BTL NEDERLAND

Insights

ISSN 2590-0811

December 2023 - April 2024 | volume 7 | number 1

The Tetrafluoro-λ^6-sulfanyl Compounds: *Highlight*

trans-SF_4

BTL NEDERLAND

Insights

ISSN 2590-0811

December 2023 - April 2024 | volume 7 | number 1

Table of contents

The tetrafluoro-λ^6-sulfanyl compounds: *Highlight*

BTL NEDERLAND

Insights

ISSN 2590-0811

December 2023 - April 2024 | volume 7 | number 1

The Tetrafluoro-λ^6-sulfanyl Compounds: *Highlight*

Atef S. Iskander[*]

In the field of fluorination, various fluorinated reagents have been demonstrated, which elegantly exploit their adaptive characteristics. In this context, the *trans*-tetrafluoro-λ^6-sulfanyl (*trans*-SF_4) moiety is envisioned to be the building blocks of the next generation of bioactive molecules. The *trans*-SF_4-contianing molecules owing to their characteristic structural and chemical properties could serve as a promising alternative of conventional bioisosteres. Furthermore, the *trans*-trifluoromethyl tetrafluorosulfanyl (*trans*-SF_4CF_3) moiety is a unique group for the incorporation into organic molecules due to their strong electron-withdrawing and steric effects, which strongly influence the reactivity of any molecule into which it is substituted. This highlight focuses on the recent development in the synthetic methodologies and applications of these groups, illustrating their interesting potential in the field of bioactive compounds. This highlight is anticipated to stimulate eclectic ideas toward further development in this area in drug design and beyond.

KEYWORDS: Hypervalent sulfur fluorides, Tetrafluoro-λ^6-sulfanyl moiety, Radical fluorinating agents, Trifluoromethyl tetrafluoro-λ^6-salfanes, Bioisostere compounds.

1. Introduction

The fluorinated molecules have a great impact on various fields of chemistry. The incorporation of fluorine atoms (F) into a suitable position of organic molecules has a great influence in modifying the physicochemical properties of these molecules, due to the high electronegativity and lipophilic nature of F atoms.[1] They play an important role in drug discovery and positron emission tomography. Sulfur-fluorine molecules are characterized by their versatile bond modalities and unique functionalities. The pentafluoro-λ^6-sulfanyl (SF_5) molecules have characteristic physicochemical properties such as high electronegativity, hydrophobicity, and bulkiness. Evidences have proven that several SF_5-containing bioactive molecules possess distinctive pharmacological

* BTL Nederland, L. Wentstraat 240, 1018 MS Amsterdam, Netherlands.

E-mail: info@btlnederland.org

http://www.btlnederland.org

properties including potent activity, target selectivity, and metabolic stability.[2,3] Likewise, the tetrafluoro-λ^6-sulfanyl (SF_4) moiety has unique physicochemical properties, that can serve as a unit of liquid crystals.[4,5] Liquid crystal materials exhibit both orientational order and fluidity, and have been recognized in the display industry, and recently in the cross-field of material science and biomedicine due to their biocompatibility, multifunctionality, and responsiveness.[6] Moreover, SF_4 moiety has interesting geometric features that enable it to connect two linearly independent functional groups *via* the central hypervalent sulfur atom in either *cis* or *trans* configuration of R-SF_4-R' molecules (Figure 1a).[5] The hexa-coordinated *trans*-SF_4 configuration, which allows the construction of linear structures *via* the axial bonds, has the ability to act as a unique linker structure of organic molecules. In addition, the SF_4 moiety has the potential to serve as a bio-isostere of non-conjugated linear motifs analogous to linear scaffolds for drug design such as bicycle-[1.1.1]-pentane (BCP), alkynes, *p*-substituted benzenes, and cubanes (Figure 1b).[7,8] Notably, the construction of molecules bearing polar hydrophobic groups can effectively modulate the biological activity by reducing the energy of desolvation while facilitating ligand dipolar interactions.
Herein, this highlight focuses on the recent advances in the synthetic methodologies of both the *trans*-SF_4-substituted and *trans*-SF_4CF_3-substituted organic molecules, and their applications, illustrating their interesting potential in bioactive compounds. It aims to stimulate new ideas for further development in this area.

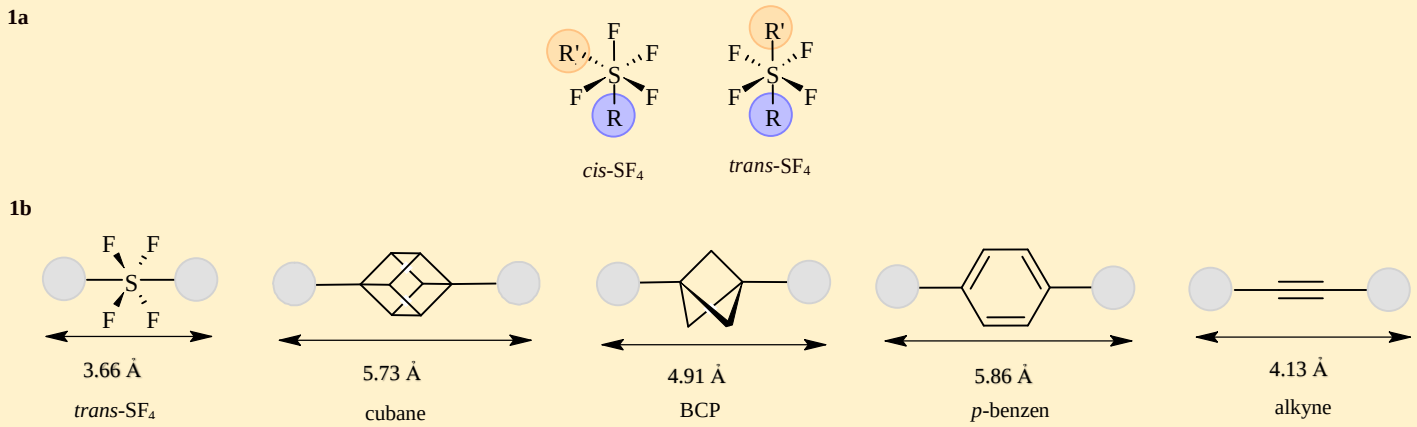


Figure 1. a) R-SF_4-R' molecules with *cis*- and *trans*-geometry. b) Structures and lengths (calculated, CH_3) of linear connective motifs of the bioisostere compounds.[9]

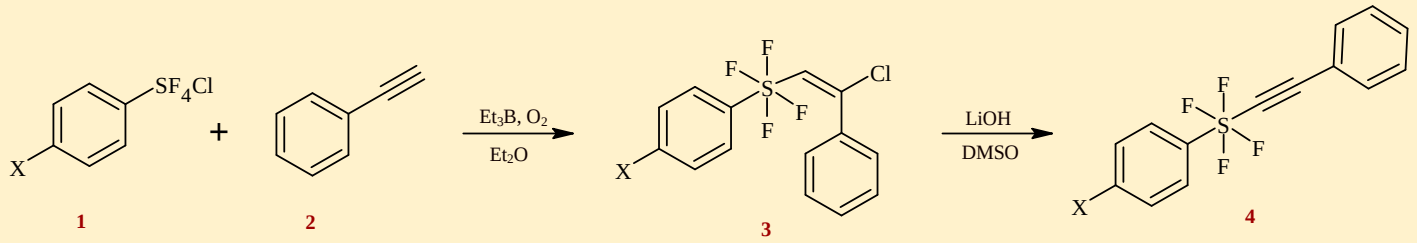
2. Synthetic methodologies of SF_4-containing compounds

The SF_4 compounds have characteristic structural and chemical properties, which may have potential as a building block of bioactive compounds, as well as a unique linker structure of organic molecules. Despite the extraordinary potential of SF_4-containing molecules, the synthetic methodologies are limited. This section therefore focuses on some recent synthetic procedures of SF_4-containing molecules.

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1

2.1. Construction of trans-SF_4-alkynyl structures

Welch and co-workers demonstrated a practical procedure to prepare 2-(aryl tetrafluoro-λ^6-sulfanyl)-ethynylbenzene **4**, through the radical addition of chlorotetrafluorosulfanyl arenes **1** to ethynylbenzene **2**, followed by elimination reaction (Scheme 1).[10,11] X-Ray crystallographic analysis of the product revealed that the axial bonds of the *trans*-SF_4 linked the arenes and ethynyl benzene moieties in almost linear geometry. The nature of substituents bound to SF_4-group affected the reactivity of the products.



Scheme 1. Synthesis of 2-(aryl tetrafluoro-λ^6-sulfanyl)- ethynylbenzene.

2.2. Synthesis of trans-SF_4-containing two non-conjugated N-heterocycles

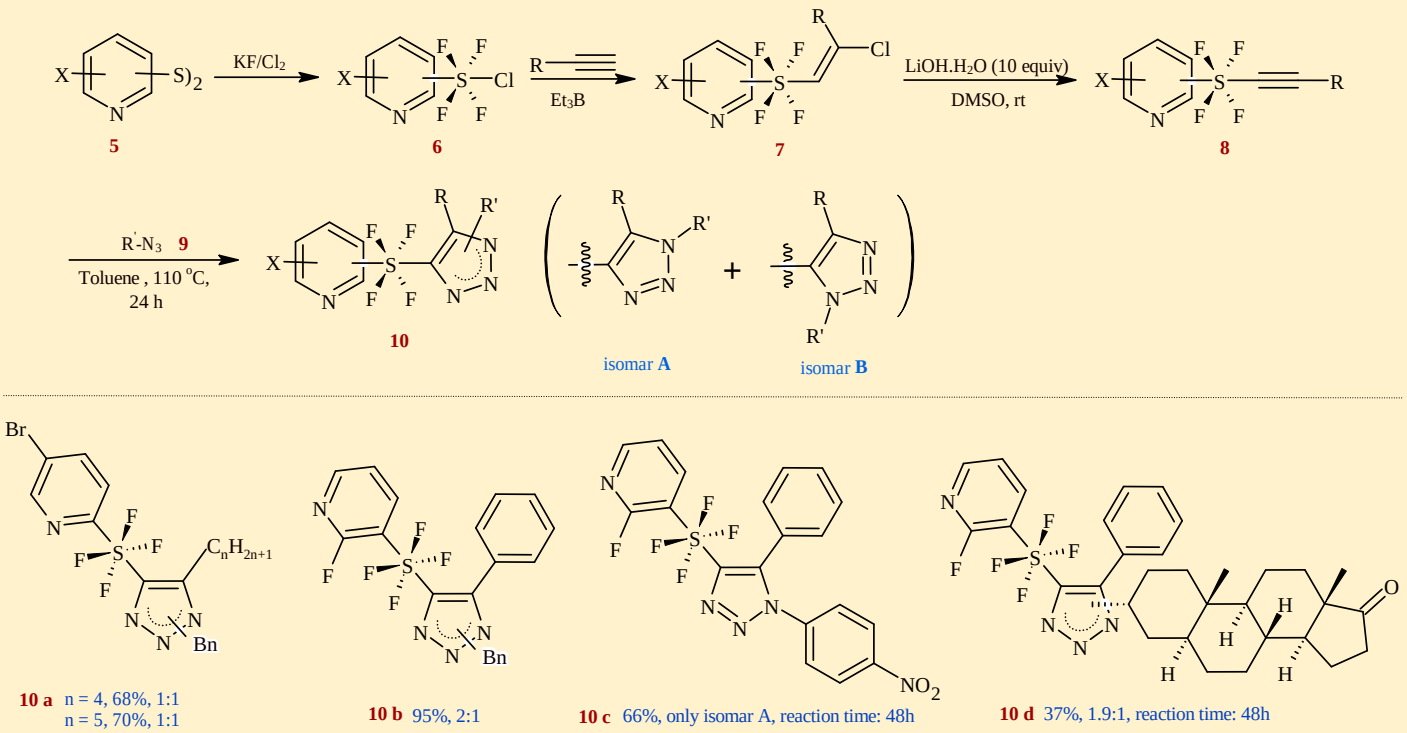
Since pyridines and triazoles are among the most common occurring *N*-heterocycles in medicinal chemistry, the use of *trans*-SF_4 moiety as a rod-like linear linker for these two molecules provides an interesting physiochemical profile related to the linear structure and the fluorinated *N*-heterocycles. In 2018, Shibata and coworkers reported a synthetic method for a linear connection between pyridine and triazole rings *via* the *trans*-SF_4 moiety, based on thermal Huisgen 1,3-dipolar cycloaddition between pyridine SF_4-alkynes and azides.[5] The radical addition of pyridine tetrafluorosulfanyl chlorides **6** (Py-SF_4-Cl), which were prepared from pyridine disulfides **5** ((Py-S)$_2$) with KF/Cl_2 by oxidation chloro-tetrafluorination, to alkynes gave pyridine *trans*-SF_4-alkenes **7**, followed by elimination reaction to provide pyridine *trans*-SF_4-alkynes **8**. Then, reaction of **8** with azides **9** under thermal Huisgen 1,3-dipolar cycloaddition conditions afforded the eccentric fluorinated heterocycles **10** with potential bioactive and surface properties in high yield (Scheme 2).[5] Being a thermal reaction, the regioisomers A and B were obtained in a 2:1 ratio.

BTL NEDERLAND

Insights

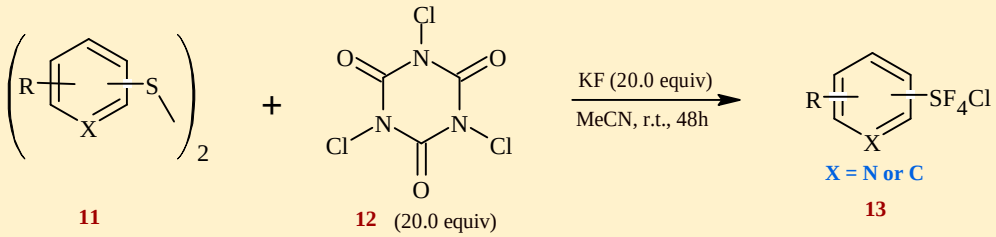
ISSN 2590-0811

December 2023 - April 2024 | volume 7 | number 1



Scheme 2. Synthesis of *trans*-SF_4 connected pyridine and triazole molecules *via* a cycloaddition reaction.

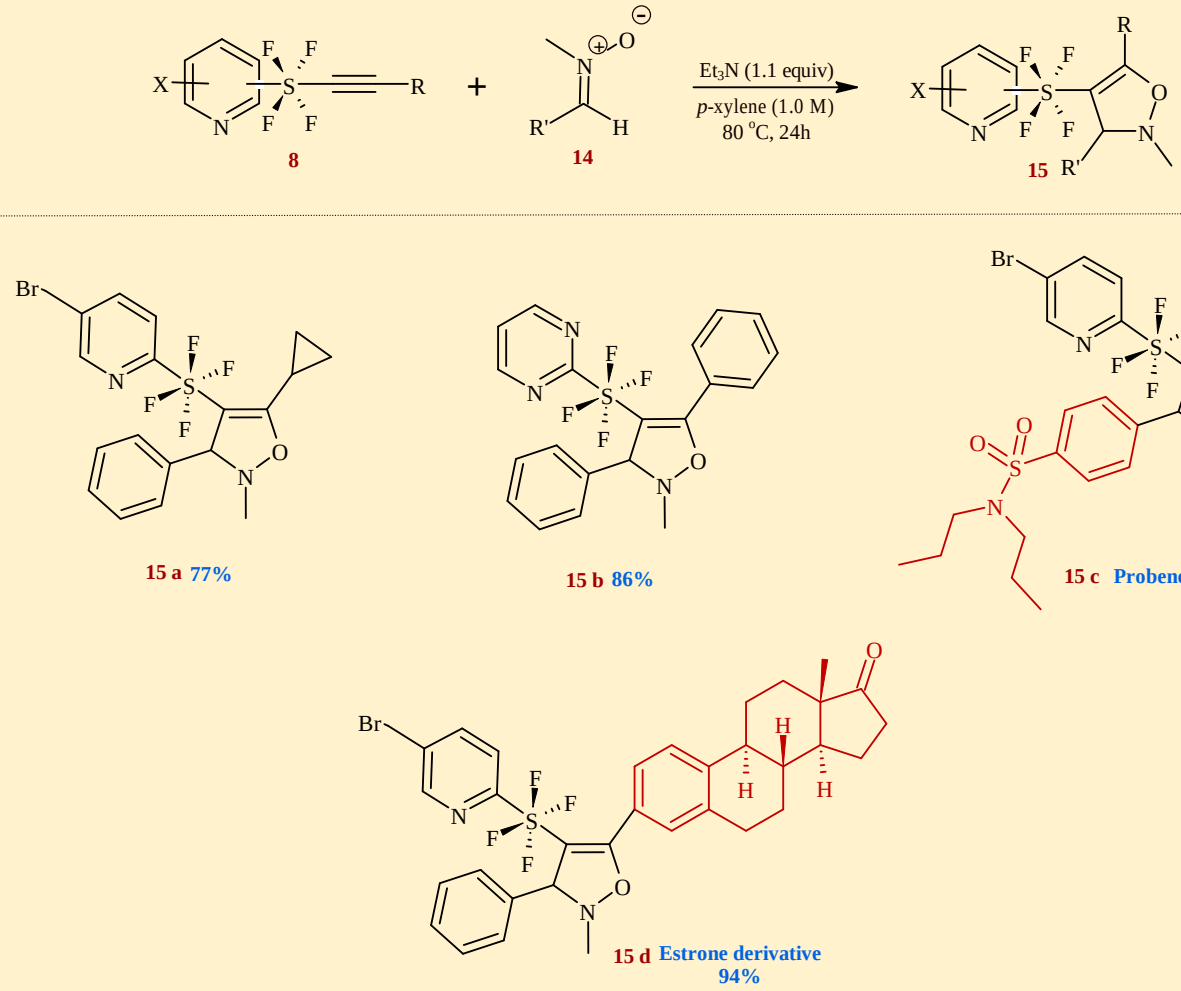
Notably, the synthesis of aryl and heteroaryl tetrafluoro-λ^6-sulfanyl chlorides (Ar-SF_4Cl) **13** can be obtained from diaryl disulfides **11** using trichloroisocyanuric acid (TCCA) **12** and potassium fluoride in acetonitrile (Scheme 3).[12]



Scheme 3. Synthesis of aryl and heteroaryl tetrafluoro-λ^6-sulfanyl chlorides.

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1

To further advance the library of SF_4-linked heterocycles, the pyridine-SF_4-isoxazolines **15** were prepared *via* the regioselective 1,3-dipolar cycloaddition of pyridine-SF_4-alkynes **8** and nitrones **14** in the presence of triethylamine (Scheme 4).[14]



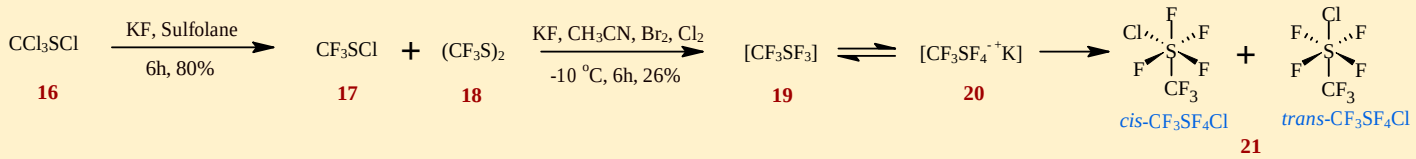
Scheme 4. Synthesis of pyridine-SF_4-isoxazolines.

2.3. Synthesis of CF_3SF_4-Cl

The reduction of the energy required for desolvation and support dipolar interactions by polar hydrophobic groups, which are characterized by large lipophilicity increments (Π) along with high Hammett substituent parameters (σ_p), can harmonize the biological activity.[9] The SF_4-containing functional groups can have steric and electronic effects on molecules. For example, the CF_3SF_4 group has a large Connolly volume,

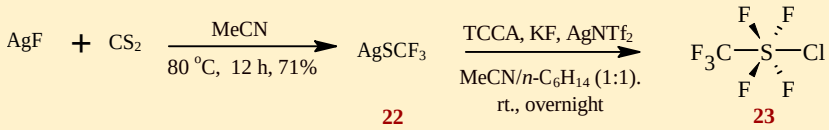
BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1

138.93 Å^3,[9,15] and surface area, 156.76 Å^2,[9,15] compared to pentafluoro-λ^6-sulfanyl (SF_5) groups. The experimentally determined lipophilicity partition coefficient of the CF_3SF_4 is estimated to be 2.13 (Π_p),[9,15] which is remarkably higher than that of the SF_5 group (1.23),[9,15] making the CF_3SF_4 moiety one of the most hydrophobic groups known. The Hammett substituent parameter, (σ_p), of the CF_3SF_4 and SF_5 is 0.68.[9] However, regardless the magnitude of the electron withdrawing influence of either group, polarization has a strong influence on reactivity. Thus, the strong electron-withdrawing effect of the CF_3SF_4 moiety in combination with steric effects strongly influences the reactivity of any molecule into which it is substituted. In view of the remarkable polar hydrophobicity of CF_3SF_4 moiety, Welch and co-workers, reported a two-step synthetic procedure for CF_3SF_4Cl based on a scalable oxidative chlorofluorination of a mixture of **17** and **18**, prepared from commercially available perchloromethyl mercaptan **16** (Scheme 5).[9]



Scheme 5. Synthesis of CF_3SF_4Cl.

In addition, Qing and coworkers reported a silver-promoted synthesis of *trans*-CF_3SF_4Cl under safe gas-reagent free conditions.[13] The procedure employed silver trifluoromethanethiolate **22** as a substrate, in the presence of trichloroisocyanuric acid, potassium fluoride, and silver(I) bis(trifluoromethanesulfonyl)imide ($AgNTf_2$) in *n*-hexane/CH_3CN, yielding the *trans*-CF_3SF_4Cl **23** (Scheme 6).[13]



Scheme 6. Silver-mediated synthesis of *trans*-CF_3SF_4Cl under safe gas-reagent free.

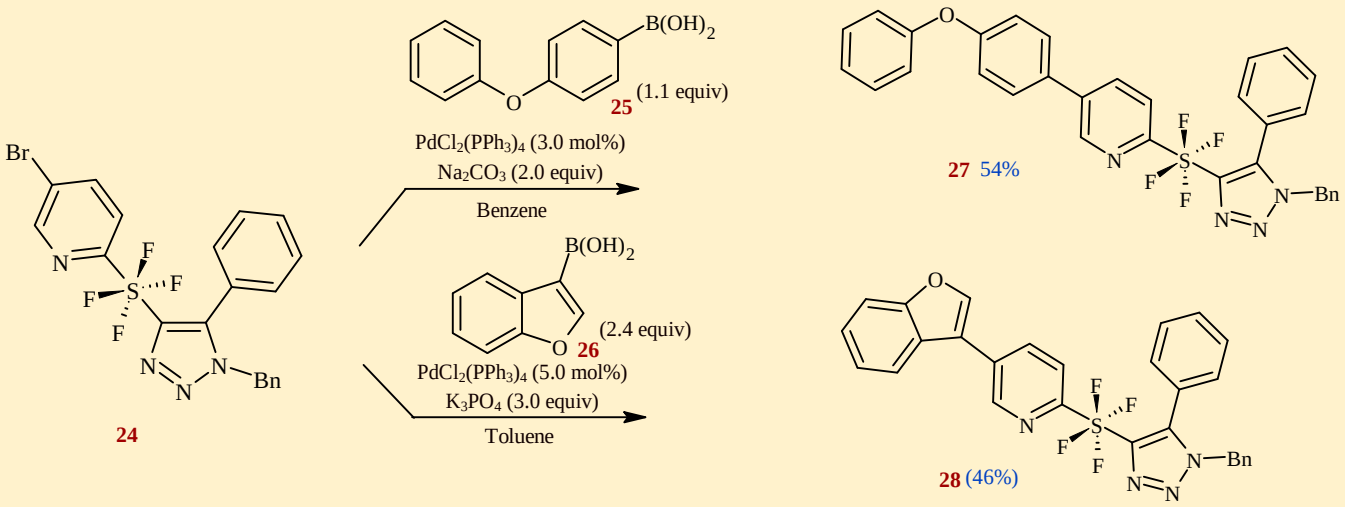
3. Applications of SF_4-moiety

The strategic incorporation of F atoms into organic molecules significantly modulates their physical, chemical, and biological properties, and depends on the ability to introduce the F atoms at appropriate positions of the molecules. Indeed, various fluorination reagents have been designed to achieve such a goal, including, the radical fluorinating agents and others. In contrast to these reagents, the potential of SF_4-containing molecules with the combination of strong electron negativity and high lipophilicity induced by four F atoms with a hypervalent sulfur atom leads to unique properties of the SF_4 moiety. In fact, the amphoteric nature of SF_4

group leads to its abundant Lewis acidic and basic reactivities, which can form adducts with molecules *via* a variety of interaction motifs.

3.1. Reactivity of trans-SF_4 containing heterocyclic molecules

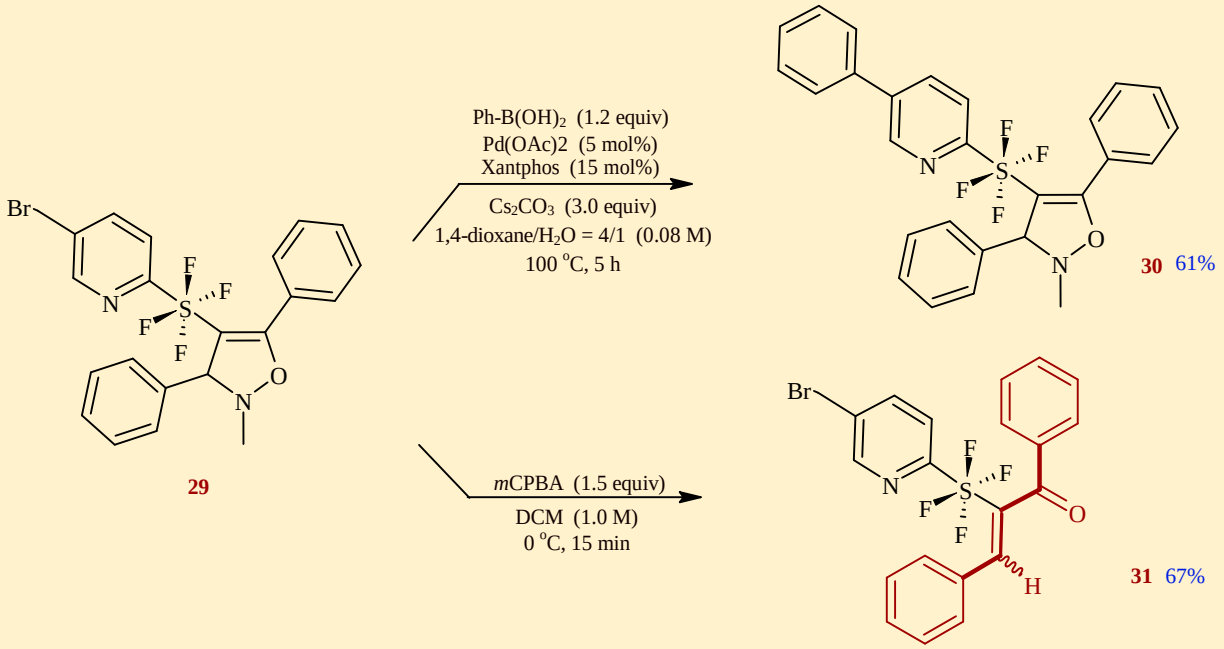
The *trans*-SF_4 linked pyridine and triazole derivatives underwent Suzuki coupling *via* the bromo-substituent on pyridine. The fluorinated heterocyclic compound **24** reacted with boronic acid derivatives to provide the corresponding coupled products (Scheme 7).[5]



Scheme 7. Coupling of fluorinated heterocyclic compound containing SF_4 moiety **24** with both of aromatic substrates, phenoxyphenyl boronic acids **25**, and heteroaromatic substrates, benzofuran boronic acids **26**.[5]

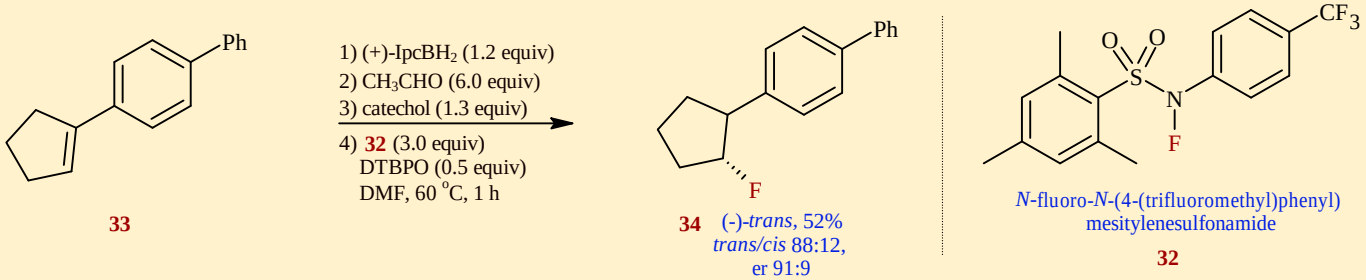
Moreover, a remarkable application of Suzuki-Miyaura coupling at the C−Br bond of the pyridine ring in pyridine-SF_4-isoxazolines **29** was achieve with phenylboronic acid (1.2 equiv) in 1,4-dioxane/water (4/1) in the presence of palladium acetate (5 mol %), Xantphos (15 mol %), and cesium carbonate (3.0 equiv) at 100 °C for 5 h, affording the coupling product **30** in 61% yield. The ring-opening reaction of **29** using *m*-chloroperoxybenzoic acid (*m*CPBA) furnished biologically attractive pyridine−SF_4-functionalized chalcone **31** in 67% yield (Scheme 8).[14]

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1



Scheme 8. Coupling of pyridine-SF_4-isoxazolines **29** with phenylboronic acid, and their ring-opening reaction.

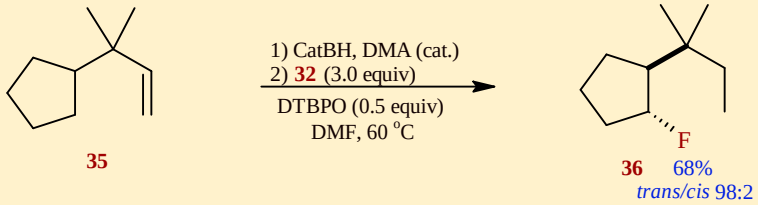
In the context of radical fluorinating reagents, The *N*-fluoro-*N*-(4-(trifluoromethyl)phenyl)mesitylenesulfonamides **32** are employed for the catecholborane-mediated enantioselective hydrofluorination of alkenes **33** in a one-pot procedure, involving a hydroboration of alkene using (+)-isopinocampheylborane ((+)-$IpcBH_2$), conversion to the diethyl boronate, transesterification to the *B*-alkylcatecholborane and a final radical fluorination, affording the fluoride **34** in 52% yield and 91:9 enantiomeric ratio (Scheme 9).[16]



Scheme 9. Synthesis of the enantioenriched (-)-*trans*-fluoride **34** from alkene **33**. DTBPO, di-*tert*-butyl peroxalate, acts as a radical initiator and can easily be prepared *via* reacting oxalyl chloride with *tert*-butyl hydroperoxide in the presence of pyridine in DMF.[16]

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1

Moreover, the radical hydrofluorination process can be achieved with suitable substrates for efficient remote fluorination *via* 1,5-hydrogen atom transfer. The hydrofluorination of terminal alkene **35** provided the fluoride **36** in 68% yield with an excellent *trans* diastereoselectivity (*trans/cis* 98:2) (Scheme 10).[16] This process is attributed to the lower nucleophilicity of primary alkyl radical, which slows the direct fluorination and favors the abstraction processes of hydrogen atom, leading to remote fluorination of unactivated C–H bonds.[16]



Scheme 10. Hydrofluorination of terminal alkenes.

3.2. *Reactivity of trans-SF_4-alkynes molecules*

In fact, the *trans*-SF_4-alkynes with heteroaryl groups are featured by enhanced stability to SF_4-molecules, leading to the construction of a variety of SF_4-linked compounds. In addition, they show outstanding reactivity toward electron-rich species, due to their highly electron-deficient nature in alkyne moiety, and their linear connection with a length of 6.23 Å would make them an alternative bioisostere than the *p*-benzene system (Figure 2).[8]

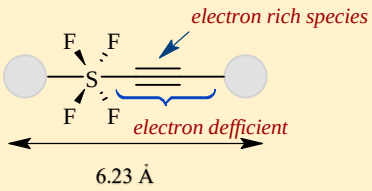
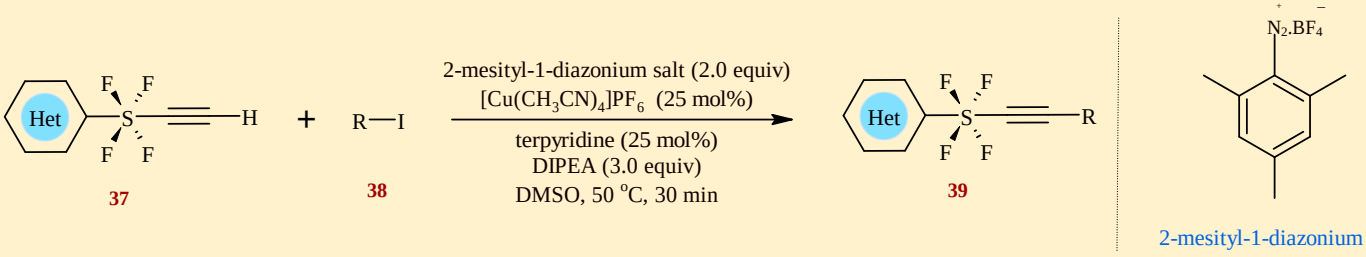


Figure 2. Structure and properties of *trans*-SF_4-alkynes.[8]

In view of these features, a Sonogashira-type cross-coupling reaction between electron-deficient SF_4-attached alkynes **37** and alkyl iodides **38** was achieved under mild conditions (Liang's conditions), affording the desired products **39** in excellent yields (Scheme 11).[8] The reaction demonstrated its versatility by accepting a diverse range of coupling partners, including pyridine/pyrimidine-SF_4-alkyne compounds; some of perfluorinated alkyl groups, and late-stage $C_{sp\text{-}sp^3}$ coupling of biologically relevant molecules as examples of bioisosteres of linear

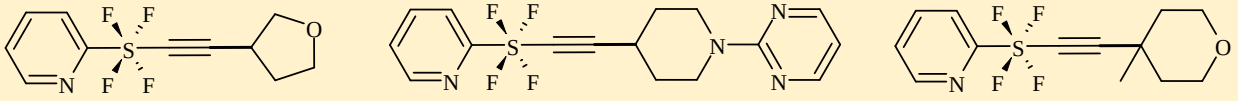
molecules. Scheme 11 depicts some of these coupling partners and the proposed mechanism. The reaction proceeds *via* a radical pathway mediated by an aryl diazonium salt and Cu catalysis, which undergoes oxidative addition of the aryl radical to Cu(II) alkyne complex, followed by reductive elimination.



37 **38** **39**

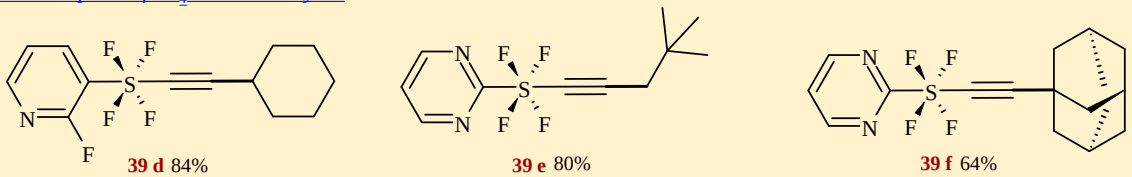
2-mesityl-1-diazonium salt

Diverse rang of alkyl iododes



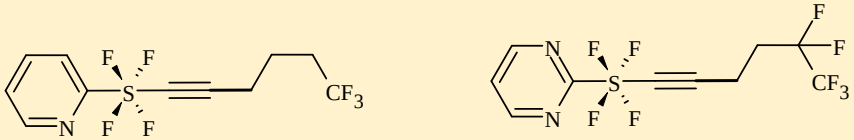
39 a 88% **39 b** 75% **39 c** 35%

Heteroaromatic parts of SF_4-terminal alkynes



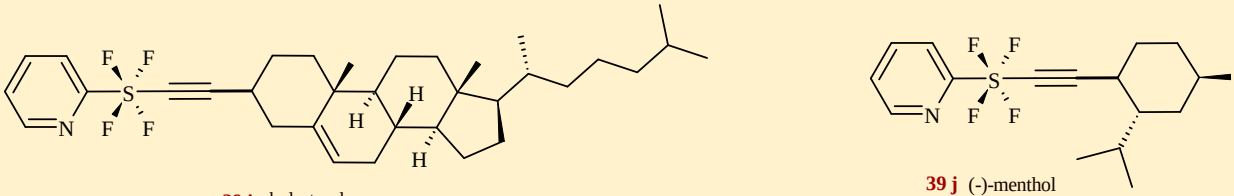
39 d 84% **39 e** 80% **39 f** 64%

Perfluorinated alkyl iodides



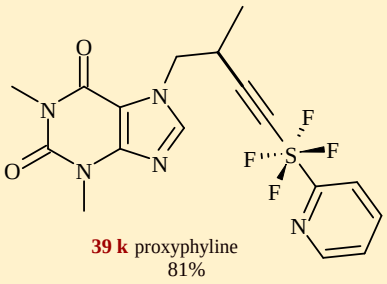
39 g 84% **39 h** 63%

Late-stage cross-coupling reactions of biologically attrective molecules

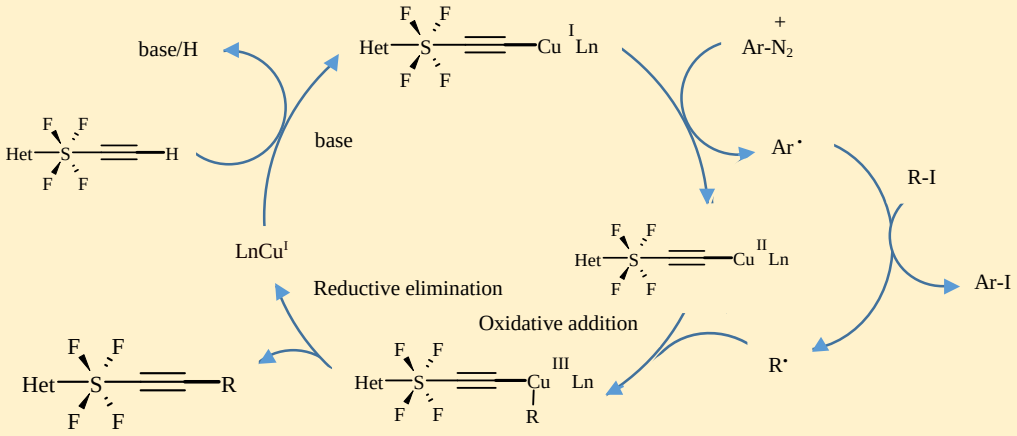


39 i cholesterol
60%; dr = 1:2

39 j (-)-menthol
70%; dr = 1:4.3



Proposed mechanism

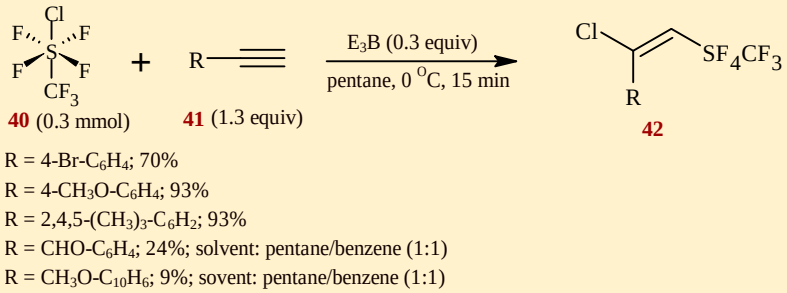


Scheme 11. Sonogashira-type cross-coupling reaction between electron-deficient SF_4-attached alkynes and alkyl iodides.

3.3. Reactivity of trifluoromethyl tetrafluoro-λ⁶-sulfanes

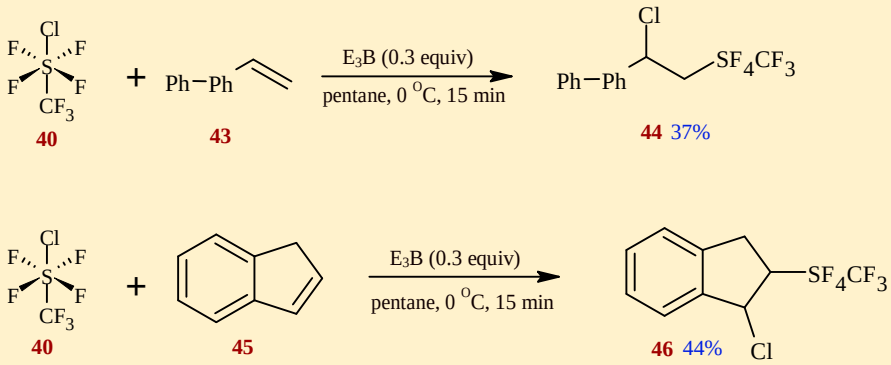
In non-polar solvents, triethylborane (Et_3B)-mediated the addition reactions of *trans*-CF_3SF_4Cl to alkenes and alkynes in pentane, affording a wide range of functionalized unsaturated compounds (Scheme 12).[9] In cases where solubility was limiting, the addition of benzene as cosolvent allowed the reaction to proceed, but with a low yield.[9]

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1



Scheme 12. Triethylborane promoted the addition of *trans*-CF_3SF_4Cl to alkynes.

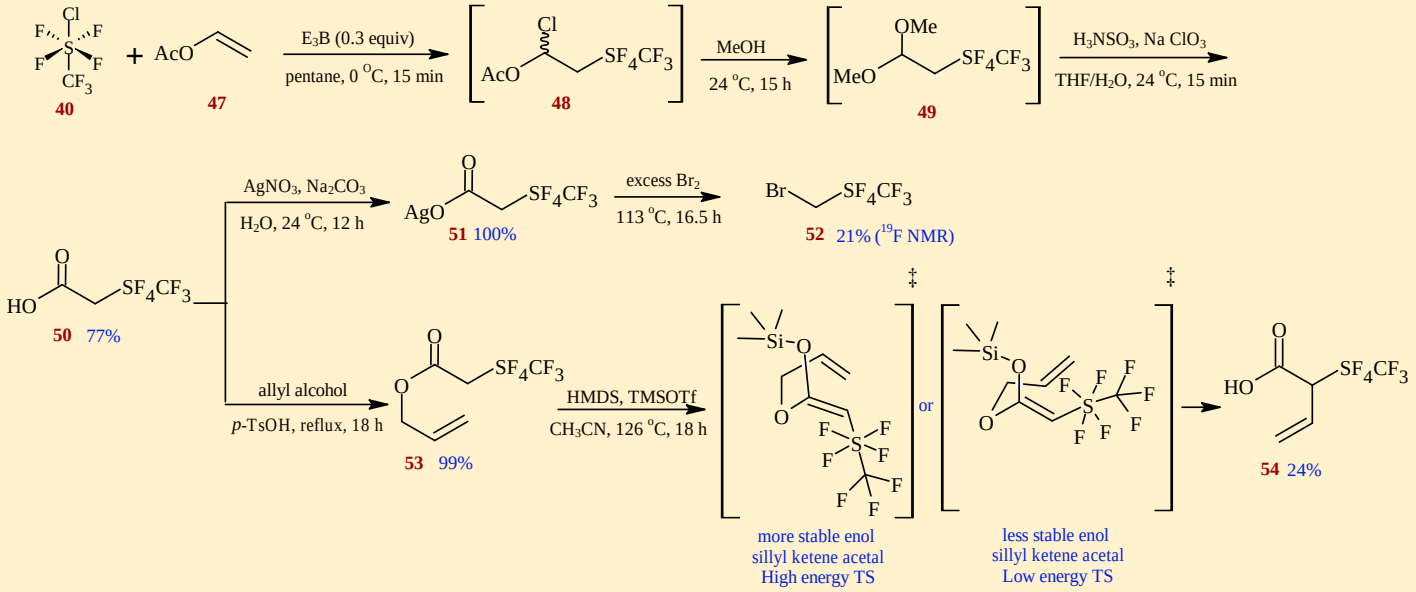
Under the same reaction conditions, the *trans*-CF_3SF_4Cl **40** was less productive for addition to internal alkenes than to terminal alkenes. Indeed, the addition to biphenylethene **43** yielded smoothly a crystalline product **44** in 37% yield (scheme 13).[9] As a special case, indene **45** reacted readily to afford product **46** in 44% yield (Scheme 13).[9]



Scheme 13. The addition of *trans*-CF_3SF_4Cl to alkynes.

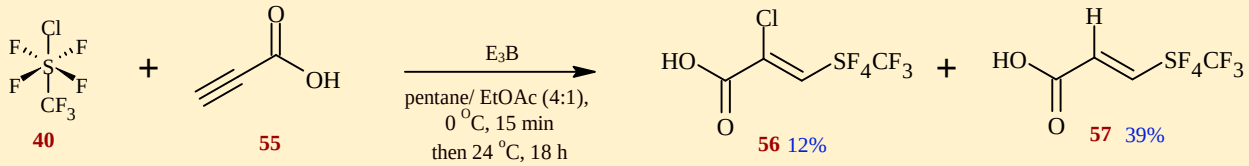
In further transformations of the CF_3SF_4 adducts, the CF_3SF_4 group is stable toward a wide range of reagents, such as bases, oxidants, reductants, acids and temperatures up to at least 125 °C. For example, the dimethyl acetal **49** was obtained from the formed adduct **48**, prepared from addition of *trans*-CF_3SF_4Cl **40** to vinyl acetate **47**, acted as a precursor to carboxylic acid **50**. Hunsdiecker decarboxylation of **51** furnished the useful CF_3SF_4-bromomethane **52** in 21% yield (^{19}F NMR), while esterification of **50** afforded allyl ester **53** in 99% yield. The Ireland-Claisen rearrangement of **53** was achieved by treatment with HMDS and TMSOTf in acetonitrile for 18 h at 126 ºC, affording **54** in 24% yield (Scheme 14).[9]

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1



Scheme 14. Transformations of vinyl acetate adducts.

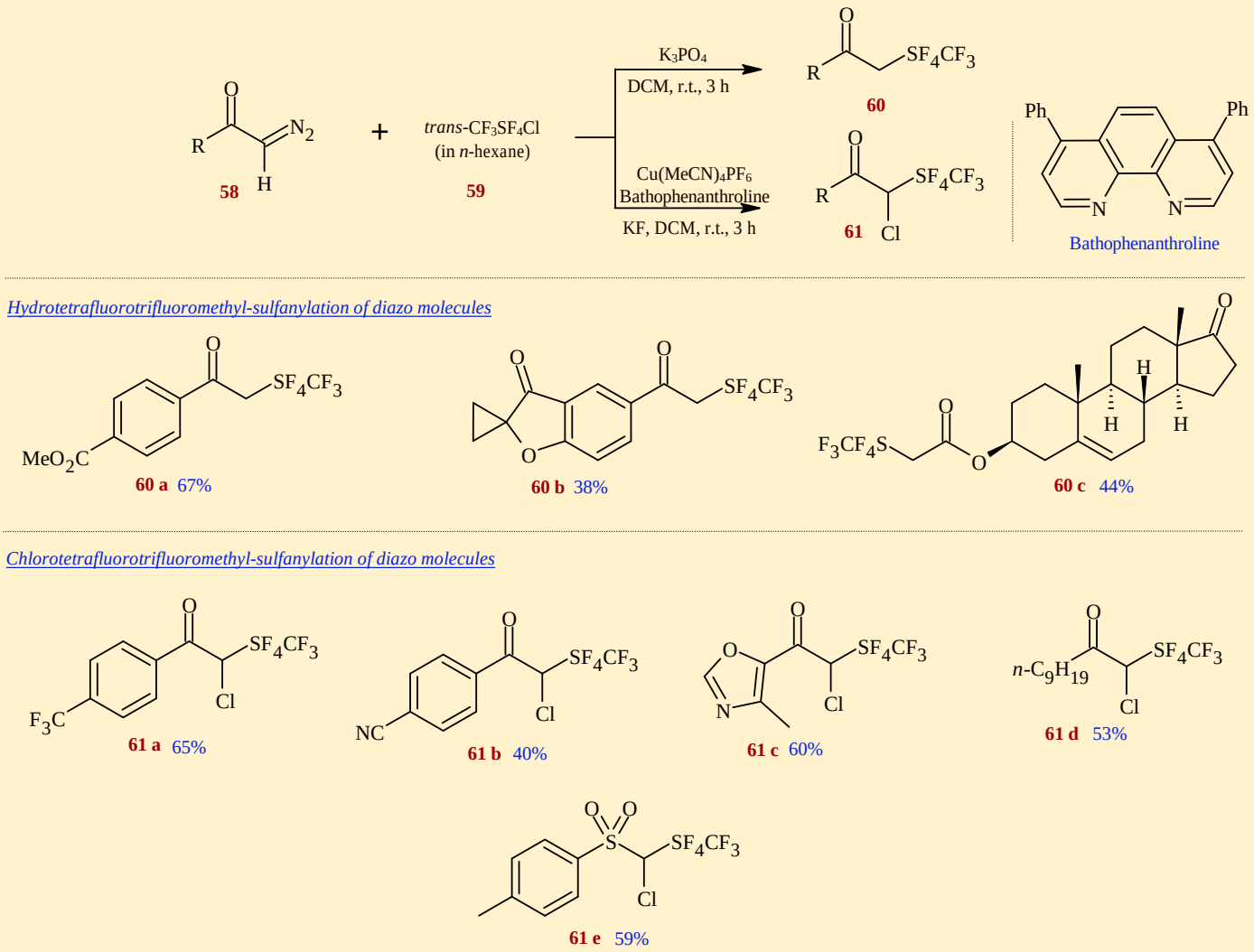
Solvent polarity constitutes an important factor in product formation, with non-polar solvents favoring radical additions, while polar solvents promote ionic addition.[9,17,18] In a more polar solvent system, 20% ethyl acetate and pentane in a 1:4 ratio, the *trans*-CF_3SF_4Cl **40** reacted with propynoic acid **55** to afford both **56** and **57** in 12% and 39% yield, respectively (Scheme 15).[9]



Scheme 15. The adducts with propynoic acid.

The trifluoromethyl tetrafluorosulfanylation of α-diazo carbonyl compounds was also demonstrated. In the presence of potassium phosphate, the hydrotetrafluorotrifluoromethyl-sulfanylation of diazo compounds was obtained in DCM at room temperature (Scheme 16),[13] while in the presence of tetrakis(acetonitrile)copper(I) hexafluorophosphate ($Cu(MeCN)_4PF_6$) as a catalyst, bathophenanthroline, and potassium fluoride as a base, the chlorotetrafluorotrifluoro-methylsulfanylations of diazo compounds was obtained in DCM at room temperature (Scheme 16).[13]

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1



Scheme 16. Hydro- and chloro-tetrafluorotrifluoromethyl-sulfanylation of diazo compounds.

3.4. The utility of trans-SF_4 moiety as a linear linker of bioactive compounds

The linkers in bioactive compounds are important structural constituents that connect different parts of the molecules, whose properties, including length, polarity, and rigidity, influence the target engagement, degradation and cell toxicity. Furthermore, the nature of the linker influences the sensitivity of binding to the surface area of the hydrophobic moiety, presumably through its influence in positioning the moiety in the binding pocket of the enzyme.[19]

On the other hand, the incorporation of fluorine atom into bioactive compounds is characterized by a peculiar combination of polarity and non-polarizability (hardness); this imbues fluorinated compounds with polar hydrophobicity, whereby desolvation of fluorinated surfaces and weak dipolar interactions in organized media drive molecular recognition.[20]

In view of the unique properties of *trans*-SF_4-alkynyl structure, such as a linear structure, high electronegativity, and hydrophobicity, Kagechika and co-workers investigated the applicability of *trans*-SF_4 moiety as a linear linker of retinoids.[21] Retinoids regulate a wide spectrum of cellular functions including cell differentiation, metabolic regulation, and inflammation. Retinoic acid (RA) signaling is one of the most important biological pathways in nature, triggered by RA interaction with nuclear receptors that control gene expression. The RA activity is mediated by members of the retinoic acid receptors (RARs) subfamily (RARα, RARβ, and RARγ), which belong to the nuclear receptor (NR) superfamily of transcription factors. RARs form heterodimers with members of the retinoid X receptors (RXRs) subfamily (RXRα, RXRβ, and RXRγ) and act as ligand-regulated transcription factors through binding specific RA response elements (RAREs) located in target genes promoters.[22]
Retinoids are a class of compounds composed of three regions: a hydrophobic, a central polyene, and a polar (usually a carboxylic acid) (Figure 3 a). Structural development of any of these elements is accompanied by change of the features of retinoid activity, such as ligand potency, receptor selectivity, and agonist/antagonist mode. There are three natural retinoids: *all trans*-RA (ATRA), 9-*cis*RA (alitretinoin), and 13-*cis*RA (isotretinoin) (Figure 3 b). Natural RA suffers from many limitations of its pharmacological use. However, synthetic analogs exhibit better administration, and have been modified to target-specific tissue and cells of interest.[23]
In their investigation: three different hydrophobic compounds of 4-[*trans*-tetrafluoro(arylethynyl)-λ^6-sulfanyl]benzoic acids linked with non-substituted phenyl **1A**, 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene **1B**, and 3,5-di-*t*-butylphenyl **1C**, were designed comparable to the structure of EC23 (an RAR-pan agonist) to evaluate the preferred size and shape of the hydrophobic component (Figure 3 c).[21]

The synthesis of these *trans*-SF_4-alkynyl derivatives was achieved *via* the radical addition of aryltetrafluorosulfanyl chloride and arylethyne, followed by elimination of hydrogen chloride. For instance, the synthesis of *trans*-SF_4-alkynyl derivative **1B** was accomplished *via* Sonogashira coupling reaction of 2-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene **62** with trimethylsilyl acetylene to provide **63**, followed by deprotection of trimethylsilyl group to furnish the arylethyne **64** (Scheme 17).[21] The methyl 4-(*trans*-chlorotetrafluoro-λ^6-sulfanyl)benzoate **68** was obtained from esterification of 4-thiolbenzoic acid **65**, followed by oxidation with iodine to afford disulfide **67**, and then, was reacted with chlorine gas in the presence of potassium fluoride. Radical addition of **64** and **68** afforded SF_4-alkenyl chlorides **69** using triethylborane as the radical initiator, followed by treatment with lithium hydroxide, and hydrolysis of the methyl ester furnished the target compound **1B**.

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1

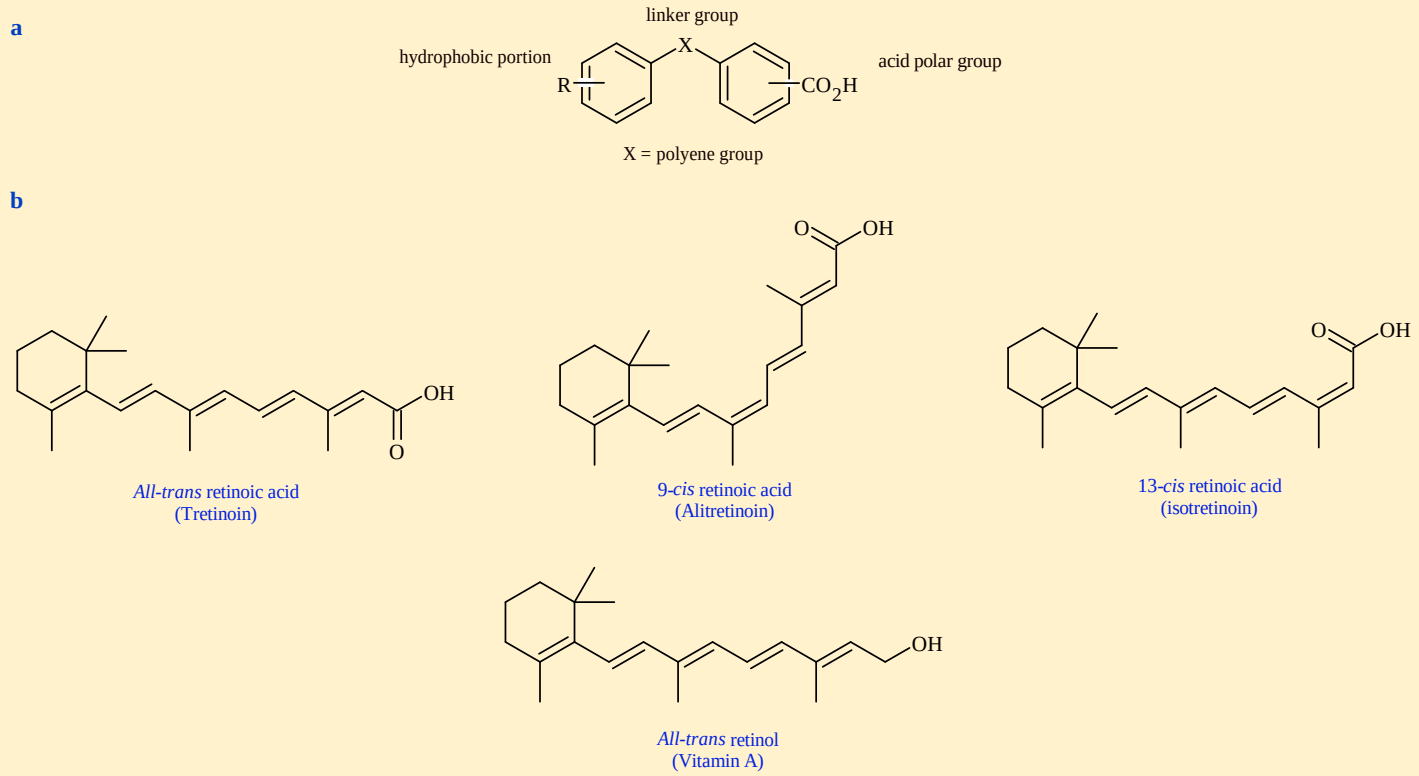
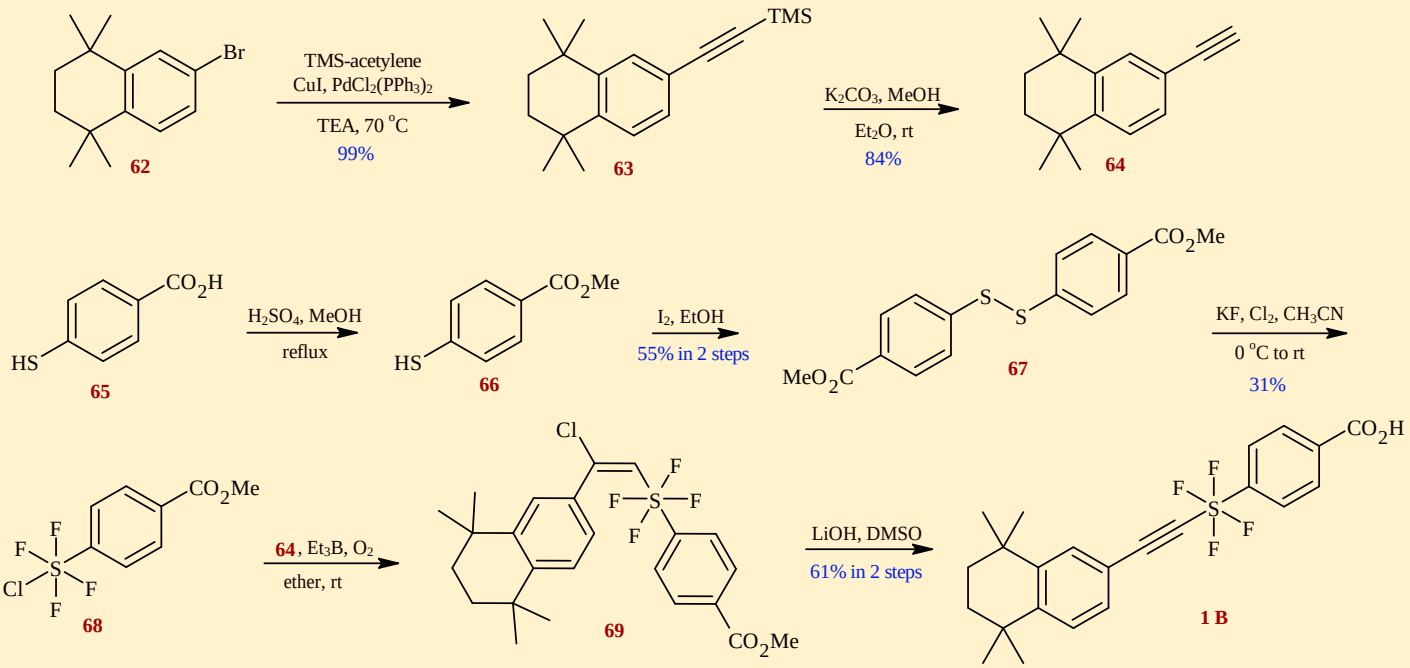


Figure 3. (a) General structure of synthetic retinoids. (b) Structures of natural retinoids, and *All-trans* retinol (Vitamin A). (c) Molecular design of retinoids containing *trans*-SF_4-alkynyl structure. Retinoic acid is the main biologically active metabolite of vitamin A. In human, the only source of vitamin A is obtained through diet, as lipophilic retinol or as carotenoids.[23]

BTL NEDERLAND
Insights
ISSN 2590-0811
December 2023 - April 2024 | volume 7 | number 1



Scheme 14. Synthesis of *trans*-SF_4-alkynyl derivative 1B.

Cell differentiation-inducing activity assay and reporter gene assay revealed that the *trans*-SF_4-alkynyl derivatives **1B** and **1C** exhibit antagonistic activity towards retinoid acid receptors (RARs). Docking studies indicated that the long linear linker alters the binding mode of the compounds with the RARα ligand-binding domain.

4. Conclusion and outlook

This highlight sheds the light on the recent advances in the synthetic methodologies of the SF_4-group and their implementation in various synthetic transformations towards the assembly of diverse alkenylations, alkynylations, and heteocyclizations, and their biological and organic product applications. The precursor for SF_4-functionalizations, Ar-SF_4Cl, can be generated from disulfides under oxidative chlorofluorination, or under gas-reagent free conditions mediated by silver catalyst for further transformations. Likewise, the CF_3SF_3Cl can be synthesized from perchloromethyl mercaptan under oxidative chlorofluorination, or from disulfides under gas-reagent free conditions mediated by silver catalyst. Taking advantages of the amphoteric nature of SF_4-group, a variety of readily adducts with molecules have been explored *via* various interaction motifs. The transformations are characterized by a remarkable polar hydrophobicity, which can harmonize the biological activity, and provide an alternative of conventional bioisosteres.

Despite the remarkable achievements in this field, there are still many issues that need to be addressed. It is anticipated that the synthetic methodologies and the applications of the functionalized SF_4-compounds will be continually developed, since only a few examples have been reported so far. The development of new functionalization linked to SF_4-moiety, that can enhance the reactivity of substituted molecules through their structural and electronic effects would be highly desirable. The discovery of new synthetic routes and reactivity of these compounds through sustainable processes based on flow chemistry would be an advantage. It is hoped that this highlight would stimulate new approaches toward further development and integration of SF_4-group in bioactive compounds.

5. References

1) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, Germany, **2013**.
2) S. Altomonte, M. Zanda, *J. Fluor. Chem.*, **2012**, *143*, 57-93.
3) M. Bassetto, S. Ferla, F. Pertusati, *Future Med. Chem.*, **2015**, *7*, 527-546.
4) D. B. Benney, D. Z. Denney, Y. F. Hsu, *J. Am. Chem. Soc.*, **1973**, *95*, 8191-8192.
5) P. Das, K. Niina, T. Hiromura, E. Tokunaga, N. Saitob, N. Shibata, *Chem. Sci.*, **2018**, *9*, 4931-4936.
6) Z. Zhang, X. Yang, Y. Zhao, F. Ye, L. Shang, *Adv. Mater.*, **2023**, *35*, 2300220.
7) R. Bychek, P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, **2022**, *61*, e202205103.
8) S. R. Narra, M. Z. Bacho, M. Hattori, N. Shibata, *Adv. Sci.*, **2023**, 2306554.
9) A. Ikeda, L. Zhong, P. R. Savoie, C. N. von Hahmann, W. Zheng, J. T. Welch, *Eur. J. Org. Chem.*, **2018**, *6*, 772-780.
10) L. Zhong, P. R. Savoie, A. S. Filatov, J. T. Welch, *Angew. Chem. Int. Ed.*, **2014**, 53, 526-529.
11) L. Zhong, A. S. Filatov, J. T. Welch, *J. Fluor. Chem.*, **2014**, *167*, 192-197.
12) I. Saidalimu, Y. Liang, K. Niina, K. Tanagawa, N. Saito, N. Shibata, *Org. Chem. Front.*, **2019**, *6*, 1157-1161.
13) X. Zhao, J.-Y. Shou, J. J. Newton, F.-L. Qing, *Org. Lett.*, **2022**, *24*, 8412-8416.
14) K. Maruno, K. Hada, Y. Sumii, O. Nagata, N. Shibata, *Org. Lett.*, **2022**, *24*, 3755-3759.
15) P. Kirsch, A. Hahn, *Eur. J. Org. Chem.*, **2006**, *2006*, 1125-1131.
16) D. Meyer, H. Jangra, F. Walther, H. Zipse, P. Renaud, *Nat. Commun.*, **2018**, *9*, 4888.
17) D. S. Lim, S. C. Ngo, S. G. Lal, K. E. Minnich, J. T. Welch, *Tetrahedron Lett.*, **2008**, *49*, 5662-5663.
18) W. R. Dolbier Jr, S. Ait-Mohand, T. D. Schertz, T. A. Sergeeva, J. A. Cradlebaugh, A. Mitani, G. L. Gard, R. W. Winter, J. S. Thrasher, *J. Fluorine Chem.*, **2006**, *127*, 1302-1310.
19) I. Gao, S. Qiao, G. M. Whitesides, *J. Med. Chem.*, **1995**, *38*, 2292-2301.
20) J. C. Biffinger, H. W. Kim, S. G. DiMagno, *ChemBioChem*, **2004**, *5*, 622-627.
21) S. Mori, N. Tsuemoto, E. Kawachi, C. Takubo, A. Tanatani,H. Kagechika, *Tetrahedron*, **2022**, *123*, 132967.
22) A. di Masi, L. Leboffe, E. De Marinis, F. Pagano, L. Cicconi, C. Rochette-Egly, F. Lo-Coco, P. Ascenzi, C. Nervi, *Mol. Aspects. Med.*, **2015**, *41*, 1-115.
23) R. Ferreira, J. Napoli, T. Enver, L. Bernardino, L. Ferreira, *Nat. Commun.*, **2020**, *11*, 4265.