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Research Article

Computationally-Guided Development of a Chelated NHC-P Iridium(I) Complex for the Directed Hydrogen Isotope Exchange of Aryl Sulfones

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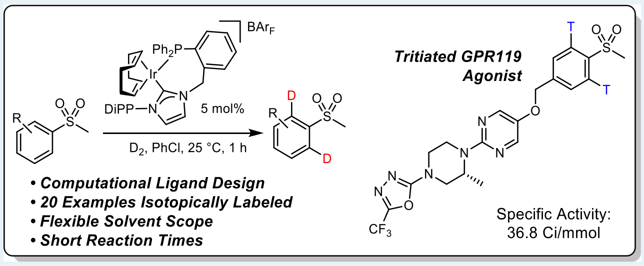
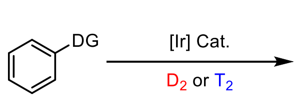
ABSTRACT: Herein, we report the rational, computationally-guided design of an iridium(I) catalyst system capable of enabling directed hydrogen isotope exchange (HIE) with the challenging sulfone directing group. Substrate binding energy was used as a parameter to guide rational ligand design via an *in silico* catalyst screen, resulting in a lead series of chelated iridium(I) NHC-phosphine complexes. Subsequent preparative studies show that the optimal catalyst system displays high levels of activity in HIE, and we demonstrate the labeling of a broad scope of substituted aryl sulfones. We also show that the activity of the catalyst is maintained at low pressures of deuterium gas and apply these conditions to tritium radiolabeling, including the expedient synthesis of a tritium-labeled drug molecule.



KEYWORDS: *rational catalyst design, hydrogen isotope exchange, iridium catalysis, C−H activation, sulfone*

The incorporation of heavy isotopes into potential drug molecules has, over time, become an indispensable tool within the pharmaceutical industry.[1] One of the most utilized methods in this area is directed hydrogen isotope exchange (HIE, Scheme 1), wherein hydrogen atoms *ortho* to a Lewis basic directing group (DG) are replaced with deuterium or tritium.[2]

Scheme 1. General Reaction Scheme for Directed HIE



Homogeneous iridium catalysts have been proven to be highly active in *ortho*-directed HIE.[3] These species have enabled the use of a broad range of directing groups in the labeling of small molecules and potential drug candidates.[4] Related to this, studies within our own laboratory have led to the development of a series of catalytically active iridium(I) NHC/phosphine complexes **1**−**2** (Figure 1), which deliver heavy isotopes of hydrogen (deuterium, D and tritium, T) to aryl and alkenyl substrates via a directed C−H activation process with a broad range of directing groups.[3d,5] Additionally, iridium(I) NHC chloride complexes of type **3** have shown utility in the labeling of primary aryl sulfonamides and aryl aldehydes.[6]

Despite these advances, however, certain high-value functionalities, common throughout pharmaceutical motifs

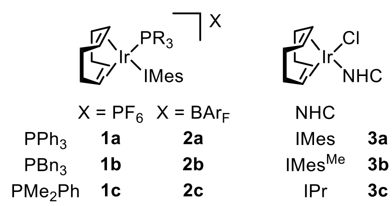


Figure 1. Ir(I) precatalysts for directed HIE.

and natural products, still present significant challenges for directed HIE. One such example is the aryl sulfone unit, which is prevalent throughout drug discovery.[7] For example, sulfones are present in antibiotics, such as dapsone and dextro-sulphenidol,[8a,b] and are also components within a range of other medicines, including the non-steroidal anti-inflammatory, rofecoxib, and the retinoid, sumarotene (Figure 2).[8c,d] However, the capacity to exploit the sulfone as a directing group in C−H activation processes,[9] including HIE,[10] is currently vastly undermet. With specific regard to HIE, Pfaltz and Muri have reported an *N*,*P*-chelated Ir(I) catalyst, which mediates deuterium labeling of a series of substrates, including

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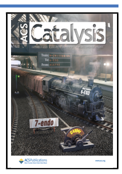

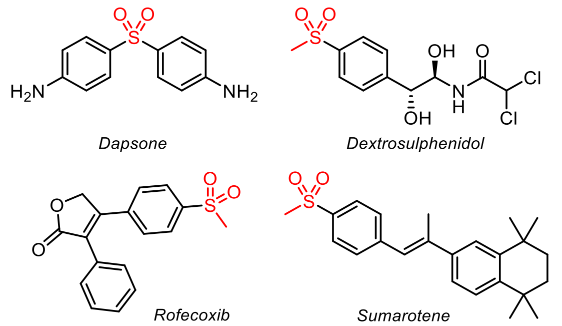

Figure 2. Examples of sulfone-containing drug molecules.

one example of a simple aryl (phenyl methyl) sulfone. This catalyst system does, however, require activation with elevated pressures (2.2 bar) of deuterium.[10a] Nonetheless, the abundance of the sulfone moiety in pharmaceutically active agents makes the ability to exploit these functional units as handles for *ortho*-directed HIE a particularly attractive goal. Additionally, applying a mechanistic approach to such a challenge has the potential to deliver an enhanced, and potentially predictive, understanding of such directed functionalization endeavors, enabling the use of sulfones in a broader range of C−H activation processes.

Current iridium-catalyzed HIE processes directed by sulfones have a range of limitations. For example, previous studies within our laboratory toward sulfone-directed HIE have employed monodentate iridium(I) catalysts, specifically NHC/phosphine **1a** and NHC/Cl analogue **3a**. When these catalyst systems were applied to the labeling of phenyl methyl sulfone **4a**, low levels of incorporation were observed (Figure 3a).[6a] We hypothesized that, in this case, substrate binding was unusually the turnover-limiting step, in contrast to less hindered directing groups where C−H activation is turnover limiting.[5c]

Bearing in mind that catalysts **1**−**3** possess very large NHC and (for **1** and **2**) phosphine ligands, coordinated in a *trans* relationship (Figure 3b), the tetrahedral nature of the sulfone directing group results in significant steric repulsion between the substrate and ligand when compared to more planar directing groups, such as acetyl. This may inhibit substrate binding, which in turn would severely limit the isotope incorporation in sulfone-derived substrates, as observed with **1a** and **3a**.[6a] We hypothesized that the use of a tethered *N*-heterocyclic carbene-phosphine ligand (NHC-P, Figure 3b) would result in a less hindered catalyst environment, more able to accommodate the sulfone unit.

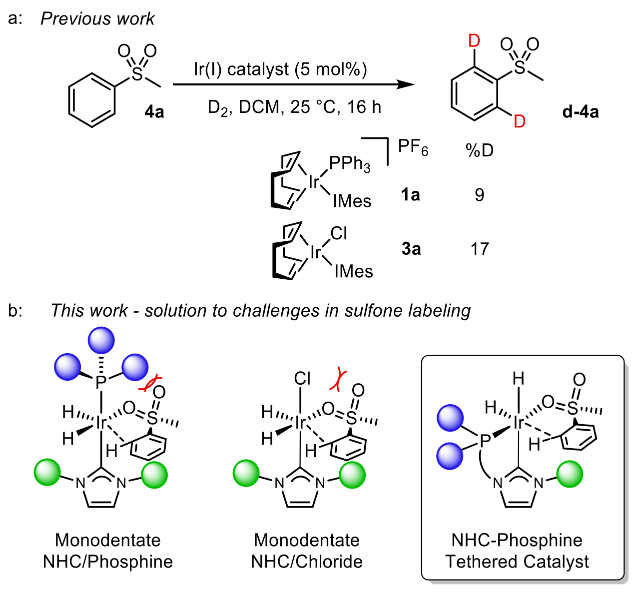

Figure 3. Sulfone labeling: Challenges with monodentate catalysts and a potential chelated catalyst solution.

The paradigm of rational ligand design is emerging as an appreciably powerful tool through which the knowledge and understanding gained from mechanistic insights allows an effective catalyst to be accessed rapidly.[11,12] We selected this approach to address the challenge of developing a broadly effective chelated catalyst system with the ability to label sulfone-bearing substrates to high levels of isotope incorporation under mild reaction conditions. Specifically, a system derived from rational, computational design would not only provide a solution to the challenge of sulfone labeling but would also potentially facilitate the application of the designed system to a more diverse array of substrate classes.

To initiate our studies, and guided by our postulate that substrate binding was limiting in the sulfone case (Figure 3), computational modeling was used to calculate the binding energy (E_{Bind}) of a model substrate methyl phenyl sulfone **4a** to catalytically relevant[5c] iridium(III) hydride complexes of varying designs (Figure 4). The binding energy was calculated

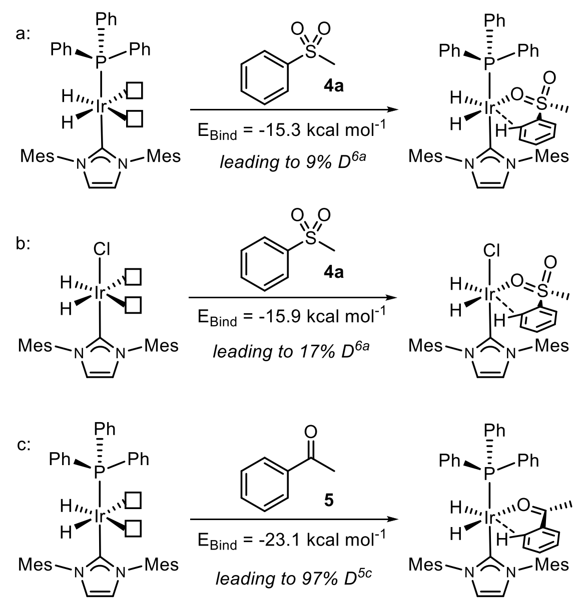

Figure 4. Calculation of binding energy with monodentate ligand systems.

using the counterpoise method, as described by Boys and Bernardi.[13] We observed that while methyl phenyl sulfone **4a** could coordinate to the monodentate NHC/phosphine iridium(III) hydride derived from **1a** (Figure 4a), a modest binding energy of only −15.3 kcal mol^{-1} was calculated, with a similarly poor binding energy of −15.9 kcal mol^{-1} for precatalyst **3a** (Figure 4b). To place these binding energies in context, when the same method was applied to the binding of acetophenone **5** (which has been shown to label to high levels using precatalyst **1a**[5c]), a significantly more negative and

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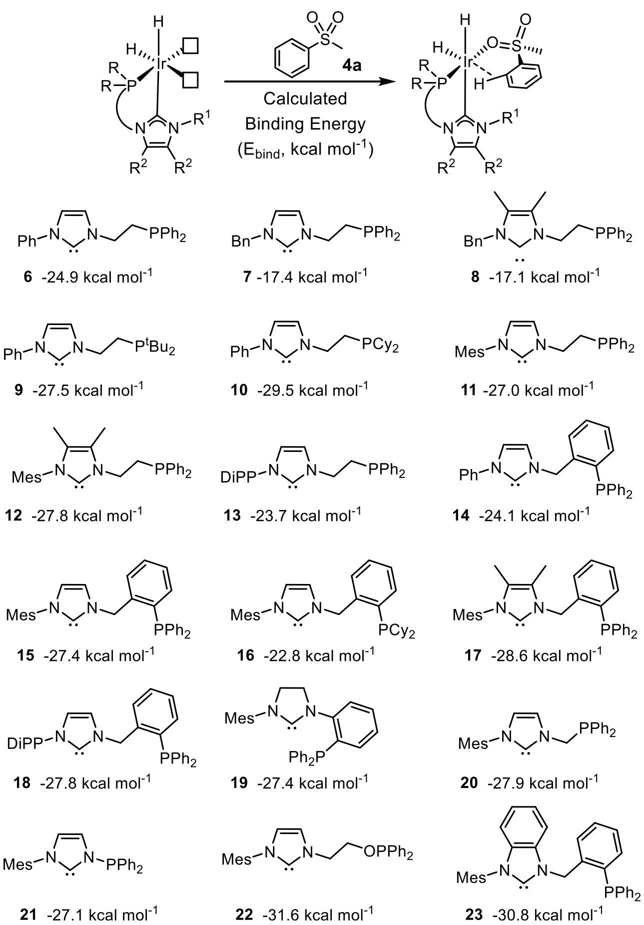
therefore more favorable binding energy of −23.1 kcal mol^{-1} was found (Figure 4c).

In terms of selecting a chelating ligand system to overcome these binding issues, a number of tethered NHC-P ligand motifs have been reported.[14] Due to the range of tethers and combinations of NHC and phosphine substituents already established, an *in silico* screening was carried out to determine which characteristics of the chelating ligand would lead to an increased sulfone binding energy, and thus a potentially effective catalyst system. Accordingly, we proposed a virtual library of eighteen structurally diverse NHC-P ligands, covering a number of chelate sizes (from four to seven membered rings), and a range of steric and electronic parameters, as dictated by the substituents on the NHC and phosphine moieties. In each case, the binding energy of methyl phenyl sulfone to the relevant chelated iridium(III) hydride was calculated (Scheme 2).

Scheme 2. *In Silico* Screen of Bidentate Ligands and the Calculated Binding Energy for Methyl Phenyl Sulfone



Firstly, it was noted that only those ligands with *N*-aryl substituents gave significantly higher sulfone binding energies than the monodentate systems (cf. **6** vs **7**). In general, ethylene tethered systems (**6**, **9**−**13**) showed a favorable range of binding energies, from −23.7 kcal mol^{-1} for **13** to −29.5 kcal mol^{-1} for **10**. Also, aryl and alkyl phosphines both gave enhanced binding energies when compared to the aforementioned monodentate catalysts. Furthermore, substitution on the backbone of the NHC appeared to deliver a moderately more favorable binding energy in some cases (cf. **12** vs **11**). The larger, benzyl-tethered ligands, **14**−**18**, also showed favorable sulfone binding energies with a similar pattern to the corresponding ethylene-bridged systems being observed in terms of the NHC substituent. Dicyclohexyl phosphinyl variant **16**, however, displayed a reduced binding energy with respect to the diphenylphosphinyl analogue **15** and, as such, no further dialkylphosphines were considered. The effect of the chelate ring size and rigidity was next examined, with the *ortho*-phenylene, **19**, methylene bridged, **20**, and directly N-P bound ligand, **21**, all displaying favorable binding energies. Interestingly, phosphite, **22**, returned the highest binding energy of all ligand variations examined. Finally, the benzimidazole-derived NHC, **23**, was also found to be favorable, resulting in a binding energy of −30.8 kcal mol^{-1}. The calculated binding energies for each of the 18 bidentate complexes, as well as monodentate complexes **1a** and **3a**, are shown graphically in Figure 5.

From this *in silico* screen, a total of six ligands (**11**, **13**, **15**, **17**, **18**, and **23**) were selected for progression based on their binding energy of methyl phenyl sulfone **4a**, coupled with their synthetic tractability in each case. The structures of the targeted iridium(I) precatalysts **24**−**29** are shown in Figure 6, with the selected ligands predicted to give complexes with a range of substrate binding energies from −23.7 to −30.8 kcal mol^{-1}. The ligands for the iridium(I) precatalysts shown were then synthesized via modification of existing literature procedures.[14d−g,15]

With the iridium(I) precatalysts **24**−**29** in hand, their labeling of methyl phenyl sulfone **4a** was investigated. This initial catalyst screen was performed at 25 °C in dichloromethane with a standard catalyst loading of 5 mol % and a reaction time of 16 h. In the majority of cases (i.e., with the exception of **25** and **27**), a marked increase in the isotope incorporation was observed compared to the monodentate systems **1a** and **3a** (Table 1).

Based on the labeling results shown in Table 1, the most promising catalyst, **29**, was selected for further optimization, beginning with a solvent screen and exploiting the versatility of the catalyst's BAr_F counterion in this regard.[5d] As shown in Figure 7, the observed incorporation reached significantly higher levels in a broad range of solvents compared to the initial labeling result in DCM. In particular, chlorobenzene and fluorobenzene delivered the highest levels of labeling, affording excellent 93 and 91% incorporations, respectively. Additionally, the use of non-halogenated solvents such as di-*iso*-propyl ether, MTBE, diethyl ether, and toluene also provided high levels (>70%) of deuterium incorporation.

Accordingly, chlorobenzene was chosen as the optimal solvent for this sulfone labeling process with catalyst **29**. Not only did this medium allow for the best incorporation from the eleven solvents examined but also additional technical advantages were delivered, in that the higher boiling nature of chlorobenzene meant that cooling to −78 °C could be avoided when exchanging the atmosphere within the reaction manifold from nitrogen to deuterium, thus simplifying the practical procedure. Notably, maintaining catalyst loadings at 5 mol %, the reaction time could be reduced to 1 h, with no drop in the observed isotope incorporation.[15] These conditions were then applied to a broad range of aryl sulfones to establish the scope of our developed process (Scheme 3). A total of eighteen additional substrates were examined, encompassing a diverse range of sulfones with generally excellent deuterium incorporation effectiveness observed throughout the series. Both electron-donating and electron-withdrawing substituents

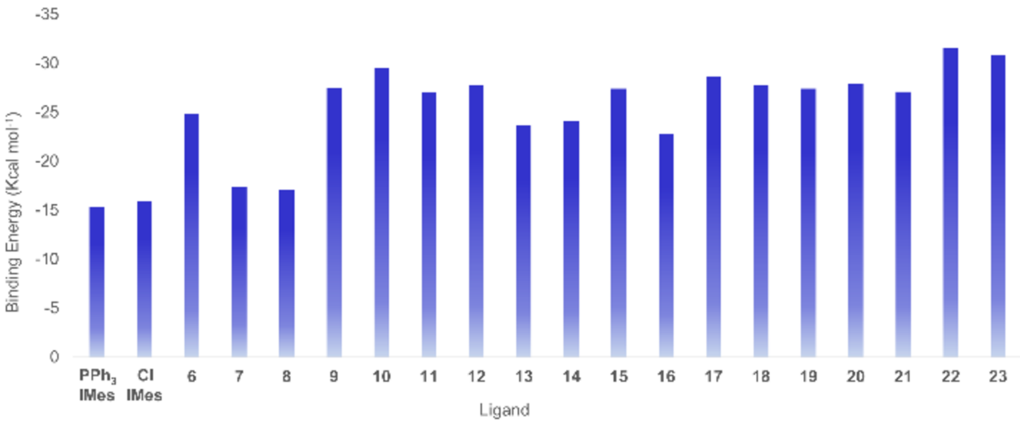


Figure 5. Calculated binding energies with sulfone 4a.

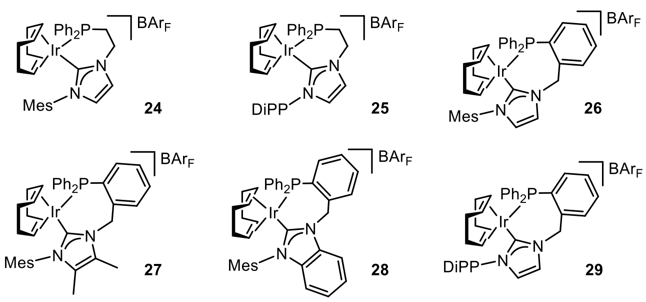
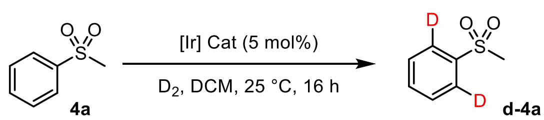


Figure 6. Summary of the targeted Iridium(I) precatalysts.

Table 1. Catalyst Screen[a]



entry	catalyst	% D incorporation[a]
1	**1a**	9[6a]
2	**3a**	17[6a]
3	**24**	35
4	**25**	12
5	**26**	23
6	**27**	13
7	**28**	36
8	**29**	43

[a]Reactions performed in triplicate.

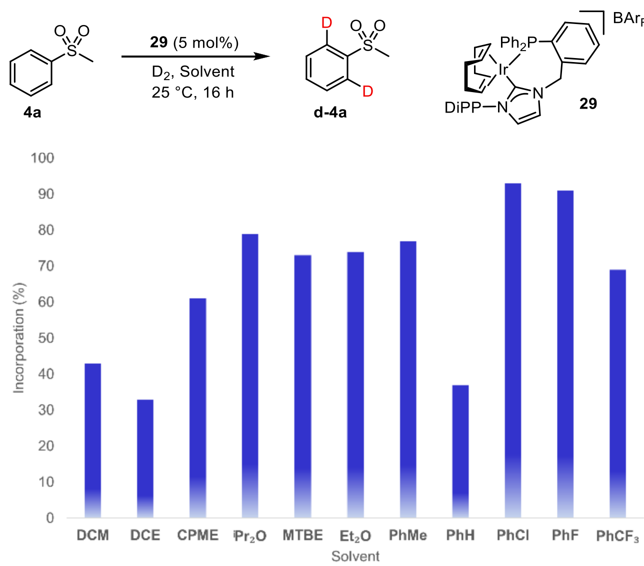


Figure 7. Solvent applicability in sulfone labeling.[15]

in the *ortho* (**4b**−**4d**) and *meta* (**4e**−**4 h**) positions of the aryl ring were well tolerated, leading to high levels of incorporation. Notably, *meta*-trifluoromethyl substrate **4 g** exhibits almost no incorporation at the considerably hindered position between both aryl substituents, but displays excellent levels of deuterium labeling at the less hindered position *ortho* to the sulfone. With less sterically encumbered *meta* substituents (**4f** and **4 h**) both positions *ortho* to the sulfone are labeled to a high degree. A range of electronically distinct *para*-substituents are also well tolerated (**4i**−**4l**, **4n**). In the case of *para*-nitro substrate **4 m**, this alternative directing group is shown to mildly outcompete the sulfone, but does not prevent an acceptable level of isotope incorporation through sulfone-directed HIE. Furthermore, restricting the orientation of the sulfone, as in cyclic substrate **4o**, did not result in a decrease in the excellent levels of incorporation generally observed. We next turned our attention to the effects of increasing the steric bulk around the sulfone group, with substrates **4p**−**4r**. While a slight decrease in the levels of incorporated deuterium were observed in diphenyl sulfone **4p** and *iso*-propyl phenyl sulfone **4q** (57 and 66%, respectively), an excellent incorporation of 80% was observed with the bulky *tert*-butyl phenyl sulfone **4r**. We also investigated labeling of benzyl methyl sulfone **4s**, where the sulfone would direct labeling via a 6-membered metallacyclic intermediate (6-mmi), which is considerably less favored than the more common 5-mmi.[5c] Nonetheless, moderate levels of incorporation were still observed in this more challenging substrate under these mild standard conditions with a low catalyst loading of 5 mol %.

To further expand the utility of our newly developed catalyst system, we investigated the effects of employing a reduced pressure of deuterium gas using a TRITEC manifold system, with these conditions more closely emulating those deployed for radiolabeling with tritium gas within a pharmaceutical industry setting. Following only minimal optimization of our standard conditions,[15] we obtained high levels of labeling under these low-pressure conditions (Scheme 4). Employing phenyl methyl sulfone **4a**, it was found that with a deuterium pressure of only ∼400 mbar, a mildly elevated catalyst loading of 7.5 mol % allowed for similar levels of deuterium

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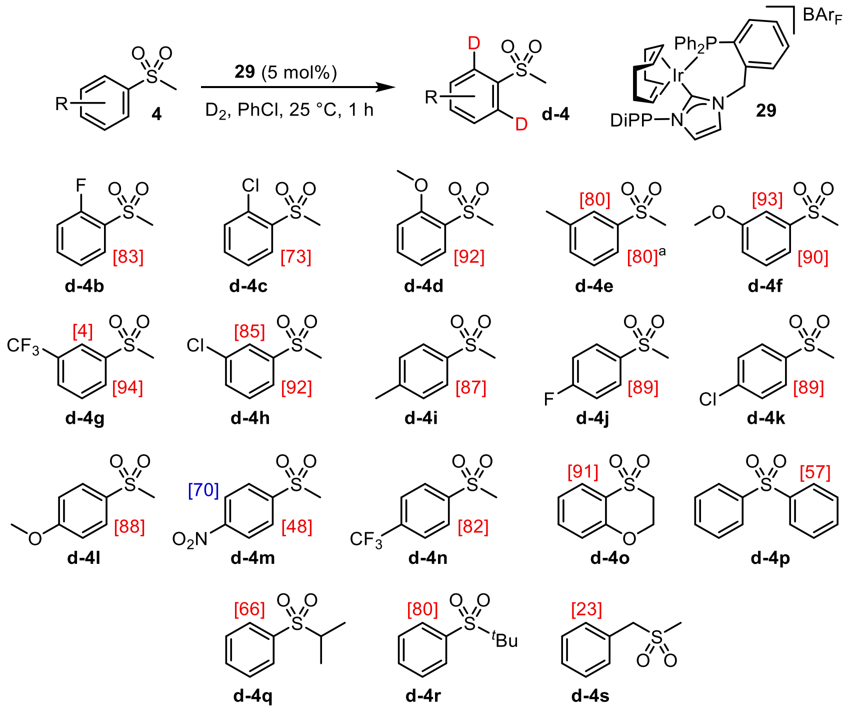
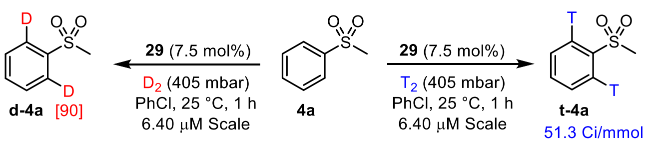
Scheme 3. Scope of Aryl Sulfone Labeling



[a]Incorporation averaged across both positions.

Scheme 4. Reduced Pressure Deuterium and Tritium Labeling of Methyl Phenyl Sulfone 4a



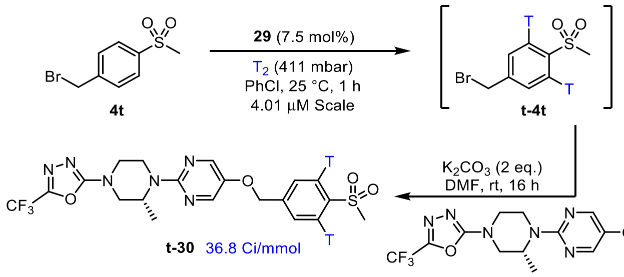
incorporation to the standard (non-TRITEC) laboratory set-up. Notably, when employing the most active catalyst reported by Pfaltz and Muri,[10a] very low levels of labeling of this same substrate, **4a**, were observed when employing 1 atm of D_2 for catalyst activation,[15] as is routinely employed with our suite of Ir(I) catalysts, including **29**. Indeed, the requirement for supra-atmospheric catalyst activation with this previously reported system may present practical challenges when applying the methodology to low-pressure tritiations (vide infra).

With a successful reduced atmosphere protocol in hand using catalyst **29**, the conditions were then applied to the tritium labeling of the same sulfone **4a**. Exposure of **4a** to 7.5 mol % of precatalyst **29** under 405 mbar of tritium gas afforded **t-4a** with a high activity of 51.3 Ci/mmol, corresponding to a tritium incorporation of 88% across both *ortho* positions. Additionally, the major mass ion of [M + 4] confirmed that the sample had indeed been labeled with two units of tritium (Scheme 4).

Finally, to further demonstrate the power of our developed catalyst as applied to radiolabeling, as shown in Scheme 5 we targeted a tritium-labeled sample of the highly potent GPR119 agonist **30**.[16] Accordingly, benzylic bromide-containing sulfone **4t** could be readily tritiated and alkylated in one pot to afford **t-30** with excellent levels of radiolabel incorporation.

In conclusion, we have employed a computationally-guided, rational ligand design approach to target a series of iridium(I) NHC-P complexes for the directed HIE of aryl sulfones. The resulting optimal complex proved to be highly active in a range of solvents, and an extensive substrate scope has been established, with high levels of deuterium incorporation being exhibited across the series. Furthermore, the catalyst system has been shown to retain its activity when applied to the low-pressure labeling systems currently used extensively in the pharmaceutical industry. Finally, the emerging iridium(I) NHC-P catalyst has been applied to tritium labeling, furnishing a selectively tritiated sample of GPR119 agonist **t-30** with high levels of specific activity. Our current studies are focused on extending our understanding of these catalytic systems in order to further refine our design process to encompass even more challenging substrates.

Scheme 5. Tritium Labeling of GRP119 Agonist 30



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03031.

Details of experimental procedures and computational methods (PDF)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

BAr_F tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
Bn benzyl
CPME cyclopentyl methyl ether
DCE 1,2-dichloroethane
DCM dichloromethane
DiPP 2,6-di-*iso*-propylphenyl
Mes 2,4,6-trimethylphenyl
MTBE methyl *tert*-butyl ether
NHC *N*-heterocyclic carbene

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