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FULL PAPER

Ruthenium-catalyzed Deuteration of Aromatic Carbonyl Compounds with a Catalytic Transient Directing Group

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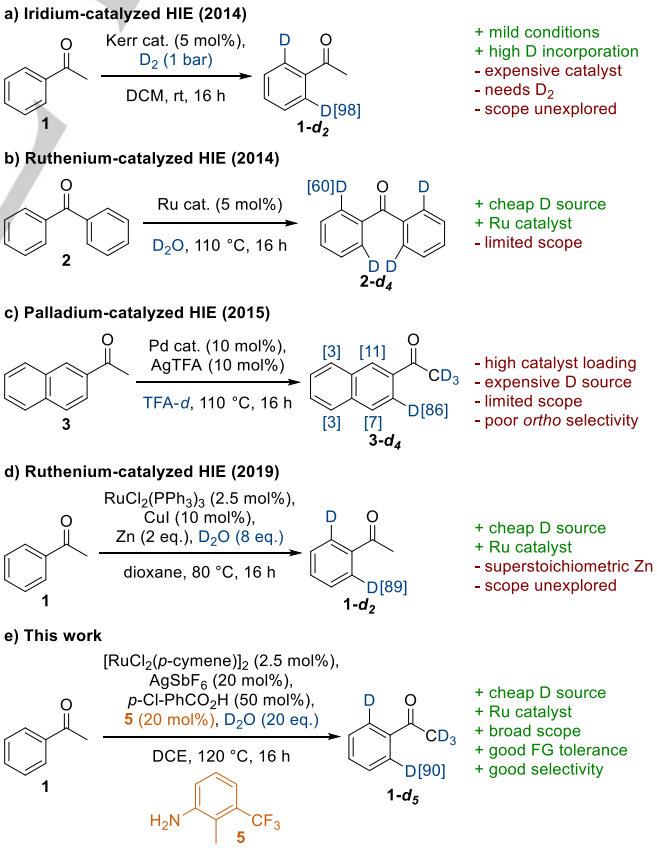
Abstract: A novel ruthenium-catalyzed C-H activation methodology for hydrogen isotope exchange of aromatic carbonyl compounds is presented. In the presence of catalytic amounts of specific amine additives, a transient directing group is formed *in situ*, which directs selective deuteration. A high degree of deuteration is achieved for *α*-carbonyl and aromatic *ortho*-positions. In addition, appropriate choice of conditions allows for exclusive labeling of the *α*-carbonyl position while a procedure for the preparation of merely *ortho*-deuterated compounds is also reported. This methodology proceeds with good functional group tolerance and can be also applied for deuteration of pharmaceutical drugs. Mechanistic studies reveal a kinetic isotope effect of 2.2, showing that the C-H activation is likely the rate-determining step of the catalytic cycle. Using deuterium oxide as a cheap and convenient source of deuterium, the methodology presents a cost-efficient alternative to state-of-the-art iridium-catalyzed procedures.

Introduction

Being an elegant approach to label a compound without altering its physical properties, structure, or biological function, the selective exchange of hydrogen for its heavier isotope deuterium continues to be of interest for many scientists.[1] Especially in the context of medicinal chemistry, the introduction of deuterium as a bioisosteric replacement of protium in specific, metabolically labile or racemization prone positions of drug candidates such as *α* carbonyl positions can mitigate deleterious pathways thanks to the kinetic isotope effect (KIE).[2] The formation of potentially toxic metabolites is thereby prevented while a more general improvement of the absorption, distribution, metabolism and excretion (ADME) properties of the drug candidate is possible at the same time.[2] The development of selective hydrogen isotope exchange (HIE) methodologies can further be important for the preparation of starting materials for KIE studies relevant for the investigation of reaction mechanisms.[3] Here, substrates with deuteration *ortho* to a functional group can be interesting.[4] In contrast, the preparation of MS standards for metabolism studies requires the incorporation of several deuterium atoms at once rather than selective deuteration to avoid overlap of unlabeled and labeled compounds in the mass spectrum.[1b] For this purpose, acetophenone derivatives are particularly attractive substrates, given their prevalence in biologically relevant compounds on the one hand, as well as the presence of two potential labeling sites in their structure on the other hand: While the slightly acidic *α* carbonyl hydrogen atoms are subject to acid- or base-catalyzed hydrogen isotope exchange (HIE),[5] the ketone moiety has also been explored as a directing group in iridium-catalyzed *ortho*-selective deuteration.[6] Having focused largely on unsubstituted acetophenone and benzophenone as substrates, excellent deuterium incorporation has been observed among others with the so-called Kerr catalyst under deuterium gas atmosphere and mild conditions (Scheme 1a).[6f]



Scheme 1. Homogeneous transition metal-catalyzed HIE of aromatic ketones.

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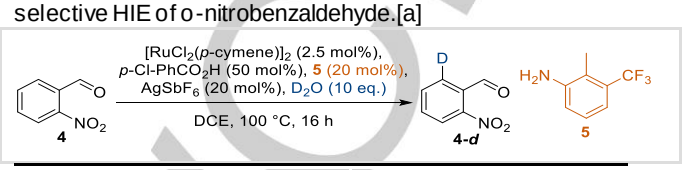
Although it would be worth investigating scope and functional group tolerance of these methodologies further, the use of alternative transition metal catalysts as well as cheaper deuterium sources is also appealing. However, attempts to replace iridium by ruthenium[7] or palladium[8] for ketone-directed HIE have been met with only limited success so far.[9] In spite of delivering moderate deuterium incorporations for benzophenones (Scheme 1b), these methodologies showed reduced or no reactivity for acetophenone derivatives.[7a,8] Moreover, using deuterated trifluoroacetic acid as deuterium source, concomitant electrophilic aromatic substitution hampers the *ortho*-selectivity of the directed palladium-catalyzed approach (Scheme 1c).[8]

Interestingly, Plietker and co-workers achieved moderate to good deuteration levels in acetophenone derivatives under ruthenium catalysis in the presence of (over)stoichiometric amounts of zinc additives (Scheme 1d).[7b] An alternative concept for homogeneous ruthenium-catalyzed aromatic HIE makes use of nitrogen containing directing groups.[7,10] Circumventing the need to pre-synthesize such directing groups, we recently reported a manganese-catalyzed deuteration of benzaldehydes in the presence of catalytic amine additives that form a transient directing group (TDG) *in situ*.[11] This concept had previously been shown to be effective under ruthenium catalysis among others[12] for the alkylation,[13] amination,[14] and radical difluoroalkylation[15] of aromatic aldehydes, but can also be used for the C–H functionalization of ketones when using palladium[16] and rhodium[17] catalysts. Building on this knowledge and aiming towards a cost-efficient procedure for the deuteration of ketones, we wish to report herein a novel useful ruthenium-catalyzed deuteration of aromatic aldehydes and ketones (Scheme 1e).

Results and Discussion

Inspired by the work on ruthenium-catalyzed functionalization of aromatic aldehydes in the presence of anilines,[13a] we investigated the deuteration of *o*-nitrobenzaldehyde as model substrate with 10 eq. of deuterium oxide as deuterium source in the presence of common ruthenium catalysts. While cyclometalated ruthenium complexes as developed in our group[18] as well as NHC ligated metathesis catalysts performed well, the best results were achieved with the simple and commercially available ruthenium chloride *p*-cymene dimer (Table 1, entry 1). Notably, the addition of *p*-chlorobenzoic acid and silver hexafluoroantimonate are necessary to activate the ruthenium complex. Alternative ruthenium precursors such as ruthenium chloride or dodecacarbonyl ruthenium(0) were not effective and the addition of various phosphine ligands slowed down the reaction. In the absence of the ruthenium catalyst no reaction took place although high deuteration was still obtained with a catalyst loading as low as 1.25 mol% (Table 1, entries 2-4). Notably, the exact substitution pattern of the transient directing group plays a minor role. A good balance between a sufficiently stable imine intermediate and good catalytic turnover is achieved with electron-deficient anilines such as *o*- and *p*-aminobenzotrifluoride as well as 2-methyl-3-trifluoromethyl aniline **5**. Further, the isolation of deuterated aldehyde could be improved without impacting the deuterium incorporation by decreasing the aniline loading to 10 mol% which lowered the amount of remaining imine after the reaction (Table 1, entry 5). No deuteration takes place in the absence of the aniline, confirming that the TDG is needed for this transformation (Table 1, entry 6). In this context, it is worth mentioning that previous attempts to deuterate aldehydes under ruthenium catalysis but without a transient directing group strategy had failed.[7a] Lowering the temperature to 80 °C diminished the deuterium incorporation significantly whereas the recovery of deuterated aldehyde was reduced at elevated temperature (Table 1, entries 7 and 8). Lastly, the scale of the reaction can be increased 10-fold without affecting deuterium incorporation and yield (Table 1, entry 9).

Table 1. Ruthenium-catalyzed and TDG-mediated *o*-selective HIE of *o*-nitrobenzaldehyde.[a]



Entry	Variation	D [%][b]	Yield [%][c]
1	none	92	75
2	no [Ru][d]	0	n.d.
3	1.25 mol% $[Ru]_2$	84	n.d.
4	0.5 mol% $[Ru]_2$	52	n.d.
5	**10 mol% 5**	**91**	**85**
6	no 5	0	n.d.
7	80 °C	35	n.d.
8	120 °C	91	65
9	10 mol% **5**, 5 mmol scale	90	84

[a] 0.5 mmol scale. Further optimization details can be found in the SI. [b] Determined by ^{1}H NMR using the aldehyde or *m*/*p*-resonances as reference. [c] Isolated yields. [d] 120 °C, 24 h.

Having established optimal reaction conditions for the ruthenium- and aniline-catalyzed deuteration of aldehydes, we explored the scope of this transformation, particularly seeking to address some of the limitations of our previously published manganese-catalyzed HIE reaction which showed diminished reactivity for sterically hindered substrates and did not tolerate free hydroxy groups.[11] Besides, slightly modified reaction conditions were needed for electron-deficient substrates. This new methodology on the other hand appears to be remarkably robust, delivering excellent deuterium incorporations and yields for both electron-deficient and electron-rich (hetero)arenes under unchanged conditions (Scheme 2). Moreover, free hydroxy groups as in vanillin are tolerated and even the sterically hindered *tert*-butylbenzaldehyde is deuterated smoothly.

Interestingly, in the case of naphthaldehyde and benzothiophene-3-carboxaldehyde, both *ortho*- and *peri*-positions are deuterated, whereas our previously reported methodology furnished exclusive labeling in the *ortho*-position.

Encouraged by these results, we attempted the TDG-enabled deuteration of aromatic ketones. Under the optimized conditions *vide supra* but in the absence of catalytic amines, only 12% deuterium incorporation in the *ortho*-positions of acetophenone was observed, confirming the challenging nature of HIE on this type of substrates (Table 2, entry 1). However,

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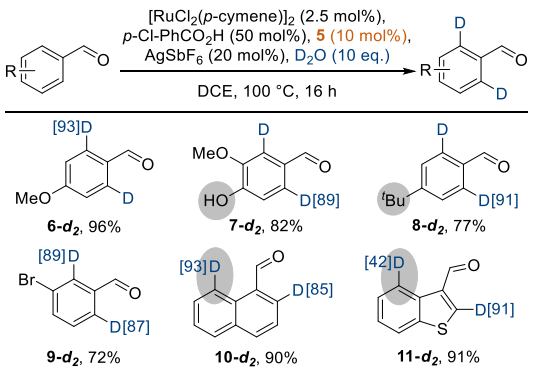
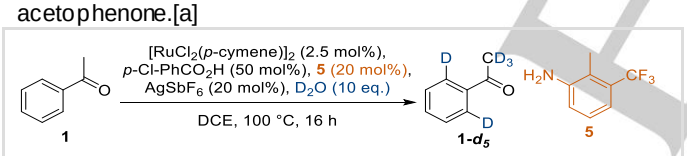
adding 20 mol% of aniline **5** as TDG, the deuteration efficiency was raised significantly (Table 2, entry 2). In contrast to the reaction on aldehydes, other anilines including *o*- and *p*-aminobenzo-trifluoride afforded moderate to low deuterium incorporation whereas *m*-aminobenzotrifluoride delivered very good results comparable to **5**. We explain this different behavior by the lower reactivity of ketones compared to aldehydes towards imine formation, requiring more nucleophilic amines. Finally, a deuteration degree of 90% could be obtained after raising the temperature and increasing the amount of deuterium oxide (Table 2, entry 3). Under these conditions, high deuteration levels are additionally achieved in the *α*-carbonyl position, furnishing an overall incorporation of five deuterium atoms per molecule.



Scheme 2. Scope of aldehydes (0.5 mmol scale). Deuterium incorporations were determined by ^{1}H NMR using the aldehyde or *m*/*p*-resonances as reference and are indicated in square brackets. Yields are given under the structures.

Table 2. Ruthenium- and TDG-catalyzed o-selective HIE of acetophenone.[a]

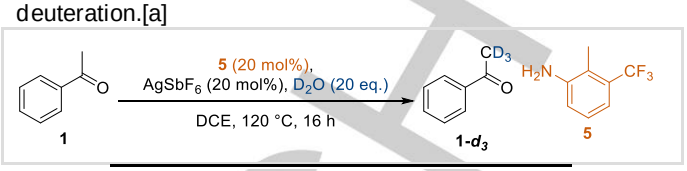


Entry	Variation	D (*o*) [%][b]	D (*α*) [%][b]
1	no TDG	12	46
2	none	74	86
3	120 °C, 20 eq. D_2O	90	90

[a] 0.5 mmol scale. Further optimization details can be found in the SI. [b] Determined by ^{1}H NMR using the resonance for the *p*-position as reference.

As shown by control experiments (Table 3), this latter reaction likely proceeds via an amine-mediated enamine formation and requires the Lewis acidic silver salt or the benzoic acid derivative as a catalyst. Indeed, in the absence of the ruthenium catalyst, ketones are solely deuterated in *α*-position. Finally, a broad range of acetophenone derivatives could be successfully converted to the *ortho*- and *α*-deuterated analogues using this newly developed methodology (Scheme 3). Substituents in *ortho*-, *meta*-, and *para*-positions were all tolerated and deuteration levels appeared to be only slightly affected by steric effects. Especially electron-rich and neutral arenes afforded very good deuterium incorporation, whereas electron-deficient acetophenone derivatives were somewhat less feasible substrates.

Table 3. Amine- and silver-catalyzed α-carbonyl deuteration.[a]



Entry	Variation	D (*α*) [%][b]
1	none	93
2	no $AgSbF_6$	62
3	no **5**	46

[a] 0.5 mmol scale. [b] Determined by ^{1}H NMR using the resonance for the *p*-position as reference.

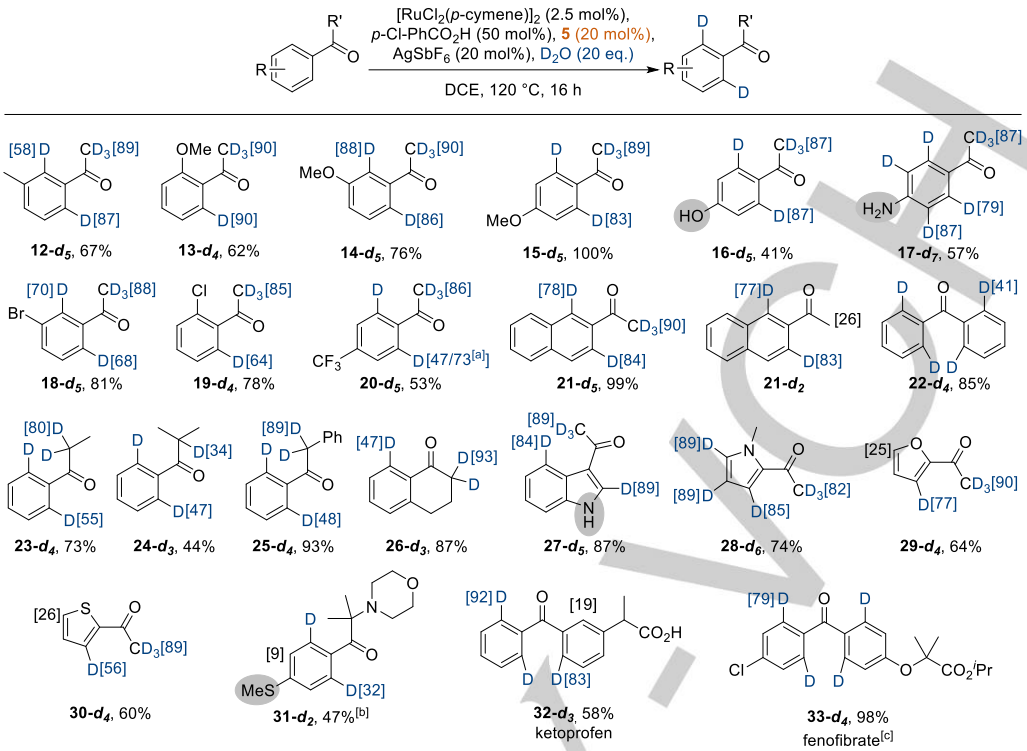
However, using 50 mol% rather than 20 mol% of the TDG, the deuterium incorporation of trifluoromethyl-substituted ketone **20** increased markedly. It can thus be deduced that the lower deuterium incorporation observed under standard conditions can be explained by the short-lived nature of the corresponding imine intermediate rather than factors involving the C-H activation step.

Furthermore, the reaction is compatible with reactive functional groups such as free alcohols (**16**), tertiary as well as free amino groups (**31** and **17**), unprotected heterocycles (**27**), and thioethers (**31**).[19] Highly electron-rich substrates such as compounds **17** and **28** engage in concomitant deuteration by electrophilic aromatic substitution, affording perdeuterated products. Increasing the chain length of acetophenone (**23**) and including branched structures (**24**) led to decreased deuterium incorporation. It thus appears that increased steric hindrance on this side of the ketone substrate interferes with either imine formation or coordination to the ruthenium catalyst.

If exclusive labeling in the *ortho*-position is desired, the deuterated compounds can simply be reacted with water under silver and amine catalysis, thus reversing the deuteration of the methyl group (**21-*d*$_2$**).

Mass spectrometric analysis of the isolated deuterated products showed that in almost all cases no non-deuterated compounds were present, rendering the herein presented procedure relevant for the preparation of isotopically labeled LC-MS standards. Besides, the preparation of deuterated pharmaceuticals is also feasible as demonstrated in the successful deuteration of marketed drugs ketoprofen (**32**) and fenofibrate (**33**).

In agreement with previous reports,[13a] it can be proposed that the ruthenium catalyst is activated by silver-mediated halide abstraction and coordination of the *p*-chlorobenzoic acid additive. At the same time, acid-catalyzed condensation of aniline and aldehyde or ketone to the imine intermediate takes place, preparing for subsequent coordination to ruthenium followed by C-H activation. For *o*-nitrobenzaldehyde, we measured a kinetic isotope effect (KIE) of 2.2, indicating that the C-H activation is likely the rate-determining step of the reaction. Its reverse finally leads to the deuterated product while the excess of deuterium oxide along with the KIE enable high conversions.



Scheme 3. Ruthenium-catalyzed HIE in the presence of a TDG: Scope of ketones. Deuterium incorporations were determined by ^{1}H NMR using the resonances for the *p*-position as reference and is indicated in square brackets. Yields are given under the structures. [a] 50 mol% TDG used. [b] 4 days reaction time. [c] 4 consecutive deuteration cycles.

Conclusion

In conclusion, we have demonstrated a novel ruthenium-catalyzed hydrogen isotope exchange reaction of aromatic aldehydes and ketones using the cheapest deuterium source as a viable alternative to the more expensive state-of-the art iridium-catalyzed methodologies. Using a catalytic transient directing group strategy, the difficulties in the C-H activation of such substrates could be mitigated. Furthermore, appropriate choice of reaction conditions allows for selective deuteration in either *ortho*- or *α*-positions or at both sites at the same time. The importance of this methodology in the context of drug design and metabolism studies is showcased by the successful preparation of deuterated analogues of marketed drugs.

Experimental Section

Representative procedure for the deuteration of aldehydes: The aldehyde (0.5 mmol), *p*-chlorobenzoic acid (39 mg, 0.25 mmol, 0.5 eq.), 2-methyl-3-trifluoromethyl-aniline (8.8 mg, 50 µmol, 10 mol%), dichloro(*p*-cymene)ruthenium(II) dimer (7.7 mg, 12.5 µmol, 2.5 mol%), and silver hexafluoroantimonate (34 mg, 0.1 mmol, 20 mol%) were weighed into a 25 mL pressure-resistant Schlenk tube equipped with a magnetic stirring bar. The Schlenk tube was evacuated and backfilled with argon three times. DCE (900 µL) and D_2O (100 µL) were added. Liquid aldehydes were also added at this stage. The reaction mixture was subsequently heated to 100 °C and stirred at this temperature for 16 hours. The resulting suspension was diluted with DCM, washed with an aqueous saturated solution of sodium bicarbonate (20 mL), and extracted with DCM (2x 20 mL). The combined organic layers were washed with distilled water (20 mL), dried over sodium sulfate and concentrated. The deuterated products were then purified by silica column chromatography with eluent systems of pentane and ethyl acetate.

Representative procedure for the deuteration of ketones. The ketone (0.5 mmol), *p*-chlorobenzoic acid (39 mg, 0.25 mmol, 0.5 eq.), 2-methyl-3-trifluoromethyl-aniline (18 mg, 0.1 mmol, 20 mol%), dichloro(*p*-cymene)ruthenium(II) dimer (7.7 mg, 12.5 µmol, 2.5 mol%), and silver hexafluoroantimonate (34 mg, 0.1 mmol, 20 mol%) were weighed into a 25 mL pressure-resistant Schlenk tube equipped with a magnetic stirring bar. The Schlenk tube was evacuated and backfilled with argon three times. DCE (300 µL) and D_2O (200 µL) were added. Liquid ketones were also added at this stage. The reaction mixture was subsequently heated to 120 °C and stirred at this temperature for 16 hours. The resulting suspension was diluted with DCM, washed with an aqueous saturated solution of sodium bicarbonate (20 mL), and extracted with DCM (2x 20 mL). The combined organic layers were washed with water (20 mL), dried over sodium sulfate and concentrated. The deuterated products were then purified by silica column chromatography with eluent systems of pentane and ethyl acetate.

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Keywords: C-H activation • hydrogen isotope exchange • ketones • ruthenium • transient directing group

[1] a) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 3022-3047; *Angew. Chem.* **2018**, *130*, 3074-3101; b) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 1758-1784; *Angew. Chem.* **2018**, *130*, 1774-1802.

[2] T. Pirali, M. Serafini, S. Cargnin, A. A. Genazzani, *J. Med. Chem.* **2019**, *62*, 5276-5297.

[3] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072; *Angew. Chem.* **2012**, *124*, 3120-3126.

[4] Recent examples: a) Q. Dherbassy, J.-P. Djukic, J. Wencel-Delord, F. Colobert, *Angew. Chem. Int. Ed.* **2018**, *57*, 4668-4672; *Angew. Chem.* **2018**, *130*, 4758-4762; b) R. A. Jagtap, C. P. Vinod, B. Punji, *ACS Catal.* **2019**, *9*, 431-441.

[5] a) C. Rappe, W. H. Sachs, *Tetrahedron* **1968**, *24*, 6287-6290; b) J. Yao, R. F. Ervilia, *J. Am. Chem. Soc.* **1994**, *116*, 11229-11233; c) C. Berthelette, J. Scheigetz, *J. Label. Compd. Radiopharm.* **2004**, *47*, 891-894; d) M. Zhan, T. Zhang, H. Huang, Y. Xie, Y. Chen, *J. Label. Compd. Radiopharm.* **2014**, *57*, 533-539; e) Y. Chang, T. Myers, M. Wasa, *Adv. Synth. Catal.* **2020**, *362*, 360-364; f) K. I. Galkin, E. G. Gordeev, V. P. Ananikov, *Adv. Synth. Catal.* **2021**, *363*, 1368-1378.

[6] a) J. R. Heys, A. Y. L. Shu, S. G. Senderoff, N. M. Phillips, *J. Label. Compd. Radiopharm.* **1993**, *33*, 431-438; b) D. Hesk, P. R. Das, B. Evans, *J. Label. Compd. Radiopharm.* **1995**, *36*, 497-502; c) G. J. Ellames, J. S. Gibson, J. M. Herbert, A. H. McNeill, *Tetrahedron* **2001**, *57*, 9487-6597; d) J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson, G. N. Nilsson, *Chem. Commun.* **2008**, 1115-1117; e) A. R. Cochrane, S. Irvine, W. J. Kerr, M. Reid, S. Andersson, G. N. Nilsson, *J. Label. Compd. Radiopharm.* **2013**, *56*, 451-454; f) J. A. Brown, A. R. Cochrane, S. Irvine, W. J. Kerr, B. Mondal, J. A. Parkinson, L. C. Paterson, M. Reid, T. Tuttle, S. Andersson, G. N. Nilsson, *Adv. Synth. Catal.* **2014**, *356*, 3551-3562, g) M. Parmentier, T. Hartung, A. Pfaltz, D. Muri, *Chem. Eur. J.* **2014**, *20*, 11496-11504; h) K. Jess, V. Derdau, R. Weck, J. Atzrodt, M. Freytag, P. G. Jones, M. Tamm, *Adv. Synth. Catal.* **2017**, *359*, 629-638.

[7] a) L. Piola, J. A. Fernández-Salas, S. Manzini, S. P. Nolan, *Org. Biomol. Chem.* **2014**, *12*, 8683-8688; b) P. Eisele, F. Ullwer, S. Scholz, B. Plietker, *Chem. Eur. J.* **2019**, *25*, 16550-16554.

[8] R. Giles, G. Ahn, K. W. Jung, *Tetrahedron Lett.* **2015**, *56*, 6231-6235.

[9] Concerning directing groups other than ketones, both ruthenium and palladium-catalyzed methodologies have been demonstrated as viable alternatives to iridium-catalyzed HIE. See ref. 7a and: a) V. Müller, R. Weck, V. Derdau, L. Ackermann, *ChemCatChem* **2020**, *12*, 100-104; b) S. Ma, G. Villa, P. S. Thuy-Boun, A. Homs, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2014**, *53*, 734-737; *Angew. Chem.* **2014**, *126*, 753-756.

[10] L.-L. Zhao, W. Liu, Z. Zhang, H. Zhao, Q. Wang, X. Yan, *Org. Lett.* **2019**, *21*, 10023-10027.

[11] S. Kopf, H. Neumann, M. Beller, *Chem. Commun.* **2021**, *57*, 1137–1140.

[12] a) P. Gandeepan, L. Ackermann, *Chem* **2018**, *4*, 199-222; b) S. St John-Campbell, J. A. Bull, *Org. Biomol. Chem.* **2018**, *16*, 4582-4595; c) B. Niu, K. Yang, B. Lawrence, H. Ge, *ChemSusChem* **2019**, *12*, 2955-2969; d) J. I. Higham, J. A. Bull, *Org. Biomol. Chem.* **2020**, *18*, 7291-7315.

[13] a) F. Li, Y. Zhou, H. Yang, D. Liu, B. Sun, F.-L. Zhang, *Org. Lett.* **2018**, *20*, 146-149; b) Z.-Y. Li, H. H. C. Lakmal, X. Qian, Z. Zhu, B. Donnadieu, S. J. McClain, X. Xu, and X. Cui, *J. Am. Chem. Soc.* **2019**, *141*, 15730-15736; c) G. Li, Q. Liu, L. Vasamsetty, W. Guo, J. Wang, *Angew. Chem. Int. Ed.* **2020**, *59*, 3475-3479; *Angew. Chem.* **2020**, *132*, 3503-3507.

[14] O. K. Rasheed, *Synlett* **2018**, *29*, 1033-1036.

[15] Y. Cheng, Y. He, J. Zheng, H. Yang, J. Liu, G. An, G. Li, *Chin. Chem. Lett.*, doi:10.1016/j.cclet.2020.09.044.

[16] a) J. Xu, Y. Liu, Y. Wang, Y. Li, X. Xu, Z. Jin, *Org. Lett.* **2017**, *19*, 1562-1565; b) J. Wang, C. Dong, L. Wu, M. Xu, J. Lin, K. Wei, *Adv. Synth. Catal.* **2018**, *360*, 3709-3715.

[17] A. E. Hande, V. B. Ramesh, K. R. Prabhu, *Chem. Commun.* **2018**, *54*, 12113-12116.

[18] P. Piehl, R. Amuso, E. Alberico, H. Junge, B. Gabriele, H. Neumann, M. Beller, *Chem. Eur. J.* **2020**, *26*, 6050-6055.

[19] Substrates 16 and 17 engage in some side reactions and thus give somewhat diminished, but nevertheless synthetically useful yields of deuterated products.

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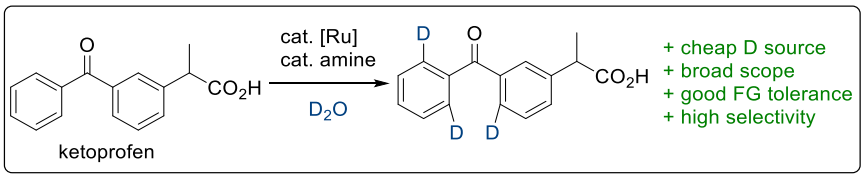

Everything is transient …: The combination of a ruthenium catalyst with amines enables the C-H activation and deuteration of aromatic carbonyl compounds in a general manner. Using D_2O as a convenient source of deuterium, high deuteration levels were achieved and the application of this methodology for the preparation of deuterated pharmaceuticals was demonstrated.

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