JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

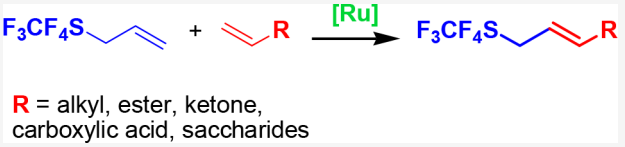
# Synthesis of *trans*-Tetrafluoro(trifluoromethyl)-$\lambda^6$-sulfanyl ($CF_3SF_4$)-Containing Olefins via Cross Metathesis

Muqian Deng, Max Wilde, and John T. Welch*

Cite This: https://doi.org/10.1021/acs.joc.3c01177 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** The cross-metathesis reactions of *trans*-tetrafluoro(trifluoromethyl)-$\lambda^6$-sulfanyl ($CF_3SF_4$)-containing olefins expand the repertoire of synthetic transformations of $CF_3SF_4$-substituted molecules. Treatment of a primary alkene and 3-$CF_3SF_4$–propene with a second-generation Hoveyda–Grubbs catalyst yielded the cross-metathesis product in good yield under very mild conditions (room temperature). $CF_3SF_4$–propene undergoes cross metathesis with substrates containing electron-withdrawing groups or electron-donating groups at room temperature or under dichloromethane reflux. The formation of the $CF_3SF_4$–propene homodimer and the utility of that dimer to undergo selective cross-metathesis reactions are described.



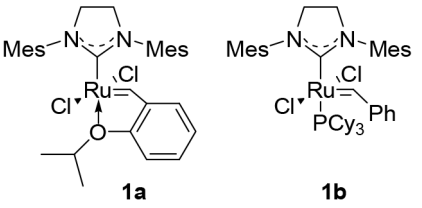

The chemistry of the *trans*-tetrafluoro(trifluoromethyl)-$\lambda^6$-sulfanyl group ($CF_3SF_4$) is little explored. The preparation of tetrafluoro(trifluoromethyl)-$\lambda^6$-sulfanyl chloride ($CF_3SF_4Cl$) and the addition of $CF_3SF_4Cl$ to aliphatic compounds was described in four accounts from the 1970s,[1−4] but recently, $CF_3SF_4Cl$ addition reactions to alkenes[5] and diazoalkanes[6] have received considerable attention. On incorporation in peptides,[7] the $CF_3SF_4$ group has been shown to have remarkable effects on the secondary structure. Unfortunately, the reactions of $CF_3SF_4$-containing building blocks have received little attention.

The tetrafluoro(trifluoromethyl)-$\lambda^6$-sulfanyl group ($CF_3SF_4$) belongs to the same class of fluorinated functionality as the pentafluorosulfanyl ($SF_5$) and trifluoromethyl groups. Incorporation of the $CF_3SF_4$ group into a molecule profoundly changes the physicochemical properties of the compound. Characteristic of these substitutions are increased lipophilicities, enhanced group dipoles, reduced heats of vaporization, and diminished dielectric constants.

The Connelly volume, 138.93 Å$^3$, and surface area, 156.76 Å$^2$, of the *trans*-$CF_3SF_4$ group are greater than the corresponding values of the pentafluorosulfanyl ($SF_5$) group,[7] 102.96 Å$^3$ and 122.71 Å$^2$. The $CF_3SF_4$ substituent is reported to be the most hydrophobic group in existence with a lipophilicity ($\pi_p$) of 2.13.[8] The $CF_3SF_4$ group has a Hammett substituent parameter $\sigma_p$ of 0.68, among the highest $\sigma_p$ values for electron-withdrawing functional groups with a predominant inductive ($-I$) effect. The calculated (B3LYP/cc-pVTZ) dipole moment of $CF_3SF_4CH_3$ of 2.301 D is comparable to that of $CF_3CH_3$ (2.267 D) and reduced relative to the dipole moment of $SF_5CH_3$ (3.310 D).

As part of our effort to expand our understanding of the influence of the $CF_3SF_4$ group on reactivity and to enhance the utility of $CF_3SF_4$-containing building blocks, we have investigated the utility of 3-*trans*-$CF_3SF_4$–propene in cross-metathesis reactions.

Olefin cross metathesis has found many applications in synthesis.[9−11] Grubbs' transformative discoveries of novel catalysts[12,13] facilitated many new synthetic strategies. Recently, there has been interest in reactions of perfluorinated olefins or partially fluorinated olefins as these olefins have shown promise in pharmaceutical agents and agrochemicals,[14] having been introduced to steroids,[15] antiprogestines,[16] fulvestrants,[17] and *O*-allylcyclodextrins[18] among other agents. The electron deficiency[19] of fluorinated alkenes renders cross-metathesis reactions of these olefins particularly challenging.




**1a** **1b**

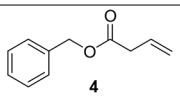
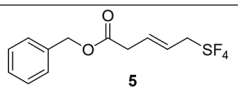
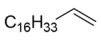
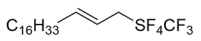
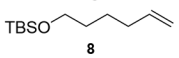
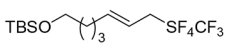
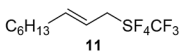
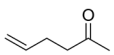
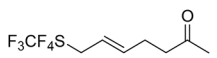
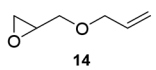
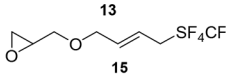
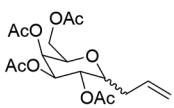
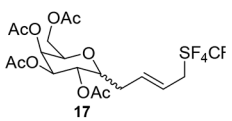
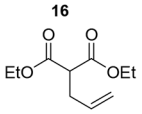
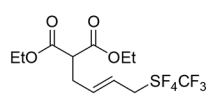
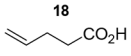
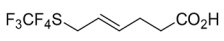
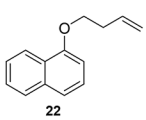
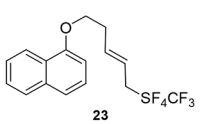
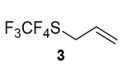
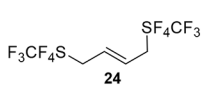
Cy = cyclohexyl Mes = 2,4,6-trimethylphenyl

The Blechert[14] group has shown that catalyst ligands strongly impact metathesis reactions with second-generation Hoveyda–Grubbs catalysts demonstrating better results. Fluorinated alkenes effectively underwent cross-metathesis reactions with second-generation Hoveyda–Grubbs catalyst **1a**.[15] It was also observed that (perfluoroalkyl)propenes such as $CF_3CF_2CF_2CH_2CH{=}CH_2$ formed homodimers in the presence of Grubbs second-generation catalyst **1b**. The homodimer

**Received:** May 26, 2023


© XXXX American Chemical Society

**Table 1. Yields for Cross Metathesis of $CF_3SF_4$ Olefin (3) with Selected Substrates**

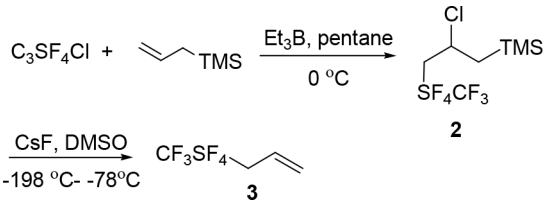
| Trial | Substrates | 1a (mol%) | Temperature | Product[a] | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 |  4 | 10 | rt |  5 | 20 |
| 2 |  6 | 10 | rt |  7 | 40 |
| 3 |  8 | 10 | rt |  9 | 55 |
| 4 |  10 | 10 | reflux |  11 | 20 |
| 5 |  12 | 10 | reflux |  13 | 40 |
| 6 |  14 | 10 | rt |  15 | 52 |
| 7 |  16 | 10 | reflux |  17 | 73[c] |
| 8 |  18 | 10 | reflux |  19 | 34 |
| 9 |  20 | 40 | reflux |  21 | 44 |
| 10 |  22 | 10 | reflux |  23 | 94 |
| 14 |  3 | 10 | reflux |  24 | 70[b] |

[a]Only the trans product was found. [b]NMR yield. [c]**16** and **17** in 11:1, $\alpha$:$\beta$, mixture[20]

$C_3F_7CH_2CH{=}CHCH_2C_3F_7$, formed by reaction of $C_3F_7CH_2CH{=}CH_2$ with **1b**, undergoes cross metathesis with second-generation Hoveyda–Grubbs catalyst **1a**.

Various *trans*-$CF_3SF_4$-containing functionalized olefins (Table 1) were prepared by cross-metathesis reactions promoted by the second-generation Hoveyda–Grubbs catalyst **1a**.

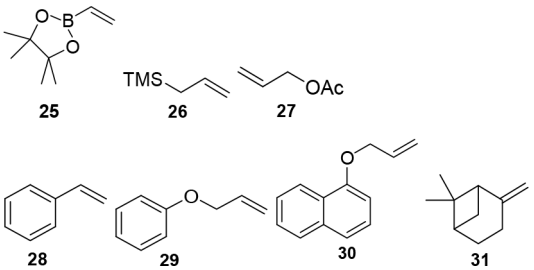
The 3-*trans*-$CF_3SF_4$–propene **3** was readily prepared as shown below (see Supporting Information for experimental details)




The cross-metathesis reaction of **3** with a variety of terminal olefins formed the products (Table 1) at room temperature or under dichloromethane reflux. Conducted in sealed tubes under an argon atmosphere, electron-rich substrates with relatively long chains (**6**, **8**, and **14**) underwent cross metathesis under mild conditions. Formation of **21** required the use of a 4-fold increase in catalyst concentration. Among the successful cross metatheses, the reaction of ester **4**, diester **18**, and short-chain alkene **10** with **3** proceeded in lower yields than the other examples.

While the $CF_3SF_4$-containing olefin (**3**) chemoselectively underwent cross metathesis with a diverse set of primary alkenes, there were several instances where the cross-metathesis process was not successful with **1a** or **1b** (see chart below). It has been suggested that the destabilization of a metallacyclobutane metathesis intermediate formed on reaction of a fluorinated olefin[21] is a result of a $\pi$ back bonding that increases the activation energy. In contrast, metallacyclobutanes are stabilized by the electron donation of strong $\sigma$ donors.

The susceptibility of *trans*-$CF_3SF_4$ olefin (**3**) to undergo cross metathesis with vinyl boronate **25** was investigated.

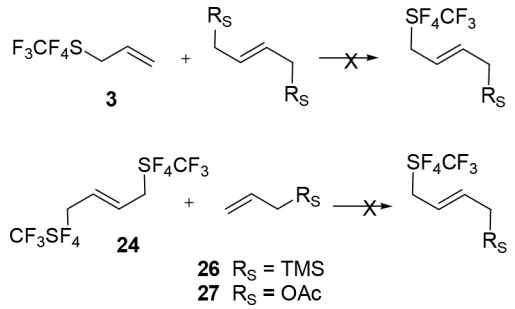





https://doi.org/10.1021/acs.joc.3c01177
J. Org. Chem. XXXX, XXX, XXX−XXX

Unfortunately, cross metathesis was unsuccessful in the presence of either second-generation Grubbs catalyst (**1b**) or second-generation Hoveyda–Grubbs catalyst (**1a**); only the homodimerization product of **3**, **24**, was formed. Based on the observation that **3** underwent rapid homodimerization, we concluded that this fluorinated olefin can be classified as a type I olefin (fast homodimerization).[22] While conditions for formation of the cross-metathesis product of **25** with **3** have not yet been identified, previously it has been reported that the cross metathesis of vinyl boronate **25** with olefins can be promoted by first-generation Grubbs catalysts.[22] Exploration of the utility of other catalysts is in progress.

Surprisingly, allyl trimethylsilane **26** and allyl acetate **27** failed to undergo cross metathesis with either **3** or the homodimerization product **24.** The failure of allyl **26** to undergo cross metathesis with **3** in the presence of **1a** was anticipated as cross-metathesis reactions of type I olefins such as **26** with a second type I olefin such as **3** are predicted to occur readily. Previously, modified Grubbs catalysts,[23] molybdenum-containing[24] or tungsten-containing catalysts,[25] have been utilized to promote the cross metathesis of allyl trialkylsilanes.




The attempted cross metathesis between allyl acetate and **3** yielded the allyl acetate homodimerization product 1,4-diacetoxy-but-2-ene (as detected by TLC) and the homodimerization product of **3**, **24**. As mentioned earlier, this result was surprising as both allyl acetate and the homodimer 1,4-diacetoxy-but-2-ene are type I olefins that would be predicted to undergo cross metathesis readily. The failure of cross metathesis was suggested to be a consequence of the difficulty of the allyl acetate ruthenium adduct to interact with the readily formed homodimer of **3**, **24**.

As the participation of $\beta$-pinene **31** in **1a**-promoted cross-metathesis reactions is known,[26] the challenge of reaction of **31** with **3** was not unexpected. Successful cross metatheses of **31** required very large excesses of the alkene partner, excesses that were not possible with the limited availability of **3**. But, the failure of **3** to undergo cross metathesis with styrene **28**, phenyl allyl ether **29**, or the naphthyl allyl ether **30** was surprising. However, 1-(but-3-enyloxy)naphthalene **22** did react to form **23** in very good yield (Table 1, trial 10). In the attempted reactions of **29** and **30**, only the homodimers were formed. The success of 1-(but-3-enyloxy)naphthalene, naphthyl ether **22** (trial 4), to yield products of cross metathesis with **3** in light of the failure of **29** and **30** is difficult to rationalize. When the chain is elongated, the metallacyclobutane required for the cross metathesis effectively formed. The origin of the unusual selectivity associated with reactions of **3** is not at all clear. Combination of the steric demand of the $CF_3SF_4$ group and the profound lipophobicity of this group may be influencing the required intermolecular interactions in an unforeseen manner. Further investigation of the origin of the unusual selectivity of **3** is under active investigation.

In summary, *trans*-$CF_3SF_4$ olefin (**3**) can undergo second-generation Hoveyda–Grubbs catalyst-promoted cross metathesis with substrates containing acid, ester, and ketone functional groups. The limitations of the utility of $CF_3SF_4$ olefin **3** in cross metathesis are likely related to the novel substituent effects of the $CF_3SF_4$ group, including the steric demand and fluorophilicity.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c01177.

Detailed experimental procedures and NMR spectra for all compounds (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

**John T. Welch** – *Department of Chemistry, University at Albany, State University of New York, Albany, New York 12222, United States;* orcid.org/0000-0002-7434-141X; Email: jwelch@albany.edu

### Authors

**Muqian Deng** – *Department of Chemistry, University at Albany, State University of New York, Albany, New York 12222, United States*

**Max Wilde** – *Department of Chemistry, University at Albany, State University of New York, Albany, New York 12222, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.3c01177

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Support of this research, in part, by National Science Foundation grants NSF-CHE 1464936 and NSF-CHE 2154772 is gratefully acknowledged.

## ■ REFERENCES

(1) Abe, T.; Shreeve, J. M. *Cis* and *Trans* Isomers of Bis (Perfluoroalkyl) Sulfur Tetrafluorides. *Inorg. Nucl. Chem. Letters* **1973**, *9*, 465–468.

(2) Abe, T.; Shreeve, J. n. M. Fluorination of Perfluoroalkylsulfenyl Chlorides, Perfluorodialkyl Disulfides, and Perfluorodialkyl Sulfides with Chlorine Monofluoride. *J. Fluorine Chem.* **1973**, *3*, 187–96.

(3) Darragh, J. I.; Haran, G.; Sharp, D. W. A. *Trans*-Chlorotetrafluoro-(Trifluoromethyl)Sulphur and It's Reactions with Olefins and Acetylenes. *J. Chem. Soc., Dalton Trans.* **1973**, 2289–2293.

(4) Darragh, J. I.; Sharp, D. W. A. Chlorofluorination Reactions of Sulfur(Iv) Fluorides. *J. Chem. Soc. D* **1969**, *15*, 864b–865.

(5) Ikeda, A.; Zhong, L.; Savoie, P. R.; Von Hahmann, C. N.; Zheng, W.; Welch, J. T. Synthesis of Trifluoromethyl Tetrafluoro-L$^6$-Sulfanyl-Substituted Alkenes, Ketones, and Acids: Polar Hydrophobic Building Blocks. *Eur. J. Org. Chem.* **2018**, *2018*, 772–780.

(6) Zhao, X.; Shou, J.-Y.; Newton, J. J.; Qing, F.-L. Trans-Trifluoromethyltetrafluorosulfanyl Chloride: Selective Synthesis and Reaction with Diazo Compounds. *Org. Lett.* **2022**, *24*, 8412.



https://doi.org/10.1021/acs.joc.3c01177
J. Org. Chem. XXXX, XXX, XXX–XXX

(7) Ikeda, A.; Capellan, A.; Welch, J. T. The Secondary Structure of a Heptapeptide Containing Trifluoromethyl-$L^6$-Tetrafluorosulfanyl Substituted Amino Acids. *Org. Biomol. Chem.* **2019**, *17*, 8079−8082.
(8) Kirsch, P.; Hahn, A. Liquid Crystals Based on Hypervalent Sulfur Fluorides: The *Trans*-(Trifluoromethyl)Tetrafluorosulfuranyl Group. *Eur. J. Org. Chem.* **2006**, *2006*, 1125−1131.
(9) Yoshida, K. In *Metathesis Reactions, Transition-Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; John Wiley & Sons, Inc., 2013; pp 721−742.
(10) Matsuo, T. Functionalization of Ruthenium Olefin-Metathesis Catalysts for Interdisciplinary Studies in Chemistry and Biology. *Catalysts* **2021**, *11*, 359.
(11) Abera Tsedalu, A. A Review on Olefin Metathesis Reactions as a Green Method for the Synthesis of Organic Compounds. *J. Chem.* **2021**, *2021*, 3590613.
(12) Grubbs, R. H.; Wenzel, A. G.; Chatterjee, A. K. *Olefin Cross-Metathesis*; Elsevier Ltd., 2007; Vol. *11*, pp 179−205.
(13) Herbert, M. B.; Grubbs, R. H. Z-Selective Cross Metathesis with Ruthenium Catalysts: Synthetic Applications and Mechanistic Implications. *Angew. Chem., Int. Ed.* **2015**, *54*, 5018−5024.
(14) Imhof, S.; Randl, S.; Blechert, S. Ruthenium Catalysed Cross Metathesis with Fluorinated Olefins. *Chem. Commun.* **2001**, *1*, 1692−1693.
(15) Eignerová, B.; Slavíková, B.; Buděsínský, M.; Dracínský, M.; Klepetárová, B.; St'Astná, E.; Kotora, M. Synthesis of Fluorinated Brassinosteroids Based on Alkene Cross-Metathesis and Preliminary Biological Assessment. *J. Med. Chem.* **2009**, *52*, 5753−5757.
(16) Robertson, J. F.; Nicholson, R. I.; Bundred, N. J.; Anderson, E.; Rayter, Z.; Dowsett, M.; Fox, J. N.; Gee, J. M.; Webster, A.; Wakeling, A. E.; Morris, C.; Dixon, M. Comparison of the Short-Term Biological Effects of 7-Alpha-9-(4,4,5,5,5-Pentafluoropentylsulfinyl)-Nonylestra-1,3,5, (10)-Triene-3,17-beta-Diol (Faslodex) Versus Tamoxifen in Postmenopausal Women with Primary Breast Cancer. *Cancer Res.* **2001**, *61*, 6739−6746.
(17) Blazejewski, J.-C. a.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seo, H.-S.; Leclercq, G. Synthesis, Characterization and Biological Evaluation of 7$\alpha$-Perfluoroalkylestradiol Derivatives. *Bioorg. Med. Chem.* **2003**, *11*, 335−345.
(18) Řezanka, M.; Eignerová, B.; Jindřich, J.; Kotora, M. Synthesis of Mono(Perfluoroalkyl) Cyclodextrins Via Cross Metathesis. *Eur. J. Org. Chem.* **2010**, *2010*, 6256−6262.
(19) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. Nitro-Substituted Hoveyda-Grubbs Ruthenium Carbenes: Enhancement of Catalyst Activity through Electronic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 9318−9325.
(20) Kramer, J. R.; Deming, T. J. Glycopolypeptides with a Redox-Triggered Helix-to-Coil Transition. *J. Am. Chem. Soc.* **2012**, *134*, 4112−4115.
(21) Tobón, P.; Gómez, S.; Restrepo, A.; Núñez-Zarur, F. Role of Substrate Substituents in Alkene Metathesis Mediated by a Ru Alkylidene Catalyst. *Organometallics* **2021**, *40*, 119−133.
(22) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.
(23) Keitz, B. K.; Endo, K.; Herbert, M. B.; Grubbs, R. H. *Z*-Selective Homodimerization of Terminal Olefins with a Ruthenium Metathesis Catalyst. *J. Am. Chem. Soc.* **2011**, *133*, 9686−8.
(24) Schowner, R.; Elser, I.; Toth, F.; Robe, E.; Frey, W.; Buchmeiser, M. R. Mono- and Bisionic Mo- and W-Based Schrock Catalysts for Biphasic Olefin Metathesis Reactions in Ionic Liquids. *Chem. Eur. J.* **2018**, *24*, 13336−13347.
(25) Elser, I.; Schowner, R.; Frey, W.; Buchmeiser, M. R. Molybdenum and Tungsten Imido Alkylidene *N*-Heterocyclic Carbene Catalysts Bearing Cationic Ligands for Use in Biphasic Olefin Metathesis. *Chem. Eur. J.* **2017**, *23*, 6398−6405.
(26) Sarmento Fernandes, L.; Mandelli, D.; Carvalho, W. A.; Caytan, E.; Fischmeister, C.; Bruneau, C. Cross Metathesis of (−)-$\beta$-Pinene, (−)-Limonene and Terpenoids Derived from Limonene with Internal Olefins. *Appl. Catal., A* **2021**, *623*, 118284.


https://doi.org/10.1021/acs.joc.3c01177
*J. Org. Chem.* XXXX, XXX, XXX−XXX