Mechanistic Study of Ru-NHC-Catalyzed Hydrodefluorination of Fluoropyridines: The Influence of the NHC on the Regioselectivity of C−F Activation and Chemoselectivity of C−F versus C−H Bond Cleavage

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Supporting Information

ABSTRACT: We describe a combined experimental and computational study into the scope, regioselectivity, and mechanism of the catalytic hydrodefluorination (HDF) of fluoropyridines, C\textsubscript{x}F\textsubscript{3}H\textsubscript{2}N (x = 0−2), at two Ru(NHC)-(PPh\textsubscript{3})\textsubscript{2}(CO)\textsubscript{2} catalysts (NHC = IPr, 1, and IMes, 2). The regioselectivity and extent of HDF is significantly dependent on the nature of the NHC: with 1 HDF of C\textsubscript{5}F\textsubscript{5}N is favored at the ortho-position and gives 2,3,4,5-C\textsubscript{5}F\textsubscript{4}H\textsubscript{3}N as the major product. This reacts on to 3,4,5-C\textsubscript{5}F\textsubscript{4}H\textsubscript{2}N and 2,3,5-C\textsubscript{5}F\textsubscript{4}H\textsubscript{2}N, and the latter can also undergo further HDF to 3,5-C\textsubscript{5}F\textsubscript{4}H\textsubscript{2}N and 2,5-C\textsubscript{5}F\textsubscript{4}H\textsubscript{2}N. para-HDF of C\textsubscript{5}F\textsubscript{5}N is also seen and gives 2,3,5,6-C\textsubscript{5}F\textsubscript{4}H\textsubscript{3}N as a minor product, which is then inert to further reaction. In contrast, with 2, para-HDF of C\textsubscript{5}F\textsubscript{5}N is preferred, and moreover, the 2,3,5,6-C\textsubscript{5}F\textsubscript{4}H\textsubscript{3}N regioisomer undergoes C−H bond activation to form the catalytically inactive 16e Ru-fluoropyridyl complex Ru(IMes)(PPh\textsubscript{3})(CO)(4-C\textsubscript{5}F\textsubscript{4}N)H. 3. Density functional theory calculations rationalize the different regioselectivity of HDF of C\textsubscript{5}F\textsubscript{5}N at 1 and 2 in terms of a change in the pathway that is operating with these two catalysts. With 1, a stepwise mechanism is favored in which a N−Ru σ-interaction stabilizes the key C−F bond cleavage along theortho-HDF pathway. With 2, a concerted pathway favoring para-HDF is more accessible. The calculations show the barriers increase for the subsequent HDF of the lower fluorinated substrates, and they also correctly identify the most reactive C−F bonds. A mechanism for the formation of 3 is also defined, but the competition between C–H bond activation and HDF of 2,3,5,6-C\textsubscript{5}F\textsubscript{4}H\textsubscript{3}N at 2 (which favors C−H activation experimentally) is not reproduced. In general, the calculations appear to overestimate the HDF reactivity of 2,3,5,6-C\textsubscript{5}F\textsubscript{4}H\textsubscript{3}N at both catalysts 1 and 2.

KEYWORDS: catalysis, hydrodefluorination, DFT, mechanism, ruthenium, pentafluoropyridine, N-heterocyclic carbene

INTRODUCTION

Efforts to develop new synthetic routes to aromatic fluorocarbons are driven primarily by the important role that C−F-containing molecules play in the pharmaceutical and agrochemical industries, as exemplified by the molecules shown in Chart 1.1 In the cases of compounds such as Tivicay or Sitagliptin,2 one hypothetical approach to the preparation of the fluorinated substrates would be via a metal-catalyzed hydrodefluorination (HDF) reaction of a pentafluorophenyl ring.3

However, significant obstacles first need to be overcome to realize such processes.4 In most of the cases of either stoichiometric or catalytic C−F bond activation reported thus far, bond cleavage becomes more difficult as the number of fluorine substituents decreases, and so whereas transforming a −C\textsubscript{\textsubscript{6}}F\textsubscript{5} group to a −C\textsubscript{\textsubscript{5}}F\textsubscript{4}H group is well-established, the second and third HDF steps that would be necessary to realize −C\textsubscript{\textsubscript{6}}F\textsubscript{3}H\textsubscript{2} and −C\textsubscript{\textsubscript{6}}F\textsubscript{2}H\textsubscript{3} groups are far more challenging.5 Second, there needs to be control of regiochemistry to allow the targeted substitution of hydrogen atoms selectively into the desired positions. In the majority of catalytic HDF reactions that employ a simple model substrate such as C\textsubscript{6}F\textsubscript{6}H, functionalization of the C−F bond at the para-position takes place to generate 1,2,4,5-C\textsubscript{6}F\textsubscript{4}H\textsubscript{2}.6 This implies that even retaining the F para to the C−C bond in all three of the structures in Chart 1 might prove to be difficult, let alone the subsequent directed HDF at the ortho- and meta-positions. A third issue relates to chemoselectivity, in driving the more thermodynamically

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favorable C–F bond activation over the competitive and kinetically favored C–H activation. In 2009, we reported the catalytic HDF of C₆F₆, C₆F₅H and C₅F₅N by the ruthenium-based complexes Ru(NHC)-(PPh₃)₂(CO)H₂ (NHC = N-heterocyclic carbene) in the presence of alkysilanes (Scheme 1). This system showed a very unusual and remarkably high regioselectivity for HDF at an ortho-position, for example, converting C₆F₅H to 1,2,3,4-C₆F₄H₂ with 98% selectivity. Density functional theory (DFT) studies were able to explain this high ortho-selectivity on the basis of a novel nucleophilic hydride attack mechanism involving either a stepwise or concerted pathway. In the former stepwise process (Pathway 1, Scheme 2), C₆F₅H initially binds in an η²-fashion (I) which permits an intramolecular hydride attack to generate a metal-stabilized Meisenheimer intermediate (II). Loss of HF then produces an LnRu–C₆F₄H complex (III) which upon protonolysis eliminates 1,2,3,4-C₆F₄H₂. In the alternative concerted process (Pathway 2), direct Ru–H/C–F exchange takes place in an intermolecular fashion to generate 1,2,3,4-C₆F₄H₂ directly in a single step. For C₆F₅H, the stepwise pathway is more accessible. Moreover, the formation of the ortho-HDF product is favored over the meta- and para-isomers. This and subsequent work also highlighted how Pathway 1 favors HDF at sites adjacent to a C–H bond, as this allows access to what would otherwise be a sterically encumbered transition state.

In the initial experimental study, we also showed that C₅F₅N was far more reactive than C₆F₅H in terms of activity (total TON) and in undergoing more than a single HDF step, resulting in the formation of trifluoro- and difluoropyridines. Using a combined experimental and computational approach, we now describe a study aimed at defining the scope, regioselectivity, and mechanism of HDF across a series of fluoroypyridines using two Ru NHC catalysts, Ru(NHC)-(PPh₃)₂(CO)H₂ (NHC = IPr, 1 or IMes 2). The study reveals that the change of NHC in these catalysts has a significant impact not only on the regioselectivity and extent of the HDF reactivity but also on the chemoselectivity through competition with an alternative C–H bond activation process. DFT calculations are used to probe the possible mechanisms of the HDF reactions and explore the competition between C–F and C–H bond activation.

### RESULTS

**Experimental Studies on the Hydrodefluorination of C₅F₅−₆Hₓ (x = 0–2) with Ru(NHC)(PPh₃)₂(CO)H₂ (NHC = IPr 1, IMes 2).** The most active of the Ru-NHC catalysts, the N-diisopropylphenyl substituted species Ru(IPr)(PPh₃)₂(CO)H₂ (1), was initially employed for the HDF of a range of fluoroypyridines with Et₃SiH as the reductant. A summary of the catalytic results is shown in Table 1. Although HDF of C₅F₅N had previously been reported, this process was reinvestigated as a benchmark for comparison to other substrates. Thus, under a standard set of reaction conditions (28 h reaction at 343 K in THF with 10 mol % loading of 1), C₅F₅N underwent 90% conversion to a mixture of five products (Entry 1), which were identified on the basis of their ¹H and ¹⁹F NMR spectra as lower fluorne-containing species resulting from up to three HDF steps. The major product was 2,3,4,5-C₅F₄H,N, formed through activation of the C–F bond ortho to the pyridyl nitrogen; taken together with the amounts of 3,4,5-C₅F₃H₂N, 2,3,5-C₅F₃H₂N and 3,4-C₅F₂H₂N, ca. 80% of the products result from cleavage of an

![Scheme 1. Ru-Catalyzed HDF of C₅F₅H to 1,2,3,4-C₅F₄H₂](image)
ortho C–F bond, supporting the high regioselectivity of the Ru system.

Increasing the temperature to 363 K (Entry 2) or reaction time to 7 days at 343 K (Entry 3) promoted additional HDF. As a result, the percentage of products resulting from more than a single HDF step increased from ca. 30% at 343 K to 51% at 363 K and to 59% with the extended time. In both reactions, 3,4,5-C₅F₃H₂N was the major product as a result of HDF at the second ortho-position. Of note is that the modified conditions did not change the amount of 2,3,5,6-C₅F₄HN formed (relative to the standard reaction), indicating that this product is inert to further HDF; indeed, only a minimal amount of HDF was observed when 2,3,5,6-C₅F₄HN was used as the substrate in a catalytic run (Entry 4). ¹H and ³¹P{¹H} NMR spectra revealed that 1 was still fully intact (vide infra).

Interestingly, changing the ortho N-substituent from F (in 2,3,5,6-C₅F₄HN) to H (in 2,3,5-C₅F₂H₃N) resurrected some, albeit modest, HDF activity, producing the difluoropyridines, 3,5-C₅F₂H₂N and 2,5-C₅F₂H₂N (Entries 5 and 6). There was no evidence for further reduction to any mono-fluoropyridine products, consistent with the general paucity of catalytic systems in the literature able to react with mono- or difluorinated substrates.⁵e

In agreement with the previous results with C₆F₆ and C₆F₅H,⁸ the Ru-IMes complex 2 proved to be a less active catalyst for the HDF of C₅F₅N, giving ca. 60% conversion in 28 h at 343 K (Entry 7). Moreover, there was now a switch in the regioselectivity of the reaction, with the para-HDF product 2,3,5,6-C₅F₄HN present as the major component of the products. In this case, attempts to bring about HDF of 2,3,5,6-C₅F₄HN itself resulted instead in the loss of catalyst 2 through competitive C–H activation to afford the fluoroarylhydride complex, Ru(IMes)(PPh₃)(CO)(4-C₅F₄N)H (3). This pathway helps to account for the poorer catalytic activity of 2 toward C₅F₅N, as the catalyst is shunted off the catalytic cycle by C–H activation of the initial product of HDF. Interestingly,
C–H cleavage was not observed when 2,3,5,6-C₅F₄HN was changed to 2,3,5-C₅F₃H₂N, although only very low HDF activity was recorded, even with prolonged reaction times (Entries 8 and 9).

Isolation and Characterization of Ru(IMes)(PPh₃)(CO)-(4-C₅F₄N)H (3).

Complex 3 was fully characterized by multinuclear NMR spectroscopy and X-ray crystallography following isolation as dark orange crystals from a stoichiometric reaction of 2 with 2,3,5,6-C₅F₄HN at 323 K for 4 days. The X-ray crystal structure (Figure 1) displayed the anticipated square-based pyramidal structure with an apical hydride ligand. π-Stacking in the molecule is evidenced by a centroid-centroid distance of 3.52 Å between the aromatic rings based on C4 and C22 and the comparatively smaller distance of 3.40 Å between the fluoropyridyl ring and the phenyl group based on C28. The associated angles between the mean-planes of pairs of adjacent rings are 4.3° (rings based on C4 and C22) and 10.2° (rings based on C22 and C28), respectively. The achievement of the

**Scheme 3. Possible Mechanisms for Catalytic HDF of C₅F₅N at 1 and 2 To Give 2,3,4,5-C₅F₄HN**

*The numbering scheme used in the text is also shown for those atoms involved in the HDF reaction, where ring carbons take the same number as their F-substituent in C₅F₅N.*
latter occurs concomitantly with substantial deviation in the phosphine ligand, such that the P1–C28–C29–C30 angle has a value of 165.6° rather than an ideal value of 180°. The Ru–C_{fluoroaryl} distance is comparable to that found in the related coordinatively saturated analogue, Ru[ICy](dppp)(CO)(4-C_{5}F_{4}N)H (ICy = 1,3-dicyclohexylimidazol-2-ylidene; dppp =1,4-bis(diphenylphosphino)propane).

The solution NMR data were consistent with the solid-state structure. The low frequency (δ = 26.9) of the Ru–H resonance was indicative of a vacant trans-coordination site, while the doublet of doublet of doublets multiplicity resulted from the expected cis-^{19}P coupling, along with coupling to the two ortho-fluorines of the static C_{5}F_{5}N ligand. This lack of free rotation about the Ru–C_{fluoroaryl} bond led to the appearance of four separate ^{19}F signals at δ = 102, −105, −116, and −124. The two lowest frequency signals were assigned to those ortho to the Ru-bound carbon atom on the basis of ^{1}H–^{19}F HOESY and HMBC spectroscopy (Supporting Information).

**Computational Studies.** DFT calculations were undertaken to establish the mechanism of fluoropyridine HDF by 1 and 2 and to probe the factors controlling the different chemoselectivities observed with these two catalyst precursors. The calculations here employed the full experimental structures, as previous studies have shown the importance of the NHC ligand architecture in both promoting HDF and dictating the selectivity of that process.\(^{10,11}\) We report free energies calculated with the BP86 functional in the gas-phase and then corrected for both THF solvent (PCM approach) and dispersion effects (Grimme’s D3 parameter set) via single point energy calculations at the BP86-optimized geometries (see Computational Details).

A general HDF catalytic cycle is shown in Scheme 3, based on the reaction of C_{5}F_{4}N at the ortho position to give 2,3,4,5-C_{5}F_{4}HN. Starting from the 6-coordinate precursors (1 or 2) catalysis is initiated by loss of PPH_{3} to give the 16e dihydride intermediate A. Calculations showed PPH_{3} dissociation to be ca. 14 kcal/mol more accessible when trans to hydride than when trans to the NHC; this was also borne out experimentally by exchange reactions with PPH_{3}d_{15} (see Figures S11 and S12, Supporting Information). Moreover, the isomer formed in the latter process readily rearranges with a minimal barrier of around 3 kcal/mol to give the lower energy form with an axial hydride. As with our previous studies on fluorooarenes,\(^{10,11}\) two pathways for the HDF step have been characterized from Intermediate A. In Pathway 1, HDF proceeds in a stepwise, intramolecular fashion via the N-bound C_{5}F_{4}N complex B\(^{15}\) and leads to an analogous adduct of the 2,3,4,5-C_{5}F_{4}HN product, C. Dissociation then gives 16e Ru hydride fluoride D, which can react with trialkylsilanes to regenerate the active dihydride A. In Pathway 2, HDF is a concerted process in which 16e A reacts with C_{5}F_{4}N in an intramolecular fashion to generate the HDF product and hydride fluoride species D directly in one step.

**Reactions of C_{5}F_{4}N at 1.** We consider first the details of these two pathways for the HDF of C_{5}F_{4}N at 1, for which reaction at the ortho position is preferred experimentally. In the following, all free energies are quoted relative to the N-bound C_{5}F_{4}N adduct B, which is set to zero. The computed free energy profiles for HDF of C_{5}F_{4}N at the ortho position via Pathways 1 (stepwise) and 2 (concerted) are compared in Figure 2, with key computed structures shown in Figure 3. The first step along Pathway 1 is C_{5}F_{4}N addition to A to give adduct B with a computed binding free energy of 7.6 kcal/mol\(^{16}\) B is most stable as this N-bound form and exhibits a Ru–N distance of 2.30 Å. The most accessible alternative π-bound isomer is 3.1 kcal/mol higher in energy than B and binds through the C=C bond. This preference contrasts that observed experimentally\(^{17}\) or in calculations\(^{18}\) on Group 10 M(PR_{3})_{2}(C_{5}F_{4}N) species where a π-bound form is preferred, and this probably reflects the greater π-basicty of the bent {M(PR_{3})_{2}} fragments in those studies. A few N-bound adducts of C_{5}F_{4}N have been structurally characterized experimentally, with the most relevant here being cis-[Re(PPh_{3})(CO)_{4}(NC_{6}F_{5})][BAr_{4}^{+}] (Ar^{2} = 3,5-C_{6}H_{3}(CF_{3})_{2}) where the Re–N distance is 2.319(5) Å\(^{19}\) Several square-planar Pt(II) σ-adducts are also known,\(^{20}\) but none to date are known for Ru.

**Figure 2.** Computed Free Energy Profiles (BP86-D3(THF), kcal/mol) for HDF of C_{5}F_{4}N following PPH_{3} loss at 1 to give 2,3,4,5-C_{5}F_{4}HN via either stepwise Pathway 1 (via B) or concerted Pathway 2 (direct from A).
Stepwise HDF along Pathway 1 proceeds through an initial isomerization of B via TS(B−C)1 \( (G = +12.2 \text{ kcal/mol}) \) to give a \( \pi \)(C,N)-bound intermediate, Int(B−C)1 \( (G = +9.9 \text{ kcal/mol}; \text{Ru}−\text{N} = 2.34 \text{ Å}; \text{Ru}−\text{C}^6 = 2.39 \text{ Å}) \). The geometry of Int(B−C)1 is set up for attack of \( \text{H}^1 \) at the ring \( \text{C}^6 \) position and this proceeds via TS(B−C)2 \( (G = +14.0 \text{ kcal/mol}) \) with transfer of \( \text{H}^1 \) from \( \text{Ru} \) onto \( \text{C}^6 \) (\( \text{Ru}−\text{H}^1 = 1.71 \text{ Å}; \text{C}^6−\text{H}^1 = 1.68 \text{ Å} \)), and elongation of the \( \text{Ru}−\text{C}^6 \) and \( \text{C}^6−\text{F}^6 \) bonds to 2.45 and 1.41 Å, respectively. The \( \text{Ru}−\text{N} \) distance is not much altered at this point (2.32 Å), but it subsequently shortens significantly to 2.22 Å in Int(B−C)2 \( (G = −2.3 \text{ kcal/mol}) \), which also features an intact \( \text{C}^6−\text{H}^1 \) bond (1.10 Å) and further elongation of the \( \text{C}^6−\text{F}^6 \) distance (1.62 Å). The \{C\text{5F}5\text{HN}\} moiety in Int(B−C)2 therefore resembles a Meisenheimer intermediate formed by the intramolecular nucleophilic (S\text{N}Ar) attack of hydride. Consistent with this picture is the lengthening of both the \( \text{C}^6−\text{C}^5 \) and \( \text{C}^6−\text{N} \) distances to 1.45 and 1.40 Å, respectively (cf. 1.40 and 1.33 Å in free \( \text{C}_3\text{F}_3\text{N} \)), while the short \( \text{Ru}−\text{N} \) distance suggests significant stabilization via \( \text{N} \rightarrow \text{Ru} \) \( \sigma \)-donation. Int(B−C)2 represents a relatively late point on the \( \text{S} \)\text{N}Ar coordinate, as evidenced by the long \( \text{C}^6−\text{F}^6 \) distance and the increased NBO negative charge on \( \text{F}^6 \) \( (−0.46 \text{ cf. an average charge of } −0.31 \text{ on the remaining ring fluorines}) \). This fluoridic character also leads to short \( (<2.2 \text{ Å}) \) \( \text{F}^6−\text{H}−\text{C} \) contacts to two methine hydrogens on the IPr isopropyl substituents. Similar stabilizing interactions were noted in our previous study on HDF of \( \text{C}_5\text{F}_5\text{H} \) and were important in directing the \text{ortho} selectivity of that process.\(^{10,11}\) The onward reaction of Int(B−C)2 involves the facile cleavage of the weakened \( \text{C}^6−\text{F}^6 \) bond via TS(B−C)3 \( (G = +2.5 \text{ kcal/mol}; \text{C}^6−\text{F}^6 = 1.79 \text{ Å}; \text{Ru}−\text{F}^6 = 3.29 \text{ Å}) \), with F-transfer to \( \text{Ru} \) to give C, the \( \text{N} \)-bound adduct of \( 2,3,4,5-\text{C}_5\text{F}_4\text{HN} \) \( (G = −39.8 \text{ kcal/mol}) \). This contrasts with the computed mechanism with \( \text{C}_6\text{F}_5\text{H} \) where HF is formed at this stage,\(^{10,11}\) and possibly reflects the much shorter \( \text{C}^6−\text{H}^1 \) bond in the present case which being essentially fully formed is resistant to deprotonation. From C the catalytic cycle would be completed by dissociation of \( 2,3,4,5-\text{C}_5\text{F}_4\text{HN} \) \( (G = −39.8 \text{ kcal/mol}) \) to give 16e \( \text{D} \) \( (G = −29.9 \text{ kcal/mol}) \) followed by reduction with \( \text{Et}_3\text{Si}−\text{H} \) to regenerate \( \text{A} \). The barrier for the latter process has been calculated to be 11.1 kcal/mol.

Along Pathway 2 the hydride ligand \text{trans} to \text{CO} in \( \text{A} \) attacks \( \text{C}_3\text{F}_3\text{N} \) directly without any prior coordination of the fluoraromatic. The HDF proceeds in one step via TS(A-D) \( (G = +18.4 \text{ kcal/mol}) \) in which the \( \text{Ru}−\text{H}^1 \) distance has lengthened to 1.86 Å and the \( \text{C}^6−\text{H}^1 \) bond is beginning to form (\( \text{C}^6−\text{H}^1 = 1.40 \text{ Å} \)). This promotes a lengthening of the \( \text{C}^6−\text{F}^6 \)
bond to 1.45 Å and, as this lies parallel to the Ru–NHC bond, this also permits two short F···H–C contacts (2.41 and 2.27 Å) to develop to the IPr ligand which may further promote this process.21 TS(A–D) leads directly to 16e D and free 2,3,4,5-
C₅F₄HN. Of the two possible mechanisms considered for the ortho HDF of C₅F₅N at 1, stepwise Pathway 1 proceeds with a lower overall barrier of 14.0 kcal/mol, and therefore, this is clearly favored kinetically over concerted Pathway 2, which has an overall barrier of 18.4 kcal/mol.

To assess the overall regioselectivity of C₅F₅N HDF at 1, the reactions at the meta and para positions were also considered via both Pathways 1 and 2. Table 2 displays the computed free energies (relative to the N-bound adduct B) of the key stationary points for these processes, alongside those already discussed for HDF at the ortho position. For Pathway 2 very similar geometries were located for TS(A–D) to that seen above for ortho activation. Barriers indicate this pathway is slightly higher for the meta position (18.7 kcal/mol) but somewhat more accessible for the para position (16.1 kcal/mol).22 Along Pathway 1, the energy of TS(B–C)2 follows the same trend, and in each case, this transition state is computed to be lower in energy than TS(A–D). This pattern of reactivity (para > ortho > meta) is consistent with a nucleophilic attack mechanism and is also seen in the S₅Ar reactions of free C₅F₅N with simple alkoxide nucleophiles.23 For ortho HDF along Pathway 1 TS(B–C)2 is higher than the subsequent F-transfer transition state TS(B–C)3 and so TS(B–C)2 is rate-determining. However, this is no longer the case for HDF at the meta and para positions as now both Int(B–C)2 and TS(B–C)3 are significantly destabilized, reflecting the fact that no N → Ru stabilization is possible when HDF occurs at the remote meta and para positions. As a result TS(B–C)3 becomes the rate-limiting transition state for HDF at the meta and para positions via Pathway 1. This situation is similar to that seen previously for the HDF of C₅F₄H, where the C–F bond cleavage step along Pathway 1 (equivalent to TS(B–C)3 here) was rate-limiting for all three ortho-, meta-, and para-HDF reactions.24 The destabilization of TS(B–C)3 for meta and para HDF along Pathway 1 moves these above TS(A–D) computed for Pathway 2. The concerted pathway is therefore favored for these reactions, although as the difference in energy between the rate-limiting transition states is very small (<0.5 kcal/mol), one might expect both pathways to be operative.

For the reaction of C₅F₅N at 1, the overall computed order of reactivity is for HDF to occur at the ortho position (via Pathway 1, ΔG² = +14.0 kcal/mol) in preference to reaction at the para position (via Pathway 2, ΔG² = +16.1 kcal/mol) with reaction at the meta position least likely (via Pathway 2, ΔG² = +18.7 kcal/mol). This qualitatively reproduces the experimental observations where ortho-HDF dominates with minor products arising from para-HDF (Table 1, Entries 1–3). Table 2 also includes the equivalent data for HDF of C₅F₅N using the IMes-based catalyst 2. ortho-HDF proceeds in a similar fashion to that seen for 1, however for meta- and para-HDF a more stable form of Int(B–C)2 is implicated in the reaction. This new species, Int(B–C)2′, lies at +6.8 kcal/mol and −0.3 kcal/mol for meta- and para-HDF, respectively, and differs from Int(B–C)2 by a rotation of the {C₅F₅HN} moiety which allows the C–F bond adjacent to the sp³ carbon to lie parallel to the Ru–IMes bond. IRC calculations show that for the Ru-IMes system Int(B–C)2′ links directly to TS(B–C)3; see Figure S20 in the Supporting Information.25 This additional feature does not, however, affect the overall barriers to HDF at 2 as para-HDF is favored through TS(A–D) at +15.9 kcal/mol, while the rate-limiting transition state for meta-HDF is TS(B–C)2 at +17.7 kcal/mol.

Comparing the HDF profiles in Table 2 shows the energies of both Int(B–C)1 and TS(B–C)2 to be 2−4 kcal/mol higher for all three HDF processes when computed with the Ru-IMes system 2. TS(A–D) is also destabilized for ortho and meta HDF, although the effect here is smaller. Most significantly a change in ortho/para selectivity is seen, the most accessible reaction at 2 being HDF at the para position (via Pathway 2, ΔG² = +15.9 kcal/mol), followed by reaction at the ortho position (via Pathway 1, ΔG² = +16.8 kcal/mol) with the meta position again least favored (via Pathway 1, ΔG² = +17.7 kcal/mol). These changes are consistent with 2,3,5,6-C₅F₄HN being the dominant HDF product formed with 2, with smaller amounts of products (2,3,4,5-C₅F₄HN and 2,3,5,6-C₅F₄HN) arising from ortho-HDF being seen (see Table 1, Entry 7). The switch in mechanism appears to be related to the greater accessibility of Int(B–C)1 when formed with the IPr catalyst 1, which is then carried through to give a lower energy for TS(B–C)2 in this case.

HDF of Lower Fluorinated Substrates at 1. With Ru-IPr catalyst 1, the major initial product, 2,3,4,5-C₅F₄HN, can undergo further HDF to give 3,4,5-C₅F₄H₃N and 2,3,5-
C₅F₄H₃N. 3,4-C₅F₄H₃N is also seen in trace amounts in these initial runs, and this can only originate from 3,4,5-
C₅F₄H₃N (see Table 1 Entries 1–3). No HDF products derived from 2,3,5-C₅F₄H₃N are apparent, possibly as this species is only formed in relatively small amounts. Indeed, if 2,3,5-C₅F₄H₃N is introduced in a separate run as the sole substrate then formation of the HDF products 3,5-C₅F₄H₃N and 2,5-C₅F₄H₃N is seen (see Entries 5 and 6). In general, HDF becomes more difficult as the number of F-substituents

### Table 2. Computed Free Energies (kcal/mol) of Key Stationary Points Associated with HDF of the ortho, meta and para Positions of C₅F₅N via Pathways 1 and 2 at Catalysts 1 (NHC = IPr) and 2 (NHC = IMes)²⁴

<table>
<thead>
<tr>
<th>pathway</th>
<th>catalyst 1</th>
<th>Int(B–C)1</th>
<th>TS(B–C)2</th>
<th>Int(B–C)2</th>
<th>TS(B–C)3</th>
<th>TS(A–D)</th>
<th>catalyst 2</th>
<th>Int(B–C)1</th>
<th>TS(B–C)2</th>
<th>Int(B–C)2</th>
<th>TS(B–C)3</th>
<th>TS(A–D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ortho</td>
<td>+9.9</td>
<td>+14.0</td>
<td>–2.3</td>
<td>+2.5</td>
<td>+18.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>meta</td>
<td>+5.3</td>
<td>+16.2</td>
<td>+14.6</td>
<td>+19.0</td>
<td>+18.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>para</td>
<td>+3.1</td>
<td>+11.2</td>
<td>+8.8</td>
<td>+16.6</td>
<td>+16.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ortho</td>
<td>+12.5</td>
<td>+16.8</td>
<td>+2.5</td>
<td>+3.1</td>
<td>+20.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>meta</td>
<td>+7.2</td>
<td>+17.7</td>
<td>+15.8</td>
<td>+6.8⁺</td>
<td>+16.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+19.3</td>
<td></td>
</tr>
<tr>
<td>para</td>
<td>+6.8</td>
<td>+14.5</td>
<td>+12.7</td>
<td>−0.3⁴⁺</td>
<td>+17.2</td>
<td>+15.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

²⁴All energies are quoted relative to adduct B at 0.0 kcal/mol for each system. An Alternative forms of Int(B–C)2 are implicated in the reaction profile: see text for details.

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<sup>21</sup> Supporting Information.25 This additional feature does not, however, affect the overall barriers to HDF at 2 as para-HDF is favored through TS(A–D) at +15.9 kcal/mol, while the rate-limiting transition state for meta-HDF is TS(B–C)2 at +17.7 kcal/mol.

<sup>22</sup> Comparing the HDF profiles in Table 2 shows the energies of both Int(B–C)1 and TS(B–C)2 to be 2−4 kcal/mol higher for all three HDF processes when computed with the Ru-IMes system 2. TS(A–D) is also destabilized for ortho and meta HDF, although the effect here is smaller. Most significantly a change in ortho/para selectivity is seen, the most accessible reaction at 2 being HDF at the para position (via Pathway 2, ΔG² = +15.9 kcal/mol), followed by reaction at the ortho position (via Pathway 1, ΔG² = +16.8 kcal/mol) with the meta position again least favored (via Pathway 1, ΔG² = +17.7 kcal/mol). These changes are consistent with 2,3,5,6-C₅F₄HN being the dominant HDF product formed with 2, with smaller amounts of products (2,3,4,5-C₅F₄HN and 2,3,5,6-C₅F₄HN) arising from ortho-HDF being seen (see Table 1, Entry 7). The switch in mechanism appears to be related to the greater accessibility of Int(B–C)1 when formed with the IPr catalyst 1, which is then carried through to give a lower energy for TS(B–C)2 in this case.

**HDF of Lower Fluorinated Substrates at 1.** With Ru-IPr catalyst 1, the major initial product, 2,3,4,5-C₅F₄HN, can undergo further HDF to give 3,4,5-C₅F₄H₃N and 2,3,5-
C₅F₄H₃N. 3,4-C₅F₄H₃N is also seen in trace amounts in these initial runs, and this can only originate from 3,4,5-
C₅F₄H₃N (see Table 1 Entries 1–3). No HDF products derived from 2,3,5-C₅F₄H₃N are apparent, possibly as this species is only formed in relatively small amounts. Indeed, if 2,3,5-C₅F₄H₃N is introduced in a separate run as the sole substrate then formation of the HDF products 3,5-C₅F₄H₃N and 2,5-C₅F₄H₃N is seen (see Entries 5 and 6). In general, HDF becomes more difficult as the number of F-substituents...
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distributions seen experimentally.

In contrast, the computational modeling of the lower reactivity of the 2,3,5,6-C₅F₄HN isomer has been less successful. This species is formed as a minor HDF product of C₅F₅N with 1 and, compared to the 2,3,4,5-C₅F₄HN isomer, is far more reluctant to undergo any further HDF reactions, despite both fluoropyridines having four remaining F-substituents (Table 1, Entry 4). HDF of 2,3,5,6-C₅F₄HN is computed to have rate-limiting transition states at 17.4 and 19.3 kcal/mol for the ortho- and meta-positions, respectively. Although these indicate a significantly lower reactivity than C₅F₅N, these barriers are both lower than the most accessible HDF transition state of the 2,3,4,5-isomer (20.3 kcal/mol), predicting that 2,3,5,6-C₅F₄HN should be amenable to HDF, in contrast to what is observed experimentally. Instead, 2,3,5,6-C₅F₄HN yields only trace amounts of the ortho HDF product under standard conditions (Table 1, Entry 4). The accessibility of HDF in 2,3,5,6-C₅F₄HN is therefore overestimated in the current approach (see Discussion below).

C–H Bond Activation of 2,3,5,6-C₅F₄HN at 2. HDF of C₅F₅N by Ru-IMes catalyst 2 leads to 2,3,5,6-C₅F₄HN and the calculations indicate this change in regioselectivity (compared to catalyst 1) arises as Pathway 2 is operative and directs HDF to the para position (see Table 2). In further contrast to the situation with 1, the IMes system then reacts further with 2,3,5,6-C₅F₄HN to give the C–H activated product 3. The computed mechanism for this process is shown in Figure 5 and

Figure 4. Free energies (kcal/mol) of rate-limiting transition states for the HDF of fluoropyridines CₓFₓ−xHₓN (x = 0–2) at catalyst 1. Two values corresponding to Pathway 1/Pathway 2 are shown for each unique C–F bond, and all energies are quoted relative to the relevant N-bound precursor adduct B at 0.0 kcal/mol. Only isomers implicated in the experimental studies are shown.

Figure 5. Computed free energy profile (BP86-D3(THF), kcal/mol) for C–H activation of 2,3,5,6-C₅F₄HN following PPh₃ loss at 2 to give 3. The inset provides barriers for the competing barriers to HDF via Pathway 1/Pathway 2. All energies are relative to the N-bound adduct of 2,3,5,6-C₅F₄HN set to 0.0 kcal/mol. The numbering of key atoms is E, +5.7 kcal/mol) for C–H activation is therefore overestimated in the current approach (see Discussion below).
HDF processes. These were therefore also computed (see inset, Figure 5) and predict an HDF barrier at the ortho-position of only 16.7 kcal/mol, indicating this process should be competitive with C–H activation. Experimentally HDF does not occur to any significant extent in this system and so it again appears that the HDF reactivity of 2,3,5,6-C₅F₄HN is being overestimated in the present calculations.

**DISCUSSION**

Catalytic HDF reactions of C₅F₅N have been explored both experimentally and computationally with the Ru-IPr and Ru-IMes catalysts 1 and 2. Experimentally HDF proceeds quite differently with these two species. With 1 HDF is favored at the ortho-position to give 2,3,4,5-C₅F₄HN which can undergo further HDF to 3,4,5-C₅F₃H₂N and 2,3,5-C₅F₃H₂N. Isolated 2,3,5-C₅F₃H₂N was also shown to undergo HDF to give 3,5-C₅F₃H₂N and 2,5-C₅F₃H₂N. The initial HDF of C₅F₅N also gives 2,3,5,6-C₅F₄HN as a minor product, but this species is then inert to any further reaction. In contrast with 2, HDF of C₅F₅N is favored at the para-position and gives 2,3,5,6-C₅F₄HN as the major product. This, however, then undergoes C–H activation to produce fluoropyridyl complex 3 which, being inactive as an HDF catalyst, shuts down any further reactivity.

DFT calculations have defined two possible mechanisms for these HDF reactions based on nucleophilic attack by a hydride ligand in either a stepwise process (Pathway 1) or a concerted process (Pathway 2). Pathway 1 involves a π-bound substrate and favors ortho-HDF as this is stabilized by a direct N → Ru interaction in the key C–F bond cleavage transition state. Pathway 2 more resembles a conventional S_NAr process and so favors reaction at the para-position. A change in the preferred pathway between catalysts 1 (Pathway 1) and 2 (Pathway 2) captures the different regioselectivities seen experimentally with C₅F₅N, despite the relatively subtle change of NHC from IPr to IMes. This change in the preferred mechanism appears to be linked to the stronger binding of the π-bound intermediate, Int(B–C)1, when formed with 1. Further calculations on the reactivity of the IPr system reproduced the trends seen in the subsequent HDF reactions of 2,3,4,5-C₅F₄HN, and correctly identified the most likely sites for the two subsequent HDF steps that give isomers of C₅F₃H₂N and C₅F₂H₃N. In most cases, experiment and calculations showed two alternative HDF processes to be in close competition, and the precise product distributions were not always correctly modeled in the calculations. However, the differences in energy that are reflected in these product distributions are small and do not represent a significant absolute error in the calculations.

A more significant issue is the apparent difficulty in modeling the reactivity of 2,3,5,6-C₅F₄HN, which the calculations indicate should be amenable to further HDF with both catalysts 1 and 2. We therefore considered (i) the functional-dependency of our results and (ii) whether an alternative mechanism may be in play. To address point (i) we first recomputed the energies of the most accessible HDF transition states of 2,3,4,5-C₅F₄HN and 2,3,5,6-C₅F₄HN at IPr catalyst 1 with a range of different functionals: BP86, BLYP, B3LYP, PBE, PBE0 (both with and without a dispersion correction); M06, M06L; B97D, B97D3 and ωB97xD, giving a total of 15 different approaches (see Table S2 in the Supporting Information). With our standard BP86-D3(THF) protocol these HDF transition states are at +20.3 kcal/mol and +17.4 kcal/mol, respectively, a difference of 2.9 kcal/mol indicating (incorrectly) a preference for HDF at 2,3,5,6-C₅F₄HN. This preference, however, is remarkably consistent across all 15 computational methods, ranging from 4.2 to 2.5 kcal/mol. Similarly, we reassessed the difference between C–H activation and HDF of 2,3,5,6-C₅F₄HN at catalyst 2. In this case the BP86-D3(THF) protocol gave barriers of 17.1 and 16.7 kcal/mol, respectively, favoring HDF by 0.4 kcal/mol; this preference was again reproduced by the other 15 methods tested. Our results are therefore not functional dependent.

To address point (ii), the possibility of an alternative mechanism, we considered the initial oxidative addition of C₅F₅N to form a Ru(IV) fluoropyridyl intermediate Ru(NHC)-(PPh₃)(CO)(F)H(C₅F₄N). This was done for NHC = IPr and gave barriers of 26.8 and 22.3 kcal/mol for activation at the ortho- and para-positions, respectively. These values rule out oxidative addition as a viable process, being between 6 to 12 kcal/mol higher than the most accessible hydride attack transition states (as well as predicting a para-selectivity not seen experimentally). At present, we are therefore unable to account for the anomalous results obtained in modeling the
reactivity of 2,3,5,6-C$_5$F$_4$HN at these Ru(NHC)(PPh$_3$)$_2$(CO)(H)$_2$ catalysts, and the reasons for this will be the subject of future work.

### CONCLUSIONS

We have reported here a joint experimental and computational study of the catalytic hydrodefluorination (HDF) reactions of C$_5$F$_5$N at Ru(NHC)(PPh$_3$)$_2$(CO)H$_2$, where NHC = IPr (1) or IMes (2). The observed reactivity is highly dependent on the NHC ligand. With catalyst 1, HDF occurs preferentially at the ortho-position to give 2,3,5,6-C$_5$F$_4$HN, while para-HDF forms 2,3,5,6-C$_5$F$_4$HN as a minor product. 2,3,5,6-C$_5$F$_4$HN can then undergo further HDF to 3,4,5-C$_5$F$_4$HN$_2$ and 2,3,5-C$_5$F$_4$HN. Isolated 2,3,5-C$_5$F$_4$HN also undergoes HDF to give 3,5-

The following reactivity of 2,3,5,6-C$_5$F$_4$HN at 1 and 2 is explained by the DFT calculations in terms of a competition between two different pathways, both based on nucleophilic attack by a hydride ligand. With 1, a stepwise process is operative that proceeds through a β-bound intermediate and favors ortho-HDF as this is stabilized by a direct N → Ru interaction in the key C–F bond cleavage transition state. With 2, a concerted process is more accessible and favors para-HDF, similar to a conventional S$_\text{N}$Ar process. The calculations give increased (but accessible) barriers for the subsequent HDF reactions to give isomers of C$_5$F$_5$H$_2$N and C$_5$F$_3$H$_2$N and also correctly identify the most reactive C–F bonds. The calculations systematically overestimate the HDF reactivity of 2,3,5,6-C$_5$F$_4$HN at both catalyst 1 (where no HDF reaction is seen experimentally) and at catalyst 2 (where C–H activation occurs preferentially).

### EXPERIMENTAL SECTION

All manipulations were carried out using standard Schlenk, high vacuum and glovebox techniques using dried and degassed solvents, unless otherwise stated. NMR spectra were recorded on Bruker Avance 400 and 500 MHz NMR spectrometers and referenced to residual solvent signals for $^1$H and $^{13}$C spectra for C$_6$D$_6$ (δ 7.15, 128.00), THF-d$_8$ (δ 3.58, 25.4) and toluene-d$_8$ (δ 2.09). $^{31}$P($^1$H) and $^{19}$F spectra were referenced externally to residual solvent signals for $^1$H and $^{13}$C spectra for C$_6$D$_6$, 298 K).

$^1$H NMR (400 MHz, C$_6$D$_6$, 298 K): δ 7.33–7.27 (m, 6H, C$_6$H$_3$), 6.98–6.88 (m, 9H, C$_6$H$_3$), 6.79 (s, 2H, C$_6$H$_3$Me$_2$), 6.74 (s, 2H, C$_6$H$_3$Me$_2$), 6.18 (s, 2H, NCH$_2$), 2.18 (s, 6H, C–CH$_3$), 2.10 (s, 6H, C–CH$_3$), 1.96 (s, 6H, C–CH$_3$), −26.20 (dd, $^3$J$_{HF}$ = 23.7 Hz, $^3$J$_{HF}$ = 6.0 Hz, $^3$J$_{HF}$ = 3.3 Hz, 1H, Ru-H). $^{13}$C($^1$H) NMR (101 MHz, C$_6$D$_6$, 298 K): δ 202.6 (br s, Ru-CO), 189.9 (d, $^3$J$_{CP}$ = 84 Hz, Ru-C$_6$H$_5$), 138.8 (s, N-C$_6$H$_5$), 136.9 (s, p-C$_6$H$_4$Me$_2$), 135.6 (s, o-C$_6$H$_4$Me$_2$), 135.5 (d, $^3$J$_{CP}$ = 93.5 Hz, P-C$_6$H$_5$), 134.0 (d, $^3$J$_{CP}$ = 11.8 Hz, PC$_6$H$_5$), 129.6 (d, $^3$J$_{CP}$ = 1.6 Hz, PC$_6$H$_5$), 129.4 (d, $^3$J$_{CP}$ = 3.1 Hz, PC$_6$H$_5$), 128.0 (s, m-C$_6$H$_4$Me$_2$), 127.9 (s, m-C$_6$H$_4$Me$_2$), 122.9 (s, NCH), 122.8 (s, NCH), 21.0 (s, CCH$_2$), 18.4 (s, CCH$_3$), 18.3 (s, CCH$_3$). $^{31}$P($^1$H) NMR (161 MHz, C$_6$D$_6$, 298 K): δ 173.9 (dq, $^3$J$_{PP}$ = 10.0 Hz, 1P), $^3$J$_{FP}$ = 12.6 Hz, 1F), $^3$J$_{FP}$ = 3.3 Hz, 1F), $^3$J$_{FP}$ = 1.6 Hz, 1F). IR (KBr, cm$^{-1}$): 1932 ($\nu_{CO}$). Anal. Calcd (%) for C$_6$H$_5$P$_2$O$_2$PN: 846.86: C, 63.82; H, 4.76; N, 4.96. Found: C, 63.63; H, 4.54; N, 5.04.

**Procedures for Catalytic HDF Experiments.** A J Young’s resealable NMR tube was charged with 1 or 2 (0.01 M), fluoropyridine substrate (0.1 M) and Et$_3$SiH (0.2 M) in THF and a standardized capillary tube of a THF solution of α,α,α-trifluorotoluene inserted. An initial $^{19}$F NMR spectrum was recorded and the tube heated to the required temperature in an oil bath. $^{19}$F NMR spectra of the products were integrated relative to the internal standard and identified by comparison to authentic samples from commercial suppliers.

**X-ray Crystallography.** Single crystals of 3 were analyzed using a Nonius Kappa CCD diffractometer. Data were collected using Mo Kα radiation throughout. Details of the data collections, solutions, and refinements are given in the Supporting Information. The structure was solved using SHELXS-97 and refined using full-matrix least-squares in SHELXL-97.

Crystallographic data for compound 3 has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1021392. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax (+44) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk].

**Computational Details.** DFT calculations were run with Gaussian 03 (Revision D.01) and Gaussian 09 (Revision D.01) Ru, P and Si centers were described with the Stuttgart RECPs and associated basis sets with additional polarization on P ($\zeta = 0.387$) and Si ($\zeta = 0.284$), and 6-31G** basis sets were used for all other atoms. Initial BP86 optimizations were performed with Gaussian 03, with all stationary points being fully characterized via analytical frequency calculations as either minima (all positive eigenvalues) or transition states (one negative eigenvalue). IRC calculations and subsequent geometry optimizations were used to confirm the minima linked by each transition state. For each transition state, several possible orientations of the fluoropyridine moiety were tested and the most stable geometries/energies are reported in the main text. PCM corrections for the effects of THF solvent ($\varepsilon = 7.43$) were computed with Gaussian 09 and dispersion corrections applied using Grimme’s D3 parameter set using the BP86-optimized geometries. Functional dependency was assessed for a number of key stationary points via single point calculations with 15 different approaches (see Table S2, Supporting Information).

**ASSOCIATED CONTENT**

**Supporting Information**

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/cs501644r.
X-ray crystallographic data for 3 (CIF)
NMR spectra for 3, phosphate exchange experiments for 1 and 2, computed structures and energies for all computational results (PDF)

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Notes
The authors declare no competing financial interest.

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■ REFERENCES

(5) Access to low F-containing products typically requires very forcing conditions and/or high catalyst loadings,
(11) NH abbreviations: IPr = 1,3-bis(2,6-disopropylphenyl)imidazol-2-ylidene; IMes = 1,3-bis(2,6-bis(trifluoromethyl)phenyl)imidazol-2-ylidene.
(14) Free energies for PPh₃/C,F,N exchange at 1 and 2 were computed to be +20.0 kcal/mol and +15.6 kcal/mol respectively at the BP86-D3(THF) level, but as reported by others, these values show a significant functional dependence (see Table S2, Supporting Information). The precise free energy change for this pre-equilibrium will affect the overall barrier for HDF; although here we have focussed on the regioselectivity of the subsequent HDF process. (a) Minenkov, A. E.; Occhipinti, G.; Jensen, V. R. J. Phys. Chem. A 2009, 113, 11833–11844.
(15) In comparison, the free energies for binding Et₂SiH or a THF solvent molecule at A are 8.0 and 0.3 kcal/mol, respectively.
(18) Other examples of this type of hydride attack mechanism proceeding with para-selectivity at C,F,N have been reported, see: (a) Beltrán, T. F.; Feliz, M.; Illas, R.; Mata, J. A.; Safont, V. S. Organometallics 2011, 30, 290–297. (b) LV, H.; Cai, Y.-B.; Zhang, J.-L. Angew. Chem., Int. Ed. 2013, 52, 3203–3207.
(20) In our previous C₅,F₅,H studies, a Ru-C₅,F₅,H fluorooaryl intermediate was located which underwent facile protonolysis by HF released in the C-F bond cleavage step. For meta- and para-HDF with C₅,F₅,N no equivalent Ru-C₅,F₅,H intermediate was located and IRCs showed TS(B-C) led directly to D + the free C₅,F₅,HN product.
(21) Analogous structures to Int(B-C)2 can be located for the IPr system with G = +3.0 kcal/mol and +11.2 kcal/mol for meta- and para-HDF respectively. However, in these cases, they do not link to TS(B-C) and so do not lie directly on the HDF reaction profile.
(22) (a) Sheldrick, G. M. Acta Crystallogr., Sect. A 1990, 46, 467–473. (b) Sheldrick, G. M. SHELXL-97, a computer program for crystal
structure refinement; University of Gottingen: Gottingen, Germany, 1997.


