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STEREOSELECTIVE FUNCTIONALIZATION OF ALKENYL-β-LACTAMS

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Abstract – Alkenyl-β-lactams, obtained by palladium-catalyzed [2+2] cycloaddition of imines with allyl halides, were functionalized in a stereoselective way by a simple deprotonation with LDA, and subsequent capture of the formed carbanion by various electrophiles. Alkyl, hydroxy and epoxy functionalities were inserted exclusively at the C-3 carbon atom of the β-lactamic system, without performing new cyclizations. High stereoselectivity was noticed with the quenching taking place preferentially at the C_α with respect to the C_γ carbon atom of the allylic moiety of the azetidinyl anion generated by deprotonation.

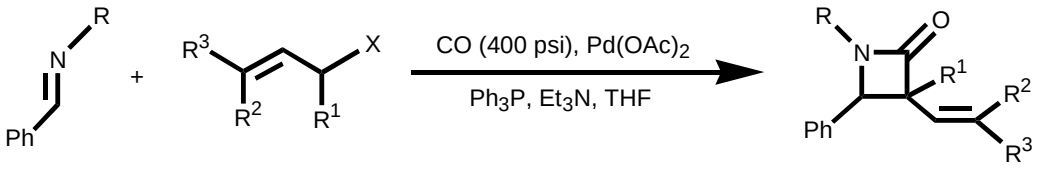
INTRODUCTION

The interest toward the chemistry of the β-lactams is enormously increased in the last decades, after the discovery of several classes of antibiotics containing the β-lactam units, such as the penicillins and the cephalosporins.[1] These compounds are used as antibacterial agents and they are useful synthetic intermediates for the preparation of heterocycles of biological and pharmaceutical interest.[2] Suitably substituted β-lactams are employed, for example, as therapeutic agents for lowering the cholesterol levels in the plasma.[3] An increasing number of studies focuses on the activity of such compounds as anticancer drugs[4] or as enzymatic inhibitors for example of the Human Leucocitary Elastase (HLE)[5] and the cysteine protease.[6] The need of more powerful and efficient β-lactamic antibiotics oriented the researchers toward the synthesis of new and variously functionalized 2-azetidinones.[4,7]

In literature, several synthetic protocols based on the palladium-catalyzed carbonylation have been reported.[8,9] Among them, particularly interesting is the [2+2] cycloaddition of allyl-phosphate under CO

pressure and in the presence of palladium complex with imines leading to β-lactams.[10]

Recently, we reported the diastereoselective synthesis of β-lactams using [2+2] cycloaddition of simple allyl halides with imines under CO pressure (400 psi) in the presence of Et_3N and catalytic amount of Pd(II) complexed by phosphine ligands (Scheme 1).[11]

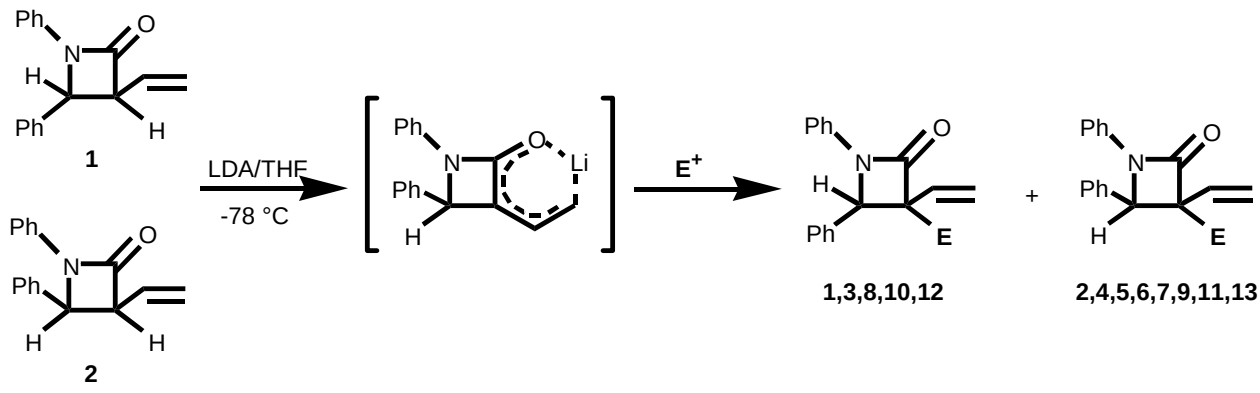


Scheme 1

A diastereoselectivity of *trans*, *trans* and *trans*, *cis*-type was noticed. Moreover, using optically pure imines, with R containing a stereocenter, through asymmetric induction we prepared alkenyl-β-lactams having more chiral stereocenters with high *trans*-type diastereoselectivity.[12] Several examples in literature suggest that the biological activity of these compounds is largely affected by the kind of substituents present on the ring.[13] We therefore considered the opportunity to functionalize the 2-azetidinone system without performing new cyclizations, as a natural extension of our previous works. This can be achieved through the generation of a stable carbanion on the ring, followed by a coupling reaction with electrophiles.

RESULTS AND DISCUSSION

1,4-Diphenyl-3-vinyl-2-azetidinones (*trans*-**1**) and (*cis*-**2**), synthetized as reported,[11,12] should have two particularly acidic hydrogens: the one linked to the C-4 carbon of benzylic type and in α position to the nitrogen atom, the other bonded to the C-3 carbon of allylic type and in α position to the carbonyl group. Treatment of **1** and **2** with a base like lithium diisopropylamide (LDA) at –78°C afforded a stable azetidinyl anion, which was trapped by various electrophiles to give β-lactams (**1-13**) functionalized exclusively at the C-3 carbon atom (Scheme 2).

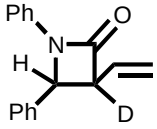
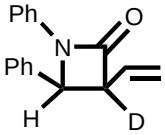
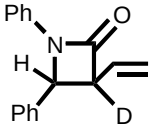
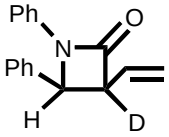
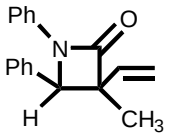
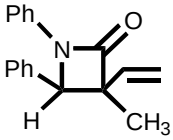
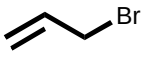
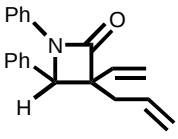
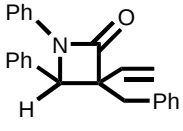


Scheme 2

This behavior could be due to the greater acidity of the hydrogen bonded to the C-3 with respect to the one bonded to the C-4. The anion conjugation, produced by the neighbouring carbonyl and vinyl groups at the C-3, results larger than that generated at the C-4 carbon by the phenyl group and by the nitrogen inductive effect.

The results of the deprotonation of **1** and **2** and the relative treatment of the azetidinyl anion with various electrophiles (H^+, D^+, R^+) are collected in Table 1.

Table 1. Functionalization of **1** and **2** with H_2O, D_2O, and RX

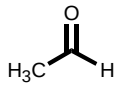
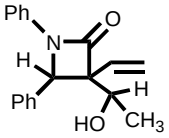
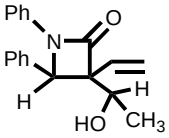
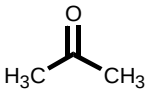
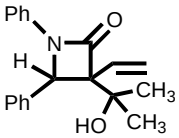
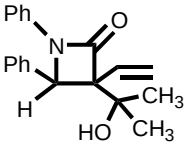
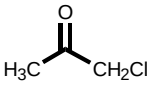
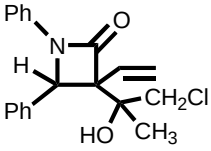
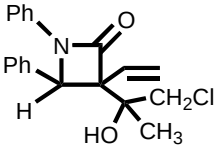
Entry	β-lactam	E	Total yield[a] [%]	Product distribution[b] [%]		
					trans	*cis*
1	**1**	H_2O	88	–	**1** (44)	**2** (56)
2	**2**	H_2O	89	–	**1** (45)	**2** (55)
3	**1**	D_2O	87	**1**+**2** (35)	 **3** (30)	 **4** (35)
4	**2**	D_2O	86	**1**+**2** (35)	 **3** (30)	 **4** (35)
5	**1**	CH_3I	97	**1**+**2** (20)	–	 **5** (80)
6	**2**	CH_3I	98	**1**+**2** (22)	–	 **5** (78)
7	**1**		95	**1**+**2** (15)	–	 **6** (85)
8	**1**	$PhCH_2Br$	80	**1**+**2** (30)	–	 **7** (70)

[a]Isolated yields. [b]Product distributions evaluated by GC and ^{1}H NMR spectroscopy.

Treating the solution of azetidinyl anions, generated indifferently by **1** or **2**, with small electrophiles such as H^+ or D^+, a diastereomeric mixture of products with almost equal ratios of *trans* and *cis* form was observed, Entries 1-4, Table 1. Probably, the formed carbanions have always the same planar structures, that makes possible for smaller electrophiles (H^+ or D^+) to bind indifferently both sides of the molecule, leading to almost equal diasteromeric ratios.

The anion's quenching reaction became stereoselective when the electrophile had larger dimensions such as an alkyl halide (Entries 5-8, Table 1). The C-3 carbon atom was substituted by the most hindered electrophile exclusively from the less hindered side, i.e. *anti* with respect to the C-4 phenyl group, leading prevailingly to the *cis* product. The transformation yields were always high for all reactions: a mixture of products (**1**) and (**2**) in almost the same ratio was recovered. These compounds, previously characterized and reported,[11] could arise from the water quenching of the anion not captured by the electrophile (Entries 1 and 2, Table 1).

Table 2. Functionalization of **1** and **2** with aliphatic aldehydes or ketones

Entry	β-lactam	E	Total yield[a] [%]		Product distribution[b] [%] *cis*	Product distribution[b] [%] *trans*
1	**1,2**		95	**1+2** (40)	 **8** (6)	 **9** (54)
2	**1**		82	**1+2** (56)	 **10** (traces)	 **11** (43)
3	**1,2**		90	**1+2** (48)	 **12** (13)	 **13** (39)

[a]Isolated yields. [b]Product distributions evaluated by GC and ^{1}H NMR spectroscopy.

When planar electrophiles, such as aliphatic aldehydes or ketones, were used in the quenching of the azetidinyl anion, a different reactivity and stereoselectivity were found. Together with the initial substrates (**1**) and (**2**) found in equal ratios, alcohols deriving from both an *anti* and a *syn* attack with respect to the C-4 phenyl group were isolated with a strong dominance of the former (% *trans* > % *cis*), Entries 1-3, Table 2.

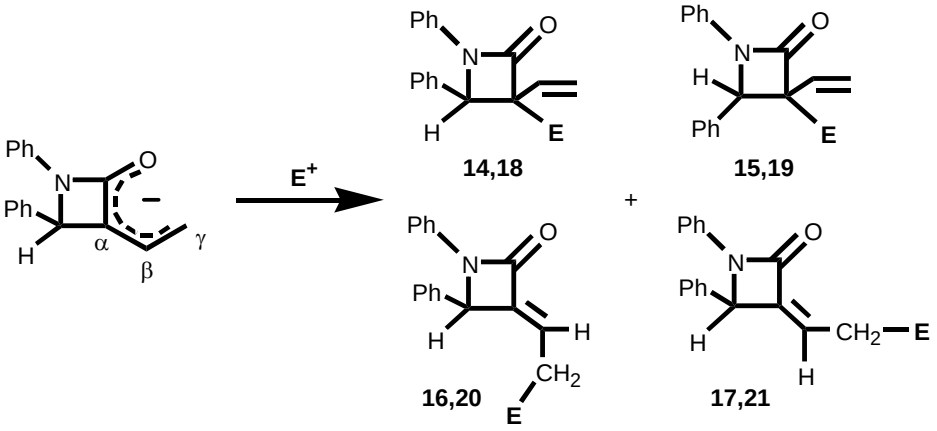
Deuterated products (**3**) and (**4**) were identified by GC-MS and ^{1}H NMR spectroscopy, as detailed in the EXPERIMENTAL. We assigned the *cis* configuration to compound (**5**) on the basis of the ^{1}H NMR

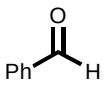
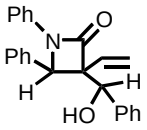
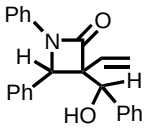
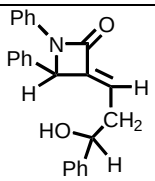
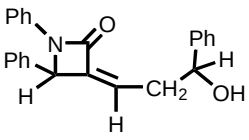
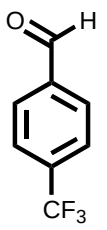
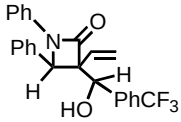
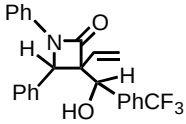
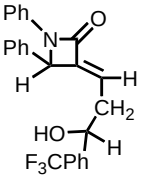
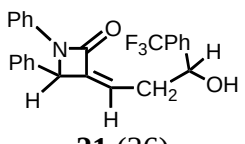
spectra. The ^{1}H chemical shift values of the vinylic system move to higher fields when the vinyl moiety is located on the same side of the phenyl for an evident case of diamagnetic anisotropy produced by the aromatic ring and felt by the vinylic hydrogens. This behaviour was previously noticed also for analogous structures and confirmed by X-Ray measurements.[11,12] Applying the above considerations we assigned the geometry to compounds (**6-13**) (Tables 1 and 2).

None of the reactions reported above led to compounds deriving from a deprotonation of the C-4 carbon. Even deprotonating with *n*-BuLi substrates doubly functionalized at the C-3 (**5**) and trapping them with electrophiles, no products functionalized at the C-4 position were observed.

When the azetidinyl anion was captured by aromatic aldehydes, two new products (**16**,**17** and **20**,**21**) were isolated, respectively (Entries 1 and 2, Table 3).

Table 3. Functionalization of **1** and **2** with aromatic aldehydes



Entry	β-lactam	E	Total yield[a] [%]	Product distribution[b] [%]				
1	**1,2**		93	**1+2** (72)	 **14** (traces)	 **15** (traces)	 **16** (3) *E*	 **17** (24) *Z*
2	**1,2**		97	**1+2** (29)	 **18** (23)	 **19** (7)	 **20** (5) *E*	 **21** (36) *Z*

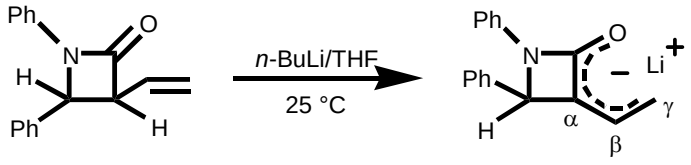
[a]Isolated yields. [b]Product distributions evaluated by GC and ^{1}H NMR spectroscopy.

Together with the expected alcohols (**14**,**15** and **18**,**19**) derived from the quenching at the C-3 carbon (the α position of the allylic moiety), we isolated in greater yield alcohols (**16**,**17** and **20**,**21**) deriving from the electrophilic quenching at the terminal carbon atom of the allylic chain on the γ position. Probably, the tridentate nature of the reacting anion influences the regioselectivity of the electrophilic attack, which may be directed to the α or γ position of the allylic moiety.[14,15] Thus α attack dominates in the irreversible reaction with alkyl halides and in the reversible additions of small aliphatic aldehydes and ketones, while γ-adducts are predominantly obtained when these latter additions were carried out with bulkier aromatic aldehydes. The lower conversion yields observed for electrophiles such as aldehydes and ketones with respect to alkyl halides could be due to the reversible nature of the addition reactions.[14,16] When γ-adducts were predominant, the stereoselectivity of γ-attack resulted always higher for the *Z* form with respect to the *E* form, with a ratio of almost 8:1 (*Z* and *E* geometries beeing referred to the vinylic moiety).

The relative configuration of **14**,**15** and **18**,**19** was determined from the ^{1}H NMR chemical shift values of the vinylic system with respect to the phenyl group beared to the C-4 carbon, as above described. The differentiation between the two isomers (**16**,**17** and **20**,**21**) was made again from the ^{1}H NMR spectra: the *Z*-**17** and *Z*-**21** isomers displayed their vinylic proton with a chemical shift value shifted upfield, whereas the *E*-**16** and *E*-**20** compounds showed a downfield chemical shift owing to the placement of this proton in the deshielding region of the neighbouring carbonyl group.[17-19]

Moreover, in order to verify if the regioselectivity was influenced by electronic effects, the ^{13}C NMR spectra of the azetidinyl anion in THF, generated deprotonating *trans*-**1** with *n*-BuLi, were recorded and the data are summarized in Table 4.

Table 4. ^{13}C NMR spectral data of the azetidinyl anion



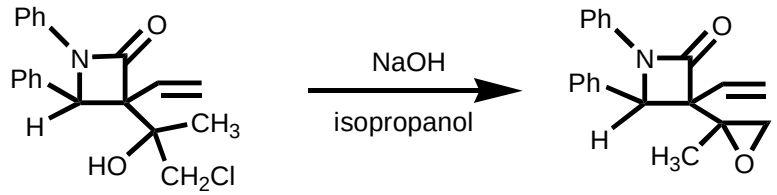
1

Carbon atom	δ (ppm) 2-azetidinone **1**	azetidinyl anion	Δ (ppm)
C_α	63.00	57.20	5.80
C_β	136.75	134.25	2.50
C_γ	115.60	115.27	0.33

As recently reported in literature for dienediolates,[20] ^{13}C NMR chemical shifts can be related to the π-electron density charges. The chemical shift displacements to higher field, as listed in Table 4, reveal a higher π-electron density on the C_α with respect to the C_γ carbon atom, which may account for a

preferential electrophilic attack to the α position of the allylic moiety, even if sterically more hindered than the γ position. Bulky electrophile such as aromatic aldehyde, however, seems to be critical to the stereochemical outcome. Both products arising from the functionalization of the C_α and the C_γ carbon atom were observed, with the prevalence of this latter (Table 3). ^{13}C NMR spectral investigations of the azetidinyl anion generated with *n*-BuLi from *cis*-**2** in THF, afforded similar results observed for *trans*-**1**. For instance, for compound *cis*-**2** we noticed chemical shift displacements towards the same values of the azetidinyl anion reported in Table 4. This behaviour strongly support the generation of a unique planar anion either starting from the 2-azetidinone *trans*-**1**or *cis*-**2**.

Finally, we showed how it is possible to insert an oxiranyl group on a β-lactam system. Employing α-chloro-ketones as electrophiles we obtained a chloridrine moiety in the chain at the C-3, as observed for the product (**13**) (Entry 3, Table 2). The treatment of **13** with NaOH in isopropanol produced a nucleophilic internal substitution with the formation of an epoxidic function in good yield (compound (**22**), Scheme 3).



13 **22**

Scheme 3

In conclusion, it was possible to functionalize, with several groups, the C-3 carbon of alkenyl-β-lactams through a simple deprotonation followed by the capture of the formed carbanion with different electrophiles. In particular, we inserted on the β-lactamic systems alkyl, hydroxy and epoxy functionalities without performing a new cyclization. The reactions turned out to be selective: whether the *cis*- or *trans*-β-lactams were used, the azetidinyl anion formed after deprotonation assumed a planar configuration and the quenching took place preferentially at the C_α carbon atom. Even if sterically more hindered than the C_γ, the C_α carbon shows higher electronic density. With bulky electrophiles it was possible to prepare both products arising from the C_α and the C_γ quenching with strong preference of the C_γ product.

EXPERIMENTAL

General Remarks: *n*-BuLi was a commercial solution in hexanes (Aldrich) and was titrated with *N*-pivaloyl-*o*-toluidine prior to use.[21] THF, lithium diisopropylamide (LDA), deuterium oxide, and all other chemicals were of commercial grade (Aldrich), and they were used without further purification. Acetaldehyde, benzaldehyde, methyl iodide, allyl bromide, benzyl chloride, chloroacetone,

α,α,α-trifluoro-*p*-tolualdehyde and acetone were of commercial grade (Aldrich) and were purified by distillation prior to use. Petroleum ether refers to the 40-60°C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 MHz and 100.62 MHz, for ^{1}H and ^{13}C, respectively); with $CDCl_3$ as solvent and TMS as internal standard (δ = 7.24 for ^{1}H spectra; δ = 77.0 for ^{13}C spectra). The IR spectra were recorded on a Perkin Elmer spectrophotometer Model 283. GC-MS spectral analyses were performed with a Shimadzu-17A gas chromatograph (5% diphenyl / 95% dimethylpolysiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with a Shimadzu GCMS-QP5050A mass-selective detector operating at 70 eV (EI). The electrospray ionisation (HR-ESI-MS) spectral experiments were carried out on a hybrid Q*q*TOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion spray ionisation source. MS (+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/ μL), dissolved in a solution 0.1% acetic acid, methanol/water 50:50 at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground respectively. Elemental analyses were performed on a Carlo Erba C, H, N analyzer. Melting points were determined using an electrothermal melting point apparatus and are uncorrected. TLC were performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatographies were performed on silica gel (63-200 mm) using petroleum ether/diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen, in oven-dried glassware using syringe/septum cap techniques.

General procedure for the functionalization of alkenyl β-lactams (1) and (2). To a stirred solution of 1 mmol of **1** and/or **2** in THF (30 mL) at –78 °C, LDA (2.0 M in hexane, 0.6 mL, 1.2 mmol) was added dropwise under nitrogen. The resulting mixture was stirred at –78 °C for 5 min, and then 1.5 mmol of the electrophile were added. The reaction was warmed up to rt and quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 1:1) to afford the pure functionalized β-lactams (**1-21**); yields: 80-98%.

1,4-Diphenyl-3-vinylazetidin-2-ones (1) and (2). Characterization data previously reported in the literature.[11]

3-Deutero-1,4-diphenyl-3-vinylazetidin-2-ones (3) and (4). Diastereomeric separable mixture in a ratio of 30/35. **3**: Yield: 65 mg (26%), 55% D, white solid, mp 98.8-99.5 °C (*n*-hexane). The ^{13}C NMR spectral data are the same of compound (**1**). In the ^{1}H NMR spectrum the double doublet at 3.73 ppm almost disappears, while the doublet at 4.81 becomes a singlet. GC-MS (70 eV); *m/z* (%): 250 (4) [M^+], 249 (4), 181 (15), 180 (25), 131 (76), 130 (100), 115 (25), 77 (54). IR ($CHCl_3$): 3050, 3020, 3000, 2910,

1740, 1600, 1370 cm^{-1}. HRMS calcd for $C_{17}H_{15}DNO$ 251.12955; found 251.12960. **4:**Yield: 75 mg (30%), 63% D, white solid, mp 85.9–85.5 °C (*n*-hexane). The ^{13}C NMR spectral data are the same of compound (**2**). In the ^{1}H NMR spectrum the double doublet at 4.29 ppm almost disappears, while the doublet at 5.33 becomes a singlet. GC-MS (70 eV); *m/z* (%): 250 (6) [M^+], 249 (7), 181 (33), 180 (45), 131 (85), 130 (100), 115 (28), 77 (70). IR ($CHCl_3$): 3050, 3020, 3000, 2910, 1740, 1600, 1370 cm^{-1}. HRMS calcd for $C_{17}H_{15}DNO$ 251.12955; found 251.12961.

3-Methyl-1,4-diphenyl-3-vinylazetidin-2-one (5). Yield: 200 mg (76%), white solid, mp 112.8-113.8 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 1.65 (s, 3H), 4.87 (s, 1H), 5.01 (d, *J* =10.0 Hz, 1H), 5.24-5.38 (m, 2H), 7.05 (t, *J* = 7.2 Hz, 1H) 7.18-7.35 (m, 9H). ^{13}C NMR (100.62 MHz): δ = 20.8, 61.7, 67.2, 117.2, 117.3, 123.8, 126.9, 128.2, 128.6, 129.0, 134.2, 135.0, 137.7, 168.7. GC-MS (70 eV); *m/z* (%): 263 (4) [M^+], 181 (35), 180 (32), 144 (58), 129 (100), 77 (60). IR ($CHCl_3$): 3060, 3000, 2960, 2900, 1730, 1600, 1590, 1370 cm^{-1}. *Anal.* Calcd for $C_{18}H_{17}NO$: C 82.09, H 6.50, N, 5.32. Found: C 82.15, H 6.53, N 5.34.

3-Allyl-1,4-diphenyl-3-vinylazetidin-2-one (6). Yield: 234 mg (81%), white solid, mp 46.8-47.8 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 2.73 (d, *J* = 7.2 Hz, 2H), 5.00 (s, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 5.19-5.31 (m, 3H), 5.45 (d, *J* = 16.3 Hz, 1H), 5.90-5.96 (m, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 7.17-7.35 (m, 9H). ^{13}C NMR (100.62 MHz): δ = 39.9, 63.9, 65.0, 117.3, 117.9, 119.4, 123.8, 127.2, 128.1, 128.6, 129.0, 132.7, 132.9, 135.0, 137.5, 167.7. GC-MS (70 eV); *m/z* (%): 289 (4) [M^+], 181 (42), 180 (32), 170 (26), 129 (100), 77 (60). IR ($CHCl_3$): 3060, 3000, 2900, 1740, 1600, 1590, 1370 cm^{-1}. *Anal.* Calcd for $C_{20}H_{19}NO$: C 83.01, H 6.62, N 4.84. Found: C 83.15, H 6.60, N 4.81.

3-Benzyl-1,4-diphenyl-3-vinylazetidin-2-one (7). Yield: 190 mg (56%), white solid, mp 90.4-91.2 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 3.20 (d, *J* = 13.9 Hz, 1H), 3.32 (d, *J* = 13.9 Hz, 1H), 5.01 (s, 1H), 5.08 (dd, *J* = 10.9, 1.3 Hz, 1H), 5.14-5.21 (m, 1H), 5.52 (dd, *J* = 17.3, 1.4 Hz, 1H), 6.98-7.35 (m, 15H). ^{13}C NMR (100.62 MHz): δ = 41.6, 63.4, 66.0, 117.4, 117.9, 123.8, 127.0, 127.2, 128.0, 128.4, 128.5, 128.9, 130.3, 133.5, 134.9, 136.1, 137.4, 167.9. GC-MS (70 eV); *m/z* (%): 339 (4) [M^+], 281 (3), 220 (12), 181 (30), 129 (100), 91 (22), 77 (28). IR ($CHCl_3$): 3060, 2920, 1740, 1600, 1490, 1375 cm^{-1}. *Anal.* Calcd for $C_{24}H_{21}NO$: C 84.92, H 6.24, N 4.13. Found: C 84.70, H 6.27, N 4.11.

3-(1-Hydroxyethyl)-1,4-diphenyl-3-vinylazetidin-2-ones (8) and (9). Diastereomeric separable mixture in a ratio of 6/54. **8:** Yield: 17.6 mg (6%), oil. ^{1}H NMR (400.13 MHz): δ = 0.74 (d, *J* = 6.3 Hz, 3H), 2.35 (br s, 1H) 4.00 (q, *J* = 6.3 Hz, 1H), 5.15 (s, 1H), 5.49 (d, *J* = 10.9 Hz, 1H) 5.62 (d, *J* = 17.6 Hz, 1H) 6.25 (dd, *J* = 17.6, 10.9 Hz, 1H), 7.06 (t, *J* = 6.8 Hz, 1H), 7.24-7.40 (m, 9H). ^{13}C NMR (100.62 MHz): δ = 17.1, 64.3, 67.7, 68.2, 117.4, 118.9, 124.1, 127.3, 128.7, 128.9, 129.1, 132.0, 133.7, 137.2, 168.0. GC-MS (70 eV); *m/z* (%): 293 (10) [M^+], 249 (13), 182 (42), 181 (95), 180 (58), 130 (80), 77 (100). IR ($CHCl_3$): 3420 (br), 3050, 2980, 1740, 1600, 1495, 1380 cm^{-1}. HRMS calcd for $C_{19}H_{20}NO_2$ 294.14950; found

294.14958. **9:** Yield: 149.4 mg (51%), white solid, mp 119.1-120.3 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 1.40 (d, *J* = 6.4 Hz, 3H), 2.30 (br s, 1H) 4.21 (q, *J* = 6.4 Hz, 1H), 5.10-5.17 (m, 2H), 5.19 (s, 1H), 5.52-5.59 (m, 1H), 7.04 (t, *J* = 6.3 Hz, 1H), 7.19-7.35 (m, 9H). ^{13}C NMR (100.62 MHz): δ = 19.0, 61.6, 70.0, 70.5, 117.4, 119.9, 123.9, 127.4, 128.2, 128.6, 129.0, 130.4, 134.7, 137.2, 166.9. GC-MS (70 eV); *m/z* (%): 293 (9) [M^+], 249 (11), 182 (45), 181 (95), 180 (55), 130 (83), 77 (100). IR ($CHCl_3$): 3420 (br), 3050, 2980, 1740, 1600, 1495, 1380 cm^{-1}. *Anal.* Calcd for $C_{19}H_{19}NO_2$: C 77.79, H 6.53, N 4.77. Found: C 77.85, H 6.55, N 4.75.

3-(1-Hydroxy-1-methylethyl)-1,4-diphenyl-3-vinylazetidin-2-ones (10) and (11). Diastereomeric separable mixture in a ratio of traces/43. **10:** traces of isomer measured by GC-MS (70 eV); *m/z* (%): 307 (13) [M^+], 292 (4), 249 (30), 182 (31), 181 (49), 180 (47), 128 (35), 77 (100), 59 (85). **11:** Yield: 107.4 mg (35%), white solid, m.p. 124.8-125.8 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 1.37 (s, 3H), 1.48 (s, 3H), 1.90 (br s, 1H), 5.11-5.17 (m, 2H), 5.39 (s, 1H), 5.56-5.63 (m, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 7.20-7.34 (m, 9H). ^{13}C NMR (100.62 MHz): δ = 26.2, 26.6, 60.9, 72.5, 74.0, 117.4, 119.6, 123.8, 127.8, 128.0, 128.5, 128.9, 131.6, 135.1, 137.2, 166.9. GC-MS (70 eV); *m/z* (%): 307 (13) [M^+], 249 (56), 182 (63), 181 (100), 180 (63), 130 (50), 77 (91). IR ($CHCl_3$): 3420 (br), 3020, 2900, 1730, 1590, 1485, 1445, 1370 cm^{-1}. *Anal.* Calcd for $C_{20}H_{21}NO_2$: C 78.15, H 6.89, N 4.56. Found: C 77.90, H 6.95, N 4.33.

3-(2-Chloro-1-hydroxy-1-methylethyl)-1,4-diphenyl-3-vinylazetidin-2-ones (12) and (13). Diastereomeric separable mixture in a ratio of 13/39. **12:** Yield: 41 mg (12%), white solid, mp 159.5-160.5 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 1.58 (s, 3H), 2.50 (br s, 1H), 3.60 (d, *J* = 11.3 Hz, 1H), 3.79 (d, *J* = 11.3 Hz, 1H), 5.05-5.19 (m, 2H), 5.51 (s, 1H), 5.65 (d, *J* = 16.4 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.18-7.32 (m, 9H). ^{13}C NMR (100.62 MHz): δ = 22.1, 52.2, 60.5, 71.9, 73.8, 117.5, 120.6, 124.0, 128.0, 128.3, 128.6, 129.0, 130.4, 134.5, 137.0, 165.4. GC-MS (70 eV); *m/z* (%): 341 (1) [M^+], 249 (9), 248 (9), 181 (90), 180 (65), 129 (45), 77 (100). IR ($CHCl_3$): 3050, 2920, 1740, 1600, 1490, 1380 cm^{-1}. *Anal.* Calcd for $C_{20}H_{20}NO_2Cl$: C 70.27, H 5.90, N 4.10. Found: C 70.30, H 5.89, N 4.07. **13:** Yield: 119.3 mg (35%), white solid, m.p. 147.0-148.0 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 1.44 (s, 3H), 2.95 (br s, 1H), 3.63 (d, *J* = 11.3 Hz, 1H), 4.29 (d, *J* = 11.3 Hz, 1H), 5.05-5.19 (m, 2H), 5.51 (s, 1H), 5.66 (d, *J* = 17.0 Hz, 1H), 7.01 (t, *J* = 7.2 Hz, 1H), 7.15-7.33 (m, 9H). ^{13}C NMR (100.62 MHz): δ = 21.9, 52.2, 60.9, 71.8, 73.1, 117.4, 120.7, 123.9, 127.8, 128.2, 128.6, 128.9, 130.4, 134.4, 137.0, 165.6. GC-MS (70 eV); *m/z* (%): 341 (5) [M^+], 249 (8), 248 (8), 181 (91), 180 (55), 129 (44), 77 (100). IR ($CHCl_3$): 3050, 2920, 1740, 1600, 1490, 1380 cm^{-1}. *Anal.* Calcd for $C_{20}H_{20}NO_2Cl$: C 70.27, H 5.90, N 4.10. Found: C 70.35, H 5.92, N 4.07.

3-Hydroxyphenylmethyl-1,4-diphenyl-3-vinylazetidin-2-ones (14) and (15). Traces of isomers measured by GC-MS spectrum. Isomer I: GC-MS (70 eV); *m/z* (%): 355 (5) [M^+], 249 (10), 181 (40), 180

(35), 130 (90), 77 (100). Isomer II: GC-MS (70 eV); *m/z* (%): 355 (6) [M^+], 249 (10), 181 (45), 180 (40), 130 (85), 77 (100).

3-(3-Hydroxy-3-phenylpropylidene)-1,4-diphenylazetidin-2-ones (16) and (17).

Diastereomeric separable mixture in a ratio of 3/24. **16:** Yield: 10.6 mg (3%), white solid, mp 137.4-138.4 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 1.80 (br s, 1H), 2.26-2.39 (m, 2H), 4.53 (dd, *J* = 7.5, 5.0 Hz, 1H), 5.32 (s, 1H), 6.35 (t, *J* = 7.9 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.20-7.42 (m, 13H). ^{13}C NMR (100.62 MHz): δ = 37.3, 62.9, 73.3, 116.9, 123.8, 124.3, 125.5, 127.1, 127.8, 128.3, 128.8, 129.0, 129.2, 136.7, 137.7, 143.2, 144.2, 161.2. GC-MS (70 eV); *m/z* (%): 355 (4) [M^+], 337 (7), 249 (30), 172 (15), 77 (100). IR ($CHCl_3$): 3480 (br), 3060, 2980, 1725, 1590, 1490, 1365, 1110 cm^{-1}. *Anal.* Calcd for $C_{24}H_{21}NO_2$: C 81.11, H 5.96, N 3.94. Found: C 81.00, H 5.94, N 3.96. **17:** Yield: 78.1 mg (22%), white solid, mp 93.8-94.8 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 2.10 (br s, 1H), 2.80-2.90 (m, 1H), 2.90-3.00 (m, 1H), 4.79-4.89 (m, 1H), 5.29 (s, 1H), 5.64 (m, 1H), 7.01 (t, *J* = 7.3 Hz, 1H), 7.20-7.31 (m, 14H). ^{13}C NMR (100.62 MHz): δ = 38.0, 62.8, 73.2, 116.8, 123.7, 125.6, 125.7, 126.5, 127.3, 127.8, 128.2, 128.4, 128.9, 136.8, 137.7, 143.0, 143.6, 161.5. GC-MS (70 eV); *m/z* (%): 355 (3) [M^+], 337 (4), 249 (85), 172 (43), 128 (36), 77 (100). IR ($CHCl_3$): 3480 (br), 3060, 2980, 1725, 1590, 1490, 1365, 1110 cm^{-1}. *Anal.* Calcd for $C_{24}H_{21}NO_2$: C 81.11, H 5.96, N 3.94. Found: C, 81.50; H 6.00, N 3.91.

3-[Hydroxy-(4-trifluoromethylphenyl)methyl]-1,4-diphenyl-3-vinylazetidin-2-ones (18) and (19).

Diastereomeric separable mixture in a ratio of 23/7. **18:** Yield: 93.1 mg (22%), white solid, mp 179.9-180.5 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 2.88 (br s, 1H), 4.85 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.16 (d, *J* = 10.9 Hz, 1H), 5.25 (s, 1H), 5.52 (s, 1H), 5.68 (d, *J* = 17.5 Hz, 1H), 6.90-6.92 (m, 2H), 7.02-7.08 (m, 1H), 7.20-7.37 (m, 7H), 7.52-7.72 (m, 4H). ^{13}C NMR (100.62 MHz): δ = 59.5, 70.2, 74.9, 117.5, 119.8, 124.1, 125.1, 125.2, 127.4, 127.5, 127.9, 128.1, 128.6, 128.7, 129.0, 134.3, 137.1, 143.4, 166.7. GC-MS (70 eV); *m/z* (%): 423 (<1) [M^+], 249 (5), 181 (32), 180 (34), 130 (100), 115 (32), 77 (67). IR ($CHCl_3$): 3430 (br), 3060, 3000, 2960, 1740, 1590, 1500, 1410, 1370, 1310, 1200 cm^{-1}. *Anal.* Calcd for $C_{25}H_{20}NO_2F_3$: C 70.91, H 4.76, N 3.31. Found: C 70.85, H 4.74, N 3.30. **19:** 29.6 mg (7%), white solid, mp 169.7-170.7 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 2.89 (br s, 1H), 4.76 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.05 (d, *J* = 10.9 Hz, 1H), 5.18 (s, 1H), 5.19 (s, 1H), 5.46 (d, *J* = 17.5 Hz, 1H), 6.50-7.00 (m, 3H), 7.11-7.24 (m, 7H), 7.52-7.60 (m, 4H). ^{13}C NMR (100.62 MHz): δ = 61.7, 69.8, 76.0, 117.4, 120.7, 124.3, 125.1, 125.14, 125.2, 127.3, 128.0, 128.4, 128.7, 129.1, 129.5, 134.0, 137.0, 143.0, 166.4. GC-MS (70 eV); *m/z* (%): 423 (<1) [M^+], 249 (4), 181 (23), 180 (32), 130 (100), 115 (29), 77 (48). IR ($CHCl_3$): 3430 (br), 3060, 3000, 2960, 1740, 1590, 1500, 1410, 1370, 1310, 1200 cm^{-1}. *Anal.* Calcd for $C_{25}H_{20}NO_2F_3$: C 70.91, H 4.76, N 3.31. Found: C 70.79, H 4.75, N 3.33.

3-[3-Hydroxy-3-(4-trifluoromethylphenyl)propylidene]-1,4-diphenylazetidin-2-ones (20) and (21).

Diastereomeric separable mixture in a ratio of 5/36. **20:** Yield: 21.1 mg (5%), white solid, mp 122.3-123.3 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 1.70 (br s, 1H), 2.20-2.34 (m, 2H), 4.49 (dd, *J* = 6.8, 5.5 Hz, 1H), 5.28 (s, 1H), 6.28 (t, *J* = 8.3 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 7.15-7.50 (m, 13H). ^{13}C NMR (100.62 MHz): δ = 37.5, 62.9, 72.6, 117.0, 124.0, 125.4, 125.5, 125.7, 125.9, 127.0, 127.1, 129.0, 129.1, 129.3, 136.6, 137.5, 144.5, 147.2, 161.1. GC-MS (70 eV); *m/z* (%): 423 (<1) [M^+], 405 (2), 355 (2), 337 (7), 249 (79), 172 (40), 77 (100). IR ($CHCl_3$): 3430 (br), 3060, 3000, 2960, 1725, 1590, 1500, 1410, 1370, 1310, 1200 cm^{-1}. *Anal.* Calcd for $C_{25}H_{20}NO_2F_3$: C 70.91, H 4.76, N 3.31. Found: C 70.85, H 4.74, N 3.29. **21:** Yield: 148.1 mg (35%), white solid, mp 94.6-95.4 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ = 1.65 (br s, 1H), 2.83-3.06 (m, 2H), 4.91-5.04 (m, 1H), 5.33 (s, 1H), 5.56-5.63 (m, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 7.20-7.65 (m, 13H). ^{13}C NMR (100.62 MHz): δ = 38.1, 62.9, 72.6, 117.0, 124.1, 125.3, 125.4, 125.9, 126.0, 126.1, 126.6, 128.7, 129.0, 129.1, 136.6, 137.5, 143.8, 147.3, 161.7. GC-MS (70 eV); *m/z* (%): 423 (<1) [M^+], 405 (1), 355 (3), 337 (5), 249 (82), 172 (43), 77 (100). IR ($CHCl_3$): 3430 (br), 3060, 3000, 2960, 1725, 1590, 1500, 1410, 1370, 1310, 1200 cm^{-1}. *Anal.* Calcd for $C_{25}H_{20}NO_2F_3$: C 70.91, H 4.76, N 3.31. Found: C 70.86, H 4.73, N 3.31.

General procedure for the epoxidation. 1 N NaOH (10 mL) was added dropwise to a stirred solution of 1 mmol (341 mg) of **13** in isopropanol (40 mL). The resulting mixture was stirred at rt for 2 h, and quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 1:1) to afford the pure functionalized β-lactams (**22**); yield: 304.2 mg (>99%) .

3-(2-Methyloxiranyl)-1,4-diphenyl-3-vinylazetidin-2-one (22). Yield: 304.2 mg (>99%), oil. ^{1}H NMR (400.13 MHz): δ = 1.50 (s, 3H), 2.70 (d, *J* = 4.8 Hz, 1H), 3.50 (d, *J* = 4.8 Hz, 1H), 5.17-5.31 (m, 3H), 5.60 (d, *J* = 17.0 Hz, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 7.19-7.38 (m, 9H). ^{13}C NMR (100.62 MHz): δ = 19.2, 52.7, 58.5, 62.7, 68.7, 117.5, 119.7, 123.9, 127.4, 128.4, 128.8, 128.9, 130.7, 134.4, 137.1, 164.4. GC-MS (70 eV) m/z (%): 305 (5) [M^+], 181 (76), 180 (73), 143 (20), 129 (40), 128 (35), 77 (100). IR ($CHCl_3$): 3010, 2910, 1740, 1600, 1490, 1380, 1200 cm^{-1}. HRMS calcd for $C_{20}H_{20}NO_2$ 306.14950; found 306.14953.

General procedure for the preparation of the azetidinyl anion. For the NMR spectral measurements, compound (**1** or **2**) (0.1 mmol) were dissolved in 0.5 mL of a mixture of THF/$CDCl_3$ in a ratio of 8/2. A ^{13}C NMR spectral experiment was performed on these solvent mixture. The NMR tube containing the mixture was cooled to –78°C and then *n*-BuLi (2.5 M in hexane, 40 μL, 0.1 mmol) was added to the tube. The mixture was vigorously stirred and placed in to the instrument probe wich was at the constant temperature of 25°C. The ^{13}C NMR spectra were then acquired.

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