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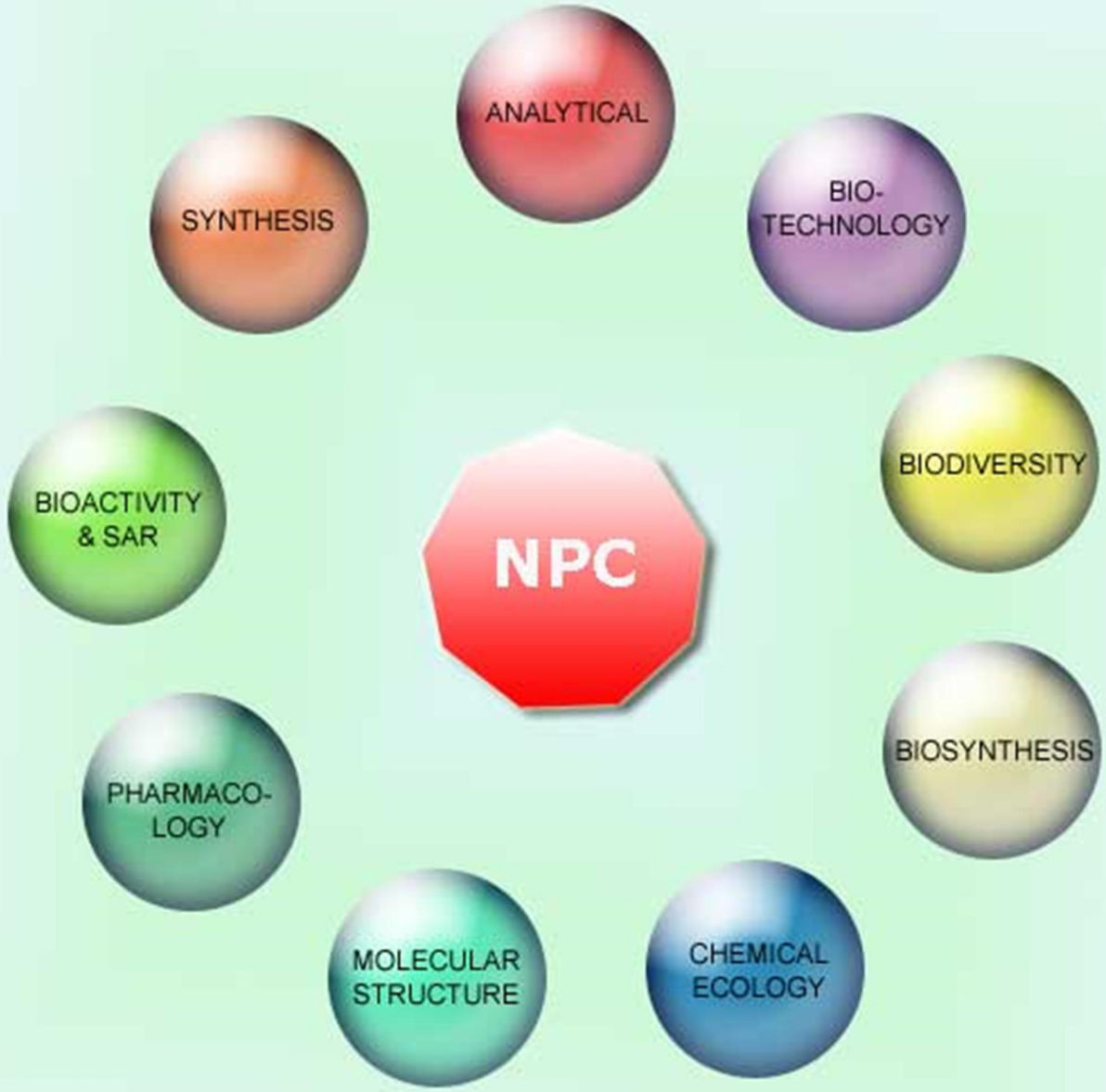

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Recent Applications and Developments of Organic Azides in Total Synthesis of Natural Products

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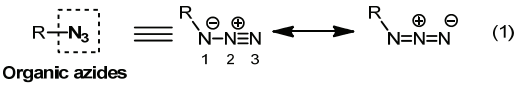
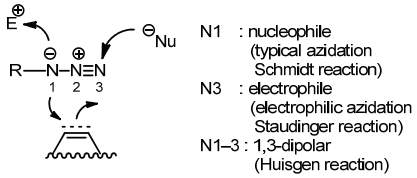
Organic azides have been exploited since their discovery because of their high reactivities. Various organic reactions using azides have been synthetically applied in chemical biology, pharmaceuticals, medicinal, and agricultural areas. In this review, we present some recent applications and developments of organic azides in the total synthesis of natural products (mostly within five years), especially alkaloids. We focus not only on application examples of organic azides, but also show their preparation methods including recently reported procedures concerning their decomposing and reducing methods in the syntheses of bioactive molecules.

Keywords: Organic azides, total synthesis, alkaloids, Schmidt reaction, 1,3-dipolar cycloaddition, Curtius rearrangement, Staudinger-aza-Wittig reaction.

In organic and medicinal chemistry, organic azides (R-N_3) have been well studied since Peter Grieß synthesized the first organic azide, phenyl azide [1,2]. After the development of Curtius rearrangement using hydrogen azide (HN_3), which produces isocyanates from corresponding acyl azides [3], many organic azide-utilizing reactions were produced. Despite their explosive and toxic properties [4], organic azides are attractive not only industrially, but also agriculturally, and pharmaceutically. For these reasons, organic azide chemistry has developed extensively [1,2,5–8]. Interestingly, natural products possessing azide groups have not been isolated to date [2], while those having 1,2,3-triazine [9] and 1,2,3-triazene structures [10] have been found in nature.

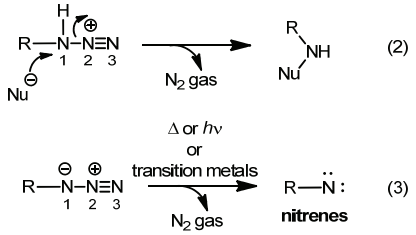


Scheme 1: Structure and resonance forms of organic azides



Scheme 2: Property of organic azides.

Structurally, azides consist of three nitrogen atoms in linear form (not straight, but bent slightly; calculated angle of N1-N2-N3 is 172.7° and R-N1-N2N3 is 115.2° in methyl azide) (Scheme 1, eq. 1)[1,2]. Organic azides show different chemical reactivities: the N1 atom can work as a nucleophile, and the N3 position nitrogen atom shows electrophilic reactivity (Scheme 2). The specific efficiency of organic azides is its character as 1,3-dipolar and this provides [3+2] cycloadditions with unsaturated bonds to give triazolines, triazoles and tetrazoles. Recently, the cyclization reactions of organic azides with alkynes (Huisgen reaction) [11] have been a focus in the area of chemical biology [12,13] and extensive reports have been published (Meldal-Sharpless click reaction or Copper-Catalyzed Azide-Alkyne Cycloaddition—CuAAC) [14–17].



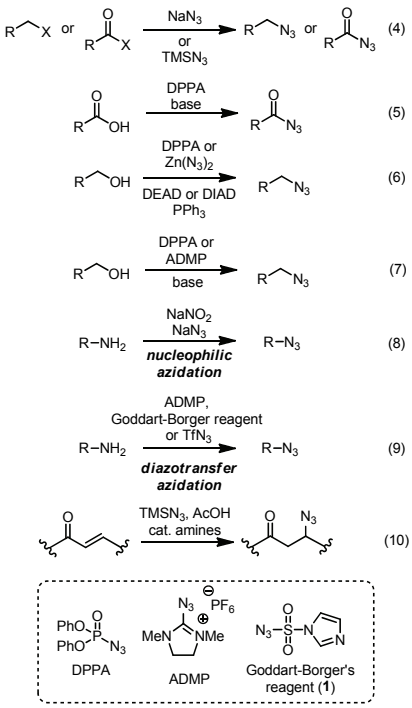
Scheme 3: Nitrogen gas-releasing reactions of organic azides

Organic azides consist of amines (N1) and the leaving group diazonium cation (N2N3) producing nitrogen gas. Actually, the bond length of N1–N2 (1.237 Å) is computationally longer than that of N2–N3 (1.156 Å) in methyl azide. Thus, azides can easily evolve nitrogen gas in many reactions (Scheme 3, eq. 2). Especially, heating conditions or photoirradiations produce nitrenes from organic azides, which are highly reactive and give aziridinations and C-H aminations (eq. 3).

In this review, we describe the more recent applications of organic azides in the synthesis of natural products. The reaction steps involving the use of this functional group as well as a description of the methods of decomposition/reduction are listed as follows: (1) preparation of organic azides; (2) C-H insertion reaction by nitrenes; (3) Curtius rearrangement; (4) Schmidt reaction; (5) [3+n] cycloaddition reaction; (6) Staudinger/aza-Wittig reaction and (7) organic azides as masked amino functional group.

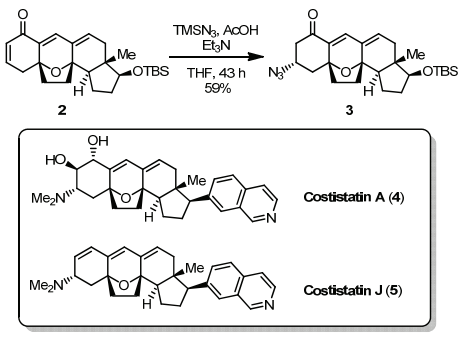
Preparation of organic azides: Before reviewing the more recent synthetic applications of organic azides, here we show their general preparation methods [4,18]. General procedures are summarized in equations 4–10 in Scheme 4. To prepare organic azides, use of volatile, toxic and highly explosive hydrogen azide should be avoided. S_N2 azidation of alkyl halides and acyl halides using nucleophilic azides, mostly sodium azide (NaN_3), is the most general method (Scheme 4, eq. 4). For transformation of alcohols and carboxylic acids, Shioiri reagent (DPPA—diphenylphosphoryl azide) is often used (eq 5) [19,20]. To replace hydroxy groups, it has been reported that Mitsunobu reaction conditions (PPh_3 and

azodicarboxylates DEAD/DIAD) can introduce azide groups with DPPA or zinc azide (eq 6) [21,22]. Direct conversion method without Mitsunobu conditions was also published (eq 7) [23]. Recently, Kitamura and co-workers demonstrated that the safer and more stable azido compound ADMP (2-azido-1,3-dimethylimidazolinium hexafluorophosphate) was a good azidation reagent [24,25]. Azides can be prepared from primary amines by way of diazoniumion formation followed by nucleophilic azidations (eq 8). Aryl azides are usually synthesized with these procedures. From primary amines, diazotransfer reaction can also deliver organic azides (eq 9). However, use of unstable and explosive trifluoromethanesulfonyl azide (TfN_3) was a problem. Recently, safer diazotransfer reagents, ADMP [24,25] and Goddart-Borger reagent (**1**) [26–28], appeared and can be used instead of TfN_3.

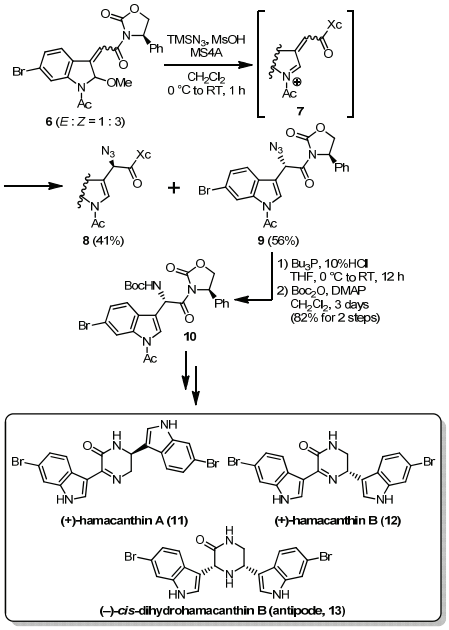


Scheme 4: General methods for introduction of azides

1,4-Addition of azides is problematic because a formal [3+2] reaction could occur as a side reaction. Miller et al. reported successful reaction conditions to perform preferential 1,4-addition of azides to α,β-unsaturated carbonyl compounds (eq 10) [29], which was recently demonstrated in the model study in total synthesis of cortistatin A **4** and J **5** by Yamashita and Hirama's group (Scheme 5) [30].



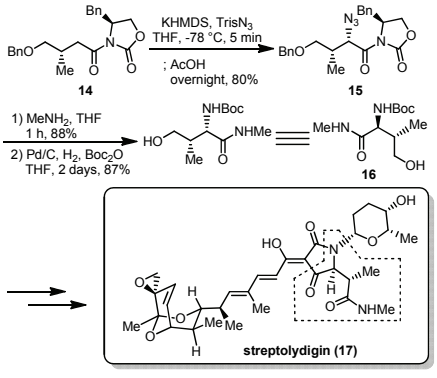
Scheme 5: 1,4-Azidation in a model study of total syntheses of costistatins A and J by Yamashita and Hirama et al.



Scheme 6: 1,4-Azidation of eniminium intermediate in total syntheses of marine bisindole alkaloids by Kawasaki et al.

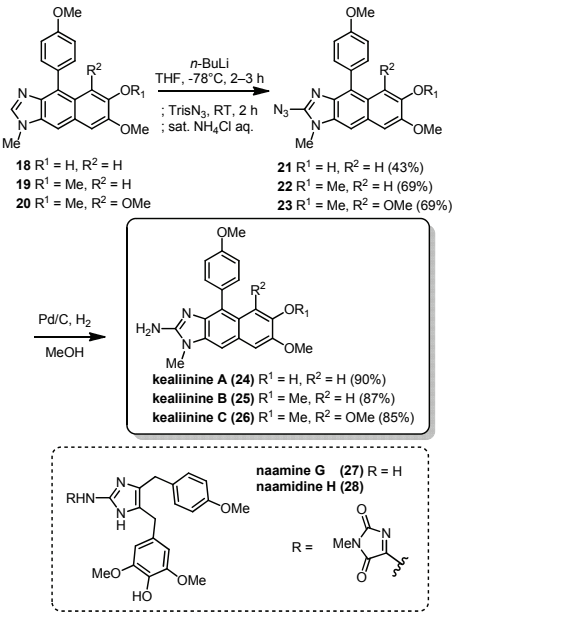
1,4-Azidation has also been reported in the total syntheses of marine bisindole alkaloids hamacanthin A (**11**), B (**12**) and the antipodode of *cis*-dihydrohamacanthin B (**13**) by Kawasaki et al. (Scheme 6) [31]. Treatment of 2-methoxyindoline derivative **6** with methanesulfonic acid generated eniminium intermediate **7**, and then 1,4-azidation proceeded with $TMSN_3$ to give a desired azide compound **9** in 56% along with its epimer **8**. The azide group in **9** was reduced with the Staudinger reaction followed by protection to afford **10**, which was converted to natural products **11**, **12** and antipode **13**.

Other carboazidations methods of unsaturated carbon-carbon bonds are presented in the section of Schmidt reaction.



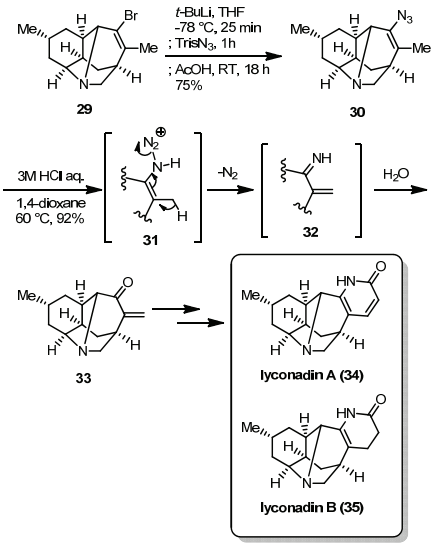
Scheme 7: Evans diastereoselective nucleophilic azidation in total synthesis of streptolydigin and its analogues by Kozmin et al.

Not only nucleophilic azidation, but also the direct introduction of azides by electrophilic azidations of carbanions have been reported, which are performed with sulfonyl azides, usually $TrisN_3$ (2,4,6-trimethylbenzenesulfonylazide). In the reaction with enolates, the proton source for the quenching reaction is critical and Evans and co-workers revealed that acetic acid was the best [32]. Kozmin et al. reported total syntheses and biological activities of streptolydigin **17** and its analogues using this stereoselective electrophilic azidation reaction (Scheme 7) [33,34].



Scheme 8:Nucleophilic Ar-azidation in total synthesis of kealiinines, naamine G and naamidine H by Lovely et al.

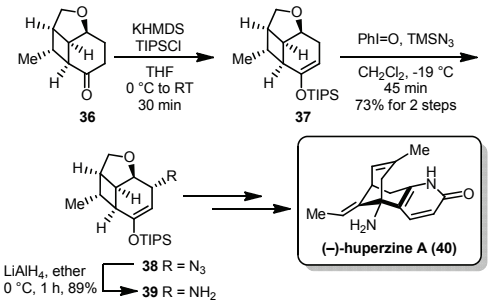
Lovely and co-workers reported the total synthesis of some components of the kealiinine family (Scheme 8) [35]. In their synthesis, the 2-aminoimidazole moieties were successfully constructed in the late stages of syntheses by way of lithiation-electrophilic azidation of the corresponding imidazoles **18**–**20**. The following hydrogenolysis gave kealiinines A **24**, B **25** and C **26**. His group also achieved concise total synthesis of related naamine G **27** and naamidine H **28** with the same strategy [36].



Scheme 9: Total synthesis of lyconadins using nucleophilic azidation by Fukuyama et al.

Very recently, Fukuyama and co-workers reported total synthesis of pentacyclic alkaloid lyconadin A **34** and B **35**(Scheme 9) [37,38]. After some investigation in modified syntheses [38], they found that nucleophilic azidation was the best way to construct the enone **33** which was essential for pyridone core synthesis. Lithiation of vinyl bromide **29** followed by trapping with Tris-N_3–acetic acid quenching gave vinyl azide **30**. Transformation of 2-methylvinyl azide moiety of **30** into enone was performed by heating in the presence of acid. The protonation of the azide triggered nitrogen evolution (Schmidt reaction) to give unsaturated imine **32**. The following hydrolysis afforded desired enone **33**.

In 1992, Magnus et al. discovered allylic azidation of triisopropylsilyl enol ethers with $TMSN_3$ in the presence of hypervalent iodines [39]. Recently, White et al. utilized this reaction to introduce an amino group in the total synthesis of huperzine A **40** (Scheme 10) [40].

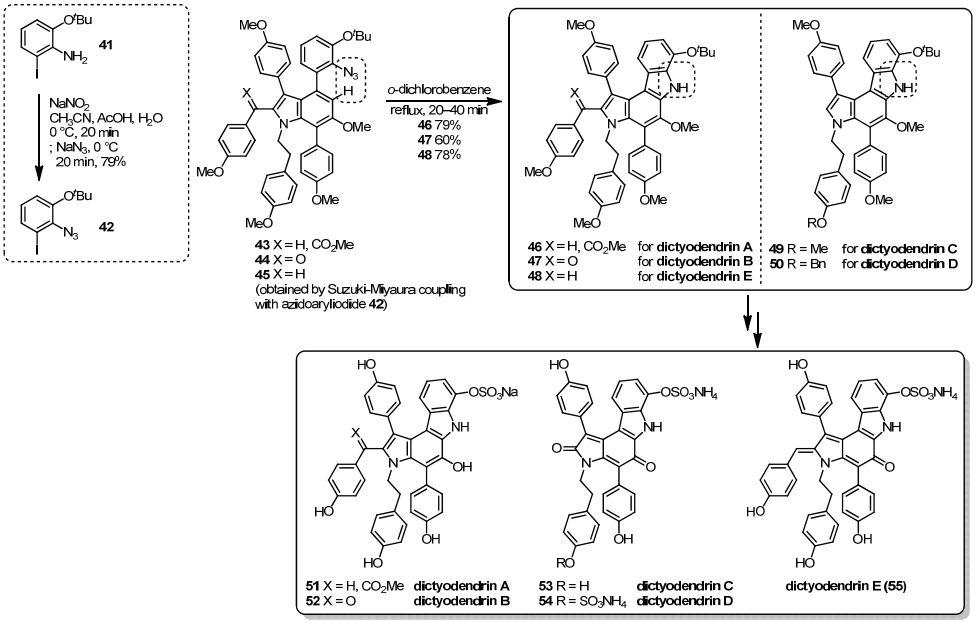


Scheme 10: White's total synthesis of huperzine A by way of the allylic C-H azidation of TIPS enol ether.

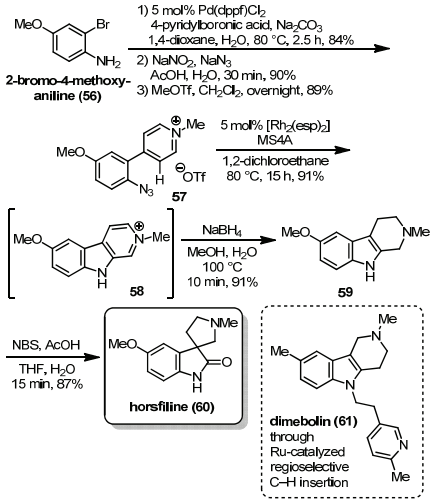
C-H insertion reaction by nitrene: As mentioned in Scheme 3, azides release nitrogen gas under high heat or photoirradiation conditions, which generates unstable but highly reactive nitrenes. These species have a special character that could accomplish C-H insertion reactions to set carbon–nitrogen bonds. Especially with *o*-azidostyrenes, thermolysis gives indoles through the C-H insertion reaction of nitrenes (Sundberg indole synthesis) [41,42]. The products are carbazoles if the reactions are performed with biarylazides [43,44].

Tokuyama et al. reported efficient total syntheses of dictyodendrins A–E **51**–**55** possessing inhibitory activity against telomerase, which were isolated from Japanese marine sponge *Dictyodendrilla verongiformis* (Scheme 11) [45,46]. Carbazole skeletons in dictyodendrins were constructed from biaryl azides **43**–**45**, which were prepared with azidoiodobenzene **42** through Suzuki-Miyaura coupling [47]. Refluxing the reaction mixture of each **43**–**45** in *o*-dichlorobenzene generated nitrenes, and the C-H insertion reactions were smoothly performed to obtain the desired carbazoles **46**–**48**, the synthetic intermediates of dictyodendrins A **51**, B **52** and E **55**. Two other dictyodendrins, C **53** and D **54**, were also successfully synthesized from **49** and **50** by the same strategy.

Also metallonitrenes are effective for C-H insertions and their activities are easily controllable by changing ligands on the metal catalysts. Thermal conditions of nitrene insertion reaction with arylazides require a high temperature, and sometimes afford products with low regioselectivity. On the other hand, with appropriate metal catalysts to form metallonitrenes, regioselective C-H insertion reactions usually occur at a lower temperature. Driver et al. exploited the use of metal catalysts for indolization reactions. They found that rhodium efficiently catalyses the reactions of nitrene insertion as demonstrated through the total synthesis of a component of a Malaysian medicinal plant *Horsfieldia superba,* (±)-horsfiline **52** from biphenyl **57** via β-carboline **58** (Scheme 12) [48]. Arylazide moiety in **57** was synthesized by S_NAr reaction from commercially available aniline **56**. Driver and co-workers also reported ruthenium-catalyzed γ-carboline synthesis from arylazides, in which was demonstrated regioselective synthesis of dimebolin **61**, a synthetic drug possessing promising activity for the treatment of Alzheimer's and Huntington's disease [49].

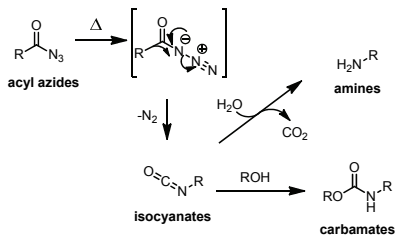


Scheme 11: Total syntheses of five dictyodendrins A–E by Tokuyama et al.

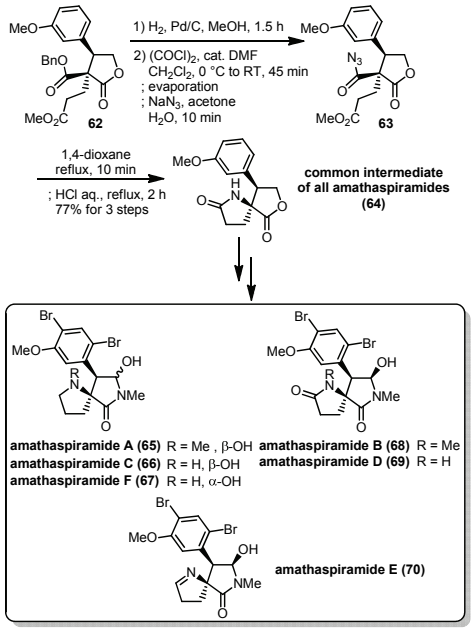


Scheme 12: Transition metal-catalyzed indole synthesis from aryl azides and its applications to synthesis of bioactive molecules by Driver et al.

Curtius rearrangement: The Curtius rearrangement is a reaction providing isocyanates from acyl azides though migration of substituents (Scheme 13). When the resulting isocyanates are treated with water, primary amines can be obtained. With alcohols, the products are carbamates, namely protected amines. Because of the usefulness and ease of reactions, Curtius rearrangement has been widely applied for the preparation of *tert*-alkyl amines by losing carbonyls.



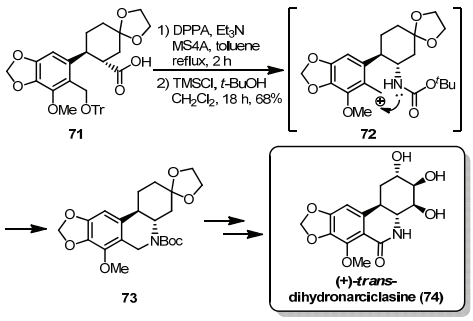
Scheme 13: Curtius rearrangement.



Scheme 14: Total syntheses of all amathaspiramides using Curtius rearrangement by Fukuyama et al.

Amathaspiramides isolated from a New Zealand marine bryozoan have densely functionalized diazaspiro[3.3]nonane frameworks which are synthetically challenging structural motifs. In 2012, Fukuyama et al. reported elegant asymmetric total syntheses, which provided all six amathaspiramides **65**–**70** from a common spirocyclic intermediate **64** (Scheme 14) [50]. The amine-containing quaternary carbon center in **56** was constructed by Curtius rearrangement followed by one-pot hydrolysis and lactamization to form a spirocyclic structure.

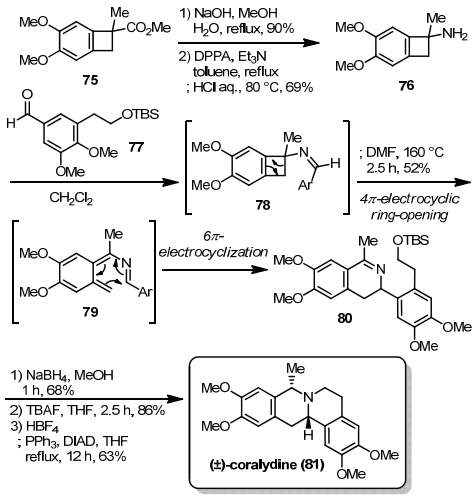
Tomioka et al. utilized Curtius rearrangement in the total synthesis of anti-cancer alkaloid *trans*-dihydronarciclasine **74** isolated from the Chinese medicinal plant *Zephyranthes candida* (Scheme 15) [51]. Acylazide was prepared from carboxylic acid **71** with DPPA



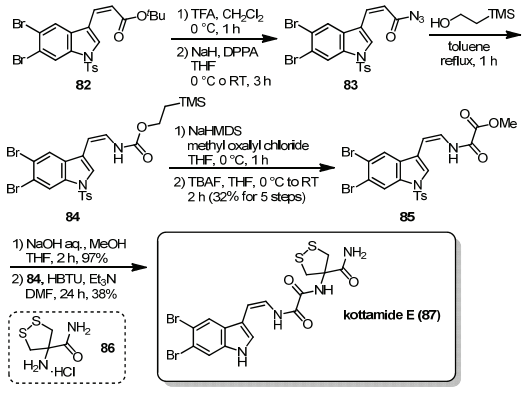
Scheme 15: Total synthesis of *trans*-dihydronarciclasine by Tomioka et al.

and the resulting isocyanate was trapped with *tert*-butanol to afford Boc-amine **72**. During this reaction, generated benzylic carbocation was captured with amide to give tricyclic compound **73**, which was delivered to (+)-*trans*-dihydronarciclasine **74**.

Baudoin and co-workers used Curtius rearrangement to construct tertiary alkylamine in the total synthesis of tetrahydroprotoberberine alkaloid coralydine **81** (Scheme 16) [52]. Their key strategy toward isoquinoline synthesis was cascade pericyclic reactions. Primary amine **76**, derived from methyl ester **75** by way of Curtius rearrangement, was coupled with aldehyde **77** to form imine **78**. Without purification of **78**, heating conditions produced dihydroisoquinoline **80** through 4π-electrocyclic ring-opening/6π-electrocyclization cascade. A further three steps furnished (±)-coralydine **81**.



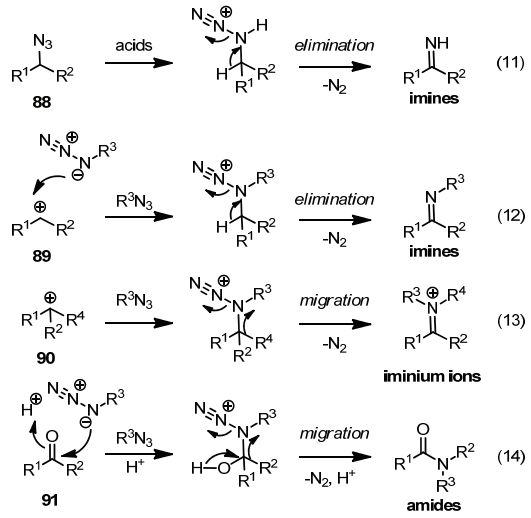
Scheme 16: Total synthesis of coralydine by Baudoin et al.



Scheme 17: Total synthesis of kottamide E by Grainger et al.

Very recently, the first total synthesis of kottamide E **87** isolated as a minor component of New Zealand ascidian was reported by Grainger and co-workers (Scheme 17) [53]. The structure of **87** features a dithiolane ring and a labile *Z*-enamide-containing indole. The unstable *Z*-enamide **84** was prepared by Curtius rearrangement of *Z*-acryloyl azide **83** followed by capturing the resulting isocyanate with 2-trimethylsilylethanol. Kottamide E **87** was obtained from Teoc-*Z*-enamide **84** in four steps.

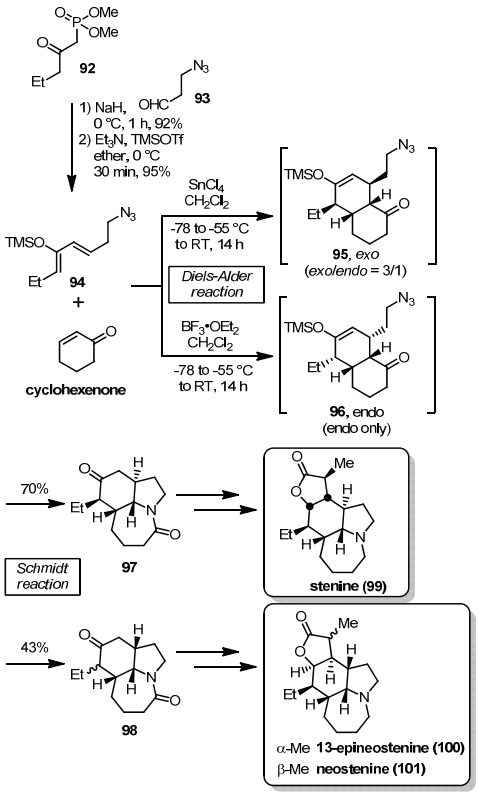
Schmidt reaction: Schmidt reaction (Schmidt rearrangement) is a rearrangement reaction of alkyl azides (Scheme 18). In the presence of acids, secondary or tertiary alkylazides lose nitrogen by elimination or migration of substitutes. The secondary alkylazides give unprotected imines (eq 11) and tertiary alkylazides produce substituted imines. This type of reaction was already shown in Scheme 8. To avoid the use of explosive HN_3, Schmidt reaction is usually performed with alkylazides and carbocations. With alkylazides, substituted imines are obtained from secondary carbocations (eq 12) [54] and iminium ions are from stable tertiary carbocations (eq 13). In most cases, Schmidt reaction has been demonstrated intramolecularly with carbonyl compounds and alkylazides, which provides amides (lactams with ring-expansion, eq 14). These reactions (Schmidt reaction with ketones and alkylazides) are also called Boyer reaction [55].



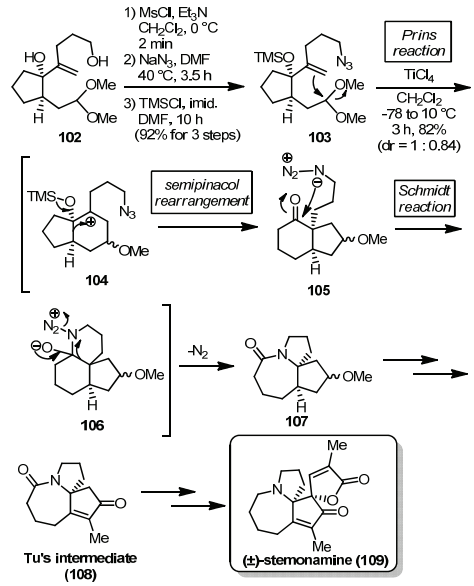
Scheme 18: Schmidt reactions.

Jeffrey Aubé has developed Schmidt reaction and reported its application to complex natural product syntheses. In 2008, Aubé and co-workers published concise and stereocontrolled total syntheses of stemona alkaloids stenine **99**, 13-epineostenine **100** and neostenine **101** associated with insecticidal anthelmintic, antitussive and various neurochemical effects (Scheme 19) [56]. Their key step was cascade Diels-Alder/intramolecular Schmidt reaction with azido diene **94** and cyclohexenone, which gave tricyclic lactam in one step. Exo/endo selectivity in the Diels-Alder reaction was excellently controlled by changing Lewis acids, and after Schmidt reaction steps, synthetic intermediate lactams **97** and **98** were obtained respectively.

Tu et al. also have studied organic azide chemistry and its application to natural product syntheses. His group achieved modified synthesis of stemonamine **109** through an elegant skeletal rearrangement by way of Prins cyclization/semipinacol rearrangement/Schmidt reaction cascade (Scheme 20) [57]. The treatment of azide **103** with titanium chloride allowed Prins



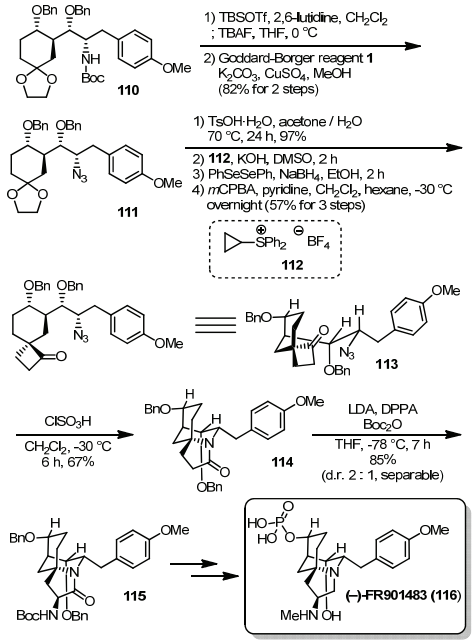
Scheme 19: Total syntheses of stenimona alkaloids by way of Diels-Alder reaction–intramolecular Schmidt reaction cascade by Aubé et al.



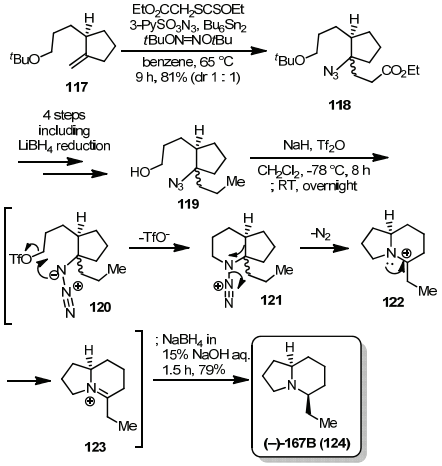
Scheme 20: Improved synthesis of stemonamine by way of Prins reaction/semi-pinacol rearrangement/Schmidt reaction cascade by Tu et al.

cyclization followed by semipinacol rearrangement to give bicyclic ketone **105**, which was subjected to the second skeletal rearrangement through Schmidt reaction in situ to provide tricyclic amide **107**. **107** was transformed into the synthetic intermediate of stemonamine **108**, which was reported in their previous total synthesis [58].

Recently, Tu et al. reported a total synthesis of immunosuppresive alkaloid FR901483 **116** (Scheme 21) [59]. The azide **111**, prepared from the amide **110** by diazo transfer, was performed with Goddard-Borger reagent **1** to afford cyclobutanone **113** via four steps. The Schmidt reaction was performed with chloroacetic acid to obtain a tricyclic lactam **114** in 67%. Tu et al. used organic azide again to construct another carbon-nitrogen bond. DPPA with $(Boc)_2O$ under basic conditions reported by Heimgartner et al. [60] successfully gave N-Boc-embedded lactam **115** which was delivered to FR901483 **116**.



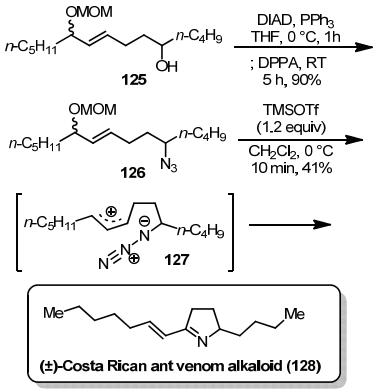
Scheme 21: Total synthesis of FR901483 using Schmidt reaction by Tu et al.



Scheme 22: Total synthesis of alkaloid (–)-167B utilizing S_N2-type Schmidt reaction by Renaud et al.

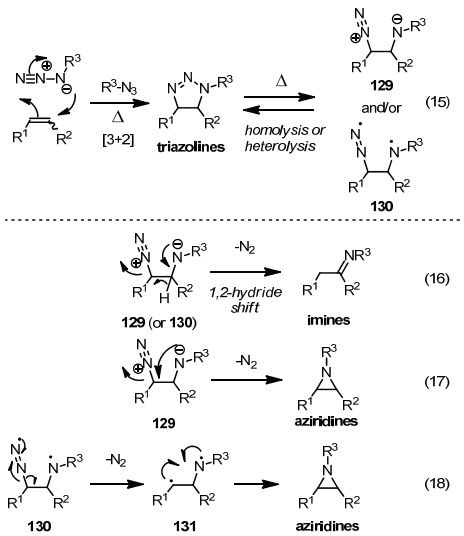
The Schmidt reaction is usually performed with carbonyls or carbocations under acid conditions. However, Renaud and co-workers developed S_N2-type Schmidt reaction under basic conditions. With triflated primary alcohol, cyclization followed by ring-rearrangement/imine formation could be performed at ambient temperature or below. They demonstrated the efficiency of this novel strategy in the total synthesis of indolizidine alkaloid 167B **124** isolated from the skin of frogs (Scheme 22) [61]. The reaction precursor of tertiary alkyl azide **119** was prepared by way of radical carboazidation of chiral methylenecyclopentane **117**, which was also developed by their group [62].

Although the Schmidt reaction could be performed by generation of carbocations, the use of more active allyl cations were limited because of the difficulty of reaction control. Tanimoto and co-workers developed the application of allylic alcohols in organic azide cyclization providing α,β-unsaturated imines which had been difficult to prepare due to their stability. With this new method, a total synthesis of Costa Rican ant venom alkaloid **128** possessing conjugated imine structure was achieved (Scheme 23) [63]. The key reaction was set in the last step of the synthesis and the cyclization precursor **126** derived from **125** by Mitsunobu azidation was successfully converted to acid-sensitive natural product **128** without a specific deprotection step.



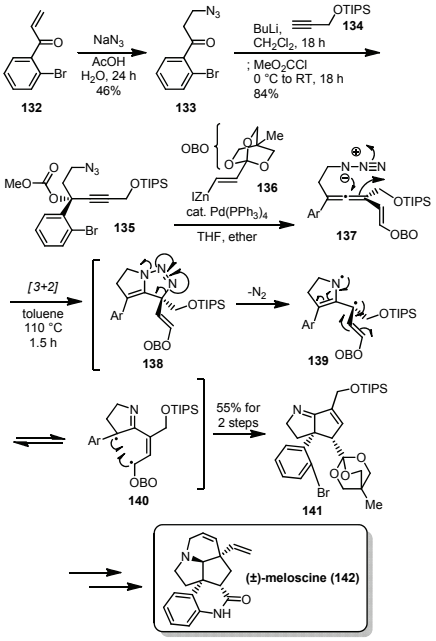
Scheme 23: Total synthesis of Costa Rican ant venom using allyl cation-mediated Schmidt-type reaction to directly form unsaturated imine by Tanimoto et al.

[3+n] Cycloaddition reactions: Organic azides can act as 1,3-dipolar and thus can provide [3+n] cycloaddition products. In most cases, [3+2] products from olefins/alkynes have been reported and recently azide-alkyne [3+2] reactions have been exploited. The reactions of organic azides with olefins give triazolines (Scheme 24). However, triazolines are unstable under heating or acid conditions, and ring-opening reactions through homolysis/heterolysis proceed (Scheme 24, eq 15). From these β-diazoamine structures **129** and/or **130**, imines (by hydride shift, eq 16) and/or aziridines (by recombination by losing N_2, eqs 17 and 18) could be obtained. The product ratio depends on the substrates. Otherwise, acid treatment of triazolines produces mostly aziridines [64,65].



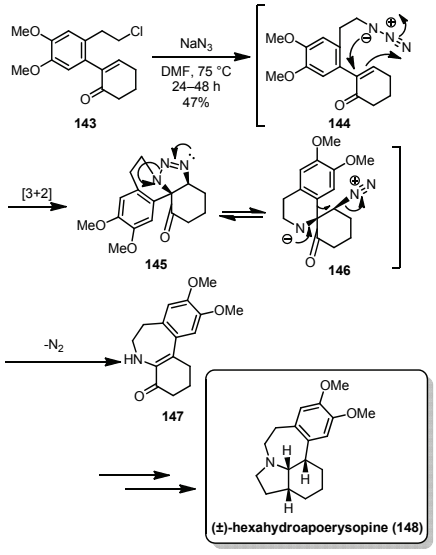
Scheme 24: Reaction mechanisms of azide-olefin [3+2] cycloaddition and further transformations.

Meloscine **142**, an extract of the Chinese medical plant *Melodinus scendan*, features an azabicyclo[3.3.0]octane core embedded in a complex pentacyclic skeleton. Feldman et al. reported its total synthesis by way of allene-azide [3+2] cyclization/ring-opening/recombination cascade as a key reaction (Scheme 25) [66].



Scheme 25: Total synthesis of meloscine performed with allenyl azide cyclization cascade by Feldman et al.

Azido-Michael addition of **132** followed by propargyl carbonate synthesis gave **135**, which was converted to azido allene **137** by Pd-catalyzed allene synthesis with organozinc **136**. Heating conditions converted **137** to triazoline **138**, which released N_2 to generate biradicals **139** and **140.** The following cyclization gave **141**, thus affording the azabicyclo[3.3.0]octane core in only one step.

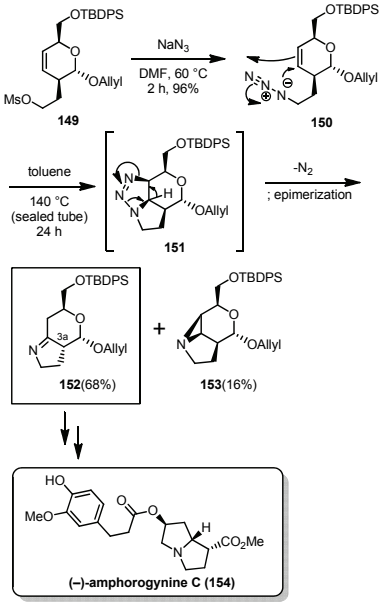


Scheme 26: Total synthesis of hexahydroapoerysopine through azide-olefin [3+2] cycloaddition followed by ring-expansion reaction by Tu et al.

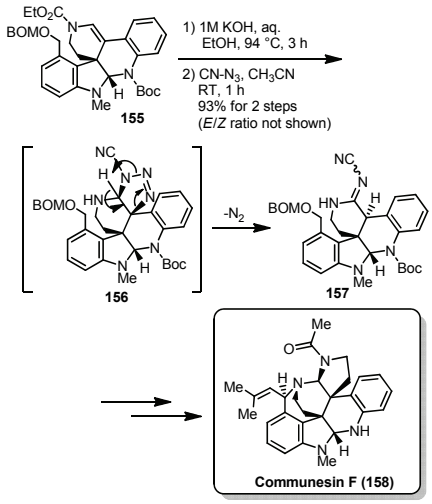
Tu et al. achieved total synthesis of polycyclic alkaloid hexahydroapoerysopine **148** by way of azide-olefin [3+2] cycloaddition/skeletal rearrangement cascade (Scheme 26) [67]. S_N2 azidation of alkyl chloride **143** with sodium azide under heating

conditions let **144** begin *in situ* [3+2] cycloaddition to form triazoline **145**. Since triazoline **145** and diazo **146** were in equilibrium, elimination of nitrogen gas along with skeletal rearrangement was proceeded by further heating to give tricyclic α-aminoenone **147**, an intermediate of (±)-hexahydroapoerysopine **148**.

Pyrrolizidine alkaloid amphorogynine C **154** was isolated from the New Caledonian plant *Amphorogynine spicata* in 1998. Mann et al. demonstrated its first total synthesis utilizing azide-olefin [3+2] cycloaddition/imine formation associated with epimerization at C-3a to afford imine **152** (Scheme 27) [68]. As reported in some articles [61,62], thermolysis of the unstable triazoline intermediate **151** released nitrogen gas to give the desired imine **152** along with undesired aziridine **153**.



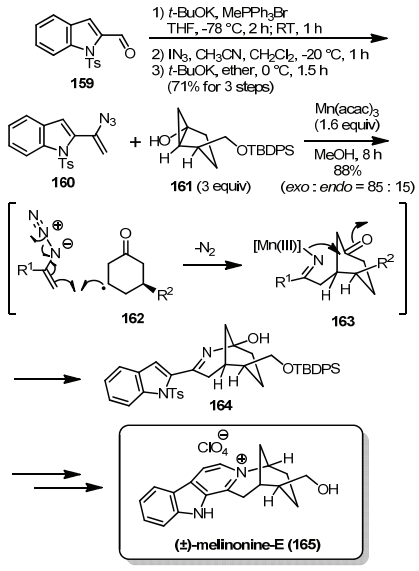
Scheme 27: Total synthesis of amphorogynine C through intramolecular azide–olefin cycloaddition by Mann et al.



Scheme 28: Azide–olefin(enamine) [3+2] cycloaddition reaction in Weinreb's total synthesis of communesin F.

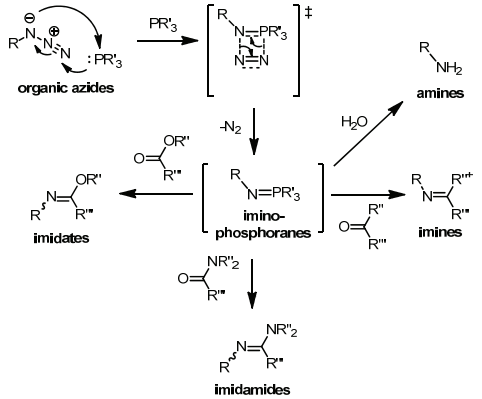
Due to the strong cytotoxicity and the intriguing complex structure, marine indole alkaloid communesin F **158** has been an attractive target for synthetic chemists. In 2010, Weinreb et al. reported a total synthesis of (±)-communesin F **158** (Scheme 28) [69,70]. To this end, azide-enamine [3+2] cycloaddition reaction was chosen. Enamide **155** was deprotected to obtain unstable enamine which was treated with cyanogen azide at room temperature in 1 h to afford the N-cyanoamidine **157** probably via triazoline **156**. Further transformation gave communesin F **158**.

Most cyclization reactions of organic azides are [3+2]. On the other hand, Chiba and co-workers developed manganese-mediated formal [3+3] cycloadditions with vinyl azides and cyclopropanols. With this method, they accomplished the total synthesis of pentacyclic indole alkaloid (±)-melinonine-E **165** (Scheme 29) [71]. Vinyl azide **160** prepared from indole-2-carboxaldehyde **159** through the Wittig reaction, iodoazidation and β-elimination was treated with cyclopropanol **151** in the presence of $Mn(acac)_3$ to obtain azacyclic compound **154** with good diastereoselectivity [72]. Imine **164** was delivered to melinonine-E **165** as a perchlorate salt in 6 steps.



Scheme 29: Total synthesis of melinonine-E demonstrated with manganese (III)-mediated formal [3+3]-annulation of vinyl azide by Chiba et al.

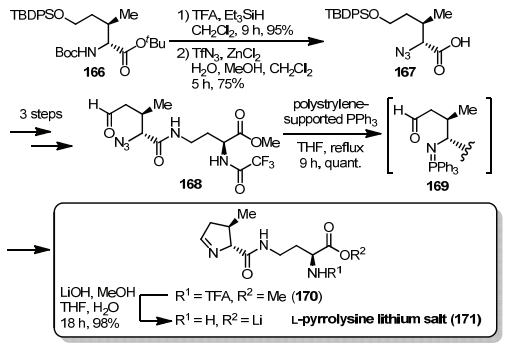
Staudinger/aza-Wittig reaction: Similar to Wittig reaction, the reactions with iminophosphoranes and carbonyls can provide imines (Scheme 30). Iminophosphoranes can be preparable by the reduction of organic azides with phosphines (Staudinger reaction) [73]. If iminophosphoranes are quenched with water, primary amines are the products and if ketones are added to the reaction



Scheme 30: Typical reaction mechanisms of Staudinger reaction and the following aza-Wittig reaction.

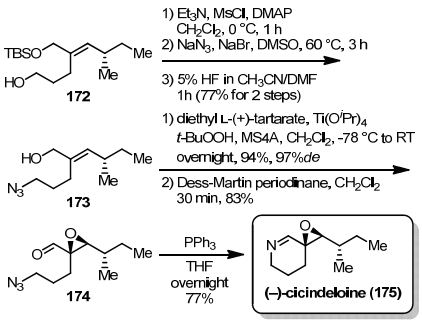
mixtures, corresponding imines can be obtained (Aza-Wittig reaction). The aza-Wittig reaction is a powerful method for small–medium ring imine formations and chemists would be free from handling reactive and highly polar amines. Especially, the intramolecular aza-Wittig reaction can afford imidates with esters, and imidamides with amides. These sequences are called the Staudinger/aza-Wittig reaction process.

L-Pyrrolysine is the newly discovered 22nd genetically encoded amino acid next to selenocysteine (21st). For biological study, pyrrolysine is an important synthetic target in order to prepare isotope-labeled molecules and modified derivatives. Kiessling et al. reported an asymmetric total synthesis of L-pyrrolysine using late-stage pyrroline-ring formation by the Staudinger/aza-Wittig reaction (Scheme 31) [74]. Aldehyde-possessing azide **168** from **167** prepared by diazo transfer with TfN_3 was reduced with polymer-supported triphenylphosphine and the resulting putative iminophosphorane **169** underwent aza-Wittig cyclization to afford pyrroline **170** in quantitative yield. Finally, global deprotection was performed to obtain lithium salt of L-pyrrolysine **171**.



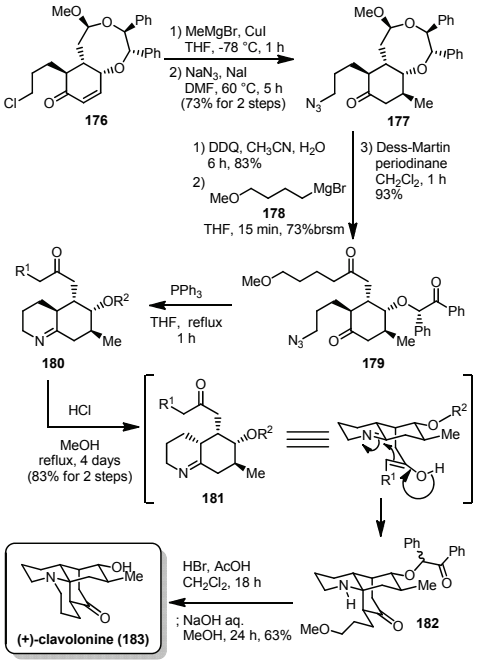
Scheme 31: Staudinger/aza-Wittig reaction in total synthesis of pyrrolysine by Kiessling et al.

In 2012, Seifert and co-workers isolated a novel cyclic imine compound possessing epoxide from the beetles *Stenus cicindeloides* and *Stenus solutus* (Scheme 32) [75]. The absolute configuration of this alkaloid cicindoloine **175** was elucidated by NMR, chiral gas chromatography and total synthesis. Through the general azidation procedure, alcohol **172** was converted to azide **173** followed by diastereoselective epoxidation and oxidation to give aldehyde **174**. The Staudinger/aza-Wittig reaction was performed in the last step of the total synthesis and successfully afforded cicindeloine **175** without chromatographic purification.



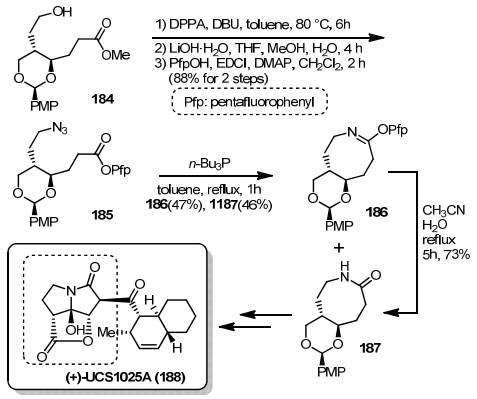
Scheme 32: Total synthesis and structure elucidation of cicindeloine by Staudinger/aza-Wittig reaction.

Fujioka achieved an asymmetric total synthesis of tetracyclic (+)-clavolonine **183**, a *lycopodium* alkaloid possessing potential anticholinesterase activity (Scheme 33) [76]. With chiral hydrobenzoin as a chiral auxiliary, azide-bearing tetrasubstituted cyclohexanone **179** was synthesized from enone **176** by S_N2 azidation and several other steps. Intramolecular Staudinger/aza-Wittig reaction of **179** with triphenylphosphine under reflux conditions gave a six-membered ring imine **180**, which was subjected to acid mediated epimerization. Subsequent intramolecular Mannich reaction gave tricyclic aminoketone **182**, which was converted to (+)-clavolonine **183** by one-pot demethylation/ring closure.



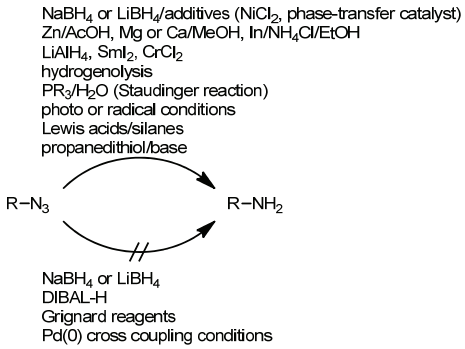
Scheme 33: Total synthesis of clavolonine using Staudinger/aza-Wittig reaction by Fujioka et al.

Kan et al. have developed an original strategy toward alkaloid synthesis using the Staudinger/aza-Wittig reaction with esters [77,78], and implemented recently in a total synthesis of antitumor antibiotic alkaloid UCS1025A **188** (Scheme 34) [79]. Azidation of primary alcohol with DPPA followed by ester exchange from methyl to active pentafluorophenyl (Pfp) ester could give **185**. The Staudinger/aza-Wittig reaction was subjected to **185** with tributylphosphine in reflux, and then cyclic imidate **186** and lactam **187** were obtained in almost 1:1 ratio. The seven-membered ring imidate **186** was successfully hydrolyzed to **187** which was delivered to (+)-UCS1025A **188**.



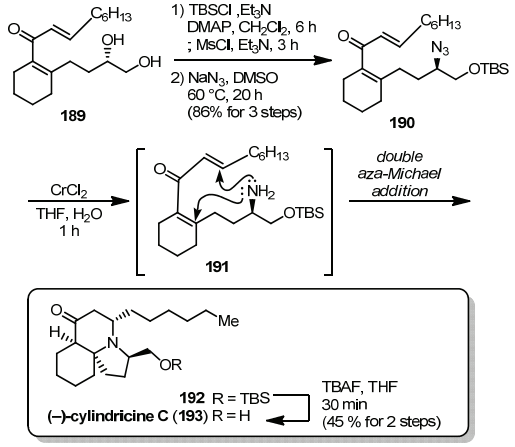
Scheme 34: Staudinger/aza-Wittig reaction cascade in total synthesis of UCS1025A by Kan et al.

Organic azides as masked amino functional groups: We have shown examples of azide-using transformation reactions. However, the major use of azides in natural product synthesis is to prepare amino groups. For high-yielding reduction of azides, many conditions have appeared, e.g. zinc metal/acetic acid, hydrogenolysis, Staudinger reactions, and other reducing agents shown in Scheme 35 [80–83].



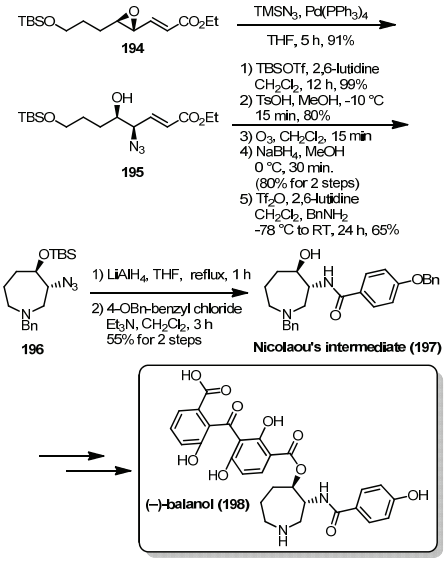
Scheme 35: Typical procedures of azide reduction to amine, and the conditions azides are tolerant.

A notable example of selective azide reduction in natural product synthesis was reported by Molander et al. in 1999 (Scheme 36) [84]. In their total synthesis of cylindricin C **193**, azide moiety in **190** had to be reduced to amine in the presence of carbonyl and conjugated olefins. After investigations, freshly prepared chromium (II) chloride solution [85–87] successfully reduced the azide chemoselectively to give primary amine **191** which gave double aza-Michael addition product spontaneously. The obtained **192** was deprotected to afford cylindricin C **193**.



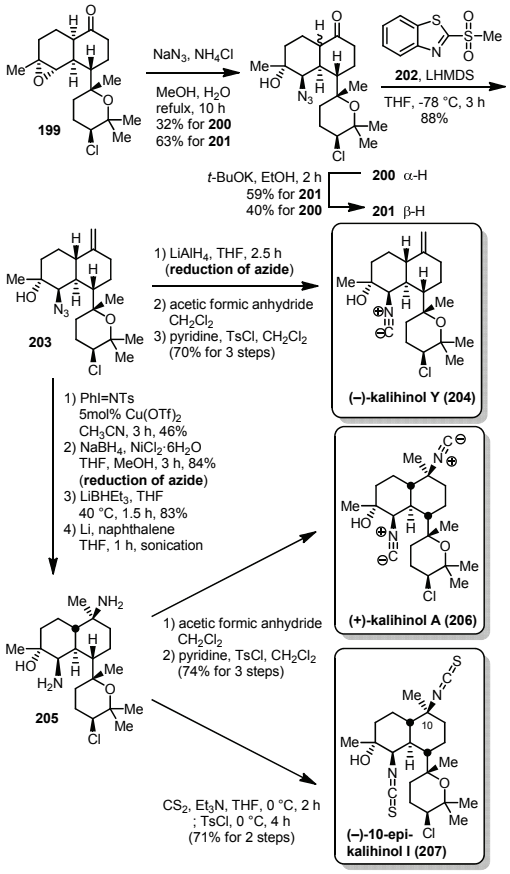
Scheme 36: Selective reduction of azide in total synthesis of cylindricine C by Molander et al.

This is an example of selective transformations of azides with reductants. However, as shown in Scheme 35, organic azides are unaffected by different reducing reagents. Especially sodium/lithium borohydride itself, Grignard reagents or Pd-catalyzed cross couplings usually do not damage organic azides (aryl azides react with metal borohydride on the other hand) [85–90]. Thus, choosing appropriate conditions and strategies, azides can work as protected amines. We have already provided some examples in Schemes 10, 20, 21, 24 and 31. Herein we show further use of azides aimed at protecting groups of amines in this section.



Scheme 37: Formal total synthesis of balanol by Muthyala et al.

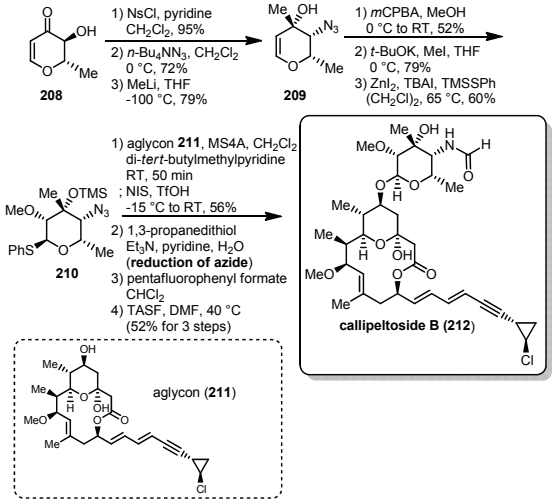
In a formal synthesis of PKC (Protein Kinase C) inhibitor (–)-balanol **198**, Muthyala et al. introduced allylic azide to allyl epoxide **194** by way of palladium-catalyzed stereospecific azidation with $TMSN_3$ (Scheme 37) [91]. A five-step transformation including ozonolysis/reductive treatment of ozonide gave azide-bearing cyclic amine **196**. The azide group in **196** was then reduced with lithium aluminum hydride and the following amidation successfully produced Nicolaou's intermediate **197** of (–)-balanol **198** [92].



Scheme 38: Total syntheses of kalihinols by Miyaoka et al.

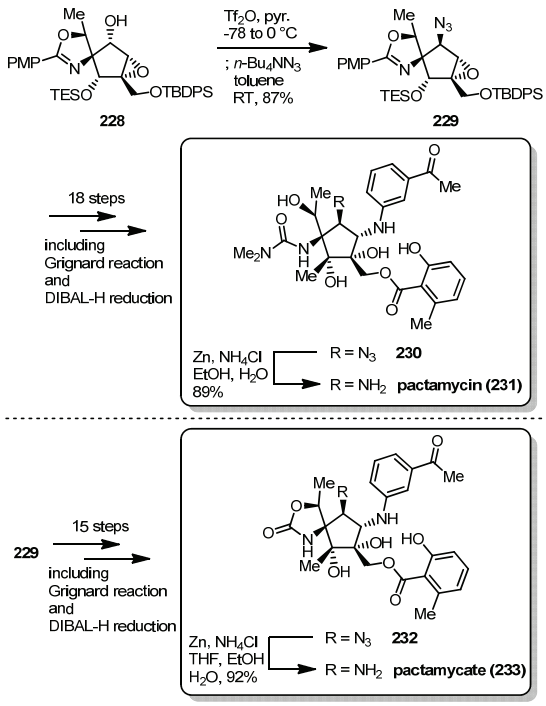
Marine sponge kalihinane-type diterpenoids possessing isocyano, isocyanato, isothiocyanato and formamide group along with chloride show extensive bioactivities like antimicrobial, anticycotic, anthelmintic, cytotoxic, antifouling, antimalarial, and ichthyotoxic properties. Miyaoka et al. achieved unified total syntheses of kalihinene diterpenoids (–)-kalihinol Y **204**, (+)-kalihinol A **206** and (–)-10-epi-kalihinol I **207** (Scheme 38) [93,94]. Ring-opening azidation followed by epimerization gave *trans*-decalin **201**, whose ketone was converted to exo-methylene **203** by Julia coupling with **202**. After three steps, including $LiAlH_4$ reduction, (–)-kalihinol Y **204** was in hand. Aziridination of **203** followed by reduction of azide with *in situ*-prepared nickel boride [95], reductive cleavage of aziridine with super hydride and removal of tosyl group by Birch reduction produced diamine **205**, which was delivered to (+)-kalihinol A **206** and (–)-10-epi-kalihinol **207**.

Cytotoxic callipeltosides were discovered from the shallow water marine sponge as minor metabolites. Ley et al. recently reported the total synthesis of callipeltoside B **212** (Scheme 39) [96]. In the synthesis of the sugar unit of **212**, azide was selected as a protecting group of the amine moiety. Nosylation, azidation followed by methyl addition gave azidated dihydropyran **209** from **208**, and further functionalizations were performed to afford protected deoxysugar **210**. After glycosylation with aglycon **211**, azide was reduced with 1,3-propanedithiol and the following formylation of resulting amine produced synthetic callipeltoside B **212**.



Scheme 39: Total synthesis of callipeltoside B by Ley et al.

Among marine natural products, dimeric pyrrole–imidazole alkaloids, biosynthetically derived from oroidin and the related alkaloids, represent unique, densely functionalized and highly nitrogen-containing polycyclic structures with multiply contiguous stereocenters including sensitive aminoacetals and halogen functional groups. With extensive effort to synthesize these complex molecules by many research groups, the total syntheses of (–)-axinellamine A **219**, B **220**, (–)-massadine chloride **222**, (–)-massadine **223**, and (–)-palau'amine **227** (reassigned structure) was finally achieved by Baran and co-workers (Scheme 41) [97–102]. Pentasubstituted cyclohexene **213** was transformed to diazide **214** by nucleophilic azidation on a multi-gram scale. After an 11-step conversion including Luche reduction ($NaBH_4$, $CeCl_3$) [103] gave spirocyclic guanidinium diazide **215**, which was a common intermediate of **219**, **220**, **222**, **223**, and **227**. With each four of further steps, diazide compounds **216**, **217** (for axinellamines), **221** (for massadines), and **224** (for palau'amine) were successfully prepared. Finally, reductions of azides by thiol or hydrogenolysis followed by additional transformations afforded totally synthetic alkaloids (–)-axinellamine A **219**, B **220**, (–)-massadine chloride **222**, (–)-massadine **223**, and (–)-palau'amine **227**.

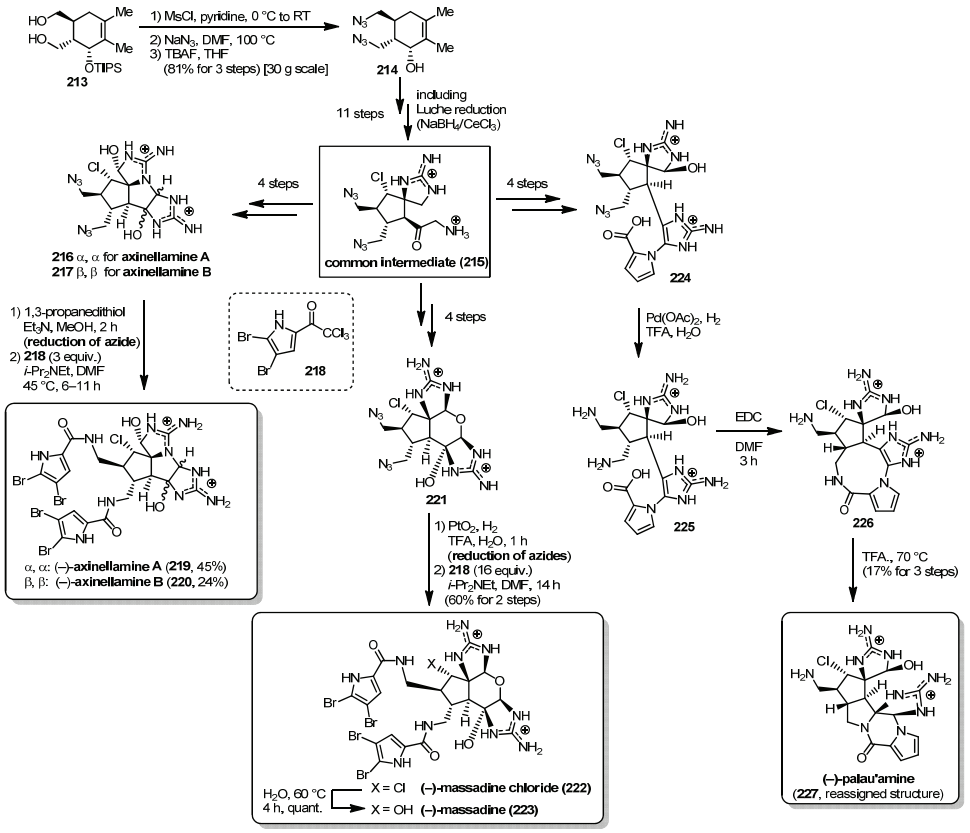


Scheme 40: Total synthesis of pacamycin and pactamycate by Hanessian et al.

Pactamycin **231** isolated in 1961 exhibited *in vitro* activity against certain Gram-positive and Gram-negative bacteria. Despite its use for pharmaceuticals being curtailed due to its strong toxicity, a highly dense-functionalized cyclopentane core (eight substitutes on a cyclopentane ring!) containing 1,2,3-triamine has been an attractive synthetic target among chemists for a long time. In 2010, almost fifty years after the isolation report, Hanessian et al. achieved the first total synthesis of **231** and pactamycate **233** (Scheme 40) [104,105]. To build up the sterically-hindered cyclopentane core, the azide was a very effective protective group because it has a linear structure and is less bulky. The prepared and highly functionalized azidocyclopentane **229** was converted to **230** in 18 steps. These steps included a Grignard reaction and a DIBAL-H reduction, but the azide group was unaffected by these reagents. Finally, an azide group in **230** was reduced to afford firstly-synthesized pactamycin **230**. Pactamycate **233** was also synthesized in similar pathway.

Summary and Outlook:

Organic azides have been exploited and the new methods developed provide us with concise syntheses of bioactive compounds. Especially, recent examples of total syntheses which use azide groups as masked amines revealed an efficiency of organic azides, aiming at step-economy synthesis. The explosive power of organic azides will undoubtedly be of great value to the fields of bioactive molecule synthesis and chemical biology.



Scheme 41: Total syntheses of oroidin alkaloids by Baran et al.

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