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Palladium-Catalyzed Aryldifluoromethylation of Aryl Halides with Aryldifluoromethyl Trimethylsilanes

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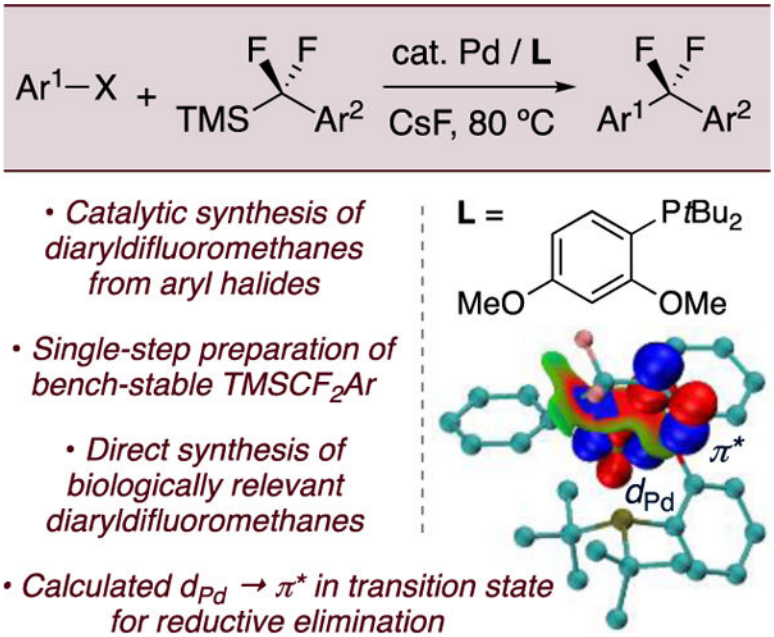
Abstract

Diaryl difluoromethanes are valuable targets for medicinal chemistry because they are bioisosteres of diaryl ethers and can function as replacements for diaryl methane, ketone, and sulfone groups. However, methods to prepare diaryl difluoromethanes are scarce, especially methods starting from abundant aryl halides. We report the Pd-catalyzed aryldifluoromethylation of aryl halides with aryldifluoromethyl trimethylsilanes ($TMSCF_2Ar$). The reaction occurs when the catalyst contains a simple, but unusual, dialkylaryl phosphine ligand that promotes transmetallation of the silane. Computational studies show that reductive elimination following transmetallation occurs with a low barrier, despite the fluorine atoms on the α-carbon, due to coordination of the difluorobenzyl π-system to palladium. The co-development of a cobalt-catalyzed synthesis of the silanes broadened the scope of the process including several applications to the synthesis biologically relevant diaryl difluoromethanes.

Graphical Abstract



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Palladium-catalyzed coupling of aryl halides with aryldifluoromethyl trimethylsilanes is shown to form diaryl difluoromethanes. A simple dialkyl(dimethoxyphenyl)phosphine ligand for palladium, stabilizing π-interactions between palladium and the difluorobenzyl ligand during reductive elimination, and a cobalt-catalyzed synthesis of the silanes enabled the reaction to form diverse products, including those possessing biological activities.

Keywords

alkylation; cross-coupling; fluorine; palladium; synthetic methods

Introduction

The replacement of two hydrogen atoms with fluorine in a methylene unit can enhance the potency, membrane permeability, metabolic stability, and clearance of bioactive molecules.[1] The high electronegativity and small size of the fluorine atom make the difluoromethylene unit a bioisostere of oxygen atoms and an analog of methylene, carbonyl, and sulfonyl groups.[1e] For these reasons, medicinal chemists have sought to incorporate difluoromethylene units into drug candidates.[2] In one example, a difluoromethylene linkage between two aryl substituents was present in the most potent inhibitor of Leukotriene A_4 (LTA_4) hydrolase, whereas other linkers, such as a methylene unit or an oxygen atom, led to less active compounds (Figure 1, top).[3a] However, the number and diversity of biologically active molecules bearing diaryl difluoromethane units is constrained by the limited synthetic routes to incorporate them.[3]

Generally, diaryl difluoromethanes are formed by the installation of two fluorine atoms at the benzylic position through radical difluorination, fluorodeoxygenation, or fluorodesulfurization (Figure 1, middle).[4] However, these methods require a reactant containing the carbon–carbon bonds in the final product and typically require toxic, harmful, or expensive reagents, such as HF, Selectfluor, and Deoxofluor. Recently, Pd-catalyzed or Pd-mediated cross-coupling reactions of aryl boronic acids with aryldifluoromethyl electrophiles have been reported that form one of the C–C bonds with a fluorine-containing reagent.[5] However, these methods require multiple synthetic steps to prepare the electrophiles, conversion of widely available aryl halides to aryl boronic acids, and 5 mol% to stoichiometric amounts of Pd.

The synthesis of diaryl difluoromethanes by catalytic coupling of aryl halides with aryldifluoromethyl nucleophiles, if it could be achieved, would occur by fewer steps and with a broad range of coupling partners, due to the wide availability and synthetic accessibility of aryl halides.[6–7] However, significant challenges confront this strategy, including the propensity of aryldifluoromethyl anions to undergo α-fluoride elimination to generate reactive arylfluorocarbenes.[8] To avoid this side reaction, Szymczak reported hexamethylborazine as a Lewis acid to trap the aryldifluoromethyl anion and reaction of the anion–borazine adducts with aryl halides and stoichiometric Pd to form diaryl difluoromethanes (Figure 1, middle).[9] However, the strong bases to deprotonate difluoromethylbenzene and the stoichiometric and expensive hexamethylborazine and

palladium reagents are major limitations of this method. Difluorobenzyl analogs ($TMSCF_2Ar$) of Ruppert's reagent ($TMSCF_3$) would be convenient reagents for this coupling process.[10] However, transmetallation of fluoroalkylsilanes to form fluoroalkyl transition-metal complexes is often slow and low-yielding,[11] and routes to these silane reagents are not well developed.

Herein, we describe the palladium-catalyzed aryldifluoromethylation of aryl halides with such aryldifluoromethyl trimethylsilanes (Figure 1, bottom). The reaction occurs with moderate loadings of Pd (typically 2 mol%) bound by a rarely used ancillary phosphine possessing weak secondary coordination. Single-turnover aryldifluoromethylation of the Pd resting state showed that the judiciously tuned dialkylaryl phosphine ligand forms a catalyst that is stable to the reaction conditions, but reactive toward transmetallation. DFT studies show the subsequent reductive elimination occurs with a low barrier, due to the presence of the benzylic π-system, causing the aryldifluoromethylation of aryl halides to occur with a broad scope. The scope of this process is complemented by the co-development of a Co-catalyzed preparation of $TMSCF_2Ar$ nucleophiles by the (trimethylsilyl)difluoromethylation of arylmagnesium bromides. The applicability of this methodology is showcased by the short synthesis of diaryl difluoromethane analogs of biologically relevant molecules.

Results and Discussion

Reaction Development

In our studies to develop a mild, widely applicable route to diaryl difluoromethanes, we sought phosphine ligands that would create palladium catalysts for the coupling of aryl bromides with $TMSCF_2Ph$ **2a** (Table 1). Prior Hiyama couplings did not encompass coupling of $TMSCH_2Ph$,[12] and it is well established that transmetallation of fluoroalkylsilanes can be slow and form fluoroalkyl transition-metal intermediate in low yield.[11] Thus, it was unclear what catalysts and conditions would lead to the desired process. The reaction of aryl bromide **1a** with **2a** catalyzed by $[Pd(allyl)Cl]_2$ and BrettPhos (**L1**), which catalyze the trifluoromethylation of aryl chlorides,[11a] formed product **3a** in good yield. However, the corresponding reaction of the more electron-deficient aryl bromide **1b** gave **3b** in moderate yield. Palladium catalysts derived from other dialkylbiaryl phosphine ligands such as CyBippyPhos (**L3**) and SPhos (**L5**) gave similar results to those with **L1**, and the reactions performed with more sterically demanding *tert*-butyl substituents (**L2** and **L4**) formed **3a** and **3b** in much lower yields. These results indicate that the steric properties of the phosphine significantly affect the coupling to afford diaryl difluoromethanes.

Based on these observations, we evaluated dialkylaryl phosphine ligands that are less sterically demanding than dialkylbiaryl phosphines. Reactions with commercially available dialkylphenyl phosphines (**L6**-**L8**) furnished varying amounts of products, and those with tBu$_2$PhP (**L7**) afforded **3a** and **3b** in higher yields than those with ligands bearing cyclohexyl (**L6**) or adamantyl (**L8**) groups. Inspired by our previous work on Pd-catalyzed coupling with *ortho*-substituted aryl phosphines,[13] we evaluated reactions with several variants of **L7**. The reactions conducted with dialkylaryl phosphines containing 2-methyl

(**L9**) or 2-dialkylamino (**L10**, **L13**, and **L14**) substituents occurred in poor yields, but the reaction with 2-anisyl-substituted ligand (**L11**) furnished **3b** in much higher yields than those with the other ligands. The higher yield than with **L12**, which contains a bulkier *tert*-butoxy substituent in the *ortho* position, is consistent with coordination by the OMe group. Modification of the electronic properties of **L11** by the inclusion of a 5-CF_3 group (**L15**) had little effect on the yields, but the incorporation of a 4-OMe group (**L16**) resulted in a catalyst that formed **3a** and **3b** in 99% and 86% yield, respectively. Reactions with ligands containing electron-donating substituents at the *para* position without an *ortho* substituent (**L17** and **L18**), or bidentate ligands (**L19**), formed **3a** and **3b** in much lower yields. Thus, we used **L16** for the remainder of our investigations.[14]

Effects of Dialkyl(bi)aryl Phosphine Ligands on Aryldifluoromethylation

To reveal the origin of the high yield of the Pd-catalyzed aryldifluoromethylation with the catalyst containing **L16**, we conducted studies on the effect of the ligand on the identity and stability of the resting state of the catalyst. We conducted these reactions with complexes of **L1** and **L7**, which represent dialkylbiaryl and dialkylaryl phosphines respectively, and a complex of **L16**. At partial conversion of **1b**, an arylpalladium bromide complex with a single phosphine ligand was detected by ^{31}P NMR spectroscopy as the catalytic resting state for the reactions with each of the ligands **L1**, **L7**, or **L16**. The structure of (**L16**)Pd(Ar)Br (Ar = C_6H_4–4-CF_3) was unambiguously confirmed by single crystal X-ray diffraction (Figure 3).[15]

We prepared arylpalladium bromide complexes ligated by **L1**, **L7**, or **L16** and studied the reactions of each of them with excess amounts of silane **2a** and CsF at 50 °C by ^{19}F NMR spectroscopy (Figure 2). (**L1**)Pd(Ar)Br reacted with **2a** and CsF at 50 °C, but the reaction occurred slowly and provided **3b** in 11% yield after 120 min, demonstrating the challenge of achieving transmetallation with **2a** (Figure 2a). At 80 °C, full conversion of (**L1**)Pd(Ar)Br occurred after 60 min, but the reaction formed **3b** in only 54% yield, along with significant amounts of side products, such as Ar–Ar (11%) and Ar–H (16%).[16] [(**L7**)Pd(Ar)Br]$_2$ reacted with **2a** and CsF within 120 min at 50 °C, signalling a faster reaction than that of (**L1**)Pd(Ar)Br (Figure 2b). However, [(**L7**)Pd(Ar)Br]$_2$ formed **3b** in only 43% yield, along with side products and several unidentified Pd species.

In contrast, the reaction of (**L16**)Pd(Ar)Br with **2a** and CsF occurred to full conversion after 180 min at 50 °C, forming **3b** in 84% yield, indicating that this complex reacts 5–10 times faster than does [(**L1**)Pd(Ar)Br] and formed **3b** in almost twice the yield of [(**L7**)Pd(Ar)Br]$_2$. Thus, replacing the biaryl group of **L1** with a single aryl group enhanced the reactivity (**L7** and **L16** vs **L1**), and installation of the 2-methoxy substituent on the phenyl ring (**L16** vs **L7**) suppressed the formation of biaryl, arene, and catalyst decomposition products.

Computational Studies on the Reductive Elimination from the Aryl(aryldifluoromethyl)palladium Complex

Because reductive elimination from α-fluoroalkyl complexes are slower than those of the non-fluorinated analogs, the observation of (**L16**)Pd(Ar)Br as the resting state of

the catalytic process, rather than (**L16**)Pd(Ar)(CF_2Ph), and the absence of an observable aryldifluoromethyl complex from the experiments with **L16** in the previous section was unexpected. The observation that (**L16**)Pd(Ar)Br reacts with **2a** at room temperature to form the diaryl difluoromethane **3b** implies that reductive elimination of the **3b** from (**L16**)Pd(Ar)(CF_2Ph) occurs at room temperature, and this rate of reductive elimination is orders of magnitude faster than the rate of reductive elimination from analogous trifluoromethyl complexes.[17–18] To gain information on the factors that lead to this difference in rate of reductive elimination between palladium trifluoromethyl and aryldifluoromethyl complexes, we computed the transition state for reductive elimination from (**L11**)Pd(Ph)(CF_2Ph). In short, interaction of the benzylic π-system with Pd facilitates reductive elimination.

The ground state of (**L11**)Pd(Ph)(CF_2Ph) containing a 2-methoxy group on the ligand is shown in Figure 4a. This complex is computed to be square planar with the methoxy and phosphino groups coordinated to Pd, in addition to the phenyl and aryldifluoromethyl ligands. The phosphino group is located *cis* to the phenyl ligand and *trans* to the aryldifluoromethyl ligand. This coordination mode of the ligand is similar to that of (**L16**)Pd(Ar)Br (Figure 3). This structure in which the aryl group is *cis* to the phosphino group was computed to be slightly lower in energy than that with the aryl group *trans* to the phosphino group (ΔG = 0.23 kcal/mol). To determine the difference between the electronic properties of the Pd aryldifluoromethyl complex and the trifluoromethyl and difluoromethyl analogs, we computed their ground state geometries and the QTAIM (quantum theory of atoms in molecules) charges at the Pd-bound carbon on the three complexes.[19] These data show that the charge of the aryldifluoromethyl complex lies between that of the two related species.

The computed transition state for reductive elimination from (**L11**)Pd(Ph)(CF_2Ph) is shown in Figure 4b. The free energy of this transition state lies only 17.3 kcal/mol above the ground state, corresponding to a half-life of 0.5 s at room temperature for the reductive elimination. This predicted fast rate explains why the aryldifluoromethyl complex is not observed as the resting state or during the reaction of (**L16**)Pd(Ar)Br with **2a** and why the catalytic process for the aryldifluoromethylation occurs with a broad scope of aryl halides, as described in the next section.

This transition state contains several structural features that are distinct from those of the ground state. The Pd–OMe distance is much longer in the transition state (2.306 Å to 2.949 Å), with the aryl group twisted out of the coordination plane in which it was present in the ground state, thereby weaking electron donation of the methoxy group to Pd. The torsion angle between C(Ph), Pd, P, and O changes from the nearly planar 171° to 124°. Concomitant with dissociation of the methoxy group is association of the aryl moiety on the aryldifluoromethyl group to form an η^3-coordination mode by rotating the Pd–CF_2Ph bond (**GS'**).

To probe the effect of π-interaction between the aryldifluoromethyl group and Pd on the calculated free energy barriers to reductive elimination, we conducted IGMH (Independent Gradient Model based on Hirshfeld partition) analysis of the transition state of reductive elimination (Figure 4c).[20] IGMH analysis classifies interactions in specific regions of a

molecular space and colors of these regions are based on whether the interactions are attractive and stabilizing (blue), repulsive and destabilizing (red), or due to van der Waals interactions (green). The IGMH plot of the transition state clearly shows blue isosurfaces between the Pd and the η^3-carbon atoms of the aryldifluoromethyl group that indicate stabilizing and bonding interactions between them.[21]

The positive charge of the Pd center calculated by QTAIM is lower in the transition state than in the connected ground state (q_{Pd}(**TS**)–q_{Pd}(**GS'**) = –0.148 e^-) because the metal is reduced during the reductive elimination process. Therefore, we considered that the stabilizing interactions in the transition state revealed by IGMH analysis might result from electron donation from orbitals on the Pd center into vacant orbitals of the electron-poor phenyl ring of the aryldifluoromethyl fragment. Indeed, the second-order perturbations in the Natural Bond Orbital analysis[22] of the transition state revealed the donor–acceptor interactions from the Pd *d* orbitals into a localized phenyl π^* orbital. Consistent with a more electron-rich metal center in **TS** than in **GS'**, the $d_{Pd} \rightarrow \pi^*$ interactions were significantly stronger in **TS** than in **GS'**. To measure the energy difference resulting from these stabilizing interactions, the Fock matrix elements corresponding to the $d_{Pd} \rightarrow \pi^*$ interaction of both **TS** and **GS'** were set to zero artificially using the NBO $DEL keyword list. Subsequent recalculation of the electronic energy of **TS** led to an increase of 8.7 kcal/mol ($\Delta G^{*\ddagger}$ = 26.0 kcal/mol).[23] In comparison, deleting these interactions in **GS'** led to an increase of only 2.8 kcal/mol (ΔG* = 5.1 kcal/mol), demonstrating that the $d_{Pd} \rightarrow \pi^*$ interaction is more stabilizing in the transition state than in the ground state. Thus, an η^3-binding mode in the transition state for reductive elimination enabled by the π-system in the aryldifluoromethyl group facilitates the C–C bond-forming step.

Scope of Aryl Halides in the Aryldifluoromethylation Reaction

The scope of our Pd-catalyzed aryldifluoromethylation with a series of aryl and heteroaryl halides is summarized in Table 2.[24] Reactions with $TMSCF_2Ph$ **2a** under the standard conditions afforded the corresponding diaryl difluoromethanes from bromobenzene (**3c**) and aryl bromides bearing electron-donating substituents (**3d**–**g**) in high yields. Reactions of **2a** with a series of electron-deficient aryl bromides bearing trifluoromethoxy, fluoro, chloro, amide, and sulfonamide groups also underwent the reaction to provide **3h**–**l**. Reaction of **1j** containing bromide and chloride occurred in good yield at the bromide, when **2a** was used as a limiting reagent to prevent a second aryldifluoromethylation at the aryl chloride. Aryl bromides containing acetal protecting groups furnished the corresponding products (**3m**–**o**) without suffering deprotection or side reactions. The reactions of aryl bromides containing *meta*- and *ortho*-substituents or extended π-systems also gave the products in high yields (**3p**–**z**). Several heteroaryl bromides were also converted to the corresponding diaryl difluoromethanes in good yields (**3aa**–**af**); however, electron-deficient bromopyridines and bromoquinolines lacking a 2-methoxy substituent did not undergo the reaction.[25] Finally, aryl chlorides underwent the coupling process to give the products in yields that were comparable to those of the corresponding bromides (**3a**–**b**, **3h**–**i**, **3r**, **3y**, and **3ae**).

The Pd-catalyzed aryldifluoromethylation was conducted with **1k** both on a gram scale and without a glovebox. Both processes, with small modifications provided **3k** in yields comparable to those under the standard conditions. For the reactions on a gram scale, it was important to ensure that adequate stirring of the CsF occurred, and for the reaction without a glovebox, **L16**·HBF_4 was used with $[Pd(allyl)Cl]_2$ as precursor to generate the active catalyst *in situ*.[26]

Evaluation of the side products of the catalytic aryldifluoromethylation revealed the formation of minor species containing a trimethylsilyl substituent on the arene (Scheme 1).[27] We considered that an activated silicate derived from **2a** and CsF could be sufficiently basic to deprotonate some aryl halides, and the resulting aryl anion could capture the trimethylsilyl group of **2a**. This overall deprotonative silylation reaction of aryl halides would lead to a silylarene under the reaction conditions.[28] Aryl and heteroaryl halides containing relatively acidic aryl C–H bonds underwent this process in combination with the catalytic process, resulting in varying amounts of trimethylsilyl-substituted aryl halides and diaryl difluoromethane side products.[29]

Changing the solvent from DME to cyclic ethers retarded this process. The deprotonative silylation of 2,4-difluorobiphenyl at the 3-position by the combination of $TMSCF_3$ and CsF in THF previously gave a lower yield of a silylarene than did that of the reaction in DME.[28b] Consistent with this literature, reactions of aryl halides in 1,4-dioxane solvent suppressed the deprotonative silylation and gave higher yields of products without just trace (**3k**) or no silylarene impurities (**3b**, **3h-i**, **3l**, **3r**, **3u**, and **3aa**–**af**).

Preparation of Aryldifluoromethyl Trimethylsilanes

Although the aryldifluoromethylation with $TMSCF_2Ph$ occurred with a wide range of aryl and heteroaryl halides, the scope in $TMSCF_2Ar$ was constrained by the limited availability of the silane reagents.[30] Prior work showed that 1,1-difluoroethylation of arylmagnesium reagents occurred with a cobalt-diamine catalyst.[31] Thus, we envisioned that a cobalt-catalyzed process could induce the coupling of $TMSCF_2Br$ with arylmagnesium reagents to prepare a range of $TMSCF_2Ar$ reagents for the coupling. Indeed, the Co-catalyzed reaction of phenylmagnesium bromide with $TMSCF_2Br$ gave aryldifluoromethyl silane **2a** in 81% yield. The active Co catalyst is prepared from cobalt(II) bromide, diamine ligand, and a sacrificial amount of phenylmagnesium bromide.[14]

Table 3 illustrates the scope of the Co-catalyzed (trimethylsilyl)difluoromethylation of arylmagnesium bromides. The reactions of electron-neutral and electron-rich 4-substituted phenylmagnesium bromides gave the corresponding $TMSCF_2Ar$ in moderate to high yields (**2a**–**d**). The arylmagnesium bromide containing an aldehyde protected as a diethyl acetal was converted to **2e** in high yield, and *meta*-substituted phenylmagnesium bromides furnished the products (**2f**–**h**). High yields from the reactions with more extended **π** systems, such as 1,1'-biphenyl and 2-naphthylmagnesium bromides (**2i**–**k**), were obtained, and a moderate yield of **2l** was observed.[32] At this point, the Co-catalyzed reactions with phenylmagnesium bromides bearing electron-deficient or *ortho*-substituents afforded the corresponding $TMSCF_2Ar$ in low yields or did not form the product.[25]

Scope of Aryldifluoromethyl Trimethylsilanes in the Aryldifluoromethylation Reaction

With a variety of $TMSCF_2Ar$ derivatives (**2a-c** and **2e-k**) in hand, we evaluated the reactivity of these silanes in the title coupling process (Table 4). $TMSCF_2Ar$ derivatives bearing electron-donating substituents on the aryl group gave the products in moderate to high yields, as long as higher loadings of Pd and **L16** or longer reaction times, or both, were used (**5a**–**c** and **5e**–**f**). A series of reactions with biphenyl- or naphthyl-substituted $TMSCF_2Ar$ reagents occurred in good yields to form **5g**–**i**, although the formation of **5h** required higher loadings of the catalyst and longer reaction time to achieve high yield. The reactions of $TMSCF_2Ar$ reagents containing 4-fluoro or 4-trifluoromethyl substituents also occurred in high yields (**5j**–**k**), and the reaction with a more sterically demanding substituent afforded **5l**, after an extended reaction time.

Synthetic Applications

To demonstrate the synthetic utility of the Pd-catalyzed aryldifluoromethylation, we used this reaction to synthesize a biologically active compound containing a difluoromethylene unit, as well as synthetic intermediates to a difluoromethylene analog of an existing bioactive diaryl ether (Scheme 2).[33] The leukotriene A_4 hydrolase inhibitor **6a** suppresses the production of leukotriene B_4 that causes inflammatory bowel disease and psoriasis.[3a] From the commercially available aryl bromide **1ag**, we synthesized **6a** in one step in 79% yield by our Pd-catalyzed aryldifluoromethylation; the previous route required three steps and gave only 15% overall yield from 4-hydroxybenzophenone (Scheme 2, top). Our coupling process also enabled the synthesis of previously unreported analogues **6b** and **6c** in a single step by varying the $TMSCF_2Ar$ coupling partner, thereby demonstrating the modularity afforded by this coupling process. We note that **6c** is a diaryl difluoromethane isostere of a diaryl ether that had been shown to be a more potent inhibitor.

We also prepared, by our method, a diaryl difluoromethane isostere of the diaryl ether fragment used to synthesize a series of pharmaceuticals that are Bruton’s tyrosine kinase (BTK) inhibitors. BTK participates in B-cell antigen receptor signaling that induces the proliferation of malignant B cells. Therefore, inhibitors of BTK are crucial for treating mantle cell lymphoma and chronic lymphocytic leukemia, and a series of molecules have been approved by the FDA that operate by this mechanism.[34] Benzoic acid **7** and pinacol boronate **8**, which are diaryl difluoromethane isosteres of the diaryl ether intermediates to the preparation of BTK inhibitors,[35–36] were prepared from products of our coupling reaction. Basic hydrolysis of product **3k** and palladium-catalyzed borylation of product **3j** formed **7** and **8**, respectively (Scheme 2, middle).[37–38]

Finally, our coupling reaction was used to prepare a difluoromethyl isostere of the diaryl ether intermediate to form Deltamethrin, which is a commercial pyrethroid ester insecticide used to control malaria.[39] As depicted in Scheme 2, we showed that aryl bromide **1ah** and **2a** coupled to form the diaryl difluoromethane, which was hydrolyzed at the acetal to give aldehyde **9a**. This aldehyde is a precursor to the cyanohydrin portion of the Deltamethrin bioisostere.[40] The synthesis of substituted analog **9b** with trifluoromethyl-substituted $TMSCF_2Ar$ **2m**, again, highlights the modularity of this method.

Conclusion

We have developed a direct, catalytic aryldifluoromethylation of aryl halides with $TMSCF_2Ar$ reagents and a palladium catalyst containing di-*tert*-butyl(2,4-dimethoxyphenyl)phosphine. The resting state of the catalyst containing this ligand is reactive toward the unusual α,α-difluorobenzyl silanes and resistant to side reactions that occur with more commonly used phosphines for cross-coupling; the arylpalladium aryldifluoromethyl complex formed by transmetallation from this silane undergoes reductive elimination with a low barrier, due to an accelerating π-interaction between Pd and the aryl ring of the difluoro-η^3-benzyl unit in the transition state. These features enable the title coupling reaction to form a wide range of diaryl difluoromethanes from broadly available aryl bromides and chlorides. The scope of this process was broadened further by the cobalt-catalyzed (trimethylsilyl)difluoromethylation of arylmagnesium bromides to access a suite of $TMSCF_2Ar$ reagents. Short, modular syntheses of pharmaceutically active compounds and a difluoromethyl analog of an agrochemical demonstrate the utility of this method. Studies toward additional, catalytic fluoroalkylation reactions of aryl halides are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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[24]. The reactions in Table 2 were conducted for 24 h instead of 12 h in Table 1, as reactions on larger scale took longer time than that of the reactions in 0.1 mmol scale, depending on the particle size of CsF and the size of the stir bar. See supporting information.

[25]. See supporting information for entries with unfruitful results.

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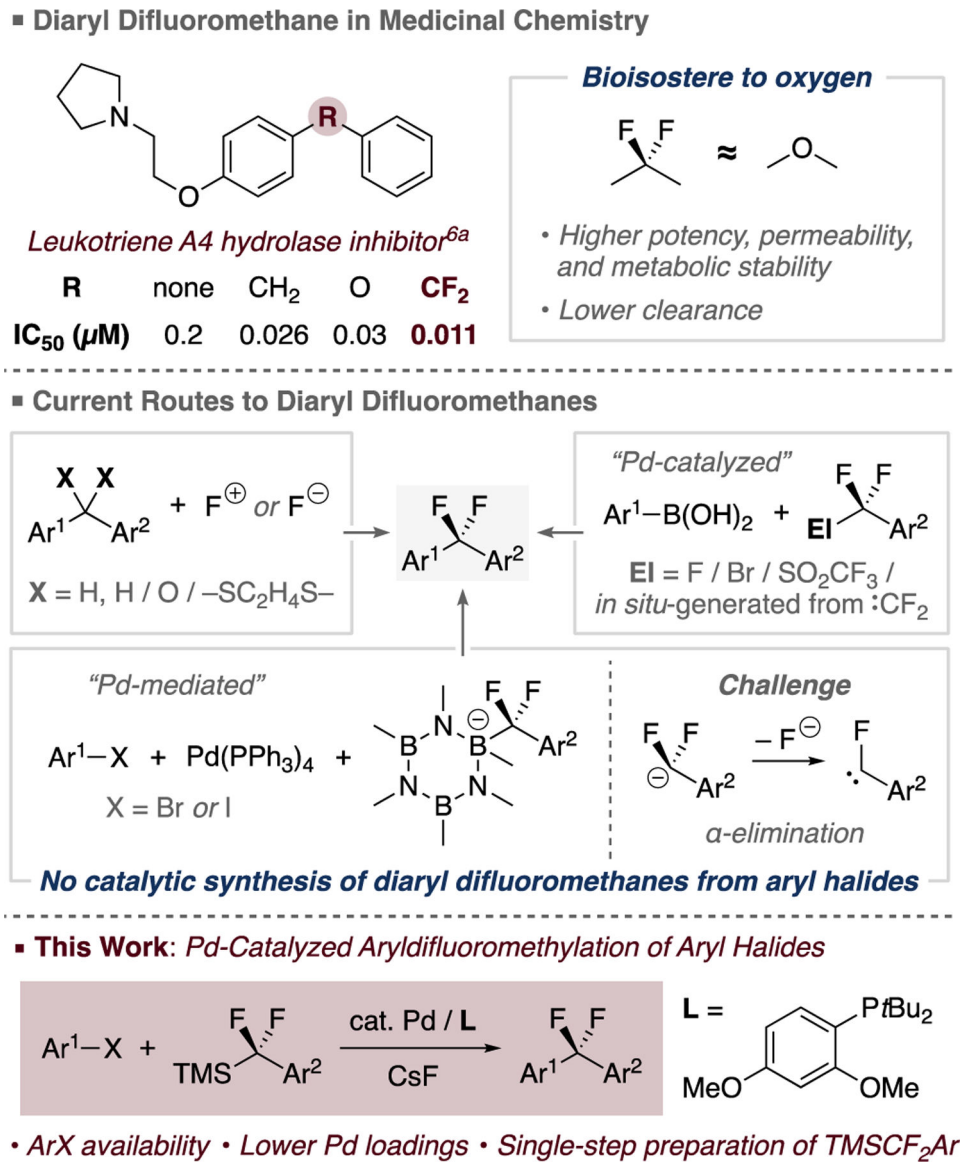


Figure 1.

Background and current work on diaryl difluoromethanes: Importance in medicinal chemistry (top), previous synthetic route (middle), and palladium-catalyzed aryldifluoromethylation of aryl halides (bottom).

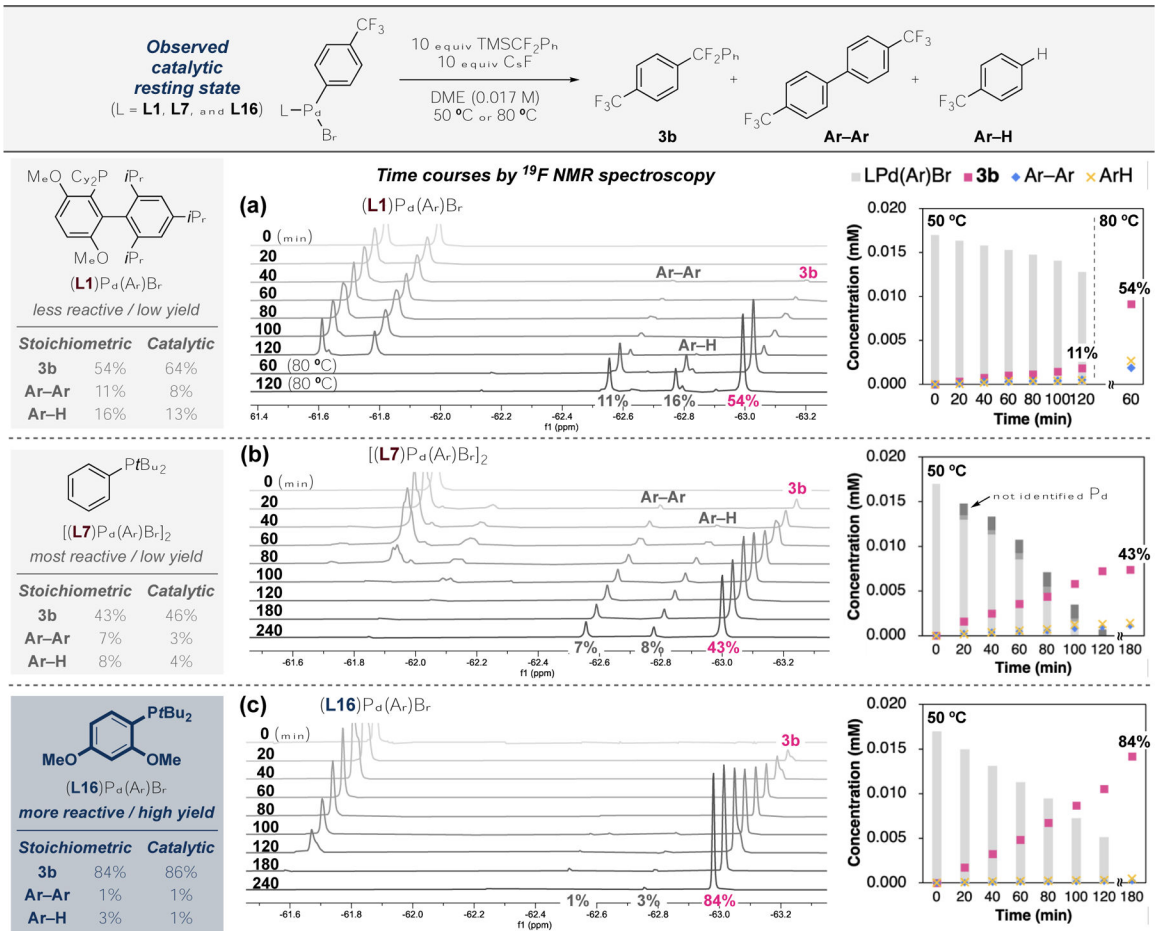


Figure 2.

Time course of reactions between an arylpalladium bromide complex, $TMSCF_2Ph$, and CsF monitored by ^{19}F NMR spectroscopy.

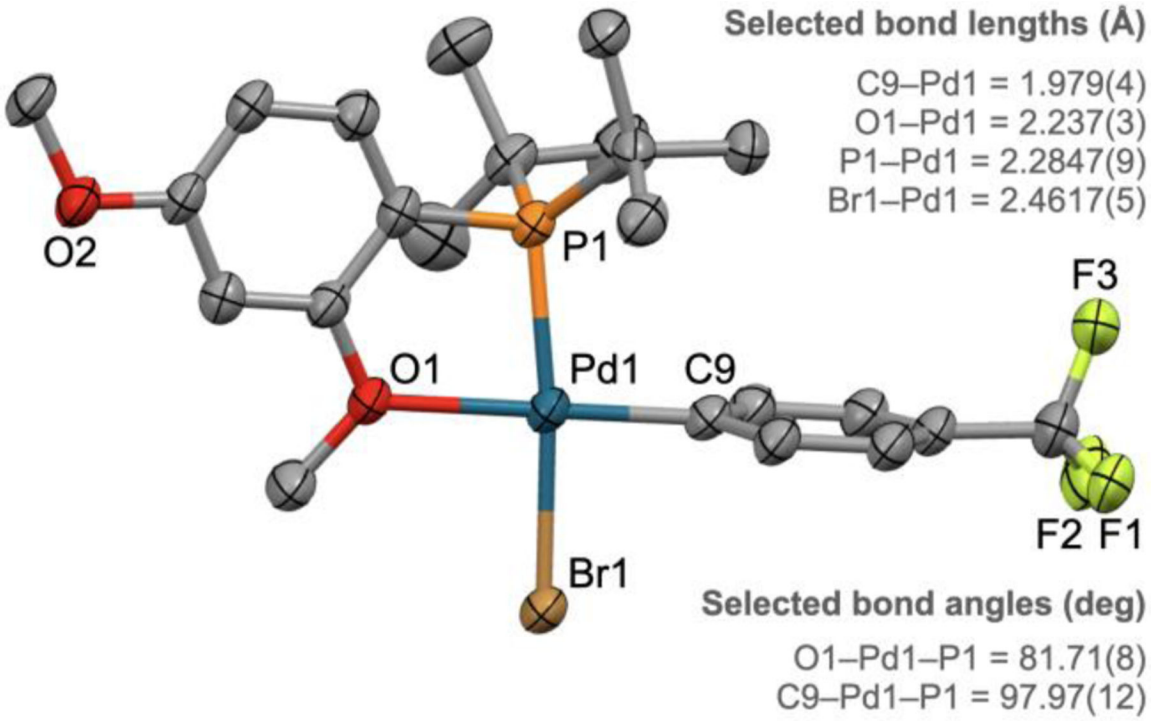


Figure 3.

Thermal ellipsoid plot of (**L16**)Pd(Ar)Br (Ar = C_6H_4–4-CF_3). Ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity.

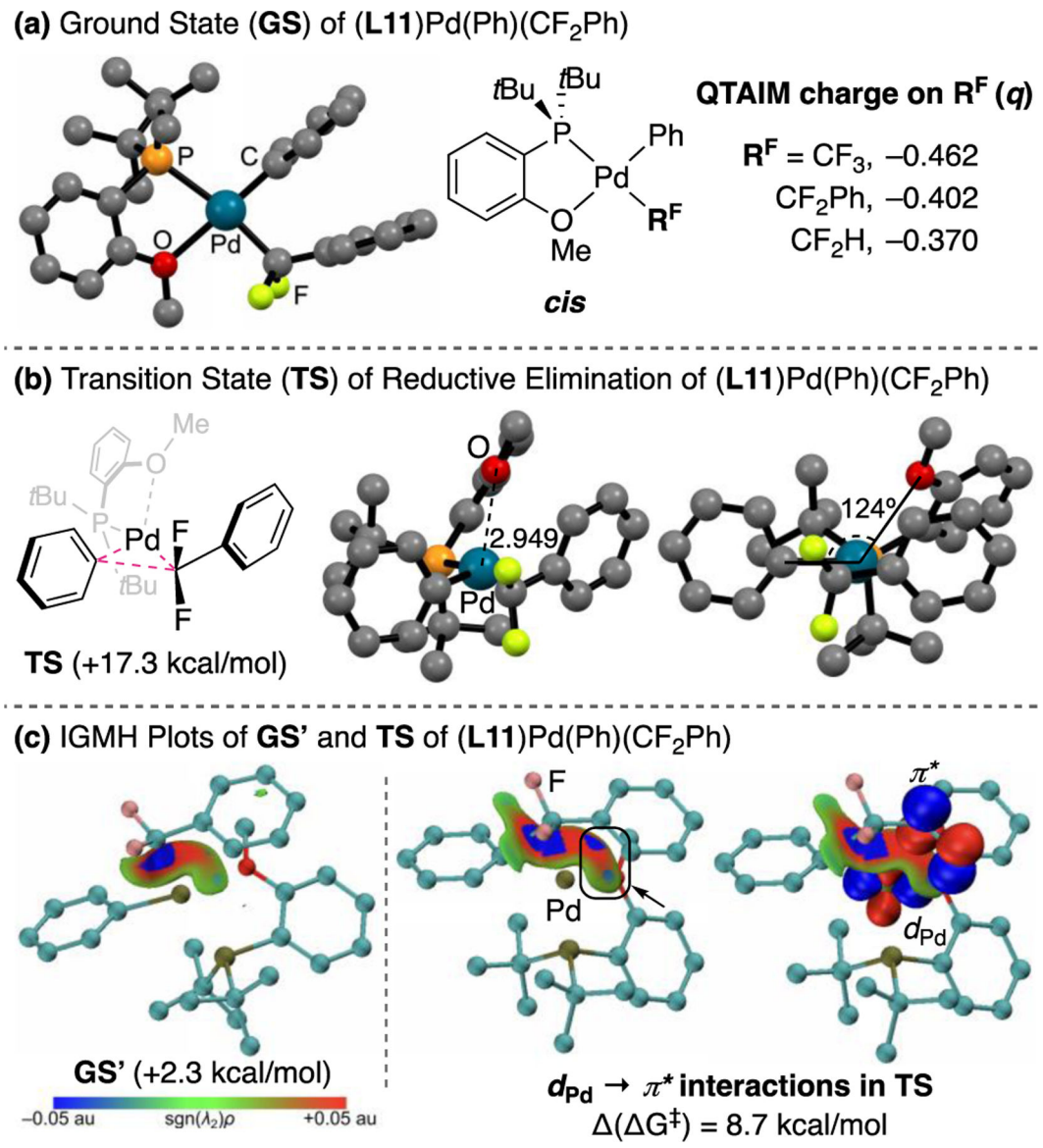
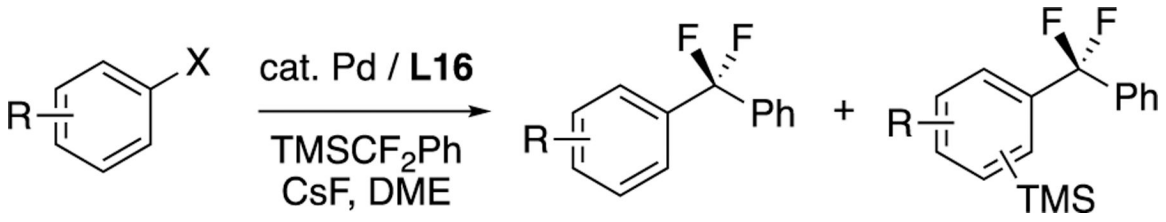
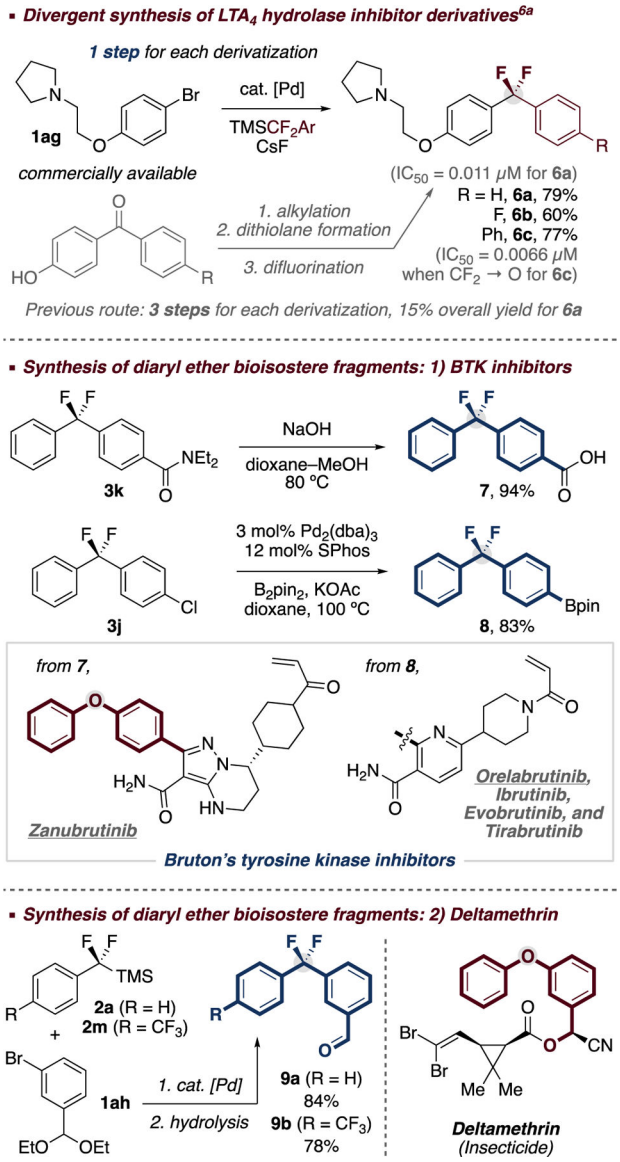


Figure 4.

Results of the computational studies on the reductive elimination from (**L11**)Pd(Ph)(CF_2Ph). Hydrogen atoms are omitted for clarity. (a) Calculated structure of the ground state and QTAIM atomic charges of fluoroalkyl fragments in corresponding ground states of palladium fluoroalkyl complexes; (b) Two views of the transition state for reductive elimination; (c) IGMH Plots of **GS'** (left), **TS** (center), and **TS** with the leading Natural Bond Orbitals responsible for the $d_{Pd} \rightarrow \pi^*$ interactions (right).



Scheme 1.
Formation of silylated side products by the deprotonative silylation.

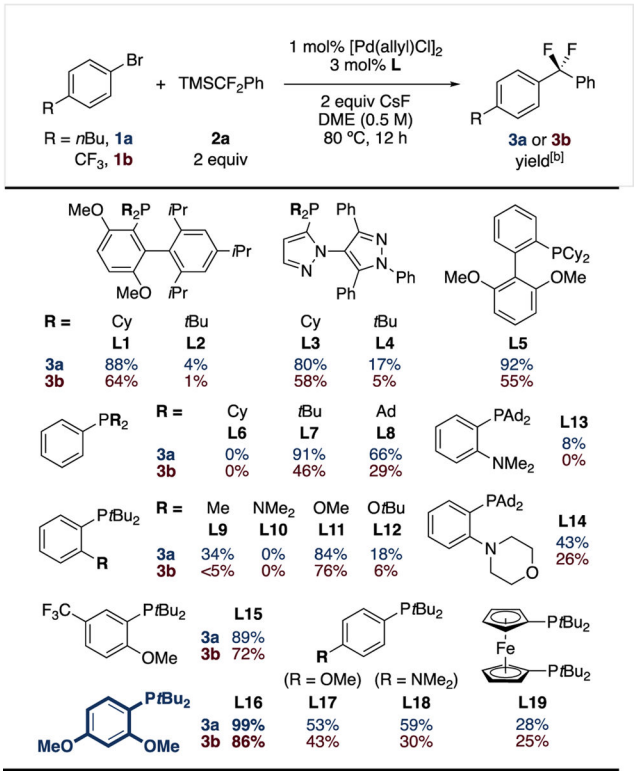


Scheme 2.

Applications to the synthesis of biologically relevant diaryl difluoromethanes

Table 1.

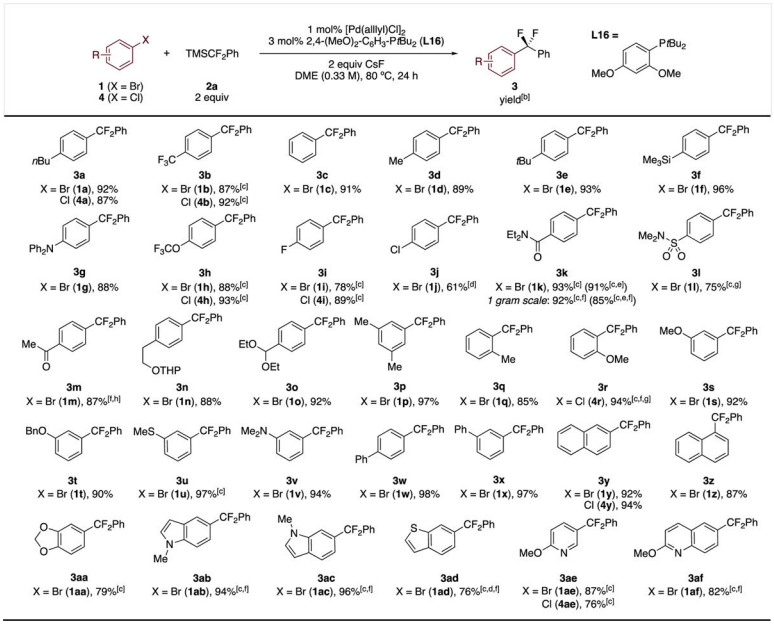
Evaluation of phosphine ligands for the Pd-catalyzed aryldifluoromethylation of aryl bromides[a]



[a]Rection conditions: **1a** or **1b** (0.10 mmol), **2a** (0.20 mmol), $[Pd(allyl)Cl]_2$ (0.001 mmol), **L** (0.003 mmol), and CsF (0.20 mmol) in DME (200 μl) at 80 °C for 12 h. [b] Yields were determined by ^{19}F NMR spectroscopy with 4,4-difluorobenzophenone as an internal standard.

Table 2.

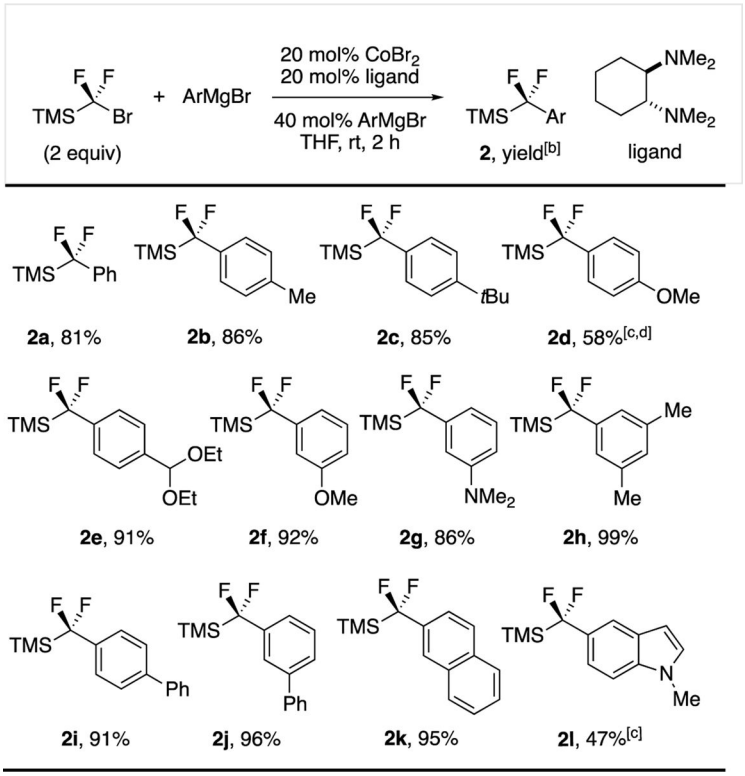
Scope of the aryldifluoromethylation with aryl halides[a]



[a]Reaction conditions: **1** or **4** (0.20 mmol), **2a** (0.40 mmol), $[Pd(allyl)Cl]_2$ (0.002 mmol), **L16** (0.0060 mmol), and CsF (0.40 mmol) in DME (600 μl) at 80 ºC for 24 h. [b] Isolated yields. [c] Dioxane was used instead of DME. [d] **1** (0.40 mmol) and **2a** (0.20 mmol) were used. [e] Isolated yield of the reaction performed without the glovebox. **L16**·HBF_4 was used instead of **L16**. [f] Reactions for 48 h. [g] $[Pd(allyl)Cl]_2$ (0.0050 mmol) and **L16** (0.015 mmol) were used. [h] 1-Bromo-4-(1,1-diethoxyethyl)benzene was used.

Table 3.

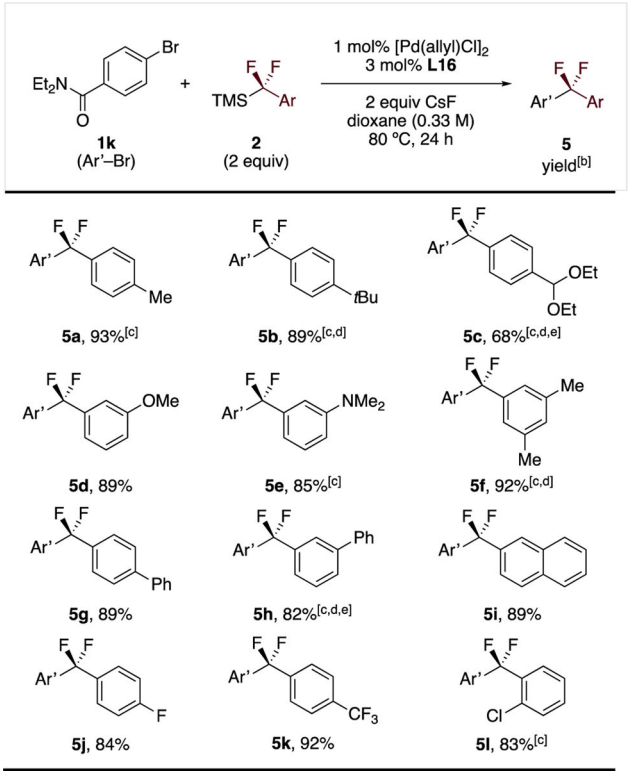
Scope of Co-catalyzed (trimethylsilyl)difluoromethylation[a]



[a]Reaction conditions: $TMSCF_2Br$ (1.0 mmol), ArMgBr (0.20+0.50 mmol), $CoBr_2$ (0.10 mmol), and ligand (0.10 mmol) in THF (4.0 ml) at room temperature for 2 h. [b] Isolated yields. [c] Yields were determined by ^{19}F NMR spectroscopy with benzotrifluoride as an internal standard. [d] Slow addition of $TMSCF_2Br$ and ArMgBr for 4 h.

Table 4.

Scope of aryldifluoromethylation with $TMSCF_2Ar$[a]



[a]Reaction conditions: **1k** (0.20 mmol), **2** (0.40 mmol), $[Pd(allyl)Cl]_2$ (0.002 mmol), **L16** (0.0060 mmol), and CsF (0.40 mmol) in dioxane (600 μl) at 80 °C for 24 h. [b] Isolated yields. [c] $[Pd(allyl)Cl]_2$ (0.0040 mmol) and **L16** (0.012 mmol) were used. [d] Reactions for 48 h. [e] 3 equiv **2** and CsF were used.