



Ruthenium(II)-Catalyzed Hydrogen Isotope Exchange of Pharmaceutical Drugs by C–H Deuteration and C–H Tritiation

Valentin Müller,^[a] Remo Weck,^[b] Volker Derdaau,^[b] and Lutz Ackermann^{*[a]}

Well-defined ruthenium(II) biscarboxylate complexes enabled selective *ortho*-deuteration with weakly-coordinating, synthetically useful carboxylic acid with outstanding levels of isotopic labeling. The robust nature of the catalytic system was reflected by a broad functional group tolerance in an operationally-simple manner, allowing the isotope labeling of challenging pharmaceuticals and bioactive heterocyclic motifs. The synthetic power of our method was highlighted by the selective tritium-labeling of repaglinide, an antidiabetic drug, providing access to defined tritium labeled therapeutics.

Hydrogen isotope exchange (HIE) of otherwise inert C–H bonds promoted by transition-metal catalysts has emerged as a valuable tool for the clarification of reaction mechanisms, as reference materials in mass-dependent analytical chemistry and for the improvement of bioactive drugs in pharmaceutical industries.^[1] Despite rapid advancements in analytical techniques over the past 20 years, the selective introduction of isotopes into a molecule, without changing its function, remains the most effective method to detect and quantify drugs and drug metabolites in a complex matrix.^[2] However, isotope-labeled pharmaceuticals are usually prepared in lengthy, multi-step procedure and require expensive labeled precursors. As an alternative strategy, the direct labeling of organic molecules through C–H late-stage activation bears great potential in this field especially for the post-synthetic modification of structurally complex molecules.^[3] This approach has recently initiated

numerous applications in the pharmaceutical industries, where the increasing impact of new therapeutics and “absorption, distribution, metabolism and excretion” (ADME) studies is leading to an increasing demand for the efficient synthesis of isotopically labeled compounds.^[4] In this context, highly selective transition metal-catalyzed HIE reactions at aromatic C–H moieties of pharmaceuticals are still one of the key challenges,^[5] because the catalyst needs to be compatible with a variety of functional groups that are commonly present in marketed pharmaceuticals. The most prominent homogeneous catalysts for the late-stage modification of drug candidates are Crabtree’s iridium catalyst^[6] and Kerr’s iridium-carbene complex,^[7] among other transition metal species.^[8] Despite the increasing synthetic abilities of metal complexes towards C–H activation of organic molecules,^[9] selective HIE of pharmaceuticals continues to be extremely rare. A recent example that addresses this synthetic challenge by the Chirik group achieved the deuteration and tritiation of pharmaceutical drugs at aromatic C–H moieties with orthogonal site selectivity relative to Crabtree’s iridium catalyst (Figure 1a).^[10] Furthermore MacMillan described the direct HIE of α -amino C–H bonds mediated by photoredox catalysis (Figure 1b).^[11] This method uses D₂O/T₂O as a promising strategy to incorporate deuterium or tritium, due to cost efficiency and its user-friendly handling.^[12] In sharp

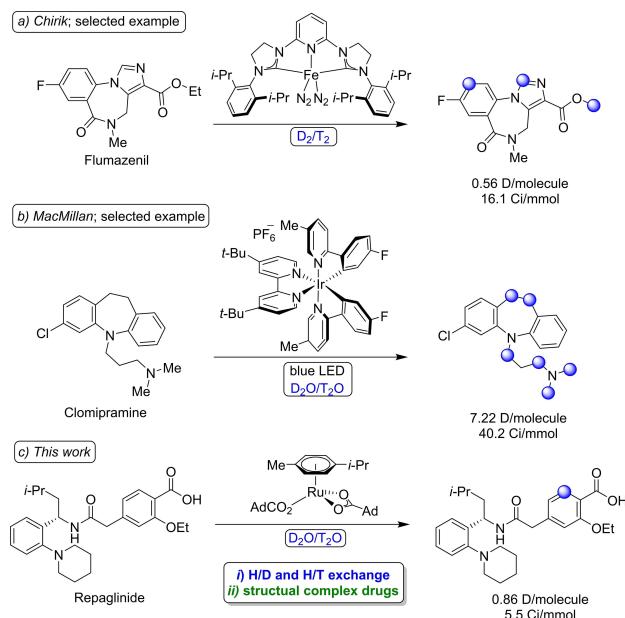


Figure 1. Labeling of pharmaceutical drugs by late-stage C–H activation.

[a] V. Müller, Prof. L. Ackermann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstrasse 2
Göttingen 37077 (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de

[b] R. Weck, Dr. V. Derdaau
R&D
Integrated Drug Discovery
Isotope Chemistry
Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
Frankfurt am Main 65926 (Germany)

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/cctc.201902051>

This manuscript is part of the Special Issue on the Sustainable and Affordable Chemistry to Meet Future Challenges in the Pharmaceutical Industry.

© 2019 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

contrast, HIE by ruthenium-catalyzed C–H activation is under-developed, with only selected examples of late-stage modification of drugs and only one example for the late-stage tritium-labeling of pharmaceuticals.^[13]

Within our program on weak chelation assistance for C–H activation,^[14] mechanistic studies had indicated the potential for a selective isotope incorporation into different structural motifs. Consequentially, we hypothesized that, instead of trapping the rutenacycle with a carbon source, the use of D₂O or T₂O could facilitate the preparation of isotope labeled compounds. Thus, we herein present a robust and selective strategy for the ruthenium-catalyzed hydrogen isotope exchange by a weakly-coordinating carboxylic acids (Figure 1c). Our approach features *inter alia* (a) the use of a versatile ruthenium(II)-catalyst, (b) deuterated water as most user-friendly isotope source, (c) selective *ortho*-deuteration of bioactive compounds and (d) tritium-labeling of a marked pharmaceutical.

We commenced our studies by probing the envisioned HIE of *p*-anisic acid by different ruthenium sources with D₂O. Notably, additive-free conditions provided poor results with the simple dichlororuthenium catalyst (entry 1). Instead, the use of well-defined ruthenium(II)biscarboxylate complexes afforded the desired HIE, with adamantly carboxylate as ligand giving the best performance in terms of yield, with excellent deuterium-incorporation (entries 2 and 3 and Table S-1 in the Supporting Information). Next, we tested different deuterium sources, as it's known for palladium, that more acidic labeling reagents led to higher deuterium-incorporation.^[15] Interestingly, methanol-*d*₄ gave a similar result (entry 4) and acetic acid-*d*₄ resulted in a reduced yield (entry 5). At a reduced reaction temperature the desired HIE did not occur in a satisfying yield (entry 6), while higher temperatures than 100 °C showed no beneficial effect (entry 7). Next, we tested the effect of air and observed that the deuterium-incorporation was unaffected by the presence of air (entry 8). To improve the yield we switched to a solvent mixture in order to avoid high polar solvents and to use the labeling agent in reduced amounts. To our delight the use of 1,4-dioxane gave excellent deuterium-incorporation (Table 1, entry 9 and Table S-1 in the Supporting Information). Control experiments verified the essential nature of the ruthenium catalyst for the HIE process.

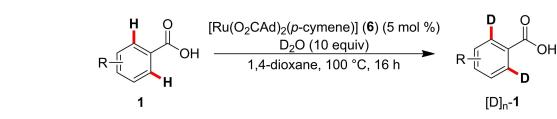
With the optimized reaction conditions in hand, we then examined the substrate scope of the ruthenium-catalyzed C–H hydrogen isotope exchange with D₂O (Scheme 1). To this end, we first evaluated various benzoic acids **1**. Electron-donating and electron-withdrawing substituents were well tolerated, yielding high labeled compounds [D]_n–**1**. With substituents in the *para* position the deuterium-labeling is good (60–85%) (**1a–c**), whereas *ortho*- and *meta*- substituted benzoic acids showed excellent deuterium-incorporation (**1f–h**, and **1j–l**). The outstanding chemoselectivity of the ruthenium(II)-carboxylate catalyst was reflected by fully tolerating valuable functional groups, such as nitro (**1d**, **1i**, **1m**), cyano (**1e**, **1n**), hydroxyl (**1o**) and amino groups (**1p**).

Furthermore, different (hetero)arenes were tested under the reaction conditions. To our delight they were obtained in a chemoselective manner, with selective and high deuterium

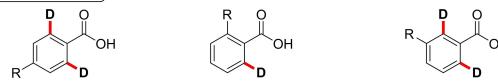
Table 1. Optimization of ruthenium-catalyzed *ortho*-deuteration^[a].

Entry	[Ru]	Solvent	D [%] ^[b]
1	[Ru(<i>p</i> -cymene)Cl ₂]	D ₂ O	19
2	Ru(OAc) ₂ (<i>p</i> -cymene)	D ₂ O	92
3	Ru(O ₂ CaD) ₂ (<i>p</i> -cymene) (6)	D ₂ O	90
4	Ru(O ₂ CaD) ₂ (<i>p</i> -cymene) (6)	CD ₃ OD	90
5	Ru(O ₂ CaD) ₂ (<i>p</i> -cymene) (6)	CD ₃ CO ₂ D	60
6 ^[c]	Ru(O ₂ CaD) ₂ (<i>p</i> -cymene) (6)	D ₂ O	60
7 ^[d]	Ru(O ₂ CaD) ₂ (<i>p</i> -cymene) (6)	D ₂ O	92
8 ^[e]	Ru(O ₂ CaD) ₂ (<i>p</i> -cymene) (6)	D ₂ O	94
9 ^[f]	Ru(O ₂ CaD) ₂ (<i>p</i> -cymene) (6)	1,4-dioxane	95
10	Ru(O ₂ CaD) ₂ (<i>p</i> -cymene) (6)	1,4-dioxane	–

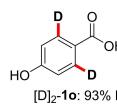
[a] Reaction conditions: **1a** (0.5 mmol), [Ru] (5.0 mol %), Solvent (1.0 mL), 16 h, 100 °C, yield of isolated products, [b] Determined by ¹H-NMR, [c] At 45 °C, [d] At 110 °C, [e] Under air, [f] With D₂O (10 equiv). Ad = 1-Adamantyl.



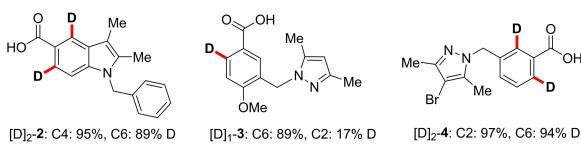
a) Benzoic acids



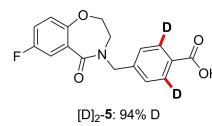
R = OMe ([D]₂-**1a**): 95% D R = OMe ([D]₁-**1f**): 98% D R = OMe ([D]₂-**1j**): C2: 96%, C6: 96% D
 R = Cl ([D]₂-**1b**): 60% D R = Cl ([D]₁-**1g**): 99% D R = Cl ([D]₂-**1k**): C2: 99%, C6: 99% D
 R = Me ([D]₂-**1c**): 94% D R = Me ([D]₁-**1h**): 97% D R = Me ([D]₂-**1l**): C2: 98%, C6: 98% D
 R = NO₂ ([D]₂-**1d**): 84% D R = NO₂ ([D]₁-**1i**): 90% D R = NO₂ ([D]₂-**1m**): C2: 98%, C6: 98% D
 R = CN ([D]₂-**1e**): 93% D R = CN ([D]₁-**1n**): C2: 90%, C6: 81% D



b) Heterocyclic acids



[D]₂-**2**: C4: 95%, C6: 89% D [D]₁-**3**: C6: 89%, C2: 17% D [D]₂-**4**: C2: 97%, C6: 94% D

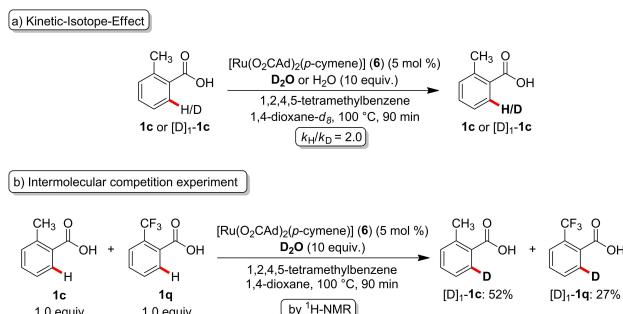


[D]₂-**5**: 94% D

Scheme 1. Ruthenium(II) biscarboxylate-catalyzed *ortho*-deuterium labeling.

incorporation in the *ortho*-position to the carboxyl group. Heterocyclic motifs, including indole (**2**), 1*H*-pyrazole (**4**) and oxazepine (**5**), were well tolerated. Importantly, in case of **3** only a poor deuteration in the C2-position was observed, probably due to steric interactions.

The rate-determining C–H activation was confirmed by an experimental KIE value of $k_H/k_D = 2.0$ (Scheme 2a). Additionally, intermolecular competition experiments with differently sub-



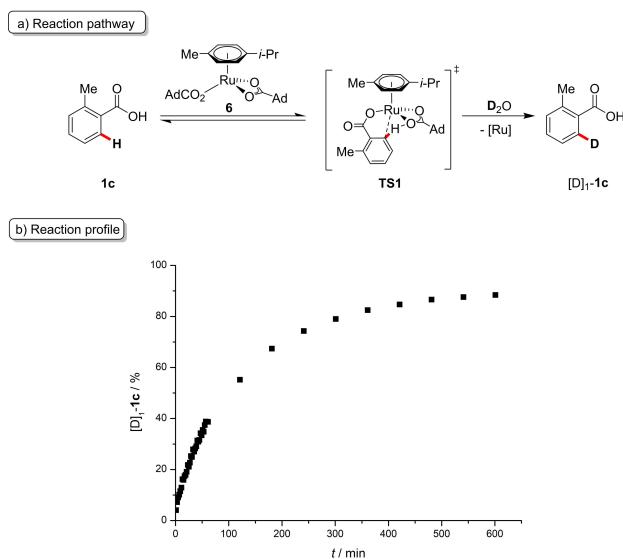
Scheme 2. Key mechanistic studies.

stituted substrates **1c** and **1q** revealed, that the more electron-donating substrate reacted preferentially, providing strong support for a base-assisted internal electrophilic type substitution (BIES) regime (Scheme 2b).^[16]

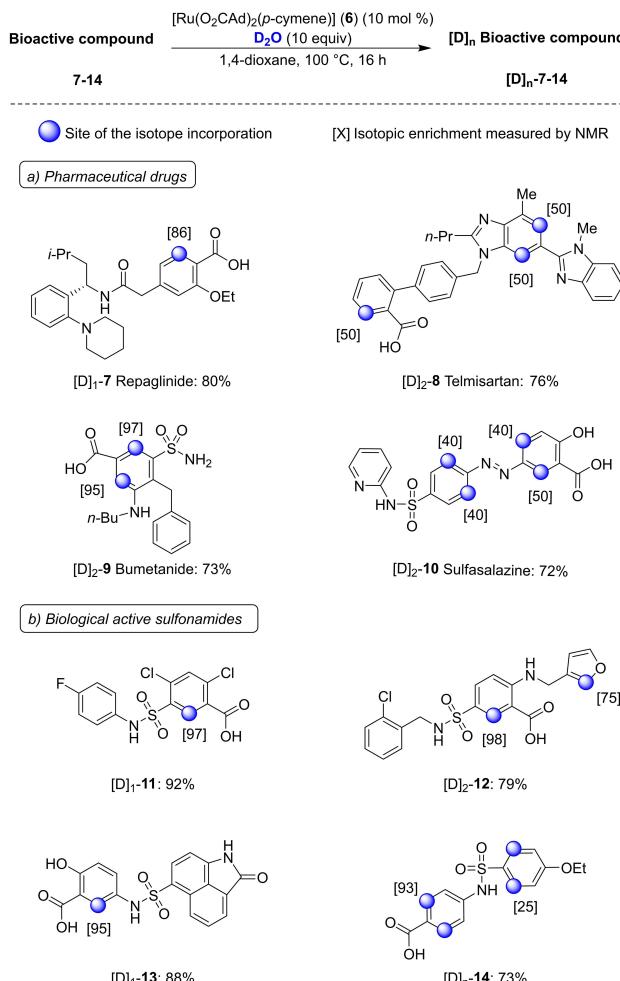
On the basis of our mechanistic findings, we propose a plausible reaction pathway for the present HIE reaction (Scheme 3a). The reaction of **1c** with the ruthenium(II)-carboxylate complex (**6**) yields a *ortho*-metallated ruthenacycle *via* a BIES C–H-activation transition state (**TS1**). H/D exchange of the hydro carboxylato ligand with a deuterium source and further deproto-demetallation then yields $[D]_1-1c$. To gain additional insights into the HIE, we followed the kinetic profile of **1c** by *in-operando* 1H -NMR spectroscopy (Scheme 3b). The synthetic utility was highlighted by the fast rate of the HIE, yielded $>78\%$ deuterium-incorporation after 5 h.

Given the excellent performance of highly functionalized (hetero)arenes, the envisioned labeling of challenging pharmaceuticals was targeted. We were pleased to find that the desired transformation could be achieved in sufficient yield and moderate to excellent deuterium-incorporation (Scheme 4).

The robustness of the C–H deuteration was highlighted by tolerating different structural motifs, like amide in repaglinide



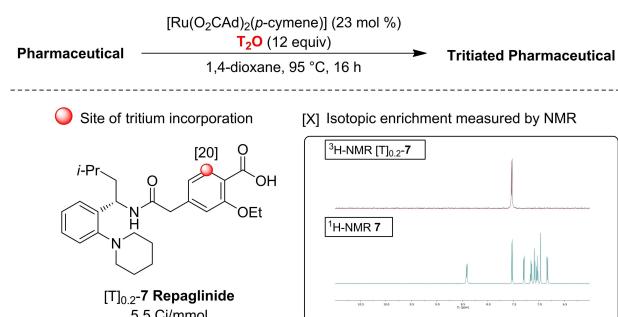
Scheme 3. Reaction pathway (a) and profile (b) of the C–H deuteration.



Scheme 4. Late-stage C–H deuteration of drugs.

(**7**), benzimidazole in telmisartan (**8**), free sulfonamide or secondary amines in bumetanide (**9**) and α -amino-pyridines as well as diazo-motifs in sulfasalazine (**10**). In addition to the generally high levels of deuterium incorporation observed for complex pharmaceuticals, we continued our studies with biologically active sulfonamides **11–14**. To our delight the catalyst showed no solubility issues^[17] and the performance was not inhibited by functional groups that often deactivate transition metal catalyst such as free amino (**11**) or hydroxyl (**13**) groups.

Based on the high performance of the H/D exchange, we became interested in the *ortho*-selective tritium labeling of pharmaceuticals with T_2O , to generate metabolically stable sites that are compatible to different functional groups. Thus, we tested the influence of different amounts of deuterium in the desired transformation. We were pleased to find that 6 equivalents of D_2O yielded 80% deuterium-incorporation (Table S-2 in the Supporting Information). In addition, we also performed the HIE of repaglinide (**7**) with freshly prepared D_2O .^[18] In this case, we observed a decreased deuterium-incorporation in the *ortho*-position (50%), which was nevertheless a promising result towards the use of T_2O . Under slightly modified reaction conditions, we performed the tritium labelling of repaglinide



Scheme 5. Tritiation of repaglinide via ruthenium catalyzed C–H-activation.

(7). Thus, were able to introduce tritium in moderate specific activity in a single step (Scheme 5).

In conclusion, we have reported on a novel ruthenium(II)-catalyzed strategy for the selective HIE of pharmaceutical drugs via late-stage diversification. Hence, carboxylate assistance enabled versatile C–H deuteration with excellent levels of isotope incorporation and functional group tolerance. In addition, we have demonstrated a step-economical access to selectively tritium labeled drugs, an essential tool for the development of new therapeutics and molecular understanding.

Acknowledgements

Generous support by the DFG (Gottfried-Wilhelm-Leibniz award to LA, and SPP1807) are gratefully acknowledged.

Keywords: C–H activation • hydrogen isotope exchange • ruthenium • pharmaceutical drugs • tritium

- [1] a) A. Mullard, *Nat. Rev. Drug Discovery* **2017**, *16*, 305; b) G. S. Timmins, *Expert Opin. Ther. Pat.* **2014**, *24*, 1067–1075; c) T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595–3611; d) B. Buscher, S. Laakso, H. Mascher, K. Pusecker, M. Doig, L. Dillen, W. Wagner-Redeker, T. Pfeifer, P. Delrat, P. Timmerman, *Bioanalysis* **2014**, *6*, 673–682; e) J. A. Krauser, *J. Labelled Compd. Radiopharm.* **2013**, *56*, 441–446; f) A. Katsnelson, *Nat. Med.* **2013**, *19*, 656; g) N. Penner, L. Xu, C. Prakash, *Chem. Res. Toxicol.* **2012**, *25*, 513–531; h) J. J. Maguire, R. E. Kuc, A. P. Davenport, in *Receptor Binding Techniques* (Ed.: A. P. Davenport), Humana Press, Totowa, NJ, **2012**, pp. 31–77; i) E. C. Hulme, M. A. Trevethick, *Br. J. Pharmacol.* **2010**, *161*, 1219–1237; j) J. Atzrodt, V. Derda, T. Fey, J. Zimmermann, *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765; *Angew. Chem.* **2007**, *119*, 7890–7911.
- [2] a) C. S. Elmore, R. A. Bragg, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 167–171; b) W. J. S. Lockley, A. McEwen, R. Cooke, *J. Labelled Compd. Radiopharm.* **2012**, *55*, 235–257; c) E. M. Isin, C. S. Elmore, G. N. Nilsson, R. A. Thompson, L. Weidolf, *Chem. Res. Toxicol.* **2012**, *25*, 532–542; d) R. Voges, J. R. Heys, T. Moenius, *Preparation of Compounds Labeled with Tritium and Carbon-14*, Wiley, Chichester, UK, **2009**; e) C. S. Elmore, *Annu. Rep. Med. Chem.* **2009**, *44*, 515–534.
- [3] J. Atzrodt, V. Derda, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 1758–1784; *Angew. Chem.* **2018**, *130*, 1774–1802.
- [4] P. H. Allen, M. J. Hickey, L. P. Kingston, D. J. Wilkinson, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 731–738.
- [5] D. Hesk, C. F. Lavey, P. McNamara, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 722–730.

- [6] a) J. J. Verendel, O. Pàmies, M. Diéguez, P. G. Andersson, *Chem. Rev.* **2014**, *114*, 2130–2169; b) J. S. Valsborg, L. Sørensen, C. Foged, *J. Labelled Compd. Radiopharm.* **2001**, *44*, 209–214; c) G. J. Ellames, J. S. Gibson, J. M. Herbert, A. H. McNeill, *Tetrahedron* **2001**, *57*, 9487–9497; d) D. Hesk, P. R. Das, B. Evans, *J. Labelled Compd. Radiopharm.* **1995**, *36*, 497–502; e) R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331–337.
- [7] a) M. Valero, R. Weck, S. Güssregen, J. Atzrodt, V. Derda, *Angew. Chem. Int. Ed.* **2018**, *57*, 8159–8163; *Angew. Chem.* **2018**, *130*, 8291–8295; b) W. J. Kerr, R. J. Mudd, M. Reid, J. Atzrodt, V. Derda, *ACS Catal.* **2018**, *8*, 10895–10900; c) W. J. Kerr, M. Reid, T. Tuttle, *Angew. Chem. Int. Ed.* **2017**, *56*, 7808–7812; *Angew. Chem.* **2017**, *129*, 7916–7920; d) W. J. Kerr, D. M. Lindsay, M. Reid, J. Atzrodt, V. Derda, P. Rojahn, R. Weck, *Chem. Commun.* **2016**, *52*, 6669–6672; e) W. J. Kerr, M. Reid, T. Tuttle, *ACS Catal.* **2015**, *5*, 402–410; f) W. J. Kerr, R. J. Mudd, L. C. Paterson, J. A. Brown, *Chem. Eur. J.* **2014**, *20*, 14604–14607; g) 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; h) G. N. Nilsson, W. J. Kerr, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 662–667.
- [8] For notable progress, see: a) C. Zarate, H. Yang, M. J. Bezdek, D. Hesk, P. J. Chirik, *J. Am. Chem. Soc.* **2019**, *141*, 5034–5044; b) M. Valero, D. Becker, K. Jess, R. Weck, J. Atzrodt, T. Bannenberg, V. Derda, M. Tamm, *Chem. Eur. J.* **2019**, *25*, 6517–6522; c) T. R. Puleo, A. J. Strong, J. S. Bandar, *J. Am. Chem. Soc.* **2019**, *141*, 1467–1472; d) A. L. Garreau, H. Zhou, M. C. Young, *Org. Lett.* **2019**, *21*, 7044–7048; e) V. H. Mai, O. B. Gadzhiev, S. K. Ignatov, G. I. Nikonorov, *Catal. Sci. Technol.* **2019**, *9*, 3398–3407; f) H. Yang, C. Zarate, W. N. Palmer, N. Rivera, D. Hesk, P. J. Chirik, *ACS Catal.* **2018**, *8*, 10210–10218; g) H. Yang, P. G. Dormer, N. R. Rivera, A. J. Hoover, *Angew. Chem. Int. Ed.* **2018**, *57*, 1883–1887; *Angew. Chem.* **2018**, *130*, 1901–1905; h) N. G. Léonard, P. J. Chirik, *ACS Catal.* **2018**, *8*, 342–348; i) R. P. Yu, J. M. Darmon, S. P. Semproni, Z. R. Turner, P. J. Chirik, *Organometallics* **2017**, *36*, 4341–4343; j) W. N. Palmer, P. J. Chirik, *ACS Catal.* **2017**, *7*, 5674–5678; k) S. K. S. Tse, P. Xue, C. W. S. Lau, H. H. Y. Sung, I. D. Williams, G. Jia, *Chem. Eur. J.* **2011**, *17*, 13918–13925; l) W. Bai, K.-H. Lee, S. K. S. Tse, K. W. Chan, Z. Lin, G. Jia, *Organometallics* **2015**, *34*, 3686–3698; m) W. J. S. Lockley, D. Hesk, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 704–715; n) M. H. Emmert, J. B. Gary, J. M. Villalobos, M. S. Sanford, *Angew. Chem. Int. Ed.* **2010**, *49*, 5884–5886; *Angew. Chem.* **2010**, *122*, 6020–6022; o) J. Atzrodt, V. Derda, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 674–685; p) J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson, G. N. Nilsson, *Chem. Commun.* **2008**, 1115–1117; q) M. H. G. Prechtli, M. Hölscher, Y. Ben-David, N. Theyssen, R. Loschen, D. Milstein, W. Leitner, *Angew. Chem. Int. Ed.* **2007**, *46*, 2269–2272; *Angew. Chem.* **2007**, *119*, 2319–2322; r) S. R. Klei, J. T. Golden, T. D. Tilley, R. G. Bergman, *J. Am. Chem. Soc.* **2002**, *124*, 2092–2093, and references cited therein.
- [9] a) S. Santoro, F. Ferlin, L. Ackermann, L. Vaccaro, *Chem. Soc. Rev.* **2019**, *48*, 2767–2782; b) J. Loup, U. Dhawa, F. Pesciaoli, J. Wencel-Delord, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 12803–12818; *Angew. Chem.* **2019**, *131*, 2–18; c) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452; d) P. Gandeepan, N. Kaplaneris, S. Santoro, L. Vaccaro, L. Ackermann, *ACS Sustain. Chem. Eng.* **2019**, *7*, 8023–8040; e) C. Sambiagio, D. Schönauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603–6743; f) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301; g) P. Naredfy, F. Jordan, M. Szostak, *ACS Catal.* **2017**, *7*, 5721–5745; h) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; i) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074–1086.
- [10] R. Pony Yu, D. Hesk, N. Rivera, I. Pelczer, P. J. Chirik, *Nature* **2016**, *529*, 195–199.
- [11] Y. Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Colletti, I. W. Davies, D. W. C. Mac Millan, *Science* **2017**, *358*, 1182–1187.
- [12] S. Bhatia, G. Spahlinger, N. Boukhamseen, Q. Boll, Z. Li, J. E. Jackson, *Eur. J. Org. Chem.* **2016**, *2016*, 4230–4235.
- [13] a) A. Palazzolo, S. Feuillastre, V. Pfeifer, S. Garcia-Argote, D. Bouzouita, S. Tricard, C. Chollet, E. Marcon, D.-A. Buisson, S. Cholet, F. Fenaille, G. Lippens, B. Chaudret, G. Pieters, *Angew. Chem. Int. Ed.* **2019**, *58*, 4891–4895; *Angew. Chem.* **2019**, *131*, 4945–4949; b) L. V. A. Hale, N. K. Szymczak, *J. Am. Chem. Soc.* **2016**, *138*, 13489–13492; c) B. Chatterjee, V. Krishnakumar, C. Gunanathan, *Org. Lett.* **2016**, *18*, 5892–5895; d) L. Piola, J. A. Fernández-Salas, S. Manzini, S. P. Nolan, *Org. Biomol. Chem.* **2014**, *12*, 8683–8688; e) L. Neubert, D. Michalik, S. Bähn, S. Imm, H. Neumann, J. Atzrodt, V. Derda, W. Holla, M. Beller, *J. Am. Chem. Soc.* **2012**, *134*,

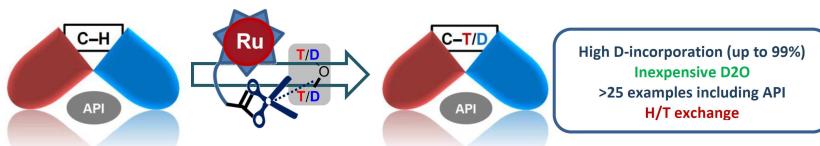
- 12239–12244; f) D. Hesk, K. Voronin, P. McNamara, P. Royster, D. Koharski, S. Hendershot, S. Saluja, V. Truong, T. M. Chan, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 131–137.
- [14] Selected examples: a) S. R. Yetra, T. Rogge, S. Warratz, J. Struwe, W. Peng, P. Vana, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 7490–7494; b) Y. Qiu, C. Tian, L. Massignan, T. Rogge, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5818–5822; *Angew. Chem.* **2018**, *130*, 5920–5924; c) K. Korvorapun, N. Kaplaneris, T. Rogge, S. Warratz, A. C. Stückl, L. Ackermann, *ACS Catal.* **2018**, *8*, 886–892; d) Q. Bu, T. Rogge, V. Kotek, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 765–768; *Angew. Chem.* **2018**, *130*, 773–776; e) A. Bechtoldt, M. E. Baumert, L. Vaccaro, L. Ackermann, *Green Chem.* **2018**, *20*, 398–402; f) A. Schischko, H. Ren, N. Kaplaneris, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 1576–1580; *Angew. Chem.* **2017**, *129*, 1598–1602; g) M. Moselage, J. Li, F. Kramm, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 5341–5344; *Angew. Chem.* **2017**, *129*, 5425–5428; h) A. Bechtoldt, C. Tirler, K. Raghuvarsh, S. Warratz, C. Kornhaaß, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 264–267; *Angew. Chem.* **2016**, *128*, 272–275; i) S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 5513–5517; *Angew. Chem.* **2015**, *127*, 5604–5608; j) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153–4155.
- [15] 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.
- [16] a) L. Wang, B. P. Carrow, *ACS Catal.* **2019**, *9*, 6821–6836; b) K. Naksoomboon, J. Poater, F. M. Bickelhaupt, M. Á. Fernández-Ibáñez, *J. Am. Chem. Soc.* **2019**, *141*, 6719–6725; c) D. Zell, M. Bursch, V. Müller, S. Grimme, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 10378–10382; *Angew. Chem.* **2017**, *129*, 10514–10518; d) W. Liu, S. C. Richter, Y. Zhang, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 7747–7750; *Angew. Chem.* **2016**, *128*, 7878–7881; e) W. Ma, R. Mei, G. Tenti, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 15248–15251.
- [17] a) D. P. Elder, R. Holm, H. L. d. Diego, *Int. J. Pharm.* **2013**, *453*, 88–100; b) K. T. Savjani, A. K. Gajjar, J. K. Savjani, *ISRN Pharmaceutics* **2012**, 1–10; c) C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Delivery Rev.* **2001**, *46*, 3–26.
- [18] M. Saljoughian, *Synthesis* **2002**, 1781–1801.

Manuscript received: October 30, 2019

Accepted manuscript online: October 30, 2019

Version of record online: ■■■, ■■■

COMMUNICATIONS



Hand in hand: Isotopic labeling by ruthenium(II)-catalyzed C–H activation *via* weak coordination enabled late-

stage drug diversification for deuteration and tritiation.

High D-incorporation (up to 99%)
Inexpensive D₂O
>25 examples including API
H/T exchange

V. Müller, R. Weck, Dr. V. Derdau,
Prof. L. Ackermann*

1 – 6

Ruthenium(II)-Catalyzed Hydrogen Isotope Exchange of Pharmaceutical Drugs by C–H Deuteration and C–H Tritiation

