Review

Synthesis of tetraarylmethanes: 1897–2022

Lai Chen[a,1], Jingqian Huo[a,1], Jinlin Zhang[a,*], Judith N. Currano[b], Haixing Guan,[c] Patrick J. Walsh[b,*], Jianyou Mao*[,d]

[a] College of Plant Protection, Hebei Agricultural University, Baoding 071000, China
[b] Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Pennsylvania 19104-6323, United States
[c] Experimental Center, Shandong Provincial Key Laboratory of Traditional Chinese Medicine for Basic Research, Key Laboratory of Traditional Chinese Medicine Classical Theory, Ministry of Education, Shandong University of Traditional Chinese Medicine, Jinan 250355, China
[d] Technical Institute of Fluorochemistry, Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China

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ABSTRACT

Tetraarylmethanes (TAMs) contain a carbon atom bound to four aryl groups. They have found diverse applications in chemistry, materials science, chemical biology and medicinal chemistry because of their unique 3-dimensional structures. As a reflection of the high demand for TAMs, over 32,000 unique TAMs have been prepared. The distinct structures of TAMs and the crowded nature of the central carbon atom require different strategies for their syntheses. Herein we present the first review on the synthesis of TAMs, from classical approaches to modern methods, including enantioselective syntheses of TAMs. We provide a critical evaluation of methods and highlight important directions for future research into the synthesis of this aesthetically pleasing and very useful class of spherical structures.

1. Introduction

Tetrahedral carbon atoms directly attached to combinations of four aryls and/or heteroaryl groups are collectively known as tetraarylmethanes (TAMs). Since Gomberg first synthesized tetraphenylmethane by heating the diazene Ph–N=N–CPh_3 in the presence of a copper promoter (≤5% yield) [1,2], chemists and materials scientists have been fascinated by these beautiful structures. Following on the heels of Gomberg's seminal disclosure, chemists began to develop improved syntheses of tetraphenylmethane and related tetraarylmethane derivatives [3]. These efforts continue today, as scientists apply modern synthetic methods to the efficient assembly of tetraarylmethanes.

In parallel with the drive to expand access to diverse tetraarylmethane derivatives, the breadth of their applications in materials science, chemistry, and chemical biology continues to grow. The unique tetrahedral disposition of the aryl groups is attractive when constructing supramolecular structures with tetrahedral or spherical topologies, including aesthetically pleasing molecular jacks [4]. As a result, TAMs have been employed in three-dimensional diamondoid networks (metal-organic frameworks, covalent organic frameworks, non-covalent self-assembled networks) [5-22], dendrimeric cores with spherical topologies [23,24], non-linear optical materials [5, 25-29], molecular devices [30-33] and machines [34-35], molecular electronic circuits [36,37], CO_2 capture [38-40], gas separation [41], and liquid crystals [42]. In the realm of medicinal chemistry, TAMs have been used in protein translocation detection [43] and drug delivery [44]. We anticipate that the applications of TAMs in medicinal chemistry will continue to increase. Researchers at AstraZeneca [45] evaluated over 9000 biologically active molecules to determine their three-dimensional structures. The vast majority of the molecules were classified as linear or disk-shaped. A small minority of the molecules were spherical, leading the authors to conclude that spherical molecules are an underexplored space in medicinal chemistry. We hypothesized that TAMs have been historically underutilized because efficient methods to access these structures are limited. The purpose of this review is to collect the most important traditional methods of synthesizing TAMs and to highlight more recent synthetically significant approaches. It is hoped that these efforts will inspire the synthetic community to continue to invent new processes for the assembly of TAMs. Before diving into the synthesis of TAMs, we briefly analyze the TAM literature.

2. A survey of the TAM literature

In order to understand research trends related to TAMs and their preparation, a survey of the literature was undertaken. The searches were designed to determine the number of unique tetraarylmethane structures that had been reported in the literature, the number of preparations of such structures that had been reported, and the number and publication years of documents that reported TAMs or their preparation. Elsevier's

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* Corresponding authors.
E-mail addresses: zhangjinlin@hebau.edu.cn (J. Zhang), pwalsh@sas.upenn.edu (P.J. Walsh), ias_jymao@njtech.edu.cn (J. Mao)
[1] These two authors contributed equally to this work.

Reaxys database and CAS's SciFinder^{n} were used for the searches, which were performed between March and June of 2022. Details of the search parameters and additional results can be found in the Supporting Information.

Search results indicated that the CAS Registry currently includes over 32,500 unique TAM structures, which have been reported in about 19,000 publications published between 1877 and the time of the searches, with about 58% appearing in journals, 42% in patents, and less than 1% in other document types (Figure 1). About 57% of these documents describe the synthesis and synthetic transformations of TAMs, and about 30% describe their use in biological studies. Analysis of the target indicators for the biologically active TAM structures indicates that they most frequently target enzymes (294 substances), signalling proteins (272 substances), and membrane proteins (175 substances). The top 5 biological applications of the substances were cardiovascular (602), anti-infective (261), antitumor (232), nervous system (223), and anti-inflammatory agents (144).

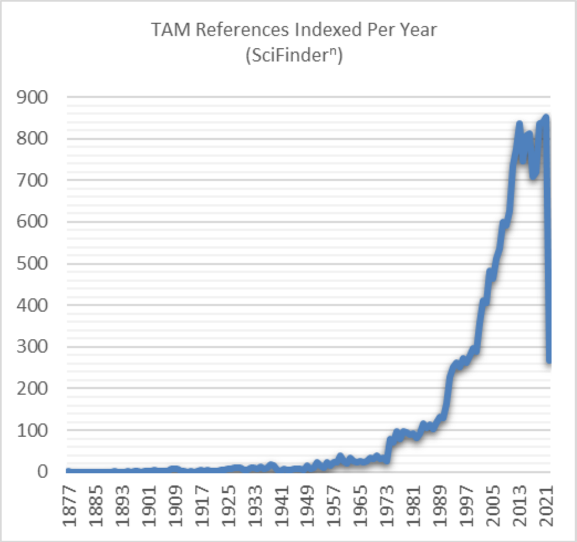


Fig 1. Results of publication year analysis of references located by SciFinder^{n} that include one or more TAM structures.

As can be seen in a plot of the number of TAM structures and reactions appearing in the literature per year (Figure 2), the number of syntheses and studies of TAMs continues to increase at a rapid pace. During a scant six-month period in late 2022, a SciFinder^{n} substructure search alert for potential TAM structures retrieved over 550 newly-registered structures, which appeared in 80 references and over 1000 reactions. 971 of the reactions have the TAM structure as one of the reaction products. These data lead us to conclude that TAMs are increasing in number, importance, and synthetic accessibility and that a review on methods of synthesizing TAMs should be beneficial to the community.

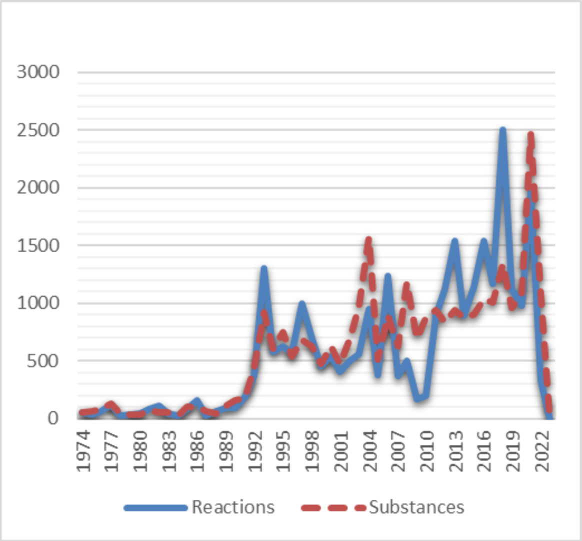


Fig 2. Results of publication year analysis of TAM structures and preparation reactions indexed in Reaxys over the past 50 years. The solid blue line indicates the number of preparation reactions indexed each year, and the dashed red line indicates the number of TAM structures indexed each year.

3. Synthesis of TAMs

3.1 Friedel-Crafts approach to TAMs

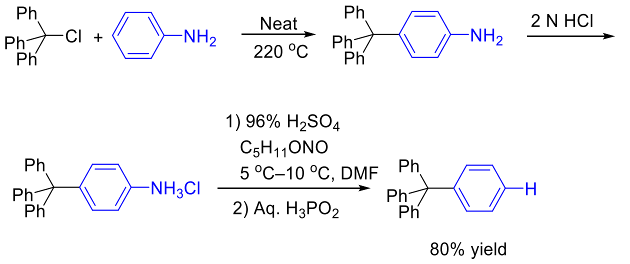
A classic and very useful approach to the synthesis of TAMs involves the Lewis acid-promoted Friedel-Crafts (F-C) alkylation of arenes with triarylmethyl-based electrophiles [46]. The strength of this approach is that many electron-rich arenes will participate as nucleophiles in such reactions and that a wide variety of triarylmethyl electrophiles are easily prepared. The downside is that the regioselectivity of the F-C reaction is governed by the electronic properties of the arene nucleophile, giving rise to classic *ortho* and *para*-substituted products. Electron-poor arenes exhibit low reactivity or complete failure to participate in F-C reactions, which is also a significant limitation to this approach. This is particularly true with relatively stable triarylmethyl carbenium ions. For example, the reaction of benzhydryl chloride (Ph_2CHCl) or benzhydrol (Ph_2CHOH) with benzene in the presence of $AlCl_3$ provides triphenylmethane in up to 70% yield. In contrast, extensive searches of the literature fail to retrieve any examples of the reaction between triphenylmethyl chloride or triphenylmethanol and benzene to provide tetraphenylmethane. The trityl cation intermediate does react with more electron-rich arenes, such as anisole, phenols [47], and anilines. Thus, alternative routes will be necessary to complement classical F-C tactics for the assembly of TAMs.

In recent years, chemists have begun to tackle long-standing deficiencies in F-C chemistry [48], including the use of catalytic rather than stoichiometric Lewis or Brønsted acids. Another improvement has been the substitution of less toxic electrophile precursors, such as alcohols, for highly reactive benzylic chlorides. Finally, chemists have long desired to develop enantioselective versions of the F-C alkylation to prepare enantioenriched TAM derivatives.

3.1.1 Friedel-Crafts approaches to TAMs with Benzyl Halide

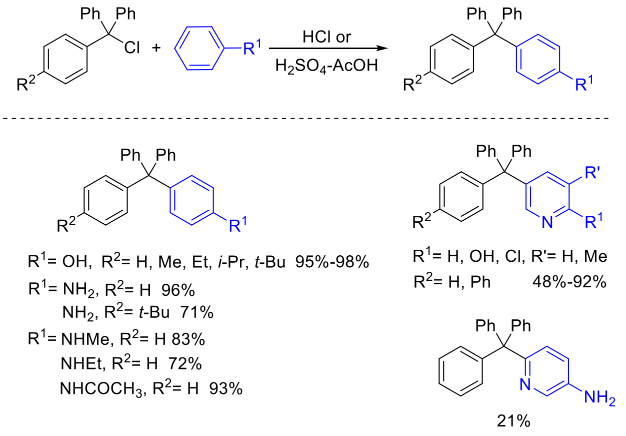
Electrophiles

After Gomberg’s groundbreaking synthesis of tetraphenylmethane in 5% yield [1], Ullmann and Münzhuber devised a more efficient route with the condensation of triphenylmethanol with aniline in a solvent-free F-C process. Subsequent diazotization and reduction furnished the parent TAM with good yields [3]. Unfortunately, the insolubility in ethanol of the charged anilinium and diazonium intermediates rendered this procedure problematic when run on a scale of 50 grams. Zimmermann and Muller revised the procedure by employing DMF in the diazotation step, in which the diazonium salt was soluble, allowing them to scale the synthesis to over 120 g of tetraphenylmethane (Scheme 1) [49].



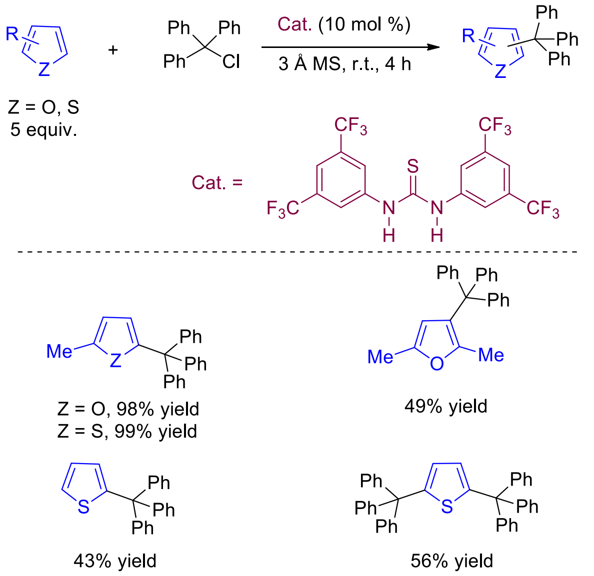
Scheme 1. Improved scalable synthesis of tetraphenylmethane.

It should be noted that triphenylmethyl chloride reacts via triphenylmethyl cation with arenes-bearing electron-donating groups, such as OH, OR, SH, NH_2, NHR, NR_2, and $NHCOCH_3$, to access TAMs (**Error! Reference source not found.**). In contrast, triphenylmethyl chloride does not react with arenes-bearing electron-withdrawing groups, including nitro, carbonyl, or halides (chloro, bromo, iodo) [50]. Nonetheless, the pyridine ring substituted with OH and NH_2 groups could produce the corresponding TAMs [51,52].



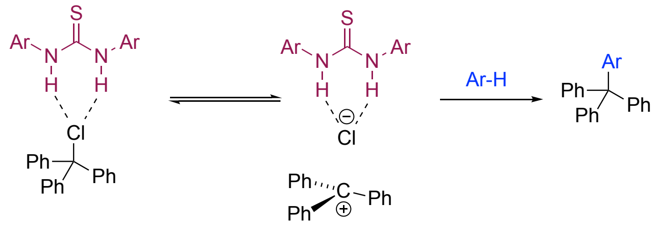
Scheme 2. Scope of the F-C reaction.

Envisioning a greener F-C process, Kotsuki and coauthors focused on using organocatalysts in place of traditional stoichiometric Lewis acid promoters [53]. They identified ureas and thioureas as potential catalysts, which are known to bind to halides, with the idea that these species could ionize trityl halides. After screening several hydrogen-bond donating catalysts, the researchers discovered that a thiourea catalyst with electron-withdrawing groups on the nitrogens performed the best (**Error! Reference source not found.**). The reaction with 5 equiv. heteroarenes proceeded at r.t. in 4 h when 10 mol% thiourea catalyst was used in the presence of 3 Å molecular sieves, which were present to absorb generated HCl. This represents an acceleration over the background reaction in the absence of a catalyst, which required about 12 h. Furans and thiofurans participated in the reaction to give the 1: 1 adduct when additional substituents hindered the formation of the di-tritylation products. The parent thiofuran gave a mixture of mono- and bis-tritylation (**Error! Reference source not found.**).



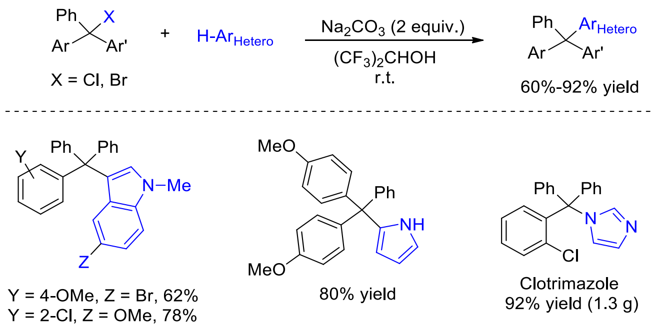
Scheme 3. Organocatalytic tritylation of heterocycles to generate TAMs.

The proposed mechanism of activation of the trityl chloride consists of hydrogen bonding between the catalyst and benzylic chloride, ionization to generate an ion pair, and attack by the nucleophilic arene (Scheme 4) [53]. We expect that the use of organocatalysts for the development of more environmentally friendly F-C reactions will continue to be important in the future.



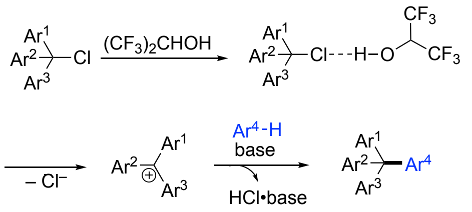
Scheme 4. Proposed action of the thiourea catalyst on the electrophile in the organocatalytic F-C tritylation of heterocycles.

While F-C reactions with trityl halide electrophiles often proceed upon heating and do not require Lewis acid mediators or catalysts, they usually require temperatures in excess of 200 °C. To circumvent some of these drawbacks, Yu, Xiao and their co-workers hypothesized that fluorinated alcohols could serve as solvents for F-C reactions of tritylchloride with nucleophilic heteroarenes. Fluorinated alcohols are good hydrogen bond donors, they stabilize ionized intermediates, and they are reluctant nucleophiles. Thus, the reaction of tritylchloride and bromide in hexafluoro isopropanol (HFIP), in the presence of electron-rich heteroarenes at r.t., resulted in F-C chemistry to provide triarylheteroaryl methanes in good to excellent yields (**Error! Reference source not found.**, 60%–92%). The heteroarenes included indole, pyrrole, and imidazole [54]. The medication clotrimazole, used to treat skin infections, was prepared on a gram scale in this fashion.



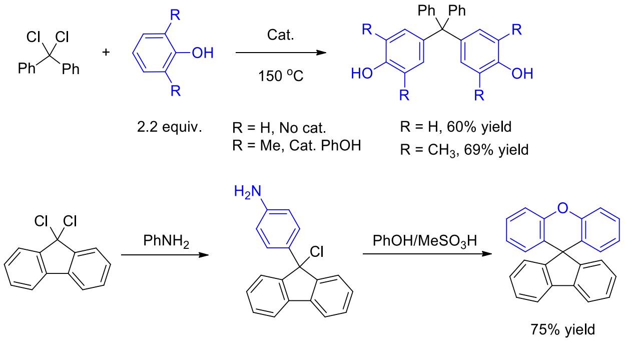
Scheme 5. Application of HFIP in the F-C reaction with electron-rich heteroarenes.

The mechanism of action of the HFIP is proposed to involve the formation of hydrogen bonds to the tritylchloride derivative, followed by ionization to generate the triarylcarbenium ion (**Error! Reference source not found.**). The cation is then attacked by the heteroarene to produce the observed TAM product.



Scheme 6. Proposed mechanism in the HFIP mediated F-C reaction with heteroarenes.

The traditional F-C reaction with benzylic halides could be applied to substrates bearing two chlorides on the same sp^3 hybridized carbon. In this case, a diarylation was performed with phenol-based nucleophiles. Thus, the reaction of dichlorodiphenylmethane with different phenols yielded 61% of the TAM (Scheme 2). With 2,6-dimethylphenol, a catalytic amount of phenol promoted the reaction. Because phenols are easily oxidized and dichlorodiphenylmethane easily hydrolyzed, the reaction was carried out under a nitrogen atmosphere with a 10% excess of phenol. These TAMs were used to prepare sulfonated aromatic poly (aryl ethers) that have potential applications in fuel cells as proton-exchange membranes [55]. In addition, 9,9’-dichlorofluorene could be used as the benzylic halide *via* two F-C alkylations with aniline and phenol, respectively, to prepare spiro[fluorene-9,9’-xanthene] (Scheme 2).

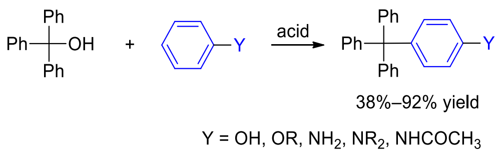


Scheme 2. Use of gem-dichloro-containing electrophiles for double F-C reactions.

3.1.2 Use of alcohol electrophiles

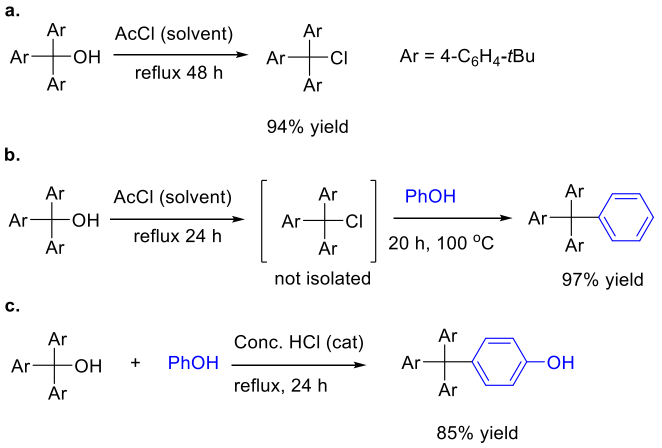
Friedel-Crafts alkylation using alcohols as the electrophile precursors have attracted attention for many years [46]. Not only are alcohols more stable and less toxic than benzylic halogens, but they are also frequently precursors to benzylic halides and, therefore, require fewer steps to prepare. Furthermore, alcohols are more environmentally friendly in these processes because H_2O is formed as the byproduct. The drawback, however, is that they require acid to promote the formation of the carbocationic intermediates, which can be problematic in the presence of acid-sensitive functional groups.

Baeyer and Villiger originally demonstrated the use of triarylmethanols as electrophiles for the synthesis of TAMs instead of triarylchloromethanes. They employed sulfuric acid and acetic acid with nucleophilic arenes. Gomberg modified the procedure by using hydrochloric acid, which exhibited cleaner reactions [51, 56]. Since then, this approach has been successfully used by other researchers and can result in greener procedures and reduce synthetic effort without compromising yields. This approach works well with nucleophilic arenes, including phenols and anilines, which give the *para*-substituted products exclusively (**Error! Reference source not found.**). Less activated toluene gave only a 36% yield of the TAM. Acetanilide gave a 38% yield of the amide-containing TAM with sulfuric acid, but could give high yields of the hydrolysis product (95%) with hydrochloric acid [50]. It was noted that the reaction using toluene as the nucleophile gave better yields with acid and $Ph_3C–OH$ than with $Ph_3C–Cl$ [50].

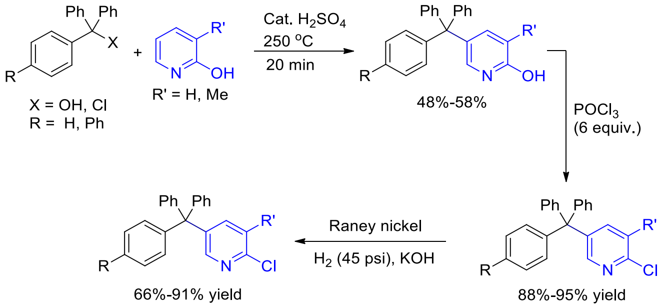


Scheme 8. Examples of reactions of Ph_3COH with arenes in the presence of acid.

In some cases, a comparison between the use of triarylchloromethanes and triarylmethanols has to be made. For example, Gibson and coworkers [57] were interested in preparing TAMs as blocking groups for rotaxanes. As shown in Scheme 3a the triarylmethanol (Ar = C_6H_4-*t*Bu) was converted to the triarylmethyl chloride by refluxing in acetyl chloride solvent for 48 h, providing 94% yield of the crude product. A one-pot procedure was reported for the conversion of the triarylmethanol to the TAM (Scheme 3b) by first treatment with refluxing acetyl chloride solvent for 24 h, evaporation of the remaining acetyl chloride and treatment with 11 equiv phenol for 20 h at 100 °C to yield the TAM in 97% yield. The authors were also able to combine triarylmethanol, excess phenol, and an acid catalyst (Scheme 3c) to yield the TAM product in 85% yield. Not only does the procedure in Scheme 3c not require acetyl chloride, but it also takes less time to prepare the desired product.

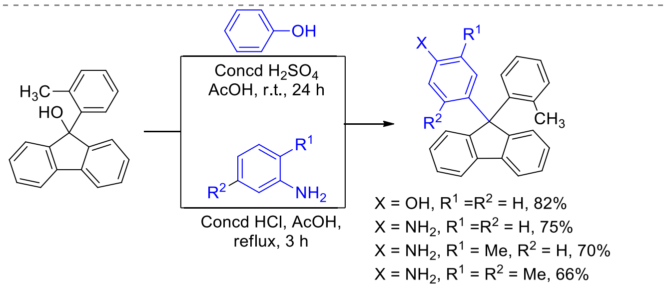


Scheme 3. Synthesis of TAMs from triarylmethanols and triarylmethyl chloride.



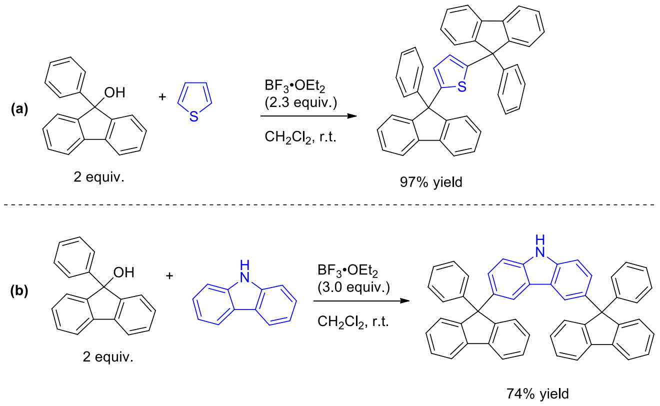
Scheme 10. Synthesis of 5-triarylpyridylmethanes.

9-Phenyl-fluoren-9-ols have become synthetic targets on account of their versatile nature as precursors to optoelectronic materials. Before these applications were discovered, researchers examined the synthesis of TAMs from 9-aryl-fluoren-9-ols. In early work, Adams and co-workers presented the preparation of the hindered tetraarylmethanes containing the fluorene substructure via the F-C type condensation of 9-hydroxy-9-o-tolylfluorene with phenol, aniline, o-toluidine, and *p*-xylidine (2,5-dimethyl aniline) in glacial acetic acid solution with sulfuric acid or hydrochloric acid. Yields ranged from 66%–82% (Scheme 11) [58].



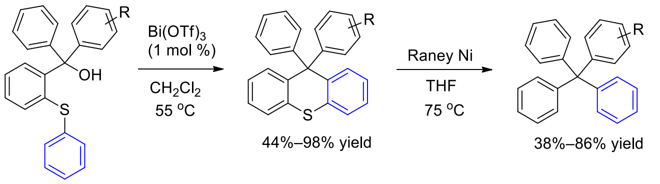
Scheme 11. Use of 9-aryl-fluoren-9-ols for the synthesis of hindered TAMs.

In a study to prepare optoelectronic materials based on TAMs, Huang and co-workers [59] reported that treatment of 9-phenyl-fluoren-9-ol with excess $BF_3{\bullet}OEt_2$ in dichloromethane at rt generated the triaryl carbocation, which could be trapped by a variety of nucleophilic arenes, including thiophenes and carbazoles (**Error! Reference source not found.**). Other trapping nucleophilic arenes included diphenyl ether. The less nucleophilic pyrene gave only a 30% yield, while *tert*-butyl benzene provided no TAM.



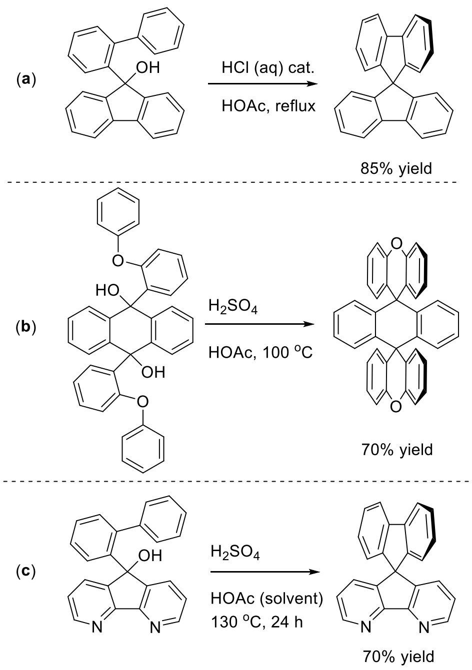
Scheme 12. Preparation of optoelectronic materials based on TAMs.

As outlined in the following paragraphs, researchers have developed F-C reactions of alcohols (and benzylic halides) that undergo ring closures to make cyclic TAMs. In one such application, Catino and co-workers reported a procedure that involves a bismuth-catalyzed F-C cyclization of a diarylthioether followed by a desulfurization reaction mediated by Raney nickel (**Error! Reference source not found.**) [60]. In addition to substituents R that would be expected to work in such a transformation, the F-C reaction with substrates containing aryl group substituted with 3-F, 4-F and 4-CF_3 was found to be viable (≥92% yield).



Scheme 13. Cyclization *via* F-C followed by desulfurization.

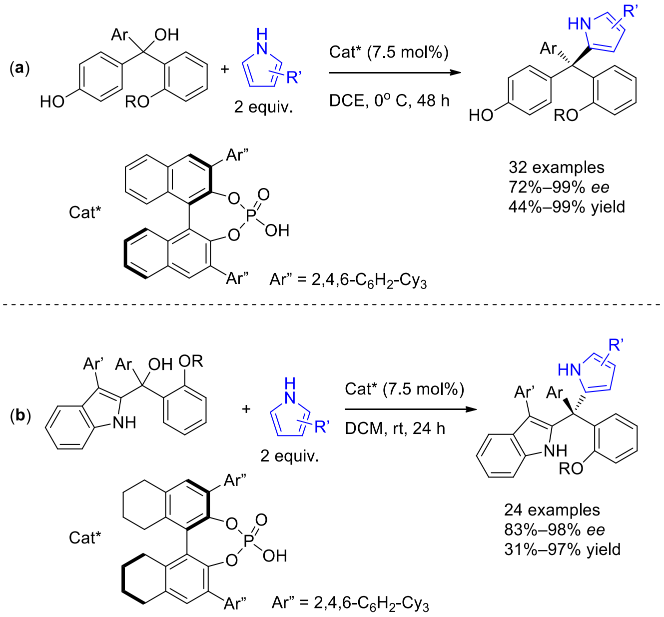
Spirocyclic fluorene-based monomers and polyfluorenes are known to be important organic semiconductors in organic electronics [61-64]. Long before this realization, however, chemists were fascinated with the reactions that form interesting fluorene-containing TAMs and spirocyclic TAMs. An early, yet elegant, example is Gomberg and Clarkson's synthesis of spirobifluorene (**Error! Reference source not found.**a) [65]. The starting alcohol can be prepared by the addition of the corresponding Grignard reagent to fluorenone. Cyclization of the alcohol with acid gives the spirocycle. This and related cyclization reactions, such as the one illustrated with xanthene and 9,10-dihydroanthracene cores (**Error! Reference source not found.**b), can be produced readily in respectable yields. Related reactions with bipy derivatives also undergo spirocyclization (**Error! Reference source not found.**c) [66] and have found multiple applications, including in OLEDs [67] and as ligands for transition metal catalysts [68]. It is noteworthy that the functionalization of 9,9-spirobifluorene was described in a review by Salbeck and co-workers [64], including enantioenriched versions. Furthermore, the spirocyclic bipy ligand can be readily brominated and elaborated by transition metal-catalyzed processes. To date, hundreds of 9,9-spirobifluorene derivatives have been successfully prepared for a myriad of applications.



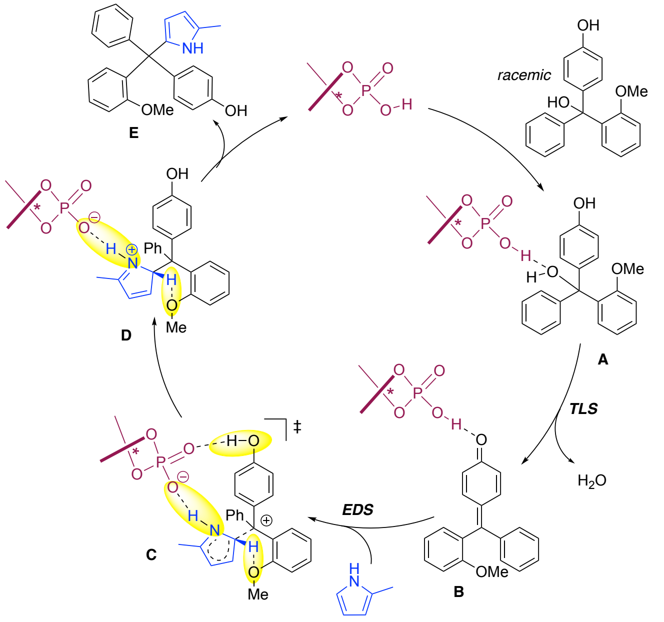
Scheme 14. Synthesis of spiran TAMs from alcohols.

3.1.3 Enantioselective approaches from alcohol electrophiles

One of the grand challenges in the synthesis and applications of TAMs is their catalytic asymmetric assembly. Given that most of the approaches to prepare TAMs involve triarylmethyl cations, an F-C reaction could be envisioned with three different aryl groups on the cationic carbon. The differentiation of the enantiotopic faces of the cation with a nucleophilic arene, however, would be quite tricky. By engineering into the substrates hydrogen bond acceptors and using enantioenriched phosphoric acid catalysts, the team of Zhu, Sun, Houk, and their co-workers were able to achieve a ground-breaking catalytic asymmetric synthesis of two classes of TAMs with high enantioselectivities (Scheme 4) [68].



Scheme 4. Catalytic asymmetric synthesis of TAMs.



Scheme 16. Proposed catalytic cycle (TLS, turnover limiting-step; EDS, enantiodetermining step).

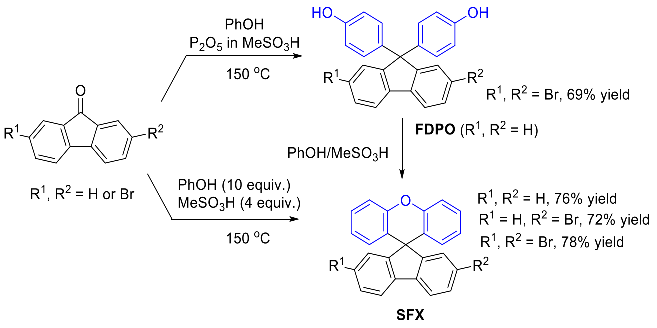
Several design features positioned the researchers for success. The first was the employment of an enantioenriched phosphoric acid catalyst capable of initiating the generation of the carbocationic intermediate and forming hydrogen bonds to well-positioned hydrogen bond acceptors on the racemic triarylmethanol. The proposed mechanism in **Error! Reference source not found.**, which is supported by experimental and computational results, starts with the acid-catalyzed elimination of water from the substrate in the turnover-limiting step. There is little difference in the rates of reaction between the reacting enantiomers and Cat* in the turnover-limiting step (TLS). A *para*-quinone methide (**B**) is proposed as an intermediate.

Independent synthesis and isolation of *para*-quinone methide **B** and subjecting it to the reaction conditions provided the TAM with the same ee, indicating that **B** is a viable intermediate. The enantiodetermining step (EDS, **C**) has key hydrogen bonding interactions highlighted. Here, the catalyst forms two key interactions with the intermediate, through the phenolic OH and to the pyrrole N–H. It was also found that a hydrogen bond between the *ortho*-OR substituent and the pyrrole C–H was an important factor in the stereodifferentiation. In the minor pathway, this interaction is prevented by unfavorable substrate-catalyst interactions. Supporting this hypothesis, the substitution of the 2-OMe group of the starting material with a 2-Me group resulted in a drop in enantioselectivity of the TAM from 96% to 52%. While the results in this work are indeed impressive, the necessity to engineer several weak interactions through specific functionality ultimately limits its scope [68]. Thus, there remains considerable room to build on this seminal report for the development of new catalysts and approaches for the synthesis of enantioenriched TAMs.

3.1.4 Use of benzophenone derivatives

With spirofluorene derivatives being widely used in optoelectronic devices, including organic light-emitting diodes (OLEDs) [69], organic photovoltaic cells (OPVs), transistors, and many other devices [70-71], the synthesis of tetraphenylmethanes containing spirocycles based on fluorene groups has received much attention. A common choice of starting materials for the synthesis of these spirocycles is fluoren-9-one.

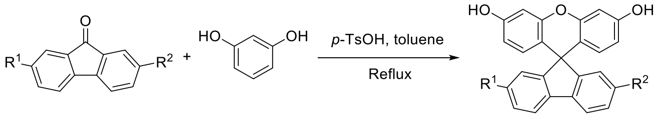
In 2006, Huang's group developed a method for the synthesis of spiro[fluorene-9,9'-xanthene] derivatives (SFX) using the F-C reaction between fluoren-9-one and phenol in the presence of excess methanesulfonic acid ($MeSO_3H$) at 150 ºC (Scheme 17). It was previously known that using Easton's reagent (10 wt% P_2O_5 in $MeSO_3H$) with fluoren-9-one and phenol at 150 ºC resulted in the formation of 4,4'-(9-fluorenylidene)diphenol (FDPO) derivatives (Scheme 17, top) [62]. The key finding of Huang's work was that using an excess of $MeSO_3H$ in the absence of P_2O_5, with longer reaction times at 150 ºC resulted in spirocycle formation in 72%–78% yield. It was also demonstrated that the parent bis(phenol) could be converted to the spirocycle (SFX) on treatment with $MeSO_3H$/phenol at 150 ºC in 55% yield, indicating that SFX is the thermodynamic product, while FDPO is a kinetic product [62].



Scheme 17. Preparation of SFX from fluorenone.

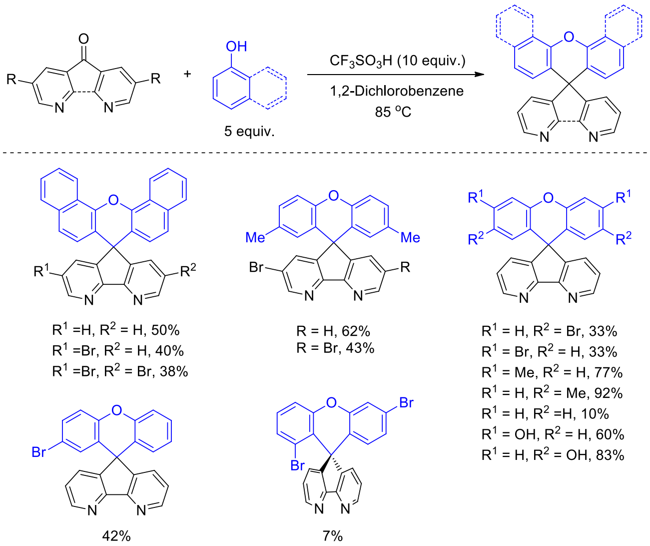
The F-C reaction between fluorenones and resorcinol has also been employed to generate SFX derivatives. Early studies by Korshak indicated that the reaction is initiated in the presence of $ZnCl_2$ at 150 ºC for 2 h, followed by the addition of concentrated hydrochloric acid for 1.5 h [73]. The scope of this reaction was not studied. Tseng and co-workers demonstrated good substrate scope with substituted fluorenones and resorcinols. The conditions were further optimized by the Zhou group [74], who found that catalytic *p*-TsOH in toluene represented improved conditions. The reaction of various 9-fluorenones with resorcinol was conducted to expand its reaction applicability (Table 1).

Table 1.
Synthesis of SFXs from F-C reaction of fluorenones and resorcinol.

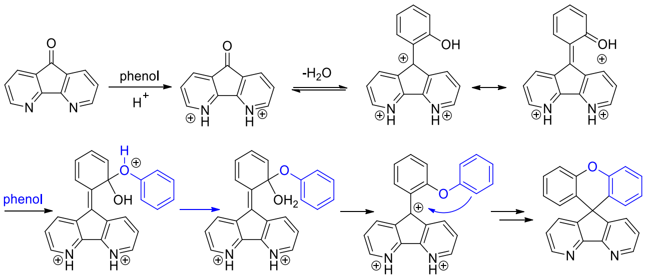


R^1	R^2	Yield/%	R^1	R^2	yield/%
Cl	Cl	86	Me	H	73
Cl	H	83	Ph	Ph	72
Br	Br	81	Ph	H	78
Br	H	80	*t*-Bu	*t*-Bu	73
Me	Me	76	CO_2Me	H	83

Spirofluorenes from fluorenone derivatives containing electron-withdrawing groups are more challenging to prepare, but have several applications. To address this issue, Huang and co-workers developed an F-C approach that they term super electrophilic-initiated carbon cationic relay, because some intermediates bear 3 positive charges. Thus, in the presence of the diazafluorenones, 5 equiv. phenol and 10 equiv. CF_3SO_3H in 1,2-dichlorobenzene at 85 ºC, spirofluorenes are generated in good to low yields (**Error! Reference source not found.**). The excess CF_3SO_3H is needed because it protonates the pyridyl nitrogens and also initiates the F-C reaction. Under highly acidic conditions, some bromide loss and bromo-migration were observed, resulting in low yields (**Error! Reference source not found.**, last entry). A possible mechanism for the cascade transformation into spirodiazafluorenes is proposed and depicted in **Error! Reference source not found.** [75]. Not surprisingly, the scope is somewhat limited by the use of the superacid CF_3SO_3H.

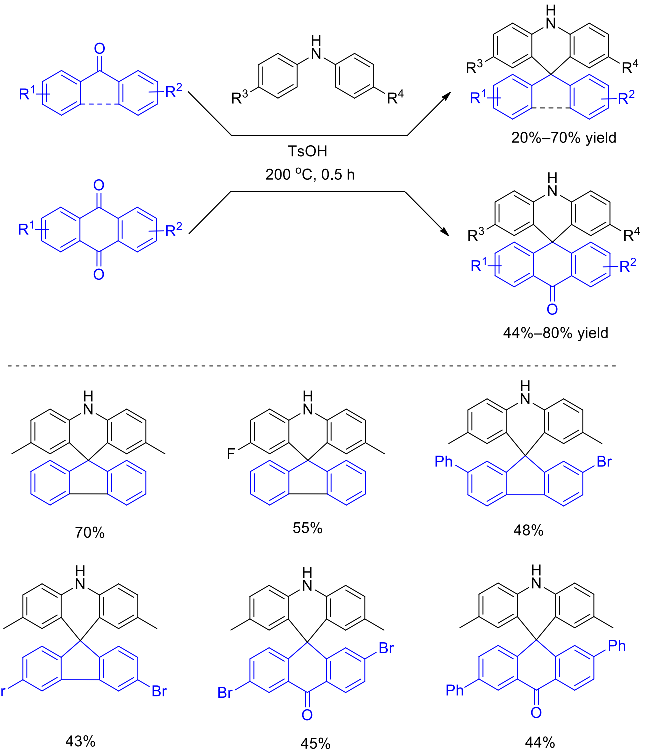


Scheme 18. F-C cyclization reaction of diazafluorenones with phenols.



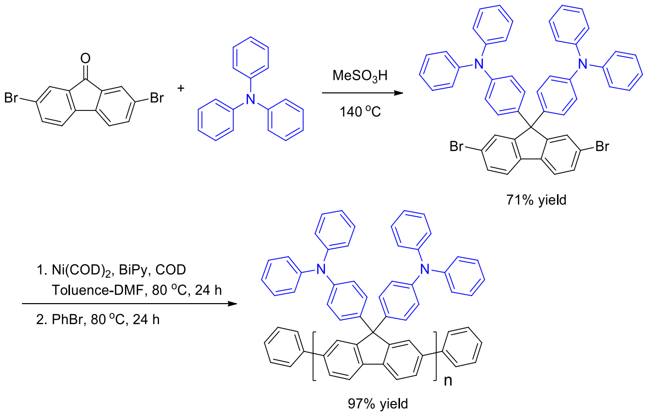
Scheme 19. Mechanism of the cationic cyclization reaction.

Spiro-acridan (SpAs) derivatives have attracted much recent attention due to their thermally activated delayed fluorescent properties, making them attractive in time-resolved imaging, lasering, and lighting applications [76-79]. However, their synthesis was time-consuming and required multiple steps. In 2021, Yang and co-workers presented a streamlined preparation of SpAs *via* TsOH-catalyzed cyclization reaction of ketones (such as fluorenones and anthraquinones) with diarylamines under solvent-free conditions (Scheme) [70]. The procedure was tolerant of halide substituents on either coupling partner [70], facilitating further elaboration. These benefits outweigh some of the low yields obtained.



Scheme 5. Construction of spiro-acridans from fluorenones and anthraquinones.

Triphenylamine-substituted polyfluorenes are stable blue-emitters with improved charge injection for light-emitting diodes [80]. In a related reaction, the condensation of dibromofluorenone with triphenylamine in the presence of methanesulfonic acid ($MeSO_3H$) was developed by Müllen's group to afford 9,9-bis(4-diphenylaminophenyl)-2,7-dibromofluorene in 71% yield (**Error! Reference source not found.**). A large excess (14 equiv.) of the amine was needed to prevent a reaction of the *para*-positions of the product with more fluorenone. Polymerization of this monomer under standard Yamamoto conditions was performed to explore its use in blue-emitting LEDs [80].

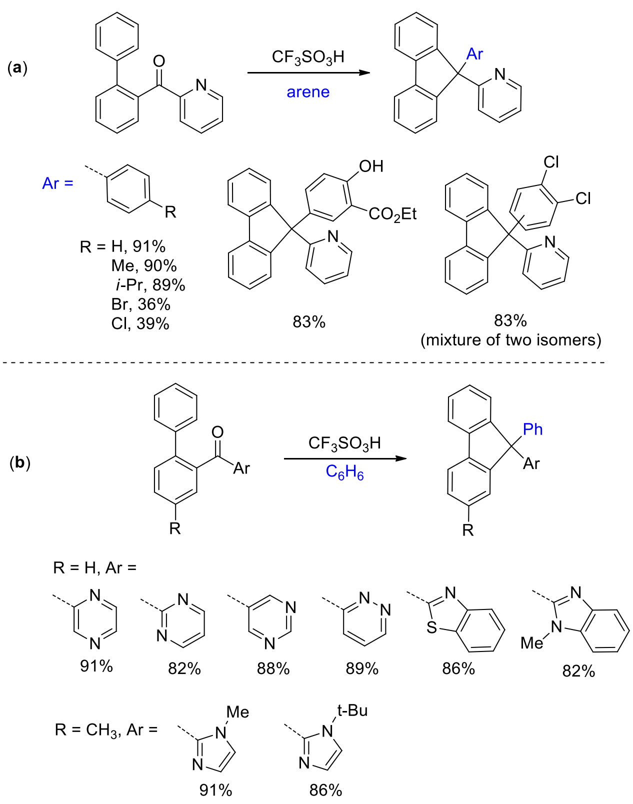


Scheme 21. Synthesis of polyfluorene from fluorenone.

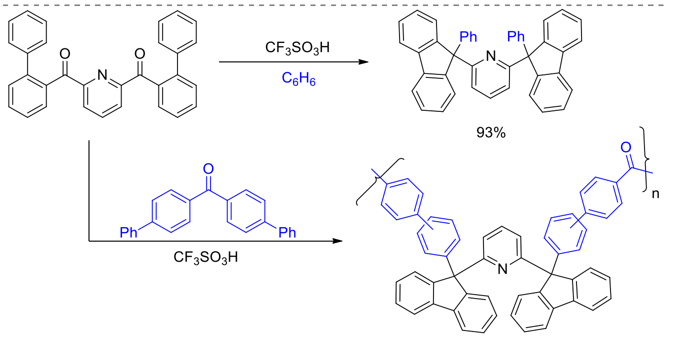
A different strategy that generates the fluorenone moiety from a biphenyl benzophenone derivative to access 9,9-diarylfluorenes was employed by the team of Ohwada, Klumpp, and coworkers. Condensation of *N*-heterocyclic biphenyl ketones with 1.5 equiv. arene nucleophile in the presence of the Brønsted superacid, triflic acid, (CF_3SO_3H, 1.4 equiv.), generated the desired TAMs (**Error! Reference source not found.**a) [81]. For benzene and benzene derivatives bearing alkyl-, bromo-, chloro-, and 1,2-dichloro groups, the condensation products formed in 36%–91% yields. Of course, regioisomers were obtained in some cases (bromo- and chlorobenzene, 1,2-dichlorobenzene), as expected in an F-C reaction of this type.

For *N*-heterocyclic substrates such as pyrazine, pyrimidine, pyridazine, and imidazole-based substrates, the condensation reactions were efficient and provided products with 82%–91% yield. Likewise, ring-fused *N*-heterocycles such as benzothiazole and benzimidazole give condensation products in 82%–86% yield (**Error! Reference source not found.**b). Ketone substrates, however, were limited to *N*-heterocyclic substituents.

When symmetric diketones with two biphenyl units on a pyridine core were employed with benzene as the nucleophilic arene, bis(fluorenyl)-pyridine derived TAMs were obtained in 93% yield (**Error! Reference source not found.**, top). When 4,4'diphenylbenzophenone was substituted for benzene as the nucleophilic arene, the stage was set for an A_2B_2-type polymerization (**Error! Reference source not found.**, bottom). It is also noteworthy that this report includes beautiful mechanistic work, including NMR characterization of the polycationic intermediates and computational comparison of the reaction profiles with cationic species.



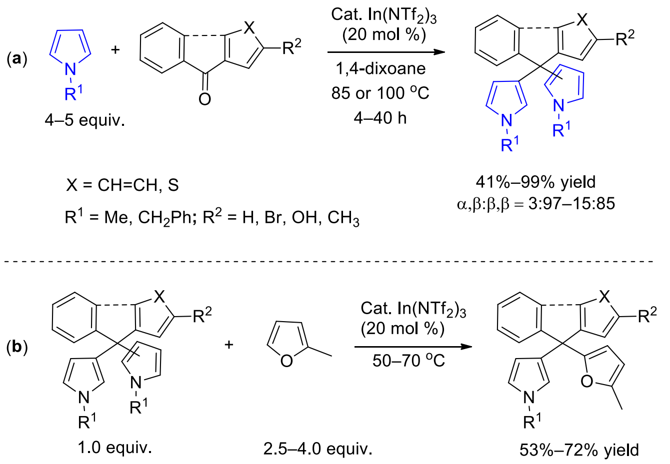
Scheme 22. Synthesis of 9,9-diarylfluorenes from *N*-heterocyclic biphenyl ketones.



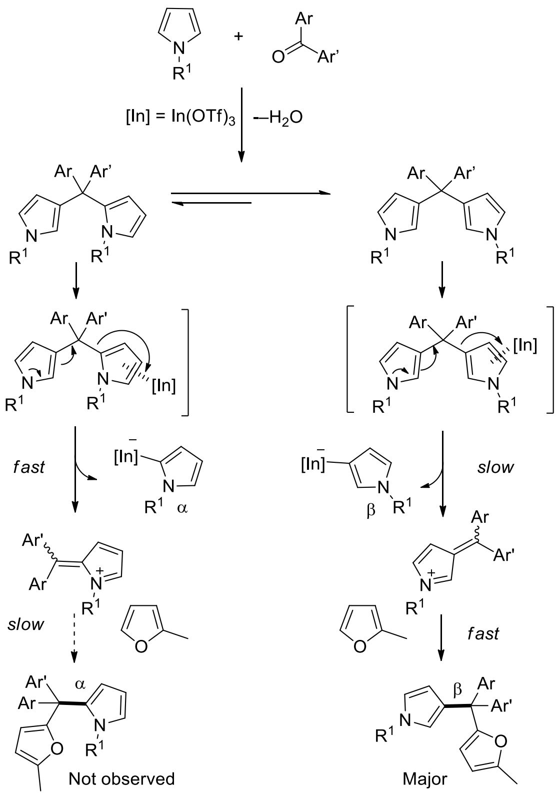
Scheme 23. Condensation reactions with a diketone.

Tsuchimoto and co-workers developed an indium-catalyzed system for the synthesis of TAMs containing pyrrolyl groups [82]. In the first stage of the process, a benzophenone or fluorenone derivative was reacted with a 5-fold excess of 1-methylpyrrole in the presence $In(NTf_2)_3$ (20 mol%) in dioxane at 85–100 ºC for 4–40 h (**Error! Reference source not found.**a). Diaryldipyrrolylmethane products were obtained in 41%–99% yields. The products were mixtures of α,β'- and β,β'-isomers with ratios > 1:5. With *N*-benzyl pyrrole, only the β,β′-isomer was observed in 70% yield. The β–isomers are favored based on steric requirements caused by the *N*-alkyl group.

Taking advantage of the reversibility of the F-C reaction with pyrroles, the authors subjected the mixtures of α,β'- and β,β'-isomers to a second F-C reaction with 2.5–4 equiv. of 2-methylfuran [and 20 mol% $In(OTf)_3$] with 53%–72% yields (**Error! Reference source not found.**b) or with 2-methoxythiophene [20 mol% $In(NTf_2)_3$] in 44%–52% yields (not shown). It is noteworthy that 1,2-dimethoxybenzene and *N,N*-dimethylaniline were not viable nucleophilic arenes in this reaction. A plausible reaction mechanism is depicted in **Error! Reference source not found.**, where the In(III) Lewis acid promotes loss of the α-pyrrole faster than the β-pyrrole, likely due to the greater stability of the α-isomeric intermediate (pathway β,α *vs.* β,β). The β-substituted intermediate leads to the product, shown here with trapping by 2-methyl furan to furnish TAMs with two heterocyclic groups.



Scheme 24. Indium-catalyzed synthesis of diaryldipyrrolylmethanes and their use to prepare other TAM derivatives.



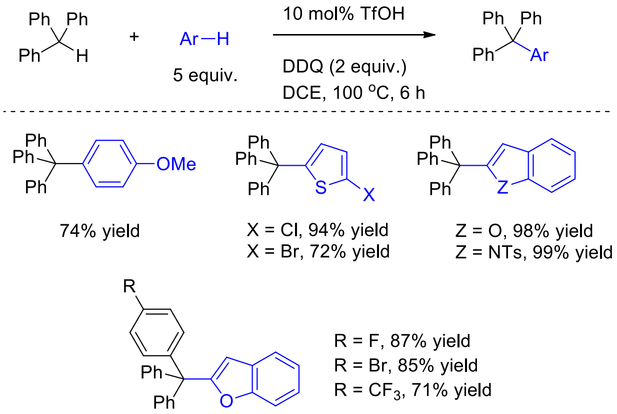
Scheme 25. Plausible reaction mechanism for the catalyzed synthesis of pyrrolyl TAMs.

3.1.5 Cross-dehydrogenative coupling processes

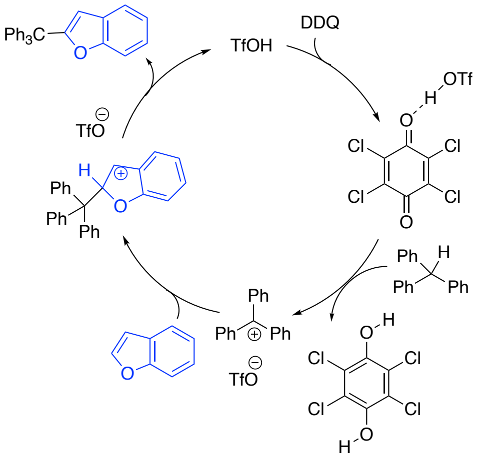
Cross-dehydrogenative coupling (CDC) is an attractive strategy for the generation of C–C bonds because it uses two C–H bonds in the coupling partners and it does not require prefunctionalization of either of the substrates [56-57, 63, 71, 83-86]. A challenge in CDC is selectivity, because substrates typically have several inequivalent C–H bonds.

An innovative approach to the F-C reaction begins with triarylmethanes and involves oxidation of the benzylic C–H bond in the presence of DDQ and triflic acid [63]. A variety of nucleophiles, including electron-rich arenes, thiophenes, benzofurans and indoles, participated in the cross-dehydrogenative coupling to afford TAMs in good to excellent yields (**Error! Reference source not found.**).

The catalytic cycle for this reaction is proposed to proceed by activation of DDQ by TfOH through a hydrogen bond (**Error! Reference source not found.**). Electron and proton transfers from the benzylic C–H to DDQ result in the formation of a triarylmethyl carbenium ion, joining the classic F-C reaction mechanism at this point. Attack by the nucleophilic arene, in this case, benzofuran, generates a resonance stabilized cation. Deprotonation of the C–H bond by triflate regenerates TfOH and liberates the F-C product [63]. This method has the advantage that it does not require oxidized triarylmethyl derivatives, opening the door to the new use of abundant triarylmethane derivatives for the preparation of TAMs.

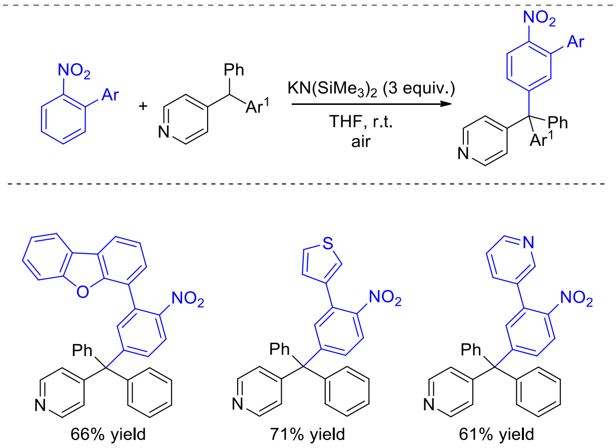


Scheme 26. Cross-dehydrogenative coupling reactions to prepare TAMs.



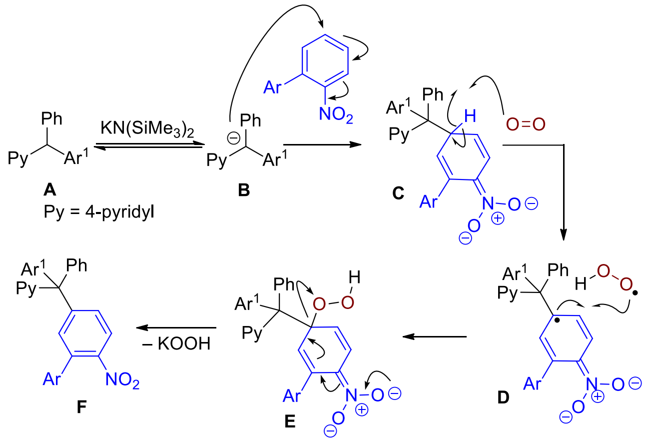
Scheme 27. Proposed mechanism of the TfOH catalyzed dehydrogenative cross-coupling reaction.

Kürti, Ess and co-workers [87] reported initial work on the synthesis of a class of cross-dehydrogenative coupling reactions under transition metal-free conditions. These researchers disclosed the innovative use of nitroarenes, which are versatile building blocks in organic synthesis, with ketone enolates under basic conditions to provide arylated products after air oxidation. Building on this work, Walsh, Liang, and coworkers advanced the use of nitroarenes as electrophiles in the arylation of triarylmethanes under basic conditions (**Error! Reference source not found.**) [88]. Yields are moderate and the reaction is currently limited to 2-aryl-substituted nitroarenes (18 examples, 43%–71% yields). Nonetheless, this route provides ready access to nitro-containing TAMs, which would be difficult to access *via* F-C chemistry.



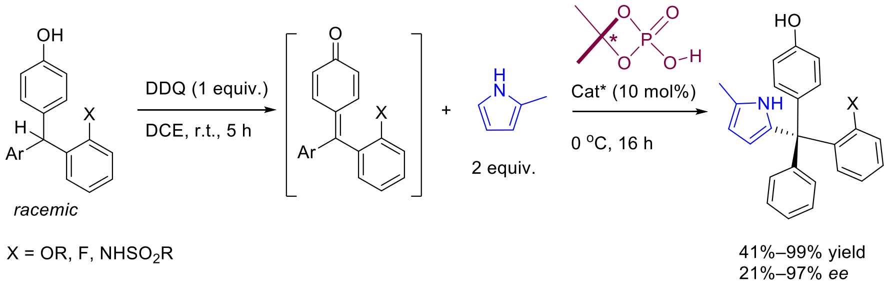
Scheme 28. Use of nitroarenes for the synthesis of TAMs.

A proposed mechanism is shown in **Error! Reference source not found.**, which involves reversible deprotonation of the triarylmethane, generating the triarylmethyl carbanion (**B**). The addition of the carbanion to the nitroarene gives the nitro-stabilized pentadienyl anion (**C**). Oxidation of **C** by dioxygen likely occurs through a free-radical process via **D** and **E**, ultimately forming the TAM.



Scheme 29. Proposed mechanism for arylation with nitroarenes.

The cross-dehydrogenative coupling reaction [56-57, 63, 71, 83-85]. described by Nambo and Crudden in **Error! Reference source not found.** was the source of inspiration for an elegant asymmetric version [63]. In this chemistry, He, Sun and their co-workers introduced a novel approach to enantioenriched TAMs (Scheme) [89]. This work is based on related efforts discussed in Scheme 4a and employs the same catalyst. A key finding of this CDC study is that the triarylmethane C–H could be oxidized to a *para*-quinone methide intermediate using DDQ with nearly quantitative conversion. Once the *para*-quinone methide was generated, the pyrrole and catalyst were added with a plan to intercept the mechanism in **Error! Reference source not found.** at intermediate **B**. Using this method, the authors reported 24 examples of enantioenriched TAMs, most of which are similar to the examples in Scheme 4a. It is notable that the *ortho*-substituent could be alkoxy, fluoro, or sulfonamide (X in Scheme). Enantioselectivities were generally excellent. The scope is somewhat limited and pyrroles with electron-withdrawing groups were not suitable. Less electron-rich arenes, including furan, 1,3,5-trimethoxybenzene, and 2-naphthol were not viable. Despite some shortcomings, this important work illuminates a pathway for further investigations employing CDC strategies.



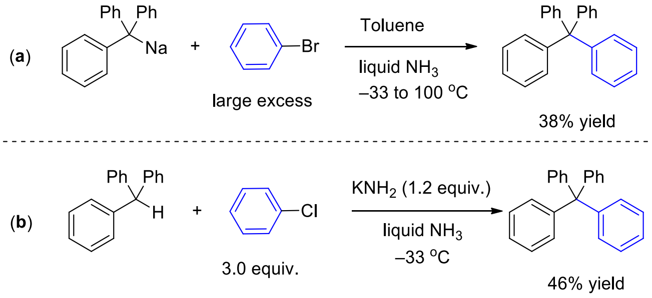
Scheme 6. Cross-dehydrogenative coupling to afford enantioenriched TAMs

3.2 Use of main group organometallics

3.2.1 Benzylic anion approach

The limitations of F-C-based methods for the preparation of certain TAMs, such as the need for an electron-rich nucleophilic arene, restrictive directing group effects of the arene substrate, and the difficulty of generating triarylmethyl cations with electron-poor aryl/heteroaryl groups, are problematic. Furthermore, some heterocycles, such as pyridines, are notoriously reluctant to undergo electrophilic aromatic substitutions. These challenges have inspired chemists to develop methods to overcome such shortcomings. A reasonably successful strategy involves the reversal of the F-C polarity by using triarylmethyl carbanions. An early study on the generation and reactivity of triarylmethylcarbanions from $Ph_3C–Cl$ and

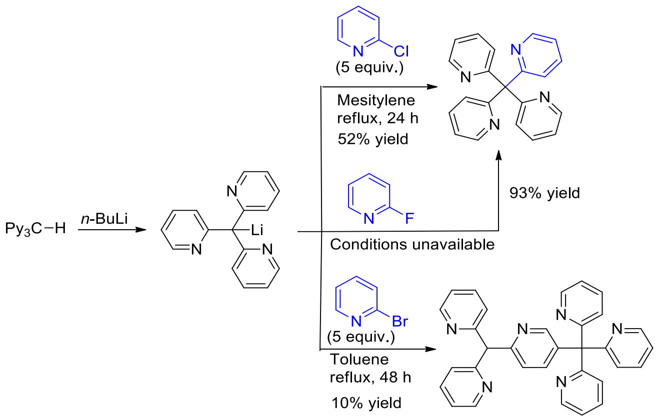
$Ph_3C–H$ with Na was published by Kraus and Kawamura. They reported the reaction between bromobenzene and triphenylmethyl sodium in liquid ammonia/toluene solution generated tetraphenylmethane in 38% yield (**Error! Reference source not found.**a) [90]. Along similar lines, Weight and Bergstrom reported that triphenylmethylpotassium, generated from $Ph_3C–H$ and KNH_2, reacted with chlorobenzene in liquid ammonia. The reaction was slow, but in the presence of KNH_2, the reaction was accelerated and gave tetraphenylmethane in 46% yield (**Error! Reference source not found.**b) [91]. Roberts provided evidence that such reactions proceed through benzyne intermediates [92]. These initial experiments demonstrate the feasibility of this approach, which proved not to be general [93]. The challenging reaction conditions and low yields inspired more practical and flexible procedures for this strategy towards TAMs.



Scheme 31. Initial studies using triarylmethyl carbanions for the preparation of TAMs.

Conceptually, the idea of reversing the polarity of reacting partners in TAM synthesis is attractive, but in practice, the examples above appear to be the best-case scenario; other substrates failed to partake in TAM generation with simple aryl halides [93]. The key to developing useful reverse polarity-based methods is changing the mechanism from the reaction on benzyne intermediates to nucleophilic aromatic substitution (S_NAr) on appropriate electrophiles. As will be seen, however, triarylmethyl carbanions with strongly electron-withdrawing groups exhibit reduced nucleophilicity.

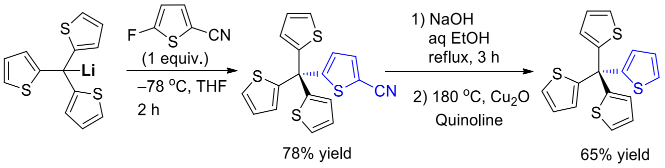
Because of the high value of heterocyclic aromatic compounds [94], the synthesis of tetrakis(heteroaryl)methanes is an area of much interest. A pioneering example was presented by Oda and co-workers, who first reported the synthesis of tetra(2-pyridyl)methane via S_NAr by the action of tris(2-pyridyl)methyl carbanion upon 2-chloropyridine [95]. The reaction required forcing conditions (refluxing mesitylene, 24 h), but provided the TAM in 52% yield (**Error! Reference source not found.**, top). The delocalization in the tripyridylmethyl carbanion likely renders this species only weakly nucleophilic. Nonetheless, the authors claim to have increased the yield to 93% by using 2-fluoropyridine [96] in place of 2-chloropyridine (**Error! Reference source not found.**, center). The authors have not published the details of this revised synthesis. Tetra(2-pyridyl)methane was oxidized to the tetra(*N*-oxide) using peracetic acid in 46% yield. Interestingly, using 2-bromopyridine with tripyridylmethyl carbanion, the reaction is believed to proceed by single electron transfer from the tripyridyl carbanion to the 2-bromopyridyne to generate a tripyridylmethyl radical that dimerizes to give an unexpected TAM (10% yield, **Error! Reference source not found.**, bottom) [95]. This mode of reactivity serves as a warning of a potential pitfall in this approach.



Scheme 32. Reactions toward the synthesis of tetrakis(2-pyridyl)methane.

Unfortunately, this approach was largely unsuccessful with tri(2-pyridyl)methyl carbanion and 4-chloropyridine (5% yield of 4-pyridyl tri(2-pyridyl)methane, not shown) [5, 97]. The reaction of lithiated tri(2-thienyl)methyl carbanion with 2-chloropyridine (refluxing xylene, 8% yield of the TAM) [95], 2-chlorothiophene, or 2,5-dichlorothiophene [96]; and the reaction of tri(4-pyridyl)methane with 4-chloropyridine (affording only 2% yield of tetra(4-pyridyl)methane) were also largely unsuccessful [5, 97].

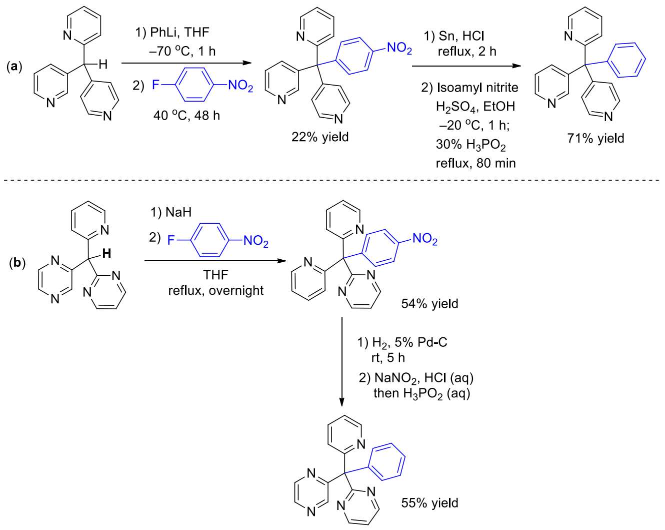
Oda and co-workers developed a work around for the above-mentioned route to tetra(2-thienyl)methanes by using a more activated electrophile for the S_NAr [96]. Thus, the reaction of lithium tri(2-thienyl)methyl carbanion with 2-fluoro-5-cyanothiophene proceeded smoothly and gave (5-cyano-2-thienyl)-tri(2-thienyl)methane in 78% yield (**Error! Reference source not found.**). Alkaline hydrolysis of the cyano group to the carboxylic acid was followed by decarboxylation at 180 °C in the presence of Cu_2O in quinoline solvent to afford the parent tetra(2-thienyl)methane in 50% overall yield from the tri(thienyl)methane [96].



Scheme 33. Improved synthesis of tetra(2-thienyl)methane.

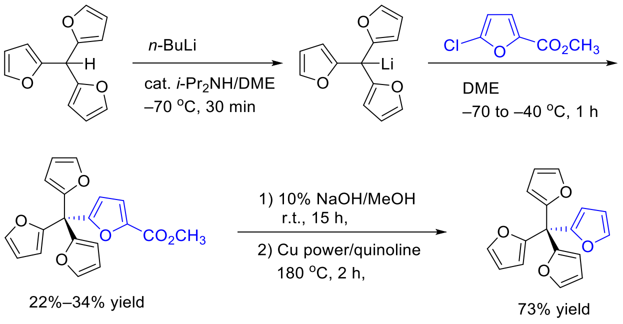
Matsumoto and co-workers also reported the synthesis of a chiral TAM bearing a phenyl and one each of 2-, 3-, and 4-pyridyl groups [phenyl-(2-pyridyl)-(3-pyridyl)-(4-pyridyl)methane], to study its chiroptical properties [5, 97]. Thus, deprotonation of (2-pyridyl)-(3-pyridyl)-(4-pyridyl)methane with PhLi at –70 °C was followed by treatment with 4-fluoronitrobenzene and gave the desired TAM derivative in 22% yield (**Error! Reference source not found.**a). Finally, the removal of the nitro group by reduction followed by a diazotization–reduction protocol afforded the target molecule, which was resolved by chiral phase HPLC for further study.

Matsumoto, Nehira, and their co-workers reported the synthesis and chiral phase resolution of the enantiomers of phenyl-pyrazinyl-2-pyridyl-2-pyrimidinylmethane (**Error! Reference source not found.**b) [98]. The key step in the preparation of the racemic TAM was again S_NAr using 4-fluoronitrobenzene (54% yield), followed by functional group interconversion [98].



Scheme 34. Synthesis of chiral a azaaryl TAM derivatives by S_NAr.

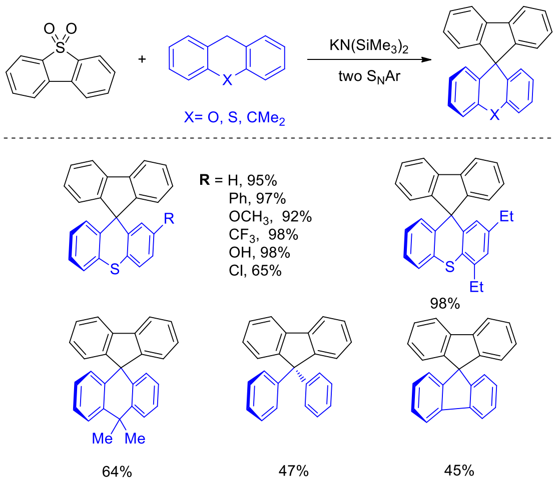
Kurata, Oda, and their group reported the synthesis of tetra(2-furyl)methane using an S_NAr on activated 2-chlorofurans [99]. Deprotonation of tri(2-furyl)methane with *n*-BuLi gave the organolithium intermediate (that was temperature sensitive, Scheme). Nonetheless, treatment of the trifurylmethyllithium with methyl 5-chlorofuran-2-carboxylate at low temperatures furnished modest amounts of the methyl ester-containing TAM. Hydrolysis and decarboxylation gave the parent tetra(2-furyl)methane. Furans are particularly useful for functionalization, as they undergo electrophilic aromatic substitution and lithiation at the 2- and 5-positions. The authors demonstrated both modes of reactivity with tetra(2-furyl)methane. Bromination with NBS at the 5-position provided the tetrabromide (75% yield), which could be metalated with *n*-BuLi and subjected to DMF to generate the tetraformyl TAM (76% yield) or subjected to Suzuki cross-coupling reactions. The parent tetra(2-furyl)methane could be directly metalated with *t*-BuLi and formylated with DMF (56% yield) [99].



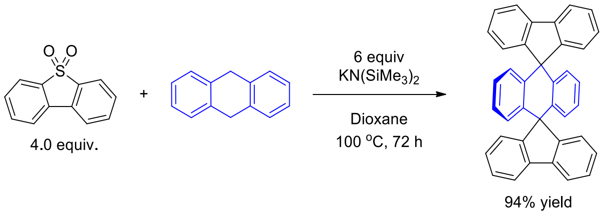
Scheme 7. Synthesis of tetra(2-furyl)methane.

Yorimitsu and co-workers introduced an innovative and practical one-pot strategy to prepare spirocyclic 9,9-diarylfluorene derivatives. The key to success was the application of dibenzothiophene dioxides, which can undergo successive S_NAr reactions to cleave the C–S bonds. Thus, in the presence of cyclic diarylmethane derivatives (1.5 equiv) and $KN(SiMe_3)_2$ (2.5 equiv) in dioxane at 80 °C, the formation of fluorene-based spirocyclic TAMs was observed in 45%–98% yields (**Error! Reference source not found.**). The procedure was also successful with 9,10-dihydroanthracene as a pro-nucleophile, giving the bis(spirocyclic) product derived from four S_NAr steps in an impressive 94% yield (**Error! Reference source not found.**). This approach enabled the synthesis of unusual spirocyclic compounds that are otherwise difficult to access, as shown in **Error! Reference source not found.** [86]. Limitations to this approach include the use of the moderately strong base $KN(SiMe_3)_2$. Thus, only base-stable functional groups can be tolerated. Less acidic diarylmethane pro-nucleophiles, such as the parent diphenylmethane, were not suitable. Despite these challenges, this approach facilitates the synthesis of a variety of novel TAMs.

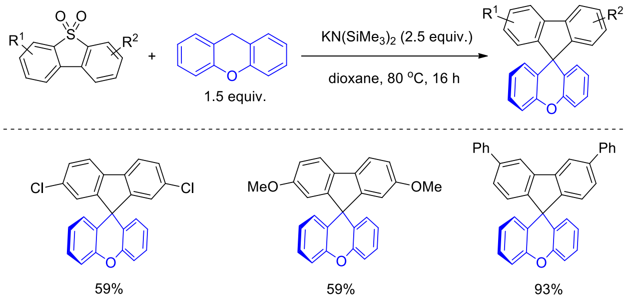
The authors also proposed a reaction mechanism involving an intermolecular S_NAr reaction of the sulfur dioxides with cyclic diarylmethylpotassium (**Error! Reference source not found.**). Next, intramolecular S_NAr cyclization takes place in the presence of $KN(SiMe_3)_2$. The intermediate sulfinic acid was isolated in 60% yield, along with spirocycle tetraarylmethanes in 39% yield. Subsequently, the sulfinic acid was exposed to $KN(SiMe_3)_2$ at 80 °C to yield tetraarylmethanes in 98% yield [85].



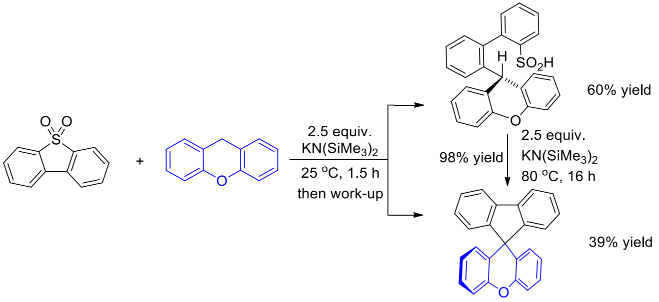
Scheme 36. Application of dibenzothiophene dioxides in the synthesis of TAMs and selected examples



Scheme 37. S_NAr with diaryl sulfones.



Scheme 38. Representative spirocycles prepared.

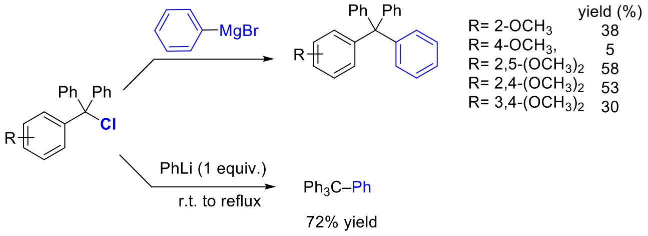


Scheme 39. Studies to probe the reaction pathway with dibenzothiophene dioxides in the synthesis of TAMs.

3.3 Aryl anion approach

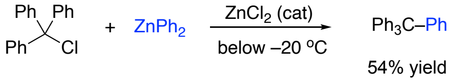
3.3.1 Grignard and organolithium reagent approaches to TAMs

Early efforts to prepare tetraphenylmethane by reaction of organometallic reagents, such as Grignard reagents, with triphenylmethyl chloride and triphenylmethyl ethers gave yields that were below 20% [56]. The yield of TAM derivatives varied when different triarylmethyl chloride derivatives were used under the same conditions, with yields reaching 58% when one of the aryl groups contained a 2-OMe substituent (**Error! Reference source not found.**) [100]. A hint of promise for the addition of aryl organometallics to triarylmethylchlorides is found in the gram scale synthesis of CPh_4 by the reaction of triphenylchloromethane and PhLi in diethyl ether, first at rt and then heating to reflux (**Error! Reference source not found.**, bottom) [101]. This method gave CPh_4 in 72% yield. The scope of this process remains to be further explored.



Scheme 40. Synthesis of TAMs from triphenylchloromethanes and organometallic reagents.

Along similar lines, it was reported that $ZnPh_2$ reacted with trityl chloride in the presence of catalytic $ZnCl_2$ to give CPh_4 in 54% yield (**Error! Reference source not found.**). The scope was not elaborated and full experimental details were not published [102].



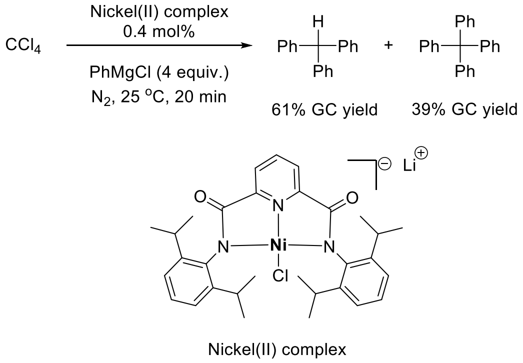
Scheme 41. Synthesis of CPh_4 catalyzed by $ZnCl_2$.

3.4 Use of TM catalysts

Transition metal-catalyzed reactions have revolutionized organic synthesis by facilitating the construction of C–C and C-heteroatom bonds. In particular, many such catalysts promote the efficient generation of *quaternary* centres *via* C–C bond-forming reactions. Despite incredible progress, applications to the synthesis of tetraarylmethanes have lagged behind other cross-coupling reactions and proved more challenging to develop. Nonetheless, the last decade has seen some advances in this area. It is worth noting that a cross-coupling approach would be complementary to the F-C synthesis, because it would not be subject to the same electronic effects that plague electrophilic aromatic substitution reactions.

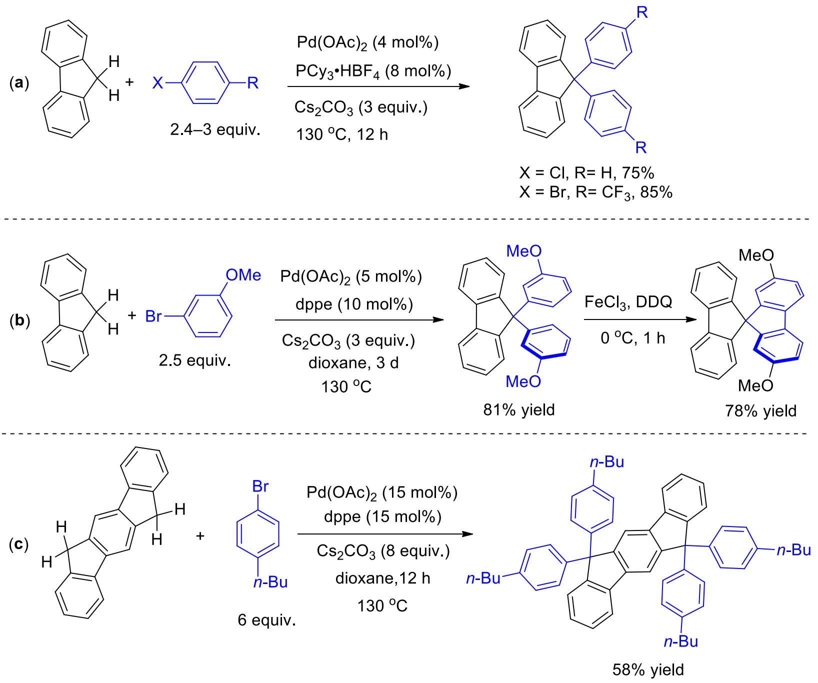
3.4.1 Transition metal-catalyzed cross-coupling approaches to TAMs.

In the early 2010's, the first successful examples of the synthesis of TAMs with transition metal-catalyzed cross-coupling methods were reported. Shortly thereafter, more general methods were introduced, as outlined below. In an intriguing initial result, an anionic nickel(II) pincer complex with a sterically bulky tridentate ligand was found to promote a Kumada-type C–C coupling of CCl_4 and PhMgCl to form a 3:2 ratio of triphenylmethane to tetraphenylmethane at room temperature in less than 20 min (**Error! Reference source not found.**). These products were not isolated, but were analyzed by GC-MS, showing only a 39% GC yield of tetraphenylmethane. No other aryl Grignard reagents were reported and no insight into the reaction mechanism was provided [103]. Given the anionic Ni(II) starting complex, it is difficult to envision a traditional coupling mechanism, even for Ni catalysts which have a wide range of oxidation states accessible [104].



Scheme 42. Ni-catalyzed construction of tetraphenylmethane.

Motivated by potential applications of diarylfluorenes in solar cells, OLEDs, and PLEDs, among others, researchers sought to prepare structures that were not accessible by F-C reactions using cross-coupling protocols. Use of fluorene, which has a particularly acidic C(sp^3)–H bond [105], as a pro-nucleophile with 3 equiv aryl halide in the presence of a Pd catalyst was explored. Use of Pd(OAc)$_2$ and PCy$_3$•HBF$_4$ or dppe enabled aryl bromides and chlorides bearing 3-OCH$_3$ or 4-CF$_3$ groups to be coupled, affording the corresponding products in 75–85% yields (**Error! Reference source not found.**a). Among them, 9,9-di(3-anisyl)fluorene could be converted to spirobifluorene in 78% yield by a radical reaction based on FeCl$_3$ and DDQ (**Error! Reference source not found.**b). This synthetic protocol was also adapted to a bis(fluorene)-based TAM in 58% yield (**Error! Reference source not found.**c) [106].



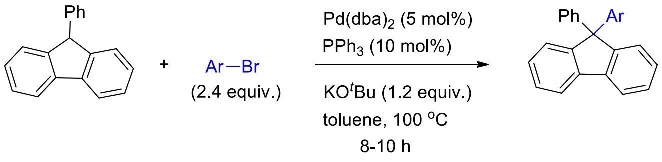
Scheme 43. Pd-catalyzed synthesis of TAMs from fluorene in one-pot.

In a related effort, an efficient Pd-catalyzed cross-coupling of monoarylfluorene with aryl bromides for the synthesis of asymmetric 9,9'-diarylfluorenes was developed (Table 2a). Most of the employed aryl bromides including bromobenzene, bromo-heterocycles, and naphthalene bromide, reacted smoothly in the presence of Pd(dba)$_2$ (5 mol%) and PPh$_3$ (10 mol%) to afford the corresponding products in 39%–65% yield (Table 2a). Electron-rich aryl bromides worked well and afforded the coupling products in good yields, while the sterically hindered 2-tolyl and 1-naphthyl resulted in relatively lower yields (45%–58%). Furthermore, heteroaryl bromides, such as 2- or 3-bromothiophene and 3-bromopyridine, gave the coupling products in 39%–65% yield. This protocol was also adapted to the difunctionalization of dibromo arenes, where the ratio of dibromoarene was reduced to 0.4 equiv. (Table 2b). These linked products might have potential utility as host materials for OLEDs. Finally, fluorene could be diarylated in a single step to afford various "symmetrical" diarylfluorenes in a 73%–92% yield (Table 2c) [107]. The systems above were not demonstrated to be viable a with a broader substrate scope that did not contain fluorene-based substrates. As outlined below, however, inroads in this area have been made.

The examples in **Error! Reference source not found.** and Table 2 employ fluorene derivatives, which are both more acidic and less sterically hindered than other substrates. To the best of our knowledge, the first example of the synthesis of TAMs *via* transition metal-catalyzed cross-coupling of non-fluorene pro-nucleophiles with aryl halides was reported in 2007. In this study, the authors focused on the synthesis of *triarylmethanes* from diarylmethanes and aryl chlorides. High yields of triarylmethanes were obtained, with TAMs observed as byproducts [108]. Under the reaction conditions using Cl$_2$Pd(NCMe)$_2$ (5 mol%), PCy$_3$ ligand, and CsOH as the base, pro-nucleophiles, such as 4-benzyl pyridine, underwent coupling in refluxing xylene to yield up to 92% 4-benzhydryl pyridine, with 8% yield of a 4-triphenylmethyl pyridine side product (**Error! Reference source not found.**). This important result served as proof-of-principle for the coupling and demonstrated that two key steps were indeed achievable: the transmetallation of the triarylmethyl carbanion with a Cs counterion to palladium and the reductive elimination of the sterically bulky CAr$_3$ substituent with a Pd-bound aryl group.

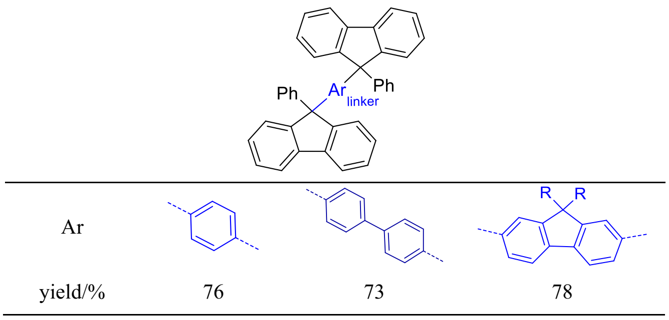
Table 2.
Pd-catalyzed preparation of TAMs from monoarylfluorene and fluorene (**a-c**)

(**a**) Monoarylation reactions.

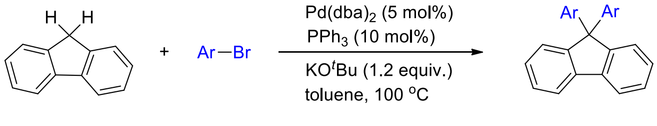


Ar	yield/%	Ar	yield/%	Ar	yield/%
4-C$_6$H$_4$Br	82	1-naphthyl	58	3-Py	65
4-C$_6$H$_4$-OMe	95	2-thiophenyl	39		
2-C$_6$H$_4$-Me	45	3-thiophenyl	54		

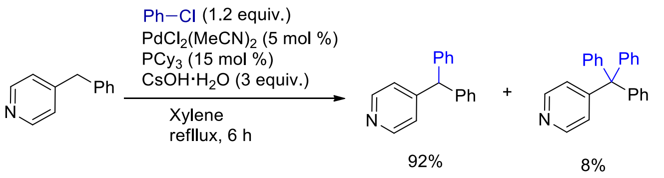
(**b**) Use of dibromoarene linkers.



(**c**) Diarylation reactions.



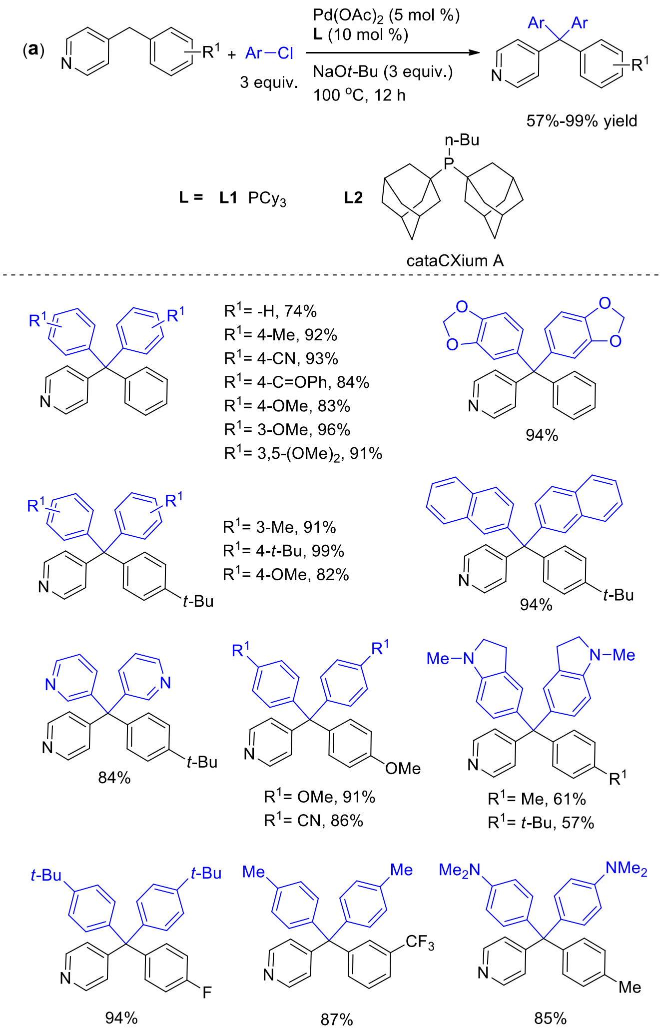
Ar	yield/ %	Ar	yield/ %	Ar	yield /%
4-C_6H_4F	73	4-C_6H_4-OMe	83	4-C_6H_4-NMe_2	74
4-C_6H_4-Cl	92	3,5-$C_6H_3(OMe)_2$	83	3,4-C_6H_3-Me_2	85
4-C_6H_4-Me	89	3-C_6H_4-OMe	89	2-naphthyl	95

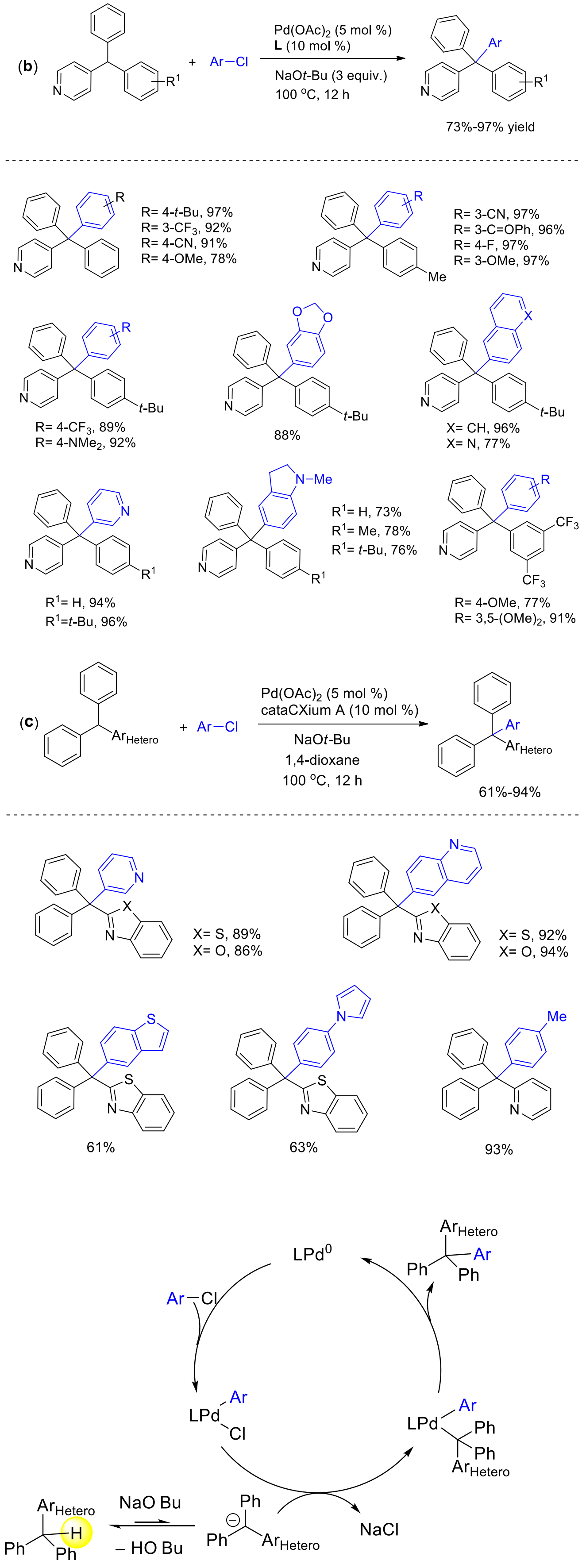


Scheme 44. Synthesis of TAM by-product by Pd-catalyzed cross-coupling.

Inspired by the results in **Error! Reference source not found.**, a more general route to TAMs was sought using palladium-catalyzed cross-coupling reactions. After screening many ligands, a system was chosen consisting of $Pd(OAc)_2$, monodentate phosphines PCy_3 or cataCXium A, and NaO*t*-Bu base for 1) the diarylation of aryl(heteroaryl)methanes (**Error! Reference source not found.**a) and 2) the arylation of diaryl(heteroaryl)methanes with aryl chlorides (**Error! Reference source not found.**b). This catalyst system enabled the introduction of various aryl groups to construct triaryl(heteroaryl)methanes in good to excellent yields. The method has an advantage over traditional cross-coupling processes that employ pre-synthesized organometallic reagents (organoboron, -zinc, and -magnesium reagents, for example). Like the approach in **Error! Reference source not found.**, this coupling involves *in situ* reversible deprotonation of the pro-nucleophile for a net C–H functionalization [63]. Heterocyclic aryl chlorides, including 3-pyridyl, 5-(*N*-methyl indole) and 6-quinolyl, participated in the coupling with the phosphine ligand cataCXium A in 61%–94% yield (**Error! Reference source not found.**c). Diaryl(4-pyridyl)methanes with phenyl and 3,5-C_6H_3-$(CF_3)_2$ also afforded TAMs. Many of the products contain chiral quaternary centres, but enantioselective versions have yet to be introduced. This method was applied to gram-scale reactions of 4-benzylpyridine with 4-chlorobenzophenone to give the product in 79% yield. A limitation of this process is the use of excess aryl halide. Furthermore, reactions with higher pK_a pro-nucleophiles, such as diphenylmethane, have not yet been achieved, leaving room for future development.

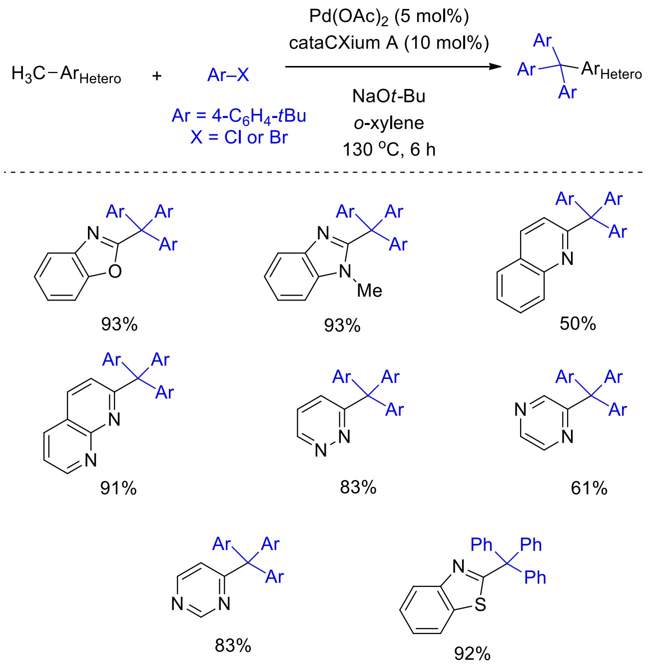
Table 3.
Pd-catalysed approach to furnish TAM derivatives (**a-c**).





Scheme 45. Pd-catalysed approach to furnishing TAM derivatives proposed reaction mechanism.

The same team adapted their catalyst system to perform the triarylation of heteroarylmethanes for the synthesis of TAMs [109]. A series of $Ar_{Hetero}–CH_3$ substrates were successfully employed with either aryl chlorides or bromides (Scheme). A variety of aryl chlorides and bromides, including heterocyclic derivatives were also reported, but are not shown here. Further advances in this area can be envisioned to involve the introduction of base metal catalysts to replace precious metals like Pd in these processes and the synthesis of TAMs without heteroaromatic groups that facilitate deprotonation.

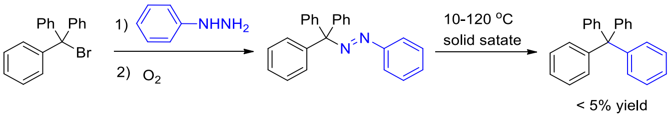


Scheme 8. Triarylation of $Ar_{Hetero}–CH_3$ pro-nucleophiles.

4. Radical approaches to TAMs

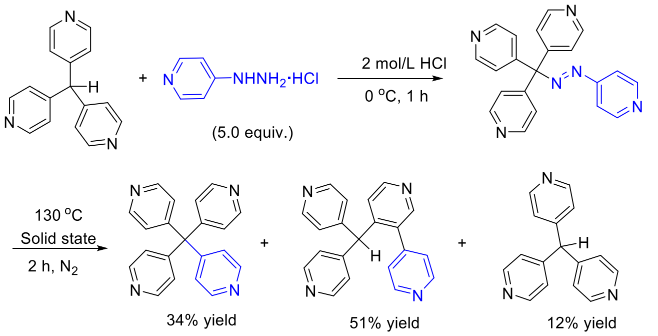
A complementary approach to the polar 2-electron processes commonly used in the synthesis of TAMs to form C–C bonds, like the F-C and cross-coupling reactions, involves the selective coupling of open-shell species. Given the recent renaissance in the application of radical species, it is surprising that this approach has not been revisited in the synthesis of TAMs.

In the first reported synthesis of tetraphenylmethane, Gomberg described the oxidation of triphenylmethanehydrazobenzene to the corresponding azo-compound. Heating this compound in the solid state to 110–120 °C resulted in the extrusion of nitrogen gas. Presumably, two carbon-centred radicals are formed and radical-radical coupling took place. While this was a landmark synthesis, the reaction suffered from low yield (<5%, **Error! Reference source not found.**) [2, 56]. Radical approaches involving heating triphenylmethane and peroxides, like benzoyl peroxide, in benzene have also been reported[110] and investigated mechanistically [111]. Likewise, the thermal decomposition of *N*-tetramethylpiperidinyl triphenyl acetate, $Ph_3C–COO–TMP$, at 146 °C in benzene generates the radical •CPh_3 which adds to benzene to give tetraphenylmethane [112]. Given that the yields of tetraphenylmethane in these radical processes are currently below 20%, and they do not compete with modern methods, they will not be covered in more detail here.



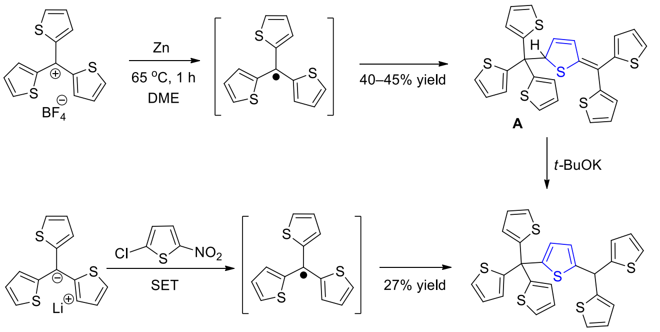
Scheme 47. Gomberg's synthesis of TAM from Ph$_3$C-N=N-Ph via radical strategy.

Following Gomberg's original decomposition of diazo compounds (**Error! Reference source not found.**) the pyrolysis of tri(4-pyridyl)-4-pyridylazomethane was examined. Solid-state pyrolysis at 130 °C for 2 h gave a 34% yield of this important supramolecular support linker (**Error! Reference source not found.**) [113]. It is noteworthy that this radical approach was ~10 times higher yielding than the method of nucleophilic aromatic substitution with 4-chloro- or 4-fluoropyridine and tri-4-pyridylmethyl anion (3% yield), which led to undesired products. Unfortunately, further expansion of the scope of this approach has not been published.



Scheme 48. Synthesis of tetra(4-pyridyl)methane from tri(4-pyridyl)-4-pyridylazomethane via radical-radical coupling.

The generation of C(Ar$_{\text{Hetero}}$)$_4$ complexes with Ar = thiophene derivatives has also been attempted using radical intermediates, but it undergoes a dimerization reaction to give an asymmetric TAM (Scheme 9). The •C(2-thienyl)$_3$ intermediate in this reaction has been generated by the reduction of tri-2-thienylmethylcarbenium tetrafluoroborate by Zn in 1,2-dimethoxyethane. Product **A** is reported to be formed in quantitative yield by NMR, but it reacts with air during purification, thus only providing a 40%–45% yield of **A**. Treatment of **A** with *t*-BuOK afforded an interesting TAM [114]. It was later found that the corresponding carbanion underwent single electron transfer (SET) with 2-chloro-5-nitrothiophene, giving the same dimer in a 27% yield [96]. The scope of reactions of the tris(2-thienyl)methyl radical has not been explored, but this intermediate may find use when paring with other aromatic radical acceptors. Additional approaches to tetrakis(2-thienyl)methane are also discussed below.

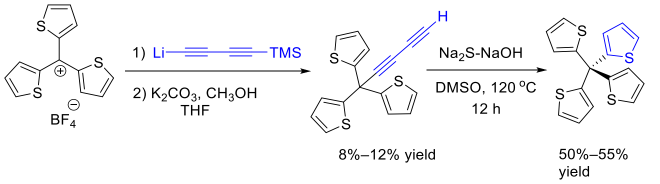


Scheme 9. The dimerization of tris(2-thienyl)methyl radical gives a tetra(2-thienyl)methane derivative.

5. Transformation of functionalized triarylmethane derivatives to TAMs

5.1 Diyne cyclization to a thiophene-based TAM.

In 2002, tetrakis(2-thienyl)methane was synthesized for the first time, although the procedure again left much room for improvement [115]. The route begins with tri-2-thienylmethylcarbenium tetrafluoroborate and the lithiated dieyne. Unfortunately, the C-butadiynylation of tris(2-thienyl)methyl cation occurred in 8%–12% yield (**Error! Reference source not found.**). The cyclization of the tris(2-thienyl)pentadiyne with sodium sulfide proceeded in 50%–55% yield (**Error! Reference source not found.**). It is noteworthy that the bromination of tetrakis(2-thienyl)methane with NBS resulted in the installation of a bromo group at the 5-position of each ring in 70% overall yield, broadening the potential utility of tetrakis(2-thienyl)methane.

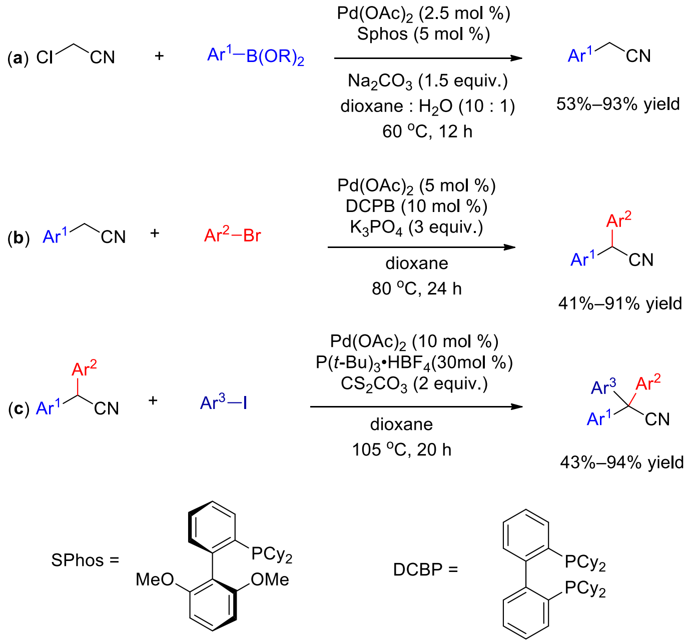


Scheme 50. Ring-forming synthesis of tetrakis(2-thienyl)methane.

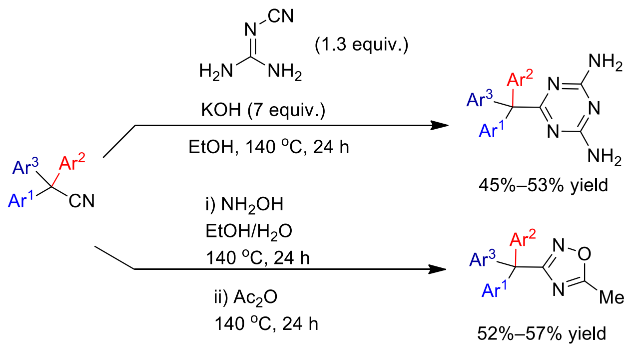
5.2 Sequencial arylation of chloroacetonitrile and heteroaryl formation.

A versatile method to build up tetraarylmethane derivatives was reported by Nambo, Crudden, and co-workers and it is based on sequential C–H arylation reactions [116]. These reactions are conducted under basic conditions that enable deprotonation of the substrate. Installation of an aryl group, however, tends to increase the acidity of the remaining benzylic hydrogens by about 6 p*K* units, potentially causing problems with over-arylation byproducts [117]. Proper choice of catalyst and base was used to circumvent this pit fall and allow for the introduction of three distinct aryl groups to give triarylmethanes.

Beginning with chloroacetonitrile, the first aryl was added via Suzuki-Miyaura cross-coupling with aryl boronic acids (Scheme a). Using a catalyst formed from Pd(OAc)$_2$ and Buchwald's SPhos, a wide range of aryl boronic acids underwent coupling to provide benzyl nitriles in yields that are generally over 80%. The second aryl is installed using 2,2′-bis(dicyclohexylphosphino)-1,1′-biphenyl (DCPB), as shown in Scheme b. These conditions exhibited good substrate scope with respect to both the aryl acetonitrile and aryl bromide coupling partners, enabling the synthesis of a variety of diarylacetonitriles in good to excellent yields. The final arylation was found to be strongly dependent on the phosphine ligand. Only a palladium complex ligated by P(t-Bu)$_3$ resulted in high yields (Scheme c). A variety of aryl and heteroaryl iodides underwent the coupling to furnish triarylacetonitriles.



Scheme 10. Sequential arylation approach to triarylacetonitriles.

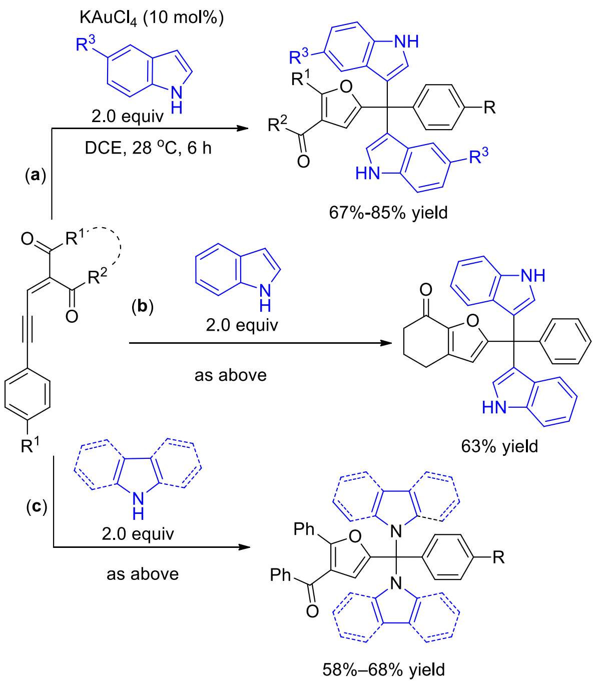


Scheme 11. Modification of the nitrile to generate heterocyclic TAM derivatives.

Transformation of the cyano into a heteroaromatic group furnishes the tetraarylmethane derivative (Scheme). This transformation was accomplished by treatment of triarylacetonitriles with cyanoguanidine or hydroxyl amine in moderate yields. Overall, this flexible method results in a concise synthesis of tetraarylmethane derivatives that would be otherwise very difficult to prepare [116]. Currently, the method is constrained by the scope of the final heteroaryl group. Further building upon this strategy could prove fruitful to broaden the classes of TAMs that can be constructed in a modular fashion.

5.3 Au and Cu-catalyzed construction of tetraarylmethanes

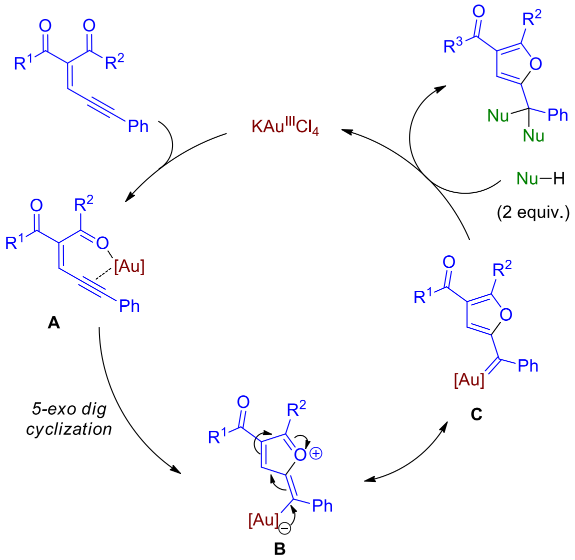
A rapid method for the construction of heterocyclic TAMs that builds a furan and incorporates two equiv of strongly nucleophilic indoles has been recently disclosed [118]. The optimized conditions employ 10 mol% KAuCl$_4$ in DCE at 28 °C, resulting in TAM assembly by forming the furan and incorporating two C-(indole) linkages in 63%–85% yields. Variations of the enynone R^1 and R^2 groups were accomplished, including cases in which R^1 ≠ R^2. In all cases, a single isomer was reported (**Error! Reference source not found.**, path a). In addition to the parent indole, indoles with R^3 = Br and OMe were prepared. Although not highlighted in **Error! Reference source not found.**, some substituents on the aryl acetylenic portion were demonstrated (R = F, Me, OMe). It was found that the diketone moiety could be cyclic (**Error! Reference source not found.**, path b) while maintaining a good yield (63%). The use of other activated heteroaromatic nucleophiles, such as pyrrole or carbazole, did not result in C–C bond formation but instead underwent C–N bond-formation (**Error! Reference source not found.**, path c). The strength of this method is the efficient formation of the TAMs. Counter balancing this feature is the need to use isomerically clean enynes and indole nucleophiles. Given the synthetic efficiency of this method, further development is warranted, including the introduction of additional nucleophiles to capture the gold carbene intermediate. Perhaps this interception could even be catalyzed by a second metal.



Scheme 53. Rapid construction of TAMs catalyzed by gold.

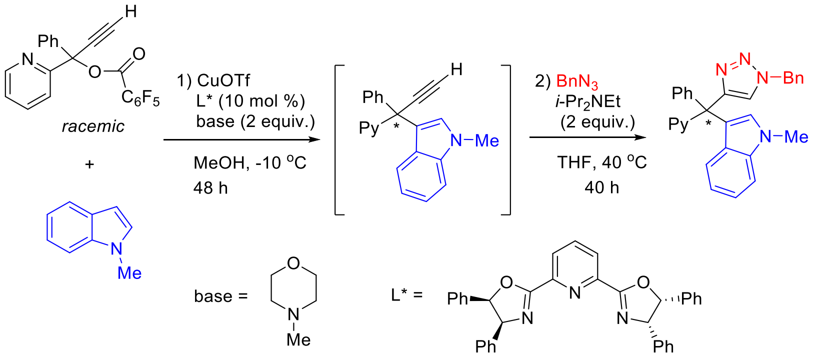
Although the details of the reaction mechanism have not been fleshed out, it is proposed that the reaction starts with the gold catalyst binding the substrates in a chelating fashion to form **A** (**Error! Reference source not found.**). Intermediate **A** is proposed to facilitate cyclization of the bound substrate through a

5-exo-dig pathway in which the *cis*-carbonyl acts as a nucleophile. A zwitterionic intermediate **B** is formed, which is in resonance with a gold carbene **C** bearing the formed furan. The electrophilic carbene is then attacked by the indole through an F-C type reaction. It can be imagined that the triarylmethylgold undergoes heterolysis to generate a triarylmethyl cation that is subsequently attacked by a second molecule of the indole [118].



Scheme 54. A plausible mechanism of Au-catalyzed cycle and substitution.

A great challenge in the preparation of tetraarylmethane derivatives is their efficient and catalytic enantioselective synthesis. Along these lines, Nishibayashi and co-workers reported the first example of a tetraarylmethane through a two-step procedure (**Error! Reference source not found.**) [119]. Employing catalytic (5 mol%) CuOTf•$(C_6H_6)_{1/2}$ and (4*S*,5*R*)-diPh-Pybox (10 mol %) in the presence of an unsymmetrical tertiary propargylic pentafluorobenzoate ester bearing phenyl and 2-pyridyl groups (**Error! Reference source not found.**) an enantioselective propargylation was conducted with *N*-methyl indole as the nucleophile. This reaction afforded the triarylmethylsubstituted acetylene as an intermediate that was not isolated or characterized. After a solvent switch, the acetylene intermediate was subjected to a Huisgen cycloaddition with benzyl azide to afford the tetraarylmethane in 28% yield over 2 steps with 78% *ee*. Although this one-pot procedure represents the first direct access to an enantioenriched tetraarylmethane, it indicates that there is considerable room for improvement.



Scheme 57. Enantioselective propargylation followed by Huisgen cycloaddition for the synthesis of an enantioenriched tetraarylmethane.

6. Conclusions

The increasing importance of TAMs in areas of basic and applied science, medicine, gas purification, and organic synthesis has resulted in the synthesis of over 32,000 unique TAM structures. Strategies such as the F-C reaction continue to be powerful methods to access TAMs, including recent advances with enantioselective F-C processes catalyzed by enantioenriched acids. The requirement of activated nucleophilic arene reaction partners and restriction to *ortho* and *para*-selectivity constrain the use of this approach. In contrast, metal-catalyzed cross-coupling reactions do not suffer this pitfall and represent a possible gateway to new TAM space. Despite the prominence of modern cross-coupling chemistry in synthesis, its application to the synthesis of TAMs has proven challenging. Nucleophilic aromatic substitutions are among the most commonly used reaction classes to form C(sp^3)–C(sp^2) linkages. Recent developments relevant to the synthesis of TAMs have successfully focused on the nature of the leaving groups. This, combined with progress in the deprotonation of weakly acidic C–H bonds, could broaden the TAM architectures accessible with S$_N$Ar reactions. Radical reactions were the first used in Gomberg's synthesis of tetraphenylmethane. The incredible progress made in the last decade in radical chemistry has not yet benefited the field of TAM synthesis. This area is ripe for development. Overall, we expect new methods for the synthesis of TAMs to increase steadily in the coming years to meet the increasing demand for these architecturally important building blocks.

Acknowledgments

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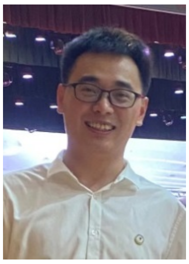
Lai Chen received his Ph.D. in Pesticide Science from Nankai University. He is currently an associate professor at Plant Protection College of Hebei Agricultural University. His research focuses on the discovery of new agrochemisticals and organic synthesis methodology.

Jingqian Huo received her Ph.D. in Pesticide Science from Hebei Agricultural University. She is currently an associate professor at Plant Protection College of Hebei Agricultural University. Her research focuses on Pesticide environmental toxicology.

Jinlin Zhang is currently dean, and an professor of Plant Protection College, Hebei Agricultural University. His research focuses on the discovery of new agrochemisticals, Pesticide environmental toxicology, and the prevention and control of alien invasive organisms.

Judith Currano is the head of the Chemistry Library at the University of Pennsylvania. Her research interests surround the development of effective methods of teaching chemical information and research and publication ethics.



Haixing Guan received his Ph.D. in Organic chemistry from Nanjing Tech University under the supervision of Prof Jianyou Mao and Prof Patrick J. Walsh in 2021. Currently, he is a lecturer at Experimental Center, Shandong University of Traditional Chinese Medicine. His research interests include TM-catalyzed cross coupling organic methodology and medicinal chemistry.

Patrick J. Walsh is a professor at the University of Pennsylvania (USA). He received his Ph.D. from UC Berkeley with Prof. R.G. Bergman and was an NSF postdoctoral fellow with K. B. Sharpless at Scripps Research Institute. His research is in the area of transition metal-catalyzed reactions, development of methods for organic synthesis and the study of reaction mechanism.

Jianyou Mao received his Ph.D. in Organic chemistry from China Agricultural University. Currently, he is a professor at School of Chemistry and Molecular Engineering, Nanjing Tech University. His research focuses on alkali-metal-catalyzed deprotonative addition of benzylic C-H bonds with toluenes and their further applications.