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# An overview of the synthetic strategies of C3-symmetric polymeric materials containing benzene and triazine cores and their biomedical applications

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C3-symmetric star-shaped materials are an emerging category of porous organic polymers with distinctive properties such as permanent porosity, good thermal and chemical stability, high surface area, and appropriate functionalization that promote outstanding potential in various applications. This review is mostly about constructing benzene or s-triazine rings as the center of C3-symmetric molecules and using side-arm reactions to add functions to these molecules. Over and above this, the performance of various polymerization processes has been additionally investigated in detail, including the trimerization of alkynes or aromatic nitriles, polycondensation of monomers with specific functional groups, and cross-coupling building blocks with benzene or triazine cores. Finally, the most recent progress in biomedical applications for C3-symmetric materials based on benzene or s-triazine have been summarized.

## 1. Introduction

Geometry in materials science relies heavily on the symmetry of molecular building components. In particular, C3-symmetric geometries are present in star-shaped molecules, dendrimers, molecular cages, metal-organic frameworks (MOFs), and covalent organic frameworks (COFs).<sup>1–5</sup> C3-symmetric conjugated aromatic compounds have applications ranging from optoelectronic and self-assembling systems to liquid crystals, mesogens, and nonlinear material optics.<sup>6–8</sup> Notably, C3-

symmetric molecules have good physicochemical characteristics, making them useful as active building blocks in electronic devices, including organic field-effect transistors (OFETs), organic photovoltaic devices (OPVs), organic solar cells (OSCs), and organic light-emitting diodes (OLEDs).<sup>9–12</sup> Further, C3-symmetric star-shaped molecules are used in various biomedical and pharmaceutical applications. For example, it was recently designed to use old drugs that function as tripod scaffold arms or as carriers of medicines with biologically active molecules immobilized on the star arms. In addition, C3-symmetric star-shaped molecules are applied in imaging cancer cells through fluorescence, as potent allosteric antagonists of P2X receptors, and in synthetic transport systems, besides their biological activities as antioxidants and antibacterials.<sup>13–17</sup> In

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variable applications.



view of these interesting applications, numerous *C*<sub>3</sub>-symmetric aromatic molecules have piqued the interest of synthetic chemists and opened up new avenues for synthesis. Synthesis of certain molecules might begin with aldol-like events involving condensation of carbonyl compounds, cyclotrimerization reactions involving alkynes, or the functionalization of appropriately geared building blocks.

Therefore, a comprehensive view summarizing these compounds' synthetic strategies and polymerization techniques is worthwhile to provide a well-organized and methodical overview. To the best of our knowledge, several other reviews have emerged concerning the chemistry of star-shaped molecules and triazine-based organic framework. However, particular attention to synthesizing *C*<sub>3</sub>-symmetric compounds based on benzene or *s*-triazine cores in an organized manner to construct the core, the reaction of side arms, as well as polymerization techniques have yet to be reported. Given this, we have covered the literature to give an example of each method and discussed the synthetic strategies in a simplified manner to provide a better understanding for future researchers to modify these methods.

## 2. Formation of the core by different trimerization reactions

### 2.1. [2+2+2] Cyclotrimerization reactions

The transition-metal-catalyzed [2+2+2] cyclotrimerization of alkynes is considered the most classical method for efficiently synthesizing benzenes and analogous aryl derivatives.<sup>18–20</sup> Mainly used catalysts consisted of Ti, Zr, Mo, Fe, Ru, Co, Rh, Ir, Ni, and Pd; however, the main challenges are chemo and regioselectivity issues, which generally result in a complex

mixture of products.<sup>21,22</sup> A limited amount of literature discovered methods to solve this problem, such as Grubbs-catalyzed 2-propynyl derivatives in DCM gave a mixture of products. Similarly, Kotha *et al.* exploited the ruthenium-catalyzed [2+2+2] cyclotrimerization reaction to generate star-shaped compounds that form various compounds, the depropargylated product and 1,2,4-trisubstituted with 1,3,5-trisubstituted, which was hard to purify by column chromatography (Table 1, entry 1-a).<sup>23</sup>

Nevertheless, K. Yang and co-workers recently reported nickel-catalyzed regioselective cyclotrimerization of terminal alkynes in good yields to synthesize *C*<sub>3</sub>-symmetry benzenes. This process features a cheap catalyst and mild reaction conditions; likewise, the NiB(OH)<sub>2</sub> complex is generated *in situ* from NiCl<sub>2</sub>·DME and tetrahydroxydiboron could act as active catalysts. The hydrogen bonding between the hydroxyl groups on boron and the terminal alkyne plays an essential role in controlling the regioselectivity by orienting the coordination of the terminal alkynes to the nickel center (Table 1, entry 1-b).<sup>24</sup>

On top of that, polymer-assisted cobalt catalysis was used to synthesize triarylbenzenes with *C*<sub>3</sub>-symmetry through the [2+2+2] cyclotrimerization of terminal aryl alkynes. A complex poly(4-vinylpyridine)-cobalt(II) system was used as a stable and reusable heterogeneous catalyst. The cobalt catalyst showed the highly selective formation of 1,3,5-triarylbenzene without forming 1,2,4-triarylbenzene. Moreover, the polymer-supported catalyst was successfully recovered and used three times (Table 1, entry 1-c).<sup>25</sup>

### 2.2. Alkenes with metal-catalysts

Palladium-catalyzed formation of tri-substituted benzene derivatives with *C*<sub>3</sub>-symmetry from alkenes bearing electron-withdrawing groups has been reported frequently.<sup>26–29</sup> Tamaso *et al.* developed a triannulation reaction by Pd(OAc)<sub>2</sub>, HPMo<sub>8</sub>V<sub>4</sub>, acetalization of acrylate with methanol, followed by trimerization reaction of the acetal by CeCl<sub>3</sub> (Table 1, entry 2-a).<sup>26</sup> Withal, a facile palladium catalyst system was developed for the highly regioselective cyclotrimerization of olefins bearing electron-withdrawing groups in PdCl<sub>2</sub>/O<sub>2</sub>/DMF (Table 1, entry 1-b).<sup>27</sup> Furthermore, S. Midya reported a room-temperature catalytic pathway for benzene derivatives with *C*<sub>3</sub>-symmetry from nitroalkenes in the presence of Pd(OAc)<sub>2</sub> (Table 1, entry 2-c).<sup>29</sup>

### 2.3. Acetyl arenes

The trimerization reaction was achieved through the use of acetyl arenes in acid-catalyzed. The cyclization occurs through a variety of catalysts, such as thionyl chloride SOCl<sub>2</sub>, 4-dodecylbenzene sulfonic acid DBSA, triflic acid CF<sub>3</sub>SO<sub>3</sub>H,<sup>30</sup> phosphoric acid,<sup>31</sup> titanium tetrachloride TiCl<sub>4</sub> (ref. 32) and silicon tetra-chloride SiCl<sub>4</sub>.<sup>33</sup>

Shimasaki *et al.* established the reaction of acetyl arenes with DBSA in xylene at 130 °C for 1 day to afford the corresponding trimerized products in 66% yield. Equally, the product was obtained in 52% yield using thionyl chloride in EtOH at 80 °C for 8 h or silicon tetrachloride in EtOH at room temperature for 15 h (60% yield) (Table 1, entry 3-a).<sup>34</sup> Also, the treatments of

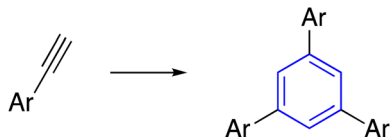
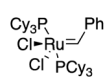
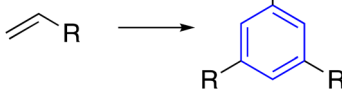
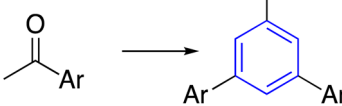
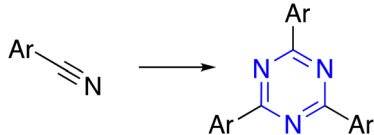
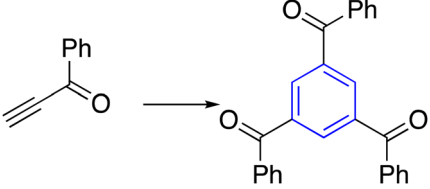
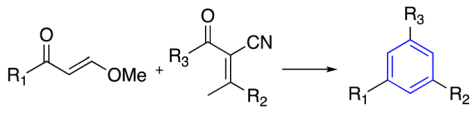
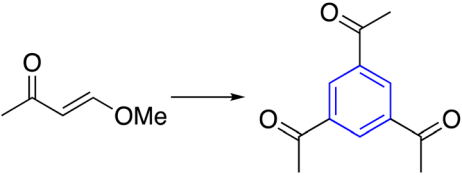
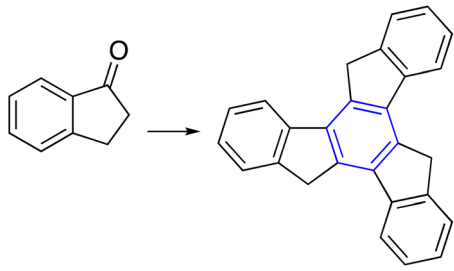


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Table 1 Synthetic strategies for cores construction by different trimerization reactions

Entry	Type of trimerization	Reaction	Reaction conditions	Ref.
1	[2+2+2] Cyclotrimerization reactions		 (a) G-1, toluene, 80 °C, 24–54 h (b) B <sub>2</sub> (OH) <sub>4</sub> , NiCl <sub>2</sub> ·DMF, CH <sub>3</sub> CN, 80 °C, 12 h (c) P4VP-CoCl <sub>2</sub> II, DIPEA, 150 °C, 24 h, N <sub>2</sub>	23 24 25
2	Alkene		(a) Pd(OAc) <sub>2</sub> , HPMo <sub>8</sub> V <sub>4</sub> , CeCl <sub>3</sub> (b) PdCl <sub>2</sub> , O <sub>2</sub> , DMF (c) Pd(OAc) <sub>2</sub> , RT	26 27 29
3	Acetyl arenes		(a) DBSA, <i>m</i> -xylene, 130 °C, 24 h. SOCl <sub>2</sub> , EtOH, 80 °C, 8 h (b) SiCl <sub>4</sub> , EtOH, 0 °C to RT, 24 h (c) CF <sub>3</sub> SO <sub>3</sub> H, toluene, 110 °C, 8 h (d) Triethyl orthoformate (e) H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> MW (f) Ethylenediamine TFA, 24 h, CH <sub>3</sub> NO <sub>2</sub>	34 35 36 37 38 39
4	Nitrile		CF <sub>3</sub> SO <sub>3</sub> H, CHCl <sub>3</sub> , 0 °C, 24 h	40
5	Alkynyl ketone		DMF, toluene, 48 h	41
6	Condensation reaction		(a) DBU, THF, RT	46
			(b) Water, 150 °C	47
			(c) TiCl <sub>4</sub> , Cl(CH <sub>2</sub> ) <sub>4</sub> Cl, 164 °C, 30 min	51

various acetylated thiophene derivatives with SiCl<sub>4</sub> in EtOH afforded the same thiophene-containing star-shaped molecule (Table 1, entry 3-b).<sup>35</sup> Okumoto and Shirota reported a CF<sub>3</sub>SO<sub>3</sub>H-catalyzed trimerization reaction to synthesize a benzene core from 4-acetylbiphenyl (Table 1, entry 3-c).<sup>36</sup> Moreover, triethyl

orthoformate was utilized to generate C<sub>3</sub>-symmetric building blocks from bromoacetophenone (Table 1, entry 3-d).<sup>37</sup> Ramshini *et al.* developed a triple condensation reaction of aryl methyl ketones catalyzed by (H<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub>)/NCP under solvent-free conditions (Table 1, entry 3-e).<sup>38</sup> Additionally,



ethylenediamine and trifluoroacetic acid were reported to afford 1,3,5-triaryl benzenes from aryl methyl ketones under mild conditions in good yields (Table 1, entry 3-f).<sup>39</sup> On the other hand, Kotha and the team treated thiophene-2-carbonitrile with  $F_3CSO_3H$  in dry chloroform at room temperature, generating the *s*-triazine as the central core in 85% yield (Table 1, entry 4).<sup>40</sup>

#### 2.4. Alkynyl ketone

Alkynyl ketones, such as benzoylacetylene derivatives, were trimerized by organocatalytic or thermally induced for synthesizing the corresponding benzene core (Table 1, entry 5). Pigge *et al.* approached (4-nitrobenzoyl) acetylene in DMF and toluene to deliver *C*<sub>3</sub>-symmetry 1,3,5-tris(4-nitrobenzoyl) benzene in 72% yield. Furthermore, Hiaki and co-workers explored the metal-free method by studying the reaction mechanism; the researchers discovered that enolate is the essential intermediate in the trimerization of alkynyl ketone to construct 1,3,5-tribenzoylbenzene under high pressure and hot water.<sup>41–45</sup>

#### 2.5. Carbonyl compounds

Benzene as a central core was synthesized by [2+4] annulation of  $\alpha,\beta$ -unsaturated carboxylic acids, or  $\alpha$ -cyano- $\beta$ -methylenes to obtain the *C*<sub>3</sub>-symmetry compounds. The  $\alpha,\beta$ -unsaturated compound was activated *via* DBU as the significant step in assembling the benzene ring, which worked as Brønsted base and nucleophile (Table 1, entry 6-a).<sup>46</sup>

More than that, the ability of enaminones to furnish *C*<sub>3</sub>-symmetry benzenes *via* cyclotrimerization in excellent yield and high regioselectivity was introduced. However, the reaction usually works under acidic media or with additives like pyridine in a number of cases. Recently, more environmentally friendly cyclotrimerized enaminones used water as the solvent and a small amount of lactic acid as a catalyst (Table 1, entry 6-b).<sup>47–50</sup>

The cyclotrimerization of cyclic ketones through an aldol trimerization reaction is a powerful tool for synthesizing trifused benzene rings. Aaron and co-workers studied certain factors that can enhance cyclotrimerizations methodology. The factor that played a substantial role in successful aldol cyclotrimerization is dehydration of the starting aldol dimer to  $\alpha,\beta$ -unsaturated ketone, while  $\beta,\gamma$ -unsaturated eliminates any possibility of producing the cyclic trimer (Table 1, entry 6-c).<sup>51,52</sup> The following Table 1 presents a summary of the above techniques.

### 3. Functionalized side arms

#### 3.1. Van Leusen oxazoles reaction

A Van Leusen oxazole reaction was utilized to synthesize star-shaped oxazole derivatives. The trisaldehyde derivative reacted with tosylmethyl isocyanide (TosMIC) in the presence of potassium carbonate and MeOH to afford the oxazole-containing star-shaped molecule. The designed trialdhyde was formed in two ways, tribromo with *n*BuLi and *N*-

formylpiperidine or formylation of tris thiophene derivative by Vilsmeier–Haack reaction using POCl<sub>3</sub> in DMF (Table 2, entry 1).<sup>53,54</sup>

#### 3.2. Wittig and related olefination

Star-shaped with alkene side arms are synthesized by an olefination in which aldehydes or ketones are reacted with phosphorus ylides to produce alkene. Frejd and co-workers examined a procedure to develop star-shaped derivatives based on amino acid (Table 2, entry 2).<sup>55</sup> To create trifunctional alkenes, Horner–Wadsworth–Emmons olefination was used. As a result of reacting 1,3,5-triformylbenzene with the Wittig reaction, a 54% yielding olefination product was obtained. Moreover, the aldol condensation is employed to form alkene in the side arms of the star-shaped compound through a condensation reaction of aldehyde and active methyl. Meier *et al.* Treated 2,4,6-trimethyl-1,3,5-triazine with various benzaldehydes in potassium hydroxide and methanol to obtain a tri-condensation product (Table 2, entry 3).<sup>56</sup>

#### 3.3. Metathesis reactions

In order to get at the pyrrole-based star-shaped molecule, ring-closing metathesis (RCM) was employed.<sup>57–59</sup> Kotha *et al.* demonstrated three different routes for synthesized pyrrole-based star-shaped *C*<sub>3</sub>-symmetric. RCM, Buchwald–Hartwig cross-coupling reaction, and Clauson–Kaas pyrrole synthesis were utilized as key steps. Interestingly, the authors employed a G-I catalyst for a one-pot ring-closing metathesis RCM and aromatization sequence (Table 2, entry 4).<sup>58</sup>

#### 3.4. Suzuki–Miyaura cross-coupling reactions

Kotha *et al.* reported a procedure for synthesizing star-shaped molecules through trimerization and Suzuki–Miyaura (SM) cross-coupling reactions. First, the acetyl thiophene refluxed with ethylenediamine in TFA and nitromethane to give the trimerized compound. Subsequent bromination by NBS provided the tribromo product, which utilized the SM cross-coupling reaction to provide star-shaped derivatives. Practically note that the tribromo compound was not formed by directly trimerized 2-acetyl-4-bromofuran. Instead, the compound was obtained by brominating the corresponding aromatic compound with NBS in DMF at room temperature (Table 2, entry 5-a).<sup>35,60</sup>

It has also been reported that star-shaped  $\alpha$ -amino acid derivatives can be produced by the trimerization of an acetyl molecule, which is then accompanied by an SM cross-coupling process. In this regard, trihalo compounds synthesized from trimerization reactions gave star-shaped AAA derivatives for SM cross-coupling with AAA-containing boronic acid (Table 2, entry 5-b).<sup>61,62</sup>

#### 3.5. Heck cross-coupling reactions

Synthesized star-shaped trihalo compounds were exploited in the Heck cross-coupling reaction to introduce a heterocycle into the star-shaped molecule. This method has been used to



Table 2 Reactions of said arms of C3-symmetric star-shaped small compound

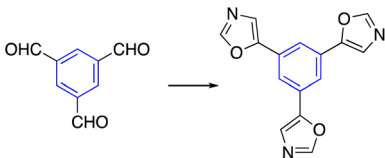
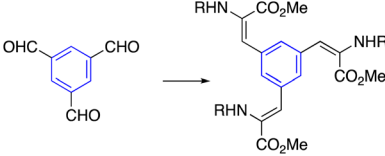
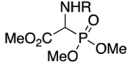
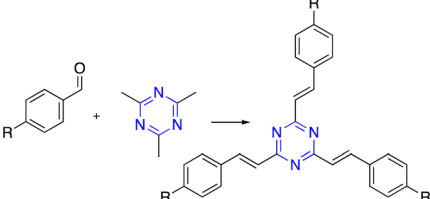
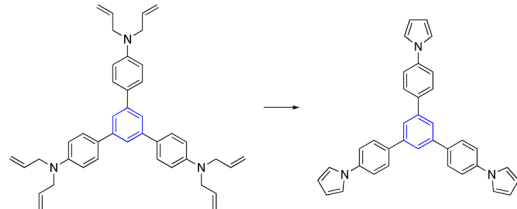
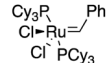
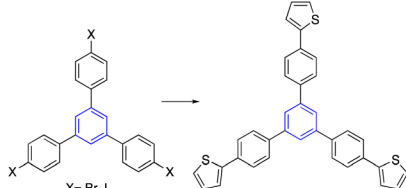
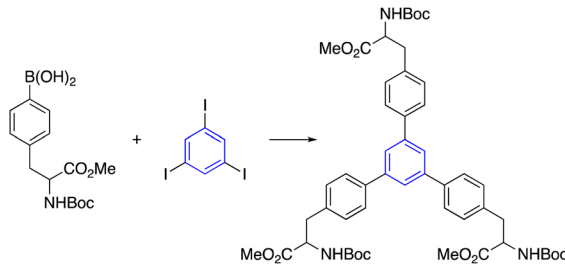
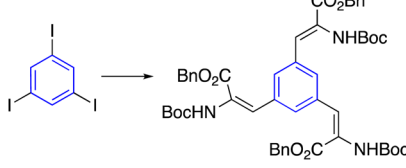
Entry	Type of reaction	Reaction	Reaction condition	Ref.
1	Van leusen oxazoles		TosMIC, K <sub>2</sub> CO <sub>3</sub> , MeOH, reflux	53
2	Wittig reaction		 N,N',N'',N'''-Tetramethyl ethylenediamine, THF, 24 h	55
3	Condensation reaction		KOH, MeOH, 3–6 days	56
4	Metathesis reactions		 G-1 CH <sub>2</sub> Cl <sub>2</sub> , 2 h	58
5	Suzuki–Miyaura cross-coupling		(a) Thiophene-2-boronic acid, Pd(PPh <sub>3</sub> ) <sub>4</sub> , THF: Toluene, Na <sub>2</sub> CO <sub>3</sub> , 90 °C	35
			(b) Pd(PPh <sub>3</sub> ) <sub>4</sub> , THF, toluene, Na <sub>2</sub> CO <sub>3</sub> , 90 °C	61
6	Heck cross-coupling		(a) NaHCO <sub>3</sub> , Bu <sub>4</sub> NCl, Pd(OAc) <sub>2</sub> , DMF, 80 °C 24 h	55
			(b) Benzoxazoe in [Pd(OAc) <sub>2</sub> ]/PPh <sub>3</sub>	63



Table 2 (Contd.)

Entry	Type of reaction	Reaction	Reaction condition	Ref.
7	Negishi cross-coupling	<p>X = Br, I</p>	<p><math>\text{Pd(PPh}_3)_4</math>, DMF, 80 °C, 12 h</p>	1
8	Stille cross-coupling		<p>Cyanuric chloride, <math>\text{Pd(PPh}_3)_4</math>, toluene, 110 °C, 4 days</p>	64
9	Sonogashira cross-coupling		<p><math>\text{Pd(PPh}_3)_4</math>, <math>\text{PPh}_3</math>, <math>\text{Et}_3\text{N}</math>, CuI, 100 °C, 3 days</p>	65

synthesize star-shaped molecules with benzoxazole, benzothiazole, and 1-methyl benzimidazole groups on their edges by palladium-catalyzed and  $\text{K}_2\text{CO}_3$  or  $\text{Cs}_2\text{CO}_3$  to produce the desired designed heterocycle (Table 2, entry 6-b).<sup>63</sup>

By using either the Horner–Wadsworth–Emmons olefination or the Heck cross-coupling reactions, Frejd and his team successfully produced star-shaped amino acid analogs with three different functions. Within the context of this investigation, a Heck cross-coupling led to the formation of a trifunctional amino acid analog. The reaction of triiodobenzene with acrylate in the presence of palladium acetate provided the coupled product. In contrast, the hydrogenation of olefin was carried out with a rhodium catalyst to give the corresponding star-shaped amino acid derivative in a good yield (Table 2, entry 6-a).<sup>55</sup>

### 3.6. Negishi cross-coupling reactions

Besides, palladium-catalyzed was employed through Negishi cross-coupling reactions to construct star-shaped molecules, which formed an established step to build the tris-AAA derivative. First, the 4-iodoacetophenone trimerization yielded the triiodo derivative. The resultant trimerized synthon was then used in a Negishi cross-coupling with palladium as a catalyst in DMF at 80 °C, yielding a compound with a 68% yield (Table 2, entry 7).<sup>1</sup>

### 3.7. Stille cross-coupling reactions

Using a Stille cross-coupling reaction between a tribromo compound and tributylstannyl analogs, we could study synthetic triazine-based star-shaped structures with  $C_3$ -symmetry. Using cyanuric chloride and the proper tributyltin or



trimethyltin precursor in toluene, Ko and co-workers created star-shaped molecules with *s*-triazine centers and substituted triphenylamine groups on their perimeter (Table 2, entry 8).<sup>63,64</sup>

### 3.8. Sonogashira cross-coupling reactions

Kim and co-workers have described the production of a molecule with a star-like structure and *C*<sub>3</sub>-symmetry by using 1,3,5-triethynylbenzene as the central core and 2,5-diphenyloxadiazole as the side arms. The compound 1,3,5-triethynylbenzene was generated when 1,3,5-tribromobenzene was treated with trimethylsilylacetylene and potassium carbonate. Second, using Sonogashira cross-coupling between the chemical and the bromo compound with [Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] as the catalyst, the required star-shaped molecule was produced with a yield of 54% (Table 2, entry 9).<sup>65</sup>

The Sonogashira cross-coupling of bromo-intermediates was accomplished by following the same approach. Since the bromine predecessors were insoluble in the MeCN. A series of tests determined that toluene is an effective solvent for carrying

out this transition. As a consequence of this, bromo-intermediates were put through a Sonogashira cross-coupling reaction with 1,3,5-triethynylbenzene in the presence of [Pd(PPh<sub>3</sub>)<sub>4</sub>]/CuI as the catalyst system and (diisopropyl)amine in toluene. This resulted in the production of coupling products with a high rate of success.

Amir and his team have created an extraordinarily efficient catalyst for the Sonogashira cross-coupling of aryl halides with aromatic and aliphatic terminal alkynes. The methodology allows the use of palladium nanoparticles immobilized on a dendritic nano-silica-triazine polymer. The processes were performed in water, the most environmentally friendly solvent. Table 2 provides an overview of these different strategies.

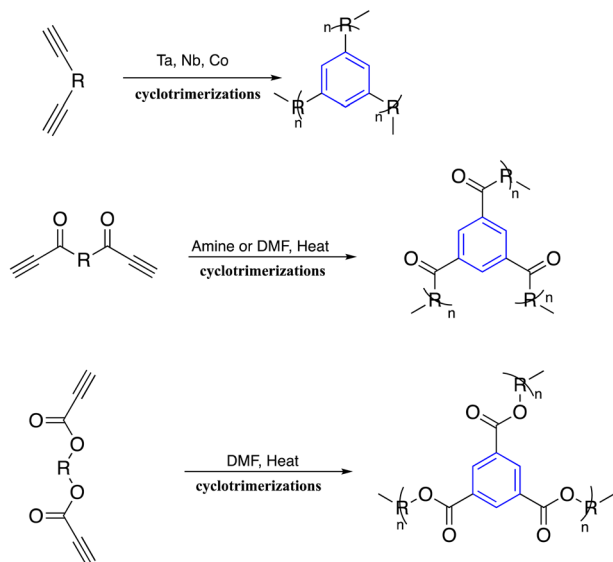
## 4. Polymerization

Polymerization techniques based on the *C*<sub>3</sub>-symmetric star-shaped molecules have been illustrated, including the trimerization of alkynes or aromatic nitriles in the existence of acidic catalysts, a polycondensation reaction of monomers containing specific functional groups, and a cross-coupling reaction containing building blocks. A brief overview of the most important, as well as common techniques, has been displayed as follows.

### 4.1. Polycyclotrimerizations

Polycyclotrimerizations of diyne molecules give *C*<sub>3</sub>-symmetric polyphenylene with benzene ring repeated units. In this context, polycyclotrimerization was uniquely synthesized in the A2 monomer approach.<sup>66–69</sup> Alkyne cyclotrimerization has been developed as a viable process for manufacturing *C*<sub>3</sub>-symmetric polymers. Tang and coworkers ran into cross-linking issues during their research, the monomers were terminal diynes connected by aromatic rings utilized. The researchers worked in molecularly engineered monomer structures and optimized polymerization conditions, and successfully synthesized *C*<sub>3</sub>-symmetric polypropylenes with high molecular weight and excellent solubility.<sup>70,71</sup>

Through further investigation, the same research team reported that the polycyclotrimerizations of bis(arylacetylenes) were started by catalysts classified as nonmetallic or



Scheme 1 Trimerization of alkyne.

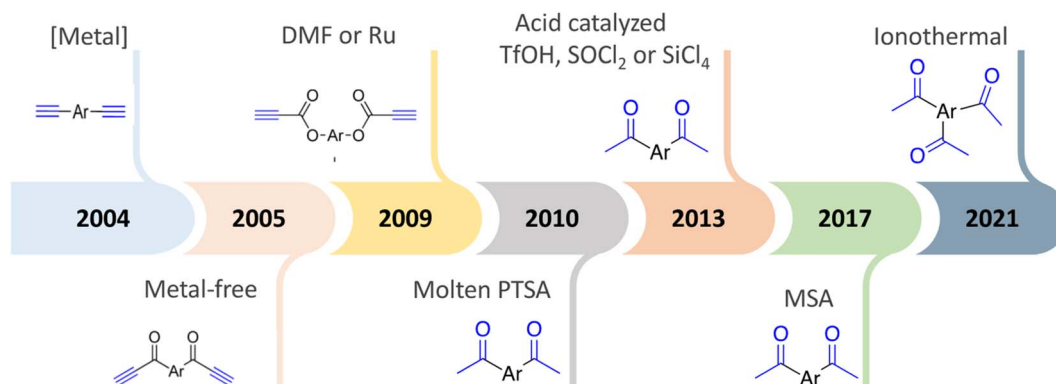
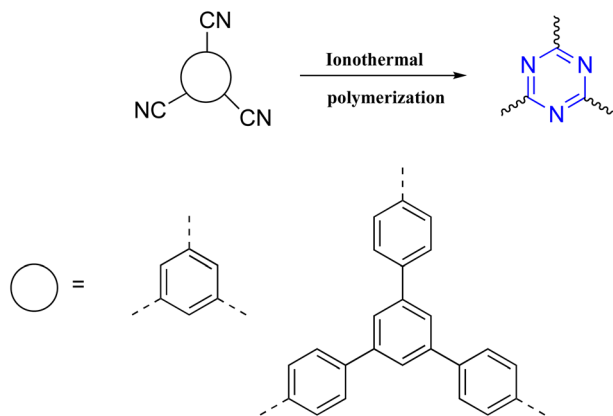


Fig. 1 *C*<sub>3</sub>-symmetric polymeric materials containing benzene core via cyclotrimerization.



Scheme 2 Trimerization of carbonitriles.

organocatalysts involving piperidine. The polymerization reaction proceeds smoothly to produce C3-symmetric poly(arylene)s with high DBs in high yields by an ionic mechanism.<sup>72,73</sup> Additionally, analysis of the monomer structure demonstrates that this polymerization reaction works for diynes where triple bonds are attached to electron-withdrawing groups. If the carbonyl bond in the aryloxyacetylene can be replaced by an ester group, the monomer synthesis becomes much more accessible. The conveniently polymerized bipropiolate monomer opened the synthetic route to the easy and economical synthesis of C3 symmetric polymers. The Tangs group investigated this possibility and showed that reflux polycyclotrimerizations of bipropiolate in DMF produce C3-symmetric polymers with perfectly branched structures and 1,3,5-regioregularity in high yields.<sup>74</sup> The synthetic sequence for this type of polymerization is shown in Scheme 1.

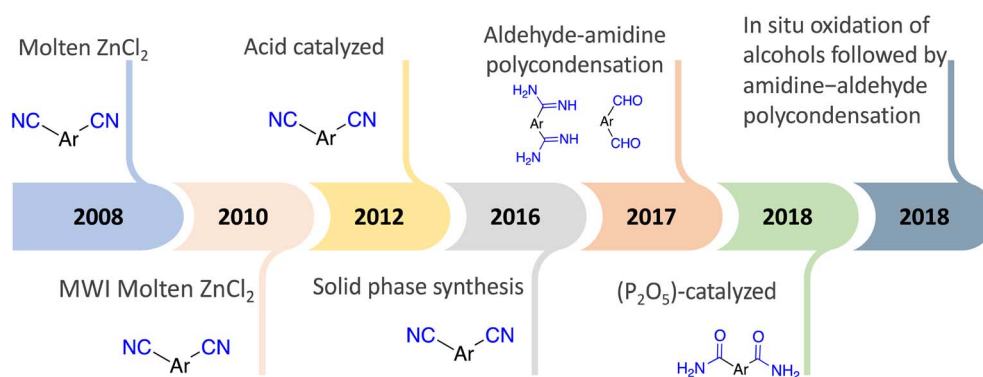
Moreover, a solvothermal method was utilized for cyclotrimerization of bifunctional acetyl arenes compounds to obtain highly porous polymers. Various acids were employed to synthesize polycyclotrimerization in solution induced, including silicon tetrachloride and molten 4-toluene sulfonic acid,<sup>75</sup> thionyl chloride,<sup>76</sup> and superacid-catalyzed.<sup>77</sup>

Zi-Hao Guo *et al.* achieved cost-effective bottom-up syntheses of organic microporous polymer networks using molten methanesulfonic acid mediated aldol triple condensation reaction.

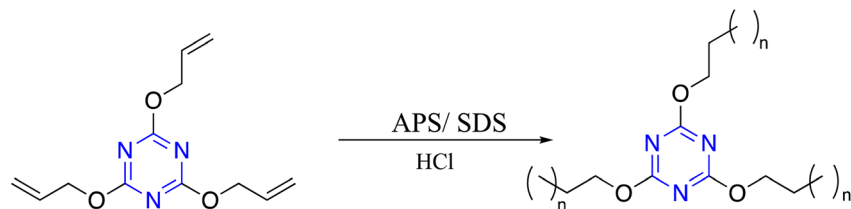
This method features inexpensive starting materials, reagents, and simple reaction procedures.<sup>78,79</sup> Recently, ionothermal conditions demonstrated that the solvent-free cyclotrimerization of methyl ketones could be driven to high conversions using molten ZnCl<sub>2</sub> as the reaction solvent, leading to a highly conjugated organic polymer.<sup>80</sup> Fig. 1 shows the development of the synthesis of C3-symmetric polymeric materials containing benzene core *via* cyclotrimerization.

On the other hand, forming triazine rings required harsh conditions. Thus, Thomas *et al.* synthesized highly stable polymers by ionothermal trimerization of nitrile groups in molten ZnCl<sub>2</sub>, which performed as a solvent and catalyst at high temperatures ranging from 400–600 °C. Further forward, in 2010, W. Zhang and co-workers enhanced the ionothermal method by utilizing a microwave-assisted that reduced the reaction time. Moreover, Cooper *et al.* developed a microwave-assisted by adding Brønsted acid trifluoromethanesulfonic acid (TFMS) as a polymerization catalyst. Furthermore, W. Huang and co-workers reported a novel TFMS acid vapor-assisted solid-phase synthetic method to construct triazine from aromatic nitrile monomers. Also, CF<sub>3</sub>SO<sub>3</sub>H-catalyzed trimerization of nitriles under both room temperature and microwave conditions was reported. This process gave significant benefits by eliminating the undesirable ZnCl<sub>2</sub> contamination and destruction of nitrile and C–H bonds. Nevertheless, CF<sub>3</sub>SO<sub>3</sub>H-catalyzed trimerization of nitriles has some limitations, such as a low synthesis temperature being required, an expensive catalyst, and brutal handling of the reaction due to the caustic and eye-irritating carcinogenic chemicals involved, along with the ice-cold saltwater considered necessary for neutralization, as illustrated in Scheme 2.<sup>81–84</sup>

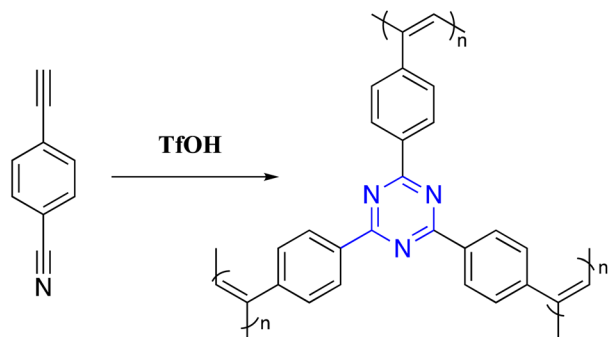
Nevertheless, to avoid harsh synthetic conditions and associated limited structural diversity K. Wang *et al.* developed a new strategy involving the condensation reaction of aldehydes and amidines to construct polymer triazine-based under mild conditions. Moreover, the phosphorus pentoxide (P<sub>2</sub>O<sub>5</sub>)-catalyzed employed as direct condensation of aromatic amide instead of aromatic nitrile to form triazine rings and likewise reported *in situ* oxidation of alcohols followed by amidine-aldehyde polycondensation, where the reaction rates were controlled by gradually generating aldehydes by *in situ* slow

Fig. 2 C3-symmetric polymeric materials containing triazine core *via* cyclotrimerization.





Scheme 3 Free radical polymerization.



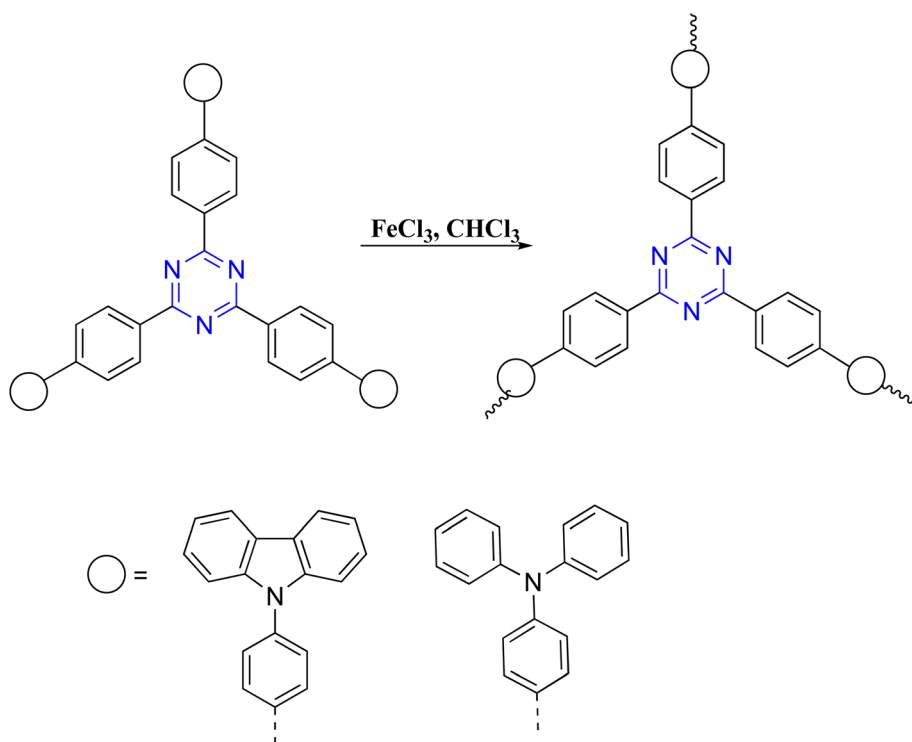
Scheme 4 Cationic polymerization.

oxidation of alcohols to form highly crystalline polymer triazine-based.<sup>84–89</sup> Fig. 2 shows the development of the synthesis of C3-symmetric polymeric materials containing triazine core *via* cyclotrimerization.

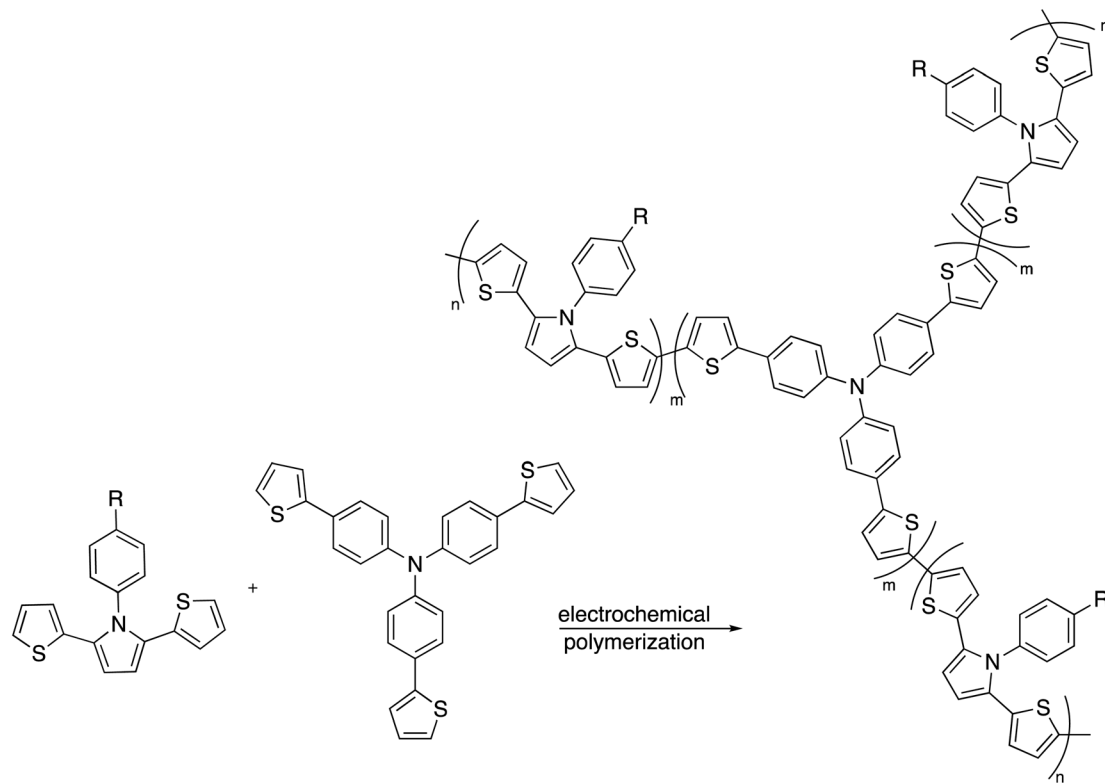
#### 4.2. Addition polymerization

Free radical polymerization is one class of addition polymerization techniques developed to synthesize C3-symmetric polymer, representing the subsequent addition of free radicals to form a polymer backbone. Modak *et al.* reported functionalized C3-symmetric polymer by simple *in situ* radical polymerization of 2,4,6-triallyloxy-1,3,5-triazine in an aqueous medium in the presence of ammonium persulfate (APS) as a radical initiator and anionic surfactant sodium dodecyl sulfate (SDS) as a template under acidic conditions. TEM image and powder XRD analysis showed the pores in the ordered 2D hexagonal structure of the material. In addition, N<sub>2</sub> sorption analysis demonstrated an excellent surface area for this C3-symmetric polymer (Scheme 3).<sup>90</sup>

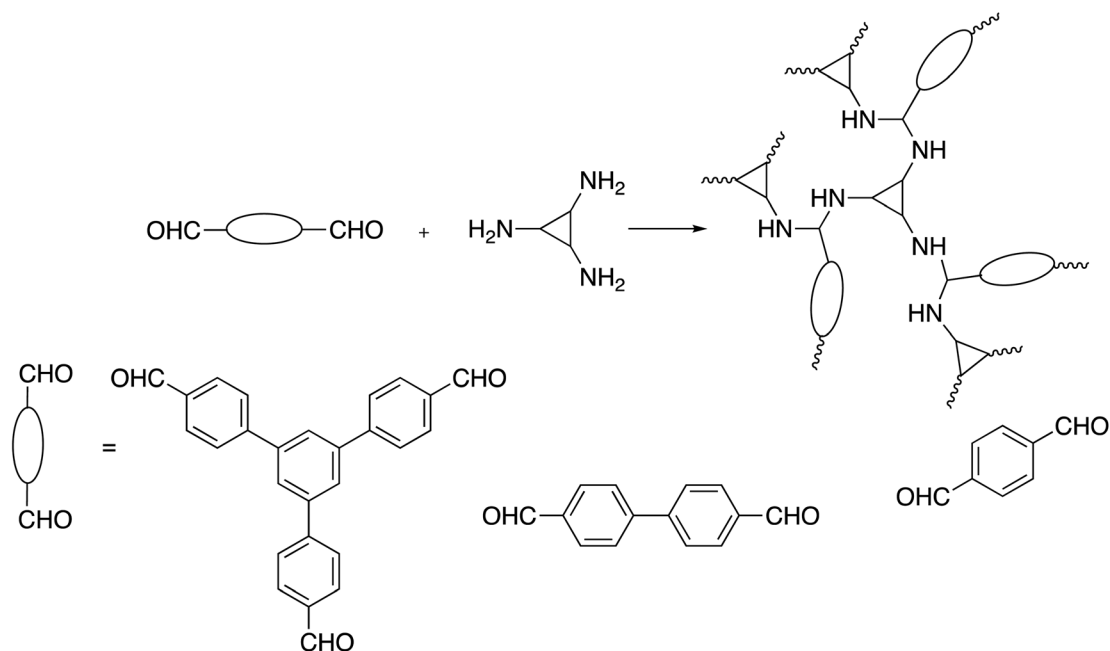
Sina and Majid developed a free-standing conjugated C3-symmetric polymer through a cationic polymerization reaction in a one-pot, low-temperature, and super-acid-catalyzed process. Bifunctional monomers with ethylene and nitrile groups were used, catalyzed by trifluoromethanesulfonic acid



Scheme 5 Oxidative polymerization.



Scheme 6 Oxidative co-polymerization.

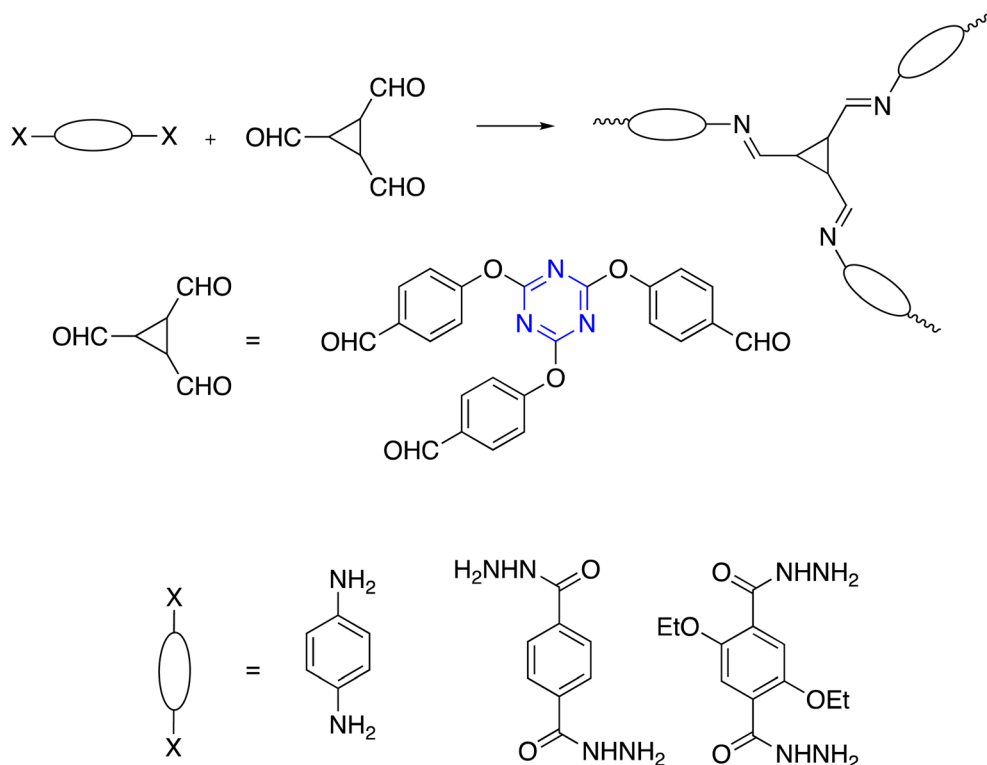


Scheme 7 Synthesis of C3-symmetry with amina networks.

( $\text{CF}_3\text{SO}_3\text{H}$ ), which provided ethynyl polymerization and nitrile cyclotrimerization. Even during the polymerization process, the hard-triple bonds are transformed into stretchable double bonds, which makes it easier to build a membrane that is both

flexible and has increased mechano-strength. This polymer showed extremely significant  $\text{CO}_2$  removal capacity up to  $3.87 \text{ mmol g}^{-1}$  ( $170.3 \text{ mg g}^{-1}$ ), and the electron richness of the conjugated skeleton increased the basicity necessary for





Scheme 8 Synthesis of C3-symmetry with imine or hydrazone networks.

interaction with CO<sub>2</sub> via dipole-quadrupole- and acid-base interactions (Scheme 4).<sup>91</sup>

#### 4.3. Oxidative coupling polymerization

The oxidative coupling polymerization of the aromatic ring in the presence of FeCl<sub>3</sub> has been reported to construct conjugated C3-symmetric organic frameworks. Mu *et al.* prepared a simplistic method for carbazole-based oxidative coupling polymerization using the 2,4,6-trisubstituted-1,3,5-triazine building block catalyzed with FeCl<sub>3</sub> in an anhydrous solvent. The three-dimensional polymer scaffolds were highly fluorescent, with a BET surface area of 840 m<sup>2</sup> g<sup>-1</sup> in the microporous regime.<sup>92</sup>

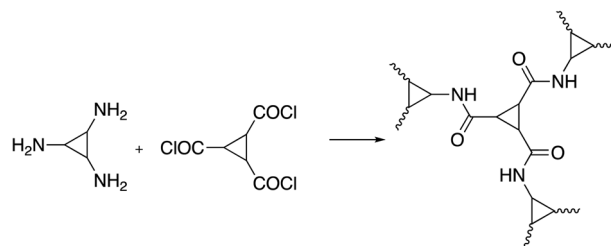
Correspondingly, chemical oxidative polymerization was employed to synthesize organic conjugated polymer containing star-shaped triphenyltriazine with C3-symmetry. Chen and co-workers designed and successfully synthesized poly[1,3,5-tris(4-diphenylamino-phenyl)triazine] through functionalized triphenylamine backbone, accompanied by FeCl<sub>3</sub>-catalyzed through oxidative chemical polymerization. The polymer powder exhibits a high surface area in 930 m<sup>2</sup> g<sup>-1</sup> and a double Peruse distribution ranging from micropores 0.55 nm to small-diameter mesopores 26 nm (Scheme 5).<sup>93</sup>

Moreover, oxidative co-polymerization was reported through an electrochemical method, the research discussed the reaction between dithienylpyrrole and tris[4-(2-thienyl)phenyl]amine in CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> to grant the C3-symmetry polymer (Scheme 6).<sup>94,95</sup>

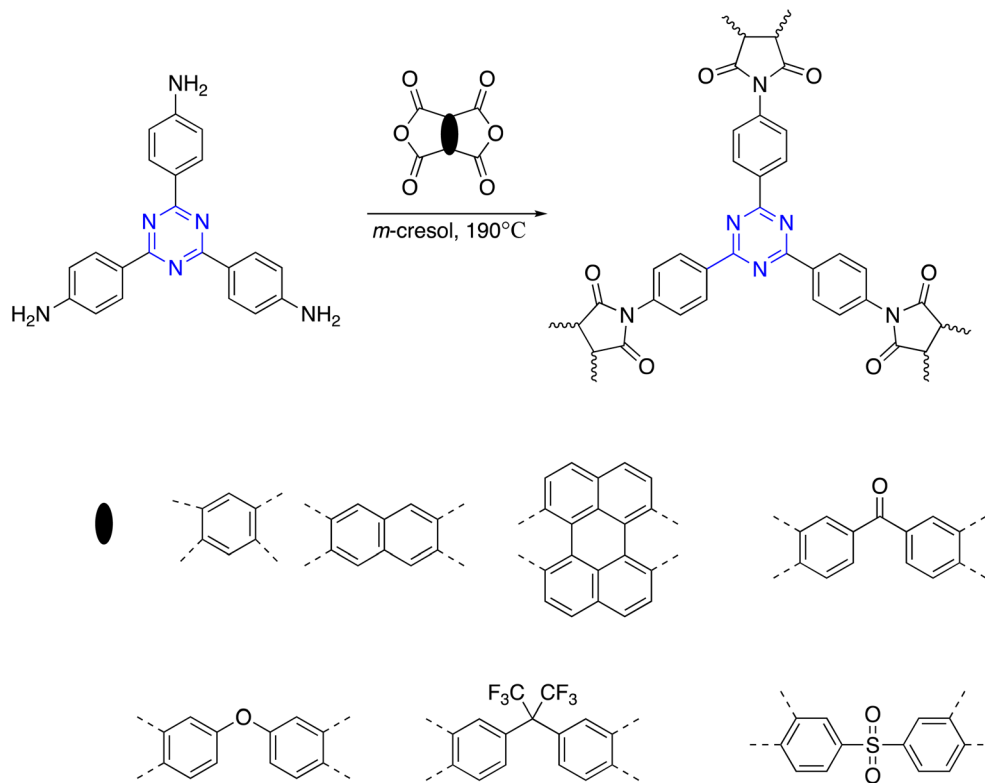
#### 4.4. Schiff-base polymerization

Schiff base chemistry is also applied to synthesize polymers with C3-symmetry via an A2 + B3 approach.<sup>96–102</sup> Müllen *et al.* reported smart condensation reactions of triamine moieties with various dialdehydes to generate highly cross-linked porous aminated networks. The polymers were prepared by microwave irradiation, one-pot, catalyst-free synthesis, and cheap and uncomplicated monomers. The polymer networks contained up to 50 wt% nitrogen, highly stable and insoluble in aqueous and organic solvents, including DMSO, MeOH, acetone, DCM, and THF (Scheme 7).<sup>96,97</sup>

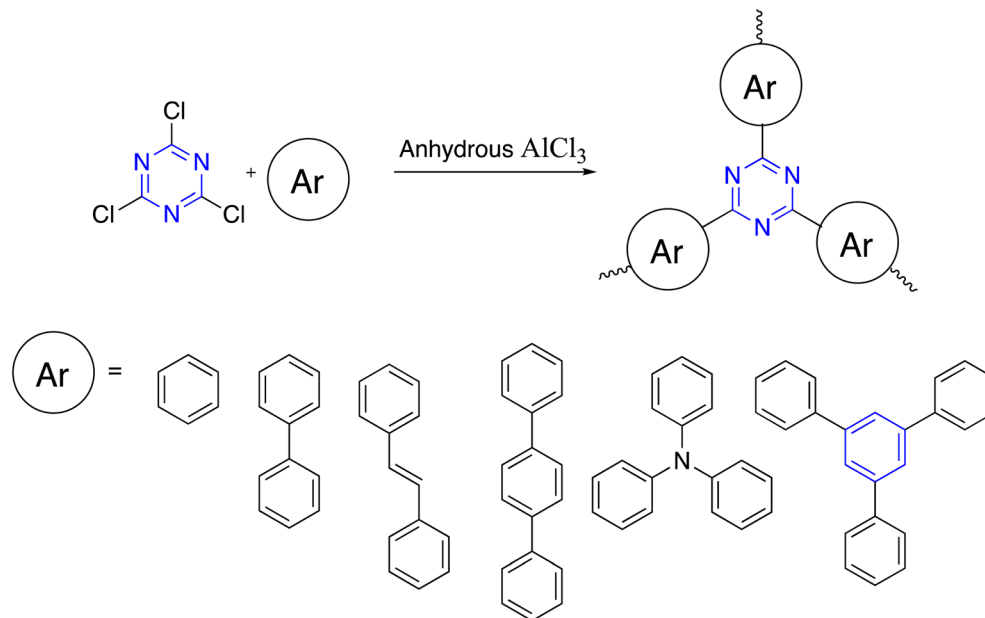
Newly, As illustrated in Scheme 8, the trialdehyde moiety was condensed with a variety of amines, which resulted in the formation of a number of imine- or hydrazone-linked<sup>103,104</sup> compounds. Through a Schiff base reaction involving 1,3,5-tris(4-formyl-phenyl)triazine and *p*-phenylenediamine or terephthalic acid dihydrazide, Pitchumani *et al.* created an imine-based polymer with C3-symmetry.



Scheme 9 Synthesis of C3-symmetry with amide networks.



Scheme 10 Synthesis of C3-symmetry with amide networks.



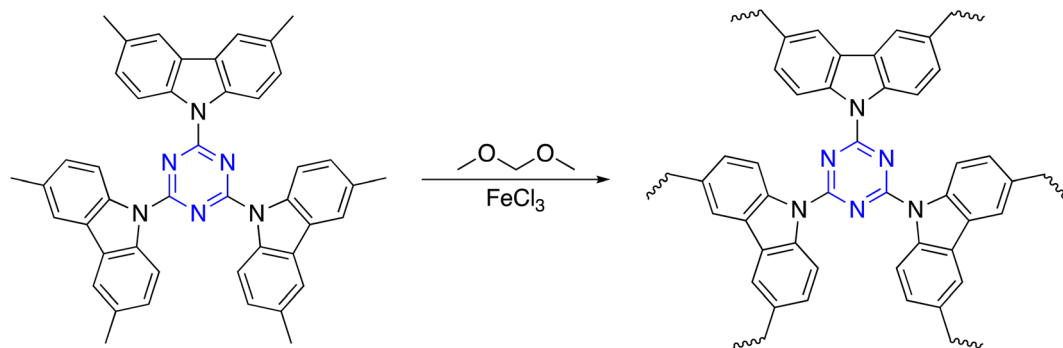
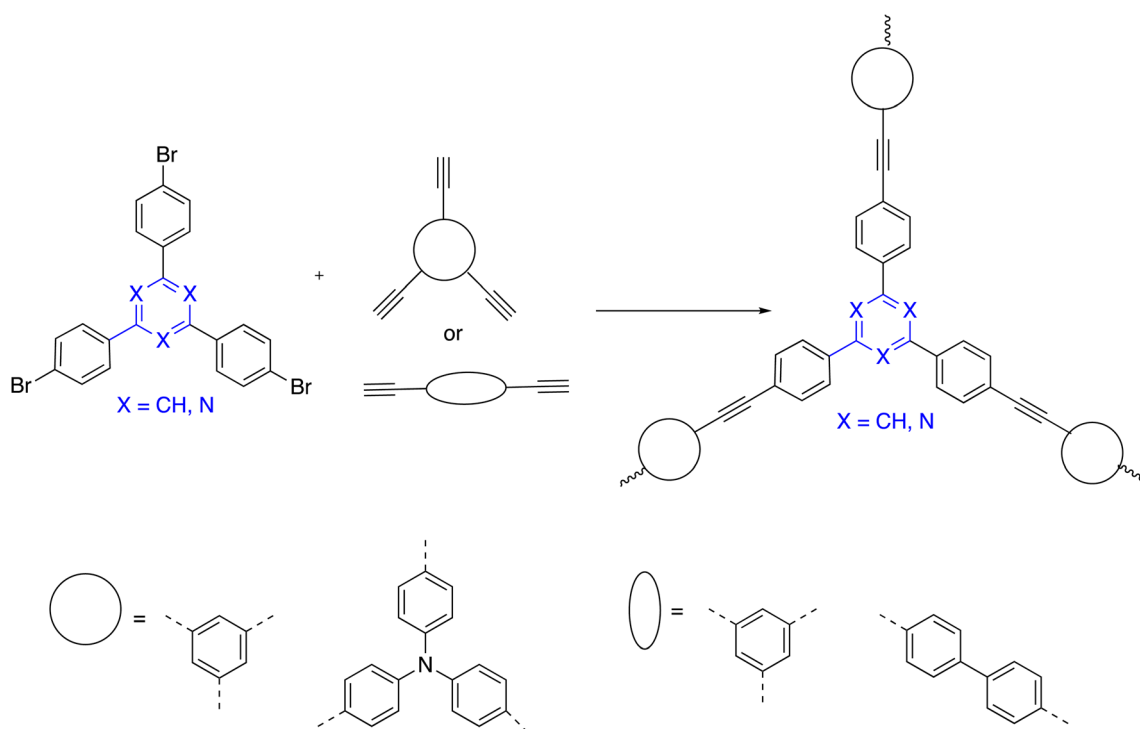
Scheme 11 Synthesis of C3-symmetry triazine-based via the Friedel–Crafts reaction.

#### 4.5. Nucleophilic substitution reaction

C3-symmetry polyamides were prepared in good yield from triamine and triacid chloride monomers through an A3 + B3 approach. Lately, Yavuz *et al.* synthesized C3-symmetry

polyamides by triamine and triacid chloride monomers by solution polymerization in two variable systems of solvents (DMAc/NMP and 1,4-dioxane) at room temperature (Scheme 9).<sup>103</sup>

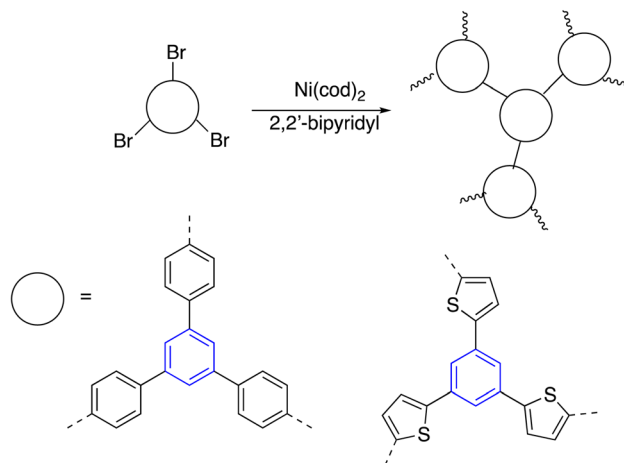


Scheme 12 Synthesis of C<sub>3</sub>-symmetry triazine-based via the Friedel–Crafts reaction.Scheme 13 Synthesis of C<sub>3</sub>-symmetry via the Sonogashira coupling reaction.

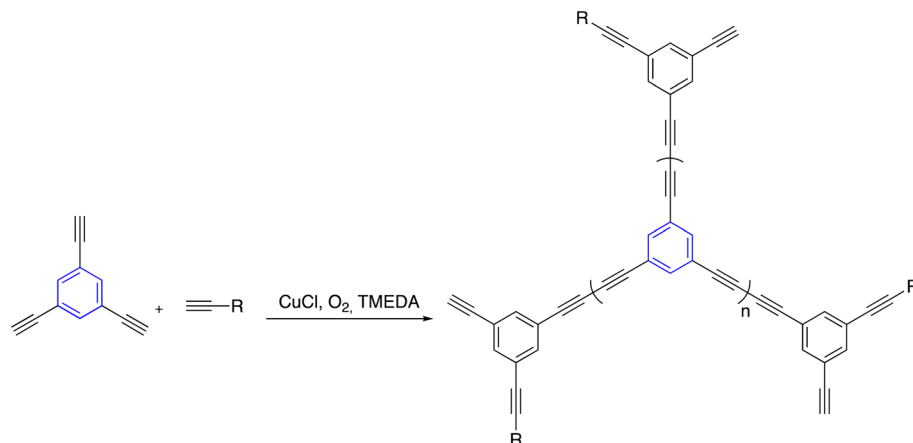
In other respects, the interaction of 2,4,6-tris(4-aminophenyl)-1,3,5-triazine and the dianhydride carried out in *m*-cresol as a solvent according to the A3 + B2 strategy resulted in the successful synthesis of C<sub>3</sub>-symmetry polyimides in excellent yield. The resulting polymer displayed significant chemical and thermal stability up to 450 °C. Moreover, the three-dimensional polymer showed a BET surface area of up to 809 m<sup>2</sup> g<sup>−1</sup> in the microporous range, as displayed in Scheme 10.<sup>104</sup>

#### 4.6. Friedel–Crafts polymerization

Friedel–Crafts reaction (FC) of cyanuric chloride and aromatic building blocks using anhydrous AlCl<sub>3</sub> or methanesulfonic as a catalyst was published. Lim and co-workers stated that microporous polymers based on an *s*-triazine unit were

Scheme 14 Synthesis of C<sub>3</sub>-symmetry via the Yamamoto coupling reaction.





Scheme 15 Synthesis of C3-symmetry via the Glaser-Hay coupling reaction.

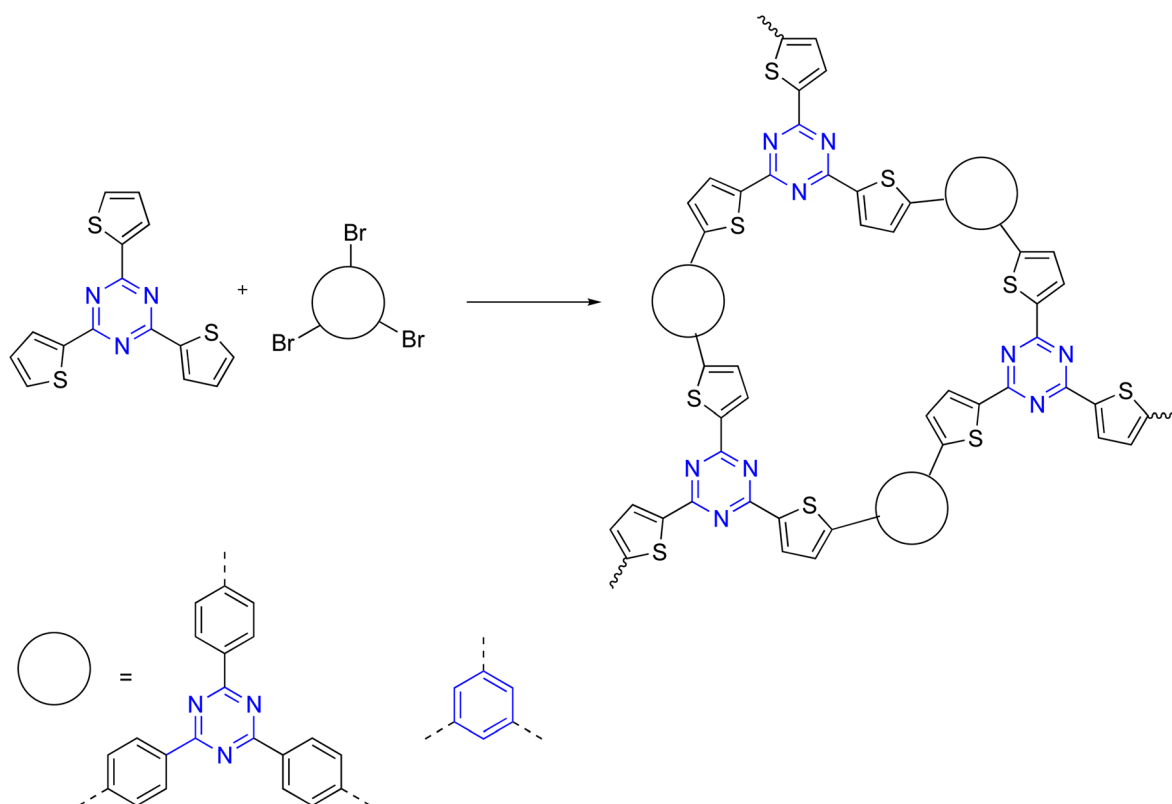
synthesized by the FC reaction of cyanuric chloride with aromatic compounds in the presence of aluminum chloride.<sup>105,106</sup> S. Xiong *et al.* developed a cost-effective approach for constructing *s*-triazine-based polymeric networks with a high BET surface area of up to 894 m<sup>2</sup> g<sup>−1</sup> that have been under the catalysis of methanesulfonic acid (Scheme 11).<sup>107</sup>

Dai *et al.* prepared C3-symmetry polymers triazine and carbazole bi-functionalized *via* FC reaction between the triazine-functionalized carbazole monomer and formaldehyde dimethyl acetal in the presence of FeCl<sub>3</sub> and 1,2-dichloroethane (DCE) (Scheme 12).<sup>108</sup>

#### 4.7. Coupling polymerizations

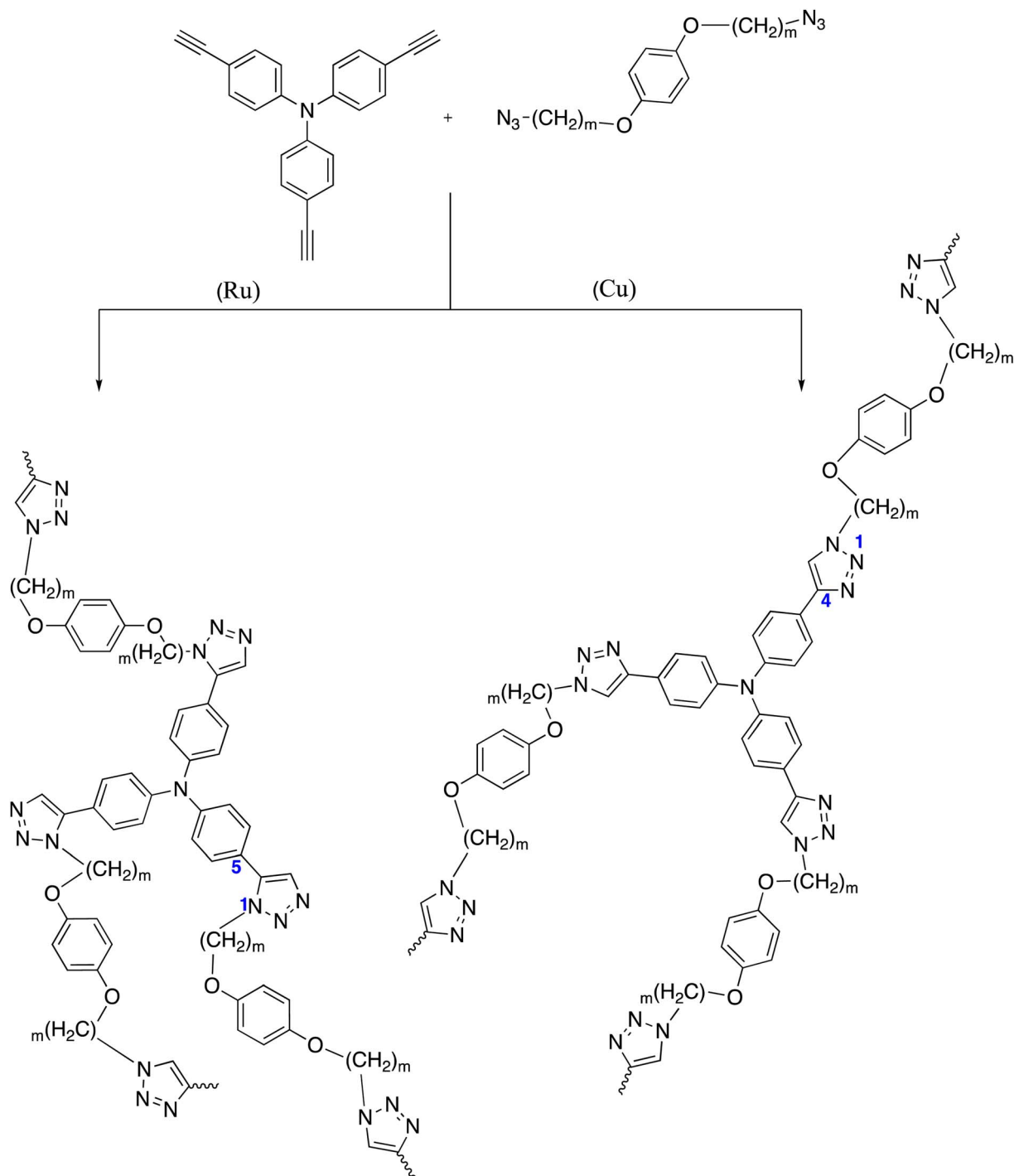
It was possible to synthesize C3-symmetry using the Sonogashira-Hagihara cross-coupling method, which was predicated on the electron-withdrawing polymers *s*-triazine and benzene and originated from trihalo and triyne or diyne monomers using an A3 + B3 or A3 + B2 strategy, correspondingly, as shown in Scheme 13.<sup>109</sup>

Xiang employed the Yamamoto reaction to significantly obtain porous organic polymers that carried out a high hydrothermal-stability. Yamamoto reaction consists of



Scheme 16 Synthesis of C3-symmetry via the direct arylation coupling reaction.





Scheme 17 Synthesis of C3-symmetry via the click reaction.

a homocoupling of aryl bromides in the presence of a Ni(0) complex. Consequently, the mentioned article operated *s*-triazine and benzene C3-symmetry star-shaped polymer under Ni-catalyzed throughout polycondensation method (Scheme 14).<sup>110</sup>

By the same token, Glaser-Hay coupling reaction was examined to synthesize co-polyenes through homopolycouplings of aryltriyne and monoyne. The coupling reaction

occurs with cuprous salts in the presence of oxygen and a base, giving soluble hyperbranched polyenes. The polymerizations were terminated by dumping the provides a good balance into acidified methanol before it reached the gel stage to avoid the network's formation (Scheme 15).<sup>111</sup>

On top of that, direct arylation polymerization was described as a synthetic technique for another class of triazine-core polymers. This was done in addition to the previous point. It



**Table 3** Selected recent examples of C3-symmetric based on benzene or s-triazine materials for biomedical applications

Entry	Core	Structure	Application	Features	Ref.
1	s-Triazine		Drug delivery of ibuprofen (IBU)	50% of the IBU was released in 5 h 75% was released in 10 h Almost the release was completed in two days	116
2	s-Triazine 1,3,5-trisubstituted benzene		Drug delivery, three different drugs, captopril, IBU, and 5-fluorouracil (5-FU)	5-FU had a 30% loading capacity and was released in 3 days	117
3	s-Triazine		Drug delivery of quercetin	Enhanced anticancer activity of quercetin	118
4	1,3,5-Trisubstituted benzene		Drug delivery of doxorubicin (DOX)	DOX had a 32.1% loading capacity, and the release was pH-responsive	119
5	1,3,5-Trisubstituted benzene		Drug delivery of doxorubicin (DOX)	Drug-loading capacity (21%)	120
6	s-Triazine		Gene delivery	Strong affinity toward nucleic acids	121
7	1,3,5-Trisubstituted benzene		Photodynamic therapy PDT and photothermal therapy PTT	Photosensitizer for PDT and PTT with enhanced antitumor efficacy	122–124



Table 3 (Contd.)

Entry	Core	Structure	Application	Features	Ref.
8	s-Triazine		Photodynamic therapy	Increase the reactive oxygen species in the tumor to improve the <i>in vivo</i> PDT effect of cancer	125
9	1,3,5-Trisubstituted benzene		Electrochemical biosensor	Accelerate signal amplification, which increase biosensor sensitivity	126
10	1,3,5-Trisubstituted benzene		Biosensor	Facilitates the migration of charge carriers and enhance the response of sensors Excellent size-exclusion effect, high selectivity, sensitivity, and reusability	127 and 128
11	1,3,5-Trisubstituted benzene		Bioimaging	Exhibits excellent specificity and can only recover its fluorescence signal upon meeting the specific targets	129

was unnecessary to pre-activate the C–H bonds in the arene monomers to carry out the coupling reaction of 2,4,6-(tri-2-thienyl)-1,3,5-triazine with multi-brominated monomers of varied geometries. The products obtained were obtained. Because of this benefit, it is possible to incorporate the triazine unit into multidimensional polymeric structures effortlessly. As a result, this provides comonomers with a considerable amount of synthetic control over the morphologies, porosities, and optoelectronic characters of triazine-core materials (Scheme 16).<sup>112</sup>

#### 4.8. Click polymerizations

Tang and co-workers studied click polymerizations by mixing diazide and triyne monomers using the normal click tools under CuSO<sub>4</sub>/sodium ascorbate catalyst in THF/water mixture. It's possible that the incompatibility between the species that are developing and the aqueous media is what caused the polymers to clump together and then precipitating. When initiating the click polymerization of triyne with diazides, a non-aqueous click of the catalyst Cu(PPh<sub>3</sub>)<sub>3</sub>Br was utilized. This was done so as to minimize the usage of an aqueous medium. The catalyzed polymerization of diazide and triyne monomers produced 1,4-triazine in 46% yield, and showed high solubility in DMSO, DMF, THF, and DCM. On the other hand, 1,5-regioselective click polymerization of diazide and triyne monomers catalyzed by Cp\*Ru(PPh<sub>3</sub>)<sub>2</sub>Cl produced soluble 1,5-triazine in 75% yield in as short as 30 min.<sup>113–115</sup> The two synthetic procedures were displayed as shown in Scheme 17.

## 5. Biomedical applications

C3-symmetric compounds that are based on benzene or s-triazine cores have high surface areas and thin structures, which allow for surface modification with various components. This further enables a wide range of applications, including biomedical, pharmaceutical, gas storage, photovoltaics, conductivity, catalysis, electrochemical sensing, and many more. Unfortunately, and according to our best of knowledge, there are a limited number of relevant studies in the biomedical applications field compared to the other fields. Therefore, the following table provides a concise summary of the most recent developments in biomedical applications, which include drug delivery, gene delivery, photodynamic therapy, photothermal therapy, biosensing, and bioimaging (Table 3).

## 6. Conclusion and outlook

To sum up, the significant properties of C3-symmetric compounds based on benzene or s-triazine cores have inspired chemists to design, synthesize, and use them in numerous applications. These consist of symmetrically porous, heteroatomic sites and multifunctional surfaces. Moreover, it has high thermal and chemical stability due to its structure via strong covalent bonds. Henceforth, synthesizing these materials requires additional effort to be simplified to achieve effortless, cheaper, and acceptable methods. Our review article

will assist future researchers in developing synthetic methodologies. Likewise, the choice of an organic linker or precursor can also be explored by employing our overview.

## Conflicts of interest

There are no conflicts to declare.

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