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

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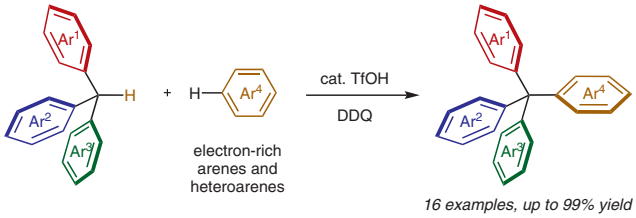
Dedicated to Professor Victor Snieckus, colleague, mentor, and friend on the occasion of his 80th birthday.



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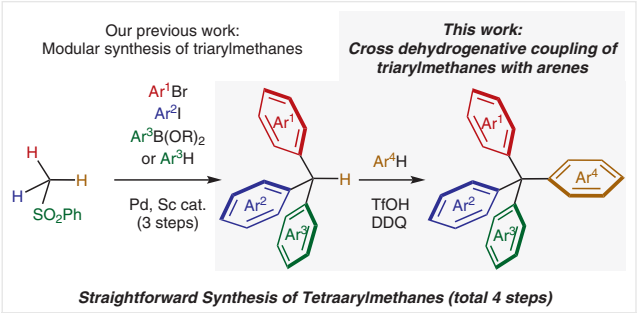
Abstract The formal cross-dehydrogenative coupling of triarylmethanes with arenes promoted by triflic acid and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone is described. This method provides a variety of tetraarylmethane derivatives in good to excellent yields from triarylmethanes that can be readily prepared by our previous methods. Control experiments suggest a possible catalytic cycle involving the generation of a trityl cation intermediate followed by nucleophilic addition of the arene.

Key words cross-coupling, dehydrogenation, tetraarylmethanes, triarylmethanes, arylation, organocatalysis

Polyarylated 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 toward tetraarylmethanes, which show unique chemical and physical properties as functionalized organic materials,[3] are still based on classical methods. For example, Friedel–Crafts arylations of triarylmethanol[4] or trityl chloride[5] with some electron-rich arenes or 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 nonsymmetric, tetraarylmethanes are still needed.

Our group has developed 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 three steps through either Pd- or Sc-catalyzed sequential arylations (Scheme 1).



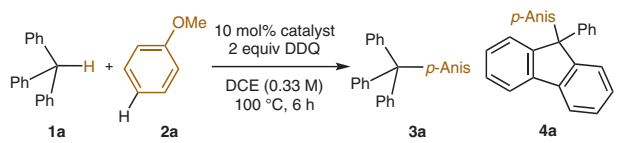
Scheme 1 The cross-dehydrogenative coupling of triarymethanes with electron-rich arenes.

We saw the next challenge as expanding our sequential arylation strategy to permit the concise synthesis of tetraarylmethanes by arylating the remaining C(sp^3)–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 a C–C bond from two different C–H bonds.[10] We envisioned that abstracting the benzylic C–H bond of triarylmethanes with an oxidant might generate reactive trityl cation intermediates that would subsequently react with nucleophilic arenes to afford tetraarylmethanes.[11] Here, we describe the cross-dehydrogenative

coupling of triarylmethanes with electron-rich arenes using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant (Scheme 1).[12]

Our initial studies focused on the use of triphenylmethane (**1a**) and anisole (**2a**) as model substrates for the formal cross-dehydrogenative coupling (Table 1). The reaction in the presence of DDQ alone gave 1-methoxy-4-tritylbenzene (**3a**) in only 10% yield (Table 1, entry 1). Inspired by previous reports on the activation of DDQ by the addition of acids,[13] several acid catalysts were screened. The addition of TFA, $BF_3{\cdot}Et_2O$, or H_2SO_4 led to increased product yields; however, the unexpected byproduct 9-(4-methoxyphenyl)-9-phenyl-9*H*-fluorene (**4a**) was also formed (entries 2–4). Triflate metal salts such as $Cu(OTf)_2$ or $Sc(OTf)_3$ improved the yield of product **3a** (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).

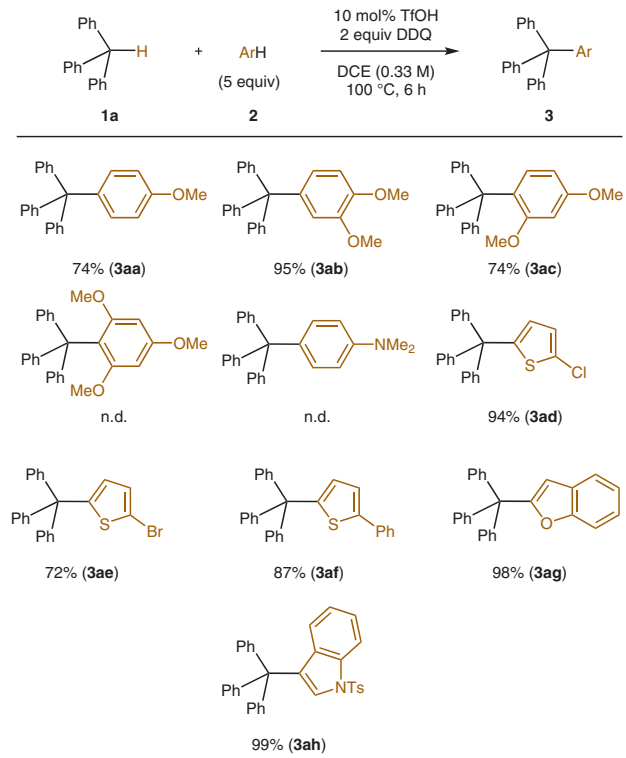
Table 1 Optimization of the Cross-Dehydrogenative Coupling of Triphenylmethane (**1a**) with Anisole (**2a**)[a]



Entry	Catalyst	Yield (%) of **3a**[b]	Yield (%) of **4a**[b]
1	–	10	<1
2	TFA	14	8
3	$BF_3{\cdot}Et_2O$	28	1
4	H_2SO_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] Yield by GC with dodecane as internal standard.
[c] Isolated yield.
[d] **2a** (3 equiv).
[e] DDQ (1 equiv).
[f] At 80 °C.

With the optimized conditions in hand, we examined the scope of the dehydrogenative coupling with regard to the arene (Scheme 2). The reaction with 1,2-dimethoxybenzene (**2b**) gave the corresponding product **3ab** in 95% yield, whereas 1,3-dimethoxybenzene (**2c**) gave a slightly decreased yield of **3ac**, 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 hetaromatics were well-tolerated. 2-Substituted thiophenes **2d–f** reacted in high yield regioselectively at the 5-position. Benzofuran (**2g**) and *N*-tosylindole (**2h**) also gave the corresponding coupling products **3ag** and **3ah** in nearly quantitative yields.



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

The structures of **3ag** and **3ah** were successfully confirmed by X-ray crystallographic analysis (Figure 1)[14]

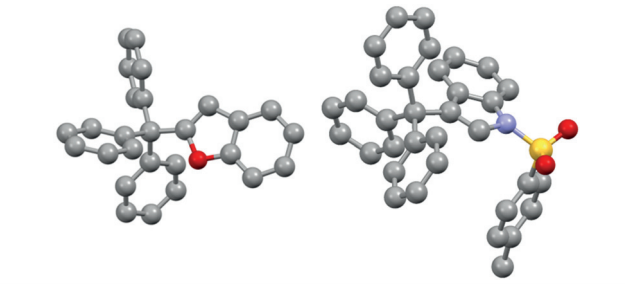


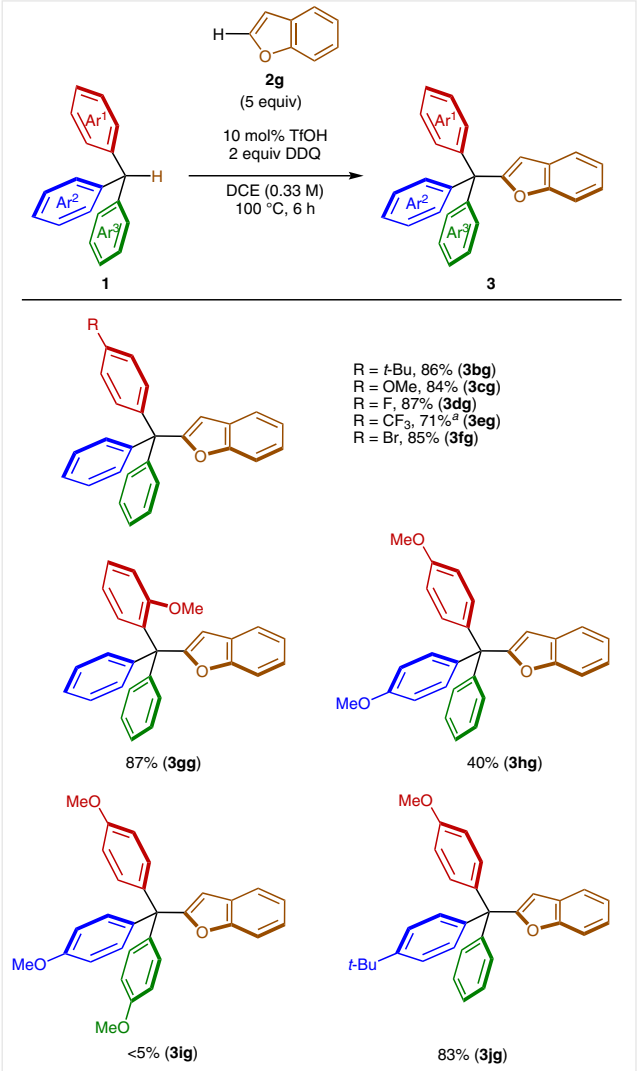
Figure 1 X-ray crystal structure of **3ag** and **3ah** (H atoms have been omitted for clarity.)

Next, we performed the reactions of various triarylmethanes **1** using 1-benzofuran (**2g**) as the coupling partner (Scheme 3). Triarylmethanes bearing 4-*tert*-butyl (**1b**), 4-methoxy (**1c**), or 4-fluoro groups (**1d**) gave the corresponding monosubstituted tetraphenylmethanes **3bg–dg** in good yields. The electron-deficient triarylmethane bearing a 4-CF_3 group (**1e**) also afforded the desired product **3eg** in moderate yield on prolonging the reaction time to 13 hours. Furthermore, a 4-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 2-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 4-methoxy groups might decrease their reactivity with arenes.[13] Notably, the nonsymmetric and highly functionalized tetrarylmethane **3jg** was obtained in good yield.

To understand the mechanism of this dehydrogenative coupling, several control experiments were conducted (Scheme 4). When the reaction of **1a** in DCE–H_2O was carried out in the absence of arenes, triphenylmethanol was obtained in 55% GC yield (Scheme 4, a). 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); therefore, the formation of **4a** through oxidative cyclization (Scholl reaction)[15,16] of **3a** can be ruled out. Ohta et al. reported the intermolecular Friedel–Crafts-type cyclization of trityl cations promoted by TfOH to afford 9-phenyl-9*H*-fluorene (**5a**), albeit in low yield.[17] To examine 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 the 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 for the dehydrogenative coupling is shown in Scheme 5. Triarylmethane **1** reacts with DDQ, which is itself activated by a catalytic amount of TfOH, to generate trityl cation intermediate **A**. Subsequently, **A** reacts with the arene to provide the desired tetraarylmethane **3** in a Friedel–Crafts fashion, along with regeneration of TfOH. As a minor reaction pathway, the formation of 9-arylfluorene **5** from **A** followed by dehydrogenative coupling with an arene gives the 9,9-diarylfluorene **4**.

In summary, we have described a new type of cross-dehydrogenative coupling of triarylmethanes with arenes under oxidative condition.[18] 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 to functionalized tetraarylmethanes, which represent useful starting points to develop new highly arylated organic materials. Further investigations toward the development of new methods for synthesizing polyarylated structures are ongoing in our laboratory.



Scheme 3 The scope of cross-dehydrogenative couplings of triarylmethanes **1** with benzofuran **2g**.
[a] Reaction time 13 h.

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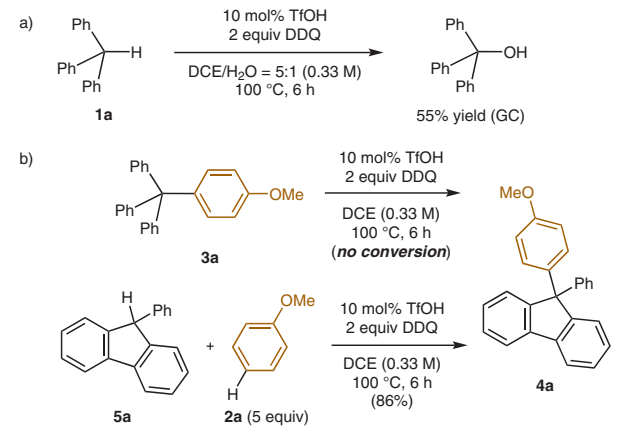
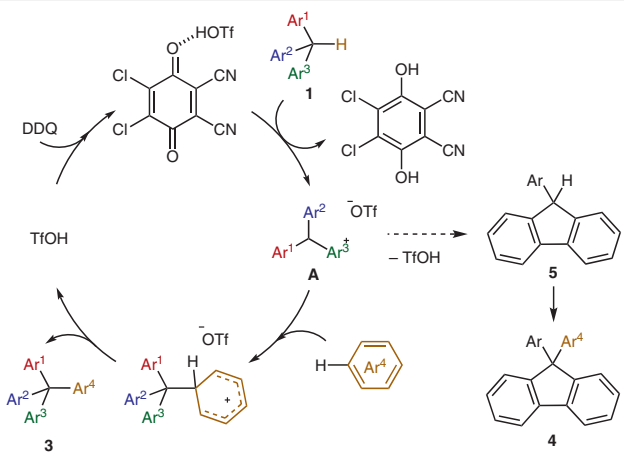


Scheme 4 Control experiments



Scheme 5 Proposed catalytic cycle for the cross-dehydrogenative coupling

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588563.

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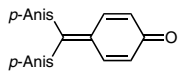

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Figure 2

(14) CCDC 1553011 and 1553012 contains the supplementary crystallographic data for compounds **3ag** and **3ah**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(18) **1-Methoxy-4-tritylbenzene (3aa); Typical Procedure**
A 10-mL sealable reaction tube equipped with a magnetic stirring bar and a septum was evacuated, flame-dried under vacuum, cooled to r.t., and backfilled with argon. The tube was then charged with Ph_3CH (**1a**; 24.4 mg, 0.1 mmol) and DDQ (45.4 mg, 0.2 mmol, 2 equiv) under a constant stream of argon. The tub was evacuated for 5 min and refilled with argon. This cycle was repeated twice more. DCE (0.3 mL), TfOH (0.9 µL, 0.01 mmol, 10 mol%), and anisole **2a** (51 µL, 0.5 mmol, 5 equiv) were added, and the vessel was sealed. The mixture was stirred at 100 °C for 6 h then cooled to r.t. 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 to give a crude product that was purified by preparative TLC (hexane–EtOAc, 50:1) to give a white solid; yield: 25.9 mg (74%).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 6.80 (dm, *J* = 9.2 Hz, 2 H), 6.80 (dm, *J* = 9.2 Hz, 2 H), 7.16–7.26 (m, 15 H). ^{13}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* calcd for $C_{26}H_{22}O$: 350.1671; found: 350.1663.