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Palladium-Catalyzed Arylation of Fluoroalkylamines

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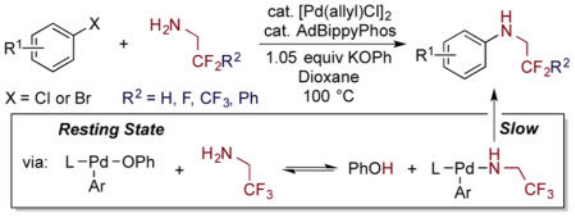
Abstract

We report the synthesis of fluorinated anilines by palladium-catalyzed coupling of fluoroalkylamines with aryl bromides and aryl chlorides. The products of these reactions are valuable because anilines typically require the presence of an electron-withdrawing substituent on nitrogen to suppress aerobic or metabolic oxidation, and the fluoroalkyl groups have steric properties and polarity distinct from those of more common electron-withdrawing amide and sulfonamide units. The fluoroalkylaniline products are unstable under typical conditions for C–N coupling reactions (heat and strong base). However, the reactions conducted with the weaker base KOPh, which has rarely been used in cross-coupling to form C–N bonds, occurred in high yield in the presence of a catalyst derived from commercially available AdBippyPhos and $[Pd(allyl)Cl]_2$. Under these conditions, the reactions occur with low catalyst loadings (<0.50 mol % for most substrates) and tolerate the presence of various functional groups that react with the strong bases that are typically used in Pd-catalyzed C–N cross-coupling reactions of aryl halides. The resting state of the catalyst is the phenoxide complex, (BippyPhosPd(Ar)OPh); due to the electron-withdrawing property of the fluoroalkyl substituent, the turnover-limiting step of the reaction is reductive elimination to form the C–N bond.



INTRODUCTION

Molecules containing aniline and aniline derivatives are common in the pharmaceutical, agrochemical, and pigment industries.[1] For example, an acetamide is found in the highest grossing prescription drug of all time (Lipitor)[2] and the most commonly administered over-the-counter pain drug (Tylenol).[3] In addition, many of the most widely applied herbicides

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Notes

The authors declare the following competing financial interest(s): A provisional patent based on this worked has been filed.

ASSOCIATED CONTENT

Supporting Information

NMR spectra (^{1}H, ^{13}C, ^{19}F, ^{31}P), HRMS, and IR spectra of all reaction products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/ jacs.5b02512.

(e.g., Metolachlor),[4] as well as common pigment chromophores (e.g., Mauveine A),[5,6] are aniline derivatives (Figure 1). Because of these important applications, numerous classical and modern methods for the preparation of anilines have been reported.[7]

Aniline derivatives containing electron-withdrawing substituents are more valuable than the parent anilines in medicinal chemistry because anilines are prone to oxidation.[1] For example, *N*-alkylanilines are susceptible to aerobic or metabolic degradation to the corresponding aniline via oxidation by cytochrome P450,[8] and the parent anilines are usually oxidized further to *N*-aryl hydroxylamines that generate carcinogenic arenium ions.[9–11] Thus, aniline derivatives, such as sulfonamides, amides, ureas, or carbamates, possessing electron-withdrawing groups are the derivatives most commonly contained in pharmaceuticals and agrochemicals.

Aniline derivatives containing fluoroalkyl groups possess electronic properties that should mitigate oxidation. Consistent with this assertion, fluoroalkylanilines have been shown to be more stable toward P450-mediated oxidation than alkylanilines lacking fluorine atoms.[12] While sharing the electronic properties of the sulfonyl and carbonyl derivatives, the solubility properties, intermolecular interactions, and steric properties of fluoroalkylanilines are distinct from those of sulfonyl and carbonyl derivatives.

The ability of fluorine atoms to change the electronic properties of neighboring atoms has led to scattered examples of medicines,[13–17] agrochemicals,[18] and dyes[19,20] containing fluoroalkylaniline groups (Figure 1), but these aniline derivatives have not been widely studied. One reason for the uncommon use of *β*-fluoroalkylanilines in these applications is that the methods to prepare such substructures are limited, particularly from the aryl halide synthetic intermediates commonly generated in medicinal chemistry. The two most commonly used methods for the preparation of *β*-fluorinated anilines (e.g., *N*-trifluoroethylaniline) are the reductive amination of trifluoroacetaldehyde[21] with the corresponding aniline derivative and S_NAr reactions.[22] However, reductive aminations form the *N*-alkyl bond, rather than the *N*-aryl bond, and S_NAr reactions require strongly electron-deficient arenes and have been shown to occur slowly with the weakly nucleophilic *β*-fluorinated amines.[23] Additionally, aryl halides can be coupled with trifluoroacetamide, but the scope of this transformation is limited and requires an additional step to generate a fluorinated aniline.[24–26]

Metal-catalyzed C–N coupling reactions could be a general method to prepare fluorinated anilines and would enable chemists to evaluate these substructures during studies on structure-activity relationships by conducting reactions on the same aryl halide intermediate as would be used to introduce other substituents from nitrogen, oxygen or carbon nucleophiles.[27] However, general conditions for cross-couplings of aryl halides with fluorinated amines have not been reported. Buchwald reported a single cross-coupling of trifluoroethylamine (with 5-bromoindazole), and this reaction occurred in moderate yield (65%).[28] In fact, the authors of this work concluded that trifluoroethylamine hydrochloride *inhibited* cross-couplings under the standard conditions developed for the amination of heteroarenes.[29] Thus, the conditions for coupling of fluoroalkylamines are distinct from

those for coupling of alkylamines or anilines, presumably due to the strong electron-withdrawing effect of the trifluoromethyl group.

We report a generally applicable coupling of aryl bromides and chlorides with primary amines containing fluorine β to nitrogen. The reaction occurs with a wide substrate scope, under mild conditions, and with inexpensive reagents, precatalysts, and ligand. One key to developing this process was revealing that strong base leads to decomposition of the product and, therefore, identifying a base that is sufficiently weak to avoid decomposition of the coupled product but sufficiently strong to induce formation of the arylpalladium-amido intermediate. A second unusual feature of the reaction is the resting state; the major palladium complex in the reaction is an adduct with the phenoxide base. A third unusual feature is the rate-limiting step. The electron-withdrawing property of the fluoroalkyl group retards reductive elimination to form the C–N bond, and kinetic studies indicate that this step has the highest energy transition state, even though the reaction is conducted with a palladium catalyst containing a class of ligand that typically leads to fast reductive elimination.

RESULTS AND DISCUSSION

Reaction Development

Due to the similar basicity of trifluoroethylamine and aniline, we hypothesized that trifluoroethylamine would couple with aryl halides under conditions reported for the coupling of aniline with aryl halides.[29] To test this hypothesis, trifluoroethylamine was allowed to react with 4-*n*-butylbromobenzene in the presence of a Josiphos-ligated catalyst that couples amines with aryl halides with broad scope under mild conditions.[29] This reaction produced **1** in 81% yield after 15 h (Figure 2a). However, the yields of reactions of more electron-rich or *o*-substituted aryl halides under these conditions reached a maximum value (50–73%, determined by ^{19}F NMR spectroscopy) within an hour and decreased at longer reaction times. This decrease in yield over time implied that the trifluoroethylaniline products are unstable under the reaction conditions.

Heating an isolated fluoroalkylaniline in the presence of NaO*t*Bu showed that NaO*t*Bu induces the decomposition of the product under the reaction conditions. Therefore, the stability of **1** was tested in the presence of various bases at 100 °C for 6 h in dioxane to determine which bases do not induce decomposition of **1**. Strong bases, such as LiHMDS, NaO*t*Bu, and KO*t*Bu, caused complete decomposition of the product **1**, whereas weaker inorganic bases and KOPh caused only minimal decomposition of **1** (Figure 2b). Although we have not identified the decomposition products, alkoxymethylanilines decompose in the presence of strong base.[30]

When coupling reactions were conducted in the presence of these weaker bases, the yields of **1** were lower than 10% with a Josiphos-ligated catalyst. Therefore, we sought combinations of palladium precursors and ligands that would catalyze the reaction under conditions with the weaker bases. Generally, the coupling reactions of amines with aryl halides catalyzed by bisphosphine-ligated Pd complexes require strong bases, whereas coupling reactions catalyzed by monophosphine-ligated Pd complexes can be conducted with weaker bases. It

has been proposed that weaker bases can be used because the amine binds more readily to an LPd(Ar)(X) containing a monophosphine than to an L_2Pd(Ar)(X) complex containing a bisphosphine.[31] The pK_a of monophosphine ligated LPd(Ar)-(X)(amine) complexes are calculated to be between 8 and 10 in H_2O,[32] and these complexes can be deprotonated by weak base.

Based on this information, we evaluated catalysts containing monophosphine ligands in the presence of weak bases for the coupling of aryl halides with fluorinated amines. Results are summarized in Table 1. The combination of $[Pd(allyl)Cl]_2$, AdBippyPhos, and KOPh catalyzed the coupling of 4-*n*-butylbromobenzene with trifluoroethylamine in high yield using just 0.10 mol % catalyst. Under these conditions, no diarylamine or diaryl ether products were observed. Phenoxides are not typical bases for Pd-catalyzed C–N coupling reactions but have been used in selected cases previously.[32–35]

Although the coupling of amines with aryl halides catalyzed by complexes of AdBippyPhos has not been reported previously, Singer at Pfizer published such couplings catalyzed by complexes of BippyPhos.[36,37] Stradiotto and co-workers recently reported the scope of C–N coupling reactions catalyzed by palladium complexes of *t*BuBippyPhos and showed that this system catalyzes the coupling of a wide variety of aryl halides and amines with low catalyst loadings.[38] Researchers at Abbot reported that palladium complexes of BippyPhos catalyze the *N*-arylation of ureas.[39] Finally, Beller has shown that the combination of palladium and AdBippyPhos catalyzes the etherification of aryl halides with primary alcohols.[40]

Other BippyPhos derivatives, all of which are commercially available and readily synthesized, form complexes that catalyze this transformation (Table 1). The reaction of trifluoroethyl-amine with 4-*n*-butylbromobenzene catalyzed by the complex generated from $[Pd(allyl)Cl]_2$ and *t*BuBippyPhos formed the product in same yield as the system derived from AdBippyPhos. However, we found the yields and conversions for reactions of aryl halides other than 4-*n*-butylbromobenzene were typically higher for reactions conducted with AdBippyPhos than for those conducted with *t*BuBippyPhos. Catalysts generated from both ligands were selective for C–N bond formation; side products from etherification with the phenoxide base and hydrodehalogenation were generally not observed. The analogous reaction conducted with CyBippyPhos as the ligand occurred in much lower yield, but the reactions of highly hindered substrates occurred in high yield when catalyzed by the complex containing this ligand (*vide inf ra*). While *t*BuBrettPhos generates a system that catalyzes the reaction in high yield, other monophosphine ligands, such as *t*BuXPhos (entry 2) or JackiePhos (entry 3), did not generate a catalyst that produces the product in greater than 10% yield. Consistent with prior observations that aryl halide aminations catalyzed by complexes ligated by bisphosphines require stronger bases, the test reaction conducted with the catalyst containing a hindered Josiphos ligand that is highly reactive for coupling of primary amines with NaO*t*Bu base did not produce any product under these conditions (entry 4).

The effects of other reaction parameters on yield were evaluated by allowing trifluoroethylamine to react with 4-*n*-butylbromobenzene in the presence of a catalyst generated *in situ* from $[Pd(allyl)Cl]_2$ and AdBippyPhos. When the catalyst was generated

from a 1:1 or 1:2 ratio of Pd to ligand the yields were nearly identical (93% vs 99%). However, full conversion of the substrate was typically achieved with lower loadings of the catalyst when a 1:2 ratio of Pd to ligand was used. For example, the reaction of trifluoroethylamine with 3-chloropyr-idine to produce **14** occurred to full conversion with a catalyst loading of 0.400 mol % when generated from a 1:1 ratio of Pd to ligand, whereas the same reaction required 0.250 mol % of catalyst to occur to completion with a 1:2 ratio of Pd to ligand. Rigorously dry and air-free conditions are not required to obtain high yields of products. The model reaction assembled in air and run with wet dioxane afforded **1** in 94% yield. A reaction conducted with sodium phenoxide, which is fully soluble in dioxane under the reaction conditions, occurred in the same yield as the reaction conducted with potassium phenoxide (entry 10).[41] Although KOPh is not available from common chemical suppliers, reactions conducted with this base generated and used *in situ* from phenol and KO*t*Bu occurred in the same yield as those initiated with isolated KOPh (entry 11).

Scope of the Arylation of Fluoroalkylamines

Figure 3 summarizes the scope of the reaction of trifluoroethylamine with a variety of aryl and heteroaryl bromides and chlorides under the conditions shown in Table 1. The minimum amount of catalyst required for each reaction to reach full conversion is reported. Electron-neutral (**1**), electron-rich (**2**–**4**), and electron-poor aryl halides (**5**–**10**) reacted to form the corresponding trifluoroethylaniline in good isolated yields within 6 h. The reactions of aryl halides possessing ortho substituents also occurred to form products **10**–**12** in high yield, but required higher catalyst loadings than reactions of less-hindered substrates. In addition, the coupling of 2,6-dimethyl-chlorobenzene occurred in good yield with 0.750 mol % catalyst; the reactions catalyzed by the system generated from CyBippyPhos as the ligand occurred in higher yield than those catalyzed by the system generated from AdBippyPhos. Although the isolated yield of **13** is moderate because the compound is volatile, the reaction occurs in 92% yield, as determined by ^{19}F NMR spectroscopy.

The reactions of a variety of heteroaryl halides were also evaluated under these conditions, including those of 2-, 3-, and 4-halopyridines, pyrimidines, quinoxalines, thiophenes, indoles, and benzothiazoles. These reactions generally occurred in the presence of low loadings of catalyst to form heteroaryl trifluoroethylanilines **14**–**23** in high yield. However, other 5-membered heteroaryl halides, such as *N*-trityl-4-chloro-pyrazole, and heteroaryl halides containing acidic N–H bonds, such as 5-bromoindole, did not react to form trifluoroethylanilines under these conditions.

The reactions of aryl halides containing functional groups that are sensitive to strong base and nucleophiles are shown in Figure 4. Unprotected acetophenones (**24** and **25**), free alcohols (**26**), acetamides (**27**), methyl cinnamate esters (**28**), and non-enolizable aldehydes (**29**) all were tolerated under the standard reaction conditions. Although competing reactions of these functional groups were not observed in most cases, small amounts of side products were observed in the reactions to form **26** and **29**. However, high yields of these products were obtained by simply increasing the number of equivalents of amine.

The combination of high functional group compatibility and the tolerance of basic functional groups should allow this reaction to occur with a wide range of medicinally relevant

compounds. For example, the coupling of Etoricoxib with trifluoroethylamine occurred with low loadings of the catalyst without undergoing side reactions (Scheme 1). It is likely that the low nucleophilicity and basicity of both KOPh and trifluoroethylamine, as well as the low solubility of KOPh in dioxane, allow for the high functional group compatibility.

To determine the scope of the fluoroalkylamines that undergo this coupling process, we evaluated our conditions for the coupling of three fluorinated amines that would form fluorinated anilines with various properties (Figure 5). Coupling with diffuoroethylamine (conjugate acid pK_a = 7.1)[42] would generate an aniline that should be less prone to oxidation than a typical aniline, while possessing two hydrogen bond donors (N–H and the C–H of CF_2H).[43] The coupling of pentafluoropropylamine (conjugate acid pK_a = 5.7)[44] was also conducted because perfluoroethyl groups have been shown to alter lipophilicity and would further suppress alkylaniline oxidation. Finally, the coupling of *β,β*-difluorophenethylamine (conjugate acid pK_a = 6.8)[45] was evaluated because phenethyl-amine moieties are present in many biologically active compounds. Both difluoroethylamine and pentafluoropropyl-amine are commercially available; difluorophenethylamine was prepared in two steps from ethyl difluorophenylacetate.

These fluoroalkylamines were allowed to react with a set of aryl halides possessing different electronic and steric properties (Figure 5, electron-rich, electron-deficient, heteroaromatic, and *ortho*-substituted). These amines reacted under our standard conditions to form the coupled products in good yields. Like the couplings of trifluoroethylamine, these reactions occurred in high yields with catalyst loadings of just 0.1–0.6 mol %. The reactions of difluoroethylamine and pentafluoropropylamine required 2 equiv of amine, presumably due to the low boiling point of these amines (68 and 50 °C, respectively). However, reactions of difluorophenethylamine occurred to full conversion of the aryl halide with just 1.1 equiv of amine.

Branched fluorinated amines and secondary fluorinated amines could react to form fluoroalkylanilines that cannot be readily prepared via reductive amination or alkylation. Therefore, the coupling of additional fluorinated amines were conducted under our standard reaction conditions. Reactions of trifluoroisopropylamine with the same subset of aryl halides used to generate the products in (see Figures 5 and 6a), occurred to high conversion but variable yield. In contrast to the reactions of primary unbranched fluoroalkylamines (e.g., trifluoroethylamine), reactions of trifluoroisopropylamine formed products from etherification of the aryl halide in certain cases. These side products were formed in greater than 10% yield from the reactions of aryl halides containing electron-withdrawing (*p*-cyano in **43**) or *ortho* (*o*-methyl in **45**) substituents, presumably because these substituents accelerate direct reductive elimination from the phenoxide resting state **54** (*vide inf ra*). The selectivity between etherification and amination was the same for reactions of aryl bromides and aryl chlorides. This result suggests that the side products are not formed by an S_NAr process, but are likely formed via the palladium catalyst, presumably by direct reductive elimination of the palladium resting state.

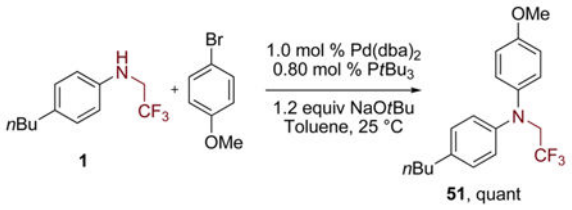
The selectivity for amination over etherification was improved by reducing the reaction temperature (80 °C instead of 100 °C), using a slightly less-hindered ligand (*t*BuBippyPhos

instead of AdBippyPhos), and by increasing the number of equivalents of amine (from 2.0 to 3.0). These modified conditions afforded higher yields from reactions of aryl halides containing strongly electron-withdrawing groups. The SFC traces of products isolated from reactions of enantiopure trifluoroisopropylamine did not contain a signal at the retention time corresponding to the minor enantiomer.

These conditions do not lead to the coupling of the same set of aryl halides with 2-(trifluoromethyl)pyrrolidine; instead, such couplings occur with the catalyst containing CyBippyPhos as ligand and with NaO*t*Bu as base (Figure 6b) at 65 °C.[46] Although reactions of representative *ortho*-substituted aryl halides or heteroaryl halides occur in moderate yield, reactions of representative electron-rich and electron-deficient aryl halides occur in high yield. The GC traces of products isolated from reactions of enantiopure 2-(trifluoromethyl)pyrrolidine did not contain a signal at the retention time corresponding to the minor enantiomer. Finally, we investigated reactions of more highly fluorinated amines; however, couplings of hexafluoroisopropylamine or bis(trifluoroethyl)amine did not produce anilines under either set of conditions.

Derivatization of the Coupled Products

As noted earlier in this paper, the fluorinated anilines produced by coupling of trifluoroethylamine with aryl halides are unstable in the presence of strong base at 100 °C (Figure 2). Thus, it was unclear if the fluorinated anilines would undergo decomposition in further transformations, such as a second arylation, acetylation, or alkylation that would be conducted under basic conditions. To address this issue, we tested the room temperature coupling of **1** with 4-bromoanisole in the presence of a catalyst for the coupling of diarylamines with aryl halides and 1.2 equiv of NaO*t*Bu (eq 1). This reaction produced diaryl



(1)

fluoroalkylamine **51** in quantitative yield. This result indicates that decomposition of fluoroalkyl anilines in the presence of strong base does not occur rapidly at room temperature. While a full evaluation of the reactions of fluoroalkylanilines is beyond the scope of this paper, this result indicates that the fluoroalkylanilines produced in this work can undergo subsequent transformations that require strong base when conducted at or near room temperature.

Mechanistic Studies of the Coupling of Aryl Halides with Fluoroalkylamines

Typical conditions for Pd-catalyzed coupling reactions to form C–N bonds include strong alkoxide or amide bases, rather than the phenoxide base in the reactions reported here. The fluorinated amines that undergo coupling under these conditions are less basic than the non-fluorinated aliphatic amines that are typically coupled with aryl halides. Therefore, we studied the mechanism of the amination of fluoroalkylamines under the catalytic reaction conditions we developed (Scheme 2) to determine the effect of the low basicity and solubility of potassium phenoxide and low nucleophilicity of the amine on the reaction. Although higher turnover numbers are observed when the reaction is conducted with the catalyst generated from AdBippyPhos as the ligand than with the catalyst generated from *t*BuBippyPhos, mechanistic studies were conducted with *t*BuBippyPhos as the ligand because multigram quantities can be prepared readily from inexpensive materials.

Identification of the Catalyst Resting State—The reaction of 4-fluorochlorobenzene (**52**) with trifluoroethylamine catalyzed by the combination of 2.5 mol % of $[Pd(allyl)Cl]_2$ and 10 mol % of *t*BuBippyPhos was conducted in an NMR tube and was monitored by ^{19}F and ^{31}P NMR spectroscopy (Scheme 2, see the Supporting Information for these spectra). At 50% conversion, the ^{31}P NMR spectrum contained two singlets in a 1:1 ratio. One singlet at 2.6 ppm corresponds to free *t*BuBippyPhos, whereas the second singlet at 38.4 ppm corresponds to the resting state of the palladium. The ^{19}F NMR spectrum of the same reaction contained resonances for 4-fluorochlorobenzene (−117.53 ppm), 4-fluoro-*N*-trifluoro-ethylaniline (**53**, −128.90 ppm), trifluoroethylamine (−76.68 ppm), and a new signal at −122.25 ppm. This signal at −122.25 ppm was tentatively assigned to an arylpalladium complex because the integration of this signal indicated that the fluoroaryl group was present in the same concentration as the palladium in the reaction. When the same reaction was conducted with potassium 4-fluorophenoxide as the base, an additional resonance at −134.09 ppm was present in the ^{19}F NMR spectrum. The intensity of this resonance was the same as that of the resonance at −122.25 ppm (attributed to an arylpalladium species). No ^{19}F NMR signals that could be attributed to a Pd amido complex were observed. The ^{31}P NMR spectrum of an identical reaction conducted with 4-fluorobromobenzene was the same as the ^{31}P spectrum of the reaction conducted with 4-fluorochlorobenzene. This observation indicates that the resting state lacks a halide ligand because the ^{31}P NMR chemical shifts of an arylpalladium chloride complex and an arylpalladium bromide complex should be distinct from each other.

Collectively, these data suggest that the catalyst resting state is [(*t*BuBippyPhos)Pd(Ar)(OPh)]. To test this hypothesis, we allowed $[Pd(allyl)Cl]_2$, *t*BuBippyPhos, 4-fluorochlorobenzene, and potassium phenoxide to react at room temperature in THF. Filtration, partial removal of the solvent, and the addition of pentane produced a yellow solid. The ^{31}P NMR spectrum of this yellow solid contained a single resonance that matched the ^{31}P spectrum of the catalyst resting state.

The structure of the catalyst resting state was unambiguously shown by X-ray diffraction to be [(*t*BuBippyPhos)Pd(Ar)-(OPh)] (**54**, Figure 7). The complex contains a dative bond between Pd and the bipyrazole backbone, an interaction that has been reported for the t_{47}

BuBippyPhos complex of $PdCl_2$ and for other Pd complexes containing bulky biaryl phosphine ligands.[48–51] This complex is stable in air in the absence of excess phenoxide, which is consistent with the ability to conduct the amination without rigorous exclusion of air.

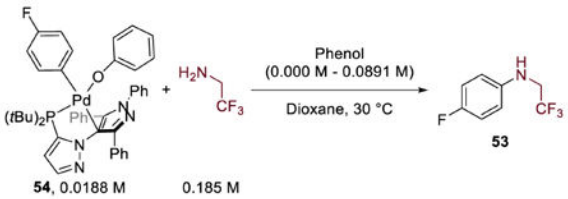
Reaction Kinetics—To assess the connection between this complex and the steps of the catalytic cycle, we determined the rate law for the reaction (Scheme 2). To increase the solubility of the base, potassium 4-*n*Bu-phenoxide was used in place of KOPh. The ^{31}P NMR spectrum of a reaction conducted with 4-*n*Bu-phenoxide was the same as that conducted with KOPh. This result indicates that the change in base does not cause a change in the catalyst resting state.

The kinetics were determined by measuring initial rates with ratios of reagents close to that of the preparative reactions and the isolated resting state as the catalyst. Due to the low boiling point of trifluoroethylamine (bp = 35 °C), the rates were measured at 50 °C, instead of the 100 °C temperature of the preparative reactions. The reaction progress was followed by the formation of fluoroalkylaniline **53** by ^{19}F NMR spectroscopy; this approach was appropriate because the mass balance of the reaction with respect to the limiting reagent (aryl halide **52**) was >98%. The reaction was conducted with 0.667 mol % of an equimolar amount of the phenoxide complex **54** and *t*BuBippyPhos as catalyst, aryl halide **52** as limiting reagent, 1.05 equiv of 4-*n*Bu-PhOK, and 2.00 equiv of trifluoroethyl-amine in dioxane.[52] The amination reaction was found to be zeroth order in 1-chloro-4-fluorobenzene and *t*BuBippyPhos; it was found to be first order in trifluoroethylamine and in palladium phenoxide complex **54**. A nearly zero, but small positive dependence on the concentration of potassium 4-*n*Bu-phenoxide was also found; an explanation for this dependence is presented below.

Two catalytic cycles that differ in the reversibility of steps and fit the kinetic data are shown in Figure 8. Both cycles include oxidative addition to form an arylpalladium halide complex, conversion of the arylpalladium halide complex to an arylpalladium fluoroalkylamido species, and reductive elimination to form Pd(0) and the C–N bond in the fluoroalkyl-aniline product. However, the first cycle (Figure 8a) involves turnover-limiting reductive elimination, whereas the second involves turnover-limiting formation of a palladium-amido complex (Figure 8b). These two cycles can be distinguished by additional kinetic experiments. If reductive elimination were turnover limiting, then formation of the palladium-amido complex would be reversible. In this scenario (Figure 8a), the amination reaction would be inverse first order in phenol because it is generated as a stoichiometric byproduct during the ligand exchange.

Determination of the order of the reaction in phenol is complex because phenol forms strong hydrogen-bond adducts with phenoxide.[53] These hydrogen bond adducts reduce the concentration of free phenol. Therefore, we monitored the initial rates of stoichiometric reactions of the palladium phenoxide **54** with trifluoroethylamine in the presence of varied concentrations of phenol (eq 2) in the absence of phenoxide base. Analysis of the initial rates (Figure 9) showed that the reaction of **54** with trifluoroethylamine is inverse first order

in phenol. This result implies that the conversion of the phenoxide to the arylamine and Pd(0) species occurs by reversible proton exchange between the amine and the

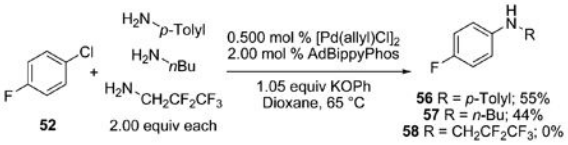


(2)

phenoxide complex, followed by irreversible reductive elimination to form the arylamine product.

The inverse order observed for phenol and the formation of strong hydrogen bonds between potassium phenoxides and phenols provides a plausible explanation for the observed partial order in potassium 4-*n*Bu-phenoxide. Excess 4-*n*Bu-phenoxide reduces the concentration of the phenol byproduct because the phenoxide hydrogen bonds to the phenol. Therefore, the concentration of free phenol is higher in reactions conducted with lower concentrations of 4-*n*Bu-phenoxide than in reactions conducted with higher concentrations of the phenoxide, and reactions conducted with higher concentrations of 4-*n*Bu-phenoxide occur faster than reactions conducted with lower concentrations of the phenoxide.

To determine the relative reactivity of different amines under these conditions, we conducted a reaction containing three distinct nitrogen nucleophiles: *n*-butylamine, *p*-toluidine, and pentafluoropropylamine (eq 3) in the presence of 1.0 mol %



(3)

catalyst. This coupling occurred to full conversion in just 30 min at 65 °C. Products arising from the couplings of *p*-toluidine and *n*-butylamine were formed in 55% and 44% yield, respectively; the product from coupling of pentafluoropropyl-amine was not observed under these conditions. The formation of products from the aryl and alkylamine over the fluoroalkyl-amine could be due to faster formation of the alkylamido or anilido complex, relative to the formation of a fluoroalkylamido complex, or from faster reductive elimination from the alkylamido or anilido complexes than from the fluoroalkyl-amido complex. Although we have not studied the origin of the observed selectivity, this result clearly demonstrates that the weak basicity of fluorinated amines dramatically changes the rate at which they react in C–N coupling reactions. Furthermore, this experiment demonstrates that

the combination of this catalyst and phenoxide base is suitable for the coupling of alkylamines and arylamines, although we have not yet studied the scope of reactions with this base in depth.

Mechanistic Conclusions

Our mechanistic data are consistent with the pathway shown in Figure 8a. Oxidative addition of the aryl halide occurs to the palladium(0) species ligated by *t*BuBippyPhos to generate a *t*BuBippyPhos(Ar)X complex. This complex reacts with phenoxide to generate the catalyst resting state, phenoxide complex **54**. Complex **54** reacts reversibly with trifluoroethylamine to form an amido complex. The transition state with the highest energy is that for reductive elimination.

It is unusual for Pd-catalyzed couplings of an aryl halide with an amine catalyzed by a complex containing a monophosphine ligand to occur with reductive elimination as the turnover-limiting step. Two prior studies, one on the coupling of benzophenone hydrazone[54] and one on the coupling of ammonia[55] with aryl halides implied that reductive elimination was the turnover-limiting step. However, these studies were conducted with palladium catalysts ligated by the bisphosphines BINAP and Josiphos, respectively. Thus, our mechanistic experiments reveal an unusual case in which aryl halide amination catalyzed by palladium ligated by a monophosphine occurs with reductive elimination as the turnover-limiting step. The reactions of the fluoroalkylamines in the current work also constitute an unusual case in which the coupling of an aryl halide with an aliphatic amine occurs by a mechanism involving turnover-limiting reductive elimination. The unusual turnover-limiting step is likely the result of the strongly electron-withdrawing property of the trifluoroethyl group. Reductive eliminations from palladium-amido complexes derived from electron-rich amines (e.g., *i*BuNH$_2$) have been shown to be faster than reductive eliminations from palladium-amido[56] complexes derived from less electron-rich amines (PhNH$_2$). Indeed, the only other case of reductive elimination as the rate-determining step in a C–N coupling reaction of an aliphatic amine catalyzed by a monophosphine ligated palladium complex was recently reported, although the authors concede they cannot exclude formation of the amido complex as the turnover-limiting step.[57]

The resting state of the catalyst in the current study is also unique for a coupling to form an arylamine and allows an unusually direct view of the formation of the amido complex. The amido complex has been proposed to form in cross-coupling reactions by coordination of the amine, followed by deprotonation of the bound amine by the base, or by formation of an alkoxide complex, followed by proton transfer to convert the alkoxide complex to an amido complex.[58] For reactions catalyzed by complexes of monophosphine complexes, the most commonly proposed mechanism is that involving coordination of the amine and deprotonation.[59,60]

Numerous groups have reported the preparation of aryl-palladium-amine complexes ligated by monophosphines and have shown that addition of amide or alkoxide base to these complexes results in the formation of anilines by reductive elimination from an arylpalladium-amido intermediates.[59,61,62] These data imply that the reactions of alkylamines catalyzed by complexes of bulky monophosphines occurs by coordination of

the amine and deprotonation by base.[63] For this reason, the direct observation of a phenoxide complex bound by a monophosphine as the resting state was unexpected. Assuming the proposed mechanism for formation of an alkylamido complex from the previous work is valid, the difference in mechanism for the reaction of alkylamines in the prior studies and the fluoroalkylamines in the current studies likely results from the large difference in Lewis basicity of the two types of amines or the different properties of phenoxide bases relative to tert-alkoxide bases. Indeed, the prior observation of an alkoxo complex during cross-coupling to form amines catalyzed by complexes of bisphosphines was made on the reaction of an arylamine mediated by NaO*t*Bu, not an alkylamine.[64,65]

CONCLUSION

In summary, we have developed conditions for the coupling of primary fluoroalkylamines with aryl bromides and aryl chlorides. The reaction occurs in high yield and can be conducted with low catalyst loadings for most substrates. The observed instability of the products toward strong bases led to the development of conditions in which weaker bases are used to promote the coupling reaction. Moreover, the combination of the low nucleophilicity of the amine and the low basicity of KOPh allows the reaction to occur in the presence of functional groups that are typically not tolerated by C–N coupling reactions. We anticipate that the products will have useful applications in pharmaceutical and agrochemical industries.

The reaction occurs with several unusual mechanistic features. First, the catalyst resting state is the phenoxide complex [(*t*BuBippyPhos)Pd(Ar)(OPh)] (**54**). The observation of this complex is the first evidence that a monophosphine-ligated arylpalladium phenoxide or alkoxide complex can be an intermediate in the coupling of aryl halides with amines. Second, the turnover-limiting step for the reaction is reductive elimination. The kinetic data provide rare evidence that reductive elimination to form a C–N bond can be rate-limiting during cross-coupling reactions to form amines catalyzed by complexes of the commonly used bulky monophosphines. These unusual features result from the selection of a base, rarely used in cross-coupling, that enabled reactions to form products valuable for medicinal chemistry, agrochemistry, and coordination chemistry, from a class of amine that is unexplored for cross-coupling reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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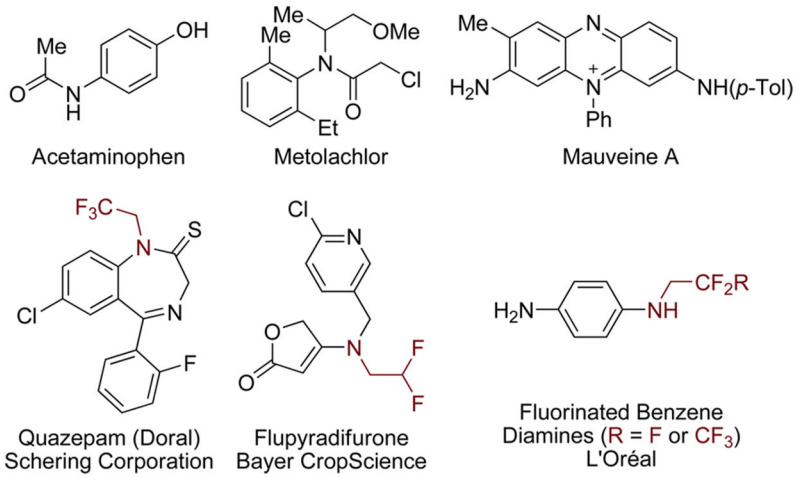
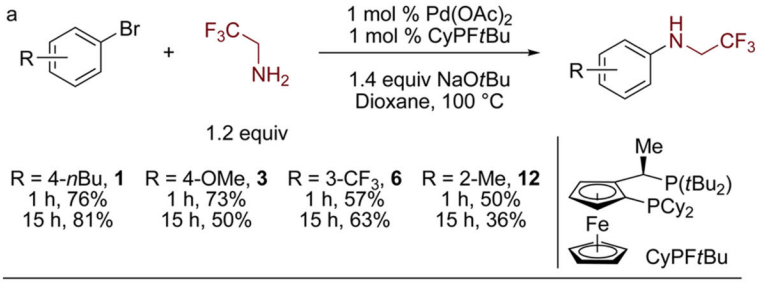
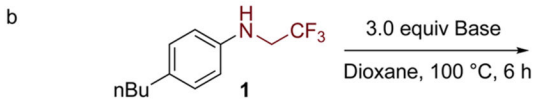


Figure 1.

Historically important aniline derivatives and recently patented fluorinated amine derivatives.





Base	LiHMDS	KO*t*Bu	NaO*t*Bu	K_3PO_4	Cs_2CO_3	PhOK
pKa Conjugate Acid	30	29.4	29.4			18
% **1** Remaining	0%	0%	9%	89%	98%	100%

Figure 2.

(a) Initial conditions for the coupling of trifluoroethylamine with aryl bromides. (b) Identification of bases that do not cause decomposition of *β*-fluoroalkylanilines as determined by ^{19}F NMR spectroscopy. The DMSO or THF pK_a values are shown for the conjugate acids of the soluble bases.

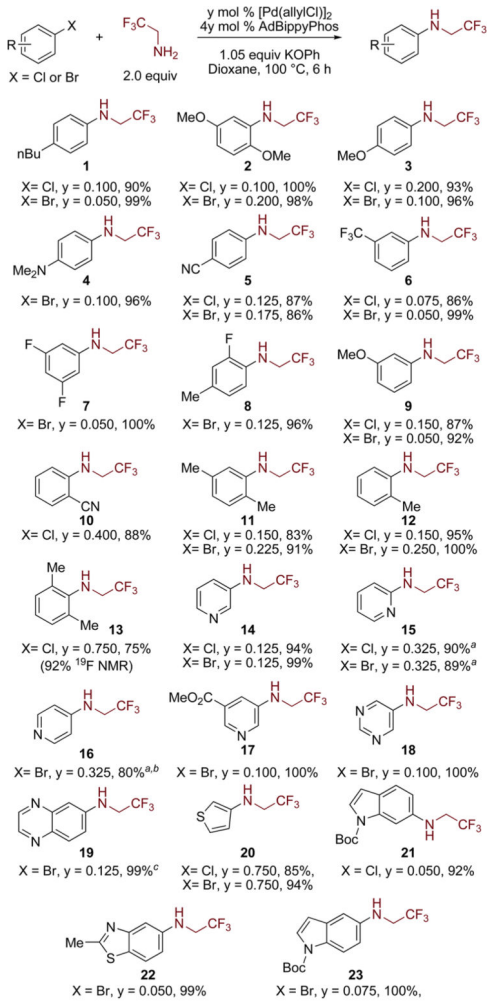


Figure 3.

Scope of the fluoroalkylamination of aryl halides. Unless otherwise stated, the yields refer to isolated material from reactions with 0.5 mmol of aryl or heteroaryl halide. [a]Yield measured by ^{1}H NMR spectroscopy. [b]The pyridinium hydrochloride salt was used with 2.05 equiv of KOPh. [c]Conducted with 0.35 mmol of aryl halide.

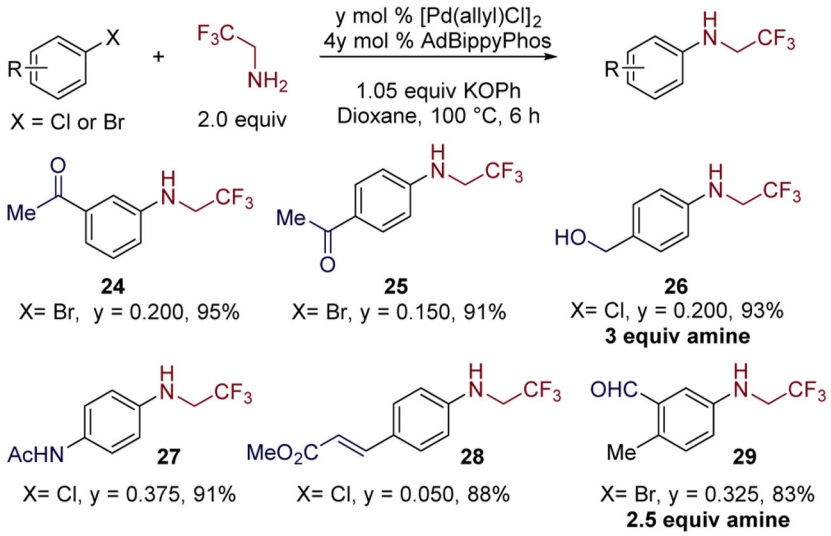


Figure 4.

Scope of the reaction of substrates containing functional groups that are sensitive to base or nucleophiles (shown in blue).

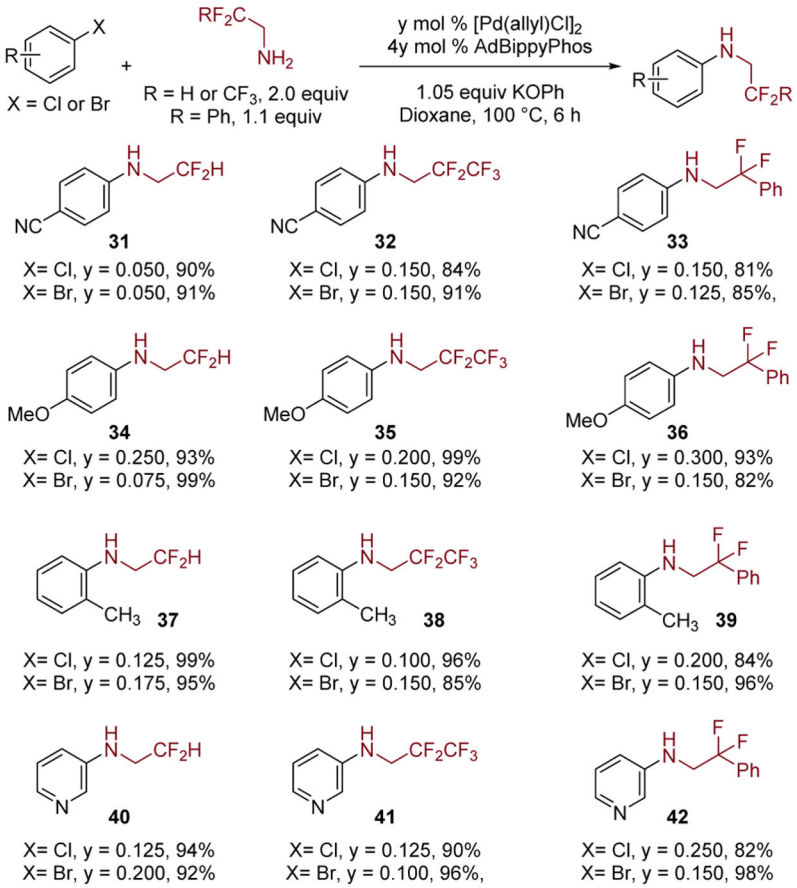


Figure 5.

Fluoroalkylanilines derived from difluoroethyl-, pentaffuor-opropyl-, and *β,β*-diffuorophenethylamine. All yields are isolated yields of 0.50 or 0.35 mmol reactions.

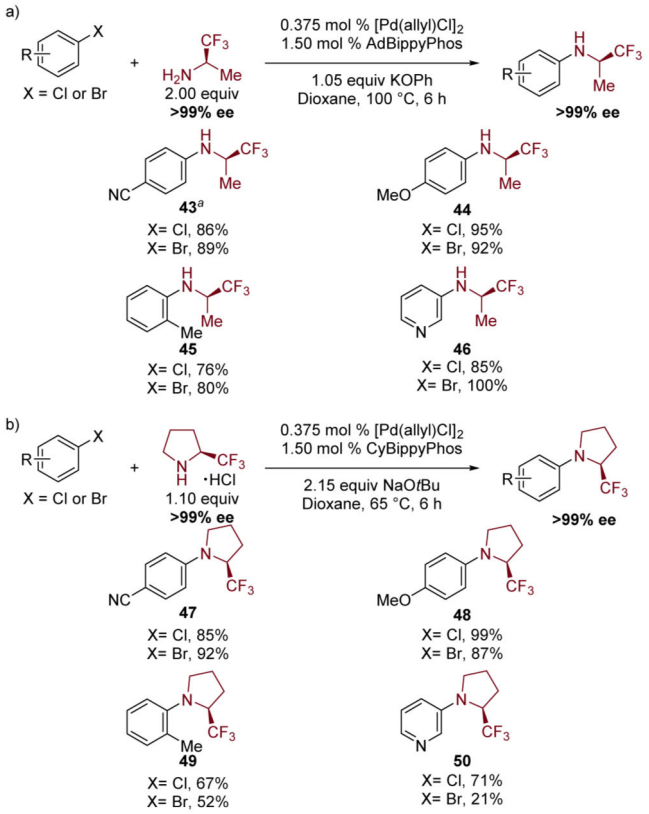


Figure 6.

Fluoroalkylanilines derived from (a) trifluoroisopropylamine and (b) 2-(trifluoromethyl)pyrrolidine. Reactions were conducted on 0.300 mmol scale; yields of products obtained from aryl chlorides are isolated yields, whereas yields of reactions of aryl bromides were determined by ^{19}F NMR spectroscopy. [a]Reaction conducted with *t*BuBippyPhos as the ligand and with 3.00 equiv of amine.

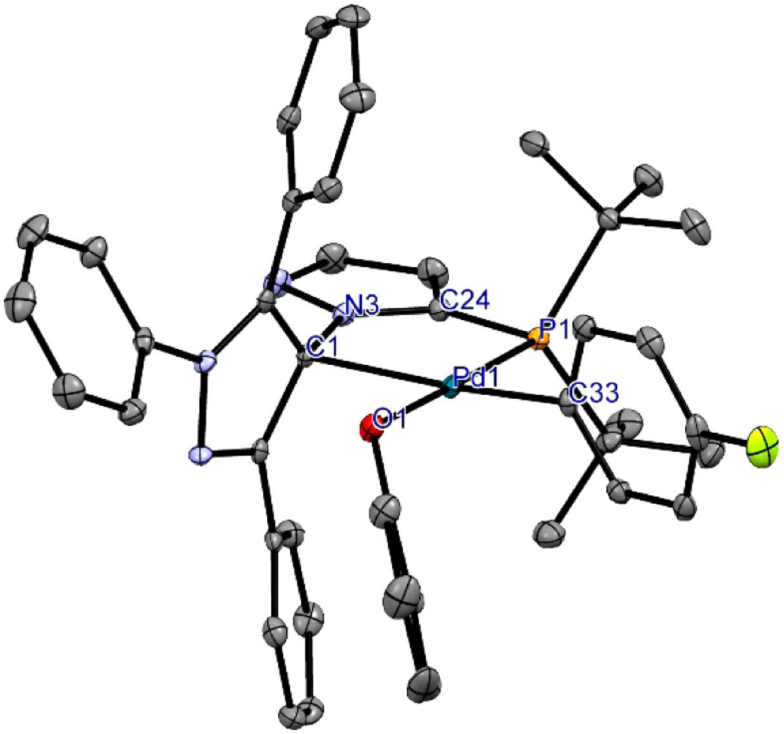


Figure 7.

Catalyst resting state **54** structure shown with 50% thermal ellipsoid. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg) of **54**: C1-Pd1 = 2.429(2); C33-Pd1 = 1.992(2); O1-Pd1 = 2.0447(14); P1-Pd1 = 2.2658(6); N3-C1-Pd1 = 103.74(12).

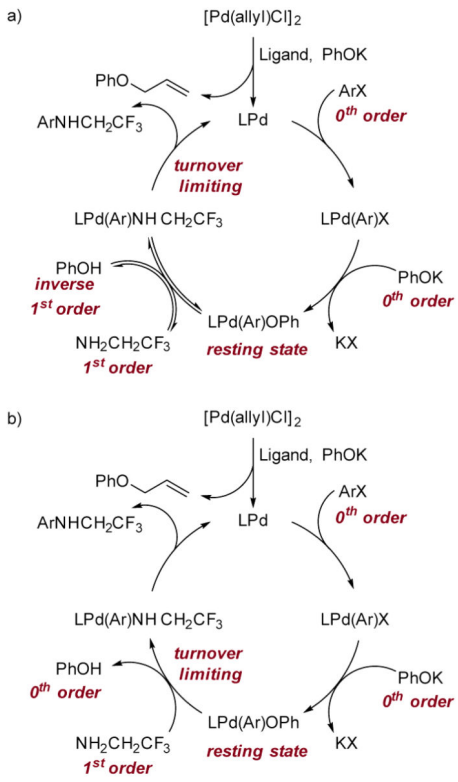


Figure 8.
Two mechanisms consistent with the observed resting state and reaction kinetics.

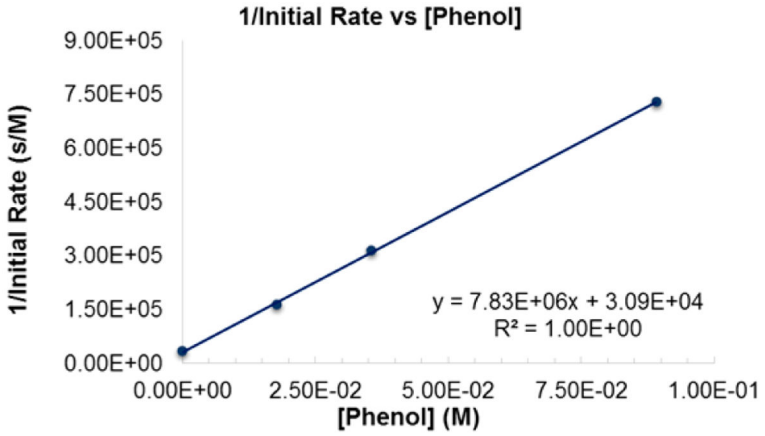
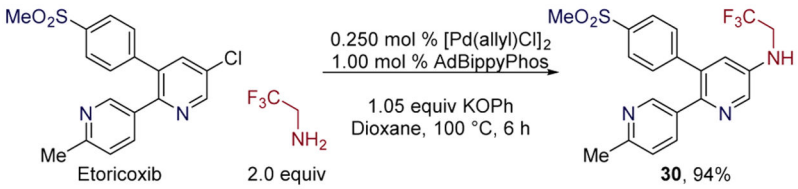
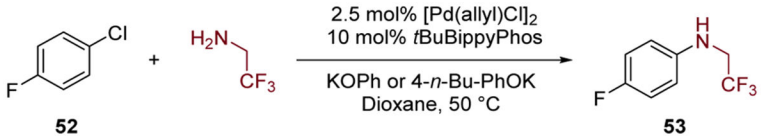


Figure 9.

Plot of 1/(initial rate) versus the concentration of phenol used to determine the reaction order in phenol.



Scheme 1.
Fluoroalkylamination of Etoricoxib

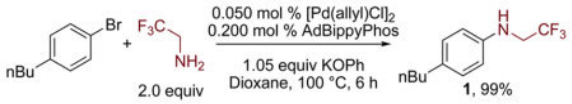


Scheme 2.

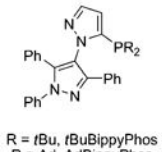
Model Reaction for Mechanistic Studies

Table 1

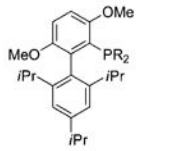
Effect of Changing Various Reaction Conditions for the Coupling of Trifluoroethylamine with 4-*n*-Butylbromobenzene



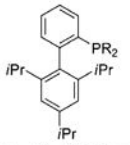
entry	deviation from standard conditions	yield[a] (%)
1	*t*BuBrettPhos instead of AdBippyPhos	88
2	*t*BuXPhos instead of AdBippyPhos	10
3	JackiePhos instead of AdBippyPhos	10
4	CyPF*t*Bu instead of AdBippyPhos	0
5	*t*BuBippyPhos instead of AdBippyPhos	100
6	CyBippyPhos instead of AdBippyPhos	20
7	1:1 metal-to-ligand ratio instead of 1:2	93
8	NaO*t*Bu instead of KOPh	43
9	assembled on benchtop with wet solvents in a vial, not in a glovebox with dried solvents	94
10	NaOPh instead of KOPh	100
11	1.10 equiv of phenol, 1.05 equiv of KO*t*Bu or NaO*t*Bu instead of isolated KOPh	100



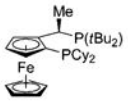
R = *t*Bu, *t*BuBippyPhos
R = Ad, AdBippyPhos
R = Cy, CyBippyPhos



R = *t*Bu, *t*BuBrettPhos
R = 3,5-bis-CF_3-Ph, JackiePhos



R = *t*Bu, *t*BuXPhos



CyPF*t*Bu

[a]Yield determined by ^{19}F NMR spectroscopy.