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Iminium ylides from carbenes and carbenoids: generation and synthetic applications

A F Khlebnikov, M S Novikov, R R Kostikov

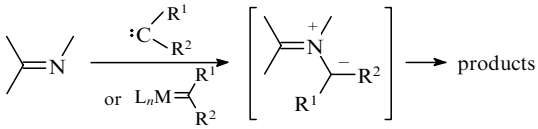
Contents

I.	Introduction	171
II.	Spectroscopic methods for identification of iminium ylides	171
III.	Ylides from metallocarbenoids	173
IV.	Ylides from halogeno carbenes	179
V.	Conclusion	190

Abstract. The carbene method for the synthesis of iminium ylides based on reactions of carbenes and metallocarbenoids with compounds containing a C=N bond is considered. Special attention is given to the use of iminium ylides in the synthesis of various classes of nitrogen-containing compounds. The bibliography includes 163 references.

I. Introduction

In recent years, iminium ylides have found wide application in organic synthesis. This is associated with the discovery of new transformations of these compounds, on the one hand, and the perfection of methods for their generation, on the other hand. About ten different procedures for the preparation of iminium ylides are known. To date, the so-called carbene method based on reactions of electrophilic carbenes or metallocarbenoids with compounds containing a C=N bond (an attack at an unshared electron pair of the nitrogen atom) is the most dynamically developing procedure.



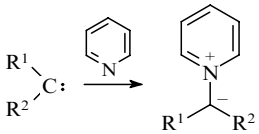
This approach allows the introduction of synthetically useful functional groups (*e.g.*, halogen atoms, alkoxycarbonyl groups) into ylides and their use in domino reactions. Recent reviews [1–6] that touch upon, to a certain degree, the problems of generation of ylides from carbenes and carbenoids cover the literature published more than ten years ago. The present review is a generalisation of the data from the last 15 years devoted to the carbene methods for the generation of iminium ylides and their successful synthetic applications.

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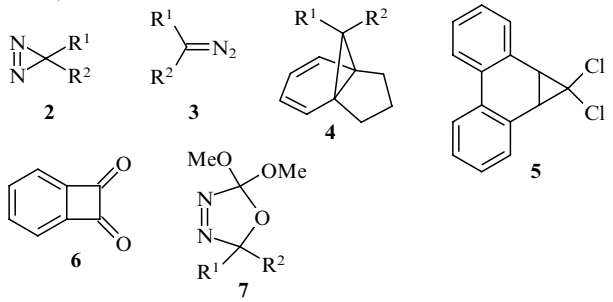
II. Spectroscopic methods for identification of iminium ylides

With rare exception, nitrogen ylides represent unstable intermediates that can nevertheless be identified by spectroscopic methods. Thus ylide species were detected by spectroscopy upon reactions of carbenes with various nitrogen-containing compounds [7] such as amines,[8–10] nitriles [8,11–13] and pyridine.[14,15] Carbenes react with pyridine at the maximum rate; therefore, this reaction is considered to be ideal for measuring absolute rates of carbene reactions and was used as a basis for the so-called 'pyridine probe technique'.[16,17] A vast array of ylides **1** have been prepared from pyridine and diverse carbenes in the past 15 years.



1

Ylides **1** are prepared in solutions or on matrices using flash vacuum thermolysis (FVT) or laser flash photolysis (LFP) of various compounds such as diazirines **2**, aliphatic diazo compounds **3**, tricyclo[4.3.1.0^{1,6}]deca-2,4-diene derivatives **4**, the adduct of dichlorocarbene with phenanthrene (**5**), bicyclo[4.2.0]octa-1,3,5-triene-7,8-dione (**6**), substituted 1,3,4-oxadiazolines **7**, *etc*.



2 **3** **4** **5** **6** **7**

The ylides **1** formed manifest a characteristic absorption in the UV or the visible region of the spectrum related to the $\pi \rightarrow \pi^*$-transition similar to the *B*-band in benzene derivatives. The wavelength of the absorption band depends on the type of the substituents R^1 and R^2 in the ylide **1**: λ_{max} = 340 – 380 nm for dialkyl- or monochloro-substituted ylides, λ_{max} = 390 – 450 nm for dihalogeno ylides and λ_{max} = 430 – 480 nm for phenyl- or carbonyl-substituted ylides. The absorption maxima of pyridi-

nium ylides in the UV region and the absolute rate constants for the formation are listed in Table 1 (for comparison, the rate constants for the reactions of carbenes with tetramethylethylene are given). These data suggest that carbenes react with pyridine several times (from 2 to 30) faster than with tetramethylethylene. The majority of carbenes react with pyridine with the rate constants ranging from 10^8 to 10^{10} litre mol^{-1} s^{-1}. Lower activities are characteristic of methoxy carbenes (presumably, by virtue of their nucleophilic nature) as well as of adamantylidene and chloro(2,2-dimethylcyclopropyl)carbene, which can be attributed to steric factors.

The activation parameters of the addition reaction of the singlet carbenes RClC**:** to pyridine have been determined:

R	E_a /kJ mol^{-1}	log A	Ref.
Ph	5.4 ± 2.0	9.7 ± 0.2	66
$PhOCH_2$	5.8 ± 0.8	10.9	67
MeOC(O)	11.1 ± 0.8	9.1 ± 0.2	40

The rates of formation of ylides (λ_{max} = 540 nm) in the reactions of phenyl- and (4-chlorophenyl)chlorocarbenes with some substituted pyridines have been determined. [68]

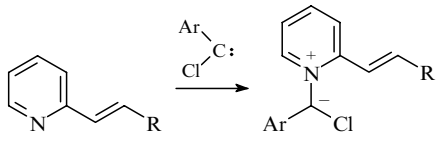
Table 1. The rate constants for the reactions of singlet carbenes R^1R^2C**:** with tetramethylethylene (TME) and pyridine (Py) and the absorption bands of ylides **1** in the UV region at room temperature.

Carbene source	R^1	R^2	k_{TME} /litre mol^{-1} s^{-1}	k_{Py} /litre mol^{-1} s^{-1}	λ_{max} /nm	Ref.
4	F	Cl	$(1.1-2.9) \times 10^8$	8×10^9	450	18
5	Cl	Cl	$(3.8 \pm 0.2) \times 10^9$	$(7.9 \pm 0.2) \times 10^9$	390	19
4	Cl	Br	6×10^9	–	407	20
4	Br	Br	2.8×10^9	5×10^9	436	20
2	Cl	Me	$(1.32 \pm 0.06) \times 10^9$	$(8.9 \pm 0.1) \times 10^9$	360	21, 22
2	Cl	Pr^i	–	$(1.1 \pm 0.3) \times 10^{10}$	–	22
2	Cl	cyclo-Pr	$(1.2 \pm 0.1) \times 10^7$	7.4×10^8	370	23
2	Cl	cyclo-Pr	–	$(4.7 \pm 0.3) \times 10^8$	–	22, 24
2	Cl		–	$(4.7 \pm 0.2) \times 10^7$	275	25
2	Cl	cyclo-Bu	–	$(2.0 \pm 0.2) \times 10^8$	375	26
2	Cl	Bu^t	–	$(2.4 \pm 0.2) \times 10^9$	376	16, 22
2	Cl	Bu^t	–	$(4.2 \pm 0.2) \times 10^9$	–	27
2	Cl	$PhCH_2$	$(1.2 \pm 0.1) \times 10^8$	$(4.2 \pm 0.2) \times 10^9$	379	28
2	Cl	$PhCH_2$	–	$(7.5 \pm 0.5) \times 10^9$	–	22, 29
2	Cl	$PhCH_2$	1.31×10^8	–	–	30
2	Cl	$4\text{-}CF_3C_6H_4CH_2$	$(5.7 \pm 0.3) \times 10^8$	$(1.4 \pm 0.2) \times 10^{10}$	380	31
2	Cl	$4\text{-}ClC_6H_4CH_2$	$(5.5 \pm 0.5) \times 10^8$	$(1.8 \pm 0.4) \times 10^{10}$	380	31
2	F	$PhOCH_2$	–	$(1.4 \pm 0.1) \times 10^{10}$	380	32
2	Cl	$PhOCH_2$	–	$(1.2 \pm 0.1) \times 10^{10}$	380	32
2	F	Ph	$(1.6 \pm 0.2) \times 10^8$	$(1.5 \pm 0.2) \times 10^9$	460	32
2	Cl	Ph	$(1.2 \pm 0.1) \times 10^8$	$(3.4 \pm 0.3) \times 10^8$	475	16, 33
2	Cl	Ph	$(2.8 \pm 0.2) \times 10^8$	$(7.6 \pm 0.9) \times 10^8$	–	26, 34
2	Cl	Ph	–	$(1.5 \pm 0.2) \times 10^9$	480	32
2	Cl	Ph	1.3×10^8	–	–	35
2	Cl	Ph	–	$(3.7 \pm 0.4) \times 10^8$	–	36
2	Cl	$4\text{-}MeC_6H_4$	1.2×10^8	$(2.9 \pm 0.3) \times 10^8$	430	37
2	Cl	$4\text{-}MeOC_6H_4$	1.4×10^7	–	–	26
2	Cl	$4\text{-}MeOC_6H_4$	–	$(2.9 \pm 0.4) \times 10^7$	460	36
2	Cl	$4\text{-}MeOC_6H_4$		$(1.58 \pm 0.05) \times 10^8$	460	37
2	Cl	$4\text{-}NO_2C_6H_4$	–	$(2.3 \pm 0.4) \times 10^9$	665	36
2	Cl	$4\text{-}NO_2C_6H_4$	–	$(7.5 \pm 0.1) \times 10^9$	605	37
2	Cl	$4\text{-}NO_2C_6H_4$	1.2×10^9	–	–	38
2	Br	Ph	–	$(1.2 \pm 0.1) \times 10^9$	480	32
2	Br	Ph	$(3.8 \pm 0.3) \times 10^8$	–	–	36
4	Cl	CN	–	5×10^9	450	39
4	Cl	CO_2Me	4.1×10^8	2×10^9	440	40
2	tetrabenzylglucosylidene		–	8.9×10^8	500	41
2	OMe	Me	–	$(6.6 \pm 0.7) \times 10^5$	380	32
2	OMe	CF_3	$(4.5 \pm 0.2) \times 10^6$	$(4.3 \pm 0.1) \times 10^9$	375	42
2	OCH_2CF_3	Me	–	$(1.6 \pm 0.2) \times 10^7$	380	32
2	OCH_2CF_3	cyclo-Pr	–	$(1.0 \pm 0.1) \times 10^6$	385	32
2	OMe	Ph	–	$(1.2 \pm 0.1) \times 10^5$	480	32
2	OMe	Ph	–	6.9×10^4	–	43
2	OCH_2CF_3	Ph	–	$(1.8 \pm 0.2) \times 10^6$	465	32
2	OAc	Ph	1×10^6	$(3.5 \pm 0.3) \times 10^7$	480	43, 44
2	OCOPh	Ph	–	$(2.1 \pm 0.1) \times 10^8$	470	43
2	$OCOBu^t$	Ph	–	$(7.4 \pm 0.1) \times 10^7$	470	43
2	$OSiMe_3$	Ph	–	–	–	45
2	Cl	MeO	–	–	472	32
2	Cl	OCH_2CF_3	–	–	400	32

Table 1 (continued).

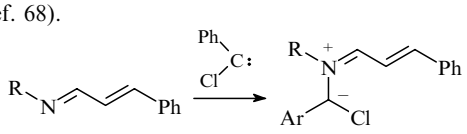
Carbene source	R^1	R^2	k_{TME} /litre mol^{-1} s^{-1}	k_{Py} /litre mol^{-1} s^{-1}	λ_{max} /nm	Ref.
2	OCH_2CF_3	$PhOCH_2$	–	$(8.6 \pm 0.9) \times 10^8$	390	32
2	OAc	$PhOCH_2$	–	$(1.03 \pm 0.06) \times 10^9$	390	32, 44
6	$-o$-$C_6H_4C(O)O-$			$(7.7 \pm 0.4) \times 10^8$	575	46
3	$-C(O)O-CMe_2-OC(O)-$		–	$(1-5) \times 10^9$ (see [a])	530	47
2	H	Cl	8.1×10^9	8×10^9	374	48
3	H	CHO	–	$(1-5) \times 10^9$ (see [a])	460	49
3	H	CO_2Et	–	$(1-5) \times 10^9$ (see [a])	430	50
2	H	cyclo-Pr	–	$(1-5) \times 10^9$ (see [a])	379	51
3	H	Ph	–	1×10^9 (see [a])	460	52
3	H	C_6F_5	–	1×10^9 (see [a])	450	53
2	H	1-adamantyl	–	1×10^9 (see [a])	370	54
2	Me	Me	–	–	364	55, 56
2	Me	Me	–	3×10^9	–	57
7	Pr	Pr	–	3×10^9 (see [a])	360	58
2	adamantylidene		–	$(1.5 \pm 0.2) \times 10^6$	337	59
2	homocuban-9-ylidene		$(0.7-1.2) \times 10^8$	3.4×10^8	400	60, 61
3	Me	Ph	–	1×10^9	450	62
2	CF_3	4-MeC_6H_4	–	4×10^8	420	63
3	$-o$-$C_6H_4CH_2-$		1.9×10^8	3.7×10^8	455–460	64, 65
3	CO_2Me	CO_2Me	–	$(1-5) \times 10^9$ (see [a])	450	47

[a] The tentative value is presented.



Ar	R	$k \times 10^{-8}$ /litre mol^{-1} s^{-1}
4-ClC_6H_4	H	2.0
	Ph	3.6 ± 0.2
	4-ClC_6H_4	4.0 ± 0.2
	4-MeC_6H_4	2.6 ± 0.2
Ph	Ph	2.3
	2-Py	3.7
	4-Py	13 ± 1

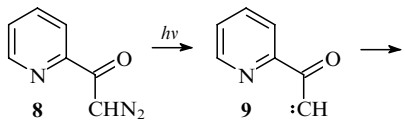
In the reaction of chloro(phenyl)carbene with *trans*-1-phenyl- and 1,5-diphenyl-4-azapenta-1,3-diene, the corresponding ylides (λ_{max} = 550 nm) are formed with the rate constants of $(1.0 \pm 0.1) \times 10^9$ and $(3.6 \pm 0.2) \times 10^8$ litre mol^{-1} s^{-1} (see Ref. 68).

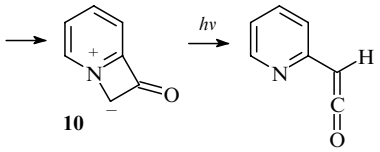


R = Me, Bn.

In all these cases, the C=C bond is inactive with respect to carbene.

Studies on matrix photolysis of 2-(diazoacetyl)pyridine (**8**) ($\nu_{C=O}$ = 1652 cm^{-1}) using time-resolved infrared spectroscopy (TRIR) have shown that compound **8** yields carbene **9**, which undergoes intramolecular cyclisation into ylide **10** with a characteristic band $\nu_{C=O}$ at 1759 cm^{-1}. Upon subsequent photolysis at $\lambda_{max} >$ 320 nm, the ylide **10** is converted into (2-pyridyl)ketene ($\nu_{C=C=O}$ = 2123–2132 cm^{-1}).[69]





Studies of reactions of triplet carbenes with pyridine revealed that in this case ylide intermediates are also formed, but the rate constants for their formation are significantly lower (by more than an order of magnitude) than the rate constants for ylide formation from singlet carbenes (Table 2). This is especially noticeable in the case of sterically hindered carbenes (*e.g.*, with a trypticenyl substituent).[71] Since the ylide formed exists in the singlet state, it was assumed that the triplet carbene first passes into the singlet state and then reacts with pyridine. Hence, the rate constant for the reaction of a triplet carbene with pyridine comprises the equilibrium constant between the triplet and the singlet carbenes. These considerations were employed for the calculation of the energies of the triplet–singlet conversions of aryl carbenes.[52,53]

It is known that the triplet diphenylcarbene is 12–16 kJ mol^{-1} more stable than the singlet one. Studies of the reaction of diphenylcarbene with pyridine have shown that the activation barrier for the formation of ylides from the triplet diphenylcarbene is equal to 8–12 kJ mol^{-1}, which is smaller than the aforementioned difference in the stabilities of states. Thus, it was suggested [69] that the mechanism of the reaction of diphenylcarbene with pyridine does not include preliminary conversion of the triplet carbene into the singlet carbene. Presumably, the triplet and singlet potential reaction surfaces are crossed in this case.[69]

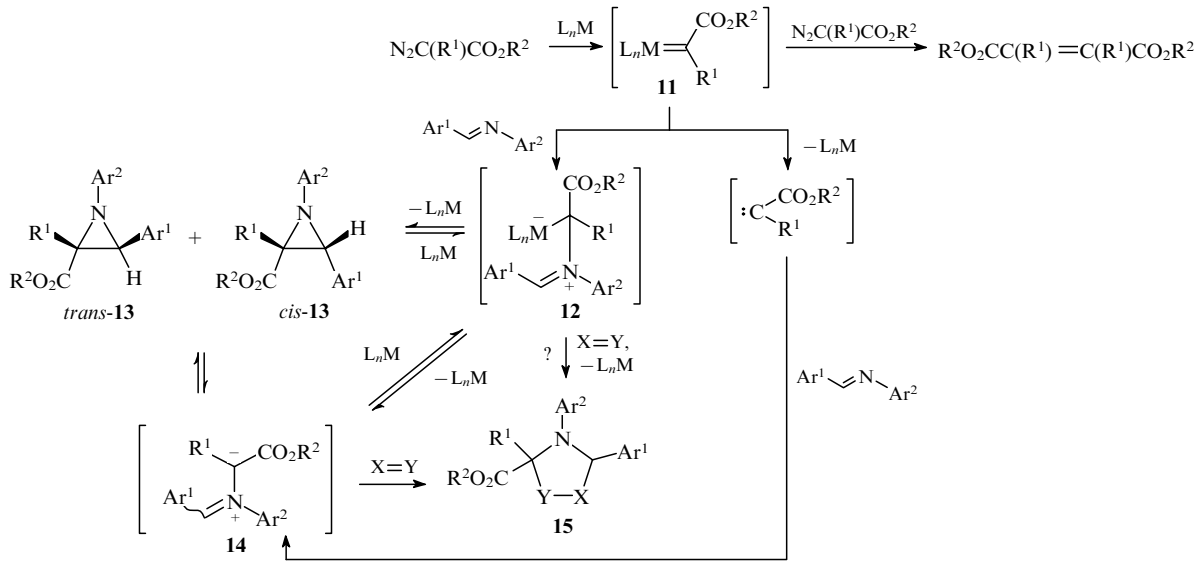
III. Ylides from metallocarbenoids

Reactions of diazo compounds with imines form the basis of an important procedure for the preparation of aziridines and aziridine-2-carboxylic acid derivatives in particular. Let us consider two main types of catalytic reactions of diazo compounds with imines leading to aziridines. The first, so-called 'carbene' type reaction (Scheme 1) consists of the reaction of a diazo compound with a metallocomplex catalyst that gives an unstable metallocarbenoid **11**. The reaction of the latter with the unshared electron pair of an imine results in the complex **12**, which either undergoes cyclisation into aziridine **13** or is converted into

Table 2. Rate constants for reactions of the triplet carbenes R^1R^2C: with pyridine, and absorption bands of ylides **1** in the UV region at room temperature.

Carbene source	R^1	R^2	k_{Py} /litre mol^{-1} s^{-1}	λ_{max} /nm	Ref.
3	H	1-naphthyl	–	535	8
3	H	Ph	9.3×10^6	450	52
3	H	Ph	$(1.9 \pm 0.3) \times 10^7$	–	53
3	H	mesityl	1.35×10^7	430	52
3	H	C_6F_5	5.1×10^7	450	53
3	Me	Ph	$(2.00 \pm 0.01) \times 10^7$	450	62
3	Me	4-$MeOC_6H_4$	$(1.01 \pm 0.03) \times 10^8$	427	62
3	Me	4-$CF_3C_6H_4$	$(2.56 \pm 0.09) \times 10^7$	520	62
3	Ph	Ph	$(2.8 - 4.2) \times 10^5$	500	70
2	Ph	trypticen-1-yl	1×10^4	380	71
2	1-naphthyl	trypticen-1-yl	1.2×10^2	380	71
2	2-naphthyl	trypticen-1-yl	6×10^3	380	71

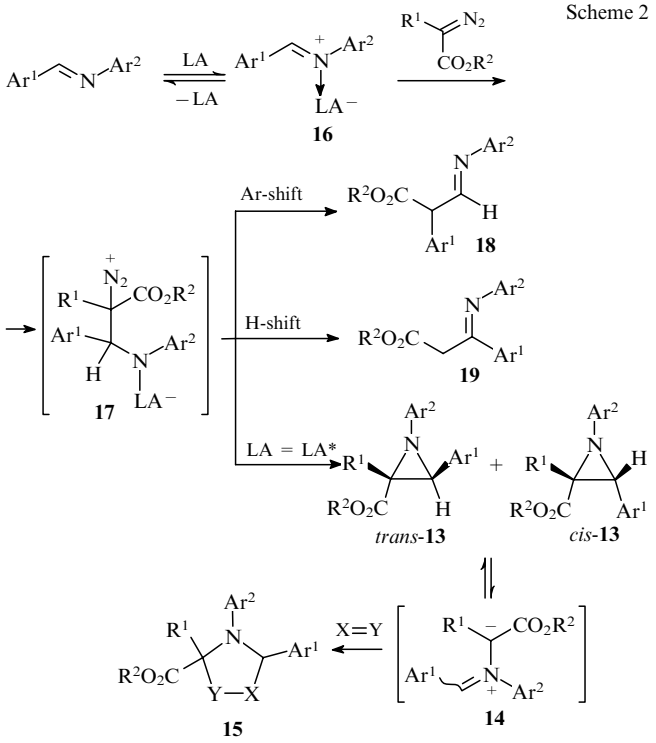
Scheme 1



azomethine ylide **14** the cyclisation of which also yields aziridine **13**. If the formation of aziridines occurs *via* the complex **12**, the use of a catalyst with chiral ligands yields optically active products. In contrast, the formation of aziridines *via* free azomethine ylide **14** would result in a racemate. In the presence of dipolarophiles X = Y, azomethine ylide **14** yields the [3 + 2]-cycloaddition products **15** which can probably be formed *via* the intermediate **12**.

The second, 'non-carbene' type reaction (Scheme 2) includes the reaction of the unshared electron pair of an imine with a Lewis acid (LA) to give a complex **16**; in certain cases, this is stable. Increased electrophilicity of the latter in comparison with the free imine favours the addition of a nucleophilic diazo compound (*e.g.*, diazoacetates) to give the intermediate **17**, which eliminates the nitrogen molecule to give aziridines **13** (the use of chiral Lewis acids LA* affords optically active products). Compounds **18** and **19** are obtained as side products in this reaction.

Scheme 2

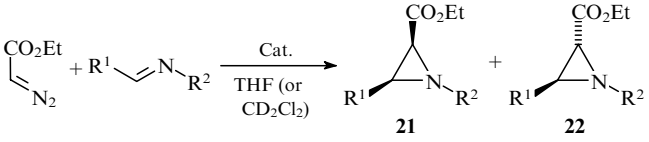


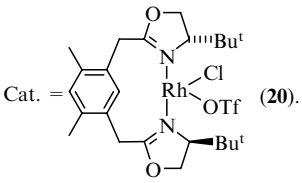
Many papers were devoted to the search for efficient catalysts for the reactions of diazoacetates (N_2CHCO_2R) with imines resulting in aziridines, especially optically active aziridines. It was shown [72] that it is upon Cu-catalysed thermolysis of ethyl diazoacetate that ethoxycarbonylcarbene formed reacted with $Bu^tCH=NMe$, $PhCH=NBu^t$ and $PhCH=NPh$ to give the corresponding 2-ethoxycarbonylaziridines (yields 15% – 30%). It was found that diazoacetates reacted *cis*-diastereoselectively to give predominantly *cis*-**13**, if Lewis acids [*e.g.*, BF_3,[73–77] $AlCl_3$,[73,76] $TiCl_4$,[73,76] $SnCl_4$,[74,76,78,79] $TiCl_2(OPr^i)_2$ [77]], salts [$Cu(OTf)_2$,[77,80] 1-butyl-3-methylimidazolium tetrafluoroborate,[81] $Ln(OTf)_3$,[82,83] $Yb(OTf)_3$,[75,77,82] $Zn(OTf)_2$ [77]] and the metal complexes {([$Cu(PF_6)(MeCN)_4$],[84] [(η^5-C_5H_5)$Fe(CO)_2$.

.(THF)]$^+$[BF_4]$^-$ (Ref. 85) and W(II)[86]} were used as catalysts. Cu(II) salts that represent catalysts for carbene reactions of diazo compounds, on the one hand, and Lewis acids, on the other hand, direct the reactions with imines along the non-carbene pathway. Chiral catalysts[84,87,88] and reaction conditions have been found that allow preparation of the corresponding aziridines with a high enantiomeric excess.[87,88]

At the same time, one cannot assert, with a full degree of confidence, that in the presence of rhodium[89–92] and rhenium[93–95] derivatives as efficient catalysts for carbene reactions of diazoesters, those resulting in aziridinecarboxylates proceed through the carbene pathway. In some cases, where the carbene pathway was suggested, the reaction was *trans*-diastereoselective[90,93–95] and was accompanied by the formation of fumarates and maleates as side products. This is considered as indirect evidence for the involvement of carbene (carbenoid) intermediates. Dirhodium acetate is especially popular,[89,92] while other derivatives, *e.g.*, [Rh(III)-K10-alumina, Rh/C], are used less frequently.[90]

The reaction of ethyl diazoacetate with imines catalysed by the mononuclear rhodium catalyst **20**,[91] results in aziridines **21** and **22**.



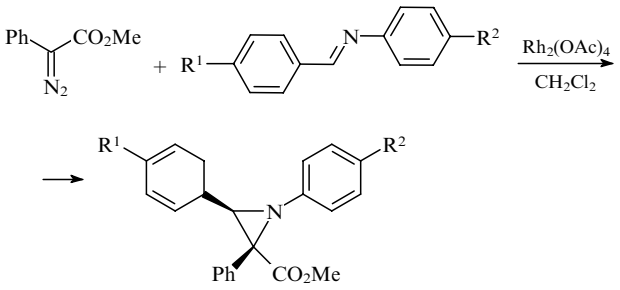


(**20**).

R^1	R^2	Solvent	Yield (**21** + **22**) (%)	Ratio **21** : **22**
Ph	Ph	THF	46	75 : 25
p-MeC_6H_4	Ph	THF	43	58 : 42
Ph	*p*-MeC_6H_4	THF	47	73 : 27
Bu^t	Ph	THF	40	70 : 30
Ph	Bn	THF	12	86 : 14
p-ClC_6H_4	*p*-MeC_6H_4	THF	43	71 : 29
p-HOC_6H_4	Ph	THF	29	90 : 10
Ph	Ph	CD_2Cl_2	36	69 : 31
p-MeC_6H_4	Ph	CD_2Cl_2	18	75 : 25
Ph	*p*-MeC_6H_4	CD_2Cl_2	10	87 : 13

The reaction with *N*-benzylideneaniline ($R^1 = R^2 = Ph$) proceeds stereoselectively with the predominant formation of the *cis*-isomer **21** (3 : 1). The diastereoselectivity and the product yields are comparable with those achieved[84] with the copper complex [$Cu(PF_6)(MeCN)_4$] as a catalyst with addition of a chiral ligand (*S*,*S*)-2,2-bis(4-phenyl-2-oxazolin-2-yl)propane. As to the enantioselectivity, this is significantly lower ($ee \leqslant 11\%$) than that reported[84] ($ee = 35\% - 44\%$). The substitution of other ligands in the chiral Rh-catalyst results in the disappearance of the catalytic activity. The yields of products for the reaction carried out in THF are higher than those in dichloromethane.

Aziridine **23** containing *cis*-aryl groups in positions 2 and 3 (see Ref. 92) is the reaction product of methyl diazophenylacetate with *N*-benzylideneanilines catalysed by $Rh_2(OAc)_4$. This reaction occurs stereoselectively. It is believed that aziridine is formed as a result of cyclisation of the intermediate azomethine ylide.

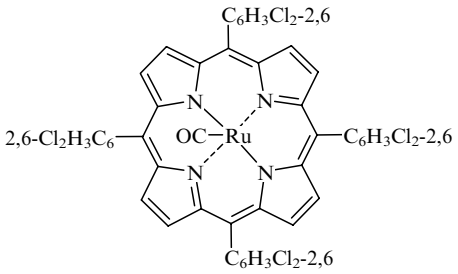


23

$R^1 = R^2 = H$ (79%); $R^1 = NO_2$, $R^2 = H$ (64%); $R^1 = H$, $R^2 = NO_2$ (89%).

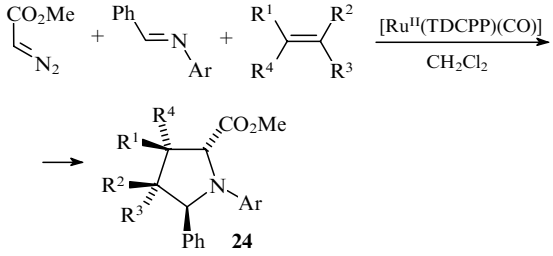
Unfortunately, in the majority of studies aimed at the synthesis of aziridine-2-carboxylates, the possibility of interconversion of aziridines of the type **13** and ylides of the type **14** under reaction conditions (especially upon heating), which might influence significantly the stereoselectivity, was not analysed. The same is true of studies devoted to the synthesis of [3 + 2]-cycloaddition products of azomethine ylides of the type **14** generated in catalytic reactions of diazo compounds with imines in the presence of dipolarophiles.

The porphyrin ruthenium complexes [Ru^{II}(TDCPP)(CO)]

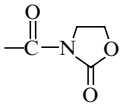


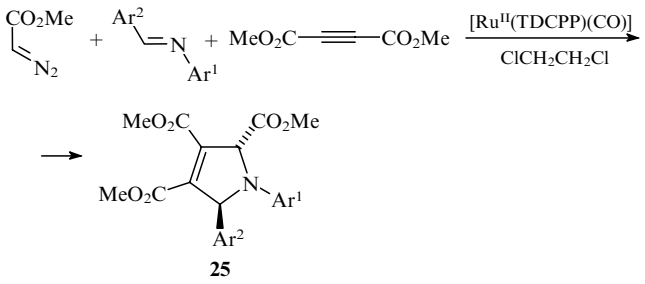
[Ru^{II}(TDCPP)(CO)]

(0.1 mol.%) catalyse a three-component coupling of α-diazo esters with *N*-benzylideneanilines and activated alkenes (or alkynes) resulting in the stereoselective formation of 2,5-*trans*-disubstituted pyrrolidines (**24**) or dihydropyrroles (**25**).[96]



24

Ar	R^1	R^2	R^3	R^4	Yield of **24** (%)
Ph	H	CO_2Me	H	H	91
4-$MeOC_6H_4$	H	CO_2Me	H	H	63
4-$MeOC_6H_4$	H	C(O)Me	H	H	57
4-$MeOC_6H_4$	H		H	H	61
4-$MeOC_6H_4$	H	CO_2Me	Me	H	45
4-$MeOC_6H_4$	H	C(O)Ph	H	Ph	51
4-$MeOC_6H_4$	−C(O)N(Ph)C(O)−		H	H	52



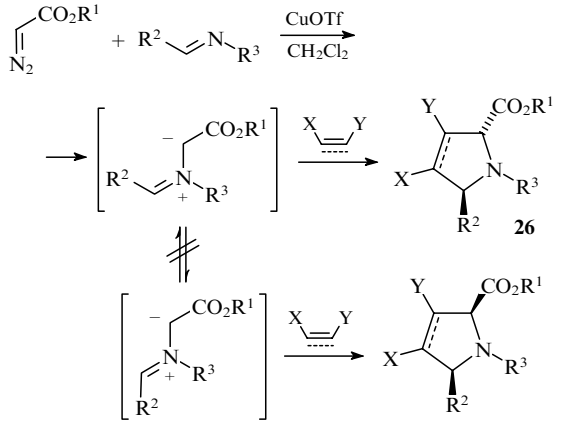
25

Ar^2 = Ph: Ar^1 = Ph (90%), 4-$MeOC_6H_4$ (84%), 4-ClC_6H_4 (85%), 3-ClC_6H_4 (69%), 2-ClC_6H_4 (0%);

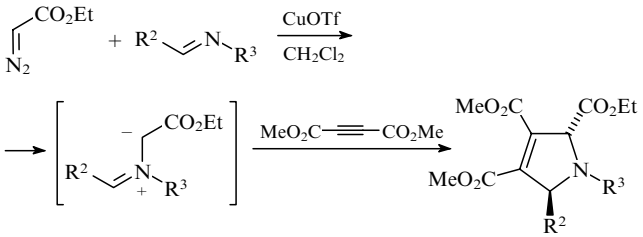
Ar^1 = Ph: Ar^2 = 4-$NO_2C_6H_4$ (59%), 4-ClC_6H_4 (92%), 4-$MeOC_6H_4$ (87%),4-MeC_6H_4 (98%), 3-$MeOC_6H_4$ (90%).

Considering the fact that porphyrin ruthenium(II) complexes form ruthenium–carbene complexes with diazo compounds, Li *et al.* suggested [96] that this reaction occurs *via* azomethine ylides, which undergo 1,3-dipolar cycloaddition with activated alkenes. In the case of non-symmetrical activated alkenes as dipolarophiles, one of two possible regioisomers was isolated. An increase in the steric crowding at the nitrogen atom of the imine hinders the reaction: *e.g.*, *N*-benzylidene-3-chloroaniline yields the cycloadduct with a lower yield than *N*-benzylidene-4-chloroaniline, whereas *N*-benzylidene-2-chloroaniline does not react at all.

Copper(I) triflate catalyses the reactions of various α-diazo esters with imines and alkenes (or alkynes) in dichloromethane to yield polysubstituted pyrrolidines (or dihydropyrroles) **26** (see Ref. 97). This reaction is stereo- and regioselective. It is suggested that the reaction of copper(I) with a diazo compound yields a metallocarbenoid, which forms an azomethine ylide with the imine, the 'carbenoid' carbon being in the *cis*-position relative to the substituent R^2. It is noteworthy that no isomerisation of the ylide takes place, since only 2,5-*trans*-adducts are formed.

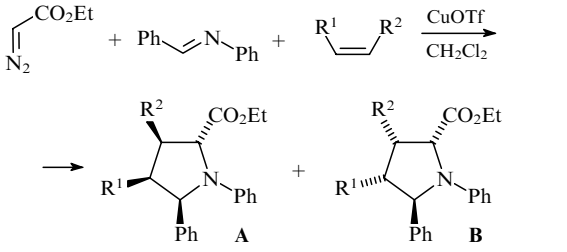


Dirhodium acetate $Rh_2(OAc)_4$ also catalyses this reaction, but the yield of the adduct of ethyl diazoacetate with dimethyl acetylenedicarboxylate (DMAD) and *N*-benzylideneaniline is lower than in the case of copper(I) triflate. Dichloromethane appeared to be the solvent of choice; in other solvents, the yields were lower and no reaction occurred in THF or DME. The effects of the substituents in *N*-benzylideneanilines on the yields of the corresponding adducts were studied in reactions of ethyl diazoacetate with dimethyl acetylenedicarboxylate and various *N*-benzylideneanilines. It was found that nitrophenyl-substituted imines do not react. It was assumed that THF or DME as the solvent and the nitro group in the imine decrease the activity of the catalyst due to complex formation.

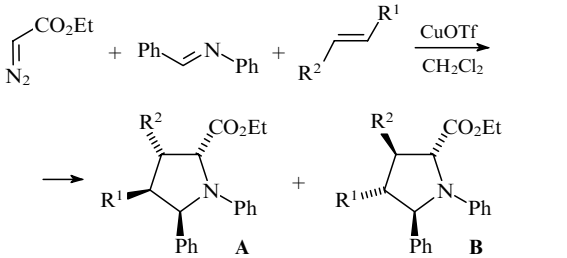


R^2 = Ph: R^3 = Ph (91%), 4-ClC_6H_4 (75%), 4-$MeOC_6H_4$ (43%), 4-$NO_2C_6H_4$ (0%), Bn (43%);

R^3 = Ph: R^2 = 4-ClC_6H_4 (77%), 2-ClC_6H_4 (74%), 4-BrC_6H_4 (79%), 4-MeC_6H_4 (86%), 4-$NO_2C_6H_4$ (0%), 4-$MeOC_6H_4$ (54%), 3-$MeOC_6H_4$ (51%), 2-furyl (94%), cyclo-C_6H_{11} (35%).



R^1	R^2	Yield (%)	**A** : **B** ratio
CO_2Me	CO_2Me	77	2 : 1
–C(O)N(Me)C(O)–		70	2 : 1
–C(O)OC(O)–		55	5 : 1

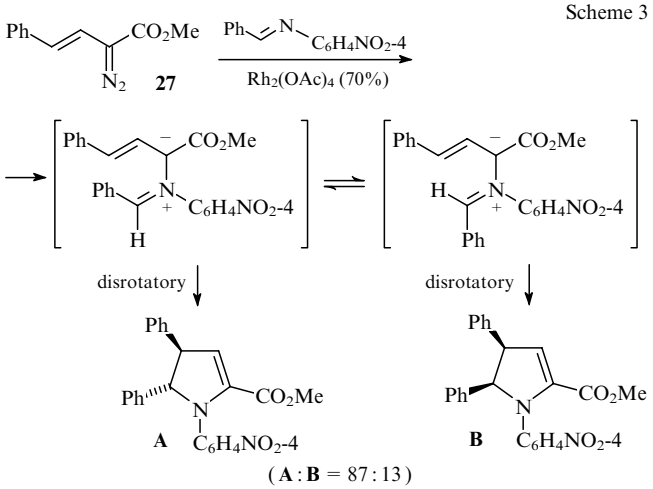


R^1	R^2	Yield (%)	**A** : **B** ratio
CO_2Et	CO_2Et	77	2 : 1
CN	CN	70	2 : 1
Ph	PhC(O)	43	5 : 1
H	CO_2Et	47	2 : 1

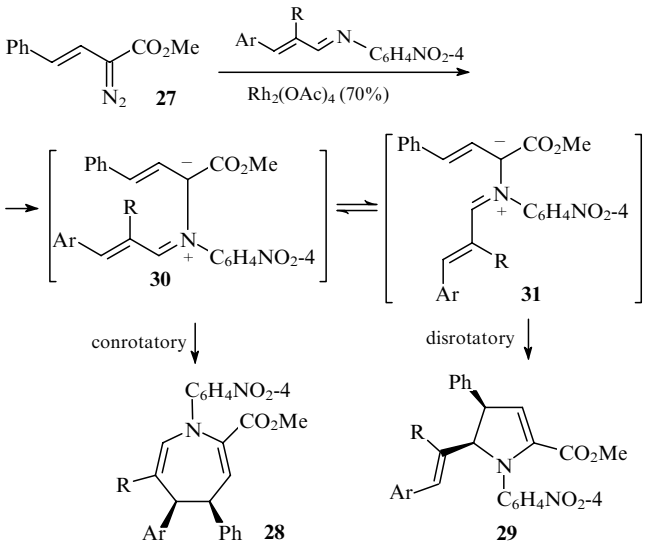
Diazostyrylacetate (**27**) is an efficient reagent for the generation of azomethine ylides containing unsaturated fragments; their cyclisation affords dihydropyrroles or dihydroazepines with a high degree of stereocontrol and in high yields.[98] The reaction of diazostyrylacetate with *N*-benzylidene-4-nitroaniline catalysed by $Rh_2(OAc)_4$ yields dihydropyrrole derivatives predominantly as the *trans*-isomer, which can be attributed to the relative configurational stability of the ylides leading to particular stereoisomers (Scheme 3).

The catalytic reaction of the ester **27** with azadienes yields a mixture of dihydroazepine **28** and dihydropyrrole **29**. The presence of a methyl group in position 3 of the azadiene strongly affects the dihydroazepine : dihydropyrrole ratio. It is assumed that the introduction of a methyl group decreases the stability of

Scheme 3



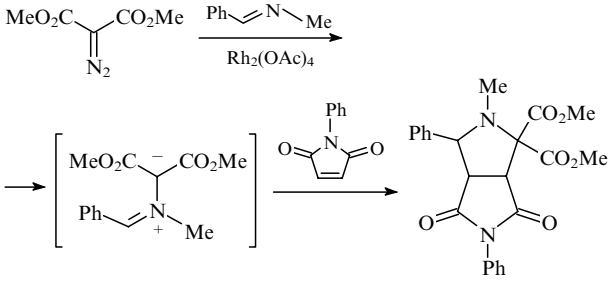
ylide **30** in comparison with ylide **31** resulting in the exclusive formation of dihydroazepine.



R	Ar	Yield of **28** + **29** (%)	Ratio of **28** : **29**
H	Ph	78	50 : 50
H	$C_6H_4NO_2$-4	78	68 : 32
Me	$C_6H_4NO_2$-4	73	100 : 0

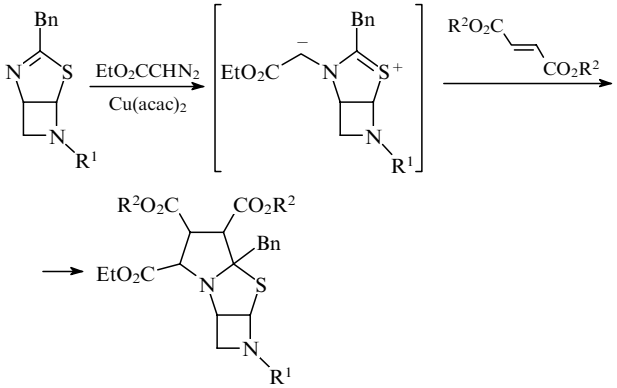
The reactions of alkenyl-substituted diazo compounds **32** with imines **33** (Scheme 4) in the presence of various catalysts including $Rh_2(OAc)_4$, $CuPF_6$, CuOTf and $Cu(OTf)_2$ have been studied.[99] It was found that the reaction of diazostyrylacetate (**32**, R = Ph) with *N*-cinnamylidene-4-nitroaniline (**33a**, Ar = Ph) catalysed by dirhodium(II) acetate yields the corresponding dihydropyrrole **34**, whereas a similar reaction catalysed by copper salts with copper(II) triflate as the catalyst of choice affords dihydropyrrole **35**. This dependence of the reaction route on the catalyst was demonstrated for a broad range of compounds (Table 3). The results obtained prompted a conclusion that dihydropyrrole **34** is formed from ylide **A** derived upon addition of the imine **33** to the metallocarbenoid, whereas dihydropyrrole **35** is formed from the intermediate **B** resulting from electrophilic addition of the activated imine **33** to the diazo compound **32**.

The reaction of *N*-methylbenzylideneamine with dimethyl diazomalonate catalysed by $Rh_2(OAc)_4$ in the presence of *N*-phenylmaleimide yielded 1,3-dipolar cycloaddition products.[100]



exo (50%), *endo* (34%)

Metallocarbenoids obtained from diazo compounds reacted with heterocyclic compounds containing C=N bonds to give iminium ylides; the 1,3-dipolar cycloaddition of the latter to fumarates or DMAD is a convenient approach to the synthesis of fused heterocyclic compounds. Some examples of these reactions are given below.[101, 102]



R^1 = $Me_2C{=}CCO_2Me$, R^2 = Me, Et.

Scheme 4

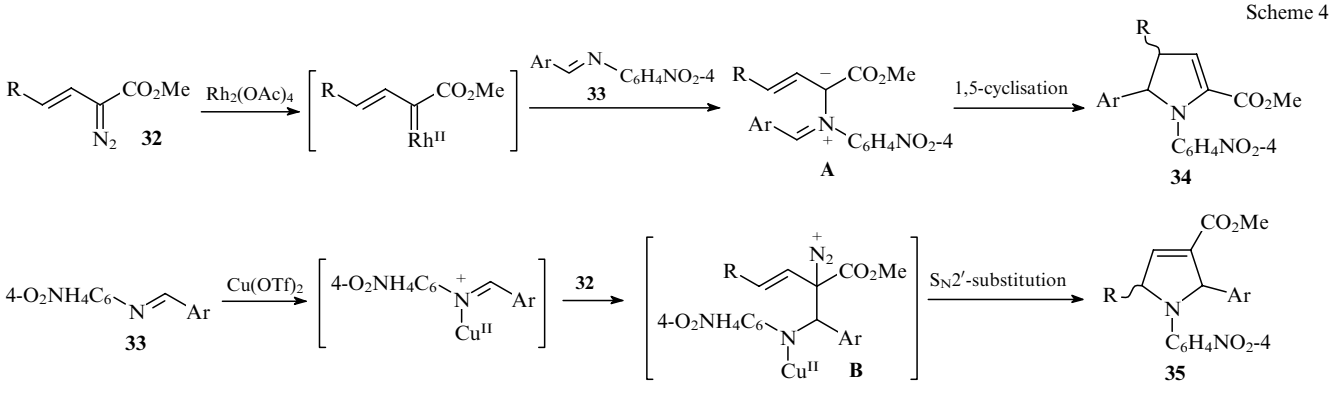
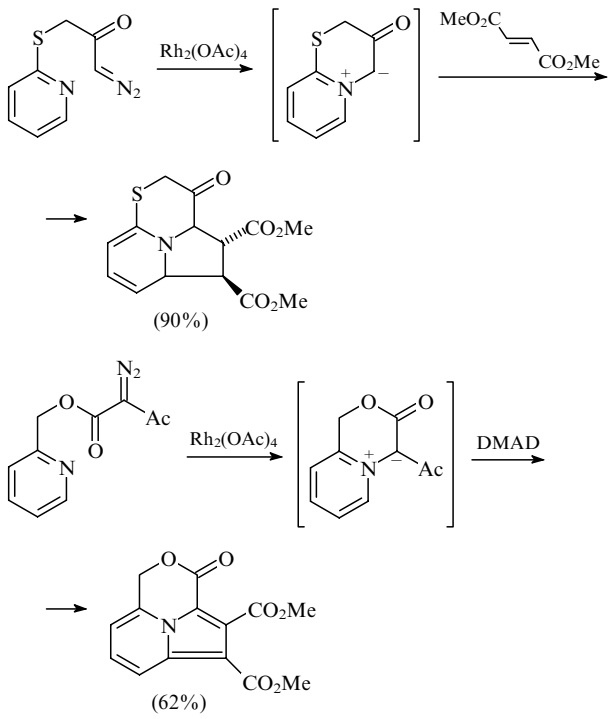
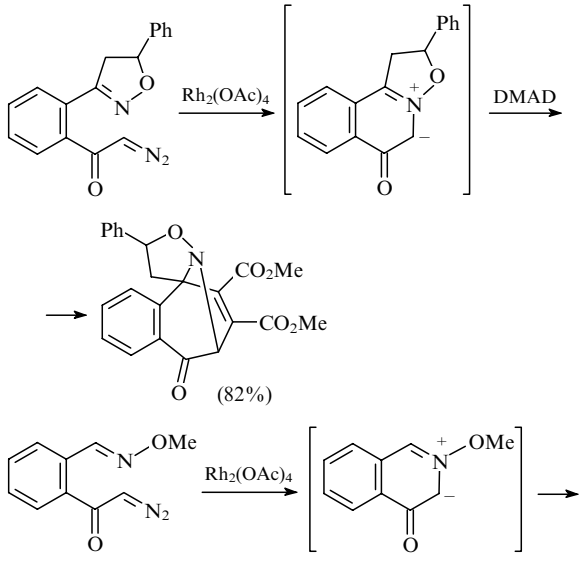


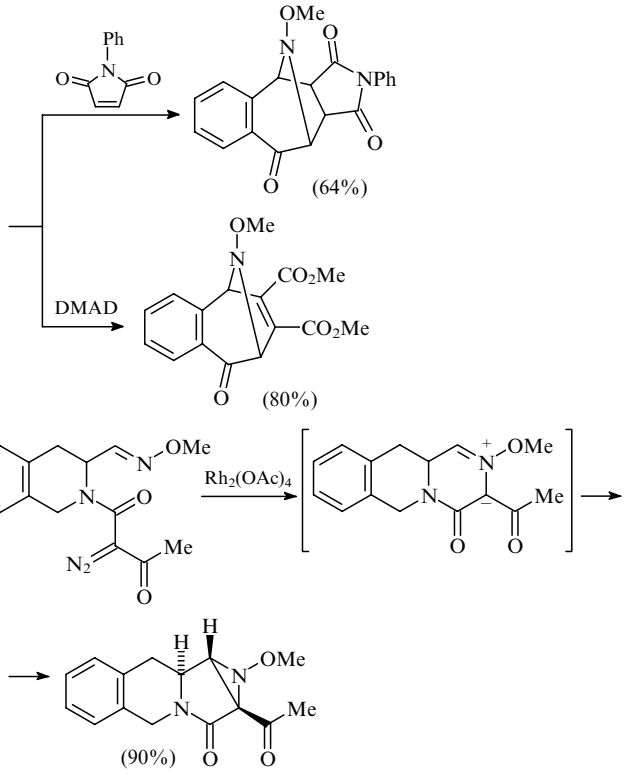
Table 3. Ratios and yields of catalytic reaction products of diazo compounds **32** with imines **33**.

R	Ar	Reaction catalysed by $Rh_2(OAc)_4$		Reaction catalysed by $Cu(OTf)_2$	
		yield of product **34**	ratio of *trans* : *cis*-isomers	yield of product **35**	ratio of *trans* : *cis*-isomers
Ph	Ph	66	< 98 : 2	67	91 : 9
Ph	4-$NO_2C_6H_4$	12	100 : 0	40	98 : 2
Ph	4-ClC_6H_4	47	100 : 0	66	96 : 4
Ph	4-MeC_6H_4	56	100 : 0	63	88 : 12
Ph	4-$MeOC_6H_4$	62	100 : 0	74	83 : 17
Me	Ph	42	90 : 10	0	
CO_2Me	Ph	51	93 : 7	0	

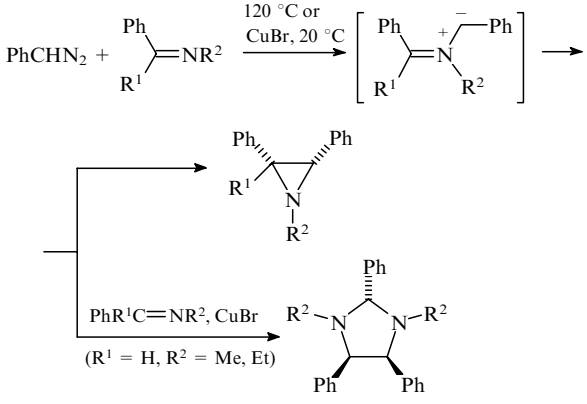


N-Ylides generated as a result of an intramolecular attack of a metallocarbenoid on the unshared electron pair of the nitrogen atom of the *N*-alkoxyimino group either yield 1,3-dipolar cycloaddition products with dipolarophiles [103] or undergo cyclisation to the corresponding aziridines.[104]





The decomposition of phenyldiazomethane in the presence of imines results in azomethine ylides which undergo conrotatory cyclisation to give *cis*-aziridines in low yields. This cyclisation competes with the 1,3-cycloaddition of the ylide (R^1 = H, R^2 = Me, Et; CuBr as the catalyst) to the imine, which results in the corresponding imidazolidine.[105]



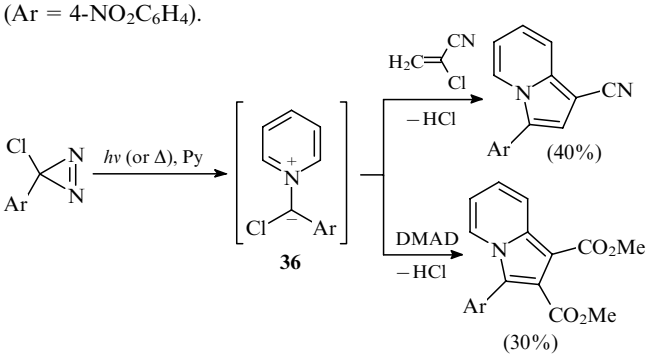
R^1 = H, Me; R^2 = Me, Et, Pr^i, Bu^t.

IV. Ylides from halogeno carbenes

1. Ylides from alkyl- and aryl(chloro)carbenes

a. 1,3-Dipolar cycloaddition

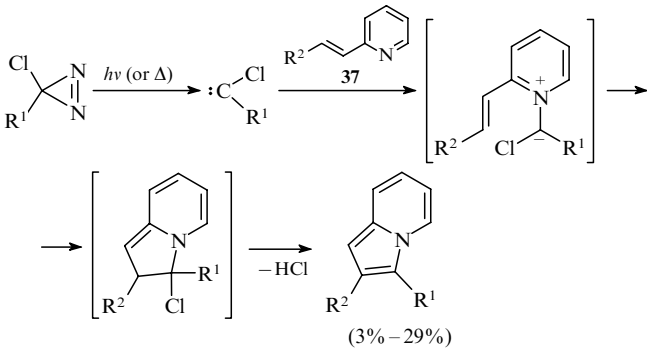
Photolysis or thermolysis of aryl chlorodiazirines in the presence of pyridine is a method for the generation of chloro-substituted pyridinium ylides **36**. Earlier studies have demonstrated the possibility of using these non-stabilised intermediates in the synthesis of indolizines by 1,3-dipolar cycloaddition to dimethyl acetylenedicarboxylate [16] and α-chloroacrylonitrile.[37] The absolute rate constants for these reactions have recently been determined. Thus the rate constant for the reaction of dimethyl acetylenedicarboxylate with the ylide **36** (Ar = Ph) is equal to $(1.57 \pm 0.06) \times 10^6$ litre mol^{-1} s^{-1} (see Refs 16 and 66). α-Chloroacrylonitrile reacts with ylides **36** regioselectively; the absolute rate constants for various Ar are equal to $(1.88 \pm 0.03) \times 10^7$ (Ar = 4-MeOC$_6$H$_4$), $(1.46 \pm 0.04) \times 10^7$ (Ar = 4-MeC$_6$H$_4$), $(7.7 \pm 0.4) \times 10^6$ (Ar = Ph) and $(2.3 \pm 0.1) \times 10^5$ litre mol^{-1} s^{-1} (Ar = 4-NO$_2$C$_6$H$_4$).



These results suggest that ylides behave as nucleophiles in the 1,3-dipolar addition.[37] The ylide prepared from 1-naphthylcarbene and pyridine undergoes cycloaddition to dimethyl fumarate [the rate constant for this reaction is equal to $(5.3 \pm 1.0) \times 10^5$ litre mol^{-1} s^{-1}].[8] The rate constants for the ylide formed from chloro (methyl)carbene and pyridine with acrylonitrile or α-chloroacrylonitrile are equal to $(2.06 \pm 0.02) \times 10^7$ and $(1.60 \pm 0.15) \times 10^8$ litre mol^{-1} s^{-1}, respectively.[21]

b. 1,5-Cyclisation

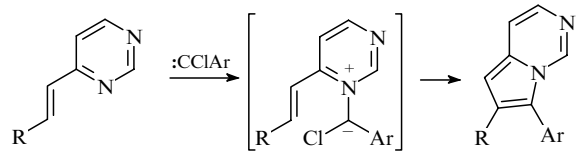
A multistep reaction of aryl(chloro)carbenes with 2-alkenylpyridines **37** and diazines, which involves ylide formation, 1,5-cyclisation and dehydrochlorination, is an alternative approach to the synthesis of indolizines and their hetero analogues.[68, 106] Kinetic studies have shown that 1,5-cyclisation under conditions of vacuum flash photolysis of aryl(chloro)diazirines in isooctane in the presence of 2-vinylpyridine (**37**, R^2 = H) is characterised by



R^1 = Ar, Bn; R^2 = H, Ar, 2-pyridyl.

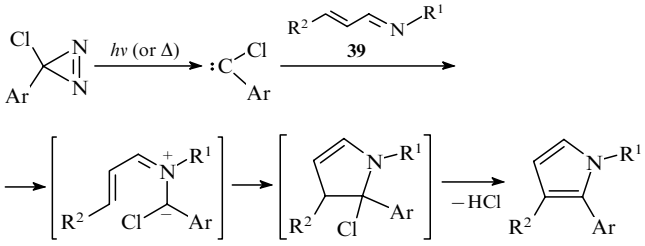
a noticeable activation barrier ($E_a \approx 50$ kcal mol^{-1}), which suggests that the transition state is somewhat compressed.[107] A phenyl substituent on the double bond favours the cyclisation by lowering this barrier to 33–37 kcal mol^{-1}. Presumably, the dehydrochlorination step is fast, since in none of the cases studied were the primary cyclisation products (*viz*., the corresponding dihydroindolizines) detected even in trace amounts.

It was shown that the addition of chloro(phenyl)carbene derived upon photolysis of 3-chloro-3-phenyldiazirine to 1-(2-pyridyl)-2-(4-pyridyl)ethylene (**37**, R^2 = 4-pyridyl) is directed to the nitrogen atom of the *para*-, rather than the *ortho*-substituted pyridine ring.[68] No target indolizine could be obtained from this substrate. However, ylides generated from 4-vinyl-and 4-styrylpyrimidines where both reactive nitrogen atoms are localised in the same ring, do undergo 1,5-cyclisation resulting in pyrrolo[1,2-*c*]pyrimidines **38**.[108]



R = H, Ph.

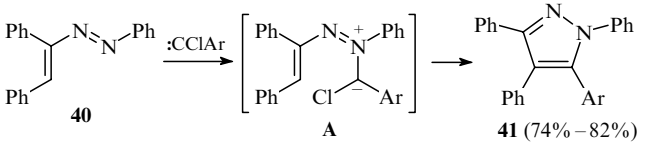
Ylides generated from azadienes **39** and aryl(chloro)carbenes represent acyclic analogues of 2-alkenylpyridinium ylides. These intermediates undergo cyclisation to give 1,2,3-trisubstituted pyrroles in yields exceeding those of the corresponding indolizines in an analogous reaction of pyridines.[68, 109] The activation parameters of the 1,5-cyclisation of the 'azadiene' ylides are as follows: $E_a = 47.0 - 51.5$ kJ mol^{-1}, log$A = 12.1 - 12.9$.



R^1 = Alk; R^2 = Alk, Ph.

This reaction occurs smoothly both upon thermolysis in boiling benzene and in the photolysis in hexane and affords pyrroles in comparable yields. This method can also be used for the preparation of 2-heteryl-substituted pyrroles starting from (chloro)-2-pyridyl- and -2-thienylcarbenes, but in this case the yields of the reaction products do not exceed 15%.[110]

The azo compound **40** contains two sites reactive with respect to aryl(chloro)carbene, however, only one of the two ylides formed affords pyrazole as a result of 1,5-cyclisation. Indeed, thermolysis of some aryl(chloro)diazirines in the presence of the azo compound **40** yields the ylide intermediate **A**; cyclisation of the latter and subsequent elimination of HCl afford the tetraaryl-substituted pyrazoles **41** in high yields.[108]

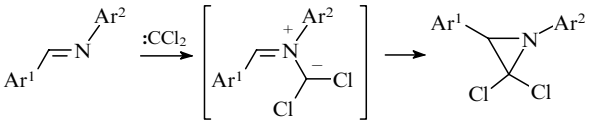


2. Ylides from dichlorocarbene

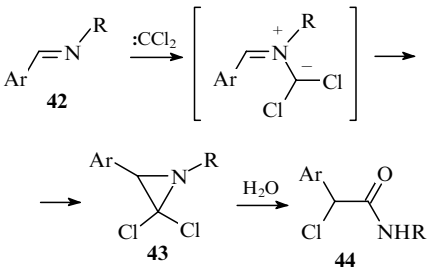
a. Azomethine ylides from dichlorocarbene

Dichloro-substituted azomethine ylides formed upon reaction of azomethines with dichlorocarbene undergo three types of conversions: (1) 1,3-cyclisation, (2) 1,3-dipolar cycloaddition to dipolarophiles and (3) 1,4-H-shift. Which particular 'stabilisation' pathway occurs depends on the structure of the ylide which, in turn, depends on the structure of the starting imine.

1,3-Cyclisation. The analysis of the dependence of the chemical behaviour of *gem*-dichloro-substituted ylides on their geometry calculated by the MNDO method has demonstrated that cyclisation to *gem*-dichloroaziridines is more typical of ylides in which the dichloromethylene fragment is turned appreciably relative to the C—N=C plane (the angle θ_1 is equal to 34–50°). This type of ylide comprises intermediates generated upon reactions of dichlorocarbene with benzophenone *N*-alkylimines and benzaldehyde *N*-aryl- and *N*-alkylimines (the latter should contain secondary or tertiary alkyl substituents at the nitrogen atom). Reactions of *N*-arylbenzylideneamines with dichlorocarbene have long been known as a convenient method for the synthesis of aziridines;[2, 111, 112] however, experimental evidence in favour of the ylide mechanism of this conversion was obtained as late as 1993.[113]

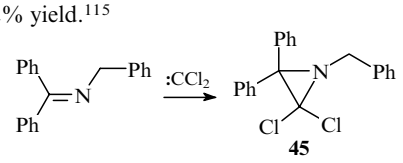


Substitution of the primary alkyl substituent at the nitrogen atom for an aryl substituent results in resinification of reaction mixtures (no aziridines could be obtained from such imines).[114] Sterically more crowded imines **42** containing an isopropyl, a cyclohexyl or a *tert*-butyl group on the nitrogen atom yield the desired aziridines **43** with dichlorocarbene generated upon treatment of chloroform with an alkali.[114] These are easily hydrolysed to the corresponding amides **44** (16%–95%) during column chromatography on silica gel. Nevertheless, some aziridines can be isolated in an analytically pure state in up to 80% yields.

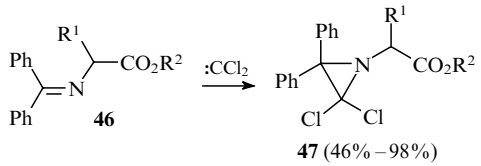


R = Pr^i, Bu^t, cyclo-C_6H_{11}.

Much more stable aziridines were prepared from benzophenone *N*-alkylimines. Thus *N*-benzhydrylidene-*N*-benzylamine reacts with dichlorocarbene to give *gem*-dichloroaziridine **45** in 72% yield.[115]

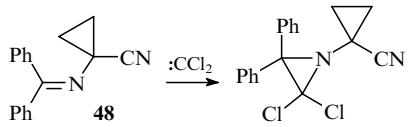


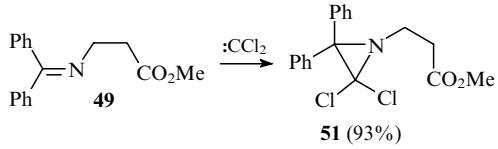
Aziridination of *N*-benzhydrylideneamino acid derivatives[114, 115] yields functionalised aziridines, which represent valuable building blocks for the synthesis of multifunctional amino acids, certain heteropolycyclic systems[116] and functionalised ketene imines, and is preparatively the most efficient among other reactions of benzophenone imines.[117] It has been found[115] that the nature of the transformation products of benzhydrylidene derivatives of glycine esters, alanine esters and related systems depends significantly on the method used for the generation of dichlorocarbene. The reaction of dichlorocarbene generated in a KOH–$CHCl_3$–$Et_3N^+CH_2Ph$ Cl^- (TEBA) system with imines **46** was used for the preparation of *gem*-dichloroaziridines **47**.



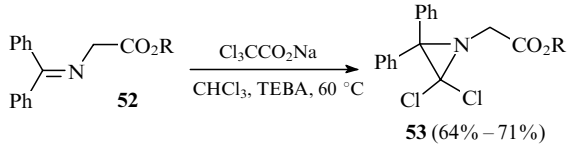
R^1 = Me, Et, Bn, CH_2=$CHCH_2$; R^2 = Me, Et.

Benzophenone imines **48** and **49** yield the corresponding aziridines **50** and **51** under identical conditions.



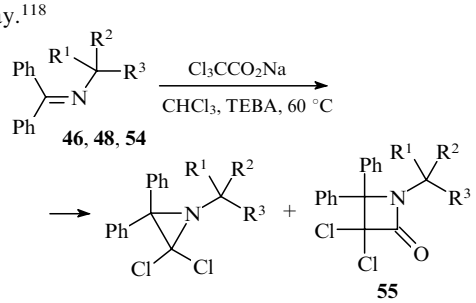


In contrast to the alanine derivatives **46**, **48** and **49**, the glycine derivatives **52** do not yield *gem*-dichloroaziridines with dichlorocarbene generated from chloroform upon alkaline treatment. Presumably, compounds **52** manifesting higher CH-acidity undergo deprotonation under the action of KOH, which changes the direction of the reaction. However, the use of a 'neutral' method of decomposition of sodium trichloroacetate for the thermocatalytic generation of dichlorocarbenes affords the desired *gem*-dichloroaziridines **53**.



R = Me, Et.

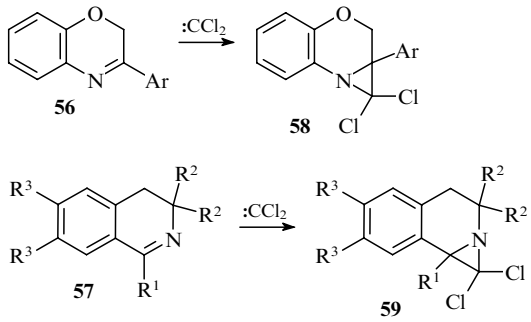
This method is also suitable for the synthesis of aziridines from sterically more crowded imines **54**; however, azetidinone **55** is formed as a side product; the relative yield of azetidinone increases with an increase in the steric volume of the substituents at the C=N bond. Studies using labelled compounds have shown that azetidine derivatives are formed through a non-carbene pathway.[118]



R^1 = H, R^2 = Alk, R^3 = CO_2Me; R^1–R^2 = CH_2CH_2, R^3 = CN.

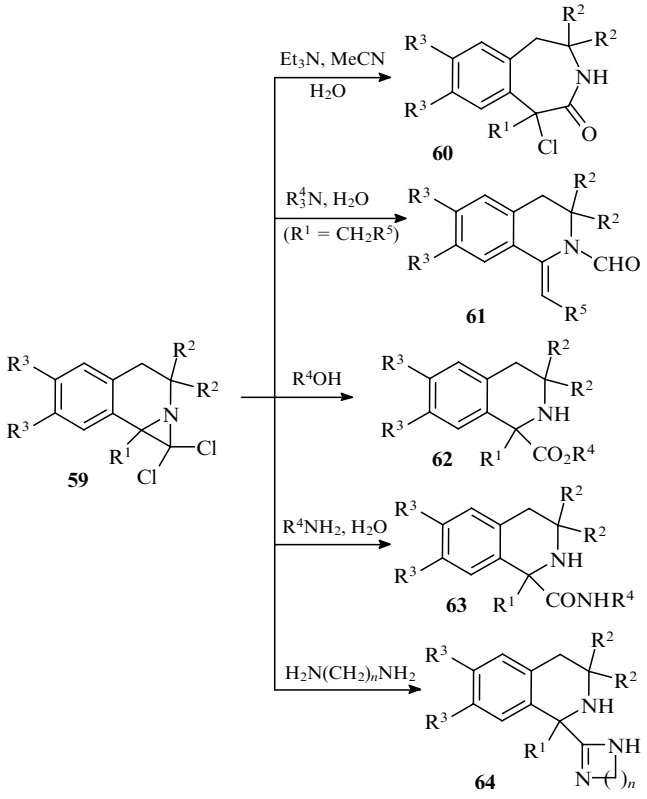
Reactions of dichlorocarbene with substrates containing an endocyclic C=N bond have found applications in the synthesis of fused aziridine compounds. Thus benzoxazines **56** and substituted 3,4-dihydroisoquinolines **57** yield aziridinobenzoxazines **58**[119]

and aziridinoisoquinolines **59**, respectively, upon reaction with dichlorocarbene.[114]



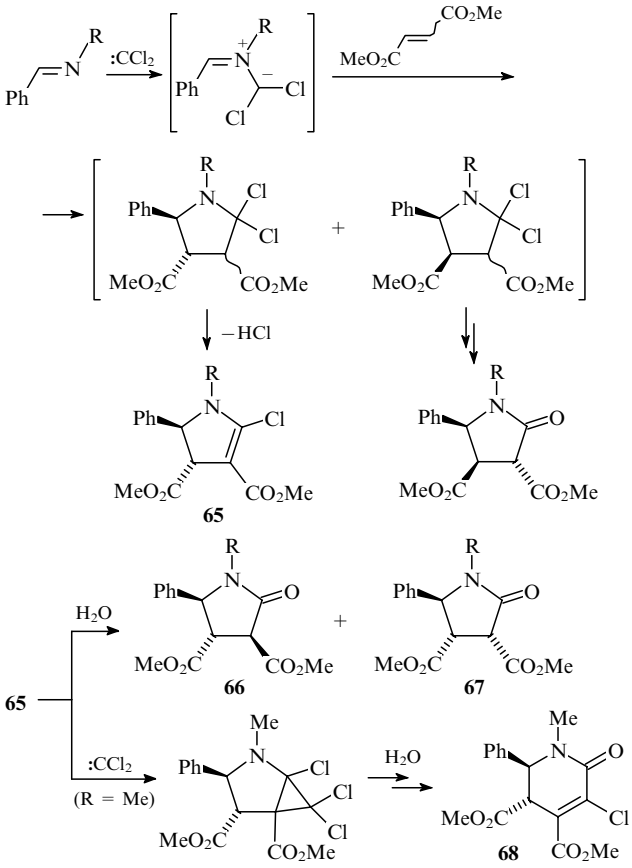
R^1 = H, Alk, Ar; R^2 = H, Alk; $R^2_2 = (CH_2)_n$ (n = 4, 5); R^3 = H, OMe.

Approaches to the cleavage of either of the non-equivalent bonds in the aziridine ring in 1,1-dichloro-1,3,4,8b-tetrahydroazirino[2,1-*a*]isoquinolines (**59**) have been developed.[120] This opens a convenient way to the synthesis of substituted 3-benzazepin-2-ones (**60**), *N*-formyltetrahydroisoquinolines **61** as well as isoquinoline-1-carboxylic acid derivatives, *viz*., esters **62**, amides **63** and cyclic amidines **64** of the imidazole and pyrimidine series.



It should be noted that 1,3-cyclisation of the aforementioned chlorinated azomethine ylides occurs at a rather fast rate, since the addition of dipolarophilic reagents containing activated double bonds to the reaction mixtures does not change the direction of the reaction with the carbene.

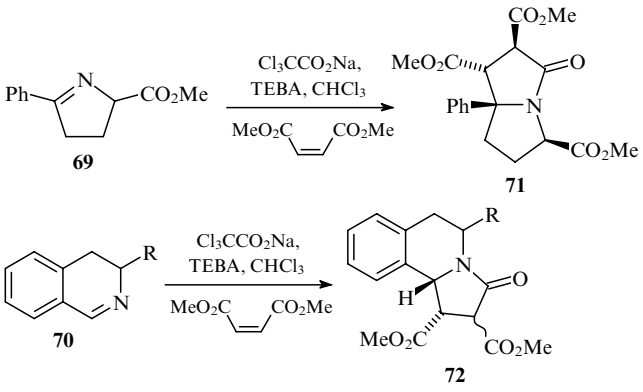
Cycloaddition. *gem*-Dichloro-substituted azomethine ylides with the dichloromethylene fragment slightly deviated from the $Cl_2C-N=C$ plane [the dihedral angle (θ) between the $Cl_2C-N=C$ and Cl_2C planes is equal to 0–30°] are not prone to yield 1,3-cyclisation products. Intermediates having such geometry are formed in reactions of dichlorocarbene with benzaldehyde *N*-alkylimines only if R = n-Alk. The cycloaddition to the electron-deficient C=C bond is the most characteristic reaction of these azomethine ylides; this can be used as a convenient method for the synthesis of some pyrrolidine and pyridine derivatives. Thus *N*-alkylimines yield the corresponding 2-chlorodihydropyrroles **65** in reactions with dichlorocarbene generated from trichloroacetate or under alkaline phase-transfer conditions and maleates or fumarates.[114] These compounds are hydrolysed to lactams **66** and **67** upon isolation by column chromatography on silica gel (the yields of the isomers vary from 27% to 66%).



R = Me, Et, Bn.

Pyridone **68** was prepared in 32% yield from *N*-benzilydene-*N*-methylamine using an excess of the source of dichlorocarbene.

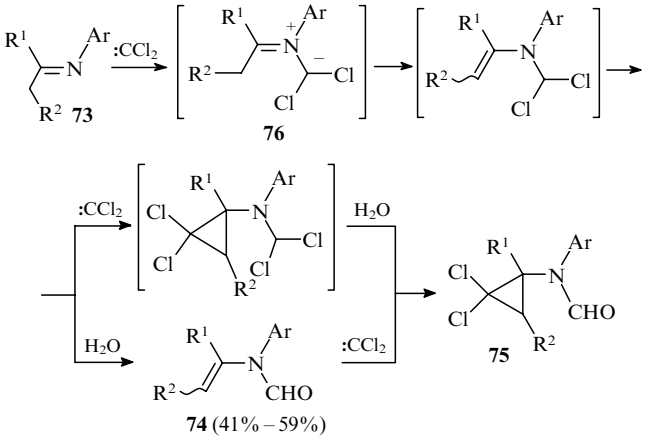
Fused cyclic compounds **71** and **72** containing a tetrahydropyrrole fragment can be prepared in this way from cyclic analogues of benzaldehyde *N*-alkylimines, *viz*., dihydropyrrole **69** and 3,4-dihydroisoquinolines **70**.[114]



R = H, Me.

1,4-H-Shift. Chlorinated ylides generated from imines of aliphatic ketones manifest specific chemical behaviour. It has been found [121] that the reaction of dichlorocarbene generated by decomposition of sodium trichloroacetate with ketone anils **73** yields predominantly enamides **74**, while the corresponding *gem*-dichlorocyclopropanes **75** (35%–42%) are formed when an

excess of the source of the carbene is used. Cyclopropanes **75** are prepared in good yields by a reaction of dichlorocarbene with isolated enamides **74** (56% – 83%).[121]



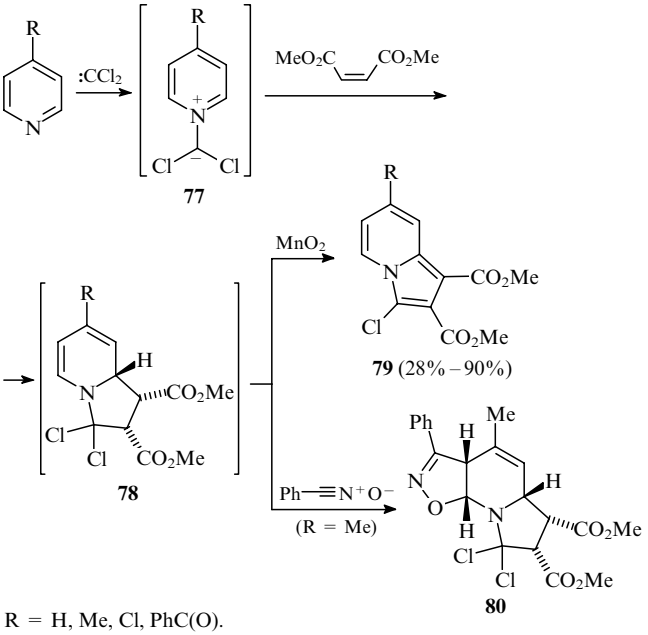
R^1 = Me, Et, cyclo-C_3H_5; R^2 = H, Me.

Studies of reactions with deuterated compounds corroborated the formation of enamides **74** *via* ylides **76** with a subsequent intramolecular 1,4-H-shift with a six-electron transition state rather than by a reaction of carbene with an enamine tautomer of imine.

b. Azinium and diazinium ylides from dichlorocarbene

Ylides generated by a reaction of dichlorocarbene with azines, diazines and their benzoannelated derivatives are convenient synthons for the chloro-substituted indolizines and their heteroatomic and benzoannelated analogues. Two different approaches to the formation of the indolizine system on the basis of azinium ylides **77** are known (Scheme 5).

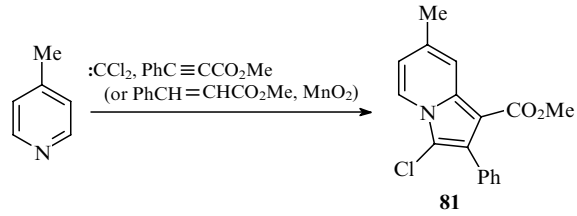
Scheme 5



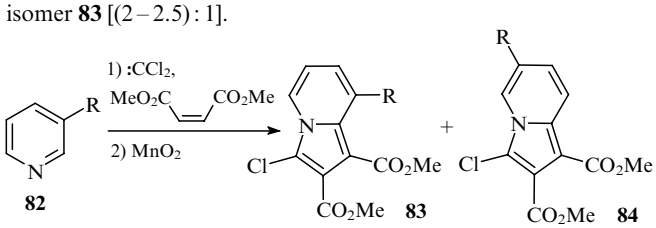
R = H, Me, Cl, PhC(O).

One of them represents a domino reaction that includes intermolecular cycloaddition of dichloroylide to an alkene-type or an alkyne-type dipolarophile. For example, the generation of dichlorocarbene using the alkaline or the trichloroacetate method in the presence of pyridines and dimethyl maleate results in unstable tetrahydroindolizines **78**, which are converted into substituted indolizines **79** (28% – 90%) upon treatment with mild oxidants (see Scheme 5).[122] The intermediate tetrahydroindolizine **78** could be identified by its adduct with benzonitrile oxide (the adduct **80**).[123]

A series of substituted indolizines have been synthesised by the reaction of 4-picoline with dichlorocarbene in the presence of various electron-deficient unsaturated compounds.[123] Indolizine **81** can be prepared from 4-picoline using methyl phenylpropiolate or methyl cinnamate (in the latter case, the product yields are significantly lower).

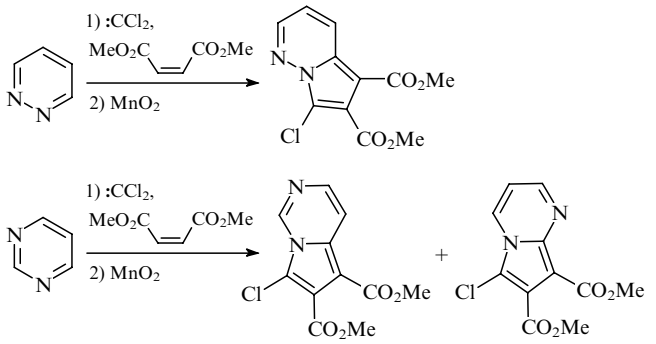


As a rule, the reactions of 3-substituted pyridines **82** yield both regioisomeric indolizines **83** and **84** with the predominance of the isomer **83** [(2 – 2.5) : 1].

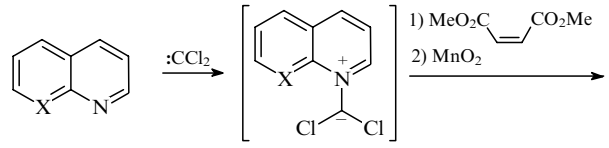


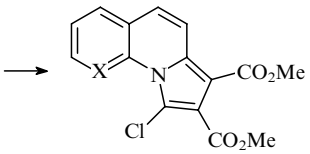
No indolizines are obtained in the reactions of 2-substituted pyridines with dichlorocarbene in the presence of dimethyl maleate.[123]

The above-described approach can be used in the synthesis of chlorinated aza-analogues of indolizines, *e.g.*, pyrrolo[1,2-*b*]pyridazines, pyrrolo[1,2-*c*]- and pyrrolo[1,2-*a*]pyrimidines.[124]



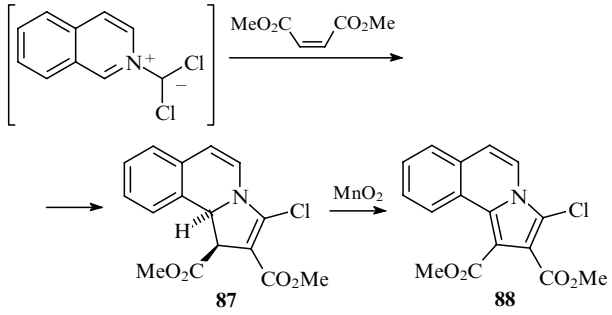
The chemical behaviour of benzoannelated analogues of azines and diazines in the above reaction has a number of specific features. Quinoline reacts slowly with dichlorocarbene in the presence of dimethyl maleate to give substituted pyrrolo[1,2-*a*]-quinoline **85** in very low yield (~5%); 8-methylquinoline reacts even more slowly. The reaction of 1,8-naphthyridine with dichlorocarbene and dimethyl maleate gave pyrrolo[1,2-*a*]naphthyridine **86** (11%). Isoquinoline is more reactive than quinoline with respect to dichlorocarbene. Besides, it produces only one of two possible structural isomers. Interestingly, in this case the use of dimethyl maleate as a dipolarophile has made it possible to isolate the intermediate chlorodihydropyrrole derivative **87** (30%), the dehydrohalogenation product of the primary cycloadduct, compound **87**, was converted into pyrroloisoquinoline **88** (80%) under the action of oxidants.





85, **86**

X = CH (**85**), N (**86**).

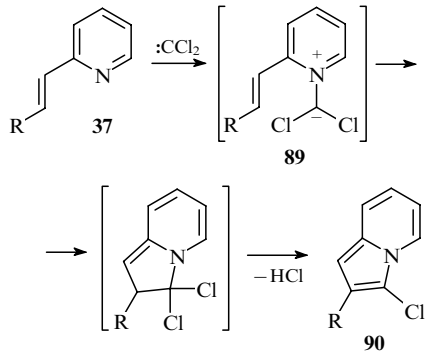


87 **88**

The syntheses of chloro-substituted pyrrolo[2,1-*a*]phthalazine, pyrrolo[1,2-*c*]quinazoline, pyrrolo[1,2-*a*]quinoxaline and pyrrolonaphthyridine systems based on analogous reactions of phthalazines, quinozalines, quinoxalines[124, 125] and benzo[*h*]naphthyridines with dichlorocarbene have been described.[126]

On the whole, intermolecular cycloaddition reactions of dichloro-substituted azinium and diazinium ylides occur regioselectively with respect to both the non-symmetrical ylide and the non-symmetrical dipolarophile. The calculation of ylides formed in reactions of pyridine, 3- and 4-substituted pyridines and isoquinoline with dichlorocarbene by the MNDO method revealed that these molecules are planar. At the same time, the plane of CCl_2 in ylides based on 2-substituted pyridines and quinoline is turned relative to the plane of the pyridine ring (26–34°). The data obtained suggest that non-planar ylides are less stable and their formation is energetically less favourable. Considering that concerted processes are sensitive to the spatial characteristics of the reactants, it can be assumed that the inertness of 2-substituted pyridines and low degree of conversion of quinolines in this reaction are due to the fact that the presence of *ortho*- and *peri*-substituents in the azine makes the corresponding ylide non-planar.

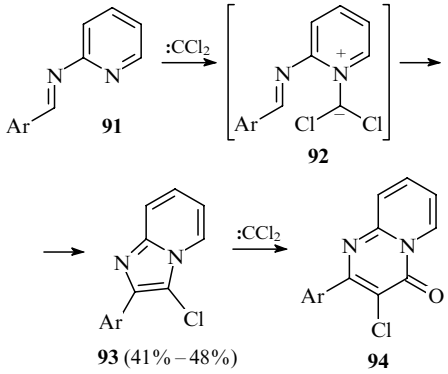
An alternative approach to the synthesis of chloro-substituted indolizine and related systems is based on the 1,5-cyclisation of the azinium dichloroylide **89** containing an unsaturated substituent in the *ortho*-position. 3-Chloro-substituted indolizines **90** can be prepared from compound **37** under conditions of generation of dichlorocarbene.[127, 128]



37 **89** **90**

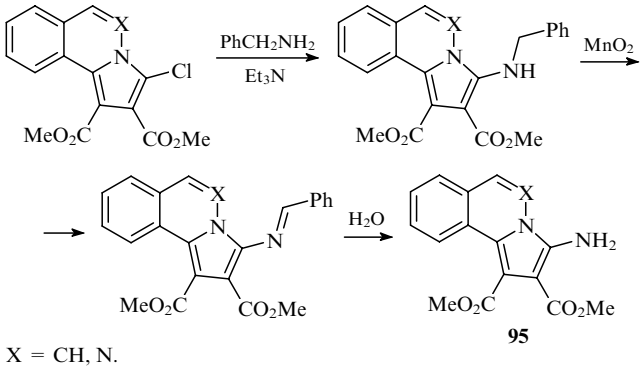
R = H, Ar, CO_2Et.

The reaction of dichlorocarbene with 2-(arylideneamino)pyridines **91** does not affect the azomethine bond C=N, but includes an attack of carbene at the nitrogen atom of pyridine, which yields pyridinium ylide **92** and makes this reaction suitable for the synthesis of 3-chloroimidazo[1,2-*a*]pyridines **93**.[129] If the aryl group in compound **91** contains no electron-withdrawing substituents, the synthetic chain can be elongated owing to the addition of carbene to the C=C bond of the imidazole ring of compound **93** with the subsequent ring expansion and the formation of chloro-substituted pyridopyrimidones **94**.



91 **92** **93** (41%–48%) **94**

Chloro-substituted heterocycles formed as a result of above-described conversions of azinium ylides are valuable intermediates for organic synthesis. Their synthetic potential has increased considerably after the discovery of a simple and efficient method for the amination of the chloropyrrole fragment,[124] which opens an access to 3-aminopyrrolo[1,2-*a*]azine-1,2-dicarboxylates **95**, which represent convenient building blocks for the synthesis of miscellaneous fused heterocyclic systems.

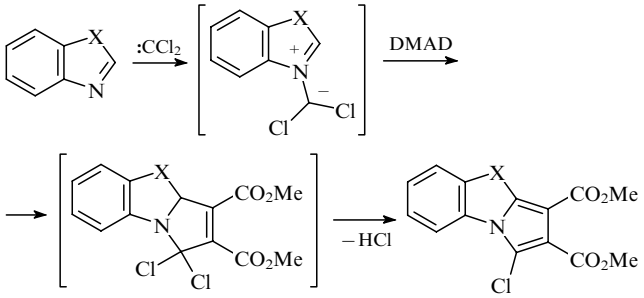


95

X = CH, N.

c. Azolium ylides from dichlorocarbene

Benzazoles afford 2,2′-bis(benzazolyl)s under conditions of generation of dichlorocarbene from $CHCl_3$ and NaOH in the presence of TEBA.[130] Although the reaction products do not contain fragments that might be generated from carbene, it was assumed that the putative mechanism involves the intermediate formation of benzazolium ylides. This mechanism was later confirmed by performing a reaction of dichlorocarbene with benzoxazole or benzothiazole in the presence of dimethyl acetylenedicarboxylate.[131] This reaction occurs through cycloaddition



96a,**b** (20%–33%)

X = O (**a**), S (**b**).

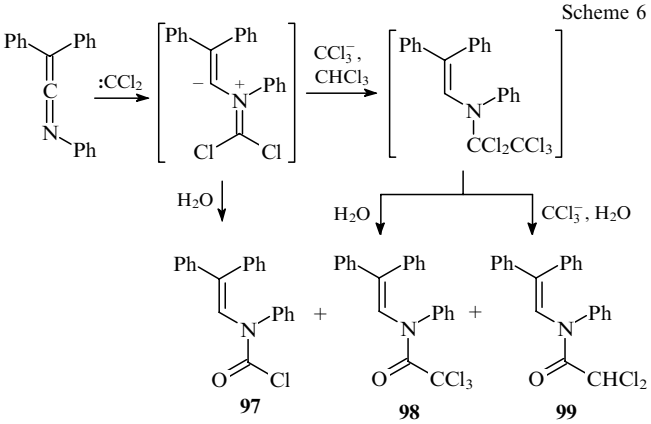
of benzazolium ylide to the triple bond of the dipolarophile with subsequent elimination of HCl, and can be employed for the preparation of pyrrolo[2,1-*b*]benzoxazoles (**96a**) and pyrrolo[2,1-*b*]benzothiazoles (**96b**).

d. Ketene imine ylides from dichlorocarbene

Calculations suggest that ketene imine ylides (alkylidene azomethine ylides) formed upon reaction of dichlorocarbene with ketene imines represent azomethine ylides with reversed polarity.[4] This difference in the electronic structure is manifested in different chemical behaviour of ketene imine ylides and ylides generated from azomethines, azines and azoles and, as a consequence, in significant changes in the array of products that might be synthesised therefrom.

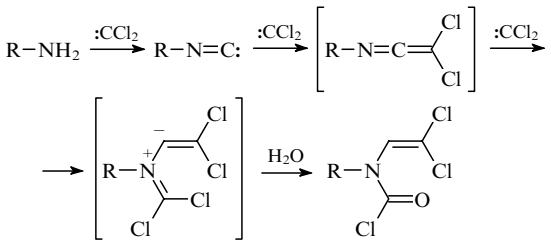
The result of the reaction of ketene imines with dihalocarbenes depends on the method used for the generation of the carbene, since its choice determines the presence or the absence of other reagents in the reaction mixture (*e.g.*, water, trichloromethyl anion, *etc.*). For example, the reaction of triphenylketene imine with dichlorocarbene generated upon thermocatalytic degradation of sodium trichloroacetate in the presence of TEBA yields three main products, *viz.*, compounds **97**–**99** (Scheme 6). Rational choice of reaction conditions (method for the generation of carbene, phase-transfer catalysts, *etc.*) allows direction of the reaction towards the formation of one of these products.[132] Thus trichloroacetamide **98** is predominantly formed upon addition of an equimolar amount of sodium trichloroacetate, while the use of an excess of trichloroacetate yields dichloroacetamide **99**. Carbamoyl chlorides **97** are the main products if dichlorocarbene is generated from $CHCl_3$ and Bu^tOK or if the phase-transfer procedure is used.[133, 134]

Scheme 6



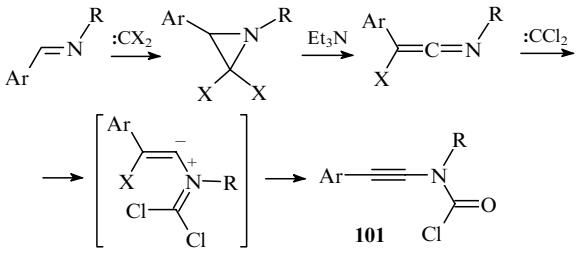
Conditions	Product yield (%)		
	97	**98**	**99**
Cl_3CCO_2Na, TEBA	8	57	9
Cl_3CCO_2Na (excess)	–	4	43
$CHCl_3$, KOH, TEBA	58	–	10
$CHCl_3$, Bu^tOK	45	–	–
$CHCl_3$, KOH, Me_4NBr	78	–	2

A convenient one-step procedure for the synthesis of *N*-(2,2-dichlorovinyl)carbamoyl chlorides **100** from the simplest compounds, *viz.*, primary amines and chloroform, has been developed.[135] The conversion of an amine into a carbamoyl chloride is an example of an unusual iterative tandem reaction successively occurring *via* isocyanide, ketene imine and ketene imine ylide, it is noteworthy that three molecules of dichlorocarbene take part in the construction of dichlorovinylcarbamoyl chloride **100**. Thus, this reaction demonstrates the feasibility of 'one-pot' assembly of the carbon skeleton from dihalogeno carbene.



100 (31%–55%)

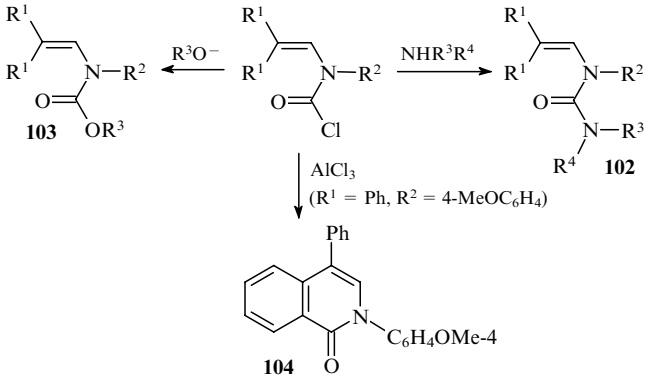
A three-step synthesis of *N*-alkynylcarbamoyl chlorides **101** from benzylideneamines is yet another example of the successful application of dihalogeno carbene as a building block for the elongation of the carbon skeleton.[136] The reaction of *C*-halogeno ketene imine with dichlorocarbene generated upon thermolysis of sodium trichloroacetate in the presence of TEBA yields a trihalogeno-substituted ketene imine ylide and is the final step of this synthetic sequence. The unusual stabilisation of the latter and the formation of a triple carbon–carbon bond result in terminal *N*-alkynylcarbamoyl chlorides **101** as the final products.



101

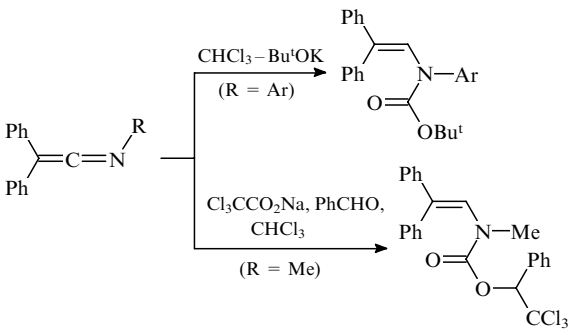
R = Ar, Bu^t; X = Cl, Br.

The carbamoyl chlorides with unsaturated substituents on the nitrogen atom thus prepared are valuable intermediates in the synthesis of various derivatives of carbamic acid (*e.g.*, ureas **102**,[133] carbamates **103**[132, 133, 137]) and heterocycles (*e.g.*, isoquinolinone **104**[134]).

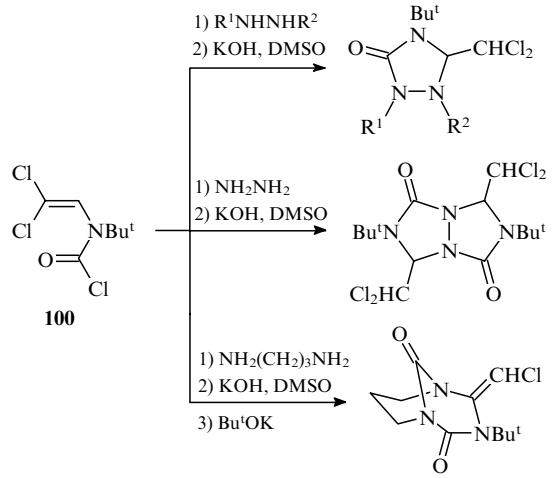


R^1, R^2, R^3, R^4 = Alk, Ar.

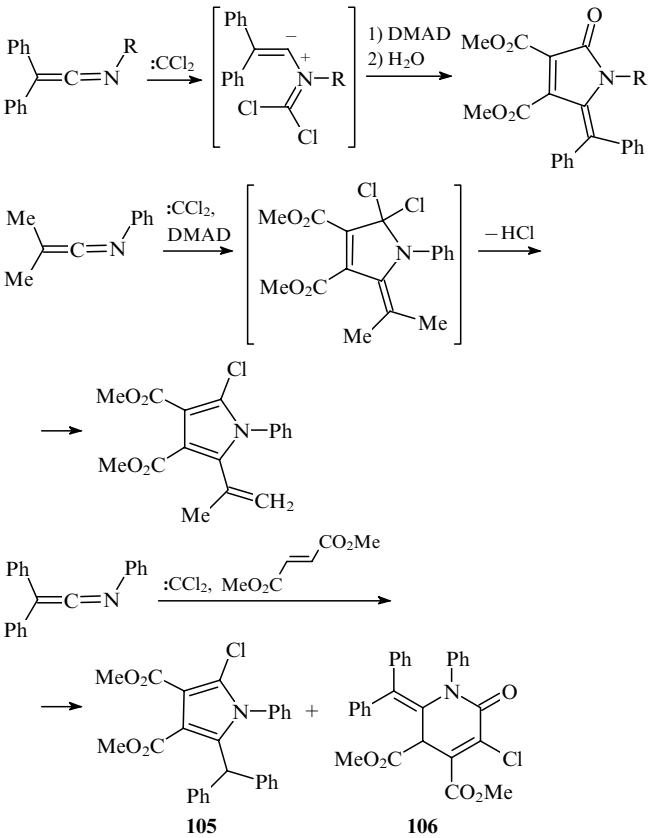
Carbamates can be prepared from the corresponding ketene imines without isolation of carbamoyl chloride.[132, 133, 137]



Dichlorovinyl-substituted carbamoyl chloride **100** was used for the preparation of various heterocyclic systems.[138] In these syntheses, compounds **100** can be regarded as synthetic equivalents of the bielectrophilic synthons $O=C^{+}N(R)C^{+}(H)CHCl_2$.



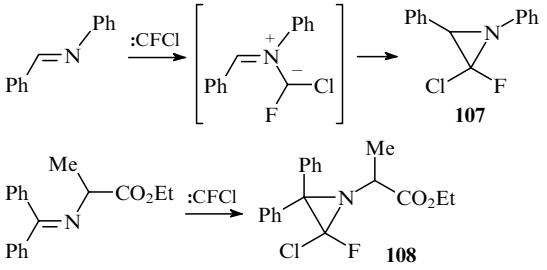
Cycloaddition of ketene imine ylides to electron-deficient alkenes [131, 139] and alkynes [131, 139, 140] occurs rather smoothly and can be used as a convenient method for the preparation of some pyrrole and pyridine derivatives.



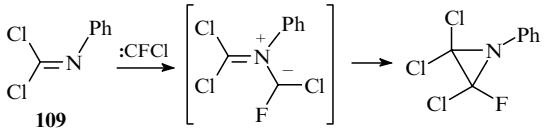
The relative yields of the reaction products, *viz*, pyrrole (**105**) and 2-pyridone (**106**), in the last-mentioned reaction can be changed by varying the ketene imine : dipolarophile ratio. Thus the use of a twofold excess of dimethyl fumarate has made it possible to obtain pyrrole (**105**) and pyridin-2-one (**106**) in 21% and 28% yields, whereas the use of a 20-fold excess afforded these compounds in 34% and 5% yields, respectively.

3. Ylides from chlorofluorocarbene

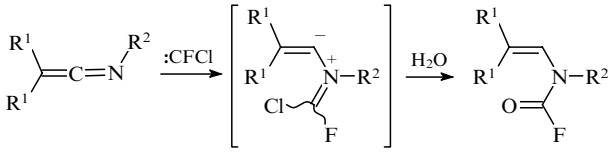
Iminiochlorofluoromethanides, *i.e.*, the intermediates in the addition of chlorofluorocarbene to the unshared electron pair of the nitrogen atom, have been studied less thoroughly. The data available suggest that the substitution of one fluorine atom for chlorine in dichloroazomethine ylides does not exert any noticeable changes in the properties of the intermediate ylides. Thus chlorofluorocarbene generated upon alkaline treatment of dichlorofluoromethane in the presence of TEBA is added to benzylideneaniline to give the corresponding *gem*-chlorofluoroazomethine ylide, which is easily cyclised to chlorofluoroaziridine **107**.[141, 142] Ethyl *N*-benzhydrylidene alaninate reacts similarly with chlorofluorocarbene to give aziridine **108** in 79% yield.[115]



Aziridine can also be prepared from the less nucleophilic imine **109**; however, in this case more drastic conditions should be used for the generation of fluorochlorocarbene, *i.e.*, thermolysis of (dichlorofluoromethyl)phenylmercury.[143]



The reactions of chlorofluorocarbene with ketene imines, which proceed *via* the intermediate ketene imine ylides **110** (chlorofluorocarbene was prepared from $CHFCl_2$ and Bu^tOK), are related to synthetically valuable reactions. The yields of carbamoyl fluorides **111** formed upon hydrolysis of ylides **110** are usually high, which makes these compounds, along with the above-mentioned carbamoyl chlorides, attractive for the synthesis of carbamic acid derivatives and various polynitrogenous heterocycles.[144]



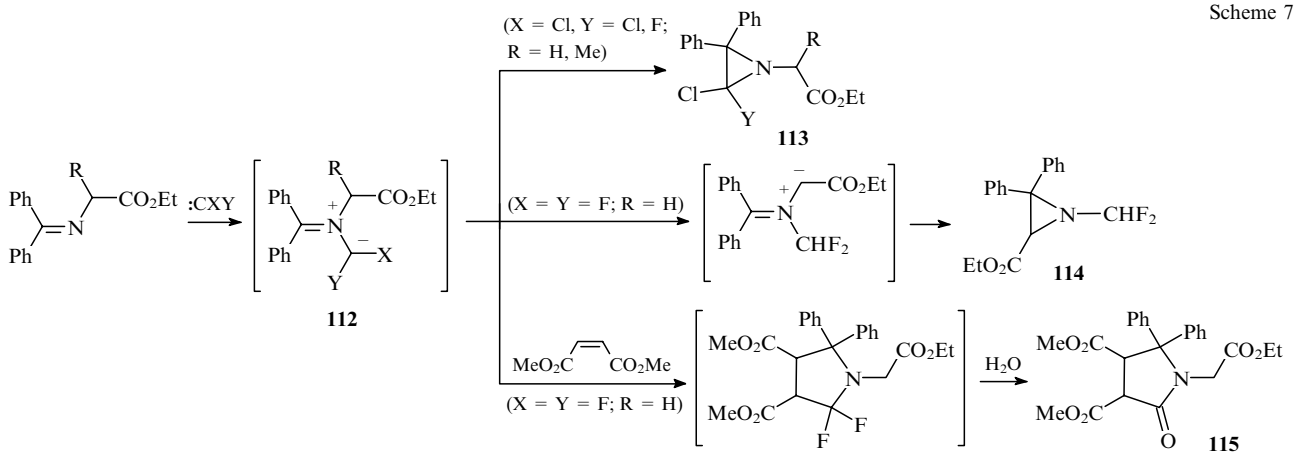
R^1, R^2 = Me, Ph.

4. Ylides from difluorocarbene

a. Acyclic azomethine ylides from difluorocarbene

It is known that difluorocarbene is much less reactive than dichloro- and chlorofluorocarbenes.[145] Nevertheless, it is reactive enough for the addition to benzaldehyde and benzophenone *N*-alkyl- and *N*-arylimines to give the corresponding difluoromethylides. The presence of two highly electronegative fluorine atoms at the ylide carbon atom is the reason for the significant changes in the chemical properties of these intermediates in comparison with dichloro- and chlorofluoro-substituted analogues. The dependence of the reactivities of iminiodihalogeno methanides on the nature of the halogen atoms is especially noticeable in the conversions of ylides generated from the corresponding dihalogeno carbenes and benzhydrylidene derivatives of amino acids (Scheme 7).[146, 147]

Scheme 7

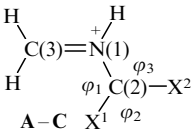


Dichloro- and chlorofluoro-substituted ylides **112** undergo cyclisation into aziridines **113** irrespective of the substituent R; the direction of the reaction does not change even in the presence of a 'dipole trap' (a dipolarophile). This conversion route is not characteristic of the difluoroylide from ethyl *N*-benzhydrylideneglycinate, which undergoes ylide–ylide isomerisation in the absence of a dipolarophile with subsequent cyclisation to aziridine **114**, whereas in the presence of dimethyl maleate it undergoes cycloaddition reaction to give pyrrolidinone **115** after hydrolysis.

According to quantum-chemical calculations (B3LYP/6-31G*), the presence of two geminal fluorine atoms in the ylide influences its geometry significantly, which changes from nearly planar (*i.e.*, characteristic of classical iminium ylides) to pyramidal (characteristic of ammonium ylides) on going from dichloro-substituted to difluoro-substituted ylides (Table 4). These results are consistent with the experimental results and *ab initio* calculations, which suggest that the presence of fluorine atoms brings about pyramidalisation of the radical centre.[148]

For this reason, difluoroylides do not cyclise to aziridines irrespective of their structures, while 1,3-dipolar cycloaddition reactions to multiple bonds, which will be considered below, are the main pathways of their conversions.

Table 4. The sum of angles $\varphi_1 + \varphi_2 + \varphi_3$ and bond lengths in ylides **A**–**C** calculated by the B3LYP/6-31G* method.

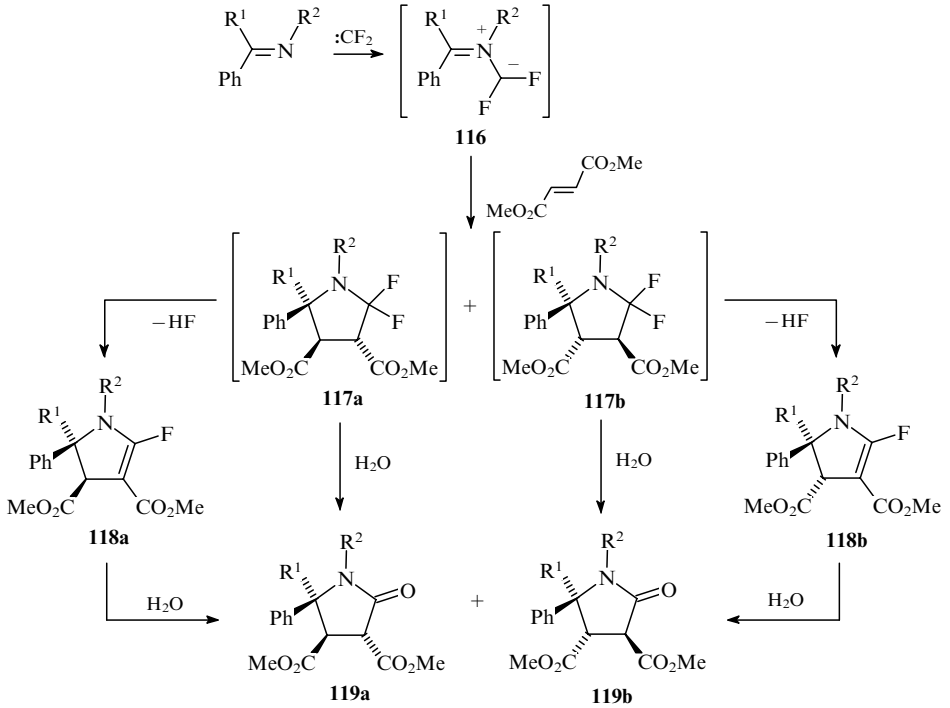


$X^1 = X^2 = Cl$ (**A**);
$X^1 = Cl$, $X^2 = F$ (**B**);
$X^1 = X^2 = F$ (**C**).

Parameters	**A**	**B**	**C**
$\varphi_1 + \varphi_2 + \varphi_3$ /deg	349	339	328
C(2)–N(1) /Å	1.35	1.36	1.39
N(1)=C(3) /Å	1.33	1.33	1.32

Addition of iminiodifluoromethanides to the C = C bond. Ylides **116** prepared by the reaction of difluorocarbene generated upon reduction of dibromodifluoromethane by lead in the presence of tetrabutylammonium bromide with benzaldehyde or benzophenone *N*-alkylimines add easily to electron-deficient alkenes, such as maleic acid esters and imides and fumaric acid esters (Scheme 8).[149–151] Primary cycloadducts formed from ylides

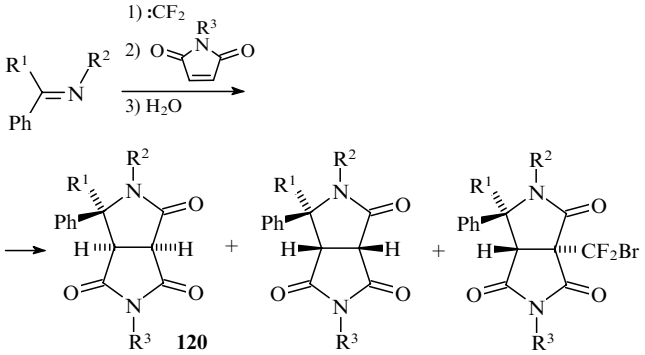
Scheme 8



R^1 = H, Ph; R^2 = Bn, CH_2CO_2Me, CH_2SiMe_3.

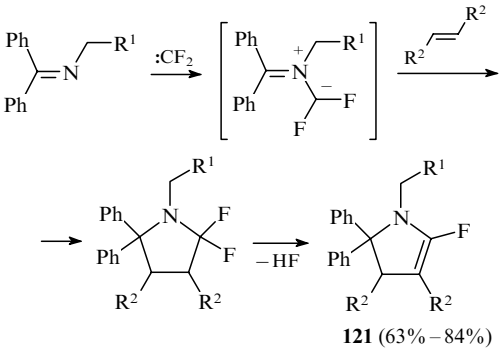
116, *viz*., pyrrolidines **117**, and their dehydrofluorination products, *viz*., dihydropyrroles **118**, are unstable and can only be detected by GC/MS. Only their hydrolytic products, *viz*., diastereomeric pyrrolidinones **119**, could be isolated.

Cycloaddition of difluoroylides prepared from benzaldehyde imines and difluorocarbene to *cis*-alkenes, *e.g., N*-phenylmaleimide, occurs *endo*-stereoselectively and gives predominanly pyrrolidinones of the type **120**, whereas *trans*-alkenes largely generate products of the type **119a**.[151] It should be noted that similar reactions with dichlorocarbene afford exclusively adducts of the type **119b**.[114]



R^1 = H, Ph; R^2, R^3 = Alk, Ar.

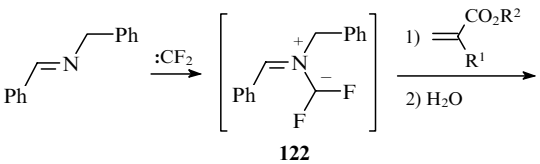
Fluorodihydropyrroles **121** prepared from benzophenone imines using fumaronitrile or dimethyl maleate as dipolarophiles are more stable and can be isolated in 63% – 84% yields.[152]

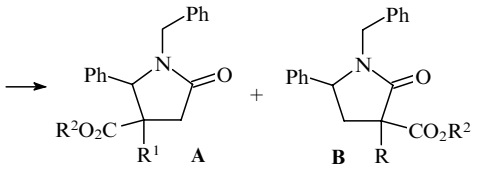


R^1 = H, Bn, CO_2Me; R^2 = CN, CO_2Me.

This methodology is applicable not only to Schiff bases, but also to substrates containing an endocyclic C=N bond. In the latter case, the reaction products represent cyclic systems that can be *ortho*-fused with fluorodihydropyrrole.[152]

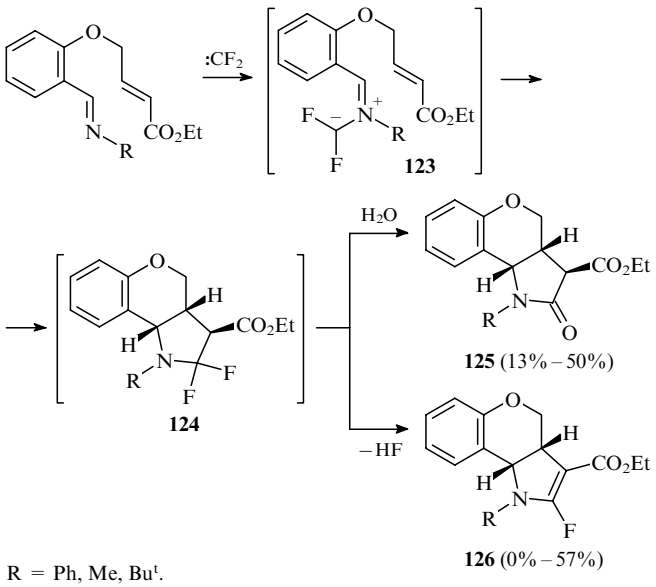
Ylides of the type **122** react easily even with alkenes containing one electron-withdrawing group; the cycloaddition may occur with either complete regioselectivity, as in the case of methyl methacrylate (where isomer **A** is formed in 77% yield), or formation of both regioisomers **A** (62%) and **B** (21%), as in the case of ethyl acrylate.[149]





R^1 = H, R^2 = Et; R^1 = R^2 = Me.

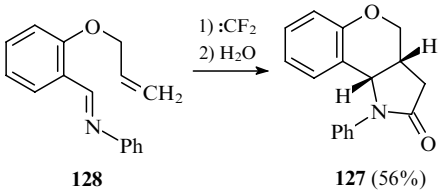
Intramolecular cycloaddition of difluoro-substituted ylides of the type **123** to the monoactivated multiple bond always gives only one regioisomeric difluoropyrrolidine **124**, which can be hydrolysed to the corresponding lactam **125**. In some cases, relatively stable fluorodihydropyrrole derivatives **126** can be isolated.[153]



R = Ph, Me, Bu^t.

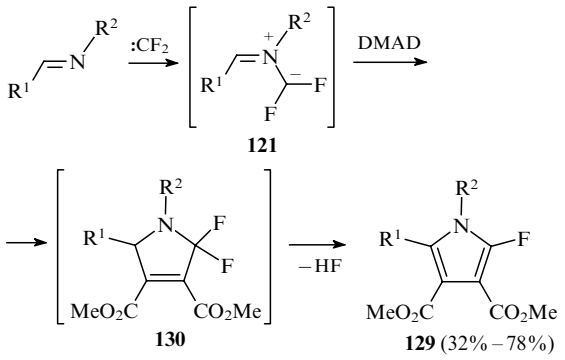
Complete *cis*-stereoselectivity is a distinguishing feature of the synthesis of compounds of the type **125** by intramolecular cycloaddition of difluoro-substituted ylides **123** generated by the carbene method, which leads to the formation of systems with only *cis*-fused rings.† An explanation of such stereoselectivity is the specificity of the carbene method for the generation of azomethine ylides, which enables preparation of *Z*-configured dipoles, this configuration, in turn, being determined by the *E*-configuration of the starting imines.

This reaction was successfully used for the synthesis of the derivative **127** containing no alkoxycarbonyl group, from imine **128** containing a terminal double bond.[153]



Addition of iminiodifluoromethanides to the C≡C bond. Addition of difluoroylides to dimethyl acetylenedicarboxylate can be employed in the synthesis of substituted 2-fluoropyrrole-3,4-dicarboxylates **129**.[158, 159]

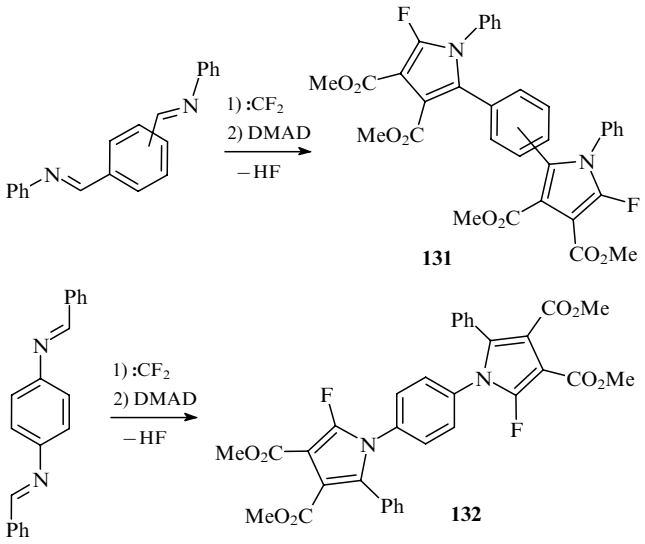
† The intramolecular cycloaddition, to the C=C bond, of non-halogenated azomethine ylides generated by non-carbene methods leading to chromeno[4,3-*b*]pyrrole derivatives has been studied.[154 – 157]



121 **130** **129** (32% – 78%)

R^1 = Ar, R^2 = Ar, furyl, alkenyl, alkynyl.

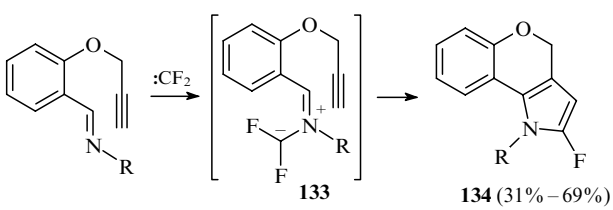
Stabilisation of the addition products, *viz*., difluorodihydropyrrole **130**, results from abstraction of HF to give a stable aromatic pyrrole system. This method was successfully used for the synthesis of compounds **131** and **132** containing two fluoropyrrole rings and the formation of a fluoropyrrole fragment in a fused polycyclic system.[159]



131

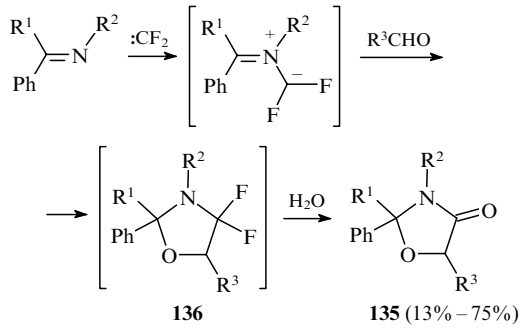
132

The addition of difluoroylides to non-symmetrical acetylenes occurs with both complete regioselectivity, as in the case of ethyl propiolate and methyl tetrolate, and the formation of both regioisomers, as in the case of methyl phenylpropiolate.[159] All these reactions include exclusive or predominant formation of 5-fluoropyrrole-3-carboxylic acid derivatives. It should be noted that the yields of the products of difluoroylide cycloaddition to this kind of monoactivated acetylene are significantly lower than those on addition to the diactivated triple bond (*e.g*., dimethyl acetylenedicarboxylate). Difluoroylides do not add to non-activated triple bonds (*e.g*., phenylacetylene). The situation is different on going to systems containing simultaneously an ylide and an acetylenic fragment. Thus the intramolecular cycloaddition of ylide **133** to a non-activated triple bond yields chromenopyrroles **134** in preparative yields.



133 **134** (31% – 69%)

Addition of iminiodifluoromethanides to the C = O bond. Studies of intermolecular cycloaddition of iminiodifluoromethanides generated from imines and difluorocarbene to the C = O bonds of various substrates have shown that these reactions usually give good yields only with aldehydes.[160] In this case, the process is characterised by complete regioselectivity and affords oxazolidin-4-one derivatives **135**, which represent hydrolysis products of the primary cycloadducts **136**. The stereoselectivity of the cycloaddition step is determined by the nature of the radical R^3 in the aldehyde: acetaldehyde reacts non-stereoselectively, while aromatic aldehydes react with the predominant formation of the *trans*-product.

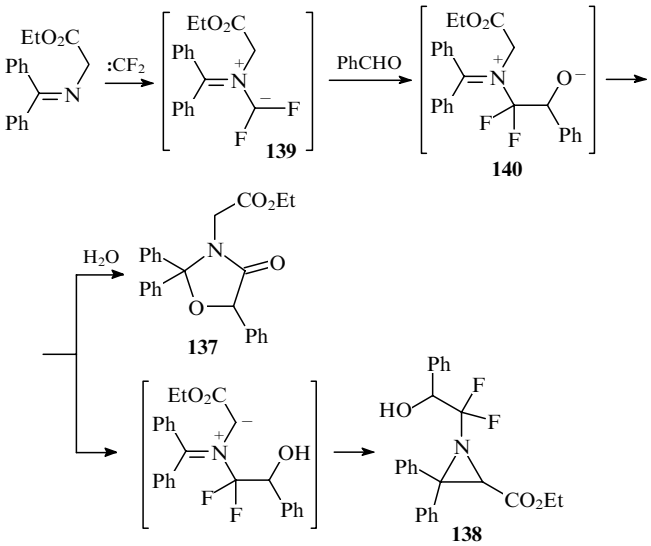


136 **135** (13% – 75%)

R^1 = H, Ph; R^2 = Bn, CH_2CO_2Me, CH_2SiMe_3; R^3 = Alk, Ar.

The reaction of ethyl *N*-benzhydrylideneglycinate with difluorocarbene in the presence of benzaldehyde yields, along with the expected cycloaddition product (oxazolidinone **137**), also aziridine **138**; it was assumed [160] that its formation includes a nucleophilic attack of the ylide on the carbon atom of the carbonyl group of benzaldehyde followed by a 1,5-H-shift and cyclisation (Scheme 9). This suggests a non-concerted cycloaddition mechanism of sterically crowded *C*,*C*-diphenyl-substituted *gem*-difluoroylides to strongly polarised multiple 'carbon – heteroatom' bonds containing a zwitter-ionic intermediate of the type **140**.

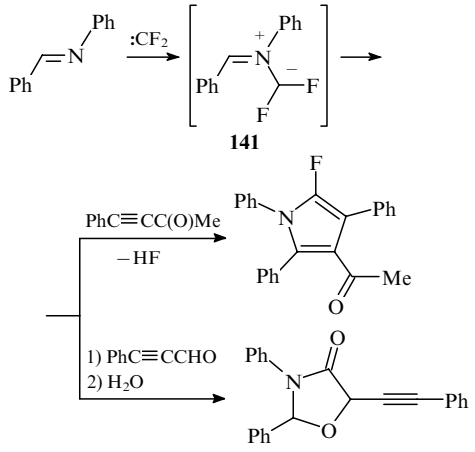
Scheme 9



139 **140** **137** **138**

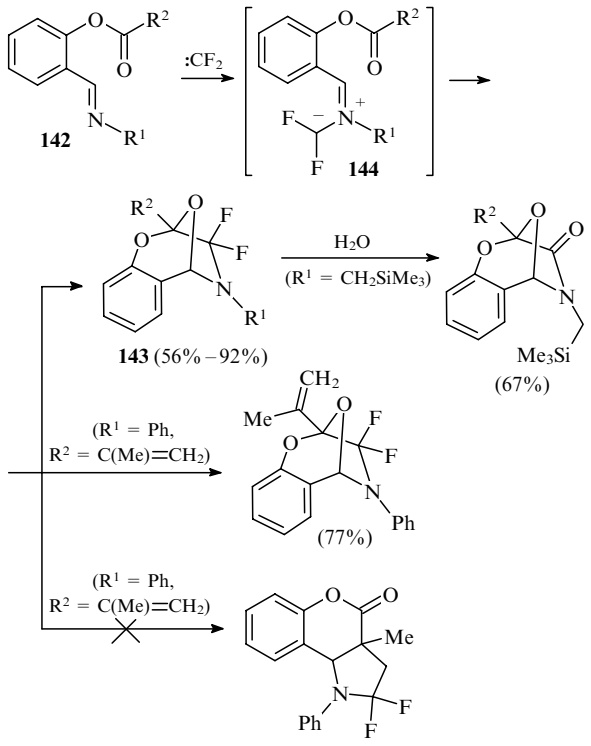
Ketones are significantly less active in the reaction with difluoro-substituted iminium ylides than aldehydes. Thus an oxazolidinone of the type **135** (R^1 = H, R^2 = Bn, R^3 = Me), the addition product of the intermediate ylide to acetone, was prepared in as low yield as 3%, whereas the carbonyl group of benzophenone is generally inactive with respect to difluoroylides.[160] The data on the chemoselectivity of the cycloaddition of difluoroylide **141** to the C = O and C ≡ C bonds of phenylpropiolaldehyde and methyl phenylethynyl ketone [159] suggest a higher reactivity of the aldehyde C = O group than the monoactivated C ≡ C group in the 1,3-dipolar cycloaddition. Substitution of the ketone for the aldehyde causes changes in the reaction

centre: thus the C≡C bond in methyl phenylethynyl ketone becomes more reactive.



The data from competitive cycloaddition of ylide **141** to various substrates containing C=O and C≡C bonds allowed the arrangement of dipolarophiles as regards their activities with respect to iminiodifluoromethanides (generated upon reactions of difluorocarbene with aromatic imines) in the following series: the C=O bond of ketones < the monoactivated C≡C bond < the C=O bond of aldehydes < the diactivated C≡C bond.[159]

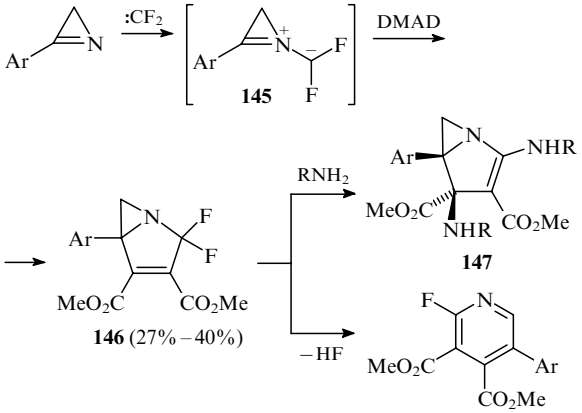
The carbonyl groups of esters are non-reactive with respect to difluoro-substituted ylides. However, the ester carbonyl can be involved in intramolecular cycloaddition reactions with a difluoroylide fragment as a dipolarophilic component. Thus azomethine ylides generated upon reaction of difluorocarbene with *N*-arylimines of the *O*-acylated salicylaldehyde **142** undergo intramolecular 1,3-dipolar cycloaddition with the ester carbonyl group. This reaction is completely regioselective and yields the 2,5-epoxy-1,4-benzoxazepine derivatives **143**.[161] The direction of a cycloaddition reaction is not changed in the presence of an alkenyl fragment on the acyl group as a competitive dipolarophile. Moreover, it has been shown that the rate of the intramolecular cycloaddition to the C=O bond of ylide **144** is comparable to the rate of intermolecular cycloaddition to one of the most reactive dipolarophiles, *viz*., dimethyl acetylenedicarboxylate.[162]



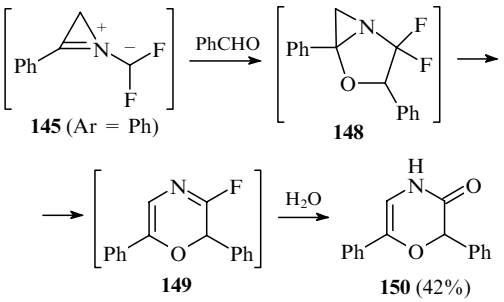
b. Cyclic ylides from difluorocarbene

Various conversions of cyclic nitrogen ylides, in particular intermolecular 1,3-dipolar cycloadditions, underlie an approach to the synthesis of *ortho*-fused nitrogenous heterocycles. At present, only three-, six- and seven-membered cyclic systems containing an endocyclic C=N bond are known; ylides could be generated from these systems under conditions of generation of difluorocarbene.

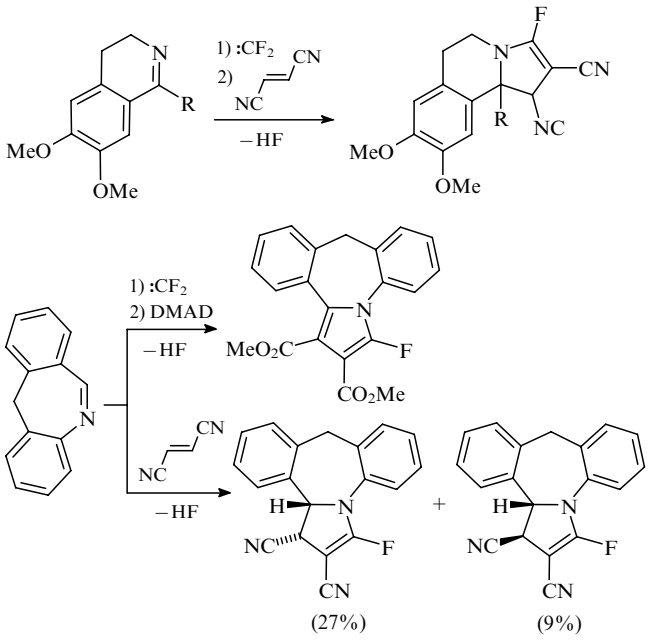
The formation of strained azirinium ylides **145** upon reaction of 3-aryl-2*H*-azirines with difluorocarbene obtained by reduction of CF_2Br_2 with active lead was confirmed by 1,3-dipolar cycloaddition to dimethyl acetylenedicarboxylate.[163] Difluoro-substituted dihydroazirino[1,2-*a*]pyrroles **146** were isolated as the reaction products. An important feature of these unusual bicyclic compounds is that they can undergo either ring expansion to give quantitative yields of 2-fluoro-substituted pyridines as valuable intermediates for the preparation of miscellaneous pyridine derivatives or transformations with the retention of the bicyclic skeleton, *e.g*., with the formation of diaminodicarboxylic acid derivatives **147**.



The reaction of ylide **145** (Ar = Ph) with benzaldehyde does not stop at the step of formation of the bicyclic derivative **148**. Presumably, in the course of the reaction, the opening of the aziridine ring takes place with the formation of 3-fluorooxazine derivative **149**, which is easily hydrolysed upon chromatographic isolation to yield lactam **150**.[163]



This approach does not allow preparation of the corresponding fused *gem*-difluorodihydropyrrole derivatives similar to compounds **146** starting from six- and seven-membered heterocycles containing a C=N bond. Nevertheless, reactions of these heterocyclic compounds with difluorocarbene in the presence of but-2-enoic and acetylenedicarboxylic acid derivatives can be used for the synthesis of polycyclic systems containing fluorodihydropyrrole and fluoropyrrole fragments, respectively.[152]



V. Conclusion

Considerable progress has been achieved in the past decade in the chemistry of 1,3-dipoles and in the study of reactivities and synthetic applications of unstable iminium ylides in particular. The perfection of the methods for matrix isolation of reactive intermediates (LFP and FVT) has made it possible to expand considerably the range of unstable ylides detected by spectroscopic methods. Recently, only analysis of 1,3-dipolar cycloaddition products to dipolarophiles has been used as indirect evidence for their existence. This trend will undoubtedly be developed in the near future, predominantly with respect to azomethine ylides; their spectral, kinetic and thermodynamic characteristics are not documented anywhere.

The great diversity of products of domino reactions of carbenes and ylides points to the high potential of this approach for designing the synthesis and assembly of the skeletons of nitrogen-containing molecules. The intramolecular 1,3-dipolar cycloaddition reaction is one of the most interesting synthetic approaches to the synthesis of polycyclic nitrogen-containing compounds and a potent tool for the stereoselective construction of complex polycyclic and bridged systems. This methodology will certainly find application in the syntheses of natural compounds and their analogues. In this context, a search for novel types of iminium ylides containing different combinations of synthetically important structural fragments (*e.g.*, functional groups, small and chemically labile rings, *etc.*) is becoming a topical task. Their conversions will lead to intermediates with high synthetic potentials, which can undergo further selective chemical transformations.

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