An oxidative carbon–carbon bond-forming reaction proceeds via an isolable iminium ion*

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Abstract: The mechanism of our previously reported DDQ-mediated oxidative C–C bond-forming reaction is investigated. We are able to trap and characterize an iminium ion intermediate with X-ray crystallography, elemental analysis, and solid-state NMR spectroscopy; to our knowledge this is the first time this putative intermediate ion has been directly observed in such cross-dehydrogenative couplings (CDCs). The intermediate can be reacted with a range of nucleophiles, including a malonate that is not amenable to a one-pot reaction protocol.

Keywords: C–C bond formation; DDQ; iminium ion; mechanism; oxidative coupling.

INTRODUCTION

In recent years, C–C bond-forming reactions have been reported where the coupling partners are not prefunctionalized to take part in such a union. Whereas regular C–C bond formation might involve pre-formation of a nucleophile and/or an electrophile (Scheme 1A), these "cross-dehydrogenative coupling" (CDC) reactions [1,2] form bonds between (for example) two sp^3 centers directly through a one-pot activation and coupling protocol (Scheme 1B [3]). Typically, one coupling partner is converted into an electrophile through oxidation, and another electron-rich coupling partner, *unaffected by the oxidative step*, attacks this electrophile. An early example, a hybrid approach of preformed nucleophile with in situ oxidation to generate an electrophile, was Mukaiyama's union of C nucleophiles with allyl ethers through an oxidation with DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone, Scheme 1C) [4]. Since then, DDQ has been used in a number of C–C bond-forming CDC processes [5–12]. DDQ is conveniently handled under ambient conditions and is inexpensive. Its reduced dihydroquinone by-product (DDQH$_2$) is easily removed from the reaction mixture during work-up and may be converted back into DDQ [13]. The successful use of catalytic DDQ for a variety of oxidative processes was recently reported [14]. Many oxidative couplings employ metals, but it is advantageous to have analogous processes that do not require metals, for the often-cited reason of toxicity of trace metals interfering with biological evaluation of the compounds synthesized.
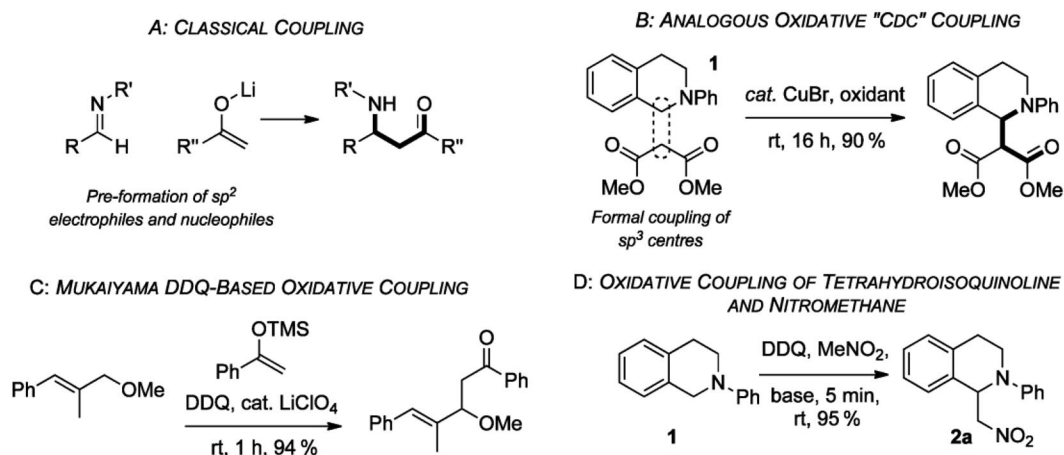
Scheme 1 Comparison of (A) traditional C–C bond formation methods with (B) CDC reactions; (C) use of DDQ as oxidant in hybrid CDC reaction; and (D) the reaction of interest in this paper.

We recently reported a CDC reaction employing DDQ that permitted the simple generation of β-nitroamines from *N*-phenyl tetrahydroisoquinoline (*N*-phenyl THIQ, **1**) and nitromethane (Scheme 1D) [15]. Reduction of the nitro moiety in the products provided new chiral vicinal diamines, structures that are widely employed in pharmaceuticals and catalyst ligands. The CDC reaction was strikingly successful, in that a near-quantitative yield of the nitroamine was obtained within a few minutes at room temperature using non-dried nitromethane under ambient conditions, representing the fastest and highest-yielding synthesis of these compounds known to us [16,17]. The effectiveness of the reaction suggested the DDQ was playing more than an oxidative role, leading us to consider the mechanism of the reaction. DDQ-mediated coupling reactions are sometimes accompanied by proposals for the reaction mechanism [5,9], though there is continuing disagreement in the literature as to the details, and different mechanisms are often given for different reactions, sometimes with no experimental proof of the presence of the proposed intermediates. Where DDQ is used to couple methylene groups adjacent to heteroatoms, it is usually supposed that a reactive iminium ion is generated in the oxidation, but to date there has been no direct evidence for this; indeed, some early papers on CDC-like reactions mediated by DDQ supposed a concerted attack of nucleophile and transfer of hydride to DDQ [18,19]. Floreancig has recently shown that in the DDQ-based oxidation of benzylic ethers, C–H bond cleavage occurs in the rate-determining step, and preformation of a reactive intermediate does not [20]. We present here what is to the best of our knowledge the first direct evidence for an iminium ion intermediate through its trapping in a solid during the reaction, and the use of this isolated iminium ion to generate a reaction product that could not be otherwise formed by a typical one-pot CDC protocol.

RESULTS AND DISCUSSION

Reaction scope

The scope of our previously reported reaction was investigated through variation of the nucleophile (Table 1). Other nitroalkanes such as nitroethane (entry 2) and nitropropane (entry 3) gave the desired β-nitroamines in good yields. Use of acetone with stoichiometric or catalytic (0.15 equiv) L-proline gave the corresponding β-ketoamine (**2d**) in good yield (entry 4) as a racemate; running the same reaction without the addition of proline also gave product but at a slower rate. A recent publication illustrating a metal- and proline-catalyzed version of this reaction showed that the enantiomeric excess of the product was low (7 % ee), likely due to racemization of the product upon isolation [21]; related

processes involving proline in the oxidative formation of other products have been shown to give higher levels of enantioenrichment [22,23]. When neat dimethyl malonate was used (entry 5), the reaction was not successful, with a complex mixture being obtained. This is possibly due to the malonate acting as the preferential substrate for oxidation by DDQ, rather than the tetrahydroisoquinoline (see below). Changing the reaction conditions to the use of a stoichiometric amount of dimethyl malonate in dichloromethane gave the same result.

Table 1 Direct DDQ-mediated oxidative addition reactions between *N*-phenyl THIQ (**1**), or the intermediate iminium ion complex (**4**), and a range of pronucleophiles.
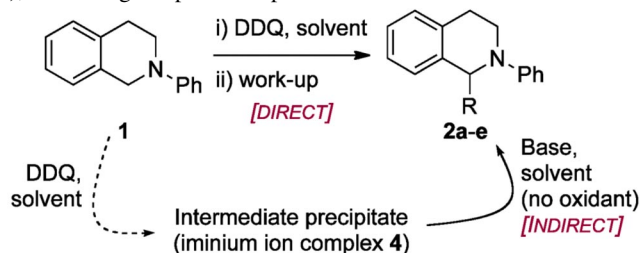
Entry	Solvent	R	Product	Direct yield (%)[a]	Indirect yield (%)[b]
1	Nitromethane	NO$_2$	**2a**	95	97
2	Nitroethane	NO$_2$	**2b**	77[c]	97[c]
3	1-Nitropropane	NO$_2$	**2c**	75[d]	95[d]
4	Acetone[e]	O	**2d**	65	94
5	Dimethyl malonate[f]	O O	**2e**	0	73

[a]Conditions: **1** (96 mM), DDQ (1.1 equiv), neat solvent, room temperature.
[b]Conditions: Complex **4** (60 mM (if solubilized)), neat solvent, *i*Pr$_2$EtN (1.1 equiv), room temperature, yield calculations based on quantity of complex used.
[c]dr 1:1.7.
[d]dr 1:1.4.
[e]Includes L-proline (0.15 equiv).
[f]Dimethyl malonate used either neat or near-stoichiometric (1.1 equiv) (for attempted direct approach) or near-stoichiometric (1.1 equiv) (indirect approach) in dichloromethane.

Isolation of a reactive intermediate

When the parent reaction between *N*-phenyl THIQ and nitromethane is run, what is notable, besides the colors normally exhibited in DDQ-mediated reactions, is the formation of a substantial amount of a precipitate; this solid disappears during basic, aqueous work-up. Specifically, a light yellow solid forms suspended in a clear, deep red solution (Fig. 1) [24].

Fig. 1 Formation of a yellow precipitate in a deep red solution during the course of the reaction shown in Scheme 1D.

When the red solution was filtered, and the filtrate worked up and purified, product **2a** was obtained in 50 % yield. The red color could arise from a charge-transfer (CT) complex [25,26] or a derived radical intermediate [27] in the reaction; alternatively, it is known that by-products of DDQ can have strong red colors, and it is possible that small amounts of similar products are responsible for the colors observed, though such products were not isolated here [28]. When the red solution was examined by UV–vis spectroscopy approximately 5 min after the start of the reaction, values of wavelengths exhibiting maximum absorbance and the extinction coefficient (assuming complete formation and dissolution of the complex and no reaction during preparation and observation) could be determined (see Supplementary Information) that are suggestive of intermediates proposed for related reactions [27]. However, it is difficult to obtain meaningful values for these variables since it is experimentally challenging to determine the position of equilibrium for the relevant processes, e.g., CT complex formation [29], and to deconvolute the mixture (CT complexes vs. radicals vs. ion pairs), though this has been achieved for a related process [30]. Kinetic studies of the first few seconds of the reaction are ongoing and will be reported in a separate article.

The implication from the yield of product obtained from the red solution is that the remaining *N*-phenyl THIQ (or a derivative thereof) is captured in the precipitate. In the above experiment, when the filtrand was treated with diisopropylethylamine (1.1 equiv) in nitromethane, further reaction product **2a** was obtained in 50 % yield (based on the amount of *N*-phenyl THIQ used at the start of the reaction), indicating that the remaining *N*-phenyl THIQ (or its derivative) is indeed present in the solid. A similar attempt to react the solid with tosic acid rather than base failed to give any product. Attention was turned to identification of this precipitate, which it was thought would allow for the positive identification of a reaction intermediate.

Allowing the parent reaction to stir for several hours gave a powder-like precipitate. Leaving the reaction mixture to stand without stirring gave a yellow precipitate that resembled flower-like crystals (shown in Fig. 1). The precipitate was isolated by careful decanting. Subsequent washing with aliquots of hexane facilitated complete removal of volatiles. While our previously reported observations of this reaction by solution-phase NMR spectroscopy suggested the presence of an iminium ion [15], analysis of the solid was hampered by it being insoluble in most organic solvents and water. The solid was therefore examined with solid-state NMR spectroscopy, using a range of 1D and 2D techniques. The results (Fig. 2) corroborate the presence of an iminium ion derived from the tetrahydroisoquinoline starting material, with a peak clearly visible at ca. 165 ppm in spectra of the precipitate which is not seen in the corresponding spectrum of the starting material (compare spectra A and D in Fig. 2). There are also ^{13}C peaks at 150–155 and 105–115 ppm that can be assigned to the DDQ molecules themselves (in spectra
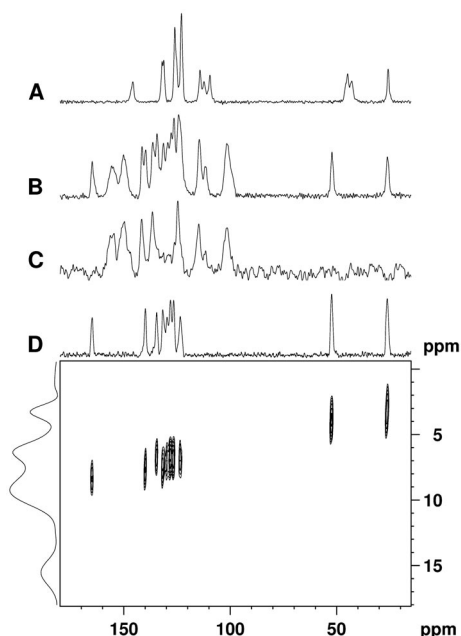
Fig. 2 Solid-state NMR spectroscopy of the precipitate formed during the reaction shown in Scheme 1d. (A) *N*-Phenyl THIQ **1**, showing all carbons (with and without attached H); (B) complex **4**, showing all carbons (with and without attached H); (C) quaternary carbons only from spectrum B, i.e., with suppression of carbons with attached H by dipolar dephasing filter; (D) ^{13}C projection from 2D HETCOR showing only those carbons with attached H, and below this is a 2D plot indicating cross-peaks only for carbons with attached H in complex **4**.

B and C), and can be distinguished from carbons in the isoquinoline moiety that possesses attached hydrogen atoms (the 2D spectrum, and the relevant projection shown in spectrum D). The broad ^1H signal around 15 ppm can be tentatively assigned to a highly deshielded phenolic H that does not give rise to a signal in the heteronuclear correlation (HETCOR) spectrum because it is only loosely associated and/or too distant to have strong interactions with the carbons in the complex.

Characterization of the precipitate by elemental analysis showed that the intermediate did not have the structure of the intuitively obvious 1:1 salt **3** (Fig. 3), but is more likely to consist of three com-

3 requires: C, 63.32; H, 3.47 %
4 requires: C, 55.96; H, 2.58 %
Observed: C, 55.97; H, 2.60 %
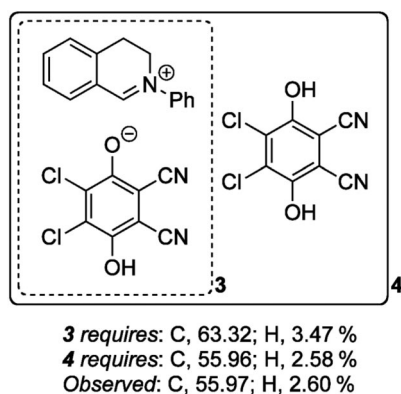
Fig. 3 Possible compositions of the precipitate formed in the reaction shown in Scheme 1d. Experimental data support structure **4** containing a second equivalent of DDQH$_2$ by-product.

ponents, with **4** being the most likely composition. This combination would account for all the DDQ used in the reaction and the remaining 50 % of starting material *N*-phenyl THIQ unaccounted for from the work-up of the filtrate.

Crystals suitable for X-ray analysis could not be obtained by growing the solid in nitromethane, but suitable crystals were obtained by reacting *N*-phenyl THIQ and DDQ in acetonitrile and allowing the mixture to stand. The X-ray crystal structure analysis (Fig. 4; see also the Supplementary Information for more data) not only directly confirmed the presence of the iminium ion in the intermediate, but also the stoichiometry of the complex, found to be as represented in **4**. The C–O bond lengths of 1.33–1.36 Å are between that of a typical C=O double bond (1.22 Å) and a C–O single bond (1.43 Å) [31]; there is a short intermolecular O–O contact between adjacent DDQ by-product molecules of 2.47 Å. These observations imply the sharing of a single negative charge, and the sharing of a mobile proton. The imine C=N bond is 1.29 Å in length, typical for such bonds, while the imine C–H bond is relatively short at 0.95 Å, and this may be due to the extended conjugation through the iminium ion intermediate. The complex appears to have an interaction of one hydroquinone molecule with the chlorine atoms of the neighboring molecule, which possibly contributes to the stacking arrangement and apparent stability of the complex.
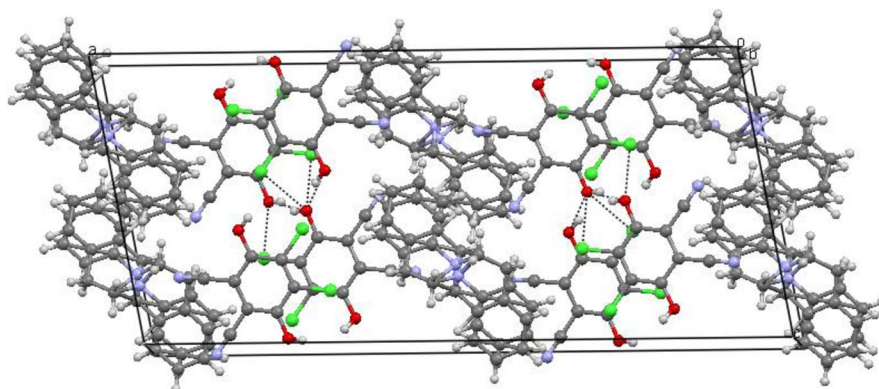
Fig. 4 Packing of the molecules in complex **4** viewed down the B-axis.

The complex crystallizes in the monoclinic space group C2/c with packing features that are different from those typically observed in structures of CT complexes. Thus, there is no alternate (or "sandwich"-like) stacking between DDQ and THIQ moieties in the crystal structure; instead, each moiety makes separate columns (as shown in Fig. 4). By packing in this way, none of the components exhibits π–π stacking; instead, the molecules are "sheared", resulting in very little overlap between the neighboring units. This type of molecular packing could be the result of non-planarity of the iminium ion unit, which also shows a two-fold orientational disorder in the crystal lattice.

Kochi has documented related structures containing radical anions derived from electron-transfer processes involving DDQ [32]; these radicals are frequently generated under rigorously anhydrous conditions, unlike the reactions performed here, though that does not preclude their persistence in a solid matrix. The solid-state NMR spectroscopy signals were not apparently broadened by a radical, but the presence of radicals in the structure of the solid cannot be ruled out here. The parent reaction has been run with the addition of the radical trap 2,6-di-*tert*-butyl-4-methyl phenol (BHT) to the intermediate suspension (addition at the start of the parent reaction is ineffective since DDQ reacts with BHT). Product was isolated with an identical yield to the reaction without the radical trap (this was also shown for a copper-catalyzed version of the same reaction) [17].

The crystal structure shows that the iminium ion appears to be well stabilized in this complex by a surrounding network of intermolecular interactions. We have shown that storage of the complex does not affect the ability of the solid to take part in subsequent reactions (vide infra), and have performed such reactions up to a year after the initial synthesis of the complex. It is possible that inclusion in a complex such as this during the reaction protects the iminium ion from unwanted side reactions, or encourages rapid initial oxidation via precipitation and hence a shift in the position of equilibrium for the reaction. This may help to explain the notably high rate and efficiency of the parent DDQ-mediated coupling reaction.

Reactions of the isolated intermediate

If the trapped iminium ion is an intermediate on the reaction pathway, it should logically react further with an added nucleophile to give the expected 1-substituted tetrahydroisoquinolines. The complex **4** was resuspended in neat nitromethane, but due to a lack of solubility in the absence of base, no reaction was observed. The addition of a stoichiometric amount of organic base (iPr$_2$EtN) to the suspension gave complete dissolution of the solid and the appearance of the desired product **2a** (Table 1, entry 1, right-hand column), which was isolated in near quantitative yield (based on the calculated amount of iminium ion present in the solid). Changing the reaction solvent to nitroethane or nitropropane again in the presence of diisopropylethylamine gave similar results, with **2b,c** (entries 2 and 3) also obtained in excellent yield. Reacting the complex with acetone in the presence of L-proline did not require the addition of diisopropylethylamine, though the reaction is slower than when base is added (entry 4).

When complex **4** was reacted with a near-stoichiometric quantity of dimethyl malonate and diisopropylethylamine in dichloromethane (entry 5), the product **2e** was successfully isolated. This result is important, as the direct one-pot CDC reaction to give this product previously failed. This highlights the synthetic benefit of isolating the reaction intermediate and allows for the synthesis of tetrahydroisoquinolines with nucleophiles that are incompatible with the oxidizing agent employed.

CONCLUSIONS

The isolation and characterization of a solid in a DDQ-mediated C–C bond-forming reaction has provided concrete evidence of a trapped iminium ion as an intermediate in the reaction pathway. The iminium ion was characterized by solid-state NMR spectroscopy, X-ray crystallography, and elemental analysis. The intermediate is itself of synthetic use, as a variety of 1-substituted tetrahydroisoquinolines can be easily prepared from this shelf-stable compound. Importantly, substrates that are otherwise inaccessible to in situ oxidative coupling methods, due to incompatibility of reagents with oxidants, can be synthesized.

EXPERIMENTAL SECTION

2-Phenyl-1,2,3,4-tetrahydroisoquinoline (1)

Iodobenzene (2.05 g, 1.12 mL, 10.0 mmol, 1.0 equiv), 1,2,3,4-tetrahydroisoquinoline (2.00 g, 1.90 mL, 15.0 mmol, 1.5 equiv) and ethylene glycol (1.11 mL, 20.0 mmol, 2.0 equiv) were added to 2-propanol (10 mL) and the reaction mixture degassed. Copper(I) iodide (0.200 g, 1.0 mmol, 0.1 equiv) and potassium phosphate tribasic (4.25 g, 20.0 mmol, 2 equiv) were added and the reaction mixture was stirred at 85 °C for 24 h. The reaction mixture was allowed to cool to rt, diethyl ether (20 mL) and distilled water (20 mL) were added and the layers separated. The aqueous phase was further extracted with diethyl ether (40 mL) and the combined organic phases were washed with brine and dried (MgSO$_4$). Concentration in vacuo gave a dark orange oily liquid, which was purified by flash column chro-

matography (20:1 hexane:ethyl acetate) to give the tetrahydroisoquinoline **1** as an off-white solid (1.18 g, 57 %).

m.p. 45–46 °C (no lit m.p.). ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.99 (2H, t, *J* 5.8, H^4), 3.56 (2H, t, *J* 5.8, H^3), 4.41 (2H, s, H^1), 6.82 (1H, t, *J* 7.2, H$^{4'}$), 6.98 (2H, d, *J* 8.8, H$^{2'}$ and H$^{6'}$), 7.10–7.19 (4H, m), 7.23–7.33 (2H, m). IR (CHCl$_3$) ν_{max}/cm^{-1} 1596, 1496. *m/z* (ESI) 210.2 (MH$^+$, 30 %), 208.3 ([M$^-$H]$^+$, 100 %). Spectroscopic data matched those in the literature [33].

1-(Nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2a)

Synthesis from 2-phenyl-1,2,3,4-tetrahydroisoquinoline 1
To a stirred solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.120 g, 0.53 mmol, 1.1 equiv) in nitromethane (5 mL) was added 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**, 0.100 g, 0.48 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 30 min, washed with saturated NaHCO$_3$ solution (25 mL), and extracted with dichloromethane (3 × 25 mL). The organic extracts were combined, washed with saturated NaHCO$_3$ solution (2 × 25 mL), dried (MgSO$_4$), and concentrated under reduced pressure to remove dichloromethane. The residue (in residual nitromethane) was purified by flash column chromatography (5:1, hexane:ethyl acetate) to give the β-nitroamine **2a** (0.121 g, 95 %) as a pale yellow crystalline solid.

Synthesis from complex 4
To the iminium ion complex (**4**, 0.200 g, 0.301 mmol, 1.0 equiv) in nitromethane (5 mL) was added diisopropylethylamine (0.043 g, 0.057 mL, 0.331 mmol, 1.1 equiv) and the reaction mixture stirred at rt until complete dissolution was observed. The reaction mixture was washed with saturated NaHCO$_3$ solution (25 mL) and extracted with dichloromethane (3 × 25 mL). The organic extracts were combined, washed with saturated NaHCO$_3$ solution (2 × 25 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (5:1, hexane:ethyl acetate) to give the β-nitroamine (0.078 g, 97 %) as a yellow oil.

m.p. 87–88 °C (lit. [17] m.p. 89–90 °C). ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.79 (1H, ddd, *J* 16.3, 10.1, 4.9, H^4), 3.09 (1H, ddd, *J* 16.3, 14.3, 7.1, H^4), 3.65 (2H, m, H^3), 4.56 (1H, dd, *J* 12.0, 8.0, H^9), 4.87 (1H, dd, *J* 12.0, 8.0, H^9), 5.55 (1H, dd, *J* 8.0, 8.0, H^1), 6.85 (1H, t, *J* 7.2, H$^{4'}$), 6.97 (2H, d, *J* 8.1, H$^{2'}$ and H$^{6'}$), 7.06–7.31 (6H, m). IR (CHCl$_3$) ν_{max}/cm^{-1} 1596, 1550, 1496, 1380. *m/z* (ESI) 208.3 ([M$^-$CH$_2$NO$_2$]$^+$, 100 %). Spectroscopic data matched those in the literature [16].

1-(Nitroethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2b)

Synthesized from **1** and **4** according to the procedure for **2a**, except for the use of nitroethane instead of nitromethane. The β-nitroamine (0.104 g, 77 % from **1**; 0.121 g, 97 % from **4**) was obtained as a yellow oil.

The ratio of diastereomers was found to be 1.7:1. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.43 (3H^{maj}, d, *J* 6.0, H^{10}), 1.59 (3H^{min}, d, *J* 6.0, H^{10}), 2.88 (2H, m, H^4), 3.41–3.55 (2H^{maj}, m, H^3) 3.74 (2H^{min}, ddd, *J* 14.0, 8.0, 6.0, H^3), 4.80 (1H^{min}, dq, *J* 6.0, 2.0, H^9), 4.95 (1H^{maj}, dq, *J* 6.0, 2.0, H^9), 5.11 (1H^{maj}, d, *J* 4.0, H^1), 5.13 (1H^{min}, d, *J* 4.0, H^1), 6.69 (1H, dd, *J* 6.0, 6.0, H$^{4'}$), 6.90 (2H, d, *J* 8.0, H$^{2'}$ and H$^{6'}$), 6.98–7.31 (6H, m). IR (CHCl$_3$) ν_{max}/cm^{-1} 3059, 2971, 2951, 1597, 1544, 1493, 1385, 1357, 747. *m/z* (ESI): 208.2 ([M$^-$CHCH$_3$NO$_2$]$^+$, 100 %). Spectroscopic data matched those in the literature [16].

1-(Nitropropyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2c)

Synthesized from **1** and **4** according to the procedure for **2a**, except for the use of nitropropane instead of nitromethane. The β-nitroamine (0.106 g, 75 % from **1**; 0.059 g, 98 % from **4**) was obtained as a yellow oil.

The ratio of diastereomers was found to be 1.4:1. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.92 (3H^{min}, t, *J* 7.2, H^{11}), 0.93 (3H^{maj}, t, *J* 7.2, H^{11}), 1.81 (1H^{maj}, dqd, *J* 14.7, 7.2, 3.3, H^{10}), 2.04–2.25 (1H + 1H^{min}, m, H^{10}), 2.81–2.94 (1H, m, H^4), 3.00–3.11 (1H, m, H$_4$), 3.46–3.69 (1H + 1H^{min}, m, H^3), 3.8 (1H^{maj}, ddd, *J* 13.8, 9.3, 5.7, H^3), 4.67 (1H^{min}, ddd, *J* 11.7, 9.6, 3.0, H^9), 4.85 (1H^{maj}, ddd, *J* 10.8, 9.3, 3.3, H^9), 5.12 (1H^{maj}, d, *J* 9.6, H^1), 5.22 (1H^{min}, d, *J* 9.3, H^1), 6.75–6.83 (1H, m), 6.91–7.00 (2H, m), 7.71–7.29 (6H, m). IR ν$_{max}$/cm^{-1} 3056, 2974, 2937, 1598, 1548, 1503, 751. *m/z* (APCI) 208.0 ([M$^-$PrNO$_2$]$^+$, 100 %), 297.9 (MH$^+$, 20 %). Spectroscopic data matched those in the literature [16].

1-(2-Oxoprop-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (2d)

Synthesis from **1**: To a solution of L-proline (0.008 g, 0.072 mmol, 0.15 equiv) in acetone (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.120 g, 0.53 mmol, 1.1 equiv) and 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1**, 0.100 g, 0.48 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 4 h, after which a saturated solution of NaHCO$_3$ (25 mL) was added and extracted into dichloromethane (3 × 25 mL). The organic extracts were combined, washed with a saturated solution of NaHCO$_3$ (2 × 25 mL), dried (MgSO$_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (7:1, hexane:ethyl acetate) to give the β-ketoamine (0.085 g, 67 %) as pale yellow stars.

Synthesis from **4**: To L-proline (0.004 g, 0.034 mmol, 0.15 equiv) in acetone (5 mL) was added the iminium ion complex (**4**, 0.150 g, 0.226 mmol, 1.0 equiv). The reaction mixture was stirred at rt until complete dissolution was observed, washed with saturated NaHCO$_3$ solution (25 mL), and extracted with dichloromethane (3 × 25 mL). The organic extracts were combined, washed with saturated NaHCO$_3$ solution (2 × 25 mL), dried (MgSO$_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (7:1, hexane:ethyl acetate) to give the β-ketoamine **2d** (0.056 g, 94 %) as a yellow oil.

m.p. 81–82 °C (no lit. m.p.). ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.07 (3H, s, H^{11}), 2.82 (2H, overlapping multiplets, one proton each from H^4 and H^9), 3.05 (2H, overlapping multiplets, one proton each from H^4 and H^9), 3.53 (1H, ddd, *J* 12.8, 8.8, 4.4, H^3), 3.65 (1H, apparent ddd, *J* 12.8, 5.2, H^3), 5.40 (1H, t, *J* 6.4, H^1), 6.78 (1H, dd, *J* 7.2, 7.2, H$^{4'}$), 6.93 (2H, d, *J* 8.0, H$^{2'}$ and H$^{6'}$), 7.13 – 7.17 (4H, m, H$^{5-8}$), 7.22–7.27 (2H, m, H$^{3'}$ and H$^{5'}$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 27.2 (C^4), 31.1 (C^{11}), 42.2 (C^3), 50.2 (C^9), 54.8 (C^1), 114.8 (C$^{2'}$ and C$^{6'}$), 118.3 (C$^{4'}$), 126.3 (C$^{6-8}$), 126.8 (C$^{6-8}$), 126.9 (C$^{6-8}$), 128.7 (C^5), 129.3 (C$^{3'}$ and C$^{5'}$), 134.4 (C^{8a}), 138.3 (C^{4a}), 148.9 (C$^{1'}$), 207.2 (C^{10}). Spectroscopic data matched those in the literature [21,34].

2-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-malonic acid dimethyl ester (2e)

Synthesized from **4** according to the procedure for **2a**, except for the use of dichloromethane as solvent and the addition of dimethyl malonate (1.1 equiv). The product **2e** (0.054 g, 73 %) was obtained as a yellow oil.

^{1}H NMR (200 MHz, CDCl$_3$): δ 2.85 (1H, dt, *J* 16.5, 5.2, H^4), 3.07 (1H, ddd, *J* 16.5, 8.4, 6.4, H^4), 3.55 (3H, s, H^{10}), 3.65 (3H, s, H^{11}), 3.60–3.70 (2H, m, H^3), 3.95 (1H, d, *J* 9.3, H^9), 5.70 (1H, d, *J* 9.3, H^1), 6.75 (1H, t, *J* 7.2, H$^{4'}$), 6.97 (2H, d, *J* 8.1, H$^{2'}$ and H$^{6'}$), 7.05–7.25 (6H, m). IR ν$_{max}$/cm^{-1} 2923, 2853, 1733, 1597, 1550, 1494, 1030, 1145, 750. Spectroscopic data matched those in the literature [16].

Synthesis of iminium ion complex (4)

To DDQ (0.109 g, 0.478 mmol, 1.0 equiv) in nitromethane or nitroethane (5 mL) was added 2-phenyl-1,2,3,4-tetrahydroisoquinoline (0.100 g, 0.478 mmol, 1.0 equiv) and the reaction mixture was left to

stand at rt for 24 h. The solvent was decanted and the residue washed with hexane (3 × 2 mL) and dried in vacuo to give the intermediate (0.157 g, 50 %) as yellow flowers.

Anal.: calcd. ($C_{31}H_{17}Cl_4N_5O_4$), C 55.96, H 2.58, N 10.53; found, C 55.97, H 2.60, N 10.58.

CCDC 800749 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <www.ccdc.cam.ac.uk/data_request/cif>.

SUPPLEMENTARY INFORMATION

Supplementary Information is available online (doi:10.1351/PAC-CON-11-01-01).

ACKNOWLEDGMENTS

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