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Studies of hydrogen isotope scrambling during the dehalogenation of aromatic chloro-compounds with deuterium gas over palladium catalysts

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Catalytic dehalogenation of aromatic halides using isotopic hydrogen gas is an important strategy for labelling pharmaceuticals, biochemicals, environmental agents and so forth. To extend, improve and further understand this process, studies have been carried out on the scrambling of deuterium isotope with protium during the catalytic deuterodehalogenation of model aryl chlorides using deuterium gas and a palladium on carbon catalyst in tetrahydrofuran solution. The degree of scrambling was greatest with electron-rich chloroarene rings. The tetrahydrofuran solvent and the triethylamine base were not the source of the undesired protium; instead, it arose, substantially, from the water content of the catalyst, though other sources of protium may also be present on the catalyst. Replacement of the Pd/C catalyst with one prepared in situ by reduction of palladium trifluoroacetate with deuterium gas and dispersed upon micronised polytetrafluoroethylene led to much reduced scrambling (typically 0-6% compared with up to 40% for palladium on carbon) and to high atom% abundance, regiospecific labelling. The improved catalytic system now enables efficient polydeuteration via the dehalogenation of polyhalogenated precursors, making the procedure viable for the preparation of MS internal standards and, potentially, for high specific activity tritium labelling.

KEYWORDS

catalysis, halogen exchange, isotope scrambling, mechanism, palladium, palladium trifluoroacetate, PTFE, reductive dehalogenation

1 | INTRODUCTION

The dehalogenation of haloaromatics is a widely utilised reaction, which is important in the preparation of labelled compounds and in the detoxification of halogenated waste. Both solution- and gas-phase procedures are employed in the reaction, as are photochemical procedures,^{1,2} metal hydrides,³⁻⁵ stannanes,^{6,7} hydrogen gas^{8,9} and various transfer hydrogen donors.^{10,11} The use of palladium complexes^{12,13} and palladium nanoparticle catalysts^{14,15} have also been investigated, whereas other powerful reductants such as samarium halides have been optimised for the process.¹⁶

Particularly relevant to the current work is a thorough investigation of hydrodechlorination by Sajiki et al.^{8,17} They studied the hydrodehalogenation of 4-chlorobiphenyl (and other chloroaromatics) with hydrogen gas under catalysis by palladium on carbon and noted the importance of the nature of the base to the efficiency of the reaction. A range of amine bases, best exemplified by triethylamine, shared the ability to promote rapid reaction, though some N-heteroaromatic bases

were strongly inhibitory. It had long been believed that the role of the base was simply to neutralise the hydrogen chloride generated in the reaction, but these workers were able to show that the amine had a more significant additional function with respect to facilitating the reaction mechanism (see later).

For many decades, dehalogenation with isotopic hydrogen gas, a palladium catalyst and triethylamine as base, has been a productive, routine, facile and common approach to labelling organic compounds with tritium.¹⁸ The reaction is site specific and proceeds in high yield. Indeed, the procedure has been widely employed in industrial research organisations and is currently offered by all the main radiolabelling contract laboratories. Hundreds of tritiated compounds have been prepared by this approach.^{19,20} Moreover, the corresponding deuterium labelling procedure has also been utilised for many years,^{21–23} either using conventional hydrogenation with deuterium gas or by transfer-hydrogenation with various deuterium donors.^{24,25}

The dehalogenation of chloroaromatics, however, generally gives low atom% abundance²⁶ due to competing isotopic scrambling reactions which introduce protium instead of deuterium or tritium at the labelling site. The presence of this undesired protium has been variously ascribed to scrambling with protiated heteroatoms in the substrate, or other protiated components of the reaction,²⁷ or with the solvent,^{28,29} especially alcohols.³⁰

We have studied several model deuterodechlorination systems over several years with the intention of identifying the nature of the scrambling processes and identifying more efficient dehalogenation systems.^{26,31,32} Our early studies utilised the dehalogenation of 2'chloroacetanilide (Figure 1) in conjunction with a deficiency of deuterium gas, to model the typical conditions of a tritiation reaction (Experimental Procedure A). Later studies used an excess of deuterium to model the conditions used in the preparation of deuterated materials for tracer studies and MS internal standards (Experimental Procedure B).

The 2'-chloroacetanilide model was particularly useful because both the degree of reaction and the percentage deuterium at the reaction site can be easily determined by ¹H-NMR due to a large isotope shift of the



FIGURE 1 Deuteration and scrambling in the deuterodehalogenation of 2'-chloroacetanilide (1)



FIGURE 2 Structures of the dehalogenation substrates used in the studies

6'-proton occasioned by deuterium substitution at the 2'position.³² This isotope effect also differentiates the 3' and 5' positions in the ¹³C-NMR of 2'-labelled acetanilides.

During the later stages of our studies, other substrates and conditions were utilised to ensure that the broad conclusions drawn were indeed general. The substrates used throughout these studies are shown in Figure 2. We now report the studies in detail.

2 | RESULTS AND DISCUSSION

Because nearly all literature dehalogenations with tritium or deuterium gas have been carried out at room temperature and at ambient pressure (sometimes somewhat lower for safety when using tritium), the reaction between deuterium gas and 2'-chloroacetanilide was studied at room temperature and with an initial deuterium pressure of 1 atm.

2.1 | Catalyst selection

An initial evaluation of a wide selection of potential catalysts was made, using the model system in Figure 1 to select a suitable catalyst for our studies. This catalyst would give a reasonable reaction rate whilst providing a sufficiently low (but not untypical) deuterium abundance in the product (Figure 3). On this basis, we excluded the metal blacks and the catalysts based upon rhodium, **FIGURE 3** Reaction extent and degree of scrambling (%H at the labelling site) found during the dehalogenation of 2'- chloroacetanilide by various active catalysts using D₂ gas, THF as solvent and triethylamine as base

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which, presumably because of the high degree of scrambling and low reactivity, are not used routinely for isotopic dehalogenation reactions. Instead, we selected 5% palladium on carbon as our model catalyst.

Like many Pd/C catalysts, this standard catalyst contains added water. Such catalysts are described as "pastes" though they are apparently dry, free-flowing powders. The water was originally added to protect against pyrophoricity, but it also ensures faster hydrogenation reactions, a phenomenon that has been ascribed to the facilitation of proton-hopping mechanisms.³³

The chosen catalyst was supplied as containing approximately 50% water, but the actual water content of the dispensed catalyst varies according to humidity. Drying at 200°C showed a weight loss of only 23.5%, whereas desiccation over activated silica gel or molecular sieve 4A showed weight losses of 23.5% and 22.8%, respectively. Rehydration of the dried catalyst by exposure to air at 98% humidity showed a weight uptake corresponding to 29%, which dropped back to approximately 24% at a humidity of 50%. Hence, a portion of the water content is easily removable and replaceable. It is possible, though, that a further portion of the water is strongly retained, maybe as chemisorbed species.

The other reaction parameters were set to provide conditions similar to those encountered in typical tritiation reactions. However, the scale was increased to enable accurate repeat analysis of the deuterium and protium in the products by spectroscopic techniques. The reaction volume was set at 2 ml, whereas the quantity of substrate was set at 0.5 mmol (Section 4: Procedure A). These conditions ensured that there would be a deficiency of deuterium in the model system because the remaining capacity of the 10 ml capacity reaction vessels used would be 8 ml (approximately 0.3 mmol D_2 allowing for solvent vapour pressure). The use of a deficiency of tritium with respect to the substrate is a common approach to atom efficiency in labelling procedures. Next, the amount of catalyst utilised was selected on the basis of initial studies, which showed that the amount of catalyst was negatively correlated with the percentage deuterium achieved in the [2'-D]acetanilide product (Figure 4); 30 mg of the catalyst was selected as a reasonable amount.

Studies also showed that the percentage deuterium was not substantially affected by the quantity of the base (triethylamine) used, provided this was greater than 1 mol/mol of substrate.

A selection of solvents was examined, and THF was chosen as a typical solvent (Figure 5). Under these conditions, the reaction was complete after 2 h.

Once the standard conditions were defined, several studies were carried out to investigate factors affecting the degree of scrambling. Of these, the most revealing were studies of the timing of substrate addition (Figure 6). These data suggest that one or more competing isotope scrambling reactions are occurring in the absence of the substrate. 4 WILEY – Radiopharmaceuticals



FIGURE 4 Effect of catalyst amount on the scrambling (%H at the labelling site) for [2'-D] acetanilide (Procedure A)

% 100 80 60 40 20 0 IDAIMettanol Methanol Ethy acetate OWH Toluene Acetone 14th Ether Ethanol ■ % Scrambling Reaction (% of theory)

FIGURE 5 Effect of solvent on the reaction extent and isotopic scrambling in the deuterodehalogenation of 2'-chloroacetanilide



To investigate these scrambling reactions further, we utilised two new chloro-substrates, 4-chlorophenylsuccinimide (**3**) and phenyl 4-chlorobenzoate (**4**), which had similar rates of reaction but which showed very different degrees of scrambling in the deuterated products: [4-D]phenylsuccinimide (43%

15

[2'-D]Acetanilide

30

Minute

360

[4-D]Benzophenone

1080

% D

80

70

0

5

scrambled) and phenyl [4-D]benzoate (only 8% scrambled).

We hypothesised that the different degree of scrambling between the substrates probably reflected different degrees of inhibition of the scrambling reactions by the substrates. Further information was provided by a study of the same two substrates under competitive conditions (Figure 7), which showed that the dehalogenation rate of 4-chlorophenylsuccinimide (3) was substantially inhibited in this case, suggesting that the phenyl 4-chlorobenzoate (4) was achieving preferential access to the reaction site, possibly by tighter binding.

The substrates 3 and 4 differ substantially in electron availability. The chlorophenyl ring in substrate 3 is electron-rich in comparison with that in substrate 4, which is electron-poor (Page 1 of the Supporting Information). Thus, the ZDO partial charges³⁴ of the carbon at the C-Cl reaction site for 3 is -0.069, whereas for 4, it is -0.0285. To check if this electron availability difference was predictive of interaction with the catalyst and hence of the precedence of the more electron-poor substrate in competitive reactions, two other pairs of compounds with significant differences in ZDO partial charge were also examined under competitive conditions. The results for each pair confirmed the behaviour: in each case, the more electron-poor substrate reacted faster and slowed the reaction of the more electron-rich substrate (Page 2 of the Supporting Information).

2.2 | Studies of the reaction parameters affecting the degree of scrambling

The scrambling of isotope between protiated hydroxylic solvents and deuterium gas over platinum group metals



 $FIGURE \ 7 \quad \ \ {\rm Reaction\ time-course\ for\ the}$

deuterodechlorination of 4-chlorophenylsuccinimide (**3**) and phenyl 4-chlorobenzoate (**4**) either alone (0.1 mmol) or under competitive conditions (0.05 mmol each) using Procedure B 5

has long been known³⁵⁻³⁸ and indeed has been exploited for the large scale preparation of high-enrichment heavy water.³⁹ The nature of the exchange mechanism is a matter of debate, but studies suggest that a hydrated proton intermediate, possibly H₃O⁺, may be a key intermediate.⁴⁰ More recently, the exchange between O-deuterated methanol and hydrogen gas over palladium on carbon has been used for the preparation of deuterium gas on a convenient and simple laboratory scale.¹⁷ It seemed likely, therefore, that a similar process might be contributing to the scrambling reaction(s) during dehalogenation. In support of this idea, carrying out the dehalogenation reaction of 2'-chloroacetanilide (1) under ordinary hydrogen gas (protium) in the presence of added deuterium oxide resulted in acetanilide partially labelled (21%D) with deuterium at the 2'-position.

2.2.1 | The effect of solvent, base and reaction product

We next undertook a series of studies of the gas-phase component of the dehalogenation reaction. Initially, we utilised phenylacetylene as a rapidly reduced surrogate to report the degree of scrambling of the deuterium gas by analysis of the styrene reduction product (Page 3 of the Supporting Information). Subsequently, the results were confirmed directly and further studies carried out, using a residual gas analyser: a quadrupole mass spectrometer that can sample and analyse small (200 μ l) quantities of isotopic hydrogen gas.

Access to this technology allowed the effects of components of the dehalogenation reaction upon the degree of isotope scrambling to be separately evaluated by analysis of the quantity of hydrogen, hydrogen deuteride and deuterium in the gas above the reaction.

The results were clear (Figure 8) and showed that scrambling took place with the solid catalyst alone, in the absence of any THF solvent or triethylamine base. Moreover, treatment of the catalyst with deuterium gas, addition of THF/CDCl₃, filtration and analysis by D-NMR showed the time-dependent generation of HOD (peak at δ 3.4 ppm in THF).

Further, reaction components were then investigated separately. This showed only minimal inhibition of the scrambling by triethylamine (though triethylamine deuterochloride was later shown to be somewhat more effective as an inhibitor), whereas the THF solvent did not inhibit the scrambling.

However, the scrambling was much reduced when the catalyst was dried over molecular sieve 4A or silica gel. Moreover, studies employing hydrogen (protium) gas and palladium on carbon catalyst treated with deuterium



FIGURE 8 Gas-phase analyses of H₂, HD, D₂ (m/z 2, 3, 4) of the effects of the individual components of the deuterodechlorination reaction. (A–D) Time-course for the reaction (at 0, 10, 20 and 40 min) in the absence of any dechlorination substrate. (E) Solid catalyst alone, no solvent or base present. (F) Catalyst plus triethylamine, no THF solvent. (G) Catalyst plus THF alone, no triethylamine. (H) Catalyst plus THF and triethylamine (spectra E–H were all recorded at 30 min reaction time)

oxide showed rapid formation of hydrogen deuteride and deuterium. Furthermore, this scrambling was increased if the catalyst had been dried previously to remove protiated water (Page 4 of the Supporting Information).

2.2.2 | The effect of the substrate on the gas scrambling

Next, the effect of the dehalogenation substrate on the extent of deuterium gas scrambling was examined, again using substrates **3** and **4**. The results are shown in Figure 9, which shows the isotopic purity of the deuterium (%D/(D + H) against time. Both substrates inhibited the scrambling reaction, but to different extents.

The degree of inhibition was then examined at two substrate concentrations (Figure 10), which showed a concentration-dependent inhibition that was more effective for substrate **4** than for substrate **3**. This is in line with the higher degree of scrambling for substrate **3** in the dehalogenation reaction and suggests that the degree of interaction (binding or reaction) with the catalyst is an important factor in the degree of scrambling experienced.

In this regard, the adsorption strength of the various monohalobenzenes to palladium catalysts have been previously shown to be I >> Br > Cl, though this need not transfer to overall reaction rate in any particular case as fast reaction requires an optimum balance between adsorption strength and carbon-halogen bond energy.¹⁰ The tight binding is particularly striking for iodocompounds and has been well characterised for iodobenzene, where thermal desorption studies⁴¹ have shown facile binding plus reduction of the phenyl to benzene by subsurface hydrogen. The palladium-bound iodine from the deiodination process is strongly bound and poisons the catalyst. Indeed, it was so tightly bound that no iodine desorption was observed until approximately 1000°C. The different binding strengths between the halogens allows for selectivity between dehalogenation sites, and this has been exploited in many labelling studies.⁴² The issue has been briefly reviewed by Filer,⁴³ who noted that in competitive dehalogenations,



FIGURE 9 Inhibition of D_2 gas scrambling by dehalogenation substrates **3** and **4**

the iodoarene always reacts first, although its reaction rate under noncompetitive conditions is often slower than the other haloarenes. It was also suggested that the strong adsorption of the iodoarene would exclude any hydrogen transfer arising from the solvent (and presumably from any other components of the reaction mixture) but would not similarly exclude the small tritium molecule from access to the active site, thus accounting for the higher specific activity that is achieved in the tritiodehalogenation of iodoarenes.

Our own studies have also shown a very powerful inhibition of deuterium gas scrambling and inhibition of dechlorination reactions by iodo-compounds (Page 5 of the Supporting Information). 7

From the earlier gas-phase experiments, it was clear that water content of the catalyst was an important contributor to the scrambling reaction(s). As noted earlier, carbon-based platinum group catalysts are usually marketed with some added or residual water to facilitate reductive reactions via 'proton-hopping'³³ a process that has been observed in real time on a catalytic surface by atomic force microscopy.⁴⁴

The role of water and water-derived species on metal surfaces has been extensively reviewed recently and the situation is complex.⁴⁵ Reactions are known in which surface-oxidised catalyst can interact with water to give OH⁻ species, whereas multiply hydrated protonated species $H^+(H_2O)_n$ may be formed on surfaces exposed to hydrogen, especially if Cl⁻ is present. The actual hydrogen species present on a specific catalyst surface will therefore reflect the preparation of the catalyst and its storage. whereas the species present during dehalogenation will reflect the actual reaction environment, the solvent, the substrate, the base, the product and by-products.

The studies reported earlier showed clearly that the catalyst is one source of the protium for the scrambling reaction(s). However, the other components of the reaction might also supply protium; hence, we examined these in turn.

2.2.3 | The solvent

The exchange of tritium from tritium gas into the reaction solvent molecules during dehalogenation reactions has been observed with polar solvents in the presence of palladium oxide and palladium on barium sulphate catalysts.⁴⁶ It is also known that cyclic ethers such as dioxan





can act as hydrogen donors under catalysis by palladium on carbon⁴⁷; hence, the solvent must be considered as a potential protium source.

To investigate this possibility, we studied the dehalogenation of **1** under standard conditions but replacing the THF solvent with $[D_8]$ THF. This gave no increase in the %D in the product [2'-D]acetanilide, suggesting that the solvent was not the source of the protium. Moreover, no increase in the protium content of the $[D_8]$ THF was detected. Similarly, analysis by GC-MS and D-NMR showed no deuterium above natural abundance levels in the protiated THF from standard deuterodehalogenation reactions.

The fact that at least some of the scrambled protium arises from water in the catalyst rather than the reaction solvent is consistent with our previous collaborative study with chemists at Janssen (Johnson & Johnson N.V.). They exposed the solvents THF, dioxan, ethyl acetate, DMA and DMF to tritium gas in the presence of a palladium on carbon catalyst. Subsequent tritium-NMR of the solvents in our laboratories showed only signals from tritiated water. No tritiated solvent resonances nor any other resonances other than HOT were detected.⁴⁸

2.2.4 | The substrate or product

Another potential source of protium could be via exchange of the aromatic protons or the NH proton of the substrate or product. However, there was no increase in the percentage of deuterium in the [2'-D]acetanilide if [amide-*N*-D]2'-chloroacetanilide was employed as substrate, nor did the aromatic protons of the [2'-D]acetanilide or 2'-chloroacetanilide become labelled. D-NMR showed only the expected deuterium at the 2'-position of the [2'-D]acetanilide.

2.2.5 | The base

Because the triethylamine contains α -methylene protons, and these are known to be prone to isotopic exchange, particularly by labilisation on metal catalysts,⁴⁹ we carried out detailed MS and NMR studies with Et₃N, Bu₃N and Hex₃N, which showed that they do not become deuterated during the reaction. Nor were any products related to the amines (other than the deuterochlorides) detected by D-NMR or GC-MS. Hence, if the base provides the protium, it is not via an exchange reaction or via a dehydrogenation/reduction sequence.

Traditionally, it has been believed that the function of the trialkylamine base in these reactions is to neutralise the hydrogen halides released, because these latter are catalyst poisons. However, although the reaction is indeed slow and often incomplete in the absence of a base, this does not seem to be their only role.

We have examined an extensive range of inorganic and organic bases (Figure 11) and found that the nature of the base^{8,9} is indeed critical for the success of the reaction and also for the %D achieved in the product. We find that the open-chain monobasic trialkylamines are particularly effective in terms of the %D obtained at the labelling site.

In our hands N,N-diisopropylethylamine (Hünig's base, DIPEA) proved the most effective trialkylamine. However, the aliphatic open chain trialkylamines (red) clearly form a favoured group (Page 6 of the Supporting Information) for the delivery of high atom % abundance labelling. Only in the case of bifunctional trialkylamines with short linkers (N,N,N,N-tetramethyl methylenediamine and N,N,N,N-tetramethylethylene diamine) was deuterium abundance lowered or the reaction inhibited, a behaviour likely to result from the chelating ability of these systems.

From our results, it is possible that *N*-methyl *N*,*N*-dialkylamines are somewhat anomalous. With the single exception of diethylmethylamine, the use of *N*-methylamines resulted in lowered %D. However, the dehydrogenation of *N*-methylamines on palladium surfaces is a known process,⁵⁰ and hence, this could contribute to the dilution of the isotope pool in these cases. It is noteworthy that the pyridines investigated resulted in little reaction or inhibited the reaction, a phenomenon previously reported^{8,9} and likely to result from strong complexation to palladium active sites on the catalyst.

Because the base, solvent, substrate and product do not appear to be the source of the isotopic scrambling, the suspicion falls next upon the remaining players: the deuterium gas itself, the catalyst, or adventitious water in the apparatus. The deuterium gas cylinders used during the studies were of 99.8% isotopic purity. Moreover, the use of flame-dried apparatus and commercial super-dried THF solvent again showed no reduction in the scrambling.

2.2.6 | The catalyst

Thus, the only identified source of protium from our studies was the catalyst, as noted earlier. Moreover, the indications were that at least some of the scrambled protium arose from water. Drying of the catalyst by heating under high vacuum did give improved deuterium abundance in the dehalogenation product, but an unacceptable degree of scrambling remained. Of course, water may not be the only catalyst source and it seems likely alkylamines. Black = %D with other bases

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and none



therefore that there are further protium sources associated with the catalyst. In this regard, palladium hydride phases have long been known⁵¹ and are catalytically active even in the absence of hydrogen gas.^{52,53}

Palladium on carbon catalysts are generally prepared in highly aqueous protiated environments often involving a final high-temperature treatment with protium gas^{54,55}; hence, the nature of the protium species associated with the metal and their migration and transformations are illdefined, though recently a proton-transfer mechanism involving water has been shown by scanning tunnelling microscopy to proceed via an H₃O⁺-like transition state.⁴⁴ In addition, the role of the carbon support in protium delivery and transport is not well understood, though it is known to be important in isotopic exchange processes via its participation in spillover mechanisms^{49,56-58}; hence, the support cannot be excluded as an ancillary source of protium.

FIGURE 12 Literature mechanism of dechlorination as modified for deuterodechlorination

2.3 | Experiments related to the dechlorination reaction mechanism

mechanism of dechlorination The of variously substituted aliphatic chlorides on palladium has been investigated in detail and has been shown to be relatively insensitive to substituent effects.⁵⁹ However, our findings relate to aromatic dehalogenation, an area for which mechanistic information has been reviewed recently⁶⁰ and are broadly consistent with a published tentative mechanism for the palladium-catalysed nonisotopic aromatic dechlorination reaction.⁹ This mechanism involves a single electron transfer (SET) from the tertiary amine to the complexed chloroaromatic to give a trialkylaminium radical cation and a chloroaromatic radical anion. Such radical anions have been proposed as intermediates in other related dechlorination systems.^{61,62} The radical



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anion then loses chloride ion to give an aryl radical before picking up deuterium. Figure 12 demonstrates the postulated process modified with respect to deuterodehalogenation.

The SET nature of the reaction was inferred from inhibition studies with the known SET inhibitors tetracyanoethylene (TCNE) and tetracyanoquinodimethane (TCNQ), and indeed, we have confirmed the very powerful inhibitory effect of TNCE in the dehalogenation of **1**. However, it should be noted that TCNE possesses metal chelation properties in addition to its radical scavenging ability and that, in addition, some stable-radical scavengers are inappropriate tools for investigating palladium-based systems because they react rapidly with palladium hydrides.⁶³

The by-product of the proposed SET reaction is a tertiary aminium radical cation, a well-characterised species produced in a range of chemical and electrochemical reactions^{64,65} and involved also in metabolic demethylations.⁶⁶ A similar SET mechanism involving formation of the triethylaminium radical cation is known to occur in the reduction of quinones where the products form a close ion-pair.⁶⁷ Moreover, the SET reduction of aryl halides by SmI₂, a one electron donor, is well known. In that case, the hydrogen arises via aryl radical abstraction from the THF solvent.⁶⁸ There is, therefore, reasonable, but not unequivocal, background support for the proposed SET mechanism.

Of relevance to the formation of triethylaminium cations is the observation that triethylamine can react with palladium on carbon to give a palladium hydride species.⁶⁹ In this reaction, an initial coordination of the triethylamine to Pd(0) is followed by insertion of palladium into an α -CH bond leading to a hydridic palladium hydride coordinated to an iminium cation (Figure 13). Such a species might be able to promote dehalogenation, as it is postulated to be the reactive agent in conjugate reduction of double bonds. Precedent for the formation of such species with palladium is known.⁷⁰

With respect to our observations of the role of the trialkylamine bases, a correlation might be expected between %D and the propensity of the amine base for SET. However, the interpretation of amine oxidation potentials (Ep) is complex. Both the ability of the incipient aminium radical cation to achieve the necessary



FIGURE 13 Putative formation of hydridic palladium species by reaction of triethylamine with palladium on carbon

planar geometry and its stabilisation by substituents are critically dependent on structure.^{64,65} For the monobasic trialkylamines acvclic and for N.N.N.Ntetramethylhexane-1,6-diamine, all of which have low anodic oxidation potentials of around Ep. 0.7 V, the achievement of planarity is facile. However, the shorter chain bis-dimethylamino systems and the cyclic alkylamines face greater steric constraints. The rather poor performance of diaza[2,2,2]bicyclooctane (DABCO) may be explained by a similar rationale. N-Methylpyrrolidine, with more favourable geometry for planarity around the nitrogen radical⁷¹ and an Ep of 0.68 V, shows intermediate behaviour.

There are, however, arguments against the proposed SET mechanism, at least as far as it implies a stoichiometric process. One is the absence of cleavage products of the quaternary Schiff base, derived from the aminium radical cation by the facile loss of a proton and an electron. The formation of this species from the aminium ion is known to be rapid, yet no trace of the expected aldehyde or secondary amine hydrolysis products could be detected by GC-MS or ¹H-NMR for the trialkylamines Et_3N , Bu_3N or Hex_3N , even when extra water was added to the reaction. Hence, the SET aspect of the reaction could well be an initiation process rather than an overall stoichiometric reaction.

A further objection is that from all the reactions that we have studied, we have been unable to identify any biphenyl-like radical-coupling products, though such products have been observed in a related palladium deuterodechlorination system where calcium metal was incorporated with the palladium catalyst to provide electron-donation.⁷² It may be that in the case of palladium on carbon, the strong adsorption of the substrate on the catalyst and the presence of surface and subsurface active hydrogen species leaves little chance for the aryl radicals to migrate and couple.

Nor have we been able to facilitate the reaction by employing radical initiators, photosensitisers, ultraviolet light of 245 and 360 nm wavelengths or visible light. Indeed, the reaction proceeds well in the dark as previously demonstrated.⁹

We noted earlier the preference of the palladium on carbon catalyst for reaction with electron-poor chloroarenes over electron-rich systems, a fact that has been ascribed, for other palladium systems, to the ability of chloroarenes to accept back-donation from Pd(0) to form reasonably stable pre-reactive complexes.⁷³ This preference for electron-poor haloarenes is typical of reactions involving oxidative addition of a chloroarene to palladium(0) species.^{74,75} Moreover, such an oxidative-addition mechanism has been advanced for the dechlorination of chloroarenes by a Pd(0) catalyst produced by

borohydride reduction of palladium (phenanthroline) dichloride.⁷⁶ It therefore seemed worthwhile to investigate the similarity between the Pd/C dehalogenation and a typical oxidative-addition system. We chose the Suzuki-Miyaura reaction as our model, because it is a typical oxidative-addition system that is compatible with our substrates and reaction conditions.^{77,78} Although heterogeneous palladium catalysts have been used for Suzuki-Miyaura and similar reactions⁷⁹⁻⁸¹ chloroarenes have generally shown low reactivity.⁸² Indeed, we found that our palladium on carbon catalyst showed little activity in a trial reaction between methyl 4-chlorobenzoate and phenylboronic acid carried out in THF in the presence of potassium carbonate. Fortunately, however, the catalyst showed greatly enhanced activity once it had been activated with deuterium gas.

We further investigated the similarities between the reactions using an ester. 4-chlorophenvl 4-chlorobenzoate (7) and an amide, N-(4-chlorophenyl)-4-chlorobenzamide (12), both of which possess electronpoor and electron-rich chloroarene rings within the same molecule. Initially we studied the deuterodechlorination of the compounds. These showed the expected preference for deuteration at the electron-poor chloroarene ring. The results from both compounds were very similar. In the case of the ester 7, (Figure 14) only around 1% of the dechlorination took place via the electron rich ring, whereas compound 12 showed only traces (approximately 0.1%) of the reaction via the electron rich site at the earliest time point and none thereafter (Page 7 of the Supporting Information).

Subsequently, we carried out the deuterodechlorination under the conditions of the Suzuki–Miyaura reaction (i.e., in the presence of phenylboronic acid and potassium carbonate at 65° C) and analysed all the products by GC-MS. We found that the

selectivity ratio between the electron-poor ring and electron-rich ring dechlorination routes had reduced from approximately 90:1 to approximately 5:1, presumably as a result of the increase in temperature from room temperature of approximately 18°C to 65°C. Interestingly however, the Suzuki-Miyaura phenylation reaction, which was occurring in parallel, also gave a similar selectivity (7:1 ratio) between phenylation at the electron-poor and electron-rich rings (Figure 15). The two reactions therefore do share very similar behaviour in that (i) both require that the catalyst is activated with hydrogen, (ii) both have a preference for electron-poor chloroarenes and (iii) both give similar ratios of products from the two routes, one via an electron-poor ring and one via an electron-rich ring. It therefore seems possible that a similar, or even the same, catalytic site is involved in both reactions and that oxidative-addition forms a component of the reaction mechanism.

The literature provides many examples of proposed dehalogenation reaction mechanisms⁶⁰ and single electron, ionic or oxidative-addition/reductive-elimination processes are all represented. Moreover, the heterogeneous nature of the catalyst has not been definitely confirmed in many, perhaps most, cases.⁸¹ Consequently, at this stage, it is not possible to confirm a definitive mechanism for the trialkylamine/palladium(0) catalysed deuterodechlorination reaction.

It is noteworthy that the deuterodechlorination reaction progresses (though less efficiently) in the absence of trialkylamines (Figure 11). As such, it may be that the actual mechanism of the dechlorination reaction is defined by the specific reagents and reaction conditions: in the current case by the use of trialkylamines as base and by the requirement for catalyst activation by hydrogen. It may even be the case that more than one mechanism is in operation or that the trialkylamine SET



FIGURE 14 Reaction time course of the deuterodechlorination of 4-chlorophenyl 4-chlorobenzoate (7)



FIGURE 15 Competitive dechlorination and Suzuki–Miyaura phenylation of 4-chlorophenyl 4-chlorobenzoate (7)

process merely acts as one step in the overall mechanism (as an initiator?). Further studies of this important reaction are therefore warranted.

2.4 | Developing a better catalytic system

Given the complexity of the palladium on carbon system, the issue for isotope chemists therefore becomes how to achieve a catalytic system that gives less scrambling and which therefore increases the quality of the labelled compounds prepared and opens the possibility of routes that are currently obviated by scrambling (e.g., polydeuterodechlorination or polytritiodechlorination). We confirmed (Figure 16) that intensive drying of the catalyst was only partially effective in this regard, as previously noted by other workers.⁴⁸ It seemed unlikely that scrambling by such catalysts could be improved unless the dechlorination reaction were made more

competitive with the scrambling reaction(s). We therefore studied the effect of additives, because admixtures with other catalytic metals have been shown to improve labelling outcomes for the rhodium black system^{83,84} and for deuterium exchange over palladium and platinum.85,86 The effect of adding, Crabtree's catalyst, (PPh₃)₃RuCl₂, Ag triflate, PtCl₂, PtO₂, RuO₂, IrO₂, Au₂O₃ was investigated but unfortunately none led to an improvement in either the extent of reaction or the %D achieved and most led to a significant reduction, possibly by increasing the H_2O/D_2 exchange reaction. An alternative would be to promote the SET mechanism. Unfortunately, the addition of AIBN and/or irradiation with ultraviolet light (360 nm) showed no clear enhancement of either the degree of reaction or of deuteration level. Similarly, 360-nm irradiation in the presence of the photosensitisers benzophenone or rhodamine 6G only resulted in reduced extent of reaction and degree of labelling (Page 8 of the Supporting Information).



FIGURE 16 Degree of scrambling in [4-D] phenylsuccinimide (from 0.1 mmol of **3**) with palladium on carbon, dried palladium on carbon and Pd(0) generated in situ from palladium trifluoroacetate

Because palladium on carbon proved intransigent in this regard, we decided to prepare a heterogeneous palladium catalyst by *in situ* reduction of Pd(II) within and during the dehalogenation reaction.

For this screen, we utilised substrate **3** because it was reactive but prone to a high degree of scrambling. With a single exception, screening a number of Pd(II) systems showed either no activity, or little reactivity with a high degree of scrambling. The exception was palladium trifluoroacetate, a catalyst precursor of Pd(0) that had previously shown exceptional activity for benzylic isotope exchange labelling.⁸⁷ Interestingly, the trifluoroacetate anion can coordinate to phosphine Pd(0) complexes in the presence of triethylamine, facilitating the oxidative addition of phenyl iodide to give anionic phenyl trifluoroacetate complexes rather than the expected phenyl iodide addition products.⁸⁸

Although the reactivity of the palladium trifluoroacetate precursor was low, the degree of scrambling was also gratifyingly very low.

The reduction of Pd(II) salts and complexes to Pd(0) can be accomplished by various reductants, including hydrogen, and the ready formation of a particulate black deposit certainly suggests that the reduction to the metal occurred in this case. However, the heterogeneous nature of the reaction has not yet been demonstrated, and the formation of low valent palladium, palladium nanocluster, colloidal palladium species or even species with different cooperating palladium oxidation states⁸⁹ is still possible.

Notwithstanding, the low activity of the catalyst still needed substantial improvement. Hence, the effect of adding a catalyst support was investigated. To minimise any scrambling arising from water in the support, a selection of dry or hydrophobic materials was used Figure 17.

All the supports gave results that were much better than palladium on carbon. But clearly the best support material was micronised polytetrafluoroethylene (PTFE). This support was therefore investigated further by varying the quantity of palladium trifluoroacetate and PTFE powder. A suitable combination was obtained when palladium trifluoroacetate (4 mg) was treated with micronised PTFE (20 mg) in THF (2 ml) and deuterium gas (8 ml). Under these conditions (Procedure C in Section 4), 0.1 mmol of the scrambling-prone 4-chlorophenylsuccinimide was completely dehalogenated in 3 h, and the amount of scrambling in the [4-D] phenylsuccinimide product was <6%.

Isolation of the solid phase from the reaction and investigation by Raman and FTIR showed no significant changes in the spectra of the PTFE support (Page 9 of the Supporting Information) though the material (now greyblack) showed fluorescence in the Raman. Microscopy showed that the micronised PTFE granules (approximately 2–5 μ m in size) aggregated to form clumps, which were now decorated by small islands of black palladium trifluoroacetate-derived material, probably Pd(0) gra nules, (approximately 1–10 μ m in size) from which the fluorescence was derived (Page 10 of the Supporting Information).

With this new catalytic system in hand, the generality of the procedure (Experimental Procedure C) was checked with a range of dehalogenation substrates of varying structure. The results were encouraging for all the substrates. They are shown in Figure 18.

Because the new catalytic system clearly reduces the isotopic scrambling, the polydehalogenation of polychloro-substrates (and presumably of polyiodo- and polybromo-substrates) becomes a viable option for preparing polydeuterated internal standards or possibly of polytritiated ligands. Some initial work in this area was therefore carried out with deuterium.

Two polychloro-substrates were investigated: 2,3,4-trichloroanisole (8), which would provide an internal standard for anisole analysis, and 2,4,6-trichlorophenyl 4-chlorobenzoate (11), which allowed comparison with the chlorinated phenyl benzoates studied previously.



FIGURE 17 Degree of scrambling in [4-D] phenylsuccinimide (from 0.1 mmol of **3**) when Pd(0) was prepared from palladium trifluoroacetate in the presence of various support materials

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FIGURE 18 Comparison of the degree of scrambling (%H/(H + D)) in the deuterated products from the dechlorination of a range of substrates using 5% palladium on carbon or a palladium catalyst generated in situ from palladium trifluoroacetate and micronised PTFE

We were pleased to find that the new catalytic system provided [2,3,4-D₃]anisole with good deuterium content $(96.5\% D_3)$ and with an unlabelled compound content of <0.01% making the compound suitable for use as an internal standard for GC-MS assay (Page 11 of the Supporting Information). The corresponding labelled compound prepared using palladium on carbon had an unlabelled anisole content of 4.7% rendering it useless for this application; 2,4,6-trichlorophenyl 4-chlorobenzoate was studied to investigate the course of the deuterodechlorination process. Halting the dechlorination of this substrate prior to the completion of the reaction enabled GC-MS analysis of the dechlorination intermediates. All the intermediates had a base peak at $106 (D-C_6H_4-CO + ion)$ showing that the dehalogenation occurred first at the electron-deficient 4-chlorobenzoate moiety. Subsequent dechlorinations resulted in $[2,4,6-D_3]$ phenyl [4-D]benzoate with a deuterium content of 87% D₄, corresponding to a scrambling of 3.35% per chlorosubstituent replaced, and a D_0 content of <0.065% (Page 12 of the Supporting Information).

3 | CONCLUSIONS

The study the deuterodechlorination of of 2'-chloroacetanilide and other chloroarenes over 5% palladium on carbon in tetrahydrofuran solution identified catalyst-bound water as a major contributor to the scrambling of isotope during the reaction, though other sources of protium may be present on the catalyst or the catalyst support. The tetrahydrofuran solvent and the triethylamine base were not sources of the protium involved in the scrambling. The degree of isotopic scrambling was greatest for substrates with electron-rich chloroarene rings. Isotopic exchange between the donor deuterium gas and catalyst water was important in the overall isotopic scrambling observed, and this exchange was inhibited by the halogenated substrate. The inhibition was concentration dependent and was greatest for substrates with electron-poor chloroarene rings.

Study of a range of bases showed that the aliphatic trialkylamines formed a favoured set, providing the highest degree of reaction and the highest abundance of isotope in the labelled product.

Competitive reaction studies have shown that the dehalogenation reaction has similarities with the heterogenous Suzuki–Miyaura reaction, and hence, the active site(s) of both reactions could be similar and oxidative addition of the chloroarene to a Pd(0) may be involved in the mechanism. However, we have confirmed the inhibition of the reaction by the radical scavenger tetracyanoethylene,⁸ and hence, the involvement of single electron species in the reaction mechanism still seems likely.

Replacement of the Pd/C catalyst with one prepared in situ from palladium trifluoroacetate and dispersed upon micronised polytetrafluoroethylene led to much reduced scrambling and to high atom % abundance, regiospecific labelling for a range of halo substrates. The new catalytic system was applicable to debromination and deiodination and was also suitable for the preparation of high-quality labelled compounds via the deuterodechlorination of polychlorinated precursors. It may also have applications to the preparation of multitritiated ligands by polytritiodehalogenation.

4 | EXPERIMENTAL

4.1 | Equipment

The deuterodehalogenation reactions were carried out using a low dead-volume stainless steel gas-transfer manifold. This enabled either high vacuum or deuterium gas to be applied to the sealed reaction tubes via a 22 gauge Luer needle, which penetrated the reaction tube septum. The manifold could be used both to evacuate the reaction tubes under high vacuum and to supply deuterium gas to the tubes from a 200-ml capacity syringe. The reaction tubes used were thick-walled test tubes of 10-ml capacity sealed with 20-mm PTFE lined aluminium crimp septa. These tubes (10-ml capacity "Discover" tubes) and septa were obtained from CEM Microwave Technology Ltd, 2 Middle Slade, Buckingham Industrial Estate, Buckingham, MK18 1WA.

NMR spectra were recorded on a Bruker AVIII500 NMR spectrometer in CDCl₃ at 500 MHz for ¹H, 100 MHz for ¹³C and 61 MHz for D and analysed by Bruker TopSpin software. Raman spectra were measured on crystalline samples supported on glass microscope slides using a ThermoScientific DXR Raman Microscope at laser frequencies of either 532 or 780 nm. Infrared spectra were recorded for crystalline samples on a sapphire anvil using an Agilent Resolutions Pro spectrometer. GC-MS analysis was performed using 1.0-µl injections of solutions at approximately 1 mg/ml in dichloromethane using an Agilent 6890N gas chromatograph coupled to a 5973 mass selective detector The column was a Phenomenex ZB-5MS, 30 m \times 0.25 mm, used with a temperature profile: 50°C (held for 3 min), ramp at 10°C per minute to 250°C and held for 2 min, or, in the case where high molecular mass compounds may be present, an injection volume of 1.0 µl at 50°C (held for 3 min), ramping to 325°C at 25°C/min (held for 6 min). The carrier gas was helium at 1.0 ml/min. Hydrogen, hydrogen deuteride and deuterium analyses were carried out using an EcoSys P residual gas analyser, ESS Ltd, Northwich CW9 7LU, UK. The molecular formulae for the labelled compounds were determined at the National Mass Spectroscopy Facility, University of Swansea, using an LTQ Orbitrap XL operating in APCI or NSI modes.

4.2 | General reagents

The tetrahydrofuran reaction solvent (>99.5%, Item 186562) and triethylamine base (Item 471283) were obtained from Merck (Sigma-Aldrich Company Ltd), The Old Brickyard, New Road, Gillingham, Dorset SP8 4XT, UK. Other solvents were of high quality (classified as anhydrous) and were obtained from either Merck (address above) or Fisher Scientific (Fisher Scientific UK Ltd, Bishop Meadow Road, Loughborough LE11 5RG, UK). Micronised PTFE powder was obtained from Hagen Automation Ltd, Greybern House, Templars Way, Sharnbrook, Bedfordshire MK441PY, UK. Graphite Powder Kasp K30050 was obtained from Carl Kammerling International Ltd, Glanydon Industrial Estate, Pwllheli LL53 5LH, UK, via Amazon.co.uk. Other general reagents were obtained from regular chemical supply houses and were used as received.

4.3 | Catalysts

The stock catalyst used throughout the studies was 5% palladium on carbon (Aldrich Item 27,670-7) and was purchased from Merck (Sigma-Aldrich Company Ltd), The Old Brickyard, New Road, Gillingham, Dorset SP8 4XT, UK This catalyst was supplied containing, nominally, 50% added water but showed a loss on drying at 200°C of only 23.5% by weight. The catalyst was stored in bulk in a tightly sealed container, and samples were dispensed rapidly into reaction tubes to ensure that the water content did not change as a result of equilibration with atmospheric moisture.

The catalysts used for comparison purposes were 10% palladium on carbon (Aldrich Item 20,569-9), rhodium black (Aldrich Item 267341), platinum black (Aldrich Item 20,591-5), palladium black (Aldrich Item 520810), platinum(IV) oxide (Aldrich Item 20,603-2), Lindlar catalyst (Aldrich Item 20,573-07), 5% palladium on calcium carbonate (Aldrich Item 21,435-3), 5% palladium on barium sulphate (Aldrich Item 27,799-1), 5% rhodium on alumina (Aldrich Item 21,2857-1G), 5% rhodium on carbon (Aldrich Item 206164-1G), dry 5% palladium on carbon (Aldrich Item 20. 568-0), 5% palladium on carbon (Engelhard item batch code 5096, BASF, Earl Road, Cheadle Hulme, Cheadle, Cheshire SK8 6OG, UK), palladium(II) oxide (Avocado Item 11895/c1485A, Alfa Aesar, Shore Road, Port Of Heysham Industrial Estate, Heysham, Morecambe LA3 2XY, UK), 1% palladium on carbon (Johnson Matthey Item 103585), Johnson Matthey 1% palladium on alumina (ATHENA experimental formulation, EPSRC consortium GR/R54576/01).

4.4 | Deuterated reagents

The deuterium gas (99.8% D) used was obtained from CK Isotopes Ltd, Office 6, Newtown Grange Farm Business Park, Leicestershire LE9 9FL, UK. $[D_8]$ Tetrahydrofuran (Item 1133640001) and $[D_4]$ methanol (Item 151947-25G) were obtained from Merck (Sigma-Aldrich Company Ltd), The Old Brickyard, New Road, Gillingham, Dorset SP8 4XT, UK.

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4.5 | Dechlorination substrates

2'-Chloroacetanilide (1), 4-chlorobenzophenone (2), ethyl 4-chlorophenylacetate (6), 4'-chlorobutyrophenone (9) and 2,3,4-trichloroanisole (8) were obtained from Merck (Sigma Aldrich, Ltd, UK), The Old Brickyard, New Road, Gillingham, Dorset SP8 4XT, UK. The precursors for the preparation of the other dehalogenation substrates were also purchased from this source. The following dehalogenation substrates were prepared as below.

4.6 | Preparation of chlorine-substituted phenyl benzoates

These were prepared using the following general procedure:

The substituted phenol (3 mmol) was dissolved in dichloromethane (10 ml) in a 20-ml glass reaction vial and triethylamine (500 μ l) was added. The substituted benzoyl chloride (3 mmol) was then added in four portions allowing the small exotherm to subside before the next addition. After 1 h, saturated sodium bicarbonate solution (5 ml) was added, the vial shaken and the aqueous layer discarded. This process was repeated with 4-M hydrochloric acid (5 ml) and then with water (3 × 5 ml). The resulting organic layer was filtered, dried with anhydrous magnesium sulphate, filtered and evaporated under a stream of dry nitrogen to give a crystalline product, which was analysed by GC-MS and ¹H-NMR. The procedure gave highly pure products in all cases.

4.6.1 | Phenyl 4-chlorobenzoate, 4

¹H-NMR (500 MHz, CDCl₃), δ 7.21 (d, 2H), 7.28 (t, 1H), 7.44 (t, 2H), 7.49 (d, 2H), 8.13 (d, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃) 121.6, 126.0, 128.0, 129.0, 129.5, 131.5, 140.1, 150.7, 164.3 ppm; m/z 232/234, 139/141 (bp), 111/113, 75, 65; ν_{max} (sapphire) 3100, 3075, 3070, 3050, 1729, 1589, 1482, 1398, 1267, 1190, 1174, 1159, 851, 742, 721, 692, 682 cm⁻¹; Raman (532-nm excitation) 3102, 3087, 3083, 3067, 3052, 1735, 1595, 1274, 1203, 1176, 1164, 1099, 1084, 1012, 869, 824, 768, 731, 636, 623, 594 cm⁻¹.

4.6.2 | 4-Chlorophenyl 4-chlorobenzoate, 7

¹H-NMR (500 MHz, CDCl₃), δ 7.16 (d, 2H), 7.39 (d, 2H), 7.48 (d, 2H), 8.12 (d, 2H); ¹³C-NMR (CDCl₃, 100 MHz) 123.00, 127.64, 129.02, 129.60, 131.45, 131.55, 140.38, 149.22, 164.10 ppm; m/z 266/268, 139/141, 111/113,

99/101, 85, 75, 63; ν_{max} (sapphire) 3102, 3080, 2920, 1742, 1591, 1481, 1400, 1263, 1201, 1170, 1160, 1070, 1009, 870, 846, 799, 747, 678, 660, 628, 530 cm⁻¹; Raman (780-nm excitation) 3080, 1744, 1593, 1260, 1193, 1161, 1098, 1069, 872, 812, 738, 628, 475, 344, 284, 267, 178 cm⁻¹.

4.6.3 | 4-t-Butylphenyl 4-chlorobenzoate, 5

¹H-NMR (500 MHz, CDCl₃) 1.34 (s, 9H), 7.12 (d, 2H), 7.41 (d, 2H), 7.46 (d, 2H), 8.13 (d, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃) 31.5, 120.9, 126.4, 128.1, 128.9, 131.6, 140.1, 148.4, 148.9, 164.5 ppm; m/z 290/288, 275/273, 141/139. 113/111, 91, 75, 65; ν_{max} (sapphire) 2963, 2910, 2860, 1744, 1590, 1509, 1398, 1366, 1257, 1199, 1172, 1087, 1077, 1011, 873, 846, 811, 749, 681, 556 cm⁻¹; Raman (532-nm excitation) 3081, 2973, 2932, 2909, 1760, 1745, 1598, 1267, 1213, 1177, 1095, 1074, 886, 820, 749, 635) cm⁻¹.

4.6.4 | 2,4,6-Trichlorophenyl 4-chlorobenzoate, 11

¹H-NMR (500 MHz, CDCl₃) 7.42 (s, 2H), 7.51 (d, 2H), 8.17 (d, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃) 126.3, 128.7, 129.2, 129.4, 129.7, 131.9, 132.3, 141.0, 143.0, 162.2 ppm; m/z 334/336/338/340, 299/301/303, 236/238, 195/197/199, 167/169/171, 139/141, 111/113, 97, 75; ν_{max} (sapphire) 3090, 2930, 2850, 1746, 1591, 1565, 1487, 1447, 1401, 1386, 1256, 1223, 1174, 1142, 1072, 1045, 1010, 852, 844, 838, 819, 806, 767, 715, 626 cm⁻¹; Raman (532-nm excitation) 3086, 1754, 1599, 1265, 1241, 1183, 1098, 1058, 871, 723, 635, 391 cm⁻¹.

Preparation of 4-halosuccinimides

The 4-haloaniline (1.5 mmol) and succinic anhydride (1.5 mmol) were ground together in the bottom of a 10-ml capacity heavy-walled pressure tube and the tube capped with a septum and heated at 140° C for 30 min. Methanol was then added, the melt broken up and the solution refluxed until only a small insoluble residue remained. The supernatant was separated, allowed to crystallise on ice for 30 min and the supernatant removed. The crystals were dried in air overnight to provide the 4-halophenylsuccinimide.

4.6.5 | 4-Chlorophenylsuccinimide; 1-(4-chlorophenyl)pyrrolidine-2,5-dione, 3

This was prepared as above but the crystalline material isolated was shown by ¹H-NMR to contain a small

amount an impurity (N,N'-(4-chlorophenyl)succinic diamide) This was removed by treating the dry solid with a mixture of dichloromethane (1.0 ml) and tetrahydrofuran (125 µl) in which the impurity was insoluble. The resulting suspension was filtered, and the filtrate evaporated under a stream of dry nitrogen to give the pure crystalline product. ¹H-NMR (500 MHz, CDCl₃), δ 2.89 (s, 4H), 7.26 (d, 2H), 7.45 (d, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃) 28.38, 127.67, 129.41, 130.35, 134.44, 175.84 ppm; m/z: 209/211, 181/183, 164/166, 157, 155, 154, 153, 146, 138, 127/129, 111/113, 90, 75, 63, 55; $\nu_{\rm max}$ (sapphire) 3098, 3058, 2987, 2947, 1703, 1491, 1378, 1164, 1089, 1014, 924, 829, 741, 711, 659, 586, 577, 450 cm⁻¹; Raman (780-nm excitation) 3078, 2978, 2944, 1771, 1592, 1432, 1382, 1266, 1176, 1091, 1013, 925, 744, 642, 580, 415, 351, 241 cm⁻¹.

4.6.6 | **4-Bromophenylsuccinimide**, **1-(4-bromophenyl)pyrrolidine-2,5-dione**, 13

¹H-NMR (500 MHz, CDCl₃) 2.89 (s, 4H), 7.20 (d, 2H), 7.60 (d, 2H) ppm; ¹³C-NMR (100 MHz) 28.4, 122.5, 127.9, 130.9, 132.4, 175.8 ppm; m/z: 255/253, 227/225, 199/197, 173, 171, 157/155, 146, 128, 118, 90, 77, 76, 73, 63, 65; ν_{max} (sapphire) 3100, 2990, 2940, 1695, 1654, 1587, 1522, 1487, 1393, 1329, 1294, 1276, 1182, 1163, 1068, 1012, 822, 667, 640, 586 cm⁻¹; Raman (532-nm excitation) 3083, 3015, 3000, 2938, 1773, 1595, 1495, 1432, 1410, 1398, 1301, 1270, 1236, 1193, 1170, 1074, 1020, 1011, 930, 734, 646, 573, 500 cm⁻¹.

4.6.7 | **4-Iodophenylsuccinimide; 1-(4-iodophenyl)pyrrolidine-2,5-dione**, 10

The above one-pot procedure proved inefficient for the preparation of the iodophenylsuccinimide. Instead, the material was prepared in two steps via acylation of the aniline (1.5 mmol) with succinic anhydride (1.5 mmol) in dichloromethane (10 ml) containing triethylamine (2 mmol) at room temperature. After washing with hydrochloric acid (4 M, 5 ml), water (5 ml), drying (MgSO₄) and evaporation, the isolated acid was cyclised to the succinimide in a mixture of tetrahydrofuran (6 ml) and acetic anhydride (1 ml) at 50°C for 4 h. The reaction mixture was partitioned between dichloromethane (10 ml) and a saturated solution of sodium bicarbonate (5 ml). Drying (MgSO₄) and evaporation gave the crystalline 4-iodophenylsuccinimide, pure by GC-MS.

¹H-NMR (500 MHz, CDCl₃) 2.90 (s, 4H), 7.0 (d, 2H), 7.8 (d, 2H) ppm; ¹³C-NMR (CDCl₃, 100 MHz), 28.38. 94.03, 128.21, 131.57, 138.35, 175.69 ppm; m/z 301, 273, 245, 219, 203, 146, 132, 118, 90, 76, 63, 55; ν_{max} (sapphire) 3086, 2927, 1695, 1483, 1388, 1294, 1184, 1164, 1011, 922, 822, 711, 670 cm⁻¹; Raman (780-nm excitation) 3071, 3007, 2929, 1764, 1583, 1483, 1391, 1261, 1229, 1166, 1055, 1011, 923, 721, 634, 565, 483, 346, 221 cm⁻¹.

4.6.8 | **4-Chloro-N-(4-chlorophenyl) benzamide**, 12

4-Chloroaniline (1 mmol) was dissolved in dichloromethane (20 ml) and triethylamine (500 μ l) was added. 4-Chlorobenzoyl chloride (1 mmol) was added in four portions over a minute, after which white crystals precipitated from the solution. After an hour, the crystals were filtered under vacuum and washed with sodium bicarbonate solution (5 ml), then with hydrochloric acid (4 M, 5 ml) and then with water (3 × 5 ml) and dried in air. GC-MS indicated that the product was pure.

¹H-NMR (500 MHz, [D₆]DMSO), δ 7.41 (d, 2H), 7.61 (d, 2H), 7.81 (d, 2H), 7.95 (d, 2H), 10.43 (s, NH); m/z 265/267, 139/141, 111/113, 99, 75; ν_{max} (sapphire) 3300, 3250, 3200, 3140, 3100, 1645, 1602, 1527, 1327, 1290, 1263, 1230, 1087, 1012, 821, 735, 684, 661 cm⁻¹; Raman (532-nm excitation) 3087, 3063, 1652, 1602, 1578, 1499, 1410, 1338, 1299, 1272, 1249, 1184, 1099, 1022, 913, 743, 637 cm⁻¹.

General Procedure A: For the deuterodehalogenation of 2'-chloroacetanilide

Palladium on carbon catalyst (30 mg) was weighed into a 10-ml capacity thick-walled test tube equipped with a magnetic stir bar. The 2'-chloroacetanilide (0.5 mmol) and the appropriate base (1 mmol) in dry THF (2 ml) were added and the tube sealed with a 20-mm aluminium PTFE lined septum and attached to the gas transfer manifold via a 22 gauge Luer needle, which penetrated the septum. The tube was stirred and then evacuated via the needle until the solvent boiled and then briefly filled with deuterium gas before being again evacuated. After refilling with deuterium gas, the tube was detached from the gas manifold needle and the reaction stirred at room temperature for 3 h. The reaction mixture was filtered free of catalyst and the filtrate partitioned between dichloromethane (10 ml) and hydrochloric acid (2 M, 10 ml). The dichloromethane layer was then washed with saturated sodium hydrogen carbonate solution (5 ml) and then twice with water (5 ml, each time). After drying and evaporation, the quality of the product and the extent of reaction were determined by GC-MS, ¹H-NMR and TLC (silica gel F₂₅₄, ethyl acetate/dichloromethane 1:3 v/v gave [4-D]acetanilide = R_f 0.4 and 2'chloroacetanilide = $R_f 0.7$).

General Procedure B: For the deuterodehalogenation of substrates using 5% palladium on carbon catalyst with an excess of deuterium

5% Palladium on carbon catalyst (15 mg) was weighed into a 10-ml capacity thick-walled test tube equipped with a magnetic stir bar. The substrate (0.1 mmol) and triethylamine (20 µl) in dry THF (2 ml) were added, and the tube sealed with a 20-mm aluminium PTFE lined septum and attached to the gas transfer manifold via a 22 gauge Luer needle, which penetrated the septum. The tube was stirred and then evacuated via the needle until the solvent boiled and then briefly filled with deuterium gas before being again evacuated. After refilling with deuterium gas, the tube was detached from the gas manifold needle and the reaction stirred at room temperature for 3 h. The products were isolated as follows: the reaction mixture was filtered free of catalyst and the filtrate partitioned between dichloromethane (10 ml) and hydrochloric acid (2 M, 10 ml). The dichloromethane laver was then washed with saturated sodium hydrogen carbonate solution (5 ml) and then twice with water (5 ml, each time). After drying and evaporation, the purity, degree of reaction and the % deuterium content were determined by GC-MS.

General Procedure C: For the deuterodehalogenation of substrates using palladium trifluoroacetate and micronised PTFE powder

Palladium trifluoroacetate (4 mg, 0.018 mmol) and PTFE powder (20 mg) were weighed into a 10-ml capacity thick-walled test tube equipped with a magnetic stir bar. The substrate (0.1 mmol) and triethylamine (20 µl) in dry THF (2 ml) were added and the tube sealed with a 20-mm aluminium PTFE lined septum and attached to the gas transfer manifold via a 22 gauge Luer needle, which penetrated the septum. The tube was stirred and then evacuated via the needle until the solvent boiled and then briefly filled with deuterium gas before being again evacuated. After refilling with deuterium gas, the tube was detached from the gas manifold needle and the reaction stirred at room temperature for 3 h. The reaction mixture became black within 10 min. The products were isolated as follows: the reaction mixture was filtered free of catalyst and the filtrate partitioned between dichloromethane (10 ml) and hydrochloric acid (2 M, 10 ml). The dichloromethane layer was then washed with saturated sodium hydrogen carbonate solution (5 ml) and then twice with water (5 ml, each time). After drying and evaporation, the quality of the product was determined by GC-MS and characterised by spectroscopic methods. The characterisation data are given below:

4.6.9 | Phenyl [4-D]benzoate

¹H-NMR (500 MHz, CDCl₃) 7.22 (d, 2H), 7.27 (t, 1H), 7.43 (t, 2H), 7. 51 (d, 2H), 8.21 (d, 2H) ppm; D-NMR (CHCl₃, 61 MHz) s, 7.70 ppm, no other resonances; ¹³C-NMR (100 MHz, CDCl₃) 121.7, 125.9, 128.5, 129.5, 129.6, 130.2, 133.0 (t, 1:1:1, J = 25 Hz), 151.0, 16 5.2 ppm; m/z 199 (3%), 116 (1%), 106 (100%), 93 (1%), 78 (40%), 65 (4%); C₁₃H₁₀DO₂ (M + H) requires 200.0816 amu, found 200.0817 amu, C₁₃H₁₃DO₂N (M + NH₃) requires 217.1082 amu, found 217.1084 amu, C₁₃H₉DO₂Na (M + Na) requires 222.0636 amu, found 222.0637 amu; ν_{max} (sapphire) 3070, 1729, 1597, 1589, 1482, 1455, 1312, 1261, 1245, 1191, 1178, 1073, 1022, 1001, 918, 852, 817, 759, 747, 689, 675, 573, 506 cm⁻¹; Raman (532-nm excitation) 3078, 1734, 1602, 1269, 1202, 1173, 1028, 991, 621 cm⁻¹.

4.6.10 | 4-t-Butylphenyl [4-D]benzoate

¹H-NMR (500 MHz, CDCl₃) 1.34 (s, 9H), 7.14 (d, 2H), 7.43 (d, 2H), 7.50 (d, 2H) 8.2 (d, 2H) ppm; D-NMR (CHCl₃, 61 MHz) s, 7.69 ppm, no other resonances; ¹³C-NMR (100 MHz, CDCl₃) 31.5, 34.5, 114.8, 121.0, 126.3, 128.5, 129.7, 130.2, 133.2 (t, 1:1:1, J = 24 Hz), 148.7, 165.4 ppm; m/z: 255 (4%), 240 (1%), 134 (1%), 106 (100%), 91 (4%), 78 (24%), 65 (1%); $C_{17}H_{18}DO_2$ (M + H) requires 256.1442 amu, found 256.1443 amu, C₁₇H₂₁DO₂N (M + NH₃) requires 273.1078 amu, found 273.1079 amu, $C_{17}H_{17}DO_2Na$ (M + Na) requires 278.1262 amu, found 278.1261 amu; v_{max} (sapphire) 3050, 2962, 2923, 2860, 1732, 1594, 1507, 1288, 1409, 1370, 1261, 1203, 1169, 1113, 1968, 1025, 1015, 908, 874, 864, 830, 806, 771, 695, 675, 650 cm⁻¹; Raman (532-nm excitation) 3079. 2979, 2438, 1737, 1603, 1450, 1271, 1212, 1181, 1081, 993, 884, 815, 738, 703 cm⁻¹.

4.6.11 | [2'-D]Acetanilide; N-(2-deuteriophenyl)acetamide

¹H-NMR (500 MHz, CDCl₃) 2.16 (s, 3H), 7.08 (t, 1H), 7.27–7.31 (cm, 2H), 7,52 (d, 1H), 7.95 (broad s. 1H) ppm; D-NMR (CHCl₃, 61 MHz) s, 7.57 ppm, no other resonances; ¹³C-NMR (100 MHz, CDCl₃) 24.5, 119.7 (weak, t, 1:1:1, J = 26 Hz), 120.0, 124.2, 128.8, 128.9, 138.1, 168.7 ppm; m/z 136 (27%), 94 (100%), 93 (11%), 92 (5%), 78 (5%), 67 (13%), 66 (15%); C₈H₈DONNa (M + Na) requires 159.0639 amu, found 159.0637 amu; ν_{max} (sapphire) 3287, 3251, 3195, 3127, 2970, 2920, 2851, 1659, 1606, 1590, 1547, 1431, 1366, 1318, 1291, 1259, 1014, 770, 743, 640 cm⁻¹: Raman (532-nm excitation) 3068,

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2934, 2278, 1669, 1599, 1541, 1481, 1375, 1299, 1268, 1236, 1167, 1130, 1059, 993, 874. 843, 669, 618, 351 $\rm cm^{-1}$

4.6.12 | [4-D]Phenylsuccinimide; 1-(4-deuteriophenyl)pyrrolidine-2,5-dione (from 4-chlorophenylsuccinimide)

¹H-NMR (500 MHz, CDCl₃) 2.90 (s, 4H), 7.29 (d, 2H), 7.48 (d, 2H, broadened by ortho-D coupling) ppm; ¹³C-NMR (100 MHz, CDCl₃) 28.40, 126.47, 128.37 (weak, t, J = 24.2 Hz), 129.11, 131.89, 176.15 ppm; D-NMR (CHCl₃, 61 MHz) 7.42 (s) no other resonances; m/z, 176, 147, 131, 121, 120, 105, 94, 93, 92, 78, 65, 56, 55; C₁₀H₉DNO₂ (M + H) requires 177.0769 amu, found 177.0764 amu; ν_{max} (sapphire) 2921, 2850, 1703, 1590, 1496, 1390, 1230, 1184, 925, 860, 817, 672, 618, 587 cm⁻¹: Raman (780-nm excitation) 3067, 2978, 2934, 1779, 1592, 1431, 1406, 1390, 1232, 1174, 1003, 987, 926, 874, 747, 702, 623, 462, 280 cm⁻¹

4.6.13 | [4-D]Phenylsuccinimide; 1-(4-deuteriophenyl)pyrrolidine-2,5-dione (from 4-bromophenylsuccinimide)

¹H-NMR (500 MHz, CDCl₃) 2.90 (s, 4H), 7.29 (d, 2H), 7.47 (d, 2H, broadened by ortho-D coupling) ppm; ¹³C-NMR (100 MHz, CDCl₃) 28.42, 126.47, 128.37 (weak, t, J = 24.9 Hz) 129.11, 131.89, 176.17 ppm; D-NMR (CHCl₃, 61 MHz) 7.42(s) ppm, no other resonances; m/z 176, 147, 131, 121, 120, 105, 94, 93, 92, 78, 65, 56, 55; C₁₀H₉DNO₂ (M + H) requires 177.0769 amu, found 177.0764 amu; ν_{max} (sapphire) 2921, 2851, 1703, 1590, 1496, 1392, 1230, 1184, 925, 868, 817, 672, 618, 587 cm⁻¹: Raman (780-nm excitation) 3067, 2974, 2935, 1775, 1592, 1431, 1391, 1232, 1175, 987, 926, 703, 624, 462 cm⁻¹

4.6.14 | Ethyl [4-D]phenylacetate; ethyl 2-(4-deuteriophenyl)acetate

¹H-NMR (500 MHz, CDCl₃) 2.27 (t, 3H), 3.60 (s, 2H), 4.15 (q, 2H), 7.28–7.33 (4H, AA'BB') ppm; ¹³C-NMR (100 MHz, CDCl₃) 14.2, 60.8, 41.4, 127.2(trace), 128.4, 129.2, 134.2, 171.6 ppm; MS: 165 (16%), 137 (1%), 120 (2%), 92 (100%), 66 (8%); ν_{max} (sapphire) 2990, 2970, 2919, 2850, 1732, 1500, 1417, 1367, 1335, 1251, 1218, 1027, 770, 660, 640, 620 cm⁻¹.

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