Supplement Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 29 April 2010, Revised 11 June 2010, Accepted 14 June 2010 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.1815

Rhodium- and ruthenium-catalysed hydrogen isotope exchange

W. J. S. Lockley[a]* and D. Hesk[b]

Metal-catalysed hydrogen isotope exchange has been widely used in the preparation of deuterium- and tritium-labelled compounds. This review details the development and utility of homogeneous and heterogeneous rhodium and ruthenium catalysts for the preparation of deuterium- and tritium-labelled compounds by hydrogen isotope exchange methodology.

Keywords: rhodium; ruthenium; homogeneous; heterogeneous; deuterium; tritium; exchange

Part I: Homogeneous Rh- and Ru-catalysed hydrogen isotope exchange

Homogeneous rhodium catalysts

The first reports of the use of rhodium trichloride hydrate in deuterium exchange appeared in 1975 as an alternative to the tetrachloroplatinate system first reported in 1967 by Garnett.[1] A solution of rhodium trichloride hydrate in a deuteroacetic acid/deuterated water mixture was found to effectively catalyse the deuteration of alkylbenzenes, halobenzenes and alkanes. Although the rate of exchange was slower than the tetrachloroplatinate system, no mineral acid stabilization was found to be necessary, thus simplifying the experimental procedure. The deuterium incorporation pattern in alkylbenzenes, which generally favoured terminal methyl and α-methylene exchange over aromatic exchange, was similar to tetrachloroplatinate. Similarly, the *ortho*-deactivation effect observed in alkyl and halobenzenes with tetrachloroplatinate was also seen with the rhodium trichloride system. A notable drawback of the rhodium trichloride system is its poor record in the labelling of halobenzenes, the result of catalyst poisoning from small amounts of hydrogen halide generated by dehalogenation.

Rhodium trichloride trihydrate was one of several catalysts studied by Jones in the tritium labelling of simple aromatic and aliphatic substrates, with ^{3}H-NMR spectrometry employed to determine the regiospecificity of incorporation.[2] An interesting selectivity difference in labelling 1,3,5-trimethylbenzene was observed, with a heterogenous platinum catalyst exclusively labelling the methyl groups, and rhodium trichloride trihydrate in acetic acid showing regiospecific incorporation in the aromatic ring.

In 1982 it was reported by Lockley that rhodium trichloride trihydrate could be used to regiospecifically label chromone-2-carboxylic acids in a DMF/deuterated water solvent at 105–110°C (Figure 1).[3]

In order to account for the high regiospecificity, it was postulated that the carboxylate was directing the catalyst to form a rhodium carbon bond and thus form a five-membered cyclometallated intermediate. Hence, in the presence of deuterated water, dissociation of this intermediate would lead to the regiospecific incorporation of deuterium. Additional studies with both deuterium and tritium in model systems showed broad applicability to regiospecific *ortho* hydrogen isotope exchange in aromatic carboxylic acids, amides, anilides and aralkylamines (Figure 2).[3]

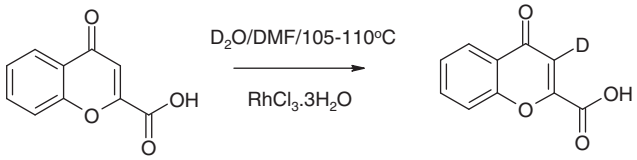
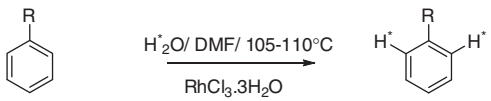


Figure 1. $RhCl_3.3H_2O$-catalysed deuterium labelling of chromone-2-carboxylic acid.



R= CO_2H, CO_2Na, $CONH_2$, CH_2NH_2, $NHCOCH_3$

Figure 2. $RhCl_3.3H_2O$-catalysed hydrogen isotope exchange of simple aromatics.

The reaction proved to be tolerant of most functional groups, with the only notable exception observed with *ortho*-halo and *ortho*-methoxy benzoic acids, where some dehalogenation and demethylation side reactions were observed. The regiospecificity as measured by ^{3}H-NMR was consistently high, thus lending further support to a proposed mechanism involving formation of a five- or six-membered cyclometallate between the directing group, the rhodium centre and the *ortho* position of the

[a]*Division of Chemical Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, UK*

[b]*Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*

**Correspondence to: W. J. S. Lockley, Division of Chemical Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK. E-mail: w.lockley@surrey@ac.uk*

aromatic ring. Further studies into the scope of the catalyst showed it could also be used to regiospecifically label some heterocyclic structures. The catalyst was also applied to the deuteration and tritiation of a broad range of pharmaceutical structures containing one or more of the required directing groups. The reaction proved to work in the majority of cases, although its utility is limited by degradation of some substrates under the reaction conditions.[4] The procedure has also been employed for the synthesis of a range of tritiated chromone carboxylate drugs at medium to high specific activity (Figure 3). The preparation of a high specific activity form of cromoglycate, an anti-allergy agent, is given below.[4]

To sodium cromoglycate (acid form, R1 = R2 = H, 5 mg) and rhodium trichloride trihydrate (1 mg) in N,N-dimethylformamide (400 μl) was added tritiated water (> 90%T, 25 Ci). The reaction vial was then sealed and heated at 90°C for 24 h. After removal of volatile and exchangeable tritium by sequential evaporation of methanol, a portion (ca. 40%) of the labelled compound was isolated by high-performance liquid chromatography using an ODS stationary phase and a methanol/aq. ammonium acetate gradient. This procedure yielded 59 mCi of the labelled cromoglycate (R1 = T, R2 = NH_4,) with a specific activity of 16.5 Ci/mmol.

More recent work by Nakagawa and co-workers confirmed the high regiospecifity of deuterium incorporation in benzoic acid and its alkali metal salts using rhodium trichloride trihydrate as catalyst.[5]

Despite the effectiveness of the catalyst, rhodium trichloride trihydrate does degrade slowly during the course of the reaction, making detailed kinetic studies difficult. Ruthenium acetylacetonate was subsequently identified as a more stable system, although it shows a much narrower scope of activity, as it is confined to the labelling of carboxylic acids. During kinetic studies, using ruthenium acetylacetonate, it was shown that the reaction was relatively insensitive to substituent effects, as there was only a modest three-fold increase in rate when going from an electron-donating subsitutent in *p*-toluic acid to a highly electron-withdrawing substituent in *p*-nitrobenzoic acid (Figure 4).[6]

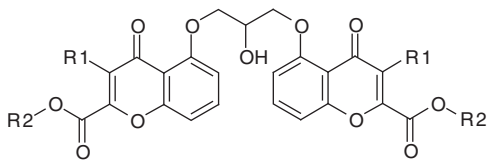


Figure 3. $RhCl_3.3H_2O$-catalysed tritium labelling of cromoglycate.

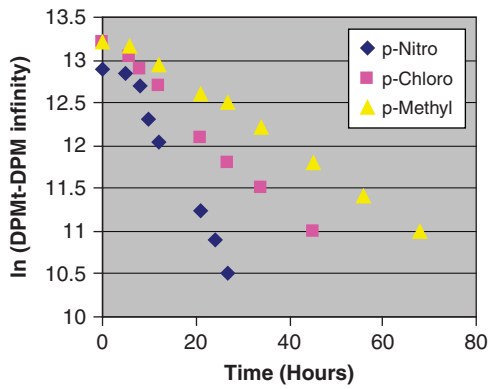


Figure 4. Detritiation of *p*-nitro, *p*-chloro and *p*-methyl benzoic acids.

It was noted that the conditions of detritiation were somewhat removed from the synthetic tritiation conditions and thus the kinetic data should be interpreted with some caution. Nevertheless, assuming a valid correlation between the conditions, this small positive Hammett reaction constant (ρ) showed that the reaction was promoted by electron-withdrawing groups. This enabled us to postulate that the rate-determining step of the reaction involved dissociation of the carboxylate oxygen–ruthenium bond, rather than formation of the ruthenium benzoate complex, as a small negative ρ value would have been expected in the latter case. Furthermore, the small ρ value ruled out formation of the ruthenium–carbon bond as the rate-determining step, as a large negative ρ value (−6 to −12) would have been expected in this case, such as is typically seen in electrophilic aromatic substitution reactions. Additional studies showed that lowering the pH reduced the rate, suggesting that the anionic form of the substrate had the highest reaction rate. Nevertheless, the reaction was devoid of a salt effect, suggesting that the rate-determining step was unlikely to involve reaction between the benzoate and a positively charged form of the catalyst.

More recently, a series of rhodium(III) hydride complexes were evaluated as catalysts for the regiospecific deuterium exchange of benzo[*h*]quinoline in deuteroacetone (Figure 5).[7]

Electron-donating phosphine ligands were found to be critical for catalyst activity. The most effective catalyst was further screened against a series of arenes and was generally found to be effective in promoting *ortho*-deuteration via a presumed five-membered cyclometallated intermediate through the hetero-aromatic nitrogen. A deuterium incorporation in the range of 60–70% was seen with most substrates after a 2-day reaction (Figure 6).

Additional amounts of deuterium (*ca.* 20%) were also incorporated in the α-position of the pyridine. Longer reaction times, up to 9 days, often resulted in almost complete deuterium exchange in the *ortho* positions. Oxygen proved to be a weaker directing group as shown by the lower incorporation observed in 2-phenylpyridine-*N*-oxide and the lack of any aromatic incorporation observed in acetophenone. While this catalyst offers a potentially viable deuterium labelling method, the use of $[D_6]$acetone as the isotope source precludes its utility for tritium labelling. Furthermore, attempts to utilize D_2O and CD_3OD as sources of isotope were unsuccessful due to the poor solubility of the catalyst in these solvents.

The complexes $RhH[P(iPr)_3]_3$ and $Rh_2H_2(\mu N_2)[P(Cy)_3)]_4$ were reported by Otsuka[8] to promote deuterium exchange in pyridine and simple mono-substituted aromatics as shown in Figure 7.

The substrate (5 mmol), D_2O (25 mmole), $RhH[P(iPr)_3]_3$ (0.1 mmol) were heated in THF (3 ml) at 80°C for 20 h.

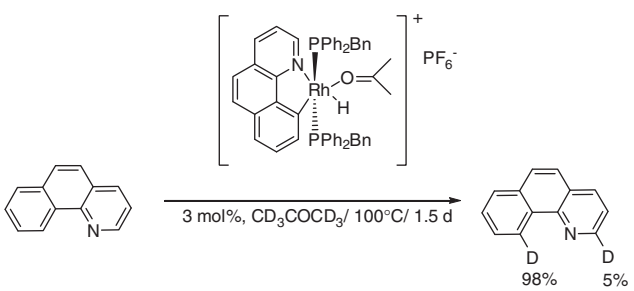


Figure 5. Deuteration of benzo[*h*]quinoline catalysed by [Rh(benzo[*h*]quinoline)(H)$(PPh_2Bn)_2$(acetone]PF_6.

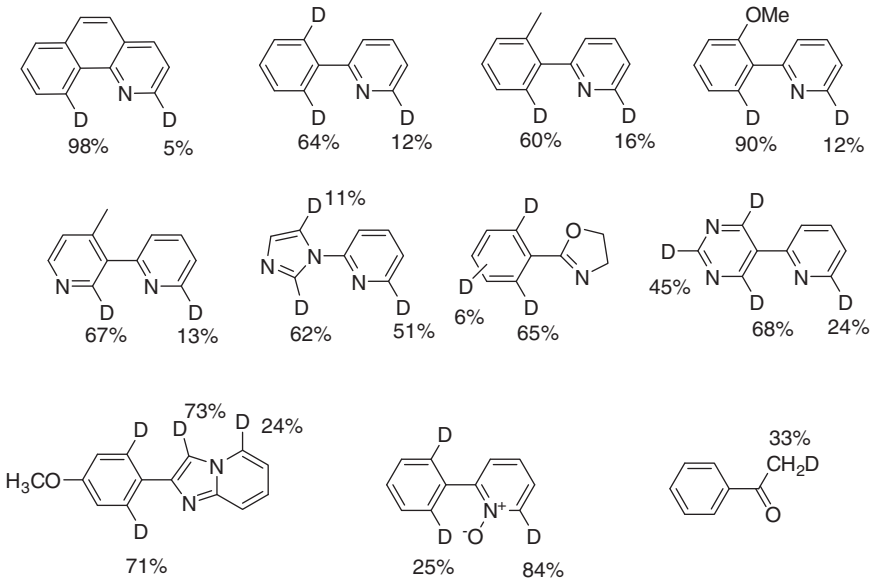


Figure 6. Deuteration of arenes.

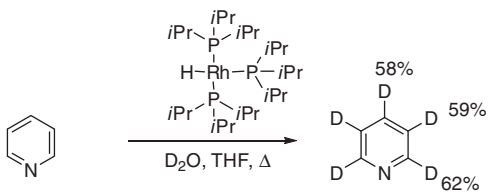


Figure 7. $RhH[P(iPr)_3]_3$-catalysed deuteration of pyridine.

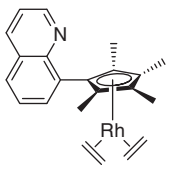


Figure 8. *Bis*(η^2-ethylene)[η^5-2,3,4,5-tetramethyl-1-(8-quinolyl)cyclopentadienyl] rhodium(I).

In the simple aromatics studied, such as toluene and anisole, the deuterium was broadly distributed across all available aromatic sites. The author's proposed mechanism suggests that in the presence of D_2O, the initial step of the reaction involves a reversible oxidative addition of D_2O to $RhH[P(iPr)_3]_3$ followed by reductive elimination of DHO from the adduct to form $RhD[P(iPr)_3]_3$. The catalytic cycle is then completed by oxidative addition of ArH, followed by reductive elimination of ArD from the adduct $RhHD(Ar)[P(iPr)_3]_3$. This mechanism also accounts for the lack of regiospecificity of deuterium incorporation, as there is no preference for one particular aromatic position over another. Deuterium incorporation was also seen in the methyl groups of toluene and anisole, which was postulated to occur via formation of a four- or five-membered cyclometallated intermediate involving the methyl group.

The remaining two examples in this section of the review arise from the area of catalytic C–H activation. In this area, research is more focused on the use of deuterium to study the mechanism of C–H activation as opposed to the identification of improved catalysts for hydrogen isotope exchange labelling. Nevertheless there are a few complexes reported in these studies that can promote deuterium exchange in simple aromatic and aliphatic substrates and hence could be worthy of further investigation. In studies of C–H activation of hydrocarbons, Enders[9] reported a rhodium(I) complex containing a hemilabile quinolyl-cyclopentadienyl ligand, which catalysed H/D exchange in olefins in the presence of visible light with perdeuterobenzene acting as the isotope source (Figure 8).

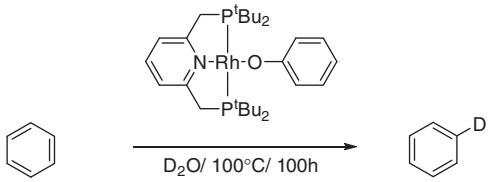


Figure 9. [(2,6-*bis*[(di-*tert*butylphosphino)methyl]pyridine)Rh(phenoxide)]-catalysed deuteration of benzene.

The complex is activated by irradiation with a high pressure mercury lamp, which results in the reversible loss of one of the ethylene ligands. Oxidative addition of perdeuterobenzene is followed by insertion of the ethylene ligand into the Rh–D bond. Hydride elimination followed by a reductive elimination of [D_5]deuterobenzene regenerates the partially deuterated mono-ethylene complex. Completion of several catalytic cycles results in complete deuteration of the ethylene ligand. The complex is also active with substituted olefins such as 2,2-dimethylbutene and vinyltrimethylsilane, where a preference for α over β exchange was observed. In contrast, 1,2-disubstituted olefins were found to be too sterically hindered for oxidative addition to the rhodium metal centre. While potentially useful for the deuterium labelling of olefins, the use of perdeuterobenzene as the isotope source precludes a similar tritium-labelling approach.

The pincer complex [(2,6-*bis*[(di-*tert*butylphosphino)methyl]-pyridine)Rh(phenoxide)] was effective in catalysing the deuteration of benzene using deuterated water at 100°C over the course of 100 h (Figure 9).[10]

No decomposition of the catalyst was observed under these conditions. The catalyst was also heated with perdeuterotoluene in water at 100°C for 335 h. Analysis (by ^{1}H NMR only) showed loss of deuterium from the *meta* and *para* positions, which supports the concept that the mechanism of de-deuteration is metal-catalyzed as opposed to proceeding via an electrophilic aromatic substitution mechanism. As D_2O was used as the isotope source, one can envisage the analogous preparation of tritiated aromatics via this approach, which might therefore provide an alternative to conventional heterogenous Pt catalysis.

Homogeneous ruthenium catalysis

The use of *tris*(triphenylphosphine)ruthenium(II) dichloride as a hydrogen isotope exchange catalyst was first reported in 1974 by Regan,[11] who applied the catalyst to the labelling of primary alcohols in the α-position by heating at temperatures from 150 to 200°C (Figure 10).

Under the conditions employed no deuteration of secondary alcohols was observed. Other Gp VIII transition metal catalysts were screened, including Wilkinson's catalyst, tetrachloroplatinate, Raney Ni, Pd/C, $(Ph_3P)_2PtCl_2$ and $(Ph_3P)_2IrCOCl$, but these proved inactive for both primary and secondary alcohols. The use of $Ru(Ph_3P)_3Cl_2$ to tritiate primary alcohols was later reported by Lešetický, who found that while the reaction proceeded rapidly at temperatures in the 180–200°C range, useful rates of exchange still occurred at temperatures as low as 130°C. Oxidation of [1-^{3}H]hexan-1-ol to caproic acid resulted in loss of >99% of the label, thus confirming that the labelling was confined to the α-position.[12]

Further studies by Jones on the labelling of primary and secondary alcohols employed ^{3}H-NMR spectroscopy and confirmed the preference for labelling α to the hydroxyl group. Upon prolonged heating, incorporation was also observed in the β positions[13] as might be expected for a reaction which progressed via an oxido-reductive cycle. Deuterium NMR studies by Al-Rawi *et al*. confirmed the earlier findings and also showed that secondary alcohols had higher β-incorporation than primary alcohols.[14] The catalyst was also used by Saljoughian to label benzyl alcohol in the methylene position, to provide an intermediate in the synthesis of 1,3-dioxa-2-phenyl[2-^{3}H]cyclohex-5-yl palmitate (Figure 11).[15] Of particular interest in this example is the presence of a favourable isotope effect during oxidation of [^{3}H]benzyl alcohol to [^{3}H]benzaldehyde as illustrated by a very modest decrease in specific activity from 186 mCi/mmol to 172 mCi/mmol.

Following on from this work, the use of the catalyst has been extended to the labelling of primary and secondary amines. An early application was in the synthesis of *N*-[^{3}H]ethyl-*N*-nitroso-*N*′-nitroguanidine using [^{3}H]ethylamine which was efficiently prepared by reaction with the catalyst and tritiated water at 140°C for 2 h. The [^{3}H]ethylamine was isolated as the hydrochloride and converted to *N*-[^{3}H]ethyl-*N*-nitroso-*N*′-nitroguanidine by the method of McKay (Figure 12).[16,17]

Subsequently, the catalyst has proven to be particularly useful in the labelling of piperidines and piperazines, which are a common functionality in pharmaceuticals. (Figure 13).

Recoveries of the tritiated product from such reactions are generally good and specific activities are generally in the 0.5–1 Ci/mmol range using tritiated water with a specific activity of 900 mCi/mmol.[18] A typical example for labelling a piperidine-containing pharmaceutical agent is further illustrated by the synthesis of [^{3}H]SCH 66336. (Figure 14).[18]

The substrate (*20 mg*) *and tris(triphenylphosphine)ruthenium*(*II*) *dichloride* (*2 mg*) *were dissolved in dioxane* (*100 μl*) *in a heavy wall*

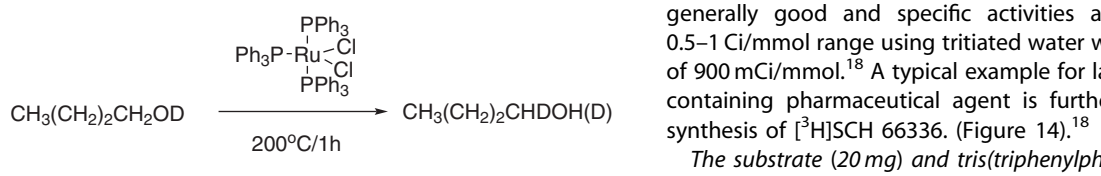


Figure 10. Preparation of [1-^{2}H]butan-1-ol.

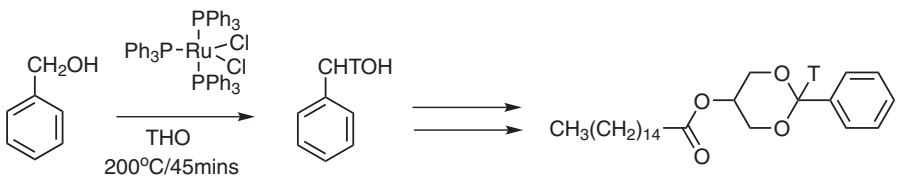


Figure 11. Preparation of [^{3}H]benzyl alcohol as an intermediate in the synthesis of 1,3-dioxa-2-phenyl[2-^{3}H]cyclohex-5-yl palmitate.

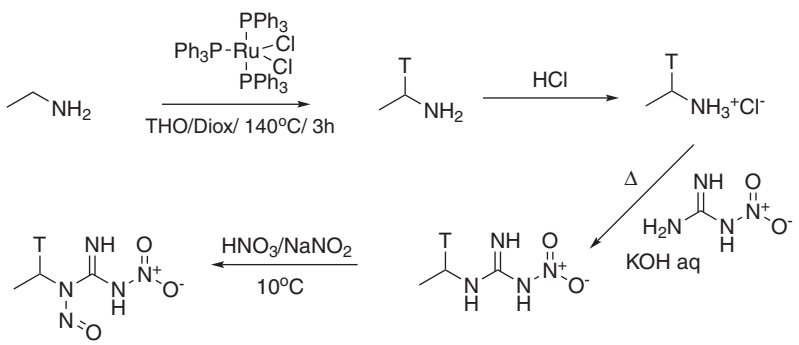


Figure 12. Preparation of [^{3}H]ethylamine as an intermediate in the synthesis of *N*-[^{3}H]ethyl-*N*-nitroso-*N*′-nitroguanidine.

tube fitted with a rubber septum. Tritiated water (900 mCi/mmol, 5 μl, 0.25 Ci) was added via syringe and the tube was frozen in liquid nitrogen, evacuated and flame sealed. The reaction was heated at 130°C for 1 h and the contents partitioned between ethyl acetate (5 ml) and sodium bicarbonate solution (0.3 M, 2 ml). The product was extracted with ethyl acetate (3 × 5 ml). The combined extracts were washed with water (2 ml), dried over anhydrous sodium sulphate, filtered and evaporated to dryness. A total of 75 mCi at a radiochemical purity of 46% and a specific activity of 1.35 Ci/mmol was isolated.

More recently, more detailed studies[19] on *tris*(triphenylphosphine)ruthenium(II) dichloride in comparison with the complexes $[Ru(\eta^6\text{-benzene})_2Cl_2]_2$, $[Ru(p\text{-cymene})_3Cl_2]_2$ and $[Ru(CO)_3Cl_2]_2$. were reported. A number of commercially available piperidines, piperazines and dialkylamines were screened with the above catalysts using both DMSO and DMF as co-solvents, with the former proving to allow for greater catalytic activity. In addition, the use of $[^2H_6]$DMSO as co-solvent allowed direct monitoring of the reactions by NMR and optimization of the reaction conditions. Heating to 150°C for 3 h in DMSO generally resulted in high deuterium incorporation for all the substrates studied. Recoveries were moderate and somewhat variable, mainly due to a competing methylation reaction arising from activation of the DMSO solvent by the catalyst. In addition, a carbonylation side reaction was observed on some occasions when using the most active catalyst, tricarbonyldichlororuthenium(II) dimer. A typical deuteration procedure is given below for the labelling of 1-(3-trifluoromethylphenyl)piperazine (Figure 15).[19]

The catalyst, $(CO)_6Ru_2Cl_4$ (6.8 mg), dry DMSO (50 μl) and deuterium oxide (10 μl) were placed in a thick-walled reaction vial and 1-(3-trifluoromethylphenyl)piperazine (10 mg) was added. The vial was capped, shaken to ensure complete dissolution and then heated for 3 h at 150°C. The product was isolated by ether extraction from aq. saturated. $NaHCO_3$ solution. The resulting crude product was dissolved in ether (0.7 ml) and a saturated solution of oxalic acid in ether (50 μl, ca. 188 mg/ml) added and allowed to stand overnight. The supernatant was then removed and the precipitated oxalate salt washed with ether (0.25 ml). Crystallization from methanol (50 μl) by slow addition of ether gave 1-(3-trifluoromethylphenyl)[2,3,5,6-^{2}H]piperazinium oxalate (8.7 mg, 63%). The overall deuteration achieved was 4.5D/molecule with the α and β positions equally labelled.

$Ru(Ph_3P)_3Cl_2$ has also been reported as an effective catalyst in the preparation of $[^2H_{10}]$cyclohexene.[20] The reaction was run under microwave conditions, employing catalytic amounts of sodium dodecylsulphate and ethanol with D_2O as the isotope source at temperatures in the 120–140°C range with a 1 h reaction time (Figure 16).

In a typical procedure, the cyclohexene (1 mmol), $Ru(Ph_3P)_3Cl_2$ (0.05 mmol), D_2O (3 ml) and SDS (0.1 mmol) were added to a 10 ml vial and microwave irradiated, with stirring. The power was varied automatically between 0 and 100 W to maintain a temperature of 140°C.

The reaction likely proceeds via a hydroruthenation/β-elimination catalytic cycle. The effect of catalytic amounts of sodium dodecylsulphate and EtOH is believed to promote the formation of a hydridoruthenium species, which can then be converted to the corresponding deuteridoruthenium species in D_2O. Either additive was equally effective at promoting the reaction when added separately and no obvious improvement was noted when they were combined in the same reaction. Deuterium enrichments as recorded by ^{1}H and ^{2}H NMR were typically > 95%, with isolated yields of 80 to 96%. Other non-substituted cyclo-olefins were also completely deuterated, but substituted cyclo-olefins such as 1-methylcyclohexane were only partially deuterated.

In the area of C–H activation, the divalent thiaruthenacycle complex *cis*-(Ru[$SC_6H_3(2\text{-}CH_2)$(6-Me)-κ^2S,C]$(PMe_3)_4$ was used by Komiya to catalyse the deuteration of the *ortho* methyl groups in 2,6-dimethylbenzene thiol under D_2 (Figure 17).[21]

In a typical procedure, cis-(Ru[$SC_6H_3(2\text{-}CH_2)$(6-Me)-κ^2S,C]$(PMe_3)_4$ (9.7 mg, 0.018 mmol) was transferred into a Schlenk tube into which [D_6]benzene (1.5 ml) was added, followed by 2,6-dimethylbenzenethiol (50 μl, 0.376 mmol). The reaction system was evacuated by several freeze–thaw cycles before D_2 (35.8 ml, 1.48 mmol) was added. The reaction was held at 30°C and a portion analysed by NMR at various time intervals.

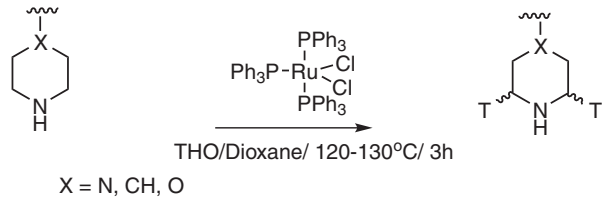


Figure 13. *Tris*(triphenylphosphine)ruthenium(II) dichloride-catalysed exchange of piperidines and piperazines.

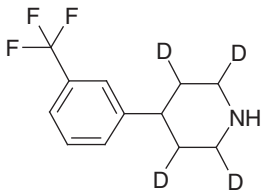


Figure 15. Labelling of 1-(3-trifluoromethylphenyl)piperazine using $(CO)_6Ru_2Cl_4$ and D_2O.

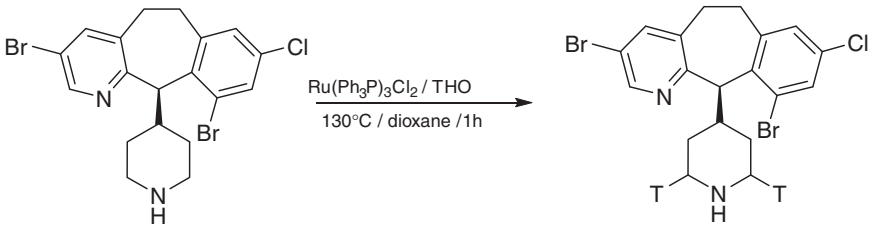


Figure 14. Preparation of precursor of [^{3}H]SCH 66336.

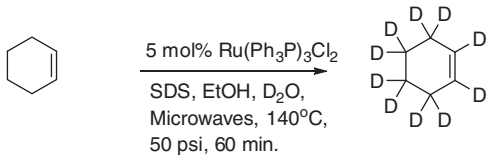


Figure 16. Deuteration of cyclohexene via $Ru(Ph_3P)_3Cl_2$-catalysed exchange with D_2O under microwave conditions.

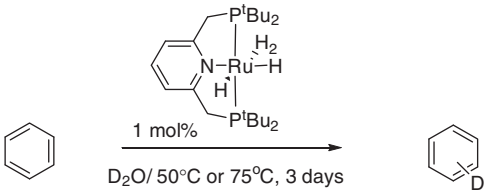


Figure 18. [Ru(dtbpmp)(η^2-H_2)H_2]-catalysed deuteration of benzene.

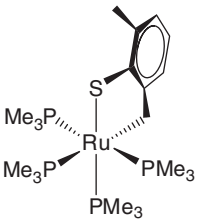


Figure 17. *cis*-(Ru[SC_6H_3(2-CH_2)(6-Me)-κ^2S,C](PMe_3)$_4$.

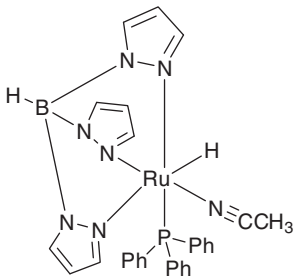


Figure 19. $TpRu(Ph_3P)_3(CH_3CN)H$.

The reaction was run using 5% catalyst in [D_6]benzene at room temperature for 5 days under a D_2 atmosphere, which allowed for direct monitoring of the enrichment by ^{1}H NMR. Approximately 60% deuterium enrichment was observed in the methyl groups with about 40% exchange in the SH group. The complex *cis*-$RuH_2(PMe_3)_4$ was also found to be active with the same substrate and to a lesser extent with 2,6-xylenol, where a 7-day reaction time was required to achieve a near 40% enrichment in the methyl groups. The authors proposed a tentative mechanism to account for SH and CH exchange, the latter likely due to the formation of a five-membered oxaruthenacycle. This was further supported by the observation that when phenol was used as a substrate, OH/D_2 exchange occurred but the *ortho* sp^2 C–H bond did not exchange, likely due to the necessity of forming an unfavourable four-membered cyclometallation intermediate.

The pincer complex [Ru(dtbpmp)(η^2-H_2)H_2] has been reported by Leitner to catalyse deuterium exchange in aromatic and heterocyclic hydrocarbons with D_2O as the isotope source (Figure 18).[22]

In a typical procedure, under an argon atmosphere, toluene (0.23 ml, 2.5 mmol) was diluted with cyclohexane (1.4 ml) and half of this solution was transferred to a Schlenk tube containing [Ru(dtbpmp)(η^2-H_2)H_2] (1 mol%). Degassed deuterated water (1 ml) was added under a stream of argon and the mixture stirred at 50°C for 3 days.

Benzene was quantitatively deuterated using 1 mol% of catalyst at 50°C within 3 days. In studies of substituted aromatics such as toluene, a clear preference for *meta* (84%) and *para* (28%) incorporation was seen over *ortho* (<5%) incorporation, suggesting the regiospecificity is influenced by a steric effect. No incorporation was observed in the methyl group. A similar steric effect was seen in naphthalene, where a preference for deuteration at the β-position (62%) over the α-position (15%) was noted. In contrast, in the case of 2,5-dimethylfuran, deuterium was incorporated in both the sp^2 positions and in the methyl groups, suggesting that the sp^3 C–H bond may be activated by coordination of the catalyst with the oxygen. This is further supported by the lack of methyl labelling in toluene as discussed above, where no such co-ordination is possible. The authors proposed a mechanism for aromatic hydrogen exchange, which involved σ-bond metathesis as the key catalytic step for the exchange process, with a strong steric effect controlling the regiospecificity of the exchange. This complex proved to be an improvement over the complex [Ru(IMes)(P-Cy_3)(η^2-H_2)$_2H_2$], which was previously reported by the same authors to have catalytic activity using perdeuterobenzene.[23] As was stated earlier, from the perspective of isotopic labelling, the use of D_2O in place of perdeuterobenzene offers a potential route to tritium labelling.

Finally the complex $TpRu(Ph_3P)_3(CH_3CN)H$ (Figure 19) has also been shown to promote modest levels of H/D exchange of simple organic solvents such as benzene, toluene, THF, 1,4-dioxane and ether with D_2O as the isotope donor.[24] Incorporation levels were generally in the 10–20% range, suggesting that further optimization of the catalyst system would be desirable before use in tritiation experiments.

The above complexes arising from research in the area of C–H activation have only demonstrated activity for the deuterium labelling of simple aromatics and aliphatics. To date there are no examples of tritium labelling by these complexes. However, those complexes employing water as the source of isotope have the potential for use as tritiation catalysts. Nevertheless the ready availability of known catalysts such as heterogenous Pt, which are highly effective for the general tritium labelling of aromatic and *N*-heteroaromatic rings, may discourage their further development.

Part II: Heterogeneous rhodium- and ruthenium-catalysed hydrogen-isotope labelling

Labelling via heterogeneous catalysis usually involves one of two approaches: 1/ general labelling mainly utilized for the preparation of highly deuterated compounds for uses such as MS internal standards and for materials science studies, and 2/ regiospecific/regioselective labelling suitable for the preparation of ^{2}H- and ^{3}H-labelled compounds for tracer studies. Although this is in some ways an artificial distinction, it is a useful way to organize the sections below.

General labelling using heterogeneous rhodium systems

Until recently most studies of general heterogeneous rhodium-catalysed isotopic exchange involved small molecule hydrocarbons.[25] These have been utilized to probe the mechanism of reduction or dehydrogenation processes taking place on the rhodium surface rather than for the purpose of isotopic labelling. In contrast, the general labelling of more complex molecules had been the province of other transition metals, mainly platinum and palladium. On occasion, though, rhodium has been utilized alone or in conjunction with other platinum group metals for high-temperature solid state isotope exchange labelling of biologicals. For more information on this widely applicable labelling technique, which can at times lead to surprisingly specific labelling outcomes, see the contribution by Nagaev, Shevchenko and Myasoedov in this Special Edition, and the references therein.

Recently, a series of studies from the Sajiki group have popularized the use of H_2/D_2O exchange systems for deuterium labelling of a wide range of organics in the presence of platinum group metals.[26] Though most of the studies have utilized a palladium or platinum catalyst, some useful methodology has also been developed for rhodium, particularly for the labelling of alkanes.[27] For this reaction, the rhodium is employed in the form of 5% rhodium on charcoal, as the presence of this lipophilic carbon support is essential for the exchange. The activating presence of hydrogen gas is also a requirement. A typical procedure is given below.

A sealed tube is charged with the substrate (0.25 mmol), 5% rhodium on charcoal (20 wt%) and D_2O (2 ml). The tube is sealed under a hydrogen atmosphere and heated at 160°C for 12–24 h.

The method has proved applicable to linear, branched and cyclic alkanes and generally results in high incorporations at all molecular sites. It is therefore a useful and general procedure. The deuterium abundances may be improved by the addition of a small quantity of cyclohexane as co-solvent. Yields are good to excellent. Typical examples of the approach are shown in Figure 20.

The authors have advanced some plausible mechanisms for the labelling based upon a key intermediate (Figure 21) reversibly formed by insertion of a H_2-Rh-D_2O complex into an alkane C–H bond. This intermediate can then undergo either (a) isotope exchange to yield the analogous rhodium deuteride followed by reductive elimination to the labelled alkane or (b) β-hydride elimination to yield the olefin, recomplexation (possibly as a rhodium π-allyl species), formation of the rhodium deuteride species and finally reductive elimination and hydrogenation to yield the deuterated hydrocarbon.

As the nature of the catalyst support is important, it is likely that the reaction occurs at the interface between the metal and the support. However, a spill-over mechanism similar to that described for high-temperature solid-phase isotope exchange elsewhere in this special issue has not been eliminated.

As might be expected, a similar labelling approach could be utilized with more functionalized compounds and this has been examined for other rhodium systems. In particular, an activated rhodium black catalyst has been prepared via sodium borodeuteride reduction of rhodium trichloride. In an early study of such hydride activated catalysts, Derdau *et al.*[28] studied the deuteration of several substrates and the results with 4-phenylbutanoic acid proved interesting. Comparison of the labelling achieved with *in-situ*-activated palladium on carbon, palladium black (from $NaBD_4$ and $PdCl_2$) and rhodium black (from $NaBD_4$ and $RhCl_3$) showed a high degree of labelling by rhodium, though the yield, at 45%, was lower than with the palladium systems.

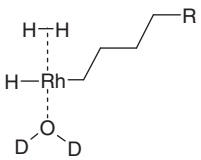


Figure 21. Proposed key intermediate in the deuterium exchange of hydrocarbons.[27]

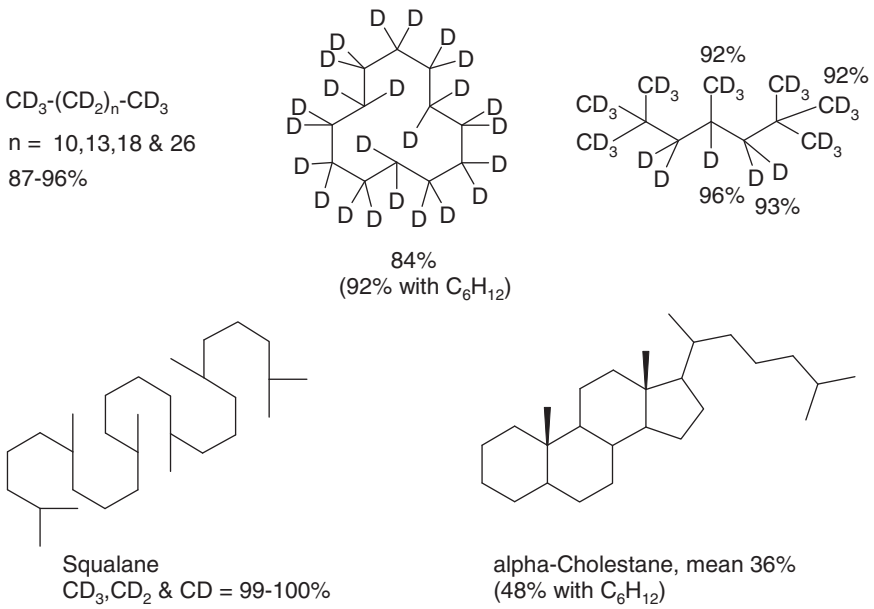


Figure 20. Labelling of various hydrocarbons by hydrogen activated rhodium on carbon and deuterium oxide.[27]

(Figure 22). Concomitant labelling at the *meta* or *para* positions was presumably absent or limited.

A more detailed study of such rhodium systems (including analogous Pt and Pd catalysts) was subsequently carried out[29] under microwave heating conditions. A range of substrate classes were examined. The results obtained with substituted anilines are tabulated below (Table 1). They show a preference for labelling *ortho* to the amino function.

Pyridines and other heterocyclics were also studied. Examples are shown in Figure 23.

Although the labelling is general, a degree of selectivity is observable, with labelling taking place preferentially at positions α to heterocyclic nitrogen or amino-substituents. A typical procedure follows.

The substrate (1 mmol) and pre-catalyst ($RhCl_3$, 10 wt%) were treated with sodium borodeuteride (99% D, 5 mol%) and deuterium oxide (99% D, 6 ml) and well stirred. When effervescence had ceased the tube was then sealed under argon and heated at 150°C for 2 h.

Yields for the procedure were generally good, but somewhat variable (30–97%).

While the methodology described in this section has proven to be very useful for the preparation of deuterated compounds, there are no reports to date of either method being adapted for tritium labelling.

Figure 22. Labelling of 4-phenylbutanoic acid by *in situ*-generated deuterium-activated rhodium black and deuterium oxide.[28]

Table 1. Labelling of substituted anilines by *in situ*-generated deuterium-activated rhodium black and deuterium oxide[29]

Substituents	% Of D *ortho* to amine	% Of D *meta* to amine
NH_2, Br	80	5
NH_2, NO_2	29	15
NH_2, OMe	82	0
NH_2, SMe	92	12
NH_2, CO_2H	89	19
NHMe, CO_2H	97	97 (Me, 4)
NMe_2, CO_2H	85	21

Regiospecific/regioselective labelling using heterogeneous rhodium

A series of very interesting studies have been carried out by Filer and co-workers using supported rhodium. This group achieved direct high specific activity labelling of the toxic glycosides, digoxin, digitoxin and ouabain using 5% rhodium on alumina in conjunction with high specific activity tritiated water at elevated temperatures for several days. The labelling was restricted to particular molecular sites (the methylene and olefinic sites on the butenolide lactone) hence its inclusion in this part of the review. The method also proved useful in obtaining labelled precursors for other biologically important compounds such as antibiotics, anti-tumour agents, antipsychotics, bile acids, etc. In addition, the same group have utilized the same catalyst with a tritium gas donor for the high specific activity labelling of some nucleic acid components, neurochemicals and toxins. For more detailed information, including structures and experimental details, see the contribution on the direct metal-catalysed tritiation of organic compounds by C N Filer in this special issue of the journal, and references therein.

The first mild, general and regiospecific ruthenium system for *N*-heteroaromatic labelling was developed[30] in 1990. The system utilized deuterium gas in perdeuteromethanol and 5% ruthenium on carbon as catalyst. Although this system utilized heterogeneous ruthenium, it will be described here since it led directly to the development of more useful rhodium systems. The ruthenium catalyst was shown to label a range of pyridines, quinolines and isoquinolines at high isotopic abundance

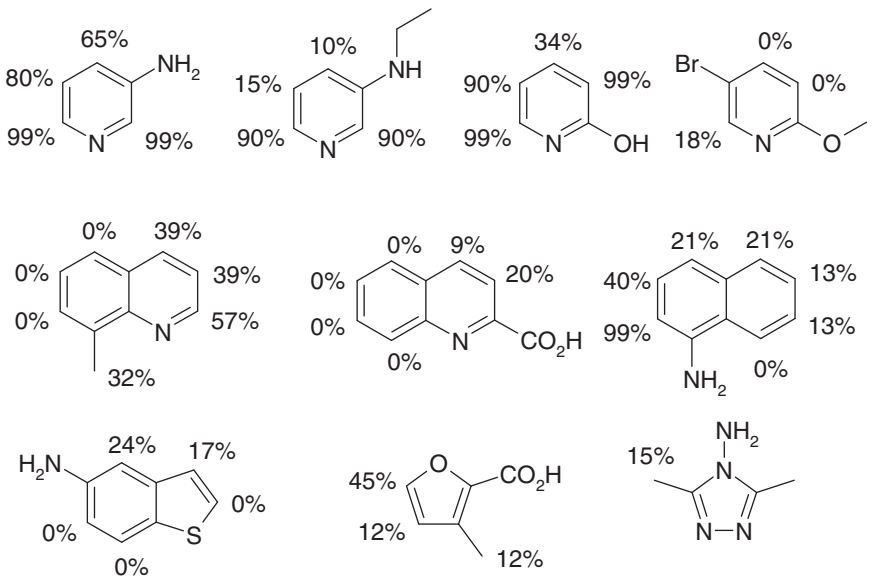


Figure 23. Labelling of various heteroaromatics by *in situ*-generated deuterium-activated rhodium black and deuterium oxide.[29]

and with good regioselectivity for the available α-positions (Figure 24).

Unfortunately subsequent studies[31] showed that much of the label originated from the perdeuteromethanol solvent. Consequently the method, while useful for deuterium labelling, had little potential for tritium. The need for 22 p.s.i. of D_2 pressure also militated against the use of tritium.

Nevertheless Lockley *et al*. was impressed by the approach and resolved to improve the procedure.[32] A range of platinum group metal catalysts were screened in parallel, utilizing deuterium gas at atmospheric pressure in a number of aprotic solvents.[32] Of these catalysts, rhodium black, ruthenium black and 5% rhodium on alumina proved many times more active than 5% Ru/C and hence showed potential for further development. As THF proved an effective and easily removable solvent, it was utilized as solvent in the subsequent screens.

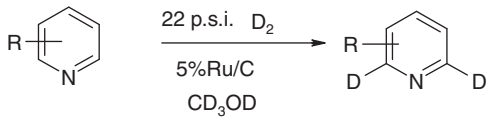


Figure 24. Labelling of pyridines by 5% ruthenium on carbon and deuterium gas in perdeuteromethanol.[30]

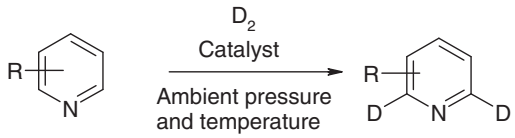


Figure 25. Labelling of pyridines and other *N*-heteroaromatics by various rhodium and ruthenium catalysts in tetrahydrofuran under mild conditions.[33]

All three catalysts proved useful for the α-labelling of *N*-heteroaromatics at ambient temperature and pressure, with rhodium black demonstrating the most general activity (Figure 25).[33]

The generality of the method was investigated using parallel chemistry studies of the labelling of a panel of *N*-heteroaromatics using the three catalysts. The panel of substrates was selected to check various aspects of the labelling process. Thus, 2-phenylpyridine was included to check for concomitant *ortho*-labelling of the phenyl group via a five-membered ring process. While 3- and 4-acetyl pyridine were included to check for concomitant labelling of the acetyl group by acid/base mechanisms in addition to potential *ortho*-labelling. 2-Bromopyridine and phthalazine were also included since these substrates had been resistant to labelling via the original 5% Ru/C system.

The results for rhodium black are shown in Figure 26.

Reactions were monitored by ^{1}H- and ^{2}H-NMR. In the reactions, the substrates (ca. 0.13 mmol) and rhodium black (Aldrich, 10 mg) in dry THF (1 ml) were stirred under D_2 gas in 10 ml capacity hydrogen tight tubes for 2 h at ambient pressure and temperature, replacing the D_2 gas twice, via evacuation and then replenishment, during the course of the exchange. (a) Indicates some concomitant decomposition or reduction under the reaction conditions.

As seen in Figure 26, the labelling procedure is general and regiospecific. In only one case (2-phenylpyridine) was any

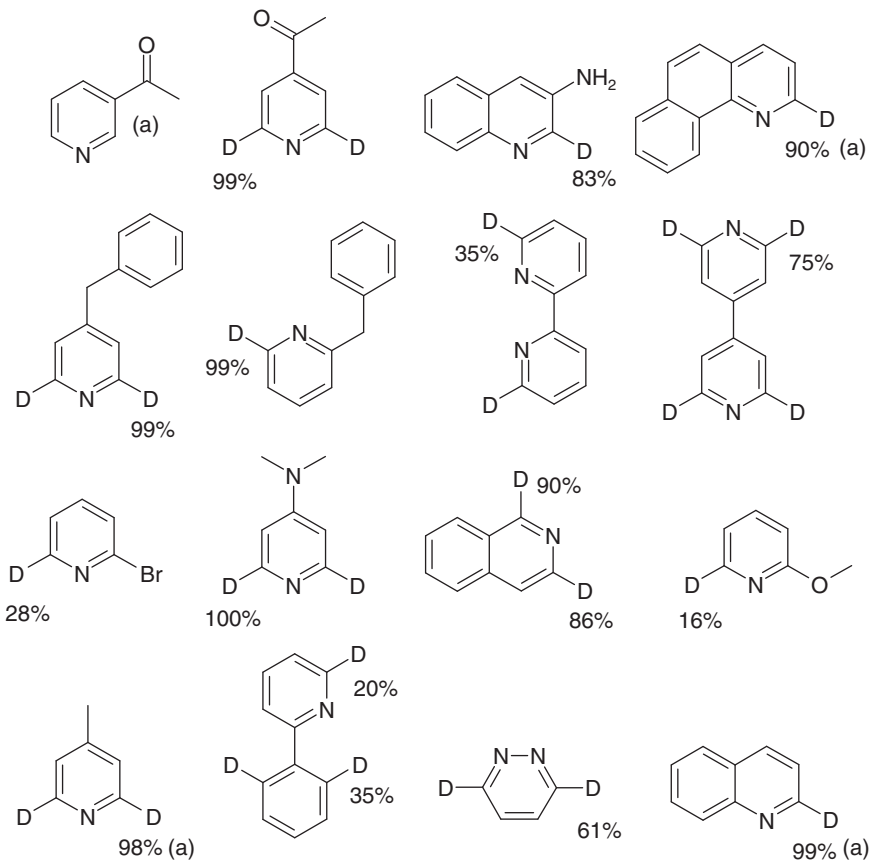


Figure 26. Labelling of pyridines and other *N*-heteroaromatics by rhodium black and deuterium gas in tetrahydrofuran under mild conditions.[33].

labelling at sites other than α to nitrogen seen, suggesting that under the correct circumstances labelling via a five-membered cyclometallated intermediate can occur. However, since several other substrates in Figure 26 could also have labelled via a five-membered cyclometallation process but showed no such labelling, it is possible that 2-phenylpyridine provides the exception rather than the rule.

The regiospecificity of the process was demonstrated in most cases by both ^{1}H and ^{2}H-NMR. In one case ^{3}H-NMR was utilized. [2,6,2′,6′-$^{2}H_4$,2,6,2′,6′-^{3}H]4,4′-bipyridyl was prepared by exchange over rhodium black with tritiated deuterium gas, prepared by acidification of a solution of tritiated sodium borohydride and sodium borodeuteride in deuterium oxide with [*O*-^{2}H]acetic acid. The labelled compound and the various isotopic NMRs are shown in Figure 27.

Similar results were obtained with the other two catalysts. These proved somewhat less active than rhodium black but in some cases this provided an advantage, thus 3-acetylpyridine, which decomposed using the rhodium black catalyst, was labelled at 99% efficiency in high yield by 5% rhodium on carbon.

Overall, a wide range of nitrogen heteroaromatics can now be labelled with deuterium (and presumably tritium) at room temperature and pressure by isotopic exchange with deuterium gas in THF in the presence of these catalysts. The labelling is rapid, isotope efficient and applicable to both electron-rich and electron-poor substrates. In a few cases, a degree of reduction accompanies the exchange and in these cases selection of the most appropriate of the new catalysts is indicated.

A typical labelling procedure is given below.

4,4′-Bipyridyl (22 mg, 0.141 mmol) and rhodium black (10 mg, 0.097 mmol) in dry THF (1.0 ml) were stirred under deuterium gas (99 atom%, 0.4 mmol) at RT and atmospheric pressure, replacing the deuterium gas after each hour to ensure displacement of the equilibrium towards complete labelling. Filtration and washing of the catalyst with a small quantity of THF followed by evaporation of the solvent gave the labelled bipyridyl (22 mg, 100% crude, pure by TLC, m.p. 108– 110°C). Crystallisation of the crude material from dichloromethane/hexane gave [2,6,2′,6′-$^{2}H_4$]4,4′-bipyridyl, 15 mg, 67%, 97.5 atom% ^{2}H). *In a parallel experiment with no change of deuterium gas the ^{2}H atom% abundance of the product was 56% (73% of theoretical) after 2 h.*

More recently, in an attempt to label the compound shown in Figure 28 at both sites a and b, Schou utilized a mixture of rhodium black (to label site a) and Crabtree's catalyst (to label site b).[34]

Instead the mixed catalysts labelled only site a, but with substantially increased incorporation, (93%D) compared with rhodium black alone (16%D). The catalytic system comprising a mixture of rhodium black and Crabtree's catalyst was subsequently investigated using a panel of 15 substrates, mainly pyridines, and was shown to lead to significant improvements in deuterium incorporation in seven cases and to either no effect or a somewhat deleterious effect in eight cases. In two cases, 2-isopropylpyridine and 4-amino-pyrimidine-5-carboxylic acid, the new system proved very effective when labelling by rhodium black alone had failed.

The reason for the improved efficiency of the new system is not clear. Investigations of the effect of various additives on the

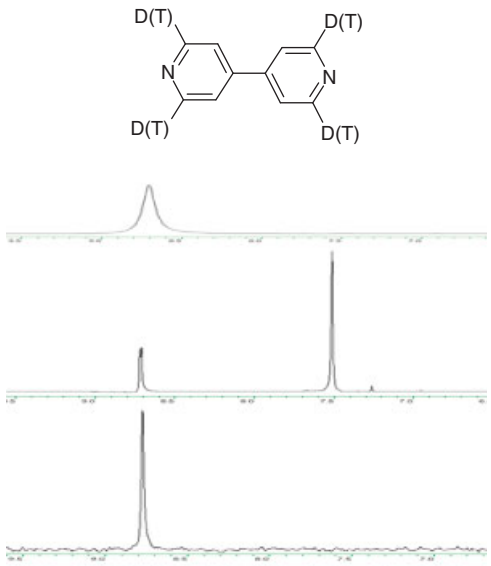


Figure 27. 4,4′-Bipyridyl labelled via rhodium black catalysis. Top NMR: ^{2}H-NMR in $CHCl_3$ of exchange product with D_2 gas, middle and bottom NMRs: ^{1}H- and ^{3}H-NMR in $CDCl_3$ of the crude exchange product with DT gas.[33]

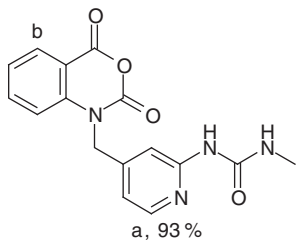


Figure 28. Labelling of a pharmaceutical agent by rhodium black and deuterium gas in combination with Crabtree's catalyst.[34]

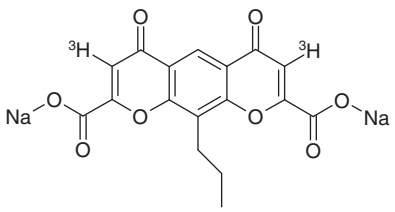


Figure 30. Tritium labelling of probicromil sodium using tritiated water at 90% abundance and 5% ruthenium on carbon catalyst.[41]

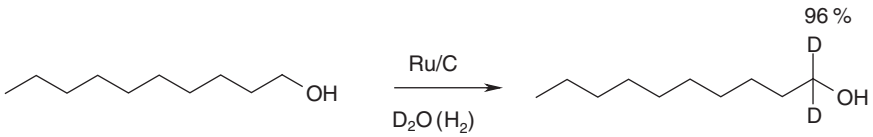


Figure 29. α-Labelling of *n*-decanol using ruthenium on carbon via an oxido-reductive process.[38]

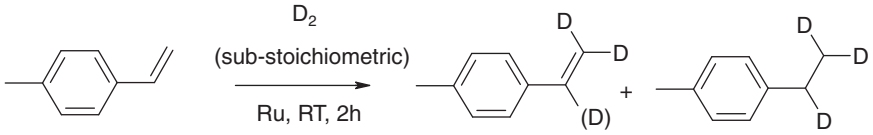


Figure 31. Exchange labelling of 4-methylstyrene using a deficiency of deuterium gas.

rhodium black labelling system were not definitive. While addition of pyridine or tricyclohexylphosphine (two of the ligands in Crabtree's catalyst) to rhodium black gave improved incorporation into the substrate, neither gave the degree of improvement seen with the Crabtree catalyst. Other investigations in the same paper showed that the reaction was heterogeneous and that the provenance of the rhodium black was important: items from Aldrich, Alfa Aesar and ABCR were active, while items from Acros and Fluka were not. X-ray powder diffraction studies were carried out and those samples possessing the lowest observed crystallinity (i.e. amorphous or highly microcrystalline) had the highest activity. Whether this is an effect of the inevitably higher surface area or of increased surface dislocations could not be determined by the technique. The observation is consistent with the finding that supported dispersed rhodium is also active in such pyridine labelling.[32,35]

General labelling via heterogeneous ruthenium systems

With the exception of the work with pyridines referred to in the previous section,[30] much less labelling work has been carried out with heterogeneous ruthenium than with rhodium. As with rhodium most isotopic exchange studies have utilized small molecule hydrocarbons to probe the mechanism of reduction or dehydrogenation processes taking place on the ruthenium surface rather than as a method for isotopic labelling.[36]

Regiospecific/regioselective labelling using heterogeneous ruthenium systems

Early studies by the Garnett group had determined that ruthenium black generated *in situ* by hydride reduction of the trichloride led to selective α-deuteration of pyridine.[37] However with the exception of the pyridines mentioned previously[30] few other regiospecific applications have been published, until recently.

As illustrated in the homogeneous catalysis section of this paper, the propensity of homogeneous ruthenium catalysts to support oxido-reductive reactions has been extensively exploited for labelling with both deuterium and tritium. Heterogeneous ruthenium shares this ability, as shown by the α-deuterium labelling of *n*-decanol at 96% abundance over 5% ruthenium on carbon[38] by reaction with the hydrogen-activated catalyst and deuterium oxide at 80°C for 24 h (Figure 29).

The Sajiki group has extended this regiospecific reaction to the α-labelling of a range of other primary and secondary alcohols.[39]The reaction is clearly proceeding via an oxido-reductive mechanism, as suggested by the utilization of the same catalyst for the oxidation of primary and secondary alcohols under an oxygen atmosphere.[40]

5% Ruthenium on carbon has also been utilized for high specific activity labelling of [^{3}H]probicromil sodium as shown below. The tritiated compound was obtained by heating the unlabelled compound with the catalyst and tritium oxide at >90% ^{3}H-abundance in DMF for 18 h, followed by HPLC purification (Figure 30).[41]

Ruthenium black has also been utilized for the regioselective labelling of styrenes at the terminal alkene positions by employing a deficiency of deuterium gas (Figure 31).

When 0.4 mol catalyst/mol of deuterium was utilized, 40% of the isotope was present in the olefin and 60% in the alkane. Both the *cis* and *trans* terminal positions of the styrene were labelled with equal efficiency.[42] Such olefin labelling by employment of traditional hydrogenation catalysts and a limited amount of isotopic hydrogen has been utilized for the tritiation of dehydroleucine,[43] cyclosporin[44] FK506,[45] and FK506 analogues.[41] Although hitherto, supported palladium rather than ruthenium had been utilized for this reaction, ruthenium black was found to be preferable to a wide range of supported and unsupported palladium catalysts when screened in the reaction above (Figure 31).

Acknowledgement

The authors thank Dr C. F. Lavey for proof reading this manuscript.

References

[1] a) J. L. Garnett, R. J. Hodges, *J. Am. Chem. Soc.* **1967**, *89*, 4546; b) M. R. Blake, J. L. Garnett, I. K. Gregor, W. Hannan, K. Hoa, M. A. Long, *J. Chem. Soc. Chem. Commun.* **1975**, 930.
[2] J. A. Al-Rawi, J. A. Elvidge, J. R. Jones, R. B. Mane, M. Saieed, *J. Chem. Res.* (*S*) **1980**, 298–299.
[3] a) W. J. S. Lockley, *Tetrahedron Lett.* **1982**, *23*, 3819–3822; b) W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1984**, *21*, 45–57; c) W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1985**, *22*, 623–630; d) D. Hesk, J. R. Jones, W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1990**, *28*, 1427–1436; e) Brief accounts of this technique and others described in this paper are given in R. Voges, J. R. Heys, T. Moenius, *Preparation of Compounds Labeled with Tritium and Carbon-14*, Wiley, Chichester, **2009**, Ch. 3, pp. 47–107. [ISBN- 978-0-470-51607-2].
[4] a) D. J. Wilkinson, W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1985**, *22*, 883–892; b) W. J. S. Lockley, D. J. Wilkinson, *J. Label. Compd. Radiopharm.* **1984**, *21*, 363–373; c) W. J. S. Lockley, D. Hesk, J. R. Jones, *J. Pharm. Sci.*, **1991**, *80*, 887–890; d) D. Hesk, J. R. Jones, W. J. S. Lockley, D. J. Wilkinson, *J. Label. Compd. Radiopharm.* **1990**, *28*, 1309–1320.
[5] A. Nakagawa, H. Hasegawa, H. Seki, K. Oohashi, *Radioisotopes* **1997**, *46*, 513–519.
[6] D. Hesk, J. R. Jones, K. B. Nolan, W. J. S. Lockley, in *Synth. Appl. Isotop. Label Compd, Proceedings of the 4th International Symposium, Toronto 1991* (Eds.: E. Buncel, G. W. Kabalka), Elsevier, Amsterdam, London, New York, Tokyo, **1992**, pp. 600–603. [ISBN-0-444-89280-X].
[7] S. Chen, G. Song, X. Li, *Tetrahedron Lett.*, **2008**, *49*, 6929–6932.
[8] T. Yoshida, T. Okano, K. Saito, S. Otsuka, *Inorganica Chimica Acta* **1980**, *44*, L135–L136.
[9] G. Kohl, R. Rudolph, H. Pritzkow, M. Enders, *Organometallics* **2005**, *24*, 4474–4781.

[10] S. M. Kloek, D. M. Heinekey, K. I. Goldberg, *Angew. Chem. Int. Ed.* **2007**, *46*, 4736–4738.
[11] S. L. Regan, *J. Org. Chem.* **1974**, *39*, 260–261.
[12] L. Lešetický, K. Sedlák, B. Fišer, *Radioisotopy* **1990**, *31*, 163–169.
[13] J. A. Al-Rawi, J. A. Elvidge, J. R. Jones, R. B. Mane, M. Saieed, *J. Chem. Res. (S)* **1980**, 298–299.
[14] J. M. Al-Rawi, N. A. Azzawi, M. S. Saieed, *J. Iraqi Chem. Soc.* **1987**, *12*, 249–259.
[15] M. Saljouhian, *J. Label. Compd. Radiopharm.* **1984**, *21*, 493–496.
[16] A. F. McKay, *J. Am. Chem. Soc.* **1949**, *71*, 1968–1970.
[17] D. Hesk, J. R. Jones, unpublished results.
[18] a) Y. Wan, J. Jacway, H. Qiu, H. Shah, C. Garlisi, F. Tian, P. Ting, D. Hesk, R. Egan, M. Billah, S. Umland, *Eur. J. Pharmacol.* **2002**, *456*, 1–10l; b) D. Hesk, D. Koharski, S. Saluja, P. McNamara, C. Magatti, D. Cesarz, S. Hendershot, J. R. Jones, in *Synth. Appl. Isotop. Label. Compd, Proceedings of the 6th International Symposium, Philadelphia 1997* (Eds.: J. R. Heys, D. G. Melillo), Wiley, Chichester, **1997**, pp. 439–443. ISBN-0471-97863-9; c) D. Hesk, D. Cesarz, C. Magatti, K. Voronin, C. Lavey, P. McNamara, D. Koharski, S. Saluja, S. Hendershot, H. Pham, V. Truong, *J. Label. Compd. Radiopharm.* **2005**, *48*, 11–23; d) D. Hesk, K. Voronin, P. McNamara, P. Royster, D. Koharski, S. Hendershot, S. Saluja, V. Truong, T. M. Chan, *J. Label. Compd. Radiopharm.* **2007**, *50*, 131–137.
[19] E. Alexakis, M. J. Hickey, J. R. Jones, L. P. Kingston, W. J. S. Lockley, *Tetrahedron Lett.* **2005**, *46*, 4291–4293.
[20] K. Ishibashi, S. Matsubara, *Chem. Lett.* **2007**, *36*, 724–725.
[21] M. Hirano, Y. Sakaguchi, T. Yajimia, N. Kurata, N. Kiomine, S. Komiya, *Organometallics* **2005**, *24*, 4799–4809.
[22] M. Prechtl, N. Hölscher, Y. Ben-David, N. Theyssen, R. Loschen, D. Milstein, W. Leitner, *Angew. Chem. Int. Ed.* **2007**, *46*, 2269–2272.
[23] D. Giunta, M. Hölscher, C. W. Lehmann, R. Mynott, C. Wirtz, W. Leitner, *Adv. Synth. Catal.* **2003**, 345, 1139–1145.
[24] C. W. Leung, W. Zheng, D. Wang, S. M. Ng, C. H. Yeung, Z. Zhou, Z. Lin, C. P. Lau, *Organometallics* **2007**, *26*, 1924–1933.
[25] a) J. M. Forrest, R. L. Burwell, B. K. C. Shim, *J. Phys. Chem.* **1959**, *63*, 1017–1021; b) R. L. Burwell, *Langmuir* **1986**, *2*, 2–11; c) J. A. Roth, B. Geller, R. L. Burwell, *J. Res. Inst. Catal. Hokkaido Univ.* **1968**, *16*, 221–243; d) D. K. Takehara, J. B. Butt, R. L. Burwell, *J. Catal.* **1992**, *133*, 294–308; e) D. K. Takehara, J. B. Butt, R. L. Burwell, *J. Catal.* **1992**, *133*, 219; f) Z. Karpinski, T. K. Chuang, H. Katsuzawa, J. B. Butt, R. L. Burwell, J. B. Cohen, *J. Catal.* **1986**, *99*, 184–197; g) A. da Costa Faro, C. Kemball, *J. Chem. Soc. Faraday Trans.* **1995**, *91*, 741–748; h) R. Brown, C. Kemball, *J. Chem. Soc. Faraday Trans.* **1996**, *92*, 281–288; i) H. Sakagami, S. Ogata, N. Takahashi, T. Matsuda, *Phys. Chem. Chem. Phys.* **2001**, *3*, 1930–1934; j) J. M. Gatica, P. Fornasiero, J. Kaspar, T. Lesage, S. Aiello, M. Daturi, *Phys. Chem. Chem. Phys.* **2002**, *4*, 381–388.
[26] a) H. Sajiki, K. Hattori, F. Aoki, K. Yasunaga, K. Hirota, *Synlett.* **2002**, 1149–1151; b) H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, K. Hirota, *Org. Lett.* **2004**, *6*, 1485–1487; c) H. Esaki, N. Ito, S. Sakai, T. Maegawa, Y. Monguchi, H. Sajiki, *Tetrahedron* **2006**, *62*, 10954–10961.
[27] T. Maegawa, Y. Fujiwara, Y. Inagaki, H. Esaki, Y. Monguchi, H. Sajiki, *Angew. Chem. Int. Ed.* **2008**, *47*, 5394–5397.
[28] V. Derdau, J. Atzrodt, W. Holla, *J. Label. Compd. Radiopharm.* **2007**, *50*, 295–299.
[29] V. Derdau, J. Atzrodt, J. Zimmermann, C. Kroll, F. Bruckner, *Chem. Eur. J.* **2009**, *15*, 10397–10404.
[30] G. M. Rubottom, E. J. Evain, *Tetrahedron* **1990**, *46*, 5055–5064.
[31] E. Alexakis, PhD thesis, University of Surrey, **2005**.
[32] E. Alexakis, J. R. Jones, W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **2005**, *48*, 534–535.
[33] E. Alexakis, J. R. Jones, W. J. S. Lockley, *Tetrahedron Lett.* **2006**, *47*, 5025–5028.
[34] S. C. Schou, *J. Label. Compd. Radiopharm.* **2009**, *52*, 376–382.
[35] a) S. C. Schou in *Synth. App. Isotop. Label. Compd., Proceedings of the 10*th *International Symposium, Chicago, 2009, J. Label Compd. Radiopharm.* **2010**, *53*, 375–380. (b) S. C. Schou, Ph.D. thesis, Faculty of Pharmaceutical Sciences, University of Copenhagen, **2010**.
[36] L. Guczi, K. V. Sarma, L. Borko, *React. Kinet. Catal. Lett.* **1999**, *68*, 95–104; (b) T. Pery, K. Pelzer, G. Buntkowsky, K. Philippot, H. H. Limbach, B. Chaudret, *Chem. Phys. Phys. Chem.* **2005**, *6*, 605–607.
[37] G. E. Calf, J. L. Garnett, *J. Chem. Soc. Chem. Commun.* **1967**, 306–307.
[38] H. Sajiki, T. Maegawa, Y. Monguchi, Y. Fujiwara, Y. Inagaki, WO 2009005069 8 Jan **2009**.
[39] T. Maegawa, Y. Fujiwara, Y. Inagaki, Y. Monguchi, H. Sajiki, *Advan. Synth. Catal.,* **2008**, *350*, 2215–2218.
[40] S. Mori, M. Takubo, K. Makida, T. Yanase, S. Aoyagi, T. Maegawa, Y. Monguchi, H. Sajiki, *Chem. Commun.* **2009**, *34*, 5159–5161.
[41] W. J. S. Lockley, unpublished results.
[42] E. Alexakis, W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **2008**, *51*, 259.
[43] G. L. Guildford, E. A. Evans, D. C. Warrell, J. R. Jones, J. A. Elvidge, R. M. Lenk, Y. S. Tang, in *Synth. Appl. Isotop. Label. Compd., Proceedings of the 1st International Symposium, Kansas City, 1982* (Eds.: W. P. Duncan, A. B. Susan), Elsevier, Amsterdam, Oxford, New York, **1983**, pp. 327–330. ISBN 0-444-42152-1.
[44] a) R. Voges, B. R. Wartburg, H. R. Loosli, in *Synth. Appl. Isotop. Label. Compd., Proceedings of the 2nd International Symposium, Kansas City, 1985* (Ed.: R. R. Muccino), Elsevier, Amsterdam, Oxford, New York, Tokyo, **1986**, pp. 371–376. ISBN-444-42612-4. b) T. Moenius, R. Voges, A. Susan, L. Jones, R. Tarapata, M. Shapiro, M. A. C. Jarema, in *Synth. Appl. Isotop. Label. Compd., Proceedings of the 4th International Symposium, Toronto, 1991* (Eds.: E. Buncell, G. W. Kabalka), Elsevier, Amsterdam, London, New York, Tokyo, **1992**, pp. 149–154. [ISBN-0-444-89280-X].
[45] H. Andres, *Tritide reagents for the synthesis of natural products*, Presentation at the R.C. Tritech Workshop, Teufen, Switzerland, June **2005**.

