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Synthesis of 6-Aryl-5-fluoropicolinate Herbicides via Halex Reaction of Tetrachloropicolinonitrile

Gregory T. Whiteker,*[†] Robert D. J. Froese,[§] Kim E. Arndt,[†] James M. Renga,[‡] Yuanming Zhu,[†] Gary A. Roth,[§] Qiang Yang,[†] Belgin Canturk,[†] and Jerzy Klosin[§]

[†]Product Design & Process R&D, Corteva Agriscience, 9330 Zionsville Road, Indianapolis, Indiana 46268, United States
[‡]Discovery Chemistry, Corteva Agriscience, 9330 Zionsville Road, Indianapolis, Indiana 46268, United States
[§]Core R&D, The Dow Chemical Company, Midland, Michigan 48674, United States

Supporting Information

ABSTRACT: The development of a new synthesis of 6-aryl-5-fluoropicolinate herbicides is described. This general route employs the halogen exchange (halex) reaction of tetrachloropicolinonitrile to give a mixture of chlorofluoropicolinonitriles. It was found that the isomeric purity of the trifluorochloropicolinonitrile fraction increased, with eventual conversion to tetrafluoropicolinonitrile. The desired product of this reaction, 3-chloro-4,5,6-trifluoropicolinonitrile, reacted with NH_3 regioselectively at the 4-position. Introduction of the aryl substituent was accomplished by initial conversion of the 6-fluoro substituent to 6-bromo using HBr in acetic acid followed by Pd-catalyzed Suzuki−Miyaura cross-coupling. The moderate regioselectivity of the halex reaction of tetrachloropicolinonitrile was studied computationally using a modified G3MP2B3* ab initio method. These computations were in agreement with the observed regioselectivity of the reaction. Recycle of the main byproduct, tetrafluoropicolinonitrile, was shown to be possible by two routes. The reverse halex reaction of tetrafluoropicolinonitrile using LiCl in DMSO gave a mixture of chlorofluoro products. In addition, scrambling of halogens between tetrafluoropicolinonitrile and tetrachloropicolinonitrile using catalytic *n*-Bu_4PCl gave a mixture of chlorofluoropicolinonitriles that could be resubjected to halex conditions to give additional 4,5,6-trifluoro-3-chloropicolinonitrile.

INTRODUCTION

Sustainable technologies that increase crop yields and lower environmental impact are critically important to meet the population growth and demographic changes predicted by 2050.[1] Minimizing crop losses due to competition from weeds is critical for agriculture intensification.[2] New herbicides should be designed to be effective at low use rates, have favorable environmental and toxicological profiles, and provide novel modes of action for managing resistance.[3] Picolinic acid herbicides have been actively researched for decades. Broadleaf herbicides of this class are members of the auxin herbicides and are widely used in cereal and pasture applications.[4] Picloram and aminopyralid are examples of commercial picolinate herbicides (Figure 1). More recently, new highly potent 6-arylpicolinate herbicides, including Arylex active,[5] DAS-534,[6] and Rinskor active,[5] have been developed by Corteva Agriscience. Arylex and Rinskor were recently commercially launched, and both provide effective control of broadleaf weeds at extremely low use rates.

The synthesis of the picolinic acid derivatives DAS-534 and Rinskor active is complicated by the presence of a fluoro substituent at the relatively unreactive 5-position of the pyridine ring. Herein we describe the development of a new synthetic route to DAS-534 and Rinskor that utilizes a regioselective halogen exchange (halex) reaction to introduce the fluorine atom at the 5-position.[7] A detailed ab initio computational study was performed to identify the factors that limit the halex regioselectivity, and these computations led to two novel strategies to recycle the overfluorinated byproduct.

DISCOVERY ROUTE

The initial syntheses of DAS-534 and Rinskor employed electrophilic fluorination of the commercial herbicide aminopyralid followed by Pd-catalyzed Suzuki−Miyaura cross-coupling (Scheme 1).[8] Although this convergent approach enabled the exploration of structure−activity relationships,[5] the fluorination of aminopyralid to give **1** occurred with low conversion that made inefficient use of the expensive fluorinating agent, Selectfluor. Since these herbicides of interest are designed for use in production of commodity crops, the cost of raw materials is highly important to develop economical synthetic routes.

A more economical and scalable route to these 6-aryl-5-fluoropicolinate herbicides was required to eventually meet our manufacturing cost targets. Approaches that formed the pyridine ring by cyclization strategies were developed,[9] but these routes suffered from lengthy reaction sequences and high raw material costs. Ideally, the 5-fluoro substituent would be introduced using a simple, inexpensive fluoride salt. The halex reaction is one of the most preferred processes to introduce fluorine into aromatic molecules.[10] In this process, a chloroarene is converted to a fluoroarene via nucleophilic aromatic substitution (S_NAr) with a fluoride salt. Halex reactions are typically performed in a polar nonprotic solvent,

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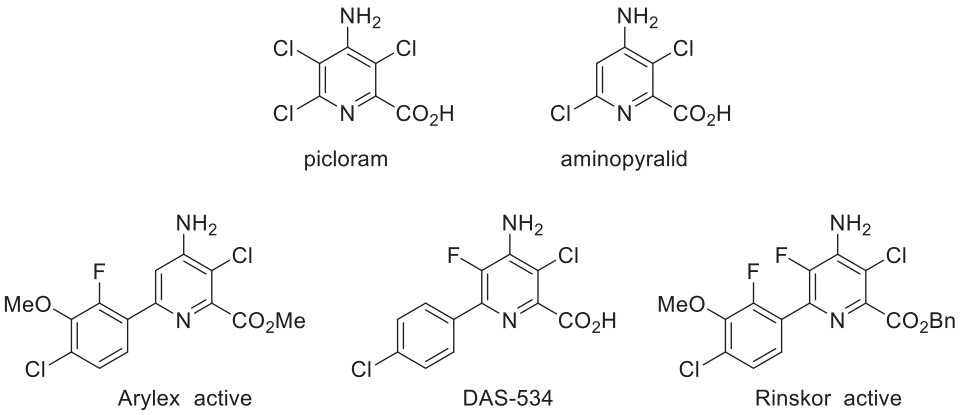
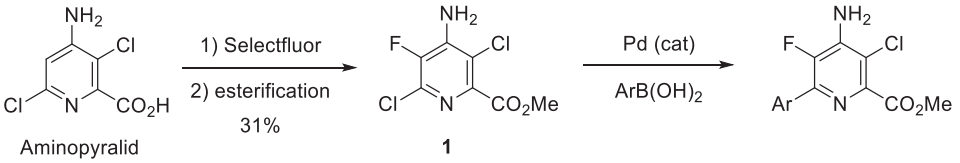
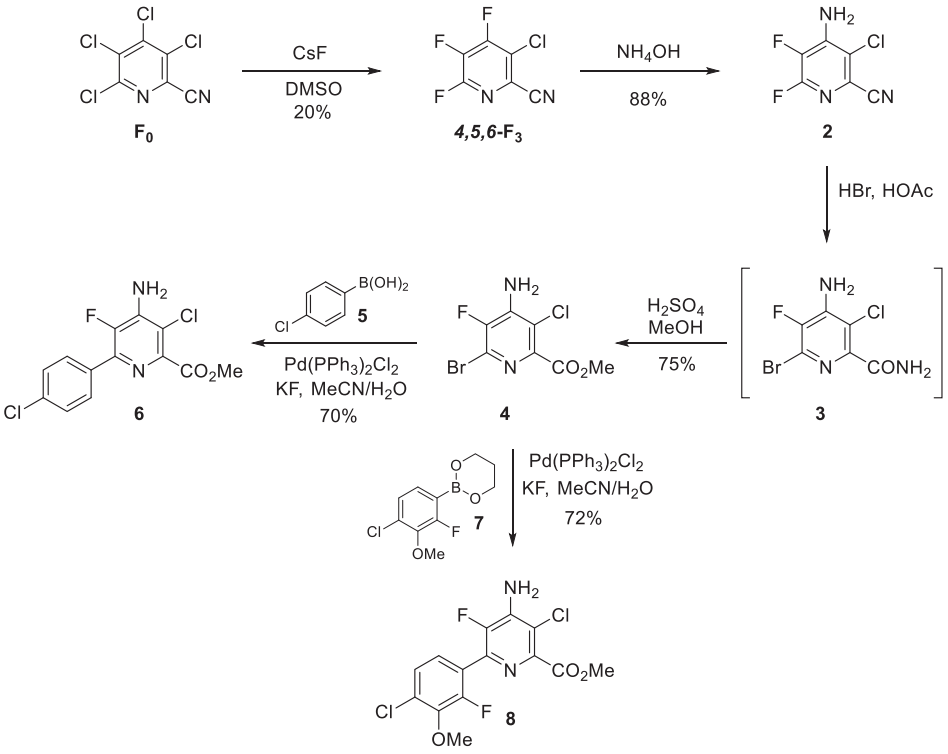


Figure 1. Structures of picolinate auxinic herbicides.

Scheme 1. Discovery Synthesis of 6-Aryl-5-fluoropicolinate Herbicides



Scheme 2. Synthesis of 6-Aryl-5-fluoropicolinates 6 and 8 via the Halex Reaction of F_0



such as dimethyl sulfoxide (DMSO) or *N*,*N*-dimethylformamide, and require the presence of an electron-withdrawing substituent on the arene.[11]

RESULTS AND DISCUSSION

Halex Route. We envisioned that tetrachloropicolinonitrile (F_0) would be an appropriate halex starting material for the synthesis of 6-aryl-5-fluoropicolinates **6** and **8** (Scheme 2). Tetrachloropicolinonitrile is produced industrially by amoxidation of picoline followed by chlorination and was readily available on a bulk scale.[12] In addition to the strongly electron-withdrawing pyridine nitrogen, the ring is further activated toward S_NAr reaction by the nitrile substituent, which could be subsequently hydrolyzed to the carboxylic acid. The halex reaction of F_0 with KF was known to produce mixtures of chlorofluoropicolinonitriles with varying degrees of fluoride substitution.[13,14] Since a successful synthesis of **6** and **8** would require selective formation of the 3-chloro-4,5,6-trifluoro isomer (***4,5,6*-F_3**),[15] we were particularly interested in maximizing the regioselectivity of this halex reaction.

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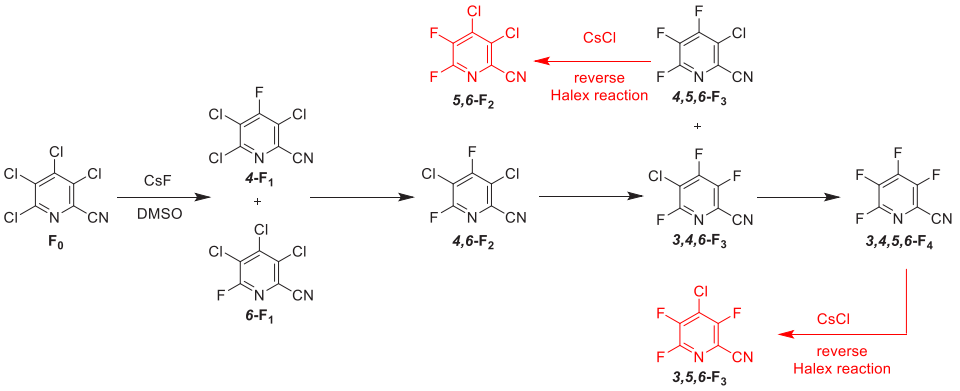
Scheme 3. Sequence of Fluorination Steps in the Halex Reaction of F_0 with CsF in DMSO[a]



[a]Reactions shown in red are due to reverse halex reactions of chloride at the 4-position.

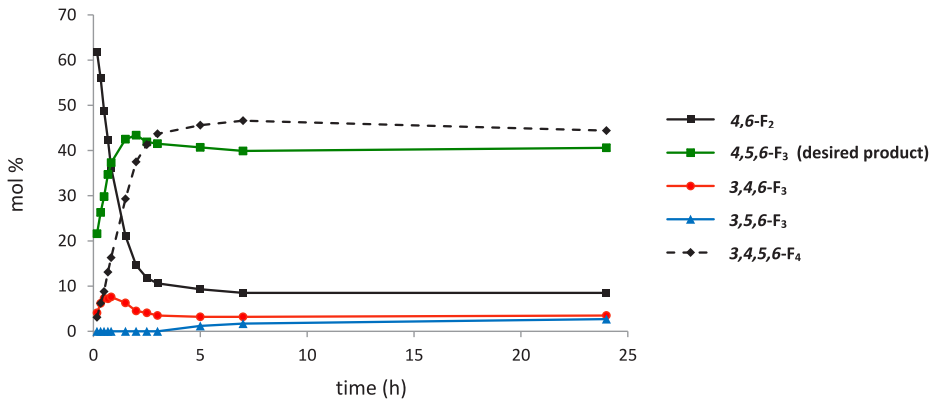


Figure 2. Reaction profile for the halex reaction of F_0 with CsF at 50 °C in DMSO.

The halex reaction of F_0 with CsF was chosen for a detailed study because of the higher solubility and reactivity of CsF compared with KF. The reaction of F_0 with 1 equiv of CsF in DMSO-d_6 was monitored by ^{19}F NMR spectroscopy. Two of the four possible monofluoro isomers, ***4*-F$_1$** and ***6*-F$_1$**, were observed at δ −95.0 and −66.5, respectively (Scheme 3). At ambient temperature, these isomers were formed in a 5:1 ratio, with ***4*-F$_1$** favored over ***6*-F$_1$**. Resonances for neither the ***3*-F$_1$** nor the ***5*-F$_1$** isomer were observed. In addition, of the six possible difluoro isomers, only a small amount of ***4,6*-F$_2$** (7%) was observed in the reaction mixture. This isomer resulted from fluorination of ***4*-F$_1$** and ***6*-F$_1$** at the 6- and 4-positions, respectively. These results confirm that the positions ortho and para to the pyridine ring nitrogen are the most activated for S_NAr reaction. The activating effect of the cyano substituent was relatively low in comparison with that of the pyridine nitrogen, as evidenced by the absence of substitution at the 3- and 5-positions at ambient temperature.

When additional CsF was supplied, more complex reaction mixtures resulted from multiple halex substitutions. The reaction progress was monitored by ^{19}F NMR spectroscopy and GC analysis. Comparison of the GC and ^{19}F NMR integrations along with correlation of resonances by comparison of coupling constants allowed resonances to be assigned to individual components of a mixture. In some cases, products could be isolated by distillation. However, some products were characterized as mixtures of isomers. Several characteristic features were used for structural assignment. ^{19}F chemical shifts and coupling constants can be used to determine the positions of fluorine atoms on the pyridine ring. Fluorine atoms at C6 exhibit chemical shifts in the δ −60 to −80 range. In addition, ^{19}F resonances for F6 are broadened by the ^{14}N quadrapole (full width at half-maximum (fwhm) = 6−8 Hz), which aids the assignment of F6. There is some overlap between the chemical shift ranges for fluorines at C3, C4, and C5, but fluorines at C4 typically give chemical shifts that are downfield relative to those of fluorines at C3 and C5. The fluorines at C3, C4, and C5 exhibit sharp ^{19}F resonances with narrow line widths (fwhm = 1−2 Hz). Assignment of the F6 resonance is also facilitated by the presence of a smaller $^1J_{F-C}$ (238−250 Hz) compared to those for all of the other fluorinated carbons (260−270 Hz). These $^{19}F-^{13}C$ one-bond coupling constants can also be observed in the ^{13}C satellites in the ^{19}F NMR spectra, allowing further confirmation of the assignments. Another particularly diagnostic ^{13}C NMR feature is the large value of $^2J_{F-C}$ between F6 and C5 (30−40 Hz). This coupling constant is much larger than all of the other two-bond $^{13}C-^{19}F$ coupling constants and provides easy assignment of C5, which can facilitate assignment of F5 by correlation to C5 with the $^1J_{F-C}$ observed in the ^{13}C NMR spectrum. Where assignments were ambiguous, computed chemical shifts from density functional theory calculations were used for further confirmation.[16]

The reaction profile for the preparative halex reaction of F_0 on a 100 g scale with 3.5 equiv of CsF in DMSO at 50 °C is shown in Figure 2. The starting material F_0 was rapidly consumed to form ***4,6*-F$_2$** as the sole difluorinated isomer. No monofluoro intermediates were observed under these con-

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ditions because of their rapid reaction with CsF. Further reaction of ***4,6*-F_2** with CsF led to two chlorotrifluoro isomers, ***4,5,6*-F_3** and ***3,4,6*-F_3**, along with the eventual formation of the tetrafluoro product, ***3,4,5,6*-F_4**. The concentration of the desired chlorotrifluoro isomer, ***4,5,6*-F_3**, rapidly peaked at 43 mol % within the first 30 min and then slowly decreased to a stable level of 40 mol %, resulting in a >10:1 ratio over the undesired isomer, ***3,4,6*-F_3** (Figure 3). After aqueous workup

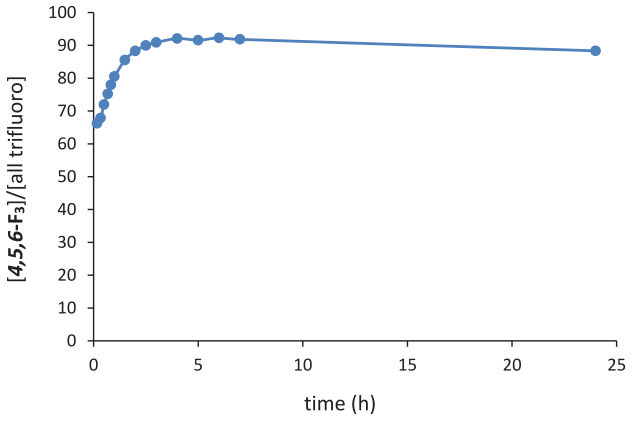

Figure 3. Change in isomeric purity (% ***4,5,6*-F_3**) of trifluorochloropicolinonitrile products in the halex reaction of F_0 with CsF at 50 °C in DMSO.

and extraction into methyl *tert*-butyl ether (MTBE), the trifluoro isomers ***4,5,6*-F_3** and ***3,4,6*-F_3** were isolated as a mixture by vacuum distillation. The desired isomer, ***4,5,6*-F_3**, was further purified by crystallization from this isomeric mixture, but only in a modest 20% yield. The structure of the major isomer as ***4,5,6*-F_3** was confirmed by ^{19}F NMR spectroscopy, which exhibited three resonances. The resonance for F6 appeared as a triplet with J_{F-F} = 23.2 Hz at δ −78.02. Inspection of the ^{13}C satellites for this resonance indicated that $^{1}J_{C-F}$ = 247 Hz. F4 gave rise to a doublet of doublets (J_{F-F} = 22.7, 18.5 Hz) at δ −114.16, and F5 exhibited a doublet of doublets (J_{F-F} = 23.7, 18.4 Hz) at δ −149.28. The ^{13}C NMR spectrum of ***4,5,6*-F_3** exhibited three resonances coupled to ^{19}F with large $^{1}J_{C-F}$ values. C6 gave rise to a resonance at δ 151.3 (ddd, J_{C-F} = 247, 13, 5 Hz) and was identified by the slightly smaller $^{1}J_{C-F}$ value. C4 and C5 gave rise to resonances with larger one-bond ^{13}C−^{19}F coupling constants at δ 154.5 (ddd, J_{F-C} = 270, 11, 7 Hz) and 138.0 (ddd, J_{F-C} = 279, 31, 13 Hz), respectively. The assignment of C5 was aided by the observation of the characteristically large $^{2}J_{F-C}$ value of 31 Hz. The structure of ***4,5,6*-F_3** was confirmed by X-ray crystallography (see the Supporting Information).

The mother liquors from the recrystallization of ***4,5,6*-F_3** contained similar amounts of ***4,5,6*-F_3** and ***3,4,6*-F3**. In addition to resonances assigned to ***4,5,6*-F_3**, the ^{19}F NMR spectrum of this mixture showed three resonances for F6 (δ −64.5), F4 (δ −113.2), and F3 (δ −137.6) of the minor isomer. The presence of a chlorine atom at C5 in the minor isomer was confirmed by ^{13}C NMR spectroscopy through the absence of a large one-bond J_{F-C} to the C5 resonance, which was identified by its diagnostic $^{2}J_{F-C}$ value of 40 Hz. Moreover, the upfield chemical shift of C5 (δ 113.44) was indicative of chlorine substitution.

Two minor products, ***5,6*-F_2** and ***3,5,6*-F_3** were observed in the halex reaction mixture by ^{19}F NMR spectroscopy. These were attributed to the reverse halex reactions of chloride ion with ***4,5,6*-F_3** and ***3,4,5,6*-F_4**, respectively (Scheme 3). The formation of these reverse halex products was consistent with our previously reported results[17] and with ab initio calculations performed on this reaction system (vide infra). After 10 min, a small amount of ***5,6*-F_2** (0.9 mol %) was observed by ^{19}F NMR spectroscopy and was proposed to result from the reaction of ***4,5,6*-F_3** with CsCl. After 30 min, the amount of ***5,6*-F_2** had decreased to 0.2 mol %. Similarly, a third trifluoro isomer, ***3,5,6*-F_3**, was found to grow to 2.5 mol % over 24 h from the reaction of ***3,4,5,6*-F_4** with chloride at the 4-position.

With a procedure in place to prepare ***4,5,6*-F_3**, the downstream chemistry was examined (Scheme 2). Amination of ***4,5,6*-F_3** was performed in a mixture of EtOAc and 14% aqueous NH_4OH to give the 4-amino derivative **2** along with a 3% yield of a regioisomer, presumably the 6-amino isomer. Recrystallization from heptane gave **2** as a single isomer in 88% yield. Next, the 6-fluoro substituent was converted to the 6-bromo or 6-chloro substituent for use in the Suzuki−Miyaura cross-coupling reactions. Our initial attempts to prepare the 6-chloro derivative involved conversion of the 6-fluoro substituent of **2** to a 6-hydrazinopyridine followed by reaction with SO_2Cl_2.[18] While this approach was effective, concerns about the potential instability of the hydrazine intermediate led us to investigate alternatives. Toward this end, heating **2** in a 33 wt % solution of HBr in acetic acid led to both halogen substitution and hydrolysis of the nitrile to give amide **3**, which was subsequently treated with H_2SO_4 and methanol at 110 °C to give methyl ester **4** in 75% yield over a one-pot, two-step sequence. The reaction of **2** with HBr in acetic acid was relatively slow and required 2 h at 120 °C in a sealed pressure vessel to reach full conversion to **3**. No bromide substitution was observed below the boiling point of acetic acid. This reaction mixture was corrosive under these conditions and required the use of a Hastelloy C reactor. Because of the formation of 1 equiv of HF under these conditions, a basic aqueous quench was employed, and appropriate personal protective equipment (Silvershield gloves and goggles) were used at all times. The Suzuki−Miyaura cross-coupling of **4** with 4-chlorophenylboronic acid (**5**) in the presence of 5 mol % $Pd(PPh_3)_2Cl_2$ with 3 equiv of KF in MeCN/H_2O at 76 °C provided the coupled product **6** in 70% yield. Similarly, the Suzuki−Miyaura coupling of **4** with boronic ester **7** gave 6-arylpicolinate **8** in 72% yield.

Although the overall yield for the conversion of F_0 to **4** was only 13% because of the modest regioselectivity of the halex reaction of F_0, this route avoided the use of the expensive fluorinating reagent Selectfluor and also enabled the preparation of larger samples of 6-arylpicolinate herbicide candidates **6** and **8** for field evaluation.

Ab Initio Computational Study. We recently described the use of G3MP2B3 ab initio calculations to study the regioselectivity of sequential halex reactions of pentachloropyridine.[17] The modified computational method (G3MP2B3*) utilized a larger basis set for the geometry optimizations, a necessity for the anionic transition states. Other slight modifications to the method were also made, and these are described in the Supporting Information.

Ab initio calculations were performed for the exhaustive halex reaction at every position and in all possible reaction sequences. Sixteen possible ground-state structures and 32 transition states were investigated computationally. The resulting G3MP2B3* enthalpies were used to investigate all

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possible halex reactions from $\mathbf{F_0}$ to ***3,4,5,6*-$\mathbf{F_4}$** (Table 1). Enthalpies of activation and/or enthalpies of reaction can be calculated mathematically from the data in Table 1. As an illustration, the activation enthalpy for the reaction of fluoride at the 3-position of ***4*-$\mathbf{F_1}$** (12.6 kcal/mol) to give ***3,4*-$\mathbf{F_2}$** is obtained by subtracting the computed enthalpy of ***4*-$\mathbf{F_1}$** (−15.7 kcal/mol) from the computed energy of transition state ***4*-$\mathbf{F_1}$(3)** (−3.1 kcal/mol). Similarly, the relative energy of any reaction can be computed by comparing the energies of the appropriate species from Table 1.

Table 1. Energies (Relative to Tetrachloropicolinonitrile, $\mathbf{F_0}$) for All Intermediates and Transition States (TSs) for the Halex Reaction of $\mathbf{F_0}$[a]

$\mathbf{F_0}$: 0.0			
2-Cyano-3,4,5,6-tetrachloropyridine TSs			
$\mathbf{F_0}$(3): 11.9	$\mathbf{F_0}$(4): 9.8	$\mathbf{F_0}$(5): 11.6	$\mathbf{F_0}$(6): 10.7
Monofluorinated Minima			
***3*-$\mathbf{F_1}$**: −14.6	***4*-$\mathbf{F_1}$**: −15.7	***5*-$\mathbf{F_1}$**: −15.2	***6*-$\mathbf{F_1}$**: −19.5
Monofluorinated TSs			
***3*-$\mathbf{F_1}$(4)**: −4.3	***3*-$\mathbf{F_1}$(5)**: −3.4	***3*-$\mathbf{F_1}$(6)**: −2.6	***4*-$\mathbf{F_1}$(3)**: −3.1
***4*-$\mathbf{F_1}$(5)**: −3.0	***4*-$\mathbf{F_1}$(6)**: −5.0	***5*-$\mathbf{F_1}$(3)**: −3.6	***5*-$\mathbf{F_1}$(4)**: −4.7
***5*-$\mathbf{F_1}$(6)**: −4.2	***6*-$\mathbf{F_1}$(3)**: −6.2	***6*-$\mathbf{F_1}$(4)**: −9.8	***6*-$\mathbf{F_1}$(5)**: −7.3
Difluorinated Minima			
***3,4*-$\mathbf{F_2}$**: −28.8	***3,5*-$\mathbf{F_2}$**: −29.7	***3,6*-$\mathbf{F_2}$**: −34.0	***4,5*-$\mathbf{F_2}$**: −29.4
***4,6*-$\mathbf{F_2}$**: −35.0	***5,6*-$\mathbf{F_2}$**: −33.5		
Difluorinated TSs			
***3,4*-$\mathbf{F_2}$(5)**: −16.5	***3,4*-$\mathbf{F_2}$(6)**: −17.0	***3,5*-$\mathbf{F_2}$(4)**: −18.5	***3,5*-$\mathbf{F_2}$(6)**: −17.2
***3,6*-$\mathbf{F_2}$(4)**: −24.0	***3,6*-$\mathbf{F_2}$(5)**: −22.3	***4,5*-$\mathbf{F_2}$(3)**: −17.0	***4,5*-$\mathbf{F_2}$(6)**: −18.2
***4,6*-$\mathbf{F_2}$(3)**: −21.0	***4,6*-$\mathbf{F_2}$(5)**: −21.4	***5,6*-$\mathbf{F_2}$(3)**: −20.5	***5,6*-$\mathbf{F_2}$(4)**: −23.0
Trifluorinated Minima			
***3,4,5*-$\mathbf{F_3}$**: −42.6	***3,4,6*-$\mathbf{F_3}$**: −48.1	***3,5,6*-$\mathbf{F_3}$**: −47.9	***4,5,6*-$\mathbf{F_3}$**: −47.7
Trifluorinated TSs			
***3,4,5*-$\mathbf{F_3}$(6)**: −30.2	***3,4,6*-$\mathbf{F_3}$(5)**: −35.0	***3,5,6*-$\mathbf{F_3}$(4)**: −36.9	***4,5,6*-$\mathbf{F_3}$(3)**: −34.0
Tetrafluorinated Minimum			
***3,4,5,6*-$\mathbf{F_4}$**: −60.9			

[a]Enthalpies are in kcal/mol at the high level, modified G3MP2B3* method. The position of attack in the transition states is denoted in parentheses.

The computations for halex reactions were consistent with the regioselectivity observed experimentally by ^{19}F NMR spectroscopy. The computed activation enthalpies for the halex reactions of $\mathbf{F_0}$ at the 4- and 6-positions were 9.8 and 10.7 kcal/mol, respectively. Barriers to exchange by fluoride at the 3- and 5-positions of $\mathbf{F_0}$ were calculated to be 11.9 and 11.6 kcal/mol, respectively. The 0.9 kcal/mol difference between the transition-state enthalpies for reaction at the 4- and 6-positions of $\mathbf{F_0}$ would lead to a predicted selectivity of 4.6:1 at room temperature, in excellent agreement with the observed 6.2:1 ratio of ***4*-$\mathbf{F_1}$** to ***6*-$\mathbf{F_1}$** determined by ^{19}F NMR spectroscopy. The activation energies for substitutions at the 3- and 5-positions of $\mathbf{F_0}$ were calculated to be >1 kcal/mol higher than the barrier to formation of ***6*-$\mathbf{F_1}$**, consistent with the absence of isomers ***3*-$\mathbf{F_1}$** and ***5*-$\mathbf{F_1}$**. The ground-state energies of ***4*-$\mathbf{F_1}$** and ***6*-$\mathbf{F_1}$** differed by 3.8 kcal/mol, which would indicate a large thermodynamic preference for ***6*-$\mathbf{F_1}$** over ***4*-$\mathbf{F_1}$**. The observed 6.2:1 ratio of 4-fluoro ***4*-$\mathbf{F_1}$** over 6-fluoro ***6*-$\mathbf{F_1}$** was consistent with kinetic rather than thermodynamic control of the halex regioselectivities.[17]

The second halex reaction can therefore only proceed by the reaction of ***4*-$\mathbf{F_1}$** and ***6*-$\mathbf{F_1}$** with fluoride. The reaction of the major 4-fluoro isomer, ***4*-$\mathbf{F_1}$**, at the 6-position was calculated to be ∼2 kcal/mol lower in energy than reactions at the 3- and 5-positions. The halex reaction of ***4*-$\mathbf{F_1}$** selectively occurred at the 6-position to give the 4,6-difluoro isomer ***4,6*-$\mathbf{F_2}$**. Likewise, the minor 6-fluoro isomer, ***6*-$\mathbf{F_1}$**, had a calculated $\Delta H^{\ddagger}$ for the reaction at the 4-position that was 2.5 and 3.6 kcal/mol lower than the $\Delta H^{\ddagger}$ values for the reactions at the 5- and 3-positions, respectively. Thus, ***6*-$\mathbf{F_1}$**, like ***4*-$\mathbf{F_1}$**, gave only the 4,6-difluoro isomer, consistent with our observation of regiospecific formation of ***4,6*-$\mathbf{F_2}$** as the sole difluoro product. The barriers to these kinetically preferred fluoride substitutions of ***4*-$\mathbf{F_1}$** and ***6*-$\mathbf{F_1}$** were 10.7 and 9.7 kcal/mol, respectively. In fact, for the first two fluoride exchanges, the barriers at the 4- and 6-positions were calculated to be in the 9.7−10.7 kcal/mol range. In addition to being kinetically preferred, ***4,6*-$\mathbf{F_2}$** is also thermodynamically favored over the other five difluoro isomers.

Therefore, the third halex substitution has only two kinetically possible pathways since ***4,6*-$\mathbf{F_2}$** can react only at the 3- or 5-position (Figure 4). The two transition-state enthalpies for reaction of ***4,6*-$\mathbf{F_2}$** with fluoride were calculated to differ by only 0.4 kcal/mol, with substitution by fluoride at the 5-position ($\Delta H^{\ddagger}$ = 13.6 kcal/mol) slightly favored over substitution at the 3-position ($\Delta H^{\ddagger}$ = 14.0 kcal/mol). The desired trifluoro isomer, ***4,5,6*-$\mathbf{F_3}$**, is therefore kinetically favored over ***3,4,6*-$\mathbf{F_3}$**. The products of these reactions, ***4,5,6*-$\mathbf{F_3}$** and ***3,4,6*-$\mathbf{F_3}$**, can further react with fluoride at their last remaining chlorinated positions to give ***3,4,5,6*-$\mathbf{F_4}$**. The barrier to fluoride substitution of the undesired 3,4,6-trifluoro isomer, ***3,4,6*-$\mathbf{F_3}$**, at the 5-position was calculated to be 13.1 kcal/mol, while that for the analogous reaction of the desired 4,5,6-trifluoro isomer, ***4,5,6*-$\mathbf{F_3}$**, at the 3-position was calculated to be

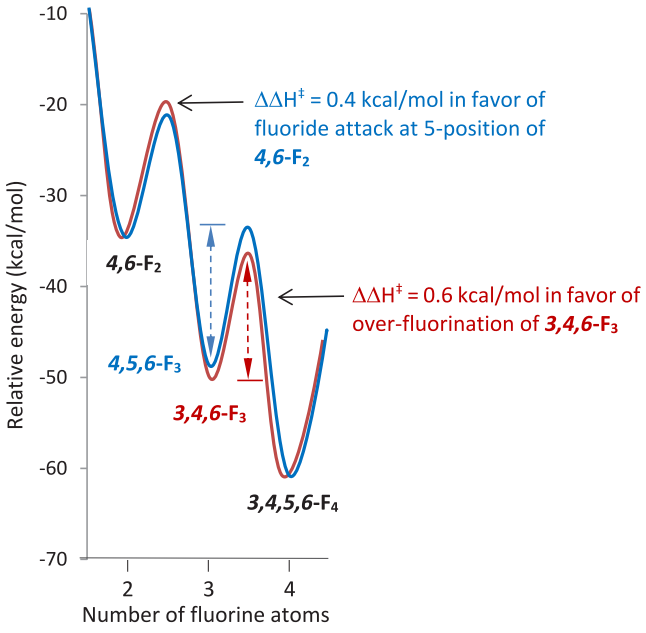

Figure 4. G3MP2B3*-calculated reaction coordinates for the halex reactions of fluoride ion with ***4,6*-$\mathbf{F_2}$**. The blue line depicts the kinetically preferred pathway to give ***4,5,6*-$\mathbf{F_3}$**. The red line depicts the less favored pathway to give ***3,4,6*-$\mathbf{F_3}$** ($\Delta\Delta H^{\ddagger}$ = 0.4 kcal/mol). The subsequent reaction of ***3,4,6*-$\mathbf{F_3}$** with fluoride to give ***3,4,5,6*-$\mathbf{F_4}$** was calculated to have $\Delta H^{\ddagger}$ = 0.6 kcal/mol lower than the corresponding reaction of ***4,5,6*-$\mathbf{F_3}$** with fluoride.

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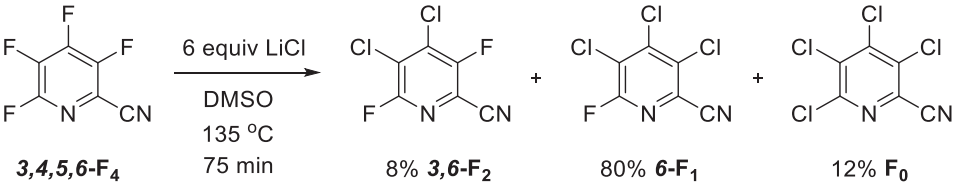
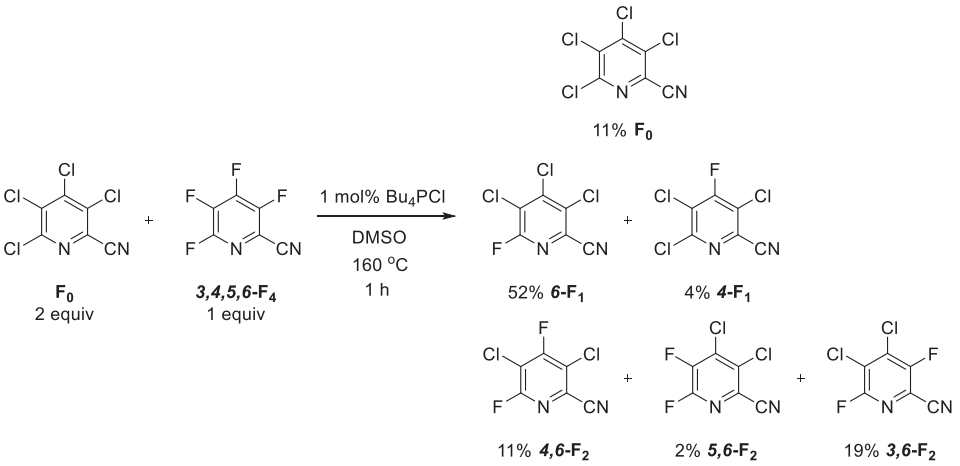
Scheme 4. Products Observed in the Reverse Halex Reaction of *3,4,5,6*-F_4 with 6 equiv of LiCl in DMSO



Scheme 5. Products Observed in the Catalytic Halopyridine Scrambling Reaction of *3,4,5,6*-F_4 and F_0



13.7 kcal/mol. On the basis of our calculations, the undesired *3,4,6*-F_3 isomer reacts faster than *4,5,6*-F_3 to give *3,4,5,6*-F_4. These calculations were consistent with our experimental observations that the ratio of *4,5,6*-F_3 to *3,4,6*-F_3 increases as the degree of fluorination increases to form *3,4,5,6*-F_4 (Figure 4). The reactivity difference between the two trifluorinated isomers is analogous to a "kinetic resolution" that increases the isomeric purity of the trifluorinated fraction at the expense of conversion to the overfluorinated product, *3,4,5,6*-F_4.

Recycle of *3,4,5,6*-F_4 by Reverse Halex and Halopyridine Scrambling Reactions. We recently showed that fluoropyridines can be converted to mixed chloropyridines by S_NAr reactions of chloride ion.[17] These reverse halex reactions can be driven by the high solubility of LiCl in DMSO. LiF has a much lower solubility in this solvent, and its precipitation provides a driving force for the reaction. Weaver recently showed that stoichiometric Me_3SiCl can also promote the reverse halex reaction of pentafluoropyridine with added chloride ion through a donor−acceptor mechanism.[19] We postulated that this could allow recycle of unwanted *3,4,5,6*-F_4 to intermediates that could be recycled for halex reactions to give *4,5,6*-F_3. A curious observation in our halex reactions was the formation of small amounts of *3,5,6*-F_3 at extended reaction times (Figure 2). Our G3MP2B3* computations indicated that *3,4,6*-F_3 was the thermodynamically most stable trifluoro isomer, with a computed $\Delta H°$ slightly lower than those for *4,5,6*-F_3 and *3,5,6*-F_3 (Table 1). Reverse halex reactions can be performed with LiCl in DMSO to give chloride substitution products that are formed by kinetic control. The reaction of *3,4,5,6*-F_4 with 1 equiv of LiCl in DMSO-d_6 at ambient temperature gave *3,5,6*-F_3 as the major product, which displayed mutually coupled ^{19}F NMR resonances at δ −83.5 (F6), −118.1 (F3), and −126.1 (F5). The lowest barrier to chloride substitution of *3,4,5,6*-F_4 ($\Delta H^‡$ = 24.0 kcal/mol) was calculated to be quite selective at the 4-position to give *3,5,6*-F_3, consistent with this experimental observation.[20] The extent of chlorination could be increased by the use of excess LiCl (Scheme 4). When the reaction of *3,4,5,6*-F_4 was performed with 6 equiv of LiCl at 135 °C in DMSO-d_6, GC and ^{19}F NMR analyses showed the formation of a mixture of *6*-F_1 (80%), F_0 (12%), and *3,6*-F_2 (8%). The reaction of the first intermediate, *3,5,6*-F_3, should occur at the 5-position to give *3,6*-F_2, with a $\Delta H^‡$ that was calculated to be 1.8 kcal/mol lower than that for chloride substitution at the 3-position (Table 1). Notably, reaction of *3,5,6*-F_3 at the 6-position was calculated to have a barrier 5.1 kcal/mol higher than that for reaction of chloride at the 5-position. These calculated barriers are consistent with the observed formation of *3,6*-F_2 as the sole difluorinated product formed by kinetic control of the regiochemistry. Difluoro intermediate *3,6*-F_2 reacted selectively at the 3-position to give *6*-F_1 as the major product, consistent with the calculated $\Delta H^‡$ values of 27.8 and 31.4 kcal/mol for the reactions at the 3- and 6-positions, respectively. Finally, reaction of *6*-F_1 with chloride can occur only at the 6-position to give F_0 with a calculated barrier of 30.2 kcal/mol.

As part of our studies of halex reactions, we have found that scrambling of chloropyridines and fluoropyridines can be accomplished using catalytic halide ion.[17] This reaction proceeds by a mechanism involving a series of reversible S_NAr reactions that scramble halogens among pyridine ring positions. When a 2:1 mixture of F_0 and *3,4,5,6*-F_4 was heated in DMSO at 160 °C for 1 h in the presence of 1 mol % *n*-Bu_4PCl, a mixture of chlorofluoropyridines was formed (Scheme 5). The product distribution showed a strong preference for isomers containing a fluorine atom at the 6-position. For example, the *6*-F_1:*4*-F_1 ratio of 13:1 from halopyridine scrambling is opposite the selectivity observed in the forward halex reaction of F_0. The regioselectivity of this forward halex reaction is driven by kinetics, while the halopyridine scrambling experiment is controlled by thermo-

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dynamics and gives ***6*-F_1**, which is more stable than ***4*-F_1** by 3.8 kcal/mol.

The reverse halex reaction and the halopyridine scrambling reaction provide strategies for recycle of ***3,4,5,6*-F_4** to obtain useful intermediates. Of the products formed in Schemes 4 and 5, only those that contain fluorine atoms at the 3-position (e.g., ***3,6*-F_2**) cannot be converted to the desired trifluorinated regioisomer ***4,5,6*-F_3** by subsequent halex reaction with fluoride. As a demonstration of this strategy, the product mixture from the catalytic halopyridine scrambling reaction of ***3,4,5,6*-F_4** and **F_0** (Scheme 5) was reacted with CsF in DMSO at 70 °C. After 2.5 h, GC showed the formation of a mixture containing ***3,4,5,6*-F_4** (61%), ***4,5,6*-F_3** (31%), ***3,5,6*-F_3** (3.4%), and ***4,6*-F_2** (4.8%), which is similar to the product composition formed by the halex reaction of **F_0** with CsF in DMSO.

CONCLUSIONS

This detailed experimental and computational study has shown that the regioselectivity of the halex reaction of tetrachloropicolinonitrile is kinetically controlled. This halex reaction is the key first step in a new synthesis of 6-aryl-5-fluoropicolinate herbicides. The first two fluoride substitution reactions produced a single regioisomer, ***4,6*-F_2**. The competition between fluoride substitution at the 3- and 5-positions of ***4,6*-F_2** favored the 5-position, producing the desired trifluoro isomer, ***4,5,6*-F_3**. The undesired trifluoro isomer, ***3,4,6*-F_3**, further reacted with additional fluoride with a lower barrier than did the ***4,5,6*-F_3** isomer to produce ***3,4,5,6*-F_4**. Although these reactions both favor the formation of the desired ***4,5,6*-F_3**, the similarity of the rates of the third and fourth fluoride substitution reactions limits the overall yield of ***4,5,6*-F_3** from the halex reaction of tetrachloropicolinonitrile. The over-fluorinated byproduct, ***3,4,5,6*-F_4**, could be recycled to useful 3-chloro intermediates by the reverse halex reaction with LiCl in DMSO (kinetic control) or by a catalytic halopyridine scrambling reaction (thermodynamic control).

EXPERIMENTAL SECTION

3-Chloro-4,5,6-trifluoropicolinonitrile (*4,5,6*-F_3). To a 1000 mL three-neck round-bottom flask equipped with a magnetic stirrer, a condenser, a heating mantle, and a N_2 inlet were charged CsF (220 g, 1447 mmol) and DMSO (500 mL). On the basis of Karl Fischer analysis, the water content of the mixture was determined to be 728 ppm. The mixture was heated at ∼60 °C and distilled under vacuum at 50−60 °C over 1 h to remove ∼200 mL of DMSO. The vacuum was broken with N_2 at 60 °C, and the mixture was cooled to 17 °C over 5 min. On the basis of Karl Fischer analysis, the water content of the mixture was determined to be 76 ppm. 3,4,5,6-Tetrachloropicolinonitrile (**F_0**) (100 g, 413 mmol) was charged under N_2 over 5 min at 17−20 °C. The resulting yellow suspension was stirred at 20 °C for 10 min and heated to 50 °C over 20 min (the reaction temperature increased to 60 °C from 50 °C because of an exotherm). The reaction mixture was stirred at 50−60 °C for 1.5 h, at which point GC analysis showed that a 39.8% total yield (area under the curve, AUC) of the combined trifluoro products was formed, along with 54.0% (AUC) ***3,4,5,6*-F_4** and 6.3% (AUC) ***4,6*-F_2**. The reaction mixture was cooled to 20 °C over 10 min and then added to H_2O (2 L) at 10−20 °C over 10 min. The mixture was extracted with MTBE (3 × 500 mL), and the combined organics were concentrated under vacuum at <20 °C to give the crude product as a brown oil (74.9 g). The resulting brown oil was charged to a 250 mL round-bottom flask fitted with a nine-tray distillation head. The content was distilled under vacuum to give 38.1 g of a colorless oil [24.5% (AUC) ***4,5,6*-F_3**] at ∼4 mmHg/and ∼50 °C and 22 g of a colorless oil [84.1% (AUC) ***4,5,6*-F_3**] at ∼2 mmHg/∼60 °C. The 22 g sample [84.1% (AUC)] was dissolved in heptanes/MTBE (22 mL, 4:1) with heating and seeded with a pure sample of the desired product, ***4,5,6*-F_3** (50 mg) at 20 °C. The resulting mixture was stirred at 20 °C for 2 h, cooled to 5 °C over 2 h, and then further stirred at 5 °C for 3 h. The resulting suspension was filtered, and the filter cake was rinsed with heptanes (2 × 40 mL). The solid was dried to afford the desired product ***4,5,6*-F_3** as a white crystalline solid (15.8 g, 19.8% yield). Mp (DSC): 43−46 °C. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.58 (ddd, J = 270.1, 10.5, 6.7 Hz), 151.38 (ddd, J_{C-F} = 246.9, 12.4, 5.3 Hz), 138.03 (ddd, J_{C-F} = 279.1, 31.4, 13.2 Hz), 124.7 (ddd, J_{F-C} = 16, 6, 2 Hz, C3), 124.4 (ddd, J_{F-C} = 16, 7, 2 Hz, C2), 112.23 (d, J_{C-F} = 3.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ −78.02 (t, J_{F-F} = 23.2 Hz), −114.16 (dd, J_{F-F} = 22.7, 18.5 Hz), −149.28 (dd, J_{F-F} = 23.7, 18.4 Hz). Anal. Calcd for $C_6ClF_3N_2$: C, 37.43; N, 14.55. Found: C, 36.91; N, 14.25. Single crystals were grown from 4:1 heptanes/MTBE.

4-Amino-3-chloro-5,6-difluoropicolinonitrile (2). A solution of ***4,5,6*-F_3** (200 g, 1.03 mol) in EtOAc (3 L) was cooled to 10 °C. NH_4OH solution (14%, 1296 g, 5.1 mol) was added at a rate that kept the temperature between 18 and 23 °C. After the addition was complete, the organic layer was separated and washed with aqueous NaCl solution (50 wt %, 500 mL) and then saturated NaCl solution (250 mL). The organic layer was concentrated under vacuum to approximately 500 mL. Heptane (1 L) was added, and the product was collected by filtration. The product was washed with pentane and dried under vacuum to give **2** as a white crystalline solid (173.8 g, 88% yield). Mp: 190−191.5 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.56 (s). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 150.03 (dd, J_{C-F} = 232.4, 12.5 Hz), 144.29 (dd, J_{C-F} = 11.4, 6.9 Hz), 133.72 (dd, J_{C-F} = 257.9, 30.8 Hz), 122.14 (dd, J_{C-F} = 19.6, 4.9 Hz), 119.31 (s), 114.25 (s). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ −91.24 (d, J_{F-F} = 24.2 Hz), −154.97 (d, J_{F-F} = 24.2 Hz). Anal. Calcd for $C_6H_2ClF_2N_3$: C, 38.02; H, 1.06; N, 22.17. Found: C, 37.91; H, 1.00; N, 22.02.

Methyl 4-Amino-6-bromo-3-chloro-5-fluoropicolinate (4). Note: The reaction mixture is heated above the boiling point of the HBr/acetic acid solution. As a safety precaution, the pressure vessel should be placed in a fume hood behind a blast shield, and the reactor should be fitted with a Hastelloy C rupture disk that is compatible with the corrosive reaction mixture. To a Hastelloy C Parr vessel were added **2** (70 g, 0.37 mol) and 33 wt % HBr in acetic acid (700 mL). The vessel was sealed and heated at 120 °C for 2 h. After cooling to room temperature, the vessel was opened, and the supernatant was transferred into a rotary evaporator and concentrated under vacuum. The concentrated residue of 4-amino-6-bromo-3-chloro-5-fluoropicolinamide (**3**) was diluted with methanol (600 mL). To this mixture was slowly added concentrated H_2SO_4 (40 g), and the reactor was sealed and heated at 110 °C for 6 h. The cooled reaction mixture was slowly poured into saturated aqueous Na_2CO_3 (2 L) and Et_2O (1 L). The Et_2O extract was dried over anhydrous $MgSO_4$, filtered, and concentrated to give a tan solid. This solid was purified by filtration through a 400 g pad of silica gel with 5%

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EtOAc in dichloromethane (DCM). The eluent was concentrated to about 100 mL, and then 400 mL of heptane was added. The resulting mixture was concentrated under vacuum to give methyl 4-amino-6-bromo-3-chloro-5-fluoropicolinate (**4**) as a fine white crystalline solid after filtration (78 g, 75% yield). Mp: 119−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 163.54 (s), 144.63 (d, J_{C-F} = 256.3 Hz), 142.60 (d, J_{C-F} = 4.9 Hz), 140.55 (d, J_{C-F} = 13.6 Hz), 125.61 (d, J_{C-F} = 21.0 Hz), 116.65 (s), 53.2 (s). ^{19}F NMR (376 MHz, $CDCl_3$): δ −128.86. EI-MS: m/z 284 ($[M]^+$). Anal. Calcd for $C_7H_3BrClFN_2O_2$: C, 29.66; H, 1.78; N, 9.88. Found: C, 30.03; H, 1.80; N, 9.91.

Methyl 4-Amino-3-chloro-6-(4-chlorophenyl)-5-fluoropicolinate (6). A 500 mL three-neck round-bottom flask equipped with a reflux condenser, an internal temperature probe, and a N_2 inlet was charged with $Pd(PPh_3)_2Cl_2$ (1.238 g, 1.764 mmol), **4** (10.0 g, 35.3 mmol), (4-chlorophenyl)boronic acid (**5**) (7.17 g, 45.9 mmol), and KF (6.15 g, 106 mmol). The flask was evacuated and purged with N_2 (×3). To the flask was added degassed MeCN/H_2O (142 mL, 3:1). The mixture was heated at 76 °C under N_2 for 8 h, cooled to room temperature, and filtered over Celite, and the filter pad was washed with MeCN (150 mL). The mixture was concentrated to about one-fourth the volume in vacuo and then extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (150 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by silica gel column chromatography (330 g of silica, gradient 0−15% EtOAc/hexanes) to yield **6** as a white solid (7.8 g, 70% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90−7.78 (m, 2H), 7.63−7.48 (m, 2H), 7.02 (br s, 2H), 3.90 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6): δ −140.15. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 165.48, 145.68 (d, J_{C-F} = 258.1 Hz), 144.59 (d, J_{C-F} = 4.6 Hz), 142.39 (d, J_{C-F} = 14.5 Hz), 140.02 (d, J_{C-F} = 8.6 Hz), 134.57, 133.43 (d, J_{C-F} = 5.3 Hz), 130.62 (d, J_{C-F} = 6.0 Hz), 129.00, 112.55 (d, J_{C-F} = 2.5 Hz), 53.14. HR-ESI-MS: $[M + H]^+$ calcd for $C_{13}H_9Cl_2FN_2O_2$, 314.0025; found, 314.0025.

Methyl 4-Amino-3-chloro-5-fluoro-6-(4-chloro-2-fluoro-3-methoxyphenyl)picolinate (8). A stream of N_2 was passed through a colorless mixture of **4** (2.8 g, 10 mmol) and 2-(4-chloro-2-fluoro-3-methoxyphenyl)-1,3,2-dioxaborinane (**7**) (3.2 g, 13 mmol) in CH_3CN (40 mL). A solution of KF (1.7 g, 30 mmol) in H_2O (20 mL) was added, and the mixture was heated to 50 °C for 20−30 min. $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol) was added, and the mixture was heated at 65 °C. The reaction was monitored by HPLC and was complete after 5 h. The reaction mixture was filtered hot through a short pad of Celite, diluted with H_2O (20 mL), and allowed to cool to ambient temperature. The product was collected by filtration and dried to give **8** as a light-tan solid (2.6 g, 72% yield). Mp: 169−170.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, J_{H-H} = 8.4 Hz, 1H), 7.32 (t, J_{H-H} = 7.7 Hz, 1H), 7.15 (s, 2H, NH_2), 3.96 (s, 3H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 164.85 (s), 153.11 (d, J_{C-F} = 252.5 Hz), 146.29 (s), 144.52 (d, J_{C-F} = 4.3 Hz), 143.74 (s), 142.75 (dd, J_{C-F} = 227.1, 14.0 Hz), 136.38 (d, J_{C-F} = 13.4 Hz), 128.58 (d, J_{C-F} = 3.2 Hz), 125.87 (s), 125.54 (d, J_{C-F} = 3.5 Hz), 122.89 (dd, J_{C-F} = 13.8, 4.0 Hz), 113.01 (d, J_{C-F} = 3.0 Hz), 61.61 (d, J_{C-F} = 4.2 Hz), 52.70 (s). Anal. Calcd for $C_{14}H_{10}Cl_2F_2N_2O_3$: C, 46.30; H, 2.78; N, 7.71. Found: C, 46.60; H, 2.68; N, 7.51.

Reverse Halogen Exchange of 3,4,5,6-Tetrafluoropicolinonitrile. A mixture of 3,4,5,6-tetrafluoropicolinonitrile (***3,4,5,6*-F_4**) (17 g, 0.1 mmol) and LiCl (25.4 g, 0.6 mol) was heated in dry DMSO (200 mL). The reaction was monitored by GC analysis of aliquots extracted into Et_2O from H_2O. The reaction mixture was heated at 120 °C for 5 min. GC showed that the starting material had been consumed, and a mixture of ***3,6*-F_2** (83% AUC) and ***6*-F_1** (14% AUC) had formed. Further heating at 135 °C for 75 min gave an 8:80:12 mixture of ***3,6*-F_2**, ***6*-F_1**, and F_0, respectively.

Halopyridine Scrambling Reaction. A mixture of F_0 (16.1 g, 66 mmol) and ***3,4,5,6*-F_4** (5.9 g, 33 mmol) was heated at 160 °C under N_2. To this stirred solution was added tetra-*n*-butylphosphonium chloride (0.36 g, 1.2 mmol). The solution was heated at 160 °C for 1 h. An aliquot was dissolved in DCM and passed through a short pad of silica gel. GC analysis showed a mixture of 11.2% F_0, 11.3% ***4,6*-F_2**, 2.3% ***5,6*-F_2**, 19% ***3,6*-F_2**, 52.6% ***6*-F_1**, and 3.6% ***4*-F_1**.

Recycle from Halopyridine Scrambling Reaction. A reaction flask fitted with a short-path distillation head was charged with finely milled CsF (35.1 g, 0.23 mol) and dry DMSO (175 mL). The reaction mixture was stirred and heated at 70−75 °C under vacuum (0.1 mm) until DMSO (75 mL) was distilled off. This slurry was cooled to 50 °C under N_2, and the molten reaction mixture from the preceding halopyridine scrambling reaction (21.7 g, 11.2% F_0, 11.3% ***4,6*-F_2**, 2.3% ***5,6*-F_2**, 19% ***3,6*-F_2**, 52.6% ***6*-F_1** and 3.6% ***4*-F_1**) was added. The reaction mixture was heated at 70 °C for 2.5 h with stirring. GC showed the presence of 61% ***3,4,5,6*-F_4**, 31% ***4,5,6*-F_3**, 3.4% ***3,5,6*-F_3**, and 4.8% ***4,6*-F_2**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00197.

^{1}H, ^{13}C, and ^{19}F NMR spectra of new compounds, crystallographic details for ***4,5,6*-F_3**, and details of the theoretical methodology and a complete set of energies and Cartesian coordinates (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: greg.whiteker@corteva.com.

ORCID

Gregory T. Whiteker: 0000-0002-9439-6696
Qiang Yang: 0000-0003-3762-5015
Belgin Canturk: 0000-0002-9848-1054
Jerzy Klosin: 0000-0002-9045-7308

Author Contributions

The manuscript was written through contributions of all authors. All of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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