EDITORS

PROFESSOR ALEJANDRO F. BARRERO
Department of Organic Chemistry,
University of Granada,
Campus de Fuentenueva, s/n, 18071, Granada, Spain
abarr@ugr.es

PROFESSOR ALESSANDRA BRACA
Dipartimento di Chimica Bioorganicae Biofarmacia,
Università di Pisa,
via Bonanno 33, 56126 Pisa, Italy
braca@farm.unipi.it

PROFESSOR DEAN GUO
State Key Laboratory of Natural and Biomimetic Drugs,
School of Pharmaceutical Sciences,
Peking University,
Beijing 100871, China
gd5958@163.com

PROFESSOR YOSHIHIRO MIMAKI
School of Pharmacy,
Tokyo University of Pharmacy and Life Sciences,\nHortinouchi 1432-1, Hachioji, Tokyo 192-0392, Japan
mimakiy@ps.toyaku.ac.jp

PROFESSOR STEPHEN G. PYNE
Department of Chemistry,
University of Wollongong,
Wollongong, New South Wales, 2522, Australia
spyne@uow.edu.au

PROFESSOR MANFRED G. REINECKE
Department of Chemistry,
Texas Christian University,
Forts Worth, TX 76129, USA
m.reinecke@tcu.edu

PROFESSOR WILLIAM N. SETZER
Department of Chemistry,
The University of Alabama in Huntsville,
Huntsville, AL 35809, USA
wsetzer@chemistry.uah.edu

PROFESSOR YASUHIRO TEZUKA
Institute of Natural Medicine
Institute of Natural Medicine, University of Toyama,
2630-Sugitani, Toyama 930-0194, Japan
tezuka@nim-u.toyama.ac.jp

PROFESSOR DAVID E. THURSTON
Department of Pharmaceutical and Biological Chemistry,
The School of Pharmacy,
University of London, 29-39 Brunswick Square,
London WC1N 1AX, UK
david.thurston@pharmacy.ac.uk

ADVISORY BOARD

Prof. Berhanu M. Abegaz
Gaborone, Botswana

Prof. Viqar Uddin Ahmad
Karachi, Pakistan

Prof. Øyvind M. Andersen
Bergen, Norway

Prof. Giovanni Appendino
Novara, Italy

Prof. Yoshinori Asakawa
Tokushima, Japan

Prof. Lee Banting
Portsmouth, U.K.

Prof. Julie Banerji
Kolkata, India

Prof. Anna R. Bilia
Florencia, Italy

Prof. Maurizio Bruno
Palermo, Italy

Prof. César A. N. Catalán
Tucumán, Argentina

Prof. Josep Coll
Barcelona, Spain

Prof. Geoffrey Cordell
Chicago, IL, USA

Prof. Ana Cristina Figueiredo
Lisbon, Portugal

Prof. Cristina Gracia-Viguera
Murcia, Spain

Prof. Dujuvuru Gunasekar
 Tirupati, India

Prof. Kurt Hostettmann
Lausanne, Switzerland

Prof. Martin A. Iglesias Arteaga
Mexico, D. F., Mexico

Prof. Leopold Jirovetz
Vienna, Austria

Prof. Vladimir I Kalinin
Vladivostok, Russia

Prof. Niel A. Koobmanally
Durban, South Africa

HONORARY EDITOR

PROFESSOR GERALD BLUNDEN
The School of Pharmacy & Biomedical Sciences,
University of Portsmouth,
Portsmouth, PO1 2DU U.K.
agrawal@naturalproduct.us

EDITORS-IN-CHIEF
DR. Pawan K. Agrawal
Natural Product Inc.
7963, Anderson Park Lane,
Westerville, Ohio 43081, USA
agrawal@naturalproduct.us

INFORMATION FOR AUTHORS

Full details of how to submit a manuscript for publication in Natural Product Communications are given in Information for Authors on our Web site http://www.naturalproduct.us.

Authors may reproduce/republish portions of their published contribution without seeking permission from NPC, provided that any such republication is accompanied by an acknowledgment (original citation)-Reproduced by permission of Natural Product Communications. Any unauthorized reproduction, transmission or storage may result in either civil or criminal liability.

The publication of each of the articles contained herein is protected by copyright. Except as allowed under national “fair use” laws, copying is not permitted by any means or for any purpose, such as for distribution to any third party (whether by sale, loan, gift, or otherwise); as agent (express or implied) of any third party; for purposes of advertising or promotion; or to create collective or derivative works. Such permission requests, or other inquiries, should be addressed to the Natural Product Inc. (NPI). A photocopy license is available from the NPI for institutional subscribers that need to make multiple copies of single articles for internal study or research purposes.

To Subscribe: Natural Product Communications is a journal published monthly. 2013 subscription price: US$2,395 (Print, ISSN# 1934-578X); US$2,395 (Web edition, ISSN# 1555-9475); US$2,795 (Print + single site online); US$595 (Personal online). Orders should be addressed to Subscription Department, Natural Product Communications, Natural Product Inc., 7963 Anderson Park Lane, Westerville, Ohio 43081, USA. Subscriptions are renewed on an annual basis. Claims for nonreceipt of issues will be honored if made within three months of publication of the issue. All issues are dispatched by airmail throughout the world, excluding the USA and Canada.
Recent Applications and Developments of Organic Azides in Total Synthesis of Natural Products

Hiroki Tanimoto* and Kiyomi Kakiuchi

Graduate School of Materials Science, Nara Institute of Science and Technology (NAIST), 8916-5 Takayama-cho, Ikoma, Nara 630-0192, Japan
tanimoto@ms.naist.jp

Received: March 15th, 2013; Accepted: April 30th, 2013

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 Azide-Alkyne Cycloaddition—CuAAC) [14–17].

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-N₃) 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 (HN₃), 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.

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

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). 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] cycladditions 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 photoradiations produce nitrenes from organic azides, which are highly reactive and give aziridinations and C-H aminations (eq. 3).

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

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 (NaN₃), 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 (PPh₃ 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 diazonium 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 (TfN₃) was a problem. Recently, safer diazotransfer reagents, ADMP [24,25] and Goddard-Borger reagent (1) [26–28], appeared and can be used instead of TfN₃.

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 Hiraama’s group (Scheme 5) [30].

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

1,4-Azidation has also been reported in the total syntheses of marine bisindole alkaloids hamacanthin A (11), B (12) and the antipode 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 TMSN₃ 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 6: 1,4-Azidation of eniminium intermediate in total synthesis of marine bisindole alkaloids by Kawasaki 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 TrisN₃ (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].
Applications of organic azides in the synthesis of natural products

Natural Product Communications Vol. 8 (7) 2013 1023

In 1992, Magnus et al. discovered allylic azidation of trisopropylsilyl enol ethers with TMSN₃ 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].

**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 α-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 C 56. 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]. Arylazole moiety in 57 was synthesized by S_N_Ar reaction from commercially available aniline 56. Driver and co-workers also reported ruthenium-catalyzed γ-carboline synthesis from arylazides, in which they demonstrated regioselective synthesis of dimebolin 61, a synthetic drug possessing promising activity for the treatment of Alzheimer’s and Huntington’s disease [49].

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-N₃-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 hydrolisis afforded desired enone 33.

In 1992, Magnus et al. discovered allylic azidation of trisopropylsilyl enol ethers with TMSN₃ 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 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 kealiinne family (Scheme 8) [35]. In their synthesis, the 2-aminomidazole 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.

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

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 C 56. 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]. Arylazole moiety in 57 was synthesized by S_N_Ar reaction from commercially available aniline 56. Driver and co-workers also reported ruthenium-catalyzed γ-carboline synthesis from arylazides, in which they 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 functionalyzed diazaspiron[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.
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 tetrahydropseudoberberine 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 dihydrososinoline 80 through 4π-electrocyclic ring-opening/6π-electrocyclization cascade. A further three steps furnished (+)-coralydine 81.

Very recently, the first total synthesis of kottamidine 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-trimethylsilyl ethanol. Kottamidine 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 substituents. 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 HN₃, 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].

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 stemonamine alkaloids stene 99, 13-epineostene 100 and neostene 101 associated with insecticidal anthelmintic, antitussive and various neurochemical effects (Scheme 19) [56]. Their key step was cascade Diels-Alder/intramolecular Schmidt reaction with azide 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
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.

Recently, Tu et al. reported a total synthesis of immunosuppressive alkaloid FR901483 116 (Scheme 21) [59]. The azide 111, prepared
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 instability. 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 N2, 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.**

Melosine 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 melosine 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 N2 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]. S2 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.

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 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.

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

**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 selencysteine (21st). For biological study, pyrolysine 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-pyrolysine 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 TN3 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-pyrolysine 171.

In 2012, Seifert and co-workers isolated a novel cyclic imine compound possessing epoxide from the beetles Stenus cinctendoides and Stenus solutus (Scheme 32) [75]. The absolute configuration of this alkaloid cincinnolone 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 cincinnoide 175 without chromatographic purification.

Fujoka 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 31: Staudinger/aza-Wittig reaction in total synthesis of pyrolysine by Kiessling et al.](image)

![Scheme 32: Total synthesis and structure elucidation of cincinnolone by Staudinger/aza-Wittig reaction.](image)

![Scheme 33: Total synthesis of clavolonine using Staudinger/aza-Wittig reaction by Fujisaka et al.](image)

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.
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/acidic acid, hydrogenolysis, Staudinger reactions, and other reducing agents shown in Scheme 35 [80–83].

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) reductants. However, as shown in Scheme 35, organic azides are tolerant.

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.

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 TMSN₃ (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].

This is 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.
Marine sponge kalihinane-type diterpenoids possessing isocyanato, isothiocyanato and formamidine group along with chloride show extensive bioactivities like antimicrobial, anticycotic, anthelmintic, cytoxic, antifouling, antimarial, and 1,3-thiourea properties. Miyaoka et al. achieved unified total syntheses of kalihinene diterpenoids (–)-kalihinol Y 204, (+)-kalihinol A 206 and (–)-10-epi-kalihinol 1 207 (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 LiAlH₄ reduction, (–)-kalihinol Y 204 was in hand. Azidination 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. N-sulfonylation, 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 aglycon (for axinellamines), and (–)-massadine (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.

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 aza-cyclopentanone 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.

References

[4] Although most reactions can be performed safely, handling and synthesis of organic azides must strongly be cared to avoid violent explosions. For general safety information of handling, see Conrow RE, Dean WD. (2008) Diazidomethane explosion. Organic Process Research & Development, 12, 1285–1286. And also chapter 1 of ref[1], chapter 2 of ref[2], and experimental section of ref[6]
Applications of organic azides in the synthesis of natural products


Synthetic Approaches to Tetracyclic Pyrrole Imidazole Marine Alkaloids
Takuya Imaoka, Makoto Iwata, Takafumi Akimoto and Kazuo Nagasawa 961

Lyngbouilloside and Related Macrolides from Marine Cyanobacteria
Abdelatif ElMarrouni, Amandine Kolleth, Raphael Lebeuf, Julian Gebauer, Sébastien Prevost, Montserrat Heras, Stelios Arseniyadis and Janine Cossy 965

Enantioselective Total Synthesis of Otteliones A and B, Novel and Powerful Antitumor Agents from the Freshwater Plant Ottelia alismoides
Tadashi Katoh 973

A New Approach to the Synthesis of Chiral Blocks for Cyclopentanoids
Airat M. Gimazetdinov, Nadezhda A. Ivanova and Mansur S. Miftakhov 981

Stereoregulated Total Synthesis of Tetrodotoxin from myo-Inositol and D-Glucose by Three Routes: Aspects for Constructing Complex Multi-Functionalized Cyclitols with Branched-Chain Structures
Ken-ichi Sato, Shoji Akai and Juji Yoshimura 987

Development of a Second Generation Palladium-Catalyzed Cycloalkenylation and its Application to Bioactive Natural Product Synthesis
Masahiro Toyota 999

Stereoselective Aminopalladation and Oxypalladation and Their Application to the Synthesis of Natural Products
Hidefumi Makabe 1005

Evolution of the Total Syntheses of Batzellasides, the First Marine Piperidine Iminosugar
Tetsuya Sengoku, Jolanta Wierzejska, Masaki Takahashi and Hidemi Yoda 1011

Recent Applications and Developments of Organic Azides in Total Synthesis of Natural Products
Hiroki Tanimoto and Kiyomi Kakiuchi 1021
### Contents

New Aspects in Natural Product Synthesis: Methodology and Strategy  
(Guest Editors: Hisahiro Hagiwara and Toshio Suzuki)

<table>
<thead>
<tr>
<th>Original Paper</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regioselective Hydroxylation and Glucosylation of α- and β-Pinenes with Cultured Cells of Eucalyptus perriniana</td>
<td>847</td>
</tr>
<tr>
<td>Kei Shimoda, Naoki Kubota, Manabu Hamada, Ken Suwada, Hatsuuyki Hamada and Hiroki Hamada</td>
<td></td>
</tr>
<tr>
<td>Synthesis of Sterically-Crowded Olefins, gem-Dihaloalkenes, Butatrienes, and Thietoketenes through the Reaction of Substituted Bornane-2-thiones or Bornane-2-selenes with Conventional Carbones or Metal Carbeneds</td>
<td>851</td>
</tr>
<tr>
<td>Kazuaki Shimada, Jun Sasaki, Anna Kishi, Shigenobu Aoyagi and Yoji Takikawa</td>
<td></td>
</tr>
<tr>
<td>Modification of Valencene by Bio- and Chemical Transformation</td>
<td>859</td>
</tr>
<tr>
<td>Yoshinori Asakawa, Toshihiro Hashimoto, Yoshiaki Nomai and Mai Furusawa</td>
<td></td>
</tr>
<tr>
<td>Enantioselective Synthesis of Natural Trinorsesquiterpene Tetralones by Chemo-enzymatic Approaches</td>
<td>863</td>
</tr>
<tr>
<td>Stefano Serra</td>
<td></td>
</tr>
<tr>
<td>Structural Factors in the Odor of α-Santalol Derivatives</td>
<td>869</td>
</tr>
<tr>
<td>Toshio Hasegawa, Hiroaki Izumi and Hideo Yamada</td>
<td></td>
</tr>
<tr>
<td>Second Generation Synthesis of the Neo-Clerodane Diterpenoid Methyl Barbascocate</td>
<td>873</td>
</tr>
<tr>
<td>Hisahiro Hagiwara, Naomi Honma, Kimihiko Kinugawa, Shota Sato, Takashi Hoshi and Toshio Suzuki</td>
<td></td>
</tr>
<tr>
<td>Synthesis of a Key Intermediate, 10-Acetyl-7-(t-butyldiphenylsiloxymethyl)-4-methylidencyclopentene, in the Synthesis of Pseudolaric Acid A</td>
<td>877</td>
</tr>
<tr>
<td>Katsuyuki Nakashima, Naoki Kikuchi, Tsukasa Takehara, Takayuki Shiozawa, Shigeru Takaoka and Motoo Tori</td>
<td></td>
</tr>
<tr>
<td>Use of RCM Reactions for Construction of Eight-Membered Carbocycles and Introduction of a Hydroxy Group at the Junction Between Five- and Eight-Membered Carbocycles</td>
<td>883</td>
</tr>
<tr>
<td>Takahiro Morimitsu, Reiko Mizutani, Katsuyuki Nakashima, Yoshiyuki Saito and Motoo Tori</td>
<td></td>
</tr>
<tr>
<td>Synthetic Approach Toward α-Aminomethyl-γ-butyrolactones from β-Lactam Synthons Elaborated by Sml-mediated Reductive Coupling Reactions</td>
<td>889</td>
</tr>
<tr>
<td>Masaki Takahashi, Takahiro Sudoh, Yusuke Murata, Tetsuya Sengoku and Hidemi Yoda</td>
<td></td>
</tr>
<tr>
<td>Formal Synthesis of (+)-Madindoline A, a Potent IL-6 Inhibitor, Utilizing Enzymatic Discrimination of Quaternary Carbon</td>
<td>897</td>
</tr>
<tr>
<td>Ken-ichi Shimizu, Mina Tomita, Kenichi Fushukitake, Sugai Mitsuru Shoji</td>
<td></td>
</tr>
<tr>
<td>Glucosylation of Taxifolin with Cultured Plant Cells</td>
<td>903</td>
</tr>
<tr>
<td>Kei Shimoda, Naoki Kubota, Manabu Hamada, Masahiro Sugamoto, Koji Ishihara, Hatsuuyki Hamada and Hiroki Hamada</td>
<td></td>
</tr>
<tr>
<td>Regioselective Hydroxylation and Glucosylation of Flavanones with Cultured Plant Cells of Eucalyptus perriniana</td>
<td>905</td>
</tr>
<tr>
<td>Ryusuke Hosoda, Yoshiyuki Horio, Kei Shimoda, Manabu Hamada, Hatsuuyki Hamada and Hiroki Hamada</td>
<td></td>
</tr>
<tr>
<td>Synthesis of Resveratrol Glycosides by Cultured Plant Cells</td>
<td>907</td>
</tr>
<tr>
<td>Kei Shimoda, Manabu Hamada, Hatsuuyki Hamada, Katsuaki Nomai and Hiroki Hamada</td>
<td></td>
</tr>
<tr>
<td>Synthesis of 3-Farnesyl Salicylic Acid, a Novel Antimicrobial from Piper multiplinervium</td>
<td>911</td>
</tr>
<tr>
<td>George A. Kraus, Divya Chaudhary, Sean Riley, Feng Liu, Allison Schlapkohl, Megan Weems and Gregory J. Phillips</td>
<td></td>
</tr>
<tr>
<td>Total Synthesis of Bisbienzyl Dibenzoefuran Asterelin A via Intramolecular Oxidative Coupling</td>
<td>915</td>
</tr>
<tr>
<td>Koshi Makino, Kenichi Harada, Masa Kubo, Hidetoshi Hikoki and Yoshii Syusaku Fukuyama</td>
<td></td>
</tr>
<tr>
<td>Cyclopentanoids from Cyclopentadien: Synthesis of (−)-Methyl jasmonate and (−)-12-Oxophytodienoic acid</td>
<td>919</td>
</tr>
<tr>
<td>Junzo Nakami, Kazuhiro Fujii, Yusuke Mizutani, Rikiyo Otagawa, Hiroshi Yamaoka and Tsutomu Inokuchi</td>
<td></td>
</tr>
<tr>
<td>Synthesis of Both Enantiomers of 12-Methyl-13-tridecanolide and 14-Methyl-15-pentadecanolide (Muscolide)</td>
<td>925</td>
</tr>
<tr>
<td>Yoshihiro Noda, Natsuki Mamiya and Hitoshi Kashiha</td>
<td></td>
</tr>
<tr>
<td>A New Variant of Fused Cyclic Ether Synthesis Based on Ireland-Claisen Rearrangement and RCM</td>
<td>929</td>
</tr>
<tr>
<td>Daisuke Domon, Kenji Kojiri, Natsumi Kawamura, Byo Katoono, Hidekoshi Kawai and Takanori Suzuki</td>
<td></td>
</tr>
</tbody>
</table>

**Review/Account**

Carvone as a Versatile Chiral Building Block for Total Syntheses of Heterocyclic Sesquiterpenoids  
Hisahiro Hagiwara  
935

Synthesis of a Hydrindene in Rings C and D of YW3699  
Reiko Mizutani, Takahiro Morimitsu, Katsuyuki Nakashima and Motoo Tori  
949

Collective Total Synthesis of PPAPs: Total Synthesis of Clusianone via Intramolecular Cyclopropanation  
Masahiro Uwamori and Masahisa Nakada  
955

*Continued inside backcover*