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# Selectivities in the reaction of vicinal diimines and acyl chlorides

Zhixin Wang [a], Ning Chen [a], Jiaxi Xu [a,b,*]

[a] State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, China
[b] Jiangxi Key Laboratory of Organic Chemistry, Jiangxi Science and Technology Normal University, Nanchang 330013, China

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ABSTRACT

The reaction of vicinal diimines and acyl chlorides in the presence of triethylamine produces 3-imino-β-lactams and/or bis-β-lactams chemo-, regio-, and stereoselectively, which are important intermediates in pharmaceutical and organic synthesis. The selectivities in the reaction have been investigated. The results indicate that all diimines react with various ketenes generated from acyl chlorides in the presence of triethylamine to give rise to *cis*-4-imino-β-lactams (mono-*cis*-β-lactams) diastereoselectively due to the electron-withdrawing property of the imino group in the vicinal diimines. Bis-β-lactams were obtained from diimines via the mono-*cis*-β-lactams as intermediates. Only ketenes with strong electron-donating substituents can react with the mono-*cis*-β-lactams to yield bis-β-lactams, affording a pair of C2-symmetric *cis*-bis-β-lactams with symmetric diimines, two or four pairs of diastereomeric bis-β-lactams with ketoaldehyde-derived unsymmetric diimines depending on the steric hindrance of their *N*-substituents. The current investigation provides very important information for the selective preparation of mono- and bis-β-lactams from vicinal diimines.



## 1. Introduction

Both 4-imino-β-lactams and bis-β-lactams are important intermediates in organic and pharmaceutical chemistry.[1,2] 4-Imino-β-lactams can be converted to 4-acyl-β-lactams, which have been widely used in the synthesis of α-amino acid derivatives[3,4] and β-amino acid derivatives[5,6] via the ring-opening. They have also been applied in the preparation of heterocyclic compounds,[7–25] alkaloids,[23,26] antibiotics,[27–31] even more complex natural products via the ring enlargement.[23,32] Bis-β-lactams have been utilized in the synthesis of fused bispyrrolidinones via one step conversion.[33,34]

Both 4-imino-β-lactams and bis-β-lactams have been prepared from the reaction of acyl chlorides and vicinal diimines in the presence of tertiary amines.[34] A few examples on the reactions of vicinal diimines and acyl chlorides have been reported previously.[34–37] Reactions of dimethylketene generated from isobutanoyl chloride and diimines formed from 2,3-butanedione and 1,2-diphenylethanedione gave rise to mono-β-lactams.[35–37] Reactions of glyoxal-derived diimines and various acyl chlorides produced *cis*-mono- and bis-β-lactams.[34] However, the diastereoselectivity in the formation of mono-β-lactams and the selectivity in the formation of mono/bis-β-lactams for the vicinal diketone-derived diimines, and the regio- and diastereoselectivities in the formation of mono-β-lactams for unsymmetric diimines generated from vicinal ketoaldehydes are still unclear to date. In our ongoing project devoted to investigate the stereoselectivity in the reaction of ketenes and imines (the Staudinger reaction), we hope to conduct the reaction of various diimines and ketenes and to study the selectivities in the reaction. Herein, we present our results on the selectivities in the reactions of vicinal diimines and acyl chlorides in the presence of triethylamine, including the diastereoselectivity in the formation of mono-β-lactams, regioselectivity in the formation of mono-β-lactams for unsymmetric diimines, the selectivity in the formation of mono- and bis-β-lactams, and the stereoselectivity in the formation of bis-β-lactams.

## 2. Results and discussion

### 2.1. Diastereoselectivity in the formation of mono-β-lactams in reactions of vicinal diketone-derived diimines and acyl chlorides

Alcaide and co-workers reported that glyoxal-derived diimines reacted with various acyl chlorides produced *cis*-mono- and bis-β-lactams stereospecifically.[34] We first hoped to investigate the diastereoselectivity in the reaction of vicinal diketone-derived diimines and representative ketenes, generated from substituted acetyl chlorides in the presence of triethylamine. A series of 2,3-butanedione-derived diimines **1a**–**d** was prepared via the reaction of 2,3-butanedione and 4-methoxyaniline (4-anisidine),[38] aniline,[38] benzylamine,[39] and dibenzylmethylamine (benzhydrylamine),

* Corresponding author. Tel./fax: +86 10 64435565; e-mail address: jxxu@mail.buct.edu.cn (J. Xu).

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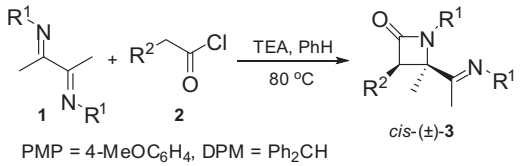
respectively, according to reported methods. Diimine **1a** reacted with various acyl chlorides **2**, including ethoxyacetyl chloride (**2a**), phthalimidoacetyl chloride (PhthNCH$_2$COCl) (**2b**), chloroacetyl chloride (**2c**), and propionyl chloride (**2d**), respectively, in benzene in the presence of triethylamine (TEA) in a molar ratio of 1:1.2:1.5 for diimine/acyl chloride/TEA (Table 1, entries 1–4). For each of cases, 4-imino-β-lactams **3aa**–**ad** were generated in satisfactory to good yields. Diimines **1b**,**c** reacted with propionyl chloride (**2d**), respectively, to afford 4-imino-β-lactams **3bd**–**cd** in satisfactory yields (Table 1, entries 5 and 6). However, diimine **1d** with bulky *N*-substituent diphenylmethyl group reacted with propionyl chloride (**2d**) to give rise to 4-imino-β-lactam **3dd** in a low yield (42%) due to the steric hindrance of the bulky diphenylmethyl group, decreasing the reaction rate (Table 1, entry 7).

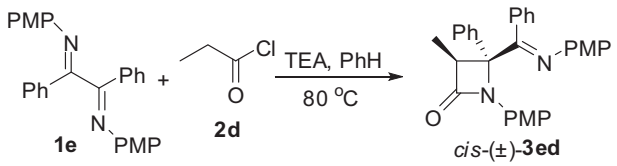
**Table 1**
Reaction of symmetric diimines **1** and acyl chlorides **2**




| Entry | Symmetric diimine **1** | | Acyl chloride **2** | | Product **3** | |
|---|---|---|---|---|---|---|
| | **1** | $R^1$ | **2** | $R^2$ | **3** | Yield[a] (%) |
| 1 | **1a** | PMP | **2a** | EtO | *cis*-**3aa** | 76 |
| 2 | | | **2b** | PhthN | *cis*-**3ab** | 87 |
| 3 | | | **2c** | Cl | *cis*-**3ac** | 70 |
| 4 | | | **2d** | Me | *cis*-**3ad** | 71 |
| 5 | **1b** | Ph | **2d** | Me | *cis*-**3bd** | 73 |
| 6 | **1c** | Bn | **2d** | Me | *cis*-**3cd** | 69 |
| 7 | **1d** | DPM | **2d** | Me | *cis*-**3dd** | 42 |

[a] Isolated yield was obtained in the ratio of **1e**/**2d** at 1:1.2 after column chromatography and recrystallization.

The reaction of aromatic vicinal diketone-derived diimines and acyl chlorides was also investigated. To observe the diastereoselectivity in the reaction, a ketene bearing weak electron-donating substituent was chosen because it may produce either *cis*-β-lactams or *trans*-β-lactams depending on different imines. Benzildiimine (**1e**) was prepared from benzil and 4-methoxyaniline and reacted with propionyl chloride (**2d**) to afford mono-β-lactam **3ed** in 50% yield in the ratio of **1e**/**2d** at 1:1.2. The yield was improved to 92% when propionyl chloride was increased to 5 equiv (Scheme 1).




**Scheme 1.** Reaction of benzildiimine (**1e**) with propionyl chloride (**2d**).

The stereostructure of products was identified on the basis of the NOESY spectra of the representative products. There existed a strong correlation between 3-hydrogen and the hydrogens in 4-methyl on the β-lactam ring in each of the mono-β-lactam products determined. Furthermore, a weak correlation between the methylene in the ethoxy group and the methyl in the acetoxime moiety in β-lactam **3aa** was also observed (Fig. 1). Both of the correlations indicate that the stereostructure of the mono-β-lactams **3aa**–**dd** is *cis*-configuration. However, the peaks of the 4-methyl on the β-lactam ring and the methyl in the acetoxime moiety in the $^1$H NMR spectra are too close for most mono-β-lactams. It is some difficult to distinguish these two singlet methyl groups. To obtain an unambiguous result on the identification of the stereostructure, one of the representative products (**3bd**) was selected to subject the X-ray single crystal diffraction (XRD) analysis. The XRD results indicate that **3bd** is indeed a *cis*-mono-β-lactam (Fig. 2),[40] further revealing that mono-β-lactams **3aa**–**dd** are in cis-configuration because **3bd** was prepared from a ketene with weak electron-donating substituent (Me) and an imine with less bulky *N*-substituent (Ph). For mono-β-lactam **3ed**, the correlation between its 3-hydrogen and 4-phenyl group was observed in its NOESY spectrum. On the other hand, benzoxime is more electron-withdrawing than acetoxime. Thus, **3ed** should be in cis-configuration.

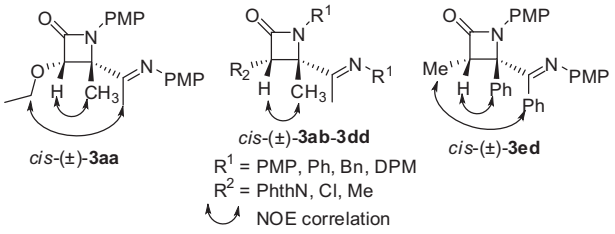



**Fig. 1.** NOE correlations in mono-*cis*-β-lactams **3aa**–**3ed**.

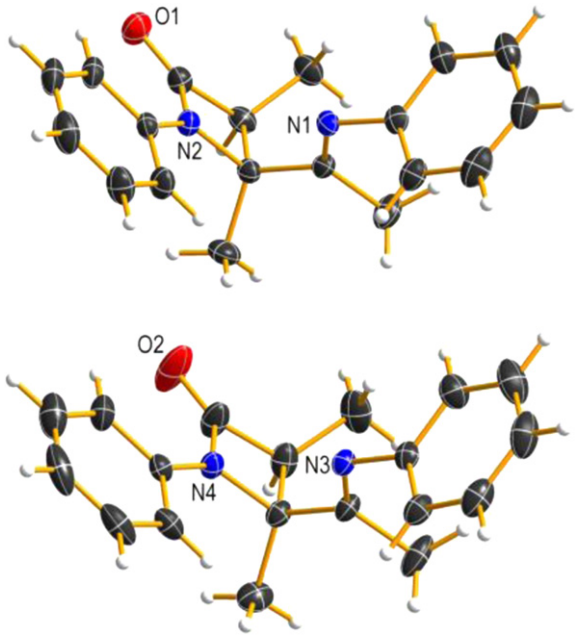
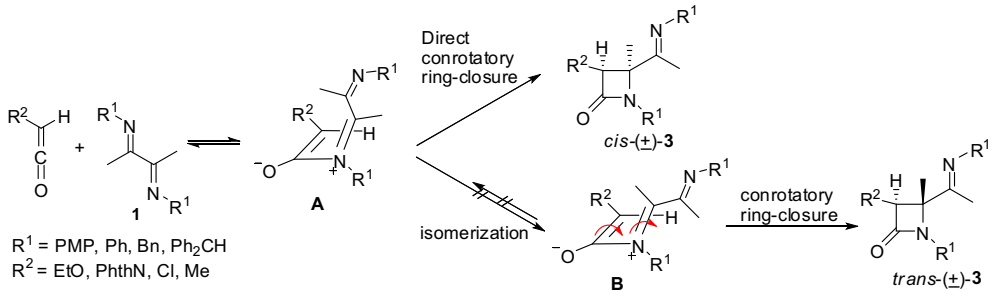



**Fig. 2.** Stereostructure of mono-β-lactam *cis*-**3bd**.

The diastereoselectivity follows our previous proposal on the stereoselectivity of the Staudinger reaction.[41–44] That is, the diastereoselectivity is a result of the competition between the direct conrotatory ring closure and the isomerization of imine moiety in the zwitterionic intermediates generated from ketenes and imines (Scheme 2). Strong electron-donating ketene substituents, strong electron-withdrawing imine *C*-substituents and bulky imine *N*-substituents prefer the formation of *cis*-β-lactams, while weak electron-donating and electron-withdrawing ketene substituents, and electron-donating imine *C*-substituents dominate the formation of *trans*-β-lactams. The results reveal that the diketone-derived diimines show similar diastereoselectivity as the glyoxal-derived diimines in the Staudinger reactions, affording mono-*cis*-β-lactams, because the imino groups derived from both formyl and acyl groups are relative strong electron-withdrawing substituents



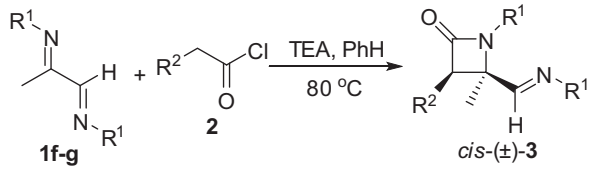

**Scheme 2.** Mechanism in the formation of mono-*cis*-β-lactams from ketenes and diimines.

in diimines, increasing the rate of ring closure. No isomerization occurs during reactions.

### 2.2. Regio- and diastereoselectivities in the formation of mono-β-lactams in the reaction of vicinal ketoaldehyde-derived unsymmetric diimines and acyl chlorides

Although diketone and glyoxal-derived diimines show similar diastereoselectivities in the reactions with acyl chlorides,[34] we are interested in the selectivity in the reaction of vicinal ketoaldehyde-derived unsymmetric diimines and acyl chlorides. Representative unsymmetric diimines **1f**–**g** with less and more bulky *N*-substituents were prepared from pyruvic aldehyde and 4-methoxyaniline and diphenylmethylamine, respectively. Unsymmetric diimine **1f** reacted with the representative acyl chlorides **2a**,**d**, respectively, in the presence of triethylamine in the molar ratio of **1**/**2**/TEA at 1:1.2:1.3 to afford the corresponding mono-*cis*-β-lactams **3fa**,**fd** in good yields (Table 2, entries 1 and 2). Unsymmetric diimine **1g** reacted with acyl chlorides **2a**–**d**, respectively, in the presence of triethylamine in the molar ratio of **1**/**2**/TEA at 1:2.5:3 to afford the corresponding mono-*cis*-β-lactams **3ga**–**gd** in satisfactory to good yields (Table 2, entries 3–6), in which more acyl chlorides were added to improve the yields because the diimine **1g** with bulky *N*-substituent.

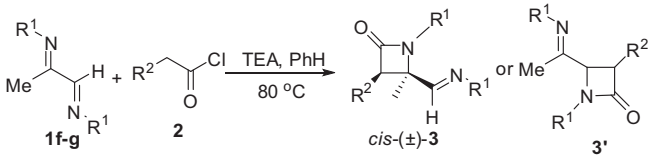
**Table 2**
Reaction of unsymmetric diimines **1** and acyl chlorides **2**




| Entry | Unsymmetric diimine **1** | | Acyl chloride **2** | | Product **3** | |
|---|---|---|---|---|---|---|
| | **1** | $R^1$ | **2** | $R^2$ | **3** | Yield[a] (%) |
| 1 | **1f** | PMP | **2a** | EtO | *cis*-**3fa** | 80 |
| 2 | | | **2d** | Me | *cis*-**3fd** | 77 |
| 3 | **1g** | DPM | **2a** | EtO | *cis*-**3ga** | 82[b] |
| 4 | | | **2b** | PhthN | *cis*-**3gb** | 84[c] |
| 5 | | | **2c** | Cl | *cis*-**3gc** | 50[c] |
| 6 | | | **2d** | Me | *cis*-**3gd** | 95[c] |

[a] Isolated yield in the ratio of **1**/**2** at 1:1.2 after column chromatography and recrystallization.
[b] Yield in ratio of **1**/**2** at 1:2.5 in dicloromethane at 25 °C.
[c] Yield in ratio of **1**/**2** at 1:2.5.

The products obtained from the reaction of diimines **1f**–**g** were identified as the structure **3** rather than **3′** (Scheme 3) because the products show a $CHCCH_3$ system with a singlet at downfield for an aldimine hydrogen, not two vicinal hydrogens (AM system) in the β-lactam ring in their $^1H$ NMR spectra. The results indicate that the ketimine in pyruvic aldehyde-derived diimines reacts with ketenes generated from acyl chlorides. For the two imine groups in the unsymmetric diimines **1f**–**g**, the ketimine is more electron-rich than the aldimine, favorably attacking ketenes in the nucleophilic addition step. On the other hand, the stable conformation of diimines **1** is *s*-trans-configuration and the ketimine attacks ketenes more predominantly than the aldimine in steric hindrance as well (**C** vs **D**, Fig. 3). These rationalize the reason why the ketimine in the unsymmetric diimines **1f**–**g** reacts with acyl chlorides **2** specifically.




**Scheme 3.** Reaction of unsymmetric diimines **1f**–**g** with acyl chlorides **2**.

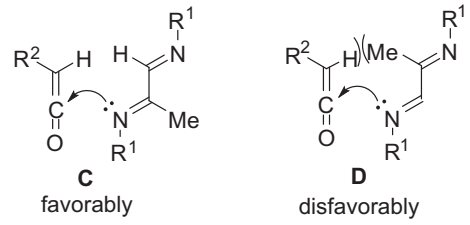



**Fig. 3.** Regioselective attacks in the reaction of unsymmetric diimines **1f**–**g** and ketenes.

The configuration of product **3fd** was determined on the basis of its NOESY spectrum (See SD for details). The correlation between 3-hydrogen and 4-methyl was observed, demonstrating that they are in the same side of the β-lactam ring. That is, the β-lactam is in cis-configuration. The diimine **1f** reacted with methylketene with weak electron-donating substituent to afford *cis*-β-lactam **3fd**, indicating that the other products from diimine **1f** and acyl chlorides **2b**–**d** should be in cis-configuration and all products from imine **1g** should be in cis-configuration as well due to bulky imine *N*-substituent.

The configuration of product **3gd** was further confirmed by 1D-NOE (Fig. 4). When 3-hydrogen on the β-lactam ring was irradiated, 3% NOE was observed for the hydrogens of 4-methyl on the β-lactam ring, which demonstrates that 3-hydrogen and 4-methyl group are in the same side of the β-lactam ring, indicating that the β-lactam is in cis-configuration.

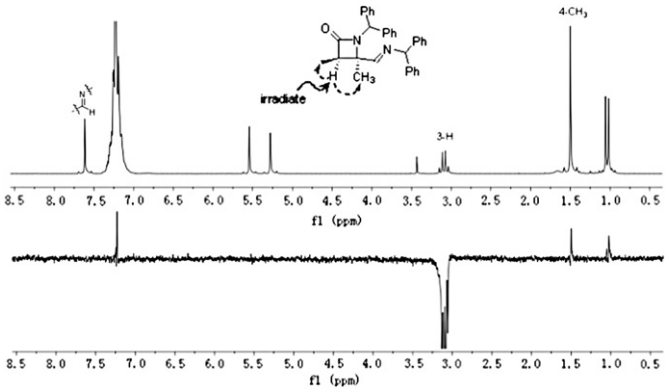
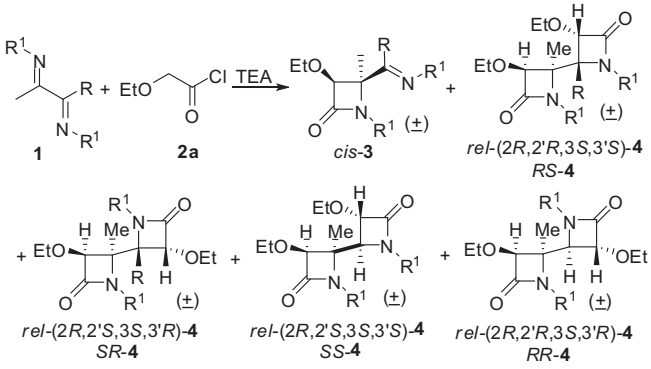



**Fig. 4.** $^1$H NMR and 1D-NOE spectra of *cis*-**3gd**.

with ethoxyacetyl chloride (**2a**), only the corresponding mono-β-lactams **3** were obtained, no bis-β-lactam was found in the reaction mixtures (also see Table 2, entries 3–6), even acyl chlorides **2b**–**d** were increased to 5 equiv, revealing that only ethoxyacetyl chloride (**2a**) can react with diimines **1** to give rise to bis-β-lactams. The results demonstrate that the electronic effect of the ketene substituents $R^2$ is very important for the formation of bis-β-lactams. Thus, the further investigation focuses on the reactions of ethoxyacetyl chloride (**2a**) and representative diimines **1a**,**f**,**g** (Table 3) and the stereostructure of the bis-β-lactam products.

We initially used symmetric diimine **1a** and ethoxyacetyl chloride (**2a**) as the model substrates to study the formation selectivity of the corresponding mono- and bis-β-lactams **3aa** and **4aa**. We conducted the reaction in different molar ratios of starting materials in the presence of TEA in dichloromethane (DCM) at room

**Table 3**
Selectivity in the reaction of diimines **1a**,**f**,**g** and ethoxyacetyl chloride (**2a**)



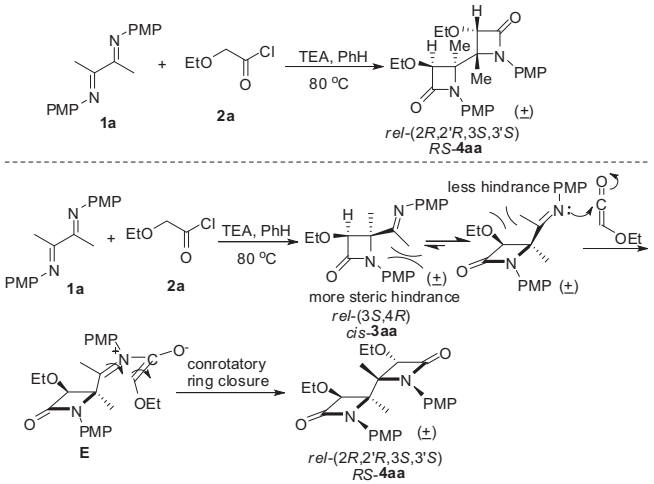

| Entry | Diimine **1** | Ratio **1**/**2a**/**TEA** | Solvent | Temp (°C) | Product | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **3** | Yield[a] (%) | **4** | Yield[a] (%) | **4** | Yield[a] (%) | **4** | Yield (%) |
| 1 | **1a** | 1:2.5:3.0 | DCM | 20 | *cis*-**3aa** | 81 | — | — | — | — | — | — |
| 2 | **1a** | 1:5:6 | DCM | 20 | *cis*-**3aa** | 81 | — | — | — | — | — | — |
| 3 | **1a** | 1:2:2.5 | PhH | 80 | *cis*-**3aa** | 63 | *RS*-**4aa** | 12 | — | — | — | — |
| 4 | **1a** | 1:2.5:3.0 | PhH | 80 | — | — | *RS*-**4aa** | 83 | — | — | — | — |
| 5 | **1f** | 1:2.5:3.0 | PhH | 80 | — | — | *RS*-**4ea** | 53 | *SR*-**4fa** | ND[b] | *SS*-**4fa** *RR*-**4fa** | ND[b] |
| 6 | **1f** | 1:5:6 | PhH | 80 | — | — | *RS*-**4ea** | 59 | *SR*-**4fa** | 11[c] | *SS*-**4fa** *RR*-**4fa** | 15[c] 9[c] |
| 7 | **1g** | 1:2.5:3.0 | DCM | 20 | *cis*-**3ga** | 82 | — | — | — | — | — | — |
| 8 | **1g** | 1:2.5:3.0 | PhH | 80 | *cis*-**3ga** | 30 | *RS*-**4ga** | 42 | *SR*-**4ga** | 9 | — | — |
| 9 | **1g** | 1:5:6 | PhH | | — | — | *RS*-**4ga** | 65 | *SR*-**4ga** | 14 | — | — |

[a] Isolated yield after column chromatography and recrystallization.
[b] Not determined.
[c] NMR yield.

## 2.3. Selectivity in the formation of mono- and bis-β-lactams in the reactions of diimines and acyl chlorides and the stereostructure of bis-β-lactams

Although Alcaide and co-workers explored the formation selectivity of mono- and bis-β-lactams in the reactions of glyoxal-derived diimines,[34] the selectivity is still unclear in the reactions of vicinal diketone-derived diimines and ketoaldehyde-derived diimines. To extend the application of the reaction in the selective preparation of various mono- and bis-β-lactams from different diimines and ketenes, we investigated the formation selectivity of mono- and bis-β-lactams in the reactions of representative vicinal diketone and ketoaldehyde-derived diimines **1** and acyl chlorides **2**. The representative diimines **1a**,**f**,**g** were screened first with acyl chlorides **2a**–**d** in the molar ratio of **1**/**2** at 1:2.5 in the presence of triethylamine in refluxing benzene at 80 °C. Except for the reactions temperature (20 °C) and in benzene at 80 °C (Table 3, entries 1–4, also see Table 1). In dichloromethane, only mono-β-lactam **3aa** was obtained in the yield of 81% whatever the molar ratio of diimine **1a** and acyl chloride **2a** varied from 1:2.5 to 1:5 (Table 3, entries 1 and 2). However, a mixture of mono-β-lactam **3aa** and bis-β-lactam **4aa** were obtained in refluxing benzene in the molar ratio of 1:2 (Table 1, entry 3) and bis-β-lactam **4aa** was obtained in a yield of 83% as sole product in the molar ratio of 1:2.5 (Table 1, entry 4, Scheme 4). The results demonstrate that diimine **1a** first reacted with one molecule of **2a** to form mono-*cis*-β-lactam **3aa** in the reaction. Mono-*cis*-β-lactam **3aa** further reacted with another molecule of **2a** to afford bis-β-lactam product **4aa**. The results also demonstrate that temperature and solvent are not key factors in the formation of mono-β-lactam. However, they are very important in the preparation of bis-β-lactams. Alcaide and co-workers also reported that high temperature is beneficial for the formation of bis-β-lactams.[34]

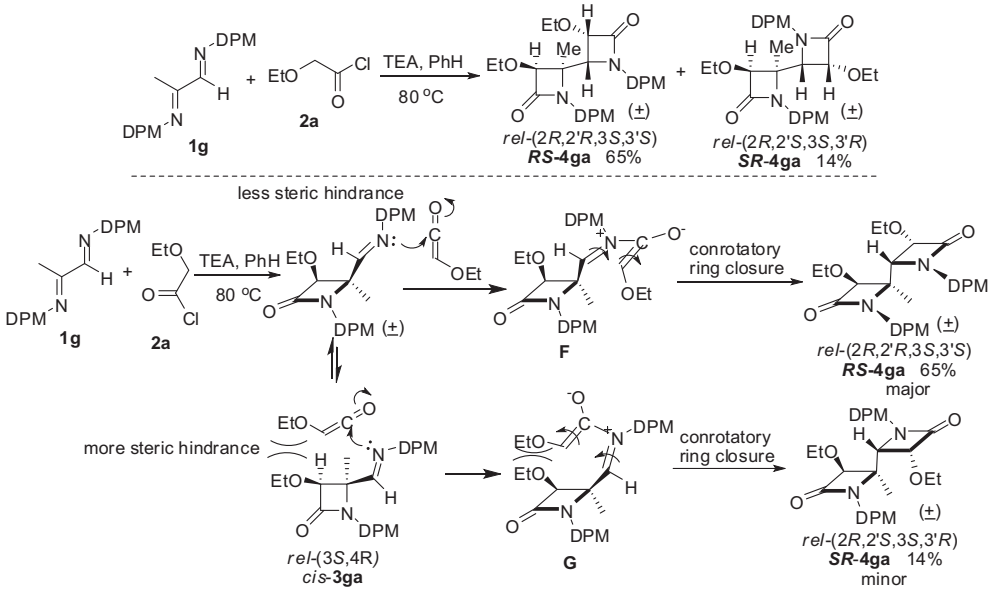
After generating the first β-lactam ring, the β-lactam ring, as bulky groups in imines, remarkably inhibits the formation of the second β-lactam ring. Thus, in order to form the second ring, a strong electron-donating ketene, such as ethoxylketene and high temperature are demanded.




**Scheme 4.** Reaction and mechanism in the formation of bis-β-lactam **4aa** from symmetric diimine **1a** and **2a**.

Secondly, we conducted the reaction of bulky unsymmetric diimine **1g** with the *N*-diphenylmethyl (DPM) group and ethoxyacetyl chloride (**2a**) (Scheme 5). As diimine **1a**, only mono-*cis*-β-lactam **3ga** was obtained in DCM in the molar ratio of **1g**/**2a** at 1:2.5 (Table 3, entry 7). However, at the same molar ratio, a mixture of mono-*cis*-β-lactam **3ga** and two different bis-β-lactams **4ga** were obtained in refluxing benzene (Table 3, entry 8). When ethoxyacetyl chloride was increased to 5 equiv, all mono-*cis*-β-lactam **3ga** was converted to the two bis-β-lactams **4ga** in yields of 65% and 14%, respectively. NMR spectra indicate that the two products are a couple of diastereoisomeric bis-*cis*-β-lactams. Their stereostructures were identified on the basis of the previous reported results[34] and the reaction mechanism. On comparison with the product *RS*-**4aa**, the major product was assigned as *RS*-**4ga** with the relative configuration of 2*R*,2′*R*,3*S*,3′*S*. It generated from *cis*-**3ga** and ethoxyketene via the more stable conformation of *cis*-**3ga** and less steric hindrance process (Top process in Scheme 5). The minor product was assigned as *SR*-**4ga** with the relative configuration of 2*R*,2′*S*,3*S*,3′*R*. It generated from *cis*-**3ga** and ethoxyketene via the less stable conformation of *cis*-**3ga** and more steric hindrance process (Bottom process in Scheme 5).

To further verify the structural identification of the products *cis*-**3ga**, *RS*-**4aa**, *RS*-**4ga**, and *SR*-**4ga**, the key representative products *cis*-**3ga**, *RS*-**4ga**, and *SR*-**4ga** were subjected single crystal X-ray diffraction analysis.[40] Their stereostructures are shown in Fig. 5. The results indicate that the XRD structures are in complete




**Scheme 5.** Reaction and mechanism in the formation of bis-β-lactams **4ga** from bulky unsymmetric diimine **1g** and **2a**.

$^{1}$H and $^{13}$C NMR spectra of **4aa** reveal that the molecule has symmetry and its NOESY spectrum indicates that both of the two lactam-rings are cis-configuration. Thus, the product **4aa** should be a C2-symmetric compound as the reported product generated from the reaction of glyoxal-derived diimine and ethoxyacetyl chloride according to the similar formation mechanism.[34] Its formation process is shown in Scheme 4. As we know, the formation of bis-β-lactam is stepwise. Hence, during the reaction, *cis*-**3aa** generated first and its less bulky conformation reacted with another molecule of ethoxyketene to produce intermediate **E**, which further underwent a conrotatory ring closure to give rise to product *RS*-**4aa** with relative configuration of 2*R*,2′*R*,3*S*,3′*S* (Only the configuration of the new generated chiral atoms is put before the compound number, similarly hereinafter.).

agreement with the structures we proposed, respectively, supporting our identification.

Finally, the reaction of unsymmetric diimine **1f** and ethoxyacetyl chloride (**2a**) was conducted. A major diastereomers of bis-β-lactams **4fa** were obtained in the yield of 53% with other three diastereomers in the molar ratio of **1f**/**2a** at 1:2.5. Similarly, the stereostructure of the major product was assigned as *RS*-**4fa** with the relative configuration of 2*R*,2′*R*,3*S*,3′*S* on the basis of NMR spectra and the formation mechanism. It generated from *cis*-**3fa** and ethoxyketene via the more stable conformation of *cis*-**3fa** and less steric hindrance process. When ethoxyacetyl chloride (**2a**) was increased to 5 equiv to improve the yields, bis-β-lactam *RS*-**4fa** increased slightly from 53% to 59%. Its other three diastereomers were obtained in yields of 15%, 11%, and 9%, respectively (See SD for

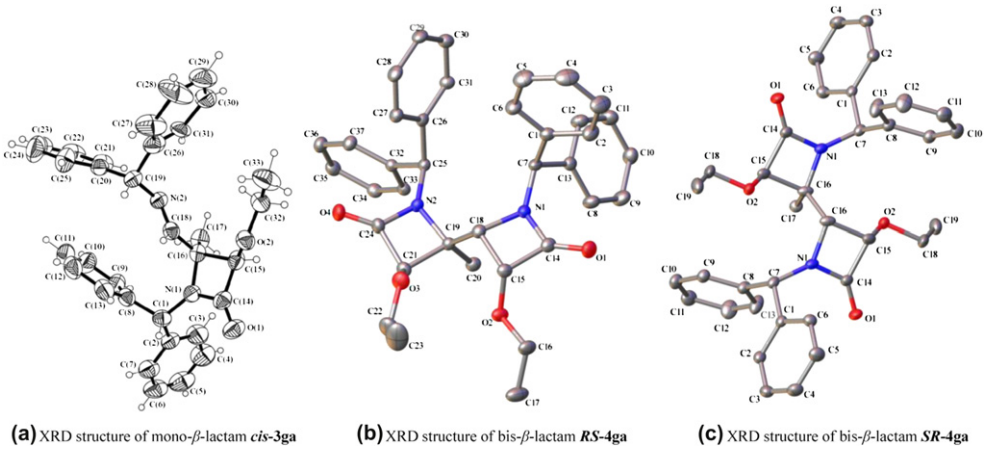



**Fig. 5.** Stereostructures of mono-β-lactam *cis*-**3ga** and bis-β-lactams *RS*-**4ga** and *SR*-**4ga**.

details). Although they are inseparable on silica gel column after many attempts, their stereostructures can be assigned on the basis of the $^1$H NMR spectrum of their mixture. In the mixture, the most isomer (15% yield) and the least one (9% yield) show trans-configuration of the β-lactam ring derived from the aldimine in diimine **1f** due to their vicinal hydrogen coupling constants of 1.6 and 1.7 Hz, respectively, while the middle one (11% yield) shows cis-configuration of the β-lactam ring derived from the aldimine due to its vicinal hydrogen coupling constant of 5.4 Hz. The results indicate that the isomerization of imine moiety in the zwitterionic intermediates generated from ethoxyketene and the aldimine in diimine **1f** occurred during the formation of the second β-lactam ring in the reaction. Thus, on the basis of the $^1$H NMR spectrum and the reaction mechanism, the stereostructures of the three bis-β-lactam products were assigned as *SS*-**4fa** with rel-(2*R*,2′*S*,3*S*,3′*S*) configuration in 15% yield, *SR*-**4fa** with rel-(2*R*,2′*S*,3*S*,3′*R*) in 11% yield, and *RR*-**4fa** with rel-(2*R*,2′*R*,3*S*,3′*R*) in 9% yield. Their formation processes are shown in Scheme 6.

Ethoxyacetyl chloride reacted with symmetric diimines prepared from glyoxal and 2,3-butanedione with 4-methoxyaniline gave rise to only a pair of enantiomers with C2 symmetry in each of cases. However, it reacted with unsymmetric ketoaldehyde-derived diimines with bulky *N*-substituents to generate two pairs of diastereomeric *cis*-bis-β-lactams, one with pseudo C2 symmetry, one with pseudo i symmetry, and with unsymmetric ketoaldehyde-derived diimines with less bulky *N*-substituents to produce four pairs of diastereomeric bis-β-lactams, two pairs with *cis*–*cis*-bis-β-lactams, two pairs with *cis*–*trans*-bis-β-lactams.

## 3. Conclusion

The selectivities in the Staudinger reaction of representative vicinal diimines and acyl chlorides have been investigated. The results indicate that all diimines react with various ketenes generated from acyl chlorides in the presence of a tertiary amine to give rise to *cis*-4-imino-β-lactams (mono-*cis*-β-lactams) due to strong electron-withdrawing imino groups as the imine *C*-substituents in the reaction. For vicinal ketoaldehyde-derived diimines, they always produce *cis*-aldimino-β-lactams because electron-rich ketimines prefer to attack ketenes favorably in both electronic and steric effects to generate zwitterionic intermediates, which favor the direct ring closure due to their electron-withdrawing aldimines. The results reveal that both the diketone-derived diimines and the ketoaldehyde-derived diimines show similar diastereoselectivity as the glyoxal-derived diimines in the formation of mono-β-lactams. Bis-β-lactams were obtained from diimines via mono-β-lactams. Only ketenes with strong electron-donating substituents can react with mono-β-lactams to yield bis-β-lactams. Ethoxyacetyl chloride reacted with symmetric diimines to afford a pair of C2-symmetric *cis*-bis-β-lactams, with unsymmetric diimines to produce two or four pairs of diastereomers depending on the steric hindrance of the diimine *N*-substituents, and the major products with pseudo C2 symmetry. The current results provide very important information for the selective preparation of mono- and bis-β-lactams from vicinal diimines.

## 4. Experimental section

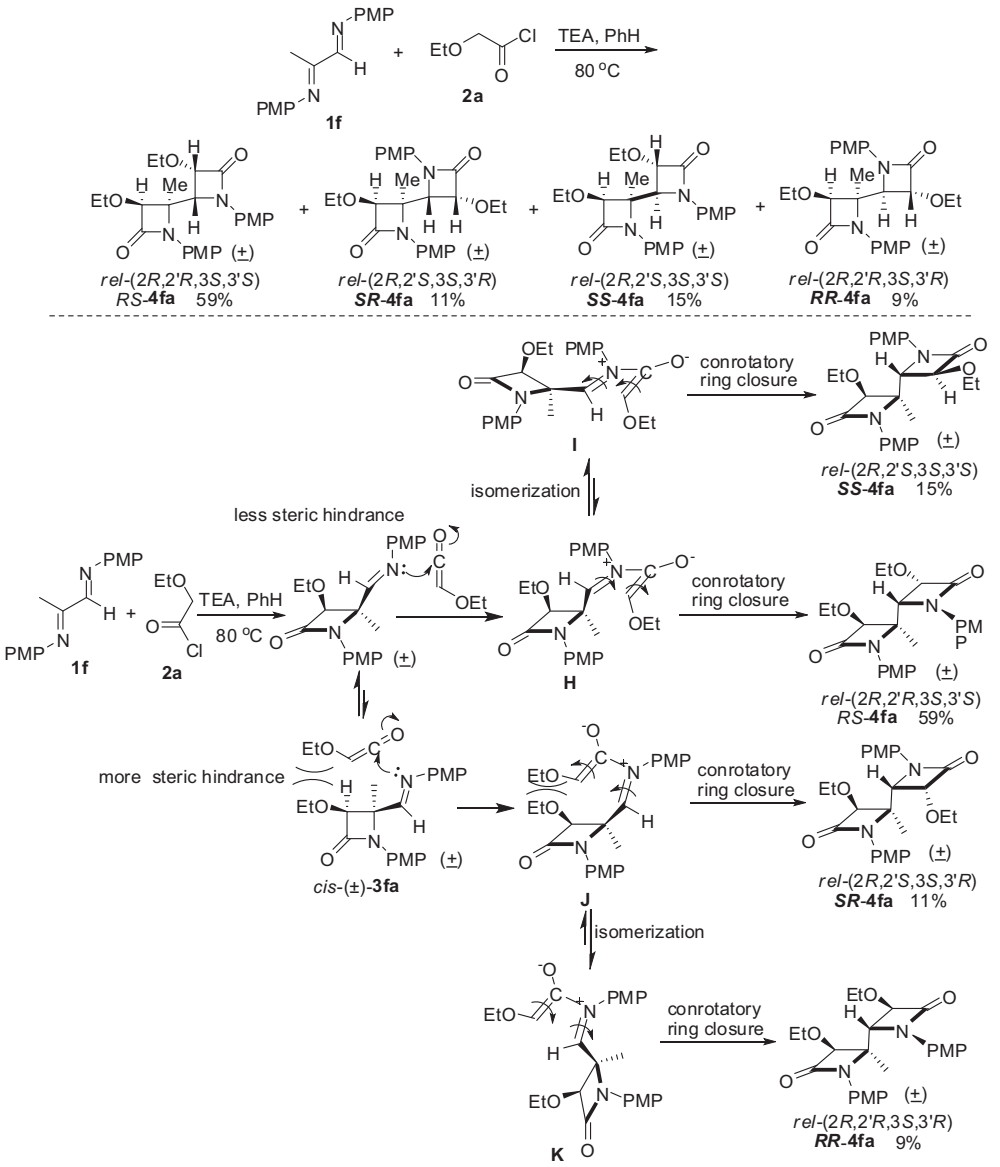
### 4.1. General

Melting points were determined on a melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded at 200, 300, or 400 MHz in $CDCl_3$ with TMS as the internal standard. $^{13}$C NMR spectra were recorded at 50.3, 75.5, or 100.6 MHz in $CDCl_3$ with $CDCl_3$ as the internal standard at 77.0 ppm. NOESY and 1D-NOE were determined from Bruker 400 plus NMR spectrometer. IR spectra were determined directly. HRMS spectra were performed on an LC/MSD TOF mass spectrometer.

Symmetric diimines **1a**–**d** were prepared from 2,3-butanedione with aniline,[38] 4-methoxyaniline,[38] benzylamine,[39] and diphenylmethylamine. Symmetric diimine **1e** was synthesized from benzil and 4-methoxyaniline. Unsymmetric diimines **1f**,**g** were derived from 30% pyruvic aldehyde aqueous solution with 4-methoxyaniline and diphenylmethylamine. All acyl chlorides **2** were generated from the corresponding carboxylic acids with $SOCl_2$ according to our reported literatures.[45,46]

### 4.2. General procedure for the reaction of vicinal diimines 1 and acyl chlorides 2

A solution of acyl chloride (1.2–5 mmol) in anhydrous benzene (5 mL) was added dropwise to a solution of diimine (1 mmol) and triethylamine (0.152–0.606 g, 1.5–6 mmol) in toluene (10 mL). The resulting mixture was stirred at 80 °C under nitrogen for 4–16 h, which was determined by TLC monitoring. The reaction mixture was then diluted with $CH_2C1_2$ (20 mL) and subsequently washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (2×10 mL). After dried over anhydrous $Na_2SO_4$ and removal of solvent, the residue was purified via recrystallization with EtOAc or a mixture of EtOAc and hexanes or via flash column chromatography (silica gel, a mixture of hexanes and EtOAc as eluent) to afford the product.




**Scheme 6.** Reaction and mechanism in the formation of bis-β-lactams **4fa** from unsymmetric diimine **1f** and **2a**.

*4.2.1. rel-(3R,4S)-3-Ethoxy-1-(4-methoxyphenyl)-4-[(E)-1-(4-methoxyphenylimino)ethyl]-4-methylazetidin-2-one (cis-**3aa**).* Reaction was conducted in 1 mmol of diimine **1a**, 1.2 mmol of acid chloride **2a**, and 1.5 mmol of $Et_3N$.

Yellowish oil, 0.288 g, yield: 75.6%. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 7.38–6.87 (m, 8H, ArH), 4.55 (s, 1H, OCH), 3.81 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.78–3.71 (m, 2H, $OCH_2$), 1.93 (s, 3H, $CH_3$), 1.88 (s, 3H, $CH_3$), 1.26 (t, $J$=7.0 Hz, 3H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 171.0, 163.1, 156.1, 155.8, 143.6, 129.80, 129.78, 119.9, 118.3, 114.3, 114.0, 90.5, 70.2, 67.4, 55.0, 19.5, 17.3, 14.9. IR (KBr) $\nu$ ($cm^{-1}$): 1754 (C=O), 1652 (C=N). HRMS (ESI) calcd for $C_{22}H_{27}N_2O_4$ $[M+H]^+$ $m/z$: 383.1965, found 383.1968.

*4.2.2. rel-(3R,4R)-1-(4-Methoxyphenyl)-4-[(E)-1-(4-methoxyphenylimino)ethyl]-4-methyl-3-phthalimidoazetidin-2-one (cis-**3ab**).* Reaction was conducted in 1 mmol of diimine **1a**, 1.2 mmol of acid chloride **2b**, and 1.5 mmol of $Et_3N$.

Colorless crystals, 0.430 g, yield: 86.9%, mp 178.0–179.5 °C $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 7.78–6.18 (m, 12H, ArH), 5.37 (s, 1H, CH), 3.82 (s, 3H, $OCH_3$), 3.69 (s, 3H, $OCH_3$), 2.09 (s, 3H, $CH_3$), 1.88 (s, 3H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 169.6, 166.7, 161.1, 156.7, 155.9, 142.7, 134.5, 131.6, 130.5, 123.7, 120.4, 119.9, 114.3, 113.9, 71.1, 64.3, 55.4, 55.3, 24.0, 17.5. IR (KBr) $\nu$ ($cm^{-1}$): 1757, 1718 (C=O), 1648 (C=N). HRMS (ESI) calcd for $C_{28}H_{26}N_3O_5$ $[M+H]^+$ $m/z$: 484.1867, found 484.1868.

*4.2.3. rel-(3R,4S)-3-Chloro-1-(4-methoxyphenyl)-4-[(E)-1-(4-methoxyphenylimino)ethyl]-4-methylazetidin-2-one (cis-**3ac**).* Reaction was conducted in 1 mmol of diimine **1a**, 1.2 mmol of acid chloride **2c**, and 1.5 mmol of $Et_3N$.

Colorless crystals, 0.221 g, yield 69.7%, mp 72.5–74.0 °C $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 7.41–6.69 (m, 8H, ArH), 4.85 (s, 1H, CHCl), 3.80 (s, 6H, $2OCH_3$), 1.96 (s, 3H, $CH_3$), 1.93 (s, 3H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 169.2, 160.0, 157.2, 156.7, 144.0, 130.2, 120.6, 119.6, 115.0, 114.8, 70.3, 65.5, 55.8, 21.0, 18.2. IR (KBr) $\nu$ ($cm^{-1}$): 1760 (C=O), 1652 (C=N). HRMS (ESI) calcd for $C_{20}H_{22}ClN_2O_3$ $[M+H]^+$ $m/z$: 373.1313, found 373.1320.

*4.2.4. rel-(3R,4R)-1-(4-Methoxyphenyl)-4-[(E)-1-(4-methoxyphenylimino)ethyl]-3,4-dimethylazetidin-2-one (cis-**3ad**).*

Reaction was conducted in 1 mmol of diimine **1a**, 1.2 mmol of acid chloride **2d**, and 1.5 mmol of $Et_3N$.

Colorless crystals, 0.249 g, yield, 70.7%, mp 188.0–190.0 °C $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.41–6.63 (m, 8H, ArH), 3.79 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.33 (q, $J$=7.5 Hz, 1H, CH), 1.88 (s, 3H, $CH_3$), 1.85 (s, 3H, $CH_3$), 1.32 (d, $J$=7.6 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 170.7, 166.8, 156.1, 155.9, 143.8, 131.0, 120.0, 118.7, 114.3, 114.2, 67.5, 56.5, 55.4, 21.7, 17.9, 9.3. IR (KBr) $\nu$ ($cm^{-1}$): 1742 (C=O), 1652 (C=N). HRMS (ESI) calcd for $C_{21}H_{25}N_2O_3$ $[M+H]^+$ $m/z$: 353.1860, found: 353.1864.

*4.2.5. rel-(3R,4R)-3,4-Dimethyl-1-phenyl-4-[(E)-1-(phenylimino)-ethyl]azetidin-2-one (cis-**3bd**).* Reaction was conducted in 1 mmol of diimine **1b**, 1.2 mmol of acid chloride **2d**, and 1.5 mmol of $Et_3N$.

Colorless crystals, 0.214 g, yield 73.2%, mp 115.0–117.0 °C $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.45–6.67 (m, 10H, ArH), 3.34 (q, $J$=7.6 Hz, 1H, CH), 1.92 (s, 3H, $CH_3$), 1.84 (s, 3H, $CH_3$), 1.34 (d, $J$=7.6 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 170.4, 167.3, 150.7, 137.5, 129.1, 123.8, 123.7, 123.5, 118.7, 117.1, 67.3, 56.6, 21.7, 18.0, 9.2. IR (KBr) $\nu$ ($cm^{-1}$): 1744 (C=O), 1653 (C=N). HRMS (ESI) calcd for $C_{19}H_{21}N_2O$ $[M+H]^+$ $m/z$: 293.1648, found 293.1655.

*4.2.6. rel-(3R,4R)-1-Benzyl-4-[(E)-1-(benzylimino)ethyl]-3,4-dimethylazetidin-2-one (cis-**3cd**).* Reaction was conducted in 1 mmol of diimine **1c**, 1.2 mmol of acid chloride **2d**, and 1.5 mmol of $Et_3N$.

Colorless crystals, 0.221 g, yield, 69.2%, mp 112–113.8 °C $^1$H NMR (200MHz, $CDCl_3$) $\delta$: 7.38–7.35 (m, 10H, ArH), 4.77 (d, $J$=15.0 Hz, 1H in $CH_2N$), 4.52 (s, 2H, $CH_2N$), 4.40 (d, $J$=15.0 Hz, 1H in $CH_2N$), 3.06 (q, $J$=7.5 Hz, 1H, CH), 1.77 (s, 3H, $CH_3$), 1.29 (s, 3H, $CH_3$), 1.13 (d, $J$=7.5 Hz, 3H, $CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$: 169.2, 168.8, 140.1, 137.1, 128.8, 128.34, 128.32, 127.4, 127.3, 126.5, 67.9, 55.6, 54.9, 45.0, 22.5, 16.3, 10.2. IR (KBr) $\nu$ ($cm^{-1}$): 1746 (C=O), 1652 (C=N). HRMS (ESI) calcd for $C_{21}H_{25}N_2O$ $[M+H]^+$ $m/z$: 321.1961, found 321.1967.

*4.2.7. rel-(3R,4R)-1-Diphenylmethyl-4-[(E)-1-(diphenylmethyl-imino)ethyl]-3,4-dimethylazetidin-2-one (cis-**3dd**).* Reaction was conducted in 1 mmol of diimine **1d**, 1.2 mmol of acid chloride **2d**, and 1.5 mmol of $Et_3N$.

Colorless crystals, 0.200 g, yield 42.3%, mp 164.0–166.0 °C $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.46–7.18 (m, 20H, ArH), 5.70 (s, 1H, CH), 5.67 (s, 1H, CH), 2.95 (q, $J$=7.5 Hz, 1H, CH), 1.84 (s, 3H, $CH_3$), 1.40 (s, 3H, $CH_3$), 1.05 (d, $J$=7.5 Hz, 3H, $CH_3$).$^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$: 168.9, 167.5, 144.0, 143.9, 141.9, 140.0, 128.8, 128.5, 128.4, 128.33, 128.27, 127.8, 127.4, 127.34, 127.28, 126.85, 126.79, 126.7, 68.4, 68.0, 62.9, 54.8, 22.8, 16.7, 10.6. IR (KBr) $\nu$ ($cm^{-1}$): 1743 (C=O), 1653 (C=N). HRMS (ESI) calcd for $C_{33}H_{33}N_2O$ $[M+H]^+$ $m/z$: 473.2587, found 473.2591.

*4.2.8. rel-(3R,4S)-1-(4-Methoxyphenyl)-4-[(E)-(4-methoxyphenylimino)(phenyl)methyl]-3-methyl-4-phenylazetidin-2-one(cis-**3ed**).* Reaction was conducted in 1 mmol of diimine **1e**, 1.2 mmol of acid chloride **2d**, and 1.5 mmol of $Et_3N$.

Yellow oil 0.239 g, yield 50.3%. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.50–6.59 (m, 18H, ArH), 3.88 (q, $J$=7.5 Hz, 1H, CH), 3.71 (s, 3H, $OCH_3$), 3.69 (s, 3H, $OCH_3$), 1.59 (d, $J$=7.4 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 168.5, 166.5, 156.3, 156.0, 142.5, 139.6, 135.5, 130.7, 128.5, 128.4, 127.9, 127.8, 127.4, 122.1, 121.5, 113.8, 113.5, 73.5, 60.4, 55.2, 12.3. IR (KBr) $\nu$ ($cm^{-1}$): 1747 (C=O), 1626 (C=N). HRMS (ESI) calcd for $C_{31}H_{29}N_2O_3$ $[M+H]^+$ $m/z$: 477.2173, found 477.2173.

*4.2.9. rel-(3S,4R)-3-Ethoxy-1-(4-methoxyphenyl)-4-[(E)-(4-methoxyphenylimino)methyl]-4-methylazetidin-2-one (cis-**3fa**).* - Reaction was conducted in 1 mmol of diimine **1f**, 1.2 mmol of acid chloride **2a**, and 1.5 mmol of $Et_3N$.

Yellow oil, 0.294 g, yield 80%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 8.14 (s, 1H, CH=N), 7.38–6.82 (m, 8H, ArH), 4.52 (s, 1H, OCH), 3.81 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.74–3.60 (m, 2H, $OCH_2$), 1.86 (s, 3H, $CH_3$), 1.20 (t, $J$=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 163.2, 162.1, 158.7, 156.6, 143.8, 130.1, 122.2, 119.1, 114.5, 114.4, 91.0, 67.4, 67.2, 55.5, 55.5, 18.2, 15.1. IR (KBr) $\nu$ ($cm^{-1}$): 1745 (C=O), 1629 (C=N). HRMS (ESI) calcd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$ $m/z$: 369.1809, found 369.1810.

*4.2.10. rel-(3R,4R)-1-(4-Methoxyphenyl)-4-[(E)-(4-methoxyphenylimino)methyl]-3,4-dimethylazetidin-2-one (cis-**3fd**).* Reaction was conducted in 1 mmol of diimine **1f**, 1.2 mmol of acid chloride **2d**, and 1.5 mmol of $Et_3N$.

Yellow oil, 0.260 g, yield 76.9%. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.99 (s, 1H, CH=N), 7.30–6.72 (m, 8H, ArH), 3.70 (s, 3H, $OCH_3$), 3.66 (s, 3H, $OCH_3$), 3.21 (q, $J$=7.6 Hz, 1H, CH), 1.76 (s, 3H, $CH_3$), 1.21 (d, $J$=7.6 Hz, 3H, $CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$: 167.0, 162.4, 158.5, 155.9, 143.5, 130.6, 121.9, 118.3, 114.3, 114.2, 63.7, 56.6, 55.3, 55.2, 19.9, 9.9. IR (KBr) $\nu$ ($cm^{-1}$): 1742 (C=O), 1644 (C=N). HRMS (ESI) calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ $m/z$: 339.1703, found 339.1709.

*4.2.11. rel-(3S,4R)-1-Diphenylmethyl-4-[(E)-(diphenylmethyl-imino)methyl]-3-ethoxy-4-methylazetidin-2-one (cis-**3ga**).* Reaction was conducted in 1 mmol of diimine **1g**, 2.5 mmol of acid chloride **2a**, and 3 mmol of $Et_3N$ in dichloromethane at room temperature.

Colorless crystals, 0.400 g, yield, 82.0%, mp 122.0–123.5 °C $^1$H NMR (300MHz, $CDCl_3$) $\delta$: 7.65 (s, 1H, CH=N), 7.29–7.12 (m, 20H, ArH), 5.52 (s, 1H, ArCH), 5.22 (s, 1H, ArCH), 4.36 (s, 1H, CHO), 3.48 (dq, $J$=9.0, 7.0 Hz, 1H in $OCH_2$), 3.26 (dq, $J$=9.0, 7.0 Hz, 1H in $OCH_2$), 1.58 (s, 3H, $CH_3$), 0.88 (t, $J$=7.0 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 165.7, 163.5, 143.0, 142.9, 139.0, 138.5, 128.4, 128.3, 127.4, 127.0, 89.9, 77.5, 67.0, 61.2, 61.2, 19.5, 14.6. IR (KBr) $\nu$ ($cm^{-1}$): 1757 (C=O), 1653 (C=N). HRMS (ESI) calcd for $C_{33}H_{33}N_2O_2$ $[M+H]^+$ $m/z$: 489.2537, found 489.2535.

*4.2.12. rel-(3S,4S)-1-Diphenylmethyl-4-[(E)-(diphenylmethyl-imino)methyl]-2-methyl-3-phthalimidoazetidin-2-one (cis-**3gb**).* Reaction was conducted in 1 mmol of diimine **1g**, 2.5 mmol of acid chloride **2b**, and 3 mmol of $Et_3N$.

Colorless crystals, 0.492 g, yield 83.5%, mp 202.0–203.0 °C $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.84 (s, 1H, CH=N), 7.59–7.07 (m, 24H, ArH), 5.79 (s, 1H, NCH), 5.18 (s, 1H, CHAr), 5.01 (s, 1H, CHAr), 1.71 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 166.6, 162.8, 143.0, 142.7, 139.0, 138.6, 134.0, 131.2, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8, 127.6, 126.9, 126.8, 126.5, 123.4, 77.5, 68.3, 63.0, 61.9, 21.7. IR (KBr) $\nu$ ($cm^{-1}$): 1766, 1722 (C=O), 1661 (C=N). HRMS (ESI) calcd for $C_{39}H_{32}N_3O_3$ $[M+H]^+$ $m/z$: 590.2434, found 590.2439.

*4.2.13. rel-(3S,4R)-1-Diphenylmethyl-4-[(E)-(diphenylmethyl-imino)methyl]-3-chloro-4-methylazetidin-2-one (cis-**3gc**).* Reaction was conducted in 1 mmol of diimine **1g**, 2.5 mmol of acid chloride **2c**, and 3 mmol of $Et_3N$.

Colorless crystals, 0.240 g, yield 50.1%, mp 115.0–116.5 °C $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.71 (s, 1H, CH=N), 7.27–7.20 (m, 20H, ArH), 5.48 (s, 1H, CHAr), 5.37 (s, 1H, CHAr), 4.67 (s, 1H, CHCl), 1.59 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 162.3, 162.0, 142.8, 142.8, 138.8, 138.6, 128.7, 128.55, 128.52, 128.37, 128.30, 128.0, 127.8, 127.7, 127.6, 127.3, 127.2, 77.4, 65.7, 64.4, 62.4, 20.2. IR (KBr) $\nu$ ($cm^{-1}$): 1768 (C=O), 1653 (C=N). HRMS (ESI) calcd for $C_{31}H_{28}ClN_2O$ $[M+H]^+$ $m/z$: 479.1885, found 479.1883.

*4.2.14. rel-(3S,4S)-1-Diphenylmethyl-4-[(E)-(diphenylmethyl-imino)methyl]-3,4-dimethylazetidin-2-one (cis-**3gd**).* Reaction was conducted in 1 mmol of diimine **1g**, 2.5 mmol of acid chloride **2d**, and 3.0 mmol of $Et_3N$.

Colorless crystals, 0.436 g, yield, 94.9%. Mp 113.0–115.0 °C $^1$H NMR (200MHz, $CDCl_3$) $\delta$: 7.62 (s, 1H, CHN), 7.26–7.20 (m, 20H, ArH), 5.55 (s, 1H, ArCH), 5.28 (s, 1H, ArCH), 3.10 (q, $J$=7.6 Hz, 1H, CH), 1.50

(s, 3H, $CH_3$), 1.04 (d, $J$=7.6 Hz, 3H, $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 169.4, 163.9, 143.2, 143.1, 140.0, 128.43, 128.39, 128.30, 128.27, 127.5, 127.4, 127.3, 127.3, 127.0, 77.6, 63.9, 61.7, 55.7, 21.4, 9.9. IR (KBr) $\nu$ ($cm^{-1}$): 1748 (C=O), 1653(C=N). HRMS calcd for $C_{32}H_{31}N_2O$ $[M+H]^+$ $m/z$: 459.2431, found 459.2440.

*4.2.15. rel-(2R,2′R,3S,3′S)-3,3′-Diethoxy-1,1′-bis(4-methoxyphen-yl)-2,2′-dimethyl-2,2′-biazetidine-4,4′-dione (RS-**4aa**).* Reaction was conducted in 1 mmol of diimine **1a**, 2.5 mmol of acid chloride **2a**, and 3 mmol of $Et_3N$.

Colorless crystals, 0.390 g, yield 83.3%, mp 223.0–225.0 °C $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 6.90–6.49 (m, 8H, ArH), 4.44 (s, 2H, OCH), 4.08–3.87 (m, 2H, $OCH_2$), 3.82–3.63 (m, 2H, $2OCH_2$), 3.72 (s, 6H, $2OCH_3$), 1.93 (s, 6H, $2CH_3$), 1.29 (t, $J$=6.9 Hz, 6H, $2CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 166.7, 157.3, 128.7, 123.8, 113.9, 90.3, 73.0, 68.1, 55.2, 23.1, 15.4. IR (KBr) $\nu$ ($cm^{-1}$): 1743 (C=O), 1635 (C=N). HRMS (ESI) calcd for $C_{26}H_{33}N_2O_6$ $[M+H]^+$ $m/z$: 469.2333, found 469.2333.

*4.2.16. rel-(2R,2′R,3S,3′S)-3,3′-Diethoxy-1,1′-bis(4-methoxyphenyl)-2-methyl-2,2′-biazetidine-4,4′-dione(RS-**4fa**).* Reaction was conducted in 1 mmol of diimine **1f**, 5 mmol of acid chloride **2a**, and 6 mmol of $Et_3N$.

Colorless crystals, yield 59%, mp 215.0–216.5 °C $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 6.97 (d, $J$=8.6 Hz, 2H, ArH), 6.82 (d, $J$=8.5 Hz, 2H, ArH), 6.46–6.44 (m, 4H, ArH), 4.83 (d, $J$=5.5 Hz, 1H, CH), 4.74 (d, $J$=5.5 Hz, 1H, CHO), 4.44 (s, 1H, CHO), 4.02–3.90 (m, 2H, $OCH_2$), 3.79–3.71 (m, 2H, $OCH_2$), 3.68 (s, 3H, $OCH_3$), 3.67 (s, 3H, $OCH_3$), 1.87 (s, 3H, $CH_3$), 1.30 (t, $J$=6.9 Hz, 3H, $CH_3$), 1.29 (t, $J$=6.9 Hz, 3H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 167.1, 166.0, 157.3, 157.1, 130.0, 129.6, 122.2, 121.8, 114.2, 114.1, 90.1, 83.5, 69.6, 68.6, 68.2, 63.9, 55.6, 20.9, 15.7. IR (KBr) $\nu$ ($cm^{-1}$): 1746 (C=O). HRMS (ESI) calcd for $C_{25}H_{31}N_2O_6$ $[M+H]^+$ $m/z$: 455.2177, found 455.2182.

*4.2.17. Mixture of rel-(2R,2′S,3S,3′S/2R,2′S,3S,3′R/2R,2′R,3S,3′R)-3,3′-diethoxy-1,1′-bis(4-methoxyphenyl)-2-methyl-2,2′-biazetidine-4,4′-dione(SS-**4fa**/SR-**4fa**/RR-**4fa**).* Reaction was conducted in 1 mmol of diimine **1e**, 5 mmol of acid chloride **2a**, and 6 mmol of $Et_3N$.

Colorless crystals, yield 35% (mixture: *SS*-**4fa**, 15%; *SR*-**4fa**: 11%; *RR*-**4fa**: 9%), mp 195–213 °C. *SS*-**4fa**: 7.26–6.55 (m, 8H, ArH), 4.57 (d, $J$=1.6 Hz, 1H, CHO), 4.52 (d, $J$=1.6 Hz, 1H, CH), 4.35 (s, 1H, CH), 4.02–3.50 (m, 4H, $2OCH_2$), 3.79 (s, 3H, OMe), 3.77 (s, 3H, OMe), 1.66 (s, 3H, Me), 1.34 (t, $J$=7.1 Hz, 1H, $CH_3$), 1.22 (t, $J$=7.1 Hz, 3H, $CH_3$). *SR*-**4fa**: 7.26–6.55 (m, 8H, ArH), 4.83 (d, $J$=5.4 Hz, 1H, CHO), 4.78 (d, $J$=5.4 Hz, 1H, CH), 4.32 (s, 1H, CH), 4.02–3.50 (m, 4H, $2OCH_2$), 3.74 (s, 3H, OMe), 3.76 (s, 3H, OMe), 1.75 (s, 3H, Me), 1.32 (t, $J$=7.0 Hz, 3H, $CH_3$), 1.30 (t, $J$=7.0 Hz, 3H, $CH_3$). *RR*-**4fa**: 7.26–6.55 (m, 8H, ArH), 4.85 (d, $J$=1.7 Hz, 1H, CHO), 4.55 (d, $J$=1.7 Hz, 1H, CH), 4.38 (s, 1H, CH), 4.02–3.50 (m, 4H, $2OCH_2$), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 1.65 (s, 3H, Me), 1.26 (t, $J$=7.0 Hz, 3H, $CH_3$), 1.17 (t, $J$=7.0 Hz, 3H, $CH_3$). IR (KBr) $\nu$ ($cm^{-1}$): 1745 (C=O). HRMS (ESI) calcd for $C_{25}H_{31}N_2O_6$ $[M+H]^+$ $m/z$: 455.2177, found 455.2180.

*4.2.18. rel-(2R,2′R,3S,3′S)-1,1′-Di(diphenylmethyl)-3,3′-diethoxy-2-methyl-2,2′-biazetidine-4,4′-dione (RS-**4ga**).* Reaction was conducted in 1 mmol of diimine **1g**, 5 mmol of acid chloride **2a**, and 6 mmol of $Et_3N$.

Colorless crystals, yield 65% mp 150.5–152.0 °C $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 7.36–6.79 (m, 20H, ArH), 5.05 (s, 1H, ArCH), 4.92 (s, 1H, ArCH), 4.54 (d, $J$=5.6 Hz, 1H, CH), 4.34 (d, $J$=5.4 Hz, 1H, CHO), 4.18 (s, 1H, CHO), 3.90–3.82 (m, 2H, $OCH_2$), 3.65 (dq, $J$=9.0, 7.1 Hz, 2H, $OCH_2$), 1.52 (s, 3H, $CH_3$), 1.23 (t, $J$=7.0 Hz, 3H, $CH_3$), 1.20 (t, $J$=7.0 Hz, 3H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 169.2, 167.4, 140.7, 139.6, 139.0, 138.8, 129.0, 128.8, 128.6, 128.4, 128.2, 127.78, 127.72, 127.68, 127.63, 89.3, 82.4, 67.9, 66.9, 65.5, 64.8, 62.5, 19.4, 15.4. IR (KBr) $\nu$ ($cm^{-1}$): 1752 (C=O), HRMS (ESI) calcd for $C_{37}H_{39}N_2O_4$ $[M+H]^+$ $m/z$: 575.2904, found 575.2905.

*4.2.19. rel-(2R,2′S,3S,3′R)-1,1′-Di(diphenylmethyl)-3,3′-diethoxy-2-methyl-2,2′-biazetidine-4,4′-dione (SR-**4ga**).* Reaction was conducted in 1 mmol of diimine **1g**, 5 mmol of acid chloride **2a**, and 6 mmol of $Et_3N$.

Colorless crystals, yield 14%, mp 125.0–126.0 °C $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 7.49–7.23 (m, 20H, ArH), 5.88 (s, 1H, ArCH), 5.84 (s, 1H, ArCH), 4.43 (d, $J$=5.4 Hz, 1H, CH), 4.20 (d, $J$=5.4 Hz, 1H, CHO), 4.12 (dq, $J$=8.9, 7.1 Hz, 1H in $OCH_2$), 4.10 (s, 1H, CHO), 3.87–3.76 (m, 2H, $OCH_2$), 3.31 (dq, $J$=8.9, 7.1 Hz, 1H in $OCH_2$), 1.55 (s, 3H, $CH_3$), 1.34 (t, $J$=7.0 Hz, 3H, $CH_3$), 1.25 (t, $J$=7.0 Hz, 3H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 167.7, 166.6, 140.2, 140.0, 139.8, 139.6, 128.9, 128.64, 128.60, 128.5, 128.4, 128.2, 127.9, 127.5, 127.3, 127.1, 89.0, 82.0, 67.1, 66.8, 65.8, 63.5, 61.9, 61.7, 18.9, 15.4, 15.3. IR (KBr) $\nu$ ($cm^{-1}$): 1752 (C=O). HRMS (ESI) calcd for $C_{37}H_{39}N_2O_4$ $[M+H]^+$ $m/z$: 575.2904, found 575.2895.

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## Supplementary data

Procedure for the preparation of diimines **1**, copies of $^1H$ and $^{13}C$ NMR and NOESY spectra of diimines **1**, mono-β-lactams **3** and bis-β-lactams **4**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.10.044. These data include MOL files and InChIKeys of the most important compounds described in this article.

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