

Catalytic Method for the Synthesis of Deuterium-Labeled *N*-Heterocyclic Carbenes Enabled by a Coordinatively Unsaturated Ruthenium *N*-Heterocyclic Carbene Catalyst

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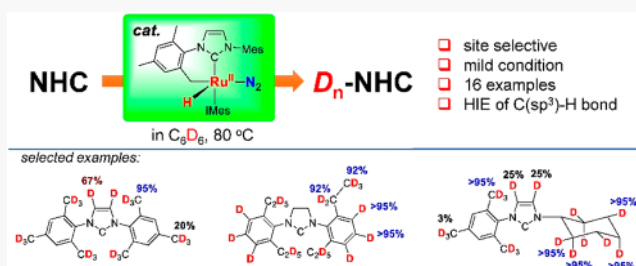
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ABSTRACT: The wide usage of *N*-heterocyclic carbenes (NHCs) has raised the quest for their deuterated molecules. Effective synthesis method to obtain them, however, has remained elusive. We present here a catalytic method for the preparation of deuterated NHCs, namely, the catalytic hydrogen–deuterium exchange reaction between NHCs and deuterated benzene using a coordinatively unsaturated Ru NHC catalyst. The catalytic system enables selective deuteration of the C(sp³)–H bonds of the alkyl groups on *N*-substituents, as well as the sterically nonhindered C(sp²)–H bonds of NHCs as demonstrated by the preparation of 16 deuterium-labeled NHCs that have a deuteration ratio on specified sites higher than 90%. The gram-scale synthesis of deuterated IMes indicated the applicability of this catalytic method. Mechanistic studies revealed that the high regio-selectivity toward those C(sp³)–H bonds on NHCs originates from the regio-selectivity of cyclometalation reactions of coordinatively unsaturated Ru NHC species.



INTRODUCTION

N-Heterocyclic carbenes (NHCs) are widely used ligands in transition metal complexes and main-group element compounds that show broad application in catalysis, medicinal chemistry, and material science.^{1–3} They are also popular catalysts in modern organo-catalysis.⁴ Along with the widespread use of NHCs, there has been growing interest in deuterium-labeled NHCs as they are envisioned useful in mechanistic studies, improving catalyst stability,⁵ and also the development of metal–NHC complexes and imidazolium salts based drugs.^{6,7} In mismatch with the soaring request, synthesis methods to obtain deuterium-labeled NHCs, however, are rarely known. As a rare example, Piers and co-workers reported the synthesis of IMes-*d*₂₂ using 1,3,5-(CD₃)₃C₆D₃ as the deuterium-labeled starting material (Figure 1a).⁸ Apart from the multistep synthesis route, an unsatisfactory aspect of the synthesis is the difficulty to access 1,3,5-(CD₃)₃C₆D₃ that relies on the high-temperature reaction of mesitylene with DMSO-*d*₆ and NaH, which has a risk of explosion.⁹ Ideally, deuterium-labeled NHCs can be synthesized from metal-catalyzed hydrogen-isotope-exchange (HIE) reactions¹⁰ of nonlabeled NHCs with deuterium sources. The catalytic HIE method should involve deuteration on C(sp³)–H and/or C(sp²)–H bonds of NHCs. A selective C(sp³)–H bond HIE reaction, however, still presents a big challenge in metal-catalyzed HIE reactions.^{11–13} Furthermore, NHCs are well-known to form strong metal–carbon(carbene) bonds with late transition metals.¹⁴ As an indication of this, solution calorimetric

investigations showed that the reaction of [Cp*RuCl]₄ with IMes to form Cp*RuCl(IMes) showed more exothermic reaction enthalpy value than the reaction of [Cp*RuCl]₄ with PCy₃ by 21 kcal/mol.¹⁵ Thus, NHCs are strongly coordinating substrates and could be poisonous to HIE metal catalysts. Associated with these challenges, catalytic method for HIE reactions of NHCs remains elusive.

In regard to this, we report herein the first catalytic method for the preparation of deuterium-labeled NHCs by using a coordinatively unsaturated Ru(II) NHC complex as catalyst (Figure 1b). This catalytic system enables selective deuteration of C(sp³)–H bonds on NHCs by taking the advantage of facile intramolecular C(sp³)–H bond activation reactions of coordinatively unsaturated Ru NHC species.^{16–24} Moreover, the catalytic system can also facilitate deuteration of sterically nonhindered C(sp²)–H bonds on NHCs. Empowered by these two features, the use of the Ru-catalyzed HIE reaction has resulted in the preparation of a variety of deuterium-labeled NHCs, including the ones having fully deuterated *ortho*-methyl and ethyl groups on *N*-aryls, the ones having fully deuterated β -methylenes on *N*-alkyl groups, as well as those

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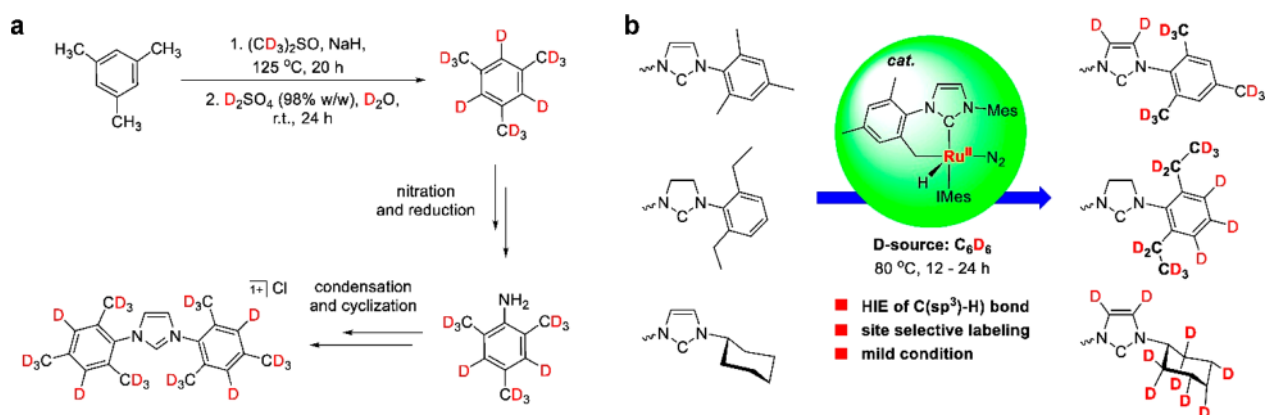


Figure 1. State of the art for synthesis of deuterated NHCs. (a) Piers' method to deuterated IMes·HCl. (b) This work: Ru-catalyzed HIE reaction of NHCs with C_6D_6 for the preparation of deuterium-labeled NHCs.

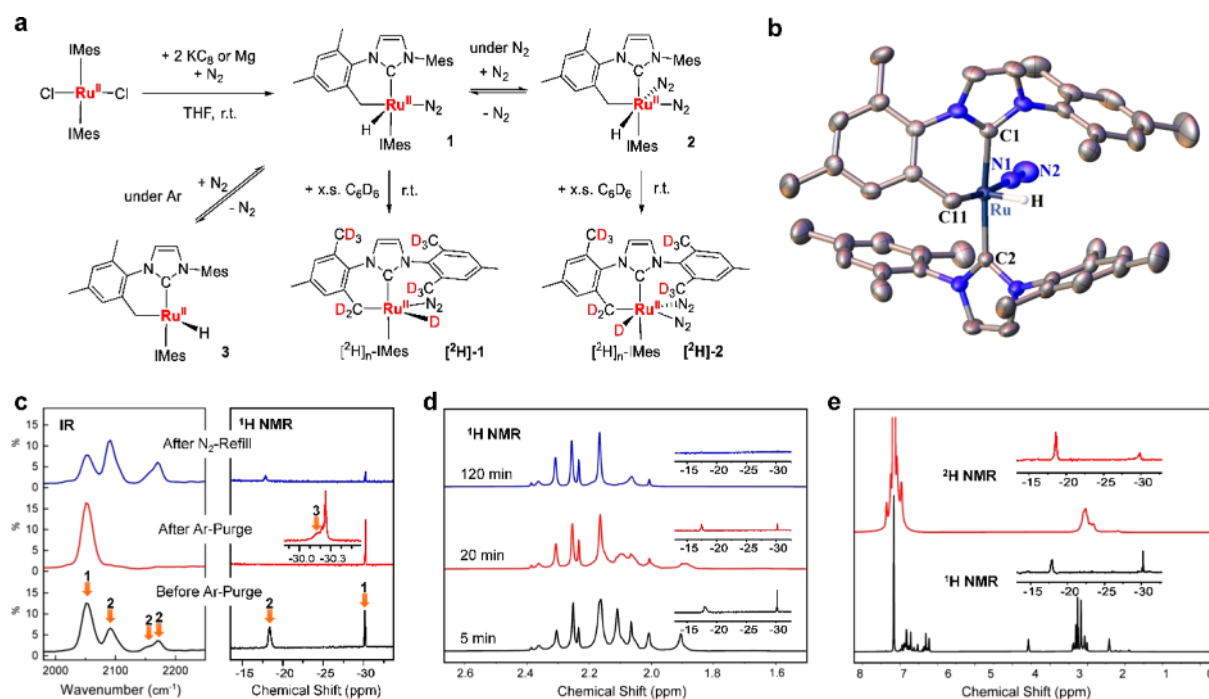


Figure 2. Synthesis, structure, and solution properties of **1**. (a) Synthesis route to **1** and its N_2 complexation and HIE reactions. (b) Molecular structure of **1** with selective atom labeling. Displacement ellipsoids are set at the 50% probability level and hydrogen atoms, beside of the hydride ligand, are omitted for clarity. (c) Characteristic infrared and 1H NMR signals of a solution of **1** in C_6D_6 under a N_2 or Ar atmosphere. (d) Selected regions of the 1H NMR spectra of a solution of **1** in C_6D_6 under a N_2 atmosphere when standing the solution at room temperature for indicated time. (e) 1H and 2H NMR spectra of a solution of **1** in C_6D_6 under a N_2 atmosphere after standing at room temperature for 2 h.

having high deuteration ratio on the nonhindered $C(sp^2)$ –H bonds of the arene fragments on NHCs, as shown below (Figure 1b).

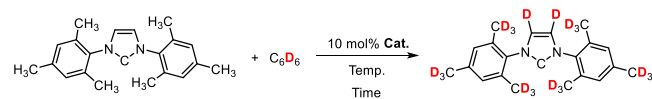
RESULTS AND DISCUSSION

Synthesis and Property of the Ru Catalyst. The catalyst used for the HIE reaction $[Ru(H)(IMes')(IMes)(N_2)]$ (**1**) (IMes = 1,3-di(2',4',6'-trimethylphenyl)-imidazol-2-ylidene, and IMes' denotes the cyclometalated IMes ligand) was obtained as a red solid in good yields from the reactions of the Ru(II) NHC complex $[RuCl_2(IMes)_2]$ with 2 equiv of KC_8 or an excess of Mg in THF under dinitrogen atmosphere (Figure 2a). Complex **1** has been characterized by 1H NMR, infrared, and UV–vis–NIR spectroscopies, as well as elemental analysis. Its molecular structure has been established by single-crystal X-ray diffraction study (Figure 2b). Comparing the structure of **1**

to that of $[RuCl_2(IMes)_2]$ (Figure S1) suggests that the interaction of $[RuCl_2(IMes)_2]$ with KC_8 might initially produce a two-coordinate Ru(0) species $Ru(IMes)_2$ that undergoes intramolecular benzylic $C(sp^3)$ –H bond oxidative addition reaction followed by the coordination of a N_2 molecule to yield **1** (Scheme S1).

An single-crystal X-ray diffraction study revealed that the Ru center in **1** is bound with an intact IMes ligand, a cyclometalated IMes ligand $[IMes']^-$, a hydride ligand, and a terminally bound N_2 molecule, forming a square pyramidal geometry (Figure 2b). The cyclometalated NHC ligand $[IMes']^-$ has the Ru–C(carbene) and Ru–C(benzyl) bond distances (2.061(2) and 2.162(2) Å, respectively) comparable to their congeners in the five-coordinate cyclometalated NHC Ru(II) complex $[RuH(sIMes')(PPh_3)_2]$ (2.045(2) and 2.162(2) Å)²⁵ and slightly shorter than those in the six-

Table 1. Catalytic Performance of Some Ru Complexes in HIE of IMes



entry	cat.	temp. (°C)	time (h)	deuteration ratio (%) ^{a,b}		
				<i>o</i> -CH ₃	<i>p</i> -CH ₃	imidazole-H
1	[Ru(H)(IMes')(IMes)(N ₂)] (1)	25	24	<1	1	<1
2	[Ru(H)(IMes')(IMes)(N ₂)] (1)	40	24	<1	1	<1
3	[Ru(H)(IMes')(IMes)(N ₂)] (1)	80	4	90	9	23
4 ^c	[Ru(H)(IMes')(IMes)(N ₂)] (1)	80	4	81	11	18
5 ^d	[Ru(H)(IMes')(IMes)(N ₂)] (1)	80	4	65	5	8
6	none	80	24	0	0	0
7	[RuCl ₂ (PPh ₃) ₃]	80	24	31	6	5
8	[RuCl ₂ (IMes) ₂]	80	24	8	1	<1
9	[Ru(H) ₂ (PPh ₃) ₄]	80	24	14	14	60
10	[Co(N ₂)(IMes)(IMes')]	80	24	12	3	16
11	[Ru(IMes') ₂ (N ₂) ₂] (4)	80	12	<1	<1	<1
12	[Ru(H)(IMes')(IMes)(CNBu ^t) ₂] (5)	80	16	<1	<1	<1

^aIMes (0.10 mmol, 0.20 mol/L), 10 mol % catalyst, and C₆D₆ (5.5 mmol, 0.50 mL) under dinitrogen (1 atm) in a J. Young NMR tube. ^bThe deuteration ratio was calculated from quantitative ¹H NMR using 1,1,1,3,3,3-hexamethyldisiloxane (0.10 mol/L) as an external standard. ^cThe concentration of IMes is 0.40 mol/L. ^dUsing 5 mol % 1.

coordinate complex [RuH(IMes')(PPh₃)₂(CO)] (2.079(2) and 2.235(2) Å, respectively).¹⁹ The hydride ligand, which is located on the difference Fourier map, sits on the apical position with the Ru–H distance (1.41(2) Å) being much shorter than that expected for second-row transition metal hydrides (1.6–1.7 Å). The short Ru–H distance might be due to underestimation of M–H distances by X-ray diffraction methods.²⁶ The N₂ ligand is *transoid* to the benzyl group and has a Ru–N separation of 1.926(2) Å and a N–N distance of 1.116(2) Å. These bond lengths, in addition with the high $\nu_{\text{N–N}}$ stretching frequency (2041 cm^{−1}) in the IR spectrum of 1 prepared from KBr pellet, indicate weak activation of the bonded N₂ ligand.²⁷

In line with its coordination unsaturation and the weak activation of the N₂ ligand of 1, solution infrared and NMR spectroscopic studies indicate that dissolution of 1 in C₆D₆ can lead to dinitrogen-coordination and -dissociation to form, presumably, the 18-e[−] complex *cis*-Ru(H)(IMes')(IMes)(N₂)₂ (2) and the 14-e[−] complex Ru(H)(IMes')(IMes) (3), respectively (Figure 2a). Under a N₂ atmosphere, the infrared spectrum of a solution of 1 in C₆D₆ shows four $\nu_{\text{N–N}}$ stretches at 2052, 2094, 2158, and 2170 cm^{−1}. After a stream of Ar was bubbling through the C₆D₆ solution, the three $\nu_{\text{N–N}}$ stretches with large wavenumbers disappeared; meanwhile, the stretch at 2052 cm^{−1} became intensified. Further replacing the Ar atmosphere with a N₂ atmosphere then resulted in the reappearance of the stretches at 2094, 2158, and 2170 cm^{−1} and the weakening of the stretch at 2052 cm^{−1} (Figure 2c). The band at 2052 cm^{−1} apparently arises from the $\nu_{\text{N–N}}$ stretch of 1 as its wavenumber is consistent with that of 1 recorded on a KBr pellet. The other three bands have their wavenumbers close to those of the $\nu_{\text{N–N}}$ stretch of *cis*-RuH₂(PCy₃)₂(N₂)₂ (2163 and 2126 cm^{−1})²⁸ and can be assigned to the $\nu_{\text{N–N}}$ stretches of the *cis*-bis(dinitrogen) complex 2 that has C₁ molecular symmetry. Being consistent with the observation from infrared spectroscopy, the ¹H NMR spectrum of a solution of 1 in C₆D₆ shows two hydride signals at −18.37 and −30.24 ppm, assignable to the hydride signals of 2 and 1, respectively. When gauged from the integral ratio of the two

hydride signals, an equilibrium constant $K = 1.6 \text{ atm}^{-1}$ can be estimated for the equilibrium between 1 + N₂ and 2 at room temperature. As the head atmosphere of the solution changes from N₂ to Ar, the hydride signals at −18.37 ppm disappeared, and the signal at −30.24 ppm became stronger. Meanwhile, a broad peak at −30.18 ppm appeared. Further replacing the head atmosphere with dinitrogen then led to the disappearance of the hydride signal at −30.18 ppm and the reappearance of the hydride signals of 2 (Figure 2c). A similar phenomenon was observed on the ¹H NMR spectra of 1 in cyclohexane-*d*₁₂ (Figure S13). The hydride signal at −30.18 ppm is then tentatively assigned as that of the 14-e[−] species Ru(H)(IMes')(IMes) (3). The attempts to isolate 2 and 3 by recrystallization the solutions of 1 under N₂ and Ar were unsuccessful.

In addition to the dinitrogen-coordination and -dissociation behavior, complex 1 can undergo facile hydrogen–deuterium exchange reactions with C₆D₆. As shown in Figure 2d, when standing a solution of 1 in C₆D₆ at room temperature under a N₂ atmosphere, the ¹H NMR signals of the hydride ligands of 1 and 2 and also part of the *ortho*-methyl and methylene hydrogen signals appearing in the range of 1.8–2.1 ppm dissipate with time. Concomitantly, the integral of the ¹H NMR signal of residual protons in C₆D₆ increases. More convincingly, the ²H NMR spectrum of the solution of 1 in C₆D₆ exhibits signals in the range of 1.8–2.5 ppm and at −18.7 and −30.2 ppm (Figure 2e), confirming the occurrence of deuterium incorporation into the *ortho*-methyl groups of NHC and hydride ligands in 1 and 2. When estimated by the relative integrals of ¹H NMR signals, holding the C₆D₆ solution of 1 at room temperature for 120 min is found to lead to a high deuteration ratio (>90%) for the *ortho*-methyl groups on the NHC ligands of the Ru NHC species. The rapid H/D exchange reaction between the Ru NHC complexes, 1 and 2, and C₆D₆ is reminiscent of that of [(IMes)Ru(H)₂(H₂)₂(PCy₃)] with C₆D₆,²³ hinting at the involvement of similar intermediates in these HIE reactions. When the solution of 1 in C₆D₆ is exposed to an Ar atmosphere, the effective deuterium incorporation into *ortho*-methyl groups was

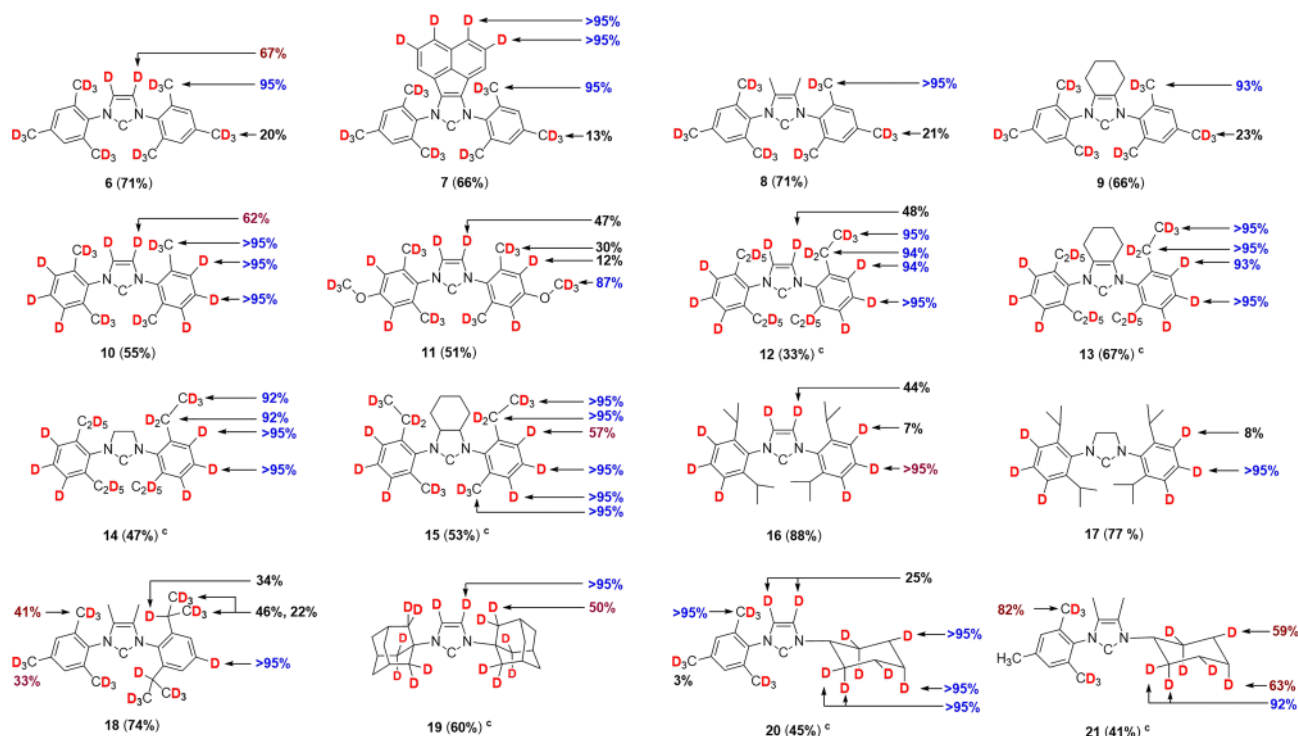


Figure 3. Deuterated NHCs prepared by catalytic HIE reactions using **1** as catalyst. Unless otherwise noted, the reaction was performed with NHC (1.0 mmol), C₆D₆ (5.0 mL), and **1** (10 mol %) at 80 °C under dinitrogen (1 atm) for 12 or 24 h. Data parenthesized is the isolated yield calculated by the mass of the isolated deuterated NHC divided by that of the NHC used for the reaction, and the data after arrow is the deuteration ratio measured via quantitative ¹H NMR analysis. Deuterium reactions were performed in two consecutive rounds. After the first run, the solvent residue was removed under vacuum, and then a new batch of catalyst **1** (10 mol %) and fresh C₆D₆ (5.0 mL) were added. The mixture was then heated to 80 °C for 24 h again.

found to reach completion in minutes (Figure S16). This observation, in conjunction with the detection of the ¹H NMR signals of proposed species **3** in the solution of **1** under Ar, implying that the enhanced rate of HIE under Ar might be due to the higher concentration of the 14-e[−] species Ru(H)(IMes')(IMes) (**3**), in line with Gunnoe's finding that the four-coordinate species [(IMes)₂Ru(H)(CO)][BAR'₄] (Ar' = 3,5-(CF₃)₂C₆H₃) can reversibly incorporate deuterium into the *ortho*-methyl groups of the IMes ligands when it is treated with D₂, whereas the five-coordinate species [(IMes)₂Ru(H)(CO)-Cl] is unreactive with D₂.²⁹ In contrast to the facile deuterium incorporation into the *ortho*-methyl groups, deuterium incorporation on the C(sp²)-H bonds and *para*-methyl groups on the NHC ligands, which show ¹H NMR signals in the ranges of 6.0–7.1 ppm and 2.1–2.5 ppm, respectively, is insignificant at room temperature under a N₂ atmosphere. Notably, while a plenty of intramolecular C–H bond activation reactions of Ru NHC complexes are scattering in literature,^{19,24,30–35} those involving HIE reaction of NHC ligands are limited to the three reports by Whittlesey,³⁶ Leitner,²⁵ and Gunnoe.²⁹

Catalytic Reaction Development. The stoichiometric deuterium incorporation reactions of **1** in C₆D₆ prompted further investigation of the catalytic HIE reaction of IMes with C₆D₆, which revealed that **1** can serve an effective catalyst for the HIE reaction at 80 °C. The initial trials by standing a solution of IMes (0.20 mol/L) with 10 mol % **1** in C₆D₆ under a N₂ atmosphere at room temperature or 40 °C for 24 h only led to deuterium incorporation into the NHC ligands on the catalyst, and the free IMes in solution was intact (entries 1 and 2 in Table 1). To our delight, the reaction run at 80 °C

resulted in the occurrence of the catalytic HIE reaction. As shown in entry 3, the reaction at the elevated temperature for 4 h afforded deuterated IMes with the deuteration ratio up to 90% on the *ortho*-methyl groups, whereas those on the *para*-methyl groups and imidazole backbone are 9 and 23%, respectively. No deuteration occurred on the *meta*-C(sp²)-H bonds that are sterically hindered. The identity of the deuterated IMes has been authenticated by comparing the NMR data of the isolated compound with those of nonlabeled IMes (Figures S56 and S57). The concentration of IMes proved a key factor affecting the deuteration ratio of the catalytic HIE reaction. Using a 10 mol % **1** as catalyst, the reaction with a concentrated solution of IMes (0.40 mol/L) in 4 h afforded deuterated IMes with a decreased deuteration ratio of 81% on the *ortho*-methyl groups (entry 4). Further elongating the reaction time to 8 h did not lead to apparent increase in deuterium-incorporation. Decreasing the catalyst loading to 5 mol % also resulted in decreased deuterium incorporation ratio on the *ortho*-methyl groups (entry 5). Control experiment showed that the reaction without the addition of the catalyst **1** did not give deuterated IMes (entry 6), revealing the indispensable role of **1** for the catalytic HIE reaction.

The catalytic performance of **1** in the HIE reaction of IMes with C₆D₆ is found superior over many other metal complexes. For example, under parallel reaction conditions, the reactions using [RuCl₂(PPh₃)₃], [RuCl₂(IMes)₂], and [Ru(H)₂(PPh₃)₄]³⁷ as catalysts gave deuterated IMes with low deuteration ratios on the *ortho*-methyl positions (31, 8, and 14%, respectively, entries 7–9). The reaction with the cobalt complex [Co(IMes')(IMes)(N₂)],³⁸ that bears similar NHC

ligands as those in **1** also gave deuterated IMes with low deuteration ratio on the *ortho*-methyl groups (12%, entry 10). The six-coordinate Ru complex $[\text{Ru}(\text{IMes}')_2(\text{N}_2)_2]$ (**4**) and $[\text{Ru}(\text{H})(\text{IMes}')(\text{IMes})(\text{CNBu}'_2)_2]$ (**5**) were found to be ineffective in catalyzing the HIE reaction (entries 11 and 12). In view of the popular use of D_2 and D_2O as deuterium sources in Ru-catalyzed HIE reactions,^{39–44} the catalytic reaction of IMes with D_2 (1 atm) and **1** (10 mol %) in C_6H_6 , and that of IMes with KOBU^t (1 equiv) and **1** (10 mol %) in D_2O were carried out, which revealed the incompatibility of the current catalytic system with these deuterium sources. The high price of C_6D_6 as compared with $\text{DMSO}-d_6$ and D_2SO_4 that are the D-source in Piers' "ab initio" synthesis of $[\text{H}]_{24}$ -IMes⁸ indicates the economic advantage of Piers' "ab initio" method in the preparation of $[\text{H}]$ -IMes in large scale. $[\text{H}]$ -IMes prepared by the current catalytic method is particularly effective to incorporate deuterium on *ortho*-methyl groups, but those on the other sites have moderate or low deuteration ratios. This is also dwarfed by Piers' method as its $[\text{H}]_{24}$ -IMes ligand has high deuteration ratio (90%) on all the deuterated sites.

Preparation of Deuterated NHCs by Catalytic HIE Reactions of NHCs with C_6D_6 . Using the optimized reaction condition, NHC (ca. 0.2 mol/L) in C_6D_6 with 10 mol % **1** as catalyst at 80 °C, the catalytic HIE reactions of different NHCs with C_6D_6 were then examined, which led to the successful preparation of 16 deuterated NHCs that feature versatile substituents.

The catalytic system proved very effective in incorporating deuterium into the *ortho*-benzylic positions of the *N*-aryl substituents of NHCs. As illustrated in Figure 3, the catalytic HIE reactions of IMes in 12 h can result in complete deuteration ($\geq 95\%$) of the *ortho*-methyl groups, giving deuterated IMes **6** in 71% isolated yield. Introducing hydrocarbyl substituents on the imidazole backbone does not affect the deuteration reaction as the IMes derivatives those have 1,8-naphthalene-fused, dimethyl-substituted, and cyclohexane-fused backbones can all be transformed into the deuterated NHCs with nearly full deuteration at their *ortho*-methyl positions (7–9 in Figure 3). In deuterated NHCs **6**–**9**, deuteration ratios on the *para*-methyl groups are generally lower than 23%, and deuteration on other $\text{C}(\text{sp}^3)\text{--H}$ bonds was not observed. The higher deuteration ratio on the *ortho*-methyl groups over other $\text{C}(\text{sp}^3)\text{--H}$ bonds hints that the cyclometalation reaction might play an important role for the observed selectivity. Selective deuteration on $\text{C}(\text{sp}^2)\text{--H}$ bonds in these NHCs were also observed as no noticeable deuterium incorporation was noticed on the *meta*- $\text{C}(\text{sp}^2)\text{--H}$ bonds of mesityl or the 2,7-positions of the naphthalene moiety of these NHCs, whereas the deuteration ratio on the 3,4,5,6-positions of the naphthalene moiety is found to be higher than 95%. This selectivity should result from the different steric nature of the $\text{C}(\text{sp}^2)\text{--H}$ bonds. In accord with this conjecture, the HIE reaction of the 2,6-dimethylphenyl-substituted NHC gave deuterated NHC **10** that has fully deuterated xylyl group. Examining the reactions with NHCs bearing heteroatom substituents indicated that the catalytic HIE reaction of 1,3-di(2',6'-dimethyl-4'-methoxyl-phenyl)-imidazol-2-ylidene mainly led to deuterium incorporation on the methoxy group (**11** in Figure 3), and no HIE reaction took place for the halogen-substituted NHCs 1,3-di(2',6'-dimethyl-4'-bromophenyl)-imidazol-2-ylidene and 1,3-di(2',4',6'-trimethylphenyl)-4,5-chloro-imidazol-2-ylidene. In the latter two cases, the

Ru catalyst might be poisoned by oxidative addition reactions with carbon–halogen bonds.⁴⁵

In addition to its fine performance in catalyzing deuteration on the *ortho*-benzylic positions of *N*-aryl NHCs, the catalytic system also enables the full deuteration of *ortho*-ethyl groups of *N*-aryl NHCs. Compared to the catalytic HIE reactions of IMes, the HIE reactions of the *N*-aryl NHCs bearing *ortho*-ethyl groups operated in decreased rates. Hence, a two-round reaction protocol has been used, leading to the successful preparation of deuterated NHCs **12**–**15**. Intriguingly, the terminal methyl groups of the ethyl moieties on these NHCs all have their deuteration ratio higher than 92%. Compound **14** has a saturated C–C backbone, and its successful preparation proved the efficacy of the catalytic system for the HIEs of imidazolin-2-ylidenes. As for the more steric demanding NHCs, 1,3-di(2',6'-diisopropylphenyl)-imidazol-2-ylidene (IPr) and 1,3-di(2',6'-diisopropylphenyl)-imidazolin-2-ylidene (sIPr), their catalytic HIE reactions were found to take place exclusively on $\text{C}(\text{sp}^2)\text{--H}$ bonds, giving deuterated NHCs **16** and **17** in good yields. The reaction of the nonsymmetric NHC, 1-(2',4',6'-trimethylphenyl)-3-(2',6'-diisopropylphenyl)-4,5-dimethyl-imidazol-2-ylidene, whose steric bulkiness is in the middle of IMes and IPr, yielded deuterated NHC **18** that has deuterium incorporation on the $\text{C}(\text{sp}^3)\text{--H}$ bonds of both mesityl and 2,6-diisopropylphenyl (Dipp), though with moderate deuteration ratios. The differentiated deuteration selectivity among **16**–**18** points out that the unsuccessful $\text{C}(\text{sp}^3)\text{--H}$ bond deuteration on **16** and **17** should result from their highly steric demanding nature that might prevent ligand-exchange reactions with **1** (*vide infra*).

Exploring the Ru-catalyzed HIE reactions with *N*-alkyl substituted NHCs revealed that the commonly used NHC 1,3-diadamantyl-imidazol-2-ylidene (IAd) is applicable. With the two-round protocol, IAd was successfully labeled on its 2-methylene positions and the imidazole backbone, yielding isotope-labeled NHC **19** with the corresponding deuteration ratios of 50 and 95% on the positions. Again, the steric property of *N*-alkyl NHCs effects the feasibility of the catalytic HIE reactions as the reactions of steric less demanding NHCs, 1,3-diisopropyl-2,4-dimethyl-imidazol-2-ylidene and 1,3-dicyclohexyl-imidazol-2-ylidene, did not produce the desired deuterated NHCs. In these cases, the catalyst might be poisoned by the formation of stable 18-electron Ru-NHC species. When the nonsymmetric NHCs 1-mesityl-3-cyclohexyl-imidazol-2-ylidene (IMesCy) and 1-mesityl-3-cyclohexyl-4,5-dimethyl-imidazol-2-ylidene (Me_2IMesCy) were used, catalytic deuterium incorporation occurred on both the mesityl and cyclohexyl groups, yielding deuterated NHCs **20** and **21** in moderate yields. Notably, the deuterated cyclohexyl rings in **20** and **21** are stereospecific as the hydrogen atoms that are *transoid* to nitrogen on the 1-, 3-, 4-, and 5-positions remain intact, and all the other 8 hydrogen atoms are fully deuterated. The stereochemistry of the deuterated cyclohexyl rings implies that these HIE reactions should origin from cyclometalation reactions. Notably, this regio-selectivity is distinct from the metal-mediated deuteration reactions of tricycloalkylphosphines.⁴⁰

While the above-mentioned catalytic HIE reactions were mainly performed in small scale (1 mmol), these reactions can be enlarged in gram-scale, showing their potential utility for the preparation of deuterated NHCs. As a demonstration, the reaction of IMes (6 mmol) with C_6D_6 using a two-round protocol was found to yield the deuterated IMes in 1.21 g with

the deuteration ratios on the *ortho*-methyl position being 92% (Figure 4). The deuterated IMes ligand was then used for the

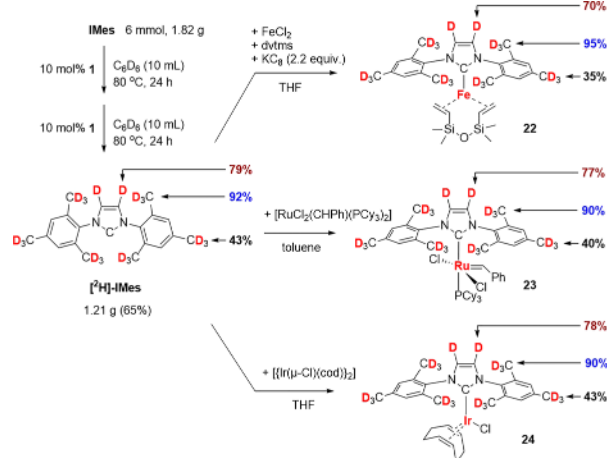


Figure 4. Gram-scale synthesis of deuterated IMes and its synthetic application to deuterated IMes-metal complexes. The deuteration ratio in the paramagnetic iron complex is determined by the ^1H NMR spectrum of $[\text{2H-IMes}]\bullet\text{HCl}$ obtained by quenching the complex with pyridine hydrochloride.

preparation of transition metal complexes, such as zero-valent iron complex **22**,⁴⁶ olefin metathesis reaction catalyst **23**,¹⁵ and iridium-based hydrogenation catalyst **24**.⁴⁷ (Figure 4).

Mechanistic Consideration. The Ru-catalyzed reaction shown above represents the first catalytic method for the

synthesis of deuterated NHCs and is adept at incorporating deuterium into the alkyl groups of the *N*-substituents with high regio-selectivity. This feature, in addition with the observed stoichiometric $\text{C}(\text{sp}^3)\text{--H}$ bond deuteration reaction of **1** (*vide supra*), suggest that these regioselective catalytic $\text{C}(\text{sp}^3)\text{--H}$ bond deuteration reactions are likely achieved via reversible cyclometalation reactions of Ru NHC complexes. Accordingly, as a representative for the catalytic $\text{C}(\text{sp}^3)\text{--H}$ bond deuteration reactions of NHCs, a catalytic cycle involving cyclometalated IMes Ru species can be proposed for the benzylic $\text{C}(\text{sp}^3)\text{--H}$ bond deuteration reaction of IMes. As shown in Figure 5a, precatalyst **1** might initially dissociate its N_2 ligand to generate the four-coordinate 14-e^- species $\text{Ru}(\text{H})(\text{IMes})(\text{IMes})$ (**3**). Once formed, **3** could then interact with C_6D_6 to yield the $\text{Ru}(\text{II})$ σ -(HD) complex $\text{Ru}(\text{HD})(\text{IMes})(\text{IMes})(\text{C}_6\text{D}_5)$ (**A**) or the $\text{Ru}(\text{IV})$ hydride complex $\text{Ru}(\text{H})(\text{D})(\text{IMes})(\text{IMes})(\text{C}_6\text{D}_5)$ (**A**) that was then converted into the deuteride complex $\text{Ru}(\text{D})(\text{IMes})(\text{IMes})$ (**B**) and $\text{C}_6\text{D}_5\text{H}$. The C--H and C--D activation reactions in the conversions of **3** to **A** and to **B** probably have oxidatively added transition states as that proposed for the $(\text{Tp})\text{Ru}(\text{PPh}_3)(\text{CH}_3\text{CN})\text{H}$ -catalyzed (Tp = hydrotris(pyrazolyl)borate) HIE reactions of CH_4 with C_6D_6 .^{48,49}

Intermediate **B** undergoes similar intramolecular HIE reaction via the intermediate $\text{Ru}(\text{HD})(\text{IMes})_2$ (**C**) or $\text{Ru}(\text{H})(\text{D})(\text{IMes})_2$ (**C**) to yield $\text{Ru}(\text{D})(\text{IMes})([\text{2H}]\text{-IMes})$ (**D**) that contains a deuterated IMes ligand. Further ligand-exchange reaction of **D** with a nonlabeled IMes ligand then releases the deuterium-labeled IMes ligand $[\text{2H}]\text{-IMes}$ and regenerates the 14-e^- species $\text{Ru}(\text{H})(\text{IMes})(\text{IMes})$ (**3**). Higher deuteration ratio on the *ortho*-benzylic positions of

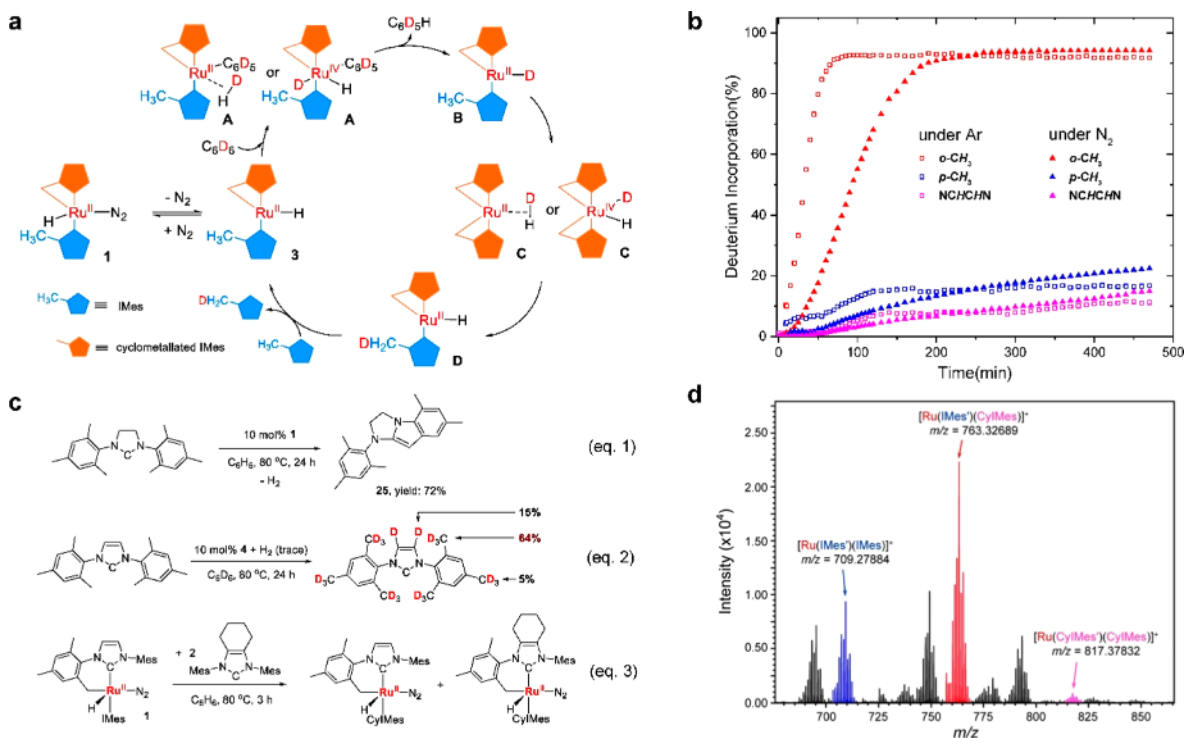


Figure 5. Mechanistic proposals and supporting evidence. (a) Proposed catalytic cycle for the catalytic HIE of IMes with C_6D_6 with **1** as catalyst. (b) Time courses of HIE reactions on the *ortho*-methyl, *para*-methyl, and backbone $\text{C}(\text{sp}^3)\text{--H}$ bonds of IMes under N_2 (1 atm) and Ar (1 atm). The reactions were performed in J. Young NMR tubes with IMes (0.1 mmol) and **1** (10 mol %) and C_6D_6 (0.5 mL) at 78°C , followed by ^1H NMR spectroscopy. (c) Reactions supporting the proposed catalytic cycle. (d) Mass spectrum of the reaction mixture formed from the reaction of **1** with CyIMes (2 equiv) in benzene at 80°C .

IMes can be realized by repeating the catalytic cycle with partially deuterated IMes and C_6D_6 as substrates.

In this proposed mechanism, **1** stands as the resting state out of the cycle. In accord with this speculation, monitoring the catalytic HIE reaction of IMes with C_6D_6 under N_2 by infrared spectroscopy has led to the detection of the characteristic ν_{N-N} stretch of **1** at 2052 cm^{-1} during the reaction course (Figure S47). The possible involvement of the 14-e^- species $Ru(H)(IMes')(IMes)$ (**3**) in the catalytic cycle gains support from the observation that the HIE reaction performed under Ar proceeded faster than that under N_2 . As depicted in Figure S5b, the catalytic deuteration reaction of IMes with C_6D_6 operating under Ar at 78°C merely needed 50 min to achieve a high deuteration ratio ($>90\%$) on the *ortho*- CH_3 positions. In contrast, the reaction run under N_2 showed an apparent induction period (ca. 20 min) and required 200 min to reach a comparable high deuteration ratio (Figure S5b). The brief induction period might be due to a temperature effect since the initial data points were collected at the early stage of the NMR monitoring experiments. During the course, the NMR sample was warmed to 78°C , and equilibrium of N_2 dissociation from Ru species has not yet been established. The different kinetic profiles are in line with the observation that the stoichiometric HIE reaction of **1** with C_6D_6 under Ar atmosphere took place faster than that under N_2 (*vide supra*). Moreover, ^1H NMR analysis on the solution of **1** in C_6D_6 or cyclohexane- d_{12} under Ar indicated the formation of a new Ru hydride species that might be $Ru(H)(IMes')(IMes)$ (**3**) (*vide supra*). As an indirect supporting evidence for the involvement of cyclometalated NHC Ru species **3**, **A–D**, in the catalytic cycle, heating a solution of 1,3-di(2',4',6'-trimethylphenyl)-imidazolin-2-ylidene (sIMes) with **1** (10 mol %) in C_6H_6 resulted in the formation of *N*-heterocyclic olefin **25** (eq 1 in Figure S5c), whose formation can be explained by the migratory insertion reaction of a cyclometalated imidazolin-2-ylidene Ru intermediate, followed by a β -H elimination step (Scheme S6). Formation of analogous *N*-heterocyclic olefin was evidenced by ^1H NMR spectroscopy when heating the solution of 1,3-di(2',6'-diethylphenyl)-imidazolin-2-ylidene with **1** (10 mol %) in C_6H_6 for 24 h. So far, attempts to detect cyclometalated IMes Ru dihydrogen or dihydride intermediates, **A** and **C**, by NMR spectroscopy were not fruitful, though similar Ru complexes supported by other ligands are documented in literature.^{50,51} However, it has been found that although the bis(cyclometalated) NHC complex $[Ru(IMes')_2(N_2)_2]$ (**4**) is ineffective in catalyzing the HIE reaction of IMes with C_6D_6 , exposing the solution of **4** to H_2 produced a mixture that effects the catalytic HIE reaction (eq 2 in Figure S5c), supporting the proposed conversion from **C** to **D** in Figure S5a. Complex **4** is reminiscent of that of Nolan's bis(cyclometalated) *N,N*-di(*tert*-butyl)imidazol-2-ylidene iridium(III) complex $[Ir(IBM')_2][PF_6]$ (IBM' denotes for the cyclometalated *N,N*-di(*tert*-butyl)imidazol-2-ylidene ligand) that is capable of incorporating deuterium into the *tert*-butyl groups of the NHC ligand when $[Ir(IBM')_2][PF_6]$ interacts with D_2 .^{52–54} In spite of the effectiveness of the mixture generated by exposing **4** to a H_2 atmosphere in promoting the catalytic deuteration reaction, the catalytic system is incapable of using D_2 as a D source. The failure might be due to the proneness of the NHC-Ru deuteride species, presumably $(NHC)_2Ru(D_2)_2$ or $(NHC)_2RuD_4$, to undergo decomposition at elevated temperature that is required for effective catalysis. This speculation gains support from the observation

that the reaction of **1** with an excess of H_2 (1 atm) in C_6D_6 at 80°C gave a black precipitate, whose identity needs further study to disclose.

The ability of NHCs to bind tightly with transition metals poses a great challenge on the development of metal-catalyzed transformations of NHCs. Hence, a key step in the proposed catalytic cycle shown in Figure S5a is the ligand-replacement reaction that converts **D** into **3**. Ligand-exchange reactions of metal–NHC complexes with exogenous NHCs are rarely known in literature.⁵⁵ As a rare example, Caddick and Cloke noted the reaction of *N,N*-di(*tert*-butyl)imidazol-2-ylidene (IBu') with $(sIPr)_2Pd$ to yield $(sIPr)(IBu')Pd$.⁵⁶ To gain evidence for the feasibility of this NHC-exchange step, the cold-spray ionization mass spectrum of the reaction mixture of **1** with 2 equiv of CyIMes in C_6H_6 was collected, which clearly showed the molecular ion peaks of $[Ru(CyIMes)(IMes')]^+$ and $[Ru(CyIMes)(CyIMes')]^+$ (Figure S5d), indicating the occurrence of the ligand-exchange reaction shown by eq 3 in Figure S5c. The attempts to use ^1H NMR to probe the NHC-exchange reaction between **1** and CyIMes was unsuccessful due to peak overlapping of the resultant ^1H NMR spectrum. No ligand-exchanged species was observed on the mixture of **1** with 2 equiv of IPr by mass spectroscopy. This observation lends credence to the speculation that the catalytic $C(sp^2)\text{--H}$ bonds deuteration reactions leading to the deuterated NHCs in Figure 3 might be achieved by the intermolecular HIE reactions of $Ru\text{--D}$ species with exogenous NHCs.

While the aforementioned catalytic cycle illustrates the catalytic benzylic $C(sp^3)\text{--H}$ bond deuteration reaction of IMes, similar catalytic cycles for the catalytic $C(sp^3)\text{--H}$ bond deuteration reactions of *ortho*-ethyl, *ortho*-isopropyl, *N*-cyclohexyl, and *N*-adamantyl on NHCs can be envisioned as relevant cyclometalation reactions of NHCs on its *N*-2,6-diisopropylphenyl,⁵⁷ *N*-isopropyl,²⁴ *N*-*tert*-butyl,⁵⁸ and *N*-adamantyl⁵⁹ are documented. On the basis of the above-mentioned mechanistic understandings, one can clearly notice that the success in the development of the catalytic method for the preparation of deuterated NHCs benefits from the use of the coordinatively unsaturated cyclometalated IMes ruthenium hydride catalyst as its ability to undergo HIE with C_6D_6 and to perform ligand replacement reaction with other NHCs satisfies the prerequisites on catalysts for catalytic $C(sp^3)\text{--H}$ bond HIE reactions. Equally important is the structural feature of NHCs that should not only be able to undergo cyclometalation reaction on $Ru(II)$ center but also have the ability to replace the IMes ligand on the precatalyst to form new coordinatively unsaturated $Ru(II)$ species. The NHCs with high deuteration ratio on $C(sp^3)\text{--H}$ bonds in Figure 3 are apparently among the ones fulfilling these requirements.

In addition to the deuteration reactions enabled by cyclometalation processes, the catalytic system also effects deuteration on *para*-methyl and *para*-OMe groups of *N*-aryls, as well as the $C(sp^2)\text{--H}$ bonds on NHCs (Figure 3). Inasmuch as these $C\text{--H}$ bonds are far away from Ru and should be hard to undergo cyclometalation reactions, it can be proposed that these $C\text{--H}$ bond deuteration reactions should not necessitate the precoordination of the carbene carbon atoms of NHCs to the ruthenium center and might be achieved by the interaction of deuteride complex $Ru(D)\text{--}(IMes')(IMes)$ (**B**) with the $C\text{--H}$ bonds of the exogenous NHC ligand. The catalytic cycles (Figure S54) should be reminiscent of that proposed in Figure S5a.

■ CONCLUSION

The first catalytic method for the preparation of deuterated NHCs has been developed by employing a coordinatively unsaturated cyclometalated IMes Ru(II) hydride complex $[\text{Ru}(\text{H})(\text{IMes})(\text{IMes})(\text{N}_2)]$ (**1**) as catalyst for the HIE reaction of NHCs with C_6D_6 . This catalytic HIE reaction enables predictable regioselective deuteration of both $\text{C}(\text{sp}^2)\text{--H}$ and $\text{C}(\text{sp}^3)\text{--H}$ bonds of NHCs, by which isotope-labeled NHCs with a high deuteration ratio on the *ortho*-alkyl groups of *N*-aryl substituents, specific $\text{C}(\text{sp}^3)\text{--H}$ bonds of *N*-alkyl groups, as well as the sterically unhindered $\text{C}(\text{sp}^2)\text{--H}$ bonds have been successfully prepared. As a demonstration for the potential synthetic utility of this the catalytic method, $[\text{H}]\text{--IMes}$ featuring fully deuterated *ortho*-methyl groups has been prepared in gram scale from the reaction of IMes with C_6D_6 , and further used for the synthesis of transition metal catalysts.

Mechanistic studies disclosed the dynamic solution behaviors of **1** of N_2 dissociation to form a new Ru(II) hydride species, the facile stoichiometric $\text{C}(\text{sp}^3)\text{--H}$ bond HIE reaction with C_6D_6 , as well as its ligand replacement reaction with other NHC ligand. These observations, in addition with the evidence of the enhanced rate of the catalytic $\text{C}(\text{sp}^3)\text{--H}$ bond HIE reaction of IMes with C_6D_6 under Ar, point to a catalytic cycle involving reversible cyclometalation reactions of coordinatively unsaturated Ru NHC species for the catalytic $\text{C}(\text{sp}^3)\text{--H}$ bond HIE reactions of NHCs, wherein the high regio-selectivity of the $\text{C}(\text{sp}^3)\text{--H}$ bond deuteration reactions should root from the selectivity of cyclometalation reaction. To our knowledge, this study also represents the first example of catalytic functionalization of NHCs. Thus, it provides a solution for the rational design of catalysts for direct, catalytic functionalization of NHCs, which are highly desired in the synthesis community.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c10071>.

Experimental procedures, characterization and data (PDF)

Accession Codes

CCDC 2106498–2106499, 2106501, 2106509, and 2112710 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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