Transition-metal-catalyzed Electrophilic Activation of 1,1-Difluoro-1-alkenes: Oxindole Synthesis via Intramolecular Amination

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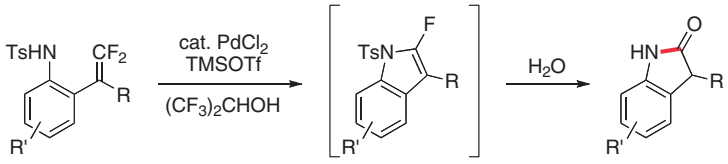

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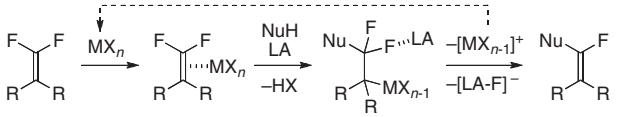
In the presence of a catalytic amount of palladium(II) chloride, β,β-difluorostyrenes bearing a sulfonamido group at the ortho position were treated with trimethylsilyl trifluoromethanesulfonate to afford oxindoles in high yield. The reactions proceeded via 5-*endo-trig* cyclization, hydrolysis, and desulfonylation. This sequence allowed the transformation of difluorostyrenes into free oxindoles in a one-pot operation.

1,1-Difluoro-1-alkenes possess electrophilic character because of the electron-withdrawing inductive effect of the two fluorine atoms.[1] Whereas they react with strong nucleophiles such as alkyllithiums and Grignard reagents, the nucleophiles that can be employed are restricted to reactive anionic species. Because of the low electron density of their alkene moiety, a limited number of electrophiles, iodine,[2] mercuric acetate,[3] tin tetrachloride,[4] and Magic Acid ($FSO_3H\cdot SbF_6$),[5] have been used for the activation of difluoroalkenes, where a stoichiometric amount of the reagent was required. Thus, their electrophilic activation in a catalytic manner is highly desirable for the transformation of 1,1-difluoro-1-alkenes.

It is widely known that transition metals, especially late transition metals, can be an electrophilic activator of alkenes because of their strong interaction with π electrons.[6] Concerning difluoroalkenes, there are reported alkene-coordinated metal complexes,[7] although they have not been utilized in the transformation of difluoroalkenes. We took notice of such transition-metal complexes and recently succeeded in the electrophilic activation of 1,1-difluoro-1-alkenes using a cationic palladium complex, $[Pd(MeCN)_4](BF_4)_2$, which allowed Friedel–Crafts-type cyclization with an intramolecular aryl group.[8]

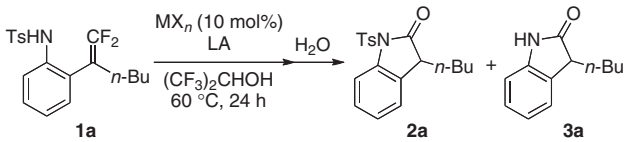
Besides the palladium catalyst, $BF_3\cdot OEt_2$ promoted the above reaction via β-fluorine elimination[8,9] and capture of a fluoride ion, which regenerated an active, cationic Pd(II) species without any reoxidants. These results showed that a combination of (i) a transition metal (MX_n) as activator of alkenes and (ii) a Lewis acid (LA) as scavenger of fluoride ions is important for the catalytic substitution of the vinylic fluorines (Scheme 1). Here, we report transition-metal-catalyzed activation of β,β-difluorostyrenes and intramolecular amination via replacement of the fluorine atom.

The starting materials, 1,1-difluoro-1-alkenes **1**, bearing a *p*-toluenesulfonamide group at the ortho position as a nucleophile,



Scheme 1. Electrophilic activation of difluoroalkenes with catalyst.

Table 1. Effects of transition-metal catalysts and Lewis acids



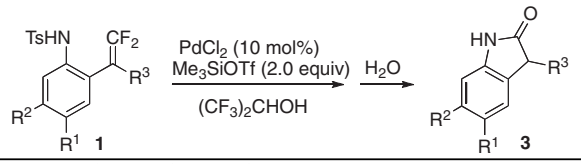
1a **2a** **3a**

Entry	MX_n	LA (equiv)	Yield/%	
			2a	**3a**
1	$[Pd(MeCN)_4](BF_4)_2$	$BF_3\cdot OEt_2$ (1.0)	0	0
2	$[Pd(MeCN)_4](BF_4)_2$	Me_3SiOTf (1.0)	10	22
3	$Pd(OAc)_2$	Me_3SiOTf (1.0)	15	34
4	$PdCl_2(PPh_3)_2$	Me_3SiOTf (1.0)	<1	<1
5	$PdCl_2$	Me_3SiOTf (1.0)	12	73
6	—	Me_3SiOTf (1.0)	0	0
7	$PdCl_2$	—	0	0
8	$PdCl_2$	Me_3SiOTf (2.0)	0	86
9	$NiCl_2$	Me_3SiOTf (2.0)	0	<5
10	$PtCl_2$	Me_3SiOTf (2.0)	0	0
11	$Cu(OAc)_2$	Me_3SiOTf (2.0)	0	37
12	$Cu(OTf)_2$	Me_3SiOTf (2.0)	0	87
13	$AgSbF_6$	Me_3SiOTf (2.0)	0	80
14	AuCl	Me_3SiOTf (2.0)	0	77

were designed to undergo aminopalladation[10] via alkene–metal complexes, leading to indole derivatives. On treatment with $[Pd(MeCN)_4](BF_4)_2$ catalyst and $BF_3\cdot OEt_2$ under the previous reaction conditions,[8] difluorostyrene **1a** gave no cyclized products (Table 1, Entry 1). However, the use of Me_3SiOTf as a fluoride ion scavenger promoted the cyclization to give the hydrolyzed products, oxindole with and without a tosyl group, **2a** and **3a** in 10% and 22% yield, respectively, instead of the expected 2-fluoroindole **4a** (Entry 2). Several palladium catalysts were tested and $PdCl_2$ provided the best total yield (85%) of the cyclic products (Entry 5). Both the metal catalyst and Me_3SiOTf were essential for this reaction (Entries 6 and 7), and the increased amount of Me_3SiOTf (2 equiv) gave free oxindole **3a** in 86% yield as the sole product (Entry 8).[11,12] Because no alkenes were observed, β-hydrogen elimination did not occur under the reaction conditions. Whereas other catalysts such as $NiCl_2$ and $PtCl_2$ were not effective, $Cu(OTf)_2$, $AgSbF_6$, and AuCl activated **1a** to afford **3a** in high yield (Entries 12–14). Under the conditions of Entry 8, no reaction occurred using Et_2O, THF, MeCN, or DMF as solvent, which confirmed the dramatic effect of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as a solvent in the activation of difluoroalkenes with the transition metal. HFIP, possessing high ionizing power with low nucleophilicity, would stabilize the cationic intermediate to promote the amination.[5]

Several difluorostyrenes **1b**–**1g** bearing other substituents were subjected to the catalytic conditions used above. The results are summarized in Table 2. The activation method was

Table 2. Synthesis of oxindoles **3** from difluorostyrenes **1**

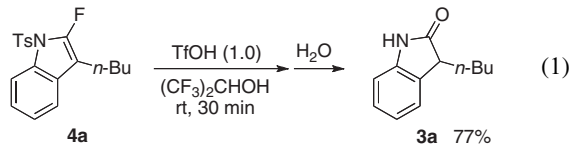


Entry	R^1	R^2	R^3	Temp/°C	Time/h	Yield/%
1	H	H	*n*-Bu	60	24	87 (**3a**)
2	H	H	H	60	2	90 (**3b**)
3	H	H	*s*-Bu	60	24	78 (**3c**)[a]
4	Cl	H	*n*-Bu	60	24	71 (**3d**)
5	Me	H	*n*-Bu	60	24	91 (**3e**)
6	H	Me	*n*-Bu	60	24	79 (**3f**)
7	OMe	H	*n*-Bu	rt	24	20 (**3g**)

[a]Diastereomeric ratio = 1:1.

effective for difluorostyrenes **1b**–**1f** (Entries 2–6). Monosubstituted difluoroalkene **1b** exhibited higher reactivity and afforded **3b** in 2 h. Difluorostyrenes **1d**–**1f** bearing a chloro or a methyl group gave the corresponding oxindoles **3d**–**3f** in high yield, whereas **1g** bearing a methoxy group underwent demethylation at 60 °C. The reaction carried out at room temperature, however, provided **3g** in 20% yield (Entry 7).

To establish the mechanism, we examined the reaction of an NH_2-bearing difluorostyrene, which gave no cyclized products. This result suggests the detosylation occurred after the cyclization of **1**. In addition, 2-fluoroindole **4a**[13] was treated with an equimolar amount of trifluoromethanesulfonic acid (TfOH) in HFIP at room temperature. Indole **4a** was transformed into oxindole **3a** in 77% yield (eq 1), which supports the claim that 2-fluoroindoles **4** would be intermediates in the above oxindole formation.

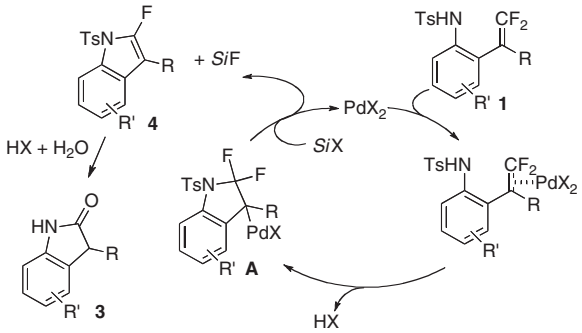


(1)

Considering the facts mentioned above, a plausible reaction mechanism for the oxindole synthesis is outlined in Scheme 2. A transition-metal catalyst would be coordinated by **1** to provide alkylmetal intermediates **A** via 5-*endo-trig* cyclization. β-Fluorine elimination should be preferentially promoted by Me_3SiOTf to regenerate the catalyst along with **4**. Finally, the hydrolysis and detosylation of **4** would occur to yield **3**.

The oxindoles obtained above are common and important components in natural products and biologically active molecules.[14] Classical methods for the synthesis of oxindoles are based on intramolecular condensation[15a] or radical cyclization.[15b] Recently, palladium-catalyzed methods, such as the Mizoroki–Heck reaction,[15c–15e] coupling reactions,[15f] and Buchwald–Hartwig-type amination[15g] have been developed, while a Wacker-type oxindole synthesis has not been reported previously.[16]

In conclusion, we have developed a transition-metal-catalyzed method for the electrophilic activation of electron-deficient 1,1-difluoro-1-alkenes, which successfully promoted their Wacker-type cyclization with an intramolecular sulfonamide group.



Scheme 2. A plausible reaction mechanism for oxindole synthesis.

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11 To a solution of **1a** (73 mg, 0.20 mmol) in HFIP (2.0 mL) was added TMSOTf (72 µL, 0.40 mmol) and $PdCl_2$ (3.5 mg, 0.020 mmol) at room temperature. After the reaction mixture was stirred for 24 h at 60 °C, the reaction was quenched with saturated aq $NaHCO_3$ and the aqueous layer was extracted twice with AcOEt. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by preparative TLC (SiO_2, hexane:AcOEt = 5:1) to afford **3a** (32 mg, 86%) as a colorless oil.
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