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Iridium-Catalyzed C-H Activation and Deuteration of Primary Sulfonamides: an Experimental and Computational Study

William J. Kerr,* Marc Reid, and Tell Tuttle*

* Department of Pure & Applied Chemistry, WestCHEM, University of Strathclyde, Glasgow G1 1XL, Scotland, UK.

KEYWORDS: iridium, C-H activation, ortho-deuteration, hydrogen-isotope exchange, sulfonamide.

ABSTRACT: Iridium-catalyzed C-H activation and ortho-hydrogen isotope exchange is an important technology for allowing access to labelled organic substrates and aromatic drug molecules, and for the development of further C-H activation processes in organic synthesis. The use of [(COD)Ir(NHC)Cl] complexes (NHC = N-heterocyclic carbene) in the ortho-deuteration of primary sulfonamides under ambient conditions is reported. This methodology has been applied to the deuteration of a series of substrates, including the COX-2 inhibitors Celecoxib and Mavacoxib, demonstrating selective complexation of the primary sulfonamide over a competing pyrazole moiety. The observed chemoselectivity can be reversed by employing more encumbered catalyst derivatives of the type [(COD)Ir(NHC)(PPh$_3$)]PF$_6$. Computational studies have revealed that, although C-H activation is rate-determining, substrate complexation or subsequent C-H activation can be product-determining depending on the catalyst employed.

INTRODUCTION

Within the realm of organic synthesis, ortho-directed aromatic C-H activation remains one of the most active current areas of research. Indeed, since the pioneering work of Murai and co-workers some twenty years ago, transition metal-catalyzed approaches to this methodology have evolved to become predictable and indispensable tools for synthetic chemists.

One particularly industry-facing facet of C-H functionalization is manifested in iridium-catalyzed hydrogen isotope-exchange (HIE, Scheme 1). To alter the properties of a drug candidate, the medicinal chemist must first have a flexible technique with which to study them. Consequently, isotopic labelling with heavy hydrogen isotopes (deuterium, D) is widely used as a means to monitor the biological fate of a potential drug molecule. Since the pioneering work of Heys in 1992, a range of iridium catalysts have been reported to efficiently deliver the required hydrogen isotope ortho to various functional handles, as well as in the absence of any directing group. In relation to this, work within our own laboratory has focused on the development of iridium(I) systems bearing mixed phosphine/N-heterocyclic carbene (NHC) ligand spheres which, owing to their steric encumbrance and electron-donating power, rank among the most active catalysts commonly used in the field.

Regardless of the many accomplishments of iridium-based HIE, a key challenge for which no general solution has been presented is C-H activation adjacent to primary sulfonamides. Related to this, the sulfa drugs derived from sulfonamides represent a significant milestone in pharmaceutical science, and, since their emergence in 1935, have been developed to produce various antibiotics, diuretics, hypoglycemic agents, and anti-hypertensive treatments. To our knowledge, primary sulfonamide substrates remain largely unexplored in C-H activation processes in a general sense. Further, only a handful of limited examples of ortho-directed deuteration labelling of primary sulfonamides have been reported (Figure 1). Through independent studies, Hesk, and later Herbert, applied commercially available Crabtree’s catalyst, to this problem. Despite these studies spanning catalyst loadings of 5 to 100 mol%, respectively, a maximum of only 15% D in benzenesulfonamide was achieved in the latter study. More successfully, Lockley applied iridium 1,3-dionate, to achieve 66% D in 4-methylbenzenesulfonamide, albeit under the high temperature of 130 °C and with a relatively elevated catalyst loading of 24 mol%. Perhaps most notably to date, Herbert applied the in-situ generated complex, to the labeling of benzenesulfonamide, achieving 85% D at room temperature, but with a substantial 52 mol% catalyst loading.

Based on our related studies in this area, we reasoned that, owing to the tetrahedral geometry of the sulfonamide group, and the fact that such HIE processes are believed to proceed via concerted C-H activation, a sterically less encumbered and more electron-rich ligand sphere would enhance the efficiency of the sulfonamide coordination and subsequent ortho-deuteration processes. In this light, we hypothesized that our catalyst, 6, would not be an effective mediator of the desired process, due mainly to the overall ligand size. In contrast, however, a complex of the class exemplified by 7, a precursor of 6, fits both the steric and electronic ligand profiles proposed above for successful deuteration of primary aryl sulfonamides, 8.

Scheme 1. Hydrogen Isotope Exchange Process

![Scheme 1](image-url)
RESULTS AND DISCUSSION

Catalyst Discovery and Optimization. We initiated our studies by testing the ability of sterically distinct catalysts 6 and 7 to mediate the ortho-deuteration of 4-methylbenzenesulfonamide under our standard labelling conditions. In agreement with our initial hypothesis, the latter system delivered far superior deuterium incorporation, and at levels currently unprecedented elsewhere in the literature (Table 1, Entry 1 vs. 4). In labelling the related substrates, methyl phenyl sulfone and N,N-dimethylbenzenesulfonamide, catalyst 6 remained inactive (Entry 1 vs. 2 and 3) whilst the activity of 7 fell markedly (Entry 4 vs. 5 and 6). Thus, catalyst 7 shows exploitable chemoselectivity for coordination of primary sulfonamides over secondary sulfonamides and sulfones.

Having identified 7 as a viable catalyst motif for labelling primary sulfonamides, we screened analogues of this system, varying the steric bulk and electron-releasing capabilities of the pendant NHC ligand (Table 2). Using Nolan and Cavallo’s Percent Buried Volume (%V_{bur}) and modified Tolman Electronic Parameter (TEP) analyses, two inferences can be drawn from this catalyst screen. Firstly, catalytic activity is negligible when %V_{bur}(NHC) falls below 33.0% (Table 2, Entries 1 and 2 vs. 3 – 7). Presumably, this is as a result of the necessity for larger ligands in order to encourage reductive elimination, releasing the labelled substrate from the active catalyst. Secondly, for NHCs of similar size, those bearing more electron-donating substituents increase catalyst activity, supporting a more facile C-H activation across the ortho C-H bonds of the substrate (for example, Entry 3 vs. 4). Overall, complex 16, the most electron-rich of all complexes tested, warranted further study. The reaction conditions were further optimized to assess the potential for labelling primary sulfonamides in reduced reaction times, whilst maintaining low catalyst loadings and ambient reaction temperature. This was achieved using a full factorial design of experiments (DoE), scrutinizing reaction time, catalyst loading, and solvent volume. Please, inside 11 experiments, we found that a small increase in catalyst loading from 5 to 6.5 mol%, employed under more dilute solvation, permitted a reduction in reaction time from 16 h to just 2 h (see ESI).

Analysis of Primary Sulfonamide Substrate Scope. We next examined the general efficacy of this methodology, applying the optimized reaction conditions to the ortho-deuteration of various primary sulfonamides (Table 3). For the parent substrate, benzenesulfonamide, 8a, an impressive and encouraging 95% D-incorporation was achieved. Similarly, para-alkyl and methoxy-benzenesulfonamides, 12 and 8b – 8d, gave excellent levels of deuteration, where only the p-tert-butyl analogue, 8c, labelled below 90% D. This suggests that...
the steric influence of the NHC ligand on the catalyst is felt even by substituent groups at such a remote position relative to the ligating center of the substrate. To demonstrate the practicality of the HIE procedure, deuteration of a simple sulfa drug, Sulfanilamide, was repeated using a five-fold increase in reaction scale, with only 4% loss in catalyst efficiency. On studying the labelling process, introduction of a bromide or nitro group to the ligating center of the substrate. To demonstrate the practicality of the HIE procedure, deuteration of Sulfanilamide was repeated using a five-fold increase in reaction scale, with only 4% loss in catalyst efficiency. On studying the labelling process, introduction of a bromide or nitro group to the ligating center of the substrate. To demonstrate the practicality of the HIE procedure, deuteration of Sulfanilamide was repeated using a five-fold increase in reaction scale, with only 4% loss in catalyst efficiency. On studying the labelling process, introduction of a bromide or nitro group to the ligating center of the substrate.

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Finally, a series of primary sulfonamides holding potentially two distinct sites of deuteration through the same sulfonamide directing group was studied. For meta-substituted benzenesulfonamides, 8l–8o, labelling was favored at the least hindered C-6 position. Most notably, for the largest meta-substituent, present in 8n, labelling occurred almost exclusively at the C-6 position. Moving to naphthalene-1-sulfonamide 8p, despite the potential for labelling via both 5- and 6-membered metallocycles, deuteration occurred exclusively at the former, and is in line with our previous observations. In the isomeric substrate, 8q, no discrimination was observed in labelling at positions C-1 and C-3, both proceeding through 5-membered metallocycles. However, as with substrates 8g and 8h, 8q suffers from low solubility in DCM, leading to only moderate levels of deuteration overall.

Table 2. Catalyst Screening for o-Deuteration of 4-Methylbenzenesulfonamide

| Entry | NHC/Complex | \( \%V^a_{\text{bur}} \) | \( \text{TEP}^{\text{ab}}/\text{cm}^3 \) | \( \%D \) | Entry | NHC/Complex | \( \%V^a_{\text{bur}} \) | \( \text{TEP}^{\text{ab}}/\text{cm}^3 \) | \( \%D \) |
|-------|-------------|----------------|-----------------|------|-------|-------------|----------------|-----------------|------|-------|-------------|----------------|-----------------|------|
| 1     |            | 26.4           | 2049.5          | 2    | 5     |            | 34.9           | 2046.7          | 96   |
| 2     |            | 30.3           | 2050.3          | 3    | 6     |            | 35.8           | 2050.2          | 93   |
| 3     |            | 33.0           | 2050.3          | 75   | 7     |            | 36.1           | 2050.8          | 95   |
| 4     |            | 33.3           | 2049.6          | 90   |       |            |                |                 |      |

\( ^a \) Values calculated from DFT-derived structures of proposed active catalyst structures. See ESI for full details.

**Competition Studies.** The true value of any catalyst system can be more fully assessed by determining its robustness in the face of additives that may act as a catalyst poison. Thus, we were keen to assess not only the activity of catalyst 16 but its ability to label primary sulfonamides in the presence of other potential directing groups. Table 4 summarizes a series of competition experiments where 11 was deuterated under the optimized reaction conditions in the presence of an equimolar quantity of a given additive. We were encouraged to find that only two of eight additives tested hindered the sulfonamide labelling process. Evidently, N-heterocyclic directing groups (Entries 1 and 2) compete for coordination to iridium, whereas carbonyl-based directing groups (Entries 3–7) and the nitro functionality (Entry 8) do not compete as readily with the iridium center. However, it should be clarified that, due to the relatively small size of each substrate, these studies mainly reflect competing directing group electronic characteristics. These studies are not believed to be representative of the steric impact of having the sulfonamide and the competing functionality in the same molecule.

**Labeling Primary Sulfonamides in Multifunctional Drug Molecules.** In a further assessment of the present ortho-deuteration protocol, we investigated its utility in labelling the more complex drug molecules, Celecoxib, 21, and Mavacoxib, 22, COX-2 inhibitors first commercialized by Pfizer. Unlike the other substrates in this study, Celecoxib possesses two
Table 3. Substrate Scope for \(\alpha\)-Deuteration of Primary Sulfonamides

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Deuteration</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>95%</td>
<td>8-d(_0) or 11 (0.215 mmol), D(_2) (balloon), DCM, 25 °C, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8b</td>
<td>97% (93%)</td>
<td>16 (6.5 mol%), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8c</td>
<td>94%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8d</td>
<td>84%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8e</td>
<td>96%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8f</td>
<td>77%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8g</td>
<td>24%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8h</td>
<td>11%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8i</td>
<td>74%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8j</td>
<td>40%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8k</td>
<td>49%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8l</td>
<td>D(_a): 95%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td></td>
<td>D(_b): 75%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8m</td>
<td>D(_a): 92%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8n</td>
<td>D(_b): 61%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8o</td>
<td>D(_b): 85%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8p</td>
<td>D(_b): 60%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
<tr>
<td>8q</td>
<td>D(_b): 33%</td>
<td>6 (0.215 mmol), D(_2) (balloon), DCM, 2 h, 25 °C. %D based on (^1)H NMR.</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: 8-d\(_0\) or 11 (0.215 mmol), 16 (6.5 mol%), D\(_2\) (balloon), DCM, 2 h, 25 °C. %D based on \(^1\)H NMR. \(^b\) Value in parenthesis is indicative of large scale reaction employing 1.075 mmol of 11. \(^c\) Values indicate level of deuterium incorporation at 40 °C. \(^d\) Ratio estimated by HRMS.

potential sites of labelling via two distinct directing groups: a primary sulfonamide and a pyrazole ring. Employing the optimized conditions described above, we compared catalysts 6 and 16 in their ability to mediate the C-H activation and deuteration labelling of 21 and 22 (Table 5). Rather unsurprisingly, the more encumbered complex 6 showed unquestionable chemoselectivity for C-H activation adjacent to the pyrazole rather than the sulfonamide (Table 5, Entries 1 and 3). This inactivity of 6 toward the sulfonamide moiety is in agreement with earlier studies (Table 1, Entry 1). However, to our surprise, employment of catalyst 16 evidenced a complete switch in the chemoselectivity of ortho-deuteration in labelling drug molecules 21 and 22 (Table 5, Entries 2 and 4). Indeed, these results are in direct contrast to that shown in the competition study involving 11 and N-phenylpyrazole (Table 4, Entry 1), where the pyrazole outcompeted the sulfonamide in coordinating and reacting at the iridium center of 16. Accordingly, such marked results called for a deeper understanding of the catalysis mechanism and, hence, the origin of the contrasting chemoselectivity of ortho-deuteration when using sterically distinct catalysts to label such multifunctional molecules as employed in this study.

Mechanistic Investigations. Based on the range of studies with various HIE catalysts, and on recent experimental and computational studies from our own laboratories, there exists an escalating body of insight surrounding the proposed mechanism for Ir-catalyzed ortho-deuteration processes. As depicted in Scheme 2 for sulfonamides, pre-catalytic Ir(I) species, 6 or 16 for example, is activated by hydrogenative loss of the cyclooctadiene (COD) ligand, generating the catalytic Ir(III) dideuteride complex, 24, stabilized by solvation or agostic interactions. Displacement of the loosely bound solvent molecules by substrate 25 produces the intermediate, 26, where the substrate is bound to iridium via the directing group and an agostic interaction from an ortho-C-H bond. Subsequent oxidative addition across the proximal C-H bond, along with simultaneous reductive elimination of the cis-deuterides, affords 27. It is worth noting that the dual redox processes
Table 4. Competition Studies to Assess Robustness and Chemoselectivity of Catalyst System

<table>
<thead>
<tr>
<th>Entry</th>
<th>Directing Group</th>
<th>X</th>
<th>%D&lt;sup&gt;a&lt;/sup&gt;</th>
<th>%D&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Entry</th>
<th>Directing Group</th>
<th>X</th>
<th>%D&lt;sup&gt;a&lt;/sup&gt;</th>
<th>%D&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>H</td>
<td>7</td>
<td>47</td>
<td>5</td>
<td></td>
<td>Me</td>
<td>93</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>H</td>
<td>7</td>
<td>19</td>
<td>6</td>
<td></td>
<td>Me</td>
<td>97</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Me</td>
<td>94</td>
<td>54</td>
<td>7</td>
<td></td>
<td>Me</td>
<td>93</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Me</td>
<td>95</td>
<td>11</td>
<td>8</td>
<td></td>
<td>H</td>
<td>97</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 11 (0.215 mmol), 19 (0.215 mmol), 16 (6.5 mol% wrt/11 + 19), D<sub>2</sub> (balloon), DCM, 2 h, 25 °C. %D based on <sup>1</sup>H NMR.

leading to 27 ensure that iridium remains in the 3<sup>+</sup> oxidation state, with Ir(V) existing in a transient sense only (vide infra).<sup>27</sup> Hydride fluxionality<sup>28</sup> then brings a deuteride cis to the activated substrate in 28, which then undergoes a second dual redox process to give the loosely bound sulfonamide in 29, which is quickly released to afford 30 and the regenerated catalyst, 24.

Our attempts to probe the reaction mechanism began by measuring the kinetic isotope effect (KIE) of the C-H activation step.<sup>29</sup> Thus, exposing substrate 12 to the reverse reaction, employing H<sub>2</sub> in place of D<sub>2</sub>, revealed a primary KIE value of approximately 3.2, indicating that C-H activation of the ortho-C-H bonds is involved in the rate-limiting step (Scheme 3). Indeed, this is similar in value to that obtained from studies of HIE with catalyst 6 and deuteratedacetophenone, 31<sup>28</sup> suggesting that both reactions proceed via a similar mechanistic process. Additionally, we observed no depletion in the activity of catalyst 16 in the deuteration of 11 when the reaction was run in the presence of Hg(0).<sup>30</sup> This supports the view that the labelling process operates under homogeneous catalysis.

**COMPUTATIONAL STUDIES**

**Substrate Binding, Catalyst Design, and Reaction Mechanism.** Based on the outcomes accumulated to this stage, we followed our experimental studies with a complementary theoretical analysis of the operative reaction mechanism.<sup>31</sup> The first task was to strengthen our original hypothesis for the catalyst design, aiming to show that catalysts such as 16 (or 7), with a relatively small coordination sphere, can bind and react with the large sulfonamide directing group more readily than encumbered catalysts such as 6. To this end, we assessed the sulfonamide binding and C-H activation enthalpies of representative catalysts 6 and 16 (cf. processes 24 to 26, and 26 to 27, Scheme 2). Interestingly, on assessing the substrate binding energies to the appropriate analogues of 34, we established that complexation of benzenesulfonamide, 25, to the activated form of 6 is more exothermic than to the equivalent activated form of 16 (34 to 35a, Scheme 4).<sup>32</sup>

However and in contrast, the rate-limiting C-H activation process is less endothermic when the smaller catalyst is employed (35a to 35b, Scheme 4). This is in qualitative agreement with our experimental findings (Table 1, Entries 1 and 4) and infers that the reduced steric encumbrance of catalyst 16 relative to 6 is essential for efficient catalytic reactivity with sulfonamide substrates.

Table 5. Chemoselective Deuterium Labeling of Celecoxib and Mavacoxib

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>X</th>
<th>%D&lt;sup&gt;a&lt;/sup&gt;</th>
<th>%D&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>Me</td>
<td>16</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>Me</td>
<td>97</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>F</td>
<td>7</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>F</td>
<td>98</td>
<td>11</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 21 or 22 (0.05 mmol), 6 or 16 (6.5 mol%), D<sub>2</sub> (balloon), DCM, 25 °C, 2 h.
Concentrating on catalyst 16, we subsequently calculated the full potential energy surface (PES) of the labelling reaction with 25. In line with our KIE studies, C-H activation was shown to be the most energetically demanding and thus rate-limiting step (36 to 37, Figure 2). Furthermore, we calculated a theoretical KIE of 3.9 for this step, showing very good agreement with the experimental estimate. As with our previous studies, the initial C-H activation step is endergonic. Comparatively, hydride fluxionality (37 to 38) is energetically neutral on the PES. Finally, the second C-H activation step (38 to 39) almost mirrors the first, and is exergonic in nature.

Chemoselectivity and Catalyst Structure. With the above insights in place, attention turned to explaining the origins of labelling chemoselectivity (Table 5). Previously, we studied the regioselectivity of labelling benzanilide which, through a single coordinating group, can undergo HIE through a 5- or a 6-membered iridacycle. In that case, a preference to label through the smaller 5-membered iridacycle was shown to originate from energetic differences in the C-H activation step, with the initial binding of the substrate proving to be insignificant. Conversely, the situation with sulfa-drugs 21 and 22 is more complex. There are now two structurally different coordinating groups, both directing ortho-deuteration through a 5-membered iridacycle. As such, it cannot be assumed that the observed labelling selectivity using catalysts 6 and 16 is resultant of the oxidative addition or the initial binding step. A detailed study of the overall substrate complexation and C-H activation pathways of Celecoxib, 21, with catalysts 6 and 16 was thus undertaken.

Firstly, we scrutinized the binding interactions and C-H activation of 21 with the larger catalyst, 6 (Figure 3). From the appropriate analogue of 34 (Scheme 4), solvated explicitly with two DCM molecules, subsequent complexation of 21 and release of solvent proved entropically favourable and enthalpically neutral for substrate binding modes, 40 and 41. However, both complexation and subsequent C-H activation are significantly lower in energy when proceeding through 40, leading to ortho-deuteration via the pyrazole. This is in agreement with experimentally observed labelling chemoselectivity (Table 5, Entry 1). Additionally, it is important to note that the energy difference in the binding modes (ΔΔGbind = 13.1 kcal mol⁻¹) is much larger than the energy difference in the C-H activation transition states (ΔΔGtrans = 0.6 kcal mol⁻¹). We can therefore infer that the observed pyrazole chemoselectivity in labelling 21 with catalyst 6 originates from the complexation event more so than the subsequent C-H activation process.

Scheme 2. Proposed Mechanism for Ir-Catalyzed HIE

Scheme 4. Calculated Energies for Binding of Benzenesulfonamide and C-H activation with Sterically Distinct Catalysts
We then sought to explore the change in labelling chemoselectivity observed upon switching from encumbered catalyst, 6, to the smaller catalyst, 16 (Table 5, Entry 2). Similarly to Figure 3, complexation and C-H activation of 21 with catalyst 16 were modelled computationally (Figure 4). Now, substrate complexation is calculated to be enthalpically disfavoured, presumably in connection with the lower electrophilicity of catalyst 16 relative to 6. Nonetheless, there is once again a clear energetic bias for complexation and subsequent C-H activation through one directing group: the sulfonamide rather than the pyrazole. In this case, discrimination between the binding modes 42 and 43 ($\Delta G_{\text{bind}} = 3.7 \text{ kcal mol}^{-1}$) is more similar in magnitude to the energy difference in the subsequent C-H activation pathways ($\Delta G_{\text{trans}} = 0.7 \text{ kcal mol}^{-1}$). Thus, we believe that chemoselective binding and labelling adjacent to the sulfonamide using the chloro/carbene catalysts is dictated by the combined influence of substrate binding and C-H activation transition state energies. The selective binding of the sulfonamide functionality in 21 by catalyst 16 is worthy of further discussion. Whereas benzenesulfonamide, 25, was predicted to bind to 16 via the nitrogen lone pair, Celecoxib, 21, binds preferentially through an oxygen lone pair, supplemented by a hydrogen bond between the amino group of the substrate and the chloride ligand of the catalyst. This highlights the flexible nature of the sulfonamide directing group, with the nitrogen or oxygen groups able to actively participate, depending on the structure of the substrate and catalyst.

CONCLUSION

In summary, we have established a general and selective method for C-H activation ortho to primary sulfonamides by applying complexes of the type [(COD)Ir(NHC)Cl], leading to highly effective levels of hydrogen-deuterium exchange. Sterically large and electron-rich NHC ligands were necessary for efficient catalysis, with complex 16 being the most active of seven such species tested. Interestingly, our most commonly used isotope exchange catalyst, 6, a more encumbered derivative of 16, was shown to be inactive towards sulfonamides.

In further exploration of the reaction scope, competition studies revealed the ability of catalyst 16 to selectively label sulfonamide, 11, in the face of ketone, ester, nitro, and various amide directing groups. Only the N-heterocycles, 1-phenylpyrazole and 2-phenylpyridine, were able to compete with 11 to reverse the chemoselectivity of labelling in these

![Figure 2. Potential Energy Surface (PES) for ortho-deuteration of benzenesulfonamide with catalyst 16, scaled according to free energy, $G_{\text{rel}}$. Details of the theoretical KIE calculation can be found in the ESI.](image-url)
orthodeuteration of primary sulfamides with catalyst 16 proceeds similarly to analogous HIE processes employing catalyst 6. Further, we have analysed the complexation modes and C-H activation pathways associated with labelling Celecoxib, 21 using catalysts 6 and 16. As a result, we can now propose that the pyrazole chemoselectivity of catalyst 6 is driven by the substrate complexation event, whereas the sulfonamide selectivity imparted by catalyst 16 is influenced by the energetics of both complexation and subsequent C-H activation. This, once again, emphasizes the importance of considering the interactions of catalyst and substrate in acute detail aligned to the overall C-H activation process, as the observed activities and chemoselectivities may be as a result of more than one contributing factor.

Work is on-going within our laboratories to extend the application of these emerging iridium catalyst species to a more expansive array of substrate classes, including sulfonamide-based molecular architectures, as well as to alternative C-H activation processes in a wider sense.

ASSOCIATED CONTENT

Details of all experimental procedures and DFT calculation (including optimized Cartesian coordinates) can be found in the electronic supporting information (ESI). This information is available free of charge via the Internet at [http://pubs.acs.org](http://pubs.acs.org).

AUTHOR INFORMATION

Corresponding Authors

*E-mail: w.kerr@strath.ac.uk
*E-mail: tell.tuttle@strath.ac.uk

Notes

The authors declare no competing financial interest.

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(24) For a recent account of robustness screening, see: Collins, K. D.; Glorius, F. Nat. Chem. 2013, 5, 597-601.


(26) The intermediacy and catalytic competency of Ir(III) dihydride complexes, derived from COD-bearing Ir(I) complexes and hydrogen gas, has strong literature precedent. See, for example, ref. 3e and 5.

(27) Such a dual redox process, with no discernible oxidative addition intermediate, can be likened to a sigma complex-assisted metathesis process. For a recent review on this topic, see: Perutz, R. N.; Sabo-Étienne, S.; Angew. Chem. Int. Ed. 2007, 46, 2578-2592.


(30) See ESI for full details.
(31) All calculations were performed in Gaussian 09 (revision A.02). The M06 density functional was used in conjunction with the 6-31G* basis set for main group non-metal atoms and the Stuttgart RSC effective core potential along with the associated basis set for Ir. Full details and references for all computational methods can be found in the ESI.

(32) Scheme 4 shows the lowest energy binding modes only. Additional higher energy conformers of benzenesulfonamide binding to both catalysts are discussed in the ESI.

(33) Similarly to reference 32, Figures 2–4 consider the lowest energy conformers of substrate binding only. Higher energy binding modes are discussed in the ESI.


- 20 examples
- Up to 98% D
- Computational studies
- Mechanistic analysis