JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 24 Sep 2015

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of symmetric bis(*N*-alkylaniline)triarylmethanes via Friedel-Crafts catalyzed reaction between secondary anilines and aldehydes

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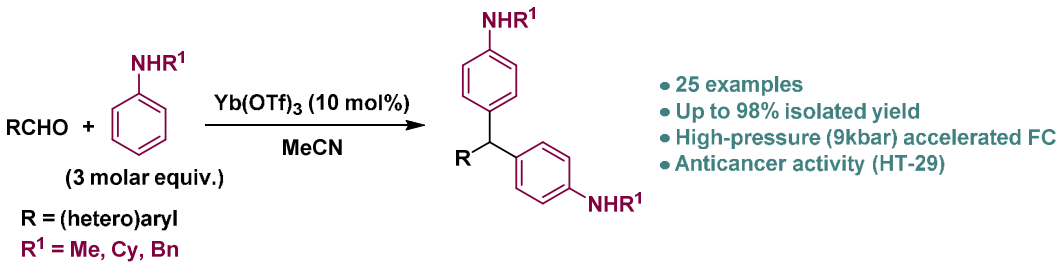


ABSTRACT: The first general protocol for the preparation of symmetric triarylmethanes bearing secondary anilines by Ytterbium-catalyzed Friedel-Crafts reaction of hetero(aryl) aldehydes and secondary anilines is reported. Mechanistic studies indicated that iminium ion intermediate is the electrophilic partner. The reaction is greatly accelerated by high-pressure (9 kbar) and showed a broad substrate scope on hetero(aryl) aldehyde. The new triarylmethanes exhibited activity against HT-29 cancer cell lines with the best result scoring an IC_{50} of 1.74 μM.

Triarylmethanes (TRAM) and related structures are important synthetic targets as they are a common motif in many dyes,[1] fluorescent probes,[2] biologically active molecules,[3] and natural products[4] (Figure 1).

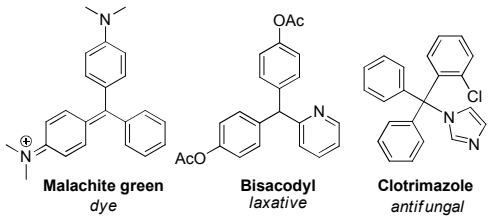
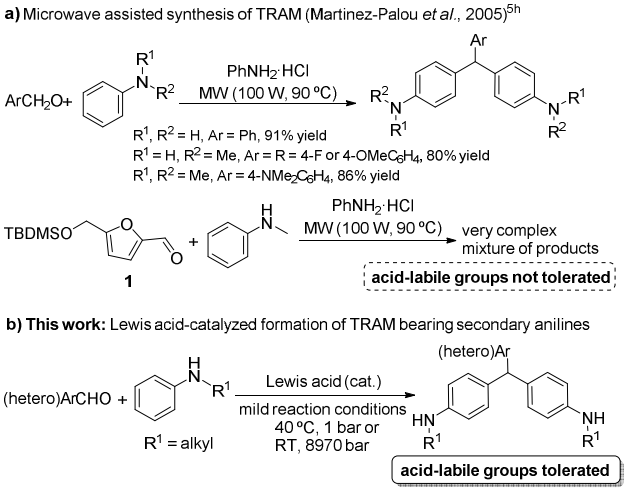


Figure 1. Selected examples of triarylmethanes

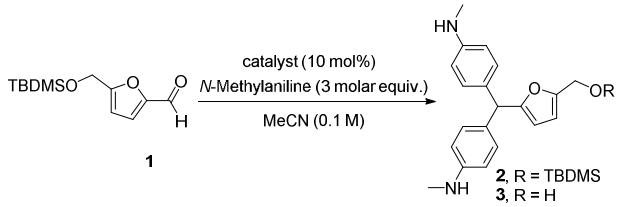
Within this family, aniline-based triarylmethanes are typically obtained via Friedel-Craft reactions between aromatic aldehydes and electron-rich tertiary anilines in the presence of Lewis or Bronsted acids under harsh conditions (reflux in solvents with high boiling points, solvent-free under heating).[1a,5] As a consequence, acid-labile functional groups or protection units are not expected to be tolerated under the current state-of-art methods. In fact, we found that TBDMS-protected 5-hydroxymethyl furfural **1**, which incorporates an *O*-silyl protection group and an acid labile furfural unit, delivered a very complex mixture of products when heated under microwave in presence aniline hydrochloride salt as catalyst – conditions reported by Martinez-Palou and co-workers (Scheme 1a)[5h]. In this way, besides the obvious need to develop milder methods to access triarylmethanes, there is also no current strategy available to directly access aniline-based triarylmethanes from secondary anilines.[6] Motivated by this literature void, we explored a novel method to access new triarylmethanes and related structures from secondary anilines and incorporating acid-sensitive functional groups, findings from which are presented herein (Scheme 1b). Based on its peculiar reactivity,[7] we envisioned that TBDMS-protected 5-hydroxymethyl furfural **1** constitutes the ideal test aldehyde substrate in combination with *N*-methylaniline to achieve our goals.



Scheme 1. Synthesis of TRAM bearing anilines

The initial screening with protected 5-hydroxymethyl furfural **1**, *N*-methylaniline and diverse acid catalysts at 40 ºC for 48 h revealed that $Yb(OTf)_3$, $LaCl_3{\cdot}7H_2O$ and $AlCl_3$ are the most suitable catalysts for this transformation, giving up to 82% yield of TRAM **2** and full conversion of **1** (Table 1, entries 1-7). Under the same reaction conditions, the protic acid PTSA only provided 33% yield of **2** whereas no product was found in absence of catalysts (Table 1, entries 1 and 2). From the initial catalyst hits, $Yb(OTf)_3$ was selected for furthers studies as $LaCl_3{\cdot}7H_2O$ and $AlCl_3$ provided irreproducible yields after three test reactions (Table 1, entries 5 and 6). Further optimization, namely temperature, time and concentration, led us to find that carrying the reaction at 40 ºC in 0.1 M acetonitrile for 34 h gives the desired TRAM **2** in quantitative yield (Table 1, entry 11). For longer reaction time or higher temperatures, TBDMS deprotection of the TRAM **2** can be detected, highlighting the importance of control of reaction conditions in the synthesis of acid-sensitive triarylmethanes.

Table 1. Reaction condition optimization for TRAM formation[a]



Entry	Catalyst	t (h)	T (°C)	Conv. (%)[b]	Yield 2 (%)[b]
1	None	48	40	50	-[c]
2	PTSA	48	40	67	33
3	See footnote[d]	48	40	up to 91	< 50
4	$ZrCl_4$	48	40	82	52
5	$LaCl_3 \cdot 7H_2O$[e]	48	40	100	72
6	$AlCl_3$[e]	48	40	94	82
7	$Yb(OTf)_3$	48	40	100	61 (60[f])[g]
8	$Yb(OTf)_3$	24	40	53	53
9	$Yb(OTf)_3$	24	50	100	45[g]
10	$Yb(OTf)_3$	32	40	83	81
11	$Yb(OTf)_3$	34	40	100	100 (98[f])
12[h]	$Yb(OTf)_3$	27	40	70	57
13[i]	$Yb(OTf)_3$	30	40	80	62

[a]Reaction conditions: **1** (0.125 mmol), *N*-methylaniline (3 molar equiv.), catalyst (10 mol%) were reacted in acetonitrile at desired temperature and time. [b]Determined by HPLC analysis of crude reaction mixture. [c]Product **2** was not observed. [d]$FeCl_3 \cdot 6H_2O$, $RuCl_3 \cdot xH_2O$, $NiCl_2$, ZnI_2, AgOTf, $CeCl_3$, $ZrCl_4$, $CoCl_2 \cdot 6H_2O$, $Cu(OTf)_2$, $GdCl_3 \cdot 6H_2O$, $BaCl_2$, $Ti(O^iPr)$. [e]Not reproducible. [f]Isolated yield after column chromatography. [g]Deprotected product **3** was also detected by TLC analysis of crude reaction mixture. [h]Reaction performed in a concentration of 0.05 M of **1**. [i]Reaction performed in a concentration of 0.2 M of **1**.

Reaction of unprotected 5-hydroxymethyl furfural (**4**, HMF – an important bioderived raw material)[8] with *N*-methylaniline catalyzed by $Yb(OTf)_3$ also smoothly produced the corresponding TRAM **3** in 91% yield after 28h (Figure 2). As summarized in Figure 2, 5-substituted hydroxymethyl furfurals bearing the hydroxyl protection groups like acetyl, benzyl and benzoyl were also well tolerated under the reaction conditions, providing the respective TRAM generally in good yields (Figure 2, compounds **5**-**7**, condition A). After achieving this important goal, we were pleased to find that benzaldehydes also produced the corresponding TRAM, despite of generally requiring longer reaction times to achieve high conversions of the starting aldehydes (Figure 2,

compounds **12**-**24**, condition A). Despite a direct correlation between the electronic nature of the substituents with the product yield was not observed, *para*-nitro substitution resulted in the highest yield (Figure 2, compound **15**). Perhaps more importantly, these mild reaction conditions tolerated *ortho*-subtitution in the benzaldehyde (Table 2, compounds **16**, **22** and **23**, condition A). On the other hand, the reaction appears to be quite sensitive to increase of steric bulkiness around the aniline nitrogen atom, as *N*-benzyl and *N*-(cylohexyl)methyl anilines presented much lower conversion compared with *N*-methyl anilines (Figure 2, compounds **8**-**9**, condition A). Tertiary *N*,*N*-dimethyl anilines were virtually unreactive under our reaction conditions (Figure 2, compounds **10**-**11**, condition A), while aniline resulted in the formation of the equivalent imine in 63% isolated yield.

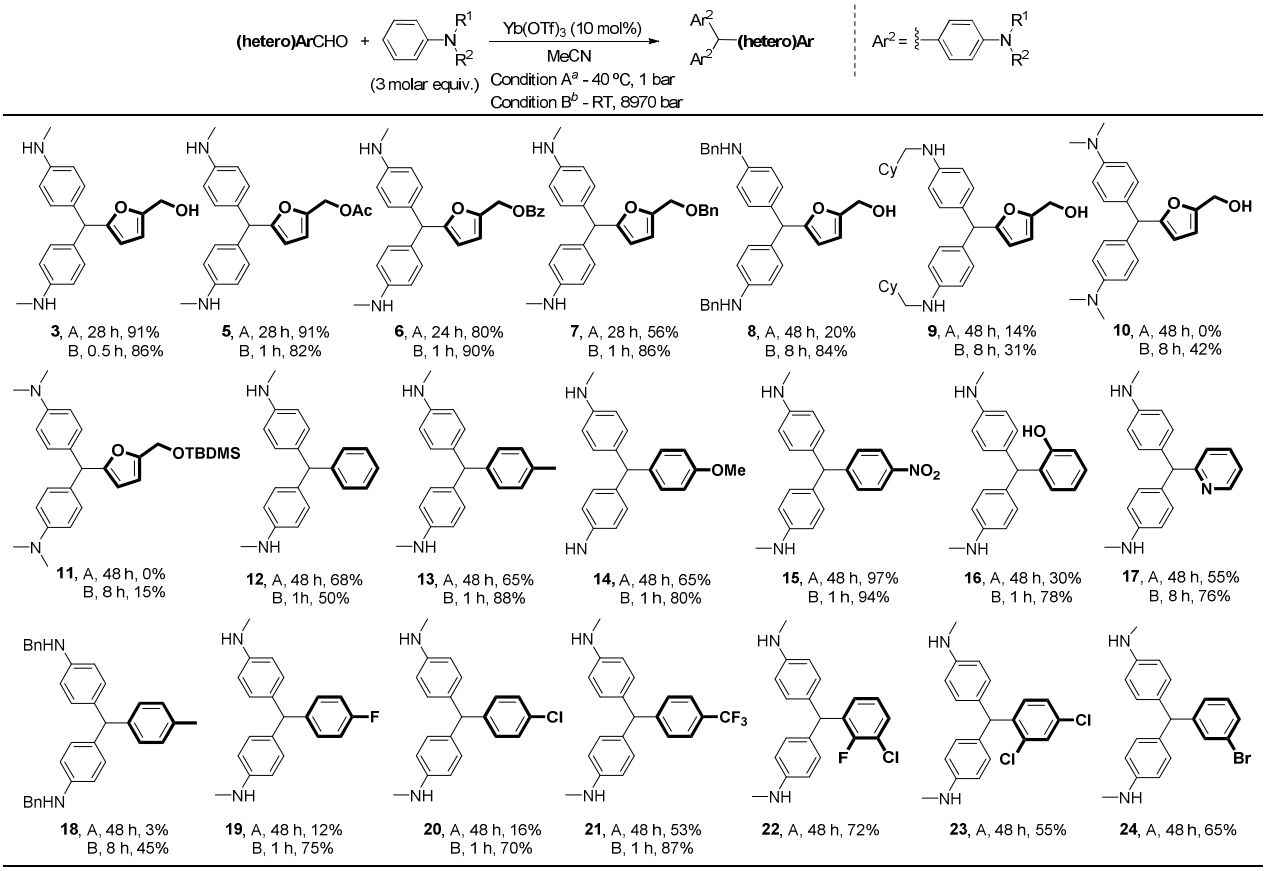
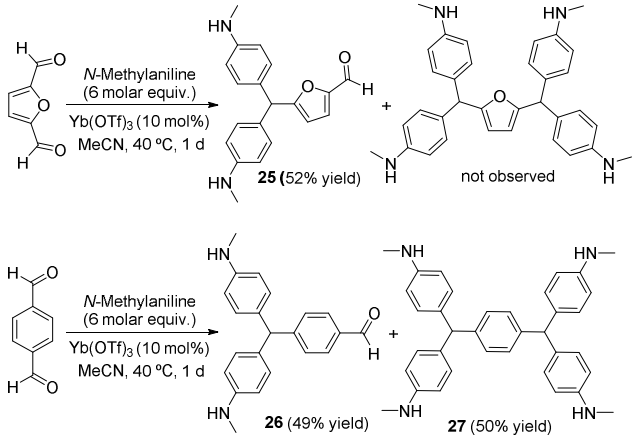


Figure 2. Substrate scope of $Yb(OTf)_3$-catalyzed reaction of aldehydes and anilines for TRAM formation. Condition A: Reaction performed at normal pressure and 40 ºC; and Condition B: Reaction performed at 8970 atm. and room temperature. For experimental details see experimental section. The yields correspond to the isolated yield after column chromatography.

Dialdehydes like 2,5-diformylfuran and terephthalaldehyde, were also studied as aldehydes for TRAM formation. The first reacted smoothly to give selectively the mono-TRAM **25**, even when 6 molar equivalents of *N*-methylaniline was used. Further extension of the reaction time to 2 days led to a very complex mixture with only traces of the product, suggesting decomposition. In opposite, when terephthalaldehyde was subjected to the same reaction conditions using 6 equivalents of *N*-methylaniline, both the corresponding TRAM **26** and the bis-TRAM **27** were obtained in a mixture of 1:1 and an overall isolated yield of 95% (Scheme 2), showing the superior stability of these products.

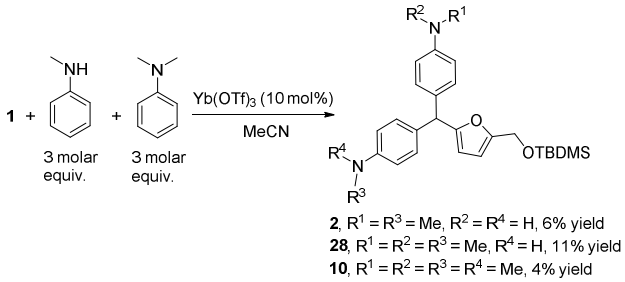


Scheme 2. Ytterbium-catalyzed Friedel-Crafts reaction between (hetero)aromatic aldehydes with *N*-methylaniline

The novel synthetic methodology to produce secondary-aniline based triarylmethanes reported herein is hypothesized to take place through a Friedel-Crafts type mechanism. This type of reaction is characterized by displaying a negative volume of activation[9] and thus is accelerated by pressure.[10] Since pressures in the range of 1-20 kbar can strongly influence the rate and the chemical equilibria of reactions,[11] we anticipated that our novel methodology could also be accelerated by applying high pressure technology.[12] The $Yb(OTf)_3$-catalyzed reaction of HMF (**4**) with *N*-methylaniline was extremely accelerated at 8970 bar, yielding the desired product in 86% after only 30 minutes at room temperature (Figure 2, compound 3, condition B). For the sake of comparison, the same reaction performed under conditions A provided only traces of product after 30 minutes.

The reaction with other (hetero)aryl aldehydes was also greatly accelerated under high-pressure conditions as summarized in Figure 2. As was observed at atmospheric pressure, several alcohol protecting groups of HMF are well tolerated offering the corresponding TRAM in 79 to 90% yield (Figure 2, compounds **5**-**7**). Substituted benzaldehydes also reacted smoothly to yield the corresponding products in up to 94% yield (Figure 2, entries **12**-**21**, condition B). Finally, secondary anilines *N*-benzylaniline and *N*-cyclohexylmethylaniline gave the increased yields of the corresponding TRAM **8** and **9** of 84% and 31%, respectively.

The current limitation of this methodology lies in the limited range of anilines that can be successfully employed, which appears to have a negative correlation with the increase of sterics around the aniline nitrogen atom. Also, the substitution degree in the aniline nitrogen impacted negatively the reaction success, since at normal pressure, the more *C*-nucleophilic tertiary anilines failed to react. These results are rather puzzling suggesting that a more complex reaction mechanism leads to a formal Friedel-Crafts product. In addition we found that a competitive reaction between *N*-methylaniline and *N*,*N*-dimethylaniline delivered a mixture of three triarylmethanes, **2**, **10** and **28** (Scheme 3).



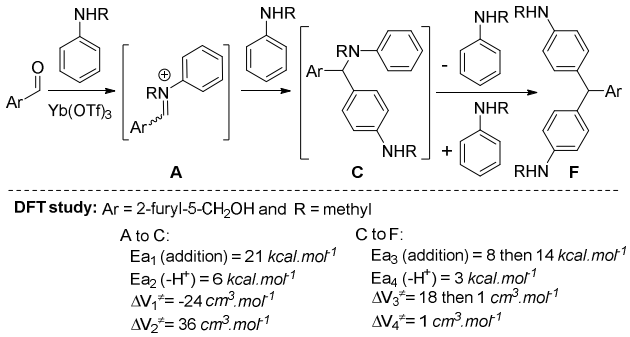
Scheme 3. Competition reaction between tertiary and secondary anilines

Based on these results, we hypothesized that the Friedel-Crafts reaction proceeds via addition of the aniline derivative to a transient iminium ion,[13] formed by the ytterbium-catalyzed reaction of secondary aniline and the aldehyde (Scheme 4). In order to further elucidate this hypothesis, conditions A between 1 and *N*-methylaniline in deuterated acetonitrile were studied by NMR. Upon, addition of the catalyst to the reaction mixture, plausible

iminium-ion and tertiary aniline intermediates were detected by ^{1}H NMR analysis.[14] Unfortunately, further characterization of these intermediates was not possible since they were neither stable to silica nor detectable by GC-MS analysis.

Kinetic isotope effect (KIE) study was conducted by submitting a 1:1 mixture of *N*-methylaniline and *N*-methylaniline-2,4,6-d_3 to intermolecular competition experiment with HMF (**4**). The observed absence of an isotope effect (KIE = 1.0) shows that C-H bond cleavage does not occur during the rate-determining step (RLS).[15] Density Functional Theory (DFT) calculations showed that the reaction of HMF (**4**) and *N*-methylaniline has the biggest energy barrier (RLS) for the Friedel-Crafts addition of the *N*-methylaniline to the iminium-ion A, and the lowest energies for the proton abstraction steps (Scheme 4). Furthermore, the calculations indicate that the second Friedel-Crafts alkylation occurs by a non-concerted fashion (the addition most probably occurs to the secondary carbocation originated by aniline disconnection rather than to the tertiary aniline C).[16]

The great acceleration of the reaction under extreme high-pressure could be attributed to the fact that the RLS occurs with a considerable negative activation volume (Scheme 4). Based on all the data gathered, we believe that under extreme high-pressure the reaction can also proceed *via* direct addition of aniline derivative to the aldehyde, as reaction with tertiary anilines under high-pressure gave the corresponding TRAM (Figure 2, compounds **12** and **13**, condition B).



Scheme 4. Proposed mechanism for TRAM formation from aldehydes and secondary anilines (See supporting information for further details on DFT results)

Finally, some of the newly synthesized TRAMs were evaluated for their antiproliferative activity towards human cancer cell lines from colon (HT-29), lung (NCI-H460) and breast (MCF-7) origin (Table 2). Interestingly, compound **12** (Ar = Ph) induced an important cancer cell growth inhibition in contrast to compound **3** (Ar = 2-furyl-5-CH_2OH) (Table 2, entries 1-2). This activity is exclusive against HT-29 cell line (determined concentration of **12** to reduce 50% of HT-29 cell viability (IC_{50}) was 5.1 μM whereas for the other cell lines tested were greater than 20 μM)[17]. Thus, the IC_{50} of several TRAM bearing substituted benzaldehydes were determined, leading to the *para*-methyl substitution in benzaldehyde (TRAM **13**) as the most promising compound, with an IC_{50} of 1.74 μM against HT-29 cell line (Table 2, entry 3). A subclone of the parental CHO cell line, which was derived from the ovary of an adult Chinese hamster (CHOK1) was also used to test toxicity of TRAM and data demonstrates that larger doses of these compounds are required to attain the IC_{50} in this model.

Table 2. Biological activity of the new TRAM derivatives

Entry	TRAM	IC_{50}(HT-29, μM)	IC_{50}(CHOK1, μM)
1	**3**	>20	ND
2	**12**	5.1 ± 3.3	>20
3	**13**	1.74 ± 2.32	14.55 ± 1.06
4	**15**	7.97 ± 3.13	>20

ND = Not determined

In conclusion, the first direct and general method for the synthesis of symmetric triarylmethane derivatives bearing secondary anilines is described. The protocol uses $Yb(OTf)_3$ as catalyst under mild reaction conditions, being compatible with protecting groups and furans. Experimental observations and DFT calculations indicate an iminium-ion catalysis, explaining the distinct reactivity of secondary anilines. Further reaction conditions investigation showed that the reaction is highly accelerated by extreme high-pressure (9 kbar). Finally, the new synthesized TRAM exhibited important antiproliferative activity against HT-29 cells and TRAM **13** present interesting biological activity.

EXPERIMENTAL SECTION

General Experimental Details

All solvents were freshly dried and distilled before use. All reactions were performed in flame dried glassware under argon atmosphere otherwise notice. Commercially available reagents were used as received without further purification otherwise notice. Flash column chromatography was carried out on silica gel 60M using an automated apparatus. Reaction mixtures were analyzed by TLC using silica gel 60, and visualization by UV and phosphomolybdic acid stain. NMR spectra were recorded at room temperature in a 300 or 400 MHz apparatus using $CDCl_3$ as solvent and $(CH_3)_4Si(^1H)$ as internal standard. All coupling constants are expressed in Hz. Elemental analysis was performed in a CHNS-O analyzer. HPLC analysis was performed using diode array detector and normal phase silica column (pore size: 110 Å; 5 μm), manual injector with 20 μL loop. Mobile phase gradient hexane/2-propanol from 99:1 to 98:2 for 10 min, flow 0.7 to 1 mL/min for 10 min. HRMS was performed using a LTQ Orbitrap XL mass spectrometer controlled by *LTQ Tune Plus 2.5.5* and *Xcalibur 2.1.0*. The capillary voltage of the electrospray ionization (ESI) was set to 3000 V. The capillary temperature was 275ºC. The sheath gas flow rate (nitrogen) was set to 5 (arbitrary unit as provided by the software seetings). The capillary voltage was 36 V and the tube lens voltage 110 V. High pressure reactions were performed in a 4 mL Teflon ampoules in a Liquid pressure vessel LV 30/16 coupled to a laboratory hydraulic press. The pressure inside the vessel (Pv) is related to the pressure from the press according to the following expression: P_v [MPa] = 3.9 × P_p [bar]. 5-Hydroxymethylfurfural (HMF, **4**) was prepared from Fructose or Glucose according to our reported protocols.[18] *O*-Protected derivatives of HMF were prepared using known protocols as recently reported by us.[19]

General procedure for reaction conditions optimization (Table 1). To a solution of **1** (30 mg, 0.125 mmol) in anhydrous acetonitrile (1.3 mL, 0.1 M), *N*-methylaniline (40 μL, 3 equiv.) was added *via* gas-tight syringe. The catalyst was added in one portion and the mixture was allowed to stir at the mentioned temperature and time under argon atmosphere. The solvent was then evaporated and the crude reaction mixture was filtered through a

small pad of silica gel. The solvent was evaporated and hexane/2-propanol was used to dilute the mixture to the appropriate concentration for HPLC analysis. R_t (**1**) = 6.2 min, λ_{max}=275 nm; R_t (**2**) = 16.2 min, λ_{max}=252 nm.

General procedure for the synthesis of triarylmethanes at atmospheric pressure (Table 2, Condition A). To a solution of aldehyde in anhydrous acetonitrile (0.1 M), desired aniline (3 molar equiv.) was added followed by the addition of $Yb(OTf)_3$ (10 mol%) in one portion. The reaction mixture was allowed to stir at the desired temperature and time described in Table 2 under argon atmosphere. The solvent was then evaporated and the product purified by column chromatography.

General procedure for the synthesis of triarylmethanes under high-pressure (Table 2, Condition B). To a proper Teflon vessel, the corresponding aldehyde, aniline (3 molar equiv.), anhydrous acetonitrile (1 mL) and $Yb(OTf)_3$ (10 mol%) were added (without argon atmosphere). Next the reactor was filled to the top with acetonitrile (approximate total volume of 2.4 mL). The reactor was introduced in the high-pressure apparatus at 8970 bar and kept for the time described in Table 2. The solvent was then evaporated and the product purified by column chromatography.

Procedure for amine competition experiment. *N,N*-Dimethylaniline (50 μL, 0.39 mmol, 3 equiv.), *N*-methylaniline (42 μL, 0.39 mmol, 3 equiv.) and $Yb(OTf)_3$ (8 mg, 0.013 mmol, 10 mol%) were sequentially added to a solution of **1** (30 mg, 0.13 mmol, 1 equiv.) in anhydrous acetonitrile (1.3 mL, 0.1 M). The reaction mixture was allowed to stir for 89 h at 40 ºC under argon atmosphere. The solvent was evaporated and the crude mixture was purified by column chromatography to yield the products **2** (6% yield), **10** (4% yield) and **28** (11% yield).

4,4'-((5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)methylene)bis(N-methylaniline) (**2**). General procedure for reaction conditions optimization (Table 1, entry 11) using **1** (0.13 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.41) afforded the product as a brown viscous liquid (54 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 2.81 (s, 6H), 4.57 (s, 2H), 5.22 (s, 1H), 5.79 (d, *J* = 2.76 Hz, 1H), 6.12 (d, *J* = 2.68 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 4H), 6.98 (d, *J* = 8.3 Hz, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ

5.2, 18.4, 25.9, 31.1, 49.3, 58.4, 107.7, 108.2, 112.5, 129.5, 131.7, 147.5, 153.3, 157.7. CHN calculated for $C_{26}H_{36}N_2O_2Si$: C: 71.51; H: 8.31; N: 6.42, found: C: 71.12; H: 8.44; N: 6.69.

(5-(bis(4-(methylamino)phenyl)methyl)furan-2-yl)methanol (**3**). General procedure A or B using 5-hydroxymethylfurfural **4** (A, 0.26 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 4:6, $R_f = 0.54$) afforded the product as a dark green viscous oil (A, 76 mg, 91%; B, 72 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (s, 6H), 4.53 (s, 2H), 5.23 (s, 1H), 5.80 (d, J = 3.1 Hz, 1H), 6.18 (d, J = 2.9 Hz, 1H), 6.54 (d, J = 8.6 Hz, 4H), 6.97 (d, J = 8.3 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 49.4, 57.6, 108.3, 108.5, 112.5, 129.4, 131.2, 147.9, 153.2, 158.5. HRMS (ESI): m/z calculated for $C_{20}H_{23}N_2O_2$ [M+H$^+$] 323.17540, found 323.17497.

(5-(bis(4-(methylamino)phenyl)methyl)furan-2-yl)methyl acetate (**5**). General procedure A or B using (5-formylfuran-2-yl)methyl acetate (A, 0.13 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, $R_f = 0.12$) afforded the product as a light green viscous oil (A, 43 mg, 91%; B, 77 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.82 (s, 6H), 4.99 (s, 2H), 5.25 (s, 1H), 5.84 (d, J = 3.1 Hz, 1H), 6.30 (d, J = 3.1 Hz, 1H), 6.56 (d, J = 8.5 Hz, 4H), 6.98 (d, J = 8.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 31.3, 49.7, 58.8, 109.2, 111.6, 112.8, 129.8, 131.5, 148.2, 148.7, 159.7, 171.1. HRMS (ESI): m/z calculated for $C_{44}H_{49}N_4O_6$ [2M+H$^+$] 729.36466, found 729.36384, m/z calculated for $C_{20}H_{21}N_2O$ [(M – CH_3COO)$^+$] 305.16484, found 305.16423.

(5-(bis(4-(methylamino)phenyl)methyl)furan-2-yl)methyl benzoate (**6**). General procedure A or B using (5-formylfuran-2-yl)methyl benzoate (A, 0.14 mmol; B, 0.29 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, $R_f = 0.18$) afforded the product as a green viscous oil (A, 48 mg, 80%; B, 110 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 6H), 5.28 (s, 2H), 5.29 (s, 1H), 5.90 (d, J = 3.1 Hz, 1H), 6.41 (d, J = 3.1 Hz, 1H), 6.56 (d, J = 8.6 Hz, 4H), 7.03 (d, J = 8.4 Hz, 4H), 7.44 (t, J = 7.5 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 8.07 (d, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 49.4, 59.0, 108.9, 111.5, 112.4, 128.4, 129.5, 129.8, 130.1, 131.1, 133.0, 148.0, 148.4, 159.4, 166.3. HRMS (ESI): m/z calculated for $C_{54}H_{53}N_4O_6$ [2M+H$^+$] 853.39596, found 853.39176, m/z calculated for $C_{20}H_{21}N_2O$ [(M – PhCOO)$^+$] 305.16484, found 305.16341.

4,4'-((5-((benzyloxy)methyl)furan-2-yl)methylene)bis(N-methylaniline) (**7**). General procedure A or B using 5-((benzyloxy)methyl)furan-2-carbaldehyde (A, 0.13 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, $R_f = 0.12$) afforded the product as a green viscous oil (A, 30 mg, 56%; B, 92 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (s, 6H), 4.44 (s, 2H), 4.51 (s, 2H), 5.26 (s, 1H), 5.83 (d, J = 3.1

Hz, 1H), 6.24 (d, *J* = 3.1 Hz, 1H), 6.54 (d, *J* = 8.6 Hz, 4H), 6.99 (d, *J* = 8.3 Hz, 4H), 7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 49.3, 64.0, 71.6, 108.5, 110.1, 112.4, 127.6, 128.0, 128.3, 129.5, 131.3, 138.1, 147.9, 150.7, 158.8. HRMS (ESI): m/z calculated for $C_{27}H_{29}N_2O_2$ [M+H$^+$] 413.22235, found 413.22170.

(5-(bis(4-(benzylamino)phenyl)methyl)furan-2-yl)methanol (**8**). General procedure A or B using 5-5-hydroxymethylfurfural **4** (A, 0.13 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 4:6, R_f = 0.85) afforded the product as a green oil (A, 12 mg, 20%; B, 104 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (s, 4H), 4.37 (s, 2H), 5.13 (s, 1H), 5.72 (d, *J* = 3.1 Hz, 1H), 6.06 (d, *J* = 3.1 Hz, 1H), 6.46 (d, *J* = 8.6 Hz, 4H), 6.87 (d, *J* = 8.5 Hz, 4H), 7.13 - 7.28 (m, 10H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.4, 49.3, 57.5, 108.6, 108.9, 113.2, 127.7, 128.0, 129.1, 129.9, 131.9, 140.0, 147.3, 153.7, 159.0. HRMS (ESI): m/z calculated for $C_{32}H_{31}N_2O_2$ [M+H$^+$] 475.23800, found 475.23707.

(5-(bis(4-((cyclohexylmethyl)amino)phenyl)methyl)furan-2-yl)methanol (**9**). General procedure A or B using 5-(hydroxymethyl)furan-2-carbaldehyde (A, 0.26 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 4:6, R_f = 0.49) afforded the product as a green oil (A, 18 mg, 14%; B, 39 mg, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 - 1.82 (m, 22H), 2.92 (d, *J* = 6.6 Hz, 4H), 4.52 (s, 2H), 5.21 (s, 1H), 5.80 (d, *J* = 3.1 Hz, 1H), 6.17 (d, *J* = 3.1 Hz, 1H), 6.51 (d, *J* = 8.6 Hz, 4H), 6.94 (d, *J* = 8.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.7, 31.4, 37.7, 49.4, 50.9, 57.8, 108.4, 108.6, 112.6, 129.5, 130.9, 147.3, 153.1, 158.8. HRMS (ESI): m/z calculated for $C_{32}H_{43}N_2O_2$ [M+H$^+$] 487.33191, found 487.33104.

(5-(bis(4-(dimethylamino)phenyl)methyl)furan-2-yl)methanol (**10**). General procedure B using 5-hydroxymethylfurfural **4** (0.26 mmol). Purification by column chromatography (Hexane/EtOAc 4:6, R_f = 0.69) afforded the product as a brown oil (38 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (s, 12H), 4.53 (s, 2H), 5.27 (s, 1H), 5.82 (d, *J* = 3.1 Hz, 1H), 6.18 (d, *J* = 3.1, Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 4H), 7.03 (d, *J* = 8.7 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.9, 49.2, 57.8, 108.4, 108.7, 112.8, 129.4, 130.6, 149.4, 153.1, 158.7. HRMS (ESI): m/z calculated for $C_{22}H_{27}N_2O_2$ [M+H$^+$] 351.20670, found 351.20656.

4,4'-((5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)methylene)bis(N,N-dimethylaniline) (**11**). General procedure B using 5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde **1** (0.26 mmol) Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.68) afforded the product as a brown viscous oil (18 mg, 15%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.93 (s, 9H), 2.94 (s, 12H), 4.63 (s, 2H), 5.30 (s, 1H), 5.85 (d, *J* = 3.1 Hz, 1H), 6.17 (d, *J* = 3.1 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 4H), 7.08 (d, *J* = 8.6 Hz, 4H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ -5.5, 18.1, 25.6, 40.5, 48.8, 58.0, 107.4, 107.9, 112.3, 129.0, 130.5, 148.9, 152.9, 157.5. HRMS (ESI): m/z calculated for $C_{28}H_{41}N_2O_2Si$ [M+H$^+$] 465.29318, found 465.29190.

4,4'-(phenylmethylene)bis(N-methylaniline) (**12**). General procedure A or B using benzaldehyde (A, 0.26 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.31) afforded the product as a blue viscous oil (A, 53 mg, 68%; B, 39 mg, 50%). The NMR data is in accordance to the literature.[20] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (s, 6H), 5.39 (s, 1H), 6.57 (d, *J* = 8.6 Hz, 4H), 6.97 (d, *J* = 8.3 Hz, 4H), 7.15 - 7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 55.3, 112.4, 125.9, 128.2, 129.5, 130.2, 133.6, 145.6, 147.6.

4,4'-(p-tolylmethylene)bis(N-methylaniline) (**13**). General procedure A or B using 4-methylbenzaldehyde (A, 0.12 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.43) afforded the product as a green oil (A, 27 mg, 65%; B, 73 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s,3H), 2.82 (s, 6H), 5.32 (s, 1H), 6.57 (d, *J* = 8.6 Hz, 4H), 6.94 (d, *J* = 8.2 Hz, 4H), 7.01 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 31.7, 55.4, 113.2, 129.4, 129.8, 130.7, 134.7, 135.8, 142.9, 147.6. HRMS (ESI): m/z calculated for $C_{22}H_{25}N_2$ [M+H$^+$] 317.20123, found 317.20069.

4,4'-((4-methoxyphenyl)methylene)bis(N-methylaniline) (**14**). General procedure A or B using 4-methoxybenzaldehyde (A, 0.13 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.32) afforded the product as a green oil (A, 28 mg, 65%; B, 69 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 6H), 3.78 (s, 3H), 5.31 (s, 1H), 6.54 (d, *J* = 8.6 Hz, 4H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 4H), 7.05 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 54.4, 55.2, 112.3, 113.5, 130.0, 130.2, 133.9, 137.7, 147.5, 157.7. CHN calculated for ($C_{22}H_{24}N_2O$): C: 79.48; H: 7.28; N: 8.43, found: C: 79.40; H: 7.55; N: 8.67.

4,4'-((4-nitrophenyl)methylene)bis(N-methylaniline) (**15**). General procedure A or B using 4-nitrobenzaldehyde (A, 0.13 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.25) afforded the product as a yellow oil (A, 44 mg, 97%; B, 87 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 6H, s), 5.43 (s, 1H), 6.55 (d, *J* = 8.6 Hz, 4H), 6.90 (d, *J* = 8.5, 4H), 7.29 (d, *J* = 8.6 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 55.2, 112.5, 123.5, 130.1, 130.2, 131.8, 146.3, 148.1, 153.6. HRMS (ESI): m/z calculated for $C_{21}H_{22}N_3O_2$ [M+H$^+$] 348.17065, found 348.17012.

2-(bis(4-(methylamino)phenyl)methyl)phenol (**16**). General procedure A or B using 2-hydroxybenzaldehyde (A, 0.13 mmol; B, 0.25 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.38) afforded the product as a green viscous oil that crystalizes in the freezer (A, 12 mg, 30%; B, 62 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 6H), 5.44 (s, 1H), 6.59 (d, *J* = 8.6 Hz, 4H), 6.83-6.85 (m, 3H), 6.99 (d, *J* = 8.4 Hz, 4H), 7.12-7.14 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 50.1, 113.0, 116.5, 120.7, 127.9, 130.3, 130.6, 131.6, 131.7, 148.2, 154.1. HRMS (ESI): m/z calculated for $C_{21}H_{23}N_2O$ [M+H$^+$] 319.18049, found 319.18032.

4,4'-(pyridin-2-ylmethylene)bis(N-methylaniline) (**17**). General procedure A or B using picolinaldehyde (A, 0.13 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.15) afforded the product as a green oil (A, 32 mg, 80%; B, 60 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (s, 6H), 5.35 (s, 1H), 6.54 (d, *J* = 8.6 Hz, 4H), 6.92 (d, *J* = 8.7 Hz, 4H), 7.17 (ddd, *J* = 0.7, 4.8, 7.8 Hz, 1H), 7.42 (dddd, *J* = 0.6, 1.7, 2.3, 7.9 Hz, 1H), 8.43 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.44-8.45 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 52.6, 112.6, 123.4, 130.3, 132.5, 137.1, 141.3, 147.7, 148.3, 151.3. HRMS (ESI): m/z calculated for $C_{20}H_{22}N_3$ [M+H$^+$] 304.18082, found 304.18042.

4,4'-(p-tolylmethylene)bis(N-benzylaniline) (**18**). General procedure A or B using 4-methylbenzaldehyde (A, 0.13 mmol; B, 0.26 mmol).Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.82) afforded the product as a green oil (A, 2 mg, 3%; B, 55 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 4.19 (s, 4H), 5.22 (s, 1H), 6.46 (d, *J* = 8.5 Hz, 4H), 6.83 (d, *J* = 8.5 Hz, 4H), 6.91-7.29 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 48.7, 54.9, 112.8, 127.3, 127.7, 128.8, 129.3, 129.4, 130.2, 134.1, 135.4, 139.7, 142.4, 146.4. HRMS (ESI): m/z calculated for $C_{34}H_{33}N_2$ [M+H$^+$] 469.26383, found 469.26257.

4,4'-((4-fluorophenyl)methylene)bis(N-methylaniline) (**19**). General procedure A or B using 4-fluorobenzaldehyde (A, 0.13 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.33) afforded the product as a green viscous oil (A, 5 mg, 12%; B, 62 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 6H), 5.36 (s, 1H), 6.57 (d, *J* = 8.6 Hz, 4H), 6.95 (d, *J* = 8.5 Hz, 4H), 7.00-7.13 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 55.0, 112.9, 115.2, 115.5, 130.6, 131.2, 131.3, 133.9, 141.8, 148.2, 160.2, 163.4. HRMS (ESI): m/z calculated for $C_{21}H_{22}N_2F$ [M+H$^+$] 321.17615, found 321.17572.

4,4'-((4-chlorophenyl)methylene)bis(N-methylaniline) (**20**). General procedure A or B using 4-chlorobenzaldehyde (A, 0.13 mmol; B, 0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.36) afforded the product as green viscous oil that crystalizes in the freezer (A, 7 mg, 16%; B, 61 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 6H), 5.22 (s, 1H), 6.44 (d, *J* = 8.6 Hz, 4H), 6.81 (d, *J* = 8.3 Hz, 4H), 6.96

(d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 55.1, 112.9, 128.8, 130.6, 131.3, 132.1, 133.5, 144.7, 148.3. HRMS (ESI): m/z calculated for $C_{21}H_{22}ClN_2$ [M+H$^+$] 337.14660, found 337.14647.

4,4'-((4-(trifluoromethyl)phenyl)methylene)bis(N-methylaniline) (**21**). General procedure A or B using 4-(trifluoromethyl)benzaldehyde (A, 0.13 mmol; B, 0.25 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.41) afforded the product as green oil (A, 26 mg, 53%; B, 80 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (s, 6H), 5.30 (s, 1H), 6.45 (d, *J* = 8.6 Hz, 4H), 6.82 (d, *J* = 8.3 Hz, 4H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 55.1, 112.4, 122.6, 125.0, 125.1, 129.7, 130.1, 132.5, 147.8, 149.7. HRMS (ESI): m/z calculated for $C_{22}H_{22}N_2F_3$ [M+H$^+$] 371.17296, found 371.17228.

4,4'-((3-chloro-2-fluorophenyl)methylene)bis(N-methylaniline) (**22**). General procedure A using 3-chloro-2-fluorobenzaldehyde (0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.62) afforded the product as green oil (66 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 6H), 5.33 (s, 1H), 6.23 (d, *J* = 8.6 Hz, 4H), 6.53-6.68 (m, 6H), 6.92 (ddd, *J* = 2.6, 6.1, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6, 47.8, 112.6, 121.2 (d), 124.3 (d), 128.6, 129.6 (d), 130.3, 131.8, 134.9 (d), 148.4, 155.0, 158.3. HRMS (ESI): m/z calculated for $C_{21}H_{21}ClFN_2$ [M+H$^+$] 355.13718 and 357.13423, found 355.13669 and 357.13349

4,4'-((2,4-dichlorophenyl)methylene)bis(N-methylaniline) (**23**). General procedure A using 2,4-dichlorobenzaldehyde (0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.68) afforded the product as green oil (53 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 6H), 5.70 (s, 1H), 6.55 (d, *J* = 8.6 Hz, 4H), 6.88 (d, *J* = 8.3 Hz, 4H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 2.2, 8.4 Hz, 1H) 7.38 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 51.7, 113.1, 127.5, 130.1, 131.0, 132.3, 132.8, 133.0, 135.9, 142.7, 148.7. HRMS (ESI): m/z calculated for $C_{21}H_{21}Cl_2N_2$ [M+H$^+$] 371.10763 and 373.10468 found 371.10748 and 373.10422.

4,4'-((3-bromophenyl)methylene)bis(N-methylaniline) (**24**). General procedure A using 3-bromobenzaldehyde (0.26 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.68) afforded the product as green oil (64 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 6H), 5.34 (s, 1H), 6.56 (d, *J* = 8.6 Hz, 4H), 6.94 (d, *J* = 8.7 Hz, 4H), 7.11 (m, 2H), 7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 55.3, 113.1, 123.2, 128.9, 129.8, 130.5, 130.9, 133.1, 133.4, 148.7, 149.0. HRMS (ESI): m/z calculated for $C_{21}H_{22}BrN_2$ [M+H$^+$] 381.09609 and 383.09404, found 381.09590 and 383.09337.

5-(bis(4-(methylamino)phenyl)methyl)furan-2-carbaldehyde (**25**). General procedure A using furan-2,5-dicarbaldehyde (0.18 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.53) afforded the product as a black oil (30 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (s, 6H), 5.33 (s, 1H), 6.13 (d, *J* = 3.5 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 4H), 6.96 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 9.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 49.7, 111.2, 112.6, 129.5, 129.7, 132.8, 148.3, 152.3, 165.9, 177.8. HRMS (ESI): m/z calculated for $C_{20}H_{21}N_2O_2$ [M+H$^+$] 321.15975, found 321.15900.

4-(bis(4-(methylamino)phenyl)methyl)benzaldehyde (**26**). General procedure A using terephthalaldehyde (0.24 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.77) afforded the product as a green oil (39 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 6H), 5.41 (s, 1H), 6.55 (d, *J* = 8.6 Hz, 4H), 6.92 (d, *J* = 8.3 Hz, 4H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 9.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 55.5, 112.4, 129.7, 130.0, 130.1, 132.2, 134.4, 147.8, 153.0, 192.1. HRMS (ESI): m/z calculated for $C_{22}H_{23}N_2O$ [M+H$^+$] 331.18049, found 331.17986.

4,4',4'',4'''-(1,4-phenylenebis(methanetriyl))tetrakis(N-methylaniline) (**27**). General procedure A using terephthalaldehyde (0.24 mmol). Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.58) afforded the product as blue viscous oil that crystalizes in the freezer (63 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (s, 12H), 5.31 (s, 2H), 6.54 (d, *J* = 8.6, 8H), 6.95 (d, *J* = 8.4 Hz, 8H), 7.03 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 54.9, 112.3, 129.0, 130.1, 133.9, 142.7, 147.5. CHN calculated for ($C_{36}H_{38}N_4$): C: 82.09; H: 7.27; N: 10.64, found: C: 82.38; H: 7.30; N: 10.43.

4-((5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)(4-(methylamino)phenyl)methyl)-N,N-dimethylaniline (**28**). Procedure for amine competition experiment using 5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde **1** (0.26 mmol). Isolated from the competion reaction. Purification by column chromatography (Hexane/EtOAc 8:2, R_f = 0.51) afforded the product as a brown viscous oil (13 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 2.83 (s, 3H), 2.94 (s, 6H), 4.62 (s, 2H), 5.28 (s, 1H), 5.84 (d, *J* = 3.1 Hz, 1H), 6.16 (d, *J* = 3.1 Hz, 1H), 6.56 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1, 18.5, 26.0, 31.0, 40.9, 49.3, 58.4, 107.8, 108.3, 112.4, 112.7, 113.1, 129.4, 129.6, 129.6, 130.9, 131.5, 147.9, 149.3, 153.4, 157.9. HRMS (ESI): m/z calculated for $C_{27}H_{39}N_2O_2Si$ [M+H$^+$] 451.27753, found 451.27723.

N-((5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)methylene)aniline. General procedure A using 5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde **1** (0.12 mmol). Purification by column chromatography

(Hexane/EtOAc 8:2) afforded the product as a brown oil (26 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.93 (s, 9H), 4.77 (s, 2H), 6.42 (d, *J* = 3.4 Hz, 1H), 6.92 (d, *J* = 3.4 Hz, 1H), 7.22 (m, 3H), 7.37 (m, 2H), 8.23 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, 18.9, 26.4, 59.3, 109.6, 117.9, 121.6, 126.6, 129.7, 148.5, 151.9, 152.2, 159.3. HRMS (ESI): m/z calculated for $C_{18}H_{26}NO_2Si$ [M+H$^+$] 316.17273, found 316.17259.

Procedure for determination of the anti-proliferative activity. Cell lines were cultivated in media RPMI-1640 with L- glutamine, and supplemented with 10% fetal bovine serum (FBS) and antibiotics, and kept in a humidified atmosphere with 5% CO_2 and at 37ºC. For determination of the anti-proliferative activity, cells were seeded in 96-well plates at a low density (0.5-1,5x10^5 cell/ml) and maintained in the incubator for approximately 24 hours. Stock solutions of the compounds to be tested were prepared in a way that the percentage of organic solvent in contact with the cells was inferior to 1%. In this situation, it is not detected any solvent-induced cytotoxicity in the used cell models. Samples were diluted in the cell culture medium with only 0.5% FBS in order to attain the desired tested concentrations ranging in the interval [0-20] μM. Incubation lasted for 48 hours to allow cells to duplicate in the presence of the compounds. At the end of the incubation period, viability was determined using neutral red and as previously explained.[21] Experimental points are an average of three repliques and IC_{50} were determined using GraphPad Prism 5.

ASSOCIATED CONTENT

Supporting Information

DFT details and atomic coordinates of all optimized species; complete biological activity data and NMR and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank the Fundação para a Ciência e a Tecnologia (SFRH/BPD/73932/2010, SFRH/BPD/73822/2010, SFRH/BPD/100433/2014, PTDC/QUI-QUI/119823/2010 and UID/DTP/04138/2013), and Fundação Calouste Gulbenkian (Prémio de Estimulo à Investigação 2012) for financial support and REDE/1518/REM/2005 and the Portuguese NMR Network (IST-UTL Center) for providing access to the MS and NMR facilities.

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(6) To the best of our knowledge, a general methodology for the direct reaction of an aromatic aldehydes and the corresponding secondary aniline is not described in the literature. However there are few examples of the preparation of triarylmethanes via this reaction: a) Microwave-assisted reaction of *N*-methylaniline and 4-fluorobenzaldehyde or 4-methoxybenzaldehyde[5h] and; b) Reaction of *N*-phenylnaphthalen-1-amine and 3-chlorobenzaldehyde or 4-nitrobenzaldehyde using a stoichiometric amount of iron(III) chloride (Li, X-L, Huang, J-H, Yang, L-M, *Org. Lett.*, **2011**, 13, 4950).

(7) As recently described by us, in contrast to furfural derivatives that undergo furan-ring opening reactions by addition of nucleophiles to C5, 5-hydroxymethylfurfural derivatives undergo ε-functionalization under similiar conditions. For further details on the peculiar reactivity of this class of compounds see Coelho, J. A. S.; Trindade, A. F.; Andre, V.; Teresa Duarte, M.; Veiros, L. F.; Afonso, C. A. M. *Org. Biom. Chem.*, **2014**, 12, 9324.

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