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Activation of 1,1-Difluoro-1-alkenes with a Transition-Metal Complex: Palladium(II)-Catalyzed Friedel−Crafts-Type Cyclization of 4,4-(Difluorohomoallyl)arenes

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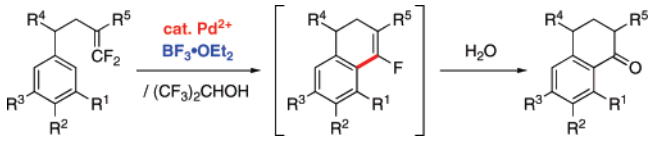
ABSTRACT



Cationic palladium(II) ([Pd(MeCN)$_4$](BF$_4$)$_2$) provides the first transition-metal-catalyzed method for electrophilic activation of electron-deficient 1,1-difluoro-1-alkenes, which allows their Friedel–Crafts-type cyclization with an intramolecular aryl group via a Wacker-type process. By using BF$_3$·OEt$_2$, the cyclization was effected by a catalytic amount of the palladium without its reoxidation.

Unactivated alkenes generally react with a wide variety of electrophiles, but not with nucleophiles. One of the best solutions to the problem of poor reactivity toward nucleophiles is activation of alkenes with transition-metal complexes, as exemplified by the Wacker reaction,[1] where water adds to an alkene−palladium(II) complex in a nucleophilic manner. This strategy has now been expanded to a variety of catalytic C−O,[2] C−N,[2a,3] and C−C[4] bond formations between alkenes and nucleophiles, which are widely applied in the synthesis of complex natural products.[5]

In contrast to unactivated alkenes, 1,1-difluoro-1-alkenes possess electrophilic character because of the electron-withdrawing inductive effect of the two fluorine atoms.[6] Whereas they react with strong nucleophiles such as alkyllithiums, their reactivity is not great enough to react with weak nucleophiles such as arenes and alkenes. Thus, electrophilic activation of 1,1-difluoroalkenes is highly desirable, while being more difficult compared with that of unactivated alkenes, because of the low electron density of difluoroalkenes. A limited number of electrophiles, iodine,[7] mercuric acetate,[8] tin tetrachloride,[9] and Magic acid (FSO$_3$H·SbF$_5$),[10]

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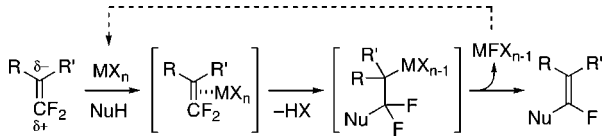
have been employed for the activation of difluoroalkenes, where a stoichiometric amount of the electrophile was required. The development of a transition-metal catalyst for the reaction of 1,1-difluoro-1-alkenes with weak nucleophiles is therefore a significant challenge.

We intended to activate 1,1-difluoro-1-alkenes with a transition-metal complex (MX_n), which would promote the reaction with a nucleophile, as shown in Scheme 1. The

Scheme 1. Activation of 1,1-Difluoro-1-alkenes with a Transition-Metal Complex



process would allow substitution by the accompanying β-fluorine elimination,[11] which might preserve the oxidation state of the metal. Thus, this reaction was expected to proceed with only a catalytic amount of metal complex without the need for a reoxidizing reagent.[12]

The starting materials, 1,1-difluoro-1-alkenes **1** bearing an aryl group as a nucleophile were designed to undergo Friedel−Crafts-type cyclization via metal−alkene complexes, leading to 4-fluorinated 1,2-dihydronaphthalene derivatives. On treatment of difluoroalkene **1a** with $AuCl_3$ in THF, which is often employed in alkene activation,[13] no cyclized products were obtained. However, the use of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP)[14] as a solvent with high ionizing power promoted the cyclization to give the hydrolyzed products, cyclic ketone **2a** along with its regioisomer **3a**, in 25% yield instead of the expected 4-fluoro-1,2-dihydrophenanthrene **5a** (Table 1, entry 1). Addition of AgOTf to $AuCl_3$ or AuCl(PPh$_3$) was examined for the generation of cationic gold complexes, which improved the yield of the cyclic ketones (entries 2 and 3). These results suggest that highly electrophilic transition-metal species can activate difluoroalkene **1a** in HFIP, and such a tendency was also observed for Ru(III) (entry 4).[15,16] In particular, a cationic palladium complex, $[Pd(MeCN)_4](BF_4)_2$,[2b,3] showed a prominent activity to give the cyclized compounds in a total yield of 49% at room temperature within 0.5 h (entry 6). The dramatic effect of HFIP as a solvent was confirmed again in the activation with Pd(II), since no reaction occurred in Et_2O, MeCN, or

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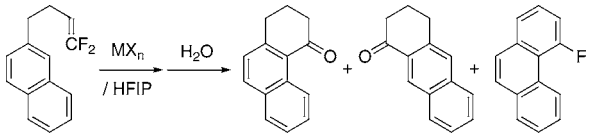
(16) No reaction occurred on treatment of **1a** with $RuCl_3$ (1 equiv) in HFIP at reflux.

Table 1. Effect of Transition-Metal Complexes in Activation of Difluoroalkene **1a**



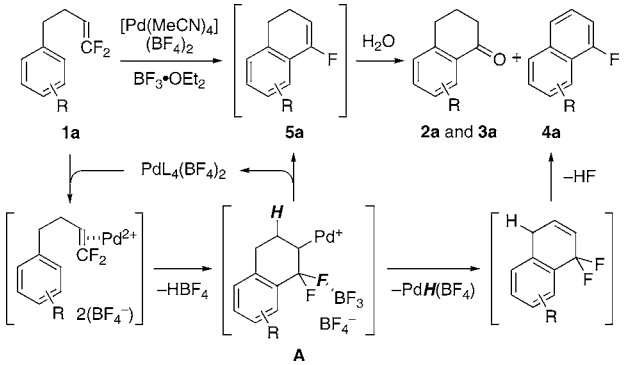
entry	MX_n (equiv)	conditions	**2a** (%)	**3a** (%)	**4a** (%)
1	$AuCl_3$ (1.0)	reflux, 6 h	24	1	0
2[a]	$AuCl_3$ (1.0)	reflux, 6 h	30	1	0
3[b]	AuCl(PPh$_3$) (1.0)	reflux, 3 h	36	4	1
4[a]	$RuCl_3$ (1.0)	reflux, 5 h	46	2	0
5[c]	$PdCl_2L_2$ (1.0)	rt, 3 h	55	0	0
6[c]	$PdL_4(BF_4)_2$ (1.0)	rt, 0.5 h	25	2	22
7[c,d]	$PdL_4(BF_4)_2$ (1.0)	120 °C, 2 h	36	3	5
8[c]	$PdL_4(BF_4)_2$ (0.05)	rt, 1 h	1	0	0
9[c,e]	$PdL_4(BF_4)_2$ (0.05)	rt, 0.5 h	86	3	5
10[c,e]	$PdL_4(BF_4)_2$ (0.01)	rt, 9 days	82	4	0

[a] AgOTf (2.0 equiv) was added. [b] AgOTf (1.0 equiv) was added. [c] L = MeCN. [d] [bmin][NTf$_2$] was used as a solvent. [e] BF_3·OEt_2 (1.0 equiv) was added.

$MeCONMe_2$. Ionic liquid, 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([bmin][NTf$_2$]), was a rather effective solvent, although it required a high temperature (entry 7).

The cationic palladium-promoted cyclization yielded not only cyclic ketones **2a** and **3a** but also fluoroarene **4a**, presumably via β-fluorine and β-hydrogen elimination from cyclized intermediate **A**, respectively (Scheme 2). The former

Scheme 2. Catalytic Activation of Difluoroalkene **1a**



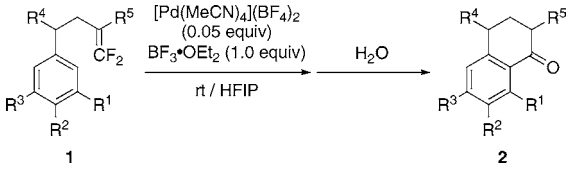
process generated a palladium fluoride species, Pd***F***$L_3(BF_4)$, which seemed to be less active. A palladium hydride species, Pd***H***$L_3(BF_4)$, formed in the latter process, turned to Pd(0). These facts prevented the catalytic turnover (Table 1, entry 8). Taking advantage of the high affinity of boron for fluorine, we tried the use of BF_3·OEt_2 with the palladium complex to accelerate the β-fluorine elimination from **A** and regenerate the active cationic species, $PdL_4(BF_4)_2$, which would make this process catalytic in palladium.

When **1a** was treated with 0.05 equiv of $[Pd(MeCN)_4](BF_4)_2$ and 1 equiv of BF_3·OEt_2 at room temperature, the

yield of cyclic ketone **2a** was raised to 86% (Table 1, entry 9).[17] Even 0.01 equiv of Pd promoted the cyclization, albeit requiring a longer reaction time (entry 10).

When several difluoroalkenes **1** bearing other substituents were subjected to the catalytic conditions obtained above, the cyclization readily proceeded to afford the corresponding cyclic ketones **2** in high yield, as shown in Table 2. This

Table 2. Cyclization of Difluoroalkenes **1**

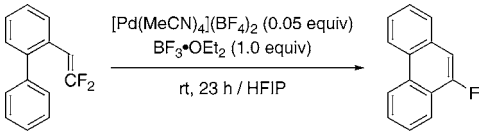


entry	R^1	R^2	R^3	R^4	R^5	time (h)	**2** (%)
1[a]	$-(CH)_4-$		H	H	H	2	89 (**2a** + **3a**)
2	H	H	H	H	H	2	89 (**2b**)
3	H	H	H	Me	H	11	83 (**2c**)
4	H	Me	H	Me	H	1	79 (**2d**)
5	H	OMe	H	Me	H	47	70 (**2e** + **2f**)[b]
6	H	H	OMe	Me	H	0.5	66 (**2f** + **2k**)[c]
7	H	OH	H	Me	H	12	78 (**2g** + **2l**)[d]
8	H	CF_3	H	Me	H	30	15 (**2h**)
9[e]	H	H	H	H	n-C_5H_{11}	22	65 (**2i**)

[a] The reaction was conducted at 0 °C. [b] The regioisomer of **2e**, 6-methoxy-4-methyl-3,4-dihydro-2*H*-naphthalen-1-one (**2f**),[18] was also obtained (**2e**/**2f** = 76/24). [c] The regioisomer of **2f**, 8-methoxy-4-methyl-3,4-dihydro-2*H*-naphthalen-1-one (**2k**), was also obtained (**2f**/**2k** = 79/21). [d] The regioisomer of **2g**, 6-hydroxy-4-methyl-3,4-dihydro-2*H*-naphthalen-1-one (**2l**),[17] was also obtained (**2g**/**2l** = 65/35). [e] $[Pd(MeCN)_4](BF_4)_2$ (0.1 equiv) and BF_3•OEt_2 (2.0 equiv) were used.

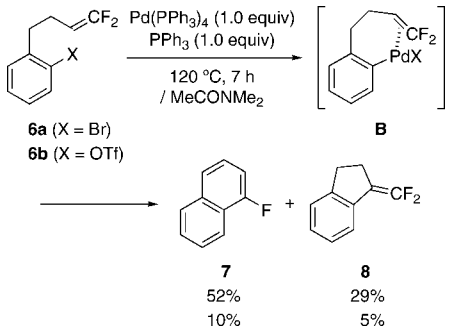
activating method was effective even for difluoroalkenes **1e**−**g** bearing a methoxy or a hydroxy group, which were unsuitable under strong acid conditions (entries 5−7). The reaction of difluoroalkene **1j** with a phenyl group tethered by an *o*-phenylene linkage afforded 9-fluorophenanthrene **5j** in 54% yield, which confirms the generation of cyclic fluoroalkenes **5** as intermediates (Scheme 3).[19]

Scheme 3. Cyclization of Difluoroalkene **1j**



The cyclization of fluoroalkenes **1** has been presumed to proceed through a Wacker-type mechanism including nucleophilic attack of the aryl group. There was, however, the possibility of a Heck-type reaction via aromatic C−H bond activation.[20] To establish the mechanism, we examined the cyclization via arylpalladium intermediate **B**, prepared by oxidative addition of **6** to Pd(0). The reaction of **6** afforded 5-*exo* cyclization product **8** as well as 6-*endo* product **7** (Scheme 4), although no 5-*exo* products were obtained in

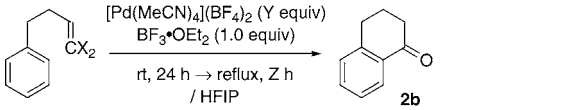
Scheme 4. Cyclization via Arylpalladium Intermediates



the cyclization of **1b** (Table 2, entry 2). These results show that the palladium-catalyzed Friedel−Crafts-type cyclization proceeds via a Wacker-type mechanism. In addition, the cyclization of **1a** occurred only in a solvent with high ionizing power like HFIP, which also supports the theory that the cyclization proceeds via the Wheland intermediates.

To elucidate the effect of fluorine on the Friedel−Crafts-type cyclizations, we compared the reactions of **1a** and the corresponding monofluoroalkene (E/Z = 5.5:1) under the same conditions. Whereas **1a** gave **2a** in 86% yield, the monofluoroalkene gave 1,2,3,4-tetrahydrophenanthrene (11% yield), 1,2,3,4-tetrahydroanthracene (4% yield), and phenanthrene (19% yield) along with a complex mixture, probably due to polymerization of the double bond. Treatment of dichloro- and dibromoalkenes **9** with a catalytic amount of Pd(II) gave only a trace amount of cyclized products, and even 1 equiv of Pd(II) did not work well (Scheme 5). These

Scheme 5. Cyclization of Dichloro- and Dibromoalkenes



results indicate that using a cationic palladium together with BF_3•OEt_2 allows a specific activation of 1,1-difluoroalkenes.

(17) The corresponding intermolecular Friedel−Crafts-type reaction between 1,1-difluoro-6-phenylhex-1-ene and 1,3-dimethoxybenzene (10 equiv) in HFIP did not proceed under these reaction conditions, and neither did the intramolecular reaction.

(18) Regioisomers **2f** and **2l** were probably obtained via spiro intermediates generated by *ipso* attack of the aromatic ring.

(19) The cyclization of **1j** was conducted in the dark to prevent photochemical 6π-electrocyclization. Lapouyade, R.; Hanafi, N.; Marand, J.-P. *Angew. Chem., Int. Ed.* **1982**, *21*, 766−767.

(20) For a review on functionalization of arenes via C−H bond activation, see: Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639.

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In conclusion, we have developed the first transition-metal-catalyzed method for the electrophilic activation of electron-deficient 1,1-difluoro-1-alkenes,[21] which successfully promotes their Friedel−Crafts-type cyclization with an intramolecular aryl group via a Wacker-type process. By adding BF_3·OEt_2, the cyclization was effected by a catalytic amount of cationic palladium without reoxidation.

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Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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