RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 20499

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

Jie-Ping Wan,*[ab] Yunfang Lin,[a] Kaikai Hu[a] and Yunyun Liu*[ab]

Received 17th January 2014
Accepted 12th March 2014

DOI: 10.1039/c4ra00475b

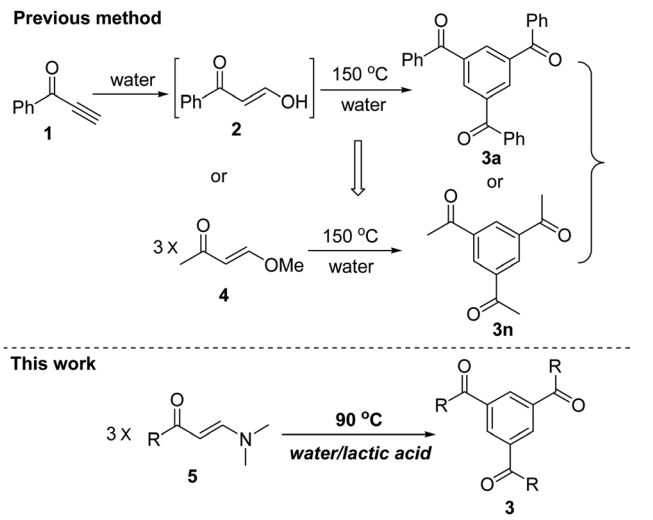
www.rsc.org/advances

The cyclotrimerization reactions of enaminones 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-triacylbenzenes.

Introduction

The construction of benzene rings is 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 been viewed as a fundamental task for the 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] cycloaddition, *etc.* have also been reported as practical protocols for providing benzenes possessing different functional substructures, respectively.

These transition-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 have restricted these methods from industrial applications. Accordingly, alternative approaches without relying on transition metal catalyst have attracted chemists' interest. 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).



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

[a]*College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P.R. China*

[b]*Key laboratory of functional small organic molecules, ministry of education, Jiangxi Normal University, Nanchang 330022, P.R. China. E-mail: wanjieping@gmail.com; chemliuyunyun@gmail.com; Fax: +86 791 88120380; Tel: +86 791 88120380*

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all products. See DOI: 10.1039/c4ra00475b

Notably, as the aza-analogs of **4**, enaminones of type **5** had also been found to be applicable for providing 1,3,5-triacylbenzenes **3** *via* cyclotrimerization, usually by performing reactions in refluxing acetic acid, sometimes with additives such as pyridine.[16] Compared with similar alkynyl ketones **1**, enaminones are advantageous for their features of easier availability, better stability and generally better regioselectivity 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 alternate AcOH.

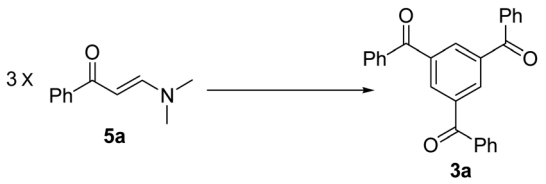
On the other hand, the 1,3,5-triacylbenzenes of type **3** are known to be highly useful compounds in organic chemistry. For example, 1,3,5-triacylbenzenes are important hosts in organic complex molecules,[17] they have also been employed as major precursors in the synthesis of dendrimers of interesting 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 approaches 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 occur when using enaminones for the synthesis of target 1,3,5-triacylbenzenes. Therefore, following our ongoing interest in enaminone-based synthesis,[22] we report herein an authentically simple and green synthesis of 1,3,5-triacylbenzenes *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 in 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).

Results and discussion

At the beginning, enaminone **5a** was subjected to cyclotrimerization in different media such as toluene, DMSO, ethyl lactate and water in the presence of LA additives. After 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 the importance of LA for promoting the reaction (entry 5, Table 1). Furthermore, low yields of corresponding products 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 and 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.

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

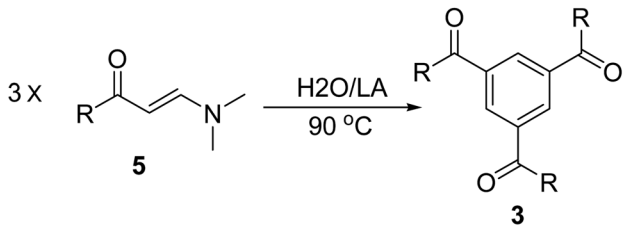


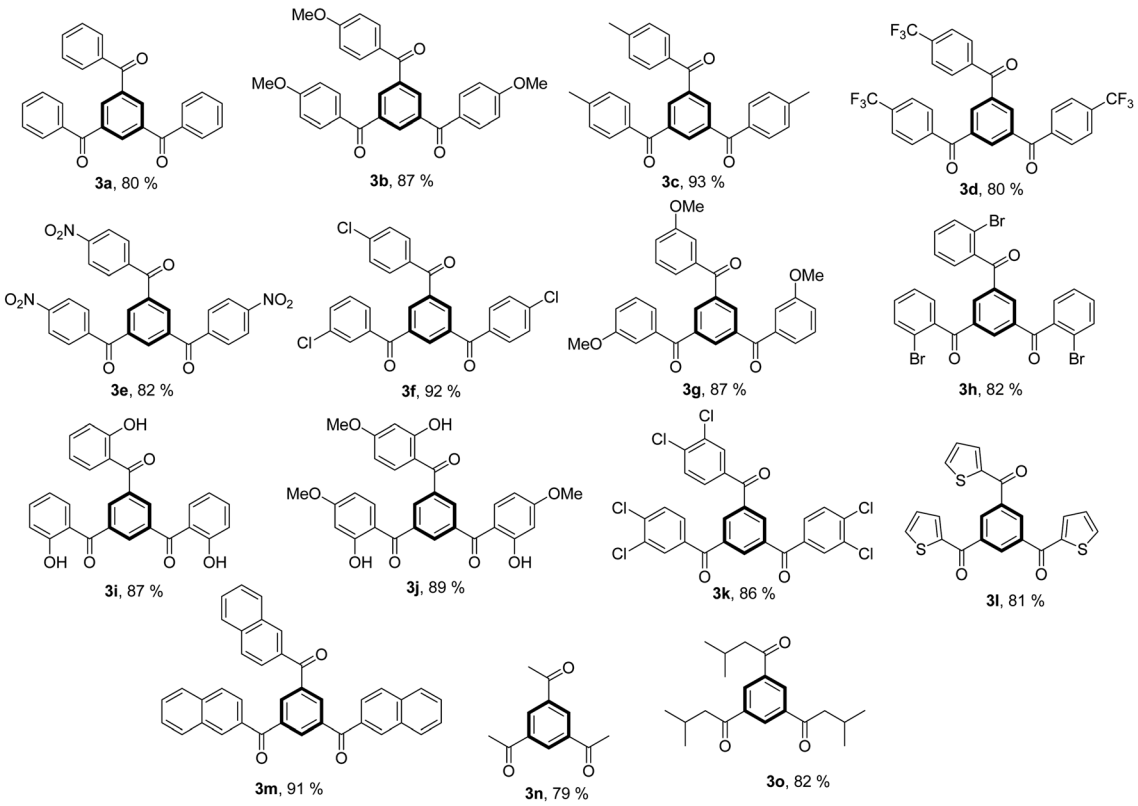
Entry	Additive	Solvent	T (°C)	Yield[b] (%)
1	LA	Toluene	100	33
2	LA	DMSO	100	26
3	LA	Ethyl lactate	100	18
4	LA	H_2O	100	77
5	No	H_2O	100	0
6	AcOH	H_2O	100	21
7	*p*-TSA	H_2O	100	30
8	L-proline	H_2O	100	Trace
9[c]	LA	H_2O	100	59
10[c]	LA	H_2O	100	74
11	LA	H_2O	110	77
12	LA	H_2O	90	80
13	LA	H_2O	80	64

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

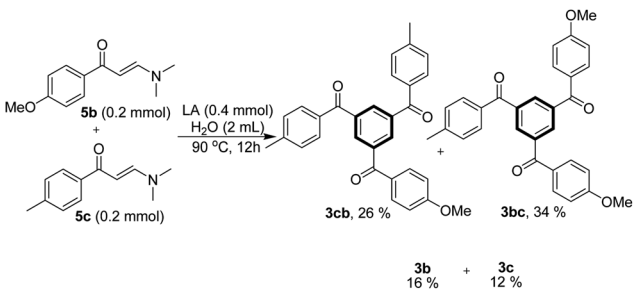
Based on the exploration of reaction conditions, we subsequently investigated the application scope by employing different enaminones under the optimal conditions. Different triacylbenzenes synthesized by this water mediated system were listed in Scheme 2. According to the results from this section, the protocol was generally applicable for 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 the 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 the alkoyl-based enaminones provided corresponding 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 simultaneously for reaction, the mixed products **3cb** and **3bc**, together with the homo-trimerized products **3b** and **3c** have all been isolated (Scheme 3).

Encouraged by the results provided by enaminone-based trimerization, we then attempted to utilize alkynes directly for



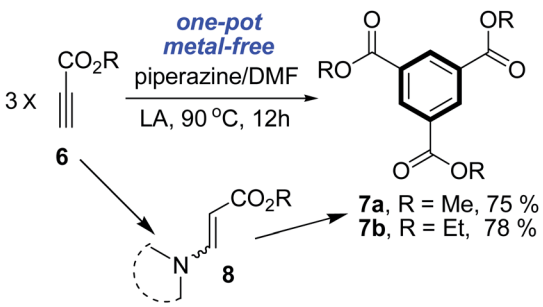


Scheme 2 Synthesis of various triaroylbenzenes. All yields are reported based on isolated products, and the reaction time is 16 h for **3e**, **3l**, 12 h for all other products.



Scheme 3 Cross-trimerization of enaminones.

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 expected trimerization and affording corresponding 1,3,5-benzenetricarboxylates **7** with good yields (Scheme 4). Based on the literature survey, presently available methods allowing for the trimerization of alkynes **6** were dominantly performed with



Scheme 4 Metal-free cyclotrimerization of electron deficient terminal alkynes.

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 conditions 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 acetal (DMF-DMA) and benzaldehyde as 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 5). 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 of 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

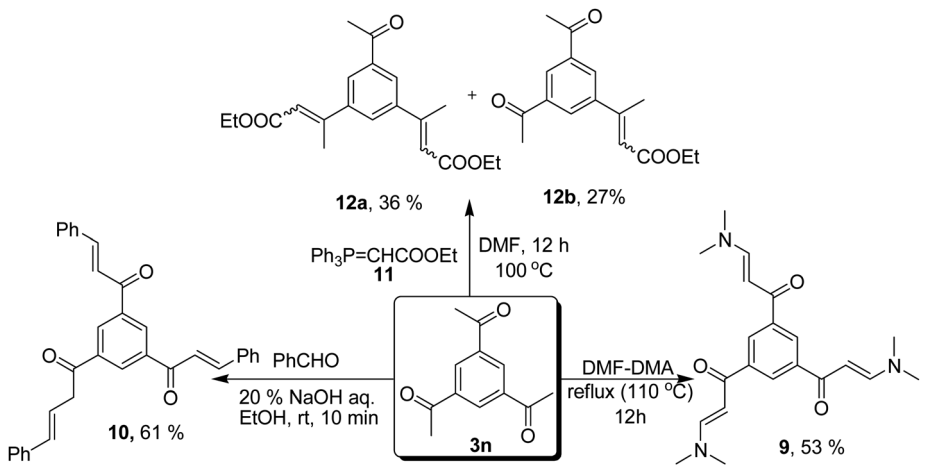
General procedure for the synthesis of 1,3,5-triacylbenzenes 3

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. Water (2 ml) 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 of the whole mixture. The resulting solution was then allowed to cool down to room temperature, followed by further cooling with ice bath until the complete precipitation of solid. The solid was then collected *via* filtration 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 resulting mixture was extracted with EtOAc (3 × 8 ml), the combined organic layer was dried over anhydrous Na_2SO_4. After filtration and removing the solvent, the residue was subjected to silica column chromatography to give target products by using eluent of mixed petroleum ether and ethyl acetate ($V_{PET} : V_{EA} = 3 : 1$).

Benzene-1,3,5-triyltris(phenylmethanone) (3a).[16c] Yellow solid; mp: 118–120 °C [lit. 119–120 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (s, 3H), 7.85 (d, 6H, J = 7.6 Hz), 7.63 (t, 3H, J = 7.2 Hz), 7.52 (d, 6H, 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; mp: 186–188 °C [lit. 177 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 3H), 7.72 (d, 6H, J = 8.0 Hz), 6.84 (d, 6H, J = 8.8 Hz), 3.75 (s, 9H); ^{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; mp: 151–153 °C [lit. 156 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (s, 3H), 7.68 (d, 6H, J = 7.6 Hz), 7.23 (d, 6H, J = 7.6 Hz), 2.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.7, 143.2, 137.4,



Scheme 5 Synthesis of different C3 symmetrical and unsymmetrical benzene derivatives.

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; mp: 127–129 °C; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.34$ (s, 3H), 7.86 (d, 6H, $J = 8.0$ Hz), 7.72 (d, 6H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 192.8$, 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; mp: 196–198 °C [lit. 196–198 °C]; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 8.41$ (d, 6H, $J = 8.8$ Hz), 8.35 (s, 3H), 8.09 (d, 6H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 192.9$, 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; mp: 161–163 °C [lit. 180 °C]; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.34$ (s, 3H), 7.79 (d, 6H, $J = 8.4$ Hz), 7.50 (d, 6H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 193.4$, 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; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.32$ (s, 3H), 7.33–7.27 (m, 9H), 7.09 (d, 3H, $J = 8.0$ Hz), 3.79 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 194.7$, 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; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.31$ (s, 3H), 7.57 (d, 3H, $J = 8.0$ Hz), 7.37–7.30 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 194.1$, 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; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.22$–8.20 (m, 3H), 7.86 (d, 3H, $J = 7.2$ Hz), 7.69–7.65 (m, 3H), 7.46–7.38 (m, 6H), 6.34 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 177.6$, 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; mp: 126–127 °C; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.12$ (d, 3H, $J = 8.0$ Hz), 7.78 (d, 3H, $J = 6.0$ Hz), 6.97 (d, 3H, $J = 9.2$ Hz), 6.84 (s, 3H), 6.28 (d, 3H, $J = 6.0$ Hz), 3.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 177.0$, 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; mp: 189–191 °C; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.26$ (s, 3H), 7.86 (d, 3H, $J = 1.6$ Hz), 7.56 (t, 6H, $J = 3.6$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 194.8$, 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; mp: 200–201 °C [lit. 203–204 °C]; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 8.42$ (s, 3H), 8.20 (d, 3H, $J = 4.8$ Hz), 7.91 (d, 3H, $J = 3.6$ Hz), 7.33 (t, 3H, $J = 4.0$ Hz); ^{13}C NMR (100 MHz, DMSO-d_3) $\delta = 186.4$, 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; mp: 209–210 °C [lit. 225 °C]; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.51$ (s, 3H), 8.18–8.15 (m, 3H), 7.94 (d, 3H, $J = 8.0$ Hz), 7.86–7.84 (m, 3H), 7.54–7.49 (m, 9H), 7.38 (t, 3H, $J = 8.0$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 198.4$, 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; mp: 167–168 °C [lit. 154–155 °C]; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.61$ (s, 3H), 2.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 196.7$, 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; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.58$ (s, 3H), 2.85 (d, 6H, $J = 7.2$ Hz), 2.27–2.20 (m, 3H), 0.93 (d, 18H, $J = 6.4$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 201.5$, 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; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.32$ (d, 3H, $J = 5.6$ Hz), 7.85 (d, 2H, $J = 8.0$ Hz), 7.76 (d, 4H, $J = 6.8$ Hz), 7.30 (d, 4H, $J = 7.6$ Hz), 6.98 (d, 2H, $J = 8.0$ Hz), 3.89 (s, 3H), 2.44 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 195.0$, 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; mp: 175–176 °C; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.30$ (d, 3H, $J = 4.0$ Hz), 7.85 (d, 4H, $J = 8.0$ Hz), 7.75 (d, 2H, $J = 8.0$ Hz), 7.30 (d, 2H, $J = 8.0$ Hz), 6.98 (d, 4H, $J = 8.0$ Hz), 3.89 (s, 6H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 194.9$, 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; found: 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 and was stirred at 90 °C for 12 h (TLC). After completion of reactions, the mixture was cooled to room temperature, distilled water was added dropwise until the solid precipitated completely. The solid was collected *via* filtration and washed with a small amount of water, then dried to give pure products.

Trimethyl benzene-1,3,5-tricarboxylate (7a)[27]

White solid; mp: 126–129 °C [lit. 144–145 °C]; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.85$ (s, 3H), 3.99 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 167.8$, 137.2, 133.8, 55.3; IR (KBr, cm^{-1}): 3099, 2993, 1713.

Triethyl benzene-1,3,5-tricarboxylate (7b)[26]

Pale yellow power; mp: 125–126 °C [lit. 127–129 °C]; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.78$ (s, 3H), 4.40–4.34 (m, 6H), 1.36 (t, 9H,

$J = 7.2$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 167.5, 136.8, 134.1, 64.3, 17.1$; 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, the 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; mp: 266–268 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.54$ (s, 3H), 7.84 (d, 3H, $J = 12.0$ Hz), 5.87 (d, 3H, $J = 12.0$ Hz), 3.16 (s, 9H), 2.95 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 190.5, 157.2, 142.9, 131.5, 94.9, 47.8, 40.1$; 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; mp: 174–175 °C [lit. 179 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.86$ (s, 3H), 7.94 (d, 3H, $J = 15.2$ Hz), 7.73–7.71 (m, 6H), 7.67 (d, 3H, $J = 15.6$ Hz), 7.47–7.44 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 189.0, 146.5, 139.1, 134.5, 131.8, 131.1, 129.1, 128.9, 121.1$; IR (KBr, cm^{-1}): 3038, 1642, 1593.

Synthesis of olefins 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 °C 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 subjected 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; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.02$ (s, 2H), 7.72 (s, 1H) 6.18 (s, 2H), 4.27–4.22 (m, 4H) 2.66 (s, 3H), 2.62 (s, 6H) 1.34 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 197.3, 166.4, 154.0, 143.3, 137.6, 128.5, 126.5, 118.7, 60. 1, 26.7, 18.0, 14.3$; 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; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.41$ (t, 1H, $J = 1.6$ Hz), 8.16 (d, 2H, $J = 1.6$ Hz), 6.13 (d, 1H, $J = 1.2$ Hz), 4.20–4.14 (m, 2H), 2.61 (s, 6H), 2.55 (s, 3H), 1.26 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 197.1, 166.5, 153.4, 143.5, 137.8, 130.1, 128.3, 119.2, 60.2, 26.8, 18.0, 14.3$; IR (KBr, cm^{-1}): 3035, 2997, 1714. ESI-HRMS calcd for $C_{16}H_{19}O_4$ $[M + H]^+$: 275.1283; found: 275.1283.

Acknowledgements

This work was financially supported by NSFC (no. 21102059 and 21202064), a project from the Department of Education of Jiangxi Province (GJJ13245) as well as NSF of Jiangxi province (20114BAB213005). The authors also thank Dr Yaqin Liu in the Department of Chemistry, Zhejiang University for her help in NMR tests.

Notes and references

1 For pioneer examples on transition metal-catalyzed [2 + 2 + 2] benzene synthesis, see: (*a*) P. E. M. Bertholet, *C. R. Hebd. Seances Acad. Sci.*, 1866, **63**, 515; (*b*) W. Reppe and W. J. Sweckendiek, *Justus Liebigs Ann. Chem.*, 1948, **560**, 104.

2 For reviews, see: (*a*) M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; (*b*) S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901; (*c*) D. L. J. Broere and E. Ruijter, *Synthesis*, 2012, **44**, 2639; (*d*) Y. Shibata and K. Tanaka, *Synthesis*, 2012, **44**, 323.

3 For selected examples on [2 + 2 + 2] cyclotrimerization for benzene synthesis, see: (*a*) V. Cadierno, S. E. Garcia-Garrido and J. Gimeno, *J. Am. Chem. Soc.*, 2006, **128**, 15094; (*b*) V. Gevorgyan, U. Radhakrishnan, A. Takeda, M. Rubina, M. Rubin and Y. Yamamoto, *J. Org. Chem.*, 2001, **66**, 2835; (*c*) J.-S. Cheng and H.-F. Jiang, *Eur. J. Org. Chem.*, 2004, 643; (*d*) M. R. Shaaban, R. El-Sayed and A. H. M. Elwahy, *Tetrahedron*, 2011, **67**, 6095; (*e*) M. Kawatsura, M. Yamamoto, J. Namioka, K. Kajita, T. Hirakawa and T. Itoh, *Org. Lett.*, 2011, **13**, 1001; (*f*) Y.-H. Wang, S.-H. Huang, T.-C. Lin and F.-Y. Tsai, *Tetrahedron*, 2010, **66**, 7136; (*g*) T. Konno, K. Moriyasu, R. Kinugawa and T. Ishihara, *Org. Biomol. Chem.*, 2010, **8**, 1718; (*h*) B. R. Galan and T. Rovis, *Angew. Chem., Int. Ed.*, 2009, **48**, 2830; (*i*) K. Yoshida, I. Morimoto, K. Mitsudo and H. Tanaka, *Tetrahedron*, 2008, **64**, 5800; (*j*) K. Murayama, Y. Sawada, K. Noguchi and K. Tanaka, *J. Org. Chem.*, 2013, **78**, 6202; (*k*) K. Tanaka, H. Hara, G. Nishida and M. Hirano, *Org. Lett.*, 2007, **9**, 1907.

4 (*a*) K.-I. Tamaso, Y. Hatamoto, S. Sakaguchi, Y. Obora and Y. Ishii, *J. Org. Chem.*, 2007, **72**, 3603; (*b*) H.-F. Jiang, Y.-X. Shen and Z.-Y. Wang, *Tetrahedron Lett.*, 2007, **48**,

7542; (*c*) H.-F. Jiang, Y.-X. Shen and Z.-Y. Wang, *Tetrahedron*, 2008, **64**, 508.
5 T. Matsuda and N. Miura, *Org. Biomol. Chem.*, 2013, **11**, 3424.
6 H. Kinoshita, H. Takahashi and K. Miura, *Org. Lett.*, 2013, **15**, 2962.
7 J.-J. Lian, A. Odedra, C.-J. Wu and R.-S. Liu, *J. Am. Chem. Soc.*, 2005, **127**, 4186.
8 A. Odedra, C.-J. Wu, T. B. Pratap, C.-W. Huang, Y.-F. Ran and R.-S. Liu, *J. Am. Chem. Soc.*, 2005, **127**, 3406.
9 C. Xi, C. Chen, J. Lin and X. Hong, *Org. Lett.*, 2005, **7**, 347.
10 J. Cordes, S. Laclef, A. J. P. White and A. G. M. Barrett, *J. Org. Chem.*, 2012, **77**, 3524.
11 L. Li, M.-N. Zhao, Z.-H. Ren, J.-L. Li and Z.-H. Guan, *Org. Lett.*, 2012, **14**, 3506.
12 For an excellent review on [3 + 3] cyclization providing benzene derivatives, see: H. Feist and P. Langer, *Synthesis*, 2007, 327.
13 (*a*) M. M. Boorum and L. T. Scott, in *Modern Arene Chemistry*, ed. D. Astruc, Wiley, New York, 2002, ch. 1; (*b*) O. De Frutos, B. Gomez-Lor, T. Granier, M. A. Monge, E. Gutierrez-Puebla and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 1999, **38**, 204; (*c*) W. Zhang, X.-Y. Cao, Z. Hong and J. Pei, *Org. Lett.*, 2005, **7**, 959; (*d*) M.-S. Yuan, Q. Fang, Z.-Q. Liu, J.-P. Guo, H.-Y. Chen, W.-T. Yu, G. Xue and D.-S. Liu, *J. Org. Chem.*, 2006, **71**, 7858; (*e*) A. W. Amick and L. T. Scott, *J. Org. Chem.*, 2007, **72**, 3412; (*f*) S. Hagen and L. T. Scott, *J. Org. Chem.*, 1996, **61**, 7198.
14 (*a*) K. Balasubramanian, P. S. Selvaraj and P. S. Venkataramani, *Synthesis*, 1980, 29; (*b*) J. Yang and J. G. Verkade, *J. Am. Chem. Soc.*, 1998, **120**, 6834; (*c*) J. Yang and J. G. Verkade, *J. Am. Chem. Soc.*, 2000, **19**, 893; (*d*) Z.-K. Yao and Z.-X. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 10864; (*e*) Q.-F. Zhou, F. Yang, Q.-X. Guo and S. Xue, *Synlett*, 2007, 215; (*f*) M. Tanaka, K. Nakamura, T. Iwado, T. Sato, M. Okada, K. Sue, H. Iwamura and T. Hiaki, *Chem. – Eur. J.*, 2011, **17**, 606.
15 T. Iwado, K. Hasegawa, T. Sato, M. Okada, K. Sue, H. Iwamura and T. Hiaki, *J. Org. Chem.*, 2013, **78**, 1949.
16 (*a*) B. Al-Saleh, M. M. Abdelkhalik, A. M. Eltoukhy and M. H. Elinagdi, *J. Heterocycl. Chem.*, 2002, **39**, 105; (*b*) I. Elghamry, *Synthesis*, 2003, 2301; (*c*) M. M. Abdel-Khalik and M. H. Elnagdi, *Synth. Commun.*, 2002, **32**, 159.
17 (*a*) F. C. Pigge, F. Ghasedi and N. P. Rath, *Tetrahedron Lett.*, 1999, **40**, 8045; (*b*) F. C. Pigge, F. Ghasedi, Z. Zheng, N. P. Rath, G. Nichols and J. S. Chickos, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2458; (*c*) F. C. Pigge, Z. Zheng and N. P. Rath, *New J. Chem.*, 2000, **24**, 183; (*d*) F. C. Pigge, F. Ghasedi and N. P. Rath, *J. Org. Chem.*, 2002, **67**, 4547.
18 (*a*) K. Matsuda, N. Nakamura, K. Takahashi, K. Inoue, N. Koga and H. Iwamura, *J. Am. Chem. Soc.*, 1995, **117**, 5550; (*b*) K. Matsuda, N. Nakamura, K. Inoue, N. Koga and H. Iwamura, *Chem. – Eur. J.*, 1996, **2**, 259–264.
19 (*a*) A. Vandendriessche, J. Thomas, C. Van Oosterwijck, J. Huybrechts, B. Dervaux, S. D'hollander, F. Du Prez, W. Dehaen and M. Smet, *Eur. Polym. J.*, 2009, **45**, 3196; (*b*) C. K. W. Jim, A. Qin, J. W. Y. Lam, J.-Z. Liu, M. Haeussler and B. Z. Tang, *Sci. China, Ser. B: Chem.*, 2008, **51**, 705–708; (*c*) H. Dong, A. Qin, C. K. W. Jim, J. W. Y. Lam, M. Haussler and B. Z. Tang, *J. Inorg. Organomet. Polym.*, 2008, **18**, 201–205.
20 (*a*) H. Meier and E. Karpouk, *Tetrahedron Lett.*, 2004, **45**, 4477; (*b*) E. Karpouk, D. Schollmeyer and H. Meier, *Eur. J. Org. Chem.*, 2007, 1983.
21 F. M. A. A. El-Taweel and M. H. Elnagdi, *J. Heterocycl. Chem.*, 2001, **38**, 981.
22 For our previous works on enamione-based organic synthesis, see: (*a*) J.-P. Wan and Y.-J. Pan, *Chem. Commun.*, 2009, 2768; (*b*) J.-P. Wan, S.-F. Gan, G.-L. Sun and Y.-J. Pan, *J. Org. Chem.*, 2009, **74**, 2862; (*c*) J.-P. Wan, C. C. J. Loh, F. Pan and D. Enders, *Chem. Commun.*, 2012, **48**, 10049; (*d*) J.-P. Wan, C. Wang and Y. Pan, *Tetrahedron*, 2011, **67**, 922; (*e*) J.-P. Wan, R. Zhou, Y. Liu and M. Cai, *RSC. Adv.*, 2013, **3**, 2477.
23 For recent references on water-mediated organic synthesis, see: (*a*) M. B. Gawande, V. D. B. Bonifácio, R. Luque, P. S. Branco and R. S. Varma, *Chem. Soc. Rev.*, 2013, **42**, 5522; (*b*) B. Li and P. H. Dixneuf, *Chem. Soc. Rev.*, 2013, **42**, 5744; (*c*) M.-O. Simon and C.-J. Li, *Chem. Soc. Rev.*, 2012, **41**, 1415; (*d*) Y. Gu, *Green Chem.*, 2012, **14**, 2091; (*e*) R. N. Nuler and A. G. Goyne, *Chem. Rev.*, 2010, **110**, 6302; (*f*) K. Kumaravel and G. Vasuki, *Green Chem.*, 2009, **11**, 1945; (*g*) W. W. Y. Leong, X. Chen and Y. R. Chi, *Green Chem.*, 2013, **15**, 1505; (*h*) D. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo and J. Wang, *Green Chem.*, 2013, **15**, 2384; (*i*) G.-X. Li and J. Qu, *Chem. Commun.*, 2010, **46**, 2653; (*j*) J.-L. Cao, S.-L. Shen, P. Yang and J. Qu, *Org. Lett.*, 2013, **15**, 3856; (*k*) E. Feng, Y. Zhou, F. Zhao, X. Chen, L. Zhang, H. Jiang and H. Liu, *Green Chem.*, 2012, **14**, 1888.
24 For representative references on lactic acid mediated green synthesis, see: (*a*) J. Yang, J.-N. Tang and Y. Gu, *Green Chem.*, 2012, **14**, 3304; (*b*) Y. Gu and F. Jérôme, *Chem. Soc. Rev.*, 2013, **42**, 9550, For examples on bio-based solvent mediated synthesis from our group, see: (*c*) Y. Liu, C. Wang, R. Zhou and J.-P. Wan, *RSC Adv.*, 2012, **2**, 8789; (*d*) Y. Liu, H. Wang, C. Wang, J.-P. Wan and C. Wen, *RSC. Adv.*, 2013, **3**, 21369.
25 For selected known references on transition metal-catalyzed cyclotrimerization of eletron deficient terminal alkynes, see: (*a*) A. Leyva-Pérez, J. Oliver-Mesaguer, J. R. Cabrero-Antonino, P. Rubio-Marqués, P. Serna, S. I. Al-Resayes and A. Corma, *ACS Catal.*, 2013, **3**, 1865; (*b*) K. Abdulla, B. L. Booth and C. Stacey, *J. Organomet. Chem.*, 1985, **293**, 103; (*c*) J. Cheng, L. Tang and J. Li, *J. Nanosci. Nanotechnol.*, 2011, **11**, 5159; (*d*) M. S. Sigman, A. W. Fatland and B. E. Eaton, *J. Am. Chem. Soc.*, 1998, **120**, 5130; (*e*) M. Herberhold, H. Yan, W. Milius and B. Wrackmeyer, *Organometallics*, 2000, **19**, 4289.
26 K. M. Al-Zayd, L. M. Nhari, R. M. Borik and M. H. Elnagdi, *Green Chem. Lett. Rev.*, 2010, **2**, 93.
27 M. P. Castaldi, S. E. Gibson, M. Rudd and A. J. P. White, *Chem. – Eur. J.*, 2006, (12), 138.