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Synthesis of 1,2-diaminotruxinic δ-cyclobutanes by BF_3-controlled [2 + 2]-photocycloaddition of 5(4*H*)-oxazolones and stereoselective expansion of δ-cyclobutanes to give highly substituted pyrrolidine-2,5-dicarboxylates†

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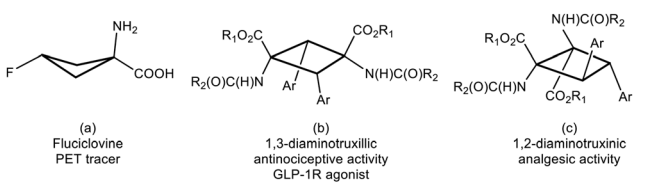
The irradiation of (*Z*)-4-arylidene-5(4*H*)-oxazolones **1a–1u** with blue light (465 nm) in the presence of the photosensitizer $[Ru(bpy)_3](BF_4)_2$ (2.5 mol%) and the Lewis acid $BF_3{\cdot}OEt_2$ (2 equiv.) in deoxygenated methanol at room temperature affords the corresponding 1,2-diaminotruxinic cyclobutane bis-amino esters **2a–2u** stereoselectively as the δ-isomer. Characterization of cyclobutanes **2** shows that the photocycloaddition takes place by the coupling of two *Z*-oxazolones in a head-to-head 1,2-*anti* way. This change in the orientation of the coupling is promoted by O- or/and N-bonding of the BF_3 additive. The δ-cyclobutanes **2** undergo a ring expansion when heated in methanol in the presence of NaOMe (1/1 molar ratio) to give densely substituted pyrrolidine-2,5-dicarboxylates **3** in a regio- and stereoselective way. The mechanism of the cyclobutane-to-pyrrolidine ring expansion has been elucidated using DFT methods.

Introduction

Amino acids are the basic components of life. The nature of their basic skeleton, the presence of alkyl or aryl lateral groups, the types of intra- and intermolecular contacts they can establish, and the type and number of substituents they have determine their role in the proteins where they are incorporated and, finally, the role of the proteins themselves.[1] Among them, amino acids with the cyclobutane skeleton are an important family of compounds due to their remarkable applications. For instance, ^{18}F-fluciclovine (1-amino-3-18F-fluorocyclobutane-1-carboxylic acid), shown in Fig. 1a, is extensively use as a PET tracer in prostate and breast cancer imaging.[2] Despite this interest, the number of synthetic methods to access these substrates is scarce.[3] This situation is even more limited if cyclobutane-bis(amino acids) are considered, and the only known method to access 1,3-diaminotruxillic (Fig. 1b) or 1,2-diaminotruxinic derivatives (Fig. 1c) is the [2 + 2]-photocycloaddition of oxazolones.[4–6] This is surprising, taking into account the high pharmacological relevance of 1,3-diaminotruxillic and 1,2-diaminotruxinic derivatives.[7]

Our group[4,5a,b,6a] and other groups[5c,6b] have made some contributions in this field. We have achieved the fully stereoselective synthesis of the esters of 1,3-diaminotruxillic acid as single isomers (epsilon isomer, Fig. 1b) by irradiation with blue light (465 nm) of orthopalladated complexes of (*Z*)-4-arylidene-5(4*H*)-oxazolones as templates.[4] We have also reported the highly efficient synthesis of 1,3-diaminotruxillic derivatives (four different isomers) in quantitative yields by the direct photoirradiation of simple 4-arylidene-5(4*H*)-oxazolones with blue light.[5a,b] In this respect, the group of Wang described a much less efficient reaction (10% yield) using high-power UV irradiation.[5c] In contrast to this relative success, the synthesis of 1,2-diaminotruxinic derivatives is almost unexplored, and



(a) Fluciclovine PET tracer
(b) 1,3-diaminotruxillic antinociceptive activity GLP-1R agonist
(c) 1,2-diaminotruxinic analgesic activity

Fig. 1 Structures and activities of some relevant cyclobutane-amino acids and bis(amino acids).

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there are only two published contributions up to now.[6] We have recently achieved the complete regio- and stereoselective synthesis of the esters of 1,2-diaminotruxinic acid as a single isomer (mu-isomer, Fig. 2, past work) by the irradiation of 4-arylidene-5(4*H*)-oxazolones with blue light in the presence of the photosensitizer $[Ru(bpy)_3](BF_4)_2$ (bpy = 2,2′-bipyridine).[6a] The exact role of the photosensitizer has been determined by laser flash photolysis, and it is the generation of the triplet excited state of the oxazolones by energy transfer from the ruthenium complex. The change of the multiplicity of the excited state from singlet to triplet changes the orientation of the reaction (head-to-tail to head-to-head) and provides full selectivity.[6a] Along the same lines, Amarante and coworkers reported in 2018 the synthesis of a different isomer (zeta-isomer) of the esters of 1,2-diaminotruxinic acid using eosin-Y as the photocatalyst (Fig. 2, past work).[6b] However, these are only precursors of the 1,2-diaminotruxinic derivatives, because one of the oxazolone rings does not undergo the necessary ring opening reaction. Despite these advancements, the synthesis of cyclobutanes as a single isomer is still a challenge, and controlled access to other isomers of 1,2-diaminotruxinic cyclobutanes is not available yet.

In this contribution we have described the regio- and stereoselective synthesis of 1,2-diaminotruxinic derivatives as the delta (δ) isomer by the [2 + 2]-cycloaddition of (*Z*)-4-arylidene-5(4*H*)-oxazolones photocatalysed by the triplet sensitizer $[Ru(bpy)_3](BF_4)_2$ in the presence of BF_3 as a Lewis acid. It is well-known that the presence of a Lewis acid can change the orientation and selectivity of a photochemical process.[8] We show here how the presence of BF_3 maintains the global orientation of the process, which takes place in a head-to-head way so 1,2-diaminotruxinic species are obtained, but changes the relative orientation of the substituents affording selectively a new isomer (Fig. 2, this work). Moreover, we also show here how further treatment of the stable 1,2-diaminotruxinic delta-cyclobutanes with a base (NaOMe) and gentle warming promotes an unexpected expansion of the cyclobutane ring giving densely substituted pyrrolidine-2,5-dicarboxylic derivatives, which can be considered as proline-like compounds (Fig. 2, this work). This new method for the synthesis of pyrrolidines is unprecedented. The importance of pyrrolidines is undeniable, not only as synthetic targets, but also due to their applications.[9] As far as we know, the expansion of aminocyclobutanes to give pyrrolidines has not been reported until now.[10]

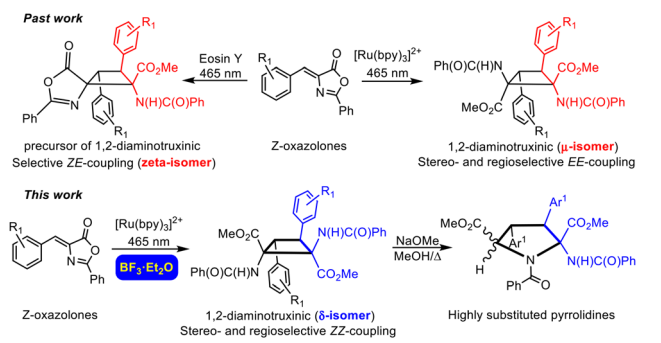

Fig. 2 Context of this research with respect to previous contributions.

Results and discussion

Synthesis and characterization of the methyl esters of delta-1,2-diaminotruxinic acids 2 in the presence of BF_3

The starting (*Z*)-4-(het)arylidene-2-phenyl-5(4*H*)-oxazolones **1a–1u** (Fig. 3) have been prepared using the known Erlenmeyer–Plöchl method.[11] Substituents of the 4-arylidene ring have been selected to cover the widest scope of electronic and steric requirements. Therefore, electron-releasing (OMe and Me) or electron-withdrawing (CN, F, Cl, Br, and CF_3) groups in the *ortho*-, *meta*- or *para*-positions of the 4-arylidene ring, as well as one example of heterocycles (thienyl-**1u**), are present in the starting materials.

The oxazolone **1a** was irradiated under the experimental conditions previously reported by us (465 nm, $[Ru(bpy)_3](BF_4)_2$ 5%, deoxygenated CH_2Cl_2, Ar, 48 h),[6a] but now in the presence of different amounts of the Lewis acid $BF_3{\cdot}OEt_2$. In all attempted cases the precipitation of variable amounts of a white solid was observed, which could not be characterized due to its complete insolubility in the usual organic solvents. Therefore, the reaction needs to be optimized. A short screening of the conditions showed that the diester of the 1,2-diaminotruxinic diacid cyclobutane **2a** was formed when using other solvents, and that the best results and the cleanest **2a** were obtained under Ar in dry and deoxygenated methanol (Fig. 3). The optimization of the amount of $BF_3{\cdot}OEt_2$ showed that a substoichiometric amount (40 mol%) was enough to achieve the maximum yield of **2a**. The amount of the photosensitizer $[Ru(bpy)_3](BF_4)_2$ was re-optimized to 2.5 mol% and the optimal reaction time was set to 24 h by monitoring the reaction by ^1H NMR. The irradiation wavelength (465 nm) was kept the same because it was the excitation wavelength of the ruthenium photocatalyst. No other photocatalysts were used (for instance, Ir(III) species) as we previously determined that this Ru(II) photosensitizer gave the best results with oxazolones.[6a] The use of other Lewis acids was also attempted ($AlCl_3$, $TiCl_4$, and BBr_3) but these reactions were much less selective and a higher variety of byproducts were detected, so all reactions were performed with $BF_3{\cdot}OEt_2$.

Complete conversion of **1a** was observed under the optimized reaction conditions, affording cyclobutane **2a** in a stereo- and regioselective way. Despite the selectivity in the for-

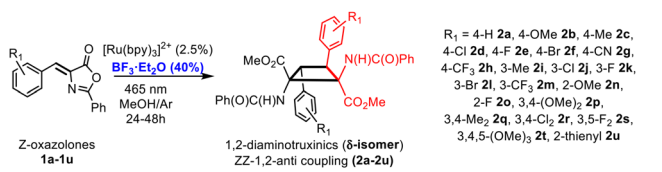

Fig. 3 Synthesis of delta isomers of cyclobutanes **2a–2u** (1,2-diaminotruxinic esters) by the [2 + 2]-photocycloaddition of (*Z*)-oxazolones **1a–1u** in the presence of BF_3.

mation of **2a** other byproducts were detected in the crude in amounts of up to 20% (^{1}H NMR), with the corresponding dehydrophenylalanine being the main one. Washing with water efficiently removed BF_3, but not dehydrophenylalanine (see the ESI†); therefore, chromatographic purification was mandatory. For this reason, the yield of pure isolated **2a** was only 34% due to the partial loss of the product during column chromatography. As is evident from Fig. 3, the reaction of the (*Z*)-oxazolone **1a** to give the diester of 1,2-diaminotruxinic acid **2a** has to involve two different steps. We propose that the [2 + 2]-photocycloaddition takes place first to give the cyclobutane, which is followed then by the ring-opening reaction of the oxazolone by methanolysis (*vide infra*).[12] Once the optimal conditions were determined, the scope of the reaction was examined. The reaction works with both electron-donating and electron-withdrawing substituents (Fig. 4), and although full conversions were determined by ^{1}H NMR of the crude after 24 h of irradiation, the isolated yields of analytically pure products were only moderate to low (20–50%) due to mandatory chromatographic purification.

As is clear from Fig. 4, the diesters of 1,2-diaminotruxinic derivatives **2** were obtained directly as unique products in all cases except for **2t**. In this case, a mixture of dispyrocyclobutane **2t*** and cyclobutane **2t** was obtained, and they were separated by column chromatography. This gives proof that the reaction takes place sequentially, first the [2 + 2]-photocycloaddition and then the ring-opening reaction.

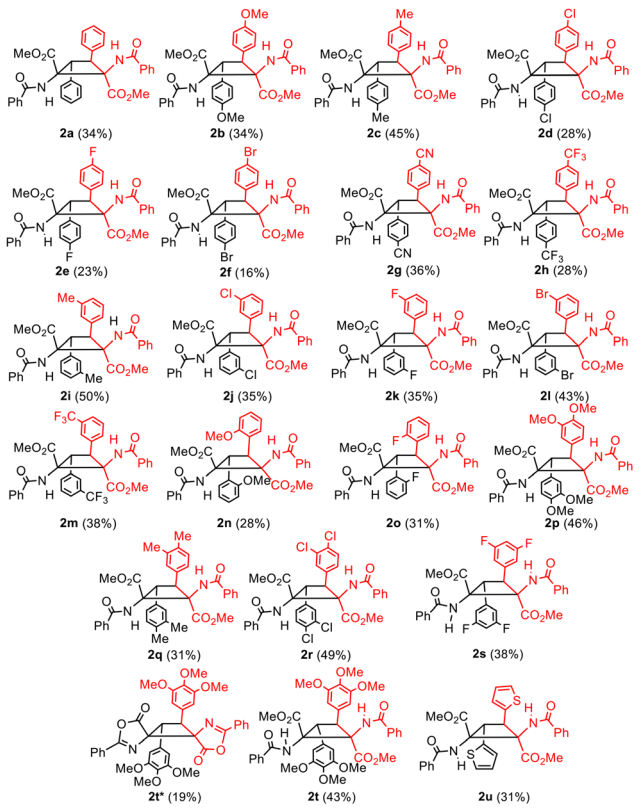

Fig. 4 Scope of the formation of cyclobutanes **2a–2u**.

While it seems that the extent of the [2 + 2]-photocycloaddition does not depend on the electronic characteristics of the substituents at the 4-arylidene ring, the steric hindrance – mainly determined by the *ortho*-, *meta*- or *para*-position of the substituent in the aromatic ring – appears to be much more critical. In fact, *para*-substituents at the 3- or 4-aryl rings of the cyclobutanes are well tolerated (**2b–2h** in Fig. 3 and 4), but those at the *meta*-position showed a more restricted scope (**2i–2m**). When the substituents were at the *ortho* position, only the cyclobutanes containing OMe (**2n**) or F (**2o**) could be obtained. As expected, two or more substituents were allowed in such 3- and 4-aryl rings, provided that they are at the *meta*/*para* positions, regardless of being electron-releasing (OMe **2p**, **2t**; Me **2q**) or electron-withdrawing (Cl **2r**, F **2s**) in nature. The reaction also takes place when heterocycles are at 3- and 4-cyclobutane positions (**2u**).

The characterization of cyclobutanes **2a–2u** has been carried out by spectroscopic and crystallographic methods. The mass spectra (ESI^+) of **2a–2u** show the presence of peaks with *m*/*z* values and isotopic distributions in agreement with the formation of the cyclobutane. In addition, the ^{1}H and ^{13}C NMR spectra of **2a–2u** show the presence of peaks reflecting the formation of a cyclobutane of high symmetry as a single isomer. This allows us to discard any isomer coming from the coupling of a *Z*-oxazolone with an *E*-oxazolone (4 isomers).[6] The comparison of the chemical shifts of cyclobutanes **2a–2u** with those reported in previous studies also allows us to discard the formation of ε-, α- and μ-isomers, already characterized.[5a,6a] Therefore, a new isomer was formed in this reaction, and there are several structures (*peri*, β, δ, and ω)[12] which can match with the NMR data. The determination of the crystal structures of the cyclobutanes **2n**, **2o** and **2s** allowed us to fully characterize the new species, and their structures are shown in Fig. 5, 6 and 7, respectively.

The three structures are isostructural and show the cyclobutane core formed by the head-to-head (1,2)-*anti* photocycloaddition of two (*Z*)-oxazolones. That is, the new isomer obtained in this reaction is the delta (δ) isomer.[13]

The three cyclobutanes show two *trans* aryl rings (2-C_6H_4OMe in **2n**, 2-C_6H_4F in **2o**, and 3,5-$C_6H_3F_2$ in **2s**) in adjacent C atoms of the cyclobutane. Each of the other two C atoms shows one CO_2Me and one N(H)C(O)Ph group, arising from the ring opening by methanolysis of the oxazolone. The relative arrangement of the two benzamido groups is *trans*, as well as that of the esters. In addition, each aryl ring is *cis* with respect to the benzamido group located in the adjacent carbon, showing that the oxazolone is not isomerized and that the geometries of the *Z*-oxazolones **1** are preserved in the cyclobutanes **2**. Therefore, the configuration of the molecule is 1,2-*trans*-2,3-*cis*-3,4-*trans*. Other internal parameters are identical, within the experimental error, to those reported by us recently,[6a] and also to those found in the literature for related systems.[14]

The comparison of the different reaction conditions used for the synthesis of the different isomers (μ-isomer: Ru, CH_2Cl_2, blue light;[6a] δ-isomer: Ru, BF_3, MeOH, blue light)

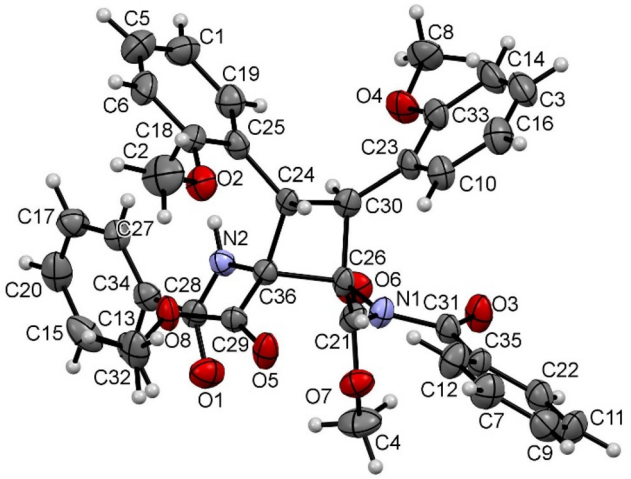

Fig. 5 X-ray molecular structure of cyclobutane **2n**. Ellipsoids are drawn at the 30% probability level.

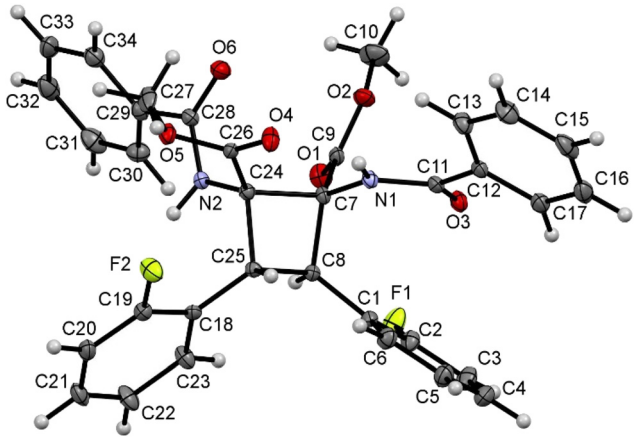

Fig. 6 X-ray molecular structure of cyclobutane **2o**. Ellipsoids are drawn at the 30% probability level.

suggests that the Lewis acid BF_3 is mainly responsible for the divergent behaviour observed. We have discarded the effect of the solvent in the obtention of different isomers because we have observed previously that the change of the solvent does not change the orientation of the photochemical reaction,[5b,6a] even if it participates in the whole process[5b] as in this case. We suggest that the role of methanol in this reaction is just the promotion of the ring-opening reaction under very smooth conditions, probably assisted by BF_3, as it has been observed by us recently for related thiazolones.[5b] In order to determine the precise role of the Lewis acid we attempted the study of the interaction between the oxazolones and BF_3 in methanol as the solvent, both in the ground state and in the excited state. The ^{1}H NMR spectra of solutions of **1a** in CD_3OD do not show changes in the shape of the signals due to the oxazolone, nor in the chemical shifts, after the addition of different amounts of $BF_3{\cdot}OEt_2$, suggesting a very weak interaction between BF_3 and **1a**, not detectable by NMR. A similar conclusion can be

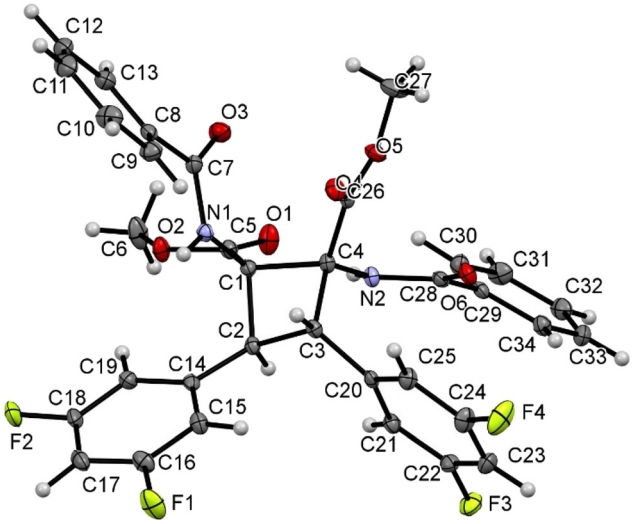

Fig. 7 X-ray molecular structure of cyclobutane **2s**. Ellipsoids are drawn at the 30% probability level.

derived from the analysis of the excitation–emission spectra of **1a** in methanol in the absence or presence of BF_3.[5b] Although the oxazolone–BF_3 interaction in methanol seems to be too weak to characterize, the different isomers obtained in the presence (δ) and absence (μ) of BF_3 suggest that this interaction exists at some point of the reaction. We can even propose that the interaction is plausible along the whole reaction path (Fig. 8), considering that the μ-isomer is not detected in presence of BF_3.

The role of BF_3 in this reaction is shown in Fig. 8 and seems to be merely steric, based on our recent study of the Ru-sensitized photocycloaddition of (*Z*)-oxazolones, where the 1,4-diradical **Int-(*ZZ*)-1** undergoes free rotation to give **Int-(*EE*)-1** before the ring closing step and formation of the μ-isomer.[6a] We propose here that the new 1,4-diradical intermediate **Int-(*ZZ*)-1-BF$_3$** would be much more sterically hindered than **Int-(*ZZ*)-1**, not allowing further rotation and giving **Int-(*ZZ*)-2-BF$_3$**. Release of BF_3 at this point should give dispyrocyclobutanes.

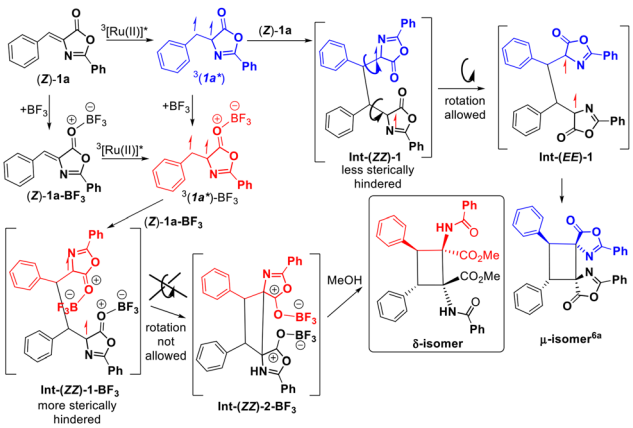

Fig. 8 Role of BF_3 in the synthesis of delta-isomers of 1,2-diaminotruxinic-cyclobutanes **2**.

In this respect, isolation of **2t*** is indirect evidence of the formation of the species **Int-(*ZZ*)-2-BF$_3$**. In addition, bonding of BF_3 to **Int-(*ZZ*)-2-BF$_3$** increases the electrophilic character of the carbonyl carbon, making it more prone to undergo nucleophilic attack from the solvent and promoting the ring opening reaction of the oxazolone, giving finally the δ-isomer of **2**.

Expansion of δ-1,2-diaminotruxinic cyclobutanes 2. Synthesis of highly substituted esters of pyrrolidine-2,5-dicarboxylic acids 3

During the synthesis of cyclobutanes **2a–2u** at short reaction times we experienced in a few cases difficulties in promoting the complete ring-opening reaction of the oxazolone at room temperature, and therefore mixtures of cyclobutanes with the heterocycles in the closed and open forms were obtained, as explained for the case of **2t** and **2t*** (see Fig. 4). In such cases we forced the complete ring-opening reaction by treatment of the mixture with a catalytic amount of NaOMe in refluxing MeOH at the end of the reaction. Surprisingly, in addition to the expected 1,2-diaminotruxinic diesters **2** we obtained a second product related to the deprotonation of such cyclobutanes **2**. Due to this unexpected additional reactivity, we decided to investigate in-depth the reactions of 1,2-diaminotruxinic diesters **2** with NaOMe in refluxing methanol. The obtained results are shown in Fig. 9.

The treatment of cyclobutanes **2** with a stoichiometric amount of NaOMe (1/1 molar ratio) in methanol at 110 °C resulted in the formation of the corresponding dimethyl 2-benzamido-3,4-diaryl-*N*-benzoyl-pyrrolidine-2,5-dicarboxylates **3**, as shown in Fig. 9. We attempted this reaction for the full set of cyclobutanes **2a–2u**, and we observed full conversion in all cases. The respective crude of the reactions showed (^{1}H NMR) a mixture of compounds, in which pyrrolidines **3** were the main components (more than 90%). In turn, pyrrolidines **3** were present as a mixture of two diastereomers in different molar ratios, one of them being clearly more abundant than the other. We attempted the separation and purification of this mixture by column chromatography. We were successful in the separation of pyrrolidines **3** into pure products in the cases where electron-withdrawing substituents (F, Cl, Br, CN, and CF_3) were present on the aryl rings (Fig. 9 and 10). In most of these cases, the separation afforded the major isomer as a single isomer (**3d**, **3e**, **3h**, **3l**, **3m**, and **3r**), while the minor isomer was always contaminated with the major one. In the other cases (**3a**, **3g**, **3k**, and **3o**) pyrrolidines could be purified,

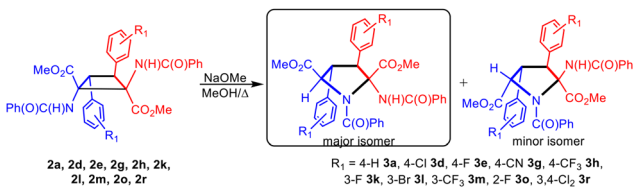

Fig. 9 Synthesis of pyrrolidines **3a–3r** by the ring expansion of cyclobutanes **2a–2r**.

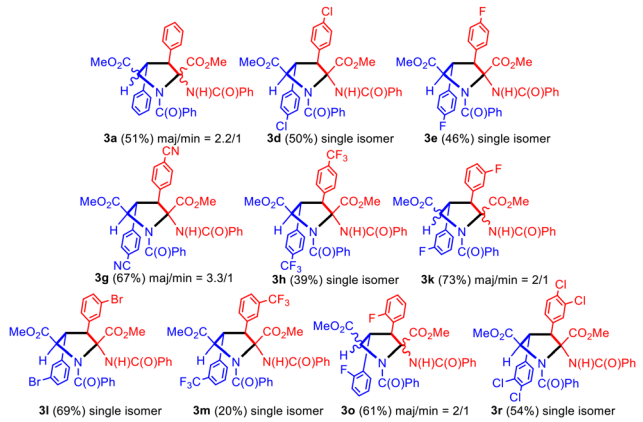

Fig. 10 Scope of the synthesis of pyrrolidine-2,5-dicarboxylates **3**.

but not separated (molar ratio in the mixture ranging from 3.3/1 to 2/1).

In general, the obtained yields were moderate to good (39% to 73%) except for **3m** (20%). Attempts to optimize the reaction showed that a lower amount of NaOMe or a lower reaction temperature resulted in lower yields of **3**. The nature of the base is critical to promote the formation of the pyrrolidines **3**. Using the couple NaOMe/MeOH (pK_a = 15.5),[15] an efficient deprotonation of the NH unit from the benzamido group can be achieved, which is the starting point of the reaction (see below). However, the use of carbonate as the base (Cs_2CO_3, pK_a = 10) in refluxing methanol results in the formation of a mixture of dehydrophenylalanine (DHPA) and pyrrolidine **3**, with DHPA being the main product of the reaction. This fact can be interpreted as a competition between the deprotonation of cyclobutane **2**, leading to pyrrolidine **3**, and the thermal retro-[2 + 2] of **2**, which affords the DHPA moiety. In line with this result, the use of acetate as the base (NaOAc, pK_a = 4.76) in refluxing methanol produces only DHPA as the reaction product. Clearly, the base has to be strong enough to promote a fast and efficient deprotonation of cyclobutane **2**, otherwise, a thermal retro-[2 + 2] takes place and the DHPA byproduct is obtained.

As is clear from Fig. 9, the reaction implies formally the expansion of a substituted cyclobutane ring, with four stereogenic centers, to give a five-membered pyrrolidine ring, also with four stereogenic centers. As far as we know, the expansion of a benzamidocyclobutane to build a pyrrolidine scaffold has not been reported previously. This methodology provides an additional and alternative synthetic pathway for the obtention of highly substituted pyrrolidine-2,5-dicarboxylates.

Due to the presence of four stereogenic centers, an important aspect of this reaction is the stereoselectivity with which it takes place considering that, *a priori*, up to 8 different stereoisomers of **3** can be obtained from **2**. As explained, pyrrolidine-2,5-dicarboxylates **3** were obtained as two diastereomers in all of the cases, from which the major diastereomer could be isolated as a unique isomer for **3d**, **3e**, **3h**, **3l**, **3m** and **3r**, while for **3a**, **3g**, **3k** and **3o** the mixture could not be separated.

The spectroscopic characterization of pyrrolidines **3** by NMR shows that the diastereomer obtained as a unique isomer (or as the major isomer for **3a**, **3g**, **3k** and **3o**) has 2*S*, 3*S*, 4*S*, 5*R*/2*R*, 3*R*, 4*R*, 5*S* configurations (Fig. 9 and 10). This arrangement can be inferred from the observation of a strong NOE effect between the H at C3 and the H at C5 (5.81 ppm and 5.30 ppm in **3o**, see the ESI†), as well as the NOE between the H at C3 and the NH of the benzamido group at C2 (8.06 ppm in **3o**), meaning that these three fragments are on the same side of the molecular plane. This was further confirmed through the determination of the crystal structure of pyrrolidine **3r** by X-ray diffraction methods (Fig. 11). Unfortunately, the determination of the structure of the minor isomers of **3a**, **3g**, **3k** and **3o** could not be performed experimentally, because no NOEs were observed after the inversion of signals associated with such species (even though the NOE was clear for the major isomer of **3o**), neither single crystals of these species could be obtained. The structural proposal for these compounds is based on DFT calculations (see below).

A molecular drawing of pyrrolidine **3r** is shown in Fig. 11. The structure confirms the formation of a five-membered pyrrolidine ring, being N-substituted by a C(O)Ph moiety and having a CO_2Me group at C1, a 3,4-$C_6H_3Cl_2$ fragment at both C2 and C3, and one ester and one benzamide functional group at C4. The five-membered ring displays the expected envelope shape, aiming to minimize intramolecular steric contacts. The relative arrangements of the substituents at each C atom (C1 to C4) show interesting changes when compared with the structure of the cyclobutane precursors **2**. The two 3,4-$C_6H_3Cl_2$ aryl rings at C2 and C3 are in mutual *trans* positions, as are in the starting cyclobutanes, and therefore it seems that this part of the molecule has not experienced changes during the ring expansion. However, the benzamido group at C4 and the 3,4-$C_6H_3Cl_2$ aryl ring at C3 are also in *trans*, while they are in *cis* in cyclobutanes **2** (see Fig. 5–7). This strongly suggests a free rotation around the C3–C4 bond during the cyclobutane expansion. The *trans* arrangement of the benzamido group and the aryl ring in the neighbour carbon was already observed in the μ-isomers of the 1,2-diaminotruxinic cyclobutanes.[6a] As a result of these geometrical arrangements, the absolute configurations of the stereogenic centers at C1, C2, C3 and C4 are R_{C1}, S_{C2}, S_{C3} and S_{C4}.

However, the molecule crystallized in the monoclinic space group *I*2/*a*, which is centrosymmetric, and therefore both enantiomers (R_{C1}, S_{C2}, S_{C3} and S_{C4} and S_{C1}, R_{C2}, R_{C3} and R_{C4}) have to be present in the unit cell. The internal C–C, C–N and C–O bond distances are identical, within the experimental error, to those found in other *N*-acyl-pyrrolidine-2,5-carboxylates.[16] There are only slight differences between the bond distances N1–C1 (1.455(3) Å) and N1–C4 (1.473(3) Å) on the one hand, and C1–C2 (1.545(3) Å) and C3–C4 (1.568(4) Å) on the other hand. Other internal parameters are in the usual ranges of distances and angles found in the literature for these types of compounds.[14]

A plausible mechanism for this reaction is shown in Fig. 12, based on DFT calculations.[17] The reaction is initiated by the methoxide anion, which deprotonates one of the two equivalent N–H bonds of the benzamide fragment in **2** and generates the corresponding N-anionic form (**2 anion** in Fig. 12), which was taken as the reference system for the energy in the potential energy surface (G = 0 kcal mol^{-1}). The N-anion charge would trigger the cyclobutane ring opening through a C–C bond cleavage in **TS1**, a step that involves an energy barrier of 22.4 kcal mol^{-1}, forming the open intermediate **intA**. This high-energy species contains the formal anionic charge at the carbon atom, and can be slightly stabilized by 1,2-shift tautomerization, to locate the negative charge at the nearby N-atom (**intB**, G = 13.6 kcal mol^{-1}). The open intermediates present free rotation allowed around the C–C bonds of the remaining carbon skeleton. From **intB**, four diastereoisomeric attack options arise, where the N-anion reacts with

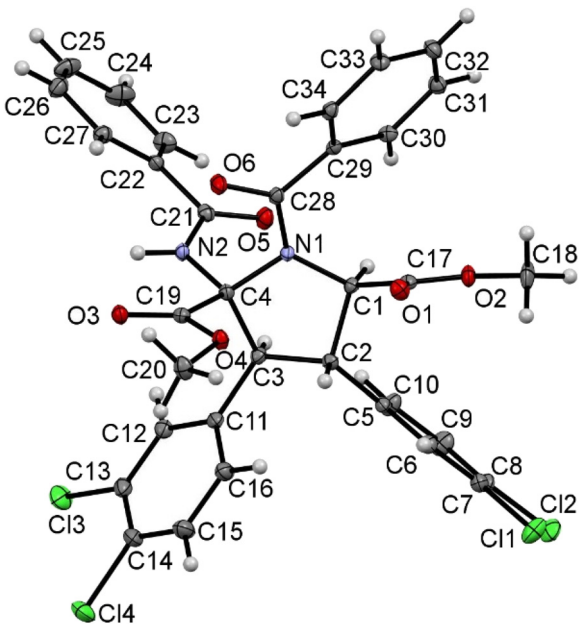

Fig. 11 X-ray molecular structure of pyrrolidine **3r**. Ellipsoids are drawn at the 50% probability level.

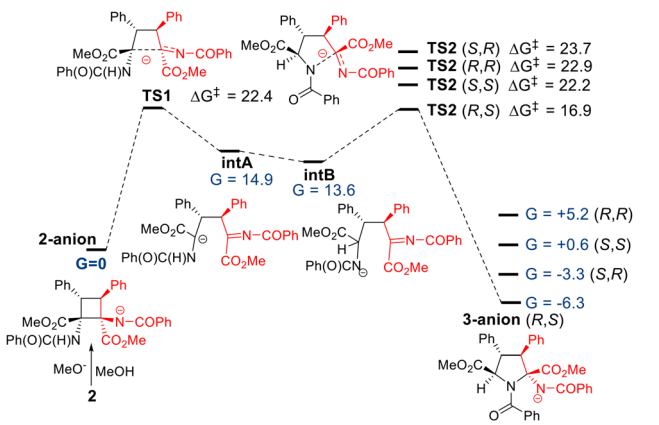

Fig. 12 Mechanism of the ring expansion of cyclobutanes **2** to give pyrrolidines **3**.

the iminic C atom, closing to the pyrrolidine **3-anion** adduct. Among the four diastereomeric final adducts, **3-anion** (*R*,*S*) is the most stable species with an energy 6.3 kcal mol^{-1} lower than the initial situation in **2a-anion**. Thus, the process is exergonic. The remaining **3a** isomers are at least 3 kcal mol^{-1} less stable than the major *R*,*S*-isomer, in agreement with our experimental results. The activation energy for the pyrrolidine ring formation in **TS2** is 16.9 kcal mol^{-1}, affordable under the reaction conditions, and interestingly, the four computed **TS2** transition states also show a clear preference in favour of the *RS*-isomer. In fact, an energy difference of at least 5 kcal mol^{-1} was noted between **TS2**-*R*,*S* and the rest of the **TS2** transition states. Thus, the formation of the *R*,*S*-isomer could be explained with either kinetic or thermodynamic conditions, according to the calculations.

However, relative energies of the transition states and the final adducts differ in the explanation of the formation of the minor experimental *SR* isomer. The energy distribution of the four isomers indicates that the second most stable adduct is the **3a-anion** (*S*,*R*), corroborating that it is formed under thermodynamic conditions, since it is kinetically the least favoured adduct **TS2** (*S*,*R*) ($\Delta G^{\ddagger}$ = +23.7 kcal mol^{-1}). As a further confirmation, the other two anions, the **3-anion** (*R*,*R*) and the **3-anion** (*S*,*S*) are much higher in energy and, as expected, they could not be obtained experimentally.

Experimental

General methods

[2 + 2]-photocycloaddition reactions were carried out under an inert (Ar) atmosphere, using dry and deoxygenated methanol from a Pure Solv MD5 solvent purification system. Purification of the compounds was carried out by flash column liquid chromatography using silica gel (70–230 μm) as the support. ^{1}H, ^{13}C and ^{19}F NMR spectra of the isolated products **2** and **3** were recorded in $CDCl_3$ or CD_2Cl_2 solutions at 25 °C (other temperatures were specified) on Bruker AV300 and Bruker AV500 spectrometers (δ in ppm, J in Hz) at ^{1}H operating frequencies of 300.13 and 500.13 MHz, respectively. ^{1}H and ^{13}C NMR spectra were referenced using the solvent signal as the internal standard, while ^{19}F NMR spectra were referenced to $CFCl_3$. The assignment of ^{1}H NMR peaks has been performed through standard 2D ^{1}H-COSY and selective 1D ^{1}H-SELNOE experiments. Typical mixing times in the case of selective 1D-SELNOE experiments were in the range of 1.2–1.8 s, as a function of the irradiated signal. These values of optimized mixing times were set equal to the longitudinal relaxation time T_1, determined using the inversion–recovery sequence. ^{13}C NMR peaks were identified using standard ^{1}H–^{13}C edited-HSQC and ^{1}H–^{13}C HMBC 2D-experiments. In both cases spectral widths of 10 ppm (^{1}H) and 200 ppm (^{13}C) were used, with average values of the coupling constants $^{1}J_{CH}$ = 145 Hz and long-range $^{n}J_{CH}$ = 10 Hz. ESI (ESI^{+}) mass spectra were recorded using an Esquire 3000 ion-trap mass spectrometer (Bruker Daltonic GmbH) equipped with a standard ESI/APCI source. HRMS and ESI (ESI^{+}) mass spectra were recorded using a MicroToF Q, API-Q-ToF ESI with a mass range from 20 to 3000 m/z and mass resolution 15 000 (FWHM). The oxazolones **1** used as starting materials were synthesized according to published methods.[11] The compound $[Ru(bpy)_3](BF_4)_2$ was also prepared following published procedures,[18] and it was stored under a protecting atmosphere (Ar) at 4 °C.

Irradiation setup

The irradiation setup used in this case was a metallic cylindrical recipient (16 cm internal diameter and 10.5 cm high) whose internal surface was covered with blue LEDs (222 diodes, 465 nm). This home-made system provided an electrical power of 18 W and used a 12 V power supply.

Crystallography

Crystals of cyclobutanes **2n**, **2o**, **2s** and pyrrolidine **3r** of quality for X-ray measurements were grown by slow diffusion of *n*-pentane into CH_2Cl_2 (**2n**, **2o**, and **2s**) or $CHCl_3$ (**3r**) solutions of the respective crude products at −18 °C for several weeks. One selected single crystal of each compound was mounted at the end of a quartz fiber in a random orientation, covered with perfluorinated oil and placed under a cold stream of N_2 gas. The data collection was performed at 123 K (**2s** and **3r**) or 153 K (**2n** and **2o**) on Oxford Diffraction Xcalibur Sapphire 3 (**2n** and **3r**), Bruker P4 (**2o**) and Bruker APEX Duo (**2s**) diffractometers, using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). A hemisphere of data were collected based on ω-scan and ϕ-scan runs. The diffraction frames were integrated using the programs CrysAlis RED[19] or SAINT[20] and the integrated intensities were corrected for absorption with SADABS.[21] The structures were solved and developed using Fourier methods.[22] All non-hydrogen atoms were refined with anisotropic displacement parameters. The H atoms were placed at idealized positions and treated as riding atoms. Each H atom was assigned an isotropic displacement parameter equal to 1.2 times the equivalent isotropic displacement parameter of its parent atom. For structure solving and refinement the SHELX-97[23] software package was used. The structures were refined to F_o^2 and all reflections were used in least-squares calculations.[24] CCDC 2177354 (**2o**), 2177355 (**2s**), and 2176207 (**3r**)† contain the supplementary crystallographic data for this paper. The structure of cyclobutane **2n** could be solved, but the low quality of the data prevented a complete refinement, so the structure has to be considered only as a connectivity scheme. For the structure of **3r** a disordered pentane molecule in the (1/2, 1/2, 1/2) plane was found, which was refined using geometrical restraints and constraints for the anisotropic thermal displacement parameters.

Computational details

All structures were optimized using density functional theory (DFT) calculations using Gaussian 16,[25] with M06-2X[26] as the functional and 6-311+G(d,p) as the basis set, introducing solvation factors with the IEF-PCM[27] method, and methanol as the solvent, as in the optimized experimental conditions. The

stationary points were characterized using frequency calculations in order to verify that they have the right number of imaginary frequencies.

Synthesis of the bis(amino acid)s δ-1,2-diaminotruxinics 2a–2u

All cyclobutane bis(amino acid)s containing the 1,2-diaminotruxinic core **2a–2u** have been prepared following the same experimental method, which is exemplified here for **2a**. See the ESI† for the details of all compounds.

Synthesis of dimethyl-1,2-bis(benzamido)-3,4-diphenylcyclobutane-1,2-dicarboxylate 2a

The oxazolone **1a** (149.45 mg, 0.60 mmol) and $[Ru(bpy)_3](BF_4)_2$ (11.2 mg, 0.015 mmol) were suspended in deoxygenated and dry methanol (4 mL) under an Ar atmosphere at room temperature. This suspension was treated with $BF_3{\cdot}Et_2O$ (34.1 mg, 0.24 mmol), and the resulting mixture was irradiated with blue light (465 nm) for 24 h at room temperature. After the reaction time the solvent was evaporated to dryness, and the solid residue was suspended in chloroform (10 mL). This suspension was washed with water (3 × 5 mL) and the organic phase was dried with anhydrous $MgSO_4$. The resulting solution, which contained cyclobutane **2a**, was purified by column chromatography using silica as the support and a mixture of ethyl acetate/*n*-hexane in a gradient from 1/9 to 3/7 ratio. Cyclobutane **2a** was isolated as a white solid by solvent evaporation. Obtained: 56.8 mg (34% yield). ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 8.30 (s, 1H, NH), 7.56 (m, 2H, H_o, CO–Ph), 7.46 (m, 3H, H_o, Ph + H_p, CO–Ph), 7.39–7.27 (m, 5H, H_m, Ph + H_m, CO–Ph + H_p, Ph), 4.93 (s, 1H, CH), 3.73 (s, 3H, OCH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz) δ 171.6, 166.7, 134.7, 133.3, 131.9, 129.1, 128.7, 128.6, 128.2, 127.0, 64.1, 53.1, 47.6. HRMS (ESI^+) *m*/*z* calcd for $C_{34}H_{30}N_2NaO_6$ $[M + Na]^+$: 585.2002, found: 585.1987.

Expansion of the cyclobutane of δ-1,2-diaminotruxínics: synthesis of pyrrolidines 3

All pyrrolidine-2,5-dicarboxylate derivatives **3** have been prepared following the same experimental method, which is discussed in detail here for **3a**. See the ESI† for the details of all compounds.

Synthesis of dimethyl-2-benzamido-1-benzoyl-3,4-diphenylpyrrolidine-2,5-dicarboxylate 3a

A solution of δ-cyclobutane **2a** (41.8 mg, 0.074 mmol) in methanol (5 mL) was treated with NaOMe (4.06 mg, 0.075 mmol), and the resulting mixture was heated at 110 °C for 1 h in a J-Young sample flask. Once cooled, the resulting solution was evaporated to dryness and the solid residue was extracted with CH_2Cl_2 (3 × 5 mL). Any insoluble solid was removed at this point by filtration through Celite. The resulting clear solution was evaporated to dryness to give impure pyrrolidine **3a**, which was purified by crystallization from CH_2Cl_2/pentane to give **3a** as a white solid. Obtained: 21.2 mg (51% yield). Pyrrolidine **3a** was characterized using NMR methods as a mixture of two diastereomers in a 2.2 : 1 molar ratio. Only the major isomer could be fully characterized by NMR. ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 8.14 (s, 1H, NH), 7.91 (m, 2H, H_o, NHCO–C_6H_5), 7.59–7.12 (m, 18H, C_6H_5), 5.28 (d, $^3J_{HH}$ = 10 Hz, 1H, H–C_5), 5.27 (d, $^3J_{HH}$ = 13.1 Hz, 1H, H–C_3), 4.27 (dd, $^3J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 10 Hz, 1H, H–C_4), 3.70 (s, 3H, C_2–$COOCH_3$), 3.10 (s, 3H, C_5–$COOCH_3$). $^{13}C\{^1H\}$NMR ($CDCl_3$, 75.5 MHz) δ 170.9, 170.8, 169.0, 167.4, 136.2, 135.2, 134.6, 133.0, 132.2, 130.9, 129.0, 129.0, 128.9, 128.7, 128.6, 128.6, 128.4, 128.2, 128.2, 127.4, 81.4, 69.7, 53.4, 53.4, 51.9, 51.8. HRMS (ESI^+) *m*/*z* calc for $C_{34}H_{30}N_2NaO_6$ $[M + Na]^+$ 585.2002, found 585.2003.

Conclusions

In conclusion, the addition of the BF_3 Lewis acid changes the outcome of the Ru-photosensitized [2 + 2]-cycloaddition of (*Z*)-4-aryliden-5(4*H*)-oxazolones. In the presence of BF_3 the δ-isomer of the 1,2-diaminotruxinic cyclobutanes **2** is obtained in moderate to low yields by the *anti*-1,2-head-to-head cycloaddition of two oxazolones, instead of the μ-isomer obtained in a free-Lewis acid reaction. The role of the Lewis acid seems to be steric in nature, hindering the free rotation in the transition state. Treatment of the δ-1,2-diaminotruxinic cyclobutanes **2** with a strong base promotes an unprecedented expansion of the cyclobutane ring affording highly substituted pyrrolidine-2,5-dicarboxylates **3** in moderate yields with a high degree of stereoselectivity.

Author contributions

S. S. synthesized the compounds, performed the chemical characterization (investigation and validation) and wrote part of the original manuscript (visualization, writing – original draft, review and editing). R. L. and E. G. B. performed the computational calculations (formal analysis and methodology) and wrote part of the original manuscript (visualization, writing, original draft, review and editing). L. R. F. performed part of the crystallographic work (formal analysis and methodology) and corrected the original manuscript (visualization, writing – original draft, review and editing). E. P. U. conceived the original idea (conceptualization), directed the research (project administration and supervision), acquired the funding (funding acquisition and resources) and wrote the original manuscript (visualization, writing – original draft, review and editing). All authors analyzed and discussed the results and reviewed the manuscript.

Conflicts of interest

There are no conflicts to declare.

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