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Review

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Pyrazolidines: synthesis, reactivity, physical and biological properties

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Dedicated to our friend Professor Leon Ghosez

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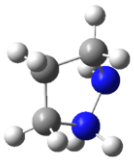
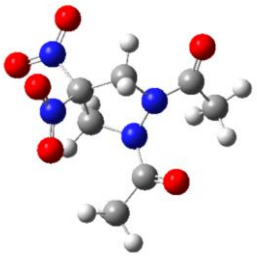
Abstract

This review summarizes the available information of monocyclic pyrazolidines (tetrahydropyrazoles) according to the following plan: synthesis; chemical properties and reactivity; structure, spectroscopic and physical properties; biological properties and drugs; and catalysts. Special stress has been placed on synthetic methodologies due to the richness of the topic. A total of **613** structural formulae plus **33** catalysts and **277** references are part of the present work.

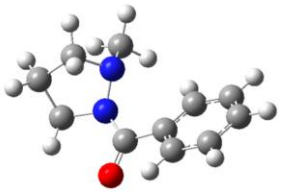


pyrazolidin-1-ium cation 11H$^+$(NOKYER)



1,1'-(4,4-dinitropyrazolidine-1,2-diyl)bis(ethan-1-one)

48 (LILLEY)



(2-methylpyrazolidin-1-yl)(phenyl)methanone

52 (BEZOLB)

Keywords: Pyrazolidines, hydrazines, [3+2] dipolar cycloadditions, catalysts, redox reactions, biological properties

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1. Introduction

The universe of pyrazoles is very vast; a classification according to their oxidation degree is represented in Figure 1. In addition to general reviews that include several of these items,[1,2] we have devoted specific reviews to the following compounds: pyrazolidinones **7**,[3] pyrazoles **8**,[4,5,6,7,8] 3-pyrazolines **9**,[9] and 2-pyrazolines **10**.[10] The present review deals with the less oxidized structure, the pyrazolidines **11**. We have published several papers on these compounds that will be cited in the corresponding sections.

This review concerns only compounds called pyrazolidines excluding fused derivatives, very numerous, that have other names (**12**-**17**, Figure 2). Exceptionally, it also includes a compound with a three membered ring linking both nitrogen atoms (1,5-diazabicyclo[3.1.0]hexane). Derivatives with a C=O exocyclic double bond, called oxo or keto pyrazolidines **1**, **3** and **7**, have been excluded also, so all the compounds reported here have three sp^3 carbon atoms in the ring except some structures with a C=C exocyclic bond.

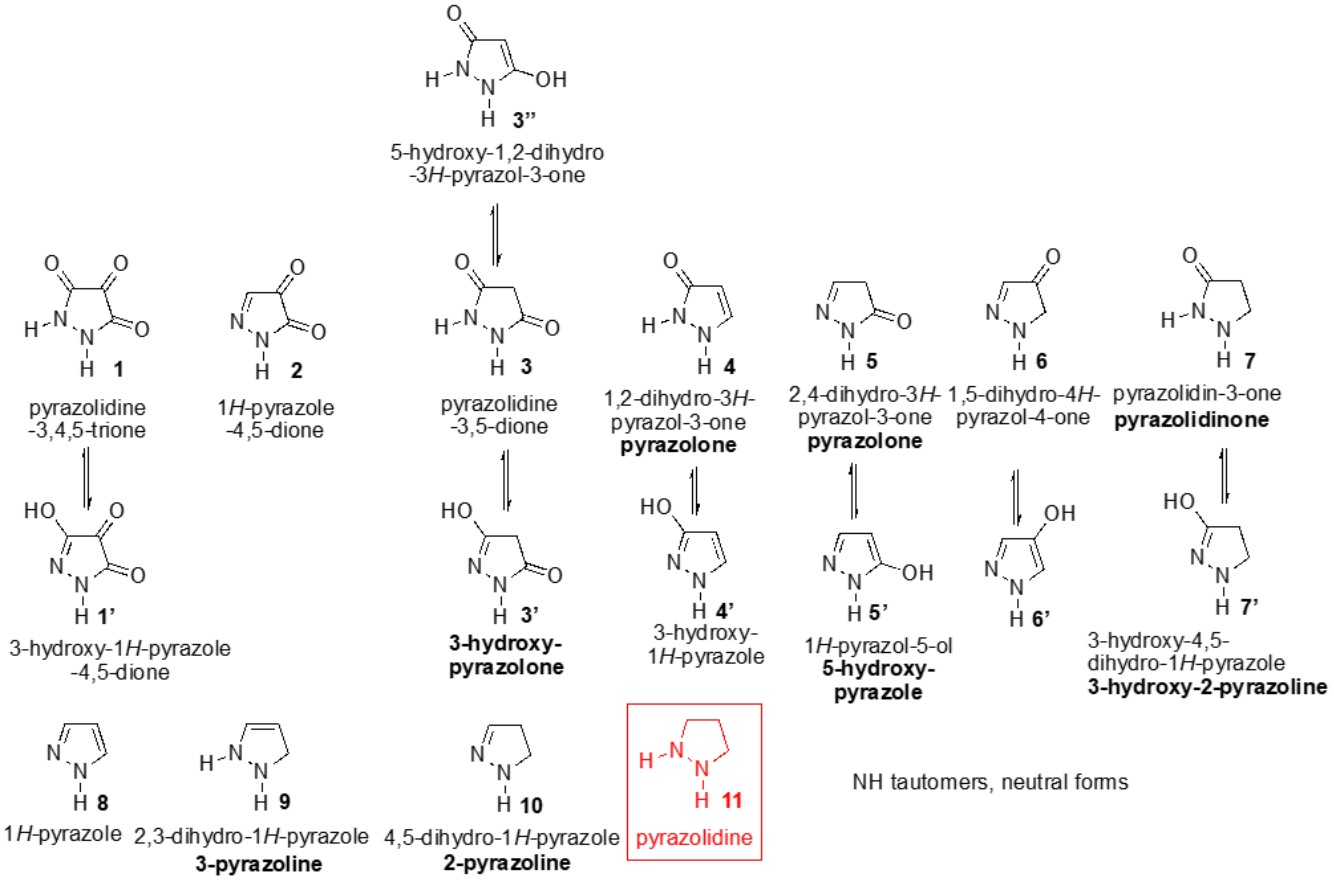


Figure 1. The universe of pyrazole structures according to their oxidation degree.

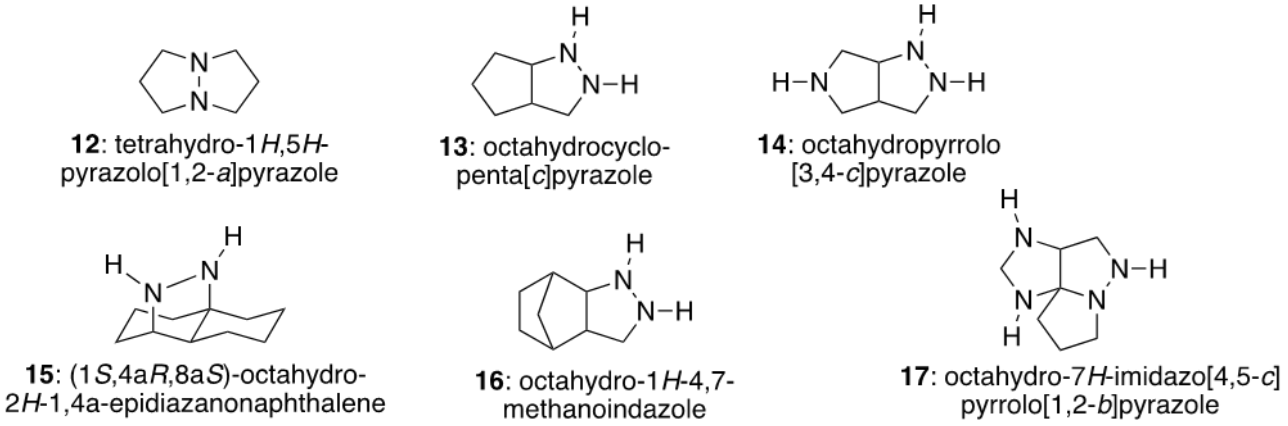


Figure 2. IUPAC names of some fused pyrazolidines.

2. Reviews

There are numerous reviews dedicated, in most cases only partly to pyrazolidines. They are reported below in chronological order and with the corresponding titles:

1,3-Dipolar Cycloadditions Past and Future. Huisgen presented his original discovery of 1,3-dipolar cycloadditions including an unpublished result (section 4.2.1) and an example of the reduction of 2-pyrazolines to pyrazolidines, see Section 4.5.2.[11]

Detection of Hindered Rotation and Inversion by NMR Spectroscopy. In this review Kessler reported a series of families presenting the title behaviors, amongst them briefly pyrazolidines. This topic is discussed in Section 6.10.[12]

Nitrogen Inversion. Experiment and Theory. Lehn described in detail his studies on the nitrogen inversion of pyrazolidines including some new results that had never been published, see Section 6.10.[13]

Intramolecular [4+2] and [3+2] Cycloadditions in Organic Synthesis. Oppolzer actualized Huisgen's review[11] and included one of his works, a [3+2] cycloaddition leading to a pyrazolidine he classified as IIIb type.[14]

Synthesis and Properties of Functionally-Substituted 1,2- Azolidines.[15] Motorina and Sviridova summarized all of the knowledge about isoxazolidines and pyrazolidines up to 1991.

Preparation of α,β-Unsaturated Ketones Bearing a Trifluoromethyl Group and Their Application in Organic Synthesis. Nenadjenko reported several examples of 3-trifluoromethyl-3-hydroxypyrazolidines and their dehydration to 2-pyrazolines, see our Sections 4.1.3 and 5.3.[16]

All of the following reviews refer to selective reactions of different classes (our sections 4.1 and 4.2), one of the brightest topics related to pyrazolidines due to the presence of three correlative sp^3 carbon atoms in their ring in addition to the regioselectivity of positions 3 and 5. Most of these reactions use specific catalysts that were optimized for the synthesis of pyrazolidines, they are reported at the end of the manuscript, numbered with a capital C, from **C1** to **C33**.

Asymmetric 1,3-dipolar cycloadditions. Pellisier provided a full review of these reactions up to 2007, including two schemes, 153 and 154, where the works of Kobayashi and Leighton were carefully described, see section 4.2.[17]

Asymmetric 1,3-dipolar cycloadditions of acrylamides. An important summary of Huisgen 1,3-dipolar cycloadditions leading, amongst other compounds, to pyrazolidines and isoxazolidines, Section 4.2.1, was described in detail in its variants normal and asymmetric.[18]

Synthesis of Cyclic Hydrazino α-Carboxylic Acids. Pyrazolidines are cyclic hydrazines. This review, although very limited, contains much useful information on the synthesis of the title compounds using different methodologies which are discussed in the corresponding sections, including double asymmetric induction.[19]

Preparation of α,β–unsaturated-trifluoromethylketones and their application in the synthesis of heterocycles. In the field of pyrazoles and their derivatives, Figure 1, compounds bearing CF_3 are of particular importance. For this reason, Nenadjenko has summarized, in an authoritative way, trifluoromethyl pyrazolidines. Note that these compounds bear in the same substituents, at positions 3 or 5, a CF_3 and an OH group, $C(OH)CF_3$.[20]

Recent Developments in Pd-Catalyzed Alkene Aminoarylation Reactions for the Synthesis of Nitrogen Heterocycles. The review by Schultz and Wolfe covers many fields, but their section 3.1 is devoted to the synthesis of pyrazolidines.[21]

Recent Developments in the Synthesis and Applications of Pyrazolidines. A Review. This review, published in 2013, is the only one exclusively devoted to pyrazolidines. The main difference with the present one is that bicyclic and oxo derivatives were included. Their part concerning "Applications" is very useful being divided into "As Therapeutic Agents", "As Peptide Mimics" and "Synthons for Diamine Ligands and Pyrazolines". We will use it in our manuscript.[22]

Recent Advances in Catalytic Asymmetric Synthesis of Pyrazoline and Pyrazolidine Derivatives. Divided into two almost equal parts, "[3+2]-Cycloaddition reactions of hydrazones; 1,3-Dipolar cycloaddition reactions

of azomethine imines with alkenes", and "Asymmetric conjugate addition/cyclization cascade reactions", it also includes bicyclic and oxo pyrazolidines.[23]

1,3-Dipolar Cycloadditions of Azomethine Imines. The review by Nájera *et al*. contains abundant information about enantio-catalyzed 1,3-dipolar cycloadditions that yield pyrazolidines.[24]

Metal-catalyzed [3+2] cycloadditions of azomethine imines and *Synthesis of Non-Racemic Pyrazolines and Pyrazolidines by [3+2] Cycloadditions of Azomethine Imines*. Svete, Pozgan *et al*. discussed the important aspect of metal-catalyzed synthesis of pyrazoles, 3-pyrazolines and pyrazolidines, including oxo and bicyclic pyrazolidines. Of particular relevance is tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (an oxo derivative of compound **12** reported in Figure 2).[25,26]

3. Theoretical calculations on simple pyrazolidines

We will report in sections 4.2.b, 6.6 and 6.10a (summarized in section 6.11) a study we carried out purposely on compounds **11**, and **18** to **47** (Figure 3), Moreover, a selection of X-ray structures was also calculated, **48** to **52**, including the Refcodes from the Cambridge Structural Database (CSD)][27] The results of that study are reported in Section 6.10.a.

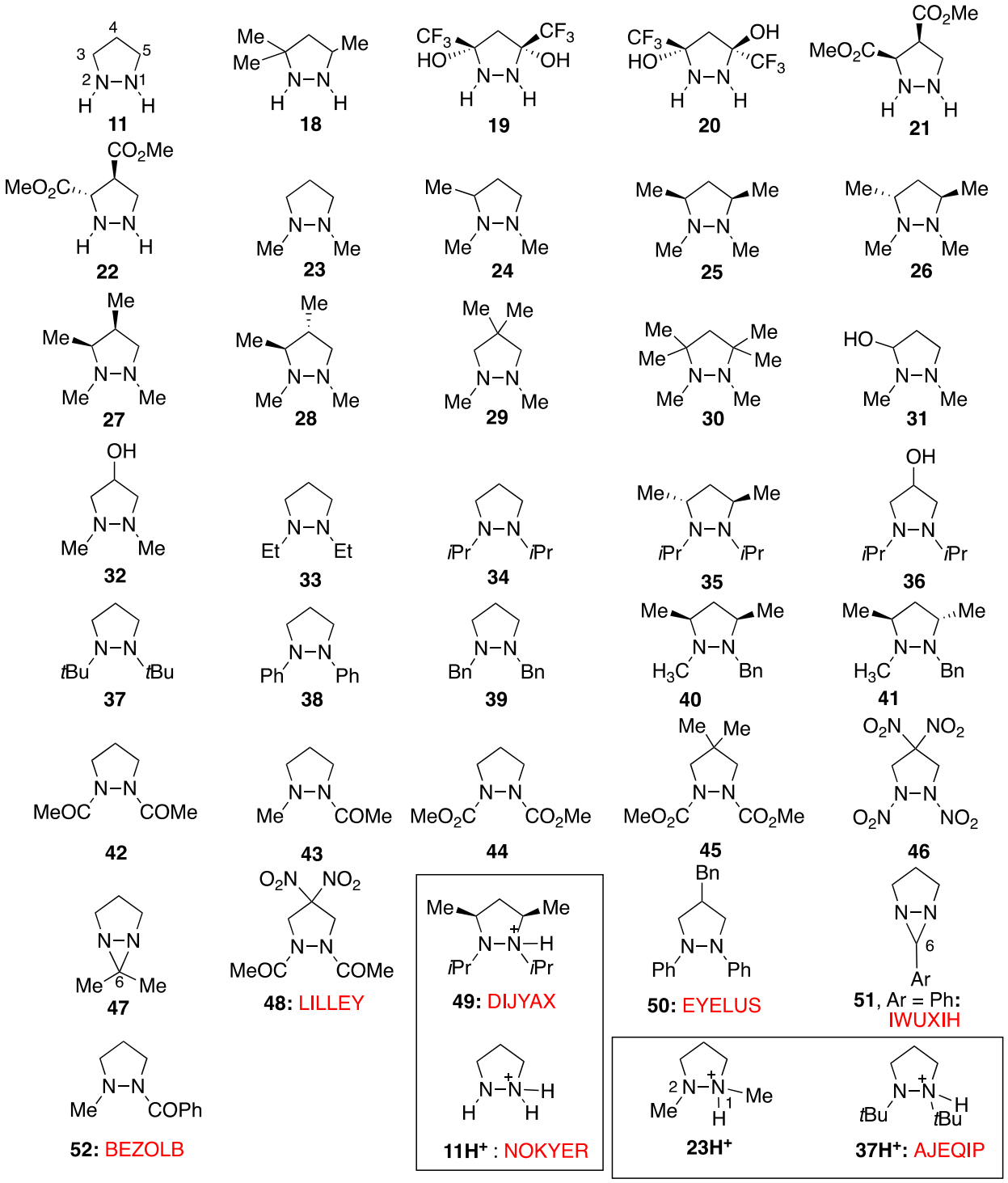
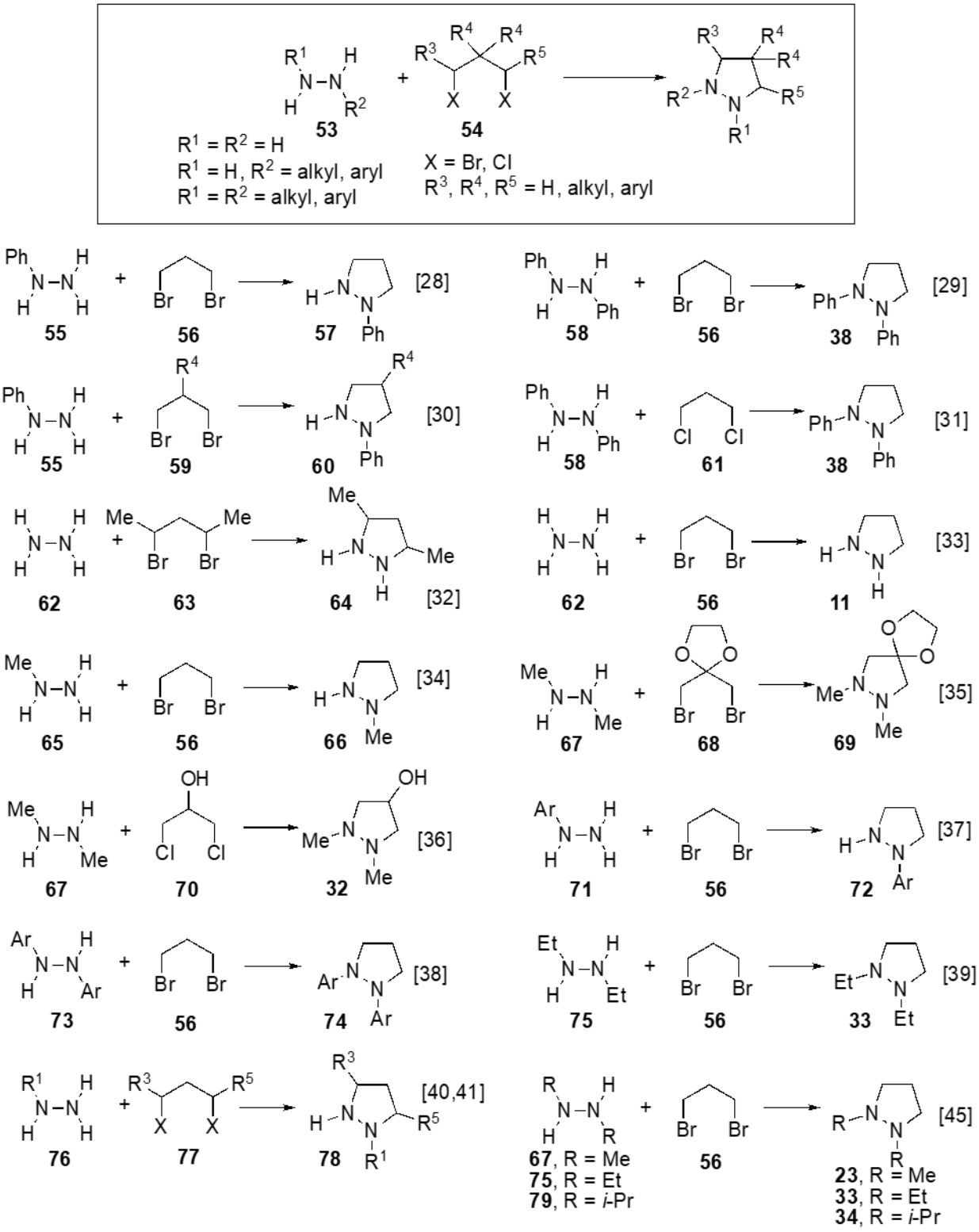


Figure 3. Calculated pyrazolidines including in red the Refcodes[27] of those whose X-ray structures have been determined.

4. Synthesis

4.1. From hydrazines and related compounds

4.1.1. With 1,3-dihalopropanes. This method, reaction of **53** and **54**, is the oldest one and has been used by great names in Chemistry, in chronological order (Scheme 1) Michaelis,[28] Wittig[29] and Büchi.[30] More recent papers correspond to the following references[31,32,33,34,35,36,37,38,39,40,41]:

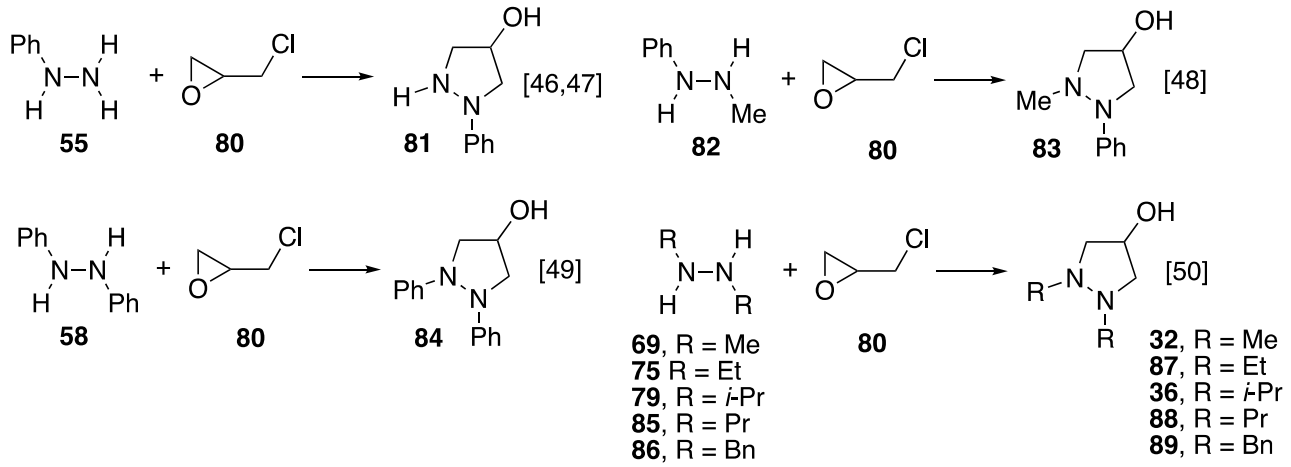


Scheme 1. Pyrazolidines prepared from hydrazines and 1,3-dihalopropanes.

In former times, the hydrazines were used as alkali-metal derivatives, for instance, the mono-sodium salt of **55**,[28,30] the di-lithium salt of **58**,[29] and the di-sodium salt of **58**.[31] In the case of **73**, the starting compounds were azobenzenes reduced electrochemically to **73**.[38] In three other cases,[42,43,44] azo compounds were used that, under the reaction conditions, were reduced to hydrazines. Pyrazolidine **87** was prepared by Varma from

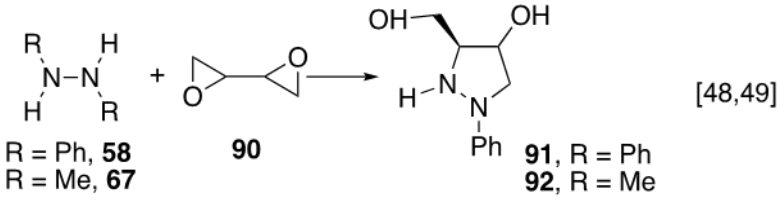
the corresponding hydrazine **75**; other *N*-substituted pyrazolidines **78** were prepared by this author from hydrazine **76**, although always as minor components of a mixture with 2-pyrazolines.[39,40,41] Pyrazolidines **78** corresponds to R^3, R^5 = H, alkyl, aryl, and for **77** X = Cl, Br, I and OTs, and used microwave (MW) and ultrasound (US) methodologies.[40,41] The syntheses of three pyrazolidines **32**, **87** and **36** from hydrazines **69**, **75** and **79** were reported by Nelsen and Hintz.[45]

Epichlorohydrin **80** is a masked 1,3-dichloro-2-hydroxypropane that reacts with different hydrazines **55**, **82**, **58**, **67**, **75**, **79**, **85** and **86** to afford 4-hydroxypyrazolidines **81**, **83, 84**, **32**, **87**, **88**, **36** and **89** (Scheme 2).[46,47,48,49,50]



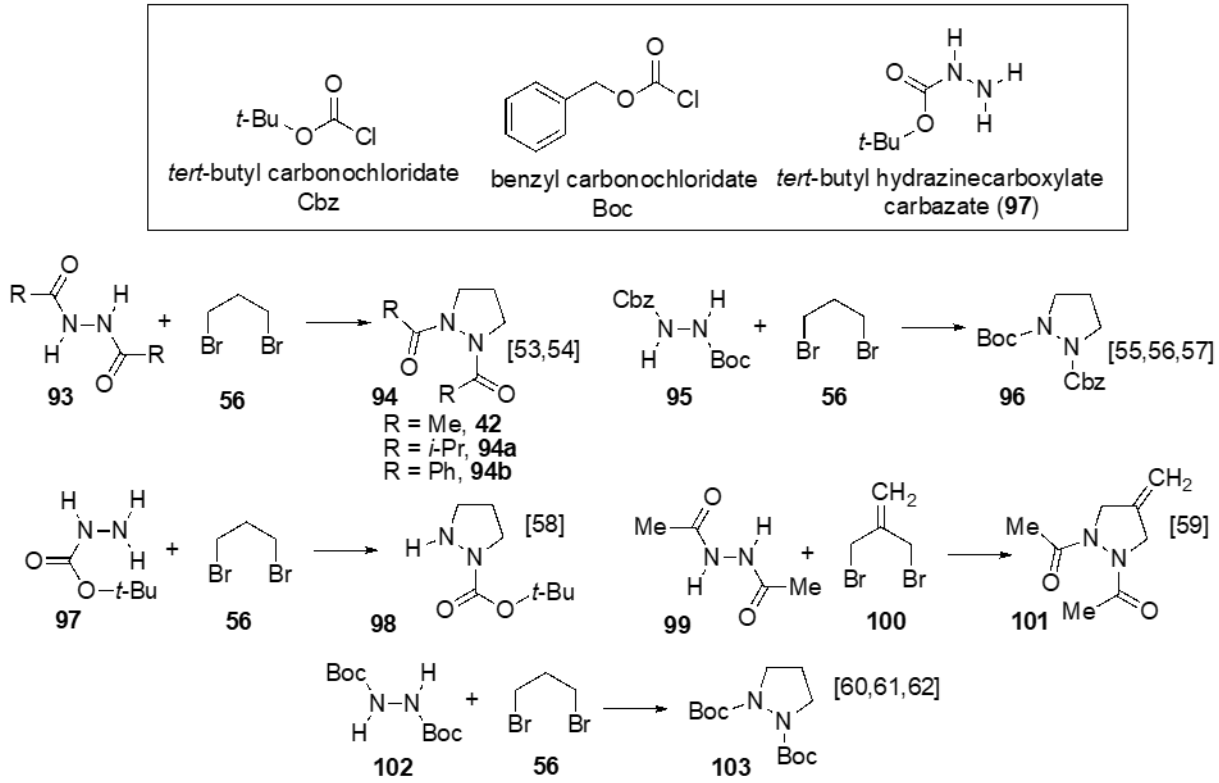
Scheme 2. Pyrazolidines prepared from hydrazines and epichlorohydrin.

2,2'-Bioxirane **90** reacts with hydrazines **67** and **58** like a 2,4-dihalobutane-1,3-diol to yield pyrazolidines **91** and **92**, Scheme 3.[51,52]



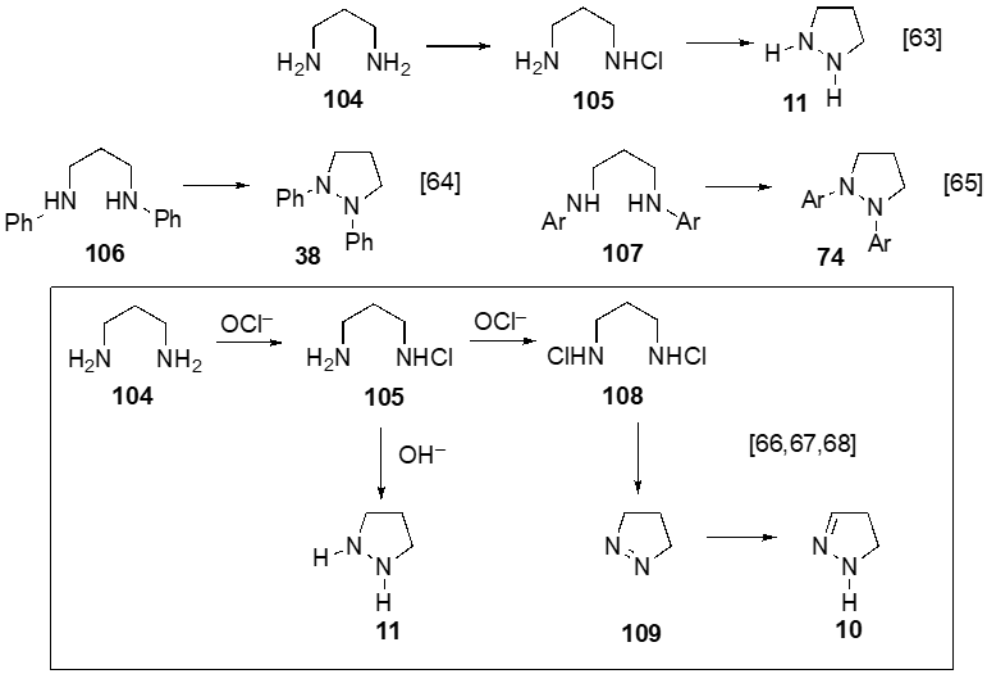
Scheme 3. Synthesis of pyrazolidines from 2,2'-dioxirane.

We have separated the acylhydrazines or hydrazides, $RCONHNH_2$ and RCONHNHOCR because, although their reactivity is similar, the resulting *N*-acylpyrazolidines **42**, **94a/b**, **96**, **98**, **101** and **103** have some characteristic properties. Moreover, the R substituents of the COR are, in most cases, typical of protein chemistry, CBz and Boc, **95** and **102** (Scheme 4). In almost all cases, 1,3-dibromopropane **56** was used with the exception of **100**. The results are reported in Scheme 4 and correspond to the references:[53,54,55,56,57,58,59,60,61,62]



Scheme 4. Pyrazolidines prepared from hydrazides.

4.1.2. By oxidation of 1,3-diaminopropanes. This procedure, although used much less than the preceding one, is the industrial method employed to prepare the parent pyrazolidine (**11**) in large amounts (framed, Scheme 5).



Scheme 5. Pyrazolidines prepared from 1,3-diaminopropanes.

Lüttringhaus and coworkers prepared **11** from the monochlorination of 1,3-diaminopropane (**104**) to afford **105** which, treated with NaOH, produced the desired compound.[63] At about the same time, Wittig oxidized 1,2-diphenyl-1,3-diaminopropane (**106**) into 1,2-diphenylpyrazolidine (**38**) using MnO_2 or MeLi followed by I_2.[64] The reaction was extended to other aryl groups (**74**, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *o*-$CH_3OC_6H_4$ and *p*-$C_2H_5OC_6H_4$) from **107** by Daniels and Martin.[65]

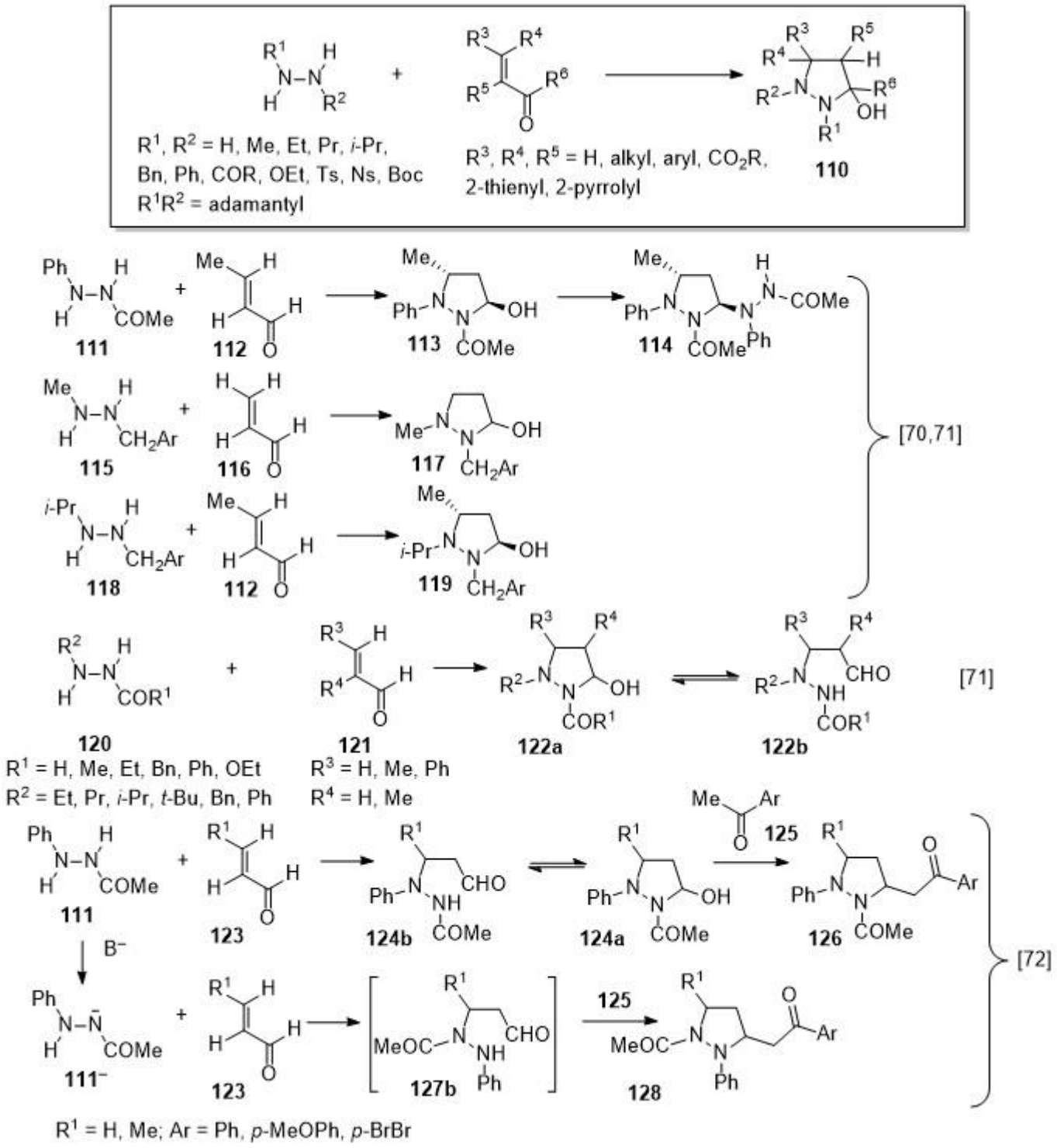
Pasquet *et al*. published three papers where they proposed a mechanism for the process and the conditions to prevent the formation of pyrazoline **10** (through **109**); they obtained **11** in 90% yield.[66,67,68] The first clear proof of oxidative N-N coupling of secondary amidolithium compounds to yield pyrazolidines was reported by Mair.[69]

4.1.3. With α,β-unsaturated carbonyl compounds. This very frequently used procedure provides 3-hydroxypyrazolidines **110**, the starting material being α,β-unsaturated carbonyl compounds. The literature results are presented in Schemes 6a and 6b.

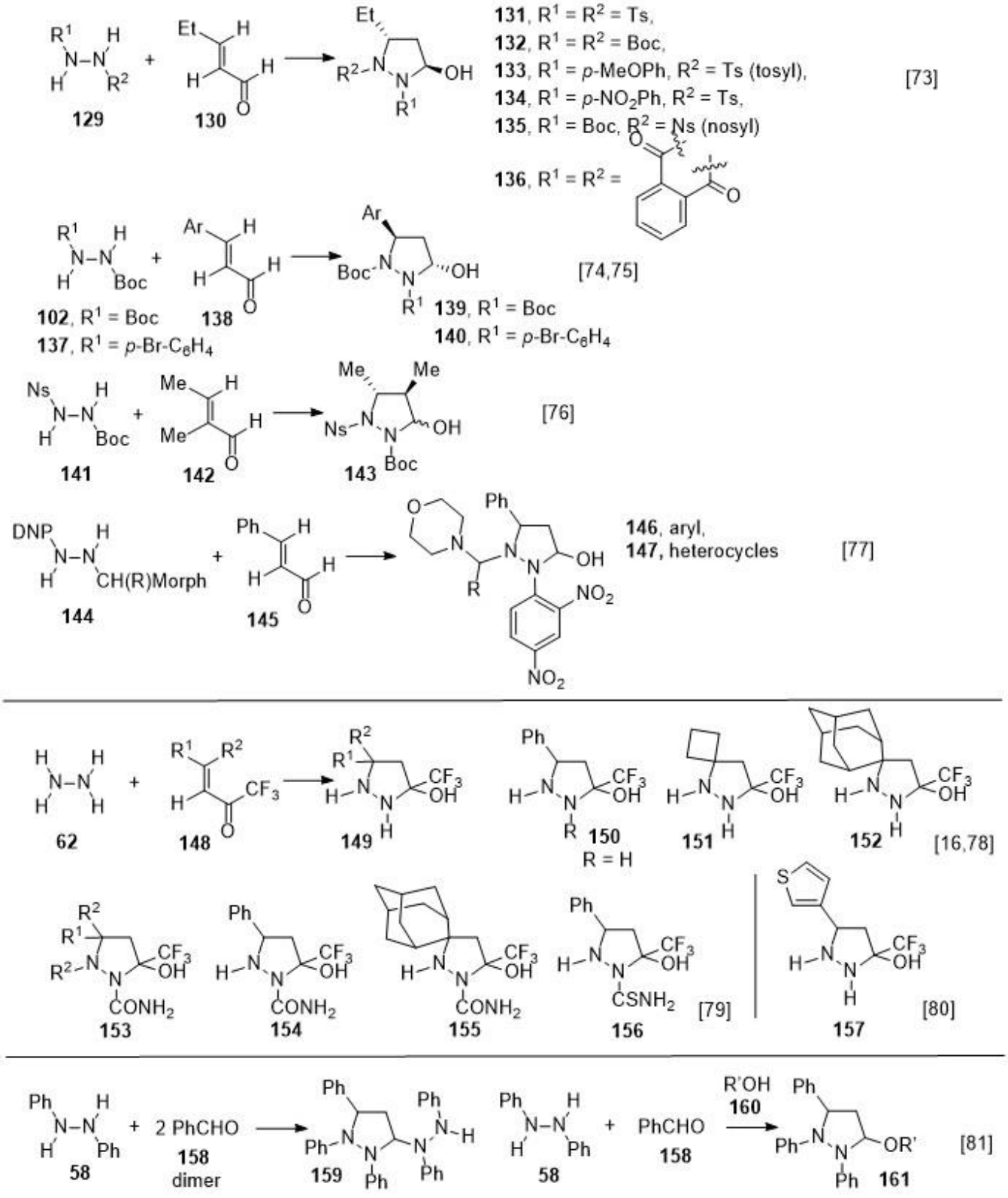
Zelenin, Sviridova, Golubeva *et al*. made the greatest contribution to this method. In 1965 they prepared a large collection of pyrazolidines; for instance, **113** from hydrazides **111** and crotonaldehyde **112**; compound **113** reacted with another molecule of **111** to afford **114**; they also prepared pyrazolidines **117** and **119**.[70] The same group carried out a similar reaction and studied the ring-chain equilibrium **122a**/**122b**.[71] In a later paper, they studied the reactivity of hydrazide **111** and its anion **111**$^-$ with α,β-unsaturated aldehydes and then with acetophenones **125**. Neutral molecule **111** and anion **111**$^-$ reacted differently, affording isomers **126** and **128** in different proportions.[72]

The natural evolution of organic chemistry led several authors in 2012 to report enantioselective synthesis of pyrazolidines. Vicario *et al*. described pyrazolidines **131-136**, using catalysts **C7** to **C11**, through an organocatalytic, enantioselective aza-Michael/hemiaminal-formation-cascade process from enals and 1,2-disubstituted hydrazides with excellent results, e.g., yields and *ee* (%) up to 99 and 92%, respectively.[73] Pyrazolidines **139** and **140** were prepared simultaneously by Zang, Wang *et al.*[74] and Córdova *et al*.[75] reacting hydrazines **102** and **137** with cinnamaldehydes **138** using, as catalyst, **C8** and other pyrrolidine catalysts. Córdova explained the resulting stereochemistry by a Michael hemiaminal cascade that favors 1,4-addition over 1,2-addition, and needs a protected hydrazine. Moyano *et al*., using Jørgensen-Hayashi catalysts, **C8** and **C10**, also obtained very high yields and a single isomer **143** (dr > 30:1).[76]

In view of medicinal chemistry applications, a series of morpholine-connected pyrazolidine derivatives **146**, **147** were prepared from the reaction between **144** and cinnamaldehyde (**145**) (see Section 7).[77]



Scheme 6a. Pyrazolidines prepared from hydrazines and α,β-unsaturated carbonyl compounds (first part).



Scheme 6b. Pyrazolidines prepared from hydrazines and α,β-unsaturated carbonyl compounds (second part).

Nenadjenko, Sanin and Balenkova initiated the use of trifluoromethyl-α,β-unsaturated ketones to prepare 5-trifluoromethyl-5-hydroxypyrazolidines **149**.[16,78] The presence of the CF_3 substituent strongly stabilizes these compounds, preventing dehydration. Compounds **150** to **152** represent some similar

compounds prepared by these authors. Starting from semicarbazides and thiosemicarbazides, 5-trifluoromethyl-5-hydroxypyrazolidines **153**-**156** have been prepared.[79] To determine the relative amounts of hydrazine and 1,1-dimethylhydrazine in a propellant, pyrazolidine **157** was prepared from the corresponding α,β-unsaturated ketone (only hydrazine can react) and its proportion determined by GC-MS.[80]

Exner *et al*. reacted hydrazobenzene (**58**) with benzaldehyde **158** to obtain compound **159** in which the OH group has been replaced by **58**. In the presence of methanol or ethanol **160**, the 5-alkoxy derivatives **161** were obtained.[81] Other authors have described hydroxypyrazolidines **162-166** (the two last ones are pyrazolidinium quaternary salts),[82] as well as the fluorinated derivatives **167**[83] and **168** (R^F = CHF_2, CF_3, $H(CF_2)_2$, $H(CF_2)_4$, C_4F_9, C_6F_{13}, only one diastereomer was obtained) (shown in Figure 4).[84]

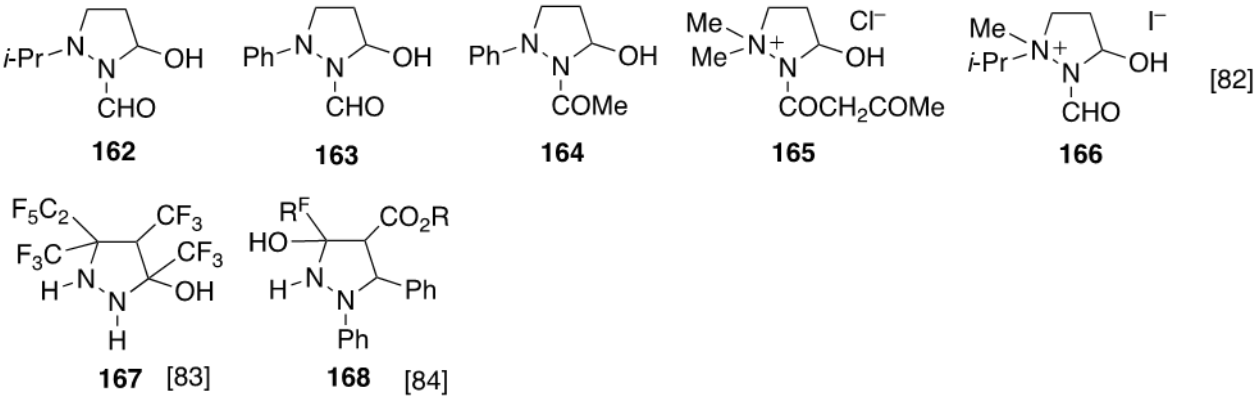
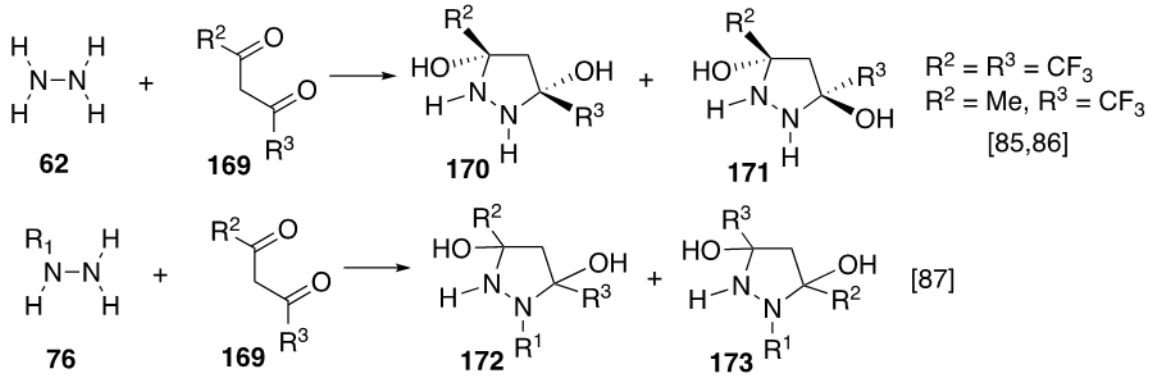


Figure 4. Other 5-hydroxypyrazolidines.

4.1.4. With β-diketones. This is a marginal section with a few examples concerning hydrazines **62** and **76** with β-diketones **169** that afford pyrazolidines **170** to **173**. 3,5-Dihydroxypyrazolidines can be isolated even when both nitrogen atoms are non-substituted, e.g., **170** and **171** (Scheme 7).[85,86,87] Reference 87, although reporting bicyclic pyrazolidines, describes a mechanistic proposal.



Scheme 7. Pyrazolidines prepared from hydrazines and β-dicarbonyl compounds.

4.1.5. Other methods involving hydrazines. The oldest methods to prepare pyrazolidines use hydrazines, either directly or through a more oxygenated form, and will appear in Sections 4.3 and 4.4. Here, we will report in Scheme 8 reactions involving hydrazines substituted in positions 1 and 2 with groups that can cyclize with the aid of a reagent.

Cyclization of an allyl precursor leads to the unexpected formation of the five-membered rings **174** with the *trans*-isomer as the main product. These products cannot arise from a 'normal' 5-*exo*-type cyclization. A large variety of cyclic α-hydrazino acid derivatives can be efficiently synthesized via this method.[88]

Selenium-induced cyclization of alkenes containing bound nucleophiles continues to attract the attention of several research groups, as it represents an efficient synthesis of a wide variety of heterocyclic compounds. *N*-AIIyl-acetohydrazides readily result in organoselenium-induced cyclization reactions promoted by phenylselenenyl sulfate ($PhSeOSO_3H$) to produce phenylseleno-*N*-acetyl pyrazolidines **177** as the thermodynamically-controlled products. A further interesting aspect of these cyclization reactions is that, in most cases, they are completely diastereoselective.[89]

The authors reported that stirring the methoxycarbonyl-protected hydrazines **178** with 0.5 equivalents of concentrated sulfuric acid in dichloromethane at room temperature overnight, resulted in complete disappearance of the staring material and isolation of **179a/b** in excellent yields.[90]

The PhSeBr-induced cyclization of 2-(but-3-en-1-yl)-1,1-dimethylhydrazine has been studied. A 5-*exo*-*trig* ring closure occurred in each case and phenylselenylmethyl-pyrazolidines were obtained. They prepared a considerable number of compounds, amongst them 1,1-disubstituted pyrazolidinium quaternary bromides, **180**.[91]

Highly stereoselective synthesis of optically active pyrazolidines **182**, and the prediction of the stereoselectivity, were accomplished by cyclization of optically active allenylhydrazine **181** with organic halides. The optimization procedure was achieved after screening several optically-active palladium catalysts, prepared *in situ* from easily available chiral ligands and $Pd(OAc)_2$ [**C4**, **C5**, **C6**, **C12**, **C13** and **C14**]. They also established a model with which the enantiopurities of the products and the diastereoselectivities of the reactions can be easily predicted.[92,93]

Pd-catalyzed alkene difunctionalization was used by Wolfe[94] to prepare **183** using as a catalyst Pd/S-Phos **C25** (see ref.[95] for a previous work by this author). An efficient and practical Pd-catalyzed intramolecular oxidative allylic amidation provides facile access to derivatives, in this way compound **185** was obtained pure from **184** in the *trans* form and with a *dr* > 30:1, using molecular oxygen (1 atm) as the sole reoxidant of Pd.[96] Similar results were reported almost simultaneously by Lalwani *et al*.[97]

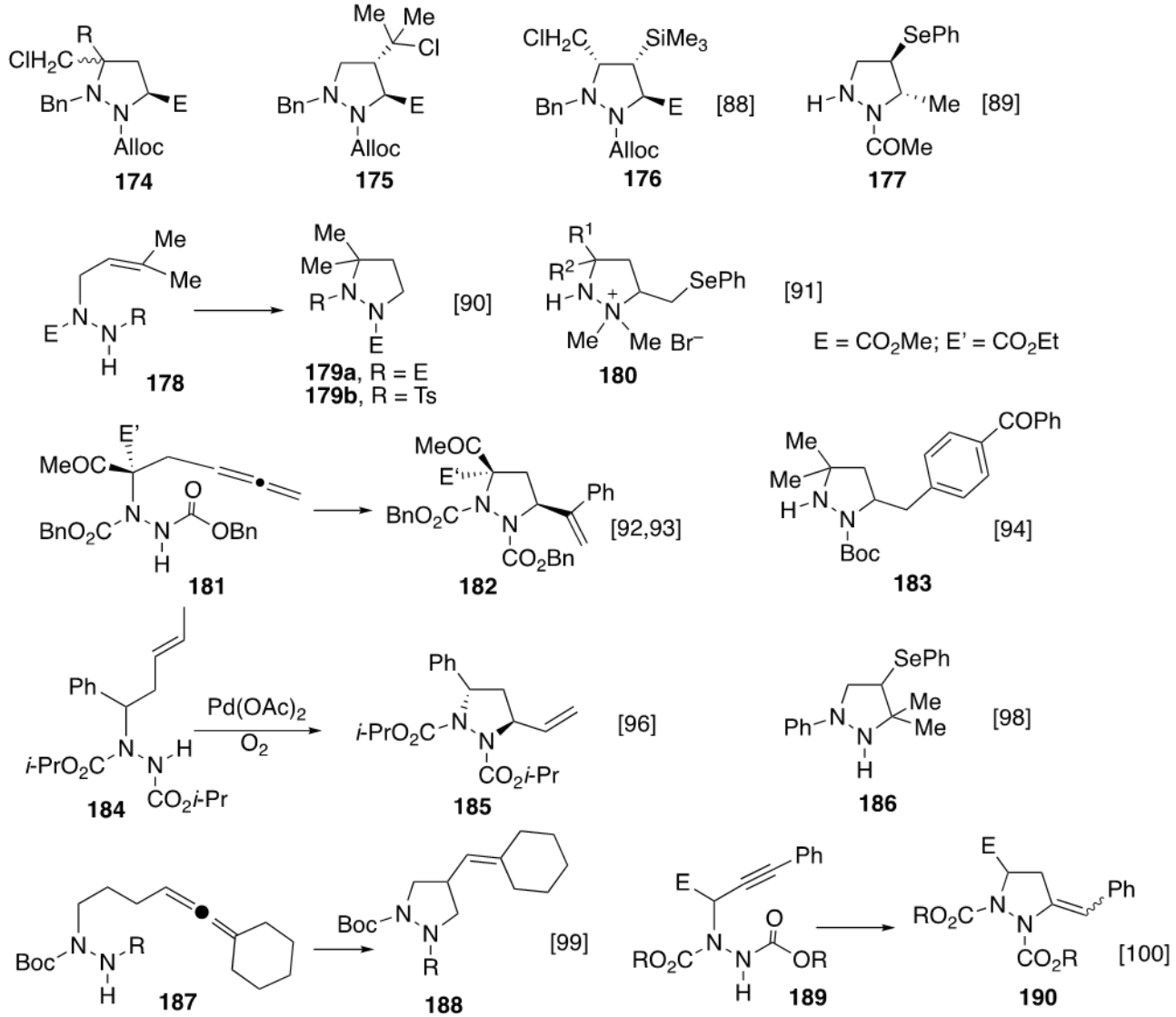
Allylhydrazines react with phenylselenenyl sulfate, produced from the reaction of diphenyl diselenide and ammonium persulfate in the presence of trifluoromethanesulfonic acid, to afford phenylseleno-substituted pyrazolidines such as 3,3-dimethyl-1-phenyl-4-(phenylseleno)-pyrazolidine (**186**). The reaction was extended to other allylhydrazines.[98]

Although paper[99] concerns mainly isoxazolidines, it also contains an important contribution to the field of pyrazolidines: gold(I)-catalyzed enantioselective synthesis of pyrazolidines **188** from mono-Boc-protected homoallenic hydrazine **187,** was achieved through an exhaustive optimization of catalysts [**C15**, **C16**, **C17** and **C18**] and protecting groups. Chiral biarylphosphinegold (I) complexes **C15** and **C18** are suitable catalysts for the enantioselective addition of nitrogen nucleophiles to allenes.[99]

Synthesis of enantio-enriched aza-proline derivatives **190** was accomplished through gold(I)-catalyzed cyclization of chiral α-hydrazinoesters bearing an alkyne group **189**. Enantioenriched α-hydrazinoesters underwent ring closure by using $Ph_3PAuCl/AgBF_4$ as a catalytic system. Under these conditions, 5-*exo*-*dig* cyclization was favored over 6-*endo*-*dig*, and aza-proline derivatives were obtained in good yields without epimerization at the stereogenic center. These results demonstrate the importance of the nature of the silver salt $AgBF_4$, the hydrazine protecting group, and alkyne substitution on the yield and selectivity of the gold-catalyzed cyclization.[100] Kerr *et al*. reported an efficient diastereoselective (and diastereodivergent)

intramolecular annulation of hydrazones and 1,1-cyclopropanediesters allowing rapid access to structurally complex pyrazolidines.[101,102]

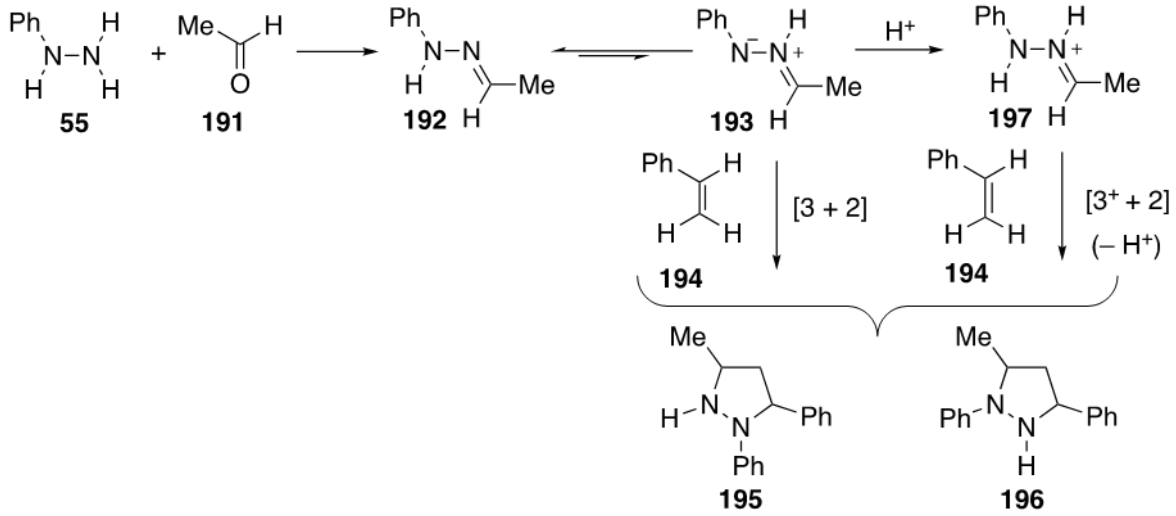
The part containing pyrazolidines bearing CF_3 groups is well summarized in the Nenajdenko review of 2011.[20]



Scheme 8. Pyrazolidines from *N,N'*-disubstituted hydrazines.

4.2. By 1,3-dipolar cycloaddition from hydrazones

This section is as important as the previous one (4.1) for preparing pyrazolidines. The methods used belong to the Huisgen [3+2] cycloaddition family of reactions[11,103]; but two variants must be distinguished ([3 + 2] and [3^+ + 2], Scheme 9). Two excellent reviews on these reactions were published by Pellissier in 2007,[17] and by Nájera, Sansano and Yus in 2015.[24]

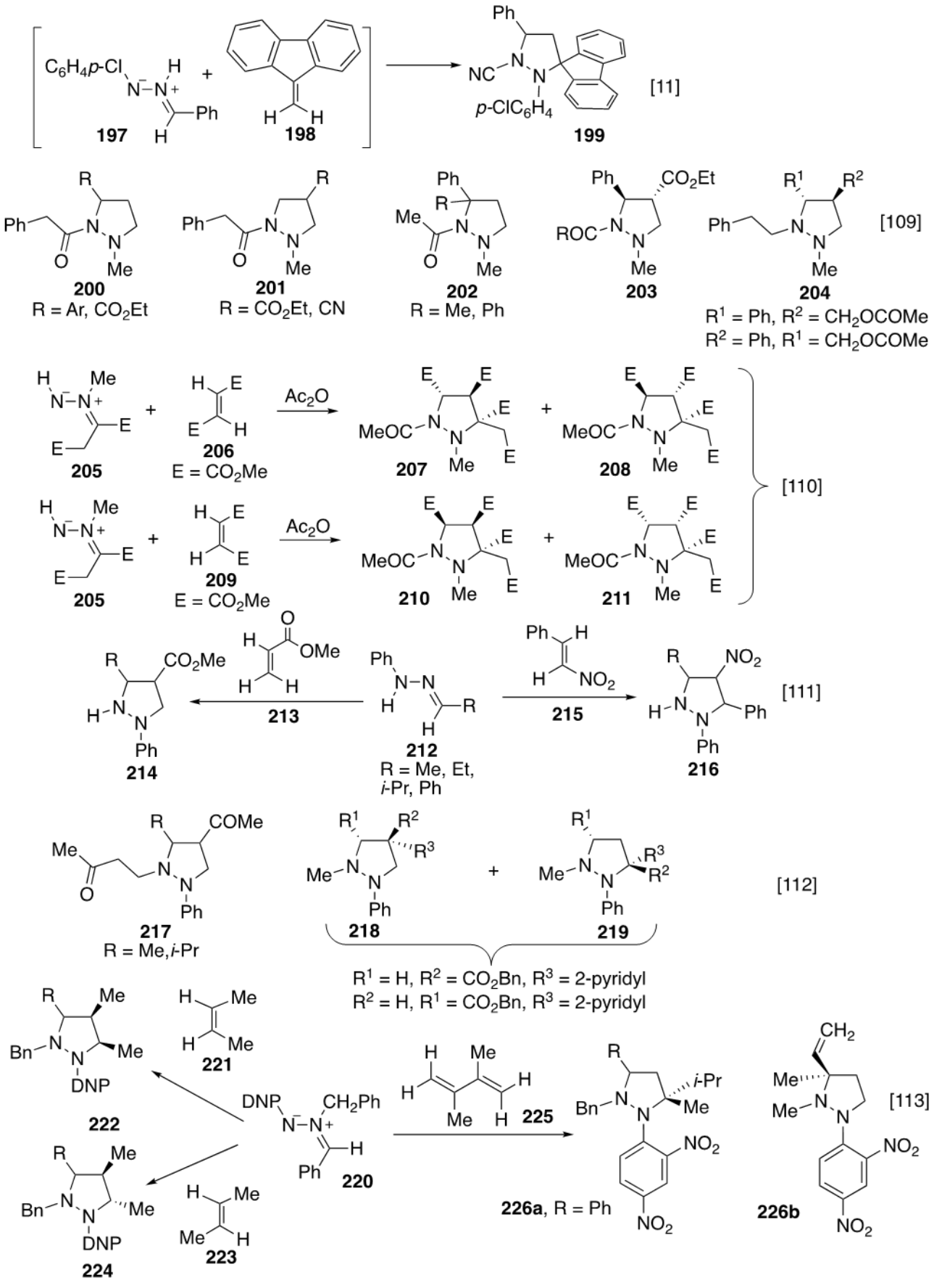


Scheme 9. The [3+2] and [3^{+}+2] variants of Huisgen cycloadditions.

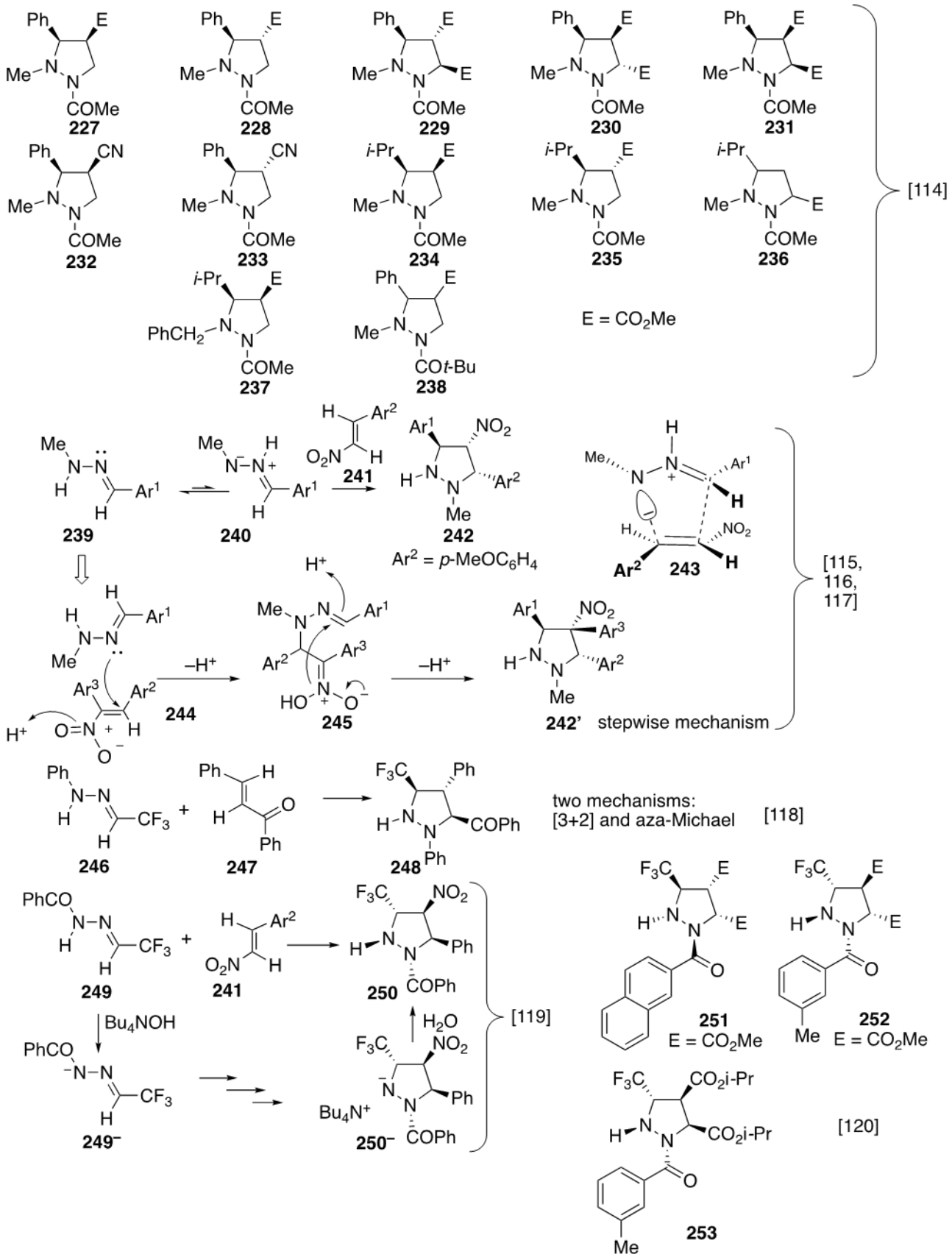
We reported in Scheme 9 the assumed reactivity of the phenylhydrazone of acetaldehyde **192** from **55** and **191**. This compound exists in tautomeric equilibrium with a dipolar form **193** (an azomethine imine)[24] that is less stable, but more reactive. Dipolar cycloaddition to styrene (**194**) affords two pyrazolidines **195** and **196** in different proportions depending on the reaction conditions. Protonation of **192** or **193** leads to a cation **197** that is also able to cycloadduct olefins to render, after losing a proton, the mixture of **195** and **196** in a different ratio. This last reaction has been called [3^{+}+2] by Schmidt,[104] who points out that Hesse reported a previous example.[105] Hamelin *et al*. consolidates the study depicted in Scheme 14, both neutral,[106,107] and protonated variants.[108]

4.2.1. Neutral hydrazones, [3+2] cycloaddition. We will first report the uncatalyzed reactions gathered in Scheme 10, that correspond to references[11,109,110,111,112,113,114,115,116,117,118,119,120]: These reactions were in some cases catalyzed by non-chiral Lewis acids.

Although the mechanism is more complex, Huisgen reported as early as 1963 pyrazolidine **199** that formally corresponds to the reaction between **197** and **198**.[11] Oppolzer, in 1970, using this procedure prepared pyrazolidines **200**-**204**;[109] compound **200** (R = Ph) was obtained by a three-component reaction between a hydrazine, paraformaldehyde and styrene. This was followed by Sucrow, who, in 1979 prepared pyrazolidines bearing four methoxycarbonyl groups **207**, **208**, **210** and **211** from dimethyl fumarate (**206**) and dimethyl maleate (**209**) and the azomethine imine **205**.[110] The reaction of phenylhydrazones **212** with methyl acrylate (**213**) and nitrostyrene [(*E*)-(2-nitrovinyl)benzene] (**215**) yields 4-methoxycarbonyl- **214** and 4-nitro-pyrazolidines **216**, respectively.[111] Grigg *et al*. reported that hydrazones of aldehydes or ketones undergo intermolecular cycloaddition to electronegative olefins via azomethine imines, formed by a formal 1,2-prototropic shift, **192**/**193**, providing the first clear analysis of these reactions. In this way, they prepared pyrazolidines **217**-**219**.[112] Cauquis and Chabaud prepared a series of pyrazolidines such as **222**, **224** and **226a/b** from azomethinimine **220** and different olefins: *cis*-2-butene (**221**), *trans*-2-butene (**223**) and 2,3-dimethyl-1,3-butadiene (**225**) for their study by mass spectrometry (section 6.6).[113]



Scheme 10a. Uncatalyzed 1,3-dipolar cycloadditions [3+2] (first part).

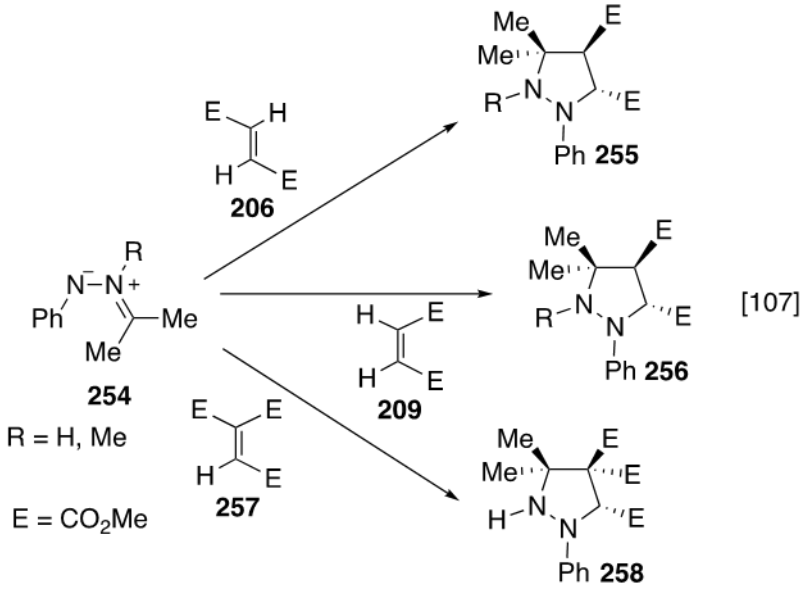


Scheme 10b. Uncatalyzed 1,3-dipolar cycloadditions [3+2] (second part).

The search of pyrazolidines as peptidomimetics led Jones *et al*. to prepare a large collection of compounds with CO_2Me and CN substituents, **227**-**238**.[114] Deng and Mani discussed if the reaction of **239**/**240** with nitrostyrenes **241** to afford **242** occurs by a concerted [2+3] dipolar cycloaddition **243** or by a stepwise mechanism (aza-Michael) involving **244** and **245**. In their first paper[115] they concluded in a concerted mechanism, but, in a subsequent paper, taking into account the possible isomerization of pyrazolidines, they preferred the stepwise mechanism.[116,117] This conclusion (see also[111]) must be considered only provisional because other authors have rejected it. In particular, Wu *et al*., after examination of the stereochemistry and regioselectivity of the reaction **246** + **247** → **248**, concluded that the mechanism is concerted; the metal salts $Sc(OTf)_3$, $In(OTf)_3$, $Yb(OTf)_3$, and $Y(OTf)_3$ could catalyze the 1,3-dipolar cycloaddition reaction.[118]

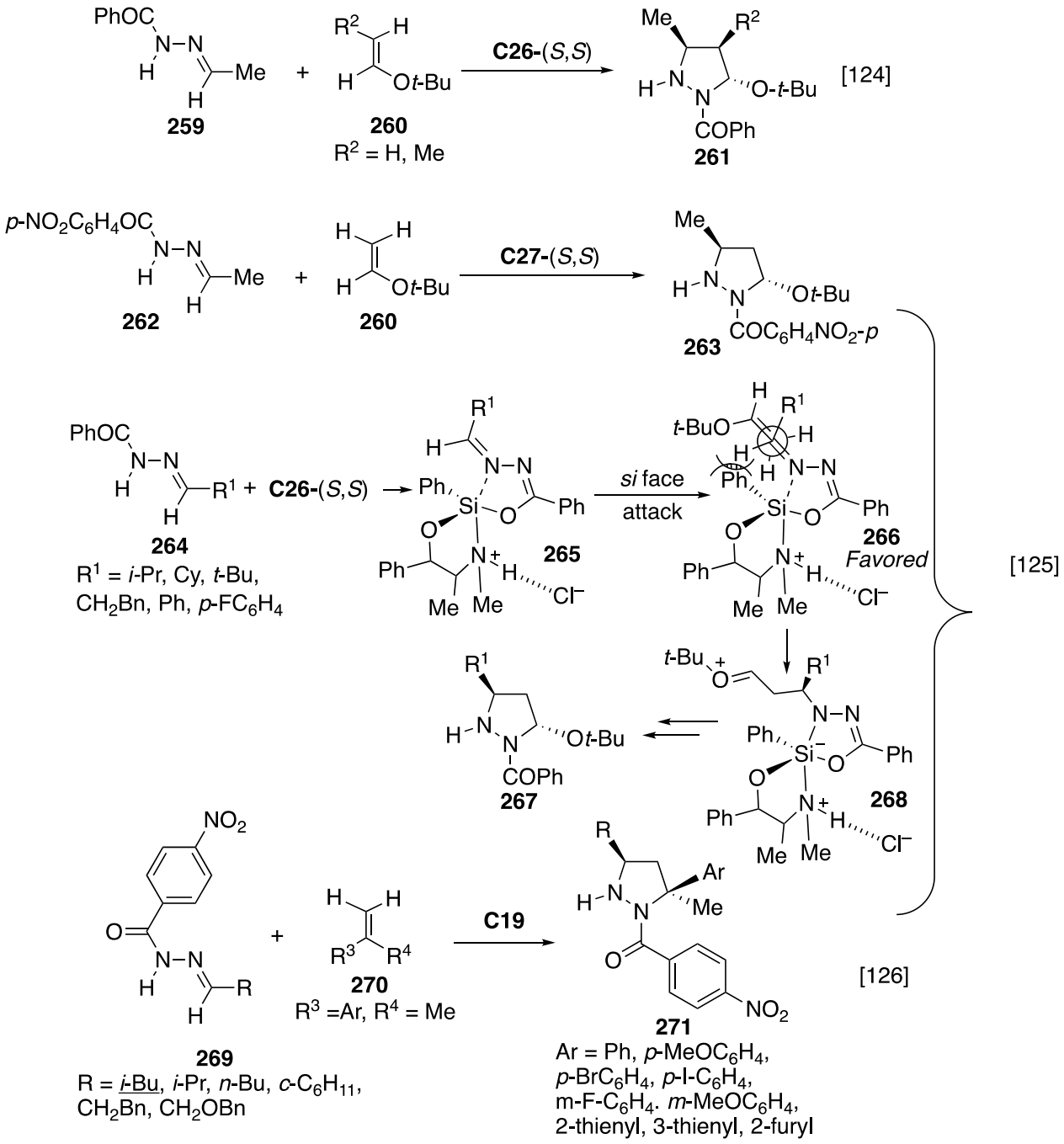
Hu *et al*.[119] have shown that basic conditions can also be used to carry out the [3+2] cycloadditions (we propose to name them [3$^-$+2]); in this way **249**$^-$ reacts with **241** to afford the tetrabutyl ammonium salt **250**$^-$ that is protonated by water to yield the desired pyrazolidine **250**. Pyrazolidines **251** to **253** were also obtained in basic conditions.

The lithium anions of phenylhydrazones also react with olefins to afford pyrazolidines;[106] this paper, and a previous one, report the experiments of Hamelin to prove that the mechanism of Scheme 11 (pyrazolidines **255** and **256**) corresponds to a [3+2] cycloaddition.[107] (4-Chlorophenyl)[(3*S*,5*S*)-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl)]methanone was obtained with a *dr* = 94/6 using $Cu(OTf)_2$ as catalyst.[121] Finally, note that heterocyclic phenylhydrazone **254** reacts with trimethyl 1,1,2-ethylenetricarboxylate (**257**) to afford a pyrazolidine bearing three ester groups at positions 4 and 5, **258**.[122]



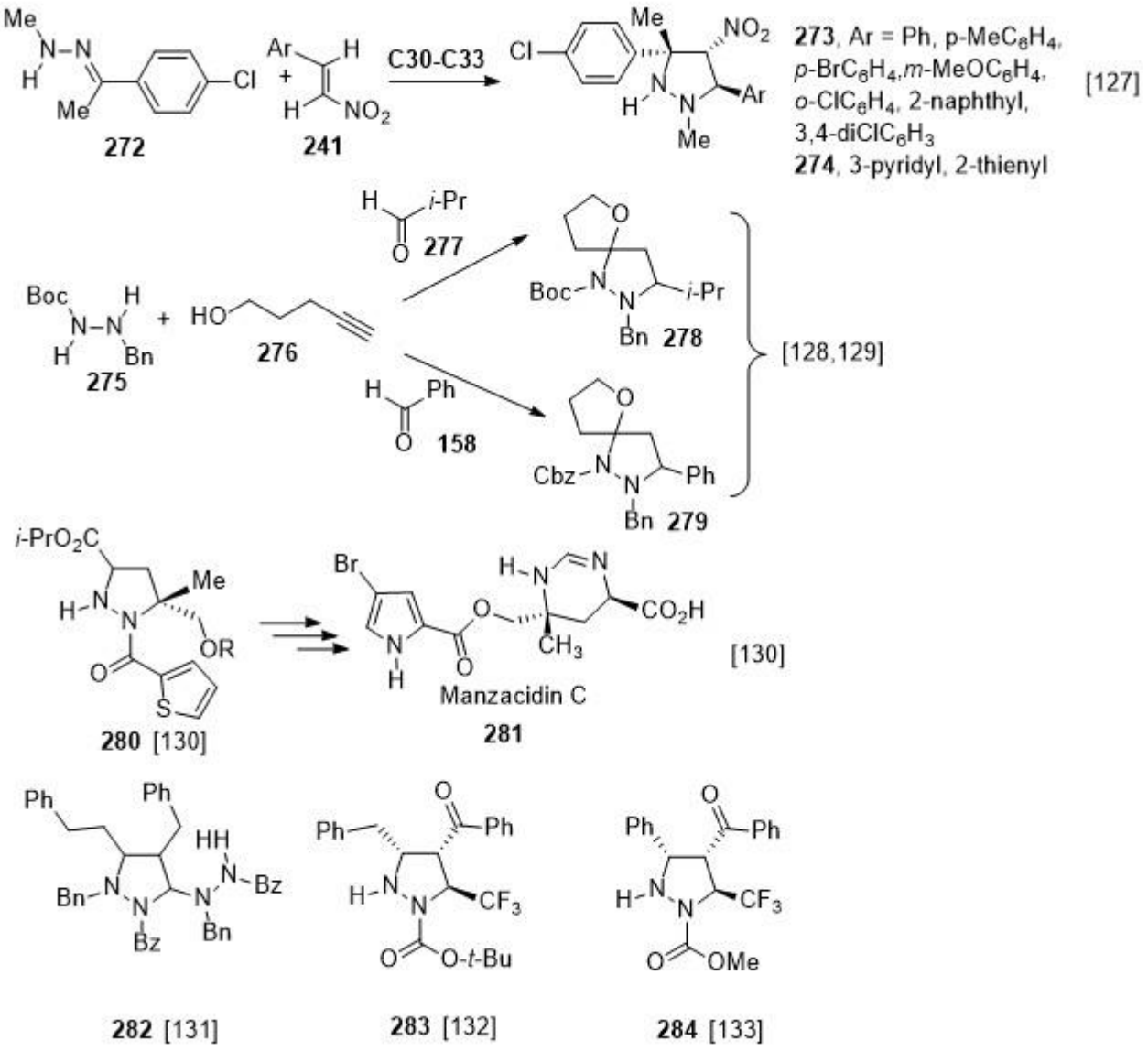
Scheme 11. Hamelin's synthesis of poly-substituted pyrazolidines **255**, **256** and **258**.

The part concerning catalyzed [3+2] cycloadditions is, in general, more recent and was aimed at obtaining stereospecific pyrazolidines; Kobayashi was the precursor of these studies, using his catalysts **C1**, **C2** and **C3** combined with $Zr(OPr)_4$ to prepare optically active pyrazolidines.[123] Scheme 12 summarizes the results reported in references. [124,125,126,127,128,129]



Scheme 12a. Catalyzed 1,3-dipolar cycloadditions [3+2] (first part).

In 2005, Leighton *et al*. developed highly diastereo- and enantioselective 1,3-dipolar cycloadditions of acylhydrazones **259** to enol ethers **260**, catalyzed by a chiral silicon Lewis acid **C26**, to prepare pyrazolidines **261**.[124] They extended these studies in a subsequent paper,[125] whereby, using similar reactants, **262** and **260**, and a similar catalyst, **C27**, they obtained pyrazolidines **263**. Furthermore, they proposed a mechanism to explain the role of the catalyst involving intermediates **265**, **266** and **268**. An asymmetric Brønsted acid-catalyzed cycloaddition using catalyst **C19** led to enantioselective pyrazolidines **271** from *N*-acyl hydrazones **269** and alkenes **270** using as chiral catalyst Rueping catalyst **C21**.[126]



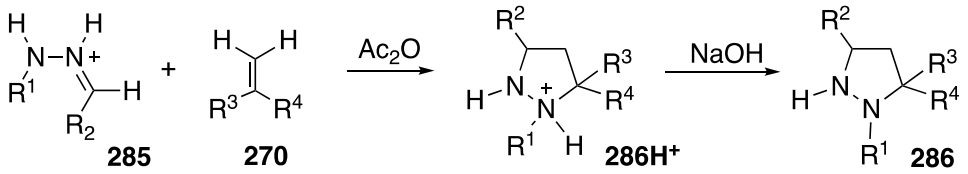
Scheme 12b. Catalyzed 1,3-dipolar cycloadditions [3+2] (second part).

Jørgensen *et al*. described a catalytic asymmetric synthesis of 4-nitro-pyrazolidines **273** and **274** from **241** and **272** using their catalysts **C30** to **C33**.[127] Krause *et al*.[128,129] reported an efficient, highly atom-economic synthesis, of hitherto unknown spirocyclic pyrazolidines **278** and **279** in a one-pot process. The gold-catalyzed three-component coupling of hydrazine **275**, pentynol (**276**) and aldehydes **277** and **158** proceeds via cycloisomerization of the pentynol to an exocyclic enol ether and subsequent [3+2]-cycloaddition of an azomethine ylide. A library of 29 derivatives with a wide range of functional groups was created in up to 97% yields.

Four pyrazolidines were reported which belong to this section, although their stereochemistry was not always indicated. Starting from pyrazolidine **280** and using a catalyst related to **C27** in five steps reached the alkaloid manzacidin C **281**.[130] Pyrazolidine **282** has a second molecule of hydrazine at position 5 similar to **114**; the catalyst is related to **C16**.[131] Pyrazolidines **283** and **284** were prepared using catalysts **C28** and **C29**.[132,133]

4.2.2. Protonated hydrazones, [3$^+$+2] cycloaddition. The first example of these reactions was described by Hesse in 1970 although he didn't use Huisgen's terminology. Protonated hydrazones **285** prepared *in situ* from R^1NHNH_2 and R^2CHO react with olefins **270** to afford pyrazolidinium salts **286H$^+$** that, upon treatment with

NaOH, yield the free pyrazolidines **286**, R^1 = Ph, COMe, COBu, COPh, COAr; R^2 = H, Me, *i*-Pr, pentyl, Ph, R^3, R^4 = H, Me, Ph, Scheme 13.[105]



Scheme 13. The first example of [3⁺+2] pyrazolidine synthesis.

Hamelin *et al*. described these reactions in a fundamental paper using a wide collection of olefins (styrene, fumarate, maleate, cinnamate, crotonate, acrylate and acrylonitrile), to prepare twelve poly-substituted pyrazolidines **287**-**298** (Figure 5, E = CO_2Me).[108]

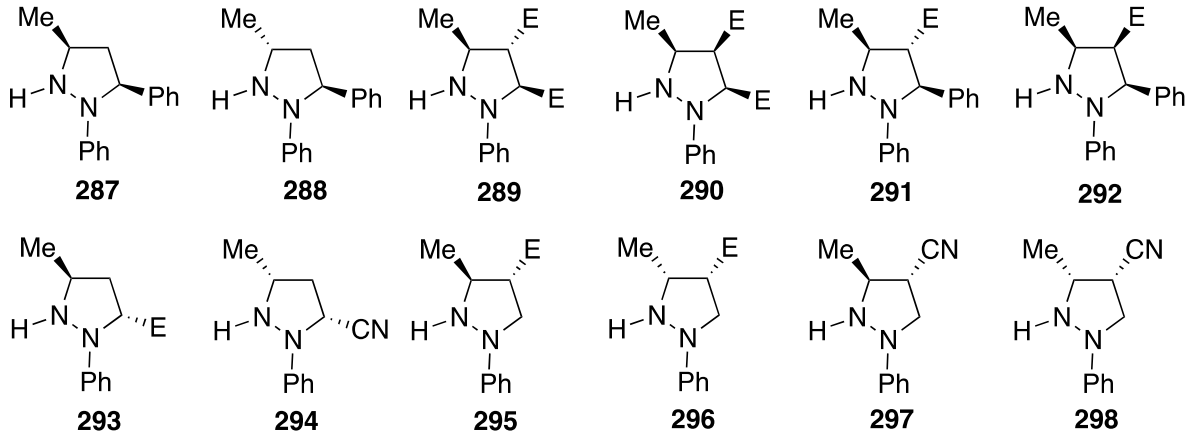
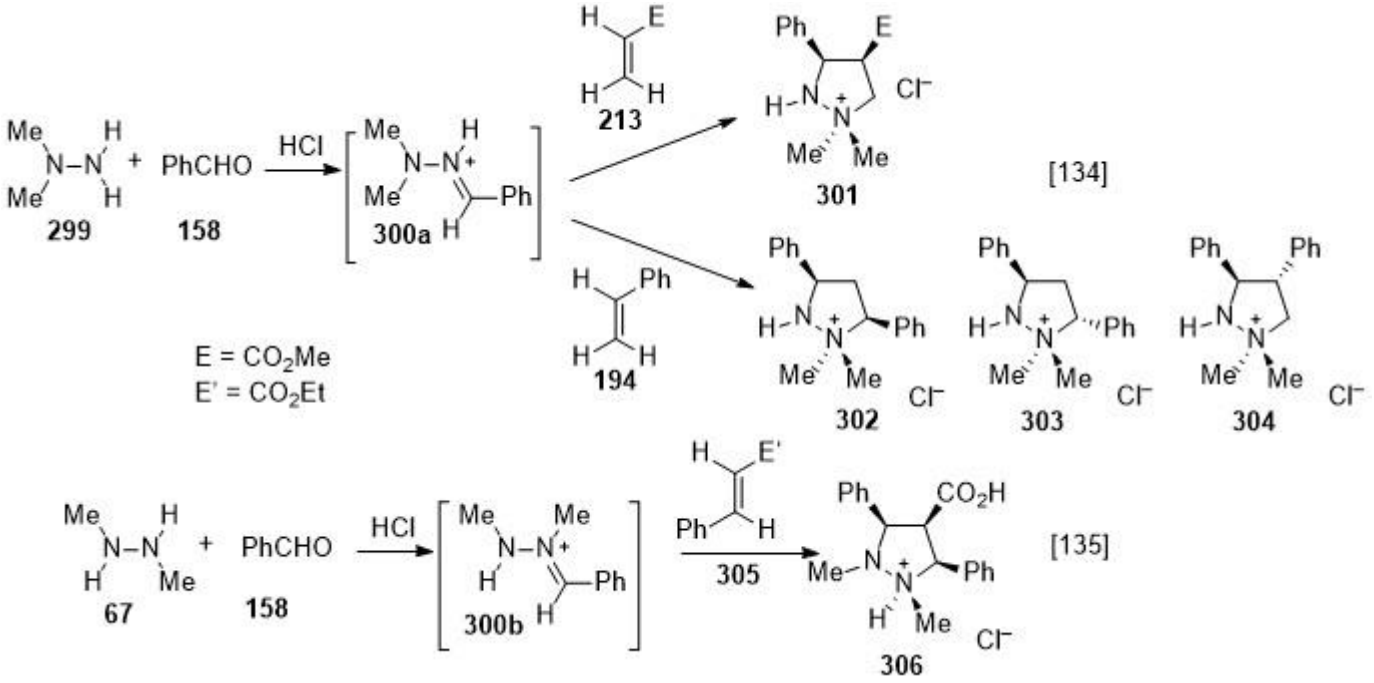


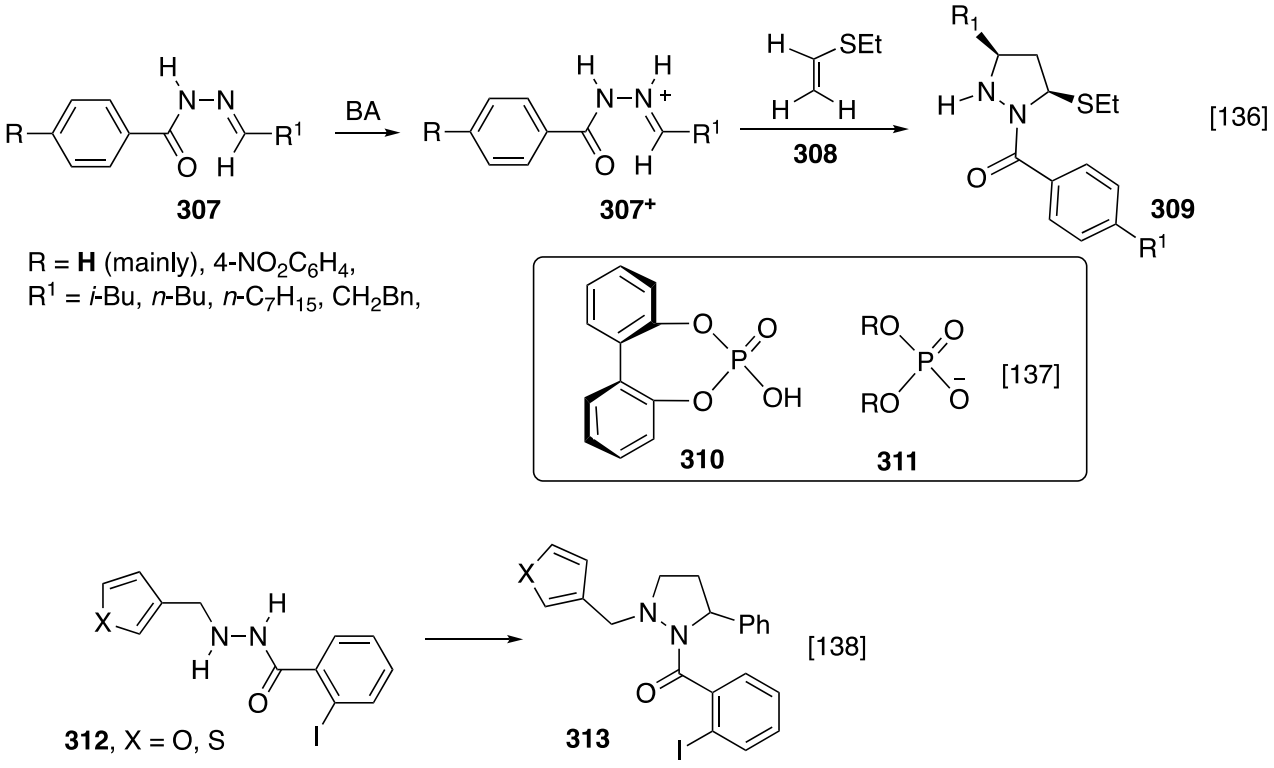
Figure 5. Functionalized pyrazolidines.

When 1,1-dimethylhydrazine (**299**) is used as starting material, it reacts with benzaldehyde (**158**) and concentrated HCl to afford the protonated hydrazone **300a** (not isolated) which reacts with methyl acrylate (**213**) and with styrene (**194**) to give analytically pure pyrazolidinium chlorides **301**-**303** (Scheme 14); the authors reject structure **304** based on ^{1}H NMR chemical shifts.[134] If cation **300b** [from 1,2-dimethylhydrazine (**67**)] is used, the reaction with ethyl cinnamate (**305**) proceeds in the same way, yielding **306** whose X-ray structure was used to establish its stereochemistry.[135]

Rueping, Houk *et al*. have studied, experimental and theoretically, the reaction of hydrazones **307** with ethyl vinyl thioether (**308**) to afford pyrazolidines **309** (Scheme 15) in the presence of Kobayashi catalyst **C2**, Leighton catalyst **C24**, Tsogoeva catalyst **C16** and Rueping catalysts **C19** and **C21**.[136] They developed a chiral Brønsted-acid-catalyzed highly-asymmetric [3⁺+2] cycloaddition reaction; the reaction affords pyrazolidine derivatives in good yields, with high diastereoselectivities and excellent enantioselectivities. The cycloaddition reaction was also carried out with ethyl vinyl ether, and the corresponding pyrazolidine derivatives were synthesized with high enantioselectivities. Furthermore, Houk *et al*. carried out DFT calculations on the [3⁺+2] cycloaddition mechanism. The alternative 1,3-dipolar [3+2] cycloaddition pathway, with azomethine imine, is less favorable due to the endergonic isomerization from hydrazone to azomethine imine; in addition, they proved that the protonation of hydrazone by Brønsted acids is crucial for the catalytic efficiency.



Scheme 14. Examples of [3⁺+2] cycloadditions.



Scheme 15. Synthesis using the [3+2] and [3⁺+2] mechanisms.

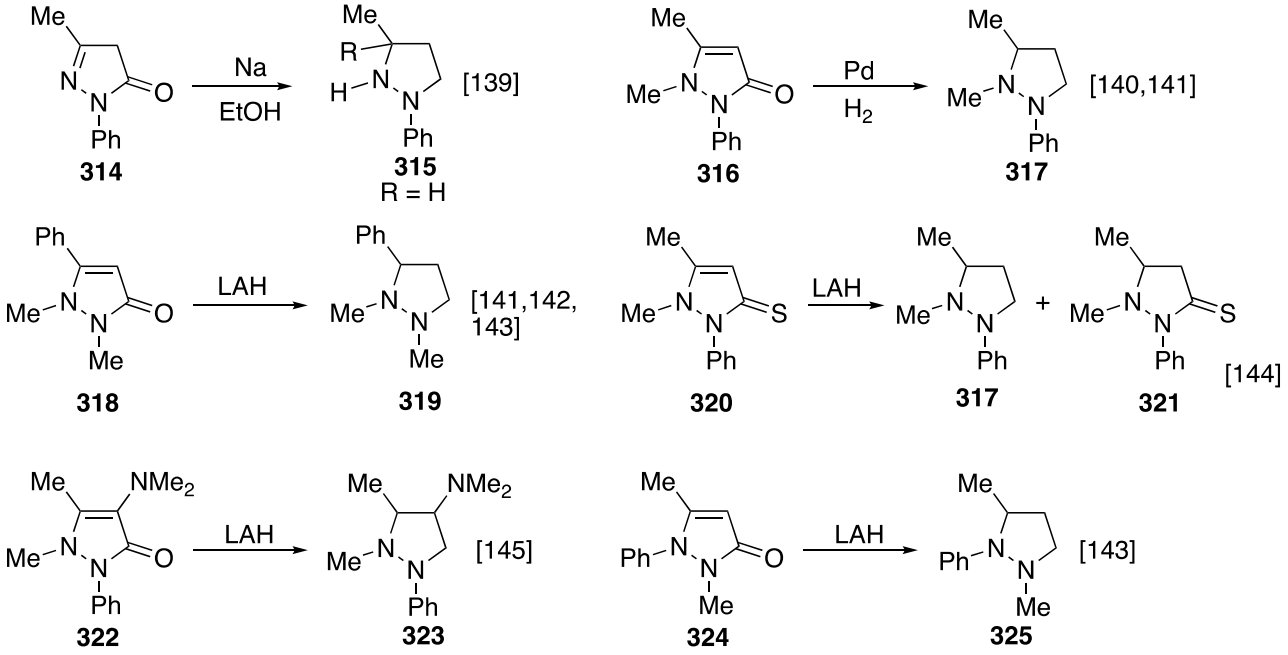
The group of Vicario, Merino *et al*. studied this mechanism, again, with a different hydrazone, leading to a tricyclic pyrazolidine (**15**, Figure 2). In order to carry out theoretical calculations, they simplified the structure of catalyst **C16** using instead **310** and **311** (Scheme 15). They employed Houk's distortion model, reaching the

conclusion that the process is an apolar, concerted one in which all the events (bond breaking/bond formation) take place in a simultaneous way. Despite the polarity of the reacting groups, the overall charge transfer is not high enough for the process to be considered polar.[137]

The three-component reaction between hydrazide **312**, *para*-formaldehyde and styrene (**194**) affords pyrazolidine **313**[138]; this publication also includes a discussion of the mechanism.

4.3. By reduction of pyrazolones and pyrazolidinones

4.3.1. Pyrazolones. This is a topic that was important in the past, but is now almost inactive, most of the publications originating from Jacquier's laboratory (Montpellier, France). In Scheme 16 we have summarized the most relevant publications[139,140,141,142,143,144,145]:



Scheme 16. Reduction of pyrazolones to pyrazolidines.

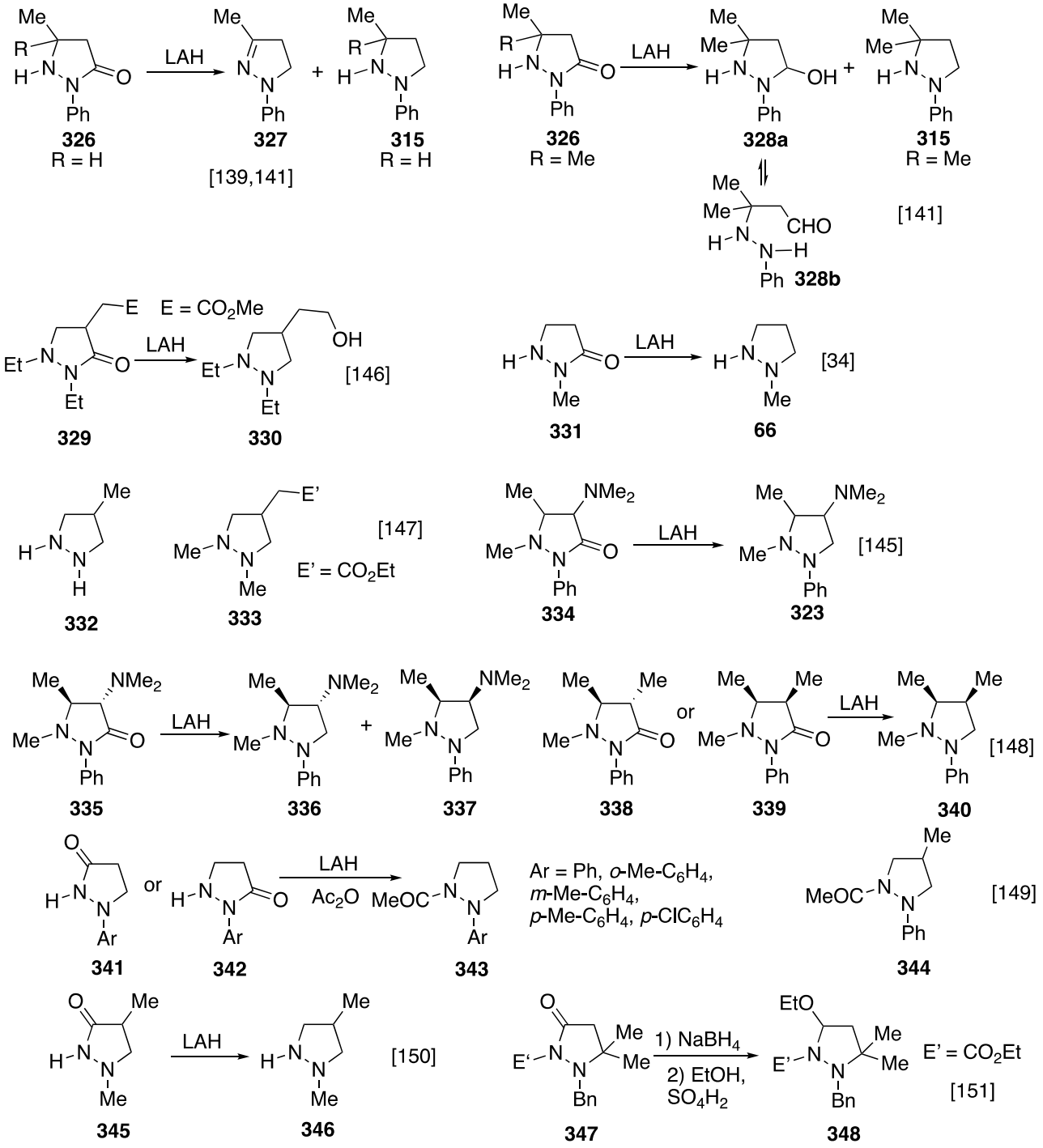
Using this method, pyrazolidines **315**, **317**, **319**, **321**, **323** and **325** were prepared from the corresponding pyrazolones **314**, **316**, **318**, **320**, **322** and **324**. Note that compound **316** is antipyrine, **320** is thiopyrine [in this example, dihydrothiopyrine (**321**) was also isolated when reducing it with lithium aluminium hydride (LAH)] and **322** is pyramidon. The replacement of H by D to determine the mechanism can be found in references [141] and[143].

4.3.2. Pyrazolidinones. Pyrazolidinones, being a degree more reduced than pyrazolones (Figure 1), are easier to reduce to pyrazolidines (Scheme 17).

In 1893, Knorr and Duden reported that the reduction of **326** by Na/EtOH affords **315** (R = H).[139] In 1966, but using lithium aluminium hydride (LAH), Montpellier's group obtained a mixture of 2-pyrazoline **327** and pyrazolidine **315** (R = H).[141] In the same paper, the reduction of **326** to afford 5-hydroxypyrazolidine **328a** (in equilibrium with the open structure **328b**) and pyrazolidine **315** was also reported;[141] replacing H by D the mechanism of the reductions was explored. The same year, Kornet reported the double reduction **329** → **330**,[146] and the following year the synthesis of 1-methyl-pyrazolidine **66** from **331**.[34] This author described in subsequent papers pyrazolidines **332** and **333**.[147]

Using LAH, the reduction **334** → **323**[145] and the synthesis of pyrazolidines **336**/**337** from **335**, and **340** were reported; the origin of the stereochemistry of C4-substituent in **336**, **337** and **340** from **338**/**339** was

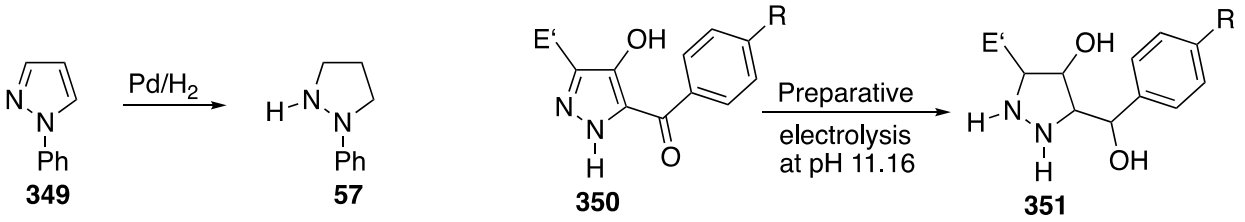
determined.[148] Reduction of any of **341/342** isomers with simultaneous acetylation affords 1-aryl-2-acetylpyrazolidine **343**; the 4-methyl analogue **344** was reported in the same paper.[149] Kornet is the author of the **345** → 1,4-dimethylpyrazolidine (**346**) reaction.[150] Finally, Speckamp reported the reduction of **347** by sodium borohydride followed by treatment with ethanol in acid medium, to give the 3-ethoxypyrazolidine **348**.[151]



Scheme 17. Reduction of pyrazolidinones to pyrazolidines.

4.4. By reduction of pyrazoles and pyrazolium salts

Pyrazoles are resistant to reduction; only two exceptions have been reported (Scheme 18). In 1923, Thoms and Schnupp used Pd/H_2 to reduce 1-phenyl-1*H*-pyrazole (**349**) to 1-phenyl-pyrazolidine **57**;[140] By preparative electrolysis, 4-hydroxy pyrazolidine **351** (E' = CO_2Et) was obtained from 4-hydroxy-1*H*-pyrazole **350**.[152]



Scheme 18. Reduction of pyrazoles.

Much more common is the reduction of pyrazolium salts. This field was explored by two groups, that of Jacquier in the 1970s (Montpellier, France)[153,154,155] and that of González Nogal in the 1990s (Valladolid, Spain).[156,157,158]

In Figure 6 are reported the pyrazolidines synthesized by the first group, **25**, **26**, **40/41**, **317**, **325**, and the remaining ones from **352** to **361**. A mechanism was proposed for the formation of these products, which were completed taking into account the incorporation of deuterium when $LiAlD_4$ is used as a reducing agent and (or) D_2O for the decomposition of the complexes.[155]

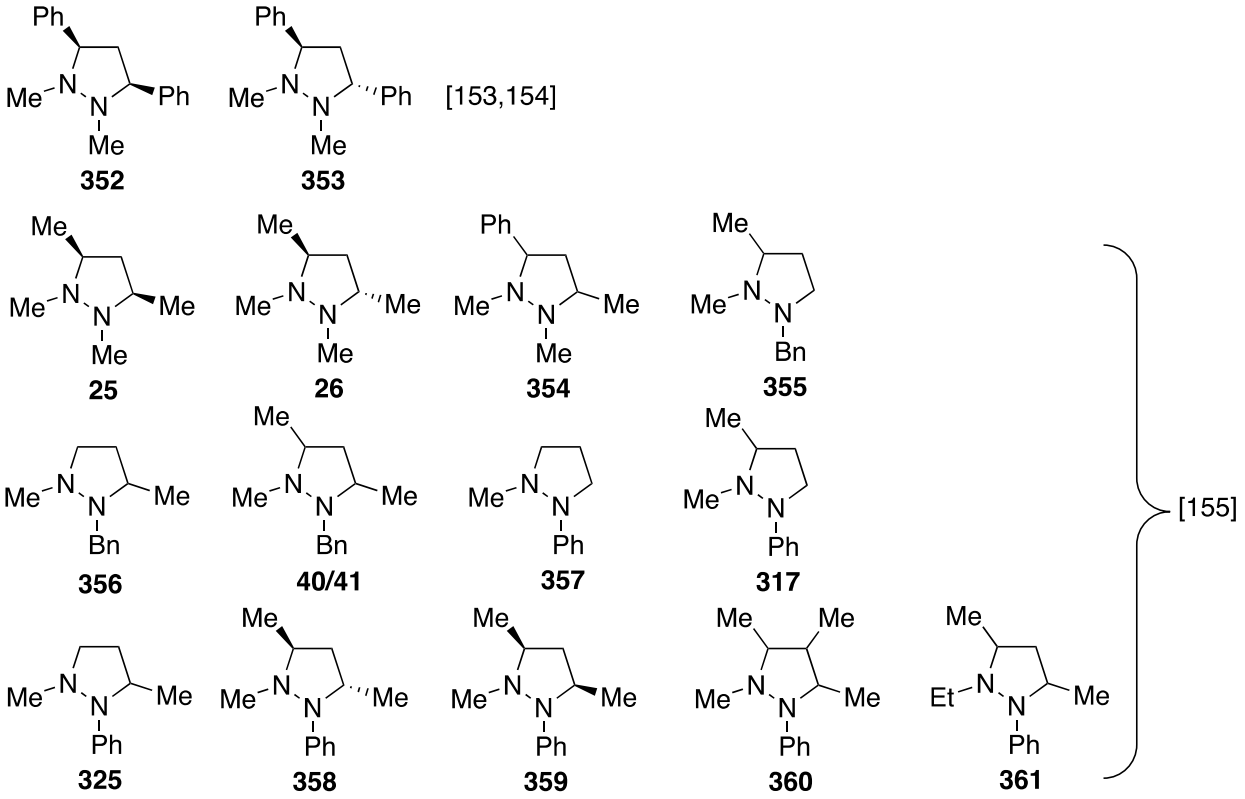


Figure 6. Pyrazolidines by reduction of pyrazolium salts, Montpellier results [153-155].

In Figure 7 there are gathered the large number of pyrazolidines obtained by the second group, **362**-**383**.[156-158] The reducing agents were $AlLiH_4$ and $NaBH_4$ and the pyrazolidines **362**-**380** were obtained mixed with pyrazolines.[156,157] The use of Grignard reagents leads to pyrazolidines with a supplementary methyl substituents, **381**-**383**.[158]

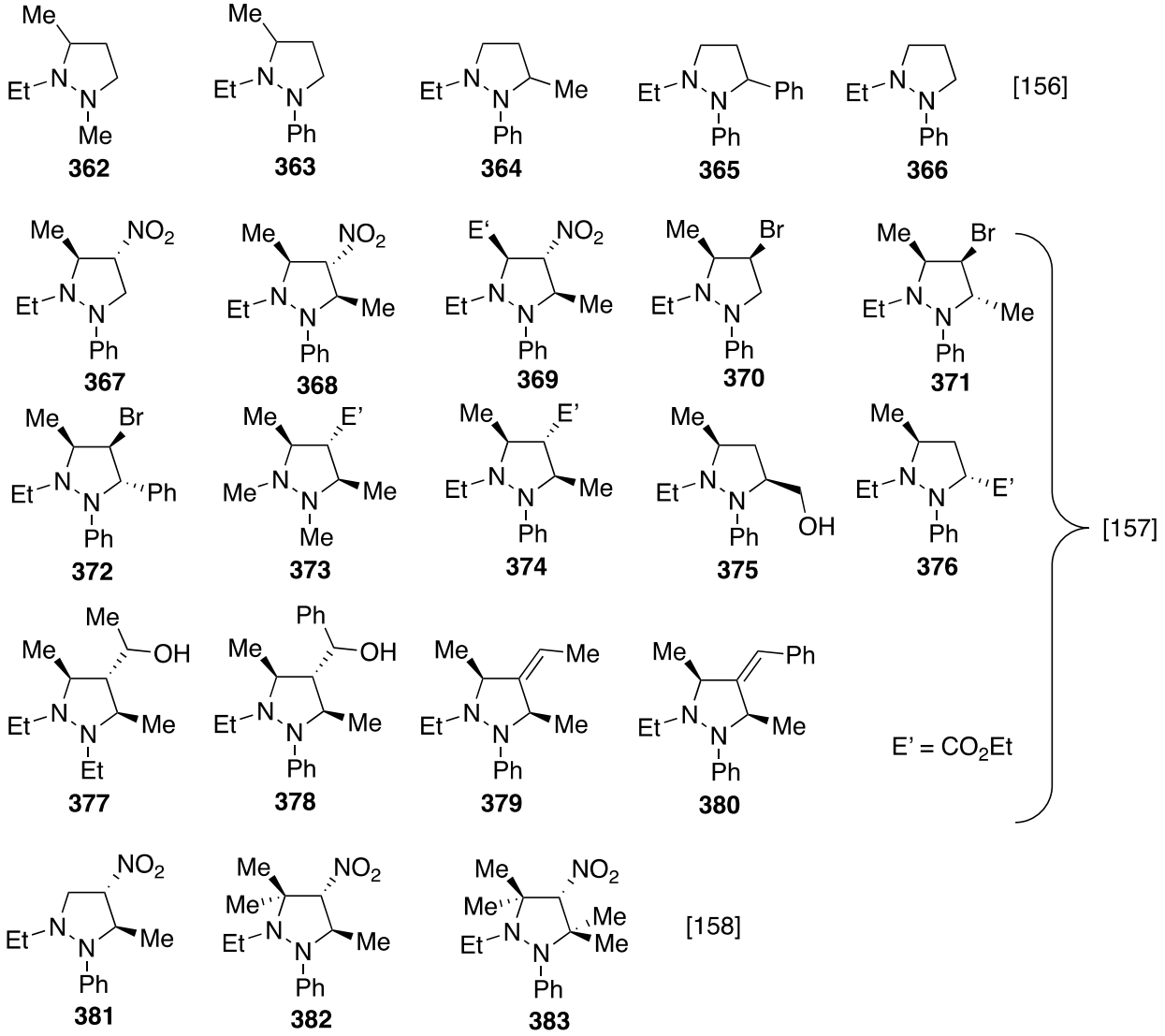
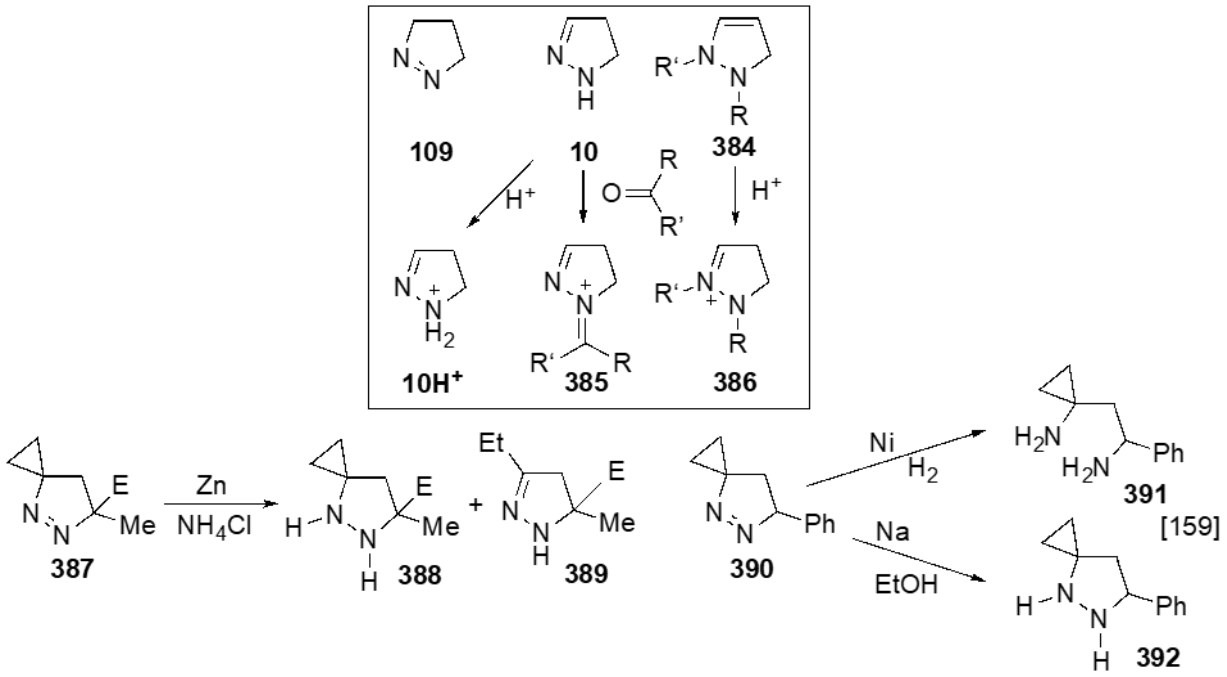


Figure 7. Pyrazolidines by reduction of pyrazolium salts, Valladolid results [156-158].

4.5. By reduction of 1-, 2- and 3-pyrazolines

We will divide this section into four subsections, depending on the pyrazoline nature: 1-pyrazoline **109**, section 4.5.1; 2-pyrazoline **10**, section 4.5.2; 3-pyrazoline **384**, section 4.5.3, and cations **385** and **386**, and section 4.5.4 (Scheme 19).

4.5.1. 1-Pyrazolines. There is only a paper reporting the reduction of 1-pyrazolines **109**, involving compounds **387** and **390** of Scheme 19.[159] The results depend on the reducing agent and together with pyrazolidines **388** and **392**, 2-pyrazoline **389** and diamine **391** are formed.

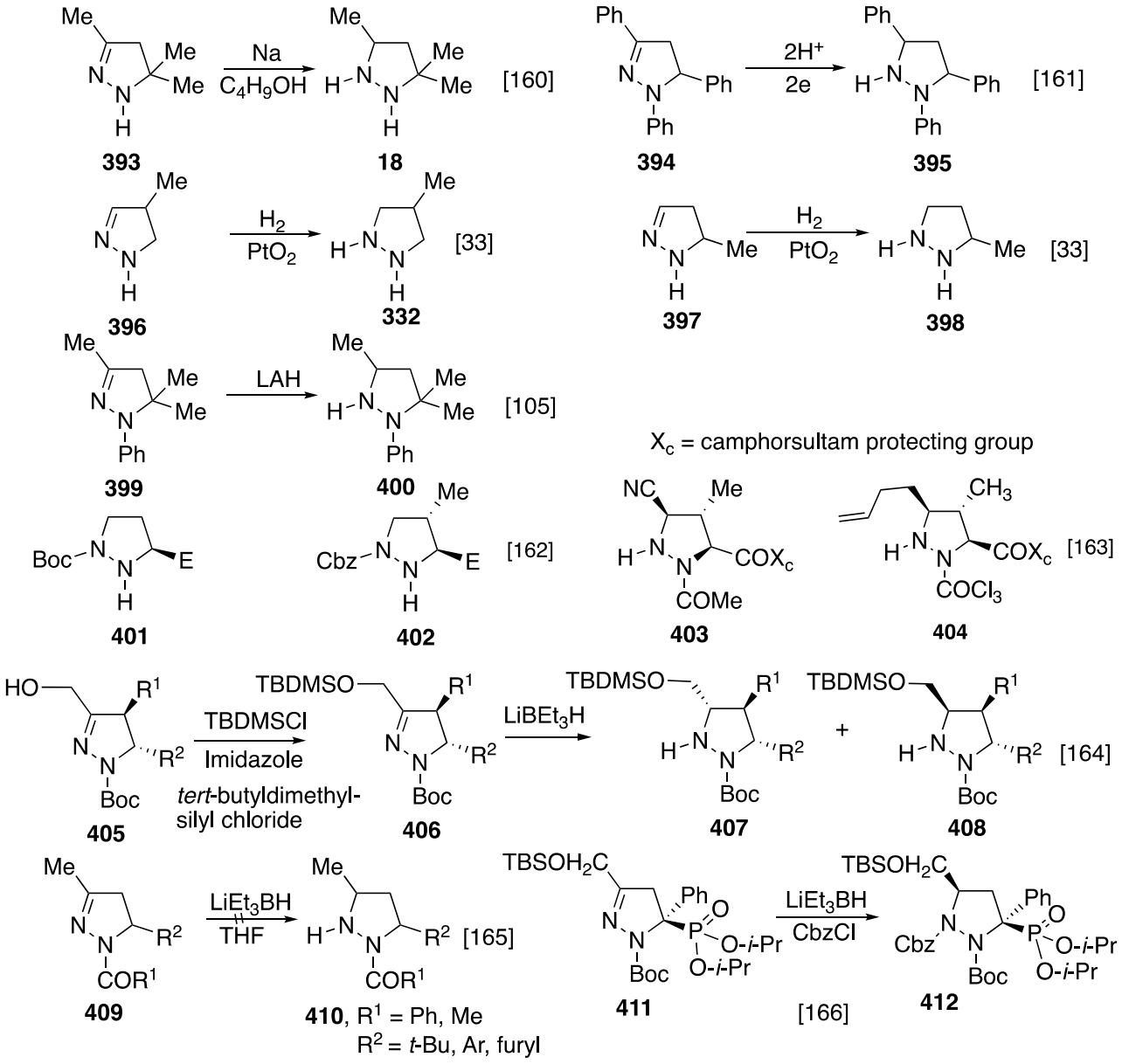


Scheme 19. Pyrazoline precursors and reduction of 1-pyrazolines.

4.5.2. 2-Pyrazolines. Different methods have successfully been used to reduce 2-pyrazolines **10** (Scheme 19) into pyrazolidines; the stereochemistry of pyrazolines is preserved in pyrazolidines (Scheme 20). Thus, Kost and Golubeva reduced 3,3,5-trimethyl-2-pyrazoline **393** with sodium in butanol into pyrazolidine **18**.[160] Polarography transforms **394** into **395**.[161] Crawford used Parr hydrogenation to carry out the synthesis of pyrazolidines **332** and **398**, pyrazolidine **18** was also prepared by this method.[33] Hesse used lithium aluminium hydride for the transformation **399 → 400**.[105]

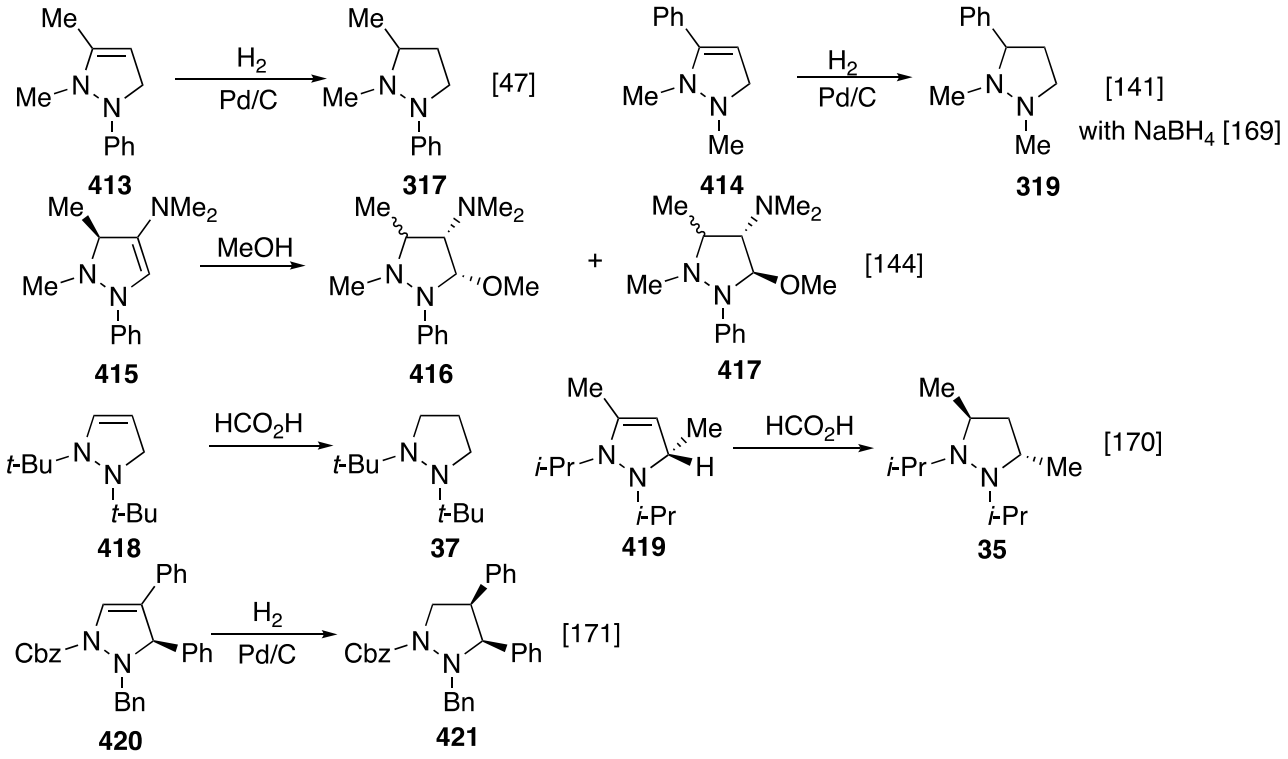
Enantioselective synthesis was used by Carreira *et al*. to prepare pyrazolidines **401**-**404**.[162,163] Barluenga *et al*. reported the sequence **405 → 406 → 407** + **408**; the diastereo-selective reduction of C=N double bond being the key step.[164] The regioselective reduction of the C=N double bond in 2-pyrazolines **409** using Superhydride ($LiEt_3BH$) gives pyrazolidines **410** with excellent levels of *cis*-diastereoselectivity.[165] Chiral 5,5-disubstituted-1*H*-pyrazoline-5-phosphonate **411** was treated with benzyl chloroformate (CbzCl) to give the protected pyrazolidine derivative **412** (97% *ee*).[166]

In the field of peptidomimetics, NCbz pyrazolidines were prepared as proline surrogates.[167] Some 2-pyrazolines proved to be extremely resistant to reduction using hydride reducing agents ($NaCNBH_3$, $LiBH_4$, $LiAlH_4$, BH_3, $LiEt_3BH$, Et_3SiH, and Bu_3SiH), catalytic reduction (H_2, Pd/C) or SmI_2; only limited success was achieved with $NaBH_4$ in refluxing methanol.[168]



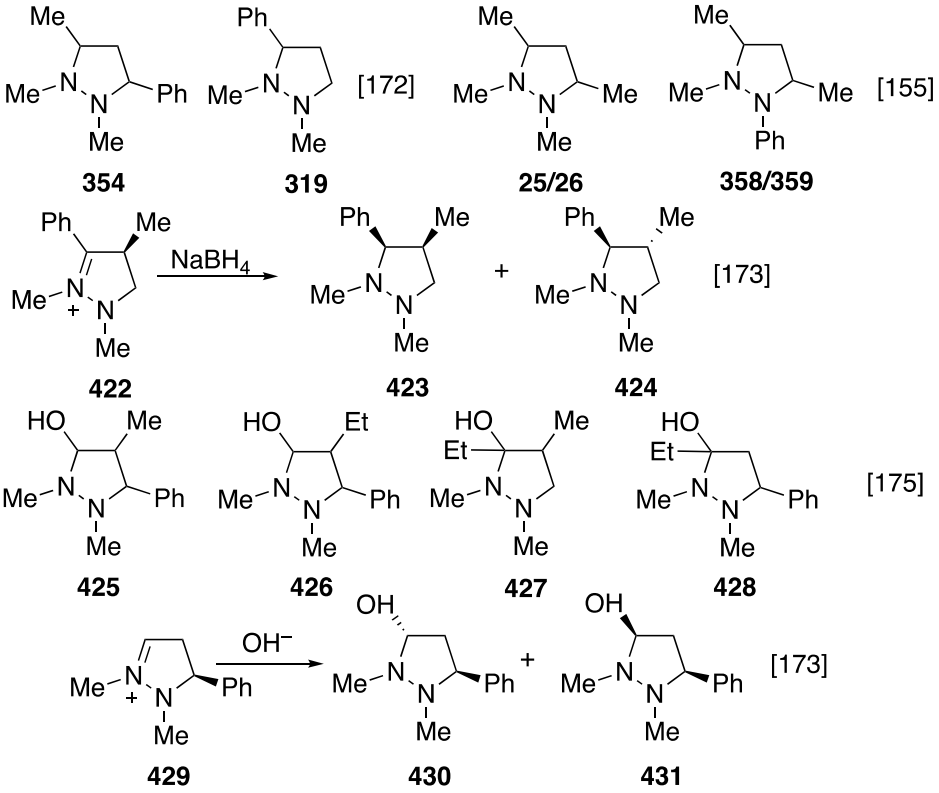
Scheme 20. Reduction of 2-pyrazolines.

4.5.3. 3-Pyrazolines. Reduction of 1-phenyl-2,3-dimethyl-3-pyrazoline (**413**) by catalytic hydrogenation affords the already reported pyrazolidine **317** (Scheme 21).[47] The transformation **414** → **319**[141] similarly proceeds using sodium borohydride.[169] Nucleophilic addition of methanol to the double bond of 3-pyrazoline **415** affords the *cis* and *trans* pyrazolidines **416** and **417**.[144] Formic acid (Leuckart-Wallach reaction) has been used to reduce pyrazolines **418** and **419** into pyrazolidines **37** and **35**.[170] Hydrogenation of **420** furnished pyrazolidine **421** bearing two phenyl groups in the *cis* conformation.[171]



Scheme 21. Reduction of 3-pyrazolines.

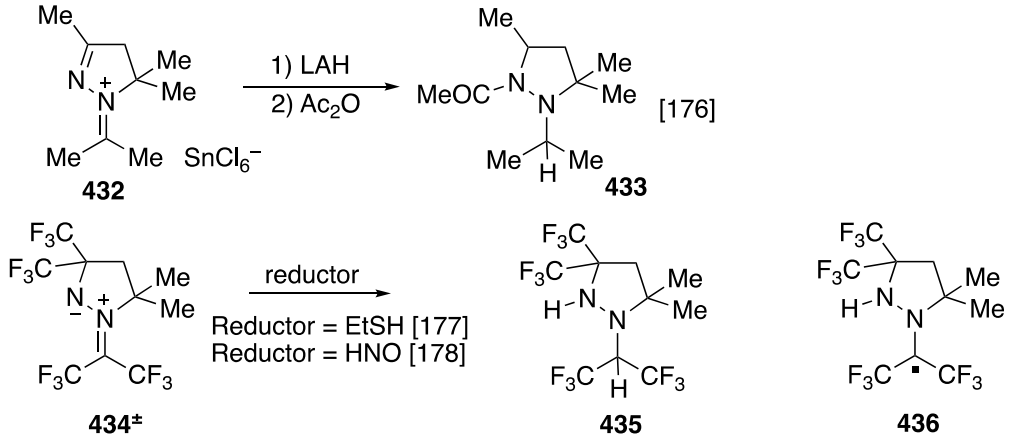
4.5.4. Pyrazolinium cations. This section includes the reduction of 3-pyrazolines **384** (Scheme 19) in the presence of Brønsted or Lewis acids, although cations **386** were not isolated (Scheme 22).



Scheme 22. Reduction of 3-pyrazolidiniums.

Pyrazolidine **354** was obtained from a mixture of pyrazoline-3, sodium borohydride and acetic acid in tetrahydrofuran; the pyrazolinium ion was formed and reduced without isolation by the hydride. A similar result was obtained using a Lewis acid, $AlCl_3$, with $AlLiH_4$, isolating pyrazolidine **319**;[172] and with I_2, which is transformed into IH during the process, pyrazolidines **25/26** and **358**/**359** were prepared.[155] Using sodium borohydride pyrazolidines **423** (30%) and **424** (70%) were obtained from the pyrazolinium salt **422**.[173] Other pyrazolines, with interesting NMR properties, were prepared using the same procedure.[174]

Addition of OH^- to type **386** cations resulted in 3-hydroxypyrazolidines **425**-**428**,[175] and, starting from **429**, pyrazolidines **430**-**431** were obtained.[173]



432 **433** **434±** **435** **436**

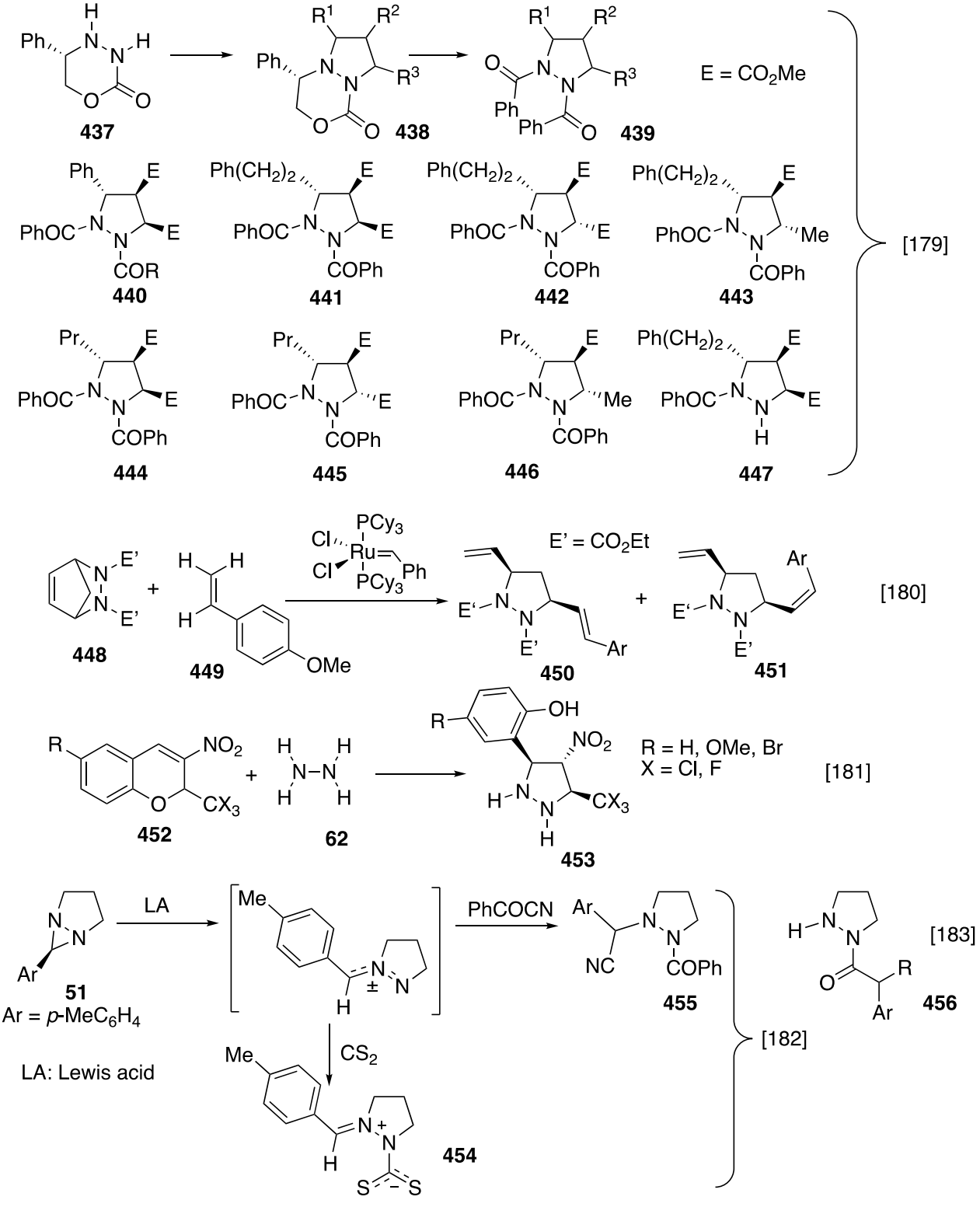
Scheme 23. Reduction of compound **432**, related to cation **385**, and zwitterion **434±**.

There is an example of reduction of a type **385** cation (Scheme 19) due to Kost (Scheme 23) **432 → 433**.[176] 2-[5,5-Dimethyl-3,3-bis(trifluoromethyl)-1-pyrazolin-l-ylio]-1,1,1,3,3,3-hexafluoro-propan-2-ide (**434±**) has been reduced by Burger[177]and by Tipping to pyrazolidine **435**, the radical **436** being postulated as intermediate (Scheme 23).[178]

4.6. Non-conventional methods

4.6.1. From other heterocycles. We have reported in Scheme 24 a series of syntheses leading to pyrazolidines that have been prepared from other heterocycles, excluding those obtained from other pyrazolidines that we will discuss in the reactivity section 5.

Based on the sequence **437** → **438** → **439**, a series of pyrazolidines **440** to **447** have been prepared.[179] The combination of a hetero-Diels–Alder reaction of **448** and **449** with ruthenium-catalyzed ring-opening cross metathesis (ROCM) renders new functionalized pyrazolidines **450** and **451**.[180] For the first time, *N,N'*-unsubstituted pyrazolidines **453** have been prepared reacting 3-nitro-2-(trichloromethyl)-2*H*-chromene (**452,** X = Cl) and 3-nitro-2-(trifluoromethyl)-2*H*-chromene (**452,** X = F) with hydrazine (**62**).[181]

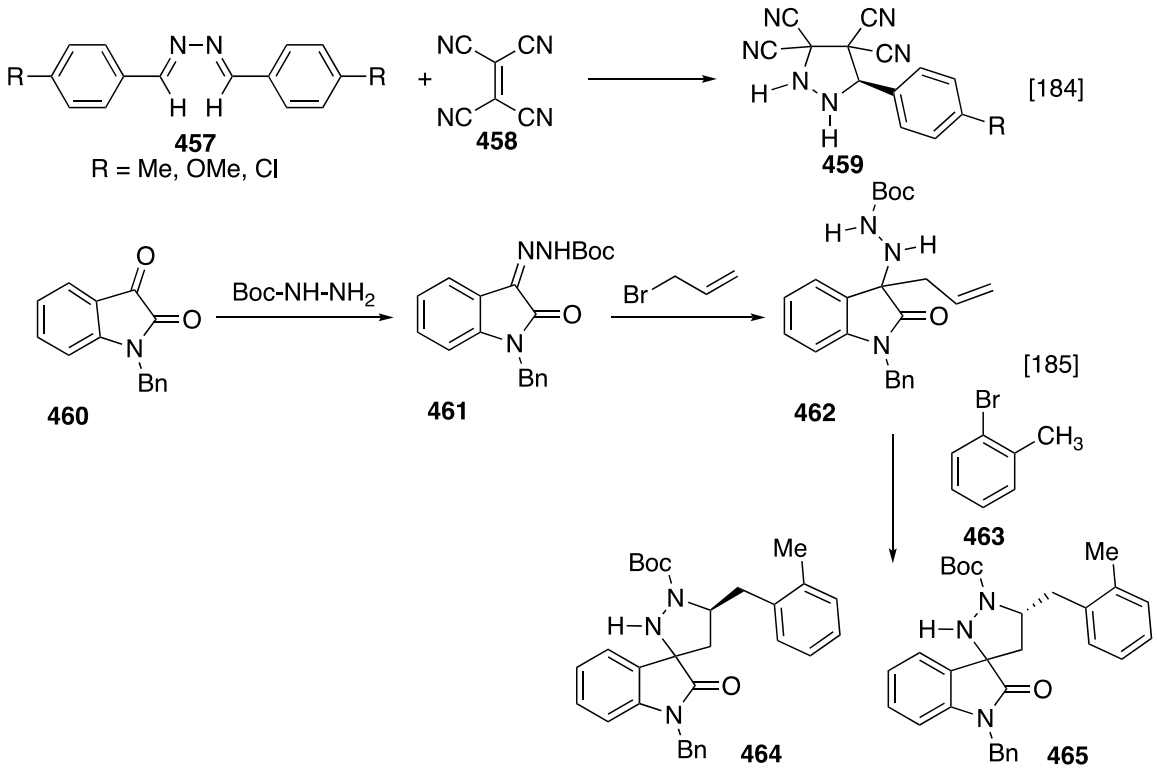


Scheme 24. Synthesis of pyrazolidines from other heterocycles.

Treatment of 6-aryl-1,5-diazabicyclo [3.1.0]hexane (**51**, Ar = *p*-MeC_6H_4) with Lewis acids affords an azomethine imine intermediate; *in situ*, reaction with carbon disulfide yields the inner salt **454.** Insertion of benzoyl cyanide affords pyrazolidines **455**;[182] a similar reaction leads to **456**.[183]

4.6.2. Other reactions. Scheme 25 corresponds to two synthetic approaches to pyrazolidines that are rather unusual. The reaction of benzaldehyde azines **457** with tetracyanoethylene (TCNE, **458**) yields a tetracyano

pyrazolidine **459** through a very complex and hypothetical mechanism.[184] Allylation of isatin **460**-derived *N*-Boc-hydrazones **461** to afford **462**, followed by a Pd-catalyzed carbo-amination reaction offers an entry to 3-spiro-pyrazolidyl-oxindoles **464** and **465**.[185]

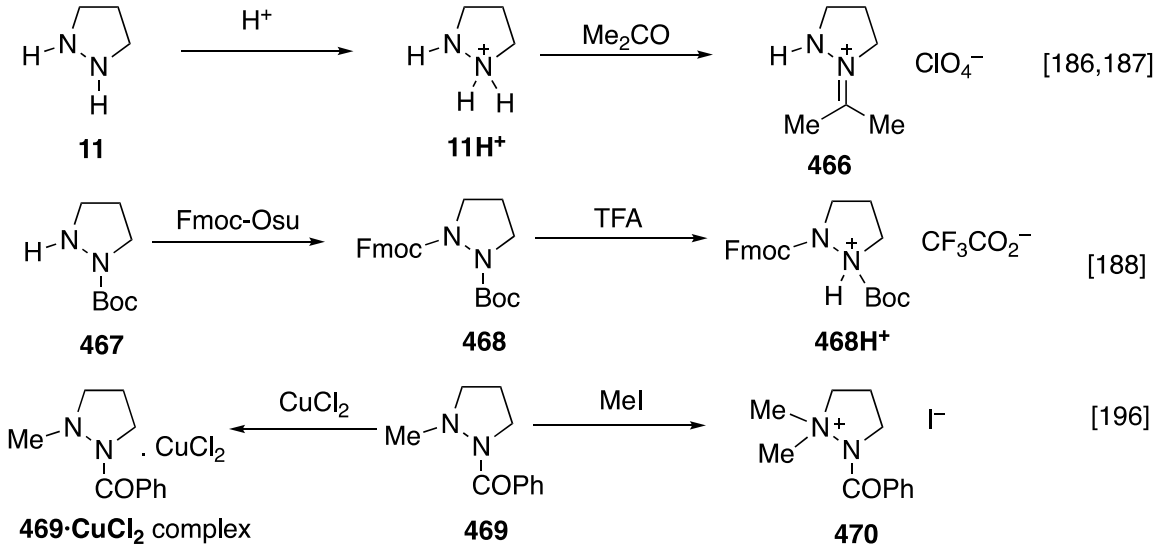


Scheme 25. Synthesis of pyrazolidines using non-conventional methods.

5. Chemical Properties and Reactivity

5.1. Protonation, basicity and quaternization

Protonation of pyrazolidines just poses a problem at the site when the molecule lacks symmetry; otherwise, the result is without ambiguity, as is the case of **11H**$^+$,[186,187] **23H**$^+$, **37H**$^+$ and **50** (Figure 3) as well as compound **306** of Scheme 14.[135] A series of protonated asymmetric pyrazolidines were prepared by treatment with HCl/AcOEt and characterized by NMR, but the protonation site was not determined.[56] Of similar structure to **306** was the pyrazolidine **468** prepared from **467** [Fmoc = 9-fluorenylmethoxycarbonyl; Fmoc-Osu = *N*-(Fmoc-oxy)-succinimide)]; in this case, the proton was attached to the NBoc, and ^{1}H and ^{13}C data were consistent with **468H**$^+$.[188] Acetone reacts with **11H**$^+$ to afford the pyrazolidinium salt **466**.[186] Inverse deprotonation reactions were reported by Hesse concerning pyrazolidine **286** (Scheme 13).[105]



Scheme 26. Protonation and quaternization of pyrazolidines.

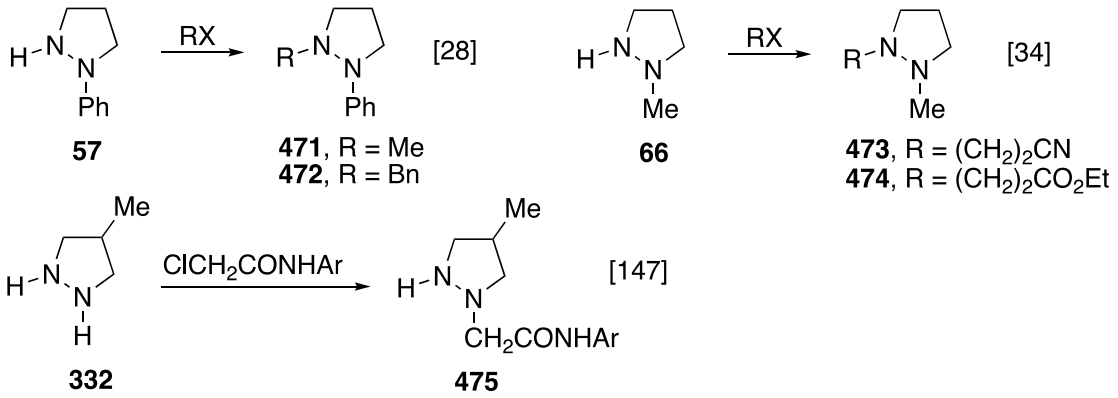
Pyrazolidines, being cyclic hydrazines, their basicity does not differ from that of these compounds, a fact that has resulted in a lack of interest to determine the pK_a of pyrazolidines. However, the ring hinders the rotation about the N-N bond, typical of hydrazines. Note that only the *gauche* conformation is a minimum on the rotational curve of hydrazine,[189,190] and few pyrazolidines can adopt such a structure. For instance, the dihedral angle between lone pairs of tetramethylhydrazine is 79º while that of pyrazolidine **12** is 12º.[191,192]

Two authors have reported the pK_as of hydrazines and pyrazolidine **11** at 25º (a)[193] and at 35º (b)[186]: hydrazine **62** 8.07 (a); 1,2-dimethylhydrazine **67** 7.52 (a), 7.32 (b); pyrazolidine **11** 7.60 (a), 7.25 (b). The hydrogen-bond acidity of 1-acyl-5-hydroxy-pyrazolidines like **122a** (Scheme 6a) and related compounds is similar to that of phenol.[194]

Quaternization of pyrazolidines has been reported in three papers, no α-effect was detected.[195] In the first one, quaternization of **469** took place on the *N*-methyl group **470** as expected.[196] In Figure 4 it was reported that in the methylation of 5-hydroxy-2-isopropylpyrazolidine-1-carbaldehyde (**162**) to **166**, again the isopropyl group was preferred to the formyl one.[82] In Scheme 14 there are also reported several quaternary salts but they were not prepared by quaternization.

5.2. Reactions on the nitrogen atoms

The alkylation of pyrazolidines is straightforward, some examples are reported in Scheme 27, from Michaelis in 1893 (**471** and **472**)[28] to Kornet in 1967 (**473** and **474**)[34] and 1969 (**475**).[147]



Scheme 27. Examples of *N*-alkylation of pyrazolidines.

Acylation (COMe, COR, COPh, COAr) of biochemical groups (Cbz, Boc), as well as tosyl and related groups, is very common, being one of the most studied reactions in pyrazolidine chemistry. Figure 8 reports the resulting compounds with the corresponding references.

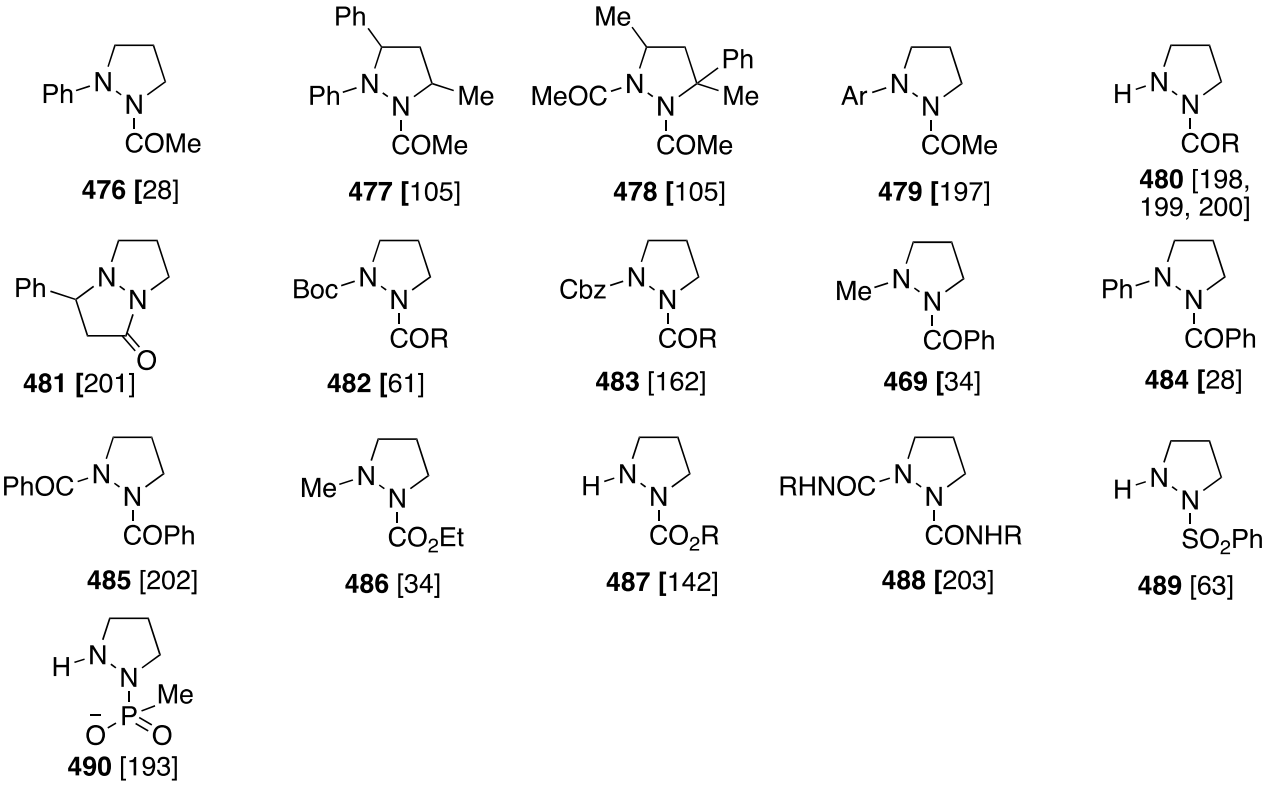
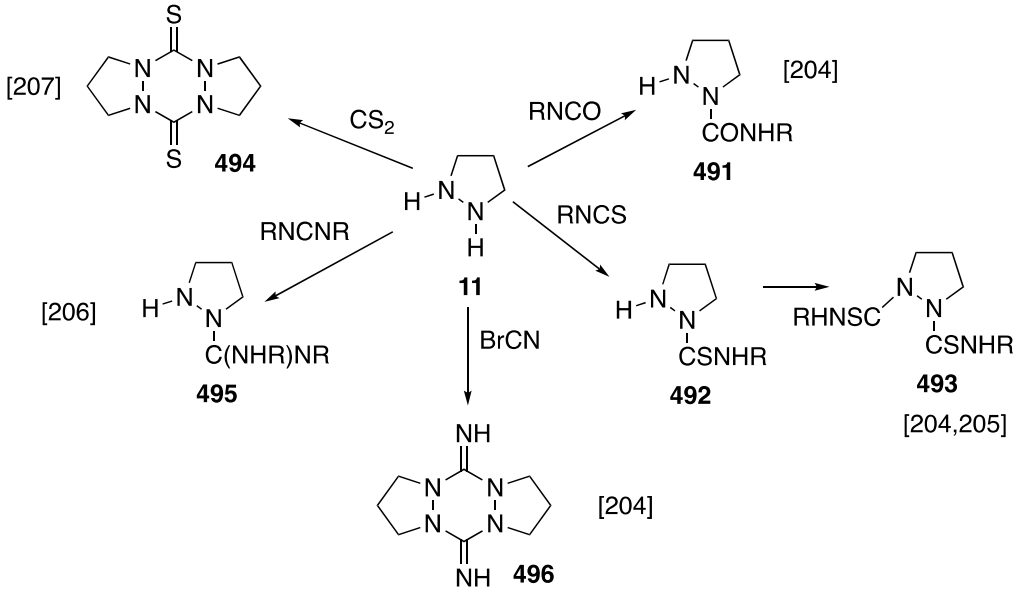


Figure 8. Acyl, tosyl and phosphinate derivatives.

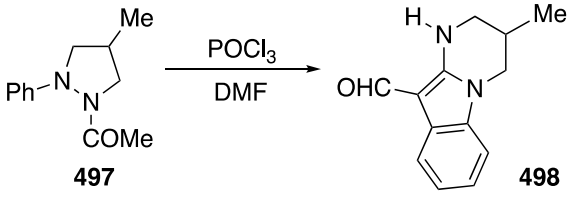
Examples of acetylation are compounds **476**-**479**,[28,105,197] and, of acylation, compound **480**,[198,199,200] including annelation leading to a bicyclic compound **481**.[201] Other results include peptidomimetics **482** and **483**,[61,162] benzoylation compounds **469**, **484** and double benzoylation **485**,[202] introduction of CO_2R groups using either ethyl chloroformate **486**[34] or 1*H*-imidazole carboxylates **487**,[142] introduction of CONHR groups using phosgene and heteroaryl amines (five- and six-membered rings) **488**,[203] tosyl **489**,[63] and phosphinyl groups **490**.[193]

Addition of pyrazolidines to a double bond of heteroallenes has been mainly studied by Morgenstern *et al*. who have prepared the compounds **491**-**496** (R = Me, CH_2=CH-CH_2, Ph, Ar, 1-naphthyl) (Scheme 28).[204,205,206] Reactions with other heteroallenes like isopropyl isocyanate,[55,56] cyclohexyl isocyanate,[142] and phenyl isothiocyanate,[207] have been reported.



Scheme 28. Addition of pyrazolidine **11** to isocyanates, isothiocyanates, carbon disulfide, carbodiimides and cyanogen bromide.

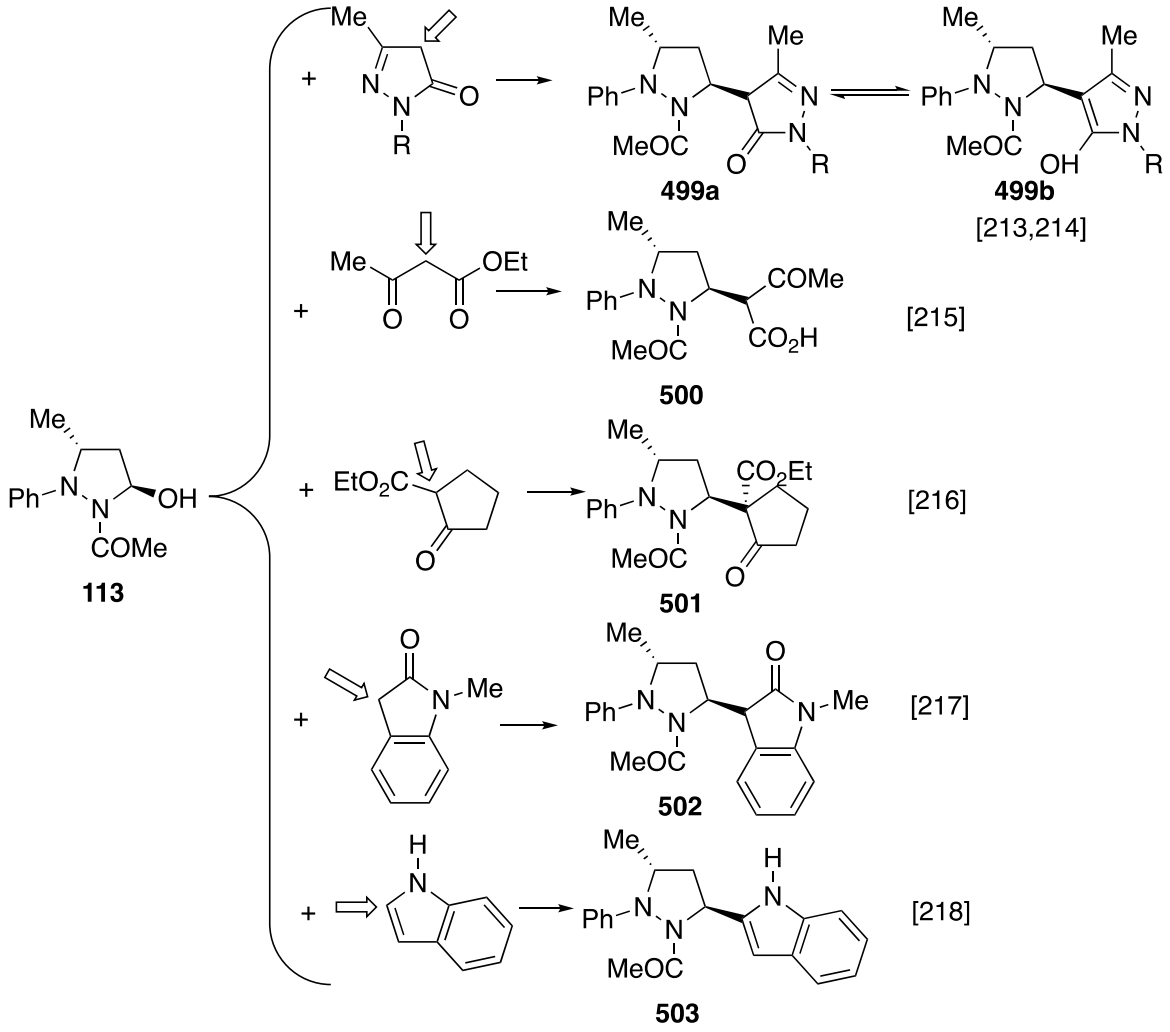
Related to these protecting groups are some deprotecting reactions. For instance, parent pyrazolidine **11** has been prepared by deprotection of diacyl-pyrazolidine CO-*i*-Bu,[53,186] and Boc.[60,62] It is possible to replace a protecting group by another, for instance, Alloc by Boc.[88] It has been shown by Kost *et al*. that *N*-acyl pyrazolidines **497** react with reagents such as $POCl_3$/DMF, called the Golubeva synthesis related to the Vilsmeier-Haack reaction,[66,208] to afford 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]indole-10-aldehyde (**498**) (Scheme 29), and related compounds.[209,210]



Scheme 29. Formation of indoles from *N*-acetyl pyrazolidines.

5.3. Reactions of the C-OH substituents and dehydration

There are two ways to transform OH to OR; the 4-hydroxypyrazolidines such as **36** are alkylated with alkyl halide to 4-alkoxypyrazolidines.[49] Treatment of the dihydroxy derivative **91** (Scheme 3) with acetyl anhydride yields a di-O-Ac compound.[52] On the other hand, 3-hydroxypyrazolidines react with alcohols to afford 3-alkoxypyrazolidines.[148,211] 5-Hydroxy and alkoxy groups can be replaced by amino,[211] hydrazino,[81] and hydrazido groups (Scheme 6a).[71] Particularly interesting is the reaction with *D*-tryptophan ethyl ester.[212]

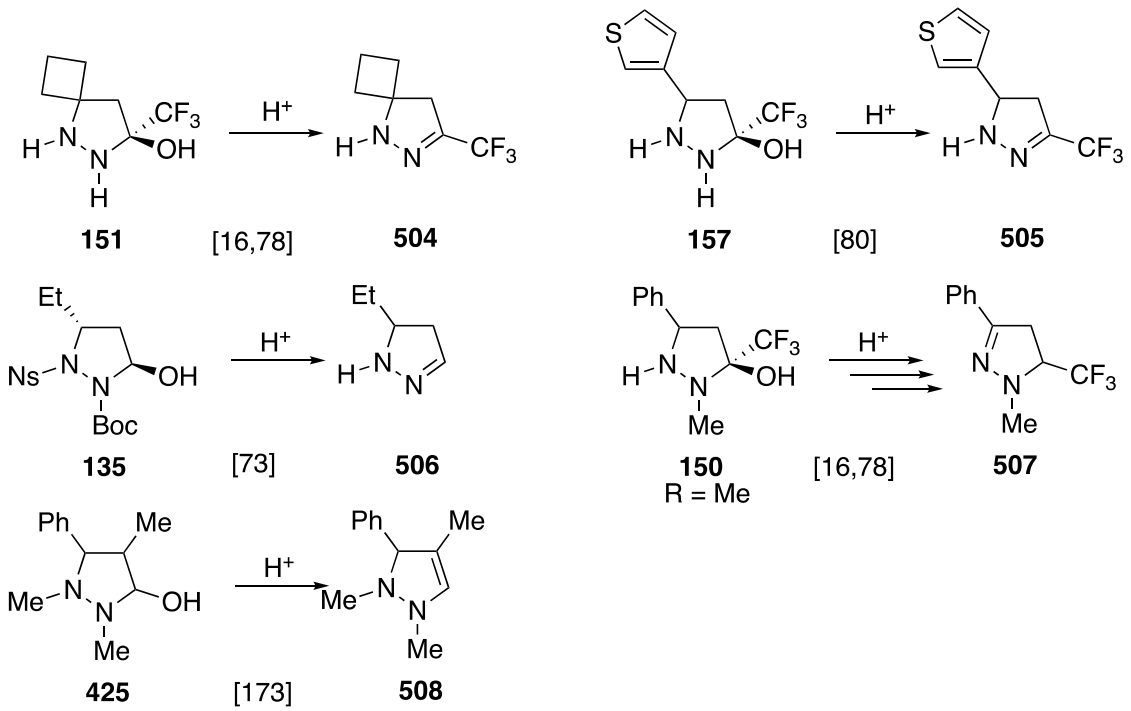


Scheme 30. Reaction of 5-hydroxypyrazolidine **113** with activated sp^3 carbon atoms.

More original is the replacement of the OH groups by both sp^3 and sp^2 C atoms. Examples of the sp^3 class are represented in Scheme 30. 5-Hydroxypyrazolidine **113** reacts with pyrazolinones to yield dimers **499** that exists as a mixture of tautomers **a** and **b**[213]; other pyrazolinones behave similarly.[214] The same compound reacts with ethyl acetoacetate to afford compound **500**.[215] Similarly, using ethyl-2-oxocyclopentane-1-carboxylate, compound **501** was obtained.[216] Finally, **113** reacts with 1-methylindolin-2-one to yield **502**.[217]

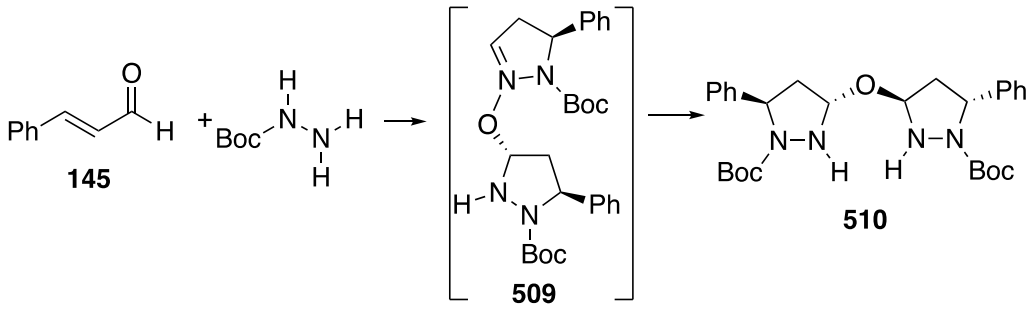
Rarer are reactions involving sp^2 carbon atoms One example is that of **113** reacting with the parent indole (other indoles and other 5-hydroxypyrazolidines were also studied) to afford **503**.[218]

Dehydration of 3- and 5-hydroxypyrazolidines to pyrazolines is an acid-catalyzed process where the OH group is protonated and leaves as water assisted by the adjacent N atom; the reason why 4-hydroxy-pyrazolidines are stable. The reaction is so easy that the CF_3 group is often necessary to isolate the hydroxypyrazolidine. Several examples are gathered in Scheme 31.



Scheme 31. Pyrazolines from hydroxypyrazolidines.

When the hydroxypyrazolidine has no substituents on the nitrogen atoms, the reaction proceeds smoothly, e.g., the syntheses of **504** and **505**.[16,78,80] The same happens if one of the substituents is easy to remove, as in the case of Boc, compound **506**.[73] If the N atom adjacent to the OH group is substituted, **150** (R = Me), then the 2-pyrazoline **507** resulted after several double-bond migrations.[16,78] Finally, *N,N'*-disubstituted compounds like **425** lead to the 3-pyrazoline **508**.[173]



Scheme 32. Hydroxypyrazolidine dimer.

Córdova *et al*. reported an interesting behavior of complex **509** formed by the reaction of **145** and Boc-NH-NH_2 (already used in Scheme 25, but not isolated) that, through an OH addition to a sp^2 carbon atom, dimerizes to **510** (Scheme 32).[75]

5.4. Reactions of substituents on the carbon atoms of the pyrazolidine ring

These reactions correspond to classical organic chemistry and will be illustrated with a few cases exemplified in Figure 9.

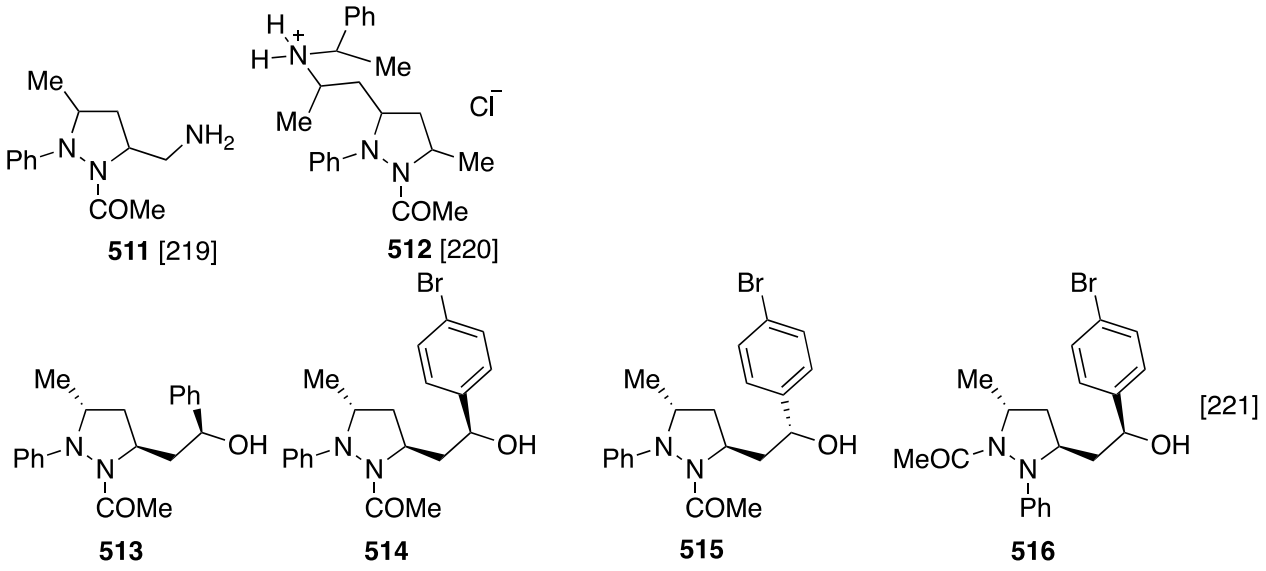


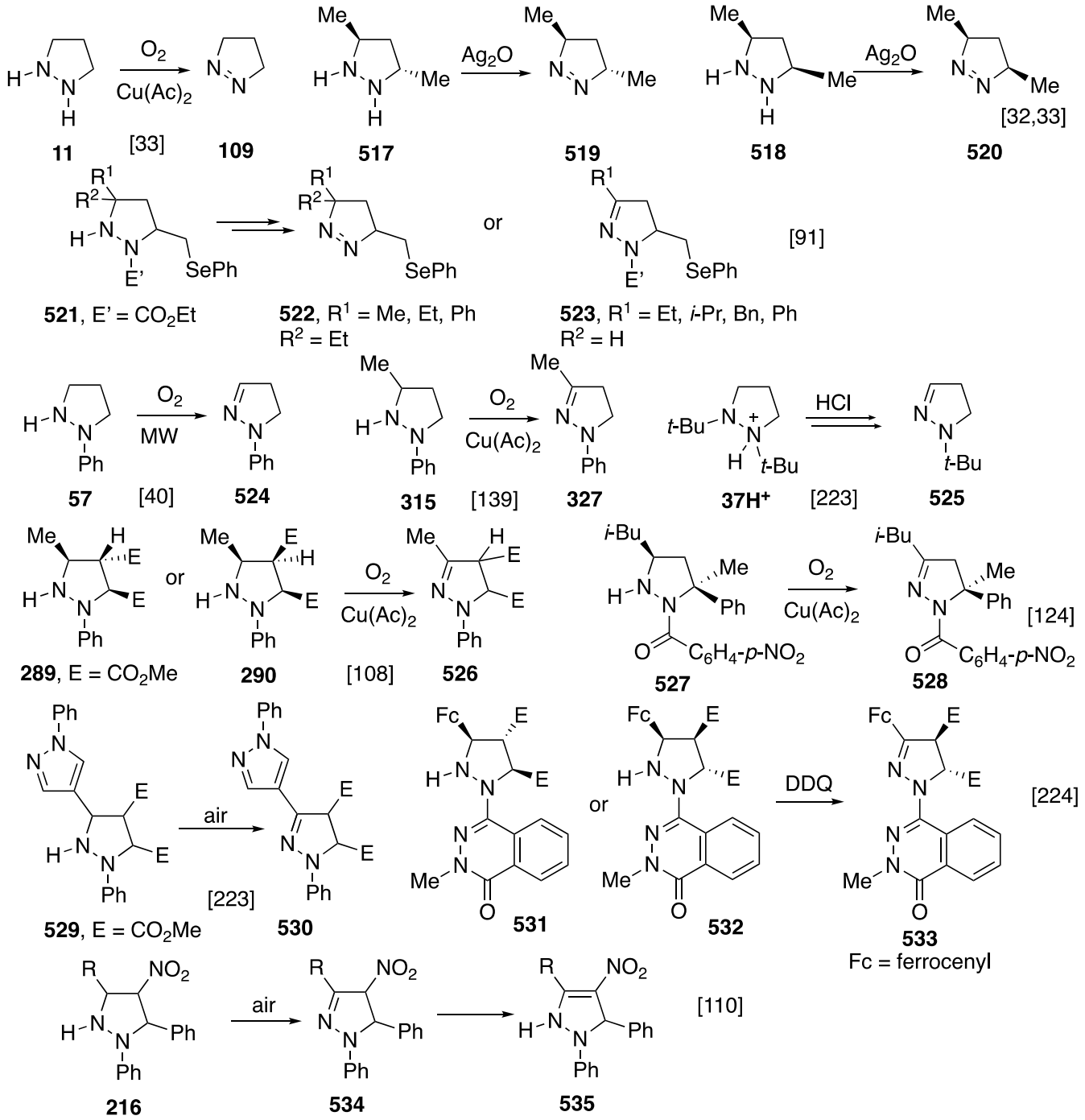
Figure 9. Some examples of pyrazolidines obtained by reaction of substituents.

Compound **511** was prepared by reduction of the corresponding nitro derivative.[219] The reduction of 3-CH_2COMe with sodium triacetoxy borohydride or sodium tripivalyloxy borohydride affords **512** that was isolated as a hydrochloride and its structure determined by X-ray crystallography.[220] Pyrazolidines **513**-**516** were prepared by the same group of authors by the reduction of the corresponding carbonyl compounds with $NaBH_4$ or $LiAlH(OBu)_3$; their structures were determined by X-ray crystallography to establish their relative *R,S*-configuration.[221] They summarized these and similar results in a subsequent work.[222]

5.5. Oxidation

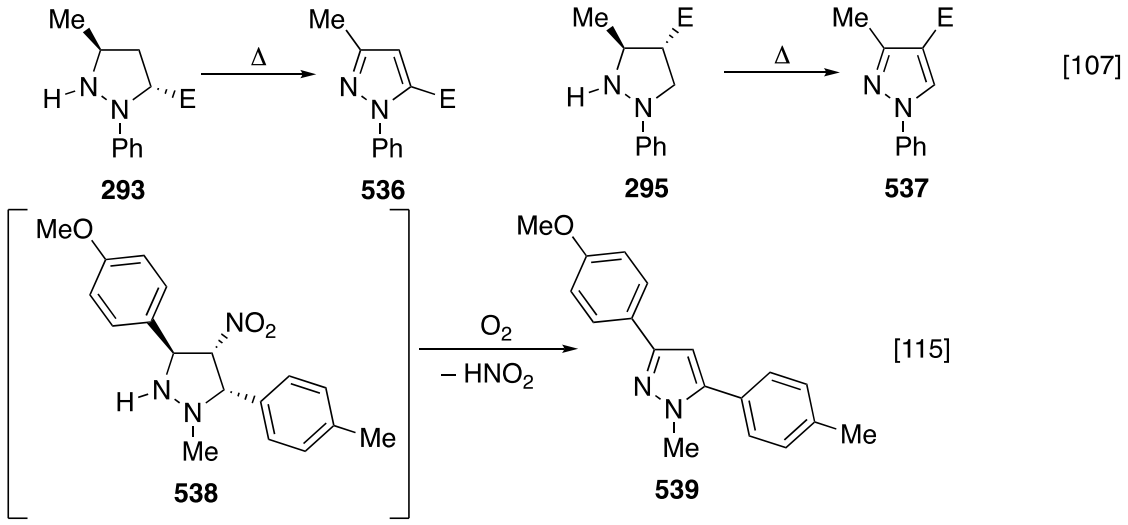
This section reports reactions that are the opposite of those discussed in Sections 4.4 and 4.5. We will start with the oxidation of pyrazolidines to pyrazolines (Scheme 33). Oxidation to 1-pyrazolines requires both nitrogen atoms of the pyrazolidine to be unsubstituted, e.g., **11, 517** and **518** to afford 1-pyrazolines **109**,[33] **519** and **520**,[32,33] or the substituents easy to remove, e.g., the ethoxy carbonyl group of **521**, depending on the experimental conditions, is eliminated giving **522** or not, yielding **523**.[91]

Oxidation to 2-pyrazolines requires that at least one N atom remains unsubstituted, as was the case for **57**, **315**, **289**/**290**, **527**, **529, 531/532** which were transformed into pyrazolidines **524**,[40] **327**,[139] **526**,[108] **528**,[124] **530**,[223] and **533,**[224] respectively. In the last example, due to the presence of a strong withdrawing group, NO_2, the reaction proceeds from **216** to the 2-pyrazoline **534**, that then tautomerizes to the 3-pyrazoline **535**.[110]



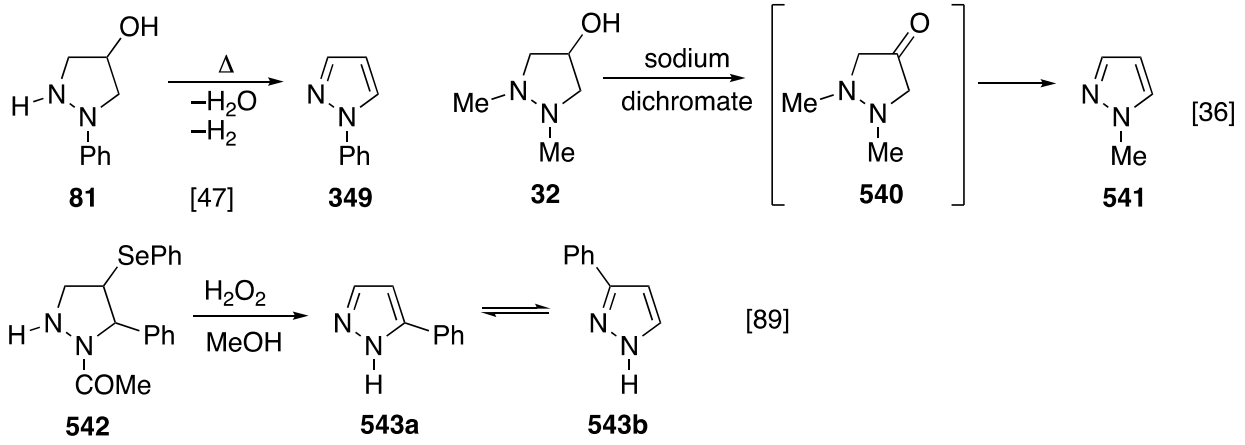
Scheme 33. Oxidation of pyrazolidines to pyrazolines.

Although the oxidation of pyrazolidines to pyrazoles occurs via pyrazolines in a two-step process, in some cases, the oxidation directly renders pyrazoles (Scheme 34). Hamelin *et al*. reported the formation of pyrazoles **536** and **537** in the synthesis of intermediates 2-pyrazolidines **293** and **295**, respectively.[107] Compound **538** was stable under N_2 but, otherwise, it is oxidized to pyrazoline (not isolated) that loses HNO_2 to yield pyrazole **539**.[115]



Scheme 34. Pyrazoles from pyrazolidines (E = CO_2Me).

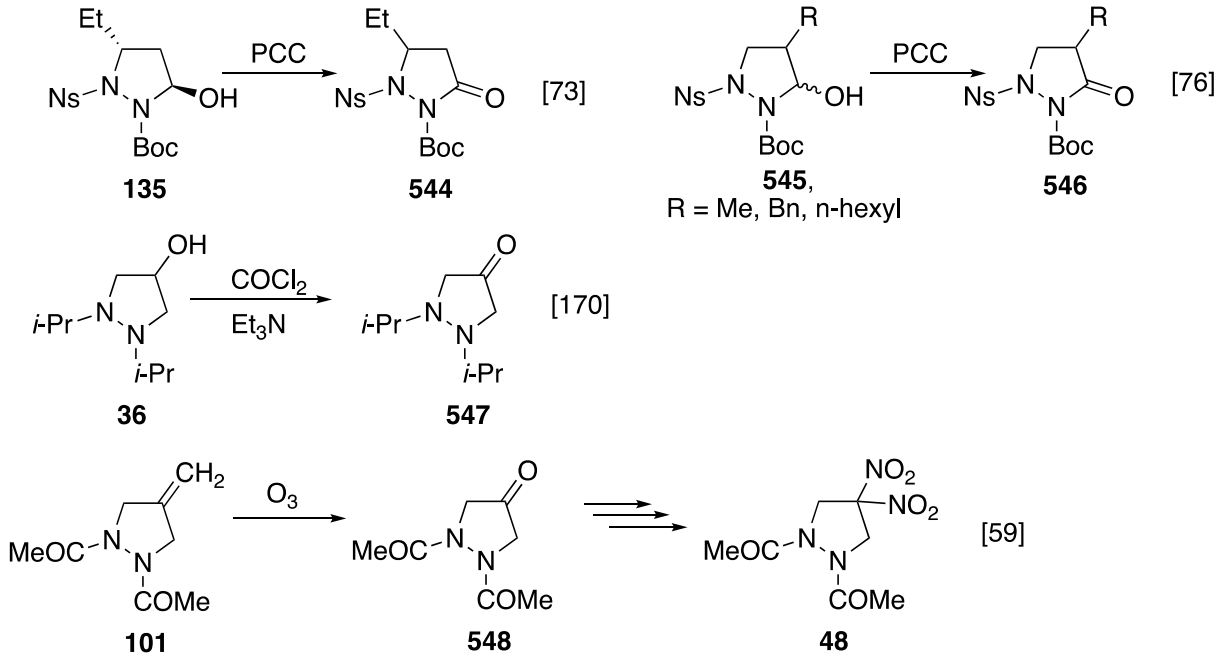
4-Hydroxypyrazolidines (Scheme 35) are oxidized to pyrazoles as in the **81** to **349** process.[47] The oxidation of **32** to 1-methyl-1*H*-pyrazole (**541**) involves presumably the 1,2-dimethyl-4-pyrazolinone (**540**)[36]



Scheme 35. Oxidation of 4-hydroxypyrazolidines to pyrazoles.

A quantitative conversion of **542** into **543** (two tautomers) was obtained by oxidation with hydrogen peroxide in methanol.[89]

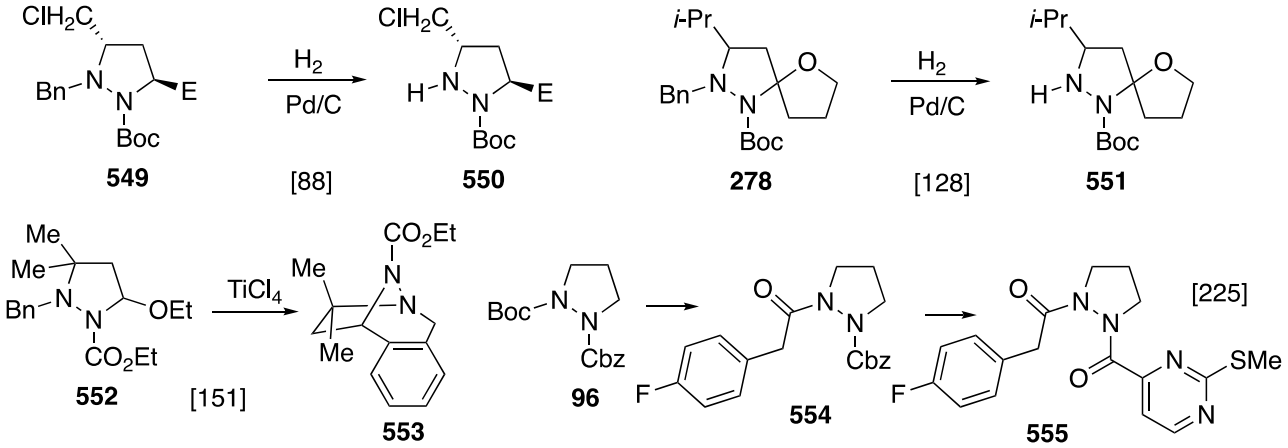
The inverse reaction to the synthesis of pyrazolidines by reduction of pyrazolidinones (Section 4.3.b) is the C-OH to C=O oxidation (Scheme 36). Different oxidizing agents have been used to carry out this reaction, PCC for **135** → **544**[73] and **545** → **546**,[76] and $COCl_2$ for **36** → **547**.[170] The vinyl group of **101** was oxidized with ozone to **548**; this compound was the precursor of **48**.[49]



Scheme 36. Oxidation of OH and C=C groups to pyrazolidinones.

5.6. Reactions of *N*-substituents

This is a very common reactivity in heterocyclic compounds and only four examples will be given in Scheme 37.

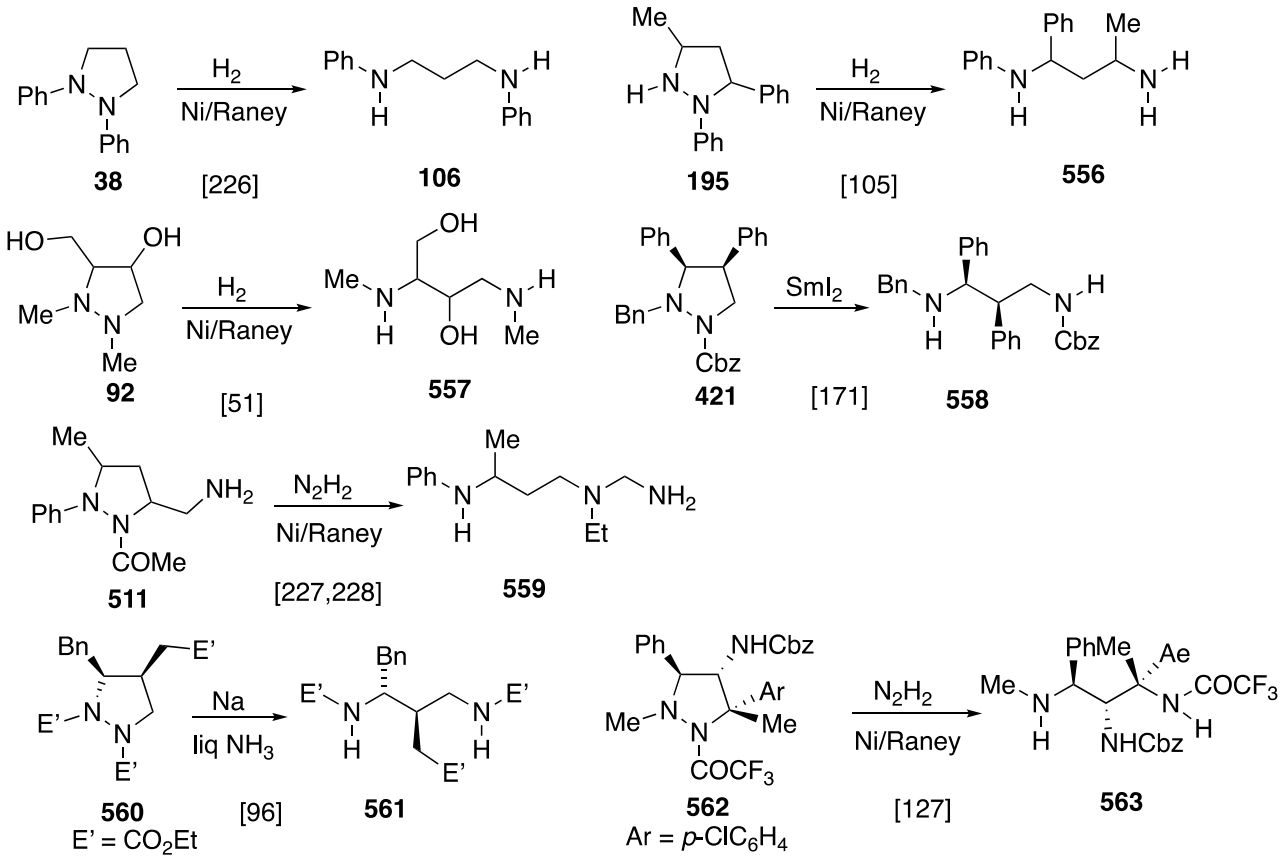


Scheme 37. Reaction of *N*-substituents.

The art of using protecting groups is exemplified in the reactions **549** → **550**[88] and **278** → **551**.[128] A bicyclic system that also involves the removal of a benzyl group was the result of treating **552** with titanium chloride to yield **553**.[151] Pyrazolidine **96** treated with two different acyl chlorides yielded first **554** and then **555**.[225]

5.7. Reduction to diamines: N–N bond breaking and ring opening

This reaction is the inverse of the synthetic method reported in Section 4.1.2. It constitutes one of the best ways to prepare 1,3-diaminopropanes **106**, **556**-**559**, **561** and **563** (Scheme 38). Hydrogen in the presence of Ni Raney was used for pyrazolidines **38**,[226] **195**,[105] **92**[51]; hydrazine over Ni/Raney for pyrazolidines **511**,[227,228] **562**;[127] samarium(II) iodide, **421**;[171] and sodium in liquid ammonia for **560**.[96]



Scheme 38. Synthesis of 1,3-diaminopropanes.

5.8. Ring-chain tautomerism

3- or 5-Hydroxy or amino pyrazolidines always exist in equilibrium with open-ring structures having a carbonyl or an imino terminal bond; the position of the equilibrium depends on the substituents and on the media. Examples of these equilibria were reported in Schemes 6a,[77,72] and 17.[141] Most publications reporting these ring-chain equilibria were due to Zelenin and coworkers such as Golubeva and Sviridova.[229,230] In their last paper, a detailed discussion of solvent effects on the equilibrium and the *E/Z* equilibrium, in the case of imines, was reported.[230]

6. Structure, Spectroscopic and Physical Properties

Spectroscopic methods, in particular NMR and IR, but also, in former times, UV, are an essential part of most organic chemistry papers. Regarding pyrazolidines, in general, such methods are never used to identify new compounds and consequently, they will not be exhaustively commented upon.

The advances in these techniques and eventually the use of theoretical methods render the information provided by them, usually in the experimental part of the manuscript, of little use. When they prove interesting *per se* they will be cited, especially the use of ^{1}H NMR, for studying dynamic processes will be discussed in detail in Section 6.10 “Conformational analysis and nitrogen inversion”. Note that there are no ^{15}N NMR data.

6.1. UV spectra

As for their UV spectra (ethanol 95), pyrazolidines of Schemes 16 and 22 are divided into two groups, depending on whether there are methyl or phenyl groups fixed on the nitrogen atoms. In the first case, 1,2-dimethylpyrazolidines, whatever the nature of the substituents in position 3 and 5, the spectra have an ending absorption around 220 nm; those C-arylated, present phenyl bands in the 250 nm region. In the second case, 1-phenyl-2-methylpyrazolidines, a similar spectrum is always observed: an inflection point in the 230 nm region (ε ~ 3000) and a peak around 275 nm (ε ~ 5000); these data are similar to those of phenylhydrazine, 241 nm, ε = 1600, 283 nm, ε = 9300.[172] Some papers where UV data are reported can be found in references.[81,141,173,174]

6.2. ESR and PES spectra

Nelsen *et al*. reported the electron spin resonance (ESR) spectra of the radical cations of pyrazolidines **23**, **33** and **34**, giving ESR splits in gauss (G) at room temperature.[231] In another work of the same year, they added the parent compound **11** and 1,2-dimethyl-4,4-diethylpyrazolidine **564** (Figure 10).[232] In this last work, they use the ESR data to deduce the *trans* conformation of these pyrazolidines, but in two different dispositions of the NR groups.

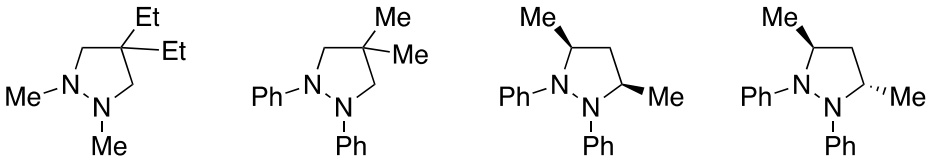
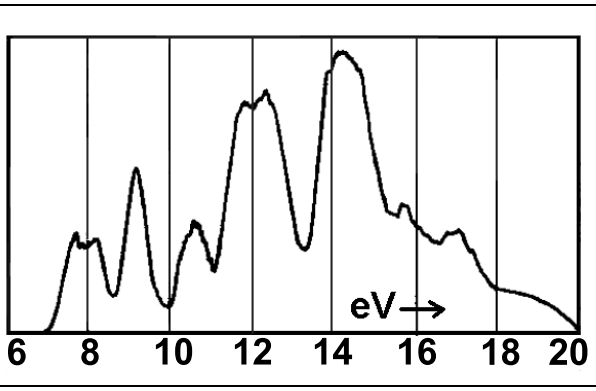


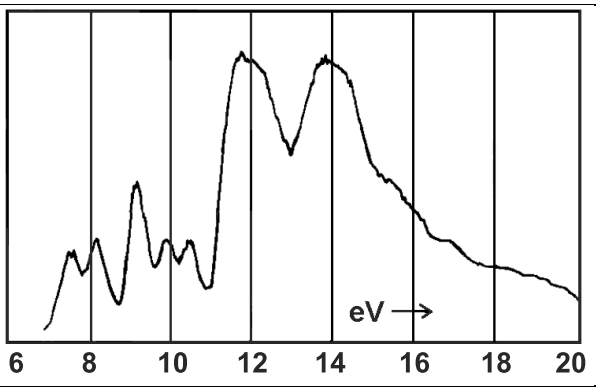
Figure 10. ESR spectroscopy. The phenyl substituents of compounds **566** and **567** are 2,5-dideuterium substituted.

A subsequent publication on the ESR spectra of pyrazolidines **38**, **565**-**567** use the data on the corresponding radical cations, hyperfine splits (*g*) to discuss their ring inversion.[233] Replacement of H3/H5 protons by methyl groups, **566**$^{\bullet+}$ and **567**$^{\bullet+}$, yields 1:2:1 triplets for the remaining H4 protons; however, there are different values for the time-averaged splittings, 13.85 G for the *cis* isomer **566**$^{\bullet+}$ and 11.70 G for the *trans* isomer **567**$^{\bullet+}$. The larger proton splitting of **566**$^{\bullet+}$ probably indicates that the steric interactions between the 3 and 5-methyl groups with the phenyl substituents force them into positions with more pseudoequatorial character.

Although entirely different, we report also the work of Rademacher *et al*., on the use of photoelectron spectroscopy (PES) in the ultraviolet region (UPS) to study 1,2-diphenylpyrazolidine (**38**) **in** comparison to 1,2-diphenylhydrazine (**58**), Figure 11.[234]



1,2-diphenylhydrazine (**58**)



1,2-diphenylpyrazolidine (**38**)

Figure 11. Modified from a picture of reference.

A similar picture of the n/π ionization bands can be found in the case of 1,2-diphenylpyrazolidine (**38**). However, the band splits are somewhat smaller. Accordingly, this is also possible that the ϕ angle has a slightly smaller value (this angle is defined as the lone pair–N–N–lone pair torsion angle, see section 5.1). This agrees well with a bisected position of the phenyl groups on an only slightly twisted five-membered ring corresponds to ϕ ≈ 130". This conclusion is consistent with that reported in section 6.10.

6.3. IR spectra

Simple pyrazolidines have no interesting bands save the OH and NH stretching ones. The most interesting are the compounds of section 5.8, which present ring chain tautomerism, because, in the open ring compounds, there is a C=O band (in the case of aldehydes at 1718 cm^{-1}, **127b,** Scheme 6a), and in the ring tautomers this band is absent.[79,141,229]

6.4. ^{1}H NMR spectra

From one of the pioneer publications in 1963[52] to the most recent ones in 2024,[235] the use of ^{1}H NMR spectroscopy has evolved considerably. In older times, the structural use of ^{1}H-^{1}H spin-spin coupling constants, SSCC, needed precise measurements of them that, in turn, required a careful analysis of the system that can be complex in molecules with multiple spin systems. Today, this is no longer the case and very few publications report rigorous analyses.

6.4.1. Ring-chain equilibrium. This fundamental question for the behavior of 3- or 5-hydroxy substituted pyrazolidines has been discussed in sections 4.1.c (**122a/b**, **124a/b**, **127b**), 4.3.b (**328a/b**) and 5.8 and will be discussed again in section 6.5.1. ^{1}H NMR is the method of choice to study these equilibria because tautomers are easily identified, and the equilibrium constant is easily measured.

6.4.2. Dynamic aspects: conformation and tautomerism. Finocchiaro *et al*. reported results on 1,2-diacylpyrazolidines **42** (Figure 3), **94a** and **94b** (Scheme 4) based on ^{1}H DNMR that will be discussed in detail in section 6.10 together with their dipole moments studies of section 6.7.[237] The tautomerism between a pyrazolin-5-one and a 5-hydroxypyrazole was studied by ^{1}H NMR, the hydroxy tautomer being predominant.[213,214]

6.4.3. Pyrazolidines bearing fluorine substituted groups. In the complex field of pyrazoles (Figure 1), pyrazolidines occupy a small space; surprisingly the number of pyrazolidines bearing substituents of the CF_3 type and higher perfluorinated alkanes, like C_2F_5, are relatively much higher. This is probably related to the synthetic methods used to prepare pyrazolidines compared to more oxidized derivatives.

Some examples are depicted in Figure 12. Both isomers of **170** are easily distinguished because, in the *cis* isomer, the protons H_A and H_B of the CH_2 group at position 4 are diastereotopic, while in the *trans* isomer, they are enantiotopic.[85]

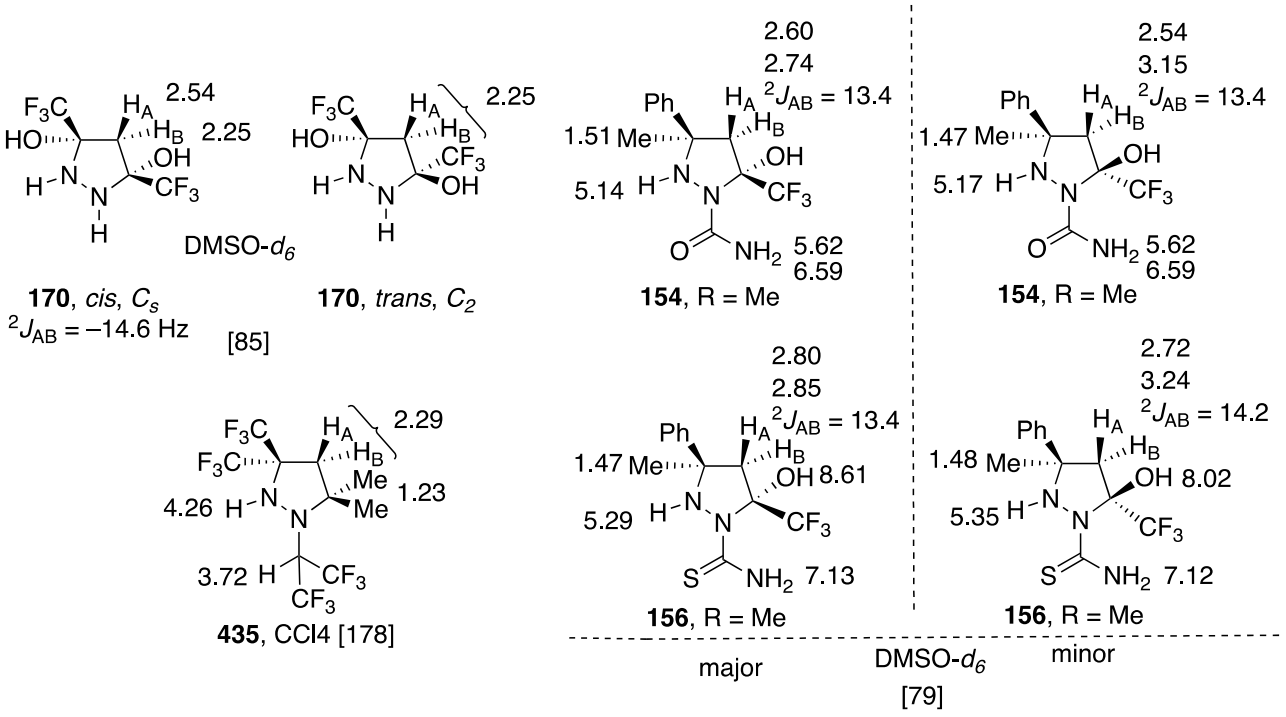


Figure 12. Some ^{1}H NMR data of fluorinated pyrazolidines.

Major and minor isomers of the series **154** and **156** were assigned using ^{1}H NMR and crystallography (FANXUN, cf. section 6.9)[79]; compound **435** shows a spectrum consistent with its symmetry.[178] Other compounds previously described also have CF_3 substituents, and their ^{1}H NMR spectra have been reported in the corresponding publications: **167**,[83] **168**,[84] **170**-**173**,[86] and **435**.[178]

6.4.4. Some interesting molecules. We have selected six pyrazolidines in Figure 13 due to the interest of their ^{1}H NMR chemical shifts and coupling constants. Besides the parent pyrazolidine **11**, a complex six-spin system that was not rigorously analyzed,[201] 1,2-dimethyl-4-hydroxypyrazolidine (**32**) where the ABX was analyzed,[36] and the spiranic ring **69** with its very simple spectrum[35] are shown.

Compound **119** shows in both *N*-substituents the effect of the chirality of the C-5 carbon atom on the diastereogenic character of the methylene protons that become AB on the benzyl and ABX_3 on the ethyl group.[71] Another spiranic pyrazolidine **388**[159] and a zwitterion **454** were also selected in Figure 13.[182]

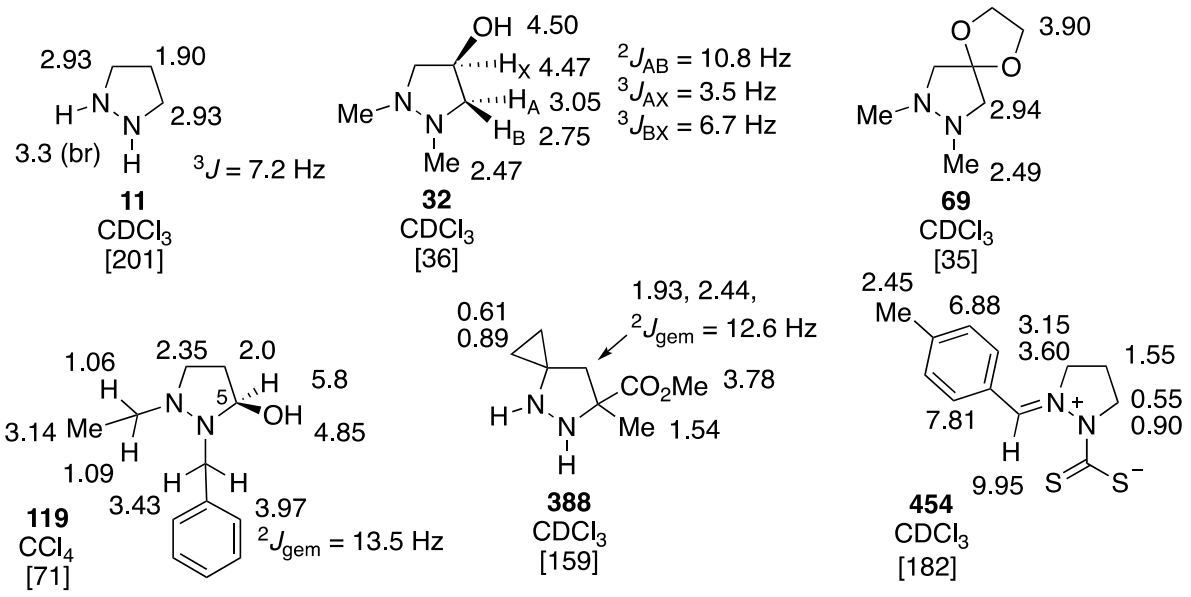


Figure 13. ^{1}H chemical shifts of some interesting molecules.

6.4.5. Some useful methods. Two methods have been used to determine the stereochemistry of 3,4 or 4,5-disubstituted pyrazolidines: the vicinal $^3J_{HH}$ SSCC because the *trans* is always larger than the *cis* (see, for instance, compound **32** in Figure 13), and Nuclear Overhauser Effect (NOE) proximity effects or the more modern NOESY version. This has been the case for compound **568**, closely related to **403**,[163] **407** (after transformation into a bicyclic structure **569** by reaction with benzyl chloroformate and tetra-butyl ammonium chloride),[164] and **410**.[165]

More detailed experiments showed how powerful this technique is when used for compounds **248**[118] and **570**.[236]

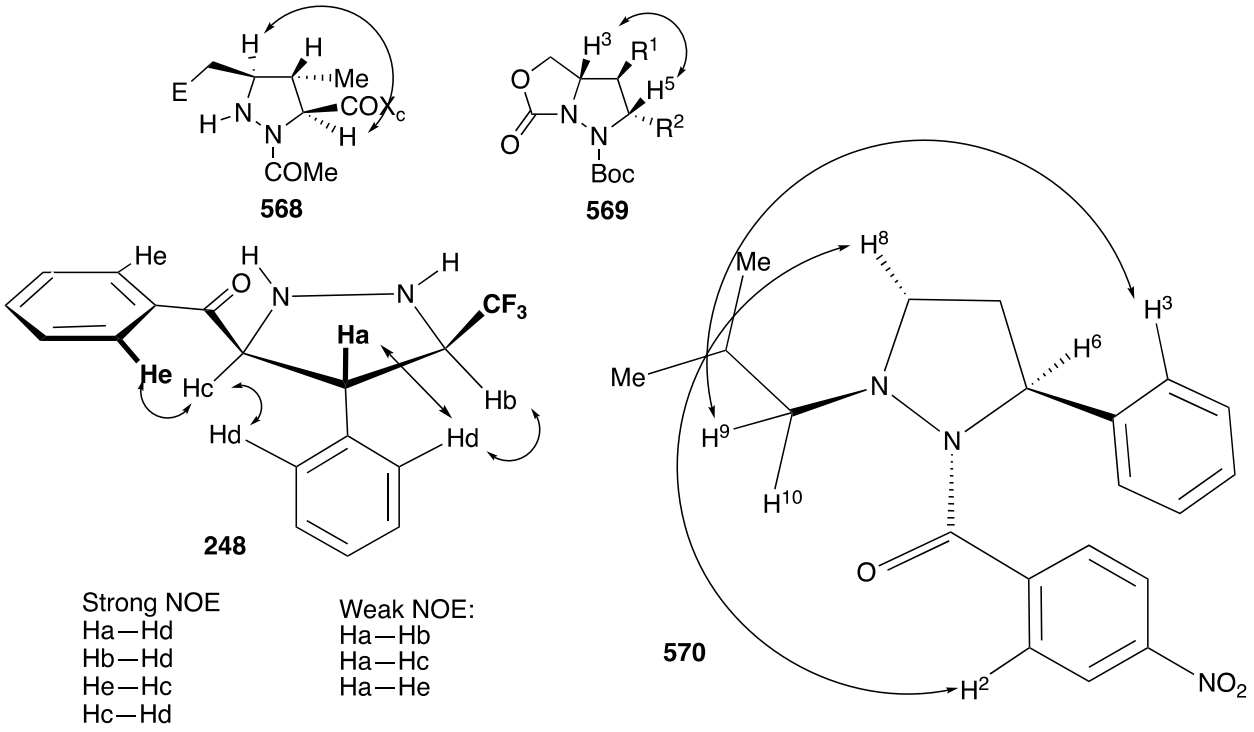


Figure 14. NOE experiments.

6.5. ^{13}C NMR spectra

We will consider four cases, leaving aside papers where ^{13}C NMR was used only as a property of the compounds, often without assigning the signals: a) ring-chain equilibrium; b) dynamic aspects (conformation and tautomerism); c) ^{13}C-^{19}F SSCC; d) some interesting molecules.

6.5.1. Ring-chain equilibrium. Although the C=O signal of **b** tautomers is different in aldehydes, ketones, esters and amides, it differs considerably in all cases from that of the C-OH group of the hydroxypyrazolidine, **a** tautomer. Besides if offers a way, taking some precautions, to determine the equilibrium by integration of the signals of both isomers.[71,216,229]

6.5.2. Dynamic aspects: conformation and tautomerism. Finocchiaro *et al*. reported in 1977 a study of the conformation of diacylpyrazolidines **42**, **94a** and **94b** that is consistent with the results obtained using dipole moments (Section 6.7) and ^{1}H DNMR (section 6.4.2).[237] Compounds **179a** and **179b**, Scheme 8, show in ^{13}C NMR broad signals for the gem-dimethyl groups at position 3, this observation was related to their ^{1}H NMR spectra.[90] The stereochemistry of compounds **407**/**408**, Scheme 20, was determined by several methods including ^{13}C NMR.[164] Although not directly related to the properties of pyrazolidines, the oxo/hydroxy prototropic tautomerism **499a**/**499b** (Scheme 30) was studied by ^{13}C NMR.[213]

6.5.3. ^{13}C-^{19}F SSCC. Pyrazolidines bearing groups with fluorine substituents, mainly CF_3, present interesting ^{13}C-^{19}F coupling constants.[79,121]

6.5.4. Some interesting molecules. We have gathered in Figure 15 four interesting molecules whose structures have been determined by ^{13}C NMR spectroscopy.[201,59,182,184]

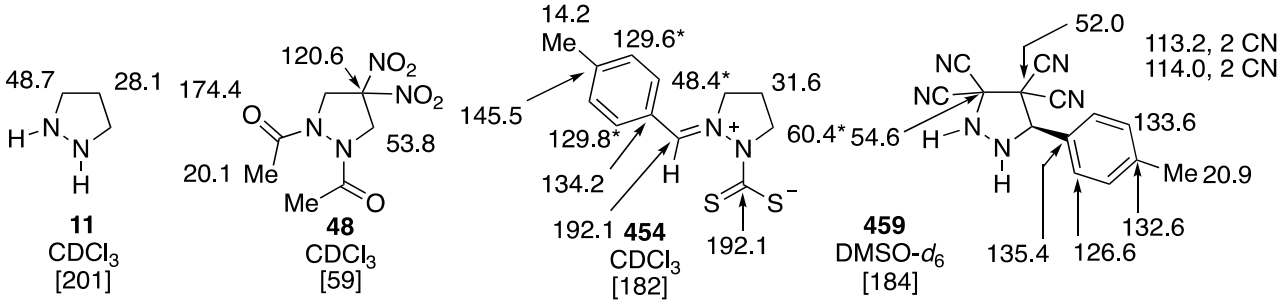


Figure 15. ^{13}C chemical shifts of some interesting molecules.

6.6. ^{19}F NMR spectra

In the year 2000, Coe *et al*. reported the NMR spectra of 5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolidin-3-ol (**167**), both ^{1}H and ^{19}F in $CDCl_3$.[83] Four of the five ^{19}F signals were not assigned, only that of the CF_2 was assigned at –111 ppm, Figure 16. No decimal figures were given indicating that the signal was large. In molecule **167**, all the carbon atoms were stereogenic; in the case of C5, that implies that the F atoms of the CF_2 group of the C_2F_5 group are anisochronous and enantiotopic; therefore, they appear as an ab system with a $^{2}J_{FF}$ geminal coupling constant. this, added to $^{3}J_{FF}$ couplings with the adjacent CF_3 group and $^{4}J_{FF}$ couplings with the CF_3 on C4, yield a very complex system for each fluorine atom that results in a broad signal. Important to note that none of the remaining signals appear split, indicating that **167** is not a mixture of compounds.

Thanks to GIAO calculations all the signals were assigned and the structure of the compound determined: it corresponds to the 3S,4*R*,5R, Figure 16.[238]

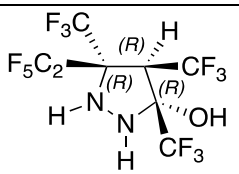
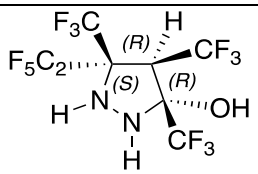
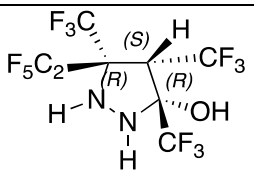
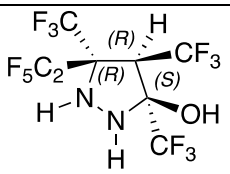
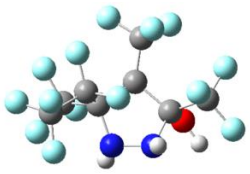
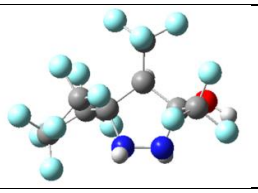
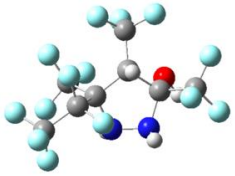
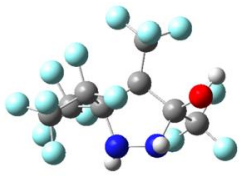
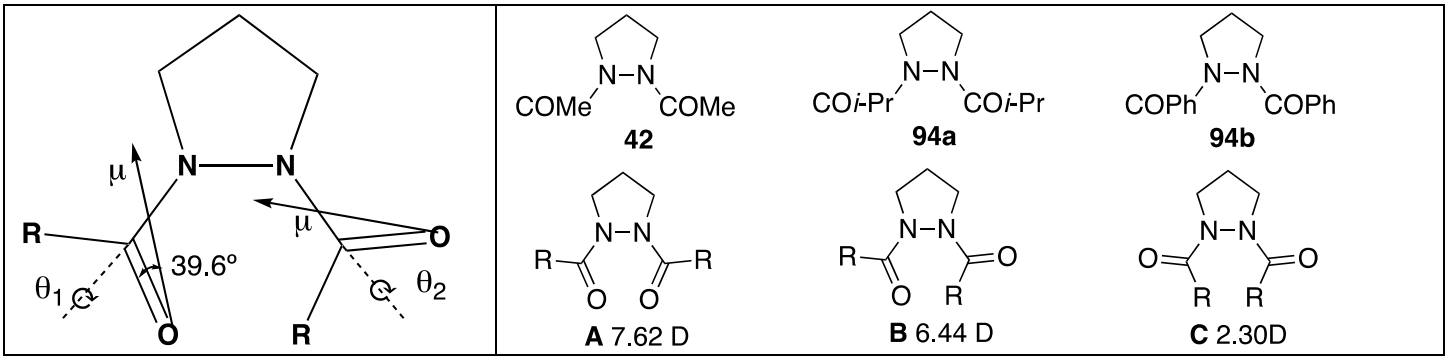
			
RRR	*RRS*	*RSR*	*SRR*
13.5 kJ·mol^{-1}	8.4 kJ·mol^{-1}	0.0 kJ·mol^{-1}	0.1 kJ·mol^{-1}
			

Figure 16. The four isomers of 5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolidin-3-ol (**167**).[238]

There are data on ^{19}F NMR on compound **168** (Figure 4)[84] and on compound **435** (Scheme 23).[178]

6.7. Dipole moments

Finocchiaro *et al*. reported a conformational study of the *N,N*-diacylpyrazolidines **42**, **94a** and **94b** based on ^{1}H DNMR (section 6.4.2) and on dipole moments (Figure 17 and Table 1).[237]



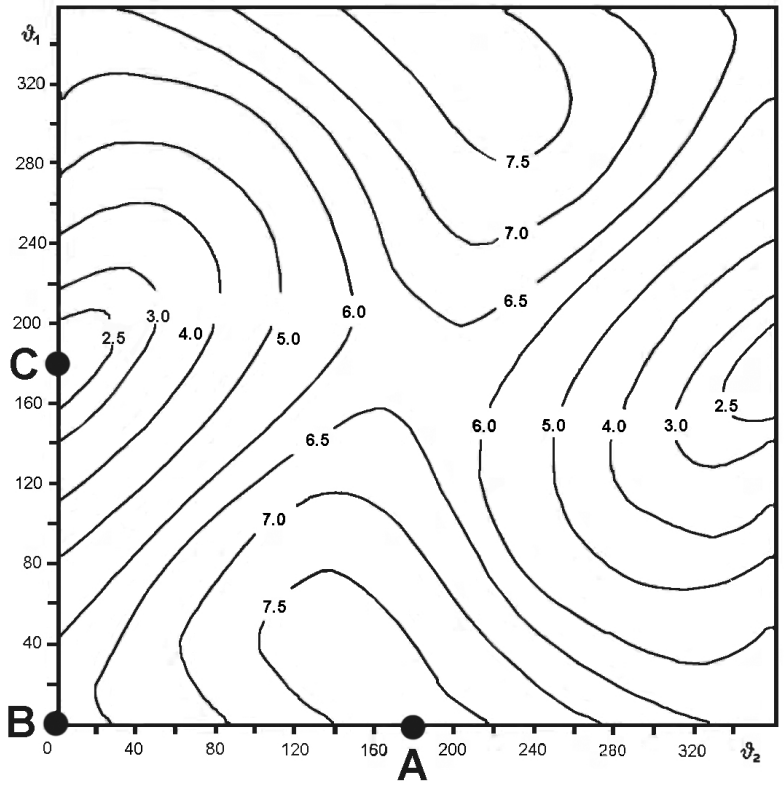


Figure 17. Contour map of calculated dipole moments (D) as a function of the two internal rotation angles ϑ_1 and ϑ_2. Black dots refer to forms **A**, **B**, and **C**.

Table 1. Dipole moments of the pyrazolidines of Figure 17

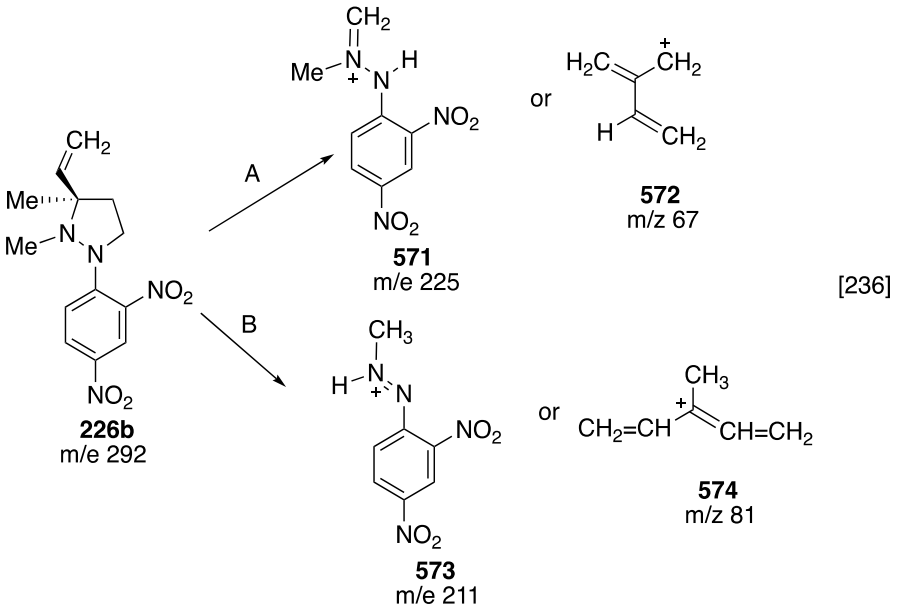
Pyrazolidine	Benzene 25 ºC	Benzene 50 ºC	(*E*)-1,2-dichloroethene
42	2.86	2.94	2.44
94a	3.10	3.15	2.39
94b	5.80	5.85	5.66

Due to kinetic restricted rotation about the amide bond, three diastereomeric forms are possible for the diacyl pyrazolidines; they are averaged through successive rotations by π radians of each acyl group. The values of Figure 17 were calculated assuming 3.84 D for each amide group and the direction depicted there. For **42** and **94a** the conformation should be **C** and for **94b** freely rotating amide groups.[237]

Hall, Katritzky *et al*. reported the calculated dipole moments of a peptidomimetic, showing that it is less polar than the triprolyl scaffold.[57]

6.8. Mass spectrometry

In the mass spectra of pyrazolidines the main fragmentation corresponds to a 1,3-dipolar-retroaddition-like process giving back the protonated form of the azomethine imine used in their synthesis.[239]



[236]

Scheme 39. Fragmentation of 2,4-dinitrophenyl-pyrazolidines.

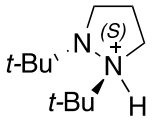
In the case of pyrazolidine **226b**, fragmentation patterns A and B corresponding to the cations **571**-**574** are found for all pyrazolidines (Scheme 39). These two fragmentation patterns can be depicted assuming that the charge of the molecular ion is localized on N-2 carrying the methyl group. Path A can be considered as a double breakage of the C-3–C-4 and N-1–C-5 bonds in β of N-2 with rearrangement of one atom of hydrogen. Path B is due to a rupture of the N-1–C-5 bond at β of N-2 with formation of a quaternary ammonium followed by breaking off the N-2–C-3 bond with rearrangement of an atom of hydrogen.[239]

The electron ionization mass spectra of six 1-thiocarbamoyl **492** and four 1-carbamoyl-pyrazolidines **491** were reported by Morgenstern (Scheme 28).[240] Metastable ion analysis and exact mass measurements were used to determine the fragmentation pathways. The main fragmentation was the same for all the pyrazolidines; the most important reaction was the loss of the thiocarbamoyl or carbamoyl substituent with concomitant hydrogen atom migration from the (thio)carbamoyl nitrogen to the ring nitrogen giving rise to ionized pyrazolidine at 72 daltons. For all the compounds studied, $[M–2H]^{+\cdot}$ion peaks formed by dehydrogenation of the original compounds were observed.

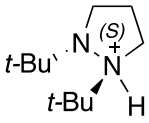
The mass spectrometric fragmentation of 19 substituted 3-amino-, 3-hydrazino-, and 3-hydroxypyrazolidines has been studied. In the gas phase these compounds exist partly as the acyclic tautomers **b**, Section 5.8.[241]

6.9. X-ray molecular structures

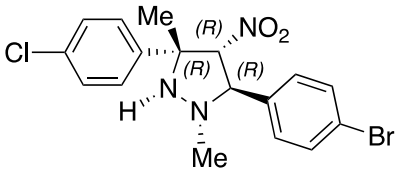
We have gathered in Figure 18 all the structures of pyrazolidines as defined in the Introduction, excluding fused derivatives; exceptionally, we have included a compound with a three-membered ring linking both nitrogen atoms **51** (a derivative of 1,5-diazabicyclo[3.1.0]hexane). We have also excluded derivatives with C=O exocyclic double bonds, so all the compounds reported here have three sp^3 carbon atoms in the ring.



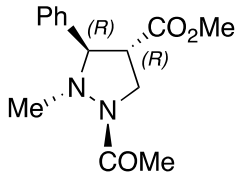
37H⁺: SO_4H^-
AJEQIP
[170]



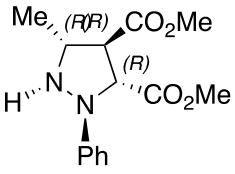
37H⁺: tosylate⁻
AJEQOV
[170]



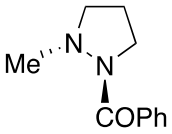
273, Ar = *p*-BrPh
BANGOP
[127]



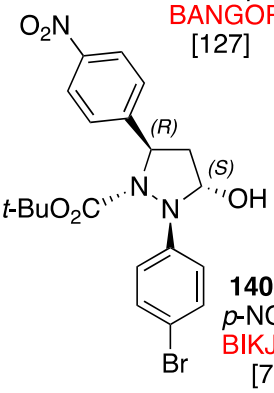
575
BATVEY
[245]



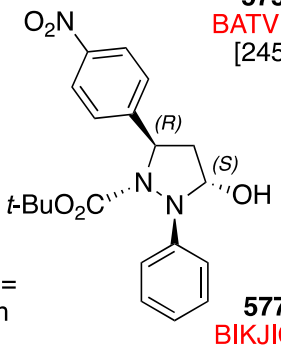
576
BETXED
[246]



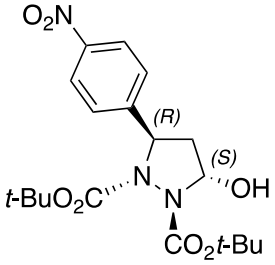
52
BEZOLB
[196]



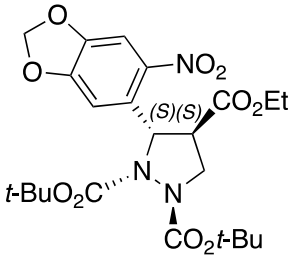
140, Ar = *p*-NO_2Ph
BIKJEM
[74]



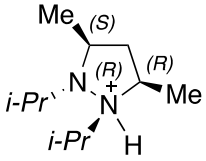
577
BIKJIC
[74]



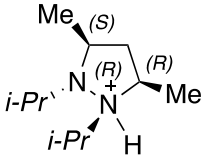
578
BIKJOW
[74]



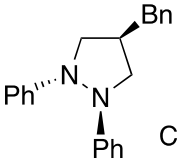
579
BUPPOT
[97]



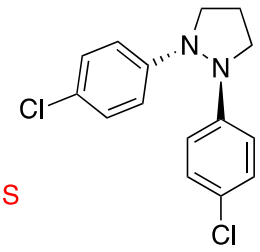
49: Cl^-
DIJYAX
[242]



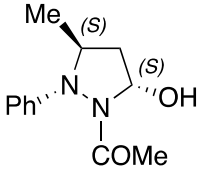
49: picrate⁻
DIJYEB
[242]



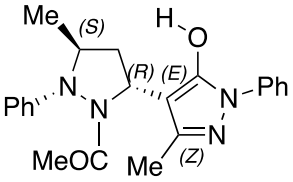
50
EYELUS
[243]



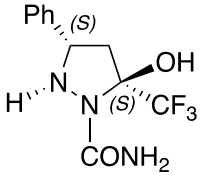
580
EYEMIH
[243]



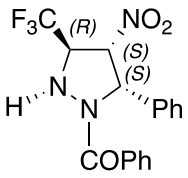
581
FAFXAL
[70,230]



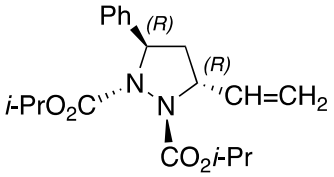
499b
FANXEX
[213,214]



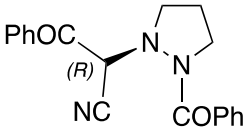
154
FANXUN
[79]



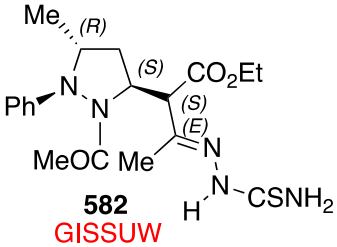
250
FECDUP
[119]



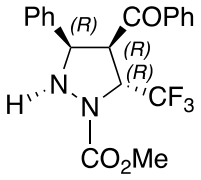
185
FOCSIB
[96]



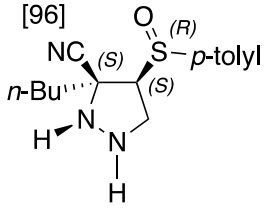
455
FUSGAC
[182]



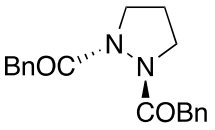
582
GISSUW
[215]



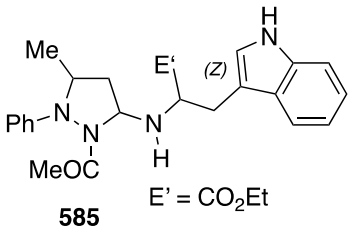
283
HEQGET
[133]



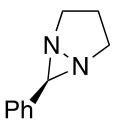
583
ICOLER
[246]



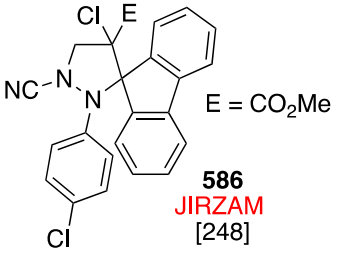
584
IRIRIL
[183]



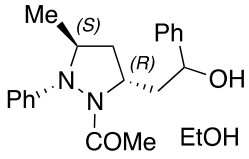
585
IWUPUL
[212]



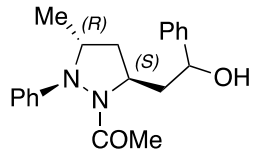
51
IWUXIH
[244]



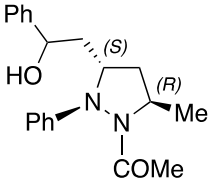
586
JIRZAM
[248]



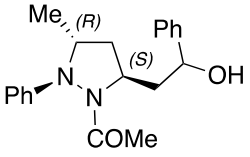
513·EtOH
LAFKOU
[221]



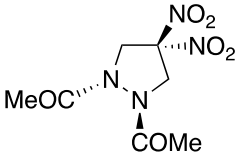
513
LAFKUA
[221]



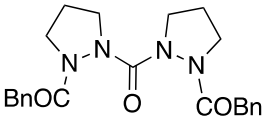
587
LAFLAH
[221]



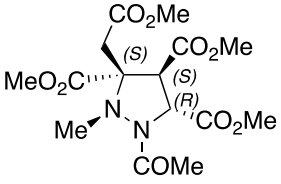
513
LAFLEL
[221]



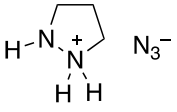
48
LILLEY
[59]



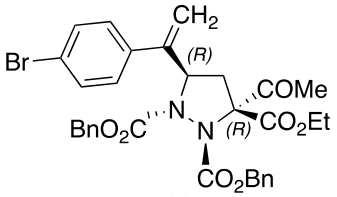
588
LINFUJ
[249]



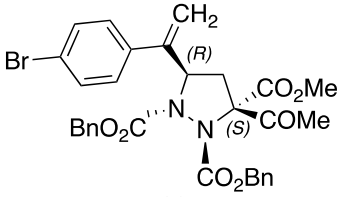
207
MXMPZE
[110]



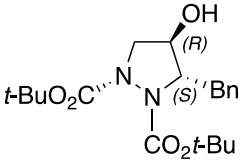
11H$^+$·N_3^-
NOKYER
[187]



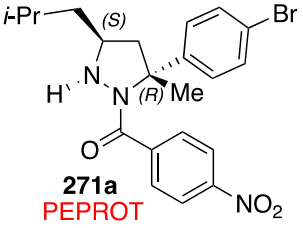
589
OBEFAD
[42]



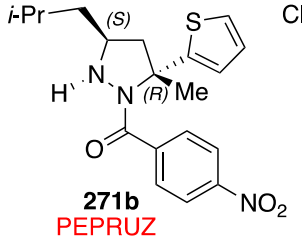
590
OBEFEH
[42]



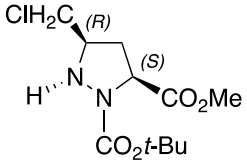
591
PAZVAP
[44]



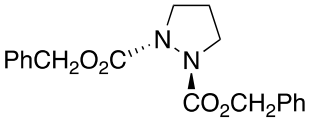
271a
PEPROT
[126]



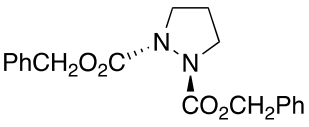
271b
PEPRUZ
[126]



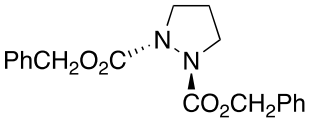
592
PEXBAV
[88]



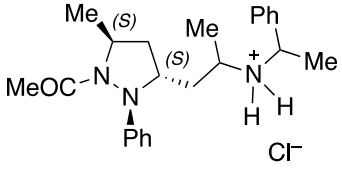
593
PILCOC
[250]



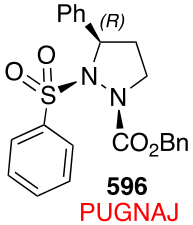
594
PILCUI
[250]



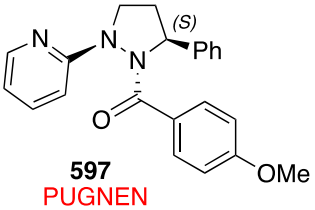
595
PILDAP
[250]



512
PONQAL
[220]



596
PUGNAJ
[236]



597
PUGNEN
[236]

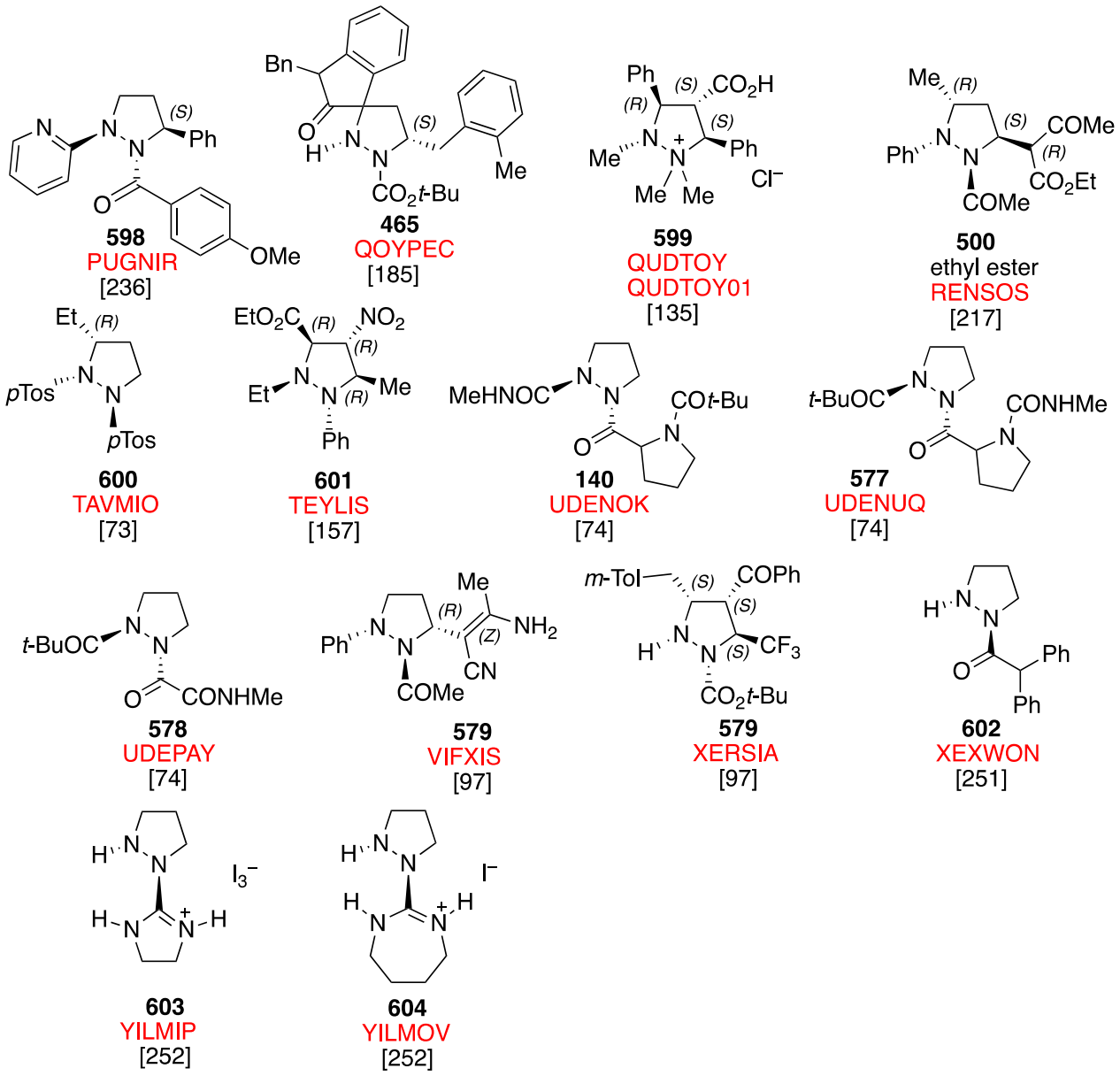


Figure 18. Pyrazolidine X-ray structures.

There are four classes of compounds in Figure 18: a) number and reference already cited; b) number new, but reference already cited, c) number already cited, but reference new (from Figure 3), and d) number and reference new. The third class of pyrazolidines are **49**:Cl^- and **49**:picrate$^-$,[242] **50** and **580**,[243] and **51**.[244] To this last class belong **575**,[245] **576**,[246] **583**,[247] **586**,[248] **588**,[249] **593**, **594** and **595**,[250] **600**,[251] as well as **603** and **604**.[252] There is a paper reporting the structures of aza-proline-containing peptides that are not gathered in the CSD.[253]

An examination of the structures of Figure 18 reveals that only relative configurations are available. Let us be clear about what this "never absolute values" implied. It implied quite a lot. Firstly, the total absence of spontaneous resolution. Secondly, that no examples of chiral chromatography were attempted. Thirdly, that salts of pyrazolidines with chiral acids were prepared. Fourthly, indirectly related to solid-state, there are no solution ^{1}H NMR experiments (section 6.4) using chiral solvents or chiral lanthanide-shift reagents.

In section 6.10.1 we discuss the theoretical calculations of the rings conformation of pyrazolidines depicted in Figure 3, **11**-**52** that include some X-ray structures **48**-**52**.[254]

6.10. Conformational analysis and nitrogen inversion

6.10.1. Ring analysis. The analysis of the conformation of the "nude" pyrazolidine ring, *i.e*., the five-membered ring without substituents, has been the objective of several studies, including those of Nelsen[255,256] and Shipman.[236] The most important contribution was that of Gaweda, Plazinska and Plazinski who, in 2020, reported the analysis of the conformation of saturated five-membered heterocycles, including the parent pyrazolidine (**11**), evaluated by MP2 calculations.[257] They used the Altona-Sundaralingam pseudorotation wheel[258] to classify the *cis* and *trans* isomers as *twist* envelopes. Note that the *cis* pyrazolidine is less stable than the *trans*.

These kind of studies was extended to all the neutral pyrazolidines of Figure 3 (**11**, **18**-**52**) using the Cremer-Pople pseudorotation wheel.[259] The computations were carried out at the B3LYP/6-311++G(d,p) level while the CREST program was used to search all possible stable conformers.[260] The ring puckering has been calculated using the parameters (Q and ϕ) proposed by Cremer and Pople (CP). The numbering for the atoms of the pyrazolidine ring start with the two nitrogen atoms as previously used in the literature.[257] Note that, in this publication, the corresponding ^{1}H and ^{13}C of the studied compounds were calculated and compared with the available experimental results.[254]

Even with this limitation, the numbering could be clockwise and counterclockwise. Since this last decision is arbitrary and depends on how the molecule is presented, we have decided to calculate for each system the CP parameters both ways. In addition, we have considered the corresponding enantiomers since they show the same energy and conformational analysis programs as CREST only provides one of the enantiomeric conformations. Thus, for each conformation, four different sets of CP parameters are calculated with the same value of Q and four different values of ϕ. Each of this sets are located in one of the four quadrants delimited by the angles [18-108º], [108-198º], [198-278º] and [278-18º].

As an example of the different conformations obtained for these molecules, the five more stable conformations of 1,2-dimethyl-3-hydroxypyrazolidine (**31**) are represented in Figure 19; all of them have the two *N*-methyl groups in a *trans* disposition. Their CP parameters are shown in Figure 20.

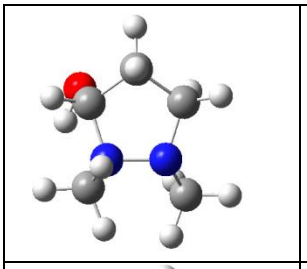
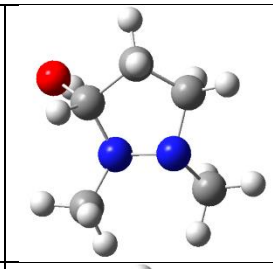
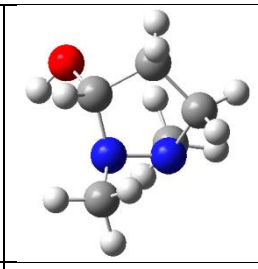
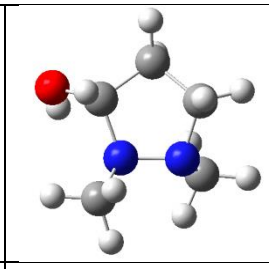
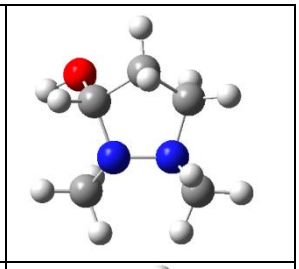
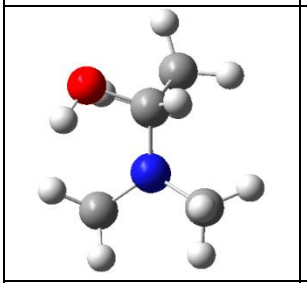
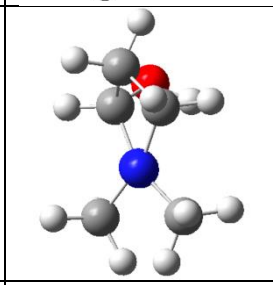
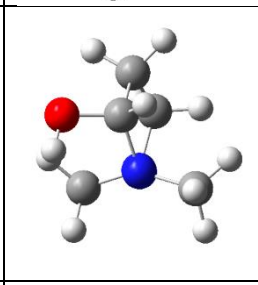
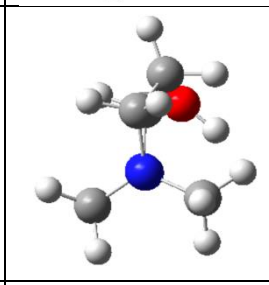
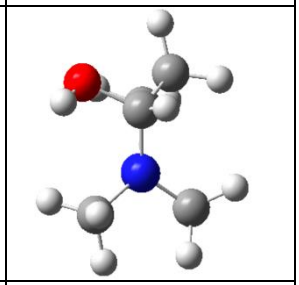
				
				
A	**B**	**C**	**D**	**E**
$C_3N_2N_1C_5$ = 111.8º	78.7º	145.6º	120.1º	106.5º
HOC_3N_2= 35.8º	30.8º	41.8º	37.4º	71.0º
q = 0.382	0.423	0.300	0.374	0.403
ϕ = 106.2	53.7	30.1	95.6	103.6
Erel = 0.0 kJ·mol^{-1}	4.7	6.6	8.0	13.0

Figure 19. The five most stable conformations of 1,2-dimethyl-3-hydoxypyrazolidine (**31**) with indication of geometrical and CP parameter and their relative energy.

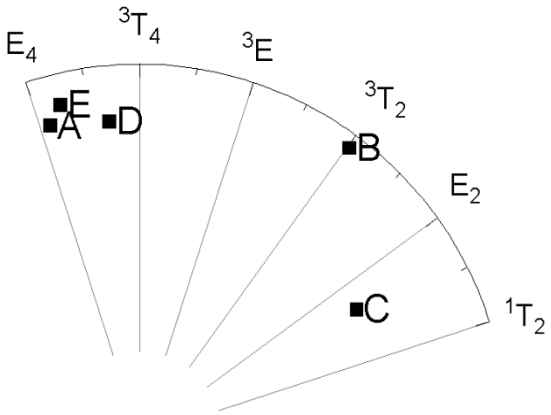


Figure 20. The five more stable conformation of **31**.

A histogram of the ϕ values in all the minimum conformations obtained for **11**, **18**-**52** (242 conformations) (Figure 21). The $^1T_2$ are the most abundant conformation in the first quadrant when all the conformations are considered (31% of the conformers). A similar conclusion is reached when only the most stable conformers for each molecule are analyzed (29% of the conformers are $^1T_2$). The population of other conformation is more dependent on the set used for the analysis, for instance, E_2 is the second most abundant conformation when all the conformers are considered (24%), but is the least one when the analysis is done with the most stable conformers (3%). The twist conformations (139 cases) are more abundant than the envelope ones (103 cases).[254]

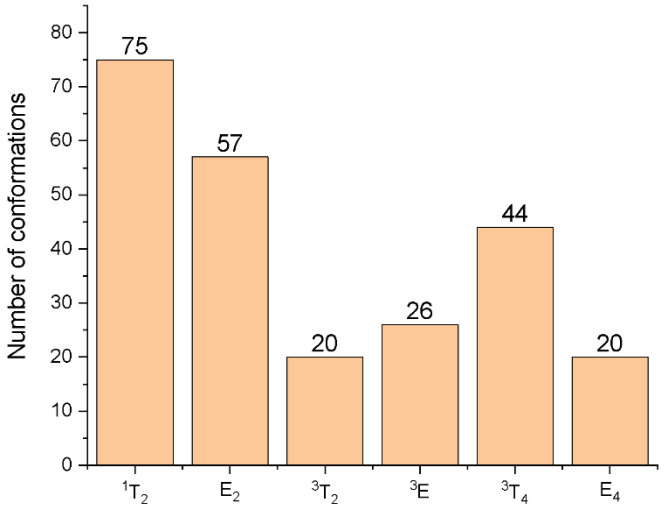


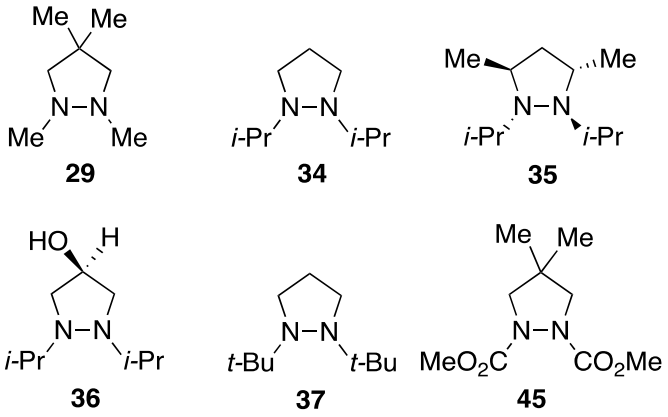
Figure 21. Histogram distribution of the conformers of all the minima obtained for **11**, **18**-**52** in the first quadrant (18-108º).

6.10.2. Nitrogen inversion. ^{1}H NMR studies were started simultaneously in Montpellier and Strasbourg in 1969-1970 on the conformation of monocyclic pyrazolidines. In the first place,[153,154] and in the second one;[13,261,262,263] although Lehn published a paper on bicyclic pyrazolidines in 1967.[264] The main conclusion from the first group was that four of the five substituents adopt an alternate structure, *e.g.*, *up-down-up-down* (the fifth is situated between an *up* and a *down*, and has no preference). They also reported the broadening of some signals when the temperature is lowered. Lehn *et al*. results were more important because they measured some inversion barriers based on energetic considerations (Table 2), came to the conclusion that the inversion of the two adjacent nitrogens must be done successively, such that at least one of the nitrogens is always pyramidal.[264]

These studies were long forgotten until Kostyanovsky developed them considerably (Table 2).[170,242,265] In the case of **35** the *up-down-up-down* conformation was blocked and in the case of **37** the barrier was too high to be measured by ^{1}H NMR and was measured by classical kinetics after the enantiomers were separated by chiral chromatography (Chirasil-β-Dex chiral stationary phase) and then racemized.

Morgenstern observed that the protons of the CH_2 adjacent to the NH have different chemical shifts while those of the remaining CH_2 are isochronous; this phenomenon may be explained in terms of the hindered nitrogen inversion in the pyrazolidine ring on the NMR time scale.[252] This conclusion should be considered with caution as only one proton is reported at 3.41 ppm, the other could be behind another signal; furthermore, it seems unlikely that NH inversion is blocked at room temperature.

Table 2. Nitrogen inversion barriers (kJ·mol^{-1}), coalescence temperature Tc (ºC)



Comp.	Lehn					Kostyanovsky				
	Tc	$\Delta G^{‡}$	$\Delta H^{‡}$	$\Delta S^{‡}$	Ref	Tc	$\Delta G^{‡}$	$\Delta H^{‡}$	$\Delta S^{‡}$	Ref
29	–45	46.4	51.0	–20.9[a]	[13,263]	---	---	---	---	
34						75	67.7	61.1	–22.2	[242,265]
35						No inversion [b]				[170]
36						55	69.2	63.8	–18.0	[265]
37						[c]		114	–15.5	[170]
45[d]		63.2			[262]					

[a] Estimated; [b] conformation blocked; [c] too high to be determined by NMR, separated by chromatography and racemized (kinetics treatment); [d] this compound belong to section 6.10.3.

6.10.3. Amide group rotation. In sections 6.7, Figure 17,[237] and 6.10.2, compound **45**,[264] some examples of N-COR pyrazolidine conformations were reported; these studies contain DNMR results. The impact of azaproline residue on peptide conformation was studied theoretically at the MP2/6-31+G** level by Che and Marshall;[266] solvation effects were studied implicitly using the polarizable continuum model, and explicitly represented by interactions with a single water molecule. These kinds of studies were developed by Reddy *et al*. using NMR and circular dichroism.[267]

Mixed aryl and amide-substituted pyrazolidines were conformationally analyzed by Shipman *et al.*[236] using the PMI (Principal Moments of Inertia) approach.[268]

6.11. Computational results

In the previous sections, 4.2.2, 6.6 and 6.10.1, we have reported results that involve different types of calculation: concerted mechanisms,[136,137] geometries,[254] NMR,[238,254] etc. It is obvious that this section will be much more important in the future, since, with the exception of reference[254] (Figure 3), structural studies are fragmentary, and cover few compounds. It is to be hoped that future publications on pyrazolidines will be accompanied by theoretical calculations. Non-concerted mechanisms also need to be supported by calculations.

7. Biological Properties and Drugs

Pyrazolidines are a class of saturated heterocyclic compounds with several representatives in the field of medicinal chemistry (Figure 22) and biochemistry (Figure 23).

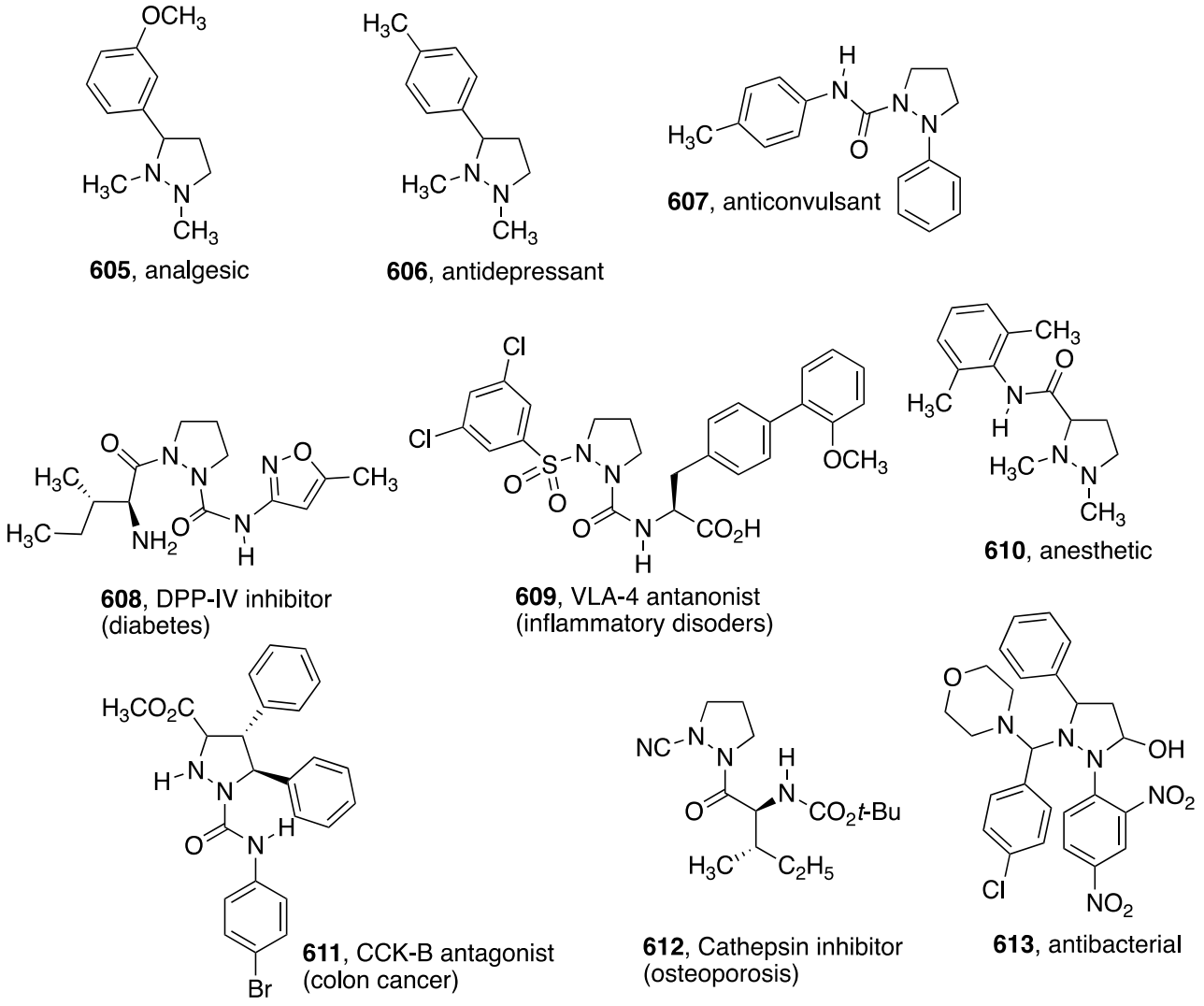


Figure 22. Some representative pyrazolidines in medicinal chemistry.

The compounds of Figure 22 were reported in the following original papers or reviews: **605,**[235] **606,**[235] **607**,[26,235] **608,**[22,235,269] **609,**[22,235] **610**,[147,270] **611**,[22,271] **612**,[200] and **613**.[77] Other publications due to Morgenstern (synthesis).[272] Guilford Pharmaceuticals (immuno-suppressant)[273] and Arribal Discovery (cannabinoids)[274] were also described.

Another field of great importance concerns the use of pyrazolidines as azaprolines (**613**) (Figure 23). Many important peptide sequences contain proline (**612**) since it confers conformational constraints to the peptide chain as the side chain cyclizes back to the backbone amide position. Thus, in an alpha helix, the possibility of forming hydrogen bonds with the previous turn is lost, and a kink will be introduced. Its activity is influenced by *cis-trans* isomerism. In epigenetics, proline isomerization is related to *cis-trans* isomerism. Only a limited number of peptidases are capable of hydrolyzing adjacent proline bonds.

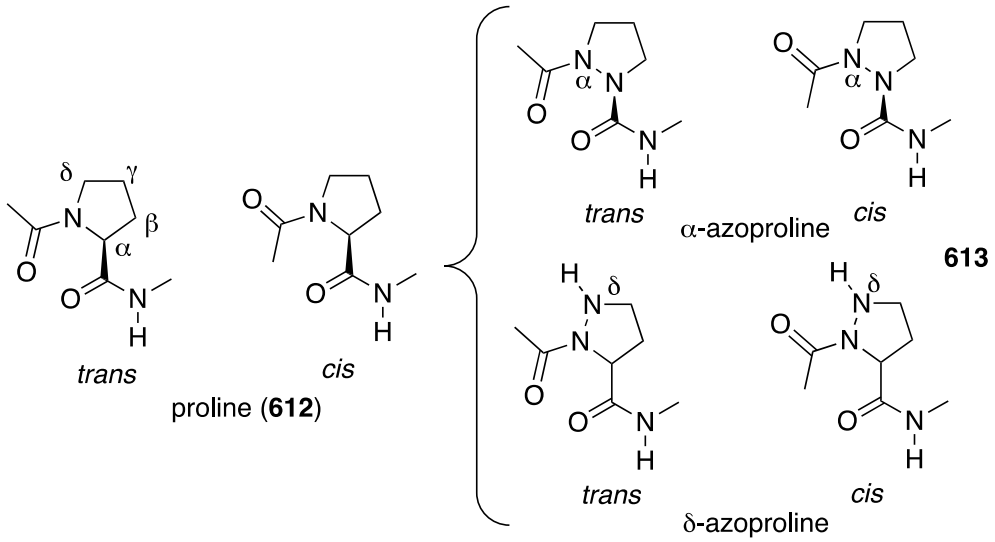
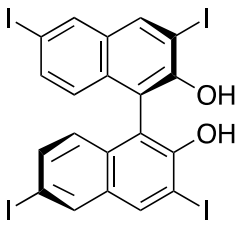


Figure 23. Structures of azaprolines.

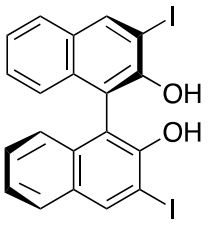
There are two classes of azaprolines **613**, the α (1,2-dicarboxy) and the δ (1,5-dicarboxy) (Figure 23). Azaproline analogs, *i.e*., pyrazolidine compounds **613**, are more resistant to protease cleavage, and have many applications as enzyme inhibitors or receptor antagonists. The results in the literature suggest that some of the corresponding azapeptides have potential therapeutic utility in the treatment of degenerative diseases. Peptides containing azaproline residues with a *cis*-amide conformation induce type IV β-turn mimetics.[58,100,188,221,266,267,275,276,277] This conclusion was based on studies of peptide conformation.

8. Catalysts

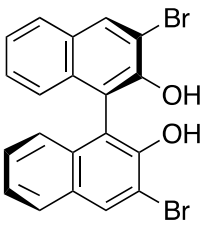
In this review, several catalysts have been used. They are reported in Figure 24 with, in red, one or several references where they were used.



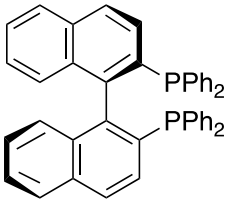
C1-(*R*)...Zr
[123]



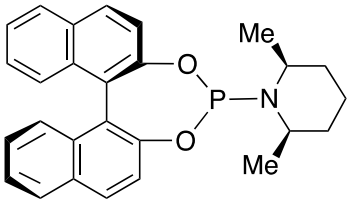
C2-(*R*)...Zr
[123,136]



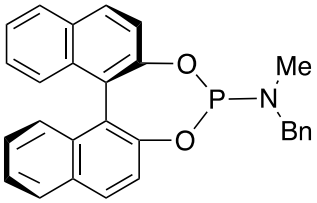
C3-(*R*)...Zr
[123]



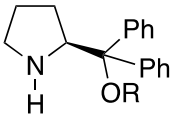
C4
[92]



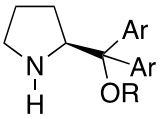
C5
[92]



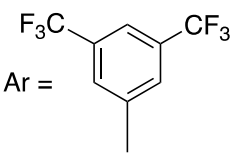
C6
[92]

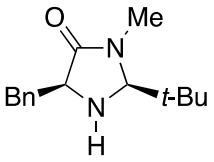


C7, R = Me
C8, R = TMS
[73, 76]

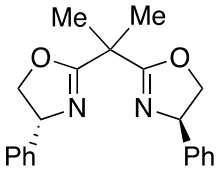


C9 R = Me
C10, R = TMS
[73, 76]

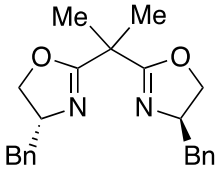




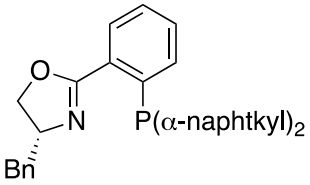
C11
[73]



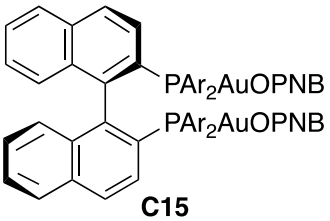
C12
[92]



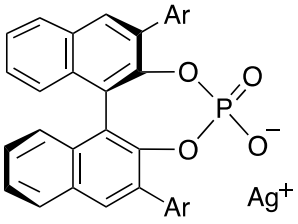
C13
[92]



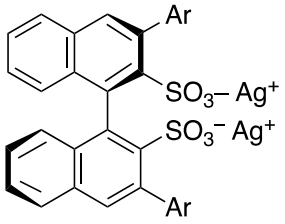
C14
[92]



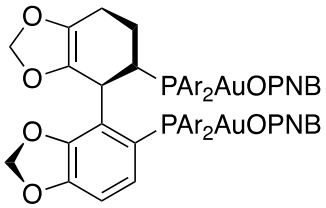
C15
[99]



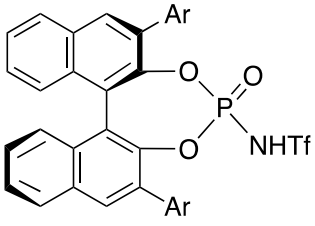
C16
[99, 136]



C17
[99]



C18
[99]



C19
[24, 126, 136]

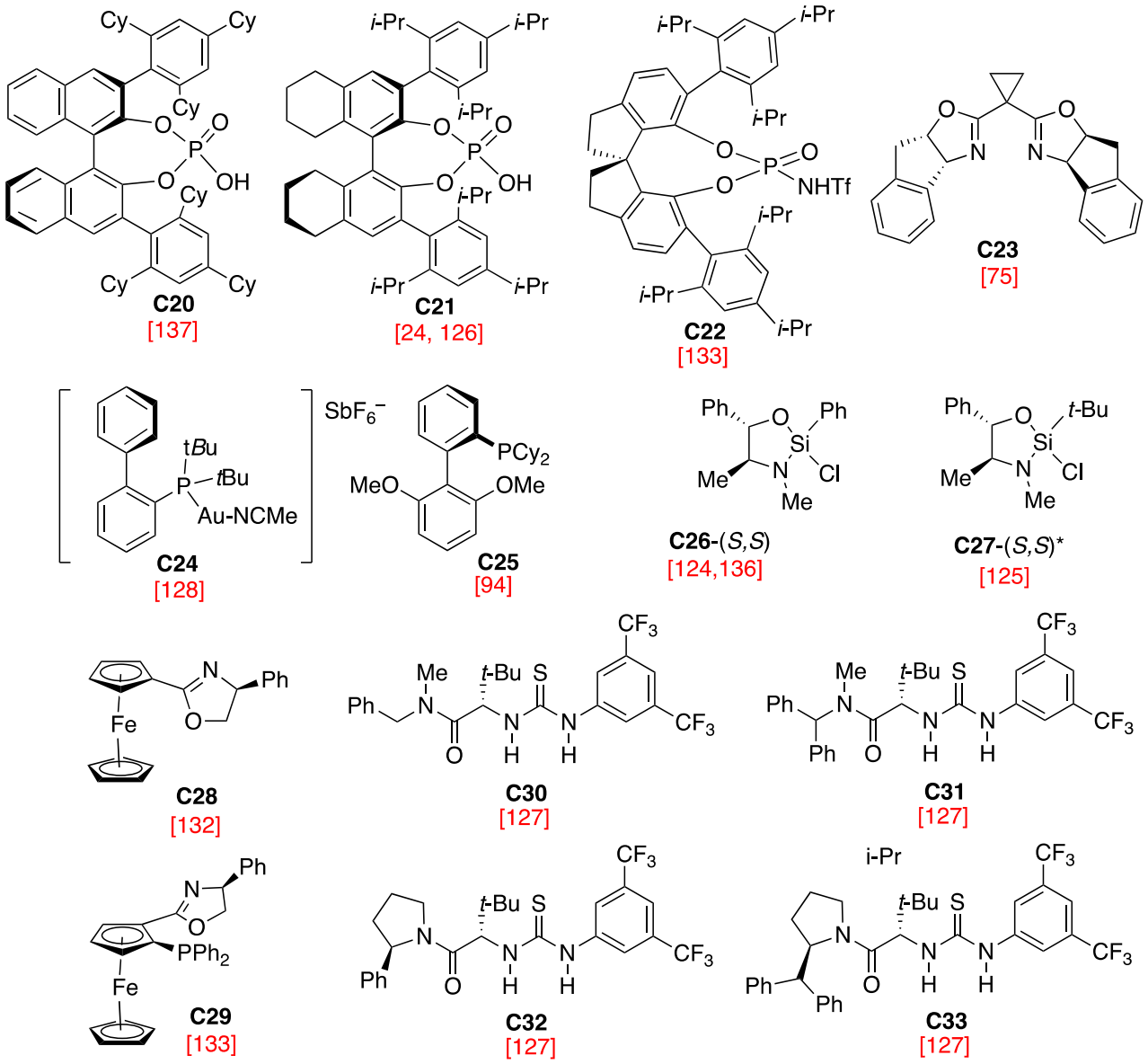


Figure 24. Structure of the catalysts.

9. Conclusions

This review shows that the, seemingly minor, field of pyrazolidines encompasses a rich variety of results. The synthetic part is well developed and up-to-date, especially regarding enantioselective methods. The reactivity remains stuck in the past and needs a resurgence, for example, in the use of pyrazolidines as starting materials to prepare complex structures, whether organic or organometallic. The structure, spectroscopic and physical properties section shows that there is abundant information regarding solid-state, X-ray structures, however, in solution, most results are old and lack quality, and the gas-phase is almost unexplored, except for some recent calculations.

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Abbreviations

MW Microwave
US Ultrasound
B3LYP Becke 3-parameter Lee Yang Parr
CCDC Cambridge Crystallographic Data Centre
DNMR Dynamic Nuclear Magnetic Resonance
GIAO Gauge Invariant Atomic Orbital
Alloc Allyloxycarbonyl
Boc *Tert*-butyloxycarbonyl
Cbz Benzyloxycarbonyl
Fc Ferrocenyl
Fmoc 9-Fluorenylmethoxycarbonyl
Fmoc-Osu *N*-(Fmoc-oxy)-succinimide
Ns Nosyl (4-nitrobenzenesulfonyl)
PCC Pyridinium chlorochromate
Xc Camphorsultam

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