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# The scope and limitations of deuteration mediated by Crabtree's catalyst

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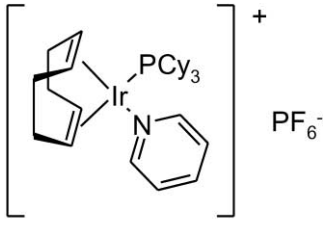
**Abstract**—Exchange of protons for deuterons mediated by Crabtree's catalyst, **1**, is directed efficiently by a functional group containing an $sp^2$-hybridised nitrogen or oxygen atom; more electron-rich substrates are, in general, deuterated more efficiently. The electronic effects of substituents in the arene ring are critical only where the directing group is poor, in which case exchange is generally promoted by electron donating substituents, but the exchange is impeded by bulky *meta*-substituents. © 2001 Elsevier Science Ltd. All rights reserved.

Over the past decade, a number of reports have appeared describing the use of iridium complexes to promote the incorporation of tritium and deuterium into arenes at positions *ortho*- to a directing group such as a carbonyl.[1–4] The isotopic hydrogen is thereby incorporated at a position where it is not particularly susceptible toward loss by metabolism or uncatalysed exchange. One of the more attractive pre-catalysts of this process, by virtue of its stability and commercial availability, is Crabtree's catalyst [(cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate, **1**]. Since the published deuteration work involving this catalyst is limited to a few examples only,[2,3] we chose to carry out a more extensive investigation of the range of substrates for which the process might be useful.




**1**

## 1. Results and discussion

Since deuterium and tritium should behave similarly in exchange processes, our investigations were carried out with the former for reasons of convenience. In order to maintain comparable conditions throughout the investigation, **1** was used in stoichiometric or near-stoichiometric quantities. This approach was intended to overcome any poisoning of the catalyst that might result from irreversible binding to the substrate. Moreover, it has been found that the binding modes of some ligands with iridium species are dependant upon the ligand/metal ratio,[4] and so we wished to keep this ratio constant. Nevertheless, it was of interest to check whether this did, indeed, correspond to an optimum catalyst/substrate ratio (Fig. 1). Using ethyl benzoate, the highest level of deuterium incorporation is observed using a 1:2 ratio of **1** to substrate, and the extent of deuteration is much reduced with greater quantities of **1**. By comparison, complete deuteration of 1-phenylpyrazole is observed in the presence of as little as 25% **1**, above which increasing the concentration of **1** has no effect. It is therefore likely that many of the figures presented below could be bettered slightly by using a smaller quantity of catalyst. Multiple runs were conducted in a few cases only, but reproducibility in these cases appears to be within 5–10%, which is sufficient to derive general trends. Since a weakly coordinating ligand is believed to be involved at several critical stages of the exchange process,[1,5] we chose to add a trace quantity of deuterium oxide to each exchange mixture. The anticipated exchange process should therefore be as illustrated in Scheme 1.

Upon examining the deuteration of a range of aromatic esters, amides, and ketones mediated by **1**, a number of trends are clear (Table 1). The deuteration of amides mediated by **1** has been reported previously,[2] and indeed this proves to be a comparatively efficient process. Not surprisingly, the process with amides is more efficient than that with esters; this appears to be principally an electronic effect associated with the electron-donating ability of the coordinating substituent, and is substantially unaffected by increasing steric demand at the amide nitrogen. This indicates that in amides it is still the oxygen that coordinates to the metal centre. Indeed, *N*,*N*-diisopropylbenzamide is essentially as good a substrate as *N*,*N*-dimethylbenzamide,

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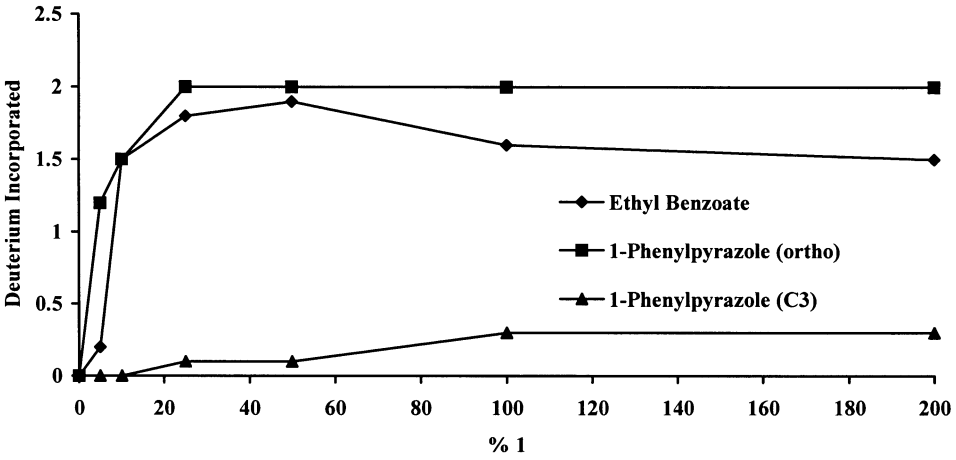
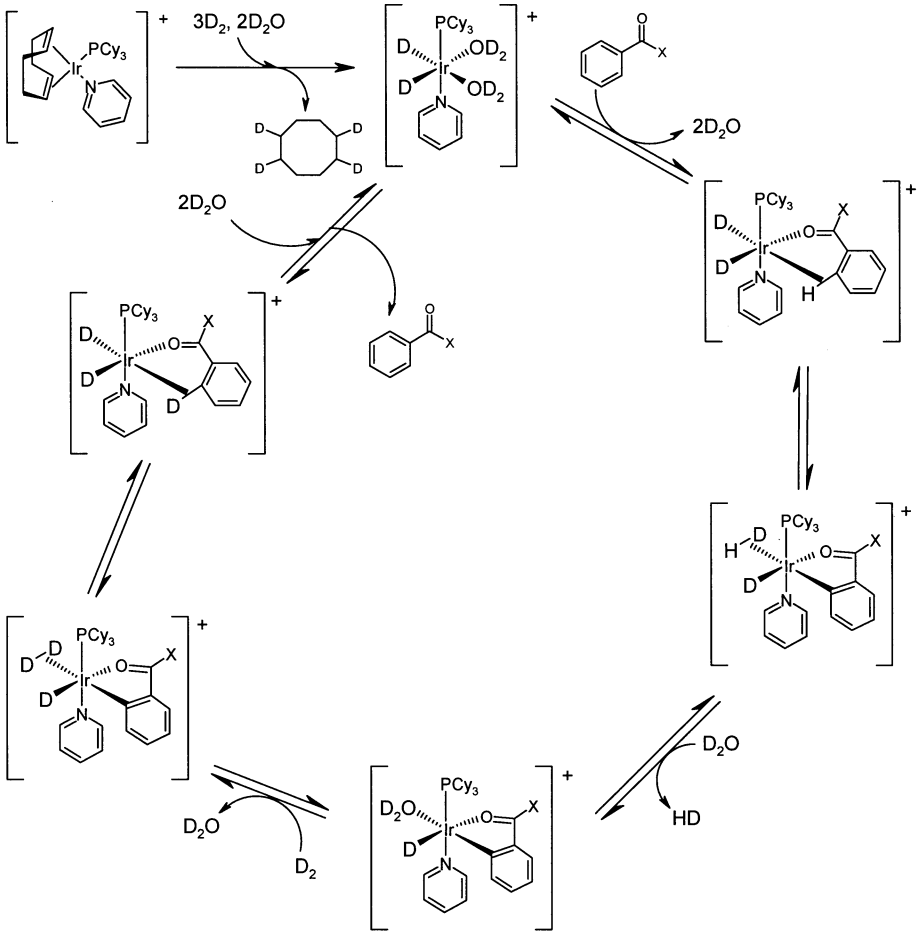



**Figure 1.** Variation of deuterium incorporation into ethyl benzoate and 1-phenylpyrazole with substrate/catalyst.

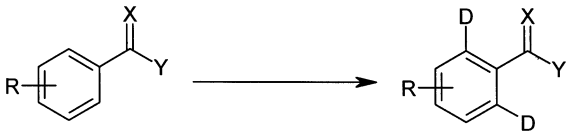
and both are superior to benzamide itself. The degree of deuteration of amides appears to be substantially unaffected by the electronic effect of substituents in the arene ring, the behaviour of *N*,*N*-dimethyl-4-methoxy and 4-nitrobenzamides being identical to that of the ring-unsubstituted species. On the other hand, electronically different ethyl benzoates give significantly differing results: the process is clearly impeded by a *para*-nitro group and assisted very slightly by a *para*-methoxy group. It may be inferred that the coordinating power of the ester is substantially improved by the presence of an electron donating substituent, leading to better deuterium incorporation; conversely, the electron-withdrawing nitro group reduces the coordinating ability of the ester, and so the level of deuteration is reduced.

It is to be expected that an *ortho*-substituent would block




**Scheme 1.** Simplified mechanism of the exchange process n the presence of deuterium oxide.

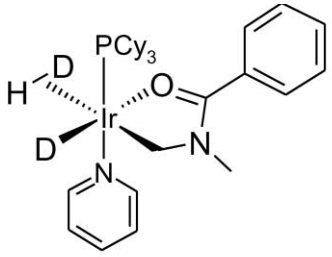
**Table 1.** Deuteration of ketone and acid derivatives mediated by **1**



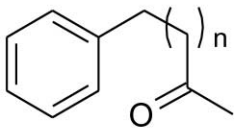

| Entry | X | Y | R | Equiv. **1** | *o*-D[a] | Notes |
|---|---|---|---|---|---|---|
| 1 | O | OEt | H | 1.0 | 1.6 | |
| 2 | O | OEt | 4-OMe | 1.3 | 1.7 | |
| 3 | O | OEt | 4-$NO_2$ | 1.2 | 0.4 | |
| 4 | O | OEt | 3-aza | 1.0 | 0.8 | 1:1 C-2/C-4 |
| 5 | O | OMe | 2-Br | 0.6 | 0.1 | No methyl benzoate detected |
| 6 | O | OMe | 2-COOMe | 1.0 | 0.1 | |
| 7 | O | OMe | 3-COOMe | 0.7 | 1.1 | No deuteration at position 2. |
| 8 | O | $NH_2$ | H | 1.1 | 1.3 | |
| 9 | O | $NMe_2$ | H | 1.1 | 1.6 | |
| 10 | O | $NMe_2$ | 4-OMe | 1.0 | 1.6 | 1.1D in *N*-Me |
| 11 | O | $NMe_2$ | 4-$NO_2$ | 1.0 | 1.6 | No D in *N*-Me |
| 12 | O | $NMe_2$ | 3-F | 1.0 | 1.9 | No D in *N*-Me |
| 13 | O | $NMe_2$ | 3-OMe | 1.0 | 1.0 | 1.8D in *N*-Me; C6/C2=9:1. |
| 15 | O | $NMe_2$ | 3-Cl | 1.0 | 1.3 | 0.3D in *N*-Me; C6/C2=8:5. |
| 16 | O | $NMe_2$ | 3-Br | 1.0 | 1.0 | No D in *N*-Me; C6/C2=8:2. |
| 17 | O | $NMe_2$ | 3-$CF_3$ | 1.0 | 1.3 | 0.7D in *N*-Me; C6/C2=9:4. |
| 18 | O | *N*-*i*-$Pr_2$ | H | 1.0 | 1.8 | 0.2D in *N*-*i*-Pr |
| 19 | O | Me | H | 1.0 | 1.5 | |
| 20 | O | Me | 4-OMe | 1.0 | 0.9 | |
| 21 | O | Me | 4-$NO_2$ | 1.1 | 1.4 | |
| 22 | O | Ph | H | | 3.4 | |
| 23 | NOMe | Me | H | | 1.6 | |
| 24 | $NNMe_2$ | Me | 4-$NO_2$ | 1.1 | 1.5 | 1.5D in *N*-Me |
| 25 | NNHPh | Me | 4-$NO_2$ | 1.0 | 1.4 | 1.3D in *N*-Ph |
| 26 | NH | NHCOOEt | H | 1.0 | 0.4 | |
| 27 | S | SMe | H | 1.0 | – | Substrate degraded |

[a] Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule.

deuteration, but it was of interest to ascertain whether the method would tolerate an *ortho*-halogen which, indeed, it does (Table 1, entry 5). However, the presence of even a relatively small *meta*-substituent substantially reduces the degree of deuteration at the adjacent 2-position: in the absence of any effect of a *para*-subsituent upon the deuteration of dimethylbenzamides, it appears that this is a steric effect. This is underlined by the comparative efficiency of deuteration of *N*,*N*-dimethyl-3-fluorobenzamide, whereas 3-bromo, 3-chloro, and 3-trifluoromethyl substituents (Table 1, entries 12–17) all impede the exchange process to at least some extent, with exchange in these substrates occurring principally at the 6-position.




**2**



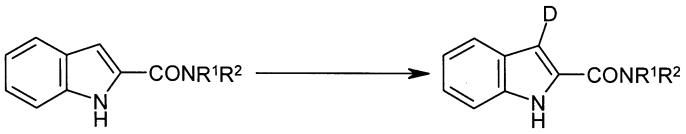

**3** (n = 0)

**4** (n = 1)

Incorporation of deuterium α- to the nitrogen of an *N*,*N*-dialkylamide is a common phenomenon. Since direction by the adjacent nitrogen would require formation of a three-membered metallacycle, it seems likely that this exchange occurs via coordination to the oxygen, as for the arene deuteration, and intermediacy of a 5-membered metallacycle such as **2**. Deuteration at a saturated carbon was not observed with ketones or esters, and although it is not restricted to amides (Table 1, entry 24), aliphatic deuteration has only been observed, so far, adjacent to nitrogen. We are presently investigating the scope of this exchange process.

Aryl ketones appear to be good substrates for the exchange process, with benzophenone and acetophenone incorporating deuterium at similar levels to *N*,*N*-dimethylbenzamide. Oddly, the presence of a *para*-methoxy group reduces the degree of deuteration of acetophenone, but a *para*-nitro group has little effect; this may reflect the existence of alternative deuteration pathways as has been suggested previously.[1] Given that amides are generally better substrates than esters, it was expected that oximes, hydrazones, or amidines would prove to be better deuteration substrates than their oxygen analogues. Nevertheless, the *O*-methyloxime and hydrazones formed from acetophenone incorporated deuterium to essentially the same extent as the ketone. Benzamidine was completely degraded within one hour in the presence of **1** and deuterium, apparently to benzonitrile, although the latter was not isolated, but characterised only by GC/MS; *N*-ethoxycarbonylbenzamidine (Table 1, entry 26) was a poor substrate. Methyl dithiobenzoate was also expected to be a good exchange

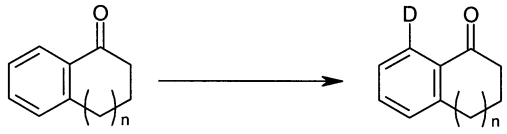
**Table 2.** Deuteration of indole-2-carboxamides mediated by **1**




| Entry | $R^1/R^2$ | Equiv. **1** | 3-D[a] | Notes |
|---|---|---|---|---|
| 1 | Me/Ph | 0.5 | 0.7 | No deuteration in Ph |
| 2 | Me/OMe | 1.1 | 0.3 | >50% degradation |
| 3 | Me/Bn | 1.2 | 0.7 | |
| 4 | H/Bu | 1.1 | 0.1 | |

[a] Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule.

**Table 3.** Deuteration of 1-indanone, tetralone, and benzosuberone mediated by **1**




| Entry | Substrate | *n* | Equiv. **1** | 7/8/9-D[a] |
|---|---|---|---|---|
| 1 | 1-Indanone | 0 | 1.0 | 0.31 |
| 2 | 1-Tetralone | 1 | 1.0 | 0.68 |
| 3 | 1-Benzosuberone | 2 | 1.0 | 0.76 |

[a] Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule.

substrate, but did not survive the deuteration conditions (Table 1, entry 27).

Deuteration at the 3-position of indole-2-carboxamides was significantly less efficient than *ortho*-deuteration of benzamides (Table 2). That the observed deuterations are iridium-mediated, rather than the consequence of electrophilic protonation (vide infra), was demonstrated by the absence of deuterium incorporation, other than at nitrogen, upon treatment of *N*-methyl-*N*-phenylindole-2-carboxamide with deuterium oxide. The Weinreb amide (Table 2, entry 2) suffered slow degradation under the exchange conditions: this did not appear to be due to reduction to the aldehyde, unless the latter was itself degraded further.

It appears that metallacycle formation from indole-2-carboxamides is less favoured than from benzamides, since a C3–H bond is less well placed to permit an agostic interaction with the metal centre. This supposition was tested further by examination of the deuteration of 1-indanone, 1-tetralone, and 1-benzosuberone, which represent a series of electronically very similar substrates, where the geometry of the carbonyl oxygen is constrained by ring formation, and which therefore differ principally in the distance between the directing heteroatom and the C–H bond into which iridium must insert in order to form a metallacycle. In this case (Table 3), there is a clear trend such that 1-indanone is the worst, and benzosuberone the best substrate. It is clear, and scarcely surprising, that increasing the distance between the directing heteroatom and the site of C–H insertion results in a reduction in deuteration. Consistent with this trend, deuterium incorporation was not observed using either phenylacetone (**3**) or benzylacetone (**4**).

Many compounds whose deuterated and tritiated derivatives would be of value in pharmaceutical development contain

**Table 4.** Deuteration of aniline, phenol, and thiophenol derivatives mediated by **1**


| Entry | Z | R | Equiv. **1** | *o*-D[a] |
|---|---|---|---|---|
| 1 | OH | H | 1.0 | 0.0 |
| 2 | OAc | H | 1.0 | 0.0 |
| 3 | $NH_2$ | H | 1.0 | 0.0 |
| 4 | NHAc | H | 1.4 | 0.8 |
| 5 | NHBoc | 2-*i*-Pr | 1.1 | 0.5 |
| 6 | $NHSO_2Me$ | H | 1.1 | 0.3 |
| 7 | NHTs | 4-Cl | 0.9 | 0.0 |
| 8 | $NMs_2$ | H | 1.2 | 0.0 |
| 9 | $NHNH_2$ | H | 1.0 | 1.0 (isolated as aniline) |
| 10 | NHN=C(Me)-*p*-$C_6H_4NO_2$ | H | 1.0 | 1.3 |
| 11 | $NO_2$ | H | 1.0 | 0.0 |
| 12 | S(O)Me | H | 1.0 | 0.1 |
| 13 | $SO_2Me$ | H | 1.0 | 0.0 |
| 14 | $SO_2NH_2$ | H | 1.0 | 0.3 |

[a] Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule.

**Table 5.** Deuteration and N–N cleavage of phenylhydrazine mediated by different percentages of **1**

| Entry | Equiv. **1** | Time (h) | Hydrazine/aniline[a] | *o*-D in hydrazine[b] | *o*-D in aniline[b] |
|---|---|---|---|---|---|
| 1 | 1.1 | 24 | 0:100 | – | 1.0 |
| 2 | 1.0 | 15 | 0:100 | – | 1.5 |
| 3 | 0.5 | 15 | 13:87 | 1.4 | 1.3 |
| 4 | 0.1 | 15 | 61:39 | 1.5 | 0.5 |

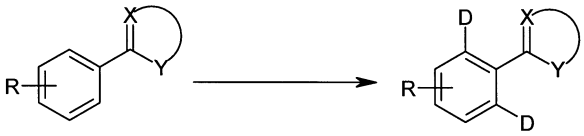
[a] Ratio from GC/MS.
[b] Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule.

arenes bound directly to heteroatoms. The deuteration of a range of model substrates of this type by **1** was therefore examined (Table 4). In practice, few of these substrates were deuterated at all, let alone efficiently; the deuteration and tritiation of acetanilide and related substrates, apparently via a six-membered metallacycle, has been reported previously.[2] We were able to reproduce the deuteration of acetanilide, and of a related *tert*-butyl-carbamate (Table 4, entries 4 and 5), although the degree of deuteration was modest, in line with the poor results obtained with phenylacetone. In the case of *N*-phenylmethanesulfonamide (Table 4, entry 6), the coordinating atom could, in principle, be either nitrogen or oxygen; the possibility that deuteration might occur via a four-membered metallacycle is suggested by the efficient exchange observed with benzosuberone (Table 3, entry 3). However, the absence of deuteration of aniline or phenol does not support this idea.

The best substrates in this group were phenylhydrazine (Table 4, entry 9) and, less surprisingly, the phenyl-hydrazone of 4-nitroacetophenone (Table 4, entry 10). In the former case, N–N cleavage is observed also, but it is almost certain that phenylhydrazine is the deuteration substrate since deuteration of aniline itself is not observed. It follows that N–N cleavage is slower than deuterium exchange, and therefore that it might be possible to recover deuterated phenylhydrazine by carrying out the exchange using a smaller quantity of **1**. Indeed (Table 5), this did prove to be the case and it is no surprise that, with the rate of N–N cleavage slowed, the deuterium incorporation improved also. Phenylhydrazine therefore represents a convenient synthon for aniline in this process.[6]

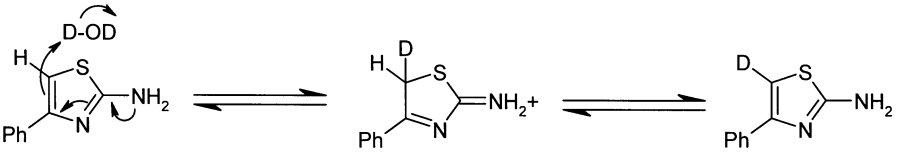
Efficient deuterium exchange was observed with a variety of aryl-substituted heterocycles (Table 6), the nature of the directing heteroatom being critical. Where deuteration is directed by an $sp^2$ nitrogen, irrespective of whether the heterocycle is π-excessive or π-deficient, deuterium incorporation is efficient in most cases. In contrast, direction by an oxygen, sulfur, or $sp^3$ nitrogen is consistently poor. These observations are consistent with a process whereby initial coordination occurs via the lone pair of the directing heteroatom; where this is coplanar with the arene ring, agostic interaction and subsequent C–H activation will be more favoured than where the directing heteroatom has lone pairs out of the plane of the arene system. This contrast is readily observed in the case of isomeric phenylthiazoles (Table 6, entries 5–7), where direction by nitrogen is efficient but direction by sulfur is poor. In these substrates, increasing the electron density of the heterocycle by amination (Table 6, entry 8) results in a further increase in

**Table 6.** Deuteration of aryl heterocycles mediated by **1**




| Entry | Heterocycle | $R^2$ | Equiv. **1** | *o*-D[a] | Notes |
|---|---|---|---|---|---|
| 1 | 2-Furyl | 4-OMe | 1.1 | 0.4 | 0.7D at furan C-2 |
| 2 | 2-Thienyl | 4-OMe | 1.0 | 0.1 | 0.7D at thiophene C-2 |
| 3 | 3,3-Dimethyloxazolin-2-yl | 2-OMe | 1.0 | 0.5 | |
| 4 | 5-Acetyl-isoxazol-3-yl | H | 1.0 | 2.0 | |
| 5 | Thiazol-2-yl | H | 1.0 | 1.6 | 1.0D at thiazole C-4 |
| 6 | Thiazol-4-yl | H | 1.1 | 1.6 | 1.0D at thiazole C-2 |
| 7 | Thiazol-5-yl | H | 1.0 | 0.2 | 0.4D at thiazole C-2 |
| 8 | 2-Aminothiazol-4-yl | H | 1.1 | 2.0 | 0.6D at thiazole C-5 |
| 9 | 2-Benzamidothiazol-4-yl | H | 1.1 | 0.6 | 0.4D in benzoyl group |
| 10 | Imidazol-4-yl | H | 0.5 | 1.8 | 0.4D at imidazole C-2 |
| 11 | Pyrazol-1-yl | H | 1.0 | 2.0 | |
| 12 | Pyrazol-3-yl | 4-Cl | 0.6 | 0.6 | Partially degrades |
| 13 | 1-Methylpyrazol-3-yl | 4-Cl | 1.0 | 1.7 | |
| 14 | 1-Methylpyrazol-5-yl | 4-Cl | 1.0 | 0.6 | |
| 15 | 2-Benzoyltetrazol-5-yl | H | 0.8 | 1.9 | 1.7D in benzoyl |
| 16 | 2-Benzyltetrazol-5-yl | H | 1.1 | 2.0 | |
| 17 | 2-Pyridinyl | H | 1.0 | 1.6 | 0.6D at pyridine C-2. |
| 18 | Pyrazinyl | H | 0.9 | 1.5 | |
| 19 | 4-Pyrimidinyl | H | 1.0 | 1.7 | |

Similar incorporation occurs with $D_2O$ alone.
[a] Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule.




**Scheme 2.** Uncatalysed deuterium exchange in 2-aminothiazoles.

deuterium incorporation, which is more than reversed when the amine is acylated (Table 6, entry 9). The isomeric pyrazoles (Table 6, entries 13 and 14) display a similar pattern. In view of the apparent efficacy of an $sp^2$-hybridised nitrogen as a coordinating centre, it was of interest to examine the deuteration of arylazines. From the few examples given, it can be seen that these are also good deuteration substrates.

It is of interest also to note that deuterium incorporation is facilitated more by heteroarenes, rather than their partially hydrogenated analogues (Table 6, entry 3). In the former case, a second heteroatom, or an electron-donating substituent can augment the electron density of the ring, and hence the binding and the efficiency of deuteration. The results for substituted imidazoles, pyrazoles, and tetrazoles are comparable to those for thiazoles but this does not, unsurprisingly, extend to annelated derivatives: 2-aminobenzothiazole, for example, was not deuterated at all.

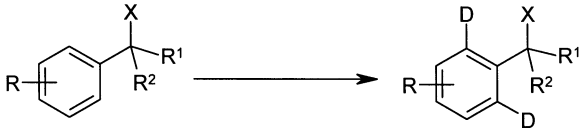
Where the pyrrole-like nitrogen of a pyrazole or a tetrazole was left unprotected, degradation of the substrate was a dominant process. In the case of 3-(4-chlorophenyl)pyrazole, some material could be recovered if a smaller quantity of **1** was used, or the reaction time was reduced, but the recovery remained poor. 3-Phenyl-5-aminopyrazole and 5-phenyltetrazole did not survive the reaction conditions at all. Given that there does not appear to be any degradation of phenylthiazoles or of 4-phenylimidazole under the reaction conditions, and in view of the observed cleavage of phenylhydrazine (vide supra), it may be that where extensive degradation occurs, this is a consequence of reductive N–N cleavage. *N*-alkylated pyrazoles and tetrazoles can, however, be good deuteration substrates (Table 6, entries 13–16). It is not surprising that the 3-arylpyrazole (entry 13) undergoes more efficient deuteration than the 5-aryl isomer (entry 14), since only the former has an $sp^2$ nitrogen in a position to direct deuteration. A similar comparison between isomeric tetrazoles could not be made, since 1-benzoyl-5-phenyltetrazole decomposes under the reaction conditions, while 1-benzyl-5-phenyltetrazole undergoes a previously observed rearrangement,[7] giving the 2-isomer without apparent degradation.

In addition to exchange in the aryl substituent, a number of aryl heterocycles incorporate deuterium in the hetero-ring as well. In most cases, the same exchange is not observed in the presence of deuterium oxide or deuterium chloride alone, indicating that it is iridium-mediated. H5 in 2-aminothiazoles, however, is exchanged by deuterium oxide alone although the exchange is suppressed by acylation of the amine; this exchange may be rationalised as illustrated in Scheme 2.

By way of contrast, H2 in 4- or 5-phenylthiazoles and H4 in 2-phenylthiazole are exchanged in the presence of **1**, but not with deuterium oxide alone; indeed, deuteration at C2 in thiazoles normally requires deprotonation by an alkyllithium base.[8] In the same manner, treatment of thiazole or benzothiazole with deuterium in the presence of **1** (one equivalent) also results in exchange at C2 (27 and 45%, respectively). Deuterium is also incorporated into the pyridine ring of 2-phenylpyridine. Since in all cases deuterium is incorporated adjacent to a pyridine-like nitrogen, and that **1** is known to mediate both the hydrogenation of imines[9] and the dehydrogenation of cyclohexenes to arenes,[10] it is possible that this exchange proceeds by means of a reversible partial hydrogenation of the heterocycle (Scheme 3).

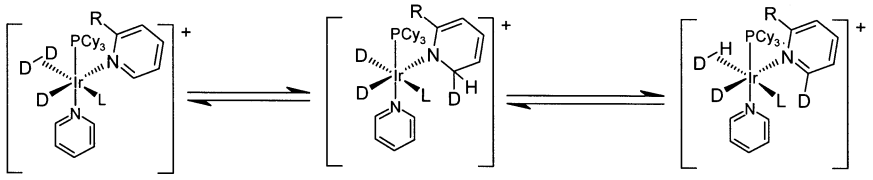
The lone pairs of benzylic amines and alcohols are not coplanar with the arene, but are nevertheless reasonably well placed to direct deuteration. In practice, modest incorporation was observed with primary and secondary benzylic amines (Table 7), but there was no incorporation into a tertiary amine. In the case of α-methylbenzylamine (Table 7, entry 4), it was expected that the Thorpe–Ingold effect

**Table 7.** Deuteration of benzylic alcohol and amine derivatives mediated by **1**




| Entry | X | $R^1$ | Equiv. **1** | *o*-D[a] |
|---|---|---|---|---|
| 1 | $NH_2$ | H | 0.4 | 1.0 |
| 2 | NHMe | H | 1.0 | 0.7 |
| 3 | $NMe_2$ | H | 1 | 0.0 |
| 4 | $NH_2$ | Me | 1.0 | 0.8 |
| 5 | OH | H | 1.0 | 0.0 |
| 6 | NHAc | H | 1.1 | 0.1 |

[a] Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule.




**Scheme 3.** Postulated process for incorporation of deuterium at C6 of pyridines.

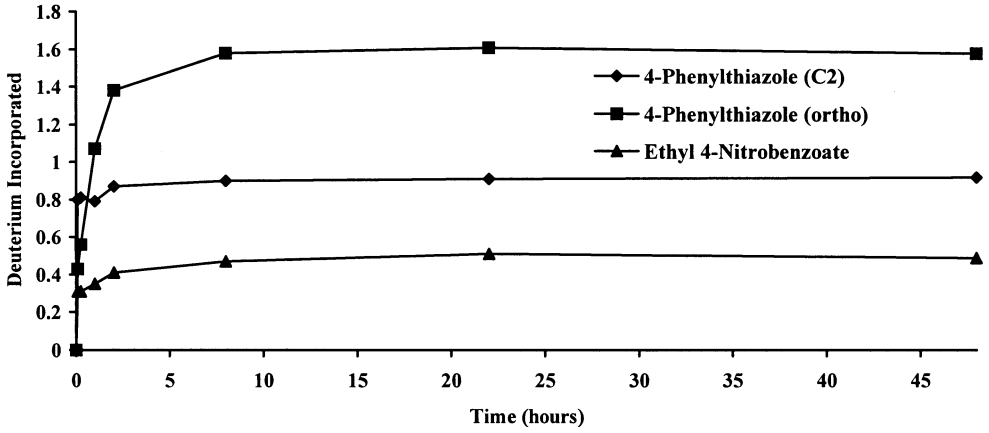



**Figure 2.** Deuterium exchange into 4-phenylthiazole and ethyl 4-nitrobenzoate (separate runs) over 48 h.

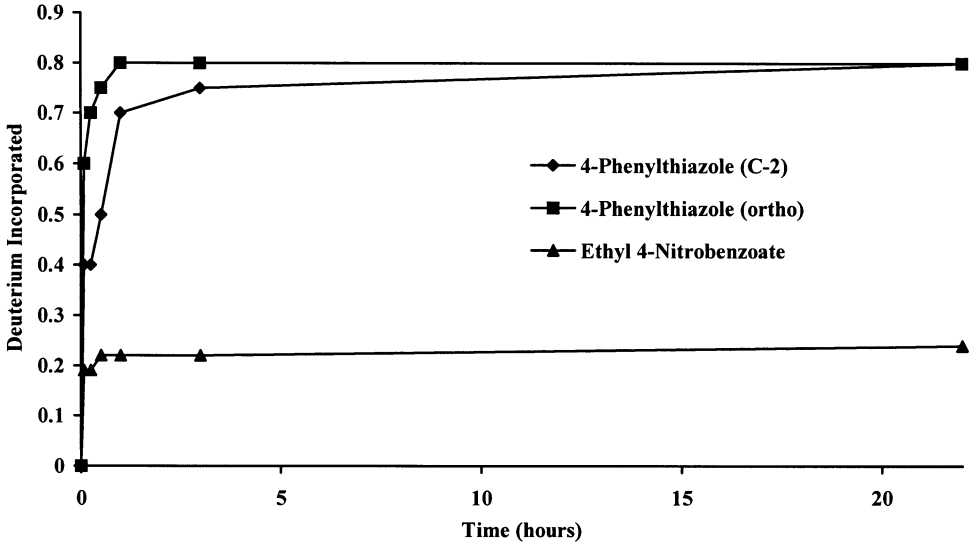



**Figure 3.** Deuterium exchange into 4-phenylthiazole and ethyl 4-nitrobenzoate (single runs) over 22 h.

might facilitate metallacycle formation and thereby exchange but, in practice, the incorporation was poorer than into benzylamine itself. It is likely, once again, that the differing results with differently-substituted amines are simply the consequence of increasing steric encumbrance at the nitrogen centre. In the cases of benzyl alcohol and *N*-benzylacetamide, the poor results presumably reflect the less nucleophilic character of the directing heteroatom.

The rate of deuteration of two representative substrates, 4-phenylthiazole and ethyl 4-nitrobenzoate, was examined by carrying out several simultaneous runs using the same mixtures of catalyst and substrate (Fig. 2) and by sampling of single exchange mixtures of each (Fig. 3). In the former case, the final deuterium incorporations are comparable to those quoted above. Nevertheless, the kinetics of the *ortho*-deuterations are clearly different to those for the deuteration at C-2 of 4-phenylthiazole, where the initial rate is very much faster: this process is essentially complete in a matter of minutes, whereas *ortho*-exchange in both substrates requires around 8 h for completion. In fact, ethyl 4-nitrobenzoate continued to incorporate small quantities of deuterium for the whole of the period studied, indicating that such extended periods are indeed necessary to ensure equilibration with

**Table 8.** Comparison between deuterations with **1** in dichloromethane and in methanol

| Substrate | Deuterium incorp. (DCM)[a] | Deuterium incorp. (MeOH)[a] |
|---|---|---|
| 4-Phenylthiazol-2-amine | 2.0 | 0.77 |
| Benzamide | 1.28 | 0.34 |
| Benzyl alcohol | 0.0 | 0.0 |
| Ethyl benzoate | 0.40 | 0.0 |
| Phenylpyrazine | 1.47 | 0.66 |

[a] Figures presented are the average number of *ortho*-deuterium atoms incorporated per molecule.

**Table 9.** Key NMR and MS data for deuteration substrates

| Substrate | Data |
|---|---|
| Acetanilide | *m/z* (EI) 135 ($M^{+\cdot}$), 93 ($PhNH_2^{+\cdot}$) |
| Acetophenone | *m/z* (EI) 120 ($M^{+\cdot}$), 105 ($PhCO^+$) |
| Acetophenone *O*-methyloxime | $\delta_H$ ($CDCl_3$) 2.25 (3H, s), 4.01 (3H,s), 7.4 (3H, m), 7.68 (2H, m, $H_{ortho}$); *m/z* (EI) 149 ($M^{+\cdot}$) |
| 5-Acetyl-3-phenylisoxazole | *m/z* (EI) 187 ($M^{+\cdot}$), 144 ($[M-CH_3CO]^+$) |
| Aniline | *m/z* (EI) 93 ($M^{+\cdot}$) |
| Benzamide | *m/z* (EI) 121 ($M^{+\cdot}$), 105 ($PhCO^+$) |
| 2-Benzamido-4-phenylthiazole | $\delta_H$ ($CD_3SOCD_3$) 7.2–8.2 (m); *m/z* (EI) 280 ($M^{+\cdot}$), 105 ($PhCO^+$). |
| Benzenesulfonamide | *m/z* (EI) 157 ($M^{+\cdot}$), 77 ($C_6H_5^+$) |
| Benzophenone | *m/z* (EI) 182 ($M^{+\cdot}$) |
| 1-Benzosuberone | $\delta_H$ ($CDCl_3$) 1.8 (4H, m), 2.7 (2H, m, H2), 2.9 (2H, m), 7.15–7.35 (2H, m), 7.4 (1H, m), 8.04 (1H, d, *J*=11 Hz, H9); *m/z* (EI) 160 ($M^{+\cdot}$) |
| Benzothiazole | *m/z* (EI) 135 ($M^{+\cdot}$), 108 ($[M-HCN]^{+\cdot}$) |
| 2-Benzoyl-5-phenyltetrazole | $\delta_H$ ($CD_3SOCD_3$) 7.4–7.7 (6H, m), 7.95 (2H, d, *J*=7.5 Hz, $H_{ortho}$ of 5-phenyl), 8.14 (2H, d, *J*=8.2 Hz, $H_{ortho}$ of benzoyl); *m/z* (EI) 222 ($M^{+\cdot}$), 105 ($PhCO^+$) |
| *N*-Benzylacetamide | $\delta_H$ ($CDCl_3$) 1.94 (3H, s), 4.35 (2H, d, *J*=6 Hz), 6.6 (br s), 7.4 (5H, m); *m/z* (EI) 149 ($M^{+\cdot}$), 106 ($BnNH^+$) |
| Benzyl alcohol | *m/z* (EI) 107 ($M^{+\cdot}$), 91 ($C_7H_7^+$) |
| Benzylamine | *m/z* (EI) 106 ($M^{+\cdot}$) |
| *N*-Benzyldimethylamine | *m/z* (EI) 135 ($M^{+\cdot}$), 134 ($[M-H]^+$) |
| *N*-Benzylmethylamine | *m/z* (EI) 121 ($M^{+\cdot}$), 120 ($[M-H]^+$), 91 ($C_7H_7^+$) |
| *N*-Benzyl-*N*-methylindole-2-carboxamide | $\delta_H$ ($CD_3SOCD_3$) 3.23 (br s, 3H), 4.80 (br s, 2H), 6.80 (1H, br s), 7.03 (dd, 1H), 7.18 (dd, 1H), 7.25–7.5 (m, 7H), 7.57 (d, 1H). *m/z* (EI) 264 ($M^{+\cdot}$), 120 (100%). |
| 2-Benzyl-5-phenyltetrazole | $\delta_H$ ($CD_3SOCD_3$) 6.00 (2H, s), 7.4 (5H, m, benzyl Ar-H), 7.55 (3H, m), 8.05 (2H, m, $H_{ortho}$ of 5-phenyl); *m/z* (EI) 258 ($M^{+\cdot}$) |
| *N*-Butylindole-2-carboxamide | $\delta_H$ ($CDCl_3$) 0.96 (3H, t), 1.4 (2H, m), 1.6 (2H, m), 3.5 (2H, m), 6.15 (1H, br s), 6.79 (1H, s, H3), 7.12 (1H, t), 7.28 (1H, t), 7.42 (1H, d), 7.63 (1H, d), 9.42 (1H, br s); *m/z* (EI) 216 ($M^{+\cdot}$), 144 (2-IndolylCO$^+$) |
| 3-Bromo-*N*,*N*-dimethylbenzamide | $\delta_H$ ($CD_3SOCD_3$) 2.98 (3H, s), 3.11 (3H, s), 7.28 (1H, m, H5), 7.34 (1H, d, *J*=7 Hz, H6), 7.55 (1H, d, *J*=8 Hz), 7.64 (1H, s, H2); *m/z* (EI) 226, 228 ($[M-H]^+$), 183, 185 ($ArCO^+$) |
| 3-Chloro-*N*,*N*-dimethylbenzamide | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 2.88 (3H, br s), 2.97 (3H, br s), 7.35 (1H, ddd, *J*=7.4, 1.5, 1.3 Hz, H4), 7.44 (1H, dd, *J*=3.8, 1.5 Hz, H2), 7.45 (1H, dd, *J*=8.0, 7.4 Hz, H5), 7.50 (1H, ddd, *J*=8.0, 3.8, 1.3 Hz, H4); *m/z* (EI) 183, 185 ($M^{+\cdot}$), 182, 184 ($[M-H]^+$), 139, 141 ($ArCO^+$) |
| 3/5-(4-Chlorophenyl)-1-methylpyrazole | $\delta_H$ ($CDCl_3$) 3.80 (s), 6.30 (d, *J*=2 Hz, H4 of 5-aryl), 6.50 (d, *J*=2 Hz, H4 of 3-aryl), 7.3–7.4 (m), 7.43 (d, *J*=8.7 Hz, $H_{ortho}$ of 5-aryl), 7.52 (d, *J*=2 Hz, H3 of 5-aryl), 7.72 (ddd, *J*=8.6, 2.7, 1.7 Hz, $H_{ortho}$ of 3-aryl); *m/z* (EI) 192 ($M^{+\cdot}$). |
| *N*-(4-Chlorophenyl)-*p*-toluenesulfonamide | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 2.31 (3H, s), 7.08 (2H, ddd, *J*=8.9. 2.7, 2.2 Hz), 7.28 (2H, ddd, *J*=8.9. 2.7, 2.2 Hz), 7.33 (2H, dm, *J*=8.3 Hz), 7.62 (2H, dm, *J*=8.3 Hz), 10.32 (1H, br s). |
| *N*,*N*-Diisopropylbenzamide | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 1.25 (12H, br), 3.62 (2H, br), 7.25 (2H, m), 7.39 (3H, m); *m/z* (EI) 205 ($M^{+\cdot}$), 105 ($PhCO^+$) |
| *N*,*N*-Dimethylbenzamide | $\delta_H$ (500 MHz, 70°C, $CD_3SOCD_3$) 2.94 (6H, s), 7.38 (2H, m), 7.42 (3H, m); *m/z* (EI) 149 ($M^{+\cdot}$), 148 ($[M-H]^+$), 105 ($PhCO^+$) |
| *N*,*N*-Dimethyl-3-fluorobenzamide | $\delta_H$ ($CD_3SOCD_3$) 2.88 (3H, br s), 2.97 (3H, br s), 7.2–7.25 (2H, m), 7.27 (1H, ddd, *J*=9.1, 2.7, 0.9 Hz, H6), 7.47 (1H, m); *m/z* (EI) 167 ($M^{+\cdot}$), 166 ($[M-H]^+$), 105 ($PhCO^+$) |
| *N*,*N*-Dimethyl-4-fluorobenzylamine | *m/z* (EI) 153 ($M^{+\cdot}$), 152 ($[M-H]^+$), 109 ($C_7H_6F^+$) |
| Dimethyl isophthalate | $\delta_H$ ($CDCl_3$) 3.93 (6H, s), 7.53 (1H, m), 8.20 (2H, d, 11 Hz, H4, H6), 8.67 (1H, s, H2); *m/z* (EI) 194 ($M^{+\cdot}$), 163 ($[M-MeO]^+$). |
| *N*,*N*-Dimethyl-3-methoxybenzamide | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 2.88 (3H, br s), 2.96 (3H, br s), 3.76 (3H, s), 6.90 (1H, dd, *J*=2.6, 1.5 Hz, H2), 6.92 (1H, ddd, *J*=7.6, 1.5, 1.1 Hz), 6.98 (1H, ddd, *J*=8.3, 2.6, 1.1 Hz, H6), 7.33 (1H, dd, *J*=8.3, 7.6 Hz); *m/z* (EI) 179 ($M^{+\cdot}$), 178 ($[M-H]^+$), 135 ($ArCO^+$) |
| *N*,*N*-Dimethyl-4-methoxybenzamide | $\delta_H$ ($CD_3SOCD_3$) 3.02 (6H, br s), 3.80 (3H, s), 6.87 (2H, d, *J*=9 Hz), 7.37 (2H, d, *J*=9 Hz); *m/z* (EI) 179 ($M^{+\cdot}$), 178 ($[M-H]^+$), 135 ($ArCO^+$) |
| 4,4-Dimethyl-2-(2-methoxyphenyl)oxazoline | $\delta_H$ ($CDCl_3$) 1.37 (6H, s), 3.87 (3H, s), 4.07 (2H, s), 6.95 (2H, m), 7.40 (1H, t), 7.71 (1H, dd, H6); *m/z* (EI) 205 ($M^{+\cdot}$) |
| *N*,*N*-Dimethyl-4-nitrobenzamide | $\delta_H$ ($CD_3SOCD_3$) 2.93 (3H, s), 3.11 (3H, s), 7.85 (2H, d, *J*=9 Hz), 8.24 (2H, d, *J*=9 Hz); *m/z* (EI) 194 ($M^{+\cdot}$), 193 ($M-H^+$), 150 ($ArCO^+$) |
| Dimethyl phthalate | *m/z* (EI) 194 ($M^{+\cdot}$), 163 ($[M-MeO]^+$). |
| *N*,*N*-Dimethyl-3-trifluoromethylbenzamide | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 2.88 (3H, br s), 2.99 (3H, s), 7.67 (1H, br dd, *J*=7.9, 7.7 Hz), 7.71 (1H, br d, *J*=7.9 Hz), 7.72 (1H, br s), 7.80 (1H, br d, *J*=7.7 Hz); *m/z* (EI) 217 ($M^{+\cdot}$), 216 ($[M-H]^+$), 173 ($ArCO^+$) |
| *N*-Ethoxycarbonylbenzamidine | $\delta_H$ ($CDCl_3$) 1.34 (3H, t, *J*=6 Hz), 4.21 (2H, q, *J*=6 Hz), 7.4 (2H, m), 7.5 (1H, m), 7.85 (2H, d, *J*=7 Hz, $H_{ortho}$); *m/z* (CI) 193 ($MH^+$), 165 ($[MH-C_2H_4]^+$). |
| Ethyl benzoate | *m/z* (EI) 150 ($M^{+\cdot}$), 105 ($PhCO^+$) |
| Ethyl 4-methoxybenzoate | $\delta_H$ ($CD_3SOCD_3$) 1.36 (3H, t, *J*=6 Hz), 3.84 (3H, s), 4.33 (2H, q, *J*=6 Hz), 6.89 (2H, d, *J*=9 Hz), 7.98 (2H, d, *J*=9 Hz); *m/z* (EI) 180 ($M^{+\cdot}$), 135 ($ArCO^+$) |
| Ethyl Nicotinate | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 1.38 (3H, t, *J*=7.1 Hz), 4.39 (2H, q, *J*=7.1 Hz), 7.35 (1H, ddd, *J*=8.0, 4.8, 0.9 Hz), 8.26 (1H, ddd, *J*=8.0, 2.1, 1.9 Hz), 8.74 (1H, dd, *J*=4.8, 1.9 Hz), 9.20 (1H, dd, *J*=2.1, 0.9 Hz); *m/z* (EI) 151 ($M^{+\cdot}$), 106 ($ArCO^+$) |
| Ethyl 4-nitrobenzoate | $\delta_H$ ($CD_3SOCD_3$) 1.40 (3H, t, *J*=7 Hz), 4.41 (2H, q, *J*=7 Hz), 8.18 (2H, d, *J*=8 Hz), 8.25 (2H, d, *J*=8 Hz); *m/z* (EI) 195 ($M^{+\cdot}$), 150 ($ArCO^+$) |
| 1-Indanone | $\delta_H$ ($CDCl_3$) 2.7 (2H, m, H2), 3.15 (2H, m), 7.2–7.5 (2H, m), 7.40 (1H, m, H5), 7.74 (1H, *d*, J=7.5 Hz, H7); *m/z* (EI) 132 ($M^{+\cdot}$) |
| 4-Methoxyacetophenone | *m/z* (EI) 150 ($M^{+\cdot}$), 135 ($ArCO^+$) |
| *N*-Methoxy-*N*-methylindole-2-carboxamide | $\delta_H$ ($CDCl_3$) 3.45 (3H, s), 3.84 (3H, s), 7.11 (1H, t), 7.28 (1H, t), 7.47 (1H, d), 7.71 (1H, d), 9.65 (1H, br s); *m/z* (EI) 204 ($M^{+\cdot}$), 144 (2-IndolylCO$^+$) |

Table 9. (*continued*)

| Substrate | Data |
|---|---|
| 2-(4-Methoxyphenyl)thiophene | $\delta_H$ ($CD_3COCD_3$) 3.81 (3H, s), 6.96 (2H, d, $J$=9 Hz), 7.08 (1H, dd, $J$=5.5, 6 Hz), 7.32 (1H, d, $J$=5.5 Hz), 7.36 (1H, d, $J$=6 Hz), 7.59 (2H, d, $J$=9 Hz); $m/z$ (EI) 190 ($M^{+\cdot}$). |
| $\alpha$-Methylbenzylamine | $m/z$ (EI) 120 ($[M-H]^+$), 106 ($[M-CH_3]^+$) |
| Methyl 2-Bromobenzoate | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 3.85 (3H, s), 7.48 (2H, m), 7.74 (2H, m); $m/z$ (EI) 214, 216 ($M^{+\cdot}$), 183, 185 ($ArCO^+$) |
| Methyl dithiobenzoate | $\delta_H$ ($CD_3SOCD_3$) 2.78 (3H, s), 7.48 (2H, t, $J$=8 Hz), 7.64 (1H, t, $J$=8 Hz), 7.96 (2H, d, $J$=8 Hz, $H_{ortho}$); $m/z$ (EI) 168 ($M^{+\cdot}$), 121 ($PhCS^+$). |
| *N*-Methyl-*N*-phenylindole-2-carboxamide | $\delta_H$ ($CD_3SOCD_3$) 3.38 (s, 3H), 6.90 (1H, t), 7.11 (1H, t), 7.27 (1H, d), 7.35 (3H, m, H4, $H_o$), 7.45 (4H, m, H3, $H_m$, $H_p$); $m/z$ (EI) 251 ($M^{+\cdot}$), 145, 107. |
| Methyl phenyl sulfoxide | $m/z$ (EI) 140 ($M^{+\cdot}$), 125 ($[M-CH_3]^+$) |
| Methyl phenyl sulfone | $m/z$ (EI) 156 ($M^{+\cdot}$), 141 ($[M-CH_3]^+$) |
| 4-Nitroacetophenone | $m/z$ (EI) 165 ($M^{+\cdot}$), 150 ($ArCO^+$) |
| 4-Nitroacetophenone dimethylhydrazone | $m/z$ (EI) 207 ($M^{+\cdot}$) |
| 4-Nitroacetophenone phenylhydrazone | $m/z$ (EI) 255 ($M^{+\cdot}$), 117 ($PhC(Me)=NH^+$) |
| Nitrobenzene | $m/z$ (EI) 123 ($M^{+\cdot}$), 77 ($C_6H_5^+$). |
| Phenol | $m/z$ (EI) 94 ($M^{+\cdot}$) |
| Phenyl acetate | $m/z$ (EI) 136 ($M^{+\cdot}$), 94 ($PhOH^{+\cdot}$). |
| Phenylhydrazine | $m/z$ (EI) 108 ($M^{+\cdot}$), 92 ($PhNH^+$). |
| 4-Phenylimidazole | $\delta_H$ ($CD_3SOCD_3$) 7.15 (1H, m), 7.35 (2H, m), 7.62 (1H, s, H5), 7.72 (1H, s, H2), 7.78 (2H, m, $H_{ortho}$); $m/z$ (EI) 144 ($M^{+\cdot}$), 116 ($[M-HCN]^{+\cdot}$) |
| *N*-Phenylmethanesulfonamide | $m/z$ (EI) 171 ($M^{+\cdot}$), 92 ($PhNH^+$) |
| *N*-Phenylmethanesulfonimide | $m/z$ (EI) 249 ($M^{+\cdot}$), 171 ($PhNHMs^{+\cdot}$), 92 ($PhNH^+$). |
| Phenylpyrazine | $\delta_H$ ($CDCl_3$) 7.5 (3H, m), 8.00 (2H, d, $J$=8 Hz, $H_{ortho}$), 8.49 (1H, br s), 8.64 (1H, br s), 9.03 (1H, s); $m/z$ (EI) 156 ($M^{+\cdot}$) |
| 1-Phenylpyrazole | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 6.53 (1H, dd, $J$=2.3, 2.0 Hz), 7.29 (1H, dt, $J$=7.6, 1.1 Hz), 7.48 (1H, dddd, $J$=8.6, 7.6, 2.2, 1.9 Hz), 7.73 (1H, dd, $J$=2.0, 0.6 Hz), 7.83 (1H, ddd, $J$=8.6, 0.9, 0.7 Hz), 8.47 (1H, dd, $J$=2.3, 0.6 Hz); $m/z$ (EI) 144 ($M^{+\cdot}$), 116 ($[M-HCN]^{+\cdot}$) |
| 2-Phenylpyridine | $\delta_H$ (500 MHz, $CD_3SOCD_3$) 7.34 (1H, ddd, $J$=7.4, 4.9, 1.2 Hz), 7.42 (1H, m), 7.48 (1H, ddm, $J$=8.0, 7.6 Hz), 7.86 (1H, ddd, $J$=8.0, 7.4, 1.8 Hz),7.94 (1H, ddd, $J$=8.0, 1.2, 1.1 Hz), 8.07 (1H, dm, $J$=8.0, Hz), 8.66 (1H, ddd, $J$=4.9, 1.8, 0.9 Hz, H6); $m/z$ (EI) 155 ($M^{+\cdot}$), 127 ($[M-HCN]^{+\cdot}$) |
| 2-Phenylpyrimidine | $\delta_H$ ($CDCl_3$) 7.20 (1H, t, $J$=6 Hz), 7.5 (3H, m), 8.46 (2H, dd, $J$=7, 3 Hz, $H_{ortho}$), 7.82 (2H, d, $J$=6 Hz); $m/z$ (EI) 156 ($M^{+\cdot}$), 103 ($PhC=N^{+\cdot}$) |
| 4-Phenylpyrimidine | $\delta_H$ ($CD_3SOCD_3$) 7.25–7.6 (3H, m), 7.65 (1H, m, Ho), 8.10 (1H, d, H5), 8.20 (1H, m, $H_o$), 8.86 (1H, d, H6), 9.24 (1H, s, H2); $m/z$ (EI) 156 ($M^{+\cdot}$), 129 ($[M-HCN]^{+\cdot}$) |
| 4-Phenylthiazol-2-amine | $\delta_H$ ($CD_3SOCD_3$) 7.05 (3H, m, H5, $NH_2$), 8.00 (2H, d, $J$=8 Hz, $H_{ortho}$); $m/z$ (EI) 176 ($M^{+\cdot}$), 134 ($[M-H_2NCN]^{+\cdot}$) |
| 2-Phenylthiazole | $\delta_H$ ($CD_2Cl_2$) 7.37 (1H, d, $J$=3.5 Hz), 7.4–7.5 (3H, m), 7.85 (1H, d, $J$=3.5 Hz), 8.0 (2H, m, $H_{ortho}$); $m/z$ (EI) 161 ($M^{+\cdot}$), 134 ($[M-HCN]^{+\cdot}$) |
| 5-Phenylthiazole | $\delta_H$ ($CD_2Cl_2$) 7.4 (3H, m), 7.58 (2H, d, $J$=8 Hz, $H_{ortho}$), 8.08 (1H, s), 8.75 (1H, s); $m/z$ (EI) 161 ($M^{+\cdot}$), 134 ($[M-HCN]^{+\cdot}$) |
| 1-Tetralone | $\delta_H$ ($CDCl_3$) 2.15 (2H, m), 2.65 (2H, m, H2), 2.97 (2H, t, $J$=6.5 Hz), 7.25 (2H, m), 7.46 (1H, m), 8.02 (1H, d, $J$=7 Hz, H8); $m/z$ (EI) 146 ($M^{+\cdot}$), 90 ($C_7H_6^+$). |

poorer substrates. Interestingly, when the exchange system was perturbed by the removal of sample (despite the continuous maintenance of a positive pressure of deuterium) the final level of *ortho*-deuteration was essentially halved. This may be a consequence of air ingress during sampling, but it appears that for both substrates, the initial rate of *ortho*-exchange is comparable to that in the undisturbed systems, but slows within little more than an hour. Exchange of thiazole-H2, interestingly, is slower than in the undisturbed system, but eventually does occur to essentially the same extent, again suggesting the operation of a different mechanism such as the reversible hydrogenation postulated above. That the observed saturation behaviour and the reduced levels of incorporation are not solely consequences of irreversible inactivation of the metal catalyst was demonstrated by addition, after 22 h, of fresh 4-phenylthiazole to the mixture containing ethyl 4-nitrobenzoate and replenishing the deuterium atmosphere. After a further 90 min, this had incorporated 1.0D in *ortho* positions, indicating that iridium species were still active. Although it is clear that shorter exposure times would suffice in many cases, deuterations carried out in the course of this work were generally allowed at least 22–24 h to reach equilibrium.

Published results indicate that iridium-mediated deuteration, in general, is intolerant of more polar, and particularly hydroxylic, solvents.[1–3] We have found, however, that the better substrates still undergo some deuteration even in neat methanol (Table 8) and good results can be obtained by using dichloromethane containing small quantities of methanol as a co-solvent. Given that sulfoxides do not appear to be good substrates (Table 4, entry 12), dimethylsulfoxide was also investigated as a co-solvent, but it was found that as little as 10% (based on the solvent volume) of DMSO completely suppressed the exchange of acetophenone with deuterium in the presence of **1**.

## 2. Conclusions

From the results presented here, it emerges that exchange of protons mediated by **1** is directed most efficiently by a functional group containing an $sp^2$-hybridised nitrogen or oxygen atom, via a five-membered metallacycle. In general, increasing the electron density at the directing heteroatom increases the degree of deuterium incorporation, although certain

substrates such as *N*-unsubstituted amidines and dithiocarboxylates do not survive the exchange conditions. The electronic effects of substituents in the arene ring are critical only where the directing group is poor, in which case exchange is generally promoted by electron donating substituents, but *meta*-substituents or bulky substituents attached to the directing heteroatom impede the exchange process. Where one *ortho*-substituent was present, there was no sign of any effect upon exchange at the other *ortho*-position, and there was no sign that an *ortho*-halogen, for instance, might be exchanged. Collateral exchange of protons adjacent to nitrogen is observed and may occur by a related C–H activation process, while deuterium incorporation into heterocycles is observed in a few cases, possibly by means of a reversible partial hydrogenation.

## 3. Experimental

### 3.1. General

Gas chromatography was performed using a Hewlett–Packard chromatograph (HP 5890) fitted with a mass-selective detector (HP 5970MSD) on a capillary column (HP1, 30 m×0.25 mm; 0.25 μm layer); the injector temperature was 250°C and the oven temperature was increased, after an initial 2 min delay, either from an initial 70–200°C at 5°C $min^{-1}$, or from an initial 100 to 240°C at 10°C $min^{-1}$. Additional low-resolution mass spectra and high resolution mass spectra were recorded using a VG Autospec magnetic sector instrument. $^1$H NMR spectra were recorded using Jeol GSX-270 and Bruker 500 instruments. (Cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate (**1**) was obtained from Fluka and from Strem

Acetophenone *O*-methyloxime,[11] 2-benzamido-4-phenylthiazole,[12] 2-benzoyl-5-phenyltetrazole,[13] 2-benzyl-5-phenyltetrazole,[14] 3-(4-chlorophenyl)-1-methylpyrazole and 5-(4-chlorophenyl)-1-methylpyrazole,[15] dimethyl-4-fluorobenzylamine,[16] 4,4-dimethyl-2-(2-methoxyphenyl)-oxazoline,[17] *N*-ethoxycarbonylbenzamidine,[18] *N*-methoxy-*N*-methylindole-2-carboxamide,[19] other indole-2-carboxamides,[20] methyl dithiobenzoate,[21] 4-nitroacetophenone dimethylhydrazone,[22] 4-nitroacetophenone phenylhydrazone,[23] *N*-phenylmethanesulfonamide and *N*-phenylmethanesulfonimide,[24] phenylpyrazine and 2-phenylpyrimidine,[25] 2- and 5-phenylthiazole,[26] and 4-phenylthiazole,[27] were prepared using published procedures. *N*-Benzylacetamide was obtained as a side-product from the benzylamine-mediated deprotection of glucose penta-*O*-acetate.[28] Ethyl esters and substituted benzamides, all of which were known compounds, were prepared by treatment of the corresponding acid chloride with ethanol or with an appropriate amine.[29] Key NMR signals and mass spectrometric ions used in the determination of deuterium incorporation levels are summarised in Table 9. Other substrates were obtained commercially, or were prepared as described below.

**3.1.1. 2-(4-Methoxyphenyl)furan and 2-(4-methoxyphenyl)thiophene.** Coupling of 4-methoxybenzenediazonium tetrafluoroborate with furan, in the presence of potassium acetate and 18-crown-6,[30] gave 2-(4-methoxyphenyl)furan (35%), mp 50–54°C (lit.[31] 55–58°C). $\delta_H$ ($CD_3COCD_3$) 3.82 (3H, s), 6.48 (1H, dd, *J*=4.5, 2.5 Hz, d), 6.67 (1H, d, *J*=4.5 Hz), 6.96 (2H, d, *J*=9.6 Hz), 7.54 (1H, d, *J*=2.5 Hz), 7.63 (2H, d, *J*=9.6 Hz); *m/z* 174 ($M^+$, 100%), 159 ($M-CH_3$), 131 (159-CO). Similarly prepared was 2-(4-methoxyphenyl)thiophene (24%), mp 104–106°C (lit.[31] 104–107°C). $\delta_H$ ($CD_3COCD_3$) 3.82 (3H, s), 6.96 (2H, d, *J*=10 Hz), 7.08 (1H, dd, *J*=4, 4 Hz), 7.31 (1H, d, *J*=4 Hz), 7.36 (1H, d, *J*=4 Hz), 7.59 (2H, d, *J*=10 Hz); *m/z* 190 ($M^+$, 100%), 175 ($M-CH_3$), 147 (175-CO).

**3.1.2. *tert*-Butyl 2-isopropylphenylcarbamate.** A solution of 2-isopropylaniline (5.481 g, 40 mmol) and di-*tert*-butyl dicarbonate (10.915 g, 50 mmol) in 1,2-dichloroethane (50 ml) was stirred for 4 h at 50–60°C, then left to cool overnight. The mixture was concentrated under reduced pressure to a low volume and passed through a short column of silica gel, eluting with ethyl acetate–hexane (1:9) to give *tert*-butyl 2-isopropylphenylcarbamate (11.503 g, 100%) as a reddish oil. $\nu_{max}$ 3344, 2967, 2932, 2870, 1731, 1714, 1703, 1587, 1514 $cm^{-1}$; $\delta_H$ ($CDCl_3$) 1.11 (6H, d, *J*=7.5 Hz), 1.50 (9H, s), 3.01 (1H, septet, *J*=7.5 Hz), 6.24 (1H, br s), 7.05–7.25 (m, 3H, 7.64 (1H, d, *J*=8.4 Hz); *m/z* ($NH_3$–CI) 253 ($MNH_4^+$), 236 ($MH^+$), 197, 180, 135 ($MH^+$–HCOO–*t*-Bu, 100%), 120; HRMS found: 253.1911 (calcd for $C_{14}H_{25}N_2O_2$ 253.1916).

**3.1.3. 4-Phenyl-2-butanone (4) and phenylacetone (3).** Magnesium (0.50 g) was dry-stirred for 30 min in a nitrogen atmosphere, then suspended in THF (7.5 ml). 1,2-Dibromoethane (0.020 ml) was added, the mixture was heated to reflux for 30 min, and 2-bromoethylbenzene (1.0 ml, 7.3 mmol) was added. After a further 15 min at reflux, the mixture was cooled and the supernatant solution was added to a solution of *N*-methoxy-*N*-methylacetamide[32] in THF (5 ml) at −20°C. After 90 min, the mixture was quenched with hydrochloric acid (1 M) and extracted twice with *tert*-butyl methyl ether. The combined organic phases were washed with aqueous sodium hydrogencarbonate, dried ($MgSO_4$), and evaporated under reduced pressure to leave 4-phenyl-2-butanone (0.783 g, 72%) as a pale yellow oil. Which was distilled at 130°C/20 mmHg (lit.[33] bp 116–118°C/20 mmHg). $\delta_H$ ($CDCl_3$) 2.12 (3H, s), 2.74 (2H, t, *J*=7.9 Hz), 2.88 (2H, t, *J*=7.9 Hz), 7.13–7.19 (3H, m), 7.2–7.3 (2H, m). *m/z* 148 ($M^+$), 133 ($M-CH_3$), 105 (100%), 91. Similarly prepared was phenylacetone (40%), bp 110°C/20 mmHg (lit.[34] bp 107–109°C/24 mmHg). $\delta_H$ ($CDCl_3$) 2.15 (3H, s), 3.69 (2H, s), 7.15–7.40 (5H, m). *m/z* 134 ($M^+$), 91 (100%).

**3.1.4. Example procedure for deuterium exchange.** A 25 ml flask containing 4-phenylthiazole (14 mg, 87 mmol) and **1** (80 mg, 100 mmol) in dichloromethane (1 ml) containing deuterium oxide (one drop) was evacuated, flushed with deuterium, and stirred for 90 h at room temperature. The crude mixture was purified directly by preparative TLC on silica gel in hexane–ethyl acetate (95:5) to give [*thiazole*-2-$^2$H, *benzene*-2,6-$^2H_2$]-4-phenylthiazole (11 mg). $\delta_H$ ($CDCl_3$) 7.36 (1H, t, *J*=7.5 Hz), 7.44 (2H, d, *J*=7.5 Hz), 8.00 (0.2H, d, *J*=7.5 Hz, *benzene*-H-2/6), 8.16 (1H, s, *thiazole*-H-5), no peak at 9.20 (*thiazole*-H-2). *m/z* 164 ($M^+$, 100%), 136 ($M-{}^2HCN$).

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## References

1. Heys, J. R. *J. Chem. Soc., Chem. Commun.* **1992**, 680. Heys, J. R.; Shu, A. Y. L.; Senderoff, S. G.; Phillips, N. M. *J. Labelled Compd. Radiopharm.* **1993**, *33*, 431. Chen, W.; Garnes, K. T.; Levinson, S. H.; Saunders, D.; Senderoff, S. G.; Shu, A. Y. L.; Villani, A. J.; Heys, J. R. *J. Labelled Compd. Radiopharm.* **1997**, *39*, 291. Shu, A. Y. L.; Saunders, D.; Levinson, S. H.; Landvatter, S. W.; Mahoney, A.; Senderoff, S. G.; Mack, J. F.; Heys, J. R. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 797. Salter, R.; Chappelle, M.; Morgan, A.; Moenius, Th.; Ackermann, P.; Studer, M.; Spindler, F. *Synthesis and Applications of Isotopically Labelled Compounds*; Pleiss, U., Voges, R., Eds.; Wiley: New York, 2001; Vol. 7, p. 63. An in situ method for complex formation and utilisation has recently been reported by ourselves: Ellames, G. J.; Gibson, J. S.; Herbert, J. M.; Kerr, W. J.; McNeill, A. H. *Tetrahedron Lett.* **2001**, *42*, 6413.
2. Hesk, D.; Das, P. R.; Evans, B. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 497. (b) Valsborg, J. S.; Sorensen, L.; Foged, C. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 209.
3. Shu, A. Y. L.; Heys, J. R. *J. Organomet. Chem.* **1996**, *524*, 87.
4. Bauer, W.; Prem, M.; Polborn, K.; Sünkel, K.; Steglich, W.; Beck, W. *Eur. J. Inorg. Chem.* **1998**, 485.
5. Shu, A. Y. L.; Heys, J. R. In *Synthesis and Applications of Isotopically Labelled Compounds*, Heys, J. R., Melillo, D. G., Eds.; Wiley: New York, 1998; p. 223.
6. N–N cleavage mediated by **1** has not been reported previously. Nevertheless, although this process is slow in the presence of a catalytic quantity of **1** at atmospheric pressure, early indications are that this is a viable synthetic method when carried out at elevated pressure.
7. Ostrovskii, V. A.; Koren, A. O. *Heterocycles* **2000**, *53*, 1421. Byard, S. J.; Herbert, J. M. *Tetrahedron* **1999**, *55*, 5931.
8. Spillane, W. J.; Kavanagh, P.; Young, F.; Dou, H. J.-M.; Metzger, J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1763.
9. Bedford, R. B.; Chaloner, P. A.; Claver, C.; Fernandez, E.; Hitchcock, P. B.; Ruiz, A. *Chem. Ind.* **1995**, *62*, 181; *Chem. Abstr.*, 123:198337.
10. Crabtree, R. H.; Parnell, C. P. *Organometallics* **1985**, *4*, 519.
11. Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016.
12. Fromm, E.; Kapeller-Adler, R.; Friedenthal, W.; Stangel, L.; Edlitz, J.; Braumann, E.; Nussbaum, J. *Liebigs Ann.* **1928**, *467*, 240.
13. Kreutzer, P. H.; Weis, J. Ch.; Bock, H.; Erbe, J.; Beck, W. *Chem. Ber.* **1983**, *116*, 2691.
14. Mihina, J. S.; Herbst, R. M. *J. Org. Chem.* **1950**, *15*, 1082.
15. Grimmett, M. R.; Lim, K. H. R.; Weavers, R. T. *Aust. J. Chem.* **1979**, *32*, 2203.
16. Jones, F. N.; Hauser, C. R. *J. Org. Chem.* **1962**, *27*, 4020.
17. Ellefson, C. R.; Prodan, K. A.; Brougham, L. R.; Miller, A. *J. Med. Chem.* **1980**, *23*, 977.
18. Pinner, A. *Ber.* **1890**, *23*, 2919.
19. Dekhan, M.; Todd, R. H. *Tetrahedron* **1994**, *50*, 6299.
20. Herbert, J. M.; McNeill, A. H. *Tetrahedron Lett.* **1998**, *39*, 2421.
21. Verkruijsse, H. D.; Brandsma, L. *J. Organomet. Chem.* **1987**, *332*, 95.
22. Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677.
23. Rector, D. L.; Folz, S. D.; Conklin, R. D.; Nowakowski, L. H.; Kaugars, G. *J. Med. Chem.* **1981**, *24*, 532.
24. King, J. F.; Lam, J. Y. L.; Skonieczny, J. *J. Am. Chem. Soc.* **1992**, *114*, 1743.
25. Ali, M.; McKillop, A.; Michell, M.; Rebelo; Wallbank, J. *Tetrahedron* **1992**, *48*, 8117.
26. Pivsa-Art, S.; Sommai, S.; Tetsuya, K.; Yoshiki, M.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn* **1998**, *71*, 467.
27. Pavlik, J. W.; Tongcharoensirikul, P.; Bird, N. P.; Day, A. C.; Barltrop, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 2292.
28. Sim, M. M.; Kondo, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 2260. Duffin, G. R.; Ellames, G. J.; Hartmann, S.; Herbert, J. M.; Smith, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2237.
29. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; 5th ed.; Longman: Harlow, 1989 pp 705, 709.
30. Beadle, J. R.; Kazeniowsky, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1594.
31. Nilsson, M.; Ullenius, C. *Acta Chem. Scand.* **1970**, *24*, 2379.
32. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
33. Jaeger, D. A.; Bolikal, D.; Nath, B. *J. Org. Chem.* **1987**, *52*, 276.
34. Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 6917.