Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/d0ob00551g

δ-Cyano substituted *para*-quinone methides enable access to unsymmetric tri- and tetraarylmethanes containing all-carbon quaternary stereocenters†

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Received 14th March 2020,
Accepted 17th April 2020

DOI: 10.1039/d0ob00551g

rsc.li/obc

para-Quinone methides bearing an electron-withdrawing cyano group at the exocyclic methylene δ-position were identified as valuable 1,6-conjugate addition building blocks for acyclic all-carbon quaternary stereocenter construction. A wide variety of electron-rich arenes as nucleophiles were tolerated, effectively furnishing diverse unsymmetrical triarylmethanes bearing all-carbon quaternary stereocenters. The robust transformable abilities of the cyano group provide a platform to access other valuable functional group-containing unsymmetrical tri- and tetraarylmethanes that are otherwise difficult to be prepared. Computational studies supported the hypothesis that the cyano group at the δ-position tunes the molecular electron-density distribution, and the stability of *para*-quinone methides is enhanced by lowering their polymerizability.

Introduction

Because of the intrinsic electrophilic property, *para*-quinone methides (*p*-QMs) have emerged as attractive and widely used building blocks in a variety of valuable organic transformations, particularly 1,6-conjugate addition reactions.[1–3] However, owing to their general instability towards polymerizability,[4] current studies suffered from significant structural limitations of *p*-QMs (Fig. 1A).[2,3] First, the existing methods typically focused on *p*-QMs bearing a mono-aryl group at the δ-position for tertiary stereocenter formation. Second, two bulky α-substituents (*e.g.*, ^{t}Bu) were prerequisite. The state of the art of structural limitations of *p*-QMs seriously hampers the advance of the promising strategy in all-carbon quaternary stereocenter construction. Accordingly, Sun developed an elegant protocol to *in situ* generate δ-electron-donating group (EDG) substituted *p*-QM intermediates through Brønsted acid catalyzed dehydration of *p*-hydroxybenzyl alcohols (Fig. 1B).[5] However, *p*-QMs bearing an electron-withdrawing group (EWG) at the δ-position might not be accessible through such a protocol. Our group adopted an oxidative C–H cleavage strategy to

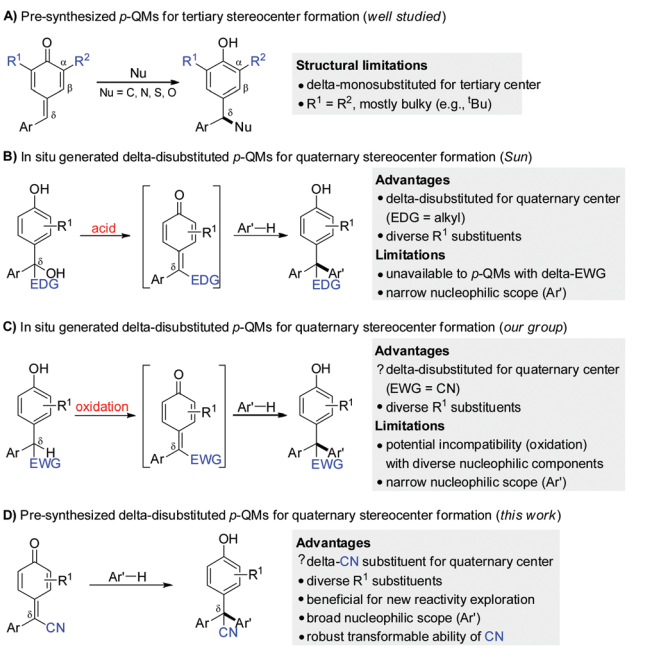

Fig. 1 Overview of the scope of *p*-QMs in 1,6-conjugate addition reactions.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ob00551g

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address such a limitation (Fig. 1C).[6] However, diverse carbon nucleophiles are not compatible with the strongly oxidative conditions, thus limiting the scope of nucleophilic components. Using pre-prepared, isolable, and storable δ,δ-disubstituted *p*-QMs as substrates can avoid the aforementioned incompatibility, and the nucleophilic component scope would be extremely expanded. We envisioned that installing an electron-withdrawing group at the exocyclic methylene δ-position would tune the molecular electron-density distribution, and the stability of the resulting *p*-QMs might be enhanced by lowering their polymerizability.[7] In light of the significance in modern pharmacology and robust transformable properties, a cyano group was placed at the δ-position for study (Fig. 1D).[8]

Triarylmethanes are privileged structure motifs in medicinal chemistry, materials science, and organic synthesis.[9] Construction of unsymmetrical triarylmethanes containing tertiary stereocenters has been extensively studied.[10] However, efficient preparation of unsymmetrical triarylmethanes bearing all-carbon quaternary stereocenters has remained underdeveloped.[11] Herein, we reported 1,6-conjugate addition of a variety of electron-rich arenes to pre-synthesized δ-CN-δ-aryl substituted *p*-QMs for preparation of diverse unsymmetrical triarylmethanes bearing all-carbon quaternary stereocenters (Fig. 1D). Further manipulation of the nitrile group provides access to a range of untouched, highly functionalized molecules of great interest. For example, unsymmetrical tetraarylmethanes, which are extraordinarily difficult to synthesize by the existing methods, can be readily prepared.[11a,b]

Results and discussion

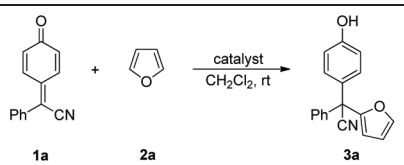
Initially, 1,6-conjugate addition of furan **2a** to δ-CN-δ-aryl disubstituted *p*-QM **1a** was selected as the model for optimization (Table 1). No reaction was observed in the absence of any catalyst (entry 1, Table 1). Brønsted acid additives such as AcOH and diphenyl phosphate proved to be futile (entries 2 and 3, Table 1). An extensive investigation of Lewis acid additives revealed that when 10 mol% of $Bi(OTf)_3$ was used, the arylation of **1a** proceeded efficiently at rt in 0.25 h, providing the expected unsymmetrical triarylmethane **3a** in 93% yield (entries 4–8, Table 1).

With the optimized conditions in hand, the scope of the quinone part of *p*-QMs was investigated (Scheme 1). *p*-QMs bearing two small substituents at the α-positions were well tolerated, as demonstrated by the formation of triarylmethane **3b** in 90% yield. α-Mono-substituted *p*-QMs **1c–1e** bearing diverse electron-donating and electron-withdrawing moieties were also suitable substrates, and the respective products **3c–3e** were isolated in 88%–92% yields.

The scope of δ-aryl substituents was next explored (Scheme 2). In general, *p*-QMs **4a–4k** bearing a wide range of electronically varied aryl moieties with different substitution patterns at the δ-position were well compatible with the mild conditions, furnishing the respective triarylmethanes **5a–5k** in 86–94% yields. Polyarene naphthalene substituted **4l** and **4m** also proved to be suitable coupling partners.

The scope of nucleophilic arene components was then evaluated (Scheme 3). A broad range of electron-rich heteroarenes proved to be well compatible with the mild conditions (Scheme 3A). Substituted furans were suitable coupling partners, as demonstrated by the generation of unsymmetrical triarylmethanes **7a** and **7b** with high efficiency. Thiophenes (**6c** and **6d**) together with pyrroles (**7e** and **7f**) and indole **7g** were also competent nucleophiles for the process. Phenols and anilines participated in the 1,6-conjugate addition reactions smoothly, affording the corresponding products **7h–7m** in 85–95% yields (Scheme 3B). Anisole derivatives (**6n** and **6o**) were also found to be well tolerated, though a slightly higher temperature was required (Scheme 3C). Electron-deficient arenes proved to be futile nucleophilic components for the method. While the scope of carbon nucleophiles was not

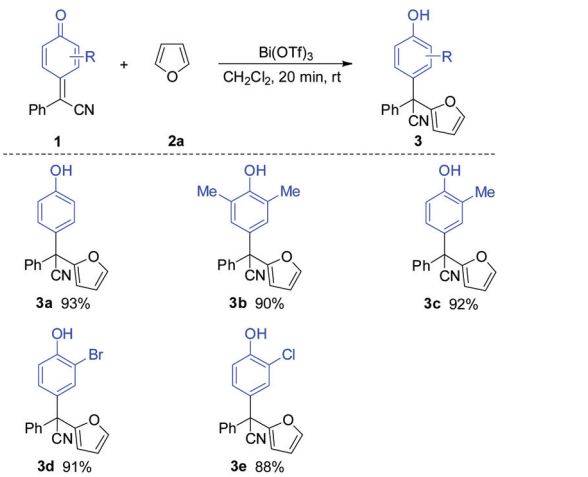
Table 1 Reaction condition optimization[a]



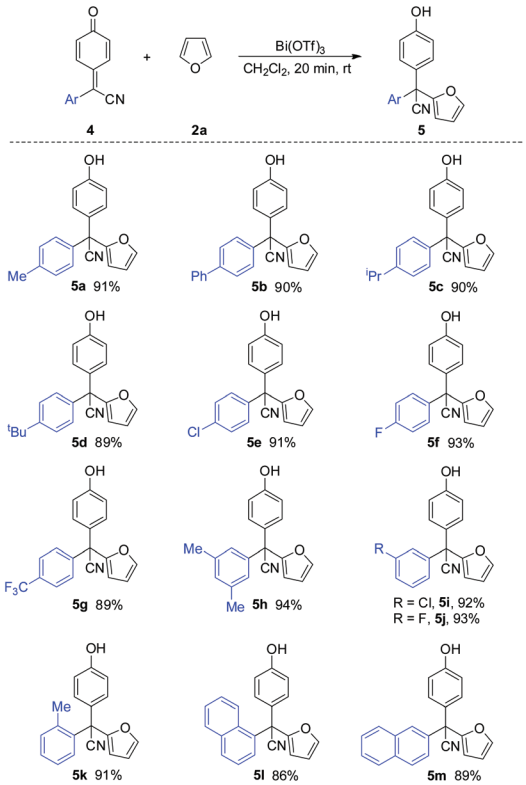
1a 2a 3a

Entry	Catalyst	Time (h)	Yield[b] (%)
1	—	24	<5
2	AcOH	24	<5
3	Diphenyl phosphate	24	<5
4	$Mg(OTf)_2$	24	<5
5	$Cu(OTf)_2$	24	10
6	$Sc(OTf)_3$	24	27
7	AgOTf	24	62
8	$Bi(OTf)_3$	0.25	93

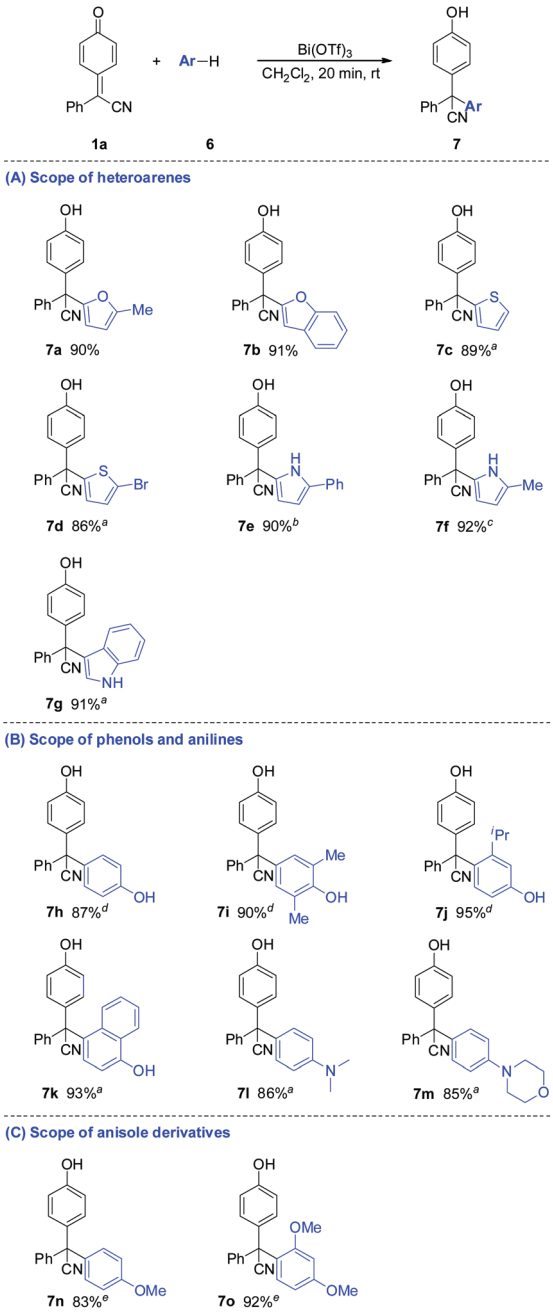
[a] Reaction conditions: a mixture of **1a** (0.1 mmol), **2a** (0.12 mmol), and catalyst (10 mol%) in CH_2Cl_2 (2 mL) at rt. [b] Yield of the isolated product. Tf = trifluoromethanesulfonyl.



Scheme 1 Scope of substituent patterns on the quinone moiety.



Scheme 2 Scope of δ-aryl moieties.

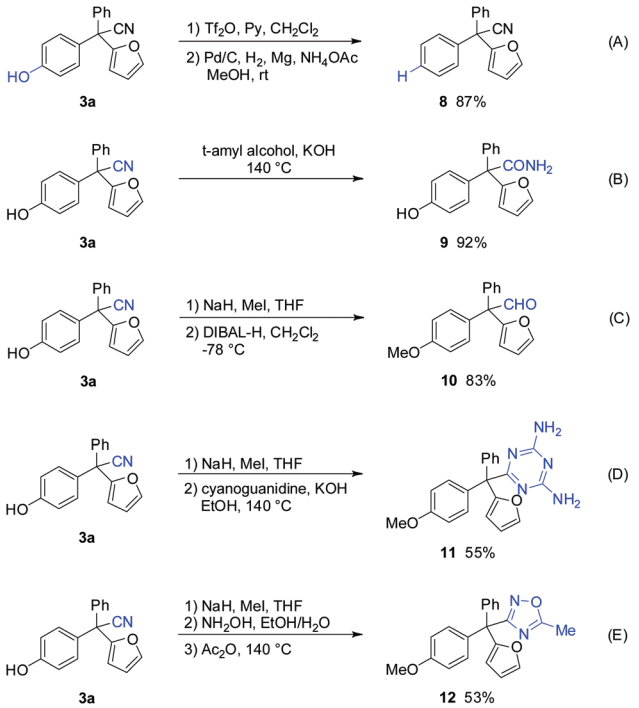


Scheme 3 Scope of nucleophilic arene components. [a] Reaction for 2 h. [b] Reaction for 12 h. [c] Reaction for 4 h. [d] Reaction for 1 h. [e] Reaction in $ClCH_2CH_2Cl$ at 70 °C for 2 h.

thoroughly examined, these results provide a proof-of-concept for the generality and modularity of δ-CN-δ-aryl disubstituted *p*-QMs as valuable 1,6-conjugate addition building blocks for constructing unsymmetric triarylmethanes containing all-carbon quaternary stereocenters.

The synthetic utilities of the method were next studied (Scheme 4). The phenolic hydroxyl group in **5g** was removed through triflation followed by Pd-catalyzed hydrogenation, affording **8** in 87% yield over two steps (Scheme 4A). The nitrile moiety can be converted into a range of valuable functional groups. For examples, **3a** underwent basic hydrolysis, giving triarylacetamide **9** in 92% yield (Scheme 4B). Moreover, the nitrile moiety in **3a** was reduced by DIBAl-H providing triarylated acetaldehyde **10** in 83% yield (Scheme 4C). Finally, the cyano group can be transformed into heteroaromatics, leading to tetraarylmethanes **11** and **12** that are otherwise difficult to be prepared (Schemes 4D and E).

δ-Aryl mono-substituted *p*-QM **1f** without any substituent on the quinone moiety is an unstable species and cannot be isolated (Fig. 2A). Instead, installing a cyano group into the δ-position of **1f** provides disubstituted *p*-QM **1a**, which has proved to be a stable, isolable, and storable species. To examine the electronic structures and their effects on the stability of the respective *p*-QMs **1f** and **1a**, we performed electrostatic potential analyses (Fig. 2B) using the Multiwfn program and natural bond orbital (NBO) analyses (Fig. 2C) using the NBO 3.1 version of Gaussian 09 at the B3LYP/6-311+g** level. The obtained molecular electrostatic potential diagrams suggested obvious differences in the electron densities around the *p*-QM substructures of **1f** and **1a** (Fig. 2B). The NBO analyses further certify the variance of atomic charges on *p*-QM motifs (Fig. 2C). Given that the instability of **1f** mainly originated from self-polymerization, several variances of partial atomic charges in **1a** by introducing an electron-withdrawing cyano group into the δ-position of **1f** merit further comment. First, the anionic property of the nucleophilic carbonyl oxygen



Scheme 4 Synthetic utilities.

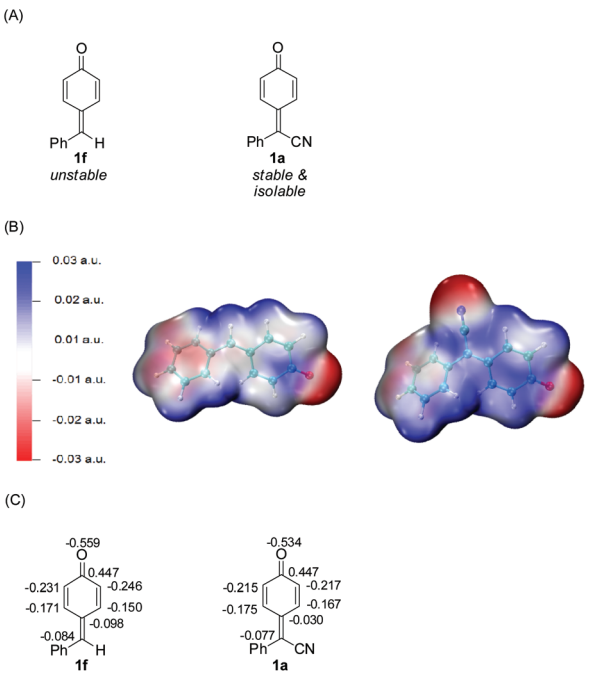


Fig. 2 (A) Two representative *p*-QMs for comparison. (B) Molecular electrostatic potential diagrams of *p*-QMs **1f** and **1a**. (C) Calculated NBO charges (in *e*) for *p*-QMs **1f** and **1a**.

in **1a** significantly diminished. Second, the cationic properties of two electrophilic β-carbons in **1a** also diminished, though no change was observed on the carbonyl carbon. Third, while the cationic property of the electrophilic δ-carbon in **1a** was somewhat enhanced, the increased steric hindrance at the δ-position might counteract the influence on electrophilicity. The calculated data support our initial hypothesis that installing an electron-withdrawing cyano group at the exocyclic methylene δ-position would tune the molecular electron-density distribution, and the thermal stability of the resulting *p*-QMs would be enhanced by lowering their polymerizability.

Conclusions

In summary, placing an electron-withdrawing cyano group into the exocyclic methylene δ-position of *p*-QMs proved to be beneficial for enhancing their stability, and thus the scope of these valuable building blocks for 1,6-conjugate addition reactions was significantly expanded. By employing pre-synthesized δ-CN-δ-aryl substituted *p*-QMs as substrates, a broad range of electron-rich arenes participated in the arylation process, providing a wide array of unsymmetrical triarylmethanes bearing all-carbon quaternary stereocenters with high efficiency. The robust transformable properties of the nitrile moiety enable facile access to other valuable functional group-containing unsymmetrical tri- and tetraarylmethanes that are otherwise difficult to be prepared. Computational studies supported the hypothesis that installing an electron-withdrawing cyano group at the exocyclic methylene δ-position would tune the molecular electron-density distribution, and the thermal stability of the resulting *p*-QMs would be enhanced by lowering their polymerizability. Ongoing studies focus on exploring the reactivities of pre-synthesized *p*-QMs bearing other valuable EWGs at the δ-position and the corresponding asymmetric variants.

Experimental

General procedure for 1,6-conjugate arylation of pre-synthesized δ-CN-δ-aryl substituted *p*-QMs with electron-rich arenes (Schemes 1–3)

To a solution of **1** or **4** (0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL) were successively added $Bi(OTf)_3$ (0.01 mmol, 0.1 equiv.) and arene **2** or **6** (0.12 mmol, 1.2 equiv.) at rt. The mixture was stirred at the same temperature for 20 min. Then the mixture was concentrated and purified by flash column chromatography (petroleum ether/ethyl acetate) to give the desired triarylmethane **3**, **5**, or **7** in good yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Science Foundation of China (21722204, 21971148).

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