

# Comparison of Iridium(I) Catalysts in Temperature Mediated Hydrogen Isotope Exchange Reactions

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The reactivity and selectivity of iridium(I) catalysed hydrogen isotope exchange (HIE) reactions can be varied by using wide range of reaction temperatures. Herein, we have done a detailed comparison study with common iridium(I) catalysts (1–6) which will help us to understand and optimize the approaches of either

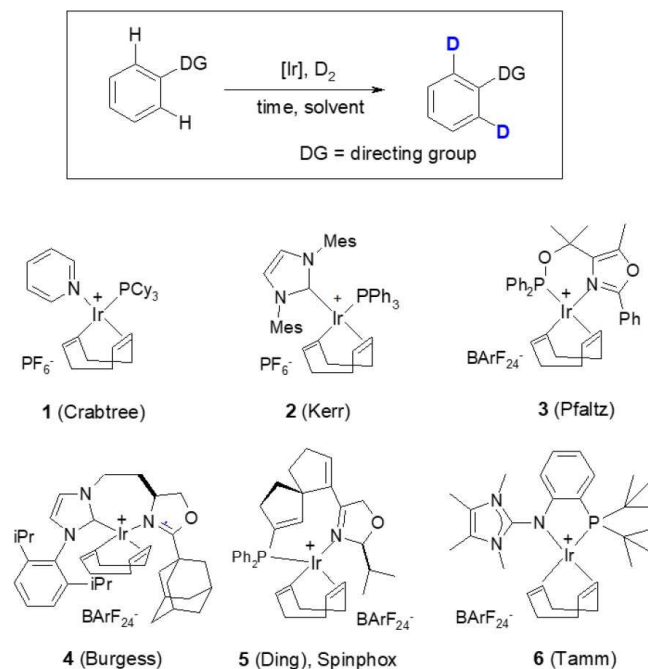
high selectivity or maximum deuterium incorporation. We have demonstrated that the temperature window for these studied iridium(I) catalysts is surprisingly very broad. This principle was further proven in some HIE reactions on complex drug molecules.

## Introduction

In recent years C–H activation in the context of late stage functionalization has become a strong tool in lead optimization of bioactive molecules in the life science academia and industry.<sup>[1]</sup> One fragment in this broader context of CH functionalization<sup>[2]</sup> and applying the principles of chemical modification of complex molecules at the latest possible time point is the hydrogen isotope exchange (HIE). Due to its simplicity the HIE method can be seen as the most fundamental of all CH functionalization reactions. HIE reactions are an elegant way for the incorporation of deuterium or tritium into complex organic molecules circumventing the need for a tedious total synthesis with several reaction steps.<sup>[3]</sup> Especially for the synthesis of tritium labelled substances a labelling procedure at the latest possible reaction step is minimizing radioactive waste and decreases the handling time with the radioactive products. Radioactive tritium labelled substances are applied as tool compounds<sup>[4,5]</sup> e.g. for understanding tissue distribution,<sup>[6]</sup> in covalent binding assays,<sup>[7]</sup> or for ADME (Absorption Distribution Metabolism Excretion) profiling of new drug candidates.<sup>[8]</sup> On the other hand deuterium labelled compounds are utilized in pharmaceutical research as internal standards for LC-MS/MS assay validation<sup>[9]</sup> for metabolic pathway elucidation<sup>[10]</sup> and more recently also as “heavy drugs”.<sup>[11]</sup> With deuterium or tritium labeling, the drug structures are not changed which gives an exact chemical or biological behavior

as compared to parent molecules. Numerous HIE protocols utilizing homogeneous or heterogeneous catalysts have already been described.<sup>[3,12]</sup>

While there have been new HIE methods published lately utilizing metals like iron,<sup>[13]</sup> cobalt<sup>[14]</sup> or ruthenium<sup>[15,16,17]</sup> the state-of-the-art-procedure utilise iridium catalysts, such as those explored by Crabtree **1**,<sup>[18,19]</sup> Kerr **2**,<sup>[20,21]</sup> Pfaltz **3**,<sup>[22]</sup> Burgess **4**,<sup>[23]</sup> Ding **5**<sup>[24]</sup> or Tamm **6**<sup>[25]</sup> (Scheme 1). Most of these catalysts are



Scheme 1. Common Iridium-catalysts (1–6) in directed HIE reactions.

commercially available and are nowadays applied regularly in HIE reactions within industry laboratories.

As an introduction of a radioactive label in a metabolically stable position is essential for the application of tritiated compounds in in-vivo experiments, it is necessary to understand the influence of the different directing groups in complex molecules.<sup>[4]</sup> In comparison to <sup>14</sup>C-labelling where a loss of the

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radioactive marker is most unlikely, the loss of tritium can happen by phase 1 metabolic enzymatic transformation, like e.g. hydroxylation. Therefore the prediction of the labelling position in complex molecules would be of great benefit to synthetic chemists<sup>[26]</sup> and avoid the necessity for many try and error experiments. One parameter to trigger reactivity and selectivity in HIE reactions is to study the effect of the reaction temperature. Even though many details on the optimization of reactions conditions in iridium catalysed HIE are already reported,<sup>[27]</sup> there is still a lacking of head to head comparison, therefore we concluded that a general comparison study with the most commonly applied catalysts 1–6 could help to use the optimized approach for either high selectivity or maximum deuterium incorporation. This way unproductive HIE reactions can be circumvented and hence it could be of great interest for many scientists.

## Results and Discussion

We began our investigations with the HIE reactions of 4-acetamido-acetophenone **7** with catalysts 1–6 in dichloromethane at various low temperatures. We had chosen this model compound as the acetamido and the ketone directing group were known to give good results in HIE reactions with iridium catalysts.<sup>[20]</sup> Beside general deuterium introduction we also evaluated the change in selectivity in the HIE reaction between position A and B (Table 1). Interestingly, depending on the used catalyst we observed strong differences in reactivities and selectivities of the deuterated products of compound **7**. At  $-80^{\circ}\text{C}$  only catalysts **1** (Crabtree, entry 6) showed reasonable reactivity ( $>25\% \text{D}$  incorporation), however with only low selectivity in favour of position B (ketone directing group). The other catalysts had increasing reactivity at lower temperatures in the order of  $6 > 2 = 4 > 5 > 3$ . For catalysts **2** (entry 10), **4** (entry 20) and **5** (entry 25) complete selectivity in favour of position B was observed at  $-30^{\circ}\text{C}$ . It is further noted that for catalysts **1**, **4**, **5** and **6** there are no big differences in the outcome of the HIE reaction of 25 or  $0^{\circ}\text{C}$ . These reactions clearly indicate that HIE reactions at lower temperature have a chance to change the reactions outcome and should be studied more intensively in the future. Kerr et al. reported the different free energy profiles for HIE reactions of aromatic compounds in the gas phase with catalyst **2** (Scheme 2). While for acetophenone a  $\Delta H$  activation energy in the transition state (**8**) of 18.13 kcal/mol (298 K) were calculated the value for acetanilide of 23.04 kcal/mol (**9**) was reported<sup>[20c]</sup> which is 4.91 kcal/mol energetically higher and in line with the observed selectivities of all used catalysts in Table 1 and 2 showing the ketone directing group of **7** the more HIE relevant one compared to acetanilide. It looks like in principle all catalysts 1–6 could either go through a five- or six-membered-ring transition state as both positions were exchanged by deuterium in the products.

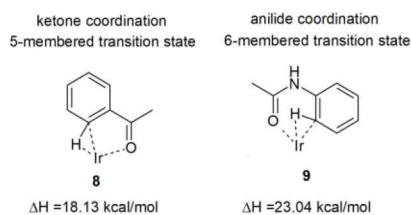
Next, we studied the HIE reaction of our model compound **7** at elevated temperatures up to  $130^{\circ}\text{C}$  (Table 2). Therefore we had to change the solvent to chlorobenzene due to the low boiling point of dichloromethane. Interestingly, catalyst **1**, **2**, **4**,

**Table 1.** Evaluations of iridium(I) catalysts 1–6 in a HIE reaction of 4-acetamido-acetophenone **7** at temperatures from  $-80^{\circ}\text{C}$  to  $25^{\circ}\text{C}$  in dichloromethane.

Entry	catalyst	T ( $^{\circ}\text{C}$ )	<b>7</b> <sub>A</sub> (D%) <sup>a</sup>	<b>7</b> <sub>B</sub> (D%) <sup>a</sup>	D <sub>total</sub> <sup>b</sup>
1	 <b>1</b> (Crabtree)	25	93	94	3.7
2		0	91	94	3.7
3		$-15$	54	87	2.8
4		$-30$	50	74	2.5
5		$-60$	33	40	1.5
6		$-80$	14	34	1.0
 <b>2'</b> (Kerr)					
7	 <b>2'</b> (Kerr)	25	92	99	3.8
8		0	30	87	2.3
9		$-15$	10	70	1.6
10		$-30$	0	38	0.8
11		$-60$	0	34	0.7
 <b>3</b> (Pfaltz)					
12	 <b>3</b> (Pfaltz)	25	0	46	1.0
13		0	0	20	0.4
14		$-15$	0	10	0.2
15		$-30$	0	0	–
16		$-60$	0	0	–
 <b>4</b> (Burgess)					
17	 <b>4</b> (Burgess)	25	67	93	3.2
18		0	51	93	2.9
19		$-15$	20	90	2.2
20		$-30$	0	50	1.0
21		$-60$	0	32	0.6
 <b>5</b> SpinPhox (Ding)					
22	 <b>5</b> SpinPhox (Ding)	25	24	82	2.1
23		0	18	81	2.0
24		$-15$	24	75	2.0
25		$-30$	0	50	1.0
26		$-60$	0	11	0.2
 <b>6</b> (Tamm)					
27	 <b>6</b> (Tamm)	25	65	94	3.2
28		0	86	91	3.6
29		$-15$	70	92	3.3
30		$-30$	21	79	2.0
31		$-60$	0	48	1.0
32		$-80$	0	13	0.3

Conditions: substrate **1** (10 mg), catalyst (5 mol%),  $\text{D}_2$  (1 atm), dichloromethane (5 mL), 4 h; <sup>a</sup> determined by  $^1\text{H-NMR}$ , <sup>b</sup> determined by LC-MS.

**5** showed their highest deuteration efficiency at  $75\text{--}100^{\circ}\text{C}$  with nearly full deuteration of the aromatic positions (entry 3, 8, 19, 24). Remarkably no H/D exchange at the  $\text{C}(\text{sp}^3)$ -positions were observed, neither at the ketone or acetanilide methyl-groups. Catalyst **3** and **6** were the most sensitive ones in relation to heat. Above  $50^{\circ}\text{C}$  the deuterium introduction decreased



**Scheme 2.** Simplified transition states in the HIE reaction of acetophenone and acetanilide with a iridium catalyst. DFT calculation values of catalyst **2** [20c]

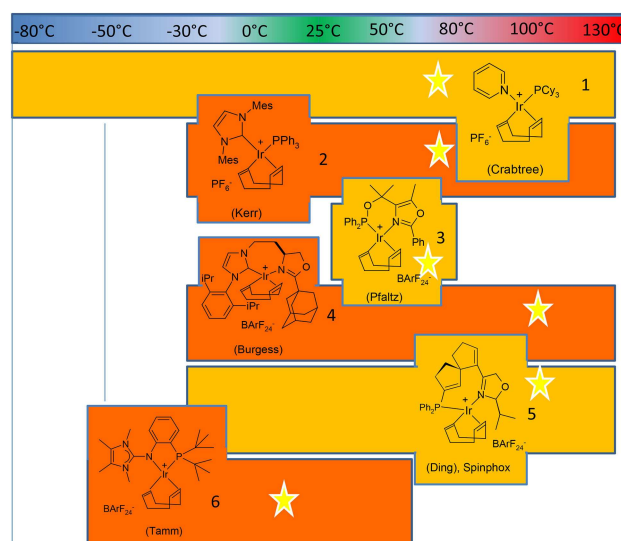
**Table 2.** Evaluations of iridium(I) catalysts 1–6 in a HIE reaction of 4-acetamido-acetophenone **7** at temperatures from 25 to 130 °C in chlorobenzene.

Entry	catalyst	T (°C)	D <sub>A</sub> (%)–7 <sup>c</sup>	D <sub>B</sub> (%)–7 <sup>c</sup>	D <sub>total</sub> <sup>d</sup>
1		25	87	94	3.6
2		50	84	99	3.7
3		75	99	99	4.0
4		100	15	68	1.8
5		130	13	64	1.6
6		25	94	92	3.8
7		50	90	99	3.8
8		75	98	99	4.0
9		100	52	81	2.7
10		130	0	47	1.0
11		25	0	45	0.9
12		50	0	48	1.0
13		75	0	35	0.7
14		100	0	0	0.1
15		130	0	0	0
16		25	63	97	3.0
17		50	58	99	3.2
18		75	62	99	3.3
19		100	98	99	4.0
20		130	49	84	2.9
21		25	35	85	2.4
22		50	79	99	3.6
23		75	79	99	3.6
24		100	96	98	3.9
25		130	8	93	1.8
26		25	56	87	3.0
27		50	23	63	1.7
28		75	30	35	1.4
29		100	8	26	0.8
30		130	0	0	0.0

Conditions: substrate **7** (1 mg), catalyst (5 mol%), D<sub>2</sub> (1 atm), C<sub>6</sub>D<sub>5</sub>Cl (0.5 mL), 4 h <sup>c</sup> determined by <sup>1</sup>H NMR, <sup>d</sup> determined by LC-MS (we have not found any significant decomposition products)

significantly indicating that the HIE activity of these catalysts drops due to undesired side reactions. These results clearly indicate that higher temperatures are having a strong effects on the outcome of the HIE reaction and should be studied more intensively as optimization parameter in the future.

Even though we know that a full picture on the efficiency and reactivity of the different catalysts 1–6 can't be given by a HIE reaction of just a single substrate we believe that together with a lot of different literature examples<sup>[20,22,29]</sup> a general statement can be made. Even though these ligated iridium catalysts seem to be remarkable stable at higher temperatures methodological studies at elevated temperature are still few in number.<sup>[23,28]</sup> Furthermore to our knowledge there is only one study on HIE reactions at –20 °C reaction temperature.<sup>[29]</sup> Nevertheless the overview in Figure 1 should only be seen as a

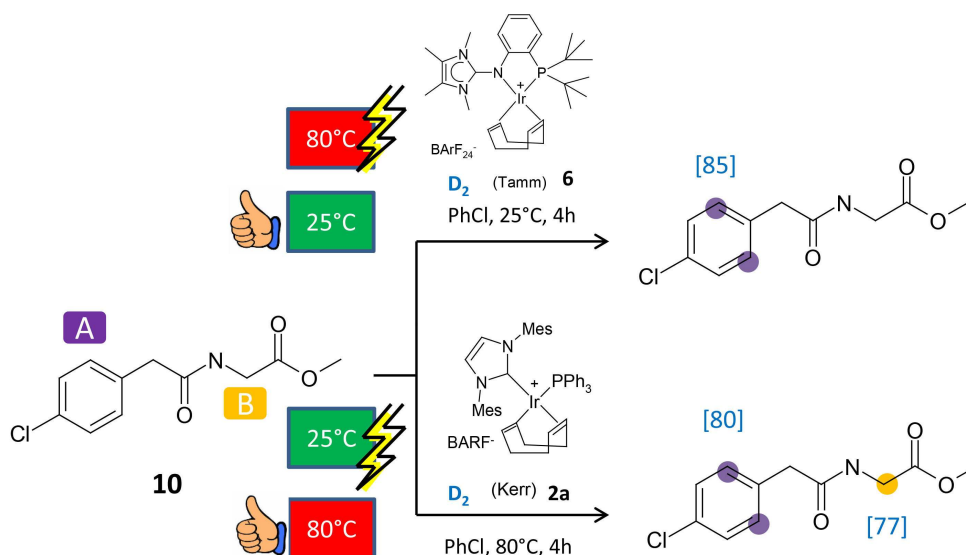


**Figure 1.** Graphical overview in which temperature window the catalysts 1–6 are efficiently working (threshold 25 %D) for HIE reactions with compound **7**; yellow star is showing highest deuterium incorporation

principal direction in which kind of temperature window the catalysts were reactive and no significant decomposition of the catalyst was observed.

Finally we were interested to demonstrate how the knowledge about different HIE reactivities and deuterium introduction efficiencies of these iridium catalysts 1–6 can influence the project planning. Therefore we identified five more complex examples where we wanted to apply different labelling conditions.

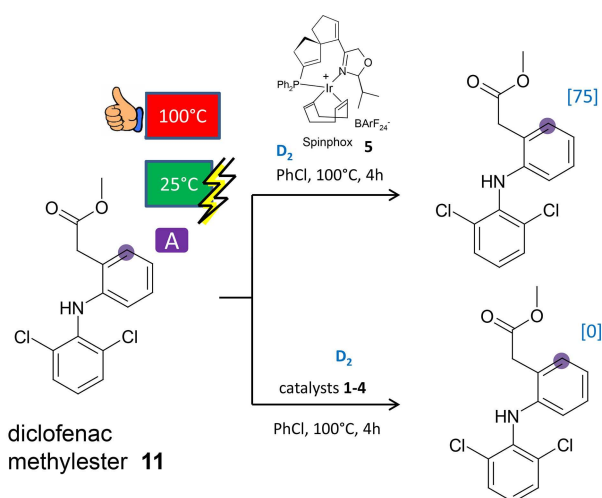
One interesting example for the different reactivity of iridium catalysts is described in Scheme 3. With catalyst **6** at 25 °C we have obtained selectively deuterium incorporation in the aromatic position A of phenylacetic amide **10**.<sup>[30]</sup> Interestingly with catalyst **2a** we obtained no deuterium introduction at all at 25 °C. However, when we increased the temperature to 80 °C we observed deuteration in both positions A and B, indicating that by increasing the temperature the transitions states for both CH-activation pathways for C(sp<sup>2</sup>)- and C(sp<sup>3</sup>)-



**Scheme 3.** HIE reaction of phenylacetic glycine amide derivative **10** with two iridium catalysts (5 mol%). No deuterated product with catalyst **2a** at 25 °C and catalyst **6** at 80 °C.

carbons are possible to be passed through. The labelling of glycine C(sp<sup>3</sup>)-positions with catalyst **2** has been demonstrated earlier by us already.<sup>[28a]</sup> With catalyst **6** we obtained only traces of deuterated product due to the prior described instability of the catalyst at temperatures above 50 °C. Unfortunately, we haven't found a catalyst or conditions to selectively introduce deuterium at the C(sp<sup>3</sup>)-position (B) only of **10** until now.

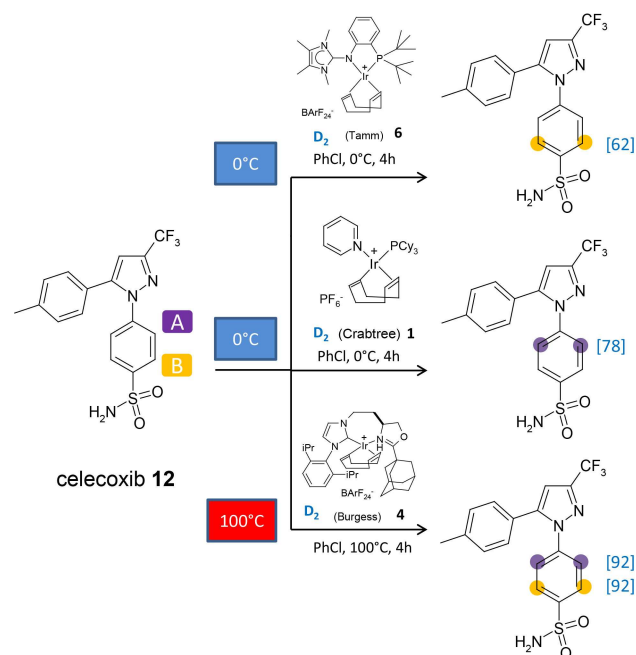
In this context we tried the HIE reaction of diclofenac methylester **11**, a NSAID drug used to treat pain and inflammatory diseases such as gout or arthritis, which was only deuterated by applying catalyst **5** at 100 °C (Scheme 4). No deuteration was observed at 80 °C degree and below with catalyst **5**, as with all other tested catalysts **1–4** at temperatures 25–100 °C. This is a remarkable result as phenyl acetic acids derivatives are core structures in a variety of important drugs,



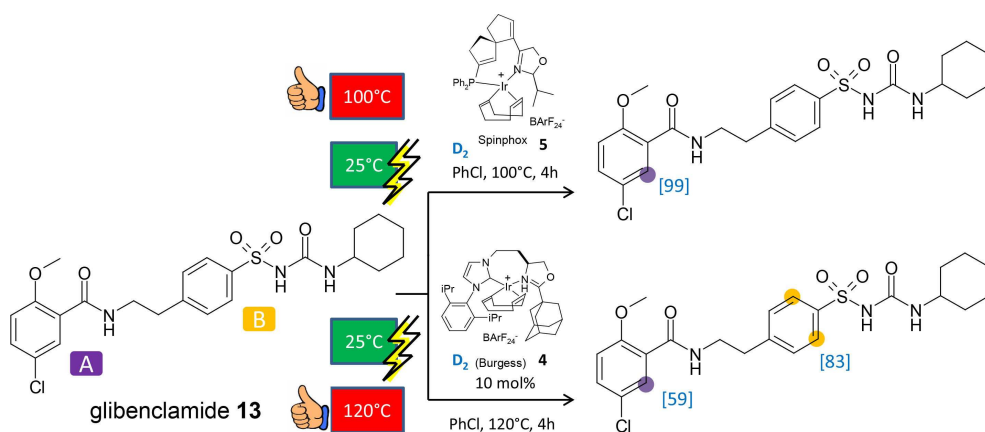
**Scheme 4.** HIE reaction of diclofenac **11** with five different iridium catalysts; no reactivity at <= 80 °C with catalysts **1–5**.

like clopidogrel, naproxene, camylofine, etc. and labelling of these compounds is still challenging.<sup>[30]</sup>

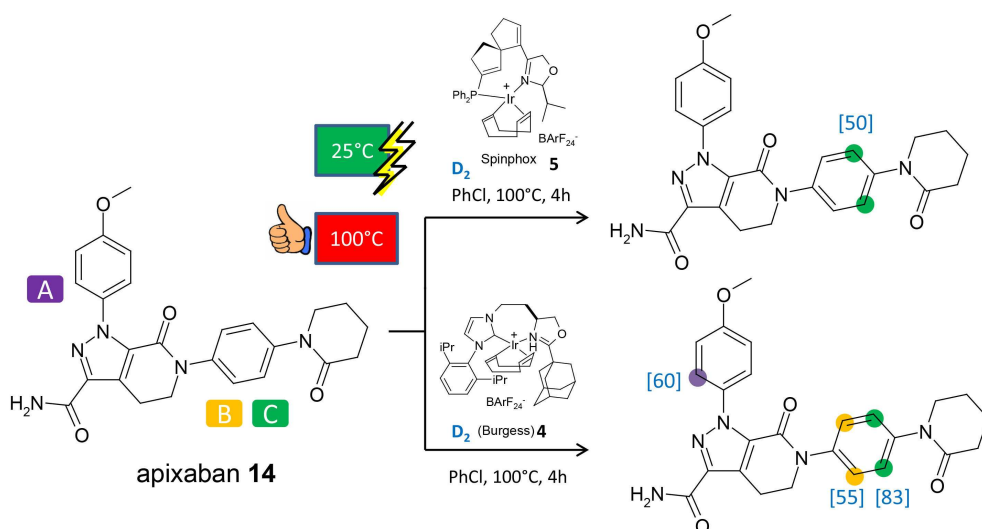
In a third example we have studied the deuteration of celecoxib **12** (Scheme 5), a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID) to treat arthritis. With catalyst **6** we observed in the HIE reaction at 0 °C only exchange in the B-position (62%D) directed by the sulfonamide group, while with catalyst **1** we found the product labelled at the A-position (78% D) only. At 80 °C this selectivity of catalyst **1** was reduced to 3:1 (60%D for position A and 20%D for B). The total amount of



**Scheme 5.** HIE reaction of celecoxib **12** with three different iridium catalysts and temperatures



Scheme 6. HIE reaction of glibenclamide **13** with two different iridium catalysts **4**, **5** at 100–120 °C; no reactivity of catalysts **4**, **5** at 25 °C.



Scheme 7. HIE reaction of apixaban **14** with two different iridium catalysts **4**, **5** at 100 °C, no reactivity at 25 °C.

introduced deuterium did not change compared to 0 °C. Interestingly, applying catalyst **4** at 100 °C both C(sp<sup>2</sup>)-positions, A and B, were exchanged completely (92%D) indicating how catalyst and temperature can trigger the HIE reaction outcome.

Next we performed HIE reactions with glibenclamide **13** (Scheme 6), an inhibitor of the ATP-sensitive potassium channels (K<sub>ATP</sub>) which is an inhibitory regulatory subunit of the sulfonylurea receptor 1 (SUR1) in pancreatic beta cells to treat diabetes mellitus type 2. With catalyst **5** at 100 °C selectively only position A was deuterated, while with catalyst **4**, as reported before,<sup>[23a]</sup> both positions A and B (59%D and 83%D) with favoring of deuterated position B was obtained. Both catalysts (**4**,**5**) showed no reactivity in reactions at 25 °C.

Finally we studied the HIE reaction of apixaban **14** (Scheme 7), a reversible direct inhibitor of factor Xa to prevent stroke, with two different iridium catalysts at the same temperature (100 °C). Interestingly, with catalyst **5** only deuteration of position C was observed, with a total of one deuterium introduced into the molecule. In comparison the HIE reaction with catalyst **4** generated a highly deuterated product with

overall four deuterium atoms, however all three possible positions A, B and C were deuterated.

## Conclusions

We have demonstrated that by applying the optimized combination of iridium catalysts and reaction temperatures different HIE reaction outcomes can be achieved. Notably the temperature window for most studied iridium catalysts **1–6** is surprisingly broad and we hope that they are applied more specifically and with greater success in the future. To use the right catalyst with the ideal reaction conditions is the trigger to either increase the selectivity or the deuterium incorporation. While rising the reaction temperature to a maximum prior facing catalyst decomposition is the key for maximum deuterium incorporation into the target molecule, on the other hand decreasing the temperature can circumvent not wanted side reactions (hydrogenation) or substrate decomposition and therefore triggers either regioselectivity and catalyst activity.

Our studies give a first aid which catalysts can be applied if very heat sensitive substrates are used. Furthermore, we believe that evaluating selectivity and reactivity of different catalysts in a comparison study of a reaction class can make the prediction of CH-functionalization reaction more reliable and understandable which could enable a greater probability of success with HIE reactions to increase effectiveness and reduce the number of reactions needed.

## Experimental Section

All chemicals were used as commercially available, unless specified otherwise. Deuterium (99.9%D) was purchased from Sigma Aldrich in 12 L bottles.  $^1\text{H-NMR}$  spectra were obtained on a Bruker Avance 300 spectrometer (Bruker, Rheinstetten, Germany). The chemical shifts are shown in ppm in reference to the shift of the residual proton of DMSO- $d_6$  ( $\delta$  2.50 ppm) or  $\text{CDCl}_3$  ( $\delta$  7.27 ppm). NMR-peaks were assigned to respective protons using a combination of NMR prediction software and 2D-NMR experiments. The NMR-spectra shown are the reference for the starting material and the product of the hydrogen-deuterium exchange. LC-MS analysis was done on an Agilent 1100 series HPLC. Using positive ESI mode, the mass of the compounds was recorded before and after deuteration. The results were normalized against the natural occurring isotopes found in the reference spectra. All reactions were carried out in a Radleys Carousel 12 parallel synthesizer.

**HIE reaction method A:** Substrate (10 mg, 1 eq) and catalyst (5 mol %, 0.05 eq) were dissolved in dichloromethane (DCM) for a total volume of 3 ml and added to a flask equipped with a stirring bar. The flasks were sealed. The flasks were then evacuated until bubbling started and filled with deuterium gas, this was repeated thrice. The flasks were sealed and the reactions were run in  $\text{D}_2$  atmosphere while stirring (500 rpm). After four hours the reaction was stopped by evacuation of the flask and evaporation of DCM. The products were analyzed by LC-MS and  $^1\text{H NMR}$ .

**HIE reaction method B:** Catalysts (5 mol%, 0.05 eq) were dissolved in chlorobenzene- $\text{D}_5$  for a total volume of 0.4 ml and added to a flask equipped with a stirring bar. The flasks were sealed. The flasks were then evacuated until bubbling started and filled with deuterium gas, this was repeated thrice. The flasks were sealed and the reaction was run in  $\text{D}_2$  atmosphere while stirring (300 RPM, at various temperature as specified), 1 h). After 1 h, substrate 7 (1 mg, 1 eq) in 0.5 mL chlorobenzene- $\text{d}_5$  were added in the reaction mixture and the reaction was further continued for another 2 h at respective temperatures. Finally, the reactions were stopped by evacuation of the flask and the products were analysed directly by  $^1\text{H NMR}$  and LC-MS.

For all data of analysis of the deuteration experiments for compounds 10–14 please look the supporting information.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** hydrogen isotope exchange · deuterium · iridium catalysis · C–H functionalization · homogeneous catalysis

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