Predictive model for the Ir-catalyzed hydrogen isotope exchange reaction

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Pharmaceutical drugs face a high rate of attrition despite strong financial support for the pharmaceutical industry.[1] A probable solution is to understand the metabolism and pharmacokinetics of a candidate drug in its early stages. One key methodology for monitoring the biological fate of a potential drug molecule is the hydrogen isotope exchange (HIE) by deuterium and tritium. In addition to the metabolic studies, HIE can also aid in deducing the reaction mechanisms. The transition metal-based catalysts facilitate HIE in a mild, effective, and selective manner.[2]

A widely used catalyst for HIE based on the iridium metal was developed by Kerr et al.[3] The catalyst generally activates the aromatic C-H groups that are ortho to a functional group (Figure 1a). However, certain functional groups seem to inhibit the catalyst toward HIE. We hypothesized that the catalyst may be bound to a functional group too strongly or not at all, which would explain the inhibition. Using data from the AstraZeneca database and high-throughput experiments, we aim to predict the success or failure of the HIE reaction with a machine learning model. We trained the model using structural and electronic features of reagents, as well as the pressure of deuterium/tritium gas used in the reaction. The model is currently under development and, once operational, is expected to significantly reduce the time, effort, and resources required for hydrogen isotope labeling experiments using the Kerr catalyst.
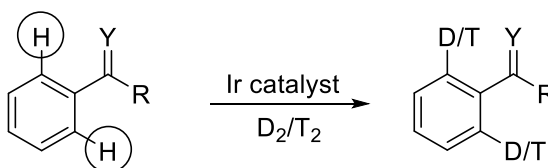
*Y and R correspond to a varying functional units,
including heteroatoms and ring systems*

Figure 1. The Ir-based catalyst developed by Kerr et el. facilitates the ortho-directed hydrogen isotope exchange.[3]

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