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N-Aryl Groups are Ubiquitous in Cross Dehydrogenative Couplings Because They Stabilize Reactive Intermediates

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Abstract: The mechanism of cross-dehydrogenative coupling (CDC) reactions has been examined by experimental and computational means. We have provided a rationale for the ubiquity of the *N*-aryl group in these reactions. The aryl substituent stabilizes two intermediates and the high-energy transition state that connects them, which together represent the rate-determining step. This knowledge has enabled us to predict new CDC substrates that react either well or poorly.

Keywords: amines, C,C coupling, mechanistic studies, radicals

Introduction

There has been considerable interest in methodology for cross-dehydrogenative coupling (CDC) reactions, given the operational simplicity of the transformations and the high product yields often obtained (Figure 1).[1] These reactions are typically one-pot procedures, where an oxidant is combined with an incoming nucleophile and an unfunctionalised substrate. The reaction products are generally formed with high

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regioselectivity and uncontrolled further reaction at the site of substitution is rarely observed. The use of phenyl-substituted tetrahydroisoquinoline **1a** has become ubiquitous in the field, with the majority of methodologies describing transformations for this motif, yet little explanation exists as to why this substrate performs so well, in part because there are few detailed mechanistic studies of this reaction class.[2] While conditions vary greatly, from the use of transition metals[3] as catalysts to metal-free[4] or photoredox[5] conditions, the substrates subjected to CDC reactions are generally similar, with variation predominantly on the aromatic rings. Elaboration of the CDC products has been demonstrated, with the methodology incorporated into the synthesis of an anthelminthic drug.[6] Through the use of synthetic and computational techniques, in this work we provide an explanation for the successful DDQ-mediated transformation of phenyltetrahydroisoquinolines (*e.g.* **1a**), the alternative reactivity of acyl-substituted tetrahydroisoquinolines and offer predictions of reactivity for other substrates.

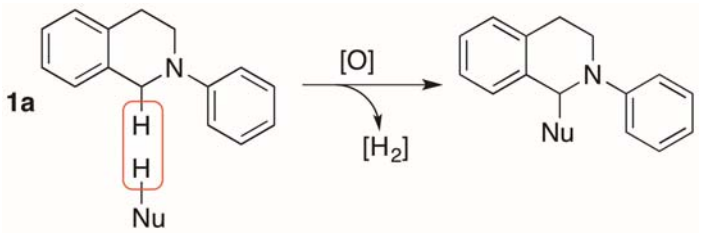

Figure 1. Schematic representation of a cross-dehydrogenative coupling reaction of phenyltetrahydroisoquinoline **1a**.

Results and Discussion

The DDQ-mediated CDC reaction of **1a**[7] has previously been shown to proceed through the corresponding iminium ion intermediate **3** (Figure 2; nucleophile is nitromethane to give **2a**),[8] with the same intermediate identified when $CuCl_2.H_2O$ was used.[2c] The isolation of **3** as a complex with the $DDQH^-$ byproduct confirmed the product of oxidation resulting from an overall hydride step, but gave little insight into the preceding steps and intermediates. The reaction between **1a** and DDQ was monitored by ^1H NMR spectroscopy (Figure 3). The appearance of a signal at ~ 9 ppm, attributed to the iminium hydrogen of **3**, was almost instantaneous. While the broad nature of the signals suggested the presence of radical intermediates, the spectra obtained did not give any further information towards the identity of these species. It was also observed that the reaction proceeded too quickly to be monitored meaningfully by NMR spectroscopy, with little difference in chemical shift or signal

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intensity observed. The addition of a stoichiometric amount of *i*Pr$_2$EtN led to the disappearance of the downfield signals representing the iminium ion intermediate **3** and appearance of the signals representing the nitromethyl product **2a**.

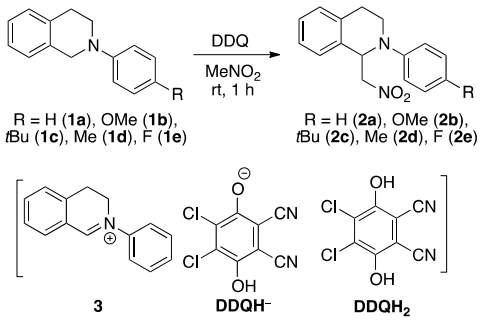

Figure 2. DDQ-mediated CDC reaction of phenyl-substituted tetrahydroisoquinolines **1** and iminium intermediate **3** derived from **1a**.

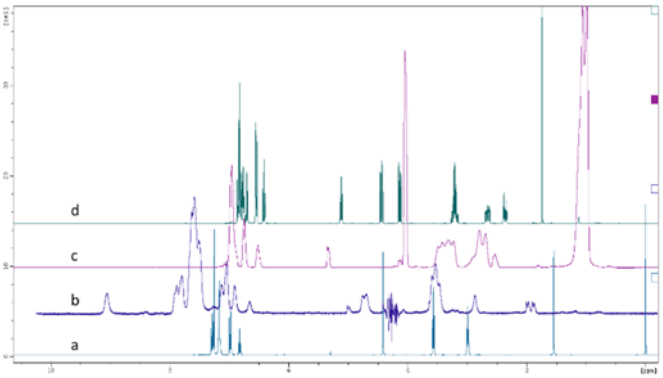

Figure 3. ^{1}H NMR spectra of a) starting material **1a**; b) the reaction of **1a** and DDQ in CD_3NO_2 after 5 minutes with solvent suppression; c) after addition of *i*Pr$_2$EtN; d) nitromethyl product **2a**.

The reaction of **1a** with DDQ was monitored by UV-vis spectroscopy (Figure 4a), with three local maxima observed immediately, corresponding to the DDQ radical anion **DDQ**$^{\bullet-}$.[9] A gradual decrease in the absorbance was observed over a period of hours. Mechanistically, this suggested the possibility of a single electron transfer (SET) step as part of the reaction pathway. Given the speed of the reaction, with an instantaneous colour change observed upon addition of the oxidant, monitoring under stopped-flow conditions allowed for spectra to be recorded at intervals of approximately 0.1 seconds (see Supplementary Information, Fig S1). Indeed, maximum absorbance was recorded after only 30 seconds. When the number of equivalents of DDQ was changed, the maximum absorbance varied accordingly (Figure 4b), which suggested that an equilibrium between the substrate/substrate

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radical cation and DDQ/DDQ radical anion existed in solution. Although this approach towards monitoring is indirect, *i.e.* only the fate of the oxidant is observed, the DDQ-mediated oxidation of other phenyltetrahydroisoquinolines was monitored in a similar manner. We note that an initial hydrogen atom transfer (HAT) mechanism has also been proposed for related processes (see below). However, based on the rapid color change observed, we believe that if HAT does play a part here, it would only be a minor contributing factor. While the same local maxima corresponding to the DDQ radical anion were observed, the rate of the reaction differed according to the substitution pattern at the *para* position of the aromatic ring (Figure 4c), with an electron-donating substituent (R = OMe, **1b**) giving a faster increase in absorbance. The resulting Hammett plot (Figure 4d, see Supplementary Information for experimental details) showed that a linear free-energy relationship existed for this step of the reaction, with the negative value of ρ (−2.138) suggesting that an electron-deficient centre is generated in the rate-limiting step.

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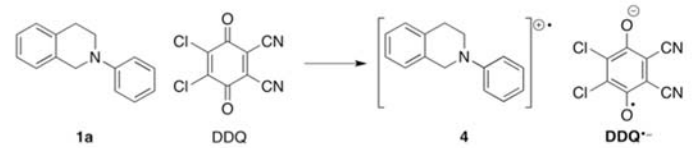

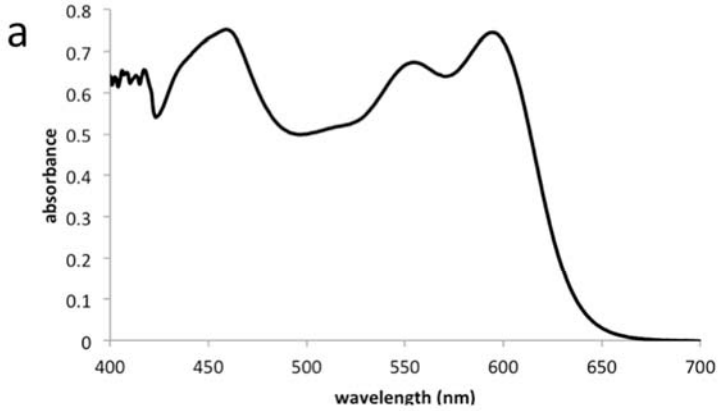

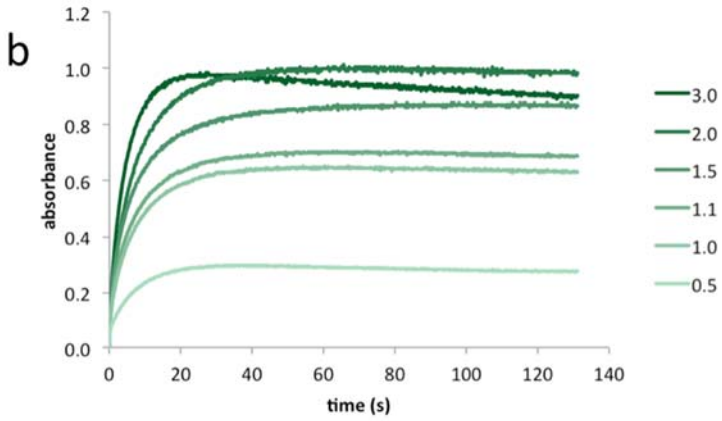

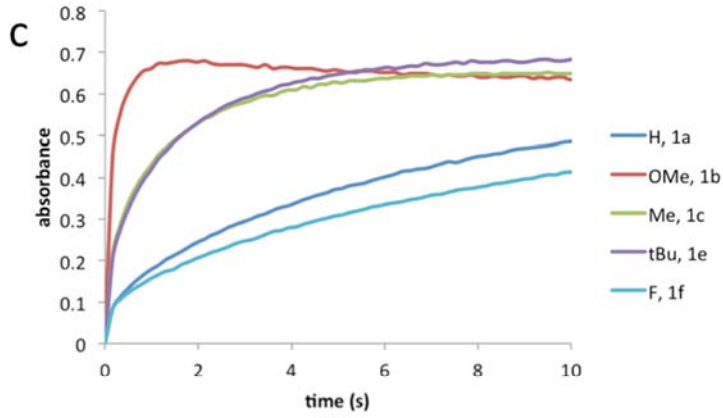

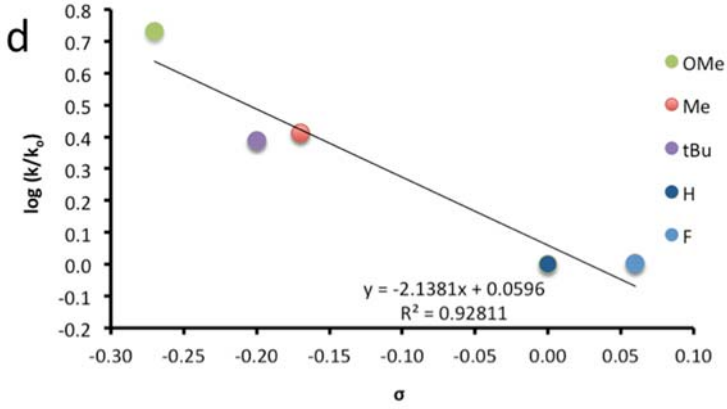

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Figure 4. UV-vis spectra (CH_3NO_2, 25 °C) of a) **1a** and DDQ (0.40 mM each) after 1 minute, with maxima at 456, 517 and 588 nm representing the DDQ radical anion $DDQ^{\bullet-}$, b) in reactions of **1a** (0.40 mM) and DDQ (0.5 – 3.0 eq.), c) in reactions of **1a**–**e** (R = H, OMe, *t*Bu, Me, F respectively) and DDQ (0.40 mM each) and d) Hammett plot of data obtained.

To gain further insight into the reaction, the reaction profile was modelled using computational means (Figure 5, see Supplementary Information for all computational methods). For the phenyl-substituted amine **1a** and other analogues, the energy difference between the starting reactants (**0**, phenyltetrahydroisoquinolines and DDQ) and the proposed radical ions (**RI**, **4** and DDQ radical anion) is small (< 20 kJ mol^{-1}), thus permitting an equilibrium to be established. Between the different analogues, the magnitude of energy difference between the starting materials and radical ions is in agreement with the difference in initial rate as derived from the UV-vis measurements. While the ionic intermediates (**Int**, iminium ion **3** and corresponding hydroxyquinone) are in a significant thermodynamic well (~ 120 kJ mol^{-1}), the barrier for hydrogen abstraction *via* the transition state **TS** (~ 80 kJ mol^{-1}, see Figure 6d for the transition state structure of **1a**) is considerable and is consistent with the slow decrease in UV-vis absorbance and hence disappearance of the DDQ radical anion $\mathbf{DDQ^{\bullet-}}$. The subsequent reaction of the iminium ion intermediate **3** with nitromethane is slightly endergonic, with the substituted products obtained in good yield. The combined experimental and computational results suggest that the DDQ radical anion $\mathbf{DDQ^{\bullet-}}$ (and hence the corresponding amine radical cation **4**) exists. At this point the results do not yet show whether this species on the reaction pathway itself or is a result of a side reaction. The transition state located could be that for either hydride or hydrogen atom transfer. Stability analysis on the closed-shell transition state **TS** wavefunctions gave $\langle S^2 \rangle$ values of ~ 0.7 (versus 0.0 for a pure singlet, 0.75 for a pure doublet and 2.0 for a pure triplet). This suggests that the transition state has a substantial biradical character derived from the proposed radical ions **RI**, which in turn suggests that the single electron transfer step is in fact on the reaction pathway. The biradical nature of the transition state is consistent with the proposed mechanism and contrary to a recently published model[10a] for a similar oxidation, in which hydride transfer was proposed.[10b,c]

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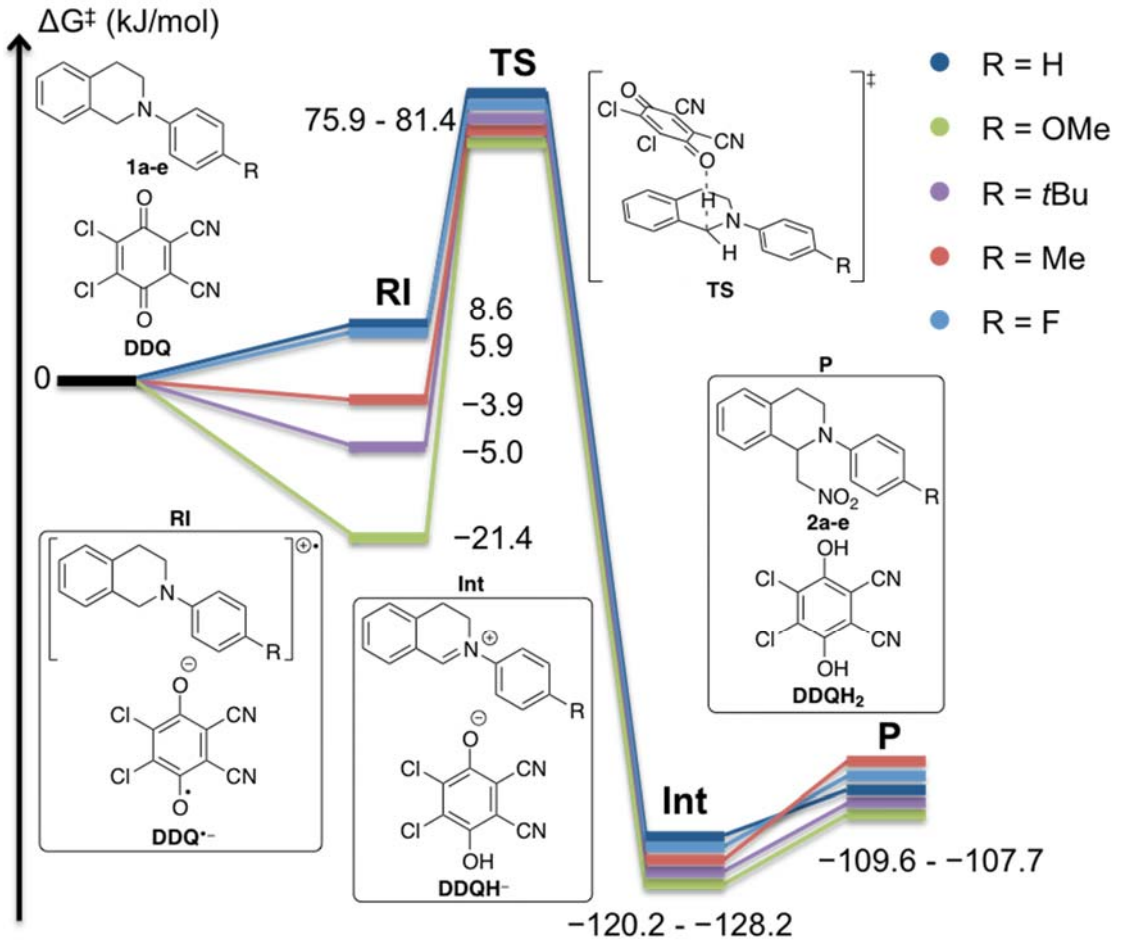

Figure 5. Profile of the reaction between **1a-f** and DDQ, calculated at B3LYP/6-31G(2df,p), with condensed phase free energies at 298 K in kJ/mol relative to reactants **1a** and DDQ; transition state structure for **1a**.

The sequence above that was experimentally observed and computationally modeled is in agreement with some mechanisms proposed for other CDC reactions (*e.g.*, an iron-catalyzed, *tert*-butyl peroxy radical-[11a], O_2-[11b,c] or DDQ-[2c] mediated CDC)[11d] but distinct from mechanisms proposed for others (*e.g.*, metal-[11e,f] or *t*BuOO•/*t*BuO•-[11g] mediated production of C-based radicals through initial hydrogen atom transfer) which may nevertheless also benefit from the stabilisation of partially-formed radicals in the relevant transition states.[11h] This highlights an important point: reactions grouped together in the literature under the term “cross dehydrogenative couplings” most likely exhibit a range of related reaction mechanisms.[2a,12]

Other synthetically more versatile protecting groups for the heteroatom, such as acyl substituents have (to date) rarely been used in substrates for CDC reactions.[13] The acyl-substituted **5** was prepared and subjected to the DDQ-

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mediated CDC reaction with nitromethane (Figure 6a). The desired product **6a** was not obtained. Instead, imide **6b** was observed, which may be associated with the involvement of water or oxygen. Using the Boc-substituted **7**, the major product isolated from the reaction with DDQ was the oxygen-bridged dimer **8a** (Figure 6b). Monitoring the production of the DDQ radical anion in the reactions of **5** and **7** as starting materials by UV-vis spectroscopy revealed only weak absorbance (Figure 6c), which suggested that the reaction mechanism for these acyl-substituted substrates was different to that for the aryl substrates **1**. Modeling of the reaction profile for these substrates showed that the pathway proposed for the aryl-substituted amines **1** (*i.e.* single electron transfer as a first step) was higher in energy than a direct oxidation of the substrate and thus likely to be unfavourable (Figure 6d). The computational results also showed that the ground-state energy of the final acyl-substituted product **6a** is similar to that of **2a** suggesting 6a is not unduly thermodynamically unstable; indeed **6a** has been synthesised and isolated by us using alternative approaches.[14]

The computational results to this point revealed that an electron-rich substituent at the heteroatom promoted oxidation *via* single electron transfer, with the atom transfer step likely to be rate determining. This suggested that modifications at the benzylic position would affect the rate (and possibly the outcome) of the reaction. Accordingly, the 1-methyl substituted phenyltetrahydroisoquinoline **9** was synthesised and subjected to a reaction with DDQ in nitromethane (Figure 7a). Even under forcing conditions (reflux for 48 hours), the desired nitromethyl product **10** was not obtained, with **9** reisolated. Monitoring of the reaction for production of the DDQ radical anion by UV-vis spectroscopy showed that single electron transfer occurred similarly to the reaction starting with **1a** (Figure 7b). That the starting material was reisolated from the reaction suggested that the single electron transfer step was reversible. Modeling of the reaction pathway of **9** by computational means showed that the barrier to electron transfer was similar to that of **1a**, but the barrier to the transition state for atom transfer was far higher (Figure 7c). The difference in the structure of the transition states can be seen in Figure 7d. According to the computational results, the atom abstraction step for **1a** was rate-limiting and hence likely to be sensitive to substitution at the benzylic position. Steric effects in **9** require that the methyl group occupy an equatorial position (Figure 7d, right), which prevents

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the coplanar arrangement of the relevant C–H bond and the heteroatom's lone pair. Subsequent resonance stabilisation in **$TS_{9\text{-}DDQ}$** does not occur, thus raising the energy of this transition state and preventing complete oxidation. By contrast, the coplanar arrangement adopted between the reacting C–H bond in substrate **1a** and the heteroatom lone pair in the transition state **$TS_{1a\text{-}DDQ}$** (Figure 7d, left) facilitates stabilisation.[2a, 15]

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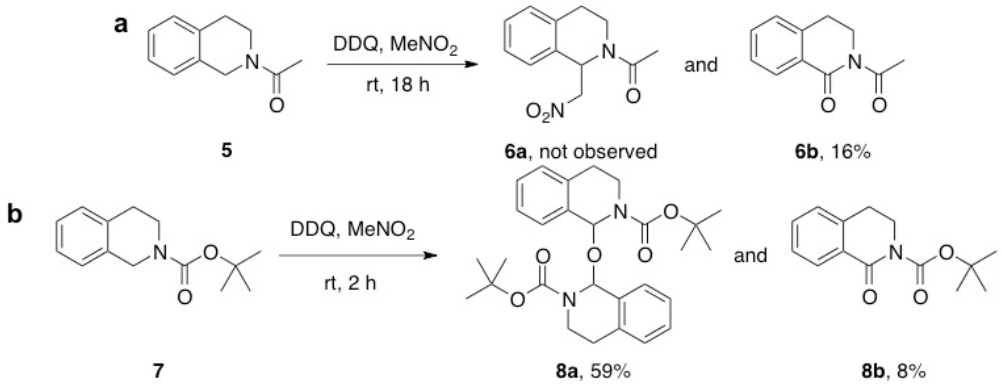

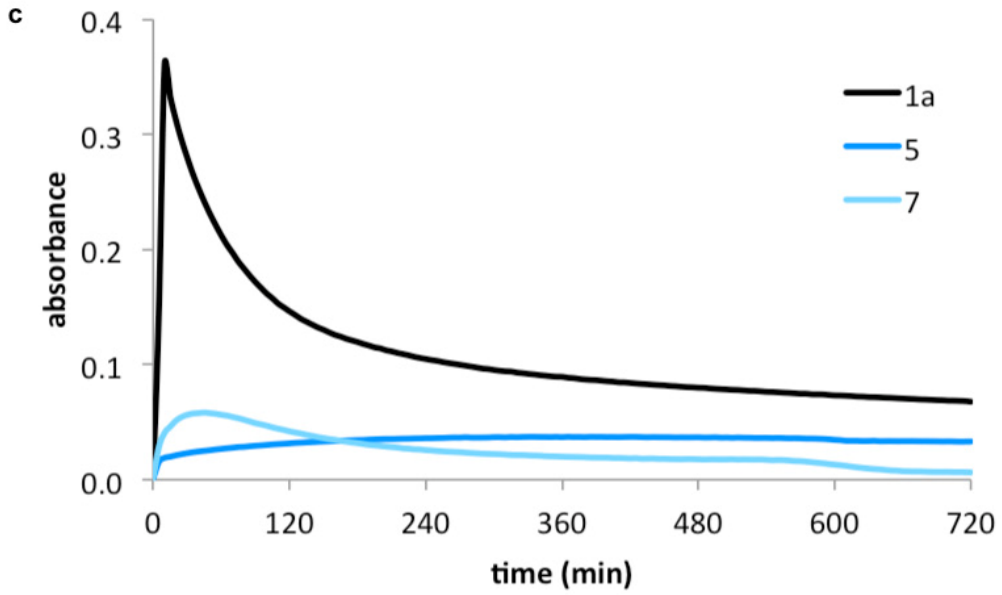

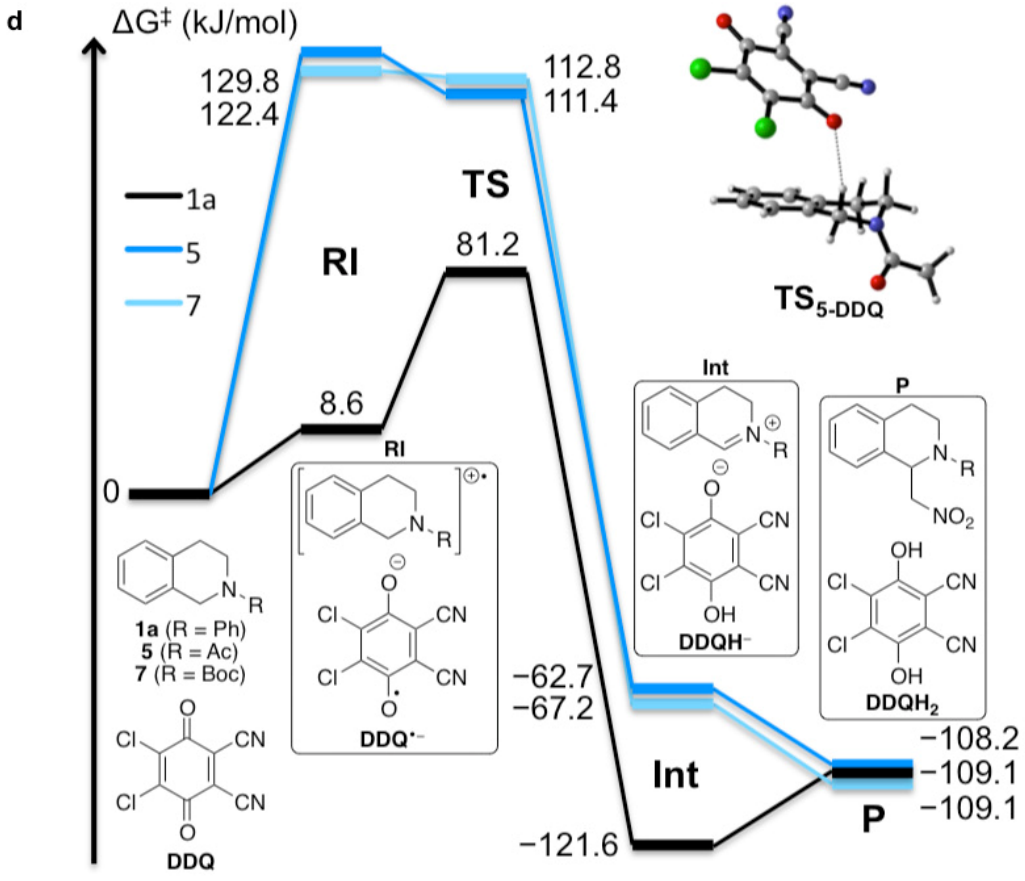

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Figure 6. DDQ-mediated reaction of a) acetyl-substituted **5** and b) Boc-substituted **7** tetrahydroisoquinolines with nitromethane; c) UV-vis absorbance at 588 nm of the reactions of **1a**, **5** and **7** with DDQ in nitromethane, monitored under stopped flow conditions, d) free energy profiles of the reactions of **1a**, **5** and **7** with DDQ in nitromethane.

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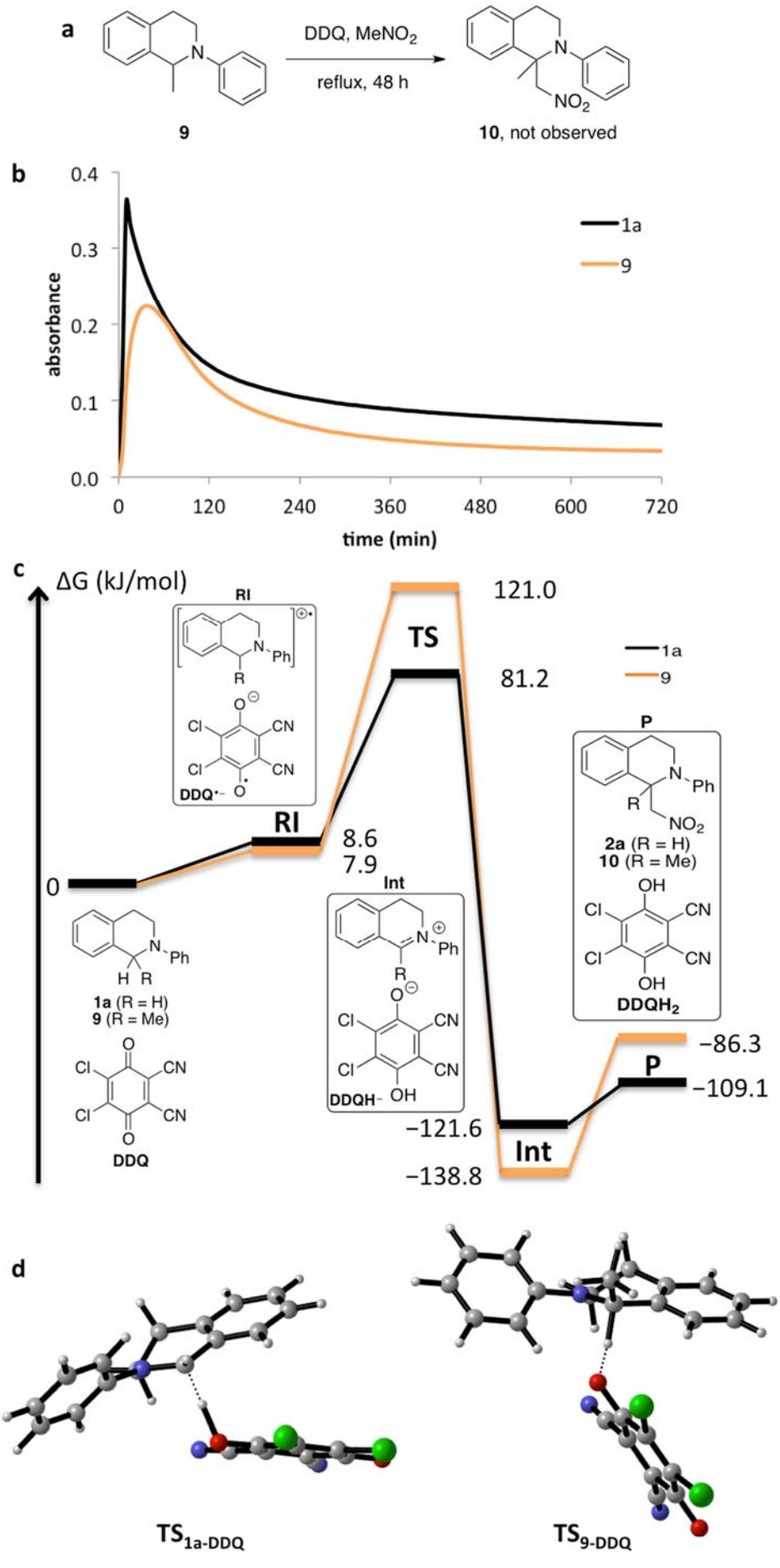

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Figure 7. a) Attempted DDQ-mediated oxidation of **9** in nitromethane; b) UV-vis absorbance at 588 nm of the reactions of **1a** and **9** with DDQ in nitromethane under stopped flow conditions; c) free energy profiles of the reactions of **1a** and **9** with DDQ in nitromethane; d) transition states for the reactions of **1a** (top) and **9** (bottom) with DDQ.

This substrate **9** presents an example where the use of computations can rationalise the experimental observations and explain the overall reactivity. As the presence of an aromatic ring at the heteroatom facilitated the reaction, it was predicted that naphthyl-substituted tetrahydroisoquinolines (**11**, Figure 8a) would also undergo the CDC reaction successfully. Subsequently, the reaction profiles of the tetrahydroisoquinolines **11a** and **11b** were calculated (Figure 8d). It was predicted that the radical intermediates arising from the 1'-naphthyl substituted **11a** would be destabilised, when compared to its analogue **11b** and the phenyl-substituted **1a**, due to the aplanar nature of the ring systems (Figure 8c and Supplementary Information, Fig S3). Conversely, the conformations and calculated energies for the 2'-naphthyl substituted **11b** are comparable to that of **1a**. Overall, the energies of the transition state, iminium ion intermediate and final products are similar for **1a**, **11a** and **11b**, suggesting that the reactions of **11a** and **11b** would proceed. Naphthyl-substituted amines **11a** and **11b** were then synthesised and subjected to a reaction with DDQ in nitromethane, with the nitromethyl products **12a** and **12b** obtained in excellent yield (Figure 8a). The reactions of **11a** and **11b** were monitored by UV-vis spectroscopy, with the maxima representing the DDQ radical anion observed in each case (Figure 8b). When comparing the rate of increase of absorbance, the aplanar **11a** showed a slower increase in absorbance than the analogue **11b**. This experimental observation was in agreement with the computational results, with the slower rate of increase corresponding to the higher energy of the radical intermediates arising from single electron transfer. Studies into the DDQ-mediated oxidative addition of nitromethane to naphthyl-substituted amines **11a** and **11b** have provided a successful example where computational predictions were successfully confirmed through experimental and spectroscopic means.[16]

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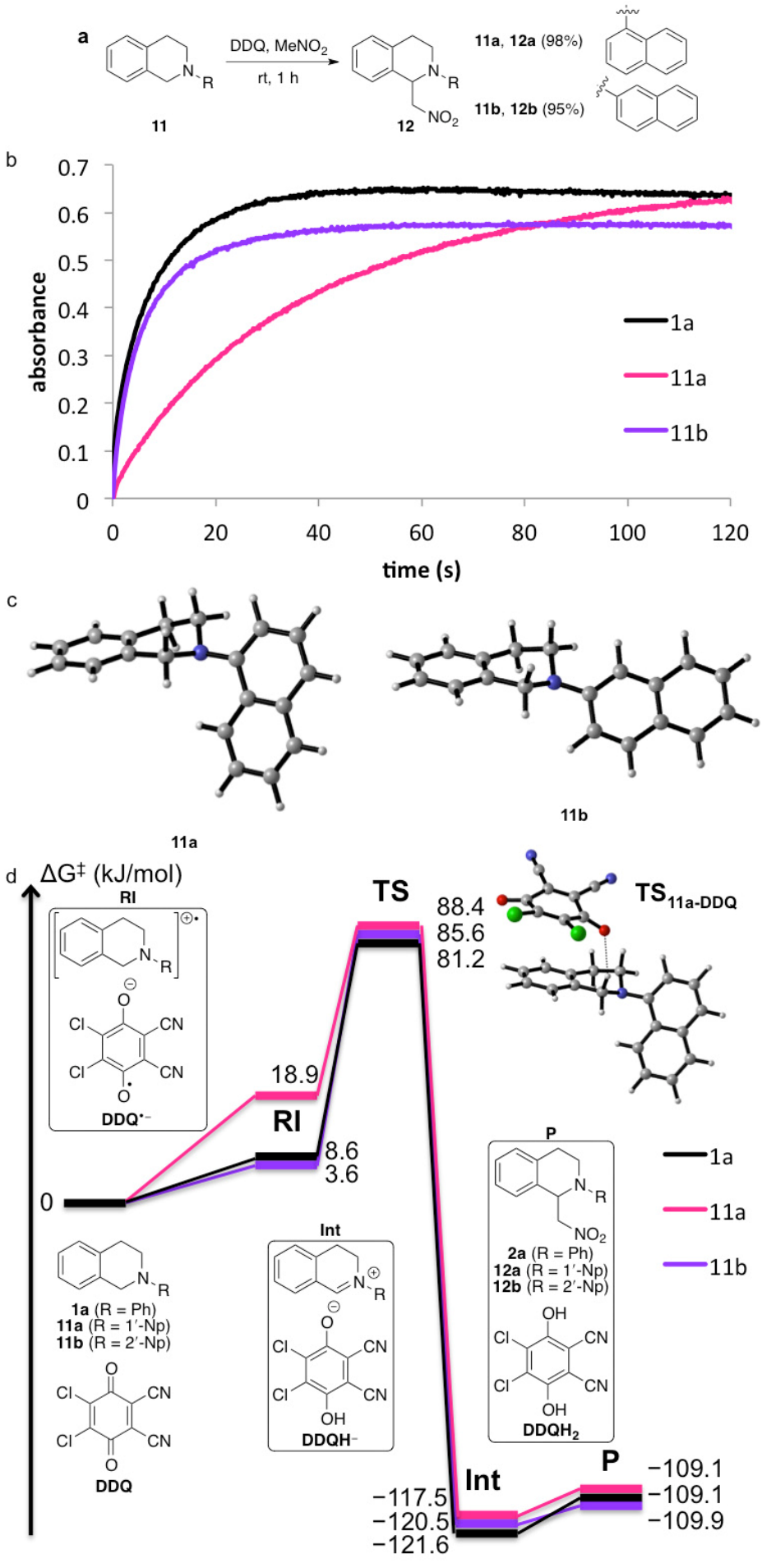

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Figure 8. a) Reaction of **11a** and **11b** with DDQ in nitromethane; b) UV-vis absorbance at 588 nm of the reactions of **11a** and **11b** with DDQ in nitromethane, with **1a** for comparisons; c) lowest energy conformations of **11a** and **11b**; d) Free energy profile of the reactions

Conclusions

We have used a variety of experimental and computational techniques to explore the mechanism of the DDQ-mediated CDC reaction of substituted tetrahydroisoquinolines. Throughout these studies, the experimental results have been in agreement with those derived computationally, with this combined approach successful in explaining the reactivity of aryl- and acyl-substituted substrates and also predicting the reaction outcome of other tetrahydroisoquinolines. The use of a phenyl substituent at the heteroatom lowers the energy of the radical intermediates (compared to when an acyl group is used) and the energy of the transition state for subsequent atom transfer, thus accounting for the extensive use of phenyltetrahydroisoquinoline **1a** as a substrate for CDC reactions. This effect is presumably resonance-based, explaining the modulating effect of substituents on the *N*-aryl ring and the lesser reported ability of alkyl groups to participate in CDC reactions. In all of the "successful" substrates discussed here, complete regioselectivity is observed with the incoming nucleophile installed at the benzylic position only. Overoxidation and further substitution of the products **2a-e**, **12a** and **12b** is not observed, as the presence of substituents at the benzylic position prevent subsequent oxidation. This was also explored with the methyl-substituted **9**, with computational results showing that the steric environment at the benzylic position prevented oxidation, thus explaining why overoxidation did not occur. The mechanistic studies showed that evaluating the stability and the geometries of the intermediate radicals could provide an initial prediction regarding the feasibility of new substrates for DDQ-mediated CDC reaction. It is common practice to suggest plausible mechanisms for CDC reactions based on extrapolation from literature examples. This may be hazardous if this class of reactions ultimately exhibits a range of reaction mechanisms. A comparison between the results obtained here and those obtained by other researchers in

the few other investigations involving physical measurements of related CDC reactions suggests that this may be the case.

Acknowledgements

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[16] While this work was being written up, an iron-catalysed synthesis of **12a** was reported, where a slower rate of reaction was indeed noted as predicted, see Ref [11b].

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