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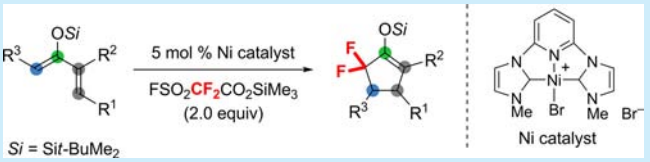
Regioselective Synthesis of α,α-Difluorocyclopentanone Derivatives: Domino Nickel-Catalyzed Difluorocyclopropanation/Ring-Expansion Sequence of Silyl Dienol Ethers

Tatsuya Aono, Hisashi Sasagawa, Kohei Fuchibe, and Junji Ichikawa*

Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan

Supporting Information

ABSTRACT: Silyl dienol ethers prepared from α,β-unsaturated ketones underwent nickel-catalyzed difluorocyclopropanation of the electron-rich alkene moiety with trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate. The subsequent vinylcyclopropane−cyclopentene rearrangement afforded silyl 5,5-difluorocyclopent-1-en-1-yl ethers in good yields. The obtained five-membered silyl enol ethers were demonstrated to be versatile intermediates for the synthesis of di- and monofluorinated cyclopentanones and cyclopentenones. A nickel difluorocarbene complex is proposed as a key intermediate in the difluorocyclopropanation.



Cyclopentanones are an important structural motif found in many natural and artificial compounds.[1] Since the introduction of fluorine substituents is known to increase the biological activities of the original molecules,[2] the pharmaceutical utilities of cyclopentanones with fluorine substituents at the position α to the carbonyl group have been taken into consideration (Figure 1).[3,4]

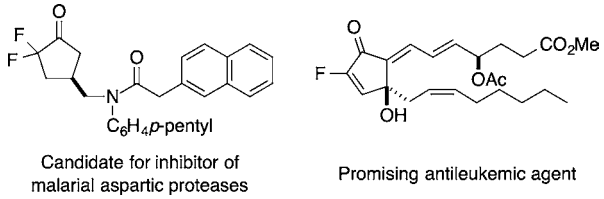
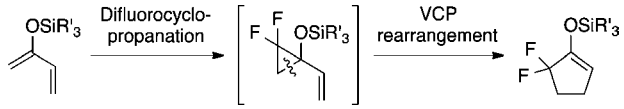


Figure 1. α-Fluorinated cyclopentanone derivatives whose biological activities have been studied.[3a,c]

To date, α,α-difluorocyclopentanone derivatives have been synthesized via two methods: double-electrophilic fluorination of cyclopentanones[5] and deoxygenative fluorination of cyclopentanones followed by oxidation.[3b] These strategies involve considerable effort because they require the construction of the carbon skeleton and the introduction of fluorine. We envisioned that the concise synthesis of α,α-difluorinated cyclopentanones would be facilitated by the combination of the difluorocyclopropanation of silyl dienol ethers and vinylcyclopropane−cyclopentene rearrangement (VCP rearrangement, Scheme 1).[6] Silyl dienol ethers, which are prepared from α,β-unsaturated ketones, are subjected to difluorocyclopropanation. The resulting 1,1-difluoro-2-vinylcyclopropanes bearing a siloxy group undergo subsequent VCP rearrangement to afford silyl 5,5-difluorocyclopent-1-en-1-yl ethers (i.e., the domino synthesis of α,α-difluorocyclopentanone derivatives).

Scheme 1. Strategy for the Domino Synthesis of α,α-Difluorocyclopentanone Derivatives



VCP rearrangements of fluorine-free vinylcyclopropanes, including siloxy-substituted ones,[7] are typically conducted at high temperatures (300−550 °C).[6] As an advantage, fluorine substitution allows the rearrangement conditions to be benign and renders the C−C bond cleavage regioselective. Dolbier reported that 1,1-difluoro-2-vinylcyclopropanes underwent facile VCP rearrangement at 200−275 °C to selectively afford 3,3-difluorocyclopent-1-enes.[8] Recently, Percy conducted the reaction of the difluorinated vinylcyclopropanes with an ester moiety at 100 °C.[9] These advantages of fluorine substitution in cyclopropane rings are ascribed to two primary reasons:[10] (i) increased ring strain[11] and (ii) elongation of the C−C bond distal to the geminal fluorine substituents.[12] We expected that the VCP rearrangement of 2-siloxy-substituted 1,1-difluoro-2-vinylcyclopropanes would readily proceed, providing the desired domino synthesis of α,α-difluorocyclopentanone derivatives.

The difluorocyclopropanation of silyl enol ethers is an issue in this strategy and needs to be addressed. In general, difluorocyclopropanations of alkenes have been extensively studied for decades using systems such as $CHClF_2$/KOH,[13] $CClF_2CO_2Na$,[14] or $PhHgCF_3$/NaI[15] to generate free difluorocarbene;[16] these methods are affected by strongly basic conditions, high reaction temperature, and the need for toxic reagents, respectively. Although useful methods for the

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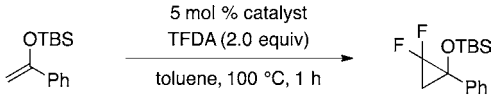
generation of free difluorocarbene have been reported in the past few years,[16b] systems for the difluorocyclopropanation of silyl enol ethers are still limited,[17] probably due to their instabilities.

Thus, we investigated the difluorocyclopropanation of silyl enol ethers with trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)-acetate (TFDA)[18] and found the first example of the metal-catalyzed difluorocyclopropanation of silyl enol ethers (Table 1, Figure 2). TFDA was originally designed to generate free difluorocarbene upon treatment with a fluoride ion. Silyl enol ether **1a** was treated with TFDA (2 equiv) in the presence of sodium fluoride (5 mol %) at 100 °C (entry 1). The desired difluorocyclopropane **2a** was obtained, although the yield was only 31% (^{19}F NMR), and a substantial amount of TFDA (0.62 equiv) remained unreacted. Since we previously reported the NHC-catalyzed generation of free difluorocarbene,[19] TFDA was treated with imidazolium, imidazolinium, or triazolium salts **3**–**5** (5 mol %) along with sodium carbonate (0.2 equiv) in the presence of silyl enol ether **1a** to afford **2a** in 53%, 56%, or 46% yield, respectively (entries 2–4). Further examination revealed that the use of a metal catalyst increased the yield of cyclopropane **2a**. Tetrakis(triphenylphosphine)nickel, -palladium, and -platinum catalysts afforded **2a** in 12–59% yields at 100 °C (entries 5–7). The use of electron-donating pincer-type NHC complexes of those metals further improved the yields (entries 8–13). In particular, nickel complex **6a** was the most effective to prepare **2a**, resulting in 73% yield (entry 8).[20] This method was also successfully applied to other substrates. Sterically hindered or cyclic silyl enol ethers **1b,c** afforded the corresponding products **2b,c** in 63% and 78% yields, respectively (eqs 1 and 2).

Table 1. Catalyst Optimization[a]



1a **2a**

entry	catalyst	**2a**[b] (%)	TFDA[b,c] (equiv)
1	NaF	31[d]	0.62
2	**3** + Na_2CO_3 (0.2 equiv)	53	
3	**4** + Na_2CO_3 (0.2 equiv)	56	
4	**5** + Na_2CO_3 (0.2 equiv)	46	
5	$Ni(PPh_3)_4$	30	
6	$Pd(PPh_3)_4$	59	
7	$Pt(PPh_3)_4$	12	
8	**6a**	72 (73)	
9	**6b**	37	
10	**7a**	64	
11	**7b**	68	
12	**7c**	62	
13	**8**	62	
14	**9** + Na_2CO_3 (0.2 equiv)	45	

[a]TFDA = $FSO_2CF_2CO_2SiMe_3$. TBS = Si*t*-BuMe_2. [b]^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}Me)_2$. Isolated yield is shown in parentheses. [c]Recovery. [d]Silyl enol ether **1a** was completely consumed.

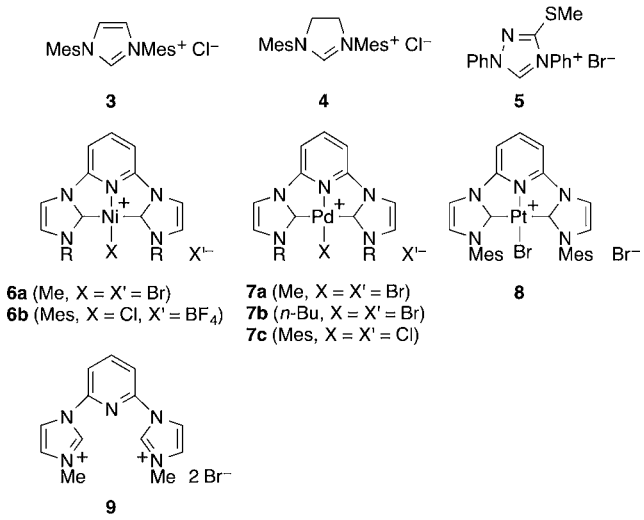
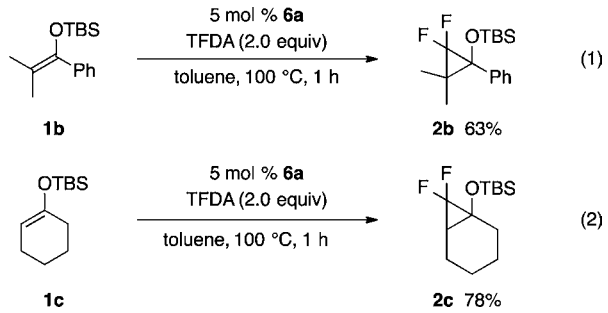


Figure 2. List of catalyst candidates (Mes = 2,4,6-trimethylphenyl).



To eliminate the possibility that the pincer-type NHC ligand served as a catalyst for the decomposition of TFDA, silyl enol ether **1a** was treated with TFDA in the presence of bis(imidazolium) salt **9** (5 mol %) and sodium carbonate (0.2 equiv, entry 14). The product **2a** was obtained in 45% yield, suggesting that the difluorocyclopropanation was more efficiently catalyzed by nickel. One reasonable mechanism for the metal-catalyzed difluorocyclopropanation is that the reaction proceeded via a nickel difluorocarbene complex, $[LNi{=}CF_2]^{2+}$ (L = pincer-type NHC ligand), which was supported by HRMS analysis of its aminolysis product, $[LNi{=}C{=}N(2,6\text{-dimethylphenyl})]^{2+}$ (see the Supporting Information).[21−23]

Importantly, there have been several reports on the preparation of transition-metal difluorocarbene complexes,[24] whereas their synthetic applications are quite rare.[25] We propose that the difluorocyclopropanation proceeds through a transition-metal difluorocarbene complex, which is an unprecedented catalytic application of the difluorocarbene complexes in organic synthesis.

Having successfully carried out the nickel-catalyzed difluorocyclopropanation of silyl enol ethers, the domino difluorocyclopropanation/VCP rearrangement sequence was examined (Table 2). Silyl dienol ether **10a** was treated with 2 equiv of TFDA in the presence of 5 mol % of nickel complex **6a** in toluene at 100 °C (entry 1). Chemoselective cyclopropanation proceeded on the oxygenated electron-rich alkene moiety followed by the expected ring expansion, affording **11a** in 61% yield along with vinylcyclopropane **12** in 16% yield. The vinylcyclopropane intermediate was completely converted to the desired cyclic silyl enol ether by conducting the reaction at 140 °C.[26] Upon treatment with 2 equiv of TFDA in the presence of 5 mol % of **6a** at 140 °C, silyl dienol ether **10a** afforded **11a** in 83% yield (entry 2). Silyl ethers **10b,c**, which bear electron-rich and -deficient aryl groups (R^1), smoothly underwent the domino process to afford the corresponding products **11b,c** in 80% and

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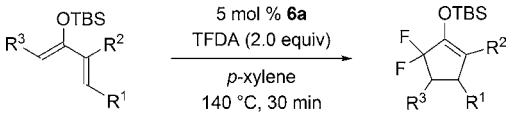
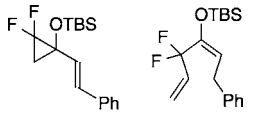
Table 2. Synthesis of Silyl 5,5-Difluorocyclopent-1-en-1-yl Ethers via Domino Difluorocyclopropanation/VCP Rearrangement[a]



10a–i 11a–i

entry	10	R^1	R^2	R^3	yield (%)
1[b]	**10a**	Ph	H	H	61,[c,d] **11a**
2	**10a**	Ph	H	H	83, **11a**
3	**10b**	C_6H_4*p*-Me	H	H	80, **11b**
4	**10c**	C_6H_4*p*-Cl	H	H	79, **11c**
5	**10d**	*n*-Pr	H	H	71, **11d**
6	**10e**	Ph	Me	H	73, **11e**
7	**10f**	Ph	Ph	H	74, **11f**
8	**10g**	Ph	Br	H	74, **11g**
9[e]	**10h**	$-(CH_2)_4-$		H	60, **11h**
10	**10i**	Ph	H	Me[f]	54, **11i**[g]

[a]TBS = Si*t*-BuMe$_2$. [b]100 °C, 40 min. [c]^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}Me)_2$. [d]Vinyl(difluoro)cyclopropane **12** was obtained in 16% yield. [e]20 mol % **6a**, NaH (2 equiv), 100 °C. [f]**10i** (*E*:*Z* = 34:66). [g]Single *trans* diastereomer. Siloxydiene **13** was obtained in 27% yield.



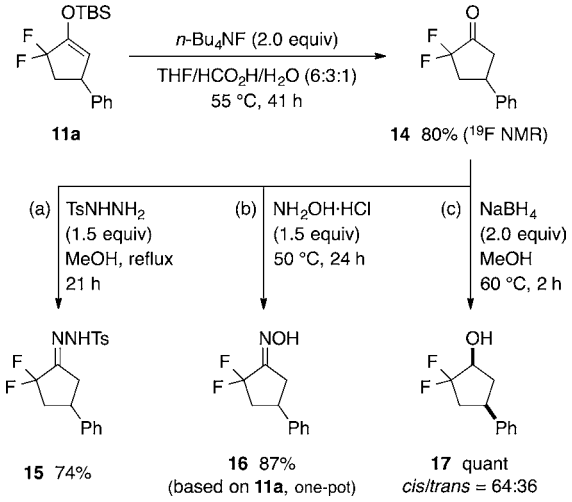
12 13

79% yields (entries 3 and 4), respectively. The reaction of alkylated substrate **10d** also worked well to give the product **11d** in 71% yield (entry 5). Substrates **10e**–**g**, which bear substituents at the internal position (R^2), similarly afforded the products **11e**–**g** in 73–74% yields (entries 6–8). Silyl enol ether **10h**, derived from cyclohexenyl methyl ketone, afforded the bicyclic silyl enol ether **11h** in 60% yield (entry 9).[27] When the substrate **10i**, bearing a methyl group as R^3, was employed, the corresponding product **11i** was obtained in 54% yield as a single *trans* diastereomer along with siloxydiene **13** (27%) as a 1,5-hydrogen shift product (entry 10).[8a,b,28] Thus, the VCP rearrangement of siloxy-substituted difluorovinylcyclopropanes was successfully accomplished for the first time.

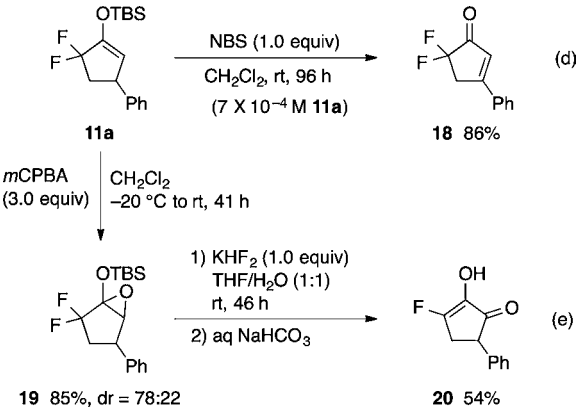
Cyclic silyl enol ethers **11** were transformed to demonstrate their utility for the synthesis of substituted α,α-difluorocyclopentanones. The hydrolysis of **11a** under acidic conditions afforded α,α-difluorocyclopentanone **14** in 80% yield (Scheme 2); this ketone was unstable toward chromatographic purification (silica gel and basic alumina) and distillation. Treatment of **14** with tosylhydrazine afforded the corresponding hydrazone **15** in 74% yield (a). The single-crystal X-ray structure analysis of **15** confirmed that the difluoromethylene unit was introduced at the position adjacent to the carbonyl group (see the Supporting Information). Cyclopentanone **14** was also derivatized to the corresponding oxime **16** in 87% yield (based on **11a**) with hydroxylamine hydrochloride in a one-pot operation (b). Treatment of cyclopentanone **14** with sodium borohydride afforded cyclopentanol **17** as a diastereomeric mixture in quantitative yield (*cis*/*trans* = 64:36, c).[29]

Furthermore, the oxidative treatment of **11** afforded functionalized fluorine-containing cyclopentenones (Scheme 3). Treatment of **11a** with *N*-bromosuccinimide (NBS) under highly

Scheme 2. Synthesis of α,α-Difluorocyclopentanone Derivatives



Scheme 3. Synthesis of Di- and Monofluorocyclopentenone Derivatives



diluted conditions (7×10^{-4} mol/L) gave difluorinated cyclopentenone **18** in 86% yield (d).[30] Oxidation of **11a** with *m*-chloroperbenzoic acid (*m*CPBA) gave the corresponding epoxide **19** in 85% yield as a diastereomeric mixture (78:22). Its desilylation with potassium hydrodifluoride led to the formation of 3-fluorinated 2-hydroxycyclopent-2-en-1-one **20** in 54% yield (e).[31] The oxygenated cyclopentenone skeleton of **20** is found in cyclotene that is used as a food additive with a caramel-like flavor.[32]

In summary, the novel metal-catalyzed difluorocyclopropanation of silyl enol ethers was accomplished using a pincer-type nickel complex. The sequential difluorocyclopropanation/VCP rearrangement of silyl dienol ethers provided synthetically useful derivatives of di- and monofluorinated cyclopentanones and cyclopentenones in good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02726.

Experimental procedures and spectra of new compounds (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: junji@chem.tsukuba.ac.jp.

Notes

The authors declare no competing financial interest.

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(21) When **6b** was treated with TFDA (1.2 equiv) in the presence of 2,6-dimethylaniline (10 equiv), the ion corresponding to the isonitrile complex was observed as a major product by HRMS analysis. See: Clark, G. R.; Hoskins, S. V.; Jones, T. C.; Roper, W. R. *J. Chem. Soc., Chem. Commun.* **1983**, 719. Free isonitrile was generated only in 4% yield (^{1}H NMR analysis) when free difluorocarbene was generated in the presence of 2,6-dimethylaniline (10 equiv).

(22) We compared the reactivities of silyl (di)enol ethers, alkynes, and alkenes in the presence or absence of the metal complex. The observed differences in reactivity suggest that the active species of our metal-catalyzed system was not free carbene. See the Supporting Information.

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