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Hydrogen-Isotope Exchange

Hydrogen-Isotope Exchange (HIE) Reactions of Secondary and Tertiary Sulfonamides and Sulfonylureas with Iridium(I) Catalysts

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Abstract: For the first time we report the optimized hydrogen-isotope exchange (HIE) conditions for the selective aromatic deuteriation of various sulfonylureas and tertiary sulfonamides, as well as for a broad range of secondary sulfonamides. Based on a comprehensive screening of readily available Ir catalysts, the Kerr-type NHC catalyst **5** proved to be most efficient in the HIE reaction of secondary sulfonamides and sulfonylureas. However, for tertiary sulfonamides, the commercially available Burgess catalyst **6**, not yet utilized in HIE reactions, resulted in a much higher incorporation of deuterium. Finally, we tested the new HIE protocol for the labelling of a series of sulfa drugs and adapted the conditions to allow for selective tritium labelling.

Introduction

Molecules labelled with isotopes are important in a wide range of different scientific fields, for example, in optoelectronics,[1] microbial ecology,[2] clinical pharmacology,[3] diagnostics,[4] proteomics,[5] metabolomics[6] and drug discovery.[7] In pharmaceutical research, stable isotope-labelled compounds are utilized as internal standards for LC–MS/MS assay validation,[8] for metabolic pathway elucidation[9] and more recently also as "heavy drugs".[10] Additionally, radioactive tritium tracers are increasingly used as discovery tools, for example, in radioligand,[11] protein[12] and covalent binding[13] assays, for photoaffinity labelling,[14] tissue distribution[15] and for the ADME (Absorption Distribution Metabolism Excretion) profiling[16] of new drug candidates. The most elegant way to introduce a hydrogen isotope (deuterium or tritium) into an organic compound is through a hydrogen-isotope exchange (HIE) reaction.[17] HIE allows for direct isotope incorporation into the target molecule itself and thus circumvents the need for additional synthetic steps (e.g., precursor synthesis or a stepwise preparation from isotopically enriched starting materials). Nowadays, the most efficient methods for selective *ortho*-directed HIE reactions (selective introduction of a hydrogen isotope at the *ortho* position next to a directing group) are based on homogeneous iridium(I) complexes, which have demonstrated a high reactivity and at the same time good functional group tolerance and regioselectivity. In the last 30 years many groups have contributed catalysts to this field, with Crabtree's $[(cod)Ir(PPh_3)(py)]PF_6$[18] and Kerr's $[(cod)Ir(IMes)(PR_3)]PF_6$,[19] both commercially available, the most popular. In particular, the latter is widely employed for the selective labelling of substrates at the *ortho* position to a broad range of directing groups, for example, ketones, acids, amides, esters and several heterocycles, including pyridines, pyrimidines, imidazoles and oxazoles.[19,20]

However, despite recent progress in the field, there are still a number of interesting functionalities that have not been fully explored or not utilized at all as directing groups, for example, sulfonamides. Secondary and tertiary sulfonamides and sulfonylureas represent particularly important structural motifs in several classes of drugs (sulfa drugs), including sulfonamide antibiotics (Figure 1), for example, sulfamethoxazole (**1**),[21] protease inhibitors for the treatment of HIV, for example, darunavir (**2**),[22] PDE5 inhibitors for the treatment of erectile dysfunction, for example, sildenafil (Viagra, **3**),[23] sulfonylureas for the treatment of diabetes mellitus, for example, glibenclamide (**4**)[24] as well as

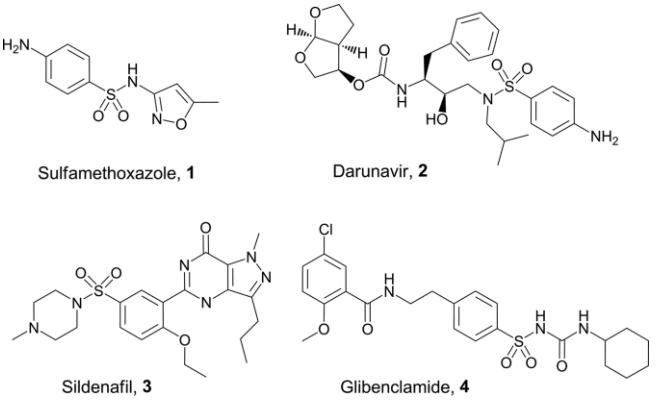

Figure 1. Secondary and tertiary sulfonamide (urea) drugs.

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non-steroidal anti-inflammatory COX-2 inhibitors of the oxicam class[25] and hepatitis C anti-viral RNA polymerase inhibitors.[26]

Recently, Kerr et al. reported a successful HIE protocol for primary sulfonamides with deuterium incorporations of up to 95 % by using a catalyst of the type [(cod)Ir(NHC)Cl] (**5**) at room temperature (Figure 2).[27] Earlier reports also described the use of Crabtree's catalyst,[28,29] iridium 1,3-dionate[30] and an in situ generated iridium–pyridine complex.[31] Although all of these methods are quite successful for HIE reactions involving primary sulfonamides, most known protocols fail to give desirable results for higher-substituted sulfonamides. For example, Kerr's NHC catalysts [(cod)Ir(NHC)PR_3] and [(cod)Ir(NHC)Cl] (**5**) yielded poor deuterium incorporations of only 7 and 8 % D, respectively, when employed at room temperature in a HIE reaction with *N*-methyl-4-methylbenzenesulfonamide (**7**).[27] For the same substrate, Pfaltz and co-workers[32] reported earlier deuterium incorporations of up to 95 % at elevated temperature (90 °C) when testing iridium P,N complexes, well known as asymmetric catalysts for double-bond reductions, for their HIE reactivity. Unfortunately, neither the yields of labelled **7** nor the application of these catalysts to the HIE of other secondary sulfonamides has been reported. Another limitation for further utilization might be the high air and moisture sensitivity of the non-commercially available catalysts, which require glove-box conditions for their preparation. To the best of our knowledge, successful HIE in tertiary sulfonamides or sulfonylureas has not yet been reported.

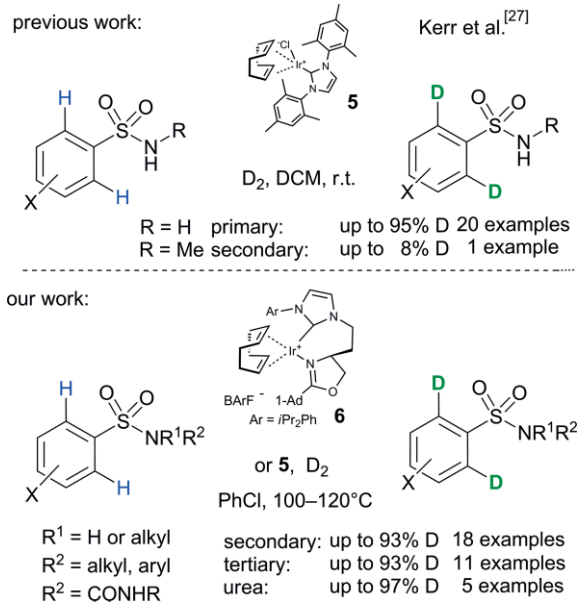


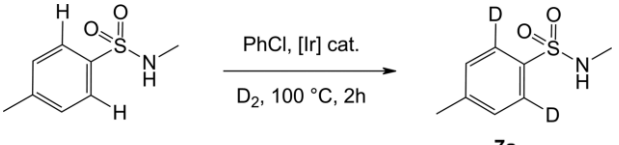
Figure 2. Previous and present work of HIE reactions with sulfonamides.

Results and Discussion

In our continuing efforts to broaden our synthetic repertoire for fast tritium labelling we became interested in a new, convenient HIE protocol as known procedures have failed for secondary and tertiary sulfonamides. Stimulated by the recent reports of Kerr[27] and Pfaltz[32] and their co-workers, we started our own studies with a careful evaluation of commercially available or readily accessible catalysts, for example, through short catalyst syntheses without the need for glove-box conditions. Even though the difference in reactivity between primary, secondary and tertiary sulfonamides might be considered moderate, our initial catalyst screening at room temperature revealed only very limited deuterium incorporation in secondary and tertiary sulfonamides in contrast to the high deuterium efficiencies reported for primary sulfonamides.[27] Clearly, substitution at the sulfonamide has a strong effect on the HIE reaction. Thus we repeated all the experiments at elevated temperatures in a high-boiling solvent like chlorobenzene (see Table 1).

To our great delight, under these conditions the [(cod)Ir(NHC)Cl] catalyst (**5**; Table 1, entry 7) as well as Burgess' catalyst [(cod)Ir{(adamantyl-oxazolyl)-ethyl(iPr_2Ph)-imidazolyl}]-

Table 1. Screening of iridium catalysts in the HIE reaction of *N*-methyl-4-methylbenzenesulfonamide (**7**).[a,b]



7 **7a**

Entry	Catalyst	D_{inc} **7a**[a,b] [%]	Yield[c] of **7a** [%]
1	[(cod)Ir(Py)PCy_3] (Crabtree)	0	91
2	[(cod)Ir(acac)]	0	96
3	[(cod)Ir($acacF_6$)]	0	94
4	[(cod)Ir(MeC_p)]	0	97
5	[(cod)Ir(NHC)PPh_3] (Kerr)	25	96
6	[(cod)Ir(NHC)PBn_3] (Kerr)	30	93
7	[(cod)Ir(NHC)Cl] (Kerr, **5**)	79	91
8	[(cod)Ir{(adamantyloxazolyl)ethyl(iPr_2Ph)imidazolyl}]BArF (Burgess, **6**)	81	94
9	[(cod)Ir$(Py)_2$]	0	92
10	[(cod)Ir(PPh_3)Cl]	0	97

[a] Reagents and conditions: substrate **7** (10 µmol, 2 mg), catalyst (10 mol-%), chlorobenzene (2 mL), D_2 (1 atm), 2 h, 100 °C. [b] Positions and percentage of deuterium incorporation were determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

BArF (**6**; entry 8) showed similar high HIE reactivity towards the secondary sulfonamide **7** selected as our model substrate. It is worth mentioning that, to the best of our knowledge, the Burgess catalyst **6**, developed as a catalyst for the asymmetric hydrogenation of olefins,[33] has never been applied in HIE reactions before. Even though both catalysts showed very similar results in this model reaction, we decided to study both to gain more insights into their differences.

Subsequent solvent screening (Table 2) with catalysts **5** and **6** revealed no or only very limited HIE reactivity in boiling methyl *tert*-butyl ether (MTBE; Table 2, entry 1), ethanol (entry 2), 2-methylhydrofuran (2MeTHF, entry 3), isopropyl acetate (entry 4), 1-butanol (entry 5) and dichloromethane (DCM, entry 8). Chlorobenzene, selected for the initial catalyst screening, turned out to be the best solvent for both catalysts (entry 6). In toluene, moderate deuteriation was observed (entry 7).

In the next optimization step we varied parameters such as temperature, time and catalyst loading (Table 3). In the model reaction of **7** with catalyst **5** (Table 3, entries 1–8), temperatures above 100 °C (entries 3–8) and a catalyst loading of 10 mol-% were needed to obtain good deuterium incorporation within 2 h. At lower temperatures (entries 1 and 2) and with a catalyst loading below 10 mol-% (entry 6) the D incorporation dropped significantly whereas a higher catalyst loading (20 mol-%) seemed to have no additional benefit (entry 7). Finally, we further investigated the scope and limitations of the reaction by using a 10 mol-% catalyst loading of **5** at 120 °C for 1 h under a deuterium atmosphere (entry 8) However, similar results were observed to those achieved at lower temperatures (100 °C) for a reaction time of 2 h (entry 3 vs. entry 8). For Burgess' catalyst **6** we found the highest deuterium incorporation at 100 °C for a 2 h reaction time and a 5 mol-% catalyst loading (entry 13). At lower temperatures (entries 9–11) a higher catalyst loading was needed to obtain a similarly large incorporation of D, whereas at higher temperatures (120 °C) the catalyst activity dropped significantly, probably due to the decomposition of the catalyst. As the best general conditions we identified 5–10 mol-% catalyst loading, a temperature of 100–120 °C and a 2 h reaction time.

For a more detailed evaluation of the scope of the reaction we first modified the alkyl and aryl substitution pattern (Figure 3). Comparing different benzene- and methanesulfonamide derivatives (**7–11**), we found that the HIE reactions with both catalysts **5** and **6** are selective for arylsulfonamides, whereas the hydrogen atoms of *N*-aryl substituents are not exchanged even in cases in which the *N*-aryl *ortho* position represents the only exchangeable hydrogen atoms, as in methanesulfonanilide **8**. This finding is in good agreement with the detailed mechanistic investigations reported previously for primary sulfonamides by Kerr and Tuttle,[27] which suggests a similar mechanism for secondary sulfonamides too.

As previously observed for other [(cod)Ir(NHC)PR_3]-type catalysts,[34] the catalytic activity of **5** is not affected by the presence of an aniline moiety and thus, like **10**, **11** is deuteriated only at the *o*-benzenesulfonamide positions. Interestingly, **6** seems to have a higher affinity than **5** towards the amine as a competing directing group, which is indicated by an additional exchange at the *o*-aniline position in **10**. Repositioning of the amino function to the other ring system in **11** resulted in exclusive *o*-aniline labelling with **6**. Similarly, the nitro function showed a better coordinating efficiency than the benzenesulfonamide moiety for both catalysts leading to 50 (with **5**) and 40 % (with **6**) deuterium exchange at the *ortho* position of the nitro group in **12**. When using acid- or ester-substituted benzenesulfonamides **13** and **14**, *ortho*-deuterium exchange next to both directing groups (ester/acid and sulfonamide) was observed, however, in this case **6** was outperformed by **5** in terms of HIE efficiency.

Table 3. Optimization of the HIE reaction of *N*-methyl-4-methylbenzenesulfonamide (**7**) in chlorobenzene.[a,b,c]

Entry	Cat	*T* [°C]	*t* [h]	Catalyst [mol-%]	D_{inc}[b,c] **7a** [%]	Yield[c,d] **7a** [%]
1	**5**	60	2	10	33	93
2	**5**	80	2	10	58	91
3	**5**	100	2	10	82	93
4	**5**	120	2	10	80	92
5	**5**	130	2	10	73	89
6	**5**	100	2	5	33	90
7	**5**	100	2	20	79	91
8	**5**	120	1	10	84	96
9	**6**	60	2	10	42	81
10	**6**	80	2	5	45	84
11	**6**	80	2	10	84	81
12	**6**	100	2	3	71	80
13	**6**	100	2	5	93	84
14	**6**	120	1	10	70	79

[a] Reagents and conditions: substrate **7** (10 µmol, 2 mg), catalyst, chlorobenzene (2 mL), D_2 (1 atm). [b] Positions and percentage of deuterium incorporation were determined by ^{1}H NMR spectroscopy. [c] Repeated three times. [d] Isolated yield.

Table 2. Solvent screening of the HIE of *N*-methyl-4-methylbenzenesulfonamide (**7**) with catalyst **5** or **6**.[a,b]

Entry	Solvent	*T* [°C]	Catalyst **5**		Catalyst **6**	
			D_{inc}[b] **7a** [%]	Yield[c] of **7a** [%]	D_{inc}[b] **7a** [%]	Yield[c] of **7a** [%]
1	MTBE	45	0	91	18	87
2	ethanol	68	0	93	0	86
3	2-MeTHF	70	0	90	0	82
4	isopropyl acetate	79	15	91	50	79
5	1-butanol	100	0	95	0	88
6	chlorobenzene	100	85	97	82	90
7	toluene	100	49	94	32	78
8	DCM	30	0	90	0	75

[a] Reagents and conditions: substrate **7** (10 µmol, 2 mg), 1 µmol catalyst, solvent (2 mL), D_2 (1 atm). [b] Positions and percentage of deuterium incorporation determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

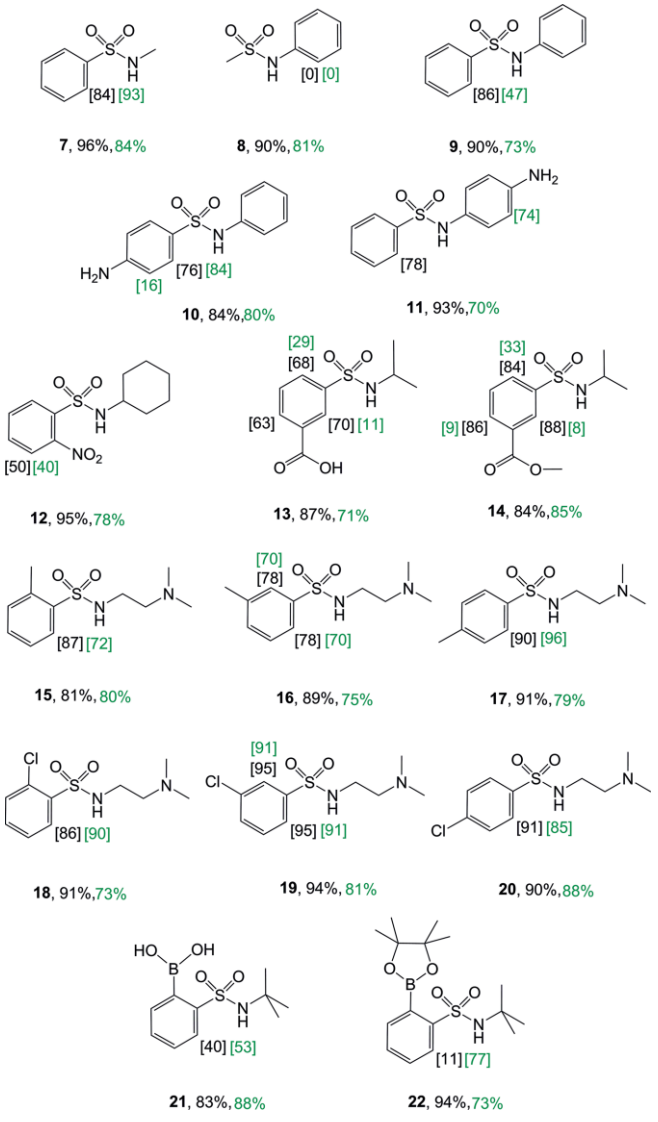


Figure 3. Products of the HIE reactions of different secondary sulfonamides with catalyst **5** and **6**.[a,b] [a] Reagents and conditions: substrate (22 μmol), 10 mol-% catalyst **5**, PhCl (1 mL), D_2 (1 atm), 120 °C, 1 h (black); substrate (22 μmol), 5 mol-% catalyst **6**, PhCl (1 mL), D_2 (1 atm), 100 °C, 2 h (green). [b] Positions and percentage of deuterium incorporation were determined by ^{1}H NMR spectroscopy. The values of D_{inc} [%] are presented in brackets. Each reaction was repeated at least twice.

Furthermore, we found no steric influence on yield and deuterium incorporation by the *ortho*-, *meta*- and *para*-substituted methyl groups in substrates **15**–**17**. Also, the presence of an electron-withdrawing chloro substituent in benzenesulfonamides **18**–**20** gave good results for deuterium incorporation, ranging from 85 to 95 % for both catalysts. The slightly better HIE efficiency observed with **6** for the boronic acid derivative **21** was more striking with the boronic ester **22** (77 % D incorporation with **6** compared with 11 % with **5**).

Although both catalysts showed good results for the HIE reactions with secondary sulfonamides **9**–**22**, with **5** tending to be superior, particularly in the presence of ester or acid functionalities, much higher deuterium incorporations were achieved for tertiary sulfonamides **23**–**31** with **6** (Figure 4). For example, the reaction of *N*,*N*-diethyl-4-chlorobenzenesulfonamide (**23**) yielded 84 % D incorporation with **6** compared with 33 % with **5**. The same tendency for better deuterium incorporation with **6** was observed with the tertiary sulfonamides **24**–**31**. Functional groups like tertiary amines, acids, esters and halogens did not affect the *ortho* selectivity or reactivity of the Burgess-catalysed aromatic HIE reaction. However, primary amines and ketones proved to be better coordinating groups than tertiary sulfonamides and this led to preferred or additional exchange at the corresponding *ortho* positions (substrates **24** and **31**). Interestingly, the presence of an alternative aromatic ring system in the pyrrole and indole derivatives **29**–**31** led to a preferred exchange in the heterocycle.

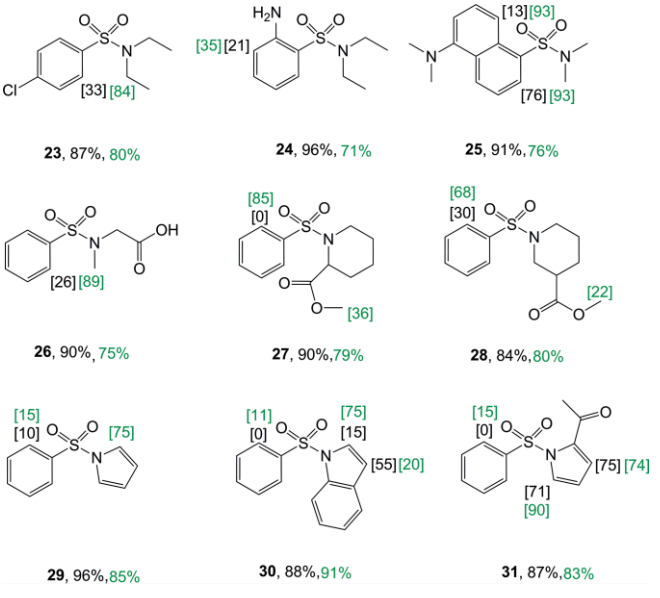


Figure 4. Products of the HIE reactions of tertiary sulfonamides with catalyst **5** and **6**.[a,b] [a] Reagents and conditions: substrate (22 μmol), 10 mol-% catalyst **5**, PhCl (1 mL), D_2 (1 atm), 120 °C, 1 h (black); substrate (22 μmol), 5 mol-% catalyst **6**, PhCl (1 mL), D_2 (1 atm), 100 °C, 2 h (green). [b] Positions and percentage of deuterium incorporation were determined by ^{1}H NMR spectroscopy. The values of D_{inc} [%] are presented in brackets. Each reaction was repeated at least twice.

Catalyst **5** performed much better in HIE reactions with sulfonylureas **32**–**34** with excellent deuterium-incorporation efficiency of up to 97 D incorporation in the case of 1-(*p*-chlorobenzenesulfonyl)-3-propylurea (**32**; Figure 5). Similarly to **14**, the presence of an ester function in **33** resulted in *ortho*-deuterium exchange next to both directing groups. For the sulfonyl amide derivative **35**, the two catalysts showed similar deuterium incorporation with 76 and 88 % D incorporation, respectively.

Finally, we tested our HIE protocol on a variety of drugs and drug-like sulfonamides and sulfonylureas (Figure 6). As expected in the HIE reaction of sulfamethoxazole (**1**) with **5**, a highly selective deuteriation of the *o*-benzenesulfonamide position (65 % D incorporation) was observed. In contrast, the treatment of **1** with **6** resulted in 0 % deuterium uptake, not even at the *o*-aniline position; we consider that an alternative stronger coordination of the catalyst at another heteroatom takes place.

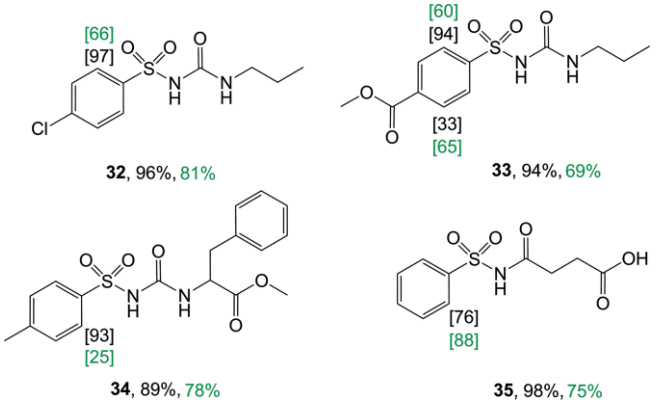


Figure 5. Products of the HIE reactions of sulfonylureas **32**–**34** and sulfonyl amide **35** with catalyst **5** and **6**.[a,b] [a] Reagents and conditions: substrate (22 µmol), 10 mol-% catalyst **5**, PhCl (1 mL), D_2 (1 atm), 120 °C, 1 h (black); substrate (22 µmol), 5 mol-% catalyst **6**, PhCl (1 mL), D_2 (1 atm), 100 °C, 2 h (green). [b] Positions and percentage of deuterium incorporation were determined by ^{1}H NMR spectroscopy. The values of D_{inc} [%] are presented in brackets. Each reaction was repeated at least twice.

The steroidal secondary sulfonamide **36** carrying the dansyl dye was deuteriated selectively at the aromatic 2- and 8-positions of the dansyl moiety next to the naphthalenesulfonamide function with 55 and 50 % D incorporation, respectively, using catalyst **5**. For the same substrate the use of catalyst **6** resulted in much lower D incorporation at the same positions, thereby confirming a general tendency to obtain better deuterium incorporation in secondary sulfonamides with catalyst **5** than with **6**. The labelling of the dansyl moiety makes it in principle possible to prepare bimodal imaging probes carrying a radioactive (tritium) and fluorophore marker.

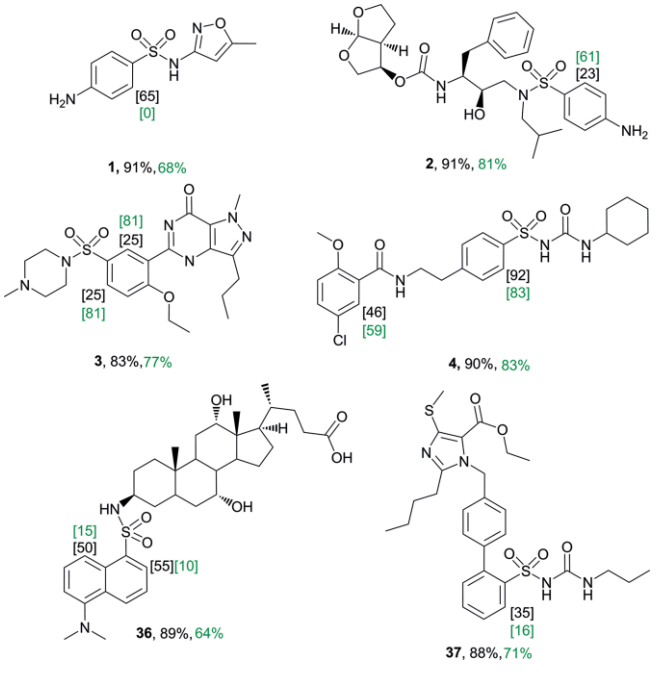


Figure 6. Products of the HIE reactions of drug-like molecules with catalyst **5** or **6**.[a,b] [a] Reagents and conditions: substrate (22 µmol), 10 mol-% catalyst **5**, PhCl (1 mL), D_2 (1 atm), 120 °C, 1 h (black); substrate (22 µmol), 10 mol-% catalyst **6**, PhCl (1 mL), D_2 (1 atm), 100 °C, 2 h (green). [b] Positions and percentage of deuterium incorporation were determined by ^{1}H NMR spectroscopy. The values of D_{inc} [%] are presented in brackets.

Interestingly, catalyst **6** proved to be superior for tertiary sulfonamides, as demonstrated for the drugs darunavir (**2**) and sildenafil (**3**), which were selectively *ortho*-deuteriated with 61 and 81 % D incorporation, respectively. The amino group in darunavir (**2**) did not change the HIE *ortho* selectivity of the catalyst, in contrast to model compound **11**. In the case of our sulfonylurea test substrates, catalyst **5** performed better than **6**, which was also found when applying the two catalysts to the exchange reactions with glibenclamide (**4**) and urea **37**. Although for substrate **37** only a moderate 35 % D incorporation was found, glibenclamide (**4**) proved to be an excellent substrate for HIE with a remarkable 92 % deuteriation of the *o*-benzenesulfonamide plus an additional 46 % at the *ortho*-amide position.

Finally, we also tested whether our HIE protocol could be applied under the special conditions required for tritium labelling. In this case typically only a 5–10-fold excess of tritium gas is utilized and therefore the reaction conditions were optimized by using a deuterium manifold system and glibenclamide (**4**) as test substrate (see the Supporting Information for details). With 10 mol-% catalyst **5** we evaluated the HIE reaction of **4** under two reduced pressures (89 and 240 mbar) with 10 equiv. D_2 at 100 °C over 2 and 5 h. Subsequently, the tritium reaction was carried out with 2.3 Ci tritium gas at 100 °C to provide tritium-labelled glibenclamide with a specific activity of 9 Ci/mmol. The ^{3}H NMR spectrum (Figure 7) of the product reveals the highly selective incorporation of tritium into the *o*-benzenesulfonamide and *o*-amide positions.[35]

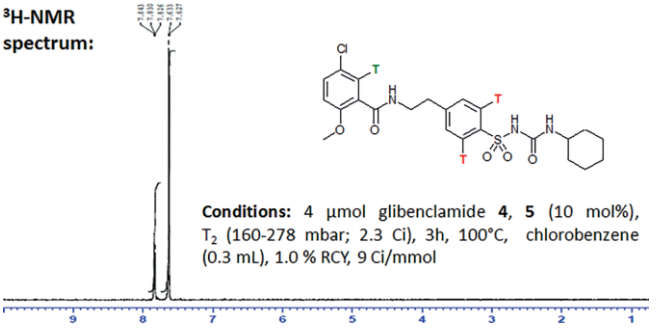


Figure 7. ^{3}H NMR spectrum of [^{3}H]glibenclamide ([^{3}H]**4**).

Conclusions

We have developed the first practical HIE protocol for the deuteriation of various secondary and tertiary sulfonamides as well as sulfonylureas based on readily available iridium NHC catalyst **5** and the commercially available Burgess catalyst **6**. The latter catalyst has not been utilized for HIE reactions before but proved to be most efficient particularly in the HIE reactions of tertiary sulfonamides, whereas for secondary sulfonamides and ureas a better deuterium incorporation was typically observed

with catalyst **5**. The method has a broad substrate scope, can be applied to sulfa drugs and in principle even be adapted to the special conditions required for selective tritium labelling. Even though some of the hydrogen-isotope incorporations achieved by this method might only be moderate, this degree of labelling is typically sufficient for tritium labelling and most related applications.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance 300 and 500 spectrometers in [D_6]DMSO. The chemical shifts (δ) are expressed in ppm and are given relative to the residual proton signal of [D_6]DMSO (δ = 2.50 ppm). NMR assignments were based on the results of additional 2D NMR experiments. The ^{1}H NMR spectra show the substrate before reaction, the substrate after the reaction with catalyst **5** and the substrate after the reaction with catalyst **6**. Silica gel column chromatography was carried out with SiO_2 (Merck, 0.063–0.200 mesh). The purity of the products was determined by using an LC–MS system with a Symmetry Shield RP18 column (3.9 × 150 mm) with a gradient program under the following conditions: mobile phase A: water (900 mL), acetonitrile (100 mL), TFA (1 mL); mobile phase B: water (100 mL), acetonitrile (900 mL), TFA (0.75 mL); flow 1.5 mL/min; detection UV 254 and 210 nm.

General Method: All screening methods were performed in a Radleys synthesis station for parallel solution-phase chemistry unless mentioned otherwise. Thus, a vial (25 mL) was charged with a stirring bar and the substrate stock solution (500 µL, 20 mM, 1 equiv.). The catalyst and solvent (1.5 mL) were added to the vial. Then the vial was sealed with an open connection to the gas inlet, evacuated until slight bubbling of the solution and refilled with deuterium gas from a balloon three times. The vial was closed and placed in the preheated synthesis station. The reaction was stirred (500 rpm) under a D_2 atmosphere (1 atm) for the appropriate time and temperature. The crude reaction mixture was purified by silica gel chromatography (MTBE/ethyl acetate, 4:1) and analysed by NMR spectroscopy.

Solvent Screening of the HIE Reaction of *N*-Methyl-4-methylbenzenesulfonamide (7) with Catalyst 5 or 6: The solvent screening was carried out with *N*-methyl-4-methylbenzenesulfonamide (**7**) in the listed solvents (500 µL, 20 mM, 1 equiv.) in the presence of catalyst **5** or **6** (1 µmol, 10 mol-%, 0.1 equiv.) at the appropriate temperature and for the stated time. The total volume of the reaction mixture was 2 mL. All reactions were performed according to the general method at the temperature and time stated in Table 2.

Optimization of the HIE Reaction of *N*-Methyl-4-methylbenzenesulfonamide (7) in Chlorobenzene: The stock solution of *N*-methyl-4-methylbenzenesulfonamide (**7**) in chlorobenzene (500 µL, 20 mM, 1 equiv.) and catalyst **5** or **6** as indicated in Table 3 (0.3–2 µmol, 3–20 mol-%, 0.03–0.2 equiv.) as well as chlorobenzene (1.5 mL) were used for the optimization of the HIE reaction. The reaction was stirred for the declared time and at the stated temperature under D_2. Every reaction was performed three times and the results are an average of the three reactions. In addition to the means, the standard deviations of the deuterium incorporation and yield were calculated.

Deuteriation of Different Sulfonamides and Sulfonylureas with Catalyst 5 or 6: Deuterium incorporation into various sulfonamides and sulfonylureas (Figure 3, Figure 4 and Figure 5) was analysed under the optimized conditions following the general method for Kerr's catalyst **5** [substrate (10 µmol), catalyst **5** (10 mol-%), PhCl (2 mL), 120 °C, 1 h] and Burgess' catalyst **6** [substrate (10 µmol), catalyst **6** (5 mol-%), PhCl (2 mL), 100 °C, 2 h].

Deuteriation of Compounds 1–4, 36 and 37: (Figure 6). Deuterium incorporation into compounds **1–4**, **36** and **37** (Figure 6) was investigated under the following conditions for Kerr's catalyst **5** [substrate (10 µmol), catalyst **5** (10 mol-%), PhCl (2 mL), 120 °C, 1 h] and Burgess' catalyst **6** [substrate (10 µmol), catalyst **6** (10 mol-%), PhCl (2 mL), 100 °C, 2 h].

Deuterium Manifold Reaction: The optimization of the deuteriation of glibenclamide (**4**) was performed in the deuterium manifold (RC TRITEC AG). Thus, the vial (1 mL) was loaded with the substrate stock solution (100/200 µL, 40 mM, 1 equiv.) and the catalyst stock solution (50/100 µL, 8 mM, 0.1 equiv.). Then the reaction mixture was frozen with liquid nitrogen, the vial was evacuated, charged with D_2 (10 equiv.) and the connection to the gas was closed. The mixture was slowly warmed to room temperature and afterwards heated to 100 °C. After the temperature was reached, the stirring (500 rpm) and the time was started. The crude reaction mixture was analysed by NMR spectroscopy.

Tritium Manifold Reaction: Based on the results in the deuterium manifold (RC TRITEC AG), the ^{3}H reaction was performed under the following conditions: glibenclamide (**4**; 2.00 mg, 4 µmol) was dissolved in chlorobenzene (0.15 mL) and then catalyst **5** (10 mol-%, 0.4 µmol) was added. The 1 mL reaction flask was adapted to a tritium manifold and the solution was frozen in liquid nitrogen. The flask was evacuated and charged with tritium (2.30 Ci, 39.3 µmol). The reaction mixture was then warmed to room temperature and whilst stirring heated at 100 °C for 2 h. After cooling to room temperature, the solvent was removed in vacuo. The labile tritium was exchanged and removed by the addition of methanol and a freeze-drying process (three times repeated). The solid residue was dissolved in dry methanol (1 mL) and purified by HPLC (Phenomenex Gemini NX C18 10 × 150 mm, 5 µm, 9 mL/min flow, ACN/water gradient program) and finally transferred through a SPE-C18 device to ethanol to give **4** [877 MBq (23.7 mCi), 1 % RCY, 3.33 GBq/mmol (9 Ci/mmol), >97 % radiochemical purity by HPLC].

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[1] For selected examples, see: a) T. D. Nguyen, G. Hukic-Markosian, F. Wang, L. Wojcik, X.-G. Li, E. Ehrenfreund, Z. V. Vardeny, *Nat. Mater.* **2010**, *9*, 345–352; b) A. M. Krause-Heuer, N. R. Yepuri, T. A. Darwish, P. J. Holden, *Molecules* **2014**, *19*, 18604–18617.

[2] For selected reviews, see: a) Z. T. Aanderud, J. T. Lennon, *Appl. Environ. Microbiol.* **2011**, *77*, 4589–4596; b) O. Uhlík, M.-C. Leewis, M. Strejcek, L. Musliva, M. Mackova, M. B. Leigh, T. Macek, *Biotechnol. Adv.* **2013**, *31*, 154–165.

[3] R. C. A. Schellekens, F. Stellard, H. J. Woerdenbag, H. W. Frijlink, J. G. W. Kosterink, *Br. J. Clin. Pharmacol.* **2011**, *72*, 879–897.

[4] For selected reviews, see: a) L. Bonfrate, I. Grattagliano, G. Palasciano, P. Portincasa, *Gastroenterol. Rep.* **2015**, *3*, 12–21; b) B. Braden, *Best. Pract. Res. Clin. Gastroent.* **2009**, *23*, 337–352.

[5] For selected reviews, see: a) O. Chahrour, D. Cobice, J. Malone, *J. Pharm. Biomed. Anal.* **2015**, *113*, 2–20; b) R. Aebersold, *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 645–665; c) L. V. Schneider, M. H. Hall, *Drug Discovery Today* **2005**, *10*, 353–363.
[6] For selected reviews, see: a) A. Chokkathukalam, D.-H. Kim, M. P. Barrett, R. Breitling, D. J. Creek, *Bioanalysis* **2014**, *6*, 511–524; b) P. Bruheimer, H. F. N. Kvitvang, S. G. Villas-Boas, *J. Chromatogr. A* **2013**, *1296*, 196–203; c) T. Toyo'oka, *J. Pharm. Biomed. Anal.* **2012**, *69*, 174–184.
[7] 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.
[8] For selected examples, see: a) E. Stovkis, H. Rosing, J. H. Beijnen, *Rapid Commun. Mass Spectrom.* **2005**, *19*, 401–407; b) A. K. Hewavitharana, *J. Chromatogr. A* **2011**, *1218*, 359–361.
[9] For selected examples, see: a) D. L. Nabb, B. Szostek, M. W. Himmelstein, M. P. Mawn, M. L. Gargas, L. M. Sweeney, J. C. Stadler, R. C. Buck, W. J. Fasano, *Toxicol. Sci.* **2007**, *100*, 333–344; b) D. Dalvie, R. S. Obach, P. Kang, C. Prakash, C. M. Loi, S. Hurst, A. N. R. Nedderman, L. Goulet, E. Smith, H. Z. Bu, *Chem. Res. Toxicol.* **2009**, *22*, 357–368; c) L. Xu, C. Woodward, S. Khan, C. Prakash, *Drug. Metab. Dispos.* **2012**, *40*, 680–693.
[10] For selected reviews, see: a) A. Katsnelson, *Nat. Med.* **2013**, *19*, 656; b) G. S. Timmins, *Expert Opin. Ther. Patents* **2014**, *24*, 1067–1075; c) S. L. Harbeson, R. D. Tung, *Med. Chem. News* **2014**, *2*, 8–22; d) T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595–3611.
[11] 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.
[12] For selected reviews, see: a) 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; b) F. M. Musteata, *Bioanalysis* **2011**, *3*, 1753–1768.
[13] For selected examples, see: T. Usui, M. Mise, T. Hashizume, M. Yabuki, S. Komuro, *Drug Metab. Dispos.* **2009**, *37*, 2383–2392.
[14] For selected reviews, see: a) E. Smith, I. Collins, *Future Med. Chem.* **2015**, *7*, 159–183; b) C. F. Filer, *J. Radioanal. Nucl. Chem.* **2009**, *281*, 521–530; c) V. T. G. Chuang, M. Otagiri, *Molecules* **2013**, *18*, 13831–13859; d) L. Dubinsky, B. P. Krom, M. M. Meijler, *Bioorg. Med. Chem.* **2012**, *20*, 554–570; e) M. S. Panov, V. D. Voskresenska, M. N. Ryazantsev, A. N. Tarnovsky, R. M. Wilson, *J. Am. Chem. Soc.* **2013**, *135*, 19167–19179; f) J. Liu, C. Liu, W. He, *Curr. Org. Chem.* **2013**, *17*, 564–579.
[15] 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.
[16] 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.
[17] For selected reviews, see: a) J. R. Heys, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 770–778; b) J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765; *Angew. Chem.* **2007**, *119*, 7890; c) G. N. Nilsson, W. J. Kerr, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 662–667; d) R. Salter, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 645–657; e) P. H. Allen, M. J. Hickey, L. P. Kingston, D. J. Wilkinson, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 731–738; f) J. Atzrodt, V. Derdau, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 674–685; g) T. Yamada, Y. Sawama, K. Shibata, K. Morita, Y. Monguchi, H. Sajiki, *RSC Adv.* **2015**, *5*, 13727–13732; h) Y. Sawama, Y. Monguchi, H. Sajiki, *Synlett* **2012**, *23*, 959–972; i) N. Modutlwa, T. Maegawa, Y. Monguchi, H. Sajiki, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 686–692.
[18] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331–337.
[19] a) J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson, G. N. Nilsson, *Chem. Commun.* **2008**, 1115–1117; b) 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.
[20] a) 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; b) A. R. Cochrane, S. Irvine, W. J. Kerr, M. Reid, S. Andersson, G. N. Nilsson, *J. Labelled Compd. Radiopharm.* **2013**, *56*, 451–454; c) P. W. C. Cross, J. M. Herbert, W. J. Kerr, A. H. McNeill, L. C. Paterson, *Synlett* **2016**, *27*, 111–115.
[21] R. Gleckman, S. Alvarez, D. W. Joubert, *Am. J. Hosp. Pharm.* **1979**, *36*, 893–906.
[22] A. K. Ghosh, Z. L. Dawson, H. Mitsuya, *Bioorg. Med. Chem.* **2007**, *15*, 7576–7580.
[23] N. K. Terrett, A. S. Bell, D. Brown, P. Ellis, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824.
[24] L. Luzi, G. Pozza, *Acta Diabetol.* **1997**, *34*, 239–244.
[25] J. G. Lombardino, E. H. Wiseman, W. M. McLamore, *J. Med. Chem.* **1971**, *14*, 1171–1175.
[26] a) L. Gerber, T. M. Welzel, S. Zeuzem, *Liver Int.* **2013**, *33*, 85–92; b) J. P. Trivella, J. Gutierrez, P. Martin, *Expert Opin. Pharmacother.* **2015**, *16*, 617–624.
[27] W. J. Kerr, M. Reid, T. Tuttle, *ACS Catal.* **2015**, *5*, 402–410.
[28] D. Hesk, P. R. Das, B. Evans, *J. Labelled Compd. Radiopharm.* **1995**, *36*, 497–502.
[29] G. J. Ellames, J. S. Gibson, J. M. Herbert, A. H. McNeill, *Tetrahedron* **2001**, *57*, 9487–9497.
[30] B. McAuley, M. J. Hickey, L. P. Kingston, J. R. Jones, W. J. S. Lockley, A. N. Mather, E. Spink, S. P. Thompson, D. J. Wilkinson, *J. Labelled Compd. Radiopharm.* **2003**, *46*, 1191–1204.
[31] P. W. C. Cross, G. J. Ellames, J. S. Gibson, J. M. Herbert, W. J. Kerr, A. H. McNeill, T. W. Mathers, *Tetrahedron* **2003**, *59*, 3349–3358.
[32] M. Parmentier, T. Hartung, A. Pfaltz, D. Muri, *Chem. Eur. J.* **2014**, *20*, 11496–11504.
[33] M. C. Perry, X. Cui, M. T. Powell, D. R. Hou, J. H. Reibenspies, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113–123.
[34] a) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, P. Rojahn, R. Weck, *Tetrahedron* **2015**, *71*, 1924–1924; b) W. J. Kerr, D. M. Lindsay, M. Reid, J. Atzrodt, V. Derdau, P. Rojahn, R. Weck, *Chem. Commun.* **2016**, *52*, 6669–6672.
[35] The tritiation was performed as a single experiment under reduced pressure and limited amount of tritium gas to demonstrate the general applicability of the method for the incorporation of tritium.

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