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Communication

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Round-Trip Oxidative Addition, Ligand Metathesis, and Reductive Elimination in a P^{III}/P^{V} Synthetic Cycle

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Supporting Information Placeholder

ABSTRACT: A synthetic cycle for aryl C–F substitution comprising oxidative addition, ligand metathesis, and reductive elimination at a C_s-symmetric phosphorus triamide (**1**, P{N[*o*-NMe–C_6H_4]$_2$}) is reported. Reaction of **1** with perfluoroarenes (Ar^F–F) results in C–F oxidative addition yielding fluorophosphoranes **1**•[F][Ar^F]. The *P*-fluoro substituent is exchanged for hydride by treatment with DIBAL-H, generating hydridophosphoranes **1**•[H][Ar^F]. Heating of **1**•[H][Ar^F] regenerates **1** by C–H reductive elimination of Ar^F–H, where experimental and computational studies establish a concerted but highly asynchronous mechanism. The results provide well-characterized examples of the full triad of elementary mechanistic aryl C–X substitution steps at a single main-group site.

Oxidative addition, ligand metathesis (transmetalation), and reductive elimination are the elementary mechanistic steps by which numerous aryl C–X substitution reactions are enabled. Round-trip sequencing of these steps is well-known for the late transition metals, enabled by the kinetically and thermodynamically favorable two-electron redox reactivity of the *d*-block elements.[1] Despite significant recent advances in oxidative addition (OA) and reductive elimination (RE) at main-group element centers,[2,3] the realization of an analogous mechanistic triad with *p*-block elements is beset by poor energetic parity among oxidation states $E^{n/n+2}$ that favors unidirectional OA or RE. For instance, low-valent group 13/14 compounds cleave aryl C–X bonds by OA (Figure 1A, *left*),[4-9] but RE from high-valent compounds of these electropositive elements is rare.[10,11] Complementarily, aryl C–H RE from high-valent Group 16/17 compounds have been described (Figure 1B, *right*),[12-15] but OA to the low-valent state of such electronegative elements is challenging.

The central position of the group 15 elements within the *p*-block results in moderate electronegativities and accessible $E^{III/V}$ redox couples[16-19] useful for aryl functionalization. Recent excellent examples by McNally[20] (for heteroaryl functionalization via a $P^V \rightarrow P^{III}$ RE step) and Cornella[21] (for functionalization of aryl boron compounds via a $Bi^V \rightarrow Bi^{III}$ RE step) are paradigmatic; nonetheless the high-valent arylpnictogen(V) intermediates are accessed via the use of an exogenous oxidant (S^{VI} reagent in the former, 'F^+' reagent in the latter), not aryl C–X OA. Indeed, while both OA[22-24] and RE[12,25] are independently known within the P^{III}/P^{V} couple, no single system exhibits the full suite of elementary steps in the aryl C–X substitution mechanism. Here, we report well-defined stoichiometric reactions atop a single phosphorus platform that trace a closed P^{III}/P^{V} synthetic loop comprising aryl C–F OA and aryl C–H RE interposed with F→H ligand metathesis (Figure 1B).[26] These results establish the redox equipoise of the P^{III}/P^{V} couple as required for OA/RE round-tripping, providing a further basis for forward-going development of group 15 promoted aryl C–X substitution chemistry.

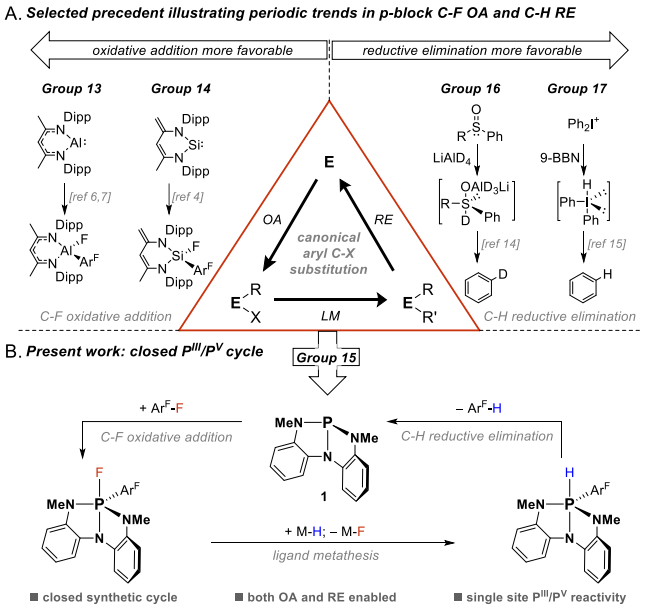

Figure 1. (A) Selected examples of main-group oxidative addition and reductive elimination reactions. (*left*) C–F oxidative addition to Group 13/14 compounds; (*right*) C–H reductive elimination from Group 16/17 compounds. (B) Phosphorus-centered two-electron redox cycle for aryl C–F substitution.

On the basis of prior research showing that C_s-symmetric σ^3-phosphorus triamide **1** undergoes reversible OA/RE of amine N–H substrates,[23] we considered whether this compound would be energetically poised to support the targeted elementary aryl substitution reactions. As depicted in Figure 2, reaction of **1** with the perfluoroarenes—aryl C–X compounds otherwise known as nucleophilic aromatic substitution (S_NAr)

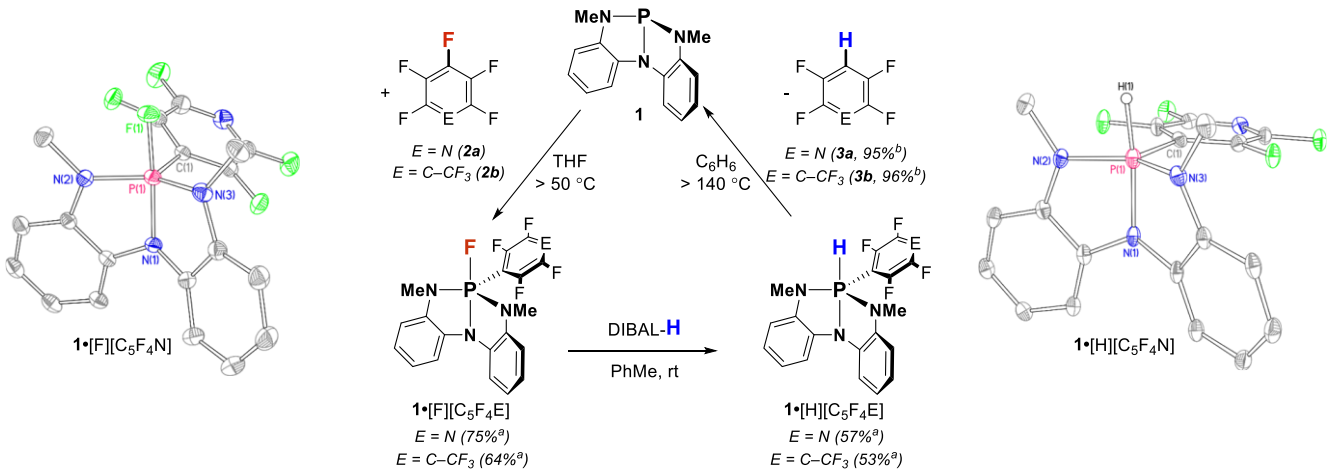

Figure 2. P^{III}/P^{V} synthetic cycle on **1** comprising aryl C–F oxidative addition, F→H ligand metathesis, and C–H reductive elimination. Thermal ellipsoid plots of intermediates **1**•[F][C_5F_4N] (left) and **1**•[H][C_5F_4N] (right) are rendered at the 50% probability level. Hydrogen atoms except H(1) in **1**•[H][C_5F_4N] are omitted for clarity. [a] Isolated yield. [b] Internal standard yield by NMR.

substrates—was selected for investigation.[27] Treatment of **1** with pentafluoropyridine (**2a**, >2 equiv) in tetrahydrofuran above 50 °C leads to the clean consumption of **1** and formation of a new species with spectral features consistent with C–F OA product **1**•[F][C_5F_4N]. The large upfield shift of the ^{31}P NMR resonance for **1**•[F][C_5F_4N] (δ –61.0 ppm) compared to **1** (δ +159.8 ppm) conforms with expectations for an increase in *P*-coordination number, and the further presence of a large coupling constant ($^1J_{P-F}$ = 768.8 Hz) confirms the formation of a P–F bond. ^{19}F NMR spectra show complementary coupling to a fluorine-19 nucleus (δ –34.67 ppm; $^1J_{F-P}$ = 765.7 Hz). Related C–F OA reactivity is observed upon reaction of **1** with other perfluoroarenes (viz. perfluorotoluene **2b** gives **1**•[F][$C_5F_4CF_3$] and perfluorobenzonitrile gives **1**•[F][C_5F_4CN]),[28] although not for simple arylfluorides.[29] σ^3-P Compounds are known to undergo addition to electron-deficient haloarenes by S_NAr, but stable σ^5-P adducts by C–F OA are not formed.[30,31] The unique reactivity of **1** is attributable to its unusual biphilicity;[32] analogous OA was not observed with common phosphorus triamides.[33]

The fluorophosphoranes obtained by C–F OA to **1** are indefinitely stable in solution at ambient temperature; diffraction quality single crystals deposit from concentrated solutions in diethyl ether upon cooling. By X-ray diffraction analysis, the solid-state structure of **1**•[F][C_5F_4N] adopts a pentacoordinate geometry intermediate between trigonal bipyramidal and square pyramidal extrema along the Berry coordinate, biased somewhat toward the former (τ = 0.60[34]). Indeed, as represented in the thermal ellipsoid plot in Figure 2 (left), the *P*-fluoro substituent of **1**•[F][C_5F_4N] is distal, but not rigorously apical, with respect to the diarylamino N_1; the fluoroheteroaryl group similarly deviates from an idealized equatorial position (Table 1). By structural comparison to known fluorophosphorane compounds, the $P_1–F_1$ bond length of **1**•[F][C_5F_4N] (1.6282(6) Å) is short relative to the average apical P–F distance (1.650 Å).[35] For reference, **1**•[F][C_5F_4N] shows a $P–F_{ax}$ distance and IR stretching frequency (687 cm^{-1}) intermediate of the polyfluorophosphoranes $MePF_4$ (1.612 Å, 720 cm^{-1}) and Me_2PF_3 (1.643 Å, 648 cm^{-1}).[36] Given the known correlation of $P–F_{ax}$ bond energy and electronegativity of the ancillary ligands,[37] we infer a high affinity of the phosphorus center for the fluoride substituent in **1**•[F][C_5F_4N][38] (*vide infra*).

Table 1. Tabulated bond distances (Å), angles (°), and δ (ppm) values for selected compounds.[a]

Metric	**1**[b]	**1**•[F][C_5F_4N]	**1**•[H][C_5F_4N]
$d(P_1–N_1)$	1.7610(12)	1.7616(8)	1.778(2)
$d(P_1–N_2)$	1.7014(14)	1.6841(9)	1.698(2)
$d(P_1–N_3)$	1.7190(13)	1.6753(9)	1.695(2)
$d(P_1–F_1/H_1)$	—	1.6282(6)	1.347(19)
$d(P_1–C_1)$	—	1.8456(10)	1.884(2)
$\angle N_1–P_1–F_1/H_1$	—	174.28(4)	172.7(10)
$\angle N_1–P_1–C_1$	—	95.62(4)	94.31(9)
$\angle N_2–P_1–N_3$	115.21(7)	139.66(5)	139.41(10)
δ ^{31}P	159.8	–61.0	–62.7

[a] See SI for full details. [b] Data from Ref. 23.

Consistent with the short P–F distance, fluoride abstraction from **1**•[F][C_5F_4N] was not accessible by treatment with $B(C_6F_5)_3$ (FIA = 107.1 kcal/mol)[39]; however, the addition of the more potent fluoride acceptor $Al(C_6F_5)_3$ (FIA = 130.0 kcal/mol) did result in fluoride transfer and formation of **1**•[C_5F_4N]$^+$[$AlF(C_6F_5)_3$]$^-$ as observed by ^{31}P NMR spectroscopy (δ +54.3 ppm). Likewise, **1**•[F][C_5F_4N] is unreactive to common borane reagents (9-BBN, HBcat) but undergoes smooth reaction instead with diisobutylaluminum hydride (DIBAL-H, 1.5 equiv) in toluene at room temperature. In this latter reaction, ^{31}P NMR spectra are consistent with an exchange of fluoride for hydride at the pentacoordinate phosphorus (δ –62.7 ppm), formulated as hydridophosphorane **1**•[H][C_5F_4N] (Figure 2); a doublet resonance with large coupling constant ($^1J_{P-H}$ = 541.7 Hz) collapses to a singlet upon proton decoupling, corroborating the presence of the P–H bond. **1**•[F][$C_5F_4CF_3$] also transforms to **1**•[H][$C_5F_4CF_3$] in the same conditions. The requirement for a strongly fluorophilic metathesis reagent would seem to imply a significant stepwise character to the exchange reaction.

Structural determination of **1**•[H][C_5F_4N] was undertaken by X-ray diffraction on a single-crystalline sample, wherein the phosphorus-bound hydrogen atom (H_1) was located in the dif-

ference Fourier map and refined isotropically. Modest distinctions are noted when comparing **1**•[F][C_5F_4N] and **1**•[H][C_5F_4N]; as depicted in Figure 2 (right), the intermediate trigonal bipyramidal/square pyramidal geometry of **1**•[F][C_5F_4N] is largely retained in **1**•[H][C_5F_4N] (τ = 0.56). With the less electronegative H substituent in place of F, a slight lengthening of the remaining four bonds to P is observed (Table 1). Overall, the geometry of **1**•[H][C_5F_4N] is comparable to the reported structures of the other hydridophosphorane molecules derived from **1**,[23] where the *P*-hydrido substituent occupies a distal position from N_1 (viz. $\angle N_1–P_1–H_1$ = 167-176°).

A solution of **1**•[H][C_5F_4E] (E = N or C–CF_3, 5-100 mM in C_6D_6) sealed in an NMR tube is stable at ambient temperature, but heating above 140 °C results in the consumption of the starting material. Time-stacked ^{31}P NMR spectra (Figure 3a) indicate that **1**•[H][C_5F_4N] (δ –62.5 ppm) is reverted to **1** (δ +160.4 ppm) through an apparent C–H RE from phosphorus(V). Simultaneous monitoring within the ^{19}F NMR channel (Figure 3b) confirms the concomitant formation of RE product 2,3,5,6-tetrafluoropyridine **3a**. Quantitative ^1H NMR analysis of the reaction under these conditions establish that the reaction proceeds cleanly (ca. 95% mass recovery).

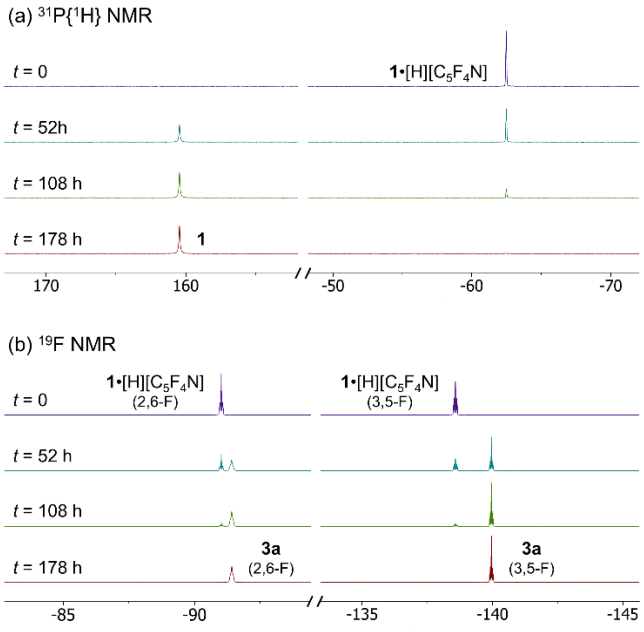

Figure 3. Time-stacked (a) $^{31}P\{^1H\}$ NMR and (b) ^{19}F NMR spectra of **1**•[H][C_5F_4N] in C_6D_6 at *t* = 0, 52, 108, and 178 h at 160 °C. Units are ppm relative to 85% H_3PO_4 (^{31}P) and $CFCl_3$ (^{19}F). See SI for unabridged spectra.

To further characterize the nature of this C–H RE, the reaction kinetics were evaluated at 160 °C by quantitative ^1H NMR spectroscopy using durene as an internal standard. As shown in Figure 4a, the concentration of **1**•[H][C_5F_4N] decays according to first-order kinetics, with a rate constant $k = 6.38\pm0.01 \times 10^{-6}$ s^{-1}. Isotope labelling studies confirm the intramolecular provenance of the C-H coupling partners; heating a solution of **1**•[D][C_5F_4N] exclusively generated D–C_5F_4N. Independentkinetic profiling of the C-H RE for **1**•[H][C_5F_4N] and **1**•[D][C_5F_4N] establish a kinetic isotope effect of k_H/k_D = 1.17±0.11.[40] Furthermore, a crossover experiment by heating a mixture of **1**•[D][C_5F_4N] and **1**•[H][$C_6F_4CF_3$] formed only D–C_5F_4N (**3a**-*d*) and H–$C_6F_4CF_3$ (**3b**) with no evidence for crossover products H–C_5F_4N (**3a**) or D–$C_6F_4CF_3$ (**3b**-*d*) (Figure 4b). Taken together, the foregoing lines of evidence inform the conclusion that the C–H RE from **1**•[H][C_5F_4E] proceeds via a unimolecular ligand coupling event.

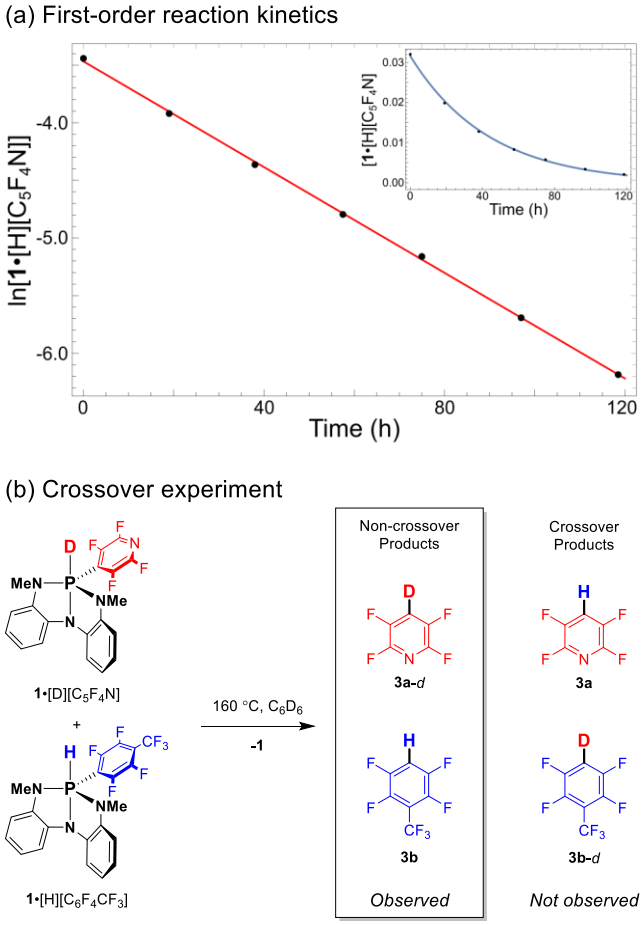

Figure 4. Experimental studies to probe into the mechanism of the H–C_5F_4E reductive elimination from **1**•[H][C_5F_4E]. (a) The first-order reaction kinetics with respect to [**1**•[H][C_5F_4N]]. (b) Crossover experiment with **1**•[D][C_5F_4N] and **1**•[H][$C_6F_4CF_3$] producing only non-crossover products.

Although a direct apical-equatorial ligand coupling is forbidden on orbital symmetry grounds,[41] DFT modelling (ωB97X-D3/def2-TZVP) identifies two candidate pathways describing concerted (albeit highly asynchronous) C–H RE mechanisms from **1**•[H][C_5F_4N]. In the first pathway, the incipient C–H bond is substantially developed prior to P–C bond cleavage in the transition structure (**TS1**, Figure 5, top). In effect, the RE has substantial character of a hydride migration from phosphorus to the carbon in the fluoroaryl group via an addition to the aromatic π^*-orbital reminiscent of concerted S_NAr[42] (see SI for details). Despite an apparent increase in $P_1–C_1$ bond order near the saddle point, no stationary point corresponding to a stable phosphonium intermediate is obtained along the reaction coordinate. Although analogous mechanisms have been suggested for other phosphorus-based ligand coupling reactions,[12,20] the high energy of this transition state ($\Delta G^{\ddagger}_{TS1}$ = 49.2 kcal/mol) likely renders such a pathway inaccessible in this case.

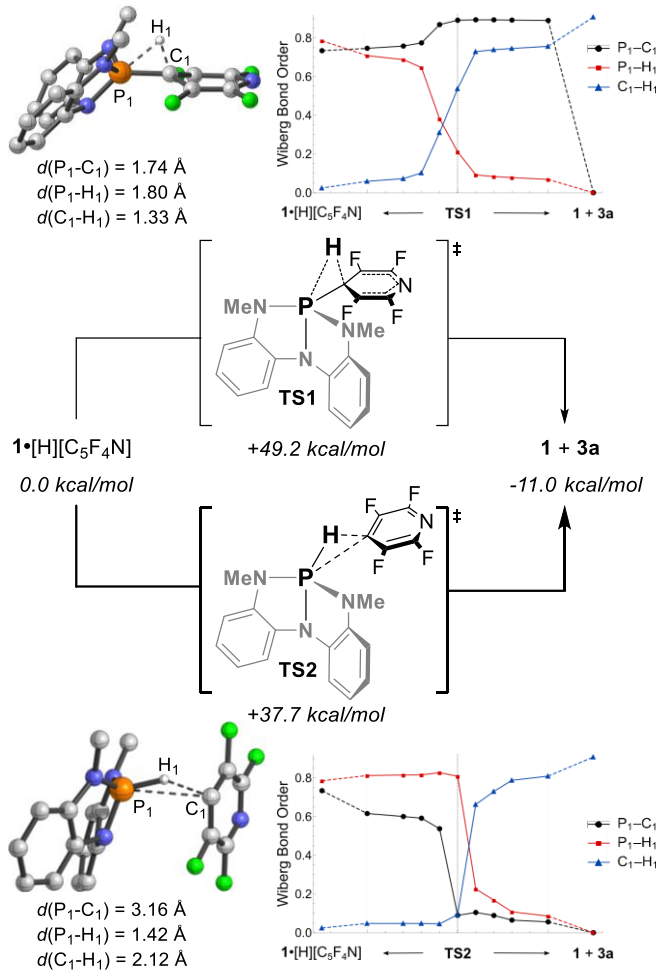

Figure 5. DFT pathways for C–H reductive elimination from **1**•[H][C_5F_4N] at the ωB97X-D3/def2-TZVP level of theory (Gibbs free energies in italics). (top) Model of **TS1** and mapping of key bond orders along the intrinsic reaction coordinates. (bottom) Model of **TS2** and mapping of key bond orders along the intrinsic reaction coordinates.

A second transition state (**TS2**, Figure 5, bottom), also located as a stationary point on the potential energy surface but lower in energy ($\Delta G^{\ddagger}_{TS2}$ = +37.7 kcal/mol), is distinguished by both the sequencing of the asynchronous bond making/breaking stages along the reaction coordinate and by the polarity of reacting P–H moiety. In **TS2**, P_1–C_1 bond elongation ($d(P_1–C_1)$ = 3.16 Å) precedes P_1–H_1 cleavage; the P_1–H_1 distance (1.42 Å) is essentially identical to starting material **1**•[H][C_5F_4N] ($d(P_1–H_1)$ = 1.42 Å). According to the natural bond orbital analysis on **TS2**, natural population analysis assigns protic character to H_1 (+0.080) and a significant second-order perturbation (17.3 kcal/mol) between the C_1 lone pair and a P_1–H_1 σ^* orbital is detected. In effect, this RE—although concerted—proceeds with high asynchronicity and resides near the boundary with a stepwise polar heterolysis/deprotonation pathway. The ensemble of experimental observations obtained to date—the temperature of reaction, kinetic unimolecularity, lack of crossover—are most consistent with **TS2** representing the operative pathway for this C–H RE.[43]

In sum, the foregoing results thus transit a closed P^{III}/P^{V} synthetic cycle for hydrodefluorination via C–F oxidative addition, F→H ligand metathesis, and C–H reductive elimination at a nontrigonal phosphorus triamide **1**. The sequencing of these elementary reactions at phosphorus is reminiscent of the role played by transition metals in aryl C–X substitution reactions,[44] but is without precedent for *p*-block compounds. The closed synthetic loop—beginning and ending with **1**—suggests that iterative cycling (i.e. catalysis) is in principle possible, but unfortunately the thermal instability of DIBAL-H is not compatible with the elevated temperature needed to promote C–H reductive elimination in this system. That said, our mechanistic models for concerted asynchronous C–H reductive elimination provide a basis for evaluating the impact of tailored alterations to **1** on the kinetics of reductive elimination with the purpose of enabling swifter C–H and related reductive elimination processes in a catalytic fashion.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures; crystallographic details; computational details; IR spectra; ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra (PDF)

Crystallographic data for $C_{19}H_{14}F_5N_4P$ (CIF)

Crystallographic data for $C_{19}H_{15}F_4N_4P$ (CIF)

Crystallographic data for $C_{21}H_{14}F_8N_3P$ (CIF)

Crystallographic data for $C_{21}H_{14}F_5N_4P$ (CIF)

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Notes

The authors declare no competing financial interests.

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