

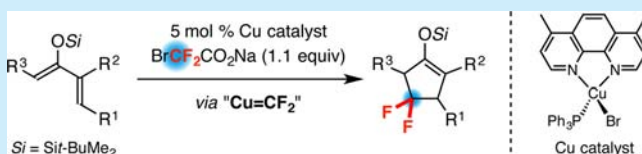
Copper(I)-Catalyzed [4 + 1] Cycloaddition of Silyl Dienol Ethers with Sodium Bromodifluoroacetate: Access to  $\beta,\beta$ -Difluorocyclopentanone Derivatives

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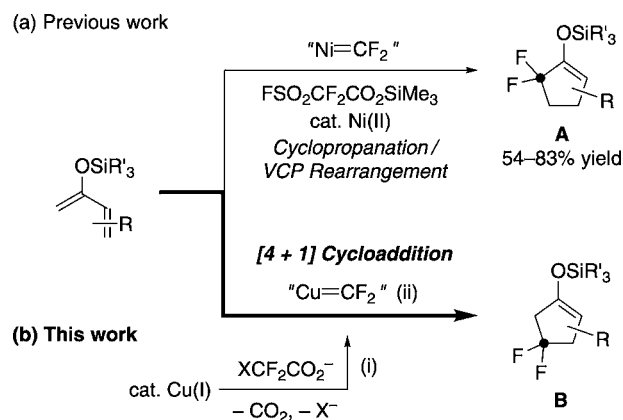
## Supporting Information

**ABSTRACT:** Silyl dienol ethers readily underwent copper(I)-catalyzed [4 + 1] cycloaddition with sodium bromodifluoroacetate to afford 4,4-difluorocyclopent-1-en-1-yl silyl ethers. On the basis of high-resolution mass spectroscopy analysis, annulation presumably proceeded via a copper(I) difluorocarbene complex, which represents an unprecedented example of [4 + 1] cycloadditions promoted by a transition metal difluorocarbene complex.



Transition metal difluorocarbene complexes,  $L_nM=CF_2$ , are highly promising intermediates for the synthesis of fluorine-containing compounds, considering the significant role of their fluorine-free counterparts in today's synthetic organic chemistry.<sup>1</sup> Despite their potential utility, however, only a limited number of reactions of difluorocarbene complexes have been reported in the past year.<sup>2</sup> Our continuous interest in transition metal difluorocarbene complexes prompted us to apply them to catalytic synthesis.

Recently, we reported the synthesis of 5,5-difluorocyclopent-1-en-1-yl silyl ethers (regioisomer A) via the domino difluorocyclopropanation/vinylcyclopropane (VCP) rearrangement sequence of silyl dienol ethers (Scheme 1a).<sup>3</sup> Silyl dienol ethers, prepared from  $\alpha,\beta$ -unsaturated ketones, were treated with trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate ( $FSO_2CF_2CO_2SiMe_3$ )<sup>4</sup> in the presence of a nickel(II) catalyst, leading to the  $\alpha,\alpha$ -difluorocyclopentanone derivatives in good yields.<sup>5</sup>

Scheme 1. Syntheses of *gem*-Difluorocyclopentanone Derivatives

Encouraged by this success, we revisited the synthesis of difluorocyclopentanone derivatives to provide the regioisomers. We report herein the [4 + 1] cycloaddition of copper difluorocarbene complexes and silyl dienol ethers, affording 4,4-difluorocyclopent-1-en-1-yl silyl ethers (regioisomer B) (Scheme 1b). It should be mentioned that the chemistry of [4 + 1] cyclizations is much less developed for five-membered ring formation compared to [3 + 2] and [2 + 2 + 1] cyclizations;<sup>6,7</sup> furthermore, the [4 + 1] cycloaddition promoted by a transition metal difluorocarbene complex has not been reported in the literature.

To conduct the desired [4 + 1] cycloaddition, we adopted a copper(I) salt as a catalyst and a halodifluoroacetate as a carbene source ( $XCF_2CO_2^-$ ) for the following reasons (Scheme 1b): (i) decarboxylation of copper(I) carboxylate is known to proceed with an activation energy of ca. 20 kcal/mol (calculated value),<sup>8</sup> and elimination of a halide ion ( $X^-$ ) from the resulting (halodifluoromethyl)copper(I) species would generate the required difluorocarbene complexes;<sup>9</sup> (ii) copper(I) carbene complexes mediated dihydrofuran formation via a [4 + 1] pathway.<sup>10</sup>

An attempted reaction with several copper(I) complexes realized the desired [4 + 1] cycloaddition as expected (Table 1). In the absence of a copper(I) complex, silyl dienol ether 1a reacted with sodium bromodifluoroacetate in acetonitrile at 50 °C to afford vinylcyclopropane 3 and  $\alpha,\alpha$ -difluorocyclopentanone-derived silyl enol ether 4 in 35 and 5% yields, respectively (entry 1). While cyclopropane 3 was produced by the reaction with free difluorocarbene generated in situ,<sup>11</sup> the undesired regioisomer A, silyl enol ether 4, was obtained from 3 via VCP rearrangement.<sup>3,12</sup> Silyl dienol ether 1a afforded the desired 4,4-difluorocyclopent-1-en-1-yl silyl ether 2a (regioisomer B) in the presence of copper(I) bromide, (phenylethynyl)copper(I), or  $SiMe_3CuCl$  in 25, 37, and 10% yields (entries 2–4), respectively.

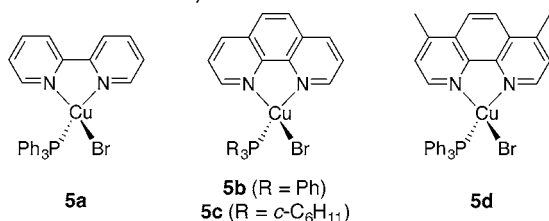
Received: July 16, 2016

Published: August 30, 2016

Table 1. Effect of Copper(I) Complex<sup>a</sup>

entry	Cu(I) complex	<i>t</i> (h)	2a (%)	3 (%)	4 (%)
1	none	15	—	35	5
2	CuBr	18	25	3	—
3	CuCCPh	15	37	10	—
4	SIMesCuCl	15	10	10	trace
5	5a <sup>b</sup>	12	39	40	2
6	5b <sup>b</sup>	12	62	11	—
7	5c <sup>b</sup>	18	51	4	—
8	5d <sup>b</sup>	12	71 (70) <sup>c</sup>	7	2

<sup>a</sup><sup>19</sup>F NMR yield based on an internal standard, (CF<sub>3</sub>)<sub>2</sub>C(C<sub>6</sub>H<sub>4</sub>p-Me)<sub>2</sub>, unless otherwise noted. TBS = Si<sup>t</sup>-BuMe<sub>2</sub>, SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene, and Phen = 1,10-phenanthroline. <sup>b</sup>5 mol %. <sup>c</sup>Isolated yield.



Product 2a was obtained with bipyridyl complex 5a or phenanthroline complexes 5b,c in 39, 62, or 51% yields (entries 5–7).<sup>13,14</sup> Eventually, dimethylphenanthroline-based complex 5d was revealed to be the most effective catalyst for the cycloaddition reaction, affording 2a in 71% yield (entry 8).<sup>15–17</sup>

The scope of the [4 + 1] cycloaddition with respect to 4,4-difluorocyclopent-1-en-1-yl silyl ethers 2 is described in Table 2.<sup>18</sup> Electron-donating and -withdrawing groups installed on the aromatic ring at the terminal position (R<sup>1</sup>) did not affect the reaction, leading to the corresponding products 2b–d in 61–70% yields (entries 2–4). 2-Naphthyl-substituted substrate 1e also afforded the product 2e in 59% yield (entry 5). Cycloaddition of alkyl-substituted substrate 1f (R<sup>1</sup> = *n*-Pr)

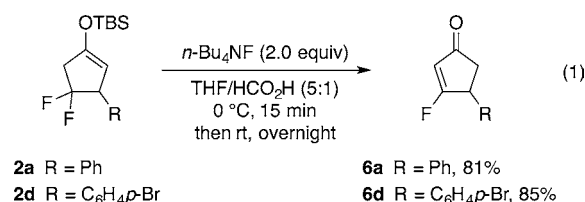
Table 2. Copper(I)-Catalyzed Synthesis of 4,4-Difluorocyclopent-1-en-1-yl Silyl Ethers<sup>a</sup>

entry	1	R <sup>1</sup>	R <sup>2</sup>	2 (%)
1 <sup>b</sup>	1a	Ph	H	70, 2a
2	1b	C <sub>6</sub> H <sub>4</sub> p-Me	H	70, 2b
3	1c	C <sub>6</sub> H <sub>4</sub> p-OMe	H	61, 2c
4 <sup>c</sup>	1d	C <sub>6</sub> H <sub>4</sub> p-Br	H	62, 2d
5	1e	2-naphthyl	H	59, 2e
6 <sup>c,d</sup>	1f	<i>n</i> -Pr	H	57, 2f
7 <sup>c</sup>	1g	Ph	Me	76, 2g
8	1h	-(CH <sub>2</sub> ) <sub>4</sub> -		63, 2h

<sup>a</sup>Isolated yield. TBS = Si<sup>t</sup>-BuMe<sub>2</sub>. <sup>b</sup>Table 1, entry 8. <sup>c</sup>2 mol % of 5d. <sup>d</sup>36 h.

worked well to afford 2f in 57% yield; however, a longer reaction time was required (entry 6). A methyl group installed at the internal position (R<sup>2</sup>) allowed the reaction to afford the desired product 2g in 76% yield (entry 7). The reaction was also applied to a cyclic system. Silyl enol ether 2h, bearing a bicyclo[4.3.0]-nonane skeleton, was efficiently synthesized from cyclic silyl dienol ether 1h in 63% yield (entry 8).

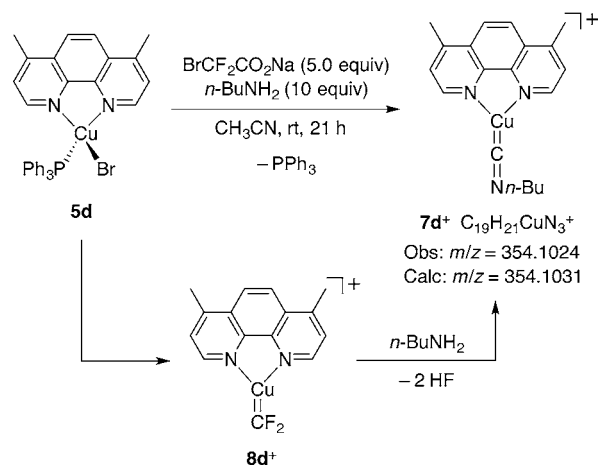
The obtained silyl enol ethers 2 are useful intermediates for  $\beta$ -fluorocyclopentenones (eq 1). Upon treatment with tetrabutyl-



ammonium fluoride in THF/HCOOH, 2a and 2d underwent desilylation and dehydrofluorination to provide 4-substituted 3-fluorocyclopent-2-en-1-ones 6a and 6d in 81 and 85% yields, respectively. Thus, the copper(I)-catalyzed [4 + 1] cycloaddition provides a variety of  $\beta,\beta$ -difluoro- and  $\beta$ -fluorocyclopentanone derivatives.<sup>5</sup>

To elucidate the reaction intermediate, we conducted the following experiment (Scheme 2). When complex 5d was treated

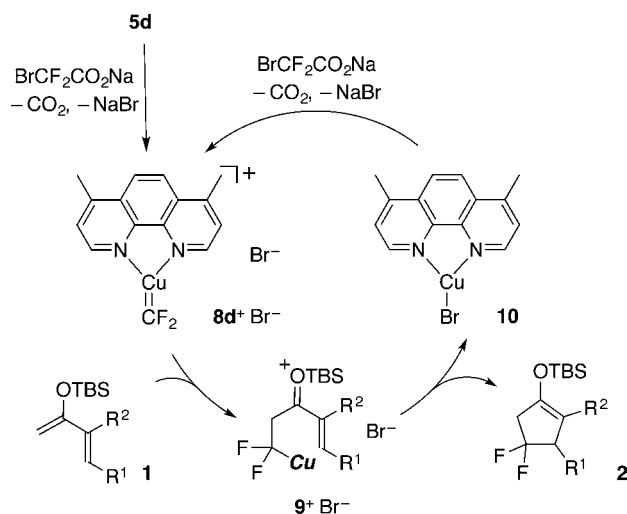
Scheme 2. HRMS Analysis of Reactive Intermediate



with sodium bromodifluoroacetate (5.0 equiv) in the presence of butylamine (10 equiv) at room temperature, isocyanide complex 7d<sup>+</sup>, losing triphenylphosphine, was observed by high-resolution mass spectroscopy (HRMS).<sup>15</sup> This fact suggested that phenanthroline-based difluorocarbene complex 8d<sup>+</sup> was generated in situ to be trapped as the aminolysis product 7d<sup>+</sup>.<sup>9b,19</sup> There remained a possibility that in situ generated free difluorocarbene produced the corresponding isocyanide (*n*-BuNC) by the reaction with butylamine, leading to the generation of 7d<sup>+</sup>. However, this possibility seems unlikely because isocyanide was not observed by <sup>1</sup>H NMR analysis on treatment of sodium bromodifluoroacetate (1.0 equiv) with butylamine (2.0 equiv) in acetonitrile at room temperature for 12 h.<sup>20,21</sup>

A plausible mechanism is proposed to account for the [4 + 1] cycloaddition process (Scheme 3). The key difluorocarbene complex 8d<sup>+</sup>Br<sup>-</sup> is generated from a catalyst precursor 5d and sodium bromodifluoroacetate through the sequence of anion

Scheme 3. Proposed Catalytic Cycle



exchange, decarboxylation, and  $\alpha$ -bromine elimination. Unlike the nickel(II) difluorocarbene complex that promoted cyclopropanation of silyl dienol ethers **1**,<sup>3</sup> copper(I) difluorocarbene complex **8d**<sup>+</sup>Br<sup>−</sup> is electrophilic enough to be nucleophilically attacked by silyl dienol ethers **1** either (I) directly on its CF<sub>2</sub> carbon or (II) on its metal center followed by migratory insertion,<sup>22</sup> to generate alkyl copper(I) species [Cu = Cu(4,7-dimethylphenanthroline)]. The intermediate **9**<sup>+</sup>Br<sup>−</sup> in turn undergoes a Michael-type ring closure<sup>10b</sup> to afford 4,4-difluorocyclopent-1-en-1-yl silyl ethers **2** ([4 + 1] cycloadducts). Thus, complex **8d**<sup>+</sup>Br<sup>−</sup> serves as a one-carbon component in the [4 + 1] cycloaddition. The resulting copper(I) species **10** reacts with the second molecule of the carbene source, BrCF<sub>2</sub>CO<sub>2</sub>Na, regenerating the difluorocarbene complex.<sup>23</sup>

In summary, [4 + 1] cycloaddition of sodium bromodifluoroacetate with silyl dienol ethers was achieved to provide  $\beta,\beta$ -difluorocyclopentanone-derived silyl enol ethers under copper(I) catalysis. High-resolution mass spectroscopy analysis suggested that the reaction would proceed via a copper(I) difluorocarbene complex. This is an unprecedented example of a cycloaddition caused by a transition metal difluorocarbene complex.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02085.

Experimental procedures and spectra of new compounds (PDF)

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### Author Contributions

J.I. conceived the project and wrote the manuscript with K.F. K.F. also planned the experiments. T.A. and J.H. carried out the experiments. All the authors discussed the experiments and results and have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research is supported by JSPS KAKENHI Grant Number JP15K05414 (K.F.), JSPS KAKENHI Grant Number JP16H01002 (J.I.), and Asahi Glass Foundation (K.F.). Kanto Denka Kogyo Co., Ltd., is acknowledged for the generous gift of ethyl bromodifluoroacetate.

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- (13) To exclude the possibility that **2a** was obtained via cyclopropane **3**, isolated **3** was subjected to the reaction conditions with **5b**, which gave no detectable amount of **2a** (<sup>19</sup>F NMR). The reactivity of copper(I)

complexes was found to be quite different from that of the nickel(II) complexes because difluorocyclopropane was not obtained in the reaction with acetophenone-derived silyl enol ether. See ref 3.

(14) In situ generation of catalyst **5b** by mixing their three components (CuBr, PPh<sub>3</sub>, and phenanthroline) in acetonitrile did not work.

(15) For more details on catalyst optimization, effect of carbene sources, and HRMS analysis, see [Supporting Information](#).

(16) For preparation of catalysts **5**, see: Ignatenko, V. A.; Deligonul, N.; Viswanathan, R. *Org. Lett.* **2010**, *12*, 3594.

(17) The dimethylphenanthroline ligand in **5d** seemed to stabilize the difluorocarbene complex due to its electron-donating properties and rigid structure.

(18) Typical procedure. To an acetonitrile suspension (1.8 mL) of copper(I) catalyst **5d** (10 mg, 0.016 mmol) and sodium bromodifluoroacetate (72 mg, 0.37 mmol) was added silyl dienol ether **1a** (88 mg, 0.34 mmol) at rt. After the reaction mixture was stirred at 50 °C for 12 h, hexane (5 mL) and saturated aqueous NaHCO<sub>3</sub> (5 mL) were added to quench the reaction at 0 °C. Organic materials were extracted with hexane five times. The combined extracts were washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexane) on silica gel which was deactivated with 15 vol % of H<sub>2</sub>O prior to use, yielding 4,4-difluorocyclopent-1-en-1-yl silyl ether **2a** as a colorless oil (74 mg, 70%).

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(20) Free isocyanide was observed by <sup>1</sup>H NMR analysis when the temperature was increased to 50 °C.

(21) Although copper(I) difluorocarbene complexes have been proposed as intermediates in some reactions, there was little evidence of complex formation.

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(23) From the result of HRMS analysis, a phosphine ligand was eliminated from the catalyst precursor **5d**. The following experiment indicated that the elimination of phosphine ligand was necessary for the reaction: the yield of **2a** decreased to 32% (<sup>19</sup>F NMR) when the reaction was conducted in the presence of 20 mol % of PPh<sub>3</sub> for 12 h (vs [Table 1](#), entry 8).