Monatshefte für Chemie 135, 649–669 (2004)
DOI 10.1007/s00706-003-0150-x

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

5-Spirocyclopropane Isoxazolidines as Versatile Intermediates in Organic Synthesis

Franca M. Cordero*, **Francesco De Sarlo,** and **Alberto Brandi**

Dipartimento di Chimica Organica 'Ugo Schiff', Università degli Studi di Firenze, 50019 Sesto Fiorentino (FI), Italy

Received November 13, 2003; accepted December 2, 2003
Published online March 18, 2004

Summary. The review outlines the various different azaheterocycles available from 5-spirocyclopropane isoxazolidines. These compounds can be regarded as versatile direct precursors of tetrahydro-, dihydropyridone and azetidinone derivatives. The current scope and limitations, and the selectivity aspects of the different processes are discussed therein.

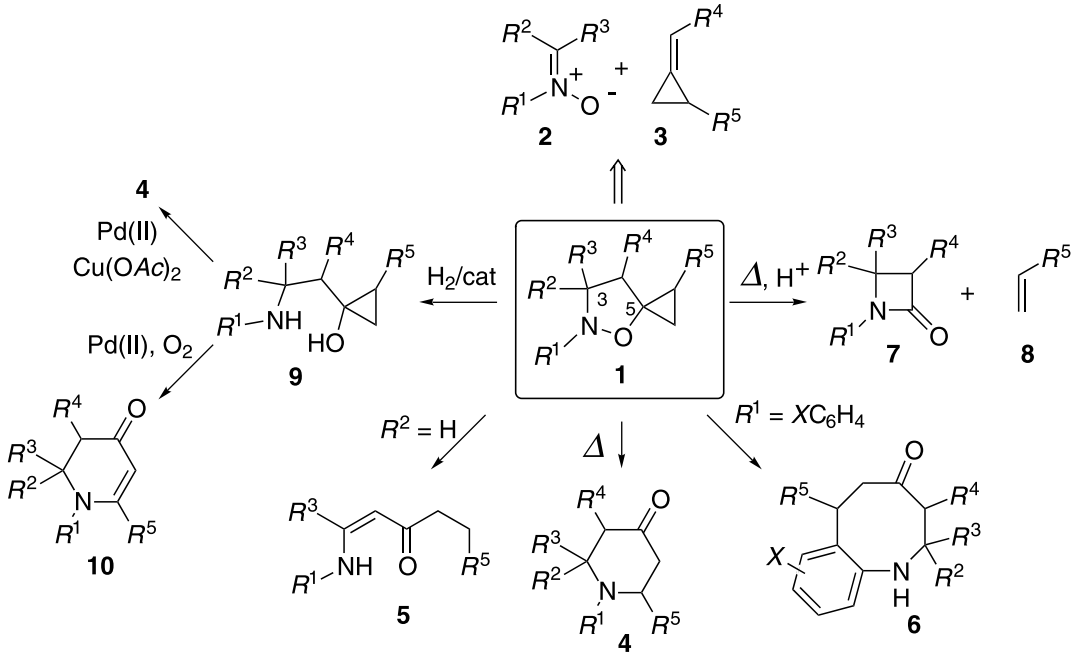
Keywords. Thermal rearrangement; Small ring system; Nitrogen heterocycles; Ring contraction; Ring expansion.

Introduction

Isoxazolidines, the saturated five-membered 1,2-N,O-heterocycles readily available from simple starting materials such as alkenes and nitrones, are useful intermediates in organic synthesis [1]. The presence of the labile N–O bond, which can be easily cleaved under mild reducing conditions, accounts for the common use of isoxazolidines as masked 1,3-aminoalcohol moieties.

5-Spirocyclopropane isoxazolidines **1**, the products of 1,3-dipolar cycloaddition of nitrones **2** and methylenecyclopropanes **3** [2, 3], possess a highly strained ring spiro-fused at the 5 position of the isoxazolidine. As the result of the unique combination of the strained small ring and the adjacent weak N–O bond, isoxazolidines **1** show a distinctive chemistry and can be converted into different azaheterocycles, such as tetrahydro-, dihydropyridone and azetidinone derivatives **4**, **10** and **7**, with a high degree of selectivity depending on the substitution pattern and the reaction conditions (Scheme 1). The extent of these transformations is quite general with only few exceptions that will be detailed below.

* Corresponding author. E-mail: franca.cordero@unifi.it
Dedicated to Prof. *Jacques Salaün* on the occasion of his 65th birthday



Scheme 1

Results and Discussion

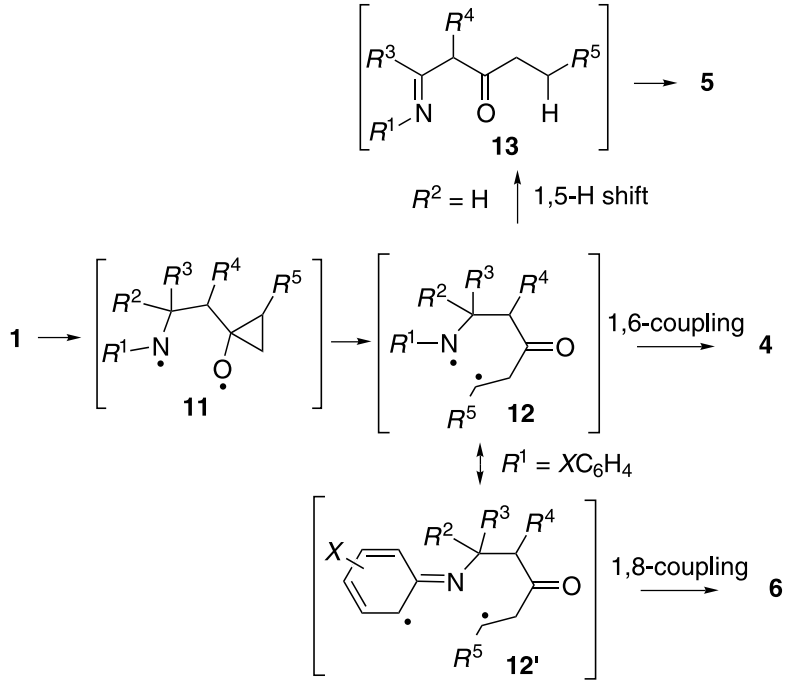
Thermal Rearrangement

Isoxazolidines are usually thermally stable compounds, in fact the 4-spirocyclopropane isomers of **1** are unaffected on heating. On the contrary, 5-spirocyclopropane isoxazolidines **1** undergo a thermally induced ring expansion to tetrahydropyridones **4** [4] by heating in solution at temperatures usually ranging from 80 to 180°C or in vapor phase between 400 and 600°C for a few seconds (flash vacuum thermolysis, FVT).

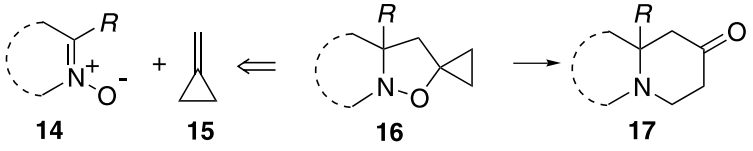
The rearrangement of **1** begins with the homolysis of the N–O bond to afford the diradical intermediate **11** which, instantaneously, undergoes the opening of the cyclopropane ring resulting in strain relief and formation of a strong C=O double bond (Scheme 2). The tetrahydropyridone **4** arises from the transient diradical **12** by intramolecular radical coupling.

The sequence 1,3-dipolar cycloaddition/thermal rearrangement (1,3-DC/TR) leading to compounds **4** is a general process, compatible with the presence of any thermally stable functional group. Moreover, it fulfills the 'atom economy' [5] criteria. When the 1,3-DC/TR process is applied to cyclic nitrones, *N*-bridgehead bicyclic ketones are obtained. In particular, five- and six-membered cyclic nitrones afford indolizidinones and quinolizidinones, respectively (Scheme 3 and Table 1).

The 1,3-DC of nitrones and alkenes occur with a high degree of stereoselectivity [1, 2]. Since the thermal rearrangement of 5-spirocyclopropane isoxazolidines does not affect the stereogenic centers on the isoxazolidine ring (Scheme 2) these maintain their configuration in the product. Therefore, the 1,3-DC/TR



Scheme 2



Scheme 3

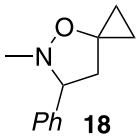
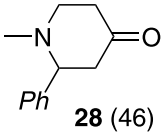
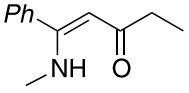
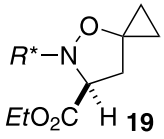
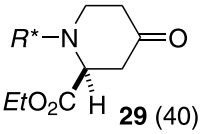
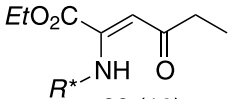
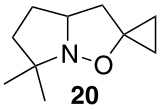
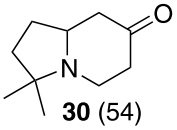
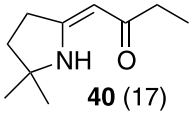
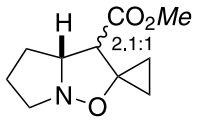
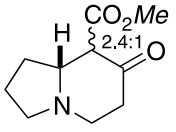
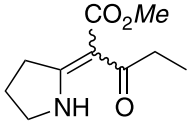
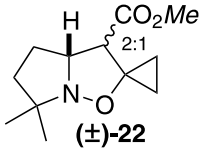
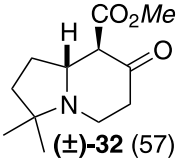
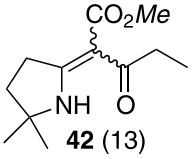
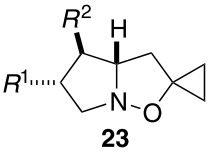
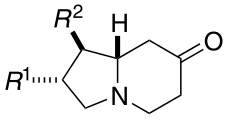
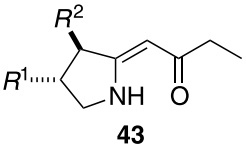
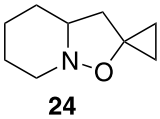
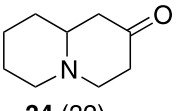
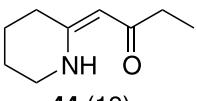
process allows a high control of the relative configuration of the new created stereogenic centers. For example, enantiomerically pure nitrones and methylenecyclopropane (*MCP*, **15**) were employed in the synthesis of **29** and **33** (Table 1, entries 2, 6, and 7). Ketones **29** and **33a** were used as intermediates in the total synthesis of the rare amino acid (2*S*)-4-oxopipecolic acid [7] and of the alkaloid (+)-lentiginosine [10], respectively.

The β-ketoesters **31**, **32**, and **35** (Table 1, entries 4, 5, and 9) epimerized under the rearrangement conditions due to tautomerization. The indolizidinone **31** was obtained as a 2.4:1 diastereomeric mixture, while the two couples of *cis*- and *trans*-adducts **22** and **25** afforded the sole thermodinamically more stable *cis*-(CO_2Me, bridgehead H) indolizidinone **32** and quinolizidinone **35**, respectively [8, 9]. Compounds **31** and **35** were used as intermediates in the formal syntheses of the racemic alkaloids eleokanine and lupinine, respectively [8, 13].

The formation of the acyclic enaminone **5** is the most characteristic side reaction that occurs during the thermal rearrangement of **1** (Scheme 1). The byproduct **5** arises from the diradical intermediate **12** through an 1,5-hydrogen atom transfer, followed by double bond migration (Scheme 2). Comparative studies proved that

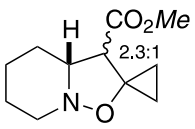
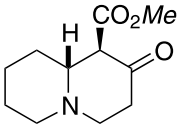
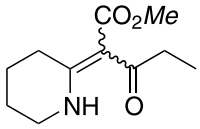
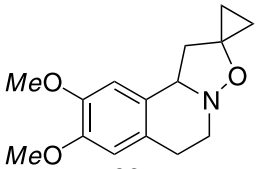
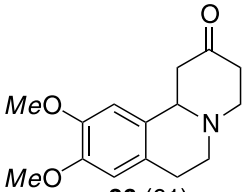
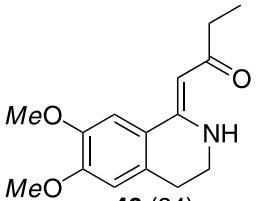
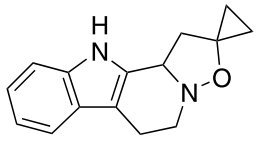
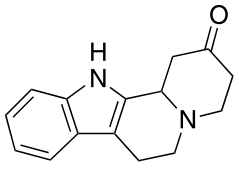
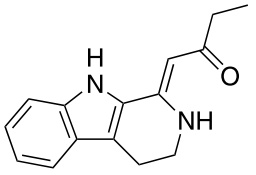
the yield of **5** is reduced, and of **4** accordingly increases, when the rearrangement is carried out under high dilution or in vapor phase. These data indicate that the 1,5-hydrogen atom shift can occur either intra- and intermolecularly, and advise

Table 1. Thermal rearrangements of 5-spirocyclopropane isoxazolidines derived from aldonitrones (**14**, $R = H$) and *MCP* or methyl 2-cyclopropylideneacetate

Entry	Adducts	Conditions	Products (Yield/%)		Ref.
1	 **18**	FVT 400°C 0.2 mm Hg	 **28** (46)	 **38** (14)	[6]
2[a]	 **19**	xylenes reflux 4 h	 **29** (40)	 **39** (10)	[7]
3	 **20**	FVT 400°C 0.2 mm Hg	 **30** (54)	 **40** (17)	[6]
4	 **(±)-21**	FVT[b] 450°C 10^{-3} mm Hg	 **(±)-31** (45)	 **41** (19)	[8]
5	 **(±)-22**	mesitylene reflux 4 h	 **(±)-32** (57)	 **42** (13)	[9]
	 **23** **a:** R^1=R^2=O*TBDPS* **b:** R^1= H, R^2=O*tBu*	xylenes reflux	 **33** **a:** R^1=R^2=O*TBDPS* **b:** R^1= H, R^2=O*tBu*	 **43** **a:** R^1=R^2=O*TBDPS* **b:** R^1= H, R^2=O*tBu*	
6	**23a**	1 h 40 min	**33a** (45)	**43a** (49)	[10]
7	(enant)-**23b**	3 h	(enant)-**33b** (52)	(enant)-**43b** (26)	[11]
8	 **24**	FVT 400°C 0.2 mm Hg	 **34** (32)	 **44** (19)	[6]

(*continued*)

Table 1 (*continued*)

Entry	Adducts	Conditions	Products (Yield/%)	Ref.
9	 **(±)-25**	FVT[b] 450°C 10^{-3} mm Hg	 **(±)-35** (46)  **45** (20)	[8]
10	 **26**	mesitylene reflux 2.5 h	 **36** (61)  **46** (34)	[12]
11	 **27**	mesitylene reflux 4 h	 **37** (50)  **47** (21)	[12]

[a] $R^* = 2,3:5,6$-diisopropylidene-α-*D*-mannofuranosyl; [b] temperature of vaporization: **21**, 70–90°C; **25**, 80–100°C

against running the 1,3-DC/TR in ''one-pot'', because highly concentrated solutions are suitable for the intermolecular cycloaddition step.

The enaminone **5** is usually obtained in minor amount than the cyclic ketone **4**, but bulky substituents such as O*TBDPS* in **23a** can hamper the six-membered ring closure and favor the formation of the acyclic product **43a** (Table 1, entry 6).

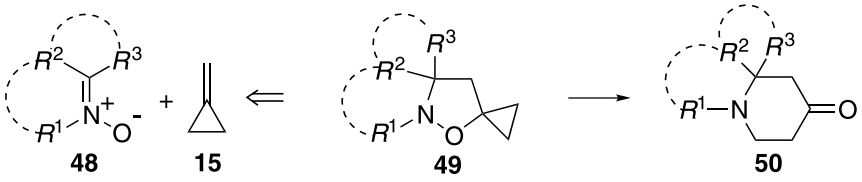
In accord to the proposed mechanism (Scheme 2), the presence of a hydrogen atom on the 3 position of the isoxazolidine ring is necessary for the formation of **5**. In fact, the 5-spirocyclopropane isoxazolidines **1** (R^2 and $R^3 \neq$ H) derived from ketonitrones rearrange exclusively into the corresponding cyclic ketones **4** (Table 2).

In these cases the 1,3-DC/TR can be successfully performed in a ''one-pot'' procedure, for example the reaction of 2-pyrroline *N*-oxide (**48b**) and *MCP* (**15**) in refluxing toluene (*ca.* 3 *M*) after 2 days afforded directly the ketone **50b** in 63% overall yield, compared with an 47% overall yield by the two-step procedure (Table 2, entry 3).

The cycloadducts **52** derived from alkylidenecyclopropane nitrones **51** by intramolecular cycloaddition are another class of 5-spirocyclopropane isoxazolidines which undergo selective thermal rearrangement to the corresponding pyridones without formation of the enaminone derivatives (Scheme 4).

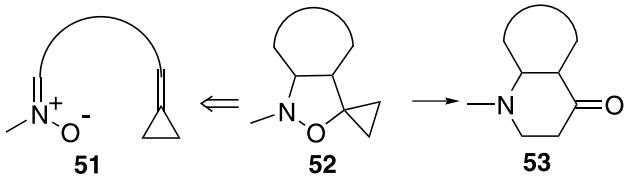
The intramolecular 1,3-DC/TR sequence affords the 2,3-fused bicyclic piperidones **53** in good yields. The second ring in **53** may be either a five- (Table 3) or a six-membered ring (Scheme 5). Larger rings are not obtainable through this approach, because the formation of the fused 5-spiro adduct is favored only by a

Table 2. Thermal rearrangements of 5-spirocyclopropane isoxazolidines derived from ketonitrones **48** (R^2 and $R^3 \neq$ H)



Entry	R^1	R^2	R^3	**49**	Conditions	**50**	Yield/%	Ref.
1	*Me*	*Ph*	*Ph*	**a**	toluene, reflux, 1 d	**a**	85	[14]
2				**a**	FVT, 400°C, 10^{-3} mm Hg	**a**	70	[14]
3	$-(CH_2)_3-$		*Me*	**b**	toluene, reflux, 2 d	**b**	60[a]	[14]
4	$-(CH_2)_3-$		CO_2Me	**c**	*o*-xylene, 130°C, 2 h	**c**	64	[15]
5	*Me*	$-(CH_2)_5-$		**d**	FVT,[b] 400°C, 10^{-3} mm Hg	**d**	42	[14]
6	*Me*	$-(CH_2)_6-$		**e**	FVT,[b] 400°C, 10^{-3} mm Hg	**e**	40	[14]

[a] when the 1,3-DC/TR was run in "one-pot" (toluene, reflux, 2 d) the yield of **50b** was 63% with respect to nitrone **48b**; [b] temperature of vaporization: **49d**, 25°C; **49e**, 40°C



Scheme 4

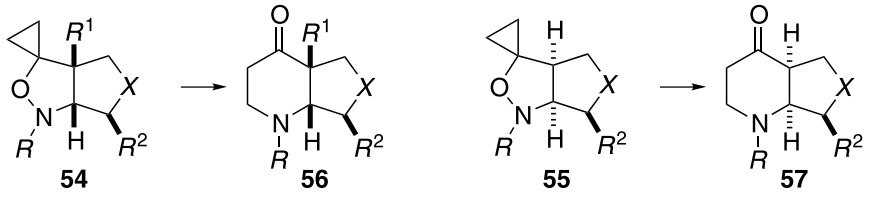
short chain of 3–4 atoms tethering the two reactive sites. Otherwise, the thermally stable bridged 4-spiro regioisomers are exclusively produced [2, 16].

The linker in **51** may consist of a carbon atom chain (Table 3, entries 1–3) or contain heteroatoms such as nitrogen (Table 3, entries 4–14; Scheme 5) and oxygen (Table 3, entry 15), hence various bicyclic and tricyclic skeletons are available through the intramolecular 1,3-DC/TR approach.

Both the *cis*- and *trans*-fused isoxazolidines **58** and **59** afforded the thermodynamically more stable *trans*-fused bicyclic ketone **60** by heating in refluxing xylenes [19]. The epimerization can be ascribed to a keto-enol equilibrium induced by the high temperature and the basicity of the compound itself. Similarly, the *cis*-fused cyclopenta[*c*]isoxazolidine **54a** afforded a mixture of *cis*- and *trans*-fused cyclopenta[*b*]pyridones **56a** (7:1 ratio) [17].

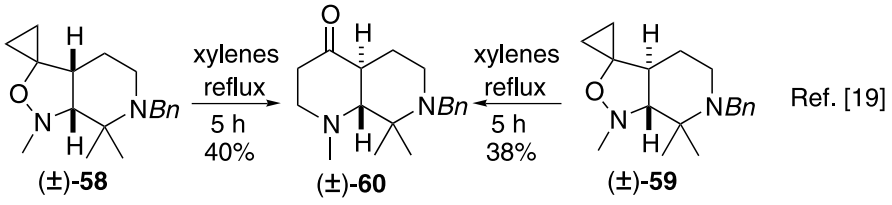
The thermal rearrangement of 5-spirocyclopropane isoxazolidines substituted on the three-membered ring **1** ($R^5 \neq$ H) is completely regioselective, as after the N–O homolysis only the more substituted cyclopropane bond breaks affording the more stable secondary radical intermediate **12** ($R^5 \neq$ H, Scheme 2). For this reason the substituent R^5 ends up exclusively on the position adjacent to the nitrogen atom in the piperidine ring, irrespective of the *endo* or *exo* position of R^5 in the starting

Table 3. Thermal rearrangements of 5-spirocyclopropane isoxazolidines derived from intramolecular 1,3-DC [17–20]



Entry	*R*	R^1	R^2	*X*	**54–55**	Conditions	**56–57**	Yield/%
								%
1	*Me*	H	H	CH_2	**54a**	*o*-xylene, 140°C, 5 h	**56a**	83[a,b]
2	*Me*	Me	H	CH_2	**54b**	mesitylene, 160°C, 16 h	**56b**	48[b]
3	*Me*	H	H	CHO*Ac*	**54c**	xylenes, reflux, 6 h	**56c**	75[a,b]
4	*Me*	H	H	N*Ts*	**54d**	xylenes, reflux, 6 h	**56d**	49[b]
5	*Me*	H	*Me*	N*Ts*	**54e**	xylenes, reflux, 6 h	**56e**	64
6	*Me*	H	*Me*	N*Ts*	**55e**	xylenes, reflux, 6 h	**57e**	63
7	*Me*	H	*Ph*	N*Ts*	**54f**	*o*-xylene, 130°C, 42 h	**56f**	53[b]
8	*Bn*	H	*Me*	N*Ts*	**54g**	*o*-xylene, 130°C, 4 h	**56g**	60
9	*Bn*	H	*Me*	N*Ts*	**55g**	*o*-xylene, 130°C, 4 h	**57g**	55
10	*THP*	H	*Me*	N*Ts*	**54h**[a]	*o*-xylene, 130°C, 6 h	**56h**[a,c]	33[b]
11	*Me*	H	CH_2Ph	N*Ts*	**54i**	xylenes, reflux, 6 h	**56i**	44
12	*Me*	H	CH_2Ph	N*Ts*	**55i**	xylenes, reflux, 6 h	**57i**	43
13	*Me*	H	CH_2-3-indolyl	N*Ts*	**54j**	*o*-xylene, 130°C, 33 h	**56j**	41
14	*Me*	H	$CH_2CH_2CH_2N$		**54k**	*o*-xylene, 126°C, 5 h	**54k**	70
15	*Me*	H	H	O	**54l**	*o*-xylene, 130°C, 36 h	**56l**	73

[a] mixture of diastereomers; [b] racemic compound; [c] **56h**: $R = H$

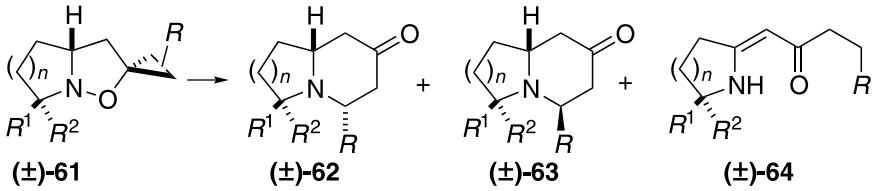


Scheme 5

adduct (Table 4). For example, the diastereomeric mixture of isoxazolidines **61** rearranges to β-substituted ketones **62–63**, besides respective enaminone side-products **64** (Table 4).

The intramolecular radical coupling of the intermediate **12** occurs with low diastereoselectivity and the two diastereomers **62** and **63** are formed in similar amounts. The bicyclic ketones **62c**, **62d**, and **63d** were used as precursors in the synthesis of the racemic alkaloids gephyrotoxin 223AB [21] and lasubine II [22] and I [23], respectively.

Table 4. Synthesis of indolizidinones **62–63** ($n = 1$) and quinolizidinones **62–63** ($n = 2$)

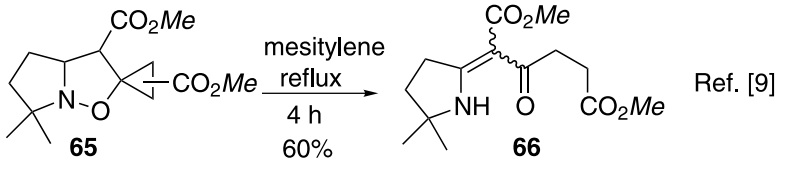


Entry	n	R^1	R^2	R	dr	Conditions	Yield/%			Ref.
					61		**62**	**63**	**64**	
a	1	*Me*	*Me*	*Ph*	2:1	toluene, reflux, 4 h	8	16	36	[21]
b	1	*Me*	H	*Ph*	1.2:1	toluene, reflux, 3 h	35	21	16	[21]
c	1	*n-Bu*	H	*n-Pr*	1.4:1	toluene, reflux, 6 h	34	24	12	[21]
d	2	H	H	2,3-(*Me*O)$_2$C$_6$H$_3$	1.2:1	mesitylene, reflux, 4 h	38	26	14	[12]

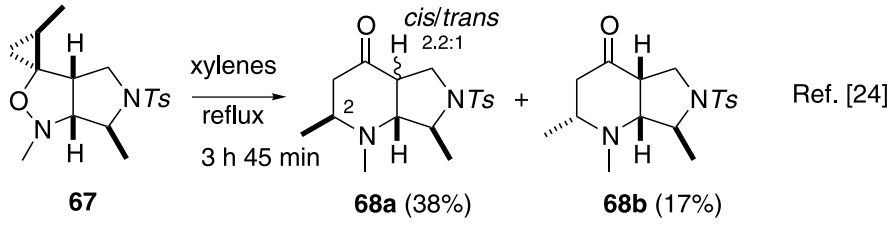
The enaminone **64a** was the main product of the rearrangement, again for the steric hindrance exerted by the *gem*-dimethyl groups in the cyclization.

The enaminone can become the exclusive rearrangement product, for example in the case of isoxazolidine **65** which afforded, by heating in solution, only the enaminone **66** in 60% yield (Scheme 6) [9]. In this case the methoxycarbonyl group on the cyclopropane ring stabilizes the corresponding diradical intermediate **12** disfavoring the annulation to **4** (Scheme 2).

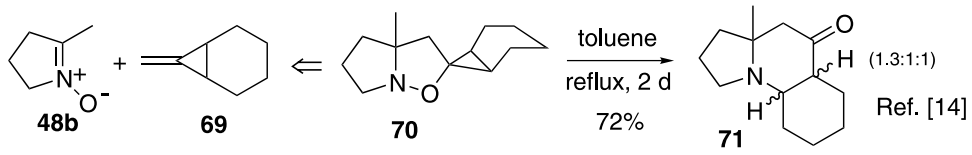
The enantiomerically pure tricyclic isoxazolidine **67**, analogous to adducts **54d–54j**, gave a diastereomeric mixture of the C-2 substituted pyrrolo[3,4-*b*]pyridinones **68** in 55% overall yield by heating in xylenes (Scheme 7) [24]. As in previous cases, the rearrangement was totally chemo- and regioselective, but the diastereoselectivity was low ($dr = 2.2{:}1$). Partial epimerization of the major product **68a** was also observed.



Scheme 6



Scheme 7



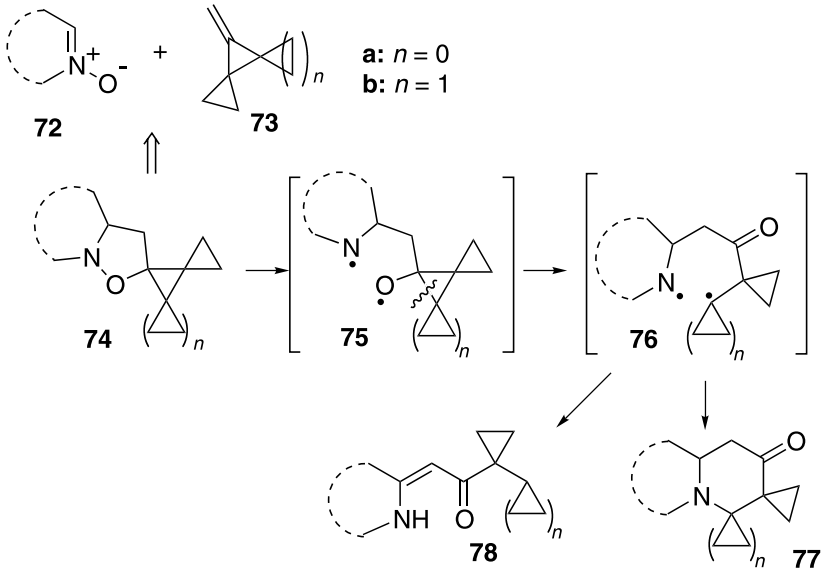
Scheme 8

The norcarane substituted isoxazolidine **70** (one diastereomer) afforded the tricyclic ketones **71** (three diastereoisomers) with similar low diastereoselectivity (Scheme 8) [14].

The adducts **74** of cyclic and acyclic nitrones **72** to methylenespiropentane (*MSP*, **73a**) and methylenedispiroheptane (*MDH*, **73b**) give a closer insight on the nature of the thermal rearrangement. Spirocyclopropane tetrahydropyridones **77** are the main products of the rearrangement besides the corresponding open chain isomers **78** (Scheme 9 and Table 5) [25].

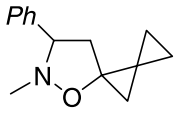
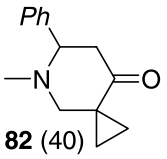
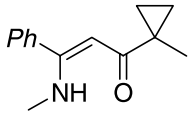
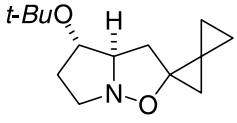
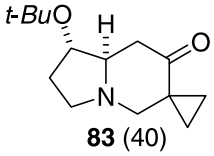
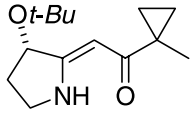
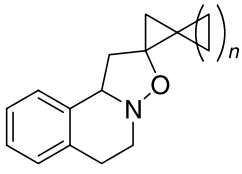
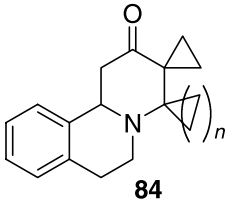
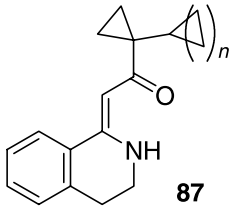
Apparently an opposite regioselectivity is observed in this case as the opening of the cyclopropane ring in the diradical intermediate **75a** leads to the primary radical **76a**. In fact, **76a** is indeed a more stable intermediate than the one with the radical on the strained cyclopropane ring. Quite striking is the lack of products deriving from a cyclopropylmethyl radical/homoallyl rearrangement, one of the fastest processes known in radical chemistry. This fact suggests that the rearrangement rate is close to the diffusion rate.

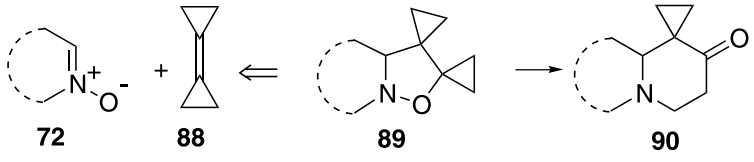
The interesting spirocyclopropane-fused ketones **77** (Scheme 9) are obtained from isoxazolidines **74** along with the open chain isomers **78** which are the main rearrangement products (Table 5). On the contrary, dispiro-fused isoxazolidines **89** (Scheme 10), the cycloadducts of nitrones and bicyclopropylidene (*BCP*, **88**) undergo the thermal rearrangement to afford almost exclusively the spiro-fused ketones **90** (Table 6).



Scheme 9

Table 5. Thermal rearrangements of 5-spirocyclopropane isoxazolidines derived from nitrones and *MSP* (**73a**) or *MDH* (**73b**) [25]

Entry	Adducts	Conditions	Products (Yield/%)	
1	 **79**	dichlorobenzene 160°C 8 h	 **82** (40)	 **85** (46)[a]
2[a]	 **80**	xylenes 125°C 6 h	 **83** (40)	 **86** (40)
	 **81**	mesitylene 160°C	 **84**	 **87**
3	**81a** ($n = 0$)	2 h	**84a** ($n = 0$, 32)	**87a** ($n = 0$, 43)
4	**81b** ($n = 1$)	3 h	**84b** ($n = 1$, 34)	**87b** ($n = 1$, 55)[a]



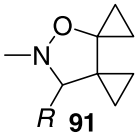
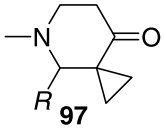
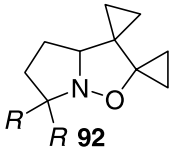
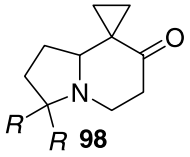
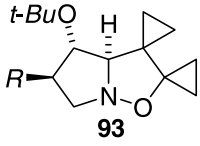
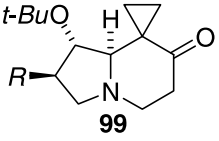
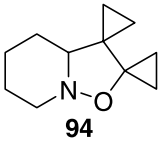
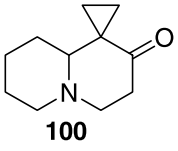
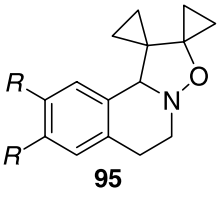
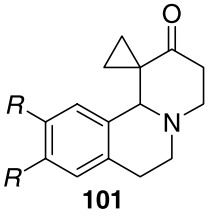
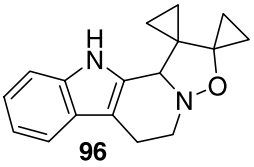
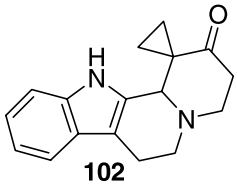
Scheme 10

As expected on the basis of the different thermal behavior observed for the 5- and 4-spirocyclopropane isoxazolidines, only the cyclopropane ring in the 5-position adjacent to the labile N–O bond in **89** is involved in the thermal rearrangement.

The ketones **77a** and **90** (Schemes 9, 10) are constitutional isomers, differentiated only by the position of the spiro-fused cyclopropane ring. Thus the 1,3-DC/TR method allows the selective production of these highly functionalized heterocycles.

It is remarkable that isoxazolidines **91**–**96**, except **95a**, rearrange selectively to the cyclic products **97**–**102**, without formation of any open-chain isomer (Table 6). This result might be ascribed to the presence of the spiro-fused cyclopropane ring that raises the rotational barriers in the diradical intermediate increasing the proportion of reactive rotamers which favor the diradical coupling (see Scheme 2) [26].

Table 6. Thermal rearrangements of bis(spirocyclopropane) isoxazolidines

Entry	Adducts	Conditions	Products	Yield/%	Ref.
	 **91**	toluene 110°C	 **97**		
1	**91a** (*R* = *Ph*)	5 d	**97a** (*R* = *Ph*)	63	[26]
2	**91b** (*R* = CO_2Me)	4 d	**97b** (*R* = CO_2Me)	61	[26]
	 **92**		 **98**		
3	**92a** (*R* = H)	xylenes, 125°C, 11 h	**98a** (*R* = H)	60	[26]
4	**92b** (*R* = *Me*)	benzene, 80°C, 7 d	**98b** (*R* = *Me*)	76	[26]
	 **93**	xylenes 125°C	 **99**		
5	**93a** (*R* = H)	8 h	**99a** (*R* = H)	80	[25]
6	**93b** (*R* = O*t-Bu*)	16 h	**99b** (*R* = O*t-Bu*)	62[a]	[25]
7	 **94**	xylenes 125°C 6 d	 **100**	68	[26]
	 **95**	xylenes 125°C	 **101**		
8	**95a** (*R* = H)	5 d	**101a** (*R* = H)	50[b]	[26]
9	**95b** (*R* = O*Me*)	2 d	**101b** (*R* = O*Me*)	67	[25]
10	 **96**	xylenes 125°C 6 d	 **102**	60	[25]

[a] yield of "one-pot" 1,3-DC/TR reaction; [b] the corresponding enaminone was isolated in 24% yield

In analogy with the derivatives of ketonitrones (Table 2) which do not afford the open-chain isomers, in general spiro-fused ketones **97**–**102** may be synthesized through the ''one-pot'' 1,3-DC/TR process with higher overall yields than by the two-step procedure [25, 26].

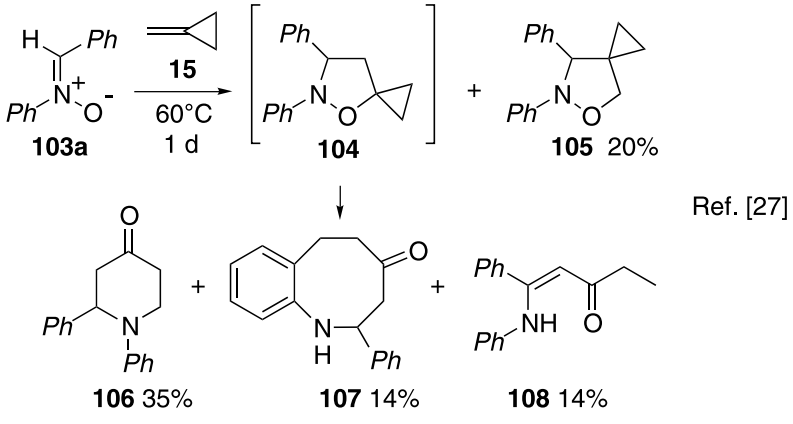
The spirocyclopropane ketones **97**–**102** are aza analogues of cytotoxic sesquiterpenes isolated from mushrooms called illudins, and the compounds **101**–**102** showed a moderate activity in cleaving a *DNA* plasmid [26].

In addition to the usual rearrangement products **4** and **5**, *N*-aryl 5-spirocyclopropane isoxazolidines **1** ($R^1 = Ar$) may afford azocinones **6** (Scheme 1) by intramolecular coupling of the diradical intermediates **12** ($R^1 = Ar$) delocalized on the *N*-aryl ring, followed by H-shift (Scheme 2). For example, benzazocine **107** was produced in moderate yield besides the tetrahydropyridone **106** and the enaminone **108**, in the rearrangement of **104** (Scheme 11) [27]. The isoxazolidine **104** in this case could not be isolated, because it slowly rearranges even at room temperature. In general, the thermal rearrangement is much easier for *N*-aryl than for *N*-alkyl isoxazolidines, probably because the transition state of the N–O cleavage, rate determining step, is stabilized by delocalization of the incipient radical on the aryl ring. DFT Calculations confirmed the experimental data giving an activation energy that is lower by about 71 kJ/mol for *N*-aryl substituted isoxazolidines than for *N*-alkyl isoxazolidines [28].

N-Phenyl substituted nitrones **103** gave with *BCP* (**88**) a more efficient domino 1,3-DC/TR process, than *MCP* (**15**) (Table 7) [29]. The symmetry of the dipolarophile and the lack of enaminone (*cf.* Table 6) led to the formation of only two products **110** and **111** with higher yields.

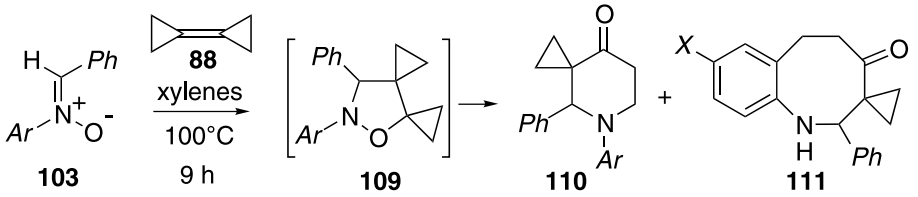
The temperature of 100°C in the domino process to **110** and **111** was necessary to carry out the cycloaddition step in reasonable reaction time, but was more than enough to induce the rearrangement of **109** which could not be isolated under the reported reaction conditions.

In order to determine the temperature required for the thermal rearrangement a more reactive dipolarophile was necessary. Ethyl cyclopropylideneacetate **112** cycloadds to nitrones even at room temperature. The 1,3-DC/TR of **103** with **112** afforded the products **114** and **115** in moderate yields at room temperature



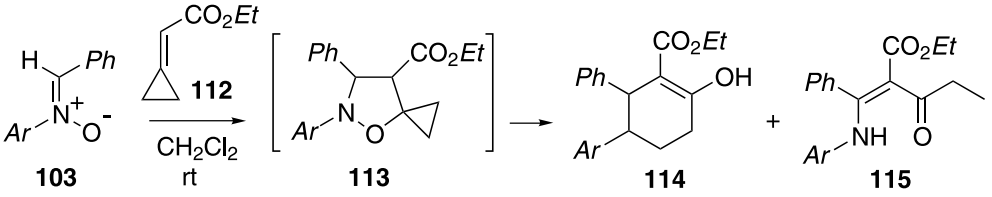
Scheme 11

Table 7. Domino 1,3-DC/TR process of *N*-aryl nitrones and *BCP* [29]



Entry	*Ar*	**110**	Yield/%	*X*	**111**	Yield/%
1	*Ph*	**a**	40	H	**a**	27
2	4-ClC_6H_4	**b**	52	Cl	**b**	20
3	4-*Me*C_6H_4	**c**	40	*Me*	**c**	21
4	4-(*Et*O_2C)C_6H_4	**d**	57	CO_2*Et*	**d**	25

Table 8. Domino 1,3-DC/TR process of *N*-aryl nitrones and cyclopropylideneacetate **112** [30]



Entry	*Ar*	Conditions	**114**	Yield/%	**115**	Yield/%
1	*Ph*	rt, 7 d	**a**	22	**a**	9
2	4-*Me*OC_6H_4	rt, 7 d	**e**	35	**e**	13
3	4-*Me*C_6H_4	rt, 7 d	**c**	36	**c**	8
4	4-(*Me*O_2C)C_6H_4	rt, 21 d, then 60°C, 4 h	**f**	34	**f**	–
5	3,5-(*Me*O_2C)$_2C_6H_3$	rt, 21 d, then 60°C, 4 h	**g**	22	**g**	2

(Table 8) [30]. Similarly to **104** and **109**, isoxazolidines **113** cannot be isolated, because they undergo the thermal rearrangement at a temperature lower than that required for the cycloaddition. The rearrangement products **114** and **115** are formed even at room temperature (Table 8), showing the dramatic effect of *N*-aryl substitution.

In addition to the influence of the *N*-aryl moiety on the rearrangement temperature, a *N*-aryl substituent effect on the propensity of the N–O to undergo homolysis was observed in adducts **113** (Table 9) [30]. In particular, electron donating substituents on the *N*-aryl ring favored the thermal rearrangement (Table 9, entries 2–3) while electron-withdrawing groups slowed it down (Table 9, entries 4–5) suggesting a polar contribution in the homolytic cleavage of the N–O bond.

Table 9. Composition of the reaction mixtures of equimolar amounts of *N*-aryl nitrones **103** and cyclopropylideneacetate **112** after 24 h at room temperature [30]

Entry	*Ar*	**103**	Conversion[a]/%	Molar ratio[a]		
				103	**113**	**114 + 115**
1	*Ph*	**a**	72	1	1.1	1.5
2	4-*Me*OC$_6$H$_4$	**e**	38	1	–	0.6
3	4-*Me*C$_6$H$_4$	**c**	45	1	–	0.8
4	4-(*Me*O$_2$C)C$_6$H$_4$	**f**	40	1	0.7	–
5	3,5-(*Me*O$_2$C)$_2$C$_6$H$_3$	**g**	52	1	1.1	<0.1

[a] calculated by ^{1}H NMR

4-Chloro-4-carbomethoxy-5-spirocyclopropane isoxazolidines (**116–118**, Table 10) derived from methyl 2-chloro-2-cyclopropylideneacetate and methyl 2-chloro-2-spiropentylideneacetate are a peculiar class of 5-spirocyclopropane isoxazolidines, because of their unusual and multiform rearrangement pathways leading to heterocycles not related to **4–5** and dependent on the structures and the reaction conditions [31]. The effect of the solvent on the rearrangement becomes crucial for these compounds (Table 10).

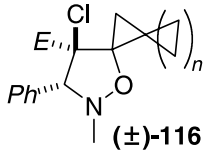
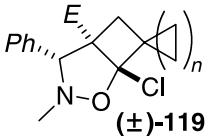
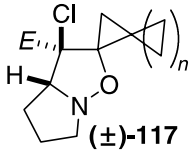
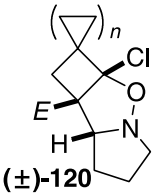
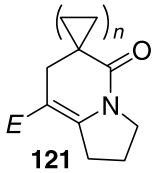
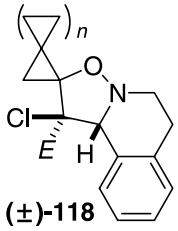
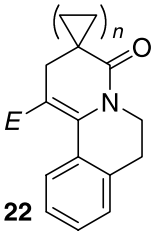
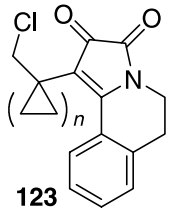
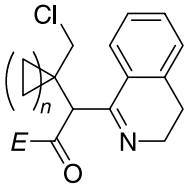
For instance, isoxazolidines **116** afforded the crystalline cyclobutane-annelated isoxazolidines **119** in high yields (82%) by heating in *DMSO* at 100°C (Table 10, entries 1–2), whereas the *cis*-(Cl, *Ph*) diastereoisomer of **116a** is stable under the same reaction conditions. The conversion of **116** in **119** is a new example of the cyclopropylmethyl chloride/cyclobutyl chloride rearrangement [32].

The adduct **117a** slowly isomerizes to **120a** at room temperature, and the process is efficiently catalyzed by Al_2O_3 (Table 10, entries 3–4). Compounds **119** are quite stable towards further thermal rearrangement, whereas compounds **120** were quantitatively converted to the indolizin-5-ones **121** by heating in *DMSO*. The same compounds **121** were formed from the isoxazolidines **117** under the same conditions with good yields (Table 10, entries 5–6). The indolizidin-5-ones **121** must form by a ring expansion of the strained cyclobutane isoxazolidine intermediates that is triggered by the abstraction of the bridgehead proton [31].

When the thermal rearrangement of isoxazolidines **118** was carried out in *DMSO* at 150°C, a different reaction pathway was observed. Although decomposition of the starting materials predominated, the benzoquinolizinones **122** were isolated in low yields (Table 10, entries 7–8). In the case of **118a** a small amount of the ketoamide **123a** was also obtained in mixture with **122a** (entry 7). When heated at 150°C in xylenes compounds **118a** and **118b** afforded the α-ketolactam **123a** and a mixture of α-ketolactam **123b** and the open chain derivative **124b**, respectively (Table 10, entries 9–10).

Up to now, the thermally induced ring expansion to tetrahydropyridones **4** is the most thoroughly explored rearrangement of 5-spirocyclopropane isoxazolidines **1**, but the same adducts **1**, under different reaction conditions, can undergo other selective skeleton reorganizations (Scheme 1).

Table 10. Rearrangement products of 4-chloro-4-methoxy-5-spirocyclopropane isoxazolidines **116**–**118** [31]

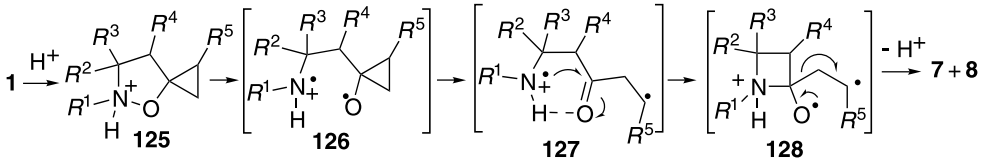
Entry	Adducts[a] **a:** $n = 0$, **b:** $n = 1$	Conditions	Products[a] (Yield/%) **a:** $n = 0$, **b:** $n = 1$		
	 **(±)-116**		 **(±)-119**		
1	**116a**	*DMSO,* 100°C, 7 h	**119a** (82)[b]		
2	**116b**	*DMSO,* 100°C, 2 h	**119b** (82)		
	 **(±)-117**		 **(±)-120**	 **121**	
3	**117a**	*DCM,* Al_2O_3, rt, 3 d	**120a** (83)[c]		
4	**117b**	*DCM,* Al_2O_3, rt, 4 h	**120b** (82)		
5	**117a**	*DMSO,* 100°C, 5 h		**121a** (83)	
6	**117b**	*DMSO,* 100°C, 3 h		**121b** (73)	
	 **(±)-118**		 **122**	 **123**	 **124**
7	**118a**	*DMSO,* 150°C, 3 h	**122a** (15)	**123a** (8)	
8	**118b**	*DMSO,* 150°C, 3 h	**122b** (21)		
9	**118a**	xylenes, 150°C, 3.5 h		**123a** (56)	
10	**118b**	xylenes, 150°C, 3 h		**123b** (16)	**124b** (40)

[a] $E = CO_2Me$; [b] the X-ray analysis was run on a crystal of isoxazolidine **119a**; [c] the conversion was 86%

Acidic Thermal Rearrangement

Recently, a new and completely different transformation of **1** which expands the scope of these compounds as synthetic intermediates was reported [33]. In particular, the adducts **1** ($R^5 = H$) undergo a ring contraction to azetidin-2-ones **7** with concurrent extrusion of ethylene (**8**, $R^5 = H$) by heating in the presence of a protic acid (Scheme 1).

The proposed mechanism of the acidic thermal rearrangement (ATR) of 5-spiroisoxazolidines is depicted in Scheme 12, and starts with the homolysis of



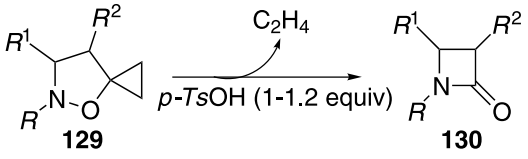
Scheme 12

the N–O bond of the protonated isoxazolidine **125** to form the biradical cation **126** which undergoes cyclopropyl ring opening and C=O formation analogously to the rearrangement under neutral conditions (Scheme 2). The absence of any formation of tetrahydropyridone **4** can be ascribed to the formation of a strong intramolecular hydrogen bond in **127** which stabilizes a conformation unsuitable for the radical coupling and with the proper stereoelectronic factors for the formation of a new C–N bond to afford **128**. Then, the four-membered intermediate **128** can undergo a radical fragmentation to the observed products **7** and **8** [33, 19].

The temperature required to trigger the transformation of **1** is significantly lower in the presence of an acid than under neutral conditions. For example, isoxazolidines **129d** and **129e** were stable at 100°C for at least 1 d, but they were totally converted after 2 h at 80°C in the presence of *p-Ts*OH (Table 11, entries 4–5). The ATR of **54** required at most 1 h in refluxing toluene/*TFA* mixture (Table 12), while higher temperatures (≥126°C) and longer reaction times (4–42 h) were required for the corresponding TR (Table 3).

β-Lactams **7** were conveniently prepared in CH_3CN, or in toluene when higher reaction temperatures were required, in the presence of 1 molar equiv. or a small excess of *p*-toluenesulfonic acid (*p-Ts*OH) or trifluoroacetic acid (*TFA*).

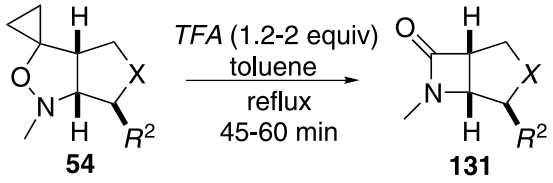
Table 11. ATR of monocyclic 5-spirocyclopropane isoxazolidines [15]



Entry	*R*	R^1	R^2	Adducts	Conditions[a]	β-Lactams	Yield/%
1	*Me*	2-ClC_6H_4	H	**129a**	90°C, 2 min	**130a**	56
2	*Me*	CO_2Et	H	**129b**	50°C, 1 h	**130b**	91
3	(*R*)-CH*MePh*	CO_2Et	H	**129c**[b]	50°C, 1 h	**130c**[b]	61[c]
4	*Me*	*Ph*	CO_2Me	*cis*-**129d**	80°C, 2 h[d]	*cis*-**130d**	30
5	*Me*	*Ph*	CO_2Me	*trans*-**129e**	80°C, 2 h[d]	*trans*-**130e**	29
6	*Bn*	*Ph*	CH_2OH	*cis*-**129f**	50°C, 1.5 h	*cis*-**130f**	67[e]
7	*Bn*	*Ph*	CH_2OH	*trans*-**129g**	50°C, 1.5 h	*trans*-**130g**	78

[a] the reactions were carried out in CH_3CN (entries 2–3, 6–7), or in toluene (entries 1, 4–5); [b] 1:1 diastereomeric mixture; [c] one pure diastereomer afforded the corresponding monobactam in 50% yield under the same conditions; [d] isoxazolidines **129d** and **129e** were recovered unchanged after 1 d at 100°C in toluene; [e] calculated with respect to 87% conversion

Table 12. ATR of 5-spirocyclopropane isoxazolidines **54** derived from intramolecular 1,3-DC [18, 19, 33]



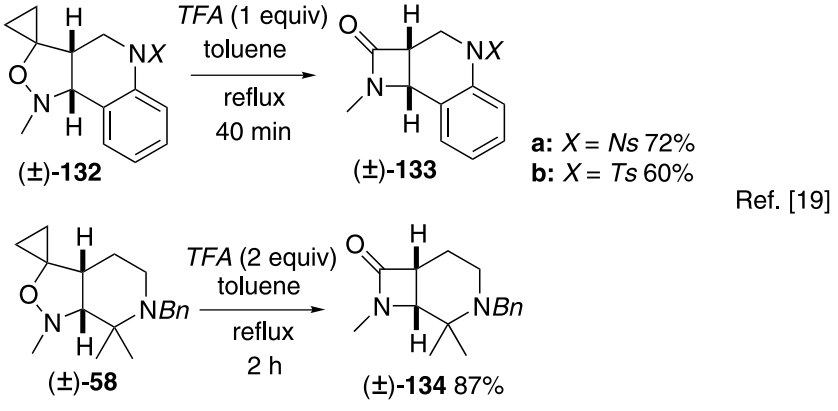
Entry	Adducts	R^2	X	β-Lactams	Yield/%
1	**54c**	H	CHO*Ac*	**131c**	63–92[a,b]
2	**54m**	*i-Pr*	N*Ts*	**131m**	63
3	**54j**	CH_2-3-indolyl	N*Ts*	**131j**	57
4	**54k**	$CH_2CH_2CH_2N$		**131k**	47
5	**54l**	H	O	**131l**	60[b]

[a] mixture of diastereomers; [b] racemic compound

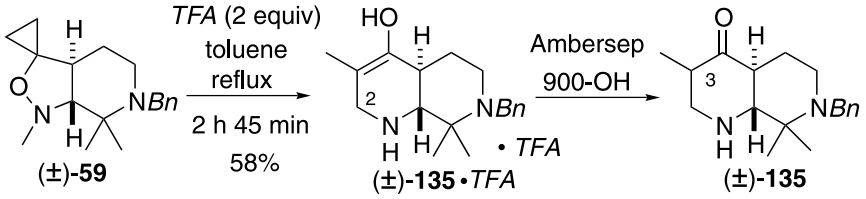
The monocyclic isoxazolidines **129** afforded monobactams **130** in the presence of *p-Ts*OH in yields ranging from 29 to 91% (Table 11). The isoxazolidines **129d** and **129e** with an alkoxycarbonyl group on the C-4 required higher temperatures to rearrange and gave the β-lactam products in lower yields than the corresponding alcohols **129f** and **129g** (Table 11, entries 4–7).

It is worth of note that stereocenters on the isoxazolidine ring, being not directly involved in the ATR (Scheme 12), retain their relative configurations in the β-lactams allowing a complete control of the stereoselectivity (Table 11, entries 4–7).

The *cis*-fused isoxazolidines **54** (Table 12) and their superior homologues **132** and **58** (Scheme 13) were converted into the corresponding 3,4-*cis*-fused azetidinones **131**, **133**, and **134** in medium to high yields.



Scheme 13



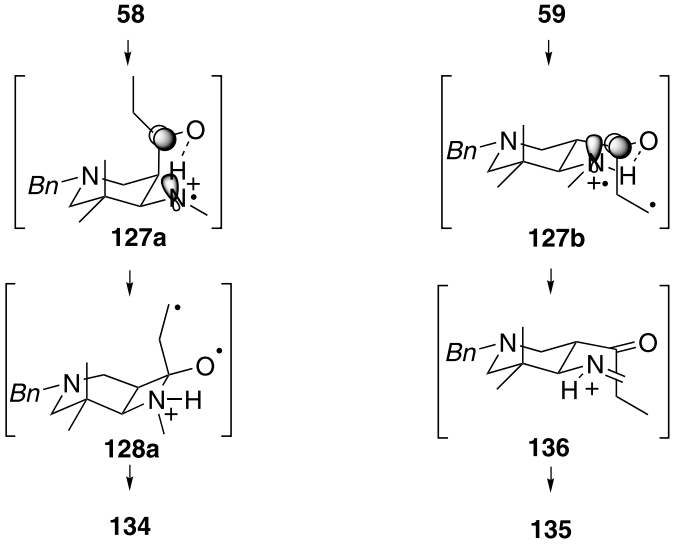
Scheme 14

The ATR of 5-spiroisoxazolidines **132**, carried out in different solvents such as toluene, CH_3CN and *Et*OH, in the presence of *p-Ts*OH, *TFA*, or HCl, afforded analogous results as long as H_2O was kept away from the reaction mixture (Scheme 13) [33, 19].

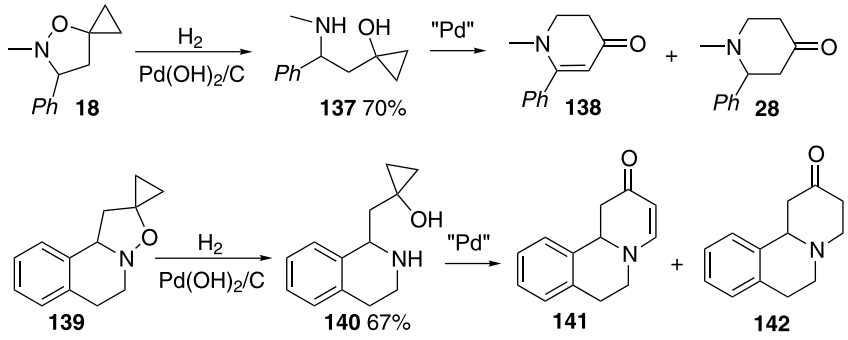
The initial data attest that the 1,3-DC/ATR approach to monobactams and to the 3,4-*cis*-fused β-lactams from nitrones and methylenecyclopropane derivatives is a general process.

The *trans*-fused isoxazolidine **59** showed a completely different behaviour compared to the *cis*-fused isomer **58** under acidic conditions (Scheme 14) [19]. In particular, **59** failed to give the strained *trans*-fused 3,8-diazabicyclo[4.2.0]octan-7-one, but afforded after treatment with a base the 3-methyloctahydro[1,7]naphthyridin-4(1*H*)-one **135**. The tetrahydropyridone **135** differs from the naphthyridinone **60** obtained by heating **58** in xylenes (Scheme 5) in the position of a methyl group which is bonded to C-3 in **135** and to N-1 in **60**.

The ATR of an isotopically labeled isoxazolidine **59** proved that the carbon atom of the *N*-methyl group in **59** ends up to the 2-position in **135** [19] and suggested that also the formation of **135** can be rationalized through the formation of a cationic diradical species such as **127**. In contrast to **127a** which affords **128a**, in the intermediate **127b** derived from **59** the stereoelectronic factors are not suitable for the closure of the four-membered ring. Therefore **127b** undergoes an



Scheme 15



Scheme 16

hydrogen transfer yielding the iminium ion **136** which can evolve to **135** through an intramolecular *Mannich* reaction (Scheme 15).

Palladium Mediated Transformation of β-Aminocyclopropanols

A new and promising two-step transformation of 5-spirocyclopropane isoxazolidines **1** to tetrahydropyridones **4** and dihydropyridones **10** was very recently described (Scheme 1) [34]. The β-aminocyclopropanols **137** and **140** prepared by hydrogenolysis of isoxazolidines **18** and **139**, respectively, were selectively converted into dihydro- and tetrahydropyridone derivatives through Pd mediated processes (Scheme 16) [34].

The product composition strongly depended on the palladium catalyst and the reaction conditions. For example, **137** afforded the sole dihydropyridone **138** by treatment with pyridine and air at 80°C in the presence of a catalytic amount of $Pd(OAc)_2$ (65% yield). Conversely, the saturated derivative **28** was obtained by treatment of **137** with $Pd(OAc)_2$, $LiOAc$, and $Cu(OAc)_2$ at 100°C (70% yield).

The two-step process N–O bond reduction followed by the Pd mediated rearrangement to **4** and **10** (Scheme 1) complements the TR of 5-spirocyclopropane isoxazolidines **1** and isoxazolines [2a, 4].

Conclusion

A rich chemistry is related to 5-spirocyclopropane isoxazolidines **1**. These compounds can be regarded as versatile direct precursors of structural units of potential synthetic interest such as tetrahydro-, dihydropyridones, and azetidinones **4**, **10**, and **7** (Scheme 1).

The simple two-step 1,3-DC/TR protocol provides a valuable access to selectively functionalized quinolizidinones, indolizidinones, and piperidinones and has been successfully applied to the synthesis of several natural compounds and their analogues [7, 8, 10–12, 21, 25].

The ATR to β-lactams **7** and the palladium catalyzed formation of dihydropyridones **10** are promising selective processes which deserve to be thoroughly explored to test their importance as new synthetic routes.

References

[1] For some reviews see: a) Tufariello JJ (1984) Nitrones. In: Padwa A (ed) 1,3-Dipolar Cycloaddition Chemistry, vol 2. Wiley, New York, p 83–168; b) Torssell KBG (1988) Nitrile oxides, Nitrones and Nitronates in Organic Synthesis. VCH, New York; c) Confalone PN, Huie EM (1988) Org React **36**: 1–173; d) Breuer E, Aurich HG, Nielsen A (1989) Nitrones, Nitronates, and Nitroxides. Wiley, New York, p 139–312; e) Padwa A (1991) In: Trost BM (ed) Comprehensive Organic Synthesis, Pergamon, Oxford, p 1069–1109; f) Frederickson M (1997) Tetrahedron **53**: 403–425; g) Gothelf KV, Jørgensen KA (1998) Chem Rev **98**: 863–909; h) Gothelf KV, Jørgensen KA (2000) Chem Commun 1449–1458; i) Karlsson S, Hogberg HE (2001) Org Prep Proced Int **33**: 103–172; j) Osborn HMI, Gemmell N, Harwood LM (2002) J Chem Soc, Perkin Trans 1 2419–2438; k) Kanemasa S (2002) Synlett **9**: 1371–1387; l) Bates RW, Sa-Ei K (2002) Tetrahedron **58**: 5957–5978; m) Gallos JK, Koumbis AE (2003) Curr Org Chem **7**: 397–425

[2] For Reviews on 1,3-Dipolar Cycloadditions of Nitrones and Methylenecyclopropanes see: a) Brandi A, Cicchi S, Cordero FM, Goti A (2003) Chem Rev **103**: 1213–1269; b) Goti A, Cordero FM, Brandi A (1996) Top Curr Chem **178**: 1–97

[3] For a Review on the Synthesis of Methylenecyclopropanes see: Brandi A, Goti A (1998) Chem Rev **98**: 589–635

[4] For a previous review see: Brandi A, Cordero FM, Goti A, De Sarlo F, Guarna A (1993) Synlett 1–8

[5] Trost BM (1991) Science **254**: 1471–1477

[6] Brandi A, Guarna A, Goti A, De Sarlo F (1986) Tetrahedron Lett **27**: 1727–1730

[7] Machetti F, Cordero FM, De Sarlo F, Guarna A, Brandi A (1996) Tetrahedron Lett **37**: 4205–4208

[8] Cordero FM, Anichini B, Goti A, Brandi A (1993) Tetrahedron **49**: 9867–9876

[9] Brandi A, Carli S, Goti A (1988) Heterocycles **27**: 17–20

[10] a) Cordero FM, Cicchi S, Goti A, Brandi A (1994) Tetrahedron Lett **35**: 949–952; b) Brandi A, Cicchi S, Cordero FM, Frignoli R, Goti A, Picasso S, Vogel P (1995) J Org Chem **60**: 6806–6812

[11] Cicchi S, Goti A, Brandi A (1995) J Org Chem **60**: 4743–4748

[12] Brandi A, Garro S, Guarna A, Goti A, Cordero F, De Sarlo F (1988) J Org Chem **53**: 2430–2434

[13] a) Taber DF, Hoerrner RS, Hagen MD (1991) J Org Chem **56**: 1287–1289; b) Tufariello JJ, Tegeler JJ (1976) Tetrahedron Lett 4037–4040

[14] Brandi A, Dürüst Y, Cordero FM, De Sarlo F (1992) J Org Chem **57**: 5666–5670

[15] Cordero FM, Salvati M, Pisaneschi F, Brandi A Eur J Org Chem, in press

[16] a) Padwa A (1984) Intramolecular 1,3-Dipolar Cycloaddition Reactions. In: Padwa A (ed) 1,3-Dipolar Cycloaddition Chemistry, vol 2. Wiley, New York, p 277–406 and references cited therein; b) Baldwin SW, Wilson JD, Aubé J (1985) J Org Chem **50**: 4432–4439; c) Aurich HG, Boutahar M, Köster H, Möbus K-D, Ruiz L (1990) Chem Ber **123**: 1999–2014

[17] Cordero FM, Brandi A (1995) Tetrahedron Lett **36**: 1343–1346

[18] Paschetta V, Cordero F, Paugam R, Ollivier J, Brandi A, Salaün J (2001) Synlett 1233–1236

[19] Cordero FM, Pisaneschi F, Salvati M, Paschetta V, Ollivier J, Salaün J, Brandi A (2003) J Org Chem **68**: 3271–3278

[20] Ferrara M, Cordero FM, Goti A, Brandi A, Estieu K, Paugam R, Ollivier J, Salaün J (1999) Eur J Org Chem 2725–2739

[21] Cordero FM, Brandi A, Querci C, Goti A, De Sarlo F, Guarna A (1990) J Org Chem **55**: 1762–1767

[22] Quick J, Meltz C, Ramachandra R (1979) Org Prep Proc Int **11**: 111–114

[23] Iida H, Tanaka M, Kibayashi C (1984) J Org Chem **49**: 1909–1912

[24] Pisaneschi F, Cordero FM, Goti A, Paugam R, Ollivier J, Brandi A, Salaün J (2000) Tetrahedron: Asymmetry **11**: 897–909

[25] Zorn C, Anichini B, Goti A, Brandi A, Kozhushkov SI, de Meijere A, Citti L (1999) J Org Chem **64**: 7846–7855
[26] Goti A, Anichini B, Brandi A, Kozhushkov S, Gratkowski C, de Meijere A (1996) J Org Chem **61**: 1665–1672
[27] Cordero FM, Goti A, De Sarlo F, Guarna A, Brandi A (1989) Tetrahedron **45**: 5917–5924
[28] Ochoa E, Mann M, Sperling D, Fabian J (2001) Eur J Org Chem 4223–4231
[29] Cordero FM, Barile I, Brandi A, Kozhushkov SI, de Meijere A (2000) Synlett 1034–1036
[30] Cordero FM, Barile I, De Sarlo F, Brandi A (1999) Tetrahedron Lett **40**: 6657–6660
[31] Zorn C, Goti A, Brandi A, Johnsen K, Noltemeyer M, Kozhushkov SI, Gratkowski C, de Meijere A (1999) J Org Chem **64**: 755–763
[32] a) Caserio MC, Graham WH, Roberts JD (1960) Tetrahedron **11**: 171–182; b) Roberts JD, Mazur RH (1951) J Am Chem Soc **73**: 2509–2520; c) Renk E, Roberts JD (1961) J Am Chem Soc **83**: 878–879; d) Klunder AJM, Zwanenburg B (1997) In: de Meijere A (ed) Houben-Weyl, vol E17c. Thieme, Stuttgart, p 2419–2437
[33] Cordero FM, Pisaneschi F, Goti A, Ollivier J, Salaün J, Brandi A (2000) J Am Chem Soc **122**: 8075–8076
[34] Cicchi S, Revuelta J, Zanobini A, Betti M, Brandi A (2003) Synlett 2305–2308