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Pd/C as heterogeneous catalyst for the direct arylation of (poly)fluorobenzenes

Shuxin Mao,[a] Xinzhe Shi,[a] Jean-François Soulé*[a] and Henri Doucet*[a]

This article is dedicated to the memory of the late Professor Keith Fagnou (1971-2009) who discovered the specific reactivity of polyfluorobenzenes in catalyzed direct arylations and received the OMCOS award in 2009.

The potential of the heterogeneous catalyst 10% Pd/C in direct arylation of (poly)fluorobenzene derivatives was investigated. In general, high yields in biaryl derivatives were obtained using tri-, tetra- and penta-fluorobenzenes. Conversely, mono- and di-fluorobenzenes exhibited a poor reactivity. The regioselectivities of the arylations were similar to those observed using homogeneous palladium catalysts. Both electron-withdrawing and electron-donating substituents such as nitrile, nitro, acetyl, ester, trifluoromethyl, *t*butyl, methoxy or methyl on the aryl bromide were tolerated. Unexpectedly, from pentafluorobenzene at 150°C, tetrafluoro-substituted [1,1'-biphenyl]-4-ols were obtained due to a regioselective formal hydroxylation; whereas, at lower temperatures the expected pentafluorobiphenyls were obtained. With the other polyfluorobenzene derivatives, no C-F bond cleavage was observed. These arylations were performed using only 1 mol% Pd/C catalyst and KOAc as inexpensive base. As Pd/C catalyst can be easily removed at the end of the reaction, as there is no contamination with phosphine ligand residues, and as the major side-products of the reaction are KOAc associated to HBr, this protocol represents a very attractive access to (poly)fluoro-substituted biphenyls in terms of cost, simplicity and sustainable chemistry.

Introduction

Many useful bioactive compounds contain a fluoro-substituted bi(hetero)aryl unit. For example, the 2,4-difluoro-1,1'-biphenyl derivative Diflunisal is a non-steroidal anti-inflammatory drug which is employed for the treatment of arthritis or dental pain (Fig 1). Flurbiprofen is also a non-steroidal anti-inflammatory drug employed for the treatment of miosis, and Tedizolid is an oxazolidinone-class antibiotic. Vorapaxar, Pitavastatin and especially Rosuvastatin, which contain heteroaryl-substituted fluorobenzenes, are also important drugs. In addition, polyfluoro-substituted bi(hetero)aryl units are very important structures in organic material science.[1] Therefore, the discovery of simple and cost effective procedures for the access to (poly)fluoro-substituted bi(hetero)aryls has potential for medicinal and material chemistry.

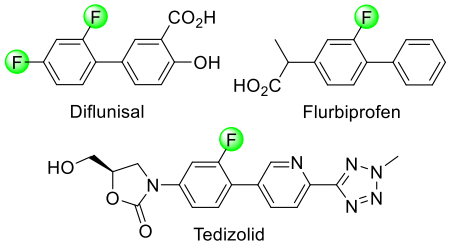

Figure 1. Examples of drugs containing a fluoro-substituted bi(hetero)aryl unit

Stille, Suzuki and Negishi couplings represent very efficient tools for the formation of a very wide variety of fluoro-substituted biaryls, but they require the preliminary synthesis of organometallic or boron derivatives and provide a stoichiometric amount of metallic or boron side products.[2] In 2006, Fagnou et al. reported the first intermolecular Pd-catalyzed arylation reaction *via* a C-H bond activation[3] using polyfluorobenzene derivatives.[4] Since these seminal results, the Pd- or Cu-catalyzed so-called direct arylations of tri-, tetra- and especially penta-fluorobenzenes[5-7] proved to be very powerful methods for the one step access to a variety of polyfluoro-substituted biaryls (Scheme 1, top).[8] However, to our knowledge, in all cases, these reactions were performed using homogeneous catalysts.

Currently, the substrate scope of the Pd-catalyzed direct arylation of benzene derivatives using heterogeneous catalysts is very limited.[9] In 2006, Fagnou et al. revealed that $Pd(OH)_2/C$ catalyst promotes the intramolecular direct arylation of a range of aryl iodides to produce 5- and 6-membred ring heterocycles.[10] To our knowledge, the intermolecular direct arylation of (poly)fluorobenzene derivatives using Pd/C catalyst has not been described yet; whereas, good results have been obtained using heteroarenes.[11] The mechanism of such Pd/C catalyzed direct arylations of heteroarenes was not elucidated;[12,13] but based on the report by Conlon et al. on the Suzuki-Miyaura reaction using Pd/C catalyst, such reactions might have a homogeneous component due to the formation of soluble Pd-species.[12a] The desorption of the palladium from Pd/C to produce soluble Pd(II) species probably occurs after the oxidative addition of the aryl halide on the Pd/C surface.

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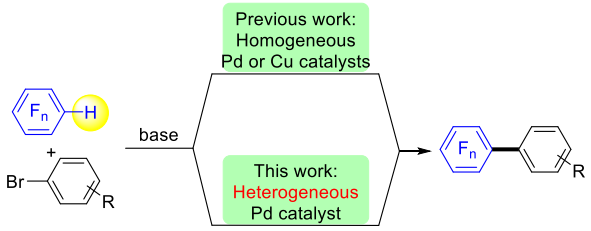
Heterogeneous Pd/C catalyst displays several advantages compared to homogeneous catalysts: 1) it is easy to handle as it is not air or moisture sensitive, 2) it can be removed by filtration, 3) it is easily available on large scale at an affordable cost, and 4) the recycling of the recovered Pd/C residues is possible is some cases or it can be remanufactured.

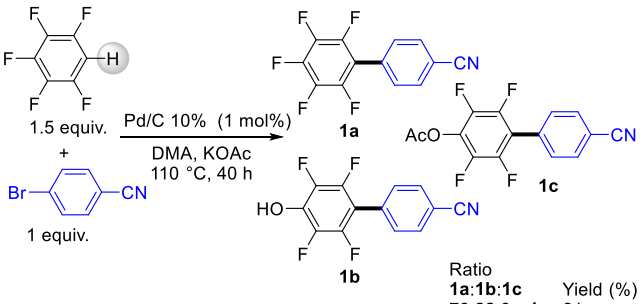


Scheme 1. Metal-catalyzed direct arylations of (poly)fluorobenzenes

As the efficiency of Pd/C catalyst in direct arylations of (poly)fluorobenzene derivatives has not been reported, its potential needed to be explored. Herein, starting from a set of (poly)fluorobenzenes, we report on their reactivity using Pd/C catalyst for direct arylations using a variety of aryl bromides.

Results and Discussion

First, we examined the reactivity of pentafluorobenzene with 4-bromobenzonitrile using Pd/C catalyst (Scheme 2). Unexpectedly, in the presence of 1 mol% of 10% Pd/C catalyst, using KOAc as base/ligand at 150 °C, almost no formation of the target product **1a** was detected by GC/MS analysis of the crude mixture, but the formation of the tetrafluoro-substituted 4-hydroxybiphenyl derivative **1b** arising from the regioselective formal hydroxylation of one of the C-F bonds was observed in 94% selectivity and in 86% yield. Conversely, the use of a lower reaction temperature of 110 °C afforded the desired pentafluoro-substituted coupling product **1a** in 78% selectivity (22% of **1b**) and 61% yield. The hydroxylation of polyfluorobenzenes in the presence of several bases had already been reported.[14a-c] However, as the formation of such 4-hydroxybiphenyls had never been observed in the course of the previous direct arylations of pentafluorobenzene using homogeneous palladium or copper catalysts,[8] the reaction outcome using our reaction conditions (150 °C, KOAc in DMA), but with $Pd(OAc)_2$ catalyst was studied. A mixture of the products **1a** and **1b** in 10:90 ratio was obtained, and **1b** was isolated in a similar yield than with Pd/C catalyst. The addition of 0.1 mL of water to the reaction mixture at 150 °C with 10% Pd/C catalyst gave a very low yield (<5%) of **1b**, and reactions using Na_2CO_3, K_2CO_3, Cs_2CO_3 or K_3PO_4 as the bases instead of KOAc gave no coupling products. Conversely, with KOPiv or NaOAc as bases instead of KOAc at 150°C, compound **1b** was obtained in good selectivities but in moderate yield with NaOAc, due to a partial conversion of 4-bromobenzonitrile. Interestingly, the use of dry DMA afforded a mixture of **1a**, **1b** and **1c** in 65:18:17 ratio, and seems to confirms that the formation of **1b** comes from the reaction of the pentafluorobenzene derivative with KOAc, producing the intermediate **1c** which is moderately stable under the reaction conditions. In order to determine if the catalytic cycle takes place on the surface of heterogeneous Pd-species or with soluble Pd-species, a drop of Hg was added to the reaction mixture. Under these conditions, no formation of traces of **1a**, **1b** or **1c** was detected by GC/MS, ^1H and ^{19}F NMR analysis of the crude mixture, and 4-bromobenzonitrile was recovered. This complete inhibition of the catalyst is typically expected when heterogeneous species including colloidal Pd(0) are active in the catalytic cycle.[15a] However, Hg(0) interaction inhibiting the activity of soluble molecular Pd-complexes has also been observed in a few cases.[15b,15c]

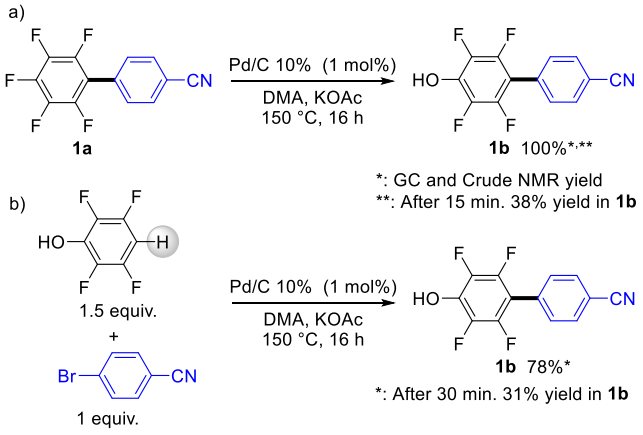


Ratio 1a:1b:1c		Yield (%)
78:22:0	**1a**	61
6:94:0	**1b**	86[a]
11:89:0	**1b**	81[b]
5:85:10	**1b**	<30[c]
-	-	0[d]
33:67:0	**1b**	5[e]
65:18:17	**1a**	35[f]
10:90:0	**1b**	73[g]
-	-	0[h]

[a]: 150 °C, 16 h
[b]: 150 °C, 16 h, KOPiv as base
[c]: 150 °C, 16 h, NaOAc as base
[d]: Using Na_2CO_3, K_2CO_3, Cs_2CO_3 or K_3PO_4 as base
[e]: Addition of 0.1 mL of H_2O
[f]: Dry DMA
[g]:$Pd(OAc)_2$ 1 mol% as catalyst, 150 °C, 16 h
[h]: 1 Drop of Hg was added.

Scheme 2. Direct arylation of pentafluorobenzene with 4-bromobenzonitrile

To elucidate the order of direct arylation and formal hydroxylation reactions in the course of this reaction, we treated the pentafluorobiphenyl **1a** by the catalytic coupling conditions (Scheme 3, a). After 15 minutes, **1b** was formed in 38%; whereas, a complete conversion of **1a** into the 4-hydroxybiphenyl **1b** was observed at 16 h. However, the reaction of 2,3,5,6-tetrafluorophenol with 4-bromobenzonitrile, under the same conditions, also afforded the 4-hydroxybiphenyl **1b** in 78% yield (31% yield after 30 min.). These results reveal that both reaction orders (direct arylation followed by hydroxylation and hydroxylation followed by direct arylation) can exist within the reaction mixture.



Scheme 3. Reactivity of **1a** and 2,3,5,6-tetrafluorophenol at 150 °C in the presence of Pd/C and KOAc

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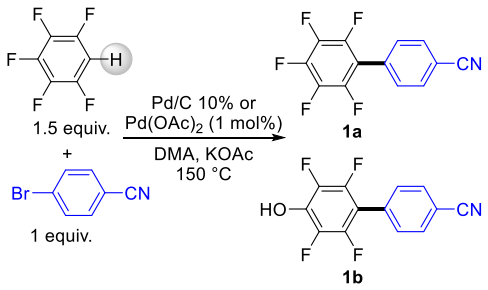
The kinetic of this reaction using both Pd/C and $Pd(OAc)_2$ catalysts was also studied (Scheme 4). An induction period was observed with Pd/C catalyst (1% conv. after 5 minutes); whereas, with $Pd(OAc)_2$ 10% conv. was observed after 5 minutes. At 15 minutes the conversions with Pd/C and $Pd(OAc)_2$ were 10% and 30%, respectively. Conversely, after 16 h, very similar results were obtained with these two catalysts. The induction period observed with Pd/C catalyst might be associated with a slow leaching of the palladium, to produce Pd nanoparticules or clusters.

Fairlamb et al. have recently studied the kinetics of homogeneous (including $Pd(OAc)_2$) and heterogeneous (including Pd/C) pre-catalysts for the direct arylation of heteroaromatics.[16a] Their initial-rate kinetic analysis revealed similarities in catalytic behaviour between Pd/C and $Pd(OAc)_2$ catalysts. The authors concluded that these dissimilar catalysts function as pre-catalysts for the formation of comparable active Pd-catalyst species (likely nanoparticules or clusters). They suggested that these species act as a palladium reservoir, the active species in the catalytic cycle consisting of leached mononuclear/lower-order Pd-species.

In order to probe the formation of soluble Pd species, we performed a hot filtration test[16b] and the catalytic activity of the resulting solution was measured (Scheme 4, b). After 30 min., the conversion of ArBr was 28%; then, the reaction mixture was filtered through a pad of celite, and 0.5 equiv. of KOAc was added to the solution which was again heated at 150 °C for 30 min. We observed that the filtrate was catalytically active, and that the reactions progressed to 50% conversion. This test supports the formation of catalytically active soluble Pd species, which may include nanoclusters, as they would not be removed by such filtration method.



a) Kinetics with Pd/C and $Pd(OAc)_2$

	Conv. of ArBr (%)		Ratio **1a**:**1b**	
Time	Pd/C	$Pd(OAc)_2$	Pd/C	$Pd(OAc)_2$
5 min.	1	10	nd	78:22
15 min.	10	30	55:45	47:53
30 min.	24	54	32:68	25:75
4 h	60	81	1:99	2:98
16 h	79	87	1:99	<1:>99

b) Hot fitration test with Pd/C catalyst:

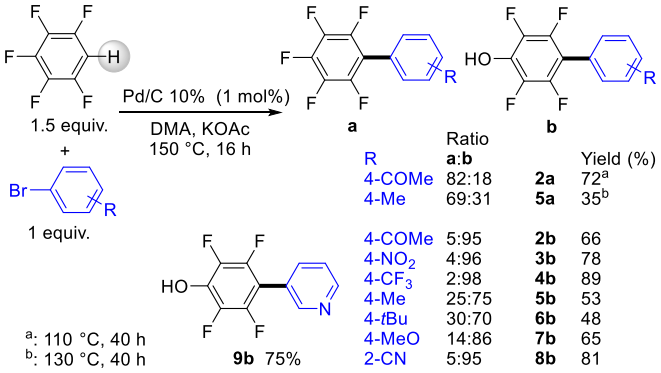
Time	Conv. of ArBr (%)	Ratio **1a**:**1b**
30 min.	28	32:68
1 h*	50	4:96

*: After 30 min., the reaction mixture was filtered (hot filtration) through a pad of celite to remove Pd/C, then 0.5 equiv. of KOAc were added to the solution which was heated at 150 °C

Scheme 4. Kinetics of the direct arylation of pentafluorobenzene with 4-bromobenzonitrile using Pd/C or $Pd(OAc)_2$ catalysts and hot filtration test

The scope for the Pd/C-catalyzed formation of the pentafluorobiphenyl derivatives **a** was briefly examined (Scheme 5). With 4-bromoacetophenone at 110 °C during 40 h, the desired product **2a** was obtained in 82% yield, and only traces of the hydroxybiphenyl derivative **2b** were detected. By contrast, the reaction of 4-bromotoluene at 130 °C during 16 h gave the pentafluorobiphenyl derivative **5a** in only 35% yield, due to the formation of an important amount of side-product **5b**; whereas, at 110 °C a low conversion of 4-bromotoluene was observed.

As the synthesis of tetrafluoro-substituted hydroxybiphenyl derivatives **b** from pentafluorobenzene had never been described, the potential of this one-pot reaction was investigated in more details using 150 °C, 40 h as the reaction conditions (Scheme 5). The influence of useful functional groups on the aryl bromide was examined, and both electron-donating substituents (e.g. nitro, acetyl, trifluoromethyl) and electron-withdrawing substituents (e.g. methyl, *t*butyl, methoxy) were tolerated. However, higher yields in hydroxybiphenyls **b** were obtained using electron-deficient aryl bromides due to an easier C-F bond cleavage. For example, with 4-bromonitrobenzene, **3b** was produced in 96% selectivity and in 78% yield; whereas, from 4-bromoanisole a mixture of **7a** and **7b** in 14:86 ratio was obtained, and **7b** was isolated in 65% yield. The structure of **7b** was confirmed by derivatization into 4-butoxy-2,3,5,6-tetrafluoro-4'-methoxy-1,1'-biphenyl.[14d] Coupling reaction with 3-bromopyridine at 150 °C afforded the hydroxybiphenyl **9b** in good yield. It should be mentioned that, in all cases, the reactions were selective in 4-hydroxybiphenyls **b**, as only the C-F bond in *para*-position to the newly formed C-C bond was transformed into a C-OH bond.



R	Ratio **a**:**b**		Yield (%)
4-COMe	82:18	**2a**	72[a]
4-Me	69:31	**5a**	35[b]
4-COMe	5:95	**2b**	66
4-NO_2	4:96	**3b**	78
4-CF_3	2:98	**4b**	89
4-Me	25:75	**5b**	53
4-*t*Bu	30:70	**6b**	48
4-MeO	14:86	**7b**	65
2-CN	5:95	**8b**	81

Scheme 5. Scope of the direct arylations of pentafluorobenzene

The Pd/C catalyst was then employed for the arylation of 1,2,3,4-tetrafluorobenzene with 4-bromotoluene and 4-bromoacetophenone (Scheme 6, a). At 150 °C after 16 h, the tetrafluorobiphenyl derivative **10** was obtained in 62% yield, without significant formation of side-products arising from the C-F bond cleavage or due to the 5,6-diarylation of this tetrafluorobenzene. At this temperature, with 4-bromoacetophenone as reaction partner, a small amount of side-product due to C-F bond cleavage was detected by GC/MS analysis of the crude mixture, but at 140 °C this side-product was not observed, and the expected tetrafluorobiphenyl **11** was isolated in 55% yield.

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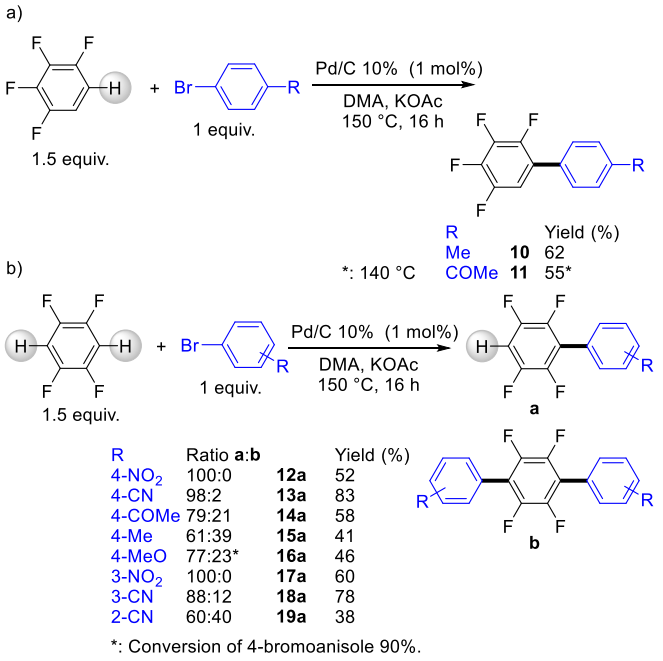
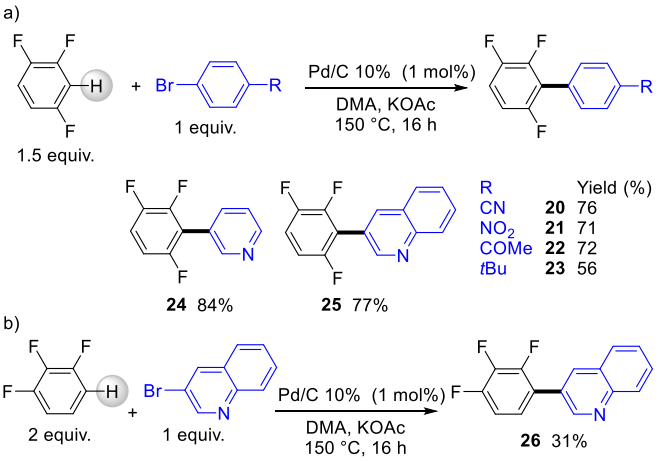
By contrast, the arylation of 1,2,4,5-tetrafluorobenzene generally afforded mixtures of mono- and di-arylated compounds (Scheme 6, b). High selectivities in favor of the formation of the mono-arylated tetrafluorobiphenyls were obtained in the presence of electron-poor aryl bromides. For example, from 3- or 4-bromonitrobenzene and 3- or 4-bromobenzonitriles, the products **12a**, **13a**, **17a** and **18a** were produced in > 88% selectivities and in 52-83% yields; whereas, 4-bromotoluene gave a mixture of the mono- and di-arylated tetrafluorobiphenyls **15a** and **15b** in a 61:39 ratio. A similar result was obtained with 4-bromoanisole affording a mixture of **16a** and **16b** in 77:23 ratio.



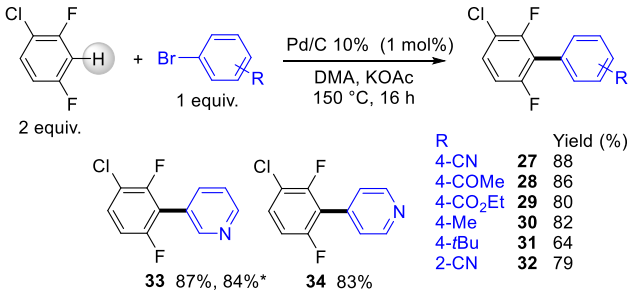
Scheme 6. Direct arylations of tetrafluorobenzenes

The reactivity of two trifluorobenzenes using Pd/C catalyst was then evaluated (Scheme 7). The arylation of 1,2,4-trifluorobenzene was very regioselective in favor of the C3-arylation. Using the electron-deficient 4-bromobenzonitrile, 4-bromonitrobenzene and 4-bromoacetophenone, the desired biaryls **20**-**22** were obtained in 71-76% yields; whereas the electron-rich 4-*tert*-butylbromobenzene gave a lower yield in the biaryl **23** due to the partial conversion of this electron-rich aryl bromide. High yields in the C3-arylation products **24** and **25** were obtained using the heteroaryl bromides, 3-bromopyridine and 3-bromoquinoline. With these six (hetero)aryl bromides, only trace amount of other regioisomers were detected by GC/MS analysis of the crude mixtures. By contrast, the coupling of 1,2,3-trifluorobenzene with 3-bromoquinoline, under the same reaction conditions, afforded **26** in only 31% yield due to a low conversion of this heteroaryl bromide, but with complete regioselectivity.



Scheme 7. Direct arylations of 1,2,3- and 1,2,4-trifluorobenzenes

1-Chloro-2,4-difluorobenzene exhibits a similar reactivity than 1,2,4-trifluorobenzene with Pd/C catalyst (Scheme 8). Again, the arylation occurred regioselectively at the C-H bond flanked by two fluorine atoms. Cyano, acetyl, ester and methyl *para*-substituents on the aryl bromide were tolerated affording the products **27**-**30** in 80-88% yields. A 2-cyano substituent on the aryl bromide was also tolerated giving rise to the biaryl **32** in 79% yield. Good yields in products **33** and **34** were also obtained using 3- and 4-bromopyridines as the heteroaryl sources. A reaction performed on a larger scale (3 mmol of 3-bromopyridine) afforded the product **33** in a similar yield of 84%.



Scheme 8. Direct arylations of 1-chloro-2,4-difluorobenzene

As expected, 1,3- and 1,4-difluorobenzenes were less reactive than 1,2,4-trifluorobenzene (Scheme 9). In the presence of 4-bromoacetophenone or 3-bromoquinoline, low yields in the target products **35**-**37** were obtained due to partial conversions of the (hetero)aryl bromides. However, with 1,3-difluorobenzene, the regioselectivities in favor of the C2-arylation products **35** and **36** were quite high (>84% according to GC/MS analysis of the crude mixtures).

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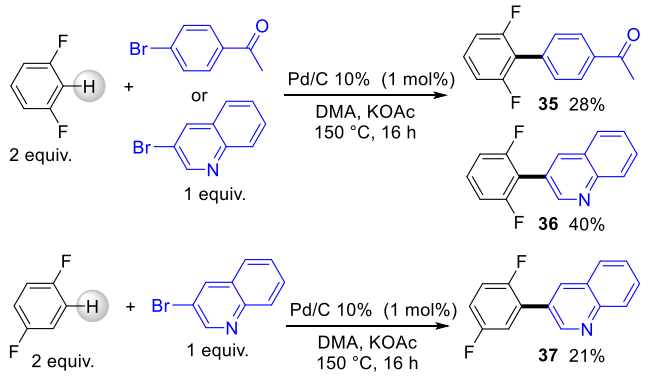
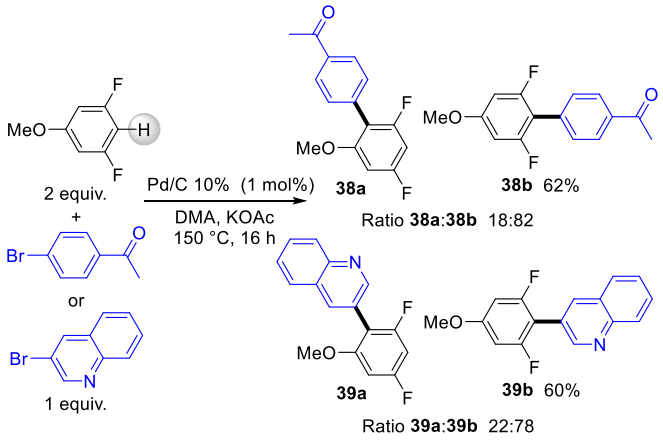


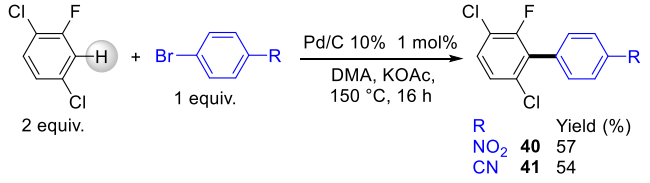
Scheme 9. Direct arylations of 1,3- and 1,4-difluorobenzenes

The arylation of 1,3-difluoro-5-methoxybenzene by 4-bromoacetophenone or 3-bromoquinoline with Pd/C catalyst afforded **38b** and **39b** in 62% and 60% yield, respectively (Scheme 10). However, moderate regioselectivities were observed in both cases, and as expected the major regioisomers **38b** and **39b** come from the arylation at the position flanked by two fluorine atoms, whereas the other regioisomers **38a** and **39a** were produced in 18% and 22% selectivities.



Scheme 10. Direct arylations of 1,3-difluoro-5-methoxybenzene

Finally, the reactivity of a mono-fluoro substituted benzene derivative using 1 mol% Pd/C catalyst was studied (Scheme 11). The coupling of 1,4-dichloro-2-fluorobenzene with 4-bromonitrobenzene or 4-bromobenzonitrile provides the expected biaryls **40** and **41** in 57% and 54% yield, respectively. The arylation took place very regioselectively at the C-H bond flanked by C-F and C-Cl bonds. No C-Cl or C-F bonds cleavages were detected, and again the regioselectivity of the coupling was similar than with a homogeneous Pd-catalyst.[6d]



Scheme 11. Direct arylations of 1,4-dichloro-2-fluorobenzene

Conclusion

In summary, the heterogeneous Pd/C catalyst was found to promote efficiently the direct arylation of a range of polyfluorobenzene derivatives. To our knowledge these are the first examples of direct arylations of polyfluorobenzenes using a heterogeneous pre-catalyst. In general, high yields in biaryl derivatives were obtained using tri-, tetra- and penta-fluorobenzenes; whereas, mono- and di-fluorobenzenes were less reactive. Unexpectedly, from pentafluorobenzene at 150°C, tetrafluoro-substituted [1,1'-biphenyl]-4-ols were obtained due to a regioselective formal hydroxylation; whereas, at lower temperatures the expected pentafluorobiphenyls were obtained. These arylations were performed using only 1 mol% Pd/C catalyst and KOAc as inexpensive base. A variety of aryl bromide substituents such as nitrile, nitro, acetyl, trifluoromethyl, ester, methyl, *tert*-butyl or methoxy was tolerated. The major by-products of these reactions are KOAc associated to HBr and Pd/C catalyst can be easily removed by simple filtration. As this protocol is phosphine-free, the products obtained by this method will not be contaminated with phosphine residues which are often observed using homogeneous catalysts. For these reasons, this protocol provides an economically viable and environmentally very attractive access to polyfluorobiphenyl derivatives.

Experimental Section

DMA (*N*,*N*-dimethylacetamide) (99%) and KOAc (99%) were purchased from Fischer. 10% Pd/C was purchased from Aldrich (Reference 205699 which is expect to conform to the following: approximately 90% <60 µm and 10% <5 µm with an average particle size of 15 µm). These compounds were not purified before use.

General procedure for the synthesis of 1-41: The reaction of the aryl bromide (1 mmol), (poly)fluorobenzene derivative (1.5 or 2 mmol) (see schemes) and KOAc (0.196 g, 2 mmol) at 110-150 °C (see schemes) during 16-40 h in DMA (3 mL) in the presence of 10% Pd/C (0.011 g, 1 mol%) under argon affords the arylation product after filtration to remove Pd residues and salts, evaporation of the solvent, and purification on silica gel.

2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-carbonitrile (1a)[17]

From 4-bromobenzonitrile (0.182 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 110 °C during 40 h, **1a** was obtained in 61% (0.164 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 8.80 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -142.7 (m), -152.9 (m), -160.9 (m).

4'-Cyano-2,3,5,6-tetrafluoro-[1,1'-biphenyl]-4-yl acetate **1c** was also isolated in low yield when using dry DMA: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 7.80 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -143.6 (dd, J = 22.5, 9.4 Hz), -152.3 (dd, J = 22.7, 9.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 166.6, 144.0 (dm, J = 248.3 Hz), 141.2 (dm, J = 241.8 Hz), 132.4, 131.6 (m), 131.0 (t, J = 2.1 Hz), 118.2, 116.2 (t, J = 16.5 Hz), 113.3, 20.0.

2',3',5',6'-Tetrafluoro-4'-hydroxy-[1,1'-biphenyl]-4-carbonitrile (1b)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **1b** was obtained in 86% (0.230 g) yield as a white solid: mp 208-210 °C.

^{1}H NMR (400 MHz, Acetone d_6, 25 °C): δ= 7.93 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H). ^{19}F NMR (376 MHz, Acetone d_6, 25 °C): δ= -147.6 (m), -163.5 (m). ^{13}C NMR (100 MHz, Acetone d_6, 25 °C): δ= 144.1 (dm, J = 244.1 Hz), 138.3 (dm, J = 241.5 Hz), 136.6 (tt, J = 14.1, 4.2 Hz), 132.5 (m), 132.3, 131.3 (t, J = 2.0 Hz), 118.1, 112.4, 108.6 (t, J = 17.2 Hz). Elemental analysis: calcd (%) for $C_{13}H_5F_4NO$ (267.18): C 58.44, H 1.89; found: C 58.38, H 2.03.

1-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-yl)ethan-1-one (2a)[4b]

From 4-bromoacetophenone (0.199 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 110 °C during 40 h, **2a** was obtained in 72% (0.206 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 8.07 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 2.66 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -142.7 (m), -153.9 (m), -161.5 (m).

1-(2',3',5',6'-Tetrafluoro-4'-hydroxy-[1,1'-biphenyl]-4-yl)ethan-1-one (2b)

From 4-bromoacetophenone (0.199 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **2b** was obtained in 66% (0.187 g) yield as a white solid: mp 260-262 °C.

^{1}H NMR (400 MHz, Acetone d_6, 25 °C): δ= 8.11 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 2.64 (s, 3H). ^{19}F NMR (376 MHz, Acetone d_6, 25 °C): δ= -147.5 (m), -163.7 (m). ^{13}C NMR (100 MHz, Acetone d_6, 25 °C): δ= 196.7, 138.5 (dm, J = 241.1 Hz), 138.3 (dm, J = 241.0 Hz), 137.2, 136.3 (tt, J = 14.1, 4.2 Hz), 132.2 (m), 130.6 (t, J = 1.9 Hz), 128.3, 109.3 (t, J = 17.5 Hz), 25.9. Elemental analysis: calcd (%) for $C_{14}H_8F_4O_2$ (284.21): C 59.17, H 2.84; found: C 59.01, H 2.69.

2,3,5,6-Tetrafluoro-4'-nitro-[1,1'-biphenyl]-4-ol (3b)

From 4-bromonitrobenzene (0.202 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **3b** was obtained in 78% (0.224 g) yield as a white solid: mp 184-186 °C.

^{1}H NMR (400 MHz, Acetone d_6, 25 °C): δ= 8.37 (d, J = 8.9 Hz, 2H), 7.80 (d, J = 8.9 Hz, 2H). ^{19}F NMR (376 MHz, Acetone d_6, 25 °C): δ= -147.4 (m), -163.4 (m). ^{13}C NMR (100 MHz, Acetone d_6, 25 °C): δ= 147.9, 144.2 (dm, J = 244.0 Hz), 138.4 (dm, J = 241.0 Hz), 136.8 (tt, J = 14.1, 4.2 Hz), 134.4 (m), 131.6 (t, J = 2.0 Hz), 123.5, 108.2 (t, J = 17.0 Hz). Elemental analysis: calcd (%) for $C_{12}H_5F_4NO_3$ (287.17): C 50.19, H 1.76; found: C 50.35, H 1.69.

2,3,5,6-Tetrafluoro-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-ol (4b)

From 4-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **4b** was obtained in 89% (0.276 g) yield as a white solid: mp 148-150 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 7.74 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -62.9 (s), -145.0 (m), -163.0 (m). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 144.2 (dm, J = 244.2 Hz), 137.8 (dm, J = 241.8 Hz), 135.0 (tt, J = 14.1, 4.2 Hz), 131.2 (m), 131.0 (q, J = 32.8 Hz), 130.8 (t, J = 2.0 Hz), 125.7 (q, J = 3.8 Hz), 124.0 (q, J = 272.2 Hz), 110.3 (t, J = 16.8 Hz). Elemental analysis: calcd (%) for $C_{13}H_5F_7O$ (310.17): C 50.34, H 1.62; found: C 50.50, H 1.69.

2,3,4,5,6-Pentafluoro-4'-methyl-1,1'-biphenyl (5a)[4c]

From 4-bromotoluene (0.171 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 130 °C during 40 h, **5a** was obtained in 35% (0.090 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 7.34-7.28 (m, 4H), 2.43 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -143.4 (m), -156.2 (m), -162.5 (m).

2,3,5,6-Tetrafluoro-4'-methyl-[1,1'-biphenyl]-4-ol (5b)

From 4-bromotoluene (0.171 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **5b** was obtained in 53% (0.135 g) yield as a white solid: mp 168-170 °C.

^{1}H NMR (400 MHz, Acetone d_6, 25 °C): δ= 7.36 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 2.39 (s, 3H). ^{19}F NMR (376 MHz, Acetone d_6, 25 °C): δ= -147.8 (m), -164.2 (m). ^{13}C NMR (100 MHz, Acetone d_6, 25 °C): δ= 144.2 (dm, J = 244.0 Hz), 138.6, 138.3 (dm, J = 242.0 Hz), 135.3 (tt, J = 14.1, 4.2 Hz), 130.1 (t, J = 1.9 Hz), 129.2, 124.5 (t, J = 2.1 Hz), 110.4 (t, J = 18.0 Hz), 20.3. Elemental analysis: calcd (%) for $C_{13}H_8F_4O$ (256.20): C 60.95, H 3.15; found: C 61.11, H 3.14.

4'-(*tert*-Butyl)-2,3,5,6-tetrafluoro-[1,1'-biphenyl]-4-ol (6b)

From 4-*tert*-butylbromobenzene (0.212 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **6b** was obtained in 48% (0.143 g) yield as a white solid: mp 108-110 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 7.51 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 1.40 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -145.2 (m), -163.8 (m). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 151.8, 144.3 (dm, J = 245.2 Hz), 137.8 (ddt, J = 241.7, 16.7, 4.6 Hz), 133.8 (tt, J = 14.0, 4.1 Hz), 129.9, 125.6, 124.3, 111.7 (t, J = 17.2 Hz), 34.7, 31.3. Elemental analysis: calcd (%) for $C_{16}H_{14}F_4O$ (298.28): C 64.43, H 4.73; found: C 64.28, H 4.50.

2,3,5,6-Tetrafluoro-4'-methoxy-[1,1'-biphenyl]-4-ol (7b)

From 4-bromoanisole (0.187 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **7b** was obtained in 65% (0.177 g) yield as a white solid: mp 170-172 °C.

^{1}H NMR (400 MHz, Acetone d_6, 25 °C): δ= 7.42 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 3.87 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -145.5 (m), -163.9 (m). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 160.0, 144.4 (dm, J = 243.0 Hz), 137.7 (dm, J = 242.0 Hz), 133.8 (tt, J = 14.1, 4.2 Hz), 131.6 (t, J = 1.9 Hz), 119.5 (m), 114.3, 111.6 (t, J = 17.4 Hz), 55.5. Elemental analysis: calcd (%) for $C_{13}H_8F_4O_2$ (272.20): C 57.36, H 2.96; found: C 57.54, H 2.78.

2',3',5',6'-Tetrafluoro-4'-hydroxy-[1,1'-biphenyl]-2-carbonitrile (8b)

From 2-bromobenzonitrile (0.182 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **8b** was obtained in 81% (0.216 g) yield as a white solid: mp 210-212 °C.

^{1}H NMR (400 MHz, Acetone d_6, 25 °C): δ = 7.99 (dd, J = 7.8, 0.8 Hz, 1H), 7.88 (td, J = 7.8, 1.3 Hz, 1H), 7.73 (td, J = 7.8, 1.3 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H). ^{19}F NMR (376 MHz, Acetone d_6, 25 °C): δ = -140.2 (m), -158.2 (m). ^{13}C NMR (100 MHz, Acetone d_6, 25 °C): δ = 144.4 (dm, J = 244.0 Hz), 138.3 (dm, J = 241.8 Hz), 137.2 (tt, J = 14.1, 4.2 Hz), 133.3, 133.2, 132.2, 131.1 (t, J = 1.9 Hz), 129.9, 116.9, 114.0, 106.9 (t, J = 18.7 Hz). Elemental analysis: calcd (%) for $C_{13}H_5F_4NO$ (267.18): C 58.44, H 1.89; found: C 58.62, H 2.08.

2,3,5,6-Tetrafluoro-4-(pyridin-3-yl)phenol (9b)

From 3-bromopyridine (0.158 g, 1 mmol) and pentafluorobenzene (0.252 g, 1.5 mmol) at 150 °C during 16 h, **9b** was obtained in 75% (0.182 g) yield as a white solid: mp 264-266 °C.

^{1}H NMR (400 MHz, DMSO d_6, 25 °C): δ = 8.69-8.64 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.55 (dd, J = 8.0, 4.8 Hz, 1H), 3.35 (bs, 1H). ^{19}F NMR (376 MHz, DMSO d_6, 25 °C): δ = -146.7 (m), -161.4 (m). ^{13}C NMR (100 MHz, DMSO d_6, 25 °C): δ = 150.7, 150.1, 144.2 (dm, J = 244.0 Hz), 138.5 (dm, J = 241.8 Hz), 138.2, 137.2 (tt, J = 14.1, 4.2 Hz), 124.3, 124.2, 106.2 (t, J = 18.1 Hz). Elemental analysis: calcd (%) for $C_{11}H_5F_4NO$ (243.16): C 54.33, H 2.07; found: C 54.39, H 2.12.

2,3,4,5-Tetrafluoro-4'-methyl-1,1'-biphenyl (10)[4a]

From 4-bromotoluene (0.171 g, 1 mmol) and 1,2,3,4-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **10** was obtained in 62% (0.149 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.07-6.98 (m, 1H), 2.41 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -139.8 (m), -143.9 (m), -155.4 (m), -157.6 (m).

1-(2',3',4',5'-Tetrafluoro-[1,1'-biphenyl]-4-yl)ethan-1-one (11)

From 4-bromoacetophenone (0.199 g, 1 mmol) and 1,2,3,4-tetrafluorobenzene (0.225 g, 1.5 mmol) at 140 °C during 16 h, **11** was obtained in 55% (0.147 g) yield as a white solid: mp 112-114 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.08 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.16-7.07 (m, 1H), 2.67 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -138.8 (m), -142.9 (m), -154.5 (m), -155.4 (m). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.4, 147.4 (dm, J = 247.8 Hz), 145.1 (dm, J = 249.1 Hz), 141.5 (dm, J = 253.2 Hz), 140.5 (dm, J = 255.0 Hz), 137.6, 137.0, 129.1 (d, J = 3.1 Hz), 128.8, 124.1 (m), 111.4 (dt, J = 19.7, 3.0 Hz), 26.7. Elemental analysis: calcd (%) for $C_{14}H_8F_4O$ (268.21): C 62.69, H 3.01; found: C 62.25, H 2.93.

2,3,5,6-Tetrafluoro-4'-nitro-1,1'-biphenyl (12a)[18]

From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,2,4,5-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **12a** was obtained in 52% (0.141 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.39 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 7.20 (tt, J = 9.5, 7.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -137.8 (dd, J = 22.0, 12.9 Hz), -143.2 (dd, J = 22.0, 12.9 Hz).

2',3',5',6'-Tetrafluoro-[1,1'-biphenyl]-4-carbonitrile (13a)[19]

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,4,5-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **13a** was obtained in 83% (0.208 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.79 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.15 (tt, J = 9.5, 7.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -137.9 (dd, J = 22.0, 12.9 Hz), -143.4 (dd, J = 22.0, 12.9 Hz).

1-(2',3',5',6'-Tetrafluoro-[1,1'-biphenyl]-4-yl)ethan-1-one (14a)[20]

From 4-bromoacetophenone (0.199 g, 1 mmol) and 1,2,4,5-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **14a** was obtained in 58% (0.155 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.08 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.12 (tt, J = 9.5, 7.0 Hz, 1H), 2.66 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -138.4 (dd, J = 22.0, 12.9 Hz), -143.4 (dd, J = 22.0, 12.9 Hz).

Diarylated product **14b** was also isolated in low yield: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.11 (d, J = 8.5 Hz, 4H), 7.64 (d, J = 8.5 Hz, 4H), 2.67 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -143.3 (s).

2,3,5,6-Tetrafluoro-4'-methyl-1,1'-biphenyl (15a)[4a]

From 4-bromotoluene (0.171 g, 1 mmol) and 1,2,4,5-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **15a** was obtained in 41% (0.098 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.06 (tt, J = 9.5, 7.4 Hz, 1H), 2.45 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -139.3 (dd, J = 22.0, 12.9 Hz), -144.0 (dd, J = 22.0, 12.9 Hz).

Diarylated product **15b** was also isolated in low yield: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.42 (d, J = 8.1 Hz, 4H), 7.32 (d, J = 8.1 Hz, 4H), 2.44 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -144.7 (s).

2,3,5,6-Tetrafluoro-4'-methoxy-1,1'-biphenyl (16a)[7a]

From 4-bromoanisole (0.187 g, 1 mmol) and 1,2,4,5-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **16a** was obtained in 46% (0.118 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40 (d, J = 8.5 Hz, 2H), 7.05-6.95 (m, 3H), 3.87 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -139.4 (dd, J = 22.0, 12.9 Hz), -144.2 (dd, J = 22.0, 12.9 Hz).

Diarylated product **16b** was also isolated in low yield: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.46 (d, J = 8.1 Hz, 4H), 7.04 (d, J = 8.1 Hz, 4H), 3.88 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -145.0 (s).

2,3,5,6-Tetrafluoro-3'-nitro-1,1'-biphenyl (17a)

From 3-bromonitrobenzene (0.202 g, 1 mmol) and 1,2,4,5-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **17a** was obtained in 60% (0.162 g) yield as a white solid: mp 158-160 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 8.39 (s, 1H), 8.36 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.73 (t, *J* = 8.3 Hz, 1H), 7.19 (tt, *J* = 9.5, 7.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -137.8 (dd, *J* = 22.0, 12.9 Hz), -143.6 (dd, *J* = 22.0, 12.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 148.4, 146.2 (dm, *J* = 249.5 Hz), 143.6 (dm, *J* = 243.5 Hz), 136.1 (t, *J* = 2.0 Hz), 129.8, 129.1 (t, *J* = 2.3 Hz), 125.3 (t, *J* = 2.2 Hz), 124.1, 119.0 (t, *J* = 16.0 Hz), 106.3 (t, *J* = 22.6 Hz). Elemental analysis: calcd (%) for $C_{12}H_5F_4NO_2$ (271.17): C 53.15, H 1.86; found: C 53.31, H 2.01.

2',3',5',6'-Tetrafluoro-[1,1'-biphenyl]-3-carbonitrile (18a)

From 3-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,4,5-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **18a** was obtained in 78% (0.196 g) yield as a white solid: mp 130-132 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 7.79-7.72 (m, 2H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.15 (tt, *J* = 9.5, 7.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -137.9 (dd, *J* = 22.1, 12.1 Hz), -143.7 (dd, *J* = 22.1, 13.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 146.3 (dm, *J* = 249.5 Hz), 143.7 (dm, *J* = 243.5 Hz), 134.5 (t, *J* = 2.1 Hz), 133.6 (t, *J* = 2.1 Hz), 132.7, 129.6, 128.8 (t, *J* = 1.4 Hz), 119.1 (t, *J* = 17.1 Hz), 118.0, 113.2, 106.2 (t, *J* = 22.6 Hz). Elemental analysis: calcd (%) for $C_{13}H_5F_4N$ (251.18): C 62.16, H 2.01; found: C 62.30, H 2.10.

2',3',5',6'-Tetrafluoro-[1,1'-biphenyl]-2-carbonitrile (19a)

From 2-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,4,5-tetrafluorobenzene (0.225 g, 1.5 mmol) at 150 °C during 16 h, **19a** was obtained in 38% (0.095 g) yield as a white solid: mp 92-94 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 7.85 (d, *J* = 8.0, 0.8 Hz, 1H), 7.74 (td, *J* = 7.8, 1.3 Hz, 1H), 7.61 (td, *J* = 7.8, 1.3 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.18 (tt, *J* = 9.5, 7.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -137.8 (dd, *J* = 22.0, 12.9 Hz), -140.8 (dd, *J* = 22.0, 12.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 146.1 (dm, *J* = 249.5 Hz), 143.6 (dm, *J* = 243.5 Hz), 133.4, 132.9, 131.5, 131.2 (t, *J* = 2.4 Hz), 129.9, 118.0 (t, *J* = 17.6 Hz), 116.9, 113.9, 107.0 (t, *J* = 22.5 Hz). Elemental analysis: calcd (%) for $C_{13}H_5F_4N$ (251.18): C 62.16, H 2.01; found: C 62.35, H 1.95.

2',3',6'-Trifluoro-[1,1'-biphenyl]-4-carbonitrile (20)[6c]

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,4-trifluorobenzene (0.198 g, 1.5 mmol) at 150 °C during 16 h, **20** was obtained in 76% (0.177 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 7.76 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.25-7.15 (m, 1H), 7.02-6.93 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -119.5 (dd, *J* = 14.8, 1.4 Hz), -137.5 (dd, *J* = 20.7, 1.6 Hz), -141.1 (dd, *J* = 20.9, 15.1 Hz).

2,3,6-Trifluoro-4'-nitro-1,1'-biphenyl (21)[6c]

From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,2,4-trifluorobenzene (0.198 g, 1.5 mmol) at 150 °C during 16 h, **21** was obtained in 71% (0.179 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 8.34 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.31-7.17 (m, 1H), 7.07-6.93 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -119.3 (dd, *J* = 14.5, 1.4 Hz), -137.2 (dd, *J* = 21.5, 2.0 Hz), -141.0 (dd, *J* = 21.0, 15.3 Hz).

1-(2',3',6'-Trifluoro-[1,1'-biphenyl]-4-yl)ethan-1-one (22)[6c]

From 4-bromoacetophenone (0.199 g, 1 mmol) and 1,2,4-trifluorobenzene (0.198 g, 1.5 mmol) at 150 °C during 16 h, **22** was obtained in 72% (0.180 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 8.08 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.25-7.14 (m, 1H), 7.04-6.93 (m, 1H).

4'-(*tert*-Butyl)-2,3,6-trifluoro-1,1'-biphenyl (23)

From 4-*tert*-butylbromobenzene (0.212 g, 1 mmol) and 1,2,4-trifluorobenzene (0.198 g, 1.5 mmol) at 150 °C during 16 h, **23** was obtained in 56% (0.148 g) yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 7.51 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.15-7.04 (m, 1H), 6.95-6.83 (m, 1H), 1.38 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -119.7 (dd, *J* = 15.2, 3.6 Hz), -137.9 (dd, *J* = 21.5, 3.6 Hz), -141.2 (dd, *J* = 21.3, 15.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ= 155.3 (ddd, *J* = 244.7, 4.9, 2.6 Hz), 151.8, 147.8 (ddd, *J* = 249.7, 14.2, 7.5 Hz), 147.7 (ddd, *J* = 244.4, 13.8, 3.7 Hz), 129.8, 125.3 (m), 120.2 (dd, *J* = 20.6, 15.0 Hz), 115.3 ddd, *J* = 19.5, 10.0, 1.3 Hz), 110.7 (ddd, *J* = 25.6, 6.8, 4.2 Hz), 34.7, 31.3. Elemental analysis: calcd (%) for $C_{16}H_{15}F_3$ (264.29): C 72.71, H 5.72; found: C 72.65, H 5.90.

3-(2,3,6-Trifluorophenyl)pyridine (24)[6c]

From 3-bromopyridine (0.158 g, 1 mmol) and 1,2,4-trifluorobenzene (0.198 g, 1.5 mmol) at 150 °C during 16 h, **24** was obtained in 84% (0.175 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 8.73 (bs, 1H), 8.66 (bs, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.25-7.11 (m, 1H), 7.03-6.93 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -119.7 (dd, *J* = 14.5, 2.6 Hz), -137.6 (dd, *J* = 21.0, 2.4 Hz), -141.3 (dd, *J* = 21.3, 15.2 Hz).

3-(2,3,6-Trifluorophenyl)quinoline (25)[6c]

From 3-bromoquinoline (0.208 g, 1 mmol) and 1,2,4-trifluorobenzene (0.198 g, 1.5 mmol) at 150 °C during 16 h, **25** was obtained in 77% (0.199 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 9.00 (s, 1H), 8.30 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.26-7.17 (m, 1H), 7.06-6.96 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ= -119.5 (dd, *J* = 14.5, 2.2 Hz), 137.5 (dd, *J* = 21.0, 2.2 Hz), -141.1 (dd, *J* = 21.3, 15.2 Hz).

3-(2,3,4-Trifluorophenyl)quinoline (26) [6c]

From 3-bromoquinoline (0.208 g, 1 mmol) and 1,2,3-trifluorobenzene (0.198 g, 1.5 mmol) at 150 °C during 16 h, **26** was obtained in 31% (0.080 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.04 (s, 1H), 8.28 (s, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.32-7.23 (m, 1H), 7.16-7.07 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -133.7 (dd, *J* = 20.5, 7.6 Hz), -138.0 (dd, *J* = 20.5, 7.6 Hz), -158.9 (t, *J* = 20.5 Hz).

3'-Chloro-2',6'-difluoro-[1,1'-biphenyl]-4-carbonitrile (27)[6d]

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1-chloro-2,4-difluorobenzene (0.297 g, 2 mmol) at 150 °C during 16 h, **27** was obtained in 88% (0.219 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.77 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.42 (td, *J* = 8.2, 5.6 Hz, 1H), 7.00 (td, *J* = 8.9, 1.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -113.8 (d, *J* = 5.7 Hz), -115.1 (d, *J* = 5.7 Hz).

1-(3'-Chloro-2',6'-difluoro-[1,1'-biphenyl]-4-yl)ethan-1-one (28) [6d]

From 4-bromoacetophenone (0.199 g, 1 mmol) and 1-chloro-2,4-difluorobenzene (0.297 g, 2 mmol) at 150 °C during 16 h, **28** was obtained in 86% (0.229 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.07 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.42 (td, *J* = 8.2, 5.6 Hz 1H), 7.00 (td, *J* = 8.9, 1.8 Hz, 1H), 2.67 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -113.7 (d, *J* = 6.2 Hz), -115.0 (d, *J* = 6.2 Hz).

Ethyl 3'-chloro-2',6'-difluoro-[1,1'-biphenyl]-4-carboxylate (29)

From ethyl 4-bromobenzoate (0.229 g, 1 mmol) and 1-chloro-2,4-difluorobenzene (0.297 g, 2 mmol) at 150 °C during 16 h, **29** was obtained in 80% (0.237 g) yield as a white solid: mp 64-66 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.14 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.38 (td, *J* = 8.2, 5.6 Hz 1H), 6.98 (td, *J* = 8.9, 1.8 Hz, 1H), 4.40 (q, *J* = 7.6 Hz, 2H), 1.41 (t, *J* = 7.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -113.7 (d, *J* = 6.2 Hz), -115.0 (d, *J* = 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.1, 158.1 (dd, *J* = 249.8, 5.7 Hz), 155.2 (dd, *J* = 251.3, 7.0 Hz), 133.0, 130.7, 130.2 (t, *J* = 1.9 Hz), 129.9 (d, *J* = 10.1 Hz), 129.6, 119.0 (dd, *J* = 19.8, 18.5 Hz), 117.3 (dd, *J* = 19.1, 4.2 Hz), 112.3 (dd, *J* = 24.2, 4.2 Hz), 61.2, 14.3. Elemental analysis: calcd (%) for $C_{15}H_{11}ClF_2O_2$ (296.70): C 60.72, H 3.74; found: C 60.57, H 4.00.

3-Chloro-2,6-difluoro-4'-methyl-1,1'-biphenyl (30)[6d]

From 4-bromotoluene (0.171 g, 1 mmol) and 1-chloro-2,4-difluorobenzene (0.297 g, 2 mmol) at 150 °C during 16 h, **30** was obtained in 82% (0.195 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38-7.26 (m, 5H), 6.95 (td, *J* = 8.9, 1.8 Hz, 1H), 2.42 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -114.1 (d, *J* = 7.6 Hz), -115.3 (d, *J* = 7.6 Hz).

4'-(*tert*-Butyl)-3-chloro-2,6-difluoro-1,1'-biphenyl (31)

From 4-*tert*-butylbromobenzene (0.212 g, 1 mmol) and 1-chloro-2,4-difluorobenzene (0.297 g, 2 mmol) at 150 °C during 16 h, **31** was obtained in 64% (0.179 g) yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.50 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.34 (td, *J* = 8.2, 5.6 Hz 1H), 6.95 (td, *J* = 8.9, 1.8 Hz, 1H), 1.37 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -114.0 (d, *J* = 7.5 Hz), -115.3 (d, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.4 (dd, *J* = 249.0, 5.7 Hz), 155.4 (dd, *J* = 250.1, 7.2 Hz), 151.7, 129.8 (t, *J* = 1.9 Hz), 128.8 (d, *J* = 9.9 Hz), 125.5, 125.4, 119.9 (dd, *J* = 19.9, 18.5 Hz), 117.0 (dd, *J* = 19.3, 4.2 Hz), 112.1 (dd, *J* = 24.6, 4.2 Hz), 34.7, 31.3. Elemental analysis: calcd (%) for $C_{16}H_{15}ClF_2$ (280.74) C 68.45, H 5.39; found: C 68.59, H 5.24.

3'-Chloro-2',6'-difluoro-[1,1'-biphenyl]-2-carbonitrile (32)[6d]

From 2-bromobenzonitrile (0.182 g, 1 mmol) and 1-chloro-2,4-difluorobenzene (0.297 g, 2 mmol) at 150 °C during 16 h, **32** was obtained in 79% (0.197 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.85 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.73 (td, *J* = 7.8, 1.3 Hz, 1H), 7.59 (td, *J* = 7.8, 1.2 Hz, 1H), 7.54-7.47 (m, 2H), 7.06 (td, *J* = 8.6, 1.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -111.9 (d, *J* = 5.3 Hz), -112.9 (d, *J* = 5.7 Hz).

3-(3-Chloro-2,6-difluorophenyl)pyridine (33)[6d]

From 3-bromopyridine (0.158 g, 1 mmol) and 1-chloro-2,4-difluorobenzene (0.297 g, 2 mmol) at 150 °C during 16 h, **33** was obtained in 87% (0.195 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.73-8.61 (m, 2H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.46-7.36 (m, 2H), 6.99 (td, *J* = 8.9, 1.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -114.0 (d, *J* = 6.4 Hz), -115.3 (d, *J* = 6.4 Hz).

4-(3-Chloro-2,6-difluorophenyl)pyridine (34)

From 4-bromopyridine (0.158 g, 1 mmol) and 1-chloro-2,4-difluorobenzene (0.297 g, 2 mmol) at 150 °C during 16 h, **34** was obtained in 83% (0.187 g) yield as a white solid: mp 108-110 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.75 (d, *J* = 3.6 Hz, 2H), 7.50-7.37 (m, 3H), 7.03 (td, *J* = 8.9, 1.5 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -113.7 (d, *J* = 5.2 Hz), -114.9 (d, *J* = 5.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.0 (dd, *J* = 251.0, 5.3 Hz), 155.1 (dd, *J* = 252.6, 6.9 Hz), 149.9, 136.8, 130.7 (d, *J* = 9.7 Hz), 124.9, 117.6 (dd, *J* = 19.0, 4.2 Hz), 117.3 (dd, *J* = 19.9, 18.5 Hz), 112.5 (dd, *J* = 24.0, 4.2 Hz). Elemental analysis: calcd (%) for $C_{11}H_6ClF_2N$ (225.62) C 58.56, H 2.68 found: C 58.39, H 2.62.

1-(2',6'-Difluoro-[1,1'-biphenyl]-4-yl)ethan-1-one (35)[21]

From 4-bromoacetophenone (0.199 g, 1 mmol) and 1,3-difluorobenzene (0.171 g, 1.5 mmol) at 150 °C during 16 h, **35** was obtained in 28% (0.065 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.05 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.38-7.29 (m, 1H), 7.06-6.97 (m, 2H), 2.65 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -114.2 (s).

3-(2,6-Difluorophenyl)quinoline (36)[6d]

From 3-bromoquinoline (0.208 g, 1 mmol) and 1,3-difluorobenzene (0.171 g, 1.5 mmol) at 150 °C during 16 h, **36** was obtained in 40% (0.096 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.04 (s, 1H), 8.32 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.42-7.31 (m, 1H), 7.13-7.04 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -114.3 (s).

3-(2,5-Difluorophenyl)quinoline (37)[22]

From 3-bromoquinoline (0.208 g, 1 mmol) and 1,4-difluorobenzene (0.171 g, 1.5 mmol) at 150 °C during 16 h, **37** was obtained in 21% (0.050 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.09 (s, 1H), 8.33 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.31-7.24 (m, 1H), 7.24-7.16 (m, 1H), 7.13-7.06 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -118.1 (d, *J* = 17.5 Hz), -123.6 (d, *J* = 17.5 Hz).

1-(2',6'-Difluoro-4'-methoxy-[1,1'-biphenyl]-4-yl)ethan-1-one (38b)

From 4-bromoacetophenone (0.199 g, 1 mmol) and 1,3-difluoro-5-methoxybenzene (0.216 g, 1.5 mmol) at 150 °C during 16 h, **38b** was obtained in 82% regioselectivity and in 62% (0.162 g) yield as a white solid: mp 112-114 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.04 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 6.59 (d, *J* = 9.9 Hz, 2H), 3.86 (s, 3H), 2.66 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -113.3 (s). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.7, 160.7 (t, *J* = 14.2 Hz), 160.5 (dd, *J* = 248.7, 10.2 Hz), 136.2, 134.4, 130.6 (t, *J* = 2.1 Hz), 128.2, 109.9 (t, *J* = 19.0 Hz), 98.3 (d, *J* = 28.2 Hz), 55.9, 26.6. Elemental analysis: calcd (%) for $C_{15}H_{12}F_2O_2$ (262.26): C 68.70, H 4.61; found: C 68.98, H 4.39.

3-(2,6-Difluoro-4-methoxyphenyl)quinoline (39b)[6d]

From 3-bromoquinoline (0.208 g, 1 mmol) and 1,3-difluoro-5-methoxybenzene (0.216 g, 1.5 mmol) at 150 °C during 16 h, **39b** was obtained in 78% regioselectivity and in 60% (0.162 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.00 (s, 1H), 8.25 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 9.9 Hz, 2H), 3.86 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -113.5 (s).

3,6-Dichloro-2-fluoro-4'-nitro-1,1'-biphenyl (40)[6d]

From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.330 g, 2 mmol) at 150 °C during 16 h, **40** was obtained in 57% (0.163 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.37 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 8.7, 1.6 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -111.4 (s).

3',6'-Dichloro-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (41)[6d]

From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.330 g, 2 mmol) at 150 °C during 16 h, **41** was obtained in 54% (0.144 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.78 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.28 (dd, *J* = 8.7, 1.5 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C): δ = -111.5 (s).

Supporting information

Copies of ^{1}H, ^{19}F and ^{13}C NMR spectra of new compounds and ^{1}H NMR spectra of known compounds.

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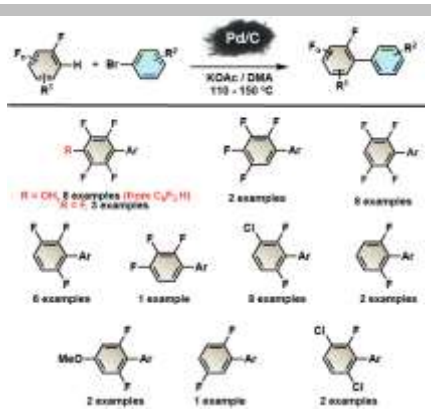
FULL PAPER

The potential of the heterogeneous catalyst Pd/C 10% in direct arylations of (poly)fluorobenzene derivatives was investigated. In general, high yields in biaryl derivatives were obtained using tri-, tetra- and penta-fluorobenzenes; whereas, mono- and di-fluorobenzenes were less reactive. Both electron-withdrawing and electron-donating substituents on aryl bromides were tolerated. The regioselectivities of the arylations were similar to those observed using homogeneous



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Pd/C as heterogeneous catalyst for the direct arylation of (poly)fluorobenzenes