Angewandte Chemie

DOI: 10.1002/anie.200801992

C–H Activation

Iridium-Catalyzed H/D Exchange at Vinyl Groups without Olefin Isomerization**

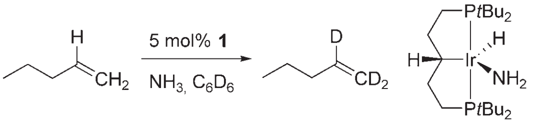
*Jianrong Zhou and John F. Hartwig**

Exchange of a hydrogen atom with a deuterium atom (H/D exchange) was one of the first catalytic C–H activation processes reported to occur by organometallic intermediates.[1] This process has experienced a renaissance recently because of the value of deuterated and tritiated compounds in the study of reaction mechanisms and biological processes.[2] In general, deuterium or tritium can be introduced during a synthesis with a deuterated or tritiated reagent, or after the synthesis is complete by H/D or H/T exchange. If regio- and stereoselective H/D or H/T exchange could be developed, the latter approach would be simpler to conduct and more cost effective than the introduction of the label during synthesis. Moreover, it would avoid the handling of tritiated synthetic intermediates.[3]

H/D exchange of aromatic hydrogen atoms is well known and has been conducted with a variety of catalysts, including acid, base, and metal complexes.[4] H/D exchange of non-activated, aliphatic C–H bonds has also been conducted with transition-metal catalysts,[5] including [Cp*Ir(PMe$_3$)],[6,7] [Cp*Ir(carbene)],[8] and [(Tp^{Me2})Ir] complexes.[9] H/D exchanges catalyzed by the recently developed systems afford a high degree of isotope incorporation, and some have been conducted with D$_2$O as the deuterium source.[10]

In contrast to H/D exchange at aryl and alkyl groups, H/D exchange at vinyl groups has not been studied extensively. Most existing examples of H/D exchange at vinyl groups have been conducted with cyclic or isolated olefins, such as cyclopentene, styrene, and *tert*-butylethylene, presumably to avoid complications from olefin isomerization.[8,11] A more general, selective H/D exchange of alkene hydrogen atoms has been limited because alkene isomerization often occurs under conditions that lead to C–H activation. For example, H/D exchange of 1-pentene[12] and 1-hexene[6,13] has caused isomerization to the more stable internal isomers at elevated temperature,[6] at room temperature,[12] and under photochemical conditions.[13] We report a catalytic system that overcomes this limitation. We show that H/D exchange catalyzed by an iridium complex containing an aliphatic pincer ligand occurs at the vinylic positions without olefin isomerization. This selectivity, along with high functional group compatibility, is demonstrated by H/D exchange between C$_6$D$_6$ and a series of olefins containing various functional groups, as well as natural products and natural product analogues.

The discovery of this H/D exchange chemistry resulted from studies with the amidoiridium hydride complex [(dtbpp)Ir(H)(NH$_2$)] (**1**) (dtbpp = 1,5-bis(di-*tert*-butylphosphino)pentan-3-yl) [Eq. (1)], that we had previously shown to form by oxidative addition of ammonia.[14] The reaction of pentene in C$_6$D$_6$ in the presence of catalytic amounts of **1** led to rapid H/D exchange of the olefinic hydrogen atoms with the C$_6$D$_6$ solvent. No isomerization of the olefin was observed, and less than 1% deuterium was incorporated into the alkyl chain, including the allylic positions.

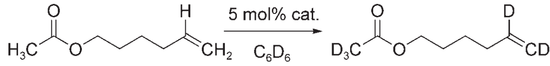


1

(1)

On the basis of this observation, a series of catalysts were evaluated for H/D exchange between C$_6$D$_6$ and 5-hexenyl acetate (Table 1). This substrate was chosen for the evaluation of catalysts because it would reveal the relative rates for H/D exchange at olefinic positions and at enolizable hydrogen atoms that are known to undergo H/D exchange in the presence of iridium catalysts.[6,8] Complex **1** catalyzed exchange at the olefinic positions faster than at the acetate.

Table 1: Selectivity pattern of H/D exchange catalysts (percentage of deuterium incorporation).



Entry	Catalyst	Conditions	α-CD$_3$	CD=C	C=CD$_2$
1	**1**	RT, 10 h	23	87	94
2	**2**	RT, 10 h	37	96	98[a]
3	**3**	RT, 3 h	32	0	52
4	**3**	RT, 10 h	74	2	61
5	**4**	RT, 10 h	0	0	0[b]
6	**4**	50 °C, 8 h	0	0	0[b]
7	**5**	RT, 10 h	0	30	6[c]
8	**5**	50 °C, 8 h	0	45	21[d]

[a] 11% hydrogenation byproduct. [b] 8% hydrogenation byproduct. [c] 4% hydrogenation byproduct. [d] 5% hydrogenation byproduct and 8% olefin isomers.

---

[*] J. Zhou, Prof. J. F. Hartwig
Department of Chemistry
University of Illinois Urbana-Champaign
600 South Matthews Ave, Box 58-6, Urbana, IL 61801 (USA)
Fax: (+1) 203-432-6144
E-mail: jhartwig@uiuc.edu

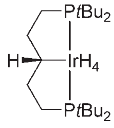
[**] We thank the DOE for support of this work and Johnson-Matthey for a gift of iridium.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200801992.

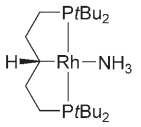
© 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

WILEY InterScience® DISCOVER SOMETHING GREAT

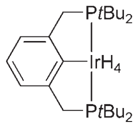
The distribution of products generated by tetrahydride **2** was similar to that produced by amido complex **1**, presumably because these two complexes react through the same active catalyst. In contrast to the iridium catalysts, rhodium analogue **3** reacted with both the terminal olefinic hydrogen atoms faster than at the internal hydrogen atoms, and it led to exchange of the enolizable hydrogen atoms.



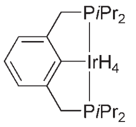
2



3



4



5

Although iridium complexes with aromatic pincer ligands readily activate aliphatic hydrogen atoms at elevated temperatures, H/D exchange at room temperature catalyzed by aromatic pincer complexes **4** and **5**[15] was much slower than that catalyzed by **1**–**3**. Because of the high reactivity of **1**, a majority of studies on the selectivity with substrates containing other functional groups were conducted with this catalyst.

Results of H/D exchange of different classes of olefins catalyzed by complex **1** are summarized in Figure 1. The efficiency of exchange for individual hydrogen atoms depended strongly on the steric environment. For example, exclusive and nearly complete deuteration at the terminal, *trans* position of the *tert*-butylethylene was achieved after 1 minute at room temperature,[12] but facile exchange was observed at similar rates with the more accessible *trans* and *cis*-terminal hydrogen atoms of vinyltrimethylsilane. Likewise, the reaction of 1-pentene led to the exchange of more than 90% of the *trans* terminal hydrogen atom after 5 minutes at room temperature, whereas less than 10% of the exchange occurred at each of its *cis* terminal and internal positions. A similar level of deuteration of 1-pentene was achieved with only 0.5 mol% of **1**, although a longer reaction time was required. Incorporation of 96% deuterium into the internal vinylic position of 1-pentene required about 20 hours with 5 mol% of **1**. H/D exchange of olefins containing amine, ester, and nitrile groups occurred at rates that were similar or slightly slower than those for H/D exchange of 1-pentene.

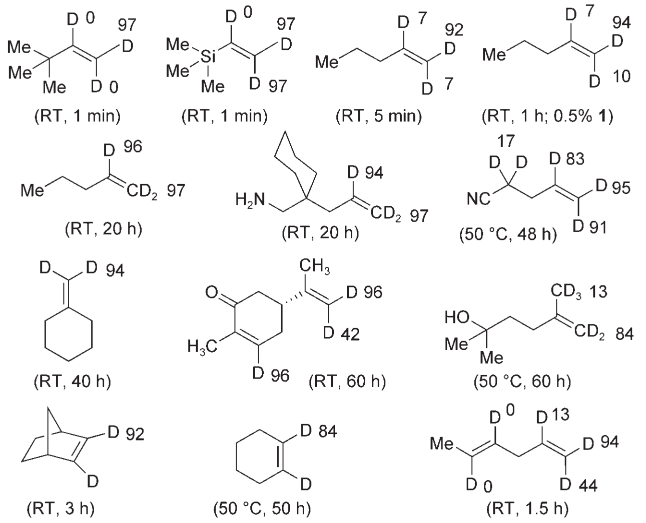


Figure 1. Percentage of deuterium incorporation into olefinic substrates catalyzed by 5 mol% **1** in C_6D_6.

H/D exchange of the olefinic hydrogen atoms of unstrained 1,1-disubstituted and *cis*-1,2-disubstituted olefins with C_6D_6 proceeded more slowly than with the vinylic hydrogen atoms of 1-pentene, but exchange did occur selectively. For example, 84% deuterium incorporation occurred exclusively at the vinyl position of cyclohexene after 50 hours at 50°C. H/D exchange of the olefinic hydrogen atoms of the strained norbornene was faster. H/D exchange of norbornene with [D_6]benzene led to 92% deuterium incorporation into the olefinic positions within 3 hours at room temperature.[16] H/D exchange with *trans*-1,2-disubstituted olefins did not occur. Thus, selective labeling of *trans*-hexa-1,4-diene was observed at the terminal double bond.

In addition to the selectivity for exchange at different olefinic C–H bonds, the method was compatible with many functional groups. As shown in Table 1 and Figure 1, these functional groups include nitriles, primary amines, unprotected alcohols, esters, and ketones. When acidic hydrogen atoms α to the functional group were present, such as those in nitrile and ester groups, partial H/D exchange with these hydrogen atoms was observed. Unactivated, aliphatic C–H bonds did not react.

Complex **1** also catalyzed H/D exchange between C_6D_6 and substituted aromatic and heteroaromatic compounds (Figure 2). The regioselectivity of H/D exchange was controlled by steric effects. For example, nearly complete H/D exchange was observed after 1 h at room temperature at the mutually *meta* position of 1,3-dibromobenzene, but negligible H/D exchange was observed at the position *ortho* to both bromines. Many heteroaromatic substrates, including substituted furans, thiophenes, pyrroles, and imidazoles also underwent deuteration. Even pyridine, which has been reported to deactivate several other iridium catalysts toward H/D exchange,[6,9] underwent H/D exchange catalyzed by **1**.

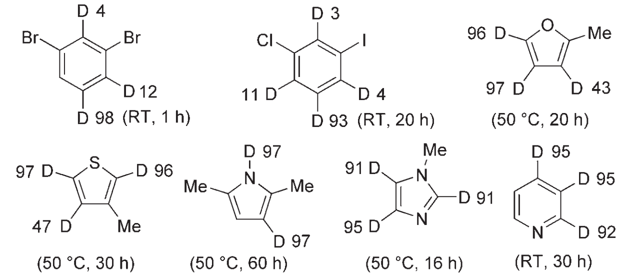


Figure 2. Percentage of deuterium incorporation into aromatic and heteroaromatic substrates catalyzed by 5 mol% **1** in C_6D_6.

The functional group tolerance and selectivity shown by the results in Figure 1 suggested that selective H/D exchange could be conducted at the vinylic positions of complex molecules. Results on H/D exchange between [D_6]benzene

© 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

and two natural products and one synthetic steroid are shown in Figure 3. Brief exposure of tiamulin to catalyst **1** in C_6H_6 led to selective labeling of one of the terminal olefinic hydrogen atoms. Exchange of the *trans* hydrogen atom was more than an order of magnitude faster than exchange of the *cis* hydrogen atom. Similar rapid H/D exchange of the olefin of forskolin occurred almost exclusively at the *trans* position. Likewise, H/D exchange of the three hydrogen atoms of the terminal olefin of altrenogest occurred over 20 hours. In each case, no detectable H/D exchange was observed by ^2H, ^1H or ^{13}C NMR spectroscopy at the internal olefins, and no isomerization of the terminal olefin to internal isomers was observed by ^1H or ^{13}C NMR spectroscopy.

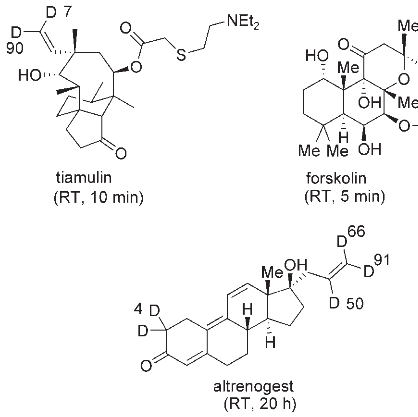
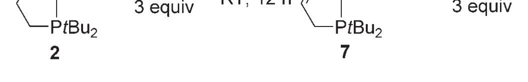


Figure 3. H/D Exchange of vinylic hydrogen atoms in complex molecules (percentage of deuterium incorporation).

To shed light on the mechanism of the H/D exchange process, we monitored the catalytic reaction by using 5 mol% of amide complex **1** by ^{31}P NMR spectroscopy. The resting state of the catalyst in the H/D exchange of [D$_6$]benzene with 1-pentene was approximately a 1:2 mixture of amide **1** and [(dtbpp)Ir(1-pentene)] (**6**). However, in the reaction of [D$_6$]benzene with *tert*-butylethylene, the resting state was approximately a 4:1 mixture of **1** and [{(tBu)$_2$PCH$_2$CH$_2$CH=CHCH$_2$P(tBu$_2$)}IrPh] (**7**). Iridium complex **7**, containing an olefin in the backbone bound to the metal, was prepared independently by the reaction of [(dtbpp)IrH$_4$] with norbornene in benzene [Eq. (2)], and its structure was determined by X-ray crystallography.[17] The structure of **7** is shown in Figure 4. The olefin on the dehydrogenated ligand[18] is bound to the iridium in an η^2 manner, and the coordination geometry around the metal is best described as square planar.

 (2)

Backbone olefin complex **7** underwent reversible H/D exchange between [D$_6$]benzene and the olefinic position that was originally the central carbon atom of the backbone in **1**.

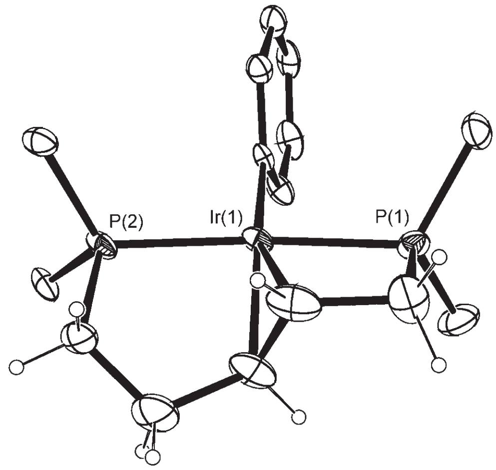
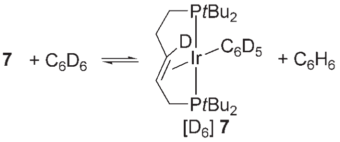


Figure 4. ORTEP diagram of **7** (thermal ellipsoids are set at 20% probability, and methyl groups have been omitted for clarity).

The equilibrium shown in Equation (3) was established within 5 minutes at room temperature. However, the H/D exchange of [D$_6$]benzene with *tert*-butylethylene, catalyzed by **7**, was slower than the reaction catalyzed by **1** (Figure 5). This result implies that olefin complex **7** is not the complex that catalyzes the majority of the H/D exchange of *tert*-butylethylene.

 (3)

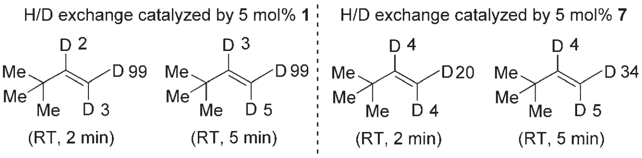
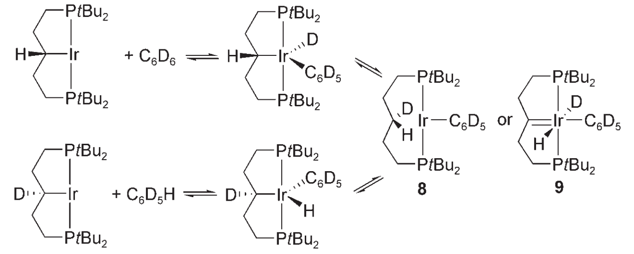


Figure 5. Comparison of catalysts **1** and **7** in H/D exchange of *tert*-butylethylene in C_6D_6.

Instead, we conclude that the H/D exchange occurs by a mechanism in which the methine position of the backbone acts as a shuttle. This proposal is supported by the observation of deuterium incorporation into that position in amide **1**. Dissolution of **1** in [D$_6$]benzene led to the growth of a ^2H NMR signal at 2.5 ppm corresponding to the backbone methine hydrogen atom in **1**. The same deuterium signal was also detected during H/D exchanges of [D$_6$]benzene with 1-pentene and *tert*-butylethylene catalyzed by 5 mol% of amide complex **1**. This intimate participation of the central hydrogen atom on the aliphatic backbone of the pincer ligand explains why iridium complex **4**, containing an aromatic ligand, does not catalyze these H/D exchanges under similarly mild conditions.[19]

Two potential mechanisms in which the methine hydrogen atom acts as a shuttle are outlined in Scheme 1. In the first



Scheme 1. Proposed pathways for the iridium-catalyzed H/D exchange in C_6D_6.

mechanism, the iridium(I) fragment, [(dtpbb)Ir^I], generated by reductive elimination of NH_3 and dissociation of the olefin from resting states **1** and **6**, could undergo oxidative addition of the aryl hydrogen atom and subsequent reversible C–H reductive elimination involving the methine carbon center on the ligand to form aryl iridium(I) complex **8**.[20] Alternatively, the complex resulting from oxidative addition of the arene could undergo reversible α-hydrogen elimination from the ligand backbone to generate iridium(III) carbene **9**.[21] We favor the reductive elimination pathway in Scheme 1 because of the facility of reductive elimination of alkanes from alkyl hydride complexes relative to α-hydrogen elimination from low-valent metal complexes. A parallel process with the vinylic C–H bonds would lead to incorporation of deuterium into the olefinic substrates.

In summary, selective deuteration of alkenes occurs in the presence of iridium catalysts containing an aliphatic pincer ligand. These reactions occur with reagents bearing a variety of auxiliary functionality without isomerization of the olefin, and these properties enable selective labeling of olefins in complex molecules. Additional studies on the mechanism of this process and reactions catalyzed by rhodium analogue **3** will be subjects of future studies.

Experimental Section

In an argon-filled glove box, a screw-capped NMR tube was charged with iridium catalyst **1** (5.6 mg, 0.010 mmol), C_6D_6 (0.50 mL), and 1-pentene (14 mg, 0.20 mmol). The tube was tightly capped and then vigorously shaken to give an orange solution. After 5 min at room temperature, the reaction mixture was exposed to air and passed through a short plug of silica gel with C_6D_6 washings to remove iridium complexes. The filtrate was judged to be pure by ^1H and ^{13}C NMR spectroscopy. The percentage of H/D exchange was based on a decrease in the integral of the ^1H NMR signals, as compared to the integral of the corresponding signals in the starting material. The ^1H NMR signals of interest were integrated relative to the resonance for allylic hydrogen atoms that do not undergo H/D exchange. The position of deuterium incorporation was also confirmed by ^2H NMR spectroscopy. The same reaction was conducted with 1 mmol 1-pentene in 2.5 mL of C_6D_6 with 5 mol% catalyst **1**, and a similar degree of H/D exchange was observed.

Received: April 28, 2008
Published online: June 24, 2008

Keywords: alkenes · C–H activation · deuterium · iridium · isomerization

[1] J. L. Garnett, R. J. Hodges, *J. Am. Chem. Soc.* **1967**, *89*, 4546.

[2] a) *Synthesis and Applications of Isotopically Labeled Compounds, Vol. 7* (Eds.: U. Pleiss, R. Voges), Wiley, New York, **2001**; b) T. H. Lowry, K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, Harper & Row, New York, **1987**; c) A. F. Thomas, *Deuterium Labeling in Organic Chemistry*, Appleton-Century-Crofts, New York, **1971**.

[3] a) T. Junk, W. J. Catallo, *Chem. Soc. Rev.* **1997**, *26*, 401; b) M. Saljoughian, P. G. Williams, *Curr. Pharm. Des.* **2000**, *6*, 1029; c) M. Saljoughian, *Synthesis* **2002**, 1781; d) J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem.* **2007**, *119*, 7890; *Angew. Chem. Int. Ed.* **2007**, *46*, 7744; e) J. R. Heys, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 770; f) W. J. S. Lockley, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 779.

[4] a) Q. X. Guo, B. J. Shen, H. Q. Guo, T. Takahashi, *Chin. J. Chem.* **2005**, *23*, 341; b) H. Sajiki, N. Ito, H. Esaki, T. Maesawa, T. Maegawa, K. Hirota, *Tetrahedron Lett.* **2005**, *46*, 6995, and references cited therein.

[5] a) J. L. Garnett, R. S. Kenyon, *J. Chem. Soc. D* **1971**, 1227; b) A. E. Shilov, A. A. Shteinman, *Coord. Chem. Rev.* **1977**, *24*, 97.

[6] C. M. Yung, M. B. Skaddan, R. G. Bergman, *J. Am. Chem. Soc.* **2004**, *126*, 13033.

[7] a) M. B. Skaddan, C. M. Yung, R. G. Bergman, *Org. Lett.* **2004**, *6*, 11; b) S. R. Klei, T. D. Tilley, R. G. Bergman, *Organometallics* **2002**, *21*, 4905; c) S. R. Klei, J. T. Golden, T. D. Tilley, R. G. Bergman, *J. Am. Chem. Soc.* **2002**, *124*, 2092; d) J. T. Golden, R. A. Andersen, R. G. Bergman, *J. Am. Chem. Soc.* **2001**, *123*, 5837.

[8] R. Corberán, M. Sanaú, E. Peris, *J. Am. Chem. Soc.* **2006**, *128*, 3974.

[9] L. L. Santos, K. Mereiter, M. Paneque, C. Slugovc, E. Carmona, *New J. Chem.* **2003**, *27*, 107.

[10] a) M. Yamamoto, K. Oshima, S. Matsubara, *Heterocycles* **2006**, *67*, 353; b) T. Kurita, K. Hattori, S. Seki, T. Mizumoto, F. Aoki, Y. Yamada, K. Ikawa, T. Maegawa, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2008**, *14*, 664, and references cited therein.

[11] a) B. Rybtchinski, R. Cohen, Y. Ben-David, J. M. L. Martin, D. Milstein, *J. Am. Chem. Soc.* **2003**, *125*, 11041; b) C. P. Lenges, P. S. White, M. Brookhart, *J. Am. Chem. Soc.* **1999**, *121*, 4385; c) J. Krüger, B. Manmontri, G. Fels, *Eur. J. Org. Chem.* **2005**, 1402.

[12] a) J. W. Faller, C. J. Smart, *Organometallics* **1989**, *8*, 602; b) J. W. Faller, H. Felkin, *Organometallics* **1985**, *4*, 1488.

[13] G. Kohl, R. Rudolph, H. Pritzkow, M. Enders, *Organometallics* **2005**, *24*, 4774.

[14] We have reported the synthesis of **1** by the oxidative addition of ammonia to the corresponding [(dtbpp)Ir(olefin)] complexes: J. Zhao, A. S. Goldman, J. F. Hartwig, *Science* **2005**, *307*, 1080.

[15] a) M. Gupta, C. Hagen, R. J. Flesher, W. C. Kaska, C. M. Jensen, *Chem. Commun.* **1996**, 2083; b) M. Gupta, C. Hagen, W. C. Kaska, R. E. Cramer, C. M. Jensen, *J. Am. Chem. Soc.* **1997**, *119*, 840; c) F. C. Liu, E. B. Pak, B. Singh, C. M. Jensen, A. S. Goldman, *J. Am. Chem. Soc.* **1999**, *121*, 4086.

[16] C. Slugovc, B. Perner, *Inorg. Chim. Acta* **2004**, *357*, 3104.

[17] CCDC-686286 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] Complexes containing a dehydrogenated dtbpp ligand have been reported for rhodium and ruthenium: a) D. G. Gusev, A. J. Lough, *Organometallics* **2002**, *21*, 2601; b) C. Crocker, R. J. Errington, R. Markham, C. J. Moulton, K. J. Odell, B. L. Shaw, *J. Am. Chem. Soc.* **1980**, *102*, 4373.

[19] For H/D exchange of arenes by ruthenium and iridium catalysts containing pincer ligands, see a) A. Träff, G. N. Nilsson, K. J.

© 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Szabo, L. Eriksson, *J. Organomet. Chem.* **2007**, *692*, 5529; b) M. H. G. Prechtl, M. Hölscher, Y. Ben-David, N. Theyssen, R. Loschen, D. Milstein, W. Leitner, *Angew. Chem.* **2007**, *119*, 2319; *Angew. Chem. Int. Ed.* **2007**, *46*, 2269.

[20] a) M. A. McLoughlin, R. J. Flesher, W. C. Kaska, H. A. Mayer, *Organometallics* **1994**, *13*, 3816; b) A. Vigalok, Y. Ben-David, D. Milstein, *Organometallics* **1996**, *15*, 1839.

[21] α-Hydrogen elimination to form iridium–carbene complexes is known: a) H. D. Empsall, E. M. Hyde, R. Markham, W. S. McDonald, M. C. Norton, B. L. Shaw, B. Weeks, *J. Chem. Soc. Chem. Commun.* **1977**, 589; b) E. Carmona, M. Paneque, L. L. Santos, V. Salazar, *Coord. Chem. Rev.* **2005**, *249*, 1729; c) E. Clot, J. Chen, D. H. Lee, S. Y. Sung, L. N. Appelhans, J. W. Faller, R. H. Crabtree, O. Eisenstein, *J. Am. Chem. Soc.* **2004**, *126*, 8795.

© 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim