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Ruthenium-Catalyzed Olefin Cross Metathesis with Tetrafluoroethylene and Analogous Fluoroolefins

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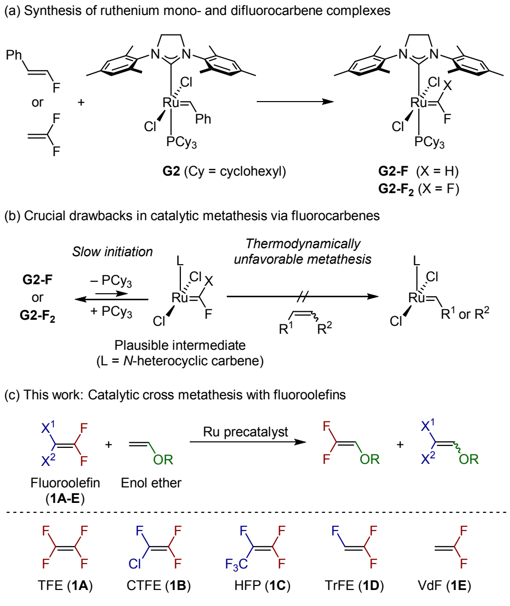
Supporting Information Placeholder

ABSTRACT: This communication describes a successful olefin cross metathesis with tetrafluoroethylene (TFE) and its analogues. A key to the efficient catalytic cycle is interconversion between two thermodynamically stable, generally considered sluggish, Fischer carbenes. This newly demonstrated catalytic transformation enables easy and short-step synthesis of a new class of partially fluorinated olefins bearing plural fluorine atoms which are particularly important and valuable compounds in organic synthesis and medicinal chemistry as well as materials and polymer industries.

Olefin metathesis is one of the most powerful and versatile catalytic transformations to construct a new carbon–carbon double bond, and has become a widely used synthetic tool in both pure and applied chemistry.[1] Despite ruthenium precatalysts having excellent tolerance toward diverse functional groups, the scarce successes underscore the incompatibility of directly halogenated olefins.[2] Focusing on directly fluorinated olefins, commonly referred to as fluoroolefins, attempts at successful olefin metathesis via fluorocarbene complexes have pointed out two crucial drawbacks in catalytic transformation.[3-8]

Ruthenium mono- and difluorocarbene complexes, **G2-F**[4] and **G2-F$_2$**,[5] respectively, have been prepared previously from the parent benzylidene counterpart **G2** with the corresponding fluoroolefins via stoichiometric metathesis (Scheme 1a). Both complexes showed no phosphine dissociation, a plausible initiation step for catalytic cycles, even at elevated temperature based on ^{31}P NMR magnetization transfer experiments, which indicated problematic initiation. Comparison of these catalytic activities for ring-opening metathesis polymerization (ROMP) of 1,5-cyclooctadiene (0.33 mol% **G2-F** or **G2-F$_2$**, CD_2Cl_2, 25 °C, 1.25 h) indicated that the initiation of **G2-F$_2$** (only 9% conversion) was much slower than that of **G2-F** (100% conversion), which emphasized the extreme sluggishness of **G2-F$_2$**. Another drawback emerged through density functional theory (DFT) calculations in regard to the Gibbs free-energy profiles of the cross metathesis of 2-norbornene with several directly halogenated olefins.[6] The results indicated a large contribution of halocarbene ligation, in particular, that of difluorocarbene, to stabilize the whole of the complexes, and this would hinder subsequent turnover. A recent study using coupled cluster theory calculation also predicted that the type of complex involving two electron negative substituents is not likely to be effective for olefin metathesis.[7] These two crucial drawbacks to olefin metathesis explained why no successful catalytic metathesis involving the difluorocarbene intermediate was reported, whereas there have been a few successes via the monofluorocarbene counterpart (Scheme 1b).[8]

Scheme 1. Olefin metathesis with fluoroolefins.

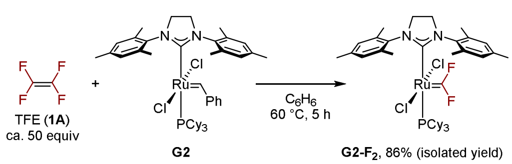


TFE, tetrafluoroethylene; CTFE, chlorotrifluoroethylene; HFP, hexafluoropropylene; TrFE,trifluoroethylene; VdF, vinylidene fluoride.

Fluoroolefins are particularly important and valuable compounds for the synthesis of many commercially successful products in the materials and polymer industries.[9] Thus far, only a limited number of fluoroolefins have been used as monomers because of a lack of suitable, inexpensive methods for their preparation. The use of olefin metathesis involving inexpensive fluoroolefins and a hydrocarbon counterpart will enable easy and short-step synthesis of a wide range of functionalized fluoroolefin monomers for exploitation in polymer chemistry, for example, as well as possible new building blocks bearing plural fluorine atoms in medicinal chemistry. TFE and its analogues are inexpensive, bulk organofluorine feedstock and are considered to be suitable starting materials for this perspective.[10]

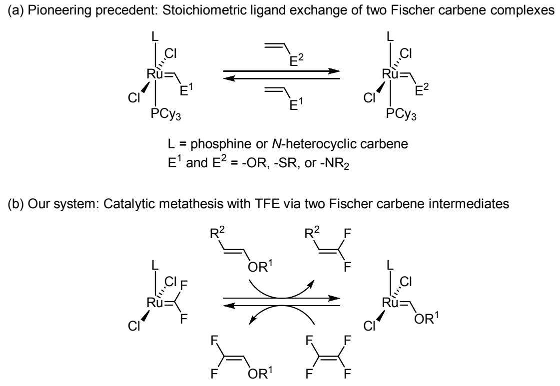
During our investigations to develop new classes of catalytic transformation with TFE, the simplest perfluoroolefin, we discovered that **G2** reacted with TFE under mild reaction conditions to afford **G2-F$_2$** in excellent isolated yield, in the same manner as with VdF (Scheme 2).[5,11] This discovery led us to accomplish the challenging catalytic cross metathesis with fluoroolefins. We herein report a successful ruthenium-catalyzed cross metathesis with TFE and its analogues (Scheme 1c). A key to the efficient catalytic cycle is interconversion between two thermodynamically stable, generally considered sluggish, Fischer carbenes.[12]

Scheme 2. Stoichiometric metathesis of G2 with TFE.



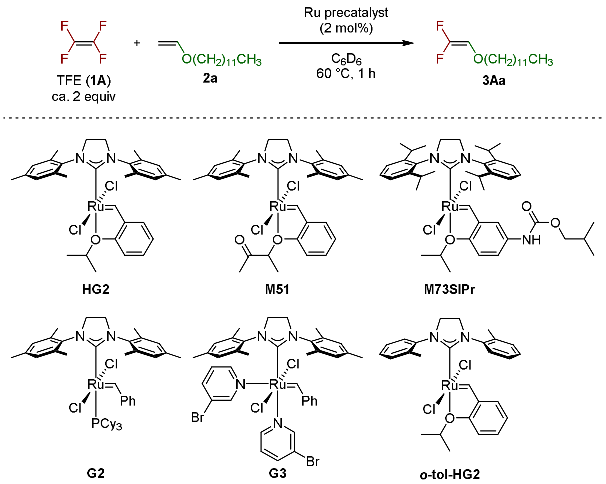
As described above, fluoroolefins serve as problematic substrates for olefin metathesis, giving insufficient or no catalytic turnover, and thereby hindering straightforward access to the corresponding functionalized fluoroolefins. After failure of our early attempts at successful catalytic cross metathesis with TFE, we designed a peculiar catalytic cycle inspired by a pioneering precedent.[13] Grubbs and co-workers have reported that a Fischer carbene reacted with a stoichiometric amount of α-heteroatom-substituted olefin to result in an equilibrium-controlled mixture of two Fischer carbenes (Scheme 3a). The ruthenium alkoxycarbenes are representative Fischer carbenes and can be readily obtained from the reaction of the parent alkylidenes with enol ethers (e.g., ethyl vinyl ether). The thermodynamic stability of alkoxycarbene strongly hinders subsequent turnover in an olefin metathesis manner, leading to the frequent use of enol ethers as a termination agent for ROMP. We hence envisioned that the interconversion between two Fischer carbenes, i.e., difluorocarbene and alkoxycarbene, would be labile, and this system could catalyze the cross metathesis of TFE and enol ethers: In the presence of TFE and enol ether, difluorocarbene and alkoxycarbene would catalytically interconvert to afford two difluorinated olefins simultaneously (Scheme 3b). We anticipated that this mutual characteristic of thermodynamic stability of difluorocarbene and alkoxycarbene would contribute suitably to our catalytic system.[14]

Scheme 3. Labile Fischer carbene interconversion.



The successful catalytic metathesis of TFE (**1A**) with dodecyl vinyl ether (**2a**) encouraged us to afford the corresponding difluorinated product **3Aa** (Table 1). A controlled experiment highlighted the essential role of the ruthenium precatalyst in this transformation (entry 1). Screening of a total of 19 ruthenium precatalysts revealed that a class of precatalysts bearing a (2-isopropoxyphenyl)methylidene moiety provided enhanced catalytic activity for this transformation (entries 2−4). The absence of a phosphine ligand was considered to contribute to the superior results.[15] **G2**, fast-initiating **G3**, and sterically less-hindered ***o*-tol-HG2** served this reaction insufficiently. (entries 5−7).

Table 1. Screening of precatalysts.[a-c]

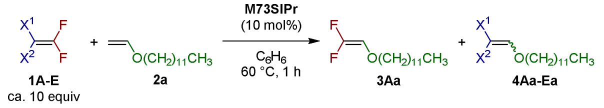


Entry	Precatalyst	Yield of **3Aa**/%[d]	TON
1	none	n.d.	−
2	**HG2**	25	12.5
3	**M51**	27	13.4
4	**M73SIPr**	23	11.7
5	**G2**	6	3.2
6	**G3**	2	1.1
7	***o*-tol-HG2**[e]	2	0.8

[a] A total of 19 precatalysts were screened; the full list is provided in the Supporting Information (SI). [b] Reaction conditions: **1A** (1 atm, ca. 0.12 mmol, ca. 2 equiv), **2a** (0.06 mmol), 1,4-bis(trifluoromethyl)benzene (0.01 mmol, internal standard for determination of ^{19}F NMR yield) and precatalyst (0.0012 mmol, 2 mol%, except for entry 1) in C_6D_6 (0.6 mL) at 60 °C for 1 h in a screw cap NMR tube. [c] n.d., not detected; TON, turnover number. [d] ^{19}F NMR yield. [e] The precatalyst was partially soluble in C_6D_6.

Not only TFE (**1A**) but also analogous fluoroolefins were capable of this transformation (Table 2). In the presence of **M73SIPr** precatalyst, these fluoroolefins could convert to provide the corresponding products under mild reaction conditions, in moderate to good yields. When 1.0 mmol of **2a** was used as the starting material, product **3Aa** was obtained in 64% isolated yield, thereby showing this transformation was scalable and catalytic (entry 1). Reaction with CTFE (**1B**) afforded a mixture of difluorinated **3Aa** (11%) and chlorofluorinated **4Ba** (51%), thus indicating turnover of 6.2 (entry 2). HFP (**1C**) and TrFE (**1D**) also gave the products **4Ca** (22%) and **4Da** (72%), respectively, whereas no **3Aa** was detected by ^{19}F NMR in these cases (entries 3 and 4). VdF (**1E**) resulted in recovery of the starting material **2a** (entry 5).[16] Neither 1,2-bis(dodecyloxy)ethylene nor symmetric fluoroolefins (the products of self metathesis from **1**, e.g., 1,2-dichloro-1,2-difluoroethylene from **1B**) was detected in the reaction mixture under these reaction conditions. The products were partially isolatable by careful chromatography, and all new compounds were characterized by NMR spectroscopy and high-resolution mass spectrometry (HRMS).[17,18] The stereochemistry of **4Ba**, **4Ca**, and **4Da** was assigned by NMR based on the coupling constants between vinylic protons and fluorines.[19]

Table 2. Catalytic cross metathesis with fluoroolefins[a-d]

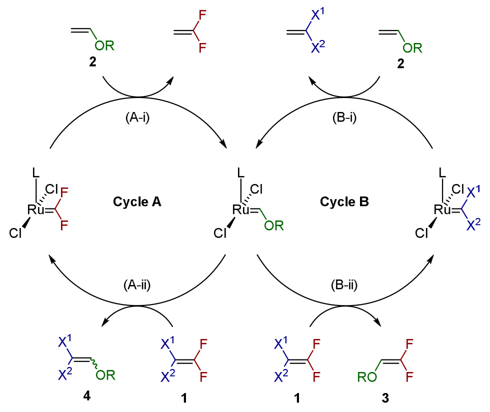


Entry	Fluoroolefin	X^1	X^2	Yield/%[e] 3Aa	Yield/%[e] 4Aa-Ea	TON
1	TFE (**1A**)	F	F	69[f] (64)		6.9
2	CTFE (**1B**)	F	Cl	11	51 [39/61]	6.2
3	HFP (**1C**)	F	CF$_3$	n.d.	22 [25/75]	2.2
4	TrFE (**1D**)	F	H	n.d.	72 [20/80]	7.2
5	VdF (**1E**)	H	H	n.d.	–[g]	–

[a] Reaction conditions: **1** (2 atm, ca. 10 mmol, ca. 10 equiv), **2a** (1.0 mmol) and **M73SIPr** precatalyst (0.1 mmol, 10 mol%) in C_6H_6 (10 mL) at 60 °C for 1 h in an autoclave. [b] n.d., not detected; TON, turnover number. [c] Isolated yields are given in parentheses. [d] *E/Z* ratios are given in square brackets. [e] ^{19}F NMR yield. [f] **4Aa** is identical to **3Aa**. [g] **4Ea** is identical to **2a**.

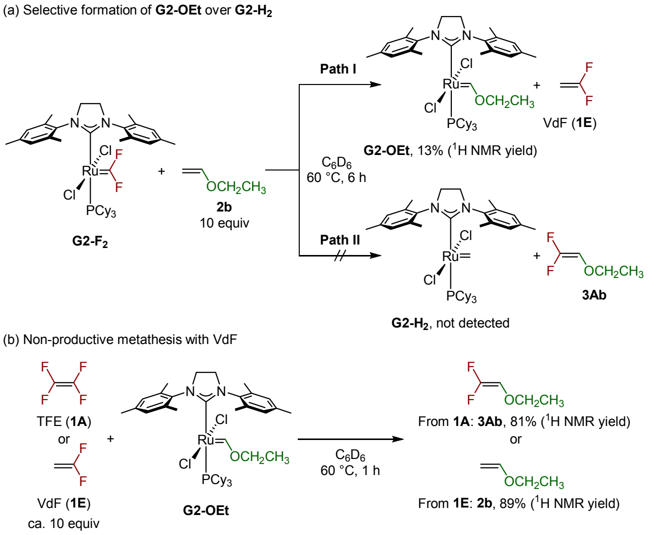
According to the simple principle regarding the interconversion of two Fischer carbene intermediates shown in Scheme 3b, the following two fundamental steps would compose the catalytic cycles: (i) fluorocarbene to alkoxycarbene conversion (Scheme 4, steps A-i and B-i) and (ii) its reverse counterpart (Scheme 4, steps A-ii and B-ii). In this situation, cycles A and B involve [Ru]=CF$_2$ and [Ru]=CX^{1}X^2 intermediates, respectively.

Scheme 4. Plausible catalytic cycles.



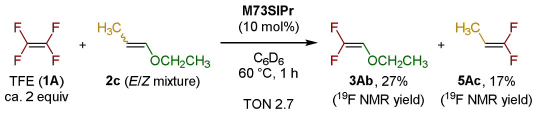
Related mechanistic studies ascertained that the expected catalytic cycle was reasonable. **G2-F$_2$** reacted with ethyl vinyl ether **2b** to afford only **G2-OEt** and VdF, whereas neither **G2-H$_2$** nor **3Ab** was observed in both ^{1}H and ^{19}F NMR spectra, showing complete regioselectivity of path I over path II (Scheme 5a). This result strongly indicated that the difluorocarbene underwent selective conversion to the alkoxycarbene according to step A-i in Scheme 4. Stoichiometric metathesis of **G2-OEt** highlighted a significant contrast between TFE and VdF (Scheme 5b). When VdF (X^1 = X^2 = H) was used as a reactant, the large energetic drawback in conversion from a Fischer carbene [Ru]=CHOR to a Schrock carbene [Ru]=CH$_2$ would hinder step B-ii in Scheme 4, thereby yielding non-productive metathesis through step A-ii. The predominant formation of **4** over **3** shown in Table 2 might also reflect a similar energetic advantage of cycle A over B. Further experimental and computational studies are now underway.

Scheme 5. Mechanistic studies.



Ethenolysis, the cross metathesis with ethylene and another olefinic counterpart featuring an internal carbon−carbon double bond, is a practical and cost-effective manufacturing process to provide high-value chemicals from bulk feedstock.[20] We hence introduced a method, “tetrafluoroethenolysis”, by which two partially fluorinated olefins could be provided in an ethenolysis manner with TFE. Indeed, in the presence of **M73SIPr** precatalyst, **2c** reacted with TFE (**1A**) to convert into two terminal olefins, **3Ab** (2.7 turnover determined by ^{19}F NMR) and **5Ac**,[21] obviously proving the feasibility of this transformation (Scheme 6). Notably, an alkyl-substituted product could be obtained via this transformation according to the principle shown in Scheme 3b.

Scheme 6. “Tetrafluoroethenolysis”.



In conclusion, we demonstrated a successful ruthenium-catalyzed cross metathesis with TFE and its analogous fluoroolefins. This newly demonstrated catalytic transformation indicates that fluoroolefins are no longer exotic substances of olefin metathesis. Furthermore, these findings prove the feasibility of a new synthetic methodology for organofluorine chemistry, such as cross metathesis with two fluoroolefins and ROMP with a cyclic fluoroolefin via Fischer carbene interconversion. Further investigations related to this work are now in progress and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

CAUTION! The International Agency for Research on Cancer (IARC) classifies TFE into “Group 2A: Probably carcinogenic to humans”,[22] and hence all manipulations using TFE must be carried out with care.

CAUTION! Under the representative reaction condition, fluoroolefins may ignite in the presence of oxygen, and hence air must be completely removed from the operating system (e.g., NMR tube and autoclave).

The authors declare the following competing financial interests: The authors are employees of Asahi Glass Co., Ltd. (AGC) and patent applications on this work have been filed.

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(8) A number of successes with α,ω-diene, one of whose carbon−carbon double bonds bears a fluorine atom, indicated certain compatibility for ring-closing metathesis, see ref. 3 and references therein.

(9) For example, see: (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, **2004**, (b) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, U.K., **2004**, and (c) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., **2006**.

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(11) Unfortunately, no perfluororuthenacyclobutane species that was a plausible intermediate for olefin metathesis with TFE was detected in the product mixture. For other perfluorometallacyclobutanes, see: (a) Iron complexes; Karel, K. J.; Tulip, T. H.; Ittel, S. D. *Organometallics* **1990**, *9*, 1276−1282, (b) cobalt complexes; Harrison, D. J.; Lee, G. M.; Leclerc, M. C.; Korobkov, I.; Baker, R. T. *J. Am. Chem. Soc.* **2013**, *135*, 18296−18299, and (c) Vicic and co-workers have reported platinum complexes during the preparation of this manuscript; Xu, L.; Solowey, D. P.; Vicic, D. A. *Organometallics* in press, DOI: 10.1021/acs.organomet.5b00045.

(12) The term “Fischer carbene” refers to a metal complex bearing a divalent carbene ligand featuring at least one α-heteroatom substitutent (e.g., halogen atom, −OR, −SR, or $-NR_2$) with lone-pair electrons.

(13) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153−2164.

(14) Likewise, Macnaughtan has proposed a similar system involving interconversion between acetoxycarbene and other Fischer carbenes in her Ph.D. dissertation, see ref. 4c.

(15) In the case of cross metathesis using 1-haloethylene and 1,2-dihaloethylene, Grela and Johnson reached a similar conclusion independently, see: (a) Sashuk, V.; Samojłowicz, C.; Szadkowska, A.; Grela, K. *Chem. Commun.* **2008**, 2468−2470 and (b) ref. 4b.

(16) We have separately confirmed that catalytic cross metathesis between enol ether and VdF actually occurred, see eqs. S1 and S2 in the SI.

(17) Although the preparation of **3Aa** has been reported previously, the NMR data are not available, see: Yang, Q.; Njardarson, J. T. *Tetrahedron Lett.* **2013**, *54*, 7080−7082.

(18) Only (*E*)- and (*Z*)-**4Ba** were inseparable chromatographically, see the SI.

(19) For compound characterization data, see the SI.

(20) For an example of ethenolysis and analogous alkenolysis, see: Nickel, A.; Ung, T.; Mkrtumyan, G.; Uy, J.; Lee, C. W.; Stoianova, D.; Papazian, J.; Wei, W. H.; Mallari, A.; Schrodi, Y.; Pederson, R. L. *Top. Catal.* **2012**, *55*, 518−523.

(21) Authentic NMR data for **5Ac** in C_6D_6 have not been reported previously, and we hence tentatively determined the formation by NMR and HRMS analyses of the reaction mixture. See the SI for details.

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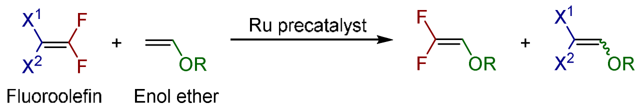

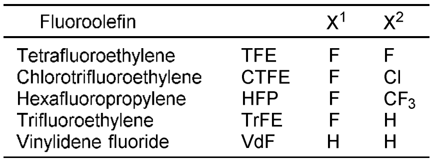

Fluoroolefin		X^1	X^2
Tetrafluoroethylene	TFE	F	F
Chlorotrifluoroethylene	CTFE	F	Cl
Hexafluoropropylene	HFP	F	CF_3
Trifluoroethylene	TrFE	F	H
Vinylidene fluoride	VdF	H	H
