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Iridium Catalysts for Hydrogen Isotope Exchange

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Contents

Abstract A history and summary of iridium-catalyzed hydrogen isotope exchange (HIE) is described. Owing to the wide range of applications served by installation of heavy and radioactive hydrogen isotopes, a wealth of synthetic labeling strategies have been forthcoming. Principle among all HIE methods are those developed using homogeneous iridium catalysts. This chapter covers major developments in (primarily homogeneous) iridium-centered catalysts for HIE. Connections to the broader fields of hydrogenation and C–H functionalization are also considered.

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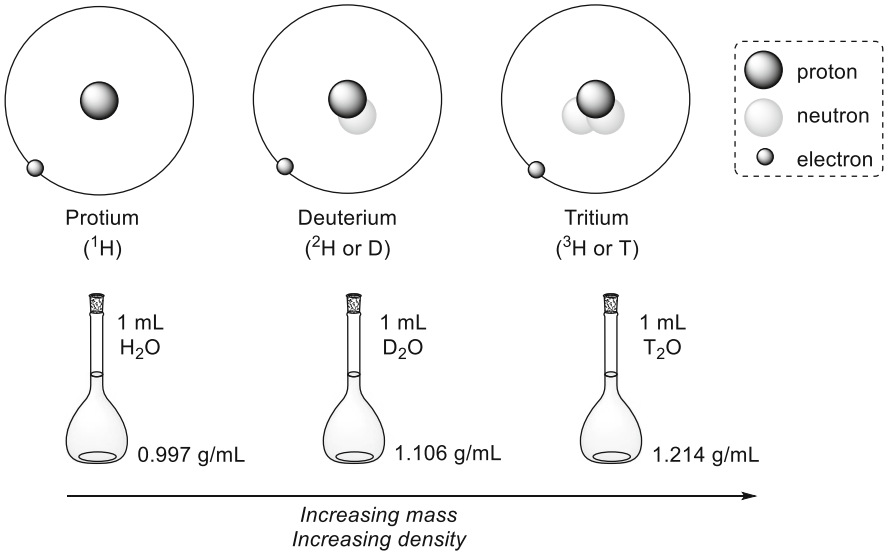
1 Introduction

1.1 Isotopes and Isotopic Labeling

Isotopes of a particular element have an identical number of protons in their respective nuclei but possess an unequal number of neutrons. Namely, they share the same atomic number but have different mass numbers, as exemplified for hydrogen (Scheme 1) [1]. The stability of an isotope is governed by the ratio of neutrons to protons within the nucleus, thus giving rise to two possible circumstances. Firstly, a *heavy isotope* of an element, such as ^{2}H or ^{13}C, has a stable nucleus and tends to be found in nature, albeit at lower abundances than their more common counterparts, ^{1}H and ^{12}C, respectively. In the alternative case, *radioisotopes*, such as ^{3}H or ^{14}C, have an unstable neutron/proton ratio and decay, via emission of radiation or particles, to form other elements, or different isotopes of the parent element.

The synthesis and supply of isotopically labeled molecules has a sustained importance in the study of metabolic processes, among myriad other processes [2]. It is therefore unsurprising that there is a large and growing body of research dedicated to the synthesis of isotopically labeled compounds. The labeling of molecules with ^{13}C or ^{14}C is most readily achieved through the use of commercially available, isotopically enriched starting materials. While such a technique ensures a regiospecific label will be present in the desired target molecule, it ultimately comes at the price of unwanted additional steps in the synthesis [3].



Scheme 1 Simplified Bohr representations of the isotopes of hydrogen

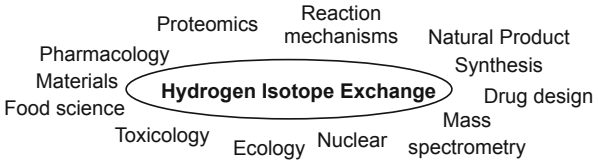
Research into deuterium (^{2}H or D) and tritium (^{3}H or T) labeling is more substantial than that for other isotopes and has been developed on a number of fronts over the past 60 years [2–22]. Further to this, key developments in synthetic strategies and analytical techniques over the past three decades are gradually making tritium labeling the preferred technique in many absorption, distribution, metabolism, excretion, and toxicology (ADMET) studies [10]. In one particularly active branch of such research, *hydrogen isotope exchange* (HIE) is commonly employed to deliver deuterium or radioactive tritium to pharmaceutical drug candidates in one synthetic step.

1.2 Applications of Hydrogen Isotope Exchange

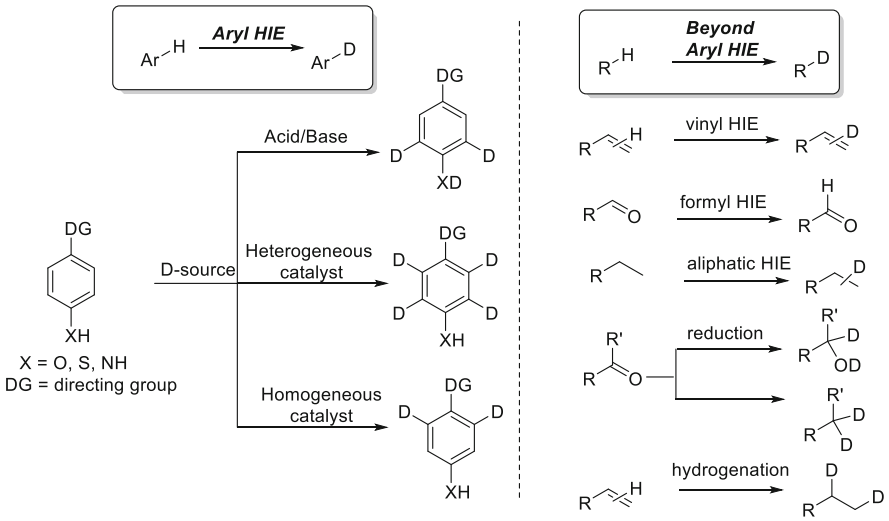
The importance of hydrogen isotope exchange (HIE), for iridium catalysts and beyond, is manifest in the wealth of reviews published in the area [2–36]. As well as circumventing the requirement for isotopically enriched starting materials in synthesizing tritiated drug candidates [3, 10], HIE can also provide analogous deuterated compounds for use as internal standards for mass spectrometry [29, 37], for kinetic isotope studies, [21, 38, 39], and for the alteration of reaction pathways in total syntheses [40]. Additionally, HIE is applied within almost every sub-discipline in life science, in nuclear science, and beyond [2]. The ability for precise measurement of isotope ratios promotes a dynamic view on biosynthetic pathways, protein turnover, and systems-wide metabolic networks and, thus, has paved the way for a number of scientific breakthroughs in biomedical research. In assessing a drug candidate's metabolic fate, the chemist must first have a flexible technique with which to study it. Consequently, *isotopic labeling* is the gold standard method by which early stage drug discovery processes are optimized. The numerous application areas for HIE are summarized in Scheme 2.

1.3 Synthetic Methods in HIE

With a broad range of existing HIE applications, there exists a wide range of synthetic methods to achieve hydrogen isotope incorporation in an ever-expanding array of substrates. While the full gamut of chemistries developed for HIE is beyond the primary focus of this chapter, it is worth covering these in brief. Firstly, the source of deuterium and tritium has varied extensively from method to method; however, some patterns exist. For deuteration, many methods have applied D_2 gas,



Scheme 2 Application areas served by hydrogen isotope exchange (HIE) technology



Scheme 3 Common synthetic transformations toward the installation of hydrogen isotopes in organic substrates

D_2O (heavy water), DCl, benzene-d_6, DMSO-d_6, and numerous deuterated alcohols. Of these isotope sources, and of direct relevance to the focus of this chapter, D_2 gas has been the preferred isotope source as it directly maps onto the preferred use of tritium gas for radiolabeling protocols [5, 7, 10, 17].

Hand in hand with the range of hydrogen isotope sources is a wide range of metal-mediated and other mediated processes for HIE (Scheme 3). Classically, these include acid- and base-mediated reactions, as well as modern variations using frustrated Lewis pairs (FLPs). Aryl labeling is most common, but many common organic transformations have been pivoted into labeling protocols. Nonetheless, metal-catalyzed HIE is dominant in HIE, covering heterogeneous and homogeneous catalysis. Such methods have been more fully reviewed elsewhere [11, 12].

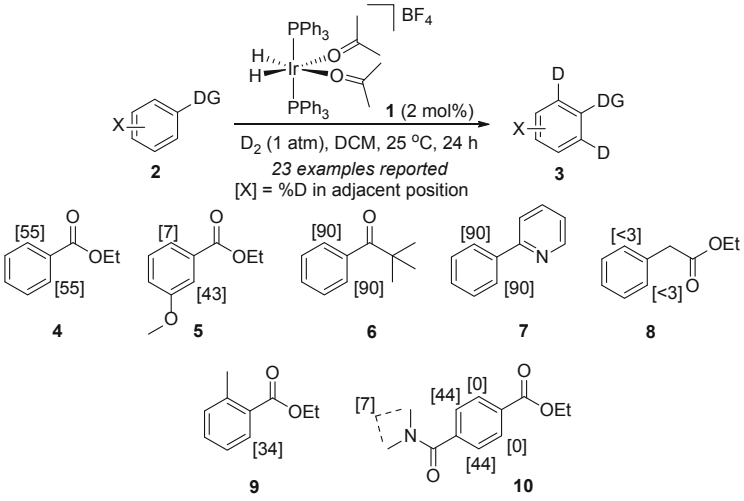
2 *Ortho*-Directed Iridium-Catalyzed HIE

Among all transition metals employed in homogeneous HIE methods, iridium is arguably the most widely studied [2, 3, 5, 6, 11–13, 15, 17, 18, 20, 22, 26, 35, 36, 41, 42], which is, in part, due to the vast and ever-expanding literature precedent in related hydrogenation reactions [31, 43–68]. Iridium was also present in some of the earliest metal-centered catalysts applied to HIE chemistries [69]. In support of this analysis of iridium's popularity in HIE, Oro and co-workers estimated that iridium accounted for 33% of all reported HIE methods, greater than for any other metal [11]. While iridium catalysts have also been applied in heterogeneous catalysis

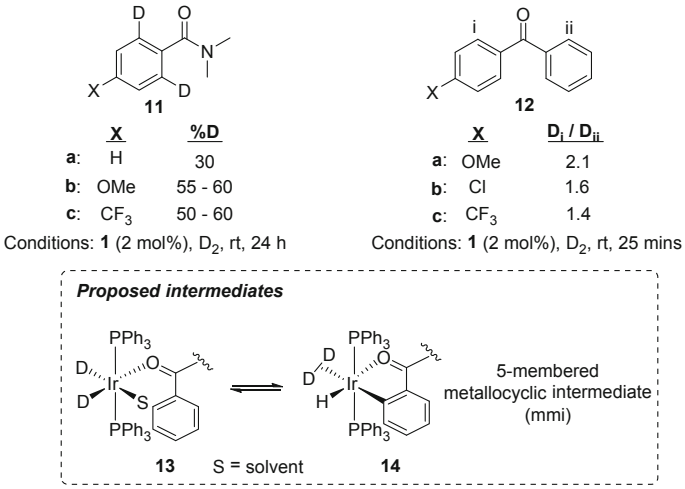
[70, 71], the focus of this chapter is on the far more expansive homogeneous iridium catalysis developments.

2.1 Early Developments in Ortho-Directed HIE

There is a clear dominance of *ortho*-HIE in the homogeneous iridium catalyst literature. In 1992, Heys demonstrated the successful *ortho*-directed deuteration of several substituted aromatic compounds using the 18-electron Ir(III) bis-phosphine dihydride complex **1** under very mild conditions (**2** → **3**, Scheme 4) [72]. Crucially for the time, Heys' investigations marked a significant advancement from Lockley's *ortho*-labeling work (with rhodium and ruthenium catalysts) [73–75]: D_2 gas replaced D_2O as the deuterium source (an advantage when considering the use of tritium), reactions operated efficiently at room temperature, and, perhaps most importantly, catalyst loadings were significantly reduced from 50 mol% to 2 mol %. Interestingly, it was noted that labeling was significantly affected by steric or electronic aspects of the substituents present on arene substrates. For example, *meta*-substituted ethyl benzoates, such as **5**, showed a consistent preference for labeling at C-2 over the less hindered C-6 position, presumably due to additional coordination assistance from *meta*-substituent lone pairs [76]. Steric hindrance from *ortho*-substitution reduced labeling efficiency (**4** vs. **9**); however, bulky α-substituted ketones such as **6** were not so adversely affected. Further to this, where substrates possessed more than one carbonyl directing group, the labeling site(s) changed according to which substituent could coordinate to the catalyst to the greatest extent (e.g., **4** vs. **10**).



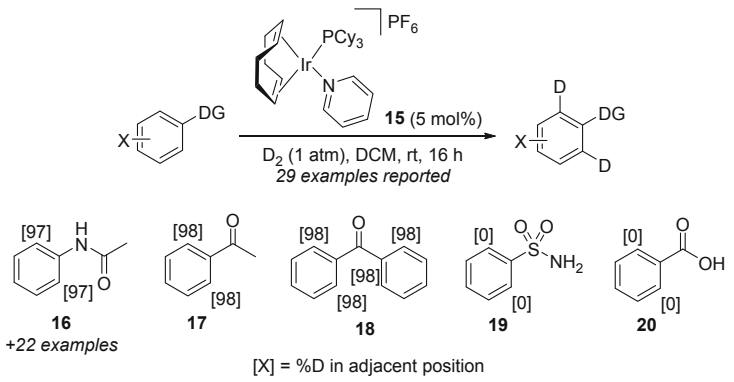
Scheme 4 Heys' Ir-catalyzed *ortho*-directed deuteration of aromatic compounds



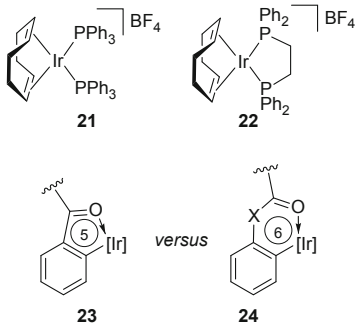
Scheme 5 Mechanistic investigations into Heys' Ir-catalyzed HIE protocol

The mild labeling conditions pioneered by Heys and co-workers, coupled with intriguing substrate-dependent regioselectivity, captured the combined interest of the industrial and academic HIE communities, resulting in a large number of subsequent studies aimed at understanding the catalytic properties of **1** and related Ir-based HIE catalysts. Firstly, Heys followed up his initial study with a more in-depth assessment of the aryl substituent effects in the labeling efficiency of ethyl benzoates and *N,N*-dimethylbenzamide substrates (Scheme 5) [72]. In a rather unexpected outcome, *para*-substitution improved the rate of labeling in both substrate types, *irrespective of substituent electronics* (e.g., **11a** vs. **11b** and **11c**). In an attempt to explain this effect, Heys monitored the rate of labeling in both rings of several monosubstituted benzophenones [72]. The substituted ring was labeled faster in every instance (**12a**–**12c**). As both rings are connected to the same carbonyl functionality, it appeared that the rate-limiting step of the overall reaction could *not* be ascribed to the initial coordination of the substrate, nor hydride fluxionality [23]. Instead, Heys suspected that some aspect of the C–H bond cleavage was rate-limiting, proposing key intermediates **13** and **14** based on available literature. At this time, the formal oxidation state of iridium intermediates involved in the C–H bond cleavage (Ir^{I} / Ir^{III} or Ir^{III}/Ir^{V}) was not clear.

Inspired by Heys, Hesk and co-workers probed the efficacy of the commercially available Crabtree hydrogenation catalyst, **15** [43], in labeling acetanilide derivatives, the first such substrates to be effectively labeled via a 6- rather than a 5-membered metallocyclic intermediate (mmi) [77]. Consistent with Heys' work, Hesk reported that deuteration was directed *ortho* to the coordinating functionality. Moreover, no clear relationship emerged regarding the electronics of *para*-substituents and labeling efficacy. Ketones **17** and **18** were also compatible with this mild labeling method; however, weakly coordinating benzenesulfonamide **19** and benzoic acid **20** were not (Scheme 6).



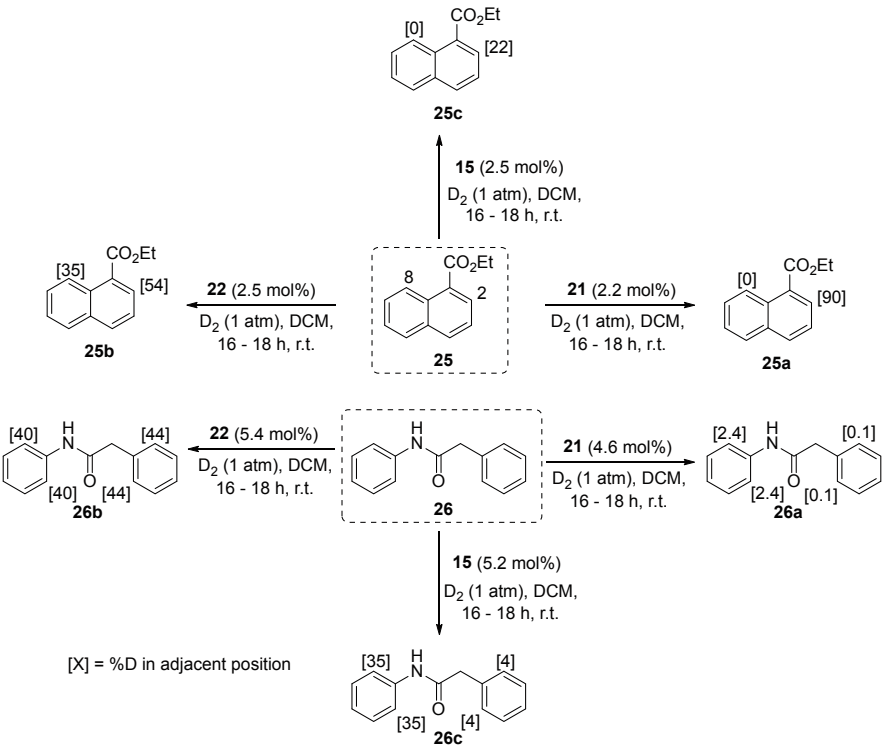
Scheme 6 Hesk's application of Crabtree's catalyst in *ortho*-HIE



Scheme 7 Mono- vs. bidentate Ir–phosphine catalysts to study *ortho*-deuteration via 5- and 6-mmis

Since Heys' and Hesk's respective discoveries of iridium catalysts for *ortho*-directed HIE, complexes **1** and **15** (and derivatives thereof, vide infra) have remained topics of high interest in HIE research [26, 78–81]. In a further key development by Heys, **21**, a precatalytic Ir(I) variant of Ir(III) catalyst **1** was compared to related bidentate pre-catalyst, **22** (Scheme 7) [82]. By the mid-1990s, it had already been hypothesized by several researchers that both 5- and 6-mmis could be formed during the C–H bond cleavage step in the *ortho*-deuteration process (**23** vs. **24**), depending on the substrate being studied; this was to be the platform on which to compare iridium catalysts **21** and **22**.

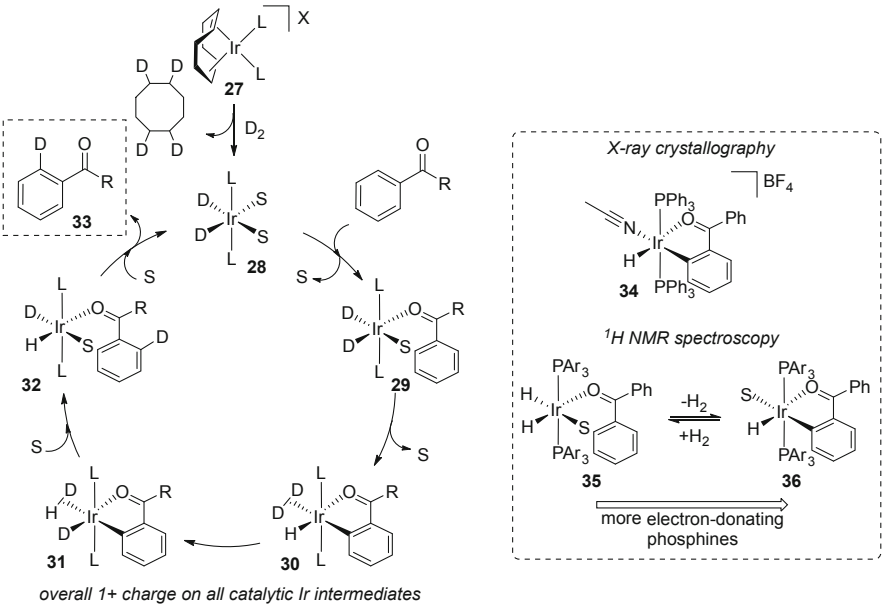
Labeling a range of substrates enabled a comparison of the mono- and bidentate phosphine complexes to be made, highlighting a preference for monodentate **21** to react through a 5-mmi only, whereas bidentate **22** could react through both a 5- and a 6-mmi. This result was exemplified in the labeling of ethyl 1-naphthoate, **25** (Scheme 8, top). Of the two available labeling sites, the monodentate complex, **21**, labeled solely at C-2. Conversely, bidentate complex **22** demonstrated the capability to direct labeling at both C-2 and C-8. When Crabtree's catalyst, **15**, was exposed to



Scheme 8 Heys' vs. Hesk's *ortho*-HIE methods for 5- and 6-mmi substrates [77, 82]

similar reaction conditions, the regioselectivity in labeling was similar to monodentate complex **21**, albeit with reduced labeling efficiency. Labeling through a 6-mmi only was also investigated. Perhaps the most remarkable findings from this study were those concerning the labeling of *N*-phenyl phenylacetamide, **26** (Scheme 8, bottom). Interestingly, the less active monodentate complex, **21**, showed selectivity for the aromatic ring adjacent to the nitrogen, **26a**, an effect emulated more efficiently by Crabtree's catalyst in **26c**. However, the bidentate catalyst **22** was able to label both rings of **26** almost indiscriminately (see **26b**). This served to show that there was potential to distinguish not only between a 5- and 6-mmi, but also between different *types* of 6-mmi, depending on the ancillary ligands employed.

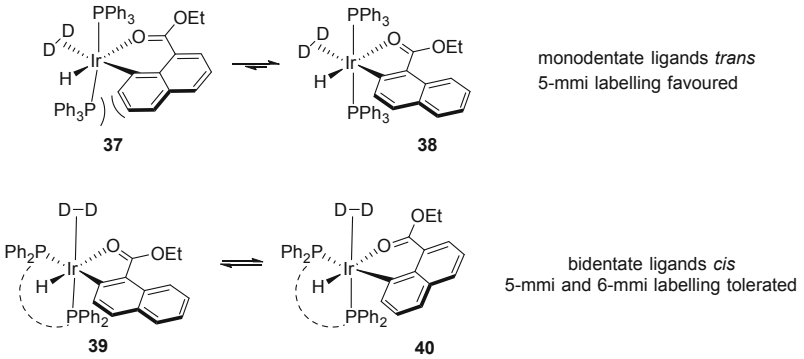
On accumulation of these data, Heys proposed a catalytic cycle by which these iridium complexes may be affecting the observed regioselective hydrogen isotope exchange (Scheme 9) [82]. Upon treatment of the Ir(I) pre-catalyst, **27**, with deuterium gas, hydrogenolysis of cyclooctadiene (COD) as d_4-cyclooctane generates the active Ir(III) catalyst, **28**, where ligands (L) are assumed to be arranged *trans* to one another when monodentate. Coordination of substrate displaces a solvent molecule (S) and is thus accepted into the coordination sphere of the iridium catalyst to give **29**. A second solvent molecule can then be displaced, allowing iridium to cleave the



Scheme 9 Heys' mechanistic analysis for homogeneous Ir-catalyzed *ortho*-HIE

nearby *ortho* C–H bond of the aryl ring to yield **30**. Transformation of species **31** to **32** is driven by a process known as *hydride fluxionality* and is central to the isotope exchange process [23]. The overall effect brings a deuteride and the activated aryl carbon into a *cis* arrangement. Subsequent C–D elimination furnishes **32**, with a deuterium atom now installed *ortho* to the directing group. Finally, the release of deuterated substrate, **33**, regenerates the resting catalytic intermediate, **28**. This mechanism invokes an all-Ir(III) catalytic cycle with C–H activation as the rate-limiting step, supporting evidence for which would take another decade to accumulate. Said evidence involved isolation and crystallographic characterization of **34** (an acetonitrile-solvated analogue of **30**) and spectroscopic studies on the evolving nature of iridium hydride equilibria as a function of ancillary ligand electronics (Scheme 9, inset) [20].

In an extension of the theory of *ortho*-directed HIE, Heys postulated that the preference for the monodentate phosphine complex, **21**, to react only via a 5-mmi, **38**, as opposed to a 6-mmi, **37**, was based on steric effects (Scheme 10) [82]. By contrast, the bidentate complex, **22**, is forced to arrange the phosphines *cis* to one another. For substrates such as **25**, this opens up a second face on the iridium complex, offering greater spatial freedom for the formation of the less planar 6-mmi, **40**, as well as the 5-mmi, **39**. By the same thought, the monodentate Crabtree's catalyst, **15**, *can* facilitate labeling through a 6-mmi as the pyridine and tricyclohexylphosphine ligands present less steric bulk than the two triphenylphosphine ligands of complex **21** and may thus exist in *cis* or *trans* form. Herbert later capitalized on this rationale to further improve bidentate catalyst **22** in



Scheme 10 Rationale for 5- vs. 6-mmi labeling selectivity with mono-/bidentate phosphine catalysts

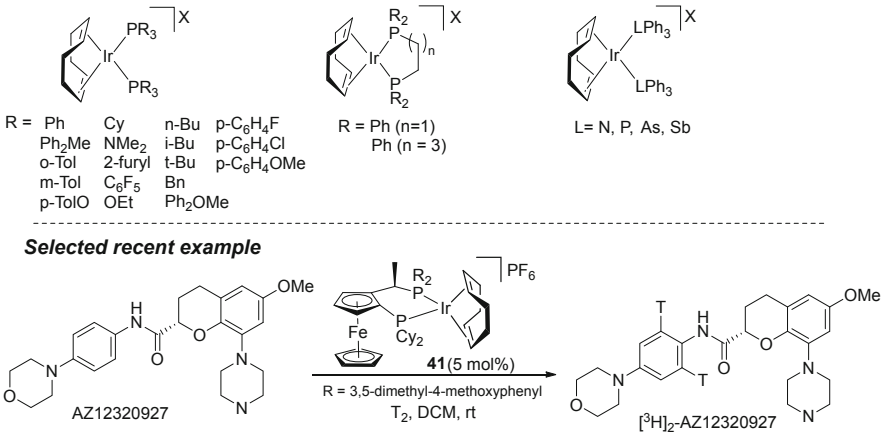
the labeling of 6-mmi substrates, changing the diphenylphosphinoethane (dppe) ligand for the sterically less encumbered arsine analogue [81].

2.2 Contemporary Methods in Ortho-Directed HIE

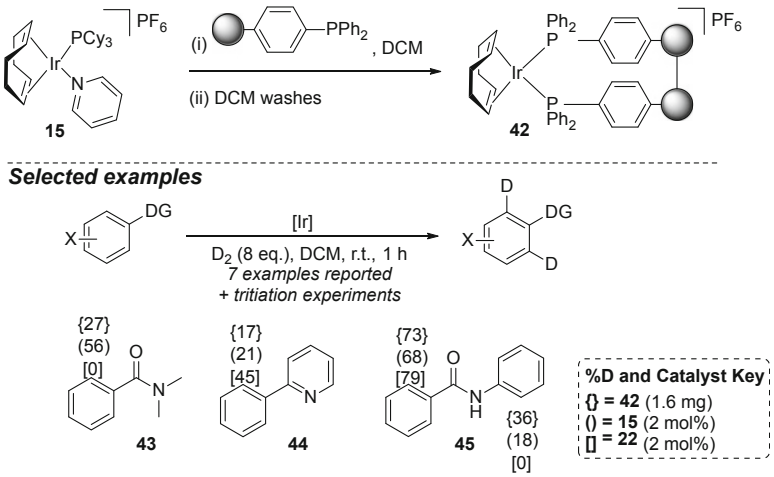
Further synthetic developments by Herbert [28, 78, 83] and later Salter [26] showed that bis-phosphine catalysts like **22** may be generated in situ from the appropriate free phosphine and commercial iridium dimer, $[Ir(COD)Cl]_2$, with comparable activity to the isolated complexes. The same authors are also separately responsible for detailed studies into alteration of the phosphine structure [26, 78, 81]. However, both parties have remarked that strong correlations between ligand properties (such as sterics or electronics) and catalyst activity are difficult to detect. The number of such ligands applied to iridium-catalyzed HIE is now extensive and includes more elaborate catalyst system like **41** (Scheme 11).

Parallel with studies into bis-phosphine systems, Crabtree's catalyst **15** has also been the subject of intense study in deuteration and tritiation, since Hesk's discovery [76, 84–89]. In one of the largest of any such study, Herbert explored an expansive substrate scope, including ketones, amides, anilides, and various heterocycles [83]. Despite the impressive array of examples reported, this study employed *at least* stoichiometric quantities of **15** and a dual D_2/D_2O isotope source, making comparisons to related *ortho*-labeling methods difficult.

In a notable crossover between bis-phosphine catalysts and Crabtree's catalyst, Hickey and co-workers developed a polymer-supported variant of Heys' bis-phosphine catalyst, **42**, which showed comparable *ortho*-HIE activity to **15** and **22**, but with the practical benefit of simple catalyst filtration at the end of the reaction (**43** vs. **44** vs. **45**; Scheme 12) [71]. Solid-supported iridium catalysts for HIE have now been adapted to flow systems [80].



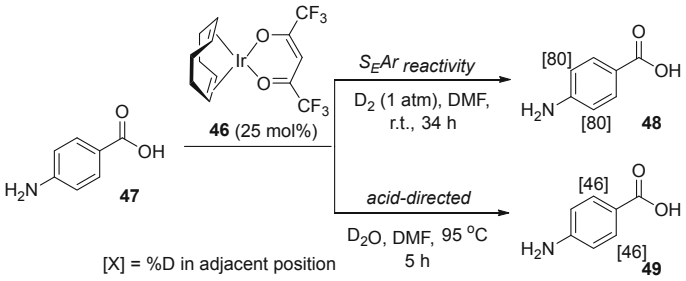
Scheme 11 An overview of bis-phosphine-ligated iridium catalysts applied in HIE



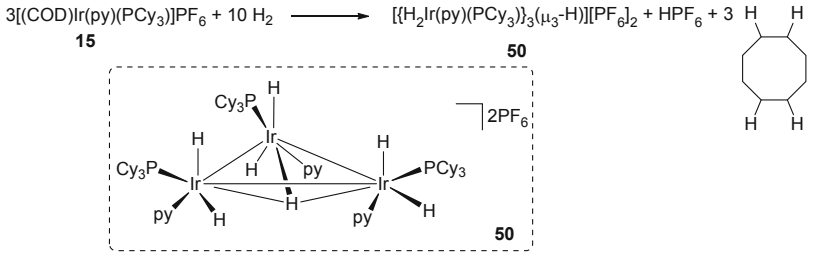
Scheme 12 Polymer-supported iridium catalyst in *ortho*-HIE

Exploring an altogether different ligand architecture, Lockley reported the application of hexafluoroacetylacetonate (hfacac)-ligated Ir(I) complex, **46**, in *ortho*-HIE (Scheme 13) [8, 10, 22, 90–92]. This catalyst has been successfully applied in the labeling of benzylic amines, benzoic acids, and primary sulfonamides, where few other Ir-based HIE catalysts have succeeded. The catalyst is one of the few iridium HIE catalysts operational in highly polar solvents such as DMF (desirable for poorly soluble drug molecules) and displays different labeling regioselectivities depending on the choice of isotope source (D_2 or D_2O; see **47** → **48** vs. **47** → **49**).

In the early 2000s, increasing interest in Crabtree's catalyst, **15**, in HIE was paralleled with investigations by other researchers to improve efficiency and



Scheme 13 Ir(I)-hfacac *ortho*-HIE catalyst and isotope source-dependent regioselectivity switch

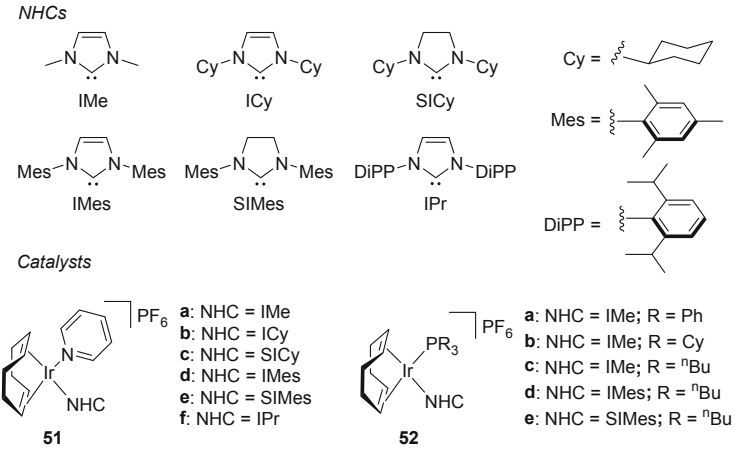


Scheme 14 Trimeric iridium cluster formed from thermal deactivation of Crabtree's catalyst

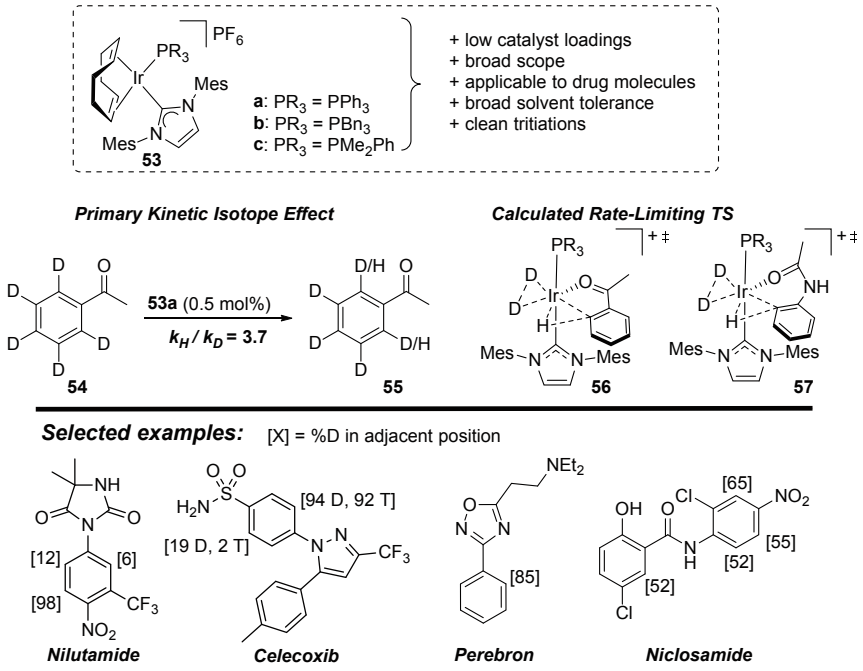
chemoselectivity in iridium-catalyzed olefin hydrogenation reactions [61]. Despite its widely reported success, **15** is known to suffer from thermal deactivation via the formation of inactive, hydride-bridged, iridium clusters (**50**, Scheme 14) [54]. Similar effects have been documented for other iridium-based complexes [66, 93].

Separate investigations by Nolan [62] and Buriak [94] toward improved thermal stability and predictable chemoselectivity of Crabtree-like hydrogenation catalysts resulted in a plethora of highly promising electron-rich, N-heterocyclic carbene (NHC)-ligated iridium catalysts (Scheme 15). Such species were first applied and published in *ortho*-HIE processes by Powell and co-workers [95]. In Powell's study, complexes **51a** and **52a**–**52c** were employed under stoichiometric (industrial "tritiation-like") conditions, with the most active variant, **52c**, shown to be superior to Crabtree's catalyst across the entire substrate range.

In a more interesting variant of this work, Kerr and co-workers studied the *catalytic* activity of complexes **51b–51f**, showing most active complex, **51e**, to be highly active over an appreciable substrate scope (5 mol% [Ir], 16 h, rt) and displaying a higher turnover frequency (TOF) than Heys' bis-phosphine catalyst, **22**. Interestingly, the smaller complexes in the series studied by Kerr (**51b** and **51c**) were completely inactive as HIE catalysts [86]. Similar investigations by the same group led to the discovery that small NHC/phosphine complexes such as **52c** were inactive as HIE catalysts, but larger variants **52d** and **52e** were active across a limited substrate scope [96].



Scheme 15 NHC-ligated iridium catalysts for hydrogenation later explored by HIE chemists



Scheme 16 Highly active NHC/phosphine *ortho*-HIE iridium catalysts

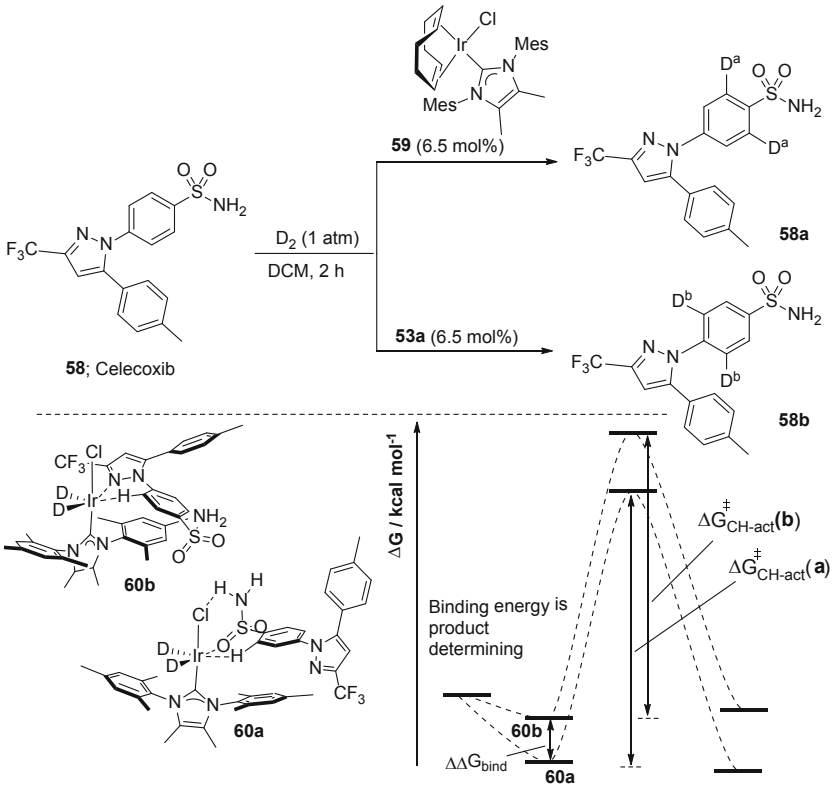
The exploration of NHC-ligated iridium HIE catalysts had revealed promising (proof-of-concept) developments beyond the popular and established works of Hesk and Heys. Kerr and co-workers later developed a synthesis of previously unattainable complexes **53a**–**53c**, bearing large phosphine *and* large NHC ligands

(Scheme 16) [97]. These complexes have proven seminal within the *ortho*-HIE domain and have among the highest activity [98], substrate/solvent scope [99, 100], and tritiation reaction cleanliness of any such catalyst reported to date. Additionally, *ortho*-HIE process with these complexes has been studied experimentally and computationally, strengthening the case for a Ir(III)-based reaction mechanism akin to that proposed by Heys [98]. More specifically, kinetic isotope effect (KIE) measurements [101] revealed that C–H bond cleavage was the rate-limiting step of the reaction (**54** → **55**), and detailed NMR studies revealed (via $^{2}J_{P-C}$ coupling information) the *trans*-geometry of the ancillary ligands [98]. The same study was also able to reveal the origins of the selective reactivity of such catalysts for 5- over 6-mmi substrates, citing dual kinetic and thermodynamic favorability for the 5-mmi. The calculated transition states **56** and **57** revealed, for the first time, the sigma-bond-assisted metathesis (sigma-CAM) process at the heart of the all-Ir(III) C–H activation step [98, 102].

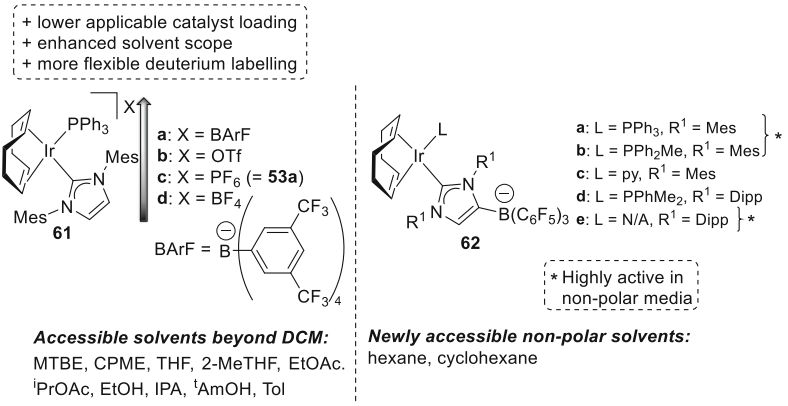
While developing a rare method for labeling primary sulfonamides, Kerr and co-workers considered directing group chemoselectivity in detail [102]. It was observed that the sulfonamide vs. pyrazole selectivity in *celecoxib* **58** varied dramatically with catalyst choice (Scheme 17). Whereas encumbered and most-often used NHC/phosphine catalysts facilitated labeling adjacent to the pyrazole moiety, giving **58b**, neutral NHC/Cl catalysts, such as **59**, facilitated selective sulfonamide labeling, delivering **58a**, for the first time. Accompanying DFT studies revealed that the substrate binding event was likely to be product-determining (**60a** vs. **60b**), even though C–H activation remained rate-limiting (Scheme 17). A similar rationale was presented for multifunctional molecules containing esters as the targeted directing group [103]. Following this, Derdau and co-workers significantly expanded on the HIE studies of competing directing groups, showing once again that calculated binding energies could serve as a semiquantitative and predictive tool for rationalizing directing group chemoselectivity in HIE [42].

Building on Kerr's work, Ir(III)-catalyzed *ortho*-HIE has continued to flourish [3, 11, 13, 15, 35, 41, 42]. From the same group, and others applying the developments therefrom, the application of bulky NHC–phosphine systems in HIE has steadily advanced in terms of the applicable substrate and solvent scope [42, 102, 104–108]. With regard to solvent scope, Kerr and Tamm have reported complementary strategies toward modifying the solubility profile of existing iridium HIE catalysts. On the one hand, Kerr explored the use of the bulky tetrakis[3,5-bis (trifluoromethyl)phenyl]borate (BArF) counterion in place of the standard hexafluorophosphate (PF_6) [104, 109], and on the other, Tamm integrated a related borate anion into the backbone of an anionic carbene ligand (Scheme 18) [110]. The wide range of solvents made applicable in extending the Kerr catalyst series through **61a**–**61d** evidenced new opportunities to tune HIE regioselectivity through simple solvent switching [104]. From Tamm's most recent developments, catalysts **62a**, **62b**, and **62e** have been identified as competent HIE catalysts in hexane and cyclohexane for the first time [110].

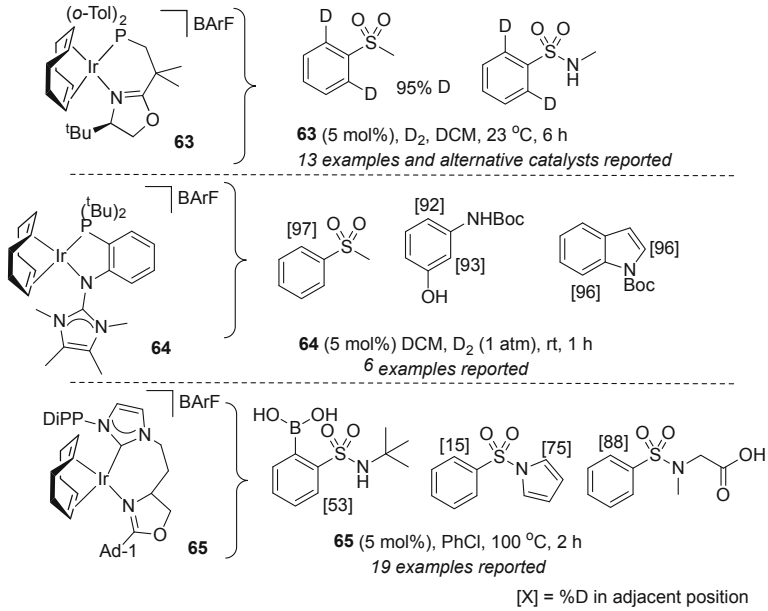
A growing community of researchers have, in more recent times, contributed a wider range of elaborated ligand spheres around tractable iridium(I) pre-catalysts. In



Scheme 17 DFT-calculated rationale for directing group selectivity using catalyst **59** and sulfonamide drug **58**



Scheme 18 Counter-anion effects explored in iridium-catalyzed *ortho*-directed HIE



Scheme 19 Modern chelated iridium catalysts expanding the range of accessible ortho-directing groups in HIE

turn, more iridium HIE catalysts have enabled applications using more challenging directing groups. A recent contribution from Pfaltz and Muri showed the application of *P*,*N*-derived bidentate ligands [111]. Most notably, these latest iridium-based HIE catalysts have been developed to be able to label *ortho* to secondary benzenesulfonamides for the first time, albeit using high temperatures and synthetically intricate ligands [111]. Along similar lines, Tamm and Derdau have reported complementary P,N- and C,N-ligated iridium catalysts able to further expand the range of accessible directing groups applicable in *ortho*-directed HIE processes (**63**–**65**, Scheme 19) [110, 112, 113].

3 Beyond *Ortho*-Directed HIE

Far from the humble beginnings of homogeneous iridium-catalyzed HIE [69], labeling of organic molecules has continued to advance along complementary lines to *ortho*-directed HIE. While some instances have been discovered as unintended by-products of desired *ortho*-labeling, [111] or to assess non-innocent ancillary ligand behaviors, [114–125] contributions have been made to labeling global aromatic, sp^3, vinyl, formyl, and heteroatom positions in a strategic manner (cf. Scheme 3). In the application domain, such developments have given

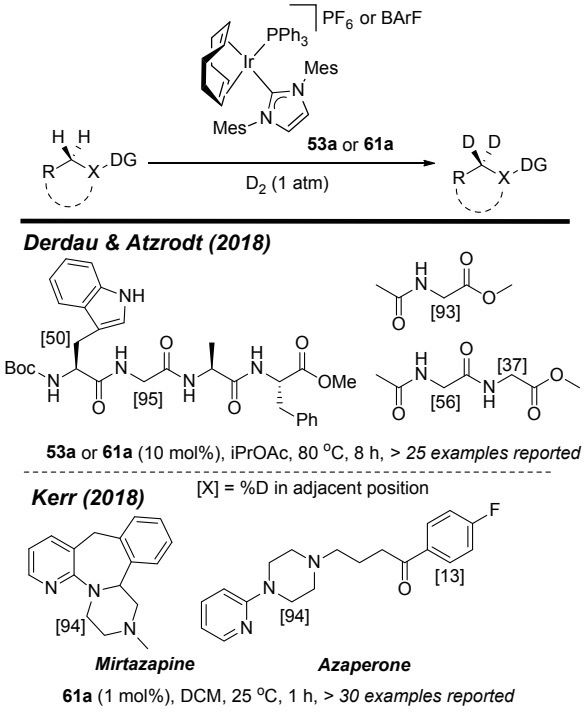
industrialists a more diverse palette of methods with which to incorporate hydrogen isotopes into an increasingly elaborate array of drug candidates.

3.1 Directed sp^3 C–H HIE Methods

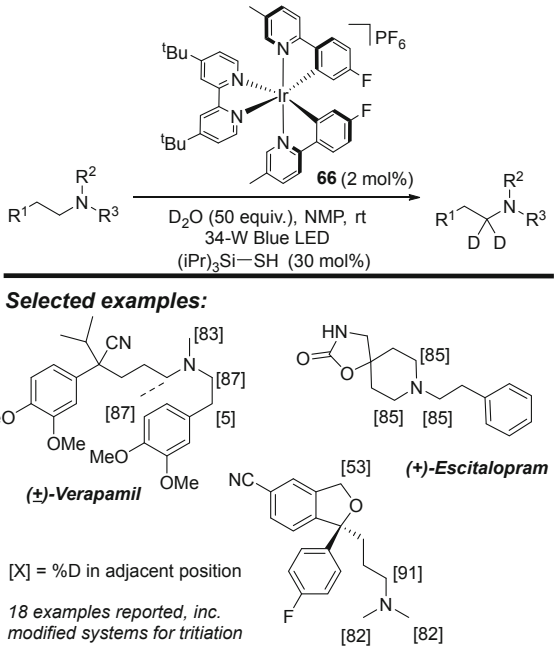
Somewhat inspired by the deep understanding of iridium catalysts and compatible directing groups for *ortho*-directed HIE protocols, significant contributions have emerged toward labeling sp^3 centers rather than aromatic sp^2 centers [15, 111, 126, 127].

Using Kerr's commercially available catalyst **53a** and **61a**, Derdau and Kerr have developed expansions of the original *ortho*-labeling methodologies, showing that the same catalyst systems can effectively label sp^3 C–H positions in complex amides and a range of drug molecules (Scheme 20).

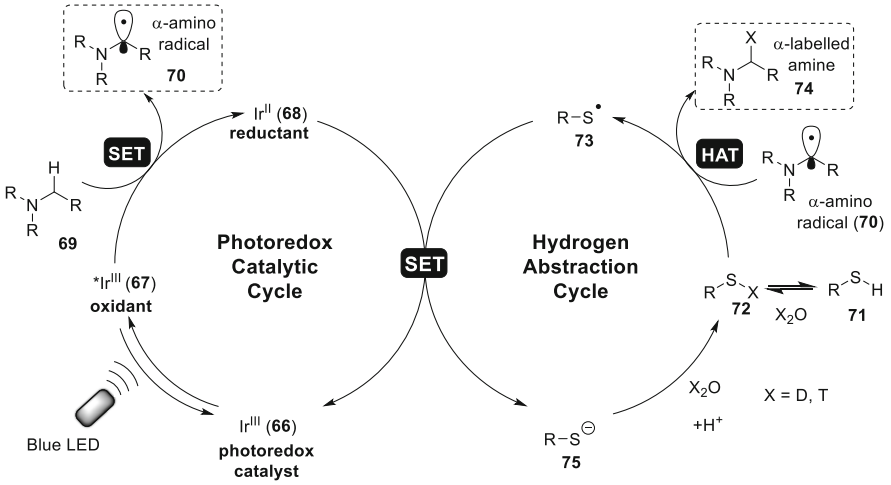
In a new paradigm for the field, MacMillan and co-workers developed a photoredox- and hydrogen atom transfer (HAT)-catalyzed method, employing an iridium(III) photocatalyst Ir(F-Meppy)$_2$ (dtbbpy)PF$_6$ [F-Meppy, 2-(4-fluorophenyl)-5-(methyl)pyridine; dtbbpy, 4,4′-di-tert-butyl-2,2′-bipyridine], **66** [128]. In combination with labeled water (D_2O or T_2O) as the isotope source, and a suitable



Scheme 20 Directed sp^3 HIE using the commercially-available iridium catalysts



Scheme 21 Selected examples from MacMillan's photoredox and hydrogen atom transfer (HAT)-mediated alpha-selective sp^3 HIE process for drug-like amines



Scheme 22 Hypothesized mechanism for photoredox- and HAT-mediated HIE

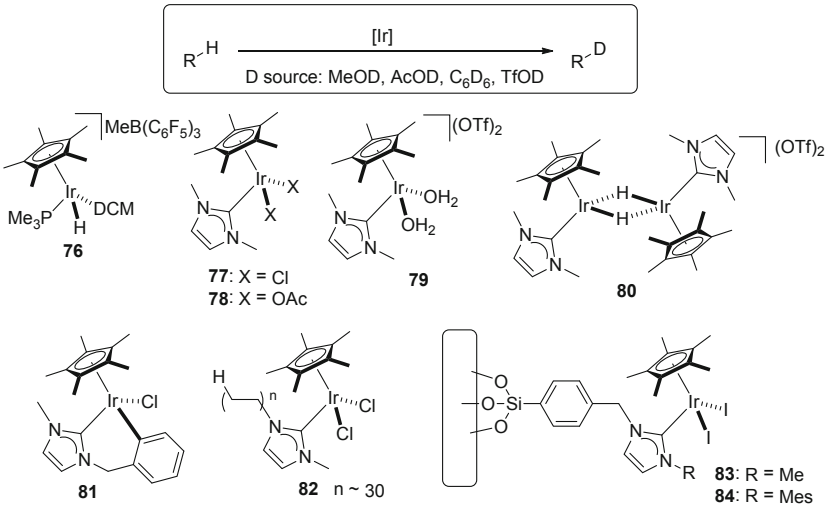
hydrogen atom donor, this method selectively delivered isotope incorporation to the sp3 a-amino sites in 18 drug molecules (Scheme 21).

The reaction is proposed to operate via coupled photoredox and hydrogen atom transfer (HAT) cycles (Scheme 22). The photoredox catalyst **66** is excited by the

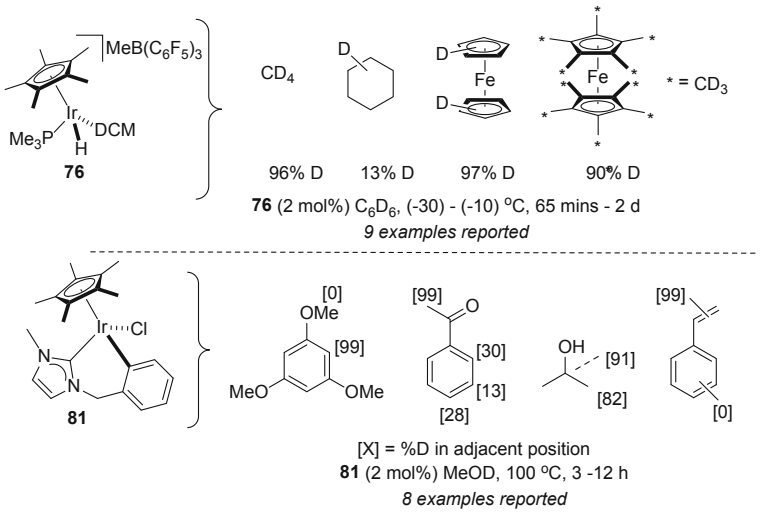
blue light-emitting diode (LED) to generate a long-lived excited state triplet **67**, a strong single electron oxidant. The catalyst then generates an alpha-amino radical **70** from **69**, and the reduced Ir(II) catalyst **68**, which is now a strong reductant. Isotopic scrambling between the labeled water source and added thiol delivers the on-cycle labeled thiol **72** from **71**, judiciously chosen due to the favorably weak S–H bond. Labeled thiol **72** (polarity matched with the nucleophilic amino radical **69**) undergoes a HAT process to generate the alpha-labeled amine product **74** and thiol radical **73**. Thereafter, the photoredox and HAT catalytic cycles converge to generate the thiolate anion **75** and regenerate the photoredox catalyst **66**. Through adjustments in the choice of photocatalyst and thiol source, this method was applicable to both deuteration and tritiation processes.

3.2 Non-ortho-HIE on Aromatic Substrates

A range of cyclopentadienyl (Cp, and derivatives thereof)-ligated iridium complexes have been shown to be active in HIE (**76–84**, Scheme 23). Principally, several nondirected and global aromatic C–H deuteration strategies have been reported and improved over several iterations of catalyst design [114, 129–136]. In 2001, Bergman and co-workers showed that complexes of the type [(Cp*)Ir(PR_3)(H)(DCM)], such as **76**, and, later, [(Cp*)Ir(PMe_3)$(H)_3$]OTf, were active in HIE across a range of aromatic and aliphatic substrates [114, 129–131]. In further iterations, Peris [132] and Ison [134, 135] reported a range of NHC-ligated complexes based on the Cp-I core. In more practically facing contributions, Thieuleux and collaborators divulged solid-supported variants of [(Cp*)Ir(NHC)] cores, **82–84** [133, 136]. Across



Scheme 23 Overview of Cp*Ir complexes applied to HIE processes



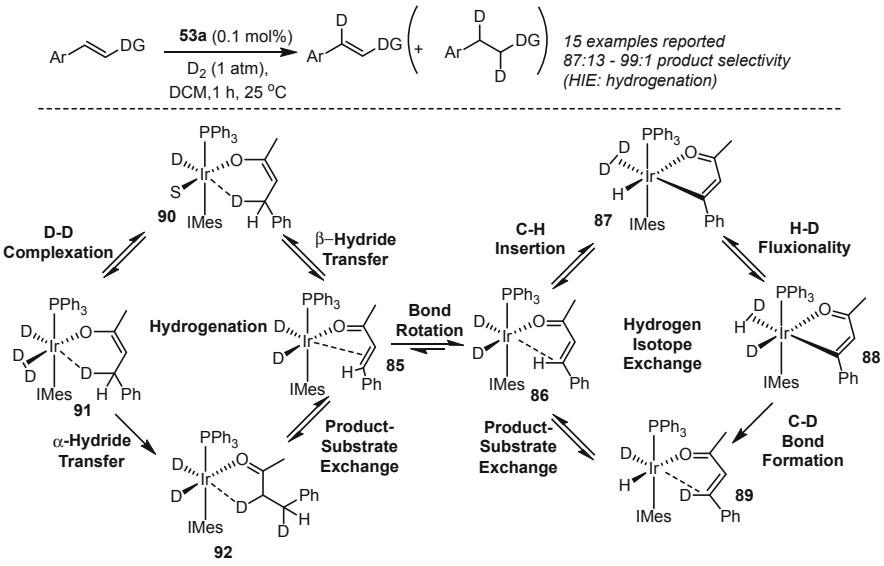
Scheme 24 Exemplar HIE processes enabled by Cp*Ir complexes

this series of publications, mechanisms of HIE were hypothesized to vary with deuterium source, solvent, and ancillary ligand combination (see Scheme 24 or exemplar transformations).

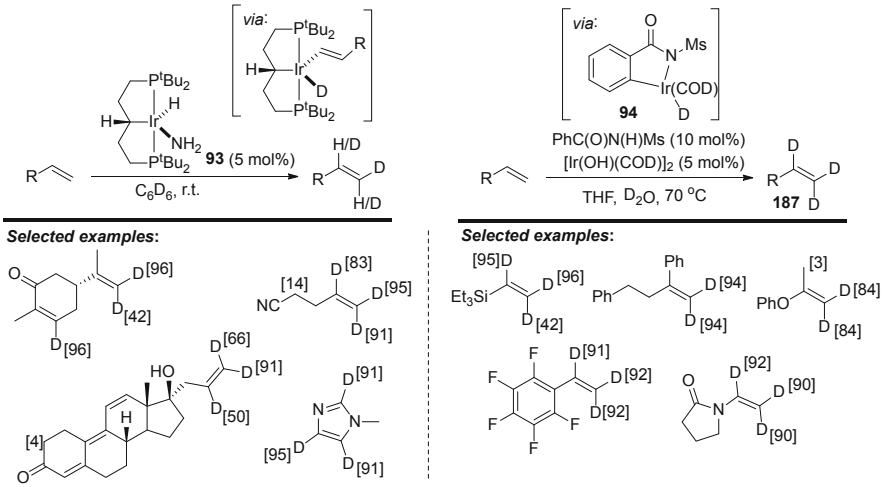
3.3 Vinyl HIE Processes

Expanding sp^2 labeling protocols beyond simple aromatic systems, a number of recent reports have shown the possibility of selectively labeling vinyl groups. Because many modern iridium HIE catalysts of the type $[(COD)Ir(L^1)(L^2)]X$ evolved from the hydrogenation literature [54, 62, 67], the labeling community has been aware of (and exploited) the reductive power of these catalyst systems to install isotopes across unsaturated moieties [10]. However, the dual HIE and hydrogenation reactivity of these iridium systems presents a challenge if the same catalyst is targeted for an HIE application, and *not* a hydrogenation. While designing HIE methods for labeling α,β-unsaturated substrates, Kerr and co-workers hypothesized that the competing reactivity could be rationalized by a equilibrating C–C bond rotation **85** to **86** upon substrate coordination (Scheme 25). For larger ligand spheres such as in catalyst **53a**, intermediate **86** would be favored, driving HIE (**86** → **87** → **88** → **89**). For smaller ligand systems, as has been observed in attempts to use Crabtree's catalyst for similar transformations [137], intermediate **85** is favored, driving hydrogenation over HIE (**85** → **90** → **91** → **92**).

Beyond re-optimizing HIE the use of catalysts in which competing hydrogenation is an issue, several methods for the chemoselective labeling of alkenes have also appeared in the iridium literature. In 2008, Hartwig reported a method where pincer complex **93** was shown to label vinyl C–H positions with selectivity largely

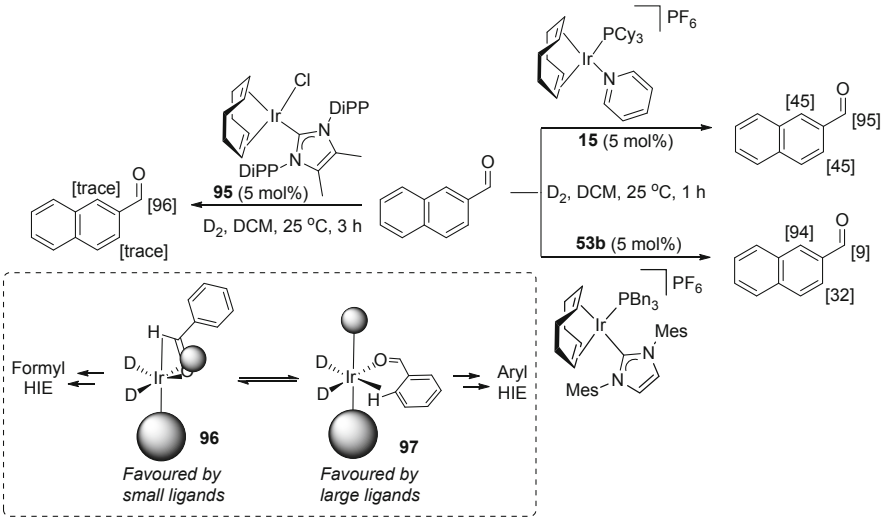


Scheme 25 Hypothesized competing HIE and hydrogenation pathways [99]



Scheme 26 Iridium-catalyzed vinyl HIE

dependent on the specific steric environment of the substrate, albeit under air and moisture sensitive conditions (Scheme 26, left) [138]. Notably, this method was applied to a series of both simple and complex organic molecules and included global labeling of aromatic and heteroaromatic substrates. A more practical variant of this method was divulged by Nishimura and co-workers [139]. Using an in situ-derived Ir(III) monohydride, **94**, and D_2O as the isotope source, an attractive range of



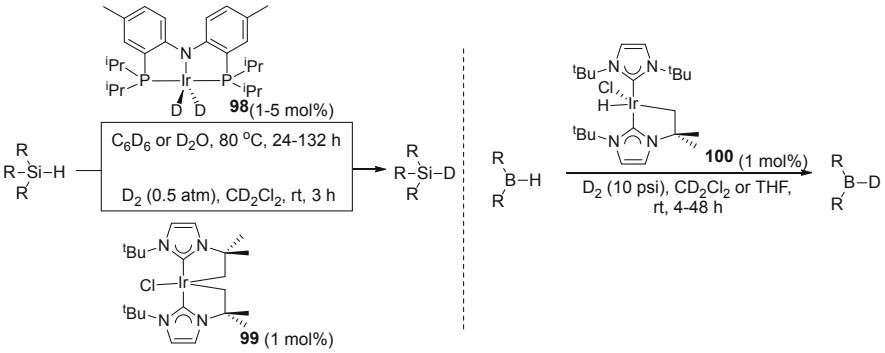
Scheme 27 Toward formyl-selective iridium-catalyzed HIE processes

mono-substituted alkenes could selectively deuterated at the vinyl or methylidene positions (Scheme 26, right).

In relation to vinyl HIE, formyl-selective methods of labeling benzaldehyde derivatives has been of notable interest, due, in part, to the synthetic handle of derivatization presented through the carbonyl functional group [140–145]. In 2010, Chapelle and co-workers showed that Crabtree's catalyst was able to deliver formyl-labeled benzaldehyde derivatives, albeit with variable selectivity against competing aryl ring labeling [142]. Kerr and co-workers used this work as inspiration to compare Crabtree's catalyst in formyl labeling vs. other competent *ortho*-HIE catalysts. Comparing catalysts **15** vs. **53b** vs. **95**, it was shown that the NHC/Cl system delivered superior formyl selectivity than either of the cationic iridium centers bearing larger ligand spheres (Scheme 27). The group accounted for these observations using a detailed mechanistic model centered around *cis-trans* isomerization of the activated Ir(III) catalyst. While intermediate **97** bearing *trans* ancillary ligands favors the approach trajectory of the aldehyde substrate that leads to aryl HIE, isomer **96** of the same catalyst enables the aldehyde to approach along a trajectory leading to formyl HIE [146].

3.4 Beyond C–H Labeling

Some of the most recent developments in isotopic labeling employing iridium catalysis have been applied to X–H moieties. While comparatively rare when compared to C–H HIE methods, heteroatom labeling can be insightful en route to establishing new carbon–heteroatom bonding–forming processes. Specifically,



Scheme 28 Iridium-catalyzed HIE for Si–H and B–H bonds

Nolan and Grubbs have independently reported on silane labeling [147, 148]. Grubbs studied catalyst **98**, while Nolan investigated **99** and **100** in Si–H and B–H labeling, respectively (Scheme 28) [149].

4 Concluding Remarks

Notwithstanding earlier pioneering developments in the field [69, 73–75, 150–152], iridium-catalyzed HIE has undergone explosive growth since Heys' use of bis-phosphine systems in the early 1990s [153]. The main thrust of developments in the field have been in *ortho*-directed HIE domain. Such is the maturity and underlying mechanistic understanding of the *ortho*-labeling subfield, that it is now influencing catalyst design strategies in the broader C–H functionalization field. Considered alteration of the iridium ligand sphere – for both Ir(I) and Ir(III) systems – has now expanded the field of HIE well beyond its *ortho*-labeling comfort zone. Iridium-catalyzed methods to install heavy and radioactive hydrogen isotopes now span global aromatic labeling, sp^3 labeling, vinyl labeling, heteroatom labeling, and combinations thereof.

Iridium-catalyzed HIE is evolving at a time when computationally supported catalyst design is reaching unprecedented levels of sophistication [154–158]. It is expected, therefore, that forthcoming developments in iridium-catalyzed HIE will be enabled by deeper exploration of predictive methods of understanding substrate–catalyst compatibility.

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References

1. Ebbing DD, Gammon SD (2005) Atoms, molecules, and ions. In: General chemistry, 8th edn. Houghton Mifflin Company, Boston
2. Atzrodt J, Derdau V, Kerr WJ, Reid M (2018) Deuterium- and tritium-labelled compounds: applications in the life sciences. Angew Chem Int Ed 57:1758–1784. https://doi.org/10.1002/anie.201704146
3. Isin EM, Elmore CS, Nilsson GN et al (2012) Use of radiolabeled compounds in drug metabolism and pharmacokinetic studies. Chem Res Toxicol 25:532–542. https://doi.org/10.1021/tx2005212
4. Filer CN (2010) Direct metal-catalyzed tritiation of organic compounds. J Label Compd Radiopharm 53:739–744. https://doi.org/10.1002/jlcr.1801
5. Nilsson GN, Kerr WJ (2010) The development and use of novel iridium complexes as catalysts for ortho-directed hydrogen isotope exchange reactions. J Label Compd Radiopharm 53:662–667. https://doi.org/10.1002/jlcr.1817
6. Allen PH, Hickey MJ, Kingston LP, Wilkinson DJ (2010) Metal-catalysed isotopic exchange labelling: 30 years of experience in pharmaceutical R&D. J Label Compd Radiopharm 53:731–738. https://doi.org/10.1002/jlcr.1825
7. Hesk D, Lavey CF, McNamara P (2010) Tritium labelling of pharmaceuticals by metal-catalysed exchange methods. J Label Compd Radiopharm 53:722–730. https://doi.org/10.1002/jlcr.1800
8. Lockley WJS, Heys JR (2010) Metal-catalysed hydrogen isotope exchange labelling: a brief overview. J Label Compd Radiopharm 53:635–644. https://doi.org/10.1002/jlcr.1851
9. Lockley WJS, Hesk D (2010) Rhodium- and ruthenium-catalysed hydrogen isotope exchange. J Label Compd Radiopharm 53:704–715. https://doi.org/10.1002/jlcr.1815
10. Lockley WJS, McEwen A, Cooke R (2012) Tritium: a coming of age for drug discovery and development ADME studies. J Label Compd Radiopharm 55:235–257. https://doi.org/10.1002/jlcr.2928
11. Di Giuseppe A, Castarlenas R, Oro LA (2015) Mechanistic considerations on catalytic H/D exchange mediated by organometallic transition metal complexes. C R Chim 18:713–741. https://doi.org/10.1016/j.crci.2015.02.006
12. Atzrodt J, Derdau V, Kerr WJ, Reid M (2018) C−H functionalisation for hydrogen isotope exchange. Angew Chem Int Ed 57:3022–3047. https://doi.org/10.1002/anie.201708903
13. Hesk D (2020) Highlights of C(sp^2)–H hydrogen isotope exchange reactions. J Label Compd Radiopharm 63:247–265. https://doi.org/10.1002/jlcr.3801
14. Junk T, Catallo WJ (1997) Hydrogen isotope exchange reactions involving C–H (D, T) bonds. Chem Soc Rev 26:401–406. https://doi.org/10.1039/CS9972600401
15. Valero M, Derdau V (2020) Highlights of aliphatic C(sp^3)–H hydrogen isotope exchange reactions. J Label Compd Radiopharm 63:266–280. https://doi.org/10.1002/jlcr.3783
16. Saljoughian M (2002) Synthetic tritium labeling: reagents and methodologies. Synthesis (Stuttg) 2002:1781–1801. https://doi.org/10.1055/s-2002-33907
17. Atzrodt J, Derdau V, Fey T, Zimmermann J (2007) The renaissance of H/D exchange. Angew Chem Int Ed 46:7744–7765. https://doi.org/10.1002/anie.200700039
18. Lockley WJS (2007) 30 Years with ortho-directed hydrogen isotope exchange labelling. J Label Compd Radiopharm 50:779–788. https://doi.org/10.1002/jlcr.1421
19. Hesk D, McNamara P (2007) Synthesis of isotopically labelled compounds at Schering-Plough, an historical perspective. J Label Compd Radiopharm 50:875–887. https://doi.org/10.1002/jlcr.1424
20. Heys JR (2007) Organoiridium complexes for hydrogen isotope exchange labeling. J Label Compd Radiopharm 50:770–778. https://doi.org/10.1002/jlcr.1428
21. Parkin G (2007) Applications of deuterium isotope effects for probing aspects of reactions involving oxidative addition and reductive elimination of H–H and C–H bonds. J Label Compd Radiopharm 50:1088–1114. https://doi.org/10.1002/jlcr.1435

22. Lockley WJS (2010) Hydrogen isotope labelling using iridium(I) dionates. J Label Compd Radiopharm 53:668–673. https://doi.org/10.1002/jlcr.1806
23. Gusev DG, Berke H (1996) Hydride fluxionality in Transition metal complexes: an approach to the understanding of mechanistic features and structural diversities. Chem Ber 129:1143–1155. https://doi.org/10.1002/cber.19961291002
24. Elander N, Jones JR, Lu S-Y, Stone-Elander S (2000) Microwave-enhanced radiochemistry. Chem Soc Rev 29:239–249. https://doi.org/10.1039/a901713e
25. Takeuchi R, Kezuka S (2006) Iridium-catalyzed formation of carbon-carbon and carbon-heteroatom bonds. Synthesis (Stuttg) 2006:3349–3366. https://doi.org/10.1055/s-2006-950284
26. Salter R (2010) The development and use of iridium(I) phosphine systems for ortho-directed hydrogen-isotope exchange. J Label Compd Radiopharm 53:645–657. https://doi.org/10.1002/jlcr.1814
27. Milstein D (2010) Discovery of environmentally benign catalytic reactions of alcohols catalyzed by pyridine-based pincer Ru complexes, based on metal–ligand cooperation. Top Catal 53:915–923. https://doi.org/10.1007/s11244-010-9523-7
28. Herbert JM (2010) Deuterium exchange promoted by iridium complexes formed in situ. J Label Compd Radiopharm 53:658–661. https://doi.org/10.1002/jlcr.1790
29. Atzrodt J, Derdau V (2010) Pd- and Pt-catalyzed H/D exchange methods and their application for internal MS standard preparation from a Sanofi-Aventis perspective. J Label Compd Radiopharm 53:674–685. https://doi.org/10.1002/jlcr.1818
30. Wiegerinck P (2011) 17th workshop of the international isotope society – central European division. The synthesis and applications of isotopes and isotopically labelled compounds. J Label Compd Radiopharm 54:278–288. https://doi.org/10.1002/jlcr.1859
31. Choi J, MacArthur AHR, Brookhart M, Goldman AS (2011) Dehydrogenation and related reactions catalyzed by iridium pincer complexes. Chem Rev 111:1761–1779. https://doi.org/10.1021/cr1003503
32. Gregson TJ, Herbert JM, Row EC (2011) Synthetic approaches to regiospecifically mono- and dilabelled arenes. J Label Compd Radiopharm 54:1–32. https://doi.org/10.1002/jlcr.1783
33. Suzuki T (2011) Organic synthesis involving iridium-catalyzed oxidation. Chem Rev 111:1825–1845. https://doi.org/10.1021/cr100378r
34. Aboagye EO, Aigbirhio FI, Allen P et al (2014) Abstracts of the 22nd international isotope society (UK Group) symposium: synthesis and applications of labelled compounds 2013. J Label Compd Radiopharm 57:178–190. https://doi.org/10.1002/jlcr.3173
35. Iglesias M, Oro LA (2018) A leap forward in iridium–NHC catalysis: new horizons and mechanistic insights. Chem Soc Rev 47:2772–2808. https://doi.org/10.1039/C7CS00743D
36. Shevchenko VP, Nagaev IY, Myasoedov NF (2019) Effect of processes occurring in the presence of metal catalysts on the main characteristics of the hydrogen isotope labeled organic compounds obtained. Radiochemistry 61:257–292. https://doi.org/10.1134/S1066362219030019
37. Lin D, Chang W (2000) Chemical derivatization and the selection of deuterated internal standard for quantitative determination – methamphetamine example. J Anal Toxicol 24:275–280. https://doi.org/10.1093/jat/24.4.275
38. Heinekey DM (2007) Transition metal dihydrogen complexes: isotope effects on reactivity and structure. J Label Compd Radiopharm 50:1063–1071. https://doi.org/10.1002/jlcr.1385
39. Lloyd-Jones GC, Muñoz MP (2007) Isotopic labelling in the study of organic and organometallic mechanism and structure: an account. J Label Compd Radiopharm 50:1072–1087. https://doi.org/10.1002/jlcr.1382
40. Quasdorf KW, Huters AD, Lodewyk MW et al (2012) Total synthesis of oxidized welwitindolinones and (−)- N -methylwelwitindolinone C isonitrile. J Am Chem Soc 134:1396–1399. https://doi.org/10.1021/ja210837b

41. Kerr WJ, Knox GJ, Paterson LC (2020) Recent advances in iridium(I) catalysis towards directed hydrogen isotope exchange. J Label Compd Radiopharm 63:281–295. https://doi.org/10.1002/jlcr.3812
42. Valero M, Kruissink T, Blass J et al (2020) C−H functionalization – prediction of selectivity in iridium(I)-catalyzed hydrogen isotope exchange competition reactions. Angew Chem Int Ed 59:5626–5631. https://doi.org/10.1002/anie.201914220
43. Crabtree RH, Felkin H, Morris GE (1977) Cationic iridium diolefin complexes as alkene hydrogenation catalysts and the isolation of some related hydrido complexes. J Organomet Chem 141:205–215. https://doi.org/10.1016/S0022-328X(00)92273-3
44. Zhu Y, Fan Y, Burgess K (2010) Carbene-metal hydrides can be much less acidic than phosphine-metal hydrides: significance in hydrogenations. J Am Chem Soc 132:6249–6253. https://doi.org/10.1021/ja101233g
45. Dobereiner G, Nova A (2011) Iridium-catalyzed hydrogenation of N-heterocyclic compounds under mild conditions by an outer-sphere pathway. J Am Chem Soc 133(19):7547–7562. https://doi.org/10.1021/ja2014983
46. Bennie LS, Fraser CJ, Irvine S et al (2011) Highly active iridium(I) complexes for the selective hydrogenation of carbon-carbon multiple bonds. Chem Commun 47:11653–11655. https://doi.org/10.1039/c1cc14367k
47. Semeniuchenko V, Exner TE, Khilya V, Groth U (2011) Homogeneous hydrogenation of electron-deficient alkenes by iridium complexes. Appl Organomet Chem 25:804–809. https://doi.org/10.1002/aoc.1841
48. Hopmann KH, Bayer A (2011) On the mechanism of iridium-catalyzed asymmetric hydrogenation of imines and alkenes: a theoretical study. Organometallics 30:2483–2497. https://doi.org/10.1021/om1009507
49. Woodmansee DH, Pfaltz A (2011) Asymmetric hydrogenation of alkenes lacking coordinating groups. Chem Commun (Camb) 47:7912–7916. https://doi.org/10.1039/c1cc11430a
50. Maurer F, Huch V, Ullrich A, Kazmaier U (2012) Development of catalysts for the stereoselective hydrogenation of α,β-unsaturated ketones. J Org Chem 77:5139–5143. https://doi.org/10.1021/jo300246c
51. Bert K, Noël T, Kimpe W et al (2012) Chiral imidate-ferrocenylphosphanes: synthesis and application as P,N-ligands in iridium(I)-catalyzed hydrogenation of unfunctionalized and poorly functionalized olefins. Org Biomol Chem 10:8539–8550. https://doi.org/10.1039/c2ob25871d
52. Song S, Zhu S-F, Yang S et al (2012) Enantioselective iridium-catalyzed hydrogenation of β,γ-unsaturated carboxylic acids: an efficient approach to chiral 4-alkyl-4-aryl butanoic acids. Angew Chem Int Ed 51:2708–2711. https://doi.org/10.1002/anie.201107802
53. Song S, Zhu S, Li Y, Zhou Q-L (2013) Iridium-catalyzed enantioselective hydrogenation of α,β-unsaturated carboxylic acids with tetrasubstituted olefins. Org Lett 15:3722–3725. https://doi.org/10.1021/ol401593a
54. Crabtree RH (1979) Iridium compounds in catalysis. Acc Chem Res 12:331
55. Song S, Zhu S-F, Yu Y-B, Zhou Q-L (2013) Carboxy-directed asymmetric hydrogenation of 1,1-diarylethenes and 1,1-dialkylethenes. Angew Chem Int Ed 125:1596–1599. https://doi.org/10.1002/ange.201208606
56. Kolychev EL, Kronig S, Brandhorst K et al (2013) Iridium(I) complexes with anionic N-heterocyclic carbene ligands as catalysts for the hydrogenation of alkenes in nonpolar media. J Am Chem Soc 135:12448–12459. https://doi.org/10.1021/ja406529c
57. Gruber S, Neuburger M, Pfaltz A (2013) Characterization and reactivity studies of dinuclear iridium hydride complexes prepared from iridium catalysts with N, P and C, N ligands under hydrogenation. Organometallics 32:4702–4711. https://doi.org/10.1021/om4007467
58. Horváth H, Kathó Á, Udvardy A et al (2014) New water-soluble iridium(I)–N-heterocyclic carbene–tertiary phosphine mixed-ligand complexes as catalysts of hydrogenation and redox isomerization. Organometallics 33:6330–6340. https://doi.org/10.1021/om5006148

59. Liu Y, Gridnev ID, Zhang W (2014) Mechanism of the asymmetric hydrogenation of exocyclic α,β-unsaturated carbonyl compounds with an iridium/BiphPhox catalyst: NMR and DFT studies. Angew Chem Int Ed 53:1901–1905. https://doi.org/10.1002/anie.201309677
60. Polo V, Al-Saadi AA, Oro LA (2014) Theoretical studies on the mechanism of iridium-catalyzed alkene hydrogenation by the cationic complex $[IrH_2(NCMe)_3(PiPr_3)]^+$. Organometallics 33:5156–5163. https://doi.org/10.1021/om500361e
61. Verendel JJ, Pàmies O, Diéguez M, Andersson PG (2014) Asymmetric hydrogenation of olefins using chiral Crabtree-type catalysts: scope and limitations. Chem Rev 114:2130–2169. https://doi.org/10.1021/cr400037u
62. Lee HM, Jiang T, Stevens ED, Nolan SP (2001) A cationic iridium complex bearing an imidazol-2-ylidene ligand as alkene hydrogenation catalyst. Organometallics 20:1255–1258
63. Vázquez-Serrano LD, Owens BT, Buriak JM (2002) Catalytic olefin hydrogenation using N-heterocyclic carbene–phosphine complexes of iridium. Chem Commun:2518
64. Perry M, Burgess K (2003) Chiral N-heterocyclic carbene-transition metal complexes in asymmetric catalysis. Tetrahedron Asymm 14:951–961
65. Zhu S-F, Xie J-B, Zhang Y-Z et al (2006) Well-defined chiral spiro iridium/phosphine-oxazoline cationic complexes for highly enantioselective hydrogenation of imines at ambient pressure. J Am Chem Soc 128:12886–12891. https://doi.org/10.1021/ja063444p
66. Smidt SP, Pfaltz A, Martínez-Viviente E et al (2003) X-ray and NOE studies on trinuclear iridium hydride phosphino oxazoline (PHOX) complexes. Organometallics 22:1000–1009. https://doi.org/10.1021/om020805a
67. Vazquez-Serrano LD, Owens BT (2006) The search for new hydrogenation catalyst motifs based on N-heterocyclic carbene ligands. Inorg Chim Acta 359:2786
68. Li S, Zhu S-F, Zhang C-M et al (2008) Iridium-catalyzed enantioselective hydrogenation of alpha, beta-unsaturated carboxylic acids. J Am Chem Soc 130:8584–8585. https://doi.org/10.1021/ja802399v
69. Garnett JL, Long MA, McLaren AB, Peterson KB (1973) Iridium(III) salts as homogeneous metal catalysts for hydrogen isotope exchange in organic compounds: a comparison with heterogeneous iridium for the deuteriation of alkylbenzenes. J Chem Soc Chem Commun 749:749. https://doi.org/10.1039/c39730000749
70. Vliegen M, Haspeslagh P, Verluyten W (2012) Alternative efficient tritium labeling of repaglinide. J Label Compd Radiopharm 55:155–157. https://doi.org/10.1002/jlcr.2913
71. Hickey MJ, Kingston LP, Lockley WJS et al (2007) Tritium-labelling via an iridium-based solid-phase catalyst. J Label Compd Radiopharm 50:286–289. https://doi.org/10.1002/jlcr.1233
72. Heys JR, Shu AYL, Senderoff SG, Phillips NM (1993) Deuterium exchange labelling of substituted aromatics using $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$. J Label Compd Radiopharm 33:431–438. https://doi.org/10.1002/jlcr.2580330509
73. Lockley WJS (1985) Regioselective labelling of anilides with deuterium. J Label Compd Radiopharm 22:623–630. https://doi.org/10.1002/jlcr.2580220612
74. Lockley WJS (1984) Regioselective deuterium labelling of aromatic acids, amides and amines using group VIII metal catalysts. J Label Compd Radiopharm 21:45–57. https://doi.org/10.1002/jlcr.2580210105
75. Hesk D, Jones JR, Lockley WJS (1990) Regiospecific tritium labeling of aromatic acids, amides, amines and heterocyclics using homogeneous rhodium trichloride and ruthenium acetylacetonate catalysts. J Label Compd Radiopharm 28:1427–1436. https://doi.org/10.1002/jlcr.2580281211
76. Heys JR, Elmore CS (2009) Meta -substituent effects on organoiridium-catalyzed ortho -hydrogen isotope exchange. J Label Compd Radiopharm 52:189–200. https://doi.org/10.1002/jlcr.1588

77. Hesk D, Das PR, Evans B (1995) Deuteration of acetanilides and other substituted aromatics using [Ir(COD)(Cy_3P)(Py)]PF_6 as catalyst. J Label Compd Radiopharm 36:497–502. https://doi.org/10.1039/C39920000680
78. Ellames GJ, Gibson JS, Herbert JM et al (2004) Ligand effects upon deuterium exchange in arenes mediated by[$Ir(PR_3)_2(cod)]^+BF_4^-$. J Label Compd Radiopharm 47:1–10. https://doi.org/10.1002/jlcr.790
79. Herbert JM (2005) The mediation of aryl ketone deuteration by [$Ir(PPh_3)_3$(cod)]BF_4. J Label Compd Radiopharm 48:317–322. https://doi.org/10.1002/jlcr.925
80. Habraken E, Haspeslagh P, Vliegen M, Noël T (2015) Iridium(I)-catalyzed ortho-directed hydrogen isotope exchange in continuous-flow reactors. J Flow Chem 5:2–5. https://doi.org/10.1556/JFC-D-14-00033
81. Herbert JM, Kohler AD, McNeill AH (2005) An improved bidentate complex of iridium as a catalyst for hydrogen isotope exchange. J Label Compd Radiopharm 48:285–294. https://doi.org/10.1002/jlcr.921
82. Shu AYL, Chen W, Heys JR (1996) Organoiridium catalyzed hydrogen isotope exchange: ligand effects on catalyst activity and regioselectivity. J Organomet Chem 524:87–93. https://doi.org/10.1016/S0022-328X(96)06413-3
83. Ellames GJ, Gibson JS, Herbert JM et al (2001) Deuterium exchange mediated by an iridium–phosphine complex formed in situ. Tetrahedron Lett 42:6413–6416. https://doi.org/10.1016/S0040-4039(01)01266-7
84. Simonsson R, Stenhagen G, Ericsson C, Elmore CS (2013) Synthesis of ximelagatran, melagatran, hydroxymelagatran, and ethylmelagatran in H-3 labeled form. J Label Compd Radiopharm 56:334–337. https://doi.org/10.1002/jlcr.3028
85. Shu AYL, Heys JR (2000) Direct, efficient and selective tritiations of paclitaxel and photoaffinity taxoids. Tetrahedron Lett 41:9015–9019. https://doi.org/10.1016/S0040-4039(00)01652-X
86. Cross P, Herbert J, Kerr W et al (2015) Isotopic labelling of functionalised arenes catalysed by iridium(I) species of the [(cod)Ir(NHC)(py)]PF_6 complex class. Synlett 27:111–115. https://doi.org/10.1055/s-0035-1560518
87. Bushby N, Killick DA (2007) Hydrogen isotope exchange at alkyl positions using Crabtree's catalyst and its application to the tritiation of methapyrilene. J Label Compd Radiopharm 50:519–520. https://doi.org/10.1002/jlcr.1236
88. Ellames GJ, Gibson JS, Herbert JM, McNeill AH (2001) The scope and limitations of deuteration mediated by Crabtree's catalyst. Tetrahedron 57:9487–9497. https://doi.org/10.1016/S0040-4020(01)00945-0
89. Valsborg JS, Sørensen L, Foged C (2001) Organoiridium catalysed hydrogen isotope exchange of benzamide derivatives. J Label Compd Radiopharm 44:209–214. https://doi.org/10.1002/jlcr.446
90. Kingston LP, Lockley WJS, Mather AN et al (2000) Parallel chemistry investigations of ortho-directed hydrogen isotope exchange between substituted aromatics and isotopic water: novel catalysis by cyclooctadienyliridium(I)pentan-1,3-dionates. Tetrahedron Lett 41:2705–2708. https://doi.org/10.1016/S0040-4039(00)00244-6
91. McAuley B, Hickey MJ, Kingston LP et al (2003) Convenient and efficient deuteration of functionalized aromatics with deuterium oxide: catalysis by cycloocta-1,5-dienyliridium (I) 1,3-dionates. J Label Compd Radiopharm 46:1191–1204. https://doi.org/10.1002/jlcr.780
92. Jones JR, Lockley WJS, Lu S-Y, Thompson SP (2001) Microwave-enhanced aromatic dehalogenation studies: a rapid deuterium-labelling procedure. Tetrahedron Lett 42:331–332. https://doi.org/10.1016/S0040-4039(00)01941-9
93. Gruber S, Neuburger M, Pfaltz A (2013) Characterization and reactivity studies of dinuclear iridium hydride complexes prepared from iridium catalysts with N,P and C,N ligands under hydrogenation conditions. Organometallics 32:4702–4711. https://doi.org/10.1021/om4007467

94. Vazquez-Serrano LD, Owens BT, Buriak JM (2006) The search for new hydrogenation catalyst motifs based on N-heterocyclic carbene ligands. Inorg Chim Acta 359:2786–2797. https://doi.org/10.1016/j.ica.2005.10.049
95. Powell ME, Elmore CS, Dorff PN, Heys JR (2007) Investigation of isotopic exchange reactions using N-heterocyclic iridium (I) complexes. J Label Compd Radiopharm 50:523–525. https://doi.org/10.1002/jlcr.1239
96. Cross PWC, Ellames GJ, Gibson JS et al (2003) Conditions for deuterium exchange mediated by iridium complexes formed in situ. Tetrahedron 59:3349–3358. https://doi.org/10.1016/S0040-4020(03)00422-8
97. Brown JA, Irvine S, Kennedy AR et al (2008) Highly active iridium(i) complexes for catalytic hydrogen isotope exchange. Chem Commun 1115. https://doi.org/10.1039/b715938b
98. Brown JA, Cochrane AR, Irvine S et al (2014) The synthesis of highly active iridium (I) complexes and their application in catalytic hydrogen isotope exchange. Adv Synth Catal 356:3551–3562. https://doi.org/10.1002/adsc.201400730
99. Kerr WJ, Mudd RJ, Paterson LC, Brown JA (2014) Iridium(I)-catalyzed regioselective C–H activation and hydrogen-isotope exchange of non-aromatic unsaturated functionality. Chem A Eur J 20:14604–14607. https://doi.org/10.1002/chem.201405114
100. Cochrane ARX, Idziak C, Kerr WJ et al (2014) Practically convenient and industrially-aligned methods for iridium-catalysed hydrogen isotope exchange processes. Org Biomol Chem 12:3598–3603. https://doi.org/10.1039/C4OB00465E
101. Simmons EM, Hartwig JF (2012) On the interpretation of deuterium kinetic isotope effects in C-H bond functionalizations by transition-metal complexes. Angew Chem Int Ed 51:3066–3072. https://doi.org/10.1002/anie.201107334
102. Kerr WJ, Reid M, Tuttle T (2015) Iridium-catalyzed C–H activation and deuteration of primary sulfonamides: an experimental and computational study. ACS Catal 5:402–410. https://doi.org/10.1021/cs5015755
103. Devlin J, Kerr W, Lindsay D et al (2015) Iridium-catalysed ortho-directed deuterium labelling of aromatic esters – an experimental and theoretical study on directing group Chemoselectivity. Molecules 20:11676–11698. https://doi.org/10.3390/molecules200711676
104. Kennedy AR, Kerr WJ, Moir R, Reid M (2014) Anion effects to deliver enhanced iridium catalysts for hydrogen isotope exchange processes. Org Biomol Chem 12:7927–7931. https://doi.org/10.1039/C4OB01570C
105. Queen AE, Hesk D, Lindsay DM et al (2020) Synthesis of [^{3}H] and [^{14}C]genipin. J Label Compd Radiopharm 63:196–202. https://doi.org/10.1002/jlcr.3832
106. Kerr WJ, Lindsay DM, Reid M et al (2016) Iridium-catalysed ortho-H/D and -H/T exchange under basic conditions: C–H activation of unprotected tetrazoles. Chem Commun 52:6669–6672. https://doi.org/10.1039/C6CC02137A
107. Atzrodt J, Derdau V, Kerr WJ et al (2015) Expanded applicability of iridium(I) NHC/phosphine catalysts in hydrogen isotope exchange processes with pharmaceutically-relevant heterocycles. Tetrahedron 71:1924–1929. https://doi.org/10.1016/j.tet.2015.02.029
108. Kerr WJ, Lindsay DM, Owens PK et al (2017) Site-selective deuteration of N -heterocycles via iridium-catalyzed hydrogen isotope exchange. ACS Catal 7:7182–7186. https://doi.org/10.1021/acscatal.7b02682
109. Kerr WJ, Mudd RJ, Owens PK et al (2016) Hydrogen isotope exchange with highly active iridium(I) NHC/phosphine complexes: a comparative counterion study. J Label Compd Radiopharm 59:601–603. https://doi.org/10.1002/jlcr.3427
110. Koneczny M, Phong Ho L, Nasr A et al (2020) Iridium(I) complexes with anionic N-heterocyclic carbene ligands as catalysts for H/D exchange in nonpolar media. Adv Synth Catal. https://doi.org/10.1002/adsc.202000438
111. Parmentier M, Hartung T, Pfaltz A, Muri D (2014) Iridium-catalyzed H/D exchange: ligand complexes with improved efficiency and scope. Chem A Eur J 20:11496–11504. https://doi.org/10.1002/chem.201402078

112. Valero M, Burhop A, Jess K et al (2018) Evaluation of a P,N-ligated iridium(I) catalyst in hydrogen isotope exchange reactions of aryl and heteroaryl compounds. J Label Compd Radiopharm 61:380–385. https://doi.org/10.1002/jlcr.3595
113. Jess K, Derdau V, Weck R et al (2017) Hydrogen isotope exchange with iridium(I) complexes supported by phosphine-imidazolin-2-imine P,N ligands. Adv Synth Catal 359:629–638. https://doi.org/10.1002/adsc.201601291
114. Klei SR, Tilley TD, Bergman RG (2002) Iridium(III) and rhodium(III) complexes bearing chelating cyclopentadienyl−phosphine ligands as C−H activation catalysts for the deuteration of hydrocarbons in D 2 O. Organometallics 21:4905–4911. https://doi.org/10.1021/om020375o
115. Kloek SM, Goldberg KI (2007) Competitive C−H bond activation and β-hydride elimination at platinum(II). J Am Chem Soc 129:3460–3461. https://doi.org/10.1021/ja0669629
116. Polukeev AV, Marcos R, Ahlquist MSG, Wendt OF (2016) Iridium hydride complexes with cyclohexyl-based pincer ligands: fluxionality and deuterium exchange. Organometallics 35:2600–2608. https://doi.org/10.1021/acs.organomet.6b00324
117. Bhattacharjee R, Nijamudheen A, Karmakar S, Datta A (2016) Strain control: reversible H 2 activation and H 2 /D 2 exchange in Pt complexes. Inorg Chem 55:3023–3029. https://doi.org/10.1021/acs.inorgchem.5b02904
118. Butschke B, Schlangen M, Schröder D, Schwarz H (2008) Competitive intramolecular aryl- and alkyl-C–H bond activation and ligand evaporation from gaseous bisimino complexes [Pt(L)(CH_3)((CH_3)$_2$S)]$^+$ (L=C_6H_5N=C(CH_3)–C(CH_3)=NC_6H_5). Helv Chim Acta 91:1902–1915. https://doi.org/10.1002/hlca.200890204
119. Crosby SH, Clarkson GJ, Rourke JP (2009) A delicate balance between sp^2 and sp^3 C−H bond activation: a Pt(II) complex with a dual agostic interaction. J Am Chem Soc 131:14142–14143. https://doi.org/10.1021/ja905046n
120. Butschke B, Ghassemi Tabrizi S, Schwarz H (2010) Ion-molecule reactions of "Rollover" cyclometalated [Pt(bipy−H)]$^+$ (bipy=2,2′-bipyridine) with dimethyl ether in comparison with dimethyl sulfide: an experimental/computational study. Chem A Eur J 16:3962–3969. https://doi.org/10.1002/chem.200902742
121. Campos J, Espada MF, López-Serrano J, Carmona E (2013) Cyclometalated iridium complexes of Bis(aryl) phosphine ligands: catalytic C–H/C–D exchanges and C–C coupling reactions. Inorg Chem 52:6694–6704. https://doi.org/10.1021/ic400759r
122. Grellier M, Mason SA, Albinati A et al (2013) Probing highly selective H/D exchange processes with a ruthenium complex through neutron diffraction and multinuclear NMR studies. Inorg Chem 52:7329–7337. https://doi.org/10.1021/ic302307m
123. Goforth SK, Walroth RC, McElwee-White L (2013) Evaluation of multisite polypyridyl ligands as platforms for the synthesis of Rh/Zn, Rh/Pd, and Rh/Pt heterometallic complexes. Inorg Chem 52:5692–5701. https://doi.org/10.1021/ic301810y
124. Benedetti M, Barone CR, Girelli CR et al (2014) H/D exchange at sp3 carbons in the coordination sphere of platinum(III). Dalton Trans 43:3669. https://doi.org/10.1039/c3dt53216j
125. Rivada-Wheelaghan O, Roselló-Merino M, Ortuño MA et al (2014) Reactivity of coordinatively unsaturated bis(N-heterocyclic carbene) Pt(II) complexes toward H2. Crystal structure of a 14-electron Pt(II) hydride complex. Inorg Chem 53:4257–4268. https://doi.org/10.1021/ic500705t
126. Kerr WJ, Mudd RJ, Reid M et al (2018) Iridium-catalyzed Csp^3–H activation for mild and selective hydrogen isotope exchange. ACS Catal 8:10895–10900. https://doi.org/10.1021/acscatal.8b03565
127. Valero M, Weck R, Güssregen S et al (2018) Highly selective directed iridium-catalyzed hydrogen isotope exchange reactions of aliphatic amides. Angew Chem Int Ed 57:8159–8163. https://doi.org/10.1002/anie.201804010

128. Loh YY, Nagao K, Hoover AJ et al (2017) Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. Science 358:1182–1187. https://doi.org/10.1126/science.aap9674
129. Golden JT, Andersen RA, Bergman RG (2001) Exceptionally low-temperature carbon−hydrogen/carbon−deuterium exchange reactions of organic and organometallic compounds catalyzed by the $Cp^*(PMe_3)IrH(ClCH_2Cl)^+$ cation. J Am Chem Soc 123:5837–5838. https://doi.org/10.1021/ja0155480
130. Klei SR, Golden JT, Burger P, Bergman RG (2002) Cationic Ir(III) alkyl and hydride complexes: stoichiometric and catalytic C–H activation by $Cp*(PMe_3)Ir(R)(X)$ in homogeneous solution. J Mol Catal A Chem 189:79–94. https://doi.org/10.1016/S1381-1169(02)00192-9
131. Skaddan MB, Yung CM, Bergman RG (2004) Stoichiometric and catalytic deuterium and tritium labeling of "Unactivated" organic substrates with cationic Ir(III) complexes. Org Lett 6:11–13. https://doi.org/10.1021/ol0359923
132. Corberán R, Sanaú M, Peris E (2006) Highly stable Cp*−Ir(III) complexes with N -heterocyclic carbene ligands as C−H activation catalysts for the deuteration of organic molecules. J Am Chem Soc 128:3974–3979. https://doi.org/10.1021/ja058253l
133. Maishal TK, Alauzun J, Basset JM et al (2008) A tailored organometallic-inorganic hybrid mesostructured material: a route to a well-defined, active, and reusable heterogeneous iridium-NHC catalyst for H/D exchange. Angew Chem Int Ed 47:8654–8656. https://doi.org/10.1002/anie.200802956
134. Feng Y, Jiang B, Boyle PA, Ison EA (2010) Effect of ancillary ligands and solvents on H/D exchange reactions catalyzed by Cp*Ir complexes. Organometallics 29:2857–2867. https://doi.org/10.1021/om100018x
135. Lehman MC, Gary JB, Boyle PD et al (2013) Effect of solvent and ancillary ligands on the catalytic H/D exchange reactivity of Cp IrIII(L) complexes. ACS Catal 3:2304–2310. https://doi.org/10.1021/cs400420n
136. Romanenko I, Norsic S, Veyre L et al (2016) Active and recyclable polyethylene-supported iridium-(N- heterocyclic carbene) catalyst for hydrogen/deuterium exchange reactions. Adv Synth Catal 358:2317–2323. https://doi.org/10.1002/adsc.201600045
137. Marek A, Pedersen MHF, Vogensen SB et al (2016) The labeling of unsaturated γ-hydroxybutyric acid by heavy isotopes of hydrogen: iridium complex-mediated H/D exchange by C⍰H bond activation vs reduction by boro-deuterides/tritides. J Label Compd Radiopharm 59:476–483. https://doi.org/10.1002/jlcr.3432
138. Zhou J, Hartwig JF (2008) Iridium-catalyzed H/D exchange at vinyl groups without olefin isomerization. Angew Chem Int Ed 47:5783–5787. https://doi.org/10.1002/anie.200801992
139. Hatano M, Nishimura T, Yorimitsu H (2016) Selective H/D exchange at vinyl and methylidene groups with D 2 O catalyzed by an iridium complex. Org Lett 18:3674–3677. https://doi.org/10.1021/acs.orglett.6b01721
140. Spletstoser JT, White JM, Georg GI (2004) One-step facile synthesis of deuterium labeled aldehydes from tertiary amides using $Cp_2Zr(D)Cl$. Tetrahedron Lett 45:2787–2789. https://doi.org/10.1016/j.tetlet.2004.02.030
141. Ariza X, Asins G, Garcia J et al (2010) Preparation of α-labeled aldehydes by base-catalyzed exchange reactions. J Label Compd Radiopharm 53:556–558. https://doi.org/10.1002/jlcr.1759
142. Chappelle MR, Hawes CR (2010) The use of metal-catalysed hydrogen isotope exchange in the contract supply of tritiated compounds. J Label Compd Radiopharm 53:745–751. https://doi.org/10.1002/jlcr.1821
143. Barnett DW, Refaei MS, Curley RW (2013) Chirally deuterated benzyl chlorides from benzyl alcohols via hexachloroacetone/polymer-supported triphenylphosphine: synthesis of protected (2 S , 3 S)-[3-^{2}H, ^{15}N]-tyrosine. J Label Compd Radiopharm 56:6–11. https://doi.org/10.1002/jlcr.3004

144. Korsager S, Taaning RH, Lindhardt AT, Skrydstrup T (2013) Reductive carbonylation of aryl halides employing a two-chamber reactor: a protocol for the synthesis of aryl aldehydes including 13 C- and D-isotope labeling. J Org Chem 78:6112–6120. https://doi.org/10.1021/jo400741t
145. Boga SB, Alhassan AB, Hesk D (2014) Efficient synthesis of ^{2}H & ^{13}C labeled benzaldehydes via regio-selective formylation. Tetrahedron Lett 55:4442–4444. https://doi.org/10.1016/j.tetlet.2014.06.053
146. Kerr WJ, Reid M, Tuttle T (2017) Iridium-catalyzed formyl-selective deuteration of aldehydes. Angew Chem Int Ed 56:7808–7812. https://doi.org/10.1002/anie.201702997
147. Fortman GC, Jacobsen H, Cavallo L, Nolan SP (2011) Catalytic deuteration of silanes mediated by N-heterocyclic carbene-Ir(III) complexes. Chem Commun 47:9723. https://doi.org/10.1039/c1cc13492b
148. Iluc VM, Fedorov A, Grubbs RH (2012) H/D exchange processes catalyzed by an iridium-pincer complex. Organometallics 31:39–41. https://doi.org/10.1021/om201049p
149. Nelson DJ, Egbert JD, Nolan SP (2013) Deuteration of boranes: catalysed versus non-catalysed processes. Dalton Trans 42:4105. https://doi.org/10.1039/c3dt33045a
150. Garnett JL, Hodges RJ (1967) Homogeneous metal-catalyzed exchange of aromatic compounds. Isotopic hydrogen labeling procedure. J Am Chem Soc 89:4546–4547. https://doi.org/10.1021/ja00993a067
151. Lockley WJS (1982) Regioselective deuteration of aromatic and α,β-unsaturated carboxylic acids via rhodium(III) chloride catalysed exchange with deuterium oxide. Tetrahedron Lett 23:3819–3822. https://doi.org/10.1016/S0040-4039(00)87716-3
152. Anderson GK, Saum SE, Cross RJ, Morris SA (1983) Homogeneous catalysts of hydrogen-deuterium exchange reactions involving cyclopentadienyl complexes of palladium and platinum. Organometallics 2:780–782. https://doi.org/10.1021/om00078a021
153. Heys R (1992) Investigation of $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$ as a catalyst of hydrogen isotope exchange of substrates in solution. J Chem Soc Chem Commun 680. https://doi.org/10.1039/c39920000680
154. Maldonado AG, Rothenberg G (2010) Predictive modeling in homogeneous catalysis: a tutorial. Chem Soc Rev 39:1891–1902. https://doi.org/10.1039/b921393g
155. Houk KN, Cheong PH-Y (2008) Computational prediction of small-molecule catalysts. Nature 455:309–313. https://doi.org/10.1038/nature07368
156. Peng Q, Duarte F, Paton RS (2016) Computing organic stereoselectivity – from concepts to quantitative calculations and predictions. Chem Soc Rev 45:6093–6107. https://doi.org/10.1039/c6cs00573j
157. Sperger T, Sanhueza IA, Schoenebeck F (2016) Computation and experiment: a powerful combination to understand and predict reactivities. Acc Chem Res 49:1311–1319. https://doi.org/10.1021/acs.accounts.6b00068
158. Balcells D, Clot E, Eisenstein O et al (2016) Deciphering selectivity in organic reactions: a multifaceted problem. Acc Chem Res 49:1070–1078. https://doi.org/10.1021/acs.accounts.6b00099