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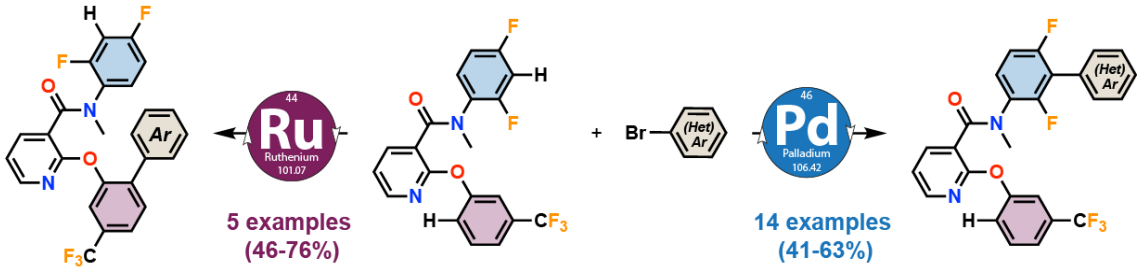
Regiodivergent late-stage Pd- or Ru-catalyzed C-H bond functionalization applied to the straightforward synthesis of *N*-methylated Diflufenican derivatives

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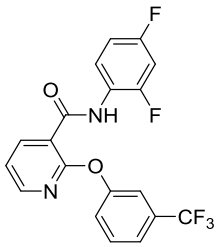
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Abstract: The late-stage C-H diversification methodology was applied to the preparation of arylated Diflufenican derivatives. Using a palladium catalyst associated to potassium pivalate, a regioselective arylation of the C-H bond flanked by the two fluorine atoms was observed. The reaction tolerated a wide range of useful functional groups on the aryl bromide. Conversely, the use of a ruthenium catalyst allowed to arylate the trifluoromethylbenzene ring of Diflufenican. To the best of our knowledge, these synthetic schemes are the first ones allowing the preparation of such arylated Diflufenican derivatives.

Late-stage functionalization of complex molecules *via* regioselective C-H bond functionalization currently represents a very hot topic in organic synthesis as it allows a fast tuning of the physical or biological properties.[1-3] So far, such late-stage functionalization has been applied to several heteroarenes or pyridine derivatives,[4] whereas, little efforts have been devoted to the C-H bond functionalization of fluorobenzene derivatives.[5,6]

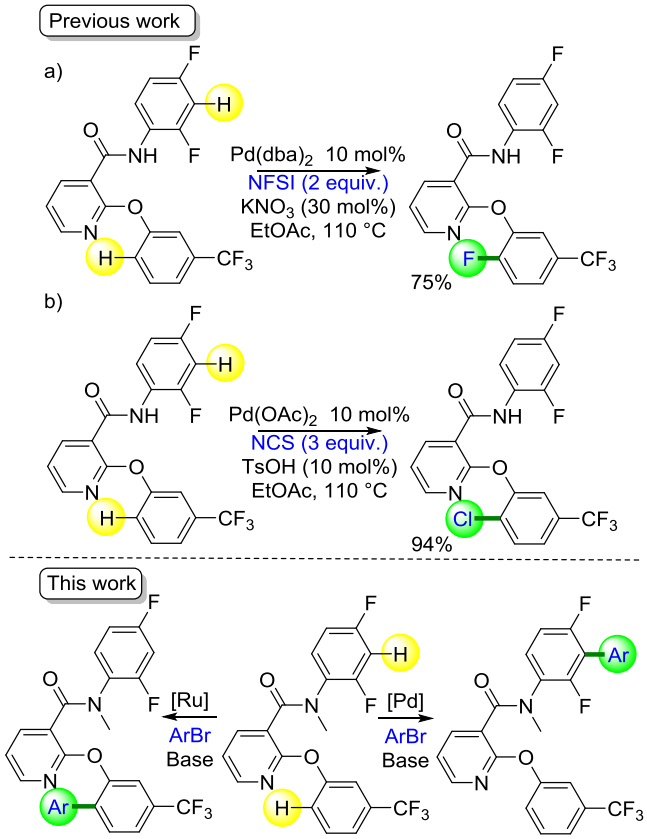
Diflufenican (Figure 1), which acts as a residual and foliar herbicide, contains a 1,3-difluorobenzene ring, a pyridine ring, a secondary amide and a trifluoromethylbenzene. Therefore, it represents a very interesting molecule in terms of C-H bond functionalization as fluoro,[4-6] amides[7] and especially pyridines, including 2-pyridyloxy[8] are known to be effective directing groups for C-H bond functionalization.



Diflufenican

Figure 1. Structure of Diflufenican.

In 2015, D.-Q. Xu, Z.-Y. Xu and coworkers reported that the trifluoromethylbenzene ring of Diflufenican could be fluorinated by NFSI (*N*-fluorobenzenesulfonimide) in the presence of a palladium catalyst (Scheme 1, a).[9] Two years later, H. Wu, G. Wu and coworkers described the chlorination of this trifluoromethylbenzene ring using NCS (*N*-chlorosuccinimide) and $Pd(OAc)_2$ catalyst (Scheme 1, b).[10] For these two reactions, the 2-pyridyloxy acts as the directing group. To the best of our knowledge, the direct functionalization of the difluorophenyl ring of Diflufenican has not been reported yet (Scheme 1, bottom right). Moreover, the Ru-catalyzed C-H bond functionalization of Diflufenican has not been investigated (Scheme 1, bottom left). Herein, we report on the reactivity of Diflufenican in Pd- and Ru-catalyzed C-H bond arylation.

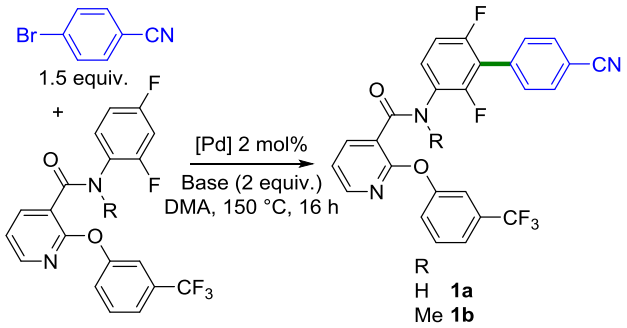


Scheme 1. Functionalization of Diflufenican *via* late-stage metal-catalyzed C-H functionalizations.

Based on our previously reported conditions for the Pd-catalyzed direct arylation of polyfluorobenzenes,[11] we first employed 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst with KOAc (2 equiv.) as the base in DMA (*N*,*N*-dimethylacetamide) at 150 °C to promote the direct arylation of the

difluorobenzene ring of Diflufenican with 4-bromobenzonitrile. However, under these reaction conditions, no formation of the desired product **1a** was obtained and both Diflufenican and the aryl bromide were recovered (Table 1, entry 1). The use of other bases such as PivOK or K_2CO_3 was also ineffective (Table 1, entries 2 and 3). We assumed this lack or reactivity was due to the formation of very stable palladium species arising from the coordination of Diflufenican. Both the pyridine unit and the secondary amide functional group could be responsible for the formation of such very stable palladium complexes. Therefore, we protected the secondary amide by methylation using iodomethane.

Table 1. Influence of the reaction conditions for palladium-catalyzed direct coupling of Diflufenican with 4-bromobenzonitrile.[a]\



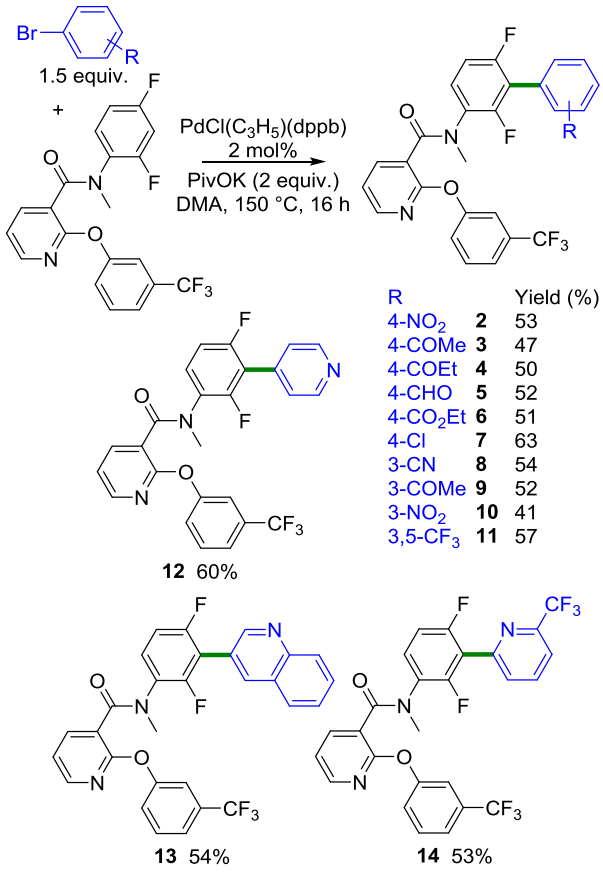
Entry	R	[Pd]	Base	Solvent	Yield in **1a** or **1b**
1	H	$PdCl(C_3H_5)(dppb)$	KOAc	DMA	0
2	H	$PdCl(C_3H_5)(dppb)$	KOPiv	DMA	0
3	H	$PdCl(C_3H_5)(dppb)$	K_2CO_3	DMA	0
4	Me	$PdCl(C_3H_5)(dppb)$	KOAc	DMA	32
5	Me	$PdCl(C_3H_5)(dppb)$	KOPiv	DMA	61
6	Me	$PdCl(C_3H_5)(dppb)$	K_2CO_3	DMA	<5
7	Me	$Pd(OAc)_2$	KOPiv	DMA	43
8	Me	$PdCl(C_3H_5)(dppb)$	KOPiv	DMF	27

[a] Diflufenican (1 mmol), 4-bromobenzonitrile (1.5 mmol), base (2 mmol), [Pd] (0.02 mmol), under argon, 16 h, 150 °C, isolated yields.

With this methylated Diflufenican, the target product **1b** was obtained in moderate yield (32%) with 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst, KOAc (2 equiv.) base in DMA (Table 1, entry 4). In order to improve the yield in **1b**, the reactivity of a few other bases was examined. With KOPiv, the yield in **1b** was improved to 61%, whereas K_2CO_3 only gave traces of the coupling product (Table 1, entries 5 and 6). Lower yields were also obtained using $Pd(OAc)_2$ as catalyst or DMF as the solvent (Table 1, entries 7 and 8). It should be mentioned that the arylation reaction was regioselective in favor of the C-H bond of the difluorobenzene unit which is flanked by two fluorine atoms. Under these conditions, no

arylation of the pyridine or trifluoromethylbenzene rings was detected, although pyridine is known to be a very good coordinating unit for palladium complexes.

Then, the scope of this reaction was studied (Scheme 2). First, a set of *para*-substituted aryl bromides was reacted with *N*-methyldiflufenican using 2 mol% $PdCl(C_3H_5)(dppb)$, KOPiv in DMA at 150 °C. The electron-withdrawing *para*-substituents nitro, acetyl, propionyl, formyl and ester on the aryl bromide were tolerated affording the target products **2**-**6** in 47-53% yields. A good yield of 63% in coupling product **7** was obtained from 4-bromo-1-chlorobenzene. No cleavage of the C-Cl bond was observed in the course of this reaction. The *meta*-substituted 3- bromobenzonitrile, 3-bromoacetophenone and 3-bromonitrobenzene led to the formation of the desired arylated Diflufenican derivatives **8**-**10** in moderate yields. From 3,5-bis(trifluoromethyl)bromobenzene, the product **11** was obtained in 57% yield.

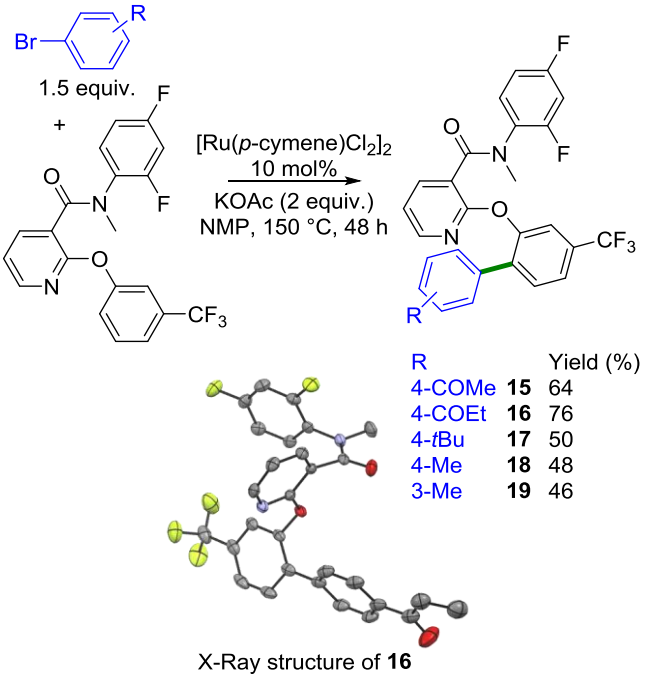


Scheme 2. Pd-catalyzed direct arylations of *N*-methyldiflufenican with a set of aryl bromides.

The *N*-containing 6-membered ring heterocycles are present in several very important drugs. Therefore, the reactivity of 4-bromopyridine and also 3-bromoquinoline for Pd-catalyzed coupling with Diflufenican was also studied. In both cases, the desired coupling products **12** and **13** were obtained in moderate yields. 2-Bromo-6-(trifluoromethyl)pyridine was also found to be reactive leading to the desired arylation product **14** in 53% yield.

Then, the reaction outcome of the Ru-catalyzed direct arylation of *N*-methyldiflufenican was studied (Scheme 3). Using $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst associated to KOAc base, which are known to be very effective conditions for the C-H arylation of 2-phenylpyridines,[3f] the regioselectivity of the arylation was different from the Pd-catalyzed reaction. It occurred regioselectively at the less hindered

ortho-position of the ether function of the trifluoromethylbenzene ring. The regioselectivity of this coupling was confirmed by X-Ray analysis of product **16**.[12] This reaction certainly proceeds *via* the coordination of the pyridine unit to ruthenium followed by a concerted metallation-deprotonation at the less hindered position of the trifluoromethylbenzene ring.[3f] From the acetyl or propionyl *para*-substituted aryl bromides, the products **15** and **16** were obtained in 64% and 76% yields, respectively. Moreover, the reaction tolerated the electron-rich aryl bromides 4-*tert*-butylbromobenzene and 4-bromotoluene providing the products **17** and **18** in 50% and 48% yield, respectively. The *meta*-substituted 3-bromotoluene, delivered the product **19** in a similar yield.



R		Yield (%)
4-COMe	**15**	64
4-COEt	**16**	76
4-*t*Bu	**17**	50
4-Me	**18**	48
3-Me	**19**	46

Scheme 3. Ru-catalyzed direct arylations of *N*-methyldiflufenican with a set of aryl bromides.

In summary, when appropriate reaction conditions are employed, the Pd- and Ru-catalyzed C-H bond functionalization of Diflufenican protected as a tertiary amide proceeds quite nicely. With a Pd-catalyst, Diflufenican was arylated at the C-H position which is flanked by two fluorine atoms. It should be mentioned that no arylation of the trifluoromethylbenzene ring was detected under these reaction conditions. In contrast, with a Ru-catalyst the arylation occurred at the less hindered *ortho*-position of the ether function of the trifluoromethylbenzene ring. These catalyst-controlled regioselective C–H bond arylation methods are the unique routes to access to this library of arylated Diflufenican derivatives. With both procedures, the arylated Diflufenican derivatives were obtained in very high regioselectivities and in moderate to good yields using air-stable catalysts, KOAc or KOPiv as inexpensive bases and aryl bromides as easily available aryl sources. These reactions tolerate a wide range of functional groups on the aryl bromide such as nitrile, nitro, acetyl, propionyl, formyl, ester, chloro. Heteroaryl bromides containing pyridine or quinoline units were also tolerated. Therefore, this late stage C-H bond functionalization methodology provides a convenient route to some functionalized (hetero)arylated Diflufenican derivatives allowing to tune the biological properties easily.

Experimental Section

Typical experiment for Pd-catalyzed arylation reactions: The reaction of the aryl bromide (0.75 mmol), *N*-(2,4-difluorophenyl)-*N*-methyl-2-(3-(trifluoromethyl)phenoxy)nicotinamide (0.204 g, 0.5 mmol) and PivOK (0.140 g, 1 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (6.1 mg, 2 mol%) in DMA under argon at 150 °C during 16 h, affords the arylated diflufenican derivatives **1b** and **2**-**14** after cooling, evaporation of the solvent and filtration on silica gel (pentane/ether).

Typical experiment for Ru-catalyzed arylation reactions: The reaction of the aryl bromide (0.75 mmol), *N*-(2,4-difluorophenyl)-*N*-methyl-2-(3-(trifluoromethyl)phenoxy)nicotinamide (0.204 g, 0.5 mmol) and KOAc (0.098 g, 1 mmol) in the presence of $[Ru(p\text{-Cymene})Cl_2]_2$ (18.7 mg, 10 mol%) in NMP under argon at 150 °C during 48 h, affords the arylated diflufenican derivatives **15**-**17** after cooling, evaporation of the solvent and filtration on silica gel (pentane/ether).

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Keywords: Catalysis • Palladium • Ruthenium • C-H bond functionalization • arylation

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