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Developing Efficient Nucleophilic Fluorination Methods and Application to Substituted Picolinate Esters

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Supporting Information

ABSTRACT: This report describes nucleophilic fluorination of 3 and 5-substituted picolinate ester substrates using potassium fluoride in combination with additive promoters. Agents such as tributylmethylammonium or tetraphenylphosphonium chloride were among the best additives investigated giving improved fluorination yields. Additionally, the choice of additive promoters could influence the potential formation of new impurities such as alkyl ester exchange. Other parameters explored in this study include additive stoichiometry, temperature influence on additive degradation, solvent selection, product isolation by solvent extraction, and demonstration of additive recycling.

INTRODUCTION

Aryl fluorides are extremely important structural motifs that are featured prominently in pharmaceuticals, agrochemicals, organic materials, and biological imaging agents.[1] An increasing number of fluorine-containing biologically active molecules have been developed for pharmaceutical and agrochemical applications (Figure 1). Despite rising pharmaceutical and agrochemical prevalence, the selective fluorination of arenes remains a difficult task. As a result, significant recent efforts have focused on the development of new synthetic procedures for the formation of C_{Aryl}–F bonds.[2,3]

Halex reactions are a class of nucleophilic substitutions where a carbon–halogen bond ($C–X_1$) is converted to new and different carbon–halogen ($C–X_2$). For this study, halex reactions specifically refer to the conversion of aryl–Cl bonds to aryl–F bonds using a nucleophilic fluoride source. Halex reactions, typically run in polar aprotic solvents, require extreme temperatures (greater than 150 °C) largely due to the poor solubility of metal fluoride salts such as cesium fluoride (CsF) and potassium fluoride (KF).[4] KF is much more economical than CsF but usually less reactive. Traditionally, common halex substrates require an electron-withdrawing group to activate the aryl ring towards nucleophilic attack. These factors often present challenges for developing efficient fluorination methods for aromatic and heteroaromatic motifs.

Recently, our efforts have focused on the development of mild, selective methods to fluorinate aromatic systems. One strategy developed in our laboratories utilizes the combination of copper triflate $Cu(OTf)_2$ and KF to convert a variety of aryl potassium trifluoroborates to the corresponding fluorinated products in good yield.[5] This methodology has a wide range of functional group compatibility (Figure 2). Additionally, we developed methodology for high yielding fluorination of heteroarenes utilizing adaptations to the anhydrous tetrabutylammonium fluoride (TBAF) protocol.[6] Unique to this adaptation was the ability to premix some of the heteroarene substrates with tetrabutylammonium cyanide before adding hexafluorobenzene, thus enabling in situ generation of anhydrous TBAF. This strategy telescoped the fluorination procedure into a single one pot process. Overall, the anhydrous TBAF agent exhibited good solubility in a wide range of solvent systems, thus delivering a potent fluoride source under much milder room temperature conditions. Moving forward, we wanted to apply the better solubility properties associated with nucleophilic fluoride agents such as anhydrous TBAF toward cheaper, less soluble metal fluorides such as KF. This paper will discuss efforts to utilize additives that would enhance reactivity of KF and apply this methodology toward less active heteroarene substrates (e.g., specifically picolinate ester motifs).

RESULTS AND DISCUSSION

To investigate reaction parameters (additives, solvent selection, stoichiometry, temperature) for effective nucleophilic substitution using metal fluorides, monochloro picolinate esters **6** and **9** were chosen. Two complementary synthetic approaches for these substrates are outlined (Scheme 1). Ethyl-3-chloro-6-chloropicolinate (**6**) was prepared via the two-step procedure[6] outlined in Scheme 1. Fisher esterification of 3,6-dichloropicolinic acid followed by a Suzuki cross-coupling with phenyl boronic acid afforded **6** in 38% yield (for two steps). Preparation of **9** utilized 2,3-dichloro-6-(trichloromethyl)-pyridine as the starting material. After purification of **7** by recrystallization from methanol, treatment with concentrated sulfuric acid followed by a solvent quench using 2-propanol directly afforded **8** in good yield. A subsequent Suzuki cross-coupling with phenyl boronic acid afforded **9** in 94% yield.

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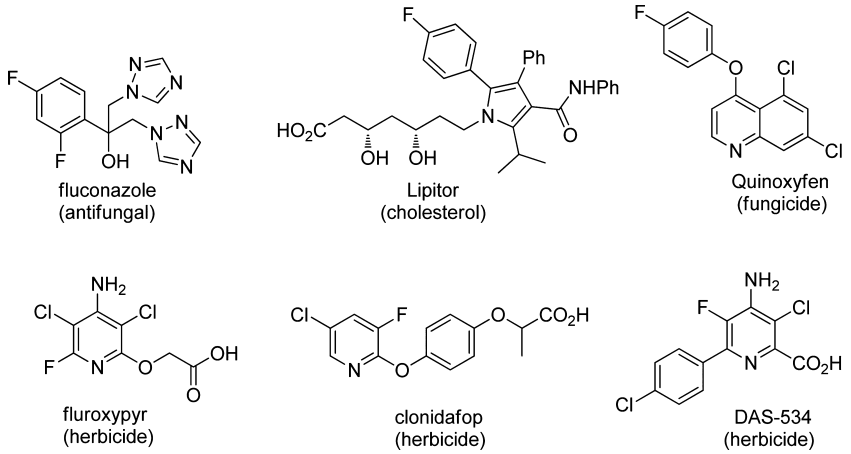


Figure 1. Representative aryl fluoride containing actives.

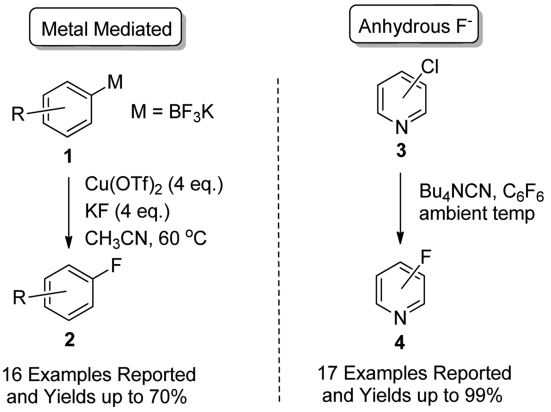
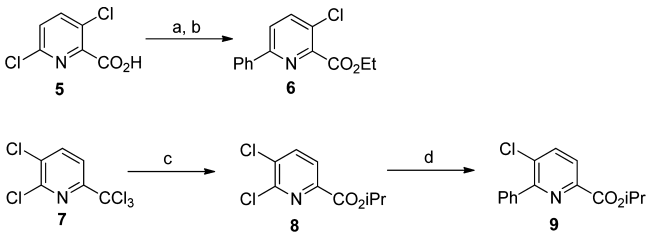


Figure 2. Mild and selective fluorination strategies for arenes and heteroarenes.

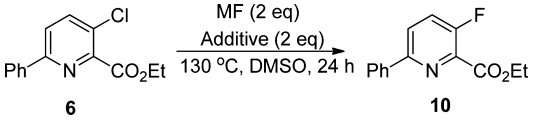
Scheme 1. Synthetic approaches to picolinate model substrates 6 and 9[a]



[a](a) EtOH, H_2SO_4, then Na_2CO_3, 73% yield; (b) $PhB(OH)_2$, $Pd(Ph_3P)_4$, KF, 52% yield; (c) H_2SO_4, 130 °C; then *i*-PrOH, 70 °C, 86% yield; (d) $PhB(OH)_2$, $Pd(Ph_3P)_2Cl_2$, KF, CH_3CN, 94% yield.

Initial efforts surveyed promoters that could improve nucleophilic substitution activity when used in combination with metal fluorides. We aimed to increase the reactivity of KF to be comparable to that of CsF through the use of additives. To establish a control, a baseline fluorination yield was measured for both CsF and KF without additives (Table 1 and 2; entries 1−2 respectively). CsF afforded higher observed yields than KF for both substrates **6** and **9**. To standardize screening conditions and to investigate fluorination additives, each reaction incorporated two equivalents of both potassium fluoride and available phase transfer agents such 18-crown-6,[7] quaternary ammonium salts,[8] and phosphonium salts.[9] In the case of substrate **6** (Table 1), none of the surveyed phase

Table 1. Fluorination of 6 using various additives at 130 °C



6 **10**

entry[a]	additive	MX	% yield[b]
1	none	CsF	34
2	none	KF	0
3	18-crown-6	KF	5
4	Bu_4NCl	KF	8
5	Bu_4NBr	KF	0
6	Me_4NCl	KF	2
7	$Bu_4N[(Ph)_3SiF_2]$	KF	9

[a]Conditions: picolinate (1 equiv), PTC additive (2 equiv), MF (2 equiv), DMSO, 130 °C. [b]In-pot yield determination by ^{19}F NMR or GC.

transfer catalyst (PTC) agents used along with KF increased yields of **10** above 10%, and mostly unreacted starting material was observed. As yields of desired product **10** were consistently low (presumably due to the C3 substitution pattern), our attention next focused on using substrate **9**, which presented a better opportunity to fine-tune conditions towards enhancing fluorination yields.

A much larger survey of PTC's agents was conducted using **9** as a substrate (Table 2). The results of this screen showed several trends. First, longer alkyl or aromatic chains on the PTC additive (such as Bu vs Me) provided higher fluorination yields. Second, PTC agents with a chloride anion generated relatively higher yields than the same PTC additive paired with a different anion. From the screening results, several promising leads, tetrabutylammonium chloride (Bu_4NCl), bis-(triphenylphosphoranylidene)ammonium chloride ($[Ph_3P{=}N{=}PPh_3]Cl$), tetrabutylphosphonium chloride (Bu_4PCl), and tetraphenylphosphonium chloride (Ph_4PCl), were identified as additives that generated fluorination yields of >75% when starting with **9**.

Among the PTC candidates explored, Bu_4NCl and Ph_4PCl are the most promising. Both of these reagents were subsequently evaluated over a wider equivalent range with the goal of using substoichiometric quantities of the PTC. However, as shown in Figure 3, the yield of **12** diminished as the equivalents of PTC was lowered. Fluorination yields greater than 50% were still achieved when using 0.5 equiv of PTC

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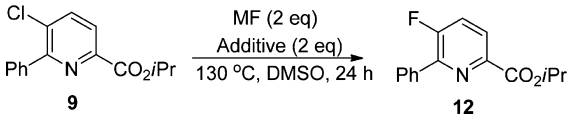
Table 2. Fluorination of 9 using various additives at 130 °C



entry[a]	additive	MX	% yield[b]
1	none	CsF	83
2	none	KF	10
3	$Bu_4NF(X\ H_2O)$	KF	11
4	Bu_4NCl	KF	86
5	Bu_4NBr	KF	23
6	Bu_4NI	KF	13
7	Me_4NF	KF	20
8	Me_4NCl	KF	54
9	Me_4NBr	KF	12
10	Me_4NI	KF	13
11	Bu_4NCPF_6	KF	17
12	Bu_4NOTf	KF	15
13	$Bu_4N[(Ph)_3SiF_2]$	KF	46
14	Bu_4NCN	KF	23
15	Bu_4NBF_4	KF	23
16	$[Ph_3P{=}N{=}PPh_3]Cl$	KF	75
17	Bu_4PCl	KF	75
18	Ph_4PCl	KF	99
19	$MePh_3PBr$	KF	0

[a]Conditions: picolinate (1 equiv), PTC additive (2 equiv), MF (2 equiv), DMSO, 130 °C. [b]In-pot yield determination by ^{19}F NMR or GC.

together with 2.0 equiv of KF in DMSO at 130 °C. When the same range of equivalents was explored at a higher jacket temperature set point of 150 °C, the yields increased at low loadings of additive (~30–40% at 0.1 equiv PTC). Diminished yields were observed for both Bu_4NCl and Ph_4PCl at loadings between 1.0 and 2.0 equiv when heated at 150 °C. These results show that effective fluorination is achievable when utilizing a larger excess of PTC agents but at temperatures no higher than 130 °C.

With lead candidates chosen, our efforts next focused on several additional parameters such as commercial availability of PTC, solvent selection, PTC side chemistry, and product isolation. These reaction parameters were explored to further develop a scalable process that could efficiently fluorinate challenging picolinate substrates such as **9**.

Bulk pricing[10] was obtained for 50% Bu_4NCl in water (~$25/kg). In contrast, bulk pricing for tributylmethylammonium chloride (Bu_3MeNCl), structurally similar to Bu_4NCl, was estimated to be ~$8/kg as a 75 wt % solution in water, and pricing for Ph_4PCl was found to be ~$40/kg. Thus, significant savings in raw material costs would be possible if Bu_3MeNCl affords similar fluorination performance to Bu_4NCl. Alternatively, cost savings would be achievable if a viable recycle strategy for additives such as Ph_4PCl could be developed. In fact, treating **9** under similar conditions (two equivalents of both KF and 98% Bu_3MeNCl in DMSO at 130 °C) afforded a 75% in-pot yield of **12**, which was comparable to previous results using Bu_4NCl as the additive. Several estimates were modeled to gauge the relative cost ranges anticipated to prepare **12** in a single chemical step (Table 3). For this exercise, only

Table 3. Estimated relative cost scenarios for the fluorination of picolinate 9

entry	MF	PTC	PTC recycle	% yield	cost[a] ($)
1	CsF	none	none	83	78
2	KF	none	none	10	133
3	KF	Bu_4NCl	0%	86	140
4	KF	Bu_3MeNCl	0%	75	44
5	KF	Ph_4PCl	0%	80	161
6	KF	Ph_4PCl	90%	80	31

[a]Cost of reagents required for fluorination/kg of fluorinated product.

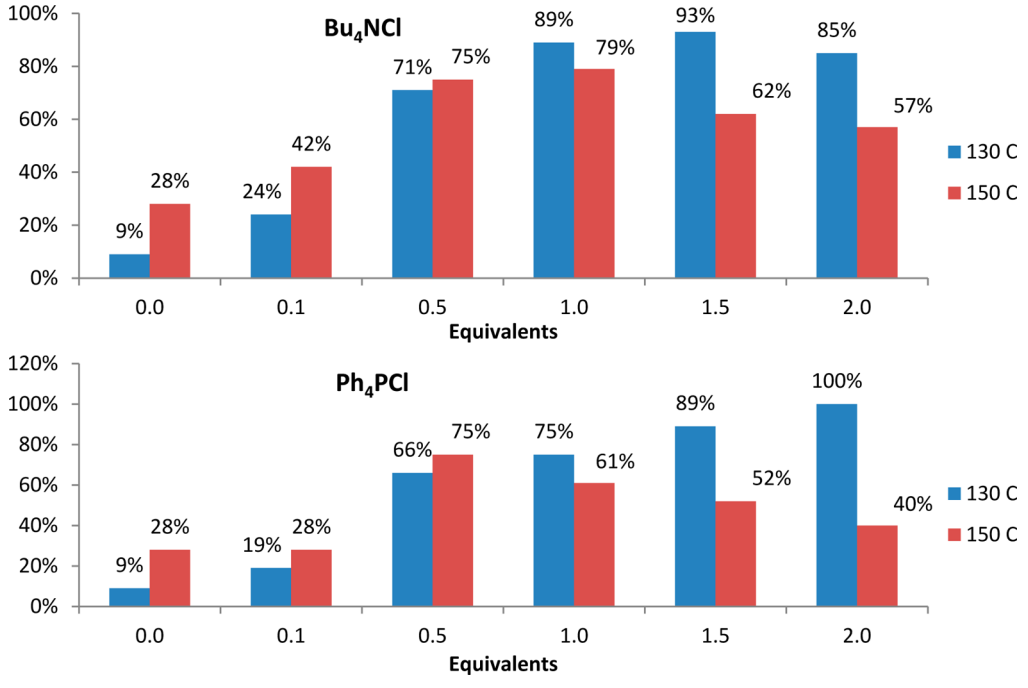


Figure 3. Temperature and stoichiometry influence on yields of **12** in DMSO.

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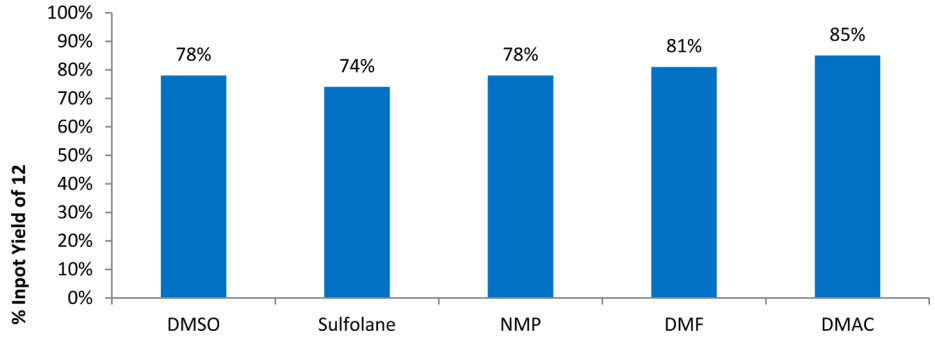

Figure 4. Observed fluorination yield of **12** for various common polar solvents.

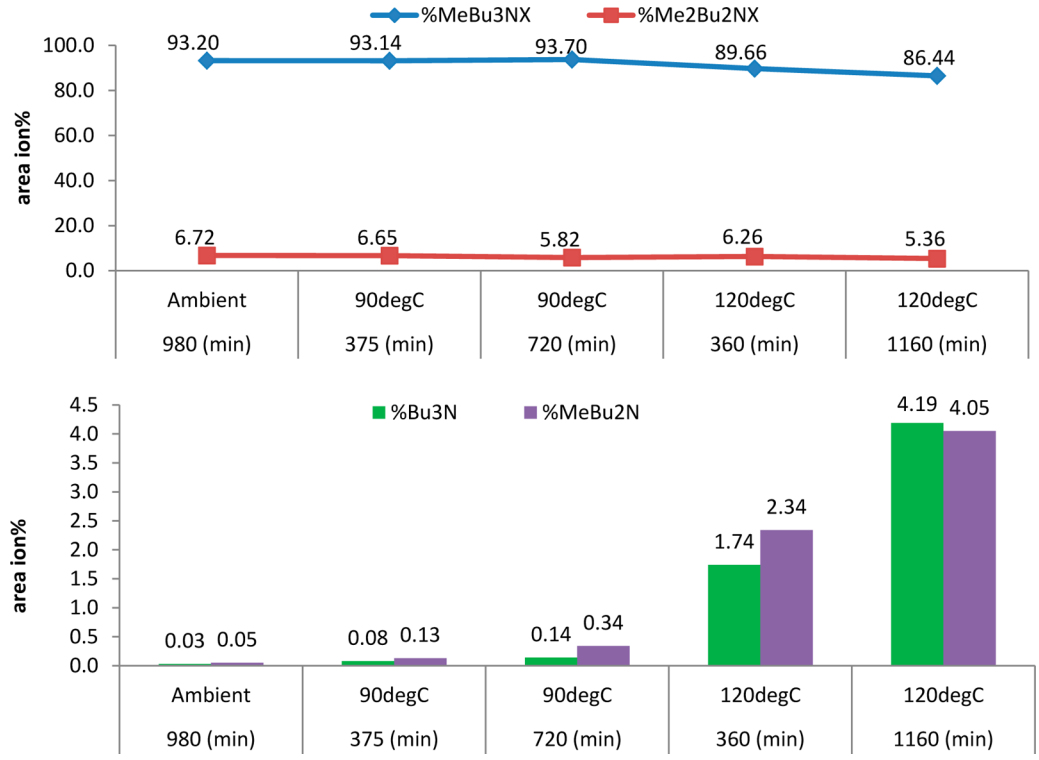

Figure 5. Measured degradation of the Bu_3MeNCl/KF mixture.

the cost of the raw materials required for fluorination was included. It was assumed that the reaction solvent (DMSO) would be recovered for recycling at an 80% rate. These cost estimations (Table 3) suggested that Bu_3MeNCl and Ph_4PCl (at a recycling rate of 90%) could be viable additives to consider for fluorination studies.

Our initial additive screening efforts focused on reaction parameters where DMSO was the solvent medium; however, it became prudent to identify other process-friendly solvents that could alleviate potential scale-up problems associated with DMSO.[11] Amide solvents (e.g., NMP) as well as less toxic solvents (e.g., sulfolane) were evaluated under standard screening reaction conditions, and the fluorination yields were compared to DMSO results (Figure 4). For this effort, 98% Bu_3MeNCl was chosen as the additive without further purification or drying efforts. All of these solvents were screened in a drybox (0.5 g of **9** at 130 °C for 24 h), and the crude reaction mixtures were analyzed for in-pot yields by GC. Overall, the observed fluorination yields exhibited a range spanning 74−85%. While these solvents were all viable candidates to replace DMSO, sulfolane was considered the optimal option due to lower toxicity. As will be discussed in a later section of this report, sulfolane was also an effective solvent for developing a product isolation strategy associated with this fluorination approach.

As previously mentioned, good fluorination yields (>70%) required adding an excess of PTC to promote KF efficiency. Quaternary ammonium salts (such as Bu_3MeNCl) are likely degrading competitively at the elevated reaction temperatures associated with this process and thus depend upon excess molar equivalents to compensate. The stability of quaternary ammonium salts has been previously studied, and typical byproducts include the formation of trialkylamines.[12] As part of the current studies, we sought to better understand the degree of Bu_3MeNCl decomposition by measuring relative concentrations of active species as a function of time and temperature. A thermal study evaluated a prepared mixture of Bu_3MeNCl and KF (45:55) in DMSO, and the solution was stirred for set time intervals at ambient temperature, 90 and 120 °C, respectively (Figure 5). ESI/LC/MS spectroscopy was employed to approximate relative area ion % concentrations

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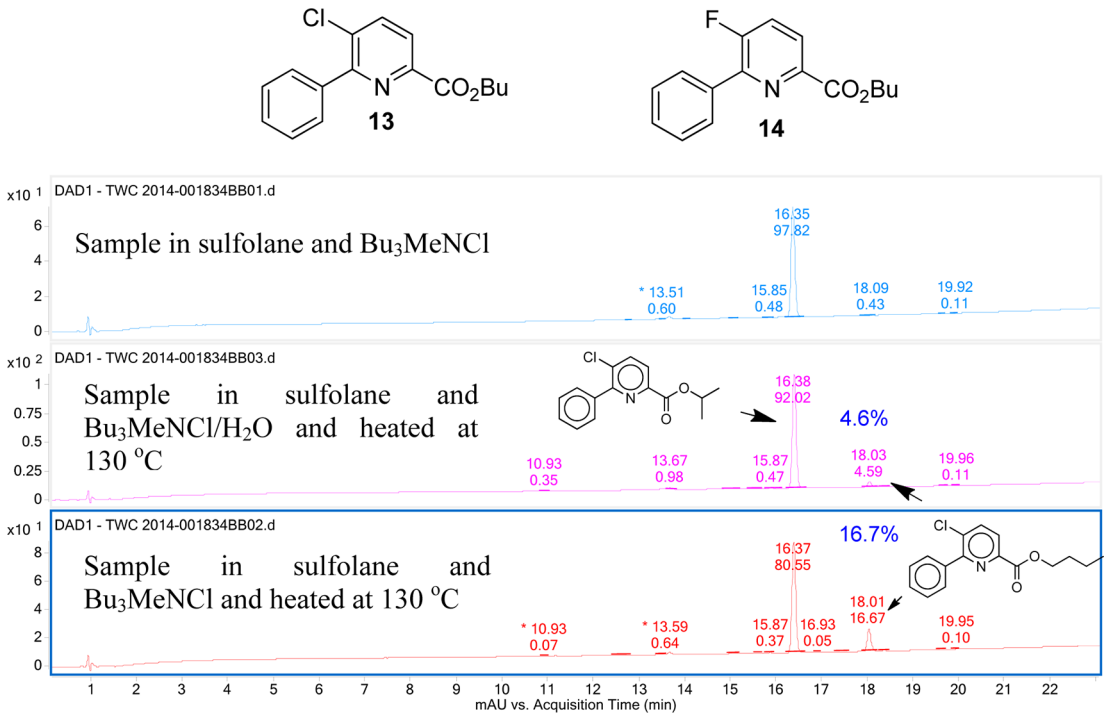

Figure 6. Observed ester exchange products from the Bu_3MeNCl additive.

for species such as quaternary ammonium cations as well as tertiary amine byproducts.

Two different quaternary ammonium cations (Bu_3MeNX and Bu_2Me_2NX) were detected in this mixture. After stirring at ambient temperature for about 16 h, the relative concentrations of Bu_3MeNX and Bu_2Me_2X were 93.20% and 6.72%, respectively. The relative concentration of two tertiary amines, tributylamine (Bu_3N) and dibutylmethylamine (Bu_2MeN), were both less than 0.1%. The mixture temperature was then subsequently raised to 90 °C and then analyzed after stirring for 6.25 and 12 h, respectively. At 90 °C, very little change in relative concentrations of either quaternary ammonium cation or tertiary amine was observed. However, degradation was detected as the mixture was subsequently heated to 120 °C for an additional period of time. The relative Bu_3MeNX concentration dropped about 8% after stirring at 120 °C for 19.3 h. Correspondingly, the sum total concentration increase of both Bu_3N and Bu_2MeN equaled 8% within the same time span. Thus, this preliminary evidence suggested that degradation of active Bu_3MeNX under typical halex reaction temperatures should occur slowly as a competing reaction pathway.

Besides thermal degradation under reaction conditions, Bu_3MeNCl can promote the formation of ester exchange byproducts **13** and **14** (Figure 6). For example, partial conversion to **13** was observed after extended heating of **9** with excess Bu_3MeNCl in sulfolane at 130 °C. Water likely does not play a direct role in ester exchange, as heating **9** in the presence of "wet" Bu_3MeCl gave less of **13** (Figure 6). A slow increase in the concentration of **14** was also observed during fluorination reactions, suggesting a similar ester exchange effect. Fortunately, a strategy to circumvent ester exchange could involve substituting another PTC that cannot deliver an alkyl substituent in place of Bu_3MeNCl. As proof of concept, heating a mixture of **9** and Ph_4PCl in sulfolane at 130 °C generated no ester exchange byproducts; thus giving a viable means to shut down this pathway. A later section of this report will discuss observed ester exchange byproduct formation with respect to larger scale fluorination batch runs using either Bu_3MeNCl or Ph_4PCl promoters.

Isopropyl-5-fluoro-6-phenylpicolinate (**12**) exists as a viscous, colorless oil making product isolation from reaction mixtures more challenging. Our efforts investigated an isolation strategy that could alleviate the need for chromatography by using a liquid extraction approach. A viable option would ideally partition the reaction mixture between an organic solvent and water. In principle, the organic solvent component would prefer to extract only **12** and simultaneously reject more polar reaction components such as PTC additive, reaction solvent, and other polar species to the aqueous phase. To test the feasibility of this extraction strategy, three organic solvents were compared. Toluene, hexanes, and isopar C were selected due to low miscibility with water as well as the ability to solubilize **12**. For this study, the reaction mixture (containing ~4.5 wt % of **12**) was partitioned between a 4:1 volume ratio of the chosen organic solvent and water. The organic phase was sequentially washed with first a dilute aqueous HCl solution (to remove tertiary alkyl amine byproducts) followed by a final water wash. Concentrating the organic extract afforded the product oil, and then both % product recovery and purity were estimated by GC analysis (Table 4).

Both toluene and hexanes demonstrated excellent (>95%) recovery yield of **12** from the crude reaction mixture. Isopar C

Table 4. Solvent comparison of the product isolation efficiency

	extraction solvent		
	toluene	isopar C	hexane
% recovery of isolated **12** from rxn mix[a]	95.4%	87.8%	97.2%
calc. purity of **12** in isolated product[a]	68.9%	86.8%	87.1%

[a]Purity and recovery yield estimated using GC analysis.

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Table 5. Results for reaction scale-up batches

batch	PTC	PTC (equiv)	KF (equiv)	% conv. of **9**	% inpot yield **12**[a]	% Yield **12** in isolated prod.[a,b]	% yield **14** in isolated prod.[a,b]	% recov. **9** in isolated prod.[a,b]
1[c]	Bu_3MeNCl	2.0	2.0	95	81	76	3	5
2[d]	Bu_3MeNCl	1.0	3.0	91	75	69	3	8
3[d]	Bu_3MeNCl	1.9	2.0	87	72	68	4	12
4[e]	Bu_3MeNCl	2.0	2.0	95	NA[f]	72	5	5
5[g]	Ph_4PCl	2.0	2.0	99	80	59	0	0
6[h]	Ph_4PCl	0.1[i]	2.0[j]	94	88	90	0	6

[a]Conditions: Yields measured by GC assay. [b]For the isolated product, the yield of component calculated based on **9** as the limiting reagent. [c]Added **9**, 98% Bu_3MeNCl, KF, and dry sulfolane (<100 ppm water), 130 °C, 24 h. [d]75% Bu_3MeNCl in water, sulfolane, **9**, toluene; vacuum distillation; then KF, 130 °C, 24 h. [e]98% Bu_3MeNCl used as PTC. [f]Reaction mixture taken directly through isolation. [g]98% Ph_4PCl used as PTC. [h]Aqueous Ph_4PCl/sulfolane/recovered **9** from batch 5 was reused. [i]Added additional 10% mol of fresh Ph_4PCl to existing Ph_4PCl recovered from batch 5. [j]Added fresh KF (2 equiv) to existing KF recovered from batch 5.

exhibited slightly diminished capacity for extracting the desired product (88% recovery); however, the purity of the isolated product from isopar C was similar to purity obtained when using hexanes to extract. Several observations were noted from the isolated product mixtures. First, isolated product contained very low concentrations of Bu_3MeNCl regardless of the extraction solvent utilized.[13] Second, product isolated from isopar C and hexanes appeared to not contain any residual sulfolane. Strikingly, isolated product from the toluene extraction run contained observable levels of sulfolane, which also explained the much lower estimated purity (~69%). Overall, these preliminary results indicated aliphatic solvents such as hexanes or isopar C offer good potential for efficient product separation from the reaction mixture. With a better understanding of side product chemistry and an isolation strategy, we next proceeded to explore conditions to demonstrate scale-up of this methodology.

This scale up demonstration specifically utilized additives Bu_3MeNCl and Ph_4PCl and also leveraged aforementioned process insights from the smaller scale studies. A total of six batches at increased (18−26×) scale were performed using 9−13 g of **9** (Table 5). Batch 1 involved directly scaling up reaction conditions similar to drybox conditions. In this example, all of the reaction components were carefully weighed into a 200 mL Schlenk flask inside the drybox.[14] The flask was sealed using a rubber stopper to hold the inert atmosphere from the drybox, and the vessel was subsequently transported to a fume hood and heated at 130 °C for 24 h with magnetic stirring. For the remaining scale-up examples (batches 2−6), a more traditional reactor setup utilized a 500 mL three-neck round-bottom flask fitted with mechanical stirring and vacuum distillation capabilities. Batches 2 and 3 incorporated a 75 wt % solution of Bu_3MeNCl in water as the PTC additive. As previously discussed, the moderate thermal stability of this PTC agent required drying temperatures less than 120 °C to minimize degradation. Azeotropically drying the reaction mixture at reduced pressure using toluene as a cosolvent was the approach demonstrated for batches 2 and 3. During the azeotropic distillation, the vacuum was adjusted between 26 and 80 mmHg as the pot temperature was gradually raised from ambient temperature to no higher than 120 °C. Under these drying conditions, about 27 mL of toluene was used per 1 g of starting material **9**. Fortunately about 80% of the toluene could be easily recovered after completing the drying step, and the reaction mixture usually contained less than 300 ppm water.[15] Dry KF[16] was quickly added in one portion to the vessel under a pad of nitrogen, and the mixture was subsequently heated to 130 °C for approximately 21 to 24 h. When using two equivalents of 75 wt % Bu_3MeNCl (e.g., batch 3), the azeotropic drying required more toluene to obtain reaction moisture levels below 300 ppm. Batch 4 incorporated process conditions similar to batches 2 and 3 except solid 98% Bu_3MeNCl was substituted as the PTC additive. Batch 5 was very similar to batch 4 except the PTC additive was substituted with 98% Ph_4PCl. Batch 6 investigated the feasibility of recycling the aqueous Ph_4PCl/sulfolane mixture recovered from batch 5. In this run, the reactor was charged with the aqueous PTC solution, and the water was removed by vacuum distillation. LC analysis of the mixture indicated the presence of leftover **12** from batch 5 (which explains the lower isolated yield reported), and this material was carried into the subsequent reaction steps associated with batch 6. For the azeotropic drying step in batch 6, the reactor was loaded with a fresh 10 mol % portion of Ph_4PCl followed by **9** in toluene. After completing the drying step, the reactor was charged with fresh KF (2 equiv) and the reaction heated at 130 °C for 24 h.

Overall, batch results produced in-pot yields consistent with conditions explored in the previous screening studies. Fluorination performance also gave comparable yields regardless of whether solid PTC agent was utilized (e.g., batches 1, 4, 5, and 6) or an aqueous solution (batches 2 and 3). The conversion of starting material **9** for all batches was good to excellent, and most of unreacted **9** could be accounted for in the isolated product mixture. As anticipated, ester exchange was also observed for batches 1−4 employing Bu_3MeNCl as the additive. For these batches, the isolated product yield after solvent extraction was predominantly a mixture of starting material **9** and fluorinated esters **12** and **14**. The observed yield range for **12** and **14** in the isolated product was 68−76% and 3−5%, respectively. When the PTC additive was switched to Ph_4PCl (batch 5 and 6), only **12** was observed in comparable yields and with no ester exchange byproduct formation. For batch 5, the observed yield of 59% was slightly lower than for the batches (1−4) following product isolation by solvent extraction with hexanes. As previously mentioned, unrecovered **12** in the Ph_4PCl recycle stream from batch 5 was subsequently carried into batch 6 which accounted for the boost in observed product yield. Toluene was utilized as the extraction solvent, producing much better recovery of **12**; however, sulfolane was also retained in the product mixture (giving an estimated 45% purity of **12** for batch 6). Further optimization of this extraction procedure using toluene will be considered in future work.

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CONCLUSION

Efficient nucleophilic fluorination of 3 and 5-substituted picolinate ester substrates was accomplished using potassium fluoride in combination with additive promoters. Agents such as tributylmethylammonium or tetraphenylphosphonium chloride were among the best additives screened improving fluorination in-pot yields up to 81%. Additionally, the choice of additive promoter influenced the formation of new impurities such as alkyl ester exchange. Other parameters explored in this study include additive stoichiometry, temperature effects on additive degradation, solvent selection, product isolation by solvent extraction, and demonstration of additive recycling.

EXPERIMENTAL SECTION

All stock solutions were made using volumetric glassware. All liquid reagents were dispensed by difference from syringes. All reagents were weighed out in a nitrogen-filled drybox with exclusion of air and moisture, unless otherwise noted. All reagents were purchased from common suppliers and dried over P_2O_5 prior to use unless otherwise noted. NMR spectra were recorded on a 700 MHz (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C), 500 MHz (500.10 MHz for ^{1}H; 125.75 MHz for ^{13}C, 470.56 MHz for ^{19}F), or 400 MHz (400.52 MHz for ^{1}H; 100.71 for ^{13}C; 376.87 MHz for ^{19}F) NMR spectrometer with the residual solvent peak ($CDCl_3$: ^{1}H: δ = 7.27 ppm, ^{13}C: δ = 77.16 ppm) used as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm) (δ) relative to tetramethylsilane. Multiplicities are reported as follows: br (broad resonance), s (singlet), d (doublet), t (triplet), q (quartet), hept (heptuplet), m (multiplet). Coupling constants (J) are reported in Hz. NMR yields were determined using trifluorotoluene (10 uL/rxn) as an internal standard. GC inpot yields were determined using either 2-phenylpyridine or biphenyl as an internal standard. Gas chromatography was carried out on a Shimadzu 17A or Agilent 6850 Network GC. HPLC was performed on a Agilent 1100 or PerkinElmer 200 series system series system. Purification by preparative chromatography was performed using either CombiFlash Rf 200 or CombiFlash Rf Mm Hgent systems.

Purification of 2,3-Dichloro-6-(trichloromethyl)-pyridine by Recrystallization.[17] To a 1 L jacketed reactor fitted with mechanical stirring, reflux condenser, and nitrogen inertion was charged 2,3-dichloro-6-(trichloromethyl)pyridine (420 g, 1.6 mol); methanol (218 g, 6.8 mol) was added, and the mixture was stirred for 5−10 min with a jacket temperature at 40 °C. The solution was then bottom drained into a 1 L conical flask and the flask was placed into a refrigerator. After allowing the solution to stand overnight, the product precipitated out of solution. The precipitate was suction filtered through a glass fritted funnel, and the cake was allowed to fully deliquor. The material was dried under vacuum to obtain 2,3-dichloro-6-(trichloromethyl)pyridine as a white crystalline solid: (339 g, purity was 95.7% by GC assay using biphenyl as an internal standard, 77.3% recovery): mp = 37−40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H).

Preparation of Isopropyl-5,6-dichloropicolinate. To a three-necked 500 mL round-bottom flask fitted with a thermocouple, mechanical stirrer and a condenser vented to a knockout pot, and then to an aqueous sodium hydroxide scrubber was added concentrated H_2SO_4 (39.2 g, 0.4 mol) and sulfolane (41.0 g, 0.3 mol). The reaction mixture was warmed to 130 °C, and 2,3-dichloro-6-(trichloromethyl)pyridine (100.0 g, 0.4 mol) prewarmed to 60 °C was added in portions over 40 min. Degassing to the caustic trap was observed. The mixture was stirred at 130 °C for 3 h and then cooled to 50 °C overnight. The mixture was warmed to 70 °C, and isopropyl alcohol (123.6 g, 2.1 mol) was added slowly via the addition funnel over 55 min. Rapid degassing of HCl gas was observed. The reaction mixture was stirred at 70 °C for an additional 1 h. The reaction mixture was poured over crushed ice (400 g), and the slurry was allowed to precipitate for 1 h in a refrigerator. The solids were collected by vacuum filtration, and the cake was washed with a 50:50 mixture of isopropyl alcohol/water (100 g) and then by water (200 g). The white solid was allowed to air-dry to constant weight. Isopropyl-5,6-dichloropicolinate was obtained as a white solid (76.9 g, 0.3 mol, 86% yield, >98% purity). mp = 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$-d_3) δ 7.96 (d, J = 8.1 Hz, 1H); 7.88 (d, J = 8.1 Hz, 1H); 5.29 (hept, J = 6.3 Hz, 1H); 1.40 (d, J = 6.3 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.9, 149.4, 146.7, 139.4, 134.5, 124.5, 70.4, 21.9; HRMS ESI$^+$. (m/z): $[M + H]^+$ calcd for $C_9H_{10}Cl_2NO_2$: 234.0083. Found: 234.0101

Preparation of Isopropyl 5-Chloro-6-phenylpicolinate. In a 1 L 4-neck round-bottom flask equipped with a mechanical overhead stirrer was charged KF (39.9 g, 688 mmol), water (125 mL), and acetonitrile (500 mL). The mixture was stirred until all of the solids dissolved. To this biphasic mixture was added phenylboronic acid (42.0 g, 344 mmol) and then isopropyl 5,6-dichloropicolinate (53.6 g, 229 mmol). The resultant suspension was sparged with N_2 gas for 15 min, and then bis(triphenylphosphine)palladium chloride (4.0 g, 5.7 mmol) was added. The bright yellow suspension was sparged with N_2 for further 15 min, and then the mixture was heated to 55 °C. At the 28 h mark the reaction was deemed complete by HPLC analysis. The heating mantle was removed and the mixture cooled to ambient temperature. The mixture was diluted with EtOAc (250 mL). The layers were separated, and the organic layer was washed with water (2 × 100 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL) and the organic layers combined. The combined organic layers were then washed with brine (1 × 100 mL) and SiO_2 (161 g) added. The solvent was removed by a rotary evaporator, and the crude product was purified by CombiFlash chromatography (750 g column) to afford cream colored solid weighing 59.7 g (94% yield). mp = 40−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.2 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 7.81−7.76 (m, 2 H), 7.50−7.43 (m, 3 H), 5.32 (hept, J = 6.3 Hz, 1 H), 1.42 (d, J = 6.4 Hz, 6 H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1, 156.7, 146.8, 138.9, 137.6, 133.6, 129.8, 129.2, 128.1, 124.2, 69.8, 22.0; HRMS ESI$^+$. (m/z): $[M + H]^+$ calcd for $C_{15}H_{15}ClNO_2$: 276.0786. Found: 276.0822.

General Procedure for Halex Additive Screening with Ethyl-3-chloro-6-phenylpicolinate. A stock solution of substrate (**6**) in DMSO was made in a volumetric flask to a final concentration of 50 mg **6**/0.5 mL DMSO. All solids (metal fluorides/phase-transfer-catalyst/additives) were weighed into a 4 mL vial equipped with a micro stir bar. The stock solution of **6** in DMSO was then added (0.5 mL), and the vial was sealed with a Teflon-lined screw cap. The reaction vial was removed from the N_2 drybox and placed on an IKA heating/stirring plate with temperature probe, equipped with an aluminum heating block. The reaction was heated/stirred at the specified temperature (generally 130 or 150 °C) for the given amount of time (generally 24 h). After the reaction was

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complete, it was allowed to cool to room temperature, diluted with methylene chloride, and internal standards (trifluorotoluene and 2-phenyylpyridine) were added. Yields were determined by ^{19}F NMR and GC.

General Procedure for Halex Additive Screening with Isopropyl-5-chloro-6-phenylpicolinate. Isopropyl-5-chloro-6-phenylpicolinate (50 mg), and all other solids (metal fluorides/phase-transfer-catalyst/additives) were weighed into a 4 mL vial equipped with a micro stir bar. DMSO (0.5 mL) was then added, and the vial was sealed with a Teflon-lined screw cap. The reaction vial was removed from the N_2 drybox and placed on an IKA heating/stirring plate with temperature probe, equipped with an aluminum heating block. The reaction was heated/stirred at the specified temperature (generally 130 or 150 °C) for the given amount of time (generally 24 h). After the reaction was complete, it was allowed to cool to room temperature, diluted with DCM, and internal standards (trifluorotoluene and 2-phenyylpyridine). Yields were determined by ^{19}F NMR and GC.

Preparation of Isopropyl-5-fluoro-6-phenylpicolinate Using Cesium Fluoride. The reaction was carried out in a glovebox. To a glass jar equipped with a stir bar was added isopropyl 5-chloro-6-phenylpicolinate (1.1 g, 3.9 mmol), cesium fluoride (1.2 g, 8.0 mmol), and DMSO (anhydrous grade, 8.5 g). The mixture was heated to 120 °C on a heating block for 19 h. A sample was taken and analyzed by GC, which indicated that this reaction was complete. The mixture was cooled to room temperature. The salts were removed by filtration and washed with 3 g of DMSO. The mixture was poured into a separatory funnel with 12 g of water and extracted with three 12 g portions of ethyl acetate. The organic phase was then washed with three 12 g portions of water and dried over anhydrous $MgSO_4$. The solvent was removed with a rotary evaporator. The concentrated crude product was purified using column chromatography eluting with an ethyl acetate/hexanes mixture (1:5) to give 0.9 g of isopropyl-5-fluoro-6-phenylpicolinate as a pale yellow liquid (81% yield, ∼100% purity by GC area, 98% purity by LC area). GC/MS results were consistent with the chemical formula of isopropyl-5-fluoro-6-phenylpicolinate (**11**): 70 eV EIMS (GC) m/z = 259 (8.3%), 174 (12.5%), 173 (100%), 172 (35.4%), 145 (9.4%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 3H), 7.57 (dd, J = 10.4, 8.5 Hz, 1H), 7.53−7.44 (m, 3H), 5.33 (hept, J = 6.3 Hz, 1H), 1.44 (d, J = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9 (s), 159.2 (d, J = 267 Hz), 146.4 (d, J = 12 Hz), 144.6 (d, J = 4.8 Hz), 134.7 (d, J = 5.6 Hz), 129.8, 129.2 (d, J = 5.9 Hz), 128.6, 125.5 (d, J = 5.5 Hz), 124.7 (d, J = 21 Hz), 69.7, 22.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.8.

Preparation of Isopropyl-5-fluoro-6-phenylpicolinate Using Tributylmethylammonium Chloride in Schlenk Equipment. A 200 mL Schlenk flask equipped with a magnetic stir bar and thermowell fitted onto the 24/40 ground glass joint was brought into a glovebox with nitrogen inertion. To this vessel was sequentially charged 9.30 g (33.73 mmol) of 5-chloro-6-phenylpicolinate followed by 16.00 g (67.84 mmol) of 98% tributylmethylammonium chloride followed by 4.0 g (68.9 mmol) of anhydrous potassium fluoride and then finally 169.6 g (1.4 mol) of dry sulfolane (Karl Fisher <100 ppm). The Schlenk flask was sealed with a rubber septum in the port containing the stopcock, and the stopcock was left open (the flask was essentially padded with nitrogen). The flask was then removed from the glovebox and allowed to heat to 130 °C with magnetic stirring. After 24 h, LC analysis indicated a 2:23:1 ratio of starting material to isopropyl-5-fluoro-6-phenylpicolinate to butyl-5-fluoro-6-phenylpicolinate. After cooling to <35 °C, the crude reaction mixture (191.2 g) was collected. GC analysis (using biphenyl as an internal standard) indicated the reaction mixture contained 3.7 wt % of isopropyl 5-fluoro-6-phenylpicolinate which corresponded to a calculated 80.8% inpot yield. The remaining 184.9 g of this crude reaction mixture (which contained 3.7 wt % of isopropyl 5-fluoro-6-phenylpicolinate) was partitioned between 203.9 g of water and 34.7 g of hexanes in a 500 mL separatory funnel. The mixture was allowed to stand for 5 min, and then the top organic phase was separated and saved. The bottom aqueous phase was extracted with a second 36.0 g portion of hexanes. The combined organic phases were sequentially washed with 50.6 g of 1 M aqueous HCl and then 51.9 g of water. The top organic phase was separated and concentrated on a rotovap at 40 °C and <20 mmHg vacuum to remove light organics. This gave 7.6 g of light orange oil in 76.1% yield and 87.1% purity (as determined by GC analysis using biphenyl as an internal standard). The isolated product also contained 3.5 wt % butyl-5-fluoro-6-phenylpicolinate (2.9% yield based on starting material) and 6.1 wt % isopropyl-5-chloro-6-phenylpicolinate (5.0% recovery of starting material).

Preparation of Isopropyl-5-fluoro-6-phenylpicolinate Using Tributylmethylammonium Chloride via an Azeotropic Drying Method. The reaction assembly consisted of a three-neck 500 mL round-bottom flask fitted with mechanical stirring, a heating mantle, and inertion was achieved by passing ambient nitrogen through a packed bed of drierite. The reaction vessel was fitted with a modified Dean−Stark distillation head which contained a three-way stopcock on the receiver arm, and this stopcock was set to divert collected distillate to a subsequent reservoir 250 mL round-bottom flask. To the reactor was loaded 29.4 g (93.4 mmol) of 75 wt % tributylmethylammonium chloride in water followed by 175.2 g (1.5 mol) of sulfolane that was premelted at 50−60 °C. To the reaction mixture was added a solution of 13.0 g (47.2 mmol) of isopropyl-5-chloro-6-phenylpicolinate in 132.8 g (1.4 mol) of toluene. The reaction was evacuated (∼24 mmHg) and heated from 22 to 92 °C, and toluene distillate (104.7 g) was collected over a 42 min period. Karl Fisher analysis of the reaction mixture indicated 2271 ppm of water. To the reaction vessel was charged another 87.4 g (1.0 mol) of fresh toluene. The reaction was evacuated (∼24 mmHg) and heated from 28 to 96 °C, and toluene distillate (76.7 g) was collected over an 18 min period. Karl Fisher analysis of the reaction mixture indicated 413 ppm of water. To the reaction vessel was charged a final 86.80 g (0.94 mol) of fresh toluene. The reaction was evacuated (∼24 mmHg) and heated from 27 to 83 °C to distill of the toluene over a 20 min period. Karl Fisher analysis of the reaction mixture indicated 133 ppm of water. After cooling the vessel to below 40 °C under nitrogen inertion, 5.5 g (94.8 mmol) of anhydrous potassium fluoride was shot added through a reaction port, and the mixture was heated to 130 °C with stirring. After 23 h, LC analysis indicated a 3:5:1 ratio of starting material to isopropyl-5-fluoro-6-phenylpicolinate to butyl-5-fluoro-6-phenylpicolinate. The reaction vessel contents (209 g) were transferred to 1 L flask. GC analysis (using biphenyl as an internal standard) indicated the reaction mixture contained 4.2 wt % of isopropyl 5-fluoro-6-phenylpicolinate which corresponded to a calculated 71.7% inpot yield. To the reactor was loaded 202.6 g of water for rinsing. This water wash was then transferred to the 1 L flask containing the reaction

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mixture. This mixture was subsequently transferred to a 1 L separatory funnel. The reaction vessel was rinsed with 35.5 g of hexanes, and this rinse was transferred to 1 L separatory funnel. After mixing, the phases were allowed to settle for 5 min, and then the top organic phase was separated and saved. The bottom aqueous phase was extracted with a second 35.0 g portion of hexanes. The combined organic phases were sequentially washed with 54.3 g of 1 M aqueous HCl and then 51.4 g of water. The top organic phase was separated and concentrated on a rotovap at 40 °C and <20 mmHg vacuum to remove light organics. This gave 11.4 g of light orange oil in 68.4% yield and 73.5% purity (as determined by GC analysis using biphenyl as an internal standard). The isolated product also contained 4.9 wt % butyl-5-fluoro-6-phenylpicolinate (4.2% yield based on starting material) and 14.0 wt % isopropyl-5-chloro-6-phenylpicolinate (12.0% recovery of starting material).

Preparation of Isopropyl-5-fluoro-6-phenylpicolinate Using Tetraphenylphosphonium Chloride via an Azeotropic Drying Method. The reaction assembly consisted of a three-neck 500 mL round-bottom flask fitted with mechanical stirring, a heating mantle, and inertion was achieved by passing ambient nitrogen through a packed bed of drierite. The reaction vessel was fitted with a modified Dean−Stark distillation head which contained a three-way stopcock on the receiver arm, and this stopcock was set to divert collected distillate to a subsequent reservoir 250 mL round-bottom flask. To the reactor was loaded a slurry of 13.0 g (47.2 mmol) of isopropyl-5-chloro-6-phenylpicolinate and 35.7 g (95.1 mmol) of 98% tetraphenylphosphonium chloride in 87.9 g (1.0 mol) of toluene, and then an additional 41.7 g (0.5 mol) toluene flush was added to the vessel. To the reaction vessel was charged 181.70 g (1.51 mol) of sulfolane that was premelted at 50−60 °C. The reaction was evacuated (16−21 mmHg) and heated from 26 to 107 °C, and toluene distillate (105.2 g) was collected over a 35 min period. Karl Fisher analysis of the reaction mixture indicated 72 ppm of water. After cooling the vessel to below 40 °C under nitrogen inertion, 5.7 g (98.5 mmol) of anhydrous potassium fluoride was shot added through a reaction port, and the mixture was heated to 130 °C with stirring. After 23 h, LC analysis indicated a full consumption of isopropyl-5-chloro-6-phenylpicolinate. The reaction mixture was cooled to 80 °C (this avoided tetraphenylphosphonium chloride from precipitating out of solution) and the vessel contents (231 g) were transferred to 1 L flask. GC analysis (using biphenyl as an internal standard) indicated the reaction mixture contained 4.2 wt % of isopropyl 5-fluoro-6-phenylpicolinate which corresponded to a calculated 80.2% inpot yield. The reactor was rinsed with 203.0 g of water and this wash was then transferred to the 1 L flask containing the reaction mixture. This mixture was subsequently transferred to a 1 L separatory funnel. The reaction vessel was rinsed with 34.0 g of hexanes and this rinse was transferred to 1 L separatory funnel. After mixing, the phases were allowed to settle for 5 min, and then the top organic phase was separated and saved. The bottom aqueous phase was extracted with a second 37.0 g portion of hexanes. The combined organic phases were washed with 51.7 g of water. The top organic phase was separated and concentrated on a rotovap at 40 °C and <20 mmHg vacuum to remove light organics. This gave 7.8 g of dark orange oil in 58.7% yield and 91.9% purity (as determined by GC analysis using biphenyl as an internal standard).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The Supporting Information contains NMR data which illustrates the product purity obtained from using the three different extraction solvents (toluene, isopar C, and hexanes).

(14) The hexanes extraction procedure was applied to this batch and the results are summarized in Table 4.

(15) Halex reactions performed best with **9** when water levels were below 300 ppm. Higher concentrations of water resulted in a lower product yield and incomplete starting material conversion.

(16) For these experiments, KF (spray dried material purchased from Aldrich) was further dried at 120 °C under a flow of nitrogen for 12 h. The dried material was transferred to a nitrogen drybox and then milled using a coffee blender.

(17) 2,3-Dichloro-6-(trichloromethyl)pyridine feed was initially ~85% pure (contaminated with other chloropyridine byproducts). Thus, recrystallization was required to get the purity greater than 95% for the subsequent steps to prepare isopropyl-5,6-dichloropicolinate.

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