Evaluation of a P,N-Ligated Iridium(I) Catalyst in Hydrogen Isotope Exchange Reactions of Aryl and Heteroaryl Compounds

Mégane Valero[a], Annina Burhop[a], Kristof Jess[b], Remo Weck[a], Matthias Tamm[b],*, Jens Atzrodt[a],* and Volker Derdau[a],*

[a] M. Valero, A. Burhop, R. Weck, Dr. Jens Atzrodt, Dr. Volker Derdau, R&D, Integrated Drug Discovery, Isotope Chemistry & Metabolite Synthesis, Sanofi Germany
Industriepark Höchst, G876, 65926 Frankfurt/Main
E-mail: Jens.Atzrodt@sanofi.com; Volker.Derdau@sanofi.com
[b] Dr. Kristof Jess, Prof. Dr. Matthias Tamm, Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Hagenring 30, 38106 Braunschweig, Germany

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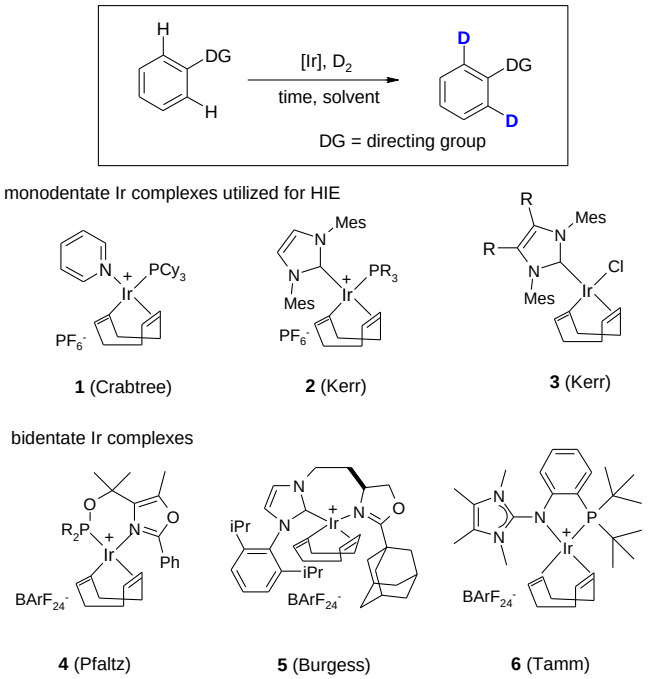
Abstract: We have developed a novel and efficient iridium-catalyzed hydrogen isotope exchange (HIE) reaction method with secondary and tertiary sulfonamides at ambient temperatures. Furthermore *N*-oxides and phosphonamides have been successfully applied in HIE reactions with moderate to excellent deuterium introduction.

Introduction

Commercial catalysts developed by Crabtree and Kerr (scheme 1), *i.e.* [(cod)Ir(PPh_3)(py)]PF_6 (**1**)[1] and [(COD)Ir(IMes)(PR_3)]PF_6 (**2**),[2] utilizing T_2 gas as tritium source have leveraged the routine use of HIE[3] for highly selective tritium labelling of organic molecules.[4] The very high selectivity of the H/T exchange for the *ortho*-position next to a directing group enables a specific tritium introduction into biologically and chemically stable positions. In consequence, those HIE methods facilitated a possibility to overcome metabolic stability issues associated with earlier tritiation methods.[5] Thus today, tritium tracers are widely utilized for ADME-profiling[6,7] of new drug candidates but also as a discovery tool for photoaffinity labelling[8] and for radioligand,[9] protein[10] and covalent binding[11] assays. In particular, Kerr's catalysts **2** and **3** are widely applied for mild and selective *ortho*-labelling employing a broad range of directing groups such as ketones, amides, esters, primary sulfonamides and several heterocycles.[12] Despite recent progress, a number of interesting functionalities, ubiquitous throughout drug motives, still present significant challenges for established HIE protocols.

Some of those limitations could be recently overcome by introduction of a new generation of Ir-catalysts with bidentate ligands. The highly air- and moisture-sensitive, non-commercial catalysts **4** with phosphine-oxazoline P,N ligands, originally developed by Pfaltz for asymmetric hydrogenation of olefins, proved efficient also in the HIE reaction of weakly coordinating substrates such as sulfones and secondary sulfonamides.[13] Based on a comprehensive screening of readily available Ir-catalysts, we recently identified another hydrogenation catalyst to have also an appreciable HIE capacity, *viz.* the commercial, air-stable Burgess catalyst **5**.[14] With this catalyst, we have developed the first practical HIE protocol for selective *ortho*-deuteration of various secondary and tertiary sulfonamides as well as sulfonyl ureas.[15] A similar reactivity was also observed for monodentate Kerr catalysts of the type [(COD)Ir(NHC)Cl] (**3**),[16] which proved even more efficient in the HIE reaction of secondary sulfonamides and ureas, while **5** resulted in greater deuterium incorporation for tertiary sulfonamides.[**Error! Bookmark not defined.**a] This method was also applied to sulfo drugs and even adopted to the special conditions required for selective tritium labelling (5–10 eq. of T_2 gas, low pressure). However, the elevated temperatures of 100–120°C required to obtain reasonable deuterium incorporation still remains an important limitation of this method.[**Error! Bookmark not defined.**]



Scheme 1: Mono- and bidentate Ir complexes utilized for HIE

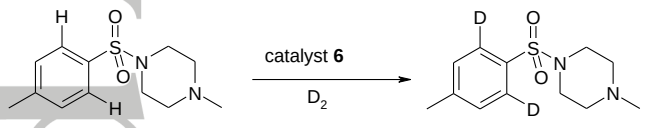
Recently, we have developed another C-H activation catalysts, [(tBuP,NMe)Ir(cod)]$BArF_{24}$ (**6**), with bidentate P,N ligands bearing the imidazolin-2-imine group[17] as an electron-rich nitrogen donor group.[18] In addition to the high HIE reactivity for known directing groups such as acetyl, heterocycles, sulfones, nitro groups and benzyl amines, **6** proved to be also highly active for H/D exchange of Boc-protected anilines, which had not been recognized previously as a directing group for HIE. After optimization, even substrates with the weakly coordinating methoxy group showed a good degree of deuteration.[Error! Bookmark not defined.] In continuous efforts to broaden our synthetic repertoire for fast tritium labelling, we have further investigated the substrate scope of **6** in more detail and wish to report on expanded applications of the new catalyst system **6**.

Results and Discussion

We started to evaluate Tamm's catalyst **6** in the HIE reaction of tertiary sulfonamide **7** in different solvents at room temperature.

To our delight, we found high deuterium incorporation in chlorobenzene (Table 1). The catalytic HIE reaction with our model substrate **7** was strongly influenced by the solvent. In most solvents, none or only poor deuterium exchange was observed; however, high deuterium incorporation was found in chlorobenzene (entry 9). The strong influence of chlorobenzene in HIE reactions has been observed earlier,[Error! Bookmark not defined.,Error! Bookmark not defined.] however the effect is still lacking a full theoretical understanding.

Table 1: Solvent screening of catalyst **6** in the HIE reaction with tertiary sulfonamide **7**.[a]



7 **7a**

Entry	Solvent	%D **7a**[b]	Yield **7a**[c] [%]
1	dichloromethane	22	72
2	chloroform	12	72
3	MTBE	11	79
4	ethanol	0	80
5	cyclohexane	15	67
6	MeTHF	0	81
7	isopropylacetate	0	79
8	1-butanol	0	83
9	chlorobenzene	82	78
10	fluorobenzene	16	65
11	toluene	0	70

[a] Conditions (repeated three times): substrate **7** (10 µmol, 2.5 mg), catalyst **6** (10 mol%), solvent (2 mL), D_2 (1 atm), rt, 2 h . [b] Positions and percentage of deuterium incorporation determined by 1H NMR. [c] Isolated yield.

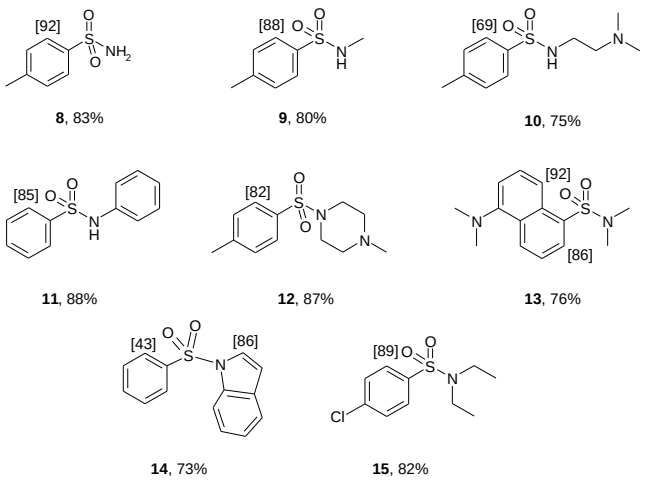
In the next step, we tried to find optimized conditions for a subsequent broader substrate screening (Table 2). We modified catalyst content and reaction time and found that generally 10 mol-% catalyst **6** are needed to obtain high deuterium introduction for substrate **7** within two hours (entry 9). Even though higher excess of deuterium was used in the optimization reactions, the deuteration reached a plateau after 30 min (entry 7) not proceeding significantly by longer reaction times up to 6h (entry 10).

Table 2: Optimization of catalyst content and reaction time in the HIE reaction of tertiary sulfonamide **7**.[a]

Entry	Catalyst **6** [mol%]	Time [min]	%D **7a**[b]
1	3	300	0
2	5	300	0
3	7,5	120	32
4	10	5	15
5	10	10	44
6	10	15	69
7	10	30	80
8	10	60	82
9	10	120	85
10	10	300	89

[a] Conditions (repeated two times): substrate **7** (10 µmol, 2.5 mg), catalyst **6**, chlorobenzene (2 mL), D_2 (1 atm), rt. [b] Positions and percentage of deuterium incorporation determined by ^{1}H NMR. [c] Isolated yield.

We then studied the HIE reaction of sulfobenzenes under the optimized reaction conditions (Scheme 2). Even though for the the level of labelling achieved after 30 min was not significantly lower than after 120 min, we choosed a reaction time of 2h for all further substrate screening to avoid any potential kinetic differences. The catalyst revealed high reactivity and deuterium incorporation in the HIE reactions of primary, secondary and even tertiary sulfonamides. In the case of the primary sulfonamide **8**, catalyst **6** showed similar degree of deuteratium incorporation as compared to the results reported by Kerr with catalyst **3** at room temperature, however with a higher amount of catalyst (10 mol%).[**Error! Bookmark not defined.**] Interestingly, with **6** secondary (**9**–**11**) and tertiary (**12**–**15**) sulfonamides underwent successful HIE reactions at room temperature as well, which was achieved previously with catalysts **3** and **5** only at elevated temperatures (> 80–120°C).[**Error! Bookmark not defined.**]



8, 83% **9**, 80% **10**, 75%

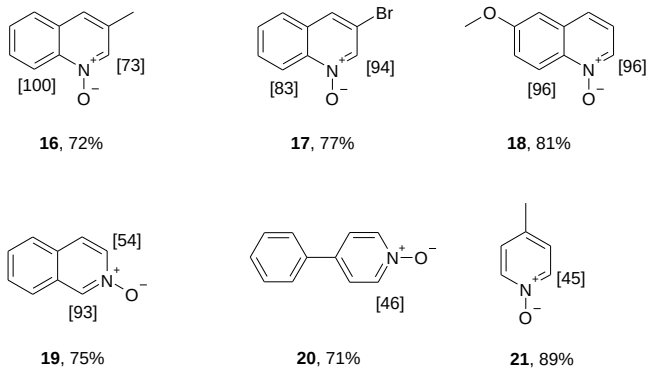
11, 88% **12**, 87% **13**, 76%

14, 73% **15**, 82%

Scheme 2: HIE reactions of sulfobenzenes catalyzed by **6**.[a,b] a) Conditions: substrate (22 µmol), catalyst **6** (10mol%), chlorobenzene (2 mL), D_2 (1atm), rt, 2 h. b) Positions and percentage of deuterium incorporation determined by ^{1}H NMR and confirmed by LC-MS isolated yields, all reactions have been repeated at least twice.

Next, we examined N-oxides as substrates for the directed HIE reaction with catalyst **6** (scheme 3). *N*-Oxides have rarely been described as directing groups in HIE reactions,[19] which would in principle enable the labeling of pyridines or quinolines after reductive cleavage of the N-O bond. This HIE approach can be convenient if direct labeling in the *ortho*-positions of the heterocyclic nitrogen atom (Rh black, D_2O[20] or THF-D_2[21]) cannot be accomplished or if higher specific activities in the case of tritium introduction are required.

In particular, the deuteration of the quinolone moiety in substrates **16**–**18** proceeded considerably well and selectively, irrespective of other aromatic substituents. The 2- and 8-positions of 3-methylquinoline *N*-oxide **16** were deuterated in 73% and 100%, respectively. Similar results were obtained for 3-bromoquinoline *N*-oxide **17** and 6-methoxyquinoline *N*-oxide **18** with deuterium incorporation in these positions higher than 80%. Interestingly, the level of deuterium introduction dropped to approx. 50% at the 3-position in isoquinoline *N*-oxide **19** and in simple pyridine *N*-oxides **20** and **21**. Since the 1-position of isoquinoline *N*-oxide **19** was still exchanged by deuterium in 93%, a significant electronic effect can be considered as the steric differences between the 1- and 3-position are comparatively small.

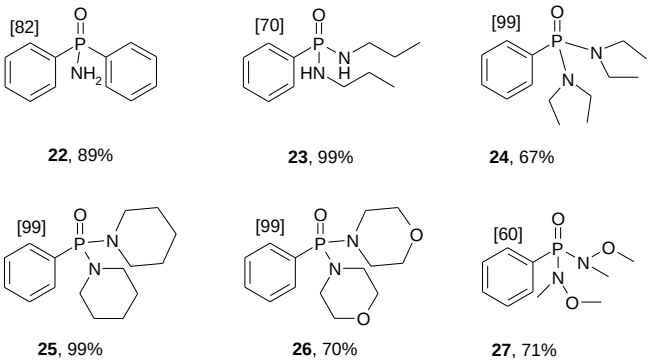


16, 72% **17**, 77% **18**, 81%

19, 75% **20**, 71% **21**, 89%

Scheme 3: HIE reactions of N-oxides catalyzed by **6**.[a,b] a) Conditions: substrate (5 µmol), catalyst **6** (10mol%), chlorobenzene (2 mL), D_2 (1atm), rt, 2 h. b) Positions and percentage of deuterium incorporation determined by ^{1}H NMR and confirmed by LC-MS, isolated yields, all reactions have been repeated at least twice.

Furthermore, we have examined phosphonamides as they have never been applied in *ortho*-directed HIE reactions before (Schema 4). To our great delight, we found good to excellent H/D exchange in the reaction of primary **22** (82%), secondary **23** (70%), and tertiary phosphonamides **24–27** (60–99%).



22, 89% **23**, 99% **24**, 67%

25, 99% **26**, 70% **27**, 71%

Scheme 4: HIE reactions of phosphonamides catalyzed by **6**.[a,b]
a) Conditions: substrate (10 µmol), catalyst **6** (10mol%), chlorobenzene (1 mL), D_2 (1atm), rt, 2 h. b) Positions and percentage of deuterium incorporation determined by ^{1}H NMR and confirmed by LC-MS, isolated yields, all reactions have been repeated at least twice.

Conclusion

We have extended the use of the newly discovered catalyst **6** by evaluation of the HIE reaction with sulfonamides, *N*-oxides and phosphonamides under mild reaction conditions. The results emphasize the usefulness of this air-stable catalyst and, in the case of sulfonamides, it seems to be more active than other commercially available iridium catalysts.

Experimental Section

General: All substrates and solvents were obtained from commercial suppliers and used without further purification, except for the phosphonamides **23**-**27** (the preparation is described in the supporting information). Catalyst **6** was synthesized according to procedures reported earlier.[Error! Bookmark not defined.] All labelling reactions were carried out on Radleys Synthesis station for parallel solution phase chemistry. Flash column chromatography was carried out using Merck kieselgel 60 silica gel (particle size: 63-200). The level and regioselectivity of deuterium incorporation in the substrate was determined by ^{1}H-NMR. ^{1}H (300, 500 MHz) and ^{13}C (75, 125 MHz) NMR spectra were obtained on Bruker spectrometers in the solvents indicated. Chemical shifts

are reported in ppm. Coupling constants are reported in Hz and refer to ^{3}J H-H couplings, unless otherwise stated. The distribution of hydrogen isotopes in the products was determined by a liquid chromatography-mass spectrometry (LC-MS) system with a Symmetry Shield RP18 column, 3.9 x 150 mm, with a gradient program. LC column conditions were as follows: 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 rate: 0.6 mL/min; Detection: UV 254 nm and UV 210 nm.

General deuteration procedure: To a carousel tube was added the substrate of choice (10 µmol, unless otherwise stated) in solution (500 µL) and iridium(I) catalyst (1.5 mg, 1.0 µmol, 10mol%, unless otherwise stated) in solution (500 µL) under air. The desired solvent (1 mL) was added unless otherwise stated, rinsing the inner walls of the tube. The tube was sealed. The flask was evacuated and flushed with deuterium via a balloon three times. After sealing the flask, the reaction was started and a red to clear/yellow colour change was observed. The reaction mixture was stirred for 2 h at room temperature. To the solution was added 1 mL dichloromethane and the mixture was transferred into a flask. The solvent was evaporated in vacuo. The residue was purified by chromatography with MTBE/ethylacetate (4/1) or DCM/MeOH (95/5), depending on the substrate polarity. The product was analyzed by LC-MS and ^{1}H-NMR. The level and regioselectivity of deuterium incorporation in the substrate was determined by ^{1}H-NMR. The integrals were calibrated against a peak corresponding to a position not expected to be labelled.

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Keywords: hydrogen isotope exchange; iridium, deuterium, catalysis

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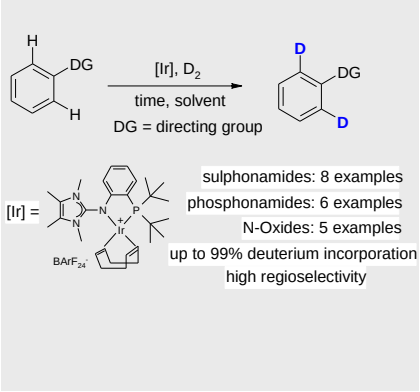
FULL PAPER

We have developed an efficient iridium-catalyzed hydrogen isotope exchange (HIE) reaction method with secondary and tertiary sulfonamides at ambient temperatures applying a recently discovered P,N-ligated iridium catalyst. Furthermore N-oxides and phosphonamides have been successfully applied in HIE reactions with moderate to excellent deuterium introduction.



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