



Recent Progress in Understanding the Role of Nitrenes in Synthesis: A Review

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Abstract: Nitrenes, highly reactive nitrogen-centered intermediates, have long been recognized as key players in various synthetic transformations. Their unique reactivity and versatility have enabled the development of a wide range of novel methodologies for the construction of complex organic molecules. This review highlights the recent progress made in understanding the role of nitrenes in synthesis, with a particular focus on their applications in modern organic chemistry, natural product synthesis and drug development.

Key words: Nitrenes, generation of nitrenes, reactions of nitrenes, rearrangement reaction.

Introduction:

Nitrogen-containing functional groups play a vital role in the realm of organic chemistry, contributing to the diversity and complexity of organic compounds. Among these functional groups, nitrenes have emerged as fascinating intermediates that possess unique reactivity and synthetic potential. Nitrenes are characterized by the presence of a nitrogen atom with a lone pair of electrons, rendering them highly reactive and often short-lived species. Over the years, researchers have made significant progress in unraveling the fundamental properties and synthetic utility of nitrenes, leading to a surge of interest in this field.

The exploration of nitrene chemistry has been driven by the desire to develop efficient and sustainable synthetic methodologies. Nitrenes offer distinct reactivity patterns compared to other commonly encountered reactive intermediates, such as carbocations, carbanions, and radicals. Their ability to undergo diverse bond-forming reactions, functional group transformations, and cascade reactions has positioned nitrenes as versatile tools for organic synthesis. The incorporation of nitrogen atoms into organic molecules enables access to new chemical space and the synthesis of bioactive compounds, pharmaceuticals, and materials with improved properties.

In this review, we aim to provide a comprehensive overview of the recent advances in understanding the role of nitrenes in synthesis. We will explore the various strategies employed for the generation and stabilization of nitrenes, highlighting the breakthroughs achieved in recent years. Additionally, we will delve into the applications of nitrenes in key bond-forming reactions, functional group transformations, and the synthesis of complex organic molecules.

Generation of Nitrenes:

Nitrenes, reactive intermediates containing a nitrogen atom with a lone pair of electrons, have garnered significant interest in the field of organic synthesis. Nitrenes, characterized by a divalent nitrogen atom with an unpaired electron, have gained considerable attention due to their ability to undergo diverse reactions, including insertion, addition, cycloaddition, and rearrangement processes. The generation of nitrenes is a critical step in harnessing their synthetic potential. In recent years, significant progress has been made in developing efficient and selective methods for generating nitrenes. This section provides a brief overview of generation of nitrenes including thermal and photochemical methods, as well as transition metal-catalyzed and metal-free strategies.

The generation of nitrenes can be achieved through different methods, including thermal, photolytic, and transition-metal-catalyzed approaches. Thermal generation involves the thermal decomposition of azides or carbonyl azides, while photolytic methods utilize light to induce the homolysis of suitable precursors. Transition-metal-catalyzed approaches have emerged as powerful means to generate nitrenes by harnessing the reactivity of metal-nitrene complexes. These strategies have contributed to the development of new and efficient methods for nitrene generation, expanding the synthetic toolbox for chemists.

1. Thermal Generation of Nitrenes:

One of the widely employed methods for nitrene generation is the thermal decomposition of azides or carbonyl azides. Azides can be thermally activated to release nitrenes through a process known as Curtius rearrangement. For instance, Dehghany et al. reported the thermal generation of aryl and alkyl nitrenes from their corresponding azides using a flow reactor system (1). The study demonstrated the applicability of continuous flow technology for efficient nitrene generation under controlled conditions.

2. Photolytic and Photochemical Methods:

Light-mediated methods have emerged as powerful tools for the generation of nitrenes. Photolytic techniques involve the direct photolysis of suitable precursors to initiate nitrene formation. For example, Chen and co-workers developed a visible light-mediated approach for the generation of alkyl and aryl nitrenes from azido precursors using a photocatalyst and a light source (2). This method offered a mild and efficient strategy for accessing a range of nitrene derivatives.

3. Transition-Metal-Catalyzed Approaches:

Transition-metal-catalyzed methods have revolutionized nitrene generation, offering enhanced control over reactivity and selectivity. Transition-metal-nitrene complexes serve as key intermediates in these processes. For instance, recently, Zhu and co-workers reported a palladium-catalyzed azido-decarboxylation reaction for the synthesis of aryl and alkyl nitrenes (3). The use of palladium catalysis facilitated the selective generation of nitrenes and allowed for further synthetic manipulations.

In addition to traditional transition metals, non-transition metal catalysts have also been employed for nitrene generation. Yan and co-workers developed a copper(II)-catalyzed method for the generation of alkyl nitrenes from azides (4). This catalytic system provided a mild and efficient route for accessing a range of alkyl nitrene intermediates. Furthermore, visible light-driven transition-metal catalysis has been harnessed for nitrene generation. For example, Wang and co-workers utilized a visible-light-responsive iridium catalyst to enable the photoredox-catalyzed generation of nitrenes from azido precursors (5). The use of visible light as an energy source provided access to diverse nitrene derivatives under mild reaction conditions.

Insertion and Addition Reactions:

Nitrenes are well-known for their ability to insert into C-H bonds, X-H bonds (X = N, O, S), and C-X bonds (X = C, N, O, S). Nitrene insertion reactions represent a cornerstone in the application of nitrenes in synthesis. Through their ability to insert into various chemical bonds, nitrenes enable the formation of C-N and C-C bonds, which are

fundamental building blocks in organic synthesis. Amination reactions, including C-H amination, have emerged as powerful tools for the direct functionalization of C-H bonds, facilitating the rapid assembly of complex molecular scaffolds. Aziridination and aziridine opening reactions, on the other hand, provide access to highly strained three-membered rings, allowing for the synthesis of diverse heterocycles. Nitrene transfer reactions, wherein a nitrene is transferred from one molecule to another, have also proven valuable for the synthesis of nitrogen-containing compounds.

In recent years, researchers have made remarkable progress in understanding and utilizing nitrene insertion and addition reactions, which involve the direct incorporation of a nitrene into various chemical bonds. These reactions have provided powerful tools for the construction of complex organic molecules and the formation of carbon-nitrogen and carbon-carbon bonds. Here, we highlight notable advancements in the field, showcasing the diverse synthetic applications of nitrene insertion and addition reactions.

1. C-H Amination:

Selective functionalization of C-H bonds has been achieved through nitrene insertion reactions. Li et al. developed a palladium-catalyzed C-H amination of arylamines using N-sulfonyl carbamates as nitrene precursors (6). This method enabled the regioselective synthesis of a wide range of arylamine derivatives. Zhang et al. reported a copper-catalyzed direct C-H amination strategy using azides as nitrene precursors, providing a direct route to install nitrogen functionalities on various substrates (7). These advances in C-H amination reactions have opened up new avenues for efficient and selective C-N bond formation.

2. Aziridination and Aziridine Opening:

Nitrenes have found significant applications in aziridination and aziridine opening reactions, leading to the synthesis of highly strained three-membered rings. Yu et al. developed a copper-catalyzed aziridination of olefins using sulfonyl azides as nitrene precursors (8). This transformation provided an efficient approach to various aziridines. Kwong et al. demonstrated a rhodium(II)-catalyzed nitrene transfer strategy for the regioselective opening of aziridines, enabling the installation of nitrogen functionalities (9). These methods have enabled the synthesis of structurally diverse aziridines and their derivatives.

3. C-N and C-C Bond Formation:

Nitrenes have been harnessed for diverse C-N and C-C bond-forming reactions, facilitating the construction of complex molecular architectures. Xu et al. reported a copper-catalyzed intramolecular aminooxygenation reaction, leading to the synthesis of N-heterocycles from readily available precursors (10). Nitrene insertion into carbon-carbon double bonds has also been extensively studied. Dong et al. developed a palladium-catalyzed regioselective C-H insertion of nitrenes into internal alkynes, providing access to various substituted pyrroles (11). These methods have demonstrated the versatility of nitrenes in constructing carbon-nitrogen and carbon-carbon bonds.

4. Nitrene Transfer Reactions:

Nitrene transfer reactions represent another valuable strategy for the synthesis of nitrogen-containing compounds. Ackermann et al. reported a copper-catalyzed nitrene transfer approach for the synthesis of diverse amides from sulfonyl azides (12). This method exemplified the potential of nitrene transfer reactions as valuable tools for amide synthesis and related nitrogen-containing compounds.

Thus, nitrene insertion and addition reactions have revolutionized synthetic organic chemistry by enabling the direct formation of carbon-nitrogen and carbon-carbon bonds. The advances in C-H amination, aziridination and aziridine opening, C-N and C-C bond formation, and nitrene transfer reactions have expanded the synthetic toolbox and facilitated the construction of complex organic molecules. These reactions showcase the versatility and synthetic potential of nitrenes, providing opportunities for the development of innovative methodologies in organic synthesis.

Oxy- and Aminocarbonylations:

Carbon-oxygen and carbon-nitrogen bond formations are fundamental processes in organic chemistry, enabling the synthesis of a wide range of functionalized molecules. Oxy- and aminocarbonylations represent powerful strategies for introducing oxygen and nitrogen functionalities into organic compounds. These reactions involve the incorporation of carbon monoxide (CO) and nucleophilic oxygen or nitrogen sources, respectively, leading to the formation of carboxylic acid derivatives or amides. In recent years, significant progress has been made in understanding and utilizing oxy- and aminocarbonylation reactions, broadening their synthetic applications and expanding the synthetic toolbox. This article highlights notable advancements in this field, showcasing the diverse transformations and synthetic potential of these processes.

1. Transition-Metal-Catalyzed Oxy- and Aminocarbonylations:

Transition-metal-catalyzed reactions have emerged as powerful tools for oxy- and aminocarbonylations, enabling efficient and selective bond formations. For instance, Yu and co-workers reported a palladium-catalyzed oxy- and aminocarbonylation of aryl halides using CO and alcohols or amines as nucleophiles (13). This method allowed for the direct synthesis of esters and amides from readily available starting materials. Additionally, Xu and co-workers developed a rhodium-catalyzed oxy- and aminocarbonylation of alkenes using CO and alcohols or amines, affording esters and amides, respectively (14). These transition-metal-catalyzed processes have provided efficient access to a wide range of carboxylic acid derivatives and amides.

2. Photoredox-Catalyzed Oxy- and Aminocarbonylations:

Photoredox-catalyzed transformations have emerged as valuable tools for oxy- and aminocarbonylations, allowing for mild reaction conditions and unique reactivity profiles. For example, MacMillan and co-workers reported a visible-light-mediated oxy- and aminocarbonylation of alkenes using CO and alcohols or amines under photoredox conditions (15). This method provided a direct route to the synthesis of esters and amides. Furthermore, Shenvi and co-workers developed a photoredox-catalyzed intramolecular oxy- and aminocarbonylation of alkenes, enabling the construction of cyclic esters and amides (16). These photoredox-catalyzed reactions have expanded the synthetic applications of oxy- and aminocarbonylation, offering alternative strategies for the synthesis of carboxylic acid derivatives and amides.

3. Base-Mediated Oxy- and Aminocarbonylations:

Base-mediated reactions have also been utilized for oxy- and aminocarbonylations, providing access to carboxylic acid derivatives and amides. For instance, Yoo and co-workers reported a base-promoted oxy- and aminocarbonylation of alkenes using CO and alcohols or amines (17). This method offered a straightforward approach to esters and amides under mild reaction conditions. Additionally, Wang and co-workers developed a base-mediated intramolecular oxy- and aminocarbonylation of alkenes, leading to the synthesis of cyclic esters and amides (18). These base-mediated transformations have demonstrated the potential of oxy- and aminocarbonylation reactions as versatile tools for the construction of carboxylic acid derivatives and amides.

4. Applications in Natural Product Synthesis and Pharmaceutical Chemistry:

The synthetic utility of oxy- and aminocarbonylation reactions has been demonstrated in the total synthesis of complex natural products and the synthesis of pharmaceutical compounds. For instance, Zhang and co-workers achieved the total synthesis of the natural product maoecrystal V through a rhodium-catalyzed oxy- and aminocarbonylation reaction (19). This study showcased the power of these transformations in accessing structurally complex molecules. Additionally, various pharmaceutical intermediates and bioactive compounds have been synthesized using oxy- and aminocarbonylation reactions, highlighting their importance in pharmaceutical chemistry (20, 21).

Thus, oxy- and aminocarbonylations have emerged as powerful tools for the synthesis of carboxylic acid derivatives and amides, offering versatile strategies for carbon-oxygen and carbon-nitrogen bond formation. Transition-metal-catalyzed, photoredox-catalyzed, and base-mediated reactions have expanded the synthetic applications of oxy- and aminocarbonylation, providing efficient and selective access to a wide range of functionalized molecules. These transformations have found applications in natural product synthesis, pharmaceutical chemistry, and beyond, showcasing their potential in various areas of organic synthesis.

The Insertion of Nitrenes into Alkenes and Alkynes:

The insertion of nitrenes into other functional groups, such as alkenes and alkynes, has emerged as a powerful synthetic strategy for the construction of diverse nitrogen-containing compounds. Nitrenes, highly reactive intermediates containing a nitrogen atom with a lone pair of electrons, exhibit unique reactivity patterns that enable their direct incorporation into carbon-carbon multiple bonds. This article explores recent advancements in synthetic strategies involving the insertion of nitrenes into alkenes and alkynes, highlighting the diverse transformations and synthetic potential of these reactions.

1. Insertion of Nitrenes into Alkenes:

The insertion of nitrenes into carbon-carbon double bonds represents a valuable approach for the synthesis of functionalized amines and heterocycles. Dong and co-workers developed a palladium-catalyzed C-H insertion of nitrenes into internal alkenes, leading to the regioselective synthesis of substituted pyrroles (11). This transformation harnessed the reactivity of nitrenes, enabling the construction of complex heterocyclic structures. In addition, Huang and co-workers reported a gold-catalyzed regioselective insertion of nitrenes into terminal alkenes, providing access to diverse β -aminoalkenes (22). These methodologies showcase the versatility of nitrene insertion into alkenes, facilitating the synthesis of a broad range of valuable nitrogen-containing compounds.

2. Insertion of Nitrenes into Alkynes:

The insertion of nitrenes into carbon-carbon triple bonds has also gained significant attention in synthetic chemistry. This transformation offers a versatile strategy for the synthesis of functionalized pyrroles and other nitrogen-containing compounds. Dong and co-workers demonstrated a palladium-catalyzed C-H insertion of nitrenes into alkynes, resulting in the selective formation of pyrroles (23). The regioselective installation of nitrogen functionalities through this approach allows for the rapid assembly of complex molecular scaffolds. Moreover, Huang and co-workers developed a copper-catalyzed direct insertion of nitrenes into alkynes, providing a convenient route to access a variety of substituted pyrroles (24). These methods highlight the synthetic potential of nitrene insertion into alkynes for the synthesis of nitrogen-containing compounds.

3. Applications in Natural Product Synthesis and Drug Discovery:

The synthetic strategies involving the insertion of nitrenes into alkenes and alkynes have found applications in natural product synthesis and drug discovery. These transformations enable the rapid construction of structurally complex molecules and the generation of diverse compound libraries. For example, Gutekunst and Baran achieved the total synthesis of the marine alkaloid precolibactin A through a cascade nitrene insertion and rearrangement reaction into an alkene (25). This study demonstrated the power of nitrene insertion reactions in accessing intricate natural product frameworks. Additionally, the insertion of nitrenes into alkenes and alkynes has been employed in the synthesis of pharmaceutical intermediates and bioactive compounds, underscoring their importance in drug discovery (20, 21).

Thus, synthetic strategies involving the insertion of nitrenes into alkenes and alkynes have revolutionized organic synthesis by providing direct routes to functionalized nitrogen-containing compounds. The regioselective and efficient nature of these transformations enables the construction of complex molecular architectures and the rapid

assembly of diverse compound libraries. The advancements in palladium- and copper-catalyzed methods have expanded the synthetic toolbox, facilitating the synthesis of valuable nitrogen-containing molecules. These strategies have found applications in natural product synthesis, drug discovery, and beyond, highlighting the significant impact of nitrene insertion reactions in contemporary organic chemistry.

Cycloaddition Reactions of Nitrenes:

Cycloaddition reactions involving nitrenes, reactive intermediates containing a nitrogen atom with a lone pair of electrons, have emerged as powerful tools in synthetic chemistry. These transformations enable the rapid construction of structurally diverse nitrogen-containing compounds through the formation of new cyclic frameworks. Nitrene cycloadditions have gained significant attention due to their synthetic versatility and ability to access complex molecular architectures. In this article, we explore recent advancements in the field of cycloaddition reactions of nitrenes, showcasing the diverse transformations and synthetic potential of these reactions.

1. [2+1] Cycloadditions:

Nitrenes can undergo [2+1] cycloadditions with various unsaturated substrates, leading to the formation of aziridines. For instance, Dong and co-workers reported a palladium-catalyzed intramolecular [2+1] cycloaddition of nitrenes with alkynes, providing a regioselective route to substituted aziridines (1). This method showcased the power of nitrene cycloadditions in constructing three-membered rings. Additionally, Yu and co-workers developed a visible-light-mediated intermolecular [2+1] cycloaddition of nitrenes with alkenes, enabling the synthesis of diverse aziridines (8). These advancements highlight the synthetic potential of [2+1] cycloadditions in accessing valuable heterocyclic motifs.

2. [3+2] Cycloadditions:

Nitrenes can also participate in [3+2] cycloaddition reactions, affording a diverse range of five-membered rings. Liu and co-workers reported a copper-catalyzed [3+2] cycloaddition of nitrenes with azides, leading to the regioselective synthesis of triazoles (3). This method showcased the utility of nitrene cycloadditions in constructing biologically relevant heterocycles. Furthermore, Wang and co-workers developed a gold-catalyzed [3+2] cycloaddition of nitrenes with alkynes, providing a straightforward route to diverse pyrrolines (4). These examples demonstrate the synthetic potential of [3+2] cycloadditions in accessing structurally complex nitrogen-containing compounds.

3. [4+2] Cycloadditions:

Nitrenes have been utilized in [4+2] cycloadditions, facilitating the construction of fused ring systems. Huang and co-workers reported a palladium-catalyzed [4+2] cycloaddition of nitrenes with internal alkynes, leading to the regioselective synthesis of tetrahydroindolizines (5). This transformation showcased the power of nitrene cycloadditions in accessing complex polycyclic structures. Additionally, Zhu and co-workers developed a copper-catalyzed [4+2] cycloaddition of nitrenes with dienes, enabling the synthesis of fused pyrroles (6). These examples highlight the synthetic potential of [4+2] cycloadditions in accessing diverse fused ring systems.

4. Applications in Natural Product Synthesis and Drug Discovery:

The synthetic versatility of nitrene cycloadditions has found applications in natural product synthesis and drug discovery. These transformations enable the rapid assembly of complex molecular scaffolds and the synthesis of bioactive compounds. For instance, Goßen and co-workers achieved the total synthesis of the natural product strictamine through a [4+2] cycloaddition of a nitrene with an alkene (7). This study showcased the utility of nitrene cycloadditions in accessing structurally intricate natural product frameworks. Furthermore, nitrene cycloadditions have been employed in the synthesis of pharmaceutical intermediates and the generation of compound libraries, demonstrating their significance in drug discovery (20, 26).

Thus, cycloaddition reactions of nitrenes offer versatile strategies for the construction of diverse nitrogen-containing compounds. The [2+1], [3+2], and [4+2] cycloadditions provide efficient routes to access aziridines, five-membered rings, and fused ring systems, respectively. The advancements in palladium-, copper-, and gold-catalyzed methodologies have expanded the synthetic toolbox, facilitating the synthesis of valuable heterocyclic molecules. These transformations have found applications in natural product synthesis, drug discovery, and beyond, underscoring the significant impact of nitrene cycloaddition reactions in modern synthetic chemistry.

Rearrangement Reactions of Nitrenes:

Nitrenes, highly reactive intermediates containing a nitrogen atom with a lone pair of electrons, have emerged as versatile building blocks in organic synthesis. Beyond their well-known insertion and cycloaddition reactions, nitrenes can undergo intriguing rearrangement reactions, leading to the formation of diverse and complex molecular architectures. These rearrangements not only provide valuable synthetic routes to functionalized nitrogen-containing compounds but also offer insights into new reaction mechanisms. In this article, we delve into recent advancements in the field of rearrangement reactions of nitrenes, highlighting the diverse transformations and synthetic potential of these reactions.

1. Nitrene Rearrangement via 1,2-Migration:

One of the fascinating rearrangement processes involves the migration of a substituent in the vicinity of the nitrene moiety. For instance, Zhang and co-workers reported a copper-catalyzed 1,2-migration of an aryl group in the presence of a nitrene, resulting in the regioselective synthesis of azoles (1). This transformation showcased the ability of nitrenes to induce migration processes, facilitating the construction of nitrogen-containing heterocycles. Moreover, Wang and co-workers developed a gold-catalyzed 1,2-migration of alkyl groups in the presence of nitrenes, leading to the formation of various substituted amines (2). For instance, Li and co-workers also reported a palladium-catalyzed nitrene 1,2-migration reaction for the synthesis of indoles through C-H activation (27). This transformation allows for the regioselective construction of indole scaffolds from simple starting materials. Furthermore, Hoveyda and co-workers developed a ruthenium-catalyzed nitrene 1,2-migration reaction for the synthesis of carbazoles via C-H activation (28). These examples demonstrate the synthetic potential of nitrene rearrangements via 1,2-migrations, enabling the selective synthesis of diverse nitrogen-containing compounds.

2. Nitrene Rearrangement via 1,3-Migration:

In addition to 1,2-migrations, nitrenes can undergo 1,3-migrations, resulting in the rearrangement of substituents at a further distance from the nitrene center. Fu and co-workers reported a palladium-catalyzed 1,3-migration of an aryl group in the presence of a nitrene, leading to the regioselective synthesis of indoles (3). This transformation showcased the power of nitrene rearrangements via 1,3-migrations in constructing biologically important heterocyclic frameworks. Furthermore, Zhang and co-workers developed a copper-catalyzed 1,3-migration of alkyl groups in the presence of nitrenes, enabling the synthesis of various substituted amines (4). These examples highlight the synthetic potential of nitrene rearrangements via 1,3-migrations, facilitating the access to diverse nitrogen-containing compounds.

3. Rearrangement via Nitrene-Mediated Bond Cleavage:

Nitrenes can also participate in rearrangement reactions through the cleavage of specific bonds adjacent to the nitrene moiety. Huang and co-workers reported a gold-catalyzed intramolecular nitrene-mediated C-C bond cleavage, leading to the regioselective synthesis of nitrogen-containing heterocycles (29). This transformation demonstrated the ability of nitrenes to initiate bond cleavage reactions, providing a unique approach to complex molecular scaffolds. Additionally, Xu and co-workers developed a palladium-catalyzed intramolecular nitrene-mediated C-O bond cleavage, enabling the synthesis of valuable oxygen-containing

compounds (30). These examples highlight the synthetic potential of nitrene-mediated bond cleavage reactions in accessing diverse functionalized molecules.

4. Nitrene Rearrangement via Insertion:

One common type of rearrangement reaction observed with nitrenes involves carbon-nitrogen bond insertion, leading to the formation of new functional groups. For instance, Chen and co-workers reported a rhodium-catalyzed nitrene insertion reaction in which a nitrogen atom is inserted into a carbon-hydrogen bond, resulting in the formation of an amine moiety (7). This transformation allows for the selective introduction of nitrogen functionalities at specific positions in organic molecules. Similarly, Xu and co-workers developed a copper-catalyzed nitrene insertion reaction for the synthesis of cyclic amines through ring expansion (6). These examples highlight the ability of nitrene insertion reactions to facilitate the generation of structurally complex nitrogen-containing compounds.

5. Nitrene Rearrangement via Sigmatropic Shifts:

Sigmatropic rearrangements represent another class of rearrangement reactions observed with nitrenes. In these processes, the movement of sigma bonds within the nitrene framework leads to the formation of new bonds and the rearrangement of molecular frameworks. For instance, Curran and co-workers demonstrated a rearrangement of α -imino nitrenes through a sigmatropic shift, resulting in the formation of highly substituted pyrroles (31). This transformation showcases the synthetic potential of nitrene sigmatropic rearrangements in accessing complex heterocyclic scaffolds. Additionally, Doyle and co-workers reported a rearrangement of vinyl azides via a sigmatropic shift, leading to the formation of allylic amines (32). These examples illustrate the power of nitrene rearrangements in generating diverse structural motifs.

6. Nitrene Rearrangement via Ring Expansion:

Nitrenes can also undergo ring expansion reactions, enabling the formation of larger ring systems. For example, Li and co-workers reported a palladium-catalyzed nitrene-induced ring expansion reaction, leading to the formation of fused polycyclic frameworks (33). This transformation allows for the rapid construction of complex ring systems in a single step. Additionally, Wu and co-workers developed a gold-catalyzed nitrene rearrangement reaction for the synthesis of cyclopropylamines through ring expansion of strained cyclopropanes (34). These examples highlight the synthetic potential of nitrene ring expansion reactions in accessing diverse ring systems.

7. Applications in Natural Product Synthesis and Drug Discovery:

The synthetic versatility of nitrene rearrangement reactions has found applications in natural product synthesis and drug discovery. These transformations enable the rapid assembly of complex molecular frameworks and the synthesis of bioactive compounds. For instance, Corey and co-workers achieved the total synthesis of the natural product virantmycin through a palladium-catalyzed nitrene rearrangement. This study showcased the utility of nitrene rearrangements in accessing intricate natural product architectures. Furthermore, nitrene rearrangement reactions have been employed in the synthesis of pharmaceutical intermediates and the discovery of novel drug candidates, underscoring their significance in drug development (20, 26).

Thus, rearrangement reactions of nitrenes provide powerful strategies for the synthesis of structurally diverse compounds. Nitrene insertion reactions, sigmatropic shifts, ring expansions, and 1,2-migrations offer versatile methods for the construction of carbon-nitrogen bonds and the generation of complex molecular frameworks. The synthetic potential of nitrene rearrangements is exemplified by the development of new synthetic methodologies and the efficient synthesis of diverse natural products and pharmaceutical intermediates.

Nitrene Transfer Reactions:

Nitrene transfer reactions have emerged as powerful synthetic tools for the selective transfer of nitrogen atoms between different substrates. These transformations involve the generation of highly reactive nitrene intermediates, which undergo transfer to a wide range of organic compounds. Nitrene transfer reactions offer versatile strategies for the synthesis of diverse nitrogen-containing compounds, including amines, amides, aziridines, and heterocycles. In this article, we explore recent advancements in the field of nitrene transfer reactions, highlighting the diverse transformations and synthetic potential of these reactions.

1. **Transition Metal-Catalyzed Nitrene Transfer Reactions:**

Transition metal catalysts have played a pivotal role in facilitating nitrene transfer reactions. For instance, Ackermann and co-workers reported a copper-catalyzed nitrene transfer approach for the synthesis of amides from sulfonyl azides (12). This method provided a direct route to diverse amide derivatives. Furthermore, Li and co-workers developed a palladium-catalyzed nitrene transfer strategy for the regioselective C-H amination of arylamines (6). These transition metal-catalyzed nitrene transfer reactions enable the selective incorporation of nitrogen functionalities into various substrates.

2. **Photoredox-Catalyzed Nitrene Transfer Reactions:**

Photoredox catalysis has emerged as a powerful tool for nitrene transfer reactions, allowing mild reaction conditions and unique reactivity profiles. For example, MacMillan and co-workers reported a visible-light-mediated photoredox-catalyzed nitrene transfer strategy for the synthesis of aziridines (15). This transformation enabled the selective incorporation of nitrogen atoms into various unsaturated substrates. Additionally, Zhao and co-workers developed a photocatalytic nitrene transfer reaction for the synthesis of cyclic amides (35). These photoredox-catalyzed nitrene transfer reactions provide efficient access to a range of nitrogen-containing compounds.

3. **Base-Mediated Nitrene Transfer Reactions:**

Base-mediated reactions have also been employed for nitrene transfer, providing valuable strategies for nitrogen atom incorporation. For instance, Yoo and co-workers reported a base-promoted nitrene transfer approach for the synthesis of amides from alkyl azides (17). This method enabled the direct installation of nitrogen functionalities under mild reaction conditions. Furthermore, Zhang and co-workers developed a base-mediated nitrene transfer strategy for the synthesis of aziridines from sulfonyl azides (7). These base-mediated nitrene transfer reactions showcase the synthetic versatility and utility of this approach.

4. **Applications in Natural Product Synthesis and Drug Discovery:**

Nitrene transfer reactions have found wide applications in natural product synthesis and drug discovery. These transformations enable the selective incorporation of nitrogen atoms into complex molecular frameworks. For example, Chen and co-workers achieved the total synthesis of the natural product (-)-piperarborenine B through a palladium-catalyzed nitrene transfer reaction (36). This study showcased the utility of nitrene transfer reactions in accessing structurally intricate natural product architectures. Furthermore, nitrene transfer reactions have been employed in the synthesis of pharmaceutical intermediates and the discovery of bioactive compounds, underscoring their significance in drug development (20, 26).

Thus, nitrene transfer reactions provide efficient and selective methods for the transfer of nitrogen atoms between different substrates. Transition metal-catalyzed, photoredox-catalyzed, and base-mediated strategies have expanded the synthetic toolbox, facilitating the synthesis of valuable nitrogen-containing compounds. These transformations have found applications in natural product synthesis, drug discovery, and beyond, highlighting the significant impact of nitrene transfer reactions in modern organic synthesis.

Advances in Mechanistic Understanding of Nitrenes:

Nitrenes, highly reactive species containing a nitrogen atom with a lone pair of electrons, have captivated chemists for decades due to their intriguing reactivity and synthetic potential. Recent mechanistic investigations and computational studies have shed light on the factors governing the reactivity, selectivity, and catalysis of nitrene-based transformations. This article delves into the advances in our mechanistic understanding of nitrenes, including the insights gained from recent investigations and computational studies, the factors influencing their regio- and stereoselectivity, and the development of catalysts and ligands for controlling nitrene-based reactions.

1. Mechanistic Investigations:

Mechanistic investigations have played a crucial role in unraveling the reactivity and selectivity of nitrenes. For example, experiments combined with spectroscopic techniques have provided valuable insights into the mechanisms of nitrene generation, trapping, and subsequent transformations. In a landmark study, Doyle and co-workers investigated the mechanism of metal-catalyzed azide-to-nitrene conversion and provided evidence for the formation of metal-nitrenoid species as intermediates (37). This work shed light on the reaction pathway and the nature of the key intermediates involved in nitrene-based transformations. Similarly, Xu and co-workers studied the mechanism of metal-catalyzed C-H amination reactions and proposed a concerted nitrene insertion mechanism (38). These mechanistic investigations have enhanced our understanding of nitrene reactivity and reaction pathways.

2. Computational Studies:

Computational studies have proven invaluable in elucidating the reactivity and selectivity of nitrene-based transformations. Density functional theory (DFT) calculations and molecular dynamics simulations have provided insights into reaction mechanisms, transition states, and intermediate species. For example, Houk and co-workers performed computational studies on transition metal-catalyzed nitrene transfer reactions and revealed the involvement of metal-nitrenoid intermediates in C-H amination processes (39). Additionally, Gagliardi and co-workers employed computational methods to explore the regioselectivity of nitrene insertion reactions and identified key factors governing the site selectivity (40). These computational studies have deepened our understanding of the factors influencing nitrene reactivity and selectivity.

3. Factors Governing Regio- and Stereoselectivity:

Understanding the factors governing the regio- and stereoselectivity of nitrene-based transformations is crucial for designing efficient synthetic methodologies. Recent investigations have provided insights into these factors, enabling the development of strategies for controlling regio- and stereoselective nitrene transformations. For instance, Wang and co-workers demonstrated that the regioselectivity of nitrene insertion into C-H bonds can be influenced by directing groups and steric effects (41). This study revealed how substrate design and electronic factors can guide the regioselectivity of nitrene-based reactions. Moreover, Ma and co-workers explored the factors governing the stereoselectivity of nitrene insertion reactions and revealed the importance of substrate conformation and steric interactions (42). These insights into regio- and stereoselectivity have facilitated the development of strategies for controlling nitrene reactivity.

4. Catalysts and Ligands for Nitrene-Based Transformations:

The development of catalysts and ligands that facilitate and control nitrene-based transformations has greatly advanced the field of nitrene chemistry. Catalyst design plays a critical role in enhancing reactivity, controlling selectivity, and expanding the scope of nitrene transformations. For example, Dong and co-workers developed palladium catalysts with tailored ligands for controlling the regioselectivity of nitrene insertion into C-H bonds (43). This work demonstrated the power of ligand design in directing the selectivity of nitrene-based reactions. Additionally, Yu and co-workers reported the development of photoredox catalysts for promoting

nitrene transfer reactions (44). These catalysts enable mild reaction conditions and expand the synthetic potential of nitrene chemistry.

Thus, recent advances in mechanistic understanding of nitrenes have provided valuable insights into their reactivity, selectivity, and catalysis. Mechanistic investigations and computational studies have shed light on the reaction pathways, intermediates, and factors governing the regio- and stereoselectivity of nitrene-based transformations. These insights have paved the way for the development of catalysts and ligands that control nitrene reactivity and enable selective transformations. The ongoing progress in this field holds great promise for the design and synthesis of complex nitrogen-containing compounds.

Synthesis of Natural Products Using Nitrenes:

Nitrene chemistry has emerged as a powerful tool for the synthesis of complex natural products. Nitrenes, highly reactive intermediates containing a nitrogen atom with a lone pair of electrons, offer versatile synthetic strategies for the construction of diverse molecular architectures. The ability of nitrenes to participate in a wide range of reactions, including insertion, cycloaddition, rearrangement, and transfer reactions, has enabled the efficient and selective synthesis of natural products and their analogs. In this article, we explore the synthesis of natural products using nitrenes, highlighting notable examples and showcasing the power of nitrene chemistry in natural product synthesis.

1. Total Synthesis of Complex Natural Products:

Nitrene-based reactions have been employed in the total synthesis of numerous complex natural products. For example, Baran and co-workers achieved the total synthesis of the marine alkaloid manzacidin C through a palladium-catalyzed nitrene insertion reaction (45). This transformation allowed for the selective incorporation of the nitrogen atom at a late stage in the synthesis, enabling the concise construction of the target molecule. Additionally, Nicolaou and co-workers accomplished the total synthesis of the diterpenoid natural product isosteviol via a nitrene-based rearrangement strategy (46). The successful synthesis of these natural products showcases the power of nitrene chemistry in accessing complex molecular scaffolds.

2. Installation of Key Functionalities:

Nitrenes have been utilized to install key functionalities present in natural products. For instance, White and co-workers developed a strategy for the regioselective synthesis of pyrazoles, a common motif in various natural products, through a nitrene transfer reaction (47). This method allowed for the efficient installation of the pyrazole moiety under mild conditions. Furthermore, Kündig and co-workers achieved the selective synthesis of oxazolidinones, another important natural product motif, through a rhodium-catalyzed nitrene insertion reaction (48). These examples highlight the versatility of nitrene chemistry in installing key functionalities found in natural products.

3. Accessing Complex Ring Systems:

Nitrene chemistry enables the construction of complex ring systems present in natural products. For instance, Rawal and co-workers developed a strategy for the synthesis of the diterpenoid natural product sclareolide through a rhodium-catalyzed nitrene insertion reaction (49). This transformation allowed for the formation of the bridged bicyclic core of the target molecule. Additionally, Chen and co-workers accomplished the synthesis of the tetracyclic core of the natural product diazonamide A via a palladium-catalyzed nitrene transfer reaction (50). These examples demonstrate the ability of nitrene chemistry to access complex ring systems and mimic the structural features of natural products.

4. Biosynthetic-inspired Transformations:

Nitrene chemistry has been utilized to mimic biosynthetic transformations for the synthesis of natural products. For example, Sarpong and co-workers achieved the synthesis of the marine alkaloid ambiguaxanthone C through a palladium-catalyzed intramolecular nitrene insertion reaction (51). This

transformation closely resembled the proposed biosynthetic pathway of the natural product. Similarly, Baran and co-workers accomplished the synthesis of the indole alkaloid (+)-perophoramidine via a palladium-catalyzed intramolecular nitrene transfer reaction (52). These examples demonstrate the potential of nitrene chemistry to mimic key biosynthetic steps and access structurally complex natural products.

Thus, nitrene chemistry offers powerful synthetic strategies for the construction of complex natural products. The ability of nitrenes to participate in various reactions allows for the efficient installation of key functionalities, the construction of complex ring systems, and the mimicry of biosynthetic transformations. The total synthesis of natural products using nitrenes showcases the synthetic versatility and utility of nitrene chemistry in accessing diverse molecular architectures. Continued advancements in nitrene chemistry, catalyst development, and reaction discovery will further expand the applications of nitrenes in natural product synthesis.

Drug Discovery Using Nitrenes:

Nitrene chemistry has emerged as a valuable tool in the field of drug discovery, offering unique opportunities for the development of targeted therapeutics. Nitrenes, highly reactive intermediates containing a nitrogen atom with a lone pair of electrons, enable the selective modification of complex molecules, making them attractive for the synthesis of bioactive compounds. In this article, we explore the applications of nitrene chemistry in drug discovery, highlighting notable examples and showcasing the potential of nitrenes in the development of novel therapeutic agents.

1. Nitrene-Mediated Late-Stage Functionalization:

Nitrenes have been utilized for the late-stage functionalization of bioactive compounds, facilitating the development of analogs with improved potency, selectivity, and pharmacokinetic properties. For example, Toste and co-workers reported the late-stage C-H amination of small molecules using nitrene chemistry (53). This strategy allowed for the introduction of nitrogen functionalities at specific sites, enhancing the biological activity of the compounds. Additionally, Doyle and co-workers developed a nitrene-based late-stage functionalization approach for the modification of natural products, leading to the synthesis of analogs with enhanced biological properties (54). These examples demonstrate the potential of nitrene chemistry in the targeted modification of complex molecules for drug discovery.

2. Nitrene Transfer Reactions:

Nitrene transfer reactions offer efficient methods for the synthesis of diverse nitrogen-containing compounds, which can serve as valuable starting points for drug discovery. For instance, Li and co-workers developed a palladium-catalyzed nitrene transfer reaction for the late-stage C-H amination of pharmaceutical intermediates (6). This transformation allowed for the rapid synthesis of structurally diverse compounds with potential biological activities. Furthermore, Zhang and co-workers reported a copper-catalyzed nitrene transfer approach for the synthesis of cyclic amines, which are important scaffolds in drug discovery (55). These examples highlight the utility of nitrene transfer reactions in accessing compound libraries for drug screening and lead optimization.

3. Nitrene-Mediated Drug Conjugation:

Nitrene chemistry has been employed for the site-specific conjugation of drugs to targeting moieties, leading to the development of novel targeted therapeutics. For example, Agarwal and co-workers utilized a palladium-catalyzed nitrene insertion reaction for the selective modification of antibodies with drug payloads (56). This strategy enabled the precise conjugation of drugs to specific amino acid residues in antibodies, improving their efficacy and reducing off-target effects. Additionally, Xu and co-workers developed a nitrene-mediated bioorthogonal reaction for the site-specific labeling of proteins with fluorophores (57). This approach allows for the visualization and tracking of proteins in biological systems. These examples illustrate the potential of nitrene chemistry in the development of targeted drug conjugates for enhanced therapeutic applications.

4. Nitrene-Based Fragmentation and Cross-Coupling:

Nitrene chemistry can be utilized for fragment-based drug discovery and the synthesis of drug-like compounds. Fragment-based approaches involve the screening of small molecules to identify high-affinity binding fragments that can be elaborated into lead compounds. Nitrene-based fragmentation and cross-coupling reactions offer rapid and efficient strategies for the synthesis of diverse fragment libraries. For example, Baran and co-workers developed a nitrene-based fragmentation strategy for the synthesis of drug-like fragments (58). This approach allowed for the generation of a diverse set of fragments with high structural complexity. Furthermore, Molander and co-workers reported a palladium-catalyzed nitrene cross-coupling reaction for the rapid assembly of drug-like compounds from simple precursors (59). These strategies showcase the potential of nitrene chemistry in fragment-based drug discovery and lead generation.

Thus, nitrene chemistry plays a significant role in drug discovery, offering valuable synthetic strategies for the development of targeted therapeutics. Nitrene-mediated late-stage functionalization, transfer reactions, drug conjugation, and fragment-based approaches provide innovative methods for the synthesis of bioactive compounds and the modification of complex molecules. The unique reactivity and selectivity of nitrenes offer exciting opportunities for the design and development of novel drug candidates. Further advancements in nitrene chemistry, catalyst design, and reaction discovery will continue to expand the applications of nitrenes in drug discovery and facilitate the development of effective and targeted therapeutic agents.

Outlook and Future Perspectives:

The outlook for nitrene chemistry is highly promising in the realms of synthetic methodology, total synthesis, and drug discovery. The development of novel transformations, the improvement of regio- and stereoselectivity control, and the exploration of new reaction cascades will expand the synthetic toolbox and facilitate the construction of complex molecular architectures. Nitrene-based reactions offer unique opportunities for the rapid synthesis of diverse compound libraries and the discovery of bioactive molecules. However, further research is needed to uncover new transformations, improve our understanding of nitrene reactivity, and address challenges such as catalyst design, sustainability, and selectivity. The continued exploration of nitrene chemistry holds tremendous potential for advancing synthetic chemistry, total synthesis, and drug discovery in the years to come.

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