Chapter 5

NICKEL-CATALYZED NUCLEOPHILIC FLUORINATIONS OF UNACTIVATED ALKYL HALIDES

5.1. Introduction

Organofluorine compounds are attracting increased attention due to their applications in pharmaceuticals, agrochemicals, and functional materials.[1–3] Nearly 50% of drugs that were globally-approved during 2018 and 2019 contain a C–F bond,[4] as the introduction of fluorine can significantly improve a compound's lipophilicity, potency, metabolic stability, and bioavailability.[5] The high demand for fluorinated molecules has led to a number of efficient fluorination methods, particularly for the synthesis of aryl fluorides.[6] However, general methods for the preparation of alkyl fluorides remain limited despite the prevalence of these motifs in bioactive compounds (**Figure 5.1**). Consequently, the development of efficient syntheses of alkyl fluorides continues to be a central goal in organic synthesis.

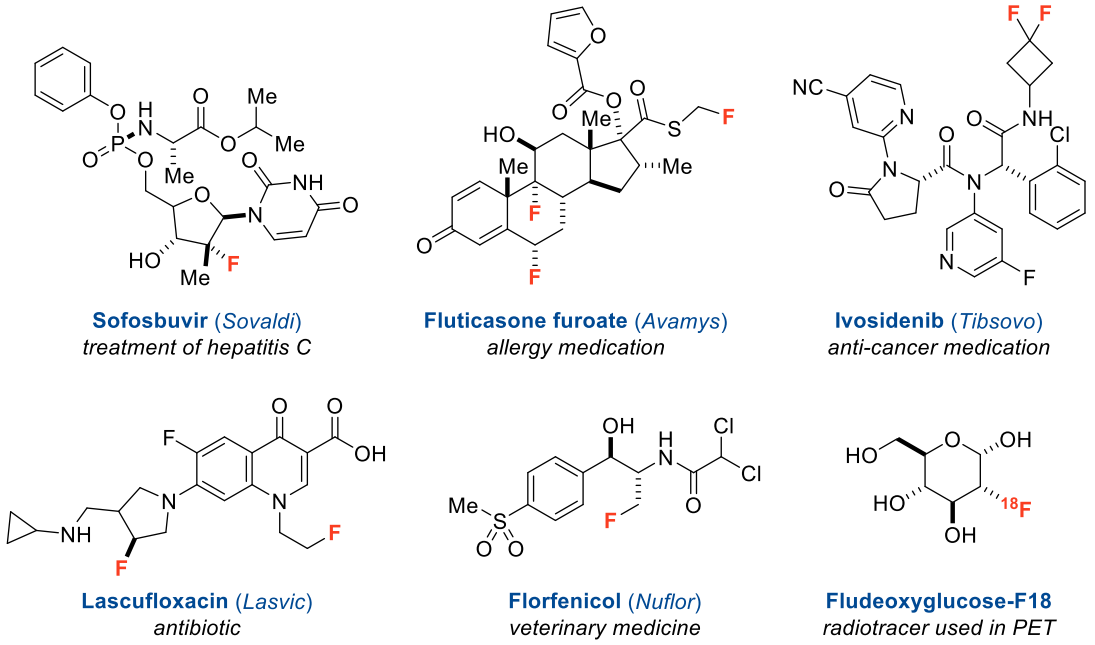


Figure 5.1. *Examples of alkyl fluorides with pharmaceutical applications.*

Among the possible methods to access alkyl fluorides, the nucleophilic fluorination of an alkyl electrophile with a metal fluoride is an especially straightforward approach. Metal fluorides (KF, CsF, AgF, etc.) are appealing sources of fluoride due to their high abundance, low cost, and ability to efficiently prepare ^{18}F-substituted radiopharmaceuticals for PET imaging.[7] However, their application to nucleophilic fluorination has been impeded by several drawbacks (**Figure 5.2**). The high lattice energies of metal fluorides result in low solubilities in organic solvents, and the propensity of fluoride to form hydrogen bonds in protic solvents undermines its nucleophilicity. In addition, the high basicity of the fluoride anion leads to side reactions of alkyl electrophiles, such as eliminations to form olefins.[8,9] Applications of metal fluorides to nucleophilic fluorination are largely restricted to specific transformations, such as allylic substitutions,[10,11] ring-opening reactions of epoxides and aziridines,[12–14] and benzylic / allylic C–H fluorinations.[15–17]

While transition metal-catalyzed nucleophilic substitution reactions have proven to be a useful strategy for the formation of otherwise challenging carbon–carbon and carbon–heteroatom bonds, this approach has limited applications in the nucleophilic fluorination of unactivated alkyl halides.[18] Mezzetti reported the ruthenium-catalyzed fluorination of *t*-butyl bromide with thallium(I) fluoride (no other examples of unactivated alkyl halides were described).[19] Weng achieved the fluorination of 1° and 2° alkyl bromides by copper(I) fluoride complexes (1.5 equiv of the copper complex was used).[20] More recently, Lalic

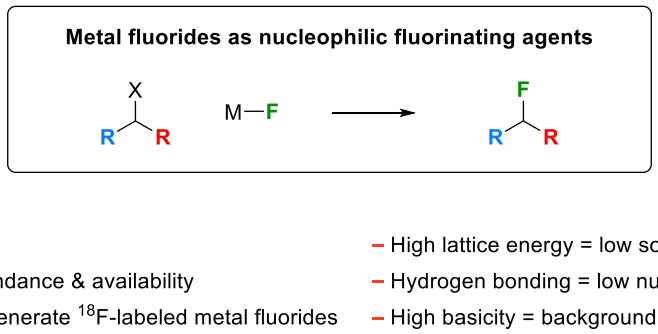


Figure 5.2. *Strengths and weaknesses of metal fluorides as nucleophilic fluorinating agents.*

disclosed the copper-catalyzed fluorination of 1° alkyl triflates using KF (not applicable to alkyl halides or to unactivated 2° or 3° alkyl triflates).[21]

To our knowledge, there is no general protocol for the transformation of a broad range of unactivated alkyl halides into alkyl fluorides via nucleophilic fluorination, although advancements in other fluorination methods have been made. For example, MacMillan reported the radical fluorination of unactivated alkyl bromides via silyl radical-mediated hydrogen atom abstraction.[22] This transformation offers a powerful approach to the synthesis of alkyl fluorides due to its mild conditions and broad functional group tolerance, although there are some limitations (low yields for 1° alkyl bromides, and a typical reaction requires 1.75 equiv of $(TMS)_3SiOH$, which is expensive).

Our lab has applied nickel-catalyzed nucleophilic substitution reactions of unactivated alkyl halides to the synthesis of a number of useful families of compounds.[23,24] While our efforts have primarily focused on carbon-based nucleophiles, nickel can serve as an effective catalyst for cross-couplings of other classes of nucleophiles as well, such as those based on boron[25] and silicon.[26] In principle, extending this approach to a metal

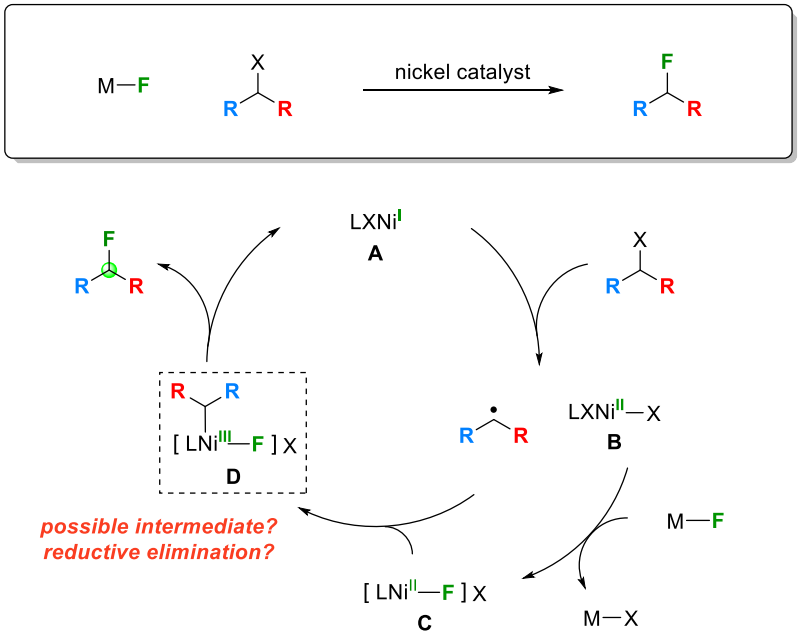
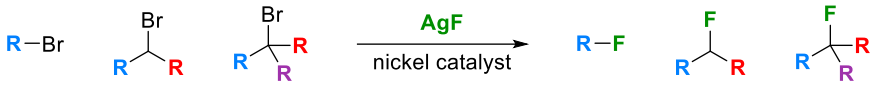


Figure 5.3. *Nickel-catalyzed nucleophilic fluorination of unactivated alkyl halides: possible pathway and challenges.*

fluoride nucleophile could grant access to unactivated alkyl fluorides from readily available starting materials (**Figure 5.3**).

Nickel's propensity to engage in single electron transfer (SET) with unactivated alkyl halides makes it an attractive catalyst for this transformation. However, nucleophilic fluorinations catalyzed by nickel have remained elusive to date; examples of alkyl fluoride synthesis catalyzed by nickel involve electrophilic fluorinations[27] and radical hydrofluorinations,[28] wherein nickel is proposed to assist in the generation of reactive intermediates but not participate directly in C–F bond formation. There are no reports of C(alkyl)–F reductive elimination from a nickel complex, although related processes have recently been studied; over the last few years, Ritter[29] and Sanford[30] have observed C(aryl)–F reductive elimination from high-valent nickel complexes.

In this chapter, we describe how the introduction of a nickel catalyst has opened the door to nucleophilic fluorinations of unactivated alkyl halides with metal fluorides. Specifically, we disclose our preliminary results in the nucleophilic fluorination of 1°, 2°, and 3° alkyl bromides, each of which was found to exhibit unique reactivity (**eq 5.1**).



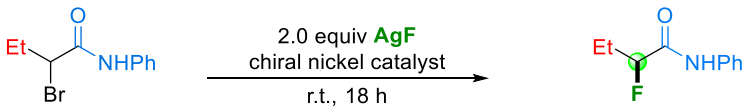
(5.1)

5.2. Results and discussion

5.2.1. Asymmetric nucleophilic fluorination of activated alkyl halides

We initially investigated the asymmetric nucleophilic fluorination of a range of racemic alkyl halides. In the presence of a chiral nickel complex, we discovered that a 2° α-bromo amide reacts with AgF to afford the fluorinated product in 11% ee (**eq 5.2**).

Upon investigating other classes of racemic electrophiles, we found that certain alkyl halides lead to the formation of racemic product (due, in some cases, to significant

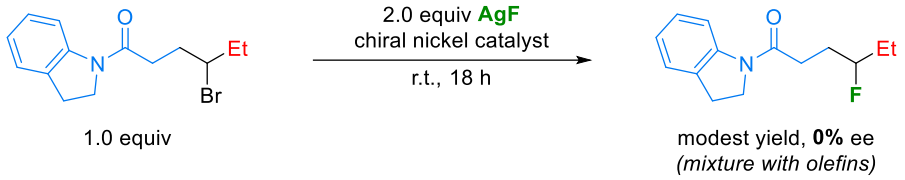


1.0 equiv

partial conversion, **11%** ee

(5.2)

background fluorination in the absence of catalyst), while others do not react at all. However, we were surprised to observe that an unactivated 2° γ-bromo amide readily undergoes substitution in the presence of a nickel catalyst (**eq 5.3**). As discussed previously, efficient nucleophilic fluorinations of unactivated alkyl halides (including non-asymmetric processes) are rare, and this result prompted us to further explore the reactivity of these traditionally challenging substrates. The following sections summarize our efforts in developing fluorinations of 2° alkyl halides (*Chapter 5.2.2*), 1° alkyl halides (*Chapter 5.2.3*), and 3° alkyl halides (*Chapter 5.2.4*).



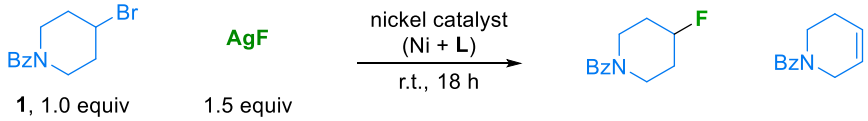
1.0 equiv

modest yield, **0%** ee
(mixture with olefins)

(5.3)

5.2.2. Nucleophilic fluorination of unactivated 2° alkyl halides

Under conditions similar to those illustrated in **eq 5.2**, unactivated, cyclic 2° alkyl bromide **1** undergoes nucleophilic fluorination with AgF in the presence of nickel and a variety of ligands (**Figure 5.4**). The relative signal intensities of the fluorinated product, the olefin byproduct, and unreacted **1** were measured by LC-MS to provide a qualitative assessment of the crude reaction mixture. In the absence of nickel and of ligand, very little product forms, and the starting material remains mostly unreacted. The addition of nickel promotes consumption of **1**, although elimination is the predominant reaction under these



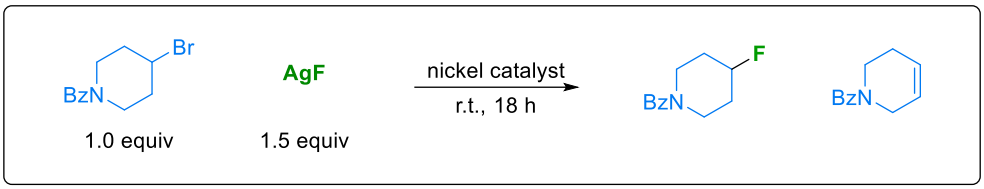
1, 1.0 equiv

1.5 equiv

conditions	product : olefin : SM
Ni + **L**	44 : 50 : 06
Ni, no **L**	16 : 61 : 23
No Ni or **L**	09 : 31 : 60

Figure 5.4. *Fluorination of unactivated, cyclic 2° alkyl bromide **1**. The relative signal intensities of product, olefin, and starting material were measured by LC-MS.*

Table 5.1. *Investigation of the fluoride nucleophile.*



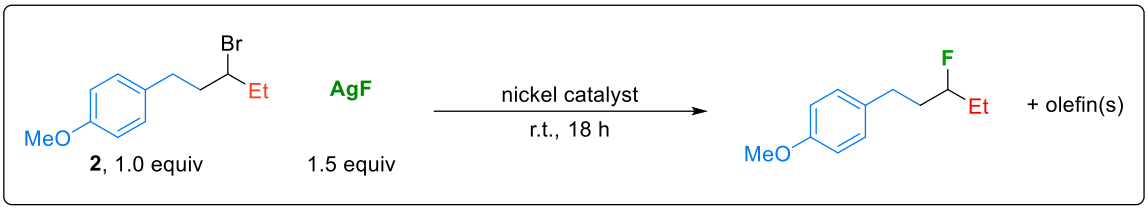
entry	nucleophile	% yield
1	AgF	~40
2	KF	0
3	CsF	0
4	TBAT	0
5	TBAF	0

conditions. However, the introduction of a range of ligands shifts reactivity in favor of fluorination.

We surveyed a range of parameters to determine the effect that different reaction conditions have on product and olefin formation. Nonpolar and ethereal solvents lead to low conversion, while polar solvents generally favor olefin formation. Lowering the temperature results in a lower yield and does not improve the ratio of product to olefin. For this 2°-substituted substrate, elimination remains a prominent side reaction that complicates reaction optimization, an issue that has hampered the development of nucleophilic fluorinations of alkyl halides.[31]

A variety of nickel precatalysts were tested, providing no benefit to the reaction outcome. In the future, the use of nickel(0) may be beneficial, as oxidative addition of the alkyl halide to form a nickel(II) intermediate, followed by comproportionation, would provide a ready mechanism for the generation of nickel(I) (complex **A**; **Figure 5.3**). Other fluoride reagents result in no reaction (**Table 5.1**). While the unique reactivity of AgF may be due to its higher solubility in organic solvents compared to alkali metal fluorides,[32] Ag(I) salts are essential additives in other nucleophilic fluorinations of alkyl halides.[33–35] The role of silver in this process will be discussed in *Chapter 5.2.4*.

Table 5.2. *Nickel-catalyzed nucleophilic fluorination of unactivated, acyclic 2° alkyl halides.*



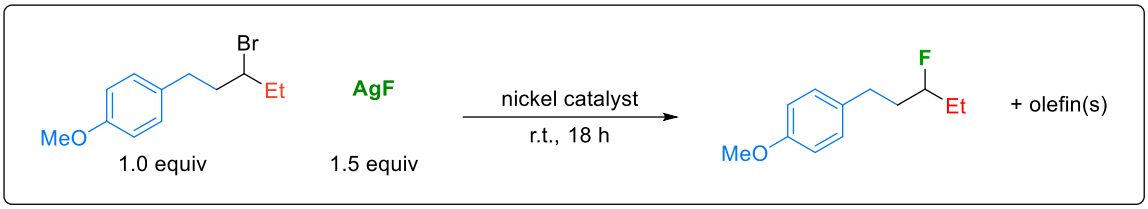
entry	X	% yield (^{19}F NMR)	% olefin (^{1}H NMR)
1	Br	45	50
2	Cl	0	0
3	OMs	0	0
4	I	35	69

Although the symmetrical structure of **1** facilitates analysis of its byproducts, we turned our optimization to unactivated, *acyclic* 2° alkyl bromide **2** to ensure that the observed reactivity is general to a wide range of 2° alkyl bromides. Using NMR spectroscopy, we found that the nucleophilic fluorination of **2** proceeds in 45% yield, with olefin byproduct(s) forming in 50% yield (**Table 5.2**, entry 1). Unactivated alkyl chlorides and mesylates do not react under these conditions, whereas alkyl iodides favor elimination (entries 2–4).

Control experiments established that nickel is necessary for this process, as reactions conducted in its absence result in minor conversion of **2** (**Table 5.3**, entries 2 and 4). While the presence of the ligand is not essential for product formation, its omission noticeably lowers the yield (entry 3). The roles of nickel and the ligand in this transformation are topics of ongoing investigation.

These preliminary results demonstrate the enticing prospect that the nickel-catalyzed nucleophilic fluorination of unactivated 2° alkyl halides is possible, although the propensity for the electrophile to undergo elimination remains a challenge. We anticipate that further investigations will lead to the discovery of conditions that minimize this side reaction.

Table 5.3. *Control reactions in the nucleophilic fluorination of acyclic 2º alkyl bromide* ***2****.*



entry	conditions	% yield (^{19}F NMR)	% olefin (^{1}H NMR)	% SM (^{1}H NMR)
1	Standard	51	49	0
2	No Ni	6	0	94
3	No **L**	40	54	0
4	No Ni or **L**	6	0	94

5.2.3. Nucleophilic fluorination of unactivated 1º alkyl halides

Applying conditions developed for the nucleophilic fluorination of **2**, we found that the fluorination of unactivated 1º alkyl bromide **3** proceeds in quantitative yield. The presence of nickel and ligand are essential for this transformation (**eq 5.4**). Remarkably, under all conditions tested, no side reactions were observed.

Attempts to duplicate these results led to product yields of 50–70%, indicating irreproducibility that may arise from the heterogeneity of the reaction mixture. We reasoned that more forcing reaction conditions could ensure the full consumption of **3**. Indeed, a reaction heated to 45 ºC results in higher conversion than a reaction run in parallel at room temperature (**Table 5.4**, entries 1 and 2). Similarly, the product yield could be improved by increasing the AgF stoichiometry or by extending the reaction time (entries 3–10). In particular, a reaction run with 3.0 equiv of AgF for 42 h led to the formation of product in 97% yield (entry 9), a result later confirmed to be reproducible.

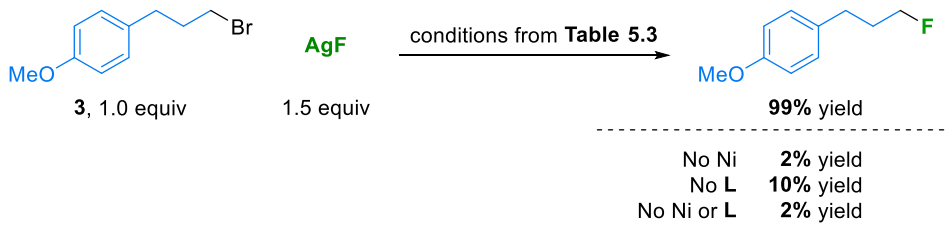


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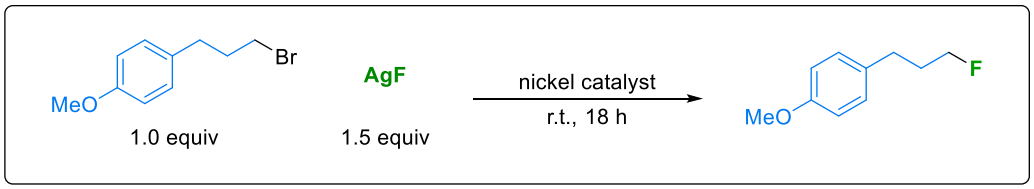
Table 5.4. *Establishing conditions for the reproducible nucleophilic fluorination of unactivated 1° alkyl bromide* ***3****.*



Effect of temperature

entry	temperature	% yield (^{19}F NMR)	% olefin (^{1}H NMR)	% SM (^{1}H NMR)
1	r.t.	59	0	41
2	45 °C	85	0	15

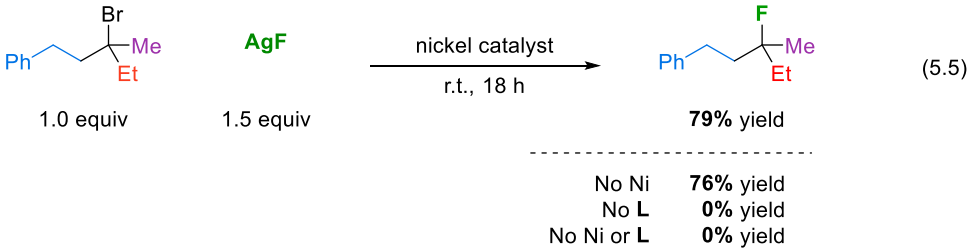
Effect of reaction time and AgF stoichiometry

entry	reaction time	equiv AgF	% yield (^{19}F NMR)	% olefin (^{1}H NMR)	% SM (^{1}H NMR)
3	18 h	1.5	46	0	54
4		2.0	66	0	34
5		3.0	73	0	27
6		5.0	60	0	40
7	42 h	1.5	82	0	18
8		2.0	87	0	13
9		3.0	**97**	0	3
10		5.0	91	0	9

5.2.4. Nucleophilic fluorination of unactivated 3° alkyl halides

Typically, methods for the generation of 1° and 2° alkyl fluorides are not applicable to or proceed sluggishly with 3° substrates[13,31,36] (and vice-versa).[37,38] Thus, the ability to apply a single method to the synthesis of alkyl fluorides bearing each of these substitution patterns in high yield would be a valuable tool in organic synthesis.

Upon surveying a range of ligands, we found that unactivated 3° alkyl bromide **4** readily reacts with AgF in the presence of a nickel catalyst, affording the fluorinated product in nearly 80% yield (**eq 5.5**). The product was formed as a mixture with olefin(s), although these side products can be separated from the fluorinated product by chromatography.



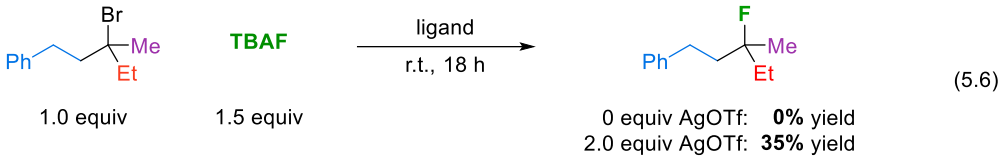
We concurrently conducted control experiments to examine the necessity of nickel and ligand in this reaction (**eq 5.5**). Surprisingly, product formation is not impacted by the removal of nickel (76% yield). To further probe this intriguing reactivity, we applied several ligands to the fluorination of **4** in the presence and absence of nickel. All ligands efficiently promoted the reaction in the absence of nickel, indicating that this process does not require nickel and likely proceeds through a pathway that is mechanistically distinct from fluorinations of 1° and 2° alkyl halides.

Subsequent experiments revealed that AgF is the only fluoride source applicable to the fluorination of **4** under these conditions, providing further support for the importance of silver in this transformation. Silver has been shown to be integral to a number of reported fluorinations. For example, silver catalysts have been applied to decarboxylative fluorinations of alkyl carboxylic acids[39] and radical fluorinations of alkylboronates.[40] These reactions are proposed to proceed through the formation of a Ag(III)–F intermediate that oxidizes the substrate and undergoes fluorine transfer with the resulting alkyl radical. Silver has also mediated fluorinations of aryl stannanes, wherein C–F bond formation is hypothesized to involve a bimetallic oxidation-reductive elimination pathway.[41]

Silver has been applied to nucleophilic fluorinations as well, such as fluorinations of α-bromoamides[35] and Pd-catalyzed fluorinations of benzylic C–H bonds.[42] In both cases, AgF is employed as the source of nucleophilic fluoride, although CsF can be applied as an effective fluorinating agent in reactions containing AgOTf as an additive. Similarly, Ag(I) salts have been found to be essential additives in the nucleophilic fluorination of unactivated 1° alkyl iodides using $TMSCF_3$[33] and aryl–OCF_2X bromides/chlorides using

KF.[34] In our case, the addition of 2.0 equiv of AgOTf enables the fluorination of 3° alkyl bromide **4** in modest yield using TBAF as the source of fluoride (**eq 5.6**).

Based on these findings, a ligated silver complex is likely a relevant intermediate in this reaction. Despite the numerous reported fluorinations catalyzed or mediated by silver, we are not aware of any examples that involve the formation of a discrete silver complex via pre-stirring of silver and a ligand. As unactivated 3° alkyl halides are relatively inert substrates, introduction of the ligand may allow for otherwise challenging processes to occur, such as the formation of a reactive intermediate (alkyl radical, carbocation, etc.) or C–F reductive elimination from silver. Mechanistic experiments to elucidate the role of silver and ligand are underway.



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5.3. Conclusions

The applications of organofluorine compounds in various fields of science have necessitated the development of efficient methods to introduce fluorine into organic molecules. While the nucleophilic fluorination of an alkyl halide using a cheap and readily-available metal fluoride represents a straightforward route to alkyl fluorides, its application in synthesis has been hindered by the low nucleophilicity and high basicity of metal fluorides. Given the propensity for nickel, an earth abundant metal, to catalyze nucleophilic substitution reactions to form C(sp^3)–heteroatom bonds, we have begun to apply nickel-based catalysts to the nucleophilic fluorination of unactivated alkyl halides. 1° alkyl bromides readily react with AgF in the presence of a nickel catalyst, forming alkyl fluorides in quantitative yields. Under similar conditions, unactivated 2° alkyl bromides afford the product in modest yields, although elimination remains a significant side reaction, and 3° alkyl bromides readily undergo fluorination with AgF through a pathway that does not require nickel. We envision that this method will serve as a powerful approach to the

synthesis of unactivated alkyl fluorides containing a range of substitution patterns, along with providing insight into the role of silver in these intriguing transformations.

5.4. Experimental section

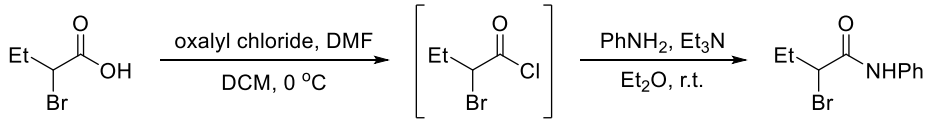
5.4.1. General information

Unless otherwise noted, reagents received from commercial suppliers were used as received. AgF was purchased from Oakwood and from Strem, and both sources yielded consistent results. All reactions were performed under an atmosphere of dry nitrogen. Solvents were purified by passage through activated aluminum oxide in a solvent-purification system.

NMR spectra were collected on a Bruker 400 MHz, or a Varian 500 MHz spectrometer at ambient temperature; chemical shifts (δ) are reported in ppm downfield from tertramethylsilane, using the solvent resonance as the internal standard. For quantitative ^{19}F NMR experiments, the center frequency (O1P) was set to be the midpoint between the product and the internal standard (4-fluorobiphenyl; –115.8 ppm). SFC analyses were carried out on an Agilent 1260 Infinity II system with Daicel CHIRALPAK® columns (4.6 × 250 mm, particle size 5 μm). LC-MS were obtained on an Agilent 6140 UHPLC-MS system in electrospray ionization (ESI+) mode. Column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle).

5.4.2. Preparation of electrophiles

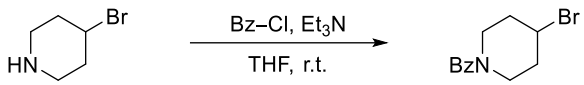
The yields have not been optimized.



2-Bromo-*N*-phenylbutanamide. An oven-dried 500 mL round bottom flask was equipped with a stir bar. The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of DCM (80 mL) and 2-bromobutanoic acid (2.55 mL, 24.0 mmol, 1.0 equiv) via syringe. The flask was cooled to 0 °C, after which oxalyl chloride (3.08 mL, 35.9 mmol,

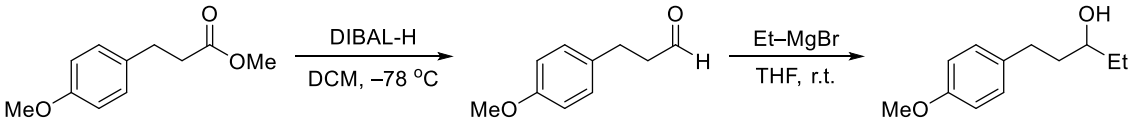
1.5 equiv) and DMF (0.19 mL, 2.40 mmol, 0.1 equiv) were added dropwise. The mixture was allowed to stir at 0 °C for 2 h. Next, the solvent was evaporated, and the flask was placed under a nitrogen atmosphere. After the residue was re-dissolved in Et_2O (240 mL), the flask was cooled to 0 °C. Following the addition of triethylamine (6.68 mL, 47.9 mmol, 2.0 equiv), aniline (2.19 mL, 24.0 mmol, 1.0 equiv) was added dropwise via syringe. Then, the solution was warmed to room temperature and allowed to stir overnight. The crude reaction mixture was washed with water (100 mL x 3) and the combined organic layers were dried over Na_2SO_4 and concentrated. The resulting yellow residue was purified by column chromatography on silica gel (2:3 EtOAc/hexanes) to yield a white solid that was then recrystallized in hexanes/THF to yield the title compound as a crystalline, white solid (3.10 g, 12.8 mmol, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.58 – 7.51 (m, 2H), 7.40 – 7.31 (m, 2H), 7.21 – 7.12 (m, 1H), 4.48 – 4.35 (m, 1H), 2.35 – 2.07 (m, 2H), 1.10 (t, *J* = 7.3 Hz, 3H).



(**4-Bromopiperidin-1-yl)(phenyl)methanone (1)**.[43] An oven-dried 100 mL round bottom flask was equipped with a stir bar and 4-bromopiperidine hydrobromide (2.71 g, 11.1 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of THF (30 mL). The flask was cooled to 0 °C, after which triethylamine (3.40 mL, 24.4 mmol, 2.2 equiv) and benzoyl chloride (1.29 mL, 11.1 mmol, 1.0 equiv) were added over 5 min via syringe. The reaction mixture was warmed to room temperature and allowed to stir overnight. Next, the solvent was evaporated, and the residue was dissolved in DCM (100 mL) and washed with water (50 mL x 2) and brine (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (2:3 EtOAc/hexanes) to yield the title compound as a white solid (2.22 g, 8.3 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 5H), 4.47 – 4.40 (m, 1H), 4.15 – 3.24 (m, 4H), 2.32 – 1.84 (m, 4H).



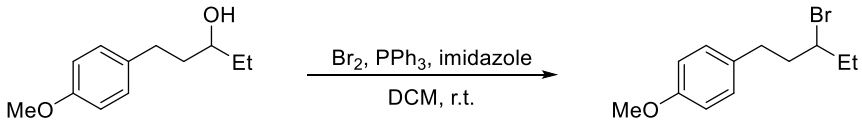
1-(4-Methoxyphenyl)pentan-3-ol.[44,45] An oven-dried 250 mL round bottom flask was equipped with a stir bar and methyl 3-(4-methoxyphenyl)propanoate (3.00 g, 15.4 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of DCM (80 mL). The flask was cooled to –78 °C, after which DIBAL-H (17.0 mL, 1.0 M in DCM, 17.0 mmol, 1.1 equiv) was over 10 min via syringe. The reaction mixture was allowed to stir at –78 °C for 1 h, after which saturated aqueous NH_4Cl (50 mL) was added, and the flask was warmed to room temperature. The organic layer was washed with water (50 mL x 2) and brine (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, yielding 3-(4-methoxyphenyl)propanal as a beige oil that was used in the next step without further purification (2.29 g, 14.0 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 – 9.79 (m, 1H), 7.15 – 7.07 (m, 2H), 6.91 – 6.80 (m, 2H), 3.78 (s, 3H), 2.93 – 2.87 (m, 2H), 2.78 – 2.72 (m, 2H).

An oven-dried 50 mL round bottom flask was equipped with a stir bar. The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of THF (20 mL) and 3-(4-methoxyphenyl)propanal (2.29 g, 14.0 mmol, 1.0 equiv) via syringe. The flask was cooled to 0 °C, and ethylmagnesium bromide (16.7 mL, 1.0 M in THF, 16.8 mmol, 1.2 equiv) was added over 5 min. The flask was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted in EtOAc (50 mL x 3), and the organic layers were washed with water (50 mL x 2) and brine (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (3:7

EtOAc/hexanes) to afford the title compound as a colorless oil (1.99 g, 10.2 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.06 (m, 2H), 6.93 – 6.77 (m, 2H), 3.79 (s, 3H), 3.59 – 3.50 (m, 1H), 2.84 – 2.47 (m, 2H), 1.83 – 1.39 (m, 5H), 0.95 (t, *J* = 7.4 Hz, 3H).



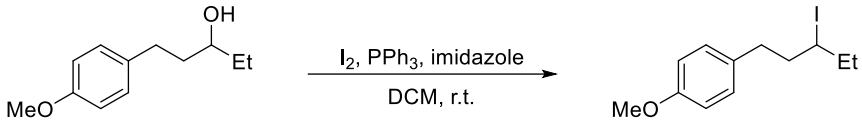
1-(3-Bromopentyl)-4-methoxybenzene (2). An oven-dried 250 mL round bottom flask was equipped with a stir bar, triphenylphosphine (5.67 g, 21.6 mmol, 1.2 equiv), and imidazole (1.47 g, 21.6 mmol, 1.2 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of DCM (90 mL). The flask was cooled to 0 ^{o}C, and then Br_2 (1.11 mL, 21.6 mmol, 1.2 equiv) was added dropwise via syringe. After the yellow / orange heterogeneous mixture was allowed to stir for an additional 10 minutes at 0 ^{o}C, 1-(4-methoxyphenyl)pentan-3-ol (3.50 g, 18.0 mmol, 1.0 equiv) was added via syringe. The reaction was warmed to room temperature and stirred overnight. The mixture was filtered through celite and concentrated to yield a yellow oil, which was then passed through a plug of silica and washed with pentane. After the pentane was evaporated, the resulting colorless oil was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to yield the title compound as a colorless oil (2.93 g, 11.4 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.08 – 6.95 (m, 2H), 4.15 – 4.04 (m, 1H), 3.94 (s, 3H), 3.04 – 2.79 (m, 2H), 2.31 – 2.15 (m, 2H), 2.06 – 1.96 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

1-(3-Chloropentyl)-4-methoxybenzene.[46] An oven-dried 40 mL vial was equipped with a stir bar and 1-(4-methoxyphenyl)pentan-3-ol (280 mg, 1.44 mmol, 1.0 equiv). The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by

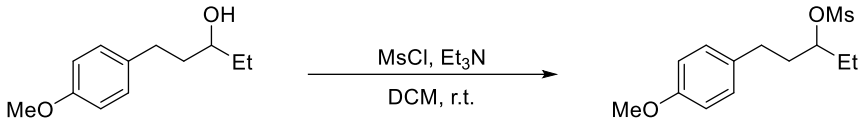
evacuating and back-filling the vial (three cycles), followed by the addition of DCM (10 mL). The vial was cooled to 0 °C, after which $SOCl_2$ (0.21 mL, 2.88 mmol, 2.0 equiv) was added dropwise via syringe and DMF (2.2 μL, 0.03 mmol, 2.0 mol %) was added via microsyringe. The reaction was warmed to room temperature and allowed to stir for 3 h. Next, the solution was concentrated, and the residue was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to yield the title compound as a colorless oil (166 mg, 0.78 mmol, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.09 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.82 – 3.75 (m, 4H), 2.88 – 2.64 (m, 2H), 2.04 – 1.91 (m, 2H), 1.88 – 1.67 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H).



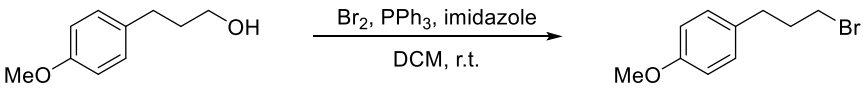
1-(3-Iodopentyl)-4-methoxybenzene. An oven-dried 40 mL vial was equipped with a stir bar, triphenylphosphine (567 mg, 2.16 mmol, 1.5 equiv), and imidazole (147 mg, 2.16 mmol, 1.5 equiv). The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the vial (three cycles), followed by the addition of DCM (10 mL). The vial was cooled to 0 °C, and then I_2 (549 mg, 2.16 mmol, 1.5 equiv) was added under a positive pressure of nitrogen. After the yellow / orange heterogeneous mixture was allowed to stir for an additional 10 minutes at 0 °C, 1-(4-methoxyphenyl) pentan-3-ol (280 mg, 1.44 mmol, 1.0 equiv) was added via syringe. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was filtered through celite and concentrated to yield a yellow oil, which was passed through a plug of silica and washed with pentane. After the pentane was evaporated, the resulting colorless oil was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to yield the title compound as a colorless oil (438 mg, 0.91 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 2H), 6.89 – 6.79 (m, 2H), 4.10 – 3.95 (m, 1H), 3.79 (s, 3H), 2.89 – 2.60 (m, 2H), 2.26 – 1.71 (m, 4H), 1.02 (t, *J* = 7.2 Hz, 3H).



1-(4-Methoxyphenyl)pentan-3-yl methanesulfonate.[47] An oven-dried 40 mL vial was equipped with a stir bar and 1-(4-methoxyphenyl)pentan-3-ol (0.86 g, 4.4 mmol, 1.0 equiv). The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the vial (three cycles), followed by the addition of DCM (15 mL). The vial was cooled to 0 ^{o}C, after which Et_3N (0.93 mL, 6.7 mmol, 1.5 equiv) and MsCl (0.52 mL, 6.7 mmol, 1.5 equiv) were added dropwise via syringe. The solution was warmed to room temperature and allowed to stir overnight. The reaction was then diluted with DCM (30 mL) and washed with water (30 mL x 3) and brine (30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (2:3 EtOAc/hexanes) to yield the title compound as a colorless oil (1.02 g, 3.8 mmol, 84% yield).

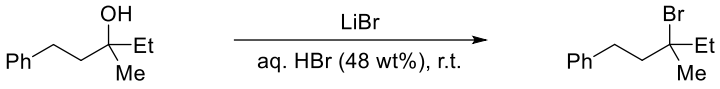
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 2H), 6.86 – 6.81 (m, 2H), 4.76 – 4.65 (m, 1H), 3.78 (s, 3H), 3.00 (s, 3H), 2.77 – 2.58 (m, 2H), 2.08 – 1.87 (m, 2H), 1.84 – 1.72 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).



1-(3-Bromopropyl)-4-methoxybenzene (3). An oven-dried 500 mL round bottom flask was equipped with a stir bar, triphenylphosphine (11.4 g, 43.3 mmol, 1.2 equiv), and imidazole (2.95 g, 43.3 mmol, 1.2 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of DCM (180 mL). The flask was cooled to 0 ^{o}C, and then Br_2 (2.22 mL, 43.3 mmol, 1.2 equiv) was added dropwise via syringe. After the yellow / orange heterogeneous mixture was allowed to stir for an additional 10 minutes at 0 ^{o}C, 3-(4-methoxyphenyl)propan-1-ol (6.00 g, 36.1 mmol, 1.0 equiv) was added via syringe. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was filtered through celite and concentrated to yield a yellow oil, which was passed through a

plug of silica and washed with pentane. After the pentane was evaporated, the resulting colorless oil was purified by column chromatography on silica gel (1:9 EtOAc/hexanes) to yield the title compound as a colorless oil (5.22 g, 22.8 mmol, 63% yield).

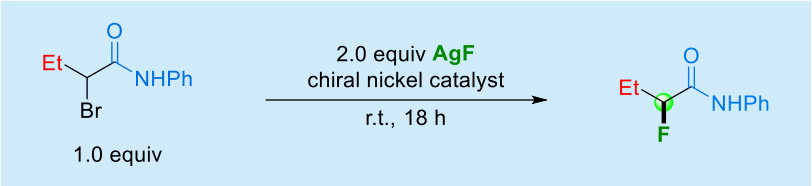
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.10 (m, 2H), 6.88 – 6.83 (m, 2H), 3.80 (s, 3H), 3.39 (t, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.19 – 2.10 (m, 2H).



(3-Bromo-3-methylpentyl)benzene (4).[25] To a 250 mL round bottom flask was added LiBr (9.74 g, 112 mmol, 2.0 equiv) and 48 wt% aqueous HBr (100 mL). The flask was cooled to 0 ^{o}C, after which 3-methyl-1-phenylpentan-3-ol (10.0 g, 56.1 mmol, 1.0 equiv) was added over 5 min. The reaction mixture was allowed to warm to room temperature and stir overnight. The mixture was then diluted with Et_2O (200 mL) and washed with water (100 mL x 2), saturated $NaHCO_3$ (100 mL x 2), and brine (100 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by vacuum distillation to yield the titled compound as a colorless oil (11.8 g, 48.9 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 5H), 2.89 – 2.73 (m, 2H), 2.19 – 1.84 (m, 4H), 1.76 (s, 3H), 1.06 (t, *J* = 7.3 Hz, 3H).

5.4.3. Nucleophilic fluorinations

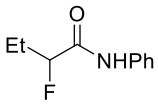


General Procedure 1 (GP-1): Asymmetric nucleophilic fluorination of 2º *α*-bromo amide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the nickel precatalyst, the chiral ligand, and AgF (25.4 mg, 0.20 mmol, 2.0 equiv). Next, solvent (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of 2-bromo-*N*-phenylbutanamide (24.2 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 18 h.

Work-up: The mixture was filtered through a small plug of silica gel, which was flushed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure.

The conversion and ee were determined via SFC analysis of the crude product mixture.

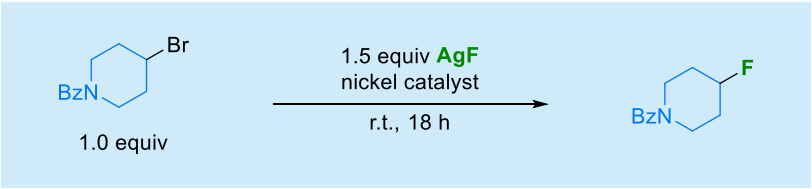


2-Fluoro-*N*-phenylbutanamide. The title compound was synthesized according to **GP-1**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.62 – 7.51 (m, 2H), 7.41 – 7.32 (m, 2H), 7.21 – 7.11 (m, 1H), 5.08 – 4.88 (m, 1H), 2.22 – 1.89 (m, 2H), 1.08 (t, *J* = 7.3 Hz, 3H).

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{10}H_{12}FNNaO$: 204.1, found: 204.1.

SFC analysis: SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-3 column (10% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times: 5.8 min, 7.1 min.

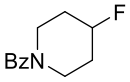


General Procedure 2 (GP-2): Nucleophilic fluorination of cyclic 2º alkyl bromide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the nickel precatalyst, the ligand, and AgF (19.0 mg, 0.15 mmol, 1.5 equiv). Next, solvent (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of (4-bromopiperidin-1-yl)(phenyl)methanone (26.8 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 18 h.

Work-up: A stock solution of 1-indanone (2.6 mg, 0.02 mmol, 0.2 equiv in 0.2 mL acetone, used as an LC-MS internal standard) was added to the vial via microsyringe. The mixture was filtered through a small plug of silica gel, which was flushed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure.

Yields were determined via LC-MS analysis of an aliquot of the crude product mixture, with 1-indanone as the internal standard.

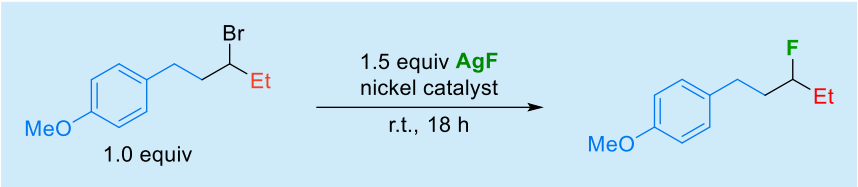


(4-Fluoropiperidin-1-yl)(phenyl)methanone. The title compound was synthesized according to **GP-2**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 5H), 5.03 – 4.79 (m, 1H), 4.07 – 3.37 (m, 4H), 2.04 – 1.70 (m, 4H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -183.2.

LC-MS (ESI-MS) *m/z* $[M+Na]^+$ calcd for $C_{12}H_{14}FNNaO$: 230.1, found: 230.1.

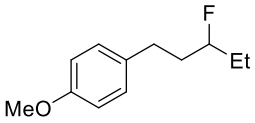


General Procedure 3 (GP-3): Nucleophilic fluorination of acyclic 2º alkyl bromide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the nickel precatalyst, the ligand, and AgF (19.0 mg, 0.15 mmol, 1.5 equiv). Next, solvent (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of 1-(3-bromopentyl)-4-methoxybenzene (25.7 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 18 h.

Work-up: A stock solution of 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.5 equiv in 0.2 mL acetone; used as a ^{1}H NMR internal standard) and a stock solution of 4-fluorobiphenyl (17.2 mg, 0.10 mmol, 1.0 equiv in 0.2 mL acetone; used as a ^{19}F NMR internal standard) were added to the vial via microsyringe. The mixture was filtered through a small plug of silica gel, which was flushed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure, and the residue was dissolved in $CDCl_3$ for NMR analysis.

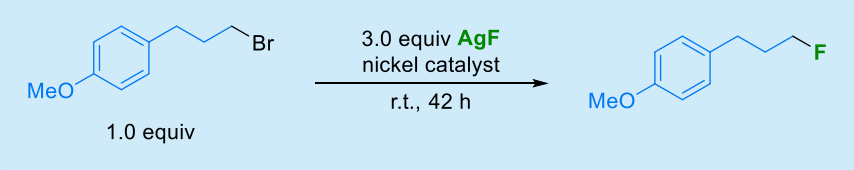
Yields were determined via ^{1}H NMR and ^{19}F NMR analysis of the crude product, with 1,3,5-trimethoxybenzene and 4-fluorobiphenyl as internal standards, respectively.



1-(3-Fluoropentyl)-4-methoxybenzene. The title compound was synthesized according to **GP-3**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.10 (m, 2H), 6.86 – 6.82 (m, 2H), 4.52 – 4.31 (m, 1H), 3.80 (s, 3H), 2.84 – 2.59 (m, 2H), 2.05 – 1.52 (m, 4H), 0.97 (t, J = 7.4 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -183.1.

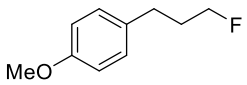


General Procedure 4 (GP-4): Nucleophilic fluorination of 1º alkyl bromide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the nickel precatalyst, the ligand, and AgF (38.1 mg, 0.30 mmol, 3.0 equiv). Next, DCM (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of 1-(3-bromopropyl)-4-methoxybenzene (22.9 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 42 h.

Work-up: A stock solution of 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.5 equiv in 0.2 mL acetone; used as a ^{1}H NMR internal standard) and a stock solution of 4-fluorobiphenyl (17.2 mg, 0.10 mmol, 1.0 equiv in 0.2 mL acetone; used as a ^{19}F NMR internal standard) were added to the vial via microsyringe. The mixture was filtered through a small plug of silica gel, which was flushed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure, and the residue was dissolved in $CDCl_3$ for NMR analysis.

Yields were determined via ^{1}H NMR and ^{19}F NMR analysis of the crude product, with 1,3,5-trimethoxybenzene and 4-fluorobiphenyl as internal standards, respectively.



1-(3-Fluoropropyl)-4-methoxybenzene. The title compound was synthesized according to **GP-4.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.11 (m, 2H), 6.90 – 6.83 (m, 2H), 4.46 (dt, *J* = 47.2, 5.9 Hz, 2H), 3.80 (s, 3H), 2.76 – 2.64 (m, 2H), 2.09 – 1.91 (m, 2H).

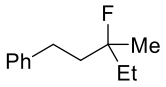
^{19}F NMR (376 MHz, $CDCl_3$) δ -220.1.

General Procedure 5 (GP-5): Nucleophilic fluorination of 3º alkyl bromide

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar, the ligand, and AgF (19.0 mg, 0.15 mmol, 1.5 equiv). Next, solvent (0.5 mL) was added, and the mixture was allowed to stir for 20 min. A solution of (3-bromo-3-methylpentyl)benzene (24.1 mg, 0.10 mmol, 1.0 equiv) in solvent (0.5 mL) was added. The vial was sealed with a septum cap, wrapped with electrical tape, and removed from the glovebox. The reaction was allowed to stir at room temperature for 18 h.

Work-up: A stock solution of 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.5 equiv in 0.2 mL acetone; used as a ^{1}H NMR internal standard) and a stock solution of 4-fluorobiphenyl (17.2 mg, 0.10 mmol, 1.0 equiv in 0.2 mL acetone; used as a ^{19}F NMR internal standard) were added to the vial via microsyringe. The mixture was filtered through a small plug of silica gel, which was flushed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure, and the residue was dissolved in $CDCl_3$ for NMR analysis.

Yields were determined via ^{1}H NMR and ^{19}F NMR analysis of the crude product, with 1,3,5-trimethoxybenzene and 4-fluorobiphenyl as internal standards, respectively.



(3-Fluoro-3-methylpentyl)benzene. The title compound was synthesized according to **GP-5.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 6.93 (m, 5H), 2.64 – 2.57 (m, 2H), 1.89 – 1.54 (m, 4H), 1.27 (d, *J* = 21.8 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -146.6.

5.5 Notes and references

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