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Editor's Choice

Silver-catalyzed Vinylic C–F Bond Activation: Synthesis of 2-Fluoroindoles from β,β-Difluoro-*o*-sulfonamidostyrenes

Takeshi Fujita, Yota Watabe, Shigeyuki Yamashita, Hiroyuki Tanabe, Tomoya Nojima, and Junji Ichikawa*
Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571

(E-mail: junji@chem.tsukuba.ac.jp)

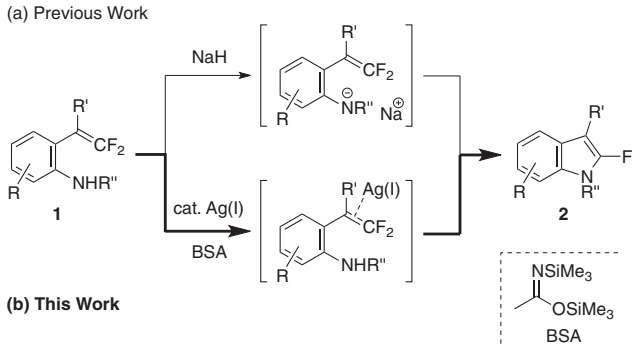
An electrophilic 5-*endo-trig* cyclization of β,β-difluoro-*o*-sulfonamidostyrenes was performed in 1,1,1,3,3,3-hexafluoropropan-2-ol using a Ag(I) catalyst and *N*,*O*-bis(trimethylsilyl)acetamide. In this process, vinylic C–F bond activation was achieved via silver-catalyzed β-fluorine elimination, accompanied by C–N bond formation, which led to the synthesis of 2-fluoroindoles.

Keywords: C–F bond activation | Silver catalyst | Fluoroindole

Because 1,1-difluoro-1-alkenes are electron-deficient substances, they readily react with strong nucleophiles at the carbon α to fluorine substituents. The nucleophilic addition, followed by β-fluorine elimination, affords monofluoroalkenes.[1] By applying the above-mentioned reaction to intramolecular cyclization, we previously synthesized ring-fluorinated hetero- and carbocyclic compounds.[2] Particularly, we achieved 5-*endo-trig* cyclization, which is disfavored in Baldwin's rules,[3] using β,β-difluoro-*o*-sulfonamidostyrenes **1** as substrates, leading to fluoroindole synthesis (Scheme 1a).[2]

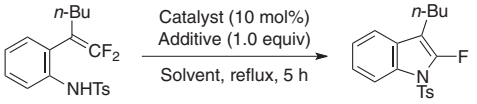
Addition–elimination reactions of 1,1-difluoro-1-alkenes with weak nucleophiles require electrophilic alkene activation,[4] recently achieved by acids[5] or transition-metal complexes.[6] Electrophilic addition–elimination of 1,1-difluoro-1-alkenes potentially exhibits a wide substrate scope by excluding basic conditions. In some cases, however, monofluoroalkene products were susceptible to hydrolysis under such acidic conditions and converted to carbonyl compounds.[5c,5g,6a,6b] We herein report a transition-metal catalysis providing 2-fluoroindoles **2** via an electrophilic 5-*endo-trig* cyclization[7] of difluorosulfonamidostyrenes **1** without hydrolysis (Scheme 1b). The use of a Ag(I) catalyst and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as a fluoride captor is highly effective for vinylic C–F bond activation[8] via the β-elimination of AgF, an unprecedented accomplishment.[9]

First, we sought suitable conditions for fluoroindole synthesis using β,β-difluorostyrene **1a** bearing a tosylamide group as a model substrate (Table 1). Heating **1a** in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP)[10,11] yielded no cyclized product in the presence of a catalytic amount of palladium complexes (Entries 2–4), although cationic Pd(II) complexes in HFIP, which are effective for carbocycle construction from β,β-difluorostyrene derivatives,[6b,6c,6d] were employed (Entries 3 and 4). While $PtCl_2$ was ineffective (Entry 5), the use of 10 mol % of $Cu(OTf)_2$ or AuCl afforded 2-fluoroindole **2a**, albeit in extremely low yield (Entries 6 and 7). As a result of screening several Ag(I) complexes (Entries 8–12), $AgSbF_6$ was found to be a prospective catalyst because the quantitative formation of **2a** was observed on the basis of the amount of $AgSbF_6$ (10 mol %) used (Entry 12).[12] Thus, with the aim of effective fluoride elimination, silylating agents were examined as fluoride captors with 10 mol % of $AgSbF_6$ (Entries 13–15). Among them, 1.0 equiv of BSA[13] drastically promoted defluorinative 5-*endo-trig* cyclization to afford **2a** in 52% yield (Entry 15). This reaction definitively proceeded with a metal



Scheme 1. Synthesis of 2-fluoroindoles **2** via 5-*endo-trig* cyclization of β,β-difluoro-*o*-sulfonamidostyrenes **1**.

Table 1. Screening of conditions for electrophilic 5-*endo-trig* cyclization of **1a**

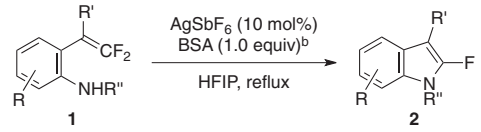


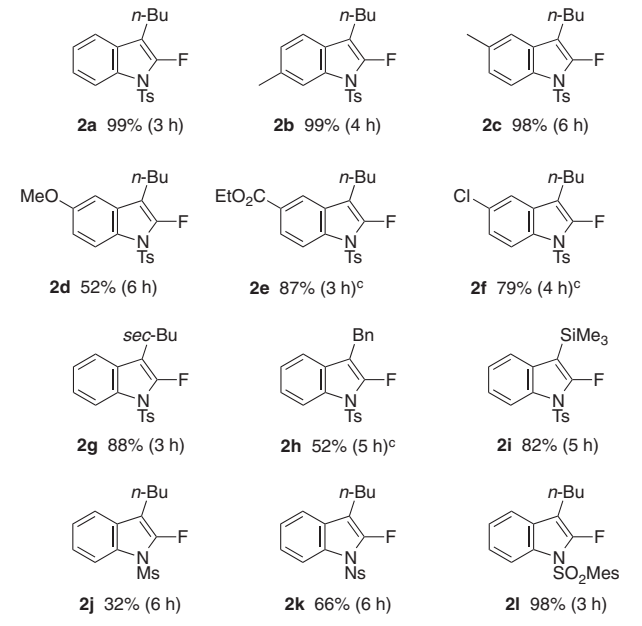
1a **2a**

Entry	Catalyst	Additive	Solvent	**2a**/%[a]
1	—	—	HFIP	N.D.[b]
2	$Pd(OAc)_2$	—	HFIP	N.D.[b]
3	$[Pd(NCMe)_4](BF_4)_2$	BF_3·OEt	HFIP	N.D.[b]
4	$PdCl_2$, AgOTf (1:2)	BF_3·OEt	HFIP	N.D.[b]
5	$PtCl_2$	—	HFIP	N.D.[b]
6	$Cu(OTf)_2$	—	HFIP	<1
7	AuCl	—	HFIP	1
8	AgF	—	HFIP	N.D.[b]
9	AgOTf	—	HFIP	6
10	$AgNTf_2$	—	HFIP	<1
11	$AgBF_4$	—	HFIP	7
12	$AgSbF_6$	—	HFIP	10
13	$AgSbF_6$	TMSImd[c]	HFIP	N.D.[b]
14	$AgSbF_6$	HMDSO[d]	HFIP	31
15	$AgSbF_6$	BSA[e]	HFIP	52
16	$AgSbF_6$	BSA[e]	Toluene	N.D.[b]
17	$AgSbF_6$	BSA[e]	CH_2Cl_2	N.D.[b]
18	$AgSbF_6$	BSA[e]	DMF	N.D.[b]
19[f]	$AgSbF_6$	BSA[e]	HFIP	quant. (99)[g]
20[h]	AgF	BSA[e]	HFIP	82 (82)[g]

[a]Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b]N.D.: not detected. [c]TMSImd: *N*-trimethylsilylimidazole. [d]HMDSO: hexamethyldisiloxane. [e]BSA: *N*,*O*-bis(trimethylsilyl)acetamide. [f]After a dropwise addition of BSA to the refluxed solution over 2 h, the mixture was stirred for another 1 h. [g]Isolated yield. [h]After a dropwise addition of BSA to the refluxed solution over 2 h, the mixture was stirred for another 3 h.

Table 2. Ag(I)-catalyzed synthesis of 2-fluoroindoles **2**[a]



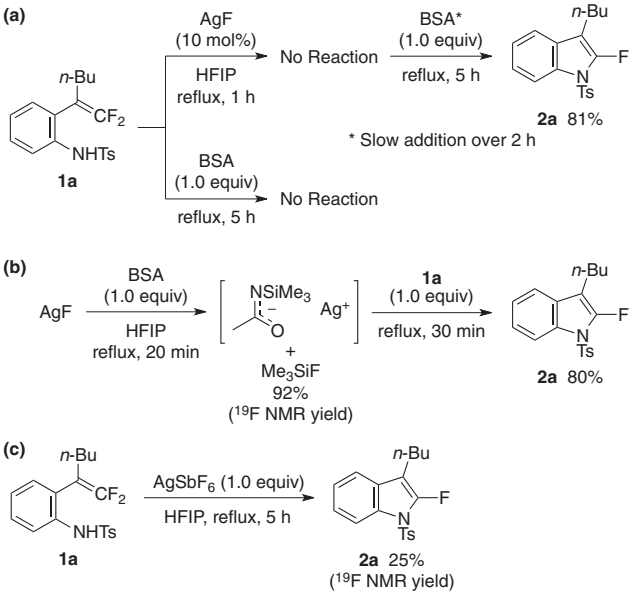


[a]Isolated yield. [b]BSA was slowly added over 2 h. [c]AgF (20 mol %) was used instead of $AgSbF_6$.

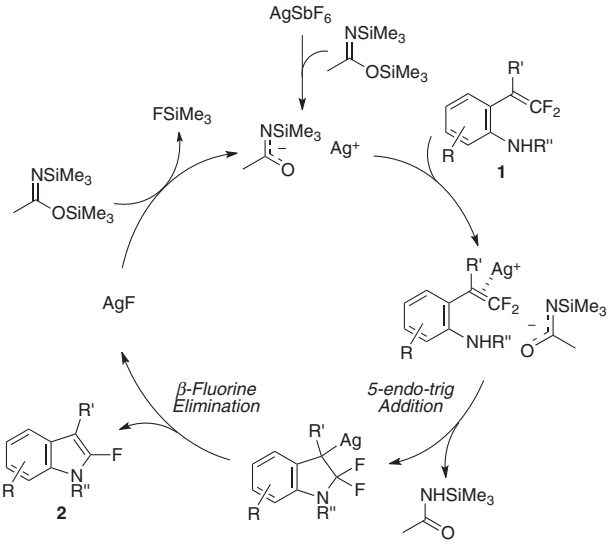
catalyst in HFIP because the formation of **2a** was not observed in the absence of the catalyst (Entry 1) or in other solvents (Entries 16–18). Eventually, the slow addition of BSA over 2 h was found to be a significant operation, which led to an almost quantitative formation of **2a** (Entry 19). Notably, the combination of 10 mol % of AgF and 1.0 equiv of BSA also successfully afforded **2a** in 82% isolated yield (Entry 20), although AgF caused no cyclization without BSA (Entry 8).

Using the above-mentioned optimal conditions, the scope of the cyclization of amidodifluorostyrenes **1** was then investigated (Table 2). β,β-Difluorostyrenes **1b** and **1c** bearing a methyl group successfully underwent cyclization, leading to an almost quantitative formation of the corresponding 2-fluoroindoles **2b** and **2c**, respectively. Ether (MeO), ester (EtO_2C), and halogen (Cl) substituents in difluorostyrenes **1d**–**1f** were tolerated in this reaction, which afforded the corresponding fluoroindoles **2d**–**2f**, while AgF was more effective than $AgSbF_6$ for the cyclization of **1e** and **1f**. Secondary alkyl (*sec*-Bu), benzyl, and silyl (Me_3Si) groups were installed instead of a primary alkyl group at the 3-position of the pyrrole rings of fluoroindoles **2g**–**2i**. The substitution of mesyl, nosyl, and mesitylenesulfonyl groups on a nitrogen atom was achieved to afford diversely sulfonylated 2-fluoroindoles **2j**–**2l**.

To gain information on the role of BSA, we performed experiments shown in Scheme 2. In the presence of 10 mol % of AgF, an HFIP solution of β,β-difluorostyrene **1a** was refluxed, and no reaction was observed (Scheme 2a; see also Entry 8, Table 1); however, further addition of a stoichiometric amount of BSA promoted 5-*endo-trig* cyclization to afford 2-fluoroindole **2a** in



Scheme 2. Mechanistic studies on Ag(I)-catalyzed cyclization of **1a**.



Scheme 3. Proposed mechanism for Ag(I)-catalyzed 5-*endo-trig* cyclization of **1a** via C–F bond activation.

81% yield. Conversely, BSA alone did not cause cyclization (Scheme 2a). When AgF was treated with BSA, trimethylsilyl fluoride was obtained in 92% yield, indicating the formation of a Ag(I) amidate complex (Scheme 2b). The addition of **1a** to the reaction mixture afforded **2a** in 80% yield (Scheme 2b). Furthermore, on treatment with a stoichiometric amount of $AgSbF_6$ in the absence of BSA, **1a** gave **2a** in only 25% yield (Scheme 2c). These results suggest that the active species is Ag(I) amidate and not $AgSbF_6$.

Based on all these observations, we propose a mechanism for the Ag(I)-catalyzed 5-*endo-trig* cyclization of β,β-difluorostyrenes **1** (Scheme 3). The reaction starts with the generation of the Ag(I) amidate complex from $AgSbF_6$ and BSA. The coordination of **1** to the Ag(I) amidate complex induces 5-*endo-trig* addition of the

sulfonamido group. Unprecedented β-elimination of AgF causes C–F bond cleavage to afford 2-fluoroindoles **2**. The reaction of AgF with BSA then regenerates Ag(I) amidate to complete the catalytic cycle.

In summary, we developed a synthetic method for the formation of 2-fluoroindoles via Ag-catalyzed vinylic C–F bond activation achieved by a 5-*endo-trig* addition/β-fluorine elimination sequence. The current method enables the simultaneous construction of an indole framework and the installation of a fluorine substituent at the 2-position. The obtained fluoroindoles are expected to constitute a new class of bioactive compounds because the indole ring and fluorine substituent are common components in pharmaceuticals.[14]

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Supporting Information is available on http://dx.doi.org/10.1246/cl.160427.

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