C(sp^2)-H Activation with Pyridine Dicarbene Iron Dialkyl Complexes: Hydrogen Isotope Exchange of Arenes Using Benzene-d_6 as a Deuterium Source.

Javier Corpas[a,b], Peter Viereck[a], Paul J. Chirik[a]*

[a]Department of Chemistry, Princeton University, Princeton, New Jersey, 08544, U.S.A.

[b]Department of Organic Chemistry, Universidad Autónoma de Madrid, c/ Fco. Tomás y Valiente 7, Cantoblanco 28049, Madrid (Spain).

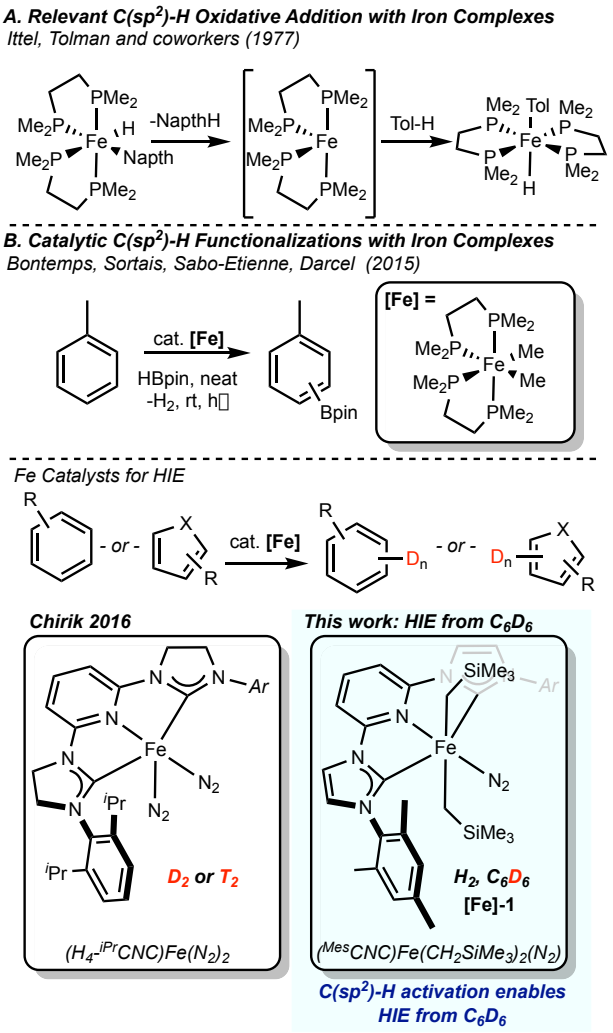
KEYWORDS: C(sp^2)-H functionalization, Hydrogen Isotope Exchange, C–H Activation, Iron catalysis, Regioselectivity.

ABSTRACT. Treatment of pyridine dicarbene iron dialkyl complexes with low (<< 1 atm) pressures of H_2 in benzene-d_6 solution promoted rapid hydrogen isotope exchange (HIE) of the C(sp^2)–H bonds in both electron-poor and -rich aromatic and heteroaromatic rings with benzene-d_6 as the deuterium source. The iron-catalyzed reaction proceeded with predictable regioselectivity, engaging sterically accessible C–H bonds including *ortho*-to-fluorine sites. The site-selectivity for the catalytic HIE reaction was studied to identify the kinetic preferences for C–H activation. Structure-activity relationship studies with a series of iron precatalysts established that introduction of substituents at the 3- and 5-positions on the pyridine of the pincer significantly accelerated HIE. Mechanistic studies identified N_2 as an inhibitor of C–H activation while H_2 serves to generate the active catalyst.

Introduction. Metal-catalyzed C–H functionalization has evolved into a transformative and widely applied method for the construction of new C–C and C–X bonds and often provides a more step-efficient and atom-economical route to complex products.[1] Because of the number of C–H bonds in most organic molecules, control of chemo- and regioselectivity is an ongoing challenge and new catalyst designs and mechanistic understanding are needed to overcome the requirements of directing group strategies.[2,3,4]

The renewed interest in the use of first-row transition metals offers the opportunity for C–H functionalization reactivity that is complementary or orthogonal to precious metals. One salient example is the high *ortho*-to-fluorine selectivity in the bis(phosphino) pyridine (PNP) cobalt-catalyzed C(sp^2)–H borylation of arenes where thermodynamic control of oxidative addition and the increased ionicity of the Co–C bond enables the unique selectivity.[5,6] Seeking to further explore the origins, generality and utility of this effect, the site-selectivity of other first transition metal catalysts that promote C–H functionalization is of interest. The high terrestrial abundance and relatively low toxicity of iron makes catalysts based on this first-row transition metal of particular interest.[7]

C–H activation with iron has a long-standing history with the first reports predating more widely known iridium examples.[6d] Ittel, Tolman and co-workers reported (dmpe)$_2$Fe(Napth)(H) (dmpe = 1,2-bis(dimethylphosphino(ethane), Napth = 2-Napthyl) as a precursor to Fe(0)-complexes that readily promote the oxidative addition of C(sp^2)-H bonds (Scheme 1A).[8] Remarkably, this family of complexes has been extended to include the oxidative addition of strong C(sp^3)-H bonds such as methane.[9] More recently, photolysis of these compounds has enabled the catalytic C(sp^2)-H borylation of arenes and heteroarenes (Scheme 1B).[10]



Scheme 1. Examples of Iron-mediated C–H activation processes.

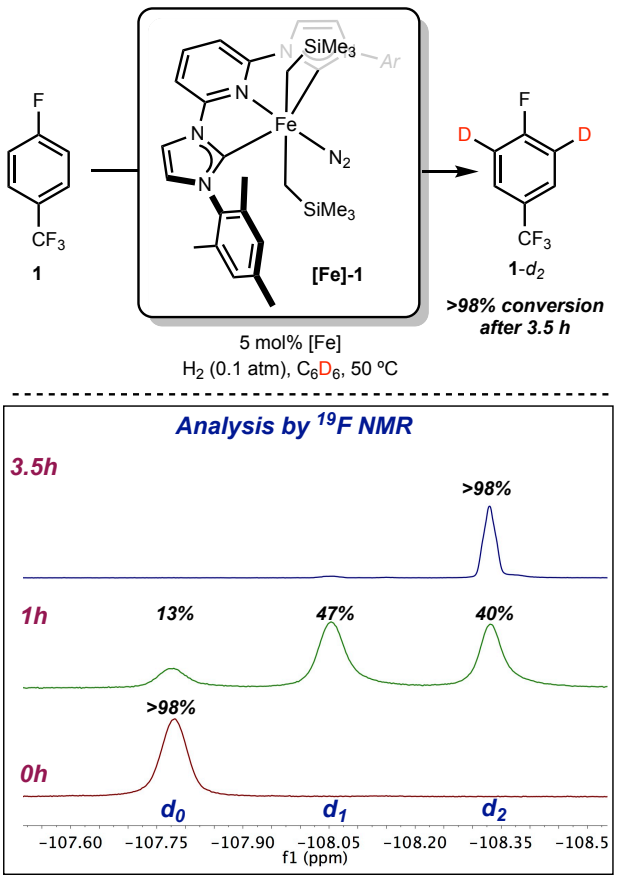
Hydrogen isotope exchange (HIE), the interchange of C–H bonds with other isotopes of hydrogen or its reverse, is a powerful probe for the determination of site selectivity in C–H functionalization reactions.[11] Catalytic HIE is also an enabling method for kinetic isotope effect studies,[12] drug discovery,[13] and ADME (absorption, distribution, metabolism, and excretion) analysis.[14] Among known catalysts for HIE, precious metals are conventional and application of directing groups is a common approach for enabling site selectivity.[15,16] Although D_2 is the most atom economical source of deuterium, D_2O and less frequently benzene-d_6 have been used as isotope sources.[17,18] Our group recently reported that (H_4-^{iPr}CNC)Fe(N_2)$_2$ ((H_4-^{iPr}CNC = 2,6-(2,6-^{i}Pr$_2$-C_6H_3-tetrahydroimidazol-2-ylidene)$_2C_5H_3N$)) promotes HIE in arenes and active pharmaceutical ingredients at low pressures (<4 atm) with site selectivity governed by steric accessibility, ignoring directing groups in reactivity that is orthogonal to iridium (Scheme 1B).[19] Spectroscopic and structural studies supported the formation of iron hydrides as catalytically relevant intermediates responsible for activation of the C–H bond.

Here we describe a systematic study of (^{Ar}CNC)Fe(^{Ar}CNC = bis(arylimidazol-2-ylidene)pyridine) complexes for HIE of C(sp^2)-H bonds of aromatic substrates using more readily prepared iron(II) dialkyl complexes as precatalysts (Scheme 1B). At low (<< 1 atm) pressures of H_2, facile C–H activation and isotope exchange was observed using benzene-d_6 as the deuterium source. Due to the availability of benzene-d_6 as a common NMR solvent, this method may prove more convenient than those employing D_2 gas. These studies enabled the elucidation of key catalyst design principles for iron pincer complexes of this type as well as site preferences for C–H site exchange.

RESULTS AND DISCUSSION

Discovery of Iron-Catalyzed HIE with Benzene-d_6 as the Deuterium Source. Our group previously reported that addition of H_2 to (3,5-^{Mes}CNC)Fe(CH_2SiMe_3)$_2$(N_2) (3,5-Me$_2$-^{Mes}CNC = 2,6-(2,4,6-Me_3-C_6H_2-imidazol-2-ylidene)$_2$-3,5-Me_2-pyridine) resulted in formation of (3,5-Me$_2$-^{Mes}CNC)Fe(H)$_2$(H_2), a compound that promotes HIE with deuterated aromatic solvents with concomitant formation of the deuterated isotopologues of the iron hydride.[20] In addition, reducing the pressure of D_2 gas in catalytic HIE reactions increased the amount of deuterium incorporation.[19] Inspired by these observations, we reasoned that even lower pressures of H_2 or D_2 gas may activate the iron catalyst for HIE with an alternative stoichiometric isotope source, ideally a common deuterated solvent.

Initial experiments were conducted with a 0.2 M solution of 1-fluoro-4-trifluoromethylbenzene (**1**) in benzene-d_6 in the presence of 5 mol% of (^{Mes}CNC)Fe(CH_2SiMe_3)$_2$(N_2) ([**Fe**]-**1**) and 0.1 atm of H_2 gas at 50 °C. Monitoring the reaction by ^{19}F NMR spectroscopy resulted in observation of two new signals after one hour identified as the d_1- and d_2-isotopologues of the arene, based on the isotopic perturbation of fluorine resonance (Scheme 2).[5f] After 3.5 hours of reaction time, only **1**-d_2 was observed where deuterium was incorporated at the 2- and 6-positions. These results demonstrate the ability of [**Fe**]-**1** to promote rapid C(sp^2)–H activation and catalytic HIE.

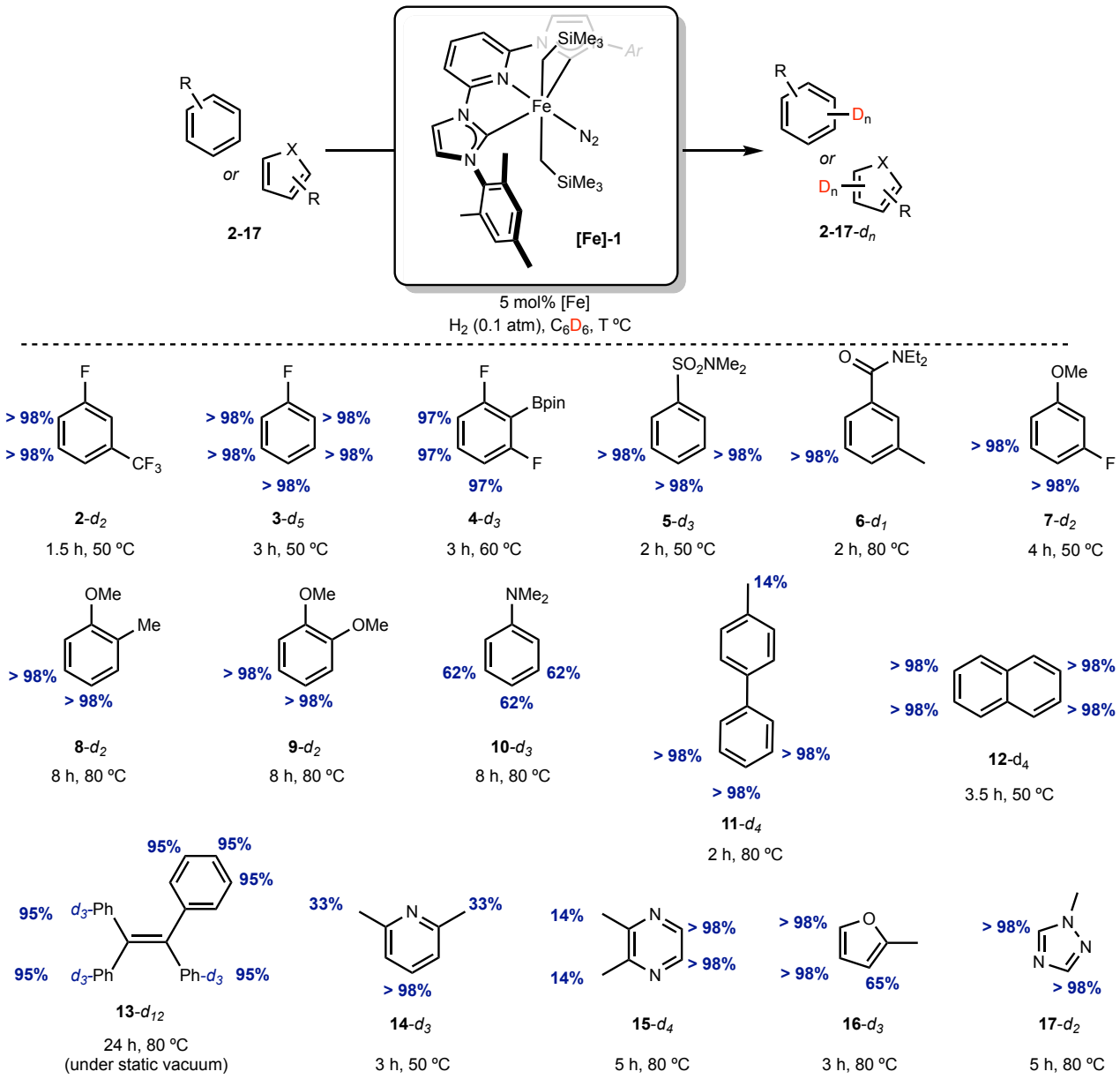


Scheme 2. Iron-catalyzed HIE of **1** with benzene-d_6 as the deuterium source. Analysis by single-scan ^{19}F NMR spectroscopy to ensure quantitative integration.

Scope of Iron-Catalyzed HIE. A series of substituted arenes and heteroarenes were evaluated for HIE using standard conditions of 5 mol% of [**Fe**]-**1**, 0.1 atm of H_2 and 0.2 M substrate in benzene-d_6 at 50 °C (Scheme 3). Complete deuteration (>98%) of 3-fluorobenzotrifluoride (**2**) in the 5- and 6-positions was observed after 1.5 hours (**2**-d_2). With fluorobenzene (**3**), all positions were deuterated to yield **3**-d_5 over the course of 3 hours. Similar reactivity was observed with other electron deficient substrates; for example the borylated *ortho*-difluoro arene **4** was isolated as **4**-d_3 with 97% deuterium incorporation at all C(sp^2)–H sites. As expected, despite the presence of a sulfonamide, a known directing group[3], only sterically accessible sites were deuterated with *N,N*-dimethylphenylsulfonamide (**5**), producing **5**-d_3 with isotopic exchange at the *meta* and *para* positions. Similarly, the amide-containing arene DEET (diethyltoluamide, **6**) was deuterated exclusively *meta*- to the amide group. With **7**, where a methoxy substituent is *meta* to fluorine, iron-catalyzed HIE occurred with complete regioselectivity and yielded **7**-d_2, although longer reaction times were required likely due to the relative electron richness of the substrate slowing C(sp^2)–H activation.

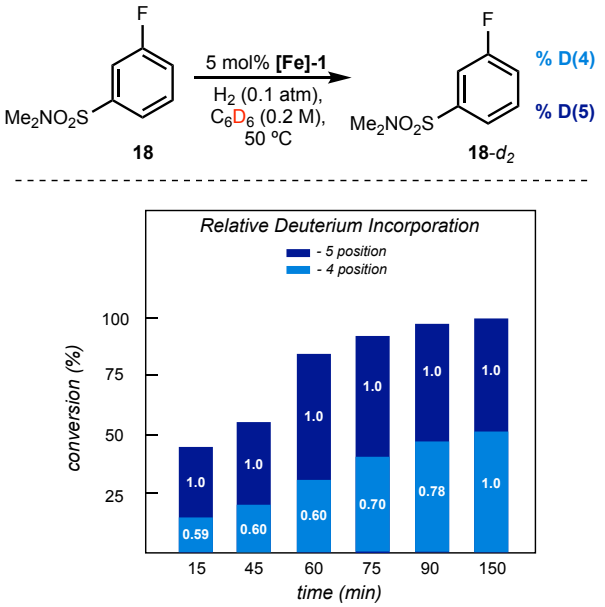
Following this trend, HIE with more electron-rich arenes such as **8** and **9** required increased temperature (80 °C) to reach full conversion to **8**-d_2 and **9**-d_2, respectively. *N,N*-dimethylaniline (**10**) proved more challenging of a substrate as lower isotopic incorporation was achieved at the *meta* and *para* positions (62% D) to **10**-d_3 even after heating the reaction mixture to 80 °C for 8 hours. Biaryls were completely deuterated at the *meta* and *para* positions of the phenyl ring of 4-phenyltoluene (**11**), while C(sp^3) –H activation at the benzylic position (14% D incorporation) was observed for the tolyl ring. Electron neutral polyaromatic substrates were also suitable substrates for iron-catalyzed HIE. When naphthalene (**12**) was subjected to the standard catalytic conditions, **12**-d_4 was obtained where only β-C–H bonds were activated while the α-positions were unaffected. As the standard conditions utilized low (<1 atm) H_2 pressures, substrates containing C=C were evaluated for HIE with the goal of promoting C–H isotopic exchange over alkene hydrogenation. Unfortunately di- and tri- substituted alkenes were not produced an intractable mixture of products arising from formation of isotopomers and isotopologues of various alkanes. However, tetraphenylethylene (**13**), was successfully deuterated at the the *meta* and *para* positions of each ring to generate **13**-d_{12} without reduction of the alkene by removing the H_2 after 1 minute of reaction time and continuing the HIE reaction under static vacuum.[21]

Finally, the reactivity of different heteroaromatic substrates was explored. *N*-heterocycles such as **14** and **15** underwent complete deuteration at the sterically accessible C(sp^2)–H bonds and also at the benzylic positions (33 and 14% D incorporation, respectively). 2-methylfuran (**16**) produced **16**-d_3 with complete deuteration at the 4- and 5-positions, while the 3-position was partially functionalized (65% D incorporation). Finally, the triazole-containing substrate **17** underwent complete deuteration at all C(sp^2)–H bonds without any detectable C(sp^3)–H functionalization, suggesting that electron-deficient C(sp^3)–H bonds are required for C(sp^3)–H activation. Substrates that were incompatible with the optimized catalytic conditions are presented in Figure S1.



Scheme 3. Scope of iron-catalyzed HIE using 0.1 mmol substrate, 5 mol% of [**Fe**]-**1**, 0.1 atm of H_2 and 0.5 mL of benzene-d_6 as the deuterium source. Reactions were conducted in J-Young NMR tubes. Deuterium incorporation was determined by a combination of ^{1}H, ^{13}C, and (where applicable) ^{19}F NMR spectroscopies and confirmed by HRMS.

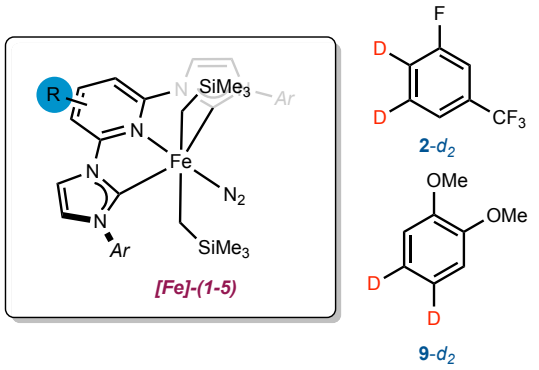
Selectivity of Iron Catalyzed C(sp²–H) Activation. Previous studies with [(PNP)Co] C(sp²)–H borylation catalysts established thermodynamic control of oxidative addition to *ortho*-to-fluorine sites governed by formation of the strongest M–C bond.[5f] To better understand the site selectivity of the C(sp²)–H activation step in iron-catalyzed HIE, the reaction between the fluorinated arene **18** and [**Fe**]-**1** was studied (Scheme 4). Monitoring the reaction by ^{2}H NMR spectroscopy established that the relative ratio of deuterium incorporation after 15 minutes was 1.0:0.59, favoring the 5-position. This trend was maintained over the course of one hour at 50 °C, after that the ratio approached 1:1 as the benzene-d_6 deuterium source was present in vast excess. These results demonstrate that C(sp²)–H activation is favored at the more sterically accessible site over *ortho*-to-fluorine sites and likely under kinetic control.[22]



Scheme 4. Relative deuteration incorporation at the 4- versus 5-position in **18** with [**Fe**]-**1** as a function of time measured by ^{2}H NMR spectroscopy. Conversions were determined by quantitative ^{13}C{^{1}H} NMR spectroscopy by comparison of the labeled and unlabeled 6-position.

Effect of Iron Precatalyst Structure on Catalytic HIE Performance. Variants of the [CNC] pincer were explored to determine the impact of substitution on catalytic HIE performance. Specifically, variations to the central pincer and the imidazolium were investigated (Scheme 5). With [**Fe**]-**1** as the precatalyst, complete deuterium incorporation was observed with the relatively electron-poor arene **2** after 1.5 h at 50 °C while the more electron-rich substrate **9** required 8 hours at 80 °C. Increasing the size of the 2,6-aryl substituents from methyl to isopropyl groups as in the case of (^{iPr}CNC)Fe(CH$_2$SiMe$_3$)$_2$(N$_2$) [**Fe**]-**2** slowed overall HIE performance. Longer reaction times of 6 h at 50 °C were required for **2**, while 48 h and 80 °C was needed for **9**. Similarly, (H$_4$-^{iPr}CNC)Fe(N$_2$)$_2$ [**Fe**]-**3**, the commercially available HIE precatalyst reported previously by our group[19] was markedly slower than [**Fe**]-**1**, requiring 5 h and 50 °C to yield quantitative formation of **2**-d_2 and 48 h and 80 °C for **9**-d_2.

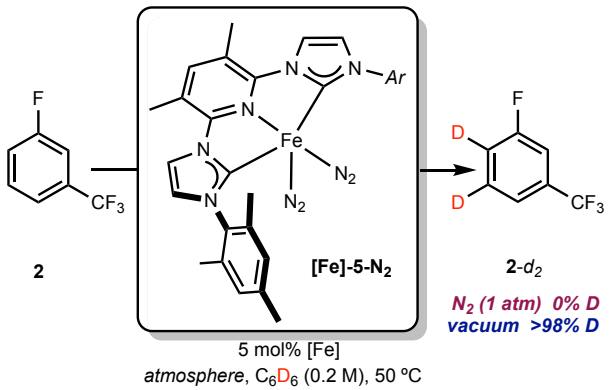
To increase the overall rate of HIE, strategies were explored to increase the rate of C(sp^2)–H activation. The iron precatalyst with a [NMe$_2$]-substituent in the 4-position of the pyridine, [**Fe**]-**4** was prepared to produce a more reducing iron center than [**Fe**]-**1**. However, no detectable improvement in catalytic HIE performance was obtained as similarly long reaction times were needed (e.g. 6 hours at 50 °C for **2** and 36 h and 80 °C for **9**). By contrast, the 3,5-dimethyl derivative [**Fe**]-**5**, exhibited a remarkable increase in the rate of HIE as the deuteration of **2** proceeded at ambient temperature in 1 hour. Similarly, the complete deuteration of **9** was accomplished in 6 hours at 45 °C. Comparing the performance of [**Fe**]-**5** to [**Fe**]-**4** demonstrates that 3- and 5-substitution has more profound impact on the rate of HIE than substitution in the 4-position of the pyridine. While the origins of this effect remain unknown, it is possible that either the LUMO lies primarily at the 3- and 5-positions, or the methyl groups distort the ligand to increase electron density at the metal center.



[Fe]	conditions for full conv. 2-d_2	9-d_2
[Fe]-1: R = H, Ar = Mes	1.5 h, 50 °C	8 h, 80 °C
[Fe]-2: R = H, Ar = Dipp	5 h, 50 °C	48 h, 80 °C
[Fe]-3: (H$_4$-^{iPr}CNC)Fe(N$_2$)$_2$	5 h, 50 °C	48 h, 80 °C
[Fe]-4: R = 4-NMe$_2$, Ar = Mes	6 h, 50 °C	36 h, 80 °C
[Fe]-5: R = 3,5-Me$_2$, Ar = Mes	1 h, 23 °C	6 h, 45 °C

Scheme 5. Evaluation of different substitution patterns in catalytic HIE performance of [(CNC)Fe]-complexes. Full conversion is defined as >98% consumption by ^{1}H or ^{19}F NMR spectroscopy.

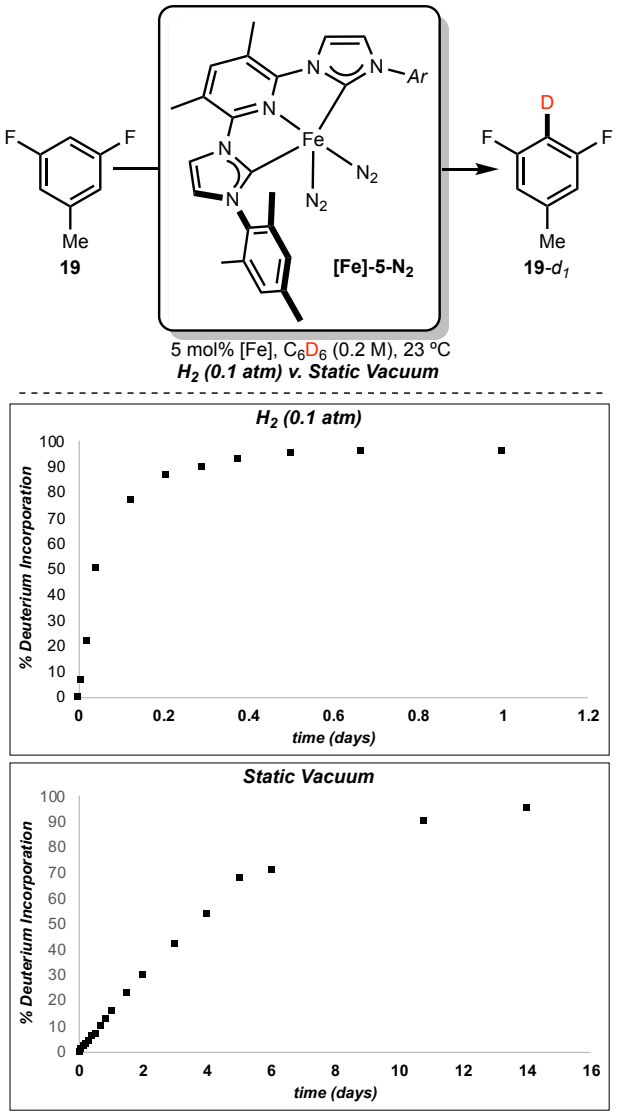
Effect of H$_2$ Pressure and Comparison of Fe(0) versus Fe(II) Precatalysts. The effect of dihydrogen on iron-catalyzed HIE was also studied. Of particular interest was whether H$_2$ was required to generate the active HIE catalyst or if oxidative addition of the C(sp^2)–H bonds of the substrate and benzene-d_6 occurred from Fe(0). To evaluate this possibility, the iron bis(dinitrogen) complex, (3,5-Me$_2$-^{Mes}CNC)Fe(N$_2$)$_2$ [**Fe**]-**5**-**N$_2$** was explored as a precatalyst for HIE with **2** in benzene-d_6 solution (Scheme 6). Under N$_2$ atmosphere, no deuterium incorporation was observed in **2** over 24 hours at 50 °C. Freeze-pump thawing the solution and continuing the reaction under static vacuum at 50 °C, gave complete conversion to **2**-d_2 was observed after 24 h. The observed inhibition of HIE in the presence of N$_2$ supports a slow substrate precoordination step prior to C(sp^2)–H activation. As the pressure of N$_2$ decreases, a large increase in HIE performance was observed.



Scheme 6. Impact of iron oxidation state of the precatalyst on HIE performance and role of N$_2$.

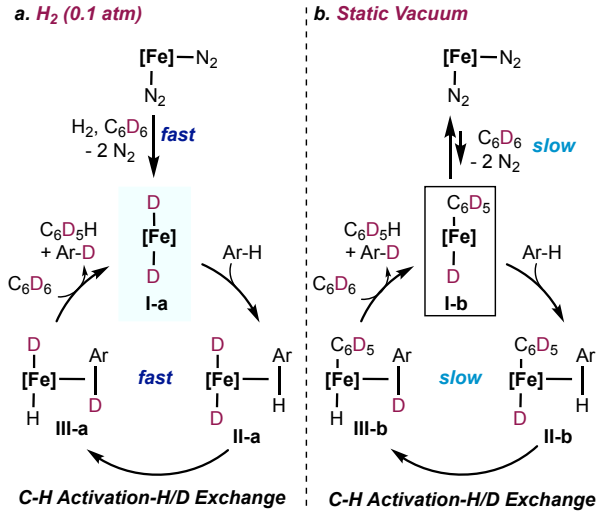
The higher reactivity of the iron(II)-based precatalysts in the presence of H$_2$ in comparison with Fe(0) complexes under vacuum supports more facile C–H activation reactivity from the iron(II) dihydride intermediate. It is also possible that the iron(0) precatalyst slowly converts to an Fe(II)-dihydride in the reaction mixture

to generate the intermediate responsible for C(sp²)–H activation. To test this hypothesis, parallel experiments monitoring the HIE activity of [**Fe**]-**5**-N_2 with **19** by ^{19}F NMR spectroscopy under 0.1 atm H_2 and vacuum were conducted (Scheme 7). **19** was selected as a representative substrate for these studies as there is only one sterically accessible C(sp²)–H site, and deuterium incorporation could be readily assayed by ^{19}F NMR spectroscopy. After 24 hours, the sample with H_2 present produced complete conversion while the reaction under vacuum proceeded to <10% conversion. In both cases, the reaction time course provided no evidence for an induction period. These findings demonstrate that [**Fe**]-**5**-N_2 likely does not form an iron hydride under vacuum and instead a distinct, less active C–H activating species and ultimately HIE catalyst was present.



Scheme 7. Effect of H_2 on iron-catalyzed HIE.

Finally, to address the observed activity differences under H_2 versus static vacuum, two catalytic cycles are proposed in Scheme 8. Under H_2 (Scheme 8a), an iron(II) dihydride intermediate rapidly forms from addition of H_2 to [**Fe**]-**5**-N_2, which then rapidly tranforms into an iron(II) dideuteride (**I-a**) through exchange with benzene-d_6, as reported previously.[20] This iron dideuteride compound is responsible for C–H activation and coordination of an arene C–H bond forming **II-a.** C–H activation leads to the formation of **III-a** that is subsequently converted to **I-a** by arene exchange with benzene-d_6 and further HIE. Under static vacuum (Scheme 8b), a similar but slower pathway is also likely operative. The initial C–H oxidative addition to form an iron(II) aryl-deuteride **I-b** was slower as evidenced by the inhibition of HIE by N_2 and the observation of [**Fe**]-**5**-N_2 during the catalytic cycle (Figure S6). Intermediate **I-b** also likely acts as a C–H activating species, however due to the increase steric encumbrance about the iron center of **I-b**, coordination to form **II-b** and subsequent C-H activation to form **III-b** are likely slower than for **I-a**. In this scenario, the pathway where **II** transforms to **III** likely involves either a redox-neutral σ-complex-assisted metathesis type mechanism[15,23] or a Fe(0/II/IV) cycle.[15,24,25]



Scheme 8. Proposed mechanisms for iron-catalyzed HIE.

Conclusions. In summary, pyridine bis(N-heterocyclic) carbene pincer-ligated iron(II) dialkyl complexes are effective precatalysts for the HIE of C(sp²)–H bonds in substituted arenes and heteroarenes under low (<1 atm) pressures of H_2 using benzene-d_6 as the isotope source. The high activity of these complexes in benzene-d_6 enabled a predictable regioselective deuteration method at unencumbered positions of different arenes with unprecedented levels of isotopic incorporation using a widely available NMR solvent as the deuterium source. The selectivity of the C(sp²)–H activation step support a kinetically controlled C(sp²)–H activation favoring *meta*-to-fluorine sites. Exploring substitution of the pincer ligand established that introduction of methyl groups in the 3- and 5-position of the central pyridine ring dramatically enhanced overall HIE activity. Dinitrogen was identified as an inhibitor of catalysis likely due to strong coordination to iron(0), d^8 intermediates while small quantities of dihydrogen generated a potent C–H activating species. These observations provide a blueprint for rational design of next generation of iron catalysts for HIE and other transformations involving the activation of C–H bonds by iron catalysts.

AUTHOR INFORMATION

Corresponding Author

* pchirik@princeton.edu

ORCID

Javier Corpas: 0000-0002-8598-578X

Peter Viereck: 0000-0003-4691-8434
Paul J. Chirik: 0000-0001-8473-2898

ASSOCIATED CONTENT

Supporting Information

Complete experimental details including pre-catalyst optimization studies, and characterization data for deuterated products. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

J. C. thanks *Ministerio de Ciencia, Innovación y Universidades* for FPU (*FPU16/03642*) and Mobility (*EST18/00649*) fellowships. Financial support was provided by the U.S. National Science Foundation Grant Opportunities for Academic Liaison with Industry (GOALI) grant (CHE-1855719).

REFERENCES

(1) (a) Trost, B. M. On inventing Reactions for Atom Economy. *Acc. Chem. Res.* **2002**, *35*, 695-705. (b) Gutekunst, W. R.; Baran, P. S. C-H Functionalization Logic in Chemical Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976-1991. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C-H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960-9009. (d) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metald-Catalyzed C-H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900-2936. (e) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J. Recent Applications of C-H Functionalization in Complex Natural Product Synthesis. *Chem. Soc. Rev.* **2018**, *47*, 8925-8967.

(2) (a) Buchanan, J. M.; Strycker, J. M.; Bergman, R. G. A Structural, Kinetic and Thermodynamic Study of the Reversible Thermal Carbon-Hydrogen Bond Activation/Reductive Elimination of Alkanes at Iridium. *J. Am. Chem. Soc.* **1986**, *108*, 1537-1550. (b) Chen, M. S.; White, M. C. A Predictable Selective Aliphatic C-H Oxidation Reaction for Complex Molecule Synthesis. *Science* **2007**, *318*, 783-787. (c) Xue, X. S.; Ji, P.; Zhou, B.; Cheng, J. P. The Essential Role of Bond Energetics in C-H Activation/Functionalization. *Chem. Rev.* **2017**, *117*, 8622-8648. (d) Curto, J. M.; Kozlowski, M. C. Chemoselective Activation of sp^3 vs sp^2 C-H Bonds with Pd(II). *J. Am. Chem. Soc.* **2015**, *137*, 18-21. (e) Zhu, Y.; Huang, K.; Pan, J.; Qiu, Xu.; Luo, X.; Qin, Q.; Wei, J.; Wen. X.; Zhang, L.; Jiao, N. Silver-Catalyzed Remote Csp^3-H Functionalization of Aliphatic Alcohols. *Nat. Commun.* **2018**, *9*, 2625-2632. (f) Hong, G.; Nahide, P. D.; Neelam, U. K.; Amadeo, P.; Vijeta, A.; Curto, J. M.; Hendrick, C. E.; VanGelder, K. F.; Kozlowski, M. C. Palladium-Catalyzed Chemoselective Activation of sp^3 vs sp^2 C-H Bonds: Oxidative Coupling to Form Quaternary Centers. *ACS Catal.* **2019**, *9*, 3716-3724.

(3) (a) Zhang, X.; Kanzelberger, M.; Emge, T. J.; Goldman, A. S. Selective Addition to Iridium of Aryl C−H Bonds Ortho to Coordinating Groups. Not Chelation-Assisted. *J. Am. Chem. Soc.* **2004**, *126*, 13192–13193. (b) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A Comprehensive Overview of Directing Groups Applied in Metal-Catalysed C-H Functionalization Chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743. (c) Gandeepan, P.; Ackerman, L. Transient Directing Groups for Transformative C-H Activation by Synergistic Metal Catalysis. *Chem* **2018**, *4*, 199-222. (d) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C-H Bond Functionalization Chemistry for the Expedient Construction of C-C Bonds. *Chem. Rev.* **2020**, *120*, 1788-1887.

(4) Hartwig, J. F. Evolution of C-H Bond Functionalization from Methane to Methodology. *J. Am. Chem. Soc.* **2016**, *138*, 2-24.

(5) (a) Obligacion, J. V.; Semproni, S. P.; Chirik, P. J. Cobalt-Catalyzed C-H Borylation. *J. Am. Chem. Soc.* **2014**, 136, 4133. (b) Su, B. Cao, Z. C.; Shi, Z. J. Exploration of Earth Abundant Transition Metals (Fe, Co, and Ni) as Catalysts in Unreactive Chemical Bond Activations. *Acc. Chem. Res.* **2015**, *48*, 886-896. (c) Obligacion, J. V.; Semproni, S. P.; Pappas, I.; Chirik, P. J. Cobalt-Catalyzed C(sp^2)-H Borylation: Mechanistic Insights Inspire Catalyst Design. *J. Am. Chem. Soc.* **2016**, *138,* 10645-10653. (d) Obligacion, J. V.; Bezdek, M. J.; Chirik, P. J. *J. Am. Chem. Soc.* **2017**, *139*, 2825-2832. (e) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C-H Activation. *Chem. Rev.* **2019**, *119*, 2192-2452. (f) Pabst, T. P.; Obligacion, J. V.; Rochette, E.; Pappas, I. Chirik, P. J. *J. Am. Chem. Soc.* ***2019****, 141*, 15378-15389.

(6) (a) Gao, K.; Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C-H Functionalization. *Acc. Chem. Res.* **2014**, *47*, 1208-1219. (b) Miao, J.; Ge, H. Recent Advances in First-Row-Transition-Metal-Catalyzed Dehydrogenative Coupling of C(sp^3)-H Bonds. *Eur. J. Org. Chem.* **2015**, *2015*, 7859-7868. (c) Wozniak, L.; Cramer, N. Enantioselective C-H Bond Functionalizations by 3d Transition-Metal Catalysts. *Trends Chem.* **2019**, *1*, 471-484. (d) Arevalo, R.; Chirik, P. J. Enabling Two-Electron Pathways with Iron and Cobalt: From Ligand Design to Catalytic Applications. *J. Am. Chem. Soc.* **2019**, *141*, 9106-9123.

(7) (a) Fürstner, A. Iron Catalysis in Organic Synthesis: A Critical Assessment of What It Takes to Make this Base Metal a Multitasking Champion. *ACS Cent. Sci.* **2016**, *2*, 778-789. (b) Shang, R. S.; Ilies, L.; Nakamura, E. Iron-Catalyzed C-H Bond Activation. *Chem. Rev.* **2017**, *117*, 9086-9139.

(8) Tolman, C. A.; Ittel, S. D.; English, A. D.; Jesson, J. P. Chemistry of 2-Naphthyl Bis[bis(dimethylphosphino)ethane] Hydride Complexes of Iron, Ruthenium, and Osmium. 3. Cleavage of sp^2 Carbon-Hydrogen Bonds. *J. Am. Chem. Soc.* **1979**, *101*, 1742-1751.

(9) Baker, M. V.; Field, L. D. Reaction of Carbon-Hydrogen Bonds in Alkanes with Bis-(Diphosphine) Complexes of Iron. *J. Am. Chem. Soc.* **1987**, *109*, 2825–2826.

(10) Dombray, T.; Werncke, C. G.; Jiang, S.; Grellier, M.; Vendier, L.; Bontemps, S.; Sortais, J. B.; Sabo-Etienne, S.; Darcel, C. Iron-Catalyzed C-H Borylation of Arenes. *J. Am. Chem. Soc.* **2015**, *137*, 4062-4065.

(11) (a) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. The Renaissance of H/D Exchange. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744-7765. (b) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. C-H Functionalization for Hydrogen Isotope Exchange. *Angew. Chem., Int. Ed.* **2018**, *57*, 3022–3047.

(12) (a) O' Ferrall, R. A. M. A Pictorial Representation of Zero-Point Energy and Tunnelling Contributions to Primary Hydrogen Isotope Effects. *J. Phys. Org. Chem.* **2010**, *23*, 572-579. (b) Gómez-Gallego, M.; Sierra, M. A. Kinetic Isotope Effects in the Study of Organometallic Reaction Mechanisms. *Chem. Rev.* **2011**, *111*, 4857-4963.

(13) (a) Katsnelson, A. Heavy Drugs Draw Heavy Interest From Pharma Backers. *Nat. Med.* **2013**, *19*, 656. (b) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. Applications of Deuterium in Medicinal Chemistry. *J. Med. Chem.* **2019**, *62*, 5276-5297.

(14) (a) Mutlib, A. E. Application of Stable Isotope-Labeled Compounds in Metabolism and in Metabolism-Mediated Toxicity Studies.

Chem. Res. Toxicol. **2008**, *21*, 1672-1689. (b) Elmore, C. S. The Use of Isotopically Labeled Compounds in Drug Discovery. *Annu. Rep. Med. Chem.* **2009**, *44*, 515–534. (c) Russak, E. M.; Bednarczyk, E. M. Impact of Deuterium Substitution on the Pharmacokinetics of Pharmaceuticals. *Ann. Pharmacother*. **2019**, *53*, 211-216.

(15) Giuseppe, A. D.; Castarlenas, R.; Oro, L. A. Mechanistic Considerations on Catalytic H/D Exchange Mediated by Organometallic Transition Metal Complexes. *C. R. Chimie* **2015**, *18*, 713-741.

(16) (a) Barefield. E. K. Parshall, G. W.; Tebbe, F. N. Catalysis of Aromatic Hydrogen-Deuterium Exchange by Metal Hydrides. *J. Am. Chem. Soc.* **1970**, *92*, 5234-5235. (b) Yung, C. M.; Skaddan, M. B.; Bergman, R. G. Stoichiometric and Catalytic H/D Incorporation by Cationic Iridium Complexes: A Common Monohydrido-Iridium Intermediate. *J. Am. Chem. Soc.* **2004**, *126*, 13033-13043. (c) Nilsson, G. N.; Kerr, W. J. The development and Use of Novel Iridium Complexes as Catalysts for *Ortho*-Directed Hydrogen Isotope Exchange Reactions. *J. Label. Comp. Radiopharm.* **2010**, *53*, 662–667. (d) Lockley, W. J. S.; Heys, J. R. Metal-Catalysed Hydrogen Isotope Exchange Labelling: a Brief Overview. *J. Labelled Comp. Radiopharm.* **2010**, *53*, 635–644. For recent applications of first-row-transition metals in HIE, see: (e) Palmer, W. N.; Chirik, P. J. Cobalt-Catalyzed Stereoretentive Hydrogen Isotope Exchange of $C(sp^3)$-H Bonds. *ACS Catal.* **2017**, *7*, 5674-5678. (f) Yang, H.; Zarate, C.; Palmer, W. N.; Rivera, N.; Hesk, D.; Chirik, P. J. Site-Selective Nickel-Catalyzed Hydrogen Isotope Exchange in *N*-Heterocycles and Its Application to the Tritiation of Pharmaceuticals. *ACS Catal.* **2018**, *8*, 10210-10218. (g) Zarate, C.; Yang, H.; Bezdek, M. J.; Hesk, D.; Chirik, P. J. Ni(I)-X Complexes Bearing a Bulky α-Diimine Ligand: Synthesis, Structure, and Superior Catalytic Performance in the Hydrogen Isotope Exchange in Pharmaceuticals. *J. Am. Chem. Soc.* **2019**, *141*, 5034-5044. (h) Yang, H.; Hesk, D. Base Metal-Catalyzed Hydrogen Isotope Exchange. *J. Label Compd. Radiopharm.* **2020**, *63*, 296–307.

(17) (a) Klei, S. R.; Golden, J. T.; Tilley, T. D.; Bergman, R. G. Iridium-Catalyzed H/D Exchange into Organic Compounds in Water. *J. Am. Chem. Soc.* **2002**, *124*, 2092-2093. (b) Prechtl, M. H.; Hölscher, M.; Ben-David, Y.; Theyssen, N.; Loschen, R.; Milstein, D.; Leitner, W. H/D Exchange at Aromatic and Heteroaromatic Hydrocarbons Using D_2O as the Deuterium Source and Ruthenium Complexes as the Catalyst. *Angew. Chem., In. Ed.* **2007**, *46*, 2269-2272.

(18) (a) Golden, J. T.; Andersen, R. A.; Bergman, R. G. Exceptionally Low-Temperature Carbon-Hydrogen/Carbon-Deuterium Exchange Reactions of Organic and Organometallic Compounds Catalyzed by the $Cp^*(PMe_3)IrH(ClCH_2Cl)^+$ Cation. *J. Am. Chem. Soc.* **2001**, *123*, 5837-5838. (b) Feng, Y.; Lail, M.; Foley, N. A.; Gunnoe, T. B.; Barakat, K. A.; Cundari, T. R.; Petersen, J. L. Hydrogen-Deuterium Exchange Between $TpRu(PMe_3)(L)X$ (L = PMe_3 and X = OH, OPh, Me, Ph, or NHPh; L = NCMe and X = Ph) and Deuterated Arene Solvents: Evidence for Metal_Mediated Processes. *J. Am. Chem. Soc.* **2006**, *128*, 7982-7994. (c) Zhou, J.; Hartwig, J. F. Iridium-Catalyzed H/D Exchange at Vinyl Groups without Olefin Isomerization. *Angew. Chem., Int. Ed.* **2008**, *47*, 5783-5787. (d) Smith, J. D.; Durrant, G.; Ess, D. H.; Gelfand, B. S.; Piers, W. E. H/D Exchange under Mild Conditions in Arenes and Unactivated Alkanes with C6D6 and D2O Using Rigid, Electron-Rich Iridium PCP Pincer Complexes. *Chem. Sci.* **2020**.

(19) Yu, R. P.; Hesk, D.; Rivera, N.; Pelczer, I.; Chirik, P. J. Iron-catalysed Tritiation of Pharmaceuticals. *Nature* **2016**, *529*, 195-199.

(20) (a) Yu, R. P.; Darmon, J. M.; Semproni, S. P.; Turner, Z. R.; Chirik, P. J. Synthesis of Iron Hydride Complexes Relevant to Hydrogen Isotope Exchange in Pharmaceuticals. *Organometallics* **2017**, *36*, 4341-4343. (b) Rummelt, S. M.; Darmon, J. M.; Yu, R. P.; Viereck, P.; Pabst, T. P.; Turner, Z. R.; Margulieux, G. W.; Gu, S.; Chirik, P. J. Synthesis, Structure, and Hydrogenolysis of Pyridine Dicarbene Iron Dialkyl Complexes. *Organometallics* **2019**, *38*, 3159-3168.

(21) Tetrasubstituted olefin **12** was subjected to the standard reaction conditions and isolated following activation of [**Fe**]-**1** with 0.1 atm H_2 for 1 min. After that the reaction was conducted under static vacuum conditions.

(22) *Ortho*-to-fluorine effect is observed in the vast majority of metal-catalyzed C-H activations of arenes due to a hyperconjugative effect between the $\sigma_{C\text{-}M}$ to $\sigma^*_{C\text{-}F}$, which stabilizes the metalated-arene species, see: (a) Selmeczy, A. D.; Partridge, M. G.; Jones, W. D.; Perutz, R. N. Selectivity in the activation of fluorinated aromatic hydrocarbons by rhodium complexes $[(C_5H_5)Rh(PMe_3)]$ and $[(C_5Me_5)Rh(PMe_3)]$. *Organometallics*, **1994**, *13*, 522−532. (b) Clot, E.; Mégret, C.; Eisenstein, O.; Perutz, R. N. Exceptional Sensitivity of Metal−Aryl Bond Energies to ortho-Fluorine Substituents: Influence of the Metal, the Coordination Sphere, and the Spectator Ligands on M−C/H−C Bond Energy Correlations. *J. Am. Chem. Soc.* **2009**, *131*, 7817−7827. (c) Clot, E.; Eisenstein, O.; Jasim, N.; MacGregor, S. A.; McGrady, J. E.; Perutz, R. N. C−F and C−H Bond Activation of Fluorobenzenes and Fluoropyridines at Transition Metal Centers: How Fluorine Tips the Scales. *Acc. Chem. Res.* **2011**, *44*, 333−348. (d) Pike, S. D.; Crimmin, M. R.; Chaplin, A. B. Organometallic Chemistry Using Partially Fluorinated Benzenes. *Chem. Commun.* **2017**, *53*, 3615-3633. See also references 8 and 5f.

(23) (a) Maseras, F.; Duran, M.; Lledós, A.; Bertrán, J. Intramolecular Atom Exchange between Molecular Hydrogen and Hydride Ligands in *cis*-$[Fe(PR_3)_4H(H_2)]^+$ Complexes. An ab Initio Theoretical Study. *J. Am. Chem. Soc.* **1992**, *114*, 2922-2928. (b) Ng, S. M.; Lam, W. H.; Mak, C. C.; Tsang, C. W.; Jia, G.; Lin, Z.; Lau, C. P. C-H Bond Activation by a Hydrotris(pyrazolyl)borato Ruthenium Hydride Complex. *Organometallics* **2003**, *22*, 641-651. (c) Perutz, R. N.; Sabo-Etienne, S. The α-CAM Mechanism: α Complexes as the Basis of α -Bond Metathesis at Late-Transition-Metal Centers. *Angew. Chem., Int. Ed.* **2007**, *46*, 2578-2592. (d) Armélin, M.; Schlangen, M.; Schwarz, H. On the Mechanisms of Degenerate Ligand Exchange in $[M(CH_3)]^+/CH_4$ Couples (M=Fe, Co, Ni, Ru, Pd, Os, Ir, Pt) as Explored by Mass Spectrometric and Computational Studies: Oxidative Addition/Reductive Elimination versus α-Complex-Assisted Metathesis. *Chem. Eur. J.* **2008**, *14*, 5229-5236.

(24) (a) Perthuisot, C.; Fan, M.; Jones, W. D. Catalytic Thermal C-H Activation with Manganese Complexes: Evidence for η^2-H_2 Coordination in a Neutral manganese Complex and Its Role in C-H Activation. *Organometallics* **1992**, *11*, 3622-3629. (b) Lee, S. H.; Gorelsky, S. I.; Nikonov, G. I. Catalytic H/D Exchange of Unactivated Aliphatic C-H Bonds. *Organometallics* **2013**, *32*, 6599-6604. (c) For a potential odd-electron pathway, see: Peterson, P. O.; Rummelt, S. M.; Wile, B. M.; Stieber, S. C. E.; Zhong, H.; Chirik, P. J. Direct Observation of Transmetalation from a Neutral Boronate Ester to a Pyridine(diimine) Iron Alkoxide. *Organometallics* **2020**, *39*, 201-205.

(25) [(CNC)Fe] complexes in the following oxidation states have been isolated including: Fe(0), Fe(II), and Fe(IV): (a) Danopoulos, A. A.; Wright, J. A.; Motherwell, W. B. Molecular N_2 Complexes of Iron Stabilised by N-Heterocyclic 'Pincer' Dicarbene Ligands. *Chem. Commun.* **2005**, 6, 784–786. (b) Danopoulos, A. A.; Pugh, D.; Smith, H.; Saßmannshausen, J. Structural and Reactivity Studies of "Pincer"

Pyridine Dicarbene Complexes of Fe^0: Experimental and Computational Comparison of the Phosphine and NHC Donors. *Chem. Eur. J.* **2009**, *15*, 5491–5502. (c) Pugh, D.; Wells, N. J.; Evans, D. J.; Danopoulos, A. A. Reactions of 'Pincer' Pyridine Dicarbene Complexes of Fe(0) with Silanes. *Dalton Trans.* **2009**, *35*, 7189–7195. (d) Darmon, J. M.; Yu, R. P.; Semproni, S. P.; Turner, Z. R.; Stieber, S. C. E.; DeBeer, S.; Chirik, P. J. Electronic Structure Determination of Pyridine N-Heterocyclic Carbene Iron Dinitrogen Complexes and Neutral Ligand Derivatives. *Organometallics* **2014**, *33*, 5423–5433.

For Table of Contents Use