Application of Vinyl Azides in Chemical Synthesis: A Recent Update

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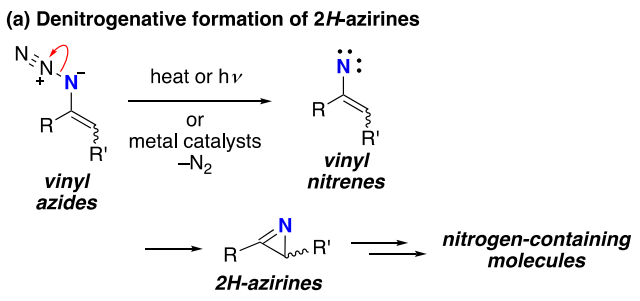
ABSTRACT: Among organic azides, vinyl azides have shown versatile chemical reactivities in recent development of new synthetic methodologies mainly for nitrogen-containing molecules. This synopsis highlights and discusses recent advances on use of vinyl azides in chemical synthesis as a radical acceptor and an enamine-type nucleophile.

Organic azides are readily available yet energetic compounds showing rich chemical reactivities for synthesis of nitrogen-containing molecules.[1] Use of organic azides for 1,3-dipolar cycloaddition with alkynes[2] should be the most frequently used method for various applications in biology,[3,4] medicine,[5] and materials chemistry.[6] Among organic azides, on the other hand, vinyl azides exhibit distinct and unique chemical reactivities from those of alkyl and aryl azides. The most common reactivity of vinyl azides is perhaps their denitrogenative conversion to highly strained 3-membered ring nitrogen-heterocycles, 2*H*-azirines via vinyl nitrene intermediates under thermal treatment, photo-irradiation, or Lewis-acid catalysis (Scheme 1a).[7] By taking advantage of rich reactivity of 2*H*-azirines, a variety of molecular transformations of vinyl azides via 2*H*-azirines have been developed.[8] Among them, thermal intramolecular aromatic C-H amination of readily available azido cinnamates for synthesis of indoles is one of the most classical but widely used process of vinyl azides (Scheme 1b).[9-11]

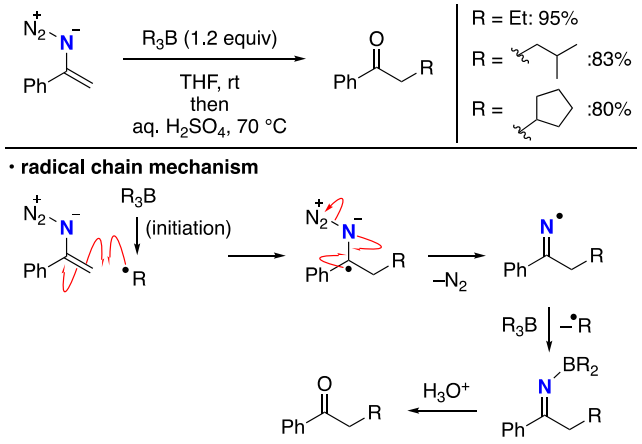
Scheme 1. Conversion of vinyl azides into 2*H*-azirines



On the other hand, new and unique synthetic methodologies have recently been emerged by the leveraging of vinyl azides either as a radical acceptor or as an enamine-type nucleophile. The aim of this synopsis is to highlight recent use of vinyl azides in chemical synthesis by taking advantage of these unprecedented reactivities.[12]

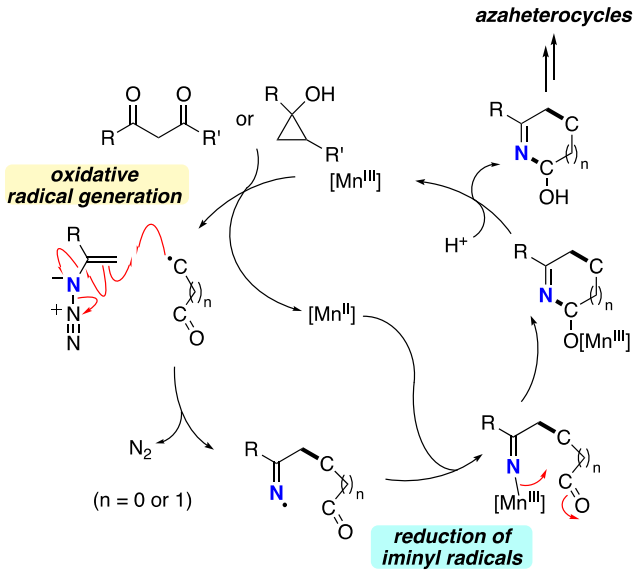
Reactivity as a radical acceptor. In 1975, Suzuki reported that treatment of α-azidostyrene (vinyl azide) with trialkyl boranes (R_3B) in THF followed by aqueous acid affords alkyl phenyl ketones in good yields.[13] Later in 1983, Roberts elucidated the mechanism of this Suzuki's reaction,[14] revealing that the process proceeds via radical chain including iminyl radicals (Scheme 2). The radical chain is initiated by generation of alkyl radicals (R•) from trialkyl boranes, that add onto vinyl azide to generate α-azido radicals. Denitrogenative fragmentation of α-azido radicals affords iminyl radicals, which react with trialkyl boranes to provide iminyl boranes along with generation of alkyl radicals, which maintain the radical chain. Acidic hydrolysis of iminyl boranes delivers ketones. This process between vinyl azide and trialkyl boranes is featured by its capability in construction of the new C-C bond and generation of iminyl radicals. However, since the seminal reports by Suzuki and Roberts, this reactivity of vinyl azides had been underutilized, especially in terms of uses of the iminyl radicals for the N-C bond formation or other molecular transformations.[15]

Scheme 2. Reactions of vinyl azides with C-radicals



Our group disclosed a concept on use of vinyl azides with Mn(III)-mediated oxidative generation of C-radicals having a keto carbonyl group from 1,3-dicarbonyl compounds or cyclopropanols for synthesis of nitrogen-heterocycles (Scheme 3).[16] It is well known that the Mn(III) complexes oxidize 1,3-dicarbonyl compounds or cyclopropanols to generate corresponding α-carbonyl or β-carbonyl radicals along with formation of the Mn(II) species (oxidative radical generation).[17] The resulting C-radicals having a carbonyl group add onto vinyl azides to generate iminyl radicals. Subsequent reduction of the iminyl radicals with the Mn(II) species forms iminyl Mn(III) species, that cyclize with the intramolecular carbonyl group to construct azaheterocyclic scaffolds with release of the Mn(III) complexes, overall enabling a redox-neutral Mn(III)-Mn(II) catalytic process.

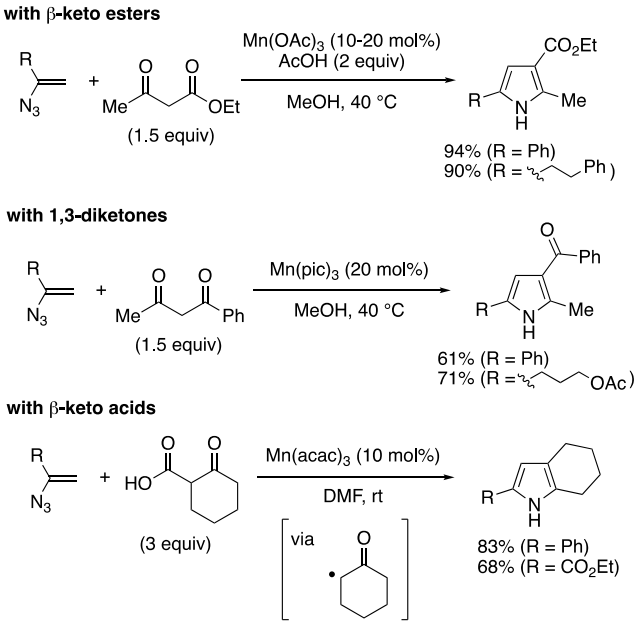
Scheme 3. Mn(III)-catalyzed reactions of vinyl azides with 1,3-dicarbonyl compounds or cyclopropanols



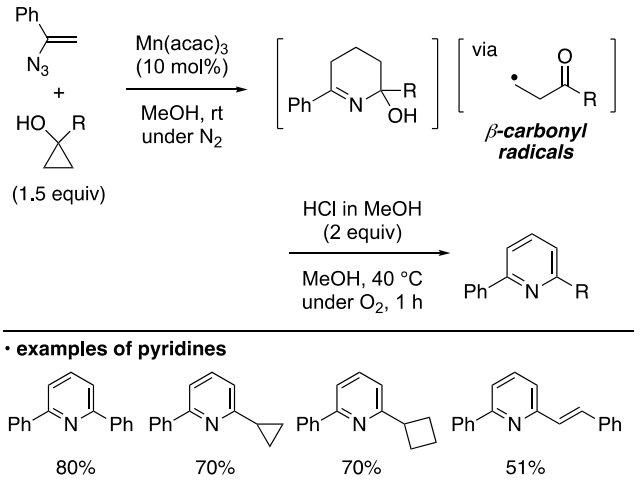
For example, the Mn(III)-catalyzed reactions of vinyl azides with 1,3-dicarbonyl compounds afford substituted *N*-H pyrroles with wide substituent compatibility (Scheme 4).[18] As for the 1,3-dicarbonyl compounds, β-keto esters, 1,3-diketones, and β-keto acids (with decarboxylation) can be used for generation of the corresponding α-carbonyl radicals for the reactions with vinyl azides.

Use of cyclopropanols as a source of β-carbonyl radicals provides a promising way to construct 6-membered ring nitrogen-heterocycles.[19] For example, the $Mn(acac)_3$-catalyzed reactions of vinyl azides with monocyclic cyclopropanols gave 2-hydroxytetrahydropyridines, that are further aromatized by aerobic treatment in the presence of acid to afford substituted pyridines (Scheme 5).

Scheme 4. Mn(III)-catalyzed synthesis of pyrroles from vinyl azides and 1,3-dicarbonyl compounds

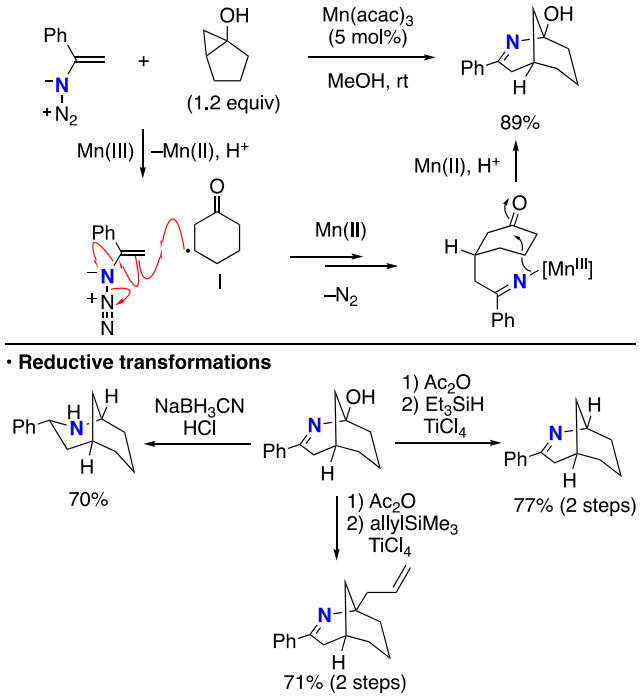


Scheme 5. Mn(III)-catalyzed synthesis of pyridines from vinyl azides and cyclopropanols



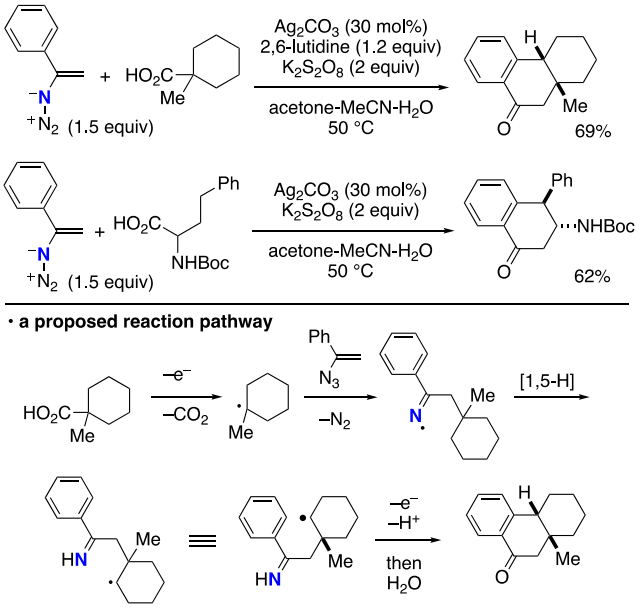
On the other hand, the reactions with bicyclic cyclopropanols, bicyclo[3.1.0]hexan-1-ols deliver unique 2-azabicyclo[3.3.1]non-2-en-1-ols. The bridgehead hydroxyl group prevents the further dehydration process (Scheme 6). These 2-azabicyclo[3.3.1]non-2-en-1-ols are readily transformed into 2-azabicyclo[3.3.1]nonanes (morphans) by subsequent treatment with $NaBH_3CN$ through stepwise double hydride reduction. On the other hand, selective reduction of the bridgehead hydroxyl group is accomplished by treatment of its acetate with hydrosilane in the presence of $TiCl_4$, furnishing 2-azabicyclo[3.3.1]non-2-ene in good yield. Use of allylsilane instead of hydrosilane allows for construction of a quaternary carbon center at the bridgehead position.

Scheme 6. Mn(III)-catalyzed reactions of vinyl azides with bicyclic cyclopropanols



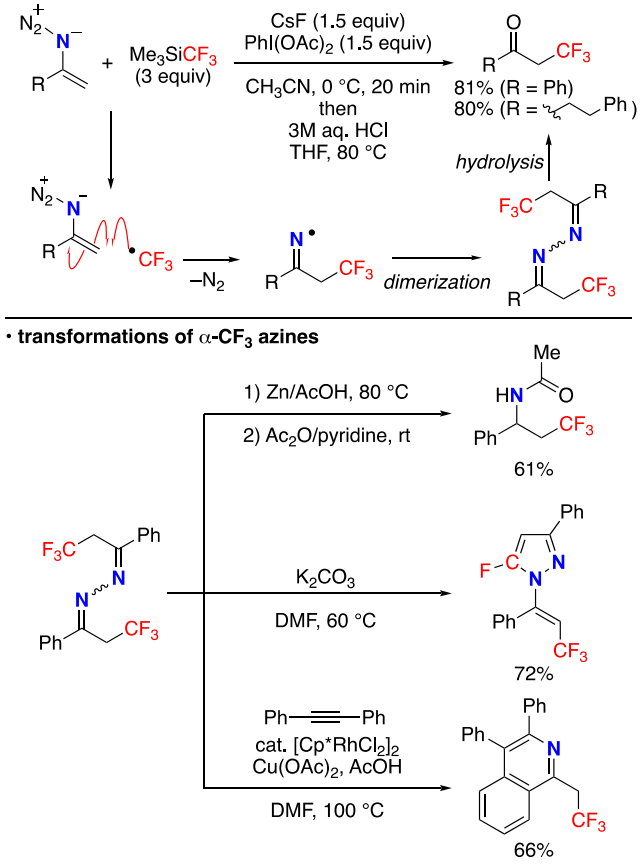
Very recently, Nevado demonstrated an elegant radical strategy for the synthesis of polycyclic ketones using α-azidostyrenes and aliphatic carboxylic acids under the Minisci-type oxidative reaction conditions (Scheme 7).[20] The process is initiated by decarboxylative generation of C-radicals from the carboxylic acids, that add to vinyl azides to give iminyl radicals. In this case, the resulting iminyl radicals undergo 1,5-H radical transfer to generate C-radicals, which in turn cyclize onto the intramolecular benzene ring. Further oxidative aromatization and hydrolysis of N-H imines furnishes the final products.

Scheme 7. Ag-catalyzed reactions of vinyl azides with aliphatic carboxylic acids



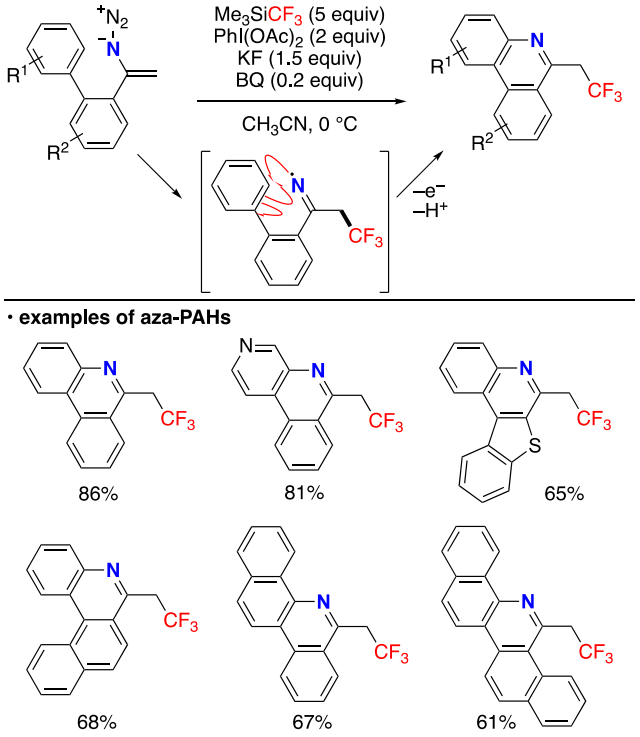
Our group developed radical trifluoromethylation of vinyl azides using $TMSCF_3$ in the presence of $PhI(OAc)_2$ and CsF (Scheme 8).[21] The CF_3-radical generated through oxidation of $TMSCF_3$ by $PhI(OAc)_2$ adds onto vinyl azides to form α-CF_3 iminyl radicals, that spontaneously dimerize to give α-CF_3 azines. The resulting α-CF_3 azines are hydrolyzed in acidic conditions to give α-trifluoromethyl ketones. Further more, they can readily be converted into β-trifluoromethyl amines, 5-fluoropyrazoles, and trifluoroethyl isoquinolines.

Scheme 8. Trifluoromethylation of vinyl azides for synthesis of α-CF_3-azines



The transient α-CF_3 iminyl radicals could be utilized for a successive radical N-C bond forming reaction with the tethered aromatic ring. This concept was extended to facile construction of trifluoroethyl substituted aza-polycyclic aromatic hydrocarbons (aza-PAHs) using readily available α-(biaryl-2-yl)vinyl azides (Scheme 9).[22]

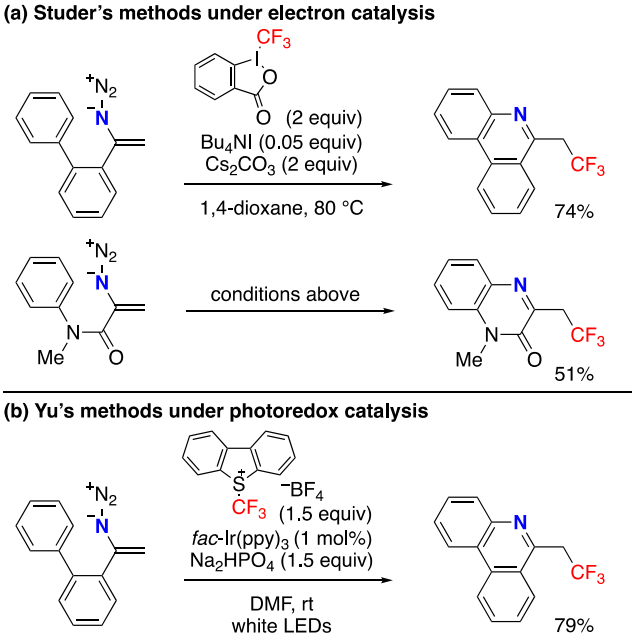
Scheme 9. Synthesis of aza-PAHs by radical trifluoromethylation of α-(biaryl-2-yl)vinyl azides



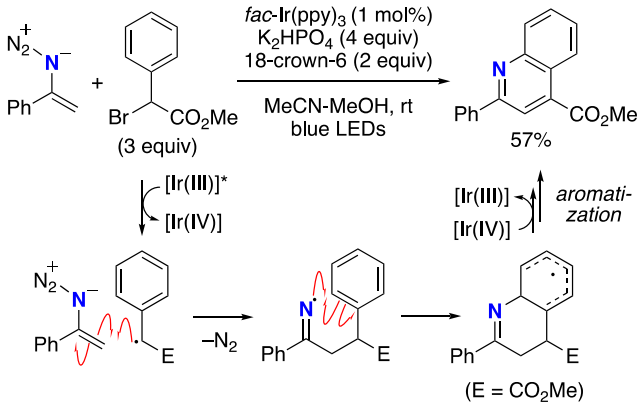
On the other hand, Studer employed the Togni's reagent for the radical trifluoromethylation of vinyl azides (Scheme 10a).[23] In this case, tetrabutylammonium iodide acted as the radical initiator, reducing the Togni's reagent to generate CF_3 radical, which reacted with α-(biaryl-2-yl)vinyl azides and 2-azido-N-phenylacrylamides, respectively, to construct trifluoroethylphenanthridines and quinoxalinones. The process, initiated by reductive generation of the CF_3 radical and terminated by oxidative aromatization, can be operated via the radical chain process under electron catalysis.[24] Similarly, Yu adopted the Umemoto's reagent for synthesis of trifluoroethyl phenanthridines under visible light photoredox catalysis (Scheme 10b).[25,26]

Zhou developed construction of quinolines from vinyl azides and 2-bromo-2-arylacetates under visible light photoredox catalysis (Scheme 11).[27] Single-electron-reduction of 2-bromo-2-arylacetates generates α-carbonyl benzyl radicals, that add onto vinyl azides to generate iminyl radicals. Subsequent N-C bond forming cyclization and aromatization via single-electron-oxidation furnishes dihydroquinolines, that are further oxidized by remaining 2-bromo-2-arylacetates under the present conditions to deliver the aromatized quinoline products.

Scheme 10. Radical trifluoromethylation of α-(biaryl-2-yl)vinyl azides under electron- and photoredox catalysis

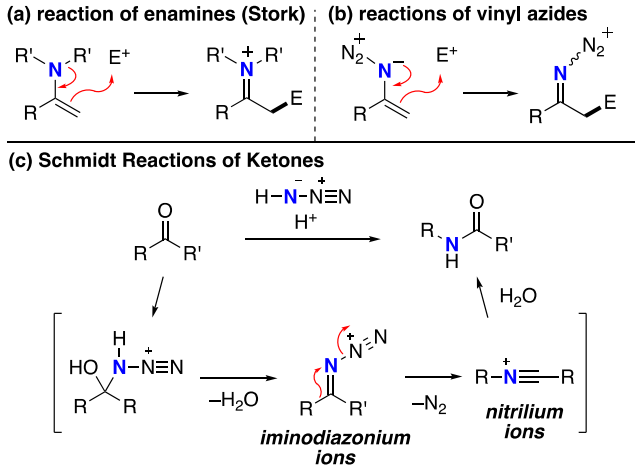


Scheme 11. Synthesis of quinolines under photoredox catalysis



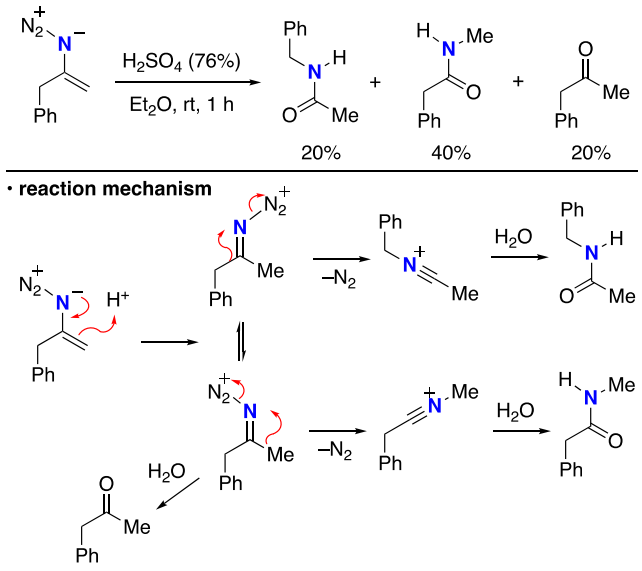
Reactivity as an enamine type nucleophile. Chemical structure of vinyl azides is analogous to that of enamines. Therefore, it could be expected that vinyl azides potentially bear the nucleophilic reactivity like enamines. The nucleophilic attack of enamines (the Stork-enamine reactions)[28] onto electrophiles (E^+) provides iminium ions (Scheme 12a), whereas that of vinyl azides should afford iminodiazonium ions (Scheme 12b), which are the reactive intermediates observed in the Schmidt reactions[29] (Scheme 12c). In the Schmidt reactions, 1,2-substituent migration of iminodiazonium ions with elimination of dinitrogen provides nitrilium ions, which are hydrolyzed to give amides.

Scheme 12. Nucleophilic reactivity of enamines and vinyl azides



In 1970, Hassner reported Brønsted-acid mediated hydrolysis of vinyl azides (Scheme 13).[30,31] For example, the reaction of 2-azido-3-phenylpropene in the presence of aqueous sulfuric acid in ether afforded a mixture of N-benzyl acetamide and N-methyl-phenylacetamide in 20% and 40% yields, respectively along with formation of phenylacetone in 20% yield. The process was initiated by protonation of 2-azido-3-phenylpropene to generate iminodiazonium ion intermediates as a mixture of the *E*- and *Z*-forms, which are supposed to be under rapid equilibrium. The Schmidt-type denitrogenative 1,2-migration of the iminodiazonium ions forms nitrilium ions, where the substituent *anti* to the N-N_2^+ bond should undergo the 1,2-migration.[32] Subsequent hydrolysis delivers the corresponding amides, whereas phenylacetone is formed via direct hydrolysis of iminodiazonium ions.

Scheme 13. Brønsted acid-mediated hydrolysis of vinyl azides

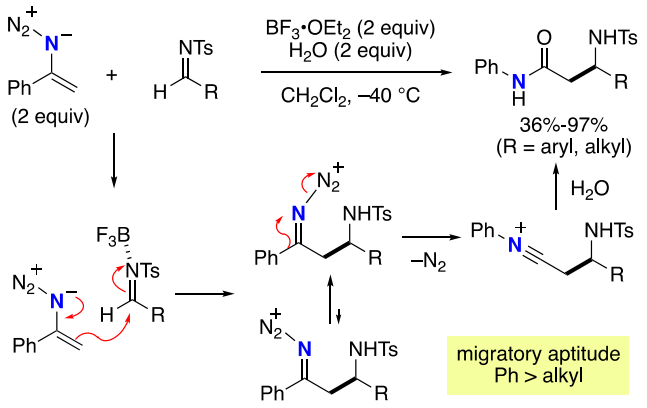


Our group recently utilized carbon-electrophiles, that accept nucleophilic attack of vinyl azides under acidic conditions to form amide products with formation of a new C-C bond. Differently from the acidic hydrolysis of vinyl azides that provided a mixture of two different amides, our reaction systems are capable of furnishing a single amide product with predictable migration selectivity by the migratory aptitude of the substitu-

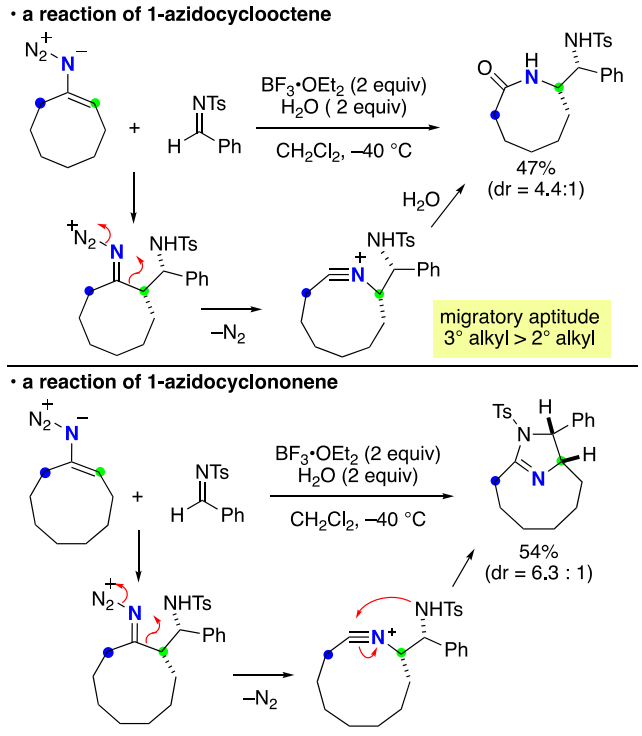
ents. For example, we found N-Ts imines are potential carbon-electrophiles for the reaction with vinyl azides in the presence of BF_3•OEt_2 and H_2O, providing β-N-Ts amino amides (Scheme 14).[33] The reactions with α-azidostyrene afford single amide products via 1,2-migration of the pheny group having higher migratory aptitude over the alkyl group in the putative iminodiazonium intermediates.

The reaction of 1-azidocyclooctene with N-Ts imine produced 9-membered ring lactam through hydrolysis of the cyclic nitrilium ion intermediate, that is formed via exclusive migration of the tertiary alkyl group from the iminodiazonium ion (Scheme 15a). Interestingly, use of 1-azidocyclononene afforded bicyclic dihydroimidazole via intramolecular cyclization of the 10-membered ring nitrilium ion with the tethered Ts-amide moiety (Scheme 15b).

Scheme 14. Reactions of vinyl azides with N-Ts imines

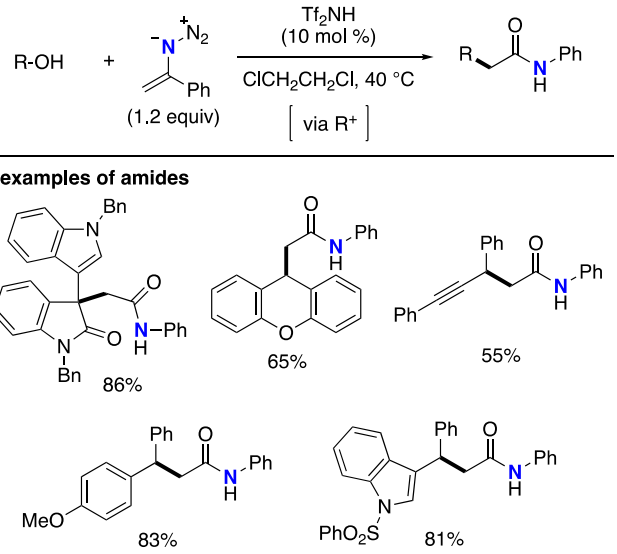


Scheme 15. BF_3-mediated reactions of cyclic vinyl azides with N-Ts imines



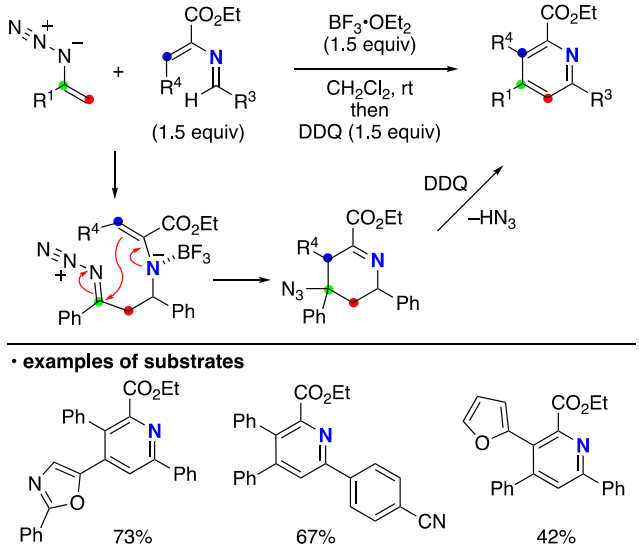
Activated alcohols could be used as the source of carbocations, that are trapped by the nucleophilic attack of vinyl azides to afford the corresponding amides.[33,34] Our group found that triflimide (Tf_2NH) efficiently serves as the specific catalysis that enables the reaction of vinyl azides with a series of alcohols as a carbocation precursor under mild reaction conditions (Scheme 16).[35,36]

Scheme 16. Tf_2NH-catalyzed reactions of vinyl azides with activated alcohols



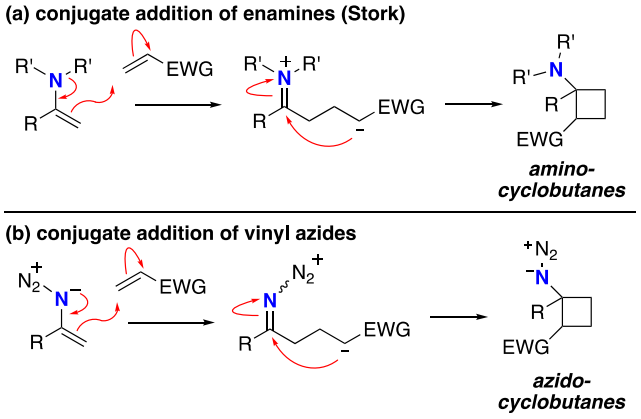
The iminodiazonium ions could be served not only as the Schmidt intermediate (for synthesis of amides via 1,2-substituent migration) but also as the π-polar electrophile, depending on tuning of the structures of carbon electrophiles. For example, use of N-alkenylaldimines instead of N-Ts ones allowed for synthesis of highly subsituted pyridines via intramolecular C-C bond formation between the resulting iminodiazonium and enamine moieties (Scheme 17).[37] The formed tetrahydropyridine intermediates could be further aromatized by subsequent treatment with DDQ to deliver the corresponding pyridines.

Scheme 17. Reactions of vinyl azides with N-alkenyl imines



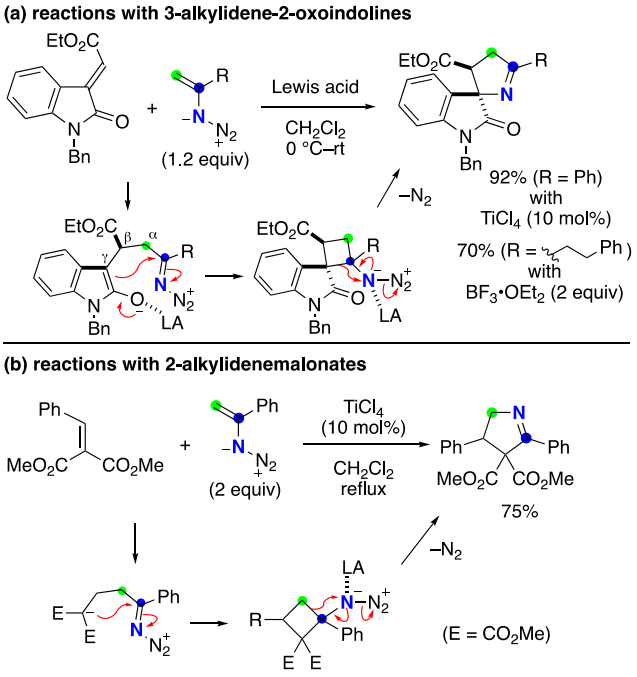
It has been known that conjugate addition of enamines to α,β-unsaturated carbonyl compounds deliver aminocyclobutanes via intramolecular C-C bond formation between the resulting iminium ion and enolate (Scheme 18a).[28] Thus, the analogous reactivity of vinyl azides could be expected in the reactions with conjugate electrophiles, that might provide azidocyclobutane intermediates via the cyclization onto the iminodiazonium ions (Scheme 18b).

Scheme 18. Conjugate addition of enamines and vinyl azides



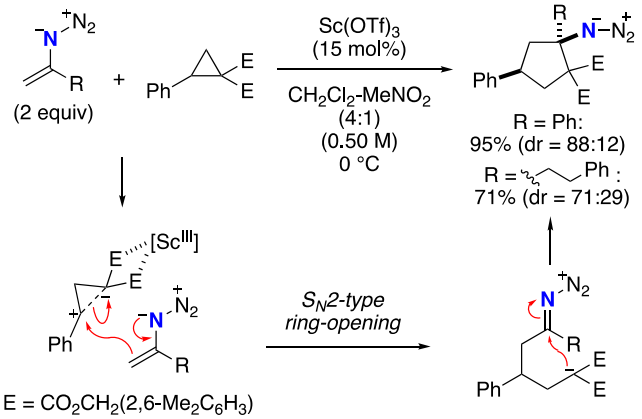
Our group disclosed that Lewis acid-mediated reactions of vinyl azides with α,β-unsaturated esters enabled efficient construction of 1-pyrroline skeletons via denitrogenative ring-expansion of the azidocyclobutane intermediates, in which the structure of the conjugate electrophiles uniquely changes the atom composition of the 1-pyrroline skeletons derived from vinyl azides (Scheme 19).[38] For example, the reactions of vinyl azides with 3-alkylidene-2-oxoindolines provided 3',4'-dihydrospiro[indoline-3,2'-pyrrol]-2-ones in diastereoselective fashion (Scheme 19a). The diastereoselective formation of azidocyclobutane intermediates is followed by denitrogenative ring-expansion of azidocyclobutanes through migration of the quaternary carbon on the 2-oxoindoline core to the nitrogen atom. On the other hand, the reactions with dimethyl 2-alkylidenemalonates afforded 4,5-dihydro-3*H*-pyrroles (Scheme 19b). The process involves cleavage of the C=C bond of vinyl azides. In this case, ring-expansion occurs via migration of the secondary carbon (marked in green) predominantly over that of the quaternary carbon, which is electronically deactivated by two methoxy carbonyl groups.

Scheme 19. Construction of 1-pyrrolines by conjugate addtion of vinyl azides



Donor-acceptor cyclopropanes[39] could be used as a 3-carbon electrophile in the reactions with vinyl azides.[40,41] Our group developed the reactions of vinyl azides and donor-acceptor cyclopropanes in the presence of $Sc(OTf)_3$ as a Lewis acid catalyst, that proceed in diastereoselective fashion to give highly functionalized azidocyclopropanes, where nucleophilic attack of vinyl azides to cyclopropanes occurs predominantly in S_N2 manner and the resulting iminodiazonium ions having a γ-carbanion subsequently cyclize to the products (Scheme 20).

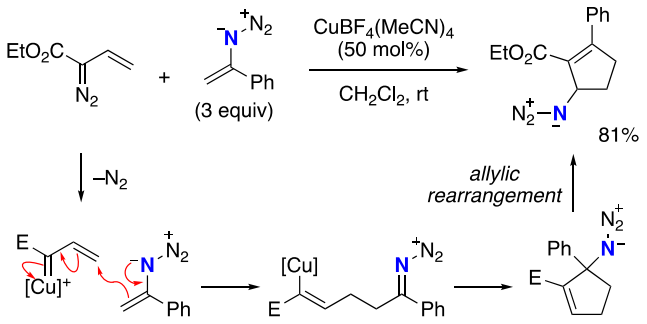
Scheme 20. Reactions of vinyl azides with donor-acceptor cyclopropanes



López reported unprecedented Cu(I)-mediated synthesis of 3-azidocyclopentenes from vinyl diazo compounds and vinyl azides through a sequence of formal [3+2]-annulation and allylic azide rearrangement (Scheme 21).[42] The process is initiated by the formation of vinyl carbene Cu complexes, that

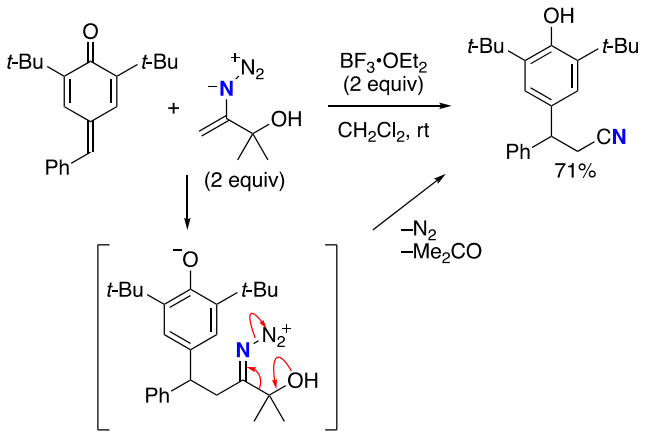
are attacked by vinyl azides to construct the 1st C-C bond. The resulting iminodiazonium ion moiety is further attacked by intramolecular vinylcopper species to build the cyclopentene scaffolds. Finally, the azido moiety was rearranged to furnish the final products.

Scheme 21. Reactions of vinyl azides with vinyl diazo compounds



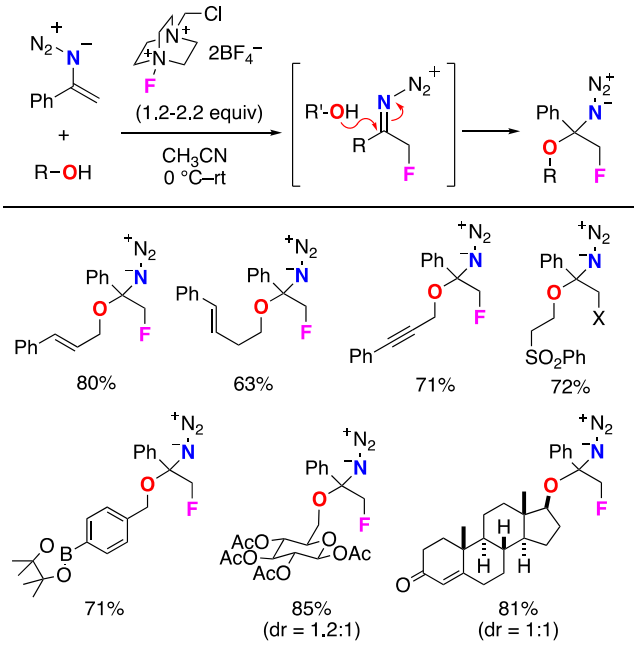
Cui disclosed a unique reactivity of 3-azido-2-methyl-3-buten-2-ol, that works as a surrogate of acetonitrile anion in the BF_3-mediated reactions with *p*-quinone methides as a conjugate electrophile (Scheme 22).[43] In this case, the corresponding iminodiazonium ion intermediates undergo denitrogenative fragmentation to give nitriles with elimination of acetone.

Scheme 22. Use of 3-azido-2-methyl-3-buten-2-ol

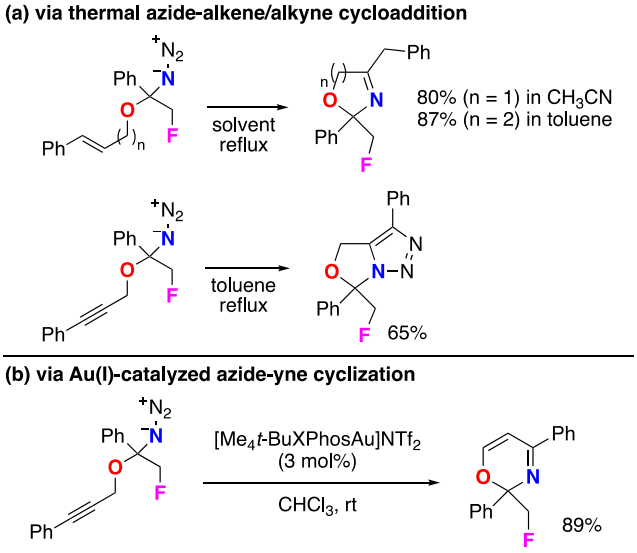


The iminodiazonoum ions could also be trapped by the external alcohol nucleophiles. Our group has developed a protocol to link variety of primary and secondary alcohols with vinyl azides through fluoroalkoxylation of vinyl azides (Scheme 23).[44] Treatment of a mixure of vinyl azides and alcohols with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (Selectfluor) in acetnitrile delivers α-alkoxy-β-fluoroalkylazides, through electrophilic fluorination of vinyl azides followed by nucleophilic addition of present alcohols onto the resulting α-fluoro-iminodiazonium ions. The linked products derived from unsaturated alcohols could be converted into flluoromethyl-containing nitrogen-heterocycles via thermal azide-alkene/alkyne cycloaddition, azide-alkyne cycloaddition (Scheme 24a) or Au(I)-catalyzed denitrogenative 6-endo-dig azide-yne cyclization (Scheme 24b).[45]

Scheme 23. Linking of alcohols with vinyl azides through alkoxyfluorination



Scheme 24. Synthesis of fluoromethyl-containing nitrogen-heterocycles



Conclusions and Future Outlook

This synopsis highlighted recent advancement of the synthetic applications of vinyl azides. The rational design of the reaction settings and chemical structures of vinyl azides as well as their reactants enabled predictable switch of the reaction courses, in which vinyl azides can serve as either a radical acceptor or an enamine-type nucleophile.[46,47] It is our strong belief that the leveraging of vinyl azides to exploit new meth-

ods to synthesize nitrogen-containing molecules of medicinal and materials importance continues to progress and thus advance our synthetic capability.

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Notes

The authors declare no competing financial interest.

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Atsushi Kaga

Shunsuke Chiba

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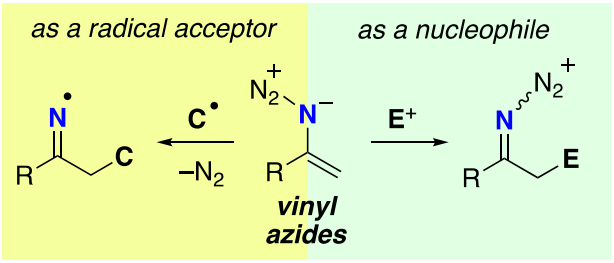
(47) *Caution:* Organic azides are potentially explosive substances that can decompose violently with the slight input of energy from external sources (heat, light, pressure, etc). All vinyl azides prepared in our works (for detailed methods to prepare vinyl azides; see the Supporting Information of our respective publications) are enough stable to be stored at least for half a year under –20 °C. We have never experienced a safety problem with these compounds.


as a radical acceptor
as a nucleophile
N
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–N2
N2+
N–
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vinyl
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N2+
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