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ARTICLE TYPE

Metal-free synthesis of 1,3,5-trisubstituted benzenes by the cyclotrimerization of enaminones or alkynes in water

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The cyclotrimerization reactions of enamiones and electron deficient terminal alkynes have been efficiently performed in water in the presence of only a small amount of lactic acid. The reactions led to the green synthesis of a variety of 1,3,5-triacylbenzenes without using any metal as catalyst. Brief investigation on different elaboration of the triacylbenzene product demonstrated the versatile synthetic application of these 1,3,5-triacylbenzene products.

Introduction

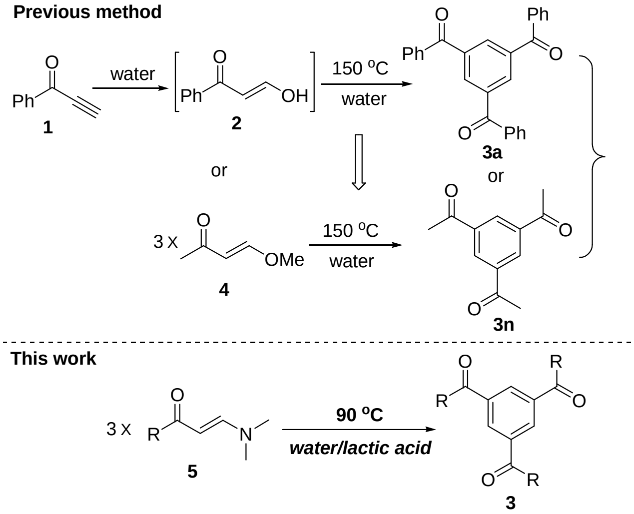
The construction of benzene ring consists of a central issue in modern organic synthesis due to the prevalent presence of benzene core in numerous natural products, medicines, agrochemicals, dyes and functional organic materials. In this regard, benzene synthesis has also been viewed as fundermental task for organic community. Among the presently known approaches towards benzene synthesis, the transition metal-catalyzed [2+2+2] cycloaddition reactions of alkynes have been regarded as the most classical one for allowing efficient synthesis of benzenes and analogous aryl derivatives.[1] By employing this tactic, benzene derivatives with broad structural diversity and dense substitutions could be readily obtained.[2-3] Besides this dominant method, other transition metal-catalyzed protocols, including the oxidative cyclization of olefins,[4] annulation reaction of cyclobutanols with alkynes,[5] intramolecular annulation of β - iodo-β-silylstyrenes with alkynes,[6] methylene transfer reactions,[7] aromatisation of enediynes,[8] the coupling reactions of alkynes and 2-bromoacrylates,[9] allylic alkylation of diketoester-dioxinones/aromatisation,[10] copper,[11] titanium or other metals-catalyzed[12] [3+3] cycloaddtion etc. have also been reported as practical protocols for providing benzenes possessing different functional substructures, respectively.

It is inarguable that these transitional-catalyzed methodologies are useful for synthesizing benzenes containing enriched functionalities, on the other hand, however, the high cost of transition metal catalysts as well as the frequently occurred regioisomeric side products restricted these methods from industrial application. Accordingly, alternative approaches without relying on transition metal catalyst have attracted chemists' interests. During the past decades, several different metal-free protocols have been successfully achieved for providing benzene products. For instance, the acid-catalyzed head-to-tail trimerization of cyclic ketones,[13] thermal induced or organocatalytic trimerization of alkynyl ketones[14] are typical protocols of the category. Recently, following their interesting work on trimerization reactions of alkynyl ketones,[14f] Hiaki and coworkers[15] have investigated the reaction mechanism and discovered that enolate **2** was the key intermediate in the trimerization of alkynyl ketone **1** to give 1,3,5-tribenzoylbenzene **3a** under the conditions of 150 °C and high pressurized hot water. In addition, 4-methoxy-3-buten-2-one **4** has also been found to similarly trimerize to give corresponding benzene derivative **3n** (Scheme 1). Notably, as the aza-analogs of **4**, enaminones of type **5** had also been found applicable for providing 1,3,5-triacylbenzenes **3** via cyclotrimerization, usually by performing reactions in refluxing acetic acid, sometimes with additive such as pyridine.[16] Compared with similar alkynyl ketones **1**, enaminones are advantageous for their features of easier availability, better stability and generally better regioseletivity when used for the synthesis of benzenes **3**. However, besides those few examples describing the trimerization of enaminones in AcOH, it is amazing that rather scarce further efforts have been devoted to improve this methodology, especially by using green media such as water to alternative AcOH.

On the other hand, the 1,3,5-triacylbenzes of type **3** are known to be highly uesful compounds in organic chemistry. For example, 1,3,5-triacylbenzenes are important hosts in organic complex molecules,[17] they have also been employed as major precursors in the synthesis of dendrimers of interesting functionality[18] as well as the highly branched polymers.[19] In addition, 1,3,5-triacetylbenzenes were the central starting materials for the photochemical synthesis of C3 symmetrical cyclophanes.[20]

Considering the fact that the cyclotrimerization of alkynyl ketones with transition metal catalysis or under harsh conditions constituted the dominant approach for synthesizing **3** at present, it is highly desirable to develop alternative protocols that overcome the challenges in alkynyl ketones-based synthesis such as troublesome preparation, short shelf life of alkynyl ketone substrates **1**. In contrast, enaminones of type **5** are easy to prepare from simple aryl/alkyl ketones,[21] considerably more stable than terminal alkynes **1**. More importantly, no isomeric side products occurs when using enaminones for the synthesis of target 1,3,5-triacylbenzenes.

Therefor, following our ongoing interests in enaminone-based synthesis,[22] we report herein an authentically simple and green synthesis of 1,3,5-triacylbenznes via the trimerization of enaminones in water/lactic acid (LA) system. This method is attractive not only for embracing the aforementioned advantages of enaminones, but also for its significance on providing a remarkably cleaner catalytic system by simply carrying out reactions in water[23] in the presence of a small amount of bio-based green chemical LA[24] (Scheme 1).

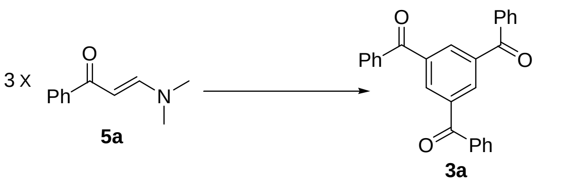


Scheme 1 Different methods for synthesizing 1,3,5-triacylbenzenes

Results and discussion

At the beginning, enaminone **5a** was subjected for cyclotrimerization in different media such as toluene, DMSO, ethyl lactate and water in the presence of LA additive. After

Table 1 Optimizing the reaction conditions of enaminone trimerization[a]

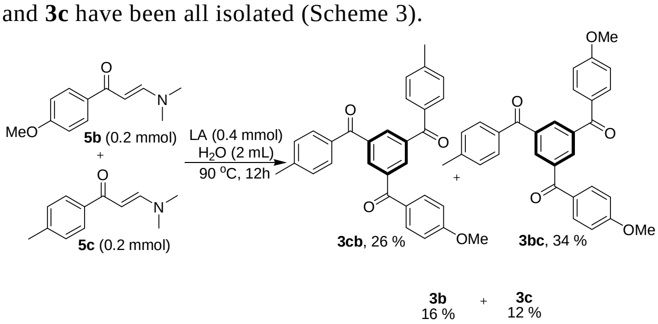


Entry	additive	Sovent	T (°C)	Yield (%)[b]
1	LA	toluene	100	33
2	LA	DMSO	100	26
3	LA	ethyl lactate	100	18
4	LA	H_2O	100	77
5	No	H_2O	100	0
6	AcOH	H_2O	100	21
7	*p*-TSA	H_2O	100	30
8	L-proline	H_2O	100	trace
9[c]	LA	H_2O	100	59
10[c]	LA	H_2O	100	74
11	LA	H_2O	110	77
12	LA	H_2O	90	80
13	LA	H_2O	80	64

[a]General conditions: 0.3 mmol **5a**, 0.4 mmol additive, 2 mL solvent, 12 h. [b]Yieds of islated product. [c]0.3 mmol LA was used in entry 9, and 0.5 mmol LA was used in entry 10.

being heated for 12 h at 100 °C (TLC), interestingly, the trimerized product **3a** was obtained in remarkably higher yield in the entry using water (entries 1-4, Table 1), while a control reaction in the absence of LA gave no desired product, which suggested importance of LA for promoting the reaction (entry 5, Table 1). Further more, low yields of correspond product have been observed in the entries employing other acid species such as AcOH, *p*-TSA or L-proline (entries 6-8, Table 1). On the other hand, increasing and decreasing the amount of LA were both unfavorable (entries 9-10, Table 1). Finally, performing the reaction at 90 °C was discovered to give slightly better yield (entries 11-13, Table 1). According to the fact that the entry utilizing 0.4 mmol LA gave evidently better yield than equivalent entry using 0.3 mmol LA, it can be tentatively concluded that LA acted not only as acid catalyst, but also as additive to facilitate the reaction by improving the solubility of substrates in water.

Based on the exploration on reaction conditions, we subsequently investigated the application scope by employing different enaminones under the optimal conditions. Different triacylbenenzes synthesized by this water mediated system were listed in Scheme 2. According to the results from this section, the protocol was generally applicable for the synthesizing a broad array of triacylbenzenes with good to excellent yields. Enaminones containing both aroyl, heteroaroyl and alkoyl backbones could be transformed solely to corresponding 1,3,5-trisubstituted benzenes. No evident impact of functional groups was observed in present examples probably because that the yields of products were determined simultaneously by electronic/steric properties of functional groups as well as solubility of the substrates in water/LA system. However, it is clear that alkoyl-based enaminones provided correspond 1,3,5-trialkoylbenzenes in slightly lower yields than their aroyl equivalents. Under the standard conditions, the cross trimerization reaction has also been investigated. When two different enaminones **5b** and **5c** were subjected simulteneously for reaction, the mixted products **3cb** and **3bc**, together with the homo-trimerized products **3b** and **3c** have been all isolated (Scheme 3).



Scheme 3 Cross-trimerizaiton of enaminones

Encouraged by the results provided by enaminone-based trimerization, we then attempted to utilize alkynes direactly for similar benzene synthesis in the presence of additional secondary amine which was expected to activate the alkynes by forming the enamino ester intermediates **8**. In the initial endeavor of performing the reaction in standard water/LA system together with secondary amine piperazine, no target benzenes of type **7** were observed. However, changing the medium to DMF was found to be capable of achieving the

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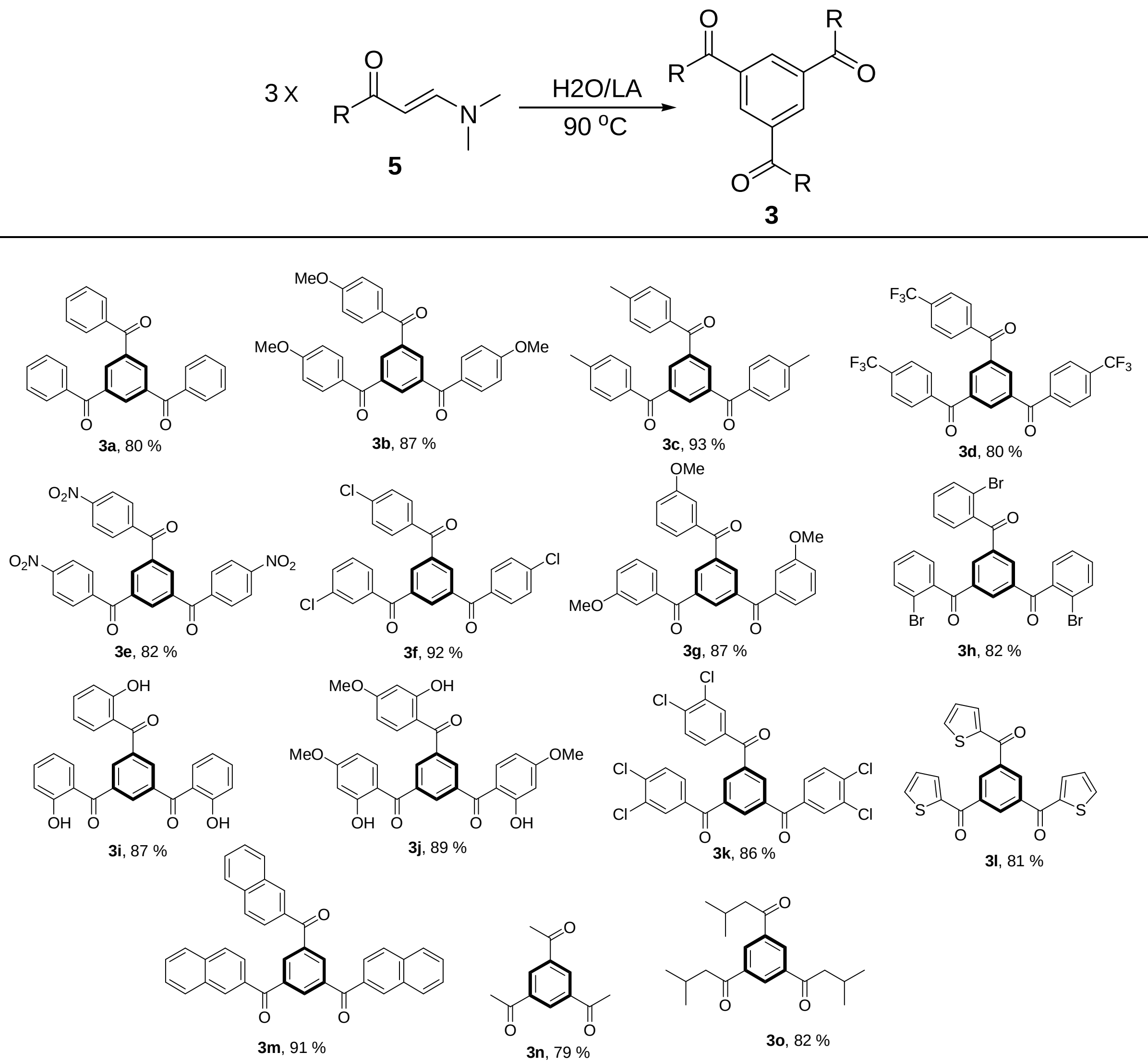
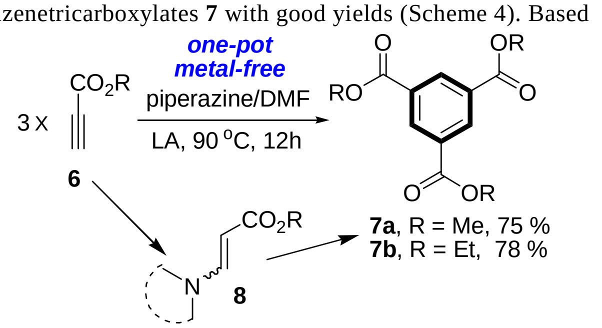


Scheme 2 Synthesis of various triaroylbenzenes. All yields were reported based on isolated products, and the reaction was 16 h for **3e**, **3l**, 12 h for all other products.

expected trimerization and affording corresponding 1,3,5-benzenetricarboxylates **7** with good yields (Scheme 4). Based



Scheme 4 Metal-free cyclotrimerization of electron deficient terminal alkynes

on the literature survey, presently available methods allowing for the trimerization of alkynes **6** were dominantly performed with transition metal catalysis,[3a, 25] therefore, realizing identical transformation under transition-metal free process was of great significance. However, attempts on running the trimerization of unactivated terminal alkynes such as phenylacetylene under identical conditionas was not successful.

Following the examination on reaction scope of this water-mediated methodology, the application for these 1,3,5-triacyl benzene products for synthesizing different derivatives was briefly investigated. Several examples on post elaboration of product **3n** were outlined in Scheme 4. Under proper conditions, employing N,N-dimethylformamide dimethyl

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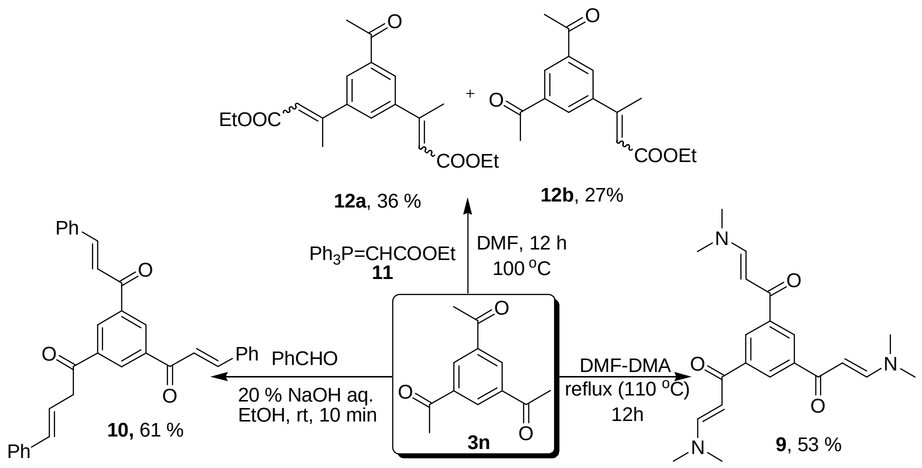

Scheme 4 Synthesis of different C3 symmetrical and unsymmetrical benzene derivatives

acetal (DMF-DMA) and benzaldehyde reaction partners provided C3 symmetrical enaminone **9** and chalcone **10**, respectively. The reactions with Wittig reagent **11**, on the other hand, led to the production of mixed mono- and double olefinated products **12a** and **12b** (Scheme 4). These results were able to partially demonstrated usefulness of the 1,3,5-triacylbenzene products for the synthesis of useful chemicals.

In conclusion, we have established a green catalytic method involving water/LA as media for efficient synthesis 1,3,5-triacylbenzenes. This method represents the first example on successful water-mediated cyclotrimerization synthesis of 1,3,5-triacylbenzenes starting from enaminones. Moreover, this transformation is also one of the few organic reactions that can be promoted or catalyzed by the nontoxic bio-based solvents.[24] More notably, the simplicity of the present catalytic conditions, the excellent conversion rate as well as specific regioselectivity of these reactions allowed for the purification of most products via chromatography-free operation (except for gummy and liquid products). Therefore, as a complement to those known methodologies, including transition metal-catalyzed alkyne trimerization and refluxing AcOH/additive promoted enaminone trimerization, such a green and facile method will reasonably be attractive for chemists in the synthesis of 1,3,5-triacylbenzenes.

Experimental section

General procedure for the synthesis of 1,3,5-triacylbenzenes 3.

Enaminone(s) **5** (0.3 mmol)/(0.2 + 0.2 mmoL for cross trimerization experiment) and LA (0.4 mmol) were charged in a 25 mL round bottom flask equipped with stirring bar. 2 mL water was added and the mixture was stirred at 90 °C for required time (Scheme 2). Upon completion of the reaction, ethanol was added dropwise to the homogeneous mixture until complete dissolvation the whole mixture. The resulted solution was then allowed to cool down to to room temperature, and further cooling with ice bath until the complete precipitation of solid. The solid was the collected via filteration and washed with a small amount of water, dried to provide pure products. For gummy and liquid products (**3g**, **3h**, **3i** and **3o**) and the entry of cross trimerization experiment, 5 mL water was added to the reaction vessel upon completion of reaction, the reusulted mixture was extracted with EtOAc (3×8 mL), the combined organic layer was dried over anhydrous Na_2SO_4. After removing the solvent, the residue was subjected to silica column chromatography to give target products by using eluent of mixted petroleum ether and ethyl acetate (V_{PET}: V_{EA}=3:1).

Benzene-1,3,5-triyltris(phenylmethanone) (3a).[16c] Yellow solid; m.p.: 118-120 °C [lit. 119-120 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ =8.40 (s, 3 H), 7.85 (d, 6 H, *J* = 7.6 Hz), 7.63 (t, 3 H, *J* = 7.2 Hz), 7.52 (d, 6 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.9, 138.2, 136.5, 134.1, 133.3, 130.1, 128.7; IR (KBr, cm^{-1}): 3088, 3034, 1721, 1224.

Benzene-1,3,5-triyltris((4-methoxyphenyl)methanone) (3b).[16a] Pale yellow solid; m.p.: 186-188 °C [lit. 177 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 3 H), 7.72 (d, 6 H, *J* = 8.0 Hz), 6.84 (d, 6 H, *J* = 8.8 Hz), 3.75 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.4, 163.3, 138.2, 132.7, 132.1, 128.7, 113.4, 55.1; IR (KBr, cm^{-1}): 3054, 2956, 1676, 1609.

Benzene-1,3,5-triyltris(*p*-tolylmethanone) (3c).[16a] Pale yellow solid; m.p.: 151-153 °C [lit. 156 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (s, 3 H), 7.68 (d, 6 H, *J* = 7.6 Hz), 7.23 (d, 6 H, *J* =7.6 Hz), 2.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.7, 143.2, 137.4, 132.8, 132.7, 129.3, 128.3, 20.7; IR (KBr, cm^{-1}): 3060, 2956, 1645, 1602.

Benzene-1,3,5-triyltris((4(trifluoromethyl)phenyl)methanone) (3d). Dark red solid; m.p.: 127-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 3 H), 7.86 (d, 6 H, *J* = 8.0 Hz), 7.72 (d, 6 H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.8, 138.7, 137.3, 133.9, 129.7, 125.3 (d, 1C, J_{C-F} = 3.7 Hz), 124.3, 121.6; IR (KBr, cm^{-1}): 3017, 1660, 1599. ESI-HRMS Calcd. for $C_{30}H_{16}F_9O_3$ $[M+H]^+$: 595.0956; Found: 595.0947.

Benzene-1,3,5-triyltris((4-nitrophenyl)methanone) (3e).[26] Pale yellow solid; m.p.: 196-198 °C [lit. 196-198 °C]; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.41 (d, 6 H, *J* = 8.8 Hz), 8.35 (s, 3 H), 8.09 (d, 6 H, *J* = 8.4 Hz) ; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 192.9, 149.9, 141.2, 136.8, 134.4, 131.1, 123.8; IR (KBr, cm^{-1}): 3086, 1656, 1526, 1337.

Benzene-1,3,5-triyltris((4-chlorophenyl)methanone) (3f).[16b] White solid; m.p.: 161-163 °C [lit. 180 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 3 H), 7.79 (d, 6 H, *J* = 8.4 Hz), 7.50 (d, 6 H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.4, 140.1, 138.1, 134.6, 133.9, 131.4, 129.1; IR (KBr, cm^{-1}): 3017, 1668, 1600.

Benzene-1,3,5-triyltris((3-methoxyphenyl)methanone) (3g).[17b] Pale yellow gummy compound; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (s, 3 H), 7.33-7.27 (m, 9 H), 7.09 (d, 3 H, *J* = 8.0 Hz), 3.79 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.7, 159.9, 138.2, 137.7, 134.1, 129.6, 122.9, 119.7, 114.3, 55.5; IR (KBr, cm^{-1}): 3019, 2938, 1663.

Benzene-1,3,5-triyltris((2-bromophenyl)methanone) (3h). Yellow gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (s, 3 H), 7.57 (d, 3 H, *J* = 8.0 Hz), 7.37-7.30 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.1, 139.2, 137.5, 135.3, 133.5, 132.0, 129.4, 127.6, 119.7; IR (KBr, cm^{-1}): 3017, 1667, 1601. ESI-HRMS Calcd. for $C_{27}H_{16}Br_3O_3$ $[M+H]^+$: 624.8650; Found: 624.8671.

Benzene-1,3,5-triyltris((2-hydroxyphenyl)methanone) (3i). Red gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22-8.20 (m, 3 H), 7.86 (d, 3 H, *J* = 7.2 Hz), 7.69-7.65 (m, 3 H), 7.46-7.38 (m, 6 H), 6.34 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.6, 156.5, 155.3, 133.7 , 125.8, 125.2, 124.9, 118.2, 113.0; IR (KBr, cm^{-1}): 3078, 1636, 1598. ESI-HRMS Calcd. for $C_{27}H_{19}O_6$ $[M+H]^+$: 439.1182; Found: 439.1192.

Benzene-1,3,5-triyltris((2-hydroxy-4-methoxyphenyl)methanone (3j). Red solid; m.p.: 126-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, 3 H, *J* = 8.0 Hz), 7.78 (d, 3 H, *J* = 6.0 Hz), 6.97 (d, 3 H, *J* = 9.2 Hz), 6.84 (s, 3 H), 6.28 (d, 3 H, *J* = 6.0 Hz), 3.90 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0, 164.1, 158.3, 154.8, 127.2, 118.8, 114.5, 112.9, 100.4, 55.8; IR (KBr, cm^{-1}): 3066, 1632, 1597. ESI-HRMS Calcd. for $C_{30}H_{25}O_9$ $[M+H]^+$: 529.1499; Found: 529.1507.

Benzene-1,3,5-triyltris((3,4-dichlorophenyl)methanone) (3k). Pale yellow solid; m.p.: 189-191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (s, 3 H), 7.86 (d, 3 H, *J* = 1.6 Hz), 7.56 (t, 6 H, *J* = 3.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 194.8, 141.1, 140.5, 138.4, 136.7, 136.5, 134.5, 133.7, 131.7; IR (KBr, cm^{-1}): 3015, 1669, 1607. ESI-HRMS Calcd. for $C_{27}H_{13}Cl_6O_3$ $[M+H]^+$: 594.8996; Found: 594.8987.

Benzene-1,3,5-triyltri(thiophen-2-ylmethanoe) (3l).[16c] Pale yellow solid; m.p.: 200-201 °C [lit. 203-204 °C]; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.42 (s, 3 H), 8.20 (d, 3 H, *J* = 4.8 Hz), 7.91 (d, 3 H, *J* = 3.6 Hz), 7.33 (t, 3 H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_3) δ = 186.4, 142.4, 138.6, 137.1, 136.9, 132.6, 129.7; IR (KBr, cm^{-1}): 3058, 1644.

Benzene-1,3,5-triyltris(naphthalen-2-ylmethanone) (3m).[16a] Pale yellow solid; m.p.: 209-210 °C [lit. 225 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51(s,3 H), 8.18-8.15 (m, 3 H), 7.94 (d, 3 H, *J* = 8.0 Hz), 7.86-7.84 (m, 3 H), 7.54-7.49 (m, 9 H), 7.38 (t, 3 H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 198.4, 142.0, 138.1, 136.5, 135.2, 133.5, 131.6, 131.6, 131.3, 130.4, 129.4, 128.1, 126.9; IR (KBr, cm^{-1}): 3047, 1651, 1608.

1, 3, 5-Acetylbenzene (3n).[16c] White solid; m.p.: 167-168 °C [lit. 154-155 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.61 (s, 3 H), 2.63 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.7, 137.9, 131.7, 26.8; IR (KBr, cm^{-1}): 3087, 1689, 1590.

1-[3,5-Bis-(3-methyl-butyvyl)-phenyl]-3-methyl-butan-1-one (3o). Red liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58 (s, 3 H), 2.85 (d, 6 H, *J* = 7.2 Hz), 2.27-2.20 (m, 3 H), 0.93 (d, 18 H, *J* = 6.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 201.5, 141.0, 133.8, 50.2, 27.5, 25.5; IR (KBr, cm^{-1}): 3015, 1689, 1593. ESI-HRMS Calcd. for $C_{21}H_{31}O_3$ $[M+H]^+$: 331.2273; Found: 331.2268.

(5-(4-methoxybenzoyl)-1,3-phenylene)bis(p-tolylmethanone) (**3cb**). Yellow gummy; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (d, 3 H, J = 5.6 Hz), 7.85 (d, 2 H, *J* = 8.0 Hz), 7.76 (d, 4 H, *J* = 6.8 Hz), 7.30 (d, 4 H, *J* = 7.6 Hz), 6.98 (d, 2 H, *J* = 8.0 Hz), 3.89 (s, 3 H), 2.44 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 195.0, 193.9, 163.9, 144.2, 138.8, 138.4, 133.9, 133.5, 132.6, 130.4, 130.3, 129.3, 129.2, 114.0, 55.4, 21.6; IR (KBr, cm^{-1}): 3010, 1720, 1689; HRMS Calcd. For $C_{30}H_{25}O_4$ $[M+H]^+$: 449.1753; Found: 449.1740.

(5-(4-methylbenzoyl)-1,3-phenylene)bis((4-methoxyphenyl)methanone) (**3bc**). White solid; m.p: 175-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, 3 H, *J* = 4.0 Hz), 7.85 (d, 4 H, *J* = 8.0 Hz), 7.75 (d, 2 H, *J* = 8.0 Hz), 7.30 (d, 2 H, *J* = 8.0 Hz), 6.98 (d, 4 H, *J* = 8.0 Hz), 3.89 (s, 6 H), 2.44 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 194.9, 193.8, 163.8, 144.2, 138.8, 138.4, 133.9, 133.4, 132.7, 132.6, 130.4, 129.3, 129.2, 114.0, 55.4, 21.7; IR (KBr, cm^{-1}): 3052, 1737, 1695; HRMS Calcd. For $C_{30}H_{25}O_5$ $[M+H]^+$: 465.1702; Foud: 465.1718.

Synthesis of 1,3,5-benzenetricarboxylates 7.

Alkyl propiolates **6** (0.3 mmol), piperazine (0.12 mol) and LA (0.4 mmol) were charged in a 25 mL round bottom flask equipped with stirring bar. 2 mL DMF was added and the mixture was stirred at 90 ℃ for 12 h (TLC). After completion of reactions, the mixture was cooled to room temperature, distilled water was added dropwise until the solid precipitated compleletly. The solid was collected via filteration and washed with a small amount of water, then dried to give pure products.

Trimethyl benzene-1,3,5-tricarboxylate (7a).[27] White solid; m.p.: 126-129 °C [lit. 144-145 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.85 (s, 3H), 3.99 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.8, 137.2, 133.8, 55.3; IR (KBr, cm^{-1}): 3099, 2993, 1713.

Triethyl benzene-1,3,5-tricarboxylate (7b).[26] Pale yellow power; m.p.: 125-126 °C [lit. 127-129 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.78 (s, 3H), 4.40-4.34 (m, 6H), 1.36 (t, 9H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.5, 136.8, 134.1, 64.3, 17.1; IR (KBr, cm^{-1}): 3099, 2994, 1715, 1240.

Synthesis of C3 symmetrical enaminone 9.

1,3,5-Acetylbenzene **3n** (0.9 mmol) was charged in a 10 mL round bottom flask equipped with stirring bar. DMF-DMA (1 mL) was added and the mixture was refluxed for 12 h (TLC). After cooling down to room temperature, water (5 mL) was added to the mixture and the resulting residue was extracted with ethyl acetate (3 × 8 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtering and removing the solvent, corresponding product **9** was obtained by subjecting the residue to silica gel column chromatography using EtOH as eluent.

1-[3,4-Bis-(3-dimethylamino-acryloyl)-phenyl]-3-dimethyl amino-propenone (9). Yellow solid; m.p.: 266-268 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.54 (s, 3 H), 7.84 (d, 3 H, *J* = 12.0 Hz), 5.87 (d, 3 H, *J* = 12.0 Hz), 3.16 (s, 9 H), 2.95 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 190.5, 157.2, 142.9, 131.5, 94.9, 47.8, 40.1; IR (KBr, cm^{-1}): 1630, 1595, 1539. ESI-HRMS Calcd. for $C_{21}H_{28}N_3O_3$ $[M+H]^+$: 370.2131; Found: 370.2128.

Synthesis of C3 symmetrical chalcone 10.

1,3,5-Acetylbenzene **3n** (0.3 mmol), benzaldehyde (0.9 mmol) and EtOH (2 mL) were charged in a 25 mL round bottom flask equipped with stirring bar. NaOH 20% aqueous solution(0.2 mL) was then slowly added. The mixture was stirred at room temperature for 10 min (TLC). Upon completion, 5 mL water was added to the mixture and the resulting residue was extracted with ethyl acetate (3 × 8 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and removing the solvent, product **10** was purified by silica gel column chromatography with the elution of mixed petroleum ether and ethyl acetate (V_{PET}: V_{EA}=5:1).

1,3,5-Tris(3-phenylpropenoyl)benzene (10).[20] White solid; m.p.: 174-175 ^oC [lit. 179 ^oC]; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.86 (s, 3 H), 7.94 (d, 3 H, *J* = 15.2 Hz), 7.73-7.71 (m, 6 H), 7.67 (d, 3 H, *J* = 15.6 Hz), 7.47-7.44 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.0, 146.5, 139.1, 134.5, 131.8, 131.1, 129.1, 128.9, 121.1; IR (KBr, cm^{-1}): 3038, 1642, 1593.

Synthesis of olefines 12a and 12b.

1,3,5-Acetylbenzene **3n** (0.3 mmol) and Witting reagent **11** (0.9 mmol) were charged with DMF (2 mL) in a 25 mL round bottom flask equipped with stirring bar. The mixture was stirred at 100 ℃ for 12 h (TLC). After cooling down to room temperature, water (5 mL) was added to the mixture and the resulting residue was extracted with ethyl acetate (3 × 8 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and removing the solvent, the residue was sujected to silica gel column chromatography with elution of mixed petroleum ether and ethyl acetate (V_{PET}: V_{EA}=10:1) to provide **12a** and **12b**.

3-[3-Acetyl-5-(2-ethoxycarbonyl-1-methyl-vinyl)-phenyl]-but-2-enoic acid ethyl ester (12a). Red liquid; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.02 (s, 2 H), 7.72 (s, 1 H) 6.18 (s, 2 H), 4.27-4.22 (m, 4 H) 2.66 (s, 3 H), 2.62 (s, 6 H) 1.34 (t, 6 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.3, 166.4, 154.0, 143.3, 137.6, 128.5, 126.5, 118.7, 60. 1, 26.7, 18.0, 14.3; IR (KBr, cm^{-1}): 3038, 2993, 1711. ESI-HRMS Calcd. for $C_{20}H_{25}O_5$ $[M+H]^+$: 345.1702; Found: 345.1698.

3-(3,5-Diacetyl-phenyl)-but-2-enoic acid ethyl ester (12b). Red liquid; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.41 (t, 1 H, *J* = 1.6 Hz), 8.16 (d, 2 H, *J* = 1.6 Hz), 6.13 (d, 1 H, *J* = 1.2 Hz), 4.20-4.14 (m, 2 H), 2.61 (s, 6 H), 2.55 (s, 3 H), 1.26 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.1, 166.5, 153.4, 143.5, 137.8, 130.1, 128.3, 119.2, 60.2, 26.8, 18.0, 14.3; IR (KBr, cm^{-1}): 3035, 2997, 1714. ESI-HRMS Calcd. for $C_{16}H_{19}O_4$ $[M+H]^+$: 275.1283; Found: 275.1283.

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