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Chelation-assisted rhodium hydride-catalyzed regioselective H/D exchange in arenes

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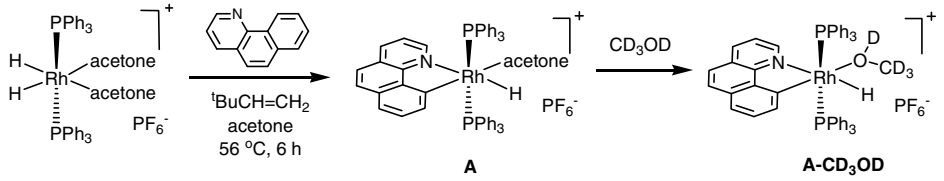
ABSTRACT

A series of air stable rhodium(III) hydride complexes are synthesized via cyclometalation of functionalized arenes, and are active catalysts for regioselective H/D exchange in various arenes via chelation-assisted C–H activation in acetone-d_6.

H/D exchange reactions have received increasing attention in that deuterium-labeled compounds have found extensive applications in mass spectrometry and NMR spectroscopy. In addition, deuterium-labeled compounds are used widely as probes in reaction mechanisms, drug metabolism, and structure elucidation of biological macromolecules.[1] Previously reported H/D exchange methods include pH-dependent exchange, which is the oldest method for this purpose, and transition metal-catalyzed H/D exchange. Homogeneous catalytic H/D exchange reactions are usually performed with D_2 or D_2O as the deuterium source owing to their low cost and low toxicity. Deuterated solvents such as CD_3COCD_3 and C_6D_6 are also used widely, which allow H/D exchange of less polar substrates. In recent years, iridium, rhodium, and ruthenium complexes have shown great potential in C–H activation of organic substrates.[2] Iridium complexes are particularly well-known for the activation of C–H bonds, and for which reasons iridium-mediated H/D exchange reactions make up by far the greatest number of publications.[3] In comparison, although rhodium catalysts have shown high activity in H/D exchange, only a few catalyst systems, such as $RhCl_3$,[4] $Rh[P(OPh)_3]_2(acac)$,[5] $C_5Me_5Rh(olefin)_2$,[6] and rhodium phosphine-aryl complexes,[2b] have been developed.

We recently synthesized a stable rhodium(III) hydride complex (**A**) via cyclometalation of benzo[*h*]quinoline in acetone (Eq. (1)). *tert*-Butylethylene behaves as a hydrogen acceptor to reversibly give $[Rh(PPh_3)_2(acetone)_2]PF_6$, which undergoes C–H oxidative addition to yield complex **A** and the analogous reactions were reported for iridium complexes.[7] Complex A was fully characterized. The hydride resonates as a doublet of triplets at δ −12.29 in the ^1H NMR spectrum, and in the $^{13}C\{^1H\}$ NMR spectrum the Rh–*C* resonates as a doublet of triplets (δ 153.08). Single crystals of complex **A** were obtained after recrystallization from methanol-d_4, and the identity of **A-CD$_3$OD** was confirmed by X-ray crystallography (Fig. 1).



(1)

We noted that the hydrogen of complex **A** could be replaced by a deuterium (>97% D) when heated in acetone-d_6 (80 °C, 3 days), although no such reaction took place for its iridium analogue. We reasoned that **A** might be an active catalyst for H/D exchange of arenes functionalized by chelating groups since step 'a' in Scheme 1 might easily occur via reversible C–H activation, and consequently the catalytic cycle could be completed.

Initial attempts to use complex **A** as a catalyst for the H/D exchange of benzo[*h*]quinoline (100 °C, 6 days, acetone-d_6) gave 97% deuteration at the 10-position (Eq. 2). We reasoned that improvement could be made by using electron-rich phosphines, since it is known that metal complexes of PMe_3, PCy_3, and P^tBu_3

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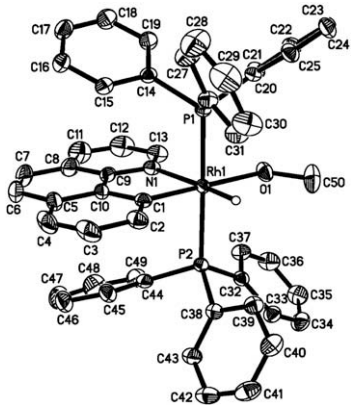
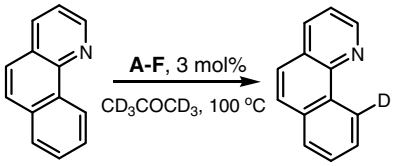


Figure 1. Molecular structure of compound **A-CD_3OD**. Selected bond distances (Å) and angles (°): C(1)–Rh(1) 1.9782(19), N(1)–Rh(1) 2.1788(17), O(1)–Rh(1) 2.2157(15), P(1)–Rh(1) 2.3396(5), P(2)–Rh(1) 2.3517(5), C(1)–Rh(1)–N(1) 81.39(8), C(1)–Rh(1)–O(1) 178.20(7), C(1)–Rh(1)–P(1) 87.83(5), N(1)–Rh(1)–P(1) 93.29 (4), O(1)–Rh(1)–P(1) 93.23(4), C(1)–Rh(1)–P(2) 85.76(5), P(1)–Rh(1)–P(2) 170.282(18).

are usually more active toward C–H activation.[8–11] Thus, we synthesized rhodium hydride complexes **A–F** (Fig. 2).



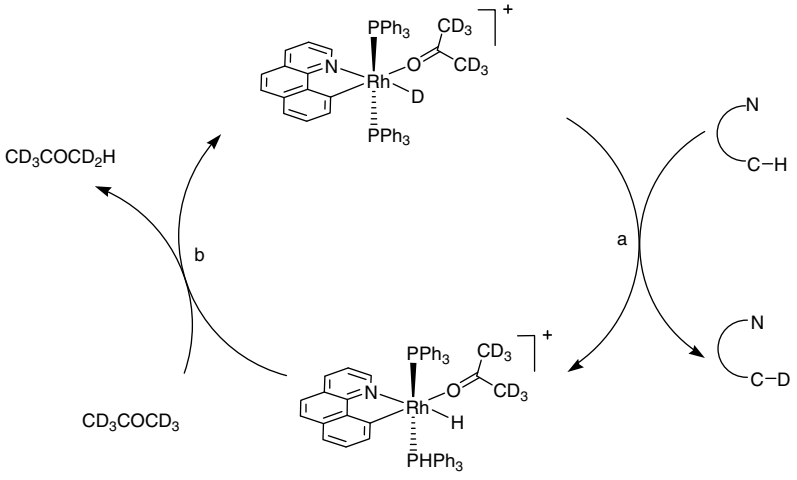
(2)

Screening of these catalysts was performed using benzo[*h*]quinoline (Eq. 2), and all these catalysts were applied with 3 mol % loading in J-Young NMR tubes in acetone-d_6 at 100 °C. The results are given in Table 1. Electron-donating phosphine ligands were

Table 1
Screening of catalysts for H/D exchange of benzo[*h*]quinoline

Catalyst	Solvent	Time (d)	D%[a]
A	CD_3COCD_3	6	97
A	CD_3COCD_3+CD_3OD	6	93
B	CD_3COCD_3	6	97
C	CD_3COCD_3	3	98
D	CD_3COCD_3	1.5	97
D	CD_3COCD_3+D_2O	2	90
E	CD_3COCD_3	3	98
F	CD_3COCD_3	7	94
$Rh(PPh_3)_3Cl$	CD_3COCD_3	2	15

[a] % Deuterium incorporation.



Scheme 1. A simplified mechanism for H/D exchange of N-functionalized arenes.

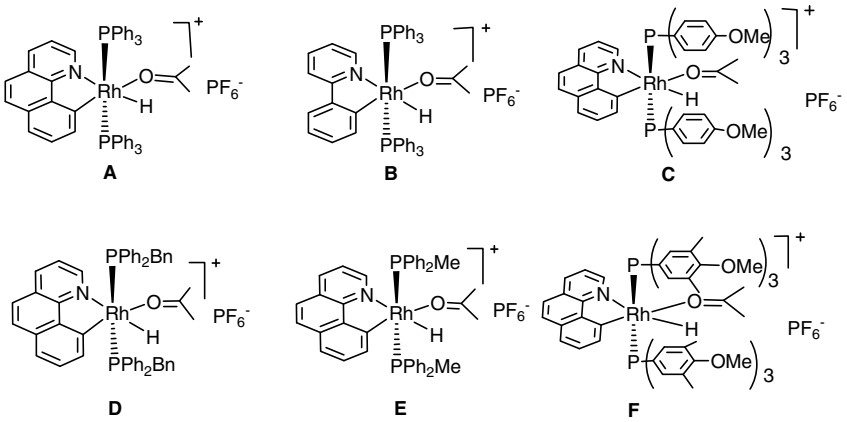
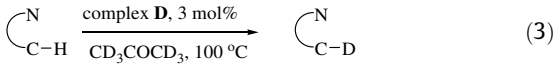


Figure 2. Rhodium hydride catalysts **A–F.**

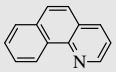
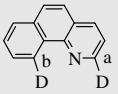
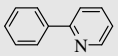
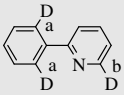
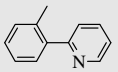
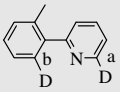
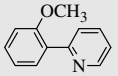
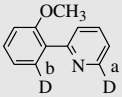
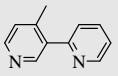
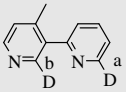
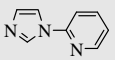
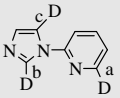
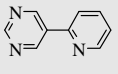
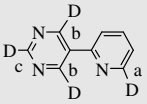
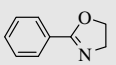
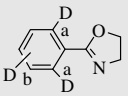
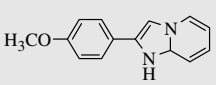
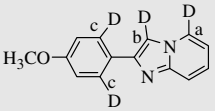
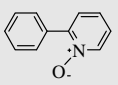
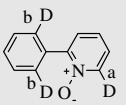
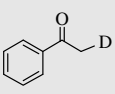
found to be crucial, and catalysts **C**, **D**, and **E** were more active than **A** or **B**. The catalytic activity of complex **F** was very low, possibly because of the introduction of more sterically congested ligands. We conclude that catalysts **D** and **E** are the best choice for this reaction. D_2O and CD_3OD are also used widely as deuterium sources for the deuteration of non-labile H atoms.[2a] Rhodium(III) hydride complexes **A**–**F**, however, are sparingly soluble in CD_3OD and are insoluble in D_2O. Catalysis was thus attempted using CD_3COCD_3/D_2O or CD_3COCD_3/CD_3OD in a 20/1 ratio to provide extra sources of active deuterium, but only lower yields were obtained. Therefore, complex **D** was retained for reactions of other substrates (Eq. 3), and the results are given in Table 2.



(3)

All the substrates under study can potentially undergo chelation-assisted C–H activation and deuteration took place predominantly at carbon atoms involved in C–H activation. In addition, the 2-position of pyridines could also be deuterated at up to 20% level. Importantly, the deuterium incorporation is reasonably regioselective for the substrates in entries 1–9, particularly for benzo[*h*]quinoline, which afforded high conversion in a short reaction time. Heys and coworkers have reported the H/D exchange reactions of benzo[*h*]quinoline and 2-phenylpyridine at the same positions, but the level of deuteration was rather low.[12] Kerr reported efficient deuteration of 2-phenylpyridine using iridium carbene catalysts and deuterium gas.[10] The phenyl group of entries 2 and 8 received nearly quantitative deuteration at the *ortho* positions only after a long reaction time, and this is because two C–H bonds need to be activated. The pyrimidine unit of 5-(pyridine-2-yl)pyrimidine

Table 2
Selective H/D exchange of arenes

Entry	Substrate	D position	Time (d)	D_{inc} %	Time (d)	D_{inc} %
1			1.5	a: 5% b: 98%		
2			2	a: 64% b: 12%	8	a: 95% b: 9%
3			2	a: 16% b: 60%	6	a: 15% b: 96%
4			2	a: 12% b: 90%	3	a: 12% b: 96%
5			2	a: 13% b: 67%	6	a: 20% b: 95%
6			2	a: 51% b:62% c:11%	6	a: 31% b:97% c: 14%
7			2	a: 24% b: 68% c: 45%	9	a: 21% b:85% c:47%
8			2	a: 65% b: 6%	7	a: 94% b: 16%
9			2	a: 24% b: 73% c: 71%	4	a: 9% b: 95% c: 94%
10			2	a: 84% b: 25%		
11			2	33%	8	81%

(entry 7) is more acidic at the 2-position, such that three positions were deuterated, which prolonged the reaction time. In entries 10 and 11, the oxygen atoms are rather poor directing groups, and the deuteration took place predominantly at the more acidic methyl group in acetophenone. We also analyzed the extent of deuterium incorporation of most substrates after 2 days, and the results are listed in Table 2, during which time the extent of deuterium incorporation achieved was 60–70% and the regioselectivity is reasonably high. In fact, the rate of deuterium exchange is very low when approaching the end of the reaction because of the lower concentration of the deuterium source.

In conclusion, we have synthesized a series of rhodium hydride complexes and explored their activity in H/D exchange reactions using acetone-d_6 as a deuterium source. They showed reasonable regioselectivity for substrates demonstrating nitrogen chelation-assistance. Rhodium complexes with stronger electron-donating phosphine groups tend to give higher catalytic activity. Development of other catalytic reactions using these rhodium hydrides is currently in progress in our laboratory.

Acknowledgment

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