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Review Article

30 Years with *ortho*-directed hydrogen isotope exchange labelling†

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Abstract: Over a 30-year period, a range of directed exchange methods have been developed to label target molecules with isotopic hydrogen. Among these methods, those involving *ortho*-direction have proved particularly useful for labelling a wide selection of drugs, drug candidates, agrochemicals, biochemicals, natural products and other significant agents with both tritium and deuterium. The approach has involved the identification of new catalysts for *ortho*-directed exchange including $RhCl_3 \cdot 3H_2O$ for the one-step labelling of carboxylic acids, amides, anilides, etc., with deuterium at high abundance, and with tritium at low and high specific activities from an isotopic water donor; CODIr($CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$), a similar and often more active catalyst with a somewhat different spectrum of directing substituents; CODIr($CF_3 \cdot CO \cdot CH_2 \cdot CO \cdot CF_3$), a catalyst for the labelling of benzylamines, anilines and heterocyclics utilizing isotopic hydrogen gas as the donor, and which is active even in dipolar aprotic solvents; and latterly, solid-phase iridium(1)-based catalysts, with activities similar to the Heys and Crabtree catalysts, which have significant advantages over their homogenous counterparts in tritium-labelling via the *ortho*-direction approach. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: $RhCl_3 \cdot 3H_2O$; CODIrAcac; $CODIrF_6Acac$; solid-phase catalyst; *ortho*-exchange

To start with, in 1977, the tritium isotope had already demonstrated its unique potential to facilitate the newly emerging, and related areas of biochemical pathway investigation and xenobiotic metabolism. Virtually all that was known of hormone elaboration had been defined by sophisticated precursor-labelling studies, and such biochemical investigations were in log-growth phase.

In my own field of terpene biochemistry, the preparation of specifically labelled mevalonates, squalenes, dolichols, juvenile hormones, sterols and steroid hormones was a prerequisite for fruitful studies. In our biochemical research laboratories at Liverpool under the direction of T. W. Goodwin and H. H. Rees, cholesterol, the key precursor in insect hormone elaboration had been labelled with tritium[1] in most of the A and B ring positions and also in key side chain locations. Some of these syntheses involved specific $^1H/^3H$ isotope exchange reactions and it was the facility of such reactions I recollected when recruited by the Metabolism Department of Fisons Pharmaceutical Division in late 1977.

The Department was facing severe challenges. The key pharmaceutical class under development by the company was a series of chromone carboxylates derived from the natural product khellin **1**. Chief amongst the compounds of interest was the anti-allergy agent sodium chromoglycate **2** marketed as an inhalation anti-asthma agent in Europe as Intal® and in North America as Cromlyn sodium®. This compound[2] is highly polar and plasma levels after inhalation of therapeutic doses are very low. The company badly needed technology to assay the compound and define its kinetics. There was also a need for metabolic investigations of related oral agents,[3] such as proxicromil, **3**. Tritium labelling was a possible solution to both these requirements. Thus, ^3H-labelled chromoglycate aerosols could provide sufficient sensitivity for kinetic investigations, whilst the same compound at high specific activity could facilitate the screening of specific antisera raised against a chromoglycate drug conjugate and also support the subsequent development of sensitive radioimmunoassays.[4] Naturally, the first approach was the base-catalysed tritium exchange

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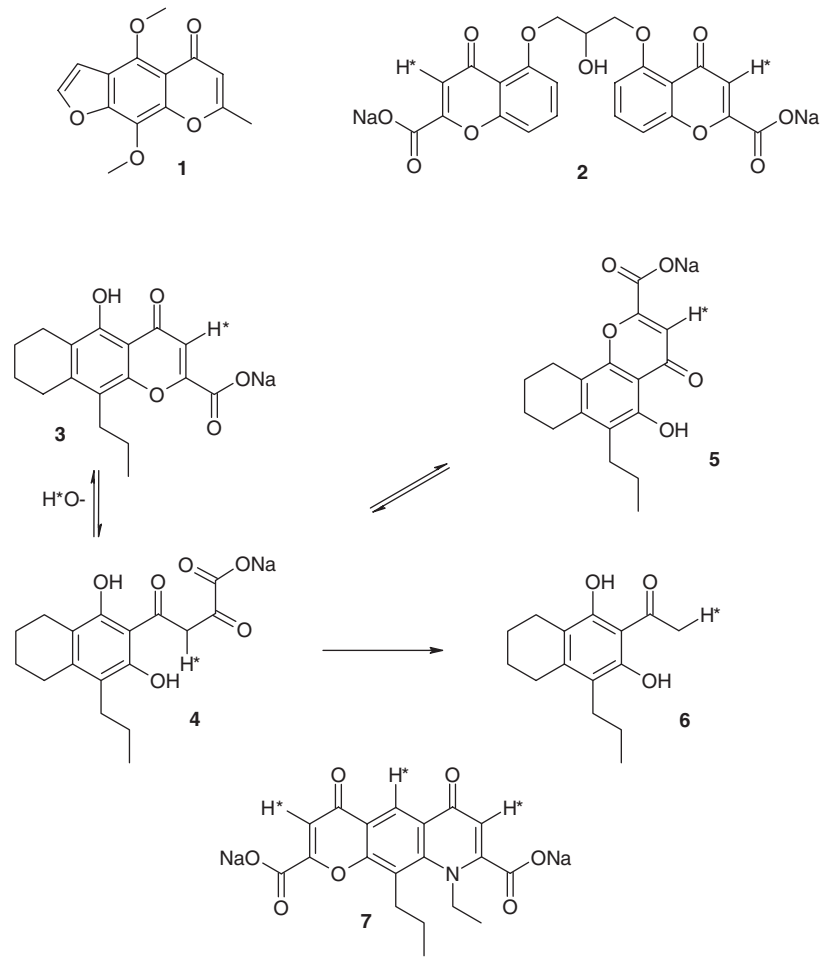
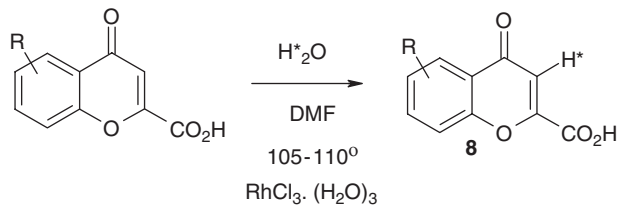


Scheme 1

which had been very successfully employed in the steroid field.

It was soon demonstrated that under strongly basic conditions the chromone ring could be opened, giving rise to a β-diketone species (Scheme 1) such as **4** which would readily undergo isotope exchange. In the case of **4** of course, recyclization would give not only labelled **3** but also its angular isomer **5**. A further drawback of this approach was the facility with which the intermediate β-diketone underwent further base-catalysed cleavage to a hydroxyacetophenone such as **6**, which itself was free to engage in further undesirable base-catalysed condensations.

An alternative approach, metal-catalysed isotopic exchange, had achieved some success in model studies[5] and even with complex agents such as steroids.[6] The existing metal catalysts, however, were unsatisfactory for our purposes since they showed little regiochemical discrimination and usually gave rise to generally labelled species.[7,8] Nevertheless, screening of many platinum group catalysts revealed one



Scheme 2

catalyst, which had been expected to lack any discrimination,[9] and which instead showed a surprising labelling regiospecificity when applied to chromone-2-carboxylates. This catalyst was rhodium(III) chloride trihydrate, [triaquotrichlororhodium(III)]. When used in DMF at 105–110°, this triaquo-catalyst[10] produced completely regiospecific labelling of the 3-position of chromone-2-carboxylates[11] to yield the labelled species, **8** (Scheme 2).

The reaction was extremely facile and, moreover, when applied to **3** no angular isomer was formed. This suggested that the labelling mechanism did not involve

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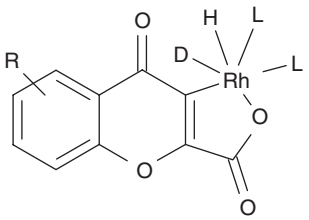
chromone ring opening. Instead we envisioned the intermediacy of some kind of five-ring chelate involving the carboxylate and a rhodium–carbon bond such as **9**.



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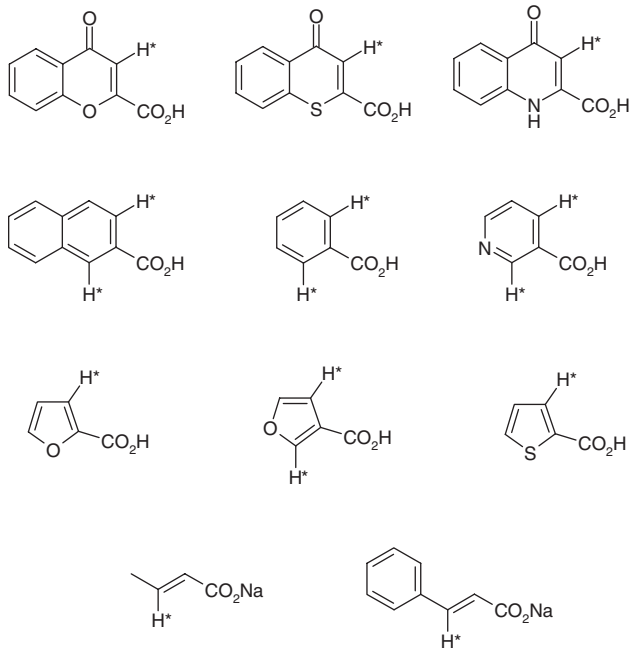
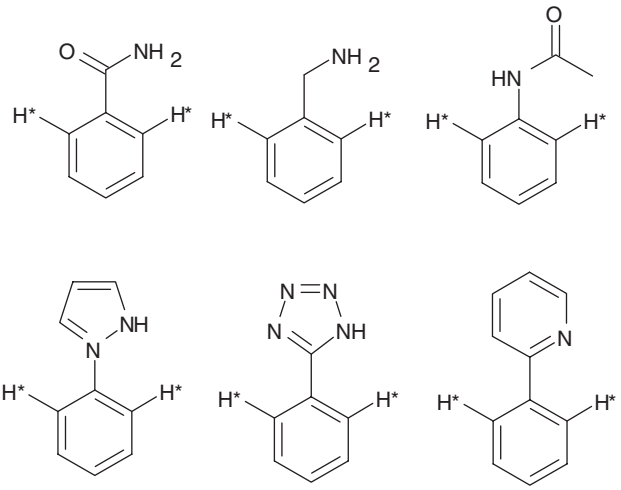
At that point in time little was known of *ortho*-metallation. Isotopic exchange into the triphenylphosphine ligands of some iridium *tris*triphenylphosphine complexes had been observed,[12] however, and somewhat later, cycloruthenated[13] and cyclorhodated[14] species were to be isolated.

If we were dealing with such cyclometallation, then the obvious next step was to try the reaction with other simple aromatic carboxylates, including substrates that could not ring open. This approach proved highly successful, (Scheme 3) and the methodology was soon shown to be useful with the tritium isotope at both low[15] and high specific activities,[16,17] allowing the labelling of two of the company's key drugs sodium chromoglycate, **1**,[16] and nedocromil sodium, **7**.[17] The method was soon extended to other directing groups (Scheme 4) such as amides, benzylamines, anilides and a range of heterocyclics.[18]



Scheme 3



Scheme 4

It was clear at this point that the approach constituted a significant advance in regiospecific labelling methodology and warranted further academic studies. Fortunately at this point, the opportunity to present the results to the wider isotopic community was provided by the first of what has become a key series of international symposia. The first symposium on the Synthesis and Applications of Isotopically Labelled Compounds was held in Kansas city in 1982, as a result of an enthusiastic and committed campaign by Bill Duncan and Alex Susan. In addition to providing an opportunity to present a preliminary account of the $RhCl_3 \cdot 3H_2O$ methodology, the symposium also offered the opportunity to meet and discuss an industrial/academic collaboration with Prof. John Jones of the University of Surrey, at that time the leading expert in ^{3}H-NMR applications, with a long track record of isotopic exchange studies.

The proposed collaboration achieved company support, and an initial investigation of the regiospecificity of the method proved very promising.[19] Next, an extremely hard-working and bright PhD student, David Hesk, was recruited to the project. David was soon producing significant advances in the methodology, demonstrating the application of the method to an increasingly wide range of drug substances[20–22] and further investigating the regiochemistry of the process.[22] Unfortunately, the $RhCl_3 \cdot 3H_2O$ labelling system proved somewhat unsuitable for detailed kinetic studies, as a result of the slow thermal decomposition of the catalyst under the labelling conditions. Instead the kinetics of the system were investigated using a closely related but more inert system, $Ru(Acac)_3$.

Although this system has a much narrower field of applicability, only functioning well with carboxylate

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substrates, it nevertheless proved very stable and suitable for kinetic detritiation studies of tritiated substrates, themselves prepared via the $RhCl_3 \cdot 3H_2O$ approach.[23] Overall, the kinetic studies showed similarities with the non-specific K_2PtCl_4 homogeneous system studied by earlier workers[24] and, taken together with the ^{3}H-NMR regiochemical studies we carried out, enabled us to further support the postulated 5-membered cyclometallated intermediate initially suggested as a key step in the reaction at Kansas City in 1982.

The applicability of such cyclometallation-based *ortho*-exchange procedures was further widened in 1992, after the publication, by Dick Heys, of a new deuterium-labelling system based around a dihydroiridium(I) catalyst he had prepared.[25] Although operative only in non-polar solvents, the system was nevertheless applicable to a whole new set of, directing groups, many of which were complementary to those active with the $RhCl_3 \cdot 3H_2O$ system. Moreover, the isotopic donor for this new system was deuterium gas. This posed an advantage for tritium-labelling applications since radiolytic decomposition should be less significant than with high specific activity water.

Studies of ligand effects[26] and applications to tritium[27] soon followed, and over the next seven years the methodology expanded to become a mainline approach to the tritiation of organic compounds. This expansion was given particular impetus by the publication of a paper[28] from David Hesk now working at Schering Plough, and who had maintained his keen interest in *ortho*-exchange methodology. The paper showed the wide applicability of the commercially available and indefinitely stable Crabtree catalyst[29] to such *ortho*-exchange labelling of a wide range of substrates, again using isotopic hydrogen gas. Now every laboratory had easy access to an effective catalyst and applications became too commonplace to reference. Indeed, so successful has the methodology become that it has led to a burgeoning of studies designed to improve the catalysts,[30] explore other practical or theoretical aspects of related iridium systems,[31] extend the ring size of the cyclometallation,[32] and so on.

Powerful though the system is, however, it has limitations. The activity was limited to a narrow range of non-polar solvents (the most effective being dichloromethane, which particularly stabilizes a key iridium dihydride species). Moreover, the purification of the tritiated product can often be problematic due to the presence of catalyst-related tritium-labelled impurities which may decompose slowly, sometimes necessitating more than one high-performance liquid chromatography purification step. Another limitation is the solubility of the substrate in the non-polar solvents required for the reaction, a major issue with polar drug substances and agrochemicals. More recently, this limitation has been successfully addressed, at least for most compound classes, by the utilization of ionic liquids.[33]

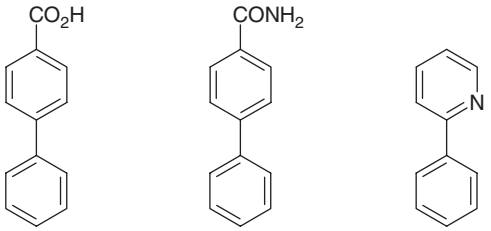
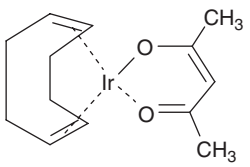


Figure 1 Screening panel.

An alternative approach, and the one adopted by my group, was to screen for catalysts that were active in dipolar aprotic solvents, by employing the newly available techniques of parallel chemistry. Given the limitation of parallel equipment for handling hydrogen gas, our initial approach was to screen for activity using deuterium oxide in DMF as the isotope donor, and leaving to a later phase the further screening and evaluation of successful hits with a deuterium gas donor.

For the initial phase, therefore, a wide range of salts and complexes of transition metals were screened in batches of 80 against three model substrates (Figure 1). Nearly all the transition metals were represented in these screens, most by several salts or complexes selected on the basis of availability and solubility. Heterogeneous metal preparations were excluded from the study, the intent being to identify homogeneous catalysts. Positive controls of $RhCl_3 \cdot 3H_2O$ and $Ru(Acac)_3$ were included in the batches.

The screen proved conventional wisdom correct, with hits limited to the precious metals (GroupVIII transition metals). As expected a number of iridium(I) systems including the Heys and Crabtree catalysts demonstrated some activity in the screens, however, the most spectacular hit[34,35] was a cyclooctadienyliridium(I) acetylacetonate, CODIrAcac, **10**.



10

This compound is a commercially available, pale yellow, air-stable, crystalline solid with a spectrum of activity similar to that of $RhCl_3 \cdot 3H_2O$. Hence, it is a

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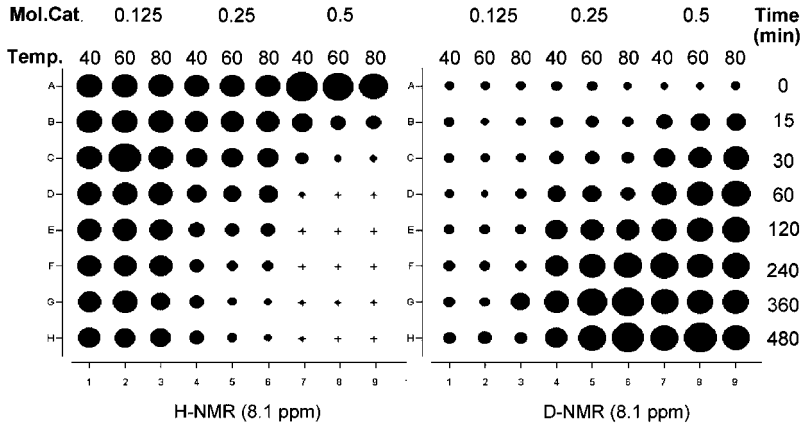
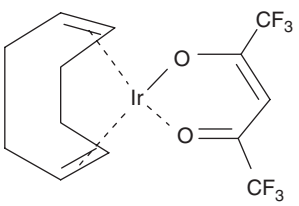


Figure 2 CODIrAcac, **10**: Optimization of labelling reaction conditions for the parameters: time, molar ratio of catalyst to substrate and temperature using high-throughput NMR (the size of the circles represents the integration of the *ortho*-proton or *ortho*-deuteron resonance of 4-phenylbenzoic acid).

catalyst of choice in the labelling of compounds with deuterium. For high-abundance deuterium-labelling applications, of course, the high molar concentrations achievable with a deuterium oxide donor prove highly advantageous when compared with the iridium(I)/deuterium gas systems.

The development of high throughput NMR analysis also provided the possibility to rapidly optimize the reaction conditions for the efficient use of the catalyst,[35] by monitoring the disappearance of the *ortho*-protons of a model substrate in the ^{1}H-NMR domain or the appearance of the corresponding *ortho*-deuterons in the ^{2}H-NMR domain. Figure 2 shows the results from a single overnight run of parallel reactions using VAST NMR.[36]

Fortunately, CODIrAcac systems are very easy to prepare, and optimization of the labelling conditions, as above, provided the information with which to set up comparative evaluations of a wide range of structural analogues of **10**, in which the acetylacetonate ligand was varied. These comparisons identified a still more active catalyst, CODIrF6Acac, **11**, a deep red-purple solid which is easily prepared in high yield in a single step and which has recently become commercially available.[37]



11

Not only was the catalyst highly active in exchanges with an isotopic water donor, but also early indications showed that for some substrates there was activity with deuterium gas, even when the reactions were run in DMF or dimethylacetamide (DMA).

By 2001 the merger between Astra and Zeneca provided an opportunity to take up an academic position at the University of Surrey. Contacts were maintained however, and a new productive academic/industrial collaboration began between myself and John Jones at Surrey and David Wilkinson and his team at AstraZeneca. Amongst the first tasks of this collaboration was an evaluation of the activity of **11** with a range of substrates using isotopic water and subsequently isotopic hydrogen gas, both in DMA.

At this point, despite the paucity of bespoke microwave equipment, John Jones's group had already pioneered the application of microwaves to isotopic labelling. Through the courtesy of CEM the opportunity presented itself to use the company's Discover microwave system to evaluate the efficacy of microwaves when applied to the reactions of **11** with a range of substrates in DMA/D_2O. These studies showed that, after optimization of the microwave conditions, exchange reactions could be carried out within 2 min at 130°C under microwave conditions, reactions that would normally be carried out for 2.5 h at 90°C under our standard thermal protocol (Table 1).

By this time the absence of reliable parallel chemistry equipment for handling hydrogen gas had led us to manufacture our own system[38] and with the availability of this apparatus the reactions of **11** with deuterium gas and a range of substrates in DMA could be studied effectively.

The results were exciting. Despite the use of DMA, a dipolar aprotic and a very good solvent, a range of benzylamines, *N*-heterocyclics and anilines were labelled at high abundance (Table 2).[37]

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Thus the method proved complementary to the existing iridium(I) systems, for which anilines and benzylamines either lacked directing ability or were very poor directors.

Tritium applications cyclooctadienyliridium systems such as the Crabtree catalyst and **11** have a drawback since activation of the catalyst involves the loss of the COD ligand as tritiated cyclooctane or cyclooctene. This is of particular concern when the catalyst is employed in stoichiometric or super-stoichiometric quantities, as is often the case in the labelling of complex polyfunctional molecules such as drugs or agrochemicals. Could the active catalytic species from **11** be generated using hydrogen instead, subsequently carrying out the labelling reaction with isotopic hydrogen? Figure 3 shows that this is indeed the case, the same degree of labelling being achieved with deuterium following an initial exposure to hydrogen as when deuterium was used throughout.

Finally, how effective would the catalyst prove with tritium and what would be the regiospecificity?

Table 1 Comparison of microwave and thermal labelling (for optimized conditions see Reference 35)

Substrate	Thermal (%)	Microwave (%)
4-Aminobenzoic acid	46	77
Antipyrine	27	41
Benzanilide	32, 0	55, 8
7,8-Benzoquinoline	75	70
2-Benzylpyridine	18	40
α,α-Dimethylbenzylamine	63	92
4-Fluorocinnamic acid	19	30
4-Methylbenzenesulphonamide	50	66
4-Methylbenzylamine	65	75
4-Phenylbenzamide	50	50
4-Phenylbenzoic acid	72	93
2-Phenylimidazole	100, 12	50, 100
2-Phenylpyridine	100	100
4-Trifluoromethylbenzylamine	57	75

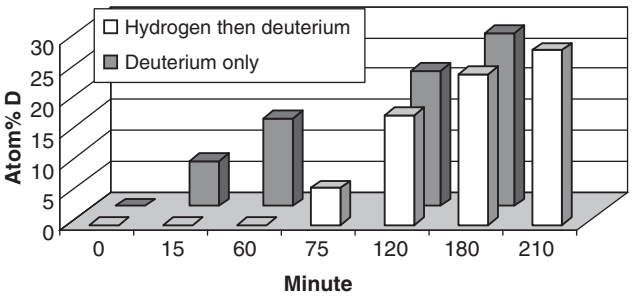

Figure 3 Isotope economy with catalyst **11**: comparison of 7,8-benzoquinoline deuteration with and without 1 h pre-incubation with hydrogen gas.

Table 2 Labelling of a range of substrates by **11** and D_2 gas in DMA

Substrate	Atom % D (no. of atoms)	Labelling assigned by
4-Aminoacetophenone	72% (2)	^{1}H-NMR/MS
4-Aminobenzoic acid	80% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Aminotoluene	77% (2)	^{1}H-NMR/MS
3-Aminoquinoline	30% (2)[a]	^{1}H-NMR/MS
7,8-Benzoquinoline	36% (1)	^{1}H-NMR/^{2}H-NMR/MS
Benzylamine	70% (2)	MS only
Biphenyl-2-ylmethylamine	38% (1)	MS only
Biphenyl-3-ylmethylamine	49% (2)	MS only
4-Dimethylaminobenzoic acid	11% (2)	MS only
N,*N*-Dimethylbenzylamine	35% (2)	^{1}H-NMR/MS
1,2-Diphenylethylamine	57% (4)	MS only
1,1-Diphenylmethylamine	50% (4)	^{1}H-NMR/^{2}H-NMR/MS
1-(4-Fluorophenyl)ethylamine	66% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Amino-2-hydroxybenzoic acid	55% (2)[b]	^{1}H-NMR/MS
4-Iodobenzylamine	42% (2)	MS only
3-Methoxybenzylamine	48% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Methoxybenzylamine	55% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Methylaminobenzoic acid	53% (2)	^{1}H-NMR/MS
4-Methylbenzylamine	69% (2)	^{1}H-NMR/^{2}H-NMR/MS
N-Methylbenzylamine	94% (2)	^{1}H-NMR/MS
1-Methyl-1-phenylethylamine	60% (2)	^{1}H-NMR/^{2}H-NMR/MS
Naphthalen-2-ylmethylamine	45% (2)	MS only
2-Phenyl-1*H*-imidazole	34% (2)	^{1}H-NMR/^{2}H-NMR/MS
2-Phenylpyridine	51% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Trifluoromethylbenzylamine	69% (2)	^{1}H-NMR/^{2}H-NMR/MS

Reaction conditions: The substrate (0.04 mmol) and catalyst (0.01 mmol) in DMA (250 μl) stirred under D_2 gas for 4 h at room temperature.[a] Ca. 30% at each of positions 2 and 4.
[b] 65% at position 5, 45% at position 3.

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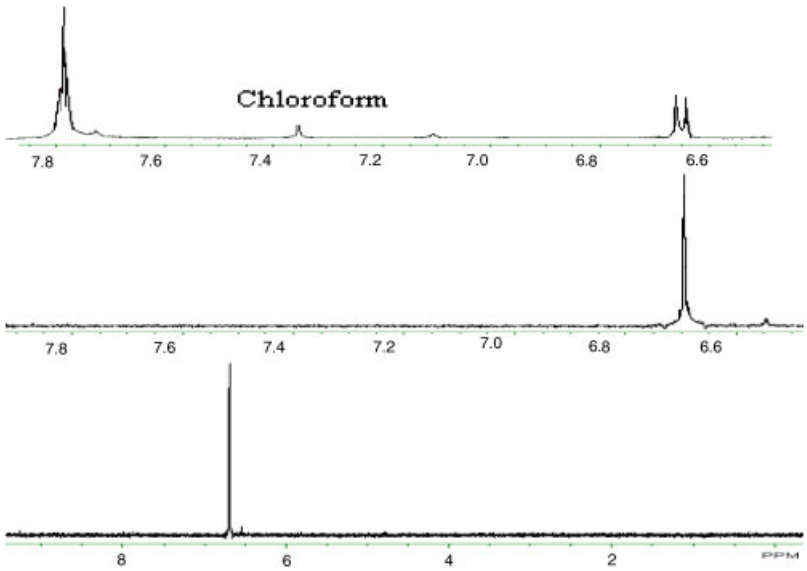


Figure 4 NMR spectra of the crude product from deuteration/tritiation of 4-aminoacetophenone catalysed by **11**. (Top spectrum: ^{1}H-NMR of the product in $CDCl_3$ showing reduction in the proton intensity at δ 6.65 ppm and partial collapse of the 2 and 6 doublet resonance at δ 7.78 ppm to a singlet, confirming deuteration at the 3 and 5 positions. Middle spectrum: ^{3}H-NMR spectrum of the same sample showing ^{3}H-labelling at the 3 and 5 positions. Bottom spectrum: as above but showing full range and absence of labelling either at the methyl group or at positions 2 and 6.) Figure available in colour online at www.interscience.wiley.com

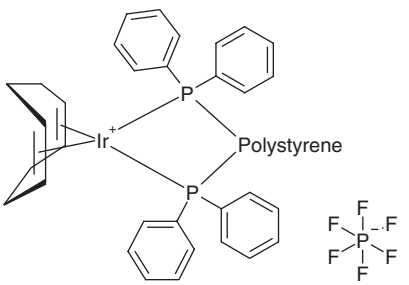
Figure 4 shows that the catalyst is indeed applicable, and that the regioselectivity for *ortho*-tritiation is high.

Such selectivity for *ortho*-labelling at the amino group in the presence of an acetyl function raised the possibility that the simple choice of catalyst could be used to select the desired labelling position within a polyfunctional molecule. The substrate in Figure 4 would certainly be orthogonally labelled, i.e. *ortho* to the acetyl group rather than the amino group, by the Crabtree or Heys catalysts. In addition, mere choice of the isotopic donor would enable selection of the labelling site with **11** (Table 3).

On completion of this work, the attention of our collaborative research focussed on the limitations of Crabtree-like catalysts. Perhaps we could address the problem of separation of labelled substrate from catalyst-related labelled impurities by the preparation of easily separated solid-phase analogues.

The auguries were not good for this approach. Previous work during another highly productive industrial/academic collaboration between Novartis, Solvias and Amersham[30] had addressed the area reasonably thoroughly and, although success had been achieved, the resultant dendrimeric catalyst was not easily synthesized and had not found general use. Instead, we sought a catalyst that would be easily accessible to anyone, whatever the level of facilities or synthetic skill.

The starting point for our campaign was obvious. We would attempt to prepare catalysts from triphenylphosphine-functionalized polystyrene, a commercially available substrate previously examined during the above collaboration and rejected due to the lack of activity in the resulting catalysts. As expected, we were not very successful. Catalysts with the nominal structure **12** were prepared by standard protocols using suspensions of the PPh_3–polystyrene in THF solvent along with the standard precursor for such syntheses, the ubiquitous $(CODIrCl)_2$. Such catalysts had been prepared before and used in olefin isomerization reactions,[39] and our catalysts were indeed active for this application. However, for isotopic exchange they showed weak activity.



12

We conjectured that it was unlikely that the solid-phase catalyst could be orders of magnitude less active compared with its homogeneous analogue, $CODIr(PPh_3)_2$, hence it seemed unadvisable to abandon the approach. Instead, we would attempt to find the problem with the system.

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Table 3 Control of labelling regiochemistry by choice of isotope donor with **11**

Substrate	Deuterium oxide donor		Deuterium gas donor	
	Atom % D (no. of sites)	Regiochemistry	Atom % D (no. of sites)	Regiochemistry
4-Aminobenzoic acid	60% (2)	2,6 (*ortho* to CO_2H)	94% (2)	3,5 (*ortho* to NH_2)
3-Aminobenzoic acid	53% (2)	Mainly 6 (*ortho* to CO_2H)	93% (1)	4 (*ortho* to NH_2)
2-Aminobenzoic acid	53% (1)	6 (*ortho* to CO_2H)	79% (1)	3 (*ortho* to NH_2)
4-Aminoacetophenone	<1.5% (2)	n.d.	83% (2)	3,5 (*ortho* to NH_2)
3-Aminoacetophenone	<2.5% (2)	n.d.	49% (2)	Mainly 4 (*ortho* to NH_2)
2-Aminoacetophenone	<5.0% (2)	n.d.	40% (1)	3 (*ortho* to NH_2)

Table 4 Comparison of the solid-phase catalyst, **12**, with homogenous CODIr(I) phosphine catalysts under kinetic conditions

Substrate	Catalyst	Labelling (location)
N,*N*-Dimethylbenzamide	Polystyrene catalyst	27% D
	Crabtree catalyst	56% D
	$CODIr(PPh_3)_2 \cdot BF_4$	0% D
	$CODIr(PPh_3)_2 \cdot PF_6$	0% D
7,8-Benzoquinoline	Polymer catalyst	14% D (at position 10)
	Crabtree catalyst	7% D (at position 10)
	$CODIr(PPh_3)_2 \cdot BF_4$	0% D
	$CODIr(PPh_3)_2 \cdot PF_6$	0% D
Benzophenone	Polystyrene catalyst	69% D *ortho*
	Crabtree catalyst	49% D *ortho*
	$CODIr(PPh_3)_2 \cdot BF_4$	81% D *ortho*
	$CODIr(PPh_3)_2 \cdot PF_6$	86% D *ortho*
4-Nitroacetophenone	Polystyrene catalyst	45% D (*ortho* to C═O)
	Crabtree catalyst	32% D (*ortho* to C═O)
	$CODIr(PPh_3)_2 \cdot BF_4$	81% D (*ortho* to C═O)
	$CODIr(PPh_3)_2 \cdot PF_6$	86% D (*ortho* to C═O)
3-Methylacetophenone	Polystyrene catalyst	79% D *ortho* D
	Crabtree catalyst	81% D *ortho* D
	$CODIr(PPh_3)_2 \cdot BF_4$	31% D *ortho* D
	$CODIr(PPh_3)_2 \cdot PF_6$	32% D *ortho* D
2-Phenylpyridine	Polystyrene catalyst	17% D (phenyl-*ortho*-D)
	Crabtree catalyst	21% D (phenyl- *ortho*-D
	$CODIr(PPh_3)_2 \cdot BF_4$	45% D (phenyl- *ortho*-D)
	$CODIr(PPh_3)_2 \cdot PF_6$	50% D (phenyl- *ortho*-D)
Benzanilide	Polystyrene catalyst	73% D *ortho* to amide, 36% D to anilide
	Crabtree catalyst	68% D *ortho* to amide, 18% D to anilide
	$CODIr(PPh_3)_2 \cdot BF_4$	79% D *ortho* to amide, 0% D to anilide
	$CODIr(PPh_3)_2 \cdot PF_6$	77% D *ortho* to amide, 0% D to anilide

Amongst other investigations, an exhaustive study of alternative preparation procedures was initiated, ultimately resulting in a protocol for the preparation of the catalyst from PPh_3–polystyrene and the Crabtree catalyst, by the displacement of the pyridine and tricyclohexylphosphine ligands. The reaction was carried out using dichloromethane rather than THF as solvent, and resulted in a catalyst that appears to be a weak dichloromethane solvate. It was highly active. Moreover, the activity could be essentially eliminated by a THF wash, explaining the original lack of activity. Thus a solid-phase catalyst[40] was obtained and, moreover, the material was easily prepared in a single step from commercially available and stable precursors. The preparation was so simple and facile, that the catalyst could easily be prepared and purified *in situ* prior to the labelling reaction.

How did the activity of the new catalyst compare with the homogeneous analogues? Table 4 shows a comparison of the various catalysts using kinetic reaction

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conditions. Clearly the solid-phase catalyst is quite comparable.

Recently, the applicability of the catalyst to the tritiation of a number of drugs and drug candidates has been evaluated and the predicted advantages of a solid-phase catalyst for such applications confirmed.[41] Studies with this labelling system and with other solid-phase catalysts are ongoing and will be reported in due course.

The above account is, of necessity, much truncated and large areas of research in directed isotope exchange techniques have been omitted. I must therefore apologize to those close colleagues whose collaborative work has not been covered in this article. I mention in particular Tracy Smith for her work on the α and β-labelling of piperidines, piperazines and secondary amines[42] and Stathis Alexakis for his development of an efficient catalytic system for the α-labelling of pyridines and other *N*-heterocyclics[43] and his still ongoing work, on the ^{2}H and ^{3}H exchange labelling of terminal alkenes over palladium catalysts.[44]

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