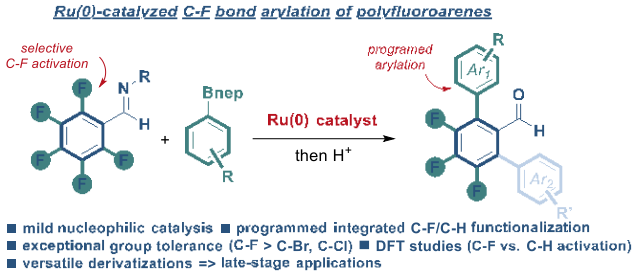
Ruthenium-Catalyzed C–F Bond Arylation of Polyfluoroarenes: Polyfluorinated Biaryls by Integrated C–F/C–H Functionalization

Jin Zhang,*,† Jiale Liu,† Xiaogang Wang,† Xinkan Yang,† Yangmin Ma,† Ran Fang,*,† Qun Zhao,*,‡ and Michal Szostak*,‡

†*College of Chemistry and Chemical Engineering, Key Laboratory of Chemical Additives for China National Light Industry, Shaanxi University of Science and Technology, Xi'an 710021, China*

‡*Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States*

Supporting Information



ABSTRACT: Fluorine containing molecules are central motifs in pharmaceuticals, agrochemicals and functional materials owing to the unique properties engendered by carbon–fluorine bonds. However, the chemoselective synthesis of multifluorinated biaryls, a motif extensively exploited in drug discovery, is challenging because of the difficulty in controlling selective fluorination. Herein, we report a site-selective arylation of C–F bonds in polyfluoroarenes enabled by a ruthenium catalyst system. The present C–F bond arylation proceeds exclusively at the ortho-position of polyfluorinated arenes through ruthenium(0) chelation to a readily modifiable directing group. A variety of broadly available polyfluoroarenes and organoboranes are applicable to this C–F bond functionalization, furnishing polyfluorinated biaryls featuring readily removable aldehyde functional handle. Notably, the present conditions enable a programmed synthesis of multifluorinated biaryls by integrated C–F/C–H functionalization by the same ruthenium catalyst. This approach is characterized by broad scope and functional group tolerance to build complex multifluorinated biaryls. The synthetic utility of this approach is highlighted by the synthesis of polyfluorinated ligands, heterocycles, pharmaceuticals and porphyrin analogues. DFT studies provide insight into the key selectivity of C–F bond activation. We fully expect that this approach will facilitate the implementation of C–F defluorination in the synthesis of polyfluorinated molecules utilizing molecules with high fluorine content.

KEYWORDS: C–F activation, ruthenium, polyfluoroarenes, arylation, DFT studies

Introduction

The unique properties of carbon–fluorine bonds render them critical in pharmaceuticals, agrochemicals and functional materials.[1] In particular, the incorporation of fluorine in drugs has a large impact on many of the essential chemical, physical and biological properties, such as adsorption, distribution and metabolism.[2] At present, >300 fluorinated pharmaceuticals have been developed, with blockbusters *Lipitor*, *Prozac* and *Januvia* (Figure 1A).[3] A major proportion of the fluorinated drug candidates feature aromatic C(sp^2)–F bonds. Despite significant efforts expanding the access to carbon–fluorine bonds, it is widely accepted that a significantly broader applicability of fluorinated molecules in drug discovery and development is limited only by the lack of synthetic access to fluorinated compounds.[4]

In general, the selective activation of C–F bonds represents a formidable challenge due to the strong dissociation energy of C–F bonds (Figure 1B).[5] The strength of C–F bonds makes them desirable to extend me tabolic stability and is responsible for the long lifetime of C–F bonds in the environment. Conversely, direct oxidative addition of C–F bonds to transition-metals requires highly reactive metals that render the process less selective.[6] Thus, the development of chemoselective C–F bond activation methods with less nucleophilic metals remains a major challenge that has prevented the area of C–F activation from broad applicability for the development of new pharmaceutical agents.

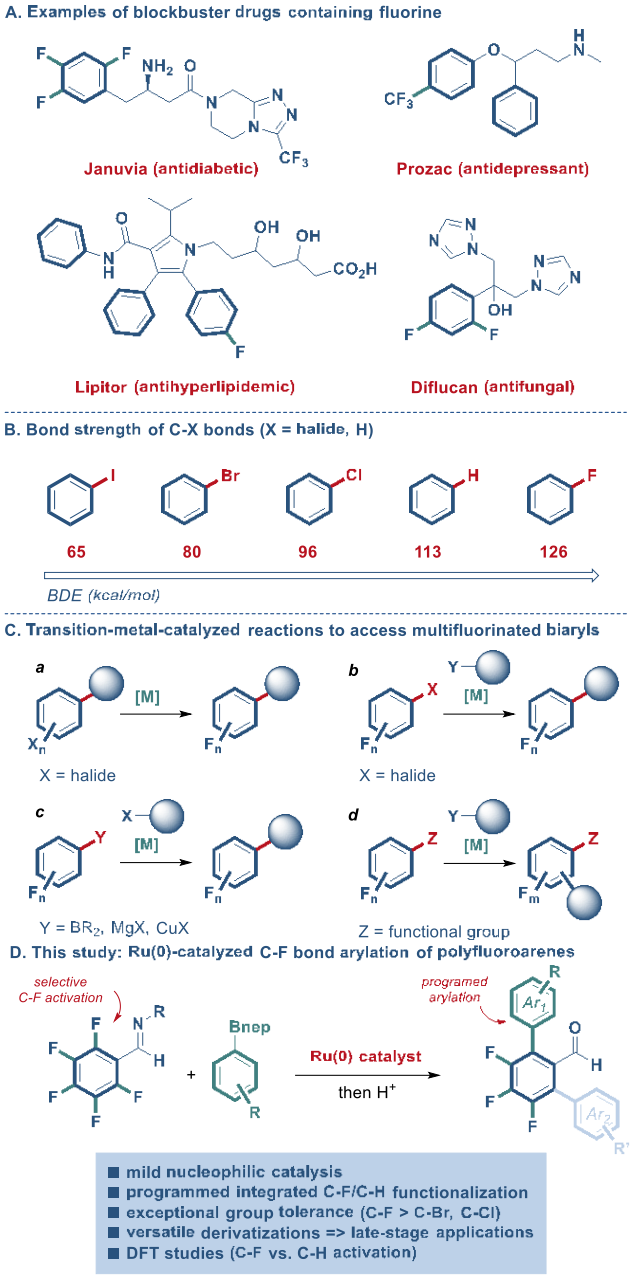


Figure 1. Context of the present work. (A) Examples of blockbuster drugs containing fluorine; (B) Bond strength of C-X bonds (X = halide, H); (C) Transition-metal-catalyzed reactions to access multifluorinated biaryls; (D) Present study: Ru(0)-catalyzed C-F bond arylation of polyfluoroarenes.

The synthesis of multifluorinated biaryls, a motif extensively exploited in drug discovery, by direct C–H or C–X fluorination is hampered by the in site-selective fluorination and the access to prefunctionalized precursors. Further, electrophilic and nucleophilic fluorination methods are limited by the lack of generality and practicality (Figure 1C).[7] In contrast, the availability of polyfluorinated arenes by exhaustive fluorination methods makes them uniquely suited for C–F bond functionalization to access mutifluorinated molecules.[8] The cleavage of C–F bonds in polyfluoroarenes is significantly more challenging than that of other aryl halides (I, Br, Cl) or equivalents (OTf). In this context, the C–H bond in polyfluoroarenes is typically weaker than the C–F bond, and the preference for selectivity in activation is heavily guided by the catalyst system.[9] The use of directing groups is an attractive method to overcome the notoriously slow oxidative addition of the C–F bond to a transition metal.[10] The feasibility of directing groups to coordinate to a metal is further desirable due to promoting the reactivity at the less reactive C–F bond with the activation selectivity opposite to SNAr and radical mechanisms. Chemo- and regioselective C–F arylation methods for the synthesis of mutiarylated biaryls are of considerable interest. The C–F vs. C–H bond activation selectivity is a fundamental process due to kinetic and thermodynamic properties of inert bond activation.[4b,11] It should be noted that the C–F/C–H activation at transition metals is a complex process involving kinetic and thermodynamic factors as well as a significant contribution from the effect of adjacent functional groups.[4b,11b-c]

Herein, we report a site-selective arylation of C–F bonds in polyfluoroarenes enabled by a ruthenium catalyst system (Figure 1C). The present C–F bond arylation proceeds exclusively at the ortho-position of polyfluorinated arenes through ruthenium(0) chelation to a readily modifiable directing group. This approach is highlighted by (1) broad scope and functional group tolerance to build complex multifluorinated biaryls and terphenyls by exploiting mildly nucleophilic ruthenium(0) catalyst system[12b,13m,n] and (2) establishing a programmed access to integrated C–F/C–H functionalization by the same ruthenium catalyst system that is not available by other methods. We demonstrate the prospective utility of this approach in drug discovery research by the synthesis of polyfluorinated ligands, heterocycles, pharmaceuticals and porphyrin analogues. We present DFT studies that give fundamental insight into the selectivity of C–F bond activation and the implementation of C–F defluorination utilizing molecules with high fluorine content. Collectively, the present method significantly advances nucleophilic ruthenium(0) catalysis for C(sp^2)–F bond activation.

Notable features of our study include (1) catalyst system that is the mildest reported to date for C–F activation of fluoroarenes owing to the mild nucleophilic nature of Ru(0); (2) the resulting broad scope and functional group tolerance to build complex multifluorinated biaryls unaccessible by other methods; (3) the programmed synthesis of multifluorinated biaryls by integrated C–F/C–H functionalization by the same ruthenium catalyst system.

Our laboratory has been interested in ruthenium catalysis as a versatile catalysis manifold for activation of inert bonds.[12] Despite the impressive advances in electrophilic, radical and nucleophilic mechanisms in ruthenium catalysis,[13] the activation of C–F bonds remains a significant challenge owing to the high bond dissociation energy of the carbon-fluorine bonds. We considered an approach based on

the relatively low nucleophilicity of ruthenium in the absence of strongly nucleophilic ligands that could interfere with selective bond activation in polyfluorinated substrates.[14] We hypothesized that using readily removable imine directing group in combination with an exceedingly selective ruthenium carbonyl $Ru_3(CO)_{12}$ would provide a mild and functional group tolerant strategy to C(sp^2)–F activation. The key feature of this design is the use of simple polyfluorinated benzaldehydes that are readily available by fluorination methods, while the products are amenable for synthetic manipulations by exploiting the traceless aldehyde handle or nucleophilic ipso substitution at the –CHO formyl group. The catalyst coordination to an auxiliary ensures high chemoselectivity[15] in C–F bond activation in that weaker C–F bonds at the remote sites are not susceptible to oxidative addition, an unselective process that is plagued by using more nucleophilic metals.

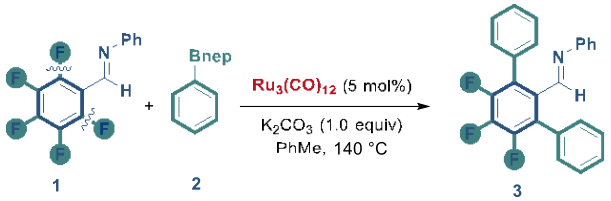
Results and Discussion

Reaction of perfluorinated benzaldehyde aldimine (**1**) was investigated as our model system (Table 1). After extensive optimization, we determined that the optimal results were obtained using N-Ph imine (**1**) as C–F functionalization substrate, neopentyl aryl boronate (**2**) as nucleophile in the presence of stoichiometric amount of K_2CO_3 (1 equiv) in toluene at 140 °C, providing the desired arylation product in 94% yield (Table 1, entry 1). Several optimization results are worth point out. Various imines were tested, and sterically non-demanding N-Ph imine is the preferred imine auxiliary with aliphatic imines leading to lower efficiency due to imine decomposition and bulky aromatic imines leading to lower conversions (Table 1, entries 2-5). Various catalysts were screened, and $Ru_3(CO)_{12}$ proved singularly effective, in agreement with our mechanistic design on chelation of ruthenium carbonyl to the imine auxiliary (Table 1, entries 6-15). Of note, related Ru(0) catalysts, such as $RuH_2(CO)(PPh_3)_3$ and $RuH_2(PPh_3)_4$ were completely ineffective (Table 1, entries 6-7) as were other Ru, Rh and Ni catalysts (Table 1, entries 8-15). Neopentyl boronate is the preferred nucleophile (Table 1, entries 16-18). Note that the use of pinacol boronate and boronic acid is also feasible (Table 1, entries 16-17), however the reaction is less efficient due to decomposition and slower transmetallation. The choice of temperature is a critical parameter in this C–F activation (Table 1, entries 19-20) with the reaction possible at 120 °C and lower temperatures resulting in incomplete conversions. Note that di-arylation product is observed as the only product at lower temperatures (di-F:mono-F >95:5), indicating coordination of the catalyst to the imine auxiliary after the first C–F activation. Optimal results are obtained using 2.5 equiv of the nucleophile (Table 1, entry 1). The reaction results in arylation of both C–F ortho-positions, indicating that the second C–F functionalization is faster than catalyst de-coordination (*vide infra*). In agreement with this finding, the use of 1.0 equiv of aryl boronate results in incomplete conversion with the di-arylation as the major product (di-F:mono-F = 87:13) (Table 1, entry 21).

A critical parameter is the use of base as minimal conversions are observed in its absence (Table 1, entry 22). Various bases were tested and K_2CO_3 proved to be the most effective (Table 1, entries 23-28). Interestingly, the base can be used in substoichiometric amount to significantly improve the yield (Table 1, entries 29-30). Hydrogen acceptors can be used in lieu of the base (Table 1, entries 30-31), however, these additives are less effective. The role of the base is not clear at this point; we hypothesize that the base might play a role in activating the catalyst to the active $Ru(CO)_4$ or act as a scavenger of residual fluoride. The main driving force for the C–F activation reaction is the formation of strong B–F bonds enabled by the efficient combination of ruthenium carbonyl and versatile auxiliary in the presence of the activator (*vide infra*). It should be noted that the catalyst coordinates to the imine auxiliary after the first C–F activation, which results in selective di-arylation. At present stage, the selective C–F bond modification through perfluorobenzaldehyde is not feasible due to decomposition under the reaction conditions.

With the optimized conditions in hand, we next investigated the capacity of this C–F activation protocol to deliver polyfluorinated biaryls (Scheme 1). As shown, a wide range of aryl organoboronates decorated with various sensitive functional groups is amenable to this reaction. It is of note that only ortho-C–F functionalization takes place, which is in contrast to radical or S_NAr protocols that result in unselective cleavage of remote C–F bonds. The reaction results in fluorinated meta-terphenyls that are important intermediates in drug discovery and functional materials owing to

Table 1. Optimization of reaction conditions[a]

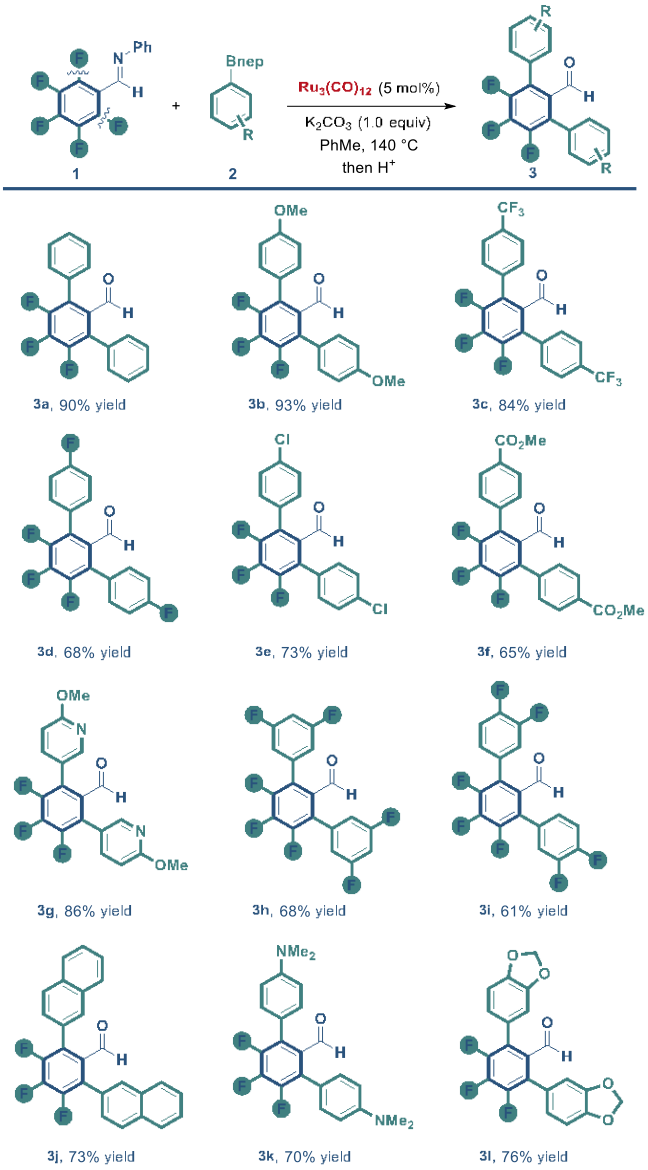


Entry	Variation from the standard conditions	Conversion[b] (%)	Yield[b] (%)
1	no change	>98	94
2	N-tBu instead of N-Ph	>98	83
3	N-Me instead of N-Ph	>98	69
4	N-Xy instead of N-Ph	>98	80
5	N-Dipp instead of N-Ph	73	60
6	$RuH_2(CO)(PPh_3)_3$	16	<5
7	$RuH_2(PPh_3)_4$	10	<5
8	$RuCl_3$	15	<5
9	$Ru(PPh_3)_2Cl_2$	32	<5
10	$[RuCl_2(p\text{-}cym)]_2$	15	<5
11	$[Ru(cod)Cl_2]_n$	18	<5
12	$[Cp^*RuCl_2]_n$	17	<5
13	$[RhCp^*Cl_2]_2$	18	<5
14[c]	$Ni(PPh_3)_2Cl_2$	39	<5

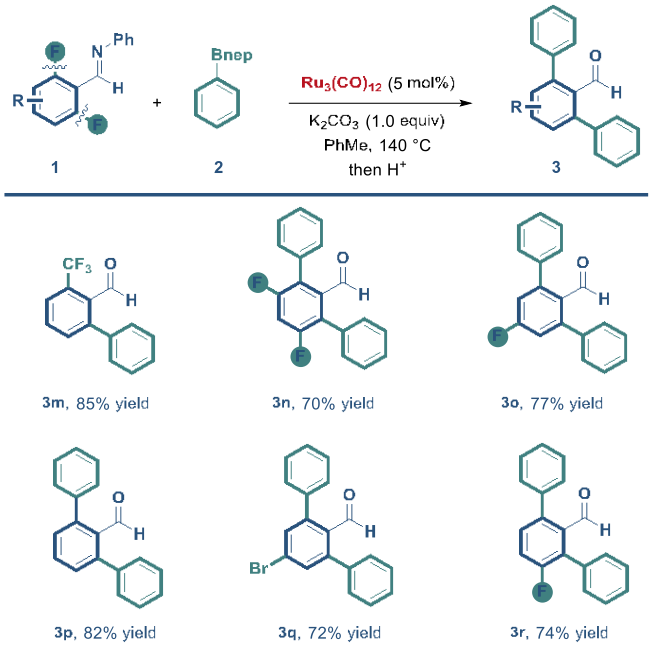
15[d]	$Ni(cod)_2$	85	<5
16	Ph-Bpin instead of Ph-Bnep	>98	72
17	Ph-$B(OH)_2$ instead of Ph-Bnep	>98	65
18[e]	Ph-$Si(OMe)_3$ instead of Ph-Bnep	85	<5
19	120 °C instead of 140 °C	>98	75
20	100 °C instead of 140 °C	41	13
21[f]	Ph-Bnep 1.0 equiv instead of 2.5 equiv	91	37
22	without K_2CO_3	>98	<10
23	$KHCO_3$ instead of K_2CO_3	>98	74
24	K_3PO_4 instead of K_2CO_3	>98	46
25	Na_2CO_3 instead of	>98	57
26	K_2CO_3	>98	65
27	$NaHCO_3$ instead of K_2CO_3	>98	5
28	Cs_2CO_3 instead of K_2CO_3	64	23
29	CsF instead of K_2CO_3	>98	70
30	K_2CO_3 0.5 equiv instead of 1.0 equiv	>98	58
31	K_2CO_3 0.1 equiv instead of 1.0 equiv	>98	65
32	acrylonitrile instead of K_2CO_3	>98	71
	norbornene instead of K_2CO_3		

[a]Conditions: imine (1.0 equiv), PhBnep (2.5 equiv), catalyst (5 mol%), additive (1 equiv), toluene (0.5 M), 140 °C, 20 h. [b]Determined by ^1H NMR and GC. [c]$Ni(PPh_3)_2Cl_2$ (10 mol%), K_2CO_3 (3 equiv). [d]$Ni(cod)_2$ (10 mol%), PCy_3 (40 mol%), NaF (2.5 equiv). [e]CsF (1.0 equiv) instead of K_2CO_3. [f]di-F:mono-F selectivity (87:13). Bnep = 5,5-dimethyl-1,3,2-dioxaborolane. See SI for details.

the properties of carbon–fluorine bonds. Electronically-diverse organoboronates are well compatible as demonstrated by the cross-coupling of neutral (**3a**), electron-rich (**3b**) and electron-deficient arenes (**3c**-**3d**). It is of note that benzylic defluorination of the CF_3 moiety is not observed, providing access to medicinally-relevant trifluoromethyl substitution. Furthermore, organoboronates with sensitive functional groups, such as chloride (**3e**) and ester (**3f**) underwent C-F bond functionalization in good yields, providing handles for further functionalization and distinguishing this protocol from more nucleophilic metals. Of note, all products contain aldehyde functional handle ready for ipso functionalization. Furthermore, heterocyclic aryl boronates are compatible as demonstrated by the cross-coupling of 3-pyridylboronate (**3g**), resulting in the synthesis of medicinally-relevant polyfluorinated pyridyl-terphenyls. Moreover, fluorinated boronates can be readily employed (**3h**-**3i**), providing access to differentially polyfluorinated terphenyls that would be challenging to prepare by other methods. Polyaromatic organoboronataes, such as naphthyl (**3j**), are competent substrates, generating conjugated polyfluorinated terphenyls that have found intensive applications in materials science. Finally, substitutions relevant in drug discovery, such as amino (**3k**) and dioxolane (**3l**), can also be used with high efficiency, establishing a pathway to polyfluorinated substitution patterns found in medicinal chemistry research.

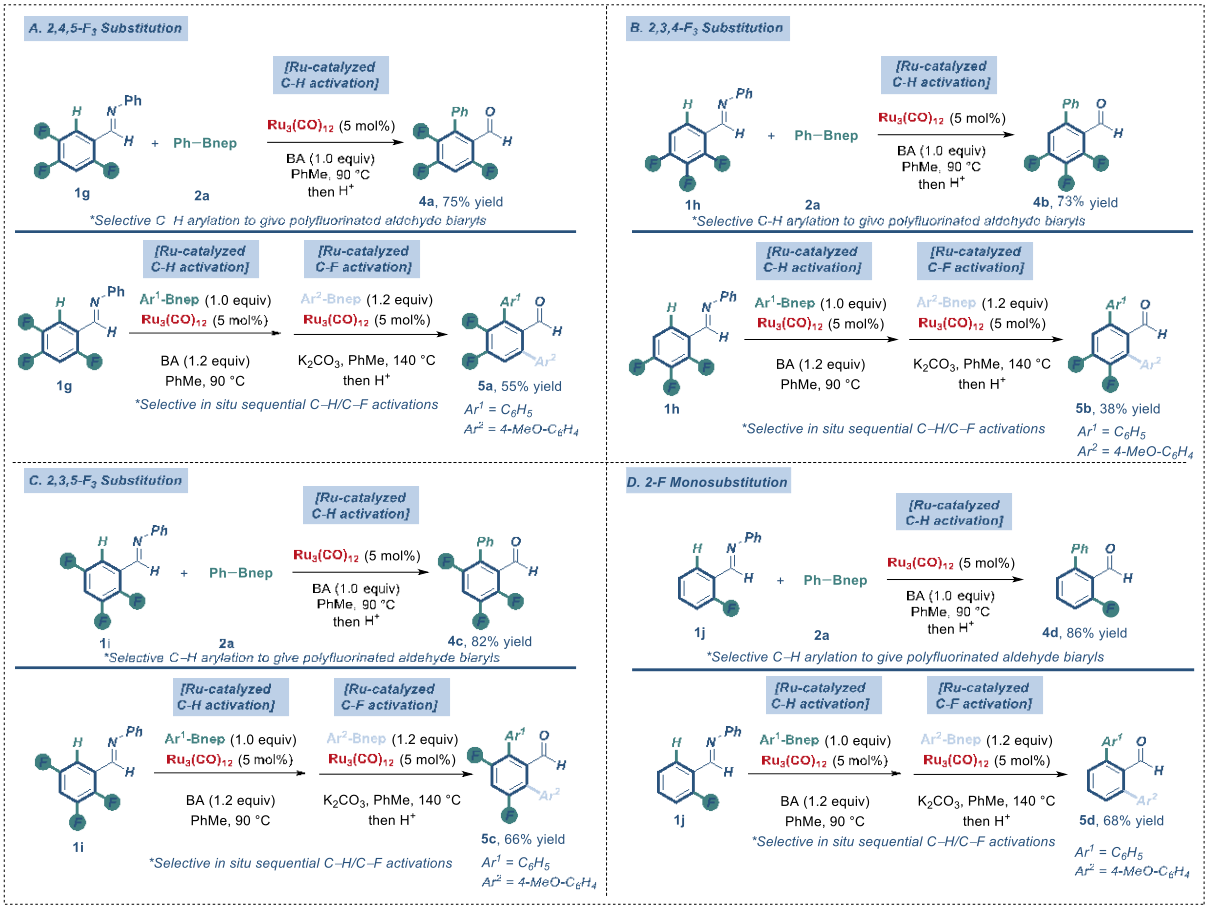


Scheme 1. Substrate scope with respect to the aryl organoboronates. Reaction conditions: Imine (1.0 equiv), Ph-Bnep (2.5 equiv), $Ru_3(CO)_{12}$ (5 mol%), K_2CO_3 (1.0 equiv), toluene (0.5 M), 140 °C, 20 h, then acidic work-up. Isolated yield.



Scheme 2. Substrate scope with respect to the polyfluoroarenes. Reaction conditions: Imine (1.0 equiv), Ph-Bnep (2.5 equiv), $Ru_3(CO)_{12}$ (5 mol%), K_2CO_3 (1.0 equiv), toluene (0.5 M), 140 °C, 20 h, then acidic work-up. Isolated yield.

Next, we investigated the C–F activation capacity of various polyfluorinated substrates (Scheme 2). Since it is established that the bond dissociation energy of the C–F bond in perfluorinated arenes is lower than in the substrates containing 3F, 2F and 1F (*vide infra*),[16] it was unclear at the outset if the mildly nucleophilic ruthenium(0) catalyst system would be capable of activating C–F bonds in unactivated polyfluorinated arenes. Pleasingly, we found that present catalyst system is general and can be used for C–F activation of even unactivated polyfluoroarenes. As such, the ortho-CF_3-substrate proved that mono- C–F activation is feasible in this system (**3m**), providing access to trifluoromethyl-biaryl aldehyde building block. Furthermore, C–F activation of tetra-fluoro-substituted (**3n**) and tri-fluoro-substituted (**3o**) arenes proceeded in good yields and with full selectivity for the ortho-C–F activation. In the extreme case, even the least activated in this series di-fluoro-benzaldehyde (**3p**) proved to be excellent substrate, demonstrating high reactivity of the ruthenium carbonyl catalyst system. We also used this screening to investigate functional group tolerance towards an aryl bromide (**3q**) and found that *the system promotes C–F cleavage in the presence of*



Scheme 3. The integrated C – F/C – H bond activations mediated by the same ruthenium carbonyl catalyst. (A) 2,4,5-F_3 substitution. (B) 2,3,4-F_3 substitution. (C) 2,3,5-F_3 substitution. (D) 2-F monosubstitution. BA = benzylideneacetone.

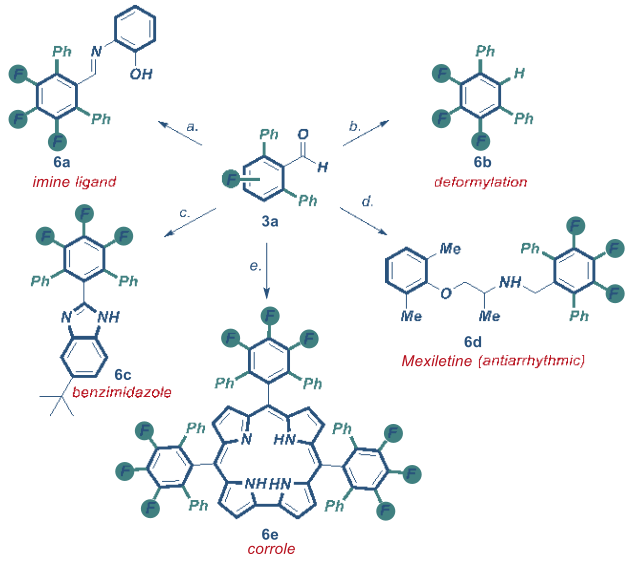
a much weaker C-Br bond. To our knowledge this is the first instance of selective C-F activation in the presence of arylbromides, reversing the traditional bond activation selectivity (Ph–Br, BDE = 80 kcal/mol; Ph–F, BDE = 126 kcal/mol) and demonstrating significant potential of ruthenium(0) catalysis in highly chemoselective C-F bond activation. Likewise, it was of interest to test the unsymmetrical tri-fluorinated arene (**3r**) since this substrate is poised for unselective defluorination via benzyne mechanism. Gratifyingly, full C-F activation selectivity for ortho-C-F bonds was observed, again showing high regioselectivity of this arylation.

The real power of this method is in the integrated C-F/C-H bond activations mediated by the same ruthenium carbonyl catalyst (Scheme 3). This unique reactivity is enabled by exploiting the differential energetics of C-H/C-F activation at Ru(0) merged with dehydrogenative C-H arylation under neutral conditions in the presence of benzylideneacetone as a mild Ru–H acceptor.[12g] The process provides expedient route to polyfluorinated terphenyls by single or two bond activation events. As shown in Scheme 3A (top), mono-C–H arylation of readily available 2,4,6-trifluoro-substituted arene can be accomplished with full C–H arylation selectivity to furnish multifluorinated biaryl (**4a**). As shown in Scheme 3A (bottom), this process can be combined in situ with C–F activation to deliver unsymmetrical polyfluorinated terphenyl (**5a**). *Of note, the reaction sequence exploits the same ruthenium carbonyl catalyst by the use of olefin acceptor and base for C–H and C–F activation, respectively.* This integrated C–F/C–H activation can be extended to other substitution patterns of polyfluorinated arenes, such as 2,3,4-tri- substitution (**4a–5a**) and 2,3,5-tri-substitution (**4b–5b**), providing polyfluorinated terphenyls that have important applications in electronics and materials science. Finally, even the least activated mono-substitution (**4c–4d**) is amenable to this integrated C–F/C–H functionalization process, attesting to the high reactivity and exquisite chemoselectivity of the ruthenium carbonyl system.

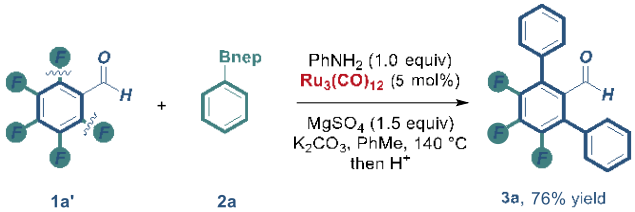
To demonstrate the prospective utility of this C–F activation protocol, we showed that this process is applicable to the synthesis of polyfluorinated ligands, heterocycles, pharmaceuticals and porphyrin analogues (Scheme 4). Thus, subjecting the polyfluorinated terphenyl (**3a**) to a standard condensation protocol with 2-aminophenol delivered fluorinated imino ligand (**6a**). The aldehyde functional handle can be readily removed by de-formylation using $[Ir(cod)Cl]_2/PPh_3$ (**6b**), serving as a traceless directing group. Furthermore, the aldehyde functional handle is a valuable precursor for the synthesis of medicinally-privileged heterocycles, such as 2-arylbenzimidazoles (**6c**). Most importantly, the C–F activation products can be exploited in the direct conjugation with pharmaceuticals owing to the presence of the aldehyde moiety as demonstrated in the condensation with an antiarrhythmic drug, *Mexiletine* (**6d**). Finally, fluorinated porphyrins have received considerable interest as biomimetic enzyme analogues. We were pleased that the polyfluorinated terphenyls can be applied to the synthesis of fluorinated corroles (**6e**), which have been used in oxygen-rebound pathway.[17] The presented examples highlight the potential impact of this ruthenium(0)-catalyzed C–F activation in medicinal chemistry research.

Another advantage of using imine auxiliary in ruthenium(0) catalysis is facile installation and compatibility with the reaction conditions, which permits to perform the $C(sp^2)$–F activation directly from the carbonyl group by in situ imine synthesis (Scheme 5).

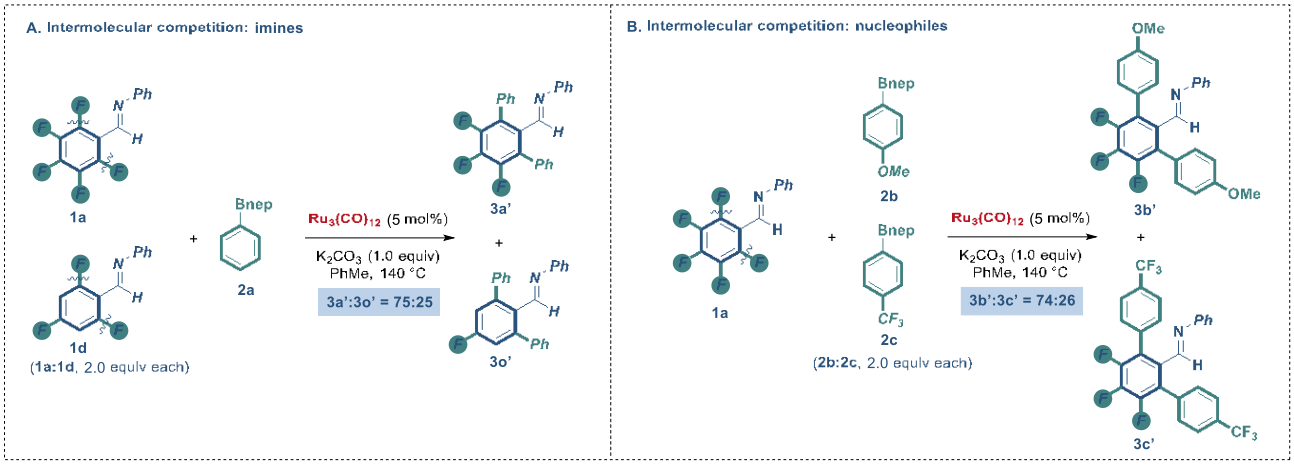
We conducted intermolecular competition studies between differently substituted arenes to gain insight into the relative reactivity of the C–F bonds and organoboronates (Scheme 6). As shown, electron-deficient fluorinated arenes are inherently more reactive (Scheme 6A; 2,3,4,5,6-F_5:2,4,6-F_3 = 75:25), consistent with the relative strength of the C–F bonds. Furthermore, electron-rich nucleophiles are more reactive (Scheme 6B, 4-MeO:4-CF_3 = 74:26), consistent with transmetallation between Ar–Ru–F and Ar–Bnep as a kinetically relevant step (*vide infra*).



Scheme 4. Synthetic transformations. Reagents and conditions: (a) 2-aminophenol, PhMe, 140 °C, 15 h, 80%; (b) $[Ir(cod)Cl]_2$, PPh_3, dioxane, 140 °C, 36 h, 61%; (c) 4-(tert-butyl)benzene-1,2-diamine, DMA, 100 °C, 18 h, 71%; (d) Mexiletine Hydrochloride, EtOH, triethylamine, sodium cyanoborohydride, methanol, tetrahydrofuran, 78 °C, 41 h, 55%; (e) pyrrole, trifluoroacetic acid, triethylamine, DDQ, THF, DCM, rt, 8 h, 11.5%.



Scheme 5. Ru(0)-catalyzed in situ C-F activation.



Scheme 6. Selectivity studies. (A) Intermolecular competition: imines. (B) Intermolecular competition: nucleophiles.

In consideration of the high efficiency of this C–F activation process, DFT studies were conducted to provide into the reaction mechanism and selectivity of C–F bond activation utilizing molecules with high fluorine content.

The computational free energy profiles for the **Re1** (2,3,4,5,6-F_5 substituted imine) and **Re3** (2,3,4,5-F_4 substituted imine) are displayed in Figure 2 and Figure 3. According to our calculation results, the first step involves the coordination of **Re1** to Ru center, generating **INT1**; this step is endergonic by 10.8 kcal/mol. Subsequent C-F activation of **INT1** occurs via a transition state **TS1** with a free energy barrier of 12.3 kcal/mol to give **INT2**, with a free energy re- of -25.1 kcal/mol. After the formation of **INT2**, the re- between **INT2** and **Re2** (neopentyl aryl boronate) via **TS2**, the corresponding intermediate **INT3**. of activation for this step is 22.1 kcal/mol free reaction energy for **INT3** is -8.4 kcal/mol relatively to **INT2**. Subsequently, there is a migration of Ph to form **INT4**. This step is exergonic by -1.7 kcal/mol, and the free energy barrier is 16.7 kcal/mol. The step for C-F activation is the rate-determining step for the whole reaction, and the free energy barrier is 23.1 kcal/mol.[18] Overall, the step for C-F activation is the rate-determining step for the whole reaction. Based on the work of Macgregor and Braun at Rh,[19] C–F bond breaking preceding interaction with the boronate ester was also calculated. However, the boronate ester was used as reactant in our work rather than a ligand. Due to the steric hindrance, we haven't located this transition state despite many attempts. Furthermore, it should be noted that the computations assume formation of $Ru(CO)_4$ as the crucial intermediate. The energy required to form $Ru(CO)_4$ was calculated, and the ΔG from 1/3 $Ru_3(CO)_{12}$ to $Ru(CO)_4$ is 4.5 kcal/mol. $Ru(CO)_4$ was directly used in the recently work by Oble and Poli.[20]

Furthermore, the selectivity of C-H and C-F activation were also calculated in our work (Figure 3). The calculation results show that the activation energy of C-H activation (**TS1'**) is 14.2 kcal/mol lower than that of C-F activation (**TS1#**). These calculated results are in agreement with the experiments. Regarding the issue of ortho selectivity, the C-F activation at the para position has been calculated. It was found that the free energy of activation is 45.8 kcal/mol, which is much larger than the design of our calculations. Based on the work of Eisenstein and Chirik,[14,11b] the effect of replacement of the meta and para C–F bonds by hydrogen were also calculated in our revised manuscript. The free energies of activation were 23.1, 24.7, 25.3, 25.7, 28.6 kcal/mol for 5F, 4F, 3F, 2F and 1F, respectively. This indicates that replacement of the meta and para C-F bonds by hydrogen has a significant effect on the free energies of activation.

It is interesting to note that the activation energy in **TS1** (pentafluorinated substrate) is 23.1 kcal/mol, while in lease **TS1#** (tetrafluorinated substrate) is 24.7 kcal/mol. We have action compared the activation energy with substrates containing would give, 3F, 2F and 1F. The activation energy of 3F, 2F and 1F is 25.3, The free energy 25.7, 28.6 kcal/mol, respectively. As expected, the fewer flu-(Figure 2), while the orine atoms, the higher the activation energy.

Conclusions

In conclusion, we have developed a site-selective arylation of C–F bonds in polyfluoroarenes by ruthenium catalysis. This approach allows to access polyfluorinated biaryls. which are of significant interest in pharmaceuticals, agrochemicals and advanced materials owing to the unique properties of carbon–fluorine bonds. This C–F arylation method is particularly notable for its exceptional functional group tolerance not achievable by other methods and the capacity to be applied in a programmed access to integrated C–F/C–H functionalization by the same ruthenium catalyst. Mechanistically, DFT studies were conducted to provide insight into the C–F vs. C–H bond activation selectivity as a fundamental process in ruthenium(0) catalysis for the synthesis of polyfluorinated molecules utilizing molecules with high fluorine content. Considering the scarcity of methods for chemoselective C–F activation of readily available multifluorinated substrates, we fully expect that this approach will facilitate further advances in mildly nucleophilic catalysis in accessing diverse fluorinated chemical space. Studies to expand the scope of $Ru_3(CO)_{12}$-catalyzed C–X functionalizations, including photochemical initiation methods, are underway in our laboratories.

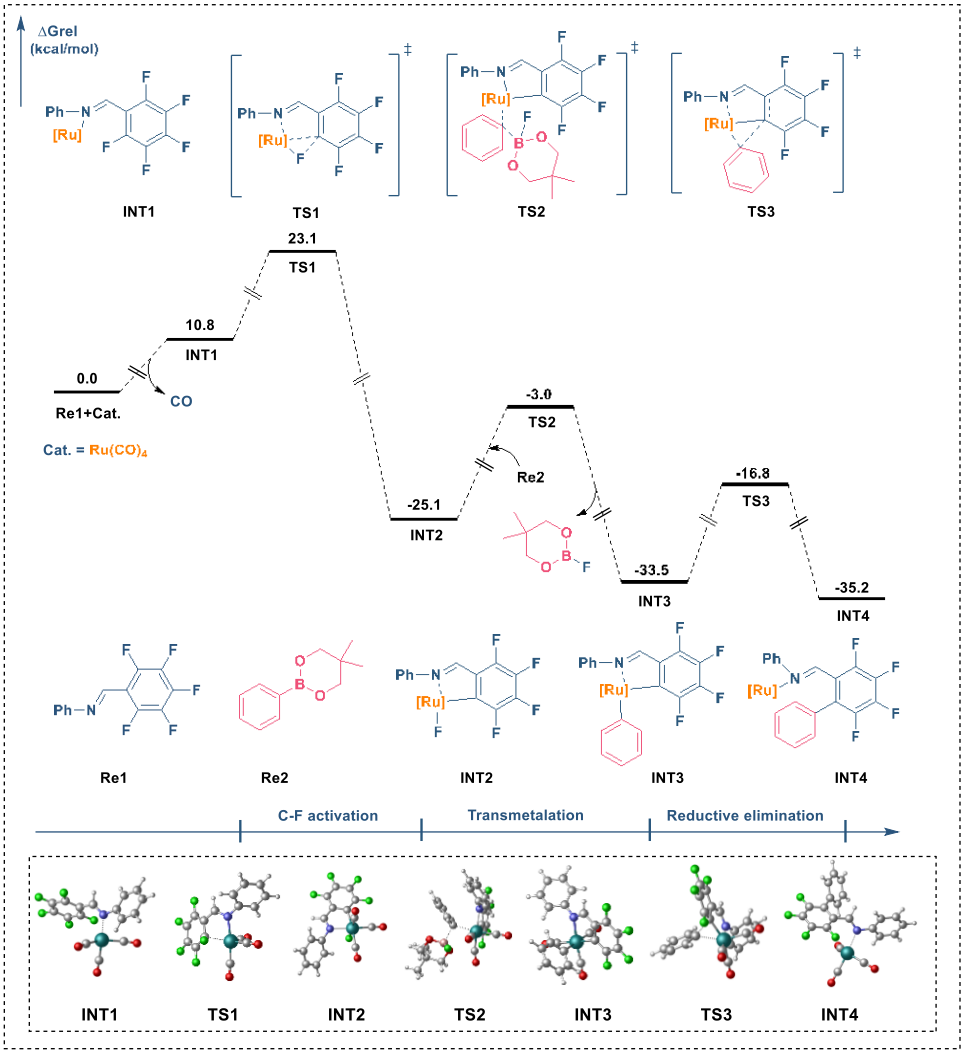


Figure 2. Free energy profiles for the Ru(0)-catalyzed C-F bond activation.

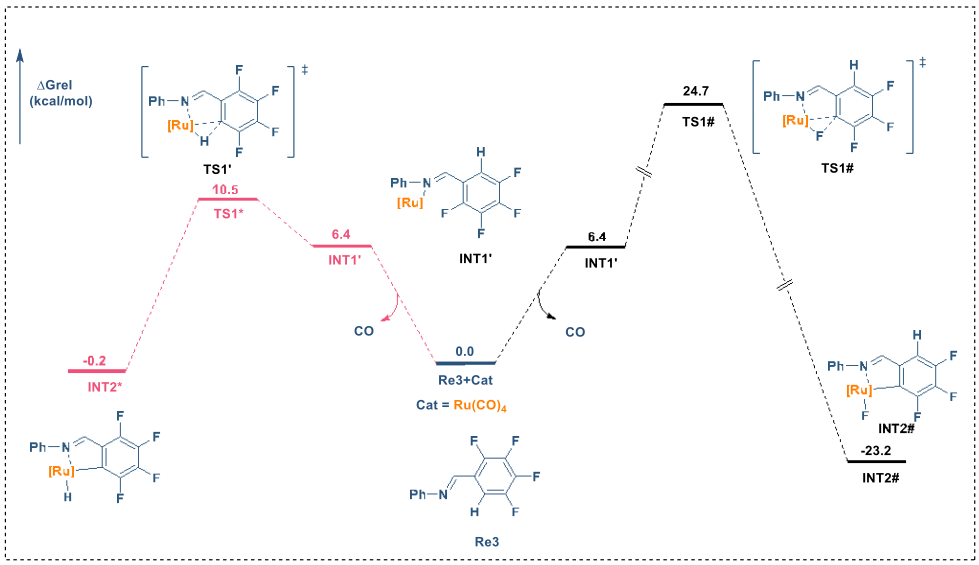


Figure 3. Free energy profiles for the selectivity of C-H and C-F activation.

AUTHOR INFORMATION

Corresponding Author

zhangjin@sust.edu.cn
fangr@lzu.edu.cn
qzhao23@jhu.edu
michal.szostak@rutgers.edu

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, computational details, coordinates and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

J.Z. thanks National Natural Science Foundation of China (No. 22179075) and Scientific Research Project of Shaanxi Province Education Department (No. 22JC018). X.Y. thanks Natural Science Basic Research Plan in Shaanxi Province of China (No. 2022JQ-126). R.F. thanks National Natural Science Foundation of China (No. 21672090). M.S. thanks Rutgers University and the NSF (CAREER CHE-1650766) for support.

REFERENCES

(1) (a) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J., Organic fluorine compounds: a great opportunity for enhanced materials properties. *Chem. Soc. Rev.* **2011,** *40*, 3496-3508. (b) Kirsch, P. *Modern Fluorooganic Chemistry: Synthesis,Reactivity, Applications*, 2nd Ed. (Wiley-VCH, Weinheim, 2013), 1-21. (c) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D., Modern Approaches for Asymmetric Construction of Carbon-Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018,** *118*, 3887-3964.

(2) (a) Mueller, K.; Faeh, C.; Diederich, F., Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007,** *317*, 1881-1886. (b) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H., Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001-2011). *Chem. Rev.* **2014,** *114*, 2432-2506. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015,** *58*, 8315-8359. (d) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A., Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **2018,** *10*, 383-394.

(3) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V., Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008,** *37*, 320-330. (b) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H., Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016,** *116*, 422-518.

(4) (a) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T., Functionalization of fluorinated molecules by transition-metal-mediated C-F bond activation to access fluorinated building blocks. *Chem Rev* **2015,** *115*, 931-972. (b) Eisenstein, O.; Milani, J.; Perutz, R. N., Selectivity of C-H Activation and Competition between C-H and C-F Bond Activation at Fluorocarbons. *Chem. Rev.* **2017,** *117*, 8710-8753. (c) C–F Bond Activation in Organic Synthesis Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119–2183. (d) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **2011**, *473*, 470–477. (e) Shen, Q.; Huang, Y. G.; Liu, C.; Xiao, J. C.; Chen, Q. Y.; Guo, Y. Review of recent advances in C-F bond activation of aliphatic fluorides. *J. Fluor. Chem.* **2015**, *179*, 4-22. (f) For additional reviews on C–F activation, see: refs. 10, 11 and 14.

(5) (a) Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies* (CRC Press, Boca Raton, FL, 2007), 211-217. (b) O'Hagan, D., Understanding organofluorine chemistry. An introduction to the C-F bond. *Chem. Soc. Rev.* **2008,** *37*, 308-319.

(6) (a) Fujita, T.; Fuchibe, K.; Ichikawa, J., Transition-Metal-Mediated and -Catalyzed C-F Bond Activation by Fluorine Elimination. *Angew. Chem., Int. Ed.* **2019,** *58*, 390-402. (b) Kang, Q.-K.; Lin, Y.; Li, Y.; Shi, H., Transition-Metal-Catalyzed Amination of Aryl Fluorides. *Synlett* **2020,** *31*, 1135-1139. (c) Fu, L.; Chen, Q.; Nishihara, Y., Recent Advances in Transition-metal-catalyzed C-C Bond Formation via C(sp^2)-F Bond Cleavage. *Chem. Rec.* **2021,** *21* (12), 3394-3410. (d) Liu, X.-W.; Echavarren, J.; Zarate, C.; Martin, R., Ni-Catalyzed Borylation of Aryl Fluorides via C-F Cleavage. *J. Am. Chem. Soc.* **2015,** *137*, 12470-12473. (e) Nohira, I.; Chatani, N., Nickel-Catalyzed Cross-Electrophile Coupling between C(sp^2)-F and C(sp^2)-Cl Bonds by the Reaction of ortho-Fluoro-Aromatic Amides with Aryl Chlorides. *ACS Catal.* **2021,** *11*, 4644-4649. (f) Ai, H.-J.; Ma, X.; Song, Q.; Wu, X.-F., C-F bond activation under transition-metal-free conditions. *Sci. China: Chem.* **2021,** *64*, 1630-1659.

(7) (a) Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T., Suzuki-Miyaura coupling reaction using pentafluorophenylboronic acid. *Org. Lett.* **2005,** *7*, 4915-4917. (b) Kinzel, T.; Zhang, Y.; Buchwald, S. L., A New Palladium Precatalyst Allows for the Fast Suzuki-Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids. *J. Am. Chem. Soc.* **2010,** *132*, 14073-14075. (c) Wei, Y.; Su, W., $Pd(OAc)_2$-Catalyzed Oxidative C-H/C-H Cross-Coupling of Electron-Deficient Polyfluoroarenes with Simple Arenes. *J. Am. Chem. Soc.* **2010,** *132*, 16377-16379. (d) Lentz, D.; Braun, T.; Kuehnel, M. F., Synthesis of Fluorinated Building Blocks by Transition-Metal-Mediated Hydrodefluorination Reactions. *Angew. Chem., Int. Ed.* **2013,** *52*, 3328-3348. (e) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A., N-Halosuccinimide/BF_3-H_2O, Efficient Electrophilic Halogenating Systems for Aromatics. *J. Am. Chem. Soc.* **2004,** *126*, 15770-15776. (f) Mueller, V.; Ghorai, D.; Capdevila, L.; Messinis, A. M.; Ribas, X.; Ackermann, L., C-F Activation for C(sp^2)-C(sp^3) Cross-Coupling by a Secondary Phosphine Oxide (SPO)-Nickel Complex. *Org. Lett.* **2020,** *22*, 7034-7040.

(8) (a) *Metal-Catalyzed Cross-Coupling Reactions and More*, de Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley: New York, 2014, 533-663. (b) Weaver, J.; Senaweera, S., C-F activation and functionalization of perfluoro- and polyfluoroarenes. *Tetrahedron* **2014,** *70*, 7413-7428. (c) Chen, Z.; He, C.-Y.; Yin, Z.; Chen, L.; He, Y.; Zhang, X., Palladium-Catalyzed Ortho-Selective C-F Activation of Polyfluoroarenes with Triethylsilane: A Facile Access to Partially Fluorinated Aromatics. *Angew. Chem., Int. Ed.* **2013,** *52*, 5813-5817. (d) Li, X.; Fu, B.; Zhang, Q.; Yuan, X.; Zhang, Q.; Xiong, T.; Zhang, Q., Copper-Catalyzed Defluorinative Hydroarylation of Alkenes with Polyfluoroarenes. *Angew. Chem., Int. Ed.* **2020,** *59*, 23056-23060.

(9) (a) Sun, A. D.; Love, J. A., Cross coupling reactions of polyfluoroarenes via C-F activation. *Dalton Trans.* **2010,** *39*, 10362-10374. (b) Wang, J.; Gao, H.; Shi, C.; Chen, G.; Tan, X.; Chen, X.; Xu, L.; Cai, X.; Huang, B.; Li, H., Recent advances in radical-based C-F bond activation of polyfluoroarenes and gem-difluoroalkenes. *Chem. Commun.* **2021,** *57*, 12203-12217. (c) Senaweera, S.; Weaver, J. D., Dual C-F, C-H Functionalization via Photocatalysis: Access to Multifluorinated Biaryls. *J. Am. Chem. Soc.* **2016,** *138*, 2520-2523.

(10) (a) Das, A.; Chatani, N., The Directing Group: A Tool for Efficient and Selective C-F Bond Activation. *ACS Catal.* **2021,** *11*, 12915-12930. (b) Capdevila, L.; Sala, J.; Ackermann, L.; Ribas, X., Nickel-Catalyzed Csp^2-OMe Functionalization for Chemoselective Aromatic Homologation En Route to Nanographenes. *Chem. - Eur. J.* **2022,** *28*, e202200625. (c) Capdevila, L.; Meyer, T. H.; Roldan-Gomez, S.; Luis, J. M.; Ackermann, L.; Ribas, X., Chemodivergent Nickel(0)-Catalyzed Arene C-F Activation with Alkynes: Unprecedented C-F/C-H Double Insertion. *ACS Catal.* **2019,** *9*, 11074-11081.

(11) (a) Jana, A.; Samuel, P. P.; Tavcar, G.; Roesky, H. W.; Schulzke, C., Selective Aromatic C-F and C-H Bond Activation with Silylenes of Different Coordinate Silicon. *J. Am. Chem. Soc.* **2010,** *132*, 10164-10170. (b) Obligacion, J. V.; Bezdek, M. J.; Chirik, P. J. C(sp2)–H Borylation of Fluorinated Arenes Using an Air-Stable Cobalt Precatalyst: Electronically Enhanced Site Selectivity Enables Synthetic Opportunities. *J. Am. Chem. Soc.* **2017**, *139*, 2825-2832. (c) See ref. 14, and references cited therein.

(12) (a) Nareddy, P.; Jordan, F.; Brenner-Moyer, S. E.; Szostak, M., Ruthenium(II)-Catalyzed Regioselective C-H Arylation of Cyclic and N,N-Dialkyl Benzamides with Boronic Acids by Weak Coordination. *ACS Catal.* **2016,** *6*, 4755-4759. (b) Nareddy, P.; Jordan, F.; Szostak, M., Recent Developments in Ruthenium-Catalyzed C-H Arylation: Array of Mechanistic Manifolds. *ACS Catal.* **2017,** *7*, 5721-5745. (c) Nareddy, P.; Jordan, F.; Szostak, M., Highly chemoselective ruthenium(II)-catalyzed direct arylation of cyclic and N,N-dialkyl benzamides with aryl silanes. *Chem. Sci.* **2017,** *8*, 3204-3210. (d) Zhao, Q.; Zhang, J.; Szostak, M., Ruthenium(0)-Catalyzed Cross-Coupling of Anilines with Organoboranes by Selective Carbon-Nitrogen Cleavage. *ACS Catal.* **2019,** *9*, 8171-8177. (e) Wang, X.; Zhang, J.; He, Y.; Chen, D.; Wang, C.; Yang, F.; Wang, W.; Ma, Y.; Szostak, M., Ruthenium(II)-Catalyzed Ortho-C-H Alkylation of Naphthylamines with Diazo Compounds for Synthesis of 2,2-Disubstituted π-Extended 3-Oxindoles in Water. *Org. Lett.* **2020,** *22*, 5187-5192. (f) Zhang, J.; Liu, Y.; Jia, Q.; Wang, Y.; Ma, Y.; Szostak, M., Ruthenium(II)-Catalyzed C-H Arylation of N,N-Dialkyl Thiobenzamides with Boronic Acids by Sulfur Coordination in 2-MeTHF. *Org. Lett.* **2020,** *22*, 6884-6890. (g) Hu, F.; Szostak, M. Ruthenium(0)-Catalyzed C–H Arylation of Aromatic Imines under Neutral Conditions: Access to Biaryl Aldehydes. *Org. Lett.* **2016**, *18*, 4186-4189.

(13) (a) Lee, D.-H.; Kwon, K.-H.; Yi, C. S., Dehydrative C-H Alkylation and Alkenylation of Phenols with Alcohols: Expedient Synthesis for Substituted Phenols and Benzofurans. *J. Am. Chem. Soc.* **2012,** *134*, 7325-7328. (b) Ackermann, L., Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C-H/Het-H Bond Functionalizations. *Acc. Chem. Res.* **2014,** *47*, 281-295. (c) Manikandan, R.; Madasamy, P.; Jeganmohan, M., Ruthenium-Catalyzed ortho Alkenylation of Aromatics with Alkenes at Room Temperature with Hydrogen Evolution. *ACS Catal.* **2016,** *6*, 230-234. (d) Ramesh, B.; Jeganmohan, M., Ruthenium-Catalyzed Remote C-H Sulfonylation of N-Aryl-2-aminopyridines with Aromatic Sulfonyl Chlorides. *Org. Lett.* **2017,** *19*, 6000-6003. (e) Ray, R.; Chandra, S.; Yadav, V.; Mondal, P.; Maiti, D.; Lahiri, G. K., Ligand controlled switchable selectivity in ruthenium catalyzed aerobic oxidation of primary amines. *Chem. Commun.* **2017,** *53*, 4006-4009. (f) Lee, H.; Mane, M. V.; Ryu, H.; Sahu, D.; Baik, M.-H.; Yi, C. S., Experimental and Computational Study of the (Z)-Selective Formation of Trisubstituted Olefins and Benzo-Fused Oxacycles from the Ruthenium-Catalyzed Dehydrative C-H Coupling of Phenols with Ketones. *J. Am. Chem. Soc.* **2018,** *140*, 10289-10296. (g) ambu, S.; Tamizmani, M.; Jeganmohan, M., Ruthenium(II)-Catalyzed Cyclization of Aromatic Acids with Allylic Acetates via Redox-Free Two-Fold Aromatic/Allylic C-H Activations: Combined Experimental and DFT Studies. *Org. Lett.* **2018,** *20*, 1982-1986. (h) Pannilawithana, N.; Yi, C. S., Catalytic Carbon-Carbon Bond Activation of Saturated and Unsaturated Carbonyl Compounds via Chelate-Assisted Coupling Reaction with Indoles. *ACS Catal.* **2020,** *10*, 5852-5861. (i) Sasmal, S.; Sinha, S. K.; Lahiri, G. K.; Maiti, D., A directing group-assisted ruthenium-catalyzed approach to access meta-nitrated phenols. *Chem. Commun.* **2020,** *56*, 7100-7103. (j) Shambhavi, C. N.; Jeganmohan, M., Ruthenium(II)-Catalyzed Redox-Neutral C-H Alkylation of Arylamides with Unactivated Olefins. *Org. Lett.* **2021,** *23*, 4849-4854. (k) Tan, X.; Hou, X.; Rogge, T.; Ackermann, L., Ruthenaelectro-Catalyzed Domino Three-Component Alkyne Annulation Expedient Isoquinoline Assembly. *Angew. Chem., Int. Ed.* **2021,** *60*, 4619-4624. (l) Pannilawithana, N.; Pudasaini, B.; Baik, M.-H.; Yi, C. S., Experimental and Computational Studies on the Ruthenium-Catalyzed Dehydrative C-H Coupling of Phenols with Aldehydes for the Synthesis of 2-Alkylphenol, Benzofuran and Xanthene Derivatives. *J. Am. Chem. Soc.* **2021,** *143*, 13428-13440. (m) *Activation of Unreactive Bonds and Organic Synthesis*, Murai, S., Ed.; Springer: Berlin, 1999. (n) Shan, C.; Zhu, L.; Qu, L. B.; Bai, R.; Lan, Y. Mechanistic View of Ru-Catalyzed C–H Bond Activation and Functionalization: Computational Advances. *Chem. Soc. Rev.* **2018**, *47*, 7552-7576.

(14) Clot, E.; Eisenstein, O.; Jasim, N.; MacGregor, S. A.; McGrady, J. E.; Perutz, R. N., C-F and C-H Bond Activation of Fluorobenzenes and Fluoropyridines at Transition Metal Centers: How Fluorine Tips the Scales. *Acc. Chem. Res.* **2011,** *44*, 333-348.

(15) Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J. Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C–H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788-802.

(16) Macgregor, S. A.; McKay, D.; Panetier, J. A.; Whittlesey, M. K. Computational study of the hydrodefluorination of fluoroarenes at $[Ru(NHC)(PR_3)_2(CO)(H)_2]$: predicted scope and regioselectivities. *Dalton Trans.* **2013**, *42*, 7386-7395.

(17) DiMagno, S.G., Biffinger, J.C., Sun, H. *Fluorinated Porphyrins and Corroles: Synthesis, Electrochemistry, and Applications.* In Fluorine in Heterocyclic Chemistry, 1st Ed., Nenajdenko, V., Ed.; Springer, Heidelberg, 2014, Vol. 1., pp. 589–620.

(18) Kozuch, S.; Shaik, S. How to Conceptualize Catalytic Cycles? The Energetic Span Model. *Acc. Chem. Res.* **2011**, *44*, 101–110.

(19) Teltewskoi, M.; Panetier, J. A.; Macgregor, S. A.; Braun. T. A Highly Reactive Rhodium(I)-Boryl Complex as a Useful Tool for C-H Bond Activation and Catalytic C-F Bond Borylation. *Angew. Chem. Int. Ed.* **2010**, *49*, 3947-3951.

(20) (a) Sala, R.; Roudesly, F.; Veiros, L. F.; Broggini, G.; Oble, J.; Poli, G. Ru-Catalyzed Carbonylative Murai Reaction: Directed C3-Acylation of Biomass-Derived 2-Formyl Heteroaromatics. *Adv. Synth. Catal.* **2020**, *362*, 2486-2493. (b) See, also ref. 13n, and references cited therein.