



HAL
open science

Direct Introduction of the 1-Fluorocyclopropyl Group via Stille Cross-Coupling – A Way of Getting Around Per- and Polyfluoroalkyl Substances (PFASs)

Florian Audet, Morgan Donnard, Armen Panossian, Philipp M Holstein,
David Bernier, Sergii Pazenok, Frédéric R. Leroux

► **To cite this version:**

Florian Audet, Morgan Donnard, Armen Panossian, Philipp M Holstein, David Bernier, et al.. Direct Introduction of the 1-Fluorocyclopropyl Group via Stille Cross-Coupling – A Way of Getting Around Per- and Polyfluoroalkyl Substances (PFASs). *Advanced Synthesis and Catalysis*, 2024, 10.1002/adsc.202400401 . hal-04655162

HAL Id: hal-04655162

<https://hal.science/hal-04655162v1>

Submitted on 21 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Direct Introduction of the 1-Fluorocyclopropyl Group *via* Stille Cross-Coupling – A Way of Getting Around Per- and Polyfluoroalkyl Substances (PFASs)

Florian Audet,^a Morgan Donnard,^a Armen Panossian,^a Philipp M. Holstein,^b David Bernier,^c Sergii Pazenok,^d and Frédéric R. Leroux^{a,*}

^a Laboratoire d'Innovation Moléculaire et Applications (UMR7042)
Université de Strasbourg, Université de Haute-Alsace, CNRS
25 rue Becquerel, 67000 Strasbourg (France)
E-mail: frederic.leroux@unistra.fr

^b Drug Discovery Sciences, Pharmaceutical Division, Bayer AG,
Aprather Weg 18 A, 42096 Wuppertal (Germany)

^c Bayer S.A.S.
14 impasse Pierre Baizet, 69263 Lyon (France)

^d Bayer CropScience AG
Alfred Nobel Straße 50, 40789 Monheim (Germany)

Manuscript received: April 9, 2024; Revised manuscript received: May 28, 2024;
Version of record online: ■■, ■■■

 Supporting information for this article is available on the WWW under <https://doi.org/10.1002/adsc.202400401>

 © 2024 The Author(s). Advanced Synthesis & Catalysis published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Abstract: We are reporting the preparation and use in cross-coupling reactions of a newly developed, bench-stable (1-fluorocyclopropyl)metalloid reagent. The Stille cross-coupling reaction described for this α -fluorinated stannane reagent is amenable to a wide range of aryl and alkenyl (pseudo)halides bearing a variety of functional groups. An enantioenriched cross-coupled product was also obtained from the corresponding 1-fluorocyclopropyltin reagent bearing an ester handle. Finally, the chemical stability of the 1-fluorocyclopropyl moiety was also demonstrated by performing several post-functionalizations.

Keywords: Cross-coupling; Cyclopropanation; Emerging Fluorinated Group; Fluorine; Palladium

The introduction of fluorine atoms in active ingredients can influence their potency as well as their selectivity by modulating crucial physico-chemical properties such as the conformation, pK_a and lipophilicity. Tuning these key properties also leads to the modification of the pharmacokinetic profile of the drug.^[1] As a result, on the one hand, a vast proportion of drugs and agrochemicals contains at least one fluorinated group, with a majority of trifluoromethyl ($-\text{CF}_3$) and monofluoro ($-\text{F}$) groups. Moreover, trifluoromethylated (hetero)aromatics are also over-represented within the family of trifluoromethylated scaffolds with a share of 83% in agrochemicals and 90% in pharmaceuticals.^[2,3] This overall lack of diversity is mainly due to the

scarcity of efficient synthetic methods to access a more diverse set of fluorinated groups.^[3] On the other hand, there has been a rising concern about per- and polyfluoroalkyl substances (PFAS) and trifluoroacetic acid (TFA) in the last few years, the latter arising mainly from the atmospheric breakdown of HCFCs and HFCs.^[4,5] Besides, TFA residues may also be generated from the degradation of fluoropolymers and trifluoromethylated pharmaceuticals and agrochemicals,^[6] although it is known that trifluoromethyl-substituted compounds do not necessarily decompose into TFA as defluorination pathways have also been witnessed.^[7,8] Nonetheless, in 2023, the European Chemicals Agency (ECHA) proposed a

universal class-based regulation of the manufacture, supply, and use of PFAS,^[9] based on the Organization for Economic Co-operation and Development (OECD) definition of PFAS.^[10] The latter is very broad, containing more than 12 000 molecules,^[11] including the ones bearing trifluoromethyl ($-\text{CF}_3$) and difluoromethylene groups ($-\text{CF}_2-$) with only a few exceptions. A recent study showed that 30% of fluorinated pharmaceuticals would fall within this PFAS definition.^[12]

In this context, efficient synthesis methods to access new, non-PFAS emerging fluorinated groups are needed to offer more alternatives to the already existing ones. We turned our attention toward small fluoroalkyl building blocks that could mimic the trifluoromethyl group.

The 1-fluorocyclopropyl moiety appeared as a very interesting target because of its appealing physicochemical properties; yet, its access remains complicated (*vide infra*). First, fluorinated cycloalkyl groups have emerged as key fragments in drug molecules.^[13] Second, the cyclopropyl ring system itself brings considerable interest in medicinal chemistry.^[14] In fact, the unique properties of cyclopropanes linked to their small size, significant ring strain and unusual bonding can contribute to improve various key properties such as potency, selectivity, aqueous solubility, oral bioavailability, metabolic stability and lipophilicity, for example, thus highlighting the importance of this structural motif in many medicinal chemistry projects.^[14–16] Besides, the 1-fluorocyclopropyl (1-FCp) group exhibits a slightly lowered lipophilicity (-0.36 in $\text{cLogD}_{7.4}$) and a similar volume ($+11.9 \text{ \AA}^3$) when compared to a trifluoromethyl group. In contrast, the acyclic 1-fluoroisopropyl analog shows a more significantly increased volume of $+24.0 \text{ \AA}^3$ in comparison to the trifluoromethyl one (Figure 1).

There are three main strategies known to date for the synthesis of a 1-FCp group attached to an aromatic ring. The first one relies on the cyclopropanation reaction of (1-fluorovinyl)arenes (Scheme 1, a). However, reported yields are generally low and most of these examples arise from patents, so that there is no comprehensive study on the scope of such reactions.^[17–25] Moreover, these cyclopropanation reactions often require diazomethane, thus necessitating

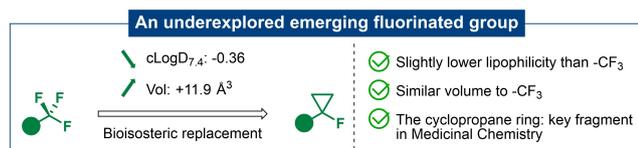
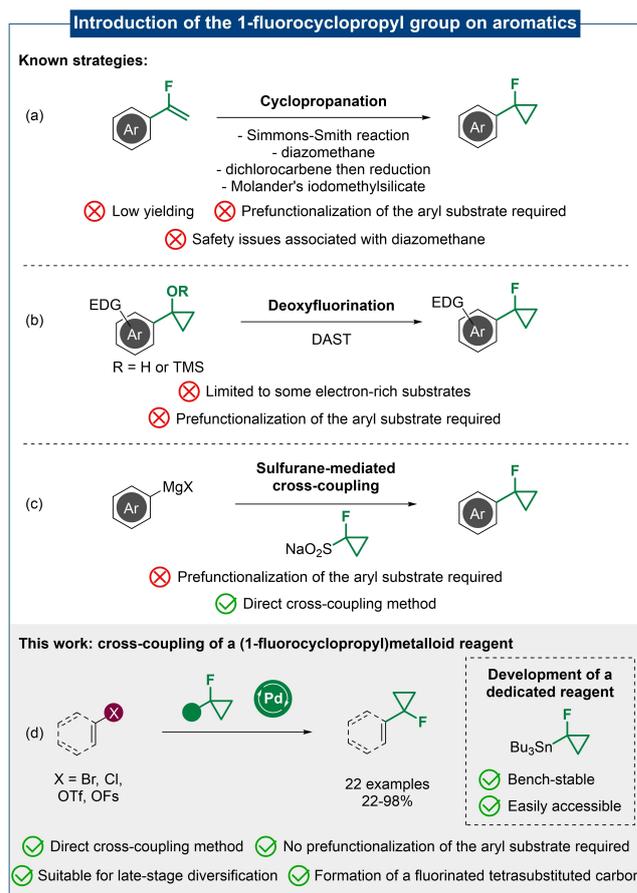


Figure 1. Predicted effect of the replacement of a trifluoromethyl group by a 1-fluorocyclopropyl one, calculated on MarvinSketch (ChemAxon).



Scheme 1. Introduction of the 1-fluorocyclopropyl group on aromatics.

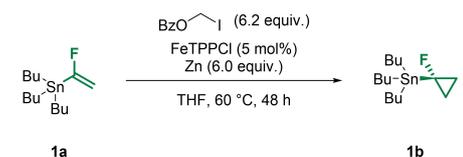
specific equipment and safety precautions that hinder their broad application in a standard research laboratory. A second strategy is based on the deoxyfluorination reaction of the corresponding cyclopropanol (Scheme 1, b). This reaction suffers from a very narrow scope due to the well-known ring-opening side-reaction, leading to the corresponding allylic fluoride.^[26–29] Therefore, it is limited to derivatives substituted by an electron-donating group since, even with an unsubstituted phenyl, the reaction yields exclusively the allylic fluoride side-product.^[27] Finally, Qin, Gutierrez and co-workers reported very recently the sulfurane-mediated installation of the 1-FCp group *via* the reaction of (hetero)aryl Grignard reagents with sodium 1-fluorocyclopropylsulfinate (Scheme 1, c).^[30] Seven examples were reported with yields in the 54–92% range. In the first two methods, the aryl substrate needs to be prefunctionalized in order to access the starting 1-fluorovinyl,^[19,31,32] or cyclopropanol,^[33] thus requiring one to three additional synthesis steps while the latter one uses Grignard reagents, showing hydrolysis-sensitivity and limited compatibility with

some ubiquitous functional groups in drug-like molecules.

Herein, we report the unprecedented palladium-catalyzed cross-coupling reaction of aryl halides with a new, bench-stable (1-fluorocyclopropyl)tin reagent, for the milder and direct introduction of the 1-fluorocyclopropyl group as a potential non-PFAS substituent. To the best of our knowledge, this work represents the first report of the synthesis and use in a palladium-catalyzed cross-coupling reactions of (1-fluorocyclopropyl)metalloid reagents, leading to the formation of a monofluorinated tetrasubstituted carbon (Scheme 1, d).

Our investigation started by evaluating the different access routes and the reactivity of potential silicon-, tin- and boron-based (1-fluorocyclopropyl)metalloid reagents. We could prepare a (1-fluorocyclopropyl)silane but it turned out to be unreactive under Hiyama cross-coupling conditions. On the contrary, we were unable to obtain any (1-fluorocyclopropyl)boronate despite our efforts (see SI for details). In order to access the key tributyl(1-fluorocyclopropyl)stannane reagent **1b**, we investigated multiple cyclopropanation reactions on tributyl(1-fluorovinyl)stannane **1a**, easily obtained *via* a Si–Sn transmetalation reaction on commercially available (1-fluorovinyl)methyldiphenylsilane.^[34] Our attempts to carry out the subsequent cyclopropanation under the Simmons-Smith conditions were unsuccessful and led to yields below 10%. This result is somewhat not surprising as vinylstannanes are known to be poor substrates in zinc-assisted carbenoid cyclopropanation strategies,^[35] and tend to rearrange in presence of the zinc(II) iodide that forms during the reaction.^[36] We then turned our attention to a recently reported Fe-catalyzed cyclopropanation method using α -acyloxy halides as carbene equivalents.^[37,38] In particular, iodomethyl benzoate (BzOCH₂I) proved to be a safer, thermally stable, alternative to diazomethane. Using this strategy with slightly adapted reaction conditions, we could obtain the key building block **1b** in an isolated yield of 58% on a 200 mg scale. The reaction was efficiently scaled-up as demonstrated by the good yield of 62% obtained on a 2 g scale and then on a 28 g scale (Table 1, entries 2 & 3). Decreasing the amount of iodomethyl benzoate and zinc by a factor of 2 led to a slightly decreased yield of 43% (Table 1, entry 4). When the reaction was carried out in DCM instead of THF, full degradation of the starting tributyl(1-fluorovinyl)stannane was observed (Table 1, entry 5). Finally, the desired product was not formed at all using FeCl₂ or CoCl₂ (Table 1, entry 6) as catalyst while only traces of product were detected using CuCl or Rh₂(OAc)₄ (Table 1, entry 7). This new reagent proved to be bench-stable, and could even be stored for several months without noticeable degradation.^[39]

Table 1. Optimization of the Fe-catalyzed cyclopropanation reaction conditions.



Entry	Deviation from optimal cond.	Yield (%) ^[a]
1	–	58
2	Reaction run on a 2.0 g scale	62
3	Reaction run on a 27.7 g scale	62
4	BzOCH ₂ I (3.1 equiv.) Zn (3.0 equiv.)	43
5 ^[b]	DCM as solvent	0
6 ^[b]	FeCl ₂ or CoCl ₂ as catalyst	0
7 ^[b]	CuCl or Rh ₂ (OAc) ₄ as catalyst	Traces

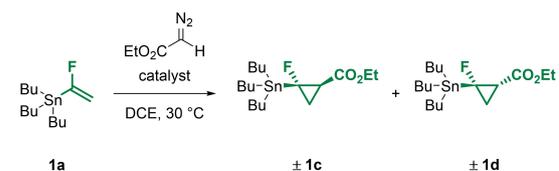
Test reactions were performed on a 0.60 mmol (200 mg) scale.

^[a] Isolated yields are given.

^[b] Test reactions performed on a 0.15 mmol (50 mg) scale with 3.0 equiv. of BzOCH₂I and 3.0 equiv. of Zn with a reaction time of 8 h.

To extend further the scope of this study we wondered if cyclopropanations using diazoacetate-type reagents could be performed on tributyl(1-fluorovinyl)stannane **1a**, yielding fluorocyclopropyl groups with an ester handle which could be further diversified. After a small optimization, the desired ethyl ester-substituted fluorocyclopropyl stannane building block was obtained in yields up to 77% as a 40:60 mixture of two diastereoisomers **1c** and **1d** (Table 2, entry 1). Replacing Rh₂(OAc)₄ by a chiral

Table 2. Cyclopropanation with ethyl diazoacetate.



Entry	Catalyst	1c : 1d ratio ^[a]	Yield (%)
1 ^[b]	Rh ₂ (OAc) ₄	40:60	77
2 ^[c]	Ru-(<i>S</i>)-Pheox	82:18	33

^[a] Ratios were determined by GC-MS analysis of the reaction mixture.

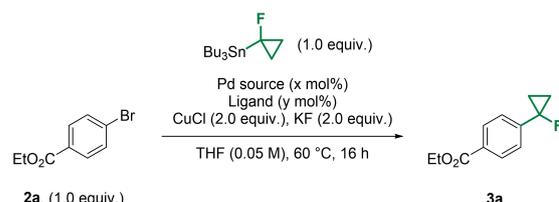
^[b] Reaction conditions (200 mg scale): EDA (10 equiv. added dropwise over 1 h), Rh₂(OAc)₄ (5 mol%), DCE, 30 °C, 2 h. The yield of the isolated mixture of diastereoisomers is given.

^[c] Reaction conditions (100 mg scale): EDA (20 equiv. added dropwise over 3 h), Ru-(*S*)-Pheox (2 mol%), DCE, 30 °C, 3 h. The yield for the isolated *syn*-**1c** diastereoisomer alone is given.

cyclopropanation catalyst – Ru-(*S*)-Pheox^[40] – afforded the desired products with the opposite diastereoselectivity (82:18). Only the major diastereoisomer **1c** could be isolated in a 33% yield (Table 2, entry 2). The enantiomeric ratio (*e.r.*) could not be determined at this stage but was measured after the Stille cross-coupling (*vide infra*).

Having a dedicated fluorocyclopropyl-transfer reagent **1b** in hand, we then explored reaction conditions that would allow its use in Stille cross-couplings. Two challenges were identified in this transformation considering (1) the slow alkyl transfer from tin compared to the more classical aryl or vinyl ones and (2) the potential competitive migration of the three butyl chains over the 1-fluorocyclopropyl one.^[41] Moreover, we could not find any closely related example of Stille coupling with α -fluoroalkylstannanes in the literature. Therefore, we started our investigation using Pd(PPh₃)₄ as catalyst in THF, in analogy to the work of McCarthy for the Stille coupling of tributyl(1-fluorovinyl)stannane **1a**.^[42] A copper salt (CuCl) and a fluoride source (KF) were also added. Indeed, it was previously proposed that in ethereal solvents like THF, the copper(I) species acts as a scavenger of the free ligands in solution, which are known to inhibit the rate-limiting transmetalation step.^[43–46] The fluoride source is used to activate tin, generating a pentavalent species while a synergistic effect of copper(I) salts and fluoride ions was also documented.^[43] Under these initial coupling conditions, the desired product was only observed in a 2% yield (Table 3, entry 1). Then, other types of ligands were investigated, starting with the bidentate XantPhos ligand affording the product in 18% yield (Table 3, entry 2). The electron-rich dialkyl(biaryl)phosphine ligands Xphos and BrettPhos were also assessed but only led to trace amounts of the desired product (Table 3, entries 3 & 4). We then turned our attention to the JackiePhos ligand, initially developed by the group of Buchwald for the *N*-arylation of secondary acyclic amides.^[47] Indeed, the use of a more electron-deficient ligand was found to facilitate the transmetalation of such bulky and weakly nucleophilic species, creating a more electrophilic and thus highly reactive Pd(II) intermediate.^[47] Similarly, organotin reagents including cyclopropylstannanes are also known to react sluggishly in the transmetalation step of palladium-catalyzed cross-couplings.^[35,48] One can also assume that having a fluorine atom in α -position relative to tin might decrease even more the nucleophilicity of the adjacent reactive center but also increase its steric congestion. Accordingly, we evaluated JackiePhos as ligand, and we were pleased to obtain the desired product in a greatly improved yield of 58% (Table 3, entry 5). This result is consistent with previous reports from the group of Biscoe on the Stille cross-coupling of secondary alkyl tricyclohexylstannanes,^[49–51] but also from the group of

Table 3. Optimization of the cross-coupling reaction conditions.



Entry	Pd source (x)	Ligand (y)	Yield (%) ^[a]
1	Pd(PPh ₃) ₄ (10)	–	2
2	Pd ₂ (dba) ₃ (5)	XantPhos (10)	18
3	Pd ₂ (dba) ₃ (5)	Xphos (20)	3
4	Pd ₂ (dba) ₃ (5)	BrettPhos (20)	2
5	Pd ₂ (dba) ₃ (5)	JackiePhos (20)	58
6	Pd(OAc) ₂ (10)	JackiePhos (20)	48
7 ^[b]	Pd ₂ (dba) ₃ (5)	JackiePhos (20)	0
8 ^[c]	Pd ₂ (dba) ₃ (5)	JackiePhos (20)	26
9 ^[d]	Pd ₂ (dba) ₃ (5)	JackiePhos (20)	15
10 ^[e]	Pd ₂ (dba) ₃ (5)	JackiePhos (20)	82
11 ^[f]	Pd ₂ (dba) ₃ (5)	JackiePhos (20)	87
12 ^[f,g]	Pd ₂ (dba) ₃ (5)	JackiePhos (20)	90

^[a] ¹H NMR yields using bromochloromethane as internal standard are reported. Isolated yields in parentheses. Test reactions performed on a 0.1 mmol scale.

^[b] Using CuI instead of CuCl.

^[c] Using CsF instead of KF.

^[d] Without CuCl and KF.

^[e] Reaction performed at 80 °C instead of 60 °C.

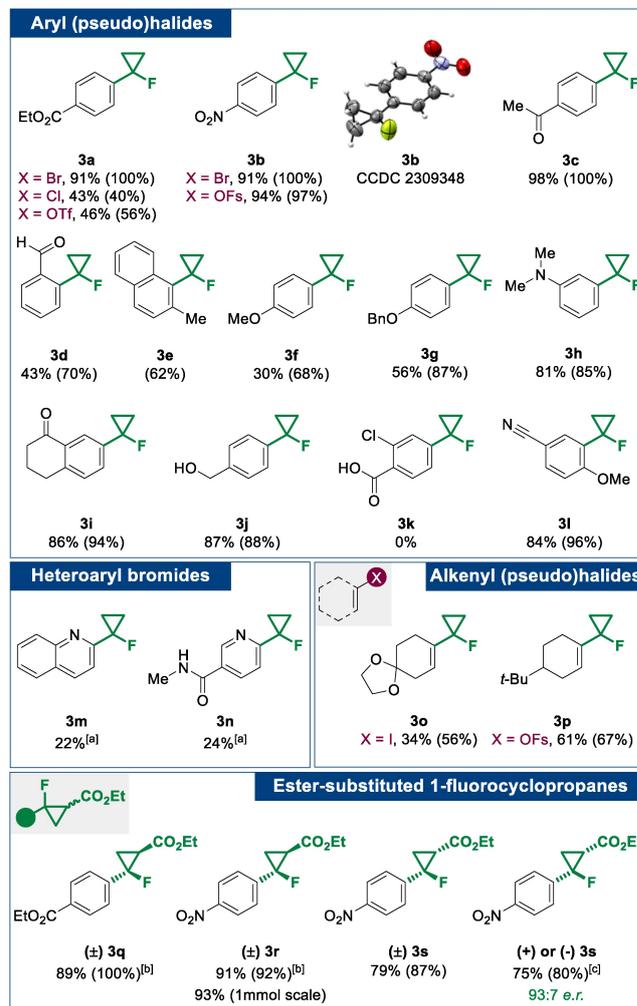
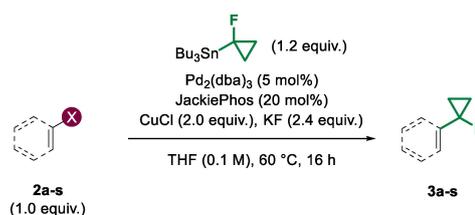
^[f] Using 1.2 equiv. of tributyl(1-fluorocyclopropyl)stannane reagent and 2.4 equiv. of KF.

^[g] Reaction performed at a 0.1 M concentration.

Fürstner, who successfully applied JackiePhos to the Stille cross-coupling of aryl iodides with cyclopropylstannanes substituted by an ethyl ester in α -position relative to the tin atom.^[52,53] Using Pd(OAc)₂ instead of Pd₂(dba)₃ as palladium source led to a slightly decreased yield (Table 3, entry 6) and the other palladium sources tested led to either similar or lower yields compared to Pd₂(dba)₃ (see SI, Table S2). Interestingly, replacing CuCl by CuI as copper salt completely inhibited the reaction and no desired product was obtained (Table 3, entry 7). The nature of the cation of the fluoride source was also decisive, as the yield dropped to 26% using CsF instead of KF (Table 3, entry 8). Similarly, the yield dramatically decreased to 15% in the absence of copper salt and fluoride source (Table 3, entry 9). Increasing the temperature to 80 °C led to a significant improvement of the yield to 82%, but in this case the migration of the butyl chain was detected in 5% yield (Table 3, entry 10). Therefore, to ensure the selectivity of the reaction toward the migration of the 1-FCp moiety, the temperature of 60 °C was retained. When performing the reaction with a slight excess of stannane reagent

1b (1.2 equiv.), the desired product was obtained in an excellent yield of 87% (Table 3, entry 11). Finally, employing a slight excess (1.2 equiv.) of tin reagent and a further excess of KF (2.4 equiv.) together with an increased concentration of 0.1 M led to a similar yield of 90% (Table 3, entry 12). These latter reaction conditions were thus selected for the rest of the study.

We started investigating the scope of this transformation with regard to aryl halides, focusing mainly on aryl bromides (Scheme 2). First, aryl bromides substituted by an ester (**2a**), a nitro (**2b**) or an acetyl (**2c**) group in *para*-position were cross-coupled in excellent to nearly isolated quantitative yields of 91–98%. In opposition to the previous reports on similar fluorinated cyclopropanes,^[54] the X-Ray structure of **2b** showed a 1-fluorocyclopropyl group where the fluorine atom stands in the plane of the benzene ring.^[55] Switching the aryl bromide **2a** to the corresponding chloride **2a-Cl** or triflate **2a-OTf** gave the desired product in lower 43 and 46% yields respectively. Interestingly, using an aryl fluorosulfonate (**2b-OFs**) gave the desired product **3b** with 94% yield, comparable to the one obtained from aryl bromide **2b**. As a result, using various aryl (pseudo)halides, the desired products could be afforded in synthetically useful yields, proving the broad applicability of the method for the late-stage diversification of advanced building blocks. Substrates bearing a substituent in *ortho*-position showed good yields, highlighting the tolerance of the reaction toward steric hindrance. As a result, 2-bromobenzaldehyde **2d** was efficiently coupled in a 70% ¹H NMR yield, although the isolated yield was lower due to the volatility of the desired product **3d**. A naphthyl derivative bearing a methyl group in position *ortho* relatively to the reactive center was also obtained in a 62% ¹H NMR yield (**3e**) but only a small fraction of pure product **3e** could be isolated. Then aryl bromides bearing an electron-donating group in *para*-position were also tested. First, *para*-bromoanisole **2f** led to the formation of the desired 1-fluorocyclopropane-substituted product **3f** in a good 68% ¹H NMR yield and a 30% isolated yield. Similarly, 1-(benzyloxy)-4-bromobenzene **2g** led to an excellent 87% ¹H NMR yield of the desired product **3g**, and a 56% isolated yield. Compounds bearing a strong electron-donating group in *para* position to the fluorocyclopropyl substituent are presumed to be slightly more sensitive and are partially degraded during flash column chromatography on silica gel. Gratifyingly, 3-(1-fluorocyclopropyl)-*N,N*-dimethylaniline **3h** was obtained in an excellent 81% isolated yield. A 1-fluorocyclopropyl-substituted tetralone **3i** was also efficiently synthesized in 86% isolated yield as well as 1-fluorocyclopropane **3j** bearing an unprotected benzylic alcohol group (87%). On the contrary, a benzoic acid derivative **2k** was not tolerated in this reaction. Finally, 3-(1-fluorocyclopropyl)-4-meth-



Reactions performed on a 0.2 mmol scale on aryl bromides unless otherwise noted. Isolated yields are given and ¹H NMR yields, using bromochloromethane as an internal standard, are given in parentheses. ^[a]Synthesized starting from 2.0 equiv. of heteroaryl bromide, 1.0 equiv. of tributyl(1-fluorocyclopropyl)stannane and 2.0 equiv. of KF. ^[b]Reaction performed on a 0.1 mmol scale. ^[c]Reaction performed on a 0.079 mmol scale.

Scheme 2. Scope of the fluorocyclopropanation via a cross-coupling reaction.

oxybenzonitrile **3l** was obtained in an excellent 84% yield emphasizing the tolerance of the reaction for both electron-withdrawing- and electron-donating-substituted arenes, as well as the good tolerance to steric hindrance, with a methoxy group in *ortho* position with regard to the reactive center in this case.

Two heteroaryl bromides were also tested. 2-Bromoquinoline and 6-bromo-*N*-methylnicotinamide afforded the corresponding desired products **3m** and **3n** in modest yields, respectively 22% and 24%, using slightly modified reaction conditions.

In an effort to extend the method beyond (hetero)aryl substrates, we wondered if alkenyl (pseudo)halides, for which the preparation was recently described in our laboratory,^[56] were suitable substrates for this Stille reaction. Alkenyl iodide **2o** and alkenyl fluorosulfonate **2p** both yielded the desired 1-fluorocyclopropane-substituted alkenyl compounds in 56 and 67% ¹H NMR yields, respectively for **3o** and **3p**. The isolated yield was slightly decreased (34%) for **3o** while it was good (61%) for **3p**.

Besides, the ester-substituted stannane reagent **1d**, was effectively cross-coupled with aryl bromides **2a** and **2b** yielding the desired products in excellent yields of 89 and 91%, respectively for **3q** and **3r**. The latter could also be synthesized on a 1 mmol scale with an unaffected yield (93%). The other diastereoisomer of this stannane reagent, **1c**, was also used in the cross-coupling reaction with **2b** and led to a similar 79% yield for **3s**. In comparison, Haufe and co-workers reported a much lower 40% yield for the cyclopropanation of the corresponding fluorovinyl moiety, 1-(1-fluorovinyl)-4-nitrobenzene, using Cu(acac)₂ and ethyl diazoacetate, thus demonstrating the added value of the present method.^[57] Finally, the same enantioenriched stannane **1c**, obtained from the asymmetric cyclopropanation with Ru-(*S*)-Pheox as catalyst, afforded the desired enantioenriched product **3s** in 75% yield, with an enantiomeric ratio (*e.r.*) determined as 93:7.

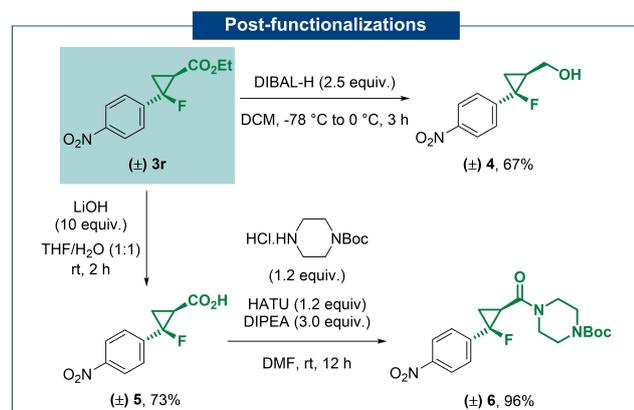
Finally, to illustrate the chemical stability of the 1-FCp group and the versatility of the ester-substituted analogs, a few transformations were performed on **3r** (Scheme 3). First, using DIBAL-H as reducing agent, the ester was converted to the corresponding alcohol **4** in a good 67% yield. This same ester could also be

saponified using lithium hydroxide in a THF/H₂O mixture affording **5** in 73% yield. This carboxylic acid was then engaged in an amide bond-forming reaction with reaction conditions that are commonly used in medicinal chemistry projects, using HATU as coupling reagent. The desired amide **6** was obtained in almost quantitative yield (96%), using *tert*-butyl piperazine-1-carboxylate hydrochloride as amine coupling partner. These few post-functionalization examples demonstrate that the 1-FCp group exhibits a good chemical stability as it remained unaltered in strongly reducing conditions (DIBAL-H), oxidative conditions (DMP treatment of a crude reaction mixture for the ease of purification, see purification protocol of **3g** in the SI) but also basic aqueous conditions and amide bond forming reactions. Therefore, this group can not only be introduced in a late-stage fashion but it could also be incorporated on an earlier stage if required in the synthesis route.

In conclusion, a bench-stable (1-fluorocyclopropyl)metalloid reagent was prepared as well as ester-substituted analogs. This tin-based reagent was employed for the introduction of the 1-FCp group onto (hetero)aryl and vinyl scaffolds by Stille cross-coupling. The electron-poor biarylphosphine JackiePhos ligand proved to be optimal for this transformation. This result could be rationalized recognizing the sluggish reaction of our fluorine-substituted organotin reagent during the transmetalation step of palladium-catalyzed cross-couplings, because of a combination of electronic and steric factors. The transformation proved to be widely applicable to variously substituted aryl and alkenyl (pseudo)halides. However, it is low yielding with heteroaromatics and a whole new catalytic system would be required to extend the scope in this direction. It is noticeable that an enantioenriched (1-fluorocyclopropyl)metalloid analog could be cross-coupled yielding the desired product with a enantiomeric ratio higher than 90:10. Finally, the chemical stability of the 1-fluorocyclopropyl moiety allowed to take advantage of the ester function chemistry in few post-functionalization reactions. Overall, this work opens the way for both early- and late-stage introduction of the 1-fluorocyclopropyl group as a promising replacement for the ubiquitous but problematic trifluoromethyl moiety, in a context of impending constraining regulation on PFAS.

Experimental Section

Caution: organotin compounds are toxic and must be handled by a trained chemist in a well-ventilated fumehood. Associated wastes should be disposed according to local waste management regulations.



Scheme 3. Post-functionalizations.

Procedure for the Synthesis of 1b

Zinc dust was activated with 2% HCl aq. solution then washed with water, EtOH, Et₂O and dried under high vacuum for several hours. A 3-necked round bottom flask fitted with a reflux condenser (Findenser-type) containing Zn dust (6.0 equiv., 2.34 g, 35.8 mmol) was dried by heating with a heat gun (maximum power) under high vacuum for 2–3 min. After cooling to room temperature and three argon/vacuum cycles, the flask was placed under argon and cooled with an ice/water bath (*ca* 0 °C). A solution of iodomethyl benzoate (6.2 equiv., 9.70 g, 37.0 mmol) in anhydrous and degassed THF (30 mL) was then added and the flask was warmed up to room temperature. After *ca* 5 min at room temperature, the heterogeneous mixture became homogeneous again (but slightly turbid), indicating the carbenoid formation. Then, a solution of tributyl(1-fluorovinyl)stannane (1.0 equiv., 2.00 g, 5.97 mmol) in anhydrous and degassed THF (30 mL) was added, and last, FeTPPCL (0.05 equiv., 210 mg, 0.300 mmol) was added. The reaction mixture was stirred at 60 °C for 48 hours. After cooling to room temperature, the reaction mixture was then diluted with Et₂O and filtered through a short pad of silica, washed again with Et₂O. The solvent was removed *in vacuo* and the crude mixture was purified by flash column chromatography on silica gel using cyclohexane as eluent to afford the product (1.29 g, 62%) as a colorless liquid.

General Procedure for the Stille Cross-Coupling Reaction

An oven-dried heavy wall, crimp cap tube was charged with Pd₂dba₃ (0.05 equiv., 9.2 mg, 0.010 mmol), JackiePhos (0.20 equiv., 32 mg, 0.040 mmol), CuCl (2.0 equiv., 40 mg, 0.40 mmol), KF (2.4 equiv., 28 mg, 0.48 mmol). It was then evacuated and backfilled with argon in three cycles before a solution of tributyl(1-fluorocyclopropyl)stannane or any stannane analog (1.2 equiv., 0.24 mmol) in anhydrous and degassed THF (2.0 mL) was added followed by the (hetero)aryl (pseudo)halide or vinyl (pseudo)halide (1.0 equiv., 0.20 mmol). The vial was tightly sealed and the resulting solution was heated up to 60 °C and stirred for 16 hours. The mixture was cooled to room temperature, filtered through a PTFE filter, rinsed with DCM and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, using the appropriate eluent system, affording the desired product.

Acknowledgements

The authors thank the CNRS (Centre National de la Recherche Scientifique, France), the Université de Strasbourg and Université de Haute-Alsace. The authors are grateful to Bayer S.A.S. for a Ph.D. grant to F.A. The company Innov'Orga is acknowledged for its contribution to this work by validating the up-scaling of the synthesis of tributyl(1-fluorocyclopropyl)stannane on a decagram scale. The French Fluorine Network (GIS Fluor) is also acknowledged. Finally, the authors also thank Dr. Emeric Wasielewski (NMR platform) and Matthieu Chessé (analytical facilities) of the LIMA (UMR7042 CNRS-Unistra-UHA), as well as the analytical facilities of the

Fédération de Chimie "Le Bel" (FR2010) of the Université de Strasbourg, who contributed, by their valuable technical and scientific support, to the achievement of this research project.

References

- [1] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.
- [2] T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16–29.
- [3] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640.
- [4] I. T. Cousins, J. C. DeWitt, J. Glüge, G. Goldenman, D. Herzke, R. Lohmann, C. A. Ng, M. Scheringer, Z. Wang, *Environ. Sci. Process. Impacts* **2020**, *22*, 2307–2312.
- [5] F. Freeling, M. K. Björnsdotter, *Curr. Opin. Green Sustain. Chem.* **2023**, *41*, 100807.
- [6] K. R. Solomon, G. J. M. Velders, S. R. Wilson, S. Madronich, J. Longstreth, P. J. Aucamp, J. F. Borrmann, *J. Toxicol. Environ. Health Part B* **2016**, *19*, 289–304.
- [7] M. Kiel, K.-H. Engesser, *Appl. Microbiol. Biotechnol.* **2015**, *99*, 7433–7464.
- [8] S. Pazenok, D. Bernier, M. Donnard, G. Hanquet, A. Panossian, F. R. Leroux, in *Patai's Chemistry of Functional Groups*, John Wiley & Sons, Ltd, **2022**, pp. 1–77.
- [9] "Per- and polyfluoroalkyl substances (PFAS) - ECHA," can be found under <https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas>, **2023**.
- [10] N. D. Tyrrell, *Org. Process Res. Dev.* **2023**, *27*, 1422–1426.
- [11] X. Lim, *Nature* **2023**, *620*, 24–27.
- [12] E. Hammel, T. F. Webster, R. Gurney, W. Heiger-Bernays, *iScience* **2022**, *25*, 104020.
- [13] O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem* **2022**, *17*, e202200365.
- [14] T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756.
- [15] Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Taylor & Francis, Boca Raton London New York, **2007**.
- [16] P. B. Karadakov, J. Gerratt, D. L. Cooper, M. Raimondi, *J. Am. Chem. Soc.* **1994**, *116*, 7714–7721.
- [17] A. Conte, H. Kuehne, T. Luebbers, P. Mattei, C. Maugeais, W. Mueller, P. Pflieger, *Anthranilamide/2-Amino-Heteroarene Carboxamide Derivatives*, **2007**, WO2007090752 A1.
- [18] N. J. Dewdney, Y. Lou, E. B. Sjogren, M. Soth, Z. K. Sweeney, *Novel Phenylpyrazinones as Kinase Inhibitors*, **2010**, WO2010000633 A1.
- [19] Z. Lu, Y. Cao, D. Zhang, X. Meng, B. Guo, D. Kong, Y. Yang, *J. Med. Chem.* **2022**, *65*, 5724–5750.
- [20] G. Liu, J. Ren, S. Yi, G. Zhang, N. Du, P. Li, C. Yuan, Y. Li, *Compound capable of being used as sodium channel regulator and application thereof*, **2022**, CN114437062 A.
- [21] Y. Tsukamoto, H. Komai, J. Kadotani, K. Koi, S. Mio, H. Takeshiba, *3-Phenoxy-4-Pyridazinol Derivative and Herbicide Composition Containing the Same*, **2004**, EP1426365 A1.

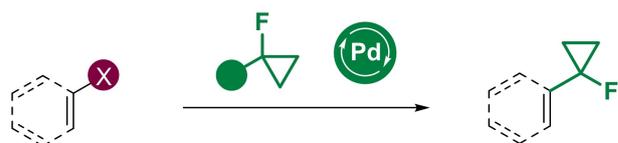
- [22] K. Nakahara, K. Fuchino, K. Komano, N. Asada, G. Tadano, T. Hasegawa, T. Yamamoto, Y. Sako, M. Ogawa, C. Unemura, M. Hosono, H. Ito, G. Sakaguchi, S. Ando, S. Ohnishi, Y. Kido, T. Fukushima, D. Dhuyvetter, H. Borghys, H. J. M. Gijzen, Y. Yamano, Y. Iso, K. Kusakabe, *J. Med. Chem.* **2018**, *61*, 5525–5546.
- [23] K.-I. Kusakabe, G. Tadano, K. Komano, K. Fuchino, K. Nakahara, *Dihydrothiazine and Dihydrooxazine Derivatives Having Bacel Inhibitory Activity*, **2015**, WO2015156421 A1.
- [24] A. Arlt, Y. C. Grande, P. Jeschke, M. Füsslein, S. Müller, H.-G. Schwarz, J. Telser, U. Ebbinghaus-Kintscher, E. Hellwege, P. Lösel, M. Linka, A. J. Damijonaitis, I. Heisler, A. Turberg, O. Mandzhulo, Y. Shermolovich, S. Mykhaylychenko, *Novel Heteroaryl-Triazole Compounds as Pesticides*, **2021**, WO2021105091 A1.
- [25] N. Papaioannou, J. M. Travins, S. J. Fink, J. M. Ellard, A. Rae, J. A. Spencer, S. S. Rankin, R. S. L. Chapman, *Heteroaryl Inhibitors of Plasma Kallikrein*, **2022**, WO2022197758 A1.
- [26] S. Kumar, R. Sharma, S. Halder, S. P. Sawargave, V. B. Deore, *Compounds for Use as Gpr120 Agonists*, **2015**, WO2015125085 A1.
- [27] M. Kirihara, H. Kakuda, M. Tsunooka, A. Shimajiri, T. Takuwa, A. Hatano, *Tetrahedron Lett.* **2003**, *44*, 8513–8518.
- [28] M. Kirihara, T. Kambayashi, T. Momose, *Chem. Commun.* **1996**, 1103–1104.
- [29] A. W. Konradi, T. T.-L. T. Lin, *Oxadiazole Compounds*, **2019**, WO2019222431 A1.
- [30] M. Zhou, J. Tsien, R. Dykstra, J. M. E. Hughes, B. K. Peters, R. R. Merchant, O. Gutierrez, T. Qin, *Nat. Chem.* **2023**, *15*, 550–559.
- [31] T. Hanamoto, T. Kobayashi, M. Kondo, *Synlett* **2001**, 0281–0283.
- [32] T. Hanamoto, T. Kobayashi, *J. Org. Chem.* **2003**, *68*, 6354–6359.
- [33] L. R. Mills, C. Zhou, E. Fung, S. A. L. Rousseaux, *Org. Lett.* **2019**, *21*, 8805–8809.
- [34] T. Hanamoto, K. Handa, T. Mido, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2497–2502.
- [35] M. Rubina, V. Gevorgyan, *Tetrahedron* **2004**, *60*, 3129–3159.
- [36] D. Seyferth, H. M. Cohen, *Inorg. Chem.* **1962**, *1*, 913–916.
- [37] L. Zhang, B. M. DeMuynck, A. N. Paneque, J. E. Rutherford, D. A. Nagib, *Science* **2022**, *377*, 649–654.
- [38] B. M. DeMuynck, L. Zhang, E. K. Ralph, D. A. Nagib, *Chem* **2024**, *10*, 1–13.
- [39] Tributyl(1-fluorocyclopropyl)stannane (**1b**) was stored under argon in a fridge. After a 4-month period, no noticeable degradation was detected by ¹H and ¹⁹F NMR analyses. The same result was obtained when storing this compound at room temperature, under air with day-light exposure. It also stands purification by flash column chromatography on silica gel and reversed-phase preparative HPLC using a mixture of acetonitrile and water.
- [40] S. Chanthamath, S. Iwasa, *Acc. Chem. Res.* **2016**, *49*, 2080–2090.
- [41] J. W. Labadie, J. K. Stille, *J. Am. Chem. Soc.* **1983**, *105*, 6129–6137.
- [42] D. P. Matthews, P. P. Waid, J. S. Sabol, J. R. McCarthy, *Tetrahedron Lett.* **1994**, *35*, 5177–5180.
- [43] S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136.
- [44] A. L. Casado, P. Espinet, *Organometallics* **2003**, *22*, 1305–1309.
- [45] X. Han, B. M. Stoltz, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
- [46] V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905–5911.
- [47] J. D. Hicks, A. M. Hyde, A. M. Cuezva, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734.
- [48] C. Cordovilla, C. Bartolomé, J. M. Martínez-Irarduya, P. Espinet, *ACS Catal.* **2015**, *5*, 3040–3053.
- [49] M. Biscoe, M. Binayeva, X. Ma, P. Ghaemimohammadi, *Chem. Sci.* **2023**, DOI 10.1039/D3SC04519F.
- [50] H. Zhao, A. T. Jose, A. Asany, S. M. Khan, M. R. Biscoe, *Org. Lett.* **2022**, *24*, 8714–8718.
- [51] X. Ma, H. Zhao, M. Binayeva, G. Ralph, M. Diane, S. Zhao, C.-Y. Wang, M. R. Biscoe, *Chem* **2020**, *6*, 781–791.
- [52] F. P. Caló, A. Zimmer, G. Bistoni, A. Fürstner, *J. Am. Chem. Soc.* **2022**, *144*, 7465–7478.
- [53] F. P. Caló, A. Fürstner, *Angew. Chem. Int. Ed.* **2020**, *59*, 13900–13907.
- [54] C. J. Thomson, Q. Zhang, N. Al-Maharik, M. Bühl, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2018**, *54*, 8415–8418.
- [55] CCDC-2309348 contains the supplementary crystallographic data for compound **3b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
- [56] C. Plaçais, S. J. Kaldas, M. Donnard, A. Panossian, D. Bernier, S. Pazenok, F. R. Leroux, *Chem. Eur. J.* **2023**, *29*, e202301420.
- [57] K. Bartels, B. Schinor, G. Haufe, *J. Fluorine Chem.* **2017**, *203*, 200–205.

RESEARCH ARTICLE

Direct Introduction of the 1-Fluorocyclopropyl Group *via* Stille Cross-Coupling – A Way of Getting Around Per- and Polyfluoroalkyl Substances (PFASs)

Adv. Synth. Catal. **2024**, *366*, 1–9

 Dr. F. Audet, Dr. M. Donnard, Dr. A. Panossian, Dr. P. M. Holstein, Dr. D. Bernier, Dr. S. Pazenok, Dr. F. R. Leroux*



X = Br, Cl,
OTf, OFs

22 examples
22–98%

- ✓ Direct cross-coupling method
- ✓ No prefunctionalization of the aryl substrate required
- ✓ Suitable for late-stage diversification
- ✓ Formation of a monofluorinated tetrasubstituted carbon