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Boron-trihalide-promoted regioselective ring-opening reactions of *gem*-difluorocyclopropyl ketones†

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Boron trihalide-promoted ring-opening reactions of *gem*-difluoro-cyclopropyl ketones to give the corresponding β-trifluoromethyl ketones and β-halodifluoromethyl ketones were described. It was found that boron trihalides act as both Lewis acids and nucleophiles and the proximal bond prefers to cleave in this transformation.

The tremendous advances in fluorinated pharmaceutical chemistry and agricultural chemistry during the past few decades clearly demonstrate the exceptional importance of fluorinated compounds.[1] As one of the important classes of selectively fluorinated molecules, *gem*-difluorocyclopropanes have received much attention due to the unique properties of the *gem*-difluorocyclopropyl group.[2] Great progress has been made on the development of new methods for the construction of this moiety.[3] But determined effort is also needed for the studies on its reactivity, especially on the ring-opening chemistry,[4] which would be expected to be a promising approach for the synthesis of unique partially fluorinated molecules. As part of our continuing interest in *gem*-difluorocyclopropane chemistry,[3k,4g,5] herein we describe the regioselective ring-opening reactions of *gem*-difluorocyclopropyl ketones leading to β-trifluoromethyl ketones and β-halodifluoromethyl ketones promoted by boron trihalides.

The ring-cleavage of *gem*-difluorocyclopropyl ketones could be promoted by nucleophiles, bases or acids with different regiochemical outcomes.[4a,b,d,e] Strong nucleophiles and strong bases could lead to distal bond scission and proximal bond scission, respectively, but both of these two routes resulted in complete loss of fluorine.[4a,b] In acid-mediated reactions, the regioselectivity was found to be an interesting issue (Scheme 1). Dolbier *et al*. reported that the Brønsted acid-promoted ring-opening reactions proceeded *via* a S_N2-type process involving
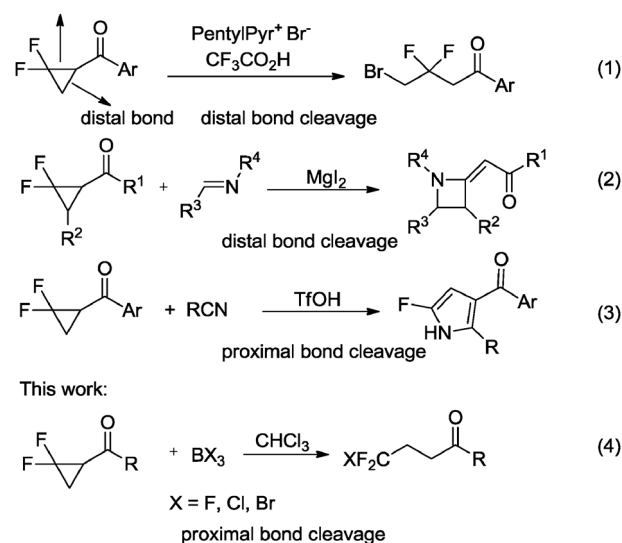
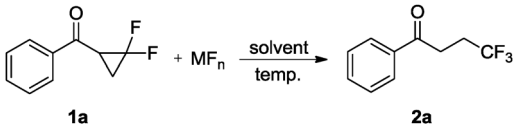**Scheme 1** The regioselectivity of ring-opening of *gem*-difluorocyclopropyl ketones.

distal bond scission (eqn (1)).[4d] Soon after this report, they described that *gem*-difluorocyclopropyl ketones would also undergo distal bond cleavage upon treatment with MgI_2 and further react with imines to give non-fluorine containing products (eqn (2)).[4e] Dolbier's results showed that the distal bond prefers to cleave in the presence of acids and soft nucleophiles. Whereas we found that triflic acid favours the proximal bond cleavage with the use of nitriles as the nucleophile and solvent. The ring-opening of *gem*-difluorocyclopropyl ketones and the subsequent cyclization with nitriles proceeded smoothly to give 2-fluoropyrroles (eqn (3)).[4g] In this communication, we found that boron trihalides could act as both Lewis acids and nucleophiles to promote ring-opening reactions *via* proximal bond cleavage to give β-trifluoromethyl ketones and β-halodifluoromethyl ketones (eqn (4)).

The initial attempt involving the reaction of phenyl *gem*-difluorocyclopropyl ketone **1a** with boron trifluoride in chloroform

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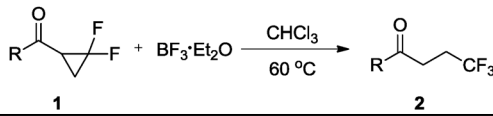
Table 1 Optimization of reaction conditions[a]

Entry	MF_n	Solvent	Temp (°C)	1a/Lewis acid[b]	2a yield[c] (%)
1	$BF_3 \cdot Et_2O$	$CHCl_3$	r.t.	1.0/2.0	41
2	ZnF_2	$CHCl_3$	r.t.	1.0/2.0	N.R.
3	CuF_2	$CHCl_3$	r.t.	1.0/2.0	N.R.
4	FeF_2	$CHCl_3$	r.t.	1.0/2.0	N.R.
5	FeF_3	$CHCl_3$	r.t.	1.0/2.0	N.R.
6	$BF_3 \cdot Et_2O$	DMSO	r.t.	1.0/2.0	N.R.
7	$BF_3 \cdot Et_2O$	CH_3CN	r.t.	1.0/2.0	N.R.
8	$BF_3 \cdot Et_2O$	THF	r.t.	1.0/2.0	N.R.
9	$BF_3 \cdot Et_2O$	DCM	r.t.	1.0/2.0	21
10	$BF_3 \cdot Et_2O$	Toluene	r.t.	1.0/2.0	26
11	$BF_3 \cdot Et_2O$	DCE	r.t.	1.0/2.0	30
12	$BF_3 \cdot Et_2O$	$CHCl_3$	40	1.0/2.0	70
13	$BF_3 \cdot Et_2O$	$CHCl_3$	60	1.0/2.0	98
14	$BF_3 \cdot Et_2O$	$CHCl_3$	60	1.0/1.0	77
15	$BF_3 \cdot Et_2O$	$CHCl_3$	60	1.0/0.5	66

[a] The reaction was carried out with 0.2 mmol of **1a** in 1 mL of solvent. [b] Molar ratio. [c] Determined by ^{19}F NMR with the use of trifluoromethyl benzene as internal standard.

was successful, even though the yield was quite low (entry 1, Table 1). Other fluoride-containing Lewis acids were not effective for this transformation (entries 2–5). Interestingly, the solvent showed a strong effect on the reaction. Polar solvents such as DMSO or CH_3CN completely suppressed the desired conversion (entries 6–8). The desired conversion only occurred in less polar solvents (entries 9–11), and chloroform seemed to be the most suitable (entry 1 *vs.* entries 9–11). The screening of reaction temperature (entries 12–13) and the substrate ratio of **1a** to boron trifluoride (entries 14–15) showed that the expected product could be obtained almost in quantitative yield as determined by ^{19}F NMR with the use of trifluoromethyl benzene as internal standard when the reaction was performed at 60 °C in the presence of 2 equiv. of boron trifluoride (entry 13).

With the optimized reaction conditions in hand (entry 13, Table 1), we next explored the substrate scope of boron trifluoride-promoted ring-opening reactions of *gem*-difluorocyclopropyl ketones (Table 2). The reaction could tolerate various substituents on the phenyl ring and resulted in moderate to excellent yields (entries 1–11). Irrespective of the electronegativity or the position of substituents on the phenyl ring in substrates, the reactions proceeded quite well to afford the desired products. In the case of methoxy substituted substrates (entries 3 and 4), a longer reaction time was needed (50 h and 56 h, respectively) in order to obtain reasonable yields, presumably because the coordination of methoxy to boron trifluoride leads to the decrease in the reactivity of boron trifluoride. Besides aromatic ketones, the reaction worked equally well for aliphatic ketones (entry 12), which means the transformation is applicable to both aromatic and aliphatic *gem*-difluorocyclopropyl ketones.

Encouraged by the successful ring-opening reaction promoted by boron trifluoride, we then examined the possibility
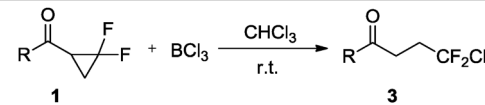
Table 2 Boron-trifluoride-promoted ring-opening of *gem*-difluorocyclopropyl ketones[a]

Entry	R	Product, yield[b]
1	Ph (**1a**)	**2a**, 95%
2	$4\text{-}CH_3C_6H_4$ (**1b**)	**2b**, 85%
3	$4\text{-}CH_3OC_6H_4$ (**1c**)	**2c**, 76%
4	$3\text{-}CH_3OC_6H_4$ (**1d**)	**2d**, 84%
5	$4\text{-}FC_6H_4$ (**1e**)	**2e**, 95%
6	$4\text{-}ClC_6H_4$ (**1f**)	**2f**, 75%
7	$4\text{-}BrC_6H_4$ (**1g**)	**2g**, 93%
8	$3\text{-}ClC_6H_4$ (**1h**)	**2h**, 70%
9	$3\text{-}BrC_6H_4$ (**1i**)	**2i**, 89%
10	$4\text{-}NO_2C_6H_4$ (**1j**)	**2j**, 77%
11	Naphthyl (**1k**)	**2k**, 83%
12	Cyclohexyl (**1l**)	**2l**, 74%

[a] Reaction conditions: **1** (0.2 mmol) and $BF_3 \cdot Et_2O$ (0.4 mmol) in $CHCl_3$ (1 mL) at 60 °C. [b] Isolated yields.

of boron-trichloride-initiated conversion. Under the same reaction conditions as above (entry 13, Table 1), the desired transformation could proceed but the reaction turned out to be quite complex as determined by ^{19}F NMR, probably because boron trichloride showed stronger Lewis acidity than boron trifluoride so more side reactions occurred at this high temperature (60 °C). Fortunately, the expected conversion proceeded quite well at room temperature and the scope of substrates was explored at this temperature (Table 3). It was found that the reaction could tolerate various functional groups on the phenyl ring (entries 1–9). The transformation is also applicable to aliphatic ketones, but the yield was relatively low (entry 10).

The above results suggested that the ring-opening reaction promoted by stronger Lewis acid required lower temperature. Indeed, boron-tribromide-initiated reaction proceeded violently at room temperature and no expected product was detected by

**Table 3** Boron-trichloride-promoted ring-opening of *gem*-difluorocyclopropyl ketones[a]

Entry	R	Product, yield[b]
1	Ph	**3a**, 63%
2	$4\text{-}CH_3C_6H_4$	**3b**, 83%
3	$4\text{-}FC_6H_4$	**3c**, 82%
4	$4\text{-}ClC_6H_4$	**3d**, 77%
5	$4\text{-}BrC_6H_4$	**3e**, 80%
6	$3\text{-}ClC_6H_4$	**3f**, 82%
7	$3\text{-}BrC_6H_4$	**3g**, 83%
8	$4\text{-}NO_2C_6H_4$	**3h**, 60%
9	Naphthyl	**3i**, 80%
10	Cyclohexyl	**3j**, 49%

[a] Reaction conditions: **1** (0.2 mmol) and BCl_3 (0.4 mL, 1 M in CH_2Cl_2) in $CHCl_3$ (1 mL) at room temperature. [b] Isolated yields.

Table 4 Boron-tribromide-promoted ring-opening of *gem*-difluorocyclo-propyl ketones[a]

Entry	R	Product, yield[b]
1	Ph	**4a**, 57%
2	4-CH$_3$C$_6$H$_4$	**4b**, 81%
3	4-FC$_6$H$_4$	**4c**, 48%
4	4-ClC$_6$H$_4$	**4d**, 71%
5	4-BrC$_6$H$_4$	**4e**, 74%
6	3-ClC$_6$H$_4$	**4f**, 58%
7	3-BrC$_6$H$_4$	**4g**, 61%
8	4-NO$_2$C$_6$H$_4$	**4h**, 54%
9	Naphthyl	**4i**, 57%
10	Cyclohexyl	**4j**, 65%

[a] Reaction conditions: **1** (0.2 mmol) and BBr$_3$ (1 mL, 0.4 M in CH$_2$Cl$_2$) in CHCl$_3$ (1 mL) at −78 °C. [b] Isolated yields.
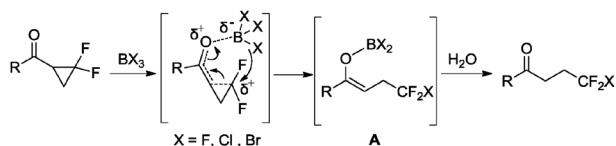
Scheme 2 Proposed mechanism for the ring-opening reactions.

^{19}F NMR. At −78 °C, the desired transformation could be observed for a variety of substrates, giving the corresponding β-bromodifluoromethyl ketones in moderate yields (Table 4).

As for the reaction mechanism, it is reasonable to conceive a pathway involving partial ring-opening of *gem*-difluorocyclopropyl ketones based on previous reports[4d–g] and the above results (Scheme 2). The coordination of ketone to boron trihalide occurred first, leading to the subsequent partial cleavage of the proximal bond. The resulting carbocation could be stabilized by the fluorines on the cyclopropane ring.[6] The intramolecular nucleophilic attack of the carbocation by a halogen anion of boron trihalide resulted in complete ring-cleavage of *gem*-difluorocyclopropane to give the intermediate **A**. Hydrolysis of intermediate **A** afforded the final product.

The distal bond or proximal bond scission depends on the reaction conditions and nucleophiles. Strong nucleophiles and weak acids promote the distal bond scission *via* S$_N$2 by attacking the less hindered carbon of the cyclopropyl group,[4d,e] while strong acids promote the proximal bond scission especially in polar solvents through the generation of α-fluorine stabilized carbocations (S$_N$1).

In conclusion, we have described ring-opening reactions of *gem*-difluorocyclopropyl ketones promoted by boron tri-halides to give corresponding β-trifluoromethyl ketones and β-halodifluoromethyl ketones. Boron trihalides were found to be able to act as both Lewis acids and nucleophiles. The proximal bond of *gem*-difluorocyclopropyl ketones prefers to cleave in the presence of boron trihalides because the two

fluorines could stabilize the resulting carbocation. This strategy represents a new method for the synthesis of β-trifluoromethyl ketones and β-halodifluoromethyl ketones, which are very difficult to obtain by other methods. The study on the ring-opening chemistry of *gem*-difluorocyclopropyl ketones and the application of this strategy to the synthesis of other important fluorinated compounds are currently underway.

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