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Nickel-Catalyzed *N*-Arylation of Fluoroalkylamines

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Abstract: *The Ni-catalyzed N-arylation of β-fluoroalkylamines with broad scope is reported for the first time. Use of the air-stable pre-catalyst (PAd2-DalPhos)Ni(o-tol)Cl allows for reactions to be conducted at room temperature (25 °C, NaOtBu), or by use of a commercially available dual-base system (100 °C, DBU/NaOTf), to circumvent decomposition of the N-(β-fluoroalkyl)aniline product. The mild protocols disclosed herein feature broad (hetero)aryl (pseudo)halide scope (X = Cl, Br, I, and for the first time phenol derived electrophiles), encompassing base sensitive substrates and enantioretentive transformations, in a manner that is unmatched by any previously reported catalyst system.*

The introduction of fluorinated substituents is an effective strategy for controlling the adsorption, distribution, metabolism, and excretion of active pharmaceutical ingredients (APIs), as well as engendering desirable performance profiles in agrochemicals.[1] In the case of β-fluoroalkylamino groups, the altered conformational preferences, acid-base properties, and hydrogen-bonding abilities arising from the included fluorine atoms allows such fragments to serve as bioisosteres for biologically important amide, sulfonamide, and related functionalities, while offering distinct physicochemical properties.[2] A recently disclosed small molecule (Gilead Sciences, GS-6207) that functions as a long-acting therapy for the treatment of HIV highlights the benefits of incorporating the β-fluoroalkylamino motif in API design.[3]

In this context, and given the prevalence of substituted anilines in top-selling pharmaceuticals and agrochemicals,[1] it is surprising that such commercial bioactive molecules featuring the *N*-(β-fluoroalkyl)aniline substructure are uncommon. One contributing factor is that the assembly of *N*-(β-fluoroalkyl)anilines by convenient disconnection strategies, such as exploiting (hetero)aryl (pseudo)halide and β-fluoroalkylamine substrates, is challenging in comparison to analogous reactions involving simple alkylamines.[4] For example, in a report from Francotte and co-workers,[5] S_NAr chemistry involving $CF_3CH_2NH_2$ is shown to require the combination of an electron-poor chloroarene, as well as forcing conditions (160 °C, 50 h), to afford the desired *N*-(β-fluoroalkyl)aniline, in keeping with established reactivity trends.[6] Despite the broad utility of metal-catalyzed Ullmann-Goldberg (Cu[7]) and Buchwald-Hartwig (Pd[8]) C-N cross-couplings, such transformations involving β-fluoroalkylamine nucleophiles have proven challenging, in some cases leading to catalyst inhibition.[9] The first cross-coupling of this type demonstrating useful scope was reported in 2015 by Brusoe and Hartwig (Figure 1),[10] in which an optimized Pd catalyst system allowed for the cross-coupling of β-fluoroalkylamines with (hetero)aryl chlorides and bromides. The use of KOPh, while non-ideal as this reagent is unavailable from common chemical suppliers and generated HOPh as a difficult-to-remove by-product, proved critical to the success of this chemistry; stronger bases including LiHMDS or MO*t*Bu (M = Na or K) were shown to decompose the desired *N*-(β-fluoroalkyl)aniline product under the conditions (100 °C) required to effect catalytic turnover. The first copper-catalyzed C-N cross-coupling of β-fluoroalkylamines was disclosed by Hu and co-workers in 2019 (Figure 1).[11] Although the use of an inexpensive and Earth-abundant base-metal Cu catalyst and K_2CO_3 in this chemistry is attractive,[12] forcing reaction conditions (110-120 °C and 5-20 mol% Cu_2O) were required, and only transformations of (hetero)aryl bromides were described.

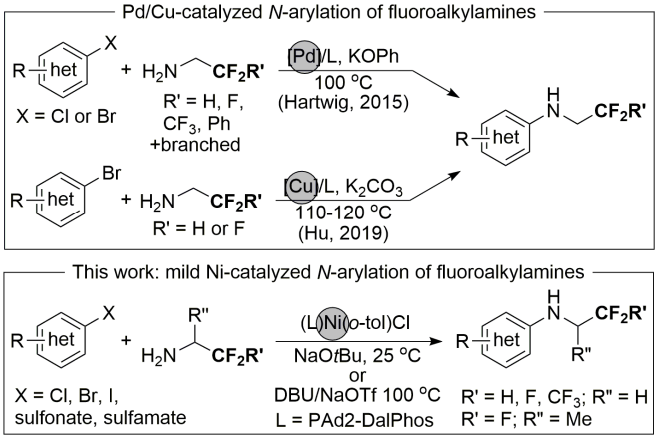

Figure 1. Metal-catalyzed *N*-arylation of fluoroalkylamines with (hetero)aryl (pseudo)halides.

Notwithstanding these and other[13],[14],[15] isolated reports detailing the synthesis of *N*-(β-fluoroalkyl)anilines by various means, important challenges remain with regard to reaction development. Particularly attractive would be the discovery of a base-metal catalyst system that could enable C-N cross-couplings of β-fluoroalkylamines with (hetero)aryl chlorides and phenol derivatives – the two most inexpensive and widely available[16] (hetero)aryl electrophile classes. Notably, such reactions of phenol-derived electrophiles involving any catalyst system are unknown. Given the sensitivity of the targeted *N*-(β-fluoroalkyl)anilines toward strong base upon heating,[10] and the low boiling points of many β-fluoroalkylamine reagents (e.g., $CF_3CH_2NH_2$, 37 °C), an optimal catalyst system would operate at room temperature and/or in combination with mild, commercially available bases. Herein we report on the establishment of such a system, which makes use of a simple, bisphosphine-ligated Ni pre-catalyst (Figure 1).

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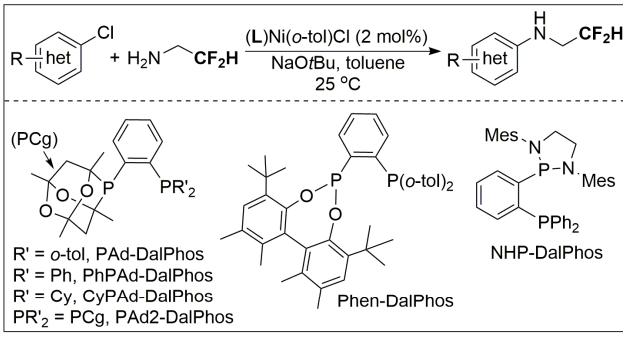
In the quest to identify a base-metal catalyst system that could facilitate the room temperature *N*-arylation of β-fluoroalkylamines, we initiated a screening campaign employing air-stable (DalPhos)Ni(*o*-tol)Cl[17] pre-catalysts, with a focus initially on reactions employing (hetero)aryl chlorides (Figure 2). These pre-catalysts were chosen on the basis of their established utility in enabling otherwise challenging C-N cross-couplings of electronically diverse nucleophile/electrophile pairings, including in many cases at room temperature with performance that meets or exceeds that of other superlative catalyst systems (e.g., Pd, Cu, Ni, and other). In positing that reactions conducted at room temperature might allow for the use of NaO*t*Bu without inducing decomposition of the *N*-(β-fluoroalkyl)aniline product,[18] we examined C-N cross-couplings of 2,2-difluoroethylamine with electron-rich, heteroaryl, and sterically hindered aryl chlorides, leading to **1a-1c** (Figure 2). Most of these pre-catalysts performed poorly, as did (**DPPF**)Ni(*o*-tol)Cl,[19] which is used widely in Ni-catalyzed C-N cross-coupling.[17f, 20] While pre-catalysts based on **PAd-DalPhos** and **Phen-DalPhos** performed well with selected electrophiles, only (**PAd2-DalPhos**)Ni(*o*-tol)Cl[17g],[21] afforded >75% conversion to each of **1a-1c** under the conditions employed. In turn, these products were obtained in synthetically useful isolated yields.[22] Throughout, no competing C-O cross-coupling products arising from NaO*t*Bu were observed.[23]



L:	1a	1b	1c
PAd-DalPhos	76%	31%	51%
PhPAd-DalPhos	<5%	<5%	13%
CyPAd-DalPhos	<5%	27%	47%
PAd2-DalPhos	**>95%** (**86%**[a])	**77%** (**75%**[a,b])	**91%** (**65%**[a,c])
Phen-DalPhos	9%	<5%	95%
NHP-DalPhos	<5%	<5%	12%
DPPF	<5%	<5%	<5%

Figure 2. Pre-catalyst screen for the Ni-catalyzed *N*-arylation of fluoroalkylamines. Reactions were conducted at 0.12 mmol scale (aryl halide, 0.24 M in toluene), with NaOtBu (1.1 equiv), and 2,2-difluoroethylamine (1.2 equiv) for 18 h (unoptimized). Reported GC yields determined on the basis of response-factor calibrated GC data using authentic material, with the mass balance corresponding to unreacted starting material. [a] Isolated yield. [b] Using 3 mol% Ni. [c] Volatile product.

The success of (**PAd2-DalPhos**)Ni(*o*-tol)Cl in enabling these room temperature reactions provided motivation for a more detailed exploration of substrate scope (Figure 3). The successful cross-coupling of 2,2-difluoroethylamine with 1-X-naphthalene electrophiles (X = Cl, Br, I, OTs, OTf) leading to **1d** established that a range of halide and sulfonate coupling partners can be used under these conditions. Catalyst loading was not exhaustively

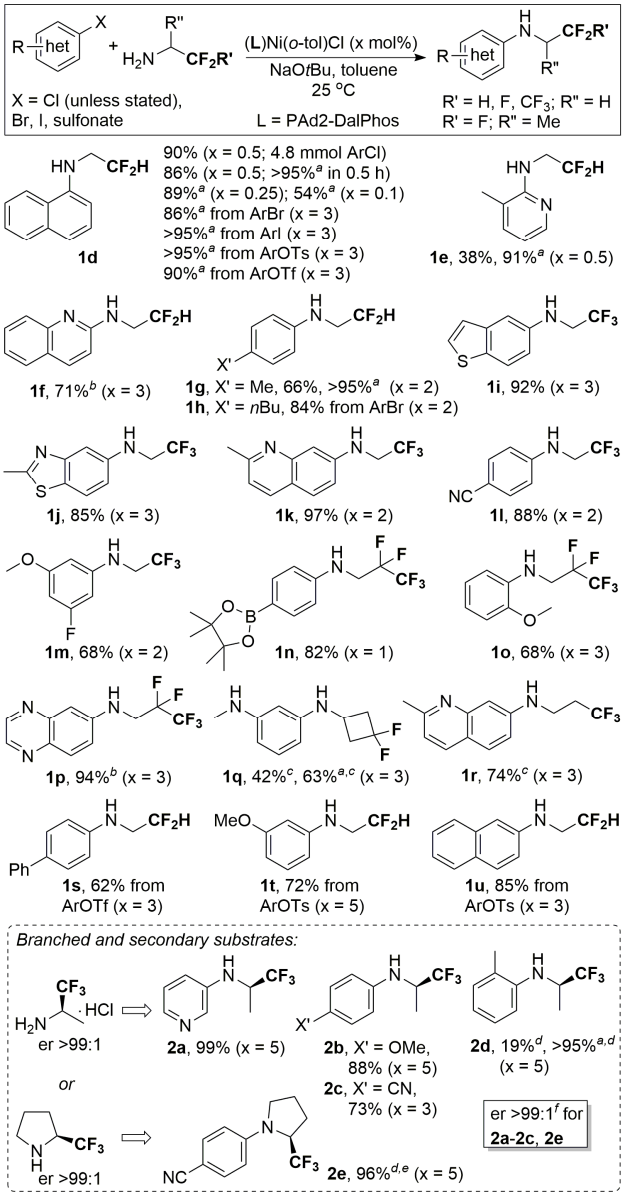


Figure 3. Scope of Ni-catalyzed *N*-arylation of fluoroalkylamines using NaO*t*Bu at room temperature. Unless indicated otherwise, isolated yields are reported from reactions conducted on 0.48 mmol scale (aryl halide, 0.24 M in toluene), with NaO*t*Bu (1.1 equiv; 2.3 equiv when using the HCl salt shown) and fluoroalkylamine (1.2 equiv) for 18 h (unoptimized). [a] Yield determined on the basis of response-factor calibrated GC data using authentic material. [b] Using 3.0 equiv amine. [c] Amine delivered as the HCl salt, and 2.3 equiv NaO*t*Bu used. [d] Conducted at 65 °C. [e] Using (**DPPF**)Ni(*o*-tol)Cl. [f] For **2d** we were unable to obtain sufficient resolution of the racemate under a range of HPLC conditions so as to allow unequivocal determination of enantioretentivity when using enantioenriched amine.

optimized on a per-substrate basis, and the amount needed to conveniently achieve high conversion to product is indicated in Figure 3 (typically 1-3 mol% Ni). While such loadings are higher than those employed with the AdBippyPhos/Pd system,[10] use of the base-metal Ni herein rather than Pd, under room temperature conditions employing commercially available NaO*t*Bu offers distinct reactivity advantages, including enabling the use of sulfonate electrophiles (leading to **1d** and **1s-1u**) not described previously in the literature for β-fluoroalkylamine C-N cross-couplings. When examining transformations of 1-

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chloronaphthalene in detail, high isolated yields of **1d** were obtained when using 0.5 mol% Ni (0.48 mmol ArCl, 86%), including in reactions where the scale was increased ten-fold (4.8 mmol ArCl, 90%). Moreover, while for convenience 18 h reaction times were employed generally, careful monitoring of such reactions revealed that >95% conversion to **1d** was achieved after only 0.5 h (0.5 mol% Ni). Synthetically useful conversion to **1d** was also achieved at both 0.25 mol% (89%) and 0.1 mol% (54%) Ni loading levels. Taken together, these observations suggest that the use of < 0.5 mol% Ni loadings and short reaction times can be employed with some substrate pairings in this room temperature chemistry.

The entries presented in Figures 2 and 3 demonstrate that a range of linear primary β-fluoroalkylamines can be efficiently cross-coupled with (hetero)aryl (pseudo)halides at room temperature using (**PAd2-DalPhos**)Ni(*o*-tol)Cl, including electron-rich and electron-poor electrophiles, and those featuring *ortho*-substitution (**1c**, **1e**, **1o**, **2d**). Heterocyclic electrophiles based on pyridine (**1b**, **1e**, **2a**), quinoline (**1f**), benzothiophene (**1i**), benzothiazole (**1j**), quinaldine (**1k**, **1r**), and quinoxaline (**1p**) core structures also proved to be suitable substrates under these room temperature conditions. Conversely, five-membered heteroaryl electrophiles were not employed with success in this chemistry. The chemoselective cross-coupling of *N*-methyl-3-chloroaniline with a cyclobutane-derived γ-fluoroalkylamine to give **1q**, as well as the successful cross-coupling of 3,3,3-trifluoropropylamine leading to **1r**, establishes the viability of using such γ-fluoroalkylamines in this chemistry.

Cross-couplings using 1,1,1-trifluoro-2-propanamine established the ability of (**PAd2-DalPhos**)Ni(*o*-tol)Cl to effect reactions involving branched primary β-fluoroalkylamines (Figure 3). Such reactions proceeded successfully with electron-rich, electron-poor, *ortho*-substituted, and heterocyclic aryl chlorides, leading to **2a**-**2d**, in a manner that did not lead to detectable racemization when using the enantioenriched nucleophile (er >99:1). While efforts to extend such reactions to 2-(trifluoromethyl)pyrrolidine were unsuccessful with (**PAd2-DalPhos**)Ni(*o*-tol)Cl, a test cross-coupling of this type using (**DPPF**)Ni(*o*-tol)Cl at 65 ºC proceeded efficiently (**2e**).

Although methoxy (**1a**, **1m**, **1o**, **1t**, **2b**), nitrile (**1l**, **2c**), fluoro (**1m**), boronic acid (**1n**), and secondary amine (**1q**) substitution on the aryl electrophile did not prove problematic in this chemistry, some limitations were encountered when we attempted to employ electrophiles featuring base-sensitive functionalities (including aldehydes, ketones, and esters) in Ni-catalyzed cross-couplings of 2,2-difluoroethylamine with NaO*t*Bu, even under room temperature conditions. In all such cases, complex reaction mixtures were obtained, which we attribute in part to degradation of the electrophile. To circumvent such issues, we sought to identify a complementary protocol that makes use of a more mild organic amine base, as has been developed lately for use in Pd-catalyzed C-N cross-coupling, including with (hetero)aryl chlorides.[18a, 24] While Buchwald and co-workers recently disclosed the first Ni-catalyzed C-N cross-couplings that make use of such a base (NEt_3) without recourse to microwave, photoredox, or electrochemical protocols and/or use of exogenous reductants, the reported transformations are restricted to reactions of (hetero)aryl triflates and anilines.[25] Given our interest in cross-couplings of aryl chlorides (as well as less reactive phenol-derived electrophiles), we selected the 'dual-base' DBU/NaOTf system[24a] (DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene) to test in C-N cross-couplings of 2,2-difluoroethylamine using (**PAd2-DalPhos**)Ni(*o*-tol)Cl as a pre-catalyst (Figure 4A). We were pleased to find that at elevated temperature (100 ºC) this protocol allowed for such cross-couplings to be achieved with otherwise base-sensitive aryl chloride or phenol-derived electrophiles bearing aldehyde, ketone, or ester functionality, leading to the desired *N*-(β-fluoroalkyl)anilines (**1d, 3a-3e**).[26] The reported cross-couplings in Figure 4A embody new and useful features that are worthy of mention with regard to the use of an amine base, including: the first examples of thermally promoted Ni-catalyzed C-N cross-couplings of non-triflate electrophiles; and the first C-N cross-couplings of aryl mesylate and sulfamate electrophiles by use of any metal catalyst.

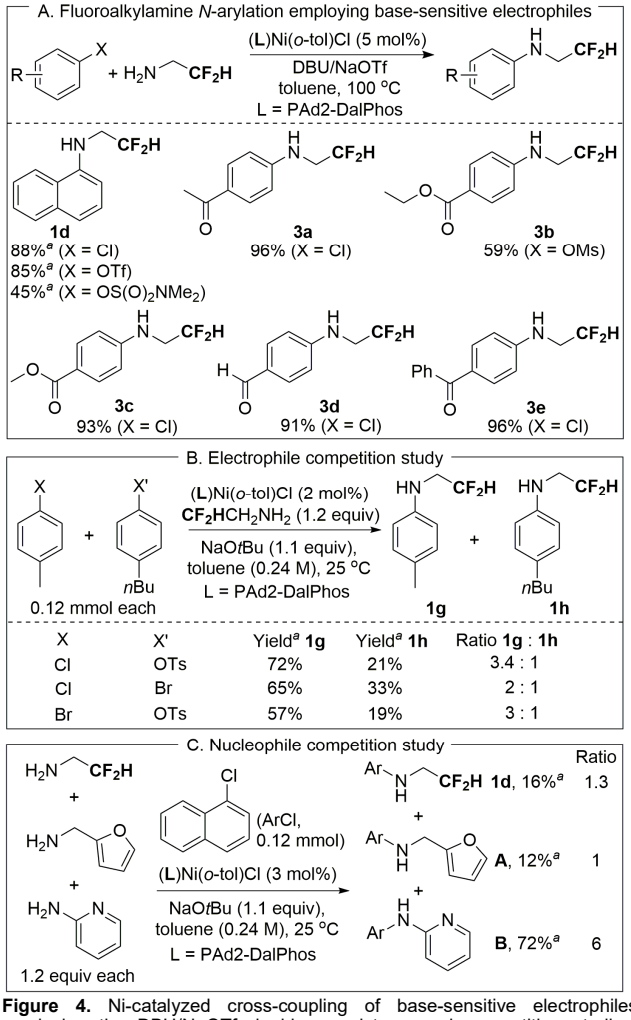

Figure 4. Ni-catalyzed cross-coupling of base-sensitive electrophiles employing the DBU/NaOTf dual-base mixture, and competition studies. Unless indicated otherwise, isolated yields are reported from reactions conducted on 0.48 mmol scale (aryl halide, 0.24 M in toluene), with DBU and NaOTf (2.0 equiv each) and fluoroalkylamine (2.0 equiv) for 18 h (unoptimized). [a] Yield determined on the basis of response-factor calibrated GC data using authentic material.

To gain insights into the reactivity preferences of the (**PAd2-DalPhos**)Ni(*o*-tol)Cl pre-catalyst in room temperature cross-couplings of β-fluoroalkylamines employing NaO*t*Bu, a selection

of competition studies were conducted. While (hetero)aryl chlorides, bromides, and phenol derivatives such as tosylates each independently proved to be viable electrophiles in this chemistry (Figure 3), the competition results presented in Figure 4B establish the Cl > Br > OTs reactivity trend in sterically and electronically similar substrates. In a complementary competition employing the heteroatom-containing nucleophiles 2,2-difluoroethylamine, furfurylamine, and 2-aminopyridine with 1-chloronaphthalene, preferential formation of the pyridine-derived aniline product (**B**) over both the alkylamine (**A**) and the β-fluoroalkylamine (**1d**) derivatives was noted. The **1d**:**A** ratio (1.3:1) indicated a modest preference for the fluorinated versus the non-fluorinated alkylamine nucleophile (Figure 4C), in contrast to competition studies reported by Hu and co-workers focusing on Cu-catalyzed C-N cross-coupling of an aryl bromide, whereby the alkylamine was preferred (3.1:1) over the β-fluoroalkylamine.[11] The competitive formation of **1d** and **A** herein also contrasts the results of studies focusing on the AdBippyPhos/Pd system, in which *p*-toluidine and *n*-butylamine nucleophiles were cross-coupled preferentially, with no conversion of the contending pentafluoropropylamine.[10] While many factors are likely to contribute to our observed selectivity, the favorable nature of 2-aminopyridine as a nucleophile in C-N cross-couplings employing (**PAd2-DalPhos**)Ni(*o*-tol)Cl was noted in our previous studies.[17g]

In summary, the Ni-catalyzed *N*-arylation of fluoroalkylamines is reported, spanning an unprecedented range of coupling partners including (hetero)aryl halides (X = Cl, Br, I), and for the first time by use of any catalyst system, phenol-derived (hetero)aryl electrophiles. Use of air-stable (**PAd2-DalPhos**)Ni(*o*-tol)Cl as a pre-catalyst in this chemistry allows for the implementation of mild reaction conditions (i.e., room temperature or use of an organic amine base), so as to avoid both degradation of the *N*-(β-fluoroalkyl)aniline product and/or base-sensitive substituents, as well as substrate/product racemization. Ongoing work is focused on expanding our mechanistic understanding of how the DalPhos ligand family engenders desirable reactivity in this and related chemistry.[27]

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Keywords: amination • cross-coupling • fluoroalkylamine • ligand design • nickel

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[21] Both **PAd2-DalPhos** and (**PAd2-DalPhos**)Ni(o-tol)Cl are in the process of being commercialized by MilliporeSigma (product numbers 919551 and 919578, respectively).

[22] In some cases, product volatility resulted in a moderate isolated yield, despite high conversion to product as determined on the basis of response factor-calibrated GC data (>85% for all transformations reported herein), in keeping with observations of Brusoe and Hartwig (ref. 10).

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[26] Efforts to use less expensive sodium trifluoroacetate in place of sodium triflate resulted in inferior catalytic performance.

[27] The authors declare the following competing financial interests: Dalhousie University has filed patents on some of the DalPhos ancillary ligands and derived nickel pre-catalysts used in this work, from which royalty payments may be derived.

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COMMUNICATION

*Ryan T. McGuire, Arun A. Yadav, and Mark Stradiotto**

Page No. – Page No.
Nickel-Catalyzed *N*-Arylation of Fluoroalkylamines

Ni-cely mild: The Ni-catalyzed *N*-arylation of β-fluoroalkylamines is reported. The mild protocols and broad (hetero)aryl (pseudo)halide scope, encompassing base sensitive substrates and enantioretentive transformations, is unmatched by any previously reported catalyst system.