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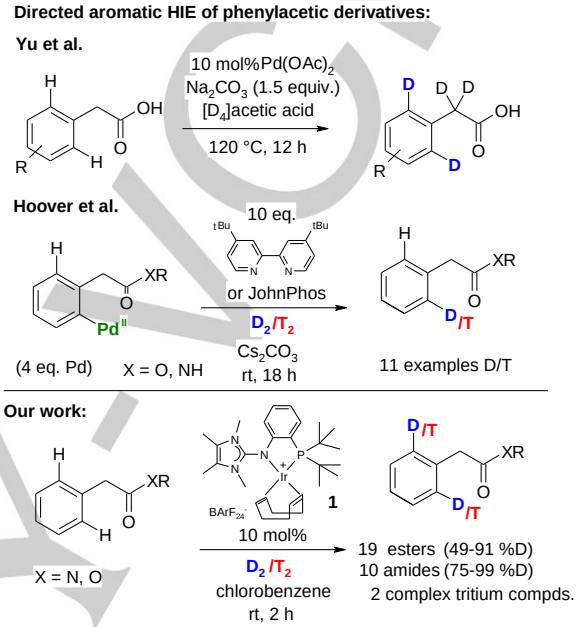
Directed Iridium-Catalyzed Hydrogen Isotope Exchange Reactions of Phenylacetic Acid Esters and Amides

Mégane Valero,[a,#] Daniel Becker,[b,#] Kristof Jess,[b] Remo Weck,[a] Jens Atzrodt,[a] Thomas Bannenberg,[b] Volker Derdau,[a,*] and Matthias Tamm[b,*]

Abstract: For the first time, a catalytic protocol for highly selective hydrogen isotope exchange (HIE) of phenylacetic acid esters and amides under very mild reaction conditions is reported. Using a homogeneous iridium catalyst supported by a bidentate phosphine-imidazolin-2-imine P,N ligand, the HIE reaction on a series of phenylacetic acid derivatives proceeds with high yields, high selectivity and with deuterium incorporation up to 99%. The method is fully adaptable to the specific requirements of tritium chemistry, and its effectiveness was demonstrated by direct tritium labeling of the fungicide benalaxyl and the drug camylofine. Further insights into the mechanism of the HIE reaction with catalyst **1** have been provided utilizing DFT calculation, NMR-studies and X-ray diffraction analysis.

Hydrogen isotope exchange (HIE) – the most fundamental of all C-H functionalization processes[1] – has become a broadly utilized strategy for the incorporation of deuterium or tritium into complex organic molecules.[2,3] In drug discovery, radioactive tritium tracers are increasingly utilized as discovery tools,[4] in covalent binding assays,[5] for tissue distribution studies,[6] for *in-vivo* profiling of new drug candidates and for other life science applications.[3,7,8] Based on homogeneous or heterogeneous catalysis, numerous HIE methods have already been described.[1,2,9] Besides an ongoing active research for C(sp^3)-H activation/deuteration,[10] particularly the selective *ortho*-directed HIE of aromatic substrates with commercial Crabtree's [11] and Kerr's catalyst [12, 13] have been investigated and successfully applied for many years. Some of the existing limitations with these classical HIE catalysts could recently be overcome by introduction of a new generation of iridium catalysts containing bidentate ligands with examples from Pfaltz[14] and Burgess.[15] We have also contributed to this field by developing the new P,N-ligated iridium catalyst **1**, which demonstrated unique reactivity features and an unprecedented HIE transition state flexibility involving 5-, 6- and even 4-membered rings.[16] As a consequence, **1** allowed to extend the scope of *ortho*-directed HIE reactions to various tertiary sulfonamides, sulfonylurea, anisoles, phosphonamides and even N-Boc-protected anilines.



Scheme 1. Known aromatic HIE reactions in comparison to our work for selective CH-activation/deuteration in phenylacetic acid esters and amides; $BArF_{24}^-$ = tetrakis[bis(3,5-trifluoromethyl)phenyl]borate.

Despite this recent progress, the selective labeling of phenylacetic acid derivatives still presents an unsolved challenge for catalytic HIE. This interesting structural motif is present in many life science products such as pharmaceutical drugs, e.g., clopidogrel, ibuprofen, naproxen etc., or fungicides like benalaxyl. In 1996, Heys studied the HIE performance of several iridium(I) complexes such as $[Ir(COD)(PCy_3)(py)]BF_4$ (PCy_3 = tricyclohexylphosphine, py = pyridine, "Crabtree's catalyst"), $[Ir(COD)(PPh_3)_2]BF_4$ and $[Ir(COD)(dppe)]BF_4$ (COD = 1,5-cyclooctadiene, dppe = diphenylphosphinoethane), and low deuterium introduction of only up to ca. 7% was found for the model substrate ethyl phenylacetate (**3**), which was ascribed to the lower preference for formation of six-membered metallacyclic intermediates upon oxidative insertion into the activated *ortho*-C–H bond. It was also shown that the latter complex containing the chelating dppe ligand was generally more effective at labeling substrates requiring the formation of six-membered metallcycles. Deuteration as well as tritiation of methyl (6-methoxynaphth-2-yl)acetate was also achieved, albeit with low deuterium (12%) and tritium (7 Ci $mmol^{-1}$) incorporation and high catalyst loadings (150 mol%).[17] Based on heterogeneous catalysis, Sajiki developed an unselective method for labeling of all aromatic protons with palladium and platinum on charcoal at 180 °C in D_2O.[18] The first selective method was reported by Yu in 2014, who discovered a palladium-catalyzed HIE reaction of phenylacetic acids with

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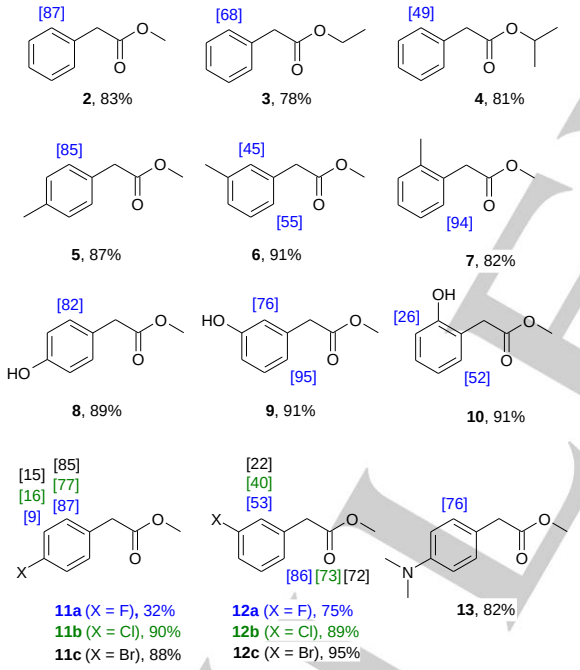
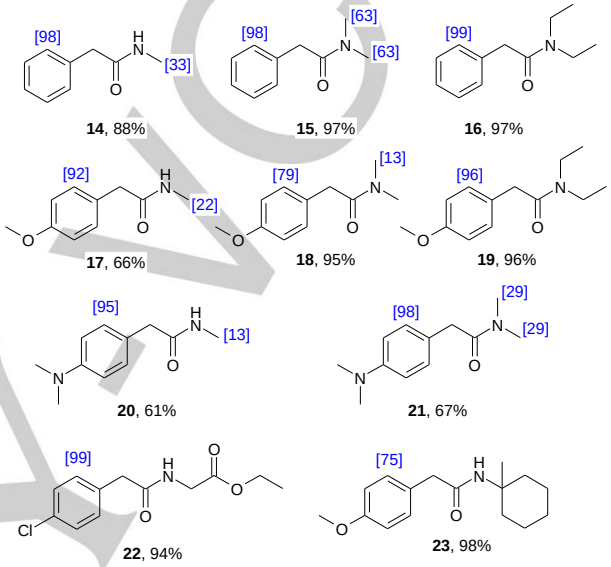
deuterated acetic acid as deuterium source (Scheme 1).[19] Recently, this approach was further improved by Hoover,[20] who generated substrate-palladium complexes, which were reduced subsequently by deuterium or tritium. However, while Yu's acetic acid method requires harsh reaction conditions (high temperature, low pH) and employs a hydrogen isotope source that is not compatible with the requirements of tritium chemistry.[21] Hoover's protocol is non-catalytic and requires a potentially troublesome precursor synthesis together with tedious removal of excess palladium and ligand. In order to circumvent these shortcomings, we became interested in developing an improved catalytic HIE method under very mild reaction conditions with D_2/T_2 as hydrogen isotope source.

We initiated our HIE studies by examining the deuteration of methyl phenylacetate (**2**) as model substrate under one atmosphere D_2 pressure. By varying the reaction parameters such as catalyst amount, solvent and temperature, optimal conditions were identified to be 10 mol% catalyst loading of **1** in chlorobenzene at room temperature. Under these conditions, a high degree of deuterium incorporation (90%) was observed for the *ortho*-position in the presence of catalyst **1**, while a screening with other established and commercially avalable iridium catalysts afforded only low levels of deuteration (< 3%D, see the Supporting Information, Table S1).



Scheme 2. HIE reaction with various phenylacetic acid esters; conditions: catalyst **1** (10 mol%), 1 atm D_2, chlorobenzene 1 mL, rt, 2 h; all reactions repeated at least twice.

Under these optimized conditions, catalyst **1** promoted *ortho*-directed deuteration of a variety of phenylacetic acid esters (**2**–**13**) with high yields, good selectivity and good to high deuterium incorporation of up to 95%D (Scheme 2). Interestingly, the efficiency of the HIE reaction depended strongly on the size of the ester function, resulting in decreasing deuterium incorporation levels in the order methyl (**2**, 87%D) > ethyl (**3**, 68%D) > isopropyl (**4**, 49%D). Additionally, the HIE reaction was somewhat sensitive towards the substitution pattern at the aryl ring. While *meta*-substitution in 3-tolylacetic acid methyl ester **6** gave 45%D and 55%D, respectively, the corresponding *para*- or *ortho*-substituted analogues gave better deuterium incorporation (85%D and 94%D). This was also observed in the halogenated substrates **11** and **12**. Interestingly, this trend was not observed for the hydroxyl-substituted esters **8**–**10**, indicating that not only steric but also electronic factors exert influence on the outcome of the HIE reaction. Increasing the reaction time to 24 h for compounds with lower deuterium incorporation like **3**, **4** or **6** had no positive effect on the final deuteration results.



Scheme 3. HIE reaction with various phenylacetic amides; conditions: catalyst **1** (10 mol%), 1 atm D_2, chlorobenzene 1 mL, rt, 2 h; all reactions repeated at least twice.

Under the general reaction conditions, *ortho*-directed deuteration of a variety of phenylacetic amides (**14**–**23**) was also achieved with high yields, good selectivity and high to excellent deuterium incorporation of up to 99%D (Scheme 3). In nearly all reactions of the N-methyl amides **14**, **15**, **17**, **18**, **20** and **21**, we observed additional deuteration at the N-methyl group with 13–33%D (**15**, 63%D) as observed previously for alkylamines containing directing groups, e.g., pyridine and pyrimidine.[22] Interestingly, these aliphatic labeling side reactions could be completely avoided by introduction of larger N-substituents like in amides **16**, **19**, **22** and **23**, indicating that excellent selectivity and deuterium incorporation can be achieved. Unfortunately, we observed no HIE reaction with primary amides or free phenylacetic acids under these reaction conditions.

We further examined the scope and limitations of this method with the more complex drug-like substrates **24**–**28** (Scheme 4). For the ibuprofen derivatives **24a**–**e**, we observed no HIE product for the primary amide **24a**,[23] but good to excellent deuterium introduction for secondary and tertiary amides **24b**–**d** (81–96%D). The corresponding ester **24e** (32%D) afforded lower deuteration efficiency compared to the amides **24b**–**d**. A remarkable selectivity and deuterium incorporation of 99%D was achieved for drug-like compound **25**[24] without labeling of the other aromatic ring systems. For both naproxen esters **26a** (75%D) and **26b** (76%D), deuteration results are identical, but interestingly, only

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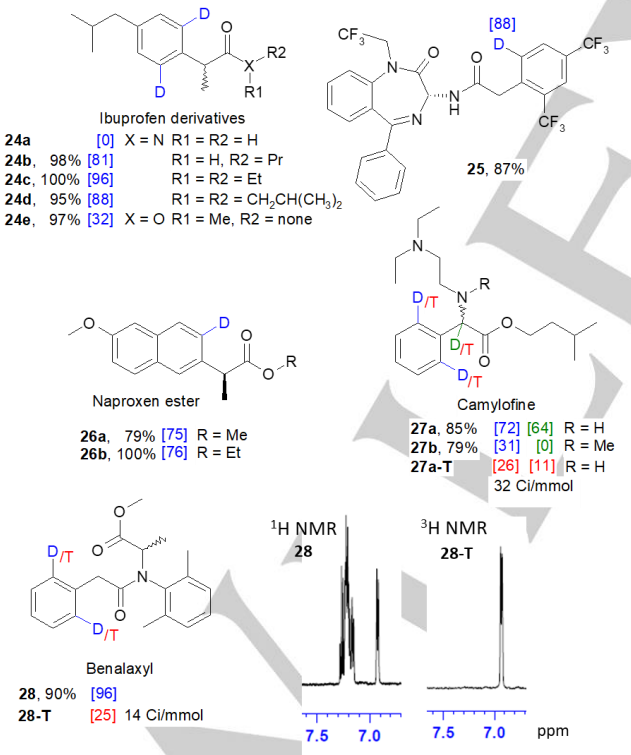
the 3-position reacted. Ester **26b** was also converted into the corresponding acid (naproxen) under basic conditions without significant loss of deuterium (for details see Supporting Information). Surprisingly, next to the expected aromatic labeling (72%D), we also observed deuteration in the benzylic position (64%D) of camylofine **27a**, a phosphodiesterase type IV inhibitor to treat stomach ache. This almost 1:1 ratio was completely reduced in favor of the aromatic position by methylation of the secondary amine function in **27b**, indicating that free NH groups have a significant effect on activity and selectivity of catalyst **1**.

Finally, we compared the results of deuteration and tritiation for two examples. While selective deuteration in the aromatic position with 72%D was found in the HIE reaction of camylofine **27a** under the optimized conditions, we observed 26%T incorporation (32 Ci/mmol specific activity in total) with 4.3 eq. of tritium gas. Benalaxyl **28**, a fungicide which inhibits the RNA polymerase I and is used in crop protection of potato and grape farming was deuterated selectively in the *ortho*-position with 96%D. Despite an expected kinetic isotope effect (D vs. T) and a much lower tritium pressure (60 mbar, 5.5 eq. vs. atmospheric deuterium pressure), a specific activity of 14 Ci/mmol was obtained, which was more than sufficient for the planned *in-vitro* studies with ^{3}H-benalaxyl (**28-T**). To the best of our knowledge, Heys reported the only other example of iridium-mediated direct tritium labeling of complex phenylacetic amides; however, this protocol required the use of 3.0–4.2 eq. of Crabtree's catalyst.[25]



Scheme 4. HIE reaction with various drug-like phenylacetic acid esters and amides; conditions: catalyst **1** (10 mol%), 1 atm D_2, chlorobenzene 1 mL, rt, 2 h; 60 mbar tritium (T_2) pressure.

Density functional theory (DFT) calculations were performed to rationalise the experimentally observed high activity of (pre-)catalyst **1** in the deuteration of phenylacetic acid derivatives. Methyl phenylacetate (**12**) was chosen as model substrate, and its binding to a cationic iridium(I) complex fragment $[(P,N)IrD_2]^+$ afforded complex **IN1** as the first stationary point on the potential energy surface (Figure 1, left). Substrate binding in intermediate **IN1** involves the carbonyl oxygen atom and an agostic *ortho*-C–H bond, which adopts an axial position *trans* to the phosphorus atom and points between the two equatorial deuterium atoms. In analogy to other mechanistic studies,[13c, 26] C–H activation represents the rate-determining step and leads to the HD complex **IN2** through σ-bond metathesis via transition state **TS1**. **IN2** is destablized by only 6.6 kcal mol^{-1} relative to **IN1** despite the formation of a less favorable six-membered metallacycle.[17] Hydride fluxionality[27] involving **TS2** gives **IN3** with a rotated HD ligand, which allows elimination and C–D bond formation through **TS3** to furnish **IN4**, which contains the *ortho*-deuterated substrate **2**-*d* (Figure 1, right). To confirm that C–H activation represents the rate-determining step, the kinetic isotope effect (KIE)[28] was studied theoretically and experimentally for the deuteration of **2** and for the hydrogenation of dideuterated (2,6-$C_6H_3D_2$)C(O)OMe (**2**-d_2), respectively (see the Supporting Information, Scheme S3, Figures S5 and S6). The calculated and experimental KIE values of 3.5 and 3.5(3) are identical within the experimental error and also in good agreement with the values derived from related reactions.[26] These findings substantiate our mechanistic proposal, and the low activation barriers associated with the C–H and C–D activation steps confirm the observed high catalytic activtiy of **1**.

While Heys has shown that arylacetates resisted efficient iridium-catalyzed HIE, the related substrates N-phenylacetamide, MeC(O)NHPh, and phenyl acetate, MeC(O)OPh, gave markedly better results, indicating that replacing the bridging unit CH_2 by NH or O is favorable to achieve *ortho*-deuteration via the formation of a six-membered metallcycle.[17] Therefore, the profile for the C–H activation step (**IN1**→**TS1**→**IN2**) was also calculated for these substrates, revealing the expected lower activation barriers and significant stabilization of the corresponding intermediates, expecially for the acetamide (NH) derivative, which can be ascribed to conjugation within the NH- and O-bridged metallacycles (see the Supporting Information, Figure S7).

Occassionally, a blue colouration of the solution was observed under the HIE reaction conditions described above, hinting at the formation of a new iridium species. A dark blue complex was isolated by stirring a solution of **1** in CH_2Cl_2 and toluene under dihydrogen atmosphere, and its ^{1}H NMR spectrum gave rise to a characteristic highfield multiplet at –28.14 ppm that collapsed to a singlet by phosphorus decoupling and could be assigned to two hydrogen atoms per ligated iridium atom by accurate integration.[29] These findings are in agreement with the composition $[(P,N)IrH_2][BArF_{24}]$ as also confirmed by elemental analysis. Single crystals of this species were obtained by slow diffusion of hexane into a saturated dichloromethane solution, and X-ray diffraction analysis afforded the molecular structure of the dicationic diiridium complex $[(P,N)_2Ir_2H_4][BArF_{24}]_2$ (**29**, Figure 2). The positions of two bridging hydrogen atoms could be refined, whereas two additional hydrogen atoms are expected to reside in terminal positions at each iridium atom presumably in a *trans*-orientation above and below the Ir_2H_2 plane as found in related systems.[30] To verify the presence of terminal hydrides, an IR spectrum of **29** was recorded in CH_2Cl_2 solution, which revealed a sharp signal at 2307 cm^{-1} (see the Supporting Information, Figure S3), which is in good agreement with the calculated IR

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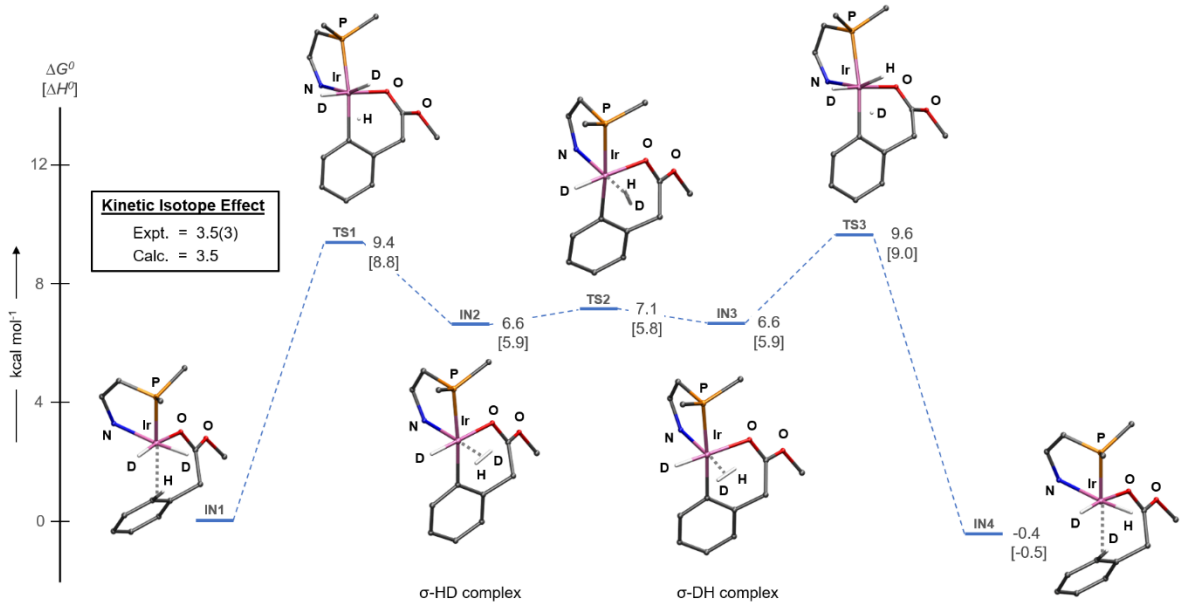

Figure 1. Potential energy profile for *ortho*-deuteration of phenyl acetic methylester (**2**) with iridium catalyst **1**, scaled to Gibbs free energy (ΔG^0). All theoretical calculations were performed according to the Density Functional Theory (DFT) method M06/6-311G(d,p) for all main group elements and a "Stuttgart 1997 ECP" – double-ξ basis set with an effective core potential – for the 5d transition metal iridium. For the stationary points, all hydrogen atoms, except for those involved in the reaction pathway, were omitted for clarity, and only a rudimentary N–C–C–P–C2 skeleton of the P,N ligand is shown.

stretching frequency of 2341 cm^{-1} (in the gas phase) and the corresponding values reported for other iridium complexes bearing terminal hydrides.[31] The Ir–Ir distance is 2.5978(4) Å and falls in the range observed for related bimetallic iridium(III) complexes featuring an Ir_2H_4 moiety with bridging and terminal hydrogen atoms.[30] However, the observation of only one highfield ^{1}H NMR resonance at –28.14 ppm indicates fast exchange between terminal and bridging positions on the NMR time scale, which could not be resolved by a variable-temperature NMR study in the range from 298 to 183 K (see the Supporting Information, Figure S2). Nevertheless, further studies are required to elucidate the hydrogen exchange mechanism in this system. Interestingly attempts to perform HIE on substrate **2** in the presence of complex **29** in chlorobenzene at room temperature afforded only marginal deuterium incorporation, indicating that this complex is not part of the catalytic cycle, but represents a deactivated form or an overly stabilized resting state, respectively.

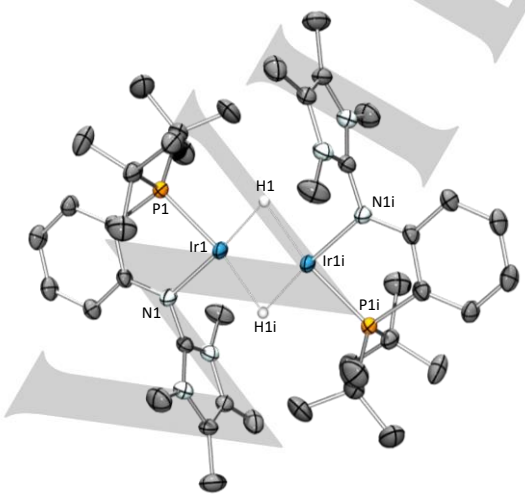

Figure 2. ORTEP diagram of the dication in the complex $[(P,N)_2Ir_2H_4][BArF_{24}]_2$ (**29**); all hydrogen atoms except for the bridging ones have been omitted for clarity; the positions of the expected terminal hydrides could not be refined.

In conclusion, we have developed the first efficient catalytic protocol for *ortho*-selective hydrogen isotope exchange (HIE) of pharmacologically important phenylacetic acid esters and amides under very mild reaction conditions. This method is fully adaptable to the specific requirements of tritium chemistry, which is demonstrated by direct tritium labeling of benalaxyl and camylofine. DFT calculations and kinetic studies give insights into the mechanism of the HIE reaction and explain the observed high activity and selectivity of catalyst **1**, which is remarkable considering the required formation of six-membered non-conjugated metallacycles upon *ortho*-C–H activation. Therefore, one of the longstanding challenges in iridium-catalyzed C–H functionalization and HIE has been solved, and we believe that our findings will stimulate further application of **1** and related catalysts in this field.

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Keywords: hydrogen isotope exchange • C-H activation • iridium • homogeneous catalysis • kinetic isotope effect

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Layout 2:

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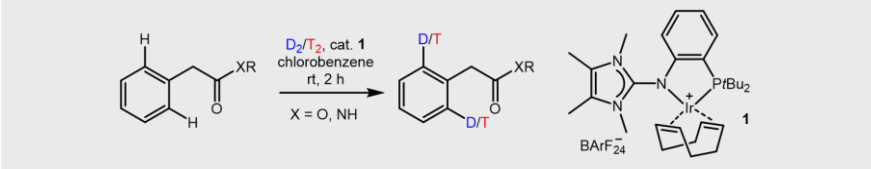

Mild, selective and efficient: The first efficient iridium-catalyzed protocol for *ortho*-selective iridium-catalyzed deuteration and tritiaton of pharmacologically important phenylacetic acid esters and amides has been developed, which proceeds smoothly despite the formation of unfavorable non-conjugated six-membered metallacyclic intermediates.

Mégane Valero, Daniel Becker, Kristof Jess, Remo Weck, Jens Atzrodt, Thomas Bannenberg, Volker Derdau, and Matthias Tamm**

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Directed Iridium-Catalyzed Hydrogen Isotope Exchange Reactions of Phenylacetic Acid Esters and Amides