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# Acid fluorides in transition metal catalysis: A good balance between stability and reactivity

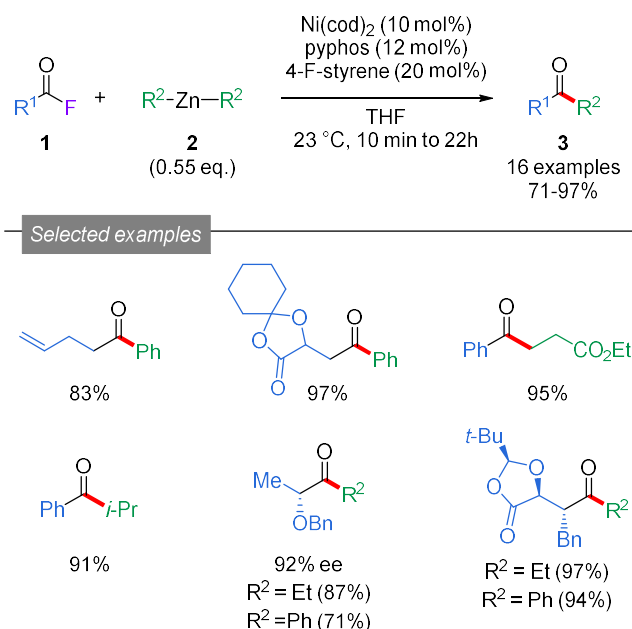
Nicolas Blanchard,<sup>[a]</sup> and Vincent Bizet\*<sup>[a]</sup>

Dedicated to Dr. Philippe Bisseret on the occasion of his retirement

**Abstract:** Several recent reports outlined the singular reactivity of acid fluorides as excellent electrophiles in transition-metal catalysis. These species undergo oxidative addition of the metal into the C-F bond; then, retention or release of the CO moiety can occur and be controlled by tuning the catalytic system and the reaction parameters. Acid fluorides, which can be derived from carboxylic acids, show good stability and high reactivity in a wide range of possible functionalizations with nucleophiles. Their use provides an interesting alternative to that of the parent carboxylic acid derivatives (acid chlorides, esters, amides, acids, or aldehydes).

Over the last two years, the development of selective transition-metal-catalyzed CF functionalization reactions has led to renewed interest in acid fluorides. The acid fluoride motif is a well-known functional group in organic chemistry; it is easily obtained from the corresponding carboxylic acid and mainly used for peptide couplings.<sup>[1]</sup> Most carboxylic acid derivatives, such as acids, acyl halides, anhydrides, esters, and amides, have been successfully used as electrophilic partners in cross-coupling reactions.<sup>[2–7]</sup> Compared to other acid halides or anhydrides, acid fluorides show higher stability towards water and neutral oxygen nucleophiles, and they are less prone to racemization. In the presence of palladium(0), nickel(0), or iridium(I) complexes, rapid oxidative addition takes place, leading to a highly electrophilic acyl PdII, NiII, or IrIII complex. The latter can then react with a wide variety of nucleophiles in a transmetalation step, following a decarbonylative or a non-decarbonylative reaction pathway depending on the ligand structure and the reaction parameters. In specific cases, the fluoride anion generated during the transmetalation elementary step is not innocent and can act as a mild base. Herein, we highlight recently developed crosscoupling reactions with acid fluorides; the specific reactivity of acid fluorides and comparative studies with other derivatives are also disclosed when available.

A groundbreaking study in this exciting field of research was reported by Rovis and Zhang. It concerns the synthesis of ketones **3** from acid fluorides **1** by a nickel(0)-catalyzed crosscoupling reaction with diorganozinc reagents **2** (Scheme 1).<sup>[8]</sup>

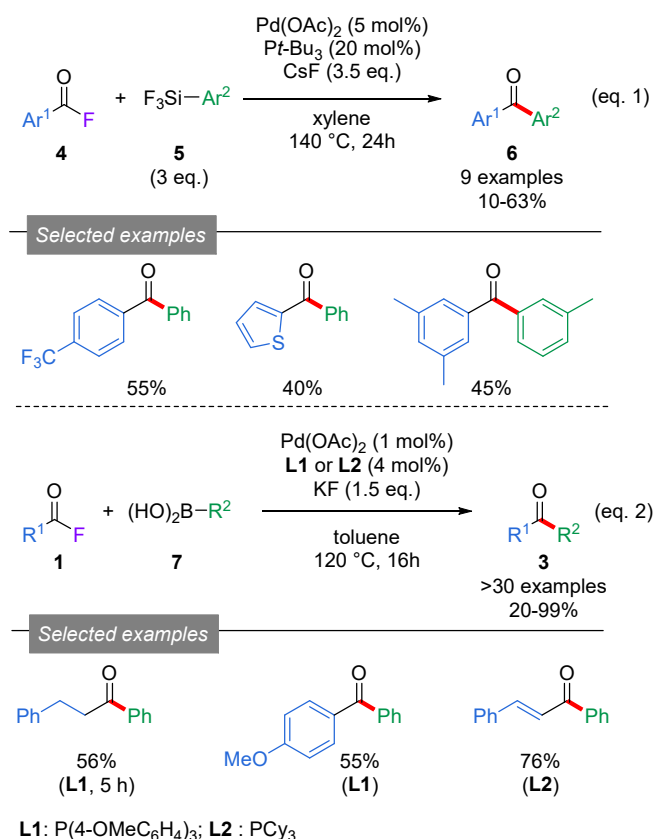


**Scheme 1.** Nickel(0)-catalyzed cross-coupling reactions of acyl fluorides **1** with diorganozinc reagents **2**.

The optimal catalytic system was based on (2-diphenylphosphinoethyl)pyridine (pyphos) as the ligand and 4-fluorostyrene as a substoichiometric additive that dramatically accelerates the reaction. The reaction proceeds, in most of the cases, in 10 to 30 min at ambient temperature, and gives the desired products in excellent yields. Remarkably, both groups of the diorganozinc species **2** are transferred, and the reaction works equally well with enantioenriched aliphatic acid fluorides without epimerization (Scheme 1, last four examples). The functional group tolerance is also worthy of note, with acetals, ethers, esters, succinimides, and alkenes being compatible. A comparative study showed that this procedure works equally well with acid chlorides, anhydrides, acyl cyanides, thioesters, pyridinyl, and aryl esters, but then usually requires slightly longer reaction times.

More recently, Hiyama-type cross-coupling reactions of benzoic acid fluorides **4** with aryl trifluorosilanes **5** were proposed by Sakai and co-workers for the generation of diaryl ketones **6** with a Pd<sup>0</sup>/Pt-Bu<sub>3</sub> catalytic system in the presence of cesium fluoride [Scheme 2, Eq. (1)].<sup>[9]</sup> However, the yields did not exceed 63%, and the scope was relatively limited. Acid fluorides and acid chlorides proved to be much more reactive than the corresponding acid bromides and anhydrides by a factor of two to three.

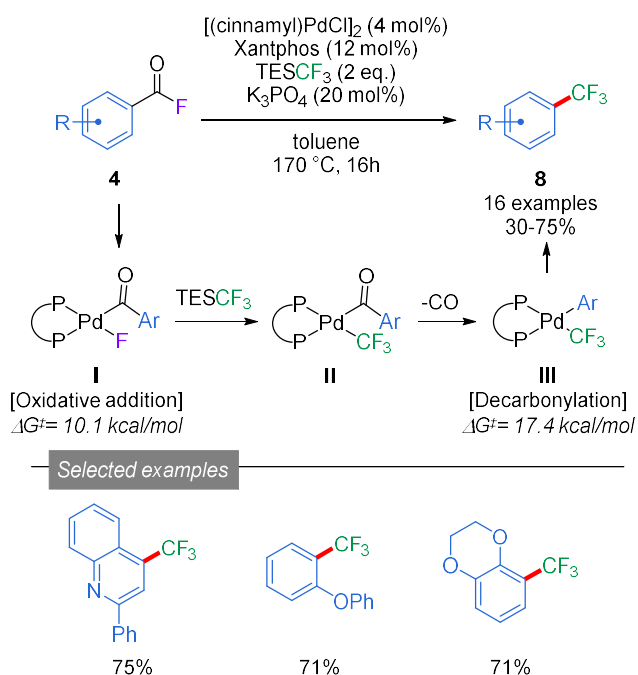
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**Scheme 2.** Palladium-catalyzed Hiyama and Suzuki-Miyaura cross coupling reactions of acid fluorides **4** (eq. 1) and **1** (eq. 2) with **5** and **7**.

The same research group subsequently developed a palladium(0)-catalyzed Suzuki-Miyaura cross-coupling of acid fluorides **1** with boronic acids **7** [Scheme 2, Eq. (2)]. Tris(4-methoxyphenyl)phosphine (**L1**) and tricyclohexylphosphine (**L2**) were found to be the best ligands for this process. Compared to the Hiyama cross-coupling [Eq. (1)], the Suzuki-Miyaura reaction is more general, and the formation of non-symmetric aryl, heteroaryl, alkyl, and alkenyl ketones **3** proceeded in moderate to high yields.<sup>[10]</sup>

The first decarbonylative coupling of acid fluorides enabled a trifluoromethylation reaction with triethyl(trifluoromethyl)silane, as reported by Schoenebeck and co-workers (Scheme 3).<sup>[11]</sup> Indeed, for the trifluoromethylation of oxidative-addition complexes, a previous report highlighted the need for the Xantphos ligand for the reductive elimination to occur, but most importantly, the formation of the Pd<sup>II</sup>F intermediate was crucial for the transmetalation step with the CF<sub>3</sub> anion.<sup>[12]</sup> Taking into account these considerations, the decarbonylative trifluoromethylation reaction of acid fluorides **4** proceeded in moderate to good yields in the presence of catalytic quantities of [(cinnamyl)PdCl]<sub>2</sub>, Xantphos, and K<sub>3</sub>PO<sub>4</sub> in toluene at high temperature, yielding trifluoromethylarenes **8**. It should be noted that under the same reaction conditions, Ar-Cl and Ar-Br substrates are totally unreactive, clearly indicating that the use of acid fluorides, and the presence of the fluoride thus generated, is key to the success of this transformation.



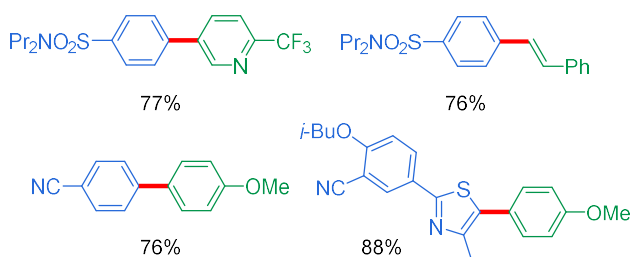
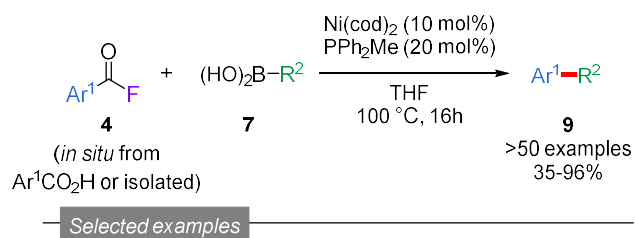
**Scheme 3.** Palladium-catalyzed decarbonylative trifluoromethylation of acid fluoride **4**

Computational studies favored a mechanism in which the oxidative-addition step has a free energy of activation of 10 kcal.mol<sup>-1</sup>, leading to complex **I**. The TS connecting complexes **II** and **III** is stabilized by favorable Xantphos-Pd interactions; in addition, it requires less distortion energy than the corresponding TS from ArCO [Pd<sup>II</sup>]F complex **I**. This mechanistic proposal is also supported by experimental results as the ketone resulting from reductive elimination of complex **II** was observed below 170 °C.

This elegant strategy works also with other nucleophiles, as exemplified by the base-free nickel-catalyzed decarbonylative Suzuki-Miyaura coupling of acid fluorides **4** with boronic acids **7** with a Ni(cod)<sub>2</sub>/PPh<sub>2</sub>Me catalytic system, or with the air-stable Ni(*o*-tolyl)(PPh<sub>2</sub>Me)<sub>2</sub>Cl complex and a catalytic amount of CsF (Scheme 4), which was reported by Sanford and co-workers.<sup>[13]</sup> Ligand screening showed that PPh<sub>2</sub>Me was essential to reach perfect selectivity for the decarbonylative arylation product **9**. The reaction proceeded smoothly with a wide variety of acid fluorides **4** and boronic acids **7** in moderate to excellent yields. It should be noted that the fluoride generated during the process acts as a mild base and activates the organoboronate intermediates; furthermore, with both nickel systems, the decarbonylation proceeds at room temperature while high temperatures are needed with palladium. A similar strategy has been used for the decarbonylative methylation or ethylation of acid fluoride using Lewis acidic trimethyl- or triethylborane and a closely related catalytic system (Ni(cod)<sub>2</sub>/dppe), which suffers from a narrower scope.<sup>[14]</sup>

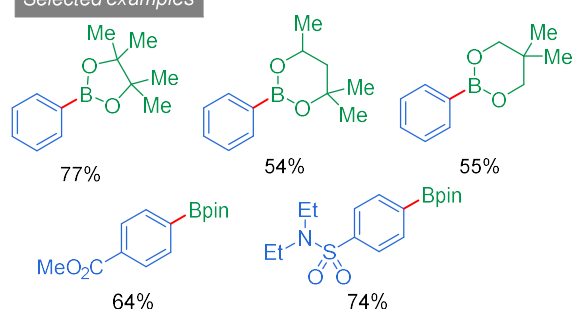
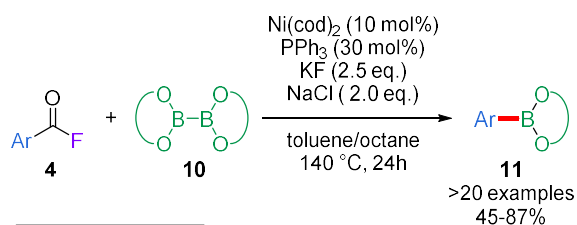
Soon after, the same group reported a nickel-catalyzed decarbonylative borylation of acid fluorides **4** (Scheme 5). An external source of fluoride (KF) is required to activate the B<sub>2</sub>pin<sub>2</sub>

(**10**), while NaCl as an additive is essential to reach satisfactory yields of products **11**.



**Scheme 4.** Nickel-catalyzed decarbonylative Suzuki-Miyaura cross coupling of acid fluorides **4**.

A comparative experiment showed that benzoyl chloride is totally unreactive under these reaction conditions, indicating that the acid fluoride plays a crucial role and that there is no conversion of the acid fluoride into the acid chloride with NaCl during the reaction. The reaction proceeds in moderate to excellent yields with good functional group tolerance; for example, an ester group in para position remained untouched.<sup>[15]</sup>

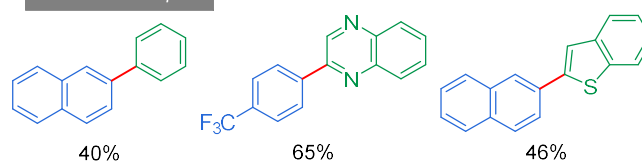
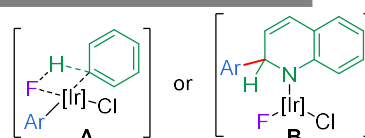
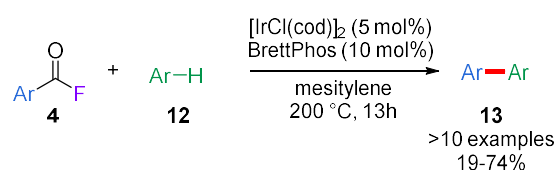


**Scheme 5.** Nickel-catalyzed decarbonylative borylation of acid fluorides **4**

The decarbonylative coupling of acid fluorides **4** can also be performed by C-H activation of arenes and heteroarenes catalyzed by a combination of [IrCl(cod)]<sub>2</sub> and BrettPhos in mesitylene at 200 °C, as shown by Tobisu and co-workers (Scheme 6). While the reaction is sensitive to steric hindrance, both electron-rich and electron-deficient (hetero)arenes **12** underwent the arylation

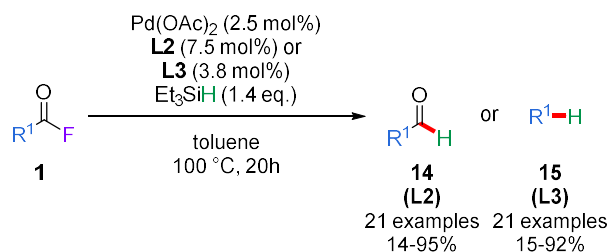
under identical conditions, providing the arylation products **13** in modest to good yields. The same holds true with regard to the acid fluoride substrates **4** even if electron-deficient ones react faster. Comparative experiments showed that acid chlorides, bromides, and anhydrides are completely unreactive in this transformation, showing once again the specific reactivity of acid fluorides. Mechanistic investigations suggested transition state **A** for arenes, where the fluoride abstracts a hydrogen atom in a CMD-like mechanism, and intermediate **B** for heteroarenes, resulting from arylation of the C=N bond.<sup>[16]</sup>

The control of reactivity and selectivity in organometallic catalysis is essential, and by careful tuning of the catalytic system and the reaction conditions, acid fluorides can evolve selectively in a decarbonylative or a non-decarbonylative pathway.

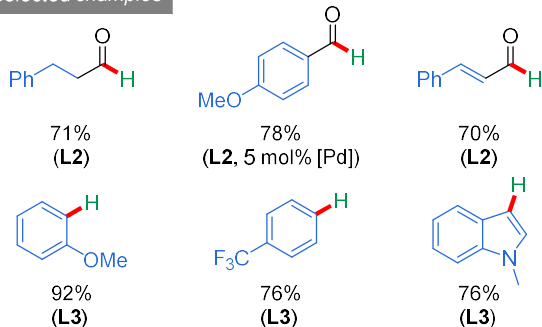


**Scheme 6.** Iridium-catalyzed decarbonylative C-H arylation of acid fluorides **4**.

This crucial control of the CO release has been addressed in the palladium-catalyzed reduction of acid fluorides **1** with triethylsilane developed by Sakai and coworkers, where the ligand fully controls the decarbonylation process (Scheme 7).<sup>[17]</sup> In the presence of the monodentate PCy<sub>3</sub> ligand (**L2**), acid fluorides **1** were converted into the corresponding aldehydes **14** without decarbonylation. However, replacing **L2** with the bidentate 1,2-bis(dicyclohexylphosphine)ethane system (**L3**) inverted the selectivity and afforded the decarbonylative reduction product **15** under otherwise identical reaction conditions. The difference in selectivity was explained by the difference in the Pd/L ratios (1:3 for **L2** vs. 1:1.5 for **L3**), leading in the former case to a coordinatively saturated oxidative-addition complex (OAC), which favors the formation of the aldehyde, while the bidentate **L3** ligand gives an OAC with a vacant coordination site, which might favor the decarbonylation step.



Selected examples



**L2:**  $\text{PCy}_3$ ; **L3:**  $\text{Cy}_2\text{P}(\text{CH}_2)_2\text{PCy}_2$

**Scheme 7.** Palladium-catalyzed reductive transformation of acid fluoride 1 with ligand-controlled decarbonylation reaction.

This brief overview of recently developed C-F functionalizations of acid fluorides with and without decarbonylation shows the high potential of this electrophilic coupling partner in catalytic reactions mediated by transition metals; we are confident that this concept will find many applications in catalysis for the synthesis of valuable compounds.

## Acknowledgements

We would like to warmly acknowledge our colleague and friend Dr. Philippe Bisseret for his long-lasting and insightful contributions to the group and his contagious and constant good mood.

**Keywords:** acid fluoride • catalysis • C-F functionalization • cross-coupling • decarbonylation

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