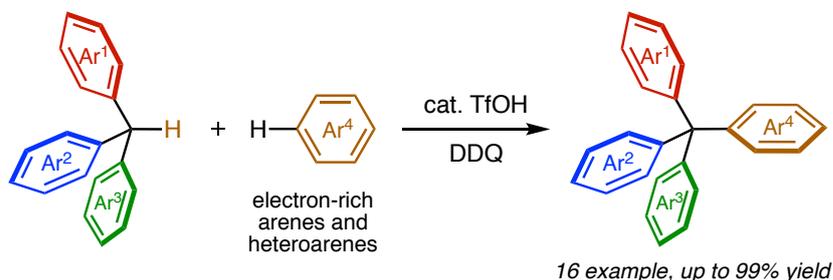


Synthesis of Tetraarylmethanes by the TfOH-Promoted Formal Cross Dehydrogenative Coupling of Triarylmethanes with Arenes

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Dedicated to Professor Victor Snieckus, colleague, mentor and friend on the occasion of his 80th birthday.

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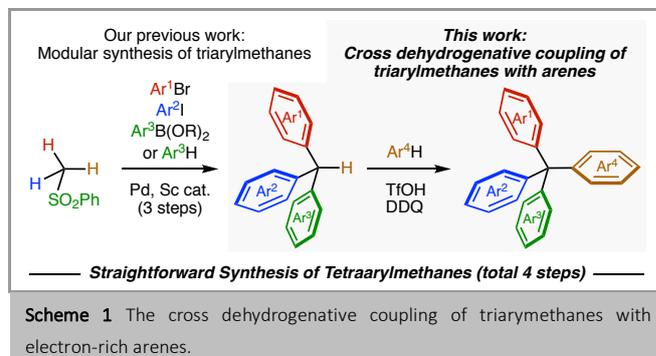
Abstract The formal cross dehydrogenative coupling of triarylmethanes with arenes promoted by TfOH and DDQ is described. This method provides a variety of tetraarylmethane derivatives in good to excellent yields from triarylmethanes that can be readily prepared by our previous methods. Control experiments suggest a possible catalytic cycle involving the generation of a trityl cation intermediate followed by nucleophilic addition of arenes.

Key words: Cross dehydrogenative coupling, Tetraarylmethane, Triarylmethane, Sequential arylation, Acid catalyst

Multiply-arylated methanes are important frameworks in medicinal chemistry and materials science.¹ A number of useful synthetic methods, including cross-coupling reactions, have been developed to access these structures, improve selectivity, and increase molecular diversity. Despite significant advances in the synthesis of di- and triarylmethanes,² synthetic routes towards tetraarylmethanes, which show unique chemical and physical properties for functionalized organic materials,³ are still based on classical methods. For example, Friedel-Crafts arylation of triarylmethanol⁴ or trityl chloride⁵ with some electron-rich arenes and the substitutions with organometallic reagents have been employed.⁶ However, these methods often require multiple steps to prepare the corresponding triarylmethyl substrates.

In a transition-metal catalyzed route, Yorimitsu and Ohshima first reported the formation of tetraarylmethanes by the Pd-catalyzed C–H diphenylation of 4-benzylpyridine.⁶ Recently, the Walsh group established Pd-catalyzed C–H arylations of di- and triarylmethanes bearing azaaryl groups to afford a variety of tetraarylmethanes.⁷ The Ni-catalyzed cross-coupling reaction of tetrachloromethane with aryl Grignard reagents has also been developed,⁸ but new synthetic methods for structurally diverse, particularly unsymmetric tetraarylmethanes are still needed.

Our group has developed the modular and selective syntheses of arylmethane derivatives using transition-metal catalysis.⁹ In particular, we have found that cheap, readily available methyl phenyl sulfone can be transformed into valuable triarylmethanes in only 3 steps through either Pd- or Sc-catalyzed sequential arylations (Scheme 1).



We saw the next challenge as expanding our sequential arylation strategy to enable the concise synthesis of tetraarylmethanes by arylating the remaining C_{sp3}-H bond in triarylmethanes. As an alternative method to deprotonative arylation,^{6,7} we focused on the cross dehydrogenative coupling approach, which has emerged as an ideal transformation to form C–C bond from two different C–H bonds.¹⁰ We envisioned that abstracting the benzylic C–H bond of triarylmethanes with an oxidant would generate reactive trityl cation intermediates, which would subsequently be reacted with nucleophilic arenes to afford tetraarylmethanes.¹¹ Herein, we describe the cross dehydrogenative coupling of triarylmethanes with electron-rich arenes using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as an oxidant (Scheme 1).¹²

Initial studies focused on triphenylmethane **1a** and anisole **2a** as model substrates for the formal cross dehydrogenative coupling (Table 1). Reaction in the presence of only DDQ gave (*p*-methoxy)tetraphenylmethane **3a** in only 10% yield (entry 1).

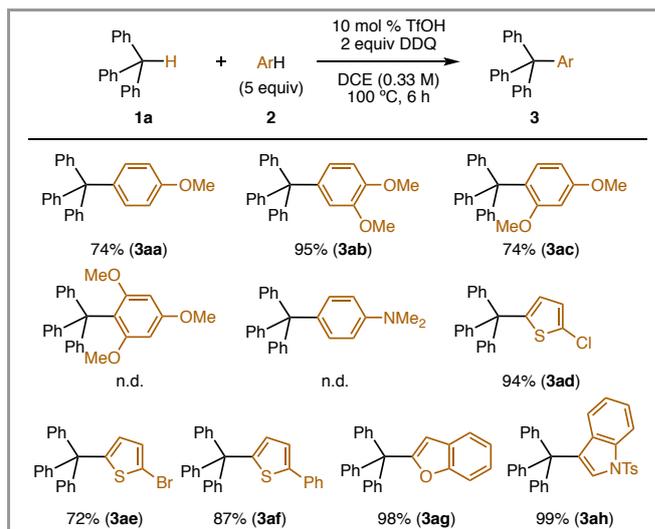
Inspired by previous reports about the activation of DDQ by the addition of acids,¹³ several acid catalysts were screened. The addition of TFA, BF₃·Et₂O, or H₂SO₄ led to increased product yields, however, an unexpected byproduct, 9-(*p*-methoxyphenyl)-9-phenylfluorene **4a**, was also formed (entries 2-4). Triflate metal salts, such as Cu(OTf)₂ and Sc(OTf)₃, improved the yield of product (entries 5 and 6), but through control experiments we showed that TfOH, potentially generated from triflate salts, was a suitable catalyst for this C–H coupling reaction. Under these simple conditions, the yield of **3a** reached 77% (entry 7). Decreasing the amount of **2a** or DDQ resulted in lower yields (entries 8 and 9), and when reaction was conducted at 80 °C, the yield was also significantly decreased (entry 10).

Table 1 Optimization of cross dehydrogenative coupling of triphenylmethane **1a** with anisole **2a**.^a

Entry	Catalyst	Yield of 3a (%) ^b	Yield of 4a (%) ^b
1	-	10	<1
2	TFA	14	8
3	BF ₃ ·Et ₂ O	28	1
4	H ₂ SO ₄	45	9
5	Cu(OTf) ₂	67	12
6	Sc(OTf) ₃	69	9
7	TfOH	77 (74) ^c	6
8 ^d	TfOH	25	24
9 ^e	TfOH	39	3
10 ^f	TfOH	49	3

^a Conditions: **1a** (1 equiv), **2a** (5 equiv), catalyst (10 mol %), DCE (0.33 M), 100 °C, 6 h. ^b GC yield was determined using dodecane as an internal standard. ^c Isolated yield. ^d 3 equiv. of **2a** was used. ^e 1 equiv. of DDQ was used. ^f Reaction was conducted at 80 °C.

With optimized conditions in hand, we examined the scope of the dehydrogenative coupling with regards to arenes (Scheme 2). Reaction with 1,2-dimethoxybenzene **2b** gave the corresponding product **3ab** in 95% yield, while 1,3-dimethoxybenzene **2c** gave a slightly decreased yield, probably due to steric effects. Indeed, no product was observed when the more electron-rich but sterically-hindered 1,3,5-trimethoxybenzene was used. Although *N,N*-dimethylaniline did not afford the desired product, electron-rich heteroareamics were well-tolerated. 2-Substituted thiophenes (**2d–2f**) reacted in high yield and selectively at the 5-position. Benzofuran **2g** and *N*-tosylindole **2h** also gave the corresponding coupling products in near quantitative yields. The exact structures of **3ag** and **3ah** were successfully confirmed by X-ray crystallographic analysis (Figure 1).



Scheme 2 The scope of cross dehydrogenative coupling of **1a** with arenes **2**.

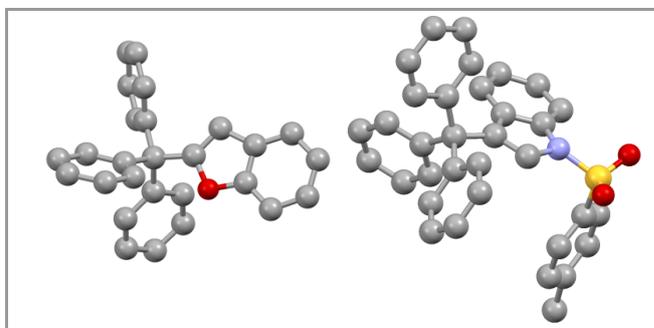
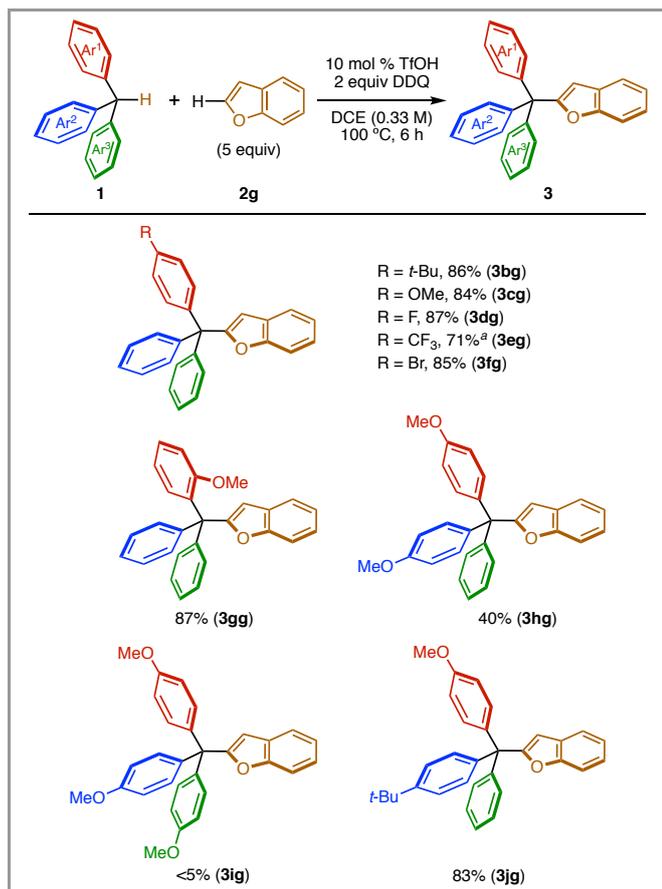


Figure 1 X-ray crystal structure of **3ag** and **3ah** (H atoms have been omitted for clarity).

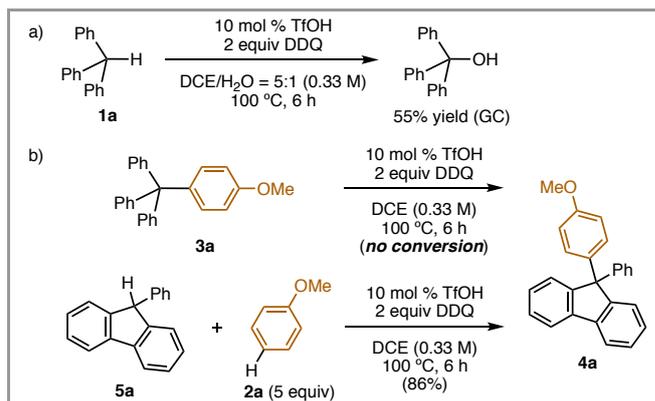
Next, we performed the reactions of various triarylmethanes (**1**) using **2g** as the coupling partner (Scheme 3). Triarylmethanes bearing *p*-*t*-butyl (**1b**), *p*-methoxy (**1c**), and *p*-fluoro (**1d**) groups were reacted to give the corresponding mono-substituted tetraphenylmethanes in good yields. The electron-deficient triarylmethane bearing *p*-CF₃ group (**1e**) also afforded the desired product **3eg** in moderate yield by prolonged reaction time. Furthermore, a *p*-bromo substituent (**1f**) was well tolerated, which will be beneficial for further transformations and is typically not compatible with metal-catalyzed cross-coupling reactions. The reaction of substrate **1g** having a bulky *o*-methoxy group proceeded with good yield giving product **3gg**. Bis(*p*-methoxyphenyl) phenylmethane **1h** and tris(*p*-methoxyphenyl)methane **1i** reacted with lower yields than **1c**, suggesting that stabilization of the newly generated trityl cation by *p*-methoxy groups may decrease reactivity with arenes.¹³ Notably, unsymmetric and highly functionalized tetraphenylmethane **3jg** was obtained in good yield.



Scheme 3 The scope of cross dehydrogenative coupling of triarylmethanes **1** with benzofuran **2g**. ^a Reaction time was 13 h.

To understand the mechanism of this dehydrogenative coupling, several control experiments were conducted (Scheme 4). When the reaction of **1a** in DCE/H₂O was carried out in the absence of arenes, triphenylmethanol was obtained in 55% GC yield (Scheme 4a). This result is consistent with the production of a trityl cation intermediate, generated from triarylmethane in the presence of TfOH and DDQ. Additionally, byproduct **4a** was not observed under standard reaction conditions (Scheme 4b), thus the formation of **4a** through oxidative cyclization (Scholl reaction^{14,15}) of **3a** can be ruled out. Ohta *et al.* has reported the intermolecular Friedel-Crafts type cyclization of trityl cations promoted by TfOH to afford 9-phenylfluorene **5a** albeit in low yield.¹⁶ Considering the possibility of the formation of **4a** through the reaction of **5a** with **2a**, we examined this reaction independently. Byproduct **4a** was obtained in 86% yield, leading us to infer that trityl cation intermediate can be converted into **5** under acidic conditions, which then reacts in a dehydrogenative coupling with arenes.

From these experiments, the proposed catalytic cycle of the dehydrogenative coupling is shown in Figure 2. Triarylmethane **1** is reacted with DDQ, which is itself activated by catalytic amount of TfOH, to generate trityl cation intermediate **A**. Subsequently, **A** is reacted with arenes to provide the desired tetraarylmethanes **3** in a Friedel-Crafts fashion along with the regeneration of TfOH. As a minor reaction pathway, the formation of 9-arylfluorene **5** from **A** followed by dehydrogenative coupling with arenes gives 9,9-diarylfluorene **4**.



Scheme 4 Control experiments

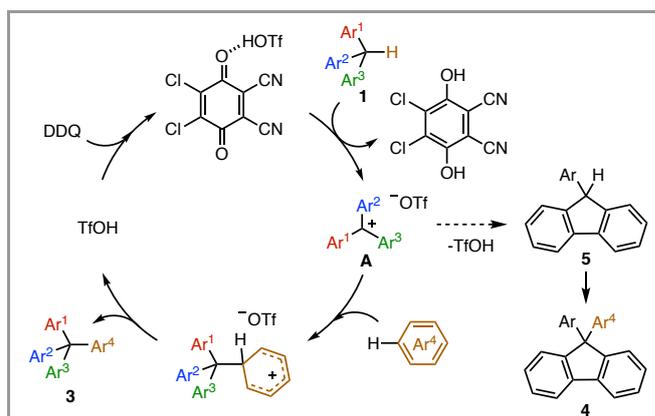


Figure 2 Proposed catalytic cycle for the cross dehydrogenative coupling.

In summary, we have described a new type of cross dehydrogenative coupling of triarylmethanes with arenes under oxidative condition. A wide range of tetraarylmethane derivatives can be easily prepared in good yields by this simple protocol. Notably, this method, combined with our previously reported methods for the synthesis of triarylmethanes results in a modular and straightforward route toward functionalized tetraarylmethanes, which represent useful starting points to develop new highly arylated organic materials. Further investigations toward the development of new synthetic methodology for multiply-arylated structures are ongoing in our laboratory.

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- (17) **Procedure for Cross Dehydrogenative Coupling of Triphenylmethane 1a with Anisole 2a.**
A 10-mL sealable reaction tube equipped with a magnetic stirring bar and a septum was evacuated, flame-dried under vacuum, cooled to room temperature and backfilled with Ar. The reaction tube was charged with triphenylmethane **1a** (24.4 mg, 0.1 mmol) and DDQ (45.4 mg, 0.2 mmol, 2 equiv) under a constant stream of argon. The mixture was evacuated under vacuum for 5 min and refilled with argon. This cycle was repeated two more times. DCE (0.3 mL), TfOH (0.9 μ L, 0.01 mmol, 10 mol %), and anisole **2a** (51 μ L, 0.5 mmol, 5 equiv) were added, and the vessel was sealed. The mixture was stirred at 100 °C for 6 h. After cooling to room temperature, EtOAc (~5 mL) was added and the solution was passed through a pad of Celite with copious washings with EtOAc. The solvent was evaporated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (hexane:EtOAc = 50:1) to afford (4-methoxyphenyl)triphenylmethane **3aa** (25.9 mg, 74% yield) as a white solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.78 (s, 3H), 6.80 (dm, J = 9.2 Hz, 2H), 6.80 (dm, J = 9.2 Hz, 2H), 7.16–7.26 (m, 15H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 55.2, 64.3, 112.7, 125.8, 127.4, 131.1, 132.2, 139.0, 147.0, 157.5. HRMS (DART) m/z calc. for $\text{C}_{26}\text{H}_{22}\text{O}$ [M] $^+$: 350.1671; found 350.1663.

