Azides

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Organic Azides: An Exploding Diversity of a Unique Class of Compounds

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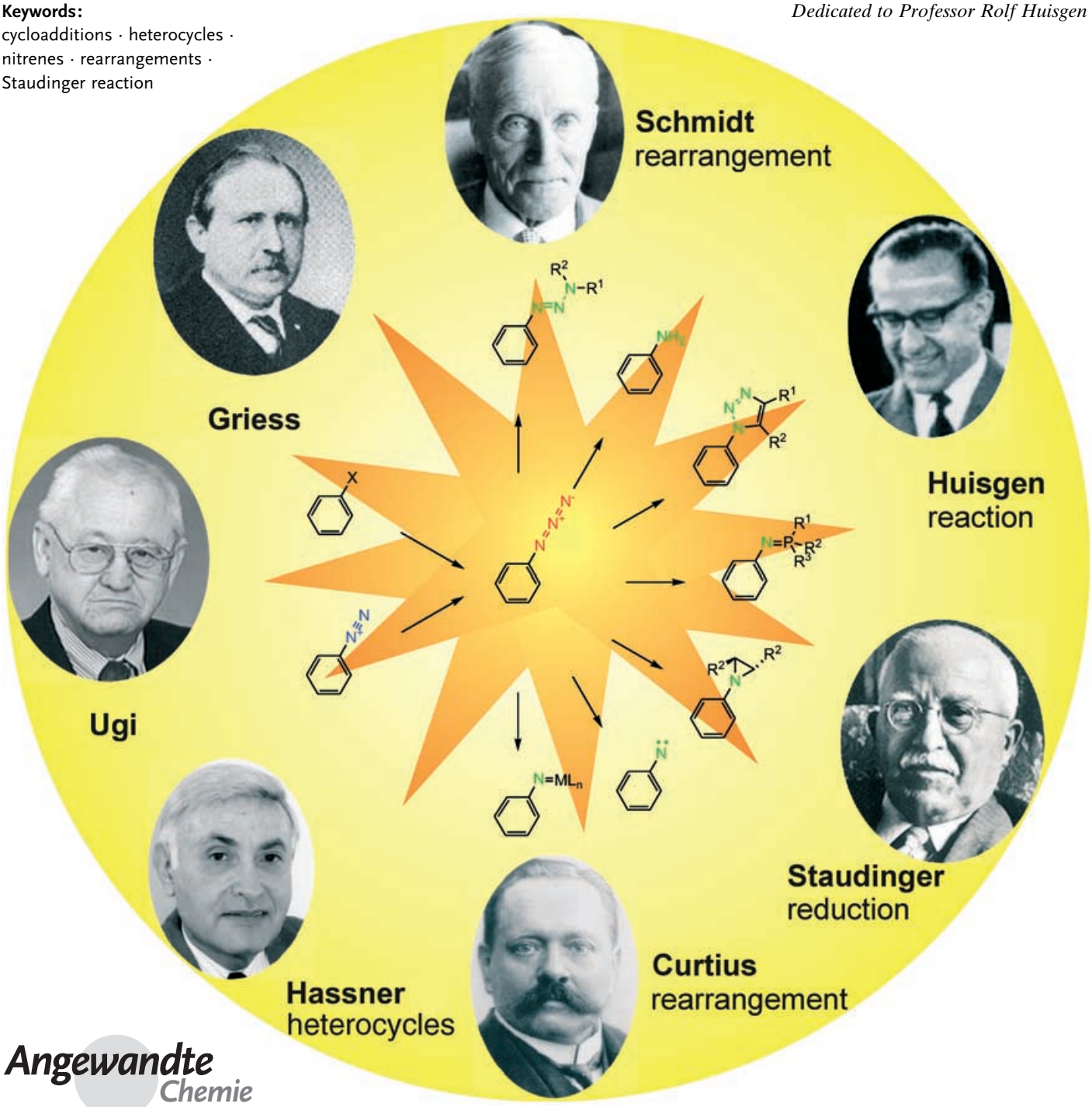
Keywords:
cycloadditions · heterocycles · nitrenes · rearrangements · Staudinger reaction

Dedicated to Professor Rolf Huisgen



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Since the discovery of organic azides by Peter Grieß more than 140 years ago, numerous syntheses of these energy-rich molecules have been developed. In more recent times in particular, completely new perspectives have been developed for their use in peptide chemistry, combinatorial chemistry, and heterocyclic synthesis. Organic azides have assumed an important position at the interface between chemistry, biology, medicine, and materials science. In this Review, the fundamental characteristics of azide chemistry and current developments are presented. The focus will be placed on cycloadditions (Huisgen reaction), aza ylide chemistry, and the synthesis of heterocycles. Further reactions such as the aza-Wittig reaction, the Sundberg rearrangement, the Staudinger ligation, the Boyer and Boyer–Aubé rearrangements, the Curtius rearrangement, the Schmidt rearrangement, and the Hemetsberger rearrangement bear witness to the versatility of modern azide chemistry.

From the Contents

1. Introduction

Since the preparation of the first organic azide, phenyl azide, by Peter Grieß in 1864 these energy-rich and flexible intermediates have enjoyed considerable interest.[1,2] A few years later Curtius developed hydrogen azide and discovered the rearrangement of acyl azides to the corresponding isocyanates (Curtius rearrangement).[3] The organic azides received considerable attention in the 1950s and 1960s[4,5] with new applications in the chemistry of the acyl, aryl, and alkyl azides. Industrial interest in organic azide compounds began with the use of azides for the synthesis of heterocycles such as triazoles and tetrazoles as well as with their use as blowing agents and as functional groups in pharmaceuticals. Thus, for example, azidonucleosides attract international interest in the treatment of AIDS.[6]

Like hydrogen azide most other azides are also explosive substances that decompose with the release of nitrogen through the slightest input of external energy, for example pressure, impact, or heat. The heavy-metal azides are used, for example, in explosives technology, in which they serve as detonators. Sodium azide is applied in airbags. The organic azides, particularly methyl azide, often decompose explosively.

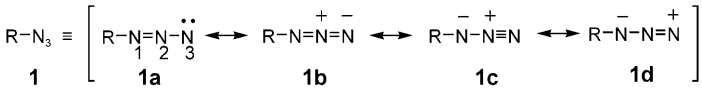
However, in spite of their explosive properties, organic azides are valuable intermediates in organic synthesis.[7,8] Thus they are used in cycloadditions, the synthesis of anilines and *N*-alkyl-substituted anilines,[9] as well as precursors for nitrenes. In this Review, which is not meant to be a comprehensive overview,[10] the fundamental characteristics of organoazide chemistry with its "explosive" diversity in modern synthetic chemistry will be illustrated. In this context, inorganic azides, purely main-group azides (such as $Te(N_3)_5$[11]), and purely structural-chemical aspects will not be discussed. After the section on their properties, the synthetic opportunities and applications of organoazides will be illustrated.

2. Physicochemical Properties of Organic Azides

The structural determination of azides originates from the initial postulation of Curtius and Hantzsch, who had suggested a cyclic 1*H*-triazirine structure [3,12,13], that was, however, rapidly revised in favor of the linear structure.

1-phenyl-1*H*-triazirine

A basis for the chemical diversity of azides comes from the physicochemical properties of azides. Some of the physicochemical properties of the organic azides can be explained by a consideration of polar mesomeric structures.[1] Aromatic azides are stabilized by



conjugation with the aromatic system. The dipolar structures of type **1c**,**d** (proposed by Pauling[14]) also compellingly explained the facile decomposition into the corresponding nitrene and dinitrogen (see Section 4.2) as well as the reactivity as a 1,3-dipole. The regioselectivity of their reactions with electrophiles and nucleophiles is explained

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on the basis of the mesomeric structure **1d** (attack on N^3 by nucleophiles, whereas electrophiles are attacked by N^1).

The angles R–N^1–N^2N^3 and RN^1–N^2–N^3 are approximately 115.2° and 172.5°, respectively (calculated for methyl azide, R = CH_3[15]). The bond lengths in methyl azide were determined as d(R–N^1) = 1.472, d(N^1–N^2) = 1.244, and d(N^2–N^3) = 1.162 Å; slightly shorter N^2–N^3 bond lengths are observed with aromatic azides. Thus an almost linear azide structure is present, with sp^2 hybridization at N^1 and a bond order of ≈2.5 between N^3 and N^2 and ≈1.5 between N^2 and N^1. Figure 1 is an example of the molecular structure of an aromatic azide.

The polar resonance structures **1b**,**c** explain the strong IR absorption at ≈2114 cm^{-1} (for phenyl azide),[17] the UV absorption (287 nm and 216 nm for alkyl azides), the weak dipole moment (1.44 D for phenyl azide), and the acidity of aliphatic azides (e.g. see Scheme 12).[18] The azide ion is regarded as a pseudohalide[19] and organic azides are similar in certain respects to organic halogen compounds. The Hammett parameters for arenes with azide groups in the *meta* and *para* positions are 0.35 and 0.10, respectively, which are comparable with those of fluoroarenes. In aromatic substitution reactions the azide group acts as an *ortho*- and *para*-directing substituent.

Whereas ionic azides such as sodium azide are relatively stable (see box), covalently bound and heavy-metal azides are thermally decomposable and in part explosive classes of compounds. For organic azides to be manipulable or non-explosive, the rule is that the number of nitrogen atoms must not exceed that of carbon and that $(N_C + N_O)/N_N \geq 3$ (N = number of atoms; Smith[20]). Synthesized but potentially explosive compounds include hexakis(azidomethyl)benzene (**2**),[16] triazidotrinitrobenzene (**3**),[21] azidotetrazole (**4**) (88 %

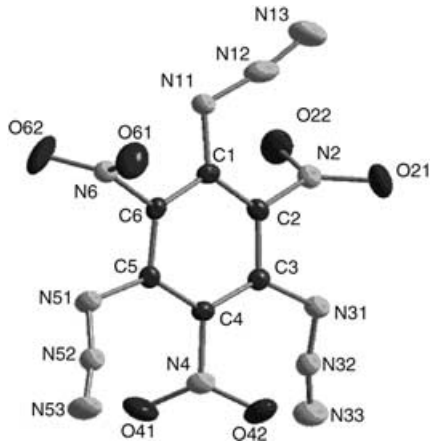
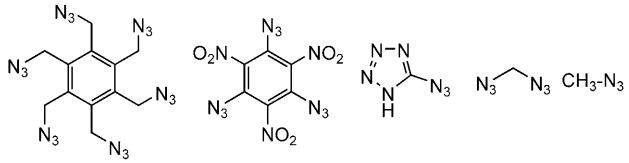


Figure 1. ORTEP representation of 1,3,5-triazido-2,4,6-trinitrobenzene with the ellipsoids of the C, N, and O atoms drawn at the 50% probability level.[16b]



Stefan Bräse was born in Kiel in 1967 and studied at Göttingen, Marseille (France), and Bangor (Wales) (PhD: Prof. Armin de Meijere). After periods of research in Uppsala (Sweden) and La Jolla (USA) he completed his Habilitation at the RWTH Aachen (Prof. Dieter Enders). In the same year he was appointed C3 professor at Bonn University. He was guest professor in Madison (USA) before taking up his current professorship at the Universität Karlsruhe (TH) in 2003. His research interests combine asymmetric catalysis, the synthesis of natural products, combinatorial chemistry, and medicinal chemistry.

Viktor Zimmermann studied chemistry at the universities of Nowosibirsk, Göttingen, and the RWTH Aachen. He completed his Diploma at the RWTH Aachen in 2002. Since then he has been working for his PhD at Bonn University (Prof. Stefan Bräse). The main topic of his research is carrier-supported combinatorial synthesis of benzotriazoles and azides.

Carmen Gil was born in Talavera de la Reina, Spain in 1972. She studied at the Complutense University of Madrid and received her PhD in 2001 at the Medicinal Chemistry Institute in Madrid (Prof. Ana Martínez). After a postdoctoral appointment at Bonn University (Prof. Stefan Bräse) as a Marie-Curie fellow, she joined the Medicinal Chemistry Institute in Madrid in 2004. Her research interests includes combinatorial chemistry applied to the synthesis of bioactive molecules.

Kerstin Knepper was born in Dortmund, Germany in 1976 and studied chemistry at the University of Dortmund. In 2001, she obtained her Diploma in chemistry (Prof. Norbert Krause). She received her PhD in 2004 at the University of Bonn (Prof. Stefan Bräse). She is currently a postdoctoral fellow with Prof. N. Winssinger (Université Louis Pasteur, Strasbourg, France). Her research interests include the solid-phase synthesis of benzannelated heterocycles, methods of organometallic chemistry, and the combinatorial synthesis of natural product analogues.

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nitrogen!),[22] and azidomethane (**6**). Diazidomethane (**5**) is prepared from sodium azide and dichloromethane.[23] Certain low-molecular-weight azides, which in practice have proved to be nonreactive, can still decompose under unexplained circumstances so that special care is needed.

Safety in the Handling of Sodium Azide and other Azides

Sodium azide is toxic (LD_{50} oral (rats) = 27 mg kg^{-1}) and can be absorbed through the skin. It decomposes explosively upon heating to above 275 °C; hence its use in airbags in the automotive industry).

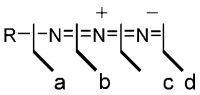
Sodium azide reacts vigorously with CS_2, bromine, nitric acid, dimethyl sulfate, and a series of heavy metals, including copper and lead. In reaction with water or Brønsted acids the highly toxic and explosive hydrogen azide is released. It has been reported that sodium azide and polymer-bound azide reagents form explosive di- and triazidomethane with CH_2Cl_2 and $CHCl_3$, respectively.[23a]

Heavy-metal azides that are highly explosive under pressure or shock are formed when solutions of NaN_3 or HN_3 vapors come into contact with heavy metals or their salts. Heavy-metal azides can accumulate under certain circumstances, for example, in metal pipelines and on the metal components of diverse equipment (rotary evaporators, freeze-drying equipment, cooling traps, water baths, waste pipes), and thus lead to violent explosions.

Some organic and other covalent azides are classified as toxic[24] and highly explosive[25], and appropriate safety measures must be taken at all times.

3. Synthesis of Organic Azides

In principle, organic azides may be prepared through five different methods: a) insertion of the N_3 group (substitution or addition), b) insertion of an N_2 group (diazo transfer), c) insertion of a nitrogen atom (diazotization), d) cleavage of triazines and analogous compounds, and e) rearrangement of azides. As the properties and the synthesis of aromatic and aliphatic azides vary considerably, the two classes of compounds will be discussed separately.[26]



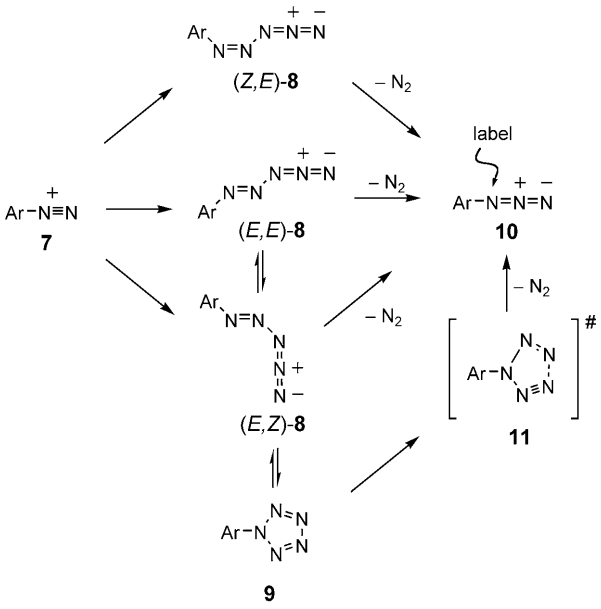
3.1. Aryl Azides

Because of their relatively high stability, aryl azides[27,28] have found biological and industrial use as photoaffinity labels,[29] as cross-linkers in photoresistors,[30] for conducting polymers,[31] and for light-induced activation of polymer surfaces[32] and are important intermediates in organic chemistry. Classic aromatic chemistry is usually the access of choice.

3.1.1. Aryl Azides from Diazonium Compounds

The older preparative methods for aryl azides are based on the reaction of diazonium salts with hydrazine[33] or *O*-benzylhydroxylamine hydrochloride.[34] The reaction of arene diazonium perbromides with ammonia also leads to aryl azides and is the oldest method for the preparation of azides.[2,34,35]

In the meantime, however, more convenient conversions of diazonium salts into aryl azides are known. Thus, aryl diazonium salts react directly with azide ions without catalysts directly to the corresponding aryl azides.[36] Alkali azides or trimethylsilyl azide act as source.[37] The latter compound is especially suitable because of its solubility in organic solvents (see Section 3.5.1). Unlike the Sandmeyer reaction, this reaction does not take place with cleavage of the C–heteroatom bond but occurs with attack of the azide on the diazonium ion with formation of aryl pentazoles and its subsequent products.[38] This reaction is sufficiently rapid even at low temperatures; *p*-chlorophenyldiazonium chloride reacts with azide ion even at −80 °C. The mechanism of this reaction (whether it occurs through a concerted [3+2] mechanism or takes place stepwise) and the nature of the intermediates have been the subject of controversial discussions since its discovery. There is a general consensus that the intermediate pentazenes and pentazoles lose dinitrogen. The corresponding azides are obtained at low reaction temperatures.[39] A pentazole structure was established for the first time by X-ray crystal-structure analysis in 1983.[40a] A British group investigated this reaction spectroscopically by ^{1}H and ^{15}N NMR spectroscopy (Scheme 1)[39] and established that



Scheme 1. Mechanism of the conversion of diazonium ions into azides.[39]

three isomeric aryl pentazenes **8**, namely the (*Z*,*E*), (*E*,*E*), and (*E*,*Z*) isomers, were formed by the attack of the azide ion at the β nitrogen atom of the diazonium ion **7**, as already postulated by Huisgen.[41] Whereas (*E*,*Z*)-**8** produces the 1-aryl pentazole **9**, (*Z*,*E*)-**8** forms the aryl azide directly by cleavage and does not rearrange to the *E* isomer. The *Z*,*E*-**8** isomer is considered to be the stereoelectronically favored product. This mechanism also explains the isotope labeling of the aryl azides found during the decomposition of labeled

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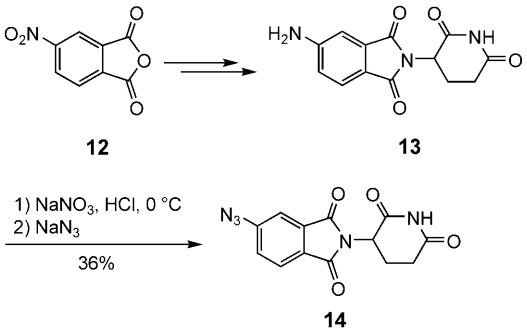
diazonium ions.[39c] Besides the isolated diazonium salts, other precursors such as benzotriazinones[42] may be used for the synthesis of aryl azides according to this scheme.

A more recent example of the decomposition of diazonium salts into the corresponding aryl azides is illustrated by the synthesis of azidothalidomide (**14**; Scheme 2).[43] The

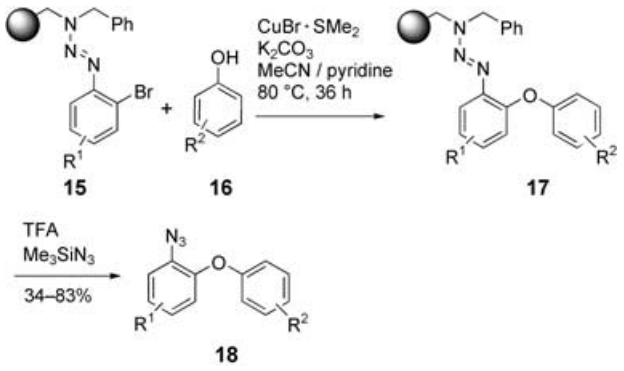


Scheme 2. Synthesis of azido-thalidomide (**14**).[43]

heterocycle was formed from nitrophthalic anhydride (**12**) by classic procedures, and the amino group in **13** was obtained by reduction. Diazotization and its subsequent reaction with sodium azide gave **14**. This compound is more active than thalidomide in the inhibition of the proliferation of human microvascular endothelial cells (HMEC) both in the presence and absence of vascular endothelial growth factors (VEGF). It was possible to demonstrate that the effect on endothelial cell growth by introduction of the azide group did not influence the affinity for the thalidomide-binding domains negatively.

A combinatorial access to aryl azides **18** is provided by the cleavage of polymer-bound aryl triazenes **15**. These aryl triazenes can be modified on the polymer support in a number of different reactions, for example, the Ullmann–Nicolaou reaction (Scheme 3). The cleavage of the resulting aryl triazenes **17** to azides **18** is then carried out in good yields in the presence of trimethylsilyl azide.[44,45]

Although the conversion of diazonium salts into aryl azides represents one of the most important reactions of this class of compounds, the need to prepare the diazonium salts is

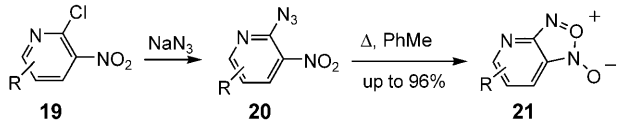


Scheme 3. Solid-phase synthesis of aryl azides **18** after a successful Ullmann–Nicolaou reaction.[44]

a severe limitation, so that in a few cases they may be synthesized only with difficulty if at all.

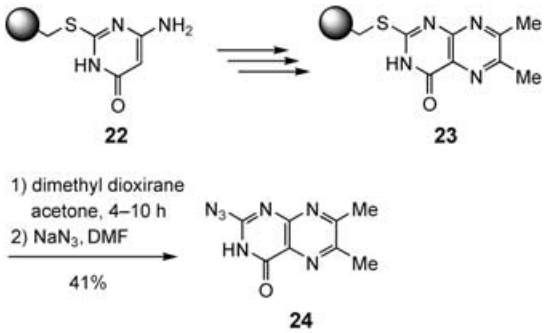
3.1.2. Nucleophilic Aromatic Substitution: S_NAr Reactions

Activated aromatic systems such as fluoro- and chloronitro arenes[46a] and a few heteroaromatic systems[46b] can undergo nucleophilic substitution by azide ions. They are generally sufficiently nucleophilic to produce aryl azides in good yields. The *ortho*-nitroazidoarenes formed react further at elevated temperatures with loss of nitrogen and formation of benzofurozane derivatives. Analogous reactivity is exhibited by the corresponding azidonitropyridine **20**, which may be prepared from chloronitropyridine **19** and sodium azide. (Scheme 4).[47]



Scheme 4. Aromatic substitution to give aryl azides.[47]

Heteroaryl sulfones are also cleaved regioselectively by azide ions. They can be used for the functionalizing cleavage of heteroaryl azides from polymeric supports, in which case the sulfur linker is first activated by oxidation to the sulfone with dimethyldioxirane (Scheme 5).[48]



Scheme 5. Functionalizing cleavage to give heteroaryl azides.[48]

If aromatic systems are provided with appropriate leaving groups, such as thallium substituents, the nucleophilic substitution can be carried out with electron-rich arenes. This aromatic substitution has been used in the total synthesis of indolactam V (**27**; Scheme 6),[49a] an indole alkaloid isolated from *Streptomyces blasmyceticum*. Alternatively, activated and deactivated aryl iodides can be converted into aryl azides under mild conditions with sodium azide in the presence of proline and copper(I) iodide.[49b]

3.1.3. Aryl Azides from Organometallic Reagents

Over the last decades, numerous methods for the preparation of aryl azides with organometallic reagents have been developed. For example, tosyl azide reacts with Grignard or

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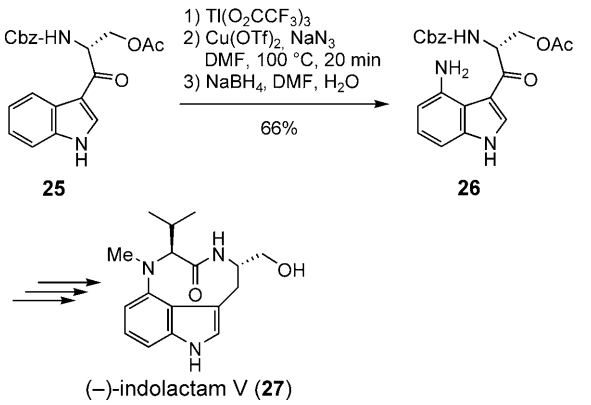
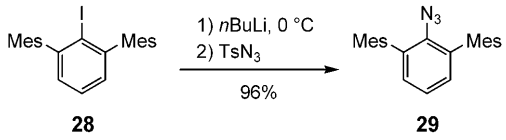


Scheme 6. Total synthesis of indolactam according to Kogan et al.[49a] Cbz = benzyloxycarbonyl; Tf = trifluoromethanesulfonyl.

lithium reagents—depending on the corresponding aryl halide—to form novel aryl azides (see also Section 3.5.2).[50] One example is the preparation of aryl azide **29** (Scheme 7).

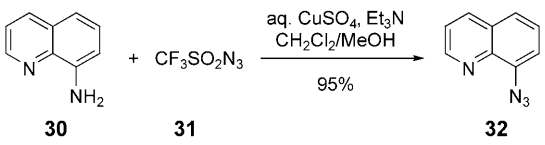


Scheme 7. Aryl azides according to Tilley and co-workers.[51] Mes = mesityl; Ts = *para*-toluenesulfonyl.

2,6-Dimesitylphenyl iodide (**28**) was initially treated with *n*-butyllithium at 0°C, and the resulting lithium salt reacted with *p*-toluenesulfonyl azide to form **29** in 96% yield.[51] Similarly, aryl amide salts (generated from the corresponding anilines and strong bases) react with tosyl azide to form the desired aryl azides.[52]

3.1.4. Aryl Azides by Diazo Transfer

In analogy to aliphatic amines (see Section 3.3.6), aryl azides and heteroaryl azides may be prepared by the reaction of anilines with triflyl azide (**31**).[53] The mild reaction conditions and very high yields make these transformations the method of choice for the preparation of numerous aromatic azides. In the typical reaction (Scheme 8) freshly prepared **31** is treated with 8-aminoquinoline (**30**) at room temperature in a mixture of dichloromethane and methanol in the presence of triethylamine and copper sulfate. The reaction produces 8-azidoquinoline (**32**) in almost quantitative yield.



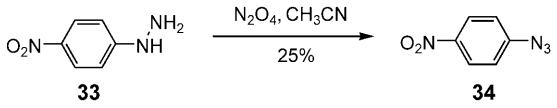
Scheme 8. Conversion of aromatic amines **30** into aryl azides **32** according to Tor and co-workers.[53]

3.1.5. Aryl Azides from Nitrosoarenes

The reaction of nitrosoarenes with hydrogen azide leads to aryl azides in good yields.[54] However, the diazonium ions must first be formed and then treated with azide ions as the second step: Thus, 2 equivalents of the explosive acid are required.

3.1.6. Diazotization of Hydrazines

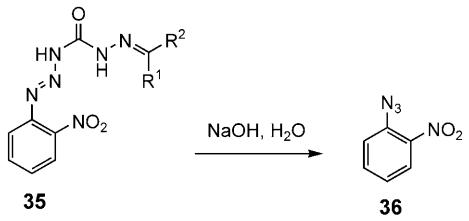
A well-established procedure that is equally suitable for the preparation of different classes of compounds such as aromatic and aliphatic azides, acyl azides, and sulfonyl azides is the reaction of hydrazines with nitrosyl ions or their precursors. N_2O_4,[55] mixtures of nitrogen oxide/oxygen,[56] nitrosyl salts,[57] and sodium nitrite[58] are particularly suitable (Scheme 9). The use of hydrazones[59] or 1-*tert*-butyl-1-aryl hydrazines,[60] which are cleaved under the reaction conditions used, is also a possibility.



Scheme 9. Conversion of the aromatic hydrazine **33** into aryl azide **34** according to Kim et al.[55,57]

3.1.7. Modification of Triazenes and Related Compounds

An older method for the preparation of azides is based on the rearrangement of triazenes into azides.[61] In particular, the base-induced cleavage of semicarbazones **35** can be used for the preparation of azides **36** (Scheme 10).[61a]



Scheme 10. Synthesis of the aryl azide **36** from the semicarbazone **35**.[61a]

3.2. Alkenyl Azides

Alkenyl azides are important as precursors for alkenyl nitrenes[62,63] and hence for the rearrangement to 2*H*-azirines.[64] A general synthetic route for alkenyl azides was developed by Hassner and co-workers.[63] In this method, the addition of iodine azide (**38**) to the double bond and the subsequent elimination of hydrogen iodide (base induced) occurs with a high degree of stereospecificity. On the one hand, exclusively vinyl azides and no allyl azides are formed from the 2-azido-3-iodoalkanes **39** and **41** formed as intermediates (with the exception of cyclopentene and cyclo-

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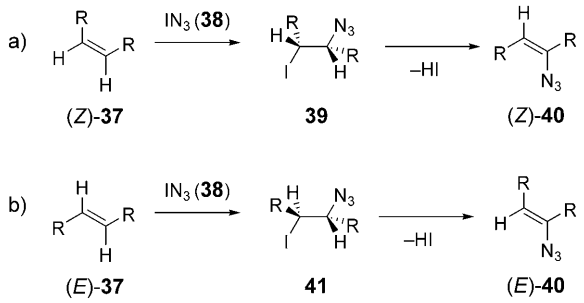
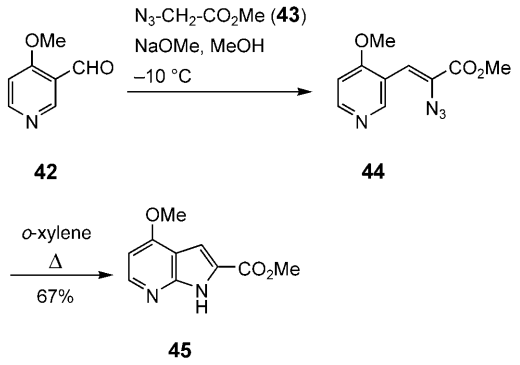
hexene adducts). On the other, the product configuration is determined by that of the starting material (Scheme 11).



Scheme 11. General synthesis of alkenyl azides **40** according to Hassner et al.[63]

An interesting access to 3-aryl-2-azidopropenoates is provided by the Knoevenagel reaction of aldehydes (e.g. **42**) and azidoacetate (e.g. **43**; Scheme 12, see also Scheme 77).[65] The subsequent thermolysis then gives the corresponding indoles or pyrroles. This reaction sequence was first described by Hemetsberger and co-workers.[66]

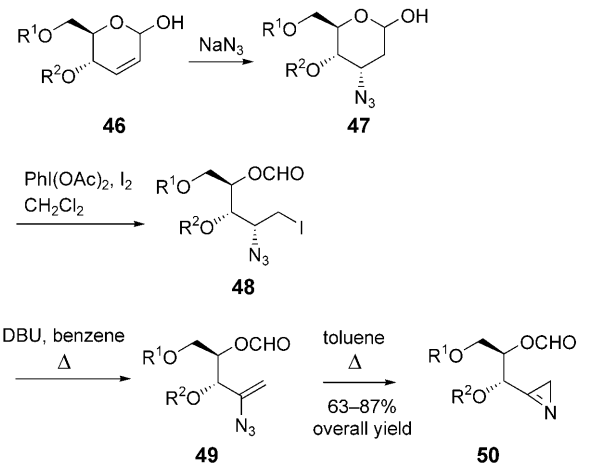


Scheme 12. Synthetic steps in the synthesis of the alkaloid varioline (**45**) and its analogues according to Molina et al.[65]

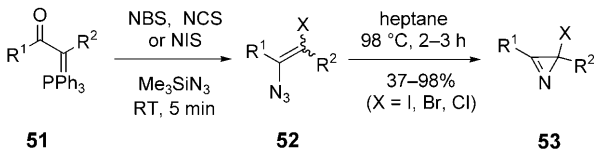
A new possibility for the synthesis of vinyl azides lies in the fragmentation of azide-substituted alkoxy radicals,[67] which are readily available from 3-azido-2,3-didesoxyhexopyranoses[68] **47** and consequently from glycals **46** and sodium azide. In the presence of an iodine source; the fragmentation initially results in vicinal iodoazides **48**, which then undergo elimination under mild conditions to the azidoalkenes **49**. This reaction sequence was used for the synthesis of 2*H*-azirines **50** (Scheme 13).

Alkenyl azides may also be prepared by conjugative addition of azide ions to activated alkynes or allenes.[69] A very convenient synthesis of 2-azidoacrylates is provided by the reaction of α,β-dibromopropanoic acid derivatives with sodium azide (see Scheme 64).[70,71]

Halogenated alkenyl azides can be formed from, among others, α-oxophosphonium ylides by reaction with *N*-halosuccinimides and trimethylsilyl azide. These haloalkenyl azides can be transformed into the corresponding 2-halo-2*H*-azirines **53** by heating to 98 °C (Scheme 14).[72]

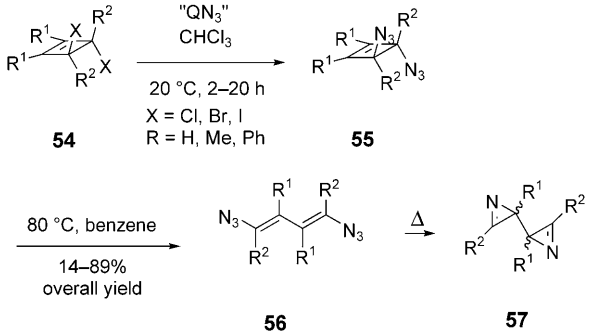


Scheme 13. Fragmentation of alkoxy radicals in the synthesis of alkenyl azides **49**.[67] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



Scheme 14. Synthesis of 2-halo-2*H*-azirines **53** via haloalkenyl azides **52**.[72] NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, NIS = *N*-iodosuccinimide.

1,4-Diazido-1,§-dienes **56** serve as precursors for biazirinyls **57** (see Scheme 65). They may be prepared in acceptable yields only by conrotatory opening of *trans*-diazidocyclobutanes **55** (Scheme 15). The latter are accessible by reaction of the *trans*-dihalocyclobutanes **54** with tributylhexadecylphosphonium azide ("QN_3").[73]



Scheme 15. Synthesis of 1,4-diazido-1,3-dienes **56** and biazirinyls **57**.[73]

3.3. Alkyl Azides

Alkyl azides were first discovered by Curtius and, after aryl azides, represent the second most important class of azide compounds. In most cases, classic nucleophilic substitution is the method of choice.

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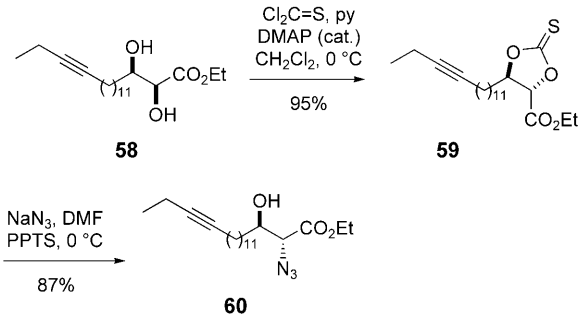
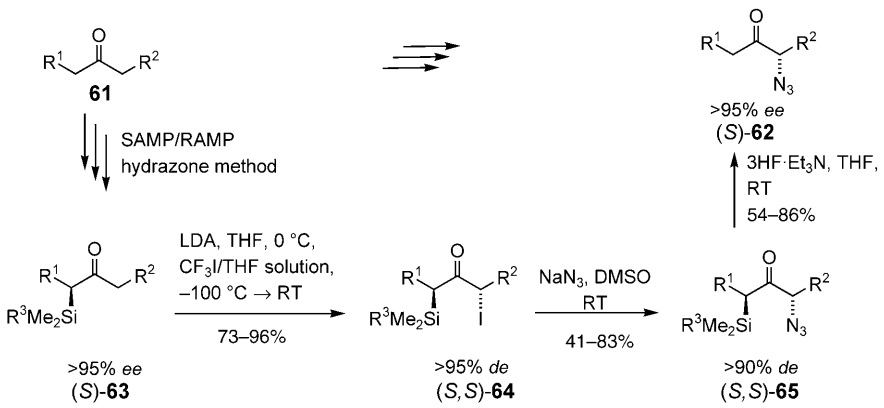
3.3.1. Classic Nucleophilic Substitution

Aliphatic azides are compounds readily accessible by nucleophilic substitution (S_N2 type) with the highly nucleophilic azide ion. Sodium azide is most commonly used as the azide source, although other alkali azides, tetraalkylammonium azides, polymer-bound azides,[74] or (as in the classic variant) the highly explosive silver azide[3] are also used. In most cases halides,[75] carboxylates,[76] and (cyclic) sulfonates[77] as well as mesylates,[78] nosylates,[79a] and triflates[79b,80] are chosen as leaving groups,[81,82] although sulfonium salts are possible substrates.[83] Besides the classic variants with DMF as solvent under thermal conditions, ionic liquids,[84] supercritical carbon dioxide,[85] or microwave radiation[86] can be used. A regioselective azide substitution at the α position of α,β-dihydroxy ester **58** via a cyclic thiocarbonate intermediate **59** was described by Bittman and co-workers in 2000 (Scheme 16).[87]



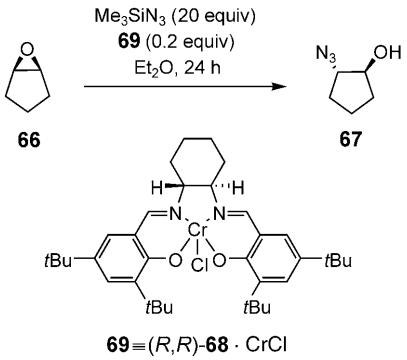
Scheme 16. Synthesis of α-azido-β-hydroxy ester **60** via a cyclic thiocarbonate intermediate **59**[87] DMAP = 4-dimethylaminopyridine, py = pyridine, PPTS = pyridinium *para*-toluenesulfonate.

The asymmetric synthesis of α-azidoketones **62** was described by Enders and Klein in 1999.[88] The key step in this reaction is a diastereoselective nucleophilic substitution of the iodine substituent in α-silylated-α′-iodoketones **64** with sodium azide. The necessary iodoketones **64** were prepared by the well-established SAMP technique. The α-azidoketones **62** are useful intermediates in the synthesis of protected and unprotected α-aminoketones (Scheme 17).



Scheme 17. Asymmetric synthesis of α-azidoketones **62** according to Enders et al.[88]

A further possibility for the synthesis of organic azides is the ring opening of epoxides by azide ions.[18] This useful reaction, which leads to α-azidoalcohols **67** and thus potentially to α-aminoalcohols and aziridines,[18] can also be carried out enantioselectively on the corresponding *meso*-epoxides **66** (Scheme 18).[89,90] A kinetic racemate separation is also possible.[91] Catalysts of choice are salen complexes **69** (salen = *N*,*N*′-bis(salicylidene)ethylenediamine, **68**)[92] with chromium as the central metal.[93] A monomeric salen structure is the reactive species with the participation of a bimetallic intermediate,[94] although macrocyclic and linear oligomer variants are significantly more active then their monomeric analogues.[95] The tolerance of biological systems towards azides also allows kinetic racemate separation of styrene epoxides with halohydrin dehalogenase from *Agrobacterium radiobacter*. The products (the *S* epoxide and the *R* azidoalcohol) were formed with excellent enantiomeric excesses.[96]



Scheme 18. Asymmetric synthesis of α-azidoalcohols **67** according to Jacobsen and co-workers.[89]

Sodium azide, either zeolite-bound[97a] or in the presence of molecular sieves,[97b] has also been used for the organic transformation of epoxides into organic azides. Glycidols, which can be readily obtained by the Sharpless epoxidation of allyl alcohols, can be opened regioselectively with titanium reagents such as $Ti(OiPr)_2(N_3)_2$.[98] In contrast, a reverse regioselectivity to Markovnikow products is achieved with aluminum reagents such as diethylaluminum azide.[99] The analogous ring opening of aziridines[100]—preferably in the presence of cerium[101] or copper[102] ions—leads to valuable 1,2-diaminoalkanes.[103–105]

S_N1 reactions are also frequently observed. Azide ions react especially readily with oxonium cations, such as are formed in the reaction of glycosyl cations. In this way thioacetals and other precursors can be transformed with azide ions in the presence of Lewis acids.[106] A stereoselective synthesis of anomeric organic azides involves the opening of oxazolines by trimethylsilyl azide and a fluoride source as described by DeShong and co-workers.[107a]

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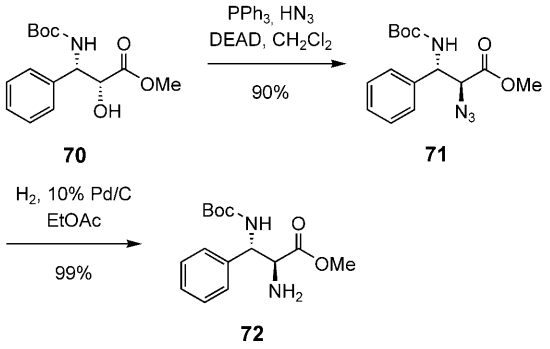
3.3.2. The Mitsunobu Reaction

A derivation of the Mitsunobu reaction published in 1967[108] provides a simple access to organic azides from alcohols.[109,110] Primary and secondary alcohols react with hydrogen azide, triphenylphosphane, and diethyl azodicarboxylate (DEAD). Secondary alcohols are of considerable interest as substrates because they react with inversion of stereochemistry. Lee et al. used this reaction as the key step in the synthesis of 2,3-diamino-3-phenylpropanoic acid derivatives **72** (Scheme 19), which are important structural elements of many biologically active compounds such as antibiotics.[111]

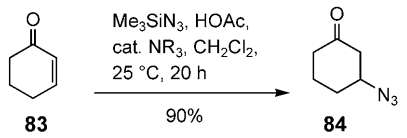


Scheme 19. Application of the Mitsunobu reaction to the asymmetric synthesis of 2,3-diamino-3-phenylpropanoic acid derivates.[111] Boc = *tert*-butoxycarbonyl.

Diphenylphosphoryl azide (DPPA) in the liquid phase[112–115] or immobilized on polymeric supports (see Scheme 125)[116] can also be used successfully in place of the explosive hydrogen azide. In 2002, Jiang et al. published the enantioselective total synthesis of hamacanthine B (**82**) in which this variant of the Mitsunobu reaction was a key reaction (Scheme 20).[117] The central chiral pyrazinone ring was formed in a Staudinger/aza-Wittig sequence (Section 4.3.3). Another Mitsunobu azide source is zinc azide.[118]Alkyl azides can also be prepared by the reaction of alcohols with a reagent combination of tetrabromomethane, triphenylphosphane, and sodium azide—comparable with the classic Appel reaction—as shown in a formal synthesis of mappicin.[119] Homada and co-workers used the Mitsunobu reaction for the preparation of biologically active peptides.[120] The substitution of hydroxy groups under Mitsunobu conditions has been carried out in the solid phase with DPPA.[121,122] In Scheme 32 (Section 3.3.8), the key step of the preparation of a sarcodictyin library by Nicolaou and coworkers is illustrated as an example.[122]

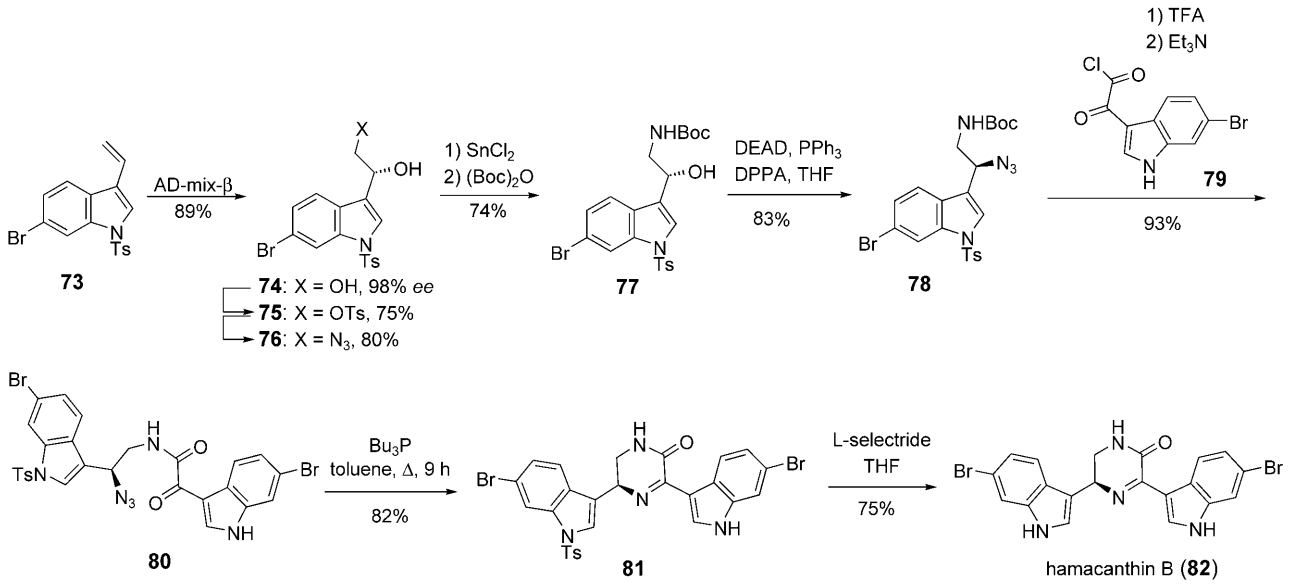
3.3.3. Polar 1,2- and 1,4-Addition Reactions

α,β-Unsaturated carbonyl compounds react with azide ions in 1,4-additions—unlike organic azides, which form triazoles. One example of this valuable method for the synthesis of alkyl azides was described by Miller and coworkers in 1999 for 2-cyclohexenone (**83**).[123,124] The source for the azide ion in this Michael-like reaction is an equimolecular mixture of trimethylsilyl azide and acetic acid, while tertiary amines as Lewis bases catalyze the reaction (Scheme 21). Other suitable Michael acceptors are glycals



Scheme 21. Conjugate addition of azide ions to cyclohexenone **83**.[123]

(Scheme 13) or quinones.[125] However, in the presence of Lewis acids (aluminum), azide ions react differently with α,β-unsaturated ketones: triazoles are formed after a hydride



Scheme 20. Enantioselective synthesis of the marine indole alkaloid hamacanthin B (**82**).[117] L-Selectride = lithium tri(*sec*-butyl)borohydride.

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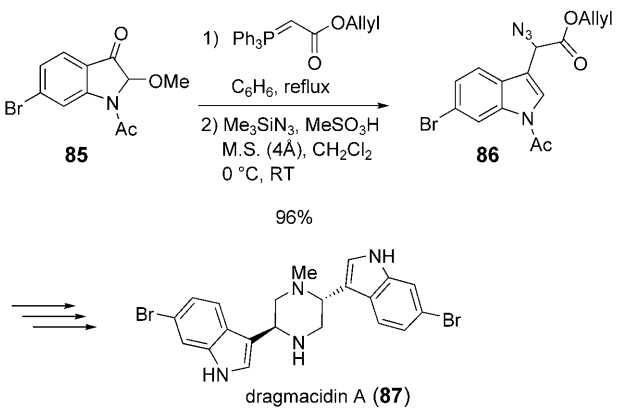
shift.[126] Kawasaki et al. used the 1,4-addition of azides to an indolenium intermediate as key step in the total synthesis of dragmacidin A (**87**; Scheme 22).[127]

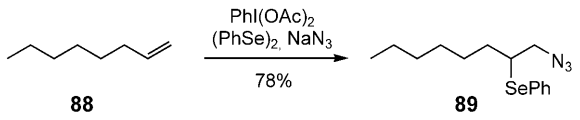


Scheme 22. Synthesis of dragmacidin A according to Kawasaki and co-workers.[127]

3.3.4. 1,2-Addition to Non-Activated Double Bonds

The addition of halogen azides to olefins was first described by Hassner and Levy in 1965.[63] This reaction eventually permitted wide access to vinyl azides (see Section 3.2).

In recent years, single- and multistep radical syntheses have become increasingly important.[128] 1,2-Addition to non-activated double bonds with azide sources can involve a radical reaction since the azidyl radical behaves as a pseudohalogen radical. The reaction of olefins with diphenyldiselenium, diacetoxyiodobenzene, and sodium azide is a radical azidoselenation (Scheme 23).[129,130b] The unusual

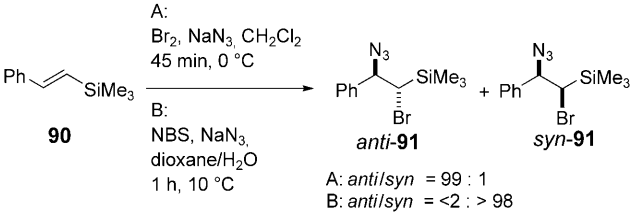


Scheme 23. Radical 1,2-addition to non-activated double bonds.[130b]

regiochemistry—the azide group is inserted at the least-substituted position—is an indication of the radical nature of this reaction. Recently Klapötke and co-workers isolated a stabilized aryl selenium azide,[131] a member of the class of selenium azides whose existence had been postulated in a number of reactions.[132] The radical azidoselenation has found interesting applications in sugar chemistry.[133]

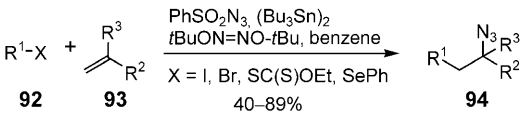
In contrast, the addition of bromoazide to alkenes by pre-electrophiles (Br_2, NBS) and azide ions is mostly polar in nature. The choice of the pre-electrophile and the substrate allows control of the stereochemistry, as shown in Scheme 24 (see also Scheme 11).[134,135]

In 2001, Renaud and co-workers described an efficient carbon–nitrogen bond formation in the reaction of radicals with sulfonyl azides.[136] In 2002, they extended this to the intermolecular addition of radicals to non-activated alkenes



Scheme 24. Polar 1,2-addition to non-activated double bonds.[134,135]

with subsequent azidation. This reaction sequence formally represents a carboazidation of alkenes and is a key step in the three-component syntheses of pyrrolidone, pyrrolizidinone, and indolizinone derivatives.[137] One example is the reaction of the terminal alkenes **93** with different radical precursors (Scheme 25).

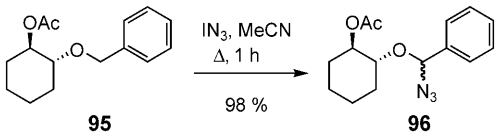


Scheme 25. Radical azide insertion according to Renaud et al.[137]

Kirschning and co-workers elegantly showed that iodoazide can be used as a polymer-bound reagent and in this way were able to convert a series of alkenes into vicinal iodoazides.[138–140] Furthermore, alkenes can be converted into β-azido alkyl mercury compounds by hydrogen azide in the presence of azide ions.[141a] Glycals can be converted into 2-desoxyglycosyl azides by the action of trimethylsilyl azide in the presence of catalytic amounts of trimethylsilyl nitrate.[141b]

3.3.5. C–H Activation

The activation of C–H bonds can also be carried out with azides. The radical azidation in the benzyl position of benzyl ethers **95** with iodoazide[25] was recently described by Viuf and Bols.[142] This reaction takes place in very good yields (74–98%) and relatively short reaction times with a number of substrates (Scheme 26). Related to this reaction is the open-



Scheme 26. Radical azidation of the benzyl position with iodoazide.[142]

ing of benzal acetals with the formation of β-azidobenzoates (azido-Hanessian reaction).[143] A domino radical iodoazide cyclization strategy was used as a key step in the formal total synthesis of (±)-aspidospermidine.[144] Hydrocarbons can also undergo radical azidation at high temperatures with the somewhat more stable hypervalent iodo reagent **98** (Scheme 27).[145]

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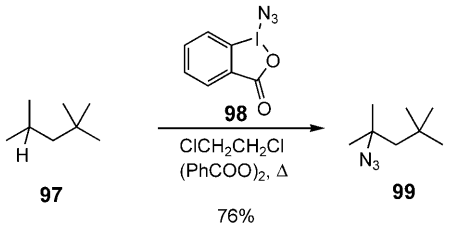
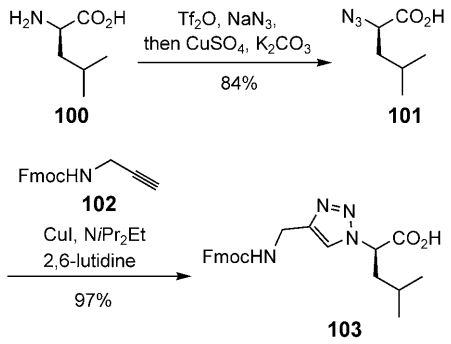


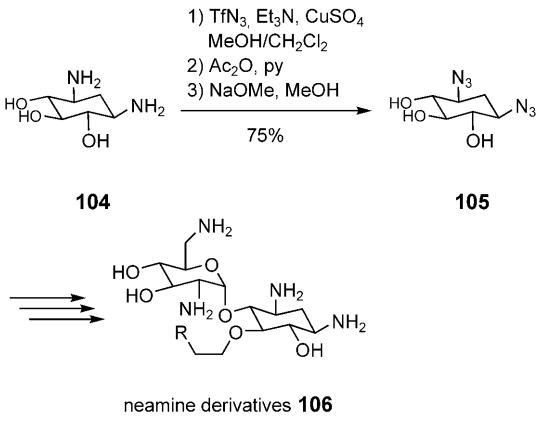
Scheme 27. Activation of the C–H bond by azidoiodinane **98** according to Zhdankin et al.[145]

3.3.6. *Diazo Transfer: A Simple Synthesis of Alkyl Azides from Amines*

Primary aliphatic amines may be converted into the corresponding azides by diazo transfer. In this way, the step involving sensitive aliphatic diazonium ions can be circumvented.[146,147] The reagent of choice for this transformation is triflyl azide (**31**), which can be prepared from trifluoromethanesulfonic anhydride and sodium azide. Aliphatic primary amines **100** give the azides **101** in the presence of a copper catalyst in exceptionally good yields.[148–150] The azides can then be converted, for example, into 1,2,3-triazoles **103** with different alkynes (Scheme 28; see Section 4.1.1). These methods were also used in the syntheses of aminoglycosides, an important group of antibiotics.[151,152] The synthesis of neamine derivatives **106** by Wong and co-workers is shown here as an example (Scheme 29).[152]



Scheme 28. Diazo transfer to primary amines and subsequent triazole synthesis according to Ghadiri and co-workers.[150] Fmoc = fluorenylmethoxycarbonyl.

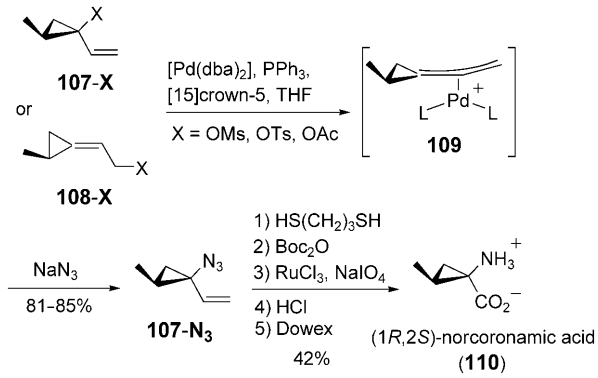


neamine derivates **106**

Scheme 29. Synthesis of neamine derivates **106** according to Wong and co-workers.[152]

3.3.7. *Azide Addition to Palladium Complexes: Synthesis of Allyl Azides*

The addition of azide ions to 1,1-substituted π-allylpalladium complexes has been used by de Meijere, Salaün, and coworkers in the synthesis of aminocyclopropanoic acids. π-Allyl palladium compounds are formed from allyl acetates **107**-OAc, **108**-OAc, or similar compounds in the presence of palladium(0) complexes and are then treated with sodium azide.[153–155] Whereas normally the addition of nucleophiles occurs at the unsubstituted end with formation of the thermodynamically less stable methylenecyclopropanes, in the case of 1,1-ethanoallylpalladium complexes **109**, azide ions give the corresponding alkenylcyclopropanes. A subsequent [3,3] rearrangement may also have occurred (Section 4.8) after the initial formation of methylenecyclopropane derivatives. The azidocyclopropane **107**-N_3 formed stereoselectively could then be transformed into (−)-(1*R*,2*S*)-norcoronamic acid (**110**) in a sequence comprising a reduction (Section 4.4.2) and an oxidative cleavage of the double bond (Scheme 30).[156] 1-Aminocyclopropanecarboxylic acid was also prepared in this way.[157] Structurally demanding π-allyl palladium complexes, which are formed according to Grigg and co-workers [158] in a cascade cyclization or by arylation of allenes,[159] could also be converted regioselectively into the corresponding allyl azides. A special feature is the fact that π-allyl complexes can also be transformed into enantiomerically pure allyl azides by the action of chiral ligands.



Scheme 30. Synthesis of (−)-(1*R*,2*S*)-norcoronamic acid (**110**) according to de Meijere, Salaün, and co-workers.[156] dba = Dibenzylideneacetone.

According to Yamamoto and co-workers π-allyl palladium complexes also play a role in the reaction of allyl carbonates, trimethylsilyl azide, and alkynyl aryl isocyanides to give indoles.[160] Allyl azides that bear a leaving group such as nitrite in the 1-position can readily fragment with the loss of this leaving group to form α,β-unsaturated nitriles.[161]

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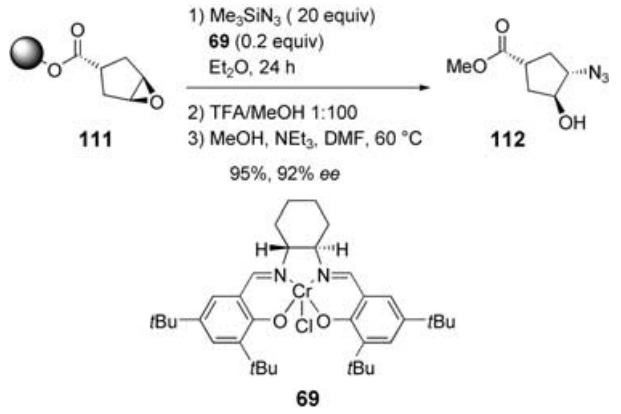
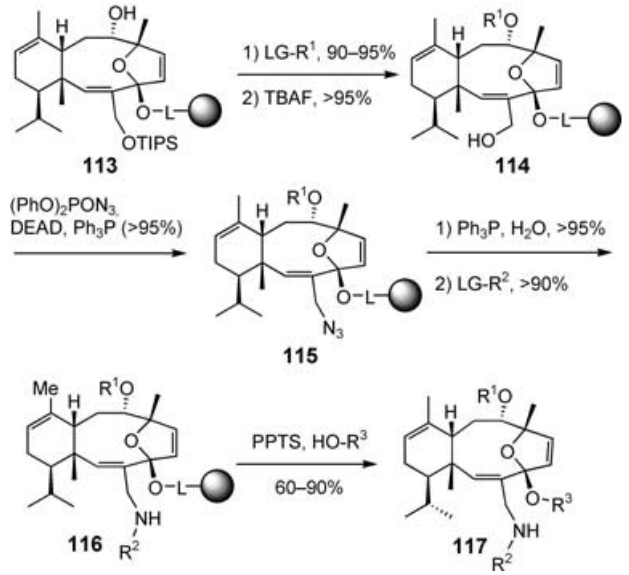
3.3.8. Solid-Phase Synthesis of Aliphatic Azides

Aliphatic azides have already been frequently synthesized on solid supports. In each case a start was made from a polymer-bound electrophile, which reacted with the corresponding azide-transfer reagent. The substitution of alkyl halides and alkyl alcohols was carried out with sodium azide[162,163] or tetra-*N*-butylammonium azide.[164] The ring opening of epoxides was carried out with sodium azide.[165,166] Jacobsen and co-workers used trimethylsilyl azide for the asymmetric ring opening of *meso*-epoxides in the solid-phase synthesis of cyclic azidoalcohols (Scheme 31).[167]

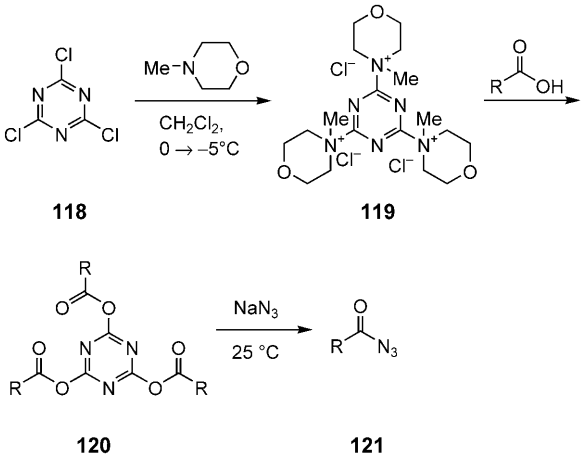


Scheme 31. Asymmetric epoxide opening on solid supports.[167] TFA = trifluoroacetic acid.

The substitution of hydroxy groups on solid-supports can be carried out under Mitsunobu conditions with DPPA[121,122,168] or under classic conditions.[169] In 1998, Nicolaou and co-workers reported the solid-phase synthesis of a sarcodictyin library with three points of diversity (Scheme 32) in which the Mitsunobu reaction played an important role.[122]



Scheme 32. Solid-phase synthesis of sarcodictyin analogues by Nicolaou and co-workers.[122] L = linker, TIPS = triisopropylsilyl, LG = leaving group, TBAF = tetrabutylammonium fluoride.



Scheme 33. Synthesis of acyl azides **121** from cyanurtrichloride **118**.[171]

3.4. Acyl Azides

Acyl azides are widespread, highly reactive reagents in organic chemistry and are used for the preparation of amides and heterocycles. Acyl azides are normally prepared from acid derivatives such as acyl chlorides or mixed anhydrides[170] with azide ions or by reaction of acyl hydrazines with nitrosyl precursors. A very mild and efficient method for the preparation of acyl azides without subsequent Curtius rearrangement (see Section 4.5.1), which would lead to the isocyanate, was described by Banddgar and Pandit in 2002 (Scheme 33).[171] In this case, different aryl, heteroaryl, alkyl aryl, and alkyl carboxylic acids are converted into the respective acyl azides **121** under mild conditions with cyanurtrichloride (**118**) in the presence of sodium azide and *N*-methylmorpholine.

Padwa et al. used the synthesis of acyl azides **123** in the preparation of substituted furans.[172] The free acids **122** are first converted into the corresponding acid chloride with thionyl chloride and then into the corresponding acyl azide **123** with sodium azide. Formation of the isocyanates **125** under Curtius conditions and subsequent reaction leads to amidofurans **126**. If the acyl azides **123** are heated in the presence of alcohols, furanamino carboxylates **124** are formed. The latter can also be prepared directly from the carboxylic acids by reaction with DPPA and alcohols in the presence of triethylamine (Scheme 34). The reaction of carboxylic acids with DPPA and subsequent Curtius rearrangement can also be used for the conversion of malonic ester derivatives **127** into α-amino acid esters **131**. In particular, the enantioselective, enzymatic desymmetrization with pig liver esterases (PLE) leads to the enantiomerically pure amino acids (Scheme 35).[173]

Enamides were prepared by Kitahara and co-workers by rearrangement of α,β-unsaturated acyl azides to alkenyl isocyanates **133** and subsequent addition of nucleo-

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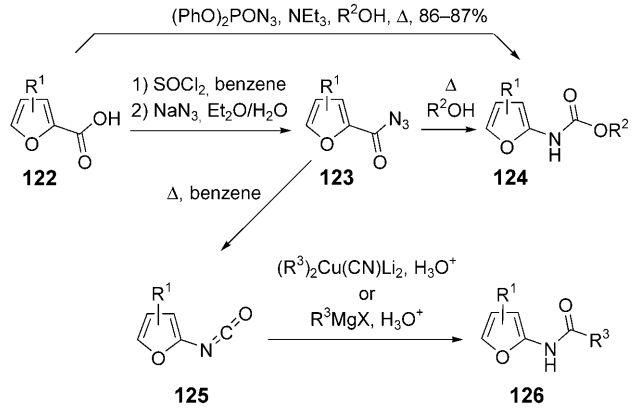
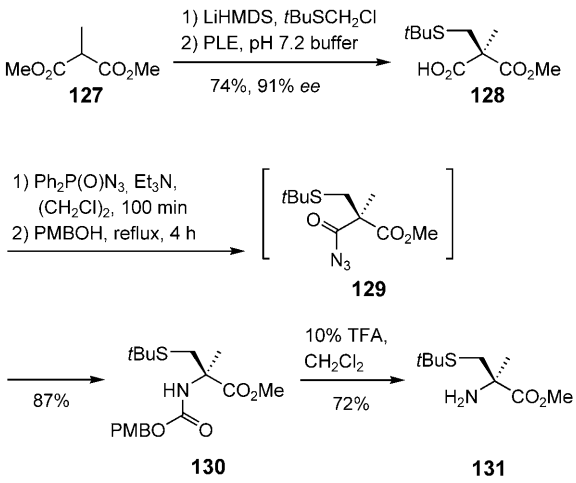


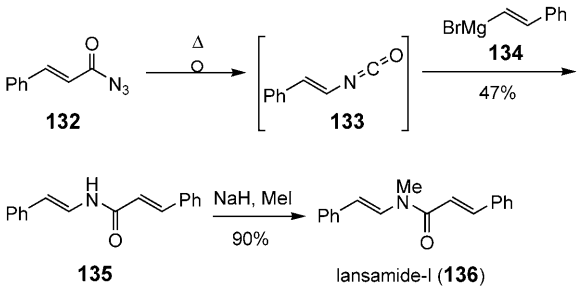
Scheme 34. Derivatization of furoic acids **122** according to Padwa et al.[172]



Scheme 35. Asymmetric conversion of the dimethyl malonate derivate **127** into α-amino acid ester **131**.[173] LiHMDS = lithium hexamethyldisilazide; PMB = *para*-methoxybenzyl.

philes.[174,175] The reaction sequence was used for the preparation of a series of natural products such as the lansiumamides A–C and lansamide-I (**136**; Scheme 36),[176] coscinamide, chondriamide, igziamide,[174] salicylihalamide,[177] apicularen A,[178] and others.[179]

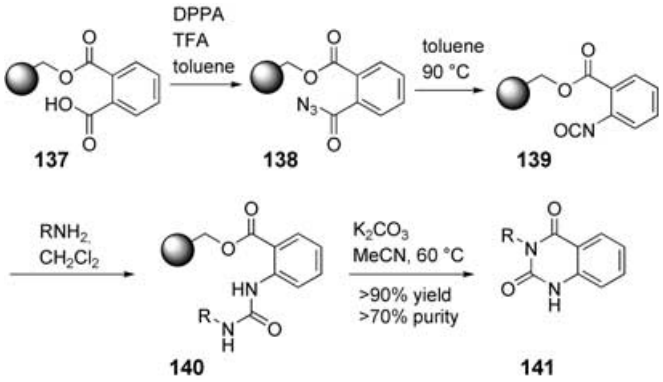
The synthesis of (poly)peptides can also be carried out with the highly reactive acyl azides[180] that are formed



Scheme 36. Total synthesis of lansamide-I (**136**) according to Taylor and co-workers.[176]

directly, for example, from DPPA and carboxylic acids. The azide unit with its ability to activate the acid group can then be replaced by nucleophiles—as already found by Curtius. Lucente and co-workers used the synthesis of acyl azides for the preparation of ergopeptides,[181] while Larsen and co-workers prepared β-1,3-glycosidically bound aminomonocarbodisaccharides.[182]

One application was described by Castelhano and co-workers in 1998 with the solid-phase synthesis of quinazoline-2,4-diones **141**.[183] Phthalic acid was first immobilized on a PEG4-PS resin and then converted into the acyl azide with DPPA in the presence of trifluoroacetic acid in toluene. Rearrangement to the isocyanate followed by reaction with a primary amine and subsequent base-catalyzed cleavage with ring closure gave the heterocycles in good yields with excellent purity (Scheme 37).



Scheme 37. Solid-phase synthesis of quinazoline-2,4-diones **141** with the generation of an acyl azide synthesis as a key step.[183]

A new variant for the preparation of acyl azides was described by Bols and co-workers. Aldehydes react with iodoazide[25] at room temperature, presumably in a radical mechanism.[184] If this reaction is carried out at elevated temperatures the acyl azides rearrange and the resulting isocyanates are captured with the formation of carbamoyl azides. Unlike acyl azides, *C*-azidoimines rearrange to tetrazoles (Scheme 145).

3.5. Heteroazides and Azide Reagents

Besides organoazides, in which the azide function is connected directly to the carbon atom, different heteroazides are of importance in organic synthesis and are briefly mentioned here.

3.5.1. Silyl azides

Silyl azides are valuable reagents in organic synthesis,[185,186] because, unlike sodium azide and hydrogen azide, they have no immediate explosive properties.[187] However, they hydrolyze in the long term to the volatile, toxic, and explosive hydrogen azide and therefore must be stored in the absence of moisture and acids. Trimethylsilyl azide (bp.

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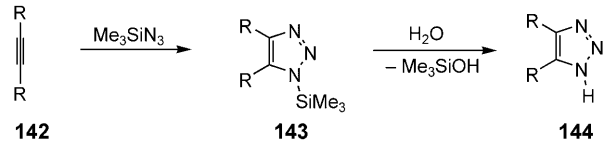
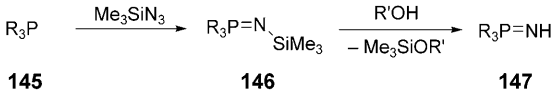
95 °C), which is also commercially available, can be prepared by photolysis of tetrakis(trimethylsilyl)-2-tetrazene[188] or by reaction of tris(trimethylsilyl)phosphate with sodium azide.[189] Most conveniently, however, it is formed from trimethylsilyl chloride by reaction with sodium azide in diglyme.[190] The higher thermal stability of trimethylsilyl azide relative to hydrazoic acid[191] can be used in the preparation of 1,2,3-triazoles from trimethylsilyl azide and acetylenes (Scheme 38).[192]



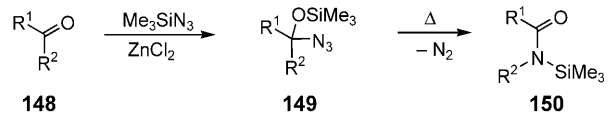
Scheme 38. Cycloadditions with trimethylsilyl azide.[192]

The facile cleavage of the Si–N bond governed the success of the synthesis of trialkyl- and triarylphosphinimines **147** from the corresponding phosphines **145** and trimethylsilyl azide (Scheme 39).[193] This reaction is significantly simpler than the reaction of phosphines with chloramine.[194]



Scheme 39. Synthesis of triaryl phosphinimines.[194]

Trimethylsilyl azide reacts with aldehydes or ketones **148** and their enol ethers with the formation of trimethylsilyloxy azides **149**, which can be transformed thermally[195a] or photochemically[195b] in a Schmidt rearrangement into *N*-trimethylsilyl amides **150** (Scheme 40) or the respective protiodesilylated amides. This reaction sequence is superior to the Schmidt reaction at least for a few derivatives because of the higher yields.[195b]



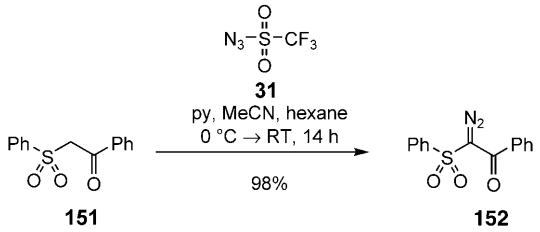
Scheme 40. Conversion of ketones into *N*-trimethylsilylamides.[195]

It was reported recently that trimethylsilyl azide can be immobilized in the solid phase as a reagent.[196]

3.5.2. *Sulfonyl Azides*

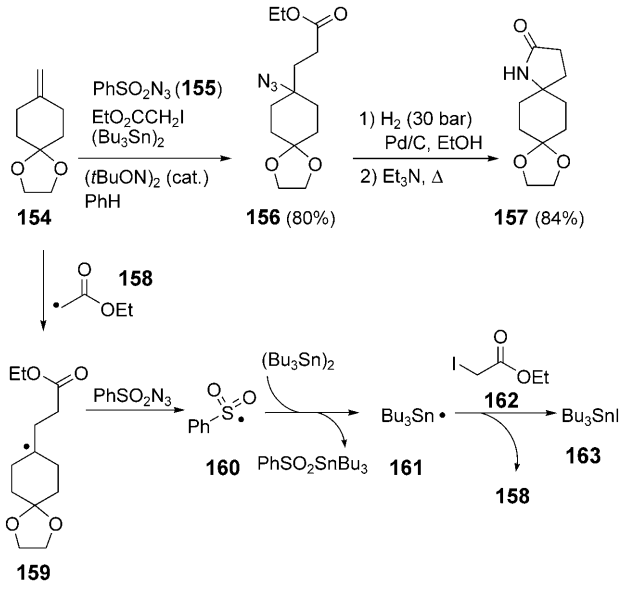
Sulfonyl azides[197] can be prepared from the corresponding sulfonyl chlorides by reaction with sodium azide in acetone.[198] These useful but sensitive[199] reagents are also available as shock-resistant solid-phase variants.[200]

The sulfonyl azides are used for diazo transfer[201] to CH-acid compounds, especially activated esters, β-ketoesters, and ketosulfones.[198,202] The enolate or enol attacks the organoazide with formation of a triazene, which after tautomerization reacts to form the diazo compound and the sulfonamide. Trifluoromethanesulfonyl azide (triflyl azide, **31**) was proposed by Charette and co-workers as a highly electrophilic diazo-transfer reagent that gives good results with activated acetic acid esters and ketones, particularly with pyridine as base (Scheme 41).[203,204]



Scheme 41. Diazo transfer with sulfonyl azide **153**.[203]

An interesting application of *p*-toluenesulfonyl azide (tosyl azide, **153**) is the proline-mediated enantioselective α-amination of aldehydes (see Scheme 46).[226] Recently sulfonyl azides, including pyridine-3-sulfonyl azide,[205] were successfully used in the azidation of nucleophilic radicals.[206] This reaction can also be used for intra- or intermolecular carboazidation of olefins. Renaud and co-workers demonstrated the use of this method in the synthesis of the spirolactam **157** (Scheme 42). The radical **158**, produced from ethyl iodoacetate, reacts with the olefin **154**, and the newly generated (nucleophilic) tertiary radical **159** extracts the azide group from phenylsulfonyl azide (**155**). The electrophilic radical **158** is, in contrast, unable to react with the sulfonyl azide. Tin-free methods are being intensively investigated, and triethyl borane appears to be a useful alternative.[207]



Scheme 42. Synthesis of spirolactam **157** by radical-induced carboazidation of olefins according to Renaud et al.[206]

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Furthermore, sulfonyl azides (especially triisopropylbenzenesulfonyl azide)[208] have been used in the electrophilic (diastereoselective) α azidation[208b] of the harder amide enolates of the Evans type[208] and ester enolates (Scheme 146)[134] for the synthesis of α-amino acid derivatives (Section 3.1.3, Scheme 7, Section 3.3.4, Scheme 25, Section 3.3.6).

Other important azides are iodoazide,[25,63,138–140,209] phosphoryl azides such as DPPA,[210] tributylhexadecylphosphonium azide ("QN_3"),[211] and *tert*-butoxycarbonyl azide (Boc azide), a transfer reagent for the *tert*-butoxycarbonyl group onto amines. The Zhdankin reagent (a stable azidoiodinone) was used for the direct azidation of hydrocarbons (see Scheme 27).[145] An important reagent is tetramethylguanidinium azide introduced by Papa[212] which has been used for the synthesis of vinyl azides,[69] among others (Section 3.2) and is advantageous for safety reasons.[213]

4. Reactions of Organic Azides

Azides can react very differently under different reaction conditions. In principle, they react with electron-deficient compounds (electrophiles) at N^1 (Section 4.6; Figure 2) and

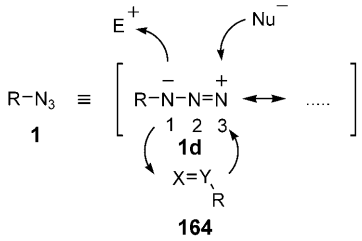


Figure 2. Reactivity of organic azides.[1]

electron-rich compounds (nucleophiles) at N^3 (Sections 4.3 and 4.4; Figure 2). There can be retention of the azide unit, but also cleavage of the nitrogen–nitrogen single bond, as in the case of nitrene chemistry. The simplest case mechanistically—an addition—has been used extensively in cycloaddition reactions.

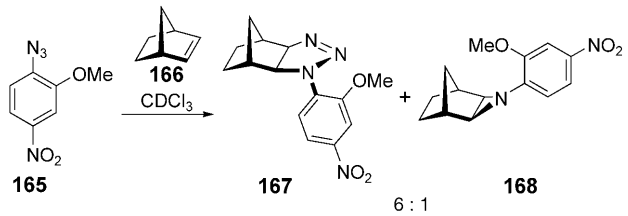
4.1. "Clicked": Cycloadditions Newly Discovered

The Huisgen reaction[214]—the cycloaddition of dipoles to dipolarophiles—also succeeds with azides as dipoles,[215] and selected dipolarophiles can be used.

4.1.1. 1H-Trazoles and Δ^2-1,2,3-Triazolines Made Simple

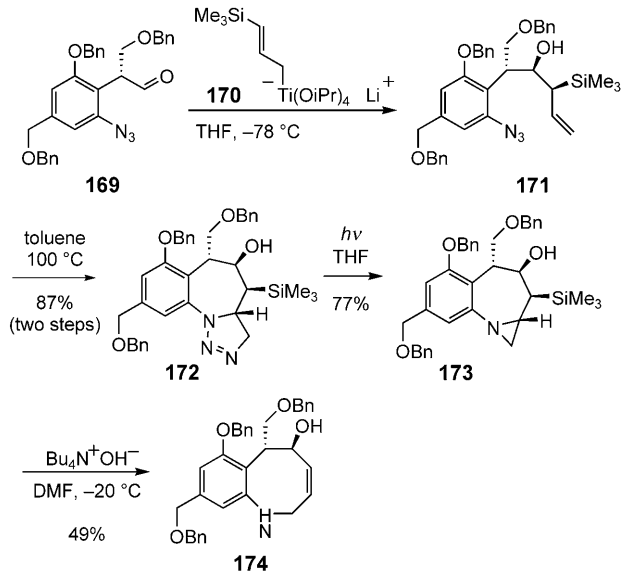
The uncatalyzed thermal cycloaddition of organic azides to alkynes and olefins allows the synthesis of 1*H*-triazoles and Δ^2-1,2,3-triazolines.[74,216,217] The addition takes place at different rates depending on the dipolarophile. Whereas strained olefins or alkynes such as norbornene and cyclooctyne[218] react readily, terminal alkenes react extremely slowly.[217b] In principle, suitable dipolarophiles include both electron-deficient and electron-rich alkenes (enol ethers such as glycans,[216f] enamines,[219a,b]; see Scheme 45) as well as magnesium acetylides.[216e] Many olefins are so unreactive, however, that intramolecular reaction control or the use of microwaves is necessary.[220]

The reaction of organoazides with alkenes is illustrated with a number of examples.[221,222] The aryl azide **165**, prepared as part of a combinatorial approach, reacted with norbornene **166** at 40 °C within 18 h and a conversion of ≈75 % with the formation of the Δ^2-1,2,3-triazoline **167** and the aziridine derivative **168** in a ratio of 6:1.[45] This ratio is temperature-dependent as the primarily formed Δ^2-1,2,3-triazoline **167** can react further to furnish the aziridine derivative **168** (Scheme 43).



Scheme 43. Cycloaddition of aryl azide **165** to norbornene.[45]

Ciufolini and co-workers demonstrated the use of intramolecular cycloadditions in their total synthesis of FR66979. After a selective Cram allylmetal addition of the titanium allyl compound **170** to an aldehyde **169** with an azide moiety through a Zimmerman–Traxler transition state, diastereoselective 1,3-dipolar cycloaddition gave the tricycle **172**. After photochemical nitrogen extrusion from the Δ^2-1,2,3-triazoline **172** and ring contraction to the aziridine **173**, an anionically induced azacyclopropylmethyl-azahomoallyl rearrangement took place (Scheme 44).[223]



Scheme 44. Part of the total synthesis of FR66979 according to Ciufolini and co-workers.[223] Bn = benzyl.

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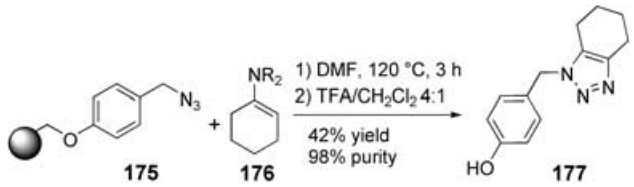
If the alkene bears a suitable leaving group, the initially formed Δ^2-1,2,3-trazoline aromatizes to the 1*H*-triazole.[224] In the case of enamines **176**, cycloaddition with organoazides **175** is usually followed by elimination of the amine group so that 1,2,3-triazoles **177** are formed (Scheme 45).[219] In a few cases, these and the analogous enol ether adducts rearrange to form β-lactams.[225]

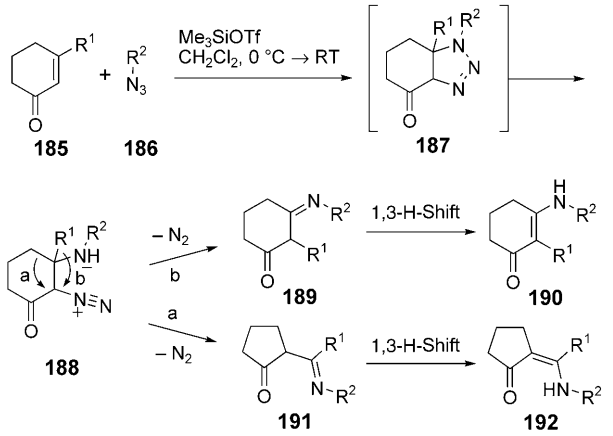


Scheme 45. Synthesis of 1,2,3-triazoles on a polymer support according to Harju et al.[219]

The enamine **180**, which is formed in a proline-mediated enantioselective α sulfamidation of 2-phenylpropanal (**178**), reacts with nosyl azide in moderate yield via the triazoline **181** to give *N*-nosyl-2-amino-2-phenylpropanal (**179**) with 89% *ee* (Scheme 46).[226] Compound **182** and the aziridine **183** are presumed to be intermediates; the latter undergoes ring opening to **184** by participation of the proline nitrogen atom to form **179** after hydrolysis.

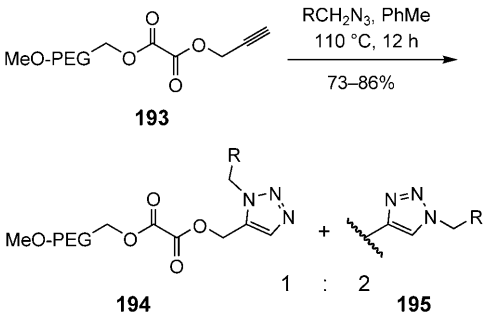
The assumed reaction mechanism is supported by work from Benati et al.[227] and Zhu et al.[228]

A series of α,β-unsaturated ketones **185** react with alkyl azides **186** under Lewis acid catalysis in a similar mechanism, as determined by Aubé and co-workers (Scheme 47).[229] Unlike the known rearrangements of this type,[230] the Lewis acid catalyzed variant takes place at low temperatures. The Δ^2-1,2,3-triazolines **187** are indeed first formed. However, they are not stable under the prevailing reaction conditions. It is a case of nonstabilized triazenes.[231] In the presence of Lewis acids, they open to amidodiazonium betaines **188**, which according to the structure of the addition product either rearrange with migration of the substituents (path b) or ring contraction occurs (path a). Endo- or exocyclic enaminones **190**/**192** are formed. Cyclohexenones usually form the (*Z*)-configured ring contraction product **192**. Cyclopentenones, in contrast, usually give aminocyclopentenones. Aziridines can also be formed.

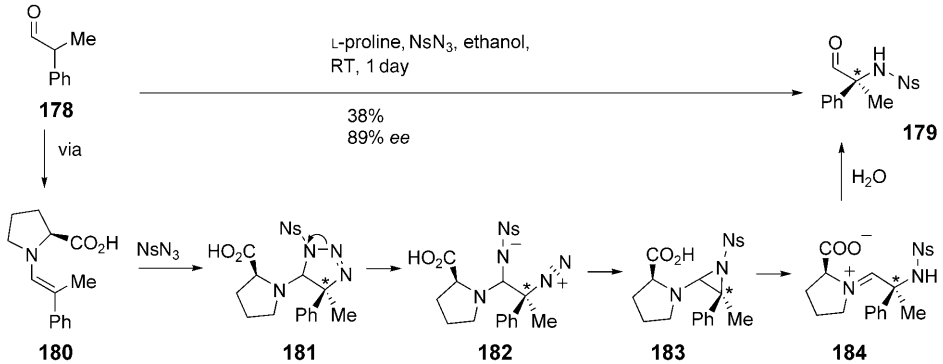


Scheme 47. Cycloaddition of alkyl azides to α,β-unsaturated ketones according to Aubé et al.[229]

Related to this reaction are the additions of arynes to azides, which lead to benzotriazoles, as Huisgen and co-workers were able to show quite early.[215,232,233] Trimethylsilylacetylene[234] and a number of strained or electronically activated alkynes react with organoazides at room temperature or below, whereas with many other alkynes the reaction must be carried out at elevated temperatures in the absence of catalysts. The cycloaddition of immobilized alkynes with organic azides has also been carried out on soluble polymers[235] (Scheme 48) and on polystyrene resins.[236,237] Furthermore, other solid-phase variants of this reaction with immobilized azide have been used for the preparation of



Scheme 48. Synthesis of 1,2,3-triazoles on a soluble polymer according to Norris et al.[235]



Scheme 46. Enantioselective α sulfamidation of 2-phenylpropanal (**178**) with tosyl azide.[226]

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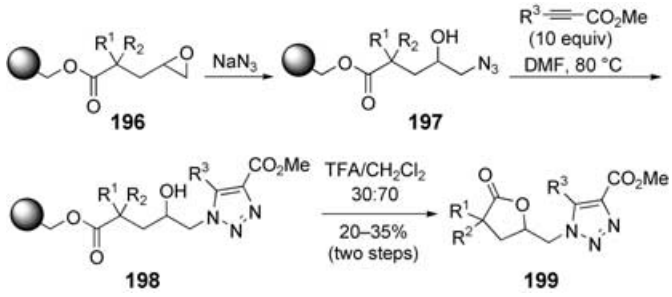
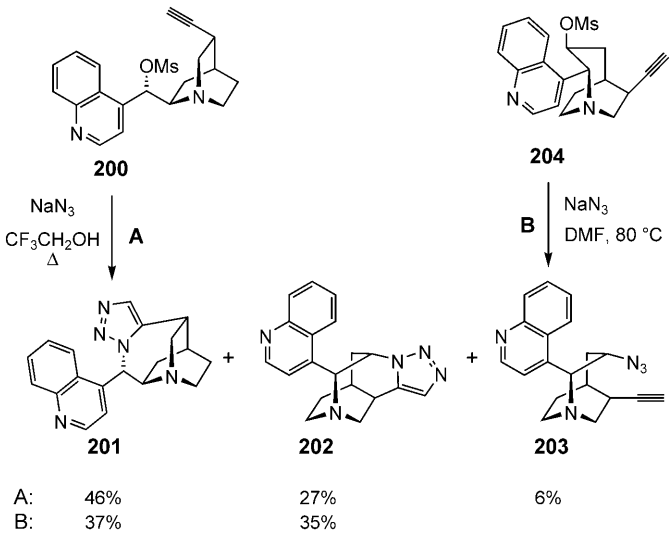
substituted 1,2,3-triazoles.[237,238] In the example shown in Scheme 49, the final product **199** is obtained by subsequent cleavage and cyclization.



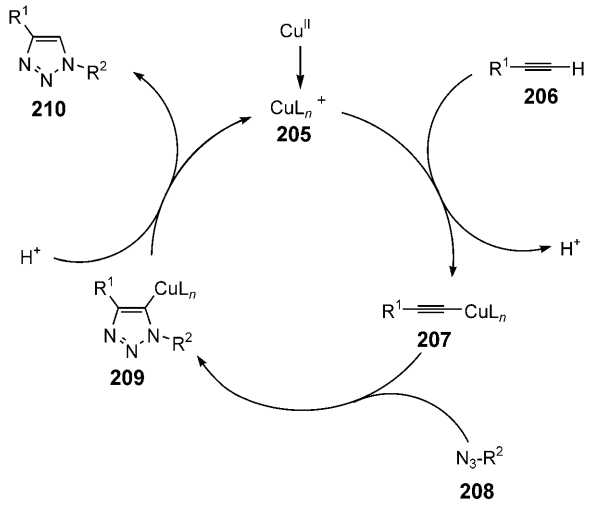
Scheme 49. Synthesis of 1,2,3-triazoles **199** on a polystyrene support according to David and co-workers.[237]

The intramolecular 1,3-dipolar cycloaddition[239] of cinchona azides to a C10–C11 alkyne and a C10–C11 alkene was demonstrated recently by Hoffmann and co-workers (Scheme 50).[240] Thus, *O*-mesylcinchonidine **200** and NaN_3 reacted to form the triazole **201** and the ring-expanded derivative **202**. Both triazoles **201** and **202** were formed with retention of configuration at C9 and C3. The 1-azabicyclo[3.2.2] rearrangement is clearly reversible.



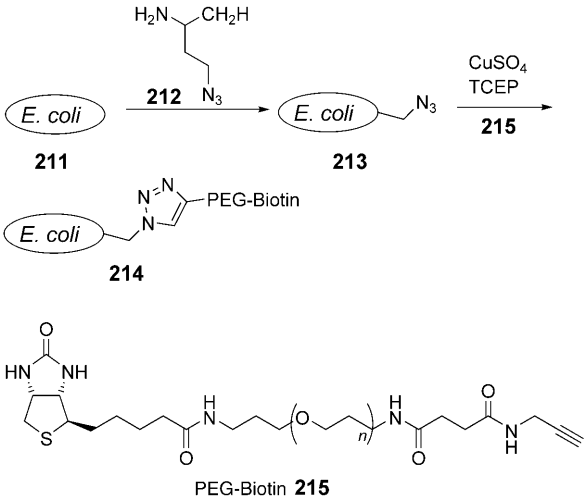
Scheme 50. Substitution, rearrangement, and cycloadditions to cinchona alkaloids according to Hoffmann and co-workers.[240] Ms = methanesulfonyl.

A breakthrough in triazole chemistry occurred with the independent observations by the groups of Meldal[241] and Sharpless[242] that the reaction of aliphatic azides **208** with terminal alkynes **206** is accelerated by copper ions, and their regioselectivity is improved (Scheme 51).[243–247] These reactions have been used frequently in recent years[248] and are also considered as a contribution to "click chemistry"[249]



Scheme 51. Possible catalytic cycle for the copper-catalyzed triazole synthesis.

because they take place under mild conditions and form complex structures. The special feature of this reaction is that it is biocompatible[250,251] and takes place particularly well in aqueous media. They can also be carried out very efficiently in organic solvents in the presence of a copper complex with appropriate ligands.[247] The sensitivity of the reaction towards copper catalysts is so high that even copper wire is sufficient to maintain the corresponding copper ion concentration. Thus it was possible, for example, to label the surface of *Escherichia coli* cells. Azidohomoalanine (**212**) was incorporated metabolically into the outer membrane protein C (OmpC), one of the most common membrane porines of *Escherichia coli*. Selective modification of the azide functionality was possible by copper-mediated [3+2] azide–alkyne cycloaddition with an alkyne **215** that carries a biotin marker (Scheme 52). The specificity of this reaction was demonstrated by Western blotting and continuous-flow cytometry.[252]



Scheme 52. Labeling of bacteria by cycloadditions.[252] TCEP = tris(2-carboxyethyl)phosphane.

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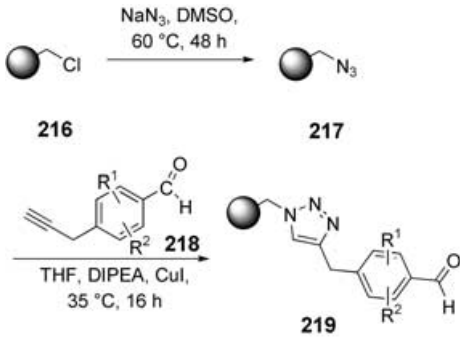
A copper-catalyzed 1,3-dipolar cycloaddition with an alkyl azide **217** in the solid phase that was synthesized starting with Merrifield resin was reported recently by Gmeiner and co-workers.[253] Based on this concept, aldehydes **218** can be immobilized to generate amides in subsequent steps (Scheme 53).



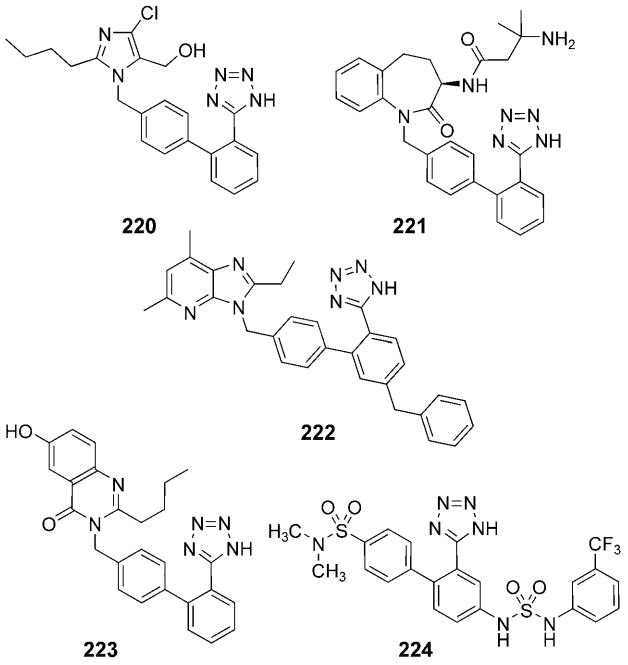
Scheme 53. Synthesis of a new family of SPOS resins by 1,3-dipolar cycloaddition through a click linker.[253] SPOS = solid-phase organic synthesis, DIPEA = diisopropylethylamine.

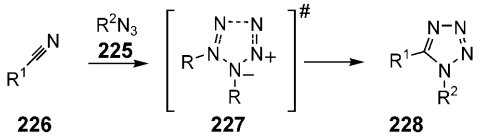
A new three-component reaction of azides, alkynes, and allyl carbonates leads to 2-allyl-1,2,3-triazoles.[254] A more recent and preparatively interesting preparation of 1,2,3-triazoles takes place through the less stable allenyl azides **586** formed from propargyl azides **585** in a [3,3] sigmatropic shift of the azide group (see Section 4.8, Scheme 144).[255]

4.1.2. *Tetrazoles*

Because of their stability towards acids and bases and oxidative and reducing conditions[256] tetrazoles are interesting building blocks and target structures in organic synthesis.[257] They are lipophilic, metabolically stable compounds,[257] carboxylic acid bioisosteres[258] and *cis*-amide isosteres in peptide chemistry,[259] and are used frequently in different pharmaceuticals such as losartan[260] and in materials science.[261] Suitably substituted biphenyltetrazoles, in particular, are potent and selective ligands for different proteins such as G protein-coupled receptors, enzymes, and ion channels. Besides their well-known antihypertensive property in pharmaceuticals such as losartan (**220**),[260] biphenyltetrazoles stimulate the release of growth hormones (e.g. **221**).[262] Furthermore, they inhibit metalloproteases (e.g. **222**, **223**)[263,264] and are chloride-channel effectors (e.g. **224**).[265]

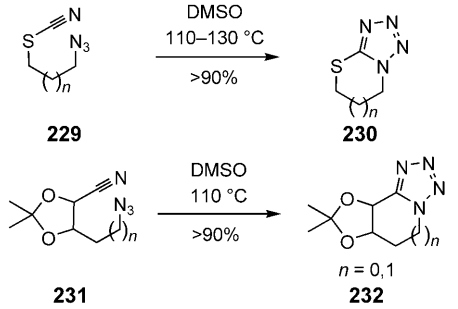
Tetrazoles **227** can be synthesized directly by a [3+2] dipolar cycloaddition between an organoazide **225** and a nitrile **226** (Scheme 54).[266] This reaction occurs through a concerted[266] and regioselective[267] [3+2] cycloaddition between an organic azide and an organic nitrile with formation of the 1,5-disubstituted product.[268] However, it only takes place sufficiently rapidly if electron-withdrawing groups are present on the nitrile,[269] or the reaction is intramolecular.[268,270] Polycyclic tetrazoles are formed in very good yields. This reaction could be improved further by the introduction of further heteroatoms such as oxygen, nitrogen, and sulfur at the nitrile terminal (thiocyanate,





Scheme 54. [3+2] Cycloaddition of nitriles **226** and organoazides **225** to give tetrazoles **228**.[266]

cyanate) (Scheme 55).[271] The spectrum of suitable azidonitriles for these intramolecular [3+2] cycloadditions is considerable, the second ring thus formed can be unsaturated or



Scheme 55. Intramolecular synthesis of tetrazoles.[271,273]

contain heteroatoms. If the necessary reaction temperature is taken as a measure of the reactivity, cyanates are more reactive in zinc-catalyzed reactions than simple nitriles. In the absence of the catalyst, however, this reactivity is reversed.[272]

If azide ions or hydrogen cyanide are used as dipoles, 1*H*-tetrazoles are formed in high yields,[274] as demonstrated by Hantzsch and Vagt more than 100 years ago.[275] The addition

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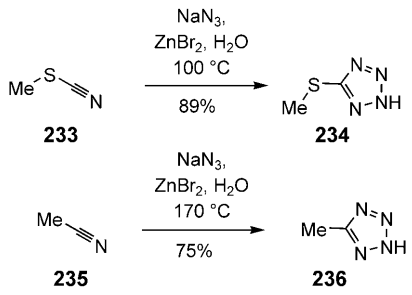
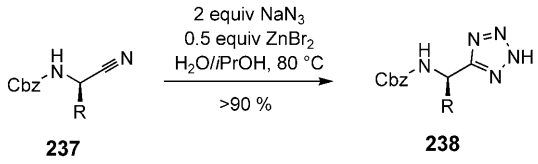
of azide ions to nitriles is accelerated by microwaves[276] or by catalysis with zinc salts (Scheme 56).[277,278] This latter discovery was used for the synthesis of, among others, chiral, enantiomerically pure tetrazoles **238** under relatively mild conditions (Scheme 57).[279]

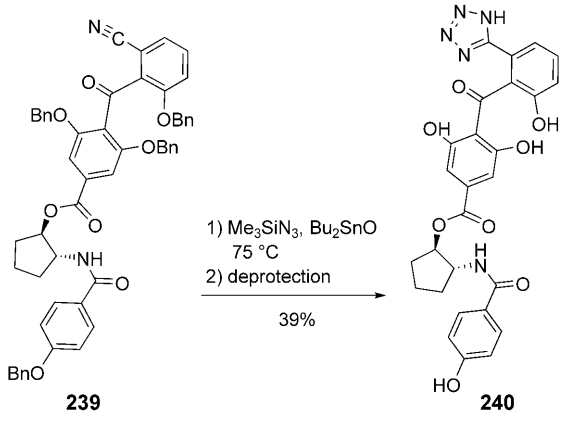


Scheme 56. [3+2] Cycloaddition of thiocyanates **233** and nitriles **235** with azide ions.[278]



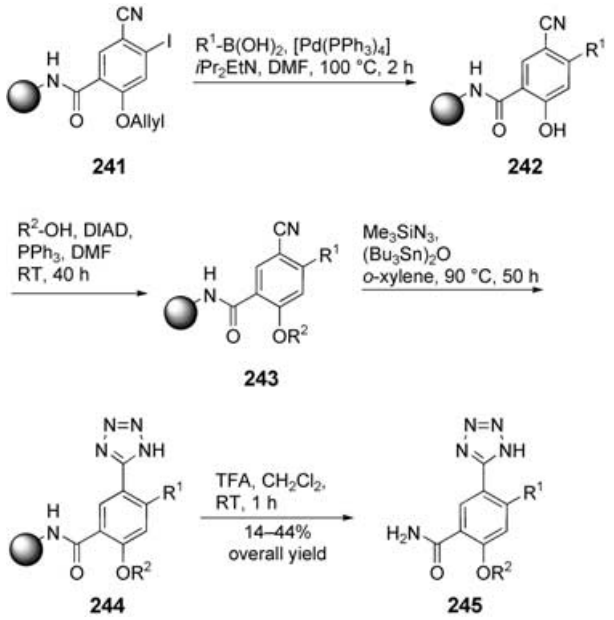
Scheme 57. Synthesis of tetrazoles **238** according to Sharpless et al.[279]

Trimethysilyl azide (in the presence of catalytic amounts of tin oxides,[280a,b] or tetrabutylammonium fluoride)[280c] and trialkyl stannyl azides[258] can act as surrogates for azide ions. They are not only more soluble in organic solvents but are probably less toxic. The tetrazoles obtained may be readily deprotected. The synthesis of the balanol analogue **240**, which has a high affinity for protein kinases A and C, is shown as an example (Scheme 58).[281]



Scheme 58. Synthesis of tetrazoles **240** according to Lampe et al.[281]

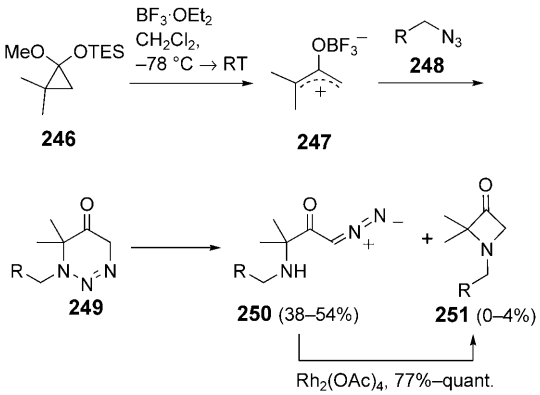
A solid-phase synthesis of biphenyltetrazoles was described recently.[282a] The formation of the tetrazole ring from polymer-bound nitriles **243** (which were prepared in two stages on the support from the iodides **241**) was achieved with Me_3SiN_3 and catalytic amounts of n-Bu_2SnO within 50 h at 90 °C in o-xylene and gave the solid-phase-bound biphenyltetrazoles **244**. Cleavage from the support with TFA/CH_2Cl_2 gave the tetrazoles **245** in good purity (Scheme 59).



Scheme 59. Synthesis of tetrazoles **245** on a polystyrene support according to Kivrakidou et al.[282] DIAD = azodicarboxylic acid diisopropyl ester.

4.1.3. Reactions of Organoazides with Other Dipolarophiles

Other π systems such as allyl cations also react with organoazides, as demonstrated by the Lewis acid induced intramolecular reaction of hydroxyazidoalkenes.[283] Thus far, however, this reaction has found little use in the synthesis of dihydrotriazines. One interesting application is the cycloaddition of aliphatic azides **248** to 2-oxyallyl systems **247** that were prepared from cyclopropanone derivatives **246** (Scheme 60).[284] The regioselective dihydrotriazines **249** formed initially fragment to give α-diazoketones **250**. The



Scheme 60. Synthesis of α-diazoketones according to Desai and Aubé.[284] TES = triethylsilyl.

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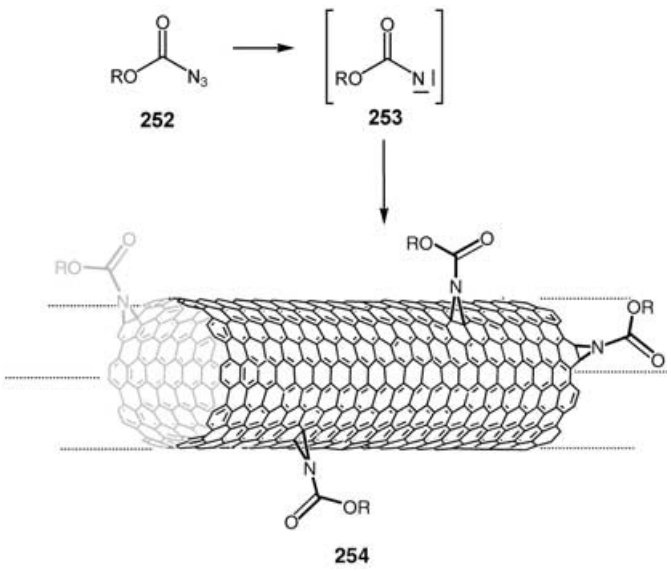
latter can be transformed into the azetidinones **251**, which otherwise only occur as by-products, in very good yields with catalytic amounts of rhodium acetate.

4.2. Nitrene Chemistry

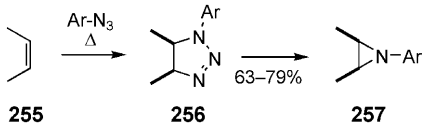
The chemistry of aryl azides (and the postulate by Tiemann[285] of nitrenes during the decomposition of azides) has a long history that stretches back to the 19th century. However, targeted photochemical rearrangements with aryl nitrenes is a relatively new area of research. Both the complexity of the possible products and the diverse applications makes this area of research of special interest. In general, nitrenes are formed either thermally or photochemically.[27d,286,287] Nitrenes are related to carbenes but have different properties.[28] A difference is drawn between singlet and triplet nitrenes, and it has been possible to detect the latter by matrix isolation experiments.[288,289] The reactions of nitrenes stretch from cycloaddition, to rearrangements, to insertion reactions. Reference is made here to the cited review articles[1] and monographs[7] for an exhaustive treatment of the very broad spectrum.

4.2.1. Intermolecular Cycloadditions of Nitrenes

The intermolecular cycloaddition of thermochemically or photolytically generated nitrenes to alkenes gives aziridines. This reaction is stereospecific as long as it occurs through singlet nitrene and can be catalyzed by metal ions. In this context, enantioselective variants have been developed which use the photolysis of aryl sulfonyl azides in the presence of copper ions.[290] Whereas acylnitrenes react in a secondary reaction to form isocyanates through a Curtius rearrangement (Section 4.5.1),[291] ethyl azidoformate usually gives the corresponding aziridines in good yields.[222] This reaction can also be used, for example, for the functionalization of carbon nanotubes (Scheme 61)[292,293]



Scheme 61. Functionalization of carbon nanotubes according to Holzinger et al.[293]



Scheme 62. Intermolecular synthesis of aziridines **257** via Δ^2-1,2,3-triazolines **256**.[295]

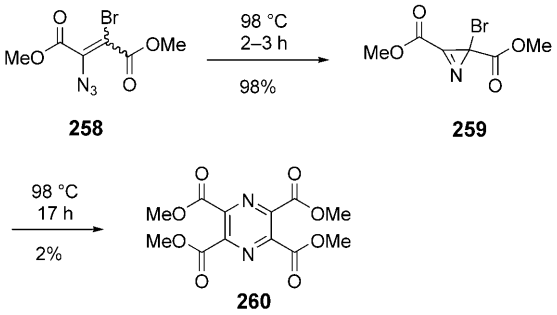
However, the cycloaddition of organoazides to alkenes is not necessarily a direct nitrene addition, as Δ^2-1,2,3-triazolines **256** can be formed which then react in a further step to aziridines **257** (Scheme 62). Both (strained) alkyl-substituted alkenes and electron-deficient or -rich alkenes such as fullerenes[294] can act as dipolarophiles.[295]

4.2.2. Intramolecular Cycloadditions of Nitrenes

4.2.2.1. Intramolecular Cycloadditions of Alkenyl Nitrenes

The (reversible) transformation of alkenyl nitrenes, which are formed by thermal or photolytic decomposition of alkenyl azides into the corresponding 2*H*-azirines,[62c,296] is a very frequently used reaction.[62,64] Recently, further reaction of the photolabile azirines has been suppressed by the use of microwaves[297] or brief heating at 150 °C in closed vessels.[70] The preparation of 2-halo-2*H*-azirines **53** was carried out with the method of Pinho e Melo et al. by heating haloazidoalkenes **52** to 100 °C (Scheme 14).[72] According to Hassner et al., 2*H*-azirines are formed from 3-monoalkylalkenylazides under thermolysis conditions.[298] The 2*H*-azirines formed react further, sometimes rapidly, with the formation of, for example, indoles (Scheme 76). Frequently found by-products are the corresponding nitriles (Scheme 93, Scheme 95)[299] or occasionally isonitriles.[300] 2-Halo-2*H*-azirines **259** with electron-withdrawing groups at C3 decompose after a few days at room temperature. Heating to ≈100 °C leads to the formation of small amounts of substituted pyrazines **260** (Scheme 63).

Recently, activated 2*H*-azirines **263** with electron-withdrawing substituents have proved to be particularly good dienophiles in *endo*-selective Diels–Alder reactions with electron-rich dienes. This was demonstrated recently in



Scheme 63. Synthesis and decomposition of 2-halo-2*H*-azirines.[72]

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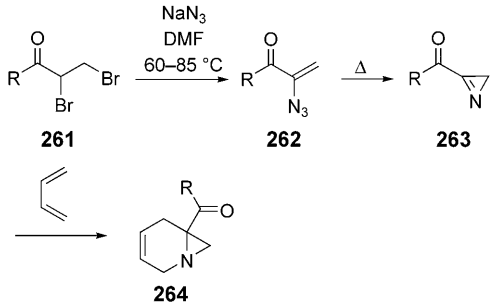
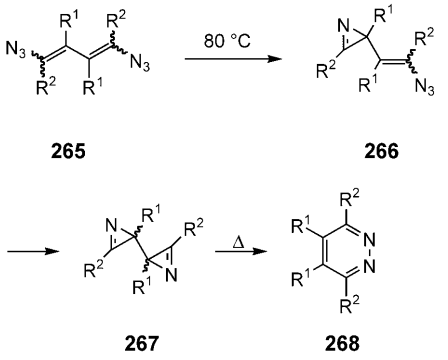
particular by Gilchrist and co-workers[301] and by Somfai and Timen[302] in the synthesis of bridged aziridines **264** (Scheme 64). The use of chiral 2*H*-azirines, chiral dienophiles, or chiral Lewis acids allows the asymmetric synthesis of such ring systems.



Scheme 64. Synthesis and Diels–Alder reactions of 2*H*-azirines.[301,302]

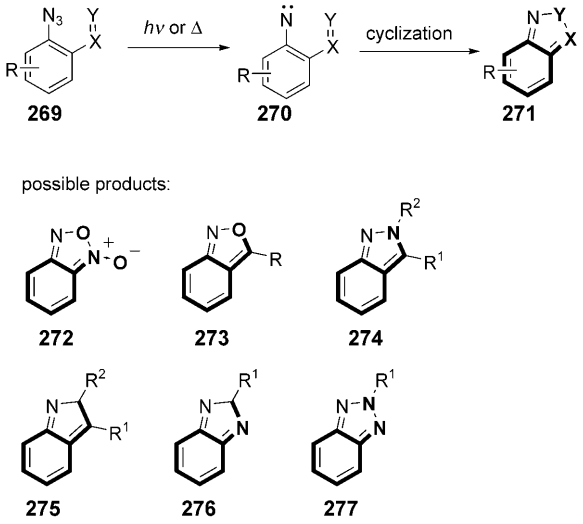
Interesting biazirinyls **267** were synthesized from 1,4-diazido-1,3-dienes **265** via 2-alkenyl-2*H*-azirines **266** intermediates (see Scheme 15). The pyridazines **268** are formed as by-products into which the biazirinyls **267** can also be converted upon heating for longer periods of time (Scheme 65).[73]



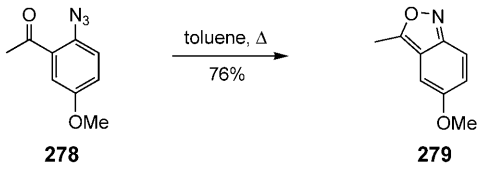
Scheme 65. Synthesis of biazirinyls.[73]

4.2.2.2. *Intramolecular Cycloadditions of Alkyl, Acyl, and Aryl Nitrenes to C=X Double Bonds*

Aryl azides with a suitable double bond in the *ortho* position decompose photochemically or thermally to form the corresponding heterocycle with loss of dinitrogen. Indazoles **274**,[303,304] benzofuroxanes **272**,[305,306] benzisoxazoles **273**,[307–311] and other heterocycles (Schemes 66 and 67) are formed amongst others. This reaction sequence was demonstrated nearly 100 years ago.[309] An electrocyclic mechanism is assumed[306b,308] in which, in a few cases, subsequent aromatization occurs through an H or alkyl shift. This applies especially to the 2*H*-indoles and 2*H*-benzimidazoles. As this latter reaction represents a formal insertion into a C–H bond, it is discussed in more detail in Section 4.2.3.1.



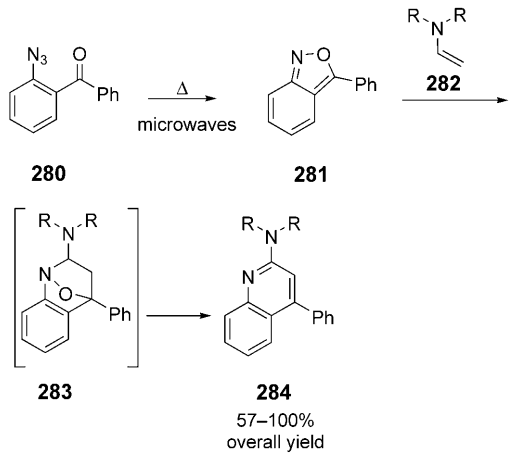
Scheme 66. Cyclization of substituted aryl azides.



Scheme 67. Thermal cyclization of *ortho*-acylaryl azides.[310]

These cycloaddition-derived heterocycles can in turn also react as reactive intermediates with further substrates, as shown in the microwave-induced synthesis of 2-aminoquinolines **284**.[312] In this synthesis, 3-aryl benzo[*c*]isoxazoles **281** react with enamines **282** to form the tricycles **283**, which then lose water. The quinolines **284** formed were isolated in good yields and with high purity after solid-phase extraction (Scheme 68).

One application, the synthesis of benzofuroxanes **286**, could be demonstrated with *ortho*-nitro resins **285**. The azides formed after displacement cyclize at approximately 70 °C to



Scheme 68. Synthesis of aminoquinolines **284** by cycloaddition of intermediate benzoisoxazoles **281**.[312]

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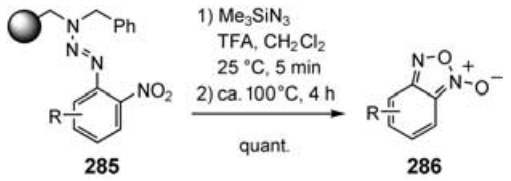
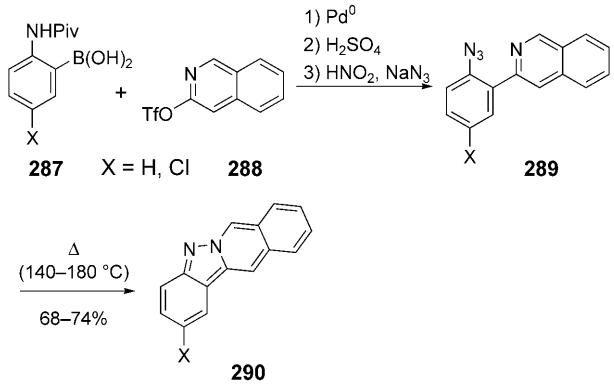
give the benzofuroxanes **286** (Scheme 69).[45a] Benzofuroxanes are biologically active compounds with considerable synthetic potential.[313] Complex heterocyclic structures can also be prepared in this way, as shown by the synthesis of indazolo[2,3-b]isoquinolines **290** (Scheme 70).[314]



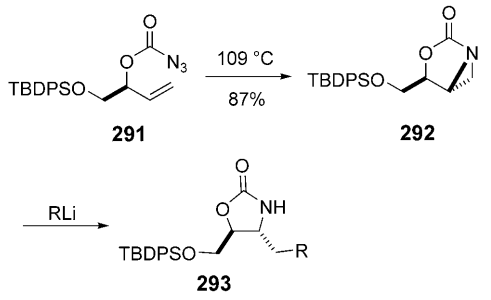
Scheme 69. Preparation of benzofuroxans **286** according to Bräse et al.[45a]



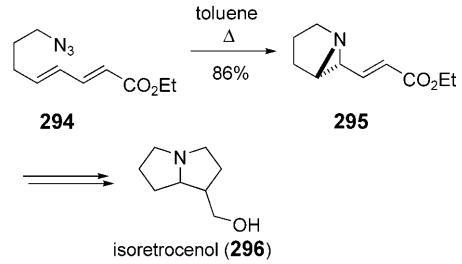
Scheme 70. Synthesis of indazolo[2,3-*b*]isoquinolines **290** according to Hajós and co-workers.[314] Piv = pivaloyl.

4.2.2.3. *Intramolecular Cycloaddition of Nitrenes to C=X Double Bonds*

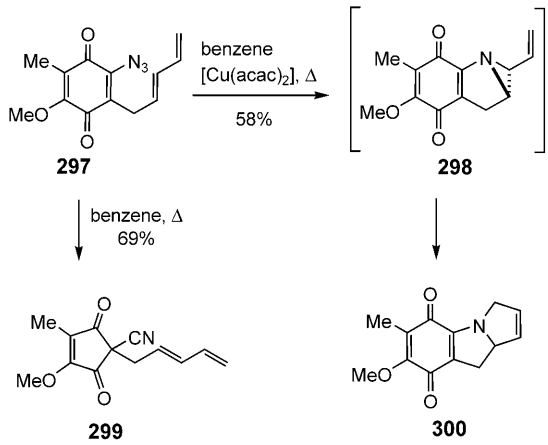
In the presence of a double bond in the nitrene precursor, which allows the formation of a relatively unstrained bicyclic system, intramolecular cycloaddition occurs with the formation of aziridine systems. This is particularly the case with the azabicyclo[3.1.0]hexane systems **292**, which can be opened regioselectively by nucleophiles (Scheme 71).[315] This reaction finds further application in the synthesis of pyrrolizidines, which can then react further to give isoretrocenol (**296**) as described by Hudlicky et al. (Scheme 72).[316] This formal nitrene–diene cycloaddition can also be carried out directly, as demonstrated in the synthesis of the tricyclic system **300** (Scheme 73).[317] In the absence of copper ions, the quinoyl nitrene rearranges to form a nitrilocyclopentenedione **299** (see also Scheme 95).



Scheme 71. Intramolecular aziridines synthesis and subsequent nucleophilic ring opening.[315] TBDPS = *tert*-butyldiphenylsilyl.



Scheme 72. Synthetic pathway for the preparation of isoretrocenol (**296**).[316]



Scheme 73. Intramolecular [4+1] cycloaddition.[317] acac = acetylacetonate.

An application of intramolecular cycloadditions of nitrenes to alkenes was demonstrated by the total synthesis of the natural product (−)-virantmycin (**308**), which was first isolated in 1981 by Ōmura and co-workers in the fermentation broth of the bacterial culture *Streptomyces nitrosporeus*, strain AM-2722.[318] This tetrahydroquinoline derivative is characterized by extremely high antiviral action against a series of different RNA and DNA viruses, although its antifungal activity is much weaker. In the 11-step total synthesis optimized by Morimoto et al.,[319c,d] the aryl azide **304** was obtained from ethyl 3-allyl-4-aminobenzoate (**301**) in a stereoselective *trans* olefination by reaction with the Still–Gennari phosphonate **303** (Scheme 74). Subsequent stereospecific photochemical nitrene addition gave the tricyclic aziridine derivative **305**, which was transformed into the methyl benzoate derivative **306** by reduction of the ester group and subsequent chemoselective oxidation to the benzaldehyde derivative. In subsequent synthetic steps, the primary alcohol **306** was converted into the corresponding methyl ether **307**. This aziridine derivative **307** was trans-

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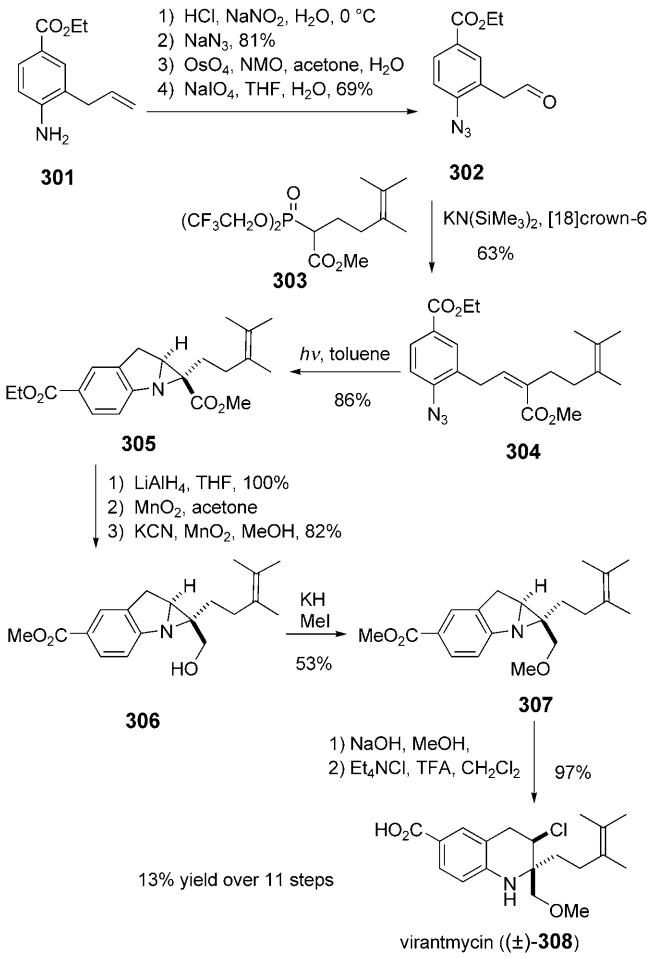


Scheme 74. Total synthesis of (±)-virantmycin (**308**) according to Morimoto et al.[319] NMO = *N*-methylmorpholine-*N*-oxide.

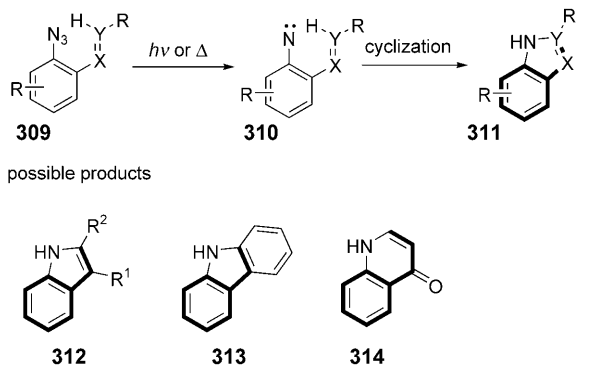
formed regioselectively and stereoselectively into (±)-virantmycin (**308**) under basic conditions. The overall yield in this total synthesis was 13% over 11 steps.

4.2.3. Insertion into C–H Bonds

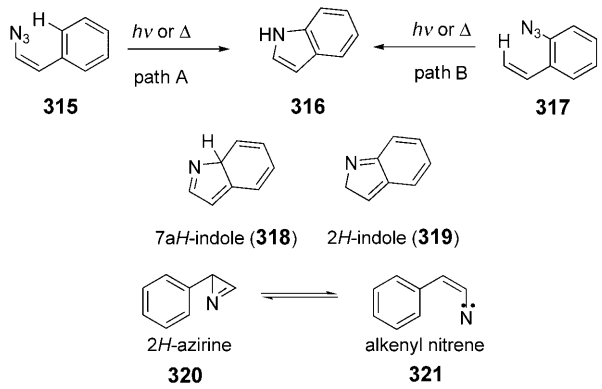
4.2.3.1. Insertion into C(sp^2)–H Bonds

The cycloadditions of nitrenes described earlier are related to insertion reactions. In particular, the formal insertion into C(sp^2)–H bonds is a frequently used reaction, which in part also follows the cycloaddition principle (Section 4.2.2.2). Thus indoles **312**,[303] carbazoles **313**,[268] and other heterocycles can be formed (Scheme 75). Early mechanistic investigations showed that the nitrogen atom in the product originates from the probable nitrene precursor.[320]

Indoles in particular are readily accessible by this reaction, and two strategies are conceivable. Either the cyclization of (*Z*)-2-aryl alkenyl nitrenes (path A) (Scheme 76) or the cyclization of 2-alkenyl aryl nitrenes (path B) can be used. 7a*H*-Indoles (path A) or 2*H*-indoles (path B) may be formulated as reactive intermediates. Viewed mechanistically, the cyclization of (*Z*)-2-aryl alkenyl nitrenes (path A) presumably involves prior intramolecular 2*H*-azirine formation, which follows reversible alkenyl



Scheme 75. Cyclization possibilities of substituted aryl azides: insertion reactions.



Scheme 76. Syntheses of indoles from organoazides.

nitrene formation and determines the necessary stereochemistry. The required azidocinnamic esters are readily formed by condensation of azidoacetic esters and aryl aldehydes (Scheme 12). This reaction, named after Isomura, Hemetsberger, and Rees,[321–323] is one of the most important indole syntheses[324,325] and was used with success in a number of natural products syntheses such as murrayquinone,[326] discorhabdin C, makaluvamine D,[327] and varioline (**45**)[65] (Scheme 12). Furthermore, this reaction is used in the synthesis of phosphodiesterase inhibitors PDE-1 (**328**) and PDE-2 (**327**), which are related to the antibiotic CC-1065 (Scheme 77).[328] The choice of the correct solvent, which also influences the thermolysis temperature, is pivotal for success. 2*H*-Azirines can otherwise occur as by-products. Dimerization can also give pyrazines.[329] The Hemetsberger reaction can also be used for the synthesis of pyrroles from αβ-unsaturated aldehydes.[330] If another accessible double bond is present in the molecule, a competitive addition to this double bond can occur which can even be the main reaction. This was used by Moody and co-workers in their total synthesis of lennoxamine (**331**) (Scheme 78).[349]

Ortho-alkenyl aryl azides also rearrange to indoles upon heating. This reaction, known as the Sundberg cyclization,[331,332] takes place by direct attack at the β-carbon atom and not after insertion into the C–H bond.[332] This reaction was recently applied to the synthesis of complex indoles

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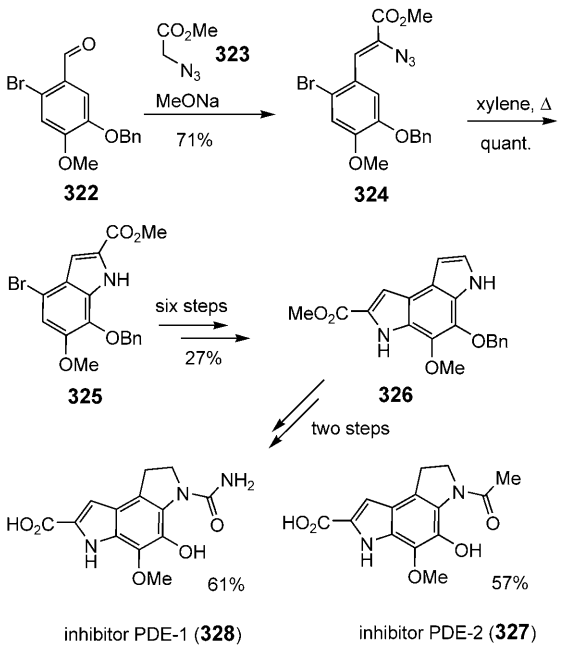
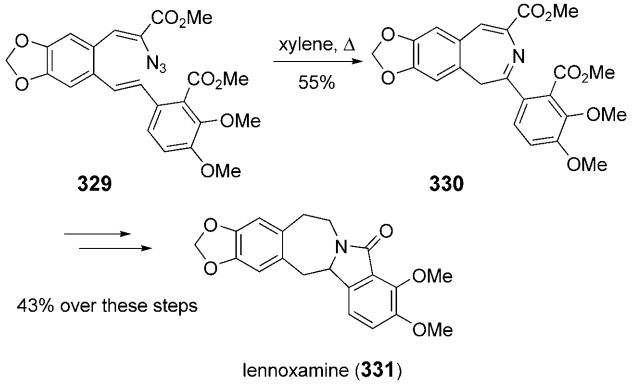


Scheme 77. Synthesis and conversion of the alkenyl azide **324** into indoles **327** and **328**.[328]



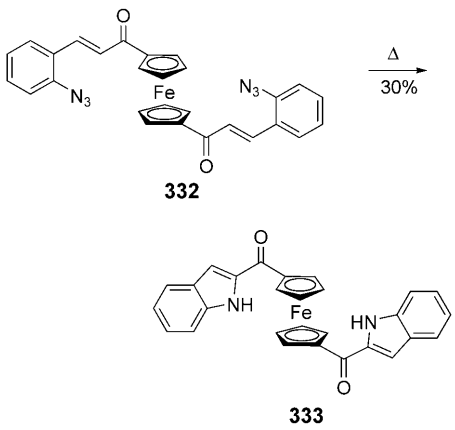
Scheme 78. Synthesis of lennoxamine (**331**) according to Moody et al.[349]

(Scheme 79).[333–335] As an alternative to thermolysis or photolysis this cyclization can also be carried out by protonation or by the action of Lewis acids with the formation of electrophilic nitrenium ions (see also Section 4.6.3).[336]

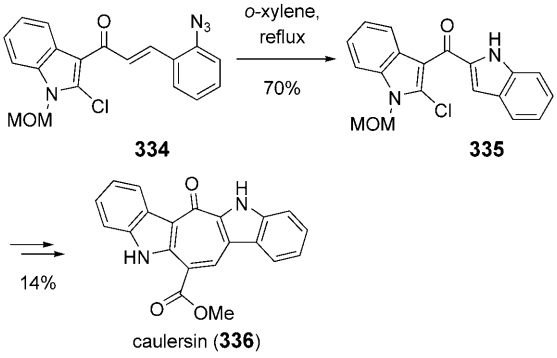
The first synthesis of the marine bisindole alkaloid caulersin (**336**) in seven steps was reported by Molina and co-workers in 1999 (Scheme 80).[337] The key step is the conversion of the azide **334** into the bisindole ketone **335** upon heating.

Other recent natural products syntheses that use this reaction pathway have been published, for example, those of the indole alkaloid meridianine from the fungus *Aplidium meridianum*,[338] novel indolecarboxylic acids related to the plant hormone indolylacetic acid,[325] and (±)-*cis*- and (±)-*trans*-trikentrin A.[339]

2-Biaryl azides decompose photochemically or thermally to carbazoles. The photolysis of azidobiaryls such as **337** with

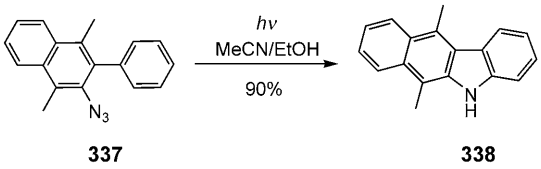


Scheme 79. Synthesis of bisindolylferrocene **333**.[333]



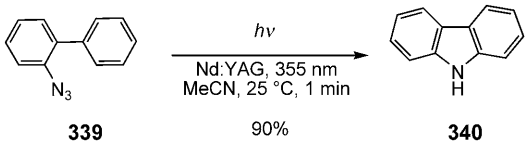
Scheme 80. Total synthesis of the marine bisindole alkaloid caulersin (**336**) according Molina et al.[337] MOM = methoxymethyl.

conventional UV lamps has been known for some time in the synthesis of carbazoles such as **338**, but this reaction has been carried out with only a few examples of substituted compounds and yields different by-products, such as the corresponding azo compounds (Scheme 81).[28,340] The use of laser



Scheme 81. Synthesis of carbazoles **338** by photolysis.[340]

light not only significantly accelerates the reaction, but also improves the selectivity of this preparatively important and extensively investigated process (Scheme 82). A further



Scheme 82. Laser-induced preparation of carbazoles **340** according to Bremus-Köbberling et al.[341]

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improvement is its execution in miniaturized photoreactors (Figure 3) which gave a greater turnover of photolysis products.[341]

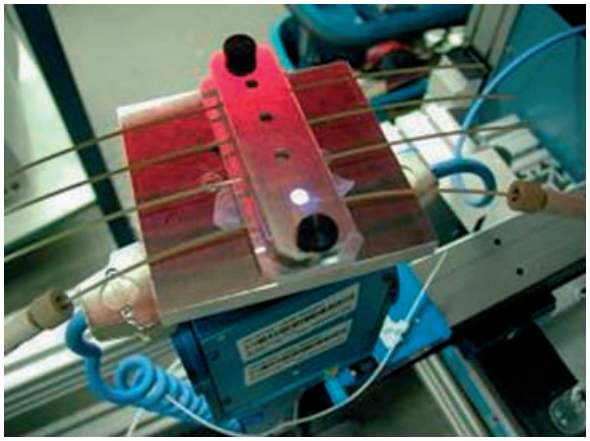
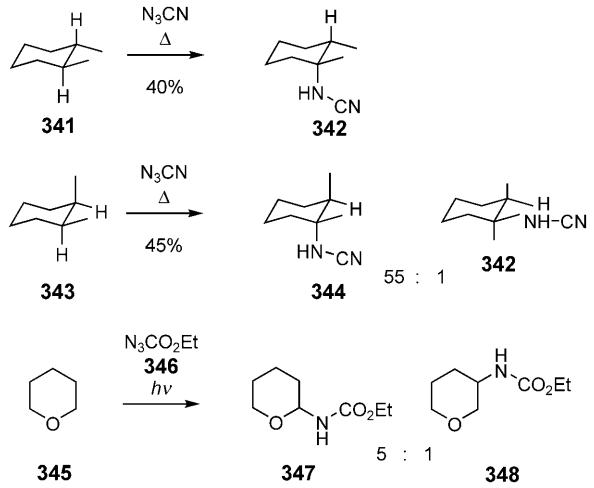


Figure 3. A miniphotoreactor for the photolysis of aryl azides. Picture reprinted with kind permission from the Fraunhofer-ILT, Aachen (Germany).[341]

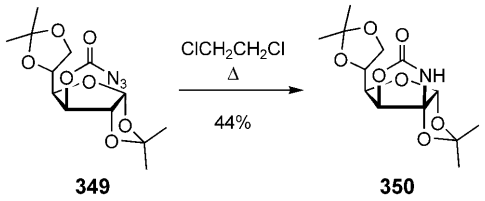
4.2.3.2. *Insertion into sp^3 C–H Bonds*

Nitrenes also undergo insertion into sp^3 C–H bonds. The selectivity of the insertion decreases from tertiary and finally to secondary to primary species. Thus statistically corrected reactivities of 25:10:1 were determined for the insertion of ethoxycarbonyl nitrene into the C–H bonds of 2-methylbutane.[342] This reaction can be both intramolecular[343] and intermolecular. These insertions usually take place with retention of configuration and regioselectively α to the oxygen atoms (Scheme 83).[345] In a few cases suitable metal catalysts have been found, although metal–nitrene complexes are not necessarily formed because these species undergo intermolecular reactions to form azoarenes.[344] An example of an intramolecular insertion of an acyl azide is the functionalization of furanose derivatives **349**

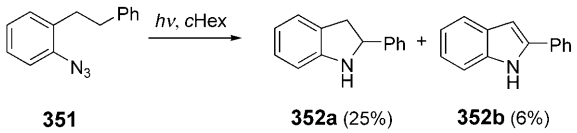


Scheme 83. Stereoselective and regioselective azide addition.[345]

(Scheme 84).[346] The newly formed rings are mostly five- or six-membered, of which the smaller rings are formed more readily. In 1995 Tomioka and co-workers synthesized 2-phenylindoline (**352a**) in this way (Scheme 85).[347] The

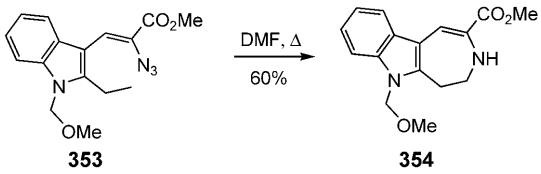


Scheme 84. Functionalization of furanose derivates.[346]



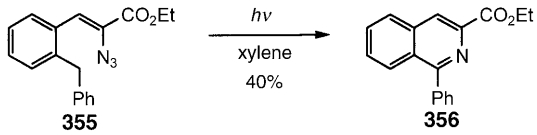
Scheme 85. Synthesis of 2-phenylindoline (**352a**) according to Tomioka et al.[347] *c*Hex = cyclohexane.

thermal decomposition of azidoacrylates **353** in refluxing DMF produces the pharmacologically important azepino[4,5-*b*]indoles **354** (Scheme 86).[348] The synthesis of isoquinolines



Scheme 86. Synthesis of azepino-[4,5-*b*]indole **354** according to Moody et al.[348]

by insertion into sp^3 C–H bonds has also been extensively investigated by Moody and co-workers.[349] In this case, the nitrene inserts into the benzhydrylic C–H bond, and the isoquinoline **356** is formed after aromatization (Scheme 87)[350]. In the case of *ortho* substituents (methyl or similar), a hydrogen atom is extracted and an imidoquinone methide is formed.[287,350]



Scheme 87. Synthesis of isoquinoline **356** according to Moody et al.[350]

4.2.4. *Addition of Nitrenes to Heteroatoms*

Nitrenes that are formed from azides react with electron-rich heteroatoms (nitrogen,[27c,351,352] sulfur, phosphorus) to form the corresponding ylides. The reaction of phosphorus compounds to form aza ylides is discussed in Section 4.3.

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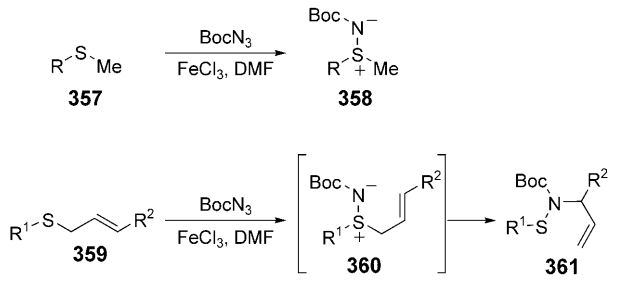
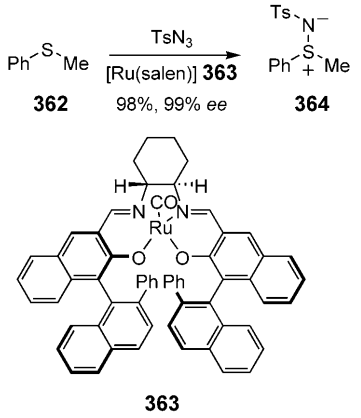
Different organoazides can be converted into sulfur ylides **358** by reaction with sulfides **357**. Bach and co-workers reported an iron-catalyzed reaction of Boc azide with organic methyl sulfides (Scheme 88).[353] These authors also showed that allyl thioethers **359** undergo a [2,3] sigmatropic shift to give α-branched allylamines **361**.[354] This reaction was extended by Van Vranken and co-workers to propargyl thioethers, which form *N*-allenylsulfenimides.[355]



Scheme 88. Azide additions according to Bach and Körber.[353,354]

A ruthenium–salen-catalyzed, highly enantioselective variant of this reaction of alkyl aryl sulfides with arylsulfonyl azides and alkoxycarbonyl azides was reported recently by Katsuki and co-workers (Scheme 89).[356] The electron-deficient and sterically demanding reagent $Cl_3C(tBu)_2COCON_3$ proved to be especially useful in the case of alkoxycarbonyl azides, which produce somewhat more readily deprotected alkoxycarbonyl aziridines. This asymmetric synthesis can be carried out with allyl sulfides in the synthesis of chiral allylamines.[357]



Scheme 89. Synthesis of enantiomerically pure sulfur ylides.[356]

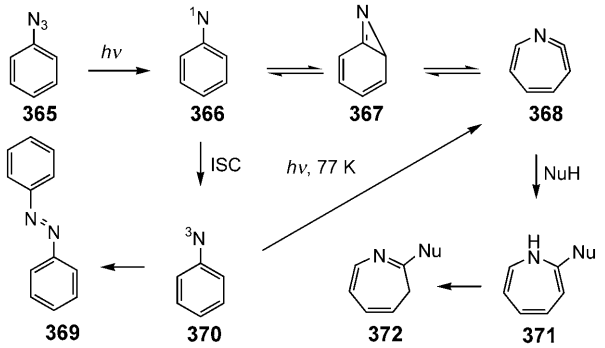
4.2.5. *Rearrangement of Nitrenes*

4.2.5.1. *Rearrangement of Acyl Nitrenes and Alkyl Nitrenes*

The rearrangement of acyl azide to isocyanates through the corresponding nitrene is well known as the Curtius rearrangement (see Section 4.5.1), whereas the general rearrangement of alkyl nitrenes is usually known as the Schmidt rearrangement (see Section 4.5.2). In the case of methyl azide (**6**) photolysis leads to methanimine, which is formed by simultaneous cleavage of dinitrogen and a 1,2-H shift.[15]

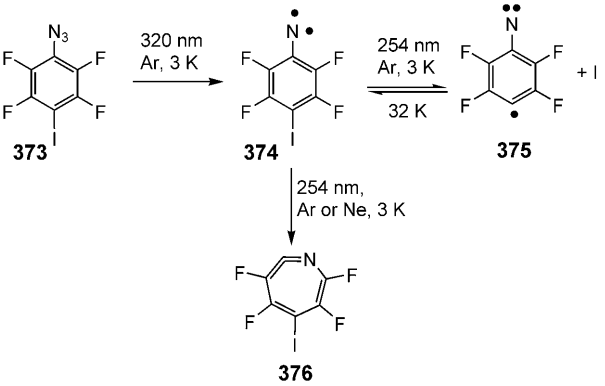
4.2.5.2. *Rearrangement of Aryl Nitrenes*

The rearrangement of aryl nitrenes by the photolysis of aryl azides leads to a broad spectrum of possible products.[358–363] As the large number of published examples would extend beyond the scope of this article, this section will be restricted to current examples. The work of Platz and co-workers in particular has helped greatly to explain the complex mechanism. In-depth analysis of reaction mixtures with matrix-isolation spectroscopy, laser flash photolysis (LFP), and modern molecular-orbital theory (MO) have all contributed to this understanding. In the photolysis of phenyl azide, various reactive intermediates are formed, of which the singlet phenyl nitrene **366** is the key molecule (Scheme 90). Intersystem crossing next gives the triplet nitrene **370**, which dimerizes to **369**. A special feature is the ring expansion of the benzazirine **367** to form the highly strained azepine derivative **368** and its subsequent products.[364] In a few cases, ring contraction to form cyanocyclopentadienes is observed.



Scheme 90. Rearrangement of aryl nitrenes.[364]

An application example was provided by Wenk and Sander in 2002 with the synthesis of 2,3,5,6-tetrafluorophenylnitren-4-yl (**375**). The intermediate **374** can also undergo iodine transfer to give dehydro-2,3,5,6-tetrafluoro-4-iodo-1*H*-azepine (**376**; Scheme 91).[365] Aryl azides with bulky *ortho* substituents react somewhat slower; the resulting benzazirines are stable for a few nanoseconds and can be detected spectroscopically (Scheme 92).[366]



Scheme 91. Synthesis of **375** according to Wenk und Sander.[365]

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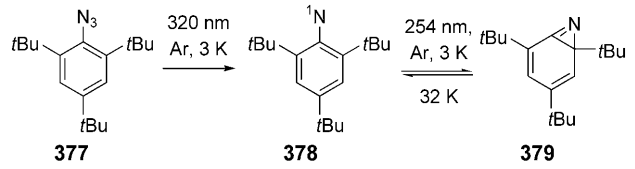
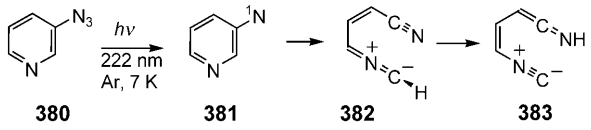
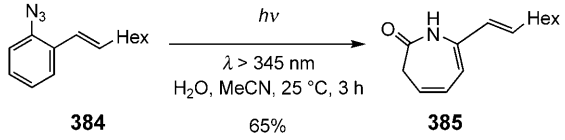


Scheme 92. Synthesis of stabilized benzazirines according to Platz et al.[366]



Scheme 93. Rearrangement of pyridylnitrenes **381**.[372]



Scheme 94. Synthesis of azepinones **385** according to Knepper and Bräse.[373a]

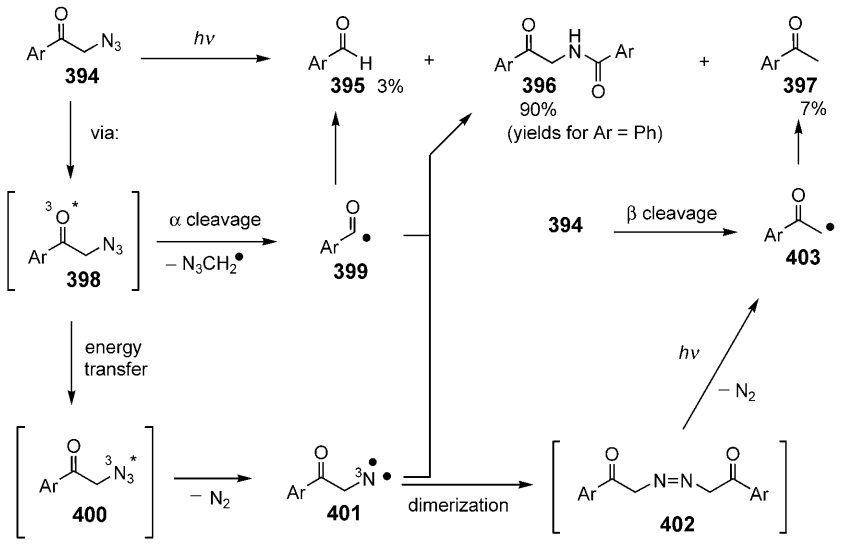
Functionalized aryl azides[367] and a few other azidopyridines[368] (see reference [369]) also rearrange under photolytic conditions in accord with this scheme. Another feature of aryl nitrenes is a reversible rearrangement between phenylnitrene and 2-pyridyl carbene, and 3-pyridyl carbene and 4-pyridyl carbene.[28,370] Furthermore, a coarctate ring opening[371] of 3-pyridyl nitrene with formation of a cyanovinylnitrile ylide complicates the reaction (Scheme 93).[372]

In the presence of water, alkenylaryl azides **384** provide access to substituted azepinones **385** by ring expansion (Scheme 94), as previously demonstrated by Scriven and co-workers.[373]

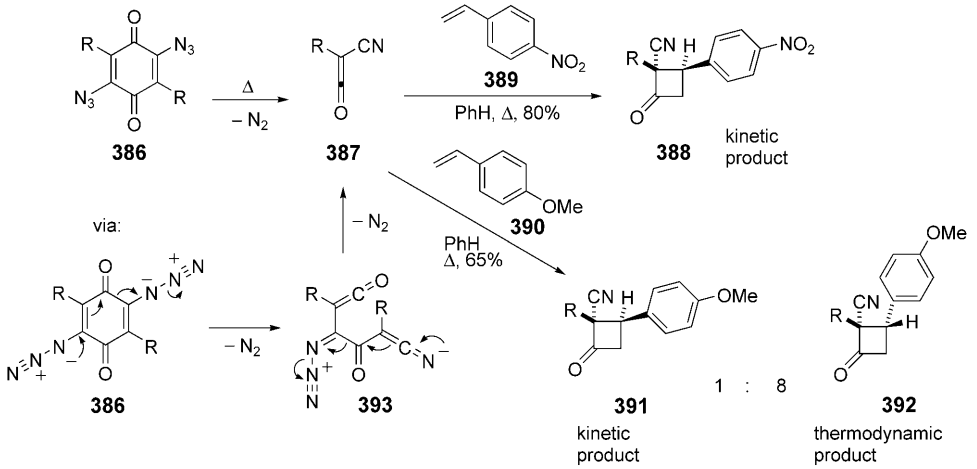
As a special case, azidoquinones usually rearrange to form nitriles (see also Scheme 73). However, 2,5-diazidoquinone (**386**) gives rise to the Moore ketene **387**, which reacts stereoselectively, for example, with styrenes **389** and **390** in intermolecular [2+2] cycloadditions to cyclobutanones **388** and **391**/**392**, respectively. Different reaction control is observed with the electron-rich styrene **390**, which gives predominantly **392** (Scheme 95).[374]

4.2.5.3. ***Fragmentation of Nitrenes***

Besides nitrene formation, alkyl azides with a photosensitive group in the α position (e.g. phenacyl azides **394**) can also react by α cleavage under radiation (Scheme 96).[375] This arises from the fact that with the supply of light the carbonyl group is first excited to the triplet state **398**. This can react either through the excited azide triplet state **400** to the triplet nitrenes **401**, or directly (by α cleavage)



Scheme 96. Fragmentation of phenacyl azides **394**.[375]



Scheme 95. Fragmentation of 2,6-diazidoquinones **386** according to Moore and synthesis of the corresponding cyclobutanone.[374]

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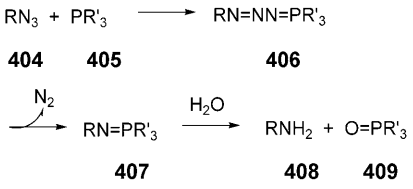
to the benzoyl radicals **399**. The benzoyl radicals **399** react predominantly with the triplet nitrenes **401** to give ketoamides **396**. Benzaldehydes **395** are formed to a small extent by H extraction. Acetophenones **397** also occur as by-products and are presumably formed by dimerization of the nitrene **401** to the azo compound **402**; direct β cleavage of **394** is also conceivable.

4.3. Nucleophilic Addition to Organoazides: Aza Ylides

As already discussed, organoazides react readily with nucleophiles. One of the most frequent applications is the attack by phosphorus nucleophiles.

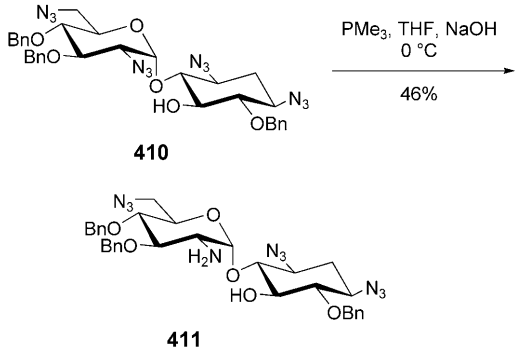
4.3.1. Azides as Amine Surrogates: The Staudinger Reduction

The Staudinger reduction was developed in 1919 by Staudinger and Meyer[376,377] as a procedure for the reduction of organoazides. This reaction involves the formation of a phosphazine intermediate **406** by nucleophilic attack of the phosphorus atom of a trialkyl or triaryl phosphine at the terminal nitrogen atom of the organoazide, which immediately loses nitrogen to form the iminophosphorane **407**.[378,379] These iminophosphoranes **407** are important reagents and intermediates in organic synthesis.[380,381] In the presence of water, the iminophosphorane **407** is spontaneously hydrolyzed to a primary amine **408** and to the corresponding phosphine oxide **409** (Staudinger reduction; Scheme 97).



Scheme 97. The Staudinger reduction.

If trimethylphosphane is used at low temperature, the organoazide—depending on its electronic properties—can be reduced chemoselectively in moderate yields in a modification of the Staudinger reaction (Scheme 98).[382]



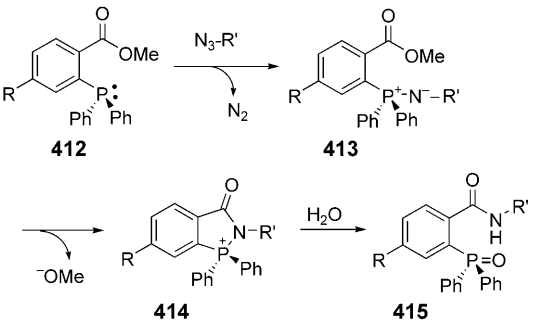
Scheme 98. Chemoselective reduction of organoazides.[382]

The Staudinger reaction between phosphines and organoazides has been used recently in the synthesis of dendrimers,[383] long-chain acyclic phosphazenes,[384] P-stereogenic phosphine oxides,[385] amides, [386] and glycosidated peptides,[387] as well as in the solid-phase synthesis of 3,5-disubstituted oxazolidine-2-ones.[388] A general Staudinger protocol has been developed for the liquid-phase parallel synthesis with fluoroalkyl-chain-modified triphenylphosphines which permits an extraction of the otherwise relatively poorly separable triphenylphosphane oxide into an organofluorous phase.[389]

4.3.2. The Staudinger Ligation

The intermediate in the Staudinger reaction is an iminophosphorane with a nucleophilic nitrogen atom. Vilarrasa and co-workers showed that this nitrogen atom can attack an acyl donor in an intermolecular or intramolecular reaction.[390] The amide is obtained as the final product after hydrolysis of the amidophosphonium salt. Thioamides can also be prepared by a coupling of thiocarboxylic acids and alkyl azides with triarylphosphines.[391]

Saxon and Bertozzi reported a modification of the Staudinger reaction for the first time in 2000—the intramolecular Staudinger ligation.[392,393] This generates an amide bond starting from organoazides and specifically functionalized phosphines.[393] This reaction takes place by nucleophilic attack at the organoazide to form an aza-ylide intermediate. A methoxycarbonyl group on one of the aryl rings of the phosphine traps the aza-ylide **413** to yield, after hydrolysis, an amidic phosphine oxide **415** (Scheme 99).[394] The reaction is



Scheme 99. The Staudinger ligation according to Saxon and Bertozzi.[393]

compatible with a large number of functional groups and therefore has various uses in organic synthesis and biological chemistry. The reaction has already been used in the investigation of cellular metabolism of synthetic azidosugars,[395] for biological labeling,[396,397] and for immobilization of substrates to surfaces.[398,399] The Staudinger ligation has been used successfully by Bertozzi and co-workers even on living organisms such as a mouse.[396b]

Bertozzi and co-workers recently reported an ELISA (enzyme-coupled immunosorbent assay) based on the Staudinger ligation (azido-ELISA).[398] A potential substrate, in this case a sugar, is equipped with an azide functionality and a

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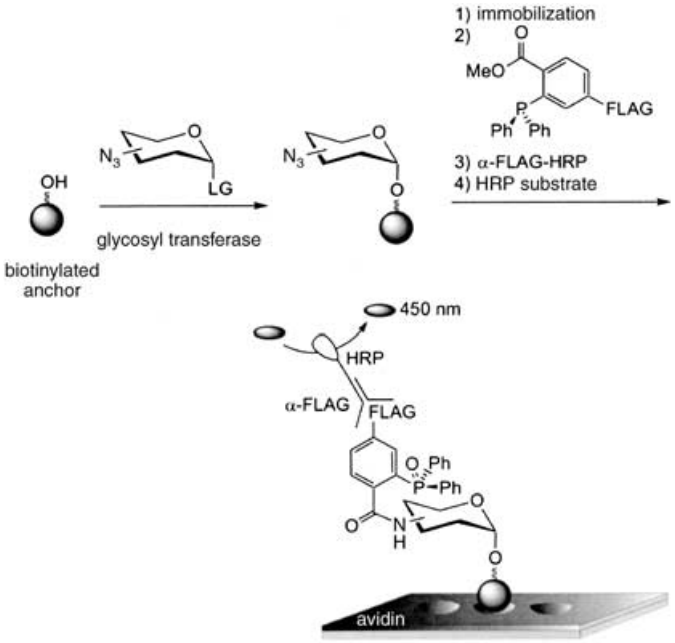
biotin anchor by an enzyme-induced coupling. This allows binding to an avidine-coated surface. The Staudinger reaction with a α-phosphinylbenzoic acid ester that bears a short peptide chain forms a conjugate. The short peptide chain (FLAG) can then be recognized by a specific monoclonal antibody (α-FLAG) to which a horseradish peroxidase is attached (α-FLAG-HRP). A substrate for this peroxidase then gives a signal at 450 nm. This system allows rapid screening of different glycosyl transferases, but should also be transferable to other systems (Scheme 100).

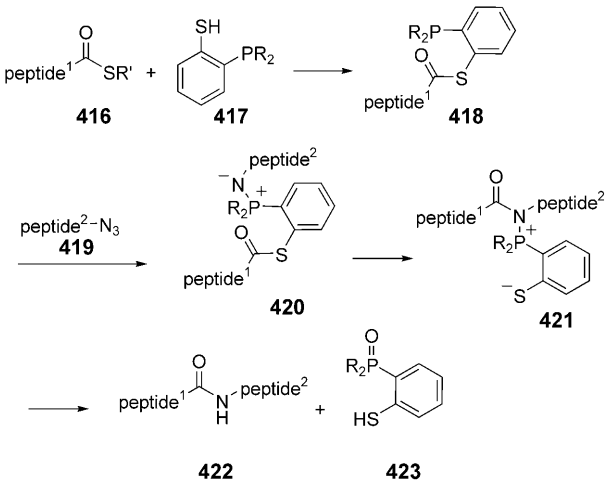


Scheme 100. Azido-ELISA according to Bertozzi and co-workers.[398]

The Staudinger ligation was applied to peptide synthesis by Raines, Kiessling, and co-workers. In this case, an amide bond is formed between a peptide fragment with a C-terminal phosphinylthioester **418** and a further peptide fragment **419** with N-terminal azide functionality (Scheme 101).[400] The reaction can be used to obtain dipeptides in high yields with retention at the α carbon atom[401,402] and is useful for the preparation of tetra- and pentapeptides.[403] The solid-phase synthesis of peptides and proteins under the conditions depicted was recently described in detail.[404]

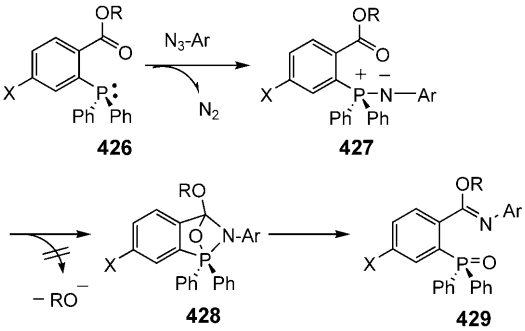
Modified Staudinger reactions with activated carboxylic acids are applied in the liquid- and solid-phase synthesis of glycosyl amides **425** (Scheme 102);[405a] stereoselective methods are also known.[405b] The reaction conditions are compatible with Boc and Fmoc protecting-group strategies, which are common in solid-phase synthesis and may be used in the synthesis of glycopeptides.

This reaction can also be applied to aryl azides and, in particular, to purinyl azides to obtain ligated material. The main product from this ligation contains a relatively stable imidate compound. *O*-Alkoxycarbonyltriaryl phosphines react somewhat differently with aryl azides. After Staudinger ligation, they form *O*-alkyl imidates **429** (Scheme 103).[406]



Scheme 101. Peptide synthesis by Staudinger ligation.[400]

Scheme 102. Coupling of amino acids to glycosyl azides **424** by Staudinger ligation for the preparation of glycoamino acids **425**.[405] DIC = diisopropylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole.



Scheme 103. Staudinger ligation with aryl azides.[406]

The intramolecular Staudinger ligation is a particularly efficient ring-closing reaction for the formation of medium-sized lactams that are difficult to prepare by other methods.[407]

4.3.3. The Aza-Wittig Reaction in a New Light

As described, the azide functionality is very useful for the synthesis of other nitrogen compounds. The reaction of iminophosphoranes **430**[381]—obtainable by Staudinger reaction from organic azides and phosphorus(III) reagents—with carbonyl compounds **431** has frequently been used for the synthesis of imines **433** by the aza-Wittig reaction (Scheme 104).[76,380,381,408–410]

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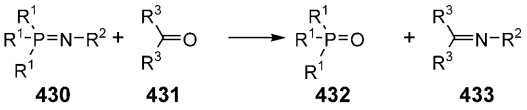
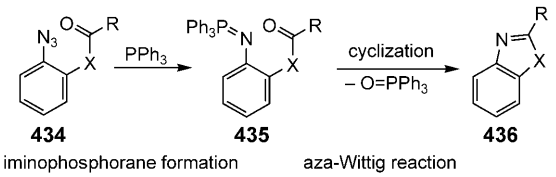


Scheme 104. Aza-Wittig reaction.

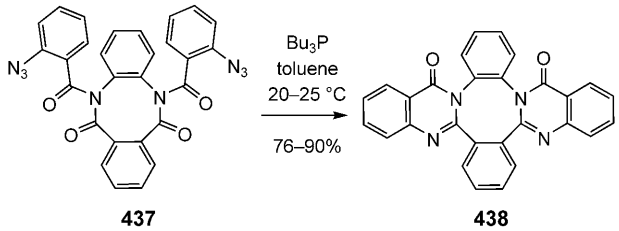
Because of its high synthetic potential, the intramolecular version of this reaction[408] is often the method of choice for the preparation of nitrogen heterocycles[411] such as isoxazolines[412] and for the synthesis of five-,[411] six-, and seven-membered nitrogen heterocycles, among others (Scheme 105).[411,413–416] A series of natural products syntheses



Scheme 105. Intramolecular aza-Wittig reaction.

uses precisely this reaction as the key step. The reactivity of the precursors is controlled by several factors: chain length, substituents at the phosphorus and nitrogen atoms of the iminophosphorane, and the chemical nature of the carbonyl group. Ester carbonyl groups are normally unreactive in the intermolecular aza-Wittig reaction, but they react in intramolecular versions and form the corresponding imino cyclization products.[76]

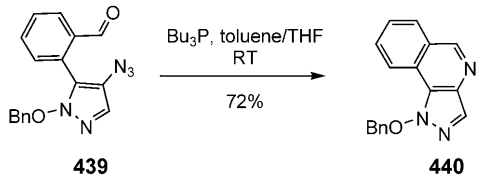
According to Eguchi et al. the reactivity of amidic carbonyl groups in intramolecular aza-Wittig reactions gives access to iminolactams.[417] Lactams can also act as substrates and give the corresponding annelated quinazolinones (for an alternative, see Section 4.6.2, Scheme 134).[413,415] This reaction can also be carried out twice, as demonstrated in the synthesis of the polyazamacrocycle **438** (Scheme 106).[418]



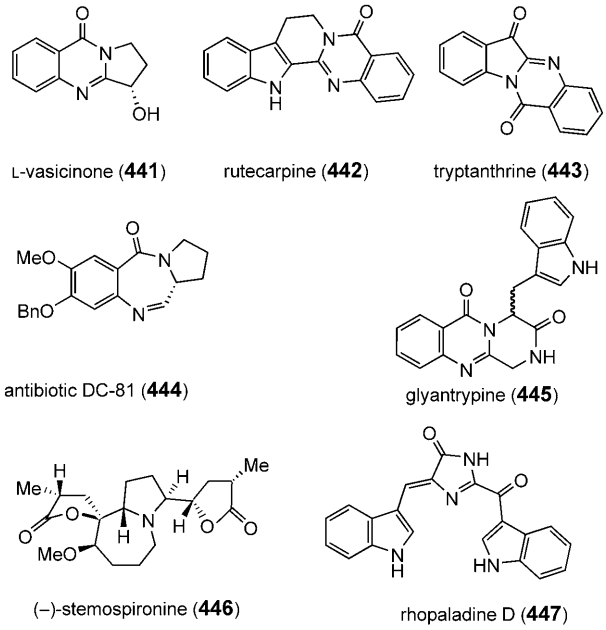
Scheme 106. Synthesis of the benzanellated polyazamacrocycle **438**.[418]

The pyridine ring of pyrazoloisoquinoline **440** was formed by a Staudinger/aza-Wittig cyclization of a formyl group with the azide group of a 4-azido-1-(benzyloxy)-5-(2-formylphenyl)pyrazole (**439**; Scheme 107).[419] Oxazoles are available from β-(acyloxy)vinyl azides and triethylphosphane.[420]

Efficient access to quinazolines by Eguchi et al. allows the synthesis of natural products in a domino Staudinger–intramolecular aza-Wittig reaction, for example, vasicinon (**441**),[421] desoxyvasicinon,[414] rutecarpin (**442**),[422] and tryp-



Scheme 107. Preparation of pyrazoloisoquinoline **440** by aza-Wittig reaction.[419]



tanthrin (**443**).[422] This methodology is particularly suitable for the synthesis of seven-membered nitrogen heterocycles such as the antitumor antibiotic DC-81 (**444**),[423–425] and for the synthesis of trifluoromethylated nitrogen heterocycles.[426] Furthermore, studies on the total synthesis of the marine alkaloids of the chartellamide group[427] and pinnatoxin A[428] by aza-Wittig reactions have been reported. Other successful examples are glyantrypine (**445**),[429] (−)-stemospironine (**446**),[430] rhopaladine (**447**),[431] ardeemin,[432] and hamacanthin A[433] and B (**82**; Scheme 20).[117]

The first total synthesis of (−)-benzomalvin A (**453**), which bears both a quinazoline-4(3*H*)-one and a 1,4-benzodiazepine-5-one unit, was reported by Eguchi and co-workers.[434,435] Both heterocycle frameworks were prepared by an aza-Wittig reaction as the key step (Scheme 108).

Enantiomerically pure 2,4-disubstituted thiazolines **455** can also be prepared efficiently from thioesters **454** in a mild Staudinger/aza-Wittig process,[436] as demonstrated in the total synthesis of apratoxin (**456**) (Scheme 109).[437]

The intramolecular aza-Wittig reaction can also be used in the synthesis of nonnatural products, as demonstrated by the synthesis of novel heterocycles based on ferrocenophanes that are used as ligands for metal ions (Scheme 110).[438] A new class of orthoacylimine-derived chiral auxiliaries have been synthesized by the reaction of the corresponding

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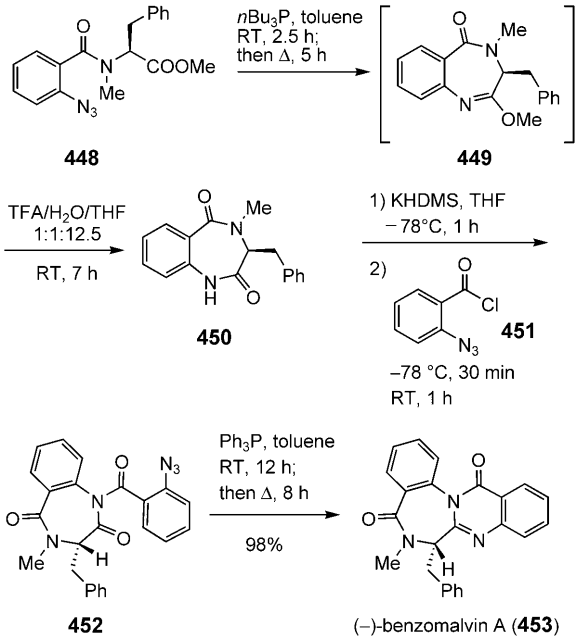
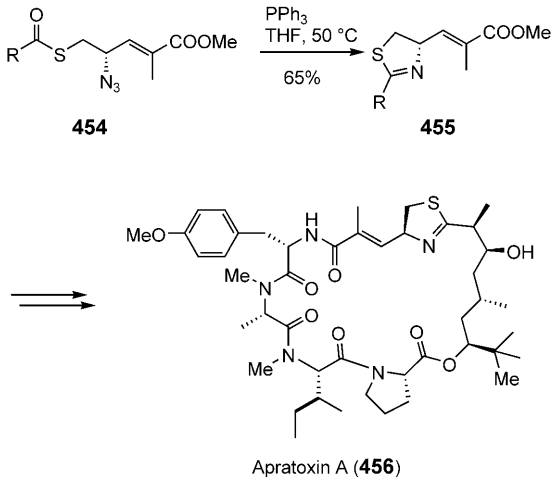
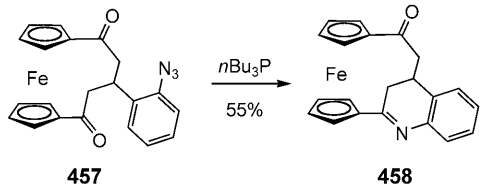


Scheme 108. Synthesis of (−)-benzomalvin A (**453**).[435]



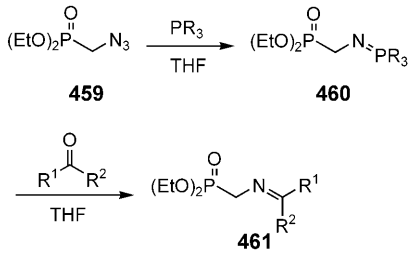
Scheme 109. Thiazole synthesis by aza-Wittig reactions in the total synthesis of apratoxin A.[437]



Scheme 110. Conversion of a ferrocenophane into the ligand **458**.[438]

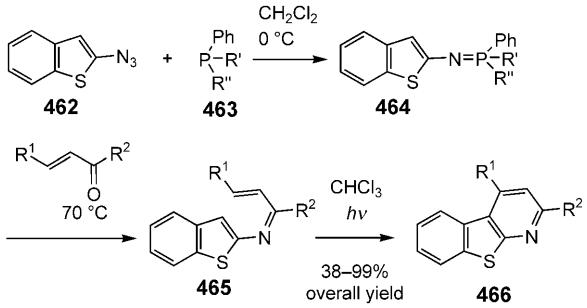
orthoacyl azides and a series of aldehydes in the presence of trialkylphosphines.[408]

The aza-Wittig reaction can thus be used for the introduction of imine units, for example, to prepare iminophosphonates **461** (Scheme 111),[439] or in keto acids for the preparation of imino acids.[440]



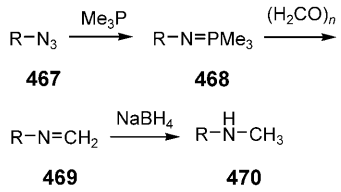
Scheme 111. Synthesis of functionalized imines **461**.[439]

The preparation of pharmacologically important benzothieno[2,3-*b*]pyridines **466** takes place by an intermolecular aza-Wittig reaction of iminophosphoranes **464** with various unsaturated aldehydes and ketones and subsequent photocyclization (Scheme 112).[441]



Scheme 112. Synthesis of benzothienopyridines **466**.[441]

A one-pot synthesis of *N*-monomethylamines **470** from organoazides **467** by Suzuki and co-workers[442] uses an aza-Wittig reaction with paraformaldehyde. The resulting imine **469** is then reduced with $NaBH_4$ to give the corresponding *N*-monomethylamine **470** (Scheme 113). Although a frequent structural motif in natural products, the *N*-monomethylamine group is at times difficult to insert without the formation of by-products.



Scheme 113. Synthesis of *N*-monomethylamines from organoazides.[442]

Owing to the potential of iminophosphoranes in the mild and neutral synthesis of nitrogen heterocycles, different solid-phase variants have been developed. Either the triarylphosphine in the aza-Wittig reaction or the substrate is immobilized on the support. The solid-phase synthesis of 1,4-benzodiazepine-2,5-diones,[443] trisubstituted guanidines,[162] oligomeric guanidines,[444] and 3*H*-quinazolin-4-ones (**475**; Scheme 114)[445] has been carried out with aza-Wittig reac-

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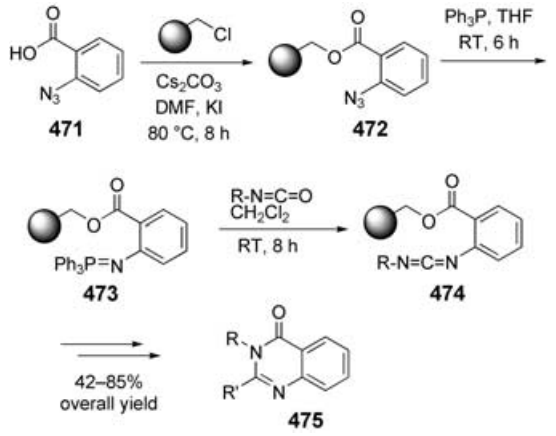


Scheme 114. Solid-phase synthesis of 3*H*-quinazolin-4-ones **475**.[445]

tions and permitted the synthesis of libraries of these classes of compounds.

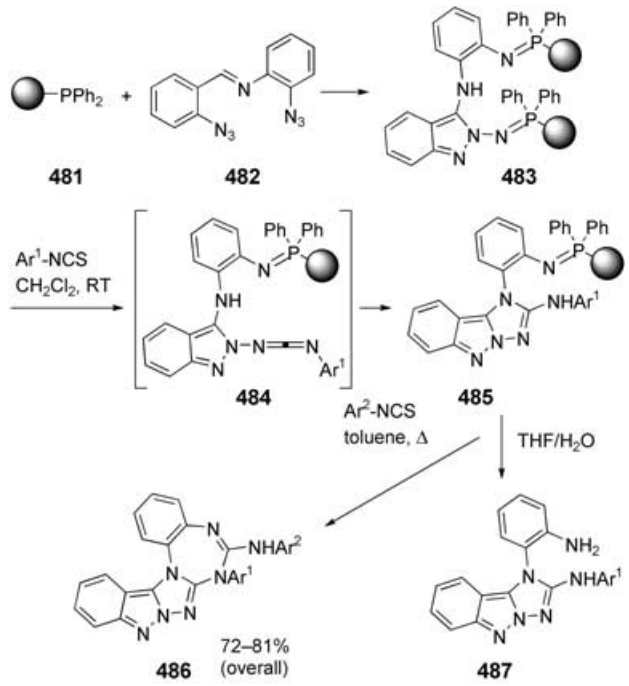
The use of the commercially available, polymer-bound diphenylphosphine (**477**) combines the advantages of solid phase synthesis with the use of polymer-bound reagents. The usual Wittig by-product triphenylphosphane oxide is normally difficult to separate from polar products, but in this way it can be readily removed as the polymer-bound diphenylphosphane oxide (**479**) by filtration (Scheme 115).[446] Owing to the high cost of the reagent **477**, it is occasionally

Scheme 115. Aza-Wittig reaction with polymer-bound diphenylphosphane.

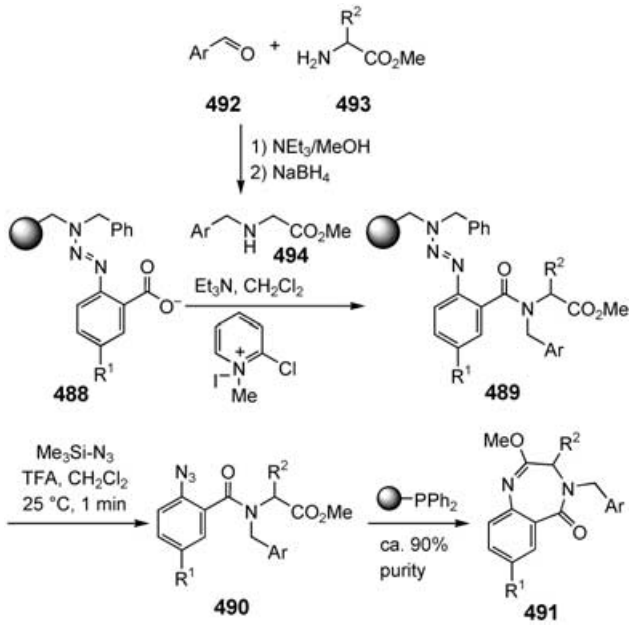
recovered, usually by reduction with trichlorosilane. In particular, the fact that the iminophosphorane **478** is polymer-bound in the first step the purification of the final product is simplified, as excess organoazide **476** can be removed before the aza-Wittig reaction.

This strategy has been used in the synthesis of condensed indazolobis(guanidines) **486** (Scheme 116),[447] amines,[448] pyrrolo[2,1-*c*][1,4]benzodiazepines such as the natural product DC-81 (**444**),[424b] pyrido[1,2-*c*]pyrimidines,[449] non-anomeric glycosidyl isothiocyanates,[450] the antitumor-active phloeodictin A1,[451] and libraries of benzodiazepine–quinaxolinone alkaloids of the circumdatin type.[452]

A combined solid-phase strategy for the synthesis of benzodiazepinones **491** starts from substituted triazene resins **488**, which were first treated with a series of *N*-benzyl amino acid esters. The latter are readily prepared by reductive amination of aryl aldehydes **492** with amino acid esters **493**. The cleavage of the resulting amide **489** in the presence of trimethylsilyl azide gave the highly functionalized aryl azides **490**. The intramolecular aza-Wittig reaction with polymer-bound triphenylphosphane then gave **491** in good yields (Scheme 117).[453]



Scheme 116. Solid-phase synthesis of condensed indazolo-bis(guanidines) **486**.[447]



Scheme 117. Solid-phase synthesis of benzodiazepinones **491**.[453]

Soluble and easily separable triphenylphosphane reagents have been prepared from noncrosslinked polystyrene (NCPS)[454] or through perfluoroalkyl-substituted triphenylphosphane[455] and are also used in the Staudinger/aza-Wittig reaction.

A new reaction sequence that includes iminophosphoranes was recently reported by Langer and co-workers. α-Azidoketones **495** are converted into allyl amides **497** with enolizable β-carbonyl compounds in a sequence of Stau-

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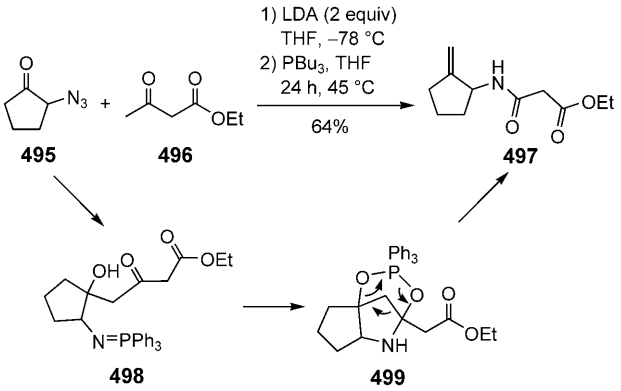
dinger–aza-Wittig–1,5-phosphonium rearrangement–fragmentation sequence (Scheme 118).[456] This reaction differs from a related reaction,[457] such that the iminophosphorane does not cyclize to the pyrrole under aza-Wittig conditions,



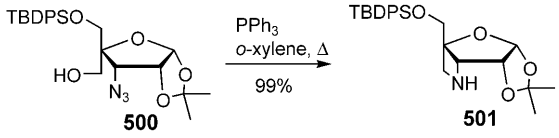
Scheme 118. A rearrangement cascade for the synthesis of allyl amides **497**.[456]

but first attacks the ketone and forms compound **499**. Ring opening of intermediate **499** and fragmentation of the resulting phosphonium oxide gives the allyl amide in a retro-Prins reaction with elimination of triphenylphosphane oxide.

At this point it must not be overlooked that alternative substrates and reagents for imine syntheses from organoazides and carbonyl compounds or their derivatives have recently been published (Section 4.6.2).

4.3.4. Reaction of Iminophosphoranes with other Electrophiles

Iminophosphoranes also react with other electrophiles, for example, epoxides or activated carbon electrophiles.[458] These intramolecular reactions take place with the formation of aziridines.[18,381] Recently, a new bridged nucleic acid monomer **501** was successfully synthesized by azetidine formation under Staudinger conditions (Scheme 119).[458a]

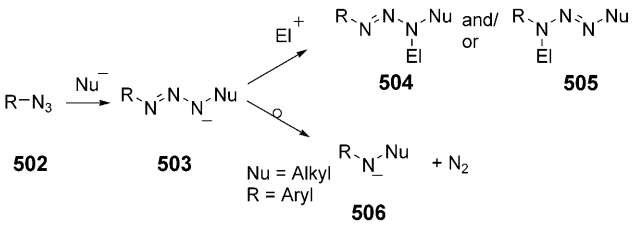


Scheme 119. Synthesis of azetidine-condensed nucleoside analogues.[458a]

4.4. Other Reactions of Organoazides with Nucleophiles

4.4.1. Reactions of Carbanions: Synthesis of Triazenes

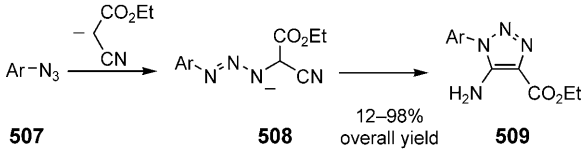
Stabilized and nonstabilized carbanions react with organoazides **502** (Scheme 120) to form triazenyl anions **503**, which can then be trapped with electrophiles—under certain circumstances regioselectively. (For the reaction with sulfonyl azides see Section 3.1.3.) This reaction is particularly useful for the preparation of the corresponding aliphatic triazenes,



Scheme 120. Synthesis of triazenes and secondary amides **506** from organoazides **502**.[9,460]

as other possible precursors (aliphatic diazonium ions) are not stable. The addition of nucleophiles to organoazides can also be used for diazo transfer[459] or for electrophilic amination of carbanions as found by Trost, Kabalka, and others,[460] because the triazenes cleave under mildly acidic conditions. However, triazenyl anions **503** that are formed by attack of aliphatic Grignard reagents on aromatic azides, are in a few cases not stable and lead to formal *N*-alkylation (Scheme 120).[9]The recently reported indium-induced Barbier synthesis of *N*-allylamines from allyl bromides and azides also probably follows a similar pattern.[461]

More than 100 years ago it was shown that in the presence of an internal electrophile the triazenyl anions **508** cyclize, for example, to triazoles **509** (Dimroth cyclization; Scheme 121).[58] Malonic, cyanoacetic, and related esters can be used.



Scheme 121. Synthesis of triazoles **509** from azides **507**.[58a]

4.4.2. Reduction of Azides to Amines

The reduction of azides[462] to the corresponding amines has been carried out with hydrogen in the presence of catalysts such as Lindlar catalyst,[78] with thiols,[463,464] complex hydrides, boranes, and phosphanes (see Section 4.3.1, Staudinger reduction).[122,409a,465–467]

Thioethers R_2S are often used in catalytic amounts; different boranes[468,469] or borohydrides[470] function as stoichiometric reducing agents. The high reactivity of the reducing agent $BHCl_2{\cdot}SMe_2$ is exploited in the selective reduction of azides in the presence of double bonds. With $BH_3{\cdot}SMe_2$, hydroboration is preferred to reduction.[469] The reduction also takes place in good yields with various metals in the presence of Lewis[471] or Brønsted acids.[472] Acyl azides can be reduced to the corresponding primary amines with lithium/DTBB (di-*tert*-butylbiphenyl) at room temperature.[473] One mild reducing agent is *N*,*N*-dimethylhydrazine, which requires the presence of catalytic amounts of iron(III) chloride.[474] A further reducing agent is SmI_2, which transforms aliphatic, aromatic, and benzoyl azides smoothly into the corresponding amines under mild conditions.[475] Analo-

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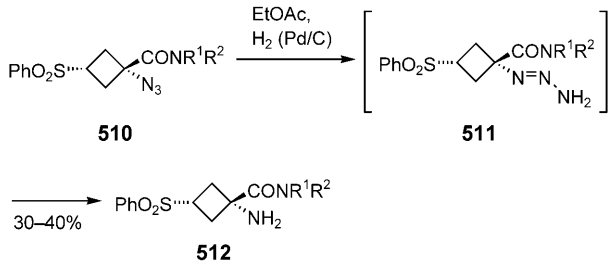
gously, the reduction also takes place with zinc borohydride,[476] sodium borohydride under Cu(II) or Co(II) catalysis,[477] sulfur-modified calcium or barium borohydrides $M^{II}(BH_2S_3)$,[478] lithium aminoborohydrides (aliphatic and benzylic azides),[479] as well as classically with lithium aluminum hydride.[480]

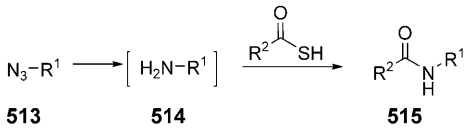
Iron(II) salts under basic conditions are also suitable reducing agents,[481] as are tetrathiomolybdates.[482] Very powerful yet selective reducing agents are the thioaryl-substituted Sn(II) complexes $Sn(SAr)_3^-$ (Bartra reagent).[483–485] Bu_3SnH is also used as reducing agent, sometimes with Ni(II) catalysis,[486,487] although a radical mechanism is assumed here.[486] Aliphatic, aromatic, and benzoyl azides can be reduced to the corresponding amines or amides by the action of trimethylchlorosilane.[488] The direct conversion of organazides into Boc-protected amines,[465,489] which provides elegant access to orthogonally protected diamines, is very attractive. The selective reduction of an azide group on an anomeric carbon atom of a saccharide by tetrathiomolybdates has also been reported, while the azide groups at other sites of the sugar were not attacked.[490] Enzymatic reductions of azides with baker's yeast[491] and lipases[491d] are also known.

The classic heterogeneous catalytic hydrogenation of aliphatic, aromatic, and sulfonyl azides with palladium on charcoal[492] as catalyst can also be carried out with other supports such as molecular sieves.[493] An interesting reduction of tertiary azides **510** to stable, monosubstituted triazenes **511** has been reported by Gaoni (Scheme 122).[494] At this point it has to be speculated whether most of the aforementioned reductions occur through triazenes.



Scheme 122. Reduction of organoazides **510** via triazene intermediate **511** according to Gaoni.[494]

A highly promising reaction is the transformation of thioacids with azides **513**, which leads directly to amides **515** (Scheme 123). Since this reaction takes place in water, it is suitable for aqueous peptide syntheses. Alkyl, acyl, and sulfonyl azides react equally well, and the amine **514** is formed in situ.[495,496]

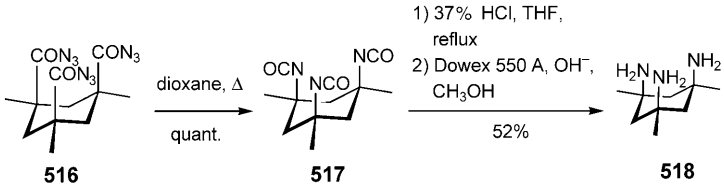


Scheme 123. Acylation of azides **513** with thiocarboxylic acids.[495]

4.5. The Curtius Rearrangement and Related Reactions

4.5.1. Curtius Rearrangement

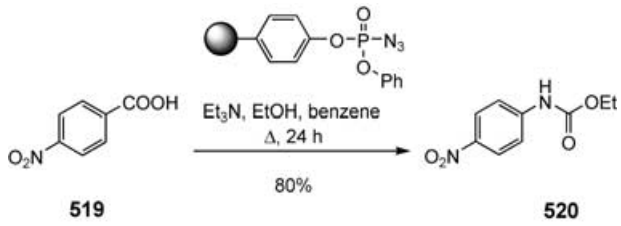
The Curtius rearrangement is a widely applicable reaction for the preparation of isocyanates and their secondary products.[497] Acid azides are photolytically decomposed to nitrenes, which in a further reaction at room temperature are converted into the isocyanates.[498] In principle, this reaction can be regarded as an aminating decarboxylation. The potential was demonstrated in a series of syntheses of complex natural products.[174,499,500] Owing to the widespread use of this reaction,[170,173,184,501,502] only a few selected examples are described here. Menger and co-workers recently reported the synthesis of 1,3,5-triaminocyclohexane **518** (in which the three amino groups adopt an axial disposition) from the Kemp triacid (Scheme 124).[503] The stereospecific triple



Scheme 124. Preparation of 1,3,5-triaminocyclohexane **518** according to Menger et al.[503]

Curtius rearrangement occurs with complete conversion in refluxing dioxane or toluene. The subsequent hydrolysis gave the triamine **518** in good yield.

Carboxylic acids and their derivatives can also be transformed directly into the corresponding amines through a Curtius rearrangement. Thus monoesters of dicarboxylic acids can be converted into amino acids.[170] Usually diphenylphosphoryl azide (DPPA) is used as the reagent; however, its use is severely restricted owing to its high toxicity. Recently Taylor prepared and successfully used a solid-phase-bound phosphoryl azide in a Curtius rearrangement (Scheme 125).[116]



Scheme 125. Curtius rearrangement with immobilized phosphoryl azide according Taylor and Lu.[116]

The Curtius rearrangement is a key step in the total synthesis of (+)-zamoanolide, a tumor-growth inhibitor.[500] Solid-phase Curtius rearrangements have also been described for the amine[504] or carboxylic acid[505] immobilized on the solid phase. The isocyanate **522** is first formed as an intermediate in a Curtius rearrangement before further transformation (Scheme 126).

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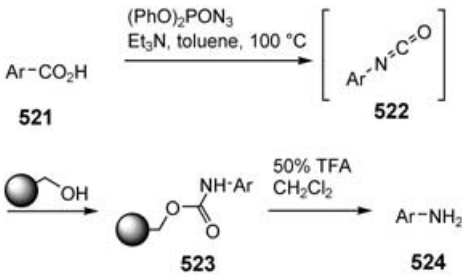
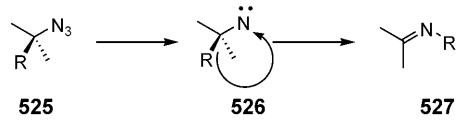


Scheme 126. Solid-phase synthesis of amines **524** according to Morishima and co-workers.[505]

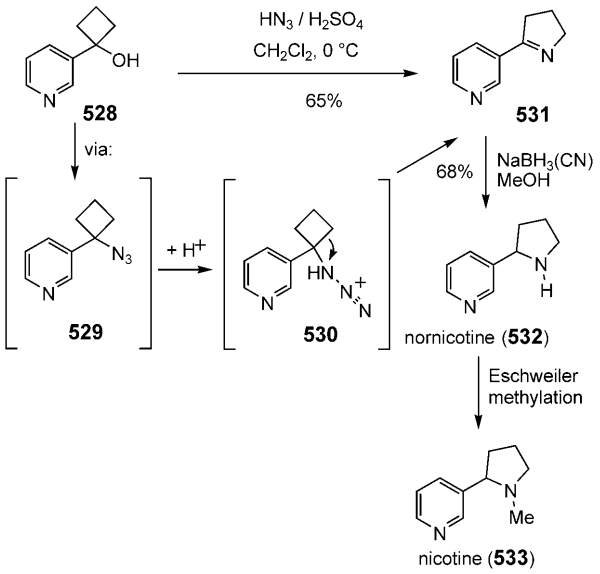
4.5.2. *The Schmidt Rearrangement*

The Schmidt rearrangement has been somewhat less extensively investigated than the Curtius rearrangement and usually takes place under pyrolysis or thermolysis conditions (Scheme 127).[506] An alkyl azide is either converted into a nitrene and further rearranges into an imine, or the rearrangement and loss of nitrogen takes place in a concerted manner.



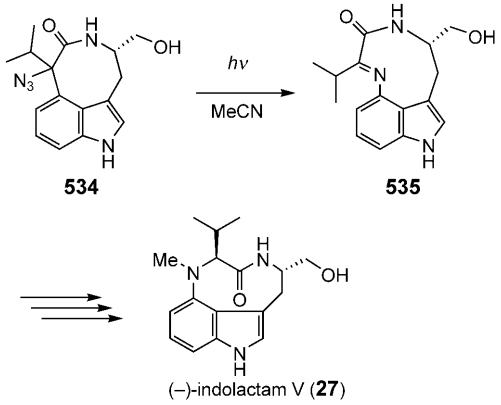
Scheme 127. Gas-phase pyrolysis of alkyl azides according to Bock et al.[506]

Andrieux and co-workers prepared tobacco alkaloids such as nicotine (**533**) with a Schmidt reaction as a key step. The intermediate in the nicotine synthesis is a cyclobutyl azide **529** (Scheme 128).[507]



Scheme 128. Synthesis of tobacco alkaloids according to Andrieux and co-workers.[507]

Another application of this rearrangement is the total synthesis of indolactam V (**27**) reported by Moody and Mascal in 1988 (Scheme 129).[508] The preparation is based on a photocyclization reaction of *N*-haloacetyltryptophan, also described by Moody and co-workers[509] and uses the α,α-dichloroisovaleryl amide of tryptophanol as starting material.



Scheme 129. Total synthesis of indolactam **27**.[508]

Further applications are found in the rearrangement of azidocubanes[147] and the synthesis of tetrazoles from fatty acids,[510] and the total synthesis of stenine.[511] In a series of examples, the Schmidt reaction takes place in the presence of Brønsted or Lewis acids. In a few of these cases, for example, in the reaction with aldehydes or ketones, the intermediate imine reacts either in an intermolecular or intramolecular fashion with a further equivalent of azide to form tetrazoles.[512]

4.6. *Reactions of Azides with Electrophiles*

Suitable electrophiles (carbon electrophiles, protons, boranes) normally react with organoazides at N^1, mostly to form initially an amine-substituted diazonium ion, which loses nitrogen. The electron-deficient nitrenium ion usually rearranges or reacts with nucleophiles.

4.6.1. *Boyer Reaction*

In the presence of Lewis acids, organoazides react with carbon electrophiles with framework expansion in analogy to the Schmidt reaction. Suitable (pre)electrophiles include ketones (Aubé[513]), epoxides, or carbenium ions, which can be obtained from alkenes or alcohols through protonation (Pearson[514]) or mercuration.[515] The aminodiazonium ion formed initially loses dinitrogen with simultaneous migration of the alkyl residue to the electron-deficient nitrogen atom. The reaction of aliphatic azides with ketones in the presence of Brønsted acids—the Boyer reaction[516]—occurs in good yields to form *N*-alkylated amides or lactams,[517] but is limited to aliphatic ketones. An improvement was brought about by the observation by Aubé and co-workers that Lewis acids can

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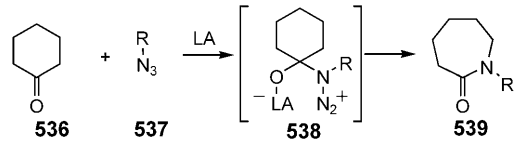
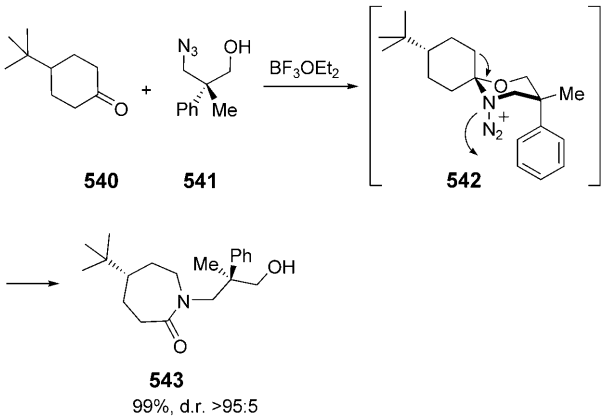
also accelerate this reaction (Scheme 130). α,β-Unsaturated ketones react through another reaction pathway (Scheme 47).



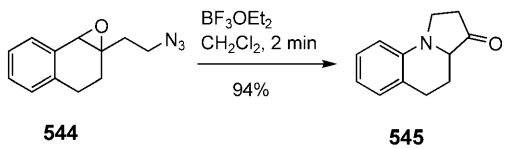
Scheme 130. Boyer reaction according to Aubé and co-workers.[513] LA = Lewis acid.

The asymmetric variant of this Boyer rearrangement was also developed by Aubé and co-workers.[518,519] Prochiral cycloalkanones **540** react with chiral 3-hydroxyalkyl azides **541** in the presence of Lewis acids and yield ring-expanded *N*-alkyl lactams **543** with high diastereoselectivity. Prior to the antiperiplanar migration, the phenyl ring in the intermediate **542** adopts an axial disposition, and the methyl group is arranged equatorially (Scheme 131). The cause of this otherwise unusual behavior lies in the interaction of the phenyl group with the electron-deficient diazonium unit.[519,520]



Scheme 131. The asymmetric Boyer reaction according to Aubé and co-workers.[518]

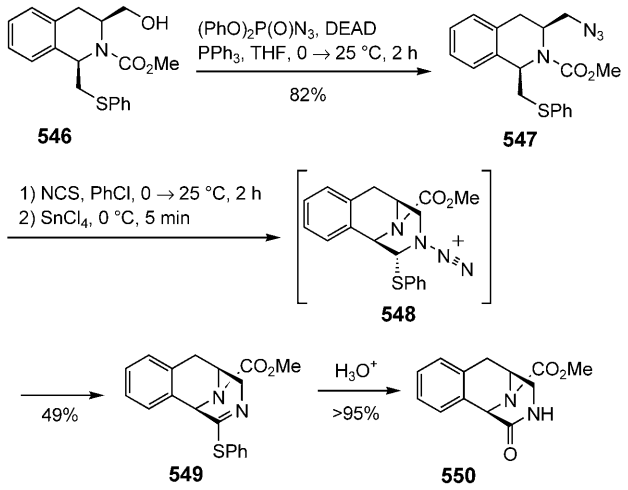
Alternatively, besides ketones, azidoalkyl-substituted epoxides such as **544** can be transformed in an intramolecular reaction (Scheme 132).[521,522] The benzylic nature of the nitrenium ion formed allows the migration of the aromatic residue, and an amino-substituted aromatic system is formed (see Scheme 136).



Scheme 132. The azido-Schmidt reaction with epoxides **544**.[522]

4.6.2. *New Electrophiles for the Synthesis of Imines from Azides: Alternatives to the Aza-Wittig Reaction*

A reaction sequence, the first stage of which is related to the organoazide Schmidt reaction, was reported by Magnus and co-workers in 2003.[523] An α-chlorinated thioether acts as the electrophile, which undergoes intramolecular attack by an alkyl azide with loss of a chloride ion. Unlike the Schmidt reaction, however, both a proton and dinitrogen are lost. The resulting thioimine **549** then releases an amide functionality under hydrolytic conditions. The overall reaction sequence thus corresponds to an aza-Wittig reaction (Scheme 133).



Scheme 133. Intramolecular alkylation of azides according to Magnus and co-workers.[523]

A related reaction sequence for the preparation of imines from azides was reported recently by Shibasaki and co-workers.[524] They observed that a number of azidoalkyl lactams **551** reacted only slowly, if at all, under Staudinger–aza-Wittig conditions with formation of the corresponding amidines. A search for suitable reagents led to oxalyl bromide/anisole as an efficient reagent combination. A bromoaminium ion is probably formed which acts as an electrophile and attacks the azide group. The resulting aminodiazonium ion **553** loses dinitrogen with migration of the bromine atom to the nitrogen atom. A dipolar mechanism has been proposed as an alternative. In any case, anisole then removes the electrophilic bromine, leading finally to the amidine **555** (Scheme 134).

4.6.3. *Nitrenium Ions by Protonation of Organoazides*

According to Bamberger, the protonation of organoazides with strong acids (e.g. TFA) gives aryl or alkyl nitrenium ions that are analogous to carbocations.[525–527] Aryl nitrenium ions are highly reactive intermediates, which react as electrophiles in either inter- or intramolecular[336] reactions with aromatic groups (Scheme 135).[526,528] The high reactivity is an argument for the carcinogenicity of such compounds.[529]

The acid-catalyzed rearrangement of azidobenzyl compounds to anilines,[530,531] which are accessible by conjugate

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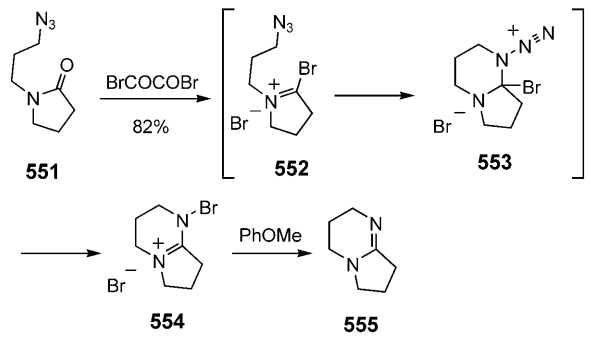
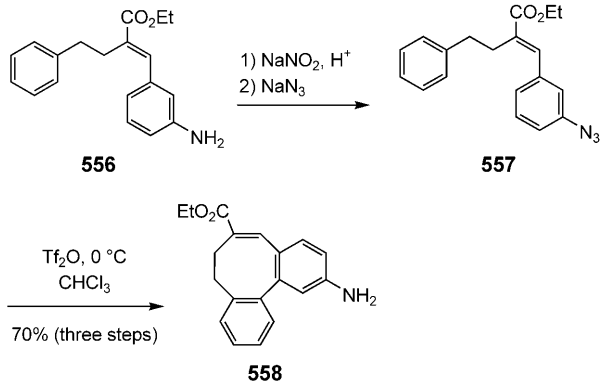
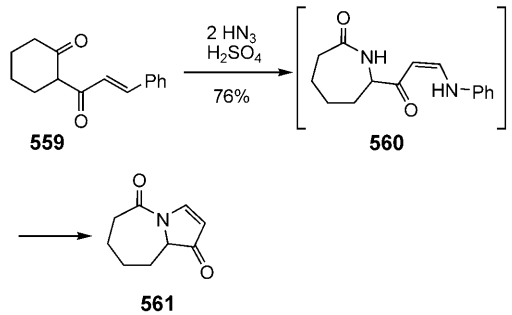


Scheme 134. Intramolecular synthesis of amidine **555** according to Shibasaki and co-workers.[524]



Scheme 135. Intramolecular cyclization of aryl nitrenium ions.[526]

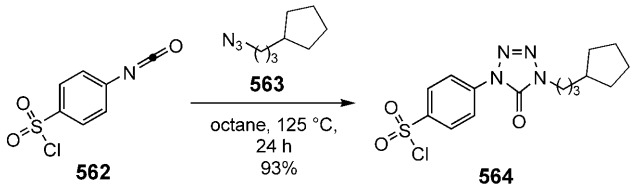
Boyer addition, also involves the participation of nitrenium ions.[532] This rearrangement takes place through an intramolecular electrophilic substitution and subsequent ring opening of the resulting aziridine to form an iminium ion. Hydrolysis then gives the aniline derivative. In the case of cyclohexanone-substituted ketones of type **559**, insertion of nitrogen atoms from 2 equivalents of HN_3 leads to the enamine **560**, and cyclization produces the unsaturated lactams **561** (Scheme 136).[533]



Scheme 136. Double rearrangement of the Schmidt type according to Casey et al.[533]

4.6.4. ***Reaction of Organoazides with Heterocumulenes***

The reaction of organic azides with aryl isocyanates takes place rapidly and in the presence of excess azide gives 1,4-disubstituted Δ^2-tetrazoline-5-ones in very good yields.[534,186] The addition is largely chemoselective, so that even sensitive functions such as the sulfonyl chloride group are not attacked (Scheme 137).[535] Alkoxycarbonyl isocyanates, sulfonyl isocyanates, and isothiocyanates react with organic azides in the same manner to form Δ^2-tetrazoline-5-ones.[536]

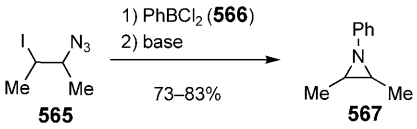


Scheme 137. Selective addition of alkyl azide **563** to 4-isocyanatobenzenesulfonyl chloride (**562**).[535]

4.6.5. ***Reaction of Organoazides with Boron Compounds***

According to an early observation by Brown et al., trialkyl boranes react with aromatic and aliphatic azides to form secondary amines.[537] The formation of nitrogen follows second-order kinetics so that a mechanism that proceeds via a nitrene intermediate is excluded. The organoboranes react reversibly with the organoazides, which subsequently react further with loss of nitrogen and simultaneous migration of the alkyl groups from the boron to the nitrogen. This reaction follows a similar but relatively older observation of Paetzold and Habereder on the decomposition of azidoboranes.[538]

As the steric demand of the alkyl residue increases, the reaction slows down significantly, and the yields decrease. Haloboranes such as monochloro-,[539] dichloro-,[540,541] and difluoroboranes[542] or their precursors such as aminoboranes in the presence of anhydrous HCl[543] can be used likewise and even advantageously[469,539] because they are more reactive. Only dibromoboranes react differently, with simultaneous formation of tetraazaborolines.[544] In the presence of alkylating agents, subsequent alkylation occurs, as in the synthesis of the aziridines **567** (Scheme 138).[539]



Scheme 138. Arylation of organoazides with boranes and subsequent intramolecular alkylation.[539]

As dichloroboranes can be prepared readily in enantiomerically pure form by diastereoselective hydroboration and subsequent transformation, α-chiral amines are readily accessible.[545] This reaction sequence also proceeds in an intramolecular fashion with the synthesis of chiral cyclic amines.[542] Under certain conditions, two alkyl groups can be transferred (Scheme 139).[543]

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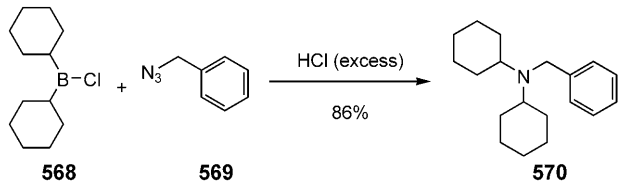


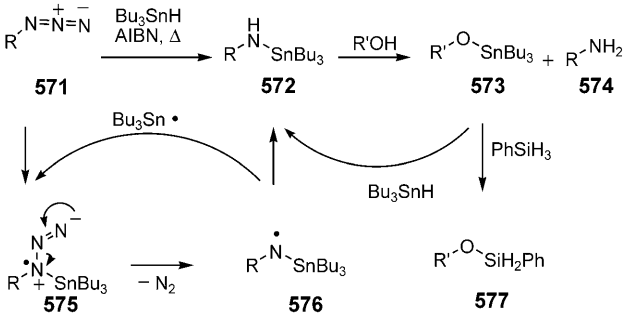
Scheme 139. Alkylation of organoazides with boranes.[543]

4.6.6. Reaction of Organoazides with Heteroelectrophiles

The reaction of aliphatic and aromatic azides with HOF/CH_3CN leads to an immediate oxidation with formation of nitro compounds. Initially, the electrophilic oxygen atom in HOF is attacked with concomitant loss of HF and dinitrogen. The nitroso compound is thus formed and reacts further to form the nitro compound. This single-step reaction is simpler than other variants.[546]

4.7. Radical Additions to Organoazides

The addition of tributyltin radicals to organoazides **571** leads initially to triazenyl radicals **575**. Loss of nitrogen leads to amine radicals **576**, which finally react with tributyltin hydride to give **572** (Scheme 140).[486a] The latter are transformed into the amines **574** with phenylsilyl hydride in the presence of alcohols. Tributyltin hydride is regenerated so that only catalytic amounts are needed.

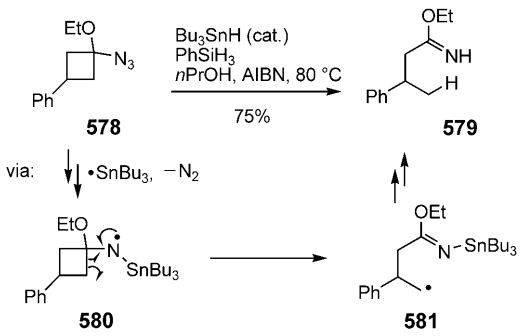


Scheme 140. Reduction of organoazides with phenylsilyl hydride under tributyltin hydride catalysis.[486] AIBN = 2,2′-azobis(isobutyronitrile).

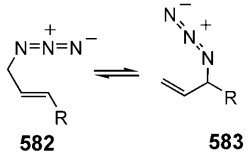
The radical reaction mechanism is confirmed by the conversion of cyclobutane azide **578** which proceeds through ring opening (Scheme 141). A few synthetically very useful azide-transfer reactions also proceed through a radical mechanism (see Scheme 27, Scheme 42).[145,206]

4.8. [3,3] Sigmatropic Rearrangements and Electrocyclizations of Organoazides

The rearrangement of allyl azides (Scheme 142) was first reported by Gagneux, Winstein, and Young in 1960, and has since then been observed with different substrates, including



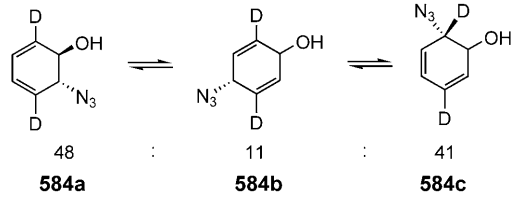
Scheme 141. Ring opening of azidocyclobutanes **578**.[486,547]



Scheme 142. Sigmatropic rearrangement of allyl azides.[549]

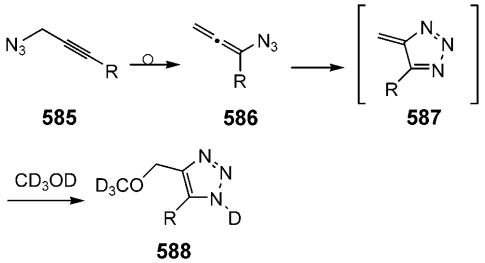
substituted cyclopropene azides.[548–551] This [3,3] sigmatropic rearrangement takes place even at low temperatures.

In the case of azidocyclohexadienes, all possible products are in thermal equilibrium (Scheme 143).[548] In some cases, a mixture of all possible products is also formed in the synthesis of allyl azides.[552]



Scheme 143. Consecutive sigmatropic rearrangements of cyclohexadienyl azides **584**.[548]

The propargyl azides **585** rearrange to the less stable allenyl azides **586** (Banert cascade, Scheme 144).[255] The short-lived allenyl azides **586** cyclize rapidly to the triazafulvenes **587**, which in the presence of a nucleophilic trapping reagent (e.g. $[D_4]$MeOH) form the corresponding 1,2,3-triazoles **588** quantitatively. In the absence of a nucleophilic trapping reagent, the allenyl azides polymerize.



Scheme 144. Preparation of 1,2,3-triazoles from allenyl azides.[255]

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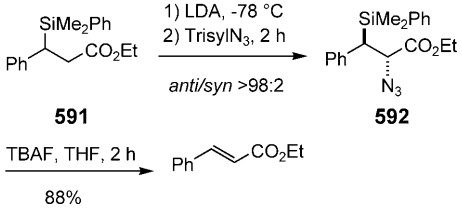
C-Azidoimines **589** can form tetrazoles **590** in a reversible electrocyclic reaction (Scheme 145).[553] These *C*-azidoimines **589** are formed, for example, in a Mitsunobu reaction of amides with trimethylsilyl azide and in most cases, rearrange directly to the tetrazoles **590**. This reaction is complementary to the cycloaddition of organoazides with nitriles.[554]

589 **590**

Scheme 145. Electrocyclization of *C*-azidoimines **589** to tetrazoles **590**.[553]

4.9. Azide Ions as Leaving Groups

Aliphatic azides can be either eliminated or substituted by suitable organic bases or nucleophiles. In this case, the property of the azide as pseudohalogen comes to the fore. Thus β-silyl azides **592** undergo *anti* elimination stereoselectively in the presence of fluoride ions to give the olefins **593**.[134] The corresponding silanes **591** are readily accessible either through haloazidation of silylalkanes (Scheme 24) or by electrophilic azidation of enolates (Scheme 146). Whereas sterically unhindered aliphatic azides are reduced smoothly to amines with Ni(II)/Bu_3SnH (see Section 4.4.2), this reagent effects substitution of the azide group by hydride with benzylic azides.[486a]



591 **592** **593**

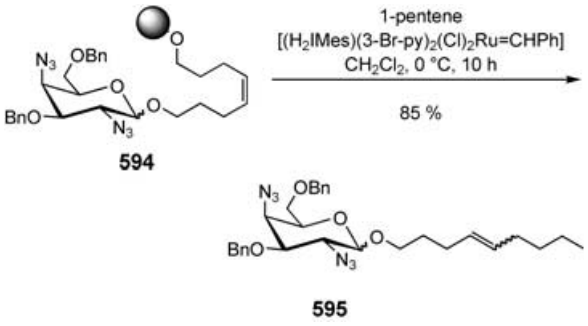
Scheme 146. Synthesis and elimination of β-silyl azides **592**.[134] Trisyl = 2,4,6-triisopropylbenzenesulfonyl.

5. Applications of Azides

5.1. Use as Protecting Groups

The azide function provides a good possibility to protect coordinating primary amines, especially in sensitive substrates such as oligosaccharides, aminoglycoside antibiotics,[152,155] glycosoaminoglycans such as heparin[556] and peptidonucleic acids (PNA).[557] Furthermore, the azide group is stable in osmium-[558] and ruthenium-induced[559] dihydroxylations or alkylations (see Scheme 44).

The protection of the amino function is carried out with, for example, triflyl azide (see Schemes 28 and 29). A more recent example of the stability of alkyl azides towards organometallic catalysts in this context was provided by Seeberger and co-workers, who demonstrated the compatibility of the azido group in cleaving alkene metathesis of saccharides (Scheme 147).[560]

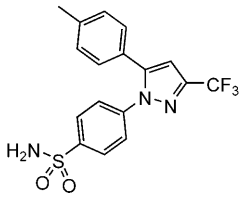


Scheme 147. Cleavage metathesis of organoazides.[560]

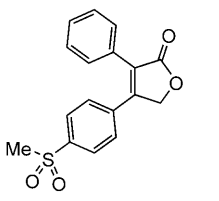
In addition to its use as a protecting group, the azide function provides other creative possibilities, for example, in the aza-Wittig reaction.

5.2. Azides as Biologically Active Compounds and in Natural Products Synthesis

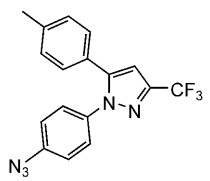
A number of syntheses for the preparation of natural products have been described in the text,[78,80,114b,386,514f,517,561] (see Schemes 6, 20, 22, 30, 36, 44, 74, 78, and 108). Although no natural products are (yet) known with an azide functionality, there is a series of potentially active compounds with this functionality. The high activity can be seen in bioisosteric comparisons of the azide group with other functional groups (see also Section 4.1.2).[562] Parallels have been drawn between the methylsulfonyl and aminosulfonyl groups. The relatively smaller azide group is slightly more lipophilic than these two groups, and, for example, interacts better with arginine units than with sulfonyl functions. Azide derivatives (such as **598**) of the COX-2 inhibitors colecoxib (**596**) and rofecoxib (**597**) are also more potent than the corresponding sulfone derivatives.[563] Comparisons between a 1,1-dichloroethyl group (as in chloramphenicol) and the azidomethyl group have shown that they exhibit similar behavior. A well-



celecoxib (**596**)



rofecoxib (**597**)



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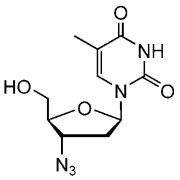


599

known example is the anti-HIV medication AZT (**599**; 3′-azido-2′,3′-didesoxythymidine).[564,565]

5.3. *Photoaffinity Labeling*

The labeling of receptor compounds and ligands with the azide functionality is used in photoaffinity labeling.[566,567] The ligand is equipped with this nitrene precursor at a position (for thalidomide see Scheme 2) that does not distort its affinity for the receptor, but yet is close enough to its target protein. The azide group is particularly suitable for this labeling since after photolysis the organoazide can be inserted into many carbon, nitrogen, oxygen, or sulfur compounds by the formation of nitrenes. An additional radioactive label can also be used to identify the ligand–protein complex (Figure 4).

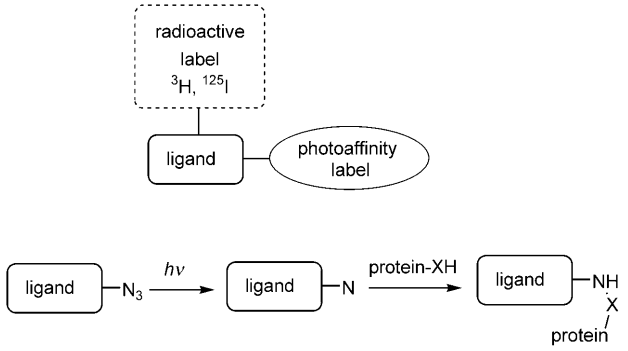
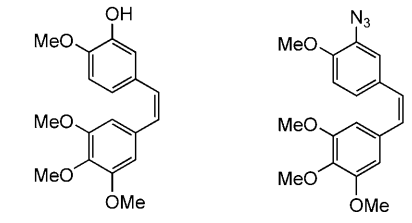


Figure 4. The principle of photoaffinity labeling.

This principle was used, for example, in the synthesis of combrestatin analogues as molecular probes for tubulin polymerization (Figure 5).[568] Furthermore, there have recently been a number of applications in medicinal chemistry.[569]

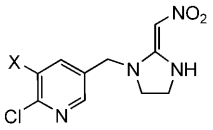


combrestatin A-4 (**600**)

azide-analogous combrestatin A-4 (**601**)

Figure 5. Aryl azides as molecular probes according to Pinney et al.[568]

This process has also been used in modern plant protection research to analyze, for example, the interaction of proteins with insecticides, as in the neonicotinoids (e.g. imidacloprid (**607**), Figure 6).[570] In this connection it was important that the biological properties of the labeled compounds differ only little from the starting compound. The lipophilicity of organic azides has a direct advantage here.



X = H: imidacloprid (**602**)
X = N_3: 5-azidoimidacloprid (**603**)

Figure 6. Heteroaryl azides as molecular probes according to Zhang and co-workers.[570]

Not only can the interaction of small molecules with proteins[571] be investigated by photolabeling with organoazides but also protein–protein [572] and protein–nucleic acid interactions.[573]

The photoaffinity labeling can also be carried out in an intramolecular fashion, which leads to crosslinking. One current example is the covalent bonding of an RNA duplex strand with an internally attached aryl azide (**606**) by photolysis. It was crucial that a hydroxy group occupied the 3-position of the aryl azide **606**, for in this way the evidence was obtained that a ketene imine or a corresponding sequential product as active species leads to the crosslink under nucleophilic attack by the antisense strand (Figure 7).[574]

6. Summary and Outlook

Organic azides have in recent times enjoyed much popularity in synthetic organic chemistry. In spite of—or perhaps because of—their partly less attractive properties (explosiveness, toxicity), a plethora of new applications has been published. In the area of cycloadditions, in particular, the discovery of new reaction conditions has led to a true "explosion" of new applications. It remains to be seen how organic azides will find use in chemical biology or in materials science.

Addendum (April 7, 2005)

Since the submission of this Review, the number of articles on organic azides has continued to increase tremendously—on average, there are more than 1000 publications a year. We refer to some of the excellent papers that have appeared most recently.[575]

Organic azides were used as flexible building blocks in the partial synthesis of some very complex natural products;[576] modern techniques in gene technology have even allowed the incorporation of biochemically modified amino acids as "proteogenes" in peptides.[577]

The 1,3-dipolar cycloaddition of alkynes with azides, an application of the Huisgen reaction in the field of "click chemistry", was discussed several times in review articles.[578] The number of applications of this useful reaction is steadily increasing.[579] The reaction has been optimized considerably, especially in biochemical applications,[580] such that larger biomolecules can also participate in this type of reaction.

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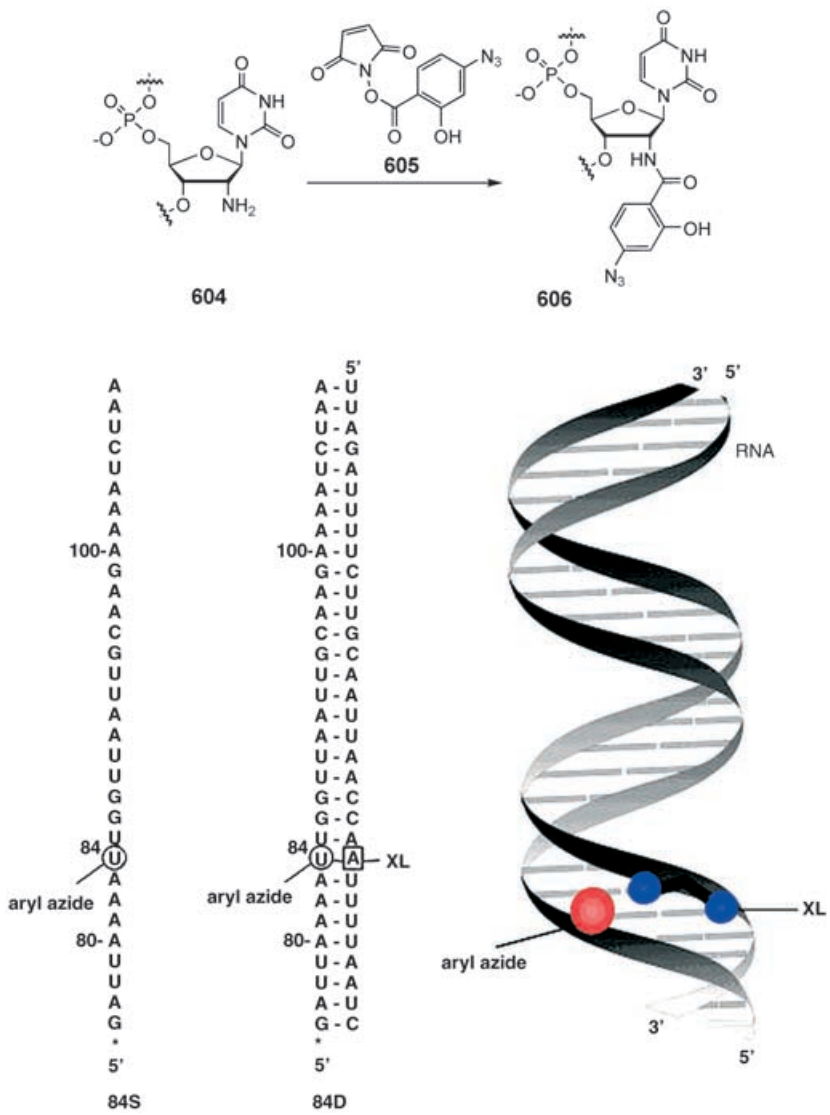

Figure 7. 3-Hydroxyaryl azides as crosslinkers according to Platz, Weeks et al.[574] *: Position of a radioactive ^{32}P label, XL = crosslinking.

Furthermore, this reaction can even take place in enzyme pockets.[581] Consequently, the mechanism of the 1,3-dipolar cycloaddition of alkynes with azides has been investigated in depth.[582] Moreover, polymers can also be prepared in this manner.[583] Azides have also been employed in other cycloadditions.[584]

The Staudinger reaction[585,586] and its application as a ligation method for the conjugation of biomolecules has been widely popular among bioorganic chemists[587] and was used in the synthesis of complex structures.[588] Investigations into the mechanism of this reaction have also been carried out.[589]

Further applications include radical reactions,[590] multicomponent reactions,[591] rearrangements,[592] and several well-known reactions such as the Curtius,[593] Hemetsberger–Knittel,[594] Schmidt,[595] Mitsunobu,[596] and Wittig (aza-Wittig)[597] reactions. Diazido iodinate (formed in situ or polymer-bound) was used in a safe azidation of aldehydes and benzyl ethers.[598] Organic azides are also important structural motifs in the field of high-energy materials, for example, in the synthesis of tetrazolylazide[599] and as precursors in materials research.[600] The rearrangement of organic azides has been investigated within organic cavitands[601] as well as spectroscopically.[602]

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