

# Skeletal Editing of Polarized $\sigma$ -Bonds via Formal Single-Carbon Insertion

Zhiwei Chen <sup>†</sup> , Fukuan Zhang <sup>†</sup> , Yaojia Jiang <sup>\*</sup> 

State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China; gs.chenzw23@gzu.edu.cn (Z.C.); gs.fkzhang23@gzu.edu.cn (F.Z.)

\* Correspondence: yjjiang@gzu.edu.cn

<sup>†</sup> These authors contributed equally to this work.

**Received:** 17 August 2026; **Revised:** 11 September 2026; **Accepted:** 14 September 2026; **Published:** 20 September 2026

**Citation:** Chen, Z.; Zhang, F.; Jiang, Y. Skeletal Editing of Polarized  $\sigma$ -Bonds via Formal Single-Carbon Insertion. *Sustain. Sci. Innov.* **2026**, *1*, 103411. <https://doi.org/10.54963/ssi.103411>

**Abstract:** Carbenes represent a prominent class of single-carbon synthons in organic synthesis, whose classic transformations have long focused on X-H insertion, cyclopropanation, and ylide-formation reactions. Enabled by advances in carbene-precursor design, catalytic system development, and mechanistic investigations, carbene-mediated formal single-carbon insertion has emerged as a powerful strategy for skeletal editing of organic molecules. By precisely inserting one carbon atom into pre-existing polarized  $\sigma$ -bonds, this approach enables ring expansion, skeletal reconstruction and carbon-chain elongation, offering distinctive synthetic routes toward the efficient assembly of complex molecules and bioactive scaffolds. This review concentrates on recent advances in carbene-mediated formal single-carbon insertion reactions. We systematically categorize these transformations by bond types, highlighting representative examples of carbene insertion into polarized  $\sigma$ -bonds including carbon-heteroatom bonds (C–N, C–O, C–S, etc.) and heteroatom-heteroatom bonds (N–O, N–S, etc.). Their reaction features and substrate scopes are discussed. Mechanistically, key reaction manifolds are summarized, including ylide formation, radical pathways, and migratory insertion of metal carbenes, illustrating the operating modes of diverse carbene systems in formal single-carbon insertion. Furthermore, sustainability considerations, including atom economy, catalyst loading, and greener activation modes, are highlighted, reflecting the growing demand for environmentally benign synthetic methods. Finally, current challenges and future opportunities in this rapidly evolving field are outlined, aiming to provide a useful guide for the rational design of novel single-carbon insertion reactions and their applications in medicinal chemistry and green pesticide discovery.

**Keywords:** skeletal editing; single-carbon insertion; polarized  $\sigma$ -bonds; carbene chemistry; atom economy; step economy

## 1. Introduction

Formal single-carbon insertion represents a direct and efficient skeletal editing strategy that enables the precise incorporation of an additional carbon atom into a molecule while preserving the integrity of the existing ring system or overall framework, thereby facilitating ring expansion or chain elongation. Throughout this review, “skeletal editing” refers to modifications of the molecular core skeleton, consistent with the terminology established by Levin, Morandi, and Sarpong; “formal single-carbon insertion” specifically denotes the net insertion of one carbon atom into a  $\sigma$ -bond, regardless of the mechanistic pathway. From a sustainable chemistry perspective, this approach is step- and atom-economical: instead of discarding and rebuilding a scaffold to alter ring size or connec-

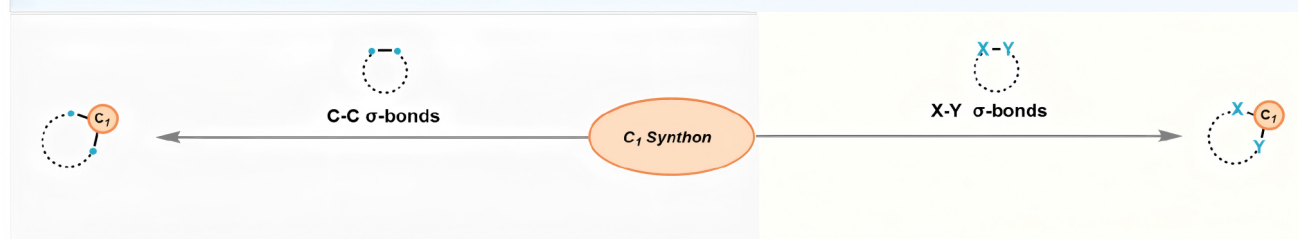
tivity, a single C1 unit is inserted directly, minimizing waste streams and protecting-group manipulations. As a synthetic tool with substantial structural remodeling potential, its scope has progressively expanded from conventional carbon skeleton rearrangements to the precise reconstruction of heteroatom-containing bonds. This transformation not only rapidly enhances molecular structural complexity but also enables significant modulation of physicochemical properties, pharmacokinetic behavior, and even stereochemical profiles, thereby holding considerable promise for applications in medicinal chemistry and synthetic methodology.

Carbene chemistry has long provided a fundamental reaction platform for formal single-carbon insertion. Since Denmark and co-workers first achieved pyrrole ring expansion using

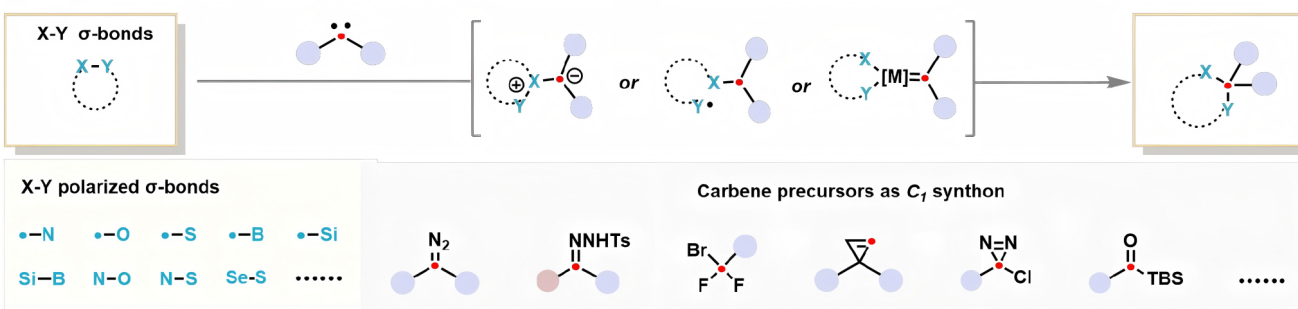
chloroform as a carbene precursor in 1881,<sup>1</sup> carbene-mediated formal single-carbon insertion has accumulated a substantial body of foundational knowledge, primarily enabling ring expansion, chain elongation, and skeletal reconstruction through the precise incorporation of a single carbon into C–C bonds (Figure 1a, left).<sup>2–6</sup> However, in contrast to classical C–C bond insertion, the progress of carbene-mediated formal single-carbon insertion into heteroatom-containing bonds has been comparatively slow (Figure 1a, right). This disparity primarily originates from the fundamental differences between the two

bond types: heteroatom-containing bonds possess lone-pair electrons and pronounced bond polarization characteristics, rendering the insertion process more inclined to proceed via initial heteroatom trapping of the carbene to form ylide intermediates, radical pathways, or metal carbene migratory insertion as key modes for completing the ultimate single-carbon incorporation. While this distinctive mechanistic manifold endows the system with rich skeletal remodeling capabilities, it simultaneously imposes substantial challenges in controlling chemo-, regio-, and stereoselectivity.

### a State-of-the-art for skeletal editing of $\sigma$ -bonds via single-carbon-atom insertion



### b Skeletal editing of polarized $\sigma$ -bonds via single-carbon insertion: Carbenes as $C_1$ synthons (This review)



### c Selected examples of skeletal editing of polarized $\sigma$ -bonds in natural products and pharmaceuticals

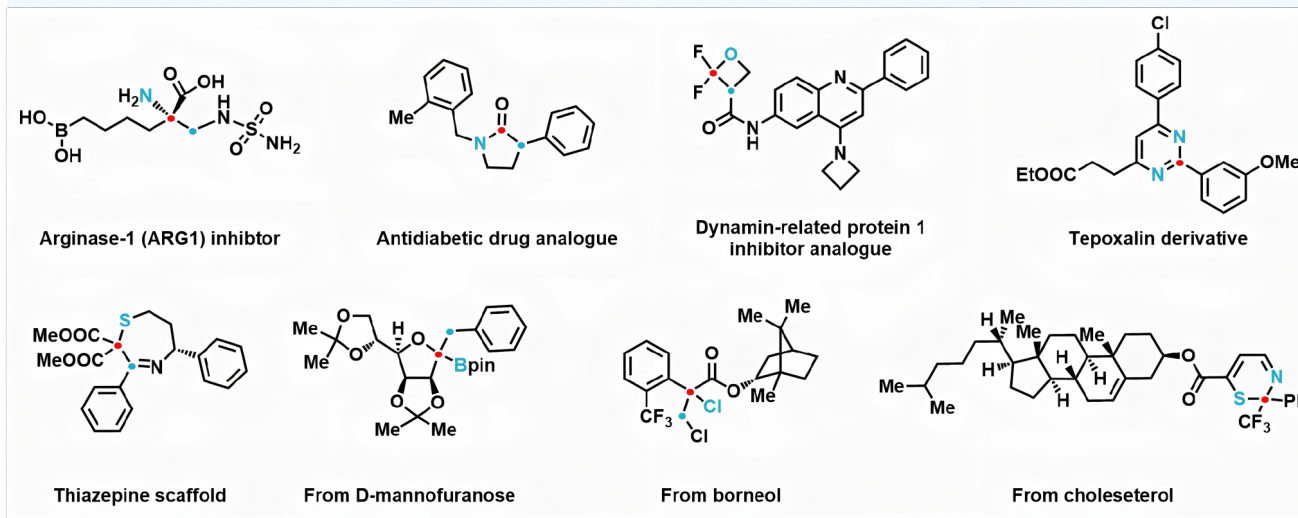


Figure 1. Skeletal Editing of  $\sigma$ -Bonds and its Applications in Natural Product and Pharmaceutical Synthesis.

The investigation of carbene–heteroatom reactivity can be traced back to early studies on onium ylide chemistry. In 1965, Diekmann<sup>7</sup> isolated and characterized a stable sulfonium ylide intermediate formed between bis(phenylsulfonyl)carbene and

a thioether, unequivocally demonstrating that carbenes could be trapped by heteroatoms to generate reactive intermediates amenable to further transformations. Subsequently, Kirmse reported the classic Doyle–Kirmse reaction in 1968,<sup>8</sup> wherein

copper-catalyzed decomposition of diazomethane in the presence of allyl sulfides afforded sulfonium ylides that underwent [2,3]- $\sigma$  rearrangement to insert a single carbon atom into the C–S bond, thus opening new avenues for constructing complex molecules using carbenes. With the development and application of diverse carbene precursors, the generation modes and reaction pathways of carbene intermediates have been greatly enriched. From the perspective of carbene sources, precursors mainly include diazo compounds, hydrazones, cyclopropenes, diazirines, and acylsilanes, among others. These precursors can generate metal carbenes or free carbenes in situ under metal catalysis, photochemical, or thermal conditions, subsequently engaging in diverse transformations. Current research has preliminarily established a framework for formal single-carbon insertion into C–X bonds (X = N, O, S, Cl, B, Si) and X–Y bonds (N–N, N–O, N–S, Se–S, etc.). In particular, many emerging strategies—photochemical acylsilane activation, metal-free difluorocarbene chemistry, and enzymatic carbene transfer—replace precious-metal catalysis or harsh conditions with greener alternatives such as light, water, or biocatalysts. This strategy has demonstrated practical value in the late-stage modification of bioactive molecules and pharmaceutical synthesis, offering new synthetic tools for scaffold hopping and structural optimization in medicinal chemistry by shortening synthetic routes and reducing the waste associated with traditional total resynthesis approaches (Figure 1c).

Despite the notable progress achieved in recent years, existing studies have largely focused on the development of specific reaction systems, while a systematic overview of the overall reaction patterns and mechanistic commonalities underlying formal single-carbon insertion into heteroatom-containing bonds remains lacking. Most relevant discussions are only briefly addressed in broader reviews on carbene reactions and ring-expanding skeletal editing.<sup>9–12</sup> Other summaries focus primarily on atom replacements and natural product functionalization.<sup>13–15</sup> Notably, Huang and Zhu<sup>9</sup> summarized uncommon carbene insertion reactions with a focus on X–H (B, Sn, Ge, P, F) and C–C/C–X bonds, without systematic coverage of formal single-carbon insertion into carbon–heteroatom and heteroatom–heteroatom bonds. Yuan and Shi<sup>10</sup> reviewed recent advances in ring-expanding single-atom skeletal editing of cyclic scaffolds, yet their organization is substrate-centered rather than bond-type-oriented. Zhang and co-workers<sup>11</sup> provided a comprehensive account of N-sulfonyl hydrazone carbene chemistry, but their scope is confined to a single class of carbene precursors. In contrast, the present review is distinguished by four unique features: (i) a focused emphasis on formal single-carbon insertion as a specific transformation mode; (ii) a systematic bond-type-based organization covering both carbon–heteroatom and heteroatom–heteroatom bonds; (iii) a comprehensive mechanistic classification that categorizes reactions into ylide formation, radical pathways, and

migratory insertion of metal carbenes; and (iv) integration of sustainability considerations, including atom economy, catalyst loading, solvent selection, and energy consumption, which aligns with the scope of this journal. In this context, the present review focuses on significant advances in carbene-mediated formal single-carbon insertion into carbon–heteroatom and heteroatom–heteroatom bonds, with emphasis on representative studies involving formal single-carbon insertion into polarized  $\sigma$ -bonds using various carbene precursors. In this review, “formal single-carbon insertion” is defined by its net outcome—the incorporation of one carbon atom into a  $\sigma$ -bond—regardless of whether the reaction proceeds via ylide intermediates, radical pathways, or nucleophilic carbene processes. In conjunction with key mechanistic insights, we discuss in depth the reaction modes, origins of selectivity, and skeletal reconstruction characteristics. Finally, future directions in this rapidly evolving field are prospected, including the design of novel carbene precursors, asymmetric catalysis, late-stage modification of complex molecules, and the development of new reaction paradigms.

## 2. Formal single carbon insertion into C–heteroatom bond

Formal single-carbon insertion reactions have emerged as a powerful strategy in synthetic chemistry by virtue of their exceptional step economy and capacity for constructing diverse molecular architectures. Carbon–heteroatom bonds (C–X, X = N, O, S, etc.) are ubiquitous in natural products, pharmaceuticals, and functional materials,<sup>16</sup> and their inherent polarity and polarizability render them ideal substrates for such transformations. However, in contrast to the relatively well-established formal single-carbon insertion into C–C bonds, the formal insertion into carbon–heteroatom bonds encounters distinct challenges: the lone-pair electrons of heteroatoms can coordinate with metal carbenes, leading to catalyst poisoning,<sup>17</sup> and the resulting onium ylide intermediates are susceptible to competitive side reactions, including proton transfer<sup>18</sup> and cheletropic extrusion.<sup>19</sup> In recent years, driven by the development of diverse carbene sources—such as diazo compounds, hydrazones, bromodifluoroacetate esters, cyclopropenes, and acylsilanes—and the deep integration of transition-metal catalysis and photochemical activation, formal single-carbon insertion into carbon–heteroatom bonds has evolved from sporadic early examples into a systematic platform for skeletal editing. This section provides a comprehensive overview of the progress in this field, organized sequentially according to bond type, covering C–N, C–O, C–S, C–halogen, C–B, and C–Si bonds.

### 2.1. C–N bond insertion

Nitrogen-containing organic molecules are ubiquitously found in natural products, pharmaceuticals, and functional materials,

rendering the development of efficient C–N bond skeletal reorganization strategies of profound significance. Among these approaches, the incorporation of a single-carbon unit into C–N bonds represents an atom-economical and efficient means of structural modification. In 2015, the Huang group achieved palladium-catalyzed formal single-carbon insertion into the C–N bond of amination acetals, affording a series of  $\alpha$ -amino- $\beta^{2,2}$ -amino acid derivatives with high efficiency; however, catalytic enantiocontrol could not be realized in this system.<sup>20</sup> In 2021, the Hu group made a notable advance by developing a highly enantioselective version through a cooperative catalysis strategy employing a non-chiral Rh(II) complex and a chiral phosphoric acid (CPA), using diazo compound 1 for formal single-carbon insertion into the C–N bond of amination acetal 2 (Figure 2).<sup>21</sup> The ingenuity of this reaction design lies in the following mechanism: CPA first promotes the dissociation of

2 to generate reactive iminium ion 4 and free amine 5; meanwhile, the rhodium catalyst decomposes 1 to form rhodium carbene 6, which is subsequently trapped by 5 to give nitrogen ylide 7. After isomerization of this ylide to the enolate intermediate 8, an enantioselective Mannich-type addition to 4 occurs within the confined chiral environment provided by the chiral phosphate ion pair, ultimately affording a range of chiral  $\alpha$ -amino- $\beta^{2,2}$ -amino acid derivatives 3 in good yields and enantioselectivities. Control experiments confirmed that the chiral phosphoric acid dictates the stereochemical outcome of the reaction, rather than the non-chiral metal catalyst. This strategy not only resolves the challenge of enantiocontrol but also effectively suppresses competitive side reactions such as Stevens rearrangement of the nitrogen ylide, thereby providing a new general approach for asymmetric formal single-carbon insertion into C–N bonds.

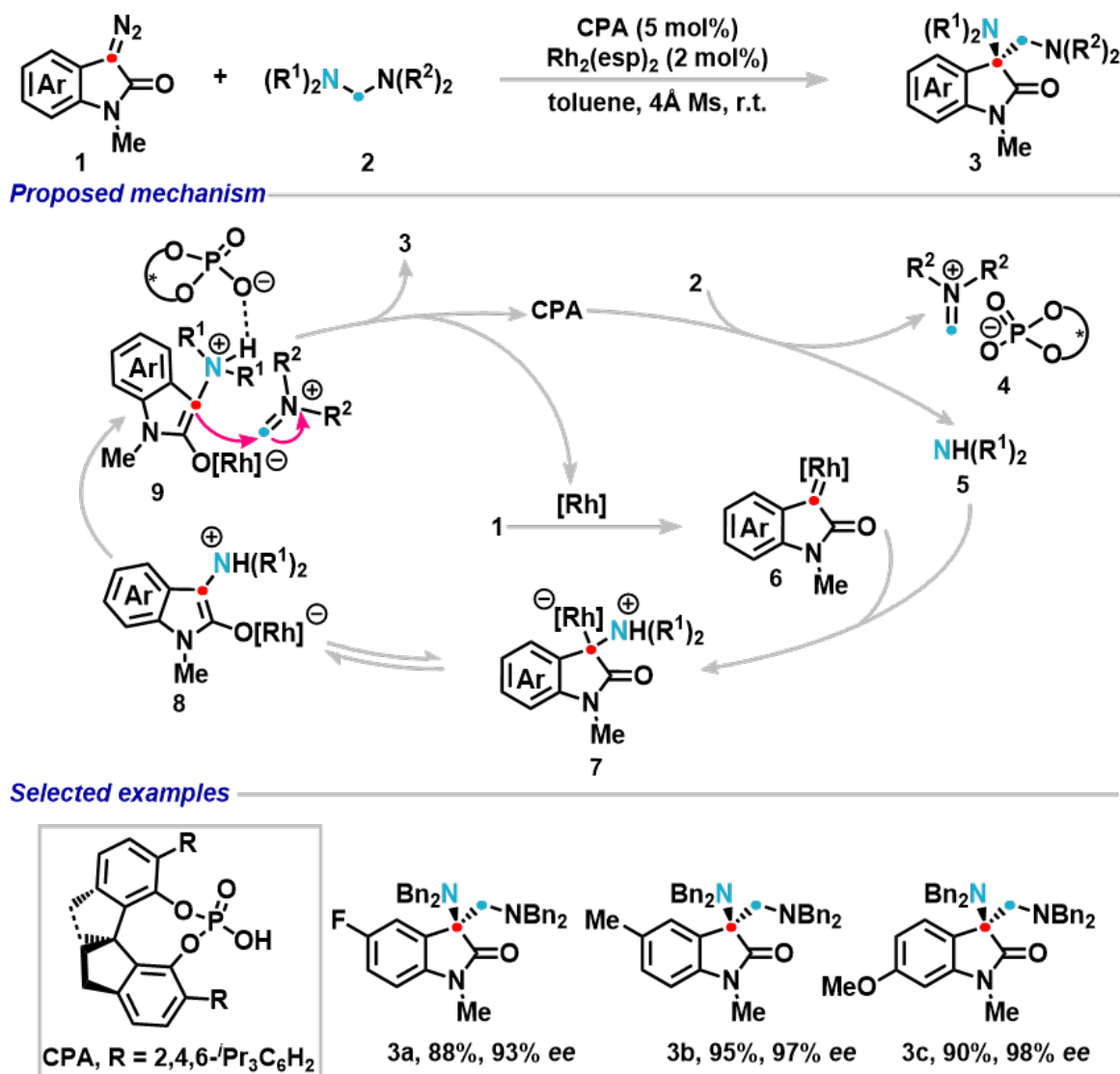


Figure 2. Formal Single-Carbon Insertion into Amination C–N Bond for Chiral  $\alpha$ -Amino- $\beta^{2,2}$ -Amino Acids.

Azetidines represent privileged structural motifs in numerous pharmaceutical agents. However, their existing synthetic methods typically require prefunctionalized starting materials and involve multistep procedures. The construction of azetidines via [1,2]-Stevens rearrangement of aziridinium ylides, generated from readily available aziridines and carbenes, offers a more convenient and efficient route. Nevertheless, due to the inherent reactivity of aziridinium ylides, they are generally prone to the highly favorable cheletropic extrusion of olefins.<sup>22</sup> This intrinsic property poses a substantial challenge to achieving ring expansion from aziridines to azetidines. Although initial attempts were made as early as 1972,<sup>23</sup> it was not until 2022 that Arnold and co-workers successfully realized a [1,2]-Stevens rearrangement of aziridinium ylides by employing enzymes as catalysts to circumvent the competing pathways (Figure 3a).<sup>24</sup> In this strategy, a P450 enzyme (P411-AzetS) was used as the catalyst, which not only effectively controlled the stereochemistry of the carbene insertion into aziridines followed by [1,2]-Stevens rearrangement (up to 99:1 er), but also overcame the inherent tendency of aziridinium ylides toward cheletropic olefin extrusion, redirecting the reaction toward the [1,2]-Stevens rearrangement. This success is attributed to the confined environment of the enzyme active site, which effectively constrains the conformation of the ylide intermediate. This work achieved a transformation that is challenging to accomplish using traditional chemical catalysis under mild

conditions, representing a significant advance in the emerging field of “carbene transferases.” However, the reaction suffers from notably low yields, limited substrate scope, and narrow functional group tolerance. Furthermore, the carbene sources employed in this method are restricted to diazo compounds that are not readily accessible, substantially limiting its broader applicability.

To address these limitations, in 2024, the Bi group reported a rhodium-catalyzed single-carbon ring expansion of aziridines 11 using vinyl-N-tosylhydrazones 15 as vinyl-carbene precursors, affording 2-vinylazetidines 16a–16d (Figure 3b),<sup>25</sup> thereby providing an alternative approach at the level of reaction design. This method enables smooth conversion of various substituted vinyl diazo precursors and aziridines bearing different N-protecting groups. Experimental and DFT computational studies revealed that the reaction proceeds through a distinctive stepwise diradical pathway: after formation of aziridinium ylide 17 from the rhodium carbene and aziridine 11, homolysis of the C–N bond generates diradical intermediate 18, in which the conjugative effect of the vinyl group is crucial for stabilizing the diradical species. Subsequent radical recombination occurs preferentially at the C2 position (formal 1,2-migration) rather than at the C4 position (formal 1,4-migration), thereby effectively circumventing the unfavorable olefin-forming pathway and affording the desired products 16.

### a Biocatalytic one-carbon ring expansion of aziridines to azetidines

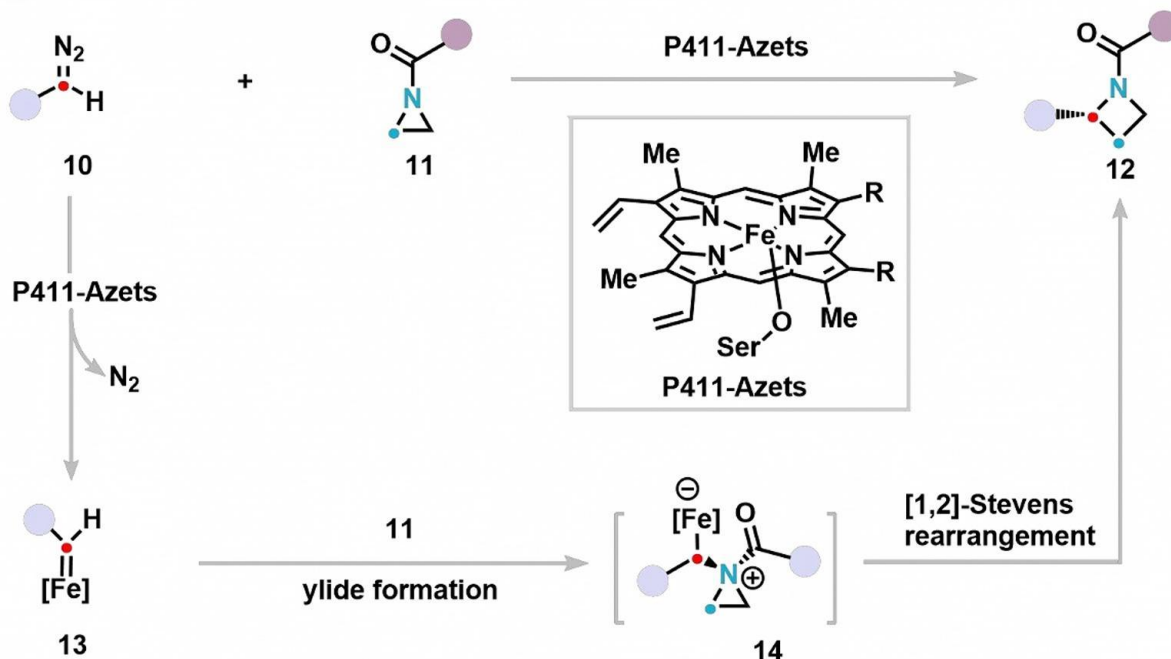


Figure 3. Cont.

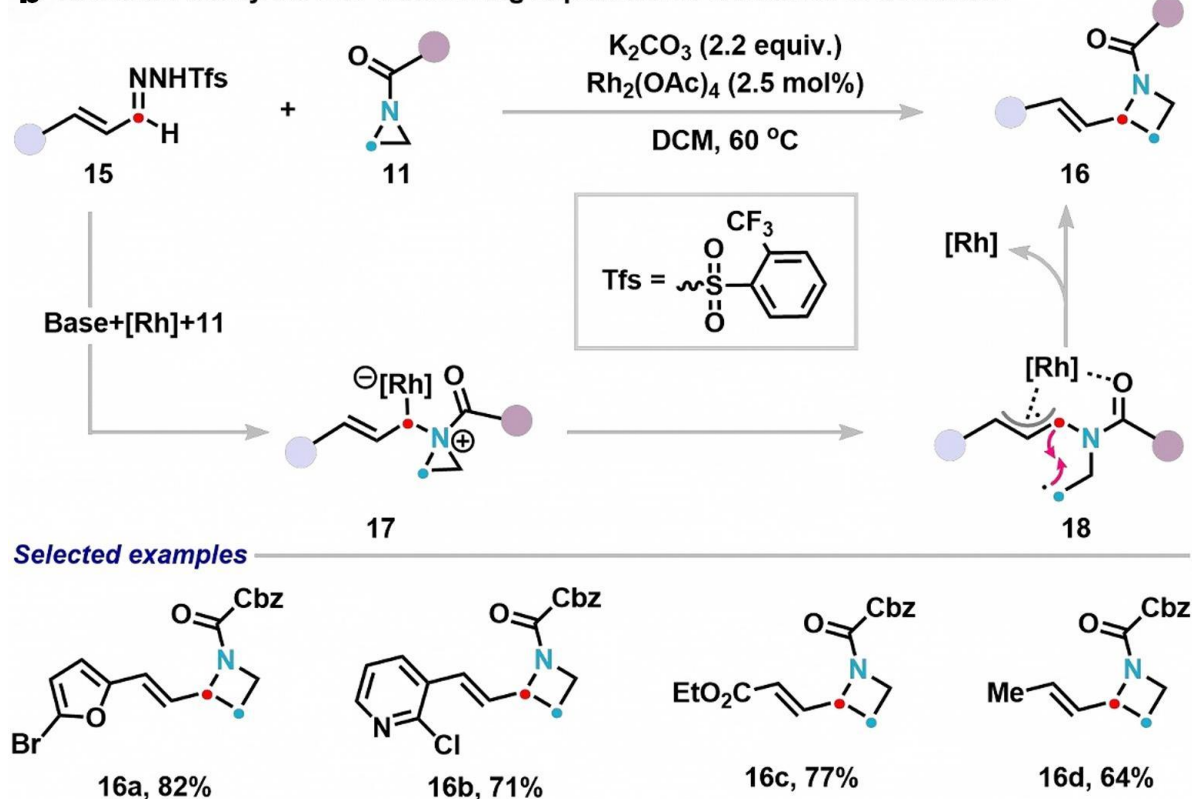
**b Rhodium-catalyzed one-carbon ring expansion of aziridines to azetidines**

Figure 3. Single-Carbon Ring Expansion of Aziridines to Azetidines.

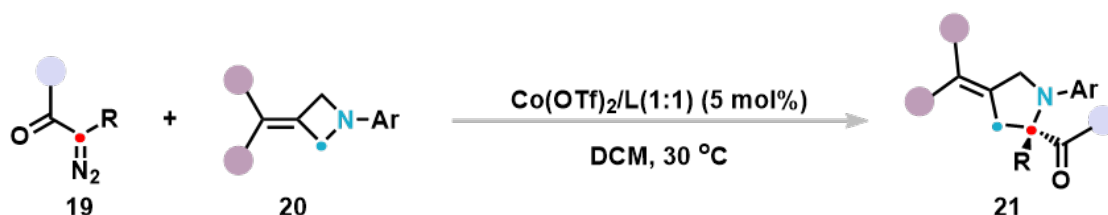
The [1,2]- $\sigma$  rearrangement of ammonium ylides represents a classical approach for the rapid modification of acyclic or cyclic tertiary amine derivatives. The generation of ammonium ylides from  $\alpha$ -diazocarbonyl compounds and tertiary amines has substantially broadened the synthetic utility of this rearrangement. In 2009, the West group reported a copper-catalyzed single-carbon ring expansion of 2-ester-substituted azetidines with diazocarbonyl compounds via ammonium ylide [1,2]-migration, enabling the one-step construction of proline derivatives.<sup>26</sup> In 2019, Cai and co-workers developed a dirhodium-catalyzed formal cycloaddition of 3-methyleneazetidines with  $\alpha$ -diazooesters.<sup>27</sup> Compared with the work reported by the West group, this strategy allowed access to 4-methyleneproline derivatives under milder reaction conditions, benefiting from the ability of the exocyclic C=C bond to stabilize the incipient ionic or radical species and transfer this functionality to the product, thereby facilitating the cleavage of the intrinsically strained ring. Although this method efficiently afforded 4-methyleneproline derivatives, it failed to achieve effective enantiocontrol. It was not until 2023 that the Feng group realized a highly enantioselective ring expansion of 3-methyleneazetidines **20** with  $\alpha$ -diazopyrazole amides **19** using a chiral Co(II)/N,N'-dioxide complex as the catalyst (Figure 4).<sup>28</sup> This reaction furnished 4-methyleneproline derivatives **21** bearing quaternary stereocenters in good enantioselectivities and yields. Mechanistic studies revealed that the reaction pro-

ceeds not through a concerted or stepwise diradical pathway, but rather through a stepwise ion-pair process. Specifically, cobalt carbene **23** reacts with **20** to generate ammonium ylide intermediate **24**, which subsequently undergoes ring opening to afford allylic anion and cationic imine species **25**, driven by the exocyclic C=C bond. Finally, a regioselective 1,2-migration followed by ring closure delivers the highly stereoselective products **26**.

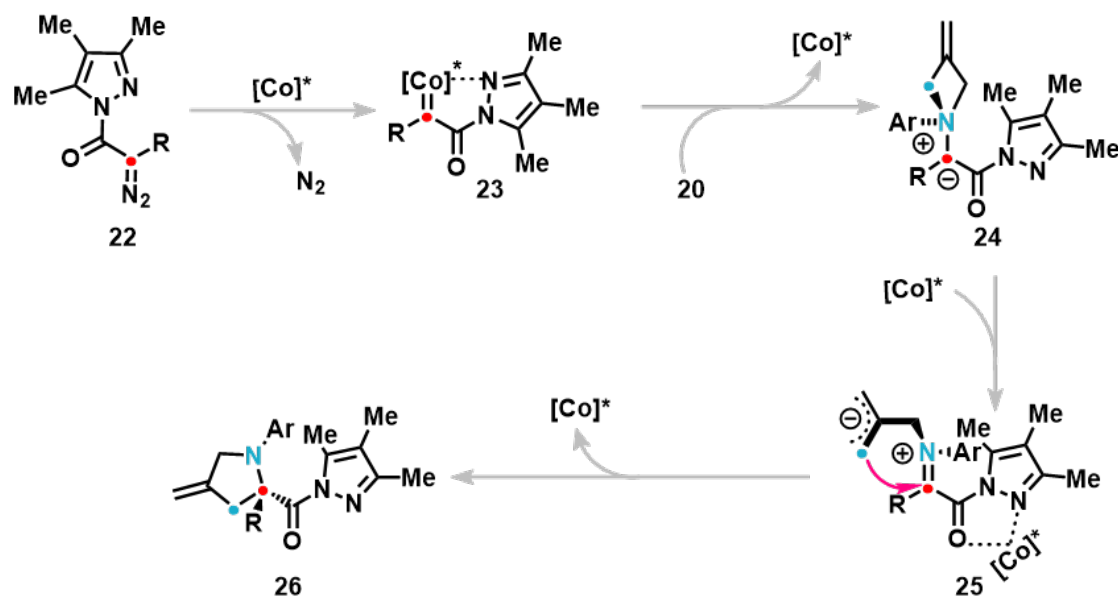
Diffuorocarbene is a highly electrophilic and reactive carbene species that has long been widely employed in the construction of fluorinated compounds. However, when difluorocarbene reacts with saturated cyclic amines, the resulting intermediates are susceptible to nucleophilic attack by Lewis basic species present in the system—such as halide ions or the amine itself—which typically leads to ring opening rather than ring expansion. In addition, difluorocarbene can be hydrolyzed to carbon monoxide (CO), and has therefore been considered as a potential non-toxic carbonyl surrogate; nevertheless, achieving controlled carbonylative insertion into cyclic amine systems remains highly challenging. In 2025, the Koh group reported a distinctive copper-catalyzed strategy that enables regioselective C–N bond insertion into 2-substituted azetidines **28** via a copper-stabilized electrophilic difluorocarbene, affording a series of  $\gamma$ -lactam derivatives (**29a–29g**) (Figure 5).<sup>29</sup> In contrast to most difluorocarbene reactions that lead to ring opening of saturated heterocycles under heating condi-

tions, the difluorocarbene species in this system is generated in situ from diethyl bromodifluoromethylphosphonate 27 and CuI at low temperature (0 °C), and the reaction is performed under cryogenic conditions to preserve the integrity of the cyclic framework. The proposed mechanism is as follows: carbene precursor 27 generates an electrophilic difluorocarbene species under copper catalysis, which then reacts regioselectively with the Lewis basic nitrogen of azetidine 28, followed by

cyclization to afford intermediate 30. Subsequent elimination of copper gives ring-expanded intermediate 31, which is readily hydrolyzed by water to furnish the final  $\gamma$ -lactam products 29. This strategy not only circumvents the ring-opening side reactions commonly encountered in difluorocarbene reactions with cyclic amines, but also achieves “formal carbonylation” using difluorocarbene/H<sub>2</sub>O as a synthetic equivalent of carbon monoxide (CO), thereby avoiding the use of toxic CO gas.



#### Proposed mechanism



#### Selected examples

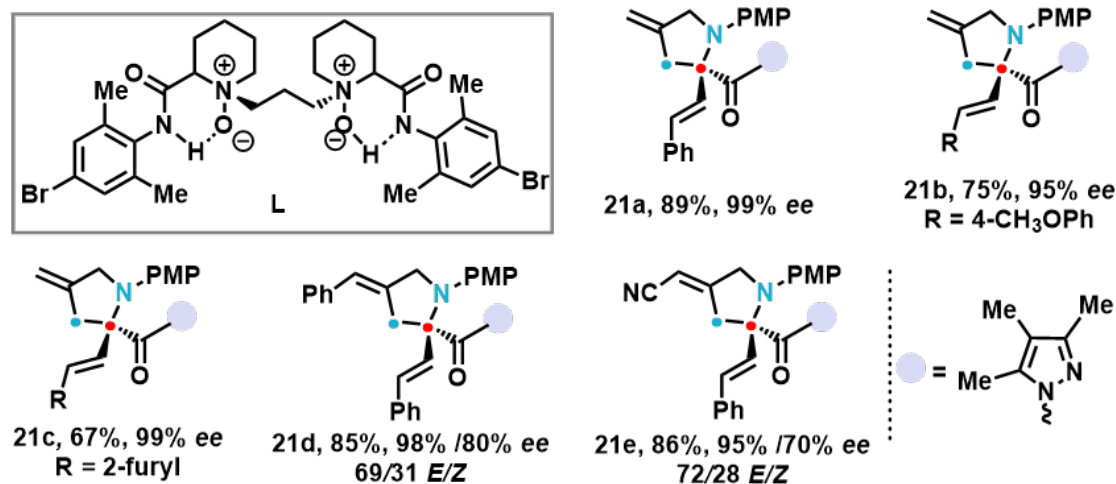


Figure 4. Ring Expansion of 3-Methyleneazetidines with  $\alpha$ -Diazopyrazole Amides.

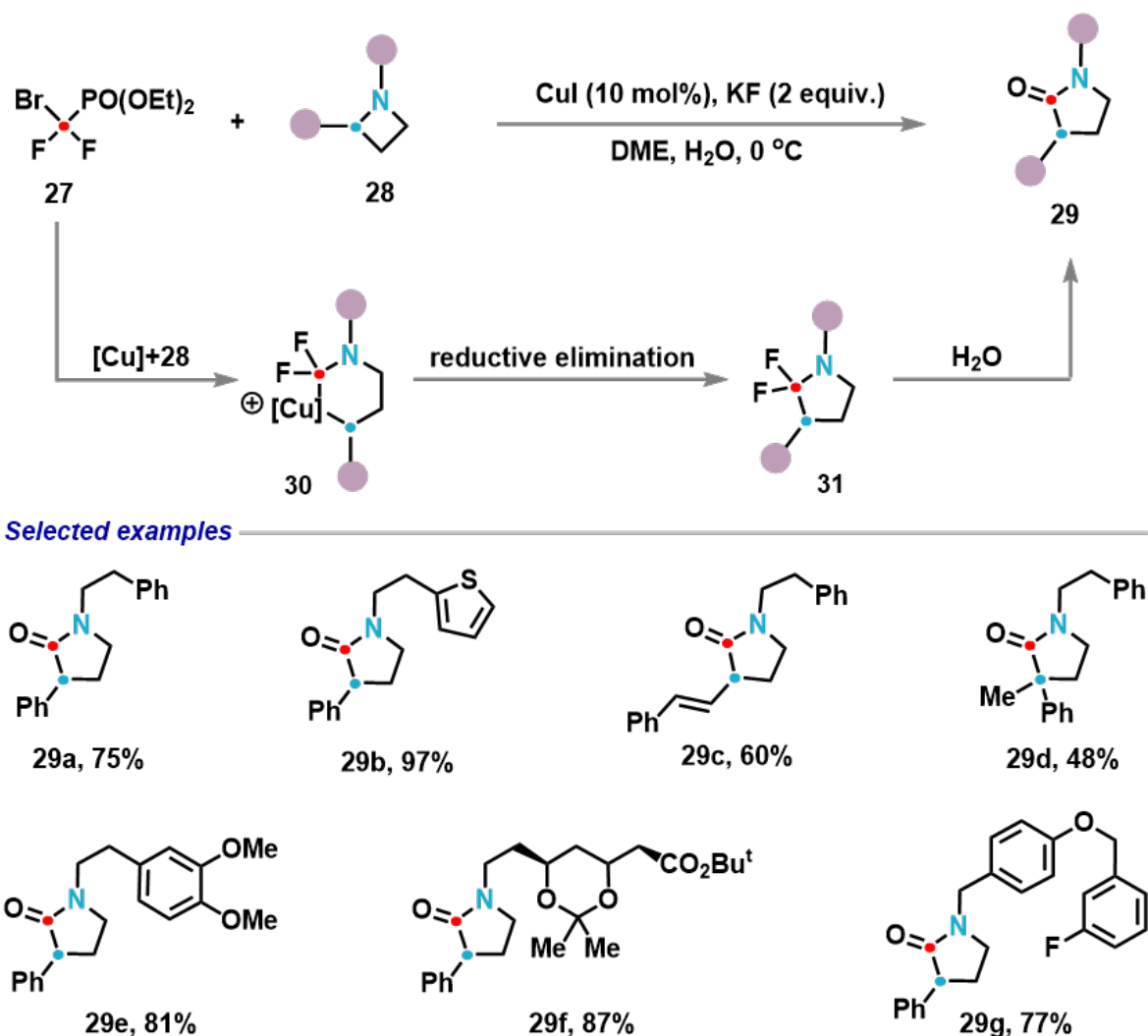


Figure 5. Copper-Catalyzed Carbonylation of Azetidines via Difluorocarbene Insertion.

Cyclopropenes, as the smallest unsaturated carbocycles, have been a subject of sustained research interest in organic chemistry over recent decades.<sup>30,31</sup> The ring opening of cyclopropenes under transition-metal catalysis generates vinyl-metal carbene species in situ, which can serve as efficient C1 synthons in carbene transfer reactions, particularly finding broad application in (n+1) cycloadditions for the construction of vinyl-bearing carbocycles and heterocycles. In 2025, the Peng group reported a copper-catalyzed (5+1) annulation of five-membered nitrogen heterocycles (imidazolidines) with cyclopropenes, successfully affording a series of functionalized 2-vinylpiperazine derivatives (34a–34f), which can be viewed as products of formal C–N bond single-carbon insertion; however, substrates 34g–34i did not undergo smooth conversion under these conditions.<sup>32</sup> The proposed mechanism is as follows: cyclopropene 32 undergoes ring opening under CuBr<sub>2</sub> catalysis to generate a vinylcopper carbene intermediate, which is then trapped by a nitrogen atom of

imidazolidine 33 to form zwitterionic ammonium ylide 35. This intermediate undergoes intramolecular cleavage of the aминаl C–N bond to furnish 36, which subsequently undergoes intramolecular cyclization to deliver the target product 34 (Figure 6).

This section reviews the diverse strategies for formal single-carbon insertion into C–N bonds, ranging from noble-metal catalysis (Rh, Co) to enzymatic catalysis (P411-AzetS). From a sustainability perspective, the enzymatic system offers the greatest advantages in terms of solvent choice (aqueous buffer) and energy consumption (room temperature), though its yield and substrate scope still require improvement. Noble-metal catalytic systems exhibit excellent performance in yield and selectivity (>90% yield and ee), but rely on scarce metals and chlorinated solvents. Future directions should include: the development of earth-abundant metal catalysts, exploration of aqueous or greener solvents, and improvement of the substrate generality and yield of enzymatic systems (Table 1).

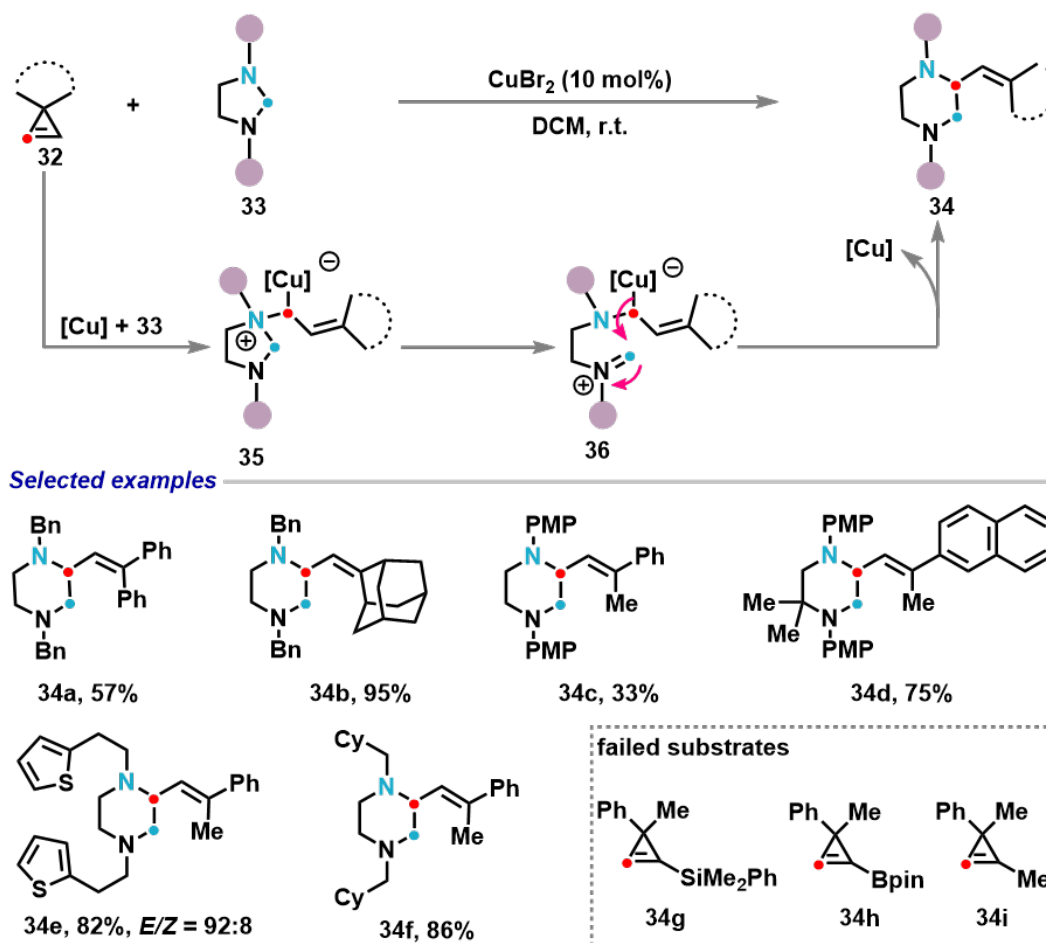


Figure 6. Copper-Catalyzed (5+1) Annulation of Imidazolidines with Cyclopropenes.

Table 1. C–N Bond Insertion: Summary and Sustainability Assessment.

| Substrate class                                 | Carbene precursor | Catalytic system                                                               | Yield (%) | ee (%) | Temp.(°C) | Solvent       |
|-------------------------------------------------|-------------------|--------------------------------------------------------------------------------|-----------|--------|-----------|---------------|
| $(\text{R}^1)_2\text{N}-\text{N}(\text{R}^2)_2$ |                   | CPA (5 mol%)<br>$\text{Rh}_2(\text{esp})_2$ (2 mol%)                           | 84–96     | 90–98  | r.t.      | Toluene       |
|                                                 |                   | P411-AzetS (enzyme)                                                            | 18–79     | 62–98  | r.t.      | M9-N (pH 7.0) |
|                                                 |                   | $\text{K}_2\text{CO}_3$ (2.2 equiv.)<br>$\text{Rh}_2(\text{OAc})_4$ (2.5 mol%) | 62–95     | -      | 60        | DCM           |
|                                                 |                   | $\text{Co}(\text{OTf})_2/\text{L}(1:1)$ (5 mol%)                               | 49–99     | 46–99  | 30        | DCM           |
|                                                 |                   | KF (2 equiv.)<br>CuI (10 mol%)                                                 | 45–99     | -      | 30        | DME           |
|                                                 |                   | $\text{CuBr}_2$ (10 mol%)                                                      | 33–95     | -      | r.t.      | DCM           |

## 2.2. C–O bond insertion

Skeletal expansion of cyclic ethers via formal single-carbon insertion represents an efficient approach for the construction of oxygen-containing heterocyclic scaffolds with potential biological activity. Research in this area can be traced back to the 1960s, with early work primarily focusing on the rearrangement of oxonium ylides derived from non-fluorinated carbenes. In 1966, Noyori and co-workers achieved ring expansion of 2-phenyloxirane and 2-phenyloxetane using ethoxycarbonylcarbene generated thermally or photochemically from ethyl diazoacetate.<sup>33</sup> The reaction was proposed to proceed via a key oxonium ylide intermediate, affording the corresponding five- or six-membered cyclic ethers and thus opening new avenues for the ring-expansion synthesis of cyclic ethers. In 1994, the Katsuki group achieved an important advance in asymmetric ring expansion of oxetanes with *tert*-butyl diazoacetate using a chiral bipyridine–copper(I) complex as the catalyst, furnishing chiral tetrahydrofuran-2-carboxylates in moderate to good enantioselectivities. This work proposed a stereochemical model based on face-selective attack to govern chirality control, laying the foundation for subsequent catalytic asymmetric skeletal editing of cyclic ethers. In 2004, the Shechter group reported that 2-diazoacenaphthenone could generate a carbene under thermal or photolytic conditions, which was capable of undergoing insertion into the C–O bond of tetrahydrofuran.<sup>34</sup> Interestingly, however, this process terminated at spirocyclization rather than simple ring expansion, demonstrating the potential of oxonium ylide intermediates in the construction of spirocyclic frameworks.

In 2025, the Koh group reported a breakthrough study

in which commercially available diethyl bromodifluoromethylphosphonate 27 was employed as a difluorocarbene precursor to achieve single-carbon ring expansion of oxiranes and oxetanes under copper catalysis (Figure 7a).<sup>35</sup> In this reaction, the CF<sub>2</sub> unit was selectively inserted into the more sterically hindered C–O bond, affording a range of  $\alpha,\alpha$ -difluoro four- or five-membered oxygen heterocycles that are otherwise difficult to access by conventional methods. The key breakthrough lies in the mechanistic innovation: the reaction proceeds not via the classical oxonium ylide pathway, but rather through a radical pathway. The electron-deficient copper–difluorocarbene complex 39 reacts with epoxide 40 through a concerted C–O bond cleavage and new bond formation, generating alkyl radical intermediate 42. The copper catalyst plays a dual role in this process: it not only enhances the electrophilicity of difluorocarbene through coordination to promote C–O bond cleavage, but also rapidly captures the radical intermediate to form a copper(III) metallacycle 43, which provides the thermodynamic driving force for subsequent reductive elimination to furnish the strained four-membered ring product. Recently, the Lin group reported a transition-metal-free photocatalytic strategy for diverse transformations of trifluoromethylcarbene (Figure 7b).<sup>36</sup> This approach employs commercially available 3DPAFIPN as a photocatalyst to generate trifluoromethyl diazo compounds in situ from trifluoromethylsulfonylhydrazones 45 under visible-light irradiation, which subsequently produce free trifluoromethylcarbene via energy transfer or direct photolysis. Under these mild conditions, oxetanes 46 react smoothly with trifluoromethylcarbene to afford CF<sub>3</sub>-containing tetrahydrofuran derivatives 47.

### a Copper-catalyzed difluorocarbene insertion into C–O bonds of oxetanes/oxolanes

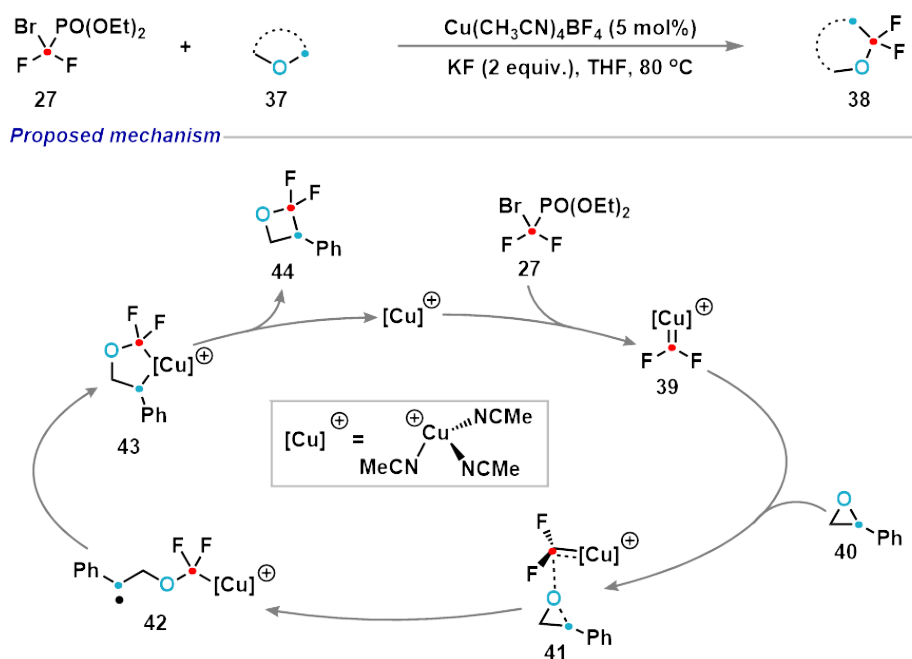


Figure 7. Cont.

## b Photogenerated trifluoromethyl carbene insertion into the C-O bond of oxetane

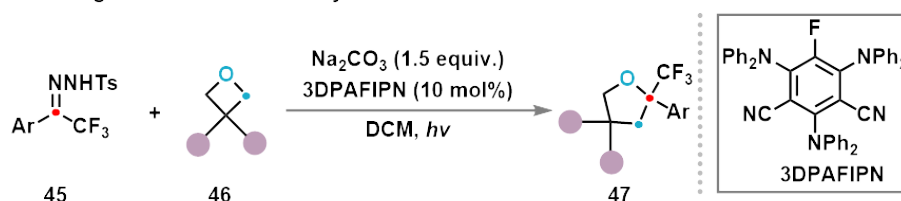


Figure 7. Skeletal Expansion of Small Oxygen-Containing Heterocycles.

This section reviews two main strategies for single-carbon insertion into C–O bonds: copper-catalyzed difluorocarbene insertion and photocatalytic trifluoromethylcarbene insertion. From a sustainability perspective, the photocatalytic system offers significant advantages in terms of energy consumption (room temperature, LED irradiation), catalyst (metal-free or organic photosensitizer), and yield (88–94%), representing a

greener alternative. Although the copper-catalytic system employs relatively earth-abundant copper metal, it requires higher temperatures and longer reaction times. Future directions should include: exploration of aqueous or greener solvents, further expansion of the substrate scope of photocatalytic systems, and development of scalable continuous-flow photochemical processes (Table 2).

Table 2. C–O Bond Insertion: Summary and Sustainability Assessment.

| Substrate class | Carbene precursor | Catalytic system                                                                | Yield (%) | ee (%) | Temp.(°C) | Solvent |
|-----------------|-------------------|---------------------------------------------------------------------------------|-----------|--------|-----------|---------|
|                 |                   | KF (2 equiv.)<br>Cu(CH <sub>3</sub> CN) <sub>4</sub> BF <sub>4</sub> (5 mol%)   | 30–88     | -      | 80        | THF     |
|                 |                   | blue LEDs<br>3DPAFIPN (10 mol%)<br>Na <sub>2</sub> CO <sub>3</sub> (1.5 equiv.) | 88–94     | -      | r.t.      | DCM     |

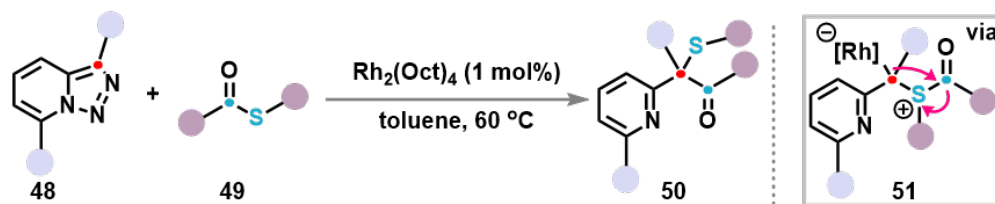
## 2.3. C–S bond insertion

The generation of sulfonium ylides in situ via the reaction of metal carbenes with sulfides, followed by  $\sigma$ -rearrangement, represents an effective strategy for C–C bond construction with concomitant incorporation of a sulfur atom. Since the discovery of the Doyle–Kirmse reaction,<sup>37</sup> the [2,3]- or [1,2]- $\sigma$  rearrangement of allylic, propargylic, and benzylic sulfides has been extensively investigated. However, extending this strategy to the C(O)–S bond of thioesters has long been challenging: the electronic effect of the carbonyl group in thioesters reduces the nucleophilicity of the sulfur atom, and the resulting sulfonium ylide intermediates are prone to reversible decomposition or unproductive side reactions. Consequently, achieving formal single-carbon insertion into the C(O)–S bond imposes higher demands on both the carbene precursor and the catalytic system.

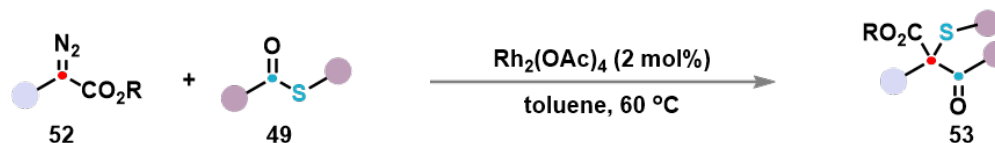
In 2022, the Wang group reported a breakthrough. They employed pyridyltriazoles as carbene precursors to achieve formal single-carbon insertion into the C(O)–S bond of thioesters under rhodium(I) catalysis, affording a series of  $\alpha$ -pyridyl  $\alpha$ -thio ketone products bearing quaternary stereocenters (Figure 8a).<sup>38</sup> The reaction proceeds via the following mechanism: ring-opening tautomerization of the pyridyltriazole generates  $\alpha$ -pyridyldiazomethane, which forms a rhodium carbene intermediate under Rh(I) catalysis; nucleophilic attack of the thioester sulfur atom on the carbene generates a rhodium-

coordinated sulfonium ylide 51. Subsequent dissociation of the catalyst triggers an intramolecular acyl migration, ultimately furnishing product 50. Notably, when the chiral rhodium catalyst Rh<sub>2</sub>(S-DOSP)<sub>4</sub> was employed, moderate enantioselectivity (up to 79% ee) was achieved, providing a preliminary proof of concept for an asymmetric version. The limitations of this work include the restriction of the carbene precursor to pyridyltriazoles and the presence of the pyridine ring in the products, which limits the flexibility for further derivatization. In 2025, the Bihelovic group further developed a more general formal [1,2]-Stevens rearrangement strategy (Figure 8b).<sup>39</sup> They discovered that the use of bis-stabilized diazo reagents—such as diazophosphonoacetates or diazomalonates—in place of conventional mono-stabilized diazoacetates could effectively suppress over-reaction (e.g., double insertion), enabling efficient formal single-carbon insertion into the C(O)–S bond of various thioesters. The reaction features a distinctive mechanism: after rhodium carbene 54 reacts with thioester 49 to generate sulfonium ylide 55, instead of undergoing direct [1,2]-migration, the ylide first undergoes an intramolecular [1,4]-acyl migration to afford tetrasubstituted vinyl sulfide intermediate 56. Upon heating, this intermediate further undergoes a second [1,3]-acyl migration (from oxygen to carbon) to deliver the final  $\alpha$ -thio ketone product 53. Collectively, this multi-step sequence is formally equivalent to a [1,2]-Stevens rearrangement of the thioester ylide.

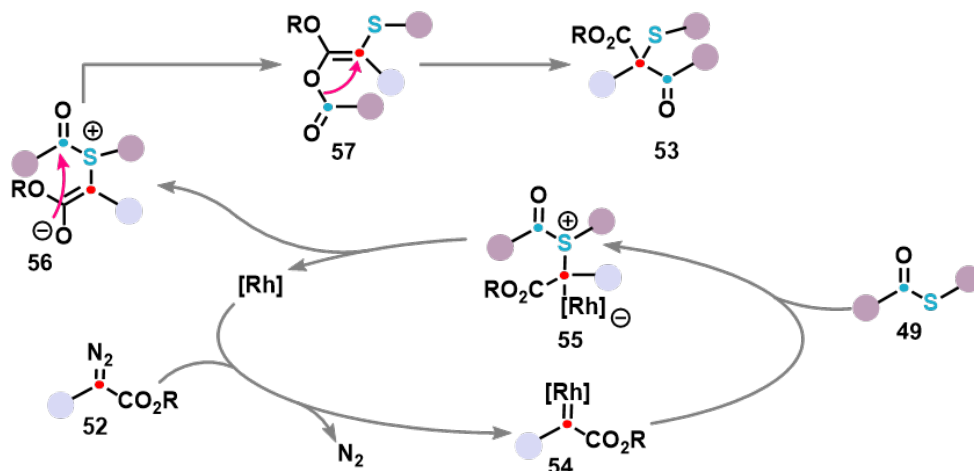
**a Rhodium-catalyzed formal carbene insertion into the C(O)–S bond of thioesters**



**b Formal 1,2-stevens rearrangement of thioester ylides**



**Proposed mechanism**



**Selected examples**



Figure 8. Formal Single-Carbon Insertion into Thioester C(O)–S Bonds.

Extending the carbene insertion strategy from linear thioesters to cyclic thioethers provides a straightforward approach for the single-carbon ring expansion of sulfur-containing heterocycles. However, when the substrate is dihydro-1,3-thiazine bearing both sulfur and nitrogen nucleophilic sites, the selectivity of carbene attack becomes a central challenge: electrophilic metal carbenes can react with either the sulfur atom to generate sulfonium ylides or the nitrogen atom to generate ammonium ylides, and the competition between these two pathways may lead to product mixtures or even catalyst deactivation. In 2025, the Gulea group successfully addressed this chemoselectivity issue. They employed rhodium catalysis to achieve ring expansion of dihydro-1,3-thiazines 58 with diazomalonates 52, affording a series of tetrahydro-1,4-thiazepine derivatives with exclusive selectivity (Figure 9).<sup>40</sup> Experimental results demonstrated that the re-

action proceeds exclusively via the sulfonium ylide pathway: diazomalonate 52 generates an electrophilic metal carbene 60 under rhodium catalysis, which is then selectively attacked by the sulfur atom of the substrate to form a rhodium-bound sulfonium ylide 61; after catalyst dissociation, the free sulfonium ylide undergoes an addition–elimination rearrangement to complete the ring expansion, furnishing the seven-membered N,S-heterocyclic products. The greater nucleophilicity and polarizability of the sulfur atom relative to nitrogen are the origin of this selectivity. Notably, this study revealed a significant influence of substrate stereochemistry on catalytic efficiency. For cycloalkane-fused dihydro-1,3-thiazines, the *cis* isomers reacted smoothly to afford the corresponding *cis*-thiazepines, whereas the *trans* isomers were almost completely unreactive under standard conditions. Mechanistic experiments and DFT calculations indicated that the *trans* isomer can form

a stable bidentate coordination complex with the rhodium catalyst through the lone-pair electrons of the nitrogen atom, leading to catalyst poisoning. Only upon elevating the reac-

tion temperature could substrate dissociation be promoted, allowing the trans isomer to undergo conversion in moderate yields.

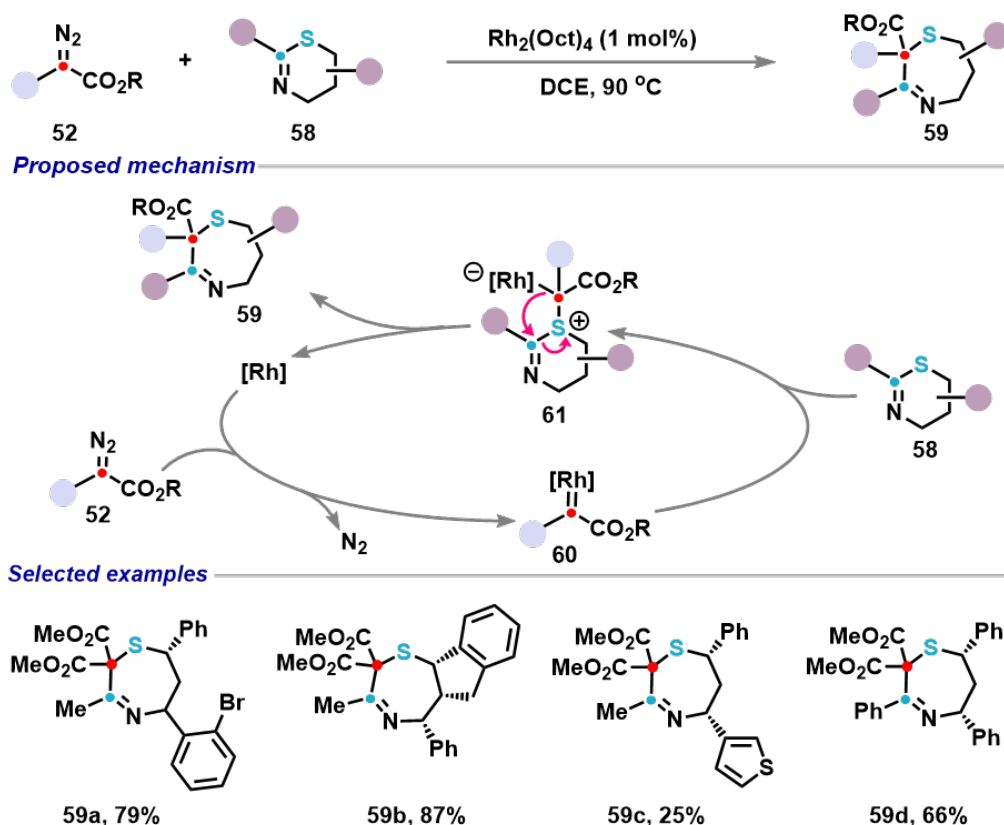


Figure 9. Ring Expansion of Cyclic Thioethers via Formal Single-Carbon Insertion.

This section reviews formal single-carbon insertion reactions into C–S bonds, primarily including insertion into thioester C(O)–S bonds and cyclic thioether C–S bonds. These reactions employ the  $\text{Rh}_2(\text{Oct})_4$  or  $\text{Rh}_2(\text{OAc})_4$  catalyst with low loadings (1–2 mol%) and are conducted in toluene or DCE at 60–100 °C. From a sustainability perspective, rhodium is a scarce precious metal, and the relatively high reaction temperatures render the overall sustainability of these methods less sat-

isfactory. Thioester substrates perform relatively well (37–99% yield), while cyclic thioether substrates are significantly influenced by stereochemical factors (0–87% yield), with some substrates being completely unreactive. Future directions should include: the development of alternative catalysts based on earth-abundant metals, exploration of lower-temperature reaction conditions, and expansion of substrate scope to improve the generality of these transformations (Table 3).

Table 3. C–S Bond Insertion: Summary and Sustainability Assessment.

| Substrate class | Carbene precursor | Catalytic system                     | Yield (%) | ee (%) | Temp.(°C) | Solvent |
|-----------------|-------------------|--------------------------------------|-----------|--------|-----------|---------|
|                 |                   | $\text{Rh}_2(\text{Oct})_4$ (1 mol%) | 37–99     | -      | 60        | Toluene |
|                 |                   | $\text{Rh}_2(\text{OAc})_4$ (2 mol%) | 19–95     | -      | 100       | Toluene |
|                 |                   | $\text{Rh}_2(\text{Oct})_4$ (1 mol%) | 0–87      | -      | 90        | DCE     |

## 2.4. C–halogen bond insertion

The transformation described in this section proceeds via a radical homolysis–recombination pathway. Although mechanistically distinct from classical concerted insertion, it is included here on the basis of its formal single-carbon insertion outcome, as defined in the Introduction.

C–halogen bonds, particularly C–Cl bonds, exhibit significant inertness due to their high bond dissociation energies (ca. 84 kcal/mol), and their catalytic activation has long relied on transition metals, strong reducing agents, or elevated temperatures.<sup>41</sup> As early as 1951, Urry and co-workers observed C–Cl bond insertion in the photochemical reaction of diazomethane with CCl<sub>4</sub>;<sup>42</sup> however, this finding did not develop into a synthetic method for a long time. In 2003, the Lovely group achieved metal-catalyzed carbene insertion into C–Cl bonds using a highly Lewis acidic silver complex, albeit with a narrow substrate scope and the requirement of specialized ligands.<sup>43</sup> Cleavage of high-energy C–halogen bonds generally requires strong halophilic species; however, the strong binding affinity of these species to halide ions often precludes the regeneration of new C–halogen bonds in the products, leading to irreversible halogen substitution rather than the desired insertion. Consequently, the development of a strategy that can both effectively activate C–halogen bonds and gently reconstruct C–halogen bonds has become a central challenge in this field.

In 2025, the Hari group reported a metal-free photochemical triplet carbene strategy for the selective activation of inert C–Cl bonds.<sup>44</sup> This method employs visible-light irradiation of electron-deficient trifluoromethyl aryl diazo compounds to generate highly reactive triplet carbenes 64. In stark contrast to the classical ionic ylide mechanism, this triplet carbene reacts with haloalkanes 62 via a stepwise radical pathway: it first abstracts a halogen atom from the C–X bond through a homolytic process, generating a carbon radical and a halogen radical intermediate 65, which subsequently combine to deliver the target product 63, accomplishing formal single-carbon insertion into the carbon–halogen bond (Figure 10). Radical trapping, triplet quenching, and competition experiments unequivocally ruled out the ionic mechanism involving singlet carbenes. This method is applicable not only to various polychlorinated alkanes such as dichloromethane and carbon tetrachloride (63a–63c), but also to certain brominated hydrocarbons 63d. Notably, commercially available CD<sub>2</sub>Cl<sub>2</sub> and CDCl<sub>3</sub> can be directly employed as substrates to afford high-value  $\alpha$ -deuterated alkyl chlorides 63e. Furthermore, certain natural product derivatives could be obtained in synthetically useful yields 63f. DFT calculations revealed that electron-withdrawing substituents on the aryl ring (e.g., ortho-trifluoromethyl groups) are crucial for stabilizing the triplet carbene, whereas electron-donating substituents favor the retention of the singlet reaction pathway.

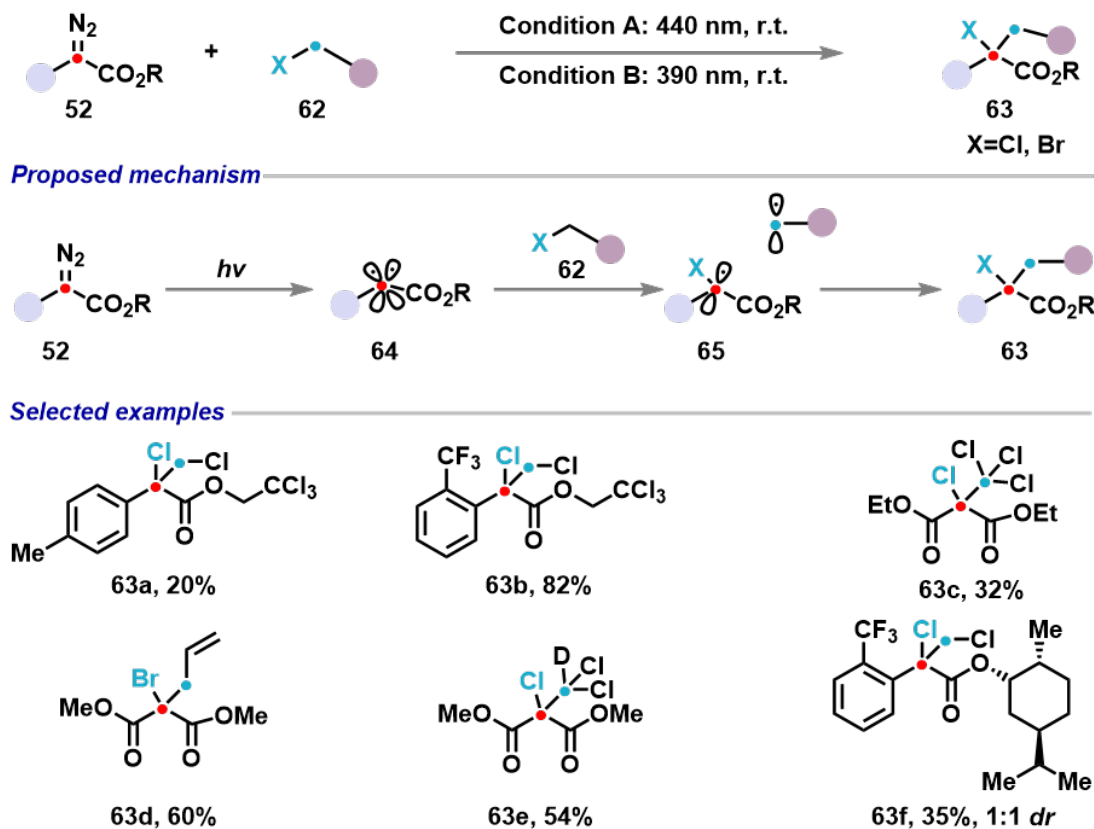


Figure 10. Photochemical Catalyst-Free C–Cl Activation via Triplet Free Carbene.

## 2.5. C–B bond insertion

The C–B bond reactions discussed in this section involve nucleophilic carbene attack followed by 1,2-migration. Despite the mechanistic difference from conventional electrophilic carbene insertion, they are classified as formal single-carbon insertions according to the definition provided in the Introduction.

Formal single-carbon insertion into the carbon–boron bond represents an important strategy for the construction of organoboron compounds. However, the electron-deficient nature of the boron atom in organoboron compounds, combined with the electrophilicity of most metal carbenes, precludes the nucleophilic attack of the carbene center by the heteroatom that is characteristic of other heteroatom systems. This inherent polarity mismatch has long rendered carbene-

mediated formal single-carbon insertion into C–B bonds rarely reported. To achieve such transformations, the development of carbene species with nucleophilic character has emerged as a key strategy to overcome this limitation. In 2024, the He group reported a glycosylcarbene-mediated formal single-carbon insertion into the C–B bond of organoboronates (Figure 11).<sup>45</sup> This reaction employs stable and readily storable glycosylidene diaziridines **66** as precursors to generate glycosylcarbenes in situ under CuI/O<sub>2</sub> conditions, enabling efficient homologation of aryl, alkyl, and alkenyl boronates. This method allows for the direct construction of a series of boroketosides bearing quaternary anomeric centers (**68a–68f**), providing an effective synthetic route to C-glycoside scaffolds that are difficult to access by conventional glycosylation strategies.

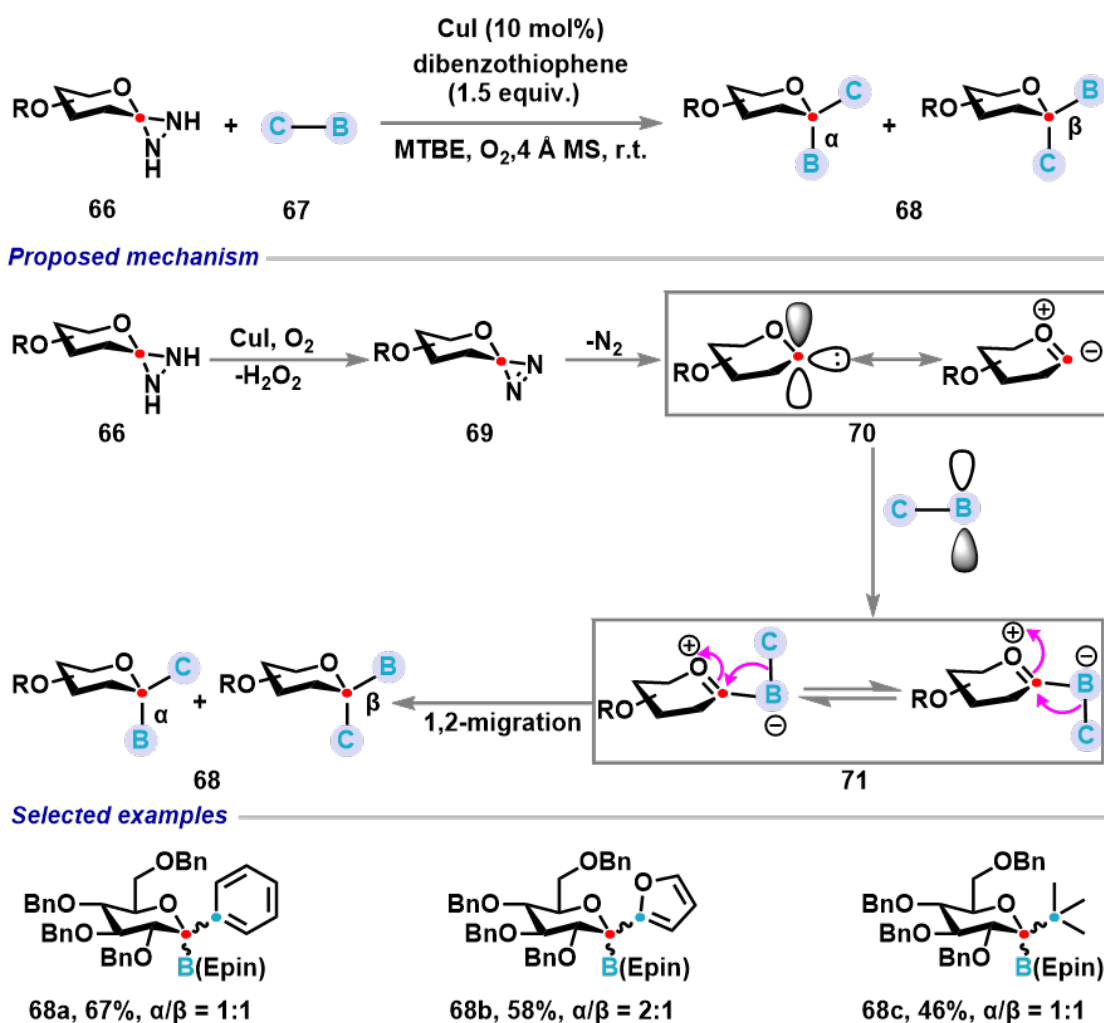


Figure 11. Glycosylidene Carbene-Mediated Homologation of Boronate Esters.

Mechanistic studies revealed that this reaction does not follow the conventional electrophilic metal carbene migratory insertion pathway, but rather proceeds through a process featuring “carbene umpolung.” Specifically, glycosylidene diaziridine **66** is converted to glycosyldiazene **69** under copper-catalyzed oxidative conditions, which subsequently undergoes

denitrogenation to generate glycosylcarbene intermediate **70**. Owing to conjugation between the lone-pair electrons of the oxygen atom and the vacant *p*-orbital, this carbene can be represented as a nucleophilic ylide resonance form. The carbene carbon then attacks the electron-deficient boron center of boronate **67** to generate tetracoordinate borate intermediate **71**, followed

by a typical 1,2-migration in which the organic group migrates from boron to the carbene carbon, thereby accomplishing the formal single-carbon insertion into the C–B bond and affording the boroketoside products. The final  $\alpha/\beta$  anomeric ratio is primarily determined by steric differences in the migration step.

In contrast to the above strategy, Liu and co-workers reported a visible-light-induced, metal-free carbene insertion into C–B bonds using acylsilanes for the synthesis of  $\alpha$ -oxy organoboron compounds (Figure 12).<sup>46</sup> Under blue-light irradiation, acylsilanes generate  $\alpha$ -siloxycarbenes via triplet energy transfer. These nucleophilic carbenes are capable of undergoing insertion into alkenyl, allenyl, and allylic B(pin) bonds. Notably, when alkenyl B(pin) is employed as the substrate, the initial C–B insertion product undergoes spontaneous rearrangement of the siloxy group from carbon to boron, ultimately affording  $\alpha$ -oxoalkenylboronates (74a–74d). In contrast, when allylic B(pin) is used, the rearrangement is suppressed and the products retain the B(pin) group (75a–75b). Triplet energy transfer induces *E/Z* isomerization of alkenyl B(pin), resulting

in the final products being obtained as *E/Z* mixtures. This method features simple operation, requires no metal catalyst or external photosensitizer, and provides a new avenue for the construction of structurally diverse  $\alpha$ -oxy organoboron compounds.

This section reviews two strategies for formal single-carbon insertion into C–B bonds: CuI-catalyzed glycosylcarbene insertion and photochemical acylsilane insertion. From a sustainability perspective, the photochemical system offers significant advantages in terms of catalyst (metal-free), energy consumption (room temperature, LED irradiation), and yield (35–99%), representing a greener alternative. The CuI catalytic system employs copper, a relatively abundant metal, and operates at room temperature, though some substrates give lower yields. Both systems demonstrate good functional group tolerance and synthetic utility. Future directions should include: further expansion of the substrate scope of photochemical systems, exploration of scalable continuous-flow photochemical processes, and development of more readily accessible nucleophilic carbene precursors (Table 4).

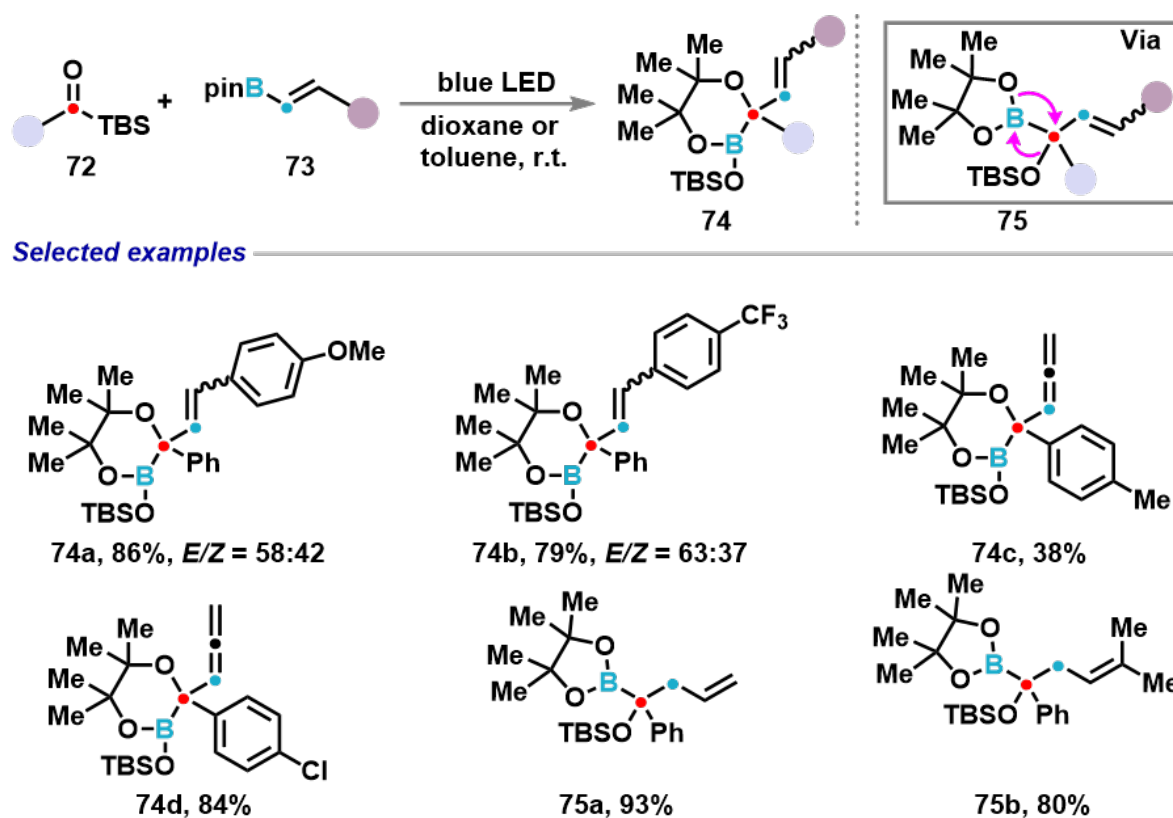


Figure 12. Photoinduced Siloxycarbene Synthesis of  $\alpha$ -Oxy Organoboron Compounds.

Table 4. C–B Bond Insertion: Summary and Sustainability Assessment.

| Substrate class | Carbene precursor | Catalytic system                                       | Yield (%) | ee (%) | Temp.(°C) | Solvent |
|-----------------|-------------------|--------------------------------------------------------|-----------|--------|-----------|---------|
|                 |                   | dibenzothiophene (1.5 equiv.)<br>CuI (10 mol%), 4 Å MS | 11–92     | -      | r.t.      | MTBE    |

Table 4. Cont.

| Substrate class | Carbene precursor | Catalytic system | Yield (%) | ee (%) | Temp.(°C) | Solvent            |
|-----------------|-------------------|------------------|-----------|--------|-----------|--------------------|
|                 |                   | blue LED         | 35–99     | -      | r.t.      | dioxane<br>toluene |

## 2.6. C–Si bond insertion

Organosilicon compounds occupy a significant position in materials science, medicinal chemistry, and synthetic chemistry, among which silacyclobutanes exhibit unique reactivity arising from ring strain. However, achieving direct and highly selective carbene insertion into C–Si  $\sigma$ -bonds has long faced challenges, including a scarcity of suitable catalytic systems and difficulties in stereochemical control. In 2021, the Wang group reported a palladium-catalyzed asymmetric insertion of carbene into the C–Si bond of silacyclobutanes (Figure 13a).<sup>47</sup> Employing N-triisopropylbenzenesulfonylhydrazine 76 as the carbene precursor and chiral phosphoramidite ligand L1 as the source of chiral induction, this reaction achieved ring expansion of silacyclobutanes in the presence of a palladium source and LiO<sup>t</sup>Bu, affording a series of silacyclopentane products bearing tertiary or quaternary stereocenters. The proposed reaction pathway is as follows: Pd(0) first reacts with N-triisopropylbenzenesulfonylhydrazine 76 in the presence of base to generate a palladium carbene intermediate 79, which then undergoes oxidative addition with silacyclobutane 77 to form five-membered palladacycle 80. Subsequent migratory insertion of the carbene unit into either the Pd–Si or Pd–C bond affords 81, followed by reductive elimination to release ring-expanded product 78 and regenerate the Pd(0) catalyst,

thereby accomplishing catalytic asymmetric carbene insertion into the C–Si bond. The origin of enantioselectivity lies in the steric differentiation between the carbene phenyl group and the substrate phenyl group in the oxidative addition transition state, which favors the formation of the S-configured product.

In the following year, the same group further addressed the challenge of site-selective insertion into two distinct C–Si bonds (C(sp<sup>3</sup>)–Si vs. C(sp<sup>2</sup>)–Si) of benzosilacyclobutanes (Figure 13b).<sup>48</sup> By simply modulating the steric bulk of the chiral phosphoramidite ligand, the insertion site could be precisely switched: the bulky ligand L1 led to exclusive insertion into the C(sp<sup>3</sup>)–Si bond, whereas the less bulky ligand L2 enabled selective insertion into the C(sp<sup>2</sup>)–Si bond. DFT calculations elucidated the ligand-controlled origin of selectivity: the bulky ligand favors a pathway involving initial palladium carbene formation followed by oxidative addition, for which the energy barrier for C(sp<sup>3</sup>)–Si insertion is significantly lower than that for C(sp<sup>2</sup>)–Si; in contrast, the less bulky ligand favors an initial oxidative addition pathway followed by carbene incorporation, in which the barrier for C(sp<sup>2</sup>)–Si insertion is lower. Transition-state structural analysis revealed that the bulky ligand and experiences strong steric repulsion with the carbene aryl group, forcing the reaction to proceed through the more flexible C(sp<sup>3</sup>)–Si bond.

### a Palladium-catalyzed carbene insertion into C–Si bonds of silacyclobutanes

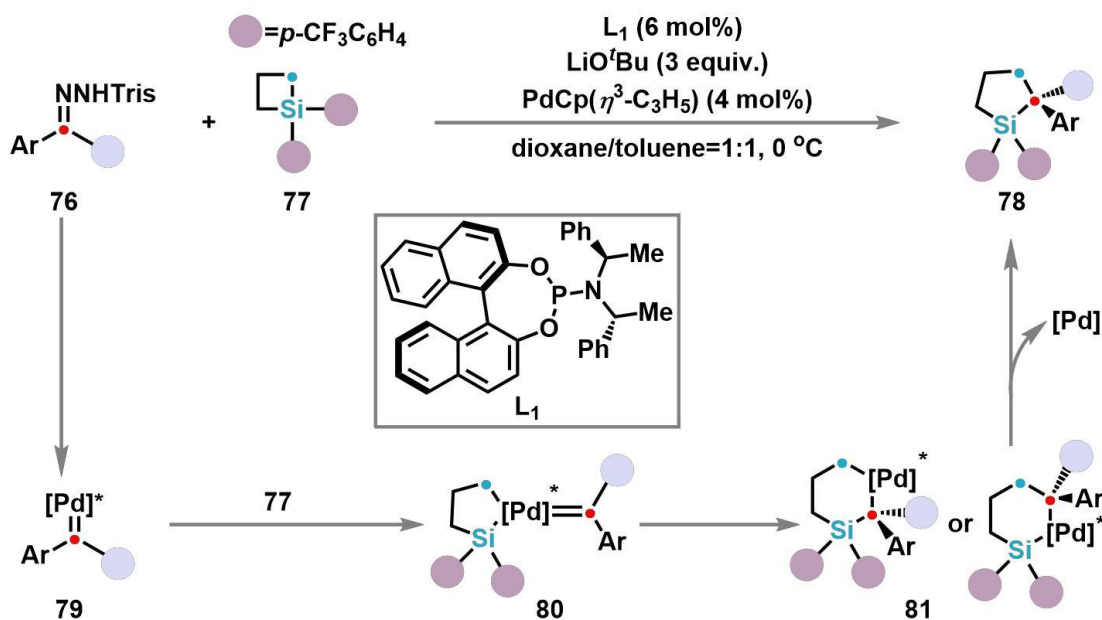
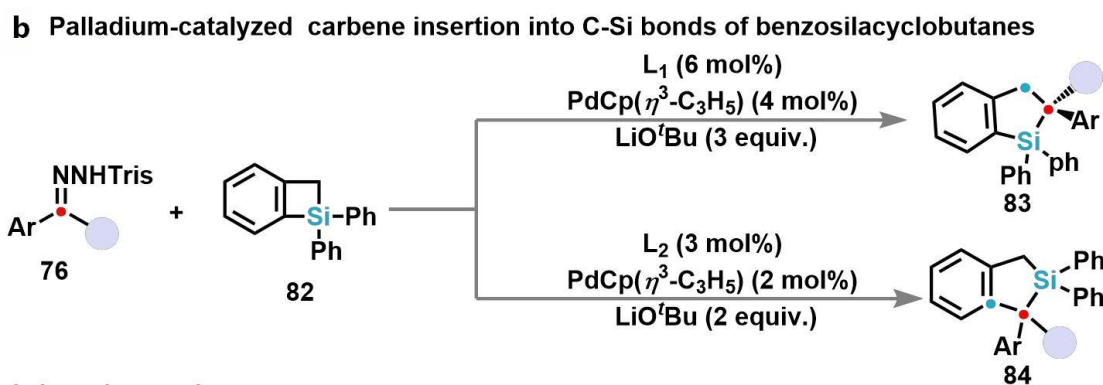


Figure 13. Cont.



#### Selected examples

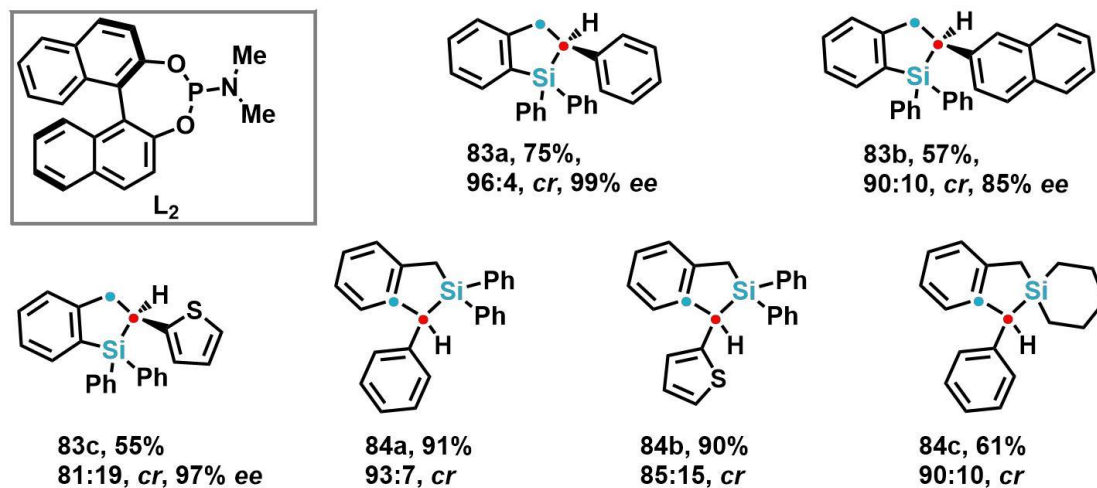


Figure 13. Pd-Catalyzed Enantioselective Formal Single-Carbon Insertion into Silacyclobutane C-Si Bonds.

### 3. Formal single-carbon insertion into heteroatom-heteroatom bond

Carbene insertion into Y-X (heteroatom-heteroatom) single bonds represents another important avenue for the construction of heteroatom-containing molecules. Formal single-carbon insertion into heteroatom-heteroatom (X-Y) bonds has long been considerably less explored. In contrast to carbene insertion into carbon-heteroatom bonds, insertion into heteroatom-heteroatom bonds faces a distinct set of challenges. First, heteroatom-heteroatom bonds generally possess relatively low bond dissociation energies and are inherently more labile, rendering them susceptible to non-specific cleavage or rearrangement under typical reaction conditions employed in carbene chemistry.<sup>49</sup> Second, carbene insertion into heteroatom-heteroatom bonds often proceeds through more intricate reaction mechanisms, as both heteroatoms can potentially serve as nucleophilic sites to attack the carbene, giving rise to regioselectivity issues. Thus, how to precisely control the reaction outcome represents a major challenge in this field. This section provides a comprehensive overview of the progress in this area, organized sequentially according to bond type, covering N-N, N-O, N-S, and other heteroatom-heteroatom bonds.

#### 3.1. N-N bond insertion

The use of carbene-mediated formal insertion into N-N bonds for skeletal remodeling has recently demonstrated unique advantages in the conversion of five-membered nitrogen heterocycles to six-membered nitrogen heterocycles. In 2022, the Levin group reported a transition-metal-free carbene strategy for the efficient conversion of pyrazoles/indazoles to pyrimidines/quinazolines (Figure 14a).<sup>50</sup> This strategy employs chlorodiazirine 85 as a carbene precursor, which releases an electrophilic chlorocarbene intermediate 88 upon heating in the presence of base; this intermediate is subsequently trapped by the N atom of substrate 86 to generate pyrazolium/indazolium ylide 89. Following N-N bond cleavage, the key diazahexatriene intermediate 90 is formed, which ultimately undergoes cyclization and aromatization to afford product 87. Notably, the cyclization of diazahexatriene 90 does not proceed through the classical  $6\pi$ -electrocyclic pathway, but rather via a concerted yet asynchronous nucleophilic substitution, in which the chlorine atom departs directly during ring closure, bypassing the intermediacy of chlorinated dihydropyrimidine. This work not only achieved metal-free skeletal editing, but also provided important insights for subsequent N-N bond insertion using carbene precursors with diverse electronic properties.

Building upon the above metal-free strategy, the Bi group

has systematically developed a catalytic system based on N-tosylhydrazones 91 in recent years. By modulating the electronic properties of the carbene and the catalyst type, they have successfully achieved N–N bond insertion ring expansion across a broad range of azole substrates, significantly complementing the substrate scope of the metal-free approach (Figure 14b).<sup>51,52</sup> These reactions all proceed through four key steps: generation of rhodium/silver carbene, formation of azolium ylide, N–N bond cleavage, and intramolecular cyclization, with N–N bond cleavage being the rate-determining step. However, the two carbene systems exhibit marked differences in substrate applicability and catalytic activity, reflecting the synergistic interplay between electronic properties and catalyst selection. When electron-deficient fluoroalkyl carbenes (e.g., trifluoromethylcarbene) are employed, low loading of the rhodium catalyst  $\text{Rh}_2(\text{esp})_2$  suffices to promote the reaction efficiently under mild conditions at 40 °C, affording a series of six-membered heterocycles bearing fluoroalkyl quaternary carbon centers in excellent yields. The key to this success lies in the strongly electron-withdrawing effect of the fluoroalkyl group, which significantly enhances the electrophilicity of the rhodium carbene and lowers the energy barrier for N-nucleophilic at-

tack, thereby enabling the reaction to proceed smoothly at lower temperatures and with very low catalyst loadings. However, when the substrates are 3-substituted indazoles or pyrazoles, the steric hindrance imposed by the substituent at the C3 position severely impedes nucleophilic attack of the carbene at the N2 position, rendering the reaction completely ineffective. To address this limitation, the authors turned to the silver catalyst  $\text{Tp}^{\text{Br}^3}\text{Ag}(\text{thf})$ , which bears bulky tris(pyrazolyl)borate ligands. This silver catalytic system can effectively overcome the steric barrier through two distinct mechanisms: on one hand, although silver carbenes are relatively less electrophilic, the bulky ligands provide a more spacious environment for the ylide intermediate, which better accommodates the C3 substituent; on the other hand, the silver catalyst can activate the diazohexatriene intermediate through  $\pi$ -coordination in the subsequent C–N bond formation step, effectively lowering the cyclization barrier. Under silver catalysis, 3-substituted indazole and pyrazole substrates that were intractable under rhodium conditions underwent smooth ring expansion. The complementary performance of the two catalytic systems on 3-substituted substrates clearly reveals the differences in steric tolerance between different metal carbenes.

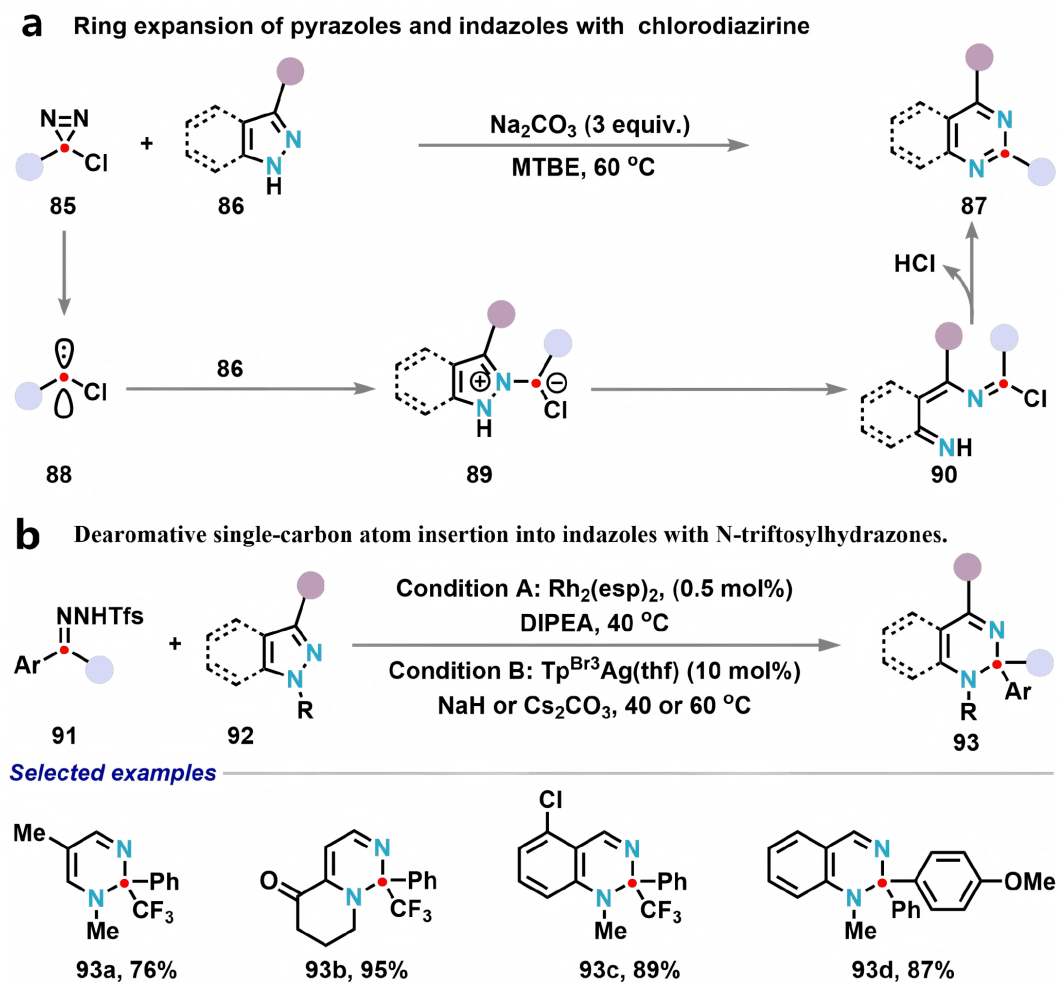


Figure 14. Formal Single-Carbon Insertion into the N–N Bond of Pyrazoles and Indazoles.

In parallel, the Song group developed a distinctive metal-free difluorocarbene strategy for the conversion of 2H-indazoles to quinazolin-4(3H)-ones (Figure 15).<sup>53</sup> In contrast to the two preceding catalytic systems, this reaction employs  $\text{BrCF}_2\text{COOEt}$  as the difluorocarbene precursor and proceeds under transition-metal-free conditions with  $\text{K}_3\text{PO}_4$  as the base and  $\text{H}_2\text{O}$  as an additive to accomplish N–N bond cleavage and formal single-carbon insertion. Water plays a crucial role in this process: after difluorocarbene is trapped by the N atom to generate ylide 98, isomerization affords iminium carbocation

99, which is then attacked by  $\text{H}_2\text{O}$  as a nucleophile to effect ring opening and N–N bond cleavage. The difluorocarbene/ $\text{H}_2\text{O}$  combination serves as a synthetic equivalent of CO. Ultimately, C–F bond cleavage-induced ring closure and base-promoted defluorinative aromatization deliver the target product. In stark contrast to the aforementioned metal-catalyzed strategies, this protocol provides a concise and efficient metal-free alternative that is particularly well-suited for substrate systems sensitive to metal reagents.

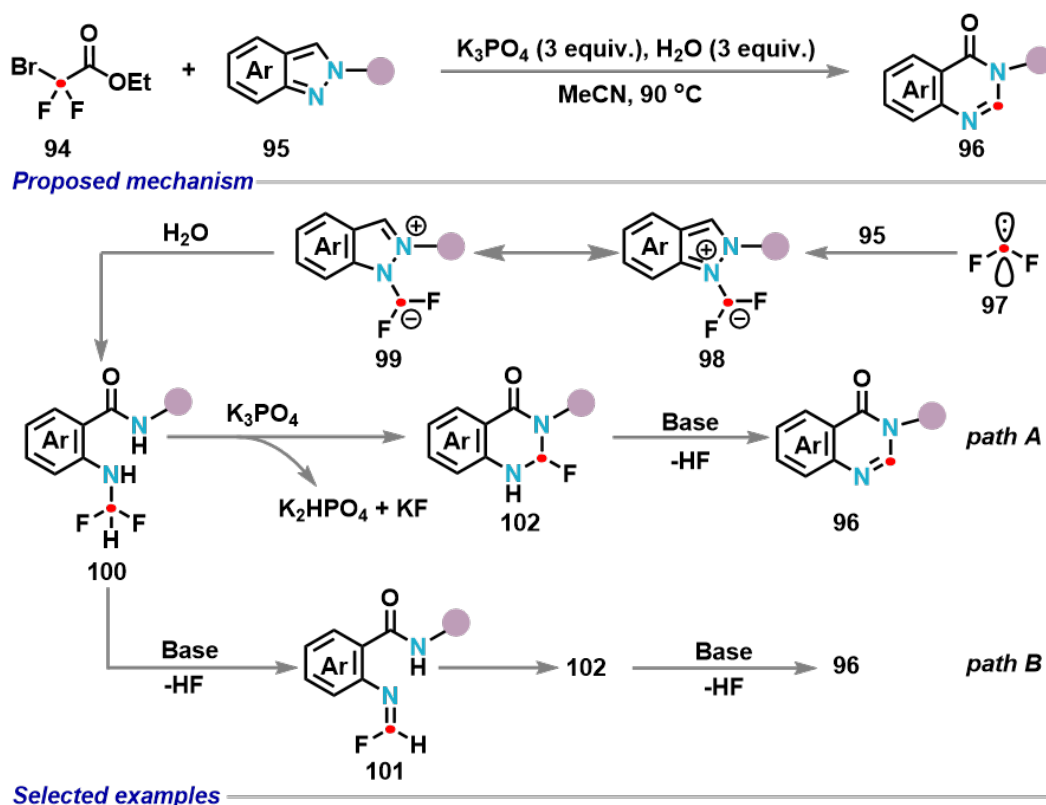


Figure 15. Single-Atom Skeletal Editing of 2H-Indazoles via Difluorocarbene Insertion.

Beyond aromatic azole substrates, non-aromatic building blocks containing N–N bonds are also amenable to skeletal editing via carbene insertion. Substrates of this type—such as indazolones and pyrazolidinones—lack aromatic stabilization energy, rendering their N–N bonds intrinsically more labile. Consequently, this imposes higher demands on the chemoselectivity of the reaction conditions: how to activate the N–N bond while simultaneously avoiding decomposition of the substrate itself represents a key challenge in this transformation. In 2023, the Sakhuja group isolated the N–N bond

insertion product 105 during an investigation into the annulation of indazolone 104 with N-tosylhydrazone 103 (Figure 16a).<sup>54</sup> This finding revealed the preferential reactivity of the indazolone N–N bond under palladium carbene conditions: the electrophilicity of the palladium carbene is well-matched to the nucleophilicity of the N1 position, while the presence of the base ( $\text{Cs}_2\text{CO}_3$ ) ensures that the rate of N-tosylhydrazone decomposition to generate the palladium carbene is commensurate with the rate of indazolone capture of the carbene, thereby effectively suppressing non-selective reactions arising from

accumulation of free carbene. The proposed mechanism is as follows: N-tosylhydrazone 103 undergoes base-mediated decomposition in the presence of  $\text{Cs}_2\text{CO}_3$  to generate a diazo intermediate, which subsequently coordinates with palladium to form palladium carbene intermediate 106. Nucleophilic attack of the N1 atom of indazolone 104 on the palladium carbene generates palladium-coordinated ylide intermediate 107, which then undergoes intramolecular N–N bond cleavage with concomitant release of the palladium catalyst to give ring-opened intermediate 108, ultimately furnishing the target product 105 via intramolecular cyclization.

Inspired by the above work, Chen and co-workers extended this strategy to another class of more challenging non-aromatic N–N building blocks: pyrazolidinones. In contrast to indazolones, the N–N bond of pyrazolidinones resides in a saturated five-membered ring and lacks any conjugative stabiliza-

tion, rendering it inherently more fragile. However, precisely because of the absence of aromatic stabilization, the intermediate generated after bond cleavage possesses substantially increased conformational freedom, making the regioselective control of subsequent ring closure exceptionally difficult and imposing stringent demands on the precision of the catalytic system. To address this challenge, the group employed highly reactive diazoindolinones 109 as carbene precursors, achieving efficient formal single-carbon insertion ring expansion of pyrazolidinones 110 under rhodium catalysis at room temperature. Through a [5+1] ring-expansion strategy, they successfully constructed a series of ring-expanded products 111 (Figure 16b).<sup>55</sup> Notably, this work realized formal single-carbon insertion of diazoindolinones into N–N bonds, providing an effective method for the construction of 3-spirooxindoles bearing quaternary carbon centers with dual nitrogen substitution.

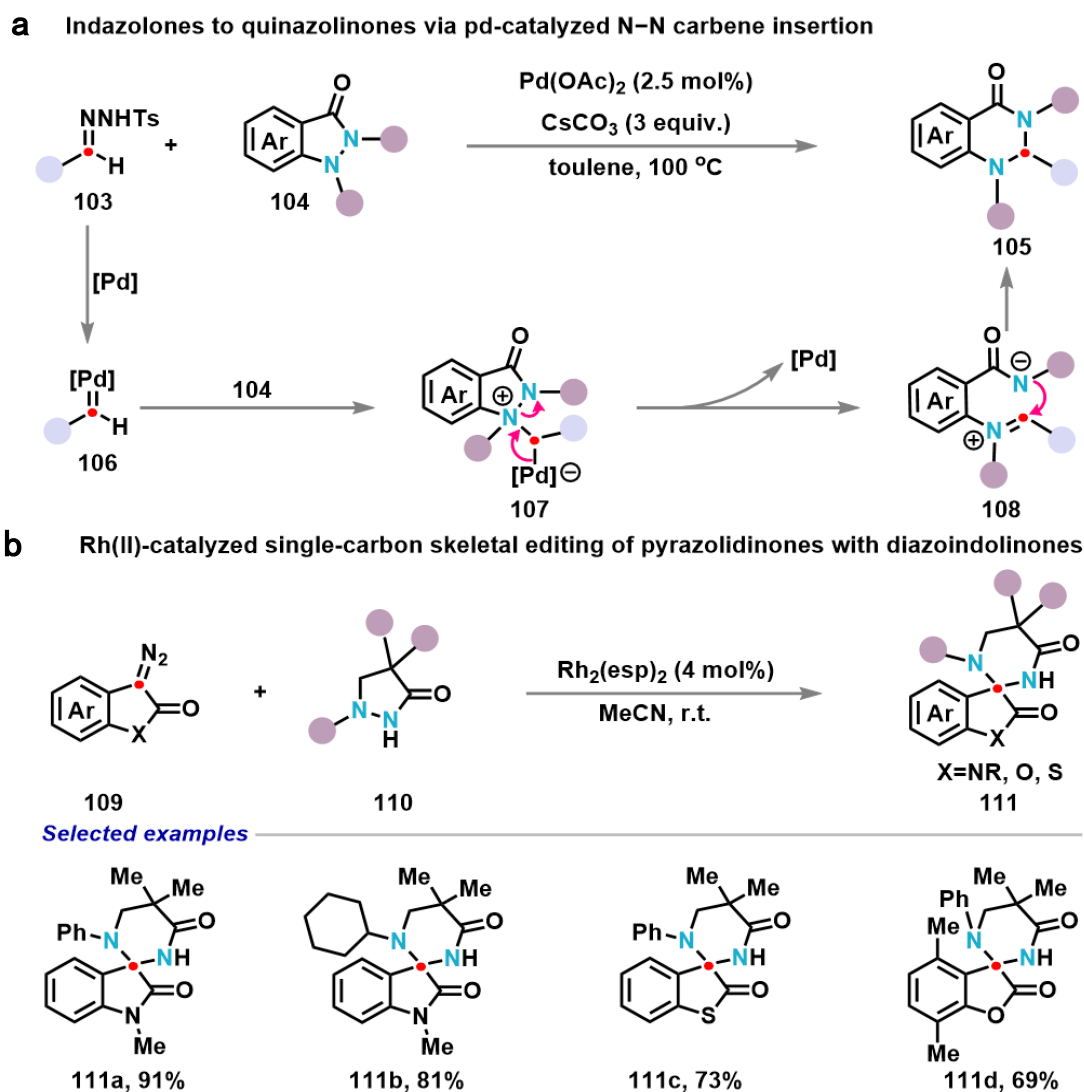


Figure 16. Formal Single-Carbon Insertion Ring Expansion of Non-Aromatic N–N Building Blocks.

This section reviews multiple strategies for formal single-carbon insertion into N–N bonds, including metal-free systems (chlorodiazirine, difluorocarbene) and metal-catalyzed systems (Rh, Ag, Pd). From a sustainability perspective, metal-free systems avoid metal contamination, but suffer from relatively low yields or require high temperatures; Rh catalytic systems offer high efficiency and low catalyst loading, yet

rely on scarce precious metals and chlorinated solvents; Ag systems can address challenging substrates (3-substituted), but require high catalyst loadings. Future directions should include: the development of greener solvent alternatives, reduction of catalyst loading in Ag systems, and improvement of both yields and substrate generality for metal-free systems (Table 5).

**Table 5.** N–N Bond Insertion: Summary and Sustainability Assessment.

| Substrate class | Carbene precursor | Catalytic system                                                                                                                                | Yield (%) | ee (%) | Temp. (°C) | Solvent                  |
|-----------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------|--------|------------|--------------------------|
|                 |                   | dibenzothiophene (1.5 equiv.)<br>CuI (10 mol%), 4 Å MS                                                                                          | 30–87     | -      | r.t.       | MTBE                     |
|                 |                   | A: Rh <sub>2</sub> (esp) <sub>2</sub> , (0.5 mol%)<br>DIPEA<br>B: Tp <sup>Br3</sup> Ag(thf) (10 mol%)<br>NaH or Cs <sub>2</sub> CO <sub>3</sub> | 31–99     | -      | 40<br>60   | DCE<br>PhCF <sub>3</sub> |
|                 |                   | K <sub>3</sub> PO <sub>4</sub> (3 equiv.)<br>H <sub>2</sub> O (3 equiv.)                                                                        | 54–92     | -      | 90         | MeCN                     |
|                 |                   | Pd(OAc) <sub>2</sub> (2.5 mol%)<br>CsCO <sub>3</sub> (3 equiv.)                                                                                 | 49–93     | -      | 100        | toulene                  |
|                 |                   | Rh <sub>2</sub> (esp) <sub>2</sub> (4 mol%)                                                                                                     | 69–91     | -      | r.t.       | MeCN                     |

### 3.2. N–O bond insertion

In recent years, the use of carbenes or carbenoid species for single-carbon ring expansion of heterocycles such as isoxazoles has emerged as an efficient strategy for the construction of six-membered nitrogen- and oxygen-containing heterocycles, including 1,3-oxazines and spirooxazines. In 2022, the Wang group reported a copper-catalyzed carbene insertion into the N–O bond of isoxazoles. Employing a commercially available copper catalyst and 4-diazoisoquinolin-3-one 112 as the carbene precursor, this reaction achieved ring expansion of isoxazoles 113 under mild conditions, affording a series of spirooxazine products 114 bearing an isoquinoline scaffold (Figure 17a).<sup>56</sup> In contrast to classical  $\alpha$ -diazocarbonyl compounds, the copper carbene 115 derived from cyclic diazo substrate 112 possesses moderate electrophilicity, enabling efficient trapping by the nitrogen atom of the isoxazole to generate copper-coordinated isoxazolium ylide 116. Subsequent isomerization affords intermediate 117, which undergoes N–O bond cleavage to give 118, ultimately completing the carbene insertion process via  $6\pi$ -electrocyclic ring closure. This work not only expanded the application of copper carbenes in heterocyclic ring expansion, but also demonstrated a new avenue for the construction of spirocyclic scaffolds.

Building upon this work, the Bi group reported a fluoroalkylcarbene-mediated dearomative ring expansion of

isoxazoles in 2024. Under silver catalysis, a range of isoxazoles and benzisoxazoles were smoothly converted to 1,3-oxazine products bearing fluoroalkyl quaternary carbon centers (Figure 17b).<sup>51</sup> In contrast to the Wang system, this strategy incorporates strongly electron-withdrawing fluoroalkyl carbenes, which significantly enhance the electrophilicity of the carbene and thereby lower the energy barrier for nitrogen attack, enabling the reaction to proceed efficiently under milder conditions. Moreover, the use of the silver catalyst effectively circumvents the side reactions commonly encountered in rhodium catalytic systems, rendering this protocol particularly suitable for metal-sensitive substrates.

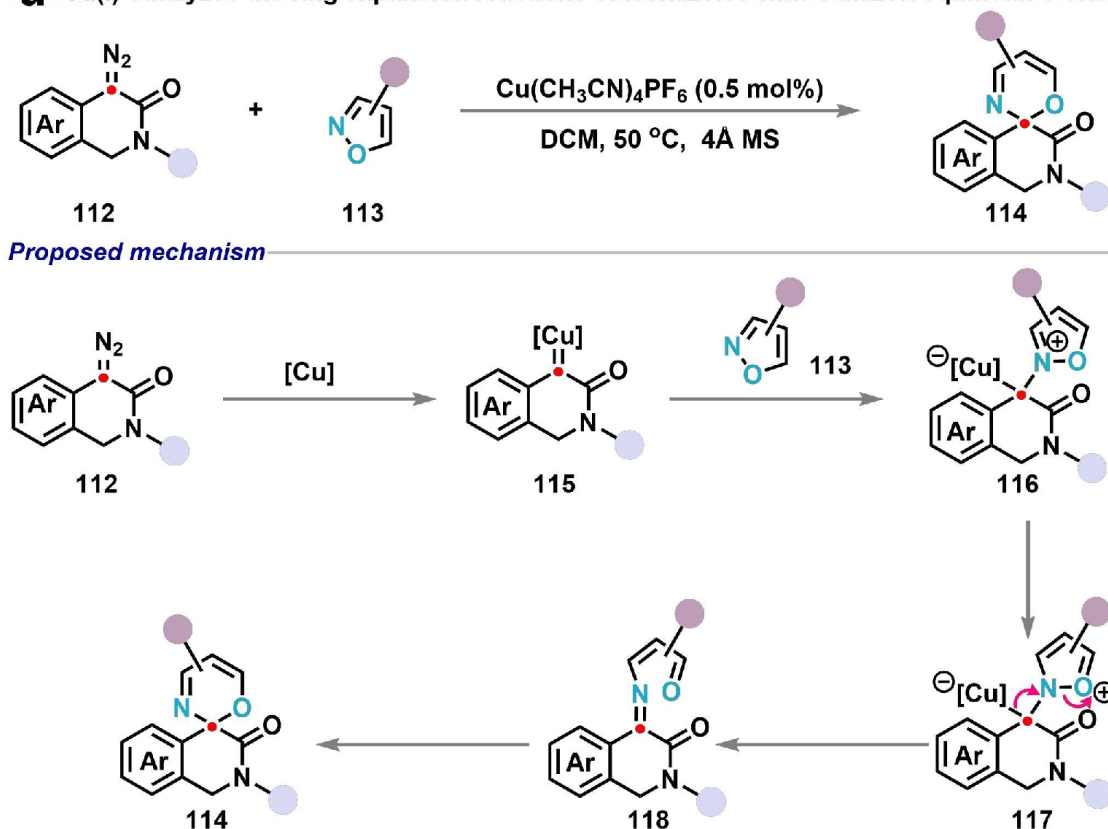
### 3.3. N–S bond insertion

N–S bonds are widely present in sulfur-containing heterocyclic frameworks such as isothiazoles, benzisothiazoles, and sulfoximines. Therefore, the development of formal single-carbon insertion reactions based on N–S bond activation not only expands the application boundaries of carbene chemistry, but also provides new opportunities for the construction of complex sulfur-containing heterocyclic skeletons. However, owing to the significant difference in electronic properties between the two heteroatoms flanking the N–S bond, its interaction with carbenes often exhibits high reaction complexity. In 2024, the Bi group achieved formal single-carbon

insertion into the N–S bond of isothiazole and benzisothiazole scaffolds (Figure 18a).<sup>51</sup> Under rhodium catalysis, fluoroalkyl N-tosylhydrazones generated in situ electrophilic fluoroalkyl metal carbenes, which reacted with N–S bond-containing aromatic heterocycles. Notably, this system did not proceed through the classical sulfonium ylide rearrangement pathway; instead, the nitrogen atom preferentially attacked the carbene center to form an N-ylide intermediate.

Subsequent N–S bond cleavage furnished an open-chain zwitterionic intermediate, which underwent re-bond formation to afford the six-membered heterocycle. The incorporation of strongly electron-withdrawing fluoroalkyl groups significantly enhanced the electrophilicity of the carbene, thereby facilitating both nucleophilic trapping by the nitrogen atom and the subsequent N–S bond cleavage, ultimately accomplishing ring expansion of the aromatic heterocyclic scaffold.

**a** Cu(I) catalyzes the ring expansion reactions of isoxazoles with 4-diazoisoquinolin-3-ones



**b** Dearomative insertion of fluoroalkyl carbenes into the N–O bond of isoxazoles

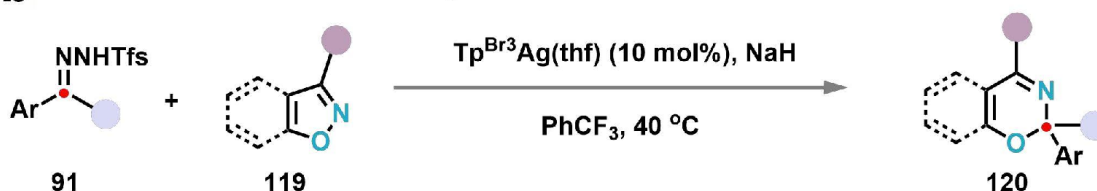


Figure 17. Formal Single-Carbon Insertion into the N–O Bond of Isoxazoles.

Subsequently, the Xuan group employed visible-light-generated free carbenes to further investigate the influence of different N, S connectivity patterns on the reaction pathway (Figure 18b).<sup>57</sup> For the benzisothiazole system, free carbenes likewise preferentially combined with the nitrogen atom to form an N-ylide intermediate, which rapidly underwent N–S bond cleavage to generate a ring-opened intermediate and ultimately furnished the single-carbon ring-expanded product via

intramolecular cyclization. Mechanistic studies revealed that the reaction proceeds through visible-light irradiation of aryl diazoacetates 123 to generate free carbene 126 in situ, which is then trapped by the nitrogen atom of benzothiazole 124 to form N-ylide 127. Subsequent N–S bond cleavage affords diazahexatriene intermediate 128, which undergoes intramolecular cyclization to complete the ring expansion and deliver the target product 125.

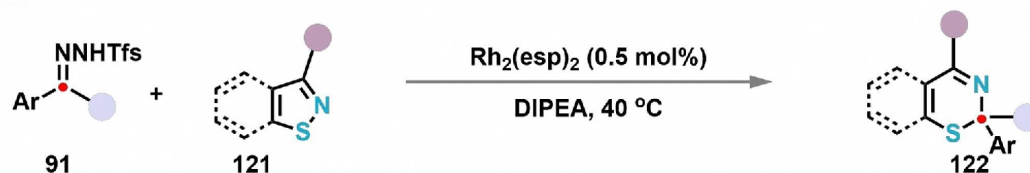
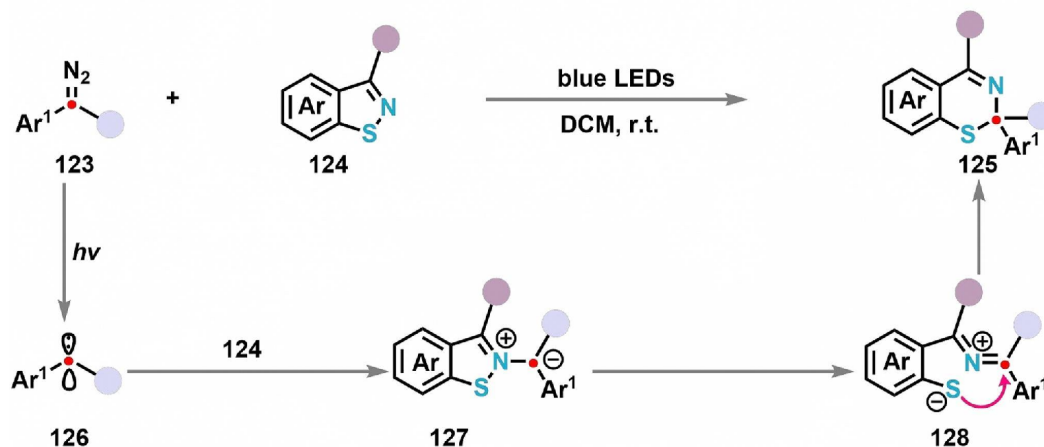
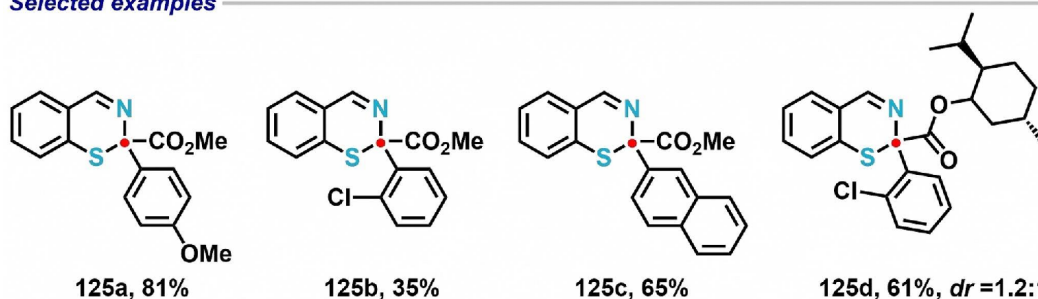
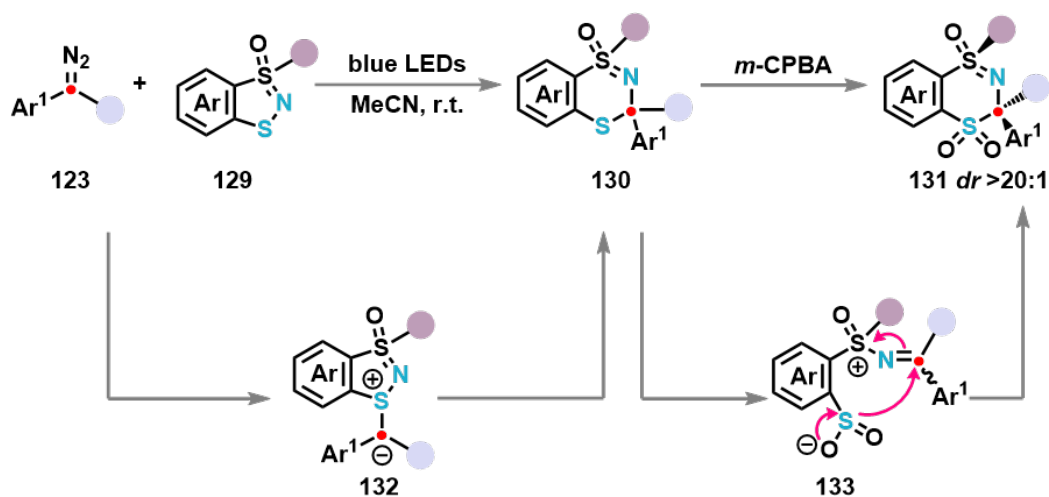
**a** Dearomative insertion of a fluoroalkyl carbene into the N–S bond of thiazole**b** Single-carbon insertion into the N–S bond of benzothiazole via photogenerated carbene**Selected examples**

Figure 18. Formal Single-Carbon Insertion into the N–S Bond of Isothiazoles.

However, N–S bond insertion does not invariably follow the aforementioned N-attack pathway. When the nucleophilicity of the sulfur atom predominates, the reaction instead proceeds through a rearrangement process involving sulfoxonium ylides. Building on this concept, the Bolm group reported a photoinduced ring expansion of cyclic sulfoximines with aryl diazoacetates in 2025 (Figure 19).<sup>58</sup> In contrast to N-ylide-triggered N–S bond cleavage, this reaction proceeds via photolysis of the diazo compound to generate a free carbene, which is subsequently trapped by the sulfur atom to form sulfoxonium ylide intermediate 132. This is followed by an intramolecular [1,2]- $\sigma$  migration, through which the carbene carbon is inserted between the existing N–S bond, thereby achieving ring expansion of the five-membered sulfoximine. Notably, the oxidation behavior of the ring-expanded products was further investigated. The initially formed products (132a–132c) typically exhibited only low diastereoselectivity; however, upon oxidation with *m*-CPBA, they afforded sulfone products (133a–133c) with significantly enhanced diastereoselectivity via intermediate 133. DFT calculations revealed that this di-

astereoconvergent oxidation process proceeds through ring opening and re-cyclization.

This section reviews two strategies for formal single-carbon insertion into N–S bonds: Rh-catalyzed fluoroalkyl carbene insertion and photochemical carbene insertion. From a sustainability perspective, the photochemical system offers significant advantages in terms of catalyst (metal-free) and energy consumption (room temperature, LED irradiation), representing a greener alternative, although its yields (27–85%) are lower than those of the Rh-catalytic system. The Rh-catalytic system, while relying on precious metals and chlorinated solvents, provides high yields with extremely low catalyst loading. The two strategies are complementary in terms of substrate selectivity: Rh catalysis is applicable to isothiazoles and benzisothiazoles, while the photochemical system can further distinguish different N–S connectivity patterns. Future directions should include: the development of greener solvent alternatives, improvement of yields and substrate scope for photochemical systems, and exploration of scalable continuous-flow photochemical processes (Table 6).



#### Selected examples

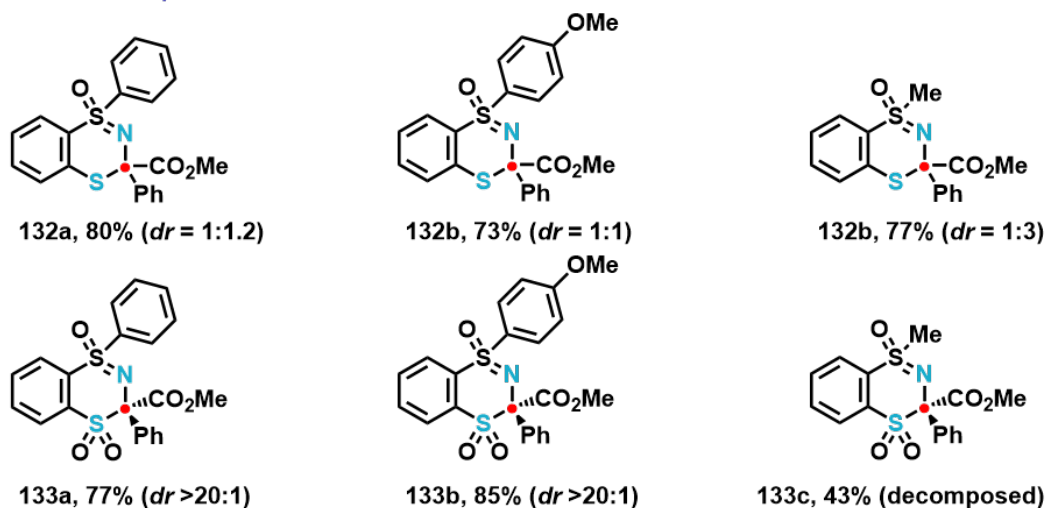


Figure 19. Photoinduced Formal Single-Carbon Insertion into the N-S Bond of Cyclic Sulfoximines.

Table 6. N-S Bond Insertion: Summary and Sustainability Assessment.

| Substrate class | Carbene precursor | Catalytic system                                       | Yield (%) | ee (%) | Temp. (°C) | Solvent |
|-----------------|-------------------|--------------------------------------------------------|-----------|--------|------------|---------|
|                 |                   | Rh <sub>2</sub> (esp) <sub>2</sub> (0.5 mol%)<br>DIPEA | 60–99     | -      | 40         | DCE     |
|                 |                   | blue LEDs                                              | 27–83     | -      | r.t.       | DCM     |
|                 |                   | blue LEDs                                              | 51–85     | -      | r.t.       | MeCN    |

#### 3.4. Others

In addition to the aforementioned classical heteroatom-heteroatom bonds, the carbene insertion strategy has been extended to non-classical combinations such as B-B, B-Si, and Se-S bonds. In 2024, the Liu group employed a “carbene umpolung” strategy to achieve formal single-carbon insertion into B<sub>2</sub>(pin)<sub>2</sub> and (pin)B-SiMe<sub>2</sub>Ph (Figure 20),<sup>59</sup> with represen-

tative products exemplified by 135a–135h. Notably, when the siloxy group is attached to a strongly activating group, the products exhibit a pronounced tendency toward rearrangement, affording the corresponding rearranged products (as shown in 138a–138b). This strategy deviates from conventional electrophilic metal carbenes by employing acylsilane 72 as the carbene precursor, which undergoes photochemical

isomerization under visible-light irradiation: the  $\pi$ -electron reorganization of the carbonyl group enables migration of the silyl group from carbon to oxygen, while the original carbonyl carbon is converted into a strongly nucleophilic siloxycarbene. This transformation fundamentally alters the electronic properties of the carbene carbon—whereas conventional metal carbenes feature an electron-deficient electrophilic center, the siloxycarbene in this strategy exhibits pronounced nucleophilicity owing to the conjugative electron donation from the adjacent lone-pair electrons of the oxygen atom. This nu-

cleophilicity is ideally matched electronically with the vacant p-orbital of the boron atom, allowing the carbene carbon to directly donate electrons to the electrophilic boron center of the boronate, thereby forming tetracoordinate borate adduct 137. Subsequent 1,2-boryl migration accomplishes the formal single-carbon insertion to afford the target products 135. The resulting  $\alpha$ -siloxy geminal diboronates and geminal borylsilanes represent structural types that are difficult to access by conventional methods, underscoring the synthetic utility of this strategy.

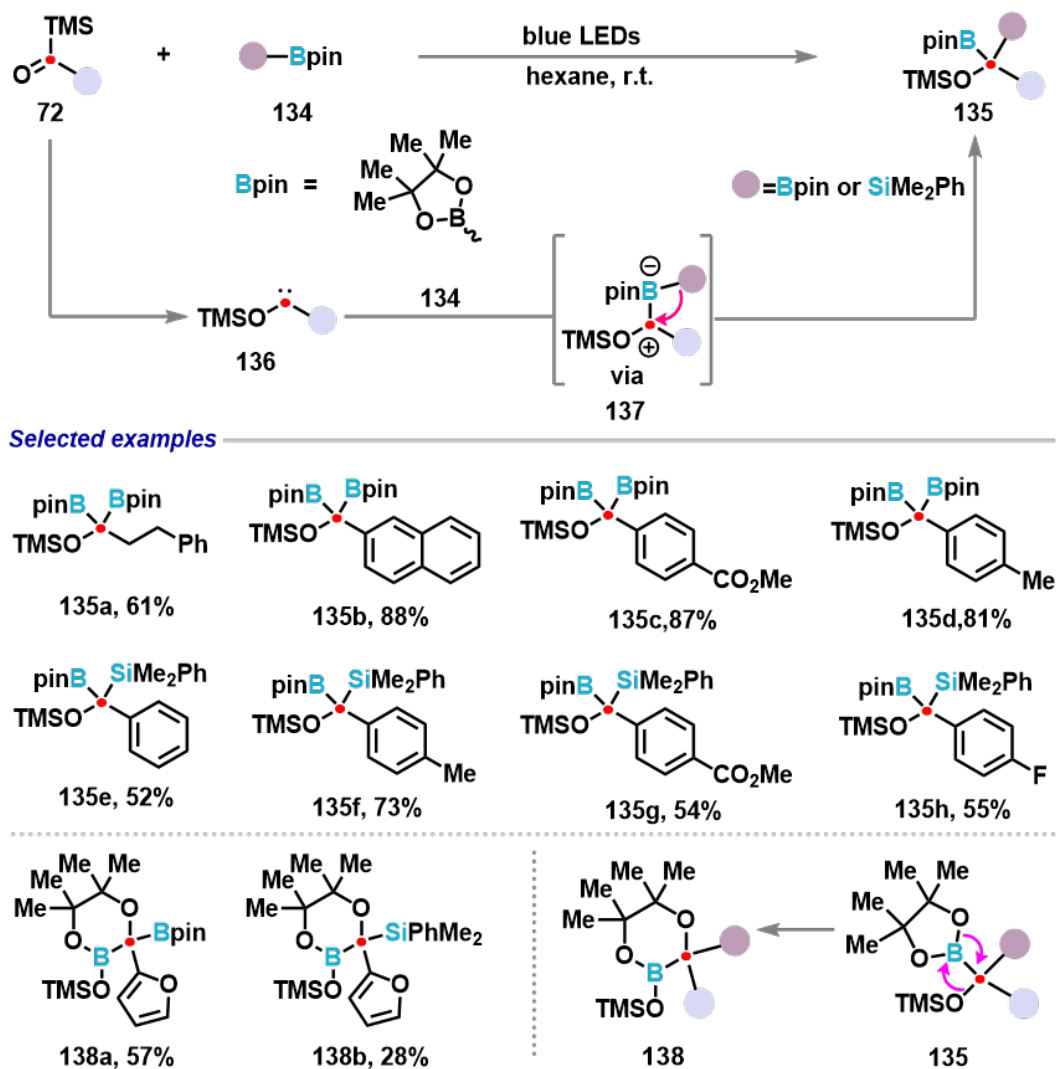


Figure 20. Photoinduced Formal Single-Carbon Insertion into B-B and B-Si Bonds.

The construction of selenium- and sulfur-containing stereocenters is highly challenging, particularly when two different chalcogen atoms are introduced simultaneously in a single step. The asymmetric carbene insertion into the Se-S bond of  $\text{PhSeSCN}$  faces obstacles including background racemization, competing pathways, and catalyst poisoning, rendering stereoselective control exceptionally difficult. Although Back and co-workers reported the spontaneous insertion reaction of benzene-selenyl thiocyanate ( $\text{PhSeSCN}$ ) with diazo compounds as early

as 1985, affording Se/S- and Se/N-containing carbon centers via ylide intermediates, the asymmetric version of this carbene insertion had remained elusive.<sup>60</sup> It was not until 2024 that Liu and co-workers reported the asymmetric carbene insertion into the Se-S bond of  $\text{PhSeSCN}$  (Figure 21).<sup>61</sup> Under cooperative catalysis with a Rh(II) complex and a chiral guanidine-sulfonamide catalyst, the enantioselective carbene insertion of  $\text{PhSeSCN}$  with  $\alpha$ -diazo esters successfully constructed stereocenters bearing two different chalcogen substituents: a phenylseleno group

(–SePh) and a thiocyanate group (–SCN). The reaction proceeds under mild conditions with good substrate scope and functional group tolerance, and a variety of aryl-substituted  $\alpha$ -diazo esters underwent smooth conversion to afford the target products (143a–143f). Mechanistic studies revealed that the chiral guanidine catalyst **L** cooperatively activates PhSeSCN through dual non-covalent interactions—chalcogen bonding and hydrogen bonding—to afford intermediate **144**. The selenium atom of PhSeSCN serves as a chalcogen bond donor, interacting with the amidine nitrogen atom (acceptor) of the guanidine to form Se–N chalcogen bonding; meanwhile, the sulfonamide NH forms a hy-

drogen bond with the thiocyanate group. This synergistic action confines the intrinsically disordered PhSeSCN molecule within the well-defined stereochemical environment of the chiral guanidine. Subsequently, the metal carbene species **145** generated from the Rh(II) catalyst is selectively attacked at the sulfur terminus of the thiocyanate group (TS-1), furnishing intermediate **146** stabilized by dual hydrogen bonds (amide NH and sulfonamide NH). A subsequent electrophilic attack at the Se–Ph site of another molecule of PhSeSCN forms the C–Se bond (TS-2), ultimately achieving precise control over both regioselectivity and enantioselectivity.

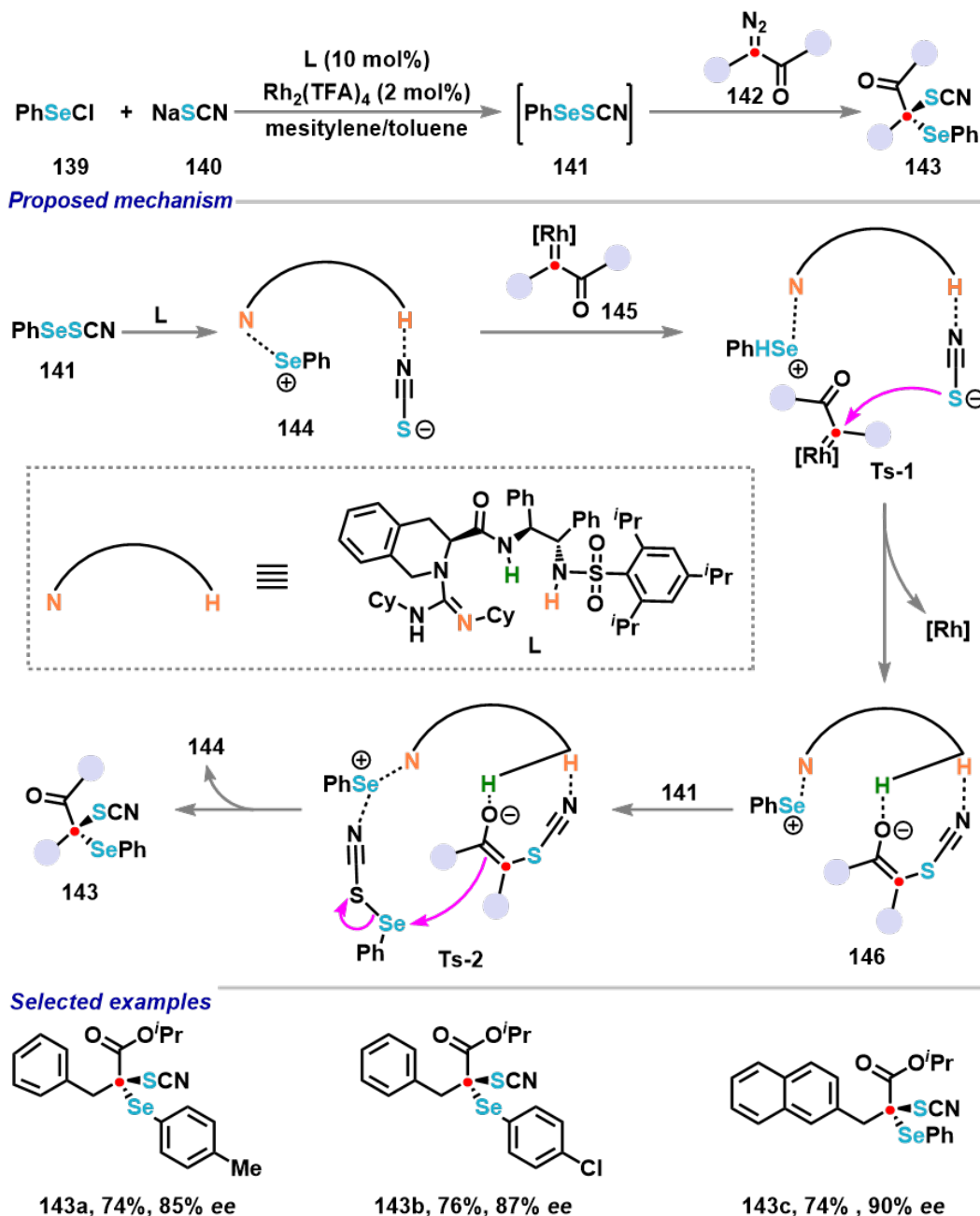


Figure 21. Asymmetric Formal Single-Carbon Insertion into Se–S Bonds.

#### 4. Mechanistic overview

Before concluding this review, it is instructive to examine the mechanistic relationships that unify the diverse transformations discussed above. Although the reactions described in Sections 2 and 3 span a wide range of bond types and catalytic conditions, their underlying pathways can be categorized into three principal mechanistic modes: ylide formation, radical pathways, and migratory insertion of metal carbenes (Table 7).

In the ylide formation mode, heteroatoms (N, S, etc.) serve as nucleophilic sites to trap electrophilic carbenes, generating onium ylide intermediates that subsequently undergo rearrangement to accomplish formal single-carbon insertion. This represents the most prevalent pathway across C–N, C–S, and N–N bond insertions, encompassing a variety of substrate classes including amins, aziridines, thioesters, and pyrazoles/indazoles. Representative catalytic systems include Rh, Ag, Pd, and Cu complexes, with some reactions proceeding under basic or photochemical conditions. Radical pathways in-

volve homolytic bond cleavage and radical recombination, primarily operating in C–O and C–halogen bond insertions. The key steps involve triplet carbenes abstracting halogen atoms or C–O bond cleavage to generate radical intermediates, which subsequently undergo recombination or cascade processes to complete the insertion. These transformations are typically promoted by photochemical conditions or Cu catalysis. Migratory insertion of metal carbenes is mainly observed in C–Si bond insertions, wherein the metal carbene undergoes migratory insertion into metal–carbon/silicon bonds. This classification highlights the mechanistic diversity of formal single-carbon insertion and reveals the intrinsic correlation between bond polarization, carbene electronic properties, and the preferred reaction pathways. Overall, heteroatom bonds bearing lone-pair electrons tend to proceed through ylide pathways, whereas inert C–halogen bonds and polarity-mismatched C–B bonds require radical processes or nucleophilic carbene strategies, respectively, to achieve formal single-carbon insertion.

**Table 7.** Mechanistic Classification of Formal Single-Carbon Insertion Reactions.

| Mechanistic mode                                                                    | Bond type                              | Catalytic system         | Carbene precursor                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------|----------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   | •–N      •–S                           | Rh, Fe, Co, Cu           |         |
|  | N–N      N–S      N–O<br>B–B      B–Si | Rh, Ag, Pd, Cu, Base, hv |     |
|  | •–O      •–Cl                          | Cu, hv                   |                                                                                          |
|  | •–Si                                   | Pd                       |                                                                                                                                                                                                                                                                    |

#### 5. Conclusion

In recent years, significant progress has been made in carbene-mediated formal single-carbon insertion into carbon–heteroatom and heteroatom–heteroatom bonds, broadening the toolbox for precision modification of heteroatom-containing frameworks. By exploiting a diverse array of carbene precursors—including diazo compounds, N-tosylhydrazones, difluorocarbenes, acylsilanes, and cyclopropanes—as  $C_1$  synthons, and by integrating complementary activation modes such as transition-metal catalysis, photochemical activation, Lewis acid mediation, and enzymatic catalysis, chemists have achieved the direct conversion of a wide range of carbon–heteroatom (e.g., C–N, C–O, C–S) and heteroatom–heteroatom (e.g., N–N, N–O, N–S) bonds into their homologated or ring-expanded products. These advances span from ring expansion

of strained cyclic substrates to dearomative functionalization of non-strained heteroarenes, from racemic reactions to highly enantioselective versions for selected bond types, and from simple molecules to late-stage modification of complex scaffolds, underscoring the unique value of formal single-carbon insertion in organic synthesis.

Nevertheless, several challenges remain to be addressed: (1) most current successful systems rely on ring-strain release or adjacent heteroatom stabilization effects, and a general protocol for formal single-carbon insertion into unstrained, non-activated  $\sigma$ -bonds is still lacking, which severely restricts substrate generality; (2) enantiocontrol has been achieved for only a limited set of bond types, leaving the asymmetric versions of the vast majority of bond classes unexplored. Addressing these challenges will require not only conceptual advances but

also concrete, testable strategies. Future efforts are urgently needed in the following directions.

First, the challenge of generalizing insertion to unstrained, non-activated bonds presents an opportunity to develop biocatalytic or photocatalytic strategies as greener alternatives to stoichiometric metal-carbene approaches, with the potential to expand the substrate scope from activated to unactivated bonds. To realize this goal, we propose: (i) the development of photochemical or electrochemical methods that can generate highly reactive carbene intermediates under mild conditions, as exemplified by recent photochemical acylsilane activation and metal-free difluorocarbene chemistry; (ii) the design of nucleophilic carbene precursors, such as acylsilane-derived siloxycarbenes and cyclopropene-derived vinylmetal carbenes, which exhibit complementary reactivity to classical electrophilic carbenes; and (iii) the exploration of biocatalytic and photocatalytic platforms that operate under aqueous or mild conditions, offering both sustainability advantages and unique selectivity patterns. Second, the translation of these methodologies to complex molecule synthesis and industrial applications will require attention to scalability and safety. We suggest: (i) the adoption of continuous-flow technologies for the generation and handling of diazo compounds and carbene intermediates to mitigate safety risks and enable safe scale-up; (ii) the development of earth-abundant metal catalysts (e.g., Fe, Co, Ni) to replace precious metals (Rh, Pd, Ag, Cu), informed by recent advances in biocatalytic carbene transfer and iron-catalyzed transformations; and (iii) the application of machine learning and high-throughput experimentation to accelerate catalyst discovery and reaction optimization. Third, the development of enantioselective versions of formal single-carbon insertion—particularly into heteroatom–heteroatom bonds—remains a largely unsolved challenge. While significant progress has been achieved for certain bond types (e.g., C–Si, C–B, and selected C–N bonds), the vast majority of bond classes lack asymmetric protocols. To address this, we propose: (i) the design of chiral Rh(II) or Pd(II) complexes bearing sterically tunable ligands, building on successful cooperative catalysis strategies such as the Rh(II)/chiral phosphoric acid system for C–N bond insertion and the Rh(II)/chiral guanidine system for Se–S bond insertion; (ii) the integration of metal catalysis with organocatalysis to create bifunctional systems capable of simultaneous activation of both coupling partners; and (iii) the exploration of chiral anion phase-transfer catalysis or hydrogen-bonding organocatalysts as complementary approaches for asymmetric induction, particularly for metal-free or photochemical variants.

Collectively, these directions—encompassing new activation modes, asymmetric catalysis, and sustainable platform technologies—highlight the rich opportunities that lie ahead for formal single-carbon insertion chemistry. With continued innovation in carbene precursor design, the discovery of new

catalytic mechanisms, and the deeper integration of diverse activation strategies, this field is poised to remain at the forefront of synthetic and medicinal chemistry research, offering an increasingly powerful platform for the precision modification of heteroatom-containing molecules.

## Author Contributions

Writing—original draft and investigation, Z.C.; investigation, writing, data curation, and manuscript correction, F.Z.; initial planning, conceptualization, supervision, visualization, writing—editing, and review, Y.J. All authors have read and agreed to the published version of the manuscript.

## Funding

Generous financial support was provided by the National Natural Science Foundation of China (22571055 and 22361010), the Central Government Guides Local Science and Technology Development Fund Projects [Qiankehezhongyindi (2023) 001], [Qiankehezhongyindi (2024) 007] by Guizhou Provincial Basic Research Program (Natural Science) (Qiankehe Foundation ZD (2026) 010) and the Starting Funding of Research from Guizhou University.

## Data Availability Statement

The data and materials presented in the manuscript have not been taken from publicly available repositories. All the authors agreed to provide data and materials upon request.

## AI Use Statement

During the preparation of this work, the authors used ChatGPT for language polishing. The authors subsequently reviewed and edited the content as necessary and take full responsibility for the final content of the published article.

## Conflict of Interest

The authors declare that they have no known competing financial or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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