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Ambivalent role of metal chlorides in ring opening reactions of 2*H*-azirines: synthesis of imidazoles, pyrroles and pyrrolinones

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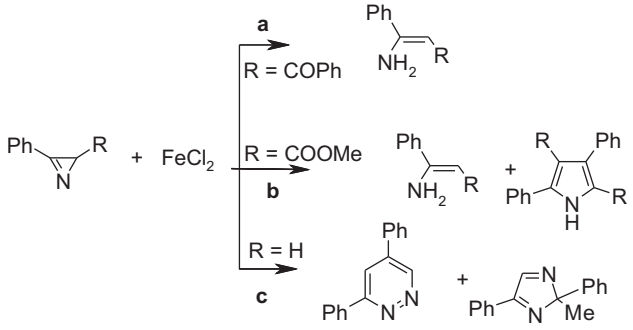
ABSTRACT

2*H*-Azirines were found to react with imines, enaminones and enaminoesters in the presence of metal salts. Imidazoles, pyrroles and new pyrrolinones derivatives are isolated in good overall yields. The role of metal salts was investigated as they can act as Lewis acids or electron donors. Mechanisms are proposed suggesting that imidazoles arise from addition of azirine to imines via radical or ionic mechanism; pyrroles and pyrrolinones are obtained from azirines with enamino derivatives when the salt acts as a Lewis acid. In the latter case the properties of the metallic compound influence the reaction regioselectivity.

1. Introduction

2*H*-Azirines are the smallest unsaturated nitrogen-containing heterocyclic rings. Due to their high reactivity they have been the object of extensive studies for various synthetic purposes and several general reviews have appeared.[1] The strain of the three-membered ring, the polarization of the C=N bond and the basicity of the nitrogen atom make 2*H*-azirines particularly attractive in organic synthesis as they are able to react with nucleophilic and electrophilic reagents and also with dienophiles or dipolarophiles in cycloadditions. The cleavage of an azirine ring gives reactive intermediates that can lead to various nitrogen-containing heterocycles. Since cleavage of each of the three bonds is possible different synthons such as vinylnitrenes, iminocarbenes and nitrile ylides can be obtained. Regioselective single C–N bond cleavage can be achieved by thermolysis of 2*H*-azirines and involves highly reactive vinylnitrenes; this cleavage can be activated by Lewis acids or by transition metal compounds.[2] Thermolysis of C–C bond of 2*H*-azirines is the less common event,[3] but it can be selectively achieved upon irradiation[1,4] and results in reaction through the formation of nitrile ylides. Cleavage of C=N bond can be obtained after initial nucleophilic attack on the polarized double bond and subsequent cleavage of the ring. Lewis acid or transition metal compound activation of this fission is reported.[5]

In the past years we have been involved in the study of cleavage reactions of heterocyclic rings under mild conditions and we found in particular that $FeCl_2$ was very efficient in the azirine ring cleavage. Reactions give different products according to the substituent at 2-position of the ring: 2-benzoyl azirines are reduced to enaminones (Scheme 1, a), 2-carboxymethyl azirines are reduced to enaminoesters (Scheme 1, b) and reaction leads also to pyrroles[6] while azirines not substituted at the 2-position give pyridazines and imidazoles[7] (Scheme 1, c).



Scheme 1. Previous work.

For all these reactions we proposed radical intermediates formed by single electron transfer from iron dichloride to the azirine in the early stages of reaction.

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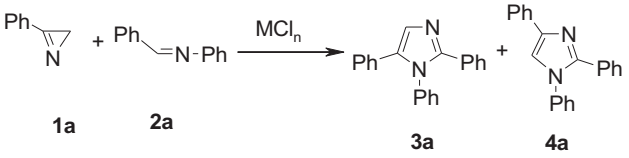
Recently, it was reported that the amination of aromatic C–H bonds can be achieved via ring opening of 2*H*-azirines induced by $FeCl_2$;[8] this reaction shows again that iron dichloride can be an efficient promoter in azirine chemistry. The authors, surprisingly, ruled out a radical pathway for the ring opening and proposed a mechanism via cleavage of the C–N single bond of azirine and formation of a vinylnitrene intermediate. It was suggested that $FeCl_2$ acts only as a Lewis acid although other Lewis acids as $AlCl_3$ or $FeCl_3$ were completely ineffective.

We found that $FeCl_2$ is able to promote reactions of azirines with imines, enaminoesters and enaminones acting both as single electron donor and Lewis acid. Radical and ionic pathways allow different azirine ring cleavages and therefore lead to different products. Use of other metal salts leads to the selective obtainment of products and clarifies the two different routes. Specifically, reactions of azirines with imines promoted by $FeCl_2$ lead to imidazoles, reactions of azirines with enaminoesters lead to pyrroles and surprisingly to pyrrolinones while reactions with enaminones lead to pyrroles and iminopyrroles.

2. Results

In the presence of $FeCl_2$, 3-phenyl-2*H*-azirine (**1a**) reacts with imine **2a** giving imidazoles **3a** and **4a** (Scheme 2). The two imidazoles arise from two different azirine bond cleavages. The structure of imidazole **3a**, corresponding to C=N cleavage, was assigned on the basis of literature data.[9a] The structure of imidazole **4a**, corresponding to C–N cleavage, was also assigned on the basis of literature data[9b] and further confirmed by comparison with data from a sample prepared by an unambiguous synthetic procedure.[9c]



Scheme 2. Reaction of azirine **1a** and imine **2a**.

Since, in principle, iron dichloride can act as Lewis acid or as one-electron donor, the reaction of azirine **1a** and imine **2a** was also performed in the presence of other Lewis acids as $AlCl_3$ or $FeCl_3$, in different amounts. Imidazoles **3a** and **4a** are obtained in different ratios as reported in Table 1. Azirine dimerization products are also always present in variable amounts.

The best overall yields are obtained when iron(III) chloride is used (Table 1, entries 6 and 7). All salts induce mainly the C=N bond cleavage but iron(II) leads to the lowest **3a**/**4a** ratio (Table 1, entries 1 and 2) while aluminium and zinc salts induce only C=N cleavage (Table 1, entries 3 and 4). The amount of iron(III) strongly influences yields and ratios **3a**/**4a**: 2 equiv are required to obtain good overall yields and higher ratio **3a**/**4a** (entries 5–7). A classical Lewis acid, $BF_3{\cdot}Et_2O$, did not give imidazoles even in traces.

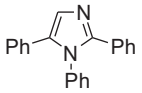
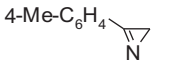
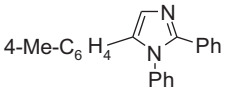
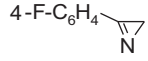
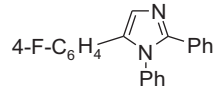
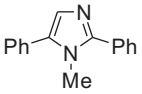
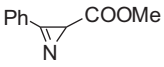
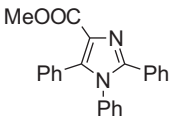
Table 1
Reactions of azirines **1a** with imine **2a** with various promoters[a]

Entry	Promoter	Equiv MCl_n	Yield (%) of **3a**	Yield (%) of **4a**	Ratio **3a**/**4a**
1	$FeCl_2$	1	13	11	1.2
2	$FeCl_{2(aq)}$	1	22	21	1.0
3	$AlCl_3$	1	15	—	
4	$ZnCl_2$	1	18	—	
5	$FeCl_3$	0.5	21	15	1.4
6	$FeCl_3$	1	42	12	3.5
7	$FeCl_3$	2	65	9	7.2

[a] Yields are given by HPLC analysis using internal standard.

Our investigation was extended to other azirines performing reactions in the presence of 2 equiv of $FeCl_3$. In all cases the main product involves the C=N bond cleavage (Table 2).

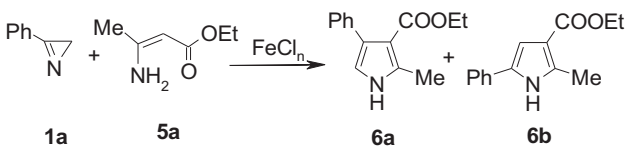
Table 2
Reactions of azirines **1a**–**d** and imines **2a**,**b** with $FeCl_3$[a,b]

Entry	Azirine **1**	Imine **2**	Yield (%)
1	 **1a**	PhCH=NPh **2a**	 **3a** (42)
2	 **1b**	PhCH=NPh **2a**	 **3b** (38)
3	 **1c**	PhCH=NPh **2a**	 **3c** (43)
4	 **1a**	PhCH=NMe **2b**	 **3d** (29)
5	 **1d**	PhCH=NPh **2a**	 **3e** (65)

[a] Yields are given after purification by column chromatography.
[b] Imidazoles arising from single bond C–N cleavage were not isolated except for reaction of **1a** with **2a**.

In previous literature, intermolecular reactions of azirine and imines were reported to proceed only via photochemical activation giving imidazoles corresponding to the C–C bond cleavage[10] whereas intramolecular reactions of iminoazirines lead to pyrazoles and involve C–N cleavage.[2k] We now found that use of Fe(III) chloride allows reaction of azirine with imines via cleavage of C=N bond.

The different behaviour of iron(II) and (III) chlorides in the cleavage of azirine ring was also studied in reactions between azirines and enaminoesters. With enaminoester **5a** in the presence of $FeCl_2$ and $FeCl_3$, 3-phenyl-2*H*-azirine (**1a**) gives pyrroles **6a** and **6b** in different ratios (Scheme 3) together with dimerization products[7] (Scheme 1).



Scheme 3. Reaction of azirine **1a** and enaminoester **5a**.

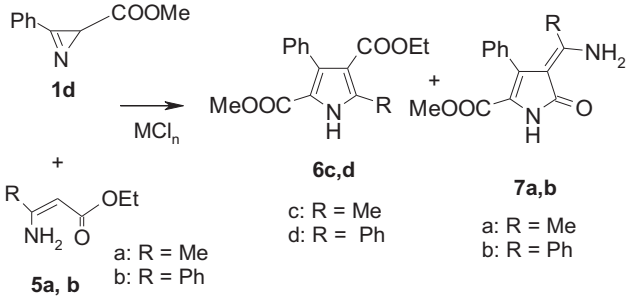
Again two different cleavages may take place and pyrroles **6a** and **6b**, corresponding, respectively, to the C=N and the C–N bond cleavages, were formed. Both structures were assigned on the basis of literature data.[11,12] Yields of pyrroles **6a** and **6b** are reported in Table 3.

Table 3
Reactions of azirine **1a** with enaminoester **5a**[a]

Entry	Promoter	Yield (%) of **6a**	Yield (%) of **6b**	Ratio **6a**/**6b**
1	$FeCl_2$	4	17	0.24
2	$FeCl_3$	18	1	18

[a] Dimerization products, coming from the reaction of azirine **1a** were also found as by products in variable low yields.

Investigations were extended to more stable 2-substituted azirine **1d**. Yields increase significantly but only one cleavage occurred and the unexpected pyrrolinones **7** were isolated. Reactions of 2*H*-azirine **1d** with enaminoesters **5a** and **5b**, carried out in the presence of various salts give pyrroles **6c**,**d** and pyrrolinones **7a**,**b** in very high overall yields (Scheme 4). Both products result from the C=N cleavage and addition to the double bond of the enaminoester with different regioselectivity. 3-Ylidene-pyrrolin-2-one derivatives **7** are new molecules,[13] never isolated before in reactions of azirines. As their benzo-condensed analogues, namely methyleneoxindoles, have pharmaceutical relevance,[14] it appeared important to try to obtain also these products in good yield. The use of different promoters leads to different ratios of products **7**/**6** as reported in Table 4.



Scheme 4. Reaction of azirine **1d** and enaminoesters **5**.

Table 4
Reactions of azirine **1d** with enaminoesters **5a**,**b**

Entry	**5**	Promoter	Solvent	Yield of products by C=N cleavage (%)	
1	**5a**	$FeCl_2$[a]	CH_3CN	**6c** (25)	**7a** (35)
2	**5a**	$FeCl_3$	CH_3CN	**6c** (25)	**7a** (55)
3	**5a**	$AlCl_3$	CH_3CN	**6c** (11)	**7a** (72)
4	**5a**	$ZnCl_2$	CH_3CN	**6c** (32)	**7a** (23)
5	**5b**	$AlCl_3$	CH_3CN	**6d** (26)	**7b** (68)
6	**5a**	$AlCl_3$	DMF	**6c** (Traces)	**7a** (Traces)

[a] Side products, coming from reaction of azirine **1d** (Scheme 1, b) were also found as in low and variable yields.

The structure of pyrrole **6c** was assigned on the basis of literature data,[15] while the structures **7a**,**b** were determined by standard analytic methods. In particular the molecular structure of **7b** was unambiguously determined through X-ray single crystal analysis[16] (Fig. 1). The stereochemistry of the exocyclic double bond is unambiguously assigned and an intramolecular H-bond between aminic hydrogen and the carbonyl oxygen is apparent.

The overall yields and the regioselectivity of the addition of the azirine **1d** to the carbon–carbon double bond of enaminoester **5a** is affected by the metal salt used: the best yields and higher selectivity are obtained when $AlCl_3$ is used (Table 4: entries 1–4), while we found a reverse selectivity when $ZnCl_2$ is used (Table 4: entry 4).

Enaminoester **5b** (R=Ph) gives also both pyrrole **6d** and pyrrolinone **7b** in very good overall yields (Table 4, entry 5) but with less selectivity than derivative **5a** (R=Me). Reactions were also performed at different temperatures as reported in Table 5. Both the yields and the regioselectivity increase with increasing temperature (entry 4).

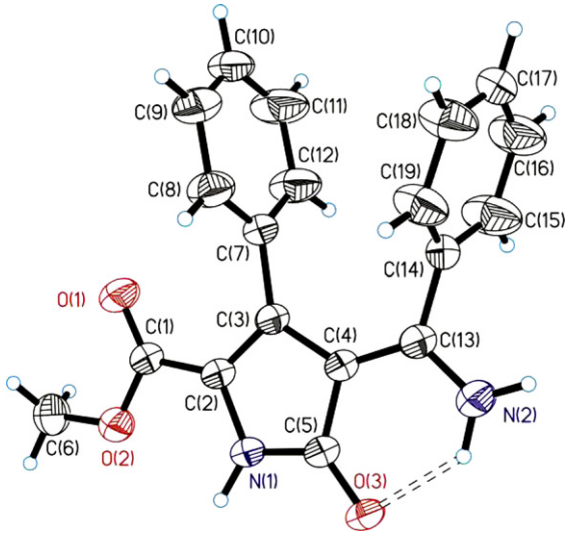


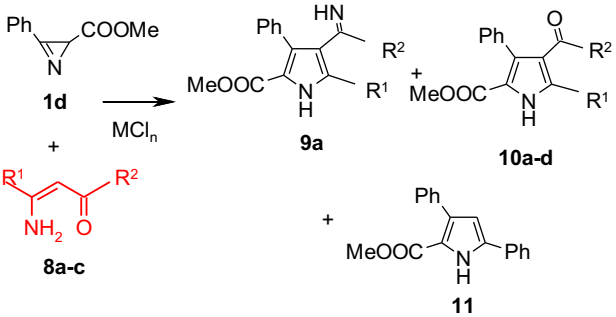
Fig. 1. A view of the molecular structure of **7b** (thermal ellipsoids drawn at 40% probability level) determined by X-ray diffraction.

Table 5
Reactions of azirine **1d** with enaminoester **5a** in the presence of $FeCl_3$ in acetonitrile

Entry	Temp (°C)	Yield (%) of **6c**	Yield (%) of **7a**	Overall yield (%)	Ratio **7a**/**6c**
1	rt	12	14	26	1.2
2	40	24	44	68	1.8
3	60	25	48	73	1.9
4	80	25	55	80	2.2

No significant change in yields of products **6c** and **7a** was found modifying the concentration of azirine **1d**.

The last investigated reaction involves azirine **1d** with enaminones **8a**–**c** in the presence of $FeCl_3$ and $AlCl_3$ giving pyrroles in good overall yields.(Scheme 5, Table 6).



Scheme 5. Reaction of azirine **1d** and enaminones **8**.

The synthesis of pyrroles **9**, **10** and **11** from reaction of azirine **1d** with enaminones occurs, as observed for the reaction with enaminoesters in the presence of non-reducing Lewis acids, only with the C=N bond cleavage in the azirine ring.

When R^1 and R^2 are phenyl groups (Table 6, entries 1 and 2) three products are formed: **9a**, **10a** and **11**. Iminopyrrole **9a** was isolated, together with pyrrole **10a**, despite the acidic condition of reaction and work up. Pyrrole **10a** can actually arise from a different attack on the carbon–carbon double bond of enaminone or from hydrolysis of **9a**. 4*H*-Pyrrole **11** arises from decarbonylation of

Table 6
Reactions of **1d** with enaminones **8a–c** in acetonitrile

Entry	8	MCl_n	Yield (%) of pyrroles			Overall yield (%)
1	**8a** R^1=R^2=Ph	$FeCl_3$	**11** (18)	**9a** (37)	**10a** (42)	97
2		$AlCl_3$	**9a** (51)	**10a** (22)	**11** (Traces)	73
3	**8b** R^1=R^2=Me	$FeCl_3$		**10b** (57)		57
4	**8c** R^1=Me; R^2=Ph	$FeCl_3$	**10c** (45)	**10d** (11)	**11** (9)	65
5		$AlCl_3$	**10c** (57)	**10d** (4)	**11** (Traces)	61

pyrrole **10a**. Aluminium trichloride (entry 2) induces more selectivity, favours the formation of pyrrole **9a** and minimizes the formation of **11**.

When R^1 and R^2 are methyl groups (Table 6, entry 3) the reaction leads only to pyrrole **10b**. In this case the imino derivative of **10b** was not isolated as it probably hydrolyses easily.

When R^1 and R^2 are different groups (Table 6, entries 4 and 5), addition of azirine to carbon–carbon double bond of enaminones takes place with different regioselectivity and pyrroles **10c** and **10d** are obtained together with pyrrole **11**.

3. Discussion

We found that $FeCl_2$ promotes reactions of azirines with imines leading to two different isomers: imidazoles **3** and **4** (Table 1, entries 1 and 2) corresponding to two different ring cleavages. Iron(II) can play different roles acting both as Lewis acid and as single electron donor.

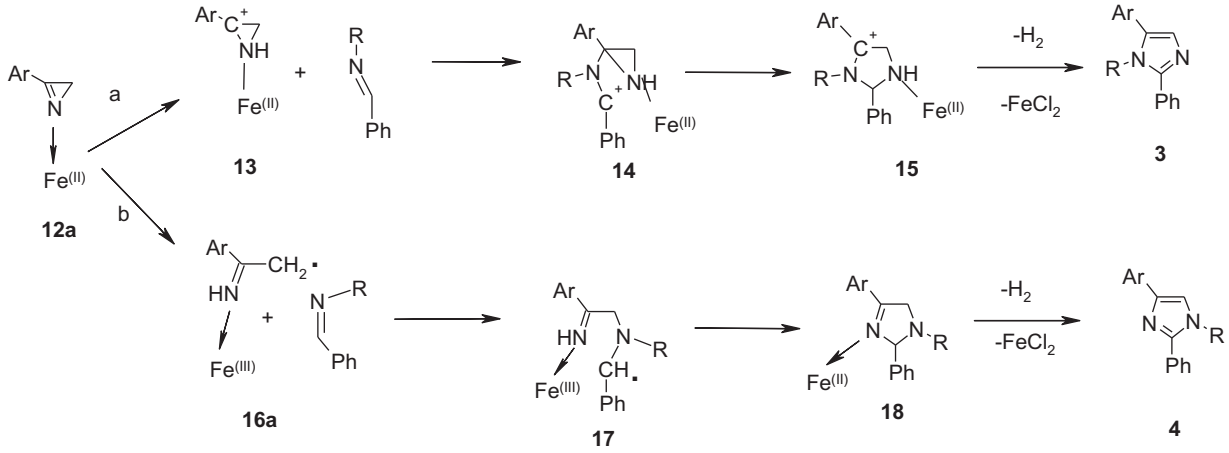
We suggest that $FeCl_2$ really exhibits both roles in the mechanism that leads to formation of **3** and **4** by two different pathways after an initial N-donor complexation to give intermediate **12a** as outlined in Scheme 6. Azirine complexes with various metals are reported in the literature.[1f,2k,17]

but in some cases, when the conformational restrictions, steric hindrance, polar effects or stabilizing groups (e.g., benzylic) are present, attack at nitrogen[18] is possible. Addition of alkyl radicals to imines has been studied in the presence of $ZnEt_2$ and both addition at the carbon atom and at the nitrogen atom of the C=N bond was observed.[19] In Scheme 6, route b, the radical attack to the nitrogen atom is justified both by the benzylic stabilization in structure **17** and by subsequent cyclization to intermediate **18** with electron transfer to the neighbouring metal.

When reactions of azirines with imines are performed with non-reducing Lewis acids as $AlCl_3$ or $ZnCl_2$, only the imidazole isomer **3** is formed (Table 1, entry 3) and, as found for $FeCl_2$, only route a of Scheme 6 is viable. When $FeCl_3$ is used, imidazole **3** is indeed the main product, especially if Fe(III) is used in large amount. Traces of Fe(II) are unavoidably present but become less influent as amounts of iron(III) increase as shown by the different **3a**/**4a** ratios obtained (Table 1, entries 5–7).

The same reactivity was discovered when azirine **1a** reacts with enaminoesters in the presence of iron(II) and iron(III). Two pyrroles are formed (Scheme 3) consistently again with two possible different ring cleavages. When $FeCl_2$ is used route b of Scheme 6 is possible and the main product comes by single bond C–N cleavage (Table 3, entry 1, ratio **6a**/**6b**=0.24); at variance, with $FeCl_3$, the main product arises by double bond C=N cleavage (Table 3, entry 2, ratio **6a**/**6b**=18).

When a more stable azirine as **1d** is used, overall yields increase (Table 4, entries 1–5). In this case $FeCl_3$ and $AlCl_3$ proved to be very efficient agents in promoting C=N cleavage. We propose that the mechanism that leads to the formation of pyrroles and pyrrolinones from azirine **1d** (Schemes 4 and 5, Tables 4–6), promoted by metal salts is, in this case, exclusively ionic and radical addition does not play any role. Indeed the properties of zinc chloride and aluminium chloride offer little scope for rationalisation based on redox pathways

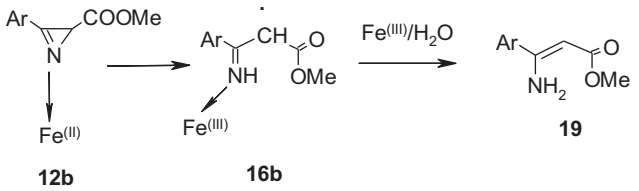


Scheme 6. Proposed mechanism for reaction of azirines with imines.

When iron(II) acts as a Lewis acid (route a) imidazole **3** is formed through attack of imine to intermediate **13** and formation of intermediates **14** and **15**. When Fe(II) acts as one-electron donor (route b) isomeric imidazole **4** is formed. In the proposed mechanism (route b), the radical addition of intermediate **16a** occurs at the iminic nitrogen and leads to **17** that, after cyclization to intermediate **18**, can afford imidazole **4** by loss of hydrogen and hydrolysis. We have already proposed in previous work[7] that radical intermediates like **16a** play a key role in azirines' dimerizations and in reactions of azirines with alkenes. Usually, radical addition to C=N iminic bond occurs at the carbon atom, (Table 4, entries 3–5). On the contrary, when Fe(II) is used, formation of radical intermediate **16b** (Scheme 7) is possible. This intermediate obtained by the initial electron transfer, however, evolves to enaminoester **19** rather than reacting with another molecule.

Products arising from reduction of azirine **1d** are always present in the crude,[6] and only the use of non-reducing Lewis acids as promoters increases yields (Table 4, entries 2–5) avoiding the formation of reduction and dimerization side products.

Surprisingly pyrrolinones and iminopyrroles are obtained beside pyrroles through the same C=N cleavage. Both products arise from attack of azirine to enaminoesters or enaminones double



Scheme 7. Reduction of azirine **1d**.

bonds with different regioselectivity, the product ratio depending upon the specific salt used and the temperature.

In order to explain these results we suggest that the azirine complex **12b** undergoes nucleophilic attack by the enaminic double bond (Scheme 8), to give intermediates **20** or **21**, which can afford the different products **22** or **23** depending upon the different intramolecular linkage with nitrogen (route a) or oxygen (route b). The role of azirine metal complexes as key intermediates is in agreement with the non-occurrence of the reaction when performed in DMF, a solvent able to give coordination highly competitive with respect to azirines (Table 4, entry 6).

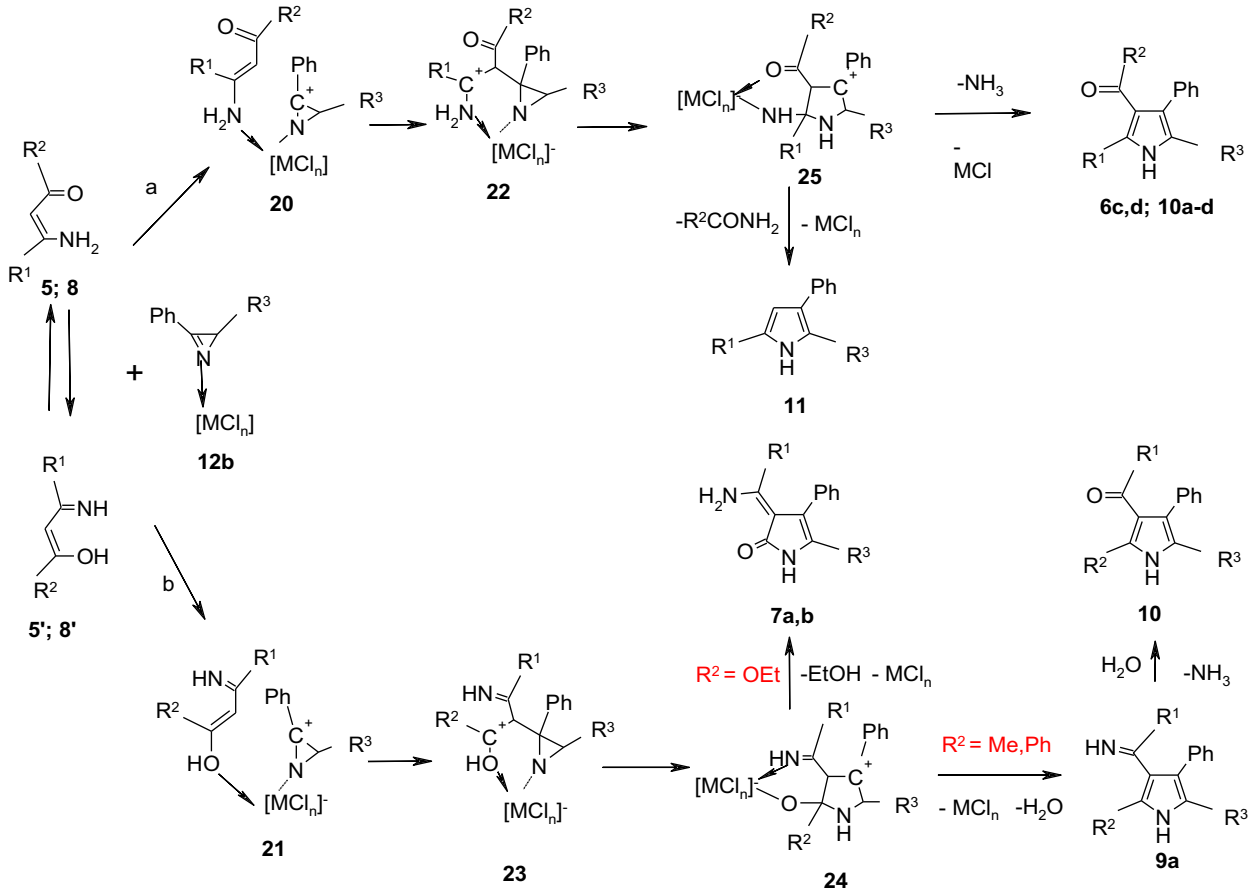
The different intermediates of the two routes can account for the different regioselectivity induced by metals. Oxophilic metals such as iron(III) and especially aluminium favour the formation of intermediates **23** and **24** that then afford pyrrolinones **7** and iminopyrrole **9a** (Table 4, entries 2,3 and 5; route b); pyrrole **10** can arise from hydrolysis of **9a**. The azophilic metal zinc favours the formation of intermediates **22** and **25** that afford pyrroles as for instance **6** (Table 4, entry 4; route a).[20]

Selectivity **7**/**6** increases as temperature increases (Table 5, entries 1–4). This is in agreement with the shift of tautomeric equilibrium from enaminic form **5** or **8** (Scheme 8, route a) to iminic form **5′** or **8′** (Scheme 8, route b) as reported in literature.[21] The proposed mechanism explains also the results obtained in the reaction of azirine **1d** with different substituted enaminoesters **5a** and **5b**. When R=Ph (**5b**), intermediates formed via route b are more stabilized and therefore the **6d**/**7b** ratio (Table 5, entry 5, ratio=0.38) is greater than the corresponding **6c**/**7a** ratio obtained from **5a** (R=Me) (Table 5, entry 3, ratio=0.15).

4. Conclusion

These results clarify the role of some metal salts in reactions of azirines with imines, enaminoesters and enaminones. The use of $FeCl_3$ allows the synthesis of imidazoles by cleavage of the azirine C=N bond, never achieved before with other methods. Up to now, reactions of azirines with enaminoesters or enaminones were known not to occur or to occur with low yields.[15] In the present investigation we found that azirines such as methyl 3-aryl-2*H*-azirine-3-carboxylate, and electron-poor enaminocarbonyl compounds react under these conditions. In particular, the synthesis of nitrogen heterocycles from azirines and enaminoesters or enaminones without loss of nitrogen atoms giving, respectively, pyrrolinones or iminopyrroles can be achieved. Although in fact pyrroles can be obtained from reaction of azirines, or even from vinyl azides with 1,3-dicarbonyl compounds, it was by no mean obvious that pyrrolinones and iminopyrroles can be synthesized by these reactions.[5a,22]

The dual role of $FeCl_2$ in reactions of azirines with imines explains the variety of obtained products. The formation of azirine complexes followed by the attack of two tautomeric forms of



Scheme 8. Proposed mechanism for the reactions with enaminones.

enaminoesters or enaminones explains the different reactivity and leads to the formation of pyrrolinones and pyrroles.

Synthesis of nitrogen heterocycles has always been a challenging goal and the use of azirines as building blocks for the preparation of pyrroles or imidazoles has always stimulated and still is of great interest.[23] Although reactions of azirines in the presence of metal complexes or Lewis acids have been studied profusely,[2,5] often by use of expensive metal complexes, we found that the use of common, inexpensive and readily available iron and aluminium salts in azirines reactions has not been sufficiently exploited and makes novel syntheses possible. The azirine ring has again proven a very useful precursor of other compounds of the nitrogen heterocyclic class.

5. Experimental section

5.1. General experimental section

NMR spectra were determined with TMS as internal standard, on a Bruker 250 MHz or on a 400 MHz instrument. MS spectra were performed on a Finnigan TSQ 70 instrument. GC–MS analyses were performed on a Agilent *6890* gas-chromatograph equipped with a 5973 mass-detector, using a HP5MS column (30 m×0.25 mm×0.25 μm); the following temperature program was employed: 40 °C (1′)//2 °C/min//45 °C (1′)//10 °C/min//200 °C (1′)//20 °C/min//280 °C (10′). IR spectra were registered with a Perkin Elmer 257 instrument or with a Nicolet Nexus FTIR spectrometer. Chromatographic separations were performed using Merck Kieselgel 60 silica gel. Melting points were determined with a Buchi 535 instrument and are uncorrected. HPLC analyses were performed on Varian 9010 equipped with a diode array detector. Azirines **1a**–**c** were prepared by thermal reaction of the corresponding azides.[24] Azirine **1d** was prepared from the corresponding isoxazole.[6] Imines **2a**,**b** and enaminoester **5a** were purchased from Aldrich. Enaminoester **5b** and enaminones **8a**–**c** were prepared from the corresponding ketoester and diketones according to standard literature procedures.[25]

5.2. General procedure for the reaction of 3-phenyl-2*H*-azirine (1a) and *N*-benzylideneaniline (2a) with different promoters

To a solution of azirine **1a** (504 mg, 4.30 mmol) in CH_3CN (43 mL), kept under stirring and under nitrogen, imine **2a** (780 mg, 4.30 mmol) and the different promoters were added. After total conversion of azirine **1a** (from 2 to 6 h except for reaction with $ZnCl_2$, which required 48 h) the crude was evaporated, washed with aq HCl 4 M or aq $NaHCO_3$ (when $AlCl_3$ or $ZnCl_2$ were used as promoters), extracted with CH_2Cl_2 and analysed by HPLC. Promoter, corresponding amount and yields are given in Table 1. Imidazoles 1,2,4-triphenyl-1*H*-imidazole[9b] (**4a**) and 1,2,5-triphenyl-1*H*-imidazole[9a] (**3a**) were then purified by column chromatography on silica gel (*n*-hexane/ethyl acetate).

5.3. General procedure for the reaction of azirine 1a–d with imines 2a,b with iron trichloride

To a solution of azirines **1a**–**d** (4.30 mmol) in CH_3CN (43 mL), kept under stirring and under nitrogen, imine **2a** or **2b** (4.30 mmol) and $FeCl_3$ (1.39 g, 8.6 mmol) were added and reaction kept at room temperature. After total conversion of azirines **1a**–**c** (from 2 to 24 h) or conversion of imine for reaction of **1d** (48 h), solvent is evaporated and 40 mL of HCl 4 M were added to the crude. The mixture was extracted with CH_2Cl_2, washed with aq $NaHCO_3$ 2%, concentrated and dried over Na_2SO_4. The crude was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate) to afford the corresponding imidazoles **3a**–**e**.

*5.3.1. Reaction of 3-phenyl-2H-azirine (**1a**) and N-benzylideneaniline (**2a**) with Fe(III).* Column chromatography on silica gel (*n*-hexane/ethyl acetate) gives 1,2,4-triphenyl-1*H*-imidazole (**4a**; 66 mg, 5%) and 1,2,5-triphenyl-1*H*-imidazole (**3a**; 535 mg, 42%).

Compound **4a**: R_f (30% ethyl acetate/*n*-hexane) 0.42; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 7.20–7.34 (m, 6H), 7.35–7.52 (m, 8H), 7.84–7.96 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 118.5, 125.0, 125.8, 127.0, 128.2, 128.4, 128.6, 128.8, 129.4, 130.1, 133.7, 138.4, 141.6, 146.9.

Compound **3a**: R_f (30% ethyl acetate/*n*-hexane) 0.19; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 7.02–7.15 (m, 4H), 7.17–7.42 (m, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 127.4, 127.9, 128.1, 128.2, 128.48, 128.53, 128.8, 129.4, 129.7, 130.4, 135.1; 137.1, 147.9.

*5.3.2. Reaction of 3-(p-tolyl)-2H-azirine (**1b**) and N-benzylidenaniline (**2a**) with Fe(III).* Column chromatography on silica gel (*n*-hexane/ethyl acetate) gave imine **2a** (73 mg, 9%), 2,5-di-*p*-tolylpyrazine[26] (85 mg, 15%); R_f (20% ethyl acetate/*n*-hexane) 0.56 and 1,2-diphenyl-5-(4-methylphenyl)imidazole[27] (**3b**; 510 mg, 38%); R_f (20% ethyl acetate/*n*-hexane) 0.11.

*5.3.3. Reaction of 3-(4-fluorophenyl)-2H-azirine (**1c**) and N-benzylideneaniline (**2a**) with Fe(III).* Column chromatography on silica gel (*n*-hexane/ethyl acetate) gave 1,2-diphenyl-5-(4-fluorophenyl)imidazole (**3c**; 580 mg, 43%).

Compound **3c**: white solid (MeOH), mp 238–240 °C. R_f (50% ethyl acetate/*n*-hexane) 0.35; FTIR (ATR) 1492, 1222, 1159 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 6.84–7.16 (m, 6H), 7.16–7.48 (m, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 115.3 (d, J=21.1 Hz); 126.0 (d, J=3.0 Hz), 128.1, 128.16, 128.21, 128.3, 128.6, 128.8, 129.4, 130.3 (d, J=8.3 Hz), 130.6, 134.1, 137.1, 148.1, 162.1 (d, J=247.7 Hz); MS: m/z 314 M$^+$, (100). Elemental analysis for $C_{21}H_{15}FN_2$: calcd. C 80.24, H 4.81, F 6.04, N 8.91; found C 80.44, H 4.83, F 6.01, N 8.86.

*5.3.4. Reaction of 3-phenyl-2H-azirine (**1a**) and N-benzylidenemethylamine (**2b**) with Fe(III).* Column chromatography on silica gel (*n*-hexane/ethyl acetate) gave 2,5-diphenyl-pirazine[28] (27 mg, 5%) [R_f (30% ethyl acetate/*n*-hexane) 0.47] and 1-methyl-2,5-diphenyl-1*H*-imidazole[29] (**3d**; 290 mg, 29%) [R_f (30% ethyl acetate/*n*-hexane) 0.10].

*5.3.5. Reaction of azirine **1d** and N-benzylidenaniline (**2a**) with Fe(III).* Column chromatography on silica gel (*n*-hexane/ethyl acetate) gave unconverted azirine **1d** (110 mg, 15%) [R_f (50% ethyl acetate/*n*-hexane) 0.53] and methyl 1,2,5-triphenyl-1*H*-imidazole-4-carboxylate (**3e**; 990 mg, 65%).

Compound **3e**: solid (ethyl acetate), mp 209–210 °C; R_f (50% ethyl acetate/*n*-hexane) 0.24; FTIR (ATR) 1717, 1213, 1145 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 3.86 (s, 3H), 6.94–7.03 (m, 2H), 7.15–7.35 (m, 11H), 7.35–7.44 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 51.7, 127.7, 128.1, 128.2, 128.65, 128.71, 128.8, 128.9, 129.18, 129.24, 129.5, 129.6, 130.8, 136.2, 140.4, 147.5, 163.6 ppm. EIMS: m/z 355 (26), 354 (M$^+$, 100), 323 (36), 322 (25), 295 (45), 180 (81), 165 (25). Elemental analysis for $C_{23}H_{18}N_2O_2$: calcd. C 77.95, H 5.12, N 7.90; found C 78.26, H 5.13, N 7.87.

5.4. General procedure for the reaction of azirine 1a with ethyl 3-aminocrotonate (5a) with different promoters

To a solution of azirine **1a** in anhydrous CH_3CN, enaminoester **5a** and $FeCl_2$ or $FeCl_3$ were added. The mixture was stirred under N_2 atmosphere at room temperature. After 2–3 h dichloromethane and a solution of aq HCl 0.1 M were added to the reaction mixture. The organic layer was washed with aq $NaHCO_3$ 5%, with H_2O, dried and concentrated.

*5.4.1. Reaction of 3-phenyl-2H-azirine (**1a**) with ethyl 3-aminocrotonate (**5a**) and iron dichloride.* To a solution of azirine **1a** (433 mg, 3.70 mmol) in anhydrous CH_3CN (37 mL), enaminoester **5a** (1.926 g, 14.91 mmol) and $FeCl_2$ (491 mg, 3.87 mmol) were added. After 3 h and work up, the crude was purified by column chromatography (*n*-hexane/ethyl acetate from 95:5 to 1:1) to give ethyl 2-methyl-5-phenyl-pyrrole-3-carboxylate[12] (**6b**; 142 mg, 17%) [R_f (50% ethyl acetate/*n*-hexane) 0.49] and ethyl 2-methyl-4-phenyl-pyrrole-3-carboxylate[11] (**6a**; 37 mg, 4%) [R_f (50% ethyl acetate/*n*-hexane) 0.27].

*5.4.2. Reaction of 3-phenyl-2H-azirine (**1a**) with ethyl 3-aminocrotonate (**5a**) and iron trichloride.* To a solution of **1a** (406 mg, 3.47 mmol) in anhydrous CH_3CN (35 mL), enaminoester **5a** (1.789 g, 13.85 mmol) and $FeCl_3$ (563 mg, 3.47 mmol) were added. After 2 h and work up, the crude was purified by column chromatography (*n*-hexane/ethyl acetate from 95:5 to 1:1) to give ethyl 2-methyl-5-phenylpyrrole-3-carboxylate (**6b**; 9 mg, 1%) and ethyl 2-methyl-4-phenylpyrrole-3-carboxylate (**6a**; 144 mg, 18%).

5.5. General procedure for the reaction of azirine 1d with ethyl 3-aminocrotonate 5a with different promoters

To a solution of 2-carbomethoxy-phenylazirine **1d** (400 mg, 2.28 mmol) in appropriate anhydrous solvent (23 mL), ethyl 3-aminocrotonate **5a** (890 mg, 6.89 mmol) and the promoter (2.28 mmol) were added. The mixture was stirred under N_2 atmosphere at 80 °C (or lower temperatures as specified in Table 5). After 3 h dichloromethane and a solution of aq HCl 0.1 M were added to the reaction mixture. The organic layer was washed with aq $NaHCO_3$ 5%, with H_2O and dried upon Na_2SO_4. By concentration, a yellow solid precipitated and the solid was filtered to give **7a**. The residue was purified by column chromatography on silica gel (from *n*-hexane/ethyl acetate 8:2 to ethyl acetate/methanol 1:1) to give 4-ethyl 2-methyl 5-methyl-3-phenyl-1*H*-pyrrole-2,4-dicarboxylate[15] **6c** [R_f (50% ethyl acetate/*n*-hexane) 0.46] and (*Z*)-methyl 4-(1-aminoethylidene)-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate **7a**. Yields are reported in Tables 4 and 5.

Compound **7a**: yellow solid (EtOH), mp 254–255 °C; R_f (ethyl acetate) 0.13; IR (KBr) 3322, 1676, 1616, 1418, 1296, 1167 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 25 °C): δ 1.56 (s, 3H), 3.43 (s, 3H), 7.15–7.25 (m, 2H), 7.27–7.40 (m, 3H), 8.54 (br s, 1H), 9.88 (s, 1H), 10.62 (br s, 1H) ppm; ^{13}C NMR (62.9 MHz, DMSO-d_6, 25 °C): δ 19.6, 50.5, 101.7, 113.3, 126.9, 127.5, 128.9, 129.6, 136.0, 160.4, 165.8 ppm; EIMS: *m*/*z* 259 (21), 258 (M^+, 100), 225 (40), 169 (24). Elemental analysis for $C_{14}H_{14}N_2O_3$: calcd. C 65.11, H 5.46, N 10.85; found C 65.36, H 5.44, N 10.81.

5.6. Reaction of azirine 1d with ethyl 3-amino-3-*phenylacrylate* (5b)

To a solution of 2-carbomethoxy-phenylazirine (**1d**; 400 mg, 2.28 mmol) in anhydrous acetonitrile (23 mL), enaminoester **5b** (1.36 g, 7.11 mmol) and $AlCl_3$ (310 mg, 2.32 mmol) were added. The mixture was stirred under N_2 atmosphere at 80 °C. After 6 h water and CH_2Cl_2 were added and the mixture washed with aq $NaHCO_3$ 10% and then with water. The organic layer was separated and dried upon Na_2SO_4. By concentration a yellow solid precipitated and the solid was filtered to give **7b**. The residue was purified by column chromatography (*n*-hexane/ethyl acetate and ethyl acetate/methanol) to give 4-ethyl 2-methyl 3,5-diphenyl-1*H*-pyrrole-2,4-dicarboxylate (**6d**; 210 mg, 26%), and (*Z*)-methyl 4-(amino(phenyl)methylene)-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (**7b**) that was combined with the precipitate (500 mg, 68%).

Compound **6d**: white solid (ethyl acetate), mp 161–162 °C; R_f (50% ethyl acetate/*n*-hexane) 0.47; IR (KBr) 3445, 3297, 1719, 1675, 1448, 1263 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ 0.86 (t, *J*=7.0 Hz, 3H), 3.67 (s, 3H), 3.96 (q, *J*=7.0 Hz, 2H), 7.30–7.70 (m, 10H), 9.30 (br s, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 13.5, 51.6, 60.0, 114.9, 119.2, 127.2 (two overlapped signals), 128.3, 128.9, 129.0, 129.9, 131.1, 133.5, 134.3, 139.0, 161.4, 164.5 ppm. EIMS: *m*/*z* 350 (21), 349 (M^+, 100), 317 (44), 304 (22), 289 (28), 272 (86), 271 (38), 245 (21), 216 (40), 189 (41). Elemental analysis for $C_{21}H_{19}NO_4$: calcd. C 72.19, H 5.48, N 4.01; found C 72.22, H 5.50, N 3.99.

Compound **7b**: yellow solid (EtOH), mp 259–260 °C; R_f (ethyl acetate) 0.29; IR (KBr) 3431, 1712, 1639, 1551, 1486, 1282 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ 3.62 (s, 3H), 5.78 (br s, 1H), 6.80–7.20 (m, 10H), 7.94 (br s, 1H), 10.74 (br s, 1H) ppm; ^1H NMR (250 MHz, DMSO-d_6, 25 °C): δ 3.46 (s, 3H), 6.70–7.20 (m, 10H), 8.71 (br s, 1H), 10.21 (s, 1H), 10.76 (br s, 1H) ppm; ^{13}C NMR (62.9 MHz, DMSO-d_6, 25 °C): δ 50.6, 101.1, 114.3, 125.6, 126.1, 127.1, 128.0, 128.4, 129.2, 130.0, 133.3, 133.9, 160.3, 165.7, 166.9 ppm; EIMS: *m*/*z* 321 (23), 320 (M^+, 100), 287 (37), 232 (26), 231 (22). Elemental analysis for $C_{19}H_{16}N_2O_3$: calcd. C, 71.24, H 5.03, N 8.74; found: C 71.23, H 5.05, N 8.71.

*5.6.1. Crystal data and structure refinement for **7b**.* Crystals of **7b** suitable for single crystal X-ray diffraction were obtained by slow evaporation of an ethyl alcohol solution. Data were collected on a Bruker P4 diffractometer at room temperature, using graphite monochromated Cu-Kα radiation (λ=1.54178 Å) and $\omega/2\theta$ scans. No absorption correction was deemed necessary. $C_{19}H_{16}O_3N_2$, M_r=320.34, monoclinic, space group *C*2/*c* (no. 15), *a*=23.6370(13), *b*=9.9330(5), *c*=17.3870(13) Å, β=127.350(6)°, *V*=3245.1(3) $Å^3$, *Z*=8, D_c=1.311 Mg m^{-3}, μ=0.734 mm^{-1}, *F*(000)=1344; 3328 reflections (2735 unique, R_{int}=0.0248). The final refinement, for 231 refined parameters converged to $wR(F^2)$=0.1584 (*R*=0.0612) for 2735 unique reflections and to $wR(F^2)$=0.1517 (*R*=0.0551) for 2372 unique reflections with $I>2\sigma(I)$, with a final goodness of fit of 1.059. The structure was solved by direct methods and refined by full-matrix least squares using the SHEXTL v2011.4-1 suite of programs.[16] Non-hydrogen atoms were treated anisotropically. Standard distances of 0.96 and 0.93 Å were used, respectively, for aliphatic and aromatic C–Hs, whereas hydrogen atoms bound to nitrogen atoms were located by Fourier methods and refined. Crystallographic data for **7b** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 871184, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk.

5.7. General procedure for the reaction of azirine 1d with enaminones 8a–c

To a solution of azirine **1d** in anhydrous CH_3CN, enaminone **8** and $FeCl_3$ or $AlCl_3$ were added. The mixture was stirred under N_2 atmosphere at 80 °C. After 30–90 min dichloromethane and a solution of aq HCl 0.1 M were added to the reaction mixture. The organic layer was washed with aq $NaHCO_3$ 5%, with H_2O, dried and concentrated. The yields are given in Table 6.

*5.7.1. Reaction of azirine **1d** with 3-amino-1,3-diphenylprop-2-en-1-one (**8a**).* To a solution of azirine **1d** (455 mg, 2.60 mmol) in anhydrous CH_3CN (23 mL), enaminone **8a** (697 mg, 3.12 mmol) and $FeCl_3$ or $AlCl_3$ (3.12 mmol) were added. After 90 min and work up, the crude was purified by column chromatography (*n*-hexane/ethyl acetate from 95:5 to 2:8), to give methyl 3,5-diphenyl-1*H*-pyrrole-2-carboxylate (**11**)[15] [R_f (50% ethyl acetate/*n*-hexane) 0.57], methyl 4-benzoyl-3,5-diphenyl-1*H*-pyrrole-2-carboxylate (**10a**) and methyl 4-(imino(phenyl)methyl)-3,5-diphenyl-1*H*-pyrrole-2-carboxylate (**9a**). The yields are given in Table 6.

Compound **10a**: pale yellow crystals (EtOH), mp 168–169 °C; R_f (50% ethyl acetate/*n*-hexane) 0.46; IR (KBr) 3280, 1696, 1651, 1447, 1258 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ 3.68 (s, 3H), 7.05–7.75 (m, 15H), 9.75 (br s, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 51.6, 118.7, 123.2, 127.2, 127.3, 127.8, 128.0, 128.6 (two overlapped signals), 129.7, 130.2, 130.4, 132.5, 132.9, 133.1, 136.9, 138.1, 161.7, 193.8 ppm. EIMS: *m*/*z* 381 (M^+, 86), 349 (27), 273 (20), 272 (100), 216 (21), 189 (31), 174 (21). Elemental analysis for $C_{25}H_{19}NO_3$: calcd. C 78.72, H 5.02, N 3.67; found: C 78.93, H 5.04, N 3.69.

Compound **9a**: pale yellow crystals (EtOH), mp 180–181 °C; R_f (50% ethyl acetate/*n*-hexane) 0.33; IR (KBr) 3267, 1695, 1676, 1446, 1292, 1271 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6, 25 °C): δ 3.64 (s, 3H), 7.05–7.65 (m, 15H), 10.39 (s, 1H), 12.31 (br s, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 51.5, 118.7, 123.4, 127.2 (two overlapped signals), 127.5, 127.9, 128.0, 128.3, 128.7, 130.0 (two overlapped signals), 130.4, 131.9, 133.1, 134.0, 138.7, 161.7, 173.2 ppm; EIMS: *m*/*z* 380 (M^+, 34), 379 (64), 347 (100), 242 (29), 173 (24), 159 (42), 158 (41), 146 (20). Elemental analysis for $C_{25}H_{20}N_2O_2$: calcd. C 78.93, H 5.30, N 7.36; found: C 78.11, H 5.32, N 7.30.

*5.7.2. Reaction of azirine **1d** with 4-amino-pent-3-en-2-one (**8b**).* To a solution of azirine **1d** (424 mg, 2.42 mmol) in anhydrous CH_3CN (24 mL), enaminone **8b** (285 mg, 2.88 mmol) and $FeCl_3$ (467 mg, 2.88 mmol) were added. After 90 min and work up, the crude was recrystallized from EtOH to give methyl 4-acetyl-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylate[15] (**10b**; 354 mg, 57%).

*5.7.3. Reaction of azirine **1d** with 3-amino-1-phenyl-but-2-en-1-one (**8c**) and aluminium trichloride.* To a solution of azirine **1d** (422 mg, 2.41 mmol) in anhydrous CH_3CN (22 mL), enaminone **8c** (470 mg, 2.92 mmol) and $AlCl_3$ (385 mg, 2.89 mmol) were added. After 30 min and work up, the crude was purified by column chromatography (*n*-hexane/ethyl acetate from 9:1 to 2:8) to give **11** in traces, methyl 4-acetyl-3,5-diphenyl-1*H*-pyrrole-2-carboxylate (**10c**; 33 mg, 4%) and methyl 4-benzoyl-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylate (**10d**; 442 mg, 57%).

Compound **10c**: white solid (EtOAc), mp 134–135 °C; R_f (50% ethyl acetate/*n*-hexane) 0.44; IR (KBr) 3273, 1698, 1669, 1447, 1258, 1217 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ 1.90 (s, 3H), 3.64 (s, 3H); 7.30–7.62 (m, 10H); 9.47 (br s, 1H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 31.3, 51.6, 118.9, 124.9, 127.7, 127.8, 128.6, 128.9, 129.2, 130.0, 131.1, 132.3, 134.1, 137.5, 161.3, 197.4 ppm; EIMS: *m*/*z* 319 (M^+, 38), 304 (22), 272 (100), 189 (22), 113 (21). Elemental analysis for $C_{20}H_{17}NO_3$: calcd. C 75.22, H 5.37, N 4.39; found: C 75.50, H 5.39, N 4.41.

Compound **10d**: white solid (EtOAc), mp 179–180 °C; R_f (50% ethyl acetate/*n*-hexane) 0.37; IR (KBr) 3287, 1695, 1672, 1636, 1447, 1277 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ 2.45 (s, 3H), 3.72 (s, 3H), 6.95–7.35 (m, 8H), 7.48–7.58 (m, 2H), 9.74 (br s, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 13.1, 51.5, 116.8, 123.1, 126.9, 127.1, 127.7, 129.4, 130.6, 131.8, 132.7, 133.4, 137.5, 138.8, 161.9, 193.8 ppm; EIMS: *m*/*z* 319 (M^+, 50), 318 (50), 287 (23), 286 (100), 210 (73), 127 (33). Elemental analysis for $C_{20}H_{17}NO_3$: calcd. C 75.22, H 5.37, N 4.39; found: C 75.53, H 5.41, N 4.37.

*5.7.4. Reaction of azirine **1d** with 3-amino-1-phenyl-but-2-en-1-one (**8c**) and iron trichloride.* To a solution of azirine **1d** (417 mg, 2.38 mmol) in anhydrous CH_3CN (22 mL), enaminone **8c** (477 mg, 2.96 mmol) and $FeCl_3$ (464 mg, 2.86 mmol) were added. After 1 h and work up, the crude was purified by column chromatography (*n*-hexane/ethyl acetate from 9:1 to 2:8) to give methyl 3,5-diphenyl-1*H*-pyrrole-2-carboxylate (**11**; 57 mg, 9%), methyl 4-acetyl-3,5-diphenyl-1*H*-pyrrole-2-carboxylate(**10d**; 86 mg, 11%) and methyl 4-benzoyl-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylate (**10c**;342 mg, 45%).

Supplementary data

^1H and ^{13}C NMR spectra for compounds **3a**, **3c**, **3e**, **4a**, **7a**, **6d**, **7b**, **10a**, **9a**, **10c** and **10d**. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.06.069.

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