Mild and Selective H/D Exchange at the β -Position of Aromatic α -Olefins by *N*-Heterocyclic Carbene-Hydride-Rhodium Catalysts**

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One of the major challenges in modern chemistry is the design of improved catalysts for controlled and selective C-H functionalization.^[1] In this context, H/D exchange reactions are valuable transformations for the preparation of isotopically labeled compounds, which have found practical applications in mechanistic investigations on catalysis, spectroscopic analysis, or monitoring of drug metabolism.^[2] Organometallic catalysts offer the potential for mild reaction conditions with a high degree of regio- and chemoselectivity.^[3,4] Although the study of H/D exchange reactions has tended to concentrate on aromatic^[2,3a-i] or aliphatic^[2,3a-d,j] compounds, there is an increasing interest in the deuteration of vinylic derivatives.^[4] Moreover, selectivity towards olefinic versus aromatic protons is an important challenge. Indeed, Milstein and co-workers have recently shown the ability of a pincer Rh^{III}-hydride catalyst to perform selective vinylic deuteration with moderate activity.^[4c]

An electron-rich ligand is often used to increase the stability of potential Rh^{III}-hydride catalysts, whereas their selectivity can be modulated by a bulky ligand, which exerts steric pressure on the interaction of substrates with the active species. *N*-heterocyclic carbene ligands (NHC) fit both these requirements^[5] as they are excellent electron-releasing groups and provide adequate steric protection in the vicinity of the metallic center.^[6] Hydride ligands are thought to play a fundamental role in the exchange step with the deuterium source, whatever the mechanism proposed.^[3,4a-e] Despite this, the number of isolated Rh^{III}-NHC-hydride derivatives remains scarce,^[7] and all such known compounds bear two NHC ligands. The presence of two bulky NHC ligands imposes a very crowded environment around the metal center, thereby reducing the reactivity.^[6c] In light of this, we envisaged the substitution of one of the quasi-hemispherical NHC ligands by a smaller planar chelate as a means of facilitating the interaction with substrates whilst maintaining a high steric induction.

Herein we report a highly active and selective H/D exchange at the β -position of aromatic α -olefins by a new rhodium(III)-*N*-heterocyclic carbene-hydride catalyst containing a bulky NHC and a chelating quinolinolate ligands. Thus, we chose 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-carbene (IPr) as encumbered NHC ligand and 8-quinolinol as a suitable hydride source upon oxidative O-H addition.^[8] Treatment of the dimer [Rh(μ -Cl)(IPr)(coe)]₂ (**1**) (coe = cyclooctene)^[7b] with 8-quinolinol gave rise to the diastereoselective formation of the 16-electron complex [RhClH(κ^2 O,N-C₉H₆NO)(IPr)] (**2**; Scheme 1). The hydride ligand resonates in the ¹H NMR spectrum at δ = -28.41 ppm as a doublet with a *J*_{H-Rh} coupling constant of 46.4 Hz.^[9] Crystallization of **2** from coordinating solvents gave the saturated species [RhClH(κ^2 O,N-C₉H₆NO)(IPr)(S)] [S = methanol (**3**); acetonitrile (**4**)]. The structure of **3** was confirmed by an X-ray diffraction analysis.^[10] The complex can be described as a distorted octahedron with the hydride *trans* to coordinated methanol and the bidentate quinolinolate ligand with its nitrogen atom *trans* to IPr.

Scheme 1. Synthesis of rhodium-NHC-hydride complexes.

Complex **2** is an active and selective catalyst for H/D exchange of α -olefins under mild conditions. High activity was observed in methanol-*d*₄ at room temperature with a 2 mol % catalyst loading. Styrene was deuterated exclusively at the vinylic positions, with concomitant lack of deuterium at the phenyl ring. Moreover, a very high selectivity for the β -position was observed, with intriguingly similar rates for both *cis* and *trans* protons (Figure 1, TOF_{1/2}^[11] of 192 h⁻¹). A conversion of 95% was reached after 3 hours at 25 °C or 20 min at 50 °C with similar selectivity. The rates observed for **3** and **4** are similar to that of **2**, since lability of the coordinated solvents on those saturated precursors should give rise to the same active species. The catalytic species are stable at room temperature. Indeed, styrene was deuterated with a similar activity and selectivity when a second load of substrate was added to a completed catalytic mixture (3 h). The selective incorporation of deuterium to olefinic versus aromatic protons has been reported previously for one Rh^{III}-hydride catalyst, although this complex shows a lower catalytic activity (80 % conversion after 24 h at 60 °C) and is not selective for α - or β -protons.^[4c]

Two main mechanisms have been postulated for H/D exchange on vinylic protons: i) oxidative addition - H/D exchange - reductive elimination,^[4b,e] or ii) H/D exchange - migratory insertion - rotation - β -elimination.^[4a,c,d] The C-H activation pathway (i) is followed with electron-rich complexes, such as Ir^I derivatives, whereas steric restrictions favor the *trans* vinylic C-H activation.^[4c] Indeed,

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aromatic protons can only be exchanged in a C-H activation mechanism. The observed selectivity for vinylic protons with similar rates for both β -protons, and the involvement of Rh^{III} -hydride precursors, therefore points to the classical insertion- β -elimination mechanism in our system.

Figure 1. H/D exchange in styrene catalyzed by **2** at 25°C.

The stoichiometric addition of styrene to **2** was monitored by NMR spectroscopy. At -30 °C the ^1H NMR spectrum shows the formation of a pair of diastereoisomers bearing a branched alkyl ligand generated by 2,1-insertion of styrene into the rhodium-hydride bond (**5a,b**; Scheme 2). The methyl groups appear as doublets ($J_{\text{H-H}} = 6.6$ Hz) in the ^1H NMR spectrum at $\delta = 0.75$ and 0.39 ppm and are coupled to the Rh-CH protons, which appear as broad signals at 5.58 and 6.15 ppm, respectively.^[12] Warming the sample to room temperature results in the formation of a new complex. The presence of two sets of diastereotopic CH_2 protons in the ^1H NMR spectrum supports the formation of the linear alkyl derivative **6** by 1,2 insertion. These experiments suggest that Markovnikov insertion products are obtained under kinetic control whereas anti-Markovnikov products are thermodynamically favored.^[13] Attempts to isolate **6** from the solution resulted in the recovery of **2**, thus showing the reversibility of the insertion process.

Scheme 2. Insertion of styrene into the rhodium-hydride bond monitored by variable-temperature NMR spectroscopy.

The high selectivity of catalyst **2** for deuteration at the β -position is remarkable. The IPr ligand is a bulky and highly electron-releasing ligand which may exert electronic and steric influence on the catalytic activity and selectivity. Its electronic influence on the selectivity should be related to its ability to control the type of olefin insertion.^[13] 1,2 insertion is responsible for α -deuteration whereas 2,1 insertion leads to β -H/D exchange. The linear alkyl derivative is thermodynamically favored, therefore H/D exchange at the α -position should occur at a higher rate under catalytic conditions. However, the high selectivity observed for β -substitution suggests that steric factors could have a stronger influence.

Figure 2 shows the proposed catalytic cycle. The relative energies of the postulated intermediates were calculated by DFT (B3LYP, kcal·mol⁻¹; Figure 3). The first step could be deuteration of the hydride ligand in **2** by CD_3OD to produce **a**. Indeed, **2** readily undergoes H/D exchange in methanol- d_4 at room temperature. The steady increase of the O-H signal in the ^1H NMR spectrum during catalytic reactions and the observation of a similar reaction rate when using CH_3OD suggest that only the deuterium atom from the O-D group are responsible for the exchange. The disposition of the alkene to the equatorial position. Two orientations (**b** and **c**) are possible for olefin coordination, with the intermediate that does not contain eclipsed aromatic rings (**b**; 0.0) being slightly more stable than **c** (1.2). In accordance with the observation that the Markovnikov insertion is kinetically favored, the pathway via **TSbd** (9.2; linear alkyl ligand) is more energetic than that via **TScf** (8.0; branched alkyl ligand). However, the energy values corresponding to the located minima for the olefin-inserted products are inverted. Thus, in accordance with the experimental observations, the linear alkyl species **d** (-20.6) is more stable than the branched alkyl derivative **f** (-13.1).

Careful observation of the structure of the alkyl ligands in **d** and **f** shows that a rotation around the $\text{C}_1\text{-C}_2$ axis of the alkyl ligand is required to exchange the proton and deuterium positions prior to H/D substitution. In the case of **d**, the steric hindrance imposed by the bis-isopropylphenyl substituents of IPr restricts this rotation due to repulsion with the phenyl group of the alkyl ligand (**e**), thus meaning that although a deuterium atom can enter the benzyl position the hydride cannot easily leave. The transition state for this rotation is highly energetic and could not be determined. However, the branched insertion process gives rise to a CH_2D terminal group (**f**) for which rotation around the $\text{C}_1\text{-C}_2$ axis is less disfavored, thus allowing exchange between proton and deuterium orientations via **TSfg** (-9.6), which is only 3.5 kcal·mol⁻¹ higher in energy than **f**. Subsequent β -elimination reforms the starting olefin but with a deuterium atom at the β -position in either a *cis* or *trans* disposition (**c_D**), thereby explaining the similar rate observed for H/D exchange for both *cis* and *trans* protons.

Figure 2. IPr-controlled steric induction for selective H/D exchange.

Figure 3. Computed potential-energy profile relative to **b** (ΔE , kcal mol⁻¹) for the olefin-insertion and alkyl-rotation processes.

A related Rh^{III}-quinolate-hydride complex bearing tricyclohexylphosphine was prepared. Although this unsaturated-phosphine analogue of **2** is unstable, we were able to prepare its acetonitrile adduct [RhClH(κ^2 O,N-C₉H₆NO)(PCy₃)(NCCH₃)] (**7**) starting from [RhCl(coe)(PCy₃)₂].

Figure 4. H/D exchange in styrene catalyzed by **7** at 25 °C.

Complex **7** also catalyzed the H/D exchange of styrene but with lower activity and selectivity than **2** or **4**. Thus, after 50 h at 25 °C the β -H/D exchange had reached 66 % conversion whereas the α -exchange was only 21 % (Figure 4). This decrease in catalytic activity can be ascribed to the higher electron-donating ability of the NHC ligand with respect to PCy₃.^[5] Catalyst **7** also favors deuteration at the β -position but with a lower selectivity than its NHC counterpart due to the different steric hindrance exerted by the two ligands. Although tricyclohexylphosphine ligand is a bulky ligand, its substituents are disposed in a *conical* fashion pointing *out* of the equatorial plane of the coordination sphere. In contrast, IPr adopts an *umbrella* type disposition with the isopropylphenyl substituents pointing *towards* the equatorial plane, thereby increasing the steric hindrance.^[6]

To elucidate the effect of the bulky electron-donating ligand on the catalytic results, we tested the hydride species generated in situ by protonation of the dimer [Rh(μ -Cl)(coe)₂]₂ with HCl as catalyst. This reaction also resulted in the exclusive deuteration of vinylic protons, but with a lower catalytic activity (Table 1, entry 15) and no discrimination between the α - and β -positions is observed.

Table 1. H/D exchange promoted by Rh^{III}-H catalysts.^a

Entry	Cat	substrate	t (h)	T (°C)	α -D ^b	β -D ^b	TOF _{1/2} (h ⁻¹) ^c
1	2		3	25	3	95	192.4
2	2		0.3	50	4	94	833.4
3	4		2	25	3	93	188.6
4	7		50	25	21	66	2.4
5	2		7	25	2	95	50.0
6	2		4	25	4	90	140.2
7	2		0.4	25	3	93	416.6
8	2		1	25	3	95	333.4
9	2		2.5	25	4	95	166.6
10	2		0.1	25	3	93	930.0 ^g
11	2		6	25	4	90	83.3
12	2		24	50	< 2	< 2	-
13 ^d	2		2	50	10	62	36.7
14	2		22	50	9	61	5.8
15	1 + HCl		0.5	50	87	86	261.0 ^g
16 ^e	2 + D ₂ O		4	50	7	95	75.0 ^g
17 ^f	2		4	25	98	2	-

^a CD₃OD with 2 mol % of catalyst. ^b (%). ^c H/D exchange at β -position. ^d 28% of 2-pentene. ^e D₂O/acetone-*d*₆ 1/4. ^f CH₃OH. ^g Calculated at final conversion.

The selectivity on the H/D exchange catalyzed by **2** is retained for a range of aromatic alkenes (Table 1), with the electron density on the aromatic ring having a major effect. Thus, introduction of electron-donating groups at the *para* or *meta* positions of the vinylic group enhances catalytic activity (entries 7, 8, and 10), whereas an electron-withdrawing CF₃ group reduces it (entry 11). Increasing the steric bulkiness of the substituents at the aromatic ring has little impact. Thus, both *p*-*tert*-butylstyrene and *o*-methylstyrene display slightly lower rates (entries 6 and 9). 2-Vinylnaphthalene is also deuterated smoothly (entry 5). Aliphatic alkenes such as 1-pentene react slowly with **2** and show similar selectivity patterns (entry 13). Concomitant isomerization to 2-pentene was also observed, although H/D exchange is 2.5 times faster than isomerization. *tert*-Butylethylene reacts slowly at 50 °C (entry 14), whereas vinylpyridine, methyl acrylate and disubstituted alkenes such as cyclooctene, α -methylstyrene, and 2-pentene do not undergo H/D exchange in the presence of **2**. Indeed, stoichiometric addition of these internal alkenes to **2** showed no insertion into the hydride bond, probably due to steric repulsion, thus suggesting that the coordination “cavity” in **2** accommodates only monosubstituted alkenes.

The use of D₂O as deuterium source was also investigated. Styrene was deuterated with a TOF_{1/2} of 75 h⁻¹ (entry 16) in a mixture of acetone-*d*₆/D₂O (4/1) at 50 °C.^[14] Another practical application of this catalytic system is the preparation of α -deuterated olefins. Thus, treatment of styrene-*d*₈ with **2** in MeOH (entry 17) gave rise to α -deuterated styrene as a result of selective D/H exchange at the β -position. Different combinations of Rh-H catalytic systems provide access to β,β' -deuterated (**2**), α,β,β' -deuterated (**1**+HCl), or α -deuterated styrene derivatives (**1**+HCl in MeOD and then **2** in MeOH).

In conclusion, we have shown that stable rhodium-IPr-hydride complexes are active and selective catalysts for H/D exchange reactions. The steric pressure exerted by the bulky IPr ligand

controls the rotation of the alkyl ligand, which in turn determines the selectivity. The design of new catalysts bearing flexible NHC ligands in order to broaden the scope of the reaction to bulkier olefins is currently underway. Indeed, these new hydride catalysts open up future opportunities for homogeneous catalysis.

Experimental Section

Full experimental details and spectroscopic data are available in the Supporting Information. Coupling constants are given in Hz

2: A solution of **1** (300 mg, 0.235 mmol) in 10 mL of toluene was treated with 8-quinolinol (68 mg, 0.470 mmol) and stirred for 45 min at r. t. The solution was concentrated to ca. 1 mL and *n*-hexane added to induce the precipitation of an orange solid, which was washed and dried under vacuum. Yield: 240 mg (76%). Anal. Calcd. for C₃₆H₄₃N₃ClORh: C, 64.33; H, 6.45; N, 6.25. Found: C, 64.14; H, 6.19; N, 6.24. ¹H NMR (400 MHz, C₆D₆, 298 K): δ 8.89, 7.21, 7.17, 7.05, 6.54, and 6.26 (H_{Quin}), -28.41 (d, 1H, J_{Rh-H} = 46.4, H_{Rh-H}). ¹³C{¹H}-APT NMR (100.6 MHz, C₆D₆, 298 K): δ 179.0 (d, J_{C-Rh} = 49.5, Rh-C_{IPr}).

Catalytic H/D Exchange. In an NMR tube, 0.01 mmol of catalyst and 0.5 mmol of olefin were dissolved in 0.5 mL of CD₃OD. The degree of H/D exchange was quantified by ¹H NMR integration with respect to hexamethyldisiloxane (2 μL, 0.01 mmol) as internal standard. Successful deuteration of the olefin was confirmed by ²H and ¹³C{¹H} NMR spectroscopy.

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- [1] a) K. Godula, D. Sames, *Science* **2006**, *312*, 67; b) S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Grudvig, *Science* **2006**, *312*, 1941; c) M. S. Chen, C. White, *Science* **2007**, *318*, 783.
- [2] J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem. Int. Ed.* **2007**, *46*, 7744.
- [3] a) C. P. Lenges, P. S. White, M. Brookhart, *J. Am. Chem. Soc.* **1999**, *121*, 4385; b) C. M. Yung, M. B. Skaddan, R. Bergman, *J. Am. Chem. Soc.* **2004**, *126*, 13033; c) R. Corberán, M. Sanaú, E. Peris, *J. Am. Chem. Soc.* **2006**, *128*, 3974; d) M. H. G. Precht, M. Hölscher, Y. Ben-David, N. Theyssen, R. Loschen, D. Milstein, W. Leitner, *Angew. Chem. Int. Ed.* **2007**, *46*, 2269; e) W. G. Brown, J. L. Garnett, *J. Am. Chem. Soc.* **1958**, *80*, 5272; f) J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson, G. Nilsson, *Chem. Commun.* **2008**, 1115; g) S. Chen, G. Song, X. Li, *Tetrahedron Lett.* **2008**, *49*, 6929; h) B. Eguillor, M. A. Esteruelas, J. García-Raboso, M. Oliván, E. Oñate, *Organometallics* **2009**, *28*, 3700; i) A. J. Hickman, J. M. Villalobos, M. S. Sandford, *Organometallics* **2009**, *28*, 5316; j) T. Maegawa, Y. Fujiwara, Y. Inagaki, H. Esaki, Y. Monguchi, H. Sajiki, *Angew. Chem. Int. Ed.* **2008**, *47*, 5394.
- [4] a) R. Cramer, *J. Am. Chem. Soc.* **1966**, *88*, 2272; b) J. W. Faller, Y. Ma, *Organometallics* **1989**, *8*, 602; c) B. Rybtchinski, R. Cohen, Y. Ben-David, J. M. L. Martin, D. Milstein, *J. Am. Chem. Soc.* **2003**, *125*, 11041; d) G. Kohl, R. Rudolph, H. Pritzkow, M. Enders, *Organometallics* **2005**, *24*, 4774; e) J. Zhou, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2008**, *47*, 5783; f) G. Erdogan, D. B. Grotjahn, *J. Am. Chem. Soc.* **2009**, *131*, 10354.
- [5] a) W. A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 1290; b) J. M. Praetorius, C. M. Crudden, *Dalton Trans.* **2008**, 4079; c) A. J. Arduengo III, L. I. Iconaru, *Dalton Trans.* **2009**, 6903; d) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612.
- [6] a) A. C. Hillier, W. J. Sommer, B. S. Yong, J. L. Petersen, L. Cavallo, S. P. Nolan, *Organometallics* **2003**, *22*, 4322; b) V. Lavallo, Y. Canac, C. Präsaug, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed.* **2005**, *44*, 5705; c) M. Yamashita, K. Goto, T. Kawashima, *J. Am. Chem. Soc.* **2005**, *127*, 7294; d) A. Fürstner, M. Alcarazo, H. Krause, C. W. Lehmann, *J. Am. Chem. Soc.* **2007**, *129*, 12676; e) S. Würtz, F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523; f) A. R. Chianese, A. Mo, D. Datta, *Organometallics* **2009**, *28*, 465; g) Y.-X. Jia, D. Katayev, G. Bernardinelli, T. M. Seidel, E. P. Kündig, *Chem. Eur. J.* **2010**, *16*, 6300.
- [7] a) J. Huang, E. D. Stevens, S. P. Nolan, *Organometallics* **2000**, *19*, 1194; b) X.-Y. Yu, B. O. Patrick, B. R. James, *Organometallics* **2006**, *25*, 4870; c) J. M. Praetorius, R. Wang, C. M. Crudden, *Eur. J. Inorg. Chem.* **2009**, 1746; d) X.-Y. Yu, H. Sun, B. O. Patrick, B. R. James, *Eur. J. Inorg. Chem.* **2009**, 1752; e) C. Y. Tang, A. L. Thompson, S. Aldridge, *Angew. Chem. Int. Ed.* **2010**, *49*, 921.
- [8] D. B. Grotjahn, C. Joubert, *Organometallics* **1995**, *14*, 5171.
- [9] A similar high-field signal and unusually high H-Rh coupling has been observed in related rhodium-hydride complexes with a vacant site in the *trans* position. See for example: a) S. Nemeh, C. Jensen, E. Binamira-Soriaga, W. C. Kaska, *Organometallics* **1983**, *2*, 1442; b) V. F. Kuznetsov, A. J. Lough, D. G. Gusev, *Inorg. Chim. Acta* **2006**, *359*, 2806; c) H. Salem, L. J. W. Shimon, G. Leitens, L. Weiner, D. Milstein, *Organometallics* **2008**, *27*, 2293.
- [10] Data for **3**: C₃₇H₄₇ClN₃O₂Rh₂CH₃OH, *M*=768.22, space group *P*2₁/*c*, *a*=10.8214(6), *b*=18.7516(11), *c*=19.1929(11) Å, β=103.7300(10)°, *V*=3783.3(4) Å³, *Z*=4, *R*=0.0357 [7759 refl., *I*>2σ(*I*)], *wR*(*F*²)=0.0987, *GoF*=1.042 (9202 unique); CCDC 784690 contains the supplementary crystallographic data for this paper.
- [11] TOF_{1/2} is the average turn-over frequency at 50% conversion.
- [12] Although an η³-benzyl structure for **5** cannot be excluded, an unsaturated square-pyramidal structure seems more likely on the basis of the ¹H and ¹³C NMR data.
- [13] a) P. J. Chirik, J. E. Bercaw, *Organometallics* **2005**, *24*, 5407; b) L.-C. Liang, P.-S. Chien, P.-Y. Lee, *Organometallics* **2008**, *27*, 3082, and references therein.
- [14] H/D exchange was not observed in pure acetone-*d*₆.