

Organic & Biomolecular Chemistry

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.

REVIEW

Reactivities of vinyl azides and their recent applications in nitrogen heterocycle synthesis

Cite this: DOI: 10.1039/x0xx00000x

Bao Hu,^{*a,b} and Stephen G. DiMagno^b

Received 00th January 2015,

Accepted 00th January 2015

DOI: 10.1039/x0xx00000x

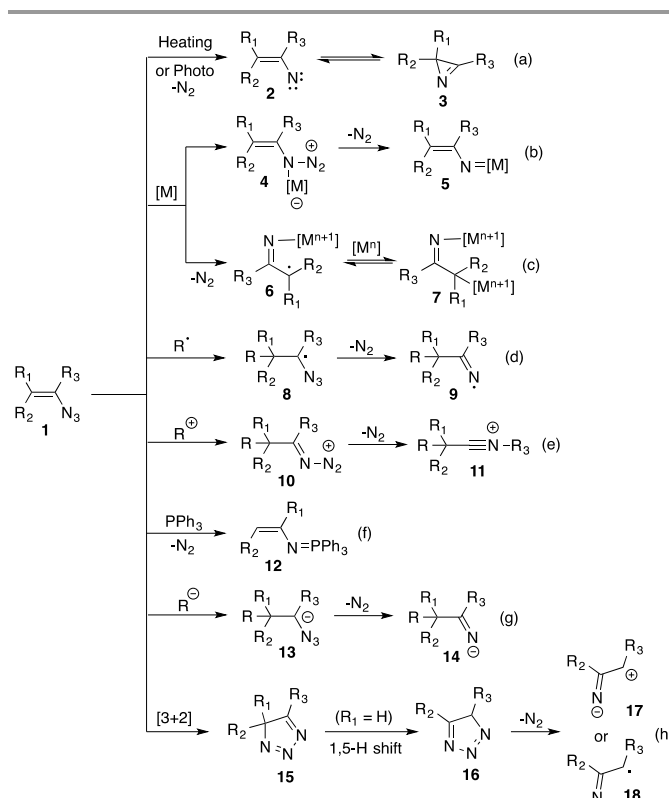
www.rsc.org/

Nitrogen heterocycles are abundant in natural products and pharmaceuticals. An emerging interest among synthetic chemists is to apply vinyl azides as a pivotal three-atom synthon for the construction of structurally complex and diverse *N*-heterocyclic skeletons. The unique features of the azide group connected to an alkene moiety permit vinyl azides to function as electrophiles, nucleophiles, or radical acceptors; their access to diverse reaction pathways provides great opportunities to generate highly reactive intermediates with often unusual or unconventional reactivities. This tutorial review will systematically illustrate the reactivities of vinyl azides and describe recent breakthroughs in the development of new transformations that create *N*-heterocycles.

1. Introduction

Since the discovery of phenyl azides by Peter Grieb in 1864,¹ numerous novel transformations of azide derivatives have emerged as rapid and versatile methods for the synthesis of a variety of complex *N*-heterocyclic systems.² However, vinyl azides have been regarded as “sleepers” among the reactive azido species, and they drew little attention over the course of the last century. Until recently, efforts to employ vinyl azides have focused largely on their use as a pivotal three-atom synthon for the formation of diverse *N*-heterocycles. The unique properties of the azide group connected to an alkene moiety permit this functional group to act as an electrophile, a nucleophile, or a radical acceptor, have turned these compounds into indispensable building blocks for organic synthesis.

One of the intriguing chemical features of vinyl azides is their ability to undergo thermolysis or photolysis to give highly strained three-membered *2H*-azirines, **3**, which can be regarded as equivalents of vinyl nitrenes, **2** (Scheme 1, eq. a).³ Transition metal-catalysed reactions of vinyl azides can form metal nitrenoids, **5**, with release of molecular nitrogen (Scheme 1, eq. b).^{2d,4} Alternatively, vinyl azides can be reduced by transition metal species to afford iminyl metal radicals, **6**, which equilibrate with iminyl metal species, **7** (Scheme 1, eq. c).⁵ In the syntheses of *N*-heterocycles, a radical pathway might also be involved, in which α -azido radicals, **8**, generated from radical species (R^\cdot), add to vinyl azides, to produce iminyl radicals, **9** (Scheme 1, eq. d).⁶ Moreover, the C=C bonds of vinyl azides can be used for the formation of new C-C or C-X (X = heteroatom) bonds with appropriate electrophiles (R^+), which results in the generation of iminodiazonium ions **10**. Subsequent Schmidt-type rearrangements might create nitrilium



Scheme 1 Chemical reactive intermediates generated from vinyl azides.

ions, **11** (Scheme 1, eq. e).⁷ Also, vinyl azides can react with PPh_3 to furnish vinyl iminophosphoranes, **12**, via the Staudinger reaction (Scheme 1, eq. f).⁸ Vinyl azides can also lead to new iminyl anions, **14**, by a process that involves Michael addition-elimination of incipient anions (R^-). The

elimination is driven by the excellent leaving-group ability of nitrogen (Scheme 1, eq. g).⁹ Recently, it was shown that an intramolecular cyclization of a vinyl azide ($R_1 = H$) takes place to generate triazolone **15**, which undergoes a 1,5-hydrogen shift to give triazolone **16**. Loss of nitrogen leads to zwitterionic (**17**) or diradical (**18**) reactive intermediates (Scheme 1, eq. h).¹⁰

One of the attractive chemical properties of vinyl azides is their ability to undergo manifold transformations. Arguably, the most important applications of vinyl azides are directed toward the synthesis of various *N*-heterocycles, and yet no comprehensive recent review categorizes the great number of transformations which vinyl azides undergo in the construction of different *N*-heterocycles.¹¹ Even this seemingly large topic encompasses a relatively small subset of the types of reactions open to vinyl azides.^{2,11} The present Review, therefore, is intended to enumerate and classify the types of possible reactive intermediates that can be generated from vinyl azides under different reaction conditions. Furthermore, this Review highlights how these diverse reaction pathways make vinyl azides outstanding building blocks in *N*-heterocycle synthesis.

2. Thermal- or photo-induced reactions of vinyl azides

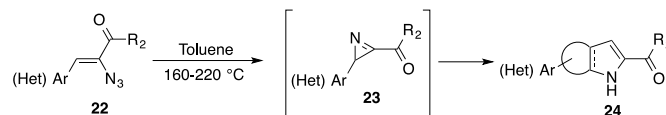
Vinyl azides are often used as precursors to vinyl nitrenes and *2H*-azirines. These reactive intermediates are accessible by thermolysis or photolysis, and they can react further in cyclization reactions or by other processes to generate nitrogenated heterocycles. In 1961, Smolinsky¹² reported the first example of the vapor phase pyrolysis of α -phenyl vinyl azide **19**. This vinyl azide furnished 2-phenylazirine **20** in 65% yield, together with a small amount of the Curtius rearrangement side product **21** (Scheme 2). Although *2H*-azirines have been studied extensively for their great synthetic potential in the synthesis of functionalized amino derivatives and *N*-containing heterocycles, most *2H*-azirines were found to be difficult to prepare and to handle because these highly strained reactive intermediates tend to be unstable.¹³ The transformation of vinyl azides into *2H*-azirines is currently the most frequently used reaction to access these strained heterocycles.

Bao Hu was born in Hunan, China in 1982. He studies chemistry at Hunan University of Science and Technology in 2001 and began his graduate studies in 2005 under the supervision of Prof. Zhongwen Wang at Nankai University, where he worked on the methylene cyclopropane 1,1-diester chemistry and total synthesis of (\pm)-bruguierol A. In 2010, he joined the faculty at Zhejiang University of Technology as an assistant professor. After a short independent research on vinyl azide chemistry, he moved to US in 2012 as a Postdoctoral Fellow with Prof. Stephen G. DiMagno at the University of Nebraska–Lincoln. His current research in DiMagno group focuses on preparation and use of diaryliodonium salts in the creation of new radiotracers for PET imaging applications.

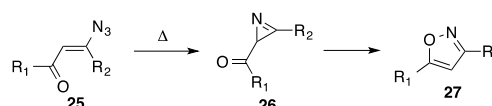


Scheme 2 Generation of *2H*-azirine from a vinyl azide by pyrolysis.

For example, continuous flow thermolysis of β -aryl vinyl azides **22** in toluene has been applied to prepare indoles and related heterocycles via *2H*-azirines intermediates **23** (Scheme 3).^{14a} However, thermolysis of β -aldehyde, ketone, or ester substituted vinyl azides **25** usually led to isoxazoles **27** through the corresponding *2H*-azirine intermediates **26** (Scheme 4).¹⁵



Scheme 3 Indole formation from thermolysis of vinyl azides via *2H*-azirines.

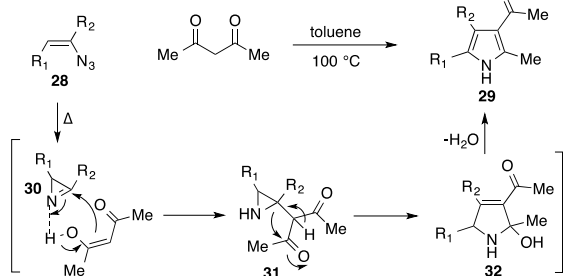


Scheme 4 Isoxazole formation from thermolysis of vinyl azides via *2H*-azirines.

Intermolecular, thermally induced reactions of vinyl azides are also possible. Chiba and Narasaka recently described the pyrolysis of vinyl azides **28** in the presence of 1,3-dicarbonyl compounds to give 2,3,4,5-tetrasubstituted *N*-H pyrroles, **29**. These products were proposed to arise from nucleophilic attack of the 1,3-diketone enol on the *2H*-azirines **30** followed by ring opening of the resulting aziridines **31**, and recyclization of the intermediates to form **32** (Scheme 5).¹⁶

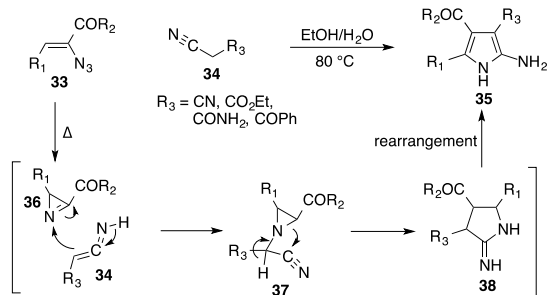
Stephen G. DiMagno is a Professor of Organic Chemistry at the University of Nebraska–Lincoln. He was born in Philadelphia, Pennsylvania in 1962. His training in organic chemistry included a BA from Swarthmore College in 1985, and a PhD in organic chemistry from UC Berkeley, under the direction of Prof. Andrew Streitwieser in 1991. His undergraduate and graduate work focused on the physical organic chemistry of radical species. During postdoctoral studies with Prof. Michael J. Therien at the University of Pennsylvania, DiMagno's research emphasis was in the synthesis and ultrafast electron transfer properties of metalloporphyrins and related heterocyclic pigments. Upon joining the University of Nebraska–Lincoln faculty in 1993, Professor DiMagno's began a research program in organofluorine chemistry that has continued to this day. Most recently, his research has particularly focused upon the introduction of fluoride (^{19}F and ^{18}F) into pharmaceutically relevant aromatic and heteroaromatic compounds.





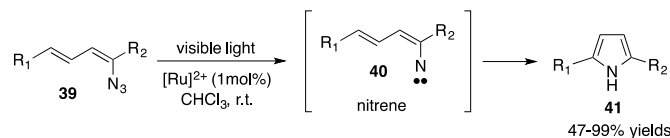
Scheme 5 Synthesis of pyrroles from vinyl azides and acetylacetone.

Condensation of α -cyano derivatives with vinyl azides has also been reported as an efficient method for the synthesis of 2-aminopyrroles (Scheme 6).¹⁷ The proposed mechanism featured the addition of α -cyano derivatives **34** onto *2H*-azirines **36**, generated from pyrolysis of vinyl azides **33**, to form azirine intermediates **37**. Ring expansion to form pyrrolidine intermediates **38**, was followed by tautomerization and oxidation to furnish the 2-aminopyrrole products, **35** (Scheme 6).



Scheme 6 Synthesis of 2-aminopyrroles from vinyl azides and α -cyano derivatives.

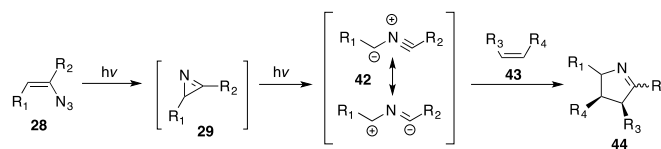
The use of visible light activated transition metal catalysts in synthesis is currently attracting increased attention.¹⁸ Important recent studies from Yoon and co-workers demonstrated that photolytic conversion of dienyln azides **39** into reactive nitrenes **40**, with visible light in the presence of a Ru photocatalyst was an attractive approach to the construction of pyrroles **41** (Scheme 7).¹⁹ The use of low-energy visible light precludes competitive photodecomposition processes typically associated with UV irradiation, and makes this approach more attractive and useful.



Scheme 7 Synthesis of pyrroles from vinyl azides by transition-metal photocatalysis.

As mentioned above, vinyl azides are typically employed as precursors to *2H*-azirines, which are themselves photochemically active substances. Under photochemical conditions, the highly strained *2H*-azirines **29** underwent ring-

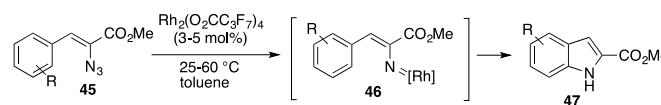
opening to yield the nitrile ylides **42**.²⁰ These 1,3-dipolar intermediates proved to be excellent [3 + 2] cycloaddition substrates for dipolarophiles **43**. The cyclization provided 3,4-dihydro-*2H*-pyrroles **44** in reasonable yields (Scheme 8).²¹



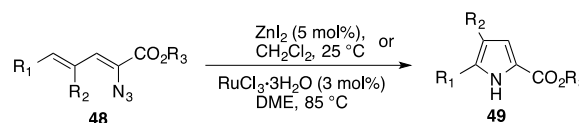
Scheme 8 Photo-induced cycloadditions of vinyl azides and electron-deficient alkenes.

3. Transition metal-catalyzed reactions of vinyl azides

Thermolysis of vinyl azides has been applied frequently in indole synthesis, however, the excessive heating often required to promote this reaction can lead to side reactions, thereby diminishing the attractiveness of this approach.¹⁴ In contrast, transition metal catalysts can generate highly reactive radical ion or metal nitrenoid intermediates under relatively mild reaction conditions. The Driver group described a Rh(II)-catalyzed intramolecular C-H bond insertion reaction that transforms vinyl azides **45** into indoles **47**. This process likely involves evolution of N_2 to form rhodium nitrenoid intermediates **46** (Scheme 9).²² Bolm and co-workers recently showed that a first row transition metal salt, Fe(II) triflate, was also a competent catalyst for heterocyclic ring closures of vinyl azides **45**.²³ More recently, this chemistry was extended to the formation of pyrroles **49**, from dienyln azides **48**. It was found that a range of transition metal salts, including Rh(II) carboxylates, $Cu(OTf)_2$, ZnI_2 , and $RuCl_3$ can promote this process efficiently (Scheme 10).²⁴

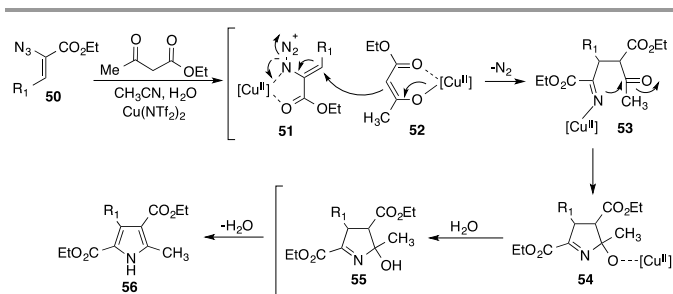


Scheme 9 Rhodium-catalyzed indole formation.



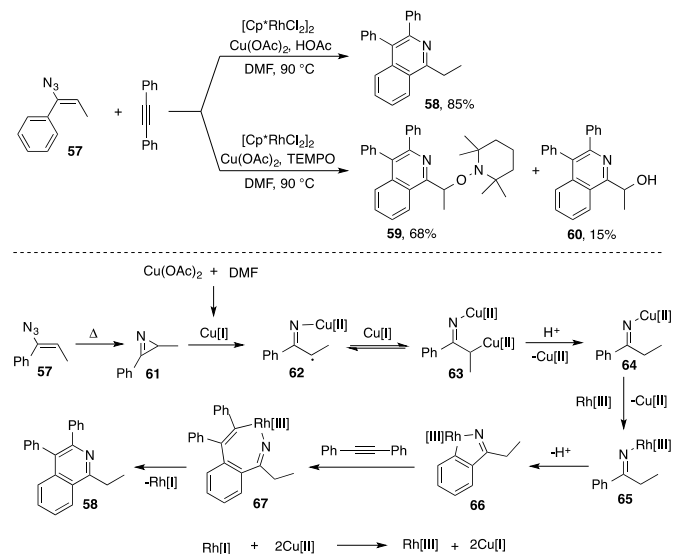
Scheme 10 Transition metal-catalyzed pyrrole formation.

For transition metal-catalyzed intermolecular reactions of vinyl azides, significant advances have been achieved by the Chiba group, who developed a Cu(II)-catalyzed synthesis of polysubstituted pyrroles **56** from vinyl azides **50** and ethyl acetoacetate (Scheme 11).^{16a} The proposed reaction mechanism included the 1,4-addition of copper enolate **52** to vinyl azides **51**, followed by elimination of dinitrogen leading to alkylideneaminocoppers **53**. Cyclization via an intramolecular nucleophilic attack on the carbonyl group, followed by dehydration, readily afforded pyrroles **56** (Scheme 11).



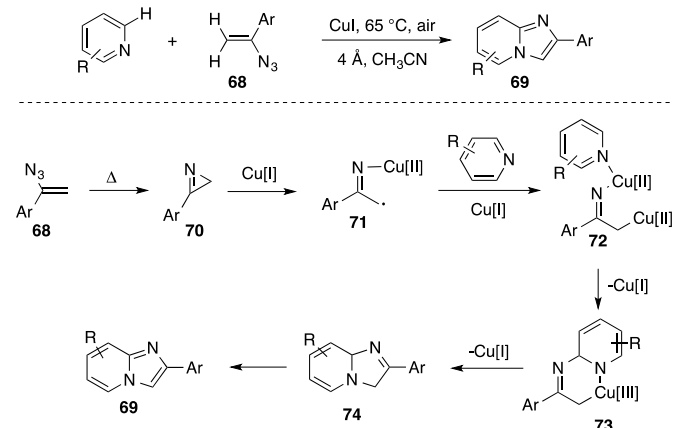
Scheme 11 Cu(II)-catalyzed pyrrole formation.

Similar efforts from the same research group revealed that highly substituted isoquinolines could be synthesized from α -aryl vinyl azides and internal alkynes under rhodium/copper bimetallic catalysis (Scheme 12).⁵ Preliminary mechanistic investigations indicated that both rhodium and copper are prerequisites for achieving catalytic activity. It was also found that benzylic radical intermediates were trapped by 2,6-di-tert-butyl-4-methylphenol (TEMPO), when it was added instead of HOAc (Scheme 12). Based on this and other experimental observations, the authors proposed a reaction mechanism that involved the reduction of Cu(OAc)₂ by DMF to generate a Cu(I) species. Vinyl azide **57** expelled N₂ to produce 2*H*-azirine **61**, which was reduced by the Cu(I) species and underwent C-N bond cleavage, affording iminyl Cu(II) radical **62**. Intermediate **62** was further reduced by a Cu(I) species and protonated to yield iminyl Cu(II) species **64**. Transmetalation with Rh(III) afforded **65**, which was proposed to form rhodacycle **66**, by C-H insertion. Subsequent insertion of diphenylethyne and C-N reductive elimination from rhodacycle **67** provided isoquinoline **58**, with generation of Rh(I) species. A redox reaction between Rh(I) and Cu(II) species was proposed as a method to regenerate the resting oxidation states of the transition metal catalysts (Rh(III) and Cu(I), Scheme 12).



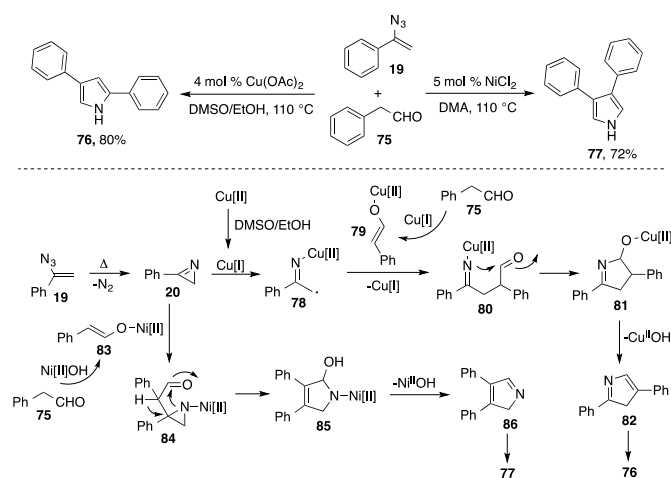
Scheme 12 Isoquinoline formation by Rh-Cu bimetallic cooperation.

Recently, the Adimurthy group reported a Cu(I)-catalyzed, oxidative C-H functionalization of pyridine derivatives with vinyl azides **68** to give imidazo[1,2- α]pyridines **69** under aerobic conditions (Scheme 13).²⁵ Similarly, thermal treatment of vinyl azides **68** led to 2*H*-azirines **70**, which underwent C-N bond cleavage in the presence of Cu(I) to generate iminylcopper(II) radicals **71**. Formation of 6-membered cyclic copper complexes **73** from reaction of pyridine derivatives and iminylcopper(II) radicals **71** occurred with the assistance of Cu(I) via iminyl copper intermediates **72**. Subsequent C-N reductive elimination of Cu(III) intermediates **73** and oxidation of **74** provided imidazo[1,2- α]pyridines **69** (Scheme 13).



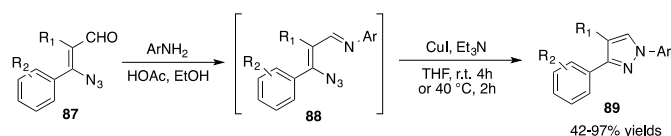
Scheme 13 Cu(I)-catalyzed C-H functionalization of pyridines with vinyl azides.

A recent study by the research group of Jiao demonstrated that 2,4- and 3,4-disubstituted pyrroles can be prepared in a regioselective fashion from vinyl azides and aryl acetaldehydes. Intriguingly, the regioselectivity could be switched by the choice of transition metal catalyst (Cu(OAc)₂ or NiCl₂, Scheme 14).²⁶ The authors proposed plausible mechanisms for these highly regioselective transformations. In the Cu-catalyzed formation of 2,4-disubstituted pyrroles, an iminylcopper(II) radical intermediate **78**, generated by pyrolysis to form the azirine **20** and reductive ring opening was proposed. A coupling reaction of Cu(II) phenylacetaldehyde enolate **79** with iminylcopper(II) radical **78** furnished γ -formyl iminylcopper(II) intermediate **80**. Intramolecular cyclization provided 2*H*-pyrrole Cu(II) intermediate **81**, which underwent dehydration and tautomerized to afford 2,4-diphenyl pyrrole **76** with regeneration of the Cu(II) catalyst. In contrast, when Ni(II), a transition metal ion less likely to support one-electron reduction, was used as a catalyst, 2*H*-azirine **20** remained intact long enough to undergo nucleophilic attack by the Ni(II) enolate of phenylacetaldehyde, **83**, giving nickel aziridine **84**. Ring-expansion and tautomerization led to the 2,5-dihydropyrrole intermediate **85**. Subsequent β -OH elimination and tautomerization produced 3,4-diphenylpyrrole **77** with regeneration of the free Ni(II) catalyst (Scheme 14).



Scheme 14 Pyrrrole synthesis switched by copper and nickel catalysts.

Copper complexes not only catalyze C-H amination reactions of vinyl azides, they can promote N-N bond forming reactions as well. The Rao group has recently developed a two-step protocol for the synthesis of 1*H*-pyrazoles **89** from vicinal vinyl azidoaldehydes **87** and aryl amines (Scheme 15).²⁷ This tandem process involves a copper-catalyzed intramolecular cyclization that occurs with loss of N₂.

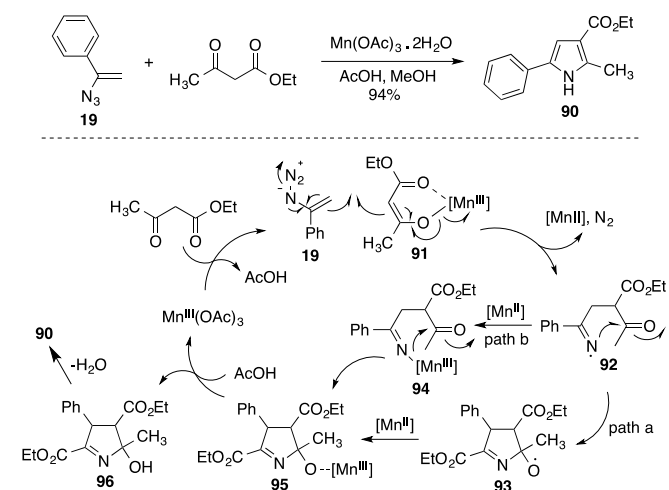


Scheme 15 1*H*-pyrazoles formation from vicinal vinyl azidoaldehydes and aryl amines.

4. Radical-initiated reactions of vinyl azides

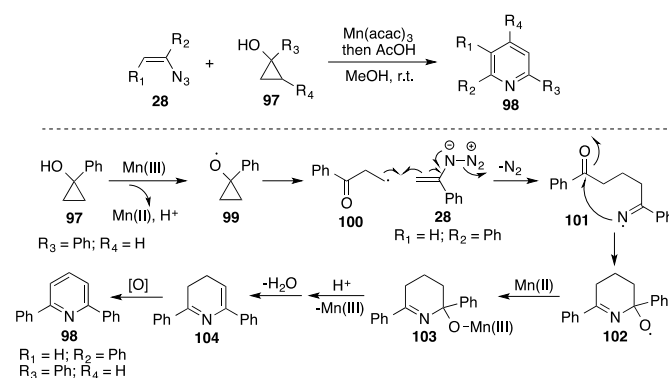
Vinyl azides participate in several different types of radical-initiated processes. Once generated, radicals add readily to the alkenyl group to produce the corresponding iminyl radicals, which in certain cases are able to undergo subsequent cyclizations to give heterocyclic amines. Pioneering research in this area was reported by Chiba group.^{28,29} Manganese(III) salts, such as Mn(OAc)₃,³⁰ are excellent one-electron oxidants, which have been widely employed to generate free radicals for cyclization reactions. Recently, Chiba and Narasaka demonstrated Mn(III)-catalyzed pyrrole formation from variously substituted vinyl azides and β-keto esters or 1,3-diketones (Scheme 16).²⁸ The reaction is thought to proceed through the addition of manganese(III) enolate **91** to vinyl azide **19** via a radical pathway, giving iminyl radical **92** with the release of a reduced Mn(II) species and dinitrogen. The resulting iminyl radical **92** undergoes an intramolecular addition to a carbonyl group to give alkoxy radical **93**, which is reduced by Mn(II) species to create Mn(III) alkoxide **95** (path a). Alternatively, reaction of iminyl radical **92** with a Mn(II) species could generate alkylideneaminomanganese(III) **94**, which can close upon the carbonyl group to give intermediate

95 (path b). Finally, protonation of **95** with acetic acid followed by dehydration of **96** produced pyrrole **90** along with regeneration of Mn(III) (Scheme 16).



Scheme 16 Mn(III)-catalyzed formal [3+2]-annulation reactions of vinyl azides and 1,3-dicarbonyl compounds.

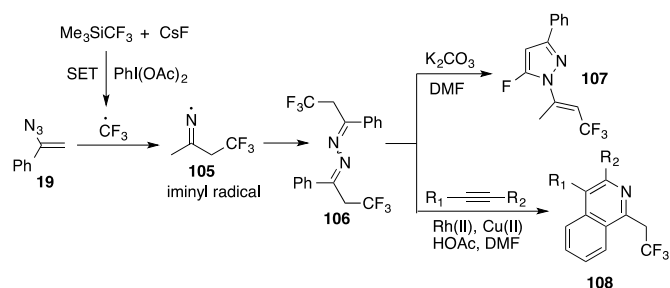
In addition to the above-mentioned Mn(III)-catalyzed [3+2] annulations of vinyl azides and 1,3-dicarbonyl compounds, the Chiba and co-workers also demonstrated [3+3] annulation reactions of vinyl azides **28** with cyclopropanols **97** for the synthesis of a series of azaheterocycles, such as pyridines **98** (Scheme 17).²⁹ The reaction likely involved the formation of a β-carbonyl radical **100**, generated by one-electron oxidation of cyclopropanol by Mn(III). Subsequent addition of β-carbonyl radical **100** to vinyl azide **28** afforded iminyl radical **101** with extrusion of dinitrogen. Subsequent intramolecular cyclization of iminyl radical **101** onto the carbonyl group would give alkoxy radical **102**. Reduction, protonation, dehydration and further oxidation afforded the pyridine product **98** (Scheme 17).



Scheme 17 Mn(III)-mediated Formal [3+3]-annulation reactions of vinyl azides and cyclopropanols.

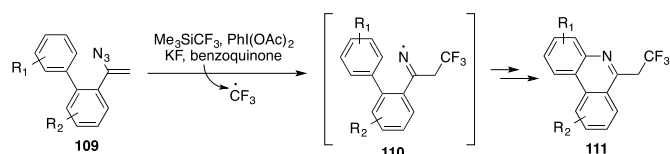
Furthering their efforts directed toward the synthesis of azaheterocycles based on radical reactions of vinyl azides, Chiba and co-workers recently disclosed a PhI(OAc)₂-mediated radical trifluoromethylation of vinyl azide **19** to generate a trifluoromethyl azine **106** (Scheme 18).³¹ The dimerization

product **106** could be transformed to 5-fluoropyrazole **107**, trifluoroethyl isoquinolines **108**, and other valuable trifluoromethylated heterocycles. Mechanistically, this reaction was likely initiated by a single-electron oxidation of Me_3SiCF_3 by $\text{PhI}(\text{OAc})_2$, leading to CF_3 radical. The CF_3 radical subsequently added to the C=C bond of vinyl azide **19** to form trifluoromethyl iminyl radical **105**, with release of a dinitrogen. Dimerization of CF_3 iminyl radical **105** gave α - CF_3 azine **106** (Scheme 18).



Scheme 18 Radical trifluoromethylation of vinyl Azides with Me_3SiCF_3 .

Drawing inspiration from these findings, the Chiba group developed an intramolecular radical cyclization of α -(biaryl-2-yl)vinyl azides **109** to construct trifluoroethyl phenanthridines **111** (Scheme 19).³² A similar mechanism was proposed: CF_3 radical generation preceded addition to the C=C bond of α -(biaryl-2-yl)vinyl azides **109** to form trifluoromethyl iminyl radicals **110**. The iminyl radicals **110** were added to the aryl group *ortho*-position to afford trifluoroethyl phenanthridines **111** after aromatization (Scheme 19).

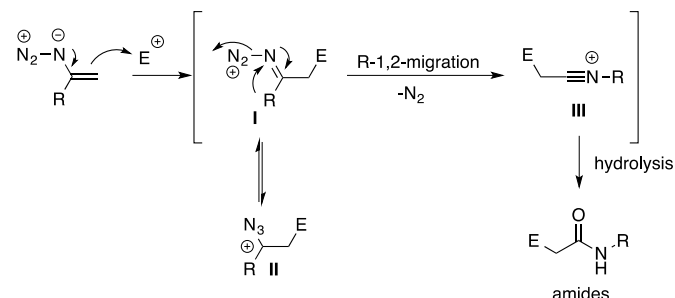


Scheme 19 Formation of trifluoroethyl phenanthridine via a radical cyclization.

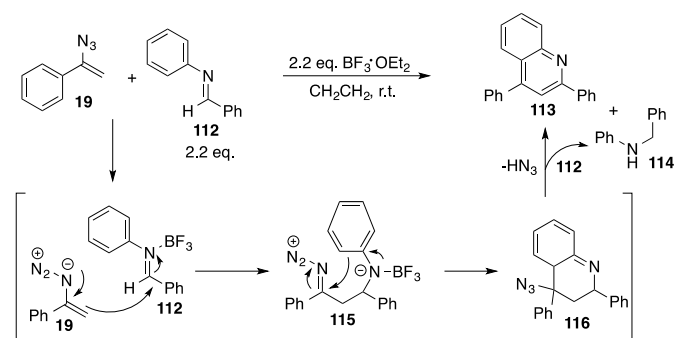
5. Lewis acid-mediated reactions of vinyl azides

Vinyl azides can act as nucleophilic enamine equivalents. Nucleophilic attack of vinyl azides onto various electrophilic species can form iminodiazonium ions **I** (Scheme 20), which are in equilibrium with α -azido ions **II**. The intermediates **I** can lose dinitrogen and undergo Schmidt-type rearrangements to form nitrilium ions **III**, which can be used for further transformations (Scheme 20). Having recognized that hydrolysis of nitrilium ions **III** provided a facile route into amides,^{33a} the Chiba group proposed a tethering strategy in which a second intramolecular nucleophile could trap α -azido ions **II** before Schmidt-type rearrangements could occur. This quite different reaction manifold ultimately relies upon azide acting as a leaving group in the construction of azaheterocycles (Scheme 21). Highly functionalized quinolines and pyridines were synthesized by a $\text{BF}_3 \cdot \text{OEt}_2$ -mediated formal [4+2]-annulation of vinyl azides and *N*-unsaturated aldimines

(Scheme 21).^{33b} In the proposed mechanism, the reaction was initiated by complexation of *N*-unsaturated aldimine **112** with $\text{BF}_3 \cdot \text{OEt}_2$, activating it to nucleophilic attack by vinyl azide **19**. This process provided iminodiazonium ion intermediate **115**, which underwent an intramolecular cyclization to form 4-azido-tetrahydroquinoline **116**. Subsequent aromatization of **116** via hydrogen transfer to another molecule of aldimine **112**, and elimination of HN_3 delivered the corresponding quinoline **113** and *N*-benzyl aniline **114** (Scheme 21).



Scheme 20 Chemical intermediates generated from nucleophilic reaction of vinyl azides with electrophilic species.

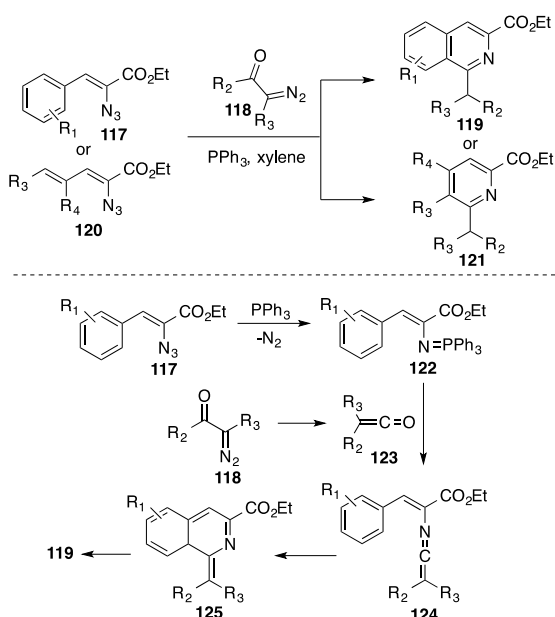


Scheme 21 Formal [4+2] annulation of vinyl azides with *N*-unsaturated aldimines.

6. PPh_3 -triggered reactions of vinyl azides

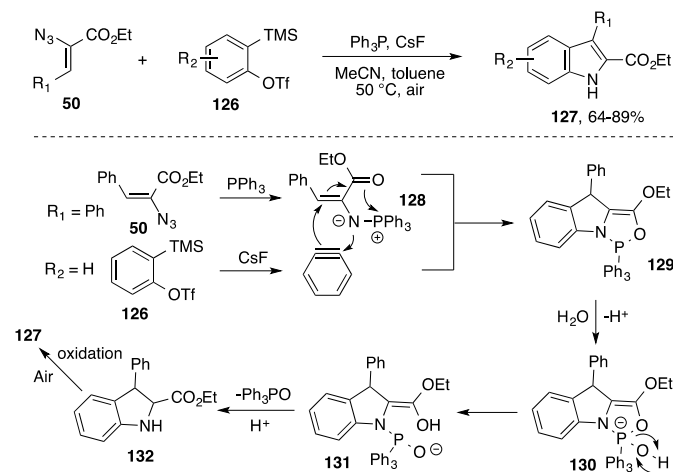
Aza-Wittig reactions of iminophosphoranes have received increased attention because of their utility in the synthesis of nitrogen heterocyclic compounds.³⁴ Vinyl azides very often appear in the form of their readily accessible synthons, vinyl iminophosphoranes, which are generated from the Staudinger reaction. The use of vinyl iminophosphoranes has been advanced significantly by the Wang group.

In 2008 and 2009, Wang and co-workers disclosed a one-pot synthesis of isoquinolines **119**, or pyridines **121** by condensation of vinyl azides **117** or **120** with α -diazocarbonyl compounds **118** (Scheme 22).³⁵ Addition of a stoichiometric amount of triphenylphosphine initiated the tandem Wolff rearrangement and aza-Wittig reactions, which was followed by a thermally-allowed electrocyclic ring closure to afford the heterocyclic core structures.



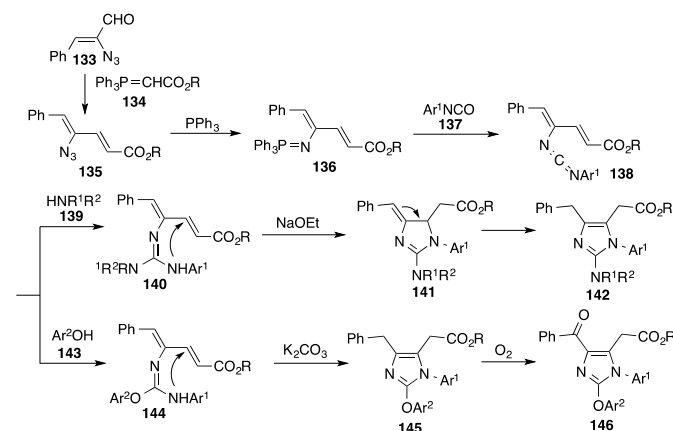
Scheme 22 A tandem Wolff rearrangement/aza-Wittig/electrocyclic reaction.

A recent study by the same research group demonstrated that vinyl azides **50** engaged benzenes **126** in an interesting transformation to furnish indoles **127** with the assistance of PPh_3 and CsF (Scheme 23).³⁶ This annulation was thought to proceed through a mechanism that involved a tandem cyclization of benzyne, generated by elimination of TMS fluoride, and vinyl iminophosphorane **128**, formed by the Staudinger reaction of vinyl azide **50** with PPh_3 , to give the tricyclic intermediate **129**. Hydrolysis of **129** afforded dihydroindole **132** and triphenylphosphine oxide, presumably with the intermediacy of **130** and **131**. Dihydroindole **132** was oxidized in air to afford indole products **127** (Scheme 23). The proposed mechanism was supported by the isolation of Ph_3PO and detection of reactive intermediate **129** by both HRMS and ^{31}P NMR in trapping experiments.



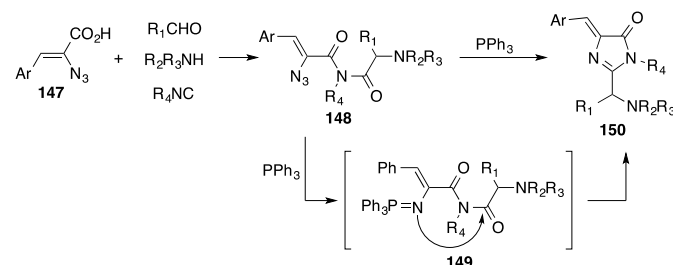
Scheme 23 Indoles formation from vinyl azides and ortho-silyl aryltriflates.

In another example of the use of vinyl azides **133** and **135** as precursors to vinyl iminophosphoranes **136**, Ding and co-workers reported syntheses of imidazole derivatives. This process proceeded through carbodiimide intermediates **138**, which could add various amines **139** or phenols **143** under base catalysis to give 1,2,4,5-tetrasubstituted imidazoles **142** (Scheme 24).³⁷ Carbodiimides **138** were derived from aza-Wittig reactions of iminophosphoranes **136** with aryl isocyanates **137**. Surprisingly, when phenols **143** were used as nucleophiles to trap the carbodiimide intermediate, 4-acylimidazoles **146** were obtained. Presumably, the expected products, **145**, were susceptible to benzylic oxidation under these basic, aerobic conditions (Scheme 24).



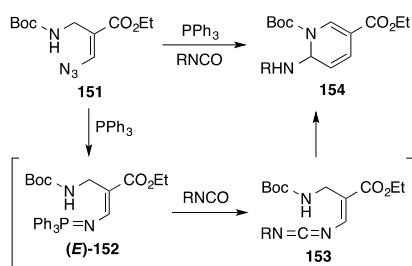
Scheme 24 Formation of 1,2,4,5-substituted imidazoles.

The coupled Staudinger/aza-Wittig strategy has also been used for the preparation of 4-arylidene-1*H*-imidazol-5(4*H*)-ones **150** (Scheme 25).³⁸ Ding and co-workers used a 4-component Ugi reaction, starting from 2-azido-3-arylacrylic acids **147**, aldehydes, secondary amines, and isocyanides to provide an elaborated vinyl azide, **148**. Upon addition of triphenylphosphine, the key vinyl iminophosphorane intermediate **149** underwent an intramolecular aza-Wittig reaction to form the densely functionalized heterocycle **150** (Scheme 25).



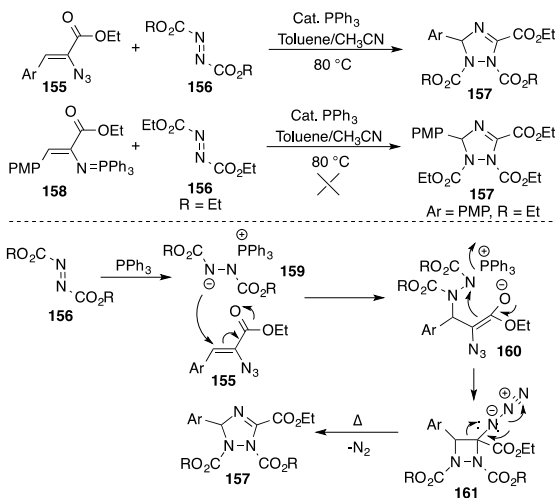
Scheme 25 A sequential Staudinger and intramolecular aza-Wittig reaction.

Similarly, treatment of vinyl azides **151** with isocyanates in the presence of PPh_3 led to the construction of dihydropyrimidines **154** (Scheme 26).³⁹ This process involved sequential Staudinger, aza-Wittig, and intramolecular cyclization reactions.



Scheme 26 A sequential Staudinger/aza-Wittig/cyclization reaction.

Triphenylphosphine and dialkyl azodicarboxylates were utilized for the formation of a Huisgen zwitterion,⁴⁰ an intermediate that plays an important role in Mitsunobu reaction.⁴¹ Recently, Lin and Wang reported a synthesis in which zwitterion **159** condensed with vinyl azides **155** to afford 1,2,4-triazolines **157** (Scheme 27).⁴² Preliminary mechanistic studies suggested that an no intermediate iminophosphorane was involved. Attempts to prepare the desired 1,2,4-triazoline product **157** (Ar = PMP, R = Et) from the reaction of diethyl azodicarboxylate (DEAD) and vinyl iminophosphorane **158** (prepared from the corresponding vinyl azide and PPh₃) failed. Because the product was not accessible directly from **158**, the authors proposed a mechanism in which the reaction is initiated by nucleophilic attack of the nitrogen of the Huisgen zwitterion **159** at the β -position of vinyl azides **155**. A subsequent cyclization of **160** released PPh₃ and gave the 1,2-diazetidine intermediate **161**, which underwent a Curtius-type rearrangement giving rise to 1,2,4-triazolines **157** with the release of a dinitrogen (Scheme 27).

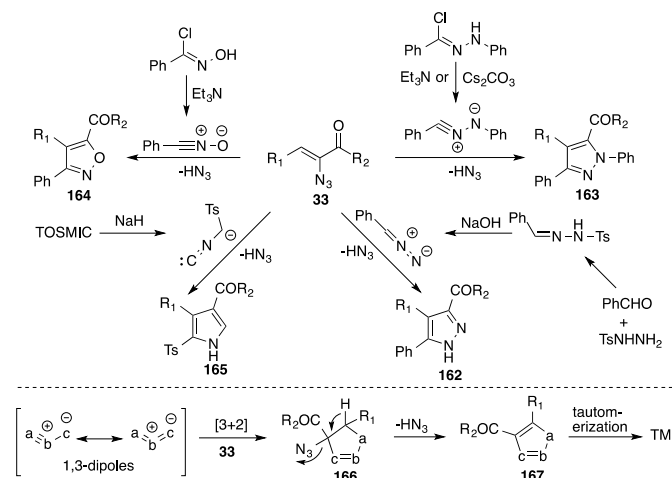


Scheme 27 A cascade reaction of the Huisgen zwitterion with vinyl azides.

7. Base-mediated reactions of vinyl azides

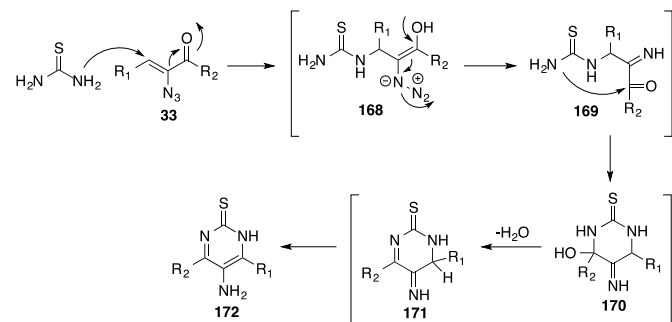
Huisgen 1,3-dipolar cycloaddition is a classic reaction in organic chemistry; the addition of 1,3-dipolar compounds to alkynes and alkenes permits facile construction of five-membered heterocyclic compounds.⁴³ The base-catalyzed cycloaddition of 1,3-dipolar compounds with electron-deficient vinyl azides **33**

is an area that has seen significant progress over the last several years (Scheme 28). This approach has provided many straightforward and operationally simple protocols for the syntheses of various heterocyclic compounds, including 1*H*-pyrazoles **162**,^{44a} pyrazoles **163**,^{44b,c} isoxazoles **164**,^{44d} and pyrroles **165**^{44e} (Scheme 28). In the above syntheses, vinyl azides function as a two-atom synthon. The azide group of vinyl azides serves as a leaving group, which is crucial for the final aromatization of the intermediate to the product. In addition, vinyl azides have been employed as three-atom (C-C-N) synthons to construct *N*-heterocyclic skeletons under basic conditions. Such reactions typically involve loss of molecular nitrogen.



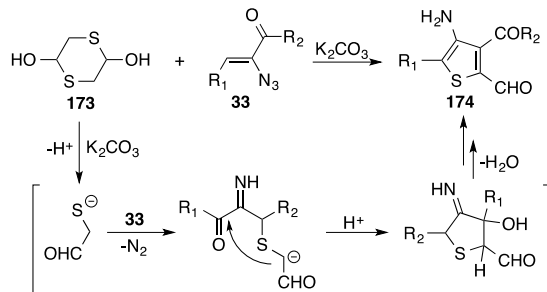
Scheme 28 [3+2] Cycloaddition of vinyl azides **33** with 1,3-dipolar compounds.

Nucleophilic species are competent to add (β -addition) to the C=C bond of vinyl azides to give anionic intermediates. The reactive intermediates, in turn, provide an opportunity for cyclization to *N*-heterocycles if an appropriate and accessible electrophilic functional group is present in the same molecule. In their preparation of 5-aminopyrimidine-2(1*H*)-thiones **172**, Yu and Zhang described the Michael addition of thiourea to vinyl azides **33** affording intermediates **168** (Scheme 29).⁴⁵ Following loss of dinitrogen, **168** formed **169**, which subsequently underwent intramolecular cyclization, dehydration, and rearrangement to provide the products **172**.

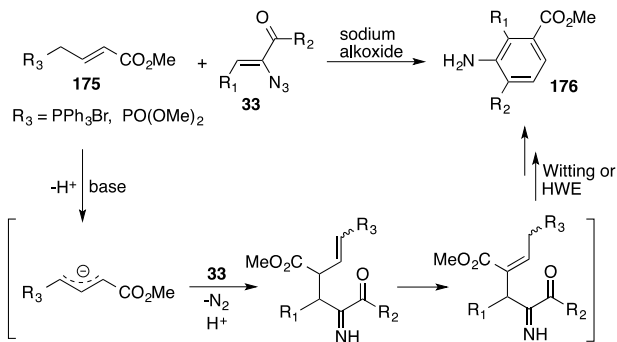


Scheme 29 Reactions of vinyl azides with thiourea.

Analogously, thiophenes **174**⁴⁶ and anilines **176**⁴⁷ have been synthesized by employing 1,4-dithiane-2,5-diol **173** (Scheme 30) and phosphorus ylide/dimethyl allylphosphonates **175** (Scheme 31) as nucleophiles for vinyl azides **33**.

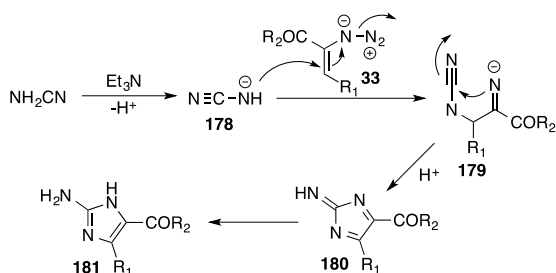


Scheme 30 Reactions of vinyl azides with 1,4-dithiane-2,5-diol.



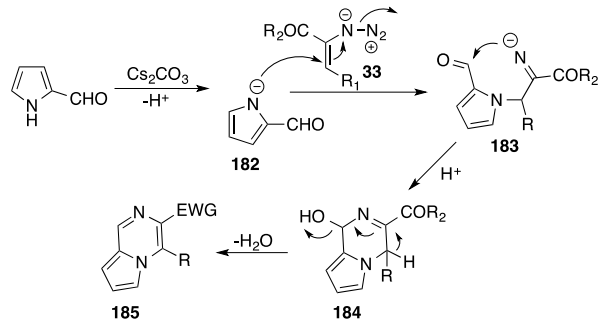
Scheme 31 Reactions of vinyl azides with phosphorus ylide/dimethyl allylphosphonate.

In above processes iminyl anions, generated from the addition of nucleophilic reagents to vinyl azides and subsequent loss of N₂, were protonated and were not available as nucleophiles for further transformations. However, it was recently demonstrated that iminyl anions can be trapped by various intramolecular electrophilic groups to construct the corresponding *N*-heterocycles. For example, Michael addition of cyanamide anion **178** to **33**, followed by elimination of N₂ afforded iminyl anions **179**, which were capable of intramolecular nucleophilic addition to the cyano group. Protonation followed by tautomerization provided 2-aminoimidazole products **181** (Scheme 32).⁴⁸



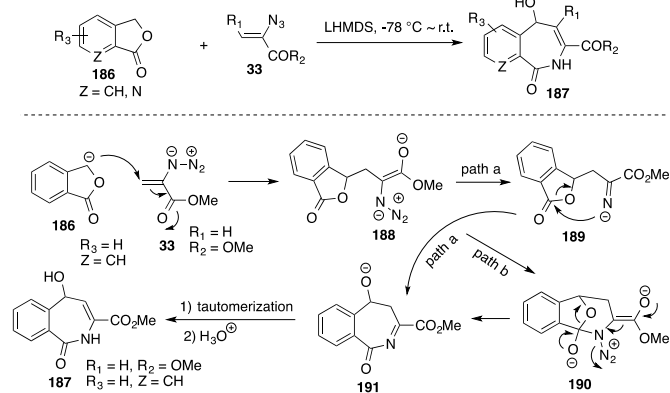
Scheme 32 A [3+2] cyclization of vinyl azides and cyanamide.

Other nucleophiles, for example the anion derived from deprotonation of pyrrole-2-carboxaldehyde, also act as a nucleophiles toward vinyl azides **33**. In this case addition initiates a [3+3] cascade process for the generation of functionalized pyrrolo[1,2- α]pyrazines **185** (Scheme 33).⁹



Scheme 33 A [3+3] cyclization of vinyl azides and pyrrole-2-carboxaldehyde.

Similarly, treatment of isobenzofuranone **186** with LHMDS and vinyl azides **33** resulted in the formation of 5-hydroxy-2-benzazepinones **187** from a [4+3] annulation (Scheme 34).⁴⁹ The proposed mechanism involved Michael addition of the benzylic anion **186** to the C=C bond of vinyl azide **33**, creating the new anion species **188**. Loss of dinitrogen gave rise to iminyl anion **189**, which underwent an intramolecular nucleophilic addition to the lactone carbonyl to generate 7-membered lactam **191** (path a). A plausible alternative second sequence leading to the same product is attack by the azido anion **188** on the lactone carbonyl prior to ring cleavage and N₂ expulsion to form intermediate **191** (path b). Tautomerization of **191** followed by protonation furnished the benzazepinone product **187** (Scheme 34).



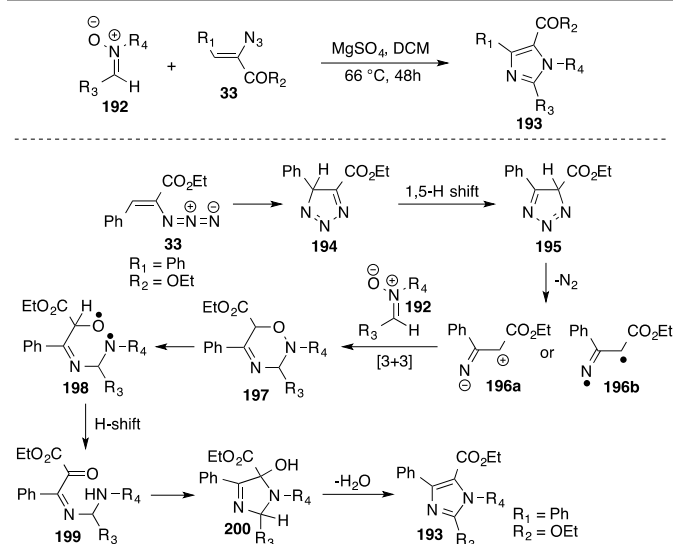
Scheme 34 A [4+3] cyclization of vinyl azides and phthalides.

8. Other miscellaneous reactions of vinyl azides

With the interest of developing a new [3+3] cycloaddition reactions of nitrones,⁵⁰ Hu et al. investigated the reaction of vinyl azides **33** with nitrones **192** and found that 1,2,4,5-tetrasubstituted imidazoles **193** were obtained instead of the possible [3+2] cycloaddition isoxazolidine products (Scheme 35).^{10a} Preliminary mechanistic investigations suggested that

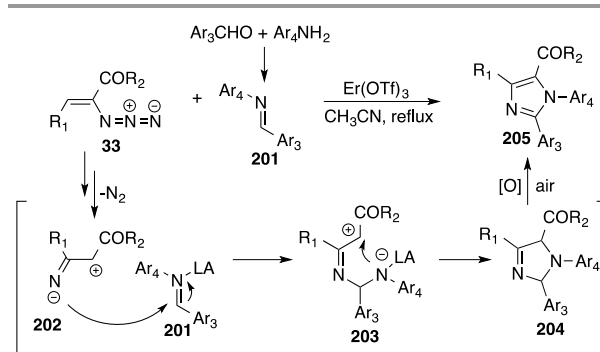
this reaction did not proceed through a 2*H*-azirine intermediate. The assignment of a radical mechanism was supported by the observation that no imidazole **193** products were obtained when 2*H*-azirine replaced vinyl azide **33**, or when the radical-trapping reagent, TEMPO (1.0 equiv) was added to the reaction of vinyl azide **33** ($R_1 = \text{Ph}$, $R_2 = \text{OEt}$) and nitrone **192** ($R_3 = R_4 = \text{Ph}$, Scheme 35).

On the basis of these results, a tentative mechanism for the domino reaction was proposed (Scheme 35). An intramolecular cyclization of vinyl azide **33** formed triazolone **194**, which underwent a 1,5-hydrogen shift to give triazolone **195**. The zwitterionic intermediate **196a**, (or biradical intermediate **196b**), was generated from the triazolone intermediate **195** by thermal elimination of dinitrogen. It was believed that the key intermediate **196** participated in a formal [3+3] cycloaddition with nitrone **192** via the zwitterionic pathway or by sequential two-electron processes, giving intermediate **197** with high regioselectivity. Homolytic cleavage of the N-O bond in **197**, followed by a hydrogen shift resulted in the formation of 5-amino ketomalonate **199**. The intermediate **200** was readily obtained via an intramolecular cyclization of **199** through nucleophilic addition of the amino nitrogen to the carbonyl group. Finally, dehydration of intermediate **200** afforded the desired product **193** (Scheme 35).



Scheme 35 Cascade reactions of nitrones and vinyl azides.

Although the proposed mechanism is quite involved, several lines of evidence support it. The key zwitterionic intermediate **202** is generated in the $\text{Er}(\text{OTf})_3$ -catalyzed reaction of vinyl azides **33** with *N*-unsaturated aldimines **201**. This reaction leads to 1,2,4,5-tetrasubstituted imidazoles **205** (Scheme 36).⁵¹ In this case the domino reaction also involves triazolone formation, a 1,5-hydrogen shift, and loss of N_2 to form zwitterionic **202**. Condensation of **202** with Lewis acid-coordinated imines **201** resulted in dihydroimidazoles **204** that were readily oxidized to furnish the imidazole products **205** (Scheme 36).



Scheme 36. A domino reaction of imines and vinyl azides.

Conclusions

In summary, vinyl azides have proven to be particularly powerful and versatile building blocks for the preparation of diverse nitrogen-containing heterocycles. The synthetic utility of vinyl azides is due mostly to their high chemical reactivity, which is driven by the excellent leaving-group ability of dinitrogen. Different timing of dinitrogen loss opens a wide variety of reaction pathways that originate from a very simple functional group. The reactions discussed in this review demonstrate that vinyl azides can generate different types of reactive intermediates for novel transformations, and that the choice of particular pathway may be influenced by heating, photolysis, transition metal catalysts, radical generation, Lewis acid coordination, and addition of PPh_3 or base. Notably, vinyl azides can undergo the intramolecular [3+2] cycloaddition, 1,5-*H* shift and denitrogenation to generate zwitterionic intermediates or biradical intermediates. We believe the formation of such intermediates from an unusual nitrogen transfer process represents a new concept for the construction of *N*-heterocycles, as well as a new reactivity pattern for vinyl azides. Although great progress has been made in vinyl azide chemistry over the last few years, there is little doubt that studies of the use of versatile vinyl azide starting material in the development of *N*-heterocycle synthesis will continue to bear fruit.

Handling azides - Warning!

Vinyl azides are classified as organic azides, which are valuable intermediates in organic synthesis. However, one should keep in mind the inherent toxicity, instability, shock sensitivity, and explosive power of azides. All users should exercise appropriate caution. Generally, the explosion danger of organic azides decreases with diminishing fraction of N_3 in the molecular mass. For organic azides to be safely handled or non-explosive, "Smith's rules" must be followed: i) the number of nitrogen atoms (N_N) must not exceed that of carbon (N_C), and ii) $(N_C + N_O)/N_N \geq 3$ ($N = \text{number of atoms}$).⁵²

In general, any azides synthesized should be stored below room temperature and in the dark. Most vinyl azides and other azides are prepared directly or indirectly from sodium azide. Sodium azide is toxic [LD_{50} oral (rats) = 27 mg/Kg] and can be

absorbed through the skin. Sodium azide should not be allowed to come into contact with any Brønsted acids, water, heavy metals such as Pb, Cu, Ba, Zn, Cd, Ni, or chlorinated solvents (CH₂Cl₂ and CHCl₃). Sodium azide reacts also vigorously with CS₂, Br₂, and dimethyl sulfate.

Acknowledgements

Bao Hu would like to thank Prof. Zhongwen Wang for his enormous amount of support and dedication to his development as a chemist. We want to thank all authors whose names are listed in the references for their contributions to the chemistry of vinyl azides. Research reported in this publication was supported by Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health under award number R01 EB015536. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The financial support by the National Natural Science Foundation of China (No. 21202148) is also gratefully acknowledged.

Notes and references

^a Institute of Industrial Catalysis, Zhejiang University of Technology, Hangzhou 310014, China. E-mail: hobao001@zjut.edu.cn

^b Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE, 68588-0304, USA. E-mail: bhu4@unl.edu

- (a) P. Grieb, *Philos. Trans. R. Soc. London*, **1864**, *13*, 377; (b) P. Grieb, *Justus Liebigs Ann. Chem.*, **1865**, *50*, 275.
- For recent reviews on organic azides, see: (a) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem., Int. Ed.*, **2005**, *44*, 5188; (b) K. Banert in *Organic Azides Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, **2010**, p. 115; (c) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.*, **2007**, *36*, 1249; (d) T. G. Driver, *Org. Biomol. Chem.*, **2010**, *8*, 3831; (e) S. Chiba, *Synlett*, **2012**, *23*, 21.
- (a) G. Smolinsky, C. A. Pryde, *J. Org. Chem.*, **1968**, *33*, 2411; (b) A. Hassner, F. W. Fowler, *J. Am. Chem. Soc.*, **1968**, *90*, 2869; (c) For recent review on vinyl azides leading to 2*H*-azirines, see: T. Patonay, J. Jekö, E. Juhász-Tóth, *Eur. J. Org. Chem.*, **2008**, 1441; (d) For early review on nitrenes, see: L. Horner, A. Christmann, *Angew. Chem., Int. Ed. Engl.*, **1963**, *2*, 599.
- (a) B. J. Stokes, T. G. Driver, *Eur. J. Org. Chem.*, **2011**, 4071; (b) G. Dequirez, V. Pons, P. Dauban, *Angew. Chem., Int. Ed.*, **2012**, *51*, 7384.
- Y. F. Wang, K. K. Toh, J.-Y. Lee, S. Chiba, *Angew. Chem. Int. Ed.*, **2011**, *50*, 5927.
- (a) A. F. Bamford, M. D. Cook, B. P. Roberts, *Tetrahedron Lett.*, **1983**, *24*, 3779; (b) P. C. Montevecchi, M. L. Navacchia, P. Spagnolo, *J. Org. Chem.* **1997**, *62*, 5846.
- (a) A. Hassner, E. S. Ferdinandi, R. J. Isbister, *J. Am. Chem. Soc.*, **1970**, *92*, 1672; (b) H. W. Moore, H. R. Sheldon, W. Weyler, Jr., *Tetrahedron Lett.*, **1969**, *10*, 1243;
- H. Staudinger, J. Meyer, *Helv. Chim. Acta.*, **1919**, *2*, 635.
- W. T. Chen, M. Hu, J. W. Wu, H. B. Zou, Y. P. Yu, *Org. Lett.*, **2010**, *12*, 3863.
- (a) B. Hu, Z. Wang, N. Ai, J. Zheng, X. H. Liu, S. Shang, Z. Wang, *Org. Lett.*, **2011**, *13*, 6362; (b) B. Hu, N. Ai, Z. Wang, X. Xu, X. Li, *ARKIVOC*, **2012**, (*vi*), 222.
- For reviews on vinyl azides, see: (a) G. L'abbé, *Angew. Chem., Int. Ed.* **1975**, *14*, 775; (b) S. Chiba, *Chimia* **2012**, *66*, 377; (c) N. Jung, S. Bräse, *Angew. Chem. Int. Ed.*, **2012**, *51*, 12169.
- (a) G. Smolinsky, *J. Am. Chem. Soc.*, **1961**, *83*, 4483; (b) G. Smolinsky, *J. Org. Chem.*, **1962**, *27*, 3557.
- For recent reviews on 2*H*-azirines, see: (a) A. F. Khlebnikov, M. S. Novikov, *Tetrahedron*, **2013**, *69*, 3363; (b) F. Palacios, A. M. O. de Retana, E. M. de Marigorta, J. M. de los Santos, *Eur. J. Org. Chem.*, **2001**, 2401.
- For recent examples, see: (a) A. G. O'Brien, F. Levesque, P. H. Seeberger, *Chem. Commun.*, **2011**, *47*, 2688; (b) P. J. Roy, C. Dufresne, N. Lachance, J.-P. Leclerc, M. Boisvert, Z. Wang, Y. Leblanc, *Synthesis*, **2005**, 2751; (c) P. J. Roy, M. Boisvert, Y. Leblanc, *Org. Synth.*, **2007**, *84*, 262; (d) P. M. Fresneda, P. Molina, S. Delgado, J. A. Bleda, *Tetrahedron Lett.*, **2000**, *41*, 4777; (e) T. Lomberget, S. Radix, R. Barret, *Synlett*, **2005**, 2080; (f) F. Lehmann, M. Holm, S. Laufer, *Tetrahedron Lett.*, **2009**, *50*, 1708.
- T. M. V. D. Pinho e Melo, C. S. J. Lopes, A. Md'A. Rocha Gonsalves, R. C. Storr, *Synthesis*, **2002**, 605.
- (a) S. Chiba, Y. F. Wang, G. Lapointe, K. Narasaka, *Org. Lett.*, **2008**, *10*, 313; (b) E. Pei J. Ng, Y. F. Wang, B. W. Q. Hui, G. Lapointe, S. Chiba, *Tetrahedron*, **2011**, *67*, 7728.
- W. Yu, W. Chen, S. Liu, J. Shao, Z. Shao, H. Lin, Y. Yu, *Tetrahedron*, **2013**, *69*, 1953.
- (a) M. N. Hopkinson, B. Sahoo, J. L. Li, F. Glorius, *Chem. Eur. J.*, **2014**, *20*, 3874; (b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.*, **2013**, *113*, 5322.
- E. P. Farney, T. P. Yoon, *Angew. Chem., Int. Ed.*, **2014**, *53*, 793.
- (a) A. Padwa, M. Dharan, J. Smolanoff, S. I. Wetmore, *J. Am. Chem. Soc.*, **1973**, *95*, 1954; (b) A. Padwa, J. Smolanoff, A. Tremper, *J. Am. Chem. Soc.*, **1975**, *97*, 4682; (c) A. Padwa; J. K. Rasmussen, A. Tremper, *J. Am. Chem. Soc.*, **1976**, *98*, 2605.
- S. Cludius-Brandt, L. Kupracz, A. Kirschning, *Beilstein J. Org. Chem.*, **2013**, *9*, 1745.
- B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pum-phrey, T. G. Driver, *J. Am. Chem. Soc.*, **2007**, *129*, 7500.
- J. Bonnamour, C. Bolm, *Org. Lett.*, **2011**, *13*, 2012.
- (a) H. Dong, M. Shen, J. E. Redford, B. J. Stokes, A. L. Pumphrey, T. G. Driver, *Org. Lett.*, **2007**, *9*, 5191; (b) W. G. Shou, J. Li, T. Guo, Z. Lin, G. Jia, *Organometallics*, **2009**, *28*, 6847.
- R. R. Donthiri, V. Pappula, N. N. K. Reddy, D. Bairagi, S. Adimurthy, *J. Org. Chem.*, **2014**, *79*, 11277.
- F. Chen, T. Shen, Y. Cui, N. Jiao *Org. Lett.*, **2012**, *14*, 4926.
- J. Hu, Y. Cheng, Y. Yang, Y. Rao, *Chem. Commun.*, **2011**, *47*, 10133.
- (a) Y. F. Wang, K. K. Toh, S. Chiba, *Org. Lett.*, **2008**, *10*, 5019; (b) E. P. J. Ng, Y. F. Wang, S. Chiba, *Synlett*, **2011**, 783; (c) E. P. J. Ng, Y. Wang, B. W. Q. Hui, G. Lapointe, S. Chiba, *Tetrahedron*, **2011**, *67*, 7728.
- (a) Y. F. Wang, S. Chiba, *J. Am. Chem. Soc.* **2009**, *131*, 12570; (b) Y. F. Wang, K. K. Toh, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.*, **2011**, *133*, 6411.

30. For reviews of Mn(OAc)₃ as an oxidant see: (a) B. B. Snider, *Chem. Rev.*, **1996**, *96*, 339; (b) G. G. Melikyan, In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, **1997**; Vol. 49, Chapter 3.
31. Y. F. Wang, G. H. Lonca, S. Chiba, *Angew. Chem. Int. Ed.*, **2014**, *53*, 1067.
32. Y. F. Wang, G. H. Lonca, M. Le Runigo, S. Chiba, *Org. Lett.*, **2014**, *16*, 4272.
33. (a) F. L. Zhang, Y. F. Wang, G. H. Lonca, X. Zhu, S. Chiba, *Angew. Chem. Int. Ed.*, **2014**, *53*, 4390; (b) X. Zhu, Y. F. Wang, F. L. Zhang, S. Chiba, *Chem. Asian J.*, **2014**, *9*, 2458.
34. For select review on aza-Wittig reactions of iminophosphoranes, see: P. Molina and M. J. Vilaplana, *Synthesis*, **1994**, 1197.
35. (a) Y. Y. Yang, W. G. Shou, Z. B. Chen, D. Hong, *J. Org. Chem.*, **2008**, *73*, 3928; (b) Z. B. Chen, D. Hong, Y.-G. Wang, *J. Org. Chem.*, **2009**, *74*, 903.
36. D. Hong, Z. B. Chen, X. F. Lin, Y. G. Wang, *Org. Lett.*, **2010**, *12*, 4608.
37. Y.B. Nie, L. Wang, M. W. Ding, *J. Org. Chem.*, **2012**, *77*, 696.
38. Y. Wang, H. Xie, Y. R. Pan, M. W. Ding, *Synthesis*, **2014**, *46*, 336.
39. Y. Nishimura, H. Chob, *Synlett*, **2015**, *26*, 233.
40. (a) Huisgen, R. In *The Adventure Playground of Mechanisms and Novel Reactions: Profiles, Pathways and Dreams*; Seeman, J. I., Ed.; American Chemical Society: Washington, DC, **1994**; p 62; (b) R. Huisgen, H. Blaschke, E. Brunn, *Tetrahedron Lett.*, **1966**, *7*, 405; (c) E. Brunn, R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **1969**, *8*, 513.
41. (a) O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.*, **1967**, *40*, 2380; (b) O. Mitsunobu, M. Yamada, T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **1967**, *40*, 935.
42. D. Hong, Y. X. Zhu, X. F. Lin, Y. G. Wang, *Tetrahedron*, **2011**, *67*, 650.
43. For a comprehensive review of 1,3-dipolar cycloadditions, see: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, **2003**.
44. (a) G. Zhang, H. Ni, W. Chen, J. Shao, H. Liu, B. Chen and Y. Yu, *Org. Lett.*, **2013**, *15*, 5967; (b) H. Zou, H. Zhu, J. Shao, J. Wu, W. Chen, M. A. Giulianotti, Y. Yu, *Tetrahedron*, **2011**, *67*, 4887; (c) Y. Li, D. Hong, P. Lu, Y. G. Wang, *Tetrahedron Lett.*, **2011**, *52*, 4161; (d) M. Hu, X. He, Z. Niu, Z. Yan, F. Zhou, Y. Shang, *Synthesis*, **2014**, *46*, 510. (e) W. Chen, J. Shao, Z. Li, M. A. Giulianotti, Y. Yu, *Can. J. Chem.*, **2012**, *90*, 214.
45. (c) Z. Shao, Q. Pan, J. Chen, Y. Yu, G. Zhang, *Tetrahedron*, **2012**, *68*, 6565.
46. B. Chen, H. Ni, X. Guo, G. Zhang, Y. Yu, *RSC Adv.*, **2014**, *4*, 44462.
47. S. Liu, W. Chen, J. Luo, Y. Yu, *Chem. Commun.*, **2014**, *50*, 8539.
48. S. Liu, J. Shao, X. Guo, J. Luo, M. Zhao, G. Zhang and Y. Yu, *Tetrahedron*, **2014**, *70*, 1418.
49. B. K. Dinda, A. K. Jana, D. Mal, *Chem. Commun.*, **2012**, *48*, 3999.
50. (a) B. Hu, J. L. Zhu, S. Y. Xing, J. Fang, D. Du and Z. W. Wang, *Chem. Eur. J.*, **2009**, *15*, 324; (b) For a recent review on nitrones, see: J. Yang, *Synlett*, **2012**, *23*, 2293.
51. K. Rajaguru, R. Suresh, A. Mariappan, S. Muthusubramanian, N. Bhuvanesh, *Org. Lett.*, **2014**, *16*, 744.
52. (a) P. A. S. Smith, *Open-Chain Nitrogen Compounds, vol. 2*, Benjamin, New York, **1966**, 211; (b) J. H. Boyer, R. Moriarty, B. de Darwent, P. A. S. Smith, *Chem. Eng. News* **1964**, *42*, 6.