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Proton or Metal? The H/D Exchange of Arenes in Acidic Solvents

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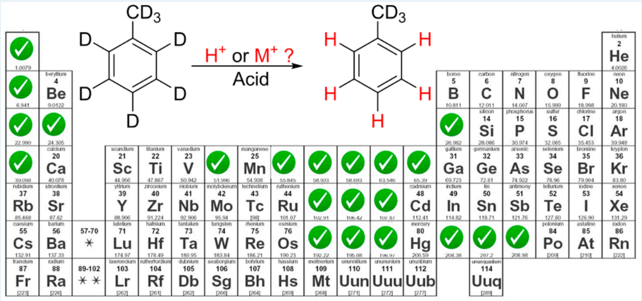
Supporting Information



ABSTRACT: The H/D exchange of arenes in acidic media by transition-metal and main-group-metal complexes and common inorganic salts was studied. The influence of Lewis acidity, anions, charge, and ligands was evaluated. The results indicate that the determination of H/D exchange activity in acidic media is not related to the formation of metal−carbon bonds (i.e., C−H activation). The combined experimental data (regioselectivity, activation energy, kinetics, isotope effects, solvent effects) and DFT calculations point toward a proton catalysis mechanism. Thus, highly Lewis acidic metal compounds, such as aluminum(III) triflate, were extraordinarily active for the H/D exchange reactions. Indeed, the degree of H/D exchange reactivity allows for a comparative measurement of Lewis acidities.

KEYWORDS: *acids, H/D exchange, benzene, toluene, Lewis acid, CH activation*

■ INTRODUCTION

The metal-mediated H/D exchange of hydrocarbons in the presence of a deuterium source is a ubiquitous concept in organometallic chemistry[1] and is indispensable for the pharmaceutical industry and medical applications.[2] Also, H/D exchange reactions are commonly used for the investigation of reaction mechanisms.[3] This method has been employed extensively in the field of sp^2 hydrocarbon C−H functionalization chemistry,[4] and the observation of H/D exchange processes between C−H bonds and deuterated acids (or vice versa) is often used to propose reaction pathways that involve organometallic intermediates. In this contribution, we present studies of H/D exchange between arenes and acids using an extensive series of metals. The combined experimental and computational results indicate that the reactivity studied herein is not likely a result of metal-mediated C−H activation involving organometallic intermediates. Instead, Brønsted acids, generated in situ, are likely the source of the H/D exchange. Furthermore, we propose that the observed H/D exchange reactivity provides a quantitative method for a comparison of Lewis acidity.

One approach to activate hydrocarbon C−H bonds relies on the generation of electron-deficient late-transition-metal compounds that react via an electrophilic pathway with sp^2- or even sp^3-hybridized carbon atoms.[5] Throughout this paper the term "C−H activation" therefore refers to a metal-mediated pathway involving the formation of metal−carbon bonds. Whereas the generation of Lewis acidic materials is crucial for heterogeneous approaches,[6] acidic media such as sulfuric acid,[7] trifluoroacetic acid (HOTFA),[8] and acetic acid (HOAc)[8i,9] also play a fundamental role in homogeneous reactions for hydrocarbon functionalization. These acidic solvents are generally weakly coordinating to the metal catalyst, and they can promote the dissociation of anionic ligands by stabilizing the formation of cationic intermediates. The dissociated anion can also serve as a base to deprotonate a coordinated C−H bond. This very well known effect[10] has also been studied in depth by means of density functional theory (DFT) calculations.[11] Additionally, formally cationic transition-metal complexes with weakly coordinating counterions such as tetrafluoroborate, hexafluorophosphate, triflate, and BAr^F (Ar^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) are frequently employed in order to increase the electrophilicity of the transition-metal catalyst.[12]

Highly electrophilic transition-metal species are frequently formed via in situ exchange of coordinating halides by reaction with silver salts of more weakly coordinating anions (Scheme 1). This approach has been used extensively for the investigation of H/D exchange activity of transition-metal complexes in acidic media.[12a−c,13] However, recently it has been proposed that proton catalysis can dominate in trifluoroacetic acid.[13b] Accordingly, the abstraction of halide ligands by silver cations leads to the formation of "naked" transition-metal compounds. These transition-metal compounds subsequently

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Scheme 1. In Situ Exchange of Strongly Coordinating Halide Ligands (X) for Weakly Coordinating Anions (BF_4^-) in Trifluoroacetic Acid (HOTFA)

$$L_mMX_n + n\,AgBF_4 \longrightarrow \left[L_mM^{n+}\,n\,BF_4^-\right] + n\,AgX$$

$$\left[L_mM^{n+}\,n\,BF_4^{n-}\right] \xrightarrow{\text{HOTFA}} \left[L_mM^{n+}\,n\,OTFA^-\right] + n\,HBF_4$$

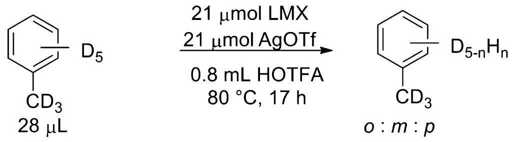
coordinate protic solvent molecules to generate a very weakly bound proton such as that in Scheme 1, formally HBF_4, which then initiates H/D exchange of aromatics by a protic aromatic substitution mechanism ($^{Ar}S_E$, Lewis acid catalyzed, electrophilic aromatic substitution). Similarly, proton catalysis versus transition-metal catalysis has been considered in the cases of oxidative diacetoxylation,[14] olefin hydroarylation,[15] and olefin hydroamination.[16] It is also known that trifluoroacetic acid itself is sufficiently acidic to mediate (very slowly) H/D exchange of aromatic compounds, an observation which was used to determine the degree of ortho/para−meta selectivity for electrophilic aromatic substitution mechanisms in 1958.[17] Stronger acids such as sulfuric acid and superacids are very well known to protonate aromatics.[18] Triflic acid is even capable of reversibly protonating more challenging, nonaromatic substrates such as isobutane.[19] On the basis of these observations, we reasoned that some arene H/D exchange reactions may result from in situ generation of protons rather than metal-mediated C−H bond breaking and formation of organometallic intermediates. Furthermore, we considered the possibility that such H/D exchange reactions in acidic media could provide a measure for the Lewis acidity of a transition-metal compound. Consequently, the H/D exchange reactions studied herein would be expected to be related to the electrophilicity of the metal catalyst rather than the ability of the metal to react directly with a C−H bond.

In order to resolve these issues, we carried out a study on the H/D exchange reactivity of arenes in acids using a series of main-group-metal and transition-metal catalysts with weakly coordinating anions. These studies include ligand and anion effects, kinetic data, the measurement of isotope effects, and DFT calculations. We show that the exchange reactions are proton mediated and that the reaction protocol allows for a straightforward determination of the Lewis acidities. For the compounds studied herein, it is the metal's Lewis acidity that influences the rate of H/D exchange, not the ability to mediate reactions with C−H bonds.

■ RESULTS AND DISCUSSION

In order to reduce the amount of relatively price intensive deuterated trifluoroacetic acid as solvent, we decided to investigate the H/D exchange of perdeuterated toluene in protio trifluoroacetic acid (Scheme 2). The choice of toluene as a substrate allows for the easy determination of the regioselectivity of the reaction, which was analyzed by ^1H NMR spectroscopy. A first screening with different silver salts aiming at determining the appropriate reaction conditions revealed that $AgBF_4$ and AgOTf (OTf = triflate) are catalytically potent catalysts at a reaction temperature of only 80 °C, whereas other silver salts (AgCl, AgOAc, AgOTFA (OTFA = trifluoroacetate), $AgNO_3$, $AgPF_6$) did not lead to activity higher than that of the background reaction within the margin of error (Figure 1).

Scheme 2. Reaction Protocol in Trifluoroacetic Acid



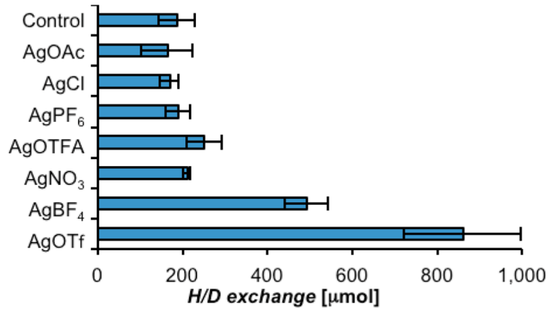


Figure 1. H/D exchange of toluene-d_8 in the presence of silver salts in HOTFA. Reaction conditions: 28 μL of toluene-d_8, 21 μmol of silver salt, 0.8 mL of HOTFA, 80 °C, 17 h. Control: no addition of silver salt.

All metal salts studied in this investigation (except $MgSO_4$ in HOTFA; vide infra) are entirely soluble in HOTFA and HOAc. We determined a very high degree of ortho/para selectivity in case of the catalyzed ($AgBF_4$, o:m:p = 0.7:0.0:0.3; AgOTf, o:m:p = 0.7:0.1:0.2) and noncatalyzed runs (o:p = 0.6:0.4; meta < threshold)). It is very revealing that the activity seems to be reflected by the acidity of the corresponding Brønsted acids. For example, $AgBF_4$ ("HBF_4") turned out to be less active than AgOTf ("HOTf").[20] The reaction with $AgBF_4$ was studied in more detail in order to draw conclusions about the mechanism. Here we determined the rate laws for the concentration of catalyst and substrate, the isotope effect, and the activation energy. The reaction follows pseudolinear (∼30% conversion) kinetics until 18 h of reaction time at 80 °C under our standard conditions (and shows a very strong preference for exchange of the ortho/para positions ((o/p):m > 9:1; Figure S1, Supporting Information). The rate laws regarding toluene-d_8 and $AgBF_4$ were determined by measuring the H/D exchange yield after less than 30% conversion and by approximating from these data the initial reaction rate.

The reaction shows a first-order rate law with respect to substrate (Figure 2) and silver salt concentration (Figure 3). Thus, the rate for H/D exchange is given by rate = [toluene][$AgBF_4$]. Thus, we conclude that the silver compound is indeed the catalytically relevant compound in the reaction mixture.

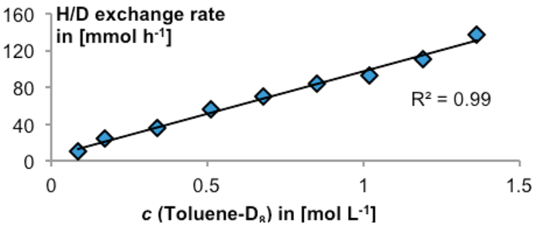


Figure 2. First-order reaction in toluene-d_8. Reaction conditions: 42 μmol of $AgBF_4$, 0.8 mL of HOTFA, 80 °C, 17 h. Data were acquired from less than 30% of maximum conversion.

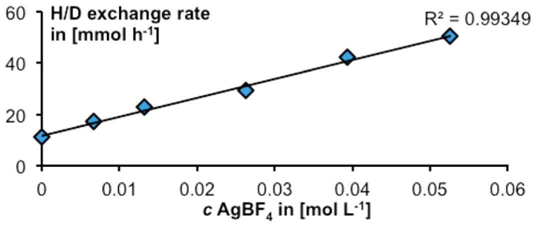


Figure 3. First-order reaction in $AgBF_4$. Reaction conditions: 28 μL of toluene-d_8, 0.8 mL of HOTFA, 80 °C, 4 h.

Eyring analyses were performed for H/D exchange of toluene-d_8 (ortho and para positions) in HOTFA in the presence and absence of $AgBF_4$ (Figure 4). The Eyring analysis revealed that the reaction has an overall reaction barrier $\Delta G^\ddagger$ of 26.0(1.5) kcal mol^{-1} at 293 K with a noncatalyzed $\Delta G^\ddagger$ of 26.4(2.7) kcal mol^{-1}. The relatively high, negative entropic contribution $\Delta S^\ddagger$ of −38(2) cal K^{-1} (noncatalyzed $\Delta S^\ddagger$ = −40(3) cal K^{-1}) is in line with an associative reaction mechanism. The comparison of $\Delta H^\ddagger$ in the presence ($\Delta H^\ddagger$ = 14.9(0.9) kcal mol^{-1}) and absence of $AgBF_4$ ($\Delta H^\ddagger$ = 14.8(1.1) kcal mol^{-1}) confirms that the activity is largely determined by entropy. Consequently, it appears very likely that the same (protio-catalytic) reaction pathway dominates for both cases. The inverse effect between protio and deutero toluene (Figures S2 and S3, Supporting Information), which was determined to be 0.8 for the ortho and para positions, is in line with a rate-determining transition state developing sp^3 character and is therefore in agreement with a protio-catalytic mechanism.[3c] Although some organometallic pathways have also been reported to lead to inverse isotope effects, arguably in most cases normal isotope effects have been observed.[3c]

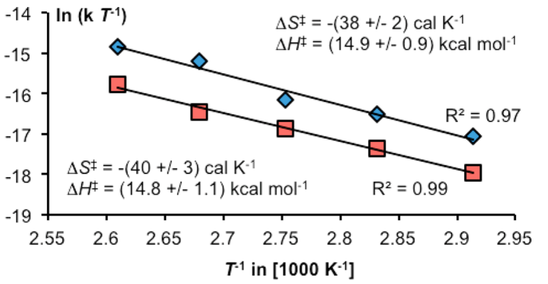


Figure 4. Eyring analysis for H/D exchange of toluene-d_8 in the presence (in blue, diamonds) and absence (in red, squares) of $AgBF_4$ in HOTFA.

Consequently we reasoned that both silver salts and other metal salts with weakly coordinating anions should be catalytically active. Our analysis of a series of commonly available salts revealed, as expected, that sodium salts of tetrafluoroborate (turnovers (TO) = 30), triflate (TO = 50), and perchlorate (TO = 50) anions also show efficient H/D exchange (Figure 5). It is unexpected that sodium cations could serve to mediate C−H activation of arenes.

In contrast, the hexafluorophosphate salts of potassium (TO = 14) and thallium(I) (TO = 18) showed only very moderate activity, which is similar to that of $AgPF_6$ (Figure 1; TO = 9). $NaBAr^F$, which decomposed rapidly under the reaction conditions, did not lead to considerable H/D exchange over the background reaction.

As the triflate salts led to the highest activity, we studied the influence of the cation for this anion (Figure 6). Bismuth(III), iron(III), and aluminum(III) triflate salts are the most active with nearly quantitative H/D exchange (TO = 66). These trivalent metals even led to quantitative exchange of the meta position, which was not observed in the case of the other triflate salts. $Al(OTf)_3$ also effected quantitative exchange of the ortho/para position after only 3 h at 40 °C.

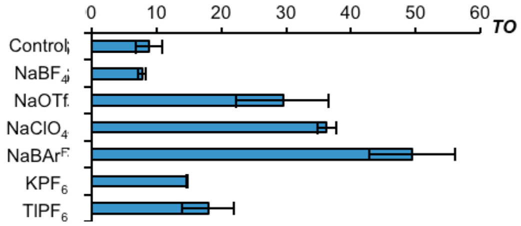


Figure 5. H/D exchange of toluene-d_8 with main-group-metal salts of weakly coordinating anions. Reaction conditions: 28 μL of toluene-d_8, 21 μmol of salt, 0.8 mL of HOTFA, 80 °C, 17 h.

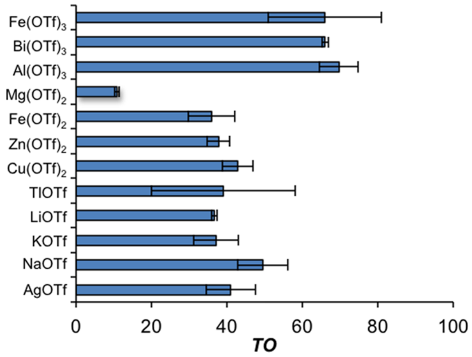


Figure 6. H/D exchange of toluene-d_8 in the presence of triflate salts in HOTFA. Reaction conditions: 28 μL of toluene-d_8, 21 μmol of salt, 0.8 mL of HOTFA, 80 °C, 17 h.

Upon lowering the catalyst concentration and increasing the content of toluene-d_8 (112 μL of toluene-d_8, 1 μmol of $Al(OTf)_3$) at only 60 °C, we obtained an impressive 2250 turnovers after 3 h, which corresponds to a turnover frequency (TOF) of 0.2 s^{-1}. For all of the other salts tested, with the exception of $Mg(OTf)_2$, which is insoluble in trifluoroacetic acid, TOs of approximately 45 were determined. Apparently, every metal salt with triflate counterions is catalytically potent, as long as it is soluble in HOTFA.

Finally, a series of transition-metal complexes and $PbCl_2$, which represent typical compounds for CH activation reactivity, was investigated (Figure 7). We resorted to the in situ exchange of the corresponding halide complexes with silver triflate according to Scheme 1. In all cases the formation and immediate precipitation of AgCl or AgBr was observed after the addition of the silver triflate. With the exception of $Ru(PPh_3)_3Cl_2$ (where a precipitate of assumed Ru(s) formed), all metals turned out to be highly active after the addition of AgOTf. The addition of AgOTf led to superior results in comparison to the same reactions using the tetrafluoroborate anion (Figure S4, Supporting Information). In addition, the oxidation state seems to be relevant. For example, Au(III) in the form of $AuCl_3$ is more active than the gold(I) precursor AuCl.

The iridium compound investigated showed considerably less H/D exchange reactivity than the corresponding rhodium compound. Similarly, the $Pt(NHC)_2Br_2$ complex showed higher reactivity than $Pd(NHC)_2Br_2$. Consequently, we

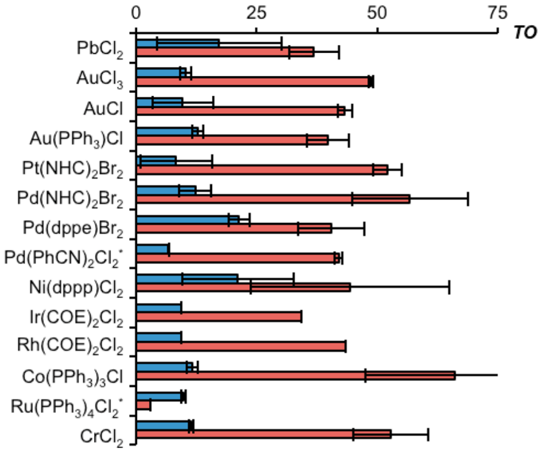


Figure 7. H/D exchange of toluene-d_8 in the presence of in situ generated transition-metal triflate salts (in red) and without addition of silver triflate (in blue). Reaction conditions: 28 μL of toluene-d_8, 21 μmol of transition-metal catalyst, 0.8 mL of HOTFA, 80 °C, 17 h. A stoichiometric amount of AgOTf was added to the halide content. (*) In the cases of Ru(PPh$_3$)$_4$Cl$_2$ and Pd(PhCN)$_2$Cl$_2$ formation of M(s) was observed. Abbreviations: COE, cyclooctene; dppe, 1,2-bis-(diphenylphosphino)ethane; dppp, 1,3-bis(diphenylphosphino)-propane; (NHC)$_2$, 1,1′-dimethyl-3,3′-methylenediimidazoline-2,2′-diylidene.

conclude that it is not sufficient for an efficient catalytic event that the anions be weakly coordinating; in addition, an appropriate cation must be chosen. The nature of the L-type ligands seems to have an influence on the catalyst activity as well, but the influence of an ancillary ligand seems to be less important than that of the transition metal or the selection of an anion.

H/D exchange reactions of benzene were also studied, since it is a more frequently investigated substrate in the literature.[12a−c,13a,b] Benzene provided fewer turnovers than toluene (AgOTf, 110 °C, 17 h; TO = 13). It is likely that the donating methyl group of toluene enhances reactivity with the Brønsted acid. In fact, the reactivity of one C−H bond in benzene should be very similar to that of the less reactive meta position of toluene. We determined that the degree of meta regioselectivity for toluene could be related to the catalytic activity for benzene H/D exchange using transition-metal compounds. Figure 8 shows the correlation between the regioselectivity measured for toluene (in cases where no paramagnetic line broadening was observed) and the turnovers obtained for benzene. Indeed, catalysts such as AuOTf or TlOTf, which in the case of toluene provide access to a very high degree of (ortho/para):meta selectivity, turned out to show only few turnovers with benzene. In contrast, highly active triflate salts in benzene such as Al(OTf)$_3$ had also exchanged the meta position in the case of toluene. In fact, we think that the regioselectivity for toluene is a much better measure for the overall reactivity than the determined turnovers for benzene, as it represents an intramolecular competition reaction between the more reactive ortho/para positions and the less reactive meta position. Consequently, errors in the experimental setup, such as weighing a defined amount of metal salt, cancel intrinsically.

The H/D exchange reactivity and regioselectivity in the case of toluene can most likely be attributed to proton catalysis. Therefore, the catalytic activity of the metal triflates is directly related to their Lewis acidity, since increased Lewis acidity enhances the proton exchange pathway. Consequently, we propose the measurement of the regioselectivity (or H/D exchange activity) for toluene for the very facile determination of relative Lewis acidities. In fact, it has also been proposed that H/D exchange reactivity in the gas phase can be used for the determination of the acidities of solid catalysts.[21] It is noteworthy in this context that the determination of strong acidities still remains challenging.[20,22]

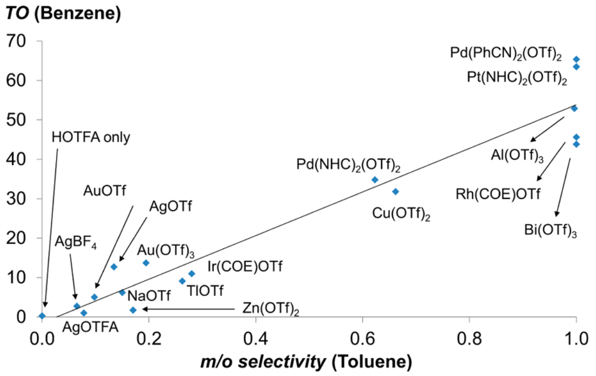


Figure 8. Correlation of meta:ortho regioselectivity for toluene with turnovers obtained for benzene. Reaction conditions: 28 μL of toluene-d_8 (24 μL of benzene-d_6), 21 μmol of metal catalyst, 0.8 mL of HOTFA, 80 °C (benzene, 100 °C), 17 h. In the case of Ir, Rh, Pd, Pt, and Au in situ generation of triflates was carried out by addition of AgOTf in a stoichiometric amount relative to the halide content. In the case of Fe, Co, Ni, and Cr the determination of regioselectivity was not possible due to broadening of the resonances.

The reactivity of a selection of salts was also examined in acetic acid (Figure 9). As acetic acid (pK_A = 4.8) is a much weaker acid than trifluoroacetic acid (pK_A = 0.2), other reaction pathways such as organometallic C−H activation might become more favorable.[11d,13b] As in trifluoroacetic acid, aluminum(III) triflate was the most active salt, showing quantitative H/D

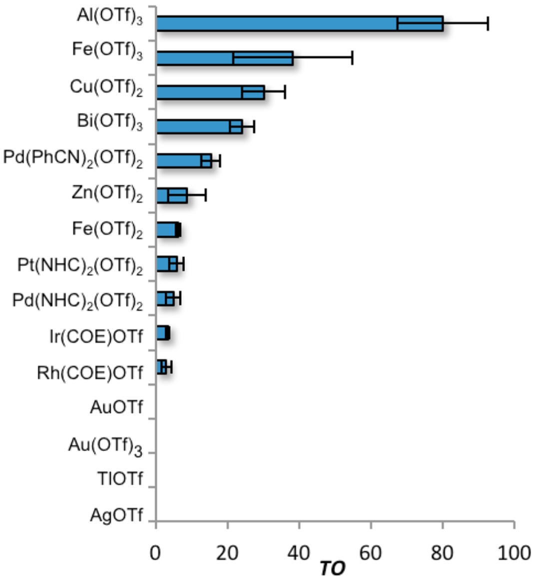
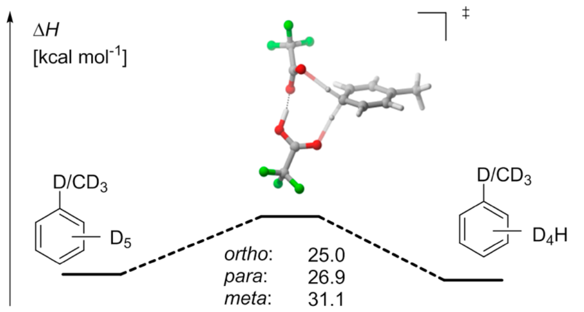


Figure 9. H/D exchange of toluene-d_8 in acetic acid. Reaction conditions: 24 μL of benzene-d_6, 21 μmol of metal catalyst, 0.8 mL of HOAc (5 vol % acetic anhydride), 150 °C, 17 h. In the case of Pd, Ir, Au, and Rh in situ generation of triflates was carried out by addition of AgOTf in a stoichiometric amount relative to the halide content.

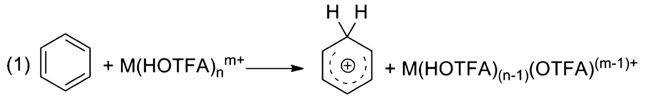
exchange (TO = 80) after 17 h at 150 °C. For the Cu, Fe, Bi, Pt, Pd, Zn, Ir, and Rh compounds, H/D exchange was observed. In contrast, the metals that provided only moderate or very low catalytic activity in HOTFA (alkali metals, Ag, Tl, Mg, Au) did not lead to efficient turnover in HOAc. In conclusion, the trends observed in strongly acidic HOTFA are also observed in HOAc, albeit with lower overall activity. We did not observe reactivity with $\mathrm{Al(OTf)_3}$ in a nonacidic solvent such as methanol.

In order to model the reactivity of the H/D exchange reaction, we employed DFT calculations using the Jaguar 7.6 software package (M06/LACV3P**++//B3LYP/LACVP**), including corrections for solvent effects by the PBF Poisson–Boltzmann implicit continuum solvation model.[23] First, we modeled the H/D exchange mediated by only trifluoroacetic acid in order to evaluate the validity of the computational method employed (Scheme 3). The computational predictions for the activation energy ($G^{\ddagger}$) are in excellent agreement with the experimental results, where we determined experimental $\Delta G^{\ddagger}$ values of 26.4 kcal $\mathrm{mol^{-1}}$ for the ortho and para positions (DFT: 26.6 and 27.6 kcal $\mathrm{mol^{-1}}$, respectively).

Scheme 3. DFT Calculated Reaction Barriers for H/D Exchange of Toluene-d_8 by HOTFA



For the case of metal catalysis, a substantial number of reaction pathways are possible. Therefore, a number of simplifications were made. According to our proposed mechanism, trifluoroacetic acid (i.e., neutral HOTFA and uncharged $^{-}$OTf) coordinates to the metals, which accordingly carry a formally positive charge equivalent to the number of trifluoroacetic acid ligands or uncoordinated triflate anions. Consistent with this, our calculations revealed that the ground states in HOTFA are compounds with protonated OTFA ligands. We therefore hypothesized that the catalytic activity of the catalysts should be reflected in the reaction enthalpy for the formation of the Wheland[24] complex (i.e., σ complex or arenium intermediate) referenced to the metal–trifluoroacetic acid complexes. The overall reaction barrier of the H/D exchange should be correlated to the formation of a positively charged Wheland complex, as shown in eq 1. Figure 10 shows the results from the calculations for a series of metals, with further details given in the Supporting Information.



$$(1)\quad \mathrm{C_6H_6} + \mathrm{M(HOTFA)}_n^{m+} \longrightarrow [\mathrm{C_6H_7}]^{+} + \mathrm{M(HOTFA)}_{(n-1)}(\mathrm{OTFA})^{(m-1)+}$$

Our computational results are in agreement with our experimental results. The $\mathrm{Fe^{III}}$, $\mathrm{Al^{III}}$, and $\mathrm{Bi^{III}}$ salts, which experimentally were shown to be the most active ones, were also predicted by DFT to be the most acidic metal complexes. Similarly, the low catalytic reactivity of silver and gold in the oxidation state +1 was reflected in the computational results. In addition, the good to moderate catalytic activity of copper, iron, and zinc in the oxidation state +2 were effectively predicted by the DFT calculations. Our $\mathrm{Fe^{III}}$ computations appear to be overestimated in comparison to the experimental results; this may be due to the ferric ion's relatively complicated chemistry in acetic acid[25] or to the variability in its spin state (we assumed a sextet, as that was the most stable state in HOTFA). The DFT results reflect that proton catalysis is most likely the dominating mechanism of H/D exchange in the cases studied.

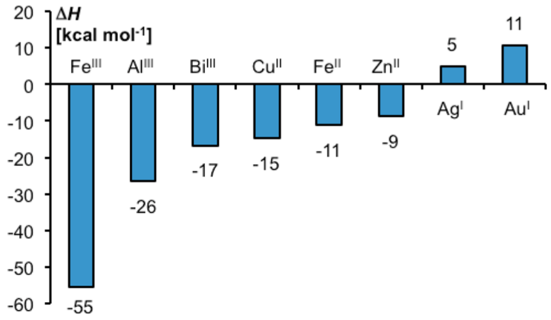


Figure 10. Reaction enthalpy for formation of Wheland complex according to eq 1. Ground states of $\mathrm{Fe^{II}}$, $\mathrm{Al^{III}}$, $\mathrm{Bi^{III}}$, $\mathrm{Cu^{II}}$, $\mathrm{Fe^{II}}$, and $\mathrm{Zn^{II}}$ coordinate six molecules of HOTFA, and $\mathrm{Ag^{I}}$ and $\mathrm{Au^{I}}$ coordinate two molecules of HOTFA. $\mathrm{Fe^{II}}$ is a singlet, and $\mathrm{Fe^{III}}$ is a doublet. Other spin states were calculated to be higher in energy.

■ CONCLUSIONS

In summary, we studied the catalytic H/D exchange of toluene and benzene in trifluoroacetic and acetic acid for a series of transition-metal and main-group-metal compounds. We also investigated the influence of the ligand, counterion, and metal and carried out DFT calculations. We showed that in the presence of weakly coordinating anions such as triflate, proton catalysis (i.e., Lewis acid catalyzed, electrophilic aromatic substitution) is likely the dominant mechanism in trifluoroacetic acid. We also obtained very strong indications that Lewis acid catalysis is important in acetic acid. Since only two acids have been tested as reaction media, no generalization of the acid catalysis pathway can be made. Nevertheless, our results indicate that precautions have to be taken when interpreting the H/D exchange reactivity of main-group-metal and transition-metal compounds in acidic solvents. These results indicate that the regioselectivity of the reaction with toluene can serve as a predictive tool for both the catalyst activity and the reaction pathway as well as a method for the comparative determination of Lewis acidities. The catalytic activity of the metals is dependent on the coligands employed. Perhaps most salient, these results suggest that extreme caution has to be taken when interpreting ligand effects for the study of H/D exchange catalysis with aromatic substrates in acidic media in the context of organometallic C–H activation chemistry. Accordingly, whereas the acidity of a transition-metal compound can be correlated to its electrophilicity, it is not necessarily a measure of C–H activation reactivity.

■ EXPERIMENTAL SECTION

General Methods. All catalytic reactions were run in screw-cap or J. Young NMR tubes. All reported values are the mean of at least two runs. All chemicals were obtained by common commercial suppliers and used as received without further purification. Measurements of the NMR spectra were performed on Bruker AC 300-P, Avance III 600, and Varian Inova 500 MHz instruments. The bis-NHC complexes were synthesized according to procedures reported in the literature.[26]

Standard Procedure for the H/D Exchange Reactions. The metal compound was weighed directly into the NMR tube in a N_2-filled glovebox. The NMR tube was brought out of the glovebox, and the indicated amount of toluene-d_8 was quickly added. Silver triflate was rapidly added in the form of 0.8 mL of a freshly prepared diluted solution in HOTFA or HOAc (containing 5% acetic anhydride). The diluted solutions were prepared in the glovebox. The NMR tube was sealed and immersed in a hot oil bath for the indicated time. After the mixture was cooled to room temperature, 30 μL of a 1/9 v/v solution of $MeNO_2$ and HOTFA (HOAc) as a standard and a capillary which contained DMSO-d_6 were added. The reaction was then analyzed by ^{1}H NMR spectroscopy and the H/D exchange determined by comparing the integral intensity of the protio toluene (benzene) signals to the signal of the $MeNO_2$ standard.

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501620f.

> Experimental details, representative ^{1}H NMR spectrum, details of kinetic experiments, determination of the isotope effect, and computational details including *xyz* coordinates of calculated structures (PDF)

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Notes

The authors declare no competing financial interest.

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