Burgess Iridium(I)-Catalyst for selective Hydrogen Isotope Exchange

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Abstract

We have evaluated the commercially available Burgess catalyst in Hydrogen Isotope Exchange (HIE) reactions with several substrates bearing different directing group functionalities and have obtained moderate to high (50-97%D) deuterium incorporations. The broad applicability in HIE reactions makes the Burgess catalyst a possible alternative compared to other commercially available iridium(I)catalysts.

Keywords: hydrogen isotope exchange, CH-activation, deuterium, Burgess catalyst

Introduction

Hydrogen isotope exchange (HIE)[1] is widely utilized for selective installation of C–D[2] or C–T[3] bonds in organic molecules. The HIE approach enables a direct incorporation of deuterium or tritium into the desired target molecule and thus circumvents the need for additional synthetic steps (e.g. precursor synthesis or multi-step routes from isotopically labelled building blocks).[4]

Homogeneous iridium(I) catalysts[5] have proved to be highly efficient for selective label introduction at the *ortho*-position next to a directing group, with commercial Crabtree's catalyst [(COD)Ir(PPh_3)(py)]PF_6 **1**[6] and Kerr's catalysts [(COD)Ir(IMes)(PR_3)]PF_6 **2**[7] being the most prominent such catalysts applied today (scheme 1). Both catalysts utilize molecular hydrogen isotopes (D_2/T_2) which is especially beneficial for selective tritium labelling[8] because T_2 is a convenient tritium source.[9] In particular, Kerr's catalysts can be used under very mild reaction conditions at room temperature for selective labeling of a broad range of substrates with different directing groups, including e.g. ketones, amides, esters, aldehydes, primary sulfonamides, and several heterocycles.[10] Despite recent progress, a number of interesting functionalities found ubiquitously throughout drug motifs still present significant challenges for established HIE protocols.

Some of these limitations have been recently overcome by the introduction of a new generation of Ir-catalysts with bidentate P,N or NHC,N ligand structure. An early example was reported by Pfaltz *et al.* which utilized the non-commercial hydrogenation phosphine-oxazoline P,N catalyst **4** in the HIE

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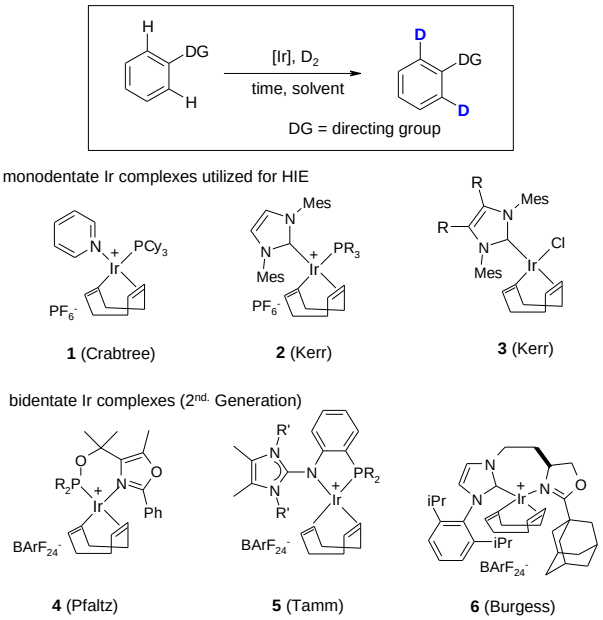
reaction of different functionalities including more challenging sulfones and sec. sulfonamides.[11] Another new class of bidentate iridium(I) catalysts with phenylene-bridged hybrid phosphine-imidazolin-2-imine P,N ligands has been recently introduced by Tamm.[12] Tamm's catalyst **5** showed remarkable performance with a broad range of known directing groups, and even promoted selective H/D exchange at aromatic Boc-protected amines, benzyl amines and methoxy derivatives, which had not been recognized previously as directing groups for *ortho* selective HIE.[12]



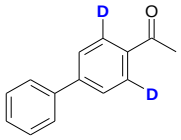
Scheme 1: mono- and bidentate Ir complexes utilized for HIE.

Based on a comprehensive screening of readily available Ir-catalysts, we recently identified another bidentate hydrogenation catalyst that displays a remarkable HIE capacity - the commercially available, air stable Burgess catalyst **6**.[13] Burgess catalyst **6** was initially developed for asymmetric hydrogenation of olefins but hasn't been applied for HIE before.[14] However, with this catalyst we were able to develop the first practical HIE protocol for selective *ortho*-deuteration of various secondary and tertiary sulfonamides, as well as for sulfonyl ureas.[15] A similar reactivity was found for the mono-dentate Kerr catalyst of type [(COD)Ir(NHC)Cl] **3.**[15,16] The method can be applied to sulfa drugs and even adopted to the special conditions required for selective tritium labelling. Based on these exciting results we became interested in investigating **6** further as a potential new catalyst for *ortho* selective HIE. Thus, here we would like to report initial results evaluating the scope and limitation of Burgess catalyst **6** in HIE reactions with different types of directing groups.

Results and discussion

We started our studies with a solvent screen of three model compounds, 4-phenylacetophenone **7**, 2-phenylimidazole **8** and 1-naphthylamine **9** in a HIE reaction with Burgess catalyst **6** at room temperature (table 1). 4-phenylacetophenone **7** and 2-phenylimidazole **8** were selected as model substrates due to their different polarity/basicity and because both are known to work well in the HIE reaction with Kerr catalyst **2**. In contrast 1-naphthylamine **9** was selected because aromatic amines represent a much more challenging functionality for HIE reactions and have been successfully labelled only utilizing iridium dionates.[17] In an initial solvent screen (table 1), catalyst **6** showed a very good performance in the HIE reaction with both model substrates **7** and **8** at room temperature in a broad range of different solvents. Only 2-methyltetrahydrofuran (entry 5),[18] alcohols (entry 3 and 9) or fluorobenzene (entry 6) resulted in considerable lower deuterium incorporations in substrates **7** or **8**. Good deuterium incorporations for 1-naphthylamine **9** (selectively in the peri-position)[19] were only observed in dichloromethane and MTBE. As the highest deuterium introduction efficiency of the model substrates was found in dichloromethane[7b] we decided to test all following reaction in this solvent.

Table 1: Solvent screening of the HIE reaction of 4-phenylacetophenone **7**, 2-phenylimidazole **8** and 1-naphthylamine **9** with Burgess catalyst **6** in different solvents.[a,b]



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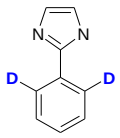

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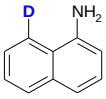

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Entry	Solvent	**7** %D[b]	**8** %D[b]	**9** %D[b]
1	dichloromethane	96	91	81
2	MTBE	89	95	70
3	ethanol	18	80	22
4	cyclohexane	82	87	16
5	2-MeTHF	9	6	13
6	fluorobenzene	16	88	18
7	isopropylacetate	83	70	41
8	methylcyclohexane	88	91	15
9	1-butanol	12	78	22
10	toluene	97	54	24
11	chlorobenzene	85	73	33

[a]Conditions: substrate **7**, **8** or **9** (25 µmol), Burgess catalyst **6** (10 mol%), solvent (2 mL), D_2 (1 atm), rt 2h; [b]percentage of deuterium incorporation determined by LC-MS; position of deuterium determined by ^{1}H-NMR.

Next we optimized the catalyst loading required to obtain deuterium incorporations in the model reactions with **6** (table 2). While for ketone **7** a catalyst loading of 3 mol% was already sufficient to

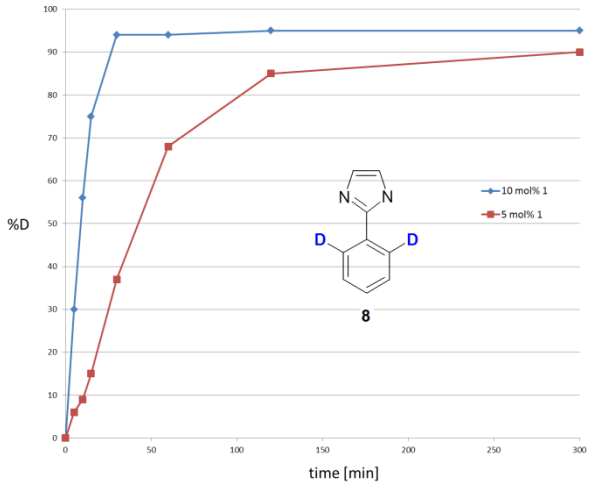
obtain >90%D, for imidazole **8** and 1-naphylamine **9** at least 10 mol% of **6** were needed to obtain similar incorporation levels (room temperature, 2h).

Table 2 Screening of catalyst amount in the HIE reaction of 4-phenylacetophenone **7**, 2-phenylimidazole **8** and 1-naphthylamine **9** with Burgess catalyst **6** in dichloromethane.[a,b]

Entry	Catalyst **6** (mol%)	**7** %D[b]	**8** %D[b]	**9** %D[b]
1	1	51	5	10
2	3	93	11	12
3	5	95	49	19
4	7	96	80	22
5	10	96	91	78

[a]Conditions: substrate **7**, **8** and **9** (25 µmol), Burgess catalyst **6**, dichloromethane (2 mL), D_2 (1atm), rt, 2h.
[b]percentage of deuterium incorporation determined by LC-MS.

Because of the strong influence of the catalyst loading observed in the HIE reaction of **8**, we conducted a kinetic study in order to investigate the influence of the reaction time (scheme 2). In a series of HIE reactions, **8** was treated either with 5 or 10 mol% of **6**. The reactions were stopped after certain time points and the deuterium incorporation was measured by LC-MS. The resulting time/conversion curves depicted in scheme 2 revealed a much faster reaction with 10 mol% of **6**, with the final deuteration grade achieved after 30 min. In contrast, with a 5 mol% catalyst loading the reaction proceeded much slower and took 5h to yield 90%D. From this experiment we concluded that a catalyst loading of 10 mol% of **6** and a reaction time of 2h might be a good compromise for a standard screening protocol when testing new substrates.



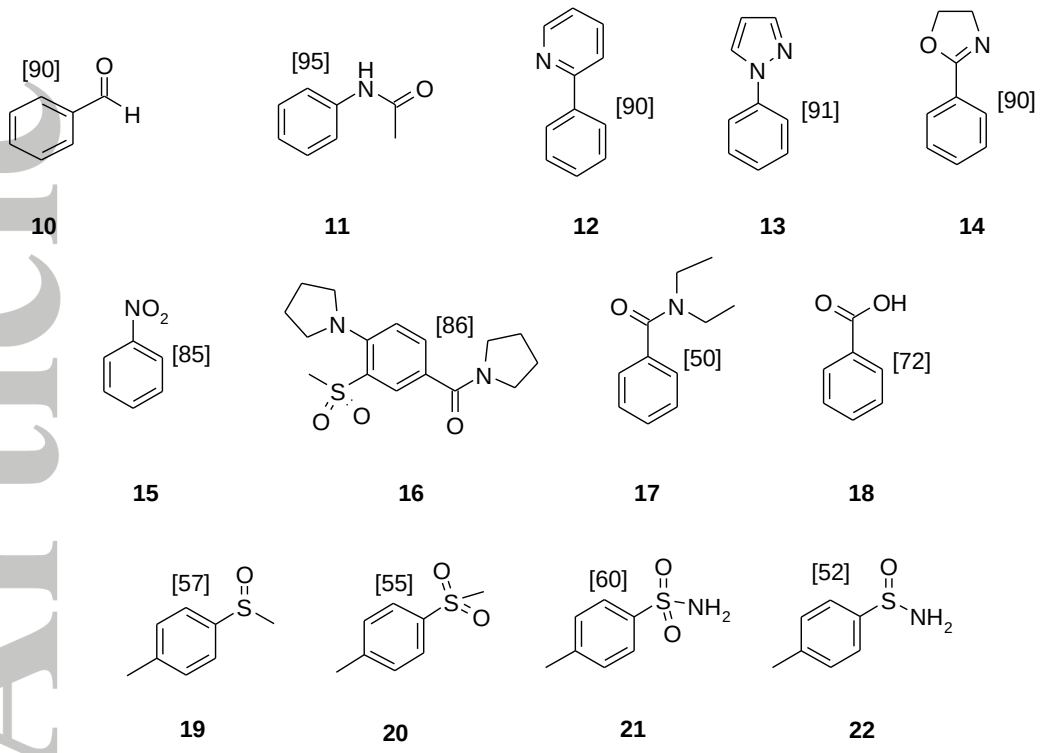
Scheme 2: Time /conversion curve for HIE reaction of **8** with catalyst **6** at room temperature.[20]

Table 3 Tolerability testing in the HIE reaction of 4-phenylacetophenone **7** and 2-phenylimidazole **8** with Burgess catalyst **6** with several additives.[a,b]

Entry	Additive	%D **7** (1 eq Add.)	%D **7** (10 eq Add.)	%D **8** (1 eq Add.)	%D **8** (10 eq Add.)
1	-	96	96	91	91
2	water	93	94	95	95
3	ethanol	95	95	95	92
4	HCl (1N)	92	14	93	10
5	NaOH (1N)	95	95	90	92
6	NEt_3	43	44	92	16
7	acetonitrile	11	12	90	48
8	TSA	95	93	95	45

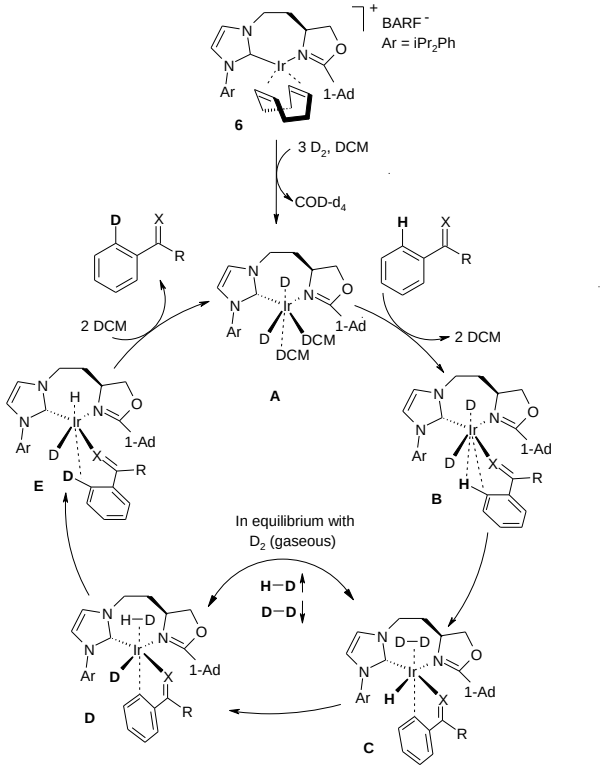
[a]Conditions: 4-phenylacetophenone **7** or 2-phenylimidazole **8** (12,5 µmol), Burgess catalyst **6** (0,125 µmol), dichloromethane (1 mL), D_2 (1atm), rt, 2h. [b]percentage of deuterium incorporation determined by LC-MS; TSA = toluene sulphonic acid

Furthermore we examined the tolerability of Burgess catalyzed HIE reactions with **7** and **8** towards several additives. Interestingly, the reaction was not influenced by addition of 1 or 10 eq. of water or ethanol (table 3, entry 2 and 3). While 1 eq. or 10 eq of HCl (entry 4) had significant effects in the HIE reaction of both compounds, even 10 eq. of 1N sodium hydroxide (entry 5) had no influence on the deuteration result. The addition of 1 or 10 eq. of an organic base like triethylamine (entry 6) changed the outcome dramatically, however not in the same way for both compounds. Surprisingly the effect of acetonitrile differed between compound **7** and **8** (entry 7). While only 1 eq. of acetonitrile inactivated the catalyst in the reaction with ketone **7**, with imidazole **8** the HIE reaction worked well. However, the deuteration of **8** was also decreased in the presence of 10 eq. of acetonitrile to 48%D. With toluene sulphonic acid (TSA) there was no effect in the HIE reaction with compound **7**, however a significant decrease of deuteration was observed with 10 eq. of TSA for compound **8** (entry 8).



Scheme 3: Substrate evaluation of HIE reaction with Burgess catalyst **6**, [a]Conditions: substrate (12,5 µmol), Burgess catalyst **6** (0,125 µmol), dichloromethane (1 mL), D_2 (1atm), rt, 2h. [b]percentage of deuterium incorporation determined by ^{1}H-NMR.

The Burgess catalyzed HIE reaction worked well to give deuterium levels above 90% with aromatic substrates containing ketone (**7**), imidazole (**8**), aldehyde (**10**), N-acyl (**11**), pyridine (**12**), pyrazine (**13**) or oxazole (**14**) moieties as directing groups (scheme 3). Reasonable to moderate hydrogen/deuterium exchange (50-86 %D) was found in reactions with amine (**9**), nitro (**15**), amide (**16**, **17**) and carboxylic acid (**18**) functions. For sulfobenzenes, e.g. sulfoxide (**19**), sulfone (**20**), primary sulfonamide (**21**) and sulfonbenzamide (**22**) a moderate deuterium incorporation level was also observed, with deuterium levels between 50-60%D. These results demonstrate the broad applicability of the Burgess catalyst **6** in HIE reactions.[15, 21]



Scheme 4: Plausible mechanism of HIE catalyzed by **6**.

According to the mechanism recently discussed by Kerr[16] the directed HIE reaction is started by hydrogenation of the COD moiety (scheme 4). The free positions in the active iridium complex **A** are proposed to be solvent and deuterium. The substrate displaces the solvent and coordination of the iridium takes place at the heteroatoms of the directing group (**B**). Next, the metal inserts into the CH-bond by a sigma-complex assisted metathesis process and the hydrogen atom is bound in the coordination sphere of the iridium(III) metal (**C**). Between complexes **C** and **D** there are several equilibria steps wherein H-D and D-D bonds are exchanged and exchange with the gaseous deuterium depot is possible. In the reductive elimination step a deuterium atom is transferred to the sp^2-carbon (**E**). Finally the substrate is eliminated from the iridium complex and substituted by two solvent molecules (**A**).

Conclusion

In summary, we have evaluated the commercial Burgess catalyst **6** in HIE reactions and obtained moderate to high (50-97%D) deuterium incorporations using several directing group functionalities. Its broad applicability in HIE reactions makes the Burgess catalyst **6** a possible alternative to commonly used Crabtree's **1** or Kerr's **2** and thus it may complement the synthetic repertoire for fast tritium labelling in the future.

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Experimental Section

General

^{1}H spectra were obtained on Bruker Avance 300 spectrometers in d_6-DMSO. The chemical shifts (δ) are expressed in ppm and are given relative to the residual proton signal of dmso-d_6 (δ 2.50 ppm). NMR assignments were made using additional 2D NMR experiments. The ^{1}H NMR spectra listed below show sequential the substrate before reaction, the substrate after the reaction with catalyst **6**. Silica-gel column chromatography was carried out with SiO_2 (Merck, 0.063-0.200 mesh). The purity of the products was determined by an LC-MS system with a Symmetry Shield RP18 column, 3.9x150 mm with a gradient program under the following conditions: 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 1.5 mL/min; detection UV 254 nm and UV 210 nm.

General method: All screening methods were performed in a Heidolph synthesis 1 station. A vial (25 mL) was equipped with a stirring bar and the substrate stock solution (500 µL, 20 mM, 1 eq.). The catalyst (10 mol-%) and the solvent (1.5 mL) were added and the vial was sealed. Then the vial was evacuated until slight bubbling of the solution and refilled with deuterium gas from a balloon. This procedure was repeated three times. The reaction was shaken under D_2 atmosphere (1 atm) at room temperature for 2 h. The crude reaction mixture was purified by silica gel chromatography (MTBE/ethylacetate, 4/1) and analyzed by LCMS and ^{1}H-NMR.

(for further details and NMR results see supporting information)

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18 We propose that 2-MeTHF coordinates to the iridium catalyst in competition to the substrate. In comparison to MTBE the coordination seems to be much stronger as demonstrated by deuterium introduction of <20% with model compounds **7**,**8** and **9**.

19 The transition state seems to work only in a five membered ring iridium-arene complex (for the peri position) and not *via* a four-membered ring necessary to exchange the hydrogen in the 2-position of 1-naphthylamine **9**.

20 A faster and more efficient deuterium exchange was observed in the kinetic study as compared to the screening results in table 2 under similar conditions (entry 3 after 2 h). The reason for this small discrepancy may be a different experimental set-up with Heidolph parallel Synthesizer (with shacking) utilized for all screening reactions in contrast to the kinetic studies performed in a 50 mL flask with stirring.

21 We did not observe deuterium pressure dependency in any of our performed iridium-catalyzed HIE reactions.