Room Temperature Regioselective Catalytic Hydrodefluorination of Fluoroarenes with trans-[Ru(NHC)4H2] via a Concerted Nucleophilic Ru-H Attack Pathway

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Room Temperature Regioselective Catalytic Hydrodefluorination of Fluoroarenes with trans-[Ru(NHC)₄H₂] via a Concerted Nucleophilic Ru-H Attack Pathway


Abstract: The efficient and highly selective room temperature hydrodefluorination (HDF) of fluoroarenes by the trans-[Ru(IMe₂)₂H₂] catalyst, 3, is reported. Mechanistic studies show 3 acts directly in catalysis without any ligand dissociation and DFT calculations indicate a concerted nucleophilic attack mechanism. The calculations fully account for the observed selectivities which corroborate earlier predictions regarding the selectivity of HDF.

The presence of partially fluorinated aromatic rings in many high value pharmaceuticals and agrochemicals (e.g. I and II, Scheme 1)[1] has fuelled interest in the use of catalytic hydrodefluorination (HDF) as a route to such functionalities by F/H substitution of perfluorinated substrates.[2-4] However, to achieve this the development of more active and more selective HDF catalysts is still required, as highlighted by the very specific substitution patterns in I and II. This is challenging as HDF becomes increasingly difficult as the number of fluoride substituents decreases, and this difficult process must be achieved with a high degree of regiocontrol. Chemoselectivity is also an issue, as selective C-F activation must be targeted over potentially deactivating C-H activation pathways.

Scheme 1. Examples of commercially important fluorinated molecules.

In previous work on HDF catalysis using N-heterocyclic carbene (NHC) ruthenium hydride complexes we have combined experimental and computational data to develop a mechanistic framework for the logical design of new catalysts with improved activity and regiocontrol. While our first catalyst system, [Ru(IPr)(PPh₃)₂(CO)H] (I)[3,4], showed only modest activity, catalytic HDF of CF₃C₆H₄ at 70 °C did proceed with a remarkably high and very unusual ortho-regioselectivity to give 1,2,3,4-C₆F₄H₂.[5,6] DFT studies on the HDF of CF₃C₆H₄ characterised two mechanisms based on the nucleophilicity of a hydride ligand in the 5-coordinate intermediate A formed via PPh₃ loss from I (Scheme 2).[7,8] These were a concerted pathway in which F/H exchange occurred in a single step, or, after fluoroarene coordination (B), a stepwise pathway featuring insertion into the Ru-H bond, HF elimination and protonolysis of Ru-aryl intermediate D to release C₆F₅H₂ and Ru-F species E. These two pathways exhibited different kinetic selectivities, the concerted mechanism leading to the para-HDF product 1,2,4,5-C₆F₄H₂, while the stepwise process favoured ortho-HDF and formation of 1,2,3,4-C₆F₄H₂. Overall, the stepwise pathway proved more accessible and so accounted for the observed regioselectivity.

Scheme 2. Nucleophilic hydride attack mechanism in [Ru(IPr)(PPh₃)₂(CO)H] catalysed HDF.

Having identified hydride nucleophilicity as a key element in these Ru-catalysed HDF reactions we turned to the more electron-rich, trans-dihydride complex [Ru(IPr)(PPh₃)(PPh₃)₂H₂] (2).[9,10] This did indeed give higher activity, with CF₃ being converted to difluorobenzene through four HDF cycles at 90 °C. However, this was counterbalanced by poorer regioselectivity, with both the 1,2- and 1,4-isomers of CF₃C₆H₄ being formed. We reasoned that this may reflect the lability of the PPh₃ ligands in this system, resulting in a mixture of 5- and 6-coordinate Ru species in solution. The former could access both stepwise and concerted pathways, while for the latter, the concerted process would be the only option. We now report on catalytic HDF with a new catalyst, trans-[Ru(IMe₂)₃H₄] (3).[11] In this system the use of four strongly bound NHC ligands aims both to enforce coordinative saturation and enhance hydride nucleophilicity. We show that 3 is capable of taking CF₃ to 1,4-C₆F₄H₂ at room temperature; moreover the intermediate steps all occur in a highly selective fashion. DFT calculations rationalise the observed outcomes.

The trans-dihydride complex 3 (Scheme 3) was reported previously by Wolf upon reduction of [Ru(IMe₂)₃Cl] with LiAlH₄, although it could only be obtained as an impure solid in low yield.[12] If KCS/H₂ is instead used as the reductant, 3 can be isolated as an analytically pure yellow microcrystalline solid in high (80%) yield (Scheme 3). The high
symmetry of the molecule led to a very simple $^1$H NMR spectrum consisting of just three resonances at $\delta = 3.37, 1.97$ and $-8.14$ ppm in a 24:24:2 ratio.

Upon addition of a stoichiometric amount of CsF to a benzene solution of 3 at room temperature, rapid HDF took place to afford [Ru(Imes)$_2$H]$^+$ (4) and CsF.[13] The X-ray structure of 4 (ESI) confirmed the same trans-H-Ru-F geometry as found in [Ru(Et$_2$Me)$_2$(PPH$_3$)$_2$H]$^+$ (5), albeit with a lengthening of the Ru-F distance (2.307(8) Å vs 2.264(2) Å). 4 exhibits approximate $C_s$ molecular symmetry around the H-Ru-F axis. The presence of the weakly coordinated fluoride ligand trans to hydride is reflected in the low frequency of the Ru-H chemical shift of 4 ($\delta = -23.19$ ppm). Addition of 5 equiv Et$_2$SiH to 4 brought about the rapid and clear formation of 3 at room temperature (Scheme 3).[14]

Table 1 summarizes the results of catalytic HDF with 3 (5 mol%) in benzene with a silane as reductant. CsF$_2$ underwent two HDF cycles within ca. 5 min (TOF > 480 h$^{-1}$) at room temperature to give the para-HDF product, 1,2,4,5-CsF$_4$H$_2$. The reaction is therefore notable not only for taking place at room temperature,[15] but also in that 3 exhibits a different regioselectivity to 1. 1,2,4,5-CsF$_4$H$_2$ continued to react further, albeit far more slowly, undergoing another two HDF cycles over ca. 1 month to ultimately give 1,4-CsF$_4$H$_2$ (entry 1). When the HDF of CsF$_2$ was performed at 90 °C, full conversion to 1,4-CsF$_4$H$_2$ was complete in 10 h (entry 1). The formation of low fluorine-content products was investigated using a range of less fluorinated substrates (entries 2-5). HDF of 1,2,4,5-CsF$_4$H$_2$: first formed 1,2,4-CsF$_3$H$_2$, which then reacted onwards to give 1,4-CsF$_4$H$_2$ (entries 2 and 3). No further reduction of 1,4-CsF$_4$H$_2$ to CsF$_4$H$_2$ was observed, although fluorobenzene could be formed from both the 1,2- and 1,3-isomers of CsF$_3$H$_2$ (entries 4 and 5). No reduction to benzene was observed.[16]

Variation of the silane reductant (entries 6-10) established that those with mixed aryl/alkyl substituents (PhMe$_2$SiH, Ph$_2$MeSiH), as well as secondary alkyl silanes (Et$_2$SiH$_2$), performed similarly to Et$_2$SiH, although lower reactivity was found with aryl silanes (Ph$_2$SiH, Ph$_3$SiH).[17] Replacement of the Imes ligand by the less donating 1,3-dimethylimidazol-2-ylidene (Imes) ligand (Scheme 3) also had a noticeable effect, [Ru(Imes)$_2$H]$^+$ (6: ESI) displaying lower activity than 3 (entries 11 and 12). This appeared to result from the relatively poor solubility of the corresponding hydride fluoride complex, [Ru(Imes)$_2$HF]$^+$ (7: ESI) in solution; even at 90 °C, a fine yellow precipitate of 7 could be observed in catalytic HDF reactions.

Given the coordinative saturation of both 3 and 5, the potential for dissociation of an NHC from either ruthenium complex was probed. The strength of metal-NHC bonds[17] has led to carbenes being considered as innocent spectator ligands which do not dissociate readily from metal centres.[18] Indeed, no exchange between 3 and free Imes$_2$Me$_3$ (3 eq) was observed at room temperature, and so any involvement of unsaturated species such as [Ru(Im$_3$)H$_2$] can be ruled out in the HDF reactions in Table 1 conducted at room temperature. However, upon heating at 90 °C, new hydride resonances were observed in the same $\delta = -8$ ppm hydride region of the proton NMR spectrum as 3, suggesting that carbene dissociation and exchange is possible at higher temperature.[19]

To address whether any dissociated Imes could therefore play a similar role to that recently found for alkylphosphines in catalysing HDF,[20] free Imes was heated between 70-90 °C with 1,2,4-CsF$_4$H$_2$ in the presence of Et$_2$SiH. The addition product 8 (ESI) and Et$_2$SiF were formed in a 1:1 ratio (Scheme 4). Activation at the 2-position (i.e. para to H rather than para to F) was confirmed by structural characterisation of the imidazolium salt 9, which was formed when Imes and 1,2,4-CsF$_4$H$_2$ were heated together in the absence of any silane (ESI).[21] Crucially, heating 7 at 90 °C in both the presence and absence of Et$_2$SiH resulted in <15% conversion to 1,4-CsF$_4$H$_2$ upon fluoroarene elimination. This shows there is only a low level of the NHC-mediated stoichiometric HDF and confirms the need for Ru in the reactions of 3. Moreover, the absence of 8 at the end of catalytic runs with 3 shows that 16e [Ru(Imes)$_2$H$_2$] is not catalytically relevant even in the high temperature HDF runs.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat</th>
<th>Substrate</th>
<th>Reductant</th>
<th>Product</th>
<th>T [°C]</th>
<th>t [h]</th>
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<td>3</td>
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<td>Et$_2$SiH</td>
<td>1,4-CsF$_4$H$_2$</td>
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<td>1,4-CsF$_4$H$_2$</td>
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<td>10</td>
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<td>3</td>
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<td>9</td>
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<td>PhMe$_2$SiH</td>
<td>1,4-CsF$_4$H$_2$</td>
<td>25</td>
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<td>90</td>
<td>103</td>
<td>80</td>
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</table>

[a] Reaction conditions: 0.1 M fluoroarene, 0.5 M silane, 5 mol% 3 or 5, 0.5 mL CsF$_2$, conversions determined by $^1$H NMR spectroscopy. [b] Temperature raised to 90 °C after ca. 5 min at 25 °C. [c] Solvent = toluene. [d] Product distribution is % of main products/total % of all HDF products.
DFT calculations were used to account for the selectivity of the various HDF reactions in Table 1. As a stepwise HDF process based on initial NHC/fluoroarene substitution can be ruled out experimentally, the calculations focused on the concerted mechanism and applied this to the full range of fluoroarenes C₆F₆H₄⁻ (n = 0-5). The results obtained with 1,2,4-C₆F₄H₄⁻ are typical and details are provided in Figure 1. The lowest energy pathway involves attack of the hydride ligand at the C2 position of the arene and proceeds with a free energy barrier (relative to the fluoroarene) of 16.2 kcal/mol. The transition state involved, TS(3-4)₁₆⁻, features a near-linear [Ru–H¹–C2] moiety (171.9°) and elongated Ru–H and C2F2 distances of 1.90 Å and 1.41 Å respectively. As this occurs, the new C2H¹ bond begins to form (1.64 Å) and a shortening of the trans Ru–H¹ distance is seen (1.65 Å) in response to the weakening of the Ru–H¹ interaction. The orientation of the approaching fluoroarene (as defined by the C₆ plane) is offset by approximately 40° relative to the best-fit plane containing Ru and the four C2 carbons of the IMe ligands. TS(3-4)₁₆⁻ exhibits a Meisenheimer-type geometry with elongation of the C₁₆–Cortho bonds (see inset, Figure 1), although H-transfer onto C is more progressed than the C-F bond cleavage, the C2F2 bond being only 0.06 Å longer than in free 1,2,4-C₆F₄H₄⁻. The Ru–F2 distance is also rather long (3.70 Å), but characterisation via IRC calculations confirms that F2 does move onto the metal centre to generate 4 and release the 1,4-C₆F₄H₂ product all in one step. This HDF process is extremely exergonic (ΔG° = -49.9 kcal/mol).

The alternative HDF at the C1 and C4 positions of 1,2,4-C₆F₄H₄⁻ proceed via transition states TS(3-4)₄⁻ and TS(3-4)₄⁺ at +19.7 kcal/mol and +21.4 kcal/mol respectively. These display similar geometries to TS(3-4)₁₆⁻, although with somewhat longer Ru–H¹ and shorter C1/C4–H¹ distances. These later geometries (in terms of H-transfer) are consistent with the higher computed barriers which indicate a clear kinetic preference for HDF at the 2-position, in line with experiment where only that process is observed (Table 1, entry 3).

The DFT study was extended to the HDF of other fluoroarenes by 3 starting with C₆F₆. Results are shown in Figure 2(a) as calculated barriers (relative to 3) and the appropriate fluoroarene in each case) for each HDF step. As seen previously, there is a general increase in the barrier as the number of F-substituents is reduced and this is reflected in the more forcing conditions that are required experimentally to achieve HDF with lower fluorinated substrates. The pattern of the F-substituents also directs the selectivity. We have previously shown that the concerted mechanism is favoured most by the ortho-F substituents which cause a weakening of the target C-F bond; meta-F substituents also reduce barriers (although to a lesser extent), while para-F substituents can actually cause a slight increase in the barrier. These patterns are borne out here, with C₆F₆H₄⁻ reacting at the 4-position (this having two ortho-F and two meta-F substituents) and, as seen in Figure 1, 1,2,4-C₆F₄H₂ reacts at the 2-position (its ortho-F and meta-F substituents trumping the 1-position which has one ortho-F and one para-F substituent). HDF of 1,4-C₆F₄H₄⁻ has a high predicted barrier of 25.6 kcal/mol and so, experimentally, the catalytic HDF of C₆F₆ proceeds to, but stops at, 1,4-C₆F₄H₂. Figures 2(b) and (c) (and (c) is a range of other fluoroarene substrates. Both 1,2,3,4- and 1,2,3,5-C₆F₄H₄⁻ are predicted to form 1,2,4-C₆F₄H₂ and hence 1,4-C₆F₄H₄⁻ (Figure 2(b)). Figure 2(c) shows that HDF of both 1,2,3- and 1,3,5-C₆F₄H₄⁻ is predicted to be accessible (barriers of 15.4 kcal/mol and 18.6 kcal/mol respectively), and that both species will form 1,3-C₆F₃H₄⁻. The meta-disposition of the F-substituents in this isomer (compared to the unfavourable para-arrangement in 1,4-C₆F₄H₂) makes HDF to C₆F₃H₂ possible via a barrier of 21.9 kcal/mol. As expected, the ortho F atom arrangement in 1,2-C₆F₄H₂ makes HDF even more accessible (ΔG° = -20.3 kcal/mol) and so fluorobenzene can also be accessed via this route, as is indeed observed experimentally. HDF of fluorobenzene has a significantly higher barrier of 26.1 kcal/mol and is not observed.

![Scheme 4. Stoichiometric C-F activation reactions of 1,2,4-C₆F₄H₄⁻ with IMe.](image-url)

![Figure 1. Computed profiles (ωB97X-D/BP86, free energies in benzene, kcal/mol) for the HDF of 1,2,4-C₆F₄H₂ by [Ru(IMe)₄]²⁺. 3. Selected distances are shown in Å and the inset provides additional information for TS(3-4)₁₆⁻.](image-url)

![Figure 2. Selectivity of HDF for a range of fluoroarene substrates: (a) C₆F₆ gives 1,4-C₆F₄H₄⁻; (b) 1,2,3,4-C₆F₄H₂ and 1,2,3,5-C₆F₄H₄⁻ give 1,4-C₆F₄H₂; and (c) 1,3,5-](image-url)
In summary, room temperature, selective catalytic HDF of C\textsubscript{6}F\textsubscript{5} to 1,4-C\textsubscript{6}F\textsubscript{4}H\textsubscript{2} has been demonstrated with the trans-[Ru(IMe)\textsubscript{2}]+H\textsubscript{2} catalyst. Fluorobenzene can also be accessed from 1,3,5-C\textsubscript{6}F\textsubscript{3}H\textsubscript{3} and 1,2,3-C\textsubscript{6}F\textsubscript{3}H. The highly electron rich character of 3 promotes the HDF reaction, which DFT calculations show proceeds via a concerted nucleophilic attack mechanism. Experimental studies indicate that 3 acts directly in catalysis and that alternative pathways based on initial ligand loss are not relevant. This also accounts for the high selectivity observed experimentally, in contrast to earlier mixed NHC/PR\textsubscript{3} catalysts.\cite{36} Thus controlling the mechanism also controls the synthetic outcome and this insight will hopefully allow for the development of new HDF catalysts that have greater utility in synthesis.

Acknowledgements

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Keywords: hydrodefluorination • ruthenium • NHC • catalysis • DFT calculations

Measurement of the C-F barrier is indicated in kcal/mol (\textsubscript{a}) M. F. Kuehne l, D. Lentz and T. John Lowe and Anneke Lubben for experimental assistance.

(6) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.


(10) IB\textsubscript{3}Me\textsubscript{2} = 1,3,4-trimethylimidazol-2-ylidene.

(11) IPR\textsubscript{3} = 1,3,4-trimethylimidazol-2-ylidene.

(12) HDF of monofluorarenes has been reported only rarely. a) R. J. Young and V. V. Grushin, Organometallics 1999, 18, 294-296; b) S. Kuhl, R. Schneider and Y. Fort, Adv. Synth. Catal. 2003, 345, 341-344; c) ref [3j]; d) ref [3k]; e) ref [3q].

(13) HDF of monofluorobenzene can also be accessed from 1,3,5-C\textsubscript{6}F\textsubscript{3}H\textsubscript{3} and 1,2,3-C\textsubscript{6}F\textsubscript{3}H. Although more slowly (see ESI).


Efficient and selective hydrodefluorination of fluoroarenes by a trans-[Ru(NHC)₄H₂] catalyst is reported. DFT calculations indicate that the observed selectivities are fully consistent with a concerted nucleophilic attack mechanism without any prior ligand dissociation.