2*H*-Azirines as Synthetic Tools in Organic Chemistry

Francisco Palacios,*[a] Ana María Ochoa de Retana,[a] Eduardo Martínez de Marigorta,[a] and Jesús Manuel de los Santos[a]

Keywords: Asymmetric synthesis / Azirines / Nitrogen heterocycles / Peptides

The versatility and the high synthetic potential including the asymmetric syntheses of 2*H*-azirines as valuable precursors for the preparation of a wide range of polyfunctional acyclic and cyclic compounds, is discussed.

1. Introduction

Azirine is the term used to describe the smallest nitrogen unsaturated heterocyclic system, with two carbon atoms and one double bond in a three-membered ring. The theoretical, biological applications, and the synthetic chemistry of these heterocycles have been extensively explored since the mid-1960s. A number of general reviews on azirines have appeared in this period.[1] This microreview will focus on the chemistry of monocyclic 2*H*-azirines; the chemistry of fused-ring azirines will not be discussed.

[a] Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco,
Apartado 450, 01080 Vitoria, Spain
Fax: (internat.) + 34-945/130756
E-mail: qoppagaf@vf.ehu.es

Interest in these nitrogen-containing heterocycles stems from the general influence of ring strain upon chemical reactivity and the potential for their derivatives to act as precursors to more elaborate heterocyclic molecules. Polarization toward the more electronegative nitrogen atom would result in a shorter C−N bond and a longer C−C bond, consistent with the dimensions of 2*H*-azirines by single-crystal X-ray data.[2] The stabilities of these heterocycles are attributable not only to the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom. The strain energy associated with these heterocycles is principally owing to deformation of normal bond angles between the atoms of the ring. The total ring-strain energy of 2*H*-azirine has been estimated at about 48 kcal mol^{-1},[1e] although lower values of 44.6 and 46.7 kcal mol^{-1} have recently been reported

Francisco Palacios (right) was born in Vitoria, Spain (1951). He graduated in Chemistry from the University of Zaragoza and he received his PhD degree from the University of Oviedo in 1977 working with Prof. Dr. José Barluenga. After two years (1979−1981) of postdoctoral work with Prof. Dr. Rolf Huisgen at the Organic Chemistry Institute of the Ludwig University (Munich, Germany) working on cycloaddition reactions, he came back to the University of Oviedo as Associate Professor (1981-90) and since 1991 is a Full Professor of Organic Chemistry in the University of the Basque Country. His research interests are organic synthesis, organophosphorus chemistry (phosphorus ylides, phosphane oxides, amino phosphonates), heterocyclic chemistry, cycloaddition reactions (azadienes and 1,3-dipoles), and solid-phase synthesis.

Ana María Ochoa de Retana (second from right) was born in Beasain (Gipuzkoa, Spain) in 1959. She graduated in Pharmacy from the University of Navarra in 1982 and she received her PhD in Organic Chemistry under the direction of Prof. Antonio Monge and Prof. Juan Palop working on the synthesis and study of biological activity of heterocycles. In 1987 she moved to the University of the Basque Country and in 1995 she became Associate Professor of Organic Chemistry. Her current research interests are the synthesis of amino acids and phosphorylated heterocycles.

Eduardo Martinez de Marigorta (second from left) was born in 1961 in Vitoria-Gasteiz. He graduated in Chemistry in 1984 and received his Ph. D. at the University of Basque Country under the guidance of Dr. Esther Domínguez on the chemistry of isoquinolines and protoberberines. In 1991-1992 and 1996 he worked with Dr. Ian Fleming at the University of Cambridge on the use of silyl anions in synthesis. At the end of 1996 he joined the Faculty of Pharmacy and Dr. Palacios' group at the University of Basque Country where he is now Associate Professor of Organic Chemistry. His research interests include the chemistry of nitrogen- and phosphorus-containing compounds and their applications to the conventional and solid-phase synthesis of cyclic and acyclic compounds.

Jesús Manuel de los Santos (left) was born in Mondragón, Gipuzkoa, in 1966. He graduated in Chemistry from the University of the Basque Country in 1990 and obtained his PhD degree in 1996 under Professor F. Palacios, with distinction for his dissertation on the chemistry of β-functionalized phosphorus compounds. He then spent two years as a post-doctoral fellow with Prof. Steven M. Weinreb at the Penn State University at Pennsylvania working on the total synthesis of marine alkaloids. He is now a research associate at the University of the Basque Country. The synthetic methodology and solid-phase synthesis of small organic molecules have been his recent research topics.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

  1434−193X/01/0713−2401 $ 17.50+.50/0

using ab initio calculations at the MP2/6-31G* and B3LYP/6-31G* levels of theory, respectively.[3] According to the authors' calculations, the corresponding value for the isoelectric cyclopropene ring are about 10 kcal mol^{-1} higher than for 2*H*-azirine at the same levels of theory. The structures of 2*H*-azirine, its complexes with H^+ and Li^+, and the relative basicities of 2*H*-azirines have been calculated by semiempirical and ab initio MO methods.[4,5] These calculations showed that the azirinyl cation exhibited aromatic properties.

The general aspects of ^1H, ^{13}C, and ^{15}N NMR spectroscopy of 2*H*-azirines have been well documented. The ^1H NMR spectrum of the parent compound 2*H*-azirine shows absorptions at δ = 1.26 (*J* = 2.05 Hz) and δ = 9.93 for the protons bonded to C(2) and C(3), respectively, and in the ^{13}C NMR spectrum, C(2) resonates at δ = 14.4 and C(3) at δ = 164.2. However, the proton bonded to C(2) shows absorption between δ = 0.20 and 4.00 for substituted 2*H*-azirines and in the ^{13}C NMR spectrum these azirines show absorptions between δ = 19.0 and 45.0 for C(2) and δ = 160.0−170.0 for C(3). A good overview of the NMR characteristics of 2*H*-azirines, especially their ^{13}C NMR spectra, can be found in Nair's review.[1g]

The azirine ring has been found in several natural products. Azirinomycin[6] (**1**) (Figure 1), isolated from *Streptomyces aureus*, and its methyl ester were found to exhibit a broad spectrum of antibiotic activity in vitro against both Gram-positive and Gram-negative bacteria.[7] More recently, the azirine-containing natural products (*R*)-(−)-[8] and (*S*)-(+)-dysidazirine[9] (**2**) and (*S*)-(+)-antazirine[9] (**3**) were isolated from the marine sponge *Dysidea fragilis* (Figure 1).

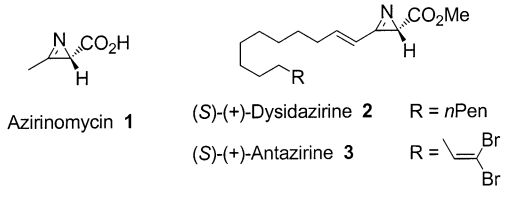
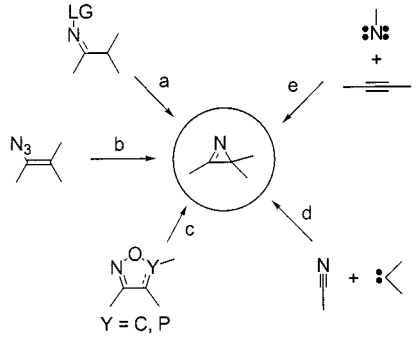


Figure 1. Azirine-containing natural products



Scheme 1

2. Synthesis of 2*H*-Azirines

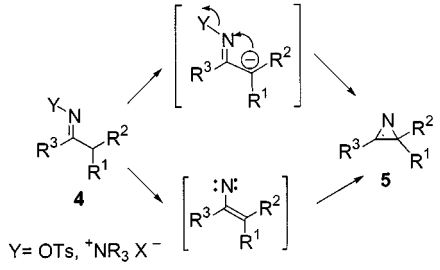
2.1. Construction of the Azirine Ring

There are two main synthetic strategies for the construction of the three-membered 2*H*-azirine ring: (a) intramolecular reactions of *N*-functionalized imines, vinyl azides, isoxazoles and oxazaphospholes (routes a, b, c; Scheme 1), and (b) intermolecular reactions between nitriles and carbenes or nitrenes and acetylenes (routes d, e; Scheme 1).

2.1.1. Intramolecular Reactions

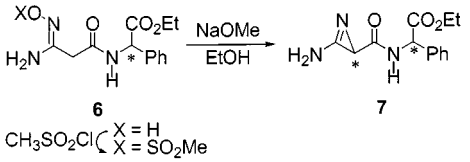
2.1.1.1. The Neber Reaction and Related Processes (Scheme 1, route a)

The first 2*H*-azirine synthesis ever reported was described by Neber et al. The azirines were formed as intermediates in the synthesis of amino ketones when treating oxime *p*-toluenesulfonates **4** (X = OTs) with base (Scheme 2).[10] The presence of strong electron-withdrawing groups in the α-position to the oxime increases the acidity of those protons, and thus favors the cycloelimination reaction under milder conditions. Modifications of the Neber reaction based on the use of ketone dimethylhydrazonium halides **4** (X = $^+NR_3X^-$) instead of oxime sulfonate esters have also been developed.[11] The Neber reaction probably occurs either through an internal concerted nucleophilic displacement or via a vinylnitrene, a reactive species formed by base-promoted loss of the leaving group on the nitrogen atom of oxime sulfonates and hydrazonium halides (Scheme 2).[1c] 4π-Electron vinylnitrenes, which are thought to be intermediates in the synthesis of 2*H*-azirines from vinyl azides (see next section), would then undergo electrocyclization to 2*H*-azirines.



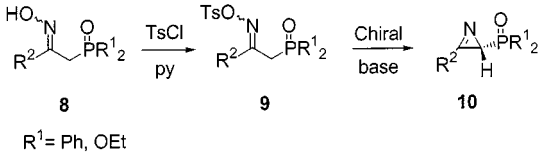
Scheme 2

The first optically active 2*H*-azirines were synthesized using the Neber reaction on an *O*-mesyl derivative of amidoxime **6** in which a chiral phenylglycine had been introduced as a chiral auxiliary. Treatment of this derivative with base gave the 3-amino-2*H*-azirine **7** in good yield and stereoselectivity (96:4) with both an exocyclic and an endocyclic stereocentre [C(2) of the azirine] (Scheme 3).[12]



Scheme 3

An impressive asymmetric synthesis of azirinecarboxylates with a chiral tertiary base, such as dihydroquinidine or quinine, in toluene has been achieved based on the Neber reaction.[13] The enantiomeric excess obtained ranged between 44 and 82%, when a stoichiometric amount of base was employed, but excellent results were also obtained when 10 mol-% of quinidine were used. The stereoselectivity is attributed to the hydrogen bond formed between the hydroxy group of the base and one of the S=O functionalities of the ketoxime. Other chiral tertiary bases without the hydroxy group, such as aspartane, brucine and strychnine, and the use of hydroxylic solvents such as ethanol did not produce any optically active heterocycles. This strategy has been applied to the first synthesis of enantiomerically enriched 2-phosphinyl-2*H*-azirines **10** (R^1 = Ph) (Scheme 4). Excellent chemical yields and enantiomeric excesses up to 82% in alkyl- and aryl-substituted azirines **10** have been obtained.[14] Precursor tosyloximes **9** were obtained by tosylation of β-oximo phosphane oxides **8**. Compounds **8** were easily prepared by addition of hydroxylamine to allenes[15] for alkyl-substituted oximes, and aryl derivatives were prepared by a condensation reaction of β-carbonyl phosphane oxides and hydroxylamines.[14b] A similar strategy has been used for the preparation of alkyl- and arylazirines **10** substituted with a phosphonate group in the 2-position (R^1 = OEt).[16] However, this method cannot be applied to the synthesis of unsubstituted azirines **10** (R^2 = H, Scheme 4) because of the inaccessibility of the corresponding tosyloximes.[17]



Scheme 4

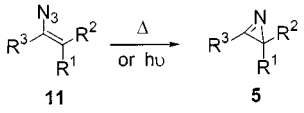
The 2*H*-azirine-2-carboxylic and the corresponding isosteric phosphonic esters obtained through this method are of particular interest because by their reduction to the corresponding aziridine followed by ring opening, nonprotein amino acids[1e,18] and their isosteric analogues can be prepared.

2.1.1.2. Pyrolysis and Photolysis of Vinyl Azides (Scheme 1, route b)

A wide range of synthetic methods have been developed for the synthesis of vinyl azides.[19] The thermal and/or photochemical treatment of vinyl azides **11** has become a general method for the synthesis of 2*H*-azirines.[1d][19a] The first azirine synthesis by pyrolysis of vinyl azides was performed in the early 1960s with yields of 50−60% of 2*H*-azirines.[20] Pyrolysis has been extended to the preparation of functionalized azirines **5** with amine, alkoxide, aldehyde, carboxylic ester, phosphane oxide, and fluorine substituents. In some cases, it is difficult to isolate the 2*H*-azirines after heating the vinyl azides, this is because of the thermal instability of these three-membered heterocycles. However, the photochemical reaction at low temperature can in some instances lead to the synthesis of azirines with little polymerization (Table 1, Scheme 5).

Table 1. Some 2*H*-azirines obtained by thermolysis/photolysis of vinyl azides

Entry	R^1	R^2	R^3	Conditions	Reference
1	H	CO_2Et	R_F	ΔT	[21]
2	$P(O)Ph_2$	H	Me	ΔT	[14a]
3	H	H	CO_2tBu	ΔT	[22]
4	CO_2Et	Br	Ph	ΔT	[23]
5	Me	Me	$CH_2P(O)(OEt)_2$	$h\upsilon$	[24]
6	$-CH_2-$		Alkyl	$h\upsilon$	[5c,25]
7	Ph	Bzl	Ph	$h\upsilon$	[26]

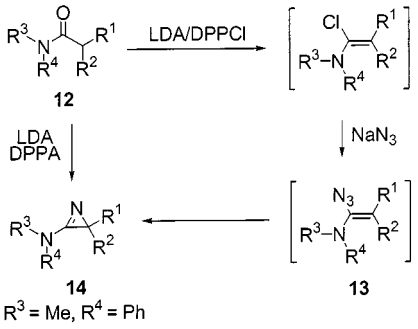


Scheme 5

The formation of 2*H*-azirines by thermolysis depends mainly on the structure of the vinyl azide.[27] Thus, azides substituted in the 1-position with aryl, alkyl, alkoxy, amine, or carboxylic groups give quite stable azirines, while hydrogen or carbonyl group substitution leads to nitriles or other heterocycles instead of the azirine ring. When carbonyl groups are present at the 2-position of the vinyl azide, oxazole formation results,[27,28] and the presence of aryl groups at the 2-position produces indoles[27] and in some cases azirines.[29] This cyclization of vinyl azides has recently been applied to the synthesis of complex compounds which are analogs of 2′-deoxyuridine, and exhibit appreciable antiviral activity.[30] The participation of nitrenes is not the only possible mechanistic pathway to the formation of 2*H*-azirines, the most widely accepted mechanism involves the concerted cyclization−elimination of N_2 assisted by the π-bond.[27,31]

An efficient synthesis of 2*H*-azirines, which most likely proceeds through a nonisolable vinyl azide **13**, involves the reaction of α-mono- or -disubstituted amide derivatives **12** and an azide source. Initially, the amide was treated with phosgene/triethylamine to isolate the corresponding α-chloro enamine which was then treated with NaN_3 and 3-

amino-2*H*-azirine was produced, probably via the azido enamine.[32] The use of the highly toxic phosgene could be avoided by the alternative reaction of the amide enolate with diphenyl phosphorochloridate (DPPCl) followed by treatment with NaN_3 (Scheme 6).[33] Another advantage of this method is that the isolation of the sensitive α-chloro enamine intermediate is not necessary, and this method has been used to prepare heterospirocyclic 3-amino-2*H*-azirines, synthons for heterocyclic amino acids.[34] More recently, diphenyl phosphorazidate (DPPA) has been used as an azide source and by substitution of the oxygen atom of amide enolates the 3-amino-2*H*-azirines can be obtained in "one pot" and with very good yields (Scheme 6).[35] The reaction is the method of choice to synthesize 2,2-disubstituted 3-amino-2*H*-azirines **14**.

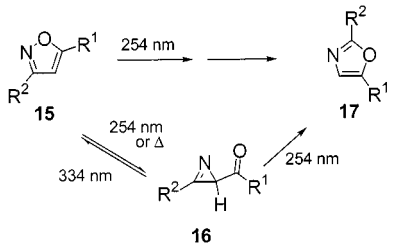


Scheme 6

For the synthesis of optically active 3-amino-2*H*-azirines, a modification of the above approach with a chiral substituent at the amino group of a thioamide has been used.[36] Chromatographic separation of the diastereomeric mixture of 3-amino-2*H*-azirines gave pure diastereoisomers which, after electrochemical cleavage of the phenylsulfonyl group, were used as synthons in the synthesis of pentapeptides.

2.1.1.3. Ring Contraction of Five- and Four-Membered Heterocycles (Scheme 1, route c)

Thermal or photochemical treatment of isoxazoles **15** produces ring contraction to acyl-2*H*-azirines **16**, which sometimes rearrange to form other heterocycles like oxazoles **17** (Scheme 7).[37] These transformations have proved to be reversible at high temperature or with a change in the irradiation wavelength. Although the thermal rearrangement of isoxazoles has produced several azirines with good yields,[37b,38] this synthesis is of limited preparative value due to the high temperatures usually needed. Ring contraction from isoxazoles to azirines can also be promoted by iron(II) catalysts. Thus, 5-alkoxy- and 5-aminoisoxazoles isomerize to 2*H*-azirines-2-carboxylic esters and to 2*H*-azirine-2-carboxamides, respectively, in nearly quantitative yield by reaction with $FeCl_2$ even in catalytic amounts.[39]



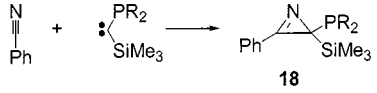
Scheme 7

Thermally induced extrusion of phosphane oxide from 1,3,5- and 1,2,5-oxazaphosphole heterocycles also leads to 2*H*-azirines by ring contraction.[40] 2*H*-Azirines can also be obtained from azete derivatives. These heterocycles are oxidized by dimethyl sulfoxide to give the 2*H*-azirine directly or, alternatively, they can be treated with 1-diazo-1-phenylethane to form the intermediate bicyclic adduct which then rearranges on thermal or photochemical treatment to generate hydrazono-2*H*-azirines.[41]

2.1.2. Intermolecular Reactions

In contrast to the cycloaddition synthesis of the parent aziridine system from nitrenes and olefins, or from carbenes and imine derivatives, the intermolecular cycloaddition reactions of carbenes to nitriles or nitrenes to alkynes is not a general method for the synthesis of azirines, as the yields obtained are usually not good enough for preparative applications. The addition of nitrenes to alkynes (Scheme 1, route e), for instance, was initially developed to find a method for the synthesis of 1*H*-azirines, but only small amounts of the isomeric 2*H*-azirines were obtained.[42] The intramolecular version of this reaction is also known, giving a much better yield of 2*H*-azirine derivatives.[43]

The other cycloaddition approach to 2*H*-azirines involves the reaction between carbenes and nitriles (Scheme 1, route d), but only a few successful syntheses have so far been achieved. 1-Naphthylcarbene (generated by ultraviolet irradiation) reacts with nitrile, but instead of the expected 2*H*-azirines, the products from trapping the intermediate nitrile ylides are isolated.[44] A better result has been obtained from the [1+2] cycloaddition reaction between a phosphanylcarbene and benzonitrile, and this reaction afforded the corresponding phosphorus-substituted 2*H*-azirine **18** in good yield (Scheme 8),[2,45] but in spite of its simplicity, no more examples of this approach have been reported to our knowledge.

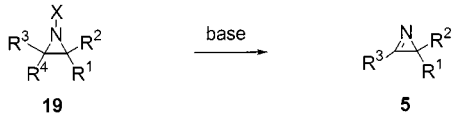


Scheme 8

2.2. Modification of the *Nitrogen*-Containing Three-Membered Ring

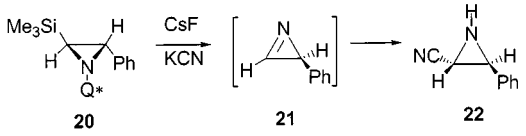
2.2.1. Elimination Reaction of Aziridines

N-Substituted aziridines **19** are prone to elimination when treated with base and thus, 2*H*-azirines **5** can be obtained in this way. Examples of this approach include *N*-chloro-,[46] *N*-sulfonyl-,[47] and *N*-acyl-substituted[48] aziridines (Scheme 9). This strategy has also been used for the asymmetric synthesis of azirinecarboxylates by the elimination of *N*-haloaziridines, which are readily obtained by treatment of aziridines with *tert*-butyl hypochlorite. Dehydrochlorination of the *N*-chloroaziridines with base (DBU) produces the corresponding 2*H*-azirines, although the yields are not good (9−39%).[49]



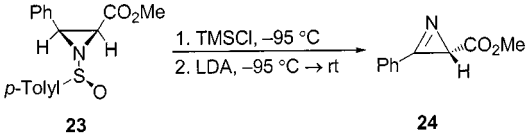
Scheme 9

Fluoride-induced elimination of silyl- and stannylaziridines, obtained by addition of nitrene to vinylsilanes and -stannanes, provide an interesting approach to azirines (Scheme 10).[50] Fluoride-mediated elimination of $SiMe_3$ and the quinazolinone ring (Q) from a chiral aziridine **20** gave optically active azirines which were not isolated, but treated with nucleophiles in the reaction media to furnish NH aziridines in high enantiomeric excess.[51]



Scheme 10

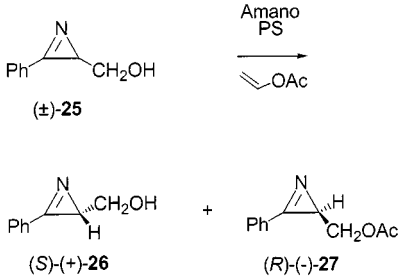
Chiral *N*-sulfinylaziridines **23** provide another elimination approach (Scheme 11). Indeed, the treatment of these derivatives with LDA/MeI afforded 2*H*-azirines **24** with high enantiomeric excess (95%) but only moderate chemical yields, and this probably because of the competitive deprotonation at C(2) followed by ring opening.[52] Improvement of the leaving ability of the *N*-sulfinyl group by treatment with TMSCl at −95 °C and then with LDA, also increased the yields to afford an elegant synthesis of 2*H*-azirine-2-carboxylates **24** with no traces of the isomeric 3-carboxylate derivatives.[53] This procedure has been applied to the first asymmetric synthesis of the marine cytotoxic antibiotic (*R*)-(−)-dysidazirine and its (*S*)-(+) epimer **2** (Figure 1).[52,53] This methodology did not work when applied to 2,2-disubstituted aziridines; however, transformation of the *N*-sulfinyl group into the *N*-tosyl group by oxidation with *m*-CPBA,[54] and treatment of the corresponding 2,2-disubstituted *N*-tosylaziridine with LDA afforded the chiral 2*H*-azirine with good yields.[55]



Scheme 11

2.2.2. Azirine Resolutions

Chemoenzymatic synthesis has recently been used for the preparation of enantiomerically pure 2*H*-azirines. Thus, (*S*)-(+)-phenyl-2*H*-azirine-2-methanol **26** and its (*R*)-(−)-acetate **27** were prepared by a lipase-catalyzed kinetic resolution of the racemic 2*H*-azirinemethanol **25** (Scheme 12). The reaction was carried out at very low temperature (−40 °C), and therefore enhanced the enantioselectivity.[56]

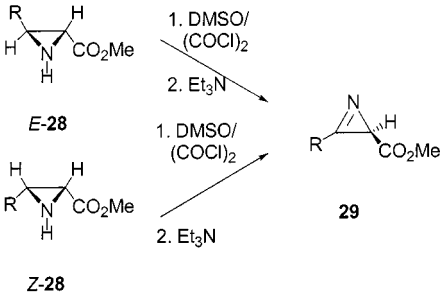


Scheme 12

2.2.3. Oxidation of Aziridines

3-Alkylaziridine-2-carboxylates have been oxidized with the Swern reagent to afford 2*H*-azirine-2-carboxylates with acceptable yields[57] and retention of configuration at C(2). This makes this method one of the first asymmetric syntheses of 2*H*-azirine-2-carboxylates **29** described in the literature (Scheme 13). Similarly to the above *N*-sulfinyl or *N*-tosyl elimination route, this procedure also gives a regioselective introduction of the double bond, which is not in conjugation with the ester function as no isomeric 2*H*-azirine-3-carboxylate has been detected. Furthermore, the oxidation of either the (*Z*) or the (*E*) isomers **28** provides the same 2*H*-azirine-2-carboxylate **29**, where the integrity of the stereogenic center at C(2) is retained. This regioselectivity resulted from the unexpected removal of the apparently less acidic C(3) proton during the base-induced *syn* elimination of the *N*-dimethylsulfonium intermediate. The reasons for this behavior are not yet clear. When the Swern oxidation was performed on a 1*H*-aziridine-2-carboxylate without a C(3) proton, the corresponding 2*H*-azirine-3-carboxylate was obtained with good yield, to provide an enantiomerically enriched azirine in which the carboxy group is conjugated with the C=N bond.[53] This methodology has been adapted to accomplish the asymmetric synthesis of azirinephosphonates substituted with an aryl group, although in

this case a mixture of both regioisomers, 2*H*-azirine-2-phosphonate and 2*H*-azirine 3-phosphonate, was obtained.[58]



Scheme 13

3. Reactivity of 2*H*-Azirines

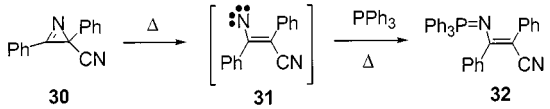
The chemistry of 2*H*-azirines, the smallest of the unsaturated nitrogen heterocycles, has been extensively explored because of the high reactivity of this ring system. Their high ring strain, reactive π-bond, lone pair of electrons on the nitrogen atom and their ability to undergo regioselective ring cleavage on thermal or photochemical excitation to give reactive species such as vinylnitrenes, iminocarbenes and nitrile ylides makes them particularly interesting in organic synthesis. They are not only capable of acting as nucleophiles and electrophiles in organic reactions, but also can act as dienophiles and dipolarophiles in cycloaddition reactions.

3.1. Thermal and Photochemical Reactions

Thermal and photochemical reactions of azirines involve regioselective opening of the strained three-membered ring, to give, for example, unstable nitrenes or nitrile ylides. These intermediates can react further in cycloaddition reactions or by other processes.

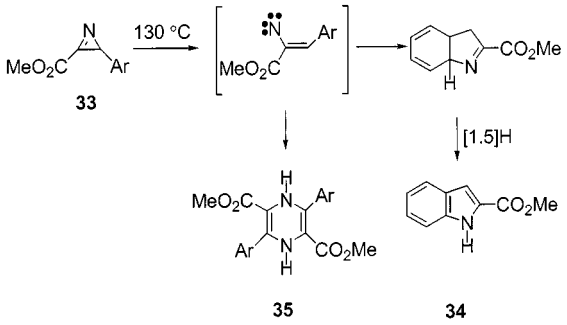
3.1.1. Thermal Reactions

The major thermal reaction of 2*H*-azirines is generally consistent with C(2)−N bond cleavage to form vinylnitrenes.[1h] Conjugated phosphazenes **32** can be trapped by thermolysis of azirine **30** in the presence of triphenylphosphane, in a similar process to that reported for the preparation of *N*-vinylphosphazenes by the Staudinger reaction of vinyl azides and phosphanes.[59] This result is consistent with the presence of transient vinylnitrenes in the thermolysis of azirines[60] (Scheme 14).



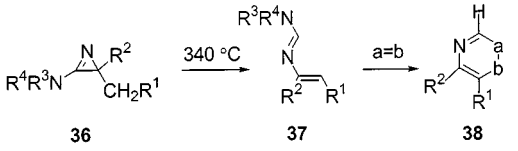
Scheme 14

Ring expansion of 2*H*-azirines to four-membered heterocycles was described when a chloroform solution of phosphonioazirine was heated at 55 °C, and the *N*-protonated azaphosphete was afforded in very high yield.[2] Likewise, thermal rearrangement of 2*H*-azirines, with an unsaturated group at the 2-position of the azirine ring, usually gives five- and six-membered nitrogen-containing heterocycles.[1,19b] Formation of these heterocycles was shown to proceed by a mechanism which involved a vinylnitrene. For example, the thermolysis of aryl-substituted azirines **33** results in the formation of indoles **34** by intramolecular electrocyclization of the intermediate vinylnitrene with the aromatic ring, as well as the formation of dihydropyrazines **35** by dimerization of the nitrene (Scheme 15).[61] Similarly, thermal treatment of azirines derived from phosphane oxide and phosphonate led to the formation of pyrazines.[17]



Scheme 15

Thermal cleavage of the C−C bond of 2*H*-azirines is less common than C(2)−N bond cleavage, and requires substantially higher temperatures. These reactions are believed to proceed with the formation of nitrile ylides which yield 2-aza-1,3-butadienes. 3-Amino-2*H*-azirines **36** can be cleaved by pyrolysis at 340−400 °C.[62] 2-Azabuta-1,3-dienes of type **37** can be formed and they are useful heterodienes for the synthesis of heterocycles **38** by a Diels−Alder reaction with dienophiles (a=b) (Scheme 16). In the last decade, 2-azadienes have proved to be excellent synthons for the preparation of nitrogen heterocycles in inter- and intramolecular reactions,[63] and less drastic methods for their preparation have recently been developed.[64] Ring expansion of 3-dimethylamino-2-methyl-2-vinyl-2*H*-azirine to pyrrole, observed on thermolysis at 340 °C, also seems to occur by breakage of the C−C bond.[65]

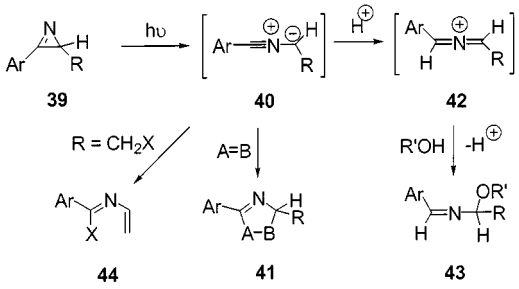


Scheme 16

3.1.2. Photochemical Reactions

2*H*-Azirines are photochemically highly active substances. Upon irradiation into their n−π* absorption bands, the strained 3-membered azirine ring opens selectively at the C−C bond in a heterolytic fashion and results in the formation of nitrile ylides. These species are 1,3-dipoles and are useful intermediates in the synthesis of acyclic

and cyclic compounds[66] (Scheme 17). On photolysis of phenyl-2*H*-azirines **39** in acetonitrile or alcohol solution with laser light, phenylnitrile ylides **40** are formed. Electron-deficient olefins react with the nitrile ylides by 1,3-dipolar cycloaddition to yield 5-membered nitrogen heterocycles **41**. But, with alcohols as solvents, the nitrile ylides are protonated[67] to yield azallenium cations **42**, which can be trapped with alcohol leading to the formation of alkoxyimine **43**. When the azirine contains a good leaving group **39** (R = CH_2X), the isomerization to 2-azadiene **44** has been reported.[68]

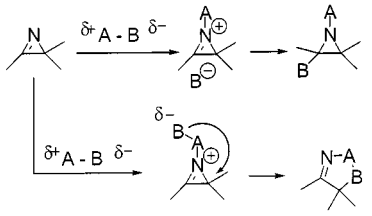


Scheme 17

Ring expansion of three-membered azirine to pentagonal heterocycles by photochemical isomerization was reported.[36b] Certain cyanoarenes can be photoexcited at relatively low wavelength (350 nm) and this excited sensitizer will then extract an electron from a 2*H*-azirine species to form a reactive intermediate, the azaallenyl radical cation. The photoinduced electron transfer (PET) intermediate is more reactive than the nitrile ylide and it will add to simple imines to give a substituted imidazole.[69] Functionalized fullerenes can also be prepared with this strategy, by an 1,3-cycloaddition reaction of aryl-2*H*-azirines.[70]

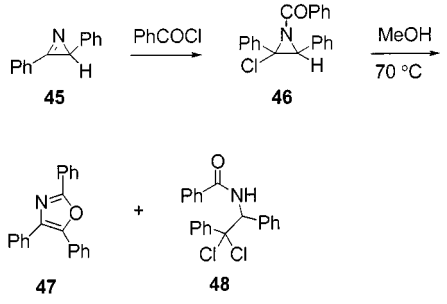
3.2. Reaction with Electrophiles and Metal-Induced Reactions

Although the basicity of the nitrogen atom in the azirine ring is much lower than in simple aliphatic imines, this system can still function as a nucleophilic reagent. Therefore, these substrates can react with a wide range of electrophilic compounds to give three- or five-membered nitrogen derivatives. In both cases the first step may be the nucleophilic attack of the azirine involving the nitrogen lone pair to the electrophilic reagent with formation of azirinium salts. Inter- or intramolecular nucleophilic attack on C(2) or C(3) of the ring system then follows (Scheme 18).



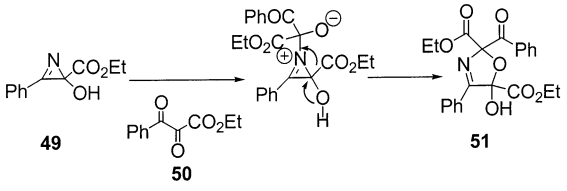
Scheme 18

The more simple base-acid reaction of 2*H*-azirines involves the protonation (AB = HX) of these heterocycles to give azirinium salts, which undergo nucleophilic attack on the carbon skeleton of the azirine ring to give acyclic and cyclic derivatives (see next section). 2*H*-Azirines also react with acylating agents such as acyl chlorides in benzene, the acyl and the chloride group has been added to the C−N double bond to give the *N*-acyl-2-chloroaziridines[71] **46** in good yield (Scheme 19). This *N*-acylaziridine is converted in polar solvents or by heating into a mixture of oxazole **47** and dichloroamide **48**. However, whereas the reaction of 3-phenyl-2*H*-azirine with acid chlorides and anhydrides in the presence of triethylamine gives the oxazole directly,[72] the reaction of 3-amino-2*H*-azirines with acyl chlorides or chloroquinones leads to acrylamidines.[47,73] 2-Chloro-*N*-vinylaziridines are obtained by reaction of the nitrogen atom of azirine and vinyl chlorides.[74]



Scheme 19

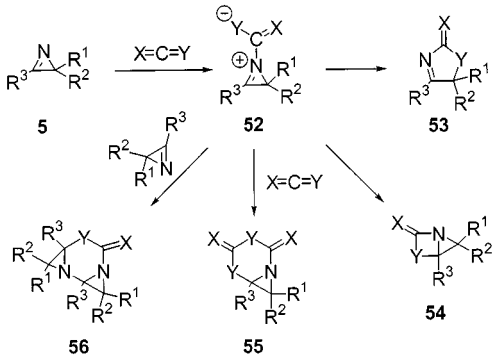
Substituted azirines react with some carbonyl compounds with ring expansion and lead to an elegant synthesis of functionalized oxazoline derivatives. The reaction of 2-hydroxy-2*H*-azirine **49** with the dioxo ester compound **50** gives 3-oxazoline[23a] **51** (Scheme 20). The reaction probably begins with a nucleophilic attack of the azirine to the reactive carbonyl linkage followed by ring opening and intramolecular nucleophilic addition with formation of the five-membered heterocycle. The mild base-promoted reaction of methyl 3-phenyl-2*H*-azirine-2-acetate with aldehydes and acetone also provides a simple route to 3-oxazolines.[75]



Scheme 20

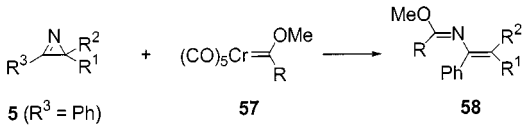
The reaction of simple 2*H*-azirines **5** with heterocumulenes has been reported to afford a wide range of mono-, bi-, and tricyclic heterocycles. Whereas monoadducts **52**, formed by reaction of 2*H*-azirine with ketenes[76] or *N*-sulfonylamines,[77] have been used for the preparation of five-membered ring systems such as 5-pyrrolin-2-one or 1,2,5-thiadiazoles **53**, bicyclic aziridines **54** have been described by the reaction of azirines and isothiocyanates.[78] Likewise,

more complex compounds have been reported when the monoadducts **52** were trapped either with a second equivalent of ketene to give the bicyclic 1,3,5-dioxazine[79] **55** or with a second equivalent of azirine to give tricyclic heterocycles[80] **56** (Scheme 21).



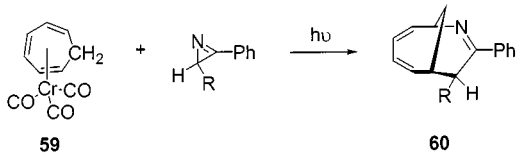
Scheme 21

The synthesis of metal-coordinated 2*H*-azirines and the reactions of azirines induced by metals have opened a new area in the chemistry of this small-ring heterocycle. Transition metal complexes were obtained by the reaction of azirine with palladium reagents[81] or with transition metal halides.[82] Hegedus et al. reported an elegant synthesis of electron-rich 2-azadienes **58** when aryl-2*H*-azirines react with Fischer carbenes[83] **57** (Scheme 22). Likewise, the reaction of azirines with wolfram or molybdenum complexes provides ring-opened compounds by initial complexation of the azirine nitrogen atom with the metal center.[83,84] 2-Phenyl-2*H*-azirine undergoes ring-opening dehydrogenative double silylation with *o*-bis(dimethylsilyl)benzene in the presence of (ethylene)bis(triphenylphosphane)platinum catalyst to give bis(silyl) enamines by insertion of the nitrogen atom between both silicon atoms.[85]



Scheme 22

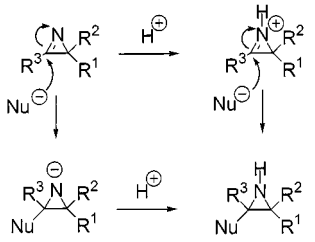
Dimerization reactions of 2*H*-azirines to pyrazines with several transition metal complexes (carbonyl complexes of Group VI metals) have been described,[86] and the bimolecular cycloaddition of dimethyl acetylendicarboxylate with 3-phenyl-2*H*-azirines in the presence of hexacarbonylmolybdenum[87] to pyrrole derivatives has been studied. Metal-mediated higher order cycloadditions for the construction of bridged heterocycles were reported by UV irradiation of tricarbonyl(cycloheptatriene)chromium(0) **59** and 3-phenyl-2*H*-azirines at 0 °C to give 7-aza-8-phenylbicyclo-[4.3.1]deca-2,4,7-trienes **60** by [6+3] cycloaddition coupling of a 1,3-dipole generated from the azirine to the cycloheptatriene ring[88] (Scheme 23).



Scheme 23

3.3. Reaction with Nucleophiles

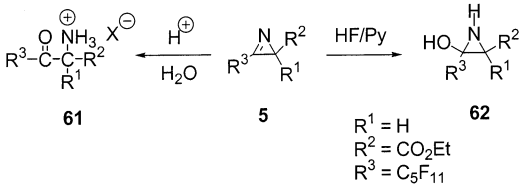
The most common reaction of azirines involves the addition of nucleophiles to the ring carbon atoms. Owing to the strain of the three-membered ring, the electrophilic character of the C−N double bond is higher than in a normal imine. Therefore, azirines react with nucleophiles at the C(3)−N double bond, to produce substituted aziridines[1f,1g] which may undergo reaction by ring opening. Both, acid-catalyzed reactions and direct additions of a wide range of nucleophilic reagents have been described (Scheme 24).



Scheme 24

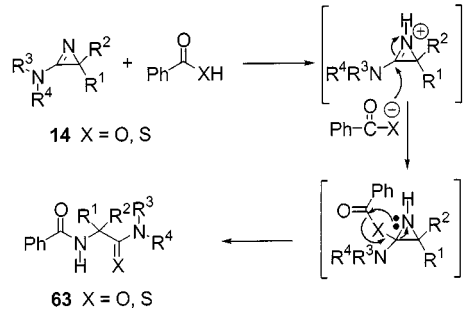
Acid catalyzed hydrolysis of azirines **5** to α-amino ketones[89] or their corresponding salts **61** represent the simplest reaction of these compounds (Scheme 25). The reaction involves initial protonation at the nitrogen atom followed by addition of water to the azirinium ion and ring opening. Interestingly, the addition of HF/Py (Olah's reagent) to a highly electrophilic 3-(perfluoroalkyl)-2*H*-azirine[21] led to a stable 2-hydroxyaziridine **62**, presumably owing to the electron-withdrawing perfluoroalkyl group. This 2-hydroxyaziridine **62** reacts with HCl to give the ring-opened α-amino ketone. 2-Methyl-3-phenyl-2*H*-azirine has been subjected to Olah's reagent to give the ring-opened compound β,β-difluoroamphetamine.[90] A protonated azirine system has also been utilized for the synthesis of acyclic and heterocyclic compounds.[89b] Treatment of 2,2-dimethyl-3-phenyl-2*H*-azirine with anhydrous perchloric acid and acetone or acetonitrile gives the oxazoline perchlorate and an imidazolinium perchlorate, while the reaction with anilinium perchlorate gives α-ammonioisobutyrophenone anil perchlorate.[91] Likewise, reaction of azirines with trimethylsilyl triflate or trityl tetrafluoroborate[92] yield azirid-

inium salts, which react with nucleophiles to give 2-aminoaziridines or further open-chain products.



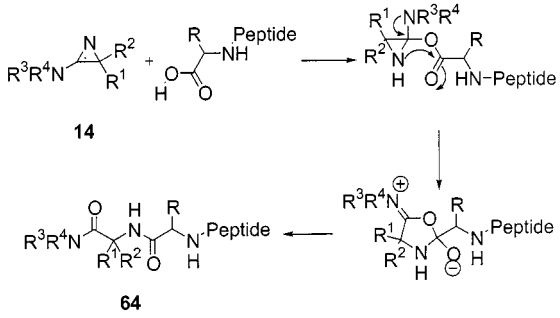
Scheme 25

Ring-opening reactions of azirines take place when carboxylic or thiocarboxylic acid react with 2,2-disubstituted-3-amino-2*H*-azirines **14** under mild conditions to furnish diamides[93] **63** (X = O) or thiodiamides[33a] **63** (X = S), respectively, in good yields (Scheme 26). In a similar way to the previously reported hydrolysis of azirines, the first step involves initial protonation on the nitrogen atom of the azirine **14**. This is then followed by the attack of the carboxylic anion on the azirinium ion, and tandem intramolecular nucleophilic addition of the nitrogen lone pair on the carboxylic group, and formation of the amide and ring opening (Scheme 26).



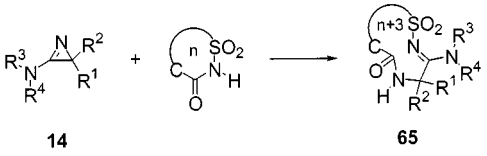
Scheme 26

The extension of this process to functionalized carboxylic acids such as amino acids, offers a very interesting synthesis of peptides with an α,α-disubstituted amino acid, as shown in Scheme 27. 3-Amino-2*H*-azirines **14** react readily with the carboxylic acid moiety of *N*-protected amino acids (first coupling step) by addition across the heterocyclic double bond followed by ring expansion to form a zwitterionic oxazolone which then undergoes ring opening to form the diamide **64**. This reaction can be regarded as a peptide chain elongation step that introduces an α,α-disubstituted amino acid onto the *C*-terminal end of a peptide, as shown in Scheme 27. This methodology has been widely applied to the formation of peptides,[1e,33b,94] and various more complex oligopeptides, particularly those with the α-aminoisobutyric acid residues such as the sequence (12−20)-nonapeptide of the ionophore alamethicin,[95] endothiodecapeptides,[96] the segment (1−10)-endothiodecapeptide of the apolar zervamicin IIA,[97] and 10-[98] and 16-membered cyclic depsipeptides[99] through acid-catalyzed direct amide cyclization.



Scheme 27

Heimgartner et al. have also shown that nucleophilic addition of amides or hydrazides to 3-amino-2*H*-azirines **14** produces triazines or oxadiazoles.[100] This reaction can also be applied to NH-acidic heterocycles with $pK_a < 8$ to give ring-enlarged heterocycles such as 1,2,5-thiadiazepine derivatives[101] **65** ($n = 4$) or 1,2,5-thiadiazacyclododecen-6-one 1,1-dioxides[102] **65** ($n = 9$) (Scheme 28). Variation of the substrate in reactions with other NH-acidic heterocycles demonstrates that the initial step in all these reactions is an activation of the 3-amino-2*H*-azirine **14** by protonation, since for substrates with $pK_a > 8$, the reaction no longer occurs.



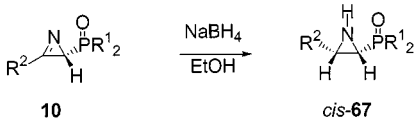
Scheme 28

Lewis acid catalyzed reactions of 3-amino-2*H*-azirines with carboxylic acid derivatives have also been reported. After activation by protonation or complexation with BF_3, 3-amino-2*H*-azirines **14** reacted with the amino group of α-amino acid esters to give 5-amino-3,6-dihydropyrazin-2(1*H*)-ones **66** by ring enlargement[103] (Scheme 29). A similar methodology was recently used for the synthesis of bis(-steroidal) pyrazines,[104] this involved a ring-fused azirine, formed in situ from a vinyl azide with a steroidal enamino ketone in refluxing dioxane and in the presence of pyridine-*p*-toluenesulfonate (PPTS).

Scheme 29

Several 2*H*-azirines have been reduced to *cis*-aziridines with lithium aluminum hydride in a highly stereospecific manner.[105] This reaction has been used for fluoro-substituted aziridine synthesis,[21] as well as for the formation of *cis*-aziridinecarboxylates.[13] Azirines derived from phos-

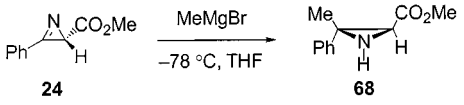
phane oxides[14a] **10** (R^1 = Ph) and phosphonates[16a] **10** (R^1 = OEt) have been reduced to aziridines using sodium borohydride, to give the *cis*-aziridines **67** exclusively (Scheme 30). The high exocyclic dihedral angle at the saturated carbon atom could hinder the nucleophilic attack of the hydride ion on the iminic bond with the bulky substituent, and the diastereoselectivity of the reduction can thus be justified. Therefore, the approach of the hydride ion is more favorable from the side opposite to the group at the 2-position and *cis*-aziridines are formed exclusively. [(2*H*-Azirin-2-yl)methyl]phosphonates have been subjected to reduction with $NaBH_4$ with the formation of disubstituted *cis*-aziridines predominating.[106]



10 *cis*-**67**

Scheme 30

Other nucleophilic reagents such as Grignard reagents have been shown to react with 2*H*-azirines to give aziridines. The few reports of the addition of Grignard reagents to 2*H*-azirines reveal that the aziridine product is formed by attack at the least hindered face.[107] However, recent results which involve the addition of methylmagnesium bromide from the more hindered face of 2*H*-azirine-2-carboxylate esters **24** have resulted in a new methodology for the asymmetric synthesis of 3,3-disubstituted aziridine-2-carboxylate esters[54] **68** (Scheme 31). These results, which contradict previous reports,[107] are likely to be a consequence of prechelation of the Grignard reagent with the ester group.

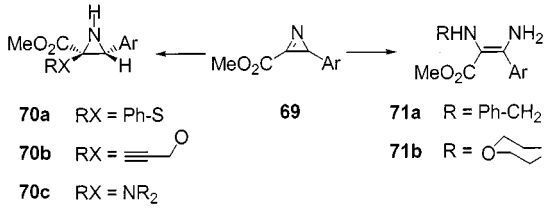


24 **68**

Scheme 31

3-Phenyl-2*H*-azirines react with lithium derivatives of 1,3-dithianes to afford *C*-functionalized aziridines or primary allylic amines.[108] This reaction of azirines with organometallic derivatives can be extended to azaenolates derived from oximes or *N*,*N*-dimethylhydrazones.[108]

2-Halo-2*H*-azirines have been used for nucleophilic substitution using potassium phthalamide and aniline as nucleophiles, and allow the preparation of new substituted 2*H*-azirines through halide displacement.[23a] However, reaction of these azirines with methylamine underwent not only halide displacement but also addition to the iminic double bond to give substituted aziridine. Electron deficient azirines such as methyl 2-aryl-2*H*-azirine-3-carboxylate **69** (Ar = 2,6-$Cl_2C_6H_3$) are highly susceptible to nucleophilic attack.[109,110] This azirine reacted readily with nucleophiles such as benzenethiol, propargyl alcohol or five-membered nitrogen heterocycles[110] to give the substituted aziridine **70** (Scheme 32). However, acyclic 3-aminoacrylates **71** are observed when azirine **69** reacted with morpholine or benzylamine, while pyrroles may be prepared by this reaction with acetylacetone.



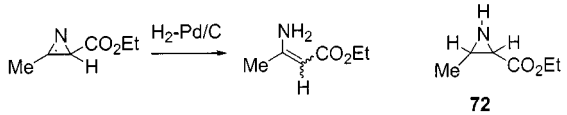
Scheme 32

Reaction of methyl 3-(2-methyl-3-phenyl-2*H*-azirin-2-yl)-prop-2-enoate with some heterocyclic nucleophiles led to the formation of 2-azadienes,[111] while the use of hydrazines as nucleophiles in methanol produced hexahydropyrrolo[3,2-*c*]pyrazol-5-ones.[112] *N*-Silylated or *N*-unsubstituted trifluoromethylaziridines may be prepared by the reaction of trifluoromethyl anion with azirines.[113] In a similar way, addition of trimethylsilyl cyanide to [(2*H*-azirin-2-yl)methyl]phosphonates yielded, stereoselectively, the highly functionalized corresponding *trans*-aziridines,[106] while the addition of cyanide to an intermediate azirine[50,114] and to 3-alkoxy-2*H*-azirines[115] has also been reported.

3.4. Oxidation and Reduction Reactions

Few examples of oxidation of azirines have been reported. The oxidation of 2*H*-azirines gave acyclic or cyclic derivatives when 2-aminoazirine and 3-chloroperbenzoic acids are used. The mechanism of the reaction seems to involve initial epoxidation of the C−N bond to produce an α-nitroso ketone and α-oximino ketones.[116] A similar mechanism may be involved in the oxidation of 2,3-diphenyl-2*H*-azirine to isoquinoline *N*-oxide.[117]

Hydrides ($LiAlH_4$, $NaBH_4$) reduce 2*H*-azirines in a highly stereospecific manner to give *cis*-aziridines (see Section 3.3). However, catalytic hydrogenation (palladium or Raney nickel catalyst) surprisingly results in the ring opening of azirines through the N−C(2) bond.[118] The imines, or primary enamines, are not usually isolated and their existence has only been inferred in most instances, given that the presence of an electron-withdrawing group on the β-carbon atom of the enamine is required in order to stabilize the primary enamine group.[119] The reduction of azirinecarboxylate to enamino ester does not seem to proceed first to the aziridine which is then reduced to the enamine, since *N*-unsubstituted aziridine **72** is not easy to reduce with hydrogen and palladium on carbon[54,55,118b] (Scheme 33). Catalytic hydrogenation of polyfunctionalized azirine with palladium on carbon caused ring enlargement to the 4-aminocoumarin derivatives by recyclization and isomerization of the initially formed imino esters.[120]

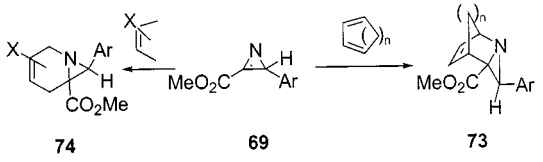


72

Scheme 33

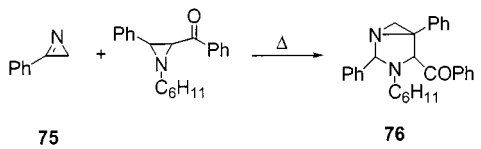
3.5. Dienophiles or Dipolarophiles in Cycloaddition Reactions

Strained cycloolefins are excellent dipolarophiles[121] and dienophiles[122] in [4+2] cycloadditions processes. In a similar way, the strained C−N double bond of 2*H*-azirine ring systems can participate not only as dienophiles but also as dipolarophiles in thermal symmetry-allowed [4+2] cycloadditions with a variety of dienes and 1,3-dipoles.[123] The reactivity of azirines as dienophiles is enhanced by the presence of an electron-withdrawing substituent on the carbon atom, but there are relatively few reports of Diels−Alder reactions of 2*H*-azirines. Methyl 2-aryl-2*H*-azirine-3-carboxylates **69** are good dienophiles and they react not only with symmetrical dienes such as cyclopentadiene, cyclohexa-1,3-diene and 2,3-dimethylbuta-1,3-diene at room temperature, but also with unsymmetrical dienes such as alkoxybutadienes, 2-trimethylsilyloxybuta-1,3-dienes, or 1-methoxy-3-trimethylsilyloxybutadiene to give bicyclic products **73**, **74** of [4+2] cycloaddition to the carbon−nitrogen double bond. The cycloadditions are *endo*-selective and the dienophile approach takes place from the less hindered face of the azirines (Scheme 34).[124] The Diels−Alder reactions of a chiral ester of 2*H*-azirine-3-carboxylic acid with cyclopentadiene is highly diastereoselective.[125] Azirines can also be used as dienophiles with very reactive cyclic dienes such as cyclopentadienone[126] or tetrazines.[127]



Scheme 34

2*H*-Azirine can also be used as dipolarophiles. Logothetis first reported that 2-aryl-3-methyl-2*H*-azirine reacts with diazomethane to produce the allyl azide.[128] Nitrile oxides can also participate in 1,3-dipolar cycloaddition with azirines. Aromatic nitrile oxides react exothermically with 2-methyl-3-phenyl-2*H*-azirines to furnish *N*,*N*′-disubstituted urea derivatives in high yield.[129] Likewise, aziridines undergo thermal ring opening in a conrotatory manner to generate azomethine ylides and these azomethine ylides can participate in 1,3-dipolar cycloaddition with 2*H*-azirines **75** to form bicyclic heterocycles[130] **76** (Scheme 35).



Scheme 35

4. Conclusion

In this microreview we have presented numerous applications of 2*H*-azirines. The reactions discussed herein demonstrate the versatility and the high synthetic potential of azirines as valuable precursors for the preparation of polyfunctionalized acyclic and cyclic compounds. Considerable progress has been made in the chemistry of azirines over the last few years. However, further attractive advances in this field may yet be seen by the creative imagination of new azirine architectures, especially their use as intermediates in the construction of metal complexes and biologically active compounds derived from nonproteinogenic amino acids and peptides. These synthetic strategies will gain importance as soon as a wide range of enantiomerically pure azirines becomes available.

Acknowledgments

The present work has been supported by the Universidad del País Vasco (UPV-170.123-G11/99), the Dirección General de Investigación, Ministerio de Ciencia y Tecnologia (Madrid, DGI, DQU2000-0217) and by the Departamento de Educación, Universidades e Investigación del Gobierno Vasco (Vitoria, PI 1998-53). J. M. d. l. S. thanks the Consejería de Educación del Gobierno Vasco for a postdoctoral fellowship.

[1] [1a] D. F. Ewing, *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds* (Ed.: M. Sainsbury), Elsevier Science B.V., Amsterdam, **1997**, vol. IVA, pp. 59−90. − [1b] S. S. Murphree, A. Padwa, *Three-Membered Ring Systems in Prog. Heterocycl. Chem.* (Eds.: E. F. V. Scriven, H. Suschitzky), Pergamon Press, Oxford, **1997**, vol. 9, pp. 43−63. − [1c] W. H. Pearson, B. W. Lian, S. C. Bergmeier, *Comp. Heterocycl. Chem. II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon Press, Oxford, **1996**, vol. 1A, chapter 1, pp. 1−60. − [1d] J. Backes, *Methoden Org. Chem. (Houben-Weyl)* **1992**, vol. E16c, pp. 317−369. − [1e] H. Heimgartner, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 238−264. − [1f] A. Padwa, A. D. Woolhouse, *Comp. Heterocycl. Chem. I* (Eds.: A. R. Katritzky, C. W. Rees, W. Lwowski), Pergamon Press, Oxford, **1984**, vol. 7, chapter 5, pp. 47−93. − [1g] V. Nair, *The Chemistry of Heterocyclic Compounds* (Ed.: A. Hassner), Wiley, New York, **1983**, vol. 42, part 1, chapter 2, pp. 215−332. − [1h] F. W. Fowler, *Adv. Heterocycl. Chem.* **1971**, *13*, 45−76.
[2] V. Piquet, A. Baceiredo, H. Gornitzka, F. Dahan, G. Bertrand, *Chem. Eur. J.* **1997**, *3*, 1757−1764.
[3] S. Calvo-Losada, J. J. Quirante, D. Suárez, T. L. Sordo, *J. Comput. Chem.* **1998**, *19*, 912−922.
[4] M. Alcamí, O. Mó, M. Yáñez, *J. Am. Chem. Soc.* **1993**, *115*, 11074−11083.
[5] [5a] K.-C. Lau, W.-K. Li, C. Y. Ng, S.-W. Chiu, *J. Phys. Chem. A* **1999**, *103*, 3330−3335. − [5b] P. M. Mayer, M. S. Taylor, M. W. Wong, L. Radom, *J. Phys. Chem. A* **1998**, *102*, 7074−7080. − [5c] K. Banert, M. Hagedorn, E. Knözinger, A. Becker, E.-U. Würthwein, *J. Am. Chem. Soc.* **1994**, *116*, 60−62.
[6] T. W. Miller, E. W. Tristram, F. J. Wolf, *J. Antibiotics* **1971**, *24*, 48−50.
[7] E. O. Stapley, D. Hendlin, M. Jackson, A. K. Miller, *J. Antibiotics* **1971**, *24*, 42−47.
[8] T. F. Molinski, C. M. Ireland, *J. Org. Chem.* **1988**, *53*, 2103−2105.
[9] C. E. Salomon, D. H. Williams, D. J. Faulkner, *J. Nat. Prod.* **1995**, *58*, 1463−1466.

[10] [10a] P. W. Neber, G. Huh, *Justus Liebigs Ann. Chem.* **1935**, *515*, 283−296. − [10b] P. W. Neber, A. Burgard, *Justus Liebigs Ann. Chem.* **1932**, *493*, 281−294.
[11] D. F. Morrow, M. E. Butler, E. C. Y. Huang, *J. Org. Chem.* **1965**, *30*, 579−587.
[12] I. P. Piskunova, A. V. Eremeev, A. F. Mishnev, I. A. Vosekalna, *Tetrahedron* **1993**, *49*, 4671−4676.
[13] M. M. H. Verstappen, G. J. A. Ariaans, B. Zwanenburg, *J. Am. Chem. Soc.* **1996**, *118*, 8491−8492.
[14] [14a] F. Palacios, A. M. Ochoa de Retana, J. I. Gil, J. M. Ezpeleta, *J. Org. Chem.* **2000**, *65*, 3213−3217. − [14b] F. Palacios, A. M. Ochoa de Retana, J. I. Gil, J. M. Alonso, unpublished results.
[15] F. Palacios, D. Aparicio, J. M. de los Santos, E. Rodríguez, *Tetrahedron Lett.* **1996**, *37*, 1289−1292.
[16] [16a] F. Palacios, A. M. Ochoa de Retana, J. I. Gil, *Tetrahedron Lett.* **2000**, *41*, 5363−5366. − [16b] F. Palacios, D. Aparicio, J. M. de los Santos, E. Rodríguez, *Tetrahedron* **1998**, *54*, 599−614.
[17] F. Palacios, A. M. Ochoa de Retana, J. I. Gil, unpublished results.
[18] [18a] J. Wu, X.-L. Hou, L.-X. Dai, *J. Org. Chem.* **2000**, *65*, 1344−1348. − [18b] F. A. Davis, H. Liu, G. V. Reddy, *Tetrahedron Lett.* **1996**, *37*, 5473−5476. − [18c] D. Tanner, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599−619.
[19] [19a] K. Banert, *Methoden Org. Chem (Houben-Weyl)* **1993**, vol. E15, part 1, pp. 818−875, 1344−1347, 2348−2349, 3105−3107. − [19b] A. Hassner, *Azides and Nitrenes − Reactivity and Utility* (Ed.: E. F. V. Scriven), Academic Press, Orlando, **1984**, pp. 35−94.
[20] G. Smolinsky, *J. Org. Chem.* **1962**, *27*, 3557−3559.
[21] M. Haddach, R. Pastor, J. G. Riess, *Tetrahedron* **1993**, *49*, 4627−4638.
[22] M. J. Alves, T. L. Gilchrist, *Tetrahedron Lett.* **1998**, *39*, 7579−7582.
[23] [23a] T. M. V. D. Pinho e Melo, C. S. J. Lopes, A. M. d'A. Rocha Gonsalves, *Tetrahedron Lett.* **2000**, *41*, 7217−7220. − [23b] T. M. V. D. Pinhoe Melo, A. M. d'A. Rocha Gonsalves, C. S. J. Lopes, *Tetrahedron Lett.* **1999**, *40*, 789−792.
[24] R. A. Abramovitch, M. Konieczny, W. Pennington, S. Kanamathareddy, M. Vedachalam, *J. Chem. Soc., Chem. Commun.* **1990**, 269−270.
[25] K. Banert, M. Hagedorn, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 103−105.
[26] K. Banert, M. Hagedorn, C. Liedtke, A. Melzer, C. Schöffler, *Eur. J. Org. Chem.* **2000**, 257−267.
[27] A. Hassner, N. H. Wiegand, H. E. Gottlieb, *J. Org. Chem.* **1986**, *51*, 3176−3180.
[28] R. W. Saalfrank, E. Ackermann, M. Fischer, U. Wirth, H. Zimmermann, *Chem. Ber.* **1990**, *123*, 115−120.
[29] T. Watanabe, H. Takahashi, H. Kamakura, S. Sakaguchi, M. Osaki, S. Toyama, Y. Mizuma, I. Ueda, Y. Murakami, *Chem. Pharm. Bull.* **1991**, *39*, 3142−3152.
[30] R. Kumar, L. I. Wiebe, E. E. Knaus, *Can. J. Chem.* **1996**, *74*, 1609−1615.
[31] D. Suarez, T. L. Sordo, *J. Am. Chem. Soc.* **1997**, *119*, 10291−10301.
[32] [32a] M. Henriet, M. Houtekie, B. Techy, R. Touillaux, L. Ghosez, *Tetrahedron Lett.* **1980**, *21*, 223−226. − [32b] M. Rens, L. Ghosez, *Tetrahedron Lett.* **1970**, 3765−3768.
[33] [33a] J. M. Villalgordo, H. Heimgartner, *Helv. Chim. Acta* **1993**, *76*, 2830−2837. − [33b] J. M. Villalgordo, H. Heimgartner, *Helv. Chim. Acta* **1992**, *75*, 1866−1871.
[34] C. Strässler, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1997**, *80*, 1528−1554.
[35] J. M. Villalgordo, A. Enderli, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1995**, *78*, 1983−1998.
[36] [36a] C. B. Bucher, H. Heimgartner, *Helv. Chim. Acta* **1996**, *79*, 1903−1915. − [36b] C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1995**, *78*, 935−946.
[37] [37a] D. A. Wunderlin, G. E. Davico, J. D. Pérez, *Int. J. Chem. Kinet.* **1992**, *24*, 31−40. − [37b] R. R. Sauers, L. M. Hadel, A. A. Scimone, T. A. Stevenson, *J. Org. Chem.* **1990**, *55*, 4011−4019. − [37c] G. Himbert, H. Kuhn, M. Barz, *Liebigs Ann. Chem.* **1990**, 403−407.
[38] B. H. Lipshutz, D. C. Reuter, *Tetrahedron Lett.* **1988**, *29*, 6067−6070.
[39] S. Auricchio, A. Bini, E. Pastormerlo, A. M. Truscello, *Tetrahedron* **1997**, *53*, 10911−10920.
[40] [40a] C. Wentrup, S. Fischer, H.-M. Berstermann, M. Kuzaj, H. Lüerssen, K. Burger, *Angew. Chem.* **1986**, *98*, 99−100; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 85. − [40b] R. Huisgen, J. Wulff, *Tetrahedron Lett.* **1967**, 917−920. − [40c] H. J. Bestmann, R. Kunstmann, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 1039−1040.
[41] U. J. Vogelbacher, M. Lederman, T. Schach, G. Michels, U. Hess, M. Regitz, *Angew. Chem.* **1988**, *100*, 304−306; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 272.
[42] [42a] D. J. Anderson, T. L. Gilchrist, G. E. Gymer, C. W. Rees, *J. Chem. Soc., Perkin Trans. 1* **1973**, 550−555. − [42b] R. Huisgen, H. Blaschke, *Chem. Ber.* **1965**, *98*, 2985−2997.
[43] R. S. Atkinson, M. J. Grimshire, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1215−1224.
[44] R. L. Barcus, L. M. Hadel, L. J. Johnston, M. S. Platz, T. G. Savino, J. C. Scaiano, *J. Am. Chem. Soc.* **1986**, *108*, 3928−3937.
[45] G. Alcaraz, U. Wecker, A. Baceiredo, F. Dahan, G. Bertrand, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1246−1248.
[46] J.-C. Guillemin, J.-M. Denis, M.-C. Lásne, J.-L. Ripoll, *Tetrahedron* **1988**, *44*, 4447−4456.
[47] R. G. Kostyanovskii, G. K. Kadorkina, S. V. Varlamov, I. I. Chervin, I. K. A. Romero-Maldonado, *Khim. Geterotsikl. Soedin* **1988**, 472−479; *Chem. Abstr.* **1989**, *110*, 114581.
[48] P. Wipf, H. Heingartner, *Helv. Chim. Acta* **1987**, *70*, 354−368.
[49] J. Legters, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 75−78.
[50] R. S. Atkinson, B. J. Kelly, *J. Chem. Soc., Chem. Commun.* **1989**, 836−837.
[51] R. S. Atkinson, M. P. Coogan, I. S. T. Lochrie, *J. Chem. Soc., Perkin Trans. 1* **1997**, 897−900.
[52] F. A. Davis, G. V. Reddy, H. Liu, *J. Am. Chem. Soc.* **1995**, *117*, 3651−3652.
[53] F. A. Davis, H. Liu, C.-H. Liang, G. V. Reddy, Y. Zhang, T. Fang, D. D. Titus, *J. Org. Chem.* **1999**, *64*, 8929−8935.
[54] [54a] F. A. Davis, H. Liu, P. Zhou, T. Fang, G. V. Reddy, Y. Zhang, *J. Org. Chem.* **1999**, *64*, 7559−7567. − [54b] F. A. Davis, P. Zhou, G. V. Reddy, *J. Org. Chem.* **1994**, *59*, 3243−3245.
[55] F. A. Davis, C.-H. Liang, H. Liu, *J. Org. Chem.* **1997**, *62*, 3796−3797.
[56] T. Sakai, I. Kawabata, T. Kishimoto, T. Ema, M. Utaka, *J. Org. Chem.* **1997**, *62*, 4906−4907.
[57] L. Gentilucci, Y. Grijzen, L. Thijs, B. Zwanenburg, *Tetrahedron Lett.* **1995**, *36*, 4665−4668.
[58] F. A. Davis, W. McCoull, *Tetrahedron Lett.* **1999**, *40*, 249−252.
[59] [59a] F. Palacios, E. Herrán, G. Rubiales, *J. Org. Chem.* **1999**, *64*, 6239−6246. − [59b] F. Palacios, D. Aparicio, J. M. de los Santos, *Tetrahedron* **1996**, *52*, 4857−4866. − [59c] J. Barluenga, M. Ferrero, F. Palacios, *Tetrahedron Lett.* **1990**, *31*, 3497−3500.
[60] [60a] N. Kanomata, T. Nakata, *Heterocycles* **1998**, *48*, 2551−2558. − [60b] T. Nishiwaki, *J. Chem. Soc., Chem. Commun.* **1972**, 565−566.
[61] D. Knittel, *Synthesis* **1985**, *2*, 186−188.
[62] [62a] K. Dietliker, H. Heimgartner, *Helv. Chim. Acta* **1983**, *66*, 262−295. − [62b] A. Demoulin, H. Gorissen, A.-M. Hesbain-Frisque, L. Ghosez, *J. Am. Chem. Soc.* **1975**, *97*, 4409−4410.
[63] [63a] D. L. Boger, *Chemtracts: Org. Chem.* **1996**, *9*, 149−189. − [63b] L. Ghosez, *Stereocontrolled Organic Synthesis* (Ed.: B. M. Trost), Backwell: Oxford, **1994**, pp. 193−233. − [63c] J. Barluenga, M. Tomas, *Adv. Heterocycl. Chem.* **1993**, *57*, 1−78.
[64] [64a] E. Jnoff, L. Ghosez, *J. Am. Chem. Soc.* **1999**, *121*, 2617−2618. − [64b] D. Ntirampebura, L. Ghosez, *Tetrahedron*

Lett. **1999**, *40*, 7079−7082. − [64c] F. Palacios, M. J. Gil, E. Martínez de Marigorta, M. Rodríguez, *Tetrahedron Lett.* **1999**, *40*, 2411−2414. − [64d] F. Palacios, C. Alonso, G. Rubiales, *J. Org. Chem.* **1997**, *62*, 1146−1154.
[65] L. Ghosez, A. Demoulin, M. Henriet, E. Sonveaux, M. Van Meerssche, G. Germain, J.-P. Declereq, *Heterocycles* **1977**, *7*, 895−902.
[66] [66a] K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863−909. − [66b] A. Padwa, *Comp. Org. Synth.* (Eds.: B. T. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 4, pp. 1069−1168. − [66c] H. J. Hansen, H. Heimgartner, *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), J. Wiley, New York, **1984**, vol. 1, pp. 177−290. − [66d]R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565−598.
[67] I. Naito, A. Ishida, S. Takamuku, K. Isomura, H. Isomura, *J. Chem. Soc., Perkin Trans. 2* **1992**, 1985−1992.
[68] E. Albrecht, J. Mattay, S. Steenken, *J. Am. Chem. Soc.* **1997**, *119*, 11605−11610.
[69] F. Müller, J. Mattay, *Chem. Rev.* **1993**, *93*, 99−117.
[70] J. Averdung, J. Mattay, *Tetrahedron* **1996**, *52*, 5407−5420.
[71] R. Prewo, J. H. Bieri, U. Widmer, H. Heimgartner, *Helv. Chim. Acta* **1981**, *64*, 1515−1521.
[72] S. Sato, H. Kato, M. Ohta, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1014.
[73] [73a] P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1988**, *71*, 140−154. − [73b] D. Obrecht, H. Heimgartner, *Helv. Chim. Acta* **1987**, *70*, 329−338.
[74] S.-M. Lee, T.-F. Lai, M. P. Sammes, *J. Chem. Res. (S)* **1992**, 266−267.
[75] M. C. M. Sá, A. Kascheres, *J. Org. Chem.* **1996**, *61*, 3749−3752.
[76] A. Kascheres, J. Nunes, F. Brandao, *Tetrahedron* **1997**, *53*, 7089−7096.
[77] I. Tornus, E. Schaumann, G. Adiwidjaja, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1629−1634.
[78] [78a] J. Daniel, D. N. Dhar, *Synth. Commun.* **1991**, *21*, 1649−1655. − [78b] I. Handke, E. Schaumann, R. Ketcham, *J. Org. Chem.* **1988**, *53*, 5298−5300.
[79] A. Hassner, A. S. Miller, M. J. Haddadin, *Tetrahedron Lett.* **1972**, 1353−1356.
[80] J. Daniel, D. N. Dhar, *Synth. Commun.* **1993**, *23*, 2151−2157.
[81] P. F. Dos Santos Filho, U. Schuchardt, *J. Organomet. Chem.* **1984**, *264*, 385−394.
[82] K. Dietliker, U. Schmid, G. Mukherjee-Müller, H. Heimgartner, *Chimia* **1978**, *32*, 164−166.
[83] L. S. Hegedus, A. Kramer, C. Yijun, *Organometallics* **1985**, *4*, 1747−1750.
[84] M. D. Curtis, M. S. Hay, W. M. Butler, J. Kampf, *Organometallics* **1992**, *11*, 2884−2892.
[85] N. P. Reddy, Y. Uchimaru, H.-J. Lautenschlager, M. Tanaka, *Chem. Lett.* **1992**, 45−48.
[86] H. Alper, S. Wollowitz, *J. Am. Chem. Soc.* **1975**, *97*, 3541−3543.
[87] T. Kobayashi, M. Nitta, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1057−1058.
[88] K. Chaffee, H. Morcos, J. B. Sheridan, *Tetrahedron Lett.* **1995**, *36*, 1577−1580.
[89] [89a] F. W. Fowler, A. Hassner, *J. Am. Chem. Soc.* **1968**, *90*, 2875−2881. − [89b] N. J. Leonard, B. Zwanenburg, *J. Am. Chem. Soc.* **1967**, *89*, 4456−4465.
[90] N. M. Gillings, A. D. Gee, O. Inoue, *Appl. Rad. Isot.* **1999**, *50*, 707−714.
[91] N. J. Leonard, E. F. Muth, V. Nair, *J. Org. Chem.* **1968**, *33*, 827−828.
[92] C. Bernard-Henriet, P. Hoet, L. Ghosez, R. Touillaux, *Tetrahedron Lett.* **1981**, *22*, 4717−4720.
[93] C. Jenny, H. Heimgartner, *Helv. Chim. Acta* **1989**, *72*, 1639−1646.
[94] [94a] J. Lehmann, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1999**, *82*, 888−908. − [94b] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1999**, *55*, 5359−5376.
[95] P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1990**, *73*, 13−24.
[96] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1998**, *54*, 8721−8736.
[97] J. Lehmann, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1999**, *82*, 1899−1915.
[98] J. M. Villalgordo, H. Heimgartner, *Helv. Chim. Acta* **1997**, *80*, 748−766.
[99] K. N. Koch, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2000**, *83*, 233−257.
[100] F. Magirius, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1993**, *76*, 1980−2003.
[101] T. R. Mihova, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1996**, *79*, 2067−2074.
[102] T. R. Mihova, A. Linden, H. Heimgartner, *Heterocycles* **1998**, *49*, 215−232.
[103] M. Hugener, H. Heimgartner, *Helv. Chim. Acta* **1995**, *78*, 1823−1836.
[104] M. Drögemüller, R. Jautelat, E. Winterfeldt, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1572−1574.
[105] A. Hassner, F. W. Fowler, *J. Am. Chem. Soc.* **1968**, *90*, 2869−2875.
[106] E. Öhler, S. Kanzler, *Liebigs Ann. Chem.* **1994**, 867−876.
[107] R. M. Carlson, S. Y. Lee, *Tetrahedron Lett.* **1969**, 4001−4004.
[108] R. Ben Cheikh, N. Bouzouita, H. Ghabi, R. Chaabouni, *Tetrahedron* **1990**, *46*, 5155−5166.
[109] M. J. Alves, T. L. Gilchrist, J. H. Sousa, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1305−1310.
[110] M. J. Alves, P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, T. L. Gilchrist, *Tetrahedron Lett.* **2000**, *41*, 4991−4995.
[111] M. T. Barroso, A. Kascheres, *J. Org. Chem.* **1999**, *64*, 49−53.
[112] A. Kascheres, C. M. A. Oliveira, M. B. M. de Azevedo, C. M. S. Nobre, *J. Org. Chem.* **1991**, *56*, 7−9.
[113] C. P. Félix, N. Khatimi, A. J. Laurent, *Tetrahedron Lett.* **1994**, *35*, 3303−3304.
[114] R. S. Atkinson, M. P. Coogan, I. S. T. Lochrie, *Chem. Commun.* **1996**, 789−790.
[115] L. Ghosez, F. Sancte, M. Rivera, C. Bernard-Henriet, V. Gouverneus, *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 456−461.
[116] M. H. Ansari, F. Ahmad, M. Ahmad, *Indian J. Chem., Sect. B* **1988**, *27*, 355−357.
[117] A. Hassner, B. A. Belinka, A. S. Steinfeld, *Heterocycles* **1982**, *18*, 179−185.
[118] [118a] D. J. Anderson, T. L. Gilchrist, C. W. Rees, *Chem. Commun.* **1969**, 147. − [118b] G. R. Harvey, K. W. Ratts, *J. Org. Chem.* **1966**, *31*, 3907−3909.
[119] [119a] F. Palacios, A. M. Ochoa de Retana, J. Oyarzabal, *Tetrahedron* **1999**, *55*, 5947−5964. − [119b] F. Palacios, A. M. Ochoa de Retana, J. Oyarzabal, *Tetrahedron Lett.* **1996**, *37*, 4577−4580. − [119c] G. Erker, M. Riedel, S. Kueh, T. Jodicke, E. H. Würthweisn, *J. Org. Chem.* **1995**, *60*, 5284−5290.
[120] S. Ueda, S. Naruto, T. Yoshida, T. Sawayama, H. Uno, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1013−1021.
[121] [121a] R. Huisgen, F. Palacios, K. Polborn, D. Böeck, *Heterocycles* **1999**, *50*, 353−364. − [121b] R. Huisgen, F. Palacios, *Tetrahedron Lett.* **1982**, *23*, 55−58. − [121c] R. Huisgen, F. Palacios, *Chem. Ber.* **1982**, *115*, 2242−2255.
[122] [122a] R. Huisgen, G. Mlosten, K. Polborn, F. Palacios, *Liebigs Ann./Recueil* **1997**, 187−192. − [122b] R. Huisgen, F. Palacios, unpublished results.
[123] [123a] S. M. Weinreb, *Comp. Org. Synth.* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon Press, Oxford, **1991**, vol. 5, pp. 401−450. − [123b] D. L. Boger, S. M. Weinreb, *Hetero-Diels−Alder Methodology in Organic Synthesis*, Academic Press, San Diego, **1987**, pp. 57−58.
[124] [124a] M. J. Alves, T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1* **1998**, 299−303. − [124b] P. Bhullar, T. L. Gilchrist, P. Maddocks, *Synthesis* **1997**, 271−272.

[125] M. J. Alves, J. F. Bickley, T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1399−1401.
[126] A. Padwa, J. Smolanoff, A. Tremper, *J. Org. Chem.* **1976**, *41*, 543−549.
[127] V. Nair, *J. Heterocycl. Chem.* **1975**, *12*, 183−190.
[128] A. L. Logothetis, *J. Org. Chem.* **1964**, *29*, 3049−3052.
[129] V. Nair, *J. Org. Chem.* **1968**, *33*, 2121−2123.
[130] V. Nair, *Tetrahedron Lett.* **1971**, 4831−4834.
Received December 20, 2000
[O00650]