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# Selective H/D Exchange at Vinyl and Methylidene Groups with $D_2O$ Catalyzed by an Iridium Complex

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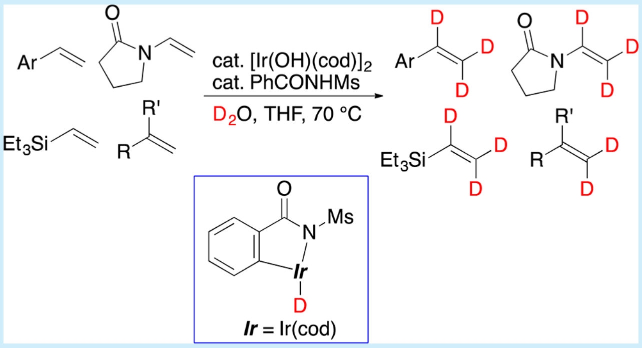
Supporting Information

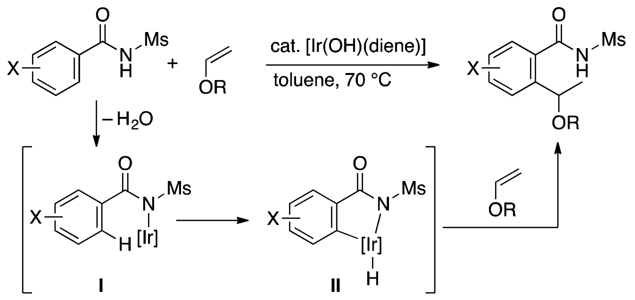
**ABSTRACT:** Selective H/D exchange at vinyl and methylidene groups of alkenes with $D_2O$ was promoted by an iridium catalyst generated in situ from a hydroxoiridium complex and *N*-mesylbenzamide.



Introduction of deuterium into organic molecules by H/D exchange reaction is a powerful method to directly synthesize deuterium-labeled compounds, which are valuable for the study of reaction mechanisms and for a variety of applications in the pharmaceutical and materials industries.[1] The development of such H/D exchange methods also enables the straightforward synthesis of tritiated compounds.[2] H/D exchange processes have been well-studied in organometallic chemistry, and diverse transition metal catalysts focusing on the synthesis of deuterated compounds have been developed.[1,3] Iridium is one of the most active catalysts for H/D exchange reactions of aromatic and aliphatic C−H bonds.[4] With the recent development of selective C−H bond functionalization, there is increasing attention on selective deuteration of alkenyl moieties.[5−9] In 2008, Zhou and Hartwig[5] reported Ir-catalyzed selective H/D exchange at vinyl groups without olefin isomerization, where the deuterium is transferred from $C_6D_6$. Iridium catalysts containing an aliphatic pincer-type ligand had high catalytic activity, which permits aromatic C−H bond deuteration also. Oro and co-workers reported Rh-catalyzed selective H/D exchange at the $\beta$-position of aromatic $\alpha$-olefins in the presence of $CD_3OD$ or $D_2O$.[6] A Ru-catalyzed H/D exchange reaction of alkenes was reported by Lin, Jia, and co-workers.[7]

We recently reported Ir-catalyzed asymmetric alkylation of aromatic *N*-sulfonylbenzamides with vinyl ethers (Scheme 1).[10] The reaction is efficiently catalyzed by a hydroxoiridium/chiral diene complex to give the branched adducts in high yields with high enantioselectivity. Hydridoiridium species **II** generated by means of *ortho* C−H activation of amidoiridium species **I** is a key intermediate. The reaction proceeds in the presence of $D_2O$ to afford deuterium incorporation into the adduct, the substrate amide, and the vinyl ether. In this deuteration, hydridoiridium **II** should undergo H/D exchange, and the following deuterium transfer to the vinyl ether should occur through reversible insertion and $\beta$-hydrogen elimination. While this deuterium-labeling experiment was thus helpful to understand the reaction mechanism, interestingly, similar deuterium incorporation was also observed for alkenes that are unreactive toward the amide. The results prompted us to apply species **II** as a catalyst for the H/D exchange reaction of alkenes using $D_2O$. Here we report that selective H/D exchange of vinyl and methylidene groups is promoted by an iridium catalyst generated in situ from a hydroxoiridium complex and *N*-mesylbenzamide.

**Scheme 1. Ir-Catalyzed Alkylation of *N*-Sulfonylbenzamides**



Our initial studies (Table 1) focused on the H/D exchange of *p*-methoxystyrene (**2a**) in the presence of an iridium complex because styrene derivatives did not undergo the alkylation of *N*-sulfonylbenzamides in our previous studies.[10] Treatment of **2a** with 20 equiv of $D_2O$ in the presence of a catalytic amount of $[Ir(OH)(cod)]_2$ (5 mol % Ir, cod = 1,5-cyclooctadiene) and amide **1a** (10 mol %), which is a good

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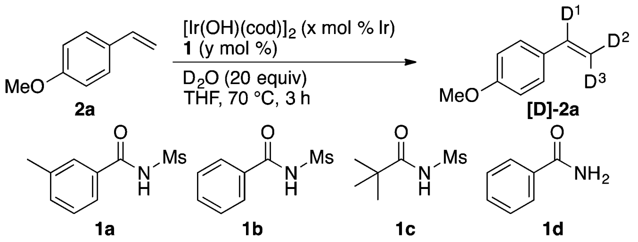
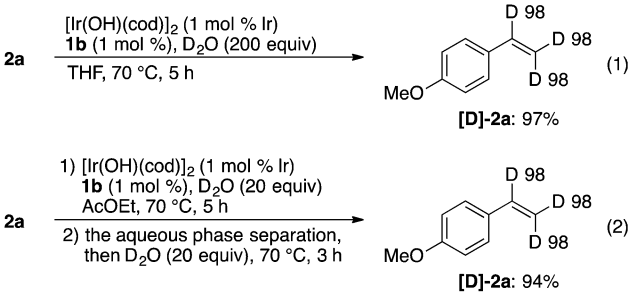
**Table 1. Ir-Catalyzed H/D Exchange of 2a with $D_2O$[a]**

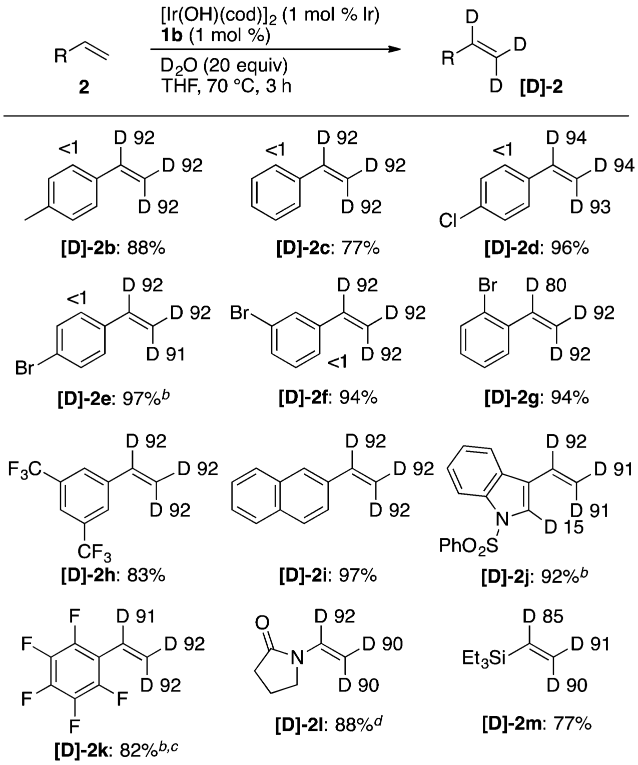


| entry | 1 | x, y | yield (%)[b] | $D^1$ [c] | $D^2$ [c] | $D^3$ [c] |
|---|---|---|---|---|---|---|
| 1 | 1a | 5, 10 | 98 | 92 | 92 | 90 |
| 2 | 1b | 5, 10 | 99 | 91 | 91 | 91 |
| 3 | 1c | 5, 10 | 96 | 0 | 0 | 0 |
| 4 | 1d | 5, 10 | 92 | 0 | 0 | 0 |
| 5 | – | 5, 0 | 94 | 0 | 0 | 0 |
| 6 | 1b | 0, 5 | 97 | 0 | 0 | 0 |
| 7 | 1b | 5, 5 | 99 | 92 | 91 | 91 |
| 8 | 1b | 1, 1 | 88[d] | 92 | 91 | 91 |
| 9 | 1b | 0.1, 0.1 | 94[d] | 90 | 90 | 90 |
| 10[e] | 1b | 0.1, 0.1 | 96[d] | 92 | 91 | 91 |

[a] Reaction conditions: **2a** (0.10 mmol), amide **1**, $[Ir(OH)(cod)]_2$, and $D_2O$ (20 equiv) in THF (0.40 mL) at 70 °C for 3 h. For entry 8, 0.50 mmol of **2a** was used. For entries 9 and 10, 5.00 mmol of **2a** was used. See the Supporting Information for details. [b] Determined by $^1H$ NMR analysis using nitromethane as an internal standard. For entries 3–6, the percentages of recovered **2a** are shown. [c] Deuterium contents (%) were determined by $^1H$ NMR analysis. [d] Isolated yield. [e] For 20 h.



**Scheme 2. Ir-Catalyzed H/D Exchange of Vinyl Groups[a]**



[a] Reaction conditions: **1b** (1 mol %), $[Ir(OH)(cod)]_2$ (0.0025 mmol, 1 mol % Ir), **2a** (0.50 mmol), and $D_2O$ (10 mmol, 20 equiv) in THF (0.40 mL) at 70 °C for 3 h. Isolated yields are shown. Deuterium contents were determined by $^1H$ NMR analysis. [b] Performed with 2 mol % Ir. [c] Deuterium contents were determined by $^1H$ NMR analysis of 1,2,4,5-tetrafluoro-3-methoxy-6-(vinyl-$d_3$)benzene derived from [**D**]-**2k**. [d] Performed with 5 mol % Ir.

substrate in the Ir-catalyzed *ortho*-alkylation with vinyl ethers,[10] in THF at 70 °C for 3 h gave deuterated [**D**]-**2a** (Table 1, entry 1). The deuterium was selectively introduced into the vinyl group of **2a** ($D^1$–$D^3$, 90–92%), and no deuterium was detected on the aromatic ring or the methoxy group. The high catalytic activity was also observed when a catalytic amount of *N*-mesylbenzamide (**1b**) was used (entry 2), whereas the use of either *N*-mesylpivalamide (**1c**) (entry 3) or benzamide (**1d**) (entry 4) did not promote the H/D exchange. The combined use of $[Ir(OH)(cod)]_2$ and amide **1b** was essential for the present reaction (entries 5 and 6). An equimolar amount of amide **1b** with respect to iridium was enough to promote the reaction (entry 7). The H/D exchange was achieved by use of a reduced amount of the catalyst (entries 8–10): a high level of deuterium incorporation was observed in the reaction with only 0.1 mol % Ir catalyst for a prolonged reaction time (20 h) (entry 10). The observed deuterium contents are close to the maximum theoretical level of deuteration attainable under the reaction conditions (92.9% for 1 mol % Ir catalyst).[11] The reactions in other solvents, such as toluene, 1,4-dioxane, acetonitrile, and ethyl acetate, also displayed the same level of deuterium incorporation as observed in THF under a 5 mol % loading of the Ir catalyst.[11]

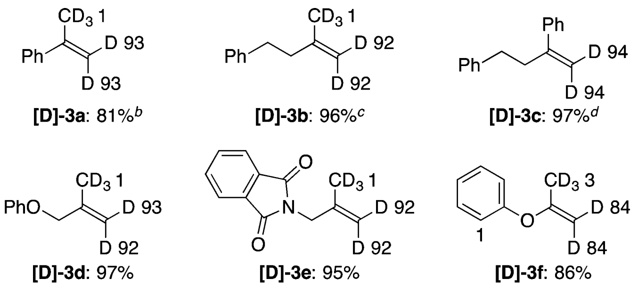
Higher deuterium content (98%) was achieved by the use of a quite large excess of $D_2O$ (200 equiv) (eq 1). Alternatively, treatment of **2a** twice with $D_2O$ (20 equiv each) by replacing the first $D_2O$ phase with fresh $D_2O$ led to the exchange of vinylic protons with 98% deuterium incorporation (eq 2).

Scheme 2 summarizes the results obtained for the H/D exchange of vinyl groups with $D_2O$ (20 equiv). Vinyl arenes **2b**–**k** are good substrates, giving the deuterated alkenes [**D**]-**2b**–**k** in high yields with high deuterium contents; the H/D exchange selectively occurred at the vinyl group, and only a trace amount of deuterium at the *ortho* positions of the phenyl group was observed for **2b**–**f**. Chloro (**2d**) and bromo groups (**2e**–**g**) were tolerated in the reaction. In the reaction of 3-vinylindole **2j**, a significant amount of deuterium at the 2-position (15%) was observed. The present catalytic system was successfully applied to the H/D exchange of pentafluorostyrene (**2k**) and *N*-vinylpyrrolidone (**2l**), which are useful monomers for important synthetic materials, fluorinated polymers[12] and poly(*N*-vinylpyrrolidone),[13] respectively. The H/D exchange of vinyl silane **2m** took place efficiently. Unfortunately, the present catalytic system cannot be applied to the H/D exchange of terminal alkenes having allylic protons such as 1-octene because of fast isomerizations into inactive internal alkenes.

It should be noted that the hydroxoiridium/amide **1b** catalyst displayed high catalytic activity toward the H/D exchange of methylidene groups without isomerization of the alkenes

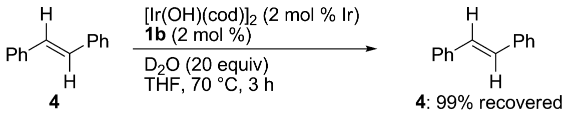
(Scheme 3). The reaction of α-methylstyrene (**3a**) with $D_2O$ gave [**D**]-**3a**, whose methylidene group was selectively deuterated, with only a small amount of deuterium incorporation observed at the methyl group (1% D). Besides simple alkenes **3b** and **3c**,[14] allylic ether **3d**, allylic imide **3e**, and isopropenyl ether **3f** were deuterated at the methylidene groups with high regioselectivity. To the best of our knowledge, there have been no reports on the catalytic selective H/D exchange reaction of methylidene groups of alkenes having aromatic rings.[15]

**Scheme 3. Ir-Catalyzed H/D Exchange of Methylidene Groups**[a]

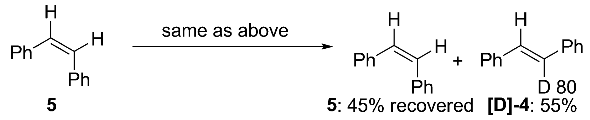


[a]The reactions of alkenes **3** were performed in the presence of $[Ir(OH)(cod)]_2$ (2 mol % Ir), amide **1b** (2 mol %), and $D_2O$ (20 equiv) in THF at 70 °C for 3 h. Isolated yields are shown. Deuterium contents were determined by $^1H$ NMR analysis. [b]For 20 h. [c]Performed with 5 mol % Ir. [d]Performed with 5 mol % Ir for 14 h.

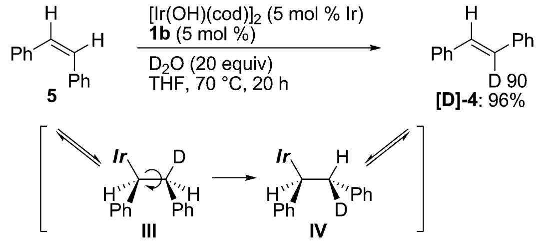
The H/D exchange reaction of *trans*-stilbene (**4**) did not take place at all (eq 3), whereas *cis*-stilbene (**5**) was transformed into monodeuterated *trans*-stilbene ([**D**]-**4**) in the presence of $D_2O$ (eq 4). Complete conversion of **5** was achieved in the presence of 5 mol % Ir catalyst after 20 h to give [**D**]-**4** in 96% yield, which contained 90% deuterium (eq 5). The observed isomerization of **5** accompanied by the monodeuteration can be explained by an insertion/*β*-elimination mechanism; a bond rotation in alkyliridium species **III** occurs to form conformer **IV**, which leads to the formation of *trans*-stilbene. However, the rotation from **IV** to **III** leading to *cis*-stilbene is disfavored because of its steric effect. The present selectivity is different from that observed in the Ru catalysis by Lin, Jia, and co-workers, who reported that deuterated *trans*-stilbene was formed from both *trans*-stilbene and *cis*-stilbene.[7]



(3)



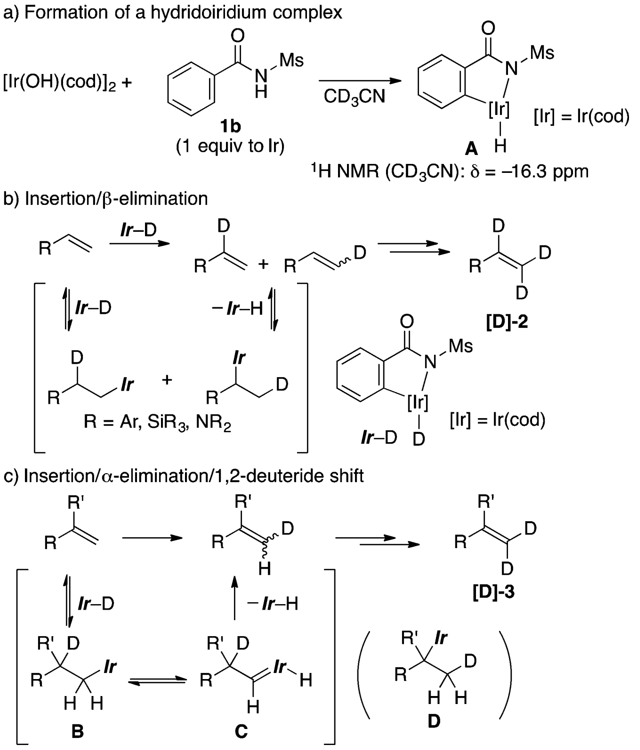
(4)



(5)

The pioneering studies on *α*-elimination in alkyliridium complexes by Crabtree and co-workers provide us mechanistic insight into the present H/D exchange reaction.[16,17] They reported that a stoichiometric reaction of the iridium dihydride $IrD_2(OCOCF_3)(P(4\text{-}FC_6H_4)_3)_2$ with *α*-methylstyrene gave a monodeuterated product, which was proposed to be formed by way of *α*-elimination followed by *β*-elimination.[16a] An alternative reaction pathway involving alkane C−H activation has been proposed in subsequent studies.[16b] We observed the formation of the hydridoiridium species **A** (intermediate **II** in Scheme 1) by $^1H$ NMR spectroscopy in the reaction of $[Ir(OH)(cod)]_2$ with **1b** in $CD_3CN$ (Scheme 4a).[11] In our catalytic system, an insertion/*β*-elimination route (Scheme 4b) via aryldeuterioiridium ***Ir*****-D** is most likely to permit the H/D exchange of vinyl groups in Table 1 and Scheme 2. In the H/D exchange of methylidene groups shown in Scheme 3, primary alkyliridium **B** formed by the insertion possibly undergoes *α*-elimination to form carbene complex **C**, and a subsequent 1,2-deuteride shift[18] gives the deuterated compound (Scheme 4c).[19] The *α*-elimination route is consistent with the fact that the isomerization of the alkene moiety caused by species **D** was not observed for the methylidene compounds.[20]

**Scheme 4. Plausible Reaction Pathways**


a) Formation of a hydridoiridium complex

b) Insertion/β-elimination

c) Insertion/α-elimination/1,2-deuteride shift

In summary, we have developed an Ir-catalyzed selective H/D exchange of vinyl and methylidene groups that is promoted by an iridium catalyst generated in situ from a hydroxoiridium complex and *N*-mesylbenzamide. Experimental studies are underway to gain detailed mechanistic insights into the present catalytic system.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01721.

Experimental procedures and NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(19) Deuterium exchange on species **C** and reverse $\alpha$-migration and $\beta$-elimination could also allow the H/D exchange of **3**.

(20) An alternative pathway is that the Ir−H(D) species adds in a 2,1-fashion to form *tert*-alkyliridium **D** having an agostic interaction with the formed Me group. Rapid rotation of the agostic Me followed by $\beta$-elimination would result in D incorporation into the methylene positions as observed. Exchange of the nonagostic Me with the agostic Me followed by $\beta$-elimination would result in minor D incorporation into the Me group as observed (e.g. 1% D incorporation into Me in the reaction of $\alpha$-methylstyrene). For an example of the dynamics of the $\beta$-agostic isopropylpalladium complex, see: Tempel, D. J.; Brookhart, M. *Organometallics* **1998**, *17*, 2290.