Evaluation of a P,N-Ligated Iridium(I) Catalyst in Hydrogen Isotope Exchange Reactions of Aryl and Heteroaryl Compounds

Mégane Valero[a], Annina Burhop[a], Kristof Jess[b], Remo Weck[a], Matthias Tamm[b]*, Jens Atzrodt[a] and Volker Derdau[a].*

Abstract: We have developed a novel and efficient iridium-catalyzed hydrogen isotope exchange (HIE) reaction method with secondary and tertiary sulphonamides at ambient temperatures. Furthermore N-oxides and phosphonamides have been successfully applied in HIE reactions with moderate to excellent deuterium introduction.

Introduction

The catalytic activation of carbon–hydrogen bonds has been in the spotlight of research for several decades.[1, 2] Besides numerous investigations on C–H activation and C–H functionalization towards C–C,[3] C–X,[4] C–N,[5] or C–O,[6] bond formation, particularly the hydrogen isotope exchange (HIE)[7] for selective installation of C–D[8] and C–T[9] bonds is of practical importance. The HIE reaction enables a direct deuteration or tritium labeling of the desired target molecule without the need for additional synthetic steps e.g., precursor synthesis or multi-step routes from isotopically labelled building blocks. Thus, HIE is commonly employed to deliver deuteration or tritium into organic molecules.[10]

Both hydrogen isotopes are well known for their utility in mechanistic, spectroscopic and tracer studies with applications in almost every sub-discipline of the life sciences.[11] Deuterium proved to be an indispensable analytical tool for relative and absolute quantification,[12] for delineation of metabolic pathways[13] and for investigation of responses to various stimuli.[14] The evolution of the LC/MS technologies in recent years and the ability for precise measurement of isotope ratios promotes a dynamic view on biosynthetic pathways, protein turnover, and systems-wide metabolic networks and thus has paved the way for a number of scientific breakthroughs in biomedical research.[15] Selective deuterium incorporation (“heavy drugs”) can alter ADME properties and may result in potential beneficiary properties such as reduced systemic clearance, higher systemic exposure as well as reduced formation of toxic or reactive metabolites while retaining the potency of the original drug.[16] In order to gain qualitative and quantitative assessment of drug distribution, metabolism and excretion in preclinical species and in the human body,[17] tritium is another essential tool for determining the fate of the drug molecule and for distinguishing drug-related from endogenous components in complex biological systems.[18] Thus, tritium tracers are widely utilized for ADME-profiling[19, 20] of new drug candidates but also as discovery tool for photoaffinity labelling[21] and for radioligand,[22] protein[23] and covalent binding[24] assays.

Additionally, the commercial catalysts developed by Crabtree and Kerr, i.e. [(cod)Ir[(PPh3)3(py)]PF6 (1)[25] and [(COD)Ir(IMes)(PR3)]PF6 (2),[26] utilizing T2 gas as tritium source have leveraged the routine use of HIE for highly selective tritium labelling of organic molecules.[27] The very high selectivity of the H/T exchange for the ortho-position next to a directing group enables a specific tritium introduction into biological and chemical stable positions. In consequence, those HIE methods facilitated a possibility to overcome metabolic stability issues associated with earlier tritiation methods. These had created a rather conservative attitude of ADME scientists towards the use of tritium-labelled compounds in the past.[28] In particular, Kerr’s catalysts are widely applied for mild and selective ortho-labelling employing a broad range of directing groups such as ketones, amides, esters, primary sulphonamides, aldehydes and several heterocycles.[29] Despite recent progress, a number of interesting

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Supporting information for this article is given via a link at the end of the document. ((Please delete this text if not appropriate))
functionalties, ubiquitous throughout drug motives, still present significant challenges for established HIE protocols.

Some of those limitations could be recently overcome by introduction of a new generation of Ir-catalysts with bidentate ligands. The highly air- and moisture-sensitive, non-commercial catalysts 4 with phosphine-oxazoline P,N ligands, originally developed by Pfaltz for asymmetric hydrogenation of olefins, proved efficient also in the HIE reaction of weakly coordinating substrates such as sulphones and secondary sulphonamides. Based on a comprehensive screening of readily available Ir-catalysts, we recently identified another hydrogenation catalyst to have also a remarkable HIE capacity, viz. the commercial, air-stable Burgess catalyst 5. With this catalyst, we have developed the first practical HIE protocol for selective ortho-deuteration of various secondary and tertiary sulphonamides as well as sulphonyl ureas. A similar reactivity was also observed for monodentate Kerr catalysts of the type [(COD)Ir(NHC)Cl] which proved even more efficient in the HIE reaction of secondary sulphonamides and ureas, while 5 resulted in greater deutrium incorporation for tertiary sulphonamides. This method was also applied to sulphur drugs and even adopted to the special conditions required for selective tritium labelling (5–10 eq. of T2 gas, low pressure). However, the elevated temperatures of 100–120°C required to obtain reasonable deutrium incorporation still remains an important limitation of this method.

Recently, we have developed another C-H activation catalysts, [(tBuP,NMe)Ir(cod)]BArF24 (6), with bidentate P,N ligands bearing the imidazolin-2-imine group as an electron-rich nitrogen donor group. In addition to the high HIE reactivity for known directing groups such as acetyl, heterocycles, sulphones, nitro groups and benzyl amines, 6 proved to be also highly active for H/D exchange of Boc-protected anilines, which had not been recognized previously as a directing group for HIE. After optimization, even substrates with the weakly coordinating methoxy group showed a remarkable degree of deuteration. In continuous efforts to broaden our synthetic repertoire for fast HIE reactions, we have further investigated the substrate scope of 6 in more detail and wish to report on expanded applications of the new catalyst system 6.

Results and Discussion

We started to evaluate Tamm’s catalyst 6 in the HIE reaction of tertiary sulphonamide 7 in different solvents at room temperature. To our great delight, we found high deutrium incorporation in chlorobenzene (Table 1). The catalytic HIE reaction with our model substrate 7 was strongly influenced by the solvent. In most solvents, none or only poor deutrium exchange was observed; however, high deutrium incorporation was found in chlorobenzene (entry 9). The strong influence of chlorobenzene in HIE reactions has been observed earlier however the effect is still lacking a full theoretical understanding.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>%D 7a[%]</th>
<th>Yield 7a[%]</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>dichloromethane</td>
<td>22</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>chloroform</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>MTBE</td>
<td>11</td>
<td>79</td>
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<td>0</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>cyclohexane</td>
<td>15</td>
<td>67</td>
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<tr>
<td>6</td>
<td>MeTHF</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
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<td>isopropylacetate</td>
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<td>79</td>
</tr>
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<td>chlorobenzene</td>
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<tr>
<td>11</td>
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\[][Conditions: substrate 7 (10 µmol, 2.5 mg), catalyst 6 (10 mol%), solvent (2 mL), D2 (1 atm), rt, 2 h. Positions and percentage of deutrium incorporation determined by 1H NMR. Isolated yield.

We then studied the HIE reaction of sulphobenzenes under the optimized reaction conditions (Scheme 2). The catalyst revealed high reactivity and deutrium incorporation in the HIE reactions of primary, secondary and even tertiary sulphonamides. In the case of the primary sulphonamide 8, catalyst 6 showed similar degree of deuterium incorporation as compared to the results reported by Kerr with catalyst 3 at room temperature. Interestingly, with 6 secondary (9–11) and tertiary (12–15) sulphonamides underwent successful HIE reactions at room
temperature as well, which was achieved previously with catalysts 3 and 5 only at elevated temperatures (> 80–120°C).[32]

**Scheme 2**: HIE reactions of sulphobenzenes catalyzed by 6.a,b

a) Conditions: substrate (22 µmol), catalyst 6 (10mol%), chlorobenzene (2 mL), D₂ (1 atm), rt, 2 h. b) Positions and percentage of deuterium incorporation determined by ¹H NMR and confirmed by LC-MS isolated yields, all reactions have been repeated at least twice.

Next, we examined N-oxides as substrates for the directed HIE reaction with catalyst 6 (scheme 3). N-Oxides have rarely been described as directing groups in HIE reactions,[36] which would in principle enable the labeling of pyridines or quinolines after reductive cleavage of the N-O bond. This HIE approach can be convenient if direct labeling in the ortho-positions of the heterocyclic nitrogen atom (Rh black, D₂O[37] or THF-D₂[38]) cannot be accomplished or if higher specific activities in the case of tritium introduction are required.

In particular, the deuteration of the quinolone moiety in substrates 16–18 proceeded considerably well and selectively, irrespective of other aromatic substituents. The 2- and 8-positions of 3-methylquinolin N-oxide 16 were deuterated in 73% and 100%, respectively. Similar results were obtained for 3-bromoquinolin N-oxide 17 and 6-methoxyquinolin N-oxide 18 with deuteration incorporation in these positions higher than 80%. Interestingly, the level of deuterium introduction dropped to approx.50% at the 3-position in isoquinoline N-oxide 19 and in simple pyridine N-oxides 20 and 21. Since the 1-position of isoquinoline N-oxide 19 was still exchanged by deuterium in 93%, a significant electronic effect can be considered as the steric differences between the 1- and 3-position are comparatively small.

**Scheme 3**: HIE reactions of N-oxides catalyzed by 6.a,b

a) Conditions: substrate (5 µmol), catalyst 6 (10mol%), chlorobenzene (2 mL), D₂ (1 atm), rt, 2 h. b) Positions and percentage of deuterium incorporation determined by ¹H NMR and confirmed by LC-MS isolated yields, all reactions have been repeated at least twice.

Furthermore, we have examined phosphonamides as they have never been applied in ortho-directed HIE reactions before. To our great delight, we found good to excellent H/D exchange in the reaction of primary 22 (82%), secondary 23, (70%) and tertiary phosphonamides 24–27 (60–99%).

**Scheme 4**: HIE reactions of phosphonamides catalyzed by 6.a,b

a) Conditions: substrate (10 µmol), catalyst 6 (10mol%), chlorobenzene (1 mL), D₂ (1 atm), rt, 2 h. b) Positions and percentage of deuterium incorporation determined by ¹H NMR and confirmed by LC-MS, isolated yields, all reactions have been repeated at least twice.

**Conclusion**

We have extended the use of the newly discovered catalyst 6 by evaluation of the HIE reaction with sulphonamides, N-oxides and phosphonamides under mild reaction conditions. The results emphasize the usefulness of this air-stable catalyst, and in the case of sulphonamides, it seems to be more active than other commercially available iridium catalysts.
Experimental Section

General: All substrates and solvents were obtained from commercial suppliers and used without further purification, except for the phosphonamides 23-27 (the preparation is described in the supporting information). Catalyst 6 was synthesized according to procedures reported earlier.[35] All labelling reactions were carried out on a Heidolph Synthesis 1 Liquid 16 device. Flash column chromatography was carried out using Merck kieselgel 60 silica gel (particle size: 63-200). \(^1\)H (300, 500 MHz) and \(^{13}\)C (75, 125 MHz) NMR spectra were obtained on Bruker spectrometers in the solvents indicated. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to \(^3\)J H-H couplings, unless otherwise stated. The distribution of hydrogen isotopes in the products was determined by a liquid chromatography-mass spectrometry (LC-MS) system with a Symmetry Shield RP18 column, 3.9 x 150 mm, with a gradient program. LC column conditions were as follows: mobile phase A: water (900 mL), acetonitrile (100 mL), TFA (1 mL) mobile phase B: water (100 mL), acetonitrile (900 mL), TFA (0.75 mL), Flow rate: 0.6 mL/min; Detection: UV 254 nm and UV 210 nm.

General deuteration procedure: To a carousel tube was added the substrate of choice (0.086 mmol, unless otherwise stated) and iridium(I) catalyst (0.0043 mmol, 10 mol%, unless otherwise stated) under air. The desired solvent (1 or 2 mL) was added, rinsing the inner walls of the tube. The tube was then sealed at the screw cap (with gas inlet left open) under air before initiating the carousel shaking motion (720 rpm) and setting the reaction temperature (25 °C). The flask was twice evacuated and flushed with deuterium via a balloon. The carousel tube gas inlet was then closed, creating a sealed atmosphere of deuterium. After sealing the flask, the reaction timer was started, and a quick red to clear/yellow colour change was observed. The reaction mixture was stirred for 2 h before removing excess deuterium and replacing with air. The yellow solution was then washed with DCM and transferred to a single necked flask before removing the solvent under reduced pressure. The residue was filtered through a short plug of silica, eluting with MTBE/ethylacetate (4/1) (2 x 3 mL) or DCM/MeOH (95/5) depending on the substrate of choice. An LC-MS sample (~2 μL) was taken directly from the combined filtered fractions. The solvent was evacuated again and the residue analysed directly by \(^1\)H-NMR. The level and regioselectivity of deuterium incorporation in the substrate was determined by \(^1\)H-NMR. The integrals were calibrated against a peak corresponding to a position not expected to be labelled.

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We have developed an efficient iridium-catalyzed hydrogen isotope exchange (HIE) reaction method with secondary and tertiary sulphonamides at ambient temperatures applying a recently discovered P,N-ligated iridium catalyst. Furthermore N-oxides and sulphonamides at ambient time, solvent

directing group

[Ir] = 

DG = directing group

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FULL PAPER

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HIE reactions with moderate to excellent deuterium incorporation.