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Hydrogen isotope labelling using iridium(I) dionates

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The cyclooctadienyliridium(I) dionates provide an alternative *ortho*-labelling approach to the more conventional iridium catalysts reviewed elsewhere in this special issue. The catalysts are utilized in DMF or DMA, removing potential problems of substrate insolubility in the solvents conventionally used for exchange labelling. Moreover, while readily prepared in a single step, the catalysts are also commercially available. In most cases recoveries are high, while the labelling achieved is both efficient and regiospecific. In addition, the reaction conditions are simple, requiring only conventional laboratory facilities and equipment.

Keywords: dionate; acetylacetonate; tritium; deuterium; ortho-labelling

Introduction

While most applications of iridium(I)-catalysed isotope-exchange labelling have utilized the Crabtree/Heys-like catalysts, certain other applications are better achieved using cyclooctadienyliridium(I) dionate catalysts, hence this review of their action and uses.

The dionate catalysts were initially developed following a screening process designed to identify catalysts which were even more effective than the rhodium chloride trihydrate *ortho*-labelling system previously utilized very effectively for the labelling of a wide range of substrate classes with deuterium and tritium.[1]

The original rhodium system suffered from a limited set of reaction conditions since the salt was insoluble in non-polar solvents and has a limited thermal stability. As a consequence, labelling conditions were restricted to isotopic water in a DMF or DMA solvent, with a temperature window of just 105–110°C. It was hoped that novel catalysts would be discovered which were free of such limitations (Figure 1).

Results and discussion

Screening an aromatic carboxylic acid, carboxamide and *N*-heterocyclic substrate panel (Figure 2) against a very wide range of potential transition metal salts and complexes, and including rhodium trichloride trihydrate as a positive control, gave a list of hits of which the most active was the simple, and commercially available, cyclooctadienyliridium(I) acetylacetonate (1, CODIrAcac).[2]

This catalyst which is a neutral complex, and hence soluble in most solvents, proved to have some advantages over the other iridium(I) systems in use at the time, catalysing the deuteration of a wide range of substrates, many of which contained directing groups which were ineffective with the typical Crabtree or Heys catalysts. Moreover the substrates could be labelled in dipolar aprotic solvents such as DMF and DMA, which was useful for polar agents such as pharmaceuticals, agrochemicals, etc.[2,3]

A typical example of labelling at high abundance by using this catalyst in a single exchange cycle is given below.

4-Phenyl[2,6-$^2H_2$]benzoic acid

4-Phenylbenzoic acid (100 mg) is heated with commercial cyclooctadienyliridium(I) pentan-1,3-dionate (1, 20 mg) in a mixture of DMF (6.6 ml) and deuterium oxide (3.3 ml) at 90°C for 2 h. The resulting solution is cooled, partitioned between ethyl acetate (30 ml) and 5% w/v aqueous sodium hydrogen carbonate solution (10 ml). The aqueous layer is separated, acidified with dilute hydrochloric acid to pH < 3, and the precipitated product re-extracted into ethyl acetate (10 ml). After the removal of the solvent under reduced pressure, crystallization of the resulting solid from hot methanol (2.0 ml) yields 4-phenyl[2,6-$^2H_2$]benzoic acid (75 mg, 74%, m.p. 223–225°C). Characterization by ^{2}H-NMR (61.4 MHz in [$^1H_6$]DMSO) shows a single resonance at δ8.1 ppm (ortho to carboxyl) with no other resonances detectable. The atom% abundance of deuterium by MS is 97%, calculated for the two exchangeable positions.

Later studies of the same catalyst by Fels *et al.*[4] confirmed our earlier results. Thus the high *ortho*-regioselectivity of the process was demonstrated yet again, this time with more substrates including benzylamines and acetophenone oxime, while DMA and DMF were again shown to be particularly good solvents for the labelling reaction. The authors reconfirmed the strict stereochemical requirements for efficient labelling. This requires the coordinating heteroatom of the directing group to be four bonds distant from the hydrogen atom to be exchanged,

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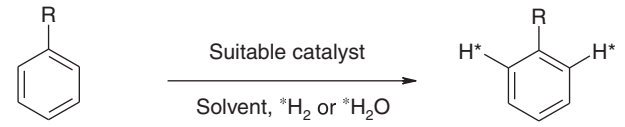


Figure 1. General labelling approach for *ortho*-labelling of substituted aromatics.

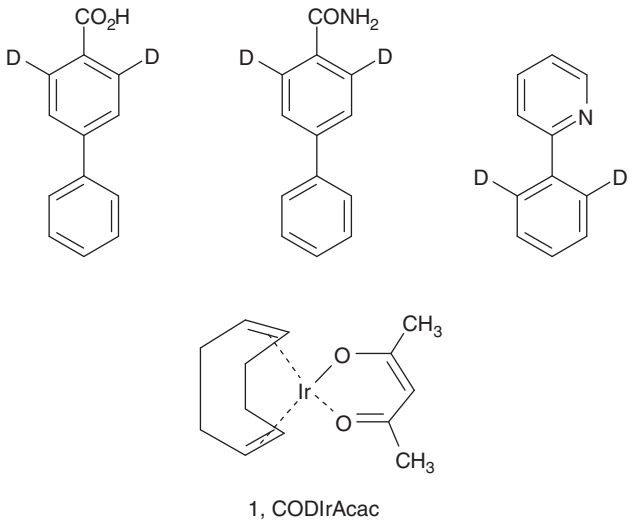


Figure 2. Screening panel of substrates (labelling positions with catalyst 1 are shown).

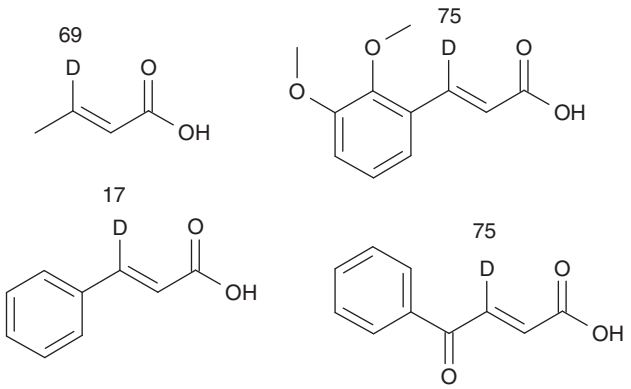


Figure 3. β-Labelling of α,β-unsaturated acids (%D, Fels *et al*).[4]

suggesting a five-ring cyclometallated intermediate involving the catalytic iridium atom. They also reinvestigated the time and temperature requirements of the labelling reaction previously studied in detail by parallel NMR studies.[3] In the same paper some novel work with non-aromatic systems such as crotonic and cinnamic acids was reported (Figure 3), confirming the applicability of the system to the β-labelling of α,β-unsaturated acids, as previously observed for the $RhCl_3\ 3H_2O$ catalytic system.[1]

In addition, the catalyst was applied with some modest success to the labelling of α,β-unsaturated ketones, though such moderate ligands would be expected to compete poorly with the DMA solvent, leading to the low abundances achieved.

The same authors have studied the efficacy of several cyclooctadinenyliridium(1) catalysts, including 1, with extensively substituted aromatics, though the work has only been described in abstract form at the time of writing.[5]

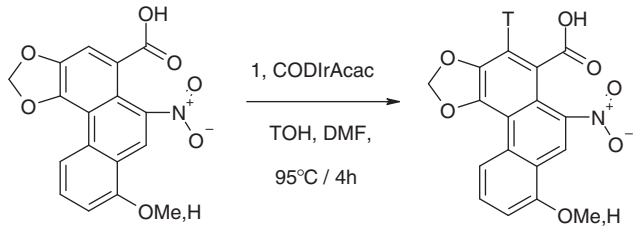


Figure 4. Tritium labelling of aristolochic acid I (OMe) and II (H) using CODIrAcac, 1. (Wu *et al*).[6]

One advantage of the new catalyst with respect to the conventional iridium(I) systems is the stability of easily reduced substituents under the non-reductive reaction conditions. Thus, the catalyst has been employed for the labelling of two aristolochic acids (aristolochic acids I & II) with tritium at intermediate specific activity (Figure 4) despite the vulnerable nitro-substituent.[6]

Treatment of the aristolochic acid in DMF with the catalyst and tritiated water in DMF at 95°C for 4 h yielded the labelled compound with a specific activity essentially the same as the commercial tritiated water used (50 Ci/ml) implying that the reaction was at, or near to, equilibrium and that there was no significant equilibrium isotope effect. There are, as yet, no published examples of the use of the system for labelling at very high specific activity, though any limitation is likely to be occasioned by radiolytic behaviour rather than by problems with the catalytic system *per se*.

The authors also proposed a plausible mechanism for the labelling reaction. Figure 7 incorporates the key aspects of the process.

Further examples of the use of CODIrAcac in the preparation of two tritiated pharmaceutical agents are given in the paper by Hesk, Lavey and McNamara in this Special Issue of the journal.

Next-generation catalysts

However, compound 1, while an excellent catalyst when used with an isotopic water donor, was rapidly reduced to iridium metal when exposed to hydrogen. In an attempt to optimize the activity of the dionate catalysts and, hopefully, to develop systems which would also allow the use of isotopic hydrogen we prepared a very wide range of dionate analogues. Screening of these analogues identified two further catalysts (Figure 5, structures 2 and 3) both with activities considerably greater than the simple acetylacetonate 1.

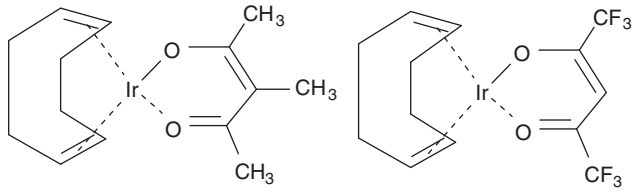
Thus 2 (CODIrMeAcac) was easily prepared, stable at room temperature and in air and proved much more active than 1 for isotopic water exchanges, while retaining similar substrate specificity. The catalysts were stable and could be employed over a wide temperature range in DMF or DMA. Moreover, labelling could be carried out within 2 min by employing microwave heating at 130°C.[3]

However, it was the fluorinated system (3, $CODIrF_6Acac$), which proved most interesting. Not only was the material more active than the simple acetylacetonate, it was also active at lower temperature and had a better spectrum of activity against a range of functional group directors. The figure below shows examples of the labelling obtained for a range of substrates under competitive conditions using both thermal and micro-

wave heating (Figure 6). It should be noted that utilization of a larger amount of catalyst, a higher temperature or a longer reaction time usually enables complete deuteration.

Despite the wide applicability it should be noted that the dionates have a strict requirement for 5-ring intermediates, hence they have only a weak ability to label anilides. The system of choice for anilide labelling, via a D_2O donor, remains the $RhCl_3$ $3H_2O$ catalyst and, for a D_2 donor, the Crabtree or Heys catalysts.

$CODIrF_6Acac$, 3, is easily prepared from the ubiquitous [di-chlorobis[1,2,5,6-η)-1,5-cyclooctadiene]diiridium (the so-called 'COD iridium chlorodimer') in a single trivial reaction, as illustrated below. It is stable for years if stored at -20° under nitrogen. Moreover, it is now commercially available. The preparation below is general and, with the substitution of the appropriate dionate, can also be utilized for the preparation of 2 (CODIrMeAcac) in 81% yield.



2, CODIrMeAcac 3, $CODIrF_6Acac$

Figure 5. Second generation catalysts from structure optimization and screening.

Cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentan-2,4-dionate, 3 ($CODIrF_6Acac$)

Commercial [di-μ-chlorobis(1,2,5,6-η)-1,5-cyclooctadiene]diiridium (300 mg) is stirred under nitrogen in degassed ether (6.0 ml) at which point it is only partly dissolved. Commercial 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (0.3 ml) in ether (0.6 ml) is then added via a syringe and the reaction stirred for 10 min. Sodium hydroxide solution (1M, 1.25 ml) is then added, dropwise via a syringe. During this phase the remaining crystals of precursor dissolve and the mixture becomes a deep claret colour. Water (3.0 ml) is then added, again via a syringe, and the biphasic mixture stirred under nitrogen for a further 20 min. The ether layer is evaporated under a slow stream of nitrogen leaving suspended clumps of fine claret-coloured crystals. The aqueous supernatant is decanted and the crystals washed twice more by decantation with 2.0 ml portions of water. Finally, the crystals are filtered and dried over silicagel overnight to leave cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentan-2,4-dionate, (3, $CODIrF_6Acac$) (412.5 mg, 91%) as a fine free-flowing stable red-purple solid. ^{1}H-NMR:$\delta(CDCl_3)$ 1.75 (4H, q, J = 7.5 Hz), 2.30 (4H, m), 4.31 (4H, s), 6.32 (1H, s) ppm. ^{13}C-NMR:$\delta(CDCl_3)$ 31.1, 62.6, 93.1, 118.5 (quartet), 174.3 (quartet)

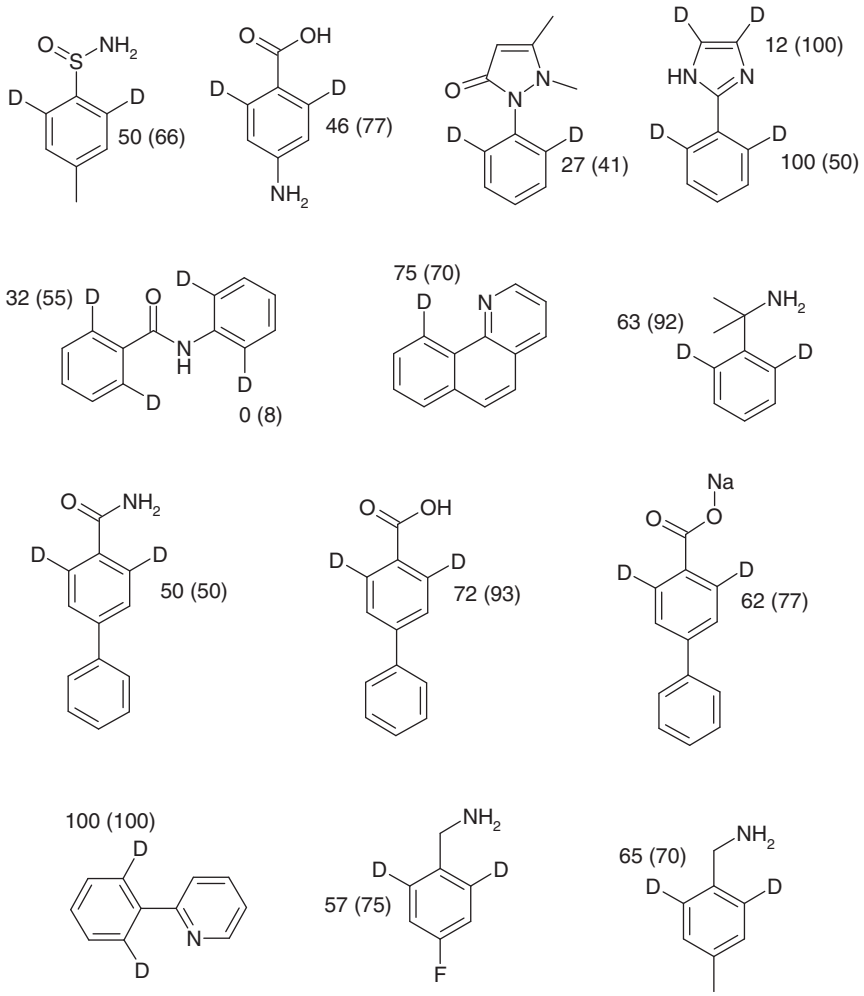


Figure 6. Percentage deuteration of various substrates by $CODIrF_6Acac$, 3, under competitive conditions, using thermal and (microwave) heating.

ppm. MS (EI mode) m/z 508/506 (mol. ion), 301−292 (cluster) amu. Found C 30.55%, H 2.91%, Required C 30.67%, H 2.91%.

The sulphonamide group has traditionally been a less useful director than other functional groups, however sulphonamides may now be conveniently labelled using 3. The reaction work-up in the preparation below is unoptimized but the preparation is included since it is typical of the high degree of labelling achievable in a single exchange cycle when using an isotopic water donor.

4-Methyl[2,6-$^2H_2$]benzenesulphonamide using catalyst 3 (CODIrF$_6$Acac)

4-Methylbenzenesulphonamide (50 mg) is dissolved in DMA (2 ml) containing cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentan-2,4-dionate (3, 29 mg) and D_2O (1 ml) added; the vial is then heated at 95°C for 5 h. The resulting reaction mixture is partitioned between sodium hydroxide solution (1M, 3 ml) and diethyl ether (4 ml) and the aqueous layer separated. The ether is washed with water (2 × 0.5 ml) and the aqueous layers combined. After acidification with 10% v/v hydrochloric acid solution, the resulting cloudy solution is extracted twice with ether (8 ml), the ether extracts combined and washed with a minimum volume of water. The ether is blown to dryness under a stream of nitrogen and the residue is recrystallized from chloroform/hexane to yield the labelled compound (27 mg, 50% unoptimized, m.p.135°C). The ^{1}H-NMR ([$^2H_6$]DMSO) shows only a singlet resonance at δ7.36 ppm and no detectable residual proton intensity at δ7.7 ppm. The ^{2}H-NMR (61.4 MHz, [$^1H_6$]DMSO) shows a single deuteron resonance at δ7.7 ppm (ortho to sulphonamide).

Further examples of the use of CODIrF$_6$Acac in the preparation of tritiated α-methylbenzylamine and of a tritiated pharmaceutical agent are given in the paper by Hesk, Lavey and McNamara in this special issue of the journal.

Catalytic cycles have been proposed[4,6] for the dionate system which are similar to those advanced for analogous metal-catalysed exchanges.[7] Figure 7 summarizes the key aspects; solvent or water displacement of the cyclooctadiene ligand, a formal chelate-assisted oxidative addition of the aromatic substrate, isotopic exchange with the isotope donor and finally reductive elimination to yield the labelled product. While reasonable, the proposed mechanism is speculative in that no appropriate kinetic studies have yet been carried out on the reaction. Moreover, the possibility that the dionate rather than the cyclooctadiene ligand is displaced during the formation of the active species has not been precluded.

Labelling with an isotopic hydrogen gas donor

The new catalyst, CODIrF$_6$acac, 3, was also of particular interest to us in that it is resistant to the formation of iridium metal on exposure to hydrogen gas. This is presumably because of greater stabilization by the fluorinated dionate ligand once the cyclooctadiene ligand has been removed by hydrogenation. The compound is therefore able to act as a catalyst for hydrogen isotope exchange using an isotopic hydrogen donor.[8]

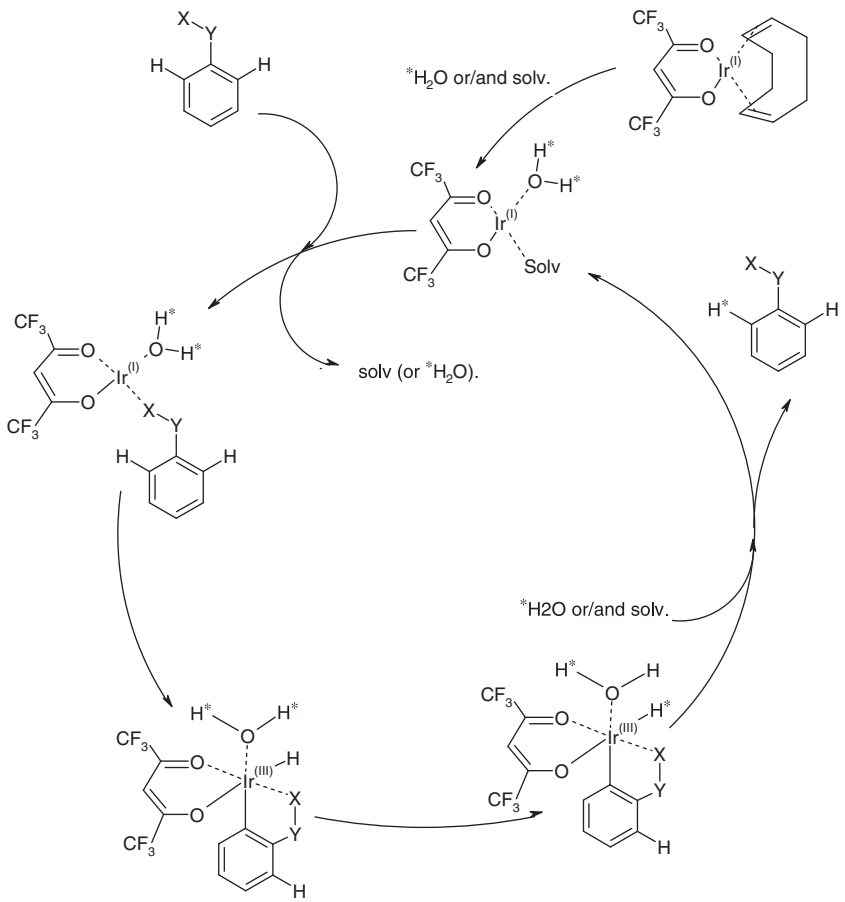


Figure 7. Proposed catalytic cycle for the exchange of an aromatic containing a directing group Y-X by CODIrF$_6$Acac, 3, and isotopic water.

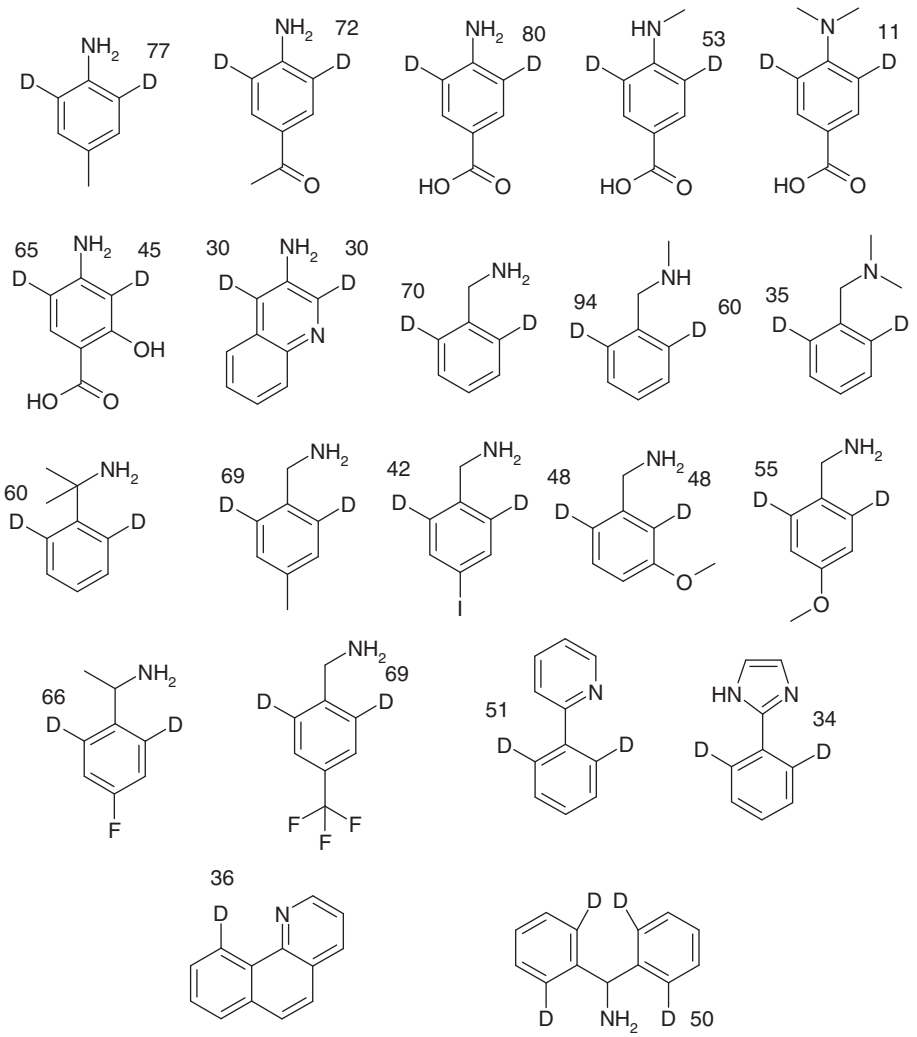


Figure 8. Percentage deuterium at the indicated positions for a range of substrates using $CODIrF_6Acac$, 3, with deuterium gas at ambient pressure and temperature in DMA solvent.

Figure 8 shows the labelling achieved for a range of subjects using catalyst 3 with deuterium gas at ambient pressure and temperature in DMA solvent.

Moreover, pre-treatment of the system with hydrogen gas showed no effect upon the labelling efficiency when the hydrogen was subsequently replaced by deuterium. This isotope-sparing should significantly reduce radioactive waste (tritiated cyclooctane and cyclooctene) when the catalyst is used with tritium.

Typical deuteration protocol for anilines and benzylamines

The substrate amine (0.04 mmol) and catalyst (3, $CODIrF_6Acac$, 0.01 mmol) are dissolved in DMF or DMA (250 μl) and stirred under deuterium gas for 34 h at room temperature and atmospheric pressure. The labelled substrate is isolated by a diethyl ether/hydrochloric acid (2 M) partition, followed by basification of the aqueous extract with NaOH solution (1 M), extraction with diethyl ether, drying with anhydrous magnesium sulphate and finally removal of the solvent under a stream of dry carbon dioxide free nitrogen. At this point the labelled amine is usually sufficiently pure for reliable analysis by ^{1}H- and ^{2}H-NMR and LC-MS.

A typical reaction follows:

4-Aminoaceto[3,5-^{2}H, 3,5-^{3}H]phenone, 1-(4-amino[3,5-^{2}H, 3,5-^{3}H]phenyl)ethanone

Cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentan-2,4-dionate (3, $CODIrF_6Acac$, 5 mg) and 4-aminoacetophenone (5.4 mg) were dissolved in N,N-dimethylacetamide (0.3 ml) and stirred under an atmosphere of deuterium gas for 1 h. A tracer quantity of tritium gas was then admitted and the reaction allowed to proceed for a further 3 h. The reaction was partitioned between aqueous sodium hydrogen carbonate solution (5% v/v, 3 ml) and chloroform (6 ml) and the chloroform layer separated and evaporated under a stream of dry nitrogen to yield 4-aminoaceto[3,5-^{2}H,3,5-^{3}H]phenone. The ^{1}H-NMR of the product showed it to be $>$ 90% pure with a deuterium abundance of $>$ 60% at the 3 and 5 positions. The ^{3}H-NMR of the product showed the expected resonance at δ6.7 ppm for the 3- and 5-positions. Moreover, no labelling was detectable at the positions of the acetyl methyl group or the 2- and 6-positions.

The nature of the actual catalyst in these isotopic hydrogen reactions is uncertain. As can be seen from Figure 8, the spectrum of substrates to which the catalyst may be applied is

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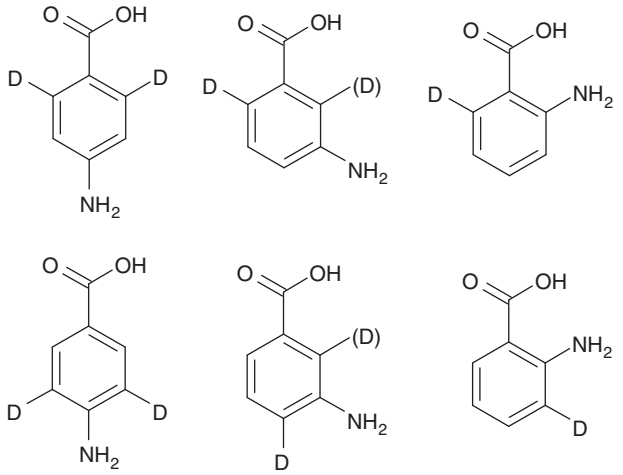

Figure 9. Selective labelling by CODIrF$_6$Acac, 3, (a) *ortho* to the carboxyl group by the D_2O system (top) and (b) *ortho* to the amino group (bottom) by the D_2 system.

very different from that when isotopic water is used as the isotope donor (Figure 6). The best substrates are the anilines and benzylamines. While the latter may be labelled using both of the deuterium donors, the labelling of the anilines only occurs with the deuterium gas system. This implies that the active form of the catalyst is different for the two isotope donors.

Moreover, the deuterium gas labelling reaction demonstrates an induction period while the active species is formed. This could reflect the simple hydrogenation/decomplexation of the cyclooctadiene ligand and the formation of an iridium hydride catalyst. However, given the substrate selectivity of the catalytic system, which differs from that of typical iridium dihydride mediated exchanges, it may also reflect the further reduction of the species to an active iridium(0) species. It is unlikely that this species is iridium metal since iridium isolated from prolonged reaction between 3 and D_2 was inactive, as was commercial iridium black. Moreover, the addition of mercury, usually considered as a test for heterogeneity, showed no consistent inhibition of the labelling.

The difference in substrate specificity between the D_2O and the D_2 donor systems can of course be exploited for selective labelling.[9] Figure 9 shows an example: the selective labelling of aminobenzoic acid isomers by the two systems.

The functional group specificity of catalyst 3 therefore displays useful orthogonal activity to that of the Heys and Crabtree catalysts. Thus 3 displays useful labelling of acids (D_2O) and benzylamines (D_2O and D_2) and anilines (D_2) which are not very effective directors with the conventional catalysts, but it is ineffective for esters, and anilides which are good directors for these catalysts.

One drawback with the isotopic hydrogen gas systems, which is not present with the isotopic water exchanges, is the reduction of nitro-groups to yield the corresponding *ortho*-labelled aniline. Not all reducible functions are reduced, however, with halogenated arenes, including aromatic iodides, tolerating the exchange conditions well.

Both CODIrAcac, 1, and CODIrF$_6$Acac, 3, are now commercially available making it simple to include them when screening for suitable catalytic labelling procedures.

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