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LETTER

Oxidative functionalization of benzylic C–H bonds by DDQ†

Victor S. Batista,* Robert H. Crabtree,* Steven J. Konezny, Oana R. Luca and Jeremy M. Praetorius

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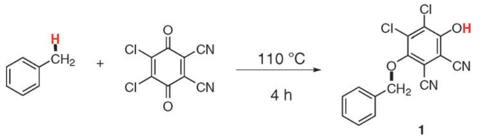
C–H activation of the methyl group of toluene and related $ArCH_3$ derivatives by 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) gives insertion products, $ArCH_2O[C_6Cl_2(CN)_2]OH$ *via* a rate-determining hydride abstraction by DDQ. The resulting benzylic ether can undergo reactions with phosphines to give benzylic phosphonium salts (Wittig reagents) and with phosphites to give phosphonate esters (Horner–Wadsworth–Emmons reagents).

High potential quinones, such as 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ), are powerful oxidants capable of performing a wide variety of organic transformations. DDQ is a highly oxidizing quinone that is indefinitely stable in dry conditions. It is widely employed for dehydrogenation of organic molecules to form aromatic and α,β-unsaturated carbonyls; and the oxidation of activated methylene and hydroxy groups to carbonyl compounds.

Our group has recently investigated DDQ as an electrocatalyst for the dehydrogenation of secondary amines and *N*-containing heterocycles,[1] with the goal of using the heterocycles as liquid phase carriers for storing $n(H^+ + e^-)$ in a virtual hydrogen storage scheme that avoids the need for free H_2 at any stage.[2] We demonstrated that the active quinone could be electrochemically regenerated after the dehydrogenation of *N*-phenylbenzylamine, allowing near quantitative yield of the corresponding imine with only catalytic amounts of DDQ. Although the regeneration of DDQ occurs at high potential (~0.9 V), this provides precedent for the use of organic oxidants as organocatalysts in electrochemical applications.

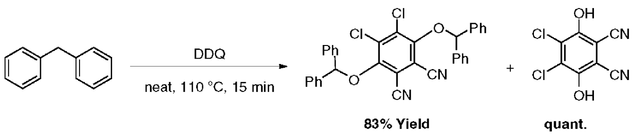
While screening the stoichiometric reaction of DDQ with other potential energy carriers, a highly coloured material precipitated from reactions run in refluxing toluene. A control reaction in the absence of the heterocycle but still in toluene as solvent gave the same dark colour and highly coloured precipitate. After sixteen hours at reflux, the dark precipitate was collected by filtration and washed with diethyl ether to give **1** as a pale purple solid in 78% yield (eqn (1)). Crystallization of this material yielded light purple crystals suitable for X-ray crystallography,† which showed that the product results from the oxidative insertion of DDQ into a $C(sp^3)$-H bond of toluene (Fig. 1). Activation of secondary benzylic and vinylic positions by DDQ has previously been reported and has been a topic of much interest in C–C bond forming reactions.[3,4]



(1)

The C–C bond lengths of the hydroquinone fragment of **1a** indicate that DDQ has undergone a complete two-electron reduction from the quinone to the arene form upon insertion into the C–H bond of toluene.

The oxidation of benzylic C–H bonds by DDQ to give quinol ethers, such as **1a**, has been reported previously, but only with substrates that were considerably more activated,[5–7] *e.g.* 3-(*p*-methoxyphenyl)propene.[8] Furthermore, reactions with these activated substrates give significant amounts of 2 : 1 (substrate:DDQ) products, $ArCH_2O[C_6Cl_2(CN)_2]OCH_2Ar$, whereas toluene only gives **1a**.[9] For example, reaction of DDQ with diphenylmethane gave $(Ph_2CH)O[C_6Cl_2(CN)_2]O(CHPh_2)$ in 82% yield, along with a stoichiometric amount of $HO(C_6Cl_2(CN)_2)OH$, as the only products (eqn (2)).[10]



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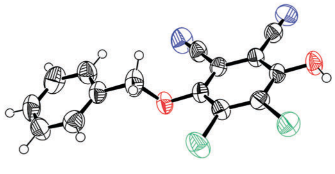

Fig. 1 ORTEP diagram of **1a** (50% probability elipsoids): one of the two independent molecules in the asymmetric unit shown.

Yale Chemistry Department, 225 Prospect St., New Haven, CT 06511, USA. E-mail: victor.batista@yale.edu, robert.crabtree@yale.edu; Fax: +1 203 432 6144; Tel: +1 203 432 6672, +1 203 432 3915

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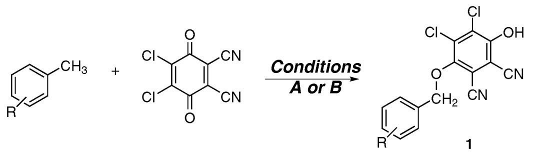


(3)

Table 1 Reaction of arylmethanes with DDQ

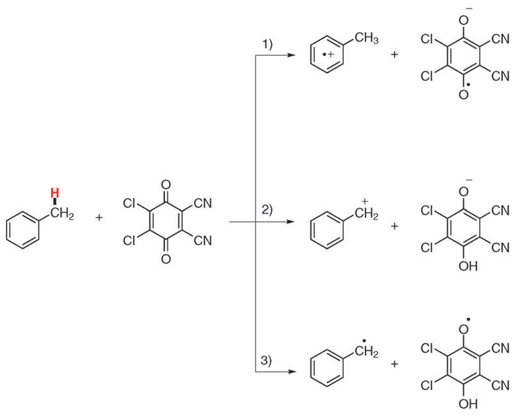
Entry	Substrate	Conditions[a]	Time (h)	% Yield[b]
1	*p*-H (**1a**)	A	16	78
2	*p*-Ph (**1b**)	B	16	67
3	*p*-Cl (**1c**)	A	16	65
4	*p*-Cl (**1c**)	B	22	60
5	*p*-tBu (**1d**)	A	18	81
6	*p*-F (**1e**)	B	24	40
7	*m*-F (**1f**)	A	18	68

[a] A: neat 2 mmol DDQ in 2 mL of $ArCH_3$, 110 °C, Ar; B: 1.5 equiv. of DDQ, 0.4 M $ArCH_3$ in PhCl, 140 °C in a sealed tube. [b] Isolated yields.

The scope of the reaction was explored with a series of substituted toluenes featuring electron-withdrawing or weakly electron-donating groups to give the analogous products (Table 1). For substrates available on large scale, the reaction could be performed in neat reactant giving the analogous C–H insertion products after precipitation with diethyl ether. In the case of substrates conveniently available in only modest quantities, such as 4-fluorotoluene, the same reactions occurred at 140 °C in PhCl. All reactions gave the expected products and were obtained in moderate to good yields in all cases but took somewhat longer with substrates having more electron withdrawing substituents.

Mechanistic investigations

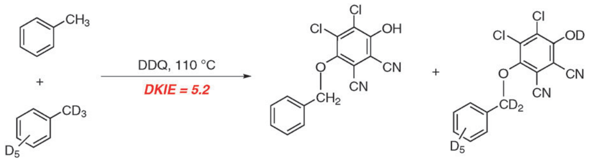
An experimental-computational combined study gave insight into the mechanism of benzylic C–H activation by DDQ. For the C–H activation, the three most plausible scenarios (Scheme 1) are: (1) Electron transfer from the arylmethane to DDQ to generate the radical cation of toluene and the radical anion of DDQ, followed by hydrogen atom transfer to generate the tolyl cation and $[DDQ\text{-}H]^-$ in a two-step process; (2) Hydride transfer from toluene to DDQ generating the tolyl cation and $[DDQ\text{-}H]^-$ in a single step; (3) Hydrogen atom transfer from toluene to DDQ generating the tolyl radical and $[DDQ\text{-}H]^\bullet$ in a single step.



Scheme 1 Possible mechanistic pathways for the C–H abstraction from toluene by DDQ.

From competition experiments, the linear free energy relationship and the deuterium kinetic isotope effect (DKIE) were both determined in order to help differentiate the three plausible mechanisms. The linear free energy relationship was determined by competition experiments: toluene and the other arylmethane were both dissolved in deuterated tetrachloroethane (d_2-TCE) along with 0.1 equiv. of DDQ and heated to 105 °C for 16 h after which time the product ratio was determined from ^1H NMR data. The results of the competition experiments obey a good linear correlation ($R^2 = 0.96$) with the substituent σ^+ values[11] and show a ρ^+ value of −3.60. The large, negative ρ^+ value indicates a significant positive charge buildup on the benzylic carbon in the rate-determining transition state.

To differentiate between a two-step mechanism involving electron transfer followed by transfer of the hydrogen atom from a single-step mechanism, the deuterium kinetic isotope effect of the reaction was investigated. A similar competition experiment was carried out comparing protiated and deuterated toluene, yielding a primary DKIE of 5.2 (eqn (4)).



(4)

This large, primary DKIE is strongly indicative of C–H bond breaking occurring during the rate-determining transition state as was previously observed by Floreancig and coworkers.[12] The primary DKIE combined with the large negative ρ^+ value is consistent with a one-step mechanism and more specifically rate-determining hydride abstraction from toluene by DDQ. There are, however, various radical mechanisms that show better correlation with σ^+ rather than σ values,[13,14] a fact that has been ascribed to the presence of a highly polar transition state.[15] The magnitude of the ρ^+ values observed in these instances is believed to be a function of the electronegativity difference between the substrate and the reactive species; in our case toluene and DDQ, respectively.

Thus, to differentiate between a hydride mechanism and a radical mechanism with a highly polar transition state, the reaction coordinate was investigated with DFT calculations of solution-phase free energies at the BH&H/6-311++G(d,p) level. The overall reaction is found to be exergonic, releasing 28.7 kcal/mol. Initially, as previously calculated for the dehydrogenation of *N*-phenylbenzylamine by DDQ,[1] toluene and DDQ form a charge transfer complex; in this instance leading to a stabilization of 0.7 kcal/mol. From this ground state, reaction coordinates corresponding to both hydrogen radical and hydride abstraction were calculated to determine both transition state energies and the ground state energies of the required intermediates.

Reaction to form the radical pair proceeds through a transition state that requires 36.7 kcal/mol. Conversely,

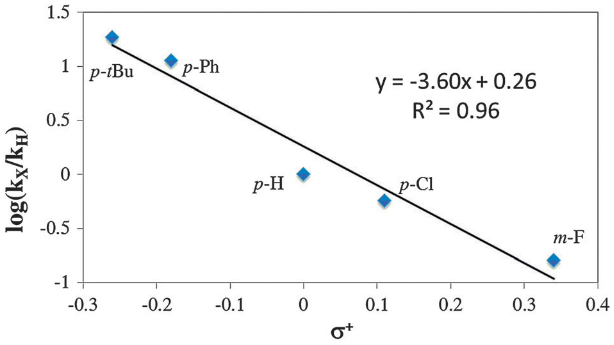


Fig. 2 Linear free energy relationship of the relative rates of reaction determined from competition experiments of toluene and substituted arylmethane with 0.1 equivalents of DDQ in d_2-TCE. The relationship is plotted as the log of product ratios from the competition reactions *versus* reported σ^+ constants for the arylmethane substituent employed in the competing substrate.

hydride abstraction to give an ion pair requires an input of only 24.5 kcal/mol and is clearly favoured over the radical mechanism by a $\Delta\Delta G^{\ddagger}$ of >12 kcal/mol (Fig. 2). Formation of the products from these two sets of intermediate pairs is likely a fast reaction of low barrier, limited only by reorganization of the two molecules to align the reactive carbon and oxygen atoms by a mutual rotation. We therefore conclude from our experimental and computational results that C–H activation of toluene and its derivatives most likely occurs through a hydride mechanism as depicted in Scheme 1 and Fig. 3.

Our mechanistic results are further corroborated by a previous report detailing the reaction of 1,1-disubstituted tetralins with high potential quinones to form the corresponding 1,2-substituted naphthalenes. For example, reaction of 1,1-dimethyltetralin with two equivalents of DDQ in refluxing toluene was reported to give 1,2-dimethylnapthalene in 84% yield (Scheme 2).[16] The skeletal rearrangement of 1,1-dimethyltetralin in this reaction implicates methyl migration in conjugated carbocation intermediates. It was also observed that similar molecules lacking benzylic C–H bonds, such as octahydrooctamethylanthracene, did not undergo dehydrogenation under analogous conditions.

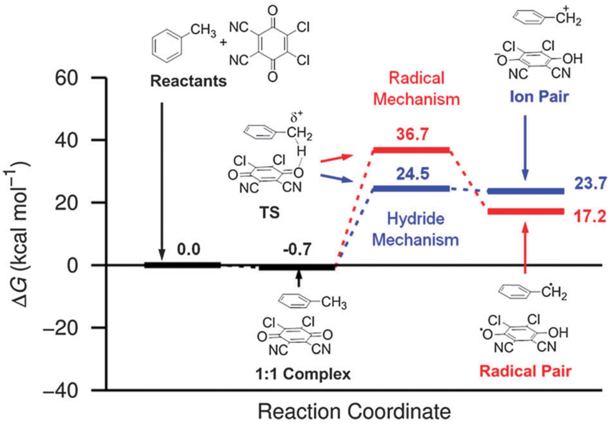
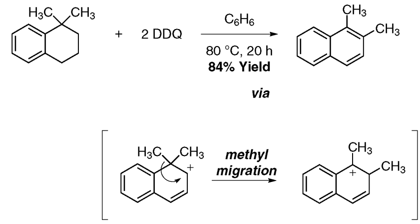


Fig. 3 Free energy diagram for the hydrogen abstraction from the methyl group of toluene by DDQ, with the radical pathway shown in red and the hydride pathway shown in blue.

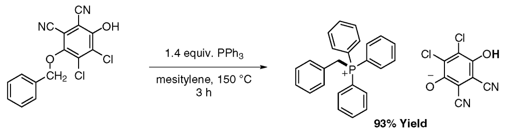


Scheme 2 The previously reported reaction of 1,1-dimethyltetralin with DDQ to form 1,2-dimethylnaphthalene and the cationic intermediates proposed to account for the observed rearrangement.

Nucleophilic displacement from $ArCH_2(DDQ)H$

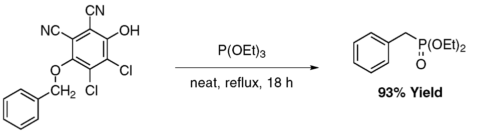
Given the extremely electron-withdrawing nature of the hydroquinone ring in the products we postulated that these groups would serve as satisfactory leaving groups in substitution reactions. Unfortunately, this same reasoning also makes the proton of the –OH of this molecule fairly acidic and thus only non-basic nucleophiles could be employed. To suit this restriction we investigated the reaction of **1a** with triphenylphosphine. The product of this reaction, benzyl(triphenyl)phosphonium salt, is a well-known reagent in the Wittig reaction for the synthesis of alkenes. Thus, alkenes could be accessed from aldehydes and arylmethanes in three steps.[17]

Triphenylphosphine and **1a** react in refluxing mesitylene to give the expected benzyl(triphenyl)phosphonium salt **2** in 93% yield (eqn (5)). The product is isolated as a precipitate from the reaction mixture, initially as a black solid, but following extraction from CH_2Cl_2 and recrystallization from acetone/diethyl ether is obtained as a light brown solid.



(5)

Using the same idea, Horner–Wadsworth–Emmons reagents, such as diethyl benzylphosphonate can also be prepared. This can be done in an analogous manner to preparation from benzyl bromide. **1a** reacts with triethylphosphite to give the phosphonate in 93% yield after purification (eqn (6)). These reagents undergo similar olefination reactions with aldehydes, generally with higher E/Z ratios than their phosphonium counterparts.



(6)

Conclusions

We have isolated benzylic ethers resulting from the oxidative C–H activation of arylmethanes by DDQ. These products were isolated for a number of relatively unactivated substrates. A combination of experimental and computational studies suggests that this C–H activation occurs through hydride abstraction from the benzylic methyl group by DDQ. Furthermore, we have demonstrated that the benzylic ether products can be reacted with phosphines to generate phosphonium reagents suitable for the Wittig reaction. We have now developed a synthetic pathway to generate β-substituted styrenes from arylmethane and aldehyde starting materials.

Acknowledgements

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