Special Issue Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 30 April 2013, Revised 03 June 2013, Accepted 04 June 2013 Published online 19 July 2013 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.3084

Application of neutral iridium(I) *N*-heterocyclic carbene complexes in *ortho*-directed hydrogen isotope exchange†,‡

Alison R. Cochrane,[a] Stephanie Irvine,[a] William J. Kerr,[a]* Marc Reid,[a] Shalini Andersson,[b] and Göran N. Nilsson[b]

Bench-stable complexes of the type [Ir(COD)(NHC)Cl] (NHC = *N*-heterocyclic carbene) have been investigated within the field of hydrogen isotope exchange. By employing a sterically encumbered NHC within such complexes and catalyst loadings of only 5 mol%, moderate to high deuterium incorporations were achieved across a range of aromatic ketones and nitrogen-based heterocycles. The simple and synthetically accessible catalysts reported herein present alternatives to phosphine-based species and increase the available labelling systems with respect to established iridium-based isotope exchange methodologies.

Keywords: *ortho*-hydrogen isotope exchange; *N*-heterocyclic carbene; deuteration; iridium

Introduction

In order to alter the properties of a drug candidate, the chemist must first have a flexible technique with which to study them. To this end, hydrogen isotope exchange (HIE) is widely used as a means to monitor the biological fate of a potential drug molecule.[1,2] Indeed, since the pioneering work of Garnett approaching half a century ago,[3,4] research in the field of HIE has undergone a remarkable evolution, with key developments in synthetic strategies and analytical techniques making this the preferred method in many absorption, distribution, metabolism, and excretion studies.[1]

Despite notable advances in heterogeneous[5–11] and even organocatalytic labelling protocols,[12] it is homogeneous transition metal-catalysed HIE methodologies that have received greatest attention from the pharmaceutical industry. More specifically, the development of *ortho*-directed HIE procedures have allowed for the site-selective, and thus predictable, labelling of aromatic substrates.[13–15] The ultimate benefit of such processes is manifested in the ability to label fully functionalised drug candidates in one synthetic step, with no dependence on (or necessity for) isotopically enriched starting materials. Indeed, since Lockley's discovery in the early 1980s that aromatic carboxylic acids and anilides could be labelled regioselectively using $RhCl_3$,[16–18] a series of notable advances in *ortho*-directed HIE have emerged in the 30 years that have followed. From 1992 onwards, the most remarkable advances have centred on iridium-based catalysts akin to those first pioneered by Heys.[19,20] In this regard, manipulation of the catalyst coordination sphere has spawned a selection of useable Ir(I) species, including those that employ *bis*-phosphine,[21–26] bidentate phosphine,[21,27] arsine[23,27] and acetoacetate[28,29] ligand systems. Among these, commercially available *Crabtree's catalyst*, [(COD)Ir(PCy_3)(py)]PF_6,[30] is perhaps the most widely used, despite the regular necessity for stoichiometric quantities of catalyst.[22,31–34]

To circumvent issues of high catalyst loadings, our efforts have focused on novel mixed NHC-phosphine systems, [(COD)Ir(NHC)(PR_3)]PF_6, **1**, as a means of introducing hydrogen isotopes with enhanced levels of overall efficiency (Figure 1). Preliminary studies in this area have now allowed expedient access to a series of novel iridium complexes,[35] many of which were previously inaccessible.[36,37] Moreover, by judicious and careful manipulation of the ligands supporting the iridium centre, these electron-rich and sterically encumbered catalysts have emerged to become some of the most active species known in this area of labelling chemistry.[14,35,38] Additionally, and outside of labelling science, the utility of these catalysts has recently been extended, with these species now proving to be highly active in the selective reduction of alkenes[39] and in *Z*-selective dimerization of terminal alkynes.[40]

With close regard to the overall steric bulk of these complexes, we have shown previously that more encumbered ligand systems produce the most efficient catalysts.[35] In relation to this, and with the recent expansion in the range of NHC ligands applicable in this area of chemistry, high-yielding syntheses of

[a]*Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, UK*

[b]*Medicinal Chemistry, AstraZeneca, R&D Mölndal, Mölndal SE-431 83, Sweden*

**Correspondence to: Professor William J. Kerr, Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, UK.*
E-mail: w.kerr@strath.ac.uk

† *This article is published in Journal of Labelled Compounds and Radiopharmaceuticals* as a special issue on *Special Issue IIS 2012 Heidelberg Conference*, edited by *Jens Atzrodt* and *Volker Derdau, Isotope Chemistry & Metabolite Synthesis, DSAR-DD, Sanofi-Aventis Deutschland GmbH, Industriepark Höchst G876, 65926 Frankfurt am Main, Germany*.

‡ *Supporting information may be found in the online version of this article.*

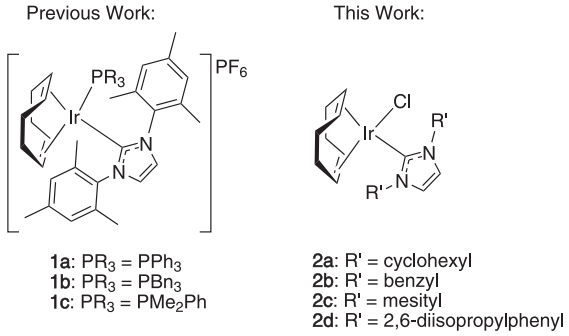


Figure 1. HIE catalysts under study.

catalyst intermediate structures, [(COD)Ir(NHC)Cl], **2a-d**, have facilitated the synthesis and diversification of structural analogues of catalysts **1a-c**. Moreover, as we have routinely synthesised structures **2a-c** en route to more intricate catalyst systems such as **1**, we were curious to note whether or not complexes of type **2** were catalytically active within HIE processes in their own right. In this article, we report for the first time on the application of the less elaborate complexes **2a-d** in *ortho*-directed HIE processes, comparing their overall utility relative to our more established catalyst systems.

Experimental

For full details on all experimental procedures, including catalyst syntheses and individual labelling reaction processes, please see the *Supporting Information*.

Synthesis of catalyst 2c[41a]

A stock solution of 1 M sodium ethoxide was prepared by dissolving sodium metal (0.25 g) in ethanol (10 mL). A solution of η^4-cycloocta-1,5-dieneiridium(I) chloride dimer (0.400 g, 0.595 mmol) in dry benzene (10 mL) was prepared in a flame-dried Schlenk tube under argon. To the benzene solution was added 1 M sodium ethoxide (1.2 mL, 1.2 mmol), resulting in a red to yellow colour change. After stirring the solution for 10 min at r.t., 1,3-dimesitylimidazolium chloride (0.406 g, 1.191 mmol) was added in one portion. The solution was stirred for 72 h at 45°C under Ar, resulting in a gradual colour change from yellow to orange. The solvent was subsequently removed in vacuo, and the residue purified directly via flash column chromatography, eluting the yellow fraction with ethyl acetate/hexanes (1:1). The combined yellow fractions were concentrated under reduced pressure. The desired yellow, crystalline solid precipitated from the resultant oil on addition of petroleum ether.

FTIR (neat): 3092, 3009, 2916, 2876, 1609 and 1485 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99–6.96 (2 × bs, 4H, ArH), 6.93 (s, 2H, ArH), 4.14–4.10 (m, 2H, COD CH), 2.96–2.94 (m, 2H, COD CH), 2.34 (s, 12H, $ArCH_3$), 2.14 (s, 6H, $ArCH_3$), 1.74–1.59 (m, 4H, COD CH_2) and 1.33–1.21 (m, 4H, COD CH_2).
^{13}C NMR (100 MHz, $CDCl_3$): δ 181.0, 138.8, 137.6, 136.3, 134.6, 133.0, 129.7, 128.3, 123.5, 82.8, 66.1, 51.6, 33.7, 29.2, 21.4, 19.9 and 15.5.

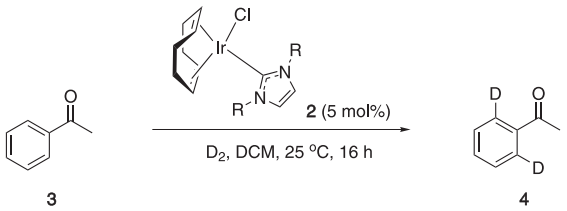
Standard hydrogen isotope exchange procedure

A flame dried and argon cooled 100 mL three-neck round bottomed flask, equipped with two stopcock valves and a suba seal, was charged with the iridium complex (5 mol%) and dry dichloromethane (2.5 mL), followed by the substrate (0.215 mmol). The suba seal was replaced by a glass stopper fitted with a Teflon® sleeve, and the reaction vessel was cooled to −78 °C in a dry ice/acetone bath, prior to being purged twice with nitrogen. The flask was then evacuated and filled with deuterium gas via balloon. The flask was removed from the slurry and allowed to warm to room temperature. (NOTE: the glass stopper must be physically restrained as the reaction mixture warms to room temperature). The reaction mixture was then allowed to stir vigorously at room temperature for 16 h. The level of isotope incorporation into the substrate was determined by ^{1}H NMR analysis of the reaction products. As such, the residual proton signal from the site of incorporation was compared against that of a site where incorporation was not expected to occur. Each reaction was carried out in duplicate.

Results and discussion

In our initial experiments, chloro-carbene complexes **2a-d** were employed in the *ortho*-directed labelling of acetophenone, **3**, under our optimised reaction conditions (Scheme 1, Table 1).[35] Interestingly, whereas complexes **2a** and **2b**, holding sterically smaller NHC ligands, failed to catalyse the reaction to any appreciable extent, more encumbered analogues **2c** and **2d** proved to be remarkably efficient HIE catalysts. This supports our previous hypothesis that a sterically encumbered coordination sphere is a necessary trait in such HIE catalyst systems.[35,41] Having said this, it is also evident from these reference reactions that, in moving from the optimum system in **2c** to an even more encumbered NHC, as in **2d**, catalyst efficiency deteriorates. Indeed, all attempts to form HIE catalysts of type **1** from **2d** have thus far failed,[42] indicating that the ligand sphere around the iridium centre is already too congested and cannot accommodate the introduction of a phosphine ligand.

Having identified **2c** as a highly efficient catalyst in the labelling of acetophenone, we were keen to investigate the effective substrate scope of this system (Scheme 2, Table 2). Towards this aim, a series of *para*-substituted aryl ketones were

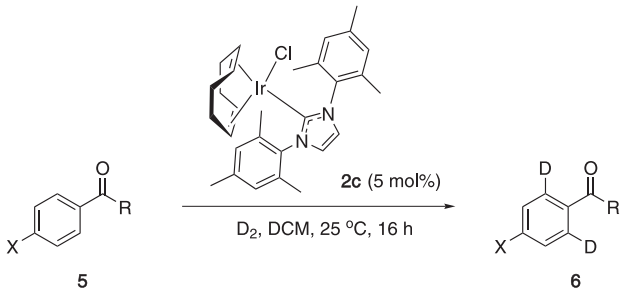


Scheme 1. Catalyst screening.

Table 1. Labelling of acetophenone

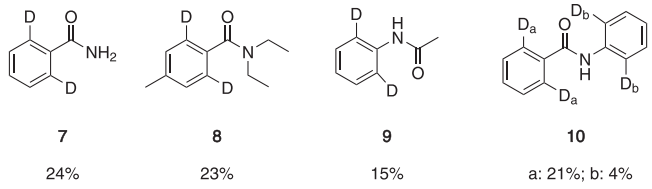
Entry	Catalyst	% D[‡]
1	**2a**	7
2	**2b**	5
3	**2c**	97
4	**2d**	87

[a]Average incorporation into the positions shown over two separate reaction runs; the percentage given refers to the level of D incorporation over the total number of positions possible, e.g. 97% for the two possible positions in Entry 3 indicates 1.94 D incorporation.



5 6

Scheme 2. Labelling of aryl ketones.



7 8 9 10

24% 23% 15% a: 21%; b: 4%

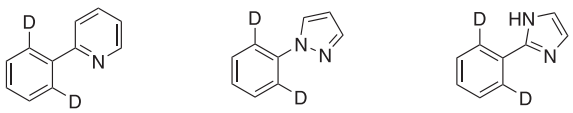
Conditions: **2c** (5 mol%), D_2 (1 atm), DCM (2.5 mL), 25 °C, 16 h

Figure 2. Labelling of aryl amides.

Table 2. Labelling of aryl ketones

Entry	X	R	% D[a]
1	OMe	Me	97
2	Ph	Me	84
3	F	Me	77
4	Cl	Me	76
5	Br	Me	62
6	I	Me	15
7	H	Ph	94
8	H	Et	93
9	H	*n*-Bu	62
10	H	*t*-Bu	41

[a]Average incorporation into the positions shown over two separate reaction runs; the percentage given refers to the level of D incorporation over the total number of positions possible.



11 12 13

88% 93% 96%

Conditions: **2c** (5 mol%), D_2 (1 atm), DCM (2.5 mL), 25 °C, 16 h.
% D reported as an average of two runs.

Figure 3. Labelling of *N*-based heterocyclic compounds.

studied, with good to excellent levels of deuterium incorporation being achieved for both electron-donating and electron-withdrawing substitution (Entries 1 and 2–4, respectively). However, on moving to bromo-derivatives or iodo-derivatives, the labelling efficiency of **2c** proved to be less effective (Entries 5 and 6, respectively); this reduced exchange efficiency could be a consequence of the relatively and perceived lowered electrophilicity of the chloro-carbene catalyst in combination with less readily coordinating substrates. Our investigations then progressed toward labelling more sterically encumbered aryl ketones. Pleasingly, benzophenone and 1-phenyl-1-propanone were both found to undergo highly efficient *ortho*-labelling with **2c** (Entries 7 and 8, respectively). On labelling further extended and branched alkyl derivatives of acetophenone, more moderate levels of deuterium incorporation were achieved under the operative reaction conditions (Entries 9 and 10).

To further investigate the variety of substrates amenable to deuterium labelling with chloro-carbene catalyst **2c**, a series of aryl amides was investigated. Unfortunately, in all cases, lowered levels of deuterium incorporation were observed (Figure 2). This observation held true for benzamide, **7**, and toluoyl amide, **8**, which would be labelled via a five-membered metallocycle (5-mmi), and for acetanilide, **9**, in which deuterium would be incorporated via a more energetically demanding 6-mmi. Interestingly, in the case of benzanilide, **10**, which has the capacity to be labelled via both 5-mmi and 6-mmi, almost exclusive labelling in the *a*-ring (via a 5-mmi) was found, albeit with low overall levels of D incorporation. These findings are in contrast to those reported previously when catalysts **1a-c** were employed, with high levels of deuterium incorporation having been achieved across all substrates **7-10**.[35] Despite the good general levels of effectiveness found to this stage with catalyst **2c**, this highlights a notable limitation in the utility of this species and, indeed, demonstrates the necessity for the use of cationic NHC-phosphine complexes of the type **1** towards achieving the widest possible substrate scope.

In our final study, we investigated the propensity for **2c** to mediate *ortho*-HIE using nitrogen-based heterocyclic functionalities as the key directing group. As such, we are pleased to report the highly efficient labelling with pyridine, **11**, pyrazole, **12**, and imidazole, **13**, using catalyst **2c** under the remarkably mild reaction conditions shown in Figure 3.

Conclusions

The results presented herein show that synthetically accessible chloro-carbene complexes, such as **2c** and **2d**, bearing sterically encumbered NHC ligands, are effective catalysts for the *ortho*-directed labelling of simple organic substrates. Moreover, complex **2c** proved to be more generally efficient than **2d**, suggesting an optimal ligand size in the former species; for further studies showing the more limited applicability of **2d**, see the *Supporting Information*. Although this overall study provides more direct evidence for the necessity for more elaborate and activated complexes, such as **1**, this work expands the range of HIE catalysts available to the labelling chemist, with the establishment of *ortho*-directed HIE protocols using a simple and readily accessible chloro-iridium(NHC) species. Moreover, this work also supports our further explorations into the development of extended novel catalysts for application in HIE and other transformations.

Acknowledgements

The authors are grateful to both AstraZeneca (ARC, SI) and The Carnegie Trust (MR) for funding. Mass spectrometry data was acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Conflict of Interest

The authors did not report any conflict of interest.

References

[1] E. M. Isin, C. S. Elmore, G. N. Nilsson, R. A. Thompson, L. Weidolf, *Chem. Res. Toxicol.* **2012**, *25*, 532.
[2] For a recent review, see: W. J. S Lockley, A. McEwen, R. Cooke, *J. Label. Compd. Radiopharm.* **2012**, *55*, 235.
[3] J. L. Garnett, R. J. Hodges, *J. Am. Chem. Soc.* **1967**, *89*, 4546.
[4] M. R. Blake, J. L. Garnett, I. K. Gregor, W. Hannan, K. Hoa, M. A. Long, *J. Chem. Soc., Chem. Commun.* **1975**, 930.
[5] J. R. Jones, W. J. S. Lockley, S.-Y. Lu, S. P. Thompson, *Tetrahedron Lett.* **2001**, *42*, 331.
[6] S. Matsubara, Y. Yokota, K. Oshima, *Chem. Lett.* **2004**, *33*, 294.
[7] S. Matsubara, Y. Yokota, K. Oshima, *Org. Lett.* **2004**, *6*, 2071.
[8] H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, K. Hirota, *Org. Lett.* **2004**, *6*, 1458.
[9] H. Sajiki, T. Kurita, H. Esaki, F. Aoki, T. Maegawa, K. Hirota, *Org. Lett.* **2004**, *6*, 3521.
[10] Y. Sawama, Y. Monguchi, H. Sajiki, *Synlett* **2012**, *23*, 959.
[11] M. L. J. Hickey, L. P. Kingston, W. J. S. Lockley, P. Allen, A. Mather, D. J. Wilkinson, *J. Label. Compd. Radiopharm.* **2007**, *50*, 286.
[12] S. Duttwyler, A. M. Butterfield, J. S. Siegel, *J. Org. Chem.* **2013**, *78*, 2134.
[13] P. H. Allen, M. J. Hickey, L. P. Kingston, D. J. Wilkinson, *J. Label. Compd. Radiopharm.* **2010**, *53*, 731.
[14] a) G. N. Nilsson, W. J. Kerr, *J. Label. Compd. Radiopharm.* **2010**, *53*, 662; b) R. Simonsson, G. Stenhagen, C. Ericsson, C. S. Elmore, *J. Label. Compd. Radiopharm.* **2013**, *56*, 334.
[15] J. R. Heys, *J. Label. Compd. Radiopharm.* **2007**, *50*, 770.
[16] W. J. S. Lockley, *Tetrahedron Lett.* **1982**, *23*, 3819.
[17] W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1984**, *21*, 46.
[18] W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1985**, *22*, 623.
[19] J. R. Heys, *J. Chem. Soc., Chem. Commun.* **1992**, 680.
[20] J. R. Heys, A. Y. L. Shu, S. G. Senderoff, N. M. Phillips, *J. Label. Compd. Radiopharm.* **1993**, *33*, 431.
[21] A. Y. L. Shu, W. Chen, J. R. Heys, *J. Organomet. Chem.* **1996**, *524*, 87.
[22] G. J. Ellames, J. S. Gibson, J. M. Herbert, W. J. Kerr, A. H. McNeill, *Tetrahedron Lett.* **2001**, *42*, 6413.
[23] P. W. C. Cross, G. J. Ellames, J. S. Gibson, J. M. Herbert, W. J. Kerr, A. H. McNeill, T. W. Mathers, *Tetrahedron* **2003**, *59*, 3349.
[24] G. J. Ellames, J. S. Gibson, J. M. Herbert, W. J. Kerr, A. H. McNeill, *J. Label. Compd. Radiopharm.* **2004**, *47*, 1.
[25] J. R. Heys, C. S. Elmore, *J. Label. Compd. Radiopharm.* **2009**, *52*, 189.
[26] R. Salter, *J. Label. Compd. Radiopharm.* **2010**, *53*, 645.
[27] J. M. Herbert, A. D. Kohler, A. H. McNeill, *J. Label. Compd. Radiopharm.* **2005**, *48*, 285.
[28] L. P. Kingston, W. J. S. Lockley, A. N. Mather, E. Spink, S. P. Thompson, D. J. Wilkinson, *Tetrahedron Lett.* **2000**, *41*, 2705.
[29] B. McAuley, M. J. Hickey, L. P. Kingston, J. R. Jones, W. J. S. Lockley, A. N. Mather, E. Spink, S. P. Thompson, D. J. Wilkinson, *J. Label. Compd. Radiopharm.* **2003**, *46*, 1191.
[30] R. H. Crabtree, H. Felkin, G. E. Morris, *J. Organomet. Chem.* **1977**, *144*, 205.
[31] D. Hesk, P. R. Das, B. Evans, *J. Label. Compd. Radiopharm.* **1995**, *36*, 497.
[32] M. Vliegen, P. Haspeslagh, W. Verluyten, *J. Label. Compd. Radiopharm.* **2012**, *55*, 155.
[33] S. C. Schou, *J. Label. Compd. Radiopharm.* **2009**, *52*, 376.
[34] D. Hesk, C. F. Lavey, P. McNamara, *J. Label. Compd. Radiopharm.* **2010**, *53*, 722.
[35] J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson, G. N. Nilsson, *Chem. Commun.* **2008**, 1115.
[36] L. D. Vázquez-Serrano, B. T. Owens, J. M. Buriak, *Chem. Commun.* **2002**, 2518.
[37] L. D. Vázquez-Serrano, B. T. Owens, J. M. Buriak, *Inorg. Chim. Acta* **2006**, *359*, 2786.
[38] Catalysts **1a-c** are available commercially from Strem Chemicals.
[39] L. S. Bennie, C. J. Fraser, S. Irvine, W. J. Kerr, S. Andersson, G. N. Nilsson, *Chem. Commun.* **2011**, *47*, 11653.
[40] C. D. Forsyth, W. J. Kerr, L. C. Paterson, *Synlett* **2013**, *24*, 587.
[41] For a comprehensive study on quantifying NHC characteristics, see: a) R. A. Kelly III, H. Clavier, S. Giudice, N. M. Scott, E. D. Stevens, J. Bordner, I. Samardjiev, C. D. Hoff, L. Cavallo, S. P. Nolan, *Organometallics* **2008**, *27*, 202; b) H. Clavier, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 841.
[42] A. R. Cochrane, *PhD Thesis*, University of Strathclyde, **2012**.