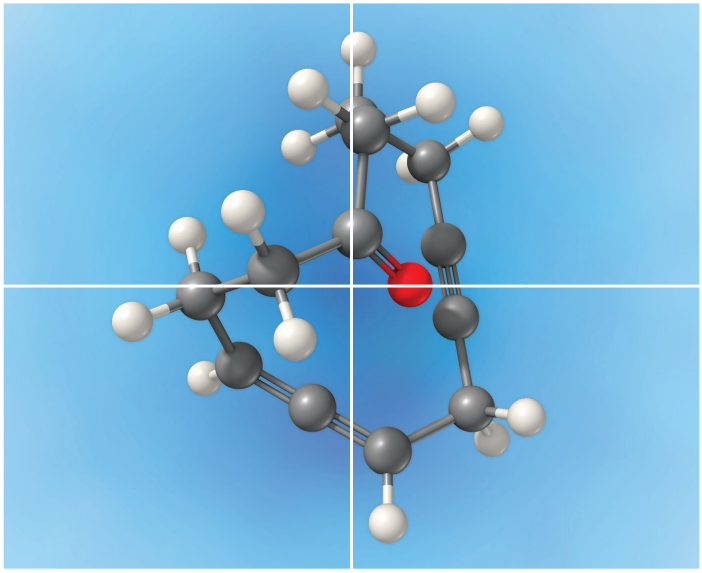
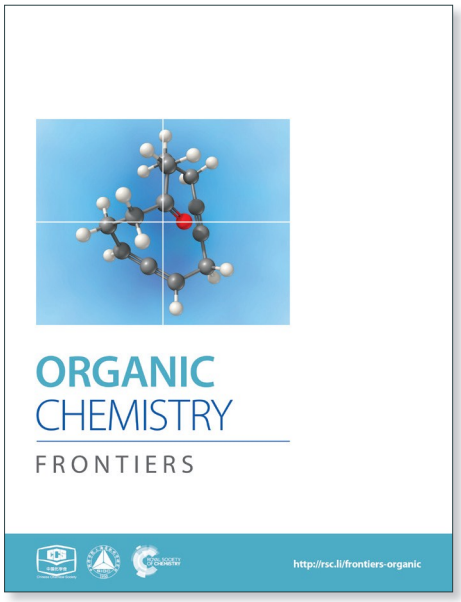
# ORGANIC CHEMISTRY

## FRONTIERS



Accepted Manuscript




This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

# New Developments of Ketonitrones in Organic Synthesis

Wei-Min Shi, Xiao-Pan Ma, Gui-Fa Su*, Dong-Liang Mo*

Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources, Ministry of Education of China and School of Chemistry & Pharmaceutical Sciences, Guangxi Normal University, 15 Yu Cai Road, Guilin 541004, China

**Abstract:** Nitrone chemistry has been widely developed for a long history and many reviews have outlined its rich transformation chemistry. However, most of these reviews are involving aldonitrones due to their easy preparation and high reactivity. In recent years, *N*-substituents *α, β*-unsaturated ketonitrones and *N*-vinyl nitrones have attracted much attention of synthetic chemists to develop novel methodologies for their preparation and transformation. Various properties and new transformations of these nitrones have been discovered and applied into the synthesis of important heterocycle scaffolds. This review describes some recent breakthroughs in the development of new transformation of these nitrones. These new reactions include novel strategies for preparation of *N*-substituents *α, β*-unsaturated ketonitrones or *N*-vinyl nitrones, new rearrangement of nitrones, reaction of nitrones with dipolarophiles such as alkynes, allenes and isocyanates.

## INTRODUCTION

The chemistry of nitrones has been well developed in the literature since its discovery more than a century ago.[1] Nitrones are widely not only recognized as important building blocks in the synthesis of various natural and biologically active compounds, [2] but also used as both spin-trap reagents[3] and therapeutic agents.[4] Most of these early studies have focused on exploring 1,3-dipole character of nitrones in [3+2] dipolar cycloadditions with dipolarophiles to construct functionalized five-membered heterocycles which are important intermediates in organic synthesis.[5] The dipolarophiles are including alkenes,[6] alkynes,[7] allenes[8] and other cumulated double bonds.[9] Some of other applications involving nitrones are also studied well, such as synthesis of *β*-lactams by copper-catalyzed [2+2] cycloaddition with terminal alkynes,[10] [3+2] cycloaddition with methylenecyclopropane, [11] [3+3] cycloaddition with cyclopropanes,[12] [3+3] cycloaddition with vinylcarbenes,[13] [4+3] cycloaddition with cyclobutanes,[14] and [2+2+3] cycloaddition with 1,6-enynes to give tricyclic 1,2-oxazepanes,[15] umpolung of nitrones by $SmI_2$ for C−C bond formation with electrophiles.[16] However, most of these transformations are applied with *N*-alkyl/*N*-aryl aldonitrones, *N*-alkyl/*N*-aryl ketonitrones (Figure 1, type I), [17a] or *N*-alkyl/*N*-aryl *α,β*-unsaturated aldonitrones[17b-c] due to their easy preparation and high reactivity. There are only few applications for *N*-substituents *α,β*-unsaturated ketonitrones (Figure 1, type II) [18] or *N*-vinyl nitrones (Figure 1, type III) [19] in the past decades because of their challenges of synthesis. Hence it is not surprising that the properties of these nitrones are unclear and desirable to be studied. Recently, not

only some new methods for synthesis of *N*- substituents *α,β*-unsaturated ketonitrones (type II) and *N*-vinyl nitrones (type III) have been developed but also novel transformations of these nitrones have been demonstrated in organic synthesis. A varies of transformations have shown that the nature of these nitrones are distinguished and interesting in the reaction. In this review, we focus on describing several recent developments of preparation of *N*-substituents *α,β*-unsaturated ketonitrones (type II) or *N*-vinyl nitrones (type III) as well as novel transformations involving these nitrones, which are including: 1) synthesis of *N*-substituents *α,β*-unsaturated ketonitrones and *N*-vinyl nitrones, 2) the new rearrangement of ketonitrones, 3) the reaction of ketonitrones with alkynes, 4) the reaction of ketonitrones with allenes, 5) the reaction of ketonitrones with isocyanates.

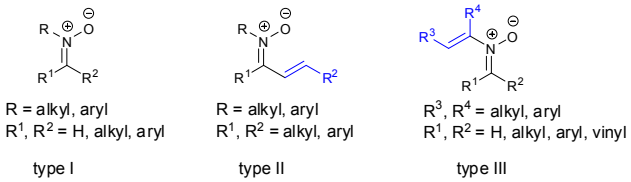



**Figure 1** Different Type of Nitrones

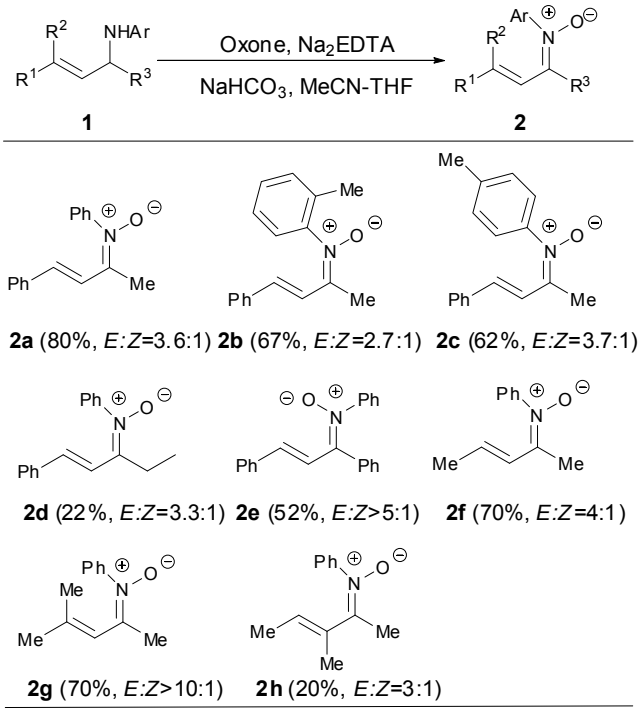
## 1 Novel Strategies in Synthesis of Ketonitrones

Various methodologies have been reported for preparation of nitrones. But most conveniently and commonly used methods are by condensing *N*-monosubstituted hydroxylamines and carbonyl compounds,[20] or by oxidation of the corresponding hydroxylamines,[21] imines,[22] amines[23] or alkylation of aldoxime.[24] The reaction of *N*-substituted hydroxylamines and aldehydes is typically facile and gives *N*-substituted aldonitrones in high yields under mild conditions. However, except for

the intra-molecular variant, condensation of *N*-substituted hydroxylamines with corresponding ketones usually requires harsh conditions and the scope of the reaction is limited. Up to now, no directed condensation of *N*-aryl hydroxylamines with *α,β*-unsaturated ketones has been developed except for successful condensation of *N*-alkyl hydroxylamine with *α,β*-unsaturated ketones.[25]

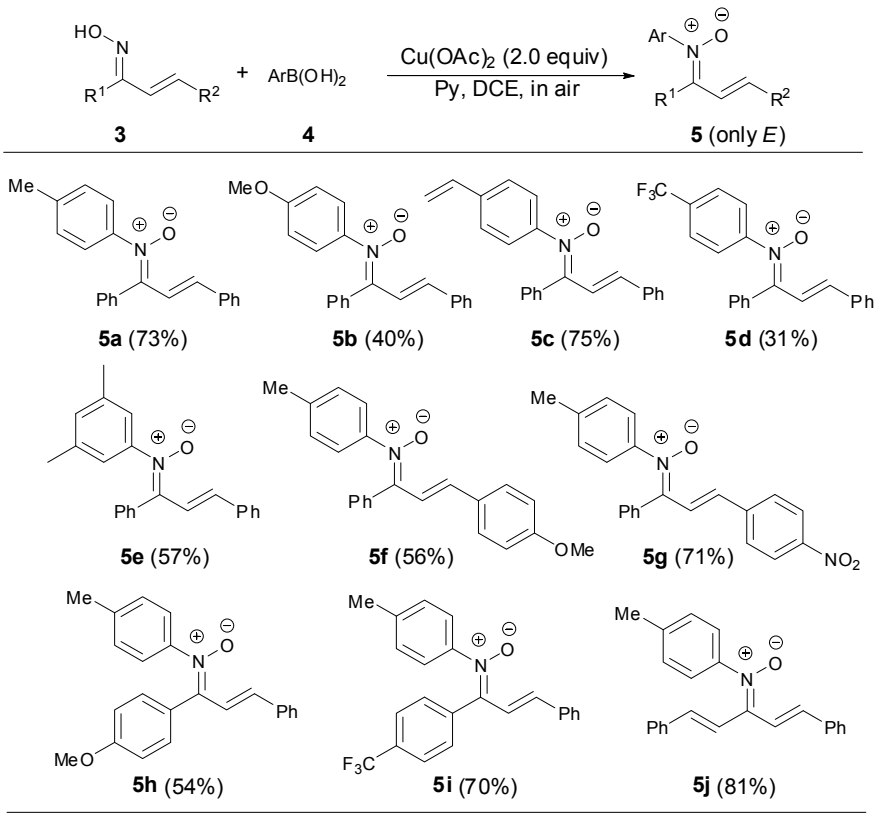
### 1.1 Preparation of Type II Nitrones

In 2012, Yang and coworkers developed a modular approach to *N*-aryl *α,β*-unsaturated ketonitrones by oxidation of *N*-allyl anilines with Oxone which was prepared by condensation of anilines and enals followed by alkylation of the resulting *α,β*-unsaturated imines.[26] This method was general and efficient access to diversely substituted *N*-aryl *α,β*-unsaturated ketonitrones in good yields. The C=C bonds of nitrones **2** appeared to be all generated in the *E*-geometry while the C=N double bonds of the nitrone **2** were formed as *E, Z*-mixtures in ratios ranging from 2:1 to >10:1. The *N*-substituted groups in nitrones were tolerated *para*-, *meta*- or *ortho*-substituted on the aryl ring. It was worth noting that the *α*- and *β*-positions of *N*-aryl *α,β*-unsaturated ketonitrones could be further substituted with methyl group (**2g** and **2h**).



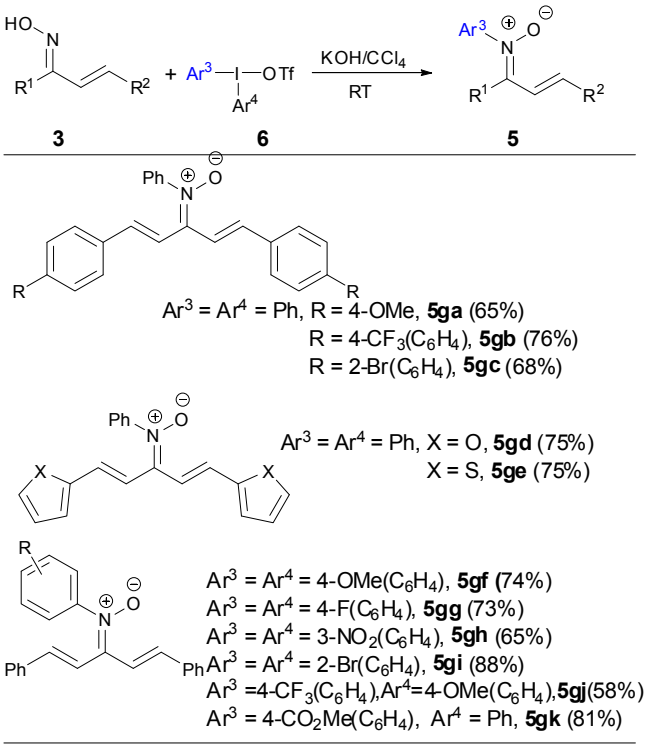

**Scheme 1** Synthesis of *N*-aryl *α,β*-unsaturated Ketonitrones by Oxidation of Aniline

In 2013, Anderson and coworkers found that *N*-aryl *α, β*-unsaturated ketonitrones can be prepared by copper-mediated cross-coupling reaction of chalcone oximes with various arylboronic acids in good yields (Scheme 2).[27] The scope of nitrones was tolerated aryl, vinyl, bromide, nitro groups. The geometry of chalcone oxime **3** has no effect on the formation of *N*-aryl *α, β*-unsaturated ketonitrones with *E*-isomer as major products. It is a very useful transformation that only the *E*-isomer nitrones were obtained after fast column chromatography. However, this copper-mediated coupling reaction was not suitable for *ortho*-substituted arylboronic acids.



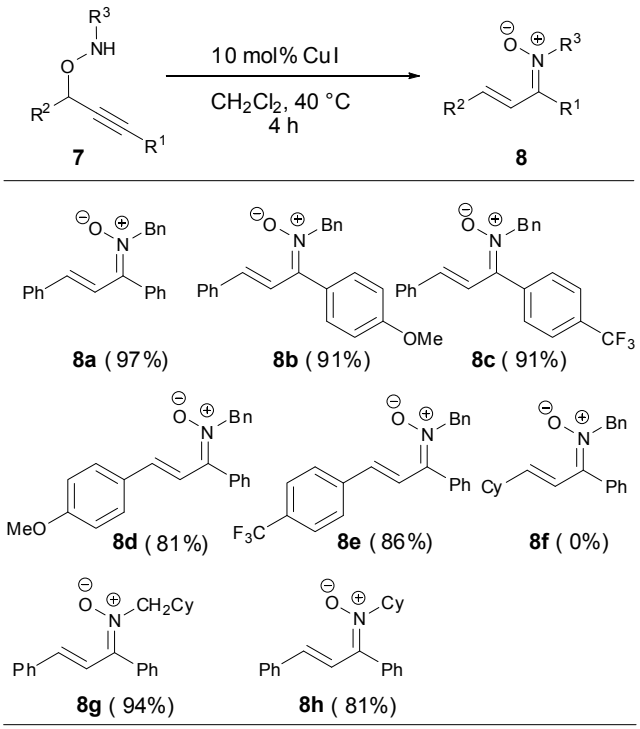

**Scheme 2** Synthesis of *N*-aryl Ketonitrones by Copper-mediated Reaction

In order to resolve the aforementioned drawbacks of requirement of copper salts and synthesis of *ortho*-substituted *N*-aryl *α,β*-unsaturated ketonitrones, a simple and efficient transition-metal free method to prepare *N*-aryl *α, β*-unsaturated ketonitrones was developed by Mo and coworkers in 2015 (Scheme 3). [28] The reaction showed good functional group tolerance for both electron-rich and electron-deficient substituents on both oximes and diaryliodonium salts. When unsymmetrical diaryliodonium salts were tested, the *N*-arylation reaction proceeded with high chemoselectivity and electron-deficient aryl moieties were preferentially transferred to the nitrones. The nitrones can be easily prepared in gram scale in good yields. A DFT calculation revealed a rational formation of nitrone via *O*-attack diaryliodonium salts and [1,3]-phenyl migration of *O*-coordinated oximate complex.



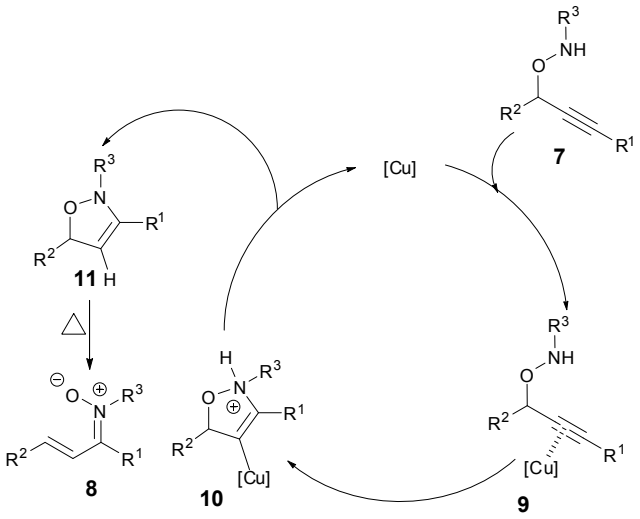

**Scheme 3** Synthesis of *N*-Aryl Ketonitrones by Diaryliodonium Salts

In 2014, A Cu-catalyzed rearrangement of propargloxyamines to synthesize the *N*-alkyl *α,β*-unsaturated ketonitrones with excellent yields was developed by Nakamura and coworkers (Scheme 4). [29] The $R^1$ and $R^2$ substituted group in propargloxyamines **7** were tolerated various aryl substituted groups. However, the reaction failed when the $R^2$ group is alkyl substituent in substrate **7f**.



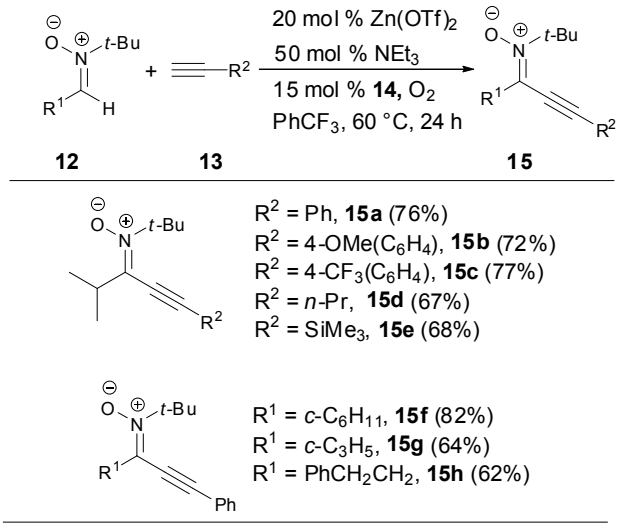

**Scheme 4** Synthesis of *N*-alkyl Ketonitrones by Copper-catalyzed Reaction

A plausible mechanism was proposed based on isolation of the intermediate **11** (Scheme 5). The π-acidic Cu catalyst coordinated to the alkyne **7** to form intermediate **9**. Nucleophilic attack of the nitrogen atom onto the electrophilically activated C-C triple bond occurred in a 5-*endo* manner, leading to the cyclized Cu-vinyl intermediate **10**. Subsequent protonolysis of Cu-vinyl intermediate afforded 3-isoxazoline **11** while regenerating Cu catalyst. An aryl substituent at the propargylic position would promote the electrocyclic ring opening **11** to provide *N*-alkyl *α,β*-unsaturated ketonitrones **8**.




**Scheme 5** A Plausible Mechanism of Formation of *N*-alkyl *α,β*-unsaturated Ketonitrones

Recently, Studer and coworkers developed a mild, simple zinc triflate catalyzed cross-dehydrogenative coupling (CDC) between aldonitrones and terminal alkynes to synthesize alkynylnitrones in good yields by using cheap, readily available 3,3'-tertra-tert-butyldipheno-quinone (**14**) and dioxygen as oxidants (Scheme 6).[30] The nitrones were easily converted to important 3,5-disubstituted isoxazoles.

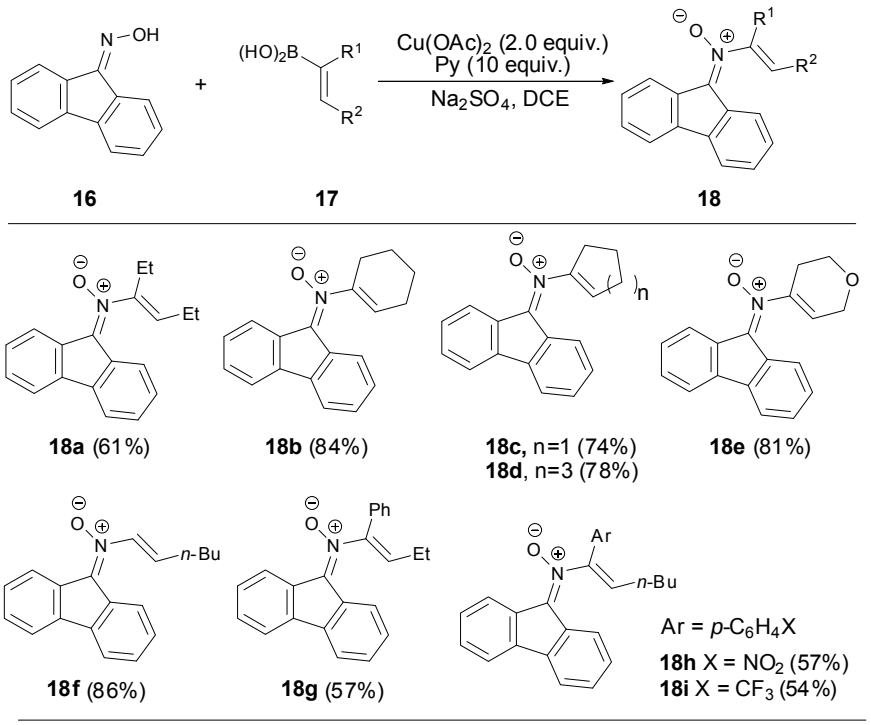



**Scheme 6** Synthesis of *N*-Alkyl Alkynylnitrones

### 1.2 Preparation of Type III Nitrones

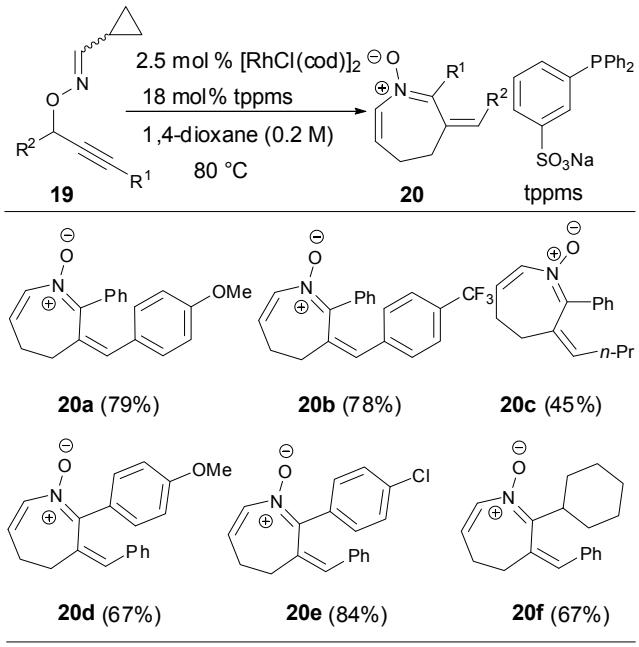
*N*-vinyl nitrones are unusual compounds that have rarely been targeted as synthetic intermediates due to the challenges for their preparation by traditional methods. Most of previous examples about *N*-vinyl nitrones were reported as side products or proposed intermediates.[31] No general practical synthesis of *N*-vinyl nitrones has been reported. In 2006, Denmark and Montgomery revealed that *N*-vinyl aldonitrones could be prepared from nitroalkenes and aldehydes in four steps with good yields.[19] Sammakia group developed a two-step method to synthesize the *N*-vinyl aldonitrones *via* condensation of an α-chloroaldehyde with a substituted benzylhydroxylamine and sequence of a 1,4-elimination.[32] However, it is not suitable for synthesis of *N*-vinyl ketonitrones.

In 2012, Anderson and coworkers developed an efficient and simple methodology to prepare *N*-vinyl ketonitrones *via* copper-mediated cross-coupling reaction of 9-fluorenone oxime with various vinylboronic acids.[33] The exact structure of *N*-vinyl ketonitrone **18** was determined by X-ray crystallography. A variety of vinylboronic acids were applied into preparing the *N*-vinyl nitrones from moderate to good yields (54%-86%). As shown in Scheme 7, the best results were obtained using cyclic vinyl boronic acids and *trans*-monosubstituted vinylboronic acids. This reaction provided a practical method for synthesis of *N*-vinyl ketonitrones which allowed further facile investigation of *N*-vinyl ketonitrones.



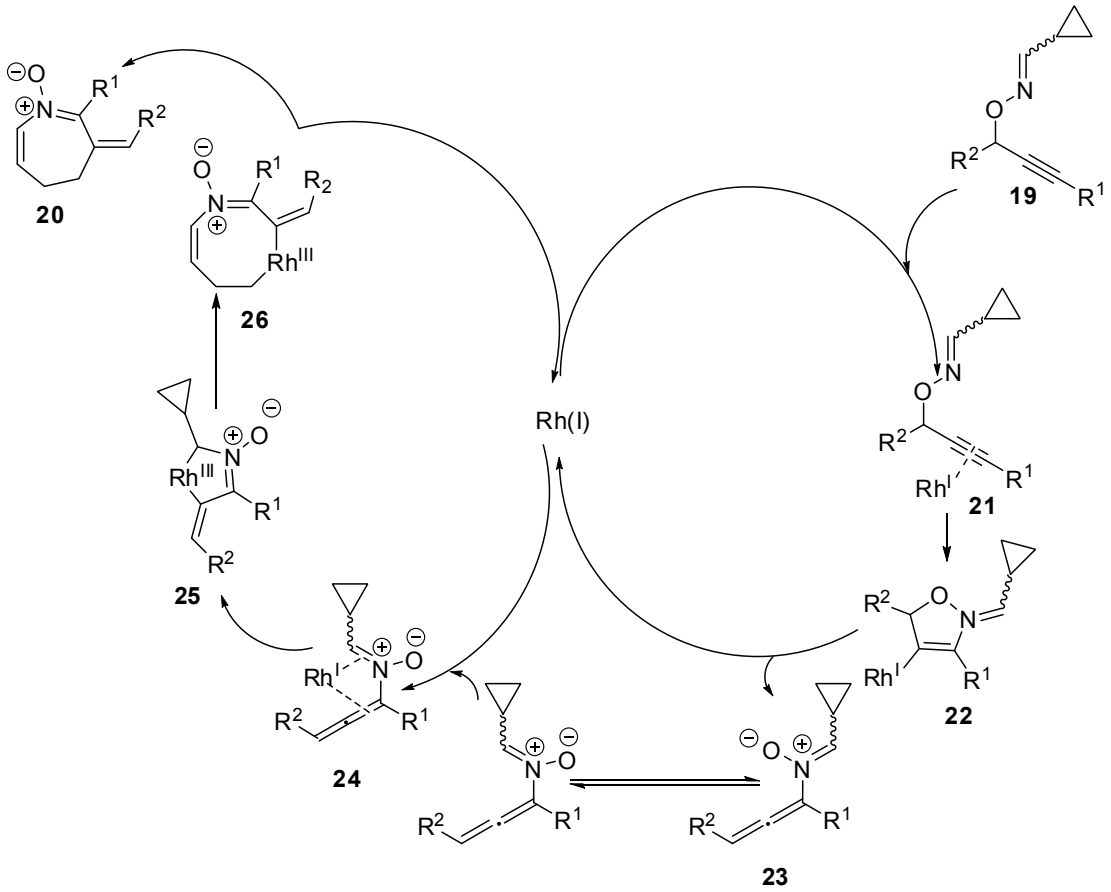

**Scheme 7** Synthesis of *N*-vinyl Ketonitrones by Copper-mediated Reaction

Nakamura and coworkers reported a reaction of *O*-propargylic cyclopropyl cabaldoximes in the presence of rhodium catalysts to provide an azepine *N*-vinyl nitrones from good to high yields through a tandem 2,3-rearrangement and heterocyclization (Scheme 8).[34] The scope of substrates was tolerated different $R^1$ and $R^2$ substituents in substrate **19**. The geometry of the imines has no effect on the formation of azepine *N*-vinyl nitrones.



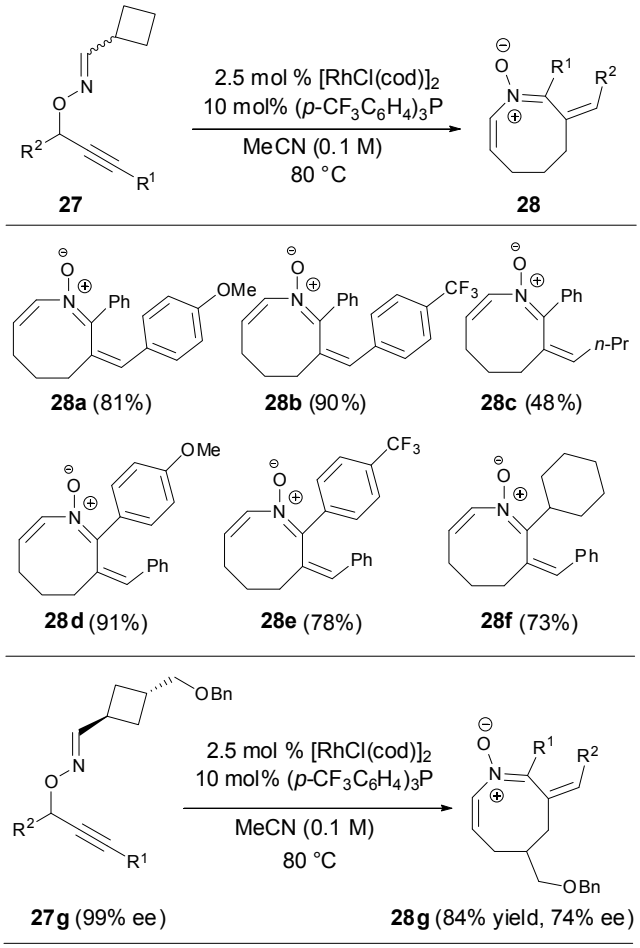

**Scheme 8** Synthesis of *N*-vinyl Ketonitrones by Rh-catalyzed Reaction

A plausible mechanism was proposed for the formation of product **16** from *O*-propargylic cyclopropyl cabaldoximes **19** (Scheme 9). The Rh catalyst coordinated to the triple bond of alkyne **20** to form $\pi$-complex **21**. Nucleophilic attack by the nitrogen atom to the activated $\pi$-complex **21** would lead to five-membered cyclic vinylrhodium intermediate **22**. Cleavage of carbon-oxygen bond and elimination of the Rh-catalyst afforded *N*-allenylnitrone intermediate **23**. The formation of *s-cis* isomer of *N*-allenylnitrone allows the $\eta^4$-coordination to the Rh-catalyst from the opposite side of $R^2$, as show in the intermediate **24**. The formation of aza-rhodacycle **25** and ring expansion involving selective cleavage of the less hindered carbon-carbon bond would give eight-membered aza-rhodacycle **26**. Finally, the reductive elimination of the Rh-catalyst produced azepine *N*-vinyl nitrone **20**.




**Scheme 9** A Plausible Mechanism of Formation of Azepine *N*-vinyl Nitrone **20**

More recently, Nakamura and coworkers revealed that azocine derivatives can be prepared from *O*-propargylic oximes *via* a Rh-catalyzed 2,3-rearrangement and heterocyclization cascade reaction (Scheme 10).[35] More importantly, the chirality of substrate was maintained throughout the cascade process to provide the corresponding optically active azocines.

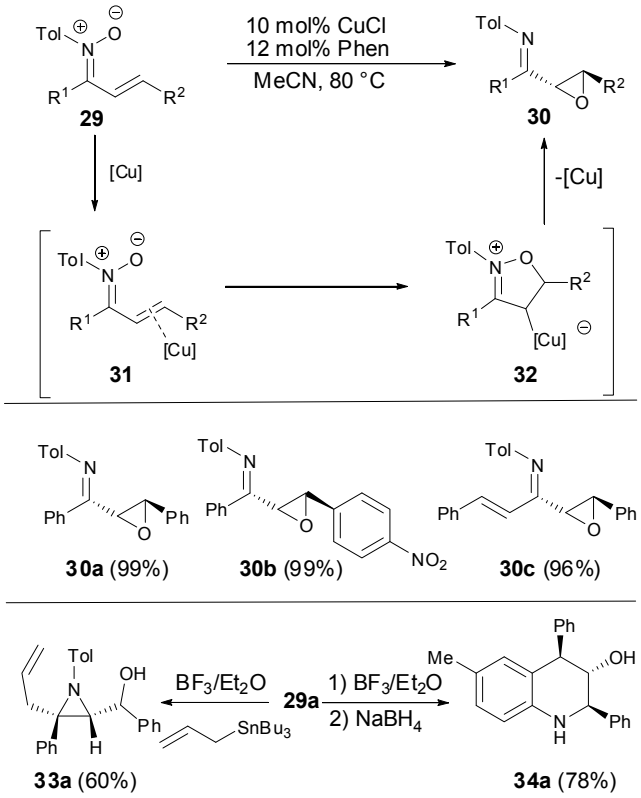



**Scheme 10** Synthesis of azocines by Rh-catalyzed reaction.

## 2 The New Rearrangement of Ketonitrones

Recently, Anderson and coworker found that the rearrangement of *N*-aryl *α,β*-unsaturated nitrones can form epoxyketimines in the presence of catalytic amounts of CuCl and 1,10-phenanthroline (Phen) (Scheme 11).[27] The reaction proceeded *via* nucleophilic attack of the nitrone oxygen atom on the electrophilically activated carbon-carbon double bond. Subsequent N−O bond cleavage of **31** resulting cyclized intermediate **32** took place oxygen-atom transfer reaction to *α,β*-epoxyketimines **30** in high yields and excellent diastereoselectivity. Treatment of epoxyketimine **30a** with $BF_3/Et_2O$ followed by reduction with $NaBH_4$ efficiently

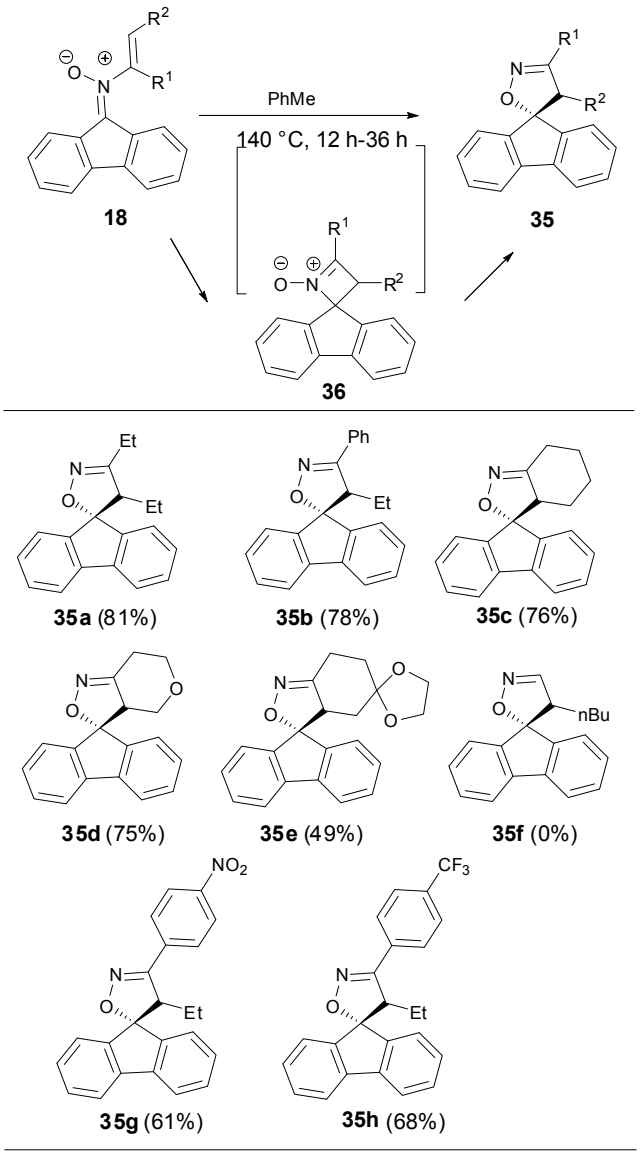
afforded tetrahydroqinolines **34a** in 78% yield as a single diastereomer. Exposure of epoxyketimine **30a** to an allylic tin reagent in the presence of $BF_3/Et_2O$ provided trisubstituted aziridine **33a** in 60% yield as a single diastereomer.




**Scheme 11** Copper-catalyzed Oxygen-atom Transfer Reaction

A thermal rearrangement of fluorenone *N*-vinyl nitrones **18** to provide spiroisoxazolines **35** has been observed by Anderson and coworkers (Scheme 12).[33] The reaction proceeded well above 120 ˚C, however, no conversion of the *N*-vinyl nitrone to spiroisoxazoline was observed below 100 ˚C and only the starting material was recovered. The scope of this rearrangement was broad with both disubstituted and cyclic vinyl nitrones tolerated as substrates. However, monosubstituted *N*-vinyl nitrone was decomposed when the reaction ran above 120 ˚C. Although there was no

definite evidence for the mechanism of this transformation now, the author proposed an optional intermediate **36** by a 4$\pi$ electron cyclization or perhaps from isomerization of nitrone to oxaziridines

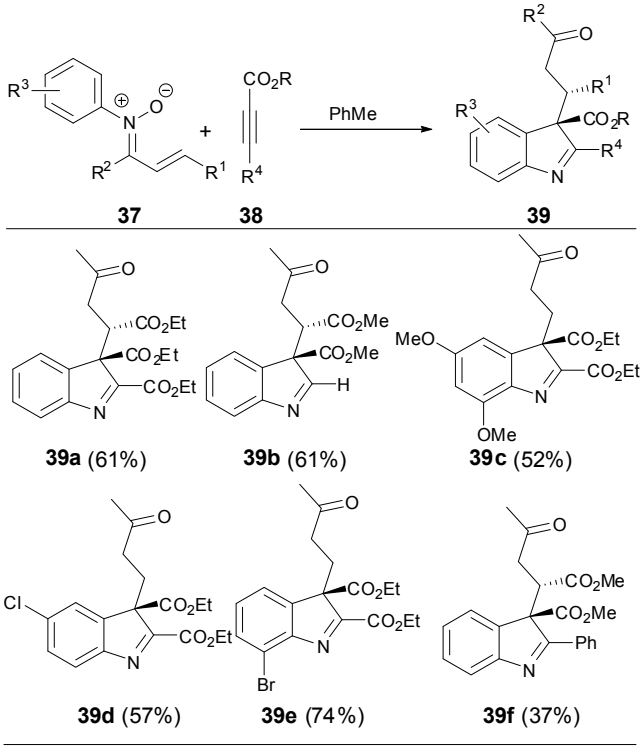



**Scheme 12** Thermal Rearrangement of *N*-vinyl Nitrones

## 3 The Reaction of Ketonitrones with Alkynes

In 2012, Yang and coworkers[36] found that when *N*-aryl *α,β*-unsaturated ketonitrones were treated with activated alkynes, C3-quaternary indolenines were

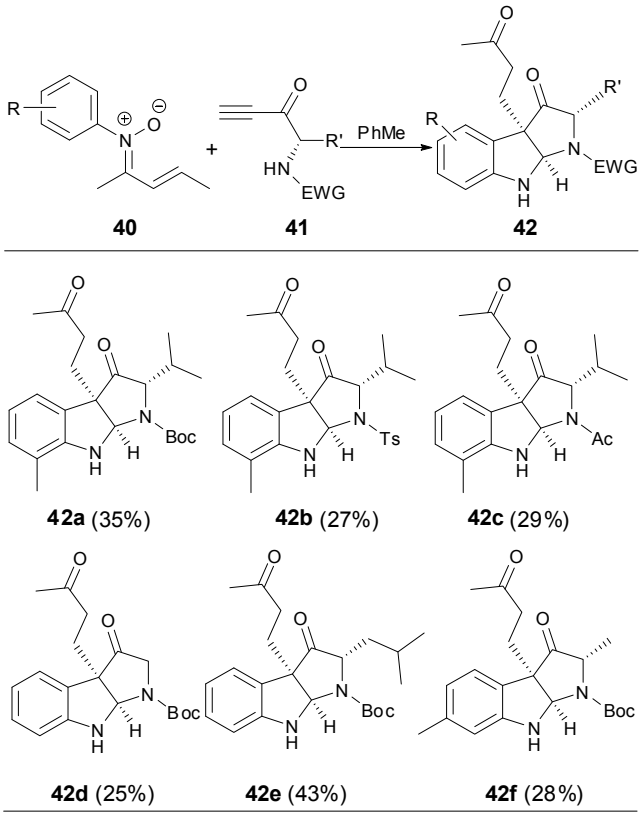
obtained with concomitant formation of two adjacent quaternary and tertiary chiral centers in high diastereoselectivity, which are versatile intermediates in synthesis of indole-containing structural motifs in natural products and pharmaceutical compounds (Scheme 13). This transformation provided an effective approach to synthesis of complex indole-containing compounds. The reaction likely started from stepwise [5+2] cycloaddition of *N*-aryl *α,β*-unsaturated ketonitrones with activated alkynes, which further underwent a series of transformations including [3,3]-sigmatropic rearrangement, tautomerization and intra-molecular condensation to afford C3-quaternary indolenine.




**Scheme 13** [5+2] Cycloaddition of *N*-aryl Nitrones with Activated Alkynes

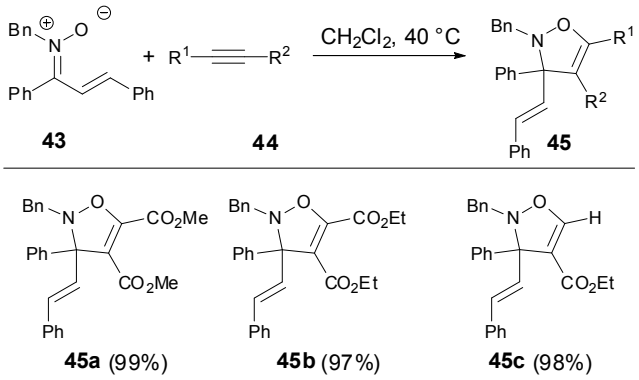
Based on the above results, in the presence of an appending *N*-nucleophilic center at the activated alkyne, the initial formation of C3-quaternary indolenines might be

followed by spontaneous *N*-cyclization to form the additional heterocycle of pyrrolindoline in one step.[37] However, pyrrolindoline products **42** were isolated with low yields (Scheme 14).



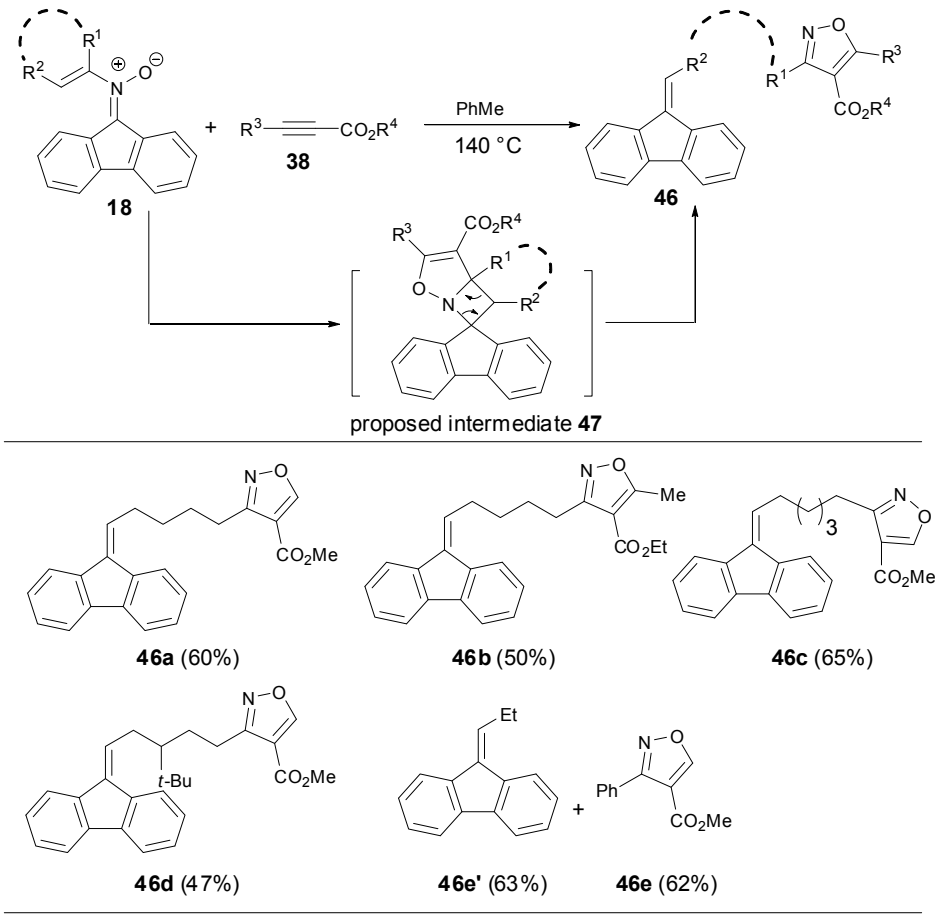

**Scheme 14** [5+2] Cycloaddition of *N*-aryl Nitrones with Activated *N*-nucleophilic center Alkynes.

Recently, Nakamura and coworkers found *N*-alkyl *α,β*-unsaturated ketonitrones underwent [3+2] cycloaddition reactions to construct corresponding 2-isoxazoline in excellent yields with mild conditions when treated with electron-deficient alkynes (Scheme 15).[29]




**Scheme 15** [3+2] Cycloaddition of *N*-alkyl Nitrones with Activated Alkynes.

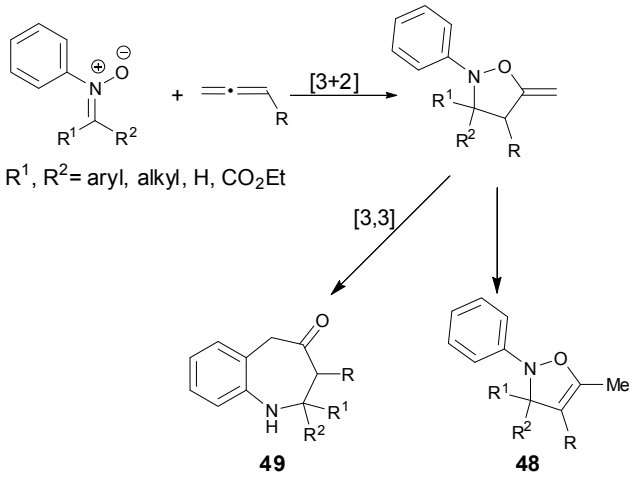
Anderson and coworkers have shown that during the studies of thermal rearrangements of fluorenone *N*-vinyl nitrones **18**, it provided fluorine-tethered isoxazoles **46** in good yields while treatment with electron-deficient alkynes to test for [3+2] cycloaddition reactivity of *N*-vinyl nitrones (Scheme 16).[33] Both the linear alkenyl and cyclo-alkenyl *N*-substituents nitrones underwent an analogous transformation with either terminal or internal alkynes **38** to afford alkyne addition and C−C bond cleavage products **46**. An alternative mechanism for the preparation of tethered-isoxazoles or mixtures of fluorenes and isoxazoles might involve an initial interaction between the electron-deficient alkyne and the *N*-vinyl nitrone prior to cycloreversion. This result has revealed that the reactivity of fluorenone-based *N*-vinyl nitrones differed significantly from the intra-molecular [4+2] cycloaddition chemistry and provided a new access to [3+2] cycloaddition chemistry.




**Scheme 16** Cycloaddition of *N*-vinyl Nitrones with Activated Alkynes

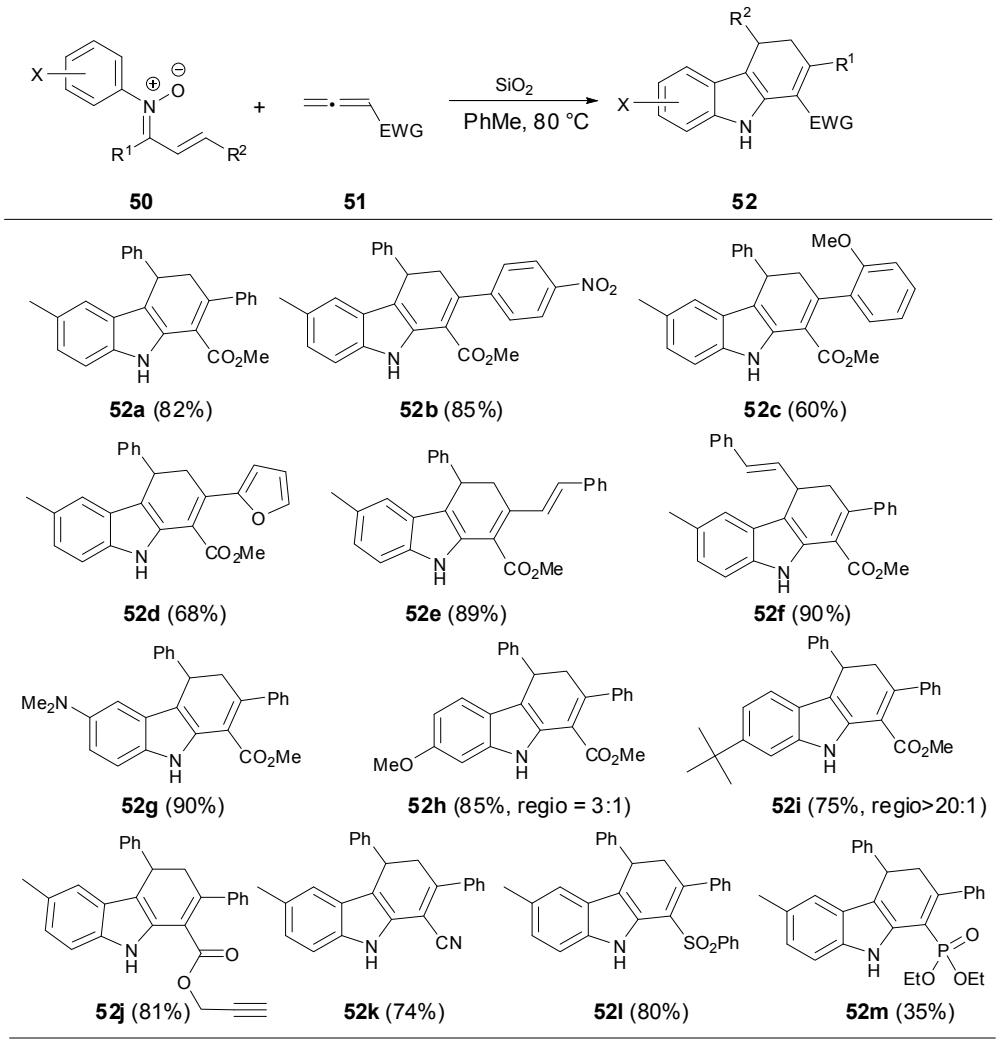
## 4 The Reaction of Ketonitrones with Allenes

Cycloaddition reactions are powerful methods for the synthesis of cyclic compounds. The cycloaddition reactions of *N*-aryl nitrones with allenes have been studied in the past.[38] In these cases, the [3+2] cycloaddition products **48** were obtained or the [3+2] cycloaddition intermediates went through a [3,3]-rearrangement to form benzazepine compounds **49** (Scheme 17).



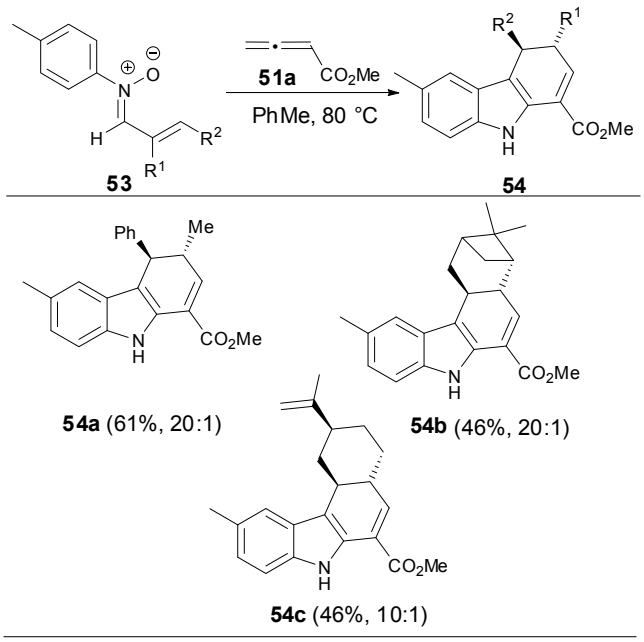

**Scheme 17** Cycloaddition of *N*-aryl Nitrones with Allenes

In 2014, Anderson and coworkers reported a new solvent-controlled cascade process of *N*-aryl *α,β*-unsaturated nitrones with electron-deficient allenes to prepare dihydrocarbazoles or dihydropyridoindoles (Scheme 18).[39] The reactions proceeded smoothly under metal-free conditions in high yields and excellent diastereoselectivity. Firstly, the author found *N*-aryl *α,β*-unsaturated nitrones were treated with allenoates under $SiO_2$ as additive in toluene, dihydrocarbazoles were obtained with high yields and high regioselectivity of the C-C bond formation which was controlled by steric hindrance on *N*-substituents.



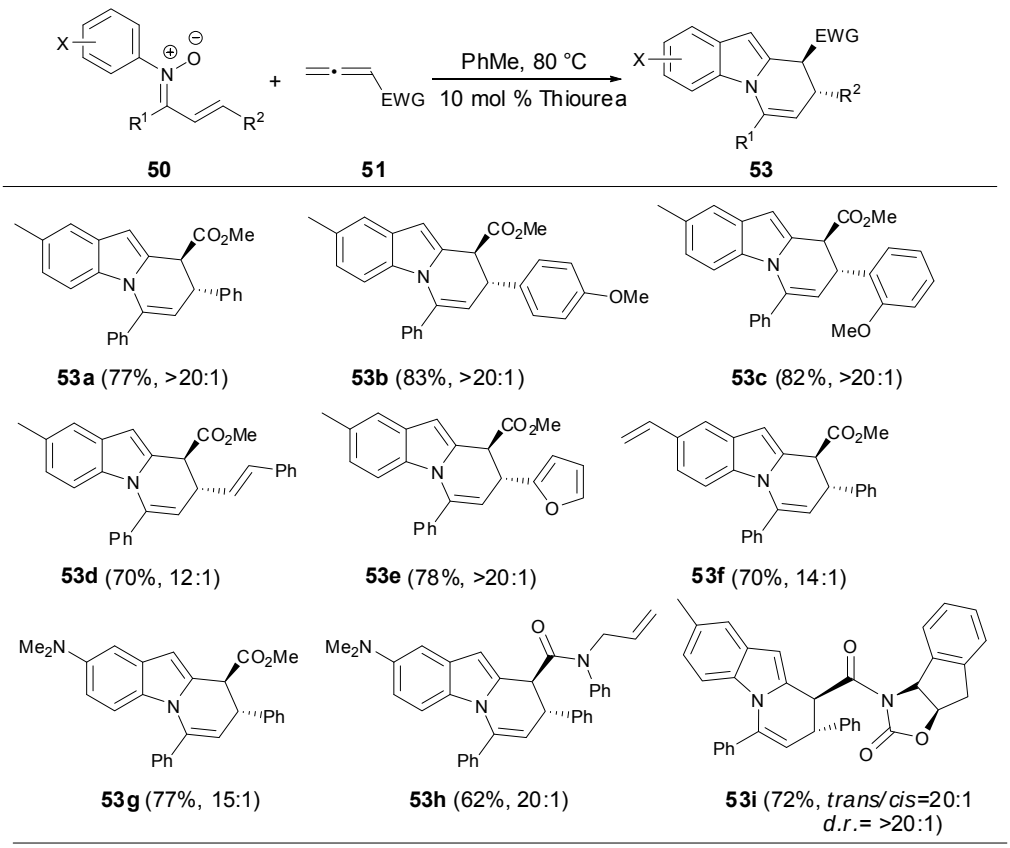

**Scheme 18** Reaction of *N*-aryl Nitrones with Allenes in PhMe.

In order to investigate the relative stereoselectivity for preparation of dihydrocarbazoles, the reaction of *N*-aryl *α,β*-disubstituted nitrones and allenes were examined. As shown in the scheme 19, the dihydrocarbazoles were favoring the *trans*-isomers in moderate yields. These results suggested that the relative stereochemistry of dihydrocarbazole products **54** can be controlled by *N*-aryl *α,β*-disubstituted nitrones.



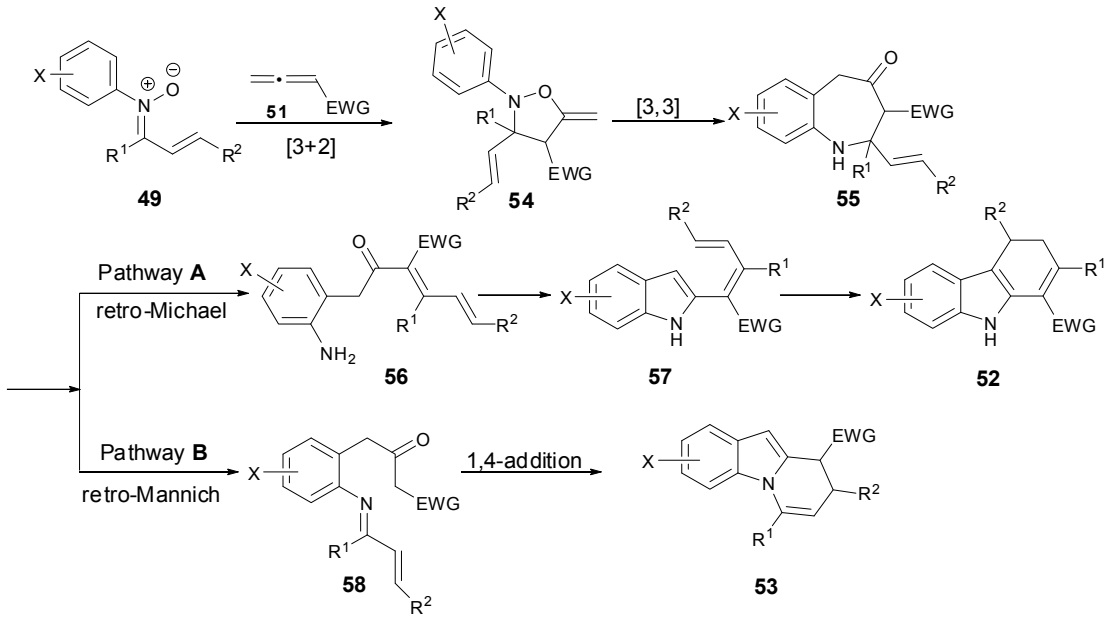

**Scheme 19** The Studies of Diastereoselectivity on Reaction of *N*-aryl Nitrones with allenes

During the screen of solvents, the author found that the formation of dihydropyridoindole was strongly favored in EtOAc and *i*-PrOAc. The yields and diastereoselectivity of dihydropyridoindoles were significantly increased by addition 10 mol% of thiourea catalyst and molecular sieves. The scope of the cascade process for preparation of dihydropyridoindoles was tolerated not only a variety of electron-rich and electron-deficient arene substituents nitrones but also with a range of *N*-aryl substituents (Scheme 20). Moreover, the relative and absolute stereochemistry of dihydropyridoindole formation can be controlled through the cascade process by using oxazolidinone chiral auxiliaries (**53i**).



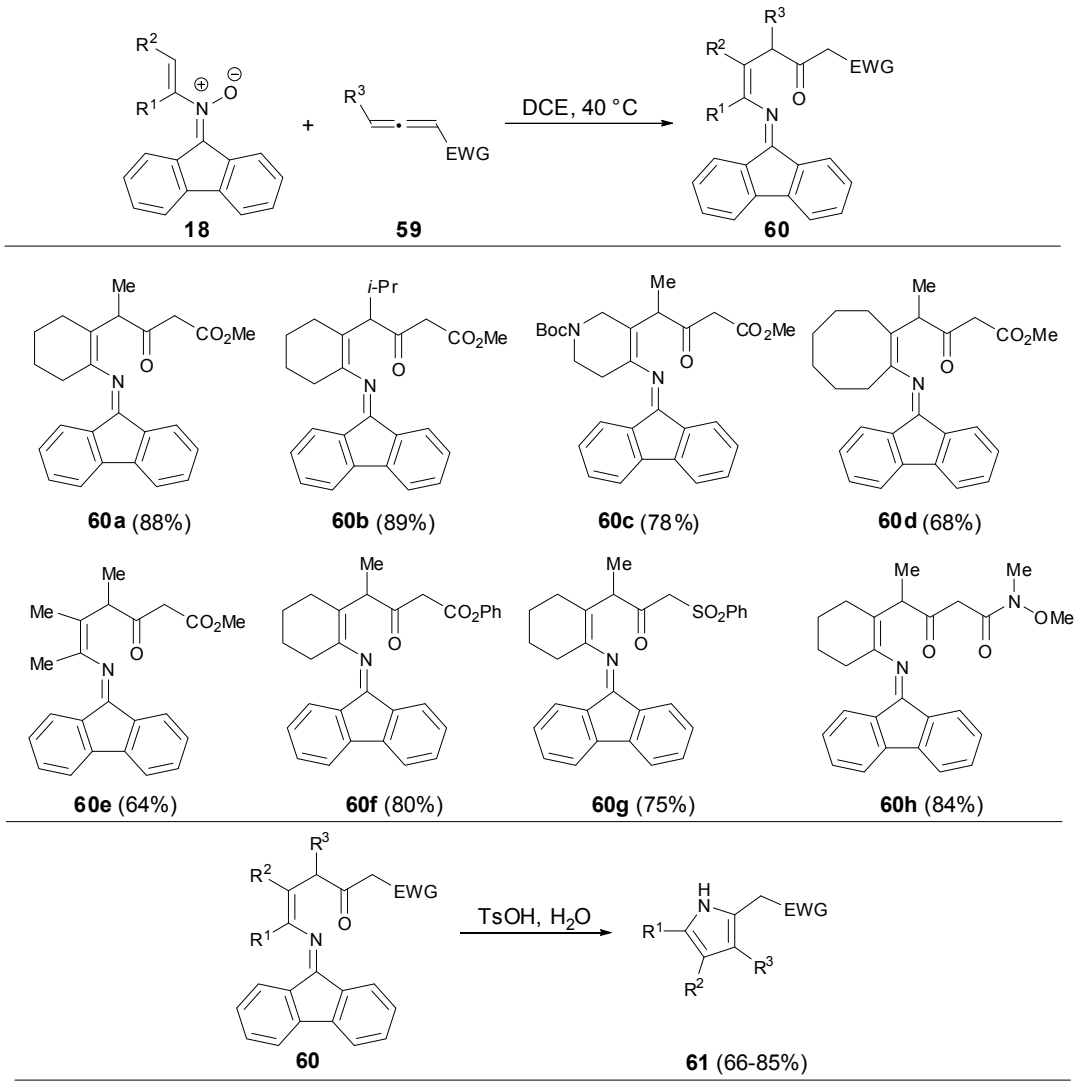

**Scheme 20** Synthesis of Dihydropyridoindole by *N*-aryl Nitrones with Allenes

Based on the literature and experiment data, the author proposed a rational mechanism (Scheme 21). An initial [3+2]-cycloaddition of nitrone and allene regioselectively provided exomethylene isoxazolidine **54**, which then underwent a [3,3]-rearrangement to give benzazapine **55**. For pathway A, a retro-aza-Michael addition followed by intra-molecular condensation of resulting aniline then afforded dienyl indole **57**. The dienyl indole went through a subsequent conjugate addition or 6π-electrocycliczation to provide dihydrocarbazoles after proton transfer. As for pathway B, a retro-Mannich reaction formed imine **58** which then underwent a [4+2] cycloaddition or a stepwise 1,4-addition of the *β*-ketoester enolate to the *α,β*-unsaturated imine to provide dihydropyridoindole after a subsequent elimination.



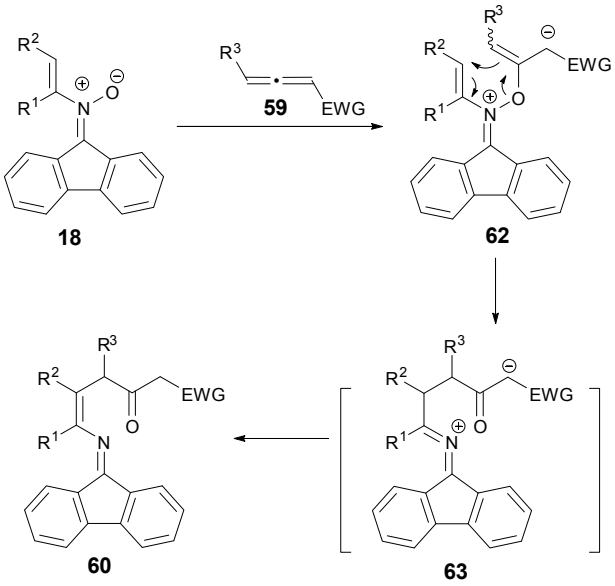

**Scheme 21** A Plausible Mechanism for Reaction of *N*-aryl Nitrones with Allenes

Recently, Anderson and coworkers found fluorenonylimine protected 1,4-enamino ketones can be prepared through the [3,3]-rearrangement of dialkenylhydroxylamines which were generated from the addition of *N*-alkenylnitrones to electron-deficient allenes (Scheme 22).[40] This reaction was particularly well tolerated cycloalkenyl nitrone substitutents and electron-deficient allenes. The fluorenonylimine protected 1,4-enamino ketones could be effectively transferred to pyrroles, 1,4-dinones and furans.




**Scheme 22** Reaction of *N*-vinyl Nitrones with Allenes

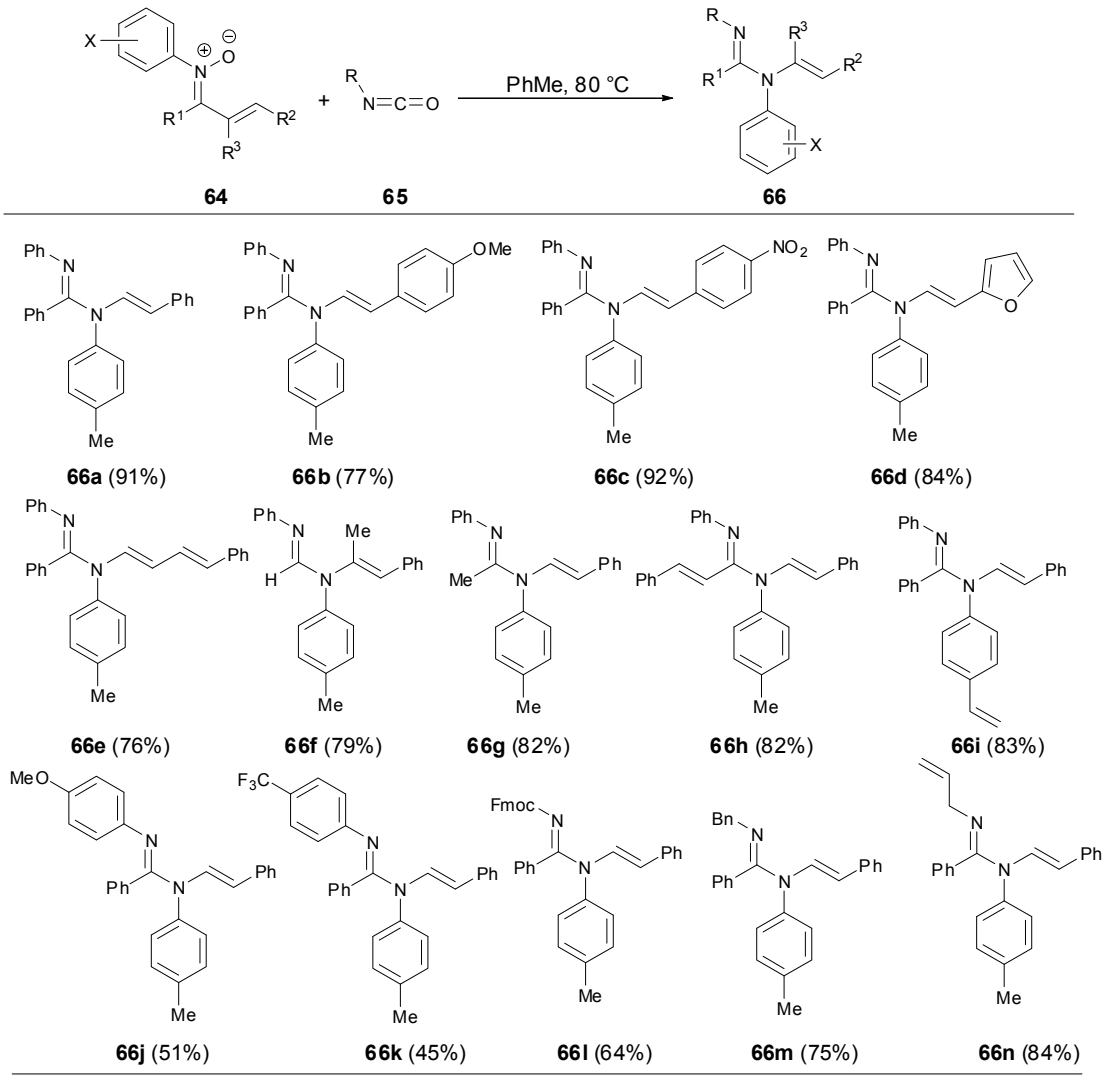
A plausible mechanism was proposed for the conversion of *N*-alkenylnitrones and allenes to 1,4-enamino ketones by either $^{1}H$ or $^{13}C$ NMR spectroscopy monitoring during the conversion of a mixture of **18** and **59** to **60** in DCE-$d_4$ (Scheme 23). Addition of nitrone to electron-deficient allene could form intermediate **61**, which could go through a [3,3]-rearrangement to form azallenium **62** and a subsequent proton transfer to form **58**.




**Scheme 23** Plausible Mechanism for Reaction of *N*-vinyl Nitrones with Allenes

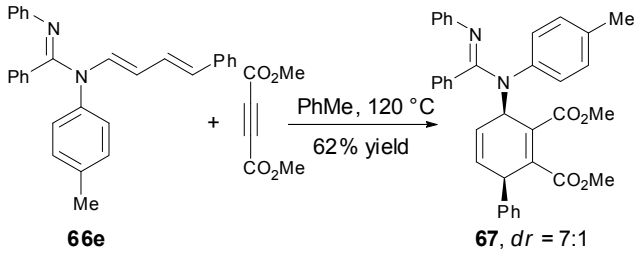
## 5 The Reaction of Ketonitrones with Isocyanates

The cycloaddition reaction of *N*-aryl nitrones with isocyanates have been developed in past decades.[41] However, Anderson and coworkers have revealed that *N*-styrenyl amidines can be prepared from *N*-aryl *α,β*-unsaturated nitrones and isocyanates (Scheme 24).[42] The scope of nitrones was tolerated not only a variety of different substitution patterns on the nitrone component but also different *N*-aryl substituents nitrones including halogen, vinyl and naphthyl substitutions. The mechanism studies showed that the transformation proceeded through an initial cycloaddition of a nitrone to an isocyanate to form an oxadiazolidinone and followed by a subsequent $CO_2$ elimination and styrenyl migration. This transformation provided a new route to *N*-alkenyl amidines which are challenging to access by traditional methods for amidine synthesis.




**Scheme 24** Reaction of *N*-aryl Nitrones with Isocyanates.

The *N*-alkenyl amidines **66e** underwent a [4+2] cycloaddition reaction with dimethylacetylene dicarboxylate (DMAD) to provide the cycloadduct **67** with good yield and good diastereoselectivity, which demonstrated the synthetic utility of the enamine functionality (Scheme 25).



**Scheme 25** [4+2] Reaction of *N*-alkenyl Amidine with DMAD.

## CONCLUSION

Copper-mediated cross coupling reaction from readily available oximes with aryl- or vinyl boronic acids under mild conditions, Rh- or Cu-catalyzed rearrangement of propargloxyamines to prepare *N*-substitutents *α,β*-unsaturated ketonitrones or *N*-vinyl nitrones have been developed. Using different dipolarophiles such as alkynes, allenes, isocyanates to test the reactivity of these nitrones have revealed that these nitrones involved new reactive intermediates and provided a variety of useful organic transformations. Although these contributions and significant progress have been made by researchers, many challenges still remain in nitrone chemistry. More efficient, simple and practical methodologies for preparing *N*-substitutents *α,β*-unsaturated ketonitrones or *N*-vinyl nitrones will more easily shed more light on the potential transformations of nitrones. The better understanding transformations of these nitrones can provide more inspiration on new reaction design. To explore more transformation of nitrones in organic synthesis, especially *N*-vinyl nitrones, remains a great challenge and high demand. We hope that our review will inspire more explorations in the field of nitrone chemistry.

## ACKNOWLEDGEMENT

This work is dedicated to Professor Xue-Long Hou (from Shanghai Institute of Organic Chemistry) on the occasion of his 60th birthday. Financial support from Oversea 100 Talents Program of Guangxi Education, Basic Research Program of

Guangxi Normal University (grant No. 2014ZD005), National Natural Science Foundation of China (21562005, 21262007, 21462008), Ministry of Education of China (IRT1225), and Guilin Science and Technology Development Fund (20110331) are greatly appreciated.

## FOOTNOTES

To whom correspondence should be addressed.

Email for G. F. S: gfysglgx@163.com;

Email for D. L. M: moeastlight@mailbox.gxnu.edu.cn;

The authors declare no competing financial interest.

## REFERENCES

1 For some early reviews, see: (a) L. I. Smith, *Chem. Rev.* 1938, **38**,193; (b) J. Hamer, A. Macaluso, *Chem. Rev.* 1964, **64**, 473.

2 For some reviews, see: (a) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* 1998, **98**, 863; (b) K. Rück-Braun, T. H. E. Freysoldt, F. Wierschem, *Chem. Soc. Rev.* 2005, **34**, 507; (c) H. Pellissier, *Tetrahedron* 2007, **63**, 3235; (d) V. Nair, T. D. Suja, *Tetrahedron* 2007, **63**, 12247; (e) A. Brandi, F. Cardona, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Eur. J.* 2009, **15**, 7808; (f) C. Nájera, J. M. Sansano, *Org. Biomol. Chem.* 2009, **7**, 4567; (g) M. Kissane, A. R. Maguire, *Chem. Soc. Rev.* 2010, **39**, 845; (h) A. J. M. Burrell, I. Coldham, *Curr. Org. Synth.* 2010, **7**, 312.

3 (a) H. Zhang, J. Joseph, J. Vasquez-Vivar, H. Karoui, C. Nsanzumuhire, P. Martasek,

P. Tordo, B. Kalyanaraman, *FEBS Lett.* 2000, **473**, 58; (b) F. A. Villamena, S. Xia, J. K. Merle, R. Lauricella, B. Tuccio, C. M. Hadad, J. L. Zweier, *J. Am. Chem. Soc.* 2007, **129**, 8177.

4 (a) R. A. Floyd, *Ageing cell* 2006, **5**, 51; (b) J. E. Slemmer, J. J. Shacka, M. Sweeney, J. T. Weber, *Curr. Med. Chem.* 2008, **15**, 404; (c) A. Piperno, S. V. Giofre, D. Iannazzo, R. Romeo, G. Romeo, U. Chiacchio, A. Rescifina, D. G. Piotrowska, *J. Org. Chem.* 2010, **75**, 2798.

5 For some early reviews, see: (a) R. Huisgen, *Angew. Chem. Int. Ed.* 1963, **2**, 565; (b) D. S. C. Black, R. F. Crozier, V. C. Davis, *Synthesis* 1975, **1975**, 205; (c) A. Padwa, *Angew. Chem. Int. Ed.* 1976, **15**, 123; (d) W. Opplzer, *Angew. Chem. Int. Ed.* 1977, **16**, 10; (e) C. P. Dell, *J. Chem. Soc., Perkin Trans 1* 1998, 3873.

6 For some examples with alkenes, see: (a) P. N. Confalone, E. M. Huie, *Org. React.* 2004, **36**, 1; (b) N. Morita, K. Fukui, J. Irikuchi, H. Sato, Y. Takano, I. Okamoto, H. Ishibashi, O. Tamura, *J. Org. Chem.* 2008, **73**, 7164; (c) T. B. Nguyen, A. Martel, R. Dhal, G. Dujardin, *Org. Lett*. 2008, **10**, 4493; (d) C. M. Qin, H. M. L. Davies, *J. Am Chem. Soc.* 2013, **135**, 14516; (e) R. Lahiri, A. Palanivel, S. A. Kulkarni, Y. D. Vankar, *J. Org. Chem.* 2014, **79**, 10786.

7 For some examples with alkynes, see: (a) C. Lu, A. V. Dubrovskiy, R .C. Larock, *J. Org. Chem.* 2012, **77**, 2279; (b) S. Bhunia, C. J. Chang, R. S. Liu, *Org. Lett.* 2012, **14**, 5522; (c) C. S. Mckay, M. Chigrinova, J. A. Blake, J. P. Pezaccki, *Org. Biomol. Chem.* 2012, **10**, 3066; (d) Y. Q. Zhang, J. L. Zhang, *Chem. Commun.* 2012, **48**,

4710; (e) Z. S. Qi, M. Wang, X. W. Li, *Org. Lett.* 2013, **15**, 5440; (f) R. P. Temming, L. Eggermont, M. B. van Eldijk, J. C. M. van Hest, F. L. van Delft, *Org. Biomol. Chem.* 2013, **11**, 2772; (g) L. Wozniak, O. Staszewska-Krajewska, M. Michalak, *Chem. Commun.* 2015, **51**, 1933.

8 For some examples with allenes, see: (a) J. J. Tufariello, S. A. Ali, H. O. Klingele, *J. Org. Chem.* 1979, **44**, 4213; (b) A. Padwa, S. P. Carter, Y. Chiacchio, D. N. Kline, *Tetrahedron Lett.* 1986, **27**, 2683; (c) A. Padwa, M. Matzinger, Y. Tomioka, M. K. Venkatramanan, *J. Org. Chem.* 1988, **53**, 955; (d) T. Wirth, S. Blechert, *Synlett* 1994, **1994**, 717; (e) X. Wu, R. S. Na, H. L. Liu, J. Liu, M. Wang, J. C. Zhong, H. C. Guo, *Tetrahedron Lett.* 2012, **53**, 342; (f) G. H. Li, W. Zhou, X. X. Li, Q. W. Bi, Z. Wang, Z. G. Zhao, W. X. Hu, Z. L. Chen, *Chem. Commun.* 2013, **49**, 4770; (g) J. Malinina, T. Q. Tran, A. V. Stepakov, V. V. Gurzhiy, G. L. Starova, R. R. Kostikov, A. P. Molchanov, *Tetrahedron Lett.* 2014, **55**, 3663.

9 For some examples with isocyanates, ketenes, ketenimines, see: (a) S. P. Joseph, D. N. Dhar, *Tetrahedron* 1988, **44**, 5209; (b) N. Murai, M. Komatsu, Y. Ohshiro, T. Agawa, *J. Org. Chem.* 1977, **42**, 448; (c) K. Namitharan, K. Pitchumani, *Org. Lett.* 2011, **13**, 5728.

10 (a) M. Kinugasa, S. Hashimoto, *Chem. Commun.* 1972, 466; (b) M. M.C. Lo, G. C. Fu, *J. Am. Chem. Soc.* 2002, **124**, 4572; (c) R. Shintani, G. C. Fu, *Angew. Chem. Int. Ed.* 2003, **42**, 4082; (d) M. C. Ye, J. Zhou, Z. Z. Huang, Y. Tang, *Chem. Commun.* 2003, 2554; (e) S. Stecko, A. Mames, B. Furman, M. Chmielewski, *J. Org. Chem.*

2009, **74**, 3094; (f) J. H. Chen, S. H. Liao, X. L. Sun, Q. Shen, Y. Tang, *Tetrahedron Lett.* 2012, **68**, 5042; (g) S. Santoro, R. Z. Liao, T. Marcelli, P. Hammar, F. Himo, *J. Org. Chem.* 2015, **80**, 2649.

11 (a) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* 2003, **103**, 1213; (b) T. Q. Tran, V. V. Diev, G. L. Starova, V. V. Gurzhiy, A. P. Molchanov, *Eur. J. Org. Chem.* 2012, **2012**, 2054; (c) D. L. Mo, T. Yuan, C. H. Ding, L. X. Dai, X. L. Hou, *J. Org. Chem.* 2013, **78**, 11470.

12 (a) I. S. Young, M. A. Kerr, *Angew. Chem. Int. Ed.* 2003, **42**, 3023; (b) I. S. Young, J. L. Williams, M. A. Kerr, *Org. Lett.* 2005, **7**, 953; (c) C. A. Carson, M. A. Kerr, *Angew. Chem. Int. Ed.* 2006, **45**, 6560; (d) M. K. Sibi, Z. Mz, C. P. Jasperse, *J. Am. Chem. Soc.* 2005, **127**, 5764; (e) Y. B. Kang, X. L. Sun, Y. Tang, *Angew. Chem. Int. Ed.* 2007, **46**, 3918; (f) H. B. Yang, M. Shi, *Org. Biomol. Chem.* 2012, **10**, 8236; (g) C. M. Braun, E. A. Congdon, K. A. Nolin, *J. Org. Chem.* 2015, **80**, 1979.

13 (a) X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* 2011, **133**, 16402; (b) X. Xu, M. O. Ratnikov, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* 2011, **13**, 6122; (c) Y. Qian, X. Xu, X. Wang, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* 2012, **51**, 5900; (d) X. Wang, Q. M. Abrahams, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* 2012, **51**, 5907; (e) X. F. Xu, P. J. Zavalij, M. P. Doyle, *Chem. Commun.* 2013, **49**, 10287.

14 (a) R. Shintani, S. Park, W. L. Duan, T. Hayashi, *Angew. Chem. Int. Ed.* 2007, **46**, 5901; (b) R. Shintani, M. Murakami, T. Hayashi, *J. Am. Chem. Soc.* 2007, **129**,

12356; (c) A. C. Stevens, C. Palmer, B. L. Pagenkopf, *Org. Lett.* 2011, **13**, 1528.

15 S. A. Gawade, S. Bhunia, R. S. Liu, *Angew. Chem. Int. Ed.* 2012, **51**, 7835.

16 (a) G. Masson, P. Cividino, S. Py, Y. Vallée, *Angew. Chem. Int. Ed.* 2003, **42**, 2265; (b) D. Riber, T. Skrydstrup, *Org. Lett.* 2003, **5**, 229; (c) J. Marco-Contelles, *Angew. Chem. Int. Ed.* 2004, **43**, 2198; (d) P. Cividino, S. Py, P. Delair, A. E. Greene, *J. Org. Chem.* 2007, **72**, 485.

17 (a) J. Yang, *Synlett* 2012, **23**, 2293; (b) M. P. S. Ishar, K. Kumar, R. Singh, *Tetrahedron Lett.* 1998, **39**, 6547; (c) T. Ghosh, C. Bandyopadhyay, *Tetrahedron Lett.* 2004, **45**, 6169; (c) K. Wittstein, A. B. García, M. Schürmann, K. Kumar, *Synlett* 2012, **23**, 227.

18 G. Bartoli, E. Marcantoni, M. Petrini, *J. Org. Chem.* 1990, **55**, 4456.

19 S. E. Denmark, J. I. Montgomery, *J. Org. Chem.* 2006, **71**, 6211.

20 (a) P. N. Confalone, E. M. Huie, *Org. React.* 1988, **36**, 1; (b) K. B. G. Torssell, *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; H. Feuer, Ed.; VCH Publishers: New York, 1988.

21 (a) S. Cicchi, M. Corsi, A. Goti, *J. Org. Chem.* 1999, **64**, 7243; (b) S. Cicchi, M. Marradi, A. Goti, A. Brandi, *Tetrahedron Lett.* 2001, **42**, 6503; (c) R. Saladino, V. Neri, F. Cardona, A. Goti, *Adv. Synth. Catal.* 2004, **346**, 639.

22 (a) F. Busqué, P. de March, M. Figueredo, J. Font, T. Gallagher, S. Milán, *Tetrahedron: Asymmertry* 2002, **13**, 437; (b) G. Soldaini, F. Cardona, A. Goti, *Org.*

*Lett.* 2007, **9**, 473.

23 (a) M. Forcato, W. A. Nugent, G. Licini, *Tetrahedron Lett.* 2003, **44**, 49; (b) C. Gella, E. Ferrer, R. Alibes, F. Busque, P. de March, M. Figueredo, J. Font, *J. Org. Chem.* 2009, **74**, 6365; (c) M. Forcato, M. Mba, W. A. Nugent, G. Licini, *Eur. J. Org. Chem.* 2010, **2010**, 740; (d) M. Abrantes, I. S. Goncalves, M. Pillinger, C. Vurchio, F. M. Cordero, A. Brandi, *Tetrahedron Lett.* 2011, **52**, 7079.

24 (a) K. Nakama, S. Seki, S. Kanemasa, *Tetrahedron Lett.* 2002, **43**, 829; (b) S. K. Hota, A. Chatterjee, P. K. Bhattacharya, P. Chattopadhyay, *Green Chem.* 2009, **11**, 169.

25 (a) S. Franco, F.L. Merchan, P. Merino, T. Tejero, *Synth. Commun.* 1995, **25**, 2272; (b) J. Y. Pfeiffer, A. M. Beauchemin, *J. Org. Chem.* 2009, **74**, 8381.

26 T. S. Hood, C. B. Huehls, J. Yang, *Tetrahedron Lett.* 2012, **53**, 4679.

27 D. L. Mo, L. L. Anderson, *Angew. Chem. Int. Ed.* 2013, **52**, 6722.

28 X. P. Ma, W. M. Shi, X. L. Mo, X. H. Li, L. G. Li, C. X. Pan, B. Chen, G. F. Su, D. L. Mo, *J. Org. Chem.* 2015, **80**, 10098.

29 I. Nakamura, T. Onuma, R. Kanazawa, Y. Nishigai, M. Terada, *Org. Lett.* 2014, **16**, 4198.

30 S. Murarka, A. Studer, *Org. Lett.* 2011, **13**, 2746.

31 (a) M. L. M. Pennings, D. N. Reinhoudt, S. Harkema, G. J. Van Hummel, *J. Am. Chem. Soc.* 1980, **102**, 7570. (b) M. L. M. Pennings, D. N. Reinhoudt, *J. Org.*

*Chem.* 1982, **47**, 1816. (c) R. Grigg, T. R. Perrior, G. J. Sexton, S. Surendrakumar, T. Suzuki, *Chem. Commun.* 1993, 372. (d) F. Heaney, B. M. Kelly, S. Bourke, O. Rooney, D. Cunningham, P. McArdle, *J. Chem. Soc., Perkin Trans. 1* 1999, 143. (e) H. S. Yeom, E. So, S. Shin, *Chem. Eur. J.* 2011, **17**, 1764.

32 R. E. Michael, K. M. Chando, T. Sammakia, *J. Org. Chem.* 2015, **80**, 6930.

33 D. L. Mo, D. A. Wink, L. L. Anderson, *Org. Lett.* 2012, **14**, 5187.

34 I. Nakamura, M. Okamoto, Y. Sato, M. Terada, *Angew. Chem. Int. Ed.* 2012, **51**, 10816.

35 I. Nakamura, Y. Sato, K. Takeda, M. Terada, *Chem. Eur. J.* 2014, **20**, 10214.

36 C. B. Huehls, T. S. Hood, J. Yang, *Angew. Chem. Int. Ed.* 2012, **51**, 5110.

37 C. B. Huehls, J. H. Huang, J. Yang, *Tetrahedron* 2015, **71**, 3593.

38 (a) A. Padwa, D. N. Kline, K. F. Koehler, M. Matzinger, M. K. Venkatramanan, *J. Org. Chem.* 1987, **52**, 3909; (b) A. Padwa, W. H. Bullock, D. N. Kline, J. Perumattam, *J. Org. Chem.* 1989, **54**, 2862.

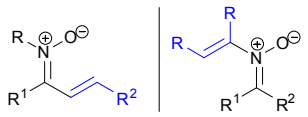
39 D. L. Mo, D. A. Wink, L. L. Anderson, *Chem. Eur. J.* 2014, **20**, 13217.

40 W. H. Pecak, J. W. Son, A. J. Burnstine, L. L. Anderson, *Org. Lett.* 2014, **16**, 3440.

41 (a) A. M. T. Bell, J. Bridges, R. Cross, C. P. Falshaw, B. F. Taylor, G. A. Taylor, I. C. Whittakeer, M. J. Begley, *J. Chem. Soc., Perkin Trans. 1* 1987, 2593; (b) T. Ritter, E. M. Carreira, *Angew. Chem. Int. Ed.* 2005, **44**, 936.

42 D. L. Mo, W. H. Pecak, M. Zhao, D. A. Wink, L. L. Anderson, *Org. Lett.* 2014, **16**, 3696.

TOC Entry




Various vinyl ketonitrones are prepared in new strategies and applied to synthesize heterocycles in organic synthesis.