ChemComm

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Journal:	*ChemComm*
Manuscript ID	CC-COM-04-2022-001938.R2
Article Type:	Communication

COMMUNICATION

Nucleophilic strategies to construct –CF_2– linkages using borazine-CF_2Ar reagents

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Michael M. Wade Wolfe,[a] Shuo Guo,[a] Lucy S. Yu,[a] Trenton R. Vogel,[a] Joseph W. Tucker,[b] Nathaniel K. Szymczak*[a]

Using a Lewis acid-quenched CF_2Ph^- reagent, we show C–C bond formation through nucleophilic addition reactions to prepare molecules containing internal –CF_2– linkages. We demonstrate C(sp^2)-C(sp^3) coupling using both S_NAr reactions and Pd-catalysis. Finally, C(sp^3)-C(sp^3) bonds are forged using operationally simple S_N2 reactions that tolerate medicinally-relevant motifs.

The development of new reagents and synthetic strategies to install fluorine into organic molecules has been a highly targeted pursuit over the past two decades.[1] Many recent pharmaceutical compounds[2] and agrochemicals[3] contain C–F bonds as prominent motifs, which often improve properties compared to their non-fluorinated counterparts (higher metabolic stability and lipophilicity).[2] Among the organofluorine motifs, –CF_3 groups are the most common, which likely stems from available synthetic methods and the wide abundance of trifluoromethylating sources such as Me_3Si-CF_3,[4, 5] and related radical[6] and electrophilic reagents.[7] In contrast, there are significantly fewer routes to install internal C–F bonds,[8-17] some of which require potentially explosive reagents (deoxyfluorination).[18] A consequence of limited general synthetic strategies to access $ArCF_2$-R motifs is that although several promising bioactive compounds contain $ArCF_2$-R groups (Figure 1),[19, 20] the number of candidates amenable to bioactivity studies are low. Within the last several years, transition metal catalysis has become an increasingly popular strategy to install CF_2R motifs.[21-26] The Zhang group has recently advanced this field by using halodifluoromethyl arenes[27, 28] and alkanes[29] as radical/electrophilic partners in conjunction with organonucleophiles to form products with internal –CF_2– linkages. The Crudden and Baran groups have investigated difluoromethyl aryl and difluoroalkyl sulfones, another class of radical/electrophilic reagents that can be further transformed into $ArCF_2R$ products.[30-32] Unlike the –CF_3 group, orthogonal nucleophilic methodologies to install –CF_2Ar groups remain largely underdeveloped.[33-36] We anticipated that a Lewis-acidic boron based scaffold could provide broad routes to related compounds with –CF_2Ar functionality.

Our group recently reported a strategy to access anionic –CF_2Ar reagents stabilized by a borazine Lewis acid, enabling a diverse array of chemical transformations from simple H–CF_2Ar precursors.[37] We previously found that hexamethylborazine Lewis-acid adducts of $[CF_2Ar]^-$ (Ar = Ph; **1a**) react with select electrophilic substrates through 1,2-addition (ketones, imines), C-H functionalization of electron deficient (hetero)arenes, and stoichiometric cross coupling.[37] In this manuscript we report additional strategies to use this reagent to construct new C-C bonds (Figure 1c).

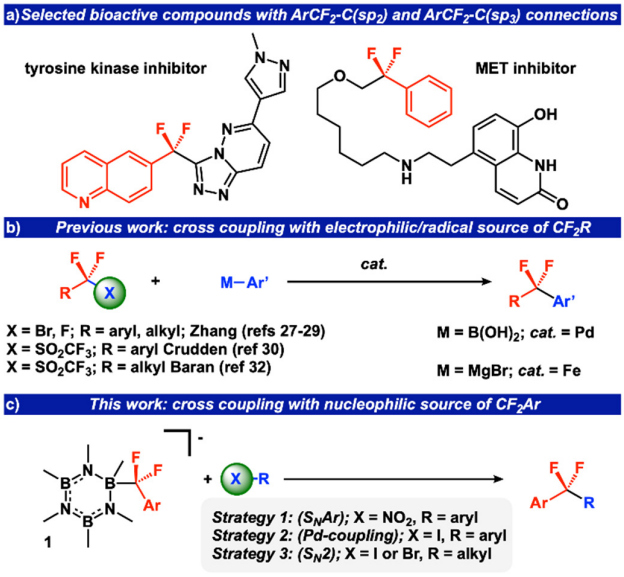

Figure 1. a) Bioactive compounds with an $ArCF_2$-R motifs. b) Previous work: cross-coupling reactions of aryl and alkyl CF_2X. c) This work: nucleophilic strategies to form C-C_F bonds.

We targeted a series of general reactions to enable C(sp^2)-C(sp^3) coupling across electronically diverse arenes. Nucleophilic aromatic substitution, S_NAr, is a powerful strategy that leverages the inherent reactivity of electron deficient arenes toward strong nucleophiles, including –CF_2Ar^-.[37, 38] Importantly, the arene reactivity in these types of reactions is dominated by the strength of the electron withdrawing

[a] University of Michigan: 930 N. University Ave., Ann Arbor, MI. 48109.
[b] Medicine Design, Pfizer Inc.: Eastern Point Rd., Groton, CT. 06340.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

groups.[38] We first evaluated the reactivity limits of electron deficient *para*-substituted nitro arenes using **1a** as the nucleophile to form phenyl difluoromethylene arene products. When 1 equiv. **1a** was introduced to 1.2 equiv. of 1,4-dinitrobenzene (Hammett σ value of *p*-NO_2 = 0.78) in THF solvent at room temperature, **3a** formed in 37% yield (Figure 2). In contrast, when the less electron deficient substrates, 1,4-cyanonitrobenzene (σ of *p*-CN = 0.66) and 4-nitrobenzotrifluoride (σ of *p*-CF_3 = 0.54) were subjected to identical conditions, **3b** and **3c** formed in only 11% and 4% yield respectively. When 1,4-bromonitrobenzene (σ of *p*-Br = 0.23) was used, 1% of the S_NAr product **3d** was formed. These results establish clear electronic limits to form C(sp^2)-CF_2Ar bonds using an S_NAr methodology.[39]

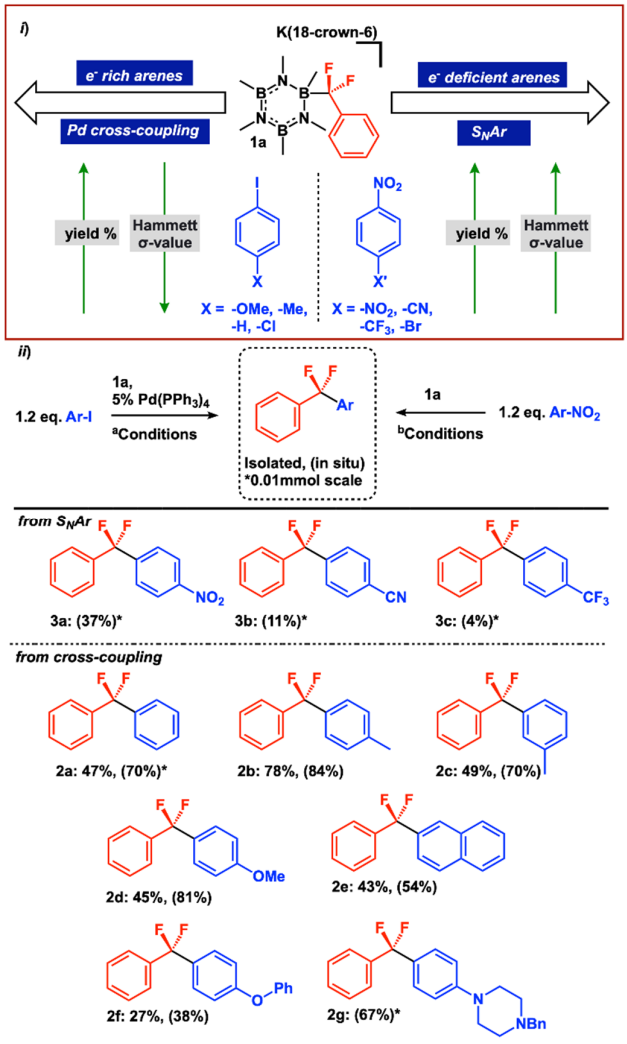

Figure 2. i) Electronic trends with Pd catalyzed cross-coupling and S_NAr. ii) Scope in cross coupling and S_NAr. In situ yields measured by ^{19}F NMR with respect to an internal standard, trifluoromethyl anisole. Mass purity of isolated samples measured by ^{19}F NMR with respect to an internal standard, trifluoromethyl anisole. [a]Conditions: reactions performed in toluene (0.02M) at 25 °C, 16h with 5 mol% $Pd(PPh_3)_4$. [b]Conditions: reactions performed in THF (0.02M) at 25 °C, 18h.

To access electron-neutral and rich C(sp^2)-CF_2Ar products, we targeted catalytic cross-coupling. Unlike S_NAr reactions, Pd-mediated cross coupling can functionalize even unactivated aryl–halogen bonds. For this reaction type, aryl iodides were selected as ideal substrates because they readily undergo oxidative addition. We previously reported stoichiometric cross coupling of phenyl iodide with **1a** in the presence of 1 eq. of $Pd(PPh_3)_4$,[37] at 0.02 M concentration and sought to translate these results to a catalytic version.

To modify stoichiometric reaction conditions to be catalytic with respect to $Pd(PPh_3)_4$, we held the concentration of Pd constant (0.02 M, 10 mol%), while increasing the concentration of **1a** and Ph-I to 0.2 M. When a THF solution containing these reagents was combined and mixed at 50 °C, **2a** formed in 35% yield after 20 h. Dilution of the concentration of **1a** and Ph-I to 0.02M resulted in an improvement to 60% yield. Unfortunately, other commonly used Pd catalysts did not significantly improve yields (see **Table S1** for more details). In contrast, analysis of the solvent effects revealed that non-polar solvents, such as toluene and DME improved the reaction to over 80% (8 TON) yield. Finally, when the catalyst loading was reduced to 5%, we obtained 65 % yield (13 TON) in DME or 72% yield (14 TON) in toluene. Further decreasing the catalyst loading to 2% caused a dramatic decrease in yield to 3%. We also observed that while a slight excess (1.2 equiv) phenyl iodide improved the yield, super-stoichiometric quantities were detrimental to productive catalysis. Based on our observation that the solvent had a larger impact on the reaction than selection of ligand, we questioned whether in the current system, $Pd(PPh_3)_4$ might actually serve as a precursor to a heterogeneous Pd catalyst. We found that the rate profiles were identical with and without added Hg, consistent with an active homogeneous catalyst. (see S41)

The yield for catalytic cross coupling improved with simple electronic variations to the aryl iodide. Moderately electron-rich substrates (4-iodotoluene and 4-iodoanisole) improved the chemical yields to form **2b** and **2d** in 84% and 81% yields respectively. In conjunction with this observation, electron neutral substrates performed comparably to iodobenzene, (3-iodotoluene and 2-iodonaphthylene) forming the products **2c** (70% yield) and **2e** (54% yield). The more sterically encumbered derivatives (2-iodotoluene and 1-iodonaphthylene) performed poorly toward catalysis, (1 TON or less) in formation of **2i** and **2h**. We ascribe this steep decline in yield to the transmetalation step becoming more difficult and slower than uncatalyzed decomposition of **1a** to difluoromethyl benzene. Larger electron rich substrates performed in moderate to good yield **2f** (38%) and **2g** (67%).

Other limitations of the method included electron deficient arenes and N-heterocyles, which provided 1 TON or less (see SI). In these cases, difluoromethyl benzene was the major product. We hypothesize that this dramatic decrease in catalytic activity is due to a combination of detrimental factors: 1) electron-deficient Pd intermediates having lower rates of reductive elimination, and 2) increased acidity of the iodoarene causing an increase in the rate of formation of difluoromethyl benzene. Overall, the S_NAr and Pd-catalyzed cross coupling reactions demonstrate that **1a** can be used to effect C(sp^2)-C(sp^3) coupling reactions spanning both electron deficient (S_NAr) and electron rich (cross-coupling) arenes.

To complement the above methodology, we sought to evaluate C(sp^3)-C(sp^3) bond formation with **1a**. S_N2 reactions represent an attractive application of carbon nucleophiles, and although such transformations are known for select perfluorinated TMS reagents (CF_3, C_2F_5, $C(CF_3)_3$, $C(CF_3)_2(C_3F_7)$),[40] they have not been reported using TMS-CF_2Ar reagents. We found that when either 1-iodobutane or 1-bromobutane were allowed to react with **1a** at elevated temperature (90 °C) in toluene, the corresponding C-C coupled product ((1,1-difluoropentyl)benzene; **4a**) formed in 83% and 84% chemical yield, respectively. These simple substrates demonstrate the feasibility of an S_N2 pathway that outcompetes the undesired E2 pathway. Finally, we found that the method tolerates other $^-CF_2Ar$ nucleophiles for nucleophilic substitution with 1-iodobutane as a representative electrophile, forming **4b** and **4c** in 59% and 70% isolated yield.

We evaluated the scope of this methodology with both benzyl and alkyl electrophiles. Benzyl bromide proved to be more challenging as a substrate, forming 1,1-difluoro-1,2-diphenylethane (**4d**) in 52% chemical yield. For this substrate, the remaining mass balance was difluorotoluene. We propose a competitive deprotonation pathway for this substrate at the benzylic CH_2 site, noting the high basicity of $PhCF_2$-.[37] Indeed, for more acidic substrates, 4-(bromomethyl)fluorobenzene and 4-(bromomethyl)benzonitrile, **4f** and **4g** were only formed in 19% and 25% yield respectively. Surprisingly, for a benzyl bromide containing less acidic benzylic -CH_2- groups (p-OMe-benzyl bromide), we found lower yields of the S_N2 reaction to form **4e**. This result highlights a needed balance of the benzylic carbon electrophilicity compared to its acidity. Substitution patterns distal (α vs. γ) to the electrophilic site provided higher yields of products. Electrophiles containing ether and thioether moieties were compatible, with **4h** and **4i** forming in 72% and 59% yield, respectively. Finally, **4j**, which contains an *N*-methyl aniline was formed in 75% yield, highlighting the versatility of the approach.

We evaluated the viability of this method in the presence of biologically-active compounds, such as oxetanes, terpenes, and steroids. Oxetanes have been shown to act as a bioisostere, mimicking conformational and electronic properties of *gem*-dimethyl and carbonyl substitutions, while imparting improved physiochemical properties to target molecules.[41] In other applications, fluorinated oxetanes are desirable functional groups that undergo polymerization under photoinduced or cationic conditions.[42] We found that an oxetane is retained under the reaction conditions with substrate **4k**, which formed in 93% chemical yield. Compared to prior routes to fluorinated oxetanes (acid-promoted ring closure of fluorinated diols[43]), our methodology enables a 1-step route from a commercially available electrophile. Geranyl bromide is a derivative of a terpene alcohol, and although it is unstable to electrophilic and radical fluorination strategies, it formed **4l** in 55% yield. Finally, a stereochemically complex steroid-derived alkyl halide was tolerated, with **4m** forming in 75% yield.

We next evaluated whether the S_N2 pathway could provide access to fluoroalkylated units that are readily diversifiable. ICH_2SiMe_3 has been used as a $-CH_2-$ linchpin in the total syntheses of Cephalotaxus esters.[44] We found that, even though $I\text{-}CH_2SiMe_3$ contains a competitive $-SiMe_3$ Lewis acidic site, it cleanly reacted with **1a** at room temperature to form (2,2-difluoro-2-phenylethyl)trimethylsilane (**4n**) in 97% yield. We next examined allyl bromide, which is a highly reactive electrophile whose terminal olefin product can easily undergo either reductive or oxidative functionalization reactions. We found that substrate **4o**, formed in 50% yield. To demonstrate the feasibility of a tandem reaction sequence, this product underwent hydroboration to afford **4p** in 18% yield over two steps with 53% selectivity for the **4p**. Overall, access to both of these reaction products establishes that S_N2 fluoroalkylation can be used as a key intermediate step in a larger reaction sequence to form high value products from simple building blocks.

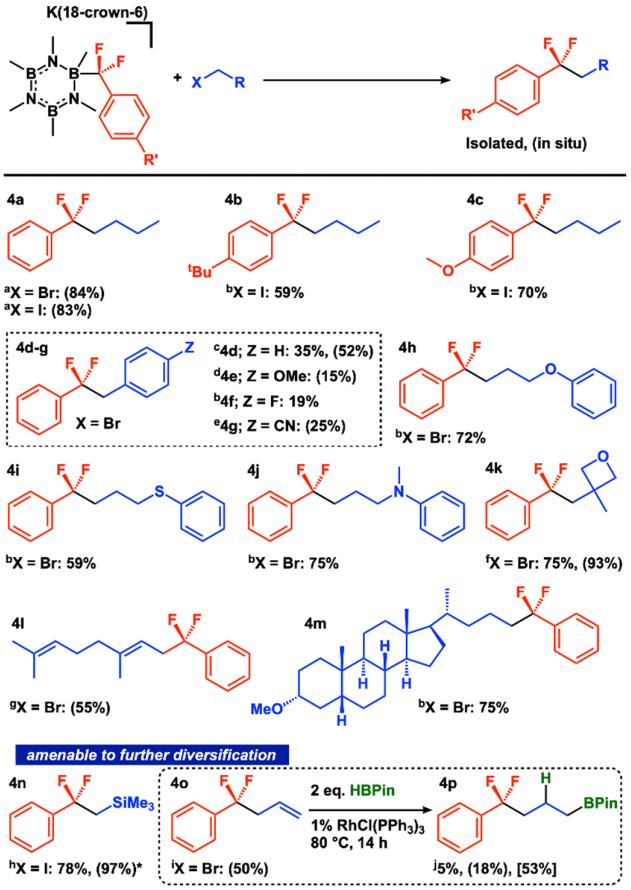

Figure 3. S_N2 reactions with alkyl halides. In situ yields measured by ^{19}F NMR with respect to an internal standard, $PhOCF_3$ or PhF. [a]1 eq. $[B]CF_2Ar$ (0.02 mmol), 1.2 eq. RCH_2X, 90 °C, 30 min in toluene (0.02M). [b]1.5 eq. $[B]CF_2Ar$, 1 eq. RCH_2X (0.25 mmol), 90 °C, 12 h in toluene (0.02M). [c]1 eq. $[B]CF_2Ar$ (0.3 mmol), 1.2 eq. RCH_2X, 80 °C, 18 h in THF (0.02M). [d]Same as [c] but on a 0.01 mmol scale. [e]Same as [b] but on a 0.1 mmol scale. [f]1 eq. $[B]CF_2Ar$ (0.3 mmol), 1.2 eq. RCH_2X, 25 °C, 18 h in THF (0.02M). [g]1 eq. $[B]CF_2Ar$ (0.15 mmol), 1.5 eq. RCH_2X, 23 °C, 12 h in toluene (0.02M). [h]Same as [f] but on a 0.1 mmol scale. [i]Same as [f] but stopped after 3.5 h. [j]After formation of **4o**, solids removed by filtration and allyl bromide removed by vacuum. **4p** heated to 80 °C in 15 mL THF in the presence of pinacol borane (2eq.) and $RhCl(PPh_3)_3$ for 14 h. Yields for **4p** were determined over two steps. *isolated in 1:1 mixture with hexamethylborazine. [selectivity for product].

In conclusion, we demonstrated an operationally simple approach that uses nucleophilic $PhCF_2^-$ precursors for both Pd-catalyzed and metal-free (S_NAr and S_N2) C-C coupling reactions.

The latter approach offers a distinct advantage when compared to RCF_2-Br reagents, whose reactions require a metal mediator.[29] Importantly, we show that these methods tolerate substrates that are amenable to further diversification, potentially highlighting this methodology as a modular route to incorporate $–CF_2–$ linkages within a longer reaction sequence.

Acknowledgments

This work was supported by the NSF (CHE 1955284). We thank Dr. Kevin Hesp and Dr. Jisun Lee at Pfizer for helpful discussions and Troy Zehnder for Mass Spectrometry assistance.

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