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)₄H₂] 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 fluorine 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)H₂) (1),[5,6] showed only modest activity, catalytic HDF of C₆F₆ at 70 °C did proceed with a remarkably high and very unusual ortho-regioselectivity to give 1,2,3,4-C₄F₄H₂. DFT studies on the HDF of C₆F₆ 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-C₄F₄H₂, while the stepwise process favoured ortho-HDF and formation of 1,2,3,4-C₄F₄H₂. 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)H₂] 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(IEt₂Me)₂(PPh₃)H₂] (2).[9,10] This did indeed give higher activity, with C₆F₆ 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 C₆F₄H₂ 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)₄H₂] (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 C₆F₆ to 1,4-C₄F₄H₂ at room temperature; moreover the intermediate steps all occur in a highly selective fashion. DFT calculations rationalised the observed outcomes.

The trans-dihydride complex 3 (Scheme 3) was reported previously by Wolf upon reduction of [Ru(IMe₂)₂Cl₂] with LiAIH₄, although it could only be obtained as an impure solid in low yield.[12] If KCSH 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 1H 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 C$_6$F$_6$ to a benzene solution of 3 at room temperature, rapid HDF took place to afford [Ru(IMe$_3$)$_2$]HF (4) and C$_6$F$_5$H$_2$.[13] The X-ray structure of 4 (ESI) confirmed the same trans-H-Ru-F geometry as found in [Ru(IEt$_2$)$_2$]HF (5), albeit with a lengthening of the Ru-F distance (2.3070(18) Å vs 2.264(2) Å). 4 exhibits approximate Cs 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 eq Et$_3$SiH to 4 brought about the rapid and clean 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. C$_6$F$_5$ 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-C$_6$F$_5$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-C$_6$F$_5$H$_2$ continued to react further, albeit far more slowly, undergoing another two HDF cycles over ca. 1 month to ultimately give 1,4-C$_6$F$_5$H$_2$ (entry 1). When the HDF of C$_6$F$_5$ was performed at 90 °C, full conversion to 1,4-C$_6$F$_5$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-C$_6$F$_5$H$_2$ first formed 1,2,4,5-C$_6$F$_5$H$_2$, which then reacted onwards to give 1,4-C$_6$F$_5$H$_2$ (entries 2 and 3). No further reduction of 1,4-C$_6$F$_5$H$_2$ to C$_6$F$_5$H$_2$ was observed, although fluorobenzene could be formed from both the 1,2- and 1,3-isomers of C$_6$F$_5$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$_3$SiH$_2$), performed similarly to Et$_3$SiH, although lower reactivity was found with aryl silanes (Ph$_2$SiH, Ph$_3$SiH).[14] Replacement of the IMe$_3$ ligand by the less donating 1,3-dimethylimidazol-2-ylidine (IMe$_2$) ligand (Scheme 3) also had a noticeable effect. [Ru(IMe)$_2$]HF (6) ESI displayed lower activity than 3 (entries 11 and 12). This appeared to result from the relatively poor solubility of the corresponding hydride fluoride complex, [Ru(IMe)$_2$]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 carbene formation and dissociation. Indeed, no exchange between 3 and free IMe$_3$Me$_2$ (3 eq) was observed at room temperature, and so any involvement of unsaturated species such as [Ru(IMe$_2$=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 IMe$_3$ could therefore play a similar role to that recently found for alkylphosphines in catalysing HDF,[20] free IMe$_3$ was heated between 70-90 °C with 1,2,4-C$_6$F$_5$H$_2$ in the presence of Et$_3$SiH. The addition product 8 (ESI) and Et$_3$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 IMe$_3$ and 1,2,4-C$_6$F$_5$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$_3$SiH resulted in <15% conversion to 1,4-C$_6$F$_5$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 1te [Ru(IMe$_2$=H)$_2$] is not catalytically relevant even in the high temperature HDF runs.

![Scheme 3. Synthesis and hydrodefluorination chemistry of trans-[Ru(NHC)H$_2$].](image)

<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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<tbody>
<tr>
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<td>3</td>
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<td>1,4-C$_6$F$_5$H$_4$</td>
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<td>9</td>
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<td>PhMe$_2$SiH</td>
<td>1,4-C$_6$F$_5$H$_4$</td>
<td>25</td>
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<tr>
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<td>103</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 C$_6$F$_5$H$_2$ conversions determined by $^{19}$F 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.[22] 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 C_{n}F_{2n}H_{n} (n = 0-5). The results obtained with 1,2,4-C_{6}F_{5}H_{3} 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 3 + free 1,2,4-C_{6}F_{5}H_{3}) of 16.2 kcal/mol. The transition state involved, TS(3-4)_{HF}, features a near-linear (Ru−H−C) moiety (171.9°) and elongated Ru−H and C2-F2 distances of 1.90 Å and 1.41 Å respectively. As this occurs, the new C2-H bond begins to form (1.64 Å) and a shortening of the trans Ru−H distance is seen (1.65 Å) in response to the weakening of the Ru−H 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)_{HF} exhibits a Meisenheimer-type geometry with elongation of the C_{para}-C_{ortho} bonds (see inset, Figure 1), although H-transfer onto C is more progressed than the C-F bond cleavage, the C2-F2 bond being only 0.06 Å longer than in free 1,2,4-C_{6}F_{5}H_{3}. 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-C_{6}F_{5}H_{2} product all in one step.[23] This HDF process is extremely exergonic (ΔG = −49.9 kcal/mol).

The alternative HDF at the C1 and C4 positions of 1,2,4-C_{6}F_{5}H_{3} proceed via transition states TS(3-4)_1 and TS(3-4)_4 at +19.7 kcal/mol and +21.4 kcal/mol respectively. These display similar geometries to TS(3-4)_{HF}, although with somewhat longer Ru−H and shorter C1/C4−H 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 C_{4}F_{8}. 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,[40] 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.[40] These patterns are borne out here, with C_{6}F_{5}H reacting at the 4-position (this having two ortho-F and two meta-F substituents) and, as seen in Figure 1, 1,2,4-C_{6}F_{5}H_{3} 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-C_{4}F_{8}H_{1} has a high predicted barrier of 25.6 kcal/mol and so,

![Figure 1](image1.png)

**Figure 1.** Computed profiles (ωB97X-D/BP86, free energies in benzene, kcal/mol) for the HDF of 1,2,4-C_{6}F_{5}H_{3} by [Ru(IMe)4H]+. 3. Selected distances are shown in Å and the inset provides additional information for TS(3-4)_{HF}.

![Figure 2](image2.png)

**Figure 2.** Selectivity of HDF for a range of fluoroarene substrates: (a) C_{6}F_{8} gives 1,4-C_{6}F_{5}H_{2}; (b) 1,2,3,4-C_{6}F_{5}H_{3} and 1,2,3,5-C_{6}F_{5}H_{3} give 1,4-C_{6}F_{5}H_{2}; and (c) 1,3,5-


4


The test calculations were run with Gaussian 03/09 and were based on geometries optimised with the BP86 functional. Energies were re-computed with the 6-31+G(d) functional and quoted free energies include a correction for C,H$_4$ solvent (PCM approach). See ESI for full details.

Test calculations including the effect of benzene solvent in the optimisation procedure gave similar results. See ESI for details.
Hydrodefluorination

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.

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