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Synthesis of Symmetric Bis(*N*-alkylaniline)triarylmethanes via Friedel–Crafts-Catalyzed Reaction between Secondary Anilines and Aldehydes

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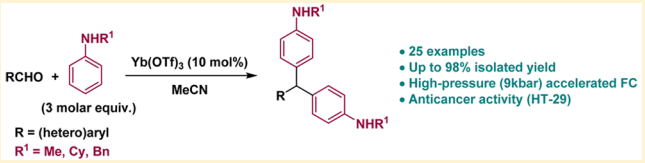
Supporting Information

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 the iminium ion intermediate is the electrophilic partner. The reaction is greatly accelerated by high pressure (9 kbar) and showed a broad substrate scope on the 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).

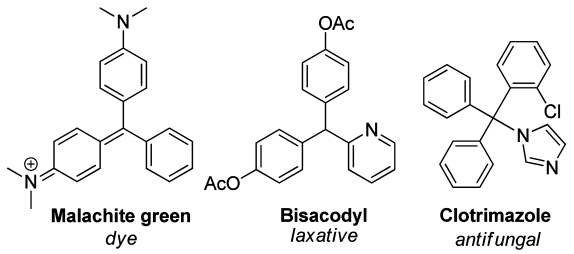
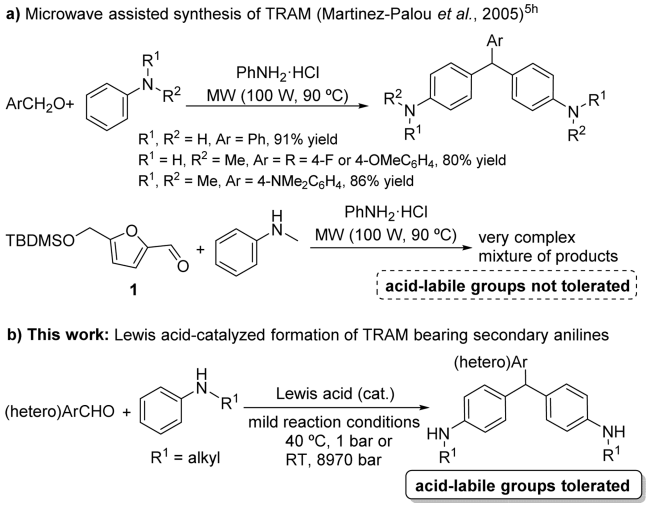


Figure 1. Selected examples of triarylmethanes.

Within this family, aniline-based triarylmethanes are typically obtained via Friedel–Crafts 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 or 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-the-art methods. In fact, we found that *tert*-butyldimethylsilyl (TBDMS)-protected 5-hydroxymethylfurfural **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 the presence of 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-hydroxymethylfurfural **1** constitutes the ideal test aldehyde substrate in combination with *N*-methylaniline to achieve our goals.

Scheme 1. Synthesis of TRAM-Bearing Anilines



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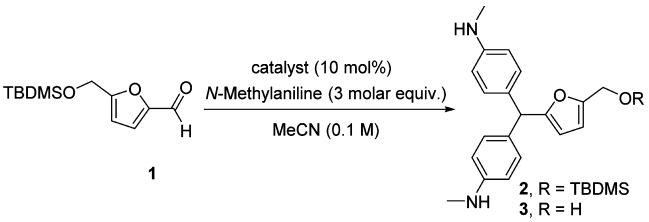
The initial screening with protected 5-hydroxymethylfurfural **1**, *N*-methylaniline, and diverse acid catalysts at 40 °C for 48 h revealed that $Yb(OTf)_3$, $LaCl_3{\cdot}7H_2O$, and $AlCl_3$ are the most suitable catalysts for this transformation, giving up to 82% yield of TRAM **2** and full conversion of **1** (Table 1, entries 1−7).

Table 1. Reaction Condition Optimization for TRAM Formation[a]



entry	catalyst	*t* (h)	*T* (°C)	conv (%)[b]	yield of **2** (%)[b]
1	none	48	40	50	[c]
2	PTSA	48	40	67	33
3	[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), and catalyst (10 mol %) were reacted in acetonitrile at desired temperature and time. [b]Determined by HPLC analysis of the 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 at a concentration of 0.05 M of **1**. [i]Reaction performed at a concentration of 0.2 M of **1**.

Under the same reaction conditions, the protic acid PTSA (*p*-toluenesulfonic acid) only provided 33% yield of **2**, whereas no product was found in the absence of catalysts (Table 1, entries 1 and 2). From the initial catalyst hits, $Yb(OTf)_3$ was selected for further 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 °C 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.

Reaction of unprotected 5-hydroxymethylfurfural (**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 28 h (Figure 2). As summarized in Figure 2, 5-substituted hydroxymethylfurfurals bearing 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 generally requiring longer reaction times to achieve high conversions of the starting aldehydes (Figure 2, compounds **12**−**24**, condition A). Even though 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*-substitution in the benzaldehyde (Table 2, compounds **16**, **22**, and **23**, condition A). On the other hand, the reaction appears to be quite sensitive to an increase of steric bulkiness around the aniline nitrogen atom, as *N*-benzyl and *N*-(cyclohexyl)methylanilines presented a conversion much lower than that with *N*-methylanilines (Figure 2, compounds **8** and **9**, condition A). Tertiary *N*,*N*-dimethylanilines were virtually unreactive under our reaction conditions (Figure 2, compounds **10** and **11**, condition A), while aniline resulted in the formation of the equivalent imine in 68% isolated yield.

Dialdehydes, such as 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 equiv 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. Conversely, when terephthalaldehyde was subjected to the same reaction conditions using 6 equiv 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.

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 min at room temperature (Figure 2, compound **3**, condition B). For the sake of comparison, the same reaction performed under condition A provided only traces of product after 30 min.

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 79−90% yield (Figure 2, compounds **5**−**7**). Substituted benzaldehydes also reacted smoothly to yield the corresponding products in up to 94% yield (Figure 2, compounds **12**−**21**, condition B). Finally, secondary anilines *N*-benzylaniline and *N*-cyclohexylmethylaniline gave increased yields of the corresponding TRAMs **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 negatively impacted the reaction success because, at normal pressure, the more C-nucleophilic

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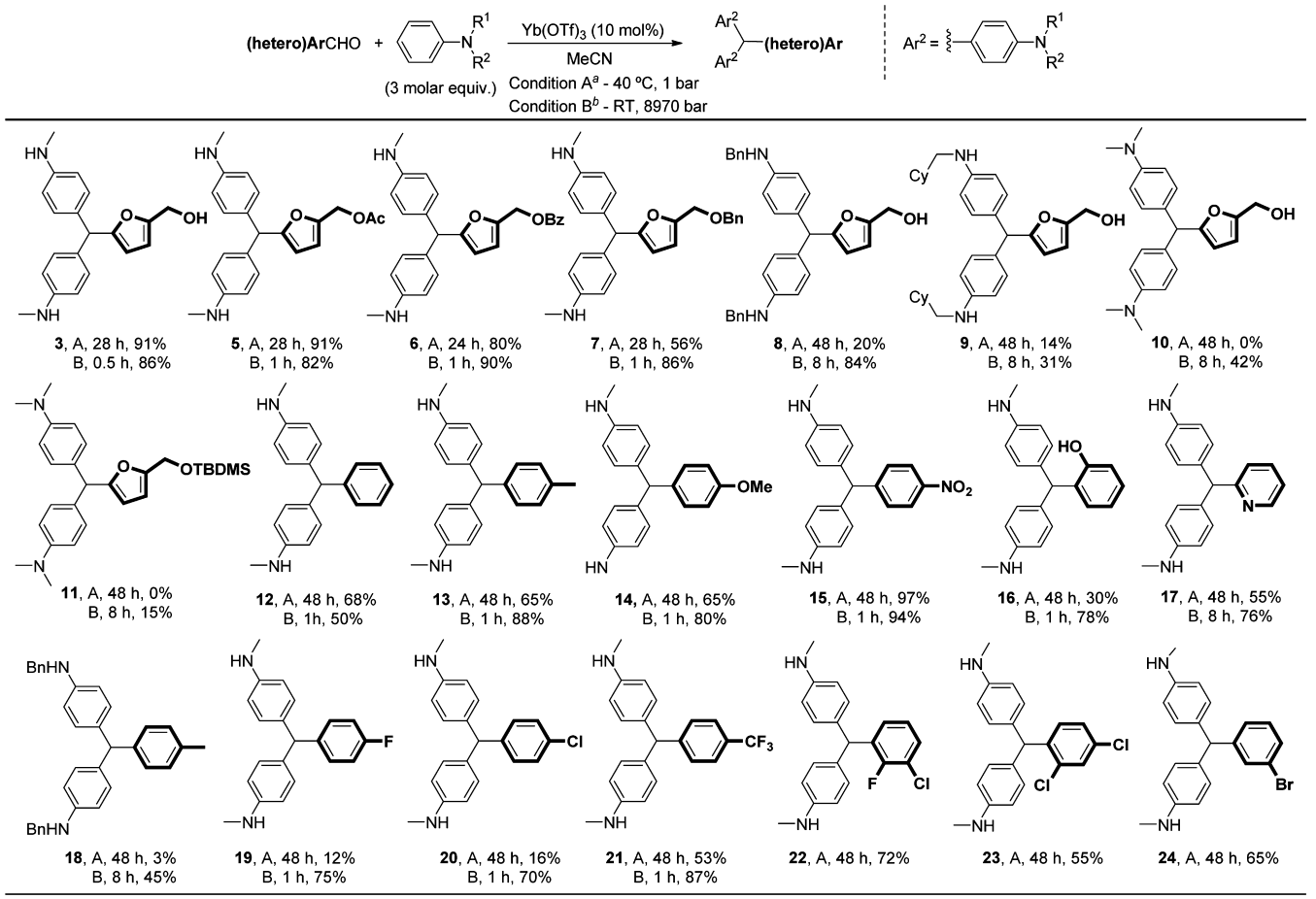
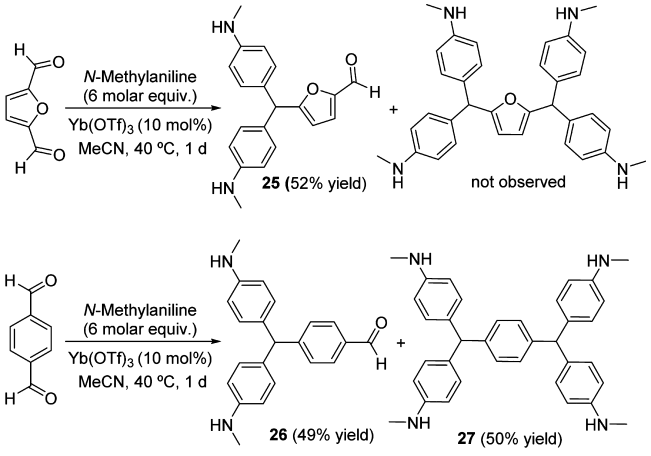
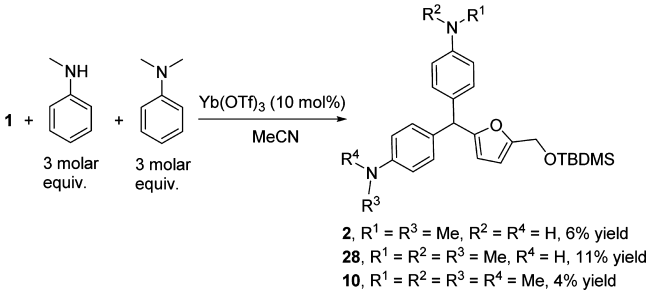


Figure 2. Substrate scope of the $Yb(OTf)_3$-catalyzed reaction of aldehydes and anilines for TRAM formation. **Condition A**: Reaction performed at normal pressure and 40 °C. **Condition B**: Reaction performed at 8970 atm and room temperature. For experimental details, see the Experimental Section.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

Scheme 2. Ytterbium-Catalyzed Friedel–Crafts Reaction between (Hetero)aromatic Aldehydes with *N*-Methylaniline



Scheme 3. Competition Reaction between Tertiary and Secondary Anilines



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).

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, condition A between **1** and *N*-methylaniline in deuterated acetonitrile was studied by NMR. Upon addition of the catalyst to the reaction mixture, plausible iminium ion and tertiary aniline intermediates were detected by ^1H NMR analysis.[14] Unfortunately, further characterization of these intermediates was not possible because they were neither stable to silica nor detectable by GC-MS analysis.

A 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 an intermolecular competition experiment with

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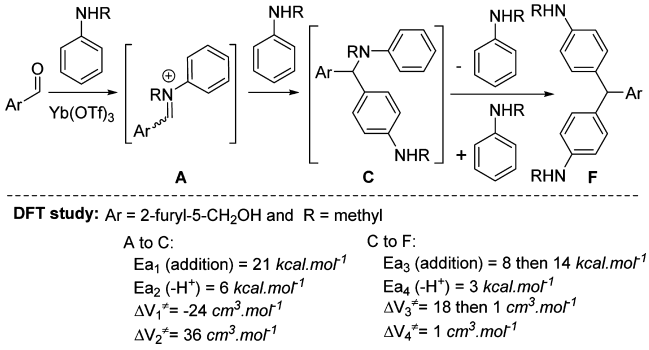
Scheme 4. Proposed Mechanism for TRAM Formation from Aldehydes and Secondary Anilines (See Supporting Information for Further Details on DFT Results)



DFT study: Ar = 2-furyl-5-CH_2OH and R = methyl

A to C:
Ea_1 (addition) = 21 *kcal.mol*$^{-1}$
Ea_2 ($-H^+$) = 6 *kcal.mol*$^{-1}$
$\Delta V_1^{\neq}$ = -24 *cm*^{3}*.mol*$^{-1}$
$\Delta V_2^{\neq}$ = 36 *cm*^{3}*.mol*$^{-1}$

C to F:
Ea_3 (addition) = 8 then 14 *kcal.mol*$^{-1}$
Ea_4 ($-H^+$) = 3 *kcal.mol*$^{-1}$
$\Delta V_3^{\neq}$ = 18 then 1 *cm*^{3}*.mol*$^{-1}$
$\Delta V_4^{\neq}$ = 1 *cm*^{3}*.mol*$^{-1}$

HMF (**4**). The observed absence of an isotope effect (KIE = 1.0) shows that C−H bond cleavage does not occur during the rate-limiting step (RLS).[15] DFT calculations showed that the reaction of HMF (**4**) and *N*-methylaniline had 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 in a nonconcerted fashion (the addition most probably occurs with the secondary carbocation that originated from aniline disconnection rather than from 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 an aniline derivative to the aldehyde, as the reaction with tertiary anilines under high pressure gave the corresponding TRAM (Figure 2, compounds **12** and **13**, condition B).

Finally, some of the newly synthesized TRAMs were evaluated for their antiproliferative activity toward human cancer cell lines from colon (HT-29), lung (NCI-H460), and breast (MCF-7) origin (Table 2). Interestingly, compound **12**

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.

(Ar = Ph) induced an important cancer cell growth inhibition in contrast to compound **3** (Ar = 2-furyl-5-CH_2OH) (Table 2, entries 1 and 2). This activity is exclusive against the 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, it was greater than 20 μM).[17] Thus, the IC_{50} values 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 the 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 the toxicity of TRAM, and data demonstrate that larger doses of these compounds are required to attain the IC_{50} in this model.

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 the catalyst under mild reaction conditions, which is compatible with protecting groups and furans. Experimental observations and DFT calculations indicate an iminium ion catalysis, explaining the distinct reactivity of secondary anilines. Investigation of further reaction conditions showed that the reaction is highly accelerated by extreme high pressure (9 kbar). Finally, the newly synthesized TRAM exhibited important antiproliferative activity against HT-29 cells, and TRAM **13** presents 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 unless noted otherwise. Commercially available reagents were used as received without further purification unless noted otherwise. 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 hertz. Elemental analysis was performed in a CHNS-O analyzer. HPLC analysis was performed using a diode array detector and normal phase silica column (pore size: 110 Å; 5 μm) and manual injector with a 20 μL loop. Mobile phase gradient was hexane/2-propanol from 99:1 to 98:2 for 10 min, and flow was 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 275 °C. The sheath gas flow rate (nitrogen) was set to 5 (arbitrary unit as provided by the software settings). The capillary voltage was 36 V, and the tube lens voltage was 110 V. High-pressure reactions were performed in a 4 mL Teflon ampule in a liquid pressure vessel, LV 30/16, coupled to a laboratory hydraulic press. The pressure inside the vessel (P_v) 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 Condition Optimization (Table 1). To a solution of **1** (30 mg, 0.125 mmol) in anhydrous acetonitrile (1.3 mL, 0.1 M) was added *N*-methylaniline (40 μL, 3 equiv) via a gastight syringe. The catalyst was added in one portion, and the mixture was allowed to stir at the mentioned temperature and time under an 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) was added the desired aniline (3 molar equiv) 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 an 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 were added the corresponding aldehyde, aniline (3 molar equiv), anhydrous acetonitrile (1 mL), and $Yb(OTf)_3$ (10 mol %)

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(without argon atmosphere). Next, the reactor was filled to the top with acetonitrile (approximate total volume of 2.4 mL). The reactor was introduced into 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 the Amine Competition Experiment. *N,N*-Dimethylaniline (100 μL, 0.78 mmol, 3 equiv), *N*-methylaniline (84 μL, 0.78 mmol, 3 equiv), and $Yb(OTf)_3$ (16 mg, 0.026 mmol, 10 mol %) were sequentially added to a solution of **1** (60 mg, 0.26 mmol, 1 equiv) in anhydrous acetonitrile (2.6 mL, 0.1 M). The reaction mixture was allowed to stir for 89 h at 40 °C under an 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 condition 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 calcd 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* calcd 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, 82%): ^{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* calcd for $C_{44}H_{49}N_4O_6$ [2M + H^+] 729.36466, found 729.36384, *m*/*z* calcd 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* calcd for $C_{54}H_{53}N_4O_6$ [2M + H^+] 853.39596, found 853.39176, *m*/*z* calcd 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* calcd 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* calcd 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* calcd 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* calcd 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* calcd 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 are 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* calcd 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*

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J. Org. Chem. 2015, 80, 10404−10411

= 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 calcd 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 calcd 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 crystallizes 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 calcd 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, 22 mg, 55%; 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 calcd 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 calcd 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 calcd 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 crystallizes 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 crystallizes 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 calcd 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), which was 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,

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J. Org. Chem. 2015, 80, 10404−10411

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 calcd 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 (imine) 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 calcd for $C_{18}H_{26}NO_2Si$ [M + H$^+$] 316.17273, found 316.17259.

Procedure for the Determination of the Antiproliferative Activity. Cell lines were cultivated in RPMI-1640 medium with L-glutamine, supplemented with 10% fetal bovine serum (FBS) and antibiotics, and kept in a humidified atmosphere with 5% CO_2 and at 37 °C. For determination of the antiproliferative activity, cells were seeded in 96-well plates at a low density (0.5−1.5 × 10^5 cell/mL) and maintained in the incubator for approximately 24 h. Stock solutions of the compounds to be tested were prepared in such a way that the percentage of organic solvent in contact with the cells was less than 1%. In this situation, no solvent-induced cytotoxicity was detected 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 of 0−20 μM. Incubation lasted for 48 h 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 replicates, and IC_{50} values were determined using GraphPad Prism 5.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01875.

DFT details and atomic coordinates of all optimized species; complete biological activity data and NMR and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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