Hydrogen Isotope Exchange

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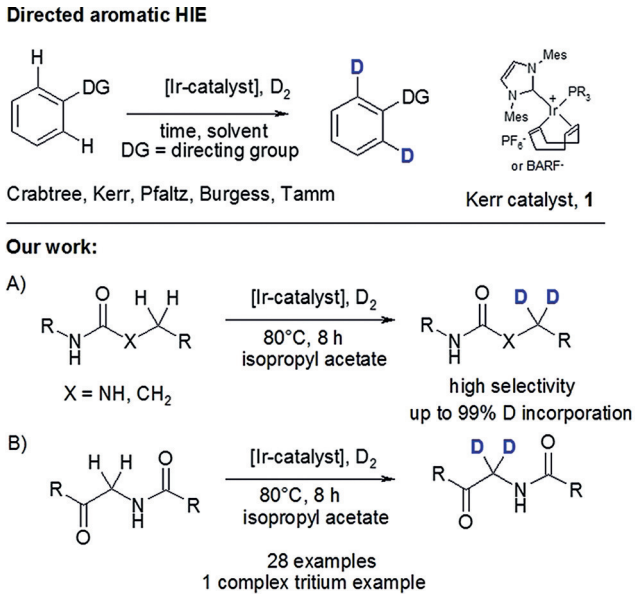
Highly Selective Directed Iridium-Catalyzed Hydrogen Isotope Exchange Reactions of Aliphatic Amides

Mégane Valero, Remo Weck, Stefan Güssregen, Jens Atzrodt, and Volker Derdau**

Abstract: *For the first time, we describe highly selective homogeneous iridium-catalyzed hydrogen isotope exchange (HIE) of unactivated C(sp^3) centers in aliphatic amides. When using the commercially available Kerr catalyst, the HIE with a series of common antibody–drug conjugate (ADC) linker side chains proceeds with high yields, high regioselectivity, and with deuterium incorporation up to 99 %. The method is fully translatable to the specific requirements of tritium chemistry and its effectiveness was demonstrated by direct tritium labelling of a maytansinoid. The scope of the method can be extended to simple amino acids, with high HIE activity observed for glycine and alanine. In di- and tripeptides, a very interesting protecting-group-dependent tunable selectivity was observed. DFT calculations gave insight into the energies of the transition states, thereby explaining the observed selectivity and the influence of the amino acid protecting groups.*

Circumventing the need for additional synthetic steps, 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 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] and for absorption distribution metabolism excretion (ADME) profiling of new drug candidates.[7,8] Numerous HIE methods based on homogeneous or heterogeneous catalysis have already been described.[1,2,9] Recent research has strongly focused on selective *ortho*-directed HIE reactions of aromatic substrates based on homogeneous iridium(I) complexes, with the commercial Crabtree's catalyst[10] and Kerr's catalyst[11,12] (**1**) being the most prominent catalysts applied today. Even though a new generation of bidentate catalyst systems such as those from the groups of Pfaltz,[13] Burgess,[14] and Tamm[15] have extended the scope of aromatic *ortho*-directing HIE (Scheme 1), this is still restricted to C(sp^2) carbons.



Scheme 1. Known aromatic HIE reactions in comparison to our work for selective C(sp^3)–H activation/deuteration in aliphatic amides.

In contrast and in spite of very active research, selective C(sp^3)–H activation/deuteration still remains challenging. Recent examples based on homogeneous Ru catalysis include the Beller group's α,β-deuteration of biologically relevant amine,[16] a selective and stereoretentive deuteration of α-chiral amines reported by Szymczak and co-workers,[17] and a regioselective labelling of aliphatic alcohols from Linand and co-workers.[18] Additionally, Pieters and co-workers developed a process for the selective and enantiospecific C(sp^3)–H activation/ deuteration of α-amino groups in amino acids using heterogeneous Ru nanoparticles,[19] and Chirik and co-workers reported a cobalt-catalyzed stereoretentive HIE of arylarenes.[20] However, all of these methods either require harsh reaction conditions, air-sensitive, non-commercial catalysts, or procedures that are not compatible with the requirements of tritium chemistry.[21] A first example for direct installation of tritium at α-amino C(sp^3)–H bonds is a photoredox-mediated hydrogen atom transfer (HAT) reaction reported by MacMillan and co-workers that utilizes an iridium(III) photocatalyst and D_2O/T_2O as an isotope source.[22] However, a preferred tritium source is tritium gas since it is both less toxic than T_2O and is routinely handled with modern manifold systems.[23] To ensure full translatabil-

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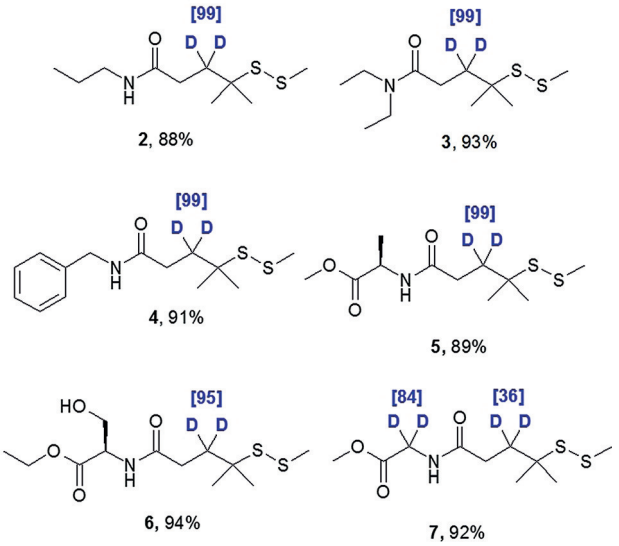
ity to tritium chemistry, we envisaged for our iridium-catalyzed approach for C(sp^3)–H labelling of aliphatic amides the use of only gaseous D_2/T_2 as a hydrogen isotope source (Scheme 1). A similar strategy was very recently applied by Pieters and co-workers to the sulfur-atom-directed radio-labelling of substrates by Ru/C-catalyzed C(sp^3)–H activation.[24] We became particularly interested in developing a HIE labelling approach for the preparation of ^{3}H-labelled maytansine analogues (for DM4 (**8a**) structure information, see Scheme 3), which are the cancer-killing cytotoxic payload in a series of antibody–drug conjugates (ADCs)[25] and are typically synthesized by a tedious and low-yielding multistep synthesis.[26]

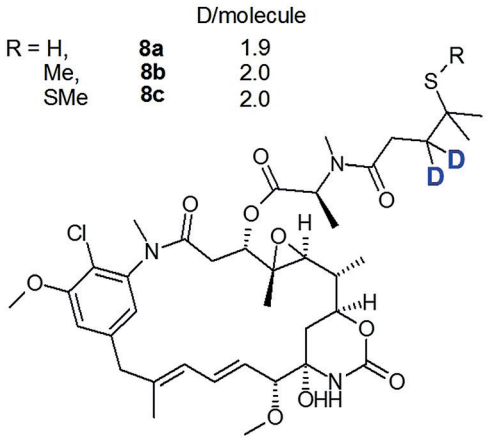
We started our studies by examining the DM4 side-chain precursors **2**–**4** as substrates andvarying reaction parameters such as catalyst, solvent, and temperature. While all attempts at room temperature gave no deuterium incorporation at all, intensive screening at higher temperature (50 °C) revealed that catalyst **1** shows high and selective HIE activity at aliphatic positions (see the Supporting Information). A catalyst loading of 10 mol % **1** in isopropyl acetate at 80 °C proved to be optimal.

Under our optimized conditions, we obtained almost complete deuterium incorporation of 95–99 % for simple amide derivatives **2**–**4**, as well as for the alanine or serine conjugates **5** and **6** (Scheme 2). The reaction is very selective



Scheme 2. HIE reaction with DM4 side-chain precursor substrates. Conditions: catalyst **1** (10 mol %), isopropylacetate 1 mL, 80 °C, 3 h.

for the β-amide carbon, with no deuterium incorporation into an aromatic or benzyl position in **4** or the α-amino acid position in compounds **5** and **6**. Next we tested the HIE conditions on maytansine (**8a**–**c**) itself. To our delight, high deuterium incorporation was observed by LC–MS for all DM4 analogues tested, including DM4 (**8a**) itself, as well as the main DM4 metabolite Me-DM4 (**8b**) and protected DM4-SMe (**8c**; Scheme 3). As expected, the aromatic proton signals in the ^{1}H-NMR spectrum of **8a**–**c** appeared



Scheme 3. HIE reaction with different DM4 derivatives (**8a**–**c**). Conditions: catalyst **1** (10 mol %), isopropylacetate, 80 °C, 3 h.

unchanged, thus indicating that only aliphatic positions were involved in the HIE reaction. However, a clear confirmation of the labelling position was not possible because of a highly complex aliphatic region in the ^{1}H-NMR spectra of **8a**–**c**. We thus decided to run a tritium experiment under similar conditions to enable ^{3}H-NMR for determination of the labelling positions in **8c**.

In spite of an expected kinetic isotope effect (D vs. T) and a much lower tritium pressure (60 mbar, 7 equivalents vs. atmospheric deuterium pressure),[27] a specific activity of 10–30 Ci mmol^{-1}[28] was obtained, which was more than sufficient for the planned in vivo studies with ^{3}H-DM4 and corresponding ^{3}H-ADCs. The high β-position selectivity of the HIE reaction was consistent with that observed for the model substrates and was confirmed by ^{3}H-NMR (ratio α to β-position 6:94, Figure 1).

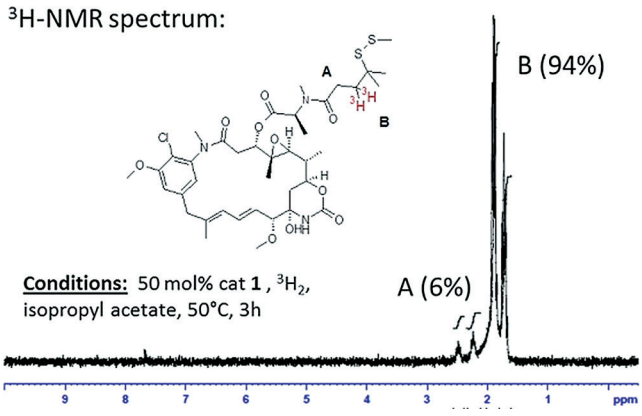
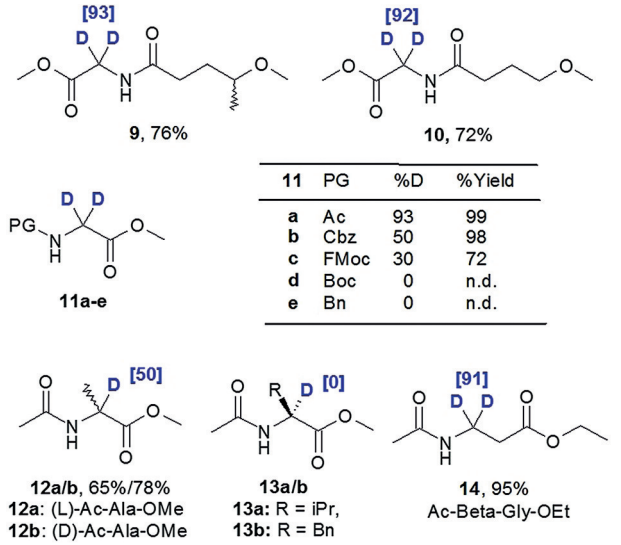


Figure 1. ^{3}H-NMR of ^{3}H-DM4-SMe (**8c**).

During the screening of DM4 side-chain model substrates, an interesting observation attracted our attention. The very high β-selectivity observed for **5** and **6** was lost in the glycine-containing substrate **7**. In this case, two positions were reactive with a clear preference for the α-glycine protons (84 %) in comparison to the β-amide position (36 %). A

complete change in selectivity in favor of the α-amino acid protons was observed in glycine conjugates with structurally modified side chain motifs (**9** and **10**; Scheme 4). In both cases, excellent deuterium incorporation in the glycine



11	PG	%D	%Yield
a	Ac	93	99
b	Cbz	50	98
c	FMoc	30	72
d	Boc	0	n.d.
e	Bn	0	n.d.

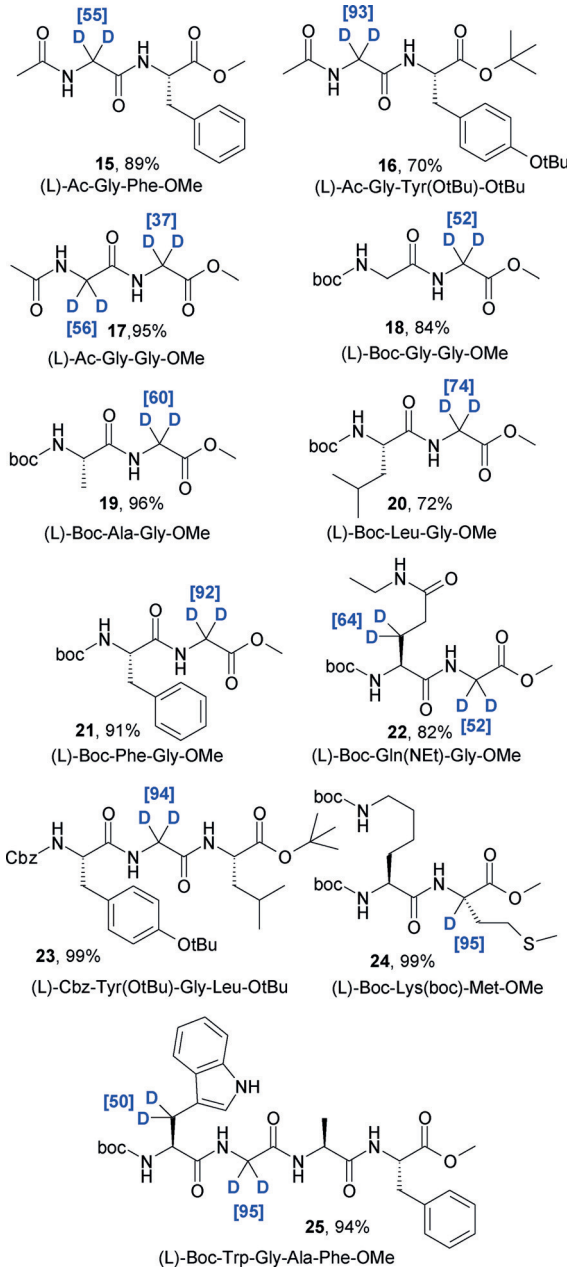
Scheme 4. HIE reaction with simple amino acids. Conditions: catalyst **1** (10 mol%), isopropylacetate 1 mL, 80°C, 8 h.

position was observed, while the β-amide position wasn't labelled at all. Obviously even small steric changes in the substrates may have a strong effect on the selectivity and outcome of the HIE, which inspired us to investigate this reaction on amino acid derivatives in more detail.

First, we investigated the influence of the protecting group in glycine methyl ester (Scheme 4). Unfortunately, high deuterium incorporation was observed only for the acetyl-protected substrate, while more synthetically versatile protecting groups such as Cbz (**11b**) or Fmoc (**11c**) resulted only in moderate deuteration. For Boc (**11d**) or Bn (**11e**), no deuterium incorporation was observed under these conditions.

Next, we tested different acetyl-protected amino acid methyl esters for their applicability in the HIE reaction. The addition of a methyl group in the α-position, as in Ac-Ala-OMe (**12**), resulted in a lower deuterium intake (50%D), which was independent of whether the D- or L-amino acid was used. For both **12a** and **12b**, complete retention of stereo information was observed, as demonstrated by chiral HPLC analysis, which is fully explained by the predicted concerted 5-membered transition-state mechanism (Figure 3). Sterically more demanding amino acids such as Ac-Leu-OMe (**13a**) or Ac-Phe-OMe (**13b**) displayed no deuteration at all. In contrast Ac-βGly-OMe (**14**) gave a high deuterium incorporation similar to that observed for glycine (**11a**).

The high sensitivity of the HIE reaction towards the steric properties of the amino acid enables an interesting selectivity towards glycine in different dipeptides, which can be tuned even by the choice of protecting group (Scheme 5). Dipeptides with N-terminal glycine are selectively labelled in the glycine position as long as acetyl is used as the protecting



Scheme 5. HIE reaction with dipeptides. Conditions: catalyst **1** (10 mol%), isopropylacetate 1 mL, 80°C, 8 h.

group (**15**, **16**). The steric demand of the C-terminal amino acid doesn't influence the deuterium yield strongly, as demonstrated by an excellent 93% incorporation observed for Ac-Gly-Tyr(OtBu)-OtBu (**16**).

If a more sterically demanding protecting group is used, for example, Boc instead of Ac, the selectivity of the HIE reaction is completely switched to the C-terminal glycine. For example, in Boc-Gly-Gly-OMe (**18**), only the C-terminal glycine is labelled, while in Ac-Gly-Gly-OMe (**17**), both positions can be exchanged. This effect is even more pronounced for more sterically demanding N-terminal amino acids, resulting in good deuterium incorporation for Boc-Leu-Gly-OMe (**20**; 74%) and Boc-Phe-Gly-OMe (**21**; 92%). In line with previous findings, protons in both the

α-glycine and β-amide positions of Boc-Gln(NEt)-Gly-OMe (**22**) underwent exchange.

The method can also be extended to longer peptides, as demonstrated by the excellent D incorporation obtained for tripeptide Cbz-Tyr(OtBu)-Gly-Leu-OtBu (**23**; 94%) and tetrapeptide Boc-Trp-Gly-Ala-Phe-OMe (**25**; 95%). Like **22**, the β-amide protons in **25** also exchanged well. The unexpected methionine selectivity of the HIE reaction in **24** will be investigated further and the results reported in in due course.

For better understanding of the pronounced glycine selectivity of the HIE reaction and the underlying mechanism, we performed density functional theory (DFT) calculations (M06 functional)[29] following the approach successfully applied by Kerr et al.[12c,30,31] based on the mechanism suggested by Heys and co-workers.[32] The constructed free-energy profile with catalyst **1** and compound **11a** is shown in Figure 2. After initial iridium coordination (**26**), the insertion product **28a** is reached via transition state **27**. The equilibrium between **28a** and **28b** goes via a low-barrier transition state. Following HIE to **28b**, the deuterated iridium adduct **30** is formed. We found that the relative energies of the transition states for the oxidative addition step **27** (+23.8 kcal mol^{-1}) and the reductive elimination step **29** (+24.1 kcal mol^{-1}) are significantly higher than those that were calculated for HIE reactions with catalyst **1** at aromatic C(sp^2) carbons like benzaldehydes (+18.6 kcal mol^{-1}),[12c] which might be the reason why elevated temperatures are needed. Comparison of the relative transition-state energies ($\Delta\Delta G_{trans}$) for the reaction with catalyst **1** revealed +4.3 kcal mol^{-1} for Ac-Ala-OMe (**12**) and +7.3 kcal mol^{-1} for Boc-Gly-OMe (**11d**) compared to Ac-Gly-OMe (**11a**). These results are fully consistent with the experimental findings and explain the different deuterium incorporation for **11a** (93%D), **11d** (0%D), and **12** (50%D). According to the calculations at 80°C, the 5-membered transition state of **11d** (Figure 3) is present with only 0.003% of all species, which explains why **11d** is not deuterated at all. Furthermore, sterically more demanding amino acids increase the $\Delta\Delta G_{trans}$ values in the transition states in the order Gly (**11a**) < Ala (**12**) < Phe (**13b**). Overall, we found that the proposed mechanism is well in line with the experimental observations. Our results show that the observed energetic differences of C(sp^3) and C(sp^2) labelling can be attributed to increased steric demands of the substrate.

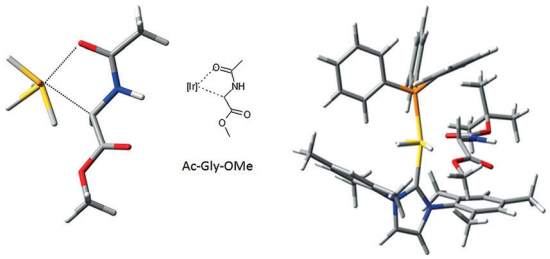


Figure 3. 5-Membered transition state of catalyst **1** (without ligands) with Ac-Gly-OMe (**11a**; left) or Boc-Gly-OMe (**11d**; right).

In conclusion, we have developed a new method for highly selective hydrogen isotope exchange (HIE) of unactivated C(sp^3) centers in aliphatic amides. Using the commercially available Kerr catalyst, the HIE reaction on a series of common linker side chains of antibody–drug conjugates (ADCs) proceeds with high yields, high regioselectivity, and deuterium incorporations up to 99%. The method is fully translatable to the specific requirements of tritium chemistry, which is demonstrated by the direct tritium labelling of the maytansine DM4. The scope of the method can be extended to simple amino acids, with high HIE activity for glycine and alanine. In di- and tripeptides, a very interesting protecting group-dependent tunable selectivity was observed. DFT calculations gave insight into the mechanism and steric requirements of the HIE reaction and explain the observed selectivity and the influence of the amino acid N-protecting groups.

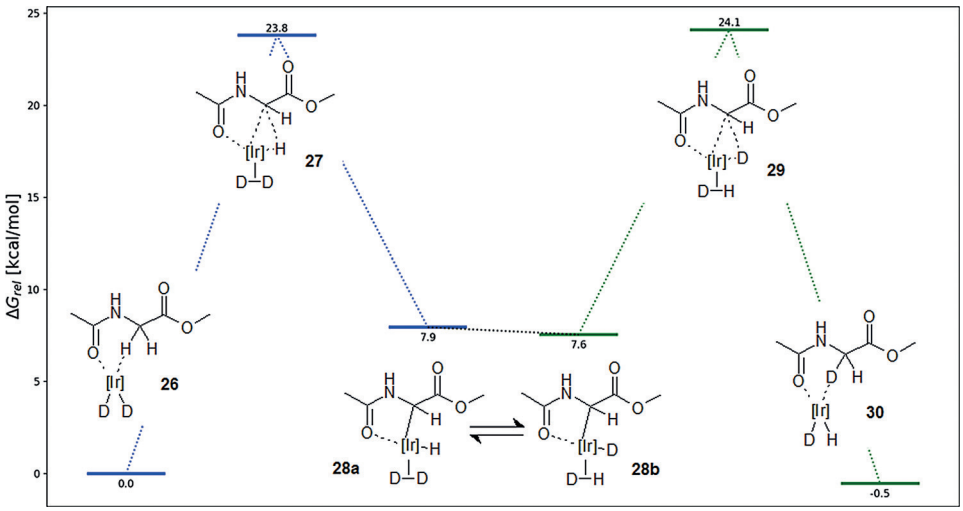


Figure 2. Calculated free-energy profile for selective deuteration of Ac-Gly-OMe (**11a**) with catalyst **1** (ligands not drawn).

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

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[1] J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 3022–3047; *Angew. Chem.* **2018**, *130*, 3074–3101.
[2] J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765; *Angew. Chem.* **2007**, *119*, 7890–7911.
[3] J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 1758–1784; *Angew. Chem.* **2018**, *130*, 1774–1802.
[4] For selected reviews see: a) C. S. Elmore, R. A. Bragg, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 167–171; b) A. Krauser, *J. Labelled Compd. Radiopharm.* **2013**, *56*, 441–446; c) W. J. S. Lockley, A. McEwen, R. Cooke, *J. Labelled Compd. Radiopharm.* **2012**, *55*, 235–257; d) A. E. Mutlib, *Chem. Res. Toxicol.* **2008**, *21*, 1672–1689.
[5] For selected reviews see: a) J. J. Maguire, R. E. Kuc, A. P. Davenport, *Methods Mol. Biol.* **2012**, *897*, 31–77; b) E. C. Hulme, M. A. Trevethick, *Br. J. Pharmacol.* **2010**, *161*, 1219–1237; c) D. Harder, D. Fotiadis, *Nat. Protoc.* **2012**, *7*, 1569–1578; d) J. Berry, M. Price-Jones, B. Killian, *Methods Mol. Biol.* **2012**, *897*, 79–94; e) 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.
[6] For selected reviews see: a) E. G. Solon, *Chem. Res. Toxicol.* **2012**, *25*, 543–555; b) A. W. Harrell, C. Sychterz, M. Y. Ho, A. Weber, K. Valko, K. Negash, *Pharma Res. Per.* **2015**, *3*, e00173.
[7] For selected reviews, see: a) N. Penner, L. Xu, C. Prakash, *Chem. Res. Toxicol.* **2012**, *25*, 513–531; b) E. M. Isin, C. S. Elmore, G. N. Nilsson, R. A. Thompson, L. Weidolf, *Chem. Res. Toxicol.* **2012**, *25*, 532–542.
[8] For selected reviews see: a) A. Mullard, *Rev. Drug Discovery* **2017**, *16*, 305; b) R. D. Tung, *Future Med. Chem.* **2016**, *8*, 491–494; c) A. Katsnelson, *Nat. Med.* **2013**, *19*, 656; d) G. S. Timmins, *Expert Opin. Ther. Pat.* **2014**, *24*, 1067–1075; e) S. L. Harbeson, R. D. Tung, *Med. Chem. News* **2014**, *2*, 8–22; f) T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595–3611.
[9] For selected reviews, see: a) J. R. Heys, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 770–778; b) G. N. Nilsson, W. J. Kerr, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 662–667; c) R. Salter, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 645–657; d) P. H. Allen, M. J. Hickey, L. P. Kingston, D. J. Wilkinson, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 731–738; e) J. Atzrodt, V. Derdau, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 674–685.
[10] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331–337.
[11] a) J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson, G. N. Nilsson, *Chem. Commun.* **2008**, 1115–1117.
[12] a) W. J. Kerr, D. M. Lindsay, M. Reid, J. Atzrodt, V. Derdau, P. Rojahn, R. Weck, *Chem. Commun.* **2016**, *52*, 6669–6672; b) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, P. Rojahn, R. Weck, *Tetrahedron* **2015**, *71*, 1924–1929; c) 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. Nilson, *Adv. Synth. Catal.* **2014**, *356*, 3551–3562; d) A. R. Cochrane, C. Idziak, W. J. Kerr, B. Mondal, L. C. Paterson, T. Tuttle, S. Andersson, G. N. Nilsson, *Org. Biomol. Chem.* **2014**, *12*, 3598–3603.
[13] M. Parmentier, T. Hartung, A. Pfaltz, D. Muri, *Chem. Eur. J.* **2014**, *20*, 11496–11504.
[14] a) A. Burhop, R. Weck, J. Atzrodt, V. Derdau, *Eur. J. Org. Chem.* **2017**, 1418–1424; b) A. Burhop, R. Prohaska, R. Weck, J. Atzrodt, V. Derdau, *J. Labelled Compd. Radiopharm.* **2017**, *60*, 343–348.
[15] a) K. Jess, V. Derdau, R. Weck, J. Atzrodt, M. Freytag, P. G. Jones, M. Tamm, *Adv. Synth. Catal.* **2017**, *359*, 629–638; b) M. Valero, A. Burhop, K. Jess, R. Weck, M. Tamm, J. Atzrodt, V. Derdau, *J. Label. Comp. Radiopharm.* **2018**, *61*, 380–385.
[16] L. Neubert, D. Michalik, S. Bähn, S. Imm, H. Neumann, J. Atzrodt, V. Derdau, W. Holla, M. Beller, *J. Am. Chem. Soc.* **2012**, *134*, 12239–12244.
[17] L. V. A. Hale, N. K. Szymczak, *J. Am. Chem. Soc.* **2016**, *138*, 13489–13492.
[18] W. Bai, K. H. Lee, S. K. S. Tse, K. W. Chan, Z. Lin, G. Jia, *Organometallics* **2015**, *34*, 3686–3698.
[19] C. Taglang, L. M. Martinez-Prieto, I. del Rosal, L. Maron, R. Poteau, K. Philippot, B. Chaudret, S. Perato, A. Sam Lone, C. Puente, C. Dugave, B. Rousseau, G. Pieters, *Angew. Chem. Int. Ed.* **2015**, *54*, 10474–10477; *Angew. Chem.* **2015**, *127*, 10620–10623.
[20] W. N. Palmer, P. J. Chirik, *ACS Catal.* **2017**, *7*, 5674–5678.
[21] R. Voges, R. Heys, T. Moenius, *Preparation of Compounds Labeled with Tritium and Carbon-14*, Wiley, Chichester, **2009**.
[22] Y. Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Coletti, I. W. Davies, D. W. C. MacMillan, *Science* **2017**, *358*, 1182–1187.
[23] 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.
[24] L. Gao, S. Perato, S. Garcia-Argote, C. Taglang, L. M. Martinez-Prieto, C. Chollet, D.-A. Buisson, V. Dauvois, P. Lesot, B. Chaudret, B. Rousseau, S. Feuillastre, G. Pieters, *Chem. Commun.* **2018**, *54*, 2986–2989.
[25] For selected recent reviews, see: a) B. E. C. G. de Goeij, J. M. Lambert, *Curr. Opin. Immunol.* **2016**, *40*, 14–23; b) P. Polakis, *Pharmacol. Rev.* **2016**, *68*, 3–19; c) N. Diamantis, U. Banerji, *Br. J. Cancer* **2016**, *114*, 362–367; d) R. Bakhtiar, *Biotechnol. Lett.* **2016**, *38*, 1655–1664; e) E. G. Kim, K. M. Kim, *Biomol. Ther.* **2015**, *23*, 493–509; f) R. V. J. Chari, M. L. Miller, W. C. Widdison, *Angew. Chem. Int. Ed.* **2014**, *53*, 3796–3827; *Angew. Chem.* **2014**, *126*, 3872–3904; g) R. J. Y. Ho, J. Chien, *J. Pharm. Sci.* **2014**, *103*, 71–77.
[26] a) A. V. Kamath, S. Iyer, *Biopharm. Drug Dispos.* **2016**, *37*, 66–74; b) K. R. Whiteman, H. A. Johnson, M. F. Mayo, C. A. Audette, C. N. Carrigan, A. LaBelle, L. Zukerberg, J. M. Lambert, R. J. Lutz, *mAbs* **2014**, *6*, 556–566; c) H. Xie, C. Audette, M. Hoffee, J. M. Lambert, W. A. Blättler, *J. Pharmacol. Exp. Ther.* **2004**, *308*, 1073–1082.
[27] Typically, tritium reactions are conducted under reduced pressure ($\ll 1$ bar) using modern stainless-steel manifold systems to allow for safe handling and to minimize radioactive waste. The very small standard reaction scale of operation requires special preparative techniques and operator training, see also ref. [24].
[28] In the first tritiation of DM4 a specific activity of 10 Ci mmol^{-1} was achieved with 7 equiv tritium gas, in a second run 12 equiv tritium was utilized resulting in a specific activity of 30 Ci mmol^{-1}. The temperature was lowered to 50 °C due to safety reasons therefore the catalyst loading was increased to 50 mol % to compensate the kinetic effect.
[29] Details of the calculation method along with further calculation results can be found in the Supporting Information.
[30] W. J. Kerr, M. Reid, T. Tuttle, *Angew. Chem. Int. Ed.* **2017**, *56*, 7808–7812; *Angew. Chem.* **2017**, *129*, 7916–7920.
[31] W. J. Kerr, M. Reid, T. Tuttle, *ACS Catal.* **2015**, *5*, 402–410.
[32] A. Y. L. Shu, W. Chen, J. R. Heys, *J. Organomet. Chem.* **1996**, *524*, 87–93.

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