8 ^{o}C.

IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) = 2961, 2932, 2863, 1607, 1593, 1472, 1373, 1276, 1170, 1131, 1033, 998, 987, 827, 786, 702, 682.

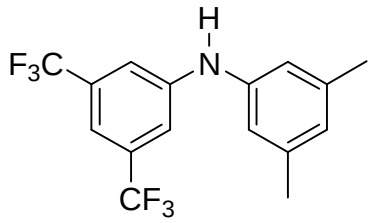
^{1}H NMR (600 MHz, $CDCl_3$): *d* = 7.23 (broad s, 1 H, Ar*H*), 7.13 (broad s, 2 H, Ar*H*), 6.89 (broad s, 1 H, Ar*H*), 6.68 (broad s, 2 H, Ar*H*), 2.31 (s, 6 H, 2 x CH_3), 1.01 (s, 9 H, C(CH_3)$_3$), 0.20 (s, 6 H, 2 x CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): *d* = 152.2, 145.5, 139.4, 131.5 (q, ^{4}J(C,F) = 33 Hz), 127.9, 127.4, 123.7 (q, ^{2}J(C,F) = 272 Hz), 119.2, 112.0, 27.9, 21.3, 20.6, -1.9.

MS (70 eV, EI): *m/z* (%) = 447 (9) [*M*]$^{+}$, 390 (100),360 (4), 294 (2), 73 (2).

HRMS (EI): *m/z* calcd. for [$C_{22}H_{27}F_6NSi$] 447.1817, found 447.1804.

Synthesis of (3,5-bis-trifluoromethyl-phenyl)-(3,5-dimethyl-phenyl)-amine



Prepared from silyl-protected amine **12c** (223 mg, 0.5 mmol) upon treatment with an excess of TBAF in 3 mL of THF at room temperature for 15 min. Flash chromatographical purification (pentane/Et_2O; 9:1) afforded the title compound (159 mg, 96 %) as a white solid.

mp.: 99–101 ^{o}C.

IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) = 3390, 2923, 1620, 1590, 1516, 1471, 1407, 1377, 1273, 1172, 1161, 1124, 1106, 1095, 1032, 998, 965, 928, 887, 879, 862, 845, 724, 699, 682, 673, 624, 607.

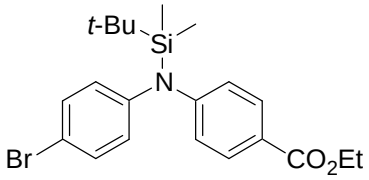
^{1}H NMR (600 MHz, $CDCl_3$): *d* = 7.34 (s, 2 H, Ar*H*), 7.30 (s, 1 H, Ar*H*), 6.77 (s, 3 H, Ar*H*), 5.89 (broad s, 1 H, N*H*), 2.32 (s, 6 H, 2 x CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): *d* = 145.6, 140.2, 139.6, 132.6 (q, ^{4}J(C,F) = 33 Hz), 125.7, 123.5 (q, ^{2}J(C,F) = 273 Hz), 118.3, 115.1, 112.7, 21.3.

MS (70 eV, EI): *m/z* (%) = 333 (100) [*M*]$^{+}$, 248 (3), 213 (1), 105 (2), 77 (2).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{13}F_6N$**]** 333.0952, found: 333.0953.

Synthesis of ethyl 4-[(4-bromophenyl)[(1,1-dimethylethyl)dimethylsilyl]amino]-benzoate (12d) (Table 1, entry 12)



Prepared according to **TP4** from 1,4-dibromobenzene (236 mg, 1.0 mmol) [Br/Mg-exchange conditions: *i*-PrMgCl·LiCl at room temperature for 3 h] and ethyl 4-aminobenzoate (231 mg, 1.4 mmol). Flash chromatographical purification (pentane/CH_2Cl_2; 4:1) afforded the title compound **12d** (304 mg, 70 %) as a pale yellow soild.

mp.: 103-105 °C

IR (neat): *?*$_{max}$ (cm^{-1}) = 3088, 2955, 2894, 2856, 1691, 1602, 1265, 1105, 805, 772.

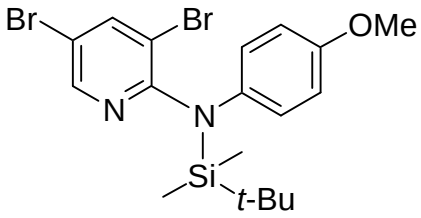
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.21 (s, 6 H, Si(C*H*$_3$)$_2$), 0.99 (s, 9 H, C(C*H*$_3$)$_3$), 1.35 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 4.31 (q, 2 H, *J* = 7.1 Hz, CH_2CH_3), 6.77 (d, 2 H, *J* = 8.8 Hz, Ar*H*), 6.93 (d, 2 H, *J* = 8.8 Hz, Ar*H*), 7.50 (d, 2 H, *J* = 8.8 Hz, Ar*H*), 7.83 (d, 2 H, *J* = 8.8 Hz, Ar*H*).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = -1.3 (Si(CH_3)$_2$), 14.7 (CH_2CH_3), 20.9 ($C(CH_3)_3$), 28.3 ($C(CH_3)_3$), 60.8 (CH_2CH_3), 118.9 (Ar*C*), 120.8 (Ar*C*H), 122.3 (Ar*C*), 130.8 (Ar*C*H), 131.4 (Ar*C*H), 132.9 (Ar*C*H), 146.7 (Ar*C*), 155.0 (Ar*C*), 166.8 (CO_2).

MS (70 eV, EI): *m/z* (%) = 435 (11) [*M*]$^+$, 378 (100), 305 (23), 297 (32).

HRMS (EI): *m/z* calc. for [$C_{21}H_{28}BrNO_2Si$] 433.1073, found 433.1071.

Synthesis of (*tert*-butyl-dimethyl-silanyl)-(3,5-dibromo-pyridin-2-yl)-(4-methoxy-phenyl)-amine (12e) (Table 1, entry 13)



Prepared according to **TP4** from 3,5-dibromopyridine (236 mg, 1.0 mmol) [reaction conditions: deprotonation with TMPMgCl·LiCl in Et_2O at T = -30 ^{o}C for 2 h] and 4-methoxy aniline (172 mg, 1.4 mmol). Purification by flash chromatography (pentane/Et_2O; 15:1) yielded **12e** as a dark oil (282 mg, 60 %).

IR (neat): ?$_{max}$ (cm^{-1}) = 2953, 2928, 2854, 1561, 1504, `464, 1421, 1365, 1285, 1243, 1209, 1179, 1147, 1105, 1034, 1024, 945, 907, 892, 837, 822, 810, 792, 778, 742, 714, 677, 649.

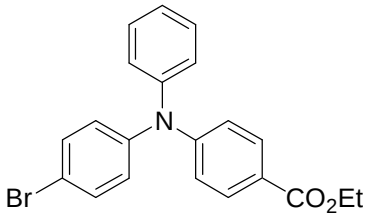
^{1}H NMR (600 MHz, $CDCl_3$): *d* = 8.26 (d, ^4J(H,H) = 2.2 Hz, 1 H, Ar*H*), 7.81 (d, ^4J(H,H) = 2.2 Hz, 1 H, Ar*H*), 6.96 (d, ^3J(H,H) = 8.8 Hz, 2 H, Ar*H*), 6.76 (d, ^3J(H,H) = 8.8 Hz, 2 H, Ar*H*), 3.78 (s, 3 H, OCH_3), 0.92 (s, 9 H, C(CH_3)$_3$), 0.17 (s, 6 H, 2 x CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): *d* = 157.2, 156.7, 146.5, 145.2, 139.0, 129.6, 115.1, 113.8, 112.5, 55.6, 28.2, 20.1, -1.5.

MS (70 eV, EI): *m/z* (%) = 472(12) [*M*]$^+$, 415 (100), 413 (51), 336 (11), 319 (7), 137 (5), 73 (16).

HRMS (EI): *m/z* calcd. for [$C_{18}H_{24}N_2(^{79}Br_2)OSi$] 470.0025, found 470.0026.

Synthesis of ethyl 4-[(4-bromophenyl)phenylamino]-benzoate (16b) (Table 1, entry 14)



Prepared according to **TP6** from *N*-lithium-ethyl-4-[(4-bromophenyl)amino]-benzoate **14b** (1.0 mmol, prepared as in **TP5**) and PhMgCl (1.79 M in THF; 0.78 mL, 1.4 mmol). Purification by flash chromatography (pentane/CH_2Cl_2; 4:1) yielded triarylamine **16b** (249 mg, 63 %) as a dark wax.

IR (neat): ?$_{max}$ (cm^{-1}) = 2693, 1705, 1590, 1485, 1258, 1171, 1097, 816, 694.

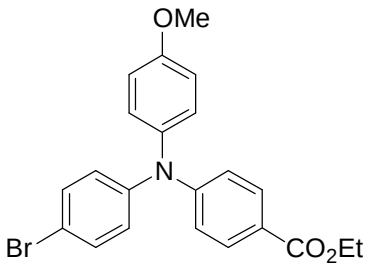
^{1}H NMR (600 MHz, $CDCl_3$): *d* = 1.37 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 4.35 (q, 2 H, *J* = 7.2 Hz, CH_2CH_3), 7.00 (dd, 4 H, *J* = 9.1, 2.9 Hz, Ar*H*), 7.11-7.15 (m, 3 H, Ar*H*), 7.31 (t, 2 H, *J* = 8.6 Hz, Ar*H*), 7.39 (dt, 2 H, *J* = 9.1, 2.9 Hz, Ar*H*), 7.88 (dt, 2 H, *J* = 9.1, 2.4 Hz, Ar*H*).

^{13}C NMR (150 MHz, $CDCl_3$): *d* = 14.6 (CH_2CH_3), 60.8 (CH_2CH_3), 117.0 (Ar*C*), 120.9 (Ar*C*H), 123.6 (Ar*C*), 124.9 (Ar*C*H), 126.0 (Ar*C*H), 127.0 (Ar*C*H), 129.9 (Ar*C*H), 131.1 (Ar*C*H), 132.8 (Ar*C*H), 146.2 (Ar*C*), 146.6 (Ar*C*), 151.7 (Ar*C*), 166.5 (CO_2).

MS (EI$^+$): *m/z* (%) = 395 (100) [*M*]$^+$, 367 (26) [*M* - CH_2CH_3]$^+$, 350 (18) [*M* – OEt]$^+$, 322 (6) [*M* – CO_2Et]$^+$, 287 (10) [*M* – Br – CH_2CH_3]$^+$, 242 (37) [*M* – Br – CO_2Et]$^+$.

HRMS (EI): *m/z* calcd. for [$C_{21}H_{18}BrNO_2$] 395.0521, found 395.0539.

Synthesis of ethyl 4-[4-bromo(4-methoxyphenyl)anilino]-benzoate (16c) (Table 1, entry 15)



Prepared according to **TP6** from *N*-lithium-ethyl-4-[(4-bromophenyl)amino]-benzoate **14b** (1.0 mmol, prepared as in **TP5**) and 4-iodoanisole (328 mg, 1.4 mmol) [I/Mg-exchange conditions: *i*-PrMgCl·LiCl at room temperature for 20 min]. Purification by flash chromatography (pentane/CH_2Cl_2; 2:1) afforded triarylamine **16c** (246 mg, 58 %) as a yellow wax.

IR (neat): ?$_{max}$ (cm^{-1}) = 2956, 2929, 1705, 1601, 1505, 1484, 1266, 1240, 1101, 825, 767, 698.

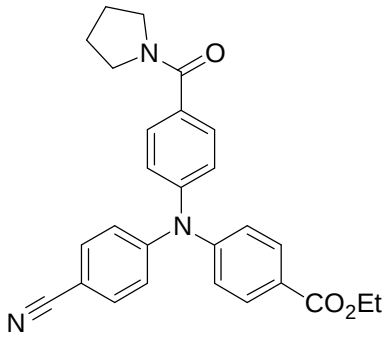
^{1}H NMR (600 MHz, $CDCl_3$): *d* = 1.36 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 3.81 (s, 3 H, OCH_3), 4.33 (q, 2 H, *J* = 7.1 Hz, CH_2CH_3), 6.88 (dd, 2 H, *J* = 6.6, 2.2 Hz, Ar*H*), 6.93 (dd, 2 H, *J* = 7.1, 2.2 Hz, Ar*H*), 6.99 (dd, 2 H, *J* = 6.6, 2.2 Hz, Ar*H*), 7.07 (dd, 2 H, *J* = 6.6, 2.2 Hz, Ar*H*), 7.37 (dd, 2 H, *J* = 6.6, 2.2 Hz, Ar*H*), 7.85 (dd, 2 H, *J* = 7.1, 1.8 Hz, Ar*H*).

^{13}C NMR (150 MHz, $CDCl_3$): *d* = 14.6 (CH_2CH_3), 55.7 (OCH_3), 60.8 (CH_2), 115.4 (Ar*C*H), 116.5 (Ar*C*), 119.7 (Ar*C*H), 122.8 (Ar*C*), 126.3 (Ar*C*H), 128.3 (Ar*C*H), 131.1 (Ar*C*H), 132.6 (Ar*C*H), 139.3 (Ar*C*), 146.2 (Ar*C*), 151.9 (Ar*C*), 157.5 (Ar*C*), 166.6 (CO_2).

MS (EI$^+$): *m/z* (%) = 427 (100) $[M]^+$, 410 (20) $[M - CH_3]^+$, 397 (6) $[M - CH_2CH_3]^+$, 382 (28) $[M - OEt]^+$.

HRMS (EI)$^+$: *m/z* calcd. for $[C_{22}H_{20}Br\ NO_3]$ 425.0627, found 425.0629.

Synthesis of 4-{4-cyano[4-(1-pyrrolidinylcarbonyl)phenyl]anilino}ethyl benzoate (16d) (Table 1, entry 16)



Prepared according to **TP6** from *N*-lithium-4-(4-cyanoanilino)ethyl benzoate **14c** (1.0 mmol, prepared as in **TP5**) and 1-(4-iodobenzoyl)-pyrrolidine (422 mg, 1.4 mmol) [I/Mg-exchange conditions: *i*-PrMgCl·LiCl at -30 °C for 45 min]. Flash chromatographical purification (pentane/EtOAc; 3:1) afforded triarylamine **16d** (250 mg, 57 %) as a greyish solid.

mp.: 163-165 °C.

IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) = 2927, 2876, 2218, 1710, 1614, 1590, 1496, 1424, 1264, 1174, 1099, 841.

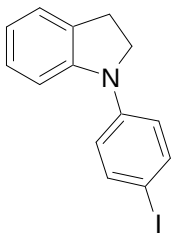
^{1}H NMR (400 MHz, $CDCl_3$): *d* = 1.37 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.86-2.00 (m, 4 H, 2 x CH_2), 3.49 (t, 2 H, *J* = 6.4 Hz, CH_2), 3.64 (t, 2 H, *J* = 6.6 Hz, CH_2), 4.36 (q, 2 H, *J* = 7.1 Hz, CH_2CH_3), 7.07-7.14 (m, 6 H, Ar*H*), 7.48-7.53 (m, 4 H, Ar*H*), 7.96 (dt, 2 H, *J* = 9.2, 2.1 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): *d* = 14.6 (CH_3), 24.6 (CH_2), 26.7 (CH_2), 46.6 (CH_2), 49.9 (CH_2), 61.2 (CH_2CH_3), 105.7 (Ar*C*), 119.2 (*C*N), 122.9 (Ar*C*H), 124.1 (Ar*C*H), 125.5 (Ar*C*H), 126.4 (Ar*C*), 129.3 (Ar*C*H), 131.5 (Ar*C*H), 133.7 (Ar*C*H), 134.2 (Ar*C*), 147.2 (Ar*C*), 150.1 (Ar*C*), 150.7 (Ar*C*), 166.1 (CO_2), 168.9 (*C*(O)N).

MS (EI^+): *m/z* (%) = 439 (56) $[M]^+$, 369 (100) $[M - N(CH_2)_4]^+$, 341 (14) $[M - C(O)N(CH_2)_4]^+$.

HRMS $(EI)^+$: *m/z* calcd. for $[C_{27}H_{25}N_3O_3]$ 439.1896, found 439.1909.

Synthesis of 2,3-dihydro-1-(4-iodophenyl)- 1*H*-indole (16e) (Table 1, entry 17)



Prepared according to **TP6** from *N*-lithium-indoline **14d** (1.0 mmol, prepared as in **TP5**) and 1,4-diiodobenzene (462 mg, 1.4 mmol) [I/Mg exchange conditions: *i*-PrMgCl·LiCl at T = 0 °C for 15 min]. Purification by flash chromatography (pentane/ 5 % CH_2Cl_2) afforded **16e** (212 mg, 66 %) as a yellow oil.

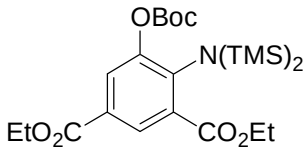
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 3.13 (t, 2 H, *J* = 8.7 Hz, C*H*$_2$), 3.92 (t, 2 H, *J* = 8.5 Hz, C*H*$_2$), 7.00 (dd, 2 H, *J* = 6.9, 2.0 Hz, Ar*H*), 7.08-7.12 (m, 3 H, Ar*H*), 7.16-7.19 (m, 1 H, Ar*H*), 7.60 (dd, 2 H, *J* = 6.9, 2.2 Hz, Ar*H*)

^{13}C NMR (150 MHz, $CDCl_3$): *d* = 28.3 (*C*H$_2$), 52.2 (*C*H$_2$), 82.6 (Ar*C*), 108.6 (Ar*C*H), 119.6 (Ar*C*H), 119.7 (Ar*C*H), 125.4 (Ar*C*H), 127.3 (Ar*C*H), 131.6 (Ar*C*), 138.1 (Ar*C*H), 144.4 (Ar*C*), 146.5 (Ar*C*)

MS (EI$^+$): *m/z* (%) = 321 (100) [*M*]$^+$, 193 (32) [*M* – I – H]$^+$.

HRMS (EI)$^+$: *m/z* calcd. for [$C_{14}H_{12}IN$] 321.1563, found 321.0013.

Synthesis of 5-*tert*-butoxycarbonyloxy-4-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-isophthalic acid diethyl ester (6a) (Scheme 1)



Prepared according to **TP1** from 5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester **2a** (338 mg, 1.0 mmol) [reaction conditions: deprotonation with TMPMgCl·LiCl at T = 0 °C for 1 h] and LiHMDS (1.0 M in THF; 2.0 mL, 2.0 mmol). Purification by flash chromatography (pentane/Et_2O; 15:1) yielded **6a** (378 mg, 76 %) as a yellow wax.

IR (neat): *?*$_{max}$ (cm^{-1}) = 2980, 2957, 2905, 1760, 1722, 1604, 1458, 1369, 1323, 1284, 1266, 1249, 1236, 1212, 1147, 1103, 1061, 1027, 928, 901, 871, 841, 826, 759, 686.

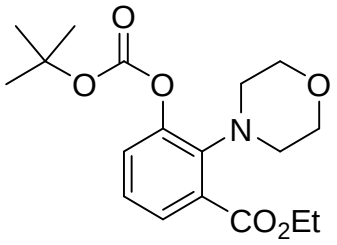
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 8.13 (d, ^{4}*J*(H,H) = 2.2 Hz, 1 H, Ar*H*), 7.96 (d, ^{4}*J*(H,H) = 2.2 Hz, 1 H, Ar*H*), 4.41 (q, ^{3}*J*(H,H) = 7.1 Hz, 2 H), 4.35 (q, ^{3}*J*(H,H) = 7.1 Hz, 4 H, C*H*$_2$), 1.58 (s, 9 H, C(C*H*$_3$)$_3$), 1.42 (t, ^{3}*J*(H,H) = 7.1 Hz, 3 H, C*H*$_3$), 1.40 (t, ^{3}*J*(H,H) = 7.1 Hz, 3 H, C*H*$_3$), 0.10 (s, 18 H, Si(C*H*$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = 166.8, 165.4, 151.4, 149.9, 145.8, 134.8, 128.0, 126.2 (2C), 83.8, 61.5, 61.3, 28.0, 14.6, 14.5, 2.0.

MS (ES): *m/z* (%) = 498 (100) [M + H]$^+$.

HRMS (ES): *m/z* calc. for [$C_{23}H_{40}NO_7Si_2$] [*M* + H]$^+$ 498.2343, found: 498.2324.

Synthesis of 3-*tert*-butoxycarbonyloxy-2-morpholin-4-yl-benzoic acid ethyl ester (21a) (Scheme 4)



Prepared according to **TP1** from ethyl-3-*tert*-butoxycarbonyloxy-benzoate (266 mg, 1.0 mmol) [reaction conditions: deprotonation with TMPMgCl·LiCl at T = 0 °C for 3 h] and *N*-lithium morpholine **17** (2.0 mmol, prepared by adding *n*-BuLi to morpholine at 0 °C and stirring for 30 min). Purification by flash chromatography (pentane/Et_2O; 7:3) yielded **21a** (214 mg, 61 %) as a white solid.

mp.: 122–123 °C.

IR (neat): ?$_{max}$ (cm^{-1}) = 2980, 2962, 2938, 2909, 2858, 1752, 1710, 1470, 1446, 1372, 1364, 1300, 1280, 1250, 1237, 1171, 1148, 1108, 1077, 1066, 1055, 1033, 938, 875, 844, 821, 775, 751, 763, 733, 721, 648, 607.

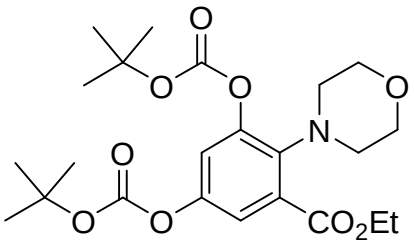
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 7.34 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.7 Hz, 1 H, Ar*H*), 7.18 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.7 Hz, 1 H, Ar*H*), 7.12 (t, ^3J(H,H) = 7.9 Hz, 1 H, Ar*H*), 4.36 (q, ^3J(H,H) = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 3.74 (t, ^3J(H,H) = 4.9 Hz, 4 H, 2 x C*H*$_2$), 3.09 (t, ^3J(H,H) = 4.9 Hz, 4 H, 2 x C*H*$_2$), 1.57 (s, 9 H, C(C*H*$_3$)$_3$), 1.39 (t, ^3J(H,H) = 7.1 Hz, 3 H, CH$_2$C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = 168.1, 151.6, 148.2, 142.5, 131.6, 127.4, 125.8, 124.5, 83.7, 67.8, 61.4, 50.7, 27.8, 14.3.

MS (70 eV, EI): *m/z* (%) = 351 (11) [*M*]$^+$, 296 (12), 251 (13), 222 (22), 207 (23), 192 (20), 176 (13), 147 (15), 57 (100).

HRMS (EI): *m/z* calcd. for [$C_{18}H_{25}NO_6$]**:** 351.1682, found: 351.1657.

Synthesis of 3,5-bis-*tert*-butoxycarbonyloxy-2-morpholin-4-yl-benzoic acid ethyl ester (21b) (Scheme 4)



Prepared according to **TP1** from 3,5-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (382 mg, 1.0 mmol) [reaction conditions: deprotonation with TMPMgCl·LiCl at T = 0 °C for 3 h.] and *N*-lithium morpholine **17** (1.6 mmol, prepared by adding *n*-BuLi to morpholine at 0 °C and stirring for 30 min). Purification by flash chromatography (pentane/Et_2O; 6.5:3.5) yielded **21b** (327 mg, 70%) as a white solid.

mp.: 78-80 °C.

IR (neat): ?$_{max}$ (cm^{-1}) = 2980, 2855, 1761, 1726, 1476, 1395, 1370, 1317, 1269, 1245, 1152, 1126, 1061, 1030, 933, 858, 780.

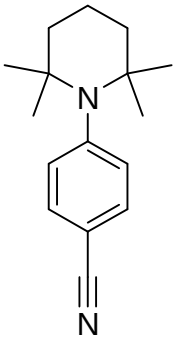
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 7.27 (d, ^4J(H,H) = 2.7 Hz, 1 H, Ar*H*), 7.13 (d, ^4J(H,H) = 2.7 Hz, 1 H, Ar*H*), 4.37 (q, ^3J(H,H) = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 3.75 (t, ^3J(H,H) = 4.4 Hz, 4 H, 2 x C*H*$_2$), 3.08 (t, ^3J(H,H) = 4.4 Hz, 4 H, 2 x C*H*$_2$), 1.58 (s, 9 H, C(C*H*$_3$)$_3$), 1.55 (s, 9 H, C(C*H*$_3$)$_3$), 1.40 (t, ^3J(H,H) = 7.1 Hz, 3 H, CH$_2$C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = 167.0, 151.1 (2 x *C*O), 148.6, 146.9, 140.1, 131.9, 119.9, 119.2, 83.9, 84.0, 67.7, 61.6, 50.7, 27.8, 27.6, 14.3.

MS (70 eV, EI): *m/z* (%) = 467 (10) [*M*]$^+$, 367 (20) [*M* - BOC]$^+$, 267 (100) [*M* – 2 × BOC]$^+$, 238 (70), 236 (37), 223 (78), 222 (20), 208 (28), 163 (40), 135 (21), 41 (25).

HRMS (EI): *m/z* calcd. for [$C_{23}H_{33}NO_9$] 467.2155, found 467.2169.

Synthesis of 4-(2,2,6,6-tetramethyl-piperidin-1-yl)-benzonitrile (22) (Scheme 4)



Prepared according to **TP2** from 4-bromobenzonitrile (182 mg, 1.0 mmol) [Br/Mg-exchange conditions: *i*-PrMgCl·LiCl at T = 0 °C for 2 h] and LiTMP **18** (2.0 mmol, prepared by adding *n*-BuLi to TMPH at -78 °C and stirring for 15 min before the mixture was allowed to reach 0 °C and was stirred for additional 15 min).[7] Purification by flash chromatography (pentane/Et_2O; 95:5) yielded **22** (155 mg, 64 %) as a pale yellow solid.

mp.: 74–75 °C.

IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) = 2969, 2929, 2869, 2226, 1600, 1500, 1459, 1378, 1363, 1276, 1260, 1245, 1173, 1129, 1104, 1036, 1016, 973, 951, 909, 864, 849, 834, 778, 655.

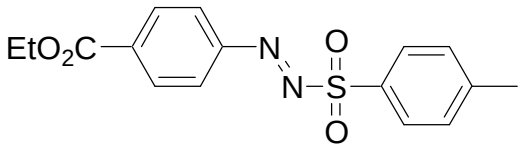
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (d, ^3J(H,H) = 8.8 Hz, 2 H, Ar*H*), 7.30 (d, ^3J(H,H) = 8.8 Hz, 2 H, Ar*H*), 1.73 (m, 2 H, CH_2), 1.57 (m, 4 H, 2 x CH_2), 1.00 (s, 12 H, 4 x CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.3, 135.2, 131.9, 119.4, 109.5, 54.7, 42.3, 29.9, 18.4.

MS (70 eV, EI): *m/z* (%) = 242 (2), 227 (100), 171 (22), 159 (14), 143 (9), 102 (7), 69 (11), 40 (10).

HRMS (EI): *m/z* calcd. for [$C_{16}H_{22}N_2$] 242.1783, found 242.1777.

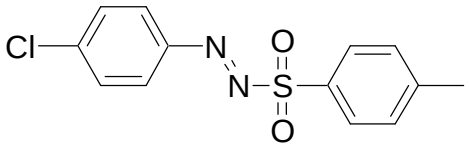
Synthesis of 4-carbetoxyphenyl-4-tolylazo sulfone



Prepared according to **TP7a** from ethyl-4-aminobenzoate (1.65 g, 10.0 mmol). The title compound (2.35 g, 71 %) was isolated after crystallisation as bright-orange platelets. The spectroscopic data matches with the literature.[8]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, 2 H, *J* = 8.9 Hz, Ar*H*), 7.86-7.81 (m, 4 H), 7.38 (d, 2 H, *J* = 8.9 Hz, Ar*H*), 4.33 (q, 2 H, *J* = 7.1 Hz, CH_2), 2.41 (s, 3 H, CH_3), 1.30 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3).

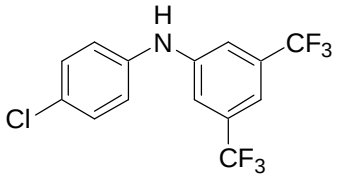
Synthesis of 4-chloro-4-tolylazo sulfone



Prepared according to **TP7b** from 4-chloroaniline (1.28 g, 10.0 mmol). The title compound (2.42 g, 82 %) was isolated after crystallisation as a yellow crystalline solid. The spectroscopic data matches with the literature.[9]

^{1}H NMR (200 MHz, $CDCl_3$): *d* = 7.85 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.73 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 7.48 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.39 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 2.42 (s, 3 H, CH_3).

Synthesis of *N*-(4-chlorophenyl)-3,5-bis(trifluoromethyl)-benzenamine



The indicated compound was synthesised according to **TP8** from 4-chloro-4-tolylazo sulfone (324 mg, 1.1 mmol) and 1-bromo-3,5-bis(trifluoromethyl)benzene (293 mg, 0.17 mL, 1.0 mmol) [Br/Mg-exchange conditions: *i*-PrMgCl·LiCl at T = 0 °C for 15 min]. Flash chromatography (pentane/5 % CH_2Cl_2) afforded the title compound (239 mg, 70 %) as an off-white solid.

mp.: 80-81 °C

IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) = 3436, 1616, 1593, 1516, 1490, 1382, 1276, 1108, 956.

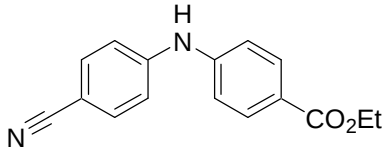
^{1}H NMR (300 MHz, $CDCl_3$): *d* = 5.95 (s, 1 H, N*H*), 7.07 (dd, 2 H, *J* = 7.7, 2.2 Hz, Ar*H*), 7.31-7.37 (m, 5 H, Ar*H*).

^{13}C NMR (75 MHz, $CDCl_3$): *d* = 113.8 (quintet, $J_{C,F}$ = 3.8 Hz), 115.8 (d, $J_{C,F}$ = 3.3 Hz), 122.0, 125.4, 129.2, 130.3, 133.2 (q, $J_{C,F}$ = 33.2 Hz), 139.3, 145.3.

MS (EI^+): *m/z* (%) = 339 (100) $[M]^+$, 320 (8) $[M - F]^+$, 303 (14) $[M - Cl]^+$, 284 (11) $[M - Cl - F]^+$.

HRMS $(EI)^+$: *m/z* calcd. for $[C_{14}H_8(^{35}Cl)F_6N]$ 339.0249, found 339.0237 (341.0200 found for $[C_{14}H_8(^{37}Cl)F_6N]$).

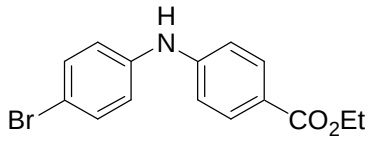
Synthesis of ethyl 4-[(4-cyanophenyl)amino]-benzoate



The indicated compound was synthesised according to **TP8** from 4-carbethoxyphenyl-4-tolylazo sulfone (366 mg, 1.1 mmol) and 4-bromobenzonitrile (182 mg, 1.0 mmol) [Br/Mg-exchange conditions: *i*-PrMgCl·LiCl at T = 0 °C for 2 h]. Flash chromatography (pentane/EtOAc; 3:1) afforded the title compound (157 mg, 59 %) as a pale yellow solid. The spectroscopic data matches with the literature.[10]

^{1}H NMR (300 MHz, $CDCl_3$): *d* = 8.01 (d, 2 H, *J* = 8.9 Hz, Ar*H*), 7.54 (d, 2 H, *J* = 8.9 Hz, Ar*H*), 7.16-7.10 (m, 4 H, Ar*H*), 6.42 (broad s, 1 H, N*H*), 4.32 (q, 2 H, *J* = 7.1 Hz, CH_2), 1.38 (t, 3 H, *J* = 7.1 Hz, CH_3).

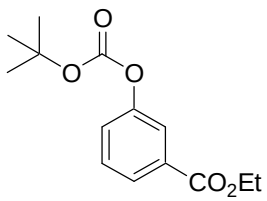
Synthesis of ethyl 4-[(4-bromophenyl)amino]-benzoate



The indicated compound was synthesised according to **TP8** from 4-carbethoxyphenyl-4-tolylazo sulfone (366 mg, 1.1 mmol) and 1,4-dibromobenzene (236 mg, 1.0 mmol) [Br/Mg-exchange conditions: *i*-PrMgCl·LiCl at room temperature for 3 h]. Flash chromatography (pentane/CH_2Cl_2; 5:1) afforded the desired diarylamine (214 mg, 67 %) as a pale yellow solid. The spectroscopic data matches with the literature.[10]

^{1}H NMR (300 MHz, $CDCl_3$): *d* = 7.92 (d, 2 H, *J* = 8.9 Hz, Ar*H*), 7.42 (d, 2 H, *J* = 8.4 Hz, Ar*H*), 7.03 (d, 2 H, *J* = 8.9 Hz, Ar*H*), 6.98 (d, 2 H, *J* = 8.4 Hz, Ar*H*), 6.15 (broad s, 1 H, N*H*), 4.33 (q, 2H, *J* = 7.1 Hz, CH_2), 1.37 (t, 2 H, *J* = 7.1 Hz, CH_3).

Synthesis of 3-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester

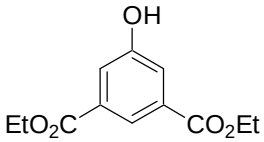


Prepared according to **TP9** from 3-hydroxy-benzoic acid ethyl ester (2.52 g, 15 mmol), DMAP (92 mg, 0.75 mmol), and Boc_2O (3.930 g, 18 mmol). Purification by flash

chromatography (pentane/Et_2O; 20:1) yielded the title product (3.80 g, 95 %) as a yellow oil. The spectroscopic data matches with the literature.[6]

^{1}H NMR (300 MHz, $CDCl_3$): *d* = 7.93–7.89 (m, 1 H, ArH), 7.85–7.82 (m, 1 H, Ar*H*), 7.44 (dt, ^3J(H,H) = 7.8 Hz, ^5J(H,H) = 0.4 Hz, 1 H, Ar*H*), 7.38–7.33 (m, 1 H, Ar*H*), 4.37 (q, ^3J(H,H) = 7.14 Hz, 2 H, CH_2), 1.56 (s, 9 H, $C(CH_3)_3$), 1.39 (t, ^3J(H,H) = 7.14 Hz, 3 H, CH_2CH_3).

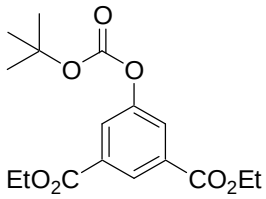
Synthesis of 5-hydroxy-isophthalic acid diethyl ester



A dry 1 L round-bottomed flask, equipped with a magnetic stirrer and a condenser, was charged with a solution of 5-hydroxy-isophthalic acid (15 g, 80 mmol) in dry ethanol (400 mL). Concentrated H_2SO_4 (1 mL) was added and the reaction mixture was refluxed overnight before the solvent was evaporated and sat. aq. NaCl solution (30 mL) was added. The reaction mixture was extracted with diethyl ether (3 x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to afford the title compound (18.2 g, 95 %) as white solid, which did not required further purification. The spectroscopic data matches with the literature.[6]

^{1}H NMR (300 MHz, $CDCl_3$): *d* = 8.21 (t, ^4J(H,H) = 1.4 Hz, 1 H, Ar*H*), 7.81 (d, ^4J(H,H) = 1.4 Hz, 2 H, Ar*H*), 6.51 (s, 1 H, Ar*H*), 4.39 (q, ^3J(H,H) = 7.1 Hz, 4 H, 2 x CH_2), 1.39 (t, ^3J(H,H) = 7.1 Hz, 6 H, 2 x CH_3).

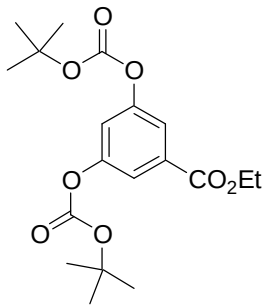
Synthesis of 5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester



Prepared according to **TP9** from 5-hydroxy-isophthalic acid diethyl ester (3.57 g, 15 mmol), DMAP (92 mg, 0.75 mmol), and Boc_2O (3.93 g, 18 mmol). Purification by flash chromatography (pentane/Et_2O; 20:1) yielded the desired product (4.82 g, 95 %) as a white solid. The spectroscopic data matches with the literature.[6]

^{1}H NMR (400 MHz, $CDCl_3$): *d* = 8.55 (t, ^4J(H,H) = 1.5 Hz, 1 H, Ar*H*), 8.02 (d, ^4J(H,H) = 1.50 Hz, 2 H, Ar*H*), 4.41 (q, ^3J(H,H) = 7.15 Hz, 4 H, 2 x CH_2), 1.57 (s, 9 H, C(CH_3)$_3$), 1.41 (t, ^3J(H,H) = 7.15 Hz, 6 H, 2 x CH_3).

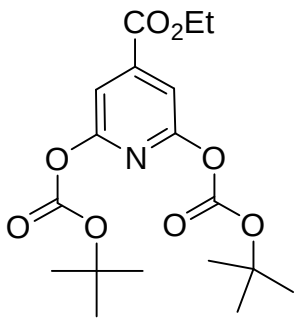
Synthesis of 3,5-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester



Prepared according to **TP9** from 3,5-dihydroxy-benzoic acid ethyl ester (15 mmol), DMAP (184 mg, 1.5 mmol), Et_3N (1 mL), and Boc_2O (7.20 g, 33 mmol). Purification by flash chromatography (pentane/Et_2O; 20:1) yielded the title product (4.82 g, 95 %) as a white solid. The spectroscopic data matches with the literature.[6]

^{1}H NMR (300 MHz, $CDCl_3$): *d* = 7.72 (d, ^4J(H,H) = 2.2 Hz, 2 H, Ar*H*), 7.27 (d, ^4J(H,H) = 2.2 Hz, 1 H, Ar*H*), 4.37 (q, ^3J(H,H) = 7.1 Hz, 2 H, CH_2), 1.55 (s, 18 H, 2 x C(CH_3)$_3$), 1.38 (t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3).

Synthesis of 4,6-bis-*tert*-butoxycarbonyloxy-pyridine-2-carboxylic acid ethyl ester



A dry 1 L round-bottomed flask, equipped with a magnetic stirrer and a condenser, was charged with a solution of 2,6-dihydroxy-isonicotinic acid (15 g, 97 mmol) in dry ethanol (600 mL). Concentrated H_2SO_4 (2 mL) was added and the reaction mixture was refluxed for 3 days, then the solvent was evaporated under reduced pressure affording a crude reaction mixture which was further treated with DMAP (0.6 g, 4.9 mmol), Et_3N (1 mL), and Boc_2O (46.6 g, 213 mmol) according to **TP9**. Purification by flash chromatography (pentane/Et_2O/Et_3N; 7:3:0.05) yielded the desired product (5.6 g, 15 %) as a white solid.

mp.: 44–45 °C.

^{1}H NMR (600 MHz, $CDCl_3$) *d* = 7.60 (s, 2 H, Ar*H*), 4.42 (q, ^3J(H,H) =7.1 Hz, 2 H, CH_2), 1.55 (s, 1 8H, 2 x $C(CH_3)_3$), 1.40 (t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$) *d* = 163.3, 156.9, 150.1, 144.7, 113.4, 84.7, 62.3, 62.3, 27.6, 14.1.

MS (70 eV, EI): *m/z* (%) = 184 (14) $[M- 199]^+$, 183 (42), 138 (7), 57 (100), 41 (13).

HRMS (FAB): *m/z* calcd. for $[C_{18}H_{25}O_8Na]$ 406.1446, found 406.1446.

[1] H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.

[2] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.

[3] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.

[4] a) D.-Y. Lee, J. F. Hartwig, *Org. Lett.* **2005**, *7*, 1169; b) K. Weigand, S. Pelka, *Org. Lett.* **2002**, *4*, 4689.

[5] K. Hori, M. Mori, *J. Am. Chem. Soc.* **1998**, *120*, 7651.

[6] A. Casarini, P. Dembech, D. Lazzari, E. Marini, G. Reginato, A. Ricci, G. Seconi, *J. Org. Chem.* **1993**, *58*, 5620.

[7] H. Salman, Y. Abraham, S. Tal, S. Meltzman, M. Kapon, N. Tessler, S. Speiser, Y. Eichen, *Eur. J. Org. Chem.* **2005**, 2207.

[8] I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 897.

[9] M.Kojima, H. Minato, M. Kobayashi, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2032.