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Sulfenylcarbenes and sulfenylnitrenes in organic synthesis

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Sulfenylcarbenes and sulfenylnitrenes are ambiphilic intermediates possessing an unoxidized sulfur atom adjacent to their reactive center. Their unique properties and tunable reactivity make them a model species for studying carbenes and nitrenes in cycloaddition reactions, atom incorporation, late-stage functionalizations, among other applications. They have gained significant attention recently and hold considerable promise for novel reaction development and discovery. Herein, we analyze the chemistry of sulfenylcarbenes and sulfenylnitrenes, emphasizing their generation and applications in contemporary organic synthesis.

Key learning points

1. Sulfur: a sustainable alternative to precious metal catalysis.
2. Metallomimetic sulfur stabilizes carbenes and nitrenes, tuning their electronic properties for chemoselective transformations.
3. Bond lengths and angles in singlet and triplet states of carbenes and nitrenes.
4. Design, development, and synthesis of several generations of sulfenyl-carbene/-nitrene precursors and their activation.
5. Drugs from drugs: late-stage skeletal editing using single carbon and nitrogen atom insertion facilitated by carbenes and nitrenes.

1. Introduction

Carbenes and nitrenes are neutral, electron-deficient intermediates that have become prominent in modern synthetic organic chemistry.[1–3] Carbenes/nitrenes are primarily classified into two types based on their electronic spin states: singlet and triplet (Fig. 1a).[3] Singlets feature a vacant p-orbital and two paired electrons in a sp^2 orbital, whereas triplets have two unpaired electrons in separate p-orbitals with parallel spins.[3–5] Specifically, singlet carbenes and nitrenes possess an empty electrophilic frontier molecular orbital and a nucleophilic lone pair of electrons.[4,5] This makes singlet carbenes/nitrenes ambiphilic reactive chemical species that can behave as both a nucleophile and electrophile, either simultaneously or sequentially.[6] However, triplet carbenes/nitrenes show diradical reactivity because they possess two unpaired electrons.[7,8]

Although carbenes and nitrenes are transient intermediates,[9–11] their reactivity and spin states are generally modulated through coordination with transition metals or *via* heteroatom substitution at the reactive center (Fig. 1b).[3,12–18] The most common transition metal carbenes/nitrenes include iron, copper, rhodium, ruthenium, silver, and gold.[3,12,19–23] Due to their versatile reactivity, carbenes and nitrenes have become indispensable tools in the synthetic chemist's toolbox, enabling C–H functionalization,[22,24] alkene metathesis,[25,26] skeletal editing,[18,27] and more.[28]

Carbenes and nitrenes stabilized by one or more adjacent unoxidized sulfur atoms are referred to as "sulfenylcarbenes" and "sulfenylnitrenes" respectively (Fig. 1b).[14,29,30] These carbenes and nitrenes are significantly unique from classical carbenes[31] and nitrenes[32] due to molecular orbital interactions between sulfur and the reactive center. Specifically, sulfenylcarbenes/nitrenes exhibit a ylide-like resonance structure resulting from a conjugate donation from sulfur's populated d-orbital into the carbene/nitrene empty p-orbital.[18,27,33] This causes sulfenylcarbenes/nitrenes to be less electrophilic than their classical counterparts.[34,35] Furthermore, this heteroatom substitution causes explicit symmetry breaking and non-degeneracy within the frontier molecular orbitals.[33] Because of this, sulfenylcarbenes/nitrenes are generally ground-state singlets (although the spin state of any given carbene/nitrene may depend on other substituents as well).[18,27,29,35] These factors combine to make sulfenylcarbenes and sulfenylnitrenes representative or even model systems for studying carbenes and nitrenes. Heteroatom substitution attenuates their reactivity, making their behavior more predictable than methylene or imidogen while avoiding the complexity introduced by metal–carbene/nitrene species.

Recently, our group has been engaged in exploring novel transformations using sulfenylcarbenes/sulfenylnitrenes chemistry.[18,27]

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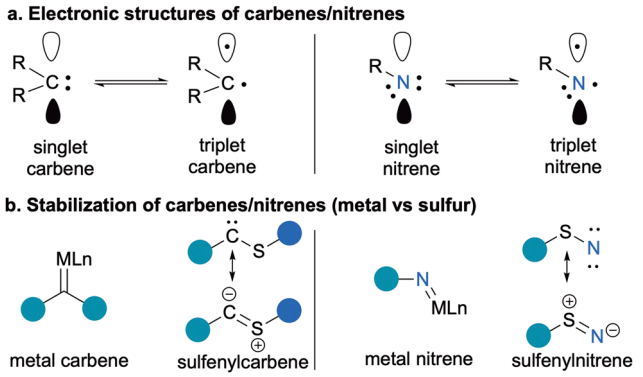

Fig. 1 Carbene and nitrene electronic structure.

Despite multiple reviews on metal carbenes/nitrenes[1,12,24,36] and heteroatom-stabilized nitrenes (*e.g.*, iodonitrenes),[37] no review has been published that focuses explicitly on the chemistry of sulfenylcarbenes and sulfenylnitrenes. Therefore, we are motivated to provide a tutorial review highlighting sulfenylcarbenes and sulfenylnitrenes and their emerging applications in organic synthesis.

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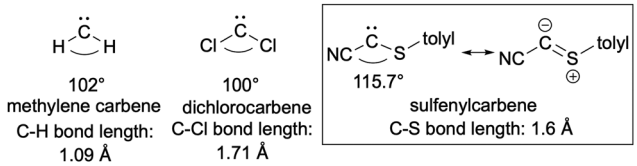

Fig. 2 Classical carbenes *versus* sulfenylcarbenes.

This tutorial review provides a comprehensive overview of the development and applications of sulfenylcarbenes and sulfenylnitrenes. We present representative examples illustrating various strategies for generating these reactive intermediates, emphasizing their use in cycloaddition reactions. Additionally, we highlight their utility in metal-free, late-stage atom incorporation. This review showcases how sulfur-based reactive species (sulfenylcarbenes and sulfenylnitrenes) can be leveraged to address common challenges in synthetic organic chemistry.

2. Sulfenylcarbenes

2.1. Introduction and origins

We will begin our discussion of sulfenylcarbenes by comparing their electronic structure, geometry, and reactivity to that of methylene and dichlorocarbene (Fig. 2).[38] The bond angle of ground state singlet methylene carbene is 102° with a C–H bond length of 1.09 Å, while the bond angle of singlet dichlorocarbene is in the range of 100° with a C–Cl bond length of 1.71 Å.[31,39] Furthermore, methylene and dichlorocarbene possess a triplet ground state.[31,39] By comparison, density functional theory (DFT) calculations indicated that cyano-sulfenylcarbene exists as a ground-state singlet with an S-C bond length of 1.6 Å and a bond angle of 115.7. Gas phase calculations on the cyano sulfenylcarbene by Sharma and coworkers revealed a 12.6 kcal mol^{-1} stabilization energy of the singlet carbene over the triplet carbene, which is in accordance with literature reported for similar carbenes.[27]

In early literature, the generation of sulfenylcarbenes is achieved by thermal decomposition of oxadiazole (**1**),[40]

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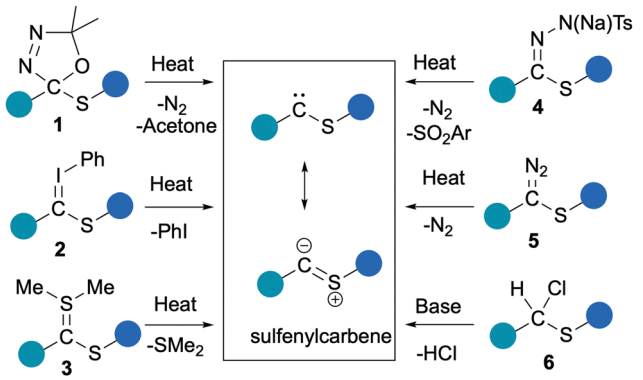


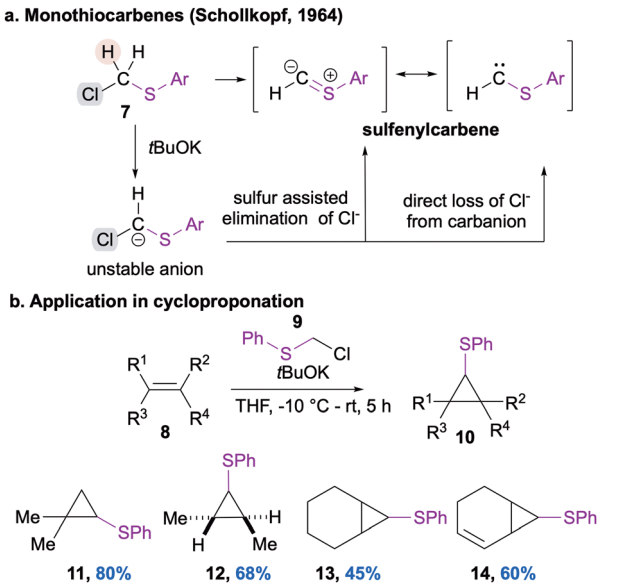
Fig. 3 Sulfenylcarbene precursors.

iodonium (**2**), and sulfonium (**3**) ylides (Fig. 3).[34] Like other carbenes, sulfenylcarbenes can also be accessed from corresponding hydrazones salts (**4**) and diazo-compounds (**5**) under thermal conditions.[41–43] The most common method for the generation of sulfenyl carbene is α-eliminations (predominantly as H–CI) from suitable precursors like **6**.[34]

Indeed, the first report of a sulfenylcarbene came early in 1964 from U. Schollkopf and coworkers (Scheme 1a).[29]

The reaction of chloromethyl arylsulfide (**7**) with base generates a highly unstable carbanion. Direct or sulfur-assisted α-elimination of chlorine from these unstable carbanions forms sulfenylcarbenes. These carbenes were trapped with alkenes to isolate stereospecific cyclopropanes *via* (2+1) cycloaddition. The reaction of sulfenylcarbene with various alkenes (**8**) in tetrahydrofuran yielded cyclopropanes (**10**) as the major product (Scheme 1b).

This basic sulfenylcarbene, also called monothiocarbene, shows stereospecific reactivity with various acyclic alkenes like isobutene, *trans*-2-butene, and cyclic alkenes like cyclohexene and cyclohexa-1,2-diene in moderate to good yields (**11–14**).



Scheme 1 First-generation sulfenylcarbenes.

This indicates that adding monothiocarbene to alkenes is likely concerted, as one might expect.

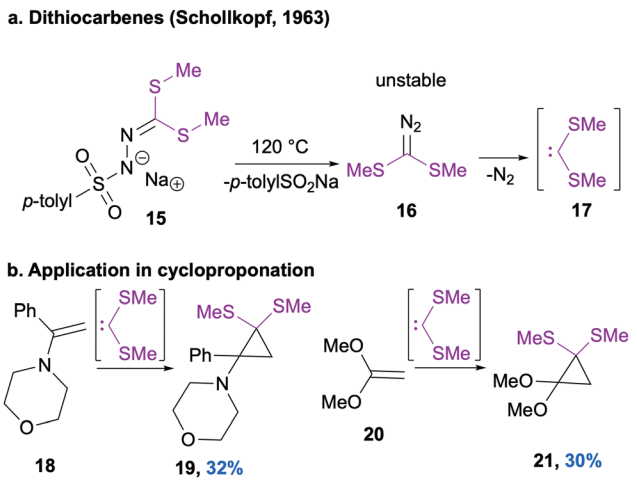
2.2. Thio sulfenylcarbenes/dithiocarbenes

The philicity of carbenes is determined by the substituents at the carbene center.[44] Generally, a carbene center possessing two donor substituents, such as oxygen or nitrogen, frequently exhibits nucleophilic properties, in contrast to the well-established electrophilic character of dihalocarbenes.[36,45] To understand the effect on carbene philicity of two sulfur substituents, we will first turn to another report from U. Schollkopf and co-workers in 1963 (Scheme 2a).[41] In this work, the generation of dithiocarbene was achieved under thermal conditions using hydrazone as a precursor. These sodium salts of hydrazones (**15**) generate diazo-compounds *in situ* at 120 °C. Diazo-compounds are highly unstable and subsequently decompose to release dithiocarbenes by liberating nitrogen gas. Dithiocarbenes are thus generated and undergo cyclopropanation with electron-rich alkenes like *N*-vinyl morpholine (**18**) and dimethoxyethylene (**20**) (Scheme 2b).

In late 1964, Lemal and coworkers also disclosed the generation of dithiocarbene from the sodium salt of hydrazones (Scheme 3a).[46] Cyclic and acyclic dithiocarbene hydrazone precursors were synthesized and thermally activated to generate carbenes. Acyclic sulfenylcarbenes were found to rapidly dimerize upon their generation, making it impossible to trap with alkenes, while cyclic carbene (**23**) was fragmented to form ethylene and carbon disulfide.

To further advance these research aims, Obata reported the generation of cyclic dithiocarbene (**25**) using the sodium salt of hydrazones in 1977 (Scheme 3b).[42] As in other reported literature, this sulfenylcarbene dimerized rapidly upon thermal or photochemical generation, making it unsuitable for synthetic transformations.

The transfer of a diazo group from sulfonyl azides to active methylene compounds is a well-established method for synthesizing diazo compounds.[47] However, methylene groups with low reactivity often require prior activation. In 1997, Benati and coworkers demonstrated the formation of cyclic dithiodiazo



Scheme 2 First-generation linear dithiocarbenes.

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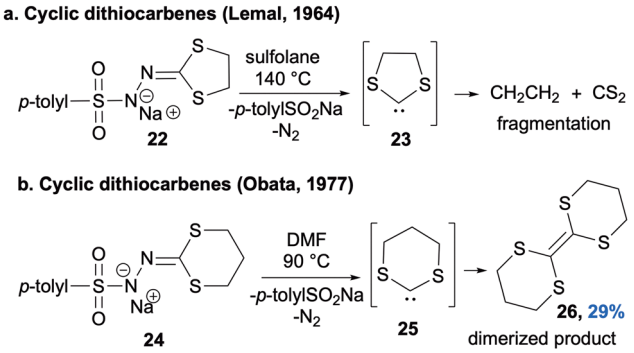
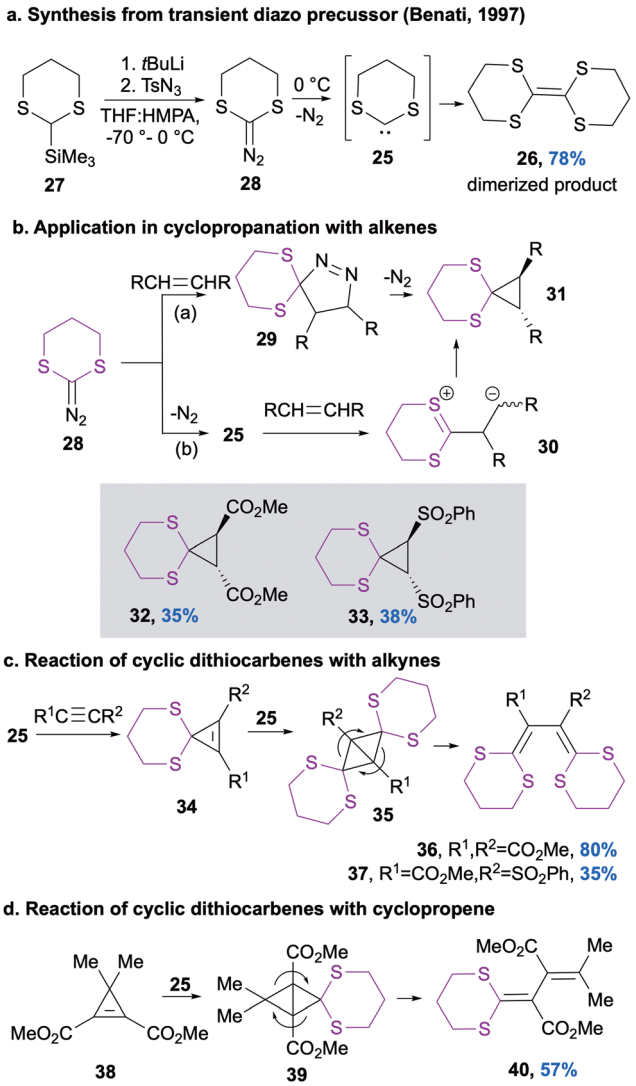


Scheme 3 First-generation cyclic dithiocarbenes.

through a diazo transfer reaction, utilizing trimethylsilane as an activator for the methylene center (Scheme 4a).[48] When compound **27** is treated with a strong base at cryogenic temperatures, a carbanion is formed, which reacts with tosyl azide to generate a transient diazo compound (**28**). When the reaction mixture was warmed to room temperature, this diazo compound (**28**) decomposes, releasing nitrogen to form sulfenylcarbene (**25**). The formation of carbene was confirmed by the isolation of the dimerized compound (**26**) as an exclusive product. Early attempts to trap these carbenes with alkenes/alkynes, including 3,4-dihydro-2*H*-pyran, 2-methylene-1,3-dithiane, diphenylacetylene, and methyl propiolate were unsuccessful with dimer by-product (**26**) being the exclusive product. However, these diazos (**28**) were found to react with strongly electrophilic *cis*/*trans* alkenes and alkynes to form non-stereospecific *trans*-cyclopropanes.



Scheme 4 Second-generation cyclic dithiocarbenes.

The non-stereospecific formation of cyclopropane with alkenes proceeds *via* two pathways. The first pathway involves a (3+2) cycloaddition, forming pyrazoline (**29**) as an intermediate (Scheme 4b). This intermediate then undergoes thermal fragmentation to yield cyclopropane **31**. An alternative pathway with the observed stereochemistry involves a stepwise reaction of singlet carbene (**25**) with alkenes, forming a zwitterionic intermediate (**30**). The scope of cyclopropanation is limited to reactions with dimethyl fumarate or dimethyl maleate and *cis*- or *trans*-1,2-bis(benzenesulfonyl)ethylene, which react with carbene (**25**) to form *trans*-cyclopropanes in 35% and 38% yield, respectively. Similarly, the trapping of carbene (**25**) with alkyne led to the formation of transient cyclopropene (**34**), which further reacts with carbene **25** to form strained bicyclo[1.1.0]butane (**35**) (Scheme 4c). The intermediate **35** undergoes ring-opening isomerization to form *cis*-diene. The process involves dimethyl acetylene dicarboxylate and 1-tosyl-2-(trimethylsilyl) acetylene, leading to corresponding bisthioacetals (**36**, **37**). This phenomenon was further supported by the reaction of cyclopropene (**38**) with carbene (**25**) to form ring-opened dithioacetal (**40**) as a major product (Scheme 4d).

In 1999, Rigby and coworkers disclosed the formation of dithiocarbene (**42**) from dithiooxadiazoline (**41**) under thermal conditions (Scheme 5a).[40] The formation of dimerized product (**43**) in the absence of trapping agent was taken as evidence for the formation of dithiocarbene **42**. These dithiocarbenes were applied in a (1+4) cycloaddition reaction with isocyanates to access 5-membered lactams (**47**) (Scheme 5b). The mechanism of the reaction involves the stepwise addition of carbenes to the isocyanates, followed by ring-closing to form intermediates **45**, **46**. The reaction of intermediate **46** with dithiocarbene **42** yielded the corresponding 5-membered lactam (**47**, **51–53**) as the major product. These products can also be obtained by N–H insertion followed by tautomerization of intermediate **46**.

This methodology was also utilized in synthesizing 6-membered lactams (**54–56**) when excess carbene precursors were used (Scheme 5c). The mechanism for forming 6-membered lactams was proposed *via* the reaction of intermediate **45** with sulfenylcarbene to generate intermediate **48**, which further cyclizes to form intermediate **49** (Scheme 5b). The slow tautomerization of intermediate **49** yields the corresponding lactam as a product. Rigby and coworkers proposed that, due to the slow tautomerization, the formation of the N–H insertion product was not observed at all in any of the substrates.

Later, in 2000, Rigby and coworkers published a full article utilizing this dithiocarbene (**42**) generated from dithiooxadiazoline

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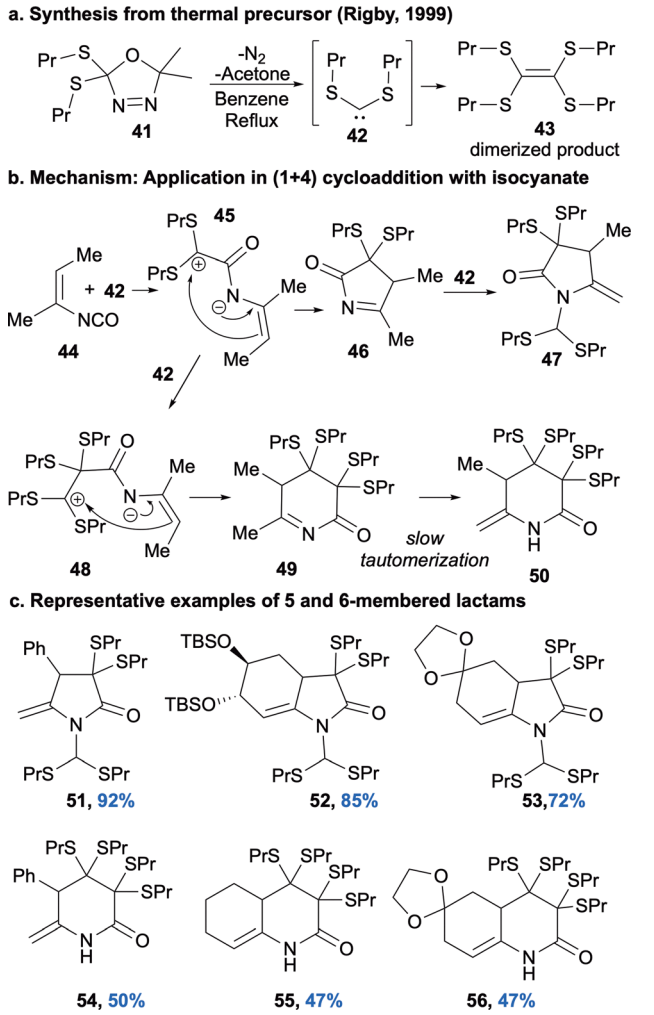


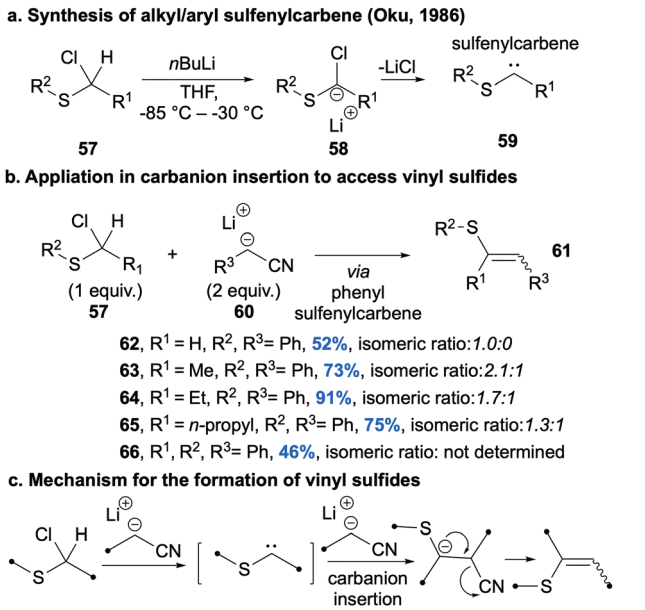
Scheme 5 Thermal generation/application of dithiocarbenes.

(**41**) under thermal conditions in cycloaddition reaction with *in situ* generated isocyanates from acyl azides.[49] The results obtained with acyl azides were similar to the direct use of isocyanates.

2.3. Alkyl/Aryl sulfenylcarbenes

In 1986, Oku and coworkers reported the synthesis of alkyl/aryl sulfenylcarbenes by α-eliminations (Scheme 6a).[50]

Treatment of sulfide halides (**57**) with a strong base generates carbanion (**58**), which then undergoes α-elimination to form sulfenylcarbene (**59**). These carbenes were then utilized in insertion reactions (Scheme 6b). Specifically, the insertion of a carbanion into these carbenes, followed by elimination, yields vinyl sulfides (**61**), which are useful synthetic intermediates.[51] This insertion reaction demonstrates compatibility with both aryl and alkyl sulfide halides, yielding the corresponding vinyl sulfides in moderate yield as mixtures of geometric isomers (**62–66**). In most cases, 2 equivalents of the anion (**60**) were used, as it also served as a base in the generation of the carbene. Oku and coworkers also performed detailed mechanistic studies to confirm the involvement of sulfenylcarbene in the formation of the product (Scheme 6c).



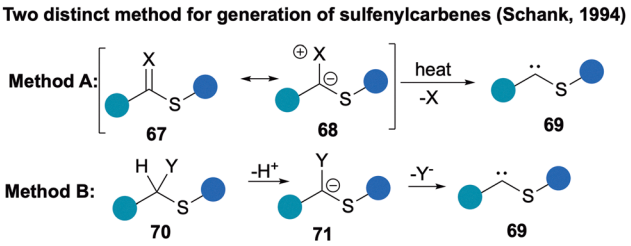
Scheme 6 Generation/application of aryl/alkyl sulfenylcarbenes.

2.4. Sulfonyl sulfenylcarbenes

In 1994, Schank and coworkers reported the synthesis of sulfonyl sulfenylcarbenes and their applications in cycloadditions.[34] They reported two distinct methods for the generation of sulfenylcarbenes (**69**): decomposition of ylides (**67**, **68**) (method A) and α-elimination from a suitable precursor (**70**, predominantly Y = Cl) (method B) (Scheme 7).

To generate sulfenylcarbene using method A, iodine (**72**) and sulfur (**73**, **74**) based ylides were synthesized from corresponding active methylene compounds (Scheme 8a). Compound **72** was found to decompose *in situ* at −10 °C, yielding diphenyl disulfide and volatile by-products. Thermal decomposition of sulfur-based ylide (**74**) in a boiling mixture (3 : 1, *cis* : *trans*) of dimethoxyethane (**75**) was found to give cyclopropane (**76**) and various other compounds determined by ^{1}H-NMR analysis (Scheme 8b).

Due to the accessibility and stability of these ylides, the application of these precursors was limited. To expand the scope of sulfonyl sulfenylcarbene, precursors capable of generating carbene *via* method B were synthesized from the corresponding active methylene compounds using a chlorinating reagent (Scheme 9). Carbene formation was observed when these precursors were introduced to an aqueous KOH solution in the presence of



Scheme 7 Schank's sulfenylcarbene generation strategies.

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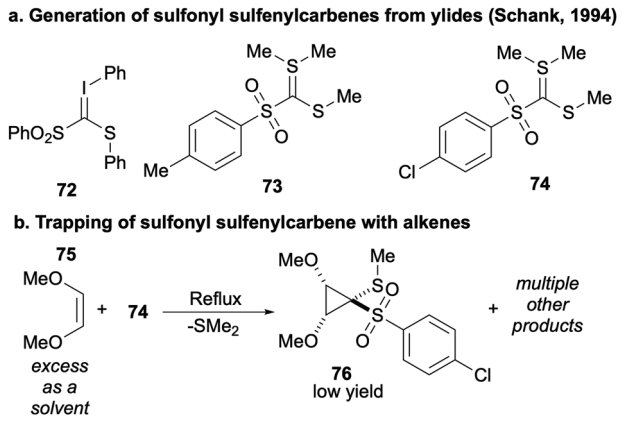
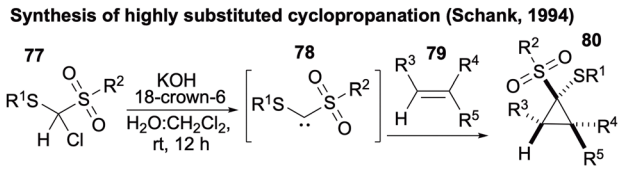


Scheme 8 Sulfonyl sulfenylcarbenes generation from ylides.

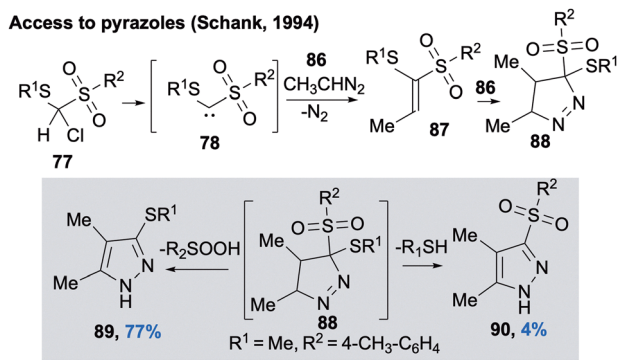


81, R^1 = Me, R^2 = 4-$CH_3C_6H_4$, R^3 = R^5 = H, R^4 = OMe, 77%
82, R^1 = Me, R^2 = 4-$CH_3C_6H_4$, R^3 = R^5 = H, R^4 = Ph, 50%
83, R^1 = R^2 = 4-$CH_3C_6H_4$, R^3 = R^5 = H, R^4 = Ph, 72%
84, R^1 = R^2 = 4-$CH_3C_6H_4$, R^3 = R^4 = OMe, R^5 = H, 56%
85, R^1 = R^2 = -(CH_2)-, R^3 = H, R^5 = R^4 = OMe, 70%

Scheme 9 Sulfonyl sulfenylcarbenes generation from α-elimination.

18-crown-6 at room temperature. These carbenes were successfully trapped with electron-rich olefins to access highly substituted cyclopropanes (**81–85**). This method was applied to the synthesis of a variety of aryl and alkyl-substituted carbene precursors and trapped with substituted olefins to access corresponding cyclopropanes. *Cis*- and *trans*-olefins were found to yield stereospecific cyclopropanes. The relative position of substituents in cyclopropanes was determined by ^{1}H-NMR and X-ray analysis.[34]

Finally, sulfonyl sulfenylcarbenes were found to react with excess diazoethane (**86**), facilitating access to pyrazoles (Scheme 10). The mechanism involves the cyclization of carbene (**78**) with diazoethane to form intermediate **87**, which further undergoes a (3+2) cycloaddition with diazoalkane to yield **88**. Intermediate **88** subsequently yields 77% of the pyrazole (**89**) containing a thioether group at the C-3 position through the loss of sulfenic acid. Similarly, a small amount of pyrazole (**90**) bearing a sulfonyl group at the C-3 position was also generated, attributed to the loss of thiol.

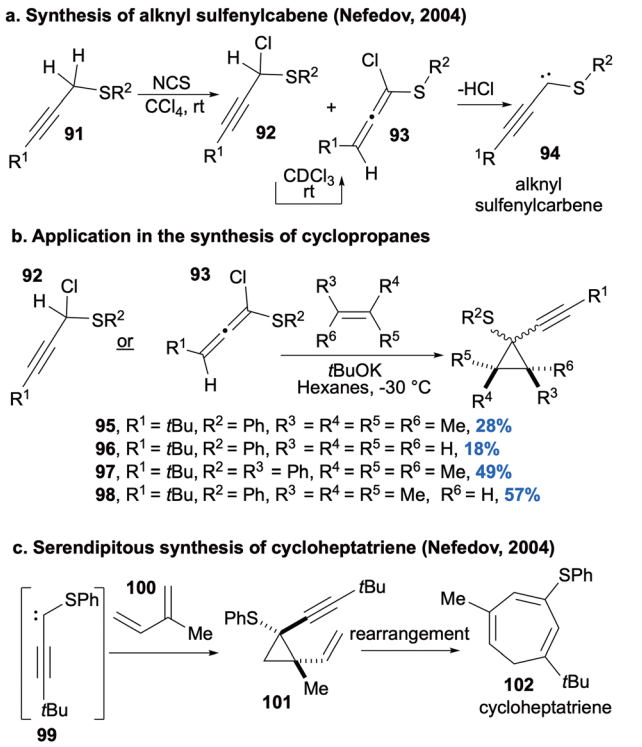


Scheme 10 Sulfonyl sulfenylcarbenes provide access to pyrazoles.

2.5. Alkynyl sulfenylcarbenes

In 2004, Nefedov and coworkers reported the synthesis of alkynyl sulfenylcarbene precursors by chlorinating corresponding active methylene compounds (**91**) (Scheme 11a).[52] Based on the substituent, acetylene-based (**92**) or allene (**93**) precursors were formed after chlorination, which were determined by ^{13}C NMR. Even though acetylene-based precursors were formed, these were found to isomerize to allene at ambient temperature. Upon subjecting these alkynyl sulfenylcarbene precursors to base, a carbanion is generated, which further undergoes α-elimination to form sulfenylcarbene (**94**). These carbenes were trapped with alkenes to synthesize highly functionalized cyclopropanes (Scheme 11b). Alkyl and aryl substituted carbene precursors were among the carbene precursors synthesized. These carbenes were successfully trapped with alkyl and aryl-substituted alkenes to obtain corresponding cyclopropanes in moderate yields (**95–98**).

To better understand the reactivity of alkynyl sulfenylcarbenes with dienes, these carbenes were trapped with *cis*-diene (**100**) (Scheme 11c). These sulfenylcarbenes selectively react with more substituted alkenes to yield two isomers of cyclopropane (**101**). While one isomer was stable enough to get isolated, the other underwent rearrangement to form cycloheptatriene (**102**). Although only a single diene substrate was used



Scheme 11 Alkynyl sulfenylcarbenes and their application.

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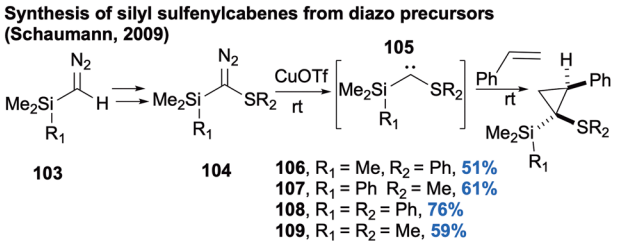
for the serendipitous synthesis of cycloheptatriene, this transformation holds significant potential for broader applications.

2.6. Silyl sulfenylcarbenes

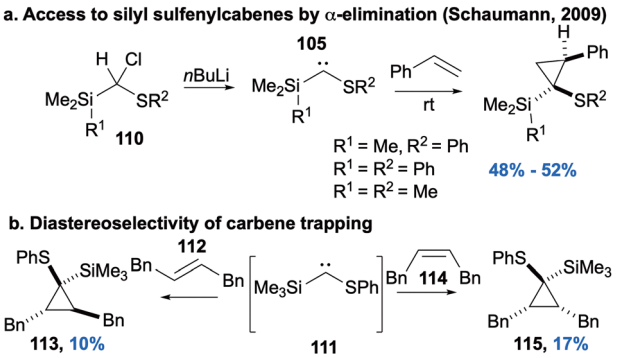
In 2009, Schaumann and coworkers reported the synthesis of diazo-based silyl sulfenylcarbene precursors (**104**) from corresponding silyl diazos (**103**) (Scheme 12).[43] These diazos were found to generate silyl sulfenylcarbene (**105**) by liberating N_2 in the presence of Cu(I)OTf. These carbenes were found to react with styrene to form cyclopropanes (**106–109**). Various silyl sulfenylcarbenes bearing alkyl/aryl thiols and silanes were successfully synthesized and trapped with styrene to yield cyclopropanes in moderate to good yield. However, these carbene precursors were utilized for cyclopropanation; these diazos were only stable in solution at room temperature.

Schaumann and coworkers also reported the alternative route for generating silyl sulfenylcarbene (Scheme 13a). Treating these precursors (**110**) with a strong base generates a carbanion, which then undergoes α-elimination to form sulfenylcarbenes. These carbenes were utilized in (2+1) cycloadditions to synthesize cyclopropanes. In this route, all these silyl sulfenylcarbenes (**105**) generated by α-elimination were also trapped by styrene to yield cyclopropanes in moderate yield.

To explore the multiplicity of these carbenes and the diastereoselectivity of cyclopropanation, reactions were conducted with *trans*- and *cis*-1,4-diphenylbut-2-ene (**112** and **114**) (Scheme 13b). Both alkenes reacted slowly with silyl sulfenylcarbene, yielding stereospecific cyclopropanes (**113** and **115**), implying a singlet nature of these carbenes. Also, DFT calculations revealed a 13.14 kcal mol^{-1} higher stability of the singlet carbene over the triplet carbene, validating experimental results.



Scheme 12 Diazo-derived silyl sulfenylcarbenes.



Scheme 13 Halide-derived silylsulfenylcarbenes.

2.7. Fluoro sulfenylcarbenes

In 2013, Kirkrihara and coworkers reported the synthesis of fluoro sulfenylcarbene (**117**) from corresponding chlorofluoromethyl phenylsulfide (**116**) (Scheme 14).[53] Upon reacting these fluoro sulfenylcarbene precursors with aqueous NaOH, a carbanion is generated, which further undergoes α-elimination to form fluoro sulfenylcarbene (**117**). These carbenes were utilized in (2+1) cycloaddition with alkenes to synthesize fluoro cyclopropanes (**118**).

Due to the instability of these cyclopropanes (**118**) during purification, sulfur oxidation was achieved to purify these cyclopropanes as a sulfoxide. Due to the oxidation of sulfur, two or three stereogenic centers (one chiral sulfur and one or two chiral carbons of the cyclopropane ring) were formed, so they were obtained as a mixture of diastereomers (**119–121**).

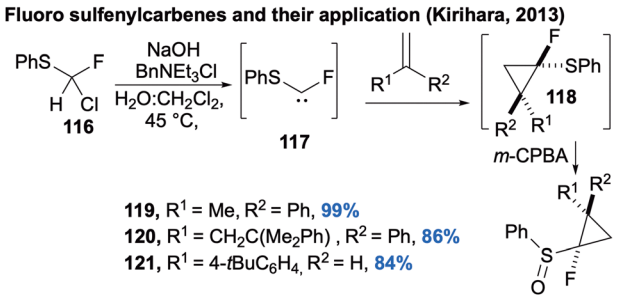
3. Sulfenylnitrenes

3.1. Introduction and origins

Nitrenes with thio-substituents are commonly referred to as sulfur-based nitrenes (Fig. 4).[54,55] Based on the different oxidation states of sulfur, there are three distinct classes of sulfur-based nitrenes: sulfonylnitrene,[54,55] sulfinylnitrene,[56] and sulfenylnitrene.[57]

Sulfenylnitrenes exist as ground-state singlets with a bond length of around 1.51 Å, which is shorter than the standard S–N single bond length of 1.7 Å in sulfenamides (Scheme 15).[35,58]

The term sulfenylnitrene was first introduced by Allison in 1975 to describe an intermediate formed during the decomposition of an enzyme-based sulfenyl azide in an activity-based study.[59] The influence of thio-substitution, particularly in sulfenylnitrenes, led to the extensive studies of these unique species.[60] Their remarkable versatility makes sulfenylnitrenes



Scheme 14 Halide-derived fluoro sulfenylcarbenes.

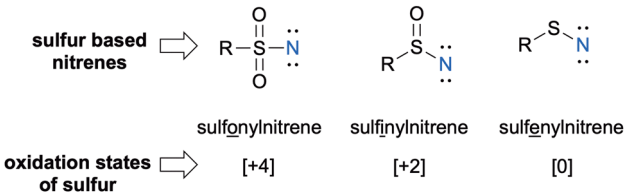


Fig. 4 Sulfur-bound nitrenes.

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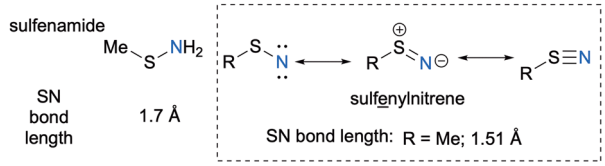


Scheme 15 N–S bond length in sulfenamide *vs.* sulfenylnitrene.

invaluable in modern organic synthesis, medicinal chemistry, and late-stage functionalization of drug molecules.[18]

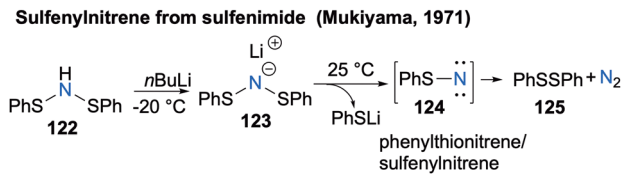
Early studies reported the generation of sulfenylnitrenes under harsh conditions, typically through the oxidation of sulfenamides or the thermal decomposition of thiazynes.[57,60] Lately, sulfenylnitrenes have been easily accessed under moderate conditions from the corresponding sulfenamide or thiazyne using heat over a broad temperature range.[35,61,62]

3.2. Sulfenimide sulfenylnitrene precursors

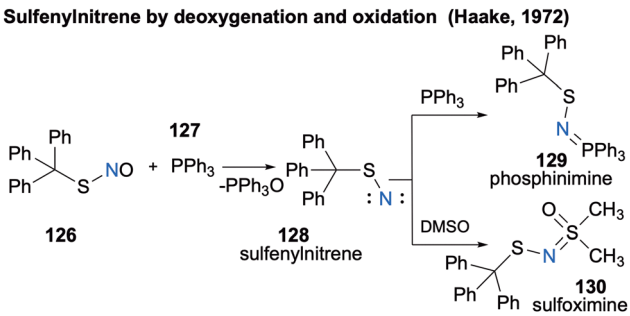
The first report on a sulfenylnitrene intermediate was published by Mukaiyama in 1971, who described it as a thionitrene (Scheme 16).[57] In this study, the treatment of the sulfenimide (**122**) with *n*-butyllithium at low temperature generates anion (**123**), which was reported to be stable up to −20 °C. This anion was postulated to generate disulfide (**125**) and nitrogen gas above this temperature *via* phenylsulfenylnitrene (**124**). The plausible mechanism for the formation of disulfide is likely the dimerization of phenylsulfenylnitrene, followed by the extrusion of nitrogen gas.

3.3. Nitrosothio sulfenylnitrene precursors

In 1972, Haake reported the formation of a sulfenylnitrene intermediate in his work (Scheme 17).[63] This intermediate was postulated as being formed during the deoxygenation of the tritylnitrosothio (**126**) compound using triphenylphosphine, ultimately leading to the formation of phosphinimine (**129**). The suggested mechanism involves generating sulfenylnitrene (**128**), followed by its dimerization reaction with triphenylphosphine to produce phosphinimine (**129**). The formation of sulfenylnitrene was further proved by the trapping of sulfenylnitrene (**128**) with dimethyl sulfoxide to access sulfoximine (**130**).



Scheme 16 First report of sulfenylnitrenes.



Scheme 17 Nitrosothio sulfenylnitrene precursors.

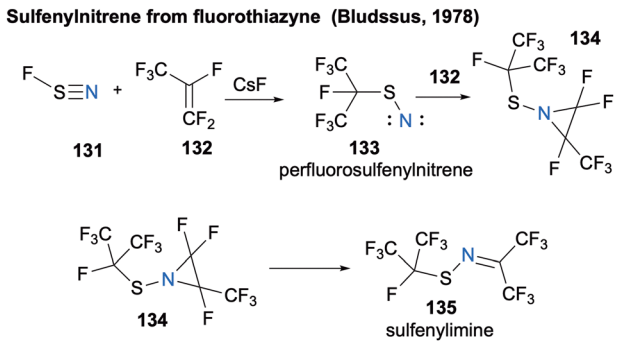
3.4. Thiazyne sulfenylnitrene precursors

In 1978, Bludssus and coworkers postulated the first aziridination reaction of sulfenylnitrene (Scheme 18).[64] However, similar aziridines were previously synthesized from corresponding amines and sulfenyl chloride.[65]

The reaction of fluorothiazyne (**131**) with perfluoropropene (**132**) in the presence of cesium fluoride gave multiple products, including sulfenylimine (**135**) (Scheme 18). The proposed pathway to sulfenylimine (**135**) involves generating perfluorosulfenylnitrene (**133**), followed by its addition to perfluoropropene (**132**). The resulting aziridine intermediate then undergoes rearrangement to yield the sulfenylimine (**135**).

In 1989, Hass and coworkers reported analogous reactions of fluorothiazyne (**131**) with perfluorolefins (Scheme 19).[66] The products obtained depended on reaction conditions and the nature of the olefins used. In reactions of thiazynes with perfluorobutadiene (**136**), the (4+2) cycloaddition product (**137**) was formed as the major product (Scheme 19a). Under UV-light, perfluoropropene was proposed to form an aziridine intermediate, which subsequently reacts with fluorothiazyne (**131**) to yield the corresponding iminosulfur difluoride derivative (**141**) along with various other products. This study by Hass strongly indicates that fluorothiazyne does not behave as a typical thiazyne compound but instead acts as a nitrene.

These thiazynes were synthesized *in situ* from corresponding azides in the presence of hexachlorocyclopentadiene (**142**) (Scheme 19b). The results showed that the intermediate thiazyne does not react with **142** as a "thiazyne" but as a "nitrene", presumably *via* an unstable (2+1) cycloaddition intermediate (**143**), rearranging to the final products. The low yields observed in this reaction were attributed to the polymerization of intermediates and their subsequent decomposition into the detected products, disulfide, and N_2, consistent with Mukiyama's report (Scheme 16).[57]



Scheme 18 Flurothiazyne precursor.

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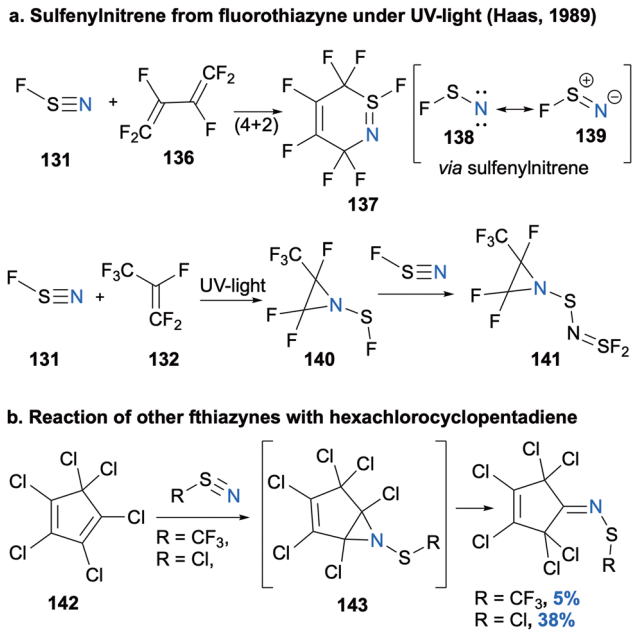
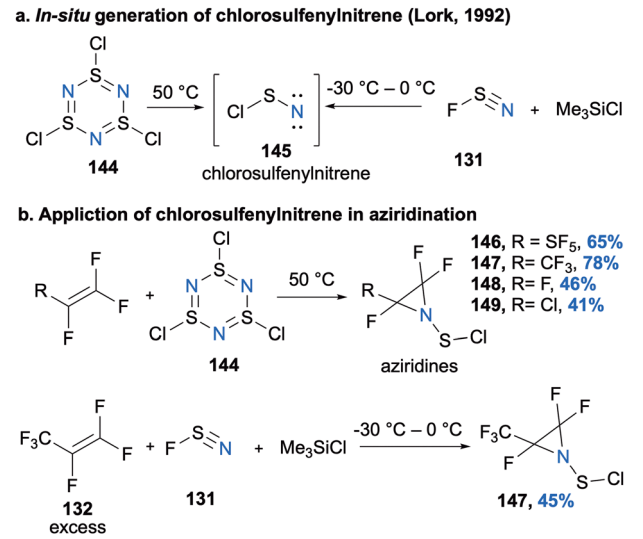


Scheme 19 UV-promoted generation of sulfenylnitrenes.

To understand the reactivities of trifluoro- and chlorothiazyne, in 1992, Lork and coworkers also reported that monomeric chlorothiazyne adds to the highly fluorinated alkenes to give the corresponding chlorosulfenylaziridines (Scheme 20).[67] In this report, monomeric chlorothiazyne is generated either from cyclic trimer (**144**) under heating conditions or by metathesis from NSF (**131**) and trimethylsilyl chloride at low temperature (Scheme 20a). Chlorothiazyne was found to react with various fluorinated alkenes *via* chlorosulfenylnitrene (**145**) to form substituted chlorosulfenylaziridines (**146–149**) in moderate yield (Scheme 20b). Similarly, chlorosulfenylnitrene generated from the metathesis of NSF was also trapped with excess alkene to form aziridine in moderate yield.

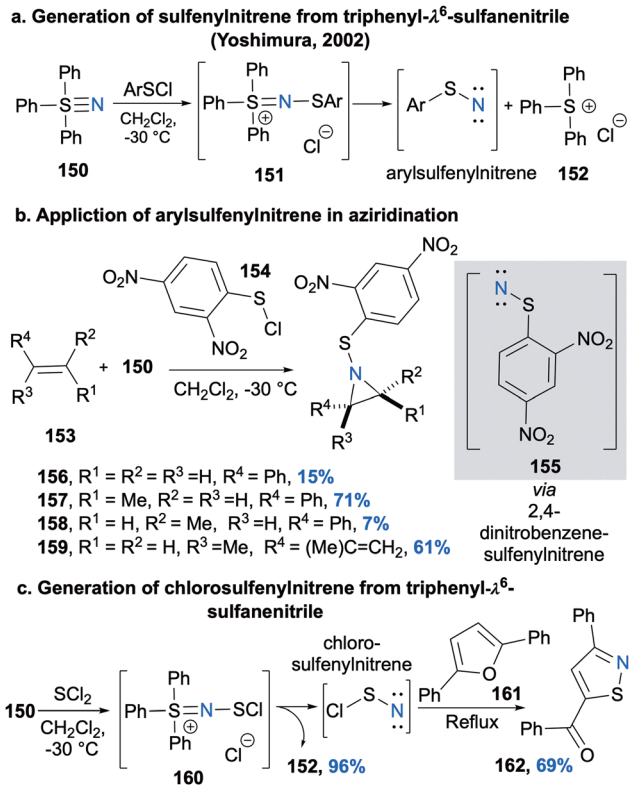


Scheme 20 *In situ* generation of halosulfenylnitrenes.

In 2002, Yoshimura and coworkers reported the generation of sulfenylnitrenes by *N*-sulfenylation of triphenyl-λ^6-sulfanenitrile (**150**) (Scheme 21).[61] The proposed mechanism for the formation of nitrene was described by the formation of N-substituted iminosulfonium salt (**151**) by the reaction of **150** with electrophiles such as arenesulfenyl chloride. The resulting salt undergoes multiple sulfur–nitrogen bond cleavage to generate sulfenylnitrene and triphenylsulfonium chloride (**152**) as a by-product (Scheme 21a). The reaction of **150** with 2,4-dinitrobenzenesulfenyl chloride (**154**) was examined in dichloromethane at −30 °C to generate 2,4-dinitrobenzenesulfenylnitrene (**155**), which was applied in aziridine formation (Scheme 21b).

Various substituted alkenes were successfully used as trapping agents to form corresponding *N*-(2,4-dinitrophenylsulfenyl) aziridines (**156–159**) in low to moderate yields. In all these reactions, by-product **152** was observed almost quantitatively. The formation of aziridine from sulfenylnitrene and butadiene contrasts with the formation of (4+2) cycloaddition product in the case of fluorothiazyne reported by Hass in 1989 (Scheme 19a).[66] Furthermore, this sulfenylnitrene shows stereospecific addition to alkenes to form corresponding aziridines.

Yoshimura also reported the *in situ* generation of chlorosulfenylnitrene by the reaction of triphenyl-λ^6-sulfanenitrile (**150**) with sulfur dichloride (Scheme 21c).[61] The mechanism for the formation of chlorosulfenylnitrene is *via* thermal decomposition of *N*-chloroiminosulfonium salt (**160**) at −30 °C in dichloromethane. This chlorosulfenylnitrene was successfully trapped with 5 equivalents of 2,5-diphenylfuran under refluxing conditions to access isothiazole (**162**).



Scheme 21 Further *in situ* generation of sulfenylcarbenes.

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3.5. Generation of Sulfenylnitrene from Sulfenamine (Oxidative Conditions)

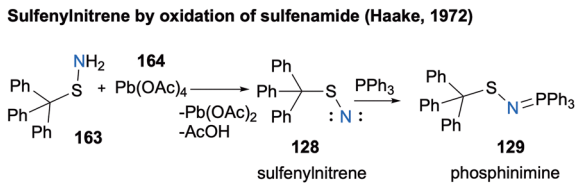
The first report of a sulfenylnitrene by oxidation of sulfenamide was reported in 1972 by Haake (Scheme 22).[63] The treatment of the sulfenamide (**163**) with lead tetra-acetate as an oxidant generates sulfenylnitrene. These nitrenes were successfully trapped with triphenylphosphine to form phosphinimine (**129**) as the only product.

In 1981, Atkinson and coworkers reported the synthesis of arylsulfenylnitrene by oxidation of arylsulfenamide and their application in aziridination (Scheme 23a).[68] The oxidation of 2,4-dinitrobenzenesulfenamide (**165**) with lead tetra-acetate generates the corresponding 2,4-dinitrobenzenesulfenylnitrene (**155**), which was successfully trapped by substituted alkenes (**166**) to access aziridines in moderate yields (**168–172**). Interestingly, electron-rich olefins were found to react better with nitrene, while electron-deficient olefins like methyl acrylate, ethyl cinnamate, and 2-acetylbenzofuran were unsuccessful for aziridine formation. Furthermore, sulfenylnitrene generated by this method shows non-stereospecific addition to *cis*-1-phenylpropene to give a mixture of *cis*- and *trans*-2-methyl-3-phenyl-substituted aziridines (**171**).

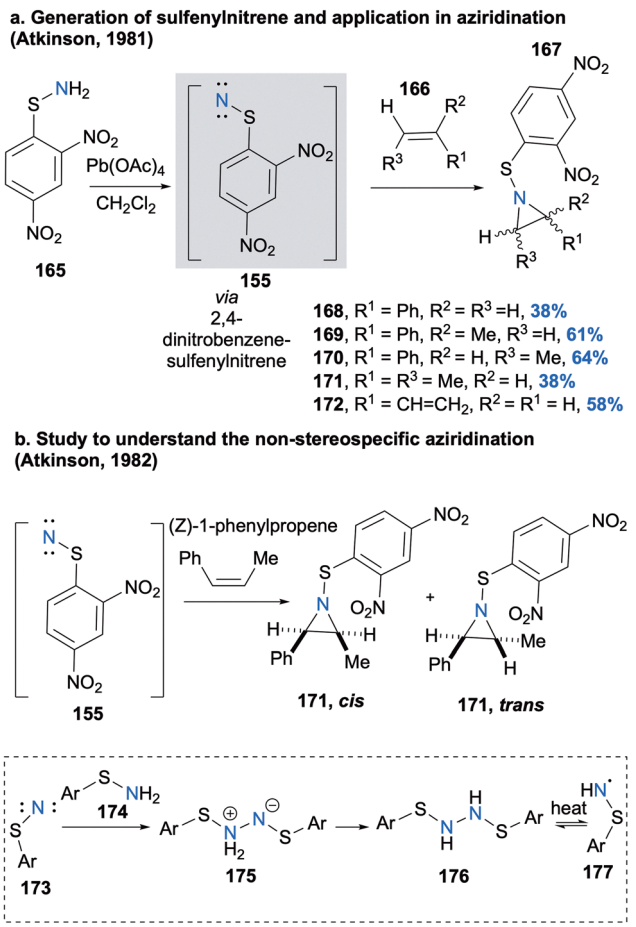
The spin state of a carbene or nitrene is commonly inferred from the stereospecificity of its addition to alkenes.[69] In 1982, Atkinson further studied to understand the spin-state and non-stereospecific aziridination of sulfenylnitrene formed under lead tetra-acetate conditions (Scheme 23b).[30] The non-stereospecific addition of sulfenylnitrene to alkenes was attributed to the generation of reactive radical species **177** by the insertion of sulfenamide to nitrene **173**. It is concluded that two intermediates are involved in adding (*Z*)-1-phenylpropene, one of which is a singlet nitrene; however, the other is not the triplet nitrene.

In 1994, Michida and coworkers also reported the synthesis of arylsulfenylnitrene by milder oxidation of arylsulfenamide and their broad application in aziridination (Scheme 24a).[62] The oxidation of 2,4-dinitrobenzenesulfenamide (**165**) with *N*-bromosuccinimide (NBS) generates the corresponding 2,4-dinitrobenzenesulfenylnitrene along with by-products, HBr and succinimide (**179**). The oxidation of **165** with NBS produces singlet (**155**) or triplet (**178**) nitrene, in accordance with the results of non-stereospecific aziridination.

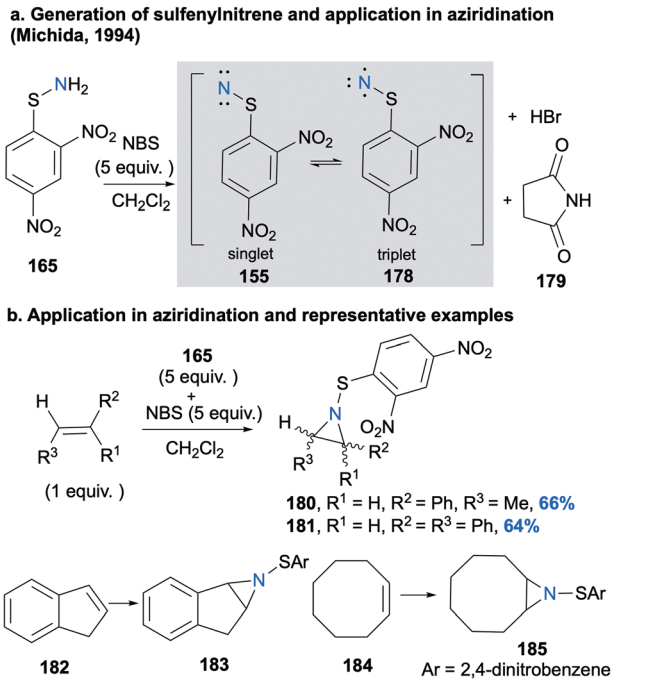
The primary reason behind non-stereospecific aziridination was the formation of a biradical intermediate. Substituted alkenes successfully trapped these nitrenes to access aziridines in moderate yields (**180** and **181**) (Scheme 24b). The application



Scheme 22 Generation of sulfenylnitrenes by oxidation with lead tetraacetate.



Scheme 23 Application of sulfenylnitrenes in aziridination.



Scheme 24 Generation and application of sulfenylnitrenes.

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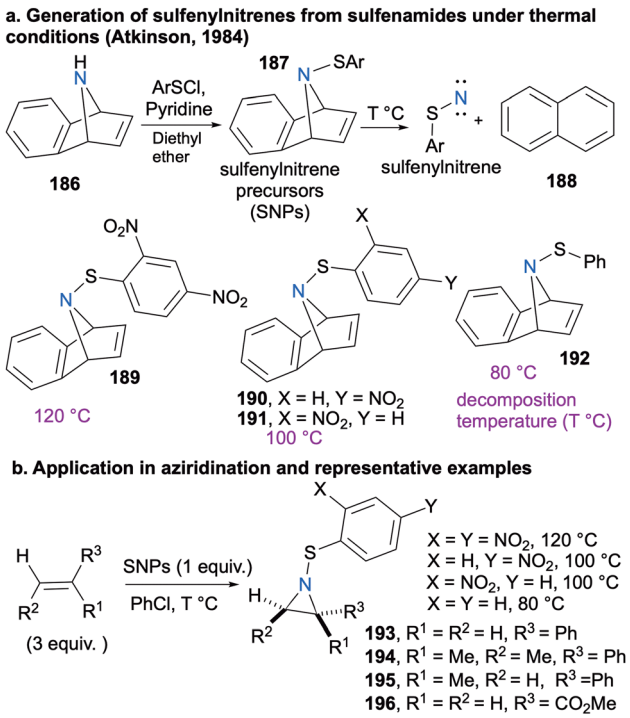
of sulfenylnitrene was further expanded to aziridination of cyclic alkenes; indene (**182**) and 1-cyclooctene (**184**) to access corresponding aziridines **183** and **185** in moderate yields.

3.6. Generation of sulfenylnitrene from sulfenamine (thermal conditions)

In 1984, Atkinson and coworkers reported the synthesis of sulfenylnitrene precursors (SNPs) that generate sulfenylnitrenes under thermal conditions by extruding bridged nitrogen (Scheme 25).[70]

These precursors were prepared as stable, crystalline compounds by treatment of 1,4-dihydro-1,4-iminonaphthalene (**186**) with the appropriate arenesulfenyl chloride and pyridine in diethyl ether (Scheme 25a). Four distinct precursors were synthesized: **189**, **190**, **191**, and **192**, which generate sulfenylnitrene under heating conditions. The decomposition temperature of the precursor was dependent on the electron-withdrawing substituent on the arene ring. SNP **189** with a 2,4-dinitro substituent decomposed at 120 °C, while **190** and **191** with mono-nitro substitution were found to decompose at 100 °C. Similarly, a simple non-substituted phenyl ring (**192**) was found to decompose at 80 °C to form the corresponding sulfenylnitrene. In all these precursors, naphthalene (**188**) was formed as a by-product.

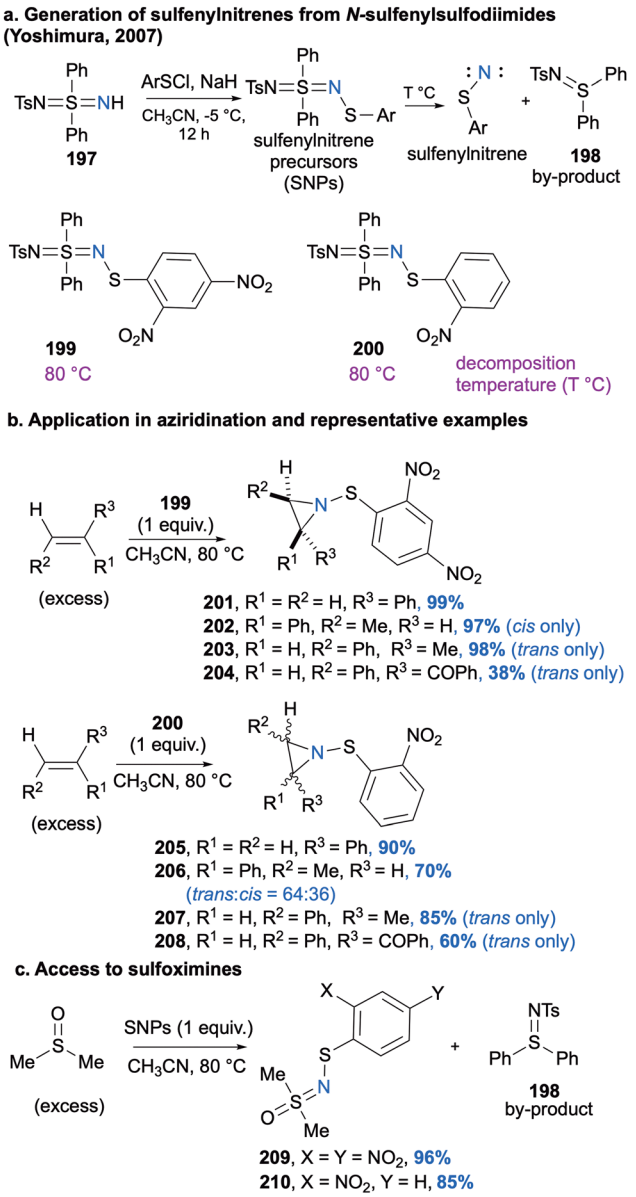
All four sulfenylnitrenes were trapped by alkenes as the corresponding stereospecific aziridines (Scheme 25b). SNP **189** decomposed within 1 hour at 120 °C in chlorobenzene solvent and, in the presence of styrene (3 equiv.), quantitative yields of aziridines (**193–196**) were observed. Similar results were obtained for other sulfenylnitrene precursors (**190–192**), but nitrene formation occurred at lower temperatures as the number of nitro groups in the aryl ring was reduced. Despite the temperature difference, stereo-specific aziridination was observed in all nitrenes. This novel extrusion pathway for nitrene generation *via* cheletropic elimination enables the exploration of alternative benzenoid-based precursors capable of generating nitrenes across a broad temperature range.



Scheme 25 Synthesis and application of thermally generated sulfenylnitrenes.

3.7. *N*-Sulfenylsulfodiimide sulfenylnitrene precursors

In 2007, Yoshimura and coworkers reported the synthesis of *N*-sulfenylsulfodimides based sulfenylnitrene precursors (SNPs) that generate sulfenylnitrenes under thermal conditions (Scheme 26a).[35] These precursors were prepared as stable, crystalline compounds by treatment of corresponding *N*-(*H*)-sulfodiimides (**197**) with the appropriate arenesulfenyl chloride and NaH in acetonitrile. Two distinct precursors were synthesized, **199** and **200**, which generate sulfenylnitrenes under heating conditions



Scheme 26 Application of sulfenylnitrenes.

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by extruding *N*-tosyl-sulfanimine (**198**) as a quantitative by-product. The decomposition temperature of both precursors was found to be 80 °C, which is relatively lower than Atkinson's thermal SNPs.

These thermally generated sulfenylnitrenes were trapped by alkenes in acetonitrile as the solvent, yielding the corresponding aziridines, similar to the results reported by Atkinson (Scheme 26b).[70] The stereospecificity is inconsistent with Atkinson's results, and the reason for this conflict is unclear. Decomposition of **199** to generate 2,4-dinitrophenylsulfenylnitrene in the presence of styrene, *trans*- and *cis*-1-phenylpropenes, and *trans*-chalcone gives the corresponding stereospecific *N*-sulfenylaziridines without any other isomer (**201–204**).

Styrene and *trans*-olefins reacted with 2-nitrophenylsulfenylnitrene in a similar manner to the dinitro analouge, though with slight differences in yield (**205–208**). While the reason for this conflict is unclear, 2-nitrophenylsulfenylnitrene with *cis*-1-phenylpropene gave a mixture of *cis*- and *trans*-aziridines (**206**). Compared to the trapping of 2,4-dinitrophenylsulfenylnitrene, the reaction of 2-nitrophenylsulfenylnitrene with electron-rich alkenes, such as styrene and 1-phenylpropenes, resulted in the reduction of yield. However, trapping with the electron-deficient chalcone (**208**) provided a higher yield than that observed for the dinitro analogue. These electronic effects suggest a change in the nature of the sulfenylnitrene, shifting from a highly electrophilic character as a nitrene to a less electrophilic one, which can be explained by the resonance structures of the sulfenylnitrene.

Yoshimura and coworkers further utilized sulfenylnitrenes in the synthesis of sulfoximines by the reaction of sulfenylnitrene with sulfoxide (Scheme 26c).[35] Both 2,4-dinitrophenylsulfenylnitrene and 2-nitrophenylsulfenylnitrene reacted with dimethyl sulfoxide to yield corresponding sulfoximines **209** and **210** in good yields. Similarly, in this case, *N*-tosyl-sulfanimine (**199**) was formed quantitatively as a by-product.

4. Applications to late-stage functionalization

4.1. Introduction to late-stage functionalization

Late-stage functionalization (LSF) has emerged as a crucial strategy in drug discovery, enabling the modification of complex molecules, including pharmaceuticals, to enhance chemical diversity within drug libraries.[71] By facilitating precise single-atom manipulations, LSF can enhance biological activity, improve metabolic stability, and accelerate drug candidate optimization while reducing the need for extensive *de novo* synthesis.[72,73]

Furthermore, given the widespread presence of nitrogen-containing heterocycles in commercial drugs,[74,75] the selective incorporation of a single carbon/nitrogen-atom into an existing molecule represents a promising scaffold-hopping approach.[76] The strategy of C/N-atom insertion into aromatic compounds using a carbene/nitrene precursor bearing a suitable leaving group provides an efficient and selective route for introducing carbon or nitrogen atoms into simple or complex molecular frameworks.[77,78]

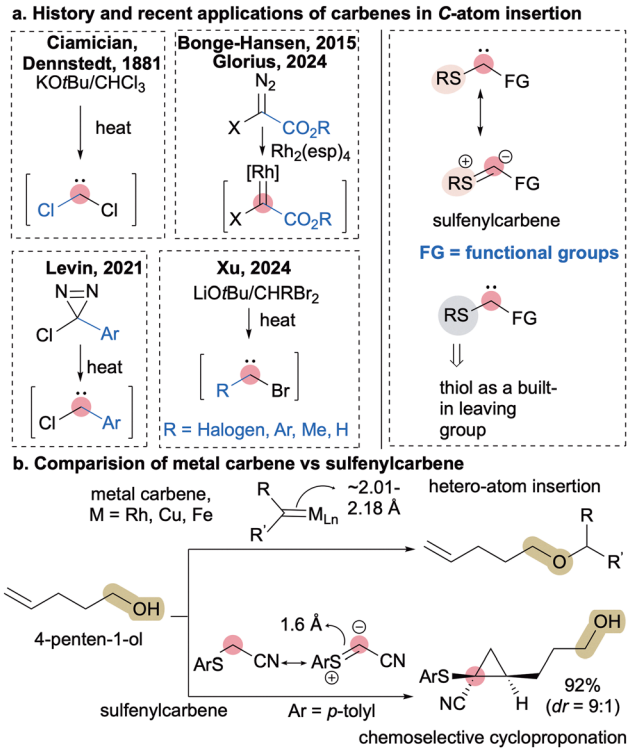
4.2. Sulfenylcarbene mediated C-atom additions to N-heterocycles

Sulfenylcarbenes may be seen as carbenes-bearing leaving groups, given that thiols are considered excellent leaving groups in organic synthesis.[27] Their potential for direct carbon-atom insertion relies on the thiol's ability to effectively act as a leaving group.[34] The resonance between sulfur and carbene center allows for the tunable reactivity of carbenes by altering the electronics of the thio substituent.[27] This enables direct carbon-atom insertion with diverse functional groups, overcoming the limitations of existing methods that allow only a narrow range of functional groups[79] or require a linchpin for most modifications.[80]

The history of the carbene-bearing leaving group goes back to 1881 when Ciamician and Dennstedt utilized chloroform to generate dichlorocarbene under basic conditions (Scheme 27a). At the time, this technique was regarded as a standard transformation of pyrroles into halo-pyridines rather than being recognized as a single C-atom insertion. In 2015, Bonge-Hansen introduced diazo compounds with leaving groups for single-carbon-atom insertion.[81] The Levin group later achieved a breakthrough in 2021 using diazirines for skeletal editing,[79] followed by Glorius with diazo precursors[80] and Xu with haloforms to access carbenes bearing a leaving group for similar insertions.[82]

In contrast to sulfenylcarbenes,[27] which are stabilized by an adjacent sulfur atom, all these carbenes reported for C-atom insertion exist either as free carbenes or as metal-carbenes.

Sulfenylcarbene undergoes chemoselective cyclopropanation with alkenes, in contrast to diazo-derived metal carbenes, which typically favor heteroatom insertions (Scheme 27b).[27]



Scheme 27 Literature reported carbenes *vs.* sulfenylcarbene.

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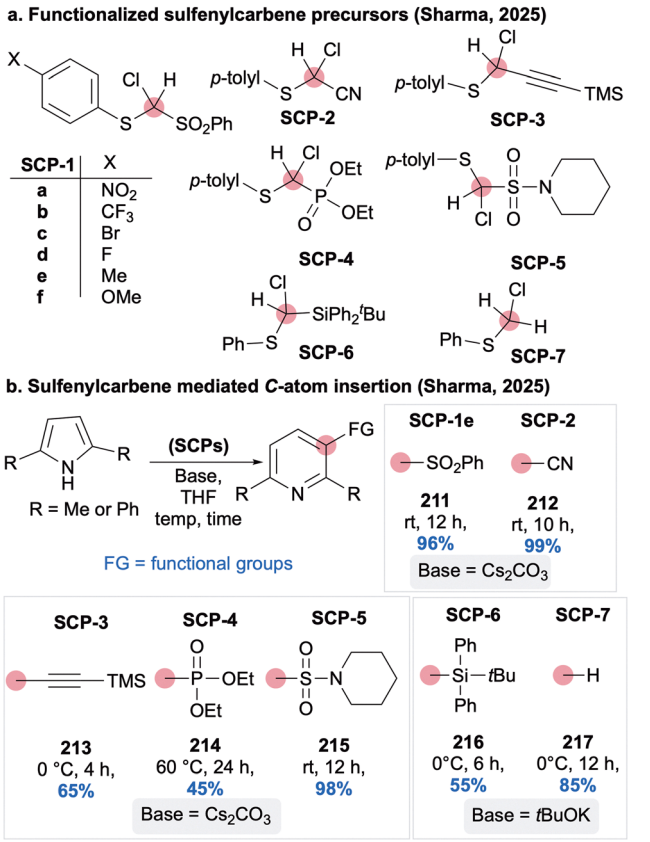
Numerous studies report that metal carbenes preferentially insert into functional groups such as –OH, –COOH, thioethers, and amines rather than reacting with π-bonds.[83–85]

In 2025, Sharma and coworkers reported the sulfenylcarbene-mediated late-stage C-atom insertion (Scheme 28).[27] This method allows the selective single C-atom insertion bearing diverse functional groups. Inspired by literature, they employed the strategy of generating an unstable carbanion, which then undergoes elimination to produce sulfenylcarbenes. This group reported the synthesis of a variety of sulfenylcarbene precursors (**SCP-1** to **SCP-7**), which include functional groups such as sulfonyl, cyano, alkyne, phosphonate, sulfonamide, and even simple hydrogen-substituted precursors (Scheme 28a).

According to initial observation, these precursors generate sulfenylcarbene under mild conditions at ambient temperature using an equilibrium base. The generation of sulfenylcarbene in the presence of 2,5-dimethyl pyrrole formed the corresponding functionalized pyridines (Scheme 28b). Optimization revealed the influence of the thio-functionality on the carbene, where electron-withdrawing groups were less effective for carbene formation. In contrast, electron-donating groups, such as **SCP-1(e–f)**, proved highly effective for robust carbene generation. The corresponding pyridine (**211**) bearing sulfonyl was formed when the thio-functionality was *para*-substituted with a methyl group. Sulfenylcarbene precursors (**SCP-2** to **SCP-6**) allow for the installation of chemically sensitive and versatile functional groups (**212** to **216**).

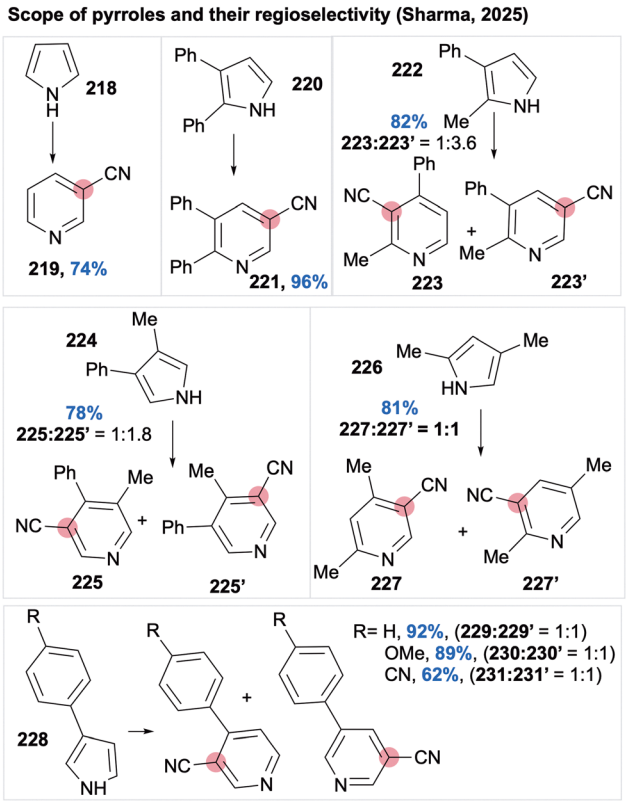


Scheme 28 Functionalized sulfenylcarbenes and their application.

Furthermore, these precursors feature modular functional groups such as nitriles,[86] which facilitate diverse functional group interconversions, and silyl groups, which are utilized in Hiyama cross-coupling reactions.[87] Critically, this method also allows the direct installation of a C–H group (**217**). Changing skeletal ring size without adding functional groups is an essential goal within LSF as it enables medicinal chemists to perform precise and targeted structure–activity relationship (SAR) studies.[72,88] Given the importance and versatility of the cyano group for post-modifications[86] and the inability of existing methods to install this important functionality, this group utilized **SCP-2** as the optimized precursor for the substrate scope study.

Their method demonstrated compatibility for carbon-atom insertion into free pyrroles (**218**) (Scheme 29).[27] The results revealed that carbon-atom insertion occurred preferentially from the sterically less hindered side of the pyrrole ring (**220**, **222**, and **224**). Interestingly, di-substituted pyrrole **226** produced a mixture of regioisomers, indicating that 2,4-disubstitution had no significant impact on the reaction's regioselectivity. Additionally, electronic variations in 3-aryl-substituted pyrroles (**228**) did not affect the regioselectivity of carbon-atom insertion. To gain deeper insights, they performed computational analyses to elucidate the underlying mechanism.

Moving on to indole, they observed excellent yields with a wide range of substrates (Scheme 30). Electron-donating and withdrawing in the aromatic ring shows compatibility, yielding quinolines (**234**, **235**) with good yield. Similarly, C-2 substitution was also tolerated (**236**).



Scheme 29 Scope of pyrroles.

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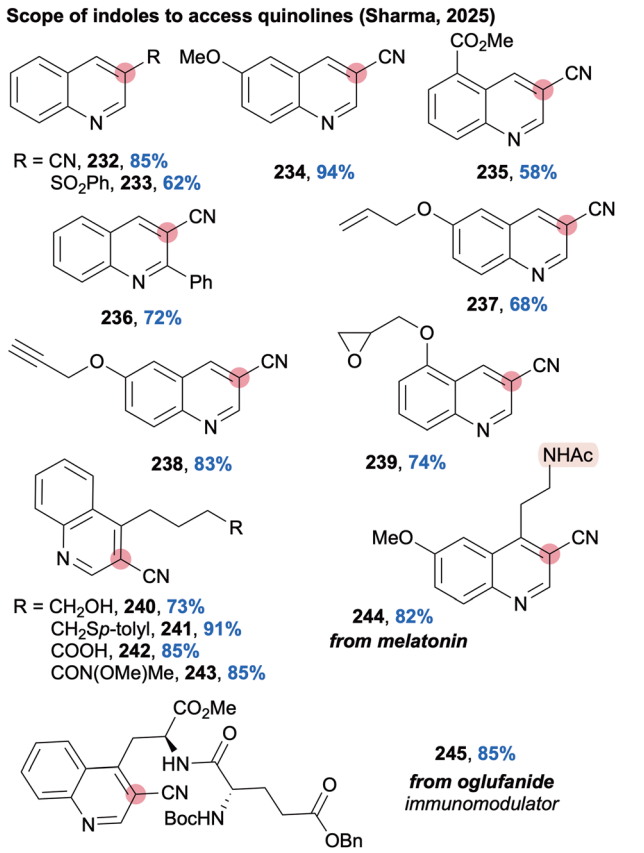
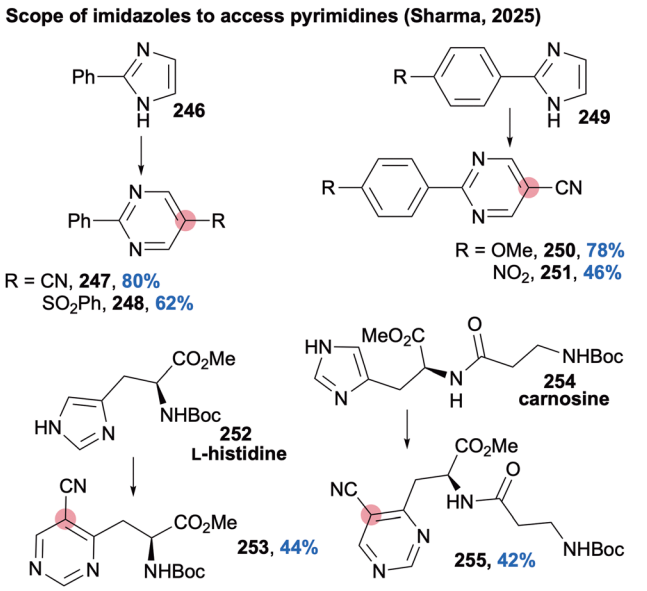


Scheme 30 Scope of indoles.

These sulfenylcarbenes exhibit high chemoselectivity for the skeletal indole double bond over the peripheral alkene (**237**) and terminal alkyne (**238**). This approach also shows compatibility with compounds featuring an epoxide (**239**), a valuable scaffold in drug design. These sulfenylcarbenes show high chemoselectivity for π-nucleophiles over σ-nucleophiles (**240**), including heteroatom lone pairs. This high chemoselectivity was investigated using DFT and likely arises from a combination of electronic properties leading sulfenylcarbenes to prefer soft nucleophiles. The method also exhibited compatibility with oxidation-sensitive functionality like thioether (**241**). Compatibility with free carboxylic acid (**242**) and its derivatives (**243**) shows the broad functional group tolerance of this method. The application of this methodology was further expanded by reacting many pharmaceutically relevant indoles, including melatonin and oglufanide, to access corresponding quinolines (**244**, **245**) in high yield.

Sharma and coworkers also applied this methodology for carbon-atom insertion into imidazoles,[27] a privileged motif in drug discovery (Scheme 31). This expansion of imidazoles to pyrimidines is particularly noteworthy, representing the first single carbon-atom expansion of this class. Interestingly, this method allows the regioselective single carbon insertion, which was further explained by DFT calculations. The broad substrate scope of this study includes various aryl-substituted imidazoles (**246**, **249**) to access corresponding pyrimidines. Additionally,



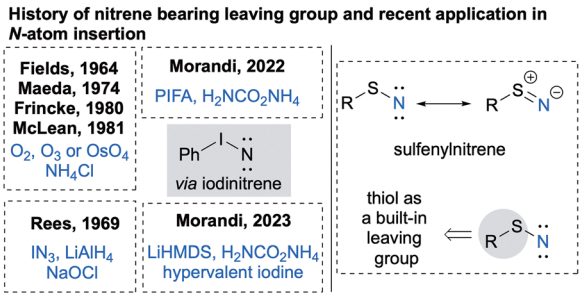
Scheme 31 Scope of imidazoles.

complex substrates include carbon-atom insertion into L-histidine (**252**) and carnosine (**254**) to access corresponding unnatural pyrimidine amino acid (**253**) and dipeptide (**255**), respectively.

This work emphasizes the ability of sulfenylcarbenes to handle a range of synthetically challenging functional groups, underscoring their versatility and broad applicability in late-stage functionalization. These sulfenylcarbene precursors, which are bench-stable and amenable to large-scale synthesis, demonstrate strong potential for commercial applications. With a metal-free, non-diazo approach, mild reaction conditions, straightforward protocols, exceptional chemoselectivity, and remarkable functional group tolerance, sulfenylcarbenes offer significant advantages. Their utility in late-stage functionalization enables the creation of novel chemical entities, opening exciting possibilities for exploring uncharted chemical space in drug discovery.

4.3. Sulfenylnitrene mediated N-atom insertion to N-heterocycles

The history of nitrene bearing leaving groups mostly involves using ammonium chloride and an oxidizing agent (Scheme 32).[89–92]



Scheme 32 History of nitrene-bearing leaving group *vs.* sulfenylnitrene.

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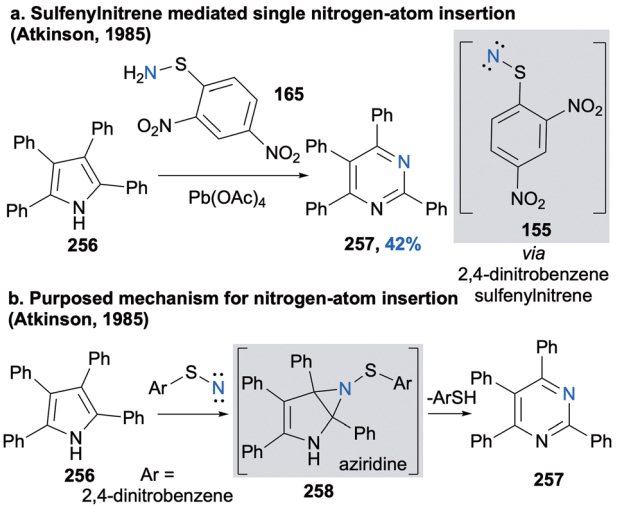
Back then, this technique was considered amozonolysis, not skeletal editing or nitrogen-atom insertion.[89] In a similar vein, the use of iodine azide to generate nitrene-bearing halogen as a leaving group was also reported.[93] Recently, a few other reports utilizing metal-based nitrene,[19] metal nitride,[94] and ammonia[95] have also emerged as N-atom insertion strategies. The breakthrough in utilizing nitrenes bearing leaving groups for nitrogen-atom insertion was reported by Morandi and coworkers, enabling late-stage skeletal editing of indoles, indenes, and pyrroles with iodonitrene.[96–98] Sulfenylnitrenes can also be considered as nitrenes bearing a leaving group, as thiol is considered a good leaving group in organic synthesis.[99]

The potential of sulfenylnitrene for nitrogen-atom insertion hinges on the thiol's ability to act as a leaving group. In 1985, Atkinson and coworkers disclosed the first report of sulfenylnitrene for the single N-atom insertion (Scheme 33).[100]

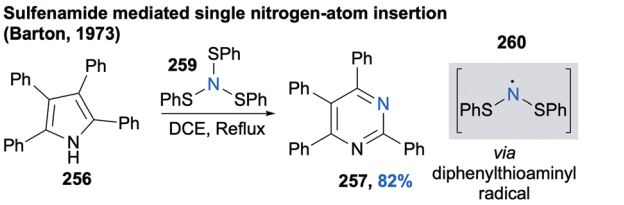
The oxidation of 2,4-dinitrobenzenesulfenamide (**165**) with lead tetra-acetate to generate 2,4-dinitrophenylsulfenylnitrene (**155**) in the presence of tetraphenylpyrrole (**256**) facilitated single nitrogen atom insertion to form 2,4,5,6-tetraphenylpyrimidine (**257**) (Scheme 33a). The mechanism involves the formation of aziridine intermediate (**258**) followed by the disrotatory ring opening to regain the aromaticity prompted by the loss of thiol (Scheme 33b).

A similar transformation was achieved by Barton and coworkers in 1973 (Scheme 34) using triphenylsulfenamide (**259**).[101] Barton and coworkers proposed a mechanism involving the formation of a diphenylthioaminyl radical (**260**) under heating conditions. In contrast, Atkinson suggested that this transformation likely proceeds through the formation of phenylsulfenylnitrene rather than exclusively following a radical pathway.[100]

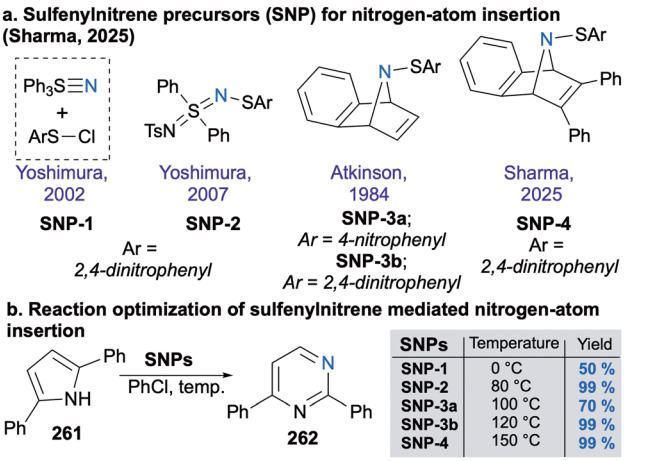
In 2025, Sharma and coworkers reported single nitrogen-atom insertion for late-stage functionalization of N-heterocycles utilizing sulfenylnitrene precursors capable of operating over a wide temperature range (Scheme 35).[18] They utilized three different types of thermal-based sulfenylnitrene precursors: triphenyl-λ^6-sulfanenitrile (**SNP-1**; Yoshimura, 2002),[61] *N*-sulfenylsulfodiimides based precursor (**SNP-2**; Yoshimura, 2007),[35] and sulfenamide based precursor (**SNP-3a/b**; Atkinson, 1984[70] & **SNP-4**; Sharma, 2025) (Scheme 35a).



Scheme 33 Early report of sulfenylnitrene-mediated nitrogen-atom insertion.



Scheme 34 Early report of nitrogen-atom insertion using sulfonamide.



Scheme 35 Sulfenylnitrene mediated-nitrogen atom insertion into N-heterocycle.

According to their initial observations, **SNP-1**, upon reaction with symmetrical 2,5-diphenylpyrrole (**261**), produced the corresponding pyrimidine (**262**) in a moderate yield (Scheme 35b). Further investigations to enhance the yield led them to **SNP-2**, **SNP-3a**, and **SNP-3b**, which furnished the corresponding pyrimidine in almost quantitative yields. These results indicate that variations in the nature of the thioaryl moiety influence both the decomposition temperature of the sulfenylnitrene precursor (**SNP**) and the yield. This is attributed to the electronic effects exerted on the central nitrogen atom of the nitrene precursor. Sharma and coworkers also introduced the distinctive precursor **SNP-4**, which generates sulfenylnitrene at an elevated temperature of 150 °C and has proven effective for nitrogen-atom insertion with a quantitative yield. Due to the synthetic feasibility and scalability, they chose **SNP-3b** as the ideal precursor for substrate scope study of pyrroles, indoles, azaindoles, and imidazoles.

Among pyrroles, they studied nitrogen-atom insertion of 3,4-substituted unsymmetrical substrates (**263**) (Scheme 36). The results indicated that nitrogen-atom insertion happened preferentially from the more electron-rich side of the pyrrole ring (**264–268**). However, electronic changes on the 3-aryl substituted pyrroles (**269**) didn't influence the regioselectivity outcomes of nitrogen-atom insertion. Similarly, trisubstituted pyrroles (**273**) were found to yield a single isomer (**274**, **275**). They also conducted computational analysis for a thorough

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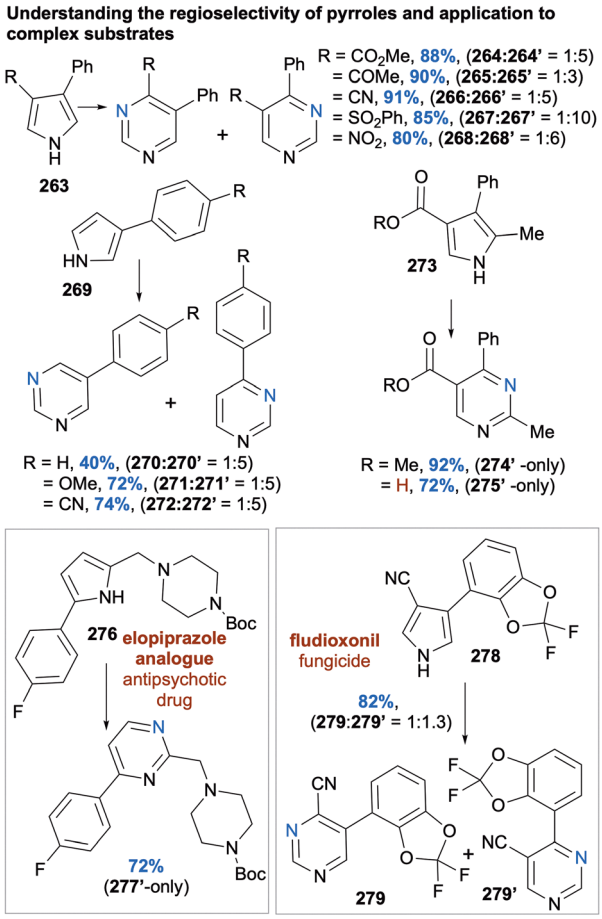


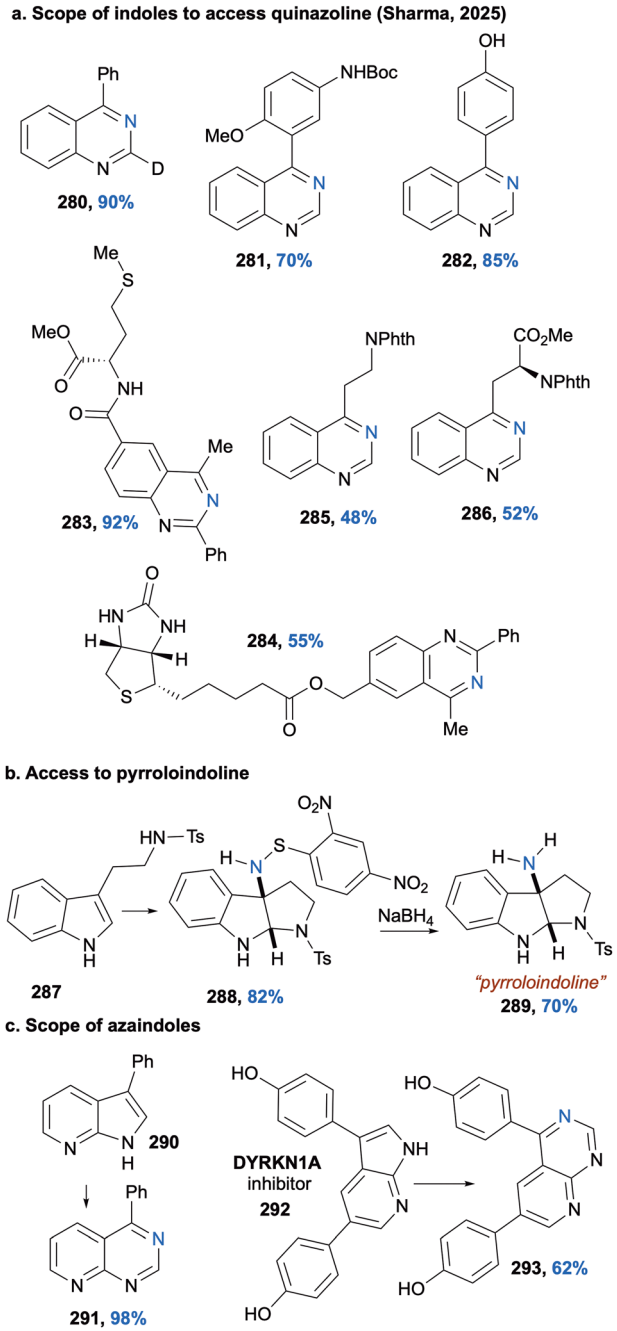
Scheme 36 Representative examples of pyrroles.

mechanistic investigation into these regioselective outcomes. To further expand the utility of this methodology, it was applied to complex bioactive pyrroles. Pyrrole-containing antipsychotic drug elopiprazole[102] (**276**) and fungicide fludioxonil[103] (**278**) were among the substrates expanded into pyrimidines successfully.

Moving onto indoles and azaindoles, they observed excellent yields with a wide range of substrates (Scheme 37). A controlled deuterium labeling experiment was conducted to rule out the possibility of peripheral C–H bond activation by these nitrenes (**280**) (Scheme 37a). An indole containing a Boc-protected amine shows compatibility, yielding quinazoline (**281**) with good yield. The method also exhibited compatibility with oxidation-sensitive functionality like phenol (**282**) and thioether (**283**), which are incompatible with the other methods, as they require potent oxidizing agents. The reaction also showed effectiveness with biotin-derivatized indole to yield the corresponding quinazoline (**284**). This showcases the compatibility of functionalities, including urea and thioether.

This method is also compatible with phthalimide-protected tryptamine and tryptophan to access their respective quinazoline products (**285**, **286**), providing access to underexplored unnatural amino acids and their derivatives.

The application of this methodology was further expanded by reacting tosyl-protected tryptamine (**287**) to access corresponding



Scheme 37 Representative examples of indoles.

pyrroloindoline (**289**) as a single diastereomer in high yield (Scheme 37b). Mechanistically, the aziridine intermediate underwent ring opening rather than ring expansion, proceeding from the same side as the aliphatic chain at the 3-position of tryptamine, resulting in exclusive *cis*-selectivity. Furthermore, the easy cleavage of the N–S bond in the thioether functionality with sodium borohydride shows the versatile applications of sulfenylnitrene. The application of this methodology was also expanded to insert single nitrogen into aza-indoles (**290**, **292**) to access corresponding N-heterocycles (Scheme 37c).

Sharma and coworkers also applied this methodology for single nitrogen-atom insertion into imidazoles,[18] a privileged

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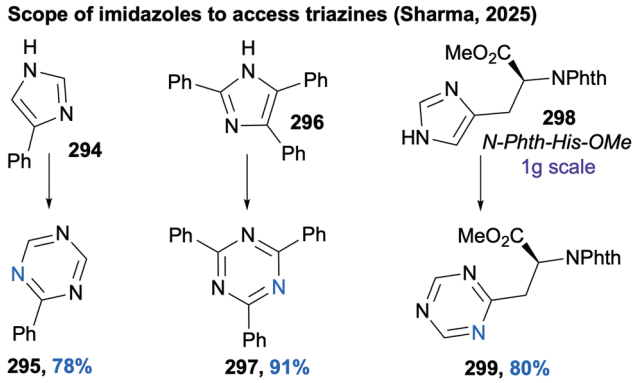

Scheme 38 Representative examples of imidazoles.

motif in drug discovery (Scheme 38).[104] Various aryl-substituted imidazoles (**294** and **296**) were successfully expanded into the corresponding 1,3,5-triazenes (**295**, and **297**). Additionally, nitrogen-atom insertion into phthalimide-protected L-histidine methyl ester (**298**) at a gram scale to access the corresponding unnatural triazine amino acid (**299**) was also achieved.

5. Conclusions and outlook

The story of sulfenylcarbenes and sulfenylnitrenes began as more or less a scientific curiosity, with early studies laying the necessary groundwork but offering limited synthetic applications. However, over the next six decades, these reactive intermediates emerged as a largely untapped reservoir of potent but controllable chemical reactivity. Likewise, it has been understood since the early days of this chemistry that the electronic structure of sulfenylcarbenes/nitrenes was unique, and our molecular-level understanding of these species has evolved alongside their synthetic applicability. Sulfenylcarbenes/nitrenes pose an interesting contrast to classical species like methylene or imidogen, as well as a complementary rather than redundant kind of behavior compared to dihalocarbenes, oxynitrenes, iodonitrenes, or metal-carbenoids/nitrenoids.

Indeed, the synthetic utility and unique electronic structure of sulfenylcarbenes/nitrenes are inherently interconnected. The typical singlet nature of these species enables diastereoselective cyclopropanation/aziridination, while heteroatom-induced reductions in electrophilicity allow for slower, more controlled reactions. It is exactly these properties that make sulfenylcarbenes/nitrenes suitable for the late-stage functionalization of drug-like molecules. Furthermore, sulfenylcarbenes/nitrenes may be generated under various experimental conditions, from oxidative and basic to additive-free thermal and photochemical conditions. This naturally enhances their usefulness in late-stage functionalizations. In parallel, the inherent leaving group ability of the thioaryl moiety may be leveraged to enable the kind of cascade cyclization/Grob-type fragmentation reactions that form the backbone of modern skeletal editing techniques.

So far, sulfenylcarbenes/nitrenes and their precursors have been applied in diastereoselective cyclopropanations and aziridinations, (3+2), (1+3), and (4+2)-cycloadditions, a variety of rearrangement reactions, and the late-stage skeletal editing of N-heterocycles. Furthermore, the chemistry of sulfenylnitrene/carbene precursors has been extensively explored, including the development of benchtop stable, scalable precursors for both intermediates. Their electronic structure has been well studied, with methods like DFT providing models that are comprehensible and accessible both computationally and from a fundamental molecular orbital perspective.

Despite over sixty years of work, this field remains young, and significant advances in the generation and application of sulfenylcarbenes and nitrenes are expected in the next decade. Specifically, there is considerable interest in the photochemical generation of sulfenylnitrenes for improved reaction times, selectivity, and yields. Sulfenylcarbenes may be applied to areas of biological relevance, including DNA-encoded libraries (DEL). Moreover, these intermediates are virtually untapped as tools for C–H functionalization and single-atom deletion but hold considerable potential in both areas. This review consolidates all historical and modern literature reports of these intermediates, providing a comprehensive starting point for experts and beginners in the fields of carbenes and nitrene chemistry.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results have been included, and no new data were generated or analyzed as part of this review.

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Notes and references

1 C. Wentrup, *Angew. Chem., Int. Ed.*, 2018, **57**, 11508–11521.
2 C. Wentrup, *Acc. Chem. Res.*, 2011, **44**, 393–404.
3 E. Gras and S. Chassaing, *Organic Reaction Mechanisms 2017*, 2020, pp. 179–212.
4 M. Nic, J. Jirat and B. Kosata, *IUPAC Compendium of Chemical Terminology Gold Book*, 2014.
5 P. F. Kuijpers, J. I. van der Vlugt, S. Schneider and B. de Bruin, *Chem. – Eur. J.*, 2017, **23**, 13819–13829.
6 H. Kim and E. Lee, *Bull. Korean Chem. Soc.*, 2022, **43**, 1328–1341.
7 Y. Guo, C. Pei and R. M. Koenigs, *Nat. Commun.*, 2022, **13**, 86.

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8 K. Hirai, T. Itoh and H. Tomioka, *Chem. Rev.*, 2009, **109**, 3275–3332.
9 L. Zhang, B. M. DeMuynck, A. N. Paneque, J. E. Rutherford and D. A. Nagib, *Science*, 2022, **377**, 649–654.
10 B. T. Boyle, N. W. Dow, C. B. Kelly, M. C. Bryan and D. W. C. MacMillan, *Nature*, 2024, **631**, 789–795.
11 H. Jung, J. Kweon, J.-M. Suh, M. H. Lim, D. Kim and S. Chang, *Science*, 2023, **381**, 525–532.
12 T. R. Roose, D. S. Verdoorn, P. Mampuys, E. Ruijter, B. U. W. Maes and R. V. A. Orru, *Chem. Soc. Rev.*, 2022, **51**, 5842–5877.
13 D. Martin, M. Melaimi, M. Soleilhavoup and G. Bertrand, *Organometallics*, 2011, **30**, 5304–5313.
14 D. Bourissou, O. Guerret, F. P. Gabbaï and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39–92.
15 Y. Cheng and O. Meth-Cohn, *Chem. Rev.*, 2004, **104**, 2507–2530.
16 W. A. Wasylenko, N. Kebede, B. M. Showalter, N. Matsunaga, A. P. Miceli, Y. Liu, L. R. Ryzhkov, C. M. Hadad and J. P. Toscano, *J. Am. Chem. Soc.*, 2006, **128**, 13142–13150.
17 J. H. Davis and W. A. Goddard III, *J. Am. Chem. Soc.*, 1977, **99**, 7111–7121.
18 B. Ghosh, P. Kafle, R. Mukherjee, R. S. Welles, D. Herndon, K. M. Nicholas, Y. Shao and I. Sharma, *Science*, 2025, **387**, 102–107.
19 Y. Luo, X. Zhang and Y. Xia, *Chin. Chem. Lett.*, 2024, **35**, 108778.
20 H. M. L. Davies and S. J. Hedley, *Chem. Soc. Rev.*, 2007, **36**, 1109–1119.
21 M. M. Díaz-Requejo and P. J. Pérez, *J. Organomet. Chem.*, 2005, **690**, 5441–5450.
22 M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704–724.
23 M. R. Rodríguez, M. Besora, F. Molina, F. Maseras, M. M. Díaz-Requejo and P. J. Pérez, *J. Am. Chem. Soc.*, 2020, **142**, 13062–13071.
24 Y. He, Z. Huang, K. Wu, J. Ma, Y.-G. Zhou and Z. Yu, *Chem. Soc. Rev.*, 2022, **51**, 2759–2852.
25 G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746–1787.
26 C. Pei, C. Zhang, Y. Qian and X. Xu, *Org. Biomol. Chem.*, 2018, **16**, 8677–8685.
27 P. Kafle, D. Herndon and I. Sharma, *J. Am. Chem. Soc.*, 2025, **147**, 13824–13832.
28 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.
29 U. Schöllkopf, G. J. Lehmann, J. Paust and H. D. Härtl, *Chem. Ber.*, 1964, **97**, 1527–1541.
30 R. S. Atkinson and B. D. Judkins, *J. Chem. Soc., Chem. Commun.*, 1979, 832–833.
31 B. A. Levi, R. W. Taft and W. J. Hehre, *J. Am. Chem. Soc.*, 1977, **99**, 8454–8455.
32 J. S. Adams and L. Pasternack, *J. Phys. Chem.*, 1991, **95**, 2975–2982.
33 D. Gerbig and D. Ley, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2013, **3**, 242–272.
34 K. Schank, A.-M. A. A. Wahab, S. Bügler, P. Eigen, J. Jager and K. Jost, *Tetrahedron*, 1994, **50**, 3721–3742.
35 T. Yoshimura, T. Fujie and T. Fujii, *Tetrahedron Lett.*, 2007, **48**, 427–430.
36 D. Zhu, L. Chen, H. Fan, Q. Yao and S. Zhu, *Chem. Soc. Rev.*, 2020, **49**, 908–950.
37 C. Hui and A. P. Antonchick, *Org. Chem. Front.*, 2022, **9**, 3897–3907.
38 E. Chinoporos, *Chem. Rev.*, 1963, **63**, 235–255.
39 P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, 1956, **78**, 4496–4497.
40 J. H. Rigby and S. Laurent, *J. Org. Chem.*, 1999, **64**, 1766–1767.
41 U. Schöllkopf and E. Wiskott, *Angew. Chem.*, 1963, **75**, 725.
42 N. Obata, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 2187–2188.
43 T. Wagner, J. Lange, D. Grote, W. Sander, E. Schaumann, G. Adiwidjaja, A. Adam and J. Kopf, *Eur. J. Org. Chem.*, 2009, 5198–5207.
44 N. I. Korotkikh, G. F. Rayenko, V. S. Saberov, V. I. Yenya, L. M. Vakhitova and A. V. Kiselyov, *Comput. Theor. Chem.*, 2024, **1238**, 114728.
45 U. H. Brinker, G. Lin, L. Xu, W. B. Smith and J.-L. Mieusset, *J. Org. Chem.*, 2007, **72**, 8434–8451.
46 D. M. Lemal and E. H. Banitt, *Tetrahedron Lett.*, 1964, **5**, 245–251.
47 B. J. Deadman, R. M. O'Mahony, D. Lynch, D. C. Crowley, S. G. Collins and A. R. Maguire, *Org. Biomol. Chem.*, 2016, **14**, 3423–3431.
48 L. Benati, G. Calestani, D. Nanni, P. Spagnolo and M. Volta, *Tetrahedron*, 1997, **53**, 9269–9278.
49 J. H. Rigby, S. Laurent, W. Dong and M. D. Danca, *Tetrahedron*, 2000, **56**, 10101–10111.
50 T. Harada, A. Karasawa and A. Oku, *J. Org. Chem.*, 1986, **51**, 842–846.
51 D. R. Williams and R. D. Gaston, *Tetrahedron Lett.*, 1986, **27**, 1485–1488.
52 K. N. Shavrin, V. D. Gvozdev, I. Y. Pinus, I. P. Dotsenko and O. M. Nefedov, *Russ. Chem. Bull.*, 2004, **53**, 2546–2553.
53 M. Kirihara, T. Ogata, A. Itou, S. Naito, M. Kishida, K. Yamazaki, H. Tabata and H. Takahashi, *Chem. Lett.*, 2013, **42**, 1377–1379.
54 D. S. Breslow, M. F. Sloan, N. R. Newburg and W. B. Renfrow, *J. Am. Chem. Soc.*, 1969, **91**, 2273–2279.
55 J. Zelenka, A. Pereverzev, U. Jahn and J. Roithová, *Chem. – Eur. J.*, 2022, **28**, e202104493.
56 T. Q. Davies, M. J. Tilby, J. Ren, N. A. Parker, D. Skolc, A. Hall, F. Duarte and M. C. Willis, *J. Am. Chem. Soc.*, 2020, **142**, 15445–15453.
57 T. Mukaiyama, T. Taguchi and M. Nishi, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 2797–2800.
58 L. Craine and M. Raban, *Chem. Rev.*, 1989, **89**, 689–712.
59 K.-S. You, L. V. Benitez, W. A. McConachie and W. S. Allison, *Biochim. Biophys. Acta, Enzymol.*, 1975, **384**, 317–330.
60 R. Mayer, D. Decker, S. Bleisch and G. Domschke, *J. Prakt. Chem.*, 1987, **329**, 81–86.
61 T. Fujii, T. Kousaka and T. Yoshimura, *Tetrahedron Lett.*, 2002, **43**, 5841–5843.

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62 T. Michida and H. Sayo, *Chem. Pharm. Bull.*, 1994, **42**, 27–30.
63 M. Haake, *Tetrahedron Lett.*, 1972, **13**, 3405–3408.
64 W. Bludssus, R. Mews, O. Glemser and G. Alange, *Isr. J. Chem.*, 1978, **17**, 137–140.
65 F. Anet, R. D. Trepka and D. J. Cram, *J. Am. Chem. Soc.*, 1967, **89**, 357–362.
66 A. Haas and T. Mischo, *Can. J. Chem.*, 1989, **67**, 1902–1908.
67 A. Lork, G. Gard, M. Hare, R. Mews, W.-D. Stohrer and R. Winter, *J. Chem. Soc., Chem. Commun.*, 1992, 898–899.
68 R. S. Atkinson and B. D. Judkins, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2615–2619.
69 R. A. Aitken, *Organic Reaction Mechanisms 1992*, 1994, pp. 205–224.
70 R. S. Atkinson, M. Lee and J. R. Malpass, *J. Chem. Soc., Chem. Commun.*, 1984, 919–920.
71 A. P. Montgomery, J. M. Joyce, J. J. Danon and M. Kassiou, *Expert Opin. Drug Discovery*, 2023, **18**, 597–613.
72 N. J. Castellino, A. P. Montgomery, J. J. Danon and M. Kassiou, *Chem. Rev.*, 2023, **123**, 8127–8153.
73 T. Huo, X. Zhao, Z. Cheng, J. Wei, M. Zhu, X. Dou and N. Jiao, *Acta Pharm. Sin. B*, 2024, **14**, 1030–1076.
74 M. M. Heravi and V. Zadsirjan, *RSC Adv.*, 2020, **10**, 44247–44311.
75 N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909.
76 Y. Hu, D. Stumpfe and J. Bajorath, *J. Med. Chem.*, 2017, **60**, 1238–1246.
77 J. Jurczyk, J. Woo, S. F. Kim, B. D. Dherange, R. Sarpong and M. D. Levin, *Nat. Synth.*, 2022, **1**, 352–364.
78 M. Peplow, *Nature*, 2023, **618**, 21–24.
79 B. D. Dherange, P. Q. Kelly, J. P. Liles, M. S. Sigman and M. D. Levin, *J. Am. Chem. Soc.*, 2021, **143**, 11337–11344.
80 F.-P. Wu, J. L. Tyler, C. G. Daniliuc and F. Glorius, *ACS Catal.*, 2024, **14**, 13343–13351.
81 M. Mortén, M. Hennum and T. Bonge-Hansen, *Beilstein J. Org. Chem.*, 2015, **11**, 1944–1949.
82 H. Guo, S. Qiu and P. Xu, *Angew. Chem., Int. Ed.*, 2024, **63**, e202317104.
83 P. Kafle, B. Ghosh, A. C. Hunter, R. Mukherjee, K. M. Nicholas and I. Sharma, *ACS Catal.*, 2024, **14**, 1292–1299.
84 B. D. Bergstrom, L. A. Nickerson, J. T. Shaw and L. W. Souza, *Angew. Chem., Int. Ed.*, 2021, **60**, 6864–6878.
85 A. C. Hunter, K. Chinthapally and I. Sharma, *Eur. J. Org. Chem.*, 2016, 2260–2263.
86 Y. Xia, H. Jiang and W. Wu, *Eur. J. Org. Chem.*, 2021, 6658–6669.
87 T. Komiyama, Y. Minami and T. Hiyama, *Synlett*, 2017, 1873–1884.
88 A. Dominguez-Huerta, X.-J. Dai, F. Zhou, P. Querard, Z. Qiu, S. Ung, W. Liu, J. Li and C.-J. Li, *Can. J. Chem.*, 2019, **97**, 67–85.
89 M. I. Fremery and E. K. Fields, *J. Org. Chem.*, 1964, **29**, 2240–2243.
90 K. Maeda, T. Mishima and T. Hayashi, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 334–338.
91 R. B. Miller and J. M. Frincke, *J. Org. Chem.*, 1980, **45**, 5312–5315.
92 D. S. Dime and S. McLean, *J. Org. Chem.*, 1981, **46**, 4999–5000.
93 D. Horwell and C. Rees, *J. Chem. Soc. D*, 1969, 1428a.
94 P. Q. Kelly, A. S. Filatov and M. D. Levin, *Angew. Chem.*, 2022, **134**, e202213041.
95 S. Liu and X. Cheng, *Nat. Commun.*, 2022, **13**, 425.
96 J. C. Reisenbauer, O. Green, A. Franchino, P. Finkelstein and B. Morandi, *Science*, 2022, **377**, 1104–1109.
97 J. C. Reisenbauer, A.-S. K. Paschke, J. Krizic, B. B. Botlik, P. Finkelstein and B. Morandi, *Org. Lett.*, 2023, **25**, 8419–8423.
98 P. Finkelstein, J. C. Reisenbauer, B. B. Botlik, O. Green, A. Florin and B. Morandi, *Chem. Sci.*, 2023, **14**, 2954–2959.
99 C. J. Stirling, *Acc. Chem. Res.*, 1979, **12**, 198–203.
100 R. S. Atkinson, B. D. Judkins, D. R. Russell and L. J. Sherry, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1967–1969.
101 D. H. Barton, I. A. Blair, P. D. Magnus and R. K. Norris, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1031–1037.
102 I. Van Wijngaarden, C. G. Kruse, R. Van Hes, J. A. Van der Heyden and M. T. Tulp, *J. Med. Chem.*, 1987, **30**, 2099–2104.
103 T. T. Brandhorst, I. R. Kean, S. M. Lawry, D. L. Wiesner and B. S. Klein, *Sci. Rep.*, 2019, **9**, 5047.
104 K. Shalini, P. K. Sharma and N. Kumar, *Der Chem. Sin.*, 2010, **1**, 36–47.

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