Computational study of the hydrodefluorination of fluoroarenes at [Ru(NHC)(PR₃)₂(CO)(H)₂]: predicted scope and regioselectivities†

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Density functional theory calculations have been employed to investigate the scope and selectivity of the hydrodefluorination (HDF) of fluoroarenes, C₆F₆–nHₙ, (n = 0–5), at catalysts of the type [Ru(NHC)–(PR₃)₂(CO)(H)₂]. Based on our previous study (Angew. Chem., Int. Ed., 2011, 50, 2783) two mechanisms featuring the nucleophilic attack of a hydride ligand at a fluoroarene substrate were considered: (i) a concerted process with Ru–H/C–F exchange occurring in one step; and (ii) a stepwise pathway in which the rate-determining transition state involves formation of HF and a Ru–H–fluoroaryl complex. The nature of the metal coordination environment and, in particular, the NHC ligand was found to play an important role in both promoting the HDF reaction and determining the regioselectivity of this process. Thus for the reaction of C₆F₅H, the full experimental system (NHC = IMes, R = Ph) promotes HDF through (i) more facile initial PR₃/fluoroarene substitution and (ii) the ability of the NHC N-aryl substituents to stabilise the key C–F bond breaking transition state through F⋯H/C interactions. This latter effect is maximised along the lower energy stepwise pathway when an ortho-H substituent is present and this accounts for the ortho-selectivity seen in the reaction of C₆F₅H to give 1,2,3,4-C₆F₄H₂. Computed C–F bond dissociation energies (BDEs) for C₆F₆–nHₙ substrates show a general increase with larger n and are most sensitive to the number of ortho-F substituents present. However, HDF is always computed to remain significantly exothermic when a silane such as Me₃SiH is included as terminal reductant. Computed barriers to HDF also generally increase with greater n, and for the concerted pathway a good correlation between C–F BDE and barrier height is seen. The two mechanisms were found to have complementary regioselectivities. For the concerted reaction the pathway is directed to sites with two ortho-F substituents, as these have the weakest C–F bonds. In contrast, reaction along the stepwise pathway is directed to sites with only one ortho-F substituent, due to difficulties in accommodating ortho-F substituents in the C–F bond cleavage transition state. Calculations predict that 1,2,3,5-C₆F₄H₂ and 1,2,3,4-C₆F₄H₂ are viable candidates for HDF at [Ru(IMes)(PPh₃)₂(CO)(H)₂] and that this would proceed selectively to give 1,2,4-C₆F₃H₃ and 1,2,3-C₆F₃H₃, respectively.

Introduction

Substituted aryl fluorides are a key component of many pharmaceuticals and agrochemicals† and will be a crucial factor in the continuing search for more effective treatments and products. Current approaches to the synthesis of aryl fluorides commonly employ traditional organic chemistry based on nucleophilic aromatic substitution. However, this approach can have drawbacks, including (i) the need for harsh reaction conditions (with implications for functional group tolerance) and (ii) limited selectivity. New methods enabling the more efficient synthesis of selectively-substituted aryl fluorides are therefore highly desirable.

Transition metal catalysis offers one attractive way to address this problem and three general strategies to implement this approach have been explored. The first (eqn (1)) resembles a cross-coupling reaction in which an aryl halide or triflate is activated at a low-valent metal centre, with X⁻/F⁻ exchange and reductive elimination then leading to the
desired aryl fluoride. While the first two steps of this process have ample precedent, the reductive elimination is challenging, although progress has been made with Pd catalysts featuring sterically demanding biaryl-based phosphine ligands. In the second approach (eqn (2)) an aryl boronate supplies the aryl group and C–F bond formation occurs after oxidation with electrophilic fluorine sources, possibly exploiting a Pd(II)/Pd(IV) cycle. The final approach (eqn (3)) targets nucleophilic C–F functionalisation via the selective defluorination of one (or more) C–F bonds in cheap and widely available perfluorinated feedstocks. We focus on this strategy here and specifically fluoroarene hydrodefluorination (HDF; Nuc = H), the simplest example of nucleophilic C–F functionalisation in which a C–F bond is replaced by a C–H bond.

Examples of the stoichiometric HDF of fluoroarenes are known for both early and late transition metals and in many cases involve the reaction of a transition metal hydride to give the corresponding transition metal fluoride and the HDF product. This apparently simple net F/H exchange, however, masks a plethora of mechanistic possibilities. With the corresponding transition metal fluoride and the HDF product. This apparently simple net F/H exchange, however, masks a plethora of mechanistic possibilities. With this was rationalised by the ‘harpoon’ mechanism that directs the site of C–F activation. Extension of HDF beyond CF3H to lower fluorinated species is rare. Johnson has reported the HDF of 1,2,4,5-C4F4H2 to give 1,2,4-C4F4H2.16a while 1,4-C6F2H4 is produced upon prolonged heating of C6F6 in benzene in the presence of [Ni([IPr]3(COD)]22 and Ph3SiH.19 In general, all these systems exhibit low catalytic activities with modest turnover numbers (TON) and frequencies (TOF), even for the most active C6F6 substrate.

Recently one of us has reported the catalytic HDF of C6F6, C6F5H and C6F3N using Ru catalysts of the type [Ru(NHC)((PPh3)3(CO)][H]1]1, where NHC = N-aryl substituted N-heterocyclic carbenes, IMes, SIMes, IPr and SIPr,22 see Scheme 1).23 Kinetic studies suggest that catalysis proceeds via initial phosphine dissociation to give a 16e intermediate, 2. HDF then gives the isolable hydride fluoride [Ru(NHC)(PPh3)3(CO)(H)(F)]3, and silane reduction completes the catalytic cycle. With NHC = SPr and C6F6 TONs of up to 200 (TOF = 0.86 h–1) could be achieved, making this one of the more active HDF catalysts to date. Intriguingly, with C6F6H HDF also proceeds with an unexpected ortho-selectivity to give 1,2,3,4-C4F4H2.42

In order to account for these observations we undertook a subsequent DFT study that revealed the HDF reaction to proceed via a novel mechanism in which a metal-bound hydride ligand acts as the nucleophile. Calculations on the full [Ru[Nmes][PPh3]3(CO)][H]2 system characterised two pathways, both stemming from the 16e intermediate 2 (Scheme 2): (i) a concerted process via TS(2–3), where hydride transfer from Ru displaces fluoride which then migrates back to the metal centre to form 1,2,3,4-C4F4H2 and 3. This stepwise process is the lower energy route and also accounts for the observed ortho-selectivity of this system, the computed activation barrier for the formation of 1,2,3,4-C4F4H2 being significantly lower than those for the formation of 1,2,3,5-C6F5H2 or 1,2,4,5-C6F5H2. The calculations also
showed that C–H activation of C₆F₅H, although kinetically accessible, would be reversible, meaning that our system can target C–F activation in the presence of C–H bonds. In addition, an alternative mechanism based on a tetrafluoro-benzyne intermediate was ruled out.

In this paper we use density functional theory calculations to explore the origins of the unusual ortho-selectivity seen in the HDF reaction of pentafluorobenzene at 1. Our calculations show that N-aryl substituted NHC ligands create a specific environment which favours C–F bond activation, particularly when this occurs ortho to a C–H bond. In addition, we provide a general analysis of the HDF reactivity of fluoroarenes, C₆F₆−nHₙ (n = 0–5), in terms of the computed C–F bond dissociation energies of these species. This is used as the basis to explore the extension of the HDF reaction to lower fluorinated substrates and to predict the regioselectivities associated with these reactions.

**Computational details**

DFT calculations were run with Gaussian 03 (Revision C.02) and results for the BP86 functional are reported. Ru, P and Si centres were described with the Stuttgart RECPs and associated basis sets, with added d-orbital polarisation on P (ζ = 0.387) and Si (ζ = 0.284). 6-31G** basis sets were used for all other atoms. Test calculations employing a range of functionals and more extended basis sets were also performed and gave similar trends (see Table S1 in the ESI†). All stationary points were fully characterized via analytical frequency calculations as either minima (all positive eigenvalues) or transition states (one negative eigenvalue) and IRC calculations and subsequent geometry optimizations were used to confirm the minima linked by each transition state. All energies are corrected for zero-point energy and, in addition, Model 1 includes a solvent correction computed via the PCM approach (THF, ε = 7.43). Note that in our initial communication we reported solvent-corrected SCF energies; the reported energies therefore differ slightly between the two studies, although the computed trends are unaffected.

**Results and discussion**

**Mechanism of HDF**

We first summarise the key results from our previous study on the mechanism of HDF of C₆F₅H with [Ru(IMes)(PPh₃)₂(CO)·(H)₂], 1, to give 1,2,3,4-C₆F₄H₂. The computed reaction profile is shown in Fig. 1 and we consider first the data in bold for Model 1, equating to solvent-corrected enthalpies for the full experimental system. The most accessible stepwise pathway starts from 16e [Ru(IMes)(PPh₃)(CO)·(H)₂], 2 (E_{THF} = +23.1 kJ mol⁻¹), formed from 1 via initial PPh₃ dissociation, which can then bind C₆F₅H to give π-arene complex, 4 (E_{THF} = +36.2 kJ mol⁻¹). Intramolecular nucleophilic attack of the cis hydride ligand at the bound arene results in the formation of species 5 (E_{THF} = +66.6 kJ mol⁻¹), in which the C₆F₅H₂ moiety resembles a Meisenheimer intermediate that is stabilised by interaction with the Ru centre. C–F bond cleavage then proceeds via TS(5–6) (E_{THF} = +83.6 kJ mol⁻¹) which features a lengthening of the C1-⋯F1 distance to 1.95 Å (see also Fig. 2[a]) and a significant computed (NBO) negative charge of −0.55 associated with F1. Characterisation of TS(5–6) shows that this highly fluoridic centre is able to deprotonate the incipient {C₆F₄H₂} moiety leading to the...
formation of a Ru-σ-aryl complex, [Ru(IMes)(PPh₃)(CO)-(o-C₆F₄H)(H)]·HF (E_{THF} = -35.3 kJ mol⁻¹), featuring a close C1⋯HF contact. The final step is protonolysis of 6ortho, with HF adding over the Ru-C₆F₄H bond to give [Ru(IMes)-(PPh₃)(CO)(H)(F)], 3, and 1,2,3,4-C₆F₄H₂ (E_{THF} = -152.1 kJ mol⁻¹). An alternative concerted pathway was also characterised in which 2 reacts directly with C₆F₅H via intermolecular nucleophilic attack of hydride, giving 3 and 1,2,3,4-C₆F₄H₂ in one step. In this case the transition state, TS(2 → 3)ortho (E_{THF} = +103.5 kJ mol⁻¹), again features a nucleophilic attack of the
hydride ligand, but the different orientation of the arene moiety permits the direct transfer of the displaced fluoride back to the metal centre (see Fig. S1†). The overall barriers for the stepwise and concerted pathways are 83.6 kJ mol$^{-1}$ and 103.5 kJ mol$^{-1}$, respectively, indicating a kinetic preference for the intramolecular stepwise reaction pathway.  

To probe the role of the metal coordination environment and solvent in promoting the HDF reaction we have considered two further computational model systems: Model 2, the full experimental system as before, but with energies computed in the gas-phase (data in italics, Fig. 1); and Model 3, gas-phase computed energies for the smaller model system, $\text{[Ru(ImMe)(PMe$_3$)$_2$(CO)(H)$_2$]}$  

Table 1 gives activation barriers computed 

![Table 1: Computed activation barriers (kJ mol$^{-1}$) for competing HDF reactions of C$_6$F$_5$H at [Ru(NHC)(PR$_3$)$_2$(CO)(H)$_2$] with Models 1, 2 and 3](image)

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<td>95.9</td>
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<tr>
<td>Model 2</td>
<td>103.3</td>
<td>132.0</td>
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<td>Model 3</td>
<td>161.3</td>
<td>176.6</td>
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| Fig. 3: Computed structure of TS(5–6)$_{\text{ortho}}$ with key distances (Å). PR$_3$ ligands are truncated at the first substituent carbon and NHC hydrogen atoms (with the exception of those Me substituents exhibiting close contacts to F3 and F4) are omitted for clarity. 

Barriers to meta- and para-C–F activation again reflect the ability of the system to stabilise the fluoridic centre formed during the C–F bond cleavage transition state. Thus in TS(5–6)$_{\text{para}}$ (Fig. 3) the breaking C3–F3 bond is oriented to one side of the NHC ligand, permitting only one short contact of 1.81 Å with an ortho-Me hydrogen of the IMes ligand. In this case the central position over the Ru–NHC bond is blocked by the spectator C4–F4 bond. Despite extensive searches we have not been able to locate a transition state in which the C3–F3 bond occupies this position, with all attempts converging on less symmetric structures as that shown in Fig. 3. The presence of only one F⋯HC contact is also a feature of TS(5–6)$_{\text{meta}}$. The implication is that the HDF of fluoroaranes at $\text{[Ru(IMes)(PR$_3$)$_2$(CO)(H)$_2$]}$ will be directed towards centres with at least one ortho-C–H bond.

It is useful to compare how the different models capture the trends in barriers to HDF. For Model 3 reaction at the ortho-position is favoured, although only by about 8 kJ mol$^{-1}$ over the para-position. As detailed above, the inclusion of the bulky IMes and PR$_3$ ligands in Model 2 significantly reduces the barrier to HDF at the ortho-position by 58 kJ mol$^{-1}$. This effect is less important for the meta- and para-positions, the reduction in barrier being only ca. 40 kJ mol$^{-1}$. This reflects the lack of any extra stabilisation gained in TS(5–6)$_{\text{para}}$ and TS(5–6)$_{\text{meta}}$ in moving from IMe to IMes: in these cases both removal of the solvent correction ($E_{\text{gas}} = +161.3$ kJ mol$^{-1}$) and use of the small model system ($E_{\text{gas}} = +161.3$ kJ mol$^{-1}$).

As mentioned above, the structure of TS(5–6)$_{\text{ortho}}$ computed with the full experimental system shows an elongation of the C1–F1 bond, with F1 being displaced towards the IMes ligand, approximately parallel to the Ru–NHC bond. The large negative charge at F1 results in the appearance of two short, stabilising F⋯HC contacts of ca. 1.91 Å to the ortho-Me substituents of the IMes ligand. In contrast, with Model 3 the IMe ligand in TS(5–6)$_{\text{ortho}}$ can only accommodate one such stabilising contact to one of the Me substituents (1.93 Å; the shortest distance to the other Me substituent is over 5.5 Å, see Fig. 2(b)). The lower overall barrier computed with Model 2 compared to Model 3 therefore arises from two effects: (i) easier substitution of phosphine; and (ii) the ability of the bulky N-aryl substituted NHC ligand to stabilise the key C–F bond breaking transition state through stabilising F⋯HC contacts. The overall barrier is also sensitive to the inclusion of solvent effects, the computed barrier reducing by a further 20 kJ mol$^{-1}$ in moving from Model 2 to Model 1.

**Origins of the ortho-selectivity**

Table 1 gives activation barriers computed via the stepwise pathway for the competing HDF reactions of C$_6$F$_5$H at [Ru(NHC)(PR$_3$)$_2$(CO)(H)$_2$] with Models 1, 2 and 3.

For Model 1 the higher barriers computed for these processes (95.9 kJ mol$^{-1}$ and 95.5 kJ mol$^{-1}$ respectively) are consistent with preferential reaction at the ortho-position to give 1,2,3,4-C$_6$F$_4$H$_2$ as the dominant species formed experimentally.  

The higher barriers to meta- and para-C–F activation again reflect the ability of the system to stabilise the fluoridic centre formed during the C–F bond cleavage transition state. Thus in TS(5–6)$_{\text{para}}$ (Fig. 3) the breaking C3–F3 bond is oriented to one side of the NHC ligand, permitting only one short contact of 1.81 Å with an ortho-Me hydrogen of the IMes ligand. In this case the central position over the Ru–NHC bond is blocked by the spectator C4–F4 bond. Despite extensive searches we have not been able to locate a transition state in which the C3–F3 bond occupies this position, with all attempts converging on less symmetric structures as that shown in Fig. 3. The presence of only one F⋯HC contact is also a feature of TS(5–6)$_{\text{meta}}$. The implication is that the HDF of fluoroaranes at $\text{[Ru(IMes)(PR$_3$)$_2$(CO)(H)$_2$]}$ will be directed towards centres with at least one ortho-C–H bond.

It is useful to compare how the different models capture the trends in barriers to HDF. For Model 3 reaction at the ortho-position is favoured, although only by about 8 kJ mol$^{-1}$ over the para-position. As detailed above, the inclusion of the bulky IMes and PR$_3$ ligands in Model 2 significantly reduces the barrier to HDF at the ortho-position by 58 kJ mol$^{-1}$. This effect is less important for the meta- and para-positions, the reduction in barrier being only ca. 40 kJ mol$^{-1}$. This reflects the lack of any extra stabilisation gained in TS(5–6)$_{\text{para}}$ and TS(5–6)$_{\text{meta}}$ in moving from IMe to IMes: in these cases both removal of the solvent correction ($E_{\text{gas}} = +161.3$ kJ mol$^{-1}$) and use of the small model system ($E_{\text{gas}} = +161.3$ kJ mol$^{-1}$).
substitution step. In contrast, the inclusion of a solvent correction is more stabilising for TS(5–6)para and TS(5–6)meta. This arises from the less symmetric geometries of these species which leads to them having larger dipole moments (8.06 D and 8.77 D, respectively, cf. 5.26 D for TS(5–6)ortho). These structures are therefore subject to greater stabilisation by the solvent dielectric and as a result, although Model 1 still favours HDF at the ortho-position, the barriers for reaction at the meta- and para-positions are only ca. 12 kJ mol⁻¹ higher in energy.

Another factor affecting the energy of these HDF transition states is the orientation of the fluoroarene. The lowest energy form of TS(5–6)ortho considered so far has the C6–H6 bond oriented toward the IMes ligand (see Fig. 4(a)) and for Model 1 this arrangement is 42 kJ mol⁻¹ more stable than the alternative where the C2–F2 is in this position (Fig. 4(b)). With TS(5–6)meta the effect is much smaller as the C–H bond is more remote from the steric bulk of the ligands; in this case the preferred orientation actually has the C–H bond oriented towards the phosphine, this being 10 kJ mol⁻¹ more stable than when it is directed towards the NHC. For TS(5–6)para only one orientation of the C6–H6 is possible. In the following, for calculations on the full model we will only report the more stable form of these two types of transition states.

In summary, the NHC ligand is a key factor in directing the regioselectivity of HDF of C₆F₄H. The steric bulk of the N-aryl NHCs favours a substrate orientation that directs an ortho-C–H bond towards the NHC; in addition the ability of the NHC substituents to stabilise the cleaving C–F bond is maximised when C–F activation occurs ortho to a C–H bond. While other factors such as solvent polarity promote HDF meta or para to a C–H bond, overall for C₆F₄H the favoured site is at the ortho-position to give 1,2,3,4-C₆F₄H₂, as seen experimentally.

**HDF of lower fluorinated substrates**

(a) **Thermodynamics.** The intrinsic properties of the full series of C₆F₆-nHₙ (n = 0–5) substrates have been considered in order to define how the number of fluorine substituents affects the energetics of HDF and also how the pattern of substitution determines regioselectivity. Eqn (4) shows the overall process for catalytic HDF and includes the favourable transformation of a silane to a fluorosilane (here Me₃SiH to Me₃SiF)

$$C₆F₆-nHₙ \quad (n = 0–5) + Me₃Si-H \rightarrow C₆F₅-nHₙ₊₁ + Me₃Si-F$$

Previously, Clot, Eisenstein, Perutz and co-workers have investigated trends in C–H bond strengths in fluoroarenes and revealed a strong dependence on the number of ortho-F substituents present. They used multiple regression techniques to show that the homolytic bond dissociation energy (BDE) of a C–H bond is increased by an average of 10.4 kJ mol⁻¹ upon replacement of an ortho hydrogen by fluorine. The effects of H/F replacement at the meta- or para-positions were much smaller, increasing the C–H BDE by only 0.3 kJ mol⁻¹ and 3.4 kJ mol⁻¹ respectively. Here, we apply a similar approach to the computed C–F homolytic BDEs for the 20 unique C–F bonds in the C₆F₆-nHₙ (n = 0–5) series. The results of the multiple regression analysis on the C–F BDEs are shown in Fig. 5(a), in which ΔD(C–F)rel is the computed C–F BDE relative to that of the C₃–F₃ (i.e. para-C–F) bond in C₆F₃H. Equivalent C–H bond data are shown in Fig. 5(b), where ΔD(C–H)rel is the C–H bond in C₆F₄H (these data differ slightly from those reported with the earlier BP86 functional as they were recomputed here with the BP86 functional and include a correction for zero-point energy). In contrast to the C–H bonds, the trend in C–F BDEs shows a general strengthening as the number of fluorine substituents is reduced. As with the C–H BDEs, the C–F BDEs depend most significantly on the number of ortho-F substituents, x (x = 0, 1, 2), with F/H replacement causing a increase in C–F BDE by 7.5 ± 0.2 kJ mol⁻¹, while at the meta- and para-positions the average increases in BDE upon F/H replacement are 2.2 ± 0.2 kJ mol⁻¹ and 0.8 ± 0.3 kJ mol⁻¹, respectively. While still dominant, the relative influence of the ortho-position is less marked than for the C–H BDEs. As a result the C–F BDE data are more evenly spread and do not show the marked clustering into three distinct groups (depending on the number of ortho-Fs present) that was a feature of the data for C–H BDEs.

Both trends in the relative C–F and C–H BDEs indicate that HDF will become progressively harder for substrates with fewer fluorine substituents, as both the C–F bond being broken will tend to be stronger and the new C–H bond being formed will tend to be weaker. This is further illustrated in Fig. 6 which plots the energy required to break the substrate C–F bond against the energy released upon forming the new C–H bond. The most favourable HDF processes are for highly fluorinated species, e.g. [i] C₆F₆ (C–F ≈ 531.9 kJ mol⁻¹) to C₆F₅H (C–H = 487.3 kJ mol⁻¹) while HDF of C₆F₃H [ii] is least favoured (C–F = 552.4 kJ mol⁻¹) to C₆H₄ (C–H = 462.5 kJ mol⁻¹). The total spread of BDEs for the C–F and C–H BDEs is rather similar (22 kJ mol⁻¹ and 25 kJ mol⁻¹ respectively) and as these trends reinforce each other the total variation in the
overall computed enthalpy change for HDF is around 47 kJ mol\(^{-1}\). However, this HDF is always exothermic as it includes the very favourable formation of Me\(_3\)SiF (\(\Delta H = -226\) kJ mol\(^{-1}\)). The overall computed enthalpy change for HDF (eqn (4)) is highlighted for selected C-F bonds.

(b) Kinetics. With C\(_6\)F\(_5\)H the rate limiting HDF transition states along the stepwise and concerted pathways both feature different degrees of C-F bond elongation (e.g. \(\text{TS}(5-6)_{\text{ortho}}\): C1\(\cdots\)F1 = 1.95 Å; \(\text{TS}(2-3)_{\text{ortho}}\): C1\(\cdots\)F1 = 1.46 Å). Elongation of the C-H distance is also computed, although this is now more marked along the concerted pathway (\(\text{TS}(2-3)_{\text{ortho}}\): C1\(\cdots\)H1 = 1.47 Å) rather than the stepwise pathway (\(\text{TS}(5-6)_{\text{ortho}}\): C1\(\cdots\)H1 = 1.14 Å). To assess how these variations are reflected in the overall barriers to HDF and the regioselectivity of this process, we have located (\(\text{TS}(5-6)\) and \(\text{TS}(2-3)\) for the full C\(_6\)F\(_n\)H\(_n\) (\(n = 0\text{--}5\)) series. For this we have employed the small Model 3, i.e. [Ru(IMe)(PMMe\(_3\))(CO)(H)]\(_2\)], which allows us to focus primarily on electronic effects\(^{16}\); the full experimental system will be considered for selected substrates in the following section.

Fig. 7 plots computed activation barriers, \(\Delta E^\ddagger_{\text{rel}}\), against \(\Delta D(C-F)_{\text{rel}}\) of the cleaving C-F bond (where \(\Delta E^\ddagger_{\text{rel}}\) is relative to the barrier for HDF at the C3-F3 bond of C\(_6\)F\(_5\)H via the concerted mechanism), while computed activation barriers for both mechanisms are reported in Fig. 8.

For the concerted mechanism a good correlation (\(R^2 = 0.965\)) between \(\Delta \Delta E^\ddagger_{\text{rel}}\) and \(\Delta D(C-F)_{\text{rel}}\) is seen across the whole range of substrates, with a general increase in barrier as the number of fluorine substituents increases. In contrast, a plot of \(\Delta \Delta E^\ddagger_{\text{rel}}\) vs. \(\Delta D(C-H)_{\text{rel}}\) shows the C-H BDE is less important (\(R^2 = 0.809\), see Fig. S4†). The nature of the \(\text{ortho}\)-substituent is again the most important factor in determining regioselectivity, with HDF via the concerted mechanism most likely to occur at sites with two \(\text{ortho}\)-F substituents, as these feature the weakest C-F bonds. Indeed a multiple regression analysis of barrier height against the substituent pattern indicates \(\text{ortho}-\text{H/F}\) substitution lowers the barrier by an average of 17 kJ mol\(^{-1}\), \(\text{meta}-\text{H/F}\) substitution lowers it by 6 kJ mol\(^{-1}\), but \(\text{para}-\text{H/F}\) substitution actually raises the barrier by 2 kJ mol\(^{-1}\). Thus for C\(_6\)F\(_5\)H, reaction at the (\(\text{para}\)) C3-position is favoured and clear kinetic preferences for reaction at the 2-position are predicted for 1,2,3,4-C\(_6\)F\(_4\)H\(_2\) and 1,2,3-C\(_6\)F\(_3\)H\(_3\) (see plain text data in Fig. 8). For 1,2,3,5-C\(_6\)F\(_5\)H\(_3\) reaction at 2-position is only marginally favoured over the 1-position. This reflects a balance
The predicted scope and regioselectivity of HDF at \([\text{Ru}(\text{IMes})(\text{PPh}_3)_2(\text{CO})(\text{H})_2]\), 1

The results on the \(\text{C}_6\text{F}_{6-n}\text{H}_n\) series with \([\text{Ru}(\text{Me})](\text{PMe}_3)_2(\text{CO})(\text{H})_2]\) (Model 3) indicate that the kinetic selectivity of HDF will in many cases change depending on the mechanism that is in operation. The calculations indicate the concerted pathway is favoured and so HDF is kinetically most accessible at sites with two ortho-F substituents. In contrast, the stepwise pathway favours sites with one ortho-F. We have already shown that the barrier to HDF along the stepwise pathway is significantly reduced by use of the bulkier IMes and PPh_3 ligands as in \([\text{Ru}(\text{IMes})(\text{PPh}_3)_2(\text{CO})(\text{H})_2]\). There is therefore the opportunity to achieve different regiochemical outcomes for HDF by varying the nature of the NHC ligand.

To test these ideas we have computed the overall barriers for the HDF reactions of a range of lower fluorinated substrates at \([\text{Ru}(\text{IMes})(\text{PPh}_3)_2(\text{CO})(\text{H})_2]\]. The activation barriers computed with Model 1 are given in Fig. 9 and show that in all cases the stepwise pathway provides the lowest energy HDF process.\(^{37}\) The most reactive C–F bond is the C1–F1 bond of \(\text{C}_6\text{F}_8\), the computed barrier of 83.6 kJ mol\(^{-1}\) being slightly below that for \(\text{C}_6\text{F}_6\) (87.8 kJ mol\(^{-1}\)). This reflects a preference for an ortho-H substituent (maximising the stabilisation of TS(5–6) through two F⋯CH interactions) over an ortho-F substituent that will tend to weaken the reacting C–F BDE. As expected, activation barriers tend to increase with lower fluorinated substrates, although with 1,2,3,4-\(\text{C}_6\text{F}_4\text{H}_2\) and 1,2,3,5-\(\text{C}_6\text{F}_4\text{H}_2\) barriers of 94.5 kJ mol\(^{-1}\) and 84.4 kJ mol\(^{-1}\) suggest reaction could still be accessible. Significantly these barriers are for reaction adjacent to an ortho-H, to give 1,2,3-\(\text{C}_6\text{F}_4\text{H}_3\) and 1,2,4-\(\text{C}_6\text{F}_4\text{H}_3\), respectively. We therefore predict that both processes could be accessible with \([\text{Ru}(\text{NHC})(\text{PPh}_3)_2(\text{CO})(\text{H})_2]\) catalysts and that if they do proceed they will retain the unusual ortho-selectivity that was first highlighted in our study of HDF of \(\text{C}_6\text{F}_3\text{H}\). Experimental studies to probe these processes are underway.

Conclusions

Density functional theory calculations have been employed to investigate the scope and selectivity of the hydrodefluorination of directing effects: at the 2-position the presence of two ortho-Fs promotes HDF but this is mitigated by the para-F; at the 1-position the combination of one ortho-F and two meta-Fs (and no para-F) results in only a slightly higher barrier. Overall, these predicted selectivities are similar to those observed for the majority of examples of transition metal mediated HDF of fluoroarenes. Indeed we expect our analysis to be quite general and to apply in cases where the C–F BDE is the factor that dominates the reactivity of a fluoroarene.

For the stepwise process the computed activation data fall into two distinct sets, depending on the number of ortho-Fs (\(x = 0, 1\) or \(x = 2\)). In both cases the trend towards increased activation barriers with lower number of F substituents is again seen, with good correlations between \(\Delta\Delta E_{\text{rel}}^f\) and \(\Delta D(C–F)_{\text{rel}}\) \((x = 0, 1; R^2 = 0.942; x = 2; R^2 = 0.949)\). The C–F BDE is again the dominant factor, as there is no correlation with \(\Delta D(C–H)_{\text{rel}}\) for \(x = 2\) \((R^2 = 0.012)\) or this is weak for \(x = 0, 1\) \((R^2 = 0.733,\) see Fig. S4\). In general with the small Model 3 \(\Delta\Delta E_{\text{rel}}^f\) is larger for the stepwise rather than the concerted pathway, although for \(x = 0\) or 1 the two pathways do become competitive with the higher fluorinated substrates (e.g. the 1-position of \(\text{C}_6\text{F}_5\text{H}\)). For \(x = 2\) all transition state structures are destabilized by the need to accommodate an ortho-F substituent near to the reacting C–F bond, and this results in a ca. 25 kJ mol\(^{-1}\) increase in \(\Delta\Delta E_{\text{rel}}^f\) compared to the equivalent reaction via the concerted pathway. The regioselectivity of HDF is therefore completely different to that seen for the concerted pathway as now the presence of two ortho-Fs increases barriers and reaction is actually preferred at sites that have one ortho-F. Thus, as discussed above, HDF at \(\text{C}_6\text{F}_5\text{H}\) via the stepwise pathway favours the (ortho) C1-position and similarly the 1-position is kinetically preferred for 1,2,3,4-\(\text{C}_6\text{F}_4\text{H}_2\), 1,2,3,5-\(\text{C}_6\text{F}_4\text{H}_2\) and 1,2,3-\(\text{C}_6\text{F}_4\text{H}_1\) (see data in bold text, Fig. 8). 1,2,4-\(\text{C}_6\text{F}_3\text{H}_3\) provides an interesting example where the substrate has two distinct C–F bonds, each of which has one ortho-F substituent. In this case the regioselectivity is governed by the meta-substituents: the F4 substituent (meta to C2) weakens the C2–F2 bond and so favours HDF at this position over C1 (which has no meta-F substituents).
(HDF) of fluoroarenes, C₆F₆₋ₙHₙ, (n = 0–5) at catalysts of the type [Ru(NHC)(PR₃)₂(CO)(H)₂]. The calculations characterise two mechanisms for the HDF process, each based on nucleophilic attack of a hydride ligand at the fluoroarene substrate. The first involves a concerted process with Ru–H/C–F exchange occurring in one step, while the second is a stepwise pathway in which the rate-determining C–F bond cleavage transition state leads to formation of HF and a Ru–σ-fluoroaryl complex. For the reaction of C₆F₆H, comparison of the full experimental system (NHC = IMes, R = Ph) with a small model system (NHC = IMe, R = Me) shows that HDF is promoted experimentally through (i) more facile initial PR₃/fluoroarene substitution and (ii) the ability of the NHC ligand to stabilise the key C–F bond breaking transition state along the stepwise pathway through stabilising F···HC interactions. This latter effect is maximised when the site of HDF has an ortho-H substituent and so accounts for the ortho-selectivity seen in the reaction of C₆F₆H to give 1,2,3,4-C₆F₄H₂.

An analysis of trends in the C–F bond dissociation energies (BDE) in C₆F₆₋ₙHₙ (n = 0–5) species shows that these generally become stronger with larger n and that the most important factor in determining the BDE is the number of ortho-F substituents. The combination of this with the opposite trend in the C–H BDEs means that the thermodynamics of HDF become somewhat less favourable with increased n. However, this process is always significantly exothermic when driven by a silane such as Me₃SiH as terminal reductant. Computed barriers also generally increase with greater n, and for the concerted pathway a good correlation between C–F BDE and barrier height is seen. In this case reaction is directed to sites with two ortho-F substituents, as these have the weakest C–F bonds. For the stepwise pathway, the difficulty of accommodating ortho-F substituents in the key C–F bond cleavage transition state means that the reaction is directed to sites with only one ortho-F substituent. Thus the two mechanisms have complementary regioselectivities. Calculations on the HDF of lower fluorinated substrates (n > 1) at [Ru(IMes)(PPh₃)₂(CO)(H)₂] predict that 1,2,3,4-C₆F₄H₂ and 1,2,3,5-C₆F₄H₂ are the most viable targets for this process and that these would both react with ortho-selectivity to give 1,2,3-C₆F₃H₃ and 1,2,4-C₆F₄H₅, respectively.

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**References**

10. We exclude from discussion here the HDF of heteroaromatic substrates such as pentafluoropyridine for which there is a rich reaction chemistry. See ref. 7b–e and references therein.
Dalton Transactions


22 NHC abbreviations: SIMes = 1,3-bis-(2,4,6-trimethylphenyl)-imidazolin-2-ylidene; SIPr = 1,3-bis-(2,6-diisopropylphenyl)-imidazolin-2-ylidene; IMes = 1,3-bis-(2,4,6-trimethylphenyl)-imidazolin-2-ylidene; IMes = 1,3-bis-(2,6-diisopropylphenyl)-imidazolin-2-ylidene; IPr = 1,3-bis-(2,6-diisopropylphenyl)-imidazolin-2-ylidene; SIPr = 1,3-bis-(2,6-diisopropylphenyl)-imidazolin-2-ylidene.; iPr = 1,3-bis-(2,6-diisopropylphenyl)-imidazolin-2-ylidene.


31 Computed free energies confirm the preference for reaction via the stepwise pathway, the barrier being 65.0 kJ mol$^{-1}$ compared to 85.0 kJ mol$^{-1}$ for the concerted pathway.

32 The corresponding solvent-corrected free energy activation barriers are 65.0 kcal mol$^{-1}$, 74.5 kJ mol$^{-1}$ and 70.3 kJ mol$^{-1}$ for reaction at the ortho-, meta- and para-positions respectively.


35 This trend is consistent with the available experimental data (C$_6$F$_6$: BDE = 485 ± 25 kJ mol$^{-1}$; C$_6$H$_2$: BDE = 525.5 ± 8.4 kJ mol$^{-1}$).

36 In all cases, when there is a choice, we have only considered the orientation of the fluoroarene that directs the ortho- or meta-C–H bonds towards the NHC ligand.

37 Although the computed barriers are always higher along the concerted pathway, it is noticeable that a preference for reaction at sites with two ortho-F substituents is retained for this mechanism, as seen with Model 3.