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Simple, practical and efficient synthesis of triarylmethanes

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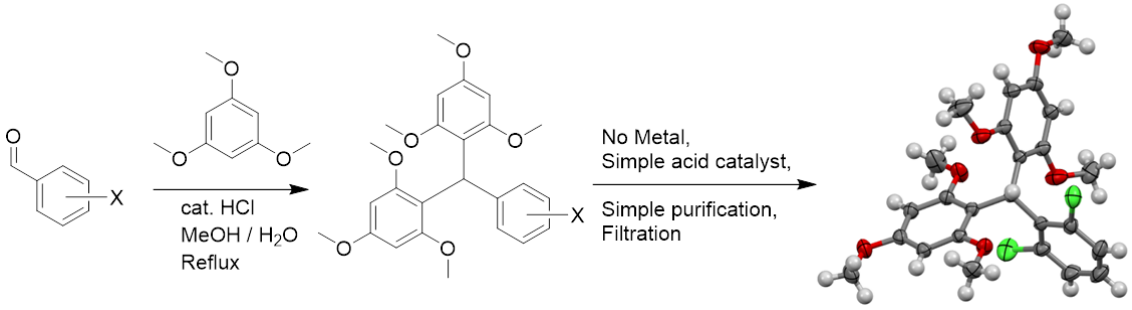
Abstract

Triarylmethanes are important building blocks for biological and material applications. Numerous methods have been described for their synthesis, often relying on harsh conditions or expensive catalysts, requiring purification(s) and sometimes lacking selectivity. Herein we describe a simple, practical and efficient synthesis of triarylmethanes, starting from an electron poor aldehyde and electron rich nucleophilic arenes, selectively giving the crystalline products in high yields after simple filtration.



Keywords: Triarylmethane, nucleophilic addition, green chemistry, crystal structure

Introduction

Triarylmethane derivatives have found applications in numerous fields, such as protective groups, organic dyes, photochromic agents, bioactive compounds and drugs, and as precursors for stable carbon-centered radicals (Figure 1).[1] Many approaches have been developed toward this scaffold, motivated by the need to access triarylmethanes bearing different functional groups selectively positioned on the aryl rings. The symmetric triarylmethanes, composed of three equivalent aromatic rings, can simply be obtained by Friedel-Crafts reaction with chloroform.[2,3] But the preparation of non-symmetric triarylmethanes, bearing two or three different aromatic rings, usually required stepwise synthetic strategies, which have been described as non-selective, difficult, and time-consuming. The Friedel–Crafts reaction and Baeyer condensation have been used for the preparation of non-symmetric triarylmethanes, in the presence of different catalysts (Figure 2), such as strong Brønsted or Lewis acids (TsOH,[4] TfOH,[5] $Sc(OTf)_3$,[6] $FeCl_3$,[7] $TiCl_4$,[8] $AlCl_3$,[9] $AuCl_3$,[10] $CuCl_2$,[11] $SnCl_4$,[12] among others), oxidants ($NaICl_2$,[13] I_2[14]), and ionic liquids.[15]

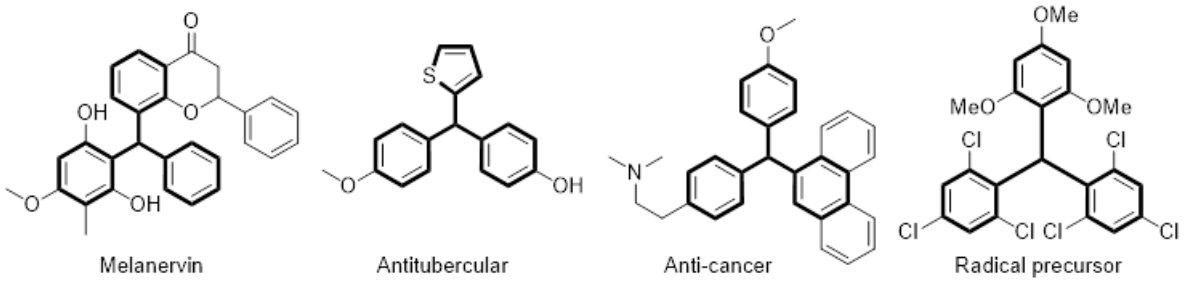


Figure 1. Examples of natural and synthetic biologically active triarylmethanes, and building blocks containing triarylmethyl moieties.

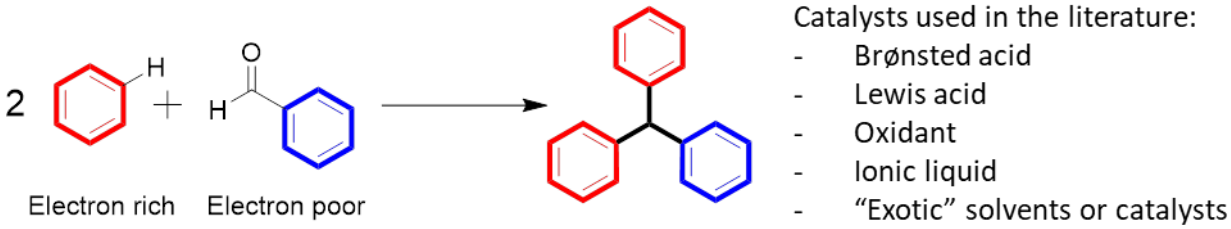


Figure 2. Friedel-Crafts reaction and Baeyer condensation toward triphenylmethane bearing electron-rich arenes.

In the course of our investigation, triarylmethane derivatives were needed as precursors of carbon-centered radicals, with both electron-donating and withdrawing substituents. In the literature, the preparation of such derivatives has been described as requiring organic salts, strong activations and difficult purification processes.[16] Here, we demonstrate that with an electron-rich arene, and a neutral or electron-poor aldehyde, only a catalytic amount of Brønsted acid is needed to obtain the product selectively and easily, in a process reminiscent of a Blanc-Quelet electrophilic aromatic substitution followed by a Friedel-Crafts alkylation.

Results and Discussion

In a preliminary experiment, pentafluorobenzaldehyde **1a** was reacted with 1,3,5-trimethoxybenzene **2** in an attempt to obtain the product of the double condensation. First, the reaction did not proceed when the reagents were mixed, with or without solvent, and warmed up. Then different acid catalysts were evaluated: $AlCl_3$ required anhydrous solvent, was not very practical, and did not give satisfactory yields; TsOH or TfOH in DCM or methanol gave better yields but required purification by chromatography, and sulfuric acid in methanol gave good yields of the product after neutralization with sodium carbonate, extraction and purification by chromatography. Finally, the best yield was obtained using concentrated hydrochloric acid as catalyst, in refluxing methanol, as the triarylmethane **3a** crystallized directly from the reaction mixture upon cooling. Using one or two equivalents of trimethoxybenzene **2** always gave the double addition product **3a**, and the unreacted aldehyde was recovered: after the first addition, the diarylmethanol is probably more reactive than the aldehyde, and therefore the reaction does not stop after the first addition. Increasing the amount of trimethoxybenzene **2** to 3 or 4 equivalents did not increase the yield, which seems to be limited only by the efficiency of the crystallization.

The scope of the reaction was tested with benzaldehyde and chlorobenzaldehydes **3b-h**, presenting different patterns of substitution with 0, 1, 2 or 3 chloro substituents (Figure 3). All compounds were isolated in good to excellent yields (70-90%) by simple filtration. The difference in yields is mainly due to the crystallization process, which was more or less efficient depending on the solubility of the corresponding triarylmethane. Attempts to broaden the scope using electron-rich benzaldehydes, with methoxy substituents (4-methoxybenzaldehyde, 2,4-dimethoxybenzaldehyde, 2,4,6-trimethoxybenzaldehyde) were unsuccessful, and the reagents were recovered after extraction.

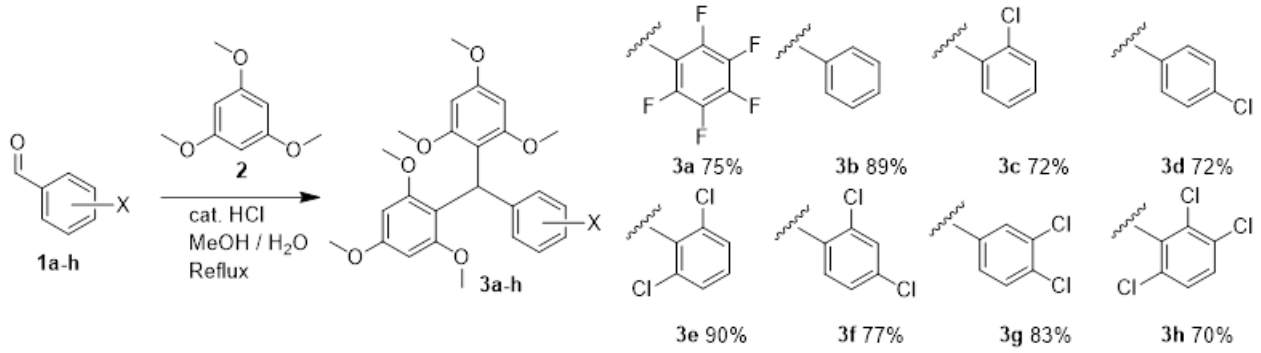


Figure 3. Simple synthetic route toward triarylmethanes, and scope of the reaction.

All the triarylmethanes **3a-h** crystallized directly from the reaction flask, and crystal structures were determined by single-crystal X-ray diffraction (Figure 4). All bond lengths and angles are in normal range, with values consistent with other triarylmethanes found in the literature, meaning that no significant distortions nor steric strains are observed in the structures.[17] All compounds present similar bond lengths and angles around the central carbon, and the three aryl substituents are not coplanar. These aryl substituents organize as a helical screw, which can adopt a right-handed or left-handed geometry, and the crystals contain a racemic mixture of both rotamers. For triarylmethanes, when the rotation around the single bond between the central carbon and the phenyl ring is blocked, such as in the case of tri(2,4,6-trichlorophenyl)methane, the two aromatic protons of each chlorophenyl substituents are diastereotopic and appear as two doublets in the NMR spectrum.[18] Here, analysis of the NMR spectra demonstrated that the aromatic protons of the

trimethoxyphenyl substituents are equivalent and appear together as one singlet, meaning that these rotamers can easily interconvert in solution, despite the steric hindrance of the methoxy groups, probably because the central carbon is less sterically cluttered.

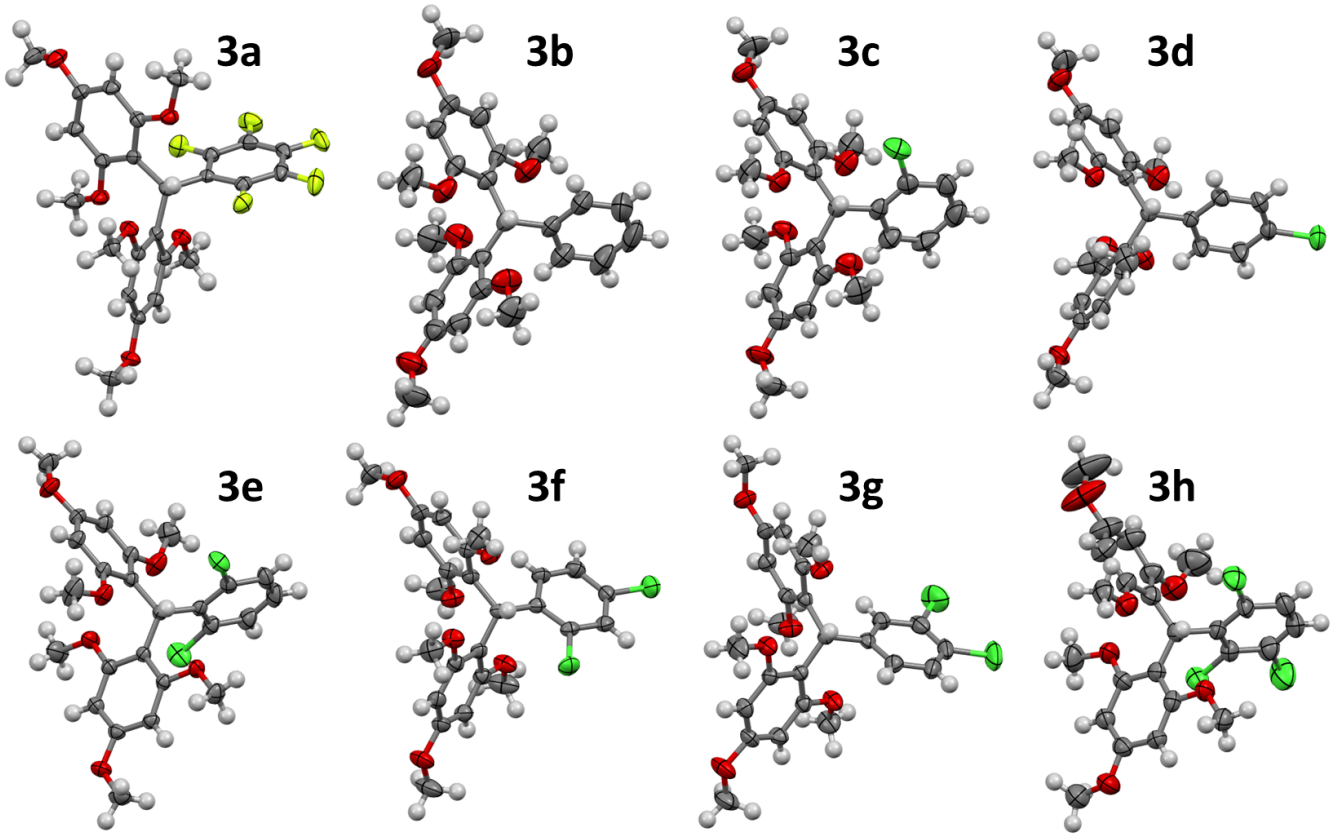


Figure 4. Structures of the compounds as revealed by single crystal X-ray diffraction (CCDC 2541525-2541532); Thermal ellipsoids are shown at the 50% probability level, hydrogen atoms are depicted with an arbitrary radius (0.30Å); C, grey; O, red; F, yellow; Cl, green; H, white.

Finally, the deprotonation of the central carbon was attempted, in order to oxidize the anion into the trityl radical.[6] Despite all our efforts, using moderate to strong bases (KOH, ^{t}BuOK, NaH, ^{n}BuLi, ^{t}BuLi) in various anhydrous solvents (DMSO, DMF, THF), the deprotonation never occurred and the starting materials were recovered.

Conclusions

A simple, practical and efficient synthesis of triarylmethanes was presented, giving the products in good to excellent yields upon crystallization from the reaction medium. The results demonstrate that this double condensation does not need exotic catalysts, as long as the aldehyde is electron poor, the nucleophilic aryl is electron rich, and the double addition is desired. Indeed, trimethoxybenzene seems to be so reactive that it does not allow the reaction to stop after the first addition: this protocol does not seem to be suitable for the synthesis of triarylmethane bearing three different aryl groups.

Experimental Section

General. All reagents were purchased from Sigma-Aldrich and used without any further purification. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 [300.13 MHz (^{1}H), 75.47 MHz (^{13}C)]. Unequivocal assignments were made on the basis of 2D HSQC ($^{1}H/^{13}C$) and HMBC experiments. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS (δ = 0), and the values of coupling constants (*J*) are given in Hertz (Hz). High-resolution mass spectra (HRMS-ESI+) were recorded on an LTQ OrbitrapTM XL hybrid mass spectrometer (Thermo Fischer Scientific, Bremen, Germany) controlled by LTQ Tune Plus 2.5.5 and Xcalibur 2.1.0. The capillary voltage of the electrospray ionization source (ESI) was set to 3.1 kV. Melting points were determined on a BUCHI Melting point apparatus and are uncorrected.

General procedure. A mixture of 1,3,5-trimethoxybenzene (2 equiv) and substituted benzaldehyde (1 equiv) in methanol (5 mL per mmol of benzaldehyde) was treated with concentrated hydrochloric acid (37%) (0.25 mL per mmol of benzaldehyde) and stirred at reflux during one hour. Upon completion, the solution was cooled down to 0 ºC in an ice bath and the solid was collected by filtration. Recrystallization from methanol afforded the pure product.

2,2'-((perfluorophenyl)methylene)bis(1,3,5-trimethoxybenzene) 3a.[19] 2,3,4,5,6-Pentafluorobenzaldehyde **1a** (1 equiv, 294 mg, 1.5 mmol) was added to a solution of 1,3,5-trimethoxybenzene **2** (2 equiv, 506 mg, 3 mmol) in methanol (10 mL). Then, concentrated HCl (1 mL) was added dropwise, and the solution was stirred at reflux during one hour. After cooling down to room temperature, the solid was collected by filtration. Recrystallization in methanol gave compound **3a** as a white crystalline solid (580 mg, 1.1 mmol, yield 75%). M.p. 140-142 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (s, 1H, C-*H*), 6.08 (s, 4H, C-H_{arom}), 3.78 (s, 6H, O-CH_3), 3.58 (s, 12H, O-CH_3) ppm. Spectral data match the literature.[19]

2,2'-(phenylmethylene)bis(1,3,5-trimethoxybenzene) 3b.[16] Benzaldehyde **1b** (1 equiv, 106 mg, 0.1 mL, 1.0 mmol) was added to a solution of 1,3,5-trimethoxybenzene **2** (2 equiv, 362 mg, 2.1 mmol) in methanol (10 mL). Then, concentrated HCl (1 mL) was added dropwise, and the solution was stirred at reflux during one hour. After cooling down to room temperature, the solid was collected by filtration. Recrystallization in methanol gave compound **3b** as a white crystalline solid (376 mg, 0.89 mmol, yield 89%). M.p. 182-184 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 – 7.11 (m, 2H, C-H_{arom}), 7.08 – 7.01 (m, 3H, C-H_{arom}), 6.22 (s, 1H, C-*H*), 6.11 (s, 4H, C-H_{arom}), 3.79 (s, 6H, O-CH_3), 3.50 (s, 12H, O-CH_3). Spectral data match the literature.[16]

2,2'-((2-chlorophenyl)methylene)bis(1,3,5-trimethoxybenzene) 3c.[16] 2-Chlorobenzaldehyde **1c** (1 equiv, 281 mg, 0.2 mL, 2.0 mmol) was added to a solution of 1,3,5-trimethoxybenzene **2** (2 equiv, 658 mg, 3.91 mmol) in methanol (15 mL). Then, concentrated HCl (1 mL) was added dropwise, and the solution was stirred at reflux during one hour. After cooling down to room temperature, the solid was collected by filtration. Recrystallization in methanol gave compound **3c** as a white crystalline solid (660 mg, 1.44 mmol, yield 72%). M.p. 192-194 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H, C-H_{arom}), 7.21 – 6.83 (m, 3H, C-H_{arom}), 6.28 (s, 1H, C-*H*), 6.10 (s, 4H, C-H_{arom}), 3.78 (s, 6H, O-CH_3), 3.50 (s, 12H, O-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 159.3, 142.9, 133.6, 130.6, 128.3, 125.9, 113.8, 92.1, 56.5, 55.3, 36.0. Spectral data match the literature.[16]

2,2'-((4-chlorophenyl)methylene)bis(1,3,5-trimethoxybenzene) 3d.[16] 4-Chlorobenzaldehyde **1d** (1 equiv, 292 mg, 2.1 mmol) was added to a solution of 1,3,5-trimethoxybenzene **2** (2 equiv, 691 mg, 4.1 mmol) in methanol (10 mL). Then, concentrated HCl (1 mL) was added dropwise, and the solution was stirred at reflux during one hour. After cooling down to room temperature, the solid was collected by filtration. Recrystallization in

methanol gave compound **3d** as a white crystalline solid (689 mg, 1.5 mmol, yield 72%). M.p. 165-167 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* 8.5 Hz, 2H, C-*H*$_{arom}$), 6.97 (d, *J* 8.5 Hz, 2H, C-*H*$_{arom}$), 6.16 (s, 1H, C-*H*), 6.10 (s, 4H, C-*H*$_{arom}$), 3.79 (s, 6H, O-C*H*$_3$), 3.51 (s, 12H, O-C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 159.4, 144.5, 129.7, 129.3, 127.2, 113.7, 91.8, 56.2, 55.3, 36.7. Spectral data match the literature.[16]

2,2'-((2,6-dichlorophenyl)methylene)bis(1,3,5-trimethoxybenzene) 3e.[16] 2,6-Dichlorobenzaldehyde **1e** (1 equiv, 850 mg, 4.9 mmol) was added to a solution of 1,3,5-trimethoxybenzene **2** (2 equiv, 1.70 g, 10.1 mmol) in methanol (30 mL). Then, concentrated HCl (1 mL) was added dropwise, and the solution was stirred at reflux during one hour. After cooling down to room temperature, the solid was collected by filtration. Recrystallization in methanol gave compound **3e** as a white crystalline solid (2.16 g, 4.39 mmol, yield 90%). M.p. 193-195 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* 7.9 Hz, 2H, C-*H*$_{arom}$), 6.92 (t, *J* 7.9 Hz, 1H, C-*H*$_{arom}$), 6.47 (s, 1H, C-*H*), 6.09 (s, 4H, C-*H*$_{arom}$), 3.78 (s, 6H, O-C*H*$_3$), 3.50 (s, 12H, O-C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 159.4, 141.1, 136.6, 128.5, 126.0, 113.5, 92.0, 56.5, 55.3, 36.6. Spectral data match the literature.[16]

2,2'-((2,4-dichlorophenyl)methylene)bis(1,3,5-trimethoxybenzene) 3f. 2,4-Dichlorobenzaldehyde **1f** (1 equiv, 269 mg, 1.54 mmol) was added to a solution of 1,3,5-trimethoxybenzene **2** (2 equiv, 519 mg, 3.08 mmol) in methanol (10 mL). Then, concentrated HCl (1 mL) was added dropwise, and the solution was stirred at reflux during one hour. After cooling down to room temperature, the solid was collected by filtration. Recrystallization in methanol gave compound **3f** as a white crystalline solid (582 mg, 1.18 mmol, yield 77%). M.p. 142-144 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* 2.1 Hz, 1H, C-*H*$_{arom}$), 7.01 (dd, *J* 8.5, 2.1 Hz, 1H, C-*H*$_{arom}$), 6.93 (d, *J* 8.5 Hz, 1H, C-*H*$_{arom}$), 6.21 (s, 1H, C-*H*), 6.09 (s, 4H, C-*H*$_{arom}$), 3.77 (s, 6H, O-C*H*$_3$), 3.50 (s, 12H, O-C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 159.4, 141.8, 134.1, 131.5, 130.6, 128.0, 125.9, 113.1, 91.9, 56.4, 55.3, 35.5; ESI-HRMS Calculated for $C_{25}H_{27}O_6Cl_2$ $[M+H]^+$ 493.1179; obtained: 493.1183.

2,2'-((3,4-dichlorophenyl)methylene)bis(1,3,5-trimethoxybenzene) 3g. 3,4-Dichlorobenzaldehyde **1g** (1 equiv, 348 mg, 1.99 mmol) was added to a solution of 1,3,5-trimethoxybenzene **2** (2 equiv, 610 mg, 3.63 mmol) in methanol (10 mL). Then, concentrated HCl (1 mL) was added dropwise, and the solution was stirred at reflux during one hour. After cooling down to room temperature, the solid was collected by filtration. Recrystallization in methanol gave compound **3g** as a white crystalline solid (822 mg, 1.67 mmol, yield 83%). M.p. 157-159 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* 8.3 Hz, 1H, C-*H*$_{arom}$), 7.12 (dd, *J* 2.1, 0.9 Hz, 1H, C-*H*$_{arom}$), 6.86 (ddd, *J* 8.3, 2.1, 0.9 Hz, 1H, C-*H*$_{arom}$), 6.13 (s, 1H, C-*H*), 6.10 (s, 4H, C-*H*$_{arom}$), 3.79 (s, 6H, O-C*H*$_3$), 3.53 (s, 12H, O-C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 146.6, 130.9, 129.9, 128.9, 127.7, 112.8, 91.7, 56.2, 55.3, 36.5; ESI-HRMS Calculated for $C_{25}H_{27}O_6Cl_2$ $[M+H]^+$ 493.1179; obtained: 493.1173.

2,2'-((2,3,6-trichlorophenyl)methylene)bis(1,3,5-trimethoxybenzene) 3h. 2,3,6-Trichlorobenzaldehyde **1h** (1 equiv, 219 mg, 1.04 mmol) was added to a solution of 1,3,5-trimethoxybenzene **2** (2 equiv, 344 mg, 2.05 mmol) in methanol (10 mL). Then, concentrated HCl (1 mL) was added dropwise, and the solution was stirred at reflux during one hour. After cooling down to room temperature, the solid was collected by filtration. Recrystallization in methanol gave compound **3h** as a white crystalline solid (375 mg, 0.705 mmol, yield 70%). M.p. 206-208 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* 8.6 Hz, 1H, C-*H*$_{arom}$), 7.08 (d, *J* 8.6 Hz, 1H, C-*H*$_{arom}$), 6.50 (s, 1H, C-*H*), 6.08 (s, 4H, C-*H*$_{arom}$), 3.78 (s, 6H, O-C*H*$_3$), 3.51 (s, 12H, O-C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 159.6, 143.4, 134.4, 126.9, 112.8, 91.8, 56.4, 55.3, 37.7; ESI-HRMS Calculated for $C_{25}H_{26}O_6Cl_3$ $[M+H]^+$ 527.0789 obtained: 527.0790.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra, and crystallographic data are provided in the Supplementary Material associated with this article.

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