

Hydrogen Isotope Exchange

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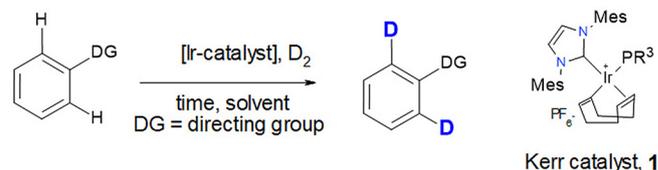
C–H Functionalization—Prediction of Selectivity in Iridium(I)-Catalyzed Hydrogen Isotope Exchange Competition Reactions

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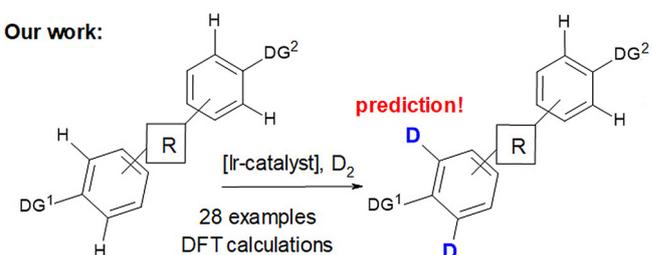
Abstract: An assessment of the C–H activation catalyst [(COD)Ir(IMes)(PPh₃)]PF₆ (COD = 1,5-cyclooctadiene, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) in the deuteration of phenyl rings containing different functional directing groups is divulged. Competition experiments have revealed a clear order of the directing groups in the hydrogen isotope exchange (HIE) with an iridium (I) catalyst. Through DFT calculations the iridium–substrate coordination complex has been identified to be the main trigger for reactivity and selectivity in the competition situation with two or more directing groups. We postulate that the competition concept found in this HIE reaction can be used to explain regioselectivities in other transition-metal-catalyzed functionalization reactions of complex drug-type molecules as long as a C–H activation mechanism is involved.

In recent years C–H functionalization of complex molecules has become a strong tool in lead optimization of bioactive molecules in the life-science industry.^[1] To increase speed and decrease costs and resources in drug-discovery research C–H functionalization reactions enable the modification of complex structures at the latest possible linear step. In this way novel chemical space can be explored and new intellectual property (IP) of compounds with already optimized pharmaceutical value can be generated. This concept is also followed in the hydrogen isotope exchange (HIE) reaction, the most fundamental of all C–H functionalization reactions (Scheme 1). The HIE reaction has become a broadly utilized and elegant method for the incorporation of deuterium or tritium into organic molecules, circumventing the need for a tedious multi-step synthesis.^[2] In drug discovery, radioactive tritium substances are used as research tools^[3,4] for example, for understanding tissue distribution,^[5] in covalent binding assays,^[6] or for ADME (absorption distribution metabolism

Directed aromatic HIE, known work



Our work:



Scheme 1. Iridium-catalyzed *ortho*-directed aromatic HIE reactions. (DG = directing group).

excretion) profiling of new drug candidates.^[7] Numerous HIE protocols utilizing homogeneous or heterogeneous catalysts have already been described.^[2,8] Even though a new generation of bidentate iridium catalyst systems such as those from Pfaltz,^[9] Burgess,^[10] and Tamm^[11] have extended the scope of the aromatic *ortho*-directing HIE reactions, (Scheme 1) the commercially available Crabtree's^[12] and Kerr's catalyst^[13,14] **1** remain the most regularly applied iridium catalysts in industry today. Interestingly new HIE applications have recently been published with great success utilizing other metals, such as iron,^[15] cobalt,^[16] or ruthenium,^[17–19] or photo-redox reactions^[20] broadening the scope also to C(sp³)-carbon atoms. Nevertheless, although there are numerous publications on the use of different directing groups such as ketones, esters, amides, carboxylic acids, nitro groups, sulfones, sulfonamides, and others, there is still a lack of understanding and prediction for how the different directing groups enable HIE if more than one directing group is present in the molecule. This understanding is especially important because the introduction of a radioactive label in a metabolically stable position is essential for the application of tritiated compounds in *in vivo* experiments.^[3] Furthermore, these predictions could also help to plan late-stage functionalization reactions and result in more complex molecules in general.

We identified several functional groups, for example, imidazole (N heterocycle), ketones, esters, amides, carbamates, acids, nitro groups, sulfones, sulfonamides, and phe-

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nols, among others, that are present repeatedly in aromatic drug molecules (based on an overview of 200 prescribed drugs in 2016 reported by Njarðarson and co-workers^[21]). Based on these findings we studied the order of the aforementioned functional groups as directing groups in a standard HIE reaction with deuterium gas as the isotope source.^[22]

Initial experiments were performed under standard HIE conditions in the presence of the commercial Kerr catalyst **1** [1 atm D₂, rt, dichloromethane (DCM), 2 h] to make our results as comparable with literature results^[23] as possible and consistent across the set. We conducted a series of competition experiments,^[24] employing two simple mono-substituted aromatic substrates in one reaction vessel (Scheme 2A), along with catalyst **1** to show which of the two directing groups enables greater deuteration in the HIE experiment. The analysis of deuterium incorporation was performed by either mass spectrometry or by ¹H NMR spectroscopy. Applying this methodology to aromatic compounds **2–10** (Table 1), we were able to determine experimentally the general relative directing-group strength in the order: imidazole **2** (heterocycle^[25]) > acetylanilide **3** ≈ ketone **4** > nitro **5** > tertiary amide **6** > aldehyde **7** > ester **8** > primary sulfonamide **9** > carbamate **10** (Scheme 2B).

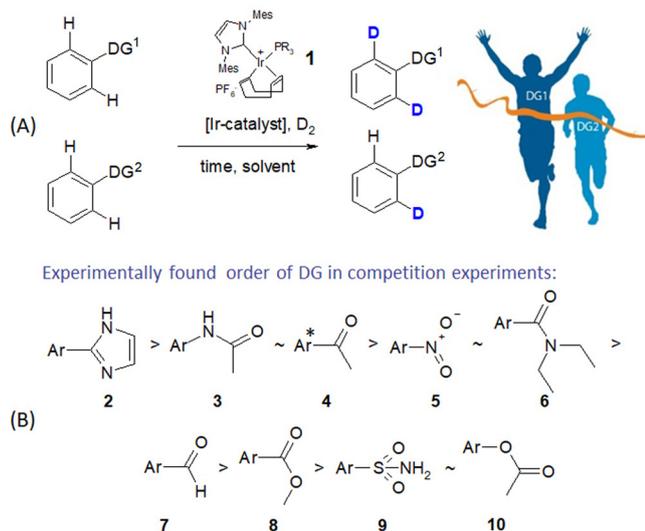
With these results in hand a prediction of the labelling positions with catalyst **1** in more complex molecules bearing these directing groups should be possible. However, to understand the theoretical background of our proposal we applied density functional theory (DFT) calculations (M06 functional),^[26] following the approach successfully applied by Kerr and co-workers,^[14c,27,28] based on the mechanism suggested by Heys and co-workers.^[29] The constructed free energy profiles (ΔG_{rel}) with catalyst **1** are shown in Figure 1 for the first step of the HIE reaction. It is reported that the rate-determining step is the most significant step in HIE reactions and the free activation energy of Ir–C–H insertion ($\Delta\Delta G_{\text{rel}}$, **2–10a**→**2–10b**) is considered to be the main parameter to explain the formation of the deuterated

Table 1: Deuterium incorporation results of the competition HIE reactions with catalyst **1** and substrates **2–10**.^[a,b]

Substrate	3	4	5	6	7	8	9	10
2	82%D	89%D	89%D	82%D	80%D	85%D	85%D	78%D
3		89%D	21%D	22%D	15%D	10%D	11%D	8%D
4		87%D	73%D	78%D	86%D	66%D	89%D	81%D
5			69%D	56%D	50%D	12%D	7%D	25%D
6			82%D	87%D	77%D	91%D	91%D	91%D
7				69%D	25%D	21%D	9%D	9%D
8				62%D	31%D	44%D	92%D	88%D
9					28%D	16%D	2%D	6%D
10					44%D	77%D	78%D	77%D
						10%D	13%D	3%D
						34%D	20%D	33%D
							12%D	11%D
							59%D	39%D
								8%D
								10%D

[a] Conditions: each substrate (1 equiv.), catalyst **1** (5 mol%, 0.05 equiv.), DCM (6 mL), D₂ (1 atm), rt, 2 h. [b] The analysis was done either by mass spectrometry (if substrate was ionizable and there was no overlapping between the two substrates) or by ¹H NMR spectroscopy.

products.^[27,28] However, the order of directing-group significance in compounds **2–10** should have differed compared with the order observed experimentally. This result is especially significant for compounds **3** and **6** with their relative free activation energies ($\Delta\Delta G_{\text{rel}}$, **2–10a**→**2–10b**) calculated to be higher than those of compounds **5**, **7**, and **8** (Table 2, Figure 1). However, in these competition experiments, which take place readily at room temperature, the relative populations of the coordination complex **2–10a** strongly influence the outcome of the overall reaction. Once the coordination complex **2–10a** has been formed, the reaction will proceed, via transition state **2–10b** and insertion product **2–10c**, to completion. This influence is reflected in the order of the calculated relative free energies $\Delta G_{\text{rel}}(\text{CC})$ of the coordination complexes **2–10a**, which matches well the order observed experimentally. For similarly coordinating directing groups (same $\Delta G_{\text{rel}}(\text{CC})$ values), in which the coordination complexes are populated almost equally (e.g. **7–9**), relative free activation energies ($\Delta\Delta G_{\text{rel}}$, **2–10a**→**2–10b**) become dominant again. This can be seen clearly for compound pairs **4a** versus **6a** (−0.3 vs. 4.6 kcal mol^{−1}) and **7a** versus **8a** (0.4 vs. 3.6 kcal mol^{−1}). This contribution is significant to understanding the processes of the C–H activation mechanism with complex substrates. It is not the rate-limiting^[14b,27,28] transition state **2–10b** that is responsible for the HIE reaction outcome in competition cases but the lower free energy $\Delta G_{\text{rel}}(\text{CC})$ of the initially formed coordination complexes **2–10a**. After the success and observations of the competition experiments, we sought to obtain more insight into the role of competing directing groups in the same molecule. We studied aromatic compounds **11–20** with at least two different substituents. Owing to the higher complexity of ¹H NMR analysis in 1,2- or 1,3-disubstituted benzenes, we focused our study on 1,4-disubstituted systems (Scheme 3). Furthermore, we have calculated the $\Delta\Delta G_{\text{rel}}(\text{CC})$ values of the two directing groups from Table 2 to demonstrate the predicted energy difference in the coordination complex combined with the experimental result. All predicted results for the deuteration



Scheme 2. Competition HIE experiment of aromatic compounds with catalysts **1** at room temperature in DCM. (Ar = Phenyl; except for **4**, Ar* = 4-biphenyl).

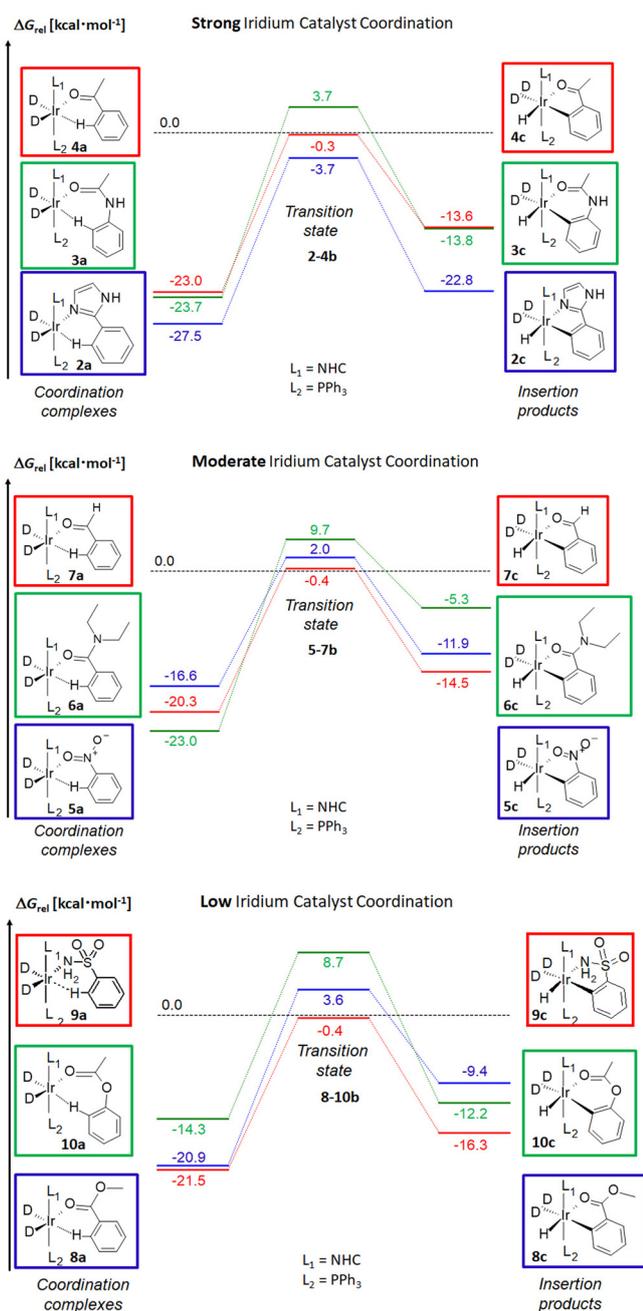


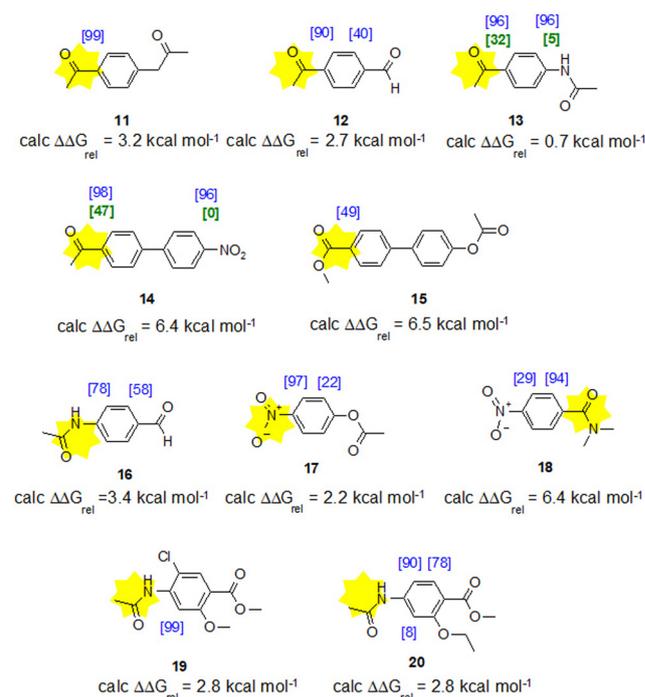
Figure 1. Relative free energies ΔG_{rel} of strong, moderate, and low substrate-iridium catalyst coordination complexes **2–10a**, transition states **2–10b**, and C–H insertion products **2–10c**.

reaction strengthen the reported order obtained in the competition experiments (Table 2 and Figure 1).

However, by this method we are able to predict the main product, but not the final deuteration result in %D. With compounds **13** and **14** it was shown that by lowering the reaction temperature to 0°C the selectivity of deuteration was shifted in favor of the ketone as the directing group (green numbers, Scheme 3), indicating that the calculated transition activation energy $\Delta\Delta G_{\text{rel}}(\text{CC})$ plays a much bigger role at temperatures below 0°C. To our delight we found a general agreement in spite of the selectivity of the main deuterated

Table 2: For different directing groups the relative free energies to form the coordination complexes **2–10a** (sorted by ΔG_{rel}) and the free activation energies $\Delta\Delta G_{\text{rel}}$ to generate **2–10c** via transition states **2–10b** are shown.

DG	ΔG_{rel} (CC) 2–10a	$\Delta\Delta G_{\text{rel}}$ (2–10a)→(2–10b)
–2-pyridine	–71.8	22.9
–N-oxide	–32.9	27.2
–NH ₂	–29.6	33.3
–CO–NH ₂	–28.6	27.5
–2-imidazole 2	–27.5	23.9
–PO(NMe ₂) ₂	–25.4	26.5
–CO–NMe ₂	–25.1	26.0
–N–CO–Me 3	–23.7	27.4
–CH ₂ COOMe	–23.1	28.5
–CO–Me	–23.0	22.7
–CO–NEt ₂ 6	–23.0	27.6
–COOH	–22.0	22.3
–SO ₂ NH ₂ 9	–21.5	23.8
–COOMe 8	–20.9	24.4
–OH	–20.9	35.8
–CO–H 7	–20.3	20.6
–SO ₂ –Me	–20.2	23.4
–CH ₂ COMe	–19.8	37.5
–NSO ₂ Me	–17.7	28.1
–OMe	–16.8	29.2
–NO ₂ 5	–16.6	18.5
–SO ₃ H	–16.6	22.9
–SO ₂ NHCONH–Me	–15.4	24.5
–OCOMe 10	–14.3	23.0



Scheme 3. HIE experiment of aromatic substrates **11–20** with deuterium gas and catalyst **1** (blue: 25°C, %D; green: 0°C, %D); the DG, as predicted by $\Delta\Delta G_{\text{rel}}(\text{CC})$, is labelled in yellow.

product according to our prediction based on the DFT calculation. To rule out an empirical finding we performed

DFT calculations with additional less common directing groups that feature in drug molecules, including sulfone, carboxylate, phenol, and phenylacetic ester groups. The directing groups were ordered according to their ΔG_{rel} energy for the formation of their coordination complex **2–10a** (Table 2).

For comparison we also added the free activation energy ($\Delta\Delta G_{\text{rel}}$, **2–10a**→**2–10b**) for the C–H activation step showing that there are significant differences between these two parameters. In groups including N-oxide, phenol, carboxylic and sulfonic acid there is a strong pH dependency present as the negative charge adds strongly to the negative $\Delta G_{\text{rel}}(\text{CC})$ in the coordination complex **2–10a**. A positive charge on the potentially coordinating heteroatom (N, O, or S) inhibits the formation of complex **2–10a** completely, explaining why drug salts from strong acids (HCl, TFA, etc.) generally fail in this HIE reaction. Furthermore, we observed a strong steric effect in the formation of complex **2–10a** demonstrated in the case of the benzamides: primary amide $-28.6 \text{ kcal mol}^{-1}$, tertiary amides CONMe_2 $-25.1 \text{ kcal mol}^{-1}$, and CONe_2 $-23.0 \text{ kcal mol}^{-1}$. We conclude that Table 2 summarizes many of the common directing groups in drug discovery and therefore should be a great help for synthesis planning and predicting outcomes in HIE reactions. However, we identified some directing groups, such as NO_2 , where there is not a perfect match between the theoretical and experimental result.

Finally, we have performed HIE reactions with catalyst **1** on complex molecules **21–29** where at least two different directing groups are present (Scheme 4). The red arrow shows the predicted main deuteration or tritiation position based on the order shown in Table 2, the blue numbers in brackets

show the %D at the relevant position from the performed deuteration experiment, the red numbers show the corresponding %T from the tritium experiment. In nearly all cases where the HIE occurs with catalyst **1** we were able to predict the correct labelling position in a competition situation independently from the hydrogen isotope source.

We consider that this finding will be a useful and general principle to understand the outcome of competition reactions in which different directing groups are present in one molecule and this knowledge can likely be transferred to further transition-metal-catalyzed C–H functionalization reactions. Other research groups have found similar regioselectivities in directed C–H functionalization competition reactions for C–C or C–X bond formations in complex molecules,^[30] by applying catalysts such as iridium,^[31] rhodium,^[32] palladium,^[33] cobalt,^[34] or ruthenium^[35] metals. Establishing convenient prediction models will be extremely beneficial.^[36] We consider that with the help of improved computer-aided tools the prediction of late-stage functionalization of complex molecules can be significantly improved by taking this competition principle into account. Together with the understanding of directing-group-enhancing transformations recently described by Dai, Yu, and co-workers^[37] this research could lead to a much broader use of C–H functionalization in lead optimization in the future.

In summary we have provided a clear order of the influence of the directing group in HIE reactions with catalyst **1**. These results not only allow predictions in regioselective HIE reactions of complex molecules, but also give a perspective to the concept of directing-group-induced late-stage functionalization in general. Understanding the influence of the directing groups could allow for a much better planning of syntheses and an increase in the successful prediction of late-stage functionalization pathways. Therefore, the success rate of these reactions could be improved, and strategic synthetic management positively influenced. With this concept we aim to improve the outcome of computer-aided predictions of HIE reactions and potentially increase the effectiveness of late-stage functionalization reactions in research.

Acknowledgements

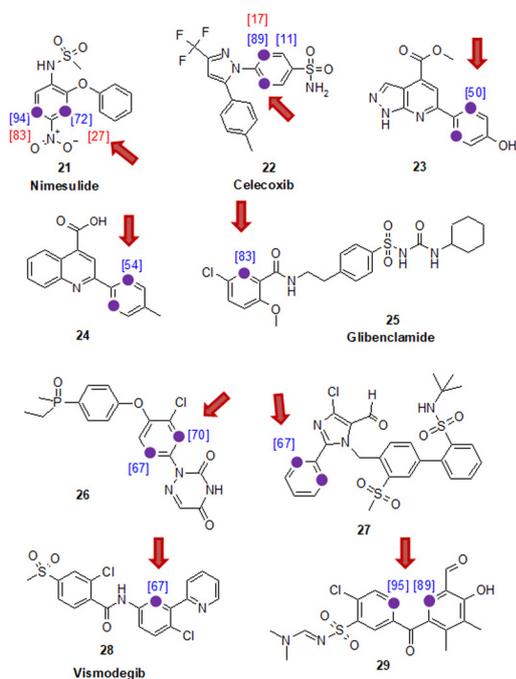
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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H functionalization · deuterium · directing groups · hydrogen isotope exchange · iridium catalysis

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Scheme 4. HIE experiment of drugs **21–29** with deuterium gas and catalyst **1**; red arrow indicates the predicted major deuteration/tritiation position based on the directing-group strength shown in Table 2.

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