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Isotopic Labeling

Iridium-Catalyzed H/D Exchange: Ligand Complexes with Improved Efficiency and Scope

Michael Parmentier,[a] Thomas Hartung,[b] Andreas Pfaltz,[a] and Dieter Muri*[b]

Abstract: Hydrogen isotope exchange (HIE) is one of the most attractive tools for the introduction of deuterium or tritium to an organic compound. Herein, iridium complexes with N,P-ligands, highly active catalysts for asymmetric double bond reductions, have been tested for their HIE capabilities. Electron-rich ligands, containing dicyclohexylphosphines or phosphinites, have been identified as excellent ligands for efficient deuterium incorporation. Substrates with strong directing groups, that is, pyridines, ketones, and amides, as well as weak ligating units, such as, nitro, sulfones, and sulfonamides, could be labeled efficiently. With the addition of tris(pentafluorophenyl) borane to the reaction mixture, also highly deactivating nitrile substituents were well tolerated in the reaction. Based on the excellent results obtained with the chiral ThrePhox ligand, a structurally simpler, achiral ligand was developed. The iridium complex containing this ligand, proved to be a powerful catalyst for HIE reactions.

Introduction

Isotopically labeled organic compounds are important tools in the research and development of new therapeutic drug candidates.[1] In particular, the demand for tritium-labeled radioligands has constantly increased over the last years due to the extended efforts in developing drugs for central nervous system (CNS) targets associated with the exploration of the corresponding receptors, performing translational studies for the selection of suitable positron emission tomography (PET) tracers, and for a rapid screening of drug candidates in preclinical adsorption, distribution, metabolism, and excretion (ADME) studies.[2] Moreover, compounds labeled with deuterium are of high importance as internal standards in mass spectrometry or for the investigation of reaction mechanisms.[3] Among the various existing labeling technologies,[4] transition-metal-catalyzed hydrogen isotope exchange (HIE) is one of the most attractive methods for the labeling of compounds with deuterium or tritium.[5] This approach enables a direct labeling of the desired compounds without laborious syntheses of adequately functionalized precursors. Platinum complexes[6] have already been applied to HIE in the sixties and the methodology was then later extended by rhodium[7] and iridium complexes.[8] Especially the work of Heys[8b] and Hesk et al.[9] in the nineties has leveraged a routine use of iridium complexes for tritium labeling and has also driven the development of new and more active catalyst systems.[8m] These catalysts allow incorporation of tritium preferentially in the *ortho* position to a directing group tolerating a variety of different functionalities present in the molecule. The incorporation should occur at a stable, that is, non-exchangeable position to avoid back-exchange in protic solvents under neutral, basic or acidic conditions with the consequence of losing the label. To date, Crabtree's catalyst is still most widely used for these types of reactions (Figure 1). Kerr's catalyst shows improved reactivity and can

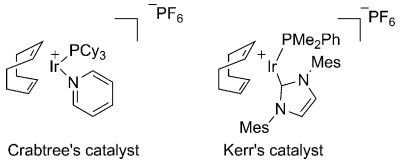

Figure 1. Crabtree's and Kerr's catalyst.

even be used in catalytic amounts for substrates bearing only weakly coordinating groups such as nitro units.[8m] Despite the levels of effectiveness shown by these established Ir-centered species, there is still room for improvement and for development of new, selective, and effective iridium-based catalysts to achieve tritium incorporation in high specific activities and across a wider substrate range.

Cationic iridium complexes bearing bidentate N,P ligands have established themselves as very efficient and selective catalysts for the enantioselective hydrogenation of functionalized and unfunctionalized alkenes.[10] Considering the analogy to Crabtree's catalyst, we expected them to also catalyze HIE reactions. The accepted mechanism of the iridium-catalyzed HIE

[a] Dr. M. Parmentier, Prof. Dr. A. Pfaltz
Department of Chemistry, University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)

[b] Dr. T. Hartung, Dr. D. Muri
Preclinical Chemistry Manufacturing Control
pRED, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124
4070 Basel (Switzerland)
E-mail: dieter.muri@roche.com

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reaction involves an octahedral cyclometalated dideuteride Ir^{III} species such as **1** (Figure 2). Ligands around the metal center stabilize the intermediates and influence the reactivity of the catalyst by changing both the electron density and steric con-

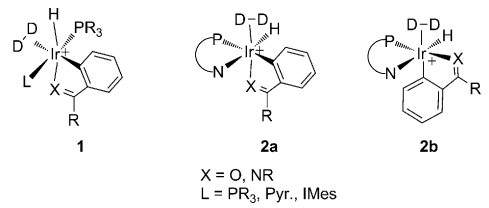


Figure 2. Structures of cyclometalated Ir^{III} intermediates bearing monodentate or bidentate ligands.

gestion.[8f,g] In addition, the rate of the cyclometalation and reductive elimination steps can be strongly affected by the electron density of the metal center and the *trans* influence of the ligands.[11] Ir^{III} species resulting from the Crabtree's or Kerr's catalyst result in a *trans* relationship between the two monodentate ligands (**1**, Figure 2).[8e,g,m,12] The use of bidentate N,P ligands leads to electronically and sterically different complexes such as **2a** or **2b** (Figure 2),[13] which possibly could show enhanced catalytic activity in HIE reactions.

Because of the potential of these bidentate N,P-ligands and the great diversity and availability of the corresponding iridium catalysts, we decided to study their use in isotope exchange reactions. Here, we report improvements of the HIE reaction with deuterium gas on representative classes of substrates catalyzed by cationic iridium complexes bearing a bidentate N,P-ligand.

Results and Discussion

As a starting point, we compiled a set of representative test compounds (Figure 3). For a preliminary screening of catalysts for *ortho*-directed HIE, classical model substrates such as 2-phenylpyridine, acetophenone, acetanilide, and phenylbenzamide were chosen. 3,5-Disubstituted substrates **5** and **6** were selected to explore steric and stereoelectronic effects of functional groups on the arene ring. Weakly coordinating functional groups such as nitro-, sulfone, and sulfonamide (**10**, **11**, **12**) were also investigated. Nitriles and pyridine-2-carbonyl derivatives are structural motifs that are widely used in drug discovery, and they can be considered as potential challenges to HIE due to their binding abilities to the metal center. They significantly reduce catalyst activity and, in most cases, even completely inhibit HIE.[14]

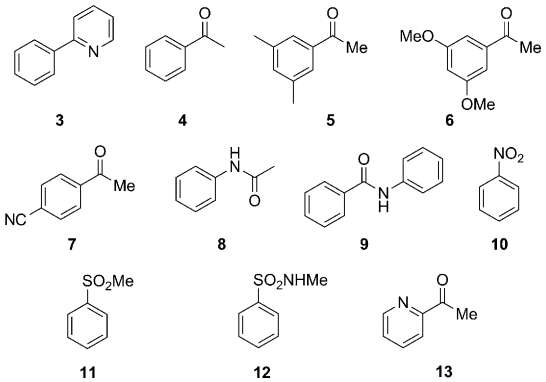


Figure 3. Structures of selected substrates.

The high modularity of N,P-ligands allows the electronic properties of the Ir catalysts to be varied, as both the nitrogen-containing part (oxazoline, oxazole, imidazoline, or pyridine) and the phosphorus moiety (diaryl or dialkyl phosphine or phosphinite) can be easily tuned. For our first screening, we selected 15 Ir-based catalysts with different backbones and electron densities to determine the most promising system (Figure 4). Because of their previous use for asymmetric hydrogenation, all catalysts selected for the first investigations were chiral. However, the HIE reaction does not require the use of an enantiomerically pure catalyst and, therefore, an achiral structurally simplified version of the most efficient catalysts will also be presented in a second part including the synthesis of the corresponding achiral N,P ligand.

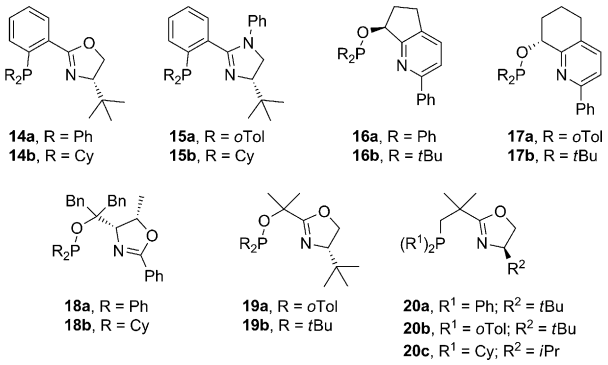
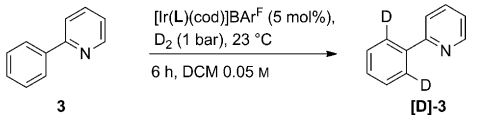


Figure 4. Structures of selected ligands.

In the initial experiments a set of model compounds were treated with different iridium catalysts in the presence of deuterium gas under standard conditions: The substrate (12.5 μmol) and Ir catalyst (0.625 μmol) were stirred in dry CH_2Cl_2 (0.25 mL) under deuterium gas (1 bar)[15] for 4, 6, or 18 h. After the reaction, labile deuterium labels were re-exchanged by washing the crude mixture with aqueous ethanol. The extent of deuterium incorporation in the model substrates was determined by MS.

Using 2-phenylpyridine **3** as substrate, good deuterium incorporation could be obtained with most of the tested iridium catalysts (Table 1). An average of 1 deuterium atom per molecule could be incorporated (D_{inc}) in the *ortho* position of the pyridine substituent using 5 mol% of the iridium catalyst derived from the phenyloxazoline ligand **14b** (Table 1, entry 2). The less electron-rich diphenylphosphine derivative **14a** led to a lower incorporation level of 0.8 D_{inc}. A stronger influence of the electronic properties of the phosphorus moiety was observed for phenylimidazoline (PHIM) ligands **15a** and **15b**.

Table 1. Deuterium incorporation in 2-phenylpyridine **3** mediated by different Ir complexes.



3 **[D]-3**

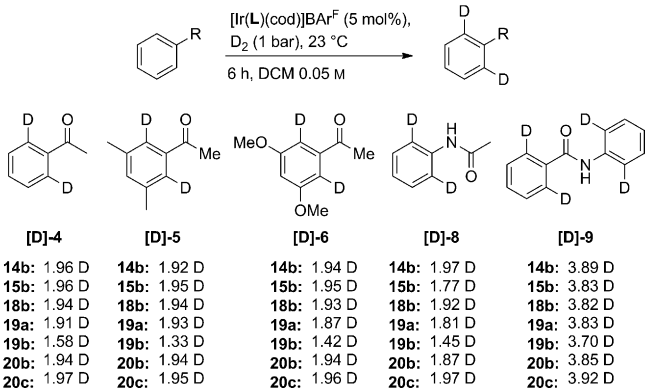
Entry	Ligand	D_{inc} (D/molecule)[a]	Entry	Ligand	D_{inc} (D/molecule)[a]
1	**14a**	0.8	9	**18a**	0.9
2	**14b**	1.0	10	**18b**	1.1
3	**15a**	0.3	11	**19a**	1.3
4	**15b**	1.4	12	**19b**	1.4
5	**16a**	0.3	13	**20a**	0.1
6	**16b**	0.5	14	**20b**	1.0
7	**17a**	0.2	15	**20c**	1.3
8	**17b**	0.1			

[a] Average number of *ortho*-deuterium atoms incorporated per molecule determined by GC-MS analysis and/or ^{1}H NMR spectroscopy.

Whereas **15a**, containing two *ortho*-tolyl substituents on the phosphorus atom, led to 0.3 D_{inc} (Table 1, entry 3), the more electron-rich dicyclohexyl phosphine analogue **15b** brought about 1.4 D_{inc} (entry 4). Up to 0.5 D_{inc} was obtained with more rigid systems such as pyridine-phosphinite ligands **16** and **17**. Electron-rich phosphinite-containing derivatives such as ThrePHOX **18b** or SimplePHOX **19b** proved to be more active and efficient deuterium incorporation up to 1.4 D_{inc} could be achieved (Table 1, entries 10 and 12). Finally, the NeoPHOX **20c** with trialkyl phosphine substituents allowed for the preparation of **[D]-3**, containing an average of 1.3 deuterium on the phenyl ring (Table 1, entry 15).

A first conclusion from these screening results is that ligands with an electron-rich phosphorus moiety are needed to achieve a good level of deuterium incorporation. Phosphinites or trialkyl phosphines can be used and are suitable for the reaction. Finally, the nitrogen-containing part of the backbone could be imidazoline or oxazoline. Rigid pyridine-phosphinite systems, which are known to be very efficient for asymmetric hydrogenation reactions of olefins,[10d] led to low deuterium levels. Taking into account all of these observations, we decided to proceed only with the most active electron-rich ligands **14b**, **15b**, **18b**, **19a**, **19b**, **20b**, and **20c**.

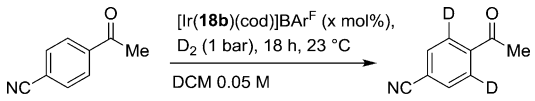
With these catalysts in hand, we tested several other typical model substrates for HIE such as acetophenone, acetanilide, and benzanilide (Scheme 1). All catalysts led to almost quantitative deuterium incorporation with a catalyst loading of 5 mol% and a reaction time of 6 h under standard conditions, favoring a reaction path through a 5- or 6-membered iridacycle. In the case of acetophenone, the catalyst containing ligand **19b** led to slightly diminished D incorporation. Sterically more demanding acetophenones **5** and **6** were investigated as well. These substrates could be labeled as well to a similar degree under standard reaction conditions. As expected, D incorporation in the *para* position of **6**, which would involve a 4-membered iridacycle, through coordination to a methoxy group, was not observed.



Scheme 1. Deuterium incorporation in acetophenone derivatives **4**–**7**, acetanilide **8**, and benzanilide **9** mediated by Ir complexes.

It is well known that cyano substituents can inhibit HIE almost completely.[14] It was therefore no surprise that the standard reaction conditions, which were successfully applied for the previously described acetophenone derivatives, led to drastically different incorporation levels in 4-acetylbenzonitrile (**7**). With all tested catalysts no H/D exchange was observed and only starting material was recovered. To gain a better understanding of this failed H/D-exchange reaction, we decided to investigate the effect of the catalyst loading and the interaction of the nitrile with the catalyst in more detail (Table 2).

Table 2. Catalyst loading effect on the HIE reaction on the 4-acetylbenzonitrile **7**.

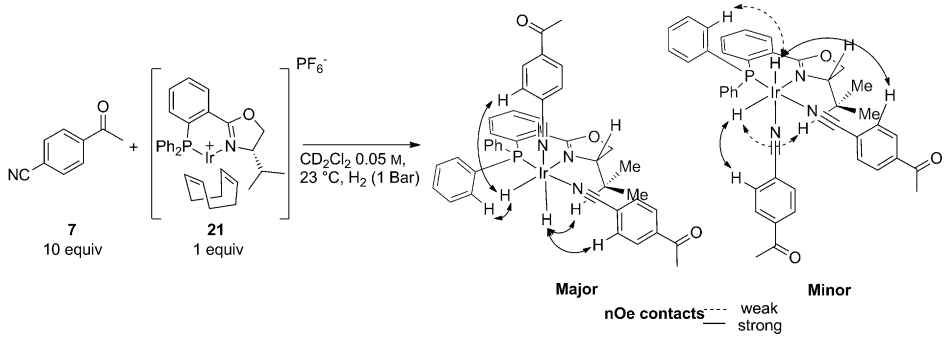


7 **[D]-7**

Entry	Catalyst loading [mol%]	Deuterium incorporation (D/molecule)[a]
1	5	0
2	40	0.3
3	60	0.9
4	105	1.5

[a] Average number of *ortho*-deuterium atoms incorporated per molecule determined by GC-MS analysis and/or ^{1}H NMR spectroscopy.

The commercially available Ir complex containing **18b** was first chosen and 0.3 D_{inc} was observed with 40 mol% catalyst loading after 18 h (Table 2, entry 2). Increasing the amount of catalyst to 60 mol% resulted in increased isotope exchange of 0.9 D_{inc} (Table 2, entry 3). Finally, a slight excess of iridium catalyst led to substantial incorporation of 1.5 D_{inc} (entry 4). These results suggest a deactivation of the catalyst by the substrate through strong coordination of the nitrile group to the metal center. ^{1}H NMR spectroscopic studies performed with the Ir catalyst **21** and 10 equivalents of substrate supported this hypothesis. Under 1 bar of hydrogen, the formation of an iridium-



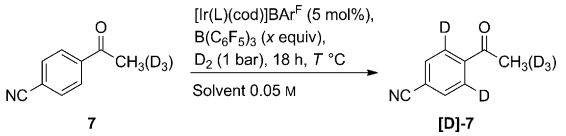
Scheme 2. Studies of the inhibition of Ir complex **21** by 4-acetylbenzonitrile **7** (the counterion $[PF_6]^-$ is omitted for clarity).

(III)-dihydride complex containing two coordinated molecules of acetylbenzonitrile was observed (Scheme 2).

The iridium metal center is acting as Lewis acid toward the nitrile group. Nuclear Overhauser effect (nOe) experiments confirmed the geometry of the complex with two strong contacts between the hydride *cis* to the phosphorus atom and the proton *ortho* to the nitrile group in the phenyl ring as major isomer (see the Supporting Information for details). With the goal to develop a reaction using only catalytic amounts of the metal complex, we decided to evaluate possible additives that could block the nitrile group by formation of a complex. After an extensive screening tris(pentafluorophenyl)borane was identified as a suitable Lewis acid in this case. The results of the HIE reaction of **7** in the presence of $B(C_6F_5)_3$ are presented in Table 3.

No deuterium incorporation was observed using the PHOX ligand **14b** in the presence of 1.1 equivalents of the borane additive at room temperature for 6 h in CH_2Cl_2 (Table 3, entry 1). Increasing both the reaction temperature to 50 °C in 1,2-dichloroethene (DCE) and the reaction time to 18 h did not give a better result (Table 3, entry 2). However, performing the reaction at 90 °C for 18 h in chlorobenzene led to 3.4 D_{inc} (Table 3, entry 4). ^1H and ^2H NMR spectroscopic experiments proved exchange at the phenyl ring as well as incorporation into the methyl group of the acetyl moiety. This latter functionalization is probably induced by the keto–enol tautomerization that can occur at such a temperature. Under the same conditions, but in the absence of tris(pentafluorophenyl)borane only an incorporation of 0.1 D_{inc} was observed (Table 3, entry 5). The complex derived from **18b** promoted the H/D exchange to 3.4 D_{inc} (Table 3, entry 6). Lowering the reaction temperature to 60 °C while simultaneously increasing the catalyst loading to 10 mol% led to a D_{inc} of 1.3 (Table 3, entry 7). The reaction time seems to be crucial as only 0.7 D_{inc} was observed after 4 h (Table 3, entry 8). Also a slight decrease in deuterium incorporation was observed when using phenylimidazoline **15b** (Table 3, entry 9) or SimplePHOX **19a** (Table 3, entry 12) as ligands. More than three deuterium atoms were incorporated with the more electron-rich NeoPHOX complex **20b** (Table 3, entry 10) and **20c** (entry 11), respectively. Finally, by using the iridium catalyst with the SimplePHOX ligand **19b** in the presence of 1.1 equivalents of the tris(pentafluorophenyl)borane additive at 90 °C (Table 3, entry 13), 4.4 deuterium atoms were incorporated adjacent to the acetyl group in the aromatic ring and in the methyl group.

Table 3. Catalyst screening for the HIE reaction on the 4-acetylbenzonitrile **7** in the presence of $B(C_6F_5)_3$ as additive.



7 [D]-7

Entry	Ligand	Conditions	$B(C_6F_5)_3$ [equiv]	D_{inc} (D/molecule)[a]
1	**14b**	CH_2Cl_2, 23 °C, 6 h	1.1	0
2	**14b**	DCE, 50 °C, 18 h	1.1	0
3	**14b**	PhCl, 23 °C, 18 h	1.1	0
4	**14b**	PhCl, 90 °C, 18 h	1.1	3.4
5	**14b**	PhCl, 90 °C, 18 h	–	0.1
6	**18b**	PhCl, 90 °C, 18 h	1.1	3.4
7	**18b**	PhCl, 60 °C, 18 h	1.1	1.3[b]
8	**18b**	PhCl, 90 °C, 4 h	1.1	0.7
9	**15b**	PhCl, 90 °C, 18 h	1.1	2.3
10	**20b**	PhCl, 90 °C, 18 h	1.1	3.2
11	**20c**	PhCl, 90 °C, 18 h	1.1	3.1
12	**19a**	PhCl, 90 °C, 18 h	1.1	1.4
13	**19b**	PhCl, 90 °C, 18 h	1.1	4.4

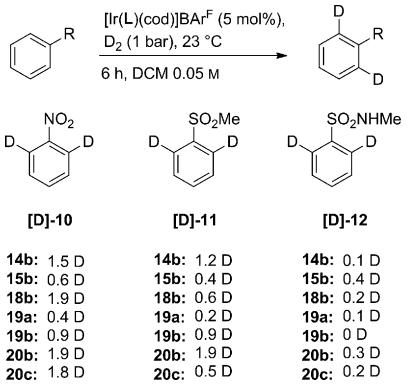
[a] Average number of deuterium atoms incorporated per molecule determined by GC-MS analysis and/or ^1H NMR spectroscopy. [b] 10 mol% of the catalyst was used.

An advantage of tris(pentafluorophenyl)borane as additive is the absence of any protons in the structure, thus avoiding the generation of radioactive waste when tritium gas is used due to potentially occurring phenyl-H/T exchange. On the other hand, the *ortho*-directing effect of the chlorine in chlorobenzene has to be monitored, as well as Cl/H exchange. Running a reaction in the absence of substrate, no H/D exchange or reduction of chlorobenzene was observed, which clearly demonstrated the suitability of this solvent for high-temperature HIE reactions.

The scope of the reaction was further explored by using weakly coordinating functionalities such as sulfones, sulfonamides, and nitro groups (Scheme 3).

These substrates required a more rigorous selection of catalysts than the previously applied arenes. Whereas catalysts with ligand **15b** or **19a** only led to low D incorporation, almost complete conversion was observed with **20b** as ligand in the case of nitrobenzene **10** and methylphenylsulfone **11**. However, sulfonamide derivative **12** could not be efficiently labeled and the best result was obtained with **15b** resulting in 0.4 D_{inc}.

Optimization of the reaction conditions for the labeling of benzenesulfonamide **12** was performed by using the most effi-

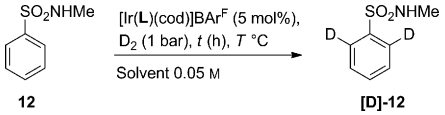


Scheme 3. Scope extension of the HIE reaction.

cient ligands **15b**, **18b**, **20b**, and **20c** identified above and by varying both solvent and temperature (Table 4).

After 6 h at room temperature in dichloromethane, an average of 0.4 deuterium per molecule could be incorporated when using **15b** as ligand (Table 4, entry 1). Increasing the temperature to 50 °C in dichloroethane improved the result to 0.5 D_{inc} (Table 4, entry 2). As already observed in the case of acetylbenzonitrile, the use of chlorobenzene at 90 °C for 18 h led to the best level of H/D exchange with an average of 1.5 D_{inc} (Table 4, entry 3). Iridium catalysts with **18b**, **20b**, and **20c** as ligands led to almost quantitative D incorporation at more elevated temperatures. NMR spectroscopic analysis showed that deuterium incorporation occurred in the *ortho* position to the sulfonamide group.

Table 4. Optimization of the reaction conditions for H/D exchange on **12** mediated by Ir complexes.

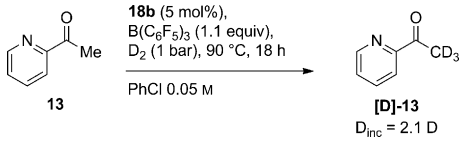


12 **[D]-12**

Entry	Ligand	Conditions	D_{inc} (D/molecule)[a]
1	**15b**	CH_2Cl_2, 23 °C, 6 h	0.4
2	**15b**	DCE, 50 °C, 18 h	0.5
3	**15b**	PhCl, 90 °C, 18 h	1.5
4	**20b**	CH_2Cl_2, 23 °C, 6 h	0.3
5	**20b**	DCE, 50 °C, 18 h	0.7
6	**20b**	PhCl, 90 °C, 18 h	1.8
7	**20c**	PhCl, 90 °C, 18 h	1.9
8	**18b**	PhCl, 90 °C, 18 h	1.9

[a] Average number of deuterium atoms incorporated per molecule determined by GC-MS analysis and/or ^{1}H NMR spectroscopy.

Strong complexation of the metal center between the nitrogen atom and the carbonyl group can be expected in the case of HIE attempts with 2-keto-substituted pyridines, a structural motif quite common in drugs and drug-like molecules. As a model substrate for this class of compounds we selected acetylpyridine **13**. Based on our results in the HIE with acetylbenzonitrile **7**, we decided to use tris(pentafluorophenyl)borane as additive in the reaction with the pyridine derivative **13** (Scheme 4).



Scheme 4. H/D exchange on **13**.

The use of 1.1 equivalents of $B(C_6F_5)_3$ significantly increased the incorporation of deuterium up to 2.1 D_{inc}. Unfortunately, NMR spectroscopic analysis of the product **[D]-13** revealed that the deuterium incorporation occurs exclusively at the methyl group. Deuteration of the methyl group could be explained by formation of a 4- or 5-membered iridacycle through coordination of the catalyst with the ketone or the pyridine N atom, respectively, followed by C–H insertion. Alternatively, deuterium incorporation could occur through boron enolate formation and subsequent D^+ transfer from an acidic iridium deuteride species to the enolate.[16] The addition of a stoichiometric amount of rhodium black to the reaction mixture, as described by Schou, neither improved the deuteration level nor changed the labeling position.[17]

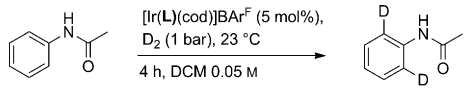
Development of an achiral Ir catalyst

Our investigation of iridium complex-catalyzed H/D exchange reactions with different substrate classes revealed that ThrePHOX **18b** is one of the most efficient N,P-ligands for this process leading to very good results in general. For that reason we aimed at designing an achiral N,P-ligand based on structure of **18b**. First, the impact of each part of the skeleton of **18b** on the HIE reaction was evaluated by choosing acetanilide **8** as test substrate under standard reaction conditions (Table 5).

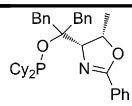
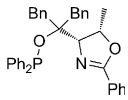
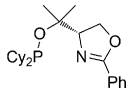
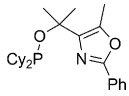
As previously observed, the electronic properties of the phosphinite moiety were crucial as replacement of the cyclohexyl groups by two phenyl groups resulted in complete loss of activity (Table 5, entries 1 vs. 2). Removing the methyl group on the oxazole ring and replacing the *gem*-dibenzyl by a *gem*-dimethyl group slightly lowered the efficiency (Table 5, entry 3). We were pleased to find that the use of achiral ligand **23**, resembling **18b**, led to high deuterium incorporation levels at only 3 mol% catalyst loading (Table 5, entry 4).

A straightforward synthetic route was designed to synthesize catalyst **26** (Scheme 5). The oxazole ring was formed by using a procedure described by Wang, providing ketone **24** in 70% yield.[18] Addition of 2 equivalents of methylmagnesium bromide afforded the tertiary alcohol **25** in 84% yield. Treatment of the alcoholate of **25** with dicyclohexylchlorophosphine led to the corresponding phosphinite derivative **23**, which was used without further purification to avoid oxidation of the phosphine moiety. The desired Ir complex **26** was obtained in 25% yield based on **25** after complexation with $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) followed by anion exchange

Table 5. Influence of phosphine ligands on the HIE of **8**.

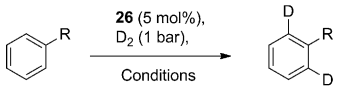


8 **[D]-8**

Entry	Ligand		D_{inc} (D/molecule)[a]
1		**18b**	1.5
2		**18a**	0
3		**22**	1.3
4		**23**	1.5[b]

[a] Average number of deuterium atoms incorporated per molecule determined by GC-MS analysis and/or ^{1}H NMR spectroscopy. [b] 3 mol% of catalyst.

Table 6. Scope of the HIE reaction mediated by achiral Ir complex **26**.



3 - 12 **[D]-3 - [D]-12**

Entry	Substrate	Conditions	$B(C_6F_5)_3$ [equiv]	D_{inc} (D/molecule)[a]
1	**3**	CH_2Cl_2, 23 °C, 6 h	–	1.3
2	**4**	CH_2Cl_2, 23 °C, 6 h	–	2.0
3	**5**	CH_2Cl_2, 23 °C, 6 h	–	2.1
4	**6**	CH_2Cl_2, 23 °C, 6 h	–	2.0
5	**7**	PhCl, 90 °C, 18 h	1.1	2.4
6	**8**	CH_2Cl_2, 23 °C, 6 h	–	1.8
7	**9**	CH_2Cl_2, 23 °C, 6 h	–	3.9
8	**10**	CH_2Cl_2, 23 °C, 6 h	–	0.4
9	**11**	CH_2Cl_2, 23 °C, 6 h	–	0
10	**12**	PhCl, 90 °C, 18 h	–	0.3

[a] Average number of deuterium atoms incorporated per molecule determined by GC-MS analysis and/or ^{1}H NMR spectroscopy.

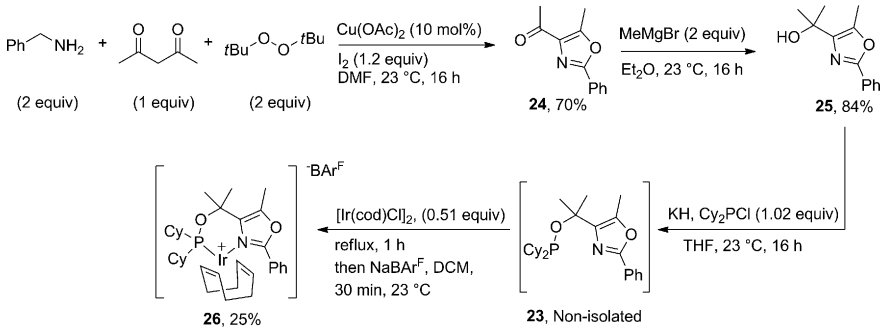
with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F$).

With the achiral Ir complex **26** in hand, the efficiency of this new catalyst for HIE was evaluated. Substrates **3**–**12** were then tested under the optimal reaction conditions previously established in the presence of 5 mol% of catalyst (Table 6).

We were pleased to see high deuterium incorporation with most of the tested substrates. For example, complete H/D exchange at the *ortho* position occurred with the acetophenone derivatives after 6 h (Table 6, entries 2–4). The use of $B(C_6F_5)_3$ as an additive for the functionalization of acetylbenzonitrile **7** was successful and D_{inc} of 2.4 was observed (Table 6, entry 5). Surprisingly, whereas nitrobenzene **10** led to excellent results with the use of **18b** as ligand (Scheme 3), low H/D exchange occurred with the achiral ligand **26** under the same reaction conditions (Table 6, entry 8).

Conclusion

Investigation of the hydrogen isotope incorporation reaction with various substrates catalyzed by iridium complexes revealed the suitability of bidentate N,P-ligands for this transformation. Highly electron-rich ligands, preferably dicyclohexylphosphines or phosphinites, are necessary to achieve high deuteration levels. ThrePHOX **18b**, NeoPHOX **20c**, SimplePHOX **19b**, and PHIM **15b** ligands were identified as the backbone of choice for the catalyst enabling both broad tolerance of substrate functionality and high efficiency. In most cases, excellent deuterium incorporation was observed when 5 mol% of an Ir catalyst derived from one of these ligands was used. Compounds with strongly coordinating substituents such as acetylbenzonitrile **7** and acetylpyridine **13** are known to be problematic substrates for the HIE process. NMR spectroscopic studies showed that the nitrile group of **7** strongly coordinated to the Ir center, resulting in loss of catalytic activity. Based on these observations, the process was modified by addition of tris(pentafluorophenyl)borane, which prevents deactivation of the catalyst by binding to the nitrile group of the substrate, and thus permits high deuterium incorporation levels. Unfortunately, 2-acetylpyridine was exclusively labeled at the methyl group. Deuterium incorporation in the aromatic ring remains a challenge in that case. The excellent results obtained with the chiral ThrePHOX ligand **18b** prompted us to develop a structurally simpler achiral analogue **23**. The Ir complex **26** derived from this ligand, which was readily prepared in a short synthetic sequence, proved to be a very efficient catalyst in the hydrogen isotope exchange reaction of a wide range of sub-



Scheme 5. Synthesis of achiral Ir catalyst **26**.

strates. Results obtained with this catalyst on drug-like molecules will be reported in due course.

Experimental Section

General information

Working techniques: Commercially available reagents were purchased from Acros, Aldrich, or Fluka and used as received. The solvents were collected from a purification column system (PureSolv, Innovative Technology Inc.) or purchased from Aldrich or Fluka in sure/sealed bottles over molecular sieves. Column chromatographic purifications were performed on Fluka silica gel 60 (Buchs, particle size 40–63 nm). The eluents were of technical grade and distilled prior to use. The dichloromethane was purchased from Aldrich ($\geq$99.5%, over molecular sieves).

Melting points: Melting points were determined on a Büchi 535 apparatus and are uncorrected.

Thin-layer chromatography: TLC plates were obtained from Machrey-Nagel (Polygram SIL/UV254, 0.2 mm silica with fluorescence indicator). UV light (254 nm) or basic permanganate solution were used to visualize the respective compounds.

NMR spectroscopy: ^{1}H NMR spectra were measured either on a Bruker Avance 400 (400 MHz) a Bruker Avance 500 (500 MHz) spectrometer or a Bruker AV 600 (600 MHz). ^{13}C NMR spectra are measured on a Bruker AV 600 (150 MHz). The chemical shifts (δ) are given in ppm. The chemical shift δ values were corrected to the signals of the deuterated solvents: $\delta=7.26$ (^{1}H NMR) and 77.16 ppm (^{13}C NMR) for $CDCl_3$; $\delta=2.05$ for [D_6]acetone, and 2.50 ppm for [D_6]DMSO. ^{31}P NMR spectra are calibrated relative to 85% phosphoric acid ($\delta=0$ ppm). ^{13}C and ^{31}P spectra were recorded ^{1}H-decoupled. The assignment of ^{1}H and ^{13}C signals was accomplished, when needed, by two-dimensional correlation experiments (COSY and HSQC). Multiplets are assigned as: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), and m (multiplet). Broad signals are assigned with: br (broad).

Mass spectrometry (MS): Mass spectra were measured on a Shimadzu spectrometer (electron ionization (EI)). ESI MS spectra were measured on a Finnigan MAT LCQ. The signals are given in mass-to-charge ratios (*m/z*). The fragments and relative intensities are given in brackets. High-resolution MS (HRMS) were measured on an Agilent QTOF 6520.

Gas chromatography (GC): Gas chromatograms were recorded on Carlo Erba HRGC Mega2 Series 800 (HRGS Mega2) instruments. Separations on achiral phases were performed on a Restek Rtx-1701 (30 m$\times$0.25 mm$\times$0.25 μmol).

Commercially available compounds and iridium complexes: Substrates **3**–**13** were purchased from Acros, Aldrich, or Fluka and used as received without further purifications. Iridium complexes arising from ligands **14a**, **14b**, **15a**, **15b**, **16a**, **16b**, **17a**, **17b**, **18a**, **18b**, **19a**, **19b**, **20a**, **20b**, **20c**, **22** and iridium complex **21** were synthesized according to literature procedures.[10e,19]

Procedures

Typical H/D exchange procedure: A vial (2.5 mL) was charged with a stirring bar and the catalyst (5 mol%, 0.625 μmol). The substrate stock solution in CH_2Cl_2 (1 equiv, 0.250 mL, 0.05 M) was added to the vial, which was placed in a high-pressure reactor. The equipment was first pressurized to 2.2 bar with deuterium gas and the pressure released to 1 bar. This procedure was then repeated twice. The reaction was performed under 1 bar D_2 atmosphere at the appropriate temperature for 18, 6, or 4 h. The solvent was then removed by bubbling argon through the solution and the crude reaction mixture was analyzed by GC/MS (EI) and/or NMR spectroscopy.

Typical H/D exchange procedure using tris(pentafluorophenyl)-boron as an additive: The substrate stock solution in PhCl (1 equiv, 0.250 mL, 0.05 M) was added to a vial (2.5 mL) containing tris(pentafluorophenyl)boron (1.1 equiv, 13.75 μmol, 7.4 mg). After stirring the mixture for 10 min at RT, the catalyst (5 mol%, 0.625 μmol) was added to the vial, which was then placed in a high-pressure reactor. The equipment was first pressurized to 2.2 bar with deuterium gas and the pressure released to 1 bar. This procedure was then repeated twice. The reaction was performed under 1 bar D_2 atmosphere at 90 °C for 18, 6, or 4 h. The solvent was then removed by bubbling argon through the solution and the crude reaction mixture was analyzed by GC/MS (EI) and/or NMR spectroscopy.

^{1}H NMR spectroscopic data of deuterated products [D]-3 to [D]-13

2-Phenylpyridine (3): ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta=$ 8.71 (d, $J=4.7$ Hz, 1H), 8.00 (d, $J=7.1$ Hz, 2H), 7.79–7.73 (m, 2H), 7.52–7.41 (m, 3H), 7.26–7.23 ppm (m, 1H). Deuterium incorporation was quantified by integration of the signal at $\delta=8.00$ ppm using the signal at $\delta=7.79$–7.73 ppm as a reference.

Acetophenone (4): ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta=7.95$ (d, $J=8.0$ Hz, 2H), 7.54 (t, $J=8.0$ Hz, 1H), 7.44 (t, $J=8.0$ Hz, 2H), 2.58 ppm (s, 3H). Deuterium incorporation was quantified by integration of the signal at $\delta=7.95$ ppm using the signal at $\delta=$ 2.58 ppm as a reference.

3,5-Dimethylacetophenone (5): ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta=7.57$ (s, 2H), 7.20 (s, 1H), 2.58 (s, 3H), 2.37 ppm (s, 6H). Deuterium incorporation was quantified by integration of the signal at $\delta=7.57$ ppm using the signal at $\delta=7.20$ ppm as reference.

3,5-Dimethoxyacetophenone (6): ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta=7.06$ (d, $J=2.4$ Hz, 2H), 6.62 (t, $J=2.4$ Hz, 1H), 3.81 (s, 6H), 2.55 ppm (s, 3H). Deuterium incorporation was quantified by integration of the signal at $\delta=7.06$ ppm using the signal at $\delta=$ 6.62 ppm as reference.

4-Acetylbenzonitrile (7): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=$ 8.02–8.07 (m, 2H), 7.75–7.81 (m, 2H), 2.65 ppm (s, 3H). Deuterium incorporation was quantified by integration of the signal at $\delta=$ 7.75–7.81 and 2.65 ppm using the signal at $\delta=8.02$–8.07 ppm as reference.

Acetanilide (8): ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta=7.54$ (s, 1H), 7.50 (d, $J=7.4$ Hz, 2H), 7.31 (t, $J=7.4$ Hz, 2H), 7.10 (t, $J=$ 7.4 Hz, 1H), 2.17 ppm (s, 3H). Deuterium incorporation was quantified by integration of the signal at $\delta=7.50$ ppm using the signal at $\delta=2.17$ ppm as a reference.

Benzanilide (9): ^{1}H NMR (400 MHz; [D_6]acetone, 25 °C, TMS): $\delta=$ 9.49 (s, 1H), 7.99 (dd, $J=7.0$, 1.2 Hz, 2H), 7.85 (d, $J=7.5$ Hz, 2H), 7.59–7.48 (m, 3H), 7.35 (m, 2H), 7.11 ppm (tt, $J=7.4$, 1.1 Hz, 1H). Deuterium incorporation was quantified by integration of the signal at $\delta=7.99$ and 7.85 ppm using the signal at $\delta=7.11$ ppm as a reference.

Nitrobenzene (10): ^{1}H NMR (400 MHz; $CDCl_3$, 25 °C, TMS): $\delta=8.25$ (dd, $J=7.7$, 1.1 Hz, 2H), 7.71 (tt, $J=7.4$ Hz, 1.1 Hz, 1H) and 7.56 ppm (t, $J=7.4$ Hz, 2H). Deuterium incorporation was quantified by integration of the signal at $\delta=8.25$ ppm using the signal at $\delta=7.71$ ppm as reference.

Methylphenylsulfone (11): ^{1}H NMR (400 MHz; [D$_6$]DMSO, 25 °C, TMS): δ = 7.93–7.97 (m, 2H), 7.65–7.69 (m, 1H) 7.56–7.61 (m, 2H), 3.07 ppm (s, 3H). Deuterium incorporation was quantified by integration of the signal at δ = 7.93–7.97 ppm using the signal at δ = 7.56–7.61 ppm as reference.

***N*-Methyl benzenesulfonamide (12)**: ^{1}H NMR (400 MHz, CDC1$_3$, 25 °C, TMS): δ = 7.88 (d, J = 6.7 Hz, 2H), 7.57–7.61 (m, 3H), 4.40 (m, 1H), 2.67 ppm (d, J = 5.4 Hz, 3H). Deuterium incorporation was quantified by integration of the signal at δ = 7.88 ppm using the signal at δ = 7.57–7.61 ppm as a reference.

2-Acetylpyridine (13): ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 8.69 (br d, J = 4.1 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.49–7.30 (m, 1H), 2.73 ppm (s, 3H). Deuterium incorporation was quantified by integration of the signal at δ = 8.69 and 2.73 ppm using the signal at δ = 7.84 ppm as a reference.

The ^{1}H NMR spectroscopic data of deuterated products **[D]-3** to **[D]-6** and **[D]-8** to **[D]-13** were consistent with the literature[8f,17,20]. Further characterizations of **[D]-7** including ^{1}H, ^{2}H, and ^{13}C NMR spectra and detailed results of the NOE study of Ir complex **21** with compound **7** are provided in the Supporting Information.

Synthesis of achiral Ir complex 26

2-(5-Methyl-2-phenyloxazol-4-yl)propan-2-ol (25): A solution of oxazole **24** (0.66 mmol, 1 equiv) in Et$_2$O (3 mL) was added dropwise to a solution of methylmagnesium bromide (3 M in ether, 1.33 mmol, 2 equiv) at room temperature, and the mixture was stirred overnight. The reaction was quenched with a 20% sulfuric acid solution (20 mL) and then extracted with Et$_2$O. The ether layer was washed with a 5% sodium bicarbonate solution (15 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent provided a yellow residue that was subjected to column chromatography using a 20% EtOAc-hexane mixture as eluent (R_f = 0.18). The desired product was obtained as yellow oil in 84% yield. M.p. 67 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 7.97 (d, J = 6.0 Hz, 2H), 7.41 (d, J = 6.0 Hz, 3H), 2.81 (s, 1H), 2.48 (s, 3H), 1.60 ppm (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$, 25 °C, TMS): δ = 158.4, 141.9, 130.0, 129.8, 128.6 (2C), 127.8, 126.0 (2C), 69.3, 30.0 (2C), 11.9 ppm; IR (neat): $\tilde{\nu}$ = = 3303, 2975, 2920, 1622, 1556, 1487, 1448, 1359, 1336, 1286, 1190, 1159, 1134, 1099, 1066, 1001, 962, 916, 852, 775, 725, 690, 659, 619 cm^{-1}; HRMS-QTOF: *m/z* calcd for [C$_{13}$H$_{16}$NO$_2$]$^+$: 218.1176 [M+H]$^+$; found: 218.1173.

Ir complex 26: In a glovebox, alcohol **25** (0.187 mmol, 1 equiv), dicyclohexylchlorophosphine (0.191 mmol, 1.02 equiv), KH (25 to 35% wt, 0.374 mmol, 2 equiv), and a magnetic stir bar were added to a dry Schlenk tube. Outside the glovebox, THF (2 mL) was added under an argon atmosphere. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo. The Schlenk tube was transferred back to the glovebox, and the residue was suspended in toluene (2 mL, dry, degassed) and filtered over a disposable HPLC-syringe filter (CHROMAFIL O-20/15 MS, pore size 20 μm). The remaining solid on the filter was rinsed with toluene (2×2 mL). After removing the filtrate from the glovebox, it was concentrated in vacuo, and the crude ligand was dissolved in CH_2Cl_2 (3 mL). This solution was added dropwise under stirring to a solution of [IrCl(cod)]$_2$ (0.0954 mmol, 0.51 equiv) in CH_2Cl_2 (1 mL). The resulting solution was heated at reflux for 1 h and cooled down to room temperature. NaBAr^F (0.206 mmol, 1.1 equiv) was added and the mixture was stirred for 30 min at room temperature. Silica gel was added and the solvent was removed in vacuo. Filtration over silica gel (40 g; h×d: 15×2.5 cm, 1st: 150 mL of Et$_2$O 2nd: 200 mL of CH_2Cl_2/Et$_2$O 1:1) led to the desired iridium complex in 25% yield as an orange solid. M.p. 180 °C; ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C, TMS): δ = 8.52 (d, J = 7.08 Hz, 2H), 7.75–7.71 (m, 9H), 7.65 (m, 2H), 7.56 (s, 4H), 5.07–5.18 (m, 1H), 4.73–4.81 (m, 1H), 3.28–3.41 (m, 2H), 243–2.65 (m, 2H), 2.57 (s, 3H), 2.35 (s, 3H), 2.10–2.33 (m, 5H), 1.59–2.01 (m, 13H), 1.16–1.48 (m, 10H), 0.97–1.14 (m, 2H), 0.50–0.67 ppm (m, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 25 °C, TMS): δ = 162.54 (s), 162.17 (q, J_{CF} = 50.1 Hz, BAr^F), 146.81 (s), 138.57 (s), 135.16 (m, BAr^F), 133.97 (s), 129.88 (s), 129.35 (s), 129.07 (qq, J_{CF} = 31.1 Hz, J_{CB} = 2.5 Hz, BAr^F), 124.92 (q, J_{CF} = 273 Hz, BAr^F), 124.43 (s), 117.83 (sept., J_{CF} = 3.8 Hz, BAr^F), 98.16 (d, J_{CP} = 9.2 Hz), 91.41 (d, J_{CP} = 12.9 Hz), 78.56 (d, J_{CP} = 4.9 Hz), 67.45 (s), 61.38 (s), 40.31 (s), 39.99 (s), 38.69 (d, J_{CP} = 2.8 Hz), 36.41 (d, J_{CP} = 36.3 Hz), 33.9 (s), 32.59 (s), 29.09 (s), 28.58 (dd, J_{CP} = 3.96, 1.33 Hz), 28.48 (s), 27.16 (d, J_{CP} = 10.8 Hz), 26.92 (d, J_{CP} = 12.5 Hz), 26.58 (d, J_{CP} = 6.9 Hz), 26.73 (s), 26.40 (br s), 26.33 (d, J_{CP} = 6.7 Hz), 24.44 (s), 13.28 ppm (s); ^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2, 25 °C): δ = 112.46 ppm; MS (+ESI) *m/z* (%): 716.3 (*M*+, 6.5), 715.3 (*M*+, 35.4), 714.3 (*M*+, 100), 713.4 (*M*+, 31.8), 712.2 (*M*+, 58.5); IR (neat): $\tilde{\nu}$ = 2933, 2860, 1699, 1544, 1485, 1452, 1353, 1271, 1114, 1001, 900, 885, 839, 763, 744, 711, 669, 576 cm^{-1}; HRMS-QTOF: *m/z* calcd for [C$_{33}$H$_{48}$IrNO$_2$P]$^+$: 714.3046; found: 714.3063; *m/z* calcd for [C$_{32}$H$_{12}$BF$_{24}$]$^-$: 863.0691; found: 863.0717.

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Keywords: C–H activation · deuterium · homogeneous catalysis · isotopic labeling · synthetic methods

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