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The use of *N*-sulfenylimines in the β-lactam synthon method: Staudinger reaction, oxidation of the cycloadducts and ring opening of β-lactams

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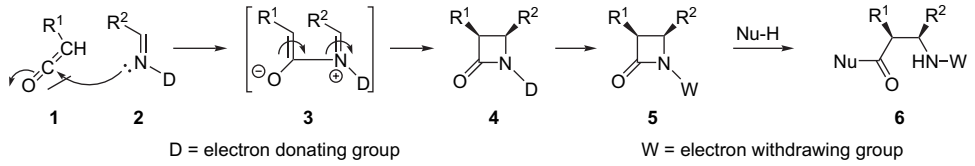
Abstract—Selected *N*-sulfenylimines act as good nucleophilic partners in the Staudinger reaction with methoxy- and benzyloxy-ketenes. The choice of diisopropylethylamine as a non-nucleophilic Lewis base for the generation of ketenes from acid chlorides is a determining factor for the success of the reaction. *N*-Sulfenyl-β-lactams are obtained in good to excellent yields and with moderate cis/trans diastereoselectivity. Then, they are quantitatively and selectively transformed to *N*-sulfinyl- or *N*-sulfonyl-β-lactams, by adjusting the oxidation state of the sulfur atom. The oxidation process induces an inversion of polarity of the nitrogen atom's substituent and allows a subsequent smooth ring opening by reaction of *N*-thiolated-β-lactams with various nucleophiles. The overall sequence provides straightforward and efficient route to highly functionalized-β-amino acid derivatives.

1. Introduction

Azetidin-2-one nucleus, a four membered cyclic amide, has been recognized as the central motif of the so-called β-lactam antibiotics, the most widely employed family of antimicrobial agent to date.[1] The increasing resistance of bacteria to the commonly used β-lactam antibiotics[2] and the recent discoveries of some azetidin-2-ones, which display a broad range of non-antibiotic enzyme-inhibitory activity, justify a renewed interest in the building of these compounds.[3] Some β-lactams have also shown anti-cancer activity.[4] Apart from their significance as bioactive agents, the β-lactams' skeleton has been also recognized as providing powerful synthetic building blocks by exploiting its strain energy, especially in the context of the synthesis of α- and β-amino acids.[5] This general procedure is known as the 'β-lactam synthon method' (Scheme 1).[6]

It is well-known that the β-lactams act as formal acylating agents towards those nucleophiles that effect cleavage of the N_1–C_2(O) bond.[7] This ring opening reaction has been shown to be applicable to β-lactam systems bearing an electron-withdrawing substituent W on the nitrogen atom of the ring **5**.[8] Staudinger's ketene–imine reaction is one of the most reliable methods available for the ring construction of β-lactams.[9] Although commonly described as a [2+2] cycloaddition, it is generally accepted that the reaction is in fact stepwise (Scheme 1). The first step of the reaction involves a nucleophilic attack of the nitrogen of imine **2** on the sp-hybridized carbon of the ketene **1** to form a zwitterionic



Scheme 1. The classical Staudinger reaction forming β-lactams followed by nucleophilic ring opening to produce stereoselectively substituted β-amino acid derivatives.

Keywords: *N*-Sulfenylimines; Staudinger reaction; *N*-Thiolated-β-lactams; β-Amino acid derivatives.
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intermediate **3**, which undergoes an electrocyclic conrotatory ring closure, or an intramolecular nucleophilic addition, to give the β-lactam ring **4**.[10]

In this process, an electron-donating substituent D on the nitrogen atom of the imine component **2** should be appropriate.[11] Consequently, to be smooth and efficient, the overall sequence of ring formation–ring opening of β-lactams requires an inversion of polarity of the nitrogen atom's substituent from electron-rich D in imine **2** to electron poor W in β-lactam **5**. As part of our program directed towards the application of the Staudinger reaction to the synthesis of peptidomimetic substitutes,[15] we wish to report here the results obtained on the basis of this strategy.[16] We chose thiolated groups as variable-polarity substituents D and W on the nitrogen centre: the electron-rich (D) sulfenyl group can be cleanly transformed to electron deficient (W) sulfinyl or sulfonyl groups by simple and selective oxidation.[17] In *N*-sulfenylimine **2** (D=SR), the sulfur group acts to enhance the nucleophilic character of the imine component of the Staudinger reaction, while in *N*-sulfinyl- and *N*-sulfonyl-β-lactam **5** the sulfur group (W=SOR or SO_2R) acts to enhance the electrophilic character of the β-lactam carbonyl through electron withdrawal. Furthermore, the sulfenyl group on the β-lactam nitrogen in **4** may be considered as a protecting group easily removable by thiophilic reagents that attack the sulfur centre to cause N–S bond cleavage and provide rapid access to *N*-unsubstituted β-lactams.[18] It is relevant to note that *N*-thiolated-β-lactams represent a broad and growing family of bioactive molecules. Recently, the finding that *N*-methylthio-β-lactams have strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* and, probably, a unique mode of action, opens the door to new investigations.[19]

In this report, we show that *N*-sulfenylimines can now be added to the list of imine partners of the Staudinger reaction.[20] In addition, we describe the subsequent oxidation of the resulting *N*-sulfenyl-β-lactams into *N*-sulfinyl- and *N*-sulfonyl-β-lactams followed by ring opening in which the cleavage of the N_1–C_2(O) bond is used for the transformation of the β-lactams. Since a variety of substituents can be stereoselectively introduced to the C-3 and C-4 positions of β-lactams, this overall procedure provides an efficient and convenient route to highly functionalized-β-amino acids, which are useful intermediates for the synthesis of enzyme inhibitors, modified peptides, chiral macromolecules and ligands or reagents for asymmetric synthesis.[21]

2. Results and discussion

2.1. Synthesis of *N*-benzenesulfenylimines

N-Sulfenylimines **8** are prepared in onestep from diphenyldisulfides, silver nitrate and aldehydes **7** following a slightly modified method described by Davis (Scheme 2).[22]

The mechanism of formation of *N*-sulfenylimines most likely involves in situ formation of the sulfenamide $PhSNH_2$. Silver ion complexes with one of the lone pairs of electrons of sulfur atom in the disulfide bond followed by nucleophilic attack by ammonia on the activated disulfide bond. The resulting sulfenamide $PhSNH_2$ condenses with aldehydes **7** giving the *N*-sulfenylimines **8** (Table 1). This synthetic procedure works well with 1 equiv of a variety of aliphatic or aromatic aldehydes, but an excess of the more reactive electron releasing substituted benzaldehydes is needed to compete with the formation of by-products.[23]

Table 1. Synthesis of *N*-benzenesulfenylimines

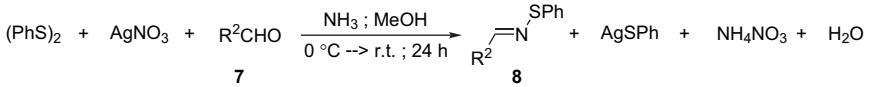
Entry	Aldehyde **7** R^2	Sulfenylimine **8**	Yield (%)	*E*:*Z*	^{15}N NMR $^2J_{NH}$ (Hz)
1	*i*-Pr	**8a**	59	80:20	5.80, 17.50
2	*t*-Bu	**8b**	62	*E*	3.50
3	C_6H_5	**8c**	81	*E*	3.30
4	*p*-$Me_2NC_6H_4$	**8d**	19	*E*	—
5	*p*-$MeOC_6H_4$	**8e**	63	*E*	3.49
6	*p*-$MeSC_6H_4$	**8f**	54	*E*	2.92
7	*p*-FC_6H_4	**8g**	79	*E*	—
8	*o*-FC_6H_4	**8h**	76	*E*	—
9	*m*-FC_6H_4	**8i**	61	*E*	—
10	*p*-$CF_3C_6H_4$	**8j**	65	*E*	—
11	*o*-$CF_3C_6H_4$	**8k**	74	*E*	4.08
12	*p*-$MeCO_2C_6H_4$	**8l**	75	*E*	2.91
13	*p*-CNC_6H_4	**8m**	55	*E*	2.91
14	*p*-$NO_2C_6H_4$	**8n**	30	*E*	—
15	*p*-Pyridyl	**8o**	13	*E*	3.49
16	*o*-Pyridyl	**8p**	11	*E*	3.49
17	*m*-Pyridyl	**8q**	19	*E*	3.50
18	3-Quinolinyl	**8r**	15	*E*	—
19	2-Furfuryl	**8s**	51	61:39	3.50, 16.30
20	2-Pyrrolyl	**8t**	47	*E*	4.07
21	2-Thiophenyl	**8u**	34	90:10	3.49, 15.73

N-Sulfenylimines can be prepared by this procedure in bulk quantities and purified by column chromatography on silica gel. The purification step is often responsible for lowering the yield of product, particularly, in the case of the most electrophilic imines. Most of the prepared *N*-sulfenylimines have an *E* configuration. *N*-Sulfenylimines derived from 2-furaldehyde **8s**, 2-thiophenecarboxaldehyde **8u** and isobutyraldehyde **8a** were isolated as mixtures of *E* and *Z* isomers; the isomeric ratios were measured by ^{1}H NMR spectroscopy and the configurations attributed by ^{15}N NMR.

The coupling constant $^2J_{NH}$ between the imine nitrogen atom and the α hydrogen is characteristic of the imine configuration.[25–30] A value of 2–6 Hz indicates an *E* imine while a value of 15–18 Hz indicates a *Z* imine (see Table 1).

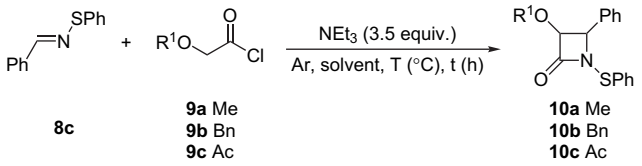
2.2. *N*-Sulfenylimines as nucleophilic partners of the Staudinger reaction

Preliminary experiments were performed with a classical model system consisting of *N*-sulfenylimine of benzaldehyde **8c** (1 equiv) and substituted ketene formed in situ



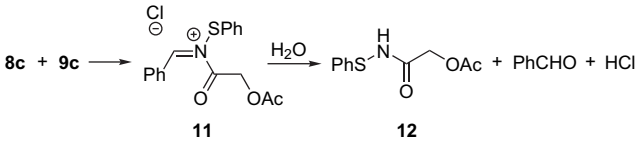
Scheme 2. Synthesis of *N*-sulfenylimines.

from substituted acetyl chloride **9** (3 equiv) and triethylamine (3.5 equiv) as the Lewis base (Scheme 3).



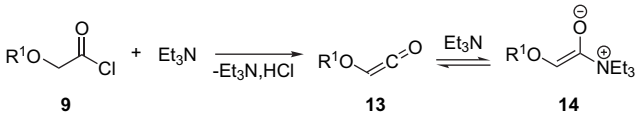
Scheme 3. Reactions between α-alkoxy acetyl chlorides, triethylamine and *N*-sulfenylimine of benzaldehyde: preliminary experiments.

The results first obtained were disappointing: use of methylene chloride at several temperatures (from 0 to 40 °C) or ethyl acetate until 80 °C resulted in the formation of mixtures in which the *N*-sulfenylimine **8c** was found as the major component along with smaller amounts of the desired β-lactams **10** (Scheme 3). Thus, when the reaction between *N*-sulfenylimine **8c** and methoxyacetyl chloride **9a** was carried out in methylene chloride, at 40 °C for 12 h, only 72% of β-lactam **10a** was formed along with 28% of recovered **8a**. However, with benzyloxyacetyl chloride **9b** no cycloadduct was detected and imine was recovered unchanged while with acetoxy-acetyl chloride **9c** only 2% of cycloadduct **10c** was obtained along with the unchanged *N*-sulfenylimine. When this later reaction was conducted without triethylamine, the *N*-acetoxy-acetyl-*N*-phenylsulfenylamine **12** was quantitatively formed. Clearly, the formation of this compound is due to the nucleophilic attack of the *N*-sulfenylimine nitrogen atom on the substituted acetyl chloride carbonyl followed by the hydrolysis of the resulting *N*-acyl-iminium salt **11** (Scheme 4).



Scheme 4. Reaction between acetoxy-acetyl chloride and *N*-sulfenylimine of benzaldehyde without triethylamine.

Naturally, we were intrigued by the remarkable difference in reactivity of *N*-sulfenylimine towards acid chlorides with or without triethylamine. It was tempting to suggest that the origin of this difference may lie in the nucleophilic competition between *N*-sulfenylimine and triethylamine, which are both able to attack the ketene carbonyl function of **13**. Thus, in the presence of an excess (3.5 equiv) of triethylamine, the likely reversible formation of the ketene-triethylamine adduct **14**[31] may prevent, or slow down, the condensation of the *N*-sulfenylimine **8** with substituted ketene **13** (Scheme 5). We decided to investigate the influence of nucleophilicity of other Lewis bases.



Scheme 5. Generation and reaction of α-alkoxy ketene with an excess of triethylamine.

A considerable improvement was observed for reactions carried out with the less nucleophilic diisopropylethylamine (Hünig's base) in boiling methylene chloride: the desired β-lactam **10a** could be formed quantitatively in 1.5 h (entry 5) (Table 2). Conversely, the more nucleophilic 1,4-diazabicyclo[2,2,2]octane (DABCO, entry 4) maximizes the side reaction described above (Scheme 5) and the complete recovery of the starting sulfenylimine **8c** was observed. With triethylamine as a Lewis base, the β-lactam product **10a** was produced relatively more slowly (entries 1–3) than with Hünig's base. We next carefully examined the other reaction conditions and found that the β-lactam products were produced in best yields by using 3 equiv of acid chloride and 3.5 equiv of Hünig's base in boiling methylene chloride under argon atmosphere.

Table 2. Reactions between *N*-sulfenylimine **8c** and methoxy-acetyl chloride **9a** in boiling CH_2Cl_2: role of the Lewis base

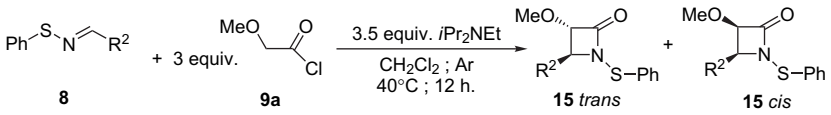
Entry	*t* (h)	Lewis base	Product ratio (%)	
			Imine **8c**	β-Lactam **10a**
1	1.5	NEt_3	87	13
2	12	NEt_3	28	72
3	18	NEt_3	9	91
4	18	DABCO	100	0
5	1.5	*i*-Pr_2NEt	0	100

Once the desired reactivity was established, we started studies to perform reactions between a series of *N*-sulfenylimines and alkoxy-ketenes formed in situ by adding diisopropylethylamine to alkoxyacetyl chlorides. α-Alkoxy-ketenes were chosen in view of the potential of 4-alkyl(aryl)-3-hydroxy-β-lactams as precursors of bioactive β-amino-α-hydroxyacids (isoserines). With methoxyketene (Table 3) and benzyloxyketene (Table 4), the corresponding β-lactam adducts were produced in most cases in good to excellent yields.

The reactions were monitored by thin layer chromatography (TLC) until complete conversion of the substrates, for 12 h with methoxyketene and for 18 h with the less reactive benzyloxyketene. As described in Tables 3 and 4 most of the imines reacted well with both methoxy- and benzyloxy-ketenes to produce β-lactam derivatives in good to excellent yields. However, the reactions of alkoxy-ketenes with *N*-sulfenylimines **8o**, **8q** and **8r**, derived from six-membered ring nitrogen heterocyclic aldehydes, failed to produce β-lactam derivatives.[32] Considering the stereochemistry, all the reactions, conducted under these conditions, were slightly stereoselective producing a mixture of cis and trans diastereoisomers. The configurations of the β-lactam products can be easily determined by the coupling constants (^3J) between the protons on C(3) and C(4) of the β-lactam ring. For *cis* β-lactam products $^3J_{cis}$ is 4.7–5.8 Hz and for trans products $^3J_{trans}$ is about 2 Hz.

With the methoxyketene, the cis diastereoisomers were generally the major products and this diastereoselectivity increased with the electron-withdrawing power of the imine substituent R^2. However, the trans diastereoisomer was obtained preferentially with imines derived from more electron-rich aldehydes (R^2=*i*-Pr, *t*-Bu, *p*-$Me_2NC_6H_4$, 2-furfuryl and 2-thiophenyl).

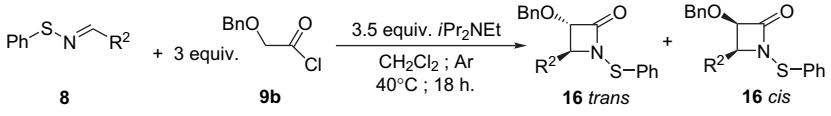
Table 3. Reactions between *N*-sulfenylimines and methoxyketene



8 **9a** **15** *trans* **15** *cis*

Entry	Imine	R^2	Yield (%)	cis/trans	β-Lactams
1	**8a**	*i*-Pr	77	34:66	**15a**
2	**8b**	*t*-Bu	79	38:62	**15b**
3	**8c**	C_6H_5	96	55:45	**15c**
4	**8d**	*p*-$Me_2NC_6H_4$	11	43:57	**15d**
5	**8e**	*p*-$MeOC_6H_4$	93	55:45	**15e**
6	**8f**	*p*-$MeSC_6H_4$	80	60:40	**15f**
7	**8g**	*p*-FC_6H_4	75	60:40	**15g**
8	**8h**	*o*-FC_6H_4	81	60:40	**15h**
9	**8i**	*m*-FC_6H_4	76	56:44	**15i**
10	**8j**	*p*-$CF_3C_6H_4$	84	63:37	**15j**
11	**8l**	*p*-$MeCO_2C_6H_4$	92	61:39	**15l**
12	**8m**	*p*-CNC_6H_4	81	70:30	**15m**
13	**8n**	*p*-$NO_2C_6H_4$	76	66:34	**15n**
14	**8p**	*o*-Pyridyl	23	43:57	**15p**
15	**8s**	2-Furfuryl	82	33:67	**15s**
16	**8u**	2-Thiophenyl	72	45:55	**15u**

Table 4. Reactions between *N*-sulfenylimines and benzyloxyketene



8 **9b** **16** *trans* **16** *cis*

Entry	Imine	R^2	Yield (%)	cis/trans	β-Lactam
1	**8a**	*i*-Pr	76	25:75	**16a**
2	**8b**	*t*-Bu	82	32:68	**16b**
3	**8c**	C_6H_5	86	55:45	**16c**
4	**8e**	*p*-$MeOC_6H_4$	91	60:40	**16e**
5	**8f**	*p*-$MeSC_6H_4$	69	54:46	**16f**
6	**8g**	*p*-FC_6H_4	66	52:48	**16g**
7	**8h**	*o*-FC_6H_4	77	40:60	**16h**
8	**8i**	*m*-FC_6H_4	74	55:45	**16i**
9	**8j**	*p*-$CF_3C_6H_4$	82	66:34	**16j**
10	**8l**	*p*-$MeCO_2C_6H_4$	78	57:43	**16l**
11	**8m**	*p*-CNC_6H_4	80	70:30	**16m**
12	**8n**	*p*-$NO_2C_6H_4$	89	76:24	**16n**
13	**8s**	2-Furfuryl	97	30:70	**16s**
14	**8u**	2-Thiophenyl	77	67:33	**16u**

Quite similar results were obtained with benzyloxyketene. A possible base-catalyzed cis/trans isomerization was experimentally ruled out, thereby confirming that kinetically controlled products were obtained: after 12 h under the usual treatment conditions (room temperature, excess sodium hydrogen carbonate) and even in the presence of stronger base (sodium hydroxide), the pure *cis* β-lactam was completely recovered and no traces of trans stereoisomer were observed.

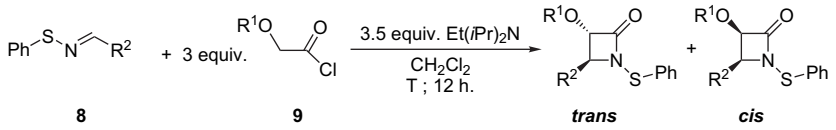
To improve the diastereoselectivity, the effect of the temperature on the product distribution was analyzed (Table 5). Experiments conducted at lower temperatures for 12 h afforded slower conversion rates of substrates (entries 3, 6, 9, 17, 18, 21 and 23) but the observed cis/trans ratios were markedly higher (ca. 85:15). These results are in good agreement with the model recently suggested by Xu[33] to explain the relative stereoselectivity of the β-lactam formation in the Staudinger reaction (Scheme 6): electron-donating (alkoxy) ketene substituents R^1 accelerate the direct ring closure, leading to a preference for *cis* β-lactam formation, while electron-donating (alkylthio) imine substituents R^3 slow the direct ring closure, leading to a preference for *trans* β-lactam formation. According to these predictions, we will show, in a following paper, that a less electron-donating (acetoxy) ketene substituent can reverse the diastereoselectivity of the reaction, leading to a much higher ratio of *trans* β-lactam products.

2.3. Transformation of the *N*-sulfenyl-β-lactams

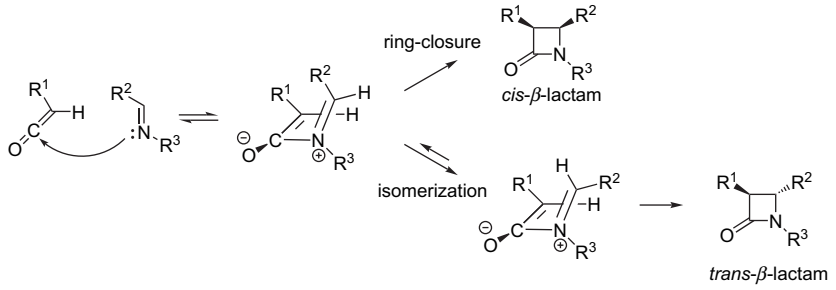
2.3.1. Nitrogen deprotection. A mild and very efficient cleavage of the N–S bond provides access to unprotected β-lactams. By reacting the representative *N*-sulfenyl-azetidinone *cis***16c** with 2-pyridinethiol and triethylamine at room temperature, a quantitative yield of the pure *cis* β-lactam derivative **17** was obtained (Scheme 7).[18]

2.3.2. Sulfur oxidation. *N*-Sulfenyl-*β*-lactams were reacted with exactly 1 equiv of *meta*chloroperbenzoic acid (*m*CpBA), in methylene chloride solution, at room temperature, to

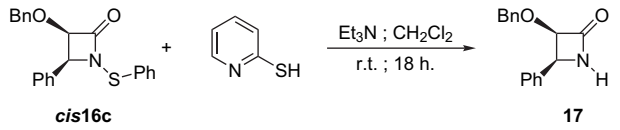
Table 5. Temperature effect on the diastereoselectivity of the reaction between *N*-sulfenylimines and alkoxy-ketenes



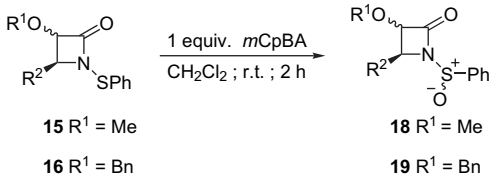
Entry	Imine	R^2	Alkoxyacetyl chloride	R^1	*T* (°C)	Conversion (%)	cis/trans
1	**8c**	Ph	**9a**	Me	40	100	55:45
2	**8c**	Ph	**9a**	Me	0	100	58:42
3	**8c**	Ph	**9a**	Me	−40	68	84:16
4	**8f**	*p*-$MeSC_6H_4$	**9a**	Me	40	100	60:40
5	**8f**	*p*-$MeSC_6H_4$	**9a**	Me	0	100	60:40
6	**8f**	*p*-$MeSC_6H_4$	**9a**	Me	−40	50	81:19
7	**8m**	*p*-CNC_6H_4	**9a**	Me	40	100	70:30
8	**8m**	*p*-CNC_6H_4	**9a**	Me	0	80	71:29
9	**8m**	*p*-CNC_6H_4	**9a**	Me	−40	17	85:15
10	**8s**	2-Furfuryl	**9a**	Me	40	100	33:67
11	**8s**	2-Furfuryl	**9a**	Me	0	100	33:67
12	**8s**	2-Furfuryl	**9a**	Me	−40	100	62:38
13	**8u**	2-Thiophenyl	**9a**	Me	40	100	45:55
14	**8u**	2-Thiophenyl	**9a**	Me	0	100	69:31
15	**8u**	2-Thiophenyl	**9a**	Me	−40	100	85:15
16	**8c**	Ph	**9b**	Bn	40	100	55:45
17	**8c**	Ph	**9b**	Bn	0	64	57:43
18	**8c**	Ph	**9b**	Bn	−40	73	77:23
19	**8f**	*p*-$MeSC_6H_4$	**9b**	Bn	40	100	54:46
20	**8f**	*p*-$MeSC_6H_4$	**9b**	Bn	0	100	67:33
21	**8f**	*p*-$MeSC_6H_4$	**9b**	Bn	−40	65	84:16
22	**8m**	*p*-CNC_6H_4	**9b**	Bn	40	100	70:30
23	**8m**	*p*-CNC_6H_4	**9b**	Bn	0	72	70:30



Scheme 6. Model for the relative stereoselectivity in the Staudinger reaction.



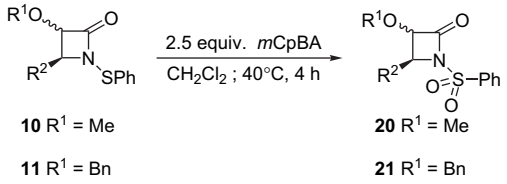
Scheme 7. Deprotection of the *N*-sulfenyl-β-lactam **16c**.



Scheme 8. Mono-oxidation of *N*-sulfenyl-β-lactams.

afford the corresponding *N*-sulfinyl-β-lactam **18** or **19** (Scheme 8). Monitoring the reaction mixtures by TLC, we observed, generally after 2 h, a quantitative and exclusive formation of the mono-oxidation products. The over-oxidation to *N*-sulfonyl-β-lactam was only detected in the presence of an excess of *m*CpBA. The two *N*-sulfinyl diastereoisomers were obtained generally in a 60:40 ratio, for *cis* and *trans* β-lactams. Very likely, the C-4 substituent (R^2) makes easier the sulfur oxidation on the less hindered side of the azetidinone nucleus whatever the C-3 substituent (OR^1) may be. The separation of the two *N*-sulfinyl diastereoisomers by flash chromatography on silica gel is generally difficult and thus, *N*-sulfinyl-β-lactams **18** and **19** are isolated as mixtures.

The di-oxidation of *N*-sulfenyl-β-lactams was conducted in boiling methylene chloride, for 4 h, by using 2.5 equiv of *m*CpBA. The corresponding *N*-sulfonyl-β-lactams **20** and **21** were quantitatively obtained (Scheme 9). However, flash chromatographic purification of the crude product afforded pure *N*-sulfonyl-β-lactams but with significant loss of material. As for *N*-sulfinyl-β-lactams **18** and **19**, it proved to be more convenient to use the crude oxidation products **20** and **21** directly in the subsequent nucleophilic β-lactams ring opening and to purify *in fine* the resulting products.



Scheme 9. Di-oxidation of *N*-sulfenyl-β-lactams.

2.4. Ring opening of *N*-sulfinyl and *N*-sulfonyl-β-lactams by nucleophilic attack

N-Sulfinyl β-lactams **18** and **19** can be cleaved at the N_1–$C_2(O)$ bond by nucleophilic reagents. With amines, monitoring the reaction mixture by TLC, we observed a total conversion, after 20 h at room temperature. The products **22–26** were obtained without isomerization: the diastereoisomeric ratio of products, due to SO chirality, is identical to that of starting materials (Table 6). In a similar way, a series of α-alkoxy β-amino acid derivatives **27–42** were prepared starting from *N*-sulfonyl-β-lactams **20** and **21**, by reactions with primary (**A–C**), secondary (**D**, **E**) amines and α-aminoester (**F**). In dichloromethane solution, *N*-sulfonyl-β-lactams reacted at room temperature with these various nucleophiles (Table 7). It is worth noting that under these conditions, *N*-sulfinyl-β-lactams logically react slowly than *N*-sulfonyl-β-lactams. Although the reactions have been shown to be complete and quantitative, the relative acyclic products were obtained in moderate chemical yields depending on the purification method. Flash chromatography afforded lower yields than the ones observed when products can be simply purified by crystallization in pentane. The products resulting from the attack of a non-symmetric secondary amine exist as mixtures of rotamers whose ratios were determined by ^{1}H NMR at room temperature. A 60 °C coalescence temperature was determined in C_6D_6 and DMSO-d_6 from the signals of the methyl groups for compounds **28** and **32**.

With ethyl glycinate (**F**), the results were similar to those obtained with primary or secondary amines: the reactions were carried out at room temperature and the products were isolated by flash chromatography on silica gel or by crystallization.

N-Sulfonyl-β-lactam ring opening was also efficient with primary, secondary and tertiary alcohols following a method described by Ojima for *N*-Boc-β-lactams.[34] The substrates, in alcoholic solution, reacted at room temperature in presence of 2 equiv of triethylamine and 0.5 equiv of *N*,*N*-dimethylaminopyridine (Table 8). Similarly, treatment of *N*-sulfonyl-β-lactam *cis***20c** with sodium methylthiolate produced the corresponding thioester **46** with essentially quantitative yield (Scheme 10).

3. Conclusion

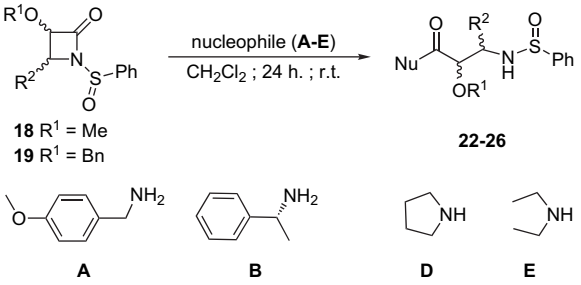
The obtained results indicate that *N*-sulfenyl-imines are new interesting partners in Staudinger cycloadditions with alkoxy-ketenes. The sulfenyl substituent is a controlling element in several aspects: (1) it enhances the nucleophilic character of the imine component thus increasing its reactivity; (2) it controls the diastereoselectivity by decreasing the direct ring closure rate versus isomerization rate of the imine moiety; (3) it behaves as an efficient protecting group that can be removed easily from the β-lactam ring; (4) it can be selectively oxidized to afford substituents of reversed polarity, which allow a smooth opening of the β-lactam ring by a variety of nucleophilic reagents. Thus, the overall sequence ketene–imine cycloaddition, oxidation and nucleophilic ring opening provides straightforward and efficient route to highly functionalized-β-amino acid derivatives.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Reactions were carried out under an atmosphere of argon. TLC was carried out on Macherey–Nagel Alugram Sil G/UV_{254}

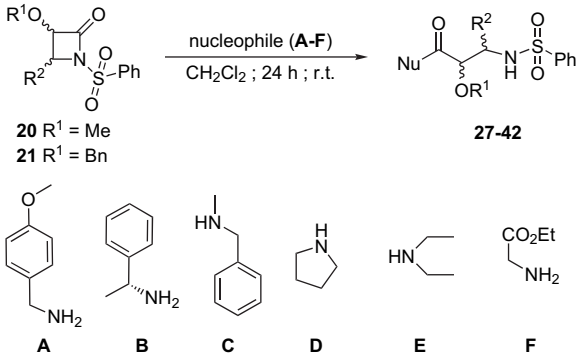
Table 6. Ring-opening of *N*-sulfinyl-β-lactams by nucleophilic attack of amines



Entry	*N*-Sulfinyl-β-lactam	R^1	R^2	Ratio[a]	Nucleophile	Yield (%)	Product
1	*trans***18c**	Me	Ph	68/32	**A**	28	**22**
2	*trans***18c**	Me	Ph	60/40	**D**	65	**23**
3	*trans***18m**	Me	*p*-CNC_6H_4	57/43	**B**	55	**24**
4	*cis***19e**	Bn	*p*-$MeOC_6H_4$	64/36	**A**	45	**25**
5	*trans***19m**	Bn	*p*-CNC_6H_4	67/33	**E**	45	**26**

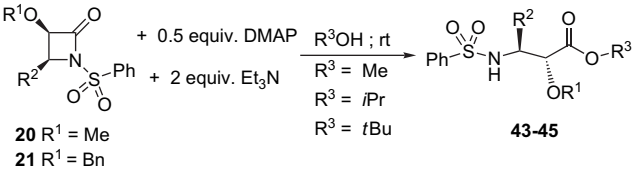
[a] Diastereoisomeric ratio of the starting *N*-sulfinyl-β-lactams.

Table 7. Ring-opening of *N*-sulfonyl-β-lactams by nucleophilic attack of amines

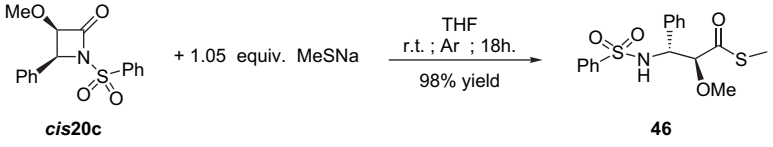


Entry	*N*-Sulfonyl-β-lactam	R^1	R^2	Nucleophile	Yield (%)	Product
1	*cis***20c**	Me	Ph	**B**	76	**27**
2	*cis***20c**	Me	Ph	**C**	47	**28**
3	*cis***20c**	Me	Ph	**D**	16	**29**
4	*cis***20c**	Me	Ph	**E**	54	**30**
5	*trans***20c**	Me	Ph	**A**	14	**31**
6	*trans***20c**	Me	Ph	**C**	34	**32**
7	*cis***20m**	Me	*p*-CNC_6H_4	**B**	26	**33**
8	*cis***20m**	Me	*p*-CNC_6H_4	**E**	44	**34**
9	*trans***20m**	Me	*p*-CNC_6H_4	**D**	12	**35**
10	*trans***21c**	Bn	Ph	**A**	39	**36**
11	*trans***21c**	Bn	Ph	**B**	32	**37**
12	*trans***21c**	Bn	Ph	**D**	57	**38**
13	*cis***21m**	Bn	*p*-CNC_6H_4	**A**	28	**39**
14	*trans***21m**	Bn	*p*-CNC_6H_4	**E**	27	**40**
15	*trans***21c**	Bn	Ph	**F**	32	**41**
16	*trans***21e**	Bn	*p*-$MeOC_6H_4$	**F**	21	**42**

Table 8. Ring-opening of *N*-sulfonyl-*β*-lactams by nucleophilic attack of alcohols



Entry	*N*-Sulfonyl-β-lactam	R^1	R^2	R^3OH	Yield (%)	Product
1	*cis***21c**	Bn	Ph	Methanol	89	**43**
2	*cis***20n**	Me	*p*-$NO_2C_6H_4$	Isopropanol	Quantit.	**44**
3	*cis***20n**	Me	*p*$NO_2C_6H_4$	*tert*-Butanol	Quantit.	**45**



Scheme 10. β-Lactam ring opening by nucleophilic attack of sodium methanethiolate.

analytical plates visualized by using UV light and by means of 5% ethanolic solution of molybdophosphoric acid. Flash chromatography was performed using Macherey–Nagel silica gel 60 (0.063–0.2 mm). NMR spectra (^1H, ^{13}C and ^{19}F) were registered on a Brücker AC 300 spectrometer using $CDCl_3$ as solvent for the samples; chemical shifts are relative to TMS as internal reference. ^{15}N NMR spectra were registered on a Brücker AC 400 spectrometer using $CDCl_3$ as solvent for the samples; chemical shifts are relative to nitromethane as internal reference. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants *J* are reported in hertz (Hz). Infrared (IR) spectra were obtained using an IR-FT Nicolet 20SXB spectrophotometer (KBr pellets) and resonances are reported in wave numbers (cm^{-1}). Melting points (mp) were determined on a capillary Büchi apparatus. Elemental analyses were performed at the University Department of Analysis on a Thermo Finnigan EA 112 (software: Thermo Finnigan Fager 300). Mass spectrometric experiments were performed using a SCIEX API III Plus triple

quadripole instrument equipped with a pneumatically assisted electrospray interface operated in positive ion mode. Samples were dissolved in 500 μL methanol and then diluted (1/1000) in a methanolic solution of ammonium acetate (3 mM). Results are reported as mass-to-charge ratio and abundance of the main fragment ions observed in the MS/MS spectra.

4.2. General procedure for the preparation of *N*-benzenesulfenylimines

In a three-necked round-bottom flask equipped with a $CaCl_2$ funnel, 2 equiv of silver nitrate was dissolved in methanol. After cooling at 0 °C, 1 equiv of diphenyldisulfide was added and dry ammonia was bubbled for 30 min while keeping the temperature at 0 °C. After this, 5 equiv of aldehyde was introduced and stirring was maintained for 18 h at room temperature. The solid formed was filtered on Celite and washed twice with methanol. The filtrate was concentrated under vacuum and the residue obtained was re-suspended in diethyl ether. Insoluble particles were filtered on Celite. The filtrate was washed with water (four times), dried over $MgSO_4$, filtered and concentrated under vacuum. Crude material obtained was purified by flash chromatography on silica gel.

4.2.1. (*E*)-*N*-Benzenesulfenylimine of benzaldehyde (8c). According to the general procedure, the following quantities of reagents and solvents were used: silver nitrate (6 g, 35.4 mmol), diphenyldisulfide (3.86 g, 17.6 mmol), benzaldehyde (9 mL, 88.6 mmol), MeOH 300 mL, Et_2O 600 mL, H_2O 480 mL. The crude product was purified by flash chromatography (pentane); 3.0 g, 81% yield of a white solid; mp 39 °C; IR 1578 cm^{-1} (C═N); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.33 (m, 1H, CH_{arom}), 7.42–7.47 (m, 5H, CH_{arom}), 7.61–7.63 (m, 2H, CH_{arom}), 7.70–7.74 (m, 2H, CH_{arom}), 8.51 (s, 1H, N═C*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 127.0, 127.1, 127.4, 128.8, 129.2, 130.4, 136.4, 137.4, 157.0 (N═*C*H); ^{15}N NMR ($CDCl_3$, 40.56 MHz) δ −71.77 (d, J=3.3 Hz, *E* imine); MS (EI) *m*/*z* (rel intensity, %) 214 (M^+, 100), 136 (12), 109 (32), 77 (23). Anal. Calcd for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57. Found: C, 73.17; H, 5.12; N, 6.47.

4.3. General procedure for cycloaddition reactions

Hünig's base (3.5 equiv) and acid chloride (3 equiv) were added, under argon at room temperature, to a 0.1 M solution of imine, in dichloromethane. The resulting mixture was stirred at 40 °C for 14 h. Then, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (×2) and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to give the crude β-lactam. A sample of crude product was used to measure the isomers ratio by ^1H NMR spectroscopy. The product was further purified by flash chromatography.

4.3.1. 3-Methoxy-4-phenyl-1-phenylsulfanyl-azetidin-2-one (15c). Treating imine **8c** (710 mg, 3.3 mmol) with methoxyacetyl chloride **9a** led to crude product (cis/trans ratio 55/45) isolated as an orange oil, which was further purified by flash chromatography (pentane/ethyl acetate 95/5); 390 mg (yellow oil) of *trans* β-lactam and 520 mg (yellow oil) of *cis* β-lactam, 96% yield. *Minor isomer*: IR 1772 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.49 (s, 3H, OCH_3), 4.47 (d, 1H, J=2.1 Hz), 4.61 (d, 1H, J=2.1 Hz), 7.18–7.35 (m, 10H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.4 (O*C*H$_3$), 66.8 (CON*C*HPh), 91.9 (*C*HOCH$_3$), 126.9, 128.5, 129.0, 129.1, 129.4, 135.6, 135.7, 170.4 (*C*═O); ES (MS) *m*/*z* (%) 286 (M^+, 1), 134 (100), 109 (10), 91 (25). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.3; N, 4.91; S, 11.24. Found: C, 67.20; H, 5.30; N, 4.89; S, 10.76. *Major isomer*: IR 1779 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.18 (s, 3H, OCH_3), 4.86 (d, 1H, J=4.9 Hz), 4.89 (d, 1H, J=4.9 Hz), 7.25–7.39 (m, 10H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.8 (O*C*H$_3$), 66.7 (CON*C*HPh), 87.0 (*C*HOCH$_3$), 128.7, 129.2, 129.6, 130.3, 133.2, 136.1, 170.7 (*C*═O). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.3; N, 4.91; S, 11.24. Found: C, 67.66; H, 5.40; N, 5.01; S, 11.06.

4.3.2. 3-Benzyloxy-4-phenyl-1-phenylsulfanyl-azetidin-2-one (16c). Treating imine **8c** (1 g, 4.7 mmol) with benzyloxyacetyl chloride **9b** led to crude product (cis/trans ratio 55/45) isolated as a yellow oil, which was further purified by flash chromatography (pentane/ethyl acetate 95/5); 656 mg (yellow oil) of *trans* β-lactam and 800 mg (yellow oil) of *cis* β-lactam, 86% yield. *Minor isomer*: IR 1779 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.64 (d, 1H, J=2.1 Hz), 4.68 (d, 1H, J=2.1 Hz), 4.75 (AB spectrum, 2H, J=11.7 Hz, $\Delta\nu$=60.6 Hz, OCH_2Ph), 7.11–7.49 (m, 15H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 67.8 (CON*C*HPh), 73.5 (O*C*H$_2$Ph), 90.4 (*C*HOAc), 127.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.3, 129.7, 129.8, 135.8, 136.0, 136.8, 170.9 (C═O); MS (ES) *m*/*z* (rel intensity, %) 362 (M^+, 1), 210 (31), 109 (12), 91 (100). *Major isomer*: IR 1775 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.31 (AB spectra, 2H, J=11.3 Hz, $\Delta\nu$=25.3 Hz, OCH_2Ph), 4.88 (d, 1H, J=4.8 Hz), 5.03 (d, 1H, J=4.8 Hz), 6.97–7.37 (m, 15H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 67.0 (CON*C*HPh), 72.8 (O*C*H$_2$Ph), 84.8 (*C*HOBn), 128.4, 128.5, 128.7, 128.8, 129.0, 129.2, 129.4, 129.6, 130.4, 133.5, 136.1, 136.5, 170.6 (C═O). Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.1; H, 5.3; N, 3.88; S, 8.87. Found: C, 72.8; H, 5.47; N, 3.78; S, 9.02.

4.3.3. *cis* 3-Benzyloxy-4-phenyl-azetidin-2-one (17). A mixture of β-lactam *cis***16c** (50 mg, 0.14 mmol), 2-thiopyridine (31 mg, 0.28 mmol) and triethylamine (38 μL, 0.28 mmol) in dichloromethane (5 mL) was stirred at room temperature (TLC monitoring). After solvent evaporation, the residue was purified by flash chromatography (dichloromethane); 33 mg (yellow solid), 98% yield; mp 152 °C; IR 1761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.30 (AB, 2H, J=11.3 Hz, $\Delta\nu$=23.2 Hz), 4.86 (d, 1H, J=4.5 Hz), 4.95 (dd, 1H, J_1=2.6 Hz, J_2=4.5 Hz), 6.42 (br s, 1H, NH), 7.20–7.22 (m, 3H), 7.32–7.41 (m, 7H); MS (EI) *m*/*z* (25 rel intensity, %) 4 (MH^+, 100), 146.

4.4. General procedure for mono-oxidation

*m*CpBA (1.1 equiv) was added to a β-lactam solution in dichloromethane (0.07 mol/L). The mixture was stirred at room temperature for 2 h (TLC monitoring). The resulting mixture was washed with saturated aqueous $NaHCO_3$ and then with a saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and then filtered. The solvent was evaporated under reduced pressure to give the crude β-lactam. The product was further purified by flash chromatography.

4.4.1. *cis* 3-Methoxy-4-phenyl-1-phenylsulfinyl-azetidin-2-one (*cis*18c). Treating 300 mg (1.05 mmol) of β-lactam *cis*15c led to 320 mg of crude product (colourless oil) containing two diastereoisomers (67/33) separated by flash chromatography (pentane/ethyl acetate 8/2); 104 mg of white oil (major diastereoisomer), 38 mg of white solid (minor diastereoisomer) and 77 mg of white oil (two diastereoisomers), 69% yield. *Major diastereoisomer*: IR 1718 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.10 (s, 3H, OCH_3), 4.80 (d, 1H, J=5.8 Hz), 5.21 (d, 1H, J=5.8 Hz), 6.92–7.21 (m, 8H, H_{arom}), 7.42–7.46 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.0 (NCHPh), 58.7 (OCH_3), 85.9 (CHOCH_3), 124.5, 127.7, 128.2, 128.4, 128.7, 131.8, 132.1, 139.0, 167.5 (C=O). *Minor diastereoisomer*: mp 135 °C; IR 1775 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.12 (s, 3H, OCH_3), 4.52 (d, 1H, J=5.4 Hz), 4.70 (d, 1H, J=5.4 Hz), 7.26–7.38 (m, 5H, H_{arom}), 7.48–7.56 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.6 (OCH$_3$), 63.5 (NCHPh), 85.8 (CHOCH$_3$), 124.9, 128.3, 128.5, 129.0, 129.5, 132.4, 133.2, 140.4, 166.4 (C=O); MS (EI) *m/z* (rel intensity, %) 302 (MH^+, 19), 168 (36), 135 (100). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.78; H, 4.83; N, 4.71.

4.4.2. *trans* 3-Methoxy-4-phenyl-1-phenylsulfinyl-azetidin-2-one (*trans*18c). Treating 200 mg (0.70 mmol) of β-lactam *trans*15c led to 209 mg of crude product (colourless oil) containing two diastereoisomers (60/40) that were not separated; IR 1789 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) two *diastereoisomers* 60/40 δ 3.42 (s, 3H, OCH_{3min}), 3.44 (s, 3H, OCH_{3maj}), 4.22 (d, 1H, J=2.4 Hz), 4.40 (d, 1H, J=2.4 Hz), 4.47 (d, 1H, J=2.9 Hz), 5.00 (d, 1H, J=2.9 Hz), 6.86–6.89 (m, 2H, H_{arom}), 6.96–7.19 (m, 10H, H_{arom}), 7.28–7.30 (m, 2H, H_{arom}), 7.39–7.53 (m, 6H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) two *diastereoisomers* 60/40 δ 58.1 (OCH$_{3maj}$), 58.4 (OCH$_{3min}$), 58.9 (CHPh$_{maj}$), 66.0 (CHPh$_{min}$), 91.0 (CHOMe$_{min+maj}$), 124.5, 124.8, 126.4, 126.6, 128.3, 128.4, 128.6, 128.7, 128.9, 129.3, 131.8, 132.2, 135.6, 136.2, 138.7, 139.6, 166.8 (C=O$_{min}$), 168.6 (C=O$_{maj}$); MS (EI) *m/z* (rel intensity, %) 302 (MH^+, 15), 168 (81), 135 (100), 125 (15).

4.4.3. *cis* 3-Benzyloxy-4-phenyl-1-phenylsulfinyl-azetidin-2-one (*cis*19c). Treating 100 mg (0.28 mmol) of β-lactam *cis*16c led to 109 mg of crude product (white oil) containing two diastereoisomers (65/35) separated by flash chromatography (pentane/ethyl acetate 9/1 and then 8/2); 18 mg of white solid (major diastereoisomer) and 18 mg of white solid (two diastereoisomers), 34% yield; *major diastereoisomer*: mp 130 °C; IR 1777 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.19 (AB spectra, 2H, J=11.2 Hz, $\Delta\nu$=35.7 Hz, CH_2Ph), 4.98 (d, 1H, J=5.7 Hz), 5.20 (d, 1H, J=5.7 Hz), 6.89–7.22 (m, 13H, H_{arom}), 7.43–7.46 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.3 (NCHPh), 72.9 (OCH$_2$Ph), 83.8 (CHOBn), 124.6, 127.8, 128.3, 128.4, 128.5, 128.7, 128.8, 131.9, 132.5, 135.7, 139.2, 167.7 (C=O); MS (EI) *m/z* (rel intensity, %) 378 (MH^+, 100), 258 (11), 252 (11), 226 (18), 193 (33), 168 (17), 125 (56), 91 (57); the minor isomer was not isolated in a pure form but was detected in the crude mixture by the characteristic NMR signals of the two protons of the β-lactam cycle: δ 4.98 (d, 1H, J=5.7 Hz) and δ 5.20 (d, 1H, J=5.7 Hz).

4.4.4. *trans* 3-Benzyloxy-4-phenyl-1-phenylsulfinyl-azetidin-2-one (*trans*19c). Treating 275 mg (0.76 mmol) of β-lactam *trans*16c led to 260 mg of crude product (yellow oil) containing two diastereoisomers (63/37) that were not separated; IR 1789 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.22 (d, 1H, J=2.36 Hz), 4.55 (d, 1H, J=2.36 Hz), 4.60 (d, 1H, J=2.83 Hz), 4.67 (AB spectra, 2H, J=11.5 Hz, $\Delta\nu$=54.1 Hz, CH_2Ph$_{min}$), 4.69 (AB spectra, 2H, J=11.6 Hz, $\Delta\nu$=65.5 Hz, CH_2Ph$_{maj}$), 4.96 (d, 1H, J=2.83 Hz), 6.72–6.75 (m, 4H, H_{arom}) 6.91–7.49 (m, 26H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) two *diastereoisomers* 63/37 δ 59.7 (CHPh$_{maj}$) 66.5 (CHPh$_{min}$), 73.1 (CH$_2$Ph$_{maj}$), 73.3 (CH$_2$Ph$_{min}$), 89.4 (CHOBn$_{maj+min}$), 124.6, 124.9, 126.6, 126.7, 128.3, 128.4, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.4, 131.8, 132.2, 135.5, 136.1, 136.2, 136.3, 138.9, 139.8, 167.1 (C=O$_{min}$), 168.7 (C=O$_{maj}$); MS (EI) *m/z* (rel intensity, %) 378 (MH^+, 100), 258 (12), 252 (30), 226 (23), 193 (55), 168 (11), 125 (59), 91 (32).

4.5. General procedure for di-oxidation

*m*CpBA (2.5 equiv) was added to a β-lactam solution in dichloromethane (0.07 mol/L). The mixture was stirred at 40 °C for 4 h (TLC monitoring). The resulting mixture was washed with a saturated aqueous $NaHCO_3$ and then with a saturated aqueous NaCl. The organic phase was dried over $MgSO_4$ and then filtered. The solvent was evaporated under reduced pressure to give the crude β-lactam. The product was further purified by flash chromatography.

4.5.1. *cis* 3-Methoxy-4-phenyl-1-phenylsulfonyl-azetidin-2-one (*cis*20c). Treating β-lactam *cis*15c (436 mg, 1.54 mmol) led to 490 mg of crude product (yellow oil) that was not purified; IR 1808 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.16 (s, 3H, OCH_3), 4.83 (d, 1H, J=5.5 Hz), 5.29 (d, 1H, J=5.5 Hz), 7.12–7.15 (m, 2H, H_{arom}), 7.20–7.34 (m, 4H, H_{arom}), 7.40–7.49 (m, 2H, H_{arom}), 7.71–7.73 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.9 (OCH_3), 64.0 (CHPh), 84.8 (CHOMe), 127.5, 128.3, 128.7, 129.1, 129.2, 131.4, 134.1, 138.7, 163.3 (C=O); MS (EI) *m/z* (rel intensity, %) 318 (MH^+, 100), 286 (37), 258 (41), 200 (20), 184 (18), 177 (17), 161 (17), 141 (86), 135 (56), 118 (12), 77 (17).

4.5.2. *trans* 3-Methoxy-4-phenyl-1-phenylsulfonyl-azetidin-2-one (*trans*20c). Treating β-lactam *trans*15c (200 mg, 0.70 mmol) led to crude product purified by flash chromatography (pentane/ethyl acetate 8/2); 187 mg of yellow oil, 84% yield; IR 1805 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.42 (s, 3H, OCH_3), 4.38 (d, 1H, J=2.5 Hz), 4.83 (d, 1H, J=2.5 Hz), 7.17–7.81 (m, 10H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 58.6 (OCH_3), 63.5 (CHPh), 90.5 (CHOMe), 126.7, 127.7, 129.1, 129.3, 129.4, 134.3, 135.1, 138.4, 164.0 (C=O); MS (EI) *m/z* (rel intensity, %) 318 (MH^+, 100), 286 (33), 258 (54), 200 (36), 184 (28), 177 (23), 161 (26), 141 (92), 135 (74), 124 (15), 118 (15), 77 (21).

4.5.3. *trans* 3-Methoxy-4-*para*cyanophenyl-1-phenylsulfonyl-azetidin-2-one (*trans*20m). Treating 117 mg (0.38 mmol) of β-lactam *trans*15m led to 131 mg of crude product (white solid) that was not purified; IR 2229 (CN), 1804 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.47 (s, 3H, OCH_3), 4.39 (d, 1H, J=2.64 Hz), 4.87 (d, 1H,

J=2.64 Hz), 7.42–7.44 (m, 2H), 7.55–7.60 (m, 2H), 7.60–7.67 (m, 3H), 7.88–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.3 (O*C*H$_3$), 59.1 (N*C*H), 85.9 (*C*HOMe), 110.5, 111.2, 124.5, 128.9, 131.7, 139.4, 143.1, 146.2, 166.9 (*C*=O); MS (EI) *m/z* (rel intensity, %) 343 (MH^+, 100), 241 (13), 184 (38), 160 (82), 141 (90), 77 (64).

4.5.4. *cis* 3-Benzyloxy-4-phenyl-1-phenylsulfonyl-azetidin-2-one (*cis*21c). Treating 426 mg (1.18 mmol) of β-lactam *cis***16c** led to 470 mg of crude product (white oil); IR 1807 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.25 (AB spectra, 2H, J=11.0 Hz, $\Delta\nu$=35.7 Hz, OC*H*$_2$Ph), 4.98 (d, 1H, J=5.5 Hz), 5.24 (d, 1H, J=5.5 Hz), 6.89–6.92 (m, 2H, H_{arom}), 7.09–7.42 (m, 10H, H_{arom}), 7.55–7.61 (m, 1H, H_{arom}), 7.68–7.71 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.3 (*C*HPh), 73.0 (O*C*H$_2$Ph), 82.6 (*C*HOBn), 127.5, 128.2, 128.3, 128.4, 128.5, 128.8, 129.1, 129.2, 131.6, 134.1, 135.5, 138.7, 163.3 (*C*=O); MS (EI) *m/z* (rel intensity, %) 411 (M+NH_4^+, 100), 394 (MH^+, 12), 209 (37), 91 (9).

4.5.5. *trans* 3-Benzyloxy-4-phenyl-1-phenylsulfonyl-azetidin-2-one (*trans*21c). Treating 123 mg (0.34 mmol) of β-lactam *trans***16c** led to crude product purified by flash chromatography (pentane/ethyl acetate 8/2); 88 mg of yellow oil; 66% yield; IR 1800 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.57 (d, 1H, J=2.6 Hz), 4.66 (AB spectra, 2H, J=11.70 Hz, $\Delta\nu$=59.1 Hz, OC*H*$_2$Ph), 4.85 (d, 1H, J=2.6 Hz), 6.89–6.92 (m, 2H, H_{arom}), 7.09–7.42 (m, 10H, H_{arom}), 7.55–7.61 (m, 1H, H_{arom}), 7.68–7.71 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 65.9 (*C*HPh), 73.4 (O*C*H$_2$Ph), 88.6 (*C*HOBn), 126.7, 127.6, 128.3, 128.6, 128.7, 128.9, 129.2, 129.3, 134.3, 134.8, 135.9, 138.3, 164.0 (*C*=O); MS (EI) *m/z* 411 (MH^+) this pseudo-molecular ion is relative to the product resulting from the nucleophilic ring opening of the β-lactam *trans***21c** by ammonia used in MS sampling.

4.6. General procedure for β-lactam opening with amines

To a solution containing the β-lactam in THF (0.04 mmol/L) was added 1.2 equiv of primary or secondary amine. Stirring was maintained at room temperature until all the starting material had reacted (TLC monitoring). The solvent was removed under vacuum and the residue was suspended in ethyl acetate. The organic layer was washed with 1 N aqueous HCl and with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography or precipitated in appropriate solvents' mixture.

4.6.1. (2*S,3*S**) 3-Benzenesulfinylamino-2-methoxy-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (23).** Treating β-lactam *trans***18c** (150 mg, 0.50 mmol) with pyrrolidine (46 μL, 0.55 mmol) led to crude product purified by flash chromatography (ethyl acetate); 120 mg of white oil (two diastereoisomers 6/4), 65% yield; IR 1633 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) *major diastereoisomer* δ 1.39–1.73 (m, 4H, N(CHC*H*)$_2$), 3.03–3.14 (m, 1H, N(C*H*CH)$_2$), 3.22–3.43 (m, 3H, N(C*H*CH)$_2$), 3.44 (s, 3H, OC*H*$_3$), 4.06 (d, 1H, J=5.0 Hz, C*H*OCH$_3$), 4.80 (t, 1H, J=5.0 Hz, NHC*H*Ph), 6.41–6.43 (m, 1H, N*H*), 6.98–7.11 (m, 5H), 7.30–7.39 (m, 2H), 7.47–7.52 (m, 2H), 7.72–7.75 (m, 1H); *minor diastereoisomer* δ 1.39–1.73 (m, 2H, N(CHC*H*)$_2$), 1.95–2.04 (m, 1H, N(CHC*H*)$_2$), 2.19–2.28 (m, 1H, N(CHC*H*)$_2$), 3.03–3.14 (m, 1H, N(C*H*CH)$_2$), 3.22–3.43 (m, 3H, N(C*H*CH)$_2$), 3.33 (s, 3H, OC*H*$_3$), 4.11 (d, 1H, J=5.1 Hz, C*H*OCH$_3$), 4.88 (t, 1H, J=5.1 Hz, NHC*H*Ph), 5.85–5.87 (m, 1H, N*H*), 6.98–7.11 (m, 5H), 7.30–7.39 (m, 2H), 7.47–7.52 (m, 2H), 7.72–7.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *major diastereoisomer* δ 23.4 (N(CH*C*H)$_2$), 25.7 (N(CH*C*H)$_2$), 45.7 (N(*C*HCH)$_2$), 45.8 (N(*C*HCH)$_2$), 53.9, 57.3, 80.9 (*C*HOCH$_3$), 125.9, 127.1, 127.6, 128.2, 130.2, 138.4, 143.3, 167.5 (*C*=O); *minor diastereoisomer* δ 23.3 (N(CH*C*H)$_2$), 25.8 (N(CH*C*H)$_2$), 45.8 (N(*C*HCH)$_2$), 45.9 (N(*C*HCH)$_2$), 57.3, 58.5, 82.0 (*C*HOCH$_3$), 125.7, 127.2, 127.9, 128.6, 130.7, 138.2, 144.9, 167.0 (C=O); MS (EI) *m/z* (rel intensity, %) 373 (MH^+, 100), 245 (26).

4.6.2. (2*R,3*S**,13*R*) 3-Benzenesulfonylamino-2-methoxy-3-phenyl-*N*-(1-phenylethyl)propionamide (27).** Treating β-lactam *cis***20c** (150 mg, 0.47 mmol) with (*R*)-1-phenylethylamine (36 μL, 0.52 mmol) led to crude product purified by flash chromatography (pentane/ethyl acetate 9/1); 47 mg of white oil (minor diastereoisomer) and 109 mg of colourless oil (major diastereoisomer), 76% yield; *minor diastereoisomer* IR 1743 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz), two *rotamers* (53/47), first rotamer δ 1.40 (d, 3H, J=6.83 Hz, NHCHC*H*$_3$), 3.19 (s, 3H, OC*H*$_3$), 3.89 (d, 1H, J=4.16 Hz, C*H*OCH$_3$), 4.06–4.12 (m, 1H, NHC*H*CH$_3$), 4.76 (dd, 1H, J_1=4.16 Hz, J_2=7.7 Hz, NHC*H*Ph), 5.56 (d, 1H, J=7.7 Hz, N*H*), 7.06–7.44 (m, 13H), 7.60–7.63 (m, 2H); second rotamer δ 1.38 (d, 3H, J=2.83 Hz, NHCHC*H*$_3$), 3.19 (s, 3H, OC*H*$_3$), 3.83 (d, 1H, J=3.96 Hz, C*H*OCH$_3$), 4.06–4.12 (m, 1H, NHC*H*CH$_3$), 4.73 (dd, 1H, J_1=3.96 Hz, J_2=7.7 Hz, NHC*H*Ph), 5.54 (d, 1H, J=7.7 Hz, N*H*), 7.06–7.44 (m, 13H), 7.60–7.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) two rotamers (53/47) δ 19.7 (NHCH*C*H$_3$), 19.8 (NHCH*C*H$_3$), 59.0, 59.1, 59.2, 59.3, 60.5 (NH*C*HPh), 60.8 (NH*C*HPh), 82.7 (*C*HOCH$_3$), 82.9 (*C*HOCH$_3$), 127.0, 127.1, 127.2, 127.4, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 132.4, 136.6, 136.7, 140.1, 140.9, 141.2, 169.5, 169.6; MS (EI) *m/z* (rel intensity, %) 439 (MH^+, 100), 335 (25), 239 (12), 207 (30), 178 (62), 135 (55), 105 (64); *major diastereoisomer* IR 1657 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz), two *rotamers* (55/45), first rotamer δ 1.14 (d, 3H, J=6.99 Hz, NHCHC*H*$_3$), 3.35 (s, 3H, OC*H*$_3$), 3.77 (d, 1H, J=3.78 Hz, C*H*OCH$_3$), 4.86–4.95 (m, 2H, NHC*H*Ph and NHC*H*CH$_3$), 6.55–6.62 (m, 1H, N*H*), 6.95–7.04 (m, 2H), 7.09–7.45 (m, 11H), 7.59–7.71 (m, 2H); second rotamer δ 1.39 (d, 3H, J=6.99 Hz, NHCHC*H*$_3$), 3.43 (s, 3H, OC*H*$_3$), 3.84 (d, 1H, J=3.96 Hz, C*H*OCH$_3$), 4.86–4.95 (m, 2H, NHC*H*Ph and NHC*H*CH$_3$), 6.71–6.74 (m, 1H, N*H*), 6.95–7.04 (m, 2H), 7.09–7.45 (m, 11H), 7.59–7.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz), two *rotamers* (55/45) δ 21.3 (NHCH*C*H$_3$), 21.6 (NHCH*C*H$_3$), 48.1, 48.2, 56.3, 56.8, 58.6, 58.7, 82.5 (*C*HOCH$_3$), 82.8 (*C*HOCH$_3$), 126.0, 126.1, 127.0, 127.4, 127.5, 128.0, 128.1, 128.5, 128.7, 128.8, 128.9, 132.2, 132.3, 135.9, 136.3, 141.0, 141.1, 142.0, 142.5, 168.9, 169.0; MS (EI) *m/z* (rel intensity, %) 439 (MH^+, 100), 335 (20), 178 (14), 135 (16). Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 5.98; N, 6.39; S, 7.31. Found: C, 65.31; H, 5.84; N, 6.28; S, 7.55.

4.6.3. (2*R,3*S**) 3-Benzenesulfonylamino-2-methoxy-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (29).** Treating

β-lactam *cis***20c** (191 mg, 0.60 mmol) with pyrrolidine (53 μL, 0.63 mmol) led to crude product purified by flash chromatography (pentane/ethyl acetate 4/6); 37 mg of white solid, 16% yield; mp 176 °C; IR 1637 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47–1.69 (m, 4H, N(CHC*H*)$_2$), 2.73–2.80 (m, 1H), 3.04–3.19 (m, 2H), 3.23 (s, 3H, OC*H*$_3$), 3.24–3.34 (m, 1H), 3.94 (d, 1H, *J*=6.1 Hz, C*H*OCH$_3$), 4.54 (dd, 1H, J_1=6.1 Hz, J_2=4.5 Hz, NHC*H*Ph), 5.25 (d, 1H, *J*=4.5 Hz, N*H*), 6.29–6.32 (m, 1H), 7.16–7.22 (m, 4H), 7.33–7.37 (m, 2H), 7.42–7.47 (m, 1H), 7.64–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.5, 26.2, 46.1, 46.4, 57.7 (O*C*H$_3$), 59.0 (NH*C*HPh), 82.8 (*C*HOCH$_3$), 127.4, 127.9, 128.1, 128.8, 132.5, 136.6, 140.0, 167.0 (*C*═O); MS (EI) *m*/*z* (rel intensity, %) 389 (MH^+, 81), 98 (100).

4.7. Procedure for β-lactam ring opening with ethyl glycinate hydrochloride

To a solution containing the β-lactam in dichloromethane (0.025 mmol/L) were added 1.2 equiv of amino ester hydrochloride salt and 1.4 equiv of triethylamine at 0 °C. Stirring was continued at room temperature until all the starting material had reacted (TLC monitoring). The solvent was removed under vacuum and the residue was suspended in ethyl acetate. The organic layer was washed with 1 N aqueous HCl and with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography or precipitated in appropriate solvents mixture.

4.7.1. (2*S,3*S**) Ethyl 3-benzenesulfonylamino-2-benzyloxy-3-phenylpropanamido-acetate (41).** Treating β-lactam *trans***21c** (50 mg, 0.13 mmol) with ethyl glycinate hydrochloride (21 mg, 0.15 mmol) and triethylamine (25 μL, 0.18 mmol) led to crude product purified by flash chromatography (pentane/ethyl acetate 7/3); 20 mg of white solid, 32% yield; IR 1749 (C═O); 1657 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, 3H, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 3.60 (dd, 1H, J_1=18.3 Hz, J_2=4.79 Hz, NHC*H*$_2$CO$_2$Et), 3.96 (dd, 1H, J_1=18.3 Hz, J_2=6.4 Hz, NHC*H*$_2$CO$_2$Et), 4.14–4.21 (m, 3H, C*H*OBn and OC*H*$_2$CH$_3$), 4.52 (AB spectra, 2H, *J*=11.3 Hz, Δν=54.5 Hz, OC*H*$_2$Ph), 4.72 (dd, 1H, J_1=7.7 Hz, J_2=5.1 Hz, NHC*H*Ph), 5.99 (d, 1H, *J*=7.7 Hz, N*H*), 6.70–6.74 (m, 1H, N*H*), 7.05–7.16 (m, 5H), 7.24–7.45 (m, 8H), 7.62–7.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2 (OCH$_2$*C*H$_3$), 40.8 (NH*C*H$_2$CO$_2$Et), 59.3 (NH*C*HPh), 61.8 (O*C*H$_2$CH$_3$), 74.1 (O*C*H$_2$Ph), 82.1 (*C*HOBn), 127.2, 127.8, 128.0, 128.2, 128.4, 128.6, 128.8, 128.9, 132.4, 136.2, 136.3, 140.3, 169.0, 169.6; MS (EI) *m*/*z* (rel intensity, %) 497 (MH^+, 100), 340 (44), 250 (72), 248 (20), 194 (28), 130 (16), 104 (32), 91 (48). Anal. Calcd for $C_{26}H_{28}N_2O_6S$: C, 62.89; H, 5.68; N, 5.73; S, 6.35. Found: C, 63.00; H, 5.65; N, 5.73; S, 6.35.

4.7.2. (2*R,3*S**) Methyl 3-benzenesulfonylamino-2-benzyloxy-3-phenyl-propanoate (43).** DMAP (62 mg (0.51 mmol)) followed by 280 μL of triethylamine was added dropwise to a solution containing 400 mg (1.02 mmol) of β-lactam *cis***21c** in methanol (37 mL). The mixture was stirred at room temperature (TLC monitoring). The solvent was then evaporated under reduced pressure and the crude mixture was dissolved in 60 mL of saturated aqueous NH_4Cl. This solution was extracted four times with 40 mL of dichloromethane. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 475 mg of yellow solid. The crude product was isolated by flash chromatography (pentane/ethyl acetate 1/1); 385 mg of yellow oil, 89% yield; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.54 (s, 3H, OC*H*$_3$), 3.92–4.01 (m, 1H, C*H*OBn), 4.41 (AB spectra, 2H, *J*=11.7 Hz, Δν=120.8 Hz, OC*H*$_2$Ph), 4.85–4.88 (m, 1H, NHC*H*Ph), 5.58–5.61 (m, 1H, N*H*), 6.95–6.97 (m, 2H), 7.12–7.30 (m, 11H), 7.60–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.3 (O*C*H$_3$), 59.3 (NH*C*HPh), 73.1 (O*C*H$_2$Ph), 80.8 (*C*HOBn), 127.1, 127.9, 128.1, 128.3, 128.4, 128.8, 132.4, 136.4, 137.6, 140.8, 170.0 (*C*═O); MS (EI) *m*/*z* (rel intensity, %) 426 (MH^+, 47), 248 (100).

4.7.3. (2*R,3*S**) *S*-Methyl 2-methoxy-3-phenyl-3-benzenesulfonylamino propanethioate (46).** In a reactor flushed with argon was dissolved 49 mg (0.69 mmol) of sodium methylthiolate in 5 mL of freshly distilled THF. A solution containing 20 mg (0.63 mmol) of β-lactam *cis***21c** in 5 mL of THF was added and stirring was continued for 18 h under argon atmosphere. The solvent was then evaporated and the residue purified by flash chromatography; 227 mg of white solid, 98% yield; IR 1676 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H, SC*H*$_3$), 3.35 (s, 3H, OC*H*$_3$), 3.85 (d, 1H, *J*=2.5 Hz, C*H*OCH$_3$), 4.90 (dd, 1H, J_1=8.88 Hz, J_2=2.46 Hz, NHC*H*Ph), 3.70 (d, 1H, *J*=8.88 Hz, N*H*), 7.31–7.39 (m, 5H), 7.46–7.51 (m, 2H), 7.69–7.72 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2 (S*C*H$_3$), 58.9 (NH*C*HPh), 60.9 (O*C*H$_3$), 89.5 (*C*HOCH$_3$), 126.9, 127.1, 127.9, 128.5, 128.7, 132.3, 137.9, 140.7, 201.3 (*C*═O).

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Supplementary data

Experimental details and characterization data of the *N*-benzenesulfenylimines **8**, 1-phenylsulfanyl-azetidin-2-ones **15** and **16**, 1-phenylsulfinyl-azetidin-2-ones **18** and **19**, 1-phenylsulfonyl-azetidin-2-ones **20** and **21** and open-chain *N*-phenylsulfonyl-β-amino acid derivatives **22**–**45**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.01.051.

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