

Palladium-Catalyzed Cascade C–H Trifluoroethylation of Aryl Iodides and Heck Reaction: Efficient Synthesis of *ortho*-Trifluoroethylstyrenes**

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Abstract: A palladium-catalyzed selective C–H bond trifluoroethylation of aryl iodides has been explored. The reaction allows for the efficient synthesis of a variety of *ortho*-trifluoroethyl-substituted styrenes. Preliminary mechanistic studies indicate that the reaction might involve a key Pd^{IV} intermediate, which is generated through the rate-determining oxidative addition of $\text{CF}_3\text{CH}_2\text{I}$ to a palladacycle; the bulky nature of $\text{CF}_3\text{CH}_2\text{I}$ influences the reactivity. Reductive elimination from the Pd^{IV} complex then leads to the formation of the aryl– CH_2CF_3 bond.

The introduction of fluorinated moieties into organic molecules can have a profound influence on their chemical and biological activities.^[1] In recent years, trifluoroethyl-containing aromatic compounds have found an increasing number of applications in the fields of medicinal chemistry and biochemistry.^[2] Therefore, the exploration of efficient methods for their synthesis has received much attention. For instance, McLoughlin and Thrower reported that a copper catalyst could promote the coupling of iodobenzene with $\text{CF}_3\text{CH}_2\text{I}$, albeit with quite low efficiency.^[3] Shibata and co-workers recently demonstrated that trifluoroethyl arenes can be synthesized through the copper-mediated trifluoromethylation of benzyl bromides with electrophilic CF_3^+ reagents.^[4] In contrast, cross-coupling reactions between $\text{CF}_3\text{CH}_2\text{I}$ and aromatic compounds are still quite challenging because of 1) the slow oxidative addition of $\text{CF}_3\text{CH}_2\text{I}$ to a Pd catalyst,^[6a] 2) the difficulty of reductive elimination from the $\text{CF}_3\text{CH}_2\text{–Pd–aryl}$ complex, and 3) the tendency of this complex to undergo β -fluoride elimination, which leads to the formation of undesired side products.^[5] More recently, the groups of Hu^[6a] and Zhou^[6b] independently delineated the palladium-catalyzed trifluoroethylation of (hetero)aryl boronic acids or esters using a unique phosphine ligand. We

speculated that the direct trifluoroethylation of aryl C–H bonds should be more attractive, but this related reaction is quite challenging. Thus far, only one example of such a transformation has been reported by Ackermann and co-workers, who employed a nickel catalyst and 8-aminoquinoline as the directing group.^[7] Herein, we report a novel palladium-catalyzed tandem process that entails the selective *ortho* C–H trifluoroethylation of aryl iodides and a Heck-type cross-coupling to efficiently provide *ortho*-trifluoroethyl-substituted styrenes.

C–H functionalization has emerged as an increasingly useful method for organic synthesis.^[8] As part of our ongoing studies on fluorination and trifluoromethylation,^[9] we were interested in testing whether the direct trifluoroethylation of aryl C–H bonds would be possible. Recently, elegant studies by the groups of Daugulis^[10a] and Chen^[10b] have demonstrated that alkyl iodides could be used as alkyl reagents to achieve C–H bond alkylation, and the oxidation of aryl–Pd or alkyl–Pd complexes generated through C–H bond activation with alkyl iodides was proposed as a key step of this process. Unfortunately, $\text{CF}_3\text{CH}_2\text{I}$ was inactive in these transformations.

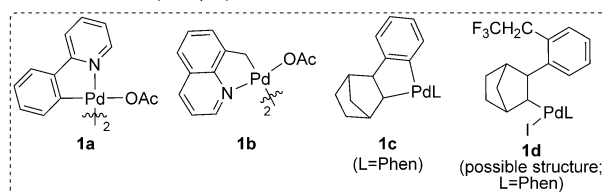
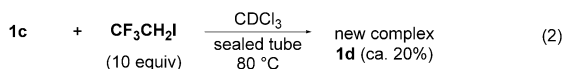
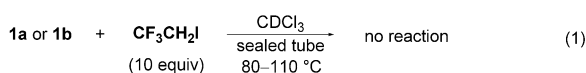
We envisioned that enhancing the nucleophilicity of the palladium intermediate might be helpful to achieve oxidative addition of $\text{CF}_3\text{CH}_2\text{I}$. To test this hypothesis, we initially investigated stoichiometric reactions of the aryl–Pd complexes **1a–c** with $\text{CF}_3\text{CH}_2\text{I}$. As shown in Equation (1), no reactions occurred between palladacycles **1a** or **1b** and $\text{CF}_3\text{CH}_2\text{I}$. When the more electron-rich palladacycle **1c** was employed, we were excited to find a new signal in the ^{19}F NMR spectrum at -62.6 ppm (t, $J = 11.6$ Hz) and two new signals in the ^1H NMR spectrum at 4.80 ppm (dq, $J = 11.6$, 15.4 Hz) and 3.76 ppm (dq, $J = 11.6$, 15.4 Hz), which match the spectrum of $\text{Ar–CH}_2\text{CF}_3$ [Eq. (2)].^[11] Furthermore, in the ESI-MS spectrum, an intense signal at m/z 539, which possibly corresponds to $[\text{1d–I}]^+$, was clearly observed.^[12] The complex **1d** might be generated through oxidation of **1c** with $\text{CF}_3\text{CH}_2\text{I}$ to generate a Pd^{IV} intermediate, followed by reductive elimination to form the $\text{C(aryl)–CH}_2\text{CF}_3$ bond.

Compounds with core structures similar to that of **1c** are important intermediates in Catellani reactions.^[13] This result intrigued us to study the catalytic trifluoroethylation of aryl C–H bonds. Initial studies were focused on the reaction of 2-iodotoluene with $\text{CF}_3\text{CH}_2\text{I}$ in the presence of catalytic amounts of palladium catalyst and ligand, norbornene, and methyl acrylate. Considering the slow oxidative addition, a number of electron-rich phosphine ligands were screened (Table 1). The phosphine ligand X-Phos was less effective, and its use led to the formation of product **3a** in only 27%

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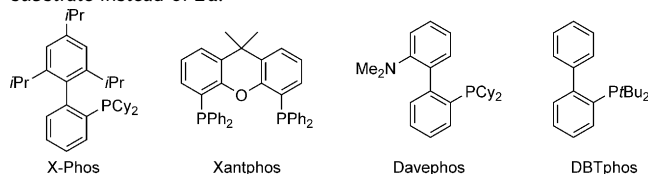
yield, and Xantphos was almost ineffective (entries 1 and 2). To our delight, when Davephos^[14] was employed, the yield of **3a** substantially improved to 50% (entry 3). In contrast, DBTPhos delivered product **3a** in a slightly lower yield (40%, entry 4). In these reactions, significant amounts of the side product **3a'** were obtained, which was generated by reductive elimination from a palladacycle such as **1c**. Furthermore, only trace amounts of the products **3a** and **3a'** were detected in the

Table 1: Optimization of the reaction conditions.^[a]

Entry	Ligand	Base	Solvent	Additive	Yield [%] 3a	3a'
1	X-Phos	Cs ₂ CO ₃	CH ₃ CN	—	27	54
2	Xantphos	Cs ₂ CO ₃	CH ₃ CN	—	6	32
3	Davephos	Cs ₂ CO ₃	CH ₃ CN	—	50	40
4	DBTPhos	Cs ₂ CO ₃	CH ₃ CN	—	40	30
5	—	Cs ₂ CO ₃	CH ₃ CN	—	trace	trace
6	Davephos	K ₂ CO ₃	CH ₃ CN	—	5	5
7	Davephos	Na ₂ CO ₃	CH ₃ CN	—	4	4
8	Davephos	Cs(OPiv) ₂	CH ₃ CN	—	26	27
9	Davephos	Cs ₂ CO ₃	toluene	—	14	37
10	Davephos	Cs ₂ CO ₃	DMF	—	38	23
11	Davephos	Cs ₂ CO ₃	DME	—	20	24
12 ^[b]	Davephos	Cs ₂ CO ₃	CH ₃ CN	—	59	26
13 ^[b]	Davephos	Cs ₂ CO ₃	CH ₃ CN	NaOAc	65	30
14 ^[b]	Davephos	Cs ₂ CO ₃	CH ₃ CN	HOAc	69	29
15 ^[b,c]	Davephos	Cs₂CO₃	CH₃CN	HOAc	76	20
16 ^[b,c,d]	Davephos	Cs ₂ CO ₃	CH ₃ CN	HOAc	0	0

[a] All of the reactions were run on a 0.2 mmol scale in CH₃CN (1 mL) in a sealed tube. Yields were determined by ¹⁹F NMR spectroscopy using *N,N*-dimethyl-trifluoroacetamide (CF₃-DMA) as an internal standard.

[b] Norbornene (3 equiv) and Cs₂CO₃ (4 equiv). [c] CF₃CH₂I (7 equiv) and DMI (50 mL) were added. [d] *ortho*-Bromotoluene was used as the substrate instead of **2a**.

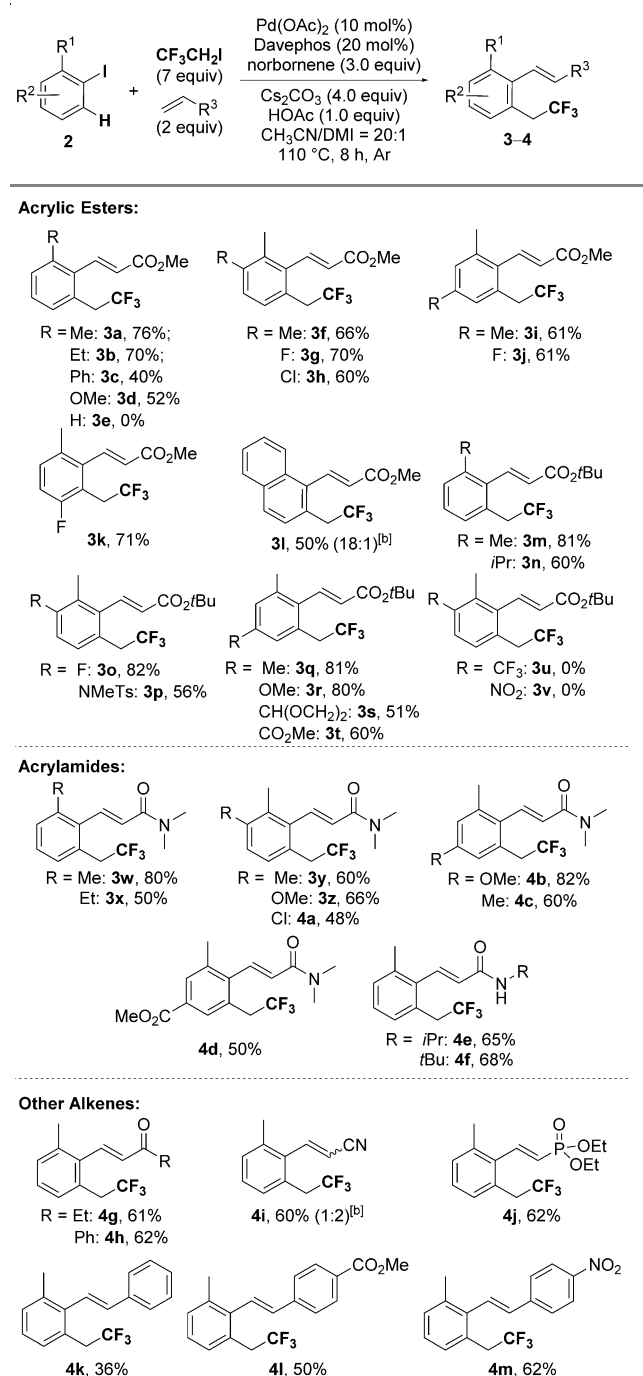


absence of a phosphine ligand (entry 5). Further optimization of the reaction conditions demonstrated that Cs₂CO₃ was the best base, and that CH₃CN was the best solvent (entries 6–11). In addition, increasing the amounts of norbornene and Cs₂CO₃ was helpful, and the yield of **3a** increased to 59% (entry 12). Furthermore, the addition of extra acetate was also beneficial, and a yield of 69% was obtained in the presence of AcOH. Finally, we found that increasing the amount of CF₃CH₂I to seven equivalents and the addition of 1,3-dimethyl-2-imidazolidinone (DMI)^[15] could improve the reaction yield to 78% (entry 15). However, *ortho*-bromotoluene was not a suitable substrate for this trifluoroethylation reaction (entry 16).

Having established optimized reaction conditions for the *ortho* C–H trifluoroethylation of aryl iodides, the substrate scope was next investigated. First, the reactions of a variety of substituted aryl iodides with acrylic esters were studied. As shown in Table 2, *ortho*-alkyl-substituted iodobenzenes with a methyl acrylate moiety could be successfully transformed into the corresponding *ortho*-CH₂CF₃-substituted styrenes **3a** and **3b** in good yields. *ortho*-Phenyl iodobenzene was also compatible with the reaction conditions and gave product **3c** in a slightly lower yield (40%). Furthermore, a methoxy substituent in the *ortho* position was also tolerated to give **3d** in moderate yield, whereas substrates with electron-poor *ortho* substituents exhibited poor reactivity in this transformation (see the Supporting Information). Simple iodobenzene also exhibited very poor reactivity (**3e**). For disubstituted iodobenzenes that bear alkyl and halide functional groups, the reactions also proceeded smoothly to generate the corresponding products (**3f–k**) in good yields. 1-Iodonaphthalene was also shown to be a good substrate and gave product **3l** in 50% yield. Among other acrylic esters, *tert*-butyl acrylate exhibited slightly higher reactivity towards trifluoroethylation to give **3m–r** in high yields. Importantly, a substrate with a bulky isopropyl group in the *ortho* position was also suitable for this transformation and generated product **3n** in 60% yield. In the *para* and *meta* positions, sulfonylamide, halide, and methyl ether substituents were tolerated (**3o–r**). In addition, an aryl iodide with a ketal group was a suitable substrate for this transformation and provided product **3s** in 51% yield.^[16] An aryl iodide with an electron-withdrawing carboxylic ester in the *para* position reacted well to give product **3t** in 60% yield. However, with trifluoromethyl or nitro groups in the *meta* position, no reaction occurred (**3u** and **3v**). All of these reactions proceeded with excellent selectivity to give the *E*-configured styrenes.

Then, various types of alkenes were investigated. As shown in Table 2, acrylamides were viable coupling partners for the reaction. Both *N,N*-bis- and *N*-mono-substituted acrylamides could undergo trifluoroethylation and cross-coupling to deliver the desired products (**3w–4f**) in moderate to good yields. Furthermore, vinyl ketones were also compatible with the reaction conditions and gave the products **4g** and **4h** in good yields. Similar reactivity was also observed with acrylonitrile (**4i**) and vinyl phosphonic ester (**4j**), but the reaction of acrylonitrile delivered a mixture of the *E* and *Z* isomers in a 1:2 ratio. Finally, a variety of substituted styrenes were considered. Compared with unsubstituted

Table 2: Substrate scope.^[a]



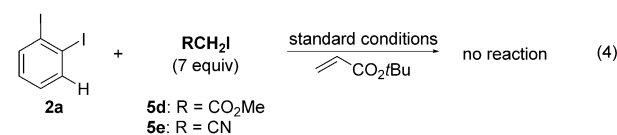
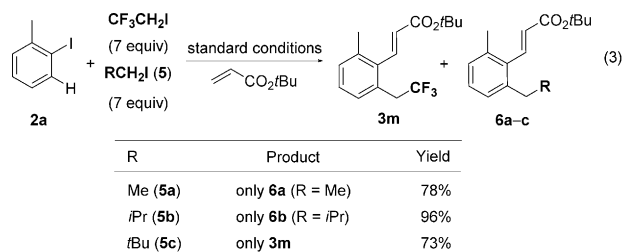
[a] Reaction conducted on a 0.2 mmol scale. Yields of isolated products are given. [b] *E/Z* ratio determined by ^1H NMR spectroscopy of the crude product.

styrene (**4k**), styrenes with electron-withdrawing groups exhibited better reactivities to give products **4l** and **4m** in satisfactory yields.

As mentioned above, oxidative addition of $\text{CF}_3\text{CH}_2\text{I}$ to a palladium complex is slower than that of normal alkyl iodides, which we thought to result from the sterically hindered nature of the CH_2CF_3 group. To test this hypothesis, a series of competition experiments were carried out. As

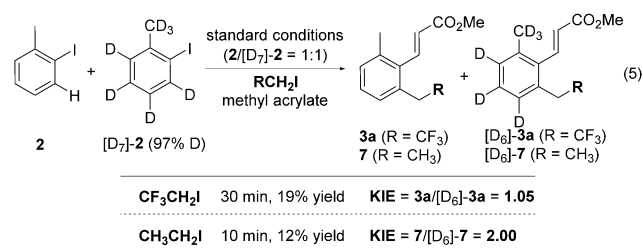
shown in Equation (3), $\text{CF}_3\text{CH}_2\text{I}$ was much less reactive than ethyl iodide (**5a**) and isobutyl iodide (**5b**), but more reactive than neopentyl iodide (**5c**). These results suggest that a steric effect indeed plays an important role in this transformation. Furthermore, with the electron-deficient alkyl iodides **5d** and **5e**, no reaction occurred [Eq. (4)], which suggests that electronic effects also influence this transformation.

To gain more insights into the mechanism, a competition experiment was carried out to determine the kinetic isotope effect (KIE) of this reaction [Eq. (5)]. With $\text{CF}_3\text{CH}_2\text{I}$, no significant kinetic isotopic effect (KIE = 1.05) was observed, indicating that C–H bond activation was not involved in the



rate-determining step. In contrast, a larger KIE effect (KIE = 2.00) was determined for the reaction of $\text{CH}_3\text{CH}_2\text{I}$, revealing a rate-determining C–H bond activation step.^[17]

As mentioned above, the formation of the side product cyclobutane **3a'** is very difficult to inhibit under the current reaction conditions, and this compound was generated by direct reductive elimination of palladacycle **C**. Meanwhile, the absence of a kinetic isotope effect suggested that



oxidative addition to palladacycle **C** might be the rate-determining step. In that case, the reaction rate of **3m** should be first-order dependent on the concentration of both intermediate **C** and $\text{CF}_3\text{CH}_2\text{I}$; in contrast, the rate for the formation of **3a'** is first-order dependent on the concentration of **C** only. Thus, the ratio in which **3m** and **3a'** are formed with varying $\text{CF}_3\text{CH}_2\text{I}$ concentration should give some information on the mechanism. As shown in Figure 1, the ratio of **3m/3a'** was linearly dependent on the concentration of $\text{CF}_3\text{CH}_2\text{I}$, which is consistent with a rate-determining oxidative addition

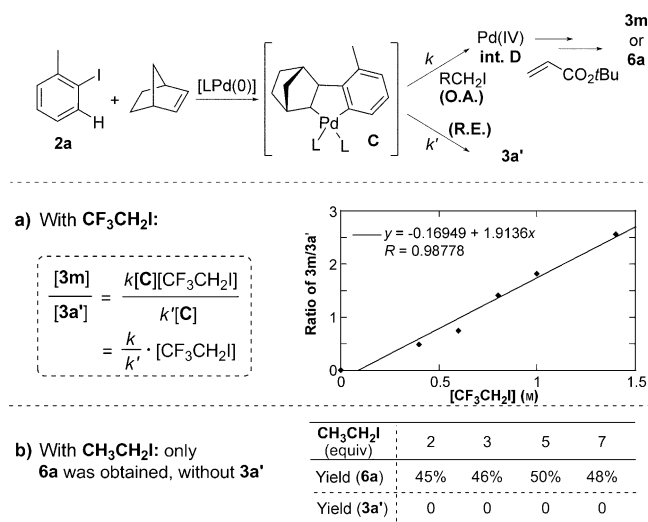
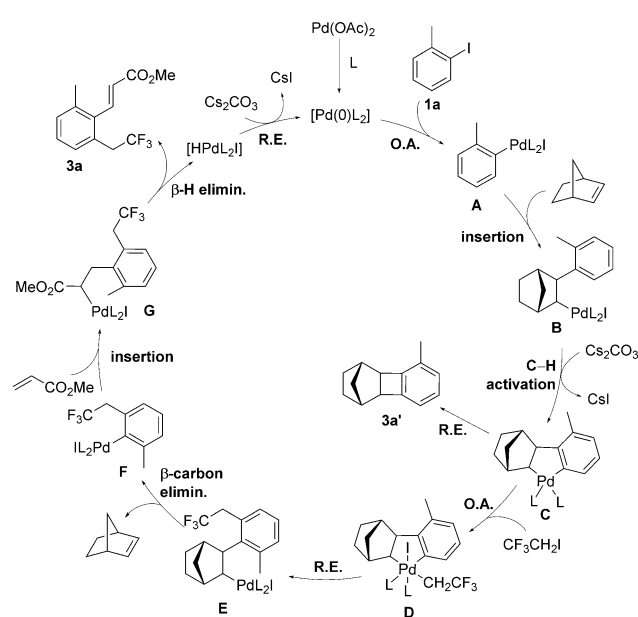


Figure 1. Reactivity of the palladacycle with RCH_2I : Oxidative addition (O.A.) versus reductive elimination (R.E.).

process (Figure 1 a). With CH_3CH_2I , however, the reactions only afforded alkylation product **6a** and not side product **3a'**, which reveals that oxidative addition of CH_3CH_2I to palladacycle **C** is much faster than reductive elimination (Figure 1 b). All of the above observations indicate that the reactivity of CF_3CH_2I towards the Catellani reaction is significantly different, and that it reacts much more slowly than normal alkyl iodides, such as CH_3CH_2I .

Finally, stoichiometric reactions were conducted with the palladium complexes **8a** and **8b**. When compound **8a** was subjected to the conditions described in Equation (6), **3a** was obtained in 36 % yield, whereas **8b** could not be transformed into **3e** under the same conditions [Eq. (7)]. This observation suggests that the *ortho* substituent plays an important role in the formation of **3a**.^[18]

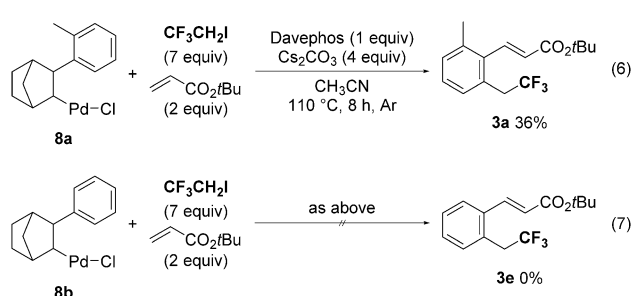
Based on the above analyses, a plausible catalytic cycle is proposed in Scheme 1. Similar to the Catellani reaction, the reaction is initiated by oxidative addition of 2-iodotoluene to the Pd^0 complex to generate aryl- Pd^{II} complex **A**. Subsequent insertion of norbornene into the C-Pd bond of **A** leads to



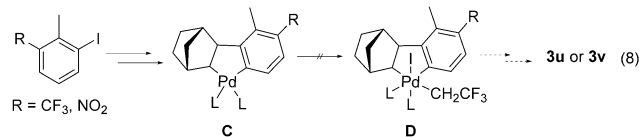
Scheme 1. Proposed mechanism.

bond formation. After β -carbon elimination of **E**, a new aryl- Pd^{II} complex **F** is released with norbornene expulsion. Finally, complex **F** reacts with the alkene in a classic Heck-type reaction to give product **3a** and to regenerate the Pd^0 catalyst. Because of the slow nature of the oxidative addition, direct reductive elimination from palladium complex **C** could deliver side product **3a'**, and enhancing the concentration of CF_3CH_2I is beneficial for the trifluoroethylation. Furthermore, for the inactive substrates (**3u** or **3v**), the strongly electron-withdrawing groups (CF_3 or NO_2) weaken the nucleophilicity of palladium complex **C**, which renders oxidation addition of CF_3CH_2I difficult and thus inhibits the trifluoroethylation process [Eq. (8)].

In conclusion, we have developed the first palladium-catalyzed selective C-H bond trifluoroethylation of aryl iodides with commercially available trifluoroethyl iodide. The reaction provides a straightforward and practical way to prepare various multi-substituted *ortho*-trifluoroethylsty-



alkyl- Pd^{II} complex **B**; then, C-H activation constructs palladacycle **C**. The following rate-determining oxidative addition of CF_3CH_2I to the strongly nucleophilic complex **C** generates Pd^{IV} intermediate **D**, which undergoes reductive elimination to yield Pd^{II} complex **E** with concomitant C-C



enes. Preliminary mechanistic studies indicate that the reaction might involve a high-valent palladium intermediate that is formed through slow oxidative addition of CF_3CH_2I to a palladacycle; this step is influenced by the bulky and possibly by the electron-withdrawing nature of CF_3CH_2I . The development of further applications of this transformation is in progress.

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