Organofluorine Chemistry

DOI: 10.1002/ange.201207304

C–F Bond Activation of Unactivated Aliphatic Fluorides: Synthesis of Fluoromethyl-3,5-diaryl-2-oxazolidinones by Desymmetrization of 2-Aryl-1,3-difluoropropan-2-ols**

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The selective synthesis of fluorinated organic compounds and the investigation of their properties have become major topics in all fields of the chemical sciences, as well as in technological applications.[1] Whereas methods for the formation of C–F bonds have been developed from the beginning of organic fluorine chemistry,[2] the application of C–F bond cleavage in poly-fluorinated carbon compounds for the preparation of partially fluorinated molecules has been less developed.[3] This is apparently due to the fact that C–F bonds are the strongest that carbon can form.[4] Research into the activation of C–F bonds of arylfluorides has a long history,[5] but aliphatic fluorides have been less frequently involved in such processes and quite forcing conditions, such as organometallic reagents or strong nucleophiles, have to be applied.[6] Thus, the development of mild and effective methods for the activation of aliphatic C–F bonds has become a stimulating topic in general organic chemistry. Although the C–F bond activation of several aliphatic fluorides with lithium reagents, Brønsted acids, Lewis acids, transition metals, or Grignard reagents has been reported in recent years,[3a,7] most of these methods require that the fluorine atom(s) should be bound in an activated position such as benzylic, allylic, α to a carbonyl (or an equivalent), on a halogenated carbon, and so on. C–F bond cleavage in an unactivated aliphatic position under mild conditions is still a challenge,[8] although the substitution of CH_2F groups by phosphine groups using R_2PLi was reported 30 years ago.[8h] Very recently, we have been able to substitute all three fluorines and another β-halogen substituent of β-trifluoromethyl-β-halostyrenes with primary amines to form vinylogous guanidinium salts.[9] As part of our research program related to the development of biologically relevant fluorine-containing molecules,[10,11] we have been interested in 3,5-diaryl-2-fluoromethyl-oxazolidin-2-ones (**1**). 3,5-Diaryl-2-trifluoromethyl-oxazolidin-2-ones (**2**) are promising agrochemicals which can act as insecticides, acaricides, ectoparasiticides, and control agents for animal parasites.[12] Although more than 4400 compounds related to **2** are registered in the SciFinder database (most of them patented),[13] no monofluoromethyl analogues, **1**, have yet been reported (Figure 1).

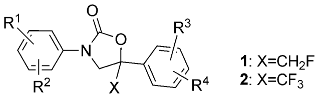
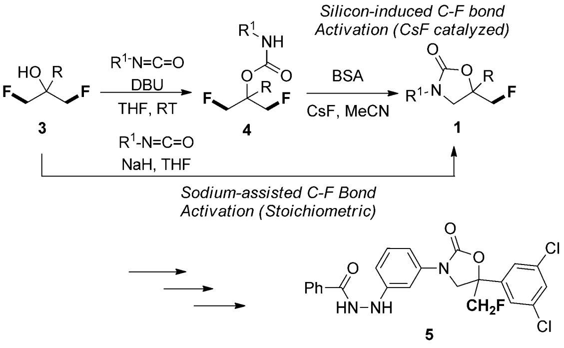


Figure 1. Biologically relevant 3,5-diaryl-2-(trifluoromethyl)-oxazolidin-2-ones.

Herein, we disclose the first general synthesis of a series of 3,5-diaryl-2-fluoromethyl-oxazolidin-2-ones **1** by a conceptually new desymmetrization of unactivated aliphatic di-fluorides with silicon-induced catalytic C–F bond-cleavage as a key step (Scheme 1). Namely, 2-aryl-1,3-difluoropropan-2-ols **3** were transformed into 3,5-diaryl-2-fluoromethyl-oxazolidin-2-ones **1** through their carbamates **4** by a mild, BSA/CsF system (BSA = bis(trimethylsilyl)acetamide) catalytic in CsF. One of the enantiotopic fluorine atoms of **4** was intramolecularly substituted to afford monofluoromethyl-oxazolidin-2-



Scheme 1. Synthesis of 3,5-diaryl-2-fluoromethyl-oxazolidin-2-ones by the desymmetrization of unactivated aliphatic fluorides using silicon-induced or sodium-assisted C–F bond-cleavage as a key step.

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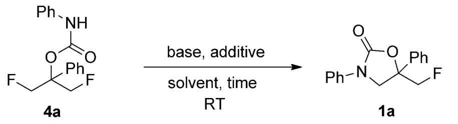
[**] This study was financially supported in part by Grants-in-Aid for Scientific Research from MEXT (Ministry of Education, Culture, Sports, Science and Technology) (24105513, Project No. 2304: Advanced Molecular Transformation by Organocatalysts) and by the Deutsche Forschungsgemeinschaft (DFG). We thank the Asahi Glass Foundation for partial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207304.

ones **1**. We also achieved the direct transformation of **3** with isocyanates, R^1-N=C=O into **1** by cascade carbamoylation/cyclization, in which the cyclization is assisted by a sodium-mediated C−F bond activation, resulting in the formation of oxazoline (Scheme 1). *N'*-{3-[5-(3,5-dichlorophenyl)-5-(fluoromethyl)-2-oxooxazolidin-3-yl]phenyl}benzohydrazide (**5**) was synthesized by this method for agricultural purposes.

Starting phenylcarbamate **4a** was prepared from 2-phenyl-1,3-difluoropropan-2-ol (**3a**) with phenylisocyanate (Ph-N=C=O) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at RT for 3 h in 93 % yield after isolation (see Table 3, entry 3). The desymmetrization/cyclization of **4a** was first attempted using a stoichiometric amount of K$_2$CO$_3$ in THF at RT. However, no reaction was observed (Table 1).

Table 1: Optimization of reaction conditions for the conversion of **4a** into **1a**.



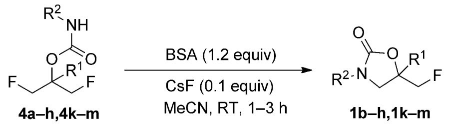
Entry	Base (equiv)	Additive	Solvent	*t* [h]	Yield [%]
1	K$_2$CO$_3$ (1.1)	–	THF	17	NR
2	Na$_2$CO$_3$ (1.1)	–	THF	17	NR
3	KOH (1.1)	–	THF	17	trace
4	NaOH (1.1)	–	THF	17	29
5	NaH (1.1)	–	THF	24	59
6	DBU (1.1)	–	THF	17	NR
7	DABCO (1.1)	–	THF	17	NR
8	TMG (1.1)	–	THF	17	38
9	P$_1$-*t*Bu (1.1)	–	THF	17	56
10	DBU (1.1)	TMSCl	THF	17	NR
11	DBU (1.1)	BSA	MeCN	3	83
12	K$_2$CO$_3$ (1.1)	BSA	MeCN	3	84
13	DBU (1.1)	BSA	THF	3	NR
14	DBU (0.1)	BSA	MeCN	6	66
15	K$_2$CO$_3$ (0.1)	BSA	MeCN	18	10
16	Cs$_2$CO$_3$ (0.1)	BSA	MeCN	1	81
17	KF (0.1)	BSA	MeCN	6	9
18	CsF (0.1)	BSA	MeCN	1	94
19	TBAF (0.1)	BSA	MeCN	4	26
20	TMAF (0.1)	BSA	MeCN	1	87

BSA = bis(trimethylsilyl)acetamide, DABCO = 1,4-diazabicyclo-[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NR = no reaction, P$_1$-*t*Bu = Phosphazene base P$_1$-*t*Bu, TMAF = tetramethylanmonium fluoride, TMG = 1,1,3,3-tetramethylguanidine, TMS = trimethylsilyl.

In the presence of other strong inorganic bases such as NaOH and NaH the desired product **1a** was obtained in 29 % and 59 % yield, respectively. Organic bases such as DBU or DABCO were ineffective for this transformation; stronger bases, TMG and P$_1$-*t*Bu, gave product **1a** in low yields. These results indicate that intramolecular substitution of alkyl fluorides by carbamates is possible in the presence of either strong inorganic or organic bases, although the conversions are not satisfactory. Thus, the activation of a C−F bond requires a synergetic effect for the transformation of **4a** to **1a**. Therefore, we investigated the addition of silylation reagents to activate the C−F bond, and so exploit the high Si−F binding energy (Table 1). Although TMSCl was not effective, the addition of BSA dramatically improved the transformation either in the presence of DBU or K$_2$CO$_3$ providing 83 % and 84 % of **1a**, respectively in 3 h. The selection of MeCN was important, as the yield of **1a** was low in THF. The amount of base can be reduced to a catalytic level, but the yield decreases slightly. Encouraged by these results, the catalytic transformation was next investigated. After screening of different bases, a catalytic amount of CsF was found to be very effective for this transformation, and provides **1a** in 94 % yield within 1 h.

With the optimized reaction conditions in hand, we screened a variety of 2-aryl-1,3-difluoromethyl-2-carbamates **4b–h**, **4k–m** (Table 2). All of these carbamates afforded the corresponding 3,5-diaryl-2-fluoromethyl-oxazolidin-2-ones **1b–h**, **1k–m**, which were isolated in good to excellent yields and with short reaction times that were almost independent of the substitution pattern on the benzene ring. The structure of **1d** was determined by X-ray analysis (Figure 2), and all the other products were assigned by analogy with **1d**.

Table 2: Scope of the silicon-induced transformation of **4** into **1**.



Entry	4	R^1	R^2	*t* [h]	1	Yield [%]
1	**4a**	Ph	Ph	1	**1a**	94
2	**4b**	3-MeC$_6$H$_4$	Ph	1	**1b**	90
3	**4c**	4-MeC$_6$H$_4$	Ph	1	**1c**	96
4	**4d**	3-MeOC$_6$H$_4$	Ph	1	**1d**	87
5	**4e**	4-FC$_6$H$_4$	Ph	1	**1e**	91
6	**4f**	3-ClC$_6$H$_4$	Ph	1	**1f**	87
7	**4g**	4-ClC$_6$H$_4$	Ph	1	**1g**	92
8	**4h**	3,5-Cl$_2$C$_6$H$_3$	Ph	2	**1h**	86
9	**4k**	C$_6$H$_5$CH$_2$CH$_2$	Ph	3	**1k**	69
10	**4l**	Ph	4-MeC$_6$H$_4$	2	**1l**	86
11	**4m**	Ph	4-BrC$_6$H$_4$	1	**1m**	88

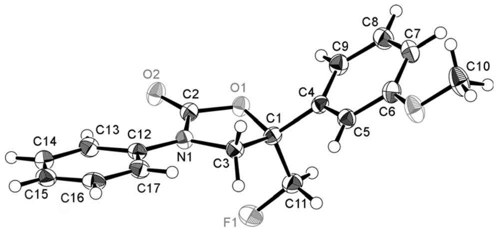
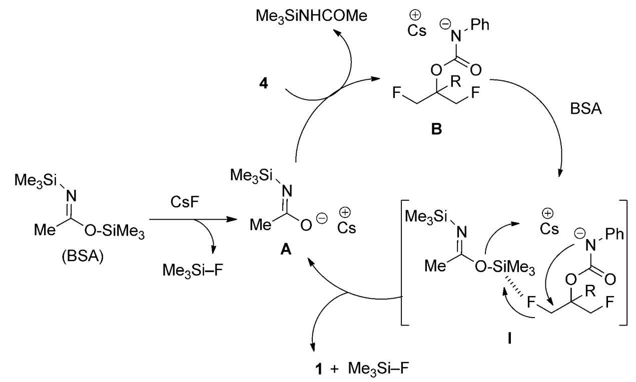


Figure 2. X-ray crystallographic structure of **1d**.[16] Thermal ellipsoids set at 50% probability.

Based on the experimental results, we propose the mechanism for the desymmetrization/cyclization reaction shown in Scheme 2. Initially, BSA was activated by CsF to provide amido anion **A**, along with the release of TMSF. Anion **A** then abstracts a proton from **4** to generate the carbamate anion **B**, along with Me$_3$SiNHCOMe. The C−F bond of **B** was next activated by interaction with the silicon

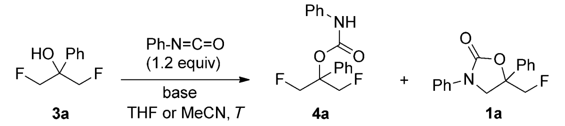


Scheme 2. Proposed reaction mechanism for the conversion of **4** into **1** by silicon-induced C–F bond activation (CsF catalyzed reaction).

atom of BSA, depicted by transition-state model **I**, to induce intramolecular cyclization, which furnishes the oxazoline product **1** and TMSF. The amido anion **A**, which is regenerated from **I**, is the true catalyst in this catalytic cycle. It is very clear that Si-containing additives accelerate/promote the reaction, but the reaction proceeds to a certain extent with organic bases even in the absence of Si-containing additives (entries 8 and 9, Table 1). This can be explained by the presumed assistance of proton abstraction in activation of the C–F bond.

We next attempted the direct transformation of **3** with R^1-N=C=O into **1** by a tandem carbamoylation/cyclization reaction (Table 3). As mentioned above, **4a** was prepared from **3a** with Ph-N=C=O in the presence of DBU, which can be used as a catalyst, but the reaction is slow (entry 1); the yield did not improve much even when used stoichiometrically (entry 2). It was greatly improved to 93 % by using an excess of Ph-N=C=O (2.0 equiv) in the presence of a stoichiometric amount of DBU (entry 3). When we added BSA to the reaction, the cyclized product **1a** was produced in 15 % yield in the presence of a catalytic amount of DBU (entry 4); this yield decreased to 8 % when using a stoichiometric amount of DBU and BSA, owing to the competitive trimethylsilylation of **3a** (entry 5). A catalytic amount of CsF also provided 22 % of **1a** in the presence of BSA (entry 6), but a stoichiometric amount of CsF was not effective for this transformation, because of the competitive trimethylsilylation of **3a** (entry 7). We next used NaH as a base, as it gave a moderate yield in the transformation of **4a** into **1a** (see Table 1, entry 5). In the presence of 1 equiv of NaH with Ph-N=C=O (1.0–2.0 equiv) in THF at 60 °C, the desired product **1a** was directly obtained in 23–27 % yield, although a large amount of **4a** remained unreacted (entries 8 and 9), presumably because of the highly hygroscopic nature of NaH. As expected, the yield of **1a** was greatly improved to 91 % by using an excess of NaH (entry 10), whereas KH was less effective for this transformation (entry 11).

Table 3: Optimization of the reaction conditions for the tandem carbamoylation/cyclization of **3a**.

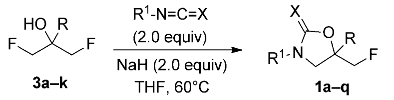


Entry	Base (equiv)	Additive	T [°C]	t [h]	Yield of **4a** [%]	Yield of **1a** [%]
1[a]	DBU (0.1)	–	RT	24	51	0
2[a]	DBU (1.05)	–	RT	24	61	0
3[b,c]	DBU (1.05)	–	RT	3	93	0
4[b]	DBU (0.1)	BSA	RT	24	36	15
5[b,d]	DBU (1.05)	BSA	RT	5	0	6
6[b]	CsF (0.1)	BSA	RT	2	0	22
7[b,d]	CsF (1.05)	BSA	RT	1	0	8
8[a]	NaH (1.0)	–	60	17	0	23
9[a,c]	NaH (1.0)	–	60	17	0	27
10[a,c]	NaH (2.0)	–	60	17	0	91
11[a,c]	KH (2.0)	–	60	17	0	39

[a] THF was used as a solvent. [b] MeCN was used as a solvent. [c] Phenyl isocyanate (2.0 equiv) was used. [d] The trimethylsilyl ether of **3a** was observed as the major product.

Under the optimized conditions, a variety of 2-aryl-1,3-difluoro-propan-2-ols **3** were investigated to determine the scope of this tandem carbamoylation/cyclization reaction. The results are summarized in Table 4. A series of 1,3-difluoropropan-2-ols, **3a**–**h**, with a variety of aromatic ring substituents, such as methyl, methoxy, fluoro, and chloro, were converted into **1a**–**h** in good yields (entries 1–8). Sterically demanding naphthyl- and biphenyl-substituted 1,3-difluoropropan-2-ols **3i** and **3j** were also compatible with the reaction conditions, and afforded products **1i** and **1j** in yields of 64 % and 94 %, respectively (entries 9 and 10). Alkyl-substituted **3k** was also readily cyclized to **1k** in 77 % yield.

Table 4: Scope of the tandem carbamoylation/cyclization of **3**.

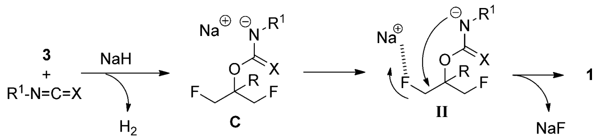


Entry	R	3	R^1	X	t [h]	1	Yield [%]
1	Ph	**3a**	Ph	O	17	**1a**	91
2	3-MeC$_6$H$_4$	**3b**	Ph	O	21	**1b**	70
3	4-MeC$_6$H$_4$	**3c**	Ph	O	9	**1c**	62
4	3-MeOC$_6$H$_4$	**3d**	Ph	O	9	**1d**	70
5	4-FC$_6$H$_4$	**3e**	Ph	O	23	**1e**	45
6	3-ClC$_6$H$_4$	**3f**	Ph	O	11	**1f**	66
7	4-ClC$_6$H$_4$	**3g**	Ph	O	9	**1g**	94
8	3,5-Cl$_2$C$_6$H$_3$	**3h**	Ph	O	21	**1h**	69
9	2-naphthyl	**3i**	Ph	O	14	**1i**	64
10	4-PhC$_6$H$_4$	**3j**	Ph	O	21	**1j**	94
11	C$_6$H$_5$CH$_2$CH$_2$	**3k**	Ph	O	14	**1k**	77
12[a]	Ph	**3a**	4-MeC$_6$H$_4$	O	11	**1l**	69
13[a]	Ph	**3a**	4-BrC$_6$H$_4$	O	23	**1m**	49
14[a]	Ph	**3a**	3-NO$_2$C$_6$H$_4$	O	11	**1n**	67
15[a]	Ph	**3a**	3,5-(CF$_3$)$_2$C$_6$H$_3$	O	23	**1o**	74
16[a]	Ph	**3a**	Ts	O	23	**1p**	15
17[a]	Ph	**3a**	Ph	S	11	**1q**	68

[a] Reaction was carried out at RT. Ts = *p*-toluenesulfonyl.

We next examined the reaction using a variety of isocyanates (Table 4, entries 12–16). The tandem reaction is almost independent of the nature of the R^1 group of isocyanates, R^1-N=C=O. Both the electron-donating tolyl group and the electron-withdrawing groups on R^1, such as *p*-bromo, *p*-nitro, and 3,5-bis(trifluoromethyl), were well tolerated to provide cyclized products **1l–o** in good yields, whereas the yield of tosyl-substituted **1p** was low (15%). Furthermore, phenylisothiocyanate, Ph-N=C=S, also reacted with **3a** under the same reaction conditions to furnish **1q** in 68% (entry 17).

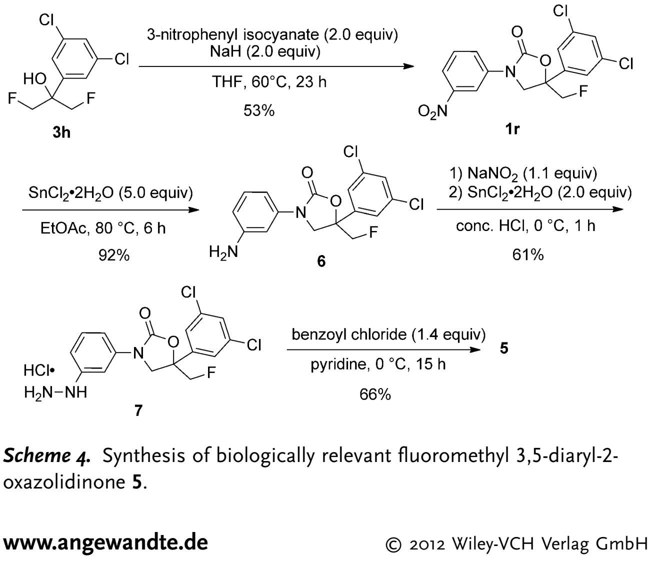
In Scheme 3, the tandem carbamoylation/cyclization pathway with C–F bond cleavage leading to fluoromethyl-oxazolidinones **1** is described. An alcohol **3** reacts with an isocyanate in the presence of NaH to furnish **C**, the carbamate sodium salt. Although the Na–F bond is slightly weaker than the C–F bond, based on the bond dissociation energies (Na–F: 477.3 kJ mol^{-1}; C–F: 513.8 kJ mol^{-1}),[14] the C–F bond of species **C** should be activated by the sodium cation to assist the intramolecular reaction via transition state **II**, resulting in cyclization and NaF elimination to give product **1**.[8e,15]



Scheme 3. Proposed tandem route for the conversion of **3** into **1** by sodium-assisted C–F bond activation (stoichiometric reaction).

Finally, we became interested in applying our method to the synthesis of **5**, a monofluoromethyl analogue of the plant disease controlling agent, 3,5-diaryl-2-trifluoromethyl-oxazolidin-2-one (**2**; Scheme 4).[12c]

In conclusion, we have developed a new method for the synthesis of biologically relevant 3,5-diaryl-2-fluoromethyl-oxazolidin-2-ones **1** and **5** by a conceptually new desymmetrization of the carbamates of 2-aryl-1,3-difluoropropan-2-ols **4** through the CsF-catalyzed silicon-induced C–F bond activation of unactivated aliphatic fluorides. A wide range of carbamates **4** proceed to furnish the corresponding fluoromethyl-oxazolidin-2-ones **1** in high to excellent yields under mild conditions. The direct transformation of 2-aryl-1,3-difluoro-isopropanols **3** with isocyanates into **1** by the carbamoylation/cyclization cascade reaction has also been achieved, in which oxazolidinone formation is induced by sodium-mediated C–F bond activation. The enantioselective desymmetrization of **4** to give **1** is now under investigation.



Scheme 4. Synthesis of biologically relevant fluoromethyl 3,5-diaryl-2-oxazolidinone **5**.

Received: September 10, 2012

Keywords: C-F bond activation · desymmetrization · fluorine · silicon · sodium

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[15] A similar transformation has been reported by Hu et.al.,[8e] although they do not mention any assistance from NaF.

[16] CCDC-898314 (**1d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.