Nickel-Catalyzed Defluorophosphonylation of Aryl Fluorides

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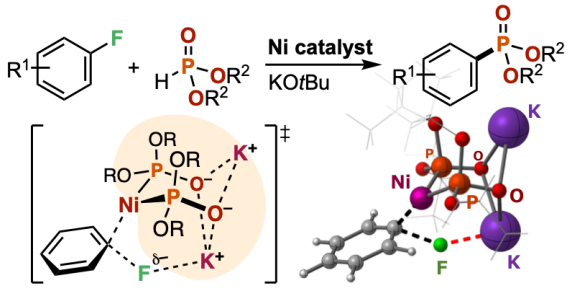


ABSTRACT: A Ni-catalyzed cross-coupling reaction between aryl fluorides and dialkyl phosphonates [HP(O)(OR)$_2$] (R = secondary alkyl groups) in the presence of potassium *tert*-butoxide as a base is reported. The reaction converted various aryl fluorides into the corresponding aryl phosphonates even when electron-donating substituents were present on the aromatic ring. The combined experimental and computational studies suggested Ni–K$^+$ cooperative action of a Ni(0) complex chelated with a strongly electron-donating ion-bridged dimeric phosphite ligand system [P(OR)$_2$O$^-$K$^+$]$_2$ that facilitates turnover-limiting C–F bond oxidative addition of aryl fluorides.

INTRODUCTION

The direct functionalization of C–F bonds has attracted increasing attention in recent years because of the increasing abundance of fluorinated compounds in pharmaceuticals[1] and other functional materials,[2] affording various opportunities for diversity-oriented synthesis through late-stage functionalization of complicated molecules. Whereas numerous methods for converting C–F bonds into C–C, C–H, C–O, and C–N bonds have been developed,[3] few methods exist for forming weaker C–P bonds toward the synthesis of organophosphorus compounds. The classical approach to C–F to C–P bond transformation involves a nucleophilic aromatic substitution (S_NAr) reaction with phosphide anions,[4] which are generated using hazardous alkali metals.[5] Würthwein and coworkers have demonstrated that silylphosphines undergo S_NAr phosphination of aryl fluorides at high temperatures (>170 °C) (Scheme 1a).[6] In these S_NAr-type reactions, the pronucleophiles are limited to secondary phosphines and phosphine oxides; the successful use of more electron-deficient phosphonic acid diesters [HP(O)(OR)$_2$] has not been reported. Organophosphonic acids [RP(O)(OH)$_2$] and their derivatives are widely used as drugs or pro-drugs,[7] chelators of metallic salts,[8] surface modifiers,[9] and phosphoantigens.[10] Thus, the development of a phosphonylation reaction for aryl fluorides is demanded. To the best of our knowledge, however, the literature contains only one example of C(sp^2)–F bond phosphonylation, which was achieved via a photoinduced single-electron-transfer (SET) process (Figure 1b)[11] that required irradiation with ultraviolet light (λ = 254 nm). We recently reported a nucleophile-dependent S_NAr reaction of non-activated aryl fluorides with potassium diorganophosphinites ($R_2PO^-K^+$) (Figure 1c).[12] In this reaction, the potassium cation plays a critical role, stabilizing the negative charge of the leaving fluoride anion. With this knowledge, we envisaged combining the unique property of the K$^+$ cation with the well-established ability of a Ni catalyst to activate C–F bonds[3,13] and thereby achieve phosphonylation of aryl fluorides (Figure 1d).[14]

Herein, we report a Ni-catalyzed cross-coupling reaction between aryl fluorides and dialkyl phosphonates [HP(O)(OR)$_2$] in the presence of potassium *tert*-butoxide (KO*t*Bu) as a stoichiometric base. The reaction uses commercially available Ni complexes as catalyst precursors and requires no exogeneous ligand. Not only electron-deficient but also electron-neutral and even electron-rich aryl fluorides were successfully converted into the corresponding aryl phosphonates. Interestingly, the present coupling reaction proceeds specifically with di-*sec*-alkyl phosphonates; no reaction occurs with primary or tertiary alkyl phosphonates. Mechanistic studies by kinetic experiments and density functional theory (DFT) calculations suggested that the catalytic cycle involves turnover-limiting oxidative addition of

the aryl fluoride to a Ni(0) complex coordinated with potassium dialkyl phosphites [$P(OR)_2O^-K^+$], which occurs through cooperative action of a Ni(0)–K^+ bimetallic system.

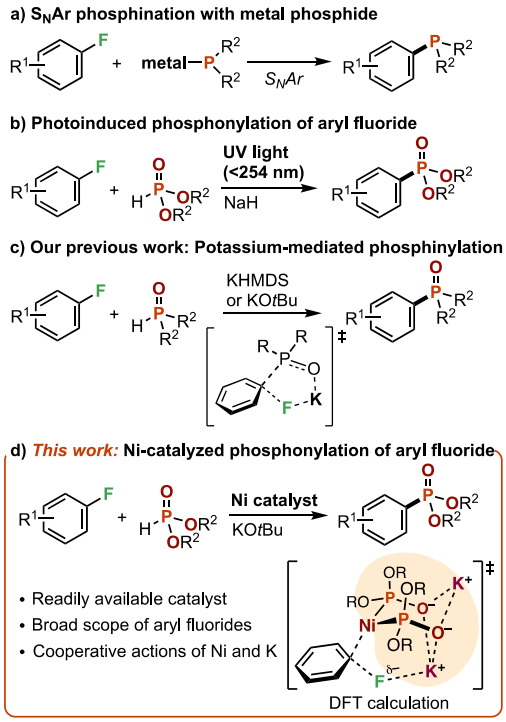
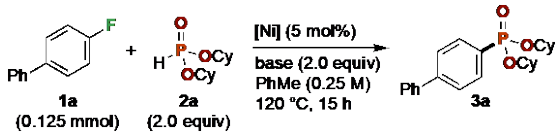


Figure 1. Defluorinative C–P bond formation reactions (KHMDS = potassium hexamethyldisilazide; KO*t*Bu = potassium *tert*-butoxide).

RESULTS AND DISCUSSION

Specifically, the reaction between 4-fluorobiphenyl (**1a**, 0.125 mmol) and dicyclohexyl phosphonate (**2a**, 0.25 mmol) in the presence of $NiBr_2$·diglyme (5 mol%, 0.00625 mmol) and KO*t*Bu (0.25 mmol) in toluene (0.5 mL) at 120 °C led to the clean and complete conversion of **2a** to the corresponding defluorinative phosphonylation product (**3a**) in quantitative yield (99% based on ^{1}H NMR spectroscopy) (Table 1, entry 1). When the amount of KO*t*Bu was decreased to 0.125 mmol (1 equiv to **1a**, 0.5 equiv to **2a**), product **3a** was not obtained, suggesting the formation of an inactive Ni species through the direct reaction of a Ni species with nondeprotonated dialkyl phosphonate **2a** (entry 2).[15] NiI_2 exhibited a catalytic performance similar to that of $NiBr_2$·diglyme (entry 3), whereas other Ni(II) complexes such as $NiCl_2$ and $Ni(acac)_2$ (acac = acetylacetonate) gave **3a** in moderate yields (entries 4–6). Notably, the Ni(0) complex $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) also catalyzed the present reaction, suggesting that Ni(0) is an active species in the catalytic process (entry 7). No reaction occurred in the absence of a Ni catalyst (entry 8). The base strongly influenced the reaction efficiency. Specifically, the use of bases that have smaller cations (e.g., NaO*t*Bu and LiO*t*Bu) in place of KO*t*Bu in entry 1 resulted in a substantial decrease in the product yield (entries 9 and 10). The addition of 18-crown-6 (2 equiv) inhibited the reaction completely, suggesting direct participation of a potassium cation in the catalysis (entry 11). The phosphonylation product **3a** was not obtained at all with less basic potassium salts such as K_2CO_3 and K_3PO_4 (entries 12 and 13). Potassium hexamethyldisilazide (KHMDS), which is sufficiently basic to deprotonate dialkyl phosphonates, also failed to give **3a** (entry 14). By contrast, the use of KHMDS with $Ni(cod)_2$ instead of $NiBr_2$·diglyme afforded **3a** in a quantitative yield, suggesting that the reduction of a Ni(II) precatalyst occurred with *tert*-butoxide but not with KHMDS (entry 15). The addition of exogeneous ligands did not substantially affect the product yield.[16]

Table 1. Ni-catalyzed phosphonylation of 4-fluorobiphenyl (1a) with dicyclohexyl phosphonate (2a).[a]



Entry	[Ni]	Base	Yield [%][b]
1	$NiBr_2$·diglyme	KO*t*Bu	99
2[c]	$NiBr_2$·diglyme	KO*t*Bu	0
3	NiI_2	KO*t*Bu	99
4	$NiBr_2$	KO*t*Bu	55
5	$NiCl_2$	KO*t*Bu	62
6	$Ni(acac)_2$	KO*t*Bu	77
7	$Ni(cod)_2$	KO*t*Bu	70
8	none	KO*t*Bu	0
9	$NiBr_2$·diglyme	NaO*t*Bu	33
10	$NiBr_2$·diglyme	LiO*t*Bu	2
11[d]	$NiBr_2$·diglyme	KO*t*Bu	0
12	$NiBr_2$·diglyme	K_2CO_3	0
13	$NiBr_2$·diglyme	K_3PO_4	0
14	$NiBr_2$·diglyme	KHMDS	0
15	$Ni(cod)_2$	KHMDS	99

[a] Reaction conditions: **1a** (0.125 mmol), **2a** (0.25 mmol), Ni complexes (0.00625 mmol, 5 mol% to **1a**), base (0.25 mmol), toluene (0.5 mL), 120 °C, 15 h. [b] ^{1}H NMR yield obtained using 1,3,5-trimethoxybenzene as an internal standard. [c] 0.125 mmol of base. [d] 18-Crown-6 (0.250 mmol, 2.0 equiv) was added.

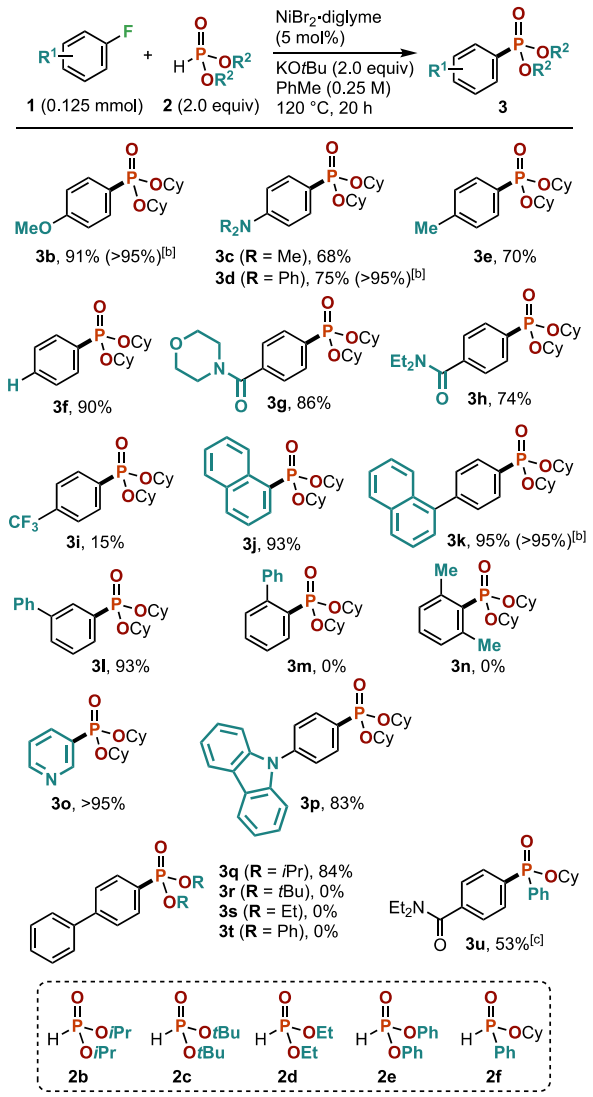
acac = acetylacetonate, cod = 1,5-cyclooctadiene, HMDS = hexamethyldisilazide.

With the optimal conditions in hand, we investigated the substrate scope (Table 2). Aryl fluorides possessing electron-donating substituents such as methoxy (OMe), dimethylamino (NMe_2), diphenylamino (NPh_2), and methyl (Me) groups participated in the phosphonylation reaction to afford the corresponding aryl phosphonates in good yields (**3b**–**3e**). Simple fluorobenzene also exhibited excellent reactivity, forming **3f** in 90% yield. Electron-withdrawing amide groups were tolerated on the aromatic ring, and the corresponding products **3g** and **3h** were obtained in 86% and 74% yields, respectively. However, the aryl fluoride with a highly electron-withdrawing trifluoromethyl group resulted in a low yield of **3i** (15% yield). π-Extended aryl fluorides were suitable substrates for the present phosphonylation reaction, and the corresponding products were obtained in excellent yields (**3j**–**3l**). However, 2-fluorobiphenyl and 1-fluoro-2,6-dimethylbenzene did not give products **3m** and **3n**. Heteroaryl fluorides were successfully converted to the

corresponding phosphonates (**3o** and **3p**). For the synthesis of **3b**,**d**,**k**, the reaction was conducted with $Ni(cod)_2$ and KHMDS because the protocol with $NiBr_2$·diglyme and KO*t*Bu produced small amounts of phosphorus-containing byproducts, which hampered the isolation of the products in pure form.

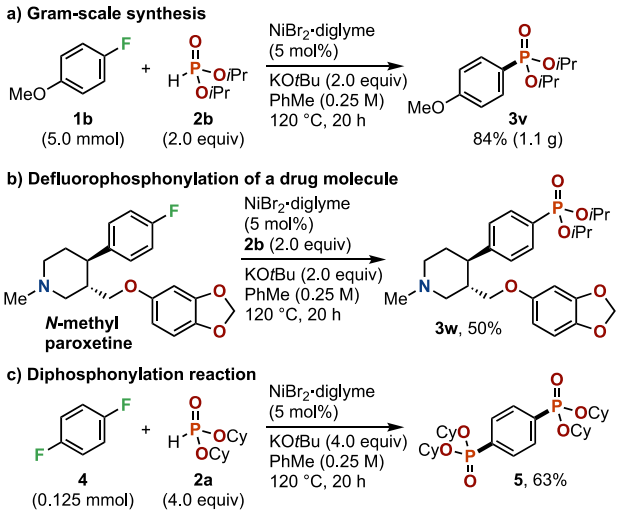
Next, the scope of dialkyl phosphonates was examined. Diisopropyl phosphite (**2b**) afforded the corresponding phosphonate **3q** in 84% yield, whereas dialkyl phosphonates with tertiary (**2c**) or primary (**2d**) *O*-alkyl groups failed to give the products (**3r**, **3s**). Diphenyl phosphonate (**2e**) also exhibited no reactivity. Thus, the present reaction was specifically possible with phosphonates with two secondary *O*-alkyl groups. This unusual reactivity trend disfavoring the smallest pronucleophile $[HP(O)(OEt)_2]$ can be explained by assuming the formation of inactive Ni species through over-coordination of the relatively small potassium diethyl phosphite ligand $[P(OEt)_2O^-K^+]$ to a Ni center or through aggregation of a Ni–$P(OEt)_2OK$ complex. Racemic phosphinate **3u** was obtained in 53% yield from 4-fluorobiphenyl and cyclohexyl phenylphosphinate (**2f**) under slightly modified reaction conditions. The synthetic applications are summarized in Scheme 1. The reaction was applicable for a gram-scale synthesis. When the reaction of aryl fluoride **1b** with phosphonate **2b** was carried out on a 5.0 mmol scale, 1.1 g of arylphosphonate **3v** was isolated (84% yield, Scheme 1a). Defluorinative phosphonylation of *N*-methyl paroxetine, an antidepressant, afforded the corresponding arylphosphonate **3w** in 50% yield, demonstrating the potential of the present protocol for the synthesis of structurally complicated organophosphorus compounds using scaffolds of biologically functional molecules (Scheme 1b). Twofold defluorophosphonylation occurred with 1,4-difluorobenzene (**4**) under slightly modified reaction conditions, affording the corresponding phenylenediphosphonic acid ester (**5**) in 63% yield (Scheme 1c).

Table 2. Scope of aryl fluorides and dialkyl phosphonates.[a]

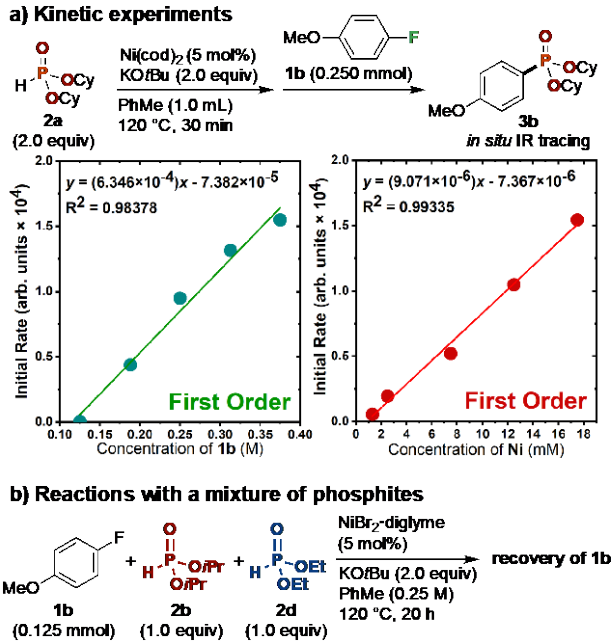


[a] Reaction conditions: **1** (0.125 mmol), **2** (0.25 mmol), $NiBr_2$·diglyme (0.00625 mmol, 5 mol% to **1**), KO*t*Bu (0.25 mmol), PhMe (0.5 mL), 120 °C, 20 h. Yields of isolated products are shown. [b] $Ni(cod)_2$ (0.00625 mmol) as catalyst, KHMDS (0.25 mmol) as base. [c] THF as a solvent, 80 °C, 20 h.

Scheme 1. Synthetic applications.



Scheme 2. Mechanistic experiments.



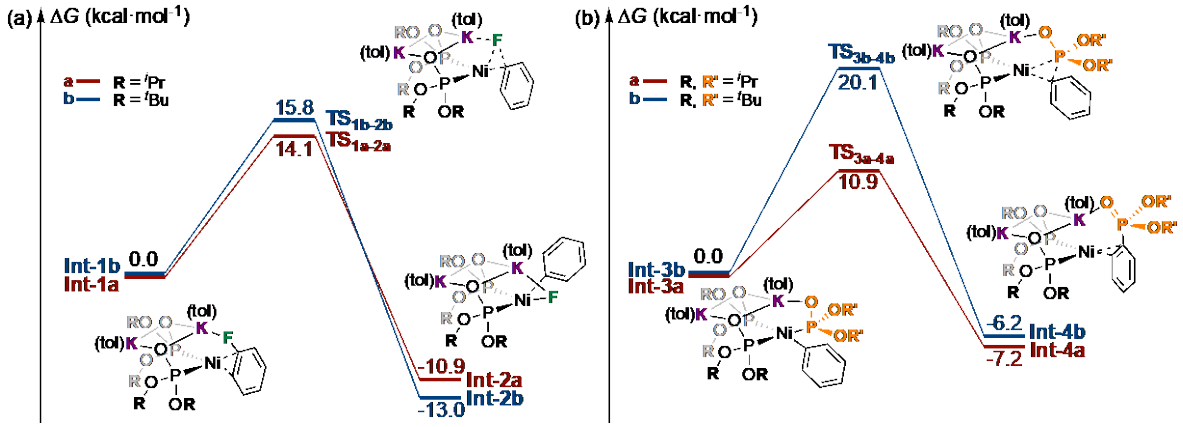


Figure 2. (a) Calculated oxidative addition pathways. (b) Calculated reductive elimination pathways.

To gain insights into the mechanism, we performed kinetic studies by *in situ* infrared (IR) spectroscopy for the reaction of potassium salt K[**2a**–H], which was formed *in situ* from **2a** and KO*t*Bu, with 4-methoxylphenyl fluoride (**1b**) promoted by $Ni(cod)_2$ in toluene at 120 °C (Scheme 2a). The rate was found to be first order in both **1b** and $Ni(cod)_2$, suggesting that a reaction of the aryl fluoride with a monomeric Ni complex would be a turnover-limiting step. However, we failed to determine the reaction order for K[**2a**–H] because of its low solubility.[16]

To explain the specific reactivity of di-*sec*-alkyl phosphonates, we conducted reactions with a mixture of phosphonates with different *O*-alkyl groups (Scheme 2b). When aryl fluoride **1b** was treated with a 1:1 mixture of diisopropyl and diethyl phosphonates (**1b** : **2b** : **2d** = 1:1:1) in the presence of $NiBr_2$·diglyme (5 mol%) and KO*t*Bu (2 equiv), no C–P coupling product was obtained, indicating that diethyl phosphonate (**2d**) inhibited the reaction of diisopropyl phosphonate (**2b**). Thus, the irreversible formation of a catalytically inactive species from **2d** and $NiBr_2$·diglyme is strongly suggested.

For computational investigations, we assume metal chelation by ion-bridged dimers of the potassium dialkyl phosphites $\{M[P(OR)_2O^-K^+]_2\}$ on the basis of analogy with the chelation by hydrogen-bonded phosphorus dimers $[(RO)_2POH\cdots{}^-OP(OR)_2]$ reported in the literature.[15,17,18] Calculations were performed at the M06/SDD,6-311+G(d,p)/SMD//M06/lanl2dz,6-31G(d) level of theory using the Gaussian 16 package. To include solvent effects, the explicit coordination of a toluene molecule to each K^+ cation was considered in all the calculations. Energy profiles are given in Figure 2 for the oxidative addition of fluorobenzene (**1f**) to the Ni(0) complex $\{Ni^0[P(OiPr)_2OK]_2\cdot(toluene)_2\}$ coordinated with two $P(OiPr)_2OK$ ligands (Figure 2a) and for reductive elimination of the arylphosphonates $[PhP(O)(OiPr)_2]$ from Ni(II) complexes $\{[P(OiPr)_2OK]_2Ni^{II}(Ph)[P(O)(OiPr)_2]\cdot(toluene)_2\}$ (Figure 2b).

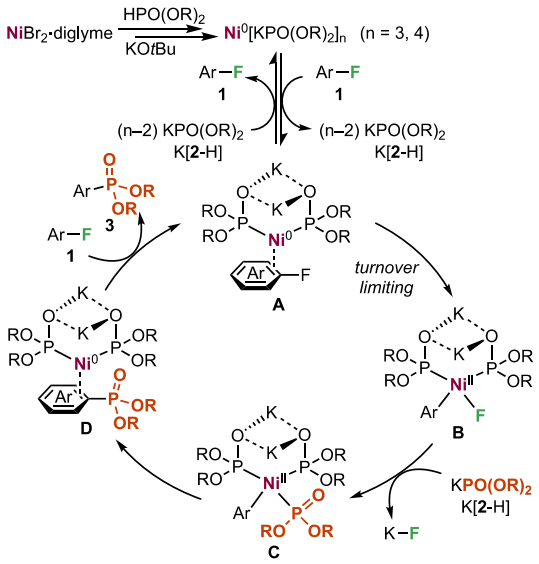
As shown in Figure 2a, the C–F bond oxidative addition of fluorobenzene to the Ni center of Ni(0) intermediate **Int-1a** (R = *i*Pr) to produce the corresponding pseudo-square-planar Ni(II) intermediate (**Int-2a**) occurs with Lewis acidic direct participation of one of the K^+ cations, as indicated by the increase of the K···F interaction (from 2.76 Å to 2.46 Å) as the reaction proceeds from **Int-1a** to transition state $\mathbf{TS_{1a-2a}}$. This process is 10.9 kcal·mol^{-1} exergonic with a barrier of 14.1 kcal·mol^{-1}, altering the P–Ni–P bite angle from 105° (for **Int-1a**) to 96° (for **Int-2a**). We reason that not only the push–pull effect of the Ni–K^+ bimetallic system but also strong electron donation by the two anionic phosphorus ligands $[P(OiPr)_2O^-]$ facilitate the C–F bond oxidative addition.[19]

We next attempted to identify a transition state for the direct reductive elimination of $PhP(O)(OiPr)_2$ from **Int-2a**; however, a reasonable transition-state structure was not found. This failure prompted us to investigate reductive elimination after ligand exchange at the Ni(II) center from the F^- anion to $P(OiPr)_2O^-$. The geometry-optimized Ni(II) complex (**Int-3a**) with three anionic P ligands adopts a pseudo-square-planar geometry. The P–Ni–P bite angle (96°) with the original two P ligands is unchanged upon this ligand exchange. The computational estimation of the relative energy between **Int-2a** and **Int-3a** is too challenging because of the insoluble natures of KF and $P(OiPr)_2OK$ in the reaction system and was therefore not pursued in the present study. Reductive elimination from **Int-3a** proceeds through $\mathbf{TS_{3a-4a}}$ with an energy barrier (10.9 kcal·mol^{-1}) much lower than that for the oxidative addition process (14.1 kcal·mol^{-1}) to afford **Int-4a** with an η^2-coordinated phosphonylbenzene via a 7.2 kcal·mol^{-1} exergonic process.

We also conducted a computational study for the less favorable reaction with the bulkier phosphorus agent di-*tert*-butyl phosphonate (R = *t*Bu). The corresponding energy diagrams are given in Figure 2 as blue lines. As in the case with diisopropyl phosphonate (R = *i*Pr), the C–F bond oxidative addition (**Int-1b**–$\mathbf{TS_{1b-2b}}$–**Int-2b**) proceeds with Lewis acidic participation of the K^+ cation, with an energy barrier of 15.8 kcal·mol^{-1}, which is only 1.7 kcal·mol^{-1} larger than that for the reaction with diisopropyl phosphate (R = *i*Pr) (Figure 2a). Thus, the oxidative addition step is likely not responsible for the lower reactivity of di-*tert*-butyl phosphonate compared with that of diisopropyl phosphate. By contrast, the change of the phosphonate alkyl groups from *i*Pr ($\mathbf{TS_{3a-4a}}$) to *t*Bu ($\mathbf{TS_{3b-4b}}$) strongly influenced the ease of reductive elimination, increasing the energy barrier to 20.1 kcal·mol^{-1} (Figure 2b). The energy barrier of $\mathbf{TS_{3b-4b}}$ is 9.2 kcal·mol^{-1} higher in energy than that for the reaction with the diisopropyl phosphonate, which is thereby deduced to be a reason for the experimentally observed inertness of $HP(O)(OtBu)_2$ (**2c**). Steric congestion in $\mathbf{TS_{3b-4b}}$ is likely responsible for the increased energy barrier.[20]

On the basis of the results of the experimental and theoretical studies, we propose the reaction mechanism shown in Scheme 3. The catalyst precursor $NiBr_2$·diglyme is activated by $P(OR)_2O^-K^+$ (K[**2**–H]) generated by deprotonation of dialkyl phosphonate **2** with KO*t*Bu to afford Ni(0) complexes $\{Ni[P(OR)_2OK]_n$ (n = 3, 4)} that chelated with a strongly electron-donating ion-bridged dimeric phosphite ligand system $[P(OR)_2O^-K^+]_2$.[21] Ligand exchange between one or two molecules of K[**2**–H] and aryl fluoride **1** gives a Ni(0) complex (**A**) η^2-coordinated with the aryl fluoride. The pronounced inhibitory effect by diethyl phosphonate **2d** is deduced to be attributable to the inertness of $Ni^0[P(OEt)_2OK]_n$ (n = 3, 4) toward ligand dissociation. Then, turnover-limiting oxidative addition of aryl fluoride **1** to the Ni center of **A** gives an aryl nickel(II) fluoride (**B**). Next, replacement of the F^- anion on the Ni center with a phosphonate anion [**2a**–H]$^-$ forms aryl(phosphonyl)nickel(II) complex **C**. Finally, reductive elimination of arylphosphonate **3** from **C** and re-coordination of aryl fluoride **1** regenerates Ni(0) complex **A** to complete the catalytic cycle.

Scheme 3. A proposed catalytic cycle.



CONCLUSIONS

In summary, Ni-catalyzed defluorinative phosphonylations of aryl fluorides with dialkyl phosphonates $[HP(O)(OR)_2]$ have been achieved using KO*t*Bu as a base. The reaction required no exogeneous ligands, and commercially available and bench-stable Ni(II) complexes exhibited high catalytic activities. Various aryl fluorides were successfully converted to the corresponding arylphosphonates irrespective of their electronic natures. The reaction proceeded specifically with di-*sec*-alkyl phosphonates. Experimental and computational mechanistic investigations suggested that Ni–K^+ cooperative action of a Ni(0) complex chelated with a strongly electron-donating ion-bridged dimeric phosphite ligand $[P(OR)_2O^-K^+]_2$ facilitates turnover-limiting C–F bond oxidative addition of aryl fluorides. Further reaction development with metal complexes with ion-bridged dimeric phosphonate ligands is underway in our laboratory.

EXPERIMENTAL SECTION

Typical Procedure for the Ni-catalyzed defluorophosphonylation of aryl fluorides

In a nitrogen-filled glovebox, $NiBr_2$·diglyme (2.2 mg, 0.00625 mmol, 5 mol%) and PhMe (0.1 mL) were placed in an oven-dried 10 mL glass tube containing a magnetic stirring bar. Next, **1a** (21.5 mg, 0.125 mmol, 1 equiv), **2a** (61.6 mg, 0.25 mmol, 2 equiv), and PhMe (0.2 mL) were added to the mixture. After stirring for 5 min, KO*t*Bu (28.1 mg, 0.25 mmol, 2 equiv) and PhMe (0.2 mL) were added, and the color of the mixture turned into orange upon stirring. The glass tube was sealed with a screw cap and was removed from the glove box. The mixture was stirred at 120 °C for 20 h. After cooling to room temperature, the dark-red reaction mixture was passed through a short plug of silica gel with a CH_2Cl_2/MeOH (9:1) eluent. Volatiles were removed by evaporation under reduced pressure. In order to remove recovered dialkylphosphonates, the crude reaction mixture was heated to 90 °C under high vacuum (140 Pa) for 12 h. After cooling to room temperature, a rsidue was purified by flash chromatography on silica gel with slow gradient elution (CH_2Cl_2/MeOH 100:0-to-98:2) followed by preparative thin layer chromatography (CH_2Cl_2/MeOH 98:2) to give **3a** as a light-brownish oil (48.4 mg, 0.12 mmol, 97% yield).

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, details of mechanistic studies, and NMR spectra (PDF).
Cartesian coordinates of optimized geometries (XYZ).

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Notes

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