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Palladium-catalyzed intermolecular fluoroesterification of styrenes: exploration and mechanistic insight†

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A novel palladium-catalyzed intermolecular oxidative fluoroesterification of vinylarenes has been developed using NFSI, one of the mildest electrophilic fluorinating reagents. The reaction presents an efficient synthetic pathway to afford a series of α-monofluoromethylbenzyl carboxylates in good to excellent yields. Rather than following an electrophilic fluorination pathway, the reaction is initiated through oxidation of Pd(0) to a Pd(II) fluoride complex by NFSI, followed by fluoropalladation of a styrene to generate an α-monofluoromethylbenzyl–Pd intermediate. Generally, reductive elimination of benzyl–Pd^{II} complexes is favored with relatively strong oxy-nucleophiles to afford C–O bonds. This reaction, however, exhibited the opposite reactivity: strong acids with weak nucleophilicity, such as CF_3CO_2H and CCl_3CO_2H, were prone to afford the fluoroesterification product, while weak acids with strong nucleophilicity, such as HOAc and BzOH, did not deliver the C–O bond product. Further mechanistic studies determined that C_{sp^3}–Pd(O_2CR), a key intermediate, was generated through ionic ligand exchange between benzyl–Pd(NZ_2) and CF_3CO_2H, and the final C–O bond was possibly formed through reductive elimination of a high-valent C_{sp^3}–Pd(O_2CR) complex *via* an S_N2-type nucleophilic attack pathway.

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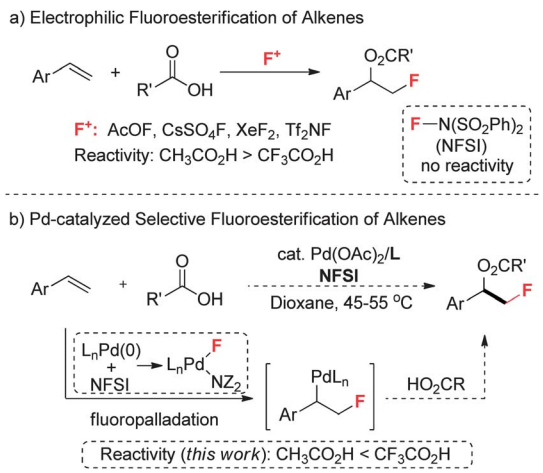
Introduction

Monofluorinated analogues of biologically active compounds are considered as potential drugs because the monofluoromethyl group can sterically mimic the methyl or hydroxymethyl group with considerably altered bioactivity and bioavailability.[1,2] Thus, efforts towards the efficient synthesis of those compounds have attracted much attention.[3] For instance, electrophilic fluorination of alkenes can be used to synthesize the corresponding monofluoro-alcohols,[4] an important moiety in biological active compounds.[5] However, such fluorooxygenation reactions are often restricted to electron-rich alkenes and required strong electrophilic fluorinating reagents,[6] such as $CsSO_4F$,[6a,b] AcOF,[6c] XeF_2,[6d] TfN_2F,[6e] and substituted *N*-fluoropyridinium salts.[6f–h] These limitations, narrow substrate scope, poor selectivity and poor functional group compatibility, can be usually overcome by employing a mild fluorinating reagent. Unfortunately, readily available *N*-fluoro-benzenesulfonimide (NFSI), one of mildest electrophilic fluorinating reagents, is inert toward fluorination of alkenes due to its low reactivity (Scheme 1a).[7] Thus, exploration of alternative approaches employing NFSI or even milder electrophilic fluorinating reagents for fluorooxygenation are in urgent need.

Palladium-catalyzed intra/inter-molecular difunctionalization of olefins represents one of the best strategies to introduce two functional groups into double bond simultaneously.[8] In addition, electrophilic fluorinating reagents have been reported as oxidants to carry out Pd-catalyzed organic transformations.[9] Therefore, we envisioned that applying a palladium catalyst might be a good strategy to achieve the fluorooxygenation of



Scheme 1 Fluoroesterification of styrene.

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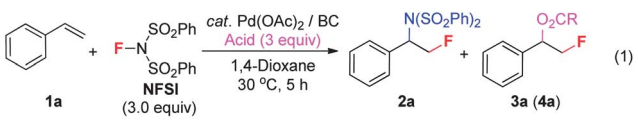
alkenes.[10] As part of our efforts to develop novel fluorination reactions,[10e,11] we disclosed a Pd-catalyzed intermolecular fluoroamination of styrene using NFSI as fluorine source.[12] In this reaction, NFSI served as a good reagent to oxidize Pd(0) to a palladium fluoride complex, and subsequent fluoropalladation of styrene was proposed as the key step to generate the α-monofluoromethyl benzyl–Pd intermediate. Based on this discovery, we speculated that if the benzyl–Pd intermediate was attacked by a carboxylic acid,[13] efficient fluoroesterification of alkenes could be expected (Scheme 1b).

Generally, reductive elimination of benzyl–Pd^{II} complexes is favoured with relatively strong oxy-nucleophiles to afford C–O bonds.[14] Herein, we reported a Pd-catalyzed fluoroesterification of styrenes, in which carboxylic acids with weak nucleophilicity but strong acidity, such as CF_3CO_2H and CCl_3CO_2H, are prone to afford the C–O bond formation product. In contrast, weak acids with strong nucleophilicity, such as HOAc and BzOH, still form C–N bonds, rather than C–O bonds. Further mechanistic studies support that the final C–O bond is derived from the reductive elimination of a high-valent C_{sp^3}–$Pd(O_2CR)$ complex.

Results and discussion

To test the above hypothesis, the reaction of **1a** was initially investigated by screening a series of carboxylic acids with different pK_a values under the previous reaction conditions (eqn (1)). We were pleased to find that fluoroesterification product **3a** or **4a** was obtained when CF_3CO_2H or CCl_3CO_2H was used as the additive. Although the yield of the desired product was low, the fluoroamination process was completely inhibited. It is noteworthy that the above two acids have much lower pK_a values and weaker nucleophilicity than $(PhSO_2)_2NH$. However, addition of HOAc or *p*-nitrobenzoic acid, which has higher pK_a values and better nucleophilicity, still afforded the fluoroamination product **2a** rather than fluoroesterification product. Upon further increasing the acidity, addition of methanesulfonic acid completely inhibited fluorination of **1a**. In comparison, trifluoroacetate salts, such as CF_3CO_2Na, CF_3CO_2Ag and CF_3CO_2Cs, did not afford any fluorination products.



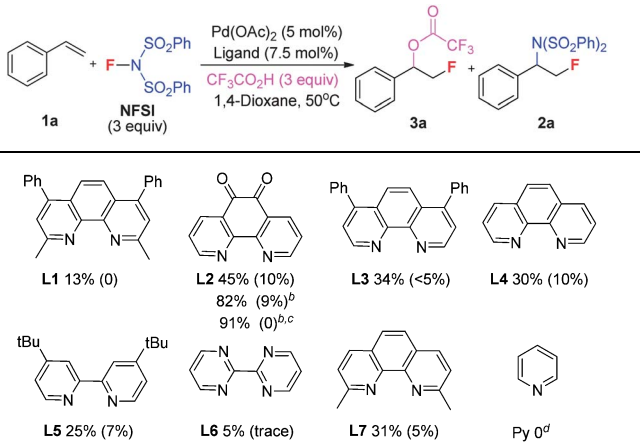
(1)

Acid (*p*K*a*)	2a	3a (4a)
CH_3CO_2H (4.76)	86%	0
p-$NO_2C_6H_4CO_2H$ (3.44)	73%	0
CCl_3CO_2H (0.65)	trace	9% (**4a** R = CCl_3)
CF_3CO_2H (0.23)	trace	13% (**3a** R = CF_3)
CH_3SO_3H (-0.26)	0	0
CF_3COOM (M = Na, Cs, Ag)	0	0

* The *pk*a of $HN(SO_2Ph)_2$ is 1.45.

Encouraged by the above interesting fluoroesterification results, further ligand effects were investigated. As shown in Table 1, bidentate nitrogen ligands were crucial to the success of the fluoroesterification. Electron-deficient ligand **L2** gave the best results (**3a**, 45% yield), combined with a small amount of fluoroamination product **2a** (10%). In contrast, pyridine was ineffective. Pd catalyst screening results showed that both Pd(II) and Pd(0) were good catalysts for this transformation,[15] and $PdCl_2$ exhibited the best reactivity to give **3a** in 82% yield. Increasing the amount of trifluoroacetic acid (5 equiv.) improved the yield of fluoroesterification (91% yield).

Table 1 Ligand screening[a]

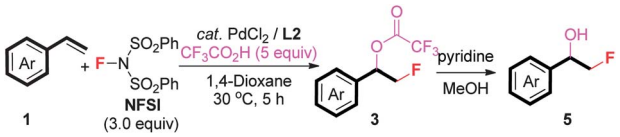


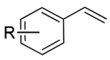
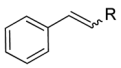
[a] All reactions were run at 0.2 mmol scale. ^{19}F NMR yield of **3a** (**2a**) with $CF_3C_6H_5$ as internal standard. [b] $PdCl_2$ (5 mol%) as catalyst. [c] 5.0 equiv. TFAH. [d] 15% pyridine.

Under the optimized reaction conditions, the substrate scope of the reaction was investigated, and the results are compiled in Table 2. The reaction of **1a** afforded the desired product **3a** in 91% yield. Due to easy hydrolysis of product **3a** on a silica gel column,[16] the desired product **3a** could be directly transformed to the corresponding alcohol **5a** in 87% yield by addition of pyridine and methanol in one pot. In addition, substrates bearing an alkyl-, aryl-, ester- or halogen-substituted benzene ring were suitable to give corresponding products **3b–3j** (or **5b–5j**) in good to excellent yields (entries 2–10). In contrast, the reactions of electron-deficient styrenes **1k** and **1l** afforded products in slightly lower yields (entries 11–12). Similarly, the reaction of α-methylstyrene **1m** smoothly proceeded to give desired product **5m** in 84% yield. Gratifyingly, internal alkenes, such as **1n–1r**, proved to be good substrates, giving products **5n–5r** with excellent regioselectivity but poor diastereoselectivity (entries 14–20).

Based on above results, the substrate scope of styrenes was further explored (Table 3). We found that more sterically hindered styrenes such as **1s**, and electron-deficient styrenes with halide (X = Cl, Br) atoms at the β-position, such as **1t** or **1u**, were compatible under these reaction conditions and yielded the desired products in moderate to good yields. 3-vinylquinoline substrate **1v** was also good for this transformation, giving product **5v** in 65% yield. The substrate **1w** with a triazole group provided corresponding product **5w** in 55% yield. In addition, styrenes with more functional groups, such as aldehyde, acid, and nitrile groups, reacted

Table 2 Pd-catalyzed fluoroesterification of styrenes[a]

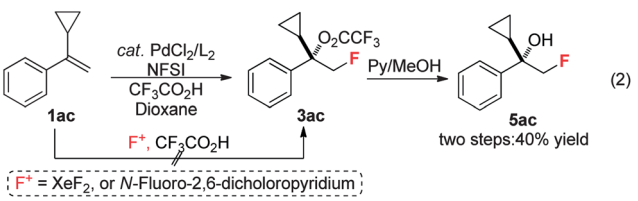


Entry		Substrate		3	Yield[b]	5	Yield[c]
1		**1a**		**3a**	91%	**5a**	87%
2		**1b**	R = *p*-Me	**3b**	89%	**5b**	83%
3		**1c**	*o*-Me	**3c**	79%	**5c**	71%
4		**1d**	*p*-^{t}Bu	**3d**	80%	**5d**	75%
5		**1e**	*p*-(*p*-F)C_6H_4	**3e**	83%	**5e**	80%
6		**1f**	*p*-CH_2Cl	**3f**	73%	**5f**	—[d]
7		**1g**	*p*-F	**3g**	91%	**5g**	85%
8		**1h**	*p*-Cl	**3h**	82%	**5h**	80%
9		**1i**	*p*-Br	**3i**	83%	**5i**	81%
10		**1j**	*p*-OAc	**3j**	80%	**5j**	80%
11		**1k**	*p*-COOMe	**3k**	57%	**5k**	50%
12		**1l**	*p*-CF_3	**3l**	53%	**5l**	43%
13		**1m**		**3m**	88%	**5m**	84%
14		*E*-**1n**	R = Me	**3n**	91% (1.4 : 1)	**5n**	81% (1.3 : 1)
15		*Z*-**1n**			97% (1 : 2.4)		87% (1 : 2.3)
16		*E*-**1o**	R = Et	**3o**	73% (2 : 1)	**5o**	70% (2 : 1)
17		*E*-**1p**	R = Ph	**3p**	91% (1.3 : 1)	**5p**	90% (1.3 : 1)
18		*Z*-**1p**			65% (1 : 1.5)		55% (1 : 1.5)
19		**1q**		**3q**	81% (1.4 : 1)	**5q**	71% (1.3 : 1)
20		**1r**		**3r**	81% (2 : 1)	**5r**	71% (2 : 1)

[a] Reactions were conducted at 0.3 mmol scale. [b] ^{19}F NMR Yield with CF_3Ph as internal standard. [c] Isolated yield based on the substrate **1** (the data in parentheses is the value of diastereoselectivity). [d] Complex result.

smoothly to afford the corresponding products in good yields. Finally, styrene **1aa** bearing a steroid motif proved to be a good substrate to give product **5aa**.[17] Estrone derivative **1ab** also afforded the corresponding ester product **3ab**, which is physiologically active and could be utilized in medicine.[18]

Furthermore, substrate **1ac**, frequently employed as a radical "clock" was subjected to the standard fluoroesterification conditions.[19] The reaction afforded the desired product **5ac** in moderate yield, which rules out the possibility of a radical pathway (eqn (2)).[20] Furthermore, product **3ac** could not be obtained through the reaction of **1ac** with strong F^+ reagents (eqn (2)), in which ring-opening of cyclopropane occurred to give complex results. This observation indicates that the electrophilic fluorination pathway is less likely.[21] Finally, unactivated olefins, such as 1-octene and allylbenzene, were found to be ineffective in this fluoroesterification reaction.

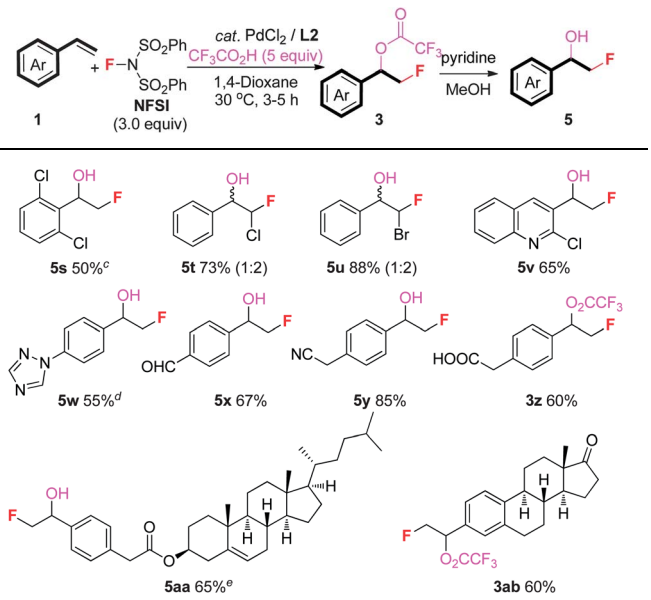


(2)

The reaction was also explored using CCl_3CO_2H, since the trichloroacetate ester products were stable enough to be handled *via* silica gel chromatography. As shown in Table 4, a variety of substrates proved suitable to afford trichloroacetate ester products **4** in moderate to good yields.

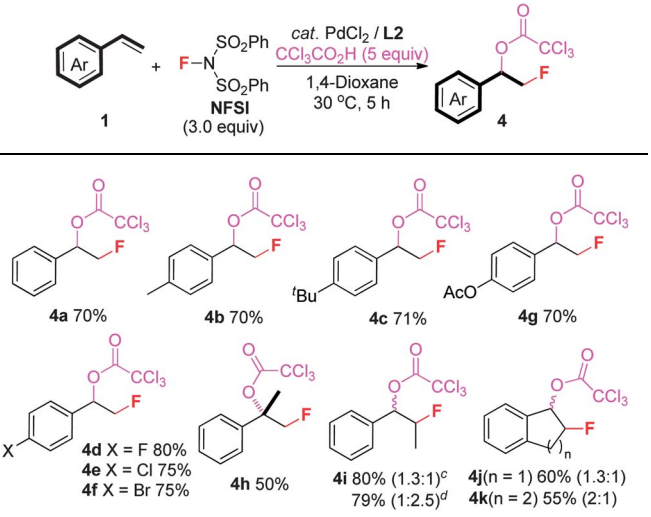
Due to the important biological activities of α-methylbenzyl thioacetates in medicinal chemistry, such as the compound illustrated below as a p38-α protein kinase inhibitor,[22] we speculated that introducing fluorine into methyl group might provide an opportunity to modulate its biological activity.

Table 3 Pd-catalyzed fluoroesterification of styrenes[a,b]



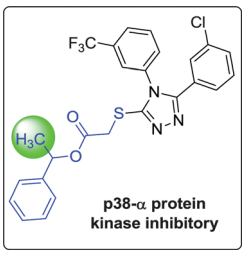
[a] Reactions were conducted at 0.2 mmol scale. [b] Isolated yield (the data in parentheses is the value of diastereoselectivity). [c] 80% conversion. [d] The ester product was hydrolysed with aq. $NaHCO_3$. [e] With $Pd(dba)_2$ (5 mol%) as catalyst.

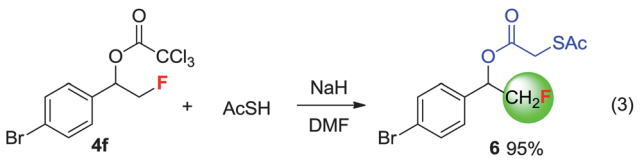
Table 4 Pd-catalyzed fluoroesterification of styrenes[a,b]

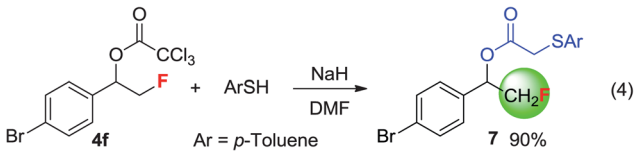


[a] Reactions were conducted with 0.3 mmol scale. [b] Isolated yield (the data in parentheses is the value of diastereoselectivity). [c] *E*-(β-methyl) styrene as substrate. [d] *Z*-(β-methyl)styrene as substrate.

Thus, the direct thiolation of product **4** was further investigated. Treatment of **4f** with thioacetic acid (AcSH) afforded substituted product **6** in 95% yield (eqn (3)). Benzylthioether **7** was also obtained from **4f** with related thiophenol in 90% yield (eqn (4)). Therefore, the sequential fluoroesterification of alkenes and thiolation provided a versatile way to build up a library of benzyl thioacetates containing a monofluoromethyl group.



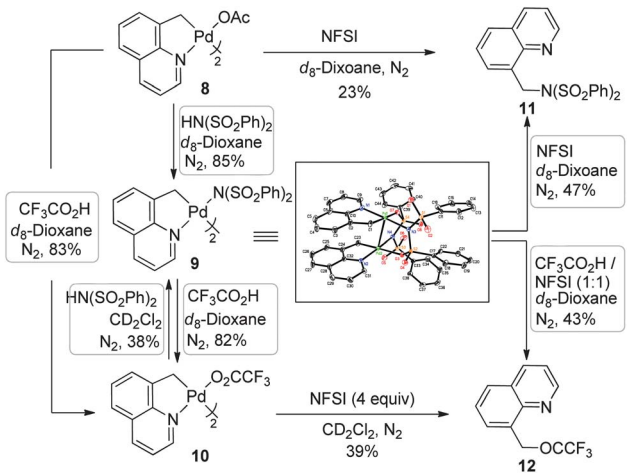




Mechanism

As proposed above, the nucleophilic attack on the benzyl–Pd^{II} complex by CF_3CO_2H is responsible for the benzyl C–O bond formation. However, a pioneering study by Yamamoto demonstrated that reductive elimination of the benzyl–$Pd^{II}(O_2CCF_3)$ complex *via* a Pd(II/0) cycle is more difficult than that of the benzyl–Pd^{II}(OAc) complex.[23] To elucidate the mechanism, benzyl–Pd complex **8** was employed to examine the C–O bond formation (Scheme 2). We found that treatment of complex **8** with either $(PhSO_2)_2NH$ or CF_3CO_2H afforded the corresponding palladium complex **9** or **10** in good yield. Complex **10** was also obtained from **9** in 82% yield, however, **9** was transformed from **10** in low yield. This ionic ligand exchange is possibly triggered due to the higher acidity of CF_3CO_2H than that of $(PhSO_2)_2NH$ or HOAc. Furthermore, complexes **8–10** were too stable to allow the formation of the corresponding C–O and C–N bonds, even with the assistance of PPh_3, bipyridine and ligand **L2**. The results indicate that C–O bond formation is unlikely to follow the reductive elimination pathway *via* Pd(0/II) cycle.

In contrast, the reductive elimination process did occur in the presence of NFSI. For instance, reductive elimination products **11** and **12** were selectively yielded from complexes **9** (47% yield) and **10** (39% yield), respectively. Product **11** could also be directly obtained from complex **8** in 23% yield without observation of the C–O bond product. In addition, product **12** could be selectively obtained from complex **9** when treated



Scheme 2 Reductive elimination processes from Pd(II) complexes.

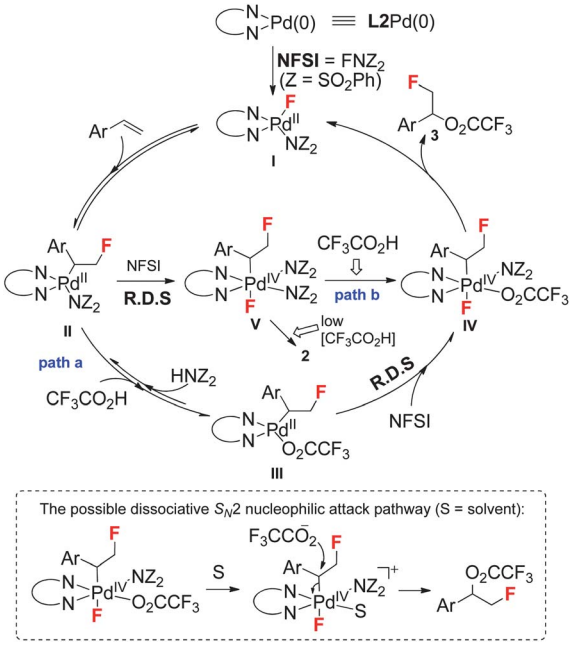
with equal equivalents of NFSI and CF_3CO_2H. The above observations suggested that the C–O bond should be derived from a high-valent Pd complex, such as a Pd(IV) or Pd(III) intermediate.[24]

Interestingly, the order of reductive elimination of high-valent C–Pd(Nu) complexes is opposite to the nucleophilicity of Nu: $CF_3CO_2^- > (PhSO_2)_2N^- > CH_3CO_2^-$. Due to easier disassociation of $CF_3CO_2^-$, reductive elimination of the palladium complex possibly involves a dissociative S_N2 nucleophilic attack pathway (Scheme 3, bottom), which is consistent with the DFT calculations on the C–N bond formation from Pd(IV) intermediate reported by Muñiz.[25,26]

Based on the above analysis, the mechanism in Scheme 3 was proposed. The reaction is initiated through oxidation of Pd(0) by NFSI to give Pd(II) fluoride complex **I**, and subsequent fluoropalladation of styrene yields intermediate **II**.[27,28] Then, two possible scenarios are presented to address the transformation from complex **II** to product **3**. The first pathway involves ligand exchange between **II** and CF_3CO_2H to give intermediate **III**, and then subsequent oxidation of **III** by NFSI generates the high-valent Pd intermediate **IV**, which undergoes S_N2-type reductive elimination to form the C–O bond (path a). For the second pathway, the transformation from Pd complex **II** to **IV** is *via* an alternative sequential process of oxidation of Pd(II) species **II**, and ligand exchange between **V** and CF_3CO_2H (path b). It is difficult to differentiate the above two pathways at present.[29]

To gain insight into the mechanism, time course experiments were conducted. As displayed in Fig. 1A, a noticeable induction period was found in the reaction with $PdCl_2$ as the catalyst. In contrast, reactions with $Pd(PPh_3)_4$ and $Pd(dba)_2$ showed a monotonic decrease in styrene concentration, and the lack of an induction period enabled us to obtain much of our kinetic data *via* initial-rates methods.

Further kinetic studies were performed using **1g** as the substrate and $Pd(PPh_3)_4$ as catalyst. The reaction rate exhibited a saturation dependence on the concentration of **1g**, and first-order dependence on the concentration of the palladium catalyst and NFSI.[30] It is interesting that the rate of **3g** formation presented a saturation dependence on the concentration of CF_3CO_2H, but the overall rate of formation of **2g** and **3g** was independent on the concentration of CF_3CO_2H (Fig. 1B). This observation is consistent with both paths a and b. In the case of low [CF_3CO_2H], the formation of a mixture of products **2g** and **3g** should be delivered from high-valent Pd complexes **V** and **IV**, which may be generated from the oxidation of both intermediates **II** and **III**, respectively, or from the ligand exchange between complex **V** and limited CF_3CO_2H. In the high [CF_3CO_2H], either rapid transfer from **II** to **III** then oxidation or rapid transfer from **V** could generate intermediate **IV**, and yield a single product **3g** from its reductive elimination (Scheme 3).



Scheme 3 Proposed mechanism.

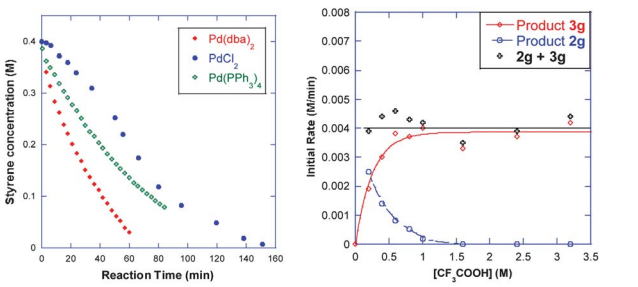


Fig. 1 (A) (left) Time course of reactions of **1g** with [Pd]/**L2**: [styrene] (0.40 M), [CF_3CO_2H] (2.00 M), [Pd] (0.02 M), [**L2**] (0.03 M), [NFSI] (1.20 M), dioxane, 30 °C; (B) (right) Dependence of the initial rate on [CF_3CO_2H]: [styrene] (0.40 M), [Pd] (0.02 M), [**L2**] (0.03 M), [NFSI] (1.20 M), [CF_3CO_2H] (0–3.5 M), dioxane, 30 °C.

Conclusions

We have developed a novel palladium-catalyzed intermolecular oxidative fluoroesterification of vinylarenes. The reaction affords monofluorinated benzyl esters in good yields. The mechanistic study shows that the key step of C–F bond formation derives from the fluoropalladation process and that subsequent C–O bond formation comes from a sequential ionic ligand exchange between the benzyl–Pd(II) intermediate and CF_3CO_2H, oxidation by NFSI, then reductive elimination of the high-valent Pd complex. Further applications of this transformation and asymmetric fluoroesterification of styrenes are in progress.

Acknowledgements

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15 For optimization of the reaction conditions, see the ESI.†

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17 Product **5aa** is hard to purify using silica gel column chromatography, due to an unidentified side product, but can be purified by HPLC.

18 Substrates **1s–1z**, **1aa** and **1ab** were treated under standard electrophilic fluorination reaction conditions; most reactions failed to give the corresponding products. For details, see the ESI.†

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20 The radical pathway was proposed in fluoroesterification of styrenes by using Tf_2NF as electrophilic fluorinating reagent, for details, see ref. 6*e*.

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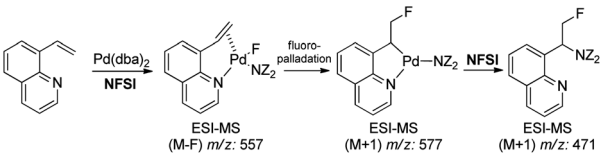
28 In order to investigate the fluoropalladation step, substrate 8-vinyl-quinoline was subjected to the reaction conditions. The reaction was monitored using ESI-MS, and the signals at *m*/*z* 557 and 577 were consistent with the coordinated Pd complex and α-monofluoromethyl benzyl–Pd complex, respectively. The latter was derived from fluoropalladation of the alkene. For details analysis, see the ESI.†



29 Based on the current results, the pathways involving radicals or carbon cations are less likely, but cannot be completely ruled out. For the case of α-methylstyrene (**1m**), however, it is difficult for the mediated S_N2 type substitution to occur on the *tertiary* carbon centre. Thus, the detailed pathway for this substrate is still unknown at the moment.

30 For more kinetic data, see the ESI.†