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

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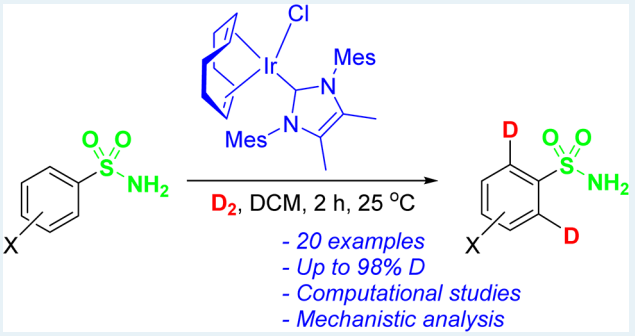
Supporting Information

ABSTRACT: Iridium-catalyzed C−H activation and *ortho*-hydrogen isotope exchange is an important technology for allowing access to labeled 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.



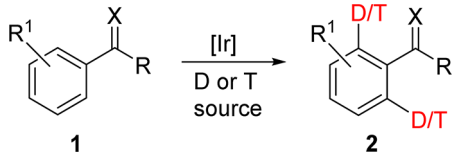
KEYWORDS: *iridium, C−H activation, ortho-deuteration, hydrogen-isotope exchange, sulfonamide*

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 20 years ago,[1] transition-metal-catalyzed approaches to this methodology have evolved to become predictable and indispensable tools for synthetic chemists.[2]

One particularly industry-facing facet of C−H functionalization is manifested in iridium-catalyzed *hydrogen-isotope exchange* (HIE, Scheme 1).[3] To alter the properties of a drug candidate, the medicinal chemist must first have a flexible technique with which to study them. Consequently, isotopic labeling with heavy hydrogen isotopes (deuterium, D_2, or tritium, T_2) is widely used as a means to monitor the biological fate of a potential drug molecule.[4] Since the pioneering work of Heys in 1992,[5] a range of iridium catalysts have been reported to efficiently deliver the required hydrogen isotope *ortho* to various functional handles,[3] as well as in the absence of any directing group.[6] 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.[3c,7]

Scheme 1. Hydrogen Isotope Exchange Process



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 antihypertensive treatments.[8] To our knowledge, primary sulfonamide substrates remain largely unexplored in C−H activation processes in a general sense.[9,10] Further, only a handful of limited examples of *ortho*-directed deuterium labeling of primary sulfonamides have been reported (Figure 1). Through independent studies, Hesk,[11] and later Herbert,[12] applied commercially available Crabtree's catalyst, **3**,[13] 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, **4**, 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 %.[14] Perhaps most notably to date, Herbert

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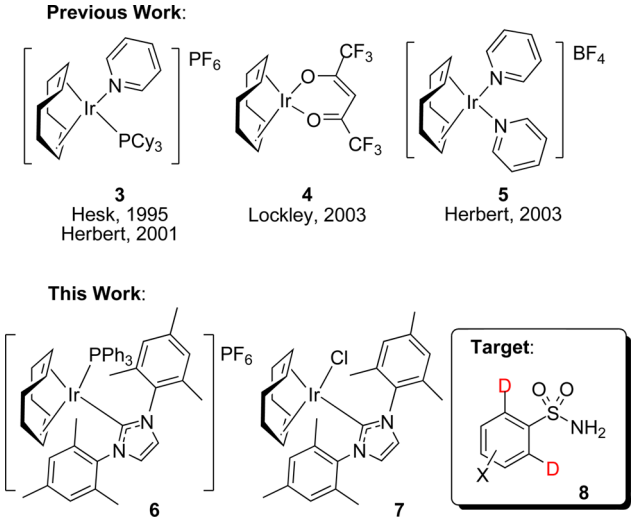


Figure 1. Past and present catalysts applied to the labeling of primary sulfonamides.

applied the in situ generated complex, **5**, to the labeling of benzenesulfonamide, achieving 85% D at room temperature, but with a substantial 52 mol % catalyst loading.[15]

On the basis of 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,[7c,16] *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**,[7a,17] 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**,[18] a precursor of **6**, fits both the steric and electronic ligand profiles proposed above for successful deuteration of primary aryl sulfonamides, **8**.

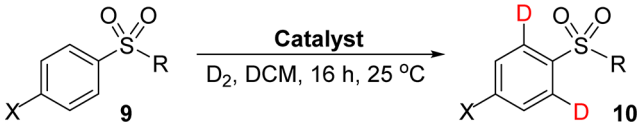
In this contribution, we divulge our exploration of an extended range of chloro carbene iridium complexes and establish that the resultant species are active catalysts for the C−H activation and labeling of primary sulfonamides under mild reaction conditions. Additionally, we report our computational analysis of the catalyst design and reaction mechanism, which establishes the origin of site-selective labeling in the presence of multiple coordinating functionalities.

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 labeling conditions.[7] 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 labeling the related substrates, methyl phenyl sulfone and *N*,4-dimethylbenzenesulfonamide, catalyst **6** remained inactive (Entry 1 vs 2 and 3) while 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 labeling primary sulfonamides, we screened analogues of this system,

Table 1. Catalyst Discovery for *o*-Deuteration of Primary Sulfonamides[a]



entry	X/R	catalyst	% D
1	Me/NH_2	**6**	12
2	H/Me	**6**	9
3	Me/NHMe	**6**	7
4	Me/NH_2	**7**	90
5	H/Me	**7**	17
6	Me/NHMe	**7**	8

[a]Conditions: **9** (0.215 mmol), **6** or **7** (5 mol %), D_2 (balloon), DCM, 16 h, 25 °C

varying the steric bulk and electron-releasing capabilities of the pendant NHC ligand (Table 2). Using Nolan and Cavallo's *Percent Buried Volume* ($\%V_{bur}$)[19] and modified Tolman Electronic Parameter (TEP)[18,20] analyses, two inferences can be drawn from this catalyst screen. First, 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 labeled substrate from the active catalyst. Second, 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**,[21] the most electron-rich of all complexes tested, warranted further study. The reaction conditions were further optimized to assess the potential for labeling primary sulfonamides in reduced reaction times, while maintaining low catalyst loadings and ambient reaction temperature. This was achieved using a full factorial design of experiments (DoE),[22] scrutinizing reaction time, catalyst loading, and solvent volume. Pleasingly, 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 Supporting Information (SI)).

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**, labeled 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 **12** was repeated using a 5-fold increase in reaction scale, with only 4% loss in catalyst efficiency. On studying *para*-halogenated substrates, very good deuteration efficiency was achieved for fluoro- and bromo-compounds, **8e** and **8f**, respectively, whereas the iodo-derivative, **8g**, gave a much lower deuterium content. The most likely explanation for these marked differences lie in the relative insolubility of **8g** in DCM. By a similar argument, a

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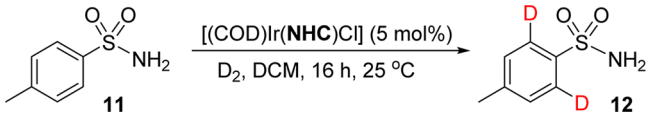
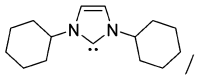
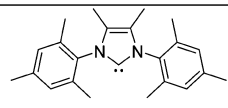
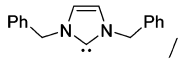
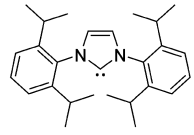
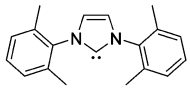
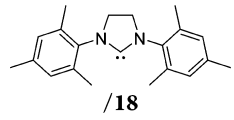
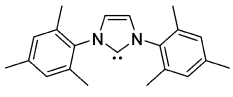
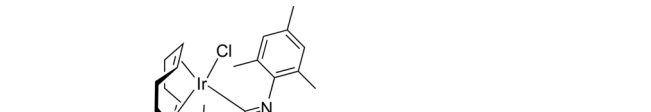
Table 2. Catalyst Screening for *o*-Deuteration of 4-Methylbenzenesulfonamide

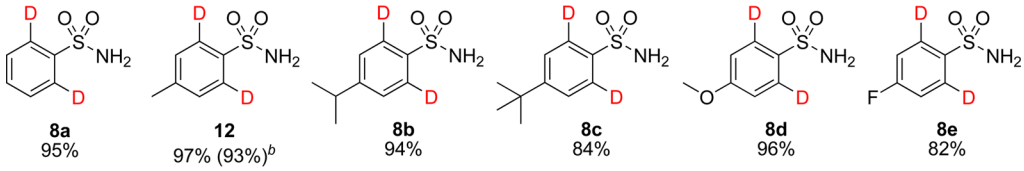


Entry	NHC/Complex	%V_{bur}[a]	TEP[20a]/ cm^{-1}	%D	Entry	NHC/Complex	%V_{bur}[a]	TEP[20a] /cm^{-1}	%D
1	 /**13**	26.4	2049.5	2	5	 /**16**	34.9	2046.7	96
2	 /**14**	30.3	2050.3	3	6	 /**17**	35.8	2050.2	93
3	 /**15**	33.0	2050.3	75	7	 /**18**	36.1	2050.8	95
4	 /**7**	33.3	2049.6	90					

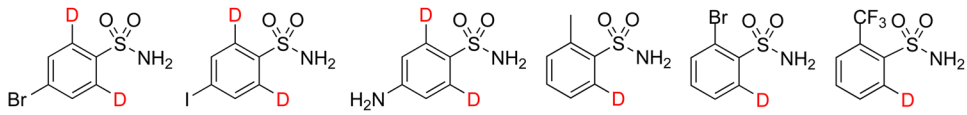
[a]Values calculated from DFT-derived structures of proposed active catalyst structures. See SI for full details.

Table 3. Substrate Scope for *o*-Deuteration of Primary Sulfonamides[a]

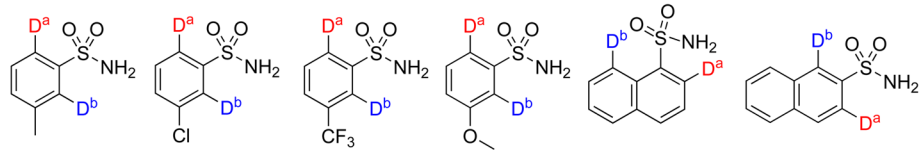




8a 95% | **12** 97% (93%)[b] | **8b** 94% | **8c** 84% | **8d** 96% | **8e** 82%



8f 77% | **8g** 24% | **8h** 11% | **8i** 74% | **8j** 40%[c] | **8k** 49%[c]



8l D^a: 95%, D^b: 85% | **8m** D^a: 75%, D^b: 61% | **8n** D^a: 92%[d], D^b: 6% | **8o** D^a: 85%, D^b: 42% | **8p** D^a: 60%, D^b: 0% | **8q** D^a: 33%, D^b: 30%

[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 parentheses 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.

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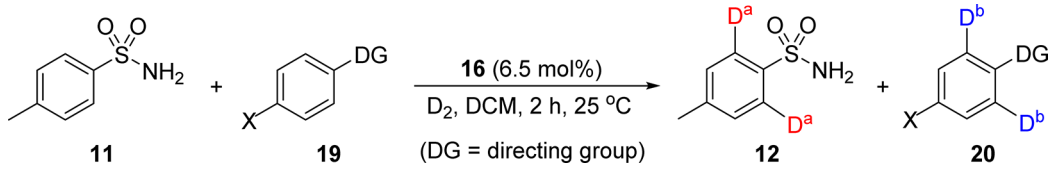
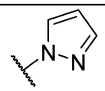
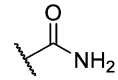
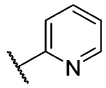
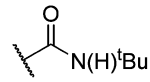
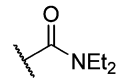
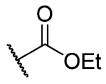
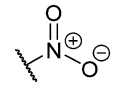
Table 4. Competition Studies to Assess Robustness and Chemoselectivty of Catalyst System[a]



11 19 12 20

Entry	Directing Group	X	%D[a]	%D[b]	Entry	Directing Group	X	%D[a]	%D[b]
1		H	7	47	5		Me	93	26
2		H	7	19	6		Me	97	10
3		Me	94	54	7		Me	93	1
4		Me	95	11	8		H	97	4

[a]Conditions: **11** (0.215 mmol), **19** (0.215 mmol), **16** (6.5 mol % wrt/**11** + **19**), D_2 (balloon), DCM, 2 h, 25 °C. %D based on ^{1}H NMR.

poor 11% D was achieved when labeling the simple sulfa drug, *Sulfanilamide*,[23] **8h**, making any rationalization based on competitive coordination of the *p*-amino group unclear. The labeling of more challenging *ortho*-substituted sulfonamides was also investigated. Whereas the methyl substituent in substrate **8i** only moderately affected the efficiency of the labeling process, introduction of a bromide or trifluoromethyl group (**8j** and **8k**, respectively) meant that gentle heating to 40 °C was required to achieve acceptable levels of deuteration in the remaining *ortho*−C-H position. In such cases, lone pairs on the heteroatoms may impede the substrate coordination to the iridium center.

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**, labeling was favored at the least hindered C-6 position. Most notably, for the largest *meta*-substituent, present in **8n**, labeling occurred almost exclusively at the C-6 position. Moving to naphthalene-1-sulfonamide **8p**, despite the potential for labeling via both five- and six-membered metallocycles, deuteration occurred exclusively at the former and is in line with our previous observations.[7] In the isomeric substrate, **8q**, no discrimination was observed in labeling at positions C-1 and C-3, both proceeding through five-membered metallocycles. However, as with substrates **8g** and **8h**, **8q** suffers from low solubility in DCM, leading to only moderate levels of deuteration overall.

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.[24] 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 labeling 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 **11**. 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 labeling the more complex drug molecules, Celecoxib, **21**, and Mavacoxib, **22**, COX-2 inhibitors first commercialized by Pfizer.[25] Unlike the other substrates in this study, Celecoxib possesses two potential sites of labeling 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 deuterium labeling 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 labeling 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.

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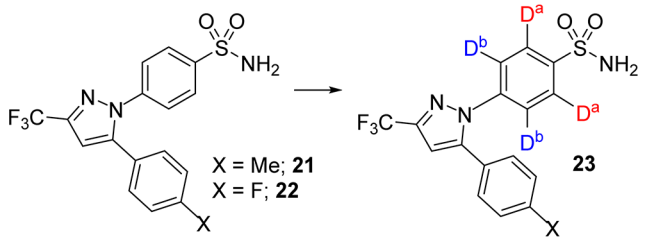
Table 5. Chemoselective Deuterium Labeling of Celecoxib and Mavacoxib[a]

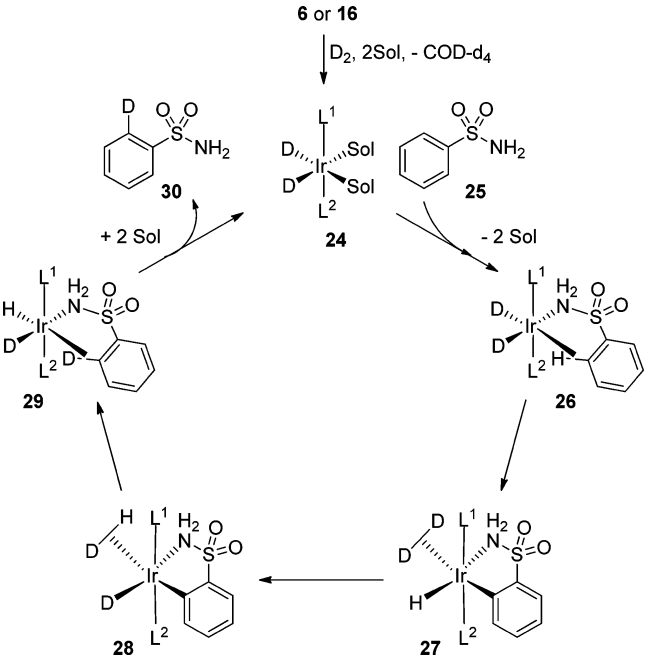


Entry	Catalyst	X	%D[a]	%D[b]
1	**6**	Me	16	95
2	**16**	Me	97	11
3	**6**	F	7	89
4	**16**	F	98	11

[a]Conditions: **21** or **22** (0.05 mmol), **6** or **16** (6.5 mol %), D_2 (balloon), DCM, 25 °C, 2 h.

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.[7c,16] As depicted in Scheme 2 for sulfonamides, precatalytic Ir(I)

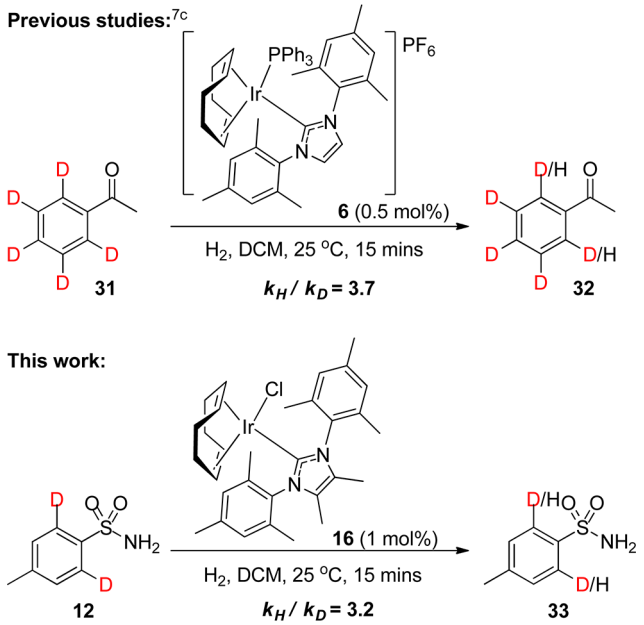
Scheme 2. Proposed Mechanism for Ir-Catalyzed HIE



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.[26] 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 leading to **27** ensure that iridium remains in the 3+ oxidation state, with Ir(V) existing in a transient sense only (*vide infra*).[27] Hydride fluxionality[28] 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.[29] Thus, exposing substrate **12** to the reverse reaction, employing H_2 in place of D_2, 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

Scheme 3. Investigation of Kinetic Isotope Effects



from studies of HIE with catalyst **6** and deuterated acetophenone, **31**,[7c] 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).[30] This supports the view that the labeling 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.[31] 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).[32]

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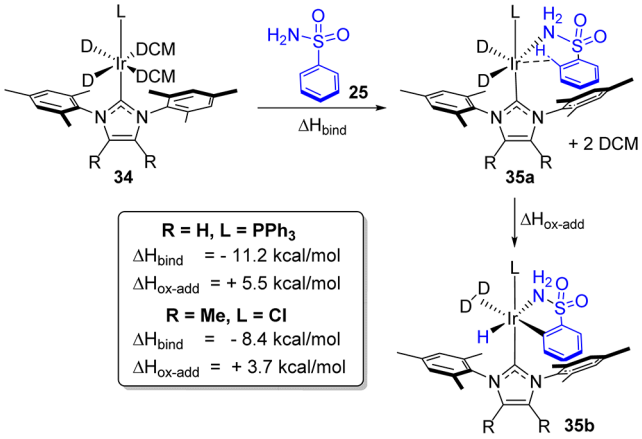
Scheme 4. Calculated Energies for Binding of Benzenesulfonamide and C−H Activation with Sterically Distinct Catalysts



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.

Concentrating on catalyst **16**, we subsequently calculated the full potential energy surface (PES) of the labeling 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,[7c] the initial C−H activation step is endergonic.[27] 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 labeling chemoselectivity (Table 5). Previously, we studied the regioselectivity of labeling benzanilide which, through a *single coordinating group*, can undergo HIE through a five- or a six-membered iridacycle.[7] In that case, a preference to label through the smaller five-membered iridacycle was shown to originate from energetic differences in the C−H activation step,[7c] 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 five-membered iridacycle. As such, it cannot be assumed that the observed labeling 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.

First, 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

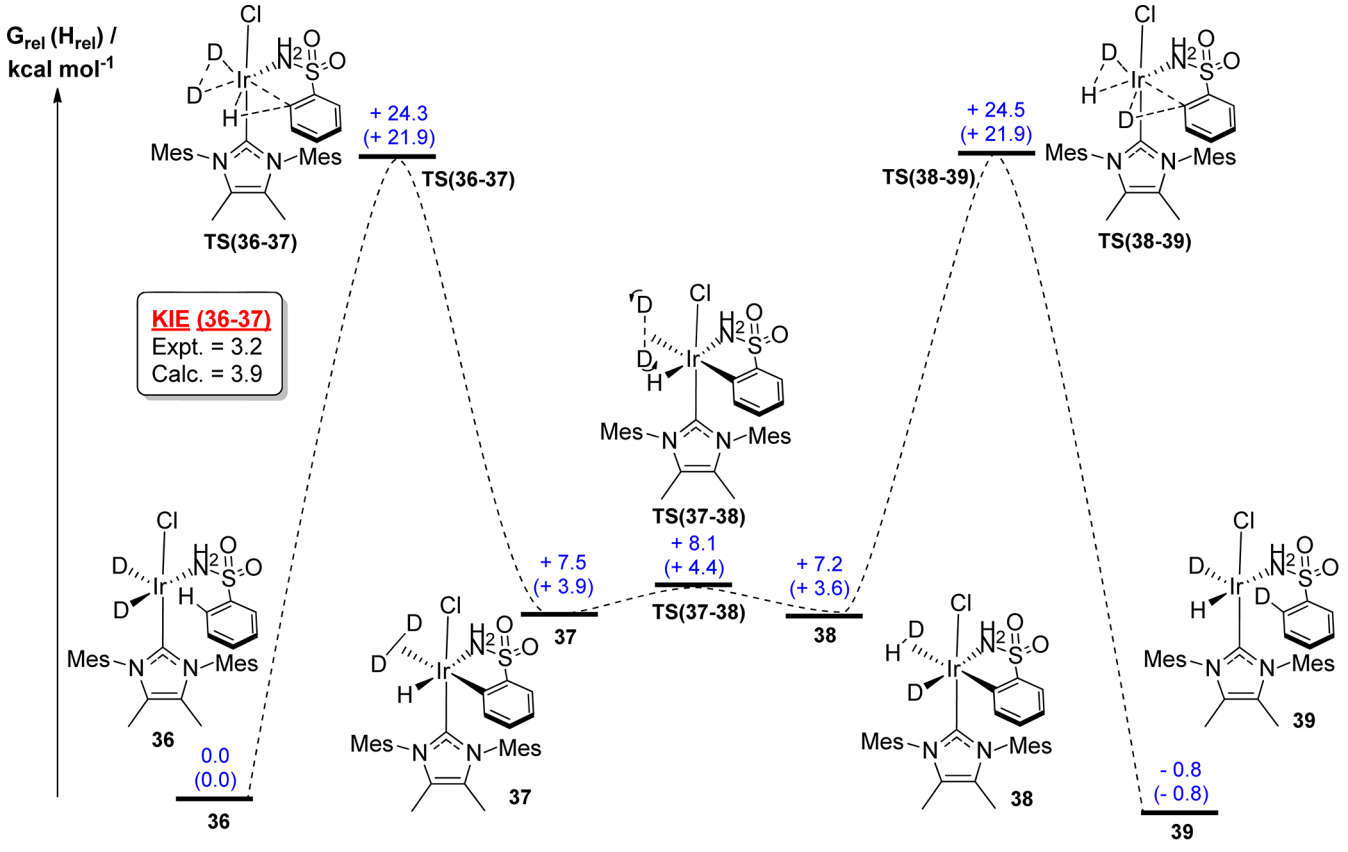


Figure 2. Potential Energy Surface (PES) for *ortho*-deuteration of benzenesulfonamide with catalyst **16**, scaled according to free energy, G_{rel}. Details of the theoretical KIE calculation can be found in the SI.

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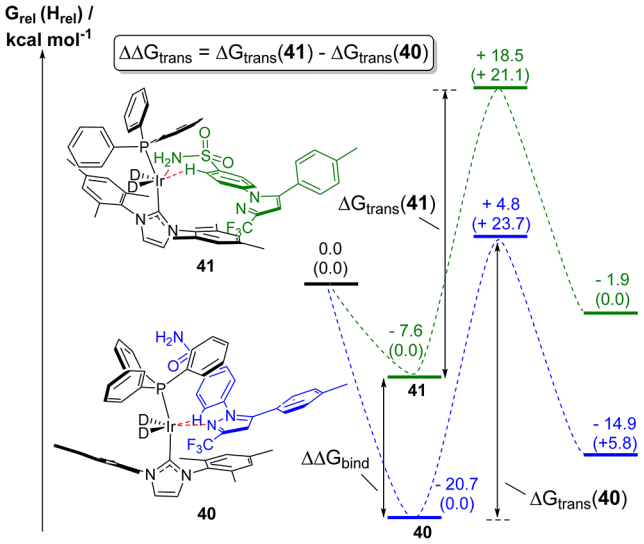

Figure 3. PES for the complexation and C−H activation of Celecoxib, **21**, with catalyst **6**. Energies are relative to the appropriate DCM solvated analogue of **34**.

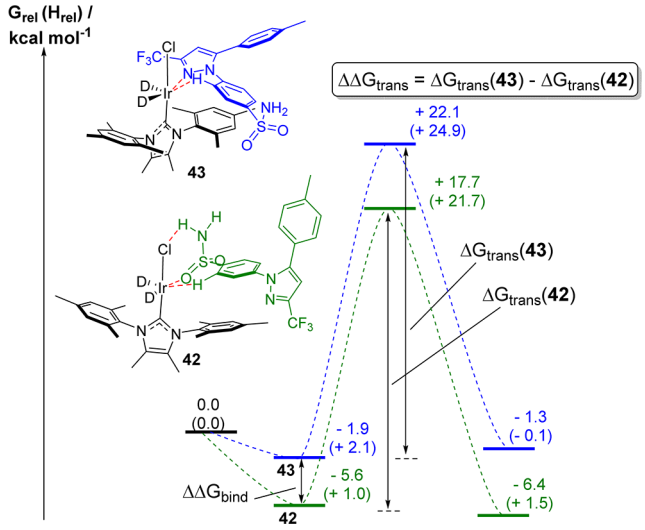

Figure 4. PES for the complexation and C−H activation of Celecoxib, **21**, with catalyst **16**. Energies are relative to the appropriate DCM solvated analogue of **34**.

release of solvent proved entropically favorable 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 labeling chemoselectivity (Table 5, Entry 1). Additionally, it is important to note that the energy difference in the binding modes ($\Delta\Delta G_{bind}$ = 13.1 kcal mol^{-1}) is much larger than the energy difference in the C−H activation transition states ($\Delta\Delta G_{trans}$ = 0.6 kcal mol^{-1}). We can therefore infer that the observed pyrazole chemoselectivity in labeling **21** with catalyst **6** originates from the complexation event more so than the subsequent C−H activation process.

We then sought to explore the change in labeling 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 modeled computationally (Figure 4).[33] Now, substrate complexation is calculated to be enthalpically disfavored, 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** ($\Delta\Delta G_{bind}$ = 3.7 kcal mol^{-1}) is more similar in magnitude to the energy difference in the subsequent C−H activation pathways ($\Delta\Delta G_{trans}$ = 0.7 kcal mol^{-1}). Thus, we believe that chemoselective binding and labeling 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.[34] 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 toward sulfonamides. Having then optimized the reaction time, catalyst loading, and dilution, through DoE techniques, a series of sulfonamides were deuterated under mild conditions using **16**. Specifically, alkyl, halogen, methoxy, trifluoromethyl, and naphthyl-substituted aryl sulfonamide derivatives were tolerated, with *ortho*-, *meta*-, and *para*-substitution having also been explored in the substrate scope. A notable limitation of this methodology lies in the poor solubility (and hence %D in the labeling reaction) of several substrates (**8g**, **8h**, and **8q**). Supplementary studies are currently ongoing within our laboratory to find reaction media alternative to DCM.

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 labeling in these studies. We have also successfully applied catalyst **16** to the *ortho*-deuteration of multifunctional sulfa-drugs Celecoxib, **21**, and Mavacoxib, **22**. Interestingly, catalyst **16** showed excellent levels of chemoselectivity toward the sulfonamide over the pyrazole directing group and in a manner completely contrary to our competition studies employing simpler substrates. Further still, we have demonstrated the ability to switch the chemoselectivity in labeling **21** and **22** by employing catalyst **6** in place of **16**. This highlights a necessity to consider more intimately the interactions between individual catalyst and substrate species.[35]

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Finally, with a combination of experimental KIE studies and computational mechanistic analyses, we have revealed that the *ortho*-deuteration of primary sulfonamides with catalyst **16** proceeds similarly to analogous HIE processes employing catalyst **6**.[7c] Further, we have analyzed the complexation modes and C−H activation pathways associated with labeling 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 ongoing 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

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs5015755.

Details of all experimental procedures and DFT calculation, including optimized Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

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