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Selective deuteration of terminal olefins with D₂O by catalysis of osmium-hydride complexes†

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An efficient catalytic system for selective deuteration of terminal olefins using D₂O as the deuterium source has been developed. A series of osmium hydride complexes of the type OsHX(CO)(PR₃)₂(L) (where X represents halides) has been evaluated as catalyst precursors for H/D exchange between olefins and D₂O. The catalytic activity of the complexes was found to depend on the ligands present. Among the complexes tested, the OsH(CO)(PPh₃)₃ complex exhibited excellent catalytic activity for the hydrogen–deuterium (H/D) exchange of terminal olefins with D₂O, especially in the presence of acetic acid. The system shows high selectivity for deuteration at terminal double bonds over internal ones. It can catalyze H/D exchange reactions of olefins without causing isomerization and can induce selective H/D exchange at the methine carbon (=CHR) over the methyldene carbon (=CH₂) for substrates RCH=CH₂ with a bulky substituent R. Additionally, these reactions can be performed on substrates with various functional groups, making this system useful for selective labeling of olefins in complex molecules.

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Introduction

Deuterium labeled compounds are of prime importance in various fields, including life science/drug discovery,¹ materials science,² and analytical chemistry,³ due to the unique properties deuterium imparts to molecules. Consequently, the development of reliable and efficient methods for producing deuterated organic compounds is of great interest and has been actively pursued in both academic and industrial laboratories.^{4,5} The production of deuterated olefins is particularly in demand, as functionalized olefins are found in natural products, synthetic drugs or bioactive molecules.⁶ Additionally, deuterated olefins serve as useful building blocks that can be transformed into various deuterium-labeled functional materials.

A common approach for obtaining deuterium labelled olefins involves conventional multistep chemical synthesis methods using deuterated precursor reagents. Examples include reductive deuteration of alkynes,^{7,8} deuteroisomerization of 2-butyne,⁹ and deuterodehalogenation of alkenylhalides.^{10–12} An alternative approach is to use direct hydrogen isotope exchange (HIE) reactions of olefins with appropriate deuterated sources. The latter approach could potentially be simpler to conduct and more cost-effective than

the approach involving multistep synthesis with labeled reagents. The process can be promoted by catalysts based on acids¹³/bases,¹⁴ enzymes¹⁵ and metal complexes.

Catalytic systems based on transition metal complexes are especially attractive and have received significant attention because their properties can be more easily tuned. H/D exchange reactions of olefins have been achieved with deuterium sources such as D₂, C₆D₆, CD₃COCD₃, CD₃OD and D₂O and with complexes of iridium,^{16,17} rhodium,^{18,19} iron,²⁰ ruthenium,^{21,22} cobalt,²³ palladium,²⁴ platinum,²⁵ and manganese.^{26,27}

Despite impressive progress, there is still a need to develop efficient catalysts for controlling or improving selectivity in metal-catalyzed H/D exchange reactions. For example, while many examples of H/D exchange reactions have been demonstrated with isolated olefins (*e.g.*, styrene and *tert*-butylethylene), selective H/D exchange reactions of isomerizable olefins (*e.g.*, 1-hexene) have achieved limited success because olefin isomerization often occurs under reaction conditions. As a rare example, Hartwig *et al.* showed that the Ir-pincer complex [(dtbpp)Ir(H)(NH₂)] (dtbpp = 1,5-bis(di-*tert*-butylphosphino)pentan-3-yl) catalyzed the selective H/D exchange reactions of olefins with C₆D₆ at the vinylic positions without olefin isomerization.¹⁵ To the best of our knowledge, there are still no catalysts demonstrated for selective H/D exchange reactions of olefins with D₂O without isomerization. Additionally, few studies have been conducted to compare the relative selectivity for H/D exchange reactions at terminal and internal vinylic positions. Furthermore, it remains a challenge to achieve selective HIE of the three olefinic protons (*e.g.*, =CHR *vs.* =CH₂) of

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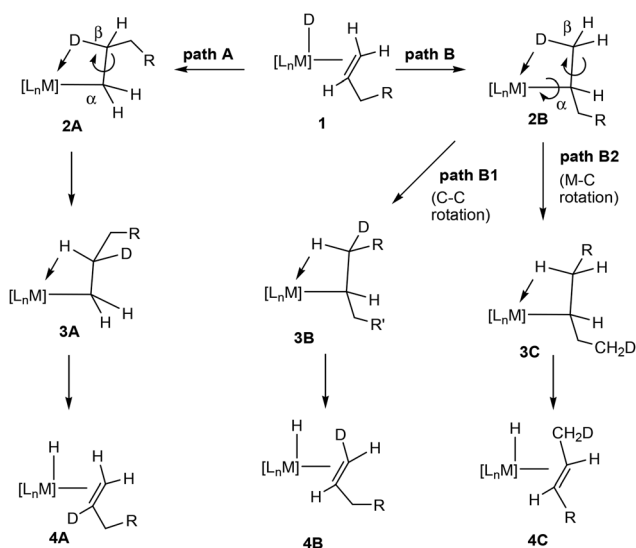


terminal olefins $\text{RCH}=\text{CH}_2$ in the absence of a directing group. In this work, we report the development of an efficient catalytic system for selective deuteration of terminal olefins with D_2O . The system shows high selectivity for deuteration at terminal double bonds over internal double bonds and can catalyze H/D exchange reactions of olefins without isomerization. It induces selective H/D exchange at the methine carbon ($=\text{CHR}$) over the methylidene carbon ($=\text{CH}_2$) for substrates $\text{RCH}=\text{CH}_2$ with a bulky substituent R.

Results and discussion

Catalyst design

In principle, a hydride complex $\text{L}_n\text{M}-\text{H}$ could catalyze the H/D exchange reaction of an olefin with D_2O if it can undergo reversible H/D exchange reactions with D_2O and reversible insertion/elimination reactions with the olefin. Scheme 1 shows three reaction pathways for intramolecular H/D exchange reactions of the olefin-deuteride complex **1** containing an isomerizable terminal olefin $\text{RCH}=\text{CH}_2$. Path A leads to deuteration at the internal vinylic carbon or methine carbon ($\text{RCH}=\text{CH}$), path B1 leads to deuteration at the terminal vinylic carbon or methylidene carbon ($=\text{CH}_2$), while path B2 leads to deuteration and isomerization. Careful examination of the reaction pathways reveals that deuteration at the vinylic positions involves $\text{C}(\alpha)-\text{C}(\beta)$ bond rotation of alkyl intermediates **2A** and **2B**, while deuteration/isomerization of the olefin involves rotation about the $\text{M}-\text{C}(\alpha)$ bond in intermediate **2B**. Thus, selective deuteration at the double bond without isomerization (paths A and B1) could only be accomplished if the rotation about the $\text{M}-\text{C}(\alpha)$ bond in intermediate **2B** is restricted (and therefore, path B2 does not proceed).



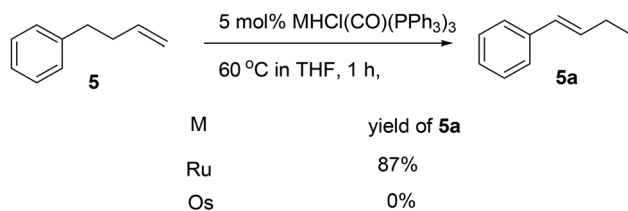
Scheme 1 Three pathways for intramolecular H/D exchange reactions of the deuterido-olefin complex **1**.

The rotational barrier of an $\text{M}-\text{X}$ bond in an $\text{L}_n\text{M}-\text{X}$ complex can be influenced by the properties of both ligands and metals. It is known that $\text{M}-\text{X}$ bond rotational barriers are generally higher for third row transition metals compared with those of analogous second row transition metals. This is exemplified by the rotational barriers of $\text{M}-\text{P}$ bonds in *trans*- $[(t\text{-Bu})_2\text{P}(i\text{-Pr})]_2\text{MCl}_2$ ($\text{M} = \text{Pd}, \text{Pt}$)²⁷ and *trans*- $[(t\text{-Bu})_2\text{PR}]_2\text{M}(\text{CO})\text{X}$ ($\text{R} = \text{H}$ and CH_3 ; $\text{M} = \text{Rh}$ and Ir ; $\text{X} = \text{Cl}, \text{Br}$, and I).²⁸

We have previously shown that the ruthenium hydride complex $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ is catalytically active for H/D exchange reactions between olefins and D_2O .²¹ Like most other reported catalysts, the H/D exchange reactions of isomerizable substrates (e.g., $\text{PhCH}_2\text{CH}=\text{CH}_2$) with the ruthenium catalyst were accompanied by isomerization, presumably due to facile rotation about the $\text{Ru}-\text{C}$ bond in ruthenium alkyl intermediates (like **2B**). Considering that the rotational barrier of an $\text{Os}-\text{C}$ bond might be higher than that of an analogous $\text{Ru}-\text{C}$ bond, we anticipated that the rotation about the $\text{Os}-\text{C}$ bond in osmium-alkyl intermediates might be more restricted. Thus, osmium hydride complexes analogous to $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ may catalyze selective H/D exchange reactions of olefins at the vinyl positions without isomerization.²⁹

To explore this possibility, we first compared the catalytic properties of $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ and $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3$ for the isomerization of $\text{PhCH}_2\text{CH}_2\text{CH}=\text{CH}_2$. *In situ* NMR experiments indicate that $\text{PhCH}_2\text{CH}_2\text{CH}=\text{CH}_2$ (**5**) in THF was completely consumed to give mainly $\text{PhCH}=\text{CHCH}_2\text{CH}_3$ (**5a**) along with a small amount (13%) of $\text{PhCH}_2\text{CH}=\text{CHMe}$ after being heated in the presence of 5 mol% of $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ at 60 °C for one hour (Scheme 2). In contrast, $\text{PhCH}_2\text{CH}_2\text{CH}=\text{CH}_2$ remained essentially unchanged when the reaction was carried out in the presence of $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3$ under similar conditions, producing only a trace amount of $\text{PhCH}_2\text{CH}=\text{CHMe}$ (ca. 4%). These results suggest that $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3$ is much less active than $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ for catalytic olefin isomerization. The lower activity of $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3$ compared with the ruthenium analog in olefin isomerization was further confirmed by the isomerization reaction of $\text{PhCH}_2\text{CH}=\text{CH}_2$ catalyzed by $\text{MHCl}(\text{CO})(\text{PPh}_3)_3$ ($\text{M} = \text{Ru}, \text{Os}$) (see the ESI†).³⁰

The observed lower activity of $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3$ compared with the ruthenium analog $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ in olefin isomerization encouraged us to investigate the catalytic properties of a series of osmium hydride complexes $\text{OsHX}(\text{CO})(\text{PR}_3)_2(\text{L})$ for selective deuteration of olefins with D_2O .



Scheme 2 Catalytic activity of $\text{MHCl}(\text{CO})(\text{PPh}_3)_3$ ($\text{M} = \text{Ru}$ and Os) in the isomerization of $\text{PhCH}_2\text{CH}_2\text{CH}=\text{CH}_2$.



Selection of catalysts and reaction conditions

To evaluate the catalytic properties of the osmium hydride complexes for H/D exchange between olefins and D₂O, we used the reaction of styrene (PhCH=CH₂, **8a**) with 13.5 equivalents of D₂O at 80 °C with a 5 mol% loading of an osmium hydride complex as the model reaction. The maximum or theoretical percentage of deuterium (%D_{theo}) incorporated at the vinyl position (which is the statistical percentage of deuterium on the oxygen of heavy water, the vinyl carbons of styrene, and osmium hydride) is approximately 90%.³¹ The results are summarized in Table 1.

The chloro complex OsHCl(CO)(PPh₃)₃ (**6a**) showed marginal catalytic activity for the reaction. When a mixture of styrene and D₂O (13.5 molar equivalents) in THF was heated in an oil bath at 80 °C for 2 hours in the presence of OsHCl(CO)(PPh₃)₃ (5 mol%), only about 5% of =CH and 2% of =CH₂ vinyl protons were replaced with deuterium (entry 1). The bromo complex OsHBr(CO)(PPh₃)₃ (**6b**) is slightly more active than chloro complex **6a** (entry 2). Iodo complex OsHI(CO)(PPh₃)₃ (**6c**) is appreciably more active than the chloro complex **6a**, leading to approximately 40% deuteration of the vinyl carbons in 2 hours (entry 3). The higher activity of the iodo complex could be related to the larger size of iodide, which can facilitate phosphine dissociation to generate the unsaturated hydride complex OsHI(CO)(PPh₃)₂ for olefin insertion. The electronic effect may also contribute to the differences in the activity. The unsaturated hydride complex OsHI(CO)(PPh₃)₂ may undergo a faster insertion/de-insertion reaction with styrene than OsHI(CO)(PPh₃)₃, similar to the insertion reaction of RuHX(CO)(P^tBuMe)₂ (X = F, Cl, and I) with HC≡CPh.³²

A key step in the H/D exchange of styrene with D₂O catalyzed by OsHX(CO)(PPh₃)₃ is the H/D exchange between osmium hydride complexes OsHX(CO)(PPh₃)₃ and D₂O to give OsDX(CO)(PPh₃)₃. This process likely proceeds through an η²-HD intermediate [Os(η²-HD)X(CO)(PPh₃)₃]⁺ and might be facilitated by an acid.³³ To test the hypothesis, we performed the catalytic reaction in the presence of a catalytic amount of acetic acid (HOAc). To our delight, the H/D exchange reaction of styrene (PhCH=CH₂, **8a**) with 13.5 equiv. of D₂O indeed proceeded much more readily in the presence of HOAc. With 5 mol% of OsHCl(CO)(PPh₃)₃ and 3 mol% of HOAc, the H/D exchange reaction at 80 °C proceeded fairly quickly (entries 4 and 5), and the percentage of deuteration at the vinylic carbons reached about 62% (69% of the %D_{theo}) in 1 hour and 82% (91% of the %D_{theo}) in 2 h. The reaction with OsHI(CO)(PPh₃)₃/HOAc proceeded at an even faster rate (entries 7 and 8), and the percentage of deuteration at the vinylic carbons reached about 83% (92% of the %D_{theo}) in 30 minutes (entry 8).³⁴ Under similar conditions, the related complex OsHCl(CO)(P(C₆H₄-*p*-CF₃)₃)₃ (**6d**) is less effective (entry 9), while OsHCl(O₂)(CO)(PCy₃)₂ (**7a**, entry 10) and OsHCl(CO)(PPh₃)(dppf) (**7b**) are totally inactive (see the ESI[†]), probably due to the difficulty of these complexes to undergo an insertion reaction with styrene. As expected, the reaction rates were temperature

dependent. For example, the H/D exchange reaction catalyzed by OsHI(CO)(PPh₃)₃/HOAc was essentially completed in 1 hour at 90 °C, but proceeded to less than 20% in 1 hour at 50 °C (see the ESI[†]).

Substrate scope of the catalytic reactions

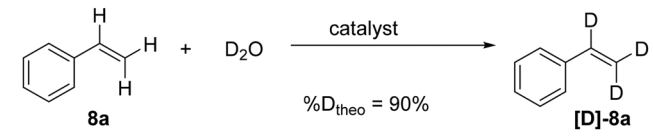
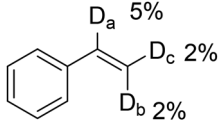
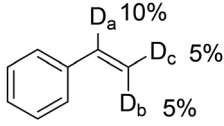
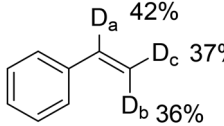
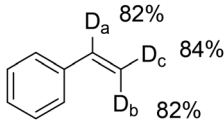
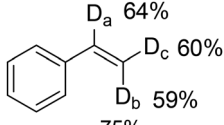
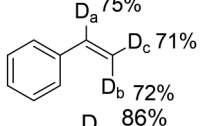
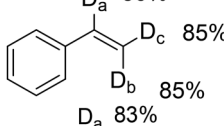
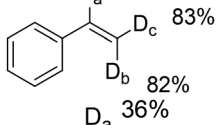
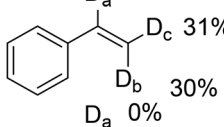
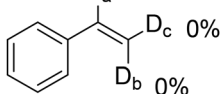
The above experiments reveal that OsHI(CO)(PPh₃)₃/HOAc is the most active catalyst for H/D exchange between olefins and D₂O. We then studied the substrate scope of this catalytic system. As shown in Scheme 3, OsHI(CO)(PPh₃)₃ effectively mediated the H/D exchange between D₂O and styrene derivatives with various functional groups, including aryl (**8b**, **8c**), alkyl (**8d**), halide (**8e–g**), ether (**8h**), ester (**8i**), NO₂ (**8j**) and CF₃ (**8k**). With a catalyst loading of 5 mol%, the scrambling of deuterium and hydrogen on the oxygen of D₂O and vinyl carbon sites was almost completed within one hour at 80 °C. Compounds with protic functional groups such as NH₂ (**8m**), carboxylic acid (**8n**) and B(OH)₂ (**8o**) also underwent smooth H/D exchange reactions with D₂O under similar reaction conditions. When the reaction was carried out with the aldehyde-functionalized derivative CH₂=CH-C₆H₄-*p*-CHO (**8l**), H/D exchange also occurred for the CHO proton, albeit at a lower rate than for the vinylic protons. 4-Vinylpyridine (**8p**) and 4-cyanostyrene were unreactive, likely due to the competing coordination of nitrogen.

The catalytic system also displayed good catalytic activity in the H/D exchange of terminal alkyl olefins with D₂O. When a mixture of 1-hexadecene (**9a**) and D₂O (13.5 molar equiv.) in THF was heated at 80 °C for 2 h in the presence of OsHI(CO)(PPh₃)₃ (5 mol%) and HOAc (3 mol%), 1-hexadecene underwent selective H/D exchange at the vinylic carbons without isomerization (Scheme 4). Selective deuteration at the vinylic carbons with minimum isomerization also occurred for terminal olefins PhCH₂CH=CH₂ (**9b**) and PhCH₂CH₂CH=CH₂ (**5**), when the reactions were carried out at 70 °C for 1 hour.³⁵ Selective deuteration of **9** and **5** is interesting, as reported systems (e.g., RuHCl(CO)(PPh₃)₃) usually induce both isomerization and deuteration. Systems capable of promoting selective H/D exchange reactions at the vinylic positions of isomerizable olefins without causing isomerization are quite rare. In this regard, Hartwig *et al.* demonstrated that the Ir-pincer complex [(dtbpp)Ir(H)(NH₂)] (dtbpp = 1,5-bis(di-*tert*-butylphosphino)pentan-3-yl) can catalyze these selective H/D exchange reactions with C₆D₆ at the vinylic positions without inducing olefin isomerization.¹⁵ To date, there appear to be no reported systems that demonstrate selective H/D exchange reactions of isomerizable olefins with D₂O without causing isomerization.

The system also promoted selective deuteration at the methine carbon (RCH=) of terminal olefins with bulky substituents (Scheme 5). For instance, when a mixture of 9-vinylanthracene (AnCH=CH₂, **10a**) and D₂O (13.5 molar equiv.) in THF was heated by an oil bath at 100 °C for 2 h in the presence of OsHI(CO)(PPh₃)₃ (5 mol%) and HOAc (3 mol%), essentially all of the methine AnCH = proton was replaced by deuterium. In contrast, only about 2% or less of the protons at the methylenic carbon (=CH₂) were replaced with deuterium. Selective



Table 1 Selection of the catalyst and conditions for H/D exchange reactions of olefins with D₂O^a

				
Entry	Osmium hydride	Additive	Reaction time	%D _{exp}
1	OsHCl(CO)(PPh ₃) ₃ (6a)	None	80 °C/2 h	
2	OsHBr(CO)(PPh ₃) ₃ (6b)	None	80 °C/2 h	
3	OsHI(CO)(PPh ₃) ₃ (6c)	None	80 °C/2 h	
4	OsHCl(CO)(PPh ₃) ₃ (6a)	HOAc ^b	80 °C/2 h	
5	OsHCl(CO)(PPh ₃) ₃ (6a)	HOAc ^b	80 °C/1 h	
6	OsHBr(CO)(PPh ₃) ₃ (6b)	HOAc ^b	80 °C/1 h	
7	OsHI(CO)(PPh ₃) ₃ (6c)	HOAc ^b	80 °C/1 h	
8	OsHI(CO)(PPh ₃) ₃ (6c)	HOAc ^b	80 °C/30 min	
9	OsHCl(CO)((p-CF ₃ C ₆ H ₄) ₃ P) ₃ (6d)	HOAc ^b	80 °C/1 h	
10	OsHCl(CO)(O ₂)(PCy ₃) ₂ (7a)	HOAc ^b	80 °C/1 h	

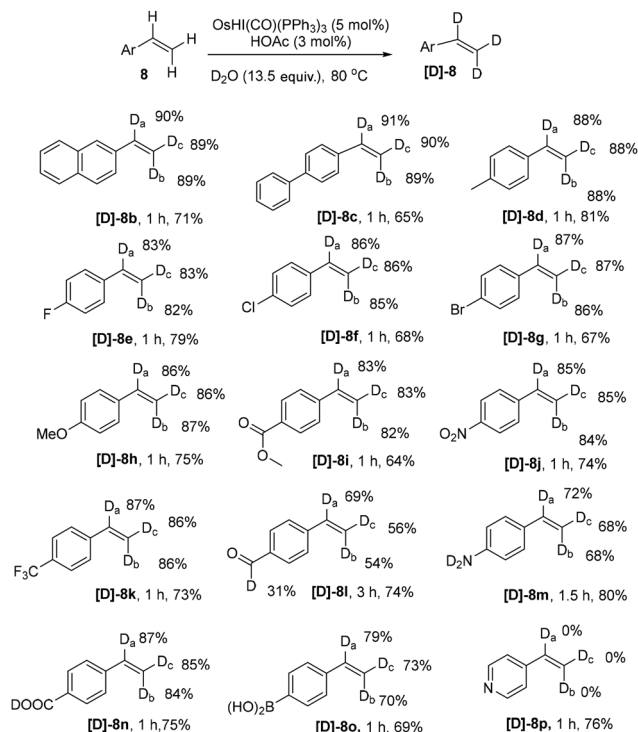
^a The reaction was carried out with 5 mol% of an osmium complex in THF (2 mL) under N₂ in a sealed Schlenk tube. %D_{theo} is the maximum or theoretical level of deuteration attainable (the statistical percentage of D among exchangeable sites of water/heavy water, acetic acid, the vinyl group of styrene and the hydride of the catalyst). %D_{exp} is the percentage of D determined experimentally. ^b 3 mol%.

deuteration at the methine carbon was also observed for Ph₂C(OH)-CH=CH₂ (**10b**) and Ph(*t*Bu)C(OH)-CH=CH₂ (**10c**).

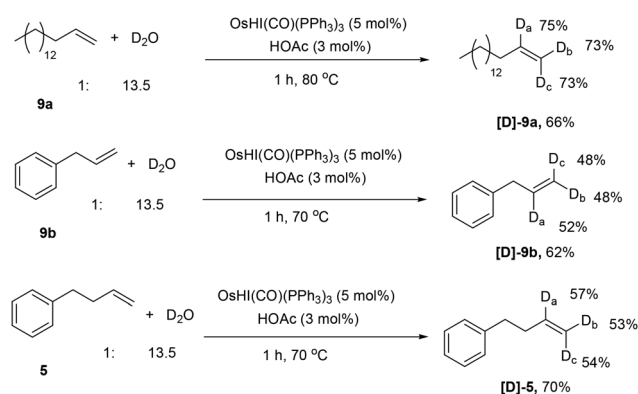
Selective deuteration at methine carbon (RCH=) or methylidene carbon (=CH₂) of terminal alkenes RCH=CH₂ via H/D

exchange reactions is both intriguing and challenging. While methylidene-selective deuteration of styrene derivatives ArCH=CH₂ with D₂O or MeOD (to give ArCH=CD₂) has been achieved using catalytic systems such as Pd(0)/PR₃/RCO₂H²³



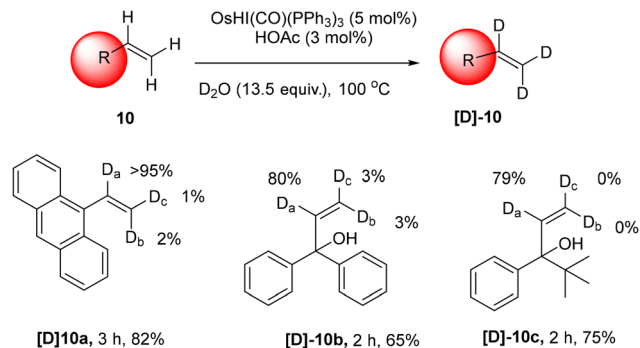


Scheme 3 Deuteration of styrene derivatives catalyzed by 5 mol% $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/3$ mol% HOAc in THF at 80°C . $\%D_{\text{theo}} = 90\%$.



Scheme 4 Selective deuteration of alkyl terminal olefins with D_2O catalyzed by 5 mol% $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/3$ mol% HOAc in THF. $\%D_{\text{theo}} = 90\%$.

and $[\text{RhCl}(\text{CH}_3\text{CN})_3(\text{IPr})]\text{CF}_3\text{SO}_3$,¹⁷ methine-selective deuteration of terminal olefins $\text{RCH}=\text{CH}_2$ (to give $\text{RCD}=\text{CH}_2$) is almost unprecedented. The most closely related work is recently reported by Stephen P. Thomas *et al.*, who observed a slight trend toward greater deuterium incorporation at the methine carbon compared to methylidene carbon in the H/D exchange reactions of $\text{RCH}=\text{CH}_2$ with CD_3OD under photocatalysis using $[\text{FeCl}_2(\text{dmpe})_2]/\text{NaOtBu}/\text{HBpin}/\text{blue light}$ ($\text{dmpe} = \text{Me}_2\text{PCH}_2\text{CH}_2\text{PMe}_2$).¹⁹ The current catalyst $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/\text{HOAc}$ represents a unique system for methine-selective deuteration of terminal olefins with bulky substituents. The

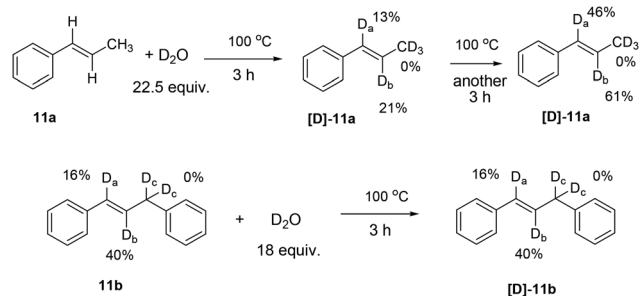


Scheme 5 Selective deuteration at the methine carbon of terminal olefins with a bulky substituent catalyzed by 5 mol% $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/3$ mol% HOAc in THF. $\%D_{\text{theo}} = 90\%$.

selectivity can be related to the steric effect as discussed in the section on reaction mechanism in the following.

It was noted that the catalytic system $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/\text{HOAc}$ exhibits significantly lower catalytic activity for the deuteration of internal olefins compared to its activity for terminal olefins (Scheme 6). For example, with a catalyst loading of 5 mol%, the H/D exchange reaction of styrene with 13.5 equivalents of D_2O is essentially complete after heating the reaction mixture at 80°C for one hour. In contrast, under the same catalyst loading, the reaction of *trans*- $\text{PhCH}=\text{CHCH}_3$ (**11a**) with 22.5 equiv. of D_2O only leads to up to 21% deuteration at the vinyl carbons after heating at 100°C for 3 hours and up to 61% deuteration after 6 hours. Similarly, the H/D exchange reaction of *trans*- $\text{PhCH}=\text{CHCH}_2\text{Ph}$ (**11b**) is also slow, with deuteration at the vinyl carbons reaching only up to 40% after heating at 100°C for three hours. Notably, deuteration only occurred at the vinylic positions in the catalytic reactions of **11a** and **11b**. *trans*-Stilbene ($\text{PhCH}=\text{CHPh}$, **11c**) and 1,1-disubstituted olefins such as $\text{PhC}(\text{Me})=\text{CH}_2$ (see the ESI[†]) are unreactive under similar conditions (100°C , 3 h). The low reactivity of internal and 1,1-disubstituted olefins can be attributed to their low tendency to undergo insertion reactions with osmium hydride complexes.

To further confirm that the system exhibits selectivity for deuteration at terminal double bonds over internal double bonds, we conducted reactions with substrates containing



Scheme 6 H/D exchange reactions of internal olefins with D_2O catalyzed by 5 mol% $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/3$ mol% HOAc .



both terminal and internal C=C double bonds. As shown in Scheme 7, under the catalysis of $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/\text{HOAc}$, 1-ethenyl-4-[(1*E*)-2-phenylethenyl]benzene (**12a**), nerolidol (**12b**), and linalyl acetate (**12c**) all underwent selective H/D exchange reactions with D_2O at the terminal double bond. For **12b** and **12c**, deuteration at the methine carbon proceeded at a higher rate than at the methine carbon, probably due to the steric effect, as will be discussed in the following.

Applications

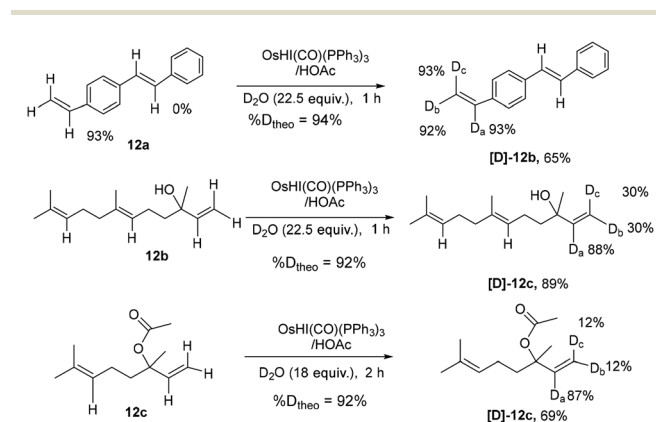
The results discussed above suggest that $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/\text{HOAc}$ may be useful for the selective deuteration of vinylic positions of complex molecules. To explore this possibility, we conducted H/D exchange reactions of D_2O with four natural products and two synthetic steroid derivatives (Fig. 1). We were pleased to find that altrenogest (**13a**) underwent a selective

H/D exchange reaction with D_2O at the terminal olefinic group without isomerization. As confirmed by ^2H and ^1H NMR, with a catalyst loading of 5 mol%, the reaction was essentially completed within one hour at 80 °C, and no H/D exchange occurred at the internal C=C double bonds. Similarly, the vinylic protons of forskolin (**13d**), sclareol (**13e**), estrone derivative **13b**, and epiandrosterone **13c** were also replaced with deuterium when they were allowed to react with D_2O at 100 °C for 2 h in the presence of $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/\text{HOAc}$. For these substrates, preferential deuteration at the methine carbon was noted, likely due to steric effect, as will be discussed in the following. In contrast, tiamulin **13f** did not undergo an H/D exchange reaction with D_2O under similar conditions, likely due to the strong coordination of S, which inhibits the olefin insertion reaction.

Mechanism for the H/D exchange reactions

Scheme 8 shows a plausible mechanism for the H/D exchange reactions of $\text{RCH}=\text{CH}_2$ (**15**) with D_2O catalyzed by $\text{OsHX}(\text{CO})(\text{PPh}_3)_3/\text{HOAc}$ (X = halide). HOAc can undergo an H/D exchange reaction with D_2O to give DOAc. The generated DOAc can then react with $\text{OsHX}(\text{CO})(\text{PPh}_3)_3$ (**6**) to give the deuteride complex $\text{OsDX}(\text{CO})(\text{PPh}_3)_3$ ([D]-**6**) probably via the η^2 -HD complex intermediate $[\text{Os}(\eta^2\text{-HD})\text{X}(\text{CO})(\text{PPh}_3)_3]\text{OAc}$ (**14**). The complex $\text{OsDX}(\text{CO})(\text{PPh}_3)_3$ ([D]-**6**) may undergo an insertion reaction with $\text{RCH}=\text{CH}_2$ via the η^2 -olefin complex intermediate $\text{OsDX}(\eta^2\text{-RCH}=\text{CH}_2)(\text{CO})(\text{PPh}_3)_3$ (**16**) (which contains two mutually *trans* PPh_3 ligands and an olefin *trans* to CO) to give an alkyl complex **16A** or **16B**. Subsequent rotation about the $\text{C}_\alpha\text{-C}_\beta$ alkyl axis of **16A** or **16B** (to give **16A'** or **16B'**) and β -H elimination would lead to the methine-deuterated olefin $\text{RCD}=\text{CH}_2$ (**17A**) or the methyldene-deuterated olefin $\text{RCH}=\text{CHD}$ (**17B**) and regenerate the active hydride complex **6**.

In line with the proposed mechanism, $\text{OsDCl}(\text{CO})(\text{PPh}_3)_3$ was identified upon the completion of the catalytic H/D exchange reaction of $\text{PhCH}=\text{CH}_2$ with H_2O catalyzed by $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3/\text{HOAc}$. Reversible olefin insertion into Os-



Scheme 7 H/D exchange of vinylic hydrogen atoms in substrates with both terminal and internal C=C double bonds (percentage of deuterium incorporation) catalyzed by 5 mol% $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/3$ mol% HOAc in THF at 100 °C.

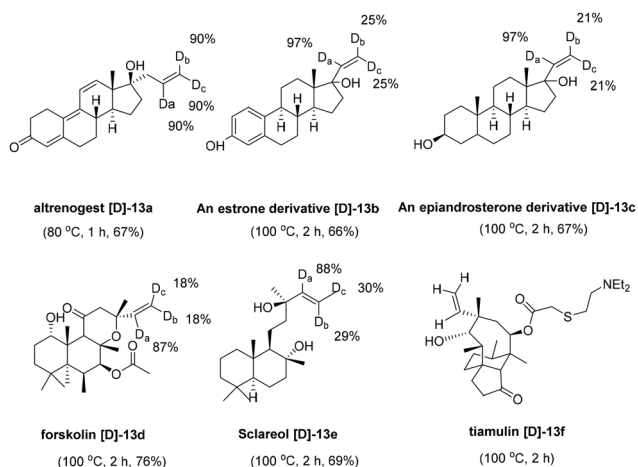
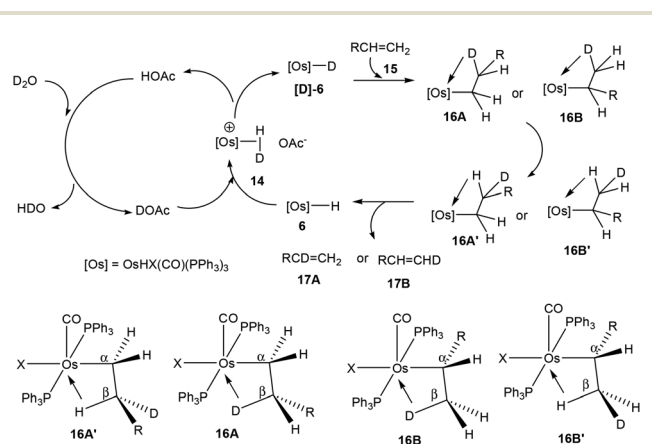


Fig. 1 H/D exchange of vinylic hydrogen atoms in complex molecules (percentage of deuterium incorporation) catalyzed by 5 mol% $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/3$ mol% HOAc in THF at 100 °C. Substrate: $\text{D}_2\text{O} = 1 : 13.5$, $\%D_{\text{theo}} = 90\%$.



Scheme 8 A plausible mechanism for the H/D exchange reactions of $\text{RCH}=\text{CH}_2$ with D_2O catalyzed by $\text{OsHI}(\text{CO})(\text{PPh}_3)_3/\text{HOAc}$.

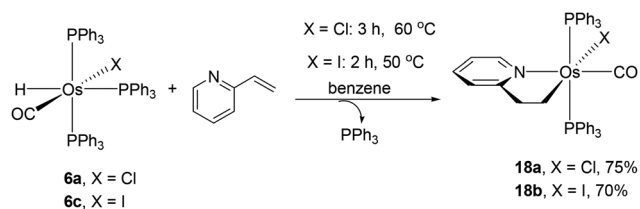


D/H bonds is one of the key processes for the catalytic H/D exchange reactions. It is known that osmium complexes such as $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3$ ³⁷ and $\text{OsHCl}(\text{CO})(\text{PiPr}_3)_2$ ^{32,38} can undergo insertion reactions with alkynes to give vinyl-osmium compounds. However, olefin insertion reactions of $\text{OsHX}(\text{CO})(\text{PR}_3)_3$ or $\text{OsHX}(\text{CO})(\text{PR}_3)_2$ are still unknown.³⁹ To verify that $\text{OsHX}(\text{CO})(\text{PPh}_3)_3$ can undergo reversible olefin insertion reactions, we studied the reactions of $\text{OsHX}(\text{CO})(\text{PPh}_3)_3$ ($\text{X} = \text{Cl}$ (**6a**) and I (**6c**)) with styrene and 2-vinyl pyridine. Both **6a** and **6b** were found to be unreactive towards styrene, implying that the insertion reaction is unfavorable. In contrast, they reacted with 2-vinyl pyridine to give the insertion products $\text{Os}(\kappa^2\text{-CH}_2\text{CH}_2\text{-C}_5\text{H}_4\text{N})\text{X}(\text{CO})(\text{PPh}_3)_3$ (**18**) containing a 1,2-dihydro-3-osmaindolizine moiety (Scheme 9). Apparently, the chelating effect can make the olefin insertion reaction thermodynamically favorable.⁴⁰ As monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR, the reaction of the chloride complex **6a** is completed in 3 h at 60 °C, while the reaction of the iodide complex **6c** is completed in 2 h at 50 °C. Thus, the iodide complex **6c** is more active than the chloride complex **6a** for olefin insertion, consistent with the observation that the iodide complex is more active than the chloride complex in catalyzing the H/D exchange reactions.

Complexes **18** have been characterized by NMR spectroscopy and elemental analysis. The structure of **18a** has also been confirmed by an X-ray diffraction study. As shown in Fig. 2, the complex adopts a distorted octahedral geometry containing a five-membered ring formed by the insertion of 2-vinylpyridine into the H–Os bond. The two PPh_3 ligands are mutually *trans*, and the chloride is *trans* to the alkyl ligand. Consistent with the solid state structure, the ^1H NMR spectra showed two methylene proton resonances at 1.93 (OsCH_2) and 2.64 (OsCH_2CH_2) ppm. The $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum shows a singlet at 43.6 ppm for OsCH_2CH_2 and a triplet at –2.71 ppm with a C–P coupling constant of 10 Hz for Os-CH_2 .

We observed experimentally that methine-selective deuteration can occur for $\text{RCH}=\text{CH}_2$ with a bulky substituent. The selectivity can be related to the steric effect. The intermediate, **16A** or **16A'** (leading to methine deuteration), is expected to be sterically more favorable than **16B** or **16B'** (leading to methylenide deuteration) when the R group is sterically bulky or demanding.

It was also noted that internal olefins ($\text{RCH}=\text{CHR}$) and 1,1-disubstituted olefins ($\text{R}_2\text{C}=\text{CH}_2$) were much less reactive than terminal olefins ($\text{RCH}=\text{CH}_2$) in the Os-catalyzed reactions.



Scheme 9 Insertion reaction of $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3$ ($\text{X} = \text{Cl}$, I) with 2-vinylpyridine.

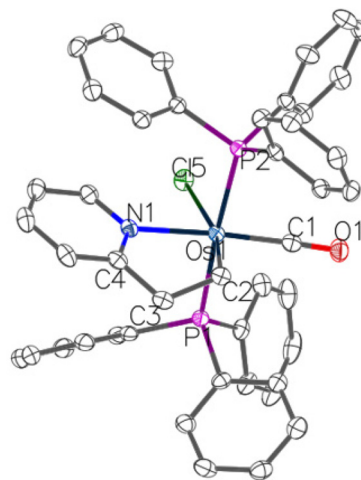


Fig. 2 The molecular structure of complex **18a** (ellipsoids at the 40% probability level). The hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Os(1)–Cl(5) 2.5169(7), Os(1)–P(1) 2.3561(7), Os(1)–P(2) 2.3653(7), Os(1)–N(1) 2.198(2), Os(1)–C(1) 1.847(2), Os(1)–C(2) 2.138(2), O(1)–C(1) 1.159(3), N(1)–C(4) 1.359(3), C(3)–C(4) 1.499(3), C(2)–C(3) 1.532(3), C(2)–Os(1)–N(1) 78.09(8), C(3)–C(2)–Os(1) 108.16(15), C(4)–C(3)–C(2) 110.80(19), N(1)–C(4)–C(3) 114.9(2), C(4)–N(1)–Os(1) 114.77(16).

The lower reactivity is likely caused by their reduced capacity to undergo insertion reactions with osmium hydride complexes to give intermediates analogous to **16** for the H/D exchange reaction. For example, the insertion reaction of $\text{OsDCl}(\text{CO})(\text{PPh}_3)_3$ with $\text{PhMeC}=\text{CH}_2$ would give $\text{Os}(\text{CH}_2\text{-CDPh(Me)})\text{CO}(\text{PPh}_3)_3$ or $\text{Os}(\text{C(Ph)Me-CH}_2\text{D})\text{CO}(\text{PPh}_3)_3$. The former insertion product is sterically unfavorable, while the latter one is unproductive for H/D exchange. The observation is perhaps not surprising, since it is commonly found that terminal olefins undergo insertion at a much greater rate than internal and 1,1-disubstituted olefins.⁴¹

Conclusions

We have discovered that the readily available hydride complex $\text{OsHCl}(\text{CO})(\text{PPh}_3)_3$ is highly effective at catalyzing H/D exchange reactions of terminal olefins with D_2O . The reaction mechanism involves H/D exchange between the osmium hydride and D_2O and reversible olefin insertion into an OsD(H) bond. This catalytic system demonstrates a high degree of selectivity for deuteration at terminal double bonds over internal double bonds. Additionally, it can catalyze H/D exchange reactions of olefins without causing isomerization. Notably, the system induces selective H/D exchange at the methine carbon ($=\text{CHR}$) rather than the methylenide carbon ($=\text{CH}_2$) for substrates $\text{RCH}=\text{CH}_2$ with a bulky substituent R. These reactions are compatible with substrates bearing a wide variety of functional groups, making this method highly versatile for the selective labeling of olefins in complex molecules.



Author contributions

G. J. conceived the project and supervised the findings of this work. W. Q. carried out the syntheses and characterization. H. H. Y. S. and I. D. W. performed XRD. G. J., W.Q. and I. D. W. wrote the manuscript and all authors contributed to the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Crystallographic data for **6d** (CCDC no. 2433118†) and **18a** (CCDC no. 2415812†) have been deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements

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