M. Nambo et al.

Letter

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

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Masakazu Nambo*^a Jacky C.-H. Yim^a Kevin G. Fowler^a Cathleen M. Crudden*a,b

^a Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Chikusa, Nagoya, 464-8602, Japan mnambo@itbm.naqoya-u.ac.jp

^b Queen's University, Department of Chemistry, Chernoff Hall, Kingston, Ontario, K7L 3N6, Canada

cruddenc@chem.queensu.ca

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 triarylmethanol⁴ or trityl chloride⁵ 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 Nicatalyzed 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 Pdor 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(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 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 M. Nambo et al.

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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 triphenvlmethane (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, BF₂·Et₂O, or H₂SO₄ led to increased product yields; however, the unexpected byproduct 9-(4-methoxyphenyl)-9-phenyl-9H-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).



Ph Ph Ph Ph 1a	+ + H 2a	equiv DDQ CE (0.33 M) 100 °C, 6 h Bh Bh Bh Bh Bh Bh Bh Bh Bh Bh Bh Bh Bh	p-Anis Ph his Ph 4a
Entry	Catalyst	Yield (%) of $\mathbf{3a}^{\mathrm{b}}$	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.

° DDQ (1 equiv). ^f At 80 °C

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-electronrich 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.)

^c Isolated yield.

^d **2a** (3 equiv).

Syn lett

M. Nambo et al.

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-CF₃ 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-H₂O was carried out in the absence of arenes, triphenvlmethanol 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-9H-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



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

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.

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Syn lett

M. Nambo et al.



Scheme 4 Control experiments



Scheme 5 Proposed catalytic cycle for the cross-dehydrogenative coupling

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Supporting Information

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M. Nambo et al.

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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 Ph₃CH (**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 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 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%).

¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (150 MHz, CDCl₃): 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 C₂₆H₂₂O: 350.1671; found: 350.1663.