

(43) International Publication Date
17 November 2016 (17.11.2016)

(51) International Patent Classification:

C07C 209/04 (2006.01) C07C 211/46 (2006.01)
C07C 209/10 (2006.01) C07C 211/48 (2006.01)
C07C 209/22 (2006.01)

(21) International Application Number:

PCT/US2016/031675

(22) International Filing Date:

10 May 2016 (10.05.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/159,816 11 May 2015 (11.05.2015) US

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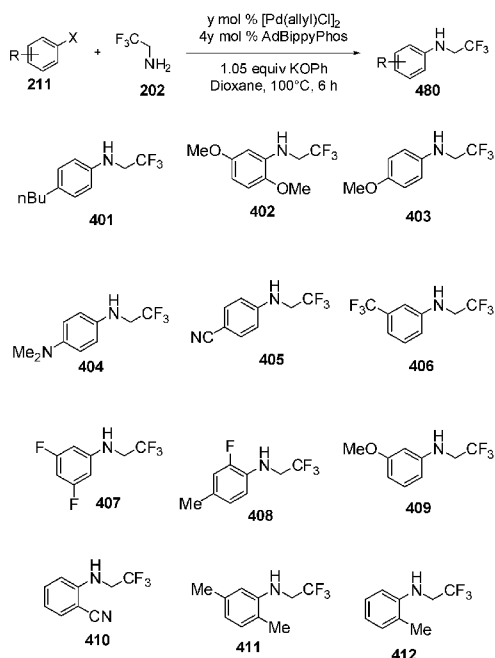
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,

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(54) Title: PALLADIUM-CATALYZED ARYLATION OF FLUOROALKYLAMINES

**FIG. 4A**

(57) Abstract: Methods for synthesizing trifluoroethyl, difluoroethyl, pentafluoropropyl, and difluorophenethyl anilines by palladium-catalyzed coupling of fluoroalkylamines with aryl bromides and aryl chlorides are provided herein. The reaction is conducted with a weaker base such as KOPh in the presence of a catalyst derived from AdBippyPhos and [Pd(allyl)Cl]₂. The reactions occur with catalyst loadings less than about 0.50 mol% 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 turn-over limiting step of the reaction is reductive elimination to form the C-N bond.



SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG). **Published:**

— *with international search report (Art. 21(3))*

PALLADIUM-CATALYZED ARYLATION OF FLUOROALKYLAMINES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims benefit of priority to U.S. Provisional Patent Application No. 62/159,816, filed May 11, 2015, entitled "PALLADIUM-CATALYZED ARYLATION OF FLUOROALKYLAMINES," which is herein incorporated by reference in its entirety.

BACKGROUND

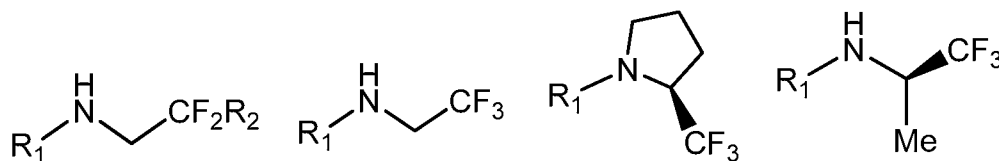
[0002] Compounds including aniline and aniline derivatives are used in the pharmaceutical, agrochemical, and pigment industries. Existing methods of forming β -fluorinated anilines use strongly electron-deficient arenes and have been shown to occur slowly with weakly nucleophilic β -fluorinated amines.

SUMMARY

[0003] Provided herein are methods of synthesizing trifluoroethyl, difluoroethyl, pentafluoropropyl, and difluorophenethyl anilines by palladium-catalyzed coupling of fluoroalkylamines with aryl halides.

[0004] One aspect involves a method of forming a fluoroalkylaniline, the method including reacting a fluoroalkylamine with an aryl or heteroaryl halide using a palladium-containing catalyst in the presence of an oxygen-containing base having a conjugate acid pKa in dimethyl sulfoxide of less than about 32. In some embodiments, the fluoroalkylaniline is enantioenriched.

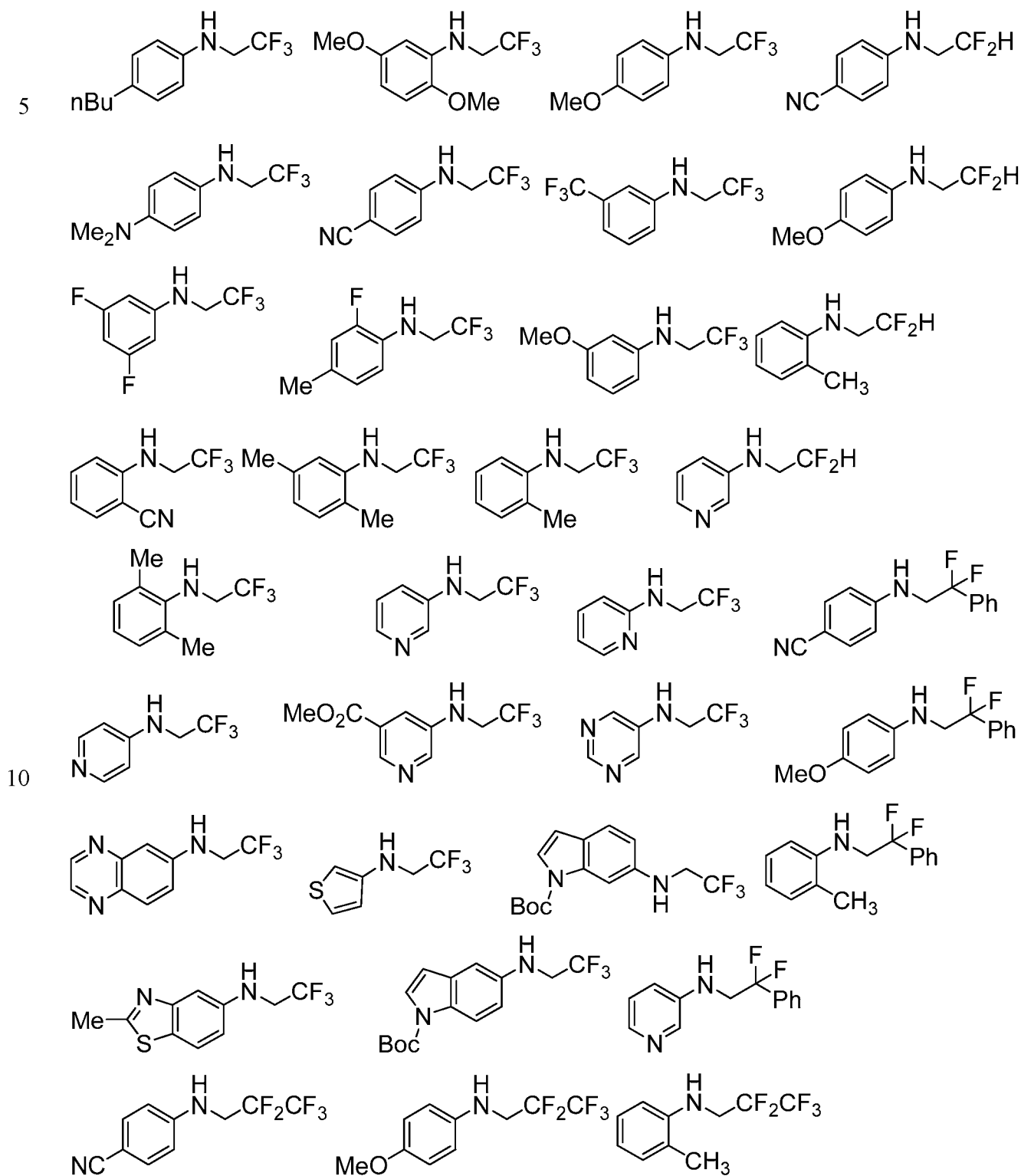
[0005] In some embodiments, the fluoroalkylaniline formed includes the structure selected from the group consisting of:

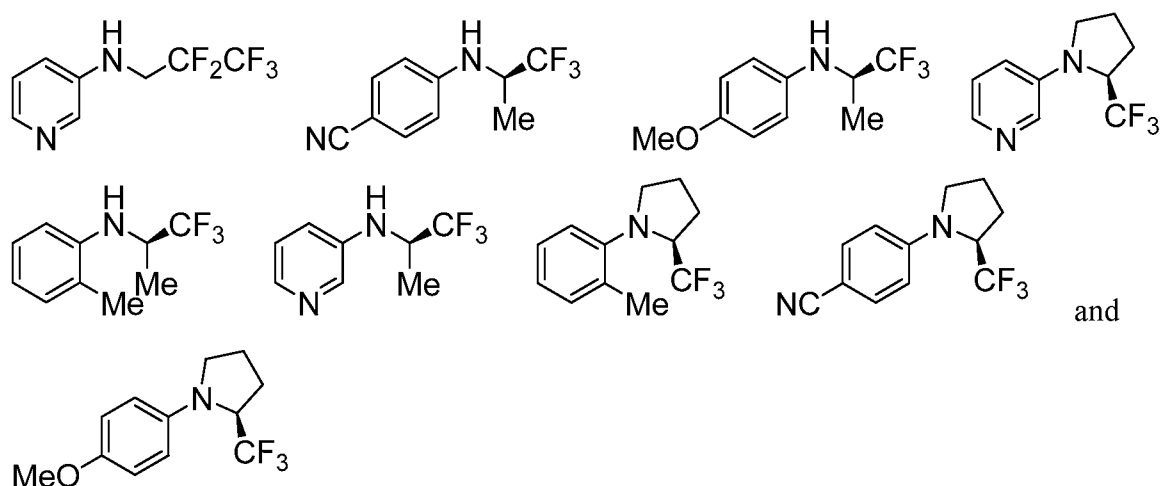


wherein R_1 is an aryl or heteroaryl group including any one or more of the following substituents: carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups including a hydrogen atom; and R_2 is any of the following organic groups: carbon-containing

organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups including a hydrogen atom.

[0006] In some embodiments, the fluoroalkylaniline formed is any of the following structures:





[0007] In various embodiments, the fluoroalkylamine is any one of trifluoroethylamine, difluoroethylamine, pentafluoropropylamine, difluorophenethylamine, trifluoroisopropylamine, and 2-(trifluoromethylpyrrolidine).

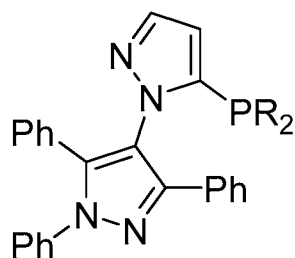
[0008] In some embodiments, the aryl or heteroaryl halide includes the chemical structure $\text{R}-\text{X}$, wherein X is selected from any one or more of the following: chlorine, bromine, and iodine; and R is an aryl or heteroaryl group including a functional group sensitive to strong base and nucleophiles. The functional group may be any of unprotected acetophenones, free alcohols, amides, unconjugated esters, cinnamate esters, nitriles, methyl aryl sulfoxide, and non-enolizable aldehydes.

[0009] In some embodiments, the aryl or heteroaryl halide includes an aryl chloride or bromide without an acidic N-H bond. In various embodiments, the aryl or heteroaryl halide is any one or more of the following: heteroaryl halides of 2-, 3-, and 4-halopyridines, pyrimidines, quinoxalines, thiophenes, indoles, and thienobenzoxazoles.

[0010] In some embodiments, the aryl or heteroaryl halide is any one or more of the following: aryl bromides, aryl chlorides, heteroaryl bromides, and heteroaryl chlorides.

[0011] In some embodiments, the base is derived from a phenoxide. In some embodiments, the base is nitrogen-free. In some embodiments, the base is KOPh.

[0012] The palladium-containing catalyst may be ligated with any one or more of the following compounds: phosphines, phophites, phosphoramidites, phosphoramides, N-heterocyclic carbenes, monophosphines, and



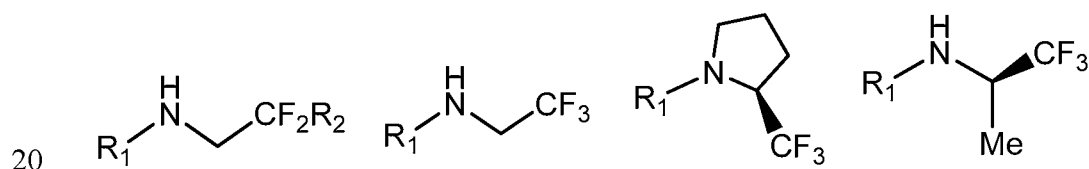
R = *t*Bu, Ad, Cy

5 [0013] The reaction may form a palladium complex including a monophosphine. In some embodiments, the ratio of palladium to ligand to form the palladium complex is about 1:2.

[0014] Another aspect involves a method of forming a fluoroalkylaniline, the method including reacting a fluoroalkylamine with an aryl or heteroaryl sulfonate or phosphate using a palladium-containing catalyst in the presence of an oxygen-containing base having a conjugate acid pKa in
10 dimethyl sulfoxide of less than about 32. The aryl or heteroaryl sulfonate or phosphate may include the chemical structure R—X, wherein X is any sulfonate or phosphate, and R is an aryl or heteroaryl group including a functional group sensitive to strong base and nucleophiles. The functional group may be any of unprotected acetophenones, free alcohols, amides, unconjugated esters, cinnamate esters, nitriles, methyl aryl sulfoxide, and non-enolizable aldehydes.

15 [0015] In various embodiments, the fluoroalkylamine is any one of trifluoroethylamine, difluoroethylamine, pentafluoropropylamine, difluorophenethylamine, trifluoroisopropylamine, and 2-(trifluoromethylpyrrolidine).

[0016] In some embodiments, the fluoroalkylaniline formed includes any of the following structures:



wherein R₁ is an aryl or heteroaryl group including any one or more of the following substituents: carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups

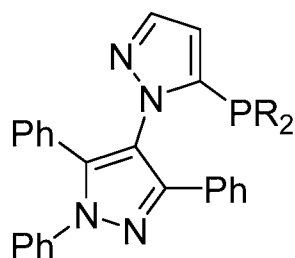
including a hydrogen atom; and R_2 is any of the following organic groups: carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups including a hydrogen atom.

[0017] In some embodiments, the aryl or heteroaryl halide is any one or more of the following:

5 aryl bromides, aryl chlorides, heteroaryl bromides, and heteroaryl chlorides.

[0018] In some embodiments, the base is derived from a phenoxide. In some embodiments, the base is nitrogen-free. In some embodiments, the base is KOPh.

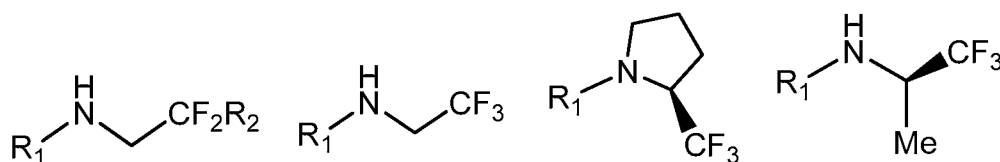
[0019] The palladium-containing catalyst may be ligated with any one or more of the following compounds: phosphines, phosphites, phosphoramidites, phosphoramides, N-heterocyclic
10 carbenes, monophosphines, and



$R = tBu, Ad, Cy$

[0020] Another aspect involves a method of forming a fluoroalkylaniline, the method including reacting a fluoroalkylamine with a halogen-containing reactant using a palladium-containing catalyst in the presence of a base, whereby the reactant is any of chloroarenes, chloroheteroarenes, bromoarenes, and bromoheteroarenes; and whereby the reactant is not
15 bromoindazole. In various embodiments, the fluoroalkylamine is any of trifluoroethylamine, difluoroethylamine, pentafluoropropylamine, difluorophenethylamine, trifluoroisopropylamine, and 2-(trifluoromethylpyrrolidine).

[0021] In some embodiments, the fluoroalkylaniline formed includes the structure selected from
20 the group consisting of:



wherein R_1 is an aryl or heteroaryl group including any one or more of the following substituents: carbon-containing organic groups, halogen-containing organic groups, sulfur-

containing organic groups, phosphorous-containing organic groups, and organic groups including a hydrogen atom; and R₂ is any of the following organic groups: carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups including a hydrogen atom.

5 [0022] Another aspect is a fluoroalkylaniline prepared by any of the above-described methods.

[0023] Another aspect is an enantioenriched fluoroalkylaniline product.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] **Figure 1** shows chemical structures of various aniline derivatives and fluorinated amine derivatives.

10 [0025] **Figure 2A** shows the chemical reaction associated with methods of certain disclosed embodiments.

[0026] **Figure 2B** is a chemical structure of CyPF*t*Bu.

[0027] **Figure 2C** shows a reactant and catalyst for experiments conducted in accordance with certain disclosed embodiments.

15 [0028] **Figure 3A** depicts chemical structures for variations of BippyPhos, BuBrettPhos, JackiePhos, and *t*BuXPhos.

[0029] **Figure 3B** depicts a reaction for coupling of trifluoroethylamine with 4-*n*-butylbromobenzene used in an experiment.

20 [0030] **Figure 4A** shows a chemical reaction of fluoroalkylation of aryl halides used for performing certain experiments in accordance with certain disclosed embodiments, as well as chemical structures for compounds derived from the experiment.

[0031] **Figure 4B** depicts chemical structures for compounds derived an experiment for fluoroalkylation of aryl halides.

25 [0032] **Figure 5** shows chemical structures of compounds having functional groups sensitive to base or nucleophiles such as the oxygen-containing functional group which are used in experiments described herein.

[0033] **Figure 6** shows chemical structures of the compounds derived from conducting an experiment in accordance with certain disclosed embodiments.

[0034] Figure 7 shows a chemical reaction used for an experiment on derivatization of coupled produced in accordance with certain disclosed embodiments.

[0035] Figure 8 shows a chemical reaction used as a model reaction for mechanistic studies.

[0036] Figure 9 is a depiction of the resting state structure of the catalyst [(*t*BuBippyPhos)Pd(Ar)-(OPh)] shown with 50% thermal ellipsoid without hydrogen atoms.

[0037] Figures 10A and 10B show example mechanisms consistent with observed resting state and reaction kinetics derived from experiments performed in accordance with certain disclosed embodiments.

[0038] Figure 11A shows the chemical reaction for reacting [(*t*BuBippyPhos)Pd(Ar)-(OPh)] to form 4-fluoro-*N*-trifluoroethylaniline.

[0039] Figure 11B is a plot of 1/Initial Rate versus the concentration of phenol used to determine the reaction order in phenol as used in an experiment.

[0040] Figures 12A and 12B show reactions performed in an experiment to form fluoroalkylanilines with retention of the high enantioerichment of the starting chiral fluoroalkylamine.

DETAILED DESCRIPTION

[0041] In the following description, numerous specific details are set forth to provide a thorough understanding of the presented embodiments. The disclosed embodiments may be practiced without some or all of these specific details. In other instances, well-known process operations have not been described in detail to not unnecessarily obscure the disclosed embodiments. While the disclosed embodiments will be described in conjunction with the specific embodiments, it will be understood that it is not intended to limit the disclosed embodiments.

INTRODUCTION

[0042] Molecules containing aniline and aniline derivatives are common in the pharmaceutical, agrochemical, and pigment industries. For example, an acetamide is found in the highest grossing prescription drug off all time (Lipitor) and the most commonly administered over-the-counter pain drug (Tylenol). In addition, many of the most widely applied herbicides (e.g. Metolachlor), as well as common pigment chromophores (e.g. Mauveine A), are aniline

derivatives (**Figure 1**). Because of these important applications, numerous classical and modern methods for the preparation of anilines have been reported.

[0043] Aniline derivatives containing electron-withdrawing substituents are more valuable than the parent anilines in medicinal chemistry because anilines are prone to oxidation. For example, *N*-alkyl anilines are susceptible to aerobic or metabolic degradation to the corresponding aniline via oxidation by cytochrome P450, and the parent anilines are usually oxidized further to *N*-aryl hydroxylamines that generate carcinogenic arenium ions. Thus, anilines derivatives, such as sulfonamides, amides, ureas, or carbamates, possessing electron-withdrawing groups are the derivatives most commonly contained in pharmacophores and agrophores.

[0044] Aniline derivatives containing fluoroalkyl groups should possess electronic properties that would mitigate oxidation. Consistent with this assertion, fluoroalkylanilines have been shown to be more stable toward P450-mediated oxidation than alkyl anilines lacking fluorine atoms. While sharing the electronic properties of the sulfonyl and carbonyl derivatives, the solubility properties, intermolecular interactions, and steric properties of fluoroalkyl anilines are distinct from those of sulfonyl and carbonyl derivatives.

[0045] **Figure 1** shows some aniline derivatives and fluorinated amine derivative examples. Compound **101** is acetaminophen, compound **103** is Metolachlor, compound **105** is Mauveine A, compound **107** is Quazepam (Doral) from Schering Corporation, compound **109** is Flupyradifurone from Bayer CropScience, and compound **111** is a generic structure of fluorinated benzene diamines from L'Oréal, where R is F or CF₃.

[0046] The ability of fluorine atoms to change the electronic properties of neighboring atoms has led to scattered examples of medicines, agrochemicals, and dyes containing fluoroalkyl aniline groups (**Figure 1**), but these aniline derivatives have not been widely studied. One reason for the uncommon use of β -fluoroalkyl anilines 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*-trifluoroethyl aniline) are the reductive amination of trifluoroacetaldehyde with the corresponding aniline derivative and S_NAr reactions. 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.

[0047] Metal-catalyzed C-N coupling reactions provides a general method for preparing fluorinated anilines and allows evaluation of these substructures as part of 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. However, general conditions for cross couplings of aryl halides with fluorinated amines have not been reported. Buchwald et al. reported a single cross coupling of trifluoroethylamine (with 5-bromoindazole), and this reaction occurred in moderate yield (65%), which is described in the publication Henderson, J. L.; Buchwald, S. L. *Org. Lett.* 2010, 12, 4442.. Buchwald et al. concluded that trifluoroethylamine hydrochloride *inhibited* cross couplings under the standard conditions developed for the amination of heteroarenes. Thus, the parameters and conditions for achieving the coupling with fluoroalkylanilines are distinct from those for coupling of alkylamines or anilines.

METHOD

[0048] Provided herein are methods associated with the synthesis of fluoroalkyl anilines such as trifluoroethyl, difluoroethyl, pentafluoropropyl, and difluorophenethyl anilines by palladium-catalyzed coupling of fluoroalkylamines with aryl bromides, aryl chlorides, aryl sulfonates, or aryl phosphates in the presence of an oxygen-containing base. In various embodiments described herein, aryl compounds may include heteroaryl compounds. The products of these reactions are valuable because anilines typically use the presence of an electron withdrawing substituent on nitrogen to suppress aerobic or metabolic oxidation, and the fluoroalkyl groups have distinct steric properties and polarity from 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, occurs in high yield in the presence of a catalyst derived from commercially available AdBippyPhos (adamantyl-BippyPhos) and $[Pd(allyl)Cl]_2$. Weaker bases suitable for use in various disclosed embodiments may have a conjugate acid pKa in DMSO (dimethyl sulfoxide) of less than about 32, less than about 25, or less than about 20. In some embodiments, any oxygen-containing base may be used. Under these conditions, the reactions occur with low catalyst loadings (less than about 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 turn-over limiting step of the reaction is reductive elimination to form the C-N bond.

[0049] In various embodiments, the synthesis of trifluoroethyl, difluoroethyl, pentafluoropropyl, and difluorophenethyl anilines by palladium-catalyzed coupling of fluoroalkylamines with
5 chloroarenes, chloroheteroarenes, bromoarenes, and bromoheteroarenes except for bromoindazole may be performed in the presence of any suitable base, including bases that do not include oxygen.

[0050] Provided herein is a method of coupling of aryl bromides and chlorides with primary amines containing fluorine β -to nitrogen. The reaction occurs with a wide substrate scope, under
10 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. In some
15 embodiments, a second feature of the reaction is the resting state for operations in which AdBippyPhos is used as a ligand; 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
20 reductive elimination.

[0051] Disclosed embodiments are also suitable for forming enantioenriched anilines. In some
embodiments, enantioenriched amines may be used to form enantioenriched anilines as disclosed
embodiments do not cause enantioenriched amines to become racemic during the reaction. In
various embodiments, a certain quantity of an enantioenriched aniline may be produced using
25 disclosed embodiments. For example, at least about 0.5 mmol, or at least about 1.0 mmol, or at
least about 5.0 mmol, or at least about 10.0 mmol of an enantioenriched aniline may be
generated. An enantioenriched compound is defined as having an enantiopurity greater than 0%
enantiomeric excess. For example, in some embodiments, an enantioenriched compound may be
in enantiomeric excess of at least 99% (w/w) over the opposite enantiomer. For example, in
30 some embodiments, an enantioenriched compound may be in enantiomeric excess of at least
95% (w/w) over the opposite enantiomer. For example, in some embodiments, an
enantioenriched compound may be in enantiomeric excess of at least 90% (w/w) over the

opposite enantiomer. For example, in some embodiments, an enantioenriched compound may be in enantiomeric excess of at least 70% (w/w) over the opposite enantiomer. In some embodiments, a highly enantioenriched compound includes only one enantiomer detectable by supercritical fluid chromatography. In some embodiments, an enantiopure sample of a fluoroalkylaniline product has only one chiral form. Any suitable primary or secondary amine including such amines that include fluorine may form an aniline under certain process conditions. For example, in some embodiments, other suitable catalysts may be selected to react with a highly fluorinated amine to yield a highly fluorinated aniline in accordance with disclosed embodiments.

EXPERIMENTAL

[0052] For the below described experiments, all reactions were conducted in an argon- or nitrogen-filled glove box unless noted otherwise. Solvents were purchased dry from commercial suppliers or were dried by eluting through a 0.33 m column of activated alumina under nitrogen. Unless specified below, all reagents were purchased from commercial suppliers. Liquid aryl and heteroaryl halides were purified by passing the neat compound through a short plug of basic alumina. Trifluoroethylamine, difluoroethylamine, and pentafluoropropylamine were purchased from commercial suppliers and stored over molecular sieves. BippyPhos ligands were purchased from Aldrich, but *t*BuBippyPhos was also prepared as described below. All palladium catalyst precursors were obtained from Strem, Aldrich, or Johnson Matthey. Potassium phenoxide and potassium 4-*n*Bu-phenoxide, Etoricoxib and difluorophenethylamine were prepared as described below. Proof of purity is demonstrated by copies of NMR spectra and by elemental analysis for the catalyst resting state.

[0053] Although alkali metal phenoxides are stable enough to be handled in air, the phenoxides used in these reactions should have contact with air minimized because metal phenoxides can undergo aerobic oxidation to produce dark colored impurities. The presence of these impurities, whether in synthesized or purchased phenoxide salts, results in much lower amination reaction yields. Without being bound by a particular theory, it is believed that the products of phenoxide oxidation may be capable of oxidizing either palladium or the BippyPhos ligand. Therefore, the phenoxides may be prepared as described herein and stored under an inert atmosphere of argon or nitrogen. Alternatively, the phenoxides can be prepared and used in situ by premixing a slight excess of phenol (1.10 equiv) with KO^tBu (1.05 equiv) or NaO^tBu (1.05 equiv) in the dioxane used to conduct the reaction. While the reaction to produce compound **401** as shown in Figure

4A can be conducted with sodium phenoxide as the base, the scope and mechanism of the reaction with potassium phenoxides is provided herein.

[0054] For the below experiments involving catalytic amination reactions, potassium phenoxide (0.525 mmol, 1.05 equiv, 69.4 mg) was added to a vial in the glove box. Solid aryl halides were added at this point (0.500 mmol, 1.00 equiv). Dioxane (2 mL minus the volume of catalyst solution to be added), benzotrifluoride (0.500 mmol, 1.00 equiv, 61.4 μ L), liquid aryl halides (0.500 mmol, 1.00 equiv), a dioxane solution of the catalyst (5.00 mM, 10.0 mM BippyPhos, 2.50 mM [Pd(allyl)Cl]₂) and trifluoroethylamine (1.00 mmol, 2.00 equiv, 78.5 μ L) were added to the vial containing potassium phenoxide. The vial was sealed with a Teflon-lined cap and removed from the glove box. The reaction was heated at 100 °C until ¹⁹F NMR spectra of aliquots showed that the reaction had occurred to greater than 95% conversion or that no additional product was being formed. The reaction was cooled to room temperature, diluted with hexanes, and filtered through a short plug of silica. The silica plug was then rinsed with ethyl acetate and concentrated to give an oil or solid, which were purified by column chromatography by eluting with EtOAc/Hexanes or MeOH/CH₂Cl₂. Some products co-elute with the phenol that is generated in the reaction. Phenol was removed from these products by passing the purified product through a plug of basic alumina, eluting with dichloromethane, or by washing an ethereal solution of the aniline with 0.1 M aqueous KOH.

EXPERIMENT 1: YIELD USING ARYL BROMIDES AND VARIOUS BASES

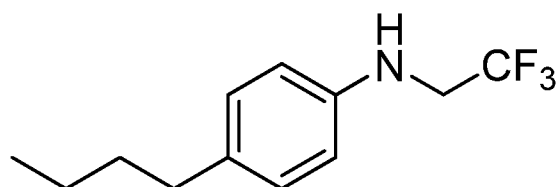
[0055] Due to the similar basicity of trifluoroethylamine and aniline, it was hypothesized that trifluoroethylamine would couple with aryl halides under conditions reported for the coupling of aniline with aryl halides. To test this hypothesis, trifluoroethylamine was allowed to react with 4-*n*-butyl bromobenzene in the presence of a Josiphos-ligated catalyst that couples anilines with aryl halides with broad scope under mild conditions. **Figure 2A** shows a chemical reaction for the coupling of trifluoroethylamine **202** with aryl bromides **201**. The reaction is catalyzed with 1 mole percent of Pd(OAc)₂ and 1 mole percent of CyPF₇Bu, with 1.4 equivalents of NaO^{*t*}Bu and dioxane at 100°C where the aryl bromide **201** is provided at 1.2 equivalents. The product is depicted in compound **203**. **Figure 2B** shows the chemical structure of CyPF₇Bu. Organic groups R for **201** and **203** of **Figure 2A** may be any of the below structures as shown in **Table 1**. The results are shown in **Table 1**.

Table 1. Conditions for Trifluoroethylamine with Aryl Bromides

Compound Number	401	3	6	12
R Group	4- <i>n</i> Bu	4-OMe	3-CF ₃	2-Me
Yield after 1 hour	76%	73%	57%	50%
Yield after 15 hours	81%	50%	63%	36%

[0056] In one trial, the reaction produced compound **401** in 81% yield after 15 hours.

Compound **401** is shown below and is also depicted in **Figure 3B**:



5 **[0057]** However, the yields of reactions of more electron-rich or *o*-substituted aryl halides under these conditions reached a maximum value (50%-73%) 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.

[0058] 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 compound **401** was tested in the presence of various bases at 100°C for 6 hours in dioxane to determine which bases do not induce decomposition of compound **401**. Strong bases, such as LiHMDS, NaO*t*Bu, and KO*t*Bu, caused complete decomposition of the product of compound **401**, whereas weaker inorganic bases and KOPh caused only minimal decomposition of compound **401** (as shown in **Table 2**). **Table 2** shows the DMSO pK_a values for soluble bases.

Table 2. Effect of Bases on Decomposition of β -fluoroalkylanilines

Base	KO <i>t</i> Bu	NaO <i>t</i> Bu	LiHMDS	K ₃ PO ₄	Cs ₂ CO ₃	PhOK
pK _a Conjugate Acid	32	32	26			18
% of Compound 401 Remaining	0%	9%	0%	89%	98%	100%

[0059] The results suggested that when coupling reactions were conducted in the presence of these weaker bases, the yields of compound **401** were lower than 10%. Weaker bases in DMSO (dimethyl sulfoxide) may have a conjugate acid pK_a of less than about 32, less than about 25, or less than about 20. In some embodiments, any oxygen-containing base may be used.

EXPERIMENT 2: VARIATION OF REACTION CONDITIONS

[0060] Combinations of palladium precursors and ligands that would catalyze the reaction under conditions with the weaker bases were evaluated. Generally, the coupling reactions of amines with aryl halides catalyzed by bisphosphine-ligated Pd complexes use 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 the three-coordinate LPd(Ar)(X) than to a four-coordinate L₂Pd(Ar)(X). The pK_a of mono-phosphine ligated LPd(Ar)(X)(amine) complexes are calculated to be between 8 and 10 in H₂O and can be deprotonated by weak base.

[0061] Based on this information, catalysts containing monodentate ligands in the presence of weak bases for the coupling of aryl halides with fluorinated amines were evaluated. Results are summarized in **Table 3**. Compound **399** of **Figure 3A** shows the chemical structure for BippyPhos, where R is *t*Bu for *t*BuBippy Phos, R is Ad for AdBippyPhos, and R is a cyclohexyl group for CyBippyPhos (cyclohexyl-BippyPhos). Compound **302** of **Figure 3B** shows the chemical structure for BrettPhos, where R is *t*Bu for *t*BuBrettPhos, or R is 3,5-bis-CF₃-Ph for JackiePhos. Compound **303** shows the chemical structure for *t*BuXPhos where R is *t*Bu.

Table 3. Effect of changing various reaction conditions for the coupling of trifluoroethylamine with 4-*n*-butyl bromobenzene

Entry	Deviation from Standard Conditions	Yield ^a
1	<i>t</i> BuBrettPhos instead of AdBippyPhos	88%
2	<i>t</i> BuXPhos instead of AdBippyPhos	10%
3	JackiePhos instead of AdBippyPhos	10%
4	CyPF <i>t</i> Bu instead of AdBippyPhos	0%
5	<i>t</i> 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 <i>t</i> Bu instead of KOPh	43%
9	Assembled on bench top with wet solvents in a vial, not in a glove box with dried solvents	94%
10	NaOPh instead of KOPh	100%
11	1.10 equiv of phenol, 1.05 equiv of KO <i>t</i> Bu or NaO <i>t</i> Bu instead of isolated KOPh	100%

^a Yield determined by ¹⁹F NMR spectroscopy

[0062] As shown in **Figure 3B**, the combination of [Pd(allyl)Cl]₂, AdBippyPhos, and KOPh catalyzed the coupling of 4-*n*-butyl bromobenzene 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 the past.

[0063] Although the coupling of amines with aryl halides catalyzed by complexes of AdBippyPhos has not previously been reported, Singer at Pfizer published such couplings catalyzed by complexes of BippyPhos, which is described in Singer, R. A.; Doré, M.; Sieser, J. E.; Berliner, M. A. *Tetrahedron Lett.* 2006, 47, 3727; and Withbroe, G. J.; Singer, R. A.; Sieser, J. E. *Org. Process Res. Dev.* 2008, 12, 480. Stradiotto and coworkers recently studied the scope of C-N coupling reaction catalyzed by palladium complexes of *t*BuBippyPhos and showed that catalysts containing this ligand catalyze the coupling of a wide variety of aryl halides and amines with low catalyst loadings, which is described in Crawford, S. M.; Lavery, C. B.; Stradiotto, M. *Chem. Eur. J.* 2013, 19, 16760. Beller has shown palladium and AdBippyPhos catalyzes the etherification of aryl halides with primary alcohols, as described in Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* 2010, 132, 11592.

[0064] Other BippyPhos derivatives, all of which are commercially available and readily synthesized, form complexes that catalyze this transformation. The reaction of trifluoroethylamine with 4-*n*-butyl bromobenzene 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, the yields and conversions for reactions of aryl halides other than 4-*n*-butyl bromobenzene 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 not observed. The analogous reaction conducted with CyBippyPhos (cyclohexyl-BippyPhos) 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 infra*). 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 use

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).

[0065] The effect of other reaction parameters on yield was evaluated by allowing trifluoroethylamine to react with 4-*n*-butyl bromobenzene 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-chloropyridine to produce compound **414** of **Figure 4B** 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.

[0066] 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 compound **401** of **Figure 4A** 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 of **Table 3**). Although KOPh is not available from common chemical suppliers, reactions conducted with this base generated and used *in situ* from phenol and KO^tBu occurred in the same yield as those initiated with isolated KOPh (Entry 11 of **Table 3**).

EXPERIMENT 3: SCOPE OF THE ARYLATION OF FLUOROALKYLAMINES

[0067] **Figures 4A** and **4B** summarize the scope of the reaction of trifluoroethylamine **202** with a variety of aryl and heteroaryl bromides and chlorides (compound **211**, where X is Cl or Br and trifluoroethylamine is provided in 2.0 equivalents) under the conditions shown in **Table 1** to generate a variety of products **480**. Unless otherwise stated herein, the yields refer to isolated material from reactions with 0.5 mmol of aryl or heteroaryl halide. The yield for those labeled “a” were measured by ¹H NMR spectroscopy. The pyridinium hydrochloride salt in those labeled “b” was used with 2.05 equivalents of KOPh. The yields associated with those labeled “c” were achieved from experiments conducted with 0.35 mmol of aryl halide. The minimum amount of catalyst used for each reaction to reach full conversion is reported. Electron-neutral (**401**), electron-rich (**402** - **404**), and electron-poor aryl halides (**405** - **410**) reacted to form the corresponding trifluoroethylaniline in good isolated yields within 6 h. Compound **401** was

obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 2.5% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.200 mol% catalyst, 90% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.100 mol% catalyst, 99% yield.

[0068] Compound **402** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 2.5% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.200 mol% catalyst, 100% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.400 mol% catalyst, 98% yield.

[0069] Compound **403** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 5.0% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.400 mol% catalyst, 93% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.200 mol% catalyst, 96% yield.

[0070] Compound **404** was obtained as a colorless oil using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 10% to 20% ethyl acetate in hexanes. This oil discolors rapidly at room temperature. The catalyst loading and isolated yield for aryl bromide was as follows: 0.200 mol% catalyst, 96% yield.

[0071] Compound **405** was obtained as a white solid using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 5.0% to 10% to 20% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.250 mol% catalyst, 87% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.350 mol% catalyst, 86% yield.

[0072] Compound **406** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 5.0% ether in pentane. This compound is volatile. The catalyst loading and isolated yield for aryl chloride was as follows: 0.150 mol% catalyst, 86% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.100 mol% catalyst, 99% yield.

[0073] Compound **407** was obtained as a colorless oil using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 5.0%

ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl bromide was as follows: 0.100 mol% catalyst, 100% yield.

5 [0074] Compound **408** was obtained as a colorless oil using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 2.5% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl bromide was as follows: 0.250 mol% catalyst, 96% yield.

10 [0075] Compound **409** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 5% to 10% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.300 mol% catalyst, 87% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.100 mol% catalyst, 92% yield.

15 [0076] Compound **410** was obtained as a light yellow solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 1.0% methanol, 25% dichloromethane in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.800 mol% catalyst, 88% yield.

[0077] Mole percentages (y) of $[Pd(allyl)Cl]_2$ and AdBippyPhos and resulting yields associated with each mole percent and halide in the reactant are shown in **Table 4** below.

Table 4. Experiment 3 Results

Compound	X	y	Yield	Compound	X	y	Yield
401	Cl	0.100	90%	411	Br	0.225	91%
401	Br	0.050	99%	412	Cl	0.150	95%
402	Cl	0.100	100%	412	Br	0.250	100%
402	Br	0.200	98%	413	Cl	0.750 ^a	75%
403	Cl	0.200	93%	414	Cl	0.125	94%
403	Br	0.100	96%	414	Br	0.125	99%
404	Br	0.100	96%	415	Cl	0.325	90% ^a
405	Cl	0.125	87%	415	Br	0.325	89% ^a
405	Br	0.175	86%	416	Br	0.325	80% ^{a,b}
406	Cl	0.075	86%	417	Br	0.100	100%
406	Br	0.050	99%	418	Br	0.100	90%
407	Br	0.050	100%	419	Br	0.125	99% ^c
408	Br	0.125	96%	420	Cl	0.750	85%
409	Cl	0.150	87%	420	Br	0.750	94%
409	Br	0.050	92%	421	Cl	0.050	85%
410	Cl	0.400	88%	422	Br	0.050	95%
411	Cl	0.150	83%	423	Br	0.075	97%

^a Yield measured by ¹H NMR spectroscopy.

^b The pyridinium hydrochloride salt was used with 2.05 equivalents of KOPh.

^c Conducted with 0.35 mmol of aryl halide

- 5 **[0078]** The reactions of aryl halides possessing ortho substituents also occurred to form products **410–412** in high yield, but used higher catalyst loadings than reactions of less-hindered substrates. Compound **411** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting

with 1.3% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.300 mol% catalyst, 83% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.450 mol% catalyst, 91% yield.

[0079] Compound **412** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 1.3% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.300 mol% catalyst, 95% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.500 mol% catalyst, 90% yield.

[0080] 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 much higher yield than those containing AdBippyPhos as ligand. Although the isolated yield of **413** is moderate because the compound is volatile, the reaction occurs in 92% yield, as determined by ¹⁹F NMR spectroscopy. Compound **413** was obtained as a colorless oil using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 1.3% to 2.5% ethyl acetate in hexanes. This compound is highly volatile. The catalyst loading and isolated yield for aryl chloride was as follows: 1.50 mol% (CyBippyPhos) catalyst, 75% yield.

[0081] 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 thiobenzoxazoles. These reactions generally occurred in the presence of low loadings of catalyst to form heteroaryl trifluoroethyl anilines **414** – **423** 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-bromo-indole, did not react to form trifluoroethylanilines under these conditions. Compound **414** was obtained as a white solid using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 20% to 50% ethyl acetate in hexanes with 0.50 % triethylamine. The catalyst loading and isolated yield for aryl chloride data is as follows: 0.250 mol% catalyst, 94% yield. The catalyst loading and isolated yield for aryl bromide is as follows: 0.250 mol% catalyst, 99% yield.

[0082] Compound **415** is known and was not isolated. The yield was determined by ¹H NMR spectroscopy by adding 1,3,5-trimethoxybenzene (0.167 mmol) at the end of the reaction. The catalyst loading and NMR yield for aryl chloride was as follows: 0.650 mol% catalyst, 90% yield

(determined by ^1H NMR). The catalyst loading and NMR yield for aryl bromide was as follows: 0.650 mol% catalyst, 89% yield (determined by ^1H NMR).

[0083] Compound **416** was produced using the general procedure except that the hydrochloride salt of the heteroaryl bromide was used. Therefore, 2.05 equiv of potassium phenoxide were added to these reactions. Compound **416** is known and was not isolated. The yield was determined by ^1H NMR spectroscopy by adding 1,3,5-trimethoxybenzene (0.167 mmol) at the end of the reaction. The catalyst loading and NMR yield for aryl bromide was as follows: 0.650 mol% catalyst, 80% yield (determined by ^1H NMR)

[0084] Compound **417** was obtained as a white solid using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 10% methanol in dichloromethane. NMR spectra were acquired in a mixture of CDCl_3 and $\text{DMSO}-d_6$. The catalyst loading and isolated yield for aryl bromide was as follows: 0.200 mol% catalyst, 100% yield.

[0085] Compound **418** was obtained as a white solid using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 10% methanol in dichloromethane. NMR spectra were acquired in a mixture of CDCl_3 and $\text{DMSO}-d_6$. The catalyst loading and isolated yield for aryl bromide was as follows: 0.200 mol% catalyst, 90% yield.

[0086] Compound **419** was obtained as a yellow solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 10% methanol in dichloromethane. The reaction was conducted on 0.38 mmol scale. The catalyst loading and isolated yield for aryl bromide was as follows: 0.250 mol% catalyst, 99% yield.

[0087] Compound **420** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 10% ether in pentane. This oil discolors rapidly at room temperature and is volatile. The catalyst loading and isolated yield for aryl chloride was as follows: 1.50 mol% catalyst, 85% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 1.50 mol% catalyst, 94% yield.

[0088] Compound **421** was obtained as a yellow solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with

2.5% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.100 mol% catalyst, 85% yield.

[0089] Compound **422** was obtained as a white solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 10% methanol in dichloromethane. The catalyst loading and isolated yield for aryl bromide was as follows: 0.100 mol% catalyst, 95% yield.

[0090] Compound **423** was obtained as a white solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 5.0% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl bromide was as follows: 0.150 mol% catalyst, 95% yield.

EXPERIMENT 4: FUNCTIONAL GROUPS SENSITIVE TO BASES OR NUCLEOPHILES

[0091] The reactions of aryl halides containing functional groups that are sensitive to strong base and nucleophiles are shown in **Figure 5**.

[0092] Unprotected acetophenones (**524** and **525**), free alcohols (**526**), acetamides (**527**), methyl cinnamate esters (**528**), and non-enolizable aldehydes (**529**) all were tolerated under the standard reaction conditions. Functional groups sensitive to bases or nucleophiles may include oxygen atoms. 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 **526** and **529**. However, high yields of these products were obtained by simply increasing the number of equivalents of amine. Compound **524** was obtained as a tan solid using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 10% to 20% to 30% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl bromide was as follows: 0.400 mol% catalyst, 95% yield.

[0093] Compound **525** was obtained as a white solid using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 5.0% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl bromide was as follows: 0.300 mol% catalyst, 91% yield.

[0094] Compound **526** was obtained as a pale yellow solid using the stated general procedure with the catalyst loading specified below. The reaction was conducted with 3.00 equivalents of trifluoroethylamine. It was purified by column chromatography, eluting with 10% to 20% to

30% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.200 mol% catalyst, 93% yield.

5 [0095] Compound **527** was obtained as a white solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 30% to 50% ethyl acetate in hexanes. NMR spectra were acquired in a mixture of CDCl_3 and $\text{DMSO}-d_6$. The catalyst loading and isolated yield for aryl chloride was as follows: 0.750 mol% catalyst, 91% yield.

10 [0096] Compound **528** was obtained as a white solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 10% to 20% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.100 mol% catalyst, 88% yield.

15 [0097] Compound **529** was obtained as a white solid using the stated general procedure with the catalyst loading specified below using 2.50 equivalents of trifluoroethylamine. After complete conversion had been reached, the reaction was cooled to room temperature and 250 μL of water was added. This was stirred for 6 hours to hydrolyze any imine that had formed, then diluted further with water and ether. The organic layer was washed 5 times with water, dried with brine and Na_2SO_4 , and concentrated. The resulting residue was purified by column chromatography, eluting with 10% to 20% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.650 mol% catalyst, 83% yield.

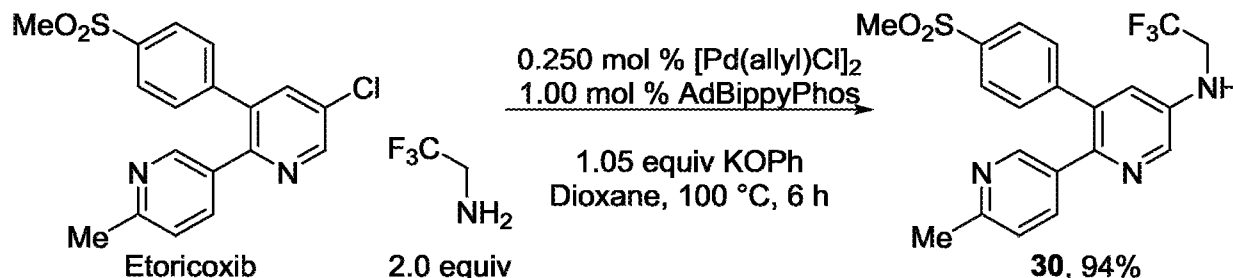
20 [0098] The resulting yields of compounds **524-529** are depicted in **Table 5**.

Table 5. Experiment 4 Results

Compound	X	y	Yield	
524	Br	0.200	95%	
525	Br	0.150	91%	
526	Cl	0.200	93%	3 equiv amine
527	Cl	0.375	91%	
528	Cl	0.050	8%	
529	Br	0.325	83%	2.5 equiv amine

EXPERIMENT 5: FLUOROALKYLANILINES DERIVED FROM DIFLUOROETHYL-,
PENTAFLUOROPROPYL-, AND β,β -DIFLUOROPHENETHYLAMINE

[0099] 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 trifluoroaniline occurred with low loadings of the catalyst without undergoing side reactions. This reaction is shown below:



[0100] Compound **30** was obtained as a white solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 1.0% triethylamine, 10% methanol in dichloromethane. The catalyst loading and isolated yield for aryl chloride was as follows: 0.500 mol% catalyst, 94% yield.

[0101] It is likely that the low nucleophilicity and basicity of both KOPh and trifluoroethylamine, as well as the low solubility of KOPh in dioxane, create the high functional group compatibility.

[0102] To determine the scope of the fluoroalkylamines that undergo this coupling process our conditions for the coupling of three fluorinated amines that would form fluorinated anilines with various properties (**Figure 5**) were evaluated. Coupling with difluoroethylamine (pKa conjugate acid = 7.1) 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 CF₂H). The coupling of pentafluoropropylamine (pKa conjugate acid = 5.7) was also conducted because perfluoroethyl groups have been shown to alter lipophilicity and would further suppress alkyl aniline oxidation. Finally, the coupling of β - β -difluorophenethylamine (pKa conjugate acid = 6.8) was evaluated because phenethylamine moieties are present in many biologically active compounds. Both difluoroethylamine and pentafluoropropylamine are commercially available; difluorophenethylamine was prepared in two steps from ethyl difluorophenylacetate.

[0103] These fluoroalkylamines were allowed to react with a set of aryl halides that contain different electronic and steric properties (electron-rich, electron-deficient, heteroaromatic, and *o*-substituted). These amines reacted under our standard conditions to form the coupled products in good yields. **Figure 6** shows the chemical structures of the fluoroalkylanilines **531-542** derived from this experiment. The yields are depicted in **Table 6** below and are isolated yields of 0.50 or 0.35 mmol reactions.

Table 6. Experiment 5 Results

Compound	X	y	Yield	Compound	X	y	Yield
531	Cl	0.050	90%	537	Cl	0.125	99%
531	Br	0.050	91%	537	Br	0.175	95%
532	Cl	0.150	84%	538	Cl	0.100	96%
532	Br	0.150	91%	538	Br	0.150	85%
533	Cl	0.150	81%	539	Cl	0.200	84%
533	Br	0.125	85%	539	Br	0.150	96%
534	Cl	0.250	93%	540	Cl	0.125	94%
534	Br	0.075	99%	540	Br	0.200	92%
535	Cl	0.200	99%	541	Cl	0.125	90%
535	Br	0.150	92%	541	Br	0.100	96%
536	Cl	0.300	93%	542	Cl	0.250	82%
536	Br	0.150	82%	542	Br	0.150	98%

[0104] Like the couplings of trifluoroethylamine, these reactions occurred in high yields with catalyst loadings of just 0.100 – 0.600 mol %. The reactions of difluoroethylamine and pentafluoropropyl amine used two equivalents of amine, presumably due to the low boiling point of these amines (68 °C and 50 °C, respectively). However, reactions of difluorophenethylamine occurred to full conversion of the aryl halide with just 1.1 equiv of amine.

[0105] Compound **531** was obtained as a white solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 20% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.100 mol% catalyst, 90% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.100 mol% catalyst, 91% yield.

[0106] Compound **532** was obtained as a white solid using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 10% to 20% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as

follows: 0.300 mol% catalyst, 84% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.300 mol% catalyst, 91% yield.

[0107] Compound **533** was obtained as a white solid using the stated general procedure with the catalyst loading specified below using 1.10 equiv of difluorophenethylamine on a 0.350 mmol scale. It was purified by column chromatography, eluting with 5% to 10% to 20% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.300 mol% catalyst, 81% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.250 mol% catalyst, 85% yield.

[0108] Compound **534** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 2.5% to 5.0% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.500 mol% catalyst, 93% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.150 mol% catalyst, 99% yield.

[0109] Compound **535** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 10% to 20% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.400 mol% catalyst, 99% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.300 mol% catalyst, 92% yield.

[0110] Compound **536** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below using 1.10 equiv of difluorophenethylamine on a 0.350 mmol scale. It was purified by column chromatography, eluting with 10% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.600 mol% catalyst, 93% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.300 mol% catalyst, 82% yield.

[0111] Compound **537** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 2.5% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.250 mol% catalyst, 99% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.350 mol% catalyst, 95% yield.

[0112] Compound **538** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 2.5% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows:

0.200 mol% catalyst, 96% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.300 mol% catalyst, 85% yield.

[0113] Compound **539** was obtained as a colorless oil using the stated general procedure with the catalyst loadings specified below using 1.10 equiv of difluorophenethylamine on a 0.350 mmol scale. It was purified by column chromatography, eluting with 2.5% to 5.0% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.400 mol% catalyst, 84% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.300 mol% catalyst, 96% yield.

[0114] Compound **540** was obtained as a colorless solid using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 1% triethylamine and 20% to 50% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.250 mol% catalyst, 94% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.400 mol% catalyst, 92% yield.

[0115] Compound **541** was obtained as a colorless solid using the stated general procedure with the catalyst loadings specified below. It was purified by column chromatography, eluting with 1% triethylamine and 20% to 50% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.250 mol% catalyst, 90% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.200 mol% catalyst, 96% yield.

[0116] Compound **542** was obtained as a colorless solid using the stated general procedure with the catalyst loadings specified below using 1.10 equivalents of difluorophenethylamine on a 0.350 mmol scale. It was purified by column chromatography, eluting with 1% triethylamine and 20% to 50% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.500 mol% catalyst, 82% yield. The catalyst loading and isolated yield for aryl bromide was as follows: 0.300 mol% catalyst, 98% yield.

EXPERIMENT 6: DERIVATIZATION OF COUPLED PRODUCTS

[0117] The fluorinated anilines produced by coupling of trifluoroethylamine with aryl halides are unstable in the presence of strong base at 100°C (**Figure 2C**). 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, the room temperature coupling of **401** with 4-bromoanisole in the presence of a catalyst for the coupling of diarylamines with aryl halides and 1.2 equivalents of NaOtBu (**Figure 7**) was tested. To a vial containing **401** (23.1 mg, 0.100 mmol, 1.00 equiv), NaOtBu (11.5 mg, 0.120 mmol, 1.20 equiv), and 4-bromoanisole (18.7 mg, 0.100 mmol, 1.00 equiv) was added a suspension of Pd(dba)₂ (0.6 mg, 0.001 mmol, 1 mol%) and PtBu₃ (0.2 mg, 0.0009 mmol, 0.9 mol%) in toluene (0.50 mL). This was allowed to stir at room temperature overnight. The next morning benzo-trifluoride (14.6 mg, 0.100 mmol, 1.00 equiv) was added, the reaction was diluted with ether, and eluted through a short plus of silica gel. The silica gel was rinsed with ether. The ¹⁹F NMR spectrum of the aliquot showed 100% conversion of the starting aniline to the **743**. The product was obtained as a colorless oil by concentrating the ethereal solution.

[0118] This reaction produced diaryl fluoroalkylamine **743** in quantitative yield. This result indicates that decomposition of fluorinated anilines in the presence of strong base does not occur rapidly at room temperature. While a full evaluation of the reactions of fluorinated anilines is beyond the scope of this paper, this result indicates that the fluoroalkylanilines produced in this work can undergo subsequent transformations that use strong base when conducted at or near room temperature.

EXPERIMENT 7: MECHANISTIC STUDIES OF THE COUPLING OF ARYL HALIDES WITH FLUOROALKYLAMINES

[0119] Typical conditions for the 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, the mechanism of the amination of fluoroalkylamines under the catalytic reaction conditions developed was studied (**Figure 8**) to determine the effect of the low basicity and solubility of potassium phenoxide and low nucleophilicity of the amine on the reaction. Although higher TON 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 readily prepared from inexpensive materials.

[0120] To identify the catalyst resting state, the reaction of 4-fluorochlorobenzene (**844**) 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 ¹⁹F and ³¹P NMR spectroscopy (**Figure 8**). At 50% conversion, the ³¹P NMR spectrum contained two singlets in a 1:1 ratio. One singlet at 2.57 ppm corresponds to free *t*BuBippyPhos, whereas the second singlet at 38.38 ppm corresponds to the resting state of the palladium. The ¹⁹F NMR spectrum of the same reaction contained resonances for 4-fluorochlorobenzene (-117.53 ppm), 4-fluoro-N-trifluoroethylaniline (**845**, -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. Compound **845** was obtained as a colorless oil using the stated general procedure with the catalyst loading specified below. It was purified by column chromatography, eluting with 2.5% ethyl acetate in hexanes. The catalyst loading and isolated yield for aryl chloride was as follows: 0.500 mol% catalyst, 90% yield.

[0121] Furthermore, when the same reaction was conducted with potassium 4-fluorophenoxide as the base, an additional resonance at -134.09 ppm was present in the ¹⁹F NMR spectrum. The intensity of this resonance was the same as that of the resonance at -122.25 ppm (attributed to an arylpalladium species). These data suggest that the phenoxide is ligated to palladium. No ¹⁹F NMR signals that could be attributed to a Pd amido complex were observed. The ³¹P NMR spectrum of an identical reaction conducted with 4-fluorobromobenzene was the same as the ³¹P spectrum of the reaction conducted with 4-fluorochlorobenzene. This observation indicates that the resting state lacks a halide ligand because the ³¹P NMR chemical shifts of an aryl palladium chloride complex and an aryl palladium bromide complex should be distinct from each other.

[0122] Collectively, these data suggest that the catalyst resting state is [(*t*BuBippyPhos)Pd(Ar)(OPh)]. To test this hypothesis, [Pd(allyl)Cl]₂, *t*BuBippyPhos, 4-fluoro-chlorobenzene, and potassium phenoxide was allowed to react at room temperature in THF. Filtration, partial removal of the solvent, and the addition of pentane produced a yellow solid. The ³¹P NMR spectrum of this yellow solid contained a single resonance that matched the ³¹P spectrum of the catalyst resting state. To a vial containing potassium phenoxide (59.5 mg, 0.450 mmol, 4.50 equiv), [Pd(allyl)Cl]₂ (36.6 mg, 0.100 mmol, 1.00 equiv), and *t*BuBippyPhos

(117 mg, 0.300 mmol, 2.30 equiv) was added THF (5 mL). This was stirred until all solids dissolved, at which time 4-fluoro-bromobenzene (74.4 mg, 0.425 mmol, 4.25 equiv, the aryl chloride can also be used) was added. The reaction was allowed to stir for 2 h, at which time the reaction was filtered through a Teflon syringe filter and concentrated to approximately 1 mL.

5 The solution was stirred rapidly, and pentane was added slowly to induce precipitation. Addition was stopped once the solution turned cloudy (approximately 2.5 mL of pentane). The cloudy solution was stirred until solids no longer precipitated, at which time 1 mL of pentane was added. The resulting suspension was filtered, washed with 3:1 pentane to ether, and dried under vacuum to produce 109 mg of a pale yellow solid. This compound was crystallized by dissolving in a
10 minimal amount of THF and layered with n-heptane. The resulting bi-phasic solution was placed in the glove box freezer (-30 °C) and allowed to stand until crystals had formed (48 h). The crystals were isolated by removing the solution by pipette. A similar procedure using dichloromethane as the solvent also produced crystals suitable for single-crystal X-ray diffraction.

15 **[0123]** The structure of the catalyst resting state was unambiguously shown by X-ray diffraction to be [(*t*BuBippyPhos)Pd(Ar)(OPh)] (**946**, Figure 9). The complex contains a dative bond between Pd and the bipyrazole backbone, which has been reported for the *t*BuBippyPhos complex of PdCl₂, and for other Pd complexes containing bulky biaryl phosphine ligands. This complex is stable in air in the absence of excess phenoxide, which is consistent with the ability to
20 conduct the catalytic amination without rigorous exclusion of air. As shown in **Figure 9**, the hydrogen atoms are omitted for clarity. Some bond lengths (Å) and angles (°) are provided herein: 45: 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).

[0124] To assess the connection between this complex and the steps of the catalytic cycle, the
25 rate law for the reaction shown in **Figure 8** was determined. To increase the solubility of the base, potassium 4-*n*Bu-phenoxide was used in place of KOPh. The ³¹P 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.

[0125] The kinetics were determined by measuring initial rates with the ratios of reagents close
30 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 perfluoroalkylaniline **845** by ^{19}F NMR spectroscopy; this approach was appropriate because the mass balance of the reaction with respect to the limiting reagent (aryl halide **844**) was greater than 98%. The reaction was conducted with 0.667 mol % of an equimolar amount of the phenoxide complex **946** and *t*BuBippyPhos as catalyst, aryl halide **844** as limiting reagent, 1.05 equiv 4-*n*-Bu-PhOK, and 2.00 equiv trifluoroethylamine in dioxane. The amination reaction was found to be 0th order in 1-chloro-4-fluorobenzene and *t*BuBippyPhos; it was found to be 1st order in trifluoroethylamine and in palladium phenoxide complex **946**. 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.

[0126] Figures **10A** and **10B** are example mechanisms that fit the kinetic data. Both mechanisms 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 fluoroalkylamido product. However, the first mechanism (**Figure 10A**) involves turnover-limiting reductive elimination, whereas the second mechanism involves turnover-limiting formation of a palladium amido complex (**Figure 10B**). These two mechanisms 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 10A**), the amination reaction would be inverse 1st order in phenol because it is generated as a stoichiometric by-product during the ligand exchange.

[0127] Determination of the order of the reaction in phenol is complex because phenol forms strong hydrogen-bond adducts with phenoxide. These hydrogen bond adducts reduce the concentration of free phenol. Therefore the initial rates of stoichiometric reactions of the palladium phenoxide **1148** as shown in **Figure 11A** with trifluoroethylamine in the presence of varied concentrations of phenol (reaction shown in **Figure 11A**) in the absence of phenoxide base were monitored. Analysis of the initial rates (**Figure 8**) showed that the reaction of **1148** with trifluoroethylamine is inverse 1st 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 phenoxide complex, followed by irreversible reductive elimination to form the arylamine product.

[0128] 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 scavenges the phenol that

is generated during the reaction. 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. Thus, reactions conducted with higher concentrations of 4-*n*Bu-phenoxide occur faster than reactions conducted with lower concentrations of this base.

5 [0129] The mechanistic data was consistent with the pathway shown in **Figure 10A**. 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 **946**. Complex **946** reacts reversibly with trifluoroethylamine to form an amido complex. The transition state with the highest energy is
10 that for reductive elimination.

[0130] 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 and one on the coupling of ammonia with aryl halides implied that reductive elimination was the
15 turn-over 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 reaction of the fluoroalkylamines in the current also constituted an unusual case in which the coupling of an
20 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 elimination from palladium amido complexes derived from electron rich amines (e.g. *t*BuNH₂) has been shown to be faster than reductive elimination from palladium amido complexes derived from less electron
25 rich amines (PhNH₂). Indeed, the only other case of reductive elimination as the slow 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.

[0131] The resting state of the catalyst in the current study is also unique for a coupling to form
30 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. For reactions catalyzed by complexes of monophosphine complexes, the most commonly proposed mechanism is that involving coordination of the amine and deprotonation because an open coordination site is available for binding of the amine.

5 [0132] Some literature shows the preparation of arylpalladium-amine complexes ligated by monophosphines and has 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. Such literature is provided in Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* 1996, 15, 2794; Biscoe, M. R.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* 10 2007, 46, 7232; and Tardiff, B. J.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *J. Org. Chem.* 2011, 77, 1056. These data imply that the reactions of alkylamines catalyzed by complexes of bulky monophosphines occur by coordination of the amine and deprotonation by base. 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 15 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. 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^tBu, not an 20 alkylamine.

EXPERIMENT 8: REACTIONS OF ENANTIOPURE FLUOROALKYLAMINES

[0133] 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 trifluoroisopropylamine and of 2-(trifluoromethyl)pyrrolidine were 25 conducted under our standard reaction conditions. Reactions of trifluoroisopropylamine with the same subset of aryl halides used to generate the products in **Figures 6** and **12A** occurred in high conversion but variable yield.

[0134] In contrast to the reactions of primary unbranched fluoroalkylamines (e.g., trifluoroethylamine), reactions of trifluoroisopropylamine formed products from etherification of 30 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 **743** of **Figure 7** or *ortho* (*o*-methyl in **845** of **Figure 8**) substituents, presumably because these substituents

accelerate direct reductive elimination from the phenoxide resting state **946** (*vide infra*). 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 a S_NAr process, but are likely formed via the palladium catalyst, presumably by direct reductive elimination of the palladium resting state.

[0135] 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.

[0136] These same conditions do not lead to the formation of product in the coupling of aryl halides with 2-(trifluoromethyl)pyrrolidine; instead, these couplings occur with the catalyst containing CyBippyPhos as a ligand and with NaOtBu as base (**Figure 12B**) at 65°C. 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, the reactions of more highly fluorinated amines were investigated. Couplings of hexafluoroisopropylamine and bis(trifluoroethyl)amine did not produce anilines under either set of conditions, however, couplings of highly fluorinated amines such as these may produce anilines under a different set of conditions. Reactions of branched fluorinated amines that have greater than about 99% enantiopurity occur with preservation of this high enantiopurity. These reactions yield highly enantioenriched compounds that are not readily prepared via existing methods. Resulting yields are shown in **Table 7** below.

Table 7. Experiment 8 Results

Compound	X	Yield
1243	Cl	86%
1243	Br	89%
1244	Cl	95%
1244	Br	92%
1245	Cl	76%
1245	Br	80%
1246	Cl	85%
1246	Br	100%
1247	Cl	85%
1247	Br	92%
1248	Cl	99%
1248	Br	87%
1249	Cl	67%
1249	Br	52%
1250	Cl	71%
1250	Br	21%

CONCLUSION

[0137] In summary, conditions for the coupling of primary fluoroalkylamines with aryl bromides
5 and aryl chlorides have been developed. 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. The products may have useful applications in pharmaceutical and agrochemical industries.

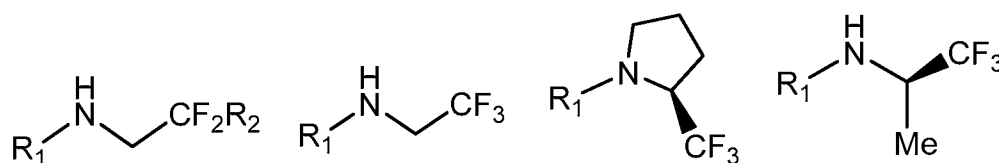
[0138] The reaction occurs with several unusual mechanistic features. First, without being bound by a particular theory, the catalyst resting state for various disclosed embodiments is the phenoxide complex $[(t\text{BuBippyPhos})\text{Pd}(\text{Ar})(\text{OPh})]$ (**946**). The observation of this complex is the first evidence that a monophosphine ligated arylpalladium phenoxide or alkoxide complex can be an intermediate in the coupling process. 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.

[0139] Although the foregoing embodiments have been described in some detail for purposes of clarity of understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. It should be noted that there are many alternative ways of implementing the processes, systems, and apparatus of the present embodiments. Accordingly, the present embodiments are to be considered as illustrative and not restrictive, and the embodiments are not to be limited to the details given herein.

CLAIMS

1. A method of forming a fluoroalkylaniline, the method comprising reacting a fluoroalkylamine with an aryl or heteroaryl halide using a palladium-containing catalyst in the presence of an oxygen-containing base having a conjugate acid pKa in dimethyl sulfoxide of less than about 32.

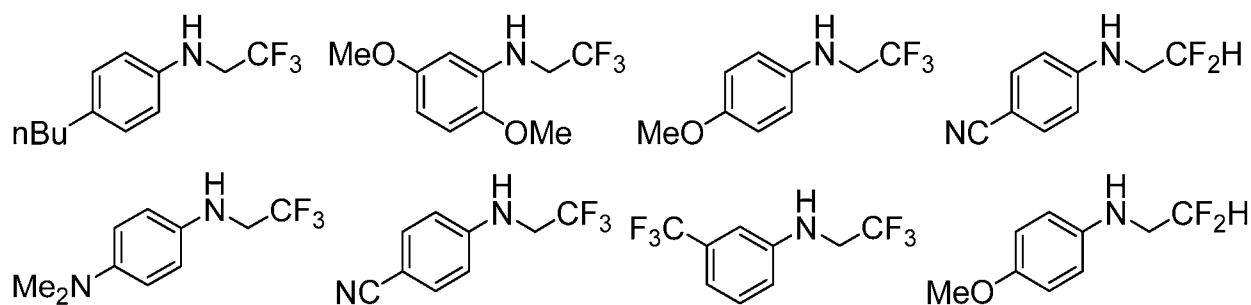
2. The method of claim 1, wherein the fluoroalkylaniline formed comprises the structure selected from the group consisting of:

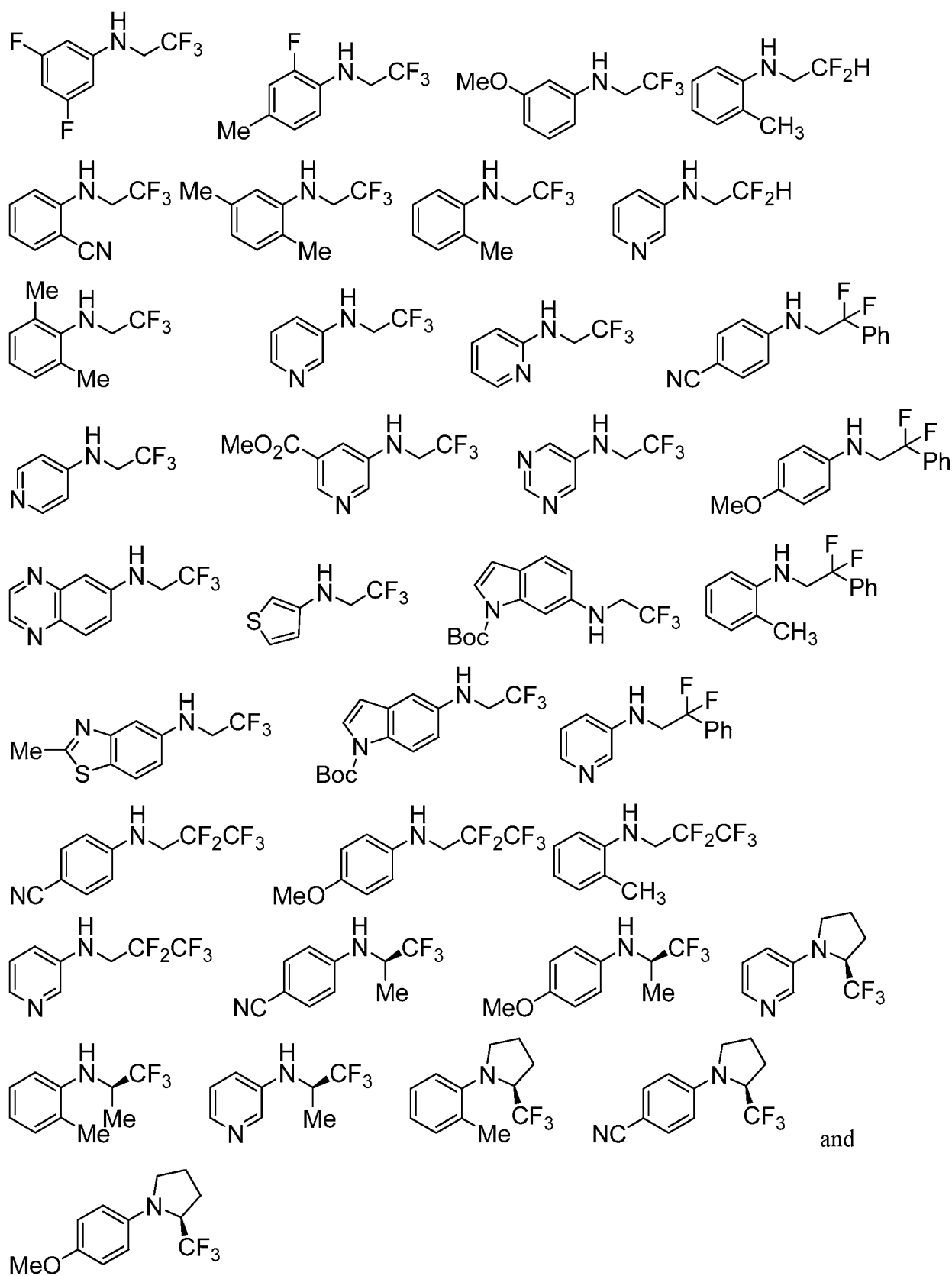


wherein R_1 is an aryl or heteroaryl group comprising one or more substituents selected from the group consisting of carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups comprising a hydrogen atom, and R_2 is an organic group selected from the group consisting of carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups comprising a hydrogen atom.

3. The method of claim 1, wherein the fluoroalkylaniline is enantioenriched.

4. The method of claim 1, wherein the fluoroalkylaniline formed is selected from the group consisting of:





5. The method of claim 1, wherein the fluoroalkylamine is selected from the group consisting of trifluoroethylamine, difluoroethylamine, pentafluoropropylamine, difluorophenethylamine, trifluoroisopropylamine, and 2-(trifluoromethylpyrrolidine).

6. The method of any of claims 1-5, wherein the aryl or heteroaryl halide comprises the chemical structure R—X, wherein X is selected from the group consisting of chlorine, bromine, and iodine, and R is an aryl or heteroaryl group comprising a functional group sensitive to strong base and nucleophiles.

7. The method of any of claims 1-5, wherein the aryl or heteroaryl halide comprises an aryl chloride or bromide without an acidic N-H bond.

8. The method of any of claims 1-5, wherein the aryl or heteroaryl halide is selected from the group consisting of heteroaryl halides of 2-, 3-, and 4-halopyridines, pyrimidines, quinoxalines, thiophenes, indoles, and thiobenzoxazoles.

9. The method of any of claims 1-5, wherein the aryl or heteroaryl halide is selected from the group consisting of aryl bromides, aryl chlorides, heteroaryl bromides, and heteroaryl chlorides.

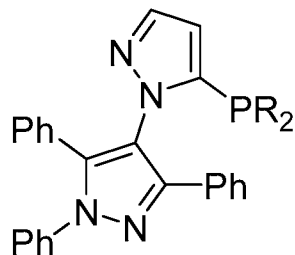
10. The method of claim 6, wherein the functional group is selected from the group consisting of unprotected acetophenones, free alcohols, amides, unconjugated esters, cinnamate esters, nitriles, methyl aryl sulfoxide, and non-enolizable aldehydes.

11. The method of any of claims 1-5, wherein the base is derived from a phenoxide.

12. The method of any of claims 1-5, wherein the base is nitrogen-free.

13. The method of any of claims 1-5, wherein the base is KOPh.

14. The method of any of claims 1-5, wherein the palladium-containing catalyst is ligated with a compound selected from the group consisting of phosphines, phosphites, phosphoramidites, phosphoramides, N-heterocyclic carbenes, monophosphines, and



R = *t*Bu, Ad, Cy

5

15. The method of any of claims 1-5, wherein the reaction forms a palladium complex comprising a monophosphine.

16. The method of claim 15, wherein the ratio of palladium to ligand to form the palladium complex is about 1:2.

10

17. A method of forming a fluoroalkylaniline, the method comprising reacting a fluoroalkylamine with an aryl or heteroaryl sulfonate or phosphate using a palladium-containing catalyst in the presence of an oxygen-containing base having a conjugate acid pKa in dimethyl sulfoxide of less than about 32.

15

18. The method of claim 17, wherein the aryl or heteroaryl sulfonate or phosphate comprises the chemical structure R—X, wherein X is selected from the group consisting of sulfonates and phosphates, and R is an aryl or heteroaryl group comprising a functional group sensitive to strong base and nucleophiles.

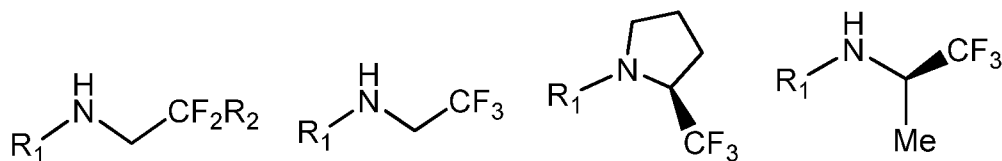
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19. The method of claim 18, wherein the functional group is selected from the group consisting of unprotected acetophenones, free alcohols, amides, unconjugated esters, cinnamate esters, nitriles, methyl aryl sulfoxide, and non-enolizable aldehydes.

25

20. The method of claim 17, wherein the fluoroalkylamine is selected from the group consisting of trifluoroethylamine, difluoroethylamine, pentafluoropropylamine, difluorophenethylamine, trifluoroisopropylamine, and 2-(trifluoromethylpyrrolidine).

21. The method of claim 17, wherein the fluoroalkylaniline formed comprises the structure selected from the group consisting of:



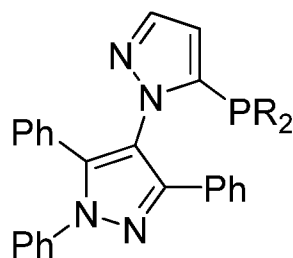
- 5 wherein R_1 is an aryl or heteroaryl group comprising one or more substituents selected from the group consisting of carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups comprising a hydrogen atom, and
- 10 R_2 is an organic group selected from the group consisting of carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups comprising a hydrogen atom.

22. The method of any of claims 17-21, wherein the base is derived from a phenoxide.

23. The method of any of claims 17-21, wherein the base is nitrogen-free.

24. The method of any of claims 17-21, wherein the base is KOPh.

- 20 25. The method of any of claims 17-21, wherein the palladium-containing catalyst is ligated with a compound selected from the group consisting of phosphines, phophites, phosphoramidites,

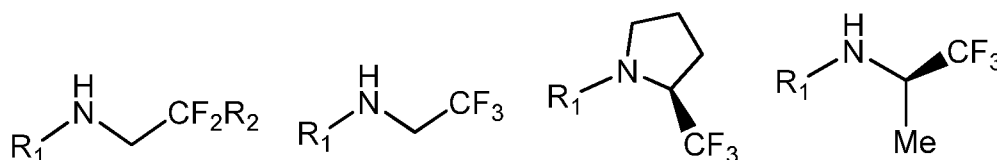


phosphoramides, N-heterocyclic carbenes, monophosphines, and $R = t\text{Bu}, \text{Ad}, \text{Cy}$.

26. A method of forming a fluoroalkylaniline, the method comprising reacting a fluoroalkylamine with a halogen-containing reactant using a palladium-containing catalyst in the presence of a base, wherein the halogen-containing reactant is selected from the group consisting of chloroarenes, chloroheteroarenes, bromoarenes, and bromoheteroarenes; and wherein the reactant is not bromoindazole.

27. The method of claim 26, wherein the fluoroalkylamine is selected from the group consisting of trifluoroethylamine, difluoroethylamine, pentafluoropropylamine, difluorophenethylamine, trifluoroisopropylamine, and 2-(trifluoromethylpyrrolidine).

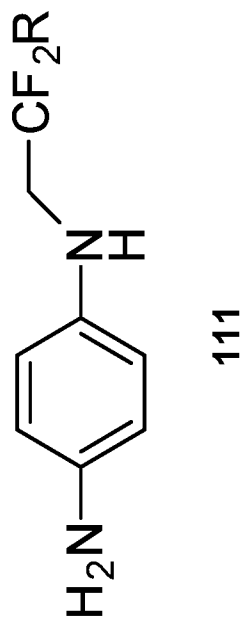
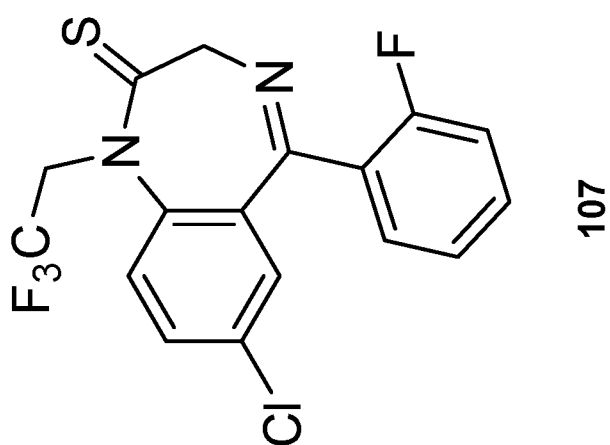
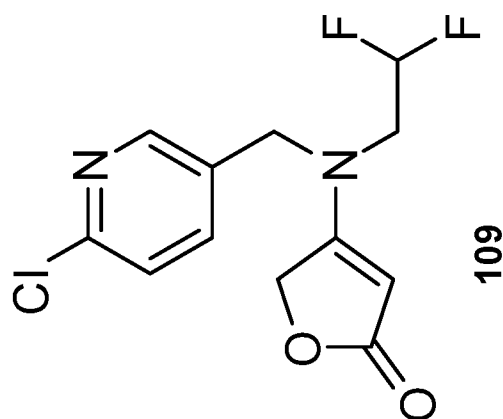
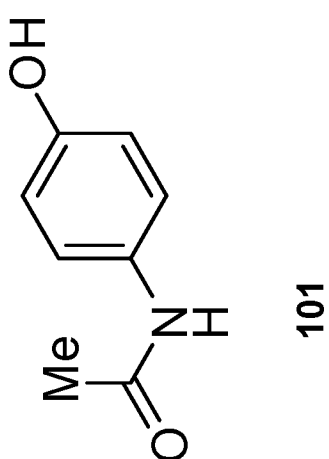
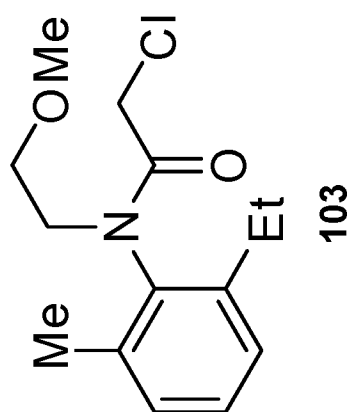
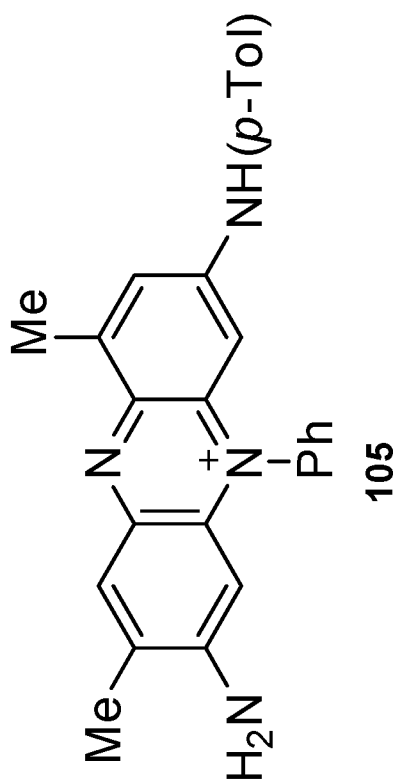
28. The method of claim 26, wherein the fluoroalkylaniline formed comprises the structure selected from the group consisting of:

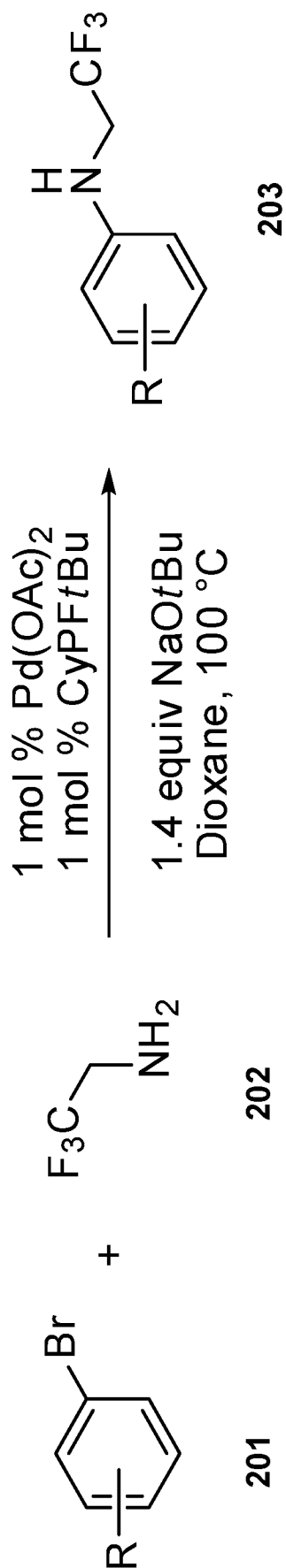
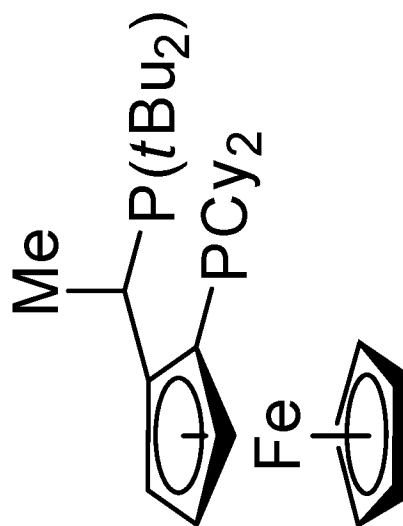
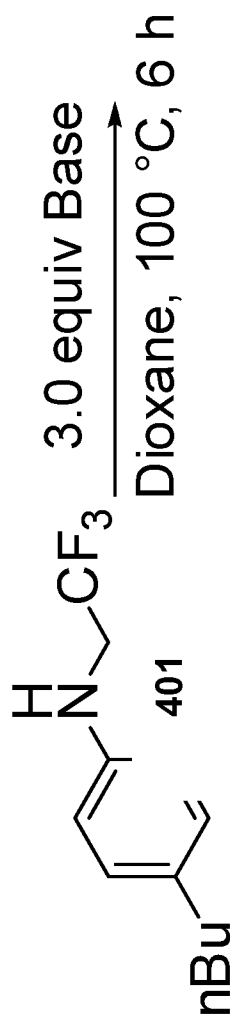


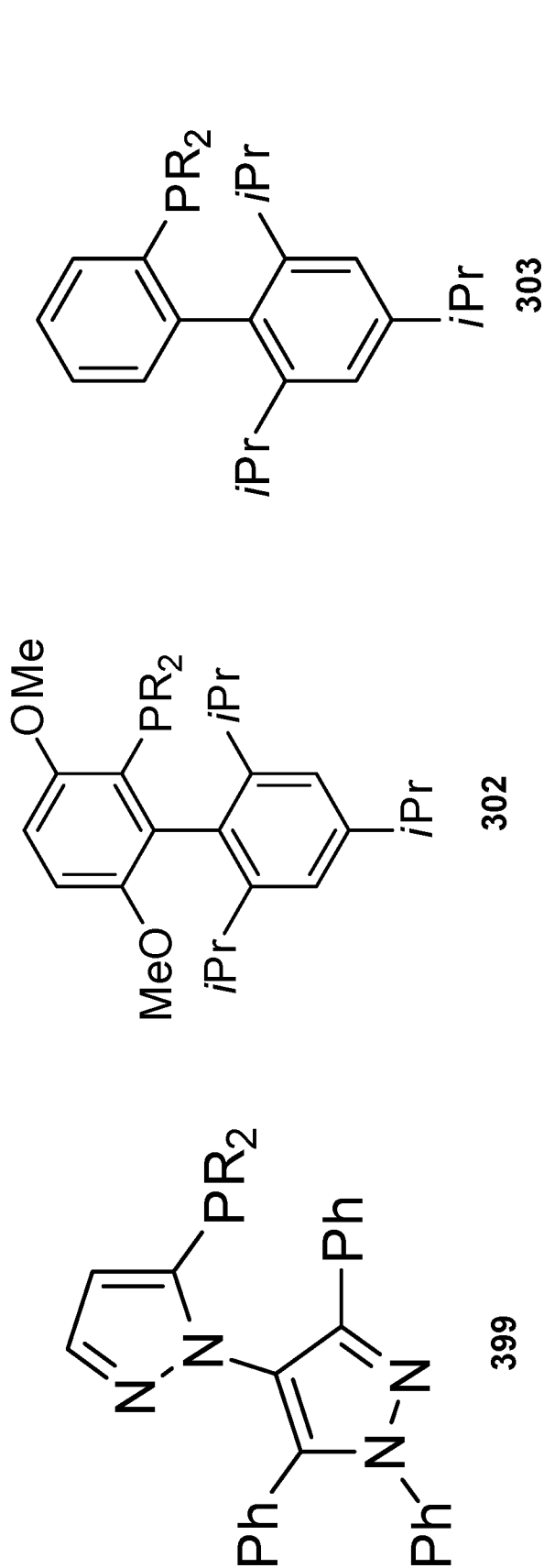
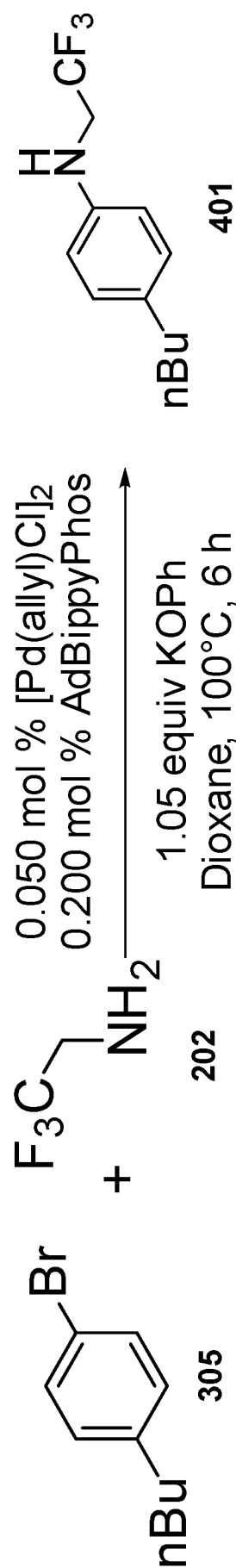
wherein R_1 is an aryl or heteroaryl group comprising one or more substituents selected from the group consisting of carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups comprising a hydrogen atom, and R_2 is an organic group selected from the group consisting of carbon-containing organic groups, halogen-containing organic groups, sulfur-containing organic groups, phosphorous-containing organic groups, and organic groups comprising a hydrogen atom.

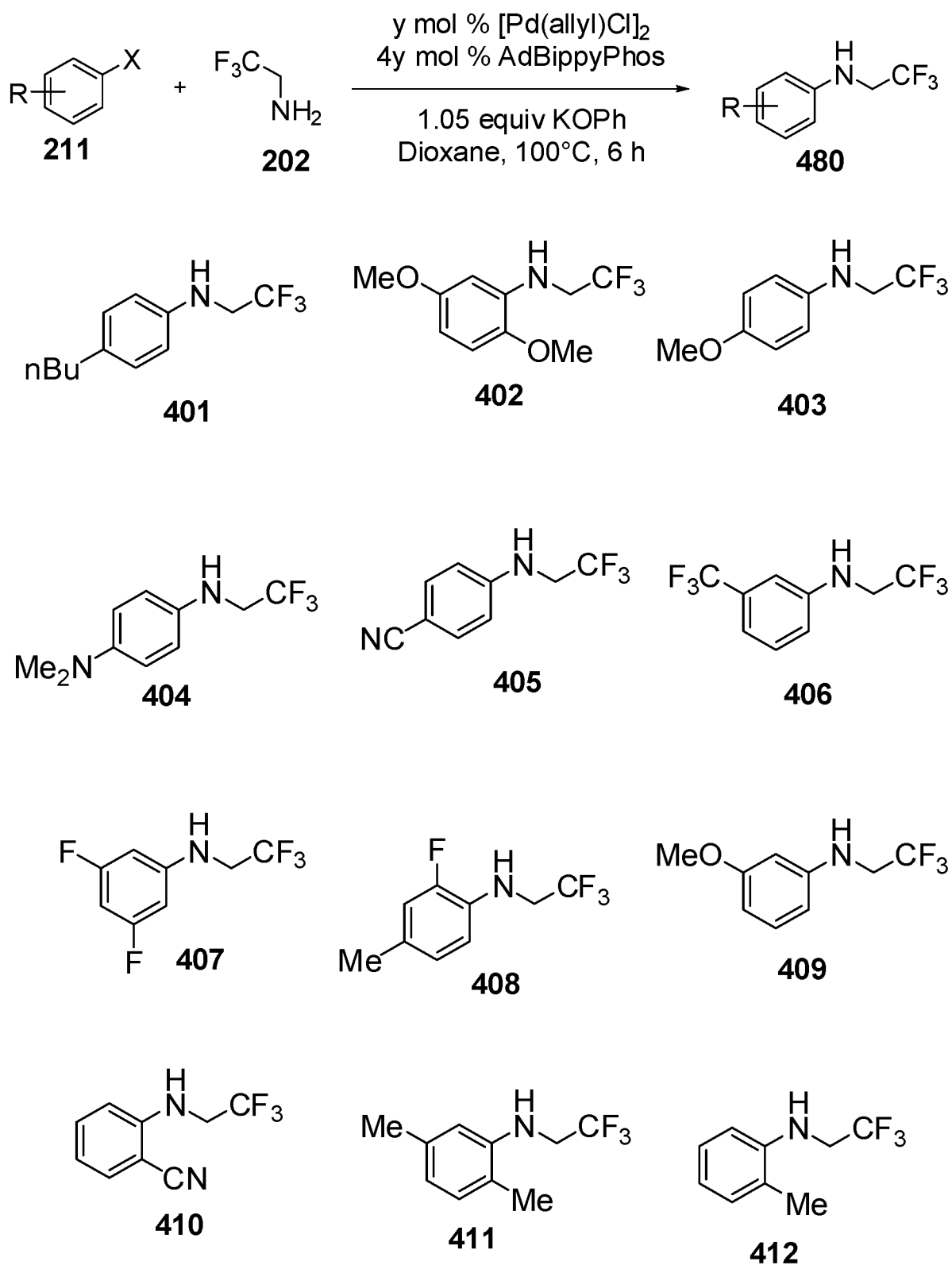
29. A fluoroalkylaniline prepared by any of the methods of claims 1-28.

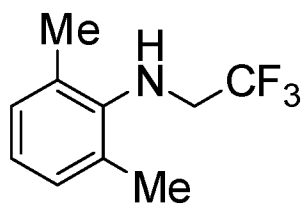
30. An enantioenriched fluoroalkylaniline product.

**FIG. 1**

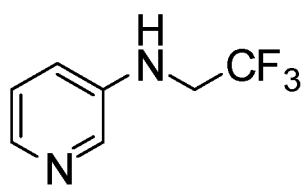
**FIG. 2A****FIG. 2B****FIG. 2C**

**FIG. 3A****FIG. 3B**

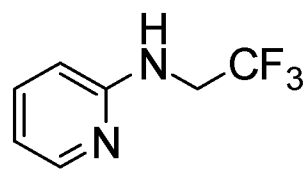
**FIG. 4A**



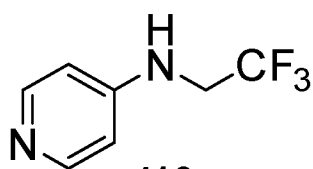
413



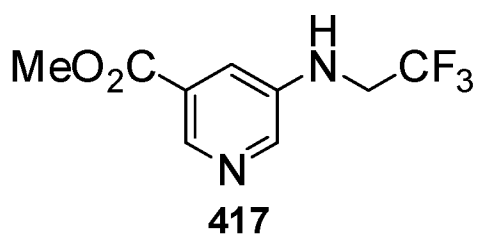
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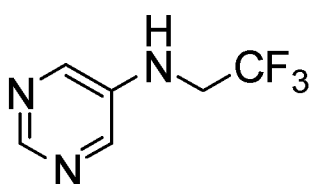
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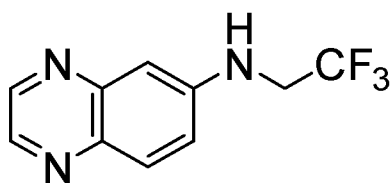
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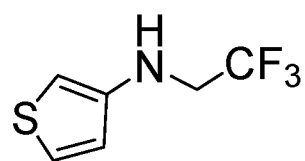
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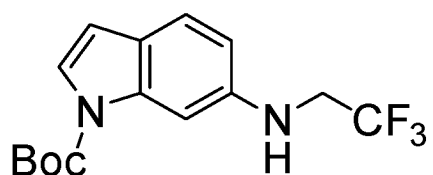
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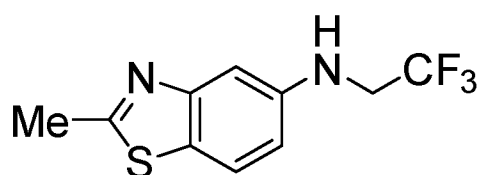
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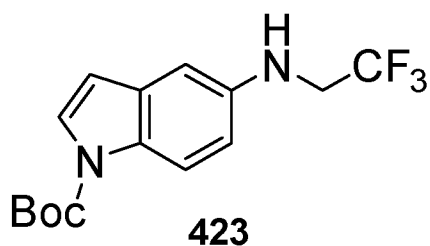
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421

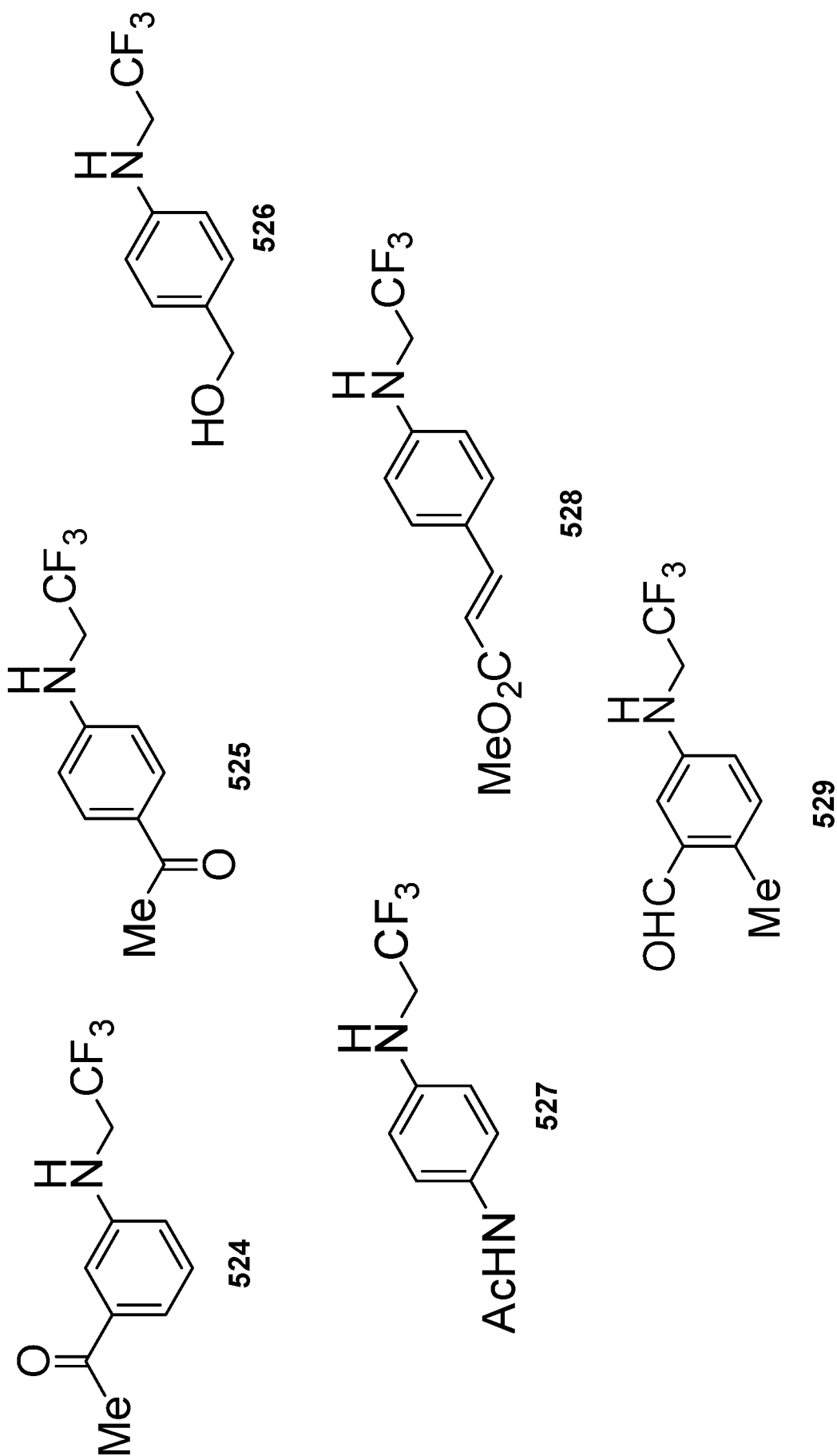


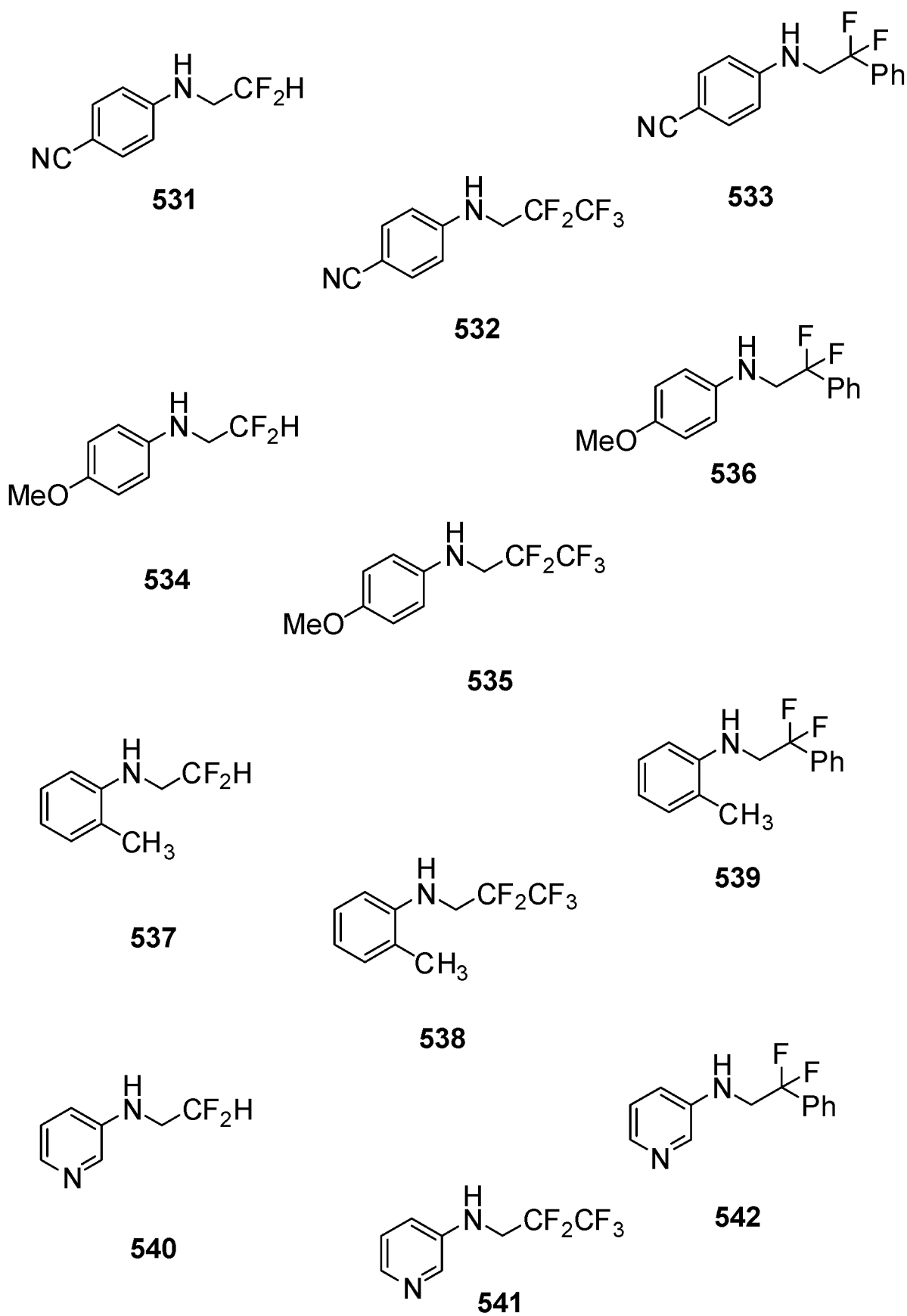
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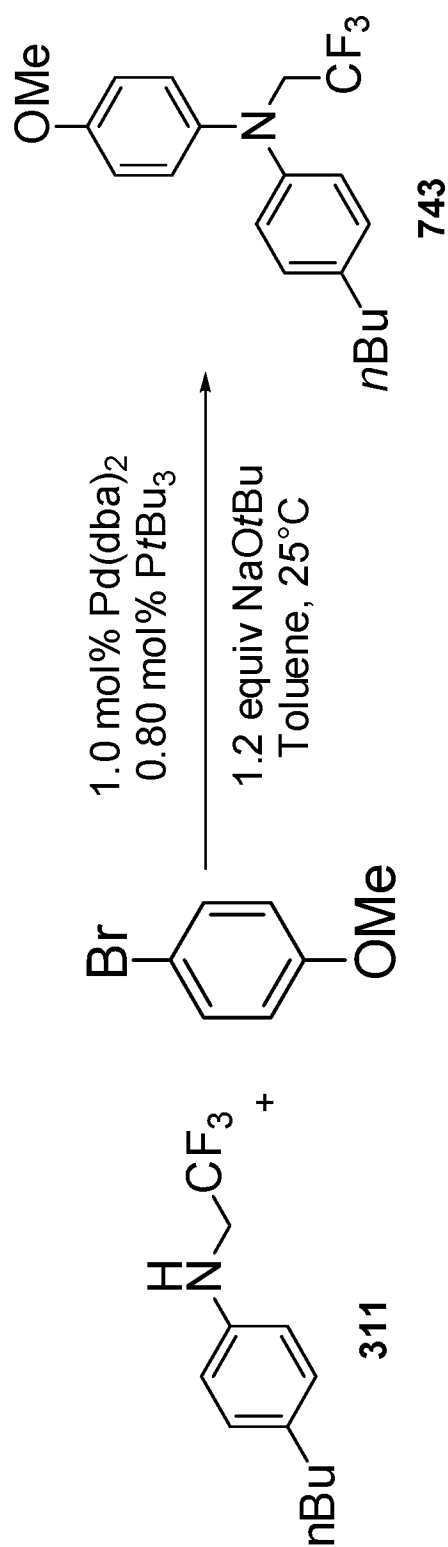


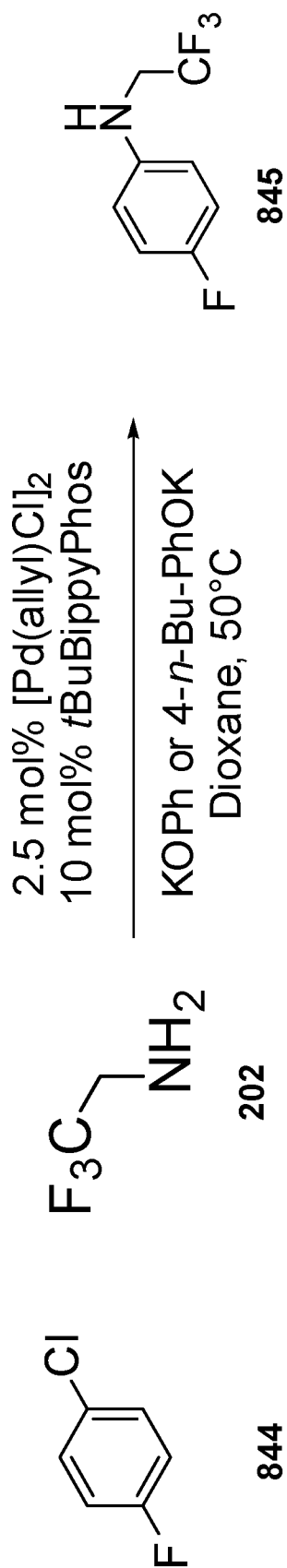
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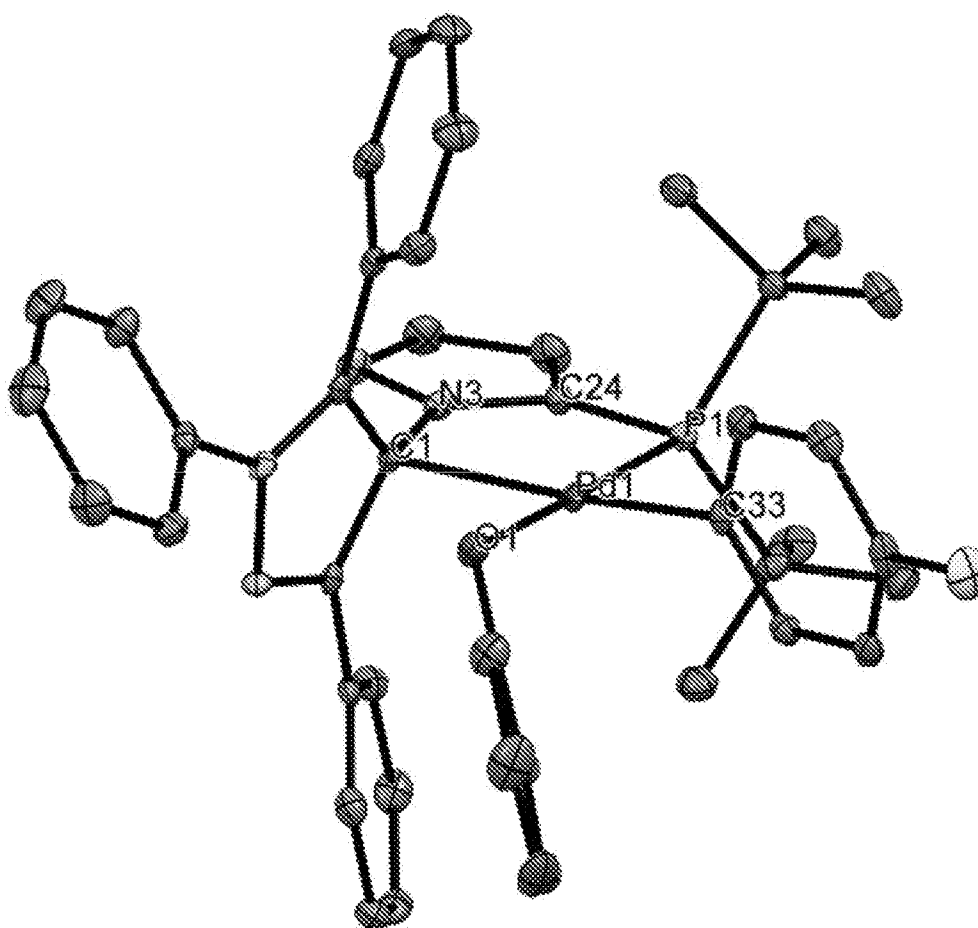
FIG. 4B

**FIG. 5**

**FIG. 6**

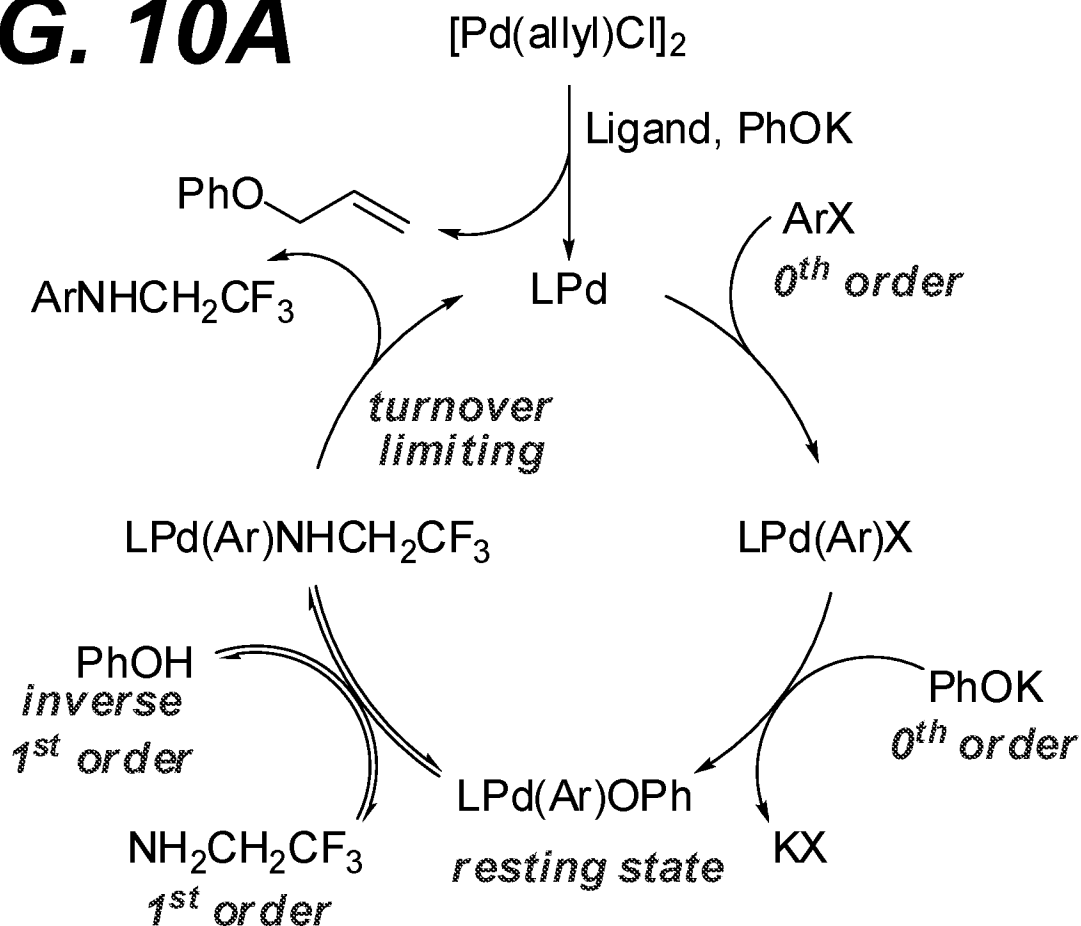
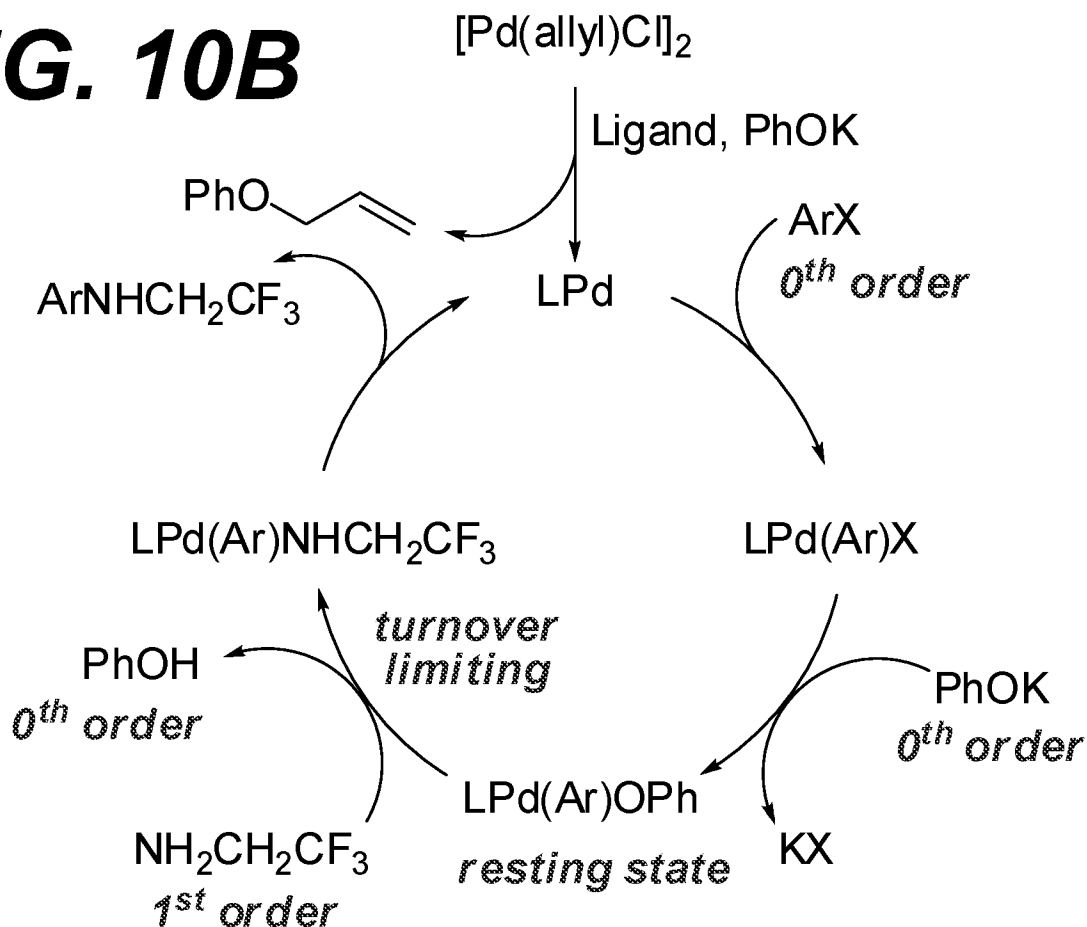
**FIG. 7**

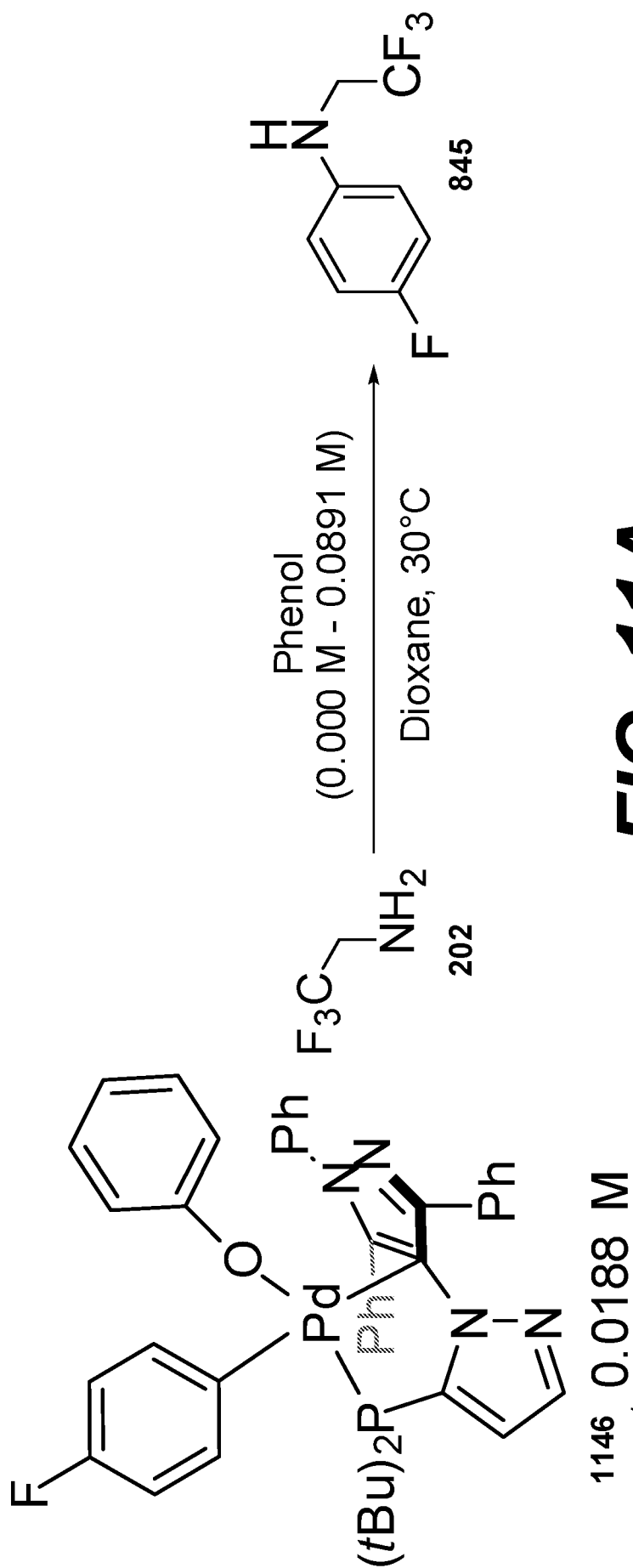
**FIG. 8**



946

FIG. 9

FIG. 10A**FIG. 10B**

**FIG. 11A**

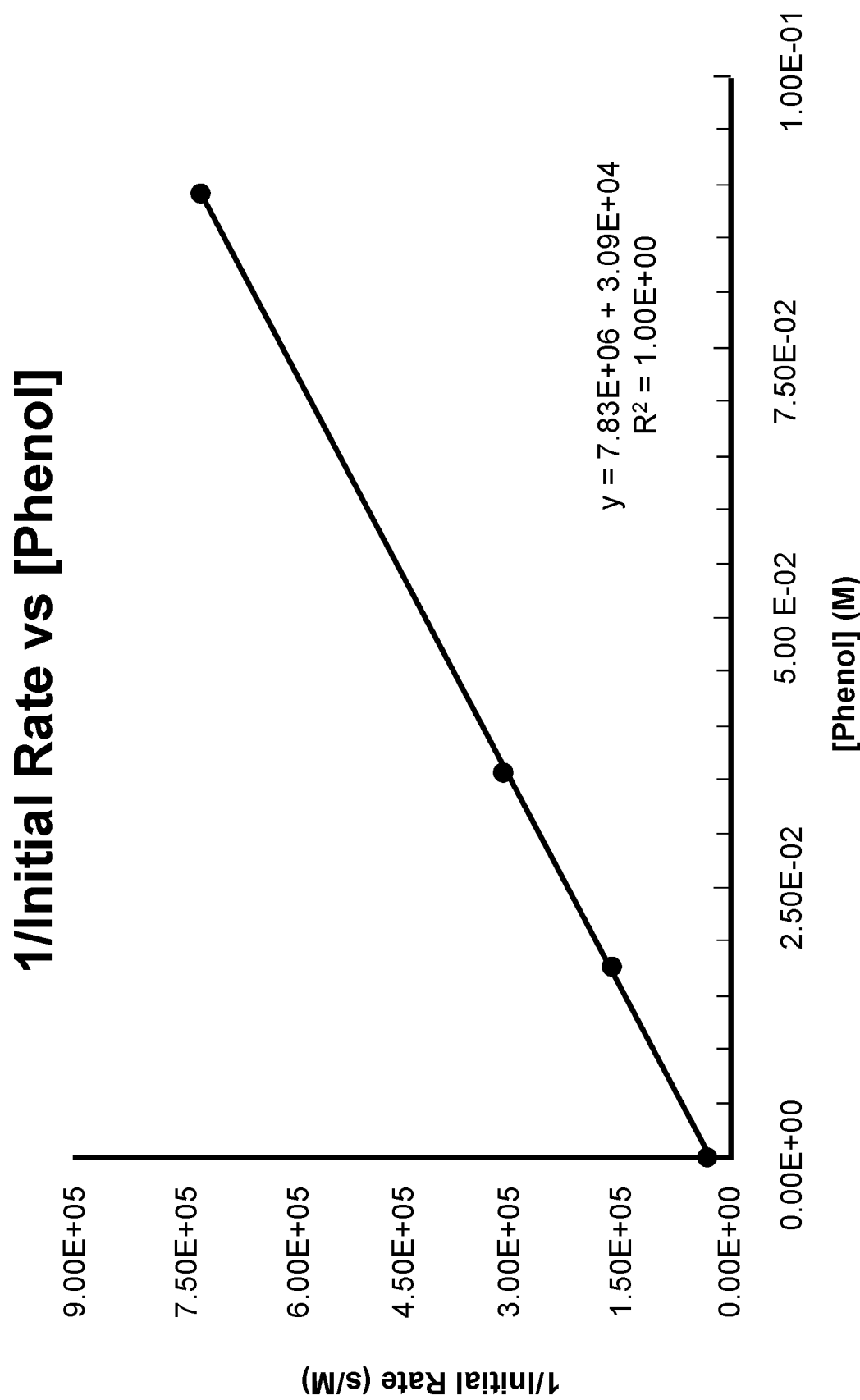
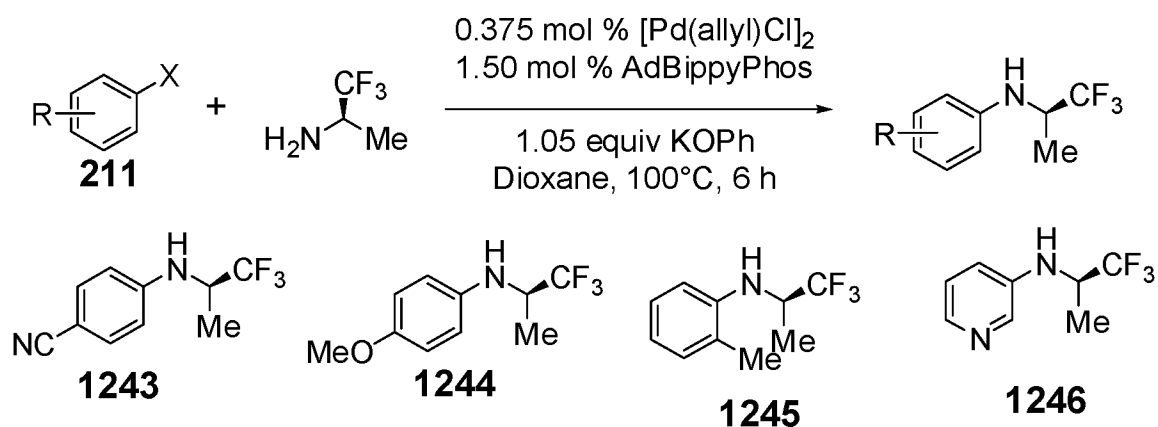
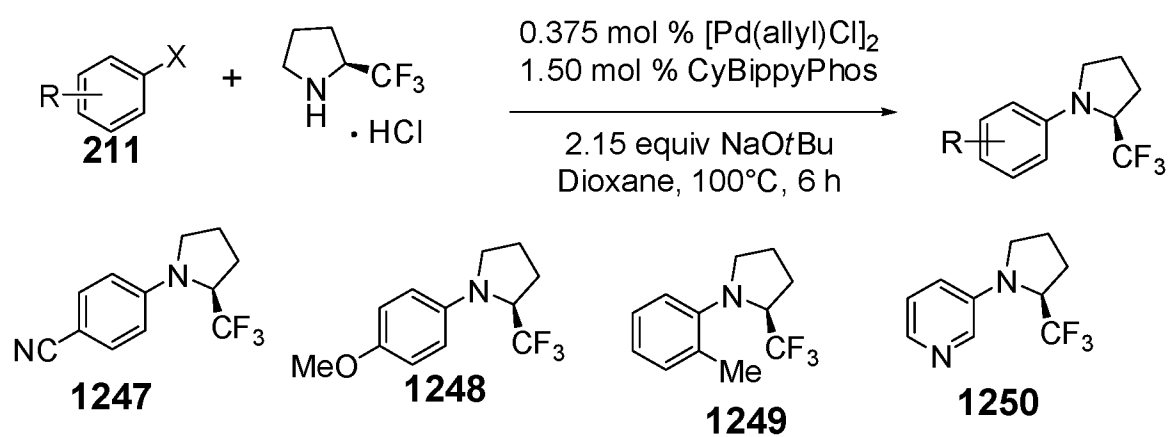


FIG. 11B

**FIG. 12A****FIG. 12B**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031675

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07C 209/04; C07C 209/10; C07C 209/22; C07C 211/46; C07C 211/48 (2016.01)

CPC - C07C 209/04; C07C 209/10; C07C 209/22 (2016.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC - C07C 209/04; C07C 209/10; C07C 209/22; C07C 211/46; C07C 211/48

CPC - C07C 209/04; C07C 209/10; C07C 209/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

IPC(8) - C07C 209/04; C07C 209/10; C07C 209/22; C07C 211/46; C07C 211/48 (2016.01); CPC - C07C 209/04; C07C 209/10; C07C 209/22 (2016.05); USPC - 564/305; 564/395; 564/479; 564/480 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, Google Scholar.

Search terms used: aryl heteroaryl halide sulfonate prepare aniline palladium

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN et al. Enantioselective Pd-Catalyzed Hydrogenation of Fluorinated Imines: Facile Access to Chiral Fluorinated Amines. Organic Letters 12 (21), pp 5075–5077, 2010. [retrieved on 11 July 2016]. Retrieved from the Internet. <http://pubs.acs.org/doi/abs/10.1021/ol1020256> entire document	30
A	US 2004/0044250 A1 (BUCHWALD et al) 04 March 2004 (04.03.2004) entire document	1-28, 30
A	US 2009/0234126 A1 (HARTWIG et al) 17 September 2009 (17.09.2009) entire document	1-28, 30
A	US 4,871,875 A (NAGATA et al) 03 October 1989 (03.10.1989) entire document	1-28, 30

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

13 July 2016

Date of mailing of the international search report

11 AUG 2016

Name and mailing address of the ISA/

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P.O. Box 1450, Alexandria, VA 22313-1450

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Blaine R. Copenhaver

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031675

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 29
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.