Organic LETTERS

Letter

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Controlled Ring-Opening of Siloxydifluorocyclopropanes for Carbocyclization: Synthesis of Difluorocyclopentenones

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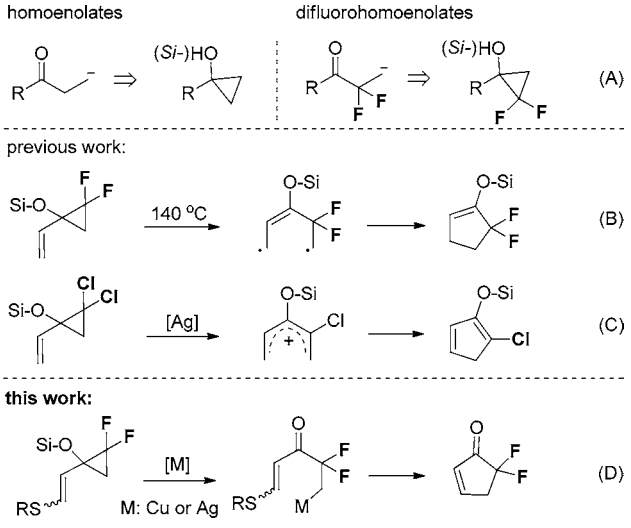
Supporting Information

ABSTRACT: A highly controlled ring opening of siloxydifluorocyclopropanes, formed by *n*BuN$_4$Br-catalyzed difluorocyclopropanation of methyl vinyl ketones bearing a *β*-alkylthio group by using TMSCF$_2$Br as a unique difluorocarbene source, results in metal difluorohomoenolates with assistance of copper or silver followed by an intramolecular addition and elimination reaction leading to *α*-*gem*-difluorocyclopentenones efficiently.

Cyclopropanols and their derivatives are widely used as homoenolate equivalents (Scheme 1A).[1,2] However, applications of their difluorinated analogs have met a substantial challenge. Organofluorides often possess remarkably enhanced chemical, physical, and bioactive properties. In view of the fact that rapid assembly of a fluorine atom into organic molecules can be achieved from fluorine-containing synthons,[3] the development of difluorocyclopropanols into the controllable difluoro-homoenol equivalents is expected to bring new opportunities to organofluorine chemistry and pharmacy.

Scheme 1. Ring Opening of Siloxydihalocyclopropanes for C−C Bond Formation



Cyclopropanols can participate in many C−C bond forming reactions[2] via metal homoenolates, for example, in nucleophilic addition onto carbonyls,[4] conjugate addition,[5] S$_N$2′ alkylation,[6] or acetylation.[7] By comparison, *gem*-dihalogenated cyclopropanols are thermodynamically unstable. Although the corresponding siloxy, acyloxy, or alkoxyl derivatives were reported to be isolable, their reactivity toward electrophiles has been proven to be difficult to control. Competitive dehalogenations often predominated the process leading to *α*-halogenated enones.[8−10] Although metal-mediated/catalyzed ring-opening cross-couplings of cyclopropanols have been also developed,[11,12] no reports have appeared of a similar C−C coupling based on siloxydihalocyclopropanes. In fact, besides a report on thermal rearrangement cyclization of difluorovinylcyclopropanol silyl ethers delivering siloxydifluorocyclopentenes via a homolytic pathway (Scheme 1B),[13,14] Ag-initiated ring openings of these compounds underwent an alternative cationic process to give siloxymonochlorocyclopentadienes (Scheme 1C).[15] To the best of our knowledge, controlled ring openings of siloxy- or acyloxy-difluorocyclopropanes are limited in the use for further protonation[9b,16,17a] or halogenation to date.[17] The corresponding anion process via metal difluorohomoenolate for C−C formation is unknown.

In the course of our research on the applications of fluoroalkylsilanes,[8,18] we recently reported a catalytic difluorocyclopropanation of enolizable ketones[8] by using TMSCF$_2$Br as a unique difluorocarbene source.[19] The *in situ* generated siloxydifluorocyclopropanes were used for the synthesis of *α*-fluorinated enones[8a] and naphthols.[8b] Considering the importance of developing siloxydifluorocyclopropanes into difluorohomoenolate equivalents along with our interest in ketene dithioacetal chemistry,[20,21] we envisioned a domino cyclization of *α*-acyl ketene dithioacetals and TMSCF$_2$Br by taking difluorohomoenolates as the key intermediates. To our delight, tandem difluorocyclopropanation, ring opening, and intramolecular addition and elimination reactions proceeded in a controllable manner. *gem*-Difluorocyclopentenones, which may be of particular interest for developing new bioactive compound candidates,[22] were obtained (Scheme 1D).

Received: May 31, 2016
Published: July 1, 2016

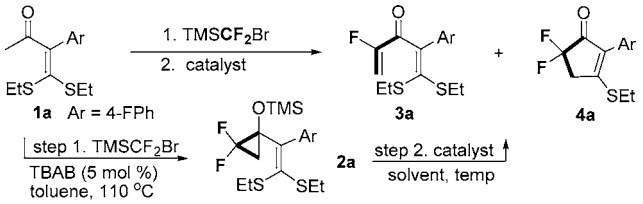
DOI: 10.1021/acs.orglett.6b01567
Org. Lett. 2016, 18, 3414−3417

We initially investigated the difluorocyclopropanation reaction of α-acetyl ketene dithioacetal **1a** with $TMSCF_2Br$. As we expected, siloxydifluorocyclopropane **2a** was obtained in almost quantitative yield under the catalysis of 5 mol % $nBuN_4Br$ (TBAB) in toluene at 110 °C for 4 h (Table 1, step 1).[8a] Then, the reaction conditions for ring opening and recyclization of **2a** were screened systematically. It was found that a high temperature and long reaction time resulted in the reaction complex. However, the use of a fluoride or a base as the deprotecting reagent at room temperature led to α-fluorinated enone **3a** (entries 1−3). Considering the formation of metal difluorohomoenolate[2c] for cyclization, we focused on screening the metal catalysts, including Fe, Ti, Zn, Cu, and Ag for ring opening of **2a** (entries 4−15). Delightfully, the reaction could give the desired *gem*-difluorocyclopentenone **4a** in 15% yield along with **3a** in 53% yield in the presence of $Cu(BF_4)_2 \cdot 6H_2O$ in DCE at 60 °C (entry 8). Gratifyingly, CuCl afforded **4a** in 89% yield (entry 10). By comparison, both CuI and $CuBF_4(MeCN)_4$ were ineffective (entries 12 and 13). In the case of silver salts as the catalyst, the reaction worked but gave **4a** in low yield (entries 14 and 15). A screen of other solvents revealed that DCE at 70 °C could provide somewhat better efficiency (entry 18).

By using the optimized reaction conditions (Table 1, entry 18), the scope of this one-pot reaction was evaluated next. A variety of α-oxo ketene dithioacetals were prepared for this cyclization strategy. As described in Scheme 2, ketene diethylthioacetals **1a−h**, bearing either an electron-donating or -withdrawing group at a different position of the phenyl ring, could afford the desired **4a−h** in excellent yields. By comparison, bulky α-alkyl substituents of **1** have a deleterious effect on the reaction.[23] **4i** and **4j** were isolated in 71% and 43% yield, respectively. **1** containing α-ester, acyl, amide, and cyano substituents also worked leading to **4k−n** and **4o′** in good yields under identical reaction conditions. Among them, **1o** with cyano as the R^1 substituent furnished amide **4o′**, which resulted from further hydrolysis of the α-cyano group of **4o**. In addition, α-propionyl ketene dithioacetals **1p** and **1q** (R^2 = Me) could also provide **4p** and **4q** in satisfactory yields. Finally, both the methylthio and benzylthio functional group were proven to be tolerated in these reactions. Corresponding 3-methylthio-/3-benzylthio-2-cyclopentenones **4r−z** were obtained in 69−93% yields.

On the basis of our knowledge on the reactivity of metal homoenolates[2,4−7] and the chemistry of ketene dithioacetals,[20,21] as well as the use of $TMSCF_2Br$ in catalytic difluorocyclopropanations of ketones,[8] it was reasonable to propose a domino mechanism as described in Scheme 3. First, the reaction of **1** with Br^--activated $TMSCF_2Br$ afforded **2** via catalytic enolization and difluorocyclopropanation. Then, upon treatment of **2** with CuCl with assistance of a halogen anion, copper alkoxide **II** was formed and converted to copper difluorohomoenolate **III** by a β-carbon elimination. Next, transfer of the coordination of copper from oxygen onto sulfur in **III** gave **IV** which allowed an addition−elimination (**IV** to **4** via **V**) leading to *gem*-difluorocyclopentenones **4** as the products. Some control experiments were then performed. The presence of a radical scavenger could not decrease the reaction efficiency (Scheme 3A), thereby excluding the free radical process. To obtain information on the sulfur-

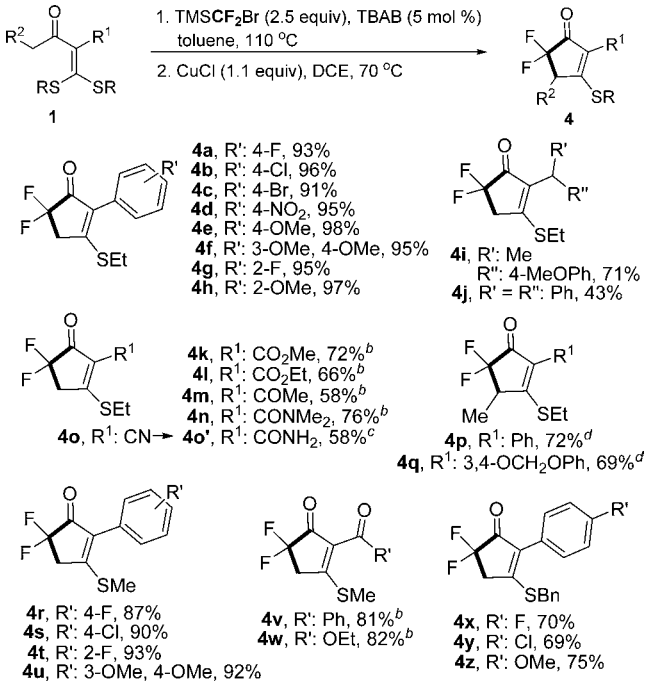
Table 1. Screening of Reaction Conditions[a]



entry	catalyst	temp (°C)	time (h)	solvent	yield (%) of 4a (3a)[b]
1	$nBuN_4F$	rt	4	toluene	– (91)
2	KF	rt	4	MeCN	– (89)
3	NaOAc	rt	6	MeCN	– (87)
4	$FeCl_3$	rt	3	DCM	– (83)
5	$TiCl_4$	rt	3	DCM	trace[c]
6	ZnI_2	rt	3	DCM	– (49)[c]
7	$Cu(OAc)_2$	rt	3	DCM	– (94)
8	$Cu(BF_4)_2 \cdot 6H_2O$	60	2	DCE	15 (53)
9	CuCl	60	10	toluene	55 (40)
10	CuCl	60	4	DCE	89
11	CuCl[d]	60	8	DCE	39 (48)
12	CuI	60	4	DCE	trace
13	$CuBF_4(MeCN)_4$	60	2	DCE	32 (61)
14	AgOTf	60	2	DCE	14 (69)
15	$AgBF_4$[e]	60	2	DCE	40 (18)
16	CuCl	60	5	MeCN	22 (50)
17	CuCl	60	5	THF	27 (47)
18	CuCl	70	3	DCE	93

[a]Conditions: Step 1: **1a** (0.5 mmol), $TMSCF_2Br$ (2.5 equiv), TBAB (5 mol %), toluene (2.5 mL), 4 h, in sealed tube; Step 2: catalyst (1.1 equiv), solvent (5 mL). [b]Isolated yields based on **1a**. [c]Along with a complex mixture. [d]With 0.5 equiv of CuCl. [e]4-FPhC=C$(SEt)_2$ was obtained in 30% yield.

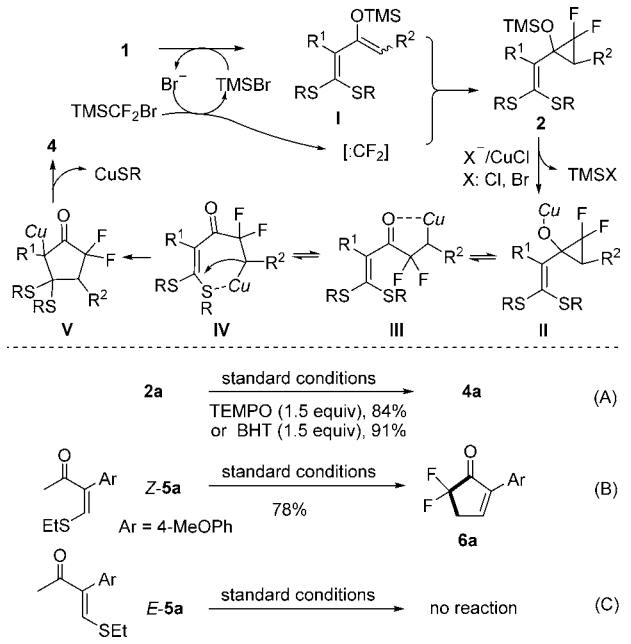
Scheme 2. Scope of Ketene Dithioacetals 1[a]



[a]Conditions: Step 1: $TMSCF_2Br$ (2.5 equiv), TBAB (5 mol %), toluene (2.5 mL), 110 °C, 4 h; Step 2: CuCl (1.1 equiv), DCE (5 mL), 70 °C, 4 h. Isolated yields. [b]Step 2: 10 h. [c]Step 2: 80 °C, 10 h. [d]CuOTf was used.

DOI: 10.1021/acs.orglett.6b01567
Org. Lett. 2016, 18, 3414−3417

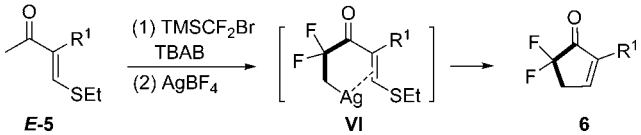
Scheme 3. Proposed Mechanism



coordination stabilization of copper homoenolate **IV** for an S_NV type reaction, we also extended the reaction to vinylogous thioesters **5**. It was found that *Z*-**5a** reacted with $TMSCF_2Br$ to afford *gem*-difluorocyclopentenone **6a** in 78% yield (Scheme 3B). By contrast, no reaction was detected in the case of *E*-**5a** as the substrate (Scheme 3C).

Interestingly, when we used $AgBF_4$, instead of CuCl, for the reactions of both *E*-**5a** and *Z*-**5a**, the cyclizations could furnish **6a** efficiently. In fact, silver salts showed reactivity in the ring opening and recyclization of **2a**, but less efficiently than in the case of CuCl (Table 1, entries 14 and 15). Compared with a required coordination between copper and the *cis*-sulfur atom for stabilization of **IV**, silver difluorohomoenolate **VI** likely contained a coordination of silver with the C−C double bond for further S_NV reaction (Table 2). Thus, we focused on extending the scope of vinylogous thioesters *E*-**5** for the cyclization strategy by the use of $AgBF_4$ as the catalyst. As we expected, all tested reactions worked well leading to **6b**−**6g** in 75−83% yields, while pure **6g** could not be obtained due to its instability toward chromatographic purification (for details, see Supporting Information (SI)). Additional experiments with a radical scavenger (TEMPO or BHT, 1.5 equiv) also excluded the free radical process.

Table 2. Domino Cyclizations of Vinylogous Thioesters[a]

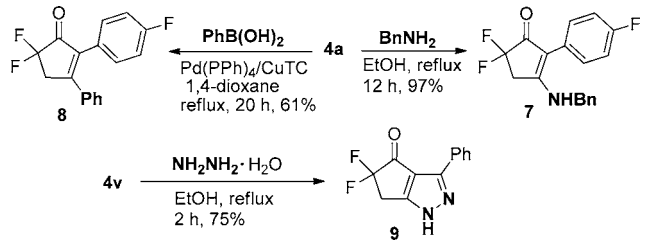


entry	R^1	product **6**	yield (%) of **6**[b]
1	4-OMePh	**6a**	81
2	3-OMe, 4-OMePh	**6b**	82
3	4-FPh	**6c**	83
4	4-ClPh	**6d**	79
5	4-BrPh	**6e**	75
6	2-FPh	**6f**	76
7	*n*Bu	**6g**	76[c]

[a]Conditions: $TMSCF_2Br$ (2.5 equiv), TBAB (5 mol %), toluene (2.5 mL), 100 °C, 4 h, then $AgBF_4$ (1.1 equiv), DCE (5 mL), 60 °C, 2 h. [b]Isolated yields. [c]Yield based on ^1H NMR. Substrates with methylthio functional group.

As described above, a new route to functionalized difluorocyclopentenones has been provided. Further transformations of **4** are presented in Scheme 4 for highlighting the synthetic potential. We first carried out a substitution[24] of **4a** by benzylamine. 3-Aminodifluoro-cyclopentenone **7** was obtained in 97% yield. Then, Pd-catalyzed cross-coupling of **4a** with $PhB(OH)_2$[21a,25] gave 3-phenyldifluorocyclopentenone **8** in 61% yield. Finally, condensation of **4v** with hydrazine afforded pyrimidodifluorocyclopentenone **9** efficiently.

Scheme 4. Transformations of Compound 4



In conclusion, we have developed a highly controlled ring opening of siloxydifluorocyclopropanes which permits generation of metal difluorohomoenolates for carbocyclization. By using $TMSCF_2Br$ as the unique difluorocarbene source, TBAB-catalyzed difluorocyclopropanations of α-acyl ketene dithioacetals produced siloxydifluorocyclopropanes. Copper difluorohomoenolates were then formed which allows an intramolecular S_NV type reaction for the construction of α-*gem*-difluorocyclopentenones. The one-pot process can be extended to the transformation of vinylogous thioesters via a silver difluorohomoenolate. The easy construction of densely functionalized building blocks from readily available starting materials makes the method well-suited for broad applications in organic synthesis and drug design.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01567.

Experimental procedures, analytical data for new compounds (PDF)

Crystallographic data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank National Natural Sciences Foundation of China (NNSFC-21372040), National Natural Science Foundation of

DOI: 10.1021/acs.orglett.6b01567
Org. Lett. 2016, 18, 3414−3417

Jilin (20140101113JC), and the State Key Laboratory of Fine Chemicals (KF1502) for funding support of this research.

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DOI: 10.1021/acs.orglett.6b01567
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