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氮宾/炔烃复分解串联反应研究进展

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摘要 在过去的几十年中, 氮宾催化转化作为一类直接构建 C—N 键的高效反应得到了飞速发展, 并被广泛应用于含氮杂环化合物的合成. 虽然已有多种类型的氮宾前体被报道, 并通过各类催化转化反应在构建结构多样性杂环化合物分子中起到了至关重要的作用, 然而, 氮宾的反应类型还是局限于胺化反应、氮杂环丙烷化反应、磺化反应等有限的几类反应. 基于氮宾前体、催化策略(或者催化剂)以及复杂分子合成的相关综述已有很多报道, 这篇综述聚焦氮宾与炔烃的加成反应, 主要是氮宾/炔烃复分解串联反应. 这类反应可以快速合成具有结构多样性的多环、稠环和螺环类含氮杂环类化合物.

关键词 氮宾; α-亚胺卡宾; 含氮杂环化合物; 氮宾/炔烃复分解; 串联反应

Recent Advances in Nitrene/Alkyne Metathesis Cascade Reaction

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Abstract Catalytic nitrene transformations to *N*-containing molecules through direct C—N bond formation have experienced a dramatic development in the last decades. Although a variety of nitrene precursors have been disclosed under the corresponding catalytic conditions, which play a principal role in the synthesis of nitrogen-containing molecules with structural complexity, the types of nitrene transfer reactions mainly limited to the amination, aziridination, sulfimidation, and few others. In this area, reviews focused on different nitrene precursors, catalytic strategy (or metal catalysts), and challenging synthesis have been well-documented. In this review, the catalytic approaches of nitrene addition with alkynes, mainly nitrene/alkyne metathesis cascade reactions are outlined, which provide expeditious access to polycyclic, fused, and spiro *N*-heterocycles with structural diversity.

Keywords nitrene; *α*-imino carbene; *N*-heterocycle; nitrene/alkyne metathesis; cascade reaction

1 Introduction

1.1 Historical retrospect

Nitrene, which was first proposed by Tiemann in 1891 as the intermediate in the Lossen rearrangement,[1] is highly reactive and has shown versatile synthetic applications in recent decades.[2] The synthetic chemistry of nitrene has a history, which could be divided into three phases according to these seminal advances (Figure 1). In phase I, the pioneering work of thermal or photochemical induced nitrene transformation was reported by Smith in 1951 for the synthesis of carbazoles using *o*-azidobiphenyls,[3] which was followed by seminal works from Lwowski,[4] Breslow,[5] and others,[6] independently. In all these early examples, the reactions involved the generation of free nitrene species under thermal or photochemical conditions using different azides as nitrene precursors for the construction of corresponding *N*-heterocycles.

The catalytic formation of metal nitrene was first disclosed by Kwart and Khan in 1967, which is a cooper-catalyzed dinitrogen extrusion of benzosulfonyl azides, followed by alkene aziridination or C—H insertion.[7] This seminal work led the nitrene chemistry to phase II. The main theme in this period was metal catalyzed aziridination

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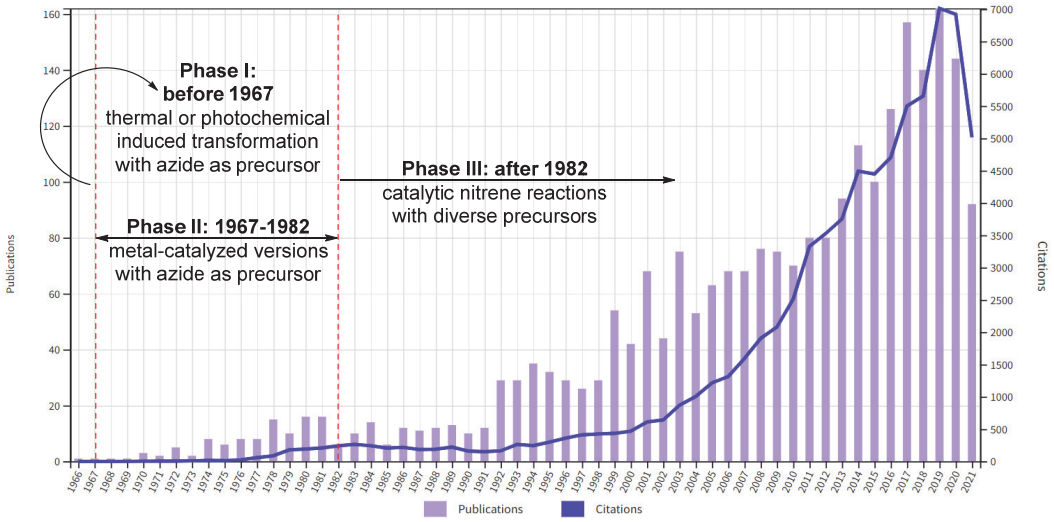


Figure 1 Publication and citation report of nitrene from Web of Science (1967～2021)

and/or amination using azide as nitrene precursor, although a few of other nitrene precursors were introduced at that time via pyrolysis or photolysis.[8-10] Thus, the progress in this area was still very slow between 1967～1982 due to the limited availability of practical and effective nitrene precursors. On the other hand, challenge remains in the control of regio-, chem-, and stereo-selectivity because the lack of robust metal catalyst.

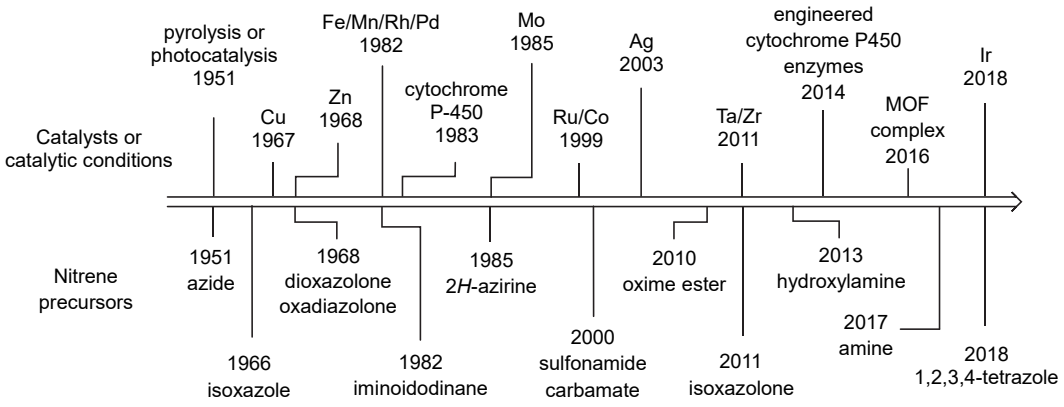
Later in 1980s, iminoidodinane[11] was introduced as nitrene precursor by Breslow[12] and Mansuy[13] independently. Following this discovery, a variety of metal catalysts have been employed to promote the nitrene formations using iminoidodinane as precursor, and the representative advances have been disclosed by Evans,[14] Jacobsen,[15] and Müller.[16] By contrast, iminoiodinanes are unstable and can be potentially explosive, which have limited their applications to large-scale synthesis. In 2000s, various sulfonamides or carbamates were employed as nitrene precursors in the presence of oxidant, such as $PhI(OAc)_2$ or PhI=O. Highly practical and selective nitrene transformations were independently reported by Che,[17] Du Bois,[18] and Dauban,[19] although the nitrene reactions were still restricted to aziridination and C—H insertion at that moment. During the last two decades, with the introduction of a variety of nitrene precursors, the catalytic nitrene transfer reactions have been emerged as a practical protocol for the direct and selective C—N bond formation with the development of robust and effective catalysts and/or catalytic strategies.[20]

1.2 Nitrene precursors and catalytic conditions

As summarized in Scheme 1, azide,[3,21] isoxazole,[8] dioxazolone,[9] and oxadiazolone[10] were employed as the nitrene precursors at early time, and generally forming free nitrene intermediates via pyrolysis or photolysis. Only Cu complexes were reported to be effective catalysts to promote the nitrene transfer using azide as precursor.[7] Until 1982, iminoiodinane was introduced as an effective nitrene precursor.[12] Since then, a variety of metal complexes were found to be compatible with this reagent, leading to the corresponding nitrene transfer reactions proceeded smoothly. With these advances in catalytic protocols, in turn, facilitated the discovery of novel nitrene precursors, including cyclic precursors:[22] 2*H*-azirine,[23] isoxazolone,[24] and 1,2,3,4-tetrazole,[25] which form the nitrene species *via* corresponding catalytic ring-opening processes; and acyclic precursors:[26] sulfonamide and carbamate,[17-19] amine,[27] and "N—O" containing amides, such as oxime ester[28] and hydroxylamine,[29] which deliver the nitrene intermediates via different catalytic oxidative approaches.

Nowadays, the strategies for the catalytic nitrene transformations could be divided into two main approaches: metal catalysis and biocatalysis (Scheme 1).[20] The latter, which was first reported by Breslow in 1983 using cytochrome P-450 as the catalyst,[12b] takes advantage of engineered natural enzymes that are capable of stereoselective oxidizing C—H bonds. Many research groups, especially the Arnold group, have disclosed effective methods to enable the direct amination of C—H bond *via* nitrene intermediates that do not regularly occur in nature.[30] Although high selectivity and turnover numbers could be realized using biocatalysis, only few laboratories have the capability or expertise to conduct the directed evolution. Thus, metal catalyzed nitrene transfer reactions still the main theme at this moment.

In fact, more than ten different transition metal complexes have been reported to be effective to promote the nitrene transfer reactions, with Cu,[7,31] Rh,[12a,32] Fe,[12a,33] Mn,[12a,34] Ru,[35-36] Co,[35,37] and Ag[38] among the more extensively used.[39] The early example of asymmetric nitrene transfer reaction using chiral copper complexes was reported by Evans[14] and Jacobsen,[15] independently. Later in early 2000s, the robust dirhodium complex, $Rh_2(esp)_2$, which is disclosed by Du Bois, displayed excellent utility for the selective late-stage functionalization.[40] The Co catalyst, typically the porphyrins supported ones that disclosed by Zhang, could be applied for homolytic activation



Scheme 1 Summary of nitrene precursors and catalysts/catalytic conditions

of sulfamoyl azide to generate the corresponding metal aminyl radical intermediates, which also show nitrene reactivity, generating the amination products with high selectivity.[37] Representative advances on the Ru catalysis were independently reported by Chi,[17] Gallo,[36a] and Brurin.[36b] The first example of Ag catalyzed intermolecular amidation of benzylic C—H bond was reported by the He group in 2003.[38c] Seminal discovers were reported after this work by Pérez,[38d] Schomaker,[38e] and Bach,[38f] independently. Recently, a novel MOF-supported complex was reported to be effective in promoting the intermolecular C(sp^3)—H amination by Lin, providing secondary amines with excellent selectivity.[41] In addition, elegant Mn and Ir catalyzed chemoselective intramolecular C(sp^3)—H amination and amidation have been disclosed recently by White[42] and Chang,[43] respectively.

1.3 Catalytic nitrene transfer reactions

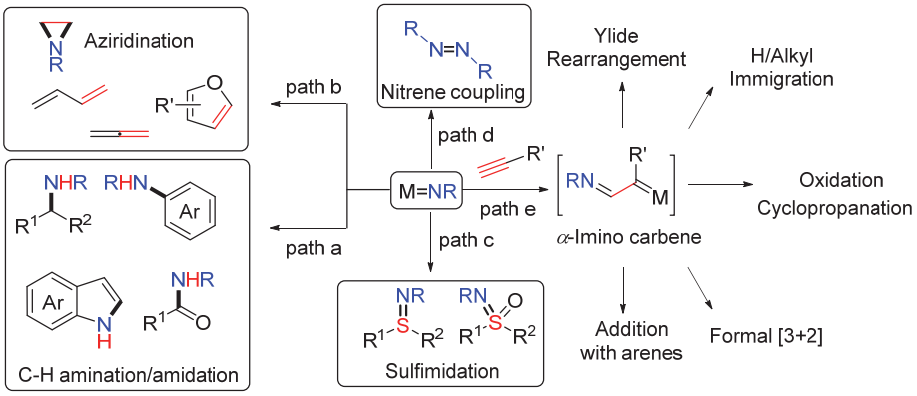
With the development of above effective metal catalysts and catalytic methods, the catalytic nitrene transformations have demonstrated broad applications in synthetic chemistry using a variety of nitrene precursors (Scheme 2).[20-22] In this context, the classic nitrene C—H amination/amidation has been expanded to previously inert C—H bonds with the discovery of novel and selective catalysts (Scheme 2, path a).[44] For examples, Driver's group has reported a rhodium-catalyzed non-aromatic C(sp^2)—H bond insertion of nitrene for the synthesis of indoles;[45] while the formylic C—H bond insertion using iminoiodinane as nitrene precursor was disclosed by Chan and coworkers.[46] On the other hand, a variety of alkene species, such as dienes, allenes, and furans, have been employed to the catalytic nitrene aziridination (path b), which formed the aziridines initially and converted to different types of *N*-heterocycles via corresponding cascade transformations or rearrangement processes.[47] Beyond these two typic nitrene transfer reactions, which have been summarized in a variety of recent review articles by researchers worldwidely,[20-22,26,45] sulfimidation (path c)[48] and nitrene coupling (path d)[49] are other two well-known nitrene transformations, although not used as extensively as C—H amination and aziridination.

In comparison to the carbene chemistry, the catalytic nitrene reactions in synthetic chemistry still in its infancy,[20a,50] the versatile reactivity, which previously realized with carbene intermediates, could be reexamined with nitrene species. For instance, nitrene/alkyne metathesis (NAM) cascade reaction, which is an analogous version of carbene/alkyne metathesis (CAM) cascade reaction,[51] has shown high efficiency for the directly construction of complex cyclic molecules with multi-bond formations in one-pot. In this type of cascade reactions, *α*-imino carbene intermediate was formed *in situ* as the key intermediate, which could be terminated by various carbene reactions, providing *N*-containing molecules or *N*-heterocycles with structural complexity and diversity (Scheme 2, path e). To increase the readability, the main text of this review article focuses on the recent advances of nitrene transfer reaction with alkynes, which has not been summarized as a specific topic yet. These reactions generally went through a nitrene/alkyne metathesis process or involved an analogous pathway via metalloradical intermediates, providing polycyclic *N*-heterocycles in one-pot. On the other hand, catalytic oxidative transformations of activated alkynes with different nitrene precursors have been reviewed by Davies,[52a] Huang,[52b] and Hashmi[52c] recently. In these reactions, although similar *α*-imino carbene intermediates were formed as in NAM process, the reaction pathway did not involve the nitrene species,[53] thus, these advances are not included in this review article.

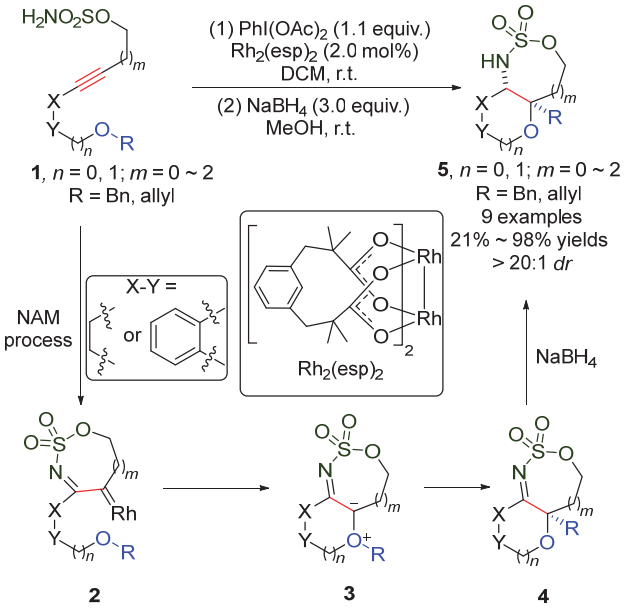
2 Nitrene/alkyne metathesis cascade reaction

2.1 NAM process terminated by ylide rearrangement

Pioneering work of catalytic nitrene/alkyne metathesis (NAM) cascade reaction of alkyne-tethered sulfamate esters was reported by Blakey in 2008.[54] In this work, the sulfamate esters with an aryl ring tethered to an alkyne species **1** converted to the nitrene intermediate after catalytic oxidation in the presence of dirhodium complex $Rh_2(esp)_2$ with bisacetoxyiodobenzene $PhI(OAc)_2$ as the oxidant, followed by an intramolecular nitrene/alkyne metathesis process to form the *α*-imino carbene intermediate **2** (Scheme 3). The



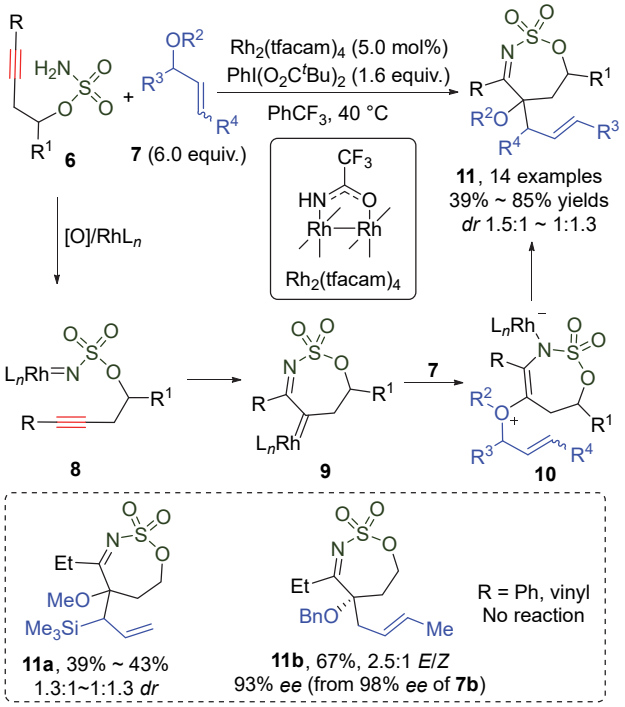
Scheme 2 Summary of catalytic nitrene transfer reactions



Scheme 3 Rh-catalyzed intramolecular cascade NAM reaction terminated by ylide rearrangement

reaction was terminated by a rearrangement procedure through the oxonium ylide intermediate **3** to give the seven-membered imines **4**. Stereoselective reduction in the presence of $NaBH_4$ could smoothly led to the stable polycyclic *N*-heterocycles **5** in moderated to high yields.

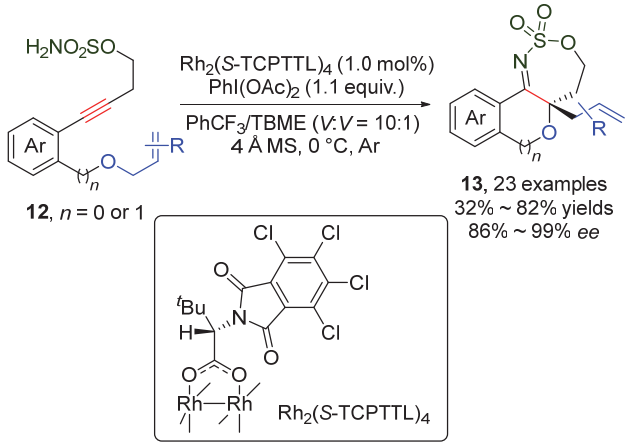
Later in 2013, the same group reported an intermolecular version of above cascade reaction through interception of the *α*-imino carbene intermediate that generated via NAM process with external allyl ethers **7** under analogous conditions using Rh_2(tfacam)$_4$ as the catalyst.[55] In this reaction, possible side reactions, including C—H amination, aziridination, cyclopropanation, and others have been successfully suppressed, providing *α*-oxyimine products **11** in good to high yields (Scheme 4). Notably, corresponding allylsilane product **11a** could be obtained in moderate yields, although with low diastereoselectivity. Moreover, the stereochemical information from enantiomerically enriched allyl ether could be efficiently transferred to the cascade product, generating the quaternary-stereocenter-bearing imine **11b** in 67% yield with 93% *ee* by using corresponding allyl ether with 98% *ee*. On the other hand, this cascade reaction limited to the internal alkyl alkynes, aryl and vinyl substituted alkynes turned out to be inert under current conditions.



Scheme 4 Rh-catalyzed intermolecular cascade NAM reaction terminated by ylide rearrangement

In 2019, Xu's group[56] has demonstrated the first asymmetric catalytic version of above cascade reaction using Rh_2(*S*-TCPTTL)$_4$ as the catalyst. This chiral dirhodium complex is an exceptionally effective catalyst for the asymmetric nitrene/alkyne metathesis cascade reaction, providing an effective approach for the synthesis of chiral tricyclic *N*-(sulfonyl)imines **13** in good yields with generally excellent enantioselectivity (Scheme 5). In this study, the chiral dirhodium catalyst is not only responsible for the *in situ* generation of the *α*-imino rhodium carbene intermediate in the presence of oxidant $PhI(OAc)_2$, but also controls the asymmetric induction step in the oxonium ylide rear-

rangement process.

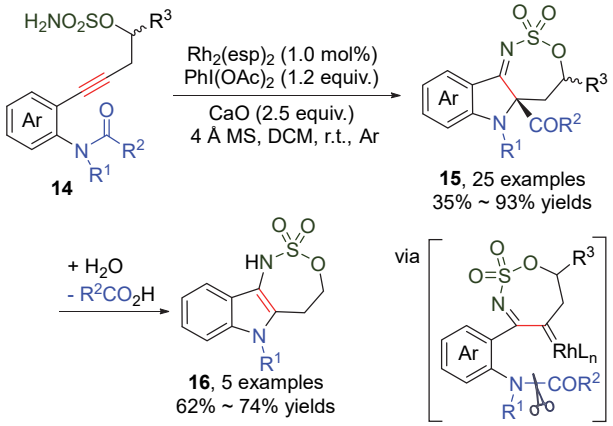


Scheme 5 Asymmetric cascade NAM reaction terminated by ylide arrangement

Based on the above results, Xu's group[75] recently reported a $Rh_2(esp)_2$-catalyzed intramolecular nitrene/alkyne metathesis cascade reaction of alkyne-tethered sulfamates **14** containing an amide group. This reaction involves a formal amide C—N bond insertion process through an ammonium ylide intermediate, followed by a selective Stevens [1,2]-acyl shift, providing a practical method for the construction of 2,2-disubstituted tricyclic 3-iminoindolines **15** in generally good yields. Moreover, these generated 3-iminoindolines could smoothly transfer to indoles **16** in the presence of water in high yields via a decarboxylation process (Scheme 6). In addition, after a brief optimization, up to 83% *ee* with 64% isolated yield could be realized for the 3-iminoindoline product **15** when $Rh_2(S\text{-TCPTTL})_4$ was introduced as the catalyst.

2.2 NAM process terminated by addition with arenes

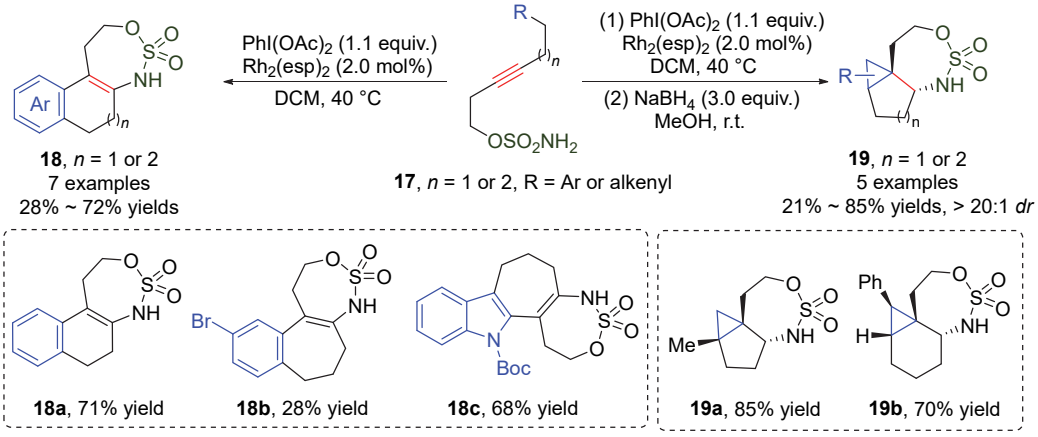
Beyond the ylide rearrangement in nitrene/alkyne metathesis cascade reaction, Blakey and co-workers[58] have realized a dirhodium-catalyzed NAM cascade reaction that terminated by addition with tethered arenes or cyclopropanation with embodied alkene species. The reaction uses



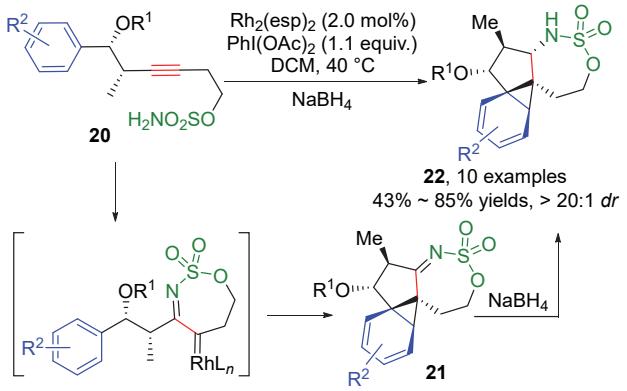
Scheme 6 Cascade NAM reaction terminated by a formal C—N bond insertion

alkyne embodied sulfamates as the *α*-imino carbene precursor, which formed via a NAM process in the presence of $Rh_2(esp)_2$ and oxidant. Then, the cascade reaction could be terminated by intramolecular aromatic C—H functionalization to produce a diverse array of heterocyclic products **18** in moderate to high yields; whereas, the *α*-imino carbene intermediate could form the cyclopropane products **19** via intramolecular cyclopropanation reaction with excellent diastereoselectivities (Scheme 7).

In 2013, Panek's group[59] has disclosed an analogous cascade approach by using chiral alkyne-tethered sulfamates **20** that produces stereochemically well-defined norcaradienes **22** in moderate to high yields and excellent diastereoselectivities under mild reaction conditions. In this reaction, the *in situ* generated *α*-imino carbene intermediate was terminated by a Buchner reaction (arene cyclopropanation) with embodied aryl group to afford unique tetracyclic norcaradiene products **21**, which finally led to the cyclic sulfamates **22** after reduction (Scheme 8). In this work, the author also found that the norcaradienes can be converted to cycloheptatrienes through a ring enlarging electrocyclization process under a transition metal or Brønsted acid catalyzed conditions in generally good yields.



Scheme 7 Cascade NAM reaction terminated by aromatic C—H functionalization or cyclopropanation



Scheme 8 Cascade NAM reaction terminated by Buchner reaction

Later in 2017, the intermolecular cascade NAM reaction that terminated by addition with aryl group has been disclosed by Pérez using copper complex $Tp^{Br3}Cu(MeCN)$ as the catalyst.[60] In this reaction, iminoiodonanes **23** were used directly as the nitrene precursors to react with alkynes **24**, leading to the *α*-imino carbene **25**, or its resonance form **25'**. The following terminating step is mainly substrate-dependent (Scheme 9). For the internal alkynes, the formed carbene intermediate could react with tethered aryl group to form the isothiazoles **26** via aromatic C—H functionalization as the major products (Scheme 9, path a), contaminating with oxidation products **27** as the minor ones (Scheme 9, path b); whereas, terminal alkynes selectively led to the oxidation products in high to excellent yields via **28**.

2.3 NAM process terminated by oxidation

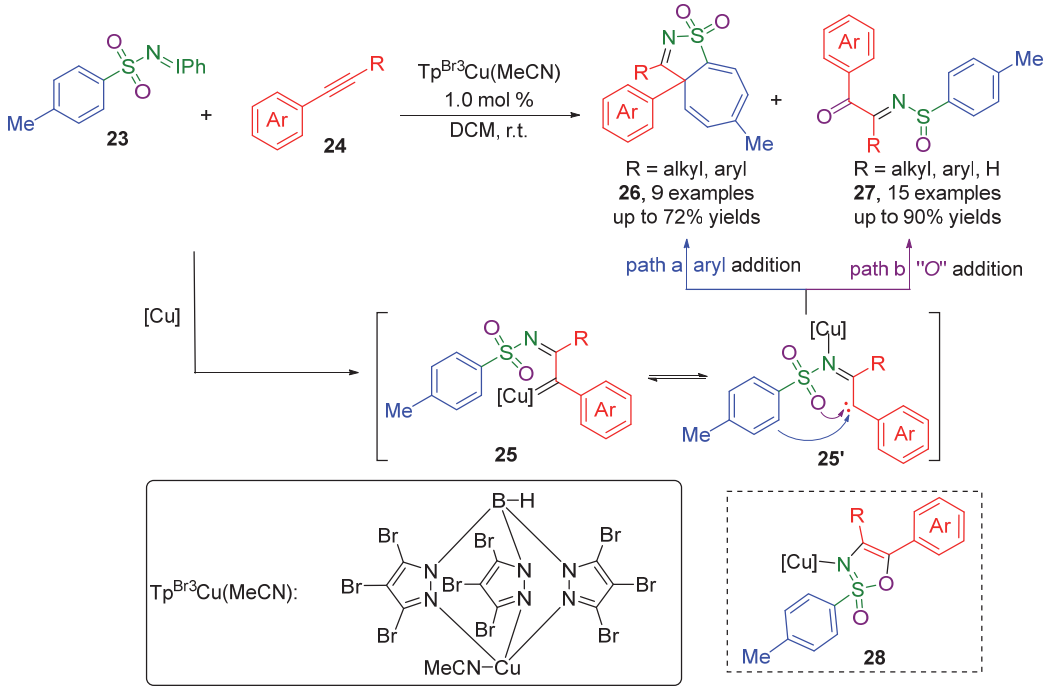
Shortly after Pérez's work, Shi's group[61] has also reported a chemoselective oxidative amination and carbonylation cascade reaction, forming aroyl group containing *N*-heterocycles **30** in good to excellent yields. This reaction went through a metal nitrene-initiated alkyne oxidation, followed by a nucleophilic trapping with water and oxidation process via carbene intermediate **31** (Scheme 10). In the case of benzyl substituted alkynes (Ar=Bn), the phenyl group migration occurred dominantly instead of addition with external water, delivering corresponding vinyl group containing derivatives in generally high yields.

2.4 NAM process terminated by 1,2-migration

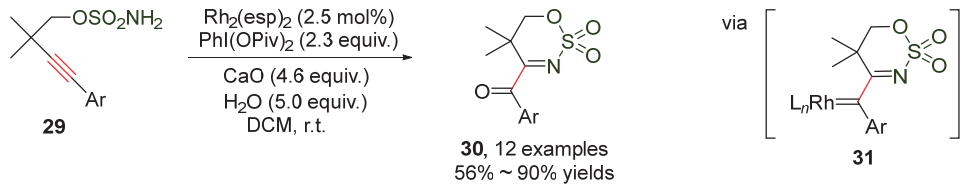
At the same time, Shi's group[62] also found that the nitrene/alkyne metathesis (NAM) cascade reaction using alkynyl-tethered sulfamates **32** could form completely different products depending on the ring size of the linkage part. When $n=0$, which is a cyclopropane linkage, the alkyl migration of the key *α*-imino carbene **33** occurred via a ring-opening manner, leading to the cyclobutane-fused heterocycles **34** in high yields (Scheme 11, path a). Whereas, when $n=1$, alkoxyl moiety migration happened dominantly, generating the methylenecyclobutane-containing heterocycles **35** in moderate to good yields (Scheme 11, path b). The detailed reaction mechanism of this divergent outcomes have been studied by the same group in 2019 through density functional theory (DFT) calculations, which well rationalized the proposed reaction pathways.[63]

2.5 Formal [3+2] annulation via metalloradical intermediate

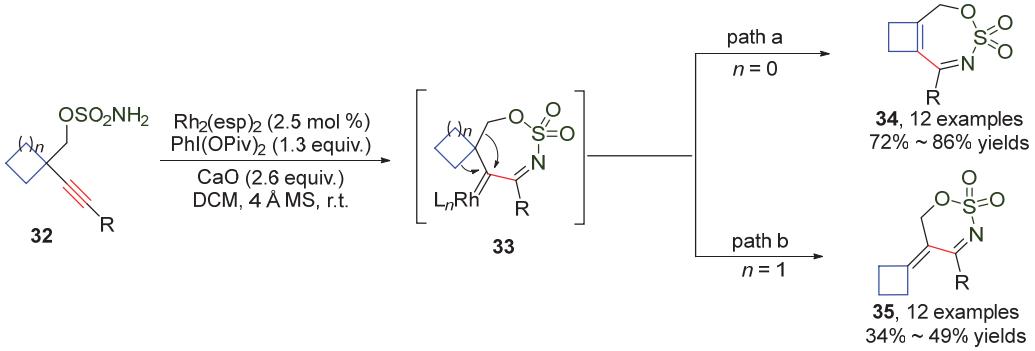
In addition to metal nitrene species, metal nitrene radical intermediates, which possesses similar reactivity in most cases, could be formed under Fe[33] or Co[37] catalysis. Recently, Chattopadhyay's group[64] has developed an iron catalyzed formal [3+2] annulation of 1,2,3,4-tetrazoles **36**



Scheme 9 Cu-catalyzed cascade NAM reaction terminated by Buchner reaction or oxidation

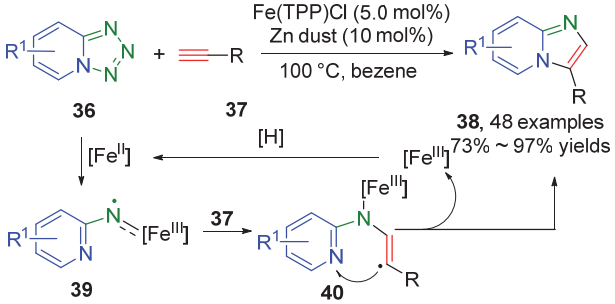


Scheme 10 Cascade NAM reaction terminated by oxidation



Scheme 11 Cascade NAM reaction terminated by 1,2-alkyl migration

with terminal alkynes **37**, which provides a practical access to pyrimidazoles **38** in good to high yields with broad substrate scope. In this work, 1,2,3,4-tetrazole has been introduced as an efficient metal nitrene radical precursor, which initially forms the key metalloradical intermediate **39** in the presence of [Fe^{II}] catalyst that generated from Fe(TPP)Cl by reduction with Zn dust. Then, addition with external alkynes led to the formal [3＋2] annulation products via γ-[Fe^{III}]-vinyl radical intermediate **40** and regenerated the [Fe^{III}] complex. The [Fe^{III}] complex was converted to [Fe^{II}] catalyst in the presence of Zn dust, and promoted the next catalytic cycle (Scheme 12).



Scheme 12 Fe-catalyzed formal [3＋2] annulation via metalloradical intermediate

3 Summary and outlooks

In this review article, we have briefly introduced the nitrene chemistry by focusing on the pioneering works, exploration of nitrene precursors, and the development of effective catalysts or catalytic conditions in the nitrene transfer reactions. Then, we have highlighted the recent advances in nitrene transfer reaction with alkynes, which has not been summarized as a specific topic yet. In this area, the general reaction pathway involved a nitrene/alkyne metathesis (NAM) process to form the key α-imino carbene or vinyl radical intermediates, and terminated by a variety of carbene reactions or annulations, providing a modular method for the expeditious construction of complex *N*-heterocycles with high atom economy and bond formation efficiency. In comparison with luxuriant carbene chemistry, the types of terminating carbene reactions in NAM cascade reaction are still limited to handful examples. On the other hand, the nitrene precursors that have been employed to the NAM reaction is generally sulfamates, and most of the NAM processes are intramolecular version, which is the main obstacle of this type of cascade reaction for the diversity-oriented synthesis. In addition, the asymmetric catalytic NAM cascade reaction remains challenging, although versatile enantioselective versions of nitrene transfer reactions have been well documented. Overcoming these drawbacks by development of effective, selective, and robust catalytic systems can open a novel field in synthetic chemistry, especially in the practical synthesis *N*-heterocycles with structural diversity.

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