C–F Activation

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Catalytic Hydrodefluorination of Pentafluorobenzene by [Ru(NHC)-$(PPh_3)_2(CO)H_2$]: A Nucleophilic Attack by a Metal-Bound Hydride Ligand Explains an Unusual *ortho*-Regioselectivity**

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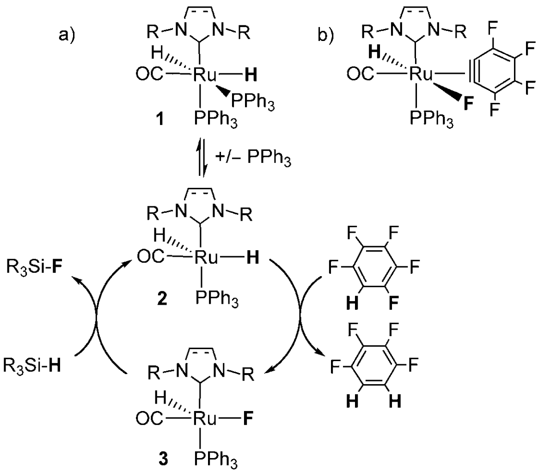
The selective synthesis of fluoroarene compounds is a subject of intense current interest, driven by the prominent role such species play in many pharmaceuticals, agrochemicals, and other industrially important products.[1] One attractive route to selectively substituted fluoroarenes involves the activation and functionalization of aromatic C–F bonds derived from readily available perfluoroarenes.[2] The simplest example of such a process is the hydrodefluorination reaction (HDF), in which fluorine is substituted for hydrogen. Catalytic HDF of C_6F_6 and C_6F_5H has been reported by Milstein et al.[3] and Holland et al.[4] using Rh and Fe catalysts.[5] However, both these systems exhibit practical problems that limit the mechanistic understanding of the HDF cycle. For example the Rh system requires high pressures of H_2 as well as a sacrificial amine to remove HF, while with Fe no C–F activation is observed in the absence of a reductant. As a consequence, the development of more active Rh or Fe catalysts has not been forthcoming.

We recently reported[6] the HDF of C_6F_6 and C_6F_5H using the ruthenium N-heterocyclic carbene (NHC) dihydride complex **1** (NHC = IMes, SIMes, IPr, SIPr;[7] see Scheme 1 a) in the presence of trialkylsilanes at 70 °C in THF. Isolation and characterization of **1** allowed detailed kinetic studies to be undertaken, and these supported a mechanism involving initial phosphine dissociation to form **2** followed by HDF of the substrate to give the Ru–F species, **3**. Isolation of this 16e complex allowed us to demonstrate its reaction with trialkylsilane in the presence of PPh_3 to regenerate catalyst **1**. The most unusual feature of this system was the high regioselectivity for the formation of 1,2,3,4-$C_6F_4H_2$ upon HDF of C_6F_5H, in complete contrast to the Milstein and Holland systems[3,4] where the 1,2,4,5-isomer dominated.

To account for the unusual *ortho*-regioselectivity we postulated the involvement of a tetrafluorobenzyne intermediate (Scheme 1 b). Such species have been reported previously[8] and could be formed here from **2** by successive C–H and *ortho*-C–F activation of C_6F_5H. However, density functional theory (DFT) calculations[9] (with NHC = IMes) have now shown that this species lies more than 200 kJ mol^{-1} above the reactants, effectively ruling it out as a viable intermediate under the conditions used experimentally.



Scheme 1. a) Catalytic hydrodefluorination (HDF) of C_6F_5H to 1,2,3,4-$C_6F_4H_2$ by **1**; b) postulated tetrafluorobenzyne intermediate.

Further calculations, however, have now allowed us to define a series of alternative pathways which are based on a novel nucleophilic attack mechanism whereby a hydride ligand reacts directly with C_6F_5H.[10] These processes produced significantly lower barriers and, moreover, the lowest-energy pathway was found to be consistent with the unusual *ortho*-regioselectivity observed experimentally. Our calculations have shown that, after initial phosphine loss from **1**, nucleophilic attack of hydride at C_6F_5H can occur through two different pathways (Scheme 2). In the concerted pathway I, the hydride is transfered from the metal onto the arene ring and the displaced fluorine migrates directly onto the metal center. In the alternative stepwise pathway II, an η^2-arene adduct, **4**, is formed prior to the hydride attack. In this case the different orientation of the arene precludes direct transfer of fluorine onto the metal. Instead an intermediate is formed, **5**, from which HF can be lost to form a σ-aryl species, **6**. Protonolysis by HF with concomitant F transfer to metal then yields 1,2,3,4-$C_6F_4H_2$ and the M–F species **3**.

The lowest-energy reaction profile for the HDF of C_6F_5H by **1** to give 1,2,3,4-$C_6F_4H_2$ is computed to proceed through pathway II, and full details are shown in Figure 1.[11] Initial

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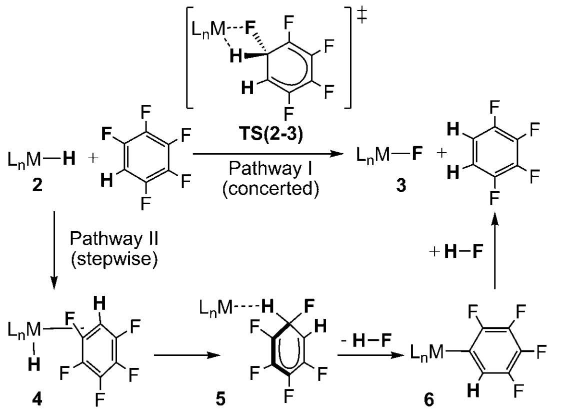


Scheme 2. Mechanisms of nucleophilic attack by a metal hydride ligand at C_6F_5H to give 1,2,3,4-$C_6F_4H_2$; L_nM = [Ru(NHC)(PPh$_3$)(CO)H].

PPh$_3$/C_6F_5H substitution gives **4** ($E = +37.7$ kJ mol^{-1} in THF[9]), in which the η^2-arene binds through the C5–C6 bond. Attack of H5 at C5 occurs through **TS(4–5)** ($E = +75.3$ kJ mol^{-1}) and gives **5** ($E = +69.5$ kJ mol^{-1}), in which the $\{C_6F_5H_2\}^-$ moiety resembles a Meisenheimer intermediate (C5–H5 1.24 Å, C5–F5 1.45 Å). This structure is also stabilized by interaction of the *ortho* position with the metal center (Ru–C6 2.28 Å). The subsequent step through **TS(5–6)** ($E = +84.1$ kJ mol^{-1}) involves elongation of the C5–F5 bond to 1.95 Å. To this point the reaction parallels nucleophilic aromatic substitution, however, rather than acting as a simple leaving group the highly fluoridic center F5 (computed charge −0.54) is able to abstract H5 to form HF. As this occurs, the remaining $\{C_6F_4H\}^-$ moiety is trapped by Ru to give **6** ($E = -40.2$ kJ mol^{-1}). The calculations suggest that HF remains loosely associated with the aryl ligand in **6** (H5···C5 1.97 Å), and so it is ideally placed to effect protonolysis of the Ru–C5 bond with concomitant F transfer to Ru. This step occurs through **TS(6–3)** ($E = -18.4$ kJ mol^{-1}) and gives [Ru(IMes)(PPh$_3$)(CO)HF] (**3**) and 1,2,3,4-$C_6F_4H_2$. Overall, HDF of C_6F_5H is a highly favorable process ($\Delta E = -168.1$ kJ mol^{-1}) and proceeds with a barrier of 84.1 kJ mol^{-1} corresponding to **TS(5–6)**.

A transition state for the concerted HDF process through pathway I was also located (Figure 2). This process involves the direct reaction of C_6F_5H with five-coordinate [Ru(IMes)(PPh$_3$)(CO)H$_2$] (**2**) to give 1,2,3,4-$C_6F_4H_2$ and **3** and proceeds through **TS(2–3)** ($E = +113.4$ kJ mol^{-1}). The structure of **TS(2–3)** features a side-on orientation of C_6F_5H, and this means that the vacant site at Ru is now readily available to accept the displaced F5 substituent directly. In contrast, in **TS(5–6)** this site is blocked by interaction with the *ortho* C6 position. Overall, the barrier computed in THF for the concerted reaction through **TS(2–3)** is 29.3 kJ mol^{-1} above that for the stepwise process through **TS(5–6)**.

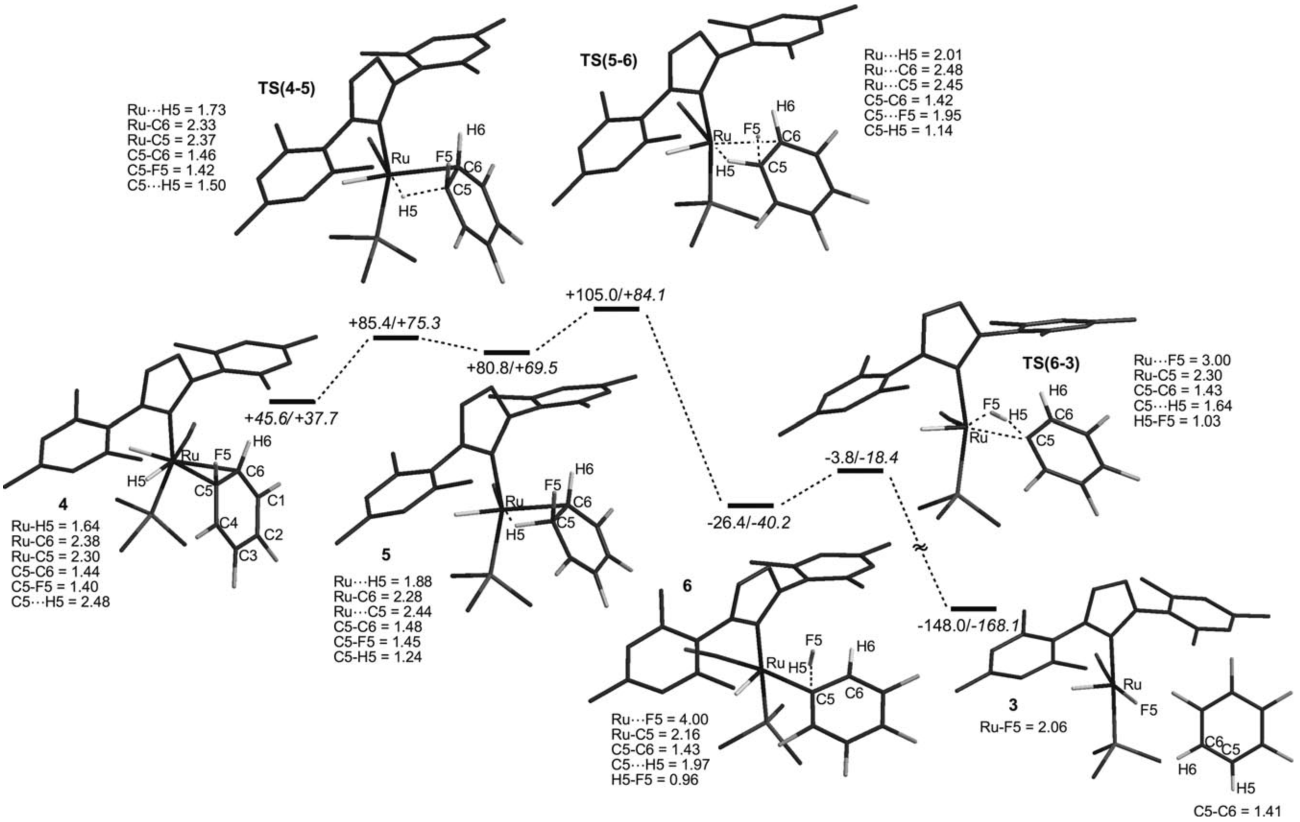
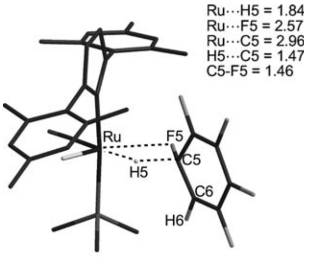


Figure 1. Computed reaction profile for HDF of C_6F_5H at [Ru(IMes)(PPh$_3$)(CO)H$_2$] to give 1,2,3,4-$C_6F_4H_2$ through pathway II. Energies (kJ mol^{-1}) are quoted relative to **1** and C_6F_5H computed separately; values in italics include a solvent correction (PCM method, THF). Selected distances are in Å. Phosphine Ph groups are truncated at the *ipso* carbon center and non-participating H atoms are omitted for clarity.



+124.7/*+113.4*
TS(2-3)

Figure 2. Computed transition state for HDF of C_6F_5H at $[Ru(IMes)(PPh_3)(CO)H_2]$ (**2**) to give 1,2,3,4-$C_6F_4H_2$ through pathway I. Energies are in $kJ\,mol^{-1}$ and the solvent-corrected values are in italics (PCM method, THF). Selected distances are in Å. Phosphine Ph groups are truncated at the *ipso* carbon center and non-participating H atoms are omitted for clarity.

We have also considered the formation of different isomers of $C_6F_4H_2$, and in all cases were able to characterize both the stepwise and concerted pathways. The lowest energy barriers computed for the formation of 1,2,3,5- and 1,2,4,5-$C_6F_4H_2$ in THF were 98.3 $kJ\,mol^{-1}$ and 99.5 $kJ\,mol^{-1}$, respectively, and in both cases corresponded to the stepwise mechanism, pathway II. The formation of 1,2,3,4-$C_6F_4H_2$ with a barrier of 84.1 $kJ\,mol^{-1}$ therefore remains the most accessible reaction, and this kinetic preference is consistent with the *ortho*-selectivity that is observed experimentally.[12,13]

The factors promoting these unusual hydride ligand nucleophilic attack reactions have been probed by calculations with a small model system featuring an N-methyl substituted carbene and PH_3 ligands. Thus, $[Ru(IMe)(PH_3)_2(CO)H_2]$ (**1′**)[7] yields barriers that are between 20 and 45 $kJ\,mol^{-1}$ higher than those computed with the full model. One reason for this difference is that the initial phosphine/C_6F_5H substitution step is more accessible for the more sterically encumbered full system. Reduced barriers for the nucleophilic attack/C–F bond cleavage steps are also seen in the full model system, and these may again reflect a more weakly bound arene. These steric effects are particularly large for the formation of the 1,2,3,4-$C_6F_4H_2$ isomer, where calculations with **1′** give a barrier 45 $kJ\,mol^{-1}$ higher than that computed for the full system.

In summary, DFT calculations have defined a novel class of reaction mechanism for the HDF of C_6F_5H catalyzed by $[Ru(IMes)(PPh_3)_2(CO)H_2]$. The key feature is the direct nucleophilic attack of a Ru hydride ligand at the fluoroarene substrate. The overall HDF process may occur either through a stepwise or a concerted pathway. The most accessible process is seen for the formation of 1,2,3,4-$C_6F_4H_2$ and involves 1) PPh_3/C_6F_5H substitution; 2) nucleophilic attack by the Ru hydride ligand at the *ortho* position on the ring; 3) HF loss and Ru fluoroaryl formation; and 4) protonolysis by HF with concomitant fluoride transfer to Ru to give 1,2,3,4-$C_6F_4H_2$ and $[Ru(IMes)(PPh_3)(CO)HF]$. This pathway has a modest computed barrier of 84.1 $kJ\,mol^{-1}$ in THF and is entirely consistent with the unusual *ortho*-regioselectivity that is observed experimentally. We believe that these results will provide a starting point for further experimental studies on transition metal hydride induced HDF and may allow the development of systems that display higher activity and additional control of regioselectivity.

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[10] Related mechanisms have been postulated for H/F exchange in C_6F_6 and C_6F_5H at $[Cp^*_2ZrH_2]$[10a] and $[\{1,3,4\text{-}(Me_3C)_3C_5H_2\}_2CeH]$.[10b] a) B. M. Kraft, W. D. Jones, *J. Organomet. Chem.* **2002**, *658*, 132–140; b) L. Maron, E. L. Werkema, L. Perrin, O. Eisenstein, R. A. Andersen, *J. Am. Chem. Soc.* **2005**, *127*, 279–292.

[11] All key stationary points were the subject of extensive conformational searching according to the protocol described in the Supporting Information.

[12] 1,2,3,4-$C_6F_4H_2$ can also be formed from an isomer of **4** in which the arene binds through the C1–C2 bond and H5 attacks C1. This process entailed a barrier of $+125.5\ \text{kJ}\,\text{mol}^{-1}$ in THF, significantly higher than the reaction shown in Figure 1.

[13] The lowest-energy pathway computed for HDF of C_6F_6 was also found to involve nucleophilic attack of the hydride ligand and had a barrier of $91.2\ \text{kJ}\,\text{mol}^{-1}$ corresponding to the stepwise pathway. This therefore supersedes the σ-bond metathesis mechanism proposed previously.[6]