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Catalytic Intermolecular Direct Arylation of Perfluorobenzenes

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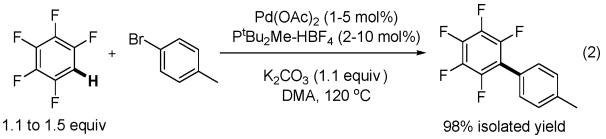
The development of new reactions capable of catalytically transforming the inert C−H bonds of organic molecules into useful functional groups is an important and very active area of research.[1] With this process, problems associated with low reactivity and selectivity are compounded by an only emerging appreciation of the mechanistic possibilities. As a consequence, the discovery of new catalytic reactivity can be of tremendous impact. An illustrative class of C−H functionalization that is limited by mechanistic understanding is direct arylation.[2,3] With these reactions, the most common mechanism of C−H bond cleavage is electrophilic aromatic substitution (S_EAr) involving reaction of an electrophilic metal catalyst with an electron-rich, nucleophilic aromatic ring.[4,5] This pathway is fundamentally limiting since the vast majority of aromatic compounds are not sufficiently nucleophilic.[6] For example, simple and electron-deficient arenes have never been successfully employed in catalytic direct arylation (eq 1) except when a basic directing group can enable the formation of a metallacycle.[7,8] New mechanistic insights that overcome these constraints and enable catalytic direct arylation to be performed with currently inaccessible arene classes would not only be of tremendous importance in biaryl synthesis but would also be transformative in the rational design of other types of catalytic arene functionalization.

Herein, we describe intermolecular direct arylation reactions of electron-deficient benzenes and associated computational studies indicating that metallacyclic intermediates are not involved. Underlying these new transformations is a mechanism that actually favors reaction with electron-deficient, C−H acidic benzenes—constituting a *complete inversion* of reactivity compared to the S_EAr pathway. Computational studies reveal the key C−H bond functionalization step occurs via a concerted arene metalation and carbon−hydrogen bond cleaving process, the accessibility of which depends directly on the acidity of the C−H bond being cleaved. These reactions are scalable, can employ a nearly equimolar ratio of the two benzene cross-coupling components, and produce perfluorobiphenyl products that have demonstrated importance in medicinal chemistry,[9] electron-transport devices,[10] organic light emitting diodes,[11] sensitizers for the photo-splitting of water,[12] and as elements in the rational design of liquid crystals.[13] It is anticipated that these new reactions will begin to replace the use of fluorobenzene organometallics in the synthesis of fluorobiaryl molecules and that the new reactivity should facilitate the design of other catalytic C−H bond functionalizations.

As a starting point, we chose to examine the direct arylation of pentafluorobenzene since this substrate would not react via a S_EAr-type process. Reaction screens were performed with 4-bromotoluene as the second coupling partner, and efforts were made to achieve conditions that were operationally simple. We were excited to find that excellent results could be obtained by reacting a nearly equimolar ratio of 4-bromotoluene and pentafluorobenzene (1:1.1) in conjunction with 1.1 equiv of potassium carbonate in dimethylacetamide (DMA, 3.0−6.0 M) at 120 °C with a catalyst generated in situ from air-stable $Pd(OAc)_2$ and the HBF_4 salt of di-*tert*-butylmethylphosphine.[14] Under these conditions, a remarkable 98% isolated yield of the cross-coupled direct arylation product can be achieved with 5 mol % of catalyst in less than 3 h of reaction time (eq 2). Even 1 mol % of palladium is sufficient to induce complete conversion if the reaction is allowed to proceed overnight.



This reaction exhibits broad scope with respect to both the aryl halide and the perfluoroarene components (Table 1). In addition to arylbromides, chlorides and iodides can also be used (entries 1 and 4). With aryl iodides, the use of 0.5 equiv of AgOTf can improve the yield as illustrated by entries 3 and 4, but its use is not imperative. Electron-donating (entries 6 and 7) and -withdrawing groups (entries 5 and 10) are compatible on the aryl halide, and heterocyclic aryl halides may also be used (entry 8). When the aryl halide contains both chlorine and bromine functionalities, high selectivity can be achieved for reaction at the aryl bromide (entry 11). If two bromine atoms are present, double direct arylation can be performed to produce valuable perfluoroterarylbenzenes in high yield (entry 12). Tetrafluoro-, trifluoro, and even some difluorobenzenes can be selectively cross-arylated. For example, 2,3,5,6-tetrafluoropyridine, 2,3,5,6-tetrafluorotoluene, and 2,3,5,6-tetrafluoroanisole all react in excellent yield and require only a slight excess of the fluorobenzene (entries 13−15).

In reactions with perfluorobenzenes having more than one potential site for reaction, mixtures of mono-, di-, and triarylation can occur, which can be minimized by using a slight excess of the fluoroarene (entries 16−22). When 1,2,3,4-tetrafluorobenzene is employed, steric encumbrance disfavors double arylation, providing synthetically useful selectivity for monoarylation with 1.1 equiv of the fluorobenzene (entry 17). With 1,3-difluorobenzene, arylation occurs selectively at the C−H bond between the two fluorine atoms in 85% yield (entry 21). Pushing the limits of these reactions, we were surprised to find that even fluorobenzene itself could be arylated, albeit in substantially lower yield (entry 23). This last result bodes well for the development of direct arylation reactions with other arenes as catalyst design improves.

Competition experiments were performed to establish the relative reactivity of different perfluoroarenes. As depicted in Figure 1, two trends emerge. First, the relative reactivity of different arenes

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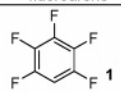
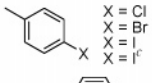
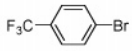
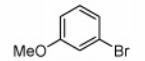
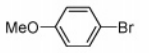
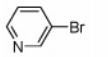
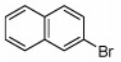
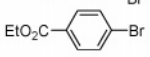
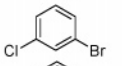
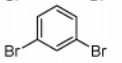
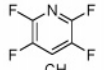
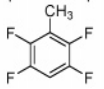
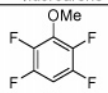
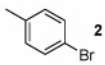
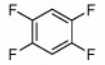
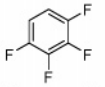
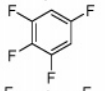
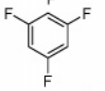
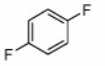
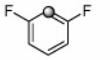
Table 1. Scope of Perfluorobenzene Direct Arylation[a]

entry	fluoroarene	aryl halide	fluoroarene equiv.	yield (%)[b]
1	 **1**	 X = Cl	1.5	57
2		X = Br	1.1	98
3		X = I	1.5	83
4		X = I[c]	1.5	95
5	**1**		1.5	89
6	**1**		1.5	85
7	**1**		1.5	76
8	**1**		1.5	78
9	**1**		1.5	91
10	**1**		1.5	83
11	**1**		1.5	96
12	**1**		3	76[f]
13		**2**	1.5	86
14		**2**	1.1	86

entry	fluoroarene	aryl halide	fluoroarene equiv.	yield (%)[b]
15		 **2**	1.1	92
16		**2**	3	79 (mono) 20 (bis)
17		**2**	1.1	68 (mono) 10 (bis)
18		**2**	3	75 (mono) 24 (bis)
19		**2**	3	69 (mono) 24 (bis) 2 (tris)
20[e]		**2**	3	42 (mono) 13 (bis)[d]
21		**2**	3	85 (mono) 9 (bis)
22[e]		**2**	3	29 (mono) 9 (bis)
23[e]		**2**	3	8

[a] Conditions: $Pd(OAc)_2$ (5 mol %), $P^tBu_2Me{\cdot}HBF_4$ (10 mol %), K_2CO_3 (1.1 equiv) added to a Schlenk tube or screw cap vial followed by addition of the fluoroarene (1.1−3 equiv), the aryl halide, and DMA and heating to 120 °C. [b] Isolated yield. [c] AgOTf added (0.5 equiv). [d] Isolated as a mixture of regioisomers. [e] 10 mol % catalyst was employed. [f] Yield of the product of double direct arylation.

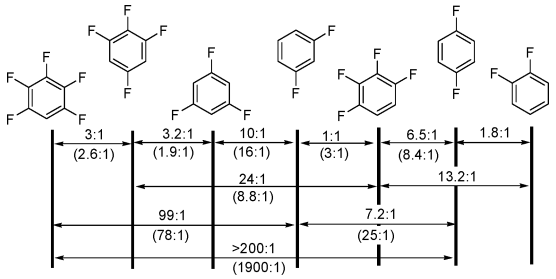
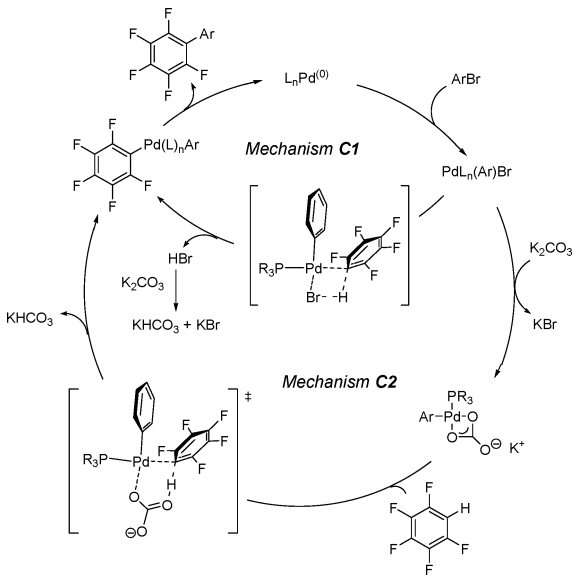


Figure 1. Competition experiments performed to determine relative reactivity. Two perfluoroarenes were reacted simultaneously in the presence of 4-bromotoluene under the standard reaction conditions, stopped at 5−10% conversion and analyzed by ^1H NMR and GCMS. Values in parentheses are determined from calculated reaction barrier difference with mechanism **C2** at 120 °C using PH_3 as the ligand.[19]

parallels relative acidities.[15] Thus, the introduction of fluorine substituents at positions remote to the C−H bond being cleaved increases the reactivity. In many cases, it is the more electron-deficient arene that reacts preferentially, which is a complete inversion in reactivity compared to other direct arylations occurring via the S_EAr mechanism. Second, direct arylation of substrates having two chemically distinct C−H bonds occurs preferentially at the most acidic C−H bond which, with perfluoroarenes, is *ortho* to a fluorine atom.[15] Computational studies indicate that this selectivity is a result of the C−H acidity and not due to a stabilizing interaction between the palladium and a fluorine substituent (vide infra). This selectivity is clearly illustrated by the reaction of 1,3-difluorobenzene which undergoes selective arylation at the 2-position. A kinetic isotope effect of 3.0 is also observed, indicating that C−H bond cleavage is a kinetically significant catalytic event.[16]

The mechanism of C−H bond cleavage has been examined by density functional theory calculations with the B3LYP[17] exchange-correlation functional and substituting PH_3 for the P^tBu_2Me ligand.[18]

Scheme 1. Proposed Catalytic Cycle of Perfluorobenzene Direct Arylation[a]



[a] For the C−H bond cleavage step, two possible mechanisms (**C1**, **C2**) are depicted involving concerted metalation of the fluoroarene and H-transfer to either a carbonate ligand or Br ligand on the catalyst.

Several distinct reaction mechanisms were explored, including oxidative addition of the arene C−H bond to the Pd center (**A**), electrophilic aromatic substitution (**B**), and concerted metalation and proton abstraction to a base (**C**).[19] Mechanism **C** is shown in Scheme 1 with two different bases and is similar to the mechanism proposed by Echavarren and Maseras for a related intramolecular direct arylation reaction.[8d] For mechanism **C**, we explored proton abstraction with various bases, including a Br ligand on $(PR_3)ArPd-$

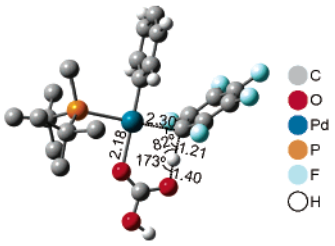


Figure 2. Calculated transition state structure for mechanism **C2** with C_6F_5H as the perfluoroarene and P^tBu_2Me as the ancillary ligand. Select H atoms have been removed for clarity.

Br (**C1**), a bicarbonate ligand on $(PR_3)ArPd-HCO_3$ that has been exchanged with the Br ligand (**C2**), an intermolecular bicarbonate ion (**C3**), and a bicarbonate ion that has added to the Pd catalyst to give $(PR_3)ArPd(Br)HCO_3$ (**C4**).

For the oxidative addition and electrophilic aromatic substitution mechanisms (**A** and **B**), all attempts to locate relevant stationary points failed. Similarly, no pathway could be located for mechanism **C3** involving intermolecular proton transfer. Instead, the bicarbonate ion was always found to first bind the Pd center and give $(PR_3)ArPd(Br)HCO_3$, which would then subsequently abstract the proton via mechanism **C4**.

Of the remaining mechanisms (**C1**, **C2**, **C4**), proton abstraction to the bicarbonate ion via mechanism **C2** was found to have the lowest reaction barrier and to give results most consistent with available experimental data (the outer pathway of Scheme 1). For example, with C_6F_5H a calculated gas phase reaction barrier of 9.9 kcal/mol was established. We note that using a continuum solvation model with a dielectric constant equal to that of bulk DMA, the barrier increases substantially for mechanisms **C1** and **C2** which might account for the need for elevated reaction temperatures. Furthermore, the computed value of k_H/k_D was found to be 3.25 at 120 °C, correlating very well with the experimental value of 3.0. We also found that the trends in calculated reaction barriers parallel the relative reactivities established experimentally (Figure 1). Product ratios using the difference in calculated reaction barriers are given in Figure 1 in parentheses. When the exponential dependence between product ratio and the calculated barrier differences is considered, the experimental and calculated ratios are in excellent agreement, lending strong support to the plausibility of this pathway. The transition state structure with C_6F_5H and P^tBu_2Me as the ancillary ligand is shown in Figure 2. Importantly, there is no indication of catalyst−fluorine interactions in any of the transition states for all the different perfluoroarenes, indicating that these reactions constitute the first time that a nondirected catalytic benzene arylation has been achieved.

While mechanism **C4**, involving a four-coordinate Pd with both Br and HCO_3^- ligands, is also energetically accessible, it gives trends that do not correlate with the competition experiments. On the other hand, mechanism **C1**, shown as the inner mechanism in Scheme 1, cannot be ruled out. Although it has a barrier larger than that of mechanism **C2**, the relative barriers are also in good agreement with the competition experiments of Figure 1.[18] Thus, it is possible that this mechanism is also active and important under certain conditions.

In conclusion, these new arylation reactions provide an efficient alternative to the stoichiometric use of organometallic reagents in the synthesis of fluorobiphenyls and the mechanistic insights lay a foundation for a more general application of direct arylation in biaryl synthesis. The absence of catalyst−fluorine interactions at the C−H bond cleaving transition state indicates that direct arylation reactions should also be accessible with other electron-deficient arenes lacking basic directing groups. Also, the relative reactivities and site selectivities indicate that C−H acidity is a new and important reaction parameter to be considered in direct arylation. This is an entirely different way of considering the design of intermolecular direct arylation reactions.

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Supporting Information Available: Details of the computational study, experimental procedures, and spectroscopic characterization of all new products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) A full account of the mechanisms explored computationally is detailed in the Supporting Information.

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