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The development and use of iridium(I) phosphine systems for ortho-directed hydrogen-isotope exchange

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Rapid and efficient iridium-mediated hydrogen-tritium exchange labeling of pharmaceutical compounds is a key methodology in the life sciences industry. A review of the development and use of iridium(I) phosphine systems for ortho-directed isotopic exchange is described to provide the reader with a comprehensive introduction to the area and to serve as a starting point for experimental investigators. Examples of useful catalyst systems and their application to different substrates types as well as potential areas for further development are discussed.

Keywords: isotope exchange; iridium catalyst; deuterium labeling; tritium labeling; regioselective labeling; catalyst development; *ortho*-labeling

Introduction

Isotope labeling of organic compounds is of high importance in the development of new drugs and therapies for the treatment of disease. Rapid and efficient labeling is the goal of many radiochemists, who need to support the urgent demands of researchers, minimize synthesis costs and reduce potential exposure to radioactivity during the course of multi-step syntheses. By far, the two most common isotopes in the pharmaceutical industry are those of carbon and hydrogen since they are the predominant atoms in most organic entities. Compounds labeled with tritium are particularly advantageous for researchers since they can be made in a rapid and cost effective manner.

Prior to the early 1990s, the most convenient tritium labeling methods involved halogen-tritium replacement, reduction of an unsaturated double bond precursor or the use of a heterogeneous catalytic exchange system, which often required optimization to achieve satisfactory results. In 1992, Dick Heys[1] reported first the use of a homogeneous iridium(I)-catalyzed exchange labeling system with the potential to rapidly produce tritium-labeled isotopomers with minimal synthetic investment. This was timely as discovery DMPK sciences were evolving to utilize rapid screening programs that required high specific activity ^{3}H-labeled compounds for basic research and lead optimization. Since then, the development of iridium(I) systems for ortho-labeling has progressed from simple systems to those that take greater advantage of additional substrate features; have increased efficiency with other substrates; allow for simpler work-up; provide alternatives to ancillary deactivating groups; offer better selectivity to sensitive moieties or result in improved solubility and reduced radioactive waste.

The advantage of iridium(I)-mediated hydrogen isotope exchange labeling is that it is one-step. Utilizing just the parent compound, catalyst and carrier-free tritium gas it can label regiospecifically at sp^2 and at some sp^3 carbons, affording a high specific activity labeled compound within just a few hours. Furthermore, sp^2 labeling is directed predominantly into metabolically stable positions, making this attractive for biological and medicinal compound development. As a result, this method has seen widespread adoption, and its applications continue to grow and develop as more experiments are conducted and new observations reported.

A recent review of the literature is available,[2] which highlights key examples of iridium(I) catalyzed labeling of simple and complex (multi-functional) substrates. In addition, a review from an historical perspective describes the key findings and rationales that led to the discovery and development of organoiridium(I) catalyzed hydrogen-isotope exchange.[3] This article concentrates specifically on the development and use of iridium(I) phosphine systems for ortho-directed isotopic exchange. The aim is to provide the reader with a comprehensive introduction to the area and serve as a starting point for experimental investigators.

Figure 1 illustrates one example of the state-of-the-art.[4] Labeling is achieved after 3 h in high specific activity and directed into three positions at room temperature under one atmosphere of carrier-free tritium gas. Work-up is simple; removal of volatile tritium and then filtration affords tritiated product in >98% radiochemical purity. This was achieved utilizing an immobilized catalyst formed from a

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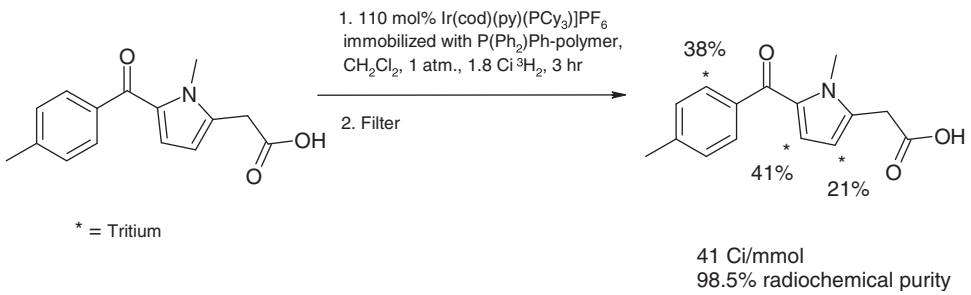

Figure 1. An example of the state-of-the-art: rapid labeling and simple product isolation.

dichloromethane solution of $[(cod)Ir(PCy_3)(py)]PF_6$ (cod = 1,5-cyclooctadiene) and a polystyrene-based ligand.

In general, the development of the iridium(I) systems for ortho-directed isotopic exchange has focused on two main areas: understanding the process of exchange, and increasing applicability to a wider and more complex range of substrates. To date, the literature contains a vast array of empirical data generated from a wide range of catalysts (both isolated and prepared *in situ*) and substrates at different ratios, reaction times and substrate purities. Therefore, caution should be exercised when making comparisons and drawing general conclusions. Examples of each catalyst considered useful to the investigator will be described. Experimental information on the synthesis of various isolated catalysts and their application in both deuterium and tritium labeling experiments is also included to provide a convenient practical resource for investigators.

Practical considerations

A key feature of this technique is that feasibility and optimization experiments can easily be carried out using the non-radioactive surrogate deuterium gas before a resort to specialist tritium labs is required. For investigators, substantial amounts of information can be generated in a relatively short timeframe, aiding the understanding of catalyst and substrate compatibility and supporting the development of improved systems. Care should be exercised, however, to ensure purity of the test substrates and reproducibility of such experiments. In addition, it should be noted that whilst most such pre-experiments transfer well to tritium, there are also exceptions that may require re-optimization.

A typical trial experiment requires a Schlenk flask or a suitable septum sealed tube, stirring bar, dichloromethane, catalyst and substrate, a source of deuterium gas (such as a regulated lecture bottle), a suitable work-up and analysis procedure as well as waste management facilities. Prior to embarking on exchange reactions, it is worthwhile periodically checking catalyst activity by running a parallel control using a suitable test substrate. This is intended to eliminate the risk of encountering false-negative outcomes as a consequence of catalyst degradation. Most complexes described herein are generally air/room temperature stable for weeks, even months; however, storage for extended periods (>6 months) should be avoided unless rigorous air/moisture/temperature precautions are in place. For regular use it is recommended that they be stored in small quantities under an argon atmosphere unless they appear to be especially stable.

Development of catalysts

The following cycle (Figure 2) illustrates the generally accepted mechanism for ortho-directed exchange. Catalyst activation requires reduction and irreversible loss of 1,5-cyclooctadiene to form a 12 valence electron cationic iridium(I) species. A further molar equivalent of tritium (or deuterium) is required for the generation of the active iridium catalyst species. 'Solv' may be solvent, additional substrate or adventitious water. After coordination of the substrate's functional group to the iridium metal center, oxidative addition occurs to form, in this case, a 5-membered metallacyclic intermediate (MMI). Next, the key step involves fluxionality of the loosely bound T-T (or D-D) to HT (or HD) followed by the reverse of the cyclometallation process and formation of the tritiated (or deuterated) product. The stereochemistry of the process, which is governed by the type of ligand bound to the metal center, will be discussed later.

The first iridium complex utilized was $[IrH_2(PPh_3)_2(CH_3COCH_3)_2]BF_4$ (**1**). This can efficiently exchange hydrogens belonging to an sp^2 or sp^3 carbon resulting in regiospecific incorporation of deuterium (or tritium) at positions 4-bonds away from the substrate's directing heteroatom. The complex facilitates deuterium labeling of a range of mono-functional substrates at very low loading (1.5–2%) such as ethyl benzoate (Figure 3), as well as a range of ring substituted aromatics[2,5] and has been used to label a complex steroid with tritium (>50 mol% loading).[6]

Like many catalysts described herein (*vide infra*), general applicability is somewhat difficult to achieve or predict. For example, deuterium labeling of methyl 3-furoate is efficient but related methyl 2-furoate fails. Other mono-functional substrates such as 4-phenylimidazole and ethyl phenylacetate also fail under these conditions whereas a range of other substrates including analogous 2-phenylimidazole label efficiently. These advantages and inconsistencies provided impetus to examine alternative catalyst systems.

Further developments originated from complexes coordinated with 1,5-cyclooctadiene, as shown previously (Figure 2). The diene affords a relatively stable, isolable pre-catalyst before it is subjected to isotopic hydrogen and lost from the coordination sphere. The pre-catalysts $[(cod)Ir(PPh_3)_2]BF_4$ (**2**), $[(cod)Ir(PMePh_2)_2]PF_6$ (**3**), $[(cod)IrP(p\text{-}MeOPh)_{32}]PF_6$ (**4**) investigated belong to the same class of monodenate complex. They can be easily synthesized (see the experimental section) or obtained commercially. All three are reasonably air/moisture stable bright-red crystalline solids, and have been tested and subsequently utilized with a range of pharmaceutical drug candidates. One of the most widely utilized pre-catalysts

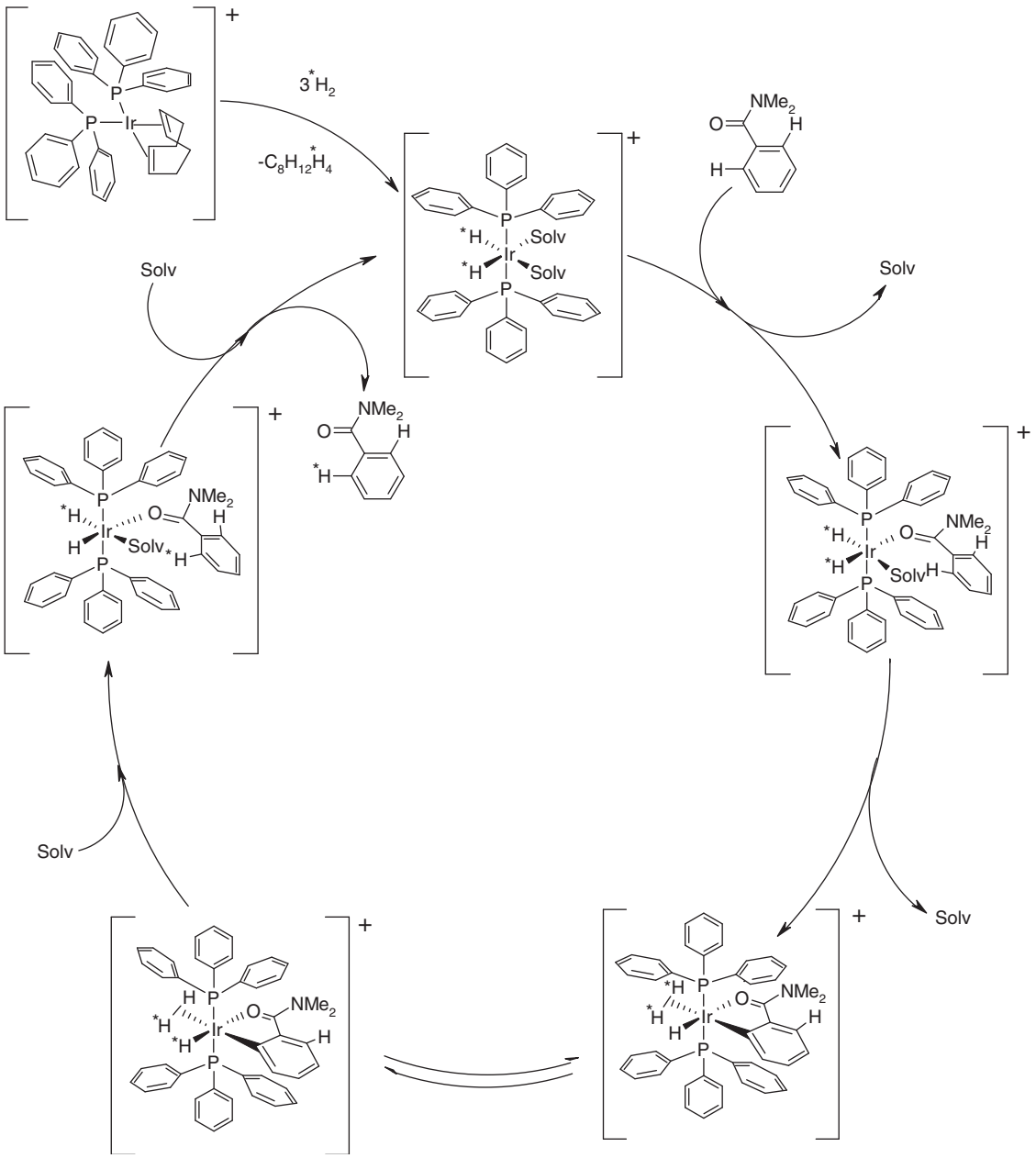

Figure 2. Generally accepted catalytic cycle of ortho-exchange using the example of $[(cod)Ir(PPh_3)_2]^+$ with isotopic hydrogen and *N,N*-dimethyl benzamide.

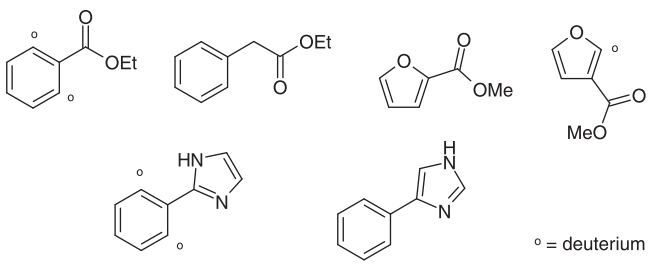

Figure 3. Deuterium labeling tests conducted on simple substrates with $[IrH_2(PPh_3)_2(CH_3COCH_3)_2]BF_4$ (**1**).

$[(cod)Ir(PPh_3)_2]BF_4$ (**2**) was shown in one study[7] to be slightly more efficient than $[IrH_2(PPh_3)_2(CH_3COCH_3)_2]BF_4$. Complex (**2**) has also been shown to support H/D/T exchange labeling at sp^3 carbons of *N,N*-dialkylamides and has been used to label a range of complex substrates – termed as having multiple ancillary functional groups (Figure 4). In this latter case, higher loadings are often required (some in excess of 300 mol%) to address sequestration of the catalyst by non-productive binding to such ancillary groups.

5- and 6-membered metallacyclic intermediates

The next notable development came from a report by Hesk *et al.*,[8] which demonstrated the application of $[(cod)Ir(PCy_3)(py)]PF_6$ (**5**) to hydrogen-deuterium exchange labeling of simple substituted acetanilides. This complex was found to catalyze ortho-labeling *via* a coordinating functional group, one additional atom away from the arene, reliably exchanging hydrogen

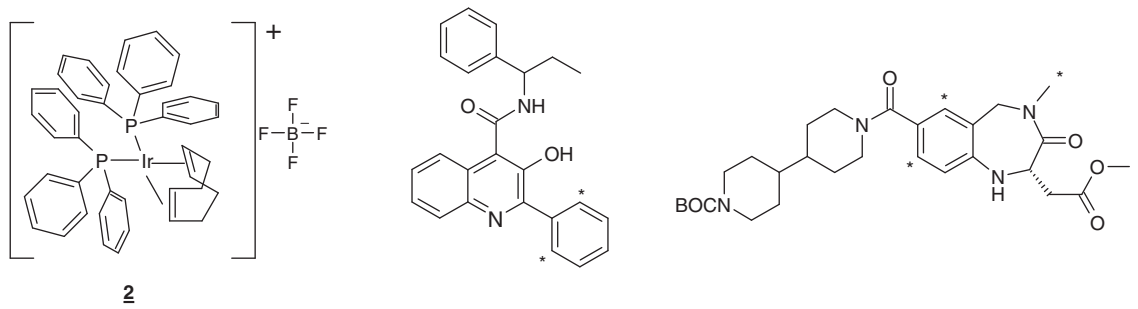

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Figure 4. Efficient tritium labeling of complex substrates with $[(cod)Ir(PPh_3)_2]BF_4$ (**2**).

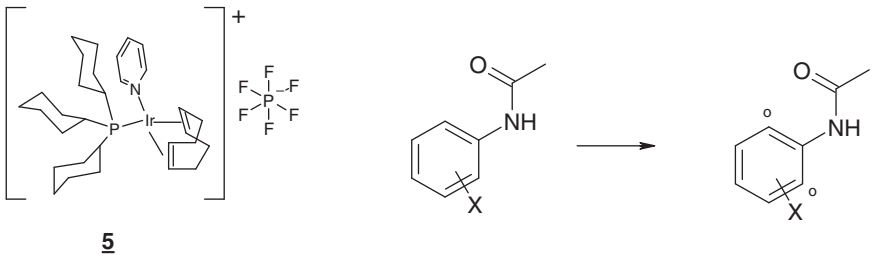

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Figure 5. *Ortho*-labeling of substituted (X = various functional groups) acetanilides with Crabtree's catalyst (**5**).

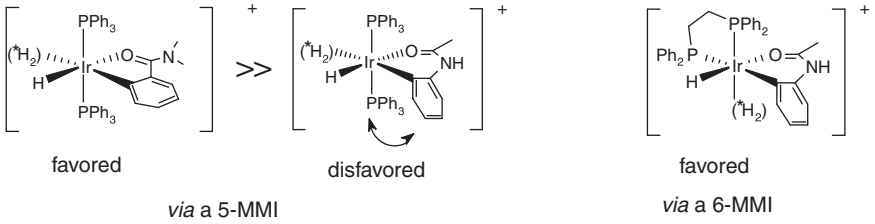

Figure 6. The effect ligand denticity has on regiospecific labeling and substrate suitability.

5-bonds away from the coordinating heteroatom (in addition to 4-bonds away – as found later). This feature therefore increased the scope of the technique to more substrates.

Also referred to as 'Crabtree's catalyst', the complex (**5**) is commercially available and facilitates exchange on a range of substrates labeling at aromatic sp^2 carbons directed by sp^2 N and O coordinating heteroatoms (Figure 5). In addition, it can facilitate 4-bond labeling at sp^3 alkyl carbons although instances in the literature are more sporadic. For a systematic study see the work of Bushby and Killick.[9] Because of its versatility, good stability and commercial availability it has become one of the most widely used exchange catalysts in industry.

Around the same time, a study comparing monodentate ligated phosphine complexes with bidentate phosphine containing complexes provided an improved understanding of what was happening mechanistically.[10] Comparing the outcome of ortho-exchange facilitated by pre-catalysts of the type $[(cod)Ir(L\text{-}L)]BF_4$ (e.g. L = CH_2PPh_2; L-L = dppe) (**6**) with pre-catalysts of the type $[(cod)Ir(L)_2]BF_4$ (eg. L = PPh_3) (**2**) clearly showed that the latter promoted labeling 4-bonds away whereas the former promoted labeling 5- as well as 4-bonds away from the directing heteroatom (Figure 6).

Since monodentate ligands tend to adopt a trans configuration, it was proposed that the formation of 6-membered metallacyclic intermediate, which requires that the arene twist out of plane with the ring, would result in steric congestion with the phenyl groups on the phosphine and disfavor subsequent catalysis. However, the formation of a smaller 5-MMI, which leaves the arene within the plane of the ring, would result in less steric encumbrance between that and the trans ligated phosphine, thus favoring subsequent catalysis.

Conversely, since the phosphine groups belonging to a bidentate ligand e.g. dppe (Figure 7) adopt a cis configuration, they reside further from the substrate's arene, resulting in less crowding in a 6-MMI. This lower energy state supports subsequent catalysis, leading to both a 5- as well as a 4-bond labeling outcome. This observation-driven hypothesis provides a reliable prediction of the labeling outcome based on ligand type alone.

A frequent exception to this rule is the monodenate Crabtree catalyst $[(cod)Ir(PCy_3)(py)]PF_6$. Because of its compact pyridine ligand, the reduced form has been shown to adopt a cis configuration with its neighboring bulky tricyclohexyl phosphine,[11] behaving in this regard like a bidentate catalyst. Attempts to push the metallacylic ring size further in a later study of the Crabtree catalyst by Ellames *et al.*[12] with phenyl acetone and benzyl acetone (potentially forming 7- and 8-MMIs respectively) failed to elicit labeled products although, as reported in later work,[13] this may not have been the optimum catalyst with which to test this hypothesis.

A useful feature of (**6**) is that it is often complimentary to Crabtree's catalyst (**5**), as demonstrated in a labeling study of

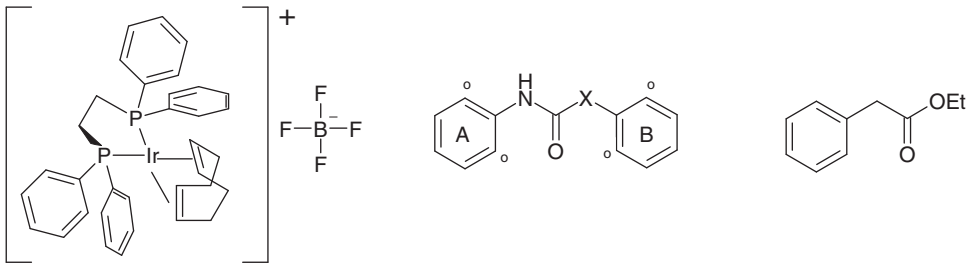

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Figure 7. Use of [(cod)Ir(dppe)]BF_4 (**6**) to facilitate phenyl ester and phenyl ketone labeling.

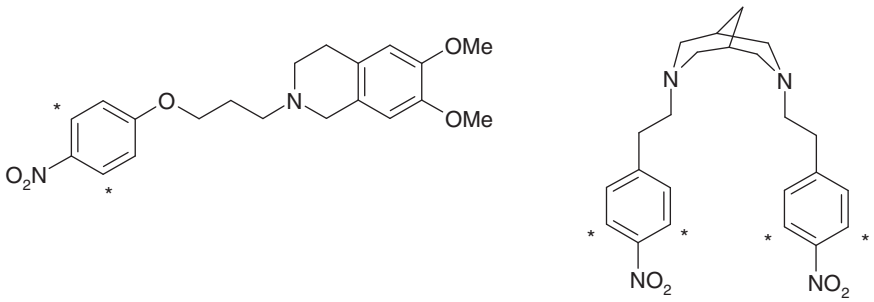

Figure 8. Use of [(cod)Ir(dppe)]BF_4 (**6**) and [(cod)Ir($EtPPh_2$)$_2$]BF_4 complexes to engage the less susceptible nitro directing group in tritium labeling.

phenyl esters and phenyl ketones. For example, the dppe-containing complex (**6**) facilitates efficient 5-bond ortho-labeling of phenyl esters (X = O) and phenyl ketones (X = C) into ring B *via* a 6-MMI (Figure 7), whereas (**5**) is a more efficient facilitator of 5-bond labeling of *N*-phenyl amides (ring A). Not all carbonyl directing substrates work, however, as is the case for ethyl phenylacetate (zero D incorporated). In general, most efficient labeling occurs when X = N. When X = O, [Ir(cod)(dppe)]BF_4 promoted efficient ortho-labeling into ring B at just over 5 mol% loading, whereas when X = C, sufficient labeling into ring B required progressively increased loadings (reaching super-stoichiometric) to attain similar results.[10] Moving to a larger ligand chelate ring size, as is the case for complexes employing dppp and dppb (dppp = $Ph_2P(CH_2)_3PPh_2$; dppb = $Ph_2P(CH_2)_4PPh_2$), diminishes labeling in ring B. As the backbone length increases, phosphine groups can potentially move away from a *cis* configuration and increase steric interaction with the substrate.

Complex (**6**) can also utilize the weaker nitro directing group, as demonstrated in the tritium labeling of the tetrahydroisoquinoline substrate (Figure 8, 225 mol% loading, 8.7 Ci/mmol). More recently, the mono-dentate analog [(cod)Ir($EtPPh_2$)$_2$]BF_4 gave reportedly good incorporation into the di-nitro substrate (Figure 8, 150 mol% loading).[4] While more air sensitive than its monodentate analogs, complex (**6**) remains a valuable addition to the current arsenal of catalysts.

At this point, a common set of useful test substrates had emerged from the literature, Figure 9. This group of substrates permits the study of 5- or 6-membered metallacyclic intermediates; sp^2 N and O coordinating groups and stereoelectronic effects brought on by substituents on the phenyl ring to be labeled. Importantly, most are commercially available. Herbert *et al.*[13] utilized a number of these substrates to help develop the dppe pre-catalyst (**6**) further, with particular emphasis on improving labeling in arylketones. Since the bond radius of arsenic is greater than that of phosphorus, it was conjectured that switching to an arsine ligand would relieve congestion between the coordinated substrate and ligand around the metal center. Thus, [(cod)Ir(edpa)]BF_4 (**7**) [edpa = ethylene 1,2-bis(diphenylarsine)] (Figure 10) was synthesized *in situ* and its activity was compared to a range of bidentate phosphine complexes as well as closely related monodenate analogs in deuterium labeling experiments of test substrates. Comparing the results, complex [(cod)Ir(edpa)]BF_4 (**7**) was shown to be markedly more efficient than (**6**) in the labeling of phenylacetone (1.7 D vs 0.6 D) and slightly more efficient for acetophenone (1.9 D vs 1.7 D). Complex (**6**) was somewhat better for acetanilide (2.0 D vs 1.5 D) as well as *N*,*N*-dimethylbenzamide (1.8 D vs 1.4 D). Application of this catalyst to the deuterium and tritium labeling of more complex substrates has not been reported thus far; however, it appears to have remarkable stability (up to 5 days) in solution and may be useful for more complex phenylacetone-containing substrates.

Since bidentate catalysts offer increased regio-labeling options, efforts have concentrated on developing this class of catalyst further with the aim of gaining higher efficiencies or increased tolerance to multi-functional substrates.

To generate a sufficient understanding of the key parameters involved, Salter *et al.*[14] established an *in situ* catalyst screening approach at low (5 mol%) loading. The screen employed a model compound, *N*-(4-methoxyphenyl)-*N*-methylbenzamide (Figure 11), designed to study sp^2 and sp^3 labeling derived from both a 5- and a 6-membered metallacyclic intermediates in one experiment. The presence of the methoxy group ensured well-resolved aromatic ortho-proton signals in the NMR and also provided a sharp standard reference integral allowing convenient analysis at each region of labeling.

With access to a large bank of ligands, some of which were rare and unavailable elsewhere, 65 catalysts were generated and screened against the test substrate. Two particularly potent

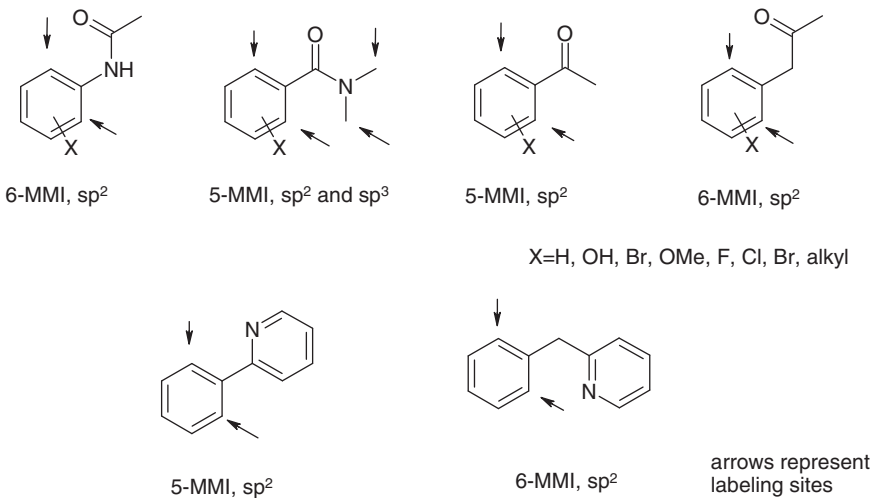

Figure 9. Useful *O* and *N* heteroatom directing test substrates for studying catalyst mediated ortho-exchange *via* 5- or 6-ring intermediates.

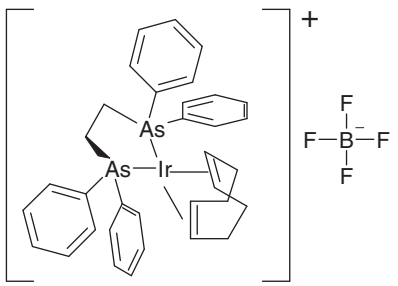

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Figure 10. Catalyst generated *in situ*.

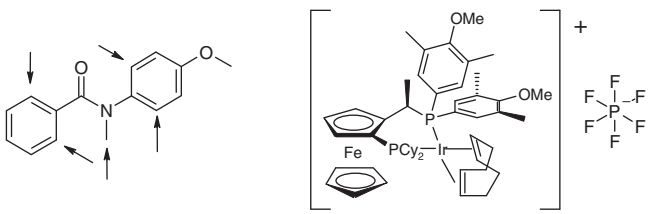

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Figure 11. The most active complex (**8**) isolated for the substrate tested. Arrows indicate the positions of labeling on the model substrate designed to allow the study of different metallacyclic intermediates in one experiment.

catalysts were identified, one of which deuterium labeled virtually all seven sites on the substrate. It was found that the 3,5-di-alkyl, 4-methoxy-substitution pattern on the phenyl phosphine group was common in the most efficient systems.

Attempts to isolate the most active pre-catalyst failed. The next best complex [(cod)Ir(PPF)]PF_6 (**8**) (PPF = [(1*R*)-1-[*bis*(4-methoxy-3,5-dimethylphenyl)phosphino]-2-[(1*R*)-1-(dicyclohexylphosphino)ethyl]ferrocene] was therefore synthesized (see experimental) and isolated as a deep claret-colored compound, stable to air and moisture at room temperature for months.

At 5–10 mol% loadings, the catalyst compared well to other known mono- and bidentate systems (for example, (**8**) gave 93% overall D incorporation in the model substrate compared to **(6)** 80% and **(5)** 54%) and efficiently labeled H-3 of methyl 2-furoate (1.0 D, 5 mol% loading) in contrast to zero incorporation using [(cod)Ir(PCy_3)(py)]PF_6 (**5**) (author, unpublished work) and [(cod)IrH_2(PPh_3)$_2$(CH_3COCH_3)$_2$]BF_4 (**1**).[1] However, it compared poorly against [(cod)Ir{P(MeOPh)$_3$}$_2$]PF_6 (**4**) in the labeling of 2-phenylpyridine (1.7 D vs 1.0 D respectively) as did all the other bidentate ligated catalysts tested in the screen. Differences in regioselective labeling was observed in the case of 2,2-dimethyl-*N*-(1-methylethyl)-*N*-(phenylmethyl)propanamide (5 mol% loading, 14 h, Figure 12; author, unpublished work). In another example, Elmore *et al.*[15] utilized (**8**) in the labeling of a compound developed for the treatment of depression since in the model experiment, the Crabtree catalyst failed to give appreciable levels (<5%) of deuterium incorporation. Hence, complex (**8**) can be a useful alternative to Crabtree's catalyst.

Other catalysts bearing analogous bidentate P-N ligands have recently emerged (Figure 13), although only preliminary results are available with 4-methylacetophenone and acetophenone substrates.[13]

Sub- vs super-stoichiometric catalyst loadings

Ortho-exchange into simple model substrates requires mostly low (5–10 mol%) catalyst loadings to support efficient levels of incorporation. Conversely, higher loadings are commonly employed in the labeling of multi-functional compounds,[16] to specifically address sequestration due to non-productive binding to ancillary functional groups. It is therefore not unusual to see reports of 1 M equivalent and above of catalyst in typical tritium labeling runs.

A drawback of high loading is the difficulty in isolating the product (which will be discussed later) or, analyzing the outcome of the deuterium pre-experiment should an excess of catalyst-derived species be present. In addition, committing large amounts of complex to a multiple screening runs rapidly depletes an often finite stock. This may be discouraging should the outcome remain unclear as a result of analytical difficulties. Lower loadings, e.g. 10–20 mol%, should therefore be initially considered with multifunctional substrates, as successful outcomes are often evident at sub-molar ratios. At higher loadings, it is sometimes better to proceed directly to the tritium run since radiochromatography facilitates easy identification of the tritium-labeled product buried in a multitude of catalyst-derived

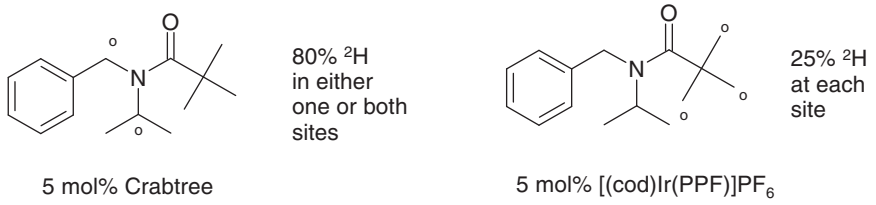

Figure 12. Regioselective differences at sp^3 carbons using different catalysts.

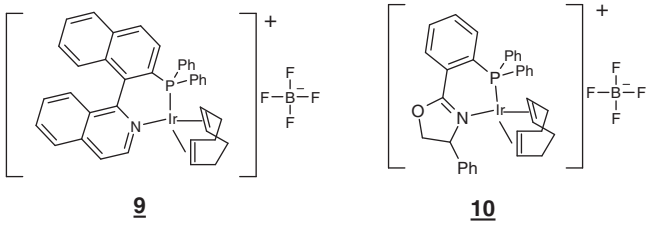

Figure 13. New classes of pre-catalyst generated *in situ*.

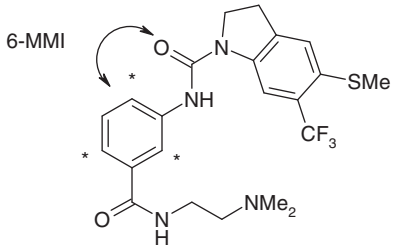

Figure 14. An exception of 6-MMI derived labeling normally not observed with a mono-dentate bis-phosphine complex. Catalyst loading was 480 mol%.

species when compared to a crude deuterium-labeled product mixture. Here, mass spectrometry may be the only source of help. In addition, isolation of even minor amounts (<1 mCi) of purified tritiated compound can confirm the site of labeling *via* proton-decoupled tritium NMR.

Reports of tritiations carried out at high loadings (>50 mol%) reveal in some cases anomalous results when compared to those observed in the 2–20 mol% range (conditions typical of deuterium modeling experiments). For example, using an overwhelming 480 mol% of monodenate $[Ir(cod)(PPh_3)_2]BF_4$ complex (**2**) with the substrate (Figure 14) and 25 equiv. of tritium gas, labeling occurred ortho to the urea as shown, which could only be envisaged to have proceeded through a 6-MMI.[16]

Stereoelectonic effects

In some cases, the effects of altering the electronic properties of the catalyst on the degree of substrate labeling can be correlated with known hypotheses.[17] In other cases, changing the electronic nature of the phosphine appears to have no detectable effect on the labeling outcome.[14] Depending on the nature of the coordinated substrate, particular stages in the catalyst cycle may become more dominant than others. In other words, strong electronic effects may be masked by steric congestion or relief, as well as by interactions with other functions if the substrate is complex. It is therefore unsurprising that to date the majority of developments have been made through trial and error rather than by rational ligand and catalyst design.

Steric effects are apparent, arising both from the ligand's architecture during the formation of 6- and/or 5-membered metallacyclic intermediates (*vide supra*) as well as from the steric constraints around the coordinating group. Until recently, it was thought that the steric effects of neighboring meta-ring substituted groups were also responsible for diminished labeling at the C-2 position; however, while this was found to be true for alkyl substituents, other groups bearing lone pairs such as methoxy- or fluoro- either reduced inhibition or promoted labeling into the C-2 position over an unencumbered C-6 position.[18] In addition, the effect on ring labeling efficiency with increasing size of the group adjacent to the coordinated heteroatom was found to be negligible in case of *N*,*N*-di-R benzamide (R = H ≈ Me = *i*Pr) in a comparative study using Crabtree's catalyst.[12]

Expanding to new coordinating groups

The majority of labeling experiments reported utilize substrates with –C(O)– and –C = N– directing groups. Less often utilized is $–NO_2$ and $–NH_2$ although the latter is particularly weak and rarely works. Considering the ubiquity of sulphones, sulphoxides and sulphonamides in medicinal compound candidates, complexes that can utilize sulphur(VI) groups for ortho-labeling are of high interest.

Ortho-labeling of methyl phenyl sulphoxide was reported[19] using *in situ* generated complexes derived from a suspension of 0.5 equiv. of $[Ir(cod)Cl]_2$, 1 equiv. of silver tetrafluoroborate and 2, 4 or 6 equivalents of pyridine. Although not characterized, the different catalyst species produced resulted in 1.6 deuteriums incorporated using 1 equiv. of pyridine; 1.8 deuteriums using 2 equiv. of pyridine and 1.3 deuteriums incorporated using 3 equiv. of pyridine. In the same study, benzene sulphonamide was also shown to be a substrate for the same *in situ* generated complex, utilizing 2 M equivalents of pyridine as ligand (**11**), resulting in the incorporation of 1.7 deuteriums (Figure 15). All the reactions were accompanied by slight precipitate of Iridium black.

In the same study, *in situ* prepared $[(cod)Ir\{P(C_6F_5)_3\}_2]BF_4$ was found to promote the labeling of benzenesulphonamide (1.1 D at 50 mol% loading) and *in situ* prepared $[(cod)Ir(PMePh_2)_2]BF_4$ (**3**) afforded labeled methyl phenyl sulphoxide (0.4 D, 50 mol% loading). Further investigations to confirm the general utility of these complexes as a means of utilizing the sulphone, the sulphoxide and the sulphonamide as a directing group has not yet appeared.

Separation – immobilized catalysts

Substrate–catalyst separation can be a major drawback in homogeneous systems. At high catalyst loadings, separation can become highly problematic, where a number of other species may be produced, and subsequent isolated yields low.

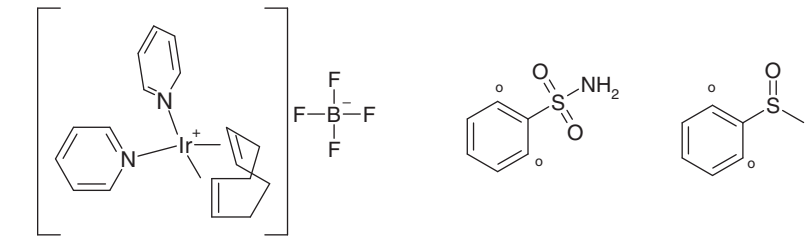

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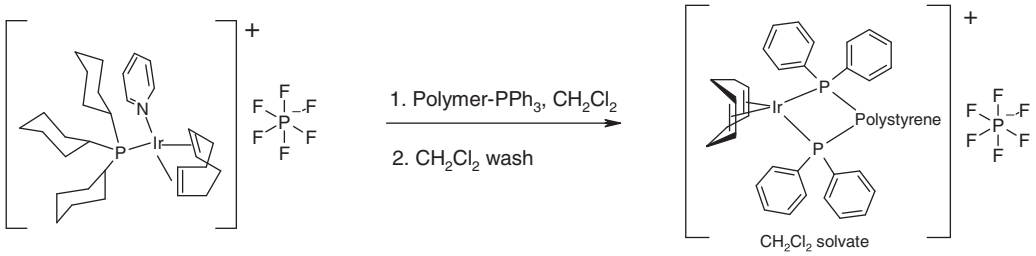
Figure 15. Application of sulphoxide and sulphonamide groups to direct *ortho*-exchange on phenyl in the presence of complexes generated *in situ* from $[(cod)IrCl]_2$, $AgBF_4$ and various ratios of pyridine.



5 12

Figure 16. A one-pot synthesis of the solid supported pre-catalyst (**12**) using a commercially available polystyrene based ligand and Crabtree's catalyst (**5**).

Therefore, the development of an easily filterable heterogeneous catalyst system that retains the advantages of its homogeneous analog is attractive.

The first reported use took advantage of modified silica supported system.[14] Synthesis of the complex was achieved by *in situ* preparation at 5 mol% loading using $[(cod)IrCl]_2$, silica supported ligand and $AgPF_6$ in methanol, followed by evaporation and reaction of dichloromethane. A second approach was tested using a catalyst prepared *in situ* with pre-synthesized dendrimer (*16PP-Ph$_2$-Cy$_2$*), which consisted of 16 ligands. After the reaction was complete, the catalyst could be conveniently filtered by syringe-assisted nano-filtration. However, both this and the silica supported system exhibited a 40% drop in efficiency at the 5-bond labeling positions of the model substrate when compared to the analogous unsupported complex, hinting at possible steric inhibition from the support.

Since both dendrimer and silica-supported ligands require significant synthetic investment, a more practical alternative using commercially available polystyrene supported triphenylphosphine ligand was developed by Bill Lockley and subsequently demonstrated with a range of substrates, Hickey *et al*.[20] The immobilized catalyst can be prepared easily by the treatment of Crabtree's catalyst (**5**) with the polymer-bound ligand in dichloromethane completely displacing both pyridine and PCy_3 ligands to furnish a red polymeric catalyst (**12**) stable for up to 2.5 months at −20°C (Figure 16). The complex exists as a dichloromethane solvate (as shown by displacement studies using NMR and reflectance IR in a separate communication with the author). It is especially important to note that catalyst activity will drop radically if washed with other solvents with greater complexing ability. Methanol, for example, will reduce the activity significantly and THF stops it. Thus, washing should be performed exclusively with dichloromethane. The catalyst was shown to compare well with Crabtree's catalyst on a range of simple substrates.

Complex (**12**) worked well in the deuterium labeling of three of the five multifunctional compounds reported[4] (Figure 17). Failure or very low incorporation was observed in two cases where Crabtree's catalyst succeeded. This may be a result of steric encumbrance between the solid support and the substrate. When applied to tritium labeling, as shown previously (Figure 2), radiochromatograms showed major peaks for product with little or no additional radioactive impurities. The ease by which this complex can be produced and utilized makes it a good choice for fast turnaround times.

Solvent development

Dichloromethane is considered to be the most versatile solvent for iridium(I)-catalyzed ortho exchange, attested by the vast majority of reactions reported in the literature to date. It dissolves a wide range of simple and complex substrates and is easy to evaporate. It ligates with, and is lost from, the iridium metal center easily at room temperature, allowing substrate and deuterium (or tritium) to participate in the exchange process efficiently. In the search for improved activity or increased substrate solubility, alternative solvents have been investigated and some have been reported to label substrates as effectively as dichloromethane. Neat acetone, for example, supports efficient labeling of 2-phenylimiadzole with catalyst (**1**).[1] Other substrates, however, fail to undergo exchange labeling in acetone, as was found in the case for propiophenone with (**1**). In a later work,[8] acetone proved to be a potent inhibitor in the labeling of acetanilide with $[(cod)Ir(PCy_3)(py)]PF_6$ (**5**) but an excellent solvent (as was THF and toluene) in the labeling of *N,N*-diethylbenzamide.[21] Acetanilide was found to be particularly sensitive to small amounts of additive acetone, and adding 5 and 10% v/v amounts to DCM inhibited labeling incrementally. DMF was found to be an even more potent inhibitor at just 5% v/v. A summary of results in neat solvents is provided in Table 1 below.

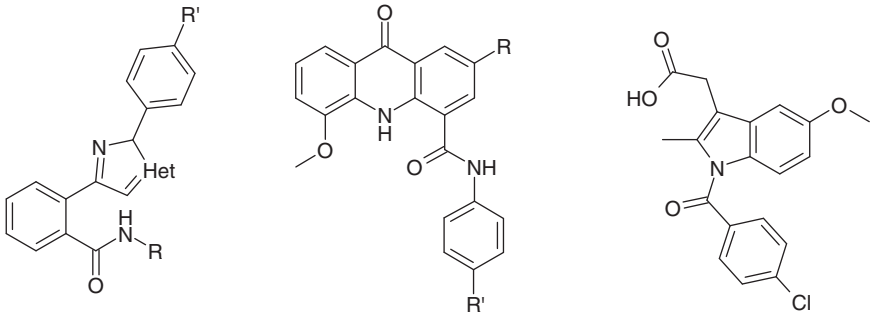
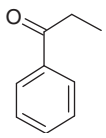
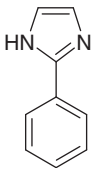
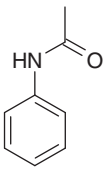
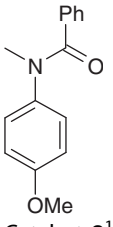
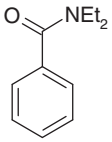


Figure 17. Complex substrates labeled successfully using the solid supported pre-catalyst (**12**).

Table 1. Overview of different solvents used in *ortho*-deuterium labeling of simple substrates with various catalysts. (++++) denotes efficient labeling. (−−−−) denotes zero or undetectable labeling. BMIM=1-butyl-3-methylimidazolium.

Solvent	 Complex **1**[1]	 Complex **1**[1]	 Complex **5**[8]	 Catalyst **8**[14]	 Complex **5**[21]
CH_2Cl_2	++++	++++	++++	++++	++++
Acetone	−−−−	++++	−−−−		+++
Ethyl acetate				++	
THF	−−−−	++++			++++
DMF		−−−−			
Dioxane			−−−−		
CH_3CN		−−			−−
Chlorobenzene				+++	
BMIM[PF_6]				+++	
Toluene					++++
DMA			−−		−−

The disparity in outcome between acetanilide and *N,N*-diethylbenzamide in acetone highlights some sensitivity to the substrate and solvent combination. The solvent should satisfy two principal requirements: provide solubility to a broad range of substrates, and support the coordination sphere as the catalytic cycle progresses, through a delicate ligating and leaving process with the iridium metal center. In this latter regard, dichloromethane is well suited to many common sp^2 N and O substrate directing groups,[22] but may be less well suited to other directing groups. Therefore, tuning the solvent to the substrate may be an important consideration. In a case where the substrate has too strong a coordinating group, the solvent may fail to displace it, often indicated by an immediate color change on the addition of the substrate to a solution of the complex. Conversely, too strong a coordinating solvent, such as acetonitrile, and the catalyst may irreversibly bind and become inactivated (Figure 2). This may explain why the strongly coordinating 2-phenylimidazole labels just as well in acetone and ethyl acetate, while propiophenone, with its weaker coordinating group, does not; or why weaker acetanilide fails to label in acetone, but the stronger ligand *N,N*-diethylbenzamide succeeds (1.2 D incorporated). Furthermore, while methanol was generally shown to be an inferior solvent to dichloromethane, it did support labeling of phenylpyrazine,[12] which has a strong directing group, in contrast to the weaker ligand ethyl benzoate, which failed to undergo exchange.

On the other hand, potent inhibitory solvents of cationic systems such as DMF, DMA and acetonitrile are essential to the optimum functioning of the catalytic hydrogen–isotope exchange cycle mediated by iridium dionate complexes (covered in another part of this special edition). Therefore, it may be possible to take advantage of alternative solvents where a reaction fails in dichloromethane, or the substrate is insoluble, provided that the substrate's coordinating group is powerful enough to compete with the new solvent.

Investigations aimed at improving ortho-labeling efficiency by adding molar equivalents of solvent additive to substrate and catalyst in dichloromethane[23] gave at best little or no improvement, and at worst suppression of deuterium incorporation.

Substrate solubility has in some cases been a limiting factor. Use of an additive solvent to improve substrate solubility in DCM, such as 5% v/v acetone, methanol or DMF, has been shown to compromise labeling efficiency of acetanilide mediated by Crabtree's catalyst.[8] Somewhat later, the emergence of room temperature ionic liquids prompted further

investigation into their use as solvents for ortho-exchange. Ionic liquids are attractive because their coordinating power can be modulated by changing the counterion. Yet, due to their ionic nature, they can provide the solvating advantage that more polar solvents offer. In a study of several ionic liquids,[24] those belonging to the class [R-MIM]PF_6 (R = Et, Butyl, Hexyl, Octyl) were found to work well, although [BMIM][PF_6] was most convenient, as it is a room temperature liquid, commercially available and less viscous than its higher chain homologs. One drawback ionic liquids have is they are non-volatile, and sometimes require a more involved separation approach. However, in cases where solubility was a limiting issue, they have often been used to good effect.

Sensitive and inhibiting functional groups

Alkene and alkyne bonds are vulnerable to reduction during exchange labeling. Some substrates bearing alkene groups have been stable to reduction although these are usually conjugated systems. In some cases they have been labeled and isolated along with some of their reduced by-products, thereby taking advantage of the slower rate of hydrogenation over exchange e.g. in (**13**) (Figure 18).[7] In other cases, complete survival of the olefin occurs as in labeling of compounds (**14**) and (**15**)[25] where Crabtree's catalyst was utilized.

The presence of an even more sensitive alkyne group on a target substrate has obstructed investigators from successfully applying this methodology. Huguenin[26] recently demonstrated an approach to circumvent undesired alkyne reduction of a target substrate through initial protection of the substrate's acetylenic bond. Complexation using cobalt octacarbonyl yielded the *bis*-tricarbonylcobalt-complexed alkyne (Figure 19). Subsequent exchange labeling using [(cod]Ir(PCy_3)(py)]PF_6 (**5**) and deprotection resulted in labeling at the C2-position of the pyridyl ring, *via* a less commonly observed 1,2-reduction/oxidation mechanism (for an example see Ellames *et al.*[12]). This approach provides a potential protection strategy for compounds containing alkyne groups.

Since a protection group strategy necessitates a departure from a one-step to a multi-step labeling approach, a useful alternative has been to identify and employ a potential intermediate for ortho-labeling, both late in the target molecule's synthesis route and deficient of inhibitory functions. The fragment, for example, could be a mono-functional aromatic ester, ketone or acid at the penultimate step of the synthetic route. The simplified substrate can thus be labeled easily, in high efficiency and coupled on the small scale with the more complex fragment, to produce the target labeled product. This approach was first successfully applied in the tritium labeling of remacemide.[27] More recently, it was presented as a common strategy in the syntheses of a multitude of complex multifunctional tritiated targets[28] albeit with tritiated water as the isotope source.

The cyano group is one of the most potent inhibitors of iridium(I) phosphine-mediated exchange labeling as attested by the sheer absence of examples in the literature. It binds strongly and in most cases irreversibly to the iridium metal center sequestering the catalyst and substrate from the exchange process.

Therefore, excess catalyst is required to occupy this group prior to exchange. Only one example exists in the literature where this has been deployed successfully (Figure 20). Here the compound was doubly labeled using 190 mol% [Ir(cod)dppe]BF_4 (**6**) with partial loss of the silyl group.[16] In spite of this, the use of super-stoichiometric loadings of catalyst does not always work. This may be a consequence of steric congestion, caused by a metal complexed-ancillary group occupying the space required for the unbound catalyst to engage with the directing group. Precipitation of a highly bound complex may also occur.

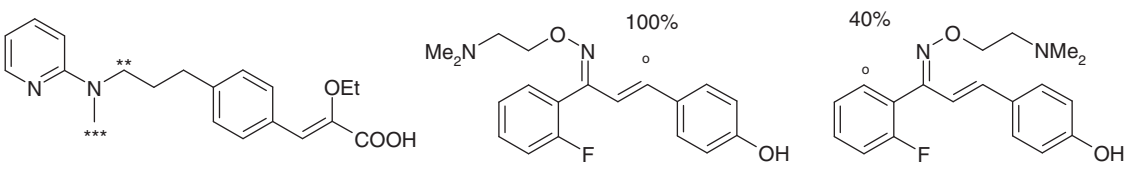
Other factors

Various substrate and catalyst concentrations have been reported. In general, a catalyst concentration of around 10 μmol/ml of solvent has been recommended[23] and has been used for many deuterium experiments. Generally, the labeling process is complete within 1–2 h. However, some *in situ* generated catalysts have been reported to take up to 120 h[13] before deuterium has been fully incorporated into the substrate. This may well be impractical for tritium experiments when facing instability issues and fast turnaround times.

In addition, the substrate has also been used as the ligand itself, although recovery was found to be generally poor and incorporation low compared to phosphine-based alternatives.[19] The same report showed that changing the molar ratio of phosphine to iridium metal using *in situ* generated complexes has a marked effect; one equivalent being less efficient than two and three equivalents and four equivalents halting the exchange entirely. In general, using two equivalents of phosphine to one equivalent of iridium metal appears to be the best and most commonly used ratio.

Waste minimization

Iridium(I) ortho-exchange can produce significant waste, especially at super-stoichiometric catalyst loadings due to non-productive reduction of the pre-catalyst's cyclooctadienyl ligand to yield tritiated cyclooctane. However, it was shown that pre-catalysts can be pre-reduced with hydrogen gas in



13 14 15

, * denotes 2 and 3 tritiums respectively

Figure 18. Olefinic groups on substrates that survived complete reduction during the course of *ortho*-exchange.

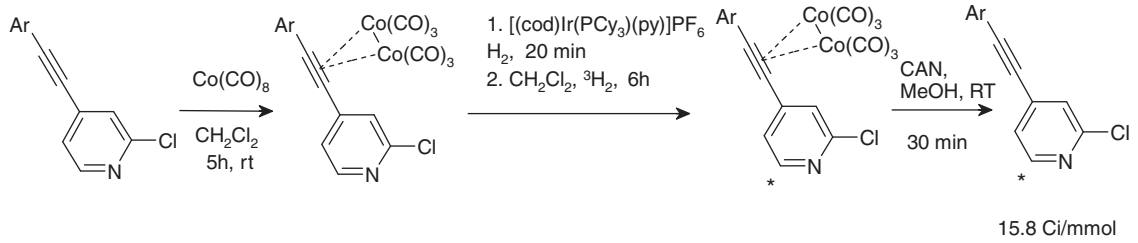


Figure 19. A protection–*ortho*-labeling–deprotection sequence employed to circumvent undesired reduction of a sensitive alkyne group.

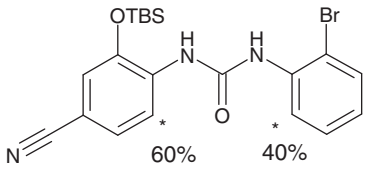


Figure 20. A rare example of successful *ortho*-labeling of a substrate bearing a nitrile group.

dichloromethane, and the excess hydrogen pumped off.[7] Subsequent reactions yield high specific activity products with no negative effects, making this an invaluable step in economic tritium use and reduced waste.

Experimental

Reagents and starting materials were obtained from common reputable commercial sources. (R)-1-{(SP)-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocenyl}ethyldicyclohexylphosphine, CAS 360048-63-1, was obtained from Sigma-Aldrich. All solvents were distilled prior to use. ^{1}H-NMR spectra were obtained from either a Bruker 300 or 400 MHz high-field NMR instrument.

Synthesis of a useful test substrate *N*-(4-methoxyphenyl)-*N*-methylbenzamide

In a two-necked flask equipped with magnetic stirrer bar, one neck fitted with a septum, the other an argon inlet was added *N*-methyl-*p*-anisidine (5.0 g, 36.4 mmol). Dichloromethane (80 ml) was added followed by benzoyl chloride (4.64 ml, 40 mmol). The solution was cooled in ice and triethylamine (5.60 ml, 40 mmol) was added dropwise while stirring (care was taken not to add base too quickly). The resulting solution was stirred overnight (12 h) before the addition of NaOH (1.0 M, 50 ml). The organic phase was separated and washed with water (2 × 25 ml), dried over Na_2SO_4, filtered and the filtrate evaporated to give a crude oil. The oil was subjected to flash chromatography eluting initially with 20% diethyl ether/80% petroleum ether (35–70°C) to remove a major non-polar impurity followed by 70% diethyl ether/30% petroleum ether (35–70°C) to give product as a colorless oil, which solidified. Recrystallization using 1:1 ethyl acetate/petroleum ether 35–70°C gave fine white plates, 7.81 g, 89%. ^{1}H NMR ($CDCl_3$) δ: 7.31 (2H, 2d superimposed, 2 × ortho –COArH), 7.22 (1H, d, para –COArH), 7.18 (2H, 2t superimposed, 2 × meta –COArH), 6.96 (2H, 2d superimposed, 2 × ortho –NArH), 6.75 (2H, 2d superimposed, 2 × meta –NarH), 3.78 (3H, s, MeO), 3.49 (3H, s, NMe).

Procedure for deuterium exchange labeling using an isolated catalyst

In a 25 ml Schlenk flask equipped with a lightly greased ground glass joint tap and containing a magnetic stirrer bar, catalyst was added (typically 5–10 mol%) followed by substrate (approximately 15 μmol) and dry dichloromethane (1 ml). A B-14 septum was fitted to the top and held in place by use of Parafilm™ wrapped around the neck. The flask was immersed in a bath of liquid nitrogen until the solution was frozen. The contents of the flask were evacuated under high vacuum and deuterium gas introduced. The flask was twice more evacuated and deuterium gas re-introduced. The flask was allowed to warm to RT and the pressure was equalized to 1 atmosphere by briefly inserting a syringe needle through the septum to relieve the excess pressure. The flask was then stirred (at least 600 rpm) at RT for 2–3 h. An aliquot (2 μl) was taken and diluted with methanol in an HPLC vial and submitted for LC-MS analysis along with a second sample containing reference unlabeled starting material. A sample was run on thin layer chromatography plate with different solvent systems to determine the system for separation. For each labeled sample, a plug of cotton wool was inserted into a pipette and loaded with 3–4 cm height of normal silica. Then, the short column was saturated with the solvent system of choice, loading with sample in a small amount of dichloromethane and eluted. The fraction was collected, evaporated and analyzed by ^{1}H-NMR to investigate the diminution of proton signals, indicating the position and extent of deuterium labeling.

Synthesis of monodentate catalyst from $[Ir(cod)Cl]_2$: example: $[(cod)Ir(PPh_3)_2]PF_6$

The following procedure was adapted from the original synthesis by Haines and Singleton.[30] To a suspension of di-μ-chlorobis(cyclo-octadiene)di-iridium(I) (47.02 mg, 70 μmol) in ethanol (2 ml) under argon was added triphenylphosphine (73.4 mg, 0.280 mmol) and the mixture stirred until the initial suspension had dissolved (*ca.* 10 min). The deep red solution was then filtered and an ethanolic solution of ammonium hexafluorophosphate (25 mg, 0.154 mmol) in 0.5 ml added *via* syringe. On addition, the solution gave a deep red precipitate that was cooled in an ice-bath then filtered under vacuum. The product, which was air stable, was washed with cold ethanol (2 ml), then cold diethyl ether (4 ml) and allowed to air dry (*ca.* 3 minutes) to give the iridium complex analytically pure as a deep red solid, 57.03 mg, 89%. ^{1}H NMR ($CDCl_3$) δ 1.97 (4H, d, 4 × CH_AH_B), 2.36 (4H, br d, 4 × CH_AH_B), 4.21 (4H, br s; 4 × CH alkene), 7.25–7.55 (30 H, m, 6 × C_6H_5).

Synthesis of a bidentate catalyst from $[Ir(cod)Cl]_2$– example: $[(cod)Ir(dppe)]PF_6$

In a Schlenk flask equipped with magnetic stirrer and septum was added $[Ir(cod)Cl]_2$ (100 mg, 149 μmol), 1,2-bis(diphenylphosphine)ethylene (dppe) (119 mg, 299 μmol). The flask was sealed with the septum and charged with argon. Methanol (5 ml) was introduced and the resulting mixture stirred for 15 min before the introduction of NH_4PF_6 (48 mg, 298 μmol) in MeOH (240 μl). The entire mixture was stirred for 1 h, then the methanol reduced to one third of its original volume by evacuation on the Schlenk line manifold. Freshly distilled degassed anhydrous diethyl ether (15 ml) was added and the resulting mixture placed in a freezer at −20°C overnight. The following day, the dark red solid was filtered off under suction and washed with cold diethyl ether (3 × 2 ml) to give the complex (**6**) 217 mg, 86%. *Note*: should the complex fail to precipitate, it is likely that too much methanol is present. The solvent should then be reduced carefully and more diethyl ether added and the solution cooled once more. ^{1}H NMR ($CDCl_3$) δ 7.60 (20H, m, aromatic), 4.61 (4H, br s, cod C*H*=C), 2.41–2.18 (12H, m, 4 × cod CH_2 and 2 × PCH_2).

Synthesis of a bidentate catalyst from $[(cod)Ir(py_2)PF_6$– synthesis of $[(cod)Ir(PPF)]PF_6$

Step 1: Preparation of $[(cod)Ir(py_2)]PF_6$. Adapted from the literature procedure of Crabtree and Morehouse.[31] To a 1:1 solution of acetone/de-oxygenated water (20 ml) and pyridine (0.7 ml) in a 100 ml Schlenk flask equipped with magnetic stirrer under argon was added di--chloro-bis(η^4-1,5-cyclooctadiene)diiridium(I) (0.42 g, 0.62 mmol) and ammonium hexafluorophosphate (0.31 g, 1.9 mmol). The mixture was allowed to stir efficiently for 2 h at room temperature. Care was taken to exclude air. The more volatile acetone was gently removed by evaporation on the Schlenk line until the volume fell to about 10 ml. The yellow solid $[(cod)Ir(py)_2]PF_6$ precipitated during this process and was collected by filtration under argon. The precipitate was washed with 10 ml of degassed water and dried under high vacuum to give 0.60 g, 79% as a bright-yellow powder. ^{1}H NMR ($CDCl_3$) δ: 8.74 (4H, 2d superimposed, o-ArH), 7.77 (2H, 2t superimposed, p-ArH), 7.50 (4H, 2d superimposed, m-ArH), 3.88 (4H, br s, olefinic C-H), 2.50 (4H, m, 4 × CH_aH_b), 1.86 (4H, m, 4 × CH_aH_b).

Step 2: Preparation of $[(cod)Ir(PPF)]PF_6$ (**8**). Adapted from the procedure of Bedford *et al.*[32] To a suspension of $[(cod)Ir(py)_2]PF_6$ (200 mg, 331 μmol) in methanol (3 ml) was added [(1*R*)-1-[*bis*(4-methoxy-3,5-dimethylphenyl)phosphino]-2-[(1*R*)-1-(dicyclohexylphosphino)ethyl]ferrocene] (235 mg, 331 μmol) and allowed to stir under argon for 1 h at room temperature (after 10 min, a bright red precipitate was observed). Half of the solvent was removed under high vacuum on the Schlenk manifold followed by the addition of de-oxygenated diethyl ether (5 ml). The mixture was cooled in an ice-salt bath at −10°C for 5 min before the solid was filtered off under suction and washed with diethyl ether (3 × 5 ml) to give 256 mg of a light red crude product. The light red solid was recrystallized from warm methanol (5 ml) to give dark red-purple crystals 213 mg (56%).

Preparation of immobilized iridium-based catalyst[20]

(1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate ('Crabtree's catalyst', 144 mg) was dissolved in dichloromethane (9 ml) and the resulting solution added to the polymer-bound triphenylphosphine (Aldrich item 3645, nominal 3 mmol of P per gram of resin, 60 mg). The reaction flask was then capped, flushed thoroughly with nitrogen and stirred for 2 h at ambient temperature. The orange supernatant was then decanted from the deep-red polymer and the polymer was washed five times by re-suspension and stirring in dichloromethane (4 ml each time). The supernatant was clear and colorless after the second wash. After drying to constant weight under vacuum, a blood-red solid was obtained (89.3 mg). The catalyst showed no loss of activity when stored for 10 weeks under nitrogen at −20°C. Only around 30% of the activity remained after the same period when stored in air at room temperature.

General labeling procedure on a tritium manifold

The substrate and iridium complex were placed in a small and long thin-necked round-bottom flask and dichloromethane was added. The contents of the flask were frozen and evacuated under high vacuum (<0.001 Torr). Carrier-free tritium gas was introduced at around 500–600 mbar. The flask was closed and allowed to warm to room temperature whereby pressure was approx. 900–1000 mbar. The solution was stirred for 2–3 h (in some cases longer reaction times are required). Stirring was stopped and the reaction flask was frozen in liquid nitrogen. The excess tritium gas was reabsorbed onto a uranium trap. Labile tritium was removed by the addition of 0.5 ml methanol and removal by static vacuum transfer to a waste ampoule. This was repeated a further two times and the ampoule flame sealed for disposal. The remaining reaction residue was subjected first to crude column chromatography to remove excess catalyst and polar material and then to reversed-phase HPLC purification to achieve better than 95% radiochemical purity. The labeled material was analyzed by LC-MS and proton decoupled high field ^{3}H-NMR and compared with the proton NMR of the unlabeled reference material to ascertain the position(s) and degree of labeling.

Conclusion

Significant contributions have emerged over the past 18 years, which have led to an improved understanding of the iridium(I)-mediated process of exchange labeling. A wide variety of catalysts have been tested and developed which often complement one another. The range of catalysts has increased from the simple monodentate to more diverse bidentate complexes, and now includes immobilized systems permitting rapid and convenient work-up. There remains no one all-purpose catalyst that serves all substrates but, having a bank of different catalysts on hand, provides a good chance of labeling success. Limitations remain, which include nitrile-containing substrates, combinations of interfering or catalyst de-activating functional groups, undesired reduction of sensitive olefinic functions and less predictable labeling at alkyl positions, when compared to aryl. Opportunities for improvement also lie in the development of catalysts that take advantage of novel directing groups (other than sp^2 O and N) or which can support potential new mechanisms of regiospecific labeling. In addition to the optimization of existing catalyst systems, entirely new C–H activation complexes are emerging[29] (covered later in this special edition), which like the iridium(I) phosphine systems were developed originally for other applications.

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