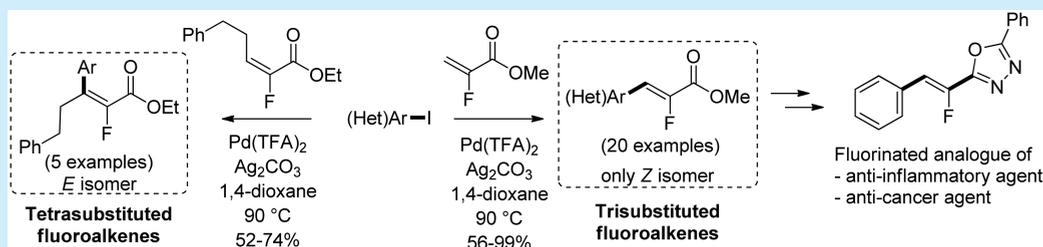


Stereospecific Synthesis of Tri- and Tetrasubstituted α -Fluoroacrylates by Mizoroki–Heck Reaction

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S Supporting Information



ABSTRACT: Ligand-free, efficient, palladium-catalyzed Mizoroki–Heck reaction between methyl α -fluoroacrylate and arene or heteroarene iodides is reported for the first time. The reaction is stereospecific and provides fair to quantitative yields of fluoroalkenes. The Mizoroki–Heck reaction starting from more hindered and usually reluctant trisubstituted acrylate, to access tetrasubstituted fluoroalkenes, is also reported. Finally, the use of a three-step synthesis sequence, including Mizoroki–Heck reaction, allows the synthesis of fluorinated analogues of therapeutic agents with high yield.

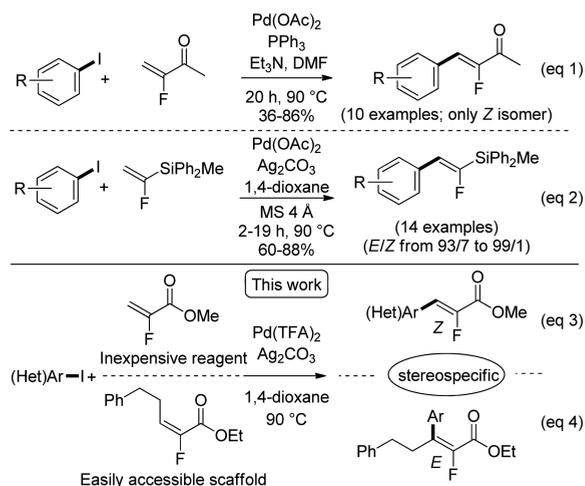
Organofluorine chemistry is an area of tremendous expansion, and the market for organofluorine fine chemicals still keeps growing every year.¹ Fluorinated molecules have applications in almost all areas of science and clearly have a crucial impact on everyday life and on modern society. Among the fluoroorganic compounds, the fluoroacrylates have been proven to be versatile compounds that have found many applications in material sciences² and medicinal chemistry³ and can also serve as relevant intermediates in the synthesis of peptidomimetics⁴ and drugs.⁵

Common efficient strategies to synthesize α -fluoroacrylates rely almost exclusively on olefination reactions with carbonyl derivatives for which many different experimental procedures have been reported⁶ (Wittig-type,⁷ Horner–Wadworth–Emmons,⁸ Peterson,^{5a} Julia–Kocienski,⁹ etc.). These reactions can lead to high *E/Z* selectivity¹⁰ or very good yields of reaction⁷ and more rarely to both excellent yield and selectivity.^{8a,11} Moreover, numerous reactions suffer from limitations such as the need for a multistep preparation of the fluorinated reagents,^{9,10b–d} the use of expensive reagents,⁸ and/or the use of harsh experimental conditions (chromium salt,^{11a} highly corrosive TiCl_4 ,^{11b} etc.). As part of our ongoing project aimed at developing new catalytic access to fluoroalkene fine chemicals,¹² we turned our attention to an efficient alternative reaction accessing to fluoroacrylates based on the Mizoroki–Heck strategy, a powerful tool to synthesize alkenes.¹³ Indeed, despite numerous reactions described with acrylates and derivatives, the Mizoroki–Heck reaction with α -fluoroacrylates has surprisingly been, to our knowledge, reported in a single example, without details about selectivity and yield of reaction, in a patent for the construction of bioactive heterocycles,¹⁴ whereas this reaction could be a general

new strategy to construct relevant fluoroalkene building blocks. As a matter of fact, complete methodological studies of the Mizoroki–Heck reaction with aryl halides have only been reported twice to produce monofluoroalkene derivatives (Scheme 1).¹⁵

Patrick et al.^{15a} reported in 2008 the synthesis of 3-fluorobenzalacetone derivatives starting from 3-fluoro-3-buten-

Scheme 1. Mizoroki–Heck Reaction between Aryl Iodides and Fluorinated Alkenes



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2-one as fluorinated reagent requiring its presynthesis through the formation of chlorofluorocarbene from the ozone depleter Freon-21 (Scheme 1, eq 1). In 2011, Hirota and Hanamoto reported the synthesis of β -aryl-(1-fluorovinyl)methyldiphenylsilane from expensive (1-fluorovinyl)methyldiphenylsilane (around \$34/mmol) as fluorinated reagent (Scheme 1, eq 2).^{15b} Recently, synthesis of fluoroalkene derivatives ((*Z*)- β -fluoro- β -(trifluoromethyl)styrene) was reported by Liu, Lu, and co-workers through a palladium-catalyzed oxidative Heck reaction.¹⁶ Herein, we report the first stereoselective, efficient synthesis of fluoroacrylate derivatives by a ligand-free Mizoroki–Heck reaction starting from methyl α -fluoroacrylate, a cheap commercially available fluorinated reagent (around \$1/mmol) (Scheme 1, eq 3). We have also succeeded accessing to tetrasubstituted fluorinated alkenes using scarce and reluctant trisubstituted alkenes as coupling partner in the Mizoroki–Heck reaction (Scheme 1, eq 4).

We started the optimization process by carrying out the reaction between α -fluoroacrylate **a** and phenyl iodide (Table 1).

Table 1. Optimization of the Fluoroalkenylation Reaction

entry	Ph-I (equiv)	a (equiv)	cat. (equiv)	base (equiv)	volume vial (mL)	yield ^d (%)
1	2	1	Pd(OAc) ₂	Ag ₂ CO ₃ (3)	10	14
2	2	1	Pd(TFA) ₂	Ag ₂ CO ₃ (3)	10	50
3	2	1	Pd(TFA) ₂	Ag ₂ CO ₃ (3)	2	73
4	1	1.5	Pd(TFA) ₂	Ag ₂ CO ₃ (3)	2	99
5	1	1.5	-	Ag ₂ CO ₃ (3)	2	0
6 ^a	1	1.5	Pd(TFA) ₂	Ag ₂ CO ₃ (3)	2	86
7	1	1.5	Pd(TFA) ₂	Ag ₂ CO ₃ (2)	2	99
8	1	1.5	Pd(TFA) ₂	Ag ₂ CO ₃ (1)	2	92
9 ^c	1	1.5	Pd(TFA) ₂	Ag ₂ CO ₃ (2)	2	98

^aYield based on isolated product after flash chromatography. ^b5 mol % of Pd(TFA)₂. ^cReaction performed at 60 °C.

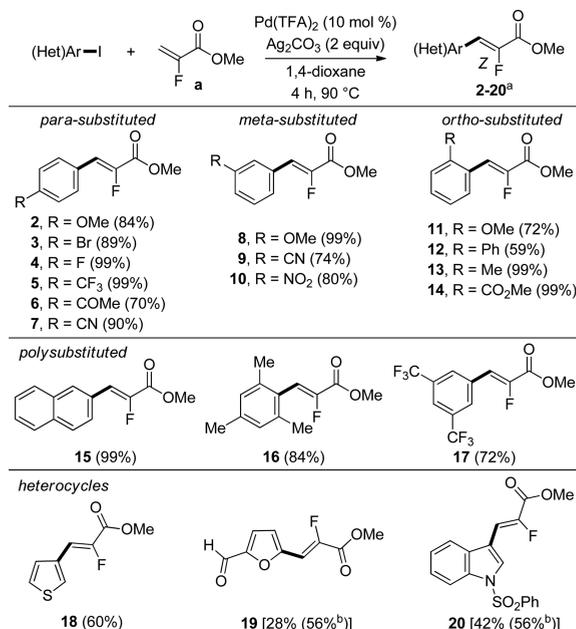
The experimental conditions described by Hirota and Hanamoto proved to be unsuccessful with a poor 14% yield of reaction (Table 1, entry 1). Among the palladium(II) or -(0) catalysts tested,¹⁷ only the more electrophilic palladium(II)-trifluoroacetate allowed us to prepare **1** with 50% yield (Table 1, entry 2). After a screening of bases, only Ag₂CO₃ proved to be efficient for the reaction to proceed.¹⁷ Taking into account the volatility of the fluorinated reagent **a**, we reduced the size of the reaction's vial, decreasing the gaseous space above the reaction liquid media, allowing us to increase the isolated yield to 73% (Table 1, entry 3). Then, to ensure sufficient quantity of the fluorinated reagent **a** in the media, we changed the number of equivalents of Ph-I/**a** from 2/1 to 1/1.5 resulting in a quantitative yield of **1** (Table 1, entry 4). As expected, the reaction did not proceed in the absence of catalyst (Table 1, entry 5). Decreasing the catalyst loading to 5 mol % allowed to obtain the product **1** in very good 86% yields (Table 1, entry 6). Pleasingly, a quantitative yield was also obtained using 2 equiv of Ag₂CO₃ (Table 1, entry 7), with 1 equiv leading to an interesting 92% yield of **1** (Table 1, entry 8). Finally decreasing the reaction temperature to 60 °C allowed us to obtain an excellent 98% yield of **1** (Table 1, entry 9). It has to be noted that it was not necessary to use dry vials, operate under inert atmosphere, or use molecular sieves^{15b} which

simplified the process. During all experiments, the methyl 3-phenyl-2-fluoroacrylate **1** was only produced as exclusive *Z*-isomer, no trace of *E*-isomer being observed in ¹⁹F NMR of the crude mixture. Typically, a 32–37 Hz coupling constant value between the vinylic proton and the fluorine atom was obtained indicating the corresponding *Z*-configuration.

We also applied our optimized procedure to other phenyl halides (Ph-Br, Ph-Cl) and pseudohalide (Ph-OTf) without success.¹⁷ Finally, using the catalytic system Pd(TFA)₂ (10 mol %)/PPh₃ (20 mol %) overnight led to the production of compound **1** in 35% yield from bromobenzene.¹⁷

We then applied our optimized procedure to substituted aryl and heteroaryl iodides (Scheme 2). For *para*-substituted aryl

Scheme 2. Scope of the Reaction with Substituted Aryl and Heteroaryl Iodides



^aYield based on isolated product after flash chromatography. ^bReaction performed overnight (12 h).

iodides, whatever the electronic effect of the substituted moiety, the reaction was efficient giving a range from 70% to quantitative yields. Dihalogenated aryl derivatives revealed to be suitable substrates giving the fluorinated acrylates **3** and **4** in high yields. Interestingly, in the presence of 4-bromophenyl iodide, the reaction was chemoselective furnishing **3** in 89% yields with a reactive C–Br bond for further catalytic reactions. Compounds **6** and **7** bearing a ketone and a nitrile moieties, respectively, which could be easily postfunctionalized, have also been synthesized in high yields.

Then, *meta*-substituted aryl iodides were studied furnishing good to excellent yields in methyl 3-aryl-2-fluoroacrylates whatever the substitution: methoxy (**8**), cyano (**9**), or nitro (**10**). Finally, *ortho*-substituted aryl iodides were engaged in the reaction with success. For example, valuable methyl 2-carboxylate phenyl iodide reacted to furnish 3-aryl-2-fluoroacrylate **14** in quantitative yield. The reaction proved to be highly efficient and tolerant toward various functional groups. Nevertheless, it has to be noted that the presence of labile hydrogen, i.e., iodophenol, iodoaniline, or iodobenzoic acid, was prohibited. No reaction occurred with those starting materials. Polysubstituted aryl

methyl α -fluoroacrylate as fluorine and alkene sources. The reaction proved to be highly tolerant in regard to numerous organic functionalities, was stereospecific, and importantly, gave good to quantitative yields in fluoroalkenes. Whereas the trisubstituted alkenes did not usually participate in the carbopalladation reaction (reluctant substrates), this reaction have been successfully extended to the use of trisubstituted (*E*)-3-alkyl-2-fluoroacrylate as substrate allowing the formation in fair to good yields of the corresponding tetrasubstituted fluoroacrylates. These results constituted the first example of the Mizoroki–Heck reaction for the synthesis of tetrasubstituted alkenes. Finally, we used this methodology to produce a fluorinated analogue of a therapeutic agent against inflammation and various types of cancer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.5b03571](https://doi.org/10.1021/acs.orglett.5b03571).

Experimental procedures, optimization tables, characterization data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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