

Palladium-Catalyzed Tandem Fluorination and Cyclization of Enynes

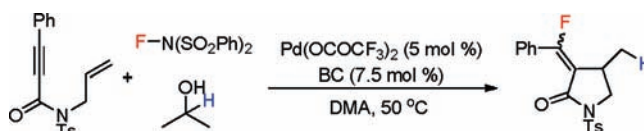
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ABSTRACT



A novel palladium-catalyzed tandem fluorination and cyclization of enynes has been developed. A favorable *cis*-fluoropalladation is proposed as a key step to construct a vinyl–F bond, and the final C_{sp^3} –Pd bond is reduced by alcohol. This transformation represents an efficient road to synthesize fluorinated lactams.

Molecules bearing a fluorine moiety significantly improve many of their properties, including solubility, bioavailability, and metabolic stability and are of great importance in pharmaceuticals.¹ Novel methods for the synthesis of fluorinated molecules based on C–F bond formation are therefore in

great demand. However, very few effective approaches are available for directly constructing a C–F bond.^{2,3} We are particularly intrigued by the prospect of developing transition-metal-catalyzed fluorination of unsaturated C–C bonds to achieve C–F bond formation under mild conditions.^{4,5}

Palladium-catalyzed cyclization of enynes is an efficient strategy for the synthesis of cyclic compounds, particularly heterocycles. Such a process is inherently atom economical and results in a significant increase in structural complexity.⁶ For instance, oxidative cyclization of enynes, initiated by nucleopalladation of alkynes, has been extensively studied (eq 1).⁷ Recently, Tse and Sanford have independently reported palladium-catalyzed enyne cyclization for the construction of bicyclic products, which was proposed to be initiated by acetoxy-palladation of the alkyne moiety and facilitated by using $PhI(OAc)_2$ as an oxidant (eq 1a).⁸

(1) (a) Welch, J. T.; Eswarakrishnan, S., Eds. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) Banks, R. E., Smart, B. E., Tatlow, J. C., Eds. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994.

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(4) For recent reviews on transition-metal-catalyzed C–F bond formation, see: (a) Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8610–8614. (b) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160–171. (c) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804–1821. For recent examples, see: (d) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134–7135. (e) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520–7521. (f) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993–5996. (g) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661–1664. (h) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150–12152.

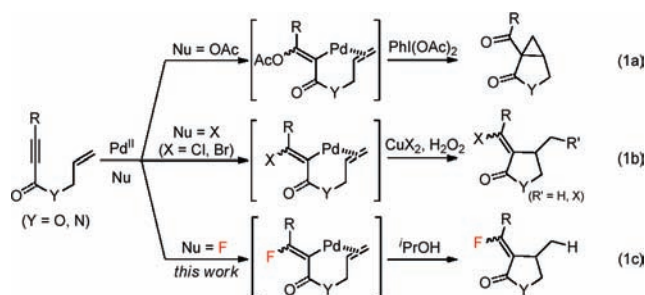
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Related cyclization initiated via halopalladation of triple bonds has been demonstrated by Lu and others (eq 1b).⁹ However, the cyclization reaction of enynes involving fluorination is unknown. This is because the challenging fluorination of triple bonds is extremely rare. So far, only gold-catalyzed fluorination of alkynes was reported by Sadighi, Gouverneur, and Nevado, respectively.¹⁰

Very recently, our group has reported a Pd(OAc)₂/BC (bathocuproine)-catalyzed intermolecular aminofluorination of vinylarenes, where a fluoropalladation of styrene was proposed as the key step for the formation of the C–F bond.^{5b} We postulate that, if fluoropalladation of triple bond occurs, the cyclization of enynes might be expected to afford the corresponding fluorinated cyclic products (eq 1c).¹¹ Importantly, the fluorination of a triple bond is also a good model to study the stereochemistry of fluoropalladation, which is a suspended question in the aminofluorination of styrenes.^{5b} Herein, we report a novel palladium-catalyzed tandem fluorination and cyclization of enynes, which is possibly initiated by a favorable *cis*-fluoropalladation of a triple bond to construct a vinyl C–F bond. Interestingly, we also observed that the newly formed C_{sp3}–Pd bond in the catalytic cycle was reduced by an alcohol, as clearly demonstrated by the deuterated experiments.



Our initial studies focused on the Pd-catalyzed cyclization of enyne **1a** with *N*-fluorobenzenesulfonimide (NFSI). We were delighted to find that a small amount of cyclic product **2a** was observed when the reaction was treated with Pd(TFA)₂/BC in DMA (*N,N*-dimethylacetamide, Table 1, entry 1). The addition of water was beneficial for the yield, but the best yield (39%) was obtained in the presence of 3 equiv of water (entry 2). A series of protic additives were investigated, and the isopropyl alcohol was proven to be the best additive to give **2a** in 67% yield (entries 3–6). When an

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Table 1. Screening Results: Pd-Catalyzed Fluorination and Cyclization of Enyne **1a**^a

entry	additive	3a yield (<i>E:Z</i>) ^{b,c}
1	none	11% (3:1)
2	H ₂ O (3 equiv)	39% (3:1)
3	HCOOH (3 equiv)	31% (3:1)
4	MeOH (3 equiv)	16% (5:1)
5	ⁱ PrOH (3 equiv)	67% (3:1)
6	BnOH (3 equiv)	52% (4:1)
7 ^c	Et ₃ SiH (10 equiv)	14% (100:0)
8 ^d	ⁱ PrOH (3 equiv)	7% (ND)
9 ^e	ⁱ PrOH (3 equiv)	NR
10 ^f	ⁱ PrOH (3 equiv)	72% (5:1)

NFSI:

3

4

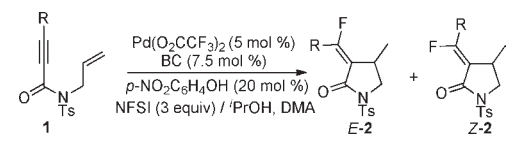
^aThe reaction conditions: **1a** (0.2 mmol), NFSI (0.5 mmol), Pd(TFA)₂ (5 mol %), BC (7.5 mol %), and additive in *N,N*-dimethylacetamide (DMA, 0.5 mL) at 50 °C. ^b¹⁹F NMR yield with trifluoromethylbenzene as internal standard, and the ratio was detected by F NMR for the crude products. ^cPd(OAc)₂ (5 mol %). ^d**3** (3 equiv) instead of NFSI. ^e**4** (3 equiv) instead of NFSI. ^f4-NO₂C₆H₄OH (20 mol %) was added.

excess of Et₃SiH was used as a reducing agent instead of ⁱPrOH, the reaction gave a single isomer *E-2a*, but in low yield (entry 7). No reaction occurred in the absence of the palladium catalyst or ligand BC. The very low conversions occurred in the presence of other fluorinating reagents, such as **3** and **4** (entries 8–9). Finally, the addition of 2,4-*tert*-butyl-phenol has no significant effect on this reaction, and the slightly better result was obtained in the presence of 4-nitrophenol (entry 10).¹²

With the optimized reaction conditions, the scope of this cyclic fluorination reaction was investigated with a variety of enynes. As summarized in Table 2, substrates **1a** and **1b** bearing electron-withdrawing groups on the nitrogen atom gave the lactams **2a** and **2b** in 70% and 66% yields with moderate *Z/E* ratios, respectively (entries 1–2). Substrate **1c** bearing a benzyl group afforded the product **2c** in 49% yield with an opposite *Z/E* ratio (entry 3). Substrate **1d** bearing an ester group produced the fluorinated lactone **2d** in a slightly lower yield (entry 4). Furthermore, the enynes **1e–1m** synthesized from aryl substituted propiolic acid were evaluated under the standard reaction conditions (entries 5–13). The substrates bearing an electron-donating group on the aromatic ring afforded a cyclic product with good yield (entries 5–8). In contrast, the yields were slightly lower for the reaction of substrates with electron-withdrawing groups (entries 9–11). A trace amount of the desired product was detected for the reaction of **1l** with a strong electron-withdrawing nitro group (entry 12). For substrate **1n**, the reaction also proceeded to give cyclic fluorinated product **2n** in moderate yield (entry 14). Unfortunately, substrates **1o** with

(12) Although the role of 4-nitrophenol is currently not understood, those observations suggest against a radical mechanism.

Table 2. Palladium-Catalyzed Tandem Fluorination and Cyclization of Enynes^a



entry	substrate	product	yield ^b	E-2:Z-2 ^c
1			70%	5:1
2			66%	3:1
3			49%	1:2
4			35%	3:1
5			70%	4:1
6			68%	3:1
7			69%	4:1
8			72%	3:1
9			56%	4:1
10			48%	8:1
11			54%	5:1
12			trace	--
13			60%	7:1
14			61% ^e	4:1
15			trace	
16			trace	
17 ^d			37%	2:1
			13%	1.6:1

^a Reactions were conducted at 0.3 mmol scale. ^b Isolated yield. ^c The ratio of *E/Z* isomers which were determined by ¹⁹F NMR. ^d 78% conversion of **1q**. ^e *E-2n* (*trans/cis* = 4:1), *Z-2n* (*trans/cis* = 2:1).

alkyl-terminated alkyne and **1p** with disubstituted alkene afforded trace amount of cyclic products (entries 15–16). The reaction of **1q** bearing an internal double bond was found to yield cyclization product **2q** in 37% yield, along with the hydrofluorination product **5** in 13% yield (entry 17). The configurations of both *E*- and *Z-2e* were determined by the X-ray crystallographic analysis (Figure 1).

Mechanistically, fluoropalladation is much less understood than chloro- or bromopalladation in part due to its scarcity. Similar to the mechanism of aminofluorination of styrene,^{5b} we proposed that this cyclization is initiated by fluoropalladation of alkyne,¹³ followed by alkene insertion into a vinyl–Pd bond to form a new C_{sp3}–Pd bond, which was reduced by

(13) A single relative fluorogoldation has been reported in ref 10a. For selected examples of chloropalladation of alkyne, see ref 7 and (a) Muniz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412–9423. (b) Yang, S.-R.; Jiang, H.; Li, Y.-Q.; Chen, H.-J.; Luo, W.; Xu, Y.-B. *Tetrahedron*. **2008**, *64*, 2930–2937. (c) Li, Y.; Liu, X.; Jiang, H.; Feng, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 3338–3341. (d) Huang, J.; Zhou, L.; Jiang, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945–1949.

(14) The alternative mechanism, which initiates by Pd(II)-catalyzed alcohol oxidation and the following Pd-hydride addition to alkene is unlikely. For details see Supporting Information.

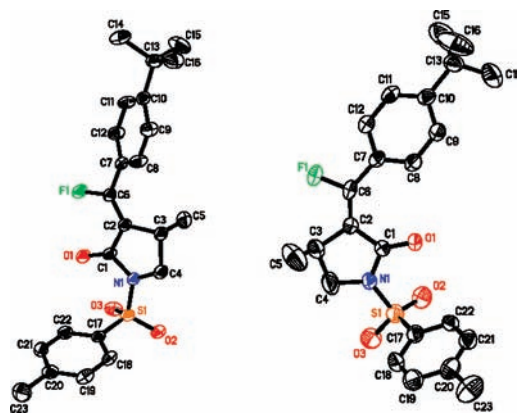
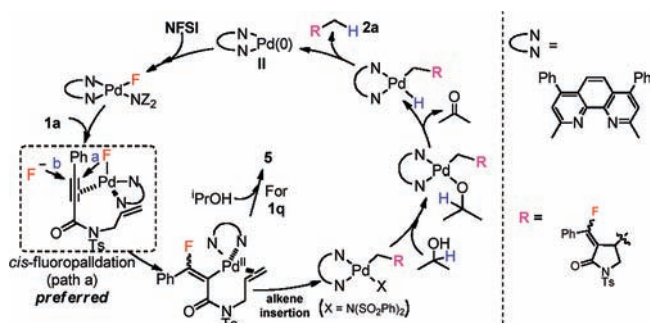


Figure 1. X-ray of *Z-2e* (left) and *E-2e* (right).

Scheme 1. Proposed Mechanism for the Palladium-Catalyzed Tandem Fluorination and Cyclization of Enyne



alcohol to give fluorinated cyclic product **2a** (Scheme 1).¹⁴ In the case of **1q**, the formation of **5** is likely generated from the reduction of a vinyl–Pd complex by alcohol.

Importantly, the formation of mixture products **2a** with an *E/Z* ratio of 5:1 indicated that both *cis*- and *trans*-fluoropalladation of the triple bond occur simultaneously and the *cis*-fluoropalladation is favored (path a, Scheme 1), which may be due to the strong interaction between fluoride and palladium.¹⁵ The less favored *trans*-fluoropalladation proceeds via *trans*-nucleophilic attack of the triple bond by a free fluoride anion which is generated from decomposition of NFSI (path b).^{16,17} When the free fluoride anion was

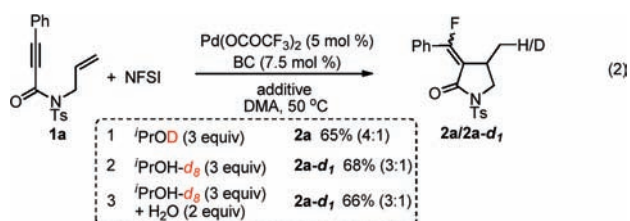
(15) For review on the interactions between fluoride and a transition metal, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.

(16) The time course experiment monitored by ¹⁹F NMR noted that the palladium-catalyzed decomposition of NFSI is prior to the cyclization of enyne. For more details, see the Supporting Information.

(17) The F[−] is possibly generated from the reaction of NFSI with a nucleophilic reagent (such as H₂O, ROH, and amine); for the details, see: (a) Antelo, J. M.; Crugeiras, J.; Leis, J. R.; Rois, A. J. *Chem. Soc., Perkin Trans. 2* **2000**, 2071–2076. (b) Roy, A.; Schneller, S. W. *Org. Lett.* **2005**, *7*, 3889–3891. (c) Giovanelli, E.; Doris, E.; Rousseau, B. *Tetrahedron Lett.* **2006**, *47*, 8457–8458.

trapped by a large excess of Et₃SiH, only *cis*-fluoropalladation occurs (Table 1, entry 7).

Lastly, we sought to investigate the origin of the proton incorporated into the cyclic product by using two deuterium-labeled isopropanols. It is surprising that no deuterium incorporating into the product was observed in the presence of ⁱPrOD. Meanwhile, deuterium labeled product **2a-d₁** was obtained when ⁱPrOH-*d*₈ was used, even in the presence of H₂O (eq 2). These observations suggest that the cleavage of a C_{sp³}-Pd bond proceeds through a sequential alcohol oxidation/reductive elimination pathway,¹⁸ in which the N(SO₂Ph)₂ anion functions as a base to promote the formation of a Pd-alkoxide intermediate (Scheme 1, right side). This unprecedented method presents a new strategy to quench the C_{sp³}-Pd bond under mild conditions. These results in eq 2 simultaneously suggest that cleavage of the C_{sp³}-Pd bond by HF is unlikely.¹⁹



In conclusion, we have developed a novel palladium-catalyzed tandem fluorination of alkyne and cyclization of enyne using NFSI as a fluorinating reagent. In this transformation, a fluoropalladation of alkyne is proposed to form a vinyl-F bond, and the relevant C_{sp³}-Pd bond is reduced by alcohol to give a fluorinated cyclic product. Further mechanistic study on this reaction is in progress.

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Supporting Information Available. Detailed experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(18) Although the palladium-catalyzed alcohol oxidation has been extensively studied, the C-Pd complex quenched by this way is unknown. This process only appears in one case to address a side reaction in aryl iodide carbonylation. For details, see: Hu, Y.; Liu, J.; Lü, Z.; Luo, X.; Zhang, H.; Lan, Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 3153–3158.

(19) If the C_{sp³}-Pd bond is cleaved by HF which generated *in situ*, the formation of the mixture of **2a** and **2a-d₁** should be expected; for details see the Supporting Information.