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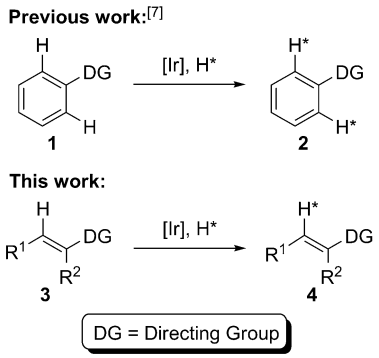
Iridium(I)-Catalyzed Regioselective C–H Activation and Hydrogen-Isotope Exchange of Non-aromatic Unsaturated Functionality

William J. Kerr,*[a] Richard J. Mudd,[a] Laura C. Paterson,[a] and Jack A. Brown[b]

Abstract: Isotopic labelling is a key technology of increasing importance for the investigation of new C–H activation and functionalization techniques, as well as in the construction of labelled molecules for use within both organic synthesis and drug discovery. Herein, we report for the first time selective iridium-catalyzed C–H activation and hydrogen-isotope exchange at the β-position of unsaturated organic compounds. The use of our highly active [Ir(cod)(IMes)(PPh_3)][PF_6] (cod = 1,5-cyclooctadiene) catalyst, under mild reaction conditions, allows the regioselective β-activation and labelling of a range of α,β-unsaturated compounds with differing steric and electronic properties. This new process delivers high levels of isotope incorporation over short reaction times by using low levels of catalyst loading.

The functionalization of aromatic C–H bonds by transition-metal-mediated C–H activation has been widely developed in the past several decades, delivering key compounds for use in an array of chemical domains.[1] In contrast, regioselective activation of olefinic C–H bonds has received much less attention, with the majority of studies to date focused upon the application of homogeneous organometallic complexes of ruthenium[2] and rhodium.[3] Indeed, very little knowledge exists surrounding the use of iridium-based complexes in this area,[4] despite their widespread activity in aromatic C–H bond activation.[1a,b,h,k,o] In relation to this, transition-metal-mediated hydrogen-isotope exchange (HIE) is a technique of increasing importance, often being used as a first step in creating new C–H activation methods and as a means to generate deuterated feed stocks for mechanistic studies.[5] Furthermore and importantly for medicinal chemists, such direct and flexible labelling processes now represent a central tool for fast and efficient incorporation of a tracer into drug candidates, enabling various metabolic, stability, and toxicity studies to be performed earlier in the drug-design process.[5a,6] Recent studies from our own laboratory[7] have disclosed a series of highly active iridium(I) catalysts of the type [Ir(cod)(IMes)(PR_3)]X (cod = 1,5-cyclooctadiene) capable of delivering heavy isotopes of hydrogen (deuterium and tritium) to aromatic molecules through an *ortho*-directed C–H insertion process under mild conditions (Scheme 1). Indeed, our developed methods have



Scheme 1. Previous and proposed labelling procedure.

enabled access to a broad spectrum of labelled new chemical entities of direct relevance to pharmaceutical partners and have provided a platform for on-going C–H activation endeavours. Expanding on our initial developments, we now report the first example of selective C–H activation and hydrogen-isotope exchange at the β-position of a range of α,β-unsaturated moieties, extending the applicability of our emerging catalyst series and addressing the requirement for mild and selective means of accessing labelled olefinic substrates.[8]

Our initial studies involved the application of conditions developed in our laboratory for the isotopic labelling of aromatic substrates.[7a] As such, (*E*)-4-phenylbutenone (**6a**) was treated with just 0.5 mol% of our iridium catalyst series (**5a–c**) in dichloromethane and exposed to 1 atm of D_2 gas (Table 1, entries 1–3).[9] As was expected, and based on the differing steric properties of our series of catalysts, varying results were obtained. Catalyst **5a**, bearing the smallest (PMe_2Ph) phosphine ligand, produced solely the reduced product **8a** with quantitative conversion (entry 1), with this result being somewhat expected due to our recent disclosure that such iridium complexes can act as extremely efficient hydrogenation catalysts.[10] Catalyst **5b**, containing the bulky yet flexible tribenzylphosphine ligand, showed high levels of deuterium incorporation, albeit with **8a** remaining as the major product (entry 2). Pleas-

[a] *Prof. Dr. W. J. Kerr, R. J. Mudd, Dr. L. C. Paterson*
Department of Pure and Applied Chemistry, WestCHEM
University of Strathclyde, 295 Cathedral Street
Glasgow, Scotland, G1 1XL (UK)
E-mail: w.kerr@strath.ac.uk

[b] *Dr. J. A. Brown*
GlaxoSmithKline R&D, Medicines Research Centre
Gunnels Wood Road, Stevenage, England, SG1 2NY (UK)

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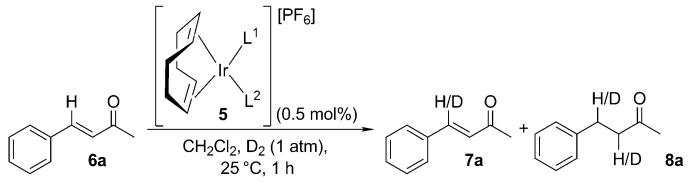
Table 1. Screening of catalysts **5a–d** for HIE of **6a**.[a]



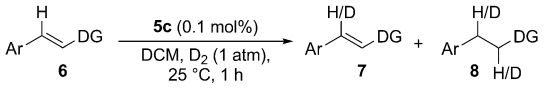
Entry	L^1, L^2	Complex	%D Incorporation in **7a**[b]	**7a**/**8a**[b]
1	IMes, $P(Me)_2Ph$	**5a**	0	0:100
2	IMes, PBn_3	**5b**	86	6:94
3	IMes, PPh_3	**5c**	95	77:23
4	Py, PCy_3	**5d**	96	46:54
5[c]	IMes, PPh_3	**5c**	88	94:6
6[d]	IMes, PPh_3	**5c**	78	99:1

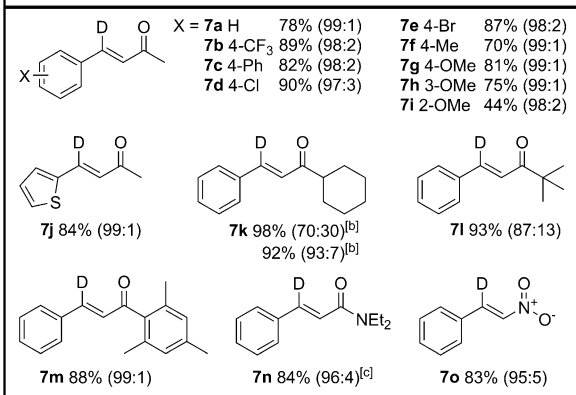
[a] Each entry displays the average of two reaction runs. [b] Calculated from the NMR spectra of crude reaction material. [c] **6a** (0.4 mmol), dichloromethane (8 mL), **5c** (0.1 mol%). [d] **6a** (0.4 mmol), dichloromethane (1 mL), **5c** (0.1 mol%).

ingly, a switch in selectivity was observed when moving to the most rigid of our catalyst range (**5c**), whereby the high level of deuterium incorporation was maintained and appreciable selectivity for the desired labelled compound was achieved (entry 3). Until recently, Crabtree's catalyst, **5d**,[11] was the most widely adopted species in the domain of iridium-catalyzed, *ortho*-directed HIE in aromatic compounds, despite the regular necessity for stoichiometric loadings.[12] In this study, Crabtree's catalyst (**5d**) displayed a similar level of deuterium incorporation to **5c**, however, with virtually no selectivity for HIE versus reduction (entry 4). On further optimization of the reaction conditions by using catalyst **5c**, we were delighted to observe that a reduction in catalyst loading to 0.1 mol% resulted in an excellent selectivity of 94:6 for the desired β-labelled enone product, **7a**, whilst maintaining high D incorporation levels (entry 5). Furthermore, increasing the concentration of the reaction delivered **7a** almost exclusively with 78% D labelling (entry 6).

With conditions in hand that produce appreciable selectivity for β-C–H activation and hydrogen-isotope exchange, we looked to further explore the capabilities of our developed system by extending the substrate scope (Table 2). In this regard, our initial focus was directed towards the manipulation of the chemical properties of the arene component present in **6**. We were pleased to find that substituents of varying electronic properties were tolerated well at the 4-position of the arene substrate, with high levels of deuterium incorporation and very good selectivities being achieved by using just 0.1 mol% catalyst loading in all cases (**7b–g**). Furthermore, steric encumbrance adjacent to the labelling position was investigated as in **6h** and **i**. Encouragingly, *meta*-substituted compound **6h** did not hinder appreciably the HIE process; however, a drop in deuterium incorporation was observed upon labelling *ortho*-substituted analogue **6i**, presumably due to an unfavourable steric interaction between the catalyst and the *ortho*-substituted aryl ring, affecting the key C–H activation process. On the other hand, the pharmaceutically relevant thiophene derivative **6j** displayed high incorporation and excellent selectivity. Our studies continued with investigations into the nature of the directing group. Notably, good incorporation levels were observed in compounds **7k–m** albeit with slightly diminished selectivity between HIE and reduction for **7k** and **l**. Presumably, this can be attributed to the nature of the intermediate formed upon directing group coordination and the reversibility of this process; as well as facilitating faster decomplexation, we envisage that the larger substrates will adopt a less planar conformation upon binding to the catalyst, potentially better suited towards the reduction pathway. Having stated this, selectivity was restored in **7k** following employment of an even lower level of catalyst loading (0.025 mol%), highlighting the level of activity presented by catalyst species **5c** for this labelling process. Finally, we were also pleased to discover that alternative directing groups such as amide or nitro functionalities

Table 2. Substrate scope with Ir catalyst **5c**.[a]

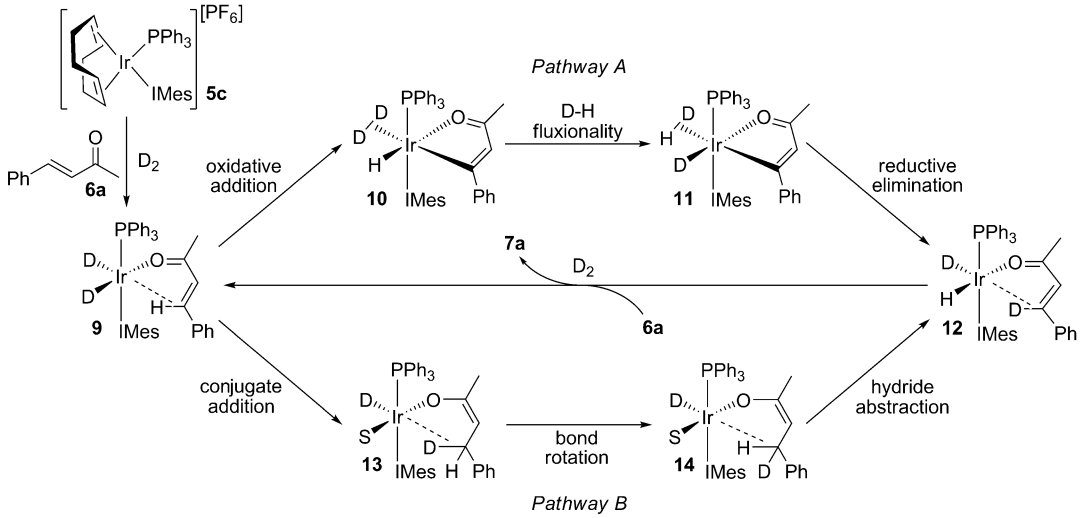




[a] Each entry displays the average of two reaction runs and the results presented as %D incorporation in **7** with the selectivity of **7**:**8** shown in parentheses. [b] 0.025 mol% of **5c** was employed. [c] 0.25 mol% of **5c** was employed.

facilitated the regioselective C–H activation and exchange process with appreciable efficiency (**6n–o**). Indeed, substrate **6o** represents, to the best of our knowledge, the first example of a nitro moiety directing such a β-C–H activation.

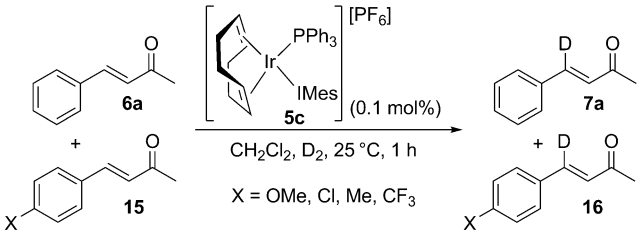
In relation to the reaction mechanism and based on Heys and co-workers original proposal in 1996,[13] we have recently disclosed experimental and computational studies which have led to escalated insight into the possible sequence of events that our "*ortho*"-directed HIE process follows.[7d] In this regard, a similar process could be envisaged for the olefinic substrates described within this contribution (pathway A in Scheme 2). Following catalyst activation with D_2, coordination of the substrate, for example, **6a**, gives intermediate **9**, in which the β-H atom is associated with the iridium centre by an agostic inter-



Scheme 2. Possible HIE mechanistic pathways; all intermediates within this process are assumed to be cationic, with the counteranions being omitted for clarity.

action, consistent with our related *ortho* aryl labelling mechanistic studies.[7d] Subsequent oxidative addition gives **10**, followed by hydride fluxionality bringing isotopic hydrogen *cis* to the activated complex as in **11**. Finally, reductive elimination and decomplexation releases the labelled product **7a** and regenerates **9** under the deuterium atmosphere. In contrast, one could also consider that the β-selective labelling process proceeds in the manner described by pathway B in Scheme 2. In this case, following the same catalyst-activation sequence to generate **9**, the intramolecular delivery of a deuteride in a conjugate manner would provide enolate-type intermediate **13** (in which S = solvent). Following bond rotation to give **14**, the cycle is completed with hydride abstraction and decomplexation.

To probe these mechanistic proposals, we conducted a series of additional experimental studies. Firstly, Hammett studies were employed, whereby competition reactions were run for the HIE of substrate **6a** versus a selected set of four *p*-substituted enone substrates (**15**, Scheme 3). By using ^{1}H NMR analysis and construction of the Hammett plot, a relatively small negative slope of −0.64 was revealed, indicating that whilst electron-donating functionality facilitates an increases in HIE, such influence does not occur during the rate-determining step of the reaction (see the Supporting Information for full details).[14] This electronic effect can be envisaged as being a result of the increased binding ability of the more electron-rich substrates with the iridium catalyst; this effect would be observed within both pathways A and B. Having stated this, the magnitude of the Hammett ρ value indicates that no significant build-up of charge is evident during the rate-limiting step of the overall process and, as such, this lends some support to mechanistic pathway A, that is, via insertion intermediate **10** as opposed to the enolate-type structure **13** proposed in pathway B. Further, it is important to note that both the (*Z*)-isomer of substrate **6a** and cyclohexenone fail to label under the developed protocols; we believe that both of these latter substrates would be unable to undergo the insertion process proposed within mechanistic pathway A (see the Supporting Information for full experimental details).



Scheme 3. Competition studies for the HIE of **6a** versus *p*-substituted enone substrates.

In relation to these preliminary mechanistic investigations, further analysis attempted to strengthen our proposals by measuring the kinetic isotope effect (KIE) within our developed HIE process. Monitoring the rate of our standard reaction, as well as the reverse process (employing H_2 in place of D_2 with fully deuterated **7a**), revealed a primary KIE value of 3.8, thus strongly indicating that C–H activation is involved in the rate-limiting step, and in line with pathway A. Indeed, if pathway B is favoured, one would expect an inverse KIE value if conjugate addition was rate determining, or a much larger KIE value ($\geq$5) for hydride abstraction.[15] Notably, the stoichiometric isolation of intermediates similar to **10** by Crabtree further supports this proposed pathway A.[4c]

In summary, we have established the first β-selective iridium-catalyzed C–H activation and hydrogen-isotope-exchange process by using our active iridium(I) catalyst, [Ir(cod)(IMes)-(PPh$_3$)]PF$_6$. Under practically accessible reaction conditions and by employing low levels of catalyst loading, very good levels of deuterium incorporation have been obtained with appreciable selectivity over the potentially competing reduction process across a series of α,β-unsaturated substrates. Additional

experimental studies have enhanced our insight into the possible mechanistic pathway being followed, whereby it is believed that a C–H activation process is the rate-limiting step of the overall transformation. Our work continues within this area to fully elucidate the mechanism of these emerging transformations and seeks to further understand the origins of our observed selectivity, with the overall aim of applying our developing techniques to a wider array of C–H activation processes.

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Keywords: C–H activation · deuterium · hydrogen isotope exchange · iridium · unsaturated compounds

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