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Introduction

Rearrangement reactions highlight the elegance of synthetic chemistry. They provide a pathway for building complex, often highly functionalized structures with remarkable precision, enabling innovations across various fields like pharmaceuticals, materials science, and agrochemicals. The ability to manipulate bond formation and cleavage in a controlled manner offers endless possibilities for the design of new molecules with specific properties or activities, underscoring the creativity and sophistication inherent in synthetic chemistry.[1]

Among various types of rearrangement, the Brook rearrangement is a fascinating and highly significant reaction within organosilicon chemistry.[2] It involves the migration of a silyl group from a carbon atom to an oxygen atom in a compound that contains an oxygen-centered anion. The Brook rearrangement has been widely exploited for the preparation of diverse organic compounds, including those used in pharmaceuticals, agrochemicals, and materials science. It also serves as an elegant example of how organosilicon chemistry can intersect with anionic and radical processes, offering a versatile tool for constructing complex molecular architectures.

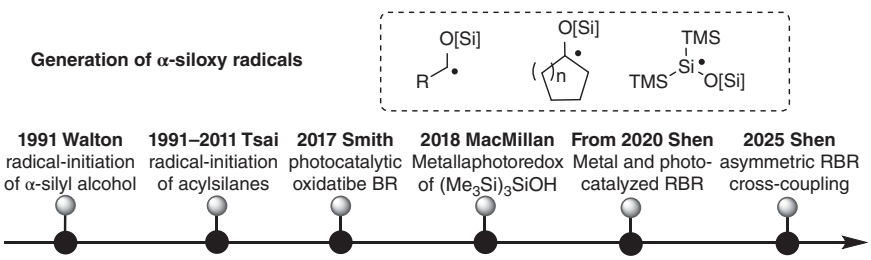
The Brook rearrangement was first observed by the Gilman group in the 1950s, but its mechanism wasn't fully understood at the time.[3] It was the Brook group that, in subsequent years, meticulously elucidated the reaction mechanism and its significance.[4] Their work clarified the crucial role of the silicon-containing alkoxide and silyl group migration, paving the way for a deeper understanding of the reactivity of organosilicon compounds. Since then, the anionic Brook rearrangement (ABR) has become a cornerstone reaction in organic synthesis, particularly for its ability to efficiently introduce functional groups and construct complex molecular frameworks.[2] ABR can be extended to achieve [1,n]-silyl transfer processes, depending on the size of the molecule and the spatial positioning of the atoms involved.[5] This ability for silyl migration is sensitive to the distance between the carbon and the heteroatom (oxygen, sulfur, nitrogen, etc.), with shorter distances generally favoring stronger and more efficient migration. This phenomenon is one of the key features that gives the ABR its remarkable versatility in organic synthesis, as it can be tuned to create a wide range of functionalized products with varying complexity. The migration of the silyl group to different atoms—sulfur, nitrogen, or oxygen—opens

Radical Brook Rearrangement, First Edition. Xiao Shen, Yunxiao Zhang and Gang Zhou.

up a whole new level of reactivity and selectivity for ABR. There are interesting variations of the ABR that involve heteroatoms like sulfur[6] and nitrogen,[7] leading to the specific types of rearrangements. Moreover, the retro-anion Brook rearrangement (r-ABR) is a fascinating counterpart to the classic ABR, and it adds another layer of versatility to organosilicon chemistry.[1c] The retro-Brook rearrangement involves the migration of a silyl group from an oxygen atom to a carbon atom, effectively reversing the direction of the migration seen in the ABR. It was first observed by the Speier group in 1952,[8] with further elucidation of its mechanism and scope coming from the West group in subsequent years.[9]

While the ABR has seen extensive exploration due to its predictable mechanism and wide applicability, the radical Brook rearrangement (RBR) has received comparatively less attention, primarily because the generation of alkoxyl radicals—which are key intermediates in RBR—is challenging. Alkoxy radicals are often less stable and harder to generate selectively, which has limited the widespread use of RBR compared to its anionic counterpart. In recent years, photocatalytic, transition-metal-catalytic and radical initiator-based strategies have been developed to overcome the challenges of generating alkoxyl radicals. These approaches have enabled chemists to harness RBR more efficiently, opening up new avenues for its use in organic synthesis. In this book, we discuss the development of RBR by summarization of the reactions based on different reactive intermediates generated from this unique radical rearrangement. Selected seminal works are briefly outlined below to provide an overview of the development of the RBR, highlighting key contributions that have shaped the evolution of this transformation.

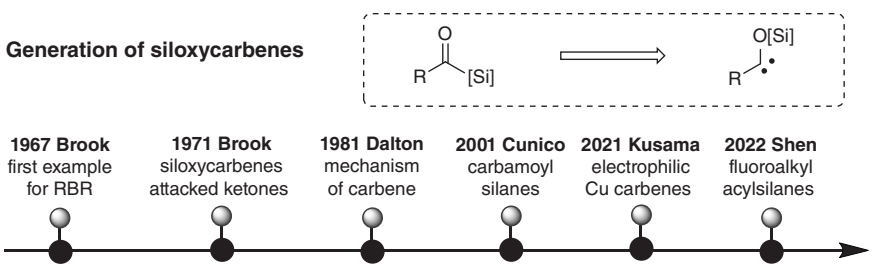
The first type of reactive intermediates is α-siloxyl carbon radicals (Scheme 1.1). In 1991, the Walton group reported the first example of the radical initiation of α-silyl alcohols, leading to the generation of α-siloxyl carbon radicals.[10] This pioneering work also demonstrated the application of these radicals in hydrogenation reactions, marking a significant advancement in the field of radical-mediated transformations involving organosilicon compounds. From 1991 to 2011, the Tsai group reported the radical initiation of bromoalkyl acylsilanes, which subsequently underwent radical cyclization and RBR processes.[11] These transformations lead to the generation of cyclic α-siloxyl carbon radicals, which are then available for further functionalization, expanding the scope of RBR. In 2017, the Smith group reported the first photoredox-catalyzed oxidative Brook rearrangement of α-silyl alcohols, enabling the generation of α-siloxyl carbon radicals.[12] These radicals were subsequently employed in alkylation and arylation reactions, demonstrating the potential of photoredox catalysis to facilitate efficient radical transformations in



Scheme 1.1 Generation of α-siloxy radicals.

organosilicon chemistry, although these reactions were proposed not to go through alkoxyl radicals. From 2018, The MacMillan group discovered that $(TMS)_3SiOH$ undergoes the RBR process to generate α-siloxyl silyl radicals, which can abstract halogen atoms from alkyl or aryl halides to form corresponding radicals that participate in further cross-coupling reactions.[13] From 2020, the Shen group has reported various metal- and photo-catalyzed RBR processes involving fluoroalkyl and alkyl α-silyl alcohols. These transformations proceeded through the generation of alkoxyl radicals, enabling the formation of a variety of functionalized products.[14] Recently, Shen's group reported the pioneering application of RBR in enantioconvergent cross-coupling of α-silyl alcohols through photoredox/nickel dual catalysis, enabling efficient access to chiral α-fluoroalkyl alcohols.[15] These work highlighted the versatility and efficiency of combining metal and photocatalysis in RBR reactions, expanding the scope of radical-based transformations in organosilicon chemistry.

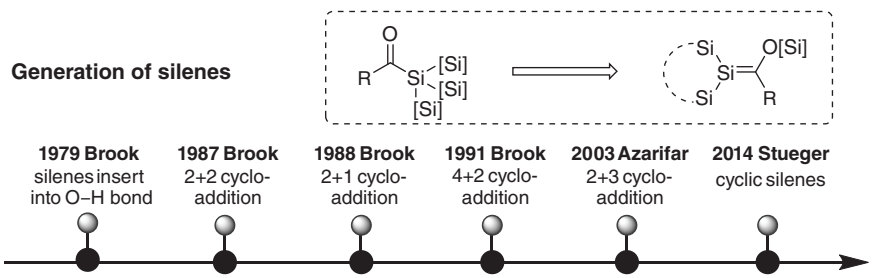
The second type of reactive intermediates generated from the RBR are siloxycarbenes (Scheme 1.2). These highly reactive species are formed when the silyl groups of acylsilanes undergo migration, leading to the generation of carbene-like intermediates stabilized by the adjacent oxygen atom. Siloxycarbenes are versatile intermediates that can undergo a variety of further transformations, such as nucleophilic addition, cyclization, or insertion reactions, making them valuable tools in synthetic chemistry. In 1967, the Brook group reported the first example of the RBR of acylsilanes, which led to the generation of siloxycarbenes.[16] These highly reactive intermediates subsequently underwent insertion reactions with the O—H bond of alcohols. In 1971, the Brook group reported the nucleophilic addition of siloxycarbenes, generated from acylsilanes, to ketones.[17] This reaction showcased the reactivity of siloxycarbenes as nucleophiles, leading to the formation of new carbon–carbon bonds and expanding the synthetic utility of these intermediates in organosilicon chemistry. Ten years later, the Dalton group provided a detailed mechanistic study of acylsilanes undergoing the RBR process to generate siloxycarbenes.[18] These intermediates were shown to insert into the O—H bond of alcohols, providing further insight into the reactivity of siloxycarbenes and their ability to participate in functional group transformations. This work contributed significantly to the understanding of the RBR mechanism and the role of siloxycarbenes in various organic reactions. Since 2001, the Cunico and Chen groups have reported that carbamoylsilanes underwent the RBR process under heating conditions to generate nucleophilic aminooxycarbenes.[19] These highly reactive intermediates can then undergo a variety of subsequent chemical transformations, expanding the



Scheme 1.2 Generation of siloxycarbenes.

scope of RBR reactions and enabling the synthesis of diverse nitrogen-containing organic compounds. In 2021, the Kusama group reported the first example of electrophilic copper-siloxycarbenes undergoing a formal [4 + 1] cycloaddition reaction with electron-rich dienes.[20] This pioneering work demonstrated the potential of siloxycarbenes, activated by copper, to engage in cycloaddition reactions, expanding the scope of their reactivity and providing a new strategy for the synthesis of cyclic structures in organosilicon chemistry. Recently, the Shen group reported that fluoroalkyl acylsilanes undergo the RBR process to generate donor-acceptor carbenes.[21] These carbenes can then participate in [2 + 1] cycloaddition reactions with both electron-rich and electron-deficient alkenes and alkynes, offering a versatile method for constructing highly functionalized compounds. This work further underscores the potential of RBR-derived intermediates in enabling diverse and selective cycloaddition reactions.

The third type of reactive intermediates generated from the RBR are silenes (Scheme 1.3). Silenes are highly reactive intermediates characterized by an electrophilic carbon–silicon double bond, which readily accepts nucleophilic attack from various nucleophiles. This reactivity makes silenes valuable for a range of transformations, such as nucleophilic additions, cycloadditions, or insertions. However, despite their intriguing reactivity, the development of reactions involving silenes has been somewhat limited, primarily due to their instability and the difficulty in generating them in a controlled and selective manner. The instability of silenes arises from the electrophilic nature of the Si═C bond, which makes them prone to decomposition or side reactions under certain conditions. In 1979, the Brook group discovered that silenes, generated from acylpolysilanes, can insert into the O—H bond of alcohols, offering a novel method for functionalizing silicon-containing compounds.[22] This finding was significant as it demonstrated the reactivity of silenes in bond insertion reactions. Additionally, the group further developed insertion reactions of silenes into N—H and C—H bonds, expanding the range of possible transformations involving these highly reactive intermediates. These advances paved the way for new synthetic strategies involving silenes, particularly in the functionalization of alcohols, amines, and hydrocarbons. Subsequently, the Brook group reported that silenes underwent a [2 + 2] cycloaddition reaction with ketones, leading to the formation of 1,2-siloxetanes. This reaction demonstrated the ability of silenes to participate in cycloaddition processes, generating cyclic siloxetane products. The ability to form such structures expanded the synthetic utility of silenes,



Scheme 1.3 Generation of silenes.

particularly in the context of organosilicon chemistry, where the introduction of silicon-containing rings can provide unique reactivity and stability, useful in the development of materials and functionalized silicon compounds.[23] They also developed [2 + 1] cycloaddition processes between silenes and isocyanides,[24] [4 + 2] cycloaddition reactions of silenes with α, β-unsaturated carbonyl compounds, dienes, and diketones.[25] In 2003, the Azarifar group reported that the N—H bond of urea underwent a formal [3 + 2] cycloaddition reaction with silenes, proceeding via two sequential nucleophilic attacks.[26] From 2014 to 2017, the Stueger group reported that acylcyclopolysilanes underwent 1,3-silyl transfer to generate cyclic silenes, which then participate in various subsequent reactions.[27] These work expanded the range of cycloaddition reactions involving silenes and contributed to the development of novel silicon-containing heterocycles, useful in materials science and medicinal chemistry.

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