Gram-Scale Synthesis of Substituted Triarylmethanes

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H2O

green condition high yield gram-scale synthesis (+) > 50 examples
facile-operational open-vessel by-product is water environmentally friendly

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Abstract A high-yield, open-vessel route for the facile-operational, gram-scale synthesis of functionalized triarylmethanes (TRAMs) is described via silica-coated magnetic nanoparticles of modified polyphosphoric acid (NiFe2O4@SiO2-PPA)-mediated intermolecular Friedel–Crafts reaction of substituted aryl aldehydes with 2 equivalents of oxygenated arenes under environmentally friendly reaction conditions. Among the overall reaction process, only water was generated as the by-product. Various reaction conditions are investigated for efficient transformation.

Key words gram-scale synthesis, triarylmethanes, magnetic nanoparticles, Friedel–Crafts reaction, environmentally friendly

Panda and co-worker analyzed these elegant synthetic methodologies of diversified TRAMs.4 Subsequently, by focusing the transition metal catalysis, Nambo and Crudden compared the synthetic routes of chiral TRAMs.5 Very recently, the Saha, Huang, and Nandi teams described the advanced development in the progress of catalytic and stoichiometric synthesis of TRAMs.6 These review papers demonstrated that the core system of symmetrically and asymmetrically substituted TRAMs could exhibit numerous unique properties, including organic functionalized materials, biologically active molecules, chemoselective metal-ion sensors, and useful synthetic building blocks.

Traditionally, the Friedel–Crafts reaction and Baeyer condensation have been two of the most commonly employed tools for the formation of TRAMs in the presence of different promoters. Several promoters have been reported, as shown in Scheme 1, including protic acid (TsOH,7 TfOH8), Lewis acid (FeCl3,9 TiCl4,10 NbCl5,11 SbCl3,12 AlCl3,13 AuCl3,14 CuCl2,15 SnCl4,16 ZrOCl217), acidic polymer (NKC-9,18 Amberlyst-15,19 Nafion-H20), oxidant (NaICl2,21 I222), clay (K10),23 ionic liquid,24 microwave irradiation, and sonication.25

Scheme 1 Synthetic routes of triarylmethanes (TRAMs)

For the related applications of triarylmethanes (TRAMs) and their derivatives, there are several review articles documented. In 1993, Duxbury outlined the first photochemical and photophysical dyestuff properties of triphenylmethane.1 Afterward, Shchepinov and Korshun provided a discussion for the applications of a bifunctional trityl cation (a deprotonated TRAMs).2 The Nair group summarized the synthetic chemistry of triaryl- and triheteroarylmethanes.3

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Recently, a number of transition-metal-catalyzed methods have emerged as an alternative route to provide structurally diverse TRAMs. The main drawbacks of the synthetic routes for these catalysts were that they were corrosive or expensive, and the apparatus for microwaving and sonication was infrequently put to use. Moreover, the desired TRAMs required a tedious workup process. Motivated by the above-mentioned literature survey, herein, we chose excellent silica-coated magnetic nanoparticles (MNP) of modified polyphosphoric acid (PPA) as a reusable, facile-operational and green solid support for the gram-scale generation of TRAMs under a mild reaction condition and open-vessel conditions. Among these synthetic catalysts towards TRAMs, to the best of our knowledge, no MNP-mediated synthetic reports have been documented. However, recent examples on chiral organophosphoric acid (OrganoPPA)-mediated enantioselective synthesis of TRAMs have been developed.31–35 To deserve to be mentioned, Zhao36 and Walsh37 have reported the novel and efficient process and repeated-cycling activation. For the synthetic applications on the combination of MNP and PPA, a few examples have been reported on the establishment of thioxoquinazolinone, β-acetamido ketone, pyranopyrazole, and chromeno[4,3-b]chromene skeletons.38–41 On the basis of the above-mentioned literature survey, herein, we present an efficient, one-step synthetic route towards TRAMs via a Friedel–Crafts reaction and Baeyer condensation of substituted aryl aldehydes and oxygenated arenes in the presence of freshly prepared silica-coated magnetic nanoparticles of modified Brønsted acids (MNP-BA) 3a–c. Among the overall reaction processes, only water was generated as the by-product. The use of nanostructured materials as support for different types of functional transformations remains an attractive field to organic chemists. The nature of the magnetic nanoparticle catalysts usually allows for facile-operational purification, an easy-recovered process and repeated-cycling activation.

The initial study commenced with the treatment of simple benzaldehyde (1a; Ar = Ph, 0.53 g, 5.0 mmol) with veratrole [2a; Ar′ = 3,4-(MeO)2C6H3; 1.38 g, 10.0 mmol]. After perusing review articles on MNP-BA-promoted synthetic applications,26–30 three that are known and well-prepared, NiFe2O4@SiO2–PPA (3a),38,39 Ni0.5Zn0.5Fe2O4@SiO2–PPA (3b),39 and CuFe2O4@SO3H (3c),41 were examined. First, by using 3a (10 mol%), only a 12% yield of 4a was obtained in the presence of MeCN (1 mL) at 25 °C for 5 hours (Table 1, entry 1). By changing the solvent to toluene, a similar yield (20%) was obtained (entry 2). However, CHCl3 and DME provided modest yields (47% and 61%, entries 3, 4). For MeNO2 and DMF, better yields (70% and 90%) were observed (entries 5, 6). From the results, we found that more polar solvent could increase the yield of 4a. With the results in mind, the optimal reaction time was surveyed next by controlling 3a as the promoter and DMF as the solvent. To increase the isolated yield, elongated times (10, 15, and 20 h) were investigated. In entries 7–9, we found that three reaction times provided yields of nearly 85%, 82%, and 80%, respectively. From the experimental results, we understood that longer reaction times (10, 15 or 20 h) did not enhance the yield of 4a.

Furthermore, reaction temperature screening was performed. By elevating the temperature to 80 °C, a 70% yield of 4a was isolated, but when the reaction was conducted at a reflux temperature (154 °C), the yield of 4a was quickly decreased to 39% (Table 1, entry 10). It is obvious that the reaction was appropriate under a room temperature-dependent condition. A possible reason could be that elevating the temperature could destroy the magnetic nanoparticle’s structure stepwise such that catalytic amounts of 3a could not promote the generation of 4a efficiently. On the basis of the above-mentioned data, DMF volumes were studied. After diluting the reaction concentration from 1 mL to 5 mL, a slightly lower yield (78%) was obtained (entry 11).

Table 1 Reaction Conditionsa

<table>
<thead>
<tr>
<th>Entry</th>
<th>MNP-BA 3a–c</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>MeCN</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>toluene</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>CHCl3</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DME</td>
<td>5</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>MeNO2</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DMF</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DMF</td>
<td>10</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DMF</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DMF</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DMF</td>
<td>10</td>
<td>70a/39d</td>
</tr>
<tr>
<td>11</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DMF</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>12</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DMF</td>
<td>10</td>
<td>82</td>
</tr>
<tr>
<td>13</td>
<td>NiFe2O4@SO3H–PPA 3a</td>
<td>DMF</td>
<td>10</td>
<td>85</td>
</tr>
<tr>
<td>14</td>
<td>Ni0.5Zn0.5Fe2O4@SO3H–PPA 3b</td>
<td>DMF</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>CuFe2O4@SO3H 3c</td>
<td>DMF</td>
<td>10</td>
<td>63a</td>
</tr>
<tr>
<td>16</td>
<td>SiO2–PPA</td>
<td>DMF</td>
<td>10</td>
<td>80</td>
</tr>
</tbody>
</table>

a Reactions were run on a 5.0 mmol scale with 1a (530 mg), 2a (1380 mg, 10.0 mmol), solvent (1 mL), and 3a–c (250 mg, ~10 mol%) at 25 °C.

b Isolated yields.

At 80 °C.

c Reflux (154 °C).

d DMF (5 mL).

e Solvent-free condition.

f Amount of 3a used: 500 mg, ~20 mol%.

g Complex unknown mixture (~10%) was isolated.
11). Under solvent-free conditions, however, a neat solution system provided similar yields (82%, entry 12). Compared with entry 6 (1 mL DMF), neither of them obtained higher yields of 4a. In entry 13, increasing the catalytic amounts (10 → 20 mol%) of 3a, the same yield (85%) of 4a was isolated. This meant that 10 mol% amount of 3a was enough to produce a better yield of 4a. Subsequently, 3b and 3c were checked. When the reaction was treated with 3b, the provided yield (70%) was lower than 3a (entry 14). According to the results, we found that NiFeO₁₂ had more reactive magnetic nanoparticles than NiₓZnₓFe₂O₄ due to the higher component of nickel increasing the yield of 4a. On the other hand, changing the source of the Brønsted acid from phosphoric acid to sulfonic acid, 3c was tested. However, 4a was isolated in a lower yield (63%) along with a 10% yield of a complex unknown mixture (entry 15). For the phenomenon of low yield, we envisioned that the sulfonic acid residue on 3c was a stronger Brønsted acid than PPA such that complex products were detected. Finally, by removing MNP-dispersion, a simple solid support of SiO₂-PPA (250 mg) was tested, and the obtained yield (80%, entry 16) was lower than 3a. Compared with 3a (entry 6, 90%) and SiO₂-PPA (entry 16, 80%), 3a provided a higher yield than SiO₂-PPA. On the basis of the results, we envisioned that MNP should also play the Lewis acid role to catalyze the reaction process such that the yield of 4a was improved from 80% to 90%. From these observations, we concluded that entry 6 provided optimal conditions for the formation of 4a (90%) via a 3a-promoted intermolecular Friedel–Crafts reaction and Baeyer condensation of 1a with 2a.

On the basis of our experimental results, a plausible mechanism for the formation of 4a is illustrated in Scheme 2. Initially, coupling 1a with 3a yields A via an intermolecular proton exchange. With the involvement of 2a, the methoxy group on 2a can trigger the para-carbon to attack the protonated carbonyl group of 1a yielding B and 3a with a phosphate ion. Following the aromatization process, 3a with a phosphate ion abstracts the proton from B to lead to C. After protonation of the hydroxyl group on C with the resulting 3a, D having an oxonium ion, can be formed. Then, by the electron-donating ability of the para-methoxy group, water can be removed from the dibenzylic position to afford E. Subsequently, by the involvement of another 2a, F is generated via the above-mentioned intermolecular addition. Finally, after dehydrogenative aromatization by 3a with a phosphate ion, 4a can be formed spontaneously along with the recovery of 3a.

To explore the substrate scope and limitations of this route, diversified aryl aldehydes 1a–x were reacted with substituted oxygenated arenes 2a–i to afford functionalized TRAMs 4a–t, 4u–ah in the presence of 3a, as shown in Table 2. With optimal conditions established (Table 1, entry 6) and a plausible mechanism proposed (Scheme 2), we found that this route allowed a direct Friedel–Crafts reaction and Baeyer condensation under mild conditions in the range of moderate to good yields (Table 2, entries 1–34, 80–94%). By controlling dioxygenated 2a as the arene source, entries 1–23 showed that different Ar groups of 1a–x with halogen (fluoro, bromo, dichloro), electron-neutral (methyl, dimethyl), electron-withdrawing (nitro, trifluoromethyl, methyl ketone, formyl) and electron-releasing (mono-, di- or tri-oxygenated) groups, and carbocyclic (2-naphthyl) and heterocyclic (2-thienyl, 2-pyridyl, 2-furyl) groups, etc. did not affect the efficient formations of 4a–x except for 4t. The
molecular structure of 4e was determined by single-crystal X-ray analysis. Also deserving mention, entry 13 showed that Ar with both one electron-withdrawing nitro group and two electron-donating oxygenated groups produced 4m in an 84% yield. Unexpectedly, 1s could produce an 84% yield of the product 4s. However, when treatment of 2a with 1t with a 2-furyl group was undertaken, no desired product 4t was isolated, and only an unidentified and unknown complex mixture was detected due to the low aromaticity of the furan ring resulting in the phenomenon (Table 2, entry 20). By the use of SiO2-PPA (Table 1, entry 16), 4t could not be still obtained. From the results, we believe that 2-furyl group was unstable under the PPA/DMF condition. For the bis-formyl group of 1u, in particular, the optimal reaction condition controlled one formyl group of 1u to react with two equivalents of 3a selectively, and the asymmetrical 4u with one formyl residue could be generated in a 90% yield (entry 21). On the other hand, when treatment of 2a (2.0 equiv) was undertaken with 1v having two kinds of different carbonyl synthons, the formyl and acetyl, respectively, only the formyl group could be converted to 4v (entry 22). However, the acetyl substituent was not initiated in the Friedel–Crafts reaction. In entry 23, 1w with one formyl and one nitrile groups showed similar results.

Table 2 Synthesis of 4a–ag and 4ah–1

<table>
<thead>
<tr>
<th>Entry</th>
<th>1, Ar</th>
<th>2, Ar’</th>
<th>4, Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a, Ph</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4a, 90</td>
</tr>
<tr>
<td>2</td>
<td>1b, 3-FC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4b, 94</td>
</tr>
<tr>
<td>3</td>
<td>1c, 4-MeC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4c, 94</td>
</tr>
<tr>
<td>4</td>
<td>1d, 4-MeOC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4d, 90</td>
</tr>
<tr>
<td>5</td>
<td>1e, 3,4-(MeO)4C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4e, 94</td>
</tr>
<tr>
<td>6</td>
<td>1f, 3,4-CH2O2C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4f, 93</td>
</tr>
<tr>
<td>7</td>
<td>1g, 4-PhC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4g, 91</td>
</tr>
<tr>
<td>8</td>
<td>1h, 2-naphthyl</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4h, 87</td>
</tr>
<tr>
<td>9</td>
<td>1i, 2-Br,4,5-(MeO)4C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4i, 89</td>
</tr>
<tr>
<td>10</td>
<td>1j, 3-MeOC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4j, 90</td>
</tr>
<tr>
<td>11</td>
<td>1k, 2-NO2C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4k, 86</td>
</tr>
<tr>
<td>12</td>
<td>1l, 3-CF3C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4l, 87</td>
</tr>
<tr>
<td>13</td>
<td>1m, 3-MeO,4-OMe,5-NO2C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4m, 84</td>
</tr>
<tr>
<td>14</td>
<td>1n, 3-(Me)2C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4n, 88</td>
</tr>
<tr>
<td>15</td>
<td>1o, 3,4-C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4o, 90</td>
</tr>
<tr>
<td>16</td>
<td>1p, 4-HOC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4p, 90</td>
</tr>
<tr>
<td>17</td>
<td>1q, 4-ClC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4q, 91</td>
</tr>
<tr>
<td>18</td>
<td>1r, 4-NO2,2-thienyl</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4r, 83</td>
</tr>
<tr>
<td>19</td>
<td>1s, 3-pyridyl</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4s, 84</td>
</tr>
<tr>
<td>20</td>
<td>1t, 2-furyl</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4t, –</td>
</tr>
<tr>
<td>21</td>
<td>1u, 4-CHOOC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4u, 90</td>
</tr>
<tr>
<td>22</td>
<td>1v, 3-MeC=OC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4v, 90</td>
</tr>
<tr>
<td>23</td>
<td>1w, 4-NCC6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4w, 93</td>
</tr>
<tr>
<td>24</td>
<td>1x, 3,4,5-(MeO)4C6H4</td>
<td>2a, 1,2-(MeO)2C6H4</td>
<td>4x, 89</td>
</tr>
</tbody>
</table>
Furthermore, after elongating the dioxygenated aliphatic carbon chain from a one-carbon 2a, 2b to a four-carbon side chain, 2c was examined. In Table 2, entries 26–28, 2c with a shorter bis-n-butoxy arm provided 4z, 4aa, and 4ab in 85%, 85% and 74% yield, respectively. With these results in hand, both 4ac (medium n-octyloxy chain) and 4ad (longer n-dodecyloxy group) could be obtained in good yields (89% and 80%, entries 29, 30).

This was a quite convenient route used to obtain TRAMs skeleton having different lipid-containing side chains. After increasing the chain number from dimethoxy 2a to tri-methoxy (for 2f), the yield of 4ae could be maintained (80%, Table 2, entry 31), and both contiguous 1,2,3-tri-n-butoxy (2g) and 1,2,3-tri-n-octyloxy (2h) also produced 4af and 4ag in good yields (82% and 81%, entries 32, 33). By the use of cold hexane as the solvent, interestingly, these nonpolar products with four-carbon, eight-carbon, and twelve-carbon side chains were dissolved easily such that the overall purification process was easy to handle. After searching the literature on the preparation of TRAMs with two to six lipid chains, however, no studies were found on related synthetic work. Therefore, the present work provides a novel route for synthesizing the TRAMs with four or six lipid-conjugated arms. In particular, no desired 4ah was detected, and 4ah-1 was obtained in only a 30% yield via the reaction of 1x (1.0 equiv) and 2i (2.0 equiv) with a separated 1,3,5-trimethoxy group (entry 34). Especially, two equivalents of 1x were installed into the formation of 4ah-1 in the presence of excess amounts of 2i (Scheme 3). This reasonable mechanism showed that the initial intermediate 1 was formed by the reaction of the same equivalent of 1x and 2i. In the next reaction of 1, a competitive behavior between 1x and 2i was formed. When the reaction of 1 treated 2i, the expected 4ah could be formed, but we could not isolate 4ah. Therefore, we envisioned that 1 preferred to react with 1x over 2i. For the generation of intermediate II, a possible reason could be that the oxygenated group on 1 can promote the para-carbon to easily attack the formyl group of 1x. After accomplishing the aromatization of II, the desired 4ah-1 was generated. This synthetic route provided highly effective four C-C bond formations. The unique tricyclic molecular structure of 4ah-1, with an anthracene core, was determined by single-crystal X-ray analysis.43

Table 2 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>1, Ar =</th>
<th>2, Ar’ =</th>
<th>4, Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1x, 3,4,5-(MeO)3C6H2</td>
<td>2b, 1,2-Ch2O2C6H4</td>
<td>4y, 84</td>
</tr>
<tr>
<td>26</td>
<td>1o, 3,4-C6H4</td>
<td>2c, 1,2-(C6H4O)3C6H4</td>
<td>4z, 85</td>
</tr>
<tr>
<td>27</td>
<td>1h, 2-naphthyl</td>
<td>2c, 1,2-(C6H4O)3C6H4</td>
<td>4a, 85</td>
</tr>
<tr>
<td>28</td>
<td>1x, 3,4,5-(MeO)3C6H2</td>
<td>2c, 1,2-(C6H4O)3C6H4</td>
<td>4ab, 84</td>
</tr>
<tr>
<td>29</td>
<td>1x, 3,4,5-(MeO)3C6H2</td>
<td>2d, 1,2-(C6H4O)3C6H4</td>
<td>4ac, 89</td>
</tr>
<tr>
<td>30</td>
<td>1x, 3,4,5-(MeO)3C6H2</td>
<td>2e, 1,2-(C6H4O)3C6H4</td>
<td>4ad, 80</td>
</tr>
<tr>
<td>31</td>
<td>1x, 3,4,5-(MeO)3C6H2</td>
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<tr>
<td>32</td>
<td>1x, 3,4,5-(MeO)3C6H2</td>
<td>2g, 1,2,3-(C6H4O)3C6H4</td>
<td>4af, 82</td>
</tr>
<tr>
<td>33</td>
<td>1x, 3,4,5-(MeO)3C6H2</td>
<td>2h, 1,2,3-(C6H4O)3C6H4</td>
<td>4ag, 81</td>
</tr>
<tr>
<td>34</td>
<td>1x, 3,4,5-(MeO)3C6H2</td>
<td>2i, 1,3,5-(MeO)3C6H4</td>
<td>4ah, –d</td>
</tr>
</tbody>
</table>

a Reactions were run on a 5.0 mmol scale with 1a–x, 2a–l (10.0 mmol), NiFe2O4@SiO2–PPA (3a; 250 mg, –10 mol%), DMF (1 mL), 10 h at 25 °C.

b Isolated yields.

c Complex unknown mixture was isolated.

d Product 4ah-1 (30%) was isolated.

Encouraged by the above experimental results, synthesis of the asymmetrical TRAMs skeletons was investigated next (Scheme 4). By involvement of NiFe2O4@SiO2–PPA (3a) as the acid support, the initial reaction of model p-tolualdehyde (1c) with the same equivalent of two oxygenated arenes 2f (1.0 equiv) and 2j (1.0 equiv) produced 4ai in an 80% yield. The experiment revealed that the formyl group on 1c could be reacted with 2f first to generate a secondary alcohol moiety (for the generation of intermediate A) followed by the sequential introduction of anisole (2j) via a well-ordered intermolecular Friedel–Crafts reaction sequence. Controlling the starting substrates 1c and 2f, 2a, 2b, and 2c produced 4aj, 4ak, and 4ai in 78%, 76% and 72% yield, respectively. By similar reaction conditions, after adjusting aldehyde 1c with an electron-neutral group to 2f with an electron-withdrawing group and changing 2f with a trimethoxy group to 2a with a dimethoxy group, four TRAMS 4am–ap were produced in a range of 70–76% yields by the reaction of 2j, 2b, 2c, and 2f. Furthermore, 4aq–as were obtained in 76–80% yields by the combination of bicyclic 1b, 2a, and 2j, 2f and 2b. This was an efficient transformation for the magnetic nanoparticle-mediated preparation of asymmetrical TRAMs skeletons.
On the basis of the abovementioned results, a linear dendrimer-like TRAMs structure was examined next (Scheme 5). Double condensation of 1,4-diformylbenzene (1u) with four equivalents of 2a produced 4at in a 58% yield along with two equivalents of water. As an extension of the NiFe2O4@SiO2-PPA (3a)-mediated synthesis of triarylmethanes (TRAMs), we were able to synthesize 11H-dibenzo[b,e]azepine skeleton (Scheme 6). 11H-Dibenzo[b,e]azepine is a versatile core in useful synthetic intermediates and bioactive molecules. Furthermore, by using 4k as the starting material, tricyclic 5 was obtained in a 40% yield in three-steps including: (1) reduction of the nitro group on 4k, (2) N-acylation of the resulting amine with excess acetyl chloride in the presence of triethylamine (Et3N), and (3) trifluoroboron etherate (BF3·OEt2)-mediated Bischler-Napieralski cyclization of the corresponding amide.
Because of the potential application of this protocol in synthesis of various TRAMs, attempts at large-scale up of the transformation would improve the significance of the results. Thus, the development of a re-used 3a-mediated 10 grams-scale route was highly in demand. As shown in Scheme 7, re-cycled 3a (2.0 g)-mediated reaction of benzaldehyde (1a, 4.24 g, 40 mmol) and veratrole (2a, 11.04 g, 80 mmol) could produce 4a in a 76% yield (11.07 g) in DMF (8 mL) at 25 °C for 5 hours. Compared with 5 mmol scale of 1a (90%, Table 2, entry 1), 40 mmol scale provided a lower yield (76%). Although the obtained yield was lower, the 10 grams-scale synthetic route of TRAMs was well-established.

In summary, we have developed a gram-scale, environmentally friendly, one-step Friedel–Crafts type route for the synthesis of symmetrical and asymmetrical functionalized triarylmethanes (TRAMs) via silica coated magnetic nanoparticles of modified polyphosphoric acid (NiFe2O4@SiO2-PPA)-mediated intermolecular condensation of substituted aryl aldehydes with 2 equivalents of oxygenated arenes. A related plausible mechanism has been proposed. The uses of various reaction conditions were investigated for efficient transformation. Further investigations regarding the synthetic application of TRAMs will be conducted and published in due course.

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry N2, with magnetic stirring. Products in organic solvents were dried with anhyd MgSO4 before concentration in vacuo. Melting points were determined with a SMP3 melting apparatus. 1H and 13C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

Scheme 6 Synthesis of 5

Scheme 7 Large-scale synthesis of 4a

The starting substrates 1a-y and 2a-j were purchased commercially and used without further purification. For three freshly prepared silica-coated magnetic nanoparticles of modified Bronsted acids (MNP-BA), NiFe2O4@SiO2-PPA (3a), Ni0.5Zn0.5Fe2O4@SiO2-PPA (3b) and CuFe2O4@SO3H (3c), these compounds were known and preparation methods were identical with those in the literature.

Triarylmethanes 4a–s, 4u–ag, and 4ah–1; General Procedure 1

NiFe2O4@SiO2-PPA (3a; 250 mg, 10 mol%) was added to a stirred solution of aryl aldehyde 1 (5.0 mmol) and oxygenated arene 2 (10.0 mmol) in DMF (1 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 5 h. Upon completion, 3a could be placed on the side wall of the reaction vessel with the aid of an external magnet, then 3a was isolated, washed with CH2Cl2 (3 × 5 mL) and dried to reuse in the next run. Then, combined DMF and CH2Cl2 solutions were concentrated under reduced pressure to afford the crude product. Purification on silica gel (hexanes/EtOAc 50:1 to 10:1) afforded compounds 4a–s, 4u–ag, and 4ah–1.

4,4′-(Phenylmethylene)bis(1,2-dimethoxybenzene) (4a)

Prepared according to the general procedure 1 from 1a (530 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 90% (1639 mg); white solid; mp 126–128 °C (recrystallized from hexanes and EtOAc).

1H NMR (400 MHz, CDCl3): δ = 7.29–7.22 (m, 1 H), 6.92–6.88 (m, 2 H), 7.14–7.12 (m, 2 H), 6.78 (d, J = 8.4 Hz, 2 H), 6.69 (d, J = 2.0 Hz, 2 H), 6.61 (dd, J = 2.0, 8.4 Hz, 2 H), 5.46 (s, 1 H), 3.84 (s, 6 H), 3.75 (s, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 148.5 (2 ×), 147.2 (2 ×), 144.1, 136.5, 129.0 (2 ×), 128.0 (2 ×), 126.0 (2 ×), 121.2 (2 ×), 112.6 (2 ×), 110.7 (2 ×), 55.7, 55.6 (2 ×), 55.5 (2 ×).


4,4′-(3-Fluorophenyl)methylene)bis(1,2-dimethoxybenzene) (4b)

Prepared according to the general procedure 1 from 1b (620 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 94% (1796 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.28–7.22 (m, 1 H), 6.92–6.88 (m, 2 H), 6.82–6.79 (m, 1 H), 6.79 (d, J = 8.4 Hz, 2 H), 6.65 (d, J = 2.0 Hz, 2 H), 6.59 (dd, J = 2.0, 8.0 Hz, 2 H), 5.43 (s, 1 H), 3.86 (s, 6 H), 3.77 (s, 6 H).

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4.4′-(p-Tolylmethylene)bis(1,2-dimethoxybenzene) (4c)
Prepared according to the general procedure 1 from 1c (600 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 94% (1777 mg); colorless solid; mp 141–143 °C (recrystallized from hexanes and EtOAc).

1H NMR (400 MHz, CDCl3): δ = 7.10 (d, J = 8.0 Hz, 2 H), 7.02 (d, J = 8.0 Hz, 2 H), 6.78 (d, J = 8.0 Hz, 2 H), 6.60 (d, J = 2.0 Hz, 2 H), 4.10 (m, 1 H), 3.86 (s, 6 H), 3.77 (s, 6 H), 2.33 (s, 3 H).


4.4′-(4-Methoxyphenyl)methylene]bis(1,2-dimethoxybenzene) (4d)
Prepared according to the general procedure 1 from 1d (680 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 90% (1777 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.03 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 8.4 Hz, 2 H), 6.67 (d, J = 2.0 Hz, 2 H), 6.60 (dd, J = 2.0, 8.4 Hz, 2 H), 5.40 (s, 1 H), 3.87 (s, 9 H), 3.76 (s, 9 H).


Tris(3,4-dimethoxyphenyl)methane (4e)
Prepared according to the general procedure 1 from 1e (830 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 94% (1989 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 6.78 (d, J = 8.4 Hz, 3 H), 6.66 (d, J = 2.0 Hz, 3 H), 6.59 (dd, J = 2.0, 8.0 Hz, 3 H), 5.38 (s, 1 H), 3.86 (s, 9 H), 3.76 (s, 9 H).


Single-Crystal X-ray Data
Crystals of compound 4e were grown by slow diffusion of EtOAc into a solution of compound 4e in CH2Cl2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 2₁, a = 10.4946(9) Å, b = 8.4754(10) Å, c = 14.0842(18) Å, V = 1149.92(2) Å³, Z = 2, dcalc = 1.226 g/cm³, F(000) = 452, 28 range 1.508–25.086°, R indices (all data) R1 = 0.1487, wR2 = 0.1290.

5-(Bis[3,4-dimethoxyphenyl)methylene]benzo[d][1,3]dioxole (4f)
Prepared according to the general procedure 1 from 1f (750 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 93% (1898 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 6.78 (d, J = 8.0 Hz, 2 H), 6.72 (d, J = 7.6 Hz, 1 H), 6.66 (d, J = 2.0 Hz, 2 H), 6.60 (t, J = 2.4 Hz, 2 H), 6.57 (dt, J = 2.0, 8.0 Hz, 2 H), 5.91 (s, 2 H), 5.35 (s, 1 H), 3.82 (s, 6 H), 3.73 (s, 6 H).


4.4′-(3-Methoxyphenyl)methylene]bis(1,2-dimethoxybenzene) (4j)
Prepared according to the general procedure 1 from 1j (680 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 90% (1777 mg); white solid; mp 108–110 °C (recrystallized from hexanes and EtOAc).
1H NMR (400 MHz, CDCl3): δ = 7.20 (t, J = 8.0 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 2 H), 6.76–6.66 (m, 5 H), 6.81 (dd, J = 2.0, 8.4 Hz, 2 H), 5.41 (s, 1 H), 3.85 (s, 6 H), 3.77 (s, 6 H), 3.74 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 135.9, 136.5, 129.1 (2 x), 121.7, 121.3 (2 x), 115.3, 112.6 (2 x), 111.2, 110.8 (2 x), 55.81, 55.75 (2 x), 55.7 (2 x), 55.0.


4.4′-(2-Nitrophenyl)methylene)bis(1,2-dimethoxybenzene) (4k)
Prepared according to the general procedure 1 from 1k (755 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 86% (1759 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.85 (dd, J = 1.2, 8.4 Hz, 1 H), 7.48 (dt, J = 1.2, 7.6 Hz, 1 H), 7.37 (dt, J = 1.2, 8.4 Hz, 1 H), 7.09 (d, J = 7.6 Hz, 1 H), 6.77 (d, J = 8.0 Hz, 2 H), 6.62 (d, J = 2.0 Hz, 2 H), 6.51 (dd, J = 2.0, 8.4 Hz, 2 H), 6.17 (s, 1 H), 3.85 (s, 6 H), 3.76 (s, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 149.7, 148.9 (2 x), 147.8 (2 x), 138.5, 134.6, 132.3, 131.7, 127.4 (2 x), 124.6, 121.3 (2 x), 112.8 (2 x), 110.8 (2 x), 55.81 (2 x), 55.79 (2 x), 50.5.


4.4′-(3-Trifluoromethyl)-2,4-bis(1,2-dimethoxy benzene) (4l)
Prepared according to the general procedure 1 from 1l (870 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 87% (1880 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.48 (d, J = 7.6 Hz, 1 H), 7.42–7.38 (m, 2 H), 7.29 (d, J = 8.0 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 2 H), 6.64 (d, J = 2.0 Hz, 2 H), 6.57 (dd, J = 2.0, 8.4 Hz, 2 H), 5.49 (s, 1 H), 3.86 (s, 6 H), 3.77 (s, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 149.7, 148.9 (2 x), 147.8 (2 x), 133.5, 131.7, 127.4 (2 x), 124.6, 121.3 (2 x), 112.8 (2 x), 110.8 (2 x), 55.81 (2 x), 55.79 (2 x), 50.5.

2-[Bis-(3,4-dimethoxyphenyl)methyl]-5-nitrothiophene (4r)
Prepared according to the general procedure 1 from 1v (785 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 83% (1723 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.78 (d, J = 4.0 Hz, 1 H), 6.82 (d, J = 8.8 Hz, 2 H), 6.73–6.70 (m, 5 H), 5.53 (s, 1 H), 3.87 (s, 6 H), 3.80 (s, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 158.3, 150.4, 149.1, 148.4, 134.3 (2 x), 128.5 (2 x), 125.8 (2 x), 120.7 (2 x), 111.9 (2 x), 111.1 (2 x), 55.9 (2 x), 55.8 (2 x), 51.9.


3-[Bis-(3,4-dimethoxyphenyl)methyl]pyridine (4s)
Prepared according to the general procedure 1 from 1s (535 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 84% (1534 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 8.49 (d, J = 4.4 Hz, 1 H), 8.43 (s, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.30 (dd, J = 4.8, 8.0 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 2 H), 6.63 (d, J = 2.0 Hz, 2 H), 6.56 (dd, J = 2.0, 8.0 Hz, 2 H), 5.46 (s, 1 H), 3.86 (s, 6 H), 3.77 (s, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 149.4, 149.1 (2 x), 147.9 (2 x), 146.5 (2 x), 140.5, 137.8, 135.0, 123.6, 121.3 (2 x), 112.5 (2 x), 111.1 (2 x), 55.88 (2 x), 55.86 (2 x), 53.4.


4-[Bis-(3,4-dimethoxyphenyl)methyl]benzaldehyde (4u)
Prepared according to the general procedure 1 from 1u (670 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 90% (1765 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 9.96 (s, 1 H), 7.79 (d, J = 8.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 6.79 (d, J = 8.4 Hz, 2 H), 6.64 (d, J = 2.0 Hz, 2 H), 6.57 (dd, J = 2.0, 8.0 Hz, 2 H), 5.50 (s, 1 H), 3.85 (s, 6 H), 3.75 (s, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 191.8, 151.5, 148.8 (2 x), 147.7 (2 x), 135.4 (2 x), 134.6, 129.9 (2 x), 129.7 (2 x), 121.3 (2 x), 112.5 (2 x), 110.9 (2 x), 55.9, 55.8 (2 x), 55.7 (2 x).


1-(3-[Bis-(3,4-dimethoxyphenyl)methyl]phenyl)ethan-1-one (4v)
Prepared according to the general procedure 1 from 1v (740 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 90% (1828 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.81 (dt, J = 1.2, 7.6 Hz, 1 H), 7.76 (t, J = 1.6 Hz, 1 H), 7.38 (t, J = 8.0 Hz, 1 H), 7.31 (dt, J = 0.4, 8.0 Hz, 1 H), 6.79 (d, J = 8.0 Hz, 2 H), 6.65 (d, J = 2.0 Hz, 2 H), 6.57 (dd, J = 2.0, 8.0 Hz, 2 H), 5.49 (s, 1 H), 3.86 (s, 6 H), 3.76 (s, 6 H), 2.54 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 198.2, 148.8 (2 x), 147.6 (2 x), 145.0, 137.2, 136.0 (2 x), 133.9, 129.0, 128.5, 126.4, 121.3 (2 x), 112.6 (2 x), 110.9 (2 x), 55.82 (4 x), 55.76, 26.6.


4-[Bis-(3,4-dimethoxyphenyl)methyl]benzonitrile (4w)
Prepared according to the general procedure 1 from 1w (655 mg, 5.0 mmol) and 2a (1380 mg, 10.0 mmol); yield: 93% (1810 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.57 (d, J = 8.4 Hz, 2 H), 7.22 (d, J = 8.0 Hz, 2 H), 6.79 (d, J = 8.0 Hz, 2 H), 6.61 (d, J = 2.0 Hz, 2 H), 6.54 (dd, J = 2.0, 8.4 Hz, 2 H), 5.47 (s, 1 H), 3.86 (s, 6 H), 3.76 (s, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 150.0, 149.0 (2 x), 147.9 (2 x), 135.1 (2 x), 132.1 (2 x), 131.0 (2 x), 121.3 (2 x), 118.9, 112.6 (2 x), 111.0 (2 x), 110.2, 55.88, 55.85 (2 x), 55.8 (2 x).


2-(Bis(3,4-di-n-butoxyphenyl)methyl)naphthalene (4aa)
Prepared according to the general procedure 1 from 1h (780 mg, 5.0 mmol) and 2c (2222 mg, 10.0 mmol); yield: 85% (2475 mg); colorless liquid.
1H NMR (400 MHz, CDCl3): δ = 7.84–7.82 (m, 1 H), 7.78 (d, J = 8.4 Hz, 1 H), 7.76–7.73 (m, 1 H), 7.51 (s, 1 H), 7.48–7.44 (m, 2 H), 7.35 (dd, J = 1.6, 8.4 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 2 H), 6.77 (dd, J = 2.0 Hz, 2 H), 6.66 (dd, J = 2.0, 8.0 Hz, 2 H), 5.60 (s, 1 H), 4.02 (t, J = 6.8 Hz, 4 H), 3.92 (t, J = 6.8 Hz, 4 H), 1.87–1.72 (m, 8 H), 1.59–1.43 (m, 8 H), 1.02 (t, J = 7.2 Hz, 6 H), 0.96 (t, J = 7.6 Hz, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 148.9 (2 ×), 147.6 (2 ×), 142.2, 136.6 (2 ×), 133.3, 133.1, 128.1, 127.8, 127.6, 127.5, 127.4, 125.8, 125.4, 121.8 (2 ×), 115.6 (2 ×), 113.5 (2 ×), 68.88 (2 ×), 68.87 (2 ×), 55.9, 31.4 (2 ×), 31.3 (2 ×), 19.2 (2 ×), 19.1 (2 ×), 13.83 (2 ×), 13.81 (2 ×).


4.4′-(3,4,5-Trimethoxyphenyl)methylene)bis(1,2-di-n-butoxy-benzene) (4ab)
Prepared according to the general procedure 1 from 1x (980 mg, 5.0 mmol) and 2c (2222 mg, 10.0 mmol); yield: 84% (2614 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 6.79 (d, J = 8.0 Hz, 2 H), 6.66 (d, J = 2.0 Hz, 2 H), 6.58 (dd, J = 2.0, 8.4 Hz, 2 H), 6.32 (s, 2 H), 5.31 (s, 1 H), 3.97 (t, J = 6.8 Hz, 4 H), 3.89 (t, J = 6.8 Hz, 4 H), 3.83 (s, 3 H), 3.72 (s, 6 H), 3.61–1.89 (m, 8 H), 1.54–1.40 (m, 8 H), 0.97 (t, J = 7.2 Hz, 6 H), 0.93 (t, J = 7.6 Hz, 6 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 152.9 (2 ×), 148.8 (2 ×), 147.5 (2 ×), 140.2, 136.8, 136.2 (2 ×), 121.6 (2 ×), 115.5 (2 ×), 113.5 (2 ×), 106.5 (2 ×), 69.0 (2 ×), 68.9 (2 ×), 60.8, 56.0 (2 ×), 55.9, 31.4 (2 ×), 31.3 (2 ×), 19.2 (2 ×), 19.1 (2 ×), 13.83 (2 ×), 13.81 (2 ×).

1,2,3,5,6,7-Hexamethoxy-9-(2,4,6-trimethoxyphenyl)anthracene (4ah-1)
Yield: 30% (786 mg); white solid; mp 169–171 °C (recrystallized from hexanes and EtOAc).

1H NMR (400 MHz, CDCl3): δ = 7.09 (d, J = 8.0 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 2 H), 6.77 (d, J = 8.4 Hz, 1 H), 6.69 (d, J = 1.6 Hz, 1 H), 6.59 (dd, J = 2.4, 8.4 Hz, 1 H), 6.57 (d, J = 8.8 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 5.75 (s, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.52 (s, 3 H), 2.32 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 152.2, 151.6, 148.6, 147.2, 142.2, 141.2, 136.8, 135.5, 130.9, 129.1 (2 ×), 128.8 (2 ×), 124.1, 121.3, 112.7, 110.7, 106.5, 65.8, 55.8 (2 ×), 55.7 (2 ×), 49.0, 20.9.


5-(p-Toly1(2,3,4-trimethoxyphenyl)methylene)benzo[d][1,3]dioxole (4ak)
Prepared according to the general procedure 2 from 1c (600 mg, 5.0 mmol), 2f (840 mg, 5.0 mmol), and 2b (610 mg, 5.0 mmol); yield: 76% (1490 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.08 (d, J = 7.6 Hz, 2 H), 7.00 (d, J = 8.0 Hz, 2 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.69 (d, J = 2.0 Hz, 1 H), 6.58–6.53 (m, 3 H), 5.73 (s, 1 H), 3.98 (t, J = 6.8 Hz, 2 H), 3.91 (t, J = 6.8 Hz, 2 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.52 (s, 2 H), 2.32 (s, 3 H), 1.83–1.70 (m, 4 H), 1.53–1.43 (m, 4 H), 0.98 (t, J = 7.6 Hz, 3 H), 0.95 (t, J = 7.2 Hz, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 152.1, 151.6, 147.5, 145.7, 142.3, 141.1, 138.3, 135.6, 130.8, 129.1 (2 ×), 128.9 (2 ×), 124.2, 122.3, 109.9, 107.8, 106.6, 60.8, 60.6, 55.9, 49.1, 21.0.


1-((3,4-Di-n-butoxyphenyl)(p-toly1)methyl)-2,3,4-trimethoxybenzene (4a1)
Prepared according to general synthetic procedure 2 from 1c (600 mg, 5.0 mmol), 2f (840 mg, 5.0 mmol), and 2c (1111 mg, 5.0 mmol); yield: 72% (1772 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.08 (d, J = 7.6 Hz, 2 H), 7.00 (d, J = 8.0 Hz, 2 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.69 (d, J = 2.0 Hz, 1 H), 6.58–6.53 (m, 3 H), 5.73 (s, 1 H), 3.98 (t, J = 6.8 Hz, 2 H), 3.91 (t, J = 6.8 Hz, 2 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.52 (s, 2 H), 2.32 (s, 3 H), 1.83–1.70 (m, 4 H), 1.53–1.43 (m, 4 H), 0.98 (t, J = 7.6 Hz, 3 H), 0.95 (t, J = 7.2 Hz, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 152.1, 151.6, 148.8, 147.4, 142.2, 141.3, 136.9, 135.4, 131.1, 129.1 (2 ×), 128.8 (2 ×), 124.2, 121.6, 115.6, 113.5, 106.5, 68.9 (2 ×), 60.57, 60.55, 55.8, 49.0, 31.4, 31.3, 20.9, 19.2, 19.1, 13.8 (2 ×).


4-((3,4-Difluorophenyl)(4-methoxyphenyl)methyl)-1,2-dimethoxybenzene (4a4m)
Prepared according to the general procedure 2 from 1y (710 mg, 5.0 mmol), 2a (690 mg, 5.0 mmol), and 2j (540 mg, 5.0 mmol); yield: 76% (1407 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.09–7.03 (m, 1 H), 7.01 (d, J = 8.8 Hz, 2 H), 6.93–6.87 (m, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.80 (d, J = 8.8 Hz, 1 H), 6.63 (d, J = 2.0 Hz, 1 H), 6.57 (dd, J = 2.0, 8.4 Hz, 1 H), 5.40 (s, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3): δ = 158.2, 150.7 (dd, J = 12.1, 127.3 Hz), 148.9, 148.2 (dd, J = 10.7, 125.1 Hz), 147.7, 141.6 (t, J = 4.6 Hz), 135.9, 135.3, 130.1 (2 ×), 125.0 (dd, J = 3.8, 6.1 Hz), 121.2, 118.0 (d, J = 17.5 Hz), 116.8 (d, J = 16.7 Hz), 113.8 (2 ×), 112.5, 110.9, 55.80, 55.76, 55.2, 54.6.

5-((3,4-Difluorophenyl)(3,4-dimethoxyphenyl)methyl)benzo[d][1,3]dioxole (4an)
Prepared according to the general procedure 2 from 1y (710 mg, 5.0 mmol), 2a (690 mg, 5.0 mmol), and 2b (610 mg, 5.0 mmol); yield: 73% (1402 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.06 (dt, J = 8.4, 10.4 Hz, 1 H), 6.90 (dt, J = 2.4, 7.6 Hz, 1 H), 6.85–6.82 (m, 1 H), 6.80 (d, J = 8.4 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.63 (d, J = 2.0 Hz, 1 H), 6.58–6.53 (m, 3 H), 5.93 (s, 2 H), 5.36 (s, 1 H), 3.86 (s, 3 H), 3.78 (s, 3 H).


13C{1H} NMR (100 MHz, CDCl3): δ = 152.6, 151.5, 150.7 (dd, J = 12.2, 131.9 Hz), 148.9, 148.2 (dd, J = 12.8, 128.8 Hz), 147.6, 142.3, 141.5 (t, J = 3.8 Hz), 135.7, 129.8, 125.01 (t, J = 3.8 Hz), 123.9, 121.2, 118.0 (d, J = 16.7 Hz), 116.7 (d, J = 17.4 Hz), 112.6, 110.9, 106.7, 60.64, 60.63; 55.9, 55.8 (2 ×), 48.7.

HRMS (ESI-TOF): m/z [M + H]+ calcd for C42H34F2O8: 651.2966; found: 651.2966.

5-((3,4-Difluorophenyl)(3,4-dimethoxyphenyl)methyl)benzo[d][1,3]dioxole (4as)
Prepared according to the general procedure 2 from 1y (710 mg, 5.0 mmol), 2a (690 mg, 5.0 mmol), and 2f (840 mg, 5.0 mmol); yield: 70% (1506 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.05 (dt, J = 8.4, 10.4 Hz, 1 H), 6.89 (dt, J = 2.4, 7.6 Hz, 1 H), 6.80–6.78 (m, 1 H), 6.78 (d, J = 3.8 Hz, 1 H), 6.63 (d, J = 2.0 Hz, 1 H), 6.58 (d, J = 8.4 Hz, 1 H), 6.54 (dd, J = 2.0, 8.8 Hz, 1 H), 6.48 (d, J = 8.8 Hz, 1 H), 5.72 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.54 (s, 3 H).

HRMS (ESI-TOF): m/z [M + H]+ calcd for C42H34F2O8: 651.2966; found: 651.2966.

1,2-Di-n-butoxy-4-((3,4-difluorophenyl)(3,4-dimethoxyphenyl)methyl)benzene (4ao)
Prepared according to the general procedure 2 from 1y (710 mg, 5.0 mmol), 2a (690 mg, 5.0 mmol), and 2c (1111 mg, 5.0 mmol); yield: 70% (1695 mg); colorless liquid.

1H NMR (400 MHz, CDCl3): δ = 7.06 (dt, J = 8.4, 10.4 Hz, 1 H), 6.90 (dt, J = 2.4, 7.6 Hz, 1 H), 6.85–6.82 (m, 1 H), 6.80 (d, J = 8.4 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.63 (d, J = 2.0 Hz, 1 H), 6.58–6.53 (m, 3 H), 5.93 (s, 2 H), 5.36 (s, 1 H), 3.86 (s, 3 H), 3.78 (s, 3 H).


13C{1H} NMR (100 MHz, CDCl3): δ = 152.6, 151.5, 150.7 (dd, J = 12.2, 131.9 Hz), 148.9, 148.2 (dd, J = 12.8, 128.8 Hz), 147.6, 142.3, 141.5 (t, J = 3.8 Hz), 135.7, 129.8, 125.01 (t, J = 3.8 Hz), 123.9, 121.2, 118.0 (d, J = 16.7 Hz), 116.7 (d, J = 17.4 Hz), 112.6, 110.9, 106.7, 60.64, 60.63; 55.9, 55.8 (2 ×), 48.7.

HRMS (ESI-TOF): m/z [M + H]+ calcd for C42H34F2O8: 651.2966; found: 651.2966.
Pd/C (10%, 30 mg) was added to a solution of 4k (409 mg, 1.0 mmol) in EtOAc (10 mL) at 25 °C. H₂ gas was installed to the reaction mixture at 25 °C. The mixture was stirred at 25 °C for 20 h. The mixture was filtered and the solvent was concentrated to afford the crude product. Without further purification, Et₃N (223 mg, 2.2 mmol) was added to a filtered and the solvent was concentrated to afford the crude product. The mixture was stirred at 25 °C for 20 h. The mixture was stirred at 0 °C for 10 min. AcCl (314 mg, 4.0 mmol) was added to the mixture at 25°C and stirred at 0 °C for 10 h. The residue was diluted with H₂O (10 mL) and the mixture was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc 50:1 to 10:1) afforded compound 1a; yield: 11.07 g (76%).

**Conflict of Interest**

The authors declare no conflict of interest.

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**Supporting Information**

Scanned photocopies of NMR spectral data for all compounds and X-ray analysis data of 4e and 4ah-1. Supporting information for this article is available online at https://doi.org/10.1055/a-1863-3443.

**References**


(43) CCDC 1981539 (4e) and 1981540 (4ah-1) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.


