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α-Substituted Vinyl Azides: An Emerging Functionalized Alkene

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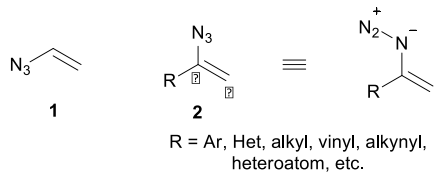
Vinyl azides are highly versatile synthons that provide access to numerous *N*-heterocycles and other functional groups. α-Substituted vinyl azides (azido vinylidenes) are a special class that display unique reactivity, able to react not only as azides, but also as radical acceptors, enamine-type nucleophiles, and even electrophiles, thus delivering a wide range of nitrogen-containing compounds and their derivatives. An impressive variety of intermediates – such as iminodiazonium ions, nitrilium ions and iminyl radicals – can be generated from vinyl azides and exploited in cycloadditions, couplings, C–H functionalizations, hydrolysis processes, and cascade reactions under transition metal / photoredox catalysis. In addition to presenting synthetic protocols to access vinyl azides, this Review offers a comprehensive coverage of the development of their multifaceted reactivity, and highlights their potential as versatile precursors for synthetic applications.

1. Introduction

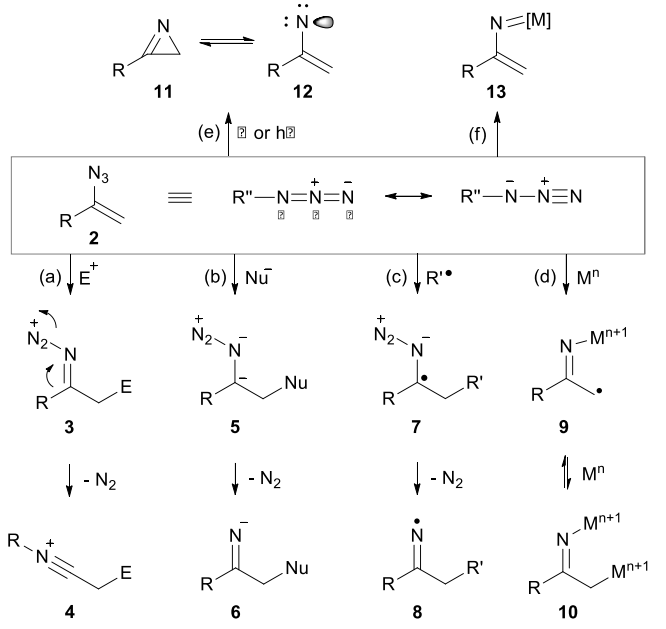
Vinyl azides, molecules that feature both alkene and azide motifs (as typified by the parent azidoethene **1**, Scheme 1) have been known for around a century.[1] However, little use was made of these dual-functionalized alkenes due to their high inherent reactivity, as well as tedious and poorly efficient syntheses.[2] Alongside the recent development of more convenient synthetic approaches, vinyl azides have been found to display multifaceted reactivity as electrophile / radical / nucleophile acceptors.[3] The conjugation of the electron-donating azide[4] with the alkene unit is in part responsible for this distinct reactivity, and the resultant variety of transformations.[3b, 3d]



Scheme 1. Vinyl azide and α-substituted vinyl azides.

As a special sub-class of vinyl azides, α-substituted vinyl azides (**2**, also termed azido vinylidenes) exhibit a unique reactivity profile (Scheme 2).[5] These electron-rich alkenes (R ≠ EWG) can display enamine-like nucleophilicity,[6] and on reaction with appropriate electrophiles (E^+, Path a) yield an iminodiazonium ion **3**. Schmidt-type rearrangement of this intermediate results in the formation of the corresponding nitrilium ion **4**, which can be hydrolysed to an amide.[7] Interestingly, azido vinylidenes can also occasionally act as nucleophile acceptors in Michael addition processes (Path b, **2**→**5**), giving iminyl anion **6** after elimination of N_2;[8] this process is facile for α-azidoesters and ketones (i.e. R = EWG).[3a, 3c, 3e] For these latter electron-deficient substrates, Lewis acid catalysts can further enhance the electrophilicity of the β-carbon atom by coordination to the carbonyl functionality.[9]

α-Substituted vinyl azides also undergo addition reactions with radicals to form α-azido radicals **7** which, on elimination of dinitrogen, lead to iminyl radicals **8** (Path c).[10] In contrast, Chiba *et al.* have recently found that metal enaminyl radicals **9** are generated by reduction of α-aryl/alkyl vinyl azides by



Scheme 2. The multifaceted reactivity of azido vinylidenes.

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transition metals, such as Cu(II) and Fe(III) species (Path d).[11] These latter radicals are in equilibrium with iminyl metal complexes **10**, which have been used for C–H functionalization, for example in *N*-heterocycle synthesis.

In addition to reactions of the alkene group with electrophiles, nucleophiles, radicals, and SET reagents, the azide motif can also behave as a 1,3-dipole,[12] or undergo decomposition into a vinylnitrene **11** and/or the corresponding 2*H*-azirine **12** (Path e).[2c, 3d, 13] As will be discussed, 2*H*-azirines are useful intermediates in organic synthesis, and therefore an important feature of the chemistry of vinyl azides.[3e, 14] This is a relatively facile decomposition pathway, with vinyl azides exhibiting lower thermal decomposition temperatures (60–70 °C) than aryl azides (140–170 °C), which likely reflects the concerted (electrocyclic) character of this 2*H*-azirine–vinylnitrene interconversion.[13a] Finally, vinyl azides can be activated by transition metal/Lewis acid catalysts (such as Pd(II), Fe(II), Cu(II), In(III)), or by PPh_3; nitrenoid intermediates **13** are thus generated via loss of dinitrogen (Path f).[12b, 15]

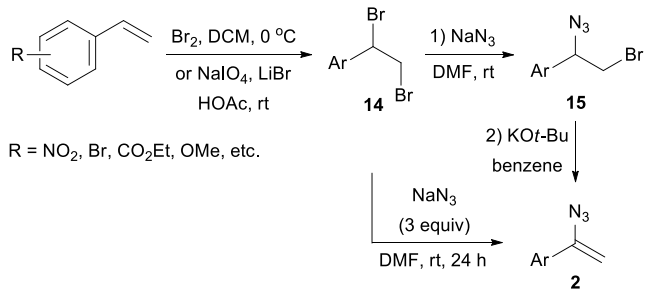
In the view of this diverse reactivity profile, we present herein a comprehensive and critical review of the wide-ranging chemistry of α-substituted vinyl azides.[3] Their popularity and diverse applications have in turn hinged on the development of mild and efficient methods for their preparation that avoid the use of explosive and toxic reagents,[2b, 16] while offering regioselectivity, and functional group compatibility.[17] The review begins with a discussion of vinyl azide synthesis, and their behavior under thermal and photochemical conditions. This is followed by sections on the various intermediates and modes of reactivity that can arise from α-substituted vinyl azides – specifically the formation of 2*H*-azirines and vinyl nitrenes, metal enaminyl radicals, iminyl radicals, their reactions as nucleophiles and electrophiles, and their participation in click chemistry.

2. Synthetic approaches to α-substituted vinyl azides

2.1 Haloazidations of alkenes

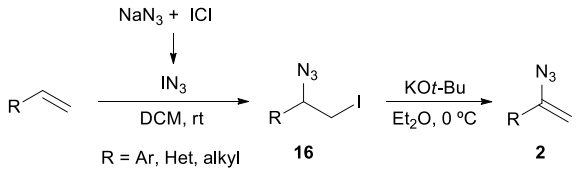
The base-induced elimination of hydrogen halides (HX) from vicinal haloazidoalkanes **15** is one of the most exploited approaches to vinyl azides.[1, 2b, 3d] Typically, 1,2-dibromides **14** (Scheme 3, easily obtained from the corresponding alkenes) are treated at room temperature with NaN_3 and a base (e.g. KO*t*-Bu),[5] or simply with excess NaN_3,[18] to afford the α-aryl vinyl azides **2** in good to excellent yields. Vicinal disulfonates are also convenient substrates, and have been employed in the preparation of α-alkynyl vinyl azides on treatment with hexadecyltributylphosphonium azide.[19] In these cases, initial azide substitution is favored at the secondary carbon atom (**14**→**15**) due to transition state stabilization. For the more challenging preparation of α-alkyl vinyl azides, the use of 1-chlorohexyl-2-tosylate precursors in place of dibromoalkanes ensures selectivity in the initial azidation step.[5]

A second classical approach to α-substituted vinyl azides is the Hassner method. First reported in 1965, this involves the



Scheme 3. Synthesis of azido vinylidenes from 1,2-dibromoalkanes.

reaction of alkenes with iodine azide (IN_3), followed by KO*t*Bu-induced elimination of HI from the resulting vicinal azidoiodoalkane **16** (Scheme 4).[2b, 16, 20] This chemistry has been applied to a range of simple (hetero)aryl- and alkyl-substituted olefins, with Markovnikov selectivity in the initial iodonium ion formation / azide ring-opening process governing regioselectivity in the formation of the α-substituted vinyl azide **2**.[2b, 20] Notably, both electronic and steric effects can influence the efficiency and regioselectivity of this alkene functionalization. As a result, moderate yields are obtained using electron-deficient aryl alkenes (e.g. 4-nitrostyrene), while the sterically hindered 3,3-dimethylbut-1-ene gave the regioisomeric terminal vinyl azide.



Scheme 4. Synthesis of azido vinylidenes *via* the Hassner protocol.

Despite the Hassner approach being widely recognized as a 'traditional' route to vinyl azides, the requirement for hazardous and highly explosive IN_3 (usually generated *in situ* from iodine chloride and NaN_3) is a serious drawback that inhibits its widespread use.[3b] IN_3 can, however, be replaced by the more stable bromine azide (BrN_3), which is generated from Br_2, HCl and NaN_3. With this reagent, different regioselectivities can be obtained by tuning the reaction conditions:[21] an ionic (Markovnikov) pathway affords the α-configured azide in polar media (in the presence of oxygen, which acts as a free radical inhibitor), whereas homolysis to an azido radical is effected on irradiation in a low polarity solvent (under an inert atmosphere), thereby affording the complementary terminal vinyl azide.

Over the last few years, a plethora of reaction conditions for generating IN_3 and BrN_3 (or their equivalents) have been developed.[22] Reagent systems such as the Sudalai halogenation ($NaIO_4$/LiBr/HOAc/NaN_3),[10d, 23] I_2/NaN_3, NXS/$TMSN_3$ (X = I, Br), $IPy_2BF_4/TMSN_3$, $PhI(OAc)_2/TMSN_3/Et_4NI$, and polymer-bound bis-azido(I)iodate have been used as azidoiodination reagents to give the Markovnikov addition products of alkenes, while *anti*-Markovnikov selectivity is afforded using NaN_3/NaI/CAN, $NaIO_4$/KI/NaN_3/AcOH, and

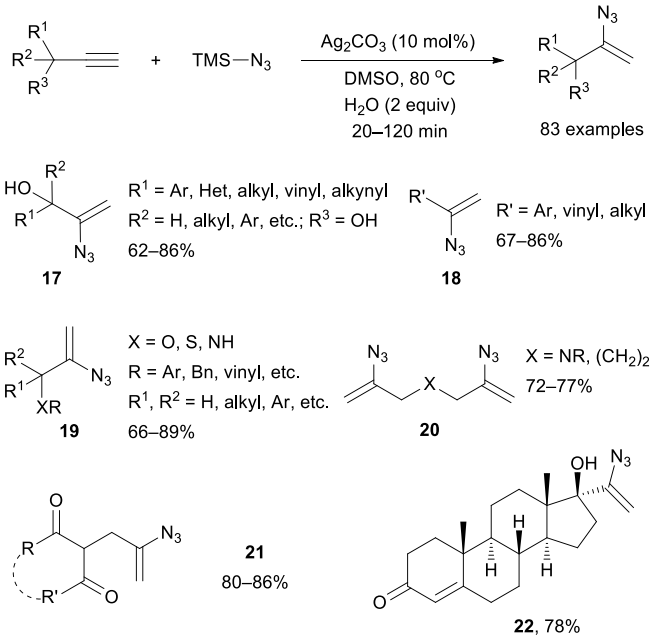
NaBr/NaN_3/oxone.[24] Notably, the polymer-bound bis-azido(I)iodate[25] is a readily available reagent that can be used to form azido vinylidenes under continuous flow conditions, thus avoiding the buildup of explosive and toxic byproducts.[26]

2.2 Hydroazidation of terminal alkynes

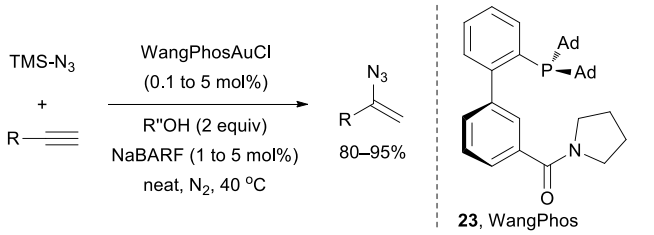
In view of the limitations of the traditional base-mediated routes to vinyl azides described above, the hydroazidation of alkynes could provide a direct, safe, and atom-economic alternative for their preparation. However, in the case of 'unactivated' alkynes (i.e., those not substituted with electron-withdrawing groups) only two preparative examples had been reported prior to 2014, namely 1-azidobut-1-en-3-yne (synthesized from reaction of butadiyne with lithium azide),[19b] and a vinyl azide intermediate isolated by Jiao and co-workers during investigations into the mechanism of nitrogenation of alkynes to nitriles (see Scheme 38).[27]

In 2014, the Bi group described a versatile, efficient and selective route for the assembly of 2-azidoallyl alcohols **17** *via* the silver-catalyzed hydroazidation of propargylic alcohols using $TMSN_3$ as the azide source, in DMSO (Scheme 5).[17c] Mechanistic studies revealed that the hydroxyl group (or water) plays an important role in stabilizing the vinyl azide product, and that a trace amount of water is required as a proton source. Hydrazoic acid (HN_3) is first formed from the silver-catalyzed reaction of $TMSN_3$ with H_2O. A silver acetylide species is then thought to be generated, which undergoes nucleophilic addition by HN_3, with protodemetallation yielding the vinyl azide.[28] The 2-azidoallyl alcohol products were further converted into useful synthons including α-carbonyl vinyl azides, and *N*-H aziridines, on treatment with pyridinium chlorochromate and K_3PO_4 respectively. Furthermore, by adding a stoichiometric amount of H_2O, the reaction was extended to simple terminal alkynes[17d] (nitriles were produced in anhydrous solvents).[27a] This latter process afforded the corresponding vinyl azides **18** in good yields, with wide substrate scope (including aryl, vinyl, and alkyl-substituted alkynes). Several other functionalized terminal alkynes, such as propargyl amines, ethers and thioethers (**19**), dialkynes (**20**), and alkynes appended to 1,3-diketones (**21**), were also efficiently converted. The method was further applied to the natural product ethisterone, which gave vinyl azide **22** in 78% yield with complete retention of the stereogenic center. Overall, this hydroazidation of alkynes offers a practical route towards new classes of vinyl azides, which are well-suited to use in further transformations.[29]

Very recently, Li and Zhang *et al.* employed a gold catalyst containing the biaryl-2-ylphosphine ligand WangPhos (**23**, Scheme 6) to synthesize vinyl azides from both unactivated terminal alkynes and internal alkynes under neat conditions.[30] The hydroazidation of terminal alkynes was realized using as little as 0.1 mol% gold catalyst at 40 °C; perhaps surprisingly, the more challenging functionalization of internal alkynes proceeded efficiently at room temperature. The 3'-amide group on ligand **23** used in this chemistry was proposed to play a significant role by acting as a general base catalyst to promote the reaction of HN_3 with the alkyne.



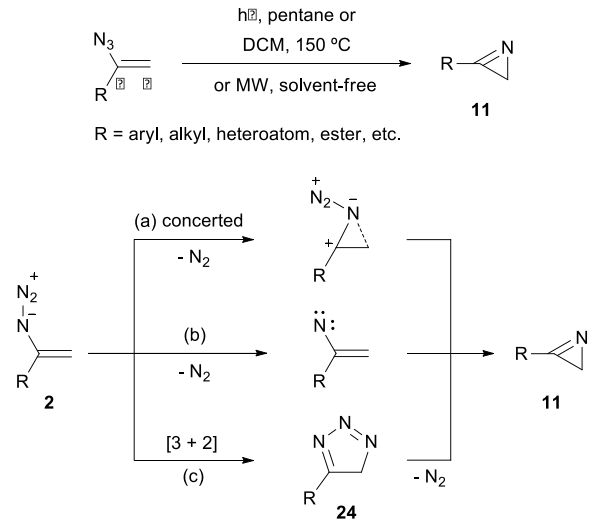
Scheme 5. Synthesis of α-substituted vinyl azides *via* hydroazidation of terminal alkynes.



Scheme 6. WangPhosAuCl-catalyzed hydroazidation of alkynes.

3. Thermolysis and photolysis of α-substituted vinyl azides

The first study of the thermolysis of vinyl azides was reported by the Smolinsky group, who studied their vapor phase pyrolysis to yield 2*H*-azirines **11** (Scheme 7); ketenimines ($RN{=}C{=}CH_2$) were obtained as a byproduct.[5] Further studies established the characteristics of the reactivity of vinyl azides (e.g. selectivity, functional group tolerance) under both thermal and photochemical conditions.[2c, 13] Their decomposition depends on several factors, including the reaction temperature and solvent, the concentration of the azide substrate, the heating time, and the electronic and steric effects of the substituents.[31] A practical method for 2*H*-azirine synthesis was thus developed by Somfai *et al.*, which involved heating a 0.1 M solution of vinyl azide in dichloromethane at 150 °C for 20 min.[32] Under these conditions, vinyl azides featuring aryl, alkyl, heteroatom, and ester substituents afforded the corresponding azirines in good to excellent yields and high purity. When the substituent at the α-position is a hydrogen atom or carbonyl (e.g., α-azidoesters and ketones), the azirine is rather unstable and usually undergoes rearrangement to a nitrile, or affords azacycles such as indoles

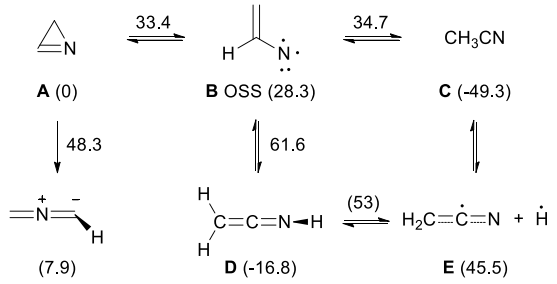


Scheme 7. Thermolysis and photolysis to 2*H*-azirines with vinyl azides.

and pyrroles.[2c, 33] Decomposition via microwave heating under solvent-free conditions has also been developed to avoid the use of low boiling solvents in a sealed tube environment.[34] 2*H*-Azirines can also be produced from vinyl azides through photochemical irradiation (λ_{max}= 350 nm),[5b, 35] and DABCO-catalyzed decomposition in toluene at 110 °C.[36]

Investigation of the reaction pathways involved in the thermal and photochemical decomposition of vinyl azides remains ongoing.[13a, 13c, 37] A concerted mechanism (Scheme 7, Path a)[38] has been proposed by L'abbé and Mathys to be energetically plausible,[39] whereas a pathway involving a singlet vinylnitrene (which can undergo symmetry-allowed electrocyclic ring closure, Scheme 7, Path b) was found to be of higher energy.[13b, 13c] Alternatively, a mechanism for the formation of 2*H*-azirines involving a tandem intramolecular [3 + 2] cyclization to a triazole intermediate (**24**, Scheme 7, Path c), followed by rearrangement and cycloreversion, is also considered energetically reasonable.[37c, 39b, 40]

CASPT2 calculations (Scheme 8) show the thermodynamic relationships between 1-azirine **A**, vinylnitrene **B**, acetonitrile **C**, and ketenimine **D**, with the thermal ring opening of **A** to the lowest singlet state open-shell singlet (OSS) vinylnitrene **B** having an activation barrier of ca. 33 kcal/mol.[41] Under flash vacuum pyrolysis conditions, ketenimine **D** can also plausibly afford the 1,3-H shift product acetonitrile **C** *via* radical pair **E**.



Scheme 8. CASPT2 calculated energies based on CASSCF(6,5) 2σ + 3π Geometries for ground and transition states in thermal reactions of 2*H*-azirine and OSS vinylnitrene (energies in kcal/mol relative to azirine).

Aside from classical UV irradiation, exposure of vinyl azides to visible light in the presence of a photoactivator ($Ru(dtbbpy)_3^{2+}$, $[Ir(dF(CF_3)ppy)_2(dtbbpy)]^+$, or organic dyes) offers a clean and selective approach to 2*H*-azirines, and generally results in good selectivity in further same-pot transformations.[42] In these cases, α-azidoesters / ketones are proposed to convert to triplet vinylnitrenes, which slowly rearrange to the corresponding 2*H*-azirines. Photocascade catalysis involving energy transfer and photoredox reactions has also been applied to vinyl azides,[42a] as exemplified by cycloadditions with dipolarophiles such as activated alkynes and aldehydes, giving pyrroles and oxazoles respectively.[43]

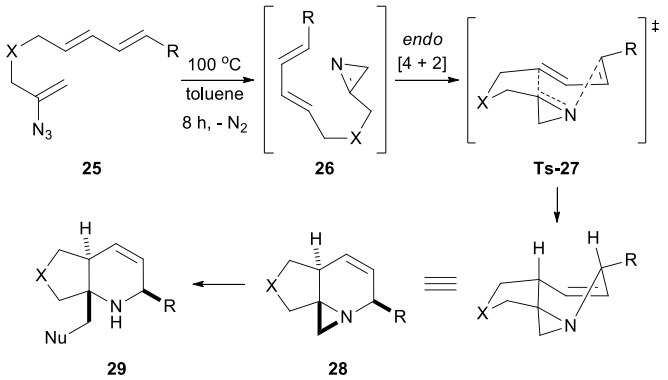
4. Applications of α-substituted vinyl azides

4.1 α-Substituted vinyl azides as 2*H*-azirine and vinylnitrene precursors

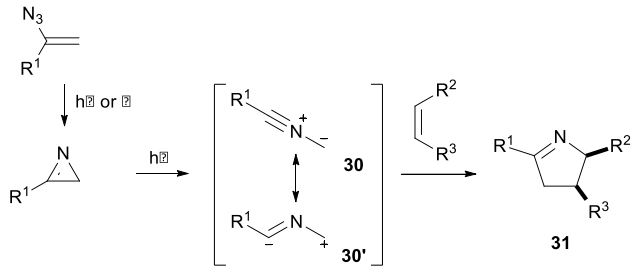
As described above, 2*H*-azirines can be generated thermally from vinyl azides, and used *in situ*. Indeed, this highly strained three-membered ring is well-recognized as a versatile reactive intermediate in organic synthesis.[14] As will be discussed, the C=N bond of the azirine has been shown to react with nucleophiles and electrophiles, and to participate in cycloadditions as a two-atom building block.

In the latter context, Shen and Xu *et al.* recently developed the first intramolecular aza-Diels–Alder reaction of a 2*H*-azirine with a non-activated diene (Scheme 9),[29d] which offers a practical and stereoselective route to *trans*-n,6,3 tricycles (n = 5-7) containing a fused aziridine ring (**28**). In this process, vinyl azide **25** decomposes to 2*H*-azirine **26**, which undergoes rapid cycloaddition with the pendent diene *via endo* transition state **Ts-27**, giving exclusive *trans* selectivity in product **28**. The aziridine in **28** underwent ring-opening reactions with various nucleophiles to yield tetrahydropyridines **29**. This chemistry contrasts with the more limited intermolecular aza-Diels–Alder reaction of 2*H*-azirines to give 1-azabicyclo[4.1.0]hept-3-ene frameworks, which requires activated dienes or azirines, and gives only modest yields and stereoselectivity.[44]

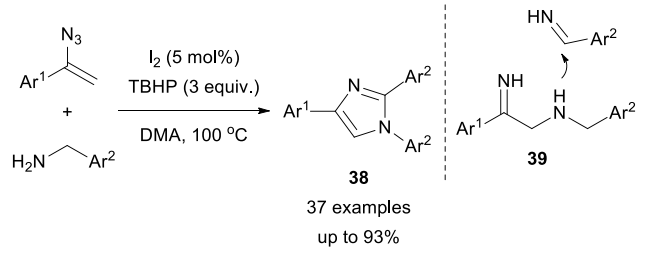
2*H*-azirines have also been widely employed as three-atom synthons (C–C–N or C–N–C) in the synthesis of *N*-containing heterocycles such as pyrroles, indoles, isoquinolines, and



Scheme 9. Stereoselective synthesis of polycycles *via* intramolecular aza-Diels-Alder cycloaddition with unactivated dienes.



Scheme 10. UV-induced [3 + 2]-cycloadditions of vinyl azides with alkenes.



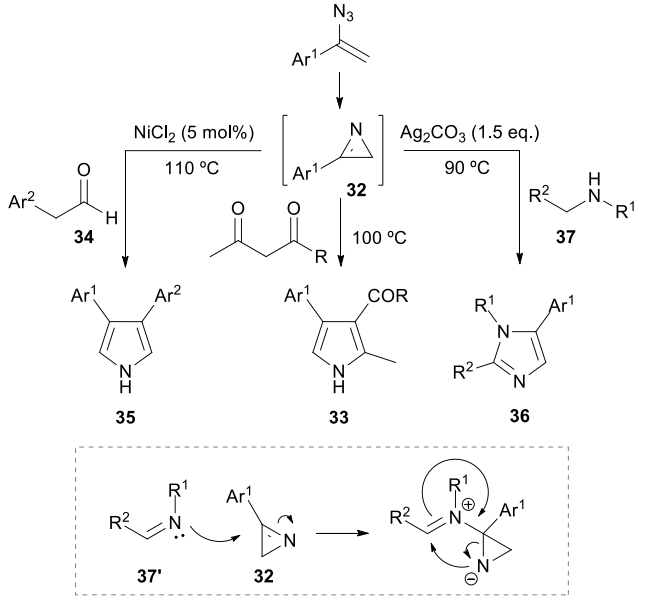
Scheme 12. Oxidative cyclization of vinyl azides with amines in the synthesis of imidazoles.

imidazoles.[14] Under UV irradiation (λ = 190–600 nm), vinyl azide decomposition and ring-opening of the resulting 2*H*-azirine yields an intermediate 1,3-dipole **30** (or **30'**, Scheme 10),[45] which can undergo [3+2]-cycloaddition with unsaturated compounds. For instance, reaction with electron-deficient alkenes results in 3,4-dihydro-2*H*-pyrroles **31**, a process that was carried out under continuous flow conditions.[26b]

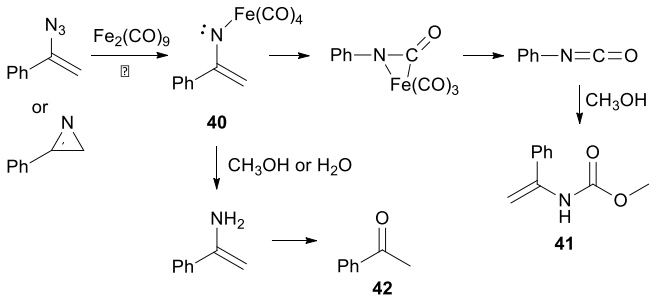
Nucleophilic ring-opening of 2*H*-azirines **32** occurs readily under either thermal or metal-catalyzed conditions (Scheme 11). Nucleophiles such as enolates derived from 1,3-dicarbonyls[46] or aryl acetaldehydes (**34**),[47] and secondary amines **37**,[48] were reacted with vinyl azides to access pyrroles (**33**, **35**) and imidazoles **36**. These reactions all proceed via initial attack at the C=N bond of the azirine, followed by fragmentation of the resulting aziridine; the inset shows this reaction between imine **37'** (formed *in situ* from secondary amine **37**), in the synthesis of imidazole **36**.[3a]

Regioisomeric imidazoles **38** were obtained in moderate to good yields from the oxidative cyclization of aryl-substituted vinyl azides and benzylamines (Scheme 12).[49] The azirine arising from the decomposition of the vinyl azide undergoes nucleophilic attack by benzylamine at the 2-position to yield imine **39**, which in turn reacts with the imine generated *in situ* by I_2/TBHT-mediated oxidation of benzylamine, delivering imidazole **38** following cyclization and expulsion of ammonia.

An iron-vinyl nitrenoid complex **40** has been employed for the synthesis of carbamate **41**, *via* reaction of either a 2*H*-azirine or vinyl azide with $Fe_2(CO)_9$ in methanol (Scheme 13). Carbonyl insertion into the nitrenoid gives an isocyanate intermediate, which on addition of methanol gives the carbamate **41**.[50] Ketone **42** was obtained as a byproduct from **40** by Neber rearrangement.[35a, 51]

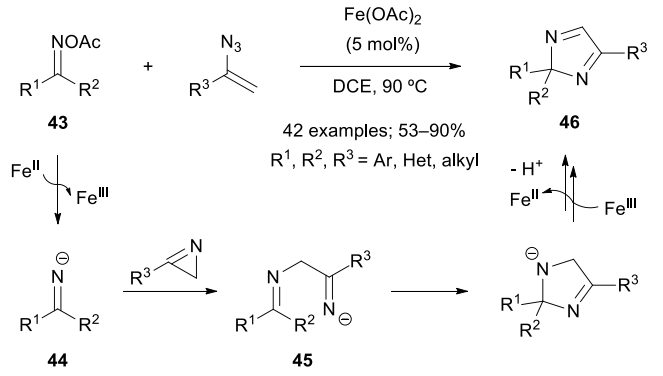


Scheme 11. Nucleophile-induced ring-opening of 2*H*-azirines.

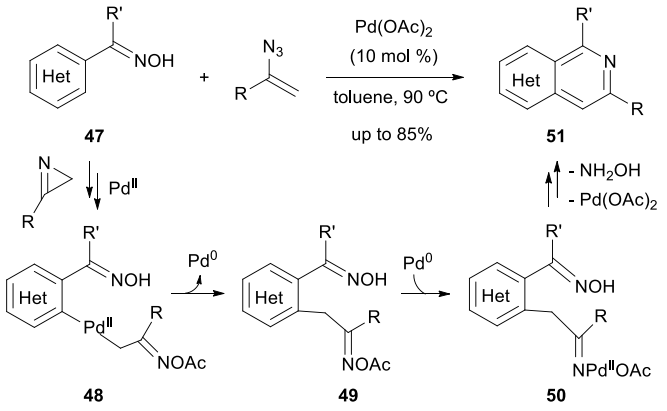


Scheme 13. Carbonyl insertion and reduction of vinyl azides for the synthesis of carbamates and ketones.

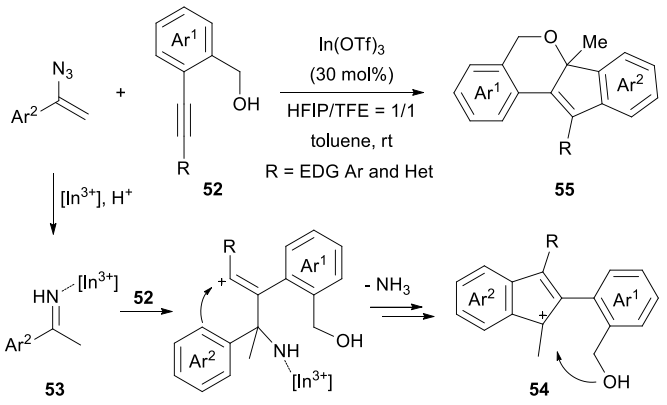
An iron(II)-catalyzed [3+2] annulation of oxime acetates **43** and vinyl azides has been developed for the synthesis of a wide range of 2,2,5-trisubstituted 2*H*-imidazoles **46** (Scheme 14).[52] Imine anion **44**, generated from **43** by Fe-mediated reduction, coupled with the 2*H*-azirine by C2–N ring opening to give intermediate **45**. This underwent cyclization / electron transfer to Fe(III), which on deprotonation afforded product **46**. A mechanism involving Michael addition of **44** to the parent vinyl azide, followed by N_2 elimination, was also proposed.



Scheme 14. $Fe(OAc)_2$-catalyzed [3 + 2] annulation of oxime acetates with azido vinylidenes.



Scheme 15. $Pd(OAc)_2$-catalyzed C–H functionalization of aryloximes for the synthesis of isoquinolines.

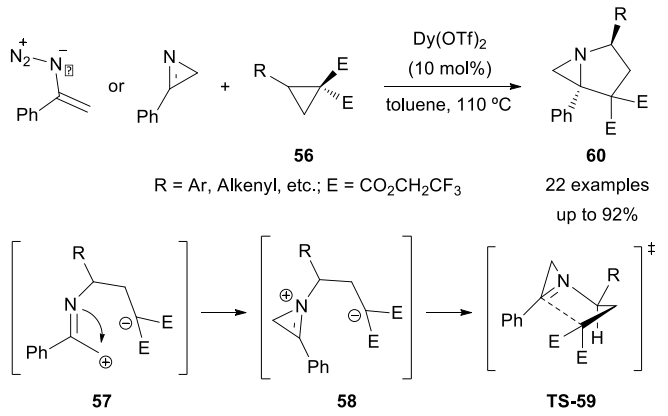


Scheme 16. $In(OTf)_3$-catalyzed tandem polycyclization of internal alkynols and α-aryl vinyl azides.

Substituted isoquinolines **51** have been prepared through the Pd(II)-catalyzed coupling of vinyl azides with oximes **47** (Scheme 15).[53] In this process, the oxime is proposed to act as an internal directing group for *ortho* C–H activation by the Pd(II) catalyst. The resulting palladacycle (not shown) can undergo migratory insertion with the 2*H*-azirine to give intermediate **48**,[54] which on reductive elimination gives oxime acetate **49**. Oxidative addition of Pd(0) into the N–OAc bond then provides intermediate **50**; cyclization of the latter yields isoquinoline **51** with release of hydroxylamine and the Pd(II) catalyst.

Vinyl azides have been used as *N*-unsubstituted imine precursors in the synthesis of pyranyl indeno[1,2-*c*]isochromenes **55** (Scheme 16).[55] In the presence of $In(OTf)_3$ catalyst, the vinyl azide is first proposed to be converted to the indium-activated imine **53**, which in turn reacts with the electron-rich alkyne of **52** via a stepwise formal [3+2] cycloaddition. The subsequent elimination of NH_3 and S_N1-type substitution of the resulting intermediate **54** results in product **55**. The use of a moderately acidic media (TFE:HFIP = 1:1) was vital for efficient reaction, as was the presence of electron-dontating aryl or heteroaryl substituent (R) on the alkyne.

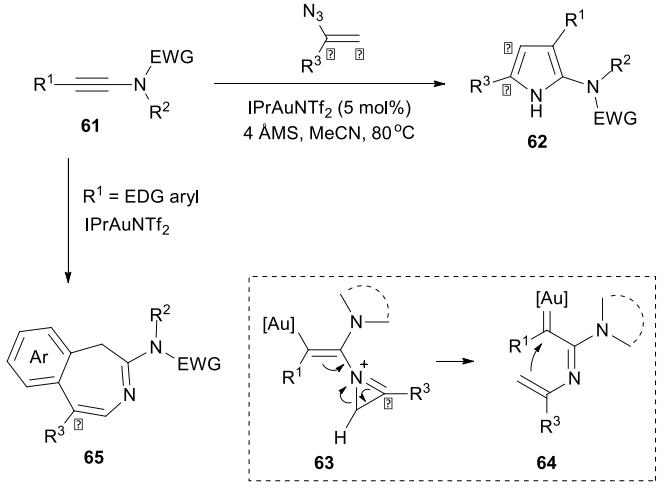
A thermally induced, $Dy(OTf)_2$-catalyzed annulation of donor/acceptor cyclopropanes **56** with vinylnitrenes has been



Scheme 17. Annulation reactions of donor/acceptor cyclopropanes with α-azidostyrene or 3-phenyl-2*H*-azirine.

developed which delivers unusual 1-azabicyclo[3.1.0]hexane scaffolds **60** with excellent diastereoselectivity (Scheme 17).[56] Both α-azidostyrene and 3-phenyl-2*H*-azirine could be used as reaction substrates, but showed different reactivity. Mechanistically, a vinyl nitrene intermediate is proposed to arise from vinyl azide decomposition, which may effect cyclopropane ring opening to give iminium ion **57**; this cyclizes to zwitterionic species **58**, which in turn undergoes Mannich-style ring closure *via* transition state **TS-59** to yield product **60**. A pathway involving S_N2 attack by the N_α atom of the vinyl azide on the activated cyclopropane, followed by cyclization to **58** with loss of dinitrogen, was also proposed.

Gold-catalyzed formal cycloadditions of ynamides with vinyl azides[57] (or, 2*H*-azirines[58]) have recently been reported (Scheme 18). These occur with tunable regioselectivity, which is highly dependent on the catalyst, the substituent of the 2*H*-azirine precursor, and the ynamide. For example, reaction of ynamides **61** with vinyl azides affords pyrroles **62**,[57-58] where the azirinium ion **63** (formed by addition of the 2*H*-azirine to the gold-activated ynamide) is proposed to undergo either direct attack by the tethered alkene, or to produce an α-imino gold carbenoid **64**, which then cyclizes to **62**. However, for ynamides bearing an electron-rich aromatic group, an

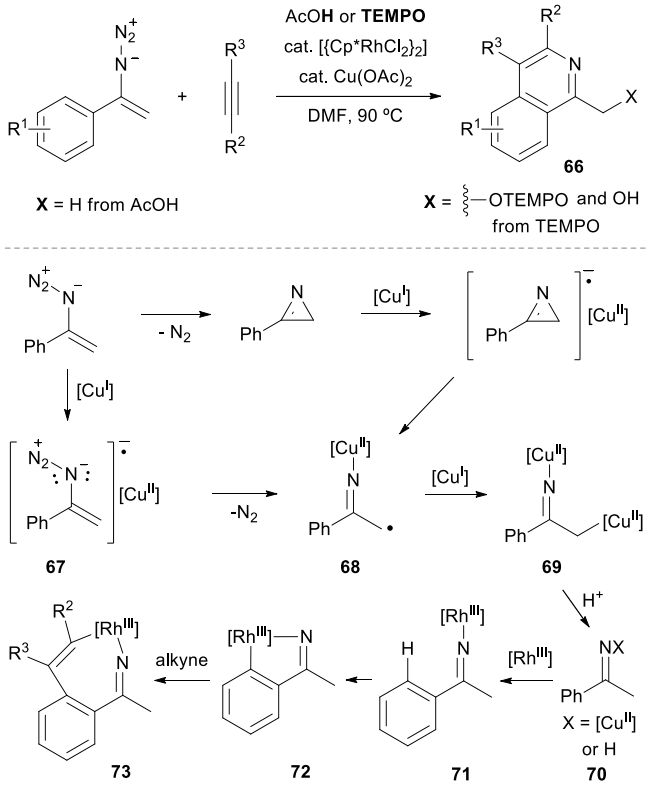


Scheme 18. [3+2] and [4+3] cycloadditions of 2*H*-azirines/vinyl azides with ynamides.

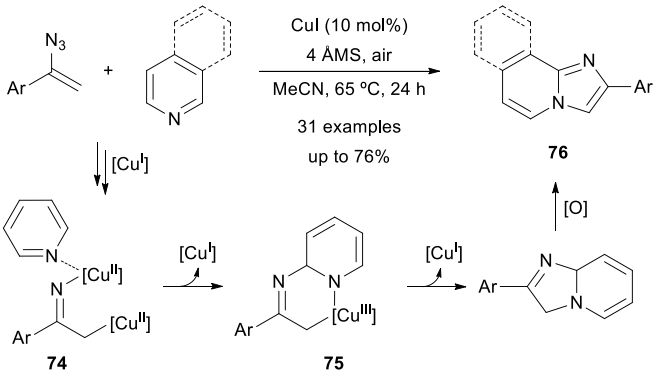
alternative [4+3] process occurs under gold-NHC catalysis to afford 1*H*-benzo[*d*]azepines **65**,[57a] possibly via attack of the phenyl (R^1) substituent of the ynamide at the C_α-position of the azirinium ion.

4.2. α-Substituted vinyl azides as a source of metal enaminyl radicals

The denitrogenative decomposition of vinyl azides in the presence of transition metal complexes was first investigated by Chiba and co-workers, in a cooperative Rh/Cu-catalyzed coupling of α-aryl vinyl azides with alkynes to form substituted isoquinolines **66** (Scheme 19).[11] The key intermediate Cu(II)-enaminyl radical **68** was proposed to be obtained either via reductive N−C2 bond cleavage of the thermally generated 2*H*-azirine, or by direct SET to the vinyl azide followed by release of N_2 from the resulting radical anion **67**. Iminyl metal species **69** was then produced from **68** by further SET from Cu(I). In this context of isoquinoline formation, an iminyl-Rh(III) species **71** was then generated by protonation of **69**, and complexation of the imine to Rh(III). This promotes C–H activation to give rhodacycle **72**, and sequential insertion of the alkyne to form intermediate **73**, reductive elimination of which results in isoquinoline **66** (with generation of Rh(I)). Finally, a redox reaction between Rh(I) and Cu(II) regenerates the required Rh(III) and Cu(I) catalysts. The formation of copper enaminyl radicals under IPrCuCl catalysis has also been reported, followed by a formal [3+2]-annulation with tetramic acids.[59]



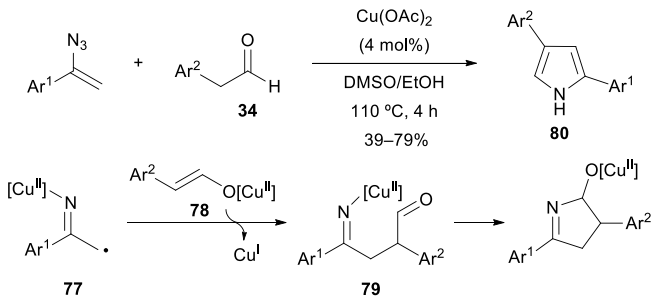
Scheme 19. Synthesis of isoquinolines by Rh–Cu bimetallic cooperation *via* Cu(II)-iminyl radical species.



Scheme 20. CuI-catalyzed C–H functionalization to imidazo[1,2-*a*]pyridines and 2-arylimidazo[2,1-*a*]isoquinolines.

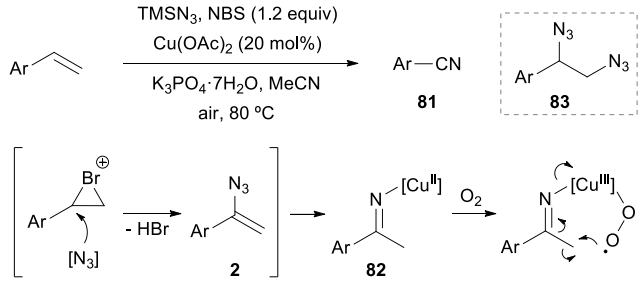
An iminyl copper(II) species **74** has similarly been suggested in the CuI-promoted coupling of pyridines and isoquinolines with vinyl azides to afford imidazo[1,2-*a*]pyridines and 2-arylimidazo[2,1-*a*]isoquinolines **76** (Scheme 20).[60] Cyclization of **74** is suggested to provide Cu(III) complex **75**, with elimination of Cu(I); sequential reductive elimination of **75**, and aerobic oxidation results in the observed heterocycle **76**.

The conversion of vinyl azides to copper(II) enaminyl radicals has further been exploited by Jiao *et al.* for the preparation of 2,4-disubstituted pyrroles **80** (Scheme 21).[47] In the presence of the copper catalyst, it is proposed that aryl acetaldehyde **34** forms the corresponding copper enolate **78**, which in turn reacts with the copper(II) enaminyl radical **77** to give intermediate **79**, with release of Cu(I). Cyclization and dehydration affords product **80**. $NiCl_2$ could also be employed as catalyst, for which an ionic pathway was proposed rather than a radical-based mechanism (see Scheme 11).



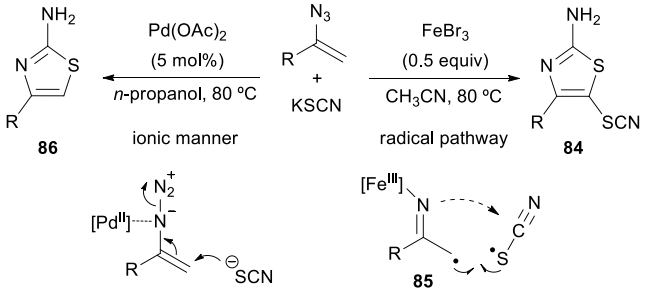
Scheme 21. 2,4-Disubsituted pyrrole synthesis under $Cu(OAc)_2$ catalysis.

Iminylcopper(II) intermediates have also been exploited in an NBS-mediated synthesis of nitriles **81** from aryl alkenes (Scheme 22).[61] BrN_3, generated *in situ* from $TMSN_3$ and NBS, furnishes the expected Markovinkov vinyl azide **2**, which is in turn converted to the Cu(II)-imine **82**. Under aerobic conditions, nitriles are formed through carbon–carbon bond cleavage of **82**, potentially via oxygen association to the copper catalyst. For substrates bearing electron-deficient aromatic rings, the formation of diazides **83** is instead favored due to the efficiency of substitution with a second azide nucleophile compared to the rate of elimination of HBr, which is compounded by poor regioselectivity in the bromoazidation.



Scheme 22. Copper-catalyzed oxidative C–C bond cleavage for the synthesis of nitriles.

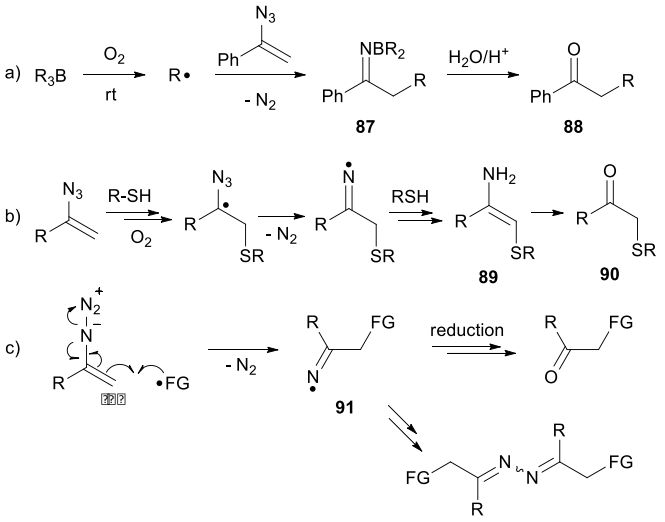
The formation of complementary thiazole products from the treatment of α-aryl vinyl azides with potassium thiocyanate, catalyzed by Fe(III) salts or $Pd(OAc)_2$, is likely explained by competition between radical and ionic pathways respectively (Scheme 23).[62] Under Fe(III) catalysis, a thiocyanate radical (·SCN) is generated by one-electron oxidation of the thiocyanate anion by Fe(III). In the presence of the reduced iron(II) species, the vinyl azide is in turn converted to enaminyl iron(III) radical **85**, which on coupling with ·SCN and cyclization yields the 2-aminothiazole scaffold. Further addition of a thiocyanate radical to this thiazole, followed by single electron oxidation and dehydrogenation, affords the final observed 4-substituted 5-thiocyano-2-aminothiazole **84**. In contrast, using 5 mol% $Pd(OAc)_2$ as catalyst, an ionic route is envisaged *via* an S_N2'-type reaction of the thiocyanate ion (with loss of molecular nitrogen); cyclization of the resulting imine affords product **86**.



Scheme 23. Synthesis of 4-substituted (5-thiocyano)-2-aminothiazoles with α-aryl vinyl azides.

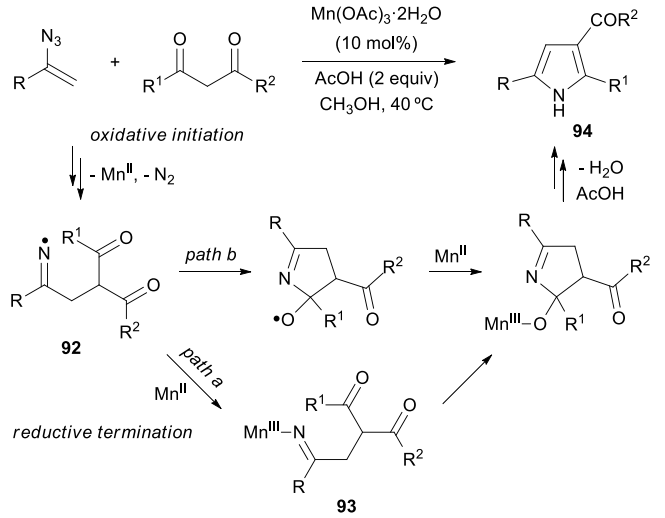
4.3 α-Substituted vinyl azides as radical acceptors

The use of vinyl azides as radical acceptors can be traced back to seminal contributions by the Suzuki group in 1975.[10a] Alkyl radicals, generated by S_H2 reaction of the corresponding trialkylborane under aerobic conditions, reacted with α-azidostyrene at room temperature in THF (with loss of nitrogen) to afford iminoborane **87**, which in turn gave butyrophenone **88** after hydrolysis (Scheme 24a).[10a, 10c] Heteroatom radicals (thiyls) were applied to further exploit this reactivity of vinyl azides, leading to sulfanylated enamines **89**, and the corresponding hydrolyzed β-keto sulfides **90** (Scheme 24b).[10b] Indeed, iminyl radicals **91** formed from addition of carbon- or heteroatom-centered radicals to the C=C bond of the vinyl azide can follow many different reaction paths, such as H-atom abstraction, dimerization, and cyclization processes, depending on the reaction conditions and substrate (Scheme 24c). The vinyl azide thus offers an attractive entry to iminyl radicals, where classical approaches can suffer from harsh conditions, challenging substrate syntheses, or reliance on toxic organotin reagents.[63]

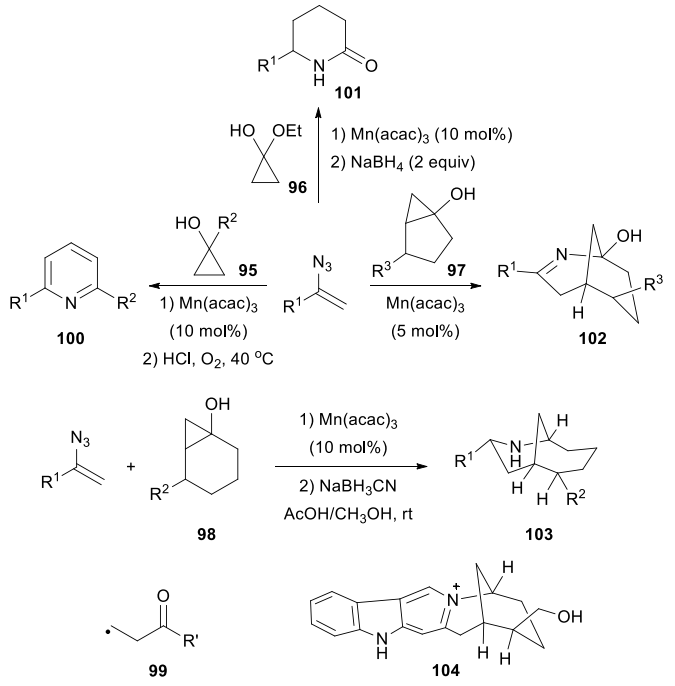


Scheme 24. Generation of iminyl radicals with vinyl azides and the further conversions.

Carbon-centered radicals can be generated under mild conditions through Mn(III) catalysis, an approach that has been extensively developed by Chiba and Narasaka. For example, a Mn(III)-catalyzed synthesis of substituted pyrroles **94** from vinyl azides and 1,3-dicarbonyl derivatives (as the carbon-centered radical precursor) has been developed, which plausibly involves a redox-netural Mn(III)/Mn(II) cycle (Scheme 25).[10d] Two key electron transfer steps are proposed: (1) oxidative generation of the carbon-centered radical from the dicarbonyl by Mn(III)→Mn(II) (oxidative initiation), which is followed by addition of the radical to the vinyl azide to generate iminyl radical **92**; (2) reduction of **92** by Mn(II) to



Scheme 25. Mn(III)-catalyzed synthesis of pyrroles from azido vinylidenes and 1,3-dicarbonyls.



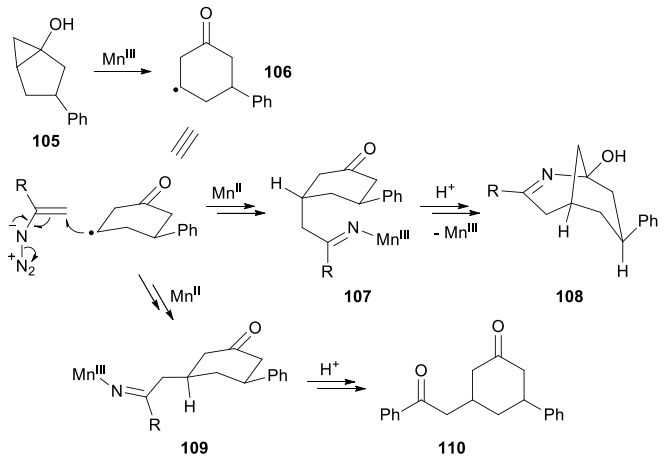
Scheme 26. Mn(III)-catalyzed formal [3+3]-annulation of vinyl azides with cyclopropanols to azaheterocycles.

form manganese(III) imine **93** (Path a), which on cyclization affords the observed *N*-heterocycle (and regenerates the Mn(III) oxidant, reductive termination). An alternative path involving cyclization of the *N*-radical **92**, followed by reduction by Mn(III) was also proposed (Path b).

Manganese(III) catalysis has been used in a number of other settings for example, α-phosphorus-substituted vinyl azides (generated from P-substituted allenes with $TMSN_3$ in DMF) have been reacted with 1,3-dicarbonyls to yield pyrroles under photochemical conditions.[64] A related decarboxylative coupling of β-keto acids and vinyl azides has also been reported: decarboxylation is occurs in the course of forming the iminyl radical, followed by cyclization to a pyrrole through a similar path to that shown in Scheme 25.[10e] Similarly, substituted 1-*H*-pyrroles were prepared in high yields *via* the Cu(II)-promoted coupling of vinyl azides with α-keto radicals, formed *in situ* from α-arylketones.[65]

An impressive approach to the synthesis of azaheterocycles employs cyclopropanol derivatives as carbon-centered radical precursors, through oxidative ring-opening (Scheme 26).[66] Again under Mn(III) catalysis, pyridines **100** and δ-lactams **101** were obtained from vinyl azides using cyclopropanols **95** and **96**, respectively. The β-carbonyl radical **99**, formed via oxidative fragmentation on reaction with Mn(III), adds to the vinyl azide to yield the iminyl radical. Reduction to the imine by Mn(II) is followed by cyclization onto the ketone; subsequent exposure to oxygen triggers aromatization, and results in pyridine **100** – overall a formal [3+3] annulation. Under similar aerobic conditions, bicyclic substrates **97** and **98** furnished 2-azabicyclo[3.3.1]non-2-en-1-ol (**102**) and 2-azabicyclo[4.3.1]decane (**103**) frameworks respectively, the latter via reduction of the initially formed imine. This radical [3+3] annulation strategy was applied to the synthesis of quaternary indole alkaloids featuring the 2-azabicyclo [3.3.1]nonane moiety, such as melinonine E (**104**).

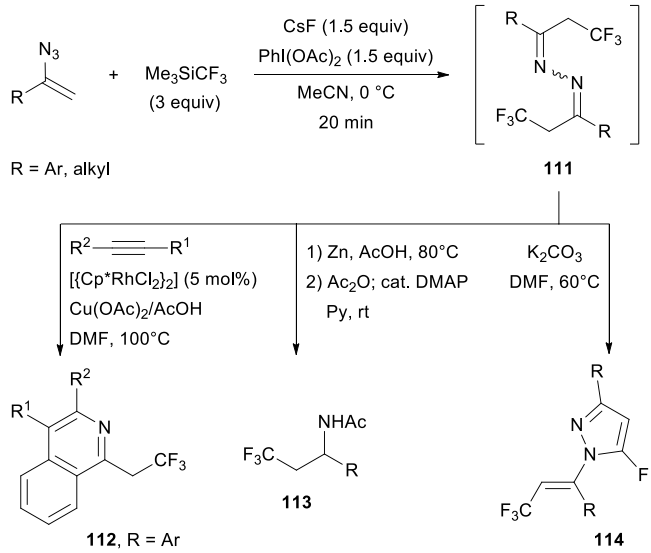
The stereocontrol observed in the synthesis of products such as **102** and **103** was further explored using compound **105** (Scheme 27).[66b] As before, the reaction initiates by oxidative fragmentation of the cyclopropane to the β-keto radical **106**, which undergoes addition to the vinyl azide. Following reduction by Mn(II), this gives rise to two diastereomers of the manganese imine (**107** and **109**), only the former of which can undergo cyclization to the bicyclic product **108**. Byproduct ketone **110** is instead observed following hydrolysis of manganese imine **109**; presumably, 1,3-diaxial interactions in the conformation of **109** required for cyclization disfavor this process. Similarly, substituted 1-*H*-pyrroles were prepared in high yields *via* the Cu(II) promoted coupling of vinyl azides with α-keto radicals, formed *in situ* from α-arylketones.[65]



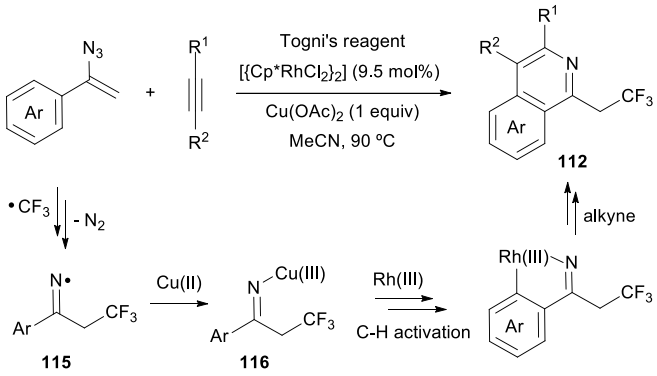
Scheme 27. Mechanism of formal [3+3]-annulation of vinyl azides with bicyclic cyclopropanols.

In 2014, Chiba and co-workers described the use of vinyl azides as efficient CF_3 radical acceptors, thus serving as precursors to various trifluoromethylated products, including *N*-heterocycles (Scheme 28).[67] The presence of CsF (1.5 equiv.) was essential in order to form a silicate complex with Me_3SiCF_3, which was susceptible to $PhI(OAc)_2$ oxidation to generate CF_3 radical. Following addition to the vinyl azide, the resulting iminyl radical underwent dimerization to afford azines **111**, which were in turn converted to a range of trifluoromethylated products, such as trifluoroethyl isoquinolines **112**, β-trifluoromethyl amines **113**, 5-fluoropyrazoles **114**, and their corresponding hydrolysis products (α-trifluoromethyl ketones). In the case of isoquinolines **112**, the nitrogen atom of **111** may function as an intramolecular directing group to facilitate Rh(III)-catalyzed aromatic C–H activation / alkenylation with internal alkynes.

Following this, an improved three component coupling for the preparation of trifluoroethyl isoquinolines **112** was achieved using Togni's reagent as the CF_3 precursor (Scheme 29).[68] The vinyl azide was first converted to iminyl radical **115**, which was in turn reduced by Cu(II) to iminyl-Cu(III) species



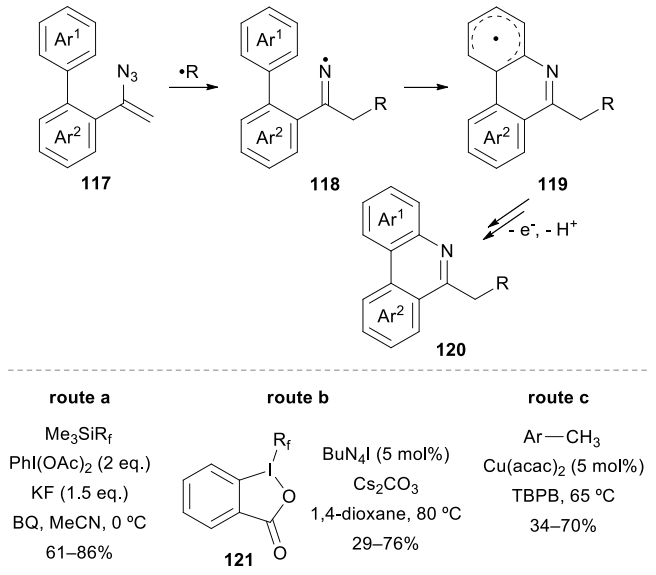
Scheme 28. $PhI(OAc)_2$-mediated radical trifluoromethylation of vinyl azides with $TMSCF_3$.



Scheme 29. Three component synthesis of trifluoroethyl isoquinolines.

116. Transmetallation to Rh(III), C–H insertion, and alkyne insertion furnished the isoquinoline core **112**.[11]

When using α-(biaryl-2-yl)vinyl azides **117** as the substrate (Scheme 30), capture of the intermediate iminyl radical **118** by the aromatic ring took place faster than dimerization, to generate radical **119**.[69] This in turn was converted to the corresponding carbocation *via* single-electron oxidation followed by the loss of H^+, affording the phenanthridine framework **120**. Using this tandem radical addition / arene functionalization strategy, various polyfluoroalkylated azapolycyclic aromatics were provided in 61–86% yields (R_f = CF_3, C_2F_5, C_3F_7, Route a).[70] Fluoroalkyl radicals could also be generated from Togni's reagent **121** in the presence of Bu_4NI (5 mol%) as an electron transfer initiator, and a stoichiometric amount of Cs_2CO_3 (Route b).[71] Thirdly (Route c), in the presence of a catalytic amount of $Cu(acac)_2$ and *tert*-butyl peroxybenzoate (TBPB) as oxidant, benzylic and cycloalkyl C(sp^3)–H bonds were activated to carbon-centered radicals, which reacted with **117** to form substituted phenanthridines through an analogous mechanism.[72] Extension to 2-azido-*N*-arylacrylamides afforded 3-trifluoromethyl substituted quinoxalin-2(1*H*)-ones in moderate yields on treatment with



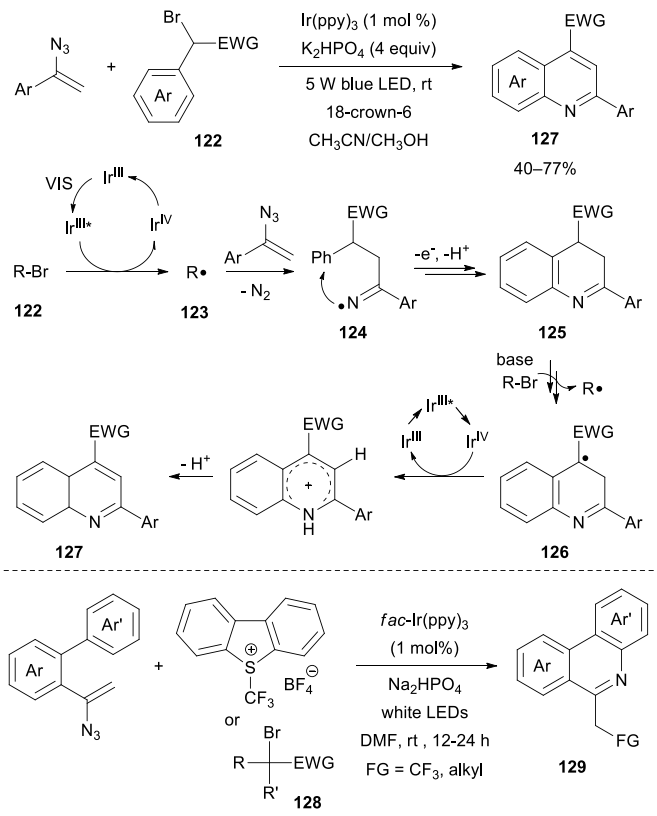
Scheme 30. Synthesis of functionalized aza-polycyclic aromatics from α-(biaryl-2-yl)vinyl azides.

Togni's reagent under CuI catalysis;[73] the alternative use of Bu_4NI (5 mol%) as catalyst led to low yields.[71]

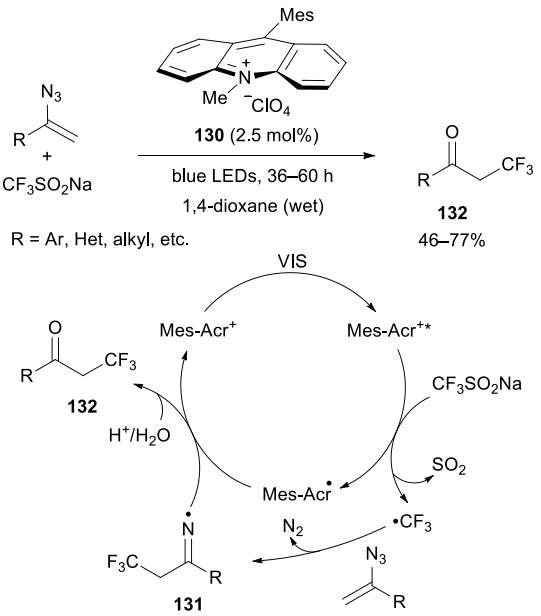
The development of visible light photoredox catalysis using transition metals has made the generation of electrophilic carbon-centered radicals possible under very mild conditions.[74] As shown in Scheme 31, oxidative quenching of the photoexcited triplet $Ir^{III}(ppy)_3$* to $Ir^{IV}(ppy)_3$ by α-carbonyl benzylbromide **122** affords the carbon-centered radical **123**.[75] Addition of this radical to the vinyl azide with expulsion of dinitrogen gives iminyl radical **124**, which in turn cyclizes onto the pendent arene to afford the dihydroquinoline core **125** (*via* SET to the $Ir^{IV}(ppy)_3$ complex to reform the Ir(III) catalyst, and deprotonation). **125** was further oxidized to the quinoline **127** through a second photocatalytic cycle, which probably involves formation of a new α-carbonyl radical **126** from **125**. A related cyclization to form 6-(fluoro)alkylated phenanthridines **129** has also been reported, where biaryl vinyl azides react with electron-deficient alkyl bromides, or Umemoto's reagent **128**, through photoredox coupling using *fac*-$Ir(ppy)_3$ as catalyst.[76]

Quin *et al.* exploited the organic photoredox catalyst *N*-methyl-9-mesityl acridinium perchlorate (**130**, Scheme 32) for the generation of trifluoromethyl radicals from the Langlois reagent (CF_3SO_2Na).[77] The oxidation of CF_3SO_2Na by activated Mes-Acr^+*, followed by loss of SO_2, affords the $CF_3^•$ radical which reacts with the vinyl azide to give iminyl radical **131**. Reduction of **131** by Mes-$Acr^•$ reforms the photocatalyst, while hydrolysis of the resulting imine affords the α-trifluoromethyl ketones **132** in good yields. Importantly, this process avoids the need for stoichiometric amounts of the strong oxidant $PhI(OAc)_2$, which can cause functional group limitations.[67]

More recently, Nevado and co-workers reported an innovative silver(I)-promoted diastereoselective synthesis of cyclic ketones **134**, initiated by the oxidative decarboxylation of a range of aliphatic carboxylic acids, including *N*-protected amino acids (**133**, Scheme 33).[29a] The iminyl radical **135**,

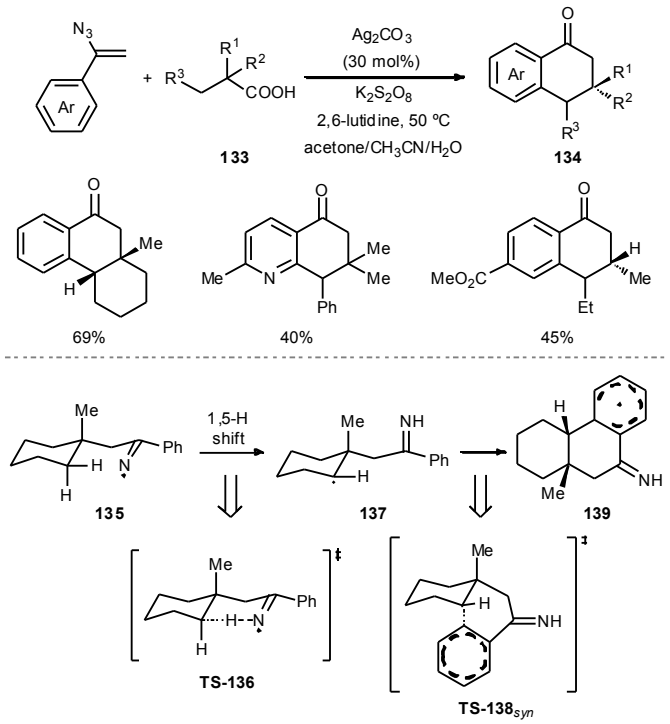


Scheme 31. Photoredox approaches for the synthesis of substituted quinolines and phenanthridines.



Scheme 32. Photoredox-catalyzed synthesis of α-trifluoromethylated ketones.

generated by trapping of the initially formed alkyl radical with the vinyl azide, is proposed to perform an intramolecular 1,5-hydrogen atom transfer to give radical **137**, which in turn undergoes addition to the arene (**139**), and finally hydrolysis to afford the cyclic ketone **134**. On the basis of DFT calculations, the 1,5-H shift of the secondary aliphatic C–H bond (**135**→**137**)

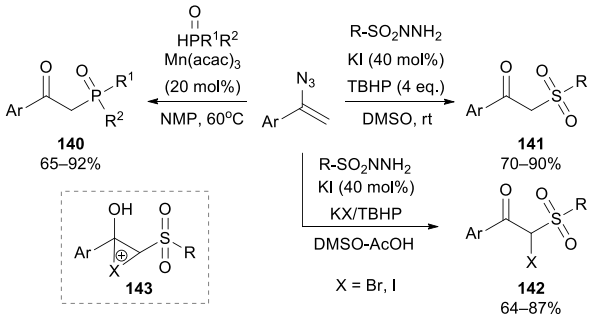


Scheme 33. Diastereoselective synthesis of elaborated ketones from aliphatic tertiary acids.

was found to be the rate-determining step (*via* transition state **TS-136**). However, the diastereoselectivity for the reaction was proposed to depend on the subsequent cyclization (**137**→**139**), with **TS-138**$_{syn}$ lower in energy than the equivalent **TS-138**$_{anti}$ due to the avoidance of unfavorable steric interactions between the axial methyl group and the arene-bearing sidechain. This reaction has been applied to the synthesis of bioactive molecules, as well as to the late-stage functionalization of natural products.

As hinted above (see Schme 24), early investigations on the addition of heteroatom radicals to vinyl azides by Montevecchi *et al.*[10b] had focused on the thiyl radical, albeit the reaction scope was limited and suffered from side reactions. However, the principle of iminyl radical formation–reduction–hydrolysis to ketones is clearly a versatile one, and progress in radical heteroatom formation has recently enabled a radical phosphorylation of vinyl azides under $Mn(acac)_3$ catalysis, which delivers β-keto phosphine oxides **140** in good yields (Scheme 34).[78] In a similar vein, sulfonyl hydrazines have been shown to be a valuable source of sulfonyl radicals in the KI/*tert*-butyl hydroperoxide-mediated oxidative coupling with vinyl azides (Scheme 34).[79] Further reaction of the resulting β-keto sulfones **141** with the corresponding potassium halide under acidic conditions affords α-halo-β-keto sulfones **142**, through putative intermediates **143**.

Very recently, a convenient and functional-group tolerant silver(I)-catalyzed aminosulfonylation reaction has been developed by our group, using readily available terminal alkynes, $TMSN_3$ as an ammonia source, and sodium sulfinates as a sulfonyl source (Scheme 35a).[80] This three-component



Scheme 34. Oxidative coupling for the synthesis of β-functionalized ketones.

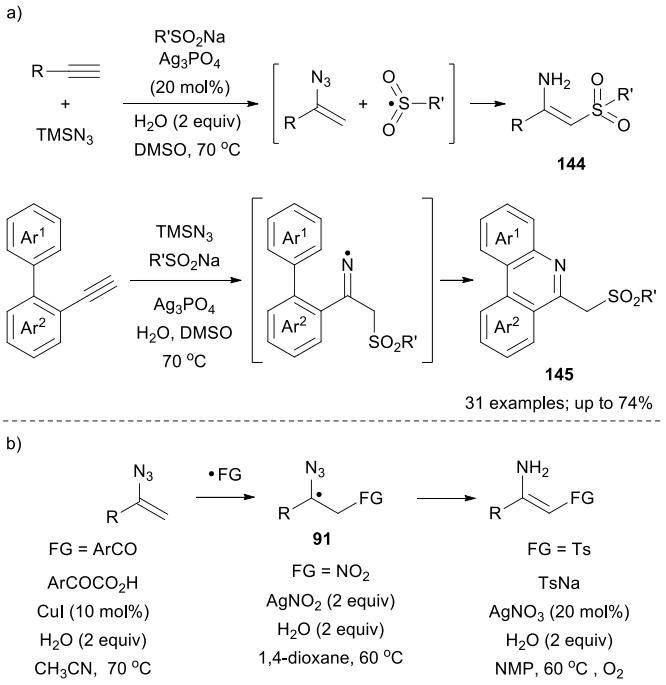
reaction proceeds through a sequence of silver-catalyzed alkyne hydroazidation, followed by attack of the sulfonyl radical onto the *in situ* generated vinyl azide. Sequential reduction and tautomerization of the resulting iminyl radical delivers the β-sulfonyl enamine **144**. Further, a silver-catalyzed tandem alkyne hydroazidation / sulfonyl radical addition / arene functionalization of diverse biphenyl acetylenes was developed for the synthesis of 6-methyl sulfonylated phenanthridines **145**.[81] This chemistry combines aspects of several of the processes outlined above, with an iminyl radical **91** generated from the vinyl azide that is formed *in situ* from the biphenyl acetylene substrate. The tandem alkyne hydroazidation and radical addition is highly convenient for the generation and consumption of the vinyl azide in a single reaction pot. Subsequent to this work, electron-deficient radicals (e.g. nitro, benzoyl, and sulfonyl radicals) have been employed by our group in additions to α-substituted vinyl azides (Scheme 35b).[82] On the basis of DFT calculations, an unusual 1,3-hydrogen atom transfer of an *in situ* generated iminyl radical intermediate was proposed to explain the generation of β-functionalized enamines.

An efficient and mild radical fluorination of vinyl azides, leading to α-fluoroketones **146**, has also been described (Scheme 36).[29b] Mechanistic studies suggested that a single-electron transfer, then fluorine atom transfer, and finally a nucleophilic addition of H_2O could be involved in the reaction pathway, with Selectfluor serving as both the oxidant and fluorine source.

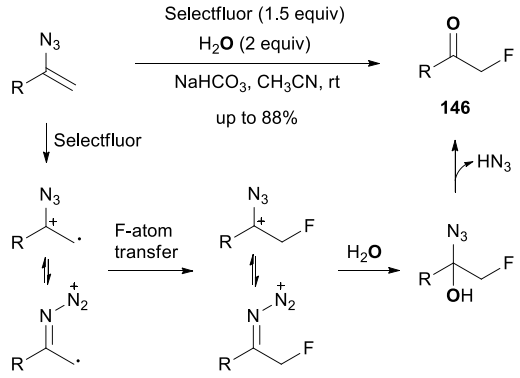
4.4 α-Substituted vinyl azides as nucleophiles

The reactivity of vinyl azides with electrophiles was first explored in the early 1970s through seminal investigations on hydrolysis[7a, 83] and bromination[84] reactions by Hassner and co-workers, which revealed the regioselective addition of electrophiles to the β-vinyl carbon of the alkenyl azide. The potential reactivity of vinyl azides as *N*-diazo enamines was further explored in other transformations, such as [3+2] cycloadditions of vinyl azides with ketenes[85] or $NOBF_4$.[6]

In the presence of aqueous acids, vinyl azides protonate to generate iminodiazonium ions **147** (Scheme 37a), which can undergo Schmidt-type 1,2-migrations to form nitrilium ions **148**;[7a, 7b] hydrolysis affords the corresponding secondary amides **149**. This method has been applied to a number of carbon-based electrophiles under Lewis acid activation (e.g.

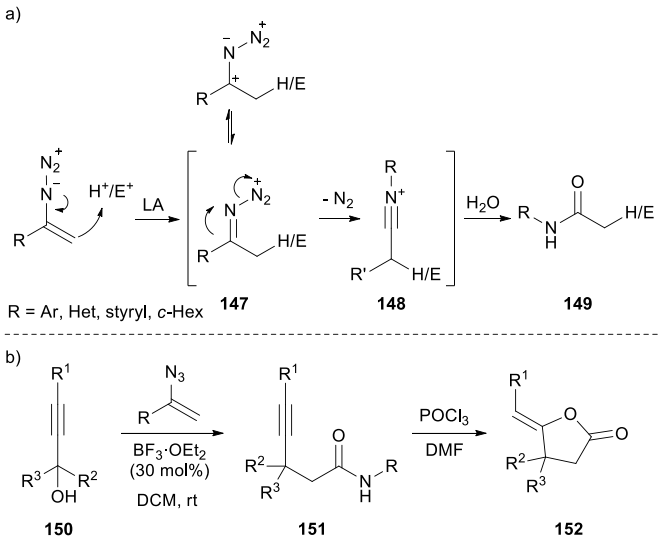


Scheme 35. Silver(I)-catalyzed aminosulfonylation reaction with terminal alkyne.



Scheme 36. Synthesis of α-fluoroketones from vinyl azides and Selectfluor.

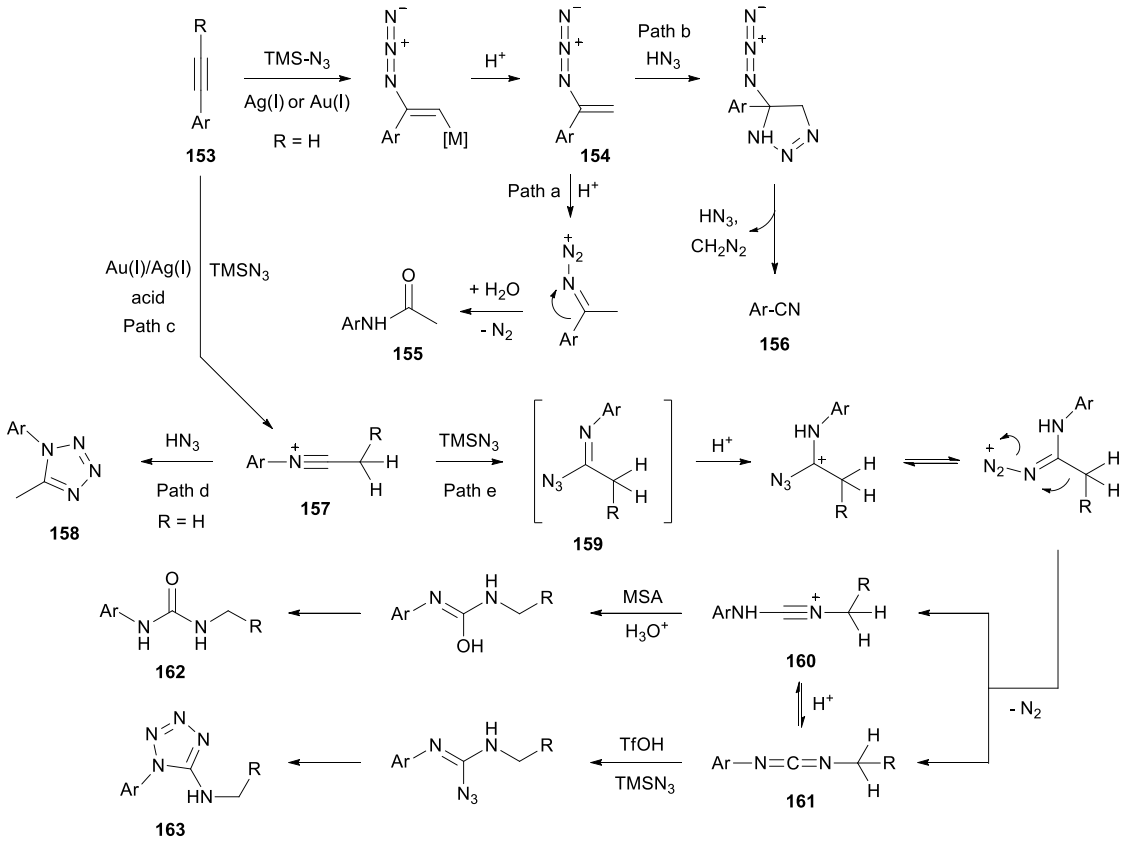
$BF_3{\cdot}OEt_2$), including *N*-tosylaldimines, benzaldehyde, ethyl glyoxal, and 2° and 3° alcohols.[7c] However, slow addition of the azide is required (5 h) to prevent its decomposition. The migratory aptitude of the substituent (i.e. R vs. CH_2E in **147**) controls which conformational isomer of amide is formed. Recently, this synthesis of amides from alkenyl azides and diverse alcohols has been improved by using triflimide (Tf_2NH) as an acid catalyst,[86] which avoids the need for stoichiometric amounts of $BF_3{\cdot}OEt_2$ or $TiCl_4$.[87] A variety of alcohols (e.g. 3-hydroxy-3-indolyloxindoles, benzylic alcohols containing aryl, indole, alkynyl, and styrene motifs) were applicable as electrophile precursors, thus leading to amides of significance in medicinal chemistry. In addition, under $BF_3{\cdot}OEt_2$ catalysis, tertiary and secondary propargyl alcohols (**150**) produced propargylic carbocation intermediates, which in turn yielded highly functionalized 4-alkynylamides **151** (Scheme 37b). Cyclization of these products under Vilsmeier conditions ($POCl_3$ / DMF) afforded dihydrofuran-2(3*H*)-ones **152**.[29c]



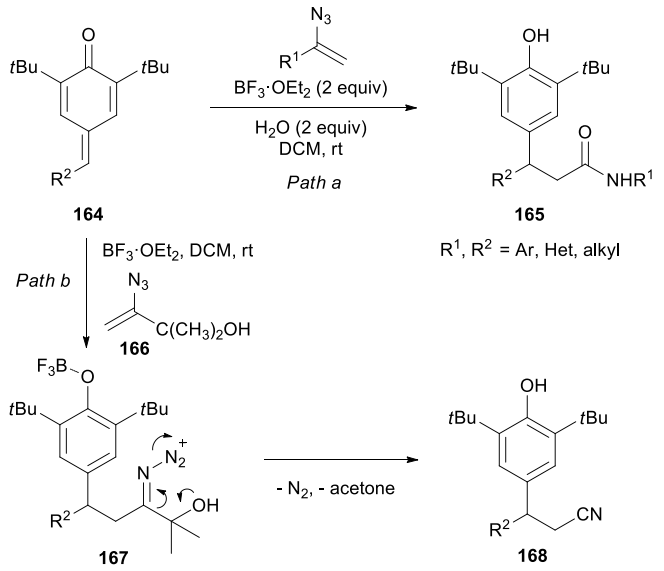
Scheme 37. Lewis acid promoted reactions of vinyl azides with carbon electrophiles.

Indeed, the tandem reaction of azides with alkynes has been widely studied;[88] under appropriate conditions, vinyl azides formed *in situ* (e.g. by metal catalyzed hydroazidation) can engage in a variety of further transformations. As shown in Scheme 38, the vinyl azide **154** derived from Au/Ag-promoted reaction of an aryl alkyne **153** with $TMSN_3$ can undergo protonation in acidic media (TFA), followed by the aforementioned Schmidt-type 1,2-rearrangement, giving amides **155** (Path a); overall, N insertion is achieved into the Csp^2–Csp bond.[27b] In the case of terminal alkynes, nitriles **156** were formed via formal Csp–Csp cleavage (Path b);[27a] in this process, the vinyl azide intermediate formed on initial silver-catalyzed hydroazidation undergoes cycloaddition with HN_3, followed by N-promoted elimination of the azide group, and diazomethane (*via* retro-[3+2] cycloaddition).[27a] When using a JohnPhos/Au(I) catalyst instead of Ag(I) (Path c), the intermediate nitrilium ion **157** underwent cycloaddition with HN3 to give N-aryltetrazoles **158** (Path d).[89] Recently, nitrilium ions **157** were also found to undergo nucleophilic addition by $TMSN_3$ to give imino azide **159**. Following protonation of **159**, a second Schmidt-type rearrangement occurs to produce a new nitrilium ion **160** (Path e), which can also be depicted as a carbodiimide **161**. Methanesulfonic acid-promoted reaction of **160/161** with adventitious water affords urea **162**, while further reaction on treatment with $TMSN_3$ and triflic acid instead generates amino tetrazole **163**.[90]

The coupling of electrophilic *p*-quinone methides **164** with vinyl azides containing aryl or alkyl functions has been exploited in the synthesis of substituted β-aryl propanamides**165** (Scheme 39, Path a).[91] Notably, when using a vinyl azide with an adjacent tertiary alcohol (**166**), reaction under $BF_3{\cdot}OEt_2$ promotion afforded exclusively the β-arylnitrile **168** (Path b). In this case, the iminodiazonium ion **167** underwent an interesting Grob-type fragmentation with release of a molecule of acetone (and nitrogen) instead of the expected Schmidt-type rearrangement.

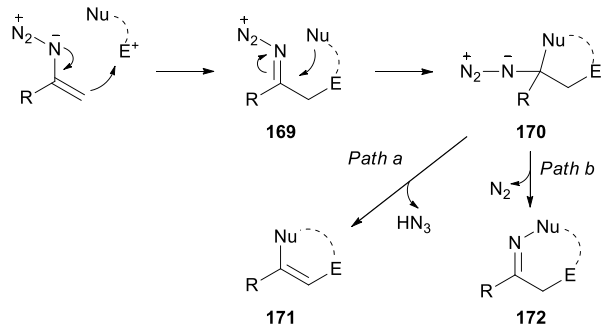


Scheme 38. Conversions of vinyl azide intermediates for the synthesis of *N*-containing compounds under gold or/and silver catalysis.



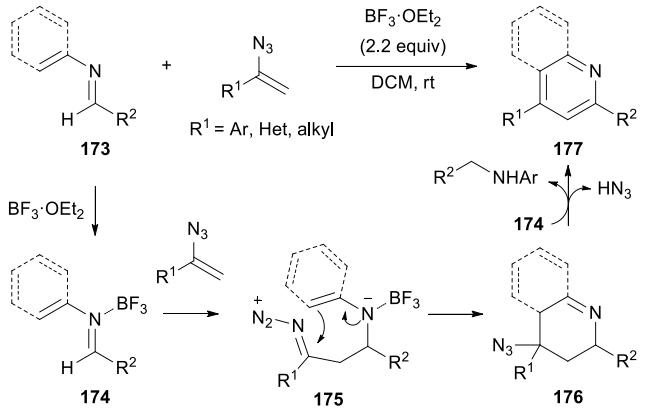
Scheme 39. Lewis acid-catalyzed coupling between vinyl azides and *p*-quinone methides.

The electrophilic C=N bond in the iminodiazonium ion intermediate **169** that results from electrophilic activation of the vinyl azide can also be trapped by nucleophiles in either an inter- or intramolecular manner, as generalized in Scheme 40.[92] When the nucleophilic group is tethered to the electrophile, ring-forming addition occurs in **169**, forming **170**. The latter can subsequently lead to unsaturated systems by elimination of HN_3 (**171**, Path a), or *via* substituent migration with release of N_2 (**172**, Path b, another Schmidt-type rearrangement). In contrast, the reaction of **169** with external nucleophiles delivers azide derivatives. Examples of these reactions are shown in the subsequent Schemes.



Scheme 40. Reactions of iminodiazonium ion intermediates with tethered nucleophiles.

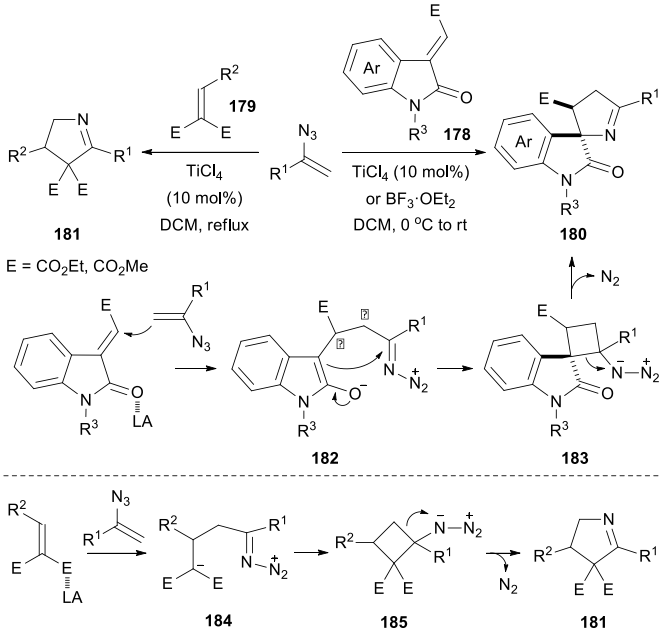
Under anhydrous conditions, $BF_3{\cdot}OEt_2$ can promote the formation of functionalized quinolines and pyridines **177** from *N*-aryl and *N*-alkenyl aldimines **173** respectively (Scheme 41).[93] This stepwise formal [4+2] annulation of the vinyl azide with the Lewis acid-activated aldimine (**174**) proceeds by cyclization of the enamine **175** to deliver 4-azido-tetrahydroquinoline pyridine **176**. Aromatization of **176** through Hantszch-like hydride transfer to another aldimine and elimination of HN_3 affords **177**. An additional equivalent of aldimine **173** is



Scheme 41. $BF_3{\cdot}OEt_2$-promoted synthesis of substituted quinolines from *N*-unsaturated aldimines.

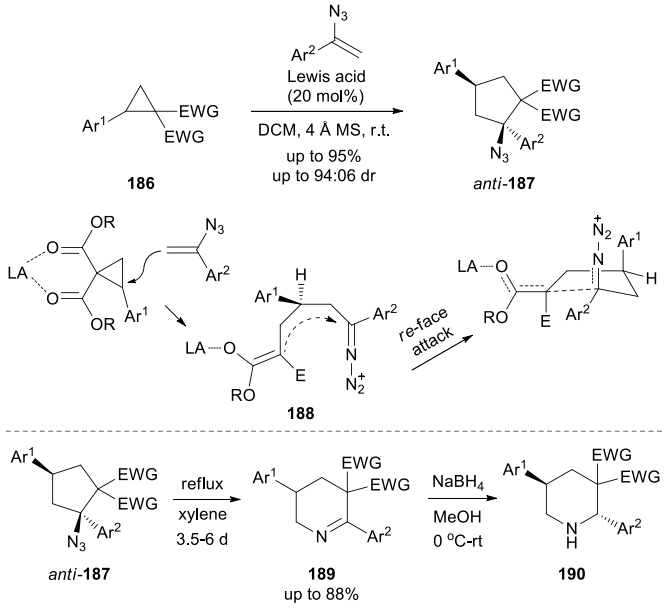
required in the reaction due to this aromatization mechanism.

Lewis acid-promoted reaction of vinyl azides and electron-poor olefins (e.g. **178** and **179**, Scheme 42) leads to the formation of 1-pyrrolines (**180** and **181** respectively).[87] The reaction is proposed to proceed through conjugate addition of the vinyl azide to the Lewis acid-activated α,β-unsaturated carbonyl, which on cyclization of the resultant enolate (**182** or **184**) gives an azidocyclobutane intermediate (**183** or **185**). In the case of azaspirocycle **180** (which is formed with high diastereoselectivity due to a well-defined open transition state in the conjugate addition process), the quaternary carbon of the 2-oxoindoline undergoes migration to the N_α atom of the azide. A similar pathway was suggested for the monocyclic 1-pyrrolines **181**, however in this case migration of the secondary carbon atom in **185** is favored over the quaternary carbon, probably due to the deactivating effect of the two methoxycarbonyl groups on the migration.



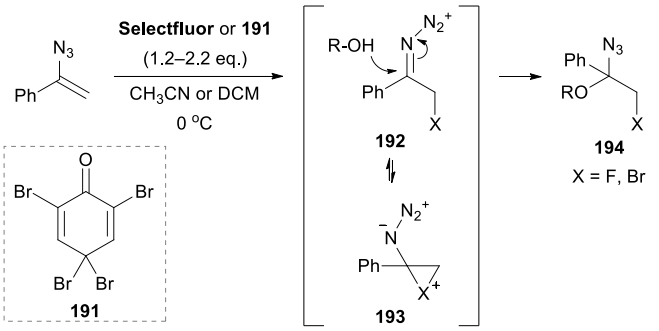
Scheme 42. Synthesis of 3',4'-dihydrospiro[indoline-3,2'-pyrrol]-2-ones and 4,5-dihydro-3*H*-pyrroles.

Vinyl azides can also engage in Lewis acid-catalyzed, diastereoselective formal [3+2] cycloadditions with donor–acceptor cyclopropanes (DAC) **186** to form azidocyclopentanes **187** at room temperature (Scheme 43)[94] – conditions that avoid the thermal formation of vinylnitrenes / 2*H*-azirines as discussed above (see Scheme 17).[56] The use of $InCl_3$ as catalyst led to excellent yields and short reaction times, but low diastereoselectivity, whereas MgI_2 provided the major product *anti*-**187** in modest yields and long reaction time, but with excellent diastereoselectivity. Mechanistically, Lewis acid activation of the DAC promotes nucleophilic attack by the alkenyl azide to give an open chain intermediate enolate **188**. This then undergoes a diastereoselective cyclization to afford the azide-substituted cyclopentane product, this selectivity presumably being due to significant conformational control effects in the cyclization transition state. *Anti*-**187** underwent thermal ring expansion to tetrahydropyridine **189**, which could be reduced to the corresponding piperidine **190** as a single diastereomer using $NaBH_4$. Equivalent chemistry using $Sc(OTf)_3$, which displayed wide substrate scope and functional group tolerance, was reported near-simultaneously by Chiba *et al*.[92a]



Scheme 43. Lewis acid-catalyzed diastereoselective cycloaddition of donor-acceptor cyclopropanes with vinyl azides.

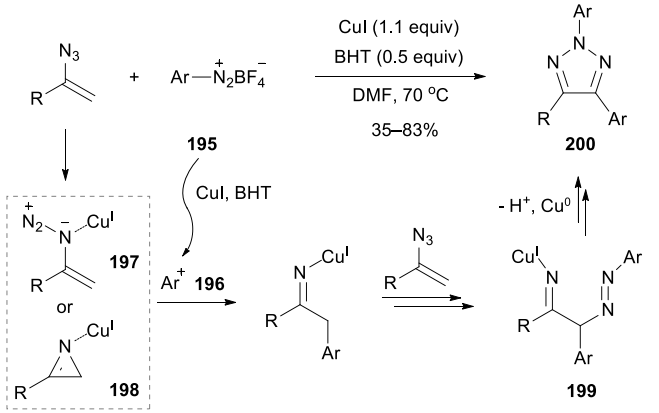
The Chiba group has recently disclosed an interesting method for the fluoro- and bromo-alkoxylation of α-azidostyrene, which enables regioselective introduction of the azide functional group into complex molecules for potential biological 'click' applications (Scheme 44).[92b] These reactions are initiated with an X^+ source (SelectFluor or 2,4,4,6-tetra-bromocyclohexa-2,5-dienone **191**), which forms an α-haloiminodiazonium ion **192**; capture of this with a wide range of primary and secondary alcohols generates aminal-type products **194**. The presence of the halogen atom (X) is proposed to stabilize transient intermediate **192** by formation of a halonium ion (**193**), which prevents the usual Schmidt-



Scheme 44. Electrophilic addition/coupling to α-alkoxy-β-haloalkyl azides.

type migration of the α-substituent (in this case, Ph). Using this chemistry, testosterone derivatives could be conjugated with a cyanine dye *via* click chemistry. The same approach has been applied to the synthesis of α-propargyloxy-β-fluoroalkylazides, which underwent gold(I)-catalyzed 6-*endo*-*dig* cyclization to afford 2*H*-1,3-oxazines in satisfactory yields.[95]

Very recently, a novel dual-functionalization at the β-carbon of a vinyl azide has been established (Scheme 45).[96] Aryldiazonium salt **195** served as a source of both an arene and a diazo group (in intermediate **199**), which then afforded a variety of N^2-substituted-1,2,3-triazoles **200** in moderate to good yields; overall, three bonds (C–C, C–N and N–N) are formed in one pot. Mechanistic studies using 2*H*-azirine, and radical inhibitors, pointed to an ionic process (namely, coupling of aryl cation **196** with intermediate **197** or **198**).

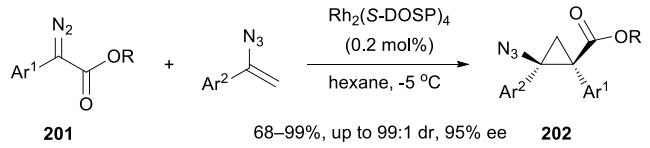


Scheme 45. CuI-promoted carboamination of azido vinylidenes by aryldiazonium salts.

4.5 Reactions between vinyl azides and metal carbenoids

The electrophilic nature of metal carbenoids renders them excellent substrates for reaction with vinyl azides, and a number of such processes have been developed.

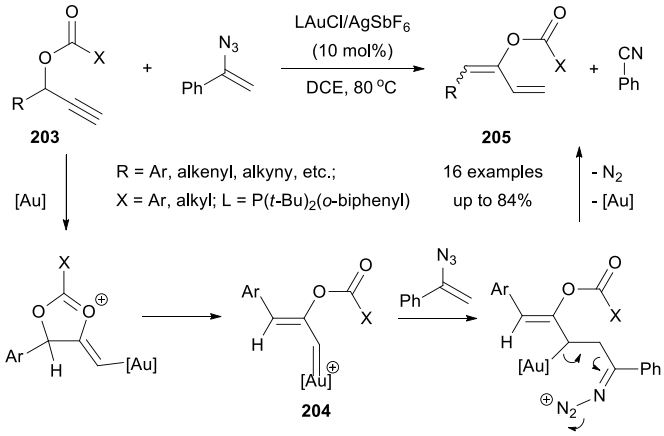
Prior to the use of vinyl azides, the stereoselective synthesis of β-azidocyclopropanes had been achieved only with poor enantioselectivity and moderate yields *via* Michael addition-initiated cyclization.[97] However, Rh_2(*S*-DOSP)$_4$ has been found to promote a highly diastereo- and enantioselective cyclopropanation of α-aryl vinyl azides using metal carbenes derived from diazo esters **201**, leading to *cis*-β-



Scheme 46. Rhodium-catalyzed stereoselective synthesis of β-azidocyclopropane esters.

azidocyclopropane esters **202** in excellent yields (up to 99:1 *dr*, 95% *ee*, Scheme 46).[98]

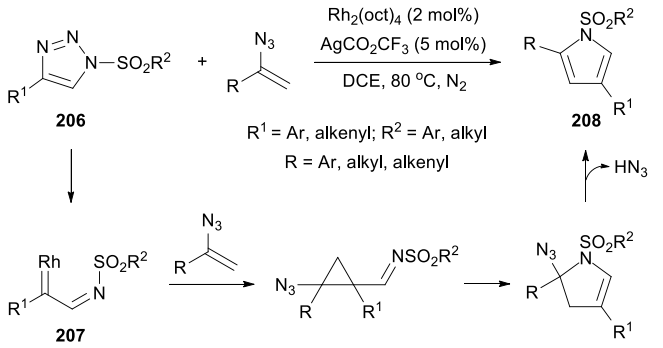
Liu and co-workers reported a gold-catalyzed reaction of vinyl azides with propargylic esters **203** that delivers buta-1,3-dien-2-yl esters **205** (Scheme 47).[99] Gold carbenoid **204** is first generated by a 5-*exo*-*dig* intitiated 1,2-carboxylate shift of propargylic esters **203**. Following nucleophilic attack on **204** by the vinyl azide, a deaurative fragmentation (loss of N_2 and benzonitrile) gives the diene product. Benzylic carbonates (R = aryl) showed excellent *Z*-selectivity (*Z*/*E* >30:1) due to the avoidance of steric effects between the arene and gold complex, while alkenyl and alkynyl substitutents gave *E*-configured products, possibly due to interaction of these groups with the initially formed gold carbene.



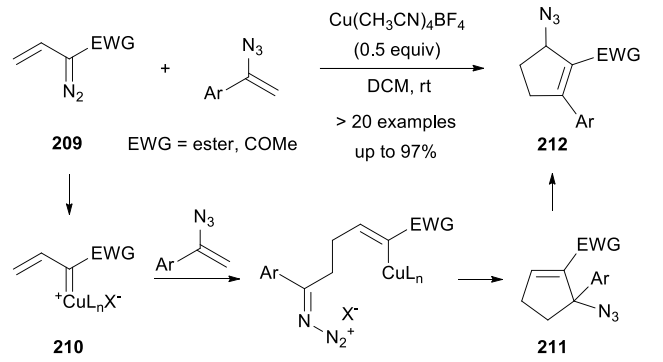
Scheme 47. Synthesis of buta-1,3-dien-2-yl esters from propargylic esters.

Recently, a formal [3+2] cyclization reaction between vinyl azides and *N*-sulfonyl-1,2,3-triazoles **206**, which uses a Rh/Ag binary metal catalyst system, has been developed (Scheme 48).[100] A range of *N*-sulfonyl pyrroles **208** were produced in high yields, in a reaction sequence thought to involve cyclopropanation of the vinyl azide with the α-iminyl rhodium carbene **207** (formed by Rh-catalyzed triazole decomposition), followed by a (possibly silver-catalyzed) cyclopropane ring expansion, and finally aromatization with loss of HN_3.

Substituted cyclopentenes **212** were obtained *via* a Cu(I)-promoted formal [3+2] cycloaddition / allylic azide rearrangement process with vinyl diazocarbonyls **209** (Scheme 49).[101] In this transformation, the vinyl azide acts as an enamine nucleophile in an S_N2'-type attack on the terminus of the copper(I) alkenylcarbene species **210**. Cyclization of the resulting alkenylcopper complex onto the imine carbon atom



Scheme 48. Rh/Ag-co-catalyzed annulation of *N*-sulfonyl-1,2,3-triazoles to *N*-sulfonyl substituted pyrroles and 2*H*-pyrazines.



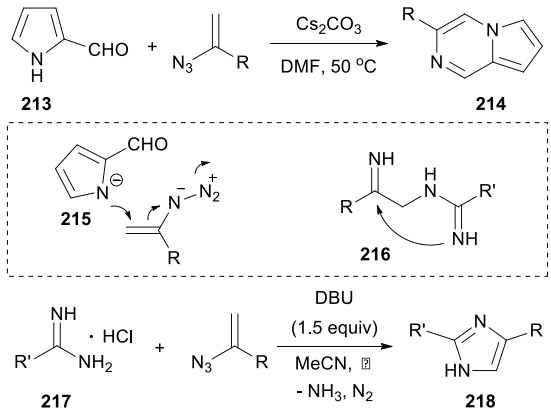
Scheme 49. [3+2] Cycloaddition/azide rearrangement to cyclopentene derivatives.

generates the azidocyclopentene **211**; [3,3]-sigmatropic rearrangement of the azide leads to the thermodynamically favored product **212**.

4.6 Vinyl azides as electrophiles

While both α-aryl / alkyl vinyl azides[8, 52, 62] and α-azido esters / ketones are capable of acting as electrophiles, the latter have seen particular use in Michael addition–elimination processes, when activated by complexation of Lewis acids with the azide and / or carbonyl group.[3a, 3c, 3e, 9] This contrasts with non-activated α-substituted vinyl azides, which under the same reaction conditions are recovered unchanged,[9b] or require more forcing conditions[8a] to promote reaction. Thus, pyrrolo[1,2-α]pyrazines **214** were afforded via the [3+3] annulation of 1*H*-2-pyrrolecarbaldehyde **213** and azido vinylidene in the presence of Cs_2CO_3 at 50 °C (Scheme 50), while the equivalent reaction with azido cinnamates proceeded at room temperature.[8a] The mechanism involves attack of the pyrrole anion **215** on the vinyl azide, with loss of N_2 leading to an imine intermediate. This undergoes cyclization onto the proximal aldehyde, and aromatization to product **214**.

Under DBU promotion, benzimidamides were generated from benzimidamide hydrochloride **217**; these highly nucleophilic species added to the vinyl azide to afford **216**. The latter in turn cyclized to give the 2,4-disubstituted-1*H*-imidazole products **218** with loss of ammonia (Scheme 50). In this [3+2] cyclization chemistry, it is the vinyl azide which acts as a C2 building block.[8b]

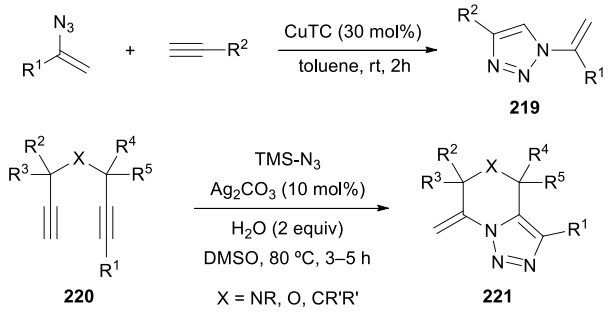


Scheme 50. Vinyl azides as electrophiles in annulations.

4.7 α-Substituted vinyl azides as cycloaddition / click partners

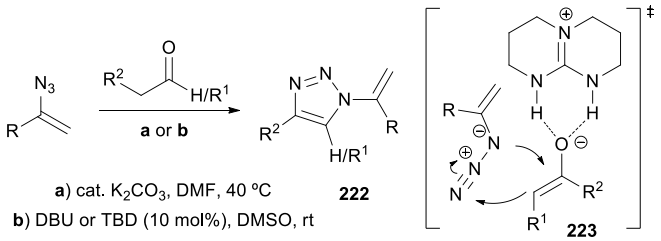
Finally, vinyl azides have also been exploited as cycloaddition partners, albeit control of reaction temperature is important in non-catalyzed reactions to avoid decomposition to the 2*H*-azirine (above 60–70 °C).[12c] Early reports showed that vinyl azides could undergo intramolecular [3+2] annulations to afford triazoline frameworks,[102] and could similarly react with a range of other electron-deficient dipolarophiles (e.g. alkenes, alkynes, nitrile oxides), albeit in a stepwise manner.[6, 103]

The azido function of the vinyl azide has been used for Cu(I)-catalyzed Huisgen-type cycloadditions with unactivated terminal alkynes.[12c] For instance, the synthesis of 1-vinyl-1,2,3-triazoles **219** was performed using copper thiophene carboxylate (CuTC) at room temperature,[17d] or at 70 °C in flow (Scheme 51).[26a] Vinyl-1,2,3-triazoles have also recently been accessed by a tandem alkyne hydroazidation / Huisgen-type cycloaddition of diynes **220** with $TMSN_3$ under silver catalysis. A range of triazoles **221** were obtained in moderate to excellent yields, including fused heterocycles containing piperidine, piperazine, morpholine, diazepine, and isoquinoline rings.[104]



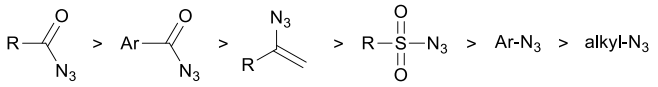
Scheme 51. Huisgen [3+2]-cycloaddition for the synthesis of 1-vinyl-1,2,3-triazoles.

The 1,3-dipolar cycloaddition of 1,3-dicarbonyl compounds with α-(hetero)aryl/alkyl vinyl azides has been achieved in the presence of a catalytic amount of K_2CO_3 in DMF at 40 °C, leading to 1-vinyl-1,2,3-triazoles **222** in good to excellent yields (Scheme 52, Conditions a).[46] In contrast, at 100 °C, 2*H*-azirine intermediates were generated which in turn were converted to pyrroles.[46] Organocatalysts such as DBU[105] and TBD (1,5,7-



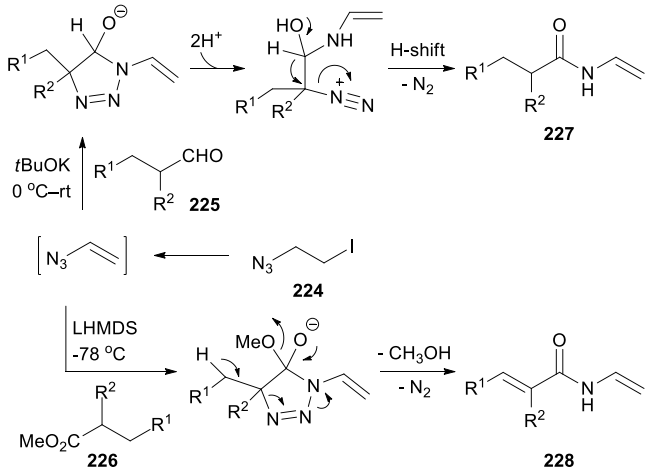
Scheme 52. Azido vinylidenes in 1,3-dipolar cycloaddition reactions.

triazabicyclo[4.4.0]dec-5-ene)[106] have also been used to promote these reactions via putative stabilized enolate **223**.[107] These processes were shown to be viable for a wide range of activated carbonyls, including ketones and aldehydes, at room temperature (Scheme 52, Conditions b). The order of reactivity of vinyl azides in azide-carbonyl [3+2]-cycloaddition relative to other azides is shown in Scheme 53.[106]



Scheme 53. Reactivity order of azide compounds in azide-carbonyl [3+2]-cycloaddition.

Very recently, a novel method has been reported for the direct synthesis of *N*-vinyl amides **227**, and α,β-unsaturated *N*-vinyl amides **228**, from α-branched aldehydes **225** and esters **226** respectively (Scheme 54).[108] A mechanism was proposed involving *in situ* generation of azidoethene (from 1-azido-2-iodoethane **224** under basic conditions); azide-enolate [3+2] annulation (as in Scheme 52) affords an intermediate triazole. For aldehydes, this process is followed by ring-opening of the triazole and a 1,2-hydride shift driven by loss of N_2, while for esters an exocyclic E2-type elimination was found to be feasible on the basis of DFT calculations.



Scheme 54. Vinyl azide–enolate [3+2] cycloaddition towards *N*-vinyl amides.

5. Summary and outlook

α-Substituted vinyl azides display a plethora of reactivity that both mirrors and goes beyond that of azides and enamines.

The ability of azido vinylidenes to act not only as nucleophiles, but also as radical acceptors and even electrophiles, has resulted in a large number of novel transformations. Furthermore, recent achievements in the *in situ* preparation of vinyl azides (for example, silver-catalyzed alkyne hydroazidation) have provided further opportunities for novel synthetic applications.

The addition of free radicals to vinyl azides has proved to be a powerful method to generate iminyl radicals in recent years, particularly in terms of the opportunities generated using visible-light photoredox catalysis, but also in other radical addition processes that enable overall difunctionalization of precursor terminal alkynes (Section 4.3). The use of metals to insert into the vinyl azide, generating metal enaminyl radicals (Section 4.2), is similarly appealing and unique to these functionalities, which has enabled exciting developments in the field of C–H functionalization, difunctionalization, and cyclization reactions.

With the significant advances in the chemistry of vinyl azides presented in this review, we hope that synthetic chemists will continue to be inspired to explore new avenues for the synthesis of *N*-containing compounds using these versatile and appealing building blocks.

Safety Notice: as with many organic azides, alkenyl azides are potentially very dangerous. Great care must be taken when handling these compounds, particularly during concentration and the physical handling of isolated products, due to the explosive potential of the azide functionality.

Notes and references

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α-Substituted Vinyl Azides: An Emerging Functionalized Alkene

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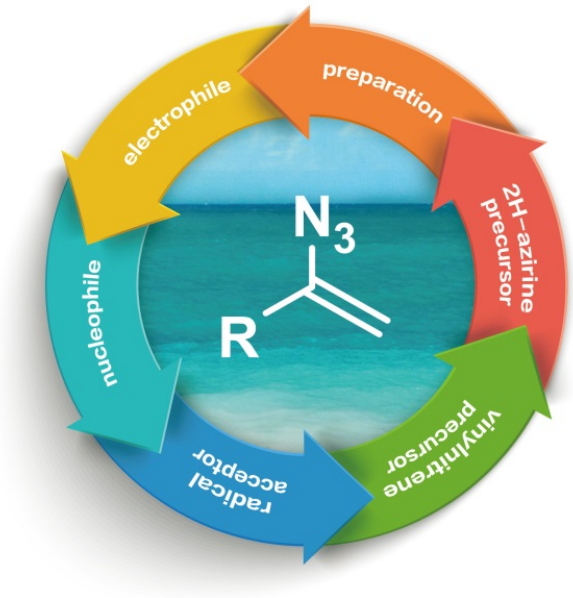

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