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Palladium-Catalyzed Iodofluorination of Alkenes Using Fluoro-Iodoxole Reagent

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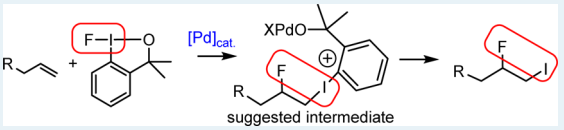
Supporting Information

ABSTRACT: The application of an air- and moisture-stable fluoroiodane reagent was investigated in the palladium-catalyzed iodofluorination reaction of alkenes. Both the iodo and fluoro substituents arise from the fluoroiodane reagent. In the case of certain palladium catalysts, the alkene substrates undergo allylic rearrangement prior to the iodofluorination process. The reaction is faster for electron-rich alkenes than for electron-deficient ones.



KEYWORDS: *fluorination, hypervalent iodines, iodofluorination, palladium catalysis, alkenes, difunctionalization*

Organofluorine compounds are important synthetic targets in the pharmaceutical and agrochemical industries because of their useful pharmacokinetic and metabolic properties.[1] In addition, the radiochemical properties of ^{18}F can be exploited in positron emission tomography (PET) diagnostics.[2] This latter application requires late-stage synthetic methods for the introduction of fluorine to the organic molecules because of the relatively short half-life of ^{18}F.[3] The large interest by the chemical industry and medical diagnostics has boosted the development of modern fluorine chemistry, which has been signified by the appearance of new fluorinating reagents, applications of catalysis, and reporting of new, selective late-stage methodologies.[3,4]

Fluorination-based difunctionalization is a useful approach for the synthesis of organofluorides. By related methods not only a fluorine but also an additional functional group can be introduced in the organic molecules.[5] Subsequently, the second functionality can be employed as a handle for additional transformations of the organofluoro compounds. In this respect, iodofluorination of alkenes is a particularly useful approach for the simultaneous introduction of both iodo and fluoro substituents to organic substrates.[6] Classical iodofluorination reactions are usually based on the use of a strong oxidant in connection with a reactive fluorine source.[7] Barluenga and co-workers[8] employed bis(pyridine)iodide tetrafluoroborate (IPy_2BF_4) for iodofluorination of alkenes. Another usual approach for iodofluorination of alkenes is the application of the *N*-iodosuccinimide (NIS)/HF system, often in the presence of a base (e.g., Et_3N, pyridine, imidazole derivatives).[9] The same type of iodofluorination can be achieved using an oxidative fluorine reagent such as $ArIF_2$ or $MeIF_2$ together with HF or I_2 as an additive.[10] These species are very reactive fluorinating and iodinating reagents that are often difficult to access, highly toxic, and hazardous to use. It would be desirable to replace the corrosive, strongly oxidizing reagents with nonhazardous stable species as well as to avoid using HF as an essential component or possible byproduct of the reaction. In this respect, transition-metal-catalyzed procedures offer attractive solutions.

Hypervalent iodine **1** is an easily accessible reagent[11] that is thermostable up to 100 °C.[12] At moderate temperatures, **1** is completely inert toward olefins in the absence of transition-metal-based or other activators. However, with suitable activation **1** can be applied to fluorinations of 1,3-diketones and 1,3-keto esters,[11a,13] in difluorination of styrenes,[14] and in fluorocyclization reactions.[12,15] A further attractive feature of this electrophilic fluorinating reagent is that it can be easily obtained from nucleophilic fluorinating reagents such as KF,[11b] which is a potentially useful feature in the synthesis of PET radioligands.[2]

During our studies of difluorination of styrenes,[14] we found that when certain palladium catalysts in the presence of **1** were used, styrenes underwent iodofluorination instead of difluorination. Expecting the above-mentioned benefits of a mild palladium-catalyst-controlled iodofluorination method, we decided to fully develop such a new synthetic transformation (Table 1). When allylbenzene (**2a**) was reacted with **1** in the presence of 5 mol % $Pd(BF_4)_2(MeCN)_4$ (**4a**), the iodofluorinated product **3a** was formed in 61% yield (Table 1, entry 1). The reaction was carried out under mild and neutral conditions without any additives. Increasing the catalyst loading to 20 mol % also increased the yield to 76% (entry 2). Surprisingly, the iodine substituent in **3a** arises from reagent **1**. This atom-economical use of iodine involves cleavage of the $C(sp^2)$–I bond in **1** and formation of a C–I bond in **3**. This also suggests an intriguing mechanism for the process.

The iodofluorination with $Pd(OCOCF_3)_2$ resulted in terminally substituted product **3a**, but the yields were lower than with **4a** (Table 1, entries 3 and 4). The reaction with $Pd(OAc)_2$ (**4b**) proceeded slower than that with **4a**. When the reaction was conducted for 18 h at 40 °C, **3a** was isolated in

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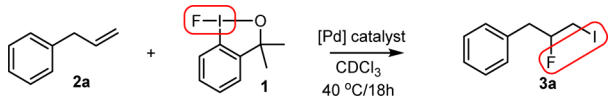
Table 1. Variation of the Reaction Conditions for Iodofluoration of Allylbenzene (2a)



entry	[Pd] catalyst	yield of **3a** (%)
1	5 mol % $Pd(BF_4)_2(MeCN)_4$ (**4a**)	61
2	20 mol % $Pd(BF_4)_2(MeCN)_4$ (**4a**)	76
3	5 mol % $Pd(TFA)_2$	41
4	20 mol % $Pd(TFA)_2$	68
5	20 mol % $Pd(OAc)_2$ (**4b**)	15
6	$PdCl_2(^tBuCN)_2$, $PdCl_2(DMSO)_2$, or $PdCl_2$(dppe)	<5
7	–	0
8	20 mol % **4a** in dioxane instead of $CDCl_3$	38
9	20 mol % **4a** in THF, MeCN, or MeOH	<5

only 15% yield (entry 5). Other palladium catalysts such as $PdCl_2(^tBuCN)_2$, $PdCl_2(DMSO)_2$, and $PdCl_2$(dppe) were inefficient for the iodofluorination (entry 6). With these catalysts or no palladium catalyst (entry 7), the starting materials **2a** and **1** remained unchanged. We employed $CDCl_3$ as a solvent, which allowed analysis of the crude reaction mixtures by ^1H and ^{19}F NMR spectroscopy. When the solvent was changed to dioxane (entry 8), the yield of **3a** decreased to 38%. When tetrahydrofuran (THF), MeCN, or MeOH was used as the solvent, formation of the iodofluorinated product was not observed (entry 9).

Subsequently, we investigated the synthetic scope of the palladium-catalyzed iodofluorination reaction (Table 2). As mentioned above, a 20 mol % loading of **4a** gave the best yield of **3a** when **2a** was used as the substrate (entry 1). When $PdCl_2(MeCN)_2$ (**4c**) was used as the catalyst (5 mol %), **3b** was formed (as a single anti stereoisomer) from **2a** (entry 2). Styrene derivative **2b** (entry 3), which is the allylic isomer of **2a**, also gave **3b** with catalyst **4c**. Compound **2c** (a structural homologue of **2a**) also gave the internal iodofluorination product **3c** with catalyst **4c** (entry 4). In this case the iodofluorination occurred at the homoallylic position with respect to the original double bond. As mentioned above (Table 1, entry 5), **4b** also catalyzed the iodofluorination, but the reaction was slower than with **4a**. When alkene **2c** was reacted at 50 °C with **1** using **4b** as the catalyst, product **3d** was formed (Table 2, entry 5). Apparently, this palladium catalyst **4b** did not induce the same rearrangement as **4c** did (cf. entries 4 and 5). The iodofluorination of allylbenzenes bearing electron-donating substituents (OMe, Me) proceeded smoothly in very clean reactions (entries 6–10). Because of the high reactivity of substrates **2d–h**, **4b** was used as the catalyst at 40 °C. The isolated yields varied between 48 and 78%. The lower yields were due to purification losses, attributable to either the volatility of the products or separation difficulties. The *p*-methoxy-substituted allylbenzene **2d** underwent iodofluorination with higher yield than its *o*-methoxy-substituted counterpart **2e** (entries 6 and 7). Fluorinated derivatives of methyl eugenol (**2f**) are useful antiseptics and anesthetics.[16] The corresponding iodofluorinated product **3g** (entry 8) could also be obtained in good yield. The difference in the isolated yields was relatively small for the *p*-methyl- (**2g**) and *o*-methyl-substituted (**2h**) analogues (entries 9 and 10).

Allylbenzene substrates with electron-withdrawing groups (**2i–k**) reacted very slowly with **1** in the presence of **4b**.

Table 2. Palladium-Catalyzed Iodofluorination with 1[a]

entry	substrate	$[Pd]_{cat.}$	product	yield (%)[b]
1	**2a**	**4a**	**3a**	76
2	**2a**	**4c**[c]	**3b**	71
3	**2b**	**4c**	**3b**	77
4	**2c**	**4c**	**3c**	86
5[d]	**2c**	**4b**	**3d**	58
6	**2d**	**4b**	**3e**	78
7	**2e**	**4b**	**3f**	53
8	**2f**	**4b**	**3g**	64
9	**2g**	**4b**	**3h**	51
10	**2h**	**4b**	**3i**	48 (76)[e]
11	**2i**	**4a**	**3j**	53
12	**2j**	**4a**	**3k**	48 (78)[e]
13	**2k**	**4a**	**3l**	53
14[d]	**2l**	**4b**	**3m**	61
15[d]	**2m**	**4c**	**3n**	54
16[f]	**2n**	**4c**	**3o**	64
17	**2o**	**4c**[c]	**3p**	40 (96)[e]
18	**2p**	**4c**[c]	**3q**	50

[a]Unless otherwise stated, substrate **2** (0.1 mmol), **1** (0.1 mmol), and the appropriate palladium catalyst (0.02 mmol, 20 mol %) in $CDCl_3$ (0.5 mL) were stirred at 40 °C for 18 h. [b]Isolated yields. [c]0.005 mmol (5 mol %) of $PdCl_2(MeCN)_2$ (**4c**). [d]The reaction was performed at 50 °C. [e]The yield was determined by ^{19}F NMR spectroscopy. [f]The reaction was performed at 60 °C.

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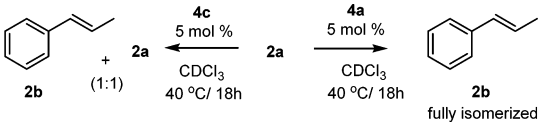
Therefore, catalyst **4a** was used for these substrates, as it has a higher catalytic activity than **4b** (cf. Table 1, entries 2 and 5). Even with the more active catalyst, the yields for iodofluorination of fluoro- (**2i**) and trifluoromethyl-substituted (**2j**) allylbenzenes were significantly lower than for the methoxy analogue (Table 2, entries 11 and 12 vs 6). *o*-Bromo substrate **2k** also underwent catalytic iodofluorination using **1** (entry 13) to afford **3l**, which contains three different halogenide handles (F, Br, I), making it a useful synthetic intermediate for substitution, elimination, and Suzuki–Miyaura coupling reactions.[17] It is noteworthy that the C(sp^2)–I bond of **1** was cleaved but the C(sp^2)–Br bond of **2k** remained intact in the catalytic iodofluorination process.

α-Methylstyrenes **2l–n** also underwent iodofluorination smoothly (Table 2, entries 14–16). In these reactions, catalysts **4b** and **4c** performed well, but the reaction temperature was raised to 50–60 °C to get full conversion of the starting materials. The lower reactivity is apparently due to the more sterically hindered double bonds in **2l–n** than in the linear analogues, such as in **2a**. Because of the mild reaction conditions, elimination of the tertiary fluorine functionality in products **3m–o** could be avoided. Like **3l**, product **3o** also has three different halogen functionalities. Simple cycloalkenes **2o** and **2p** underwent iodofluorination with **1** in the presence of catalyst **4c** (entries 17 and 18). The reaction proceeded with clean anti selectivity. Product **3p** is volatile and was isolated in only 40% yield, but the corresponding NMR yield was 96%.

We carried out mechanistic studies to understand the regioselectivity of the reaction and investigate the fate of reagent **1**. As mentioned above (Table 2, entry 2), **2a** and **1** gave internally iodofluorinated product **3b** in the presence of $PdCl_2(MeCN)_2$ (**4c**). It is well-documented that allylbenzene derivatives can easily undergo allylic rearrangement in the presence of **4c** or other Pd(II) catalysts.[18] Indeed, when we reacted **2a** with **4c** in the absence of **1**, allylic rearrangement of **2a** occurred, resulting in **2b** (Scheme 1). As we have shown

Scheme 1. Isomerization of Allylbenzene



(Table 2, entry 3), **2b** smoothly underwent iodofluorination with **1** to afford **3b**. Considering this, we concluded that **2a** undergoes allylic rearrangement (to **2b**) in the presence of **4c**, after which iodofluorination of **2b** gives product **3b** (Table 2 entry 2). Accordingly, catalyst **4c** performs a tandem catalytic rearrangement–iodofluorination sequence when **2a** is reacted with **4c**. Interestingly, under identical reaction conditions **2a** underwent allylic rearrangement even with **4a** as a catalyst. However, the reaction of **2a** and **1** in the presence of **4a** gave the terminal iodofluorinated product **3a** (Table 2 entry 1). The above results indicate that in the presence of **4a** the iodofluorination of **2a** with **1** is much faster than the rearrangement to **2b**. Conversely, in the presence of **4c** the rearrangement is faster than the iodofluorination. Both reactions are very selective, as none of these reactions resulted in mixtures of **3a** and **3b**.

Our previous studies indicated that **1** can be activated by Lewis acid catalysts[14,15] similarly to the trifluoromethyl analogue of **1**.[19] In the present reaction this activation may take place by the PdX_2 catalyst **4**. The activated complex **5** (Figure 1) undergoes electrophilic addition to the alkene to

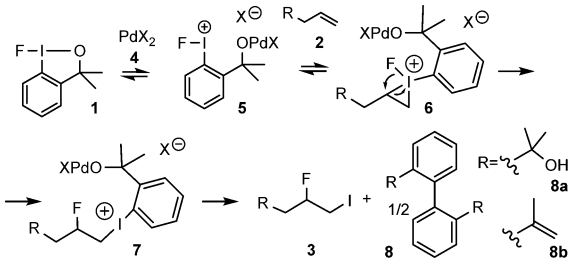


Figure 1. Plausible mechanism for the iodofluorination reaction.

give iodonium ion **6**. The electrophilic addition is in line with our findings that the reaction proceeds faster in the presence of electron-supplying substituents (OMe, Me) in the aromatic ring of the allylbenzene substrate (e.g., Table 2 entries 6–10) than in case of electron-withdrawing substituents (F, CF_3; entries 11 and 12). The next step is opening of the iodonium ring, resulting in **7**. The most intriguing process of the reaction is the cleavage of the C(sp^2)–I bond, which is most probably catalyzed by palladium. Our GC/MS studies indicated that the deiodinated aromatic ring of **1** underwent dimerization to give **8**. The molecular peaks indicating the formation of **8** could be found in the MS spectrum of the GC-separated reaction mixture. Most probably the primary product was **8a**, which underwent water elimination to give **8b**. Biphenyls with both dimethyl hydroxy and *α*-methyl ethyl substituents are also possible.

Benziodoxoles (such as **1**) are very unusual iodine sources in synthetic transformations. Mechanistic studies of these transformations are encumbered by the fact that the iodine transfer from the benziodoxole ring to the organic substrate occurs in a late stage of the reaction, as the I–F and I–O bonds have to be cleaved before the C(sp^2)–I bond cleavage. Except for our early report,[14] we found only a single recent study in which benziodoxoles were used for iodination. In that study, Rao and co-workers[20] showed that the MeO analogue of **1** can be used for Pd-catalyzed aromatic iodination. Those authors suggested an oxidative addition–reductive elimination sequence for introduction of the iodine atom to the substrate. According to Rao and co-workers,[20] this sequence may involve a Pd(II) to Pd(IV) oxidation step. We believe that a similar process may occur in the above iodofluorination reaction as well. Several studies[21] have shown that hypervalent iodines (structurally similar to **1**) are able to oxidize Pd(II) species. Mechanistic and density functional theory modeling studies to obtain a deeper understanding of this interesting C(sp^2)–I bond cleavage process are underway in our laboratory.

In conclusion, we have shown that the air- and moisture-stable fluoroiodine reagent **1** is suitable for iodofluorination of alkenes in the presence of palladium catalysts. Reagent **1** is the source of both the fluorine and iodine substituents. The reaction involves a palladium-catalyzed C–I bond formation–C(sp^2)–I cleavage sequence. For some catalysts a clean allylic rearrangement precedes the iodofluorination reaction. The presented reaction is suitable for iodofluorination of alkenes under mild neutral conditions and potentially applicable in PET diagnostics.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02022.

Detailed experimental procedures, compound characterization data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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