REVIEW

Journal of Labelled Compounds and Radiopharmaceuticals

Received 30 March 2010, Accepted 26 April 2010 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.1790

Deuterium exchange promoted by iridium complexes formed *in situ*

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For many exchange processes using iridium catalysts, the use of isolated pre-catalysts may be preferred. However, the generation and use of iridium complexes *in situ* provides a useful option where the intention is to examine a range of ligand systems or where the pre-catalyst is not readily isolated.

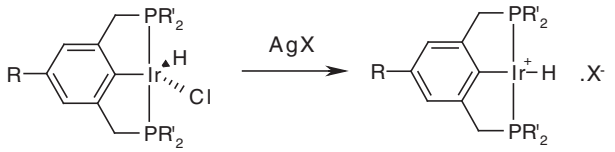
Keywords: *in situ* complexation; iridium; deuteration

Introduction

Many of the catalysts reported to mediate directed *ortho*-deuteration of functionalized arenes suffer from limited stability, both in solution and on prolonged storage. Others, particularly those with three or five formal metal-ligand bonds, are not always amenable to isolation in the first place. In many such cases, the generation of a catalyst *in situ* from stable precursors is an attractive alternative. The results obtained on deuterium exchange using complexes generated and used without isolation are in many cases only slightly inferior to (and sometimes better than) those obtained using the isolated complexes. The *in situ* generation and use of iridium catalysts has enabled the rapid evaluation of different ligands and stoichiometries (Scheme 1) without isolating the pre-catalysts. This article reviews methods for *in situ* complex formation and use along with the more important issues encountered, and attempts to summarize the scope and limitations of the methodology, highlighting some of its more important successes. It is worth noting that in all of the work reviewed, exchange has involved deuterium rather than tritium.

Methods for pre-catalyst formation and *in situ* use

Most of the work reported to date using iridium complexes prepared *in situ* has been aimed at identifying potential exchange catalysts, rather than at their use in tritiation of drug candidates. Moreover, most of the studies reported have involved the preparation and use of pre-catalysts of general form $[IrLL'(cod)]^+ \cdot X^-$ (**1**), $[IrL_3(cod)]^+ \cdot X^-$ (**2**) or $[IrL(cod)]^+ \cdot X^-$ (**3**), the anion X^- most commonly being tetrafluoroborate.



Scheme 1.

Four approaches have been reported for the generation of pre-catalysts **1**-**3** *in situ*. The generally preferred procedure involves treatment of μ-chloro-1,5-cyclooctadieneiridium(I) dimer with ligand (four molar equivalents or two molar equivalents of a bidentate ligand) and silver tetrafluoroborate (two molar equivalents) in dichloromethane.[1] After filtration to remove silver salts and dilution to the desired concentration, the resulting solution is added to the substrate and exposed to deuterium gas. The presence of the desired complex can usually be confirmed by using TLC if a standard is available or, if the complexation is performed in a deuterated solvent, by ^1H and ^{31}P NMR. The results using this method are reproducible and largely consistent with (though usually slightly poorer than) those obtained using the isolated pre-catalyst where it is available. Variation of the silver salt also permits complexes with different non-ligating counterions to be examined; hexafluorophosphate, hexafluoroantimonate and triflate complexes have all been tested, and give comparable results to tetrafluoroborate complexes.[2] Unsatisfactory results were, however, obtained using the analogue of Crabtree's catalyst, $Ir(cod)(Py)(PCy_3)^+BAr_F$, which may be due to an ion-pairing effect blocking substrate access to the iridium centre.[3] Alternatively, the complex is generated in the presence of the substrate, and the mixture exposed to deuterium without removal of the silver salts.[1] This method is not recommended, as the remaining silver salts are prone to be reduced on exposure to deuterium, as evidenced by the formation of a silver mirror on the interior of the flask. The resulting deuterons can promote degradation and inactivation of the iridium catalyst,[4] and can certainly cause acid-mediated deuterium exchange at labile sites. Although such processes can be suppressed by adding a mild inorganic base, sodium carbonate having been established as the most satisfactory, the removal of silver salts prior to use of the

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catalyst is to be preferred. Nevertheless, omission of the silver salt is not an option, as on addition of ligand to $[Ir(cod)Cl]_2$ alone, the resulting species (which would be expected to contain chloride as a fifth ligand) had a very much poorer range of activity.[1] Additionally, and despite the knowledge that the addition of sodium carbonate could be advantageous, it is preferable not to complicate the process by addition of a base. It is therefore best to filter off insoluble silver salts from the catalyst solution before addition of the substrate. A second method, closely related to that above, involves addition of a single molar equivalent each of ligand and silver tetrafluoroborate to a complex Ir(cod)(L)Cl.[5] Of the available methods, this is probably the best suited to the preparation of pre-catalysts **1** where L and L′ are different, including analogues of Crabtree's catalyst[5] and mixed phosphine/arsine complexes.[6]

In the third method, the presence of silver salts is avoided by treatment of *bis*(1,5-cyclooctadiene)iridium tetrafluoroborate with ligand (two molar equivalents) in the presence of a substrate and deuterium gas.[1] Clearly, in this case, ligand coordination will not occur until after removal of at least one cyclooctadiene unit and in some cases coordination of the substrate may be more efficient. This last method gives unreliable results when simple phosphine or arsine ligands are used. This may be a consequence of the inhibition of exchange by cyclooctadiene in the early stages of the process.[5] Nevertheless, this last method seems to be well suited to the preparation of catalysts with bidentate phosphine, *PN* and particularly arsine ligands; most *in situ* studies with the last two ligand classes were carried out using this method.[6] A final method, reported by Salter *et al*,[5] but not recommended, involves treatment of the isolable precursor, $Ir(cod)Py_2 \cdot PF_6$ with a phosphine ligand. This process is used in the preparation of Crabtree's catalyst and related complexes[7] but, in the *in situ* variant, liberated pyridine inhibits the exchange process.

The effects of reaction time and conditions have been examined in some detail, largely using the well-known complexes $Ir(cod)(PPh_3)_2^+ \cdot BF_4^-$ and Crabtree's catalyst, $Ir(cod)(Py)(PCy_3)^+ \cdot PF_6^-$.[2] Complexes of simple phosphine ligands are mostly degraded after a few hours' exposure to deuterium, and so the process reaches an apparent equilibrium after a rapid initial exchange. A result of this is that, for poorly binding substrates at least, exchange is very much less efficient at concentrations below 10 μmol/ml, although with tighter-binding substrates such as *N*-heterocycles, changes in concentration have very much less effect. Exchange is also generally best carried out at room temperature: iridium catalysts are generally degraded more rapidly at higher temperatures but, at the same time, no improvement is apparent when exchange is carried out at reduced temperatures. More surprisingly, increasing the pressure of deuterium does not result in improved exchange for the majority of substrates; it may be that at higher deuterium pressures, the rate of complex degradation is increased to a greater extent than is the rate of exchange. Adventitious water does not appear to cause a significant problem in most cases, although there is some NMR evidence that water may be binding to the iridium centre, and so measures to exclude water are worthwhile where the substrate of interest binds poorly. Addition of excess deuterium oxide results in a very different spectrum of activity, abolishing exchange into poorer substrates, but with a second deuterium oxide-driven exchange pathway apparently operating for many *N*-heterocyclic substrates in particular.

Pentamethylcyclopentiadienyliridium complexes, $Cp^*Ir(PMe_3)(Me)(CH_2Cl_2)B(Ar_F)_4$, are also formed *in situ* by a simpler procedure, in which $Cp^*Ir(PMe_3)(Me)OTf$ is treated with $NaB(Ar_F)_4$ in dichloromethane. These catalysts are effective stoichiometric mediators of deuteration in methyl esters and at β-positions in naphthalenes,[8] and *ortho* to fluorine in fluoroarenes.[9] The activation of chloroiridium(III) pincer complexes is carried out in a similar manner (Scheme 1), with the best results obtained for $X = SbF_6$; the reported activity of these complexes is limited, with modest incorporation into aromatic amides and up to 1.7 D incorporated in a nonspecific manner into 2-phenylpyridine.[10]

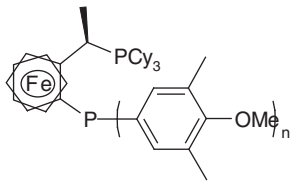
Advantages and disadvantages of *in situ* complex formation

With few exceptions, there is no advantage to be gained by preparing and using an iridium catalyst *in situ* if that catalyst is conveniently prepared and isolated, and is stable on storage for even a limited period. Nevertheless, *in situ* complexation is of considerable use in the search for new catalytic systems, permitting the rapid screening of large numbers of ligand systems, and also permitting the examination of systems where the stoichiometry would not permit isolation of a pre-catalyst, or where binding of the ligand to the metal centre is insufficiently strong to permit isolation of the pre-catalyst. More generally, the use of *in situ* complexation methods has permitted the issues of complex instability and degradation to be addressed. Many isolated pre-catalysts **1** are air-sensitive and have limited shelf lives, even when kept under an inert atmosphere. In these cases, *in situ* preparation and use of a complex is a particularly attractive option. Filtered solutions of many complexes **1** retain activity for at least 7 days when stored under nitrogen at room temperature or below. A more serious concern over stability arises after exposure of the pre-catalyst to deuterium to form the active catalyst. As shown by crossover experiments,[2] many iridium catalysts degrade before isotope exchange can proceed to completion. The degradants formed from iridium hydrogenation catalysts have been characterized in earlier work by Crabtree *et al*, and the degradation process generally appears to involve initial loss of a phosphine ligand.[4] The problem is not alleviated greatly by altering the reaction conditions, but complexes that are most readily prepared *in situ* include some where the reduced catalyst retains activity long enough to promote complete exchange.

Avoiding the need to isolate the iridium pre-catalyst provides a simple means for variation of the metal/ligand stoichiometry. At one extreme, a large excess of phosphine ligand generates a co-ordinatively saturated species, which is catalytically inactive as might be expected. At the other end of the scale, systems containing no added phosphine, where the substrate acts as its own ligand, are of interest in a limited number of cases but suffer from severe instability, with metallic iridium typically precipitating. With complexes **3**, exchange is generally poor, and the more promising results obtained involve substrates that can also act as a ligands for their own exchange.[1] More interestingly, pre-catalysts **2**, of which only $Ir(cod)(PPh_3)_3BF_4$ has been examined in detail, are particularly effective for *ortho*-exchange in ketones. The key to this efficacy appears to be improved complex stability: exchange continues for 48 h, after which time the complex still retains some activity, and results in complete *ortho*-deuteration.[11] This relative stability may be due to nothing

more than the fact that dissociation of a single ligand from **2** gives the corresponding species **1**, which can reassociate a ligand to reform **2**, which is the predominant species in solution from NMR studies.[11] Further dissociation of a ligand and subsequent inactivation is therefore rather less favoured. The price paid for this improvement in stability and activity is a very limited tolerance of steric bulk in the substrate. Moreover, it is not certain that the exchange process proceeds by the generally accepted Heys mechanism in these cases,[11] although equally it is possible that dissociation of a phosphine ligand and subsequent substrate binding occurs, feeding into the Heys mechanism.[12]

Ligands whose binding affinity for the iridium centre is moderate or poor are expected to give rise to complexes, the isolation of which would be difficult, and the stability of which is likely to be poor. These systems are therefore conveniently examined using *in situ* complexation although, in most such cases, the binding centre is not phosphorus, and so the potential for NMR investigation and therefore any useful characterization of the resulting complexes is limited. Nevertheless, complexes **1**, with relatively electron-deficient phosphines, arsines, stibines, triphenylamines, pyridines, phosphine oxides and phosphine sulfides have all been examined. In general, these complexes do not possess useful activity as isotope exchange catalysts, but complexes with pyridine and phosphine oxides have been found to have some useful if limited activity. $Ir(Py)_2(cod)PF_6$ (**1**, L = Py) is readily isolated and is the usual precursor in the synthesis of Crabtree's catalyst.[7] Although the isolated complex possesses little useful activity as an isotope exchange catalyst, the corresponding species, $Ir(Py)_2(cod)BF_4$, prepared *in situ,* was one of the more promising early leads for *ortho*-deuteration of methyl phenyl sulphoxide and benzenesulphonic acid. In this case, TLC and ^1H NMR analyses of the pre-catalyst formed *in situ* were largely consistent with data for the isolated complex, but it must still be concluded that the complex prepared *in situ* is a different (and incompletely characterized) species. Some complexes **1,** where the ligand is a phosphine oxide, are also relatively efficient mediators of *ortho*-exchange into methyl phenyl sulphoxide (although exchange is accompanied by complete reduction to methyl phenyl sulphide) and benzenesulphonic acid, although the substrate tolerance is limited and not all of the phosphine oxide complexes tested display this activity.[15]



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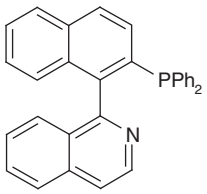

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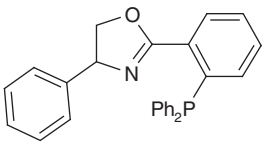

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The results obtained with complexes **2** led to a search for means to stabilize the activated iridium catalysts. The addition of a variety of hemilabile ligands to mimic the effect of the third phosphine in **2** does not extend catalyst lifetime or result in improved exchange.[2] On the other hand, complexes with bidentate ligands should retain their activity for longer than those with simple phosphines. Indeed, promising results have been obtained using complexes of bidentate phosphines[5,6] culminating in the identification of ligand **4**, where the pre-catalyst of form **1** has been isolated and has a broad general spectrum of activity.[6,13] Iridium-*PN* complexes have also been examined and activity optimized using *in situ* complexation methods,[14,15] with the iridium complexes (**1**) of QUINAP (**5**) and Phox ligand **6** both promoting up to 80% exchange into phenylacetamides, as well as into benzamides.[14] Nevertheless, it is clear from kinetic studies and crossover studies that complexes **1** with bidentate phosphine or *PN* ligands still suffer inactivation before isotope exchange reaches completion. A significant improvement in catalyst stability was, however, achieved with the discovery of the bidentate arsine complex, $Ir(cod)(Ph_2AsCH_2CH_2AsPh_2)BF_4$ (**8**). Pre-catalyst **8** has not been isolated in pure form, but it is readily formed *in situ* from $Ir(cod)_2BF_4$ and 1,2-bis(diphenylarsino)ethane.[6] Even after reduction of displaced cyclooctadiene is complete, isotope exchange mediated by **8** is slow, and complete exchange can take up to 5 days. However, the catalyst retains its activity after this time;[2] comparable results are obtained using the homologous system, $Ir(cod)(Ph_2AsCH_2CH_2CH_2AsPh_2)BF_4$ (**9**), which is a useful mediator of exchange into both benzamides and phenylacetamides.[14] The solution stability of the active catalysts derived from **8** and **9** is very much greater than that of the corresponding dppe and dppp complexes,[2] and is believed to be due to stabilization of a low oxidation state intermediate in the catalytic cycle, as a result of the greater π-acidity of arsenic compared with phosphorus.

In general, *in situ* catalyst generation is best suited for the formation and use of catalysts containing a single type of ligand. As mentioned in the preceding section, attempts to form Crabtree's catalyst *in situ* as the tetrafluoroborate salt resulted in a system that possessed little of the activity of the isolated complex. Nevertheless, using the stepwise methodology, where μ-chloro-1,5-cyclooctadieneiridium(I) dimer is treated with a stoichiometric quantity of one ligand to form the intermediate Ir(cod)LCl, and then with a second ligand in the presence of a silver salt to generate the pre-catalyst **1**, has been used successfully for the formation of some complexes bearing two different ligands.[5,6]

Conclusion

The development of methods for the *in situ* formation of iridium-based catalysts and pre-catalysts has permitted the rapid

screening of a wide variety of different ligands for *ortho*-isotope exchange in several different types of substrate. Although in many cases, this has led to identification of specific catalysts that have subsequently been isolated and used directly in this form, there are further examples where useful catalysts are best prepared by *in situ* complexation. In these cases, this represents a valuable technique for isotopic exchange into both simple and complex substrates.

Acknowledgements

The author wishes to thank Dr. R. B. Bedford (University of Bristol) for helpful discussions.

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