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Communication

Application of iridium pincer complexes in hydrogen isotope exchange reactions

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Abstract

Iridium pincer complex catalyzed hydrogen to deuterium exchange could be achieved using aromatic and heteroaromatic substrates. The reactions proceed under mild conditions and with high regioselectivity. The efficiency of the hydrogen isotope exchange reaction depends on the electronic properties of the pincer complex catalyst.

Keywords: Pincer complexes; Iridium; Catalysis; Deuterium; Hydrogen isotope exchange

Attrition or high failure rate has emerged as a central problem of modern drug development and therefore the design of drugs with optimal potency and pharmacokinetic properties as well as increased safety profile poses a major challenge. Absorption, distribution, metabolism, excretion and toxicology (ADMET) studies are widely used in drug discovery and development to help obtain an optimal balance of properties necessary to convert lead compounds into drugs that are safe and effective in humans. In order to decrease the attrition rate most pharmaceutical industries have moved towards front-loading of ADMET studies into the discovery phase to address possible clinical liabilities. Deuterium and tritium isotope labelled compounds are widely used in the ADMET studies. Hydrogen isotope exchange (HIE) reactions offer a very attractive synthetic tool to access deuterium and tritium labelled compounds.

The most important advantage of the HIE techniques is that these procedures do not require special precursors, hydrogen atoms of drug molecules can be directly exchanged with deuterium or tritium. Currently the most common catalysts employed for hydrogen isotope exchange reactions are iridium-based organometallic complexes, such as Crabtree's catalyst **1** (Scheme 1) [1].

Although, Crabtree's catalyst and other commonly employed organo-iridium complexes have an excellent performance [2] in hydrogen isotope exchange processes, use of these complexes impose certain synthetic limitations as well. One problem is the relatively low stability of these complexes, which are prone to form catalytically inactive di- and trimeric iridium species. Another problem arises from the coordinative interactions between the iridium atom of the complex and the functionalities of the labelled substrate [2,3]. These difficulties could be avoided by application of robust and highly selective iridium complexes in the HIE reactions. A possible solution for the above-mentioned problems would be application of the so-called pincer complexes as catalysts [4–6]. These complexes are known to be highly stable and easily tunable for selective organic transformations [5–13]. The synthesis of the first iridium PCP pincer complex was reported by Moulton and Shaw [7]. Several research groups, such as Jensen and co-workers [8], Goldman and co-workers [9], Leitner and Six [10], Brookhart and co-workers [11], employed these complexes as catalysts in dehydrogenation reaction of hydrocarbons. Recently, Hartwig and co-workers [13] reported a new application of iridium PCP-pincers for

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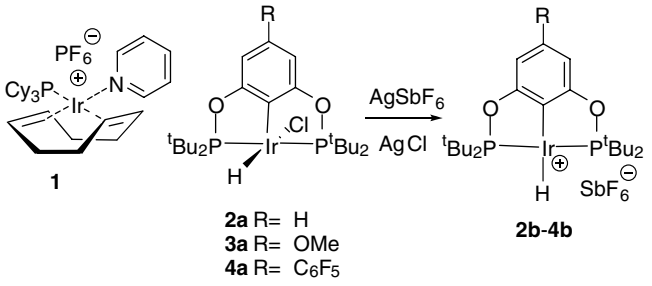


Scheme 1.

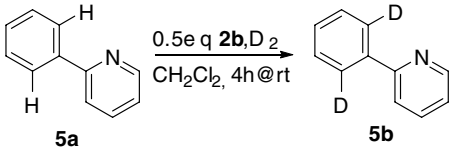
nitrogen–hydrogen bond activation in ammonia. Considering the fact that iridium pincer complexes perform well in carbon–hydrogen and nitrogen–hydrogen bond activation processes, it is appealing to attempt HIE processes with these catalysts. We have now found that iridium pincer complexes **2a**–**4a** [11] (Scheme 1) are promising catalysts in these reactions. Pincer complexes **2a**–**4a** were prepared according to the procedure reported by Brookhart and co-workers [11]. Although, complex **2a** showed some HIE activity (entry 1, Table 1 and Scheme 2), it was found that the pincer complex catalysts can be efficiently activated [11,14] by exchange of the chloride counter ion with a weakly coordinating anion via exchange with silver salts. The best results could be achieved by conversion of **2a** with $AgSbF_6$ providing **2b** as active HIE catalyst (entry 4, Table 1 and Scheme 1).

In a typical reaction, the corresponding substrate (**5a**–**b**, **7** or **8**, 40 μmol) in 1 mL CH_2Cl_2 was added to a mixture of **2a** [11] (20 μmol) and $AgSbF_6$ (20 μmol) under argon. Subsequently, the reaction mixture was saturated with deuterium gas and stirred for 4 h at room temperature. We have also compared the efficiency of the pincer complex catalysts **2b** and Crabtree's catalyst **1** in the HIE reactions under identical reaction conditions. The extent of deuterium incorporation with **1** and **2b** appeared to be very similar using phenyl pyridine (**5a**) as substrate (entry 1, Table 2). The hydrogen exchange process catalyzed by **2b** takes place with a high regioselectivity at the ortho hydrogens in **5a** (Scheme 1) as formation of **5b** could be detected by ^1H NMR analysis of the reaction mixture. The deuterium incorporation to *N*-phenylbenzamide **6a** was less extensive with pincer complex catalyst **2b** than with **1** (0.8 versus 3.7 atom, entry 2, Table 2). Interestingly, however, the deuterium incorporation with **2b** takes place regioselectively at the 2′ and 6′ ortho positions of **6a** affording product **6b** (Scheme 3). On the other hand, Crabtree's catalyst **1** mediates the hydrogen exchange for all the four ortho positions (2,6,2′ and 6′) in **6a** (entry 2, Table 2). For the catalytic HIE reaction of substrates **7** and **8** catalyst **1** clearly outperforms pincer complex **2b** (Table 2). In order to study the electronic effects of the para substituents (R) in the pincer complex catalyst, we have studied the deuterium atom

Table 1
Activation of complex **2a** by different silver agents in hydrogen isotope exchange reaction (Scheme 1)

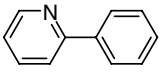
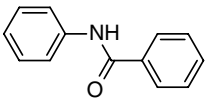
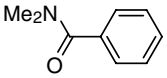
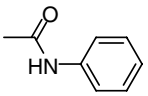
Entry	Activation agent	D_n[a]
1	–	0.7
2	$AgOCOCF_3$	0.8
3	$AgBF_4$	1.0
4	$AgSbF_6$	1.7
5	$AgSbF_6 + H_2O$	0.8

[a] Figures presented are the average number of deuterium atoms incorporated per molecule determined by LC–MS and ^1H NMR.

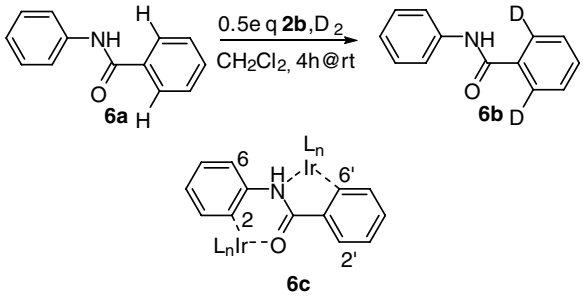


Scheme 2.

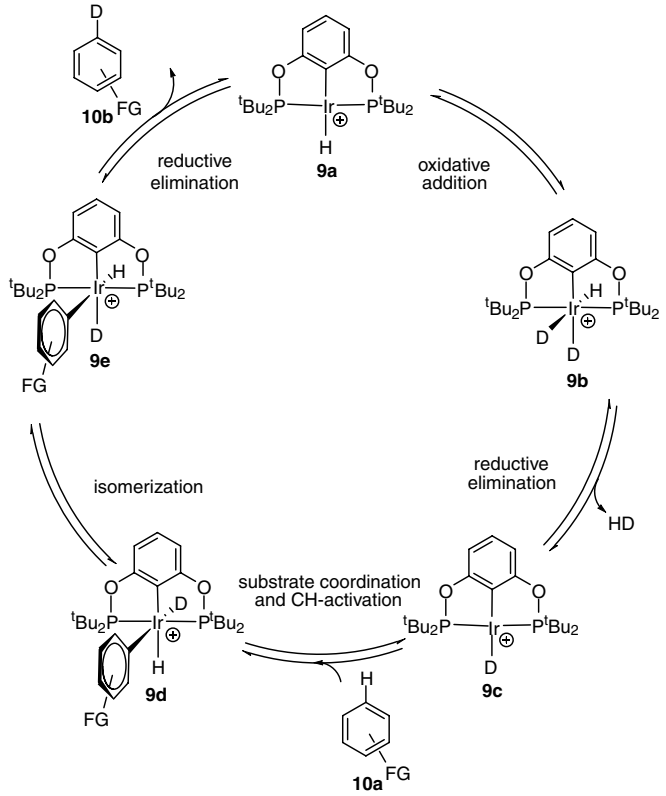
Table 2
Deuteration of substrates mediated by catalyst **2**, **3**, **4** and Crabtree's catalyst **1**[a]

Entry	Substrate	Deuterium atom incorporation[b]			
		1	**2**	**3**	**4**
1	 **5a**	1.9	1.7	1.0	0.8
2	 **6a**	3.7	0.8	0.6	1.0
3	 **7**	3.9	0	0	0
4	 **8**	1.9	0.05	0	0

[a] The transformations were performed using 20 μmol catalyst, 20 μmol $AgSbF_6$ for **2**–**4** and 40 μmol substrate in CH_2Cl_2 employing 1 atm deuterium gas. All reactions were conducted for 4 h at room temperature.
[b] Average number of deuterium atoms incorporated per molecule determined by LC–MS.



Scheme 3.



Scheme 4.

incorporation with the methoxy substituted pincer complex **3b** and the pentafluoro phenyl substituted complex **4b** (Scheme 1). Using **5a** as substrate, application of both electron donating (**3b**) and electron withdrawing (**4b**) substituents in **2b** leads to a decrease of the catalytic activity (entry 1, Table 2) in H/D exchange. Similarly, the methoxy complex **3b** is less efficient for HIE with **6a** than with **2b**, however, complex **4b** appeared to be somewhat more reactive in deuterium exchange with **6a** than with the parent complex **2b** (entry 2, Table 2). Similarly to **2b** complexes **3b** and **4b** are inactive for HIE of substrates **7** and **8**.

Skaddan and Bergman [17] studied the mechanistic aspects of the iridium catalyzed HIE reactions, showing [17] that the non-selective HIE reaction proceeds via iridium (III)/iridium (V) intermediates. Based on these results a plausible catalytic cycle is proposed for the above presented (Schemes 2 and 3 and Table 2) pincer complex catalyzed processes (Scheme 4). Accordingly, the activated intermediate **9a** undergoes oxidative addition with deuterium gas affording complex **9b**. Subsequently, reductive elimination of HD provides deutero complex **9c**, which oxidatively activates the carbon hydrogen bond of the aromatic substrate **10a** to form complex **9d**. After isomerization of **9d** to **9e** a reductive elimination affords the deuterated product **10b** recovering catalyst **9a**. Conversion of **9c** to **9d** is probably the most interesting step of the catalytic cycle determining the regioselectivity of the HIE process. As we pointed out complex **2b** induces a regioselective exchange reaction of the H2′ and H6′ ortho hydrogens of **6a** (Scheme 3). A possible explanation [15,16] for this regioselectivity of **2b** is a preferential formation of a five-membered ring intermediate of the iridium atom with the nitrogen atom and carbon atom 6′ (upper part of **6c**). Crabtree's catalyst **1** mediates the exchange of these ortho protons (i.e. H2′ and H6′) as well as the ortho protons of the aniline part (i.e. H2 and H6), thus exchange a total of four protons (entry 2, Table 2). This indicates that **1** is able to react via the above described five membered ring intermediate, and also via a six-membered intermediate involving the iridium atom, the carbon atom C6 and the carbonyl oxygen (lower part of **6c**) [15,16].

In summary, we have shown for the first time that iridium pincer complexes **2a**–**4a** are able to catalyze HIE exchange for aromatic substrates **5a** and **6a** under mild conditions. The exchange reaction takes place with a high regioselectivity for labelling of **6a**. Our studies also suggest that the catalytic activity and selectivity of the pincer complex catalysts can be fine tuned by changing of the electronic properties of the complex. Considering the above application of iridium pincer complexes represent an interesting alternative for the use of mono and bidentate iridium complexes for HIE reaction of drug like molecules.

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