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BrettPhos Ligand Supported Palladium-Catalyzed C–O Bond Formation through an Electronic Pathway of Reductive Elimination: Fluoroalkoxylation of Activated Aryl Halides

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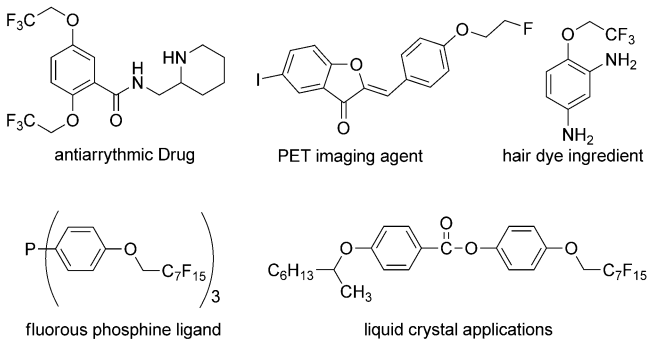
Abstract: We report an unprecedented BrettPhos ligand supported Pd-catalyzed C–O bond-forming reaction of activated aryl halides with primary fluoroalkyl alcohols. We demonstrate that the Phosphine ligand (BrettPhos) possesses the property of altering the mechanistic pathway of reductive elimination from nucleophile to nucleophile. The Pd/BrettPhos catalyst system facilitates the reductive elimination of the oxygen nucleophile through an electronic pathway.

The chemistry of fluorine has been an inviting subject for chemists for more than three decades because of fluorine's excellent and even bizarre physical and chemical properties. In fact, fluorinated organic compounds have found pervasive applications in medicinal,[1a] molecular imaging,[1b] agrochemicals,[1c] and material sciences.[1d–f] Therefore, the incorporation of the fluorine atom and fluorine-containing functional groups into organic molecules has recently received a spectacular growth of interest among chemists.[2,3]

Recently, transition-metal-catalyzed cross-coupling reactions (particularly Pd and Cu) have become a splendid tool not only to couple C–C, C–N, C–O bonds etc.,[4] but also C–F, C–CF_3, C–OCF_3, C–CF_3, and C–SCF_3 bonds. Thanks to the success of fluorination reactions under mild reaction conditions, coupling reactions involving fluorine chemistry have reached an advanced level in all branches of chemistry.[3] By popular demand, transition-metal-catalyzed cross-coupling methodologies have been shown ingress in almost all aspects of chemical syntheses.[3,4] In recent years, aryl fluoroalkyl ethers (Scheme 1) have also been paid as much attention as other fluorinated organic compounds in pharmaceuticals,[5] PET imaging,[1b,6] hair dye ingredients,[7a] pesticides,[7b] liquid-crystal display applications,[7c] fluorous chemistry,[7d] etc. Transition-metal-catalyzed C–O cross-coupling methodologies have become an efficient and alternative tool over traditional methods, such as Williamson ether synthesis, the Ullmann reaction, and alkylation of phenols, as these methods involve harsh reaction conditions, low functional-group tolerance, and carcinogenic reagents.[8]



Scheme 1. Selected examples of aryl fluoroalkyl ether containing compounds in various fields.

Various structural derivatives of phosphine ligated transition-metal-catalyzed cross-coupling methodologies offer a wide scope in the organic synthesis, were initially developed by Buchwald[9,10d,e,12c] and Hartwig groups,[10,12c] and subsequent contributions have been made by Beller[9b,c,10c,11,12c] and others[9b,c,10d,e,12] over last few decades. The electron-rich counterpart of the X-Phos ligand, the so-called electron-rich, relatively bulky BrettPhos ligand (**L1**) (Scheme 2), developed by the Buchwald group,[9f,13a] is one of the most effective supporting ligands that has promisingly facilitated several cross-coupling reactions,[3c,13,14] depicted in Scheme 3.

This catalytic system offered coupling products even with weak nucleophiles, such as a F^- anoin,[14b] trifluoromethyl anion,[14c] and trifluoromethylthio anion.[3c] However, this Pd/BrettPhos catalytic system, albeit it involves an oxidative addition step, failed to give C–O coupling reactions with relatively weak nucleophiles, such as ethyl acetohydroximate,[14e] metha-

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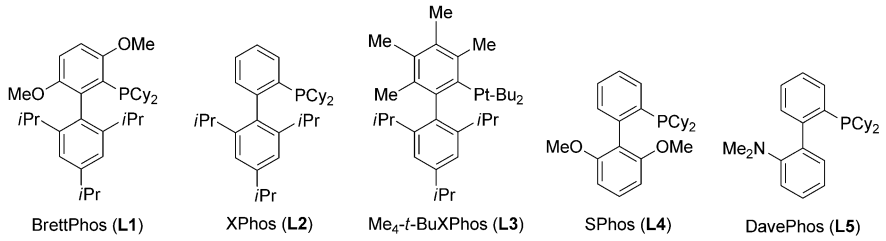
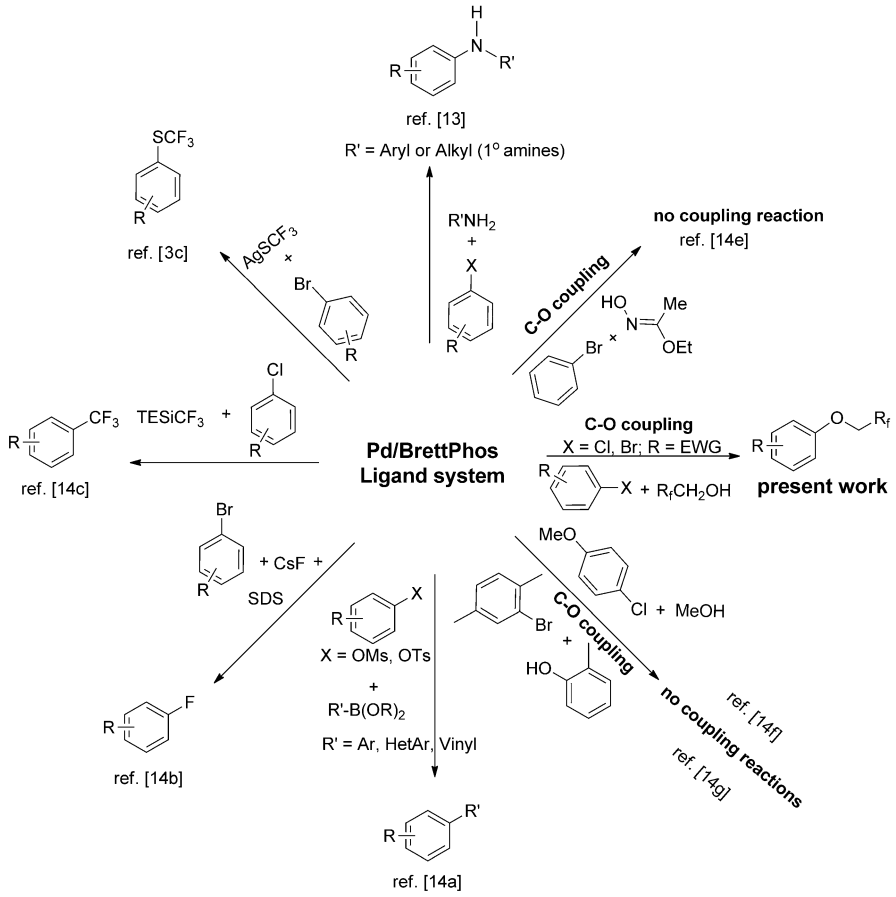


Scheme 2. Structures of the biarylphosphine ligands used for screening purposes.



Scheme 3. Examples of BrettPhos ligand supported palladium-catalyzed cross-coupling reactions.

and deactivated aryl bromides were also conducted under the same reaction conditions with another nucleophile (phenyl boronic acid) to ensure the BrettPhos ligand (phosphine ligand) possesses the property of altering the mechanistic pathway of reductive elimination from nucleophile to nucleophile (depending on the nature of the nucleophile). To the best of our knowledge, this is the first example of a Pd/BrettPhos ligand system that clearly separates the steric and electronic pathway of reductive elimination from nucleophile to nucleophile by facilitating the C–O bond formation through a pure electronic-assisted reductive elimination pathway and C–C bond formation through a steric and/or electronic pathway of reductive elimination.

A growing interest in aryl fluoroalkyl ethers in both academia and industry (Scheme 1) and a lack of efficient methodologies available for the synthesis of aryl fluoroalkyl ethers[6,7,15,16] have really kindled or interest in developing an efficient protocol for the fluoroalkoxylation of aryl halides with wide substrate scope. In fact, our study with the ligands available at hand was narrowed down by the substrate scope of the reaction. Thankfully, we were able to discern a ligand that possesses the ability of altering the mechanistic pathway of reductive elimination from nucleophile to nucleophile in cross-coupling reactions.

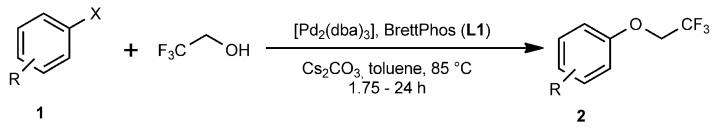
nol,[14f] and phenol[14g] (Scheme 3). To the best of our knowledge, the discrepancy observed in catalyzing the cross-coupling reactions by a given catalytic system (Pd/BrettPhos system, Scheme 3) from nucleophile to nucleophile is yet to be accounted for. In this Communication, we disentangled the aforementioned discrepancy associated with Pd/BrettPhos ligand system by an intermolecular C–O bond-forming reaction of primary fluoroalkyl alcohols with aryl bromides. Aryl chlorides were also effectively coupled by this catalytic system. We investigated the coupling reaction of 2,2,2-trifluoroethanol with electronically different aryl bromides to understand the properties of the ligands in deciding the mechanistic pathway (electronic or steric) of the reductive elimination step under optimized reaction conditions. Coupling reactions of activated

To begin with, we investigated 2,2,2-trifluoroethoxylation of *p*-bromoanisole with 2,2,2-trifluoroethanol in the presence of 0.5 mol% of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone), 1.25 mol% of commercially available BrettPhos ligand (**L1**), and a strong base, NaH, in toluene at 85 °C over 24 h. After this time, no coupling product was observed. Fortunately, we conducted the same reaction with *p*-bromoacetophenone as the substrate based on an inkling from mechanistic studies carried out by Buchwald and Hartwig groups.[17] Surprisingly, the reaction gave the desired product **2a** in about 31% yield and 51% conversion over 24 h. Thenceforth *p*-bromoacetophenone became a model substrate for further optimization of the reaction conditions. The complete optimization of the reaction

conditions are given in the Supporting Information (Table S1). The bases K_3PO_4 and Cs_2CO_3 effected the coupling reaction with complete conversion. Indeed, Cs_2CO_3 gave the desired product with 85% yield in 2.25 h. It has also been observed that when catalyst loading is reduced from 0.5 to 0.1 mol%, the catalytic activity has also been reduced. The higher catalyst loading and higher temperature gave the desired product in short reaction times of 1.5 and 0.75 h, respectively, without altering the yield of the product. No other palladium sources, such as $Pd(OAc)_2$ and $[Pd(PPh_3)_4]$, were as effective as $[Pd_2(dba)_3]$. Finally, we examined the commercially available ligands (Scheme 2) XPhos (**L2**), Me_4-*t*BuXPhos (**L3**), SPhos (**L4**), and DavePhos (**L5**); however, these ligands could not facilitate the reaction as effectively as BrettPhos ligand (**L1**). It is important to note that all the ligands with palladium catalyst could not effectively couple the nucleophile even with strong activated aryl or heteroaryl halides.[18]

With the optimized reaction conditions in hand, we further explored the coupling reaction of 2,2,2-trifluoroethanol with aryl bromides of a different electronic nature in order to understand the ligand's properties in the Pd-catalyzed coupling reactions. Also, we extended the scope of the reaction to activated aryl chlorides and the results are presented in Table 1. Aryl bromides bearing electron-withdrawing functional groups (EWG), such as –CHO, –CN, –COOEt, and $–NO_2$ at the *p*-position gave the coupling products with 2,2,2-trifluoroethanol in moderate to excellent yield (Table 1, entries 2, 4, 5, and 9). The functional groups –OMe (entry 7), –F (entry 8), and –Ph (not included in table) did not

Table 1. Palladium-catalyzed 2,2,2-trifluoroethoxylation of aryl bromides and chlorides.[a,b]



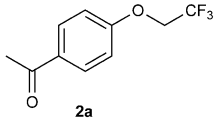
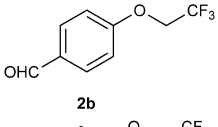
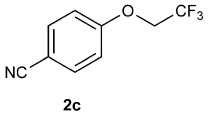
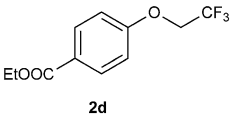
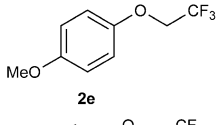
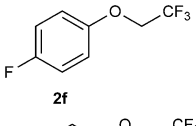
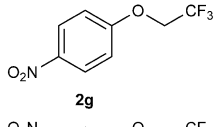
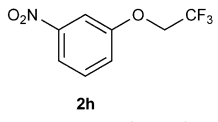
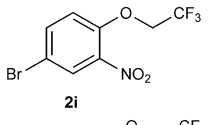
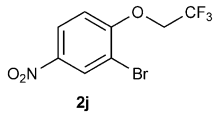
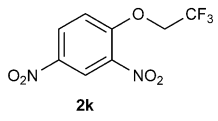
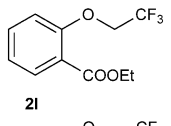
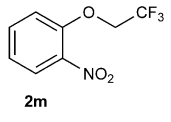
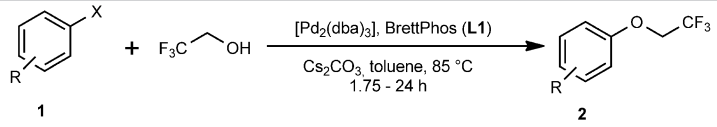
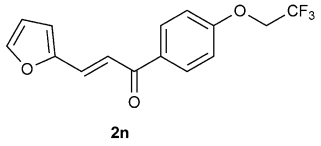
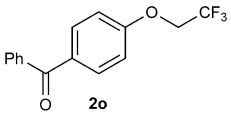
Entry	Substrate X, R	Product	Pd [mol%]	Time [h]	Yield [%][c]
1	Cl, 4-$COCH_3$; $F=0.33$; $R=0.17$[d]	 **2a**	0.5	7.0	73
2	Br, 4-CHO; $F=0.33$; $R=0.09$	 **2b**	0.5	6.0	72
3	Cl, *p*-CHO		0.5	17[e]	70
4	Br, 4-CN; $F=0.51$; $R=0.15$	 **2c**	0.5	2.0	92
5	Br, 4-COOEt; $F=0.34$; $R=0.11$	 **2d**	1.0	6.0	63
6	Cl, 4-COOEt		1.0	17[e]	60
7	Br, 4-OMe; $F=0.29$; $R=-0.56$	 **2e**	1.0	24	NR
8	Br, 4-F; $F=0.45$; $R=-0.39$	 **2f**	0.5	12	NR
9	Br, 4-NO_2; $F=0.65$; $R=0.13$	 **2g**	1.0	2.0	89
10	Cl, 4-NO_2		1.0	2.0	87
11	Br, 3-NO_2; $F=0.65$; $R=0.13$	 **2h**	1.0	12	NR
12	Br, 2-NO_2, 4-Br; Br, $R=-0.22$; NO_2, $R=0.13$	 **2i**	1.0	24	28
13	Br, 2-Br, 4-NO_2	 **2j**	1.0	20	trace
14	Br, 2-NO_2, 4-NO_2	 **2k**	0.5	1.75	92
15	Cl, 2-NO_2, 4-NO_2		0.5	1.0	74
16	Br, 2-COOEt	 **2l**	1.0	23	NR
17	Cl, 2-NO_2	 **2m**	1.0	16	38

Table 1. (Continued)

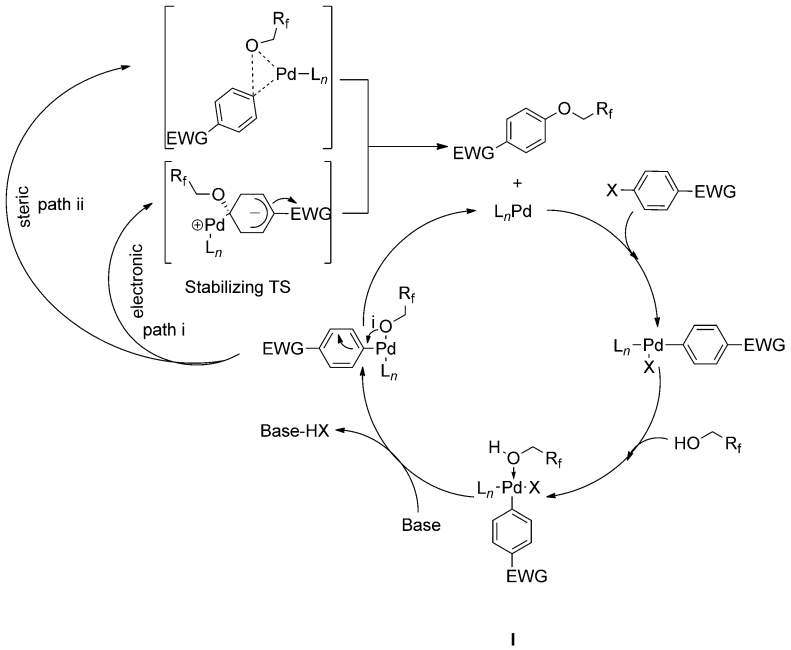


Entry	Substrate X, R	Product	Pd [mol%]	Time [h]	Yield [%][c]
18	Br, 4-	 **2n**	1.0	22	60[f]
19	Br, 4-COPh; $F=0.31$; $R=0.12$	 **2o**	1.0	4.0	92

[a] Reaction conditions: ArX (1.0 mmol), 2,2,2-trifluoroethanol (1.5 mmol), Cs_2CO_3 (1.5 mmol), $[Pd_2(dba)_3]$ (0.5 mol%), BrettPhos (1.25 mol%), toluene (3.0 mL), Ar atm., 85 °C. [b] ArX (0.6111 mmol), 2,2,2-trifluoroethanol (0.917 mmol), Cs_2CO_3 (0.917 mmol), $[Pd_2(dba)_3]$ (1.0 mol%), BrettPhos (2.5 mol%), toluene (2.0 mL), Ar atm., 85 °C. [c] Isolated yield. [d] Swan–Lapton's field (F) and resonance (R) dual substituent constants for substituent R. [e] Reaction time not optimized. NR = No Reaction. [f] 90% conversion.

give any coupling products. The functional groups $-COCH_3$ (see Table S1 in the Supporting Information), $-CN$ (entry 4), and $-NO_2$ (entry 9) gave the coupling products in very good yields in short reaction times, whereas $-CHO$ (entry 2) and $-COOEt$ (entry 5) gave the desired products in moderate yield with relatively long reaction time. This reaction trend can easily be explained with the help of the resonance constant of Swan–Lapton[19] field (F) and resonance (R) dual substituent parameters.[17a,b,20] The positive R values for the substituents indicate the electron-withdrawing extended π-resonance conjugation between the functional group and the site of interest. The negative R values for substituents indicate the electron-releasing extended π-resonance conjugation between the functional group and the site of interest. Therefore, EWG reduces the electron density accumulated at the *ipso*-carbon atom of the palladium-bound aryl group by inner-sphere attack of fluoroalkoxide in the transition state leading to a stabilization that facilitates the reductive elimination (Scheme 4, path i). In contrast, electron-releasing group (ERG) increases the electron density at the *ipso*-carbon atom of the palladium-bound aryl group, which hinders the fluoroalkoxide attack in the transition state, leading to destabilization of the transition state. Hence, the reductive elimination fails through the electronic pathway (Scheme 5, path i). This strongly suggests that this catalytic system facilitates the C–O bond formation by inner sphere nucleophilic attack of fluoroalkoxide at the *ipso*-carbon atom of the palladium-bound aryl group via a Meisenheimer complex. In general, electron-rich and -neutral aryl bromides facilitate the reductive elimination only through a concerted, symmetric, three-centered transition state, whereas for activated aryl bromides both the mechanisms may possibly occur.[17a,b]

However, it is ascertained that the Pd/BrettPhos catalytic system enables C–O bond formation only through the electronic pathway of reductive elimination (Scheme 4, path i) as this catalytic system hinders the steric pathway of reductive elimination. This can further be demonstrated by the reaction of 2,2,2-trifluoroethanol with 1-bromo-3-nitrobenzene (Table 1, entry 11), 1,4-dibromo-2-nitrobenzene (entry 12), 1,2-dibromo-4-nitrobenzene (entry 13), and 1-bromo-2,4-dinitrobenzene (entry 14). Entry 11 did not give the coupling product at all due to the m-NO_2 group, which increases the electron density at the *ipso*-carbon atom both by inductive and resonance ef-



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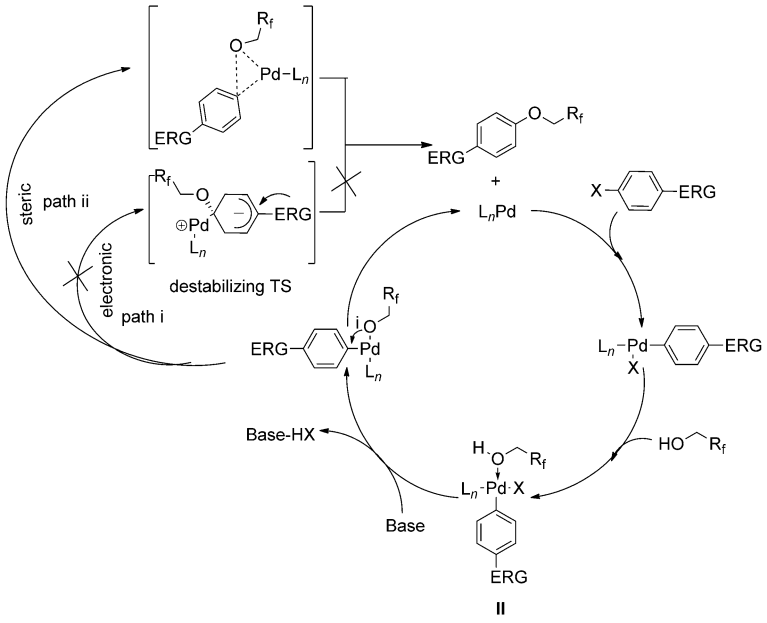
Scheme 4. Plausible mechanistic pathway of C–O reductive elimination of activated (I) aryl halides. EWG = electron-withdrawing group.

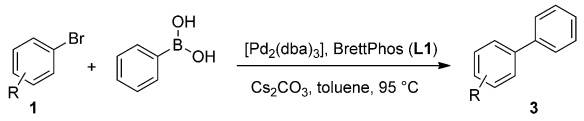


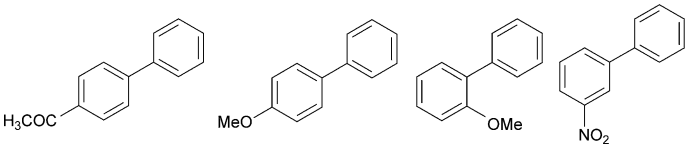
Scheme 5. Plausible mechanistic pathway of C–O reductive elimination of deactivated and neutral (**II**) aryl halides. ERG = electron-releasing group + neutral.

fects.[17b] Moreover, entries 12 and 14 offered the coupling products **2i** and **2k** in 28 and 92% yields, respectively. It is clear that the former resists the reductive elimination through the Br-atom from the *p*-position since the overall resonance effect *R* is negative ($R = -0.09$) and the later readily offered the coupling product even in low catalyst loading. On the other hand, entry 13 gave traces of product **2j**. These results suggest that both the electron-donating and steric bulkiness of the Br atom increases the electron density at the *ipso*-carbon atom of the palladium-bound aryl group resist the reductive elimination by the electronic pathway. In the case of *ortho*-substituted aryl halides, entry 16 failed to couple, whereas entry 17 offered the desired product **2m** 38% yield.[21] This may be attributed to steric overcrowding of the {Ar-Pd(L_n)-OCH_2R_f} complex system that could force the aryl group and the substituents on the aryl group out of the plane. Thus, they are probably no longer in a co-planar or nearly co-planar conformation, which results in a considerable reduction in the extent of conjugation between the substituent and the aryl group that increases electron-density at the *ipso*-carbon atom of the palladium-bound aryl group.[22] Thus, resonance stabilization plays a vital role in the electronic pathway of reductive elimination; this can be further confirmed by the reaction of 2,2,2-trifluroethanol with (*E*)-1-(4-bromophenyl)-3-(furan-2-yl)prop-2-en-1-one (entry 18) and 4-bromobenzophenone (entry 19). The former gave the desired product **2n** in 60% yield with 90% conversion over 22 h. The poor yield and incomplete conversion are due to the reduction of extended electron-withdrawing resonance π-conjugation between the carbonyl group and the palladium-bound aryl group by increased extended resonance π-conjugation between the carbonyl group and the α,β-unsaturated furfurylidene group. The latter, on the other hand, offered the desired product **2o** in 92% yield; this is a result of a *R* value of 0.12, that is, extended resonance stabilization.[23] Aryl chlorides were also coupled with 2,2,2-trifluoroethanol under the same reaction conditions but the yields were comparably low with aryl bromides in some instances (entries 1 and 15). Other aryl chlorides gave the desired products in almost equal yield with bromo analogues (entries 3, 6, and 10).

Furthermore, we were pleased to carry out a few reactions both of electron-rich and -poor aryl bromides with phenyl boronic acid[14a] (carbon nucleophile) under the same reaction conditions to explore the ligand's role in the reductive elimination step with respect to the nucleophile. The results are given in Table 2. Under the same reaction conditions, phenyl boronic acid was successfully coupled with substrates bearing a different electronic nature from activated to deactivated aryl bromides affording the desired products (**3a**–**d**) in good to very good yields (72–90%). This result strongly suggests that this catalytic system now facilitates the C–C bond formation between aryl bromides and the carbon nucleophile through a steric-assisted reductive elimination pathway (Scheme 5, path ii). However, in this case, it is difficult to ascertain the actual mechanistic pathway of reductive elimination for activated aryl bromide since both the mechanistic path-

Table 2. Coupling of phenyl boronic acid with deactivated and activated aryl bromides.[a,b]





3a (84%, 1.5 h) **3b** (90%, 16 h[c]) **3c** (72%, 3.5 h) **3d** (88%, 3 h)

[a] Reaction conditions: ArBr (1.0 mmol), phenyl boronic acid (1.5 mmol), Cs_2CO_3 (1.5 mmol), $[Pd_2(dba)_3]$ (0.5 mol%), BrettPhos (1.25 mol%), toluene (2.0 mL), Ar atm., 95 °C. [b] Yields are referred to isolated products. [c] Reaction time not optimized.

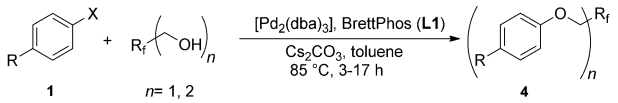
ways of reductive elimination are possible for activated aryl substrates (Scheme 4).

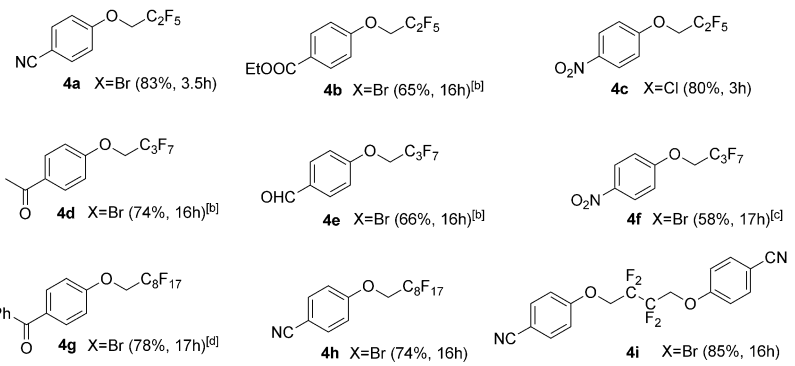
Consequently, the phosphine ligand (BrettPhos) possesses the property of altering the mechanistic pathway of reductive elimination from nucleophile to nucleophile. The Pd/BrettPhos ligand system shows a preference for the pure electronic pathway of reductive elimination towards the oxygen nucleophile, but when it comes to the carbon nucleophile, it prefers the steric or steric and electronic pathway of reductive elimination. More recently, Z. Novak et al.[18b] studied the screening of ligands with two aryl chlorides with different electronic properties, such as 4-chloroacteophenone and 4-chlorotoluene. It is interesting to note that the Pd/XPhos catalytic system facilitated the coupling reaction between 4-chloroacteophenone and sodium tetramethoxyborate in 81% yield, whereas this catalytic system failed to couple the nucleophile with 4-chlorotoluene.

Finally, we examined the reaction of activated aryl halides with commercially available higher fluorinated alcohols (Table 3) and 2-fluoroethanol (Table 4) under optimized reaction conditions. For higher fluoroalcohols, relatively more catalyst loading (1.0 mol%) was required to achieve the reaction successfully. The reactivity trend of substrates with higher fluorinated alcohols are the same as those with 2,2,2-trifluoroethanol. Those substituents with higher resonance constant values (*R*) such as cyano (**4a**, **4h** and **4i**), nitro (**4c** and **4f**), acetyl (**4d**), and benzoyl (**4g**) at *para*-position were effectively coupled with 1*H*,1*H*-perfluoropropanol, 1*H*,1*H*-perfluorobutanol, 1*H*,1*H*-perfluorononanol, and 1*H*,1*H*,4*H*,4*H*-perfluorobutan-1,4-diol (Table 3) in good to very good yields, whereas those substituents with lower resonance constant values (*R*), such as ester (**4b**) and formyl (**4e**), gave products in moderate yields. These data suggest that the extended electron-withdrawing resonance π-conjugation is an important factor for the electronic pathway of reductive elimination (Scheme 4, path i) via a Meisenheimer-type transition state. In all the reactions only 1.5 equivalents of fluoroalcohols were used.[15h]

It is also interesting to note that this catalytic system effectively coupled the activated aryl bromides with 2-fluoroethanol in short reaction times (Table 4) compared with 2,2,2-trifluoroethanol (Table 1) and other higher fluorinated alcohols (Table 3) except in the case of 1-bromo-4-nitrobenzene, which offered the desired product **5e** with 2-fluoroethanol in 3.5 h. This is a relatively longer reaction time compared to those substrates with 2,2,2-trifluoroethanol. All other aryl bromides gave the desired products (**5a**–**f**) in very good to moderate yield

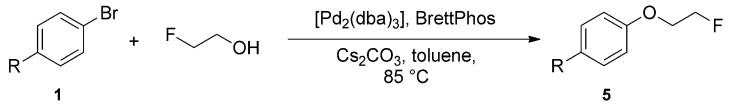
Table 3. Palladium-catalyzed 1*H*,1*H*-perfluoroalkoxylation of activated aryl halides.[a]

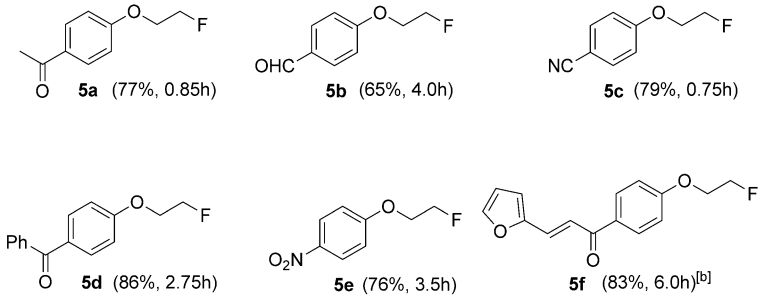




[a] Reaction conditions: ArX (0.6111 mmol, 1 equiv), 1*H*,1*H*-perifluoroalkanol ($n=1$, 0.917 mmol, 1.5 equiv; $n=2$, 0.4278 mmol, 0.7 equiv), Cs_2CO_3 (0.917 mmol, 1.5 equiv), $[Pd_2(dba)_3]$ (1.0 mol%), BrettPhos (2.5 mol%), toluene (2.0 mL), Ar atm., 85 °C, 3–17 h; isolated yields. [b] Reaction time not optimized. [c] 27% of starting material was recovered. [d] 2% of starting material was recovered.

Table 4. Palladium-catalyzed 2-fluoroethoxylation of activated aryl bromides.[a]





[a] Reaction conditions: ArBr (1.0 mmol), 2-fluoroethanol (1.5 mmol), $[Pd_2(dba)_3]$ (0.5 mol%), BrettPhos (1.25 mol%), Cs_2CO_3 (1.5 mmol), toluene (3.0 mL), Ar atm., 85 °C, isolated yields. [b] $[Pd_2(dba)_3]$ (1.0 mol%); conversion: 93%.

(65–86%) but these yields were relatively lower when compared to reactions with 2,2,2-trifluoroethanol.

In conclusion, we have disclosed a new insight into a phosphine ligand (BrettPhos) that possesses the property of altering the mechanistic pathway of reductive elimination from nucleophile to nucleophile. This Pd/BrettPhos catalytic system enabled C–O bond formation from the oxygen nucleophile by a pure electronic pathway of reductive elimination via the Meisenheimer-type transition state, whereas C–C bond formation from the carbon nucleophile occurs by a steric or steric and electronic pathway of reductive elimination. Other phosphine ligands, such as XPhos (**L2**), Me_4-*t*BuXPhos (**L3**), SPhos (**L4**), and DavePhos (**L5**) did not catalyze the C–O bond-forming reaction even with activated substrate *p*-bromoacetophenone. Moreover, we have demonstrated a clear separation of the steric and electronic pathway of reductive elimination with respect to the nucleophiles for the first time. Further, utility of this catalytic system in the C–C cross-coupling reaction of aryl halides in wide substrate scope with aryl/heteroaryl boronic acid is under progress.

Experimental Section

General procedure for the BrettPhos ligand supported palladium-catalyzed C–O cross-coupling reaction

An oven dried 5.0 mL two-neck round-bottomed flask was equipped with a magnetic stir bar, a rubber septum, condenser, and an argon balloon on the top of the condenser with the aid of an adaptor. The flask was charged with Cs_2CO_3 and dried with hot air gun under vacuum. The R.B. flask was allowed to cool under an argon atmosphere. [$Pd_2(dba)_3$] and BrettPhos ligand were added successively. The flask was then flushed with argon repeatedly three times. To this, anhydrous toluene (1.0 mL) was added by syringe and the mixture was stirred for five minutes at room temperature. A solution of aryl halides and fluoroalcohols in toluene (1.0 mL) was added to the flask by syringe. Additional toluene (1.0 mL, for rinsing) was added to the reaction flask and the flask was placed into a pre-heated oil bath at $85\pm2^{\circ}C$. The reaction mixture was stirred vigorously until completion as indicated by TLC analysis. The reaction mixture was allowed to cool to room temperature and passed through a short silica (230–400 mesh size) column eluted with chloroform or directly with hexane/ethyl acetate solvent mixture under N_2 pressure. The solvent removal under reduced pressure afforded the desired compounds as a yellow oily liquid or yellow/colorless solid.

General procedure for the BrettPhos ligand supported palladium-catalyzed C–C cross-coupling reaction

The same procedure was followed as in C–O cross-coupling reaction with a little modification. After the round-bottomed flask was allowed to cool under an Ar atmosphere, phenyl boronic acid, [$Pd_2(dba)_3$], BrettPhos, and aryl bromides were successively added. To this mixture, anhydrous toluene (2.0 mL) was added in a single addition and the flask was placed into a pre-heated oil bath at 95 °C. The reaction was left until completion, as judged by TLC analysis. The reaction mixture was treated as above.

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Keywords: alcohols · BrettPhos · C–O coupling · ethers · reductive elimination

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[23] The corresponding aryl bromides of the product **2a**–**c** and **2o** showed no product formation with 2,2,2-trifluoroethanol, even over 16 h reaction under similar experimental conditions without the Pd/ligand catalytic system (S_NAr conditions). While the corresponding aryl bromides of **2g** offered 18% of desired product with 79% conversion over 16 h (S_NAr conditions).

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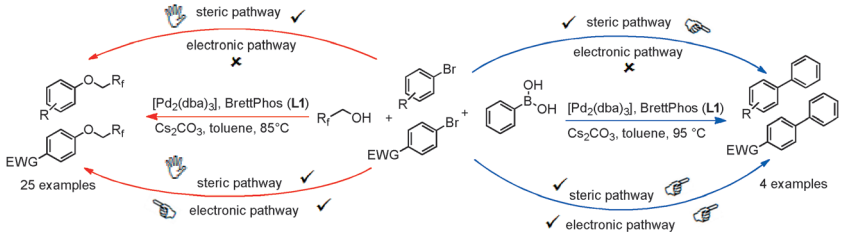

C–O coupling: A BrettPhos ligand supported Pd-catalyzed C–O bond-forming reaction of activated aryl halides with primary fluoroalkyl alcohols is reported. BrettPhos ligand (**L1**) can alter the mechanistic pathway of reductive elimination from nucleophile to nucleophile (see scheme; $R_f = -(CF_2)_nCF_3$; R = electron-releasing groups (ERGs) at *o*-, *m*- and *p*-positions, -neutral, and electron-withdrawing groups at *o*- and *m*-positions; EWG = electron-withdrawing group).

Organic Synthesis

T. M. Rangarajan, R. Singh, R. Brahma, K. Devi, R. P. Singh, R. P. Singh,* A. K. Prasad*

■■ – ■■

BrettPhos Ligand Supported Palladium-Catalyzed C–O Bond Formation through an Electronic Pathway of Reductive Elimination: Fluoroalkoxylation of Activated Aryl Halides