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Review Article

Organoiridium complexes for hydrogen isotope exchange labeling†

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Abstract: An account of the development of organoiridium-catalyzed hydrogen isotope exchange methods is given for the regioselective labeling of compounds from isotopic hydrogen gas, and their current status. The concept arose out of organometallic chemistry studies of C–H bond activation that revealed the ability of certain metal centers to interact with specific C–H bonds of molecules adjacent to coordinating heteroatoms. Initial success in labeling of model compounds with $[Ir(H)_2(acetone)_2(PPh_3)_2]BF_4$ and deuterium gas provided the stimulus for further investigations into modified catalysts, their use with tritium, and applications to the labeling of a wide variety of more complex compounds. Over time, development of mechanistic models and accumulation of empirical data have grown sufficient to permit the prediction of applicability and regioselectivity based on compound structure. Continuing development of new organoiridium catalysts is broadening the range of compound types that can be labeled. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: isotope exchange; catalytic exchange; iridium complexes; tritium exchange; deuterium exchange; regioselectivity; exchange labeling

By the mid-1980s, high specific activity tritiated compounds had become standard tools in biological, pharmaceutical and agrochemical research for investigating the interactions of small molecules with biological molecules, such as receptors and enzymes, and with more complex biological systems of many kinds. The Radiochemistry Group at Smith Kline & French Laboratories in Philadelphia had been preparing tritium-labeled pharmaceutical candidates and research tool compounds in increasing numbers as the drug research teams we supported became ever more adept at their exploitation and responded to pressures for increased research throughput. Typically, these compounds were needed at high specific activity and rapidly, in response to the fast pace of decision making in early pharmaceutical research. The compounds required in tritiated form were often one or more of a large set that medicinal chemists had prepared for early screening and biological experiments and therefore only small quantities could be made available to Radiochemistry. Moreover, synthetic intermediates were often needed in Medicinal Chemistry to prepare further analogs. All this meant that the meager chemical resources available to Radiochemistry worked against our goal for rapid preparation of labeled compounds.

We could usually depend on obtaining a few milligrams of the unlabeled target compound, but if this did not suffice, we had to resort to synthetic work. Some target compounds were amenable to aromatic halogenation, and these derivatives could be subjected to catalytic tritium–halogen replacement using tritium gas. Occasionally, an *N*- or *O*-desmethyl or unsaturated analog was available or could be readily prepared and used as a substrate for [^{3}H]methylation or catalytic [^{3}H]hydrogenation. In a few cases, we had managed to label compounds by known catalytic exchange methods, such as palladium-catalyzed benzylic hydrogen isotope exchange with tritium gas.[1] But usually such methods required a number of trials to develop workable reaction conditions, using up time and precious compound.

I imagined having a 'magic catalyst', or a suite of catalysts to choose from, that could be used with tritium gas (cheap, carrier-free and easy to handle) to predictably (based on the chemical structure of the labeling substrate) exchange-label target compounds (without substrate-specific optimization) to

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high specific activity (sufficient for receptor studies) in chemically stable sites (no loss of label under conditions of use) and be easily purifiable, so that the entire process from the identification of a need by the biologists to our delivery of a tritium-labeled investigational tool could be carried out rapidly. Some fantasy!

Of course many hydrogen isotope exchange methods were already known – exposure to various kinds of activated tritium species with or without catalysts, acid- or base- or homogeneous metal-catalyzed exchange with tritiated water, and heterogeneous metal-catalyzed exchange with tritium gas (like the benzylic labeling above). However, all these methods had serious shortcomings, such as the need for multiple trials for each compound, or difficulty achieving adequate specific activity, or the risk that the label would back-exchange during use.

The replacement of H by D or T on an sp^3 or sp^2 carbon fundamentally requires breaking and making C–H/D/T bonds, and when the carbon site is unactivated (so that the incorporated tritium would be chemically stable) such bond breaking was not easy owing to the strength of the C–H bond (ca. 95–110 kcal/mol) compared with C–H bonds of carbons activated by carbanion- or carbenium ion-stabilizing functions. In the mid-1980s I was only vaguely aware of the then-burgeoning research in the organometallic chemistry field into soluble complexes which could react with hydrocarbons to form alkyl- or aryl-metal complexes. I was intrigued about how mild the reaction conditions often were compared with the high temperatures or radical-producing photochemical conditions classically required for breaking unactivated C–H bonds. One of the stimuli for those investigations was the prospect of catalytic methods for more efficient industrial conversion of cheap hydrocarbon feedstocks into higher-value commodity chemicals. Further developed in the ensuing two decades and embraced by the synthetic organic chemistry community this chemistry has become the foundation for a variety of new synthetic transformations based on catalytic functionalization of unactivated C–H bonds.[2] But at that time the research had not extended much beyond the organometallic chemistry community, who were focusing on the properties and conditions required for what was called 'C–H bond activation'. Integral to this research were studies of the chemistry of organometal hydrides; Kubas *et al.*[3] had recently confirmed the existence of complexes containing molecular hydrogen as a ligand; and the phenomenon of fluxionality, or the rapid exchange between ligated H and H_2, in complexes containing both hydride and dihydrogen ligands, was recognized.[4] Metal centers possessing these characteristics were good candidates for exchanging atmospheric isotopic hydrogen with other molecules.

Some investigators were using deuterium as a tracer to help them gain mechanistic inferences in cases where discrete intermediates were not observable. The classic criterion for the occurrence of C–H activation (besides actual isolation of an aryl or alkyl metal hydride complex) was the observation of metal complex-mediated exchange between benzene-d_6 solvent and other hydrogens in the system. Deuteration of a complex's ancillary ligands from solvent or atmospheric deuterium was commonly observed. This type of labeling was usually regiospecific, implying cyclometalation via the insertion of the metal into a ligand C–H bond while the ligand remained attached to the metal; being intramolecular, it is favored entropically. If a complex had the capability of coordinating a donor atom in a substrate, thereby making the substrate a temporary ligand, the same regioselective labeling of the substrate might be possible (intermolecular becomes intramolecular). But the metal's coordination number must also be sufficient to simultaneously accommodate hydride and/or dihydrogen ligands, in order to mediate the required atom transfers. Some metals in the early and late transition series had these properties. The former usually had strong M–H bonds; some of the latter tended to have M–H and M–C bond strengths in better balance for the reversible transformations required.

Unfortunately, catalysts with any alacrity for exchanging tritium gas with the C–H bonds of their solvents and their own ligands would dissipate tritium profligately, even if they did exchange-label a target compound dissolved in the solution. Thus, more conditions had to be satisfied. The available literature suggested that iridium had less of a tendency to exchange hydrogens of its own ligands. But the solvent-labeling problem seemed to be a real showstopper.

At about this stage I came across one of Robert Crabtree's papers[5] which reported that $[Ir(acetone)_2(H)_2(PPh_3)_2]BF_4$ rapidly catalyzed the exchange of specific C–H bonds of 8-methylquinoline and caffeine in CH_2Cl_2 solution under deuterium gas at room temperature. Moreover, the report claimed that deuterium did not get incorporated into the solvent. Wow.

In 1989, I wrote and submitted an internal proposal to my management in SK&F Chemical Development, seeking resources to conduct an investigation into the applicability of organoiridium complexes of this type (and another organometallic system I thought had possibilities) to the catalytic exchange labeling of compounds from isotopic hydrogen gas. Resources were not forthcoming, but my supervisor Conrad

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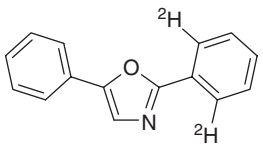
Kowalski, whom I greatly respected as a boss, scientist and friend, and who sadly died of cancer at the age of 57 in 2004, told me he would not mind if I worked on it as a back-burner effort. Over the following years I am sure I spent far more time on the project than he anticipated.

The initial 1990–91 investigations simply involved testing catalytic amounts (ca. 2 mol%) of $[Ir(acetone)_2(H)_2(PPh_3)_2]BF_4$ (a stable, sugar-like crystalline solid easily prepared in two steps from commercially available $[(cod)IrCl]_2$) on a range of model compounds having a heteroatom function with nearby aryl C–H bonds. The experiments were immediately successful[6] and showed deuterium labeling of benzoate esters, alkylphenones, benzamides, nitrobenzene and several types of heterocyclic compounds, all selectively in positions ortho to heteroatom functions. This regioselectivity suggested an intramolecular process consistent with the hypothesized intermediacy of 5-membered metallacycles, the activating heteroatom and the labeled carbon simultaneously ligated to the metal. Close substrate analogs (such as phenylacetate esters) were not labeled under these conditions, and the compound **1** was labeled only in the indicated ring, suggesting that *N*-coordination is better than *O*-coordination.



Other findings described in this paper include:

- Exchange can occur at sp^3 carbons of methyl groups of *N*-methylbenzamides.
- Noncoordinating meta-substituents (e.g. methyl) sterically inhibit C2 labeling, but coordinating meta-substituents (e.g. halogen, methoxy, nitro) can exert positive neighboring group effects on labeling at C2.
- Labeling adjacent to a directing functional group is retarded (or not) by the ancillary functional groups (intra- or intermolecularly) according to their relative coordinating ability.
- Functional groups such as nitro, halo and nitrile are not reduced.
- Catalyst activity is retained in acetone and THF solvents when the substrate coordinating function is a strong one.
- There is an indication of β-exchange labeling of α, β-unsaturated functions prior to reduction of the double bond.

These early findings, along with mechanistic hypotheses already laid out by other investigators, supported the idea that with this catalytic method it might be possible to predict with some reliability the ability to label a compound, and the position of the label so introduced, based solely on the knowledge of the compound's structure. This was a major advancement over previously developed isotope exchange methods using isotopic hydrogen gas (Lockley and Jones's $RhCl_3$-based method[7] was reliably predictable for aqueous isotope sources). An additional advantage was that, in being compatible with the presence of various reducible functionalities, the method would be complementary to catalytic dehalogenation with tritium gas, arguably the most frequently used procedure at the time for high specific activity labeling.

We appreciated the vast potential before us: The literature was rapidly expanding with the information about the influence of organometallic structure on reactivity. The efficiency or selectivity of $[Ir(acetone)_2(H)_2(PPh_3)_2]BF_4$ might be modified by changing the electronic and steric properties of the phosphine ligands and the isomerism around the metal center, substitution of P ligands by other ligands, enforcing changes in bite angles, etc., not to mention changes in solvents and other experimental conditions.

Our approach from this point was two-pronged: On the one hand, we wanted to extend the method by conducting as many experiments as possible to build up a body of empirical data – for example, by trying out a wide variety of substrates and testing the effects of modifying the catalysts and the reaction conditions. On the other hand, we wanted to develop some mechanistic understanding that would enable informed guesses as to what would be the effects of specific modifications of a catalyst on its properties; i.e. to develop the ability to *rationally design* new catalysts for labeling particular compounds or classes of interest or for exerting desired regio- or chemo-selectivities. The first was practical and easy to do; the second was mechanistic and very ambitious, as we learned. But they were not entirely separate.

On the practical front we found that a variety of other, more complex substrates could be labeled using $[Ir(acetone)_2(H)_2(PPh_3)_2]BF_4$ with deuterium gas[8] and with tritium gas.[9] We found that the intermediate in the preparation of $[Ir(acetone)_2(H)_2(PPh_3)_2]BF_4$, $[(cod)Ir(PPh_3)_2]BF_4$ (which is indefinitely stable and only one simple step away from commercially available starting material) was just as effective a catalyst. This made the comparative investigation of catalysts with different phosphine ligands (including the bidentate phosphine 1,2-*bis*(diphenylphosphinyl)ethane, or 'dppe'), as well as the commercially available $[(cod)Ir(PMePh_2)_2]BF_4$ and $[(cod)Ir(PCy_3)(py)]PF_6$ ('Crabtree's catalyst') more convenient. Our interest was to compare

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the activity and regioselectivity of complexes which differed in electronic richness and steric demand and, in the case of dppe, the enforced cis-attachment of the two phosphorus ligands to iridium (vs the trans-relationship of the monodentate bisphosphines) in the hexacoordinate octagonal structure of the putative Ir(III) active catalytic species.

During this phase of our work, a report was published[10] on the results of deuterium labeling studies using Crabtree's catalyst, led by Dave Hesk at Schering-Plough. This report showed that in addition to being active on acetophenones and benzophenones, similar to our findings with $[Ir(acetone)_2(H)_2(PPh_3)_2]BF_4$, Crabtree's catalyst was active in labeling a large series of ring-substituted acetanilides. With the presumptive coordinating heteroatom (carbonyl O) an additional bond away from the ortho C–H bond exchanged, these results implied the ability of Crabtree's to form 6-membered metallacyclic intermediates, a distinct difference in reactivity from catalytic levels of $[Ir(acetone)_2(H)_2(PPh_3)_2]BF_4$.

Our findings[11] with Crabtree's catalyst on acetanilide analogs *N*-phenyl phenylacetamide and indomethacin were consistent with Hesk's report, but we had found that Crabtree's did not label C8 of one of our test substrates, ethyl 1-naphthoate. Our cis-catalyst $[(cod)Ir(dppe)]BF_4$ did, and it was a more active (although not very stable) catalyst for labeling acetanilides and other compounds at C–H sites requiring 6-membered metallacyclic intermediates, and it was active at 5-ring sites like the monodentate bisphosphine catalysts. Generally, although, there was not a large difference in reactivity among these catalysts on labeling benzamides and related benzoyl moieties, except that the tendency of monodentate bisphosphine catalysts to also label the methyl groups of *N*-methylbenzamides was not apparent with $[(cod)Ir(dppe)]BF_4$.

In our mechanistic studies, early experiments suggested that, in the case of substituted benzoates, benzamides and benzophenones, the coordination of iridium to substrates directing heteroatom was probably not the rate-determining step in the labeling process,[8] and that the catalyst remained fully active after four days in a reaction mixture. Rate-of-deuteration studies[12] on monosubstituted benzophenones showed that para-substituents enhanced the rate of ortho-deuteration in rough proportion to their electron-donating power, and that the rate of deuteration was also in direct relation to the electron-donating ability of substituents on the phosphine ligands. Thus, proper selection of catalyst and substrate allowed some control of the ratio of labeling in different positions of these substrates. Similar catalyst–substrate selection in mono–meta-substituted benzophenones was even more powerful, giving labeling distributions ranging from equally at all four ortho positions to almost exclusively at C2 when the C3 substituent (OMe or Cl) was capable of exerting a positive neighboring effect. Observations of the metal hydride region in low-temperature ^1H NMR studies[13] of solutions of benzophenone and catalysts varying in phosphine aryl substitution (such as Figure 1) illustrated the effect of increased or decreased electron richness at the iridium center on the equilibrium between ortho-C–H intact forms and C–H cleaved (metallacyclic) forms, and this provided an explanation for the observed increase in the activity of catalysts having more electron-rich metal centers, and vice versa. We found that this equilibrium could be shifted toward the ring-opened dihydride form by the addition of more hydrogen, and completely to the metallacyclic form by the removal of hydrogen, a process that could be repeated indefinitely.

Together these kinetic and thermodynamic data led us to conclude that the C–H bond breaking by iridium is probably the rate-determining step in the catalytic cycle. We succeeded in isolating and crystallizing a stabilized version of the benzophenone complex (Ar = Ph) for X-ray crystallography (Figure 2), and it confirmed the structure of the metallacyclic species postulated to be the key intermediate in the catalytic cycle.

Labeling studies with 2-phenylpyridine had shown it to be rapidly labeled at C2′ and C6′ by several different monodentate diphosphine complexes. However, the bidentate complex $[(cod)Ir(dppe)]BF_4$ was inactive with this substrate. Low-temperature NMR studies of a solution of the dppe complex and 2-phenylpyridine under hydrogen showed rapid formation of an unsymmetrical dihydrido species and its subsequent slow conversion to a monohydrido species. We were able to crystallize the slow forming complex, and its X-ray crystal structure (Figure 3) showed it to be a metallacycle with a second molecule of 2-phenylpyridine attached. This finding combined with the NMR data indicated that under the reaction conditions the dppe complex rapidly formed a stable metallacycle with 2-phenylpyridine – one that traps the iridium complex and stops the catalytic cycle. Slowly thereafter the hydride para to one phosphine is displaced by the second pyridine.

By 1996, we had accumulated a reasonable body of results demonstrating the effectiveness and utility of $[(cod)Ir(PPh_3)_2]BF_4$ and related complexes in the tritium labeling of a variety of multifunctional, drug-like molecules[14] to high specific activity for receptor studies. These included phenylquinolines, benzazepinone amides, *N*-alkyl aminoheterocycles and complex benzamides and benzophenones. The regioselectivities

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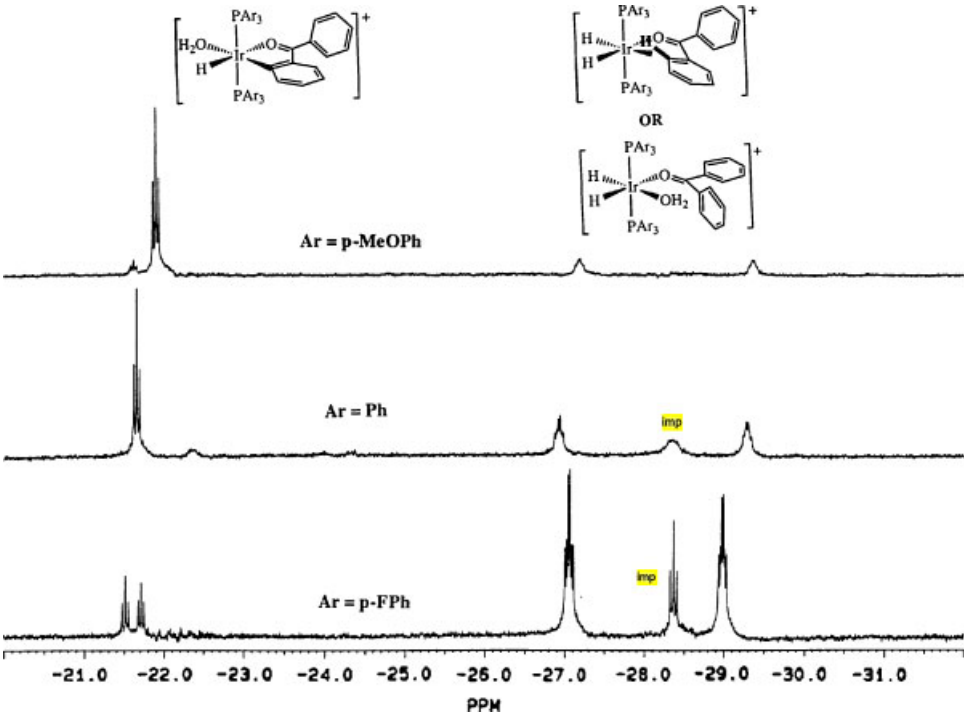

Figure 1 Hydride regions of ^{1}H NMR spectra at ca. −60°C of solutions of benzophenone and different [(cod)Ir(PAr_3)]BF_4 catalysts in the presence of D_2.

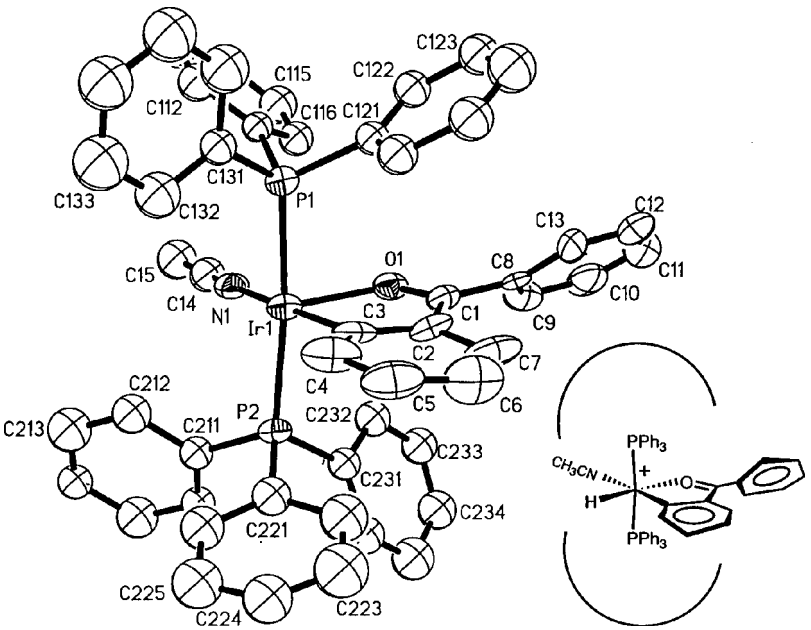

Figure 2 X-ray crystal structure of [Ir(H)(O,C2-η^2-benzophenone)(acetonitrile)(PPh_3)$_2$]BF_4.

of labeling were consistent with the previous mechanistic and model studies on simpler compounds. One unexpected result was the high degree to which methyl and methylene groups of two related compounds **2** and **3** were labeled: the specific activities of these products were 154 and 128 Ci/mmol, respectively. This level of isotope incorporation was much higher than the previous observations of partial *N*–Me labeling in benzamides[6] catalyzed by bisphosphine complexes, and suggested that the stronger-ligating nitrogens of

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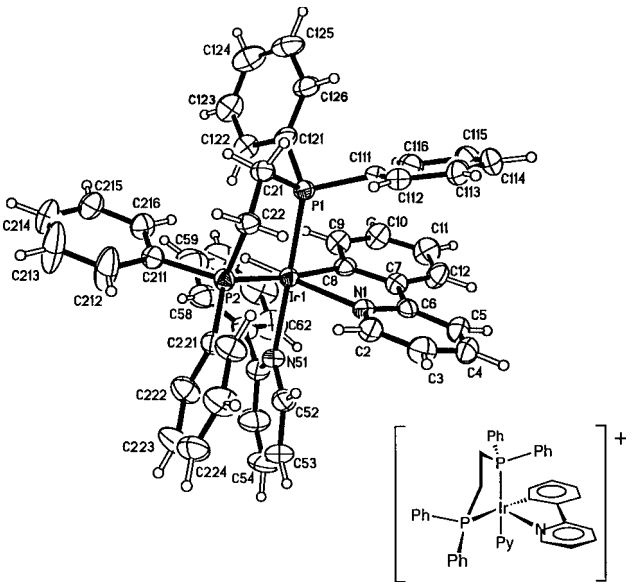
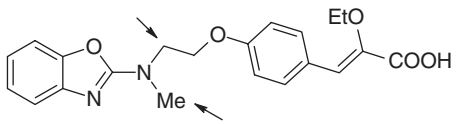


Figure 3 X-ray crystal structure of [Ir(H)(N,C2'-η^2-2-phenylpyridine)(acetonitrile)(dppe)$_2$]BF_4.

benzoxazepine and pyridine could provide a more effective entry into labeling at sp^3 carbon centers.

Although we generally observed good levels of labeling with limited amounts of tritium gas, in spite of the consumption of some tritium in reducing the cyclooctadiene ligand during catalyst activation, we began about this time[14] routinely prereducing the catalyst precursor with hydrogen *in situ*, prior to introducing



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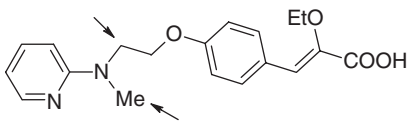

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tritium gas. This had the effect of producing less radioactive waste and reducing the nonproductive consumption of tritium. By 1999, we had achieved the tritium labeling of a large number of ligands,[15] selecting among precatalysts [(cod)Ir(PPh_3)$_2$]BF_4, [(cod)Ir(dppe)]BF_4 and [(cod)Ir(PCy_3)(py)]PF_6 according to the structural characteristics of the substrates, which by now included *N,N'*-diphenylureas, nitro-substituted benzamides, a variety of benzanilides and benzamides, sometimes multiply present in the same ring or same molecule. We achieved our first cassette labeling run, tritiating three peptidomimetic compounds as a mixture in the same solution then separating and purifying them in one HPLC run. This case was also the first in which we observed tritiation in C2 positions of pyridyl moieties within molecules. In 2000,[16] we demonstrated the utility of the organoiridium-catalyzed exchange method for direct tritiations of photoaffinity labeling compounds in the photophore moieties (benzophenone, azidobenzoyl and trifluoromethyldiazirenylbenzoyl), using paclitaxel photoaffinity ligands as a model for complex ligands in general.

By the mid-1990s more than 50% of the tritiated compounds required in SmithKline Beecham R&D in the US were being prepared by direct organoiridium-catalyzed exchange with tritium gas, and by the time of the breakup of our (by then GSK) radiochemistry group in 2002, well over a 100 high specific activity tritiated research compounds had been prepared by this approach. We rarely encountered a compound which was so insoluble in CH_2Cl_2 that this method did not work. We ran one very successful labeling of a compound in its HCl salt form, and in a few cases where the substrate formed a suspension with CH_2Cl_2, we nevertheless carried on with the exchange experiment and found that during the overnight period the compound had gone into solution and become tritiated. Perhaps, catalyst–substrate interactions served to assist solubilization. Being ignorant of this possibility earlier, we went through a time-consuming multistep sequence to prepare [^{3}H]camptothecin because we thought that it was insufficiently soluble in CH_2Cl_2 for exchange. The recent report by the US Novartis group[17] describing their very successful tritiation of camptothecin and several analogs using [(cod)Ir(PPh_3)$_2$]BF_4 showed us otherwise.

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Apart from the early work of Hesk *et al.*[10] already cited, it was only in 2000 that reports began appearing from other groups on organoiridium-catalyzed exchange using isotopic hydrogen gas. The contributions of these investigations between then and the present time have substantially increased knowledge about the effects of modifying the catalyst and broadened the range of substrate types that can be labeled.

The more significant discoveries by others, with the catalyst types already discussed, was their ability to label certain benzylamines[18,19] and the formyl positions of aryl aldehydes[20] and aliphatic aldehydes,[21] the β-positions of a nonreducible enone and an α, β-unsaturated oxime,[22] further examples of labeling of activated methyl and methylene groups adjacent to certain coordinating heteroatoms[23] and further examples of pyridine-C2 labeling.[24] The possibility of using ionic solvents for labeling more polar compounds was reported by Salter,[25] both with $[(cod)Ir(PCy_3)(py)]PF_6$ and several diphosphine complexes.

Several groups have made important advances with new organoiridium complexes in the last five years. Some of the most significant. . . .

The Solvias group published[26] their results of screening of a number of (mostly bidentate) phosphine complexes, some of which showed extraordinary activity with their model compound. My AZ Wilmington group used one of these complexes with excellent results.

The Sanofi-Aventis UK group has published extensively on their exploration of a number of variables in organoiridium-catalyzed exchange systems using deuterium gas.[19,27] They developed an *in situ* preparation of catalyst precursors in order to facilitate reaction screening and allow use of complexes that might be unstable in isolated form, and they discovered an additional substrate-directing groups and new cyclic substructures capable of being labeled. Other areas the group has investigated include the effects on catalytic activity and selectivity of phosphine:iridium stoichiometry, phosphine ligand modification, bidentate vs monodentate phosphines, and substitution of arsenic or antimony for phosphorus.

The Surrey-AZ Charnwood collaboration reported on their discovery and investigations of iridium pentadionate complexes.[28] These complexes are capable of labeling anilines (a new substrate class for organoiridium-catalyzed labeling) and benzylamines (more predictably than with catalysts mentioned so far), with heating in polar solvents such as aqueous DMF and DMA. Although first tested with D_2O as the source of isotope, the investigators found that they work with a similar range of substrates using D_2 gas and DMF or DMA solvent.[29] They revealed that, interestingly and usefully, certain bifunctional compounds can be labeled in different positions depending on whether the isotope source is D_2O or D_2. These pentadionate complexes must be acting through different mechanisms, but mechanistic investigations are complicated by the tendency of the complexes to deposit metallic iridium during the labeling reaction.

Bergman-type catalysts (e.g. $[Cp^*(PMe_3)Ir(Me)(CH_2Cl_2)][BAr_f]$, Cp^* = pentamethylcyclopentadienyl, BAr_f = tetrakis[(3,5-bistrifluoromethyl)phenyl]borate) have been shown to be capable of labeling compounds *via* deuterium gas;[30,31] use of tritium gas was reported on two substrates.[31] The regioselectivity of this labeling is not guided by coordinating functional groups (except perhaps by coordinating substituents such as halo, hydroxyl[32]), but rather is sensitive to the steric environment, so that the positions labeled tend to be different from those with the other catalyst types. Compounds lacking directing functions can be labeled, provided they do not contain strongly coordinating atoms, which deactivate the complex. So far, catalytic systems have not been developed for D_2; rather, an organoiridium–substrate adduct is first formed, then treated *in situ* with D_2 to 'hydrogenolyze' the Ir–substrate bond. In some cases, additional deuterium was found in positions neighboring the Ir–substrate bond. This must be the result of some exchange during the hydrogenolysis process; some mechanistic study has been carried out.[33]

My group at AstraZeneca demonstrated the utility of noninvasive Raman spectroscopy for real-time monitoring of catalytic deuterations (e.g. Figure 4) and tritiations.[34]

Most recently, iridium complexes having new ligand types have been reported to catalyze hydrogen isotope exchange with D_2. They include a polymer-bound organoiridium phosphine complex,[35] complexes with pincer ligands[36] and P,N ligands[37] and, in my AZ-Wilmington group, *N*-heterocyclic carbene complexes.[38]

In addition to the novel developmental work highlighted above, an increasing number of reports are appearing on the use of existing catalysts to label additional compounds. The methodology has been added by commercial custom labeling groups to their repertoire of tritiation methods. Considering the degree of confidentiality that most investigators must operate under, it seems certain that there are many more applications than have appeared in the literature.

Although this growing suite of catalysts do not make it to the level of magic (yet!), they enable more predictable, rapid and efficient labeling of certain compounds than ever before. And there is a significant potential for yet further development to broaden the applicability of organoiridium-catalyzed isotope exchange with tritium gas. However, there is also a

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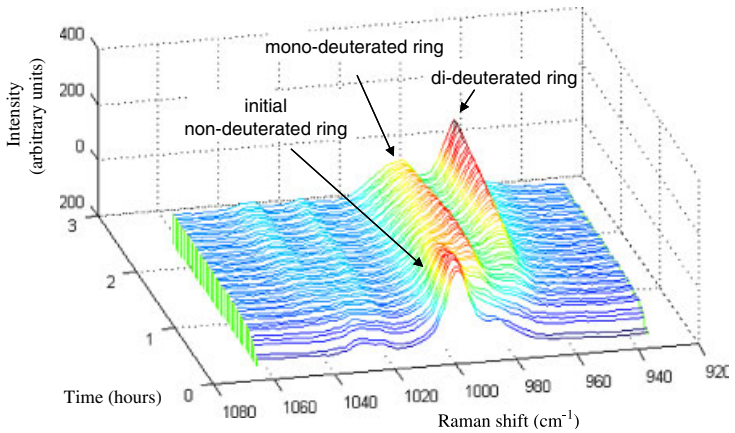

Figure 4 Raman spectroscopic monitoring of 3,5-difluorobenzoylpyrrolidine (3.9 mol% $[(cod)Ir(PPh_3)_2]BF_4$, 3.5 equiv. D_2, CH_2Cl_2, rt).

variety of other hydrogen isotope exchange methods and technologies, each with its own capabilities and specificities, and many of these are being improved and expanded as well. As the science develops on all these fronts, it becomes ever more likely that the next high specific activity tritiated compound that an investigator needs can be prepared by isotopic exchange, quickly utilizing only a few milligrams of the unlabeled compound, if he or she considers all the available exchange methods and applies the most appropriate one.

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