Chemistry

Synthesis of tetraphenylene derivatives and their recent advances
Jian-Wei Han¹,²,∗, Xiao-Shui Peng³ and Henry N. C. Wong¹,³,∗

ABSTRACT
The synthetic strategies towards tetraphenylene derivatives are comprehensively summarized in this review. Recent advances in the functionalized tetraphenylene skeleton for research into their structurally unique properties are described together with their potential applications.

Keywords: tetraphenylene, aromatic, chiral, carbocycles, eight-membered rings

INTRODUCTION
Tetraphenylene (1, Fig. 1) can also be called tetrabenzylocyclooctatetraene or tetrabenzo[8]annulene. Being a member of the polycyclic aromatic group of compounds, initial studies of 1 were centered around exploration of the planarization of cyclooctatetraene (COT) [1]. In more recent years, a tetrabenzo-derivative of COT has been investigated thoroughly due to its interesting chemical properties and theoretical relevance to the discussion of its aromaticity. However, the structure of 1 was found to be a non-planar molecule with a distinct saddle-shaped framework [2,3]. As depicted in Fig. 1, the four benzene rings of 1 form a rigid central eight-membered ring by ortho-annulation, in which two pairs of benzene rings are oriented alternatively above or below the average plane of the molecule. Therefore, the central COT of 1 is ‘non-aromatic’. Although the magnitude of inversion barrier had been controversial, with various estimations in the early years, the saddle-shaped geometry of 1 was found to be very stable, which was confirmed by neutron diffraction study and thermal experiments [4,5]. With this geometric rigidity, studies of 1 and its derivatives have led to their application in asymmetric catalysis, liquid crystalline materials, molecular devices, organic light-emitting diodes and others. More recently, the extraordinary geometric characteristics and promising chiral properties of tetrabenzenes have renewed the interest of synthetic chemists to explore new synthetic strategies and to obtain multi-substituted tetraphenylene.

The structure of tetraphenylene (1) features a central COT ring embedded in benzene rings. Pioneering work in the context of the planar or tub-shaped conformations of COTs, together with studies on their intrinsic properties and potential applications, have already been described in a series of definitive review or account articles [6–10]. The current review will focus on the synthetic methodology of tetrabenzenes, with a particular focus on recent advances in the preparation of novel tetrabenzenes derivatives with three-dimensional topology over the last 10 years.

DIRECT SYNTHESIS OF TETRAPHENYLENES
In terms of organic synthesis, tetraphenylene (1) can be viewed as a tetramer of benzene. However, to date no methods have been described for the realization of 1 by direct polymerization of benzene. The first synthesis of 1 was reported by Rapson et al. in 1943 via a copper-assisted coupling of a Grignard reagent (Scheme 1) [11]. Since then, numerous approaches towards tetrabenzenes have been documented [6–10]. Generally, the constructions of 1 and its derivatives are summarized as the following methods: (i) pyrolysis and/or metal-catalyzed dimerization of biphenylenes; (ii) the Diels–Alder cycloaddition and subsequent deoxygenation protocol, starting from cyclooctadienediyne; (iii) oxidative coupling reaction of dilithiobiphenyl derivatives; (iv) transition metal-catalyzed double coupling reactions;
Scheme 1. The first synthesis of tetraphenylenes.

Figure 1. The structure of tetraphenylenes.

(v) inter- and intramolecular cycloadditions of two ortho-phenylene-tethered triynes; (vi) the fold-in oxidative fusion reaction; (vii) the Scholl reaction; and (viii) tetrameric condensations. These methods are discussed below.

Pyrolysis and/or metal-catalyzed dimerization of biphenylenes

Despite the fact that benzyne (4) might be too reactive for tetramerization by cyclization to provide tetraphenylenes, biphenylene (5) can be viewed as a dimer of o-benzyne. Pyrolysis of 5 in liquid phase at a high temperature of 400°C afforded an essentially quantitative yield (96%) of 1, as reported by Friedman and Lindow in 1967 [12]. The effects of time and temperature on the course of the reaction showed that an efficient dimerization occurred in the liquid phase as a result of a relatively high steady-state concentration of biphenylene diradical (6) (Scheme 2). Notably, large-scale pyrolyses of biphenylene in 20 g were successfully conducted in a stainless steel bomb at 375°C for 1 h. The reaction temperature was lower when the reaction was carried out in a stainless steel bomb in comparison with glassware, therefore pyrolysis was attempted in a Vycor tube with a small piece of stainless steel tubing as a catalyst, which showed that the formation of 1 was catalyzed by the stainless steel surface. Importantly, the finding of a metal-catalyzed reaction by cleavage and reconnecting the carbon–carbon (C–C) bonds has accelerated later developments in transition metal catalysis. It is noteworthy that the yield of 1 through pyrolysis has been the highest until now. However, substituted tetraphenylene derivatives such as 8 were obtained at an extremely low yield of 6% in the pyrolysis of the corresponding tetramethyl biphenylene (7) (Scheme 3) [13].

In 1961, it was reported that when 5 was heated to a temperature of 100°C for 7 h in a sealed tube in the presence of one equivalent of bis(triphenylphosphino)nickel dicarbonyl [Ni(CO)2(PPh3)2] complex, the reaction gave a small yield of 1 as the only isolable product (Scheme 4) [14]. Later, Eisch examined various nickel complexes for this reaction, and found that the ligands attached to the metal center of nickel complexes played a crucial role in the oxidative insertion into the strained C–C bond of 5 [15]. For example, complex Ni(COD)2 was unreactive towards 5, whereas Ni(Et3P)4 reacted rapidly and

Scheme 2. Synthesis of tetraphenylenes by dimerization of benzyne.

Scheme 3. Synthesis of octamethyltetraphenylenes by pyrolysis.

Scheme 4. Synthesis of tetraphenylenes from biphenylene by Ni-catalysis.
To complement the results of Eisch, Vollhardt impressively utilized a Ni-catalyzed approach for the preparation of tetraphenylene derivatives (13 and 14) with various substituents. Thus, a mixture of tetrasubstituted tetraphenylene (13 and 14) was yielded using nickel catalysis as shown in Scheme 6 [19].

The central ring strain of 5 facilitates C–C bond cleavage by transition metals. In this way, dimerization of 5 offers an excellent opportunity to study fundamental C–C bond cleavage and formation involving heavy metals. In 1980, Stille reported that di-μ-chloro-bis(norbornadienierhodium) catalyzed the dimerization of 5 to afford 1 at 44% yield at 250°C [20]. In 1998, Jones reported that at 120°C, Pt(PEt3)3 and Pd(PEt3)3 were able to convert 5 to 1 in a catalytic manner [21,22]. In addition, Pt(PEt3)3 and Pd(PEt3)3 cleaved the C–C bond of 5 to give a metal 2,2-biphenyl complex that is also capable of catalyzing the formation of 1 from 5 via the Pt(IV) intermediate (16) (Scheme 7). The resting-state species in the catalytic cycle was the same complex whether Pt(PEt3)3 or 16 was used as the catalyst. Of note, intermediates 15 and 16 in the catalytic cycle have been identified and characterized by X-ray crystallographic analysis.

Although the strategy of pyrolysis and/or metal-catalyzed dimerization of biphenylenes yields tetraphenylenes, greater effort is needed to examine factors leading to the efficient oxidative addition of metal complexes into biphenylenes. Moreover, current procedures for the preparation of biphenylenes are unsatisfactory because they either need the use of expensive starting materials or produce biphenylenes in only small amounts. As can be seen, the tetraphenylene derivatives obtained by the dimerization of biphenylenes are very limited due to the availability of biphenylenes. In 2005, Gallagher investigated palladacycles, including a pyridine ring in the reactions with 5, for the construction of heterocyclic tetraphenylene derivatives (18a–18c).

![Scheme 5](image)

**Scheme 5.** The mechanism of cyclization of biphenylene.

Completely even at 0°C. Importantly, a dibenzo-nickelole intermediate (9) was proposed to be involved in the reaction mechanism (Scheme 5). Then, 9 lost Et3P and dimerized to a dinuclear nickel complex (10) (R = Et), whose structure was determined by an X-ray diffraction study. However, it is unfortunate that mononuclear 9 could not be isolated for structural characterization. The likely existence of 9 was nonetheless proved by its reactivity with deuterium hydrochloride (DCl), LiAlH4, and CO, leading to the respective desired products. Notably, the structures of 9 and 10 lend support to a unified mechanistic scheme for interpreting the nickel-catalyzed Reppe tetramerization reaction of acetylenes to COT [16].

Considering the classical mechanism of Reppe cyclization for COT catalyzed by nickel [16,17], Johnson isolated an asymmetric nickel–nickel bonded intermediate (11) in the reaction of 5 with bis(1,5-cyclooctadiene)nickel and a larger phosphine i-Pr3P. The solid-state crystallographic structures of dinuclear species (10) (R = i-Pr) and (11) support their role in a mechanism involving a formal Ni(III)–Ni(I) complex (Scheme 5) [18].

![Scheme 6](image)

**Scheme 6.** Synthesis of substituted tetraphenylenes.

R = Et, 13a 14%; 14a 15%
R = Ph, 13b 12%; 14b 13%
R = SiMe3, 13c 10%; 14c 11%
Scheme 7. Synthesis of tetraphenylenes from biphenylene by Pt/Pd-catalysis.

Scheme 8. Synthesis of substituted tetraphenylenes.

Scheme 9. Synthesis of tetraphenylenes by cycloaddition-deoxygenation protocol.

The corresponding products were yielded at 36, 16, and 13%, respectively (Scheme 8) [23].

Diels–Alder cycloaddition and subsequent deoxygenation protocol, starting from cyclooctadienediyne

In their initial works exploring the aromatic properties of planar COTs embedded in conjugated polycycles, Wong and Sondheimer firstly synthesized planar dibenzocyclooctadienediyne as a stable compound in 1974 [24,25]. Soon afterwards, a Diels–Alder reaction with furans was used to trap the acetylenic intermediates to furnish endoxides [26,27]; then, the arenes were constructed by extrusion of the oxygen atom from the endoxides. In 1982, a cycloaddition reaction between the highly strained planar diyne 19 with an excess of furan was undertaken to provide endoxide 20, whose deoxygenation with low-valent titanium led to the formation of 1 at a 50% yield (Scheme 9) [28]. This reaction proved to be an extremely practical ‘cycloaddition–deoxygenation protocol’, paving a new way towards the synthesis of 1 and its analogs.

Using the cycloaddition–deoxygenation protocol, Wong et al. synthesized a family of benzo-fused tetraphenylenes (21–26) by using the corresponding benzo-fused dehydro[8]annulenes and various furan derivatives (Fig. 2) [29–31]. By employing 21–26, a systematic study of host–guest interactions made by tetraphenylenes and a wide variety of guest species suggested the formation of clathrate inclusion compounds. Furthermore, a tetramethoxy derivative (26) was oxidized with silver oxide and nitric acid, affording the respective bis-quinone (27), which was found to be selective against guest molecules [30]. Utilizing this protocol, Müllen synthesized octaphenyltetraphenylene (28) as an oligophenylene precursor at a 95% yield from 19 and 1,2,3,4-tetraphenylcyclopenta-l,3-diene.

As anticipated, the crystal structure of 28 showed a boat conformation of the central eight-membered ring [32].

On the other hand, 1,16-hydroxytetraphenylene (32) was synthesized by this protocol as illustrated in Scheme 10 [33]. As can be seen, starting from dibromide 29, a diyne 30 was generated with t-BuOK. Without further isolation, 30 was allowed to go through a double Diels–Alder reaction with furan to form an endoxide. A subsequent deoxygenation with low-valent titanium furnished 1,16-dimethoxytetraphenylene (31) at an 80% yield. Eventually, treatment of 31 with boron tribromide afforded 32 at a 97% yield.

As shown in Scheme 11, Sygula reported the synthesis of buckycatcher 34 by using this protocol [34], in which two corannulenes are linked with a rigid tetraphenylene unit. Tweezer 34 could form a stable inclusion complex with fullerene C_{60} (K_a = 8.6 × 10^{3} M^{-1}, toluene-d_8, determined by NMR titrations), and an X-ray diffraction study of a mixture of 34 and C_{60} allowed the determination of the solid-state complex structure.
Figure 2. Tetraphenylenederivatives.

Similar to the aforementioned Diels–Alder cycloaddition and subsequent deoxygenation protocol, tetraphenylenol \((42)\) and its tetramethoxyl analog \((41)\) were synthesized from 1,10-dimethoxydibenzo[\(a,e\)]cyclooctene as a precursor in Wong’s laboratory \([35]\). The synthesis of 1,4,5,16-tetrahydroxytetraphenylen was realized by a stepwise Diels–Alder reaction and subsequent reductive cleavage to form the benzene ring. A further procedure of oxidation and reduction introduced another hydroxyl group on the tetraphenylen skeleton (Scheme 12).

The research group of Siegel reported a novel saddle-shaped tetraphenylen derivative \((44)\) containing two fluoranthene subunits \([36]\). The synthesis was achieved via a Diels–Alder reaction between 43 and 19 (Scheme 13). The X-ray crystallographic structure of 44 revealed a \(C_2\) symmetric molecule with a dihedral angle; the angle between the mean planes of the naphthalene and benzene units is \(19.55^\circ\). The twisting is continuous from one naphthalene subunit, through the tetraphenylen core, to the naphthalene of the other fluoranthene subunit.

Very recently, Whalley and co-workers reported the synthesis of 47 based on a strategy that was similar to the cycloaddition protocol (Scheme 14) \([37]\). Sulfoxide 45 was employed as a dienophile in the Diels–Alder reaction with 19, providing the adduct 46 at a 14\% yield. Under microwave irradiation, palladium-catalyzed arylation of 46 at 180\°C afforded 47 at a 24\% yield. Four fused benzenoid rings around the periphery of the molecule (47) provide a highly stable structure. This increased stability over the parent [8] circulene was predicted using Clar’s theory of aromatic sextets and is a result of the compound becoming fully benzenoid upon the incorporation of these additional rings.

Oxidative coupling reaction of dilithiobiphenyl derivatives

The coupling reaction of two hydrocarbon fragments with the aid of a transition metal catalyst
The protocol provides a fundamentally synthetic methodology for C–C bond formation. Following flourishing research over many decades, the coupling reaction accessible via organometallic reagents nowadays has many more possible applications. The first synthesis of tetraphenylene, as previously mentioned, was a homo-coupling reaction of Grignard reagents [11]. Soon after, Wittig prepared o-dilithiobenzene and 2,2′-dilithiobiphenyl from o-phenylenemercury (by treatment of o-dibromobenzene with sodium mercury amalgam). Next, Wittig detailed the homo-coupling reactions of dilithiobiphenyl with various transition metal chlorides [38]. Besides tetraphenylenes, biphenylenes were also generated (Scheme 15). The selectivity between the two compounds is not constant and alters dramatically depending on different reaction factors. Solvents were often found to play a distinct role. It was suggested that tetrahydrofuran (THF) favored the formation of biphenylenes, while Et₂O favored that of tetraphenylenes. Substituents on the phenyl rings also influenced the outcome of these reactions. Thus, bromo-substituted dilithiobiaryl gave tetraphenylenes (50) as major products, while methoxy-substituted dilithiobiaryl gave the corresponding tetraphenylenes as minor products in both THF and Et₂O [39].

The structural features of tetraphenylene derivatives possessing various substituents can be manipulated for a variety of uses. For example, hydroxytetraphenylenes as self-assembling building blocks and other scaffolds have been well summarized in our previous paper [8]. In 2002, Wong and co-workers accomplished the synthesis of 1,4,5,8,9,12,13,16-octamethoxyletraphenylene (54) by using this homo-coupling reaction. Moreover, deprotection and oxidation yielded the corresponding tetraquinone (55) for the study of its inclusion property (Scheme 16) [40].

As can be seen, this homo-coupling reaction could be widely applied as the principal preparative method in the realization of tetraphenylenes. Our recent work has revisited the synthesis of these target molecules of hydroxytetraphenylenes via intermolecular oxidative homo- or cross-coupling reactions of dilithio substrates mediated by copper salts [41]. We showed that the synthetic steps of each hydroxytetraphenylene were fewer than those of routes reported in previous works, and that the overall yields were also higher (Scheme 17).
In general, zinc analogs form biphenylenes as primary products rather than tetraphenylenes. However, zincobiaryls, synthesized from their corresponding dilithiobiaryls with ZnBr₂ (Scheme 18), can also undergo homo-coupling with Cu(II) to afford tetraphenylenes. Iyoda and Kabir found that transmetallation of dilithio derivatives from halogen–lithium exchange with zinc bromide give zincacyclopentadiene (61) as a reactive intermediate [42,43]. Treatment with CuBr₂ allowed further transmetallation and octamethoxytetraphenylenene (62) formed selectively at a 67% yield through a reductive elimination sequence.

Interestingly, Rajca et al. synthesized a ‘biphenylene dimer’ as a nearly planar structure [44]. The synthetic route to this symmetrical biphenylene dimer (64) was based on a Cu-mediated aryl–aryl homocoupling reaction (Scheme 19).

In 2000, Rajca and co-workers reported that a CuBr₂-mediated oxidation coupling of partially resolved (R)-2,2′-dibromo-1,1′-binaphthyl (65) gave the corresponding dimer of (R)-66 at a 20% yield with 95% enantiomeric excess (ee). The structure of 66 was determined by X-ray crystallographic analysis [45]. This method was based on the configurationally stability of 2,2′-dilithio-1,1′-binaphthyl and amplification of enantiomeric excess was observed in the coupling product (Scheme 20).

(–)-Sparteine-induced lithiation of 2,2′-dibromobiphenyl (67) and a subsequent CuBr₂-mediated enantioselective coupling reaction was also reported by Rajca et al. (Scheme 21) [46]. Optically active tetraphenylene derivatives (68) bearing t-butyls were obtained in 75–86% yields and in moderate enantioselectivities (54–64%). Nevertheless, a highly enantiomerically pure 68a (≥95% ee) was obtained after recrystallization.

Recently, Wong and co-workers developed an efficient process towards chiral tetrahydroxytetraphenylenes based on the strategy of ‘center-to-axis chirality transfer’ [47]. As depicted in Scheme 22, employing chiral butane-2,3-diol as chiral auxiliaries, diiodide (70) was prepared and allowed to undergo a CuCl₂-mediated coupling reaction to afford the optically pure tetraphenylene (71). Subsequent deprotection then led to the formation of optically pure 1,8,9,16-tetrahydroxytetraphenylenene (58) at a 95% yield (Scheme 22).

As tetraphenylenes are saddle-shaped and are inherently chiral π-conjugated scaffolds, a sequence of ortho-annulations of tetraphenylenes via rigid C–C bonds could provide oligotetraphenylenes as artificial double-stranded helical structures. In 1997, Rajca and co-workers reported the synthesis

Scheme 13. Synthesis of 44.

Scheme 14. Synthesis of tetrabenzo[8]circulene 47.

Scheme 15. Transition metal-mediated oxidative coupling.
Scheme 16. Synthesis of 53, 54 and 55.

Scheme 17. Synthesis of 32, 42, 54, 58 and 59.

of a racemic double helical octaphenylene (75), based on a CuCl2-mediated coupling reaction [48]. The random cross-coupling of 2,2′-dilithiobiphenyl salts 72 and 73 gave a tetraphenylene intermediate (74) at a 19% yield, which was subjected to oxidative coupling again with CuBr2 to furnish the target octaphenylene (75) at a 4% isolated yield (Scheme 23). However, only a racemic hydrocarbon was obtained in this procedure.

Very recently, Wong and co-workers employed both enantiopure dibromooligophenylenes and dibromotetraphenylenes in a copper-mediated coupling reaction after treatment with t-BuLi. As a result, helical frameworks of (M)-78, (M)-79 and (M)-80 were obtained in one pot (5, 6 and 9% yield, respectively). The molecular structure of (M)-80
cyclooctatetrathiophenes with different connection sequences could be achieved on the basis of the selectivity of deprotonation of bithiophene-bearing trimethylsilyl groups [51]. Analog 82c was prepared by Marsella et al. with the aim of achieving double helical oligomers (82d–e) utilizing a further coupling reaction [52].

**Transition metal-catalyzed double coupling reactions**

The usage of a large amount of lithium reagents is very inconvenient from a practical viewpoint. Palladium-catalyzed double coupling protocols, on the other hand, could provide a reliable pathway towards efficient synthesis of tetraphenylenes. In 2012, an intermolecular double Suzuki coupling reaction was disclosed by Wong and co-workers [53]. As shown in Scheme 26, the intermolecular cyclic dimerization between bromide and boronic acid would lead to a straightforward approach toward regio- and stereoselective synthesis of 2,3,10,11-tetramethoxy-tetraphenylene. Interestingly, it was found that a mixture of 84 and 85 in equal quantities was obtained, as determined by NMR analysis.

Later, a double Suzuki coupling reaction of diiodobiphenyl with a diboronate reagent was revealed to be a reliable method in the synthesis of tetraphenylene derivatives [49]. By using Pd(dppf)Cl₂ as a catalyst in dimethyl ether (DME), 1,8,9,16-tetramethoxytetraphenylene (57) was obtained at a 53% yield. It is noteworthy that the yield of 53% given by a double Suzuki coupling reaction is the highest in comparison with previous
Scheme 24. Preparation of oligophenylenes (M)-78, (M)-79 and (M)-80

reports on the preparation of tetramethoxytetraphenylene [41]. By employing this method, a biphenyl trimer (87) was achieved at a 26% yield in the presence of a catalytic amount of Pd(dppf)Cl2 (Scheme 27).

Scheme 25. Synthesis of 82 via coupling reactions.

Very recently, Wong and co-workers synthesized 6,7-bismethoxy-2,11-dihydroxytetraphenylene with this strategy [54]. As shown in Scheme 28, diiodide (88) and diborinate (89) smoothly undergo a double Suzuki reaction to yield the expected

Scheme 26. Double Suzuki coupling reaction in synthesis of 84 and 85.

28% yield (84 : 85 = 1:1, determined by ¹H NMR)
tetraphenylenes 90 and 91. However, upon selective removal of an isopropyl group and subsequent triflation, the resulting compounds are converted into chromatographically separable triflates 91a and 91b.

Thermal decomposition of cyclic dibenzoiodonium salts in the generation of biphenyl diradicals was attempted as early as 1967. It was also noted that two biphenyl diradicals could combine to form a tetraphenyleneskeleton. However, only one example of 1,16-dinitrotetraphenylenewasobtainedinan extremely low yield of 0.25% [55]. Recently, we employed dibenzoiodonium salt (92) as a double Suzuki coupling partner and, gratifyingly, 1 was obtained at a 21% isolated yield from 2,2'-biphenyldiboronic acid (Scheme 29) [56].

Scheme 27. Double Suzuki coupling reaction of diiodobiphenyl with a diboronate reagent.

Scheme 28. Preparation of tetraphenylene derivatives 90 and 91.
Besides double Suzuki reactions, Pd-catalyzed Ullmann coupling reactions of diiodobiphenyls in an attempt to construct tetraphenylenes were simultaneously reported by the research groups of Xi and Wong [57,58]. Ouyang and Xi reported one case in which Pd(t-Bu$_3$P)$_2$ catalyzed the coupling reaction of dibromobiphenyl in the presence of LiOEt. As a result, tetraphenylene (1) was gained at a 45% yield [57]. On the other hand, Wong and co-workers developed double Ullmann coupling and cross-coupling reactions catalyzed by palladium acetates in 2-butanone by utilizing sealed-tube techniques [52]. With this method, 12 tetraphenylene derivatives were synthesized directly at yields of 13–51% from the corresponding 2′-diiodobiphenyls (2) (Scheme 30). Cross-coupling between different diiodobiphenyls was therefore realized. Several examples, such as 93c, 93e, 93g, 93h and 93l were confirmed by X-ray crystallographic analyses. Furthermore, a mechanism of palladium-catalyzed double coupling reactions was proposed featuring a palladacycle in the catalytic cycle.

Very recently, Zhang and co-workers reported a facile approach for the synthesis of 1 and its
derivatives from 2-iodobiphenyls via Pd-catalyzed C–H activation [59]. A variety of substituted tetraphenylenes 94 were prepared in good yields (Scheme 31). It is noteworthy that the reaction can be performed on a gram scale with relatively high efficiency.

Inter- and intramolecular cycloadditions of two ortho-phenylene-tethered triynes

In 2009, Shibata developed a catalytic and enantioselective method for the synthesis of chiral tetraphenylenes based on a [2 + 2 + 2] cycloaddition of triynes [60–62]. This approach gave the target tetraphenylenes derivatives (96) in good yields (45–93%) with excellent enantioselectivities (up to 99%). It therefore provides a new route to access substituted tetraphenylene derivatives. The presence of a terminal alkyne in 95 is essential for this protocol, as described in the proposed mechanism. Recently, the reaction’s scope was further extended to both electron-donating and electron-withdrawing groups on the phenyl ring of 95 [62]. The results suggested that the stereocontrol was dependent on the chiral ligands employed (Scheme 32).
Scheme 32. Cycloaddition of triynes in synthesis of tetrphenylenes.

Fold-in oxidative fusion reaction

According to the report by Osuka and co-workers, tetrabenzotetraaza[8]circulene (98) can be synthesized at a good yield of 96% by a ‘fold-in’ oxidative fusion reaction of a 1,2-phenylene-bridged cyclic tetrapyrrrole (97) [63]. X-ray diffraction analysis revealed a planar square structure with a central COT with a slight alternation of bond lengths (Scheme 33).

Scholl reaction

In 2013, Sakamoto and Suzuki reported two saddle-shaped tetrabenzo[8]circulenes, which were synthesized by the Scholl reaction of cyclic octphyrylene precursors [64]. Starting materials (99) were prepared by palladium-catalyzed double Suzuki cross-coupling reactions. The Scholl reaction with Cu(OTf)_2, AlCl_3 in CS_2, provided tetrphenylene derivative 100a at only a 7% yield. The octmethyl
Scheme 33. ‘Fold-in’ oxidative fusion reaction.

Scheme 34. Scholl reaction in synthesis of 100.

Scheme 35. Tetrameric condensation in synthesis of 101 and 102.

precursor 99b, which may prevent the intermolecular oxidation, gave a much high yield of desired 100b when the Scholl reaction was preceded with FeCl3 in CH2Cl2 (Scheme 34). It was found that the structure of 100a greatly deviated from planarity, and the deep saddle-shape was confirmed by a single-crystal X-ray crystallographic study.

Tetrameric condensations

Interest in the circulenes has increased in recent years following the discovery of fullerenes. In 1970, Erdtman and Högber established a method for tetrameric condensation of quinones, in which tetroxa[8]circulene (101) (R = H) was formed in the presence of a strong acid [65]. Recently, Christensen and co-workers reported oligomerization of 2,3-disubstituted-1,4-benzoquinones substituted with hydrophobic long chains to generate various tetroxa[8]circulenes containing alkyl groups (101) (Scheme 35; Equation 1) [66]. In 2014, Wudl and co-workers reported a facile one-pot tetramerization of indolin-2-one with phosphoryl chloride for direct synthesis of C2-symmetric cyclooctatetraindole 102. Furthermore, tetra- and octa-arylated cyclooctatetraindole derivatives functionalized with fluorescent fluorene and pyrene units were synthesized and characterized (Scheme 35; Equation 2) [67].

Interestingly, Pittelkow and co-workers improved this method for the production of azatrioxa[8]circulenes (104 or 105) by condensing 3,6-dihydroxycarbazoles (103) or cross-condensing (103) with benzoquinones (Scheme 36). These [8]circulenes have a significant antiaromatic character, as can be predicted using computational methods [68].

DIRECT ELECTROPHILIC AROMATIC SUBSTITUTION OF TETRAPHENYLENES

After tetraphenylene (1) was realized, Rapson et al. immediately proceeded to perform nitration and bromination reactions on 1 to give monobromo- and tetrinitro-tetraphenlene derivatives (Scheme 37) [11]. However, the substituted positions of these products could not be determined easily. Later, Figeys and Dralants, Mislow and co-workers, and Rosdahl and Sandstrom all reported Friedel–Crafts reactions [69–73]. Figeys and Dralants accomplished the acetylation of 1 using acetyl chloride in tetrachloroethane, and 2-acryl mono-substituted products (108) were obtained at a 72% yield [69]. Mislow and co-workers treated 1 with titanium tetrachloride and dichloromethyl methylether in methylene chloride to obtain a mixture of aldehydes (109...
and 110) and other mono-substituted products on other positions accompanied by formylation of 1 is poor due to a lack of directing groups.

In 2013, Wu and co-workers reported the direct iodination of tetraphenylene derivatives 111 and 112 by using H3IO6 in combination with I2. In these reactions, tetraiodo-substituted tetraphenylenes and their iodo-substituted regioisomers were easily obtained in a non-regioselective manner [74]. The mixture was allowed to undergo a palladium-catalyzed annulation, leading to the synthesis of a series of peri-substituted [8] circulene derivatives (113), all with good yields. Compounds (113) exhibited a unique saddle-shaped structure with an [8] radialene character (Scheme 38).

In 2014, Wong and co-workers reported their efforts in the synthesis and study of dioxo-, diaza-, dithio-, and diseleno-bridged tetraphenylenes [75]. Structures of these compounds were unambiguously confirmed by X-ray crystallographic analyses, and crystallographic investigations indicated that 115, 116, 117b, 117c and 118 assumed a unique saddle-shaped structure with different packing motifs (Scheme 39).

On the basis of the aforementioned encouraging results, tetrathio[8] circulene and tetraseleno[8] circulene (120) were synthesized from octamethoxytetraphenylenes (119) by Wong’s group (Scheme 40) [76]. Structures of 120a and 120b were unambiguously confirmed by X-ray crystallographic analyses. Photophysical and electrochemical investigations of these [8] circulenes suggested their potential application as electronic materials. Furthermore, Fourier Transform Infrared Spectroscopy (FTIR), Raman and UV-visible spectra of tetrathia [8] circulene and tetraselena [8] circulene have been measured as well as interpreted in detail by density functional theory computation [77]. In particular, the neutral tetrathia [8] circulene and tetraselena [8] circulene molecules, with a slightly non-planar conformation, were demonstrated to be bifacial aromatic/antiaromatic in nature.

### LATE FUNCTIONALIZATION OF TETRAPHENYLENE DERIVATIVES

In order to study the magnitude of the inversion barriers of tetraphenylene derivatives, manipulations of functional groups of 1 were carried out after successful aromatic substitution of 1 had been achieved [69–73]. For example, 2-acetyltetraphenylene (123) was treated with methyl magnesium iodide to give alcohol 121 at a 94% yield. Tetraphenylene derivatives 121–126 were prepared in a similar way (Fig. 3). It is noteworthy that Mislow and co-workers reported the partial resolution of 126 with brucine to afford (+)-126. Furthermore, 2-acetyltetraphenylene (123) and 25 were obtained in high enantiomeric purities by repeated chromatography on swollen microcrystalline triacetylcelluloses in Wong’s laboratory [78]. Vollhardt’s group employed 14c as a starting material to synthesize a novel polycycle (131)
containing a central tetraphenylene skeleton via a five-step reaction sequence (Scheme 41) [19].

In order to study the potential applications of chiral tetraphenyles, Wong and co-workers reported an efficient resolution of racemic hydroxyltetraphenylene, as described in Scheme 42. Thus, conversion of racemic tetrahydroxyltetraphenylene 58 into its tetra-(S)-camphorsulfonate esters after esterification with (S)-camphorsulfonyl chloride resulted in two diastereomers (132a and 132b). Chromatographic separation and subsequent deprotection afforded enantiopure 1,8,9,16-tetrahydroxyltetraphenylene (58) [79,80]. The presence of hydroxyl groups in the tetraphenylene skeleton has provided openings for further chemistry through late functional group transformations.

With the chiral hydroxyltetraphenylene (58) in hand, Wong’s group started to diversify chiral tetraphenylene derivatives bearing various functional groups. As shown in Scheme 43, a useful chiral building block of 1,8,9,16-tetrakis(diphenylphosphino)tetraphenylene (137) was synthesized in four steps.

Using chiral 98 and 137 as building blocks, three enantiopure rod-like compounds (138–140) were synthesized (Fig. 4) [80]. To have a better understanding of the structures of 138–140, the results of density functional theory computation showed that their structures all seemed to be rod-like chains.

Similarly, another useful chiral building block of 1,8,9,16-tetraethynyltetraphenylene (143) was synthesized in a linear manner (Scheme 44) [81].

On the basis of the chiral unit of 143, several enantiopure helical macrocycles (144, 145 and 146; Fig. 5) containing one tetraphenylene motif were obtained. Platinum(II) complexes were prepared via coordination-driven self-assembly of 143 and platinum species in the presence of a catalytic amount of copper chloride. In particular, the helical macrocycle 146 was formed by self-assembly of (S,S)- or (R,R)-143 with a dimetallic complex under similar conditions.
Scheme 41. Synthesis of 131.

Scheme 42. Resolution of hydroxyltetraphenylene 58.

In the course of the study of polyhydroxyltetraphenylene in host–guest chemistry, Wong’s group synthesized a tweezer-like host (147) with two dibenzo-24-crown-8 moieties (Scheme 45). Preliminary investigation showed that 147 could form a 1:1 stable complex with paraquat derivative 148 in solution state, and that the association constant for the complex was determined to be $K_a = 4.59 \times 10^3$ M$^{-1}$ [53].

Furthermore, Wong and co-workers developed a series of crown ether compounds (149) and their corresponding enantiomers were derived from chiral tetrahydroxytetraphenylene 58 in enantiomerically pure forms (Scheme 46) [47]. Enantiomeric recognition properties of these hosts towards $L$- and $D$-amino acid methyl ester hydrochloride were studied by UV spectroscopic titration. The tetramer hosts exhibited the best enantioselectivities towards...
Scheme 43. Synthesis of chiral 137.

Figure 4. Chiral rod-like platinum complexes.

Scheme 44. Synthesis of chiral 143.

L- and D-alanine methyl ester hydrochloride salt, with $K_L/K_D = 4.10$ and $K_D/K_L = 3.90$, respectively.

Starting with 6,7-bis(methoxy)-2,11-dihydroxytetraphenylene, Wong reported three novel tetraphenylene-derived macrocycles (151–153) as macrocyclic hosts (Scheme 47), and 151 and 152 were characterized by X-ray diffraction studies. Structural studies on the relevant macrocyclic hosts showed that the macrocycles possessed well-defined structures with fixed conformations both in solution and in solid state. They demonstrated efficient and unique properties toward complexation with fullerenes C$_{60}$ and C$_{70}$ in toluene. Considering the applications of hydroxytetraphenylenes, several examples have shown the applications of tetraphenylenes in liquid crystalline materials. The research group of Giesselmann has prepared four series of 2,3,6,7,10,11,14,15-
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Figures 5. Chiral macrocycle based on tetraphenylenes.

Scheme 45. Synthesis of tweezer-like host including a tetraphenylenic motif.

octasubstituted octahydroxytetraphenylen derivatives (154) (Scheme 48) [82]. The study of their liquid crystal states showed that these tetraphenylen derivatives displayed mesophases or columnar phases depending on the substituents of alkyl chains. Moreover, anomalous odd–even effects among this type of tetraphenylenes were discovered.

Wong and co-workers also synthesized a group of tetraalkoxy-substituted tetraphenylenes (155 and 157) in both racemic and chiral forms, as depicted in Scheme 49 [83]. The study of their liquid crystalline properties showed that racemic compounds (157), possessing four long chains of -C12H25 and/or -(CH2CH2O)4CH3, form stacking nanosheets through self-assembly in polar solvents. In this way, amphiphilic tetraphenylenes could potentially be used as molecular building blocks for supramolecular soft nanomaterials.

In the research field of asymmetric catalysis, an N,P-ligand (S,S)-158 and a series of Brønsted
Scheme 46. Synthesis of crown ether hosts including tetraphenylene motifs.

Scheme 47. Synthesis of macrocycles including a tetraphenylene motif.

base organocatalysts based on a tetraphenylene skeleton were prepared in Wong’s laboratory (Scheme 50) [84]. By employing ligand (S,S)-158 in combination with Rh(COD)₂BF₄ as a catalyst, α-acylaminoacrylate substrates (165) were hydrogenated in quantitative yields, and with excellent enantioselectivities (94–97% ee; Scheme 51, Equation 1). In continuation of asymmetric catalysis using metal complexes, tetraphenylene-based organocatalysts 159–164 were also used in Diels–Alder reactions between anthrone and maleimides. As shown in Scheme 51, the desired Diels–Alder adduct (169) was obtained in good yields (58–92%) but only in moderate enantioselectivities (up to 43% ee). Although only two reports of asymmetric catalysis in this respect have been recorded to date, chiral catalysts based on tetraphenylene skeletons are very promising due to their unique structural features. It is believed that novel chiral tetraphenylene catalysts will appear soon and be applied in various asymmetric reactions in the near future.

Scheme 48. Tetraphenylenes as liquid crystal molecular materials.
Scheme 49. Synthesis of 155 and 157.

Scheme 50. Synthesis of chiral ligands and catalysts.

Scheme 51. Asymmetric catalysis by chiral tetraphenylenes.

**FUTURE PERSPECTIVES**

Interest in tetraphenylenes will continue in the coming years due to their intrinsic properties and potential applications. Syntheses of tetraphenylenes have recently witnessed significant progress, although the efficient synthesis of tetraphenylene derivatives in large quantities is still challenging. Therefore, to our knowledge, no tetraphenylenes are currently commercially available, which has limited their utilization in a wider sense. Thus, attempts to discover a general and efficient large-scale strategy to synthesize highly functionalized tetraphenylenes remains challenging and rewarding. We firmly believe that more tetraphenylenes will be realized in the future, and that this will lead to the exploration of more interesting characteristics and unique properties of these intriguing molecules.
FUNDING

This work was supported by the National Natural Science Foundation of China (21202186, 21272199 and 21472213) and the Croucher Foundation (Hong Kong) in the form of a CAS-Croucher Foundation Joint Laboratory Grant.

Conflict of interest statement. None declared.

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