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Accessing polysubstituted oxazolidines, pyrrolidines and imidazolidines by regioselective [3+2] annulations of ketenimines with donor-acceptor oxiranes and aziridines

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Efficient [3+2] annulations of *N*-aryl-*C,C*-diphenyl ketenimines with metallo-carbonyl and metallo-azomethine ylides, generated *via* the respective $Yb(OTf)_3$ and $Y(OTf)_3$ promoted carbon-carbon bond heterolysis of donor-acceptor oxiranes and aziridines, have been accomplished. These reactions proceeded under mild conditions and supplied a general methodology for the regioselective construction of structurally complex oxazolidines and pyrrolidines. Moreover, heating neat mixtures of *N*-aryl-*C,C*-diphenyl ketenimines and diethyl aziridine-2,3-dicarboxylates led to imidazolidine derivatives. A computational study concluded in stepwise mechanisms for these [3+2] annulations, also shedding light on its regioselectivity concernig which of the two cumulated double bonds of the ketenimine becomes involved in the reaction with the ylide.

Introduction

Dipolar [3+2] cycloaddition reactions[1] are significant tools in modern organic chemistry considering their important applications in the synthesis of carbocyclic and heterocyclic compounds containing five-membered rings, a key structural motif found in the skeleton of natural products and drugs.[2]

Ketenimines, nitrogen-containing heterocumulenes characterized by their N=C=C triatomic moiety, are versatile substrates for the preparation of structurally diverse open-chain organic compounds and, to the greatest extent, nitrogenated heterocycles.[3] The chemical behaviour of ketenimines is largely dominated by their participation in pericyclic processes such as electrocyclic ring closures, sigmatropic rearrangements and cycloadditions.[4] Despite its clear synthetic potential, the applications of ketenimines in dipolar [3+2] cycloadditions remain rather exotic. Only a few examples of this type of 1,3-dipolar cycloadditions have been reported, in which ketenimines habitually play the role of the dipolarophilic 2π system involving either its cumulated N=C or C=C double bond.[5]

Donor-acceptor oxiranes, with anion- and cation-stabilizing groups at the vicinal carbons have emerged as important starting materials to generate 1,3-dipolar carbonyl ylides due to their tendency for strain-induced ring opening. Thus, donor-acceptor oxiranes, upon treatment with Lewis acids, participate in a range of [3+2] cycloadditions resulting in five-membered oxa-heterocyclic compounds. These processes imply the formation of a metallo-carbonyl ylide via the Lewis acid promoted C-C bond cleavage of the oxirane, which is then trapped by dipolarophiles bearing multiple bonds such as alkenes,[6] indoles,[7] alkynes,[8] nitriles,[9] aldehydes[10] and imines.[11] Some of these processes are highly diastereo- and enantioselective.

On the other hand, donor-acceptor aziridines under the catalysis of Lewis acids suffer selective carbon-carbon bond heterolytic breaking to form active metallo-azomethine ylides, subsequently captured by dipolarophiles in [3+2] cycloaddition reactions to produce five-membered nitrogen heterocycles. In this manner, a series of [3+2] cycloadditions of 2,2-diester aziridines has been successfully achieved with diverse reactants including alkenes,[12] alkynes,[13] 2,3-disubstituted indoles,[14] aldehydes,[15] imines,[16] isothiocyanates[17] and donor-acceptor cyclopropanes,[18] in many cases with high levels of sterocontrol.

Within the frame of our longstanding interest on the chemistry of ketenimines,[19] we recently disclosed the intermolecular $Sc(OTf)_3$ catalyzed [3+2] annulation reaction between trisubstituted ketenimines and donor-acceptor cyclopropanes, yielding highly functionalized pyrrolidines.[20] Ketenimines participate on these cyclizations selectively involving its cumulated N=C bond as the 2π component. Based on these findings we envisaged that ketenimines might undergo similar [3+2] annulations with donor-acceptor oxiranes and aziridines (Scheme 1). We here disclose that the

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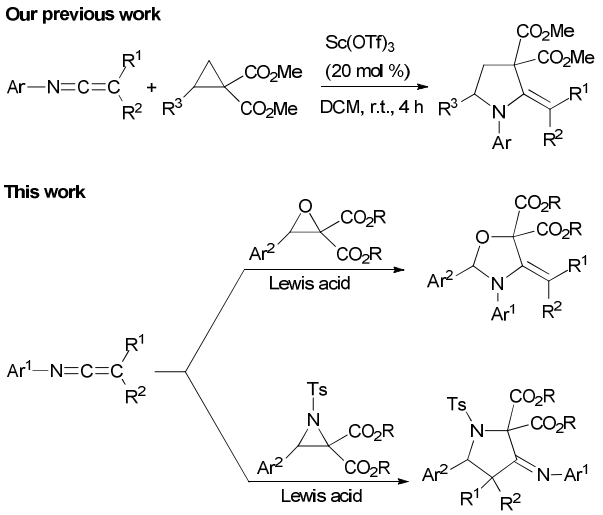
metallo-carbonyl ylides generated by the Lewis acid promoted C-C bond cleavage of donor-acceptor oxiranes are trapped exclusively by the N=C cumulated bond of ketenimines producing oxazolidines. In contrast, ketenimines use its C=C cumulated bond to capture metallo-azomethine ylides formed from the Lewis acid assisted C-C bond fragmentation of donor-acceptor aziridines yielding pyrrolidines. The mechanisms of these [3+2] annulation reactions have been computationally scrutinized by using DFT methods in order to understand the selectivity related to the cumulated double bond used by the ketenimines when reacting with both types of ylides.

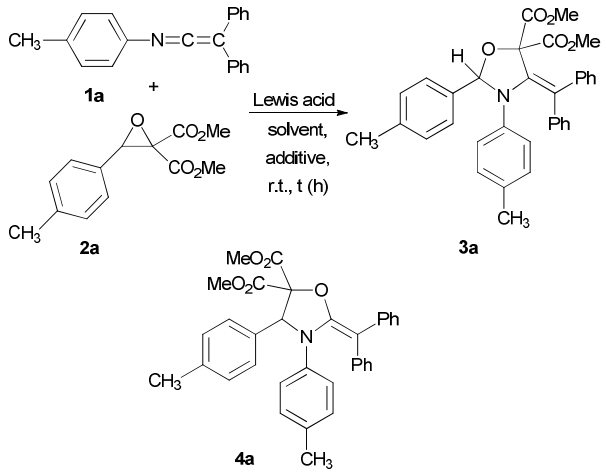


Scheme 1 [3+2] annulation of ketenimines with donor-acceptor cyclopropanes, oxiranes and aziridines

Results and Discusion

We selected the [3+2] annulation of ketenimine **1a** with the donor-acceptor oxirane **2a** as our starting point for screening different Lewis acids. The reactions were initially carried out in the presence of 25 mol% of the Lewis acid, in dichloromethane at room temperature. First no reaction was observed when using $Sc(OTf)_3$ or $Yb(OTf)_3$ as catalyst (Table 1, entries 1 and 3). Gratifyingly, the desired cycloaddition product **3a** was obtained running the reaction of **1a** with **2a** under the catalysis of the same Lewis acids but in the presence of 4 Å molecular sieves, thus showing the crucial role played by this additive (Table 1, entries 2 and 4). Other commonly used trifluoromethanesulfonate salts such as $In(OTf)_3$ and $Y(OTf)_3$ and the perchlorate salt $Ni(ClO_4)_2{\cdot}6H_2O$ (Table 1, entries 6, 8 and 10) were also shown to afford the targeted oxazolidine **3a** in low to moderate yields. The Lewis acids $Ga(OTf)_3$, $La(OTf)_3$ and $Cu(ClO_4)_2{\cdot}6H_2O$ turned out not to be catalytically active. Thus, among the catalysts essayed, $Yb(OTf)_3$ provided the best result: consumption of the starting ketenimine **1a** occurred after 6 hours affording the

Table 1 Optimization of the reaction conditions[a] of the [3+2] annulation between ketenimine **1a** and activated oxirane **2a**



entry	Lewis acid[b]	LA mol%	additive	Solvent	Time (h)	Yield[c] (%)
1	$Sc(OTf)_3$	25	none	DCM	24	0
2	$Sc(OTf)_3$	25	4 Å MS	DCM	24	52
3	$Yb(OTf)_3$	25	none	DCM	24	0
4	$Yb(OTf)_3$	25	4 Å MS	DCM	6	78
5	$Ga(OTf)_3$	25	4 Å MS	DCM	48	0
6	$In(OTf)_3$	25	4 Å MS	DCM	24	34
7	$La(OTf)_3$	25	4 Å MS	DCM	24	trace
8	$Y(OTf)_3$	25	4 Å MS	DCM	24	76
9	$Cu(ClO_4)_2$	25	4 Å MS	DCM	24	trace
10	$Ni(ClO_4)_2$	25	4 Å MS	DCM	8	75
11	$Yb(OTf)_3$	25	4 Å MS	toluene	24	40
12	$Yb(OTf)_3$	25	4 Å MS	1,2-DCE	6	97
13	$Yb(OTf)_3$	20	4 Å MS	1,2-DCE	6	97
14	$Yb(OTf)_3$	10	4 Å MS	1,2-DCE	6	77
15	$Sn(OTf)_2$	25	none	DCM	24	0
16	$Sn(OTf)_2$	25	4 Å MS	DCM	24	0
17	$Hg(OTf)_2$	25	4 Å MS	DCM	48	0
18	$Hg(ClO_4)_2$	25	4 Å MS	DCM	48	0

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.46 mmol), Lewis acid (25 mol%) and activated 4 Å MS (240 mg) in 8 mL of anhydrous solvent at room temperature, under nitrogen.

[b] $Cu(ClO_4)_2$, $Ni(ClO_4)_2$ and $Hg(ClO_4)_2$ were used as the hexahydrate salts.

[c] Isolated yields.

oxazolidine **3a** in the highest yield (78%, Table 1, entry 4). A short survey of other solvents, toluene or 1,2-dichloroethane (1,2-DCE) revealed that the reaction media has a significant effect on the yield. When the reaction was performed in toluene the yield decreased to 40% (Table 1, entry 11), whereas in 1,2-dichloroethane the yield increased to 97% (Table 1, entry 12). In 1,2-dichloroethane solution a slight reduction of the $Yb(OTf)_3$ loading to 20 mol% was not detrimental to the yield of **3a** (97%, Table 1, entry 13), although further lowering to 10 mol% decreased the yield to 77% (Table 1, entry 14).

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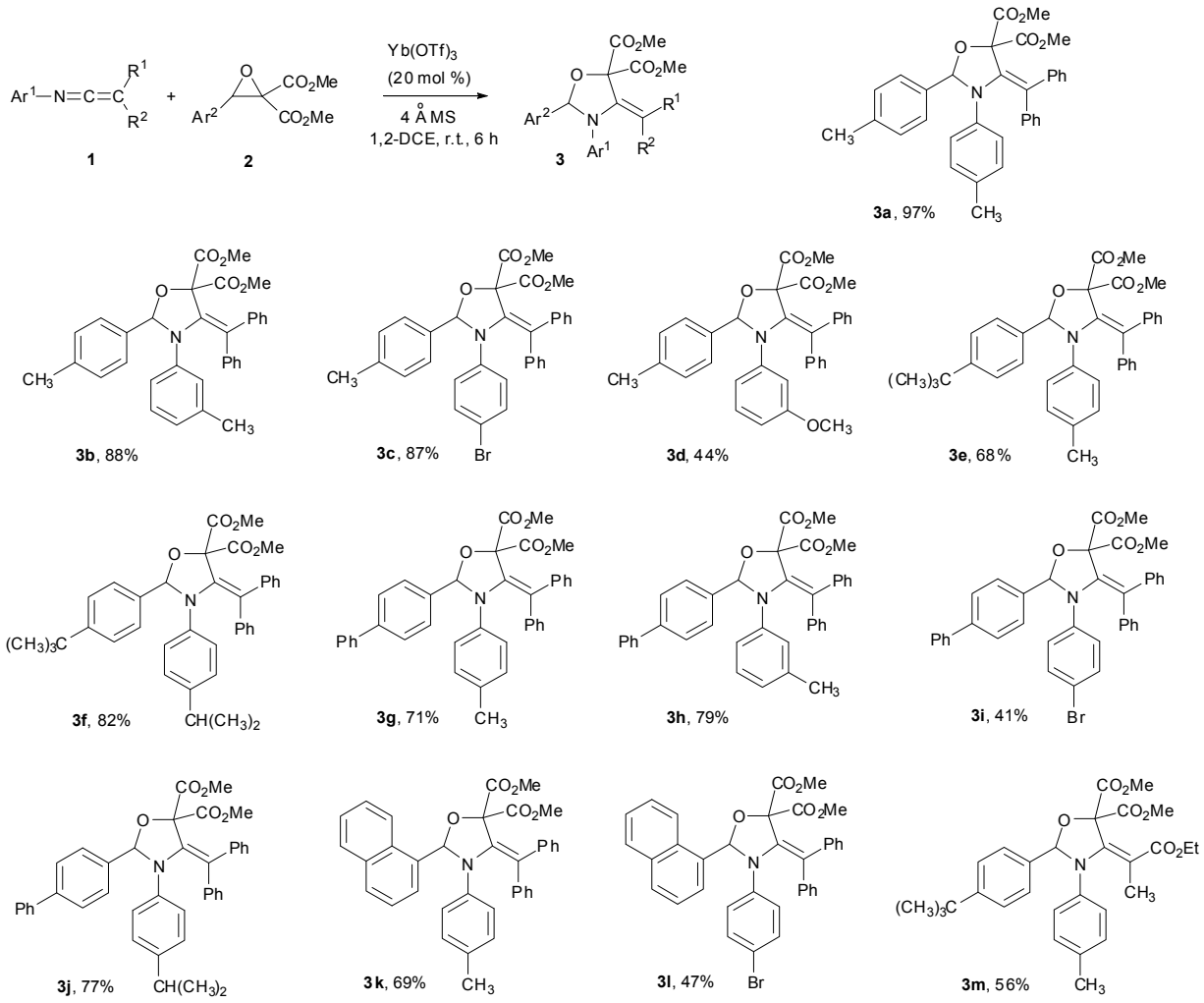

Scheme 2 Synthesis of oxazolidines **3**

It is worth to mention that the isomeric oxazolidine **4a**, which may result via C-O bond cleavage of the oxirane **2a**, was never detected under the described conditions. Moreover, the divergent synthesis of **4a** was attempted under the catalysis of $Sn(OTf)_2$, $Hg(OTf)_2$ and $Hg(ClO_4)_2{\cdot}6H_2O$ (Table 1, entries 15-18), which have been proven to be catalysts promoting the cleavage of the C-O bond of oxirane rings.[10a] Unfortunatelly these catalysts were not effective for the expected alternative annulation as complex reaction mixtures of unidentified products were obtained.

Therefore, the optimal reaction conditions were selected as follows: ketenimine **1**, donor-acceptor oxirane **2** (1.15 equiv), $Yb(OTf)_3$ (20 mol%) and 4 Å MS in anhydrous 1,2-dichloroethane (0.05 M in ketenimine **1**) at room temperature. Under these conditions the reactions of various ketenimines **1** with several donor-acceptor oxiranes **2** were investigated, and the results are shown in Scheme 2. Different electron-donating

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and electron-withdrawing groups were tolerated in the aryl moiety at the nitrogen atom of the *N*-aryl-*C,C*-diphenyl ketenimines **1**. With respect to the oxiranediesters **2** phenyl rings bearing electron-donating groups [CH_3-, $(CH_3)_3C$- and Ph] or a 1-naphthyl fragment at C3 were compatible and underwent the reaction efficiently. Meanwhile, in our hands, an electron-withdrawing group such as Cl at the *para* position of the C3-phenyl ring prevented the [3+2] annulation. This may be consequence of the destabilization of the positive charge of the carbonyl ylide intermediate by the electron deficient aryl group.

The multi-substituted oxazolidines **3** were identified by ^1H and ^{13}C NMR analyses, as well as by X-ray crystal structure determination of **3a** (Figure 1). The oxazolidine ring presents an envelope conformation, retained by the intramolecular hydrogen bond C42-H42…O4, established between the hydrogen of a phenyl moiety at the exocyclic C=C double bond and the carbonyl oxygen atom of one of the ester groups at C3. The (*E*) configuration of the exocyclic carbon-carbon double

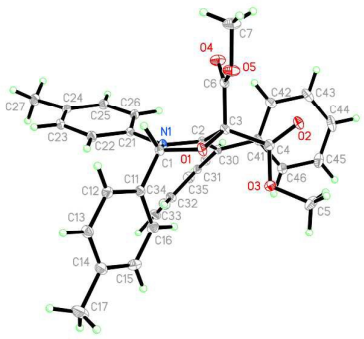


Figure 1 Solid-state molecular structure of **3a**. Thermal ellipsoids are drawn at the 50% probability level

bond of compound **3m** was determined with the help of a NOESY experiment.

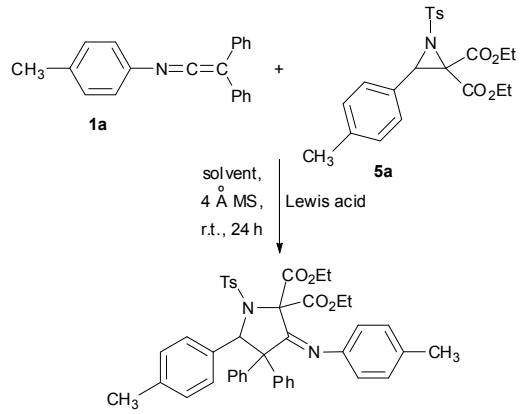
In these [3+2] annulations involving activated oxiranes the ketenimine participates as the dipolarophilic component exclusively via its N=C cumulated double bond.

Next we investigated the [3+2] annulation of ketenimines with donor-acceptor aziridines. Initial reaction development focused on the reaction of *N*-(4-methylphenyl)-*C,C*-diphenylketenimine **1a** and diethyl 3-(4-methylphenyl)-*N*-tosylaziridine-2,2-dicarboxylate **5a** as model reactants. A representative selection of trifluoromethanesulfonate salts, including $Ga(OTf)_3$, $In(OTf)_3$, $La(OTf)_3$, $Sc(OTf)_3$, $Sn(OTf)_2$, $Y(OTf)_3$ and $Yb(OTf)_3$ were tested in dichloromethane solution at room temperature in the presence of 4 Å molecular sieves (Table 2). The molecular sieves were added to the reaction medium as it is known that the starting aziridine **5a** easily undergoes Lewis acid catalysed decomposition by reacting with trace amounts of water. In this respect, a slight excess (1.1 equiv) of the *N*-tosyl aziridine **5a** was used. All the Lewis acids examined were found to catalyse the generation of the metallo-azomethine ylide from the donor-acceptor aziridine **5a** and its [3+2] annulation with ketenimine **1a**, yielding a cycloadduct identified as the multi-substituted pyrrolidine **6a**.

Notably $Y(OTf)_3$ gave the highest yield (Table 2, entry 6). With $Y(OTf)_3$ as the optimal catalyst further attempts to improve the results focused on the solvent. Alternative solvents such as toluene and 1,2-dichloroethane were tested. The reaction carried out in 1,2-dichloroethane gave **6a** in 57% yield (Table 2, entry 9), whereas in toluene only traces of the product were detected by thin layer chromatography (Table 2, entry 8). The amount of catalyst was also screened: when the loading of $Y(OTf)_3$ decreased to 20 and 10 mol% there was a significant drop in the yields of the reactions to 62% and 67%, respectively (Table 2, entries 10 and 11).

Examples of pyrrolidines **6** obtained by the [3+2] annulation of several ketenimines **1** with two different donor-acceptor aziridines **5**, promoted by $Y(OTf)_3$ as catalyst under the optimal reaction conditions of entry 6, are summarized in Scheme 3.

Table 2 Optimization of the reaction conditions[a] of the [3+2] annulation between ketenimine **1a** and activated aziridine **5a**



entry	Lewis acid	LA mol%	Solvent	Yield[b] (%)
1	$Ga(OTf)_3$	25	DCM	28
2	$In(OTf)_3$	25	DCM	73
3	$La(OTf)_3$	25	DCM	41
4	$Sc(OTf)_3$	25	DCM	65
5	$Sn(OTf)_3$	25	DCM	44
6	$Y(OTf)_3$	25	DCM	84
7	$Yb(OTf)_3$	25	DCM	68
8	$Y(OTf)_3$	25	toluene	traces
9	$Y(OTf)_3$	25	1,2-DCE	57
10	$Y(OTf)_3$	20	DCM	62
11	$Y(OTf)_3$	10	DCM	67

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.44 mmol), Lewis acid (25 mol%) and activated 4 Å MS (240 mg) in 8 mL of anhydrous solvent at room temperature, under nitrogen.

[b] Isolated yields.

Single-crystal X-ray structure of pyrrolidine **6a** showed that the pyrrolidine ring presents an envelope conformation (Figure 2), and this conformation is stabilized by a π-π stacking

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interaction between the aromatic rings of the *p*-tolyl moieties C21-C26 and C11-C16 attached to C1 and to the sulfonyl group, respectively. The distance between the centroids of these planes is 3.71 Å.

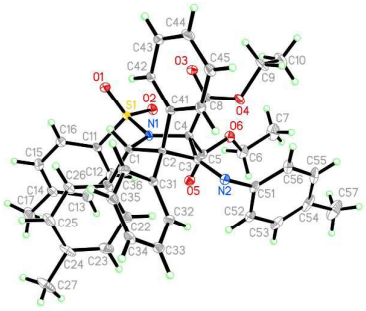
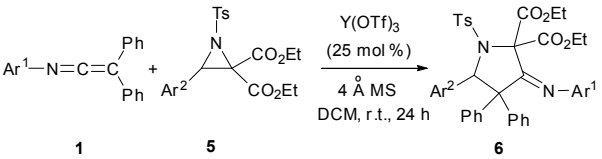
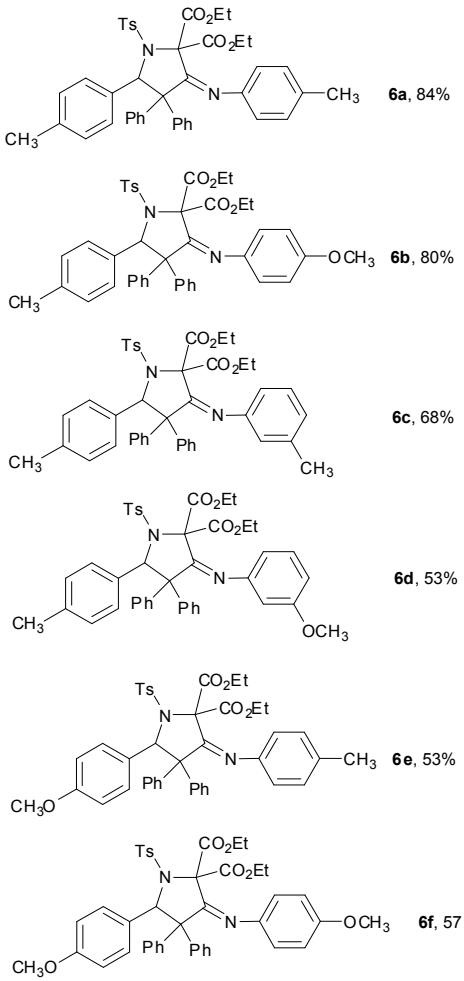


Figure 2 Solid-state molecular structure of **6a**. Thermal ellipsoids are drawn at the 50% probability level



1 **5** **6**



Scheme 3 Synthesis of pyrrolidines **6**

All these Lewis acid catalysed [3+2] annulations involving activated aziridines take place with the selective participation of the ketenimine as dipolarophile through its C=C cumulated double bond.

It is also well known that upon thermal treatment aziridines undergo electrocyclic ring-opening at the carbon-carbon bond resulting into azomethine ylides.[21] Thus, at that point of our investigation we decided to study the [3+2] cycloaddition between aziridines and ketenimines under thermal conditions as a complementary methodology. Following a brief search for optimal conditions, we found that by heating at 115-120 °C, in the absence of solvent, mixtures of ketenimines **1** and diethyl *cis*-1-(4-methylphenyl)aziridine-2,3-dicarboxylate **7** (1.5 equiv) the respective imidazolidines **8** were obtained in high yields (Scheme 4). These reactions are regio and diastereoselective affording only *trans*-adducts.

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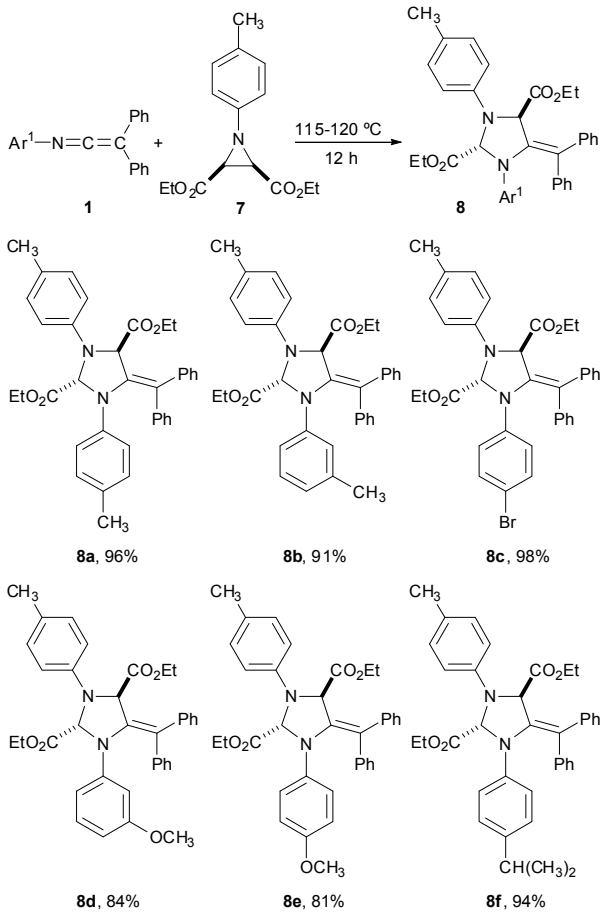


Scheme 4 Synthesis of imidazolidines **8**

The structure of products **8** was supported by an X-ray crystallographic analysis of a monocrystal of **8a** (Figure 3), allowing the assignment of the *trans* orientation of its two ethoxycarbonyl groups. The central imidazolidine ring has a slightly deflected envelope conformation.

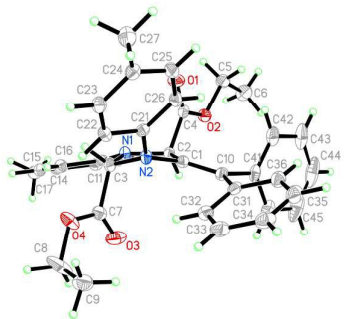
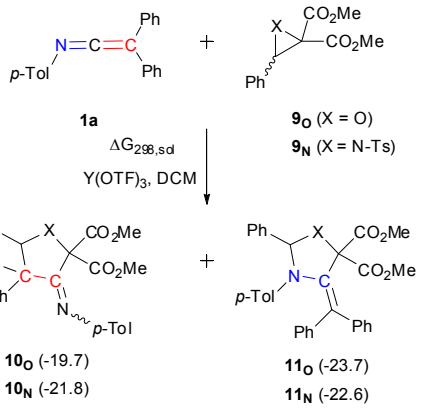


Figure 3 Solid-state molecular structure of **8a**. Thermal ellipsoids are drawn at the 50% probability level

Interestingly, under conventional heating ketenimines **1** participate in the [3+2] cycloaddition with the *in situ* generated azomethine ylide as the 2π component via its N=C double bond.



Scheme 5 Reaction free energies for the formation of the products **10** and **11** computed at the M06/6-311+G(d,p)/SDD//SMD(DCM)/B3PW91/6-31g(d)/SDD theoretical level. The Gibbs Free Energies are reported in kcal/mol (1 atm and 298 K), relative to **1a** + **9** are shown

An overview of the above results reveals that the mode in which ketenimines **1** take part as dipolarophiles in the [3+2] annulation processes significantly depends on the nature of the three-membered heterocyclic counterpart, either oxiranes **2** or aziridines **5** and **7**, as well as on the reaction conditions. A DFT study of the mechanism of these annulation reactions was performed, mainly motivated for finding an explanation to the formation, somewhat unexpectedly, of the pyrrolidines **6**, the only instances in which ketenimines react through its C=C cumulated bond.

This theoretical analysis started by computing the reaction free energies $\Delta G_{298,sol}$ of the Y-catalyzed reaction between ketenimine **1a** and the simplified aziridine $\mathbf{9_N}$ (X=N-Ts) and oxirane $\mathbf{9_o}$ (X=O), to yield the possible products resulting either *via* participation of the heterocumulenic C=C bond leading to **10** or the heterocumulenic C=N double bond leading to **11** (Scheme 5). In the case involving the oxirane $\mathbf{9_o}$ the oxazolidine $\mathbf{11_O}$ is about +4.0 kcal/mol more stable than the tetrahydrofuran $\mathbf{10_O}$.

When the aziridine $\mathbf{9_N}$ reacts with the ketenimine **1a** both potential azacyclic products $\mathbf{10_N}$ and $\mathbf{11_N}$ present very similar reaction free energies, -21.8 and -22.6 kcal/mol respectively, the diazacycle $\mathbf{11_N}$ being the most thermodynamically stable reaction product. Thus, the computations predict that the annulation of the heterocycles **9** with the ketenimine **1a** *via* its C=N double bond should drive to the most stable products **11** as far as the processes are thermodynamically controlled. It is remarkable that this mode of annulation is that experimentally observed in the reaction of ketenimines **1** with the oxiranes **2**, for yielding oxazolidines **3**, but not the case of the annulations involving aziridines **5**, that furnish pyrrolidines **6** as result of participating the C=C bond of the ketenimines **1**. For this reason, here we will comment on the results obtained for the computations related to the conversion **1a** + $\mathbf{9_N} \rightarrow \mathbf{10_N}/\mathbf{11_N}$ (see ESI for the computational study realized for the mechanism of the transformation **1a** + $\mathbf{9_O} \rightarrow \mathbf{10_O}/\mathbf{11_O}$).

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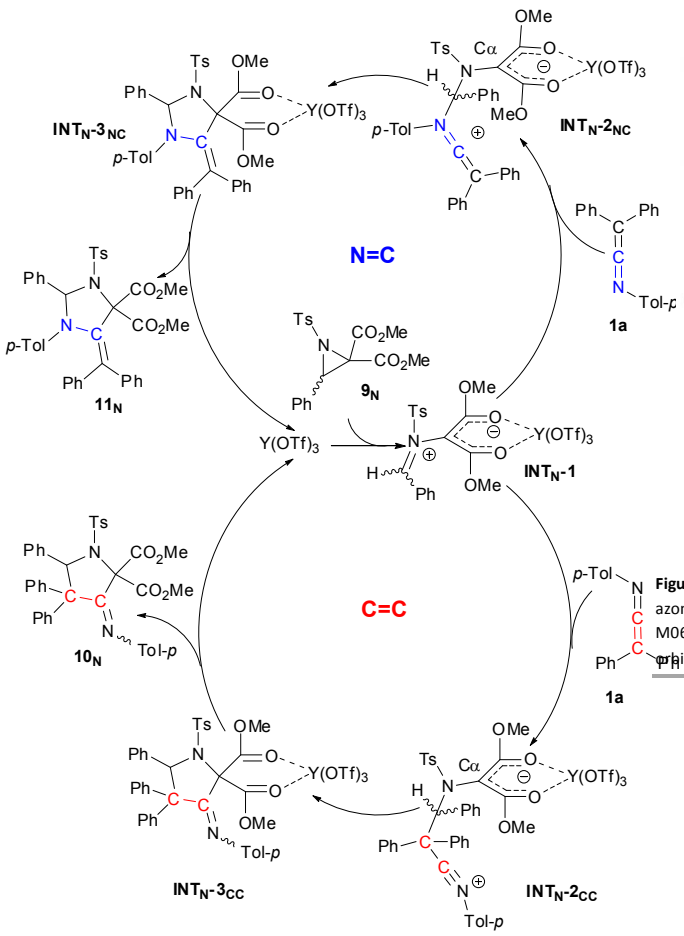

Scheme 6 Proposed mechanisms to the formation of the products **10$_N$** and **11$_N$**

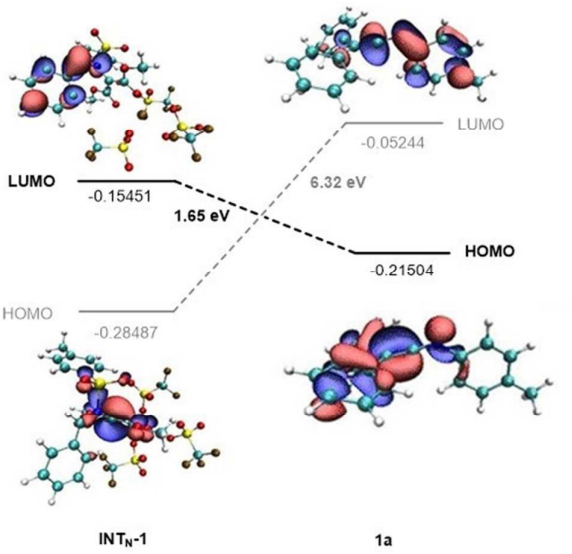

Figure 4 Frontier Molecular Orbital diagram. HOMO and LUMO levels of the azomethine ylide **INT$_N$-1** (left) and the ketenimine **1a** (right). Energies computed at M06/6-311+G(d,p)/SDD//SMD(DCM)/B3PW91/6-31g(d)/SDD theoretical level. The orbital surfaces are plotted with an isovalue of +0.04 (blue) and -0.04 (red)

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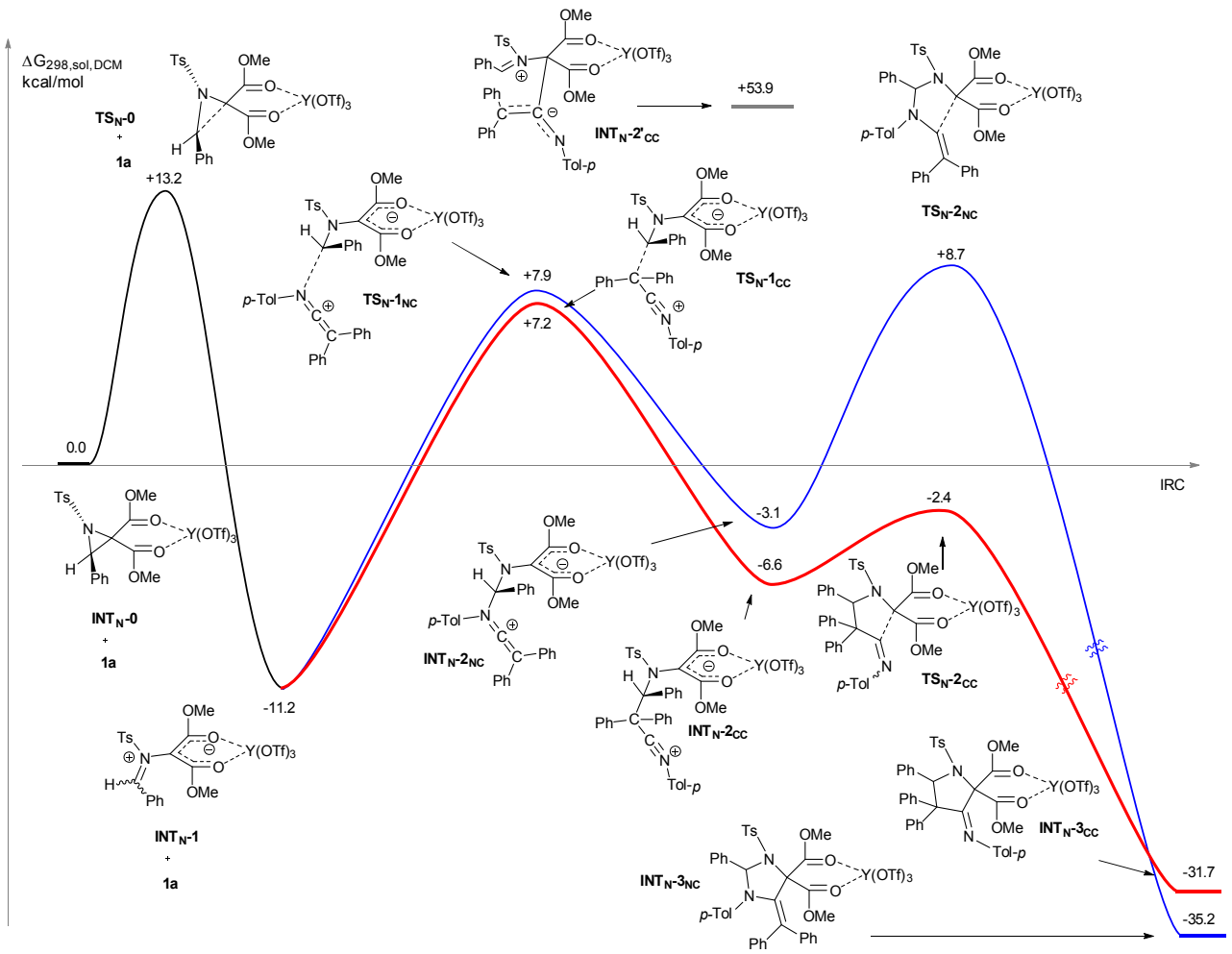

Scheme 7. Computed mechanisms for the reaction between the ketenimine **1a** and the aziridine complex $\mathbf{INT_N\text{-}0}$ to form the intermediates $\mathbf{INT_N\text{-}3_{NC}}$ (blue path) and $\mathbf{INT_N\text{-}3_{CC}}$ (red path). Computations were performed at the M06/6-311+G(d,p)/SDD//SMD(DCM)/B3PW91/6-31g(d)/SDD theoretical level. The Gibbs Free Energies of the best conformer computed are reported in kcal/mol (1atm and 298K), relative to $\mathbf{INT_N\text{-}0}$ +**1a** are shown.

Two plausible mechanisms are conceivable for the annulation of the aziridine $\mathbf{9_N}$ with the heterocumulene **1a** depending on which double bond of this last one, either C=C or N=C, is acting as 2π component in the process (Scheme 6). First, intermediate $\mathbf{INT_N\text{-}1}$ is expected to be formed after the coordination of the azacycle $\mathbf{9_N}$ to the yttrium metal through its two carbonyl groups and the further C-C bond break of the three-membered ring. At this point, either the terminal C or N atom of the ketenimine fragment could attack the electron deficient benzylic carbon atom of $\mathbf{INT_N\text{-}1}$, leading respectively to the intermediates $\mathbf{INT_N\text{-}2_{CC}}$ and $\mathbf{INT_N\text{-}2_{NC}}$. The subsequent ring-closing process at both $\mathbf{INT_N\text{-}2}$, involving the C-C bond formation between the central carbon atom of the original heterocumulene **1a** and the C_α-atom of the initial malonate moiety, would yield the annulated complexes $\mathbf{INT_N\text{-}3_{CC}}$ and $\mathbf{INT_N\text{-}3_{NC}}$. Finally, further departure of the $Y(OTf)_3$ catalyst would generate the respective five-membered heterocycles $\mathbf{10_N}$ and $\mathbf{11_N}$.

The products $\mathbf{10_N}$ and $\mathbf{11_N}$ could be also formed by inverting the order of the mechanistic steps, that is *via* an initial attack of the C_α-atom of $\mathbf{INT_N\text{-}1}$ to the electrophilic central carbon atom of the ketenimine **1a**, followed by a ring-

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closure process through the extreme C or N atom coming from the heterocumulene and the benzylic carbon atom of the ylide **INT_N-1** (see ESI). However, these alternative paths were discarded by taking into account the results of the Frontier Molecular Orbital (FMO) analysis applied to the reaction between the azomethine ylide **INT_N-1** and the ketenimine **1a** (Figure 4). The computed HOMO-LUMO gaps indicate that the more favoured attacking mode is that involving the HOMO of the ketenimine **1a** and the LUMO of the ylide **INT_N-1** (1.65 eV). The HOMO of ketenimine **1a** shows the electron density located along the C=C=N axis, while in the LUMO of the ylide **INT_N-1** it is mostly placed at the benzylic carbon atom next to the nitrogen atom. Thus, the FMO analysis supports the proposed initial attack of the extreme C/N atom of the ketenimine **1a** to the benzylic carbon atom of the ylide **INT_N-1**.

Then, the Potential Energy Surfaces (PESs) of the formation of the two possible Y-annulated complexes **INT_N-3_{CC}** and **INT_N-3_{NC}** were computed (Scheme 7). The initial aziridine complex **INT_N-0** converts into the metallo-azomethine ylide **INT_N-1** (-11.2 kcal/mol) via a ring-opening process through the transition structure **TS_N-0** ($\Delta G^{\neq}$= +13.2 kcal/mol). Next, the intermediate **INT_N-2_{CC}** is formed overpassing an energy barrier of +18.4 kcal/mol while the conversion into intermediate **INT_N-2_{NC}** requires a slightly higher energetic demand ($\Delta G^{\neq}$= +19.1 kcal/mol). Concerted transition structures were not located at this level of theory.

The computed relative energies of **TS_N-1_{NC}** and **TS_N-1_{CC}** correlate with the lengths of the forming bonds at both transition structures, **TS_N-1_{NC}** (dN-C = 2.05 Å) and **TS_N-1_{CC}** (dC-C = 2.23 Å), the shortest one determining a higher steric congestion around the respective bond and so a higher energy (Figure 5). It should be noted that the intermediate **INT_N-2'$_{CC}$** resulting of the initial C-C_α bond formation was also located but presents a relative free energy of +53.9 kcal/mol, much higher than those of the intermediates **INT_N-2_{CC}** and **INT_N-2_{NC}** (-6.6 and -3.1 kcal/mol, respectively). Once these later complexes are formed they are prone to cyclize forming a five-membered ring at **INT_N-3_{CC}** and **INT_N-3_{NC}**. Computations predict that while the intermediate **INT_N-2_{CC}** progresses quite easily toward **INT_N-3_{CC}**, whose formation takes place through **TS_N-2_{cc}** $\Delta G^{\neq}$ = +4.2 kcal/mol, the pathway driving to **INT_N-3_{NC}** could be reversible once **INT_N-2_{NC}** is formed. It is necessary to surmount an energetic barrier of +11.8 kcal/mol, via **TS_N-2_{NC}**, to get the cyclic complex **INT_N-3_{NC}**, whereas the reverse conversion toward the ylide **INT_N-1** and the ketenimine **1a** is easier, $\Delta G_r^{\neq}$= +11.0 kcal/mol.

Regarding the exocyclic N=C bond at the intermediate **INT_N-3_{CC}**, it presents a *Z* stereochemistry, matching with that found in the X-ray crystal structure of the pyrrolidine **6a**. The transition structure **TS_N-2_{CC}** shows the C=N=C_{Ar} angle of 173.8° whereas the lone pair of the N atom is located antiperiplanar respect to the forming C-C_α bond, thus finally leading to the *Z*-N=C exocyclic bond geometry of the resulting **INT_N-3_{CC}** (see ESI).

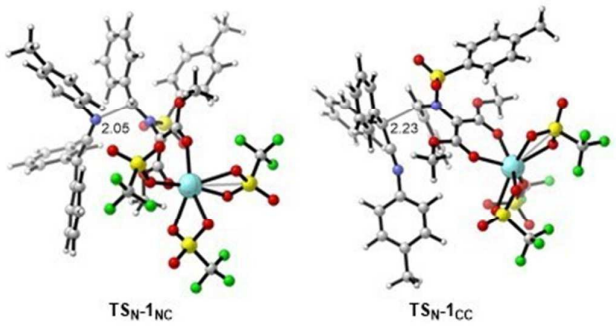

Figure 5 Computed transition structures **TS_N-1_{NC}** and **TS_N-1_{CC}** for the both proposed pathways shown in Figure 3. Distances are shown in Angstrom

In both mechanistic routes, and according to the transition-state theory, the rate-determining step is the initial attack of the ketenimine **1a** to the ylide **INT_N-1**, being the pathway leading to intermediate **INT_N-3_{CC}** the kinetically preferred by less than +1.0 kcal/mol over that ending at **INT_N-3_{NC}**. This fact suggests that both pathways are kinetically very competitive and the potential reversibility of the C=N pathway should be the key fact that would predict the formation of the experimentally obtained pyrrolidines **6**.

Conclusions

In conclusion, we have disclosed a [3+2] annulation of trisubstituted ketenimines with metallo-carbonyl and metallo-azomethine ylides obtained from Lewis acid-catalyzed C-C bond cleavages of oxirane and aziridine 2,2-diesters. This protocol allowed the efficient production, under mild conditions, of a variety of novel highly functionalized oxazolidines and pyrrolidines. Azomethine ylides generated thermally from aziridine 2,3-diesters also undergo a similar annulation with ketenimines producing imidazolidines in high yields. Computational mechanistic investigations suggested that the process leading to the oxazolidines in which the ketenimines involve its C=N bond is kinetically and thermodynamically favoured. On the other hand, the formation of the pyrrolidines, that involves the participation of the ketenimines as dipolarophiles through its C=C bond, seems to be controlled by the reversibility of the alternative pathway involving the C=N of the ketenimine.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) K. V. Gothelf, K. A. Jorgersen, *Chem. Rev.*, 1998, **98**, 863; (b) H.-W. Fruhauf, *Coord. Chem. Rev.*, 2002, **230**, 79; (c) S. Kanemasa, *Synlett*, 2002, 1371; (d) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; (e) V. Nair, T. D. Suja, *Tetrahedron*, 2007, **63**, 12247; (f) H. Pellissier, *Tetrahedron*, 2007, **63**, 3235; (g) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117; (h) N. T. Patil, Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395; (i) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051; (j) M. Bartok, *Chem. Rev.*, 2010, **110**, 1663; (k) Y. Xing, N.-X. Wang, *Coord. Chem. Rev.*, 2012, **256**, 938; (l) A. L. Cardoso, T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem*., 2012, 6479.

2 (a) M. Baumann, I. R. Baxendale, S. L. Ley, N. Nikbin, *Beilstein J. Org. Chem*., 2011, **7**, 442; (b) D. J. Newman, G. M. Cragg, *J. Nat. Prod.*, 2016, **79**, 629; (c) E. K. Davison, J. Sperry, *J. Nat. Prod*., 2017, **80**, 3060.

3 M. Alajarin, A. Vidal, F. Tovar, *Targets Heterocycl. Syst.*, 2000, **4**, 293.

4 For reviews on the chemistry of ketenimines, see: (a) H. Perst, *Science of Synthesis*, 2006, **23**, 781; (b) E. J. Yoo, S. Chang, *Curr. Org. Chem*., 2009, **13**, 1766; (c) P. Lu, Y. Wang, *Synlett*, 2010, 165; (d) M. Alajarin, M. Marin-Luna, A. Vidal, *Eur. J. Org. Chem.*, 2012, 5637; (e) P. Lu, Y. Wang, *Chem. Soc. Rev*., 2012, **41**, 5687; (f) R. H. Dodd, K. Cariou, *Chem. Eur. J*., 2018, **24**, 2297.

5 (a) M. W. Barker, W. E. McHenry, *J. Org. Chem*., 1979, **44**, 1175; (b) S. Li, Y. Luo, J. Wu, *Org. Lett.*, 2011, **13**, 4312; (c) H. Giera, R. Huisgen, K. Polborn, *Eur. J. Org. Chem*., 2005, 3781; (d) T. Aoyama, T. Nakano, K. Marumo, Y. Uno, T. Shioiri, *Synthesis*, 1991, 1163; (e) T. Aoyama, S. Katsuta, T. Shioiri, *Heterocycles*, 1989, **28**, 123; (f) A. Martvon, S. Stankovsky, J. Svetlík, *Collect. Czech, Chem. Commun*., 1975, **40**, 1199; (g) M. W. Barker, J. H. Gardner, *J. Heterocycl. Chem*., 1969, **6**, 251; (h) J. Svetlík, A. Martvon, *Collect. Czech. Chem. Commun.*, 1979, **44**, 2421; (i) W. J. Kauffman, *J. Org. Chem*., 1970, **35**, 4244; (j) H. Maas, C. Bensimon, H. Alper, *J. Org. Chem.*, 1998, **63**, 17; (k) C. Larksap, O. Sellier, H. Alper, *J. Org. Chem*., 2001, **66**, 3502; (l) N. Murai, M. Komatsu, Y. Ohshiro, Y. Agawa, *J. Org. Chem*., 1977, **42**, 448; (m) Y. Cheng, Y.-G. Ma, X.-R. Wang, J.-M. Mo, *J. Org. Chem*., 2009, **74**, 850; (n) J.-M. Mo, Y.-G. Ma, Y. Cheng, *Org. Biomol. Chem*., 2009, **7**, 5010; (o) M. Alajarin, B. Bonillo, M.-M. Ortin, R.-A. Orenes, A. Vidal, *Org. Biomol. Chem.*, 2011, **9**, 6741; (p) J. Ruiz, F. Marquinez, V. Riera, M. Vivanco, S. Garcia-Granda, M. R. Diaz, *Angew. Chem. Int. Ed*., 2000, **39**, 1821; (q) J. Ruiz, F. Marquinez, V. Riera, M. Vivanco, S. Garcia-Granda, M. R. Diaz, *Chem. Eur. J.*, 2002, **8**, 3872.

6 (a) R. Huisgen, P. de March, *J. Am. Chem. Soc*., 1982, **104**, 4953; (b) X. Yuan, L. Lin, W. Chen, W. Wu, X. Liu, X. Feng, *J. Org. Chem*., 2016, **81**, 1237.

7 (a) J. Zhang, Z. Chen., H.-H. Wu, J. Zhang, *Chem. Commun*., 2012, **48**, 1817; (b) W. Chen, Y. Xia, L. Lin, X. Yuan, S. Guo, X. Liu, X. Feng, *Chem. Eur. J*., 2015, **21**, 15104.

8 (a) R. Liu, M. Zhang, J. Zhang, *Chem. Commun*., 2011, **47**, 12870; (b) W. Chen, X. Fu, L. Lin, X. Yuan, W. Luo, J. Feng, X. Liu, X. Feng, *Chem. Commun*., 2014, **50**, 11480.

9 (a) H. Zhou, X. Zeng, L. Ding, Y. Xie, G. Zhong, *Org. Lett*., 2015, **17**, 2385; (b) H. Zhou, X. Zeng, Y. Xie, G. Zhong, *Synlett*, 2015, 1693.

10 (a) Z. Chen, Z. Tian, J. Zhang, J. Ma, J. Zhang, *Chem. Eur. J*., 2012, **18**, 8591; (b) Z. Chen, L. Wei, J. Zhang, *Org. Lett*., 2011, **13**, 1170; (c) W. Chen, L. Lin, Y. Cai, Y. Xia, W. Cao, X. Liu, X. Feng, *Chem. Commun*., 2014, **50**, 2161; (d) Z. Tian, Y. Xiao, X. Yuan, Z. Chen, J. Zhang, J. Ma, *Organometallics*, 2014, **33**, 1715.

11 J. Zhang, Y. Xiao, J. Zhang, *Adv. Synth. Catal*., 2013, **355**, 2793.

12 (a) M. Vaultier, R. Carrié, *Tetrahedron Lett*., 1978, **19**, 1195; (b) P. D. Pohlhaus, R. K. Bowman, J. S. Johnson, *J. Am. Chem. Soc*., 2004, **126**, 2294; (c) L. Li, X. Wu, J. Zhang, *Chem. Commun*., 2011, **47**, 5049; (d) A. S. Pankova, M. A. Kuznetsov, *Tetrahedron Lett*., 2014, **55**, 2499; (e) B. Wang, M. Liang, J. Tang, Y. Deng, J. Zhao, H. Sun, C.-H. Tung, J. Jia, Z. Xu, *Org. Lett*., 2016, **18**, 4614; (f) Y. Zhan, T. Liu, J. Ren, Z. Wang, *Chem. Eur. J*., 2017, **23**, 17862.

13 L. Li, J. Zhang, *Org. Lett*., 2011 **13**, 5940.

14 (a) H. Liu, C. Zheng, S.-L. You, *Chin. J. Chem*., 2014, **32**, 709; (b) H. Liu, C. Zheng, S.-L. You, *J. Org. Chem*., 2014, **79**, 1047.

15 (a) S. Grabowsky, T. Pfeuffer, W. Morgenroth, C. Paulmann, T. Schirmeister, P. Luger, *Org. Biomol. Chem*., 2008, **6**, 2295; (b) Z. Jiang, J. Wang, P. Lu, Y. Wang, *Tetrahedron*, 2011, **67**, 9609; (c) X. Wu, L. Li, J. Zhang, *Chem. Commun*., 2011, **47**, 7824; (d) Y. Liao, X. Liu, Y. Zhang, Y. Xu, Y. Xia, L. Lin, X. Feng, *Chem. Sci*., 2016, **7**, 3775; (e) X. Wu, W. Zhou, H-H. Wu, J. Zhang, *Chem. Commun*, 2017, **53**, 5661.

16 X. Wu, J. Zhang, *Synthesis*, 2014, 2147.

17 R. A. Craig II, N. R. O'Connor, A. F. G. Goldberg, B. M. Stolz, *Chem. Eur. J*., 2014, **20**, 4806.

18 A. Ghosh, A. K. Pandey, P. Banerjee, *J. Org. Chem*., 2015, **80**, 7235.

19 (a) P. Molina, M. Alajarin, A. Vidal, J. Fenau-Dupont, J. P. Declerq, *J. Org. Chem*., 1991, **56**, 4008; (b) M. Alajarin, A. Vidal, F. Tovar, A. Arrieta, B. Lecea, F. P. Cossio, *Chem. Eur. J.*, 1999, **5**, 1106; (c) F. P. Cossio, A. Arrieta, B. Lecea, M. Alajarin, A. Vidal, F. Tovar, *J. Org. Chem.*, 2000, **65**, 3633; (d) M. Alajarin, A. Vidal, F. Tovar, M.-C. Ramirez de Arellano, F. P. Cossio, A. Arreita, B. Lecea, *J. Org. Chem*., 2000, **65**, 7512; (e) M. Alajarin, A. Vidal, F. Tovar, P. Sanchez-Andrada, *Tetrahedron Lett.*, 2002, **43**, 6259; (f) M. Alajarin, A. Vidal, M.-M. Ortin, *Tetrahedron Lett.*, 2003, **44**, 3027; (g) M. Alajarin, A. Vidal, M.-M. Ortin, *Org. Biomol. Chem.*, 2003, **1**, 4282; (h) M. Alajarin, A. Vidal, M.-M. Ortin, D. Bautista, *Synlett*, 2004, 991; (i) M: Alajarin, A. Vidal, M.-M. Ortin, D. Bautista, *New J. Chem*., 2004, **28**, 570; (j) M. Alajarin, P. Sanchez-Andrada, A. Vidal, F. Tovar, *Eur. J. Org. Chem.*, 2004, 2636; (k) M. Alajarin, P. Sanchez-Andrada, A. Vidal, F. Tovar, *J. Org. Chem*., 2005, **70**, 1340; (l) M. Alajarin, A. Vidal, M.-M. Ortin, *Tetrahedron*, 2005, **61**, 7613; (m) M. Alajarin, M.-M. Ortin, P. Sanchez-Andrada, A. Vidal, *J. Org. Chem.*, 2006, **71**, 8126; (n) M. Alajarin, B. Bonillo, M.-M. Ortin, P. Sanchez-Andrada, A. Vidal, *Org. Lett*., 2006, **8**, 5645; (o) M. Alajarin, B. Bonillo, P. Sanchez-Andrada, A. Vidal, D. Bautista, *J. Org. Chem.*, 2007, **72**, 5863; (p) M. Alajarin, B. Bonillo, P. Sanchez-Andrada, A. Vidal, D. Bautista, *Org. Lett.*, 2009, **11**, 1365; (q) M. Alajarin, B. Bonillo, M. Marin-Luna, A. Vidal, R.-A. Orenes, *J. Org. Chem.*, 2009, **74**, 3558; (r) M. Alajarin B. Bonillo, P. Sanchez-Andrada, A. Vidal, *J. Org. Chem*., 2010, **75**, 3737; (s) M. Alajarin, B. Bonillo, M.-M. ortin, P. Sanchez-Andrada, A. Vidal, R.-A. Orenes, *Org. Biomol. Chem.*, 2010, **8**, 4690; (t) M. Alajarin, B. Bonillo, M.-M. Ortin, P. Sanchez-Andrada, A. Vidal, *Eur. J. Org. Chem*., 2011, 1896; (u) M. Alajarin, B. Bonillo, M. Marin-Luna, P. Sanchez-Andrada, A. Vidal, R.-A. Orenes, *Tetrahedron*, 2012, **68**, 4672; (v) M. Alajarin, B. Bonillo, R.-A. Orenes, M.-M. Ortin, A. Vidal, *Org. Biomol. Chem.,* 2012, **10**, 9523; (w) A. Vidal, M. Marin-Luna, M. Alajarin, *Eur. J. Org. Chem.*, 2014, 878.

20 M. Alajarin, A. Egea, R.-A. Orenes, A. Vidal, *Org. Biomol. Chem*., 2016, **14**, 10275.

21 For selected examples, see: (a) A. L. Cardoso, M. S. C. Henriques, J. A. Paixao, T. M. V. D. Pinho e Melo, *J. Org. Chem*., 2016, **81**, 9028; (b) W. Ren, Q. Zhao, C. Zheng, Q. Zhao, L. Guo, W. Huang, *Molecules*, 2016, **21**, 1113; (c) Y. Miyamoto, N. Wada, T. Soeta, S. Fujinami, K. Inomata, Y.

View Article Online
DOI: 10.1039/C8QO00255J

Ukaji, *Chem. Asian, J.*, 2013, **8**, 824; (d) A. S. Konev, A. A. Mitichkina, A. F. Khlebnikov, H. Frauendorf, *Russ. Chem. Bull., Int. Ed.*, 2012, **61**, 863; (e) J. Danielsson, L. Toom, P. Somfai, *Eur. J. Org. Chem.*, 2011, 607; (f) P. J. S. Gomes, C. M. Nunes, A. C. C. C. Pais, T. M. V. D. Pinho e Melo, L. G. Arnaut, *Tetrahedron Lett*., 2006, **47**, 5475; (g) A. S. Pankova, V. V. Voronin, M. A. Kuznetsov, *Tetrahedron Lett*., 2009, **50**, 5990.