# PART 4

# **Application in Bioorganic Chemistry**

Organic Azides: Syntheses and Applications Edited by Stefan Bräse and Klaus Banert © 2010 John Wiley & Sons, Ltd. ISBN: 978-0-470-51998-1

# 15

# Aza-Wittig Reaction in Natural Product Syntheses

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### 15.1 Introduction

Staudinger and Meyers reported in 1919 the first example of an aza-Wittig reagent (Scheme 15.1).<sup>1</sup> These phosphorus reagents are named  $\lambda^5$ -phosphazenes, iminophosphoranes or phosphine imines although, in this account, we will use the general term, phosphazenes. Phosphazenes were first prepared at the beginning of the last century,<sup>1</sup> but it was not until Wittig's work, more than 30 years later, that the aza-Wittig reaction became accepted practice. In an analogous manner to phosphorus ylides in the Wittig reaction, phosphazenes can also react with carbonyl compounds to afford an excellent method for the construction of C=N double bonds (Scheme 15.1).<sup>2</sup>

Since then, the Wittig and aza-Wittig reactions have undergone tremendous development and have become a powerful tool in organic synthetic strategies directed towards the construction of acyclic and cyclic compounds, mainly because the reaction is conducted in neutral solvents in the absence of catalysts, generally at mild temperatures, and usually proceeds high yields.

Numerous research papers and several reviews<sup>3</sup> have appeared describing the general use of phosphazenes as reagents and intermediates in organic synthesis. This account describes the use of the aza-Wittig reaction for the preparation of natural products by means of intermolecular and intramolecular processes. Despite the aza-Wittig strategy

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Scheme 15.1

has been developed for the synthesis of a wide type of heterocycles and their analogues, in this review we present those syntheses that exclusively lead to the preparation of natural products.

## 15.2 Intermolecular Aza-Wittig Reaction

## 15.2.1 Reaction with Carbonyl Compounds

The reaction of phosphazenes with carbonyl compounds is an excellent tool for the formation of carbon-nitrogen double bonds and this reaction seems to be one of the most efficient methods for the creation of the imine group under mild reaction conditions.<sup>4</sup>

## 15.2.1.1 Reaction of Phosphazenes with Aldehydes

The 5,11-methanomorphanthridine alkaloids are a small subclass of compounds of the *Amaryllidaceae* type first isolated by Wildman *et al.*<sup>5</sup> These natural products, produced by plants of various *Pancratium*, *Narcissus*, and *Brunsvigia* species, have a unique pentacyclic structural framework exemplified by the alkaloids (–)-pancracine, and (–)-coccinine. A very elegant synthesis of (–)-coccinine (7) and (–)-pancracine (8) has been described by Weinreb *et al.*<sup>6</sup> The corresponding imines were prepared by reaction between *N*-phenyl phosphazene 2 and functionalized aldehyde 1 (Scheme 15.2). Stereospecific cyclization was accomplished upon heating this imine/allenylsilane 3 in mesitylene at 162 °C by subsequent alkyne desilylation to afford amino acetylene 4. Subsequent transformations led to the formation of the pentacyclic structural framework 6, which can be reduced to (–)-pancracine 8 with sodium triacetoxyborohydride. In addition, enone 5 could be transformed into (–)-coccinine 7 after conversion of ketone group to the dimethyl ketal, followed by treatment with DIBALH (diisobutylaluminium hydride) for the reduction of the hydroxy ketal and cleavage of the TBS (tributylsilyl) group.

Conjugated phosphazenes have been widely used for the preparation of azadienes.<sup>7</sup> An important extension of the aza-Wittig/intramolecular electrocyclic ring closure (AW-IEC) methodology has been used in the construction of  $\beta$ -carboline alkaloids, which contain a



Scheme 15.2

phenyl acetyl or heteroaryl substituent at C-1. The reaction involves an initial formation of phosphazenes **10** by treatment of functionalized azides **9** with phosphine followed by aza-Wittig reaction with heterocyclic aldehyde to give the imine **11** (Scheme 15.3). Thermal treatment in the presence of Pd/C provides the corresponding 1-heteroarylsubstituted  $\beta$ -carbolines **12**. Finally, deprotection of the *N*-MOM (methoxymethyl) group, hydrolysis of the ester group and thermal decarboxylation afforded eudistomins A (**13a**) and M (**13b**),<sup>8a</sup> eudistomin U (**13c**),<sup>8b</sup> and nitramarine (**13d**).<sup>8c</sup> When this methodology is allowed using benzylglyoxal, the corresponding 1-phenylacetyl- $\beta$ -carboline **12** was converted into eudistomins T (**13e**) and S (**13f**).<sup>8d</sup> The same approach has been extensively used for the synthesis of other alkaloids such as xestomanzamine A (**14**),<sup>8d</sup> fascaplysin (**15**),<sup>8c</sup> the unusual group of azafluoranthrene alkaloids rufescine (**16**),<sup>8e</sup> imeluteine (**17**),<sup>8e</sup> which are biosynthetically related to the tropoloisoquinolines imerubine and grandirubine and lavendamycin (**18**)<sup>8a,8f</sup> (Figure 15.1).

#### 15.2.1.2 Reaction of Phosphazenes with Ketones

The preparation of a variety of vinylogous amides, precursors for a facile entry to the tetracyclic core of selaginoidine (26) (Scheme 15.4), was first attempted in different





Scheme 15.4

ways.<sup>9</sup> However, only the aza-Wittig reaction gave the expected results, improved by the use of microwave technology. Reaction of phosphazenes **20**, derived from azides **19**, with cyclohexanone derivatives **21** gives the corresponding imines **22** (Scheme 15.4). Subsequent condensation with carboxylic acid derivatives **23** and rapid cyclization furnished the desired hexahydroindolinone systems **25**. By the moment, with a subsequent intramolecular electrophilic substitution of furanyl derivative, related homoerythrina alkaloids can be prepared.

Aza-Wittig reaction of the phosphazene 27 with methyl or benzyl glyoxalate, followed by *in situ* reduction of the intermediate aldimine 28a,b with sodium cyanoborohydride, gives the cyclic enaminones 29a or 29b, which are the starting materials for the asymmetric synthesis of mycosporin I (30) and mycosporin-gly (31) (Scheme 15.5).<sup>10</sup>

#### 15.2.1.3 Reaction of Phosphazenes with Carboxylic Acid Derivatives

The reaction of acyl halides with phosphazenes gives an mild method for the preparation of 2,5-disustituted oxazoles.<sup>11</sup> This method has been used in the preparation of naturally occurring oxazole alkaloids, such as pimprinine analogues **35a**,<sup>12</sup> *O*-methylhalfordinol (**35b**) and annuloline (**35c**).<sup>13</sup> The preparation of five pimprinine analogues through



aza-Wittig type reaction of phosphazenes with acyl chlorides has been reported. The onepot reaction between an  $\alpha$ -azidoketone **32**, trialkylphosphine and an acyl halide leads to oxazoles **35** (Scheme 15.6). The aza-Wittig reaction between the initially formed phosphazene **33** and the acyl chloride gives an imidoyl chloride **34** which cyclizes across the enol form of the carbonyl function to give the five-membered ring.

The first synthesis of the bis(indole) alkaloid rhopaladin D (40) isolated from the marine Okinawan tunicate *Rhopalaea sp.* was achieved.<sup>14</sup> Alkaloids rhopaladins A-D showed antibacterial activity against *Sarcina lutea* and *Corynebacterium xerosis* and inhibitory activity against cyclin dependent kinase 4 and *c-erbβ*-2-kinase. The key step, construction of the central imidazolinone ring, is based on the aza-Wittig reaction of the phosphazene 37 derived from the  $\alpha$ -azido- $\beta$ -(3-indolyl)propenamide 36, and indol-3-ylglyoxylyl chloride in the presence of a base such as polymer-supported BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) as a base (Scheme 15.7). Thus, the aza-Wittig reaction followed by intramolecular cyclization of the resulting imidoyl chloride 38 proceeded smoothly to afford the cyclized product 39 as a 6:4 mixture of *E/Z* isomers. The *N*-SEM ([ $\beta$ -(trimethylsilyl)ethox] methyl) deprotection of 39 with TBAF (tetrabutylammonium fluoride) in THF at reflux gave the rhopaladin D (40).

The same strategy has been reported for the synthesis of the marine alkaloid almazole C, isolated from the red seaweed *Heraldiophylum sp.*, which showed antibacterial activity against Gram-negative pathogens. The formation of the central 2,5-disubstituted oxazole





Rhopaladin D (40) (60%)

38

Scheme 15.7



Scheme 15.8

ring was achieved using the phosphazene methodology (Scheme 15.8).<sup>15</sup> The key intermediate **43** was prepared in 70% yield by reaction of  $\alpha$ -azidoacetyl indole **41** with tributylphosphine in THF and subsequent addition of (*S*)-*N*-phthaloylphenylalanyl chloride **42**, followed by treatment with Et<sub>3</sub>N. The *N*-phthaloyl group was removed with hydrazine to give amine **44**, which was dimethylated by reductive amination with hydrogen in the presence of formaldehyde and palladium as catalysis, to give compound **45** in 90% yield. Finally, compound **45** was converted into almazole C (**46**) by deprotection of the *N*-methoxymethyl substituent with formic acid in THF (Scheme 15.8).

#### 15.2.2 Reaction with Heterocumulene Derivatives

$$R^{1}-N=PR^{2}R^{3}R^{4} \xrightarrow{X=C=O} R^{1}-N=C=X$$

$$X = NR, CR_{2}$$
Scheme 15.9

The aza-Wittig reaction of phosphazenes with heterocumulenes<sup>3a,16</sup> such as isocyanates (X = NR) and ketenes  $(X = CR_2)$  has been extensively used for the formation of carbodiimides and ketenimines, respectively (Scheme 15.9).

#### 15.2.2.1 Reaction of Phosphazenes with Isocyanates

From the range of general methods available for the construction of the carbodiimide functionality, the intermolecular aza-Wittig-type reaction of phosphazenes and isocya-



Scheme 15.10

nates seems to be an attractive method for preparation of these compounds, since it takes place under neutral conditions. In addition, this type of compounds can be subsequently used for the preparation of natural products by means of tandem or domino reactions. Aromatic phosphazenes have also been used in the synthesis of nitrogenated six-membered ring systems following the strategy of the aza-Wittig reaction and subsequent electrocyclic ring closure. The protocol has been used for the synthesis of indoloquino-line alkaloid cryptotackieine (**51**).<sup>17</sup> Thus, the phosphazenes **47**, containing an unsaturated side chain at the *ortho*-position (Scheme 15.10), participate in an aza-Wittig/electrocyclic ring closure, allowing the preparation of indolo[2,3-*b*]quinoline **50** through an electrocyclic process of **48** followed by the ring closure of **49**. Conversion of compound **50** into cryptotackieine **51** was achieved by deprotection of *N*-sulfonyl group with TBAF and subsequent microwave-promoted methylation with dimethyl sulfate followed by deprotonation.

*N*-Aromatic phosphazenes containing a triple bond reacted with heterocumulenes to give carbodiimides which can give heteropolycyclic compounds through an intramolecular [4+2] cycloaddition reaction. Thus, initial aza-Wittig reaction of phosphazene **52** (Scheme 15.11) with phenyl isocyanate and subsequent intramolecular cycloaddition of the formed carbodiimide **53** gave the quinindoline heterocycle **54**,<sup>18</sup> which was used in a straightforward formal total synthesis of cryptotackieine **51**<sup>19</sup> (neocryptolepine)<sup>20</sup> after methylation and subsequent deprotonation of the quinindoline **54**.

Usually, carbodiimides obtained by an aza-Wittig reaction of *N*-vinylic phosphazenes with isocyanates cannot be isolated.<sup>3a,21</sup> Therefore, the very reactive carbodiimides can be used as synthetic intermediates of polyheterocyclic natural products by domino processes involving aza-Wittig/intramolecular cyclization (AW-IC). In the synthesis of variolin B (**58**), the formation of the annulated 2-aminopyrimidine ring **57** is achieved from phosphazene **56** by a tandem aza-Wittig/carbodiimide-mediated intramolecular cyclization process<sup>22</sup> (Scheme 15.12).

Five-membered heterocycles were obtained when ammonia or amine nucleophiles reacted with carbodiimides, generated *in situ* from phosphazenes by a cascade process



Scheme 15.11



Scheme 15.12

involving aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization (AW-NA-IC). The strategy has also proved to be suitable for the preparation of leucettamine B (**62**).<sup>23</sup> Aza-Wittig reaction of phosphazene **59** with methyl isocyanate furnished the carbodiimide **60** in almost quantitative yield. Posterior treatment with ammonia yielded leucettamine B (**62**) through a guanidine-substituted intermediate **61**, which undergoes regioselective imidazole ring-formation across the ester and methyl amino functionality (Scheme 15.13).



Scheme 15.14

This methodology has also been used for the preparation of several alkaloids (Scheme 15.14). Syntheses of the marine alkaloids, isonaamine A (**67a**), dorimidazole A (**67b**) and preclathridine A (**67c**),<sup>24</sup> have been described by aza-Wittig reactions of phosphazenes **63** with tosyl isocyanate, followed by addition of amine **65** to the carbodiimide intermediate **64** and subsequent intramolecular cyclization of compound **66**.

#### 15.2.2.2 Reaction of Phosphazenes with Ketenes

The alkaloid (+)-cularine (72) was isolated by Manske in 1938 from plants belonging to the genera *Dicentra* and *Corydalis*.<sup>25</sup> Recently, Rodrigues *et al.* reported a diastereoselec-



tive synthesis of cularine alkaloids demonstrating the versatility of the aza-Wittig reaction for the construction of the isoquinoline core of the cularine alkaloids.<sup>26</sup> Thus, as shown in Scheme 15.15, the cascade aza-Wittig reaction/intramolecular cyclization (AW-IC) between phosphazene **68** and ketene **69** gave the 3,4-dihydroisoquinoline **70**. The corresponding aryloxenium or oxeniumoid was generated using a 1:1 ratio of the sodium salt of **70** and  $C_6F_5I(CF_3CO_2)_2$ , and cyclization product **71** (87%) was formed. Methylation of **71** followed by reduction with sodium borohydride at 0 °C for 4 h, yielded (+)-cularine (**72**) in 94% yield (Scheme 15.15). The synthesis of (+)-crassifoline (**73**), (+)-*O*-demethylcularine (**74**), (+)-sarcocapnine (**75**), and (+)-sarcocapnidine (**76**) has been reported by using the same approach (Figure 15.2).<sup>26</sup>



Figure 15.2



#### 15.3 Intramolecular Aza-Wittig Reaction

Special interest has been focused on those aza-Wittig reactions of compounds **77** (Scheme 15.16) where both the phosphazene, moiety and the carbon-oxygen double bond (C=O) (aldehydes, ketones, esters and amides) are found within one molecule.<sup>3a,27</sup> This strategy involving intramolecular aza-Wittig reactions allows a method for the preparation of five- to higher-membered heterocyclic compounds **78** under very mild reaction conditions, that are a structural feature in the skeleton of natural products.

#### 15.3.1 Functionalized Phosphazenes Containing an Aldehyde Group

An intramolecular aza-Wittig reaction with an aldehyde function allowed the stereocontrolled total synthesis of the polycyclic stemona alkaloid which characteristically contains the 1-azabicyclo[5.3.0.]decane nucleous, such as (-)-stemospironine  $(84)^{28}$  and (+)-croomine (85).<sup>29</sup> The required aldehyde **80** was prepared from the starting azide **79** by cleavage of benzyl ether and Dess-Martin oxidation of the obtained primary alcohol (Scheme 15.17). Subsequent addition of triphenylphosphine to give phosphazene **81** and *in situ* reduction of the formed imine bond of **82** in the intramolecular aza-Wittig reaction gave a seven-membered ring precursor **83** of the expected alkaloids **84** and **85**.

Phosphazenes containing an aldehyde group have been used by Yadav *et al.*<sup>30</sup> for the synthesis of the optically active (3S,4S)-hexahydroazepine core of balanol (**90**) and ophiocordin by ring expansion to the seven-membered azepine through an intramolecular aza-Wittig process as the key step. As shown in Scheme 15.18, treatment of functionalized azide **86** with triphenylphosphine in toluene at reflux temperature gave the crude imine **87** which was subjected to reduction with NaBH<sub>4</sub> in methanol followed by *in situ* protection with Boc<sub>2</sub>O and TEA (triethylamine) to give the azepine segment, which was converted into the azide **88** *via* treatment with Tf<sub>2</sub>O and 2,6-lutidine followed by NaN<sub>3</sub> displacement (Scheme 15.18). The final elaboration of the targeted hexahydroazepine moiety **89** of balanol is very straightforward. Hydrogenation of **88** in AcOEt liberated the amino group from its azido surrogate and simultaneously deprotected the benzyl ether function with PtO<sub>2</sub>. Acylation of the resulting amino alcohol delivers the product **89**, which is directly amenable to the total synthesis of (3*S*,4*S*)-balanol.



Scheme 15.18

The intramolecular aza-Wittig reaction has been successfully used for an elegant synthesis of the seven-membered nitrogen ring of (-)-stemonine (97) (Scheme 15.19). Stemona alkaloids represent a class of approximately 50 structurally novel, polycyclic metabolites isolated from monocotyledonous plants comprising the genera of Stemona, *Croomia*, and *Stichoneuron*. The total synthesis of (-)-stemonine (97) was reported for the first time by Williams et al.<sup>31</sup> nearly 75 years after its initial discovery. Cyclization to give perhydroazepine 92 via the Staudinger reaction of aldehydic azide 91 with ethyldiphenylphosphine generated the seven-membered imine by an intramolecular aza-Wittig process (Scheme 15.19). After imine formation, a reductive quench with  $NaBH_4$  gave the amine 92 in 70% yield. Stereocontrolled formation of the pyrrolidinobutyrolactone C-D ring system occurred in a single step as a consequence of an iodine-induced cyclization. Thus, treatment of 92 with  $I_2$  led to formation of 95 in reproducible yields of 42%. The synthesis of 97 was completed by simultaneous deprotection of TBS ethers followed by Dess-Martin oxidation, which resulted in isolation of the stable lactol 96. Brief exposure to Jones reagent gave synthetic (-)-stemonine (97).



Reaction conditions: (a) EtPPh<sub>2</sub>, benzene, rt, 18 h; the mixture was then concentrated in vacuo, and THF, NaBH<sub>4</sub>, and MeOH were added, 70%. (b) I<sub>2</sub>, CH<sub>2</sub>CI<sub>2</sub>/Et<sub>2</sub>O (2.5:1), rt, 48 h, 42%. (c) TBAF, THF, rt, 77%. (d) Dess-Martin periodinane, NaHCO<sub>3</sub>, CH<sub>2</sub>CI<sub>2</sub>, rt, 69%. (e) CrO<sub>3</sub>, aq H<sub>2</sub>SO<sub>4</sub>, acetone, THF, rt, 68%.

Scheme 15.19



Likewise, the antibiotic DC-81 (**99b**) can be synthesized by using the same strategy through an intramolecular reductive cyclization with polymer-supported triphenylphosphine.<sup>32</sup> Treatment of the azide **98** this polymer at room temperature afforded the intramolecular aza-Wittig compound **99a**, which, in turn, could be converted into the natural product DC-81 (**99b**) in a straightforward manner (Scheme 15.20). This strategy has also been used by Molina *et al.*<sup>33</sup> for the preparation of optically active (*R*)-enantiomer of antibiotic DC-81. A similar approach has been used for the synthesis of benzodiazocine (**100**), a novel eight-membered ring analogue to the anthramicin family of antibiotics, synthetized by O'Neil *et al.*<sup>34</sup>

#### 15.3.2 Functionalized Phosphazenes Containing a Ketone Group

Phosphazenes having a ketone substitution cyclize by an intramolecular aza-Wittig reaction to give ring systems of 5- or 6-membered heterocycles.<sup>3a</sup> In the total synthesis of (–)-dendrobine (**104**), the 5-membered nitrogen heterocycle can be formed by an intramolecular aza-Wittig reaction of the azido ketone **101** (Scheme 15.21).<sup>35</sup> Thus, treatment of **101** with triphenylphosphine gave polycyclic imine **103** via **102**. Reduction of the imine moiety with sodium cyanoborohydride from the less hindered  $\alpha$ -face, followed by reductive methylation of the amine with paraformaldehyde and formic acid, afforded the enantiomerically pure (–)-dendrobine (**104**) (Scheme 15.21). In this synthesis, six stereogenic centers were induced, each in a stereoselective fashion, from a single chiral center of the starting material.

The formation of five-membered cyclic imines through a Staudinger/intramolecular aza-Wittig reaction can also be performed by solid-phase synthesis and has been applied for the first synthesis of lanopylin  $B_1$  (**108**).<sup>36</sup> The total synthesis, which takes only four steps, starts with a phase-transfer alkylation of diethyl 2-oxopropylphosphonate **105** with a 2-iodoethyl azide, affording the azido phosphonate **106**, which undergoes a phase-transfer Horner-Emmons Wittig reaction with heptadecanal to provide the azido enone **107**. An intramolecular aza-Wittig reaction of the enone **107** with polymer-supported triphenylphosphine in toluene completed the first total synthesis of lanopylin  $B_1$  (**108**) in 76% yield (Scheme 15.22).

A similar approach has been reported for the total synthesis of the marine cyanobacterial apratoxin A (**111**).<sup>37</sup> Apratoxin A, isolated from *Lyngbya spp*. cyanobacteria, is representative of a growing class of marine cyanobacterial cyclodepsipeptides wherein discrete polypeptide and polyketide domains are merged by ester and amide or amidederived linkages. For the preparation of apratoxin A, the reaction of the azide **109** with





 $Ph_{3}P$  in anhydrous THF effected thiazoline formation by the intramolecular Staudingeraza-Wittig process to deliver C35 *O*-TBS ether **110**. Completion of the total synthesis of the cyclodepsipeptide apratoxin A (**111**) from thiazoline **110** would have required only two further operations: amide formation between proline amine and *iso*-leucine carboxylate residues and removal of the C35 *O*-TBS-protecting group (Scheme 15.23).

The formation of a tetrahydropyridine ring by means of the Staudinger reaction of azido-ketones and phosphines followed by intramolecular Aza-Witig reaction was applied



Scheme 15.23

for the synthesis of the alkaloid nigrifactine (**114a**) (Scheme 15.24), and represents the first example reported for the use of this synthetic strategy for the preparation of a natural product.<sup>38</sup> Polonicumtoxins A (**114b**), B (**114c**), and C (**114d**) are cyclic ketimine toxins isolated from the freshwater dinoflagellate *Peridinium polonicum*, which occasionally blooms in lakes and drinking water reservoirs. They exhibit extremely potent toxicity toward fish, making the dinoflagellate blooms a serious environmental problem. Yasumoto *et al.*<sup>39</sup> have reported the preparation of these compounds through a similar strategy involving an aza-Wittig procedure for the construction of the ketimine unit (Scheme 15.24). A microwave-assisted intramolecular aza-Wittig reaction was used by De Kimpe *et al.*<sup>40</sup> for the synthesis of the principal bread flavour component, 6-acetyl-1,2,3,4-tetrahydropyridine.

An optically active piperidine ring has been constructed by an intramolecular aza-Wittig reaction allowing a concise enantiospecific synthesis of nuphar piperidine alkaloids, among them (-)-anhydronupharamine (118), which has a sesquiterpenoid structure



Scheme 15.24



Scheme 15.25

with a furane and piperidine rings. Reaction of the phosphazene **116**, obtained by a Staudinger reaction of azide **115** with triphenylphosphine, in refluxing THF yielded the imine **117**. The non-isolated imine **117** was reduced with sodium borohydride in ethanol to give (–)-anhydronupharamine (**118**) stereoselectively (Scheme 15.25).<sup>41</sup>

A similar strategy has been applied for the preparation of tetrahydropyridine precursors in the synthesis of (–)-adenophorine (**123**), a rare example of a naturally occurring azasugar with hydrophobic subtituents, 1-*epi*-adenophorine or deoxynojirimycin (DNJ) variants.<sup>42</sup> Ethyl ketimine **121** was synthesized through the Staudinger/aza-Wittig sequence from compound **119**, as shown in Scheme 15.26. The use of LiAlH<sub>4</sub> yielded tetrabenzyladenophorine **122**. Deprotection of **122** yielded (–)-adenophorine (**123**).

The azaspiracids **124** (Scheme 15.27) are the causative agents of a recently defined class of human poisoning resulting from consumption of tainted shellfish. The archetypal member of this novel class of marine toxins, azaspiracid-1 (AZA1,  $R^1 = R^3 = H$ ,  $R^2 = R^4 = Me$ , Scheme 15.27), was reported by Yasumoto *et al.* as an isolated compound from the cultivated Irish mussel *Mytilus edulis*.<sup>43</sup> The azaspiracid natural products display



Scheme 15.26





Scheme 15.27



Scheme 15.28

a common spiroaminal-containing terminal domain that has inspired the development of its synthesis through a Staudinger reduction-aza-Wittig process.<sup>44</sup> The anticipated spiroaminal moiety in **128** was initially formed stereoselectively in 75% yield upon treatment of azide **125** with Et<sub>3</sub>P in benzene (Scheme 15.27). The generated phosphazene **126** undergoes an intramolecular aza-Wittig reaction with the C36 ketone to form the sixmembered cyclic imine **127**. Addition of the C33 hydroxyl group to the imine completes the cascade. Compound **128** represents the fully functionalized C27-C40 azaspiracid intermediate that is amenable to elaboration into the complete F-G-H-I ring domain.

This approach has been also used as the key step for the enantioselective synthesis of the marine indole alkaloid, hamacanthin B  $(132b)^{45}$  (Scheme 15.28), and the antipode of hamacanthin A.<sup>46</sup> The central pyrazinone ring was achieved by the reaction of azide 130 with tributylphosphine in toluene at room temperature, to afford phosphazene intermediate 131, followed by heating, to provide the expected cyclized product 132a. Deprotection of 132a led to the formation of hamacanthin B (132b) in 82% yield and keeping the configuration of the *C*- $\alpha$  of the starting azide.

#### 15.3.3 Functionalized Phosphazenes Containing an Ester Group

It is well known that the carbonyl group of esters is less reactive than that of aldehydes and ketones in an aza-Wittig reaction. However, in recent years, some reports of the intramolecular aza-Wittig reaction of phosphazenes containing ester derivatives in the molecule for the preparation of heterocyclic systems<sup>3a</sup> have appeared. In the synthesis of siamine (**135**) the treatment of  $\alpha$ -azidocinnamate **133** with triethylphosphine in benzene at room temperature gave the 1-ethoxyisoquinoline **134**.<sup>47</sup> The ester substituent of **134** was reduced in high yielding indirect sequence and finally treatment with boron tribromide resulted in simultaneous cleavage of ethyl and benzyl ethers to give siamine (**135**) (Scheme 15.29).



The formation of complex 13-membered macrocycles through a Staudinger/intramolecular aza-Wittig reaction has been applied to the total synthesis of (–)-ephedradine A (orantine) (**137b**) (Scheme 15.30).<sup>48,49</sup> (–)-Ephedradine A is a complex macrocyclic spermine alkaloid, whose one of its two macrocycles can be constructed by an intramolecular aza-Wittig strategy. In this way the formation of the 13-membered iminoether **137a** was successfully obtained by treatment of the azide **136** (Ar = *p*-BnO-C<sub>6</sub>H<sub>4</sub>) with Ph<sub>3</sub>P in refluxing toluene under high-dilution conditions (Scheme 15.30). Subsequent hydrolysis, removal of the Ns (2-nitrobenzenesulfonyl) group and simultaneous cleavage of the Cbz group and benzyl ether yielded (–)-ephedradine A (**137b**).

Methods for the preparation of seven-membered nitrogen-ring systems by the use of the intramolecular aza-Wittig reaction have increased in the last decade. This heterocycle is quite common in benzodiazepine derived alkaloids. This methodology has been applied for the first total synthesis of (–)-benzomalvin A (142) (Scheme 15.31).<sup>50,51</sup> Reaction of the starting azide 138 with tributylphosphine leads to the formation of the phosphazene intermediate 139, which under the reaction conditions affords the benzodiazepine 141 in 58% yield *via* compound 140. Benzodiazepine 141 suffered subsequent transformations to afford (–)-benzomalvin A (142).



#### 15.3.4 Functionalized Phosphazenes Containing an Amide Group

Intramolecular aza-Wittig imination reactions involving less reactive amide carbonyl groups, which are known as the Eguchi protocol, have been reported, usually suffering from low yields. As previously reported (Section 15.3.3), intramolecular aza-Wittig reaction with ester substituents allowed the preparation of benzomalvin A. The last step in this total synthesis involves an intramolecular aza-Wittig reaction of a functionalized phosphazene containing an amide moiety. Thus, the azide **143** was treated with triphenylphosphine to generate the corresponding phosphazene, which reacted with the amide function to afford (–)-benzomalvin A (**142**) in 98% yield. Benzomalvin B (**144**) can also be obtained in two steps from (–)-benzomalvin A (Scheme 15.32).<sup>51</sup>

On the other hand a convenient combination of intramolecular aza-Wittig strategy and microwave technology for the preparation of the alkaloid, cryptotackieine, which has an indolo[2,3-*b*]quinoline core, has been described.<sup>52,53</sup> Thus, treatment of 3-(*o*-azidophenyl) quinolin-2-one **145** with trimethylphosphine in nitrobenzene under microwave irradiation between 150–180 °C, after five-membered ring construction, afforded cryptotackieine (**51**) in 40% yield *via* **146** (Scheme 15.33).

The intramolecular aza-Wittig reaction of functionalized phosphazenes containing an amide moiety has been used as the key-step for the preparation of the natural product deoxyvasicinone.<sup>54</sup> Azide **149** (R = H) was obtained from **148** and pyrrolidone **147** (R = H) in the presence of sodium hydride as a base at room temperature (Scheme 15.34). Then azide **149** (R = H) was treated with tributylphosphine and the natural product deoxyvasicinone (**150**) was successfully obtained in 99% yield even at room temperature for 2 h. More recently, fused [2,1-*b*]quinazolinones, namely vasicinone, deoxyvacisinone and related heterocycles have been prepared by solid-phase methods using the intramolecular aza-Wittig reaction of a phosphazene with an amide moiety.<sup>55,56</sup> Similarly, this



E/Z 56:44

Scheme 15.32



strategy has also been used for the synthesis of optically active pyrrolo[2,1-b]-quinazoline alkaloid, (S)-(-)-vasicinone (152).<sup>57</sup> Fortunately, by this synthesis the authors have clarified that natural L-vasicinone has the (S)-configuration. After O-TBDMS (O-tert-butyldimethylsilyl) protection, o-azidobenzoylation followed by treatment of compound 149 (R = OTBDMS) with tributylphosphine afforded (S)-(-)-vasicinone (152) via the tandem Staudinger/intramolecular aza-Wittig reaction followed by TBDMS deprotection of 151 (Scheme 15.34).

Quinazoline alkaloids containing the indole skeleton such as tryptanthrin (156)<sup>58</sup> have been constructed via intramolecular aza-Wittig reaction of amide derivatives (Scheme 15.35). The fused quinazoline ring in tryptanthrin (156) could be synthesized efficiently in a one-pot procedure via the consecutive Staudinger/intramolecular aza-Wittig reaction of the corresponding azide 154 with tributylphosphine (Eguchi protocol).



Analogously, rutercarpine  $(157)^{58}$  and alkaloids such as (–)-asperlicin C (158),<sup>59</sup> circumdatin F (159),<sup>60</sup> sclerotigenin (160),<sup>60</sup> and (–)-asperlicin (161)<sup>59</sup> (Figure 15.3) containing a quinazolino[3.2-*a*][1,4]benzodiazepinedione nucleus have been prepared through an intramolecular aza-Wittig procedure involving an amide moiety in very mild reaction conditions. The modified Eguchi protocol using polymer-supported phosphine-mediated intramolecular aza-Wittig reaction relied on an efficient formation of the fused



quinazoline ring system<sup>61</sup> yielding the simplest member of the benzodiazepine-quinazolinone family, sclerotigenin (**160**). In this manner, a multi-arrayed library generation strategy has been developed for the preparation of benzodiazepine-quinazolinone alkaloid structure of the circumdatin family of natural products. Also the key step in the synthesis of pyrazino[2,1-*b*]quinazoline core, found in the (–)-fumiquinazoline G (**162**)<sup>60,62</sup> and ardeemin (**163**)<sup>63</sup> (Figure 15.3), involves annulation of a quinazolin-4-one onto an amide by reaction with tributylphosphine following the Eguchi procedure.

This route has been adapted to the synthesis of both enantiomers of the alkaloid glyantrypine (**166**). In this case, the intramolecular aza-Wittig strategy allowed the preparation of pyrazino[2,1-*b*]quinazoline ring system present in this alkaloid and many others which exhibit very interesting biological properties.<sup>64</sup> The cyclization to pyrazino[2,1-*b*] quinazoline-3,6-dione derivatives was carried out through a Staudinger/aza-Wittig sequence by treatment of compound **164** with Bu<sub>3</sub>P, which afforded compound **165** in 66% yield (Scheme 15.36). Subsequent deacetylation by addition of hydrazine hydrate gave compounds **166a,b** in good yields.

The antitumor antibiotic phloeodictine A1 (**171**) has been synthesized by Snider's group<sup>65</sup> (Scheme 15.37). The unstable azide derived from **167** was subjected to a polymer supported tandem Staudinger-aza-Wittig followed by a retro Diels-Alder reaction to afford intermediate **170**. Addition of 11-dodecenyl magnesium bromide followed by alkylation reaction and deprotection completes an efficient synthesis of phloeodictine A1 (**171**).

#### 15.4 Conclusions

In summary, this review presents recent progress in the synthesis of some natural products based on the intermolecular and intramolecular aza-Wittig reaction of phosphazenes with



Scheme 15.37

carbonyl compounds. These results indicate the importance and utility of these phosphazenes as versatile building blocks for the construction of C-N double bonds in very mild conditions, not only in the preparation of acyclic compounds, but also for heterocycle construction, ranging from simple monocyclic compounds to complex polycyclic and macrocyclic systems. In many cases, the synthesis is carried out stereoselectively and the resulting compounds are physiologically active or are potential intermediates in the synthesis of physiologically active compounds including analogues of natural products.

## Acknowledgments

The present work has been supported by the *Dirección General de Investigación del Ministerio de Ciencia e Innovación* (MICINN, Madrid DGI, CTQ2006/09323) and *Departamento de Educación Universidades e Investigación (Gobierno Vasco) – Universidad del País Vasco* (GV, IT277-07; UPV, GIU06/51).

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# 16

# Azides in Carbohydrate Chemistry

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### 16.1 Introduction

The first azide-containing sugar, a glycosyl azide, was reported in 1930 by Bertho.<sup>1</sup> Since that time various methods have been developed for the introduction of azides at different positions of sugars. A survey of available methods is given in Section 16.2. Until the late 1970s, azides contained in carbohydrate derivatives were simply used as accessible synthons for amines because of their easily performed reduction to amines. Due to their stability against a variety of reaction conditions, azides often can serve as masked amines during the course of carbohydrate synthesis. The development of the diazo transfer reaction facilitated the use of azides also as temporary protecting group for amines. This was extensively applied during the preparation of aminoglycoside derivatives (Section 16.3).

Over the last three decades, azides became an important tool especially for the synthesis of glycopeptides and -proteins. In 1978 Paulsen *et al.* developed the 'azide method' for the preparation of 1,2-*cis*-glycosides of glycosamine derivatives using 2-azido-2-deoxy-donors (Section 16.4). This reaction is widely used for the synthesis of *O*-linked glycosyl amino acid building blocks. In *N*-glycoproteins, the glycan chains are attached to the protein via a  $\beta$ -glycosyl amide. Staudinger-type reactions offer a convenient access to such structures and are applied since the 1990s for the synthesis of  $\alpha$ - and  $\beta$ -glycosyl amides directly from glycosyl azides (Section 16.5).

An enormous impact on the field of glycobiology during the last decade had the development of two bioorthogonal reactions based on azides: the copper-catalyzed azidealkyne [3+2] cycloaddition and the Staudinger ligation. Together with the possibility of *in vivo* incorporation of azide and alkyne tags into glycans and proteins, these reactions offer new options for selective labeling and manipulation of biomolecules even within

Organic Azides: Syntheses and Applications Edited by Stefan Bräse and Klaus Banert © 2010 John Wiley & Sons, Ltd. ISBN: 978-0-470-51998-1

living cells. Especially the azide-alkyne cycloaddition has been extensively applied for the chemical synthesis of neoglycoconjugates such as glycopeptide and glycoprotein mimics or multivalent glycoclusters (Section 16.6). Metabolic oligosaccharide engineering uses the biosynthetic pathways for the introduction of azide- (and alkyne-)tagged sugar moieties into the glycans of cells that can subsequently be labeled by a detectable probe. This approach is discussed in Section 16.7.

## 16.2 Synthesis of Azide-Containing Carbohydrates

A common way for the introduction of azides into carbohydrates is the nucleophilic replacement of leaving groups by the azide ion. These reactions can be divided into three groups: substitutions at the anomeric center leading to glycosyl azides, substitutions at primary, and substitutions at secondary carbon atoms.

A widely used method for the preparation of glycosyl azides<sup>2-4</sup> is the conversion of acetylated halogenoses, such as **1**, by treatment with sodium azide based on Bertho's initial work (Scheme 16.1A).<sup>1</sup> While homogeneous one-phase reactions in DMF often require elevated temperatures,<sup>5</sup> phase-transfer catalysis enables milder conditions.<sup>6</sup> One limitation of this methodology is the instability of glycosyl halides. Thus, sequential one-pot procedures have been developed that avoid the isolation of glycosyl halides.<sup>7</sup> An alternative, which circumvents the preparation of glycosyl halides completely, is the direct conversion of glycosyl acetates into the corresponding glycosyl azides using trimethylsilyl azide under Lewis acid catalysis (Scheme 16.1B).<sup>8</sup> Glycosyl azides with 1,2-*trans*-configuration are easily obtained by the described methods using acyl protecting groups due to their neighboring group participation. Glycosyl azides with 1,2-*cis*-configuration can be prepared from 1,2-*trans*-glycosyl halides in an S<sub>N</sub>2-type reaction or from etherprotected glycosyl acetates by treatment with trimethylsilyl azide.<sup>2-4</sup>



**Scheme 16.1** Preparation of glycosyl azides from (A) peracetylated glycosyl halides under classical homogeneous conditions<sup>5</sup> and under mild phase-transfer catalysis<sup>6</sup> and (B) from peracetylated sugars<sup>9</sup>

The introduction of azides at the primary carbon of carbohydrates is conveniently carried out by an  $S_N^2$  reaction. The generation of a good leaving group, such as a sulfonate, is often possible in a selective way without need for protection of the secondary hydroxy groups as was shown for GlcNAc derivative **5** (Scheme 16.2).<sup>10</sup> Subsequent substitution with sodium azide usually proceeds at elevated temperatures with good yields.

In contrast,  $S_N^2$  reactions at secondary carbons of the sugar ring system are more complex. The success of such reactions is strongly dependent on the type of sugar (stereochemistry), the position at which the  $S_N^2$  reaction is carried out, anomeric configuration, and used protecting groups. Nevertheless, this approach is widely applied for the introduction of azido groups at the ring system. For instance, the mesylate of glucoside **7** was substituted yielding 4-azido galactoside **8** under inversion of configuration (Scheme 16.3).<sup>11</sup>

Epoxides are also useful precursors for the incorporation of azido groups by nucleophilic attack. According to the Fürst-Plattner rule,<sup>12</sup> ring opening of sugar epoxides by azide ions preferentially leads to the diaxial product. For instance, 2-azido compound **10** is obtained regioselectively by opening of Cerny epoxide **9** with sodium azide (Scheme 16.4).<sup>13</sup> **10** was further converted into the suitably protected glycosyl donor **11**, which was applied in the synthesis of a heparan sulfate synthon by 1,2-*cis*-glycosylation (cf. Section 16.4).

Azides can also be introduced by radical addition to glycals. The classical azidonitration, developed by Lemieux *et al.* in 1979, is a powerful method for the preparation of







**Scheme 16.3** Replacement of a mesylate by an azido group under inversion of configuration at a secondary center of the sugar ring<sup>11</sup>



**Scheme 16.4** Regio- and stereoselective opening of Cerny epoxide **9** leads to 2-azido compound **10**, which can be further converted into glycosyl donor **11**<sup>13</sup>



**Scheme 16.5** Azidonitration of galactal **12** leads to an epimeric mixture of the 2-azido-1nitro-pyranoses **13** and **14** from which glycosyl donor **15** can be prepared directly.<sup>14</sup> CAN = cerium(IV) ammonium nitrate



**Scheme 16.6** Typical procedure for the Cu(II)-catalyzed diazo transfer.<sup>26</sup> DMAP = 4-(dimethylamino)pyridine

2-azido sugars that is still frequently used (Scheme 16.5).<sup>14</sup> It is especially useful for the synthesis of those 2-azido derivatives, whose corresponding glycosamines lack accessibility from natural sources as in the case of galactosamine. However, while the reaction is highly regioselective, in most cases epimeric mixtures of the 2-azido compounds are formed. The ratio of the epimers strongly depends on the employed glycal substrate.<sup>15</sup> The obtained 1-nitro-pyranoses can easily be converted into glycosyl donors, such as glycosyl halides,<sup>14</sup> trichloroacetimidates,<sup>16</sup> *n*-pentenyl glycosides,<sup>17</sup> or thioglycosides,<sup>18–20</sup> which are valuable building blocks for the preparation of 1,2-*cis* glycosides of *N*-acetyl-glycosamines (cf. Section 16.4). Similar methods for the synthesis of 2-azido sugars using radical addition to glycals are the azidochlorination<sup>21</sup> and the azidophenylselenation.<sup>22,23</sup>

Another possibility for the synthesis of organic azides is the diazo transfer using triflyl azide.<sup>24</sup> In contrast to the methods described above, not the entire azido group is incorporated into a molecule but an N<sub>2</sub> moiety is transferred onto an existing amine under retention of configuration. The first diazo transfer onto amino sugars was reported in 1991 by Vasella *et al.*<sup>25</sup> They treated different unprotected glycosamines with freshly prepared triflyl azide under basic conditions. After subsequent acetylation, the 2-azido sugars were isolated in good yields. This methodology was further improved by the addition of catalytic amounts of copper sulfate which leads to a much faster and more reliable reaction (Scheme 16.6).<sup>26,27</sup> Using the diazo transfer, it is possible to employ azides not only as amine synthons but also as temporary protecting groups for amines. This has been applied for example to the synthesis of aminoglycosides (Section 16.3), heparan sulfate fragments,<sup>28</sup> heparin fragments,<sup>29,30</sup> hyaluronan neoglycopolymers,<sup>31</sup> and *N*-acetyl-neuraminic acid derivatives.<sup>32</sup>

### 16.3 Azides as Protecting Groups during Aminoglycoside Synthesis

Protecting groups commonly employed for masking amino groups include alkyl carbamates such as benzyl-, *tert*-butyl-, and 9-fluorenylmethyl carbamates. If used for the protection of molecules containing multiple amino groups, however, carbamate protecting groups can seriously complicate the interpretation of NMR spectra. This is due to the occurrence of E/Z rotamers that are in slow interconversion leading to multiple sets of signals. The use of azides as protecting groups circumvents this problem. Azides are easily reduced to amines, for example by catalytic hydrogenation or by reaction with thiols or complex hydrides.<sup>4,33,34</sup> A widely applied method in carbohydrate chemistry is the Staudinger reduction using triaryl- or trialkylphosphines.<sup>35</sup> This mild procedure enables the selective reduction of azides in the presence of esters and benzyl ethers which are frequently used as OH-protecting groups. Furthermore, azides can be directly converted into carbamate-protected amines using a variant of the Staudinger reaction (cf. Section 16.5).<sup>27,36,37</sup>

Aminoglycosides are highly potent, broad-spectrum antibiotics, containing several amino groups presented on an oligosaccharide-like core.<sup>38–40</sup> Due to the appearance of bacterial strains resistant to these drugs and due to their relatively high toxicity, the synthesis of aminoglycoside derivatives with improved properties is of great interest.<sup>41</sup> Several syntheses of aminoglycoside derivatives using azides as amine protecting groups were reported,<sup>42,43</sup> for instance the preparation of analogs of neomycin B as shown in Scheme 16.7.<sup>27,44,45</sup> Starting from commercially available neomycin B (**18**), all six amino groups were converted into azides by diazo transfer. After chemical derivatization of the structure, amines were regenerated by Staudinger reduction.

In the course of these studies, it was observed that the regioselective reduction of a single azide of multiple azide-containing molecules is feasible if only one equivalent of phosphine is used.<sup>27</sup> Reduction of neamine derivative **23**, for example, gave mono-amine **24** in a yield of 46 % (Scheme 16.8). Strong evidence was presented that the selectivity is primarily determined by electronic factors with electron-deficient azides being reduced more rapidly and efficiently than electron-rich azides. In compound **23** this is the case for



**Scheme 16.7** Synthesis of aminoglycoside derivative **22** using azides as protecting groups for amines. First, the amino groups of **18** were converted into azides by diazo transfer.<sup>27</sup> After chemical remodeling of the aminoglycoside (one amino group was replaced by a hydroxy group), the amines were regenerated by Staudinger reduction<sup>44</sup>



**Scheme 16.8** Regioselective reduction of tetra-azides  $23^{27}$  and  $25.^{46,47}$  Boc-ON = 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile

the 2'-azide adjacent to the anomeric center. It was shown that the regioselectivity can be predicted on the basis of <sup>15</sup>N and, to some extent, <sup>1</sup>H NMR chemical shifts. Consequently, by introduction of electron withdrawing 4-chlorobenzoyl protecting groups in the 5- and 6-position, the selectivity can be tuned in favor for reduction of the 1-azide  $(25 \rightarrow 26)$ .<sup>46,47</sup>

### 16.4 Azides as Non-Participating Neighboring Groups in Glycosylations

Although 1,2-cis glycosides of 2-amino-2-deoxysugars are less frequently found in natural products compared to their 1,2-trans isomers, they are a common motive in important structures. In mucin-type O-glycoproteins, e.g. the glycan chains are attached to protein via an  $\alpha$ -glycosidic linkage of N-acetyl-D-galactosamine to the  $\beta$ -hydroxy group of either serine or threonine, and  $\alpha$ -glycosides of 2-acetamido-2-deoxy-D-glucose are found in the glycosaminoglycan heparan sulphate.<sup>48–51</sup> For the preparation of these 1,2-*cis* glycosides, the commonly employed N-acyl protecting groups are not suited because they lead to 1,2-trans products 29 via neighboring group participation (Scheme 16.9A).<sup>15,52,53</sup> In 1978 Paulsen et al. showed that 2-azido-2-deoxy-glycosyl halides are suitable donors in 1,2-cis glycosylations. This approach preferentially leads to  $\alpha$ -glycosides 32 either directly from  $\beta$ -glycosyl halides **30** (Scheme 16.9B)<sup>54,55</sup> or by *in situ* anomerization<sup>56</sup> of  $\alpha$ -glycosyl halides 33 (Scheme 16.9C).<sup>57</sup> Since then, the azide method has been widely used<sup>15,52,58-62</sup> and expanded by use of other glycosyl donors, such as trichloroacetimidates, <sup>16</sup> *n*-pentenyl glycosides,<sup>17</sup> and thioglycosides<sup>18-20</sup> just to name a few. The required 2-azido-2-deoxy sugars are usually prepared by azidonitration of glycals or by diazo transfer reaction of the corresponding glycosamines as described above. After glycosylation, the azide can



**Scheme 16.9** Preparation of O-glycosides of 2-amino-2-deoxysugars. (A) Use of N-acylprotected donors **27** results in 1,2-trans glycosylation due to neighboring group participation. (B) 1,2-cis glycosylation products **32** from  $\beta$ -glycosyl halides **30**<sup>54,55</sup> or (C) by in situ anomerization<sup>56</sup> of  $\alpha$ -glycosyl halides **33**<sup>57</sup>

be transformed to the natural acetamido function either in two steps by reduction of the azide and subsequent acetylation or in one step by reductive acetylation using thioacetic acid.<sup>63,64</sup>

A successful approach for the synthesis of *O*-glycopeptides is the assembly of preformed, more or less complex glycosyl amino acid building blocks by solid phase peptide synthesis (SPPS).<sup>60–62,65–67</sup> Based on initial work of Ferrari<sup>68</sup> and Paulsen,<sup>69</sup> the azide method is extensively used for the preparation of such glycosyl amino acid building blocks. Especially the synthesis of complex glycosyl amino acids is challenging. Usually, glycosylation is performed with monosaccharides followed by attachment of further sugar residues because glycosylation reactions with oligosaccharide donors and serine or threonine acceptors often proceed with unpredictable stereochemistry. Nevertheless, oligosaccharides have been successfully used in many glycosylations as illustrated by the synthesis of glycosyl threonine building block **38** reported by Danishefsky and coworkers (Scheme 16.10).<sup>64</sup>

#### 16.5 Glycosyl Azides as Precursors for Glycosyl Amides

Beside the *O*-linked glycoproteins, the more prevalent form of glycosylation of proteins is *N*-linked glycosylation.<sup>48,70,71</sup> *N*-Glycoproteins are characterized by a  $\beta$ -*N*-glycosidic linkage of the terminal *N*-acetylglucosamine of the pentasaccharide core structure to the amide nitrogen of asparagine. The conventional synthetic strategy for the preparation of such glycosyl amides starts from glycosyl amines which are reacted with activated and



**Scheme 16.10** Synthesis of glycosyl threonine building block **38** using the azide method.<sup>64</sup> The 2-azido group is introduced by azidonitration of **34** followed by preparation of donor **36**. Glycosylation using threonine as acceptor leads to 1,2-cis glycoside **37**. After conversion of the azide group to an N-acetyl group by reductive acetylation, **38** was used as building block in glycopeptide synthesis

suitably protected aspartic acid derivatives to form the amide linkage.<sup>60–62,65–67</sup> Glycosyl amines are commonly prepared either by reduction of glycosyl azides (cf. Section 16.3) or by amination of unprotected reducing sugars with saturated aqueous ammonium bicarbonate.<sup>72</sup> Recently, improved variants of the latter procedure employing microwave irradiation<sup>73,74</sup> and ammonium carbamate,<sup>75,76</sup> respectively, have been published. Drawbacks of this method are the instability of glycosyl amines and their propensity for dimerization and anomerization. Also, the preparation of  $\alpha$ -glycosyl amides is a synthetic challenge.

While the classical Staudinger reaction<sup>35</sup> leads to iminophosphoranes which can be hydrolyzed to amines under aqueous conditions (Staudinger reduction, cf. Section 16.3), the addition of acyl donors under dry conditions results in amide formation.<sup>77,78</sup> This procedure was repeatedly applied for the synthesis of glycosyl amides, thus circumventing the preparation of glycosyl amines. Initially, three-component reactions employing glycosyl azide, activated carboxyl derivative and phosphine were reported (Scheme 16.11). The reaction starts from the  $\beta$ - (**39**) or  $\alpha$ -glycoside **45** with the formation of an iminophosphorane (**40** and **42**, respectively), which is then trapped by an acylating agent in the second step. The resulting acylaminophosphonium salt (**43/46**) yields the corresponding glycosyl amide (**44/47**) upon hydrolysis. The intermediate iminophosphorane can undergo anomerization via open-chain form **41** preferring  $\beta$ -configuration. The degree of isomerization is dependent on the efficiency of iminophosphorane trapping by the acylating agent. Differently activated carboxylic acids, such as carboxylic halides,<sup>79,80</sup> anhydrides,<sup>80,81</sup> and carbodiimide-activated acids,<sup>82,83</sup> have been employed as acylating agents. While  $\beta$ -glycosyl amides **44** can be obtained easily from  $\beta$ -glycosyl azides **39**, the stereospecific



Scheme 16.11 Mechanism of the Staudinger reaction with glycosyl azides



**Scheme 16.12** Three-component Staudinger-type reaction with  $\beta$ -glycosyl azide **4** stereoselectively leads to the  $\beta$ -glycosyl amides **48**.  $\alpha$ -Glycosyl amides can only be obtained from  $\alpha$ -glycosyl azide **49** with strong acylating agents to prevent complete anomerization of the intermediate iminophosphorane<sup>80</sup>

synthesis of  $\alpha$ -glycosyl amides 47 starting from  $\alpha$ -glycosyl azides 45 is only possible with strong acylating agents which trap the intermediate iminophosphorane 42 before anomerization can take place.<sup>80</sup> Representative examples for the three-component Staudinger reaction are shown in Scheme 16.12. Rarely, the Staudinger reaction with reactive alkylphosphines and free carboxylic acids has been reported.<sup>84,85</sup> In this case, amide-bond formation is assumed to proceed in a concerted reaction without generation of an iminophosphorane intermediate.

Recently, the synthesis of glycosyl amides has also been achieved employing the traceless two-component Staudinger ligation<sup>9,86,87</sup> developed in the laboratories of Bertozzi<sup>88</sup> and Raines<sup>89,90</sup> (Scheme 16.13). Starting from glycosyl azides **50** and **55**, respectively, the initially formed iminophosphorane **52/57** reacts with an intramolecular (thio)ester group to form the acylaminophosphonium salt **53/58** from which the phosphine moiety is removed by hydrolysis with water. Using benzyl protected  $\alpha$ -glycosyl azides such as **50** 



**Scheme 16.13** Two-component traceless Staudinger ligations using phosphine-derivatized ester **51**  $(A)^9$  or thioester **56**  $(B)^{87}$ 

and stable phosphine **51** or similar esters in polar aprotic solvents such as DMF, the reaction proceeded stereo conservatively to yield predominantly  $\alpha$ -glycosyl amides (Scheme 16.13A).<sup>9</sup> The use of acetyl protected  $\alpha$ -glycosyl azides, however, resulted only in  $\beta$ -glycosyl amides due to isomerization of the less reactive iminophosphorane.

All methods described above have been used for the preparation of the  $\beta$ -glycosyl amide linkage between *N*-acetylglucosamine and the side chain of asparagine in both three-component reactions using free<sup>84,85</sup> or activated<sup>82,83</sup> carboxylic acids and two-component reactions as shown in Scheme 16.13.<sup>9,87</sup> The obtained protected glycosyl amino acids can be used as building blocks in SPPS of *N*-linked glycopeptides.<sup>91,92</sup> It was also shown that deprotected sugars can be attached to amino acids and whole peptides using the three-component reaction.<sup>92</sup> Beside Staudinger-type reactions, another route towards the synthesis of glycosyl amides is the reaction of glycosyl azides with thiocarboxylic acids.<sup>93</sup>

## 16.6 Synthesis of Glycoconjugates via Azide-Alkyne [3+2] Cycloaddition

Although the azide-alkyne [3+2] cycloaddition<sup>94</sup> (cf. Chapter 9) is known in carbohydrate chemistry for more than 50 years,<sup>95</sup> its application for the preparation of glycoconjugates became particularly attractive with the development of the copper(I)-catalyzed variant by Meldal<sup>96</sup> and Sharpless.<sup>97</sup> The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC)<sup>98,99</sup> enables the regioselective formation of 1,4-disubstituted 1,2,3-triazoles under very mild conditions even in a biological context. However, the cellular toxicity of the copper catalyst precludes applications wherein cells must remain viable. Therefore, as an alternative



**Scheme 16.14** Coupling of azide-substituted galactoside **60** to alkyne-modified  $C_{14}$  hydrocarbon **61** noncovalently bound to the microtiter well surface<sup>108</sup>

to CuAAC, strain-promoted azide-alkyne [3+2] cycloadditions have been developed that proceed at room temperature without the need for a catalyst.<sup>100,101</sup> These reactions are discussed in the next section dealing with metabolic oligosaccharide engineering. Another example of metal-free triazole formation by a tandem [3+2] cycloaddition-retro-Diels-Alder reaction has been developed by van Berkel *et al.* although no carbohydrate-related application was reported.<sup>102</sup>

CuAAC reactions have been extensively applied in carbohydrate chemistry including the synthesis of simple glycoside and oligosaccharide mimetics, glyco-macrocycles, glycoconjugates, glycoclusters, and for the attachment of carbohydrates to surfaces. The field has been thoroughly reviewed<sup>98,103–107</sup> and, therefore, we will focus on a few selected examples which are of special interest for glycobiology.

One of the first applications of CuAAC in carbohydrate chemistry was – beside the one in the seminal paper of  $Meldal^{96}$  – the immobilization of azide-substituted sugars on microtiter plates (Scheme 16.14).<sup>108</sup> The surface-bound sugars such as **62** were screened with various lectins and could be elongated by glycosyltransferase-catalyzed fucosylation. The technique was later on improved by incorporation of a cleavable disulfide bond in the linker allowing mass spectrometric characterization of the carbohydrate array.<sup>109</sup>

Neoglycopeptides and -proteins<sup>110</sup> differ from naturally occurring structures by replacement of the natural carbohydrate-peptide linkage with a non-natural one. This not only allows studying the influence of distinct structural elements on biological activity, but has many practical applications as well. Use of chemoselective ligation reactions such as



**Scheme 16.15** Application of CuAAC for the preparation of triazole-linked glycosyl amino acids **65**<sup>111</sup>



**Scheme 16.16** Preparation of tyrocidine derivatives **68** by CuAAC of propargy/glycinecontaining cyclic peptides **66** and azido-functionalized sugars **67**<sup>113</sup>

CuAAC makes glycoconjugates accessible to a broader community. Furthermore, the non-natural linkage often is more stable (both chemically and with respect to enzymatic degradation) which can lead to an increased half life of a glycoconjugate within a biological system. Scheme 16.15 depicts the synthesis of triazole-linked glycosyl amino acids **65** starting from glycosyl azides **63** and different alkyne-containing amino acids **64** which can be used as building blocks in peptide synthesis.<sup>111,112</sup>

Lin and Walsh applied CuAAC for the attachment of 21 different azido-functionalized monosaccharides **67** to 13 derivatives **66** of the cyclic decapeptide tyrocidine containing one to three propargylglycine residues at positions 3–8 (Scheme 16.16).<sup>113</sup> Head-to-tail cyclization of the peptides was accomplished using a thioesterase domain from tyrocidine synthetase. Antibacterial and hemolytic assays showed that the two best glycopeptide mimetics had a 6-fold better therapeutic index than the natural tyrocidine. CuAAC has further been used to attach carbohydrates to whole virus particles<sup>114,115</sup> and DNA.<sup>116</sup>

More challenging is the modification of bacterially expressed proteins by site-specific attachment of carbohydrates. Crucial step is the introduction of a chemical tag, which can be chemoselectively modified, into the protein. It has been shown that alkyne- and azido-modified amino acids, such as 2-amino-5-hexynoic acid (homopropargylglycine, Hpg),<sup>117</sup> 4-azidohomoalanine (Aha),<sup>118,119</sup> and with less efficiency also 3-azidoalanine, 5-azidonorvaline, and 6-azidonorleucine,<sup>120</sup> act as methionine surrogates that are acti-

vated by the methionyl-tRNA synthetase of *E. coli* and replace methionine in proteins expressed in methionine-depleted bacterial cultures. This, together with other methods for the incorporation of non-canonical amino acids into proteins,<sup>121–123</sup> offers the possibility to use azide-alkyne cycloaddition (and also Staudinger ligation<sup>124–126</sup>) not only for protein labeling within cells or on cell surfaces<sup>119,120</sup> but also for the preparation of neoglycoproteins.

Davis and coworkers expanded the diversity of chemical protein modification by a combination of this CuAAC-based labeling and disulfide bond formation via genetically engineered cysteine (Cys) residues.<sup>127</sup> Aha and Hpg, respectively, were introduced into engineered proteins by the auxotrophy-based residue-specific method. Subsequent CuAAC reactions with alkyne- and azide-substituted carbohydrates, respectively, resulted in homogeneous protein glycoconjugates. As second modification reaction, conjugation of Cys residues with substituted methanethiosulfonates was chosen. Applying these two orthogonal protein modification reactions, derivatives of the LacZ reporter enzyme carrying the tetrasaccharide sialyl Lewis X and a sulfotyrosine mimic were created that allowed detection of mammalian brain inflammation.

Recently, Merkel *et al.* reported efficient N-terminal glycoconjugation of proteins by the N-end rule.<sup>128</sup> Bulky amino acids at the second and third sequence position of the barnase inhibitor barstar efficiently prevent excision of N-terminal methionine analogue Aha introduced by the auxotrophy-based residue-specific method. The created azide tag at the protein's N-terminus was subsequently conjugated to propargyl glycosides of *N*-acetylglucosamine and N,N'-diacetylchitobiose, respectively, by CuAAC. The obtained glycoprotein mimetics show binding affinity to the lectin wheat germ agglutinin whereas the natural activity of barstar is conserved.

Lectins are carbohydrate-binding proteins other than immunoglobulins without enzymatic activity towards the recognized sugars.<sup>129-131</sup> Carbohydrate-lectin interactions are involved in numerous intra- and intercellular events during development, inflammation, immune response and cancer metastasis.<sup>132-136</sup> Multivalency appears to play an important role in lectin-mediated interactions,<sup>137-140</sup> and many lectins are found to recognize individual carbohydrate epitopes only with low affinity. Preparation of carbohydrate clusters, therefore, is a common strategy to obtain high-affinity lectin ligands.<sup>141–144</sup> Because of its robustness, CuAAC is excellently suited for the simultaneous attachment of several carbohydrate epitopes to a scaffold. Initially, Santoyo-Gonzáles and coworkers prepared different multivalent mannose clusters starting from propargyl mannosides and azidecontaining scaffolds.<sup>145</sup> This strategy as well as the opposite approach based on azidecontaining carbohydrates and alkyne-bearing scaffolds have been used intensively for the preparation of glycoclusters.<sup>98,103-107</sup> Glycosyl azides are easily produced, however, the direct attachment of a triazole to the sugar may interfere with the recognition of the carbohydrate by the protein and, therefore, linkers of varying length have been introduced between the sugar and the triazole moiety. It would be far beyond the scope of this chapter to mention all applications. Exemplarily, the asymmetrical, bifunctional dendrimer 69 containing 16 mannose units and two coumarin chromophores<sup>146</sup> and poly(methacrylate)based glycopolymer  $70^{147}$  are depicted in Scheme 16.17.

Although organic azides are stable against most reaction conditions, compounds containing multiple azide residues (like multivalent scaffolds) are potentially explosive. Therefore, several one-pot procedures to generate azides *in situ* followed by CuAAC have



**Scheme 16.17** (A) Asymmetrical, bifunctional dendrimer **69** containing 16 mannose units and two coumarin chromophores<sup>146</sup> and (B) poly(methacrylate)-based glycopolymer **70**<sup>147</sup> prepared by CuAAC and used for lectin binding studies with concanavalin A

been reported.<sup>148–154</sup> While the azides in most of these procedures are introduced by a nucleophilic substitution of a leaving group in allyl, benzyl, glycosyl, or similar position,<sup>148–152</sup> aliphatic<sup>154</sup> and aromatic<sup>153</sup> amino groups may also serve as precursors. We reported, for example a one-pot procedure for diazo transfer and subsequent CuAAC which allows the preparation of multivalent structures starting from commercially avail-



**Scheme 16.18** Sequential one-pot procedure for diazo transfer and CuAAC.<sup>154</sup> First, diamine **71** is transformed to the corresponding diazide by Cu(II)-catalyzed diazo transfer. After completion, Cu(I) required for subsequent CuAAC with **72** is generated by addition of reducing agent Na ascorbate. MW = microwave; TBTA = tris(benzyltriazolylmethyl)amine

able amine scaffolds without need for isolation of the azide-containing intermediates.<sup>154</sup> As an example, divalent glycoconjugate **73** was synthesized from diamine **71** and propargyl glycoside **72** as shown in Scheme 16.18.

Azides can also undergo [3+2] cycloaddition reactions with nitriles giving access to 1,5-disubstituted tetrazoles. *Inter*molecular reactions, however, require electron deficient nitriles and very forcing conditions to occur with sufficiently high reaction rates.<sup>155–157</sup> High yields have been reported for the reaction of sulfonyl and acyl cyanides with unhindered aliphatic azides by neat, thermal fusion.<sup>158,159</sup> *Intra*molecular [3+2] cycloaddition reactions of organic azides to nitriles occur more readily.<sup>160–164</sup> Still, they require high reaction temperatures and yields are with few exceptions<sup>165</sup> not satisfactory. When precisely positioned on a rigid carbohydrate scaffold, however, azides can undergo cycloaddition reactions with nitriles under exceptionally mild conditions. Thus, 3-azido-1,2-*O*-cyanoethylidene-3-deoxy-allopyranose was shown to form a tetrazole embedded in a bridged tetracyclic ring system even at room temperature.<sup>166</sup>

#### 16.7 Metabolic Oligosaccharide Engineering

Glycosylation of proteins is an important co- and posttranslational event that has been estimated to occur on more than 50% of eukaryotic proteins.<sup>167</sup> The glycan chains of cell-surface glycoproteins are involved in numerous recognition processes such as cell adhesion and attachment of bacteria or viruses. Inside cells, glycans direct protein trafficking and they modulate structure and activity of proteins.<sup>132–136</sup> Hence, in vivo monitoring of glycosylation processes is of utmost interest.<sup>168</sup> While fluorescent fusion proteins and other genetically encoded tags provide a means for labeling specific proteins in live cells, analogous techniques are not available for secondary gene products including glycans. Metabolic oligosaccharide engineering offers the possibility to introduce carbohydrates with unnatural structural elements into the glycans without genetic manipulation making use of the cell's biosynthetic machinery.<sup>169</sup> If suitable chemical reporter groups are introduced, subsequent addition of an exogenously delivered detectable probe allows for tagging of the glycans by a chemoselective ligation reaction. Examples for such reporter groups include ketones<sup>170,171</sup> and thiols.<sup>172</sup> However, the azido group is much more



**Scheme 16.19** Metabolic oligosaccharide engineering: peracetylated ManNAz **74** is taken up by mammalian cells and converted into an azide-containing sialic acid derivative which is incorporated into sialic acid-bearing glycans **75**. In the next step, a detectable probe **76** can be attached to **75** via Staudinger ligation<sup>124,173</sup>

suited for this approach because azides can take part in two important bioorthogonal ligation reactions, Staudinger ligation<sup>124</sup> (cf. Section 16.5) and azide-alkyne [3+2] cyclo-addition (cf. Section 16.6 and Chapter 9).

Azide derivatization of monosaccharides represents a subtle structural change that is accepted by several metabolic pathways. Thus, azide derivatives of N-acetylmannosamine (i.e. N-(azidoacetyl)mannosamine, ManNAz), N-acetylgalactosamine (i.e. N-(azidoacetyl) galactosamine, GalNAz), N-acetylglucosamine (i.e. N-(azidoacetyl)glucosamine, GlcNAz), and L-fucose (i.e. 6-azido-L-fucose) have been explored.<sup>168,169</sup> Initially, ManNAz was employed to tag sialylated cell surface glycans of mammalian cells in vitro (Scheme 16.19).<sup>124,173</sup> Cells are grown in the presence of peracetylated ManNAz 74 which can be taken up by the cells more easily than ManNAz. After de-O-acetylation by cellular esterases, resulting ManNAz is metabolized similarly to its native counterpart N-acetylmannosamine and integrated into cellular glycans. Finally, the azide-labeled glycans are reacted with a detectable probe by Staudinger ligation. GalNAz can be metabolically introduced at the core position of mucin-type O-linked glycoproteins.<sup>174</sup> Thus, a selective labeling of mucin-type glycoproteins is possible. Both, the metabolic labeling of sialylated glycans with ManNAz<sup>175</sup> and labeling of mucin-type O-glycoproteins with GalNAz<sup>176</sup> can be carried out in vivo. Analogously, GlcNAz has been used for the labeling of O-GlcNAc glycosylated proteins.<sup>177</sup> Recently, cells were labeled simultaneously with an azide- and a ketone-containing sugar.<sup>178</sup> Using orthogonal ligation reactions, glycans bearing these sugar residues can be visualized in parallel on the same cells.

In the cases mentioned so far, fluorescence labeling has been achieved by a two-step procedure. First, a biotin label<sup>124</sup> or FLAG tag (octapeptide Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Asp-Lys)<sup>173,174,177</sup> is covalently attached to the azide-containing glycan by Staudinger ligation at high concentration. In a second step, a fluorescently labeled receptor (avidin and anti-FLAG antibody, respectively) is added at lower concentration. To avoid the problem of high background fluorescence caused by the application of fluorescent dyes,



**Scheme 16.20** Generation of fluorescent triazole **80** by CuAAC of fluorogenic ethynylnaphthalimide **78** and azide-labeled glycoproteins **79** applicable for intracellular localization of fucosylated glycoconjugates<sup>179</sup>

Wong and coworkers developed a one-step labeling method based on CuAAC ligation using fluorogenic dyes (Scheme 16.20).<sup>179</sup> 6-Azido-L-fucose was applied for tagging of fucosylated proteins by metabolic oligosaccharide engineering. Reaction of alkyne-sub-stituted naphthalimide **78** and azide-modified glycoprotein **79** results in formation of fluorescent triazole **80**. Since **78** is not fluorescent, it can be applied at high concentrations without producing a background signal. The method was used for cell surface glycoprotein analysis and intracellular localization of fucosylated glycoconjugates by using fluorescence microscopy.

Other examples for the application of CuAAC for labeling and visualization of glycoproteins in cells have been published by the research groups of Bertozzi<sup>180</sup> and Wong.<sup>181</sup> The main advantage of CuAAC over Staudinger ligation is its much faster reaction kinetics. However, the use of CuAAC for applications in vivo is limited due to the cellular toxicity of copper ions. This led to the development of copper-free variants of this cycloaddition. Based on observations made by Wittig who described the exothermic cycloaddition of cyclooctyne with phenyl azide,<sup>182</sup> Bertozzi and coworkers reported the copper-free, strain-promoted cycloaddition between azides and substituted cyclooctyne **81** for covalent modification of biomolecules in living systems (Scheme 16.21).<sup>100</sup> The reaction rates were lower than those of CuAAC but comparable to those of Staudinger ligation.<sup>183</sup> The validity of the approach was demonstrated by functionalization of modified Jurkat cells with a biotin derivative of 81.<sup>100</sup> Reaction rates of the strain-promoted azide-alkyne cycloaddition could be dramatically improved by introduction of electronwithdrawing fluorine substituents in  $\alpha$  position of the triple bond (Scheme 16.21, 82–84) with the difluorinated cyclooctyne (DIFO) derivatives 83 and 84 possessing comparable kinetics to those of CuAAC.<sup>183-185</sup> Similar reaction rates were observed with dibenzocyclooctyne derivative 85.<sup>101</sup> These reactions are not regioselective but proceed chemoselectively within minutes on live cells with no apparent toxicity.<sup>101,184,185</sup> Latest application of DIFO derivative 83 is the *in vivo* imaging of membrane-associated glycans in live



**Scheme 16.21** Cyclooctyne derivatives for use in copper-free, strain-promoted azide-alkyne [3+2] cycloadditions designed by Bertozzi (**81**,<sup>100</sup> **82**,<sup>183</sup> **83**,<sup>184</sup> **84**<sup>185</sup>) and Boons (**85**<sup>101</sup>). The second-generation difluorinated derivative **84** is easier to synthesize than **83** 

developing zebrafish.<sup>186</sup> Using two derivatives **83** with different fluorophores attached, it was possible to perform a spatiotemporal analysis of glycan expression and trafficking.

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# Index

Accelerating Rate Calorimetry (ARC) 20-1 4-acetamidobenzene-sulfonyl azide 37 2-acetamido-2-deoxy-d-glucose 474 acetyl azide 60 N-acetylglycosamines 472 amide linkage 478 N-(acetyl)mannosamine 484 acetylnitrenes 323 acyl azides Curtius degradation 86 electrochemical reduction to amines 256 as peptide coupling reagents 88 synthesis 84-90 acid chloride method 84-5 anhydrides 87 direct conversion of carboxylic acids 86 - 7from aldehydes using Dess-Martin periodinane 88-9 mixed anhydrides 85-7 N-acylbenzotriazoles 89-90 acyl halides, reactions with phosphazenes 443 acyl tetrazoles, synthesis 278-9 acylaminophosphonium salt 476 iminophosphoranes 476 N-acylbentotriazoles, synthesis of acyl azides 89-90 1-epi-adenophorine 457 (-)-adenophorine 458 adenyl-peptide conjugates 299-300 adiabatic self-heating 20 Agrobacterium radiobacter AD1, halohydrin dehalogenase 66 airbags, automotive industry 41 alcalase mediated dipeptide synthesis, with amino acid amides 293

alcohols conversion to corresponding azides 70-1 direct synthesis of azides 54-5 aldehydes Dess-Martin periodinane, acyl azides 88-9 reactions with phosphazenes 440-2 alkaloids benzodiazepine derived 460 homoerythrina 221-2, 443 quinazoline 462 quinolizidine-containing 225 Schmidt rearrangements 220 stenine 225-8 alkenes carboazidation 252 reaction with halogen azides 244-5 alkenyl azides cheletropic additions 143 reactions 133 alkenyl-substituted azides 392-400 alkyl 2-azidocinnamates conversion into alkyl indole-2-carboxylates 183 conversion into indole-2-carboxylic esters 170 alkyl azides 43, 191-238 fluorosubstituted n-propyl azide 316 hydroxyalkyl azides 200-7 intermolecular sensitization 318 photochemistry 315-19 radical cyclizations 255 reactions with epoxides 216-18 reactions with alpha, beta-unsaturated ketones 214-16 reduction by single electron transfer (SET) 255 - 62

Organic Azides: Syntheses and Applications Edited by Stefan Bräse and Klaus Banert © 2010 John Wiley & Sons, Ltd. ISBN: 978-0-470-51998-1

Schmidt reactions 191-238 with carbocations 207-11 with carbonyl compounds 197-200 intramolecular 192-7 intermolecular 197-200 intramolecular vs intermolecular 192-5 metal-mediated reactions 211-14 rearrangement cascade reactions 218-20 rearrangements of hydroxyalkyl azides toward biologically relevant compounds 233-5 rearrangements in total synthesis of natural products 220-30 rearrangements in total synthesis of non-natural products 230-3 synthesis 53-76 classic nucleophilic substitutions 53-64 from amines, diazo transfer reaction 72-5 from carbon nucleophiles and electronpoor sulfonyl azides 75-6 microwave-assisted 61, 63 Mitsunobu reaction 70-1 ring opening of aziridines 68-9 ring opening of epoxides 64-8 tertiary, matrix photochemistry 316 see also hydroxyalkyl azides alkyl-substituted azides 391-400 alkyl/aminyl radicals, SET 255-62 alkylated cyclohexanone, Schmidt reactions 195 alkylnitrenes 317 N-alkylstannanaminyl radical intermediate 259 1-alkylsulfanyl-2-azidoethynes 156 alkyne-substituted peptide thioethers, enzymemediated cyclization 293 alkyne-substituted tripeptides 290 allenes, electron-deficient 121 allenyl azides 147-54 acceptor substituent, phenylsulfonyl group 153 characterization by NMR data 148 early direct reference 147 photolysis and generation of 2-methylene-2H-azirines 154 [3,3]-sigmatropic rearrangement of propargyl azides 149 allylsulfones 250 almazoles 444-6 aluminium salen azide complex 1 (catalyst) 97 Amaryllidaceae alkaloids 249, 440 Amberlite azide ion exchange resin 61 amides linkage, N-acetylglucosamine 478 vinylogous 441-2

amines, diazo transfer reaction, synthesis of alkyl azides 72–5 amino acids azide-functionalized 305 azido-substituted glycosyl amino acids 291 glycoconjugated 286 mannopyranoside and glucopyranoside derivatives 287 solid phase peptide synthesis (SPPS) 475, 478synthesis of glycopeptide mimetics, DCR 286 - 8tetrazole analogues 287-8 unnatural beta-, asymmetric synthesis 86 amino groups, masking 472 amino sugars 54 2-amino sugars, CAN procedure 242 2-amino-2-deoxysugars 475 diazo transfer reaction 472, 474 1-amino-5-azido-tetrazole 406 3-amino-2H-azirines 125 aminoglycosides, synthesis 472-4 aminoguanidine, diazotization 41 2-amino-5-hexynoic acid 480 aminohydroxylation, electron-deficient olefins 217 aminomonocarba-disaccharide, Curtius rearrangement 86 5-aminotetrazole (5-AT), synthesis from cyanoguanidine 41 aminyl radicals ability to rearrange 259-60 intermediacy in reduction of organic azides 257 SET 255-6 anhydrides, synthesis of acyl azides 87 (-)-anhydronupharamine 456-7 annuloline 443, 445 anomerization, iminophosphorane 476 anthramicins 454 anti-cancer agents 303 antibacterials aminoglycosides, synthesis 472-4 anthramicins 454 phloeodictine 464 triazole-functionalization of vancomycin 295 antigens and peptides, copper(I)-catalyzed conjugation 292 apratoxin A 454-6 Aprepitant 45 ardeemin 464 aromatic azides bisulfonyl azides, cross-linking/vulcanizing agents in polymers 47 polynuclear, photochemistry 355-63

aroyl azides 84 aroylnitrenes 322 artificial receptor prototypes 304 aryl azides 43 diazo transfer 83 from diazonium compounds 80 from hydrazines and nitrosoarenes 84 from organometallic reagents 80-2 from triazenes 82 nucleophilic aromatic substitution 76-80 electron-deficient arenes 77 radical cyclizations 255 synthesis 76-84 aryl substituted azides 400-5 4-aryl-3-butenyl azides, with TfOH yielding 3-pyrrolines 209 beta-aryl-carboxylic acids 41 aryloxenium 450 arynes 275 (-)-asperlicin C 463 (+)-aspidospermidine 224 automotive industry, airbags 41 aza-Wittig reaction 439-68 intermolecular 440-6 carbonyl derivatives 440-5 heterocumulene derivatives 445-50 intermolecular nucleophilic addition/ intramolecular cyclization (AW-NA-IC) 448 intramolecular 450-65 intramolecular cyclization (AW-IC) 447 Wittig reagents 242 azafluoranthrene alkaloids 441-2 azaisowurtzitanes 400, 401, 402 azaspiracids 457 azaspiroconjugation 133 azetidine-2-ones 186-7 from 4-azido-2-pyrrolinones 186 from cyclopropanone acetal 187 azidation carbon-centered radicals 246-7 iodine compounds, ethanesulfonyl azide 250 iodine derivatives 247-9 with sulfonyl azides 249-54 azide esters, photochemistry 325-7 azide-enriched tetrazole 406 azide-mediated ring expansions, steric interactions vs cation interactions 206 azides addition to multiple CC- and/or CN-bonds 37-43 anomeric 250 commercial-scale applications 47-8 1,3-dipolar cycloaddition reactions 269-70, 285-310

organic, reduction with metals 257-8 as protective group for amino function 46 synthesis 53-94 use on technical scale 37-47 see also acyl, alkyl and aryl azides; organoazides; sodium azide azidoacetic acid chloride, cephalosporins 45, 47 azidoacetic acid ethyl ester (AAE) 35-6 physical and chemical properties 36 alpha-azidoacetophenones 318 intramolecular sensitization 317 alpha-azidoacetyl indole 446 N-(azidoacetyl)mannosamine (ManNAz) 484 3-azidoacrolein 118 1-azidoadamantane, triplet sensitization 318 3-azidoalanine 480-1 azidoalcohols 200 acid promoted rearrangement 208 derived from limonene 263 azidoaldehyde, rearrangement pathways 196 azido alkenes, acid promoted rearrangement 208 alpha-azidoalkyl radicals, fragmentation reaction 262-3 1-azidoalk-1-ynes 154, 156, 157 azido-aminoglucopyranoside, coupled to propynoyl-dipeptide 304 1-azido-1,2-benziodoxole-3-(1H)-one 247 alpha-azidobenzyl ethers 247-8 azidobenzyl substituted azaisowurtzitanes 401 hexakis-4-azidobenzyl-hexaazaisowurtzitane 402 alpha-azido-beta-(3-indolyl)propenamide 444 2-azidobuta-1,3-dienes 126, 140 azidobutatriene, synthesis of 4-ethynyl-1,2,3triazole 153 azido carbohydrates 54 alpha-azidocinnamate 459 azidocumulenes 153 azidocyclobutanes 140 azidocyclopentadienes 129, 130, 139, 142 (3'-azido-3'-deoxythymidinyl) trimethylphosphinegold(I) 382 2-azido-3,5-dichlorobiphenyl, photochemistry 352 - 33-azido-2,3-dideoxyhexanopyranoses, preparation of 2H-azirines 167-9 4-azido-1,2-dihydronaphthalene 170 2-azido-2,2-diphenylacetic acid 288 alpha-azidoenamines 127 2-azidoethanol 200 see also azidoalcohols tris(azidoethyl)amine 397

tetrakis(azidoethyl)ammonium azide 397

azidoformamidinium salts 400 azidoformates, photolysis and thermolysis 325 azidohaloalkanes 115, 119 4-azidohomoalanine (Aha) 480 3-azido-1H-indenes 129 azidoiodinanes 247-8 azido ketals 197 azidoketones, cyclic, Schmidt reactions 194 alpha-azido-ketones, silvl enol ethers 242 azidomethane-substituted compounds 392-3 hexakis(azidomethyl) benzene 392 azidomethyl ketones, condensation with aldehydes or ethyl pyruvate 125 tetrakis(azidomethyl) silane 392, 394 tris(azidomethyl)amine 396 3-azido-3-methylbut-1-yne, synthesis and succeeding reactions 148 tris(azidomethyl)ethanol 396 tris(azidomethyl)methanol 394 tris(azidomethyl)methylammonium salts 395 2-azidonaphthalene, photolysis and pyrolysis 355 1-azido-2-nitroethyne, geometrical structure and heat of formation 156 1-azidonorbornane 316-17 6-azidonorleucine 480-1 5-azidonorvaline 480-1 1,3,5,7-tetrakis(4-azidophenyl) adamantane, DSC and TGA measurements 18 3-(o-azidophenyl) quinolin-2-one 461 3-azido-3-phenyl-3H-diazirine 54 1-azido-2-phenylethyne 154 attempts to generate and trap 155 (2-azidophenylisocyanide) pentacarbonyltungsten 381 azido phosphonate 454 (4S)-4-azido-proline 297 azidoprolines (Azp) 296 3-azidopropanol 200 beta-azidopropiophenones, intramolecular sensitization 317-18 4-azido-2-pyrrolinones, azetidin-2-ones 186 azidoquinones 115-16 azidoselenation of olefins, diphenyl diselenide 244 azido-selenenylation 131 alpha-azidostyrene photolysis 321 vapor phase pyrolysis 133 azido-substituted polyazines 407, 408 2-azido sugars 472 3-azido-3-sulfolenes 143 azido-tethered phenyl-substituted epoxides, rearrangements 219 5-azidotetrazole 406

5-azido-1*H*-tetrazole 405 1,2-bis-(5-azido-1H-tetrazolyl)ethane 406-7 3-azido-1,2,4-triazoles 405 azidotrimethylsilane 129, 131 azido-1,2,3-triphenylpropenes 122 azidyl radicals addition onto alkenes 241 cerium ammonium nitrate (CAN) 241-2 electrochemically generated 246 halogen azides 244-5 iron(III) azide 241 metal generation 241-2 aziridination, acid-promoted 217 aziridines 171-85 acid-promoted aziridination 217 cyclic sulfates and sulfites 183 enantiopure 182 from acyclic enones with alkyl azides 216 from alkenes and organic azides 172 from epoxides or 1,2-diols 181-3 from vinyl azides via 2H-azirines 183-4 nitrene intermediates 172-6 ring opening 43-4, 68-9 via triazolines 176-81 see also small ring nitrogen heterocycles azirine intermediates 140 1-azirines 320 2H-azirines 133-9, 149, 167-90 3-amino-2H-azirines 125 2,3-bridged 137-8 by thermolysis or photolysis 135 destabilized 134 exo-endo stereoisomers 138 five-membered heterocycles 139 from enazides 134 indirect syntheses from unsaturated azides 170 - 1interception by internal nucleophile 184 2-methylene-2H-azirines 154 reaction with methanol 170 reactions 136 reactions of vicinal halovinyl azides 139 thermal isomerization of halo-2H-azirines 170 balanol 451, 453 BAM friction test apparatus 10-11 barrenazines A and B 242-3 Barton esters 250-1 (-)-batzelladine D 239 benzenes, polyazido benzenes 400-1 benzenesulfonyl azide 251 benzodiazepines 460-1 benzodiazocine 454

(–)-benzomalvin A 460–2

benzo-1,2,3,4-tetrazine 1,3-dioxides 402, 405 alpha-benzoyl-azidoalkanes, photochemistry 317 benzoylaminyl radical 256 benzoyl azide isocyanates 322 photochemistry 323 benzyl azide reactions with enones 215 triplet sensitization 318 benzylamine, diazidosubstituted 401 benzyl-2H-azirine-3-carboxylate, cycloaddition to furan 185 benzylidene acetals 248 beta-carbolines, 1-heteroarylsubstituted 441 beta-turn mimics 233 CuAAC 302 peptidomimetic 234 biotin label (FLAG tag) 484-5 ortho-biphenyl azide, photolysis 348 biphenyl tetrazole, synthesis 39 2-biphenylmethyl azide, di-methyl and di-phenyl derivatives 315 ortho-biphenylyl azide, transient absorption spectra 349-51 Boc-deprotection 289 3-bromo-3-phenyl-3H-diazirine 54 alpha-bromoacetates 252 alpha-bromocarboximide-67 60 bromoimines, from glycosyl azides 263 3-tert-butoxycarbonyl-2H-azirine 170 2-(tert-butoxycarbonyloxyimino)-2phenylacetonitrile (Boc-ON) 474 3-tert-butylazirine 170 4-tert-butylcyclohexanoneanone, Scmidt reaction 202-3, 205 O-tert-butyldimethylsilyl (O-TBDMS) 462 2-tert-butylimino-2-diethylamino-1,3dimethylperhydro-1,3,2-diazaphosphorine (BEMP) 444 cage system, hexaazaisowurtzitane 400-1 calixarene scaffold 306 calorimetric methods Accelerating Rate Calorimetry (ARC) 20-1 mass loss tests 19 stability tests 19-23 Thermal Activity Monitor (TAM) 21-4 cancers anti-cancer agents 303 signal transducers and activators of transcription 3 (STAT3) dimerization 303 Candesartan 37-8

originators and commercial relevance 38

carbamate protecting groups 472-3 carbamoyl radicals, beta-fragmentation reaction 263 carbazole, formation 350 carbene trapping 156 carbenes, Skell-Woodworth hypothesis 323 carbethoxy azide, laser flash photolysis (LFP) 326 carbethoxynitrene 325 carboazidation process 252-3 carbocations, Schmidt reactions 207-11 carbodiimide-activated acids 476 carbodiimides 447 carbohydrate-lectin interactions 481 carbohydrates, azido-containing 54, 469-91 azides as non-participating neighboring groups 474-5 azides as protecting groups 472-4 metabolic oligosaccharide engineering 483-6 synthesis 470-2 carbon dioxide, supercritical 63 carbon nucleophiles, synthesis of alkyl azides 75-6 carbon-nitrogen bonds 239 carbon-centered radicals azidation 246-7 intermolecular addition to unactivated alkenes 252 carbonates, synthesis of alpha-azido alcohols 57 - 8carbonyl azides isocyanates 321-2 photochemistry 321-5 thermal decomposition 322 carboxylic acid derivatives azides, precursors for isocyanates 43, 44 reactions with phosphazenes 445-6 carboxylic acids biosteric replacement into tetrazole group 37 - 8and DPPA, Curtius rearrangement 87 synthesis of acyl azides 86-7 carboxylic halides 476 catenanes 413-36 cells metabolic oligosaccharide engineering 483-8 protein labeling within cells 481 cephalosporins and azidoacetic acid chloride 45 base structure 41 synthesis 40-2 with tetrazole or mercaptotetrazole element in side chains 42

cerium ammonium nitrate (CAN) 241-2 2-aminosugars 243 cheletropic additions, alkenyl azides 143 chimeras 300-1 beta-chloro alcohol-7 54 alpha-chloro methyl ester-5 54 1-chloro-2-alkylsulfanylethyne 156 chromium complexes, with organoazides 382 chromophores, coumarin 482 cinchona alkaloids 86 click chemistry 285-6 acceleration of Click reaction 272-4 copper-free 274-5 first catenane 423 formation of epitope mimics 294 peptides, linking with glycopeptides 294 ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) 275-7 synthesis of dihydrotriazoles 280-2 see also 1,2,3-triazole derivatives clinical trials, peptidomimetics 308 Clopidogrel 45 cobalt-catalyzed hydrohydrazination 254-5 olefins 99-101 cobalt(III) ethylenediamine complexes, cationic, with organoazides 376-7 commercial-scale azides 47-8 future of 47-8 composite propellants, energetic binders 399-400 concanavalin A, lectin binding studies 482 conjugation reactions, by 1,3-dipolar cycloaddition 301 copper complexes with organoazides 376-7, 383-4 copper(I) trifluoromethanesulfonate 383 thermal stability 376 copper-catalyzed azide-alkyne cycloaddition (CuAAC) 270-2, 285-302 addition of base 273-4 advantage of CuAAC over Staudinger ligation 485 beta-turn mimics 302 cellular toxicity 478 cyclodimerization of peptide chains 302 genetically engineered cysteine (Cys) residues 481 glycoconjugate synthesis 478-83 mechanisms 271-2, 288-90 microwave-assisted 305-6 monomeric and dimeric macrocycles 303 radiolabeling of biomolecules 307 sequential one-pot procedure for diazo transfer 483 synthesis of glycoconjugates 478-83

triazole-linked glycosyl amino acids 480 tyrocidine derivatives 480 see also 1,3-dipolar cycloaddition reactions (DCRs) copper(I) template rotaxane synthesis 424-32 proposed catalytic cycle 430 as template and catalyst 428-30 copper(I)-free cycloaddition 274-5 azide and electron-deficient strained double bond 298 cyclooctyne derivatives 486 strain-promoted 486 coumarin chromophores 482 (+)-crassifoline 450, 451 (+)-croomine 451–2 crown ethers 59 formation of pseudorotaxane complexes 417 cryptotackieine 447, 448, 461-2 cubane derivatives 394-5 cucurbiturils (CB) 415-16 (+)-cularine 450 cumulenes 148 azidocumulenes 153 Curtius rearrangement vii 43, 84, 85-7, 321-2 cyano compounds, from vinyl azides 140 cyanobacterial cyclodepsipeptides 454 cyanoguanidine, synthesis of 5-aminotetrazole (5-AT) 41 cyanuric azide 407 cyclic beta-peptoids, derivatization 295 cyclization reactions 239 enzyme-mediated, alkyne-substituted peptide thioethers 293 values of rate constants 150 cycloaddition reactions 269-84 [3+2] and [3+3] 210 with azides for synthesis of tetrazoles 278 - 80with azides for synthesis of thiatriazoles 282 concerted and diradical mechanisms 270 copper-catalyzed azide-alkyne cycloaddition (CuAAC) 270-2 copper-free click chemistry 274-5 enazides 142 Huisgen 1,3-dipolar cycloaddition 147, 269 - 70intermolecular 280 intramolecular, of azido-tethered allylic cations 210 N-sulfonyl indole 210 ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) 275-7 strain-promoted [3 + 2] 479 use of other metals 277

vinyl azides 141 see also Diels-Alder; 1,3-dipolar cycloaddition reactions (DCRs) cyclobis(paraquat-p-phenylene) (CBPQT) 417, 420 cyclobutane amine hydrochloride, one-pot synthesis 108 cyclodepsipeptides, cyanobacterial 454 cyclodextrins (CD) 415-16 cyclohexanones, 4-tertbutylcyclohexanoneanone 202-3 cyclooctynes 274 copper(I)-free strain-promoted cycloaddition 486 6,7-dimethoxyazacyclooct-4-yne 275 cyclopeptide cyclo[ProTyrProVal] 303 cyclopropanone with alkyl azides 199 ring-opening and azide trapping 199 cyclopropanone acetal 187 cysteine (Cys), genetically engineered residues 481 decarboxylative azidation, thiohydroxamates 250 (+)-O-demethylcularine 450-1 dendrimers coumarin chromophores 482 1,3-dipolar cycloaddition reactions (DCRs) 305 - 7(-)-dendrobine 454-5 deoxyhalogenosugars, zinc-induced ringopening reactions 257 deoxynojirimycin 457 deoxyvasicinone 461 Desmaele/d'Angelo approach, erythrina alkaloid ring system 222 Dess-Martin oxidation 451, 453 dialkylaluminium azides 279 diamine, azidoethyl substituted 397 1,2-diaminoalkanes, ring opening of aziridines 68 2,9-dianisyl-1,10-phenanthroline (dap) 424 diazenylimido ligands, metal complexes 384 diazidation of olefins 241 iodosyl benzene (PhIO) 243 manganese(III) salts 243 diazide 73, corresponding rotaxane 432 1,3-diazidoacetone 399 1,3-diazidobenzene derivatives 401 3,4-diazidobenzyl bromide 404 3,4-diazidobenzylamine 403 4-diazidobuta-1,3-dienes 145-7 trans-3,4-diazidocyclobutenes 145 1,2-diazidoethene substructures 129

diazidomethane 392 1-diazidomethylenamino-substituted 5-azidotetrazole 406 1,3-diazido-2-nitro-2-azapropane (DANP) 399 detonation parameters 400 diazido-substituted benzylamine 401 2,6-diazidotoluene 404 3,5-diazido-1,2,4-triazoles 405 1,3-diazido-2,4,6-trinitro-2,4,6-triazaheptane (DATH) 399 1,4-diazine 409 diazo transfer reaction amino sugars 472 glycosamines 474 imidazole-1-sulfonyl azide hydrochloride-184 74 sequential one-pot procedure 483 synthesis of alkyl azides 72-5 synthesis of aryl azides 83 triflyl azide 472 N-diazoenamines 133 see also vinyl azides diazonium compounds 80 diazotization of aminoguanidine 41 alpha, beta-dibromoketones, early synthetic methods, vinyl azides 118 dicarbonyl(cyclopentadienyl)(trans-1,2diphenyl-2-azidoethenyl)iron(II) 380 3,4-dicyanomaleic anhydride 402 cis- and trans-dicyanostilbenes 154 Diels-Alder reaction 298 azidocyclopentadienes 142 azirines as dienophiles 167, 184-5 copper(I)-free cycloaddition 298 cycloaddition, facilitating intramolecular Schmidt reaction 218 3-phenylazirine and 3-tert-butylazirine 170 retro Diels-Alder reaction 298, 479 Schmidt reactions, domino 219-20 dienones, intermolecular azide trapping 211 diethyl azodicarboxylate (DEAD) 70 diethylaluminium azide hydroazidation reactions 97 opening of trisubstituted epoxides 182 diethyl-2-oxopropylphosphonate 454 differential scanning calorimetry (DSC) 13-14 difluorinated cyclooctyne (DIFO) derivatives 485 dihydropyrazine 134 dihydrotriazoles 280-2 diisobutylaluminium hydride (DIBALH) 440 diisopropyl azodicarboxylate (DIAD) 70 dimethyl acetylenedicarboxylate 142 4-(dimethylamino)pyridine (DMAP) 472 2,2-dimethylcyclopropanone acetals 199

dinoflagellate blooms, Peridinium polonicum 456 dioxynaphthalene (DNP) derivative 420-1 dipentaerythrityl hexaazide 397 diphenyl diselenide, azidoselenation of olefins 244 4,5-bis(diphenylphosphinoyl)-4,2,6dimethylpyrimidine 145 diphenylphosphoryl azide (DPPA) 132 addition to enamines to yield β-arylcarboxylic acids 41 physical and chemical properties 34 polymer-supported 70 production 32-4 replacement 70 1,3-dipolar cycloaddition reactions (DCRs) 147, 269-70, 285-304, 414-15 backbone modifications of peptides 288-92 catalyzed by copper(I) salts 419, 420 catalyzed vs uncatalyzed versions 414 conjugation reactions of biomolecule 301 dendrimers and polymers 305-7 glycoconjugate synthesis 478-83 glycoconjugated amino acids 286-8 isotopic labeling 307-8 macrocyclization 302-5 other modifications of peptides 292-302 retro Diels-Alder reaction 298 scaffolded triazolyl-peptides 297, 306 see also copper-catalyzed azide-alkyne cycloaddition (CuAAC); cycloaddition reactions disposal of azides, and effluent streams 30 DNA oligonucleotides, conversion to 5'-azido derivatives 54 dodecaazide, synthesis 398 domino process 218 dopamine analogs, Schmidt reaction route 232 dorimidazole A 449 Eguchi protocol 461, 463 electrochemical reduction, organic azides to amines 256 electron detachment spectroscopy 331 electrostatic discharge (ESD) 6, 11-12 enamides 85 enamines 85, 207 addition of DPPA to yield β-aryl-carboxylic acids 41 enaminones 214 formation 216 enazides 133 cycloaddition reactions 142 energetic binders, for composite propellants 399-400

enones 454 Lewis-acid activation 215 reactions with benzvl azide 215 enzyme-mediated cyclization, alkynesubstituted peptide thioethers 293 Ephedradine A 460 epoxides azido-tethered, bicyclic tertiary amines 216 Lewis acid-assisted formation 216 Markovnikow regioselectivity 67 opening by azides 218 reactions with alkyl azides 216-18 ring opening 64-8, 181-3 Fuerst-Plattner rule 474 regioselective opening 183 trialkylsilyl-substituted epoxides 131 trisubstituted epoxides 182 EPR spectroscopy 329, 355 erythrina alkaloid ring system, Desmaele/d'Angelo approach 222 ESD testing 11-12 ESR spectroscopy 316-17, 325 esters MMDOC esters 250 MPDOC esters 250 estradiol, 17alpha-ethynyl-estradiol 299 estradiol-functionalized peptoids, as potential biosensors 300 ethanesulfonyl azide, azidation of iodine compounds 250 ethenylidenecyclopentadiene 121 1-ethoxyisoquinoline 459 ethyl azide, preparation 54 ethyl ketimine 457 2-ethylcyclopentanone 223 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) 234 ethyldiphenylphosphine 453 N-ethyl-2-propynamide 296 ethynyl azides 154-7 silyl-substituted 156 17alpha-ethynyl-estradiol 299 ethynylnaphthalimide, CuAAC 485 4-ethynyl-1,2,3-triazole, synthesis via azidobutatriene 153 eudistomins 441-2 Evolved Gas Analysis (EGA) 17-19 explosive potential detonation parameters 400 and N<sub>3</sub> fraction viii see also safety fall hammer equipment 7-9 fasclaplysin 442

femtosecond transient absorption spectroscopy 319, 334-5, 348, 350, 352, 357 ferrocenyl azide see iron(II) complexes with organoazides FI-18 labeling of peptides and biomolecules 307 - 8FLAG tag 484-5 fluorescence labeling 484-5 fluorescence resonance energy transfer (FRET) 289 fluorosubstituted n-propyl azide, phototransformation 316 formylnitrenes 323 fragmentation reaction, alpha-azidoalkyl radicals 262-3 friction sensitivity testing 9-11 (-)-fumiquinazoline G 464 furanyl derivatives 443 2-furoic acids 84 galactal, azidonitration 472 gamma-turn mimics 233 GAP triol, TAM measurement 22, 23 gephyrotoxin 228-9 German Federal Institute for Materials Research and Testing (BAM) 8, 10 glyantrypine 464 glycals, azidonitration 474 glycans membrane-associated, in vivo imaging 485-6 metabolic oligosaccharide engineering 483-6 tagging by chemoselective ligation reaction 483 glycidyl azide polymer (GAP) 399 glycine-oligomers, N-substituted 299 glycobiology 469-91 glycoconjugates fucosylated 485 N-terminal, N-end rule 481 synthesis 478-83 glycopeptidomimetics 286 N-glycoproteins 475-6 metabolic oligosaccharide engineering 483-6 non-natural carbohydrate-peptide linkage 479 glycosamines, diazo transfer reaction 474 glycosaminoglycans 474-5 glycosyl amides 475-8 glycosyl azides 475-8, 481 asymmetrical, bifunctional dendrimer 481-2 from bromoimines 263 one-pot procedures 481-2

reduction 476 Staudinger reaction 477 synthesis 62 glycosyl donors 471-2 glycosyl threonine building block 475-6 glycosylations 474-6 oligosaccharide donors 475 gold complexes, (3'-azido-3'-deoxythymidinyl) trimethylphosphinegold(I) 382 gold-mediated Schmidt reactions 213-14 grandirubine 441 gravimetric and calorimetric methods, stability tests 19-23 Grignard reagents 80 Grubbs catalyst 87 halides, synthesis of alkyl azides 55 halogen azides, reaction with alkenes 244-5 halohydrin dehalogenase 66 N-halosuccinimides 129 halovinyl azides 139 hamacanthin A and B 459 hand protection 6 Hassner reaction, vinyl azides 119-20 heat-flux DSC 13-14 Hemetsberger-Knittel reaction 124, 137 heptazines 407-9 Heraldiophylum sp. 444 hexaazaisowurtzitane, cage system 400-1 hexadecyltributylphosphonium azide 147, 148 in azide synthesis 62 4,5,6,7,8,9-hexahydrocycloocta-1,2,3-triazole 156 hexakis-4-azidobenzyl-hexaazaisowurtzitane 402 hexakis(azidomethyl)benzene 392 hexatriacontaazide, synthesis 398 high energy materials 391-412 histidine residues, acceleration of CuAAC 291 - 2HIV-1 envelope glycoprotein 297 HIV-neutralizing antibody 2G12 293 Hofmann elimination 397 homoerythrina alkaloids 443 homopropargylglycine (Hpg) 480 Horner-Emmons Wittig reaction 454 Huisgen 1,3-dipolar cycloaddition 147, 269-70, 285-304 see also 1,3-dipolar cycloaddition human melanocortin receptor 4 (hMC4R), alkynylated ligands 297 hyacinthacine, synthesis 253 hydrazines aryl azides 84

azidoethyl substituted 397

hydrazinium 5-azidotetrazolate 405 hydrazoic acid detonation speed 29 deutero-substitute analogue (ND) 313 and metal salts 4-5 photochemistry 312-14 products of gas phase reaction 312-13 hydride transfer reduction 386 hydroazidation reactions 95-112 azide products, one-pot protocol 106 Co-catalyzed 99-100 comparison of TsN<sub>3</sub>, azide-49 and azide-50 105 electron-deficient double bonds 96-8 influence of silane and azide 102 Lewis Acid promoted 98 mechanistic investigations 108-9 non-activated olefins 98 in situ functionalization 99 unsaturated carbonyl compounds 96 hydrogen atoms, activated, substitution by azido groups 247-8 hydroxamates 301 hydroxyalkyl azides 200-7 reactions with ketones 201 rearrangements toward biologically relevant compounds 233-5 regiochemistry of ring expansion 203 Schmidt reactions asymmetric 204 with ketones 202 bis(8-hydroxyquinolinato) copper(II)?(picrylazide) 377 imeluteine 441-2 imerubine 441 imidazole-1-sulfonyl azide hydrochloride-184 74 - 5imidazoles 405-9 imidazolinone ring 444 imidogen 312 triplet nitrene trap 313 imidoyl chloride 444 imines 440, 443 five-membered cyclic 454 six-membered cyclic 459 strained bridgehead 316 iminium ethers 200 hydrolysis, effect of pH 202 nucleophilic additions 203 iminium/acycliminium ions 249 iminoperoxide 312 iminophosphoranes acylaminophosphonium salt 476 anomerization 476

iminyl radicals, hydrogen atom transfer from azides in presence of tin hydride 262 impact sensitivity of energetic compounds 7\_9 (-)-indolizidine, synthesis 222 indolizidine-containing compounds 232-3 indoloquinolines 447 indol-3-ylglyoxylyl chloride 444 influenza treatments 45 integrin-directed multivalent peptides 306 iodine compounds ethanesulfonyl azide 250 IN<sub>3</sub> replaced by PhI(N<sub>3</sub>)<sub>2</sub> 248 source of azidyl radicals 243 iodine derivatives, azidation 247-9 2-iodoethyl azide 454 iodosyl benzene (PhIO) diazidation of olefins 243 PhIO/TMSN<sub>3</sub> 244 ionic liquids (IL), solvents for nucleophilic substitution reactions 61, 63 IR spectroscopy 313, 316 time-resolved (TRIR) 320, 323-4, 327, 330, 335, 346, 351, 358, 360, 364 iron(II) chloride, radical reactions with organic azides 261-2 iron(II) complexes with organoazides 379-82 azide functionalized chiral ferrocenophane 379 ferrocenyl azide and 1,1'-ferrocenylene azide 378 formation of azidyl radical 241 thermal decomposition of ferrocenyl azide 378 isocarbazole, catalysis of isomerization by water 349 isocyanates 39-40 carbonyl azides 321-2 from benzoyl azide 322 reactions with phosphazenes 446-50 isonaamine A 449 isothiocyanates 40 isotopic labeling, DCRs 307-8 isoxazole 118 Jurkat cells 485 keteneimines, as precursor to nitriles 320 ketenes, reactions with phosphazenes 450 ketones amino-diazomethylketones 199

with Bronsted or Lewis acids 193 cyclic azidoketones 194 reactions with hydroxyalkyl azides 201 reactions with phosphazenes 450

alpha, beta-unsaturated ketones, reactions with alkyl azides 214–16 unsymmetrical, N-insertion reactions 201-2 Koenen test 23-5 lactams 193-5 first generation Diels-Alder Schmidt approach 227 fused and bridged 230-1 hydroxyalkyl azides, reactions with ketones 201 libraries, 3-component parallel synthesis 234 macrocyclic, ring expansion process 259 N-substituted 195 lanopylin 454-5 lansiumamides 85 large-scale production, safety measures 29-52 laser flash photolysis (LFP) 317, 320-1, 323, 325-6, 328-9, 331, 333, 335, 343, 346, 348-50, 353, 357-63 laser magnetic-resonance spectroscopy 313 lasubine II 222 lavendamycin 441-2 lectins binding studies, concanavalin A 482 carbohydrate-binding proteins 481 Leishmania mexicana 289 lepadiformine, synthesis 253 leucettamine B 448-9 Linezolid 45 lithium reagents, synthesis of aryl azides 80, 83 Loracarbef 45, 47 luminescence spectroscopy 313 lycorane Amaryllidaceae alkaloids 249 macrocyclization by DCR 302-4 propargylic acid residues 305 malonic esters 87-8 manganese(III) salts, diazidation of olefins 243 Mannich pathway, vs Schmidt reactions 198 mass loss tests 19, 22 matrix metalloproteases 301 matrix spectroscopy 320, 347 mercaptotetrazoles 40-1 mercury trifluoromethanesulfonate, Schmidt reactions 212 Merrifield resin 61 mesitylmagnesium bromide 80 metabolic oligosaccharide engineering 483-8 metal complexes co-crystallized with organoazide 376 diazenylimido ligands 384

with intact, coordinating and bent organoazide ligands 384-5 with intact, coordinating and linear organoazide ligands 383-4 ligands with non-coordinating organoazide unit 377-82 other metal-coordinated ligands 385-7 metal-generated azidyl radicals 241-2 metal-mediated azide reduction 257 metal-mediated Schmidt reactions 211-14 methanethiosulfonates 481 5,11-methanomorphanthridine alkaloids 440 methionine surrogates 480-1 alpha-methoxy acrylonitriles 242 bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) 87 methyl azide bond lengths and bond angles 374 explosive risk 392 Mullikan charges 374-6 (R)-2-methylcysteine derivative, synthesis 88 methyleneazirines 153 methylene-2H-azirines 154 from azidoallenes 170 O-methylhalfordinol 443, 445 methylnitrenes 321 trans-alpha-methylstyrene, nitroazidation 242 microwave-assisted synthesis of alkyl azides 61, 63 Mitsunobu reaction, synthesis of alkyl azides 70 - 1MMDOC esters 250 molecular orbital theory 285 molybdenum complexes 386 monosaccharides, azide derivatization 484 Mosapride 45 MPDOC esters 250 Mullikan charges, methyl azide 374-6 mycosporins 444 Mytilus edulis, azaspiracids 457 N-H pyrroles 144 nanosecond laser flash photolysis 323 nanosecond transient absorption spectroscopy 364 2-naphthoyl azide 322 2-naphthoyl nitrenes 323 1-naphthyl azide, photochemistry 359 2-naphthyl nitrene, relative energies of valence isomers 357-8 naproxen, synthesis 41-3 neocryptolepine 447 neostenine 228-9 nickel(II) ethylenediamine complexes,

cationic, with organoazides 376-7

nickeloaddition reactions 277 nigrifactine 456, 457 nitramarine 441 nitrenes 312-14 alkylnitrenes 317 aroylnitrenes 322 benzyl nitrenes 318 C-H insertion product 318 formyl- and acetylnitrenes 323 imidogen 312 methylnitrene 321 molecular orbitals 313 2-naphthoylnitrenes 323 and other reactive intermediates 311-63 triplet nitrene trap 313 vinylnitrenes 320-1 nitriles, thermal reactions of vinyl azides 139 nitrimino structure 400 nitro explosives, detonation parameters 400 1-nitro-pyranoses 472 nitrogen-ring systems, seven-membered 460-1 nitroglycerine impact sensitivity values 9 Koenen test results 24 nitroguanyl azide 400 ortho-nitrophenyl azide, photolysis 354 nitrosoarenes, aryl azides 84 non-steroidal anti-inflammatory drugs 41-2 nosyl azide 101 N<sub>3</sub> fraction, and explosion danger viii nucleophiles NuH 151 nucleophilic aromatic substitution 76-80 Nuphar piperidine alkaloids 456-7

#### olefins

Co-catalyzed hydroazidation 254-5 di- and trisubstituted olefins 102, 104 diazidation 241-4 direct introduction of azide groups 96 electron-deficient, formal aminohydroxylation 217 hydroazidation reactions 95-112 mechanistic investigations 108-10 one-pot functionalization 106-8 scope 101-3 Markovnikov selectivity 102 monosubstituted 103 nitroazidation 242 oligomannosyl azides 293 ophiocordin 451 opioids, indolizidine-containing compounds 232 organoazides 373-88, 391-412 cationic metal complexes containing anions 376-7

co-crystallized with metal complexes 376 metal complexes with ligands 377-82 quantum chemistry 373-5 reacting with other metal-bound ligands 385 - 7and transition metals 373-88 organometallic reagents, synthesis of aryl azides 80-1 Oseltamivir 45, 46 oxanorbornadiene 298 oxazoles, 2,5-disubstituted 443 oxazoline ring opening 61 oxeniumoid 450 oximidines 85 oxiranes, ring opening reaction 43-4 oxyallyl cations, intramolecular reactions of azides with 211 Paclitaxel (Taxol), extraction 44 palladium catalyst for decomposition of organoazides 383 cycloaddition reactions 277 pentaerythritol tetranitrate (PETN) ESD test results 12 Koenen test results 24 pentaerythrityl tetraazide 392, 397 pentafluorophenyl 460 peptide nucleic acids (PNA) 299 peptides and antigens, copper(I)-catalyzed conjugation 292 cyclization, VEGFR1 mimics 304 cyclopeptide cyclo[ProTyrProVal] 303 1,3-dipolar cycloaddition reactions 269-70, 285 - 310backbone modifications 288-92 other modifications 292-302 FI-18 labeling 307-8 integrin-directed multivalent 306 linking with glycopeptide, CuAAC click reaction 294 macrocyclization by DCR 302-4 pseudodipeptides 298 scaffolded triazolyl-peptides 297, 306 triazole-derivatized gluten peptides 296 peptidomimetics 234 clinical trials 308 glycopeptidomimetics 286 peptidotriazoles solid-phase synthesis 289-90 synthesis by CuAAC 288-9 peptoid oligomers 299 perhydroazepine 453 Peridinium polonicum 456

phase-transfer catalysts 59 phenyl azide photochemistry 327-36 reduction to aniline 258 and simple derivatives, photochemistry 336-54 3-phenyl azirine 170 phenyl tetrazolinones 39-40 4-phenylbut-1-ene hydroazidation, influence of silane and azide 102, 104 hydrohydrazination and hydroazidation 106 2-phenyl-3-carbethoxyoxiran 44 phenylsulfonyl group, acceptor substituent for allenyl azides 153 PhIO/TMSN<sub>3</sub> 243-4 phloeodictine 464 phosphatidylethanol azide, reactions with 1–3-propargylglycinyl residues 297 phosphazenes 439-67 containing an aldehyde group 451-4 containing an amide group 461-4 containing an ester 459-61 containing a ketone group 454-9 reactions with aldehydes 440-2 reactions with carboxylic acid derivatives 445 - 6reactions with isocyanates 446-50 reactions with ketenes 450 reactions with ketones 441-5 photochemistry 311-73 acyl azides 256 alkyl azides 315-19 azide esters 325-7 carbonyl azides 321-5 hydrazoic acid 312-14 phenyl azide 327-36 and simple derivatives 336-54 polynuclear aromatic azides 355-63 vinyl azides 319-21 photoelectron spectroscopy (PES) 314, 319 phototransformation, fluorosubstituted n-propyl azide 316 (S)-N-phthaloylphenylalanyl chloride 446 picosecond transient absorption spectroscopy 352, 364 pimprinine analogues 443-4, 445 piperazine amides beta-turn mimics 291 triazole-substituted 290 piperidine alkaloids 456-7 platinum, cycloaddition reactions 277 polonicumtoxins 456 polyazido benzenes 400-1

polyazido-triazines, azido-tetrazole ring-chain isomerism 407 polyazines, azido-substituted 407 polymers, 1,3-dipolar cycloaddition reactions (DCRs) 305-7 poly(methacrylate)-based glycopolymer 482 poly(methylhydrosiloxane) (PMHS) 101 polynuclear aromatic azides, photochemistry 355-63 polyproline II (PPII) 296 potential energy surface (PES) 319 precursor azides, production 30-7 propargyl azides preparation 60, 147 [3,3]-sigmatropic rearrangement 149 unimolecular reactions 150 propargyl glycosides 481 propargyl mannosides 481 N-propargyl-beta-alanine oligomers 294-5 propargylamine Boc-protected substituted 289 click reactions with 291 propargylglycine, homopropargylglycine (Hpg) 480 1-3-propargylglycinyl residues 297 macrocyclic peptides 293 propargylic acid residues, macrocyclization of peptides 305 propellants energetic binders 399-400 LOVA 400 propynoyl-dipeptide 304 coupled to azido-aminoglucopyranoside, cyclodimerization 304 N-propynoyl-L-phenylalanine methylester 296 proteases, activity fingerprint 302 proteins carbohydrate-binding proteins 481 genetically engineered, auxotrophy-based residue-specific method 481 labeling within cells 481 pseudodipeptides 298 pteridines 77 pyrazino[2,1-b]quinazoline ring system 464 3-pyridylsulfonyl azide 253 pyrimidines 407-9 azido-substituted 408 pyrrolidino-butyrolactone CûD ring system 453 pyrrolidone 461 3-pyrrolines, 4-aryl-3-butenyl azides with **TfOH 209** 

1-pyrrolines, Schmidt reaction 209

quinazoline alkaloids 462 quinazoline-2,4-diones, solid-phase synthesis 88 [2,1-b]quinazolinones 461 quinolizidine-containing alkaloids 225 quinone derivative, hydroazidation reactions 96 - 7quinuclidinium tetrafluoroborate 232 radical reactions 239-68 azidation with iodine derivatives 247-8 organic azides with iron(II) chloride 261 - 2radical reduction of organic azides aminyl radicals 257 electrochemical reduction 256 with metals 257-8 with samarium diiodide 258-9 with silanes 260 single electron transfer (SET) 255-62 radical traps 246 receptors, artificial receptor prototypes 304 reporter groups 483-4 retro Diels-Alder reaction 298, 479 rhopaladins 444, 445 riazolopiperazines 280 ring opening azide-mediated, steric interactions vs cation interactions 206 aziridines 43-4, 68-9 epoxides 64-8, 181-3 macrocyclic lactams 259 oxazoline 61 oxiranes 43-4 sugar epoxides, Fuerst-Plattner rule 474 zinc-induced, deoxyhalogenosugars 257 rotaxanes 413-36 bistable 423 crown ethers, formation of pseudorotaxane complexes 417 Cu(I) as template and catalyst 428-32 proposed catalytic cycle 430 double-stoppering vs stepwise approach 414 (hyper)branched rotaxanes and polyrotaxanes 416 main-chain polyrotaxane 416 protecting group approach 419 pseudorotaxane blocks 417 synthesis by thermal 1,3-dipolar cycloaddition reactions (DCRs) 418 threading-followed-by-stoppering 417-19 transition metal templated approaches 424-32 rufescine 441-2

rutercarpine 463-4 ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) cycloaddition reactions 275-7 mechanism 276 triazolyl dipeptide 290 safety measures 5-7 disposal of azides, and effluent streams 30 gripping devices 6-7 large-scale production 29-52 small-scale production 3-28 safety screens 5 samarium diiodide, reduction of organic azides 258 - 9(+)-sarcocapnine 450-1 sartans (tetrazoles) 37-9 originators and commercial relevance 38 scaffolded triazolyl-peptides 297, 306 scaffolds alkyne-bearing 481 azide-containing 481 calixarene 306 Schmidt reactions alkyl azides 191-238 asymmetric 204 diastereoselectivities 205 with carbocations 207-11 with carbonyl compounds 193-207 acyclic ketones and aldehydes 196 2-alkylated cyclohexanone 195 intermolecular 197-200 intramolecular 192-7 classical, vs with alkyl azides 192 Competition between Schmidt and Mannich pathways 198 cyclic azidoketones 194 domino 219-20 history 191-2 hydroxyalkyl azides with ketones 202 metal-mediated 211-14 rearrangement cascade reactions 218-22 removal of chiral tether 205 see also alkyl azides Schmidt rearrangements, semipinacol 221, 229-30 sclerotigenin 463 selaginoidine 441, 443 self-heating rate (SHR) 211 semipinacol Schmidt rearrangements 221, 229 - 30siamine 459-60 signal transducers and activators of transcription 3 (STAT3) dimerization, cancer treatment 303

silicon analogs, tetrakis(azidomethyl) silane 392 silvl enol ethers azidation of beta-carbon 249 alpha-azido ketones 242 diazidation 243 single electron transfer (SET) 255-62 samarium diiodide, reduction of organic azides 258-9 Skell-Woodworth hypothesis, carbenes 323 small ring nitrogen heterocycles 167–90 small-scale production, safety measures 3-28, 29 - 52sodium 4-azidosulfonylbenzoate 106 sodium azide addition to isocyanate 39-40 addition to isothiocyanate 40 addition to nitriles to produce sartans (tetrazoles) 37-9 physical and chemical properties 32 production 30-1 zeolite-bound 67 solid phase peptide synthesis (SPPS) 475, 478 solvents, polar (DMF or DMSO) 58, 73 (-)-sparteine 224-5 spectroscopy electron detachment spectroscopy 331 EPR spectroscopy 329, 355 ESR spectroscopy 316-17, 325 femtosecond transient absorption spectroscopy 319, 334-5, 348, 350, 352, 357 IR spectroscopy 313, 316 laser magnetic-resonance spectroscopy 313 luminescence spectroscopy 313 matrix spectroscopy 320, 347 nanosecond transient absorption spectroscopy 364 photoelectron spectroscopy (PES) 314, 319 picosecond transient absorption spectroscopy 352, 364 time-resolved IR spectroscopy 320, 323-4, 327, 330, 335, 346, 351, 358, 360, 364 stability tests, gravimetric and calorimetric methods 19-23 stannyl azides 250 STAT3 dimerization, linear and macrocyclic inhibitors 304 Staudinger reaction 453, 476 glycosyl azides 477 three-component 477 two-component traceless ligations 478 vinyl azides 145 Staudinger-aza-Wittig process 455, 459, 462

Steel Sleeve test 23-5 Stemona alkaloid stenine 225-8 stemonamine 230 (-)-stemonine 453 (-)-stemospironine 451-2 beta-styryl azide 133 Suarez reagent 264 sugar epoxides, ring opening, Fuerst-Plattner rule 474 sugars 2-azido sugars, synthesis 472 ring-opening reactions, deoxyhalogenosugars 257 see also amino sugars; 2-azido sugars sulfates, synthesis of alkyl azides 55-7 sulfites, synthesis of alkyl azides 57 sulfonates displacement by azide ion 54 synthesis of alkyl azides 56 sulfonide azide, deprotonated, hydroazidation reaction 107 sulfonium salt, synthesis of alkyl azides 58 sulfonyl azides azidation 249-54 electron-poor, synthesis of alkyl azides 75 N-sulfonyl indole, cycloaddition reaction 210 sulfonyl tetrazoles, synthesis 278-9 sulfonylallenes, treatment with TMGA 121 sulfoximines 155 sulfoxonium ylides 156 supercritical carbon dioxide 63 symtriazidotrinitrobenzene 402 synthetic routes 3-28 safety instructions and measures 5-7 Tamiflu 45, 46 catalytic enantioselective ring opening of a meso-aziridine with TMSN<sub>3</sub> 69 tantalum(III) complexes with organoazides 384-5 tantalum(V) imido complexes 384-5 template-assembled synthetic proteins (TASPs) 293 tetra-n-butylammonium tetrafluoroborate 54 tetraazidomethane 392-3 3,4,5,6-tetraazidophthalic anhydride 402 thermolysis 405 tetraazidoquinone tetrathiafulvalene complex 400 - 1tetrabutylammonium azide (TBAA) 35-6 physical and chemical properties 36 tetrabutylammonium fluoride (TBAF) 444 reaction with trimethylsilyl azide (TMSA) 61

tetracyanoethene (TCNE) 140

tetrahydropyridine ring 455 tetramethyldisiloxane (TMDSO) 101 tetramethylguanidinium azide (TMGA) 60, 116 sulfonylallenes 121 tetrathiafulvalene (TTF) 400-1, 421 tetrazines 407-9 tetrazoles 37-9, 405-9 azide-enriched 406 1,5-disubstituted 483 synthesis 278-9 tetrazolinones 39-40 tetrazolopiperazines 280 tetrazolyl azide 405 Thermal Activity Monitor (TAM) 21-4 thermal properties of organic azides 7 thermally induced decomposition behavior 13 - 14Thermogravimetric Analysis (TGA) 16-19 thiatriazoles 282 thiazoline 455 thioacetamido nucleic acid (TANA) 299 thiocarbonates, synthesis of alpha-azido alcohols 57-8 thiohydroxamates 250 decarboxylative azidation 250 esters (MPDOC esters) 250 threonine, synthesis 475 time-resolved IR spectroscopy (TRIR) 320, 323-4, 327, 330, 335, 346, 351, 358, 360, 364 p-toluenesulfonyl azide 37 tosyl azide 75, 80, 101 tosyl isocyanate 449 transition metals and organoazides 373-88 sites with Lewis acidic properties 374 template synthesis of rotaxanes 424-32 1,3-triazenyl radicals 246, 250 intermediates 258 2,5,8-triazido-s-heptazine (TAH) 76, 407, 408 DSC measurement 15 triazidocarbenium cation 392 triazidopentaerythrite acetate (TAP-Ac) DSC measurement 16-18 infrared spectroscopic EGA 19 2,4,6-triazidopyrimidine (TAP) 408 triazido-triazine (TAT) 407 triazines 407-9 triaziridines 185-6 1,2,3-triazole derivatives 294 bis-triazole formation affording peptidic molecular receptors 305 1,4-disubstituted-1,2,3-triazoles 62, 270, 419

1,4- and 1,5-disubstituted-1,2,3-triazoles 277 4,5,6,7,8,9-hexahydrocycloocta-1,2,3triazole 156 one-pot synthesis 151 ring closure of vinyl azides 150 synthesis via short-lived allenyl azides 152 triazole-substituted piperazine amides 290 triazoles 405-9 chimeras 300-1 from aromatic amines, one-pot protocol 80, 82 libraries generated by click chemistry 301 - 2triazolocyclophanes 153 tristriazolylamine (TTA) 273 triazolyldipeptides 287 Ru(II)-catalyzed alkyne-azide cycloaddition 290tris(triazolylmethyl)amine ligand (TBTA) 271 TBTA complexes 273 triazolyl-peptides 297 F-labelled 308 ligands, covalent linkage 298 tributylphosphine 446 tributylsilyl (TBS) group 440 tributylstannylaminyl radicals, cyclization 260 tributyltin azide (TBSnA) physical and chemical properties 34 production 34-5 tributyltin hydride, radical reactions with organic azides 259-60 trichloroacetimidates 474 trienyl azide, reactions 226 triethylamine (TEA) 451 triethylsilane, thiols catalyze reduction of azides 260 trifluoromethanesulfonic acid (TfOH) 207 triflyl azide 72-3 diazo transfer reaction 472 trimethylsilyl azide (TMSA) 288 addition to isocyanate 39-40 hydroazidation reactions 97 physical and chemical properties 33 production 31-2 reaction with tetrabutylammonium fluoride 61 synthesis of alkyl azides 59 synthesis of vinyl azides 116 O-(trimethylsilyl)phenyltriflate, RuAAC 275 trinitroazidomethane 392-3 trinitrotoluene (TNT) ESD test results 12 impact sensitivity values 9 Koenen test results 24

tripentaerythrityl octaazide 397 tripeptides, alkyne-substituted 290 triphenylmethyl azide (trityl azide) DSC measurement 14-15 reactions with triptycyl azide 385 triphenylphosphane 70 triphenylphosphine 454 triplet sensitization 1-azidoadamantane 318 benzyl azide 318 tris(azidoethyl)amine 397 tris(azidomethyl)amine 396 tris(azidomethyl)ethanol 396 tris(azidomethyl)methanol 394 tris(azidomethyl)methylammonium salts 395 trispyrazolylborato ligands 384 trityl azide see triphenylmethyl azide tropoloisoquinolines 441 tryptanthrin 462-3 tungsten complexes calixarene system 385 organoazides 381 tunicates Rhopalaea sp., rhopaladins 444 tyrocidine synthetase 293 tyrosinase inhibitors 303-4 alpha, beta-unsaturated carbonyl compounds, and halogen azides 244 alpha, beta-unsaturated ketones 214-16 urotropine, synthesis of DANP and DATH 399 vanadium(III) complexes 385 vancomycin antibacterial activity, triazolefunctionalization 295 azido-substituted 295 variolin B 447 vasicinones 461-3 VEGFR1 mimics, peptide cyclization 304 vicinal azidohaloalkanes 115, 119 vicinal halovinyl azides 129, 131 reactions with 2H-azirines 139

vinyl azides 115–47 aziridines via 2*H*-azirines 183–4 early synthetic methods 115–19 nucleophilic addition of hydrazoic acid 117 nucleophilic substitution 117 one-pot procedures 118 early synthetic methods for alpha,betadibromoketones 118

1965-70 119-26 azidostyrenes via ionic or radical addition of bromine 121, 124 by dehydration of beta-azidoalcohols 124 condensation of azidomethyl ketones with aldehydes or ethyl pyruvate 125 from electron-deficient allenes 123 Hassner reaction 119-20 Hemetsberger-Knittel reaction 124, 137 nucleophilic addition of hydrazoic acid to acceptor-substituted allenes 122 halo substituted 171 new methods 126-33 addition of bromine 143 base-induced prototropic rearrangement 128 cycloaddition reactions 141, 142 DABCO-catalyzed isomerization of allyl azides 128-9 formation of cyano compounds 140 miscellaneous synthetic methods 132 [3,3]-sigmatropic rearrangement of allylic azides 126-7 treatment with electrophiles 143 treatment with nucleophiles 143 nitriles or other heterocycles 170 photochemistry 319-21 photolysis of alpha-substituted vinyl azides 320 preparation of 2H-azirines 167-9 pyrolysis of alpha-aryl substituted vinyl azides 320 reactions 133-47 ring closure 149-50 1,2,3-triazole derivatives 150 Staudinger reaction 145 synthesis of N-H pyrroles 144 vinylnitrenes 320-1 Wittig reagents 242 xanthate esters 252 xanthates 250

xestomanzamine 441–2 ylides, cyclic 356

yttrium complex of ligand-141 69

zeolite-bound sodium azide 67 zinc-induced ring-opening reactions, deoxyhalogenosugars 257