Exploring the reactivity of alkylidene malonamides: synthesis of polyfunctionalized isoxazolidinones, aziridines and oxazolines

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Dedicated to Prof. Ferenc Fülöp on the occasion of his 60th anniversary

Abstract
The reactivity of alkylidene malonamides as Michael receptors in the conjugate addition of *N,O*-bis(trimethylsilyl)hydroxylamine has been explored. Due to the presence of several different functionalities that may be selectively transformed, the products of the conjugate addition represent versatile intermediates for the synthesis of isoxazolidinones, aziridines, oxazolines or highly functionalized β-amino-amide derivatives. These novel molecules possessing unusual backbones may be exploited as scaffolds in the preparation of bioactive molecules.

Keywords: Alkylidene malonamides, conjugate addition, isoxazolidinones, aziridines, oxazolines

Introduction

Since the end of the nineteenth century, α,β-unsaturated compounds have been recognized as fundamental starting materials for the simple and economic preparation of polyfunctionalized products.[1] Indeed, their reactivity as Michael acceptors has been extensively explored and a great variety of conjugate addition methodologies have been reported in the literature.[2]

More recently, excellent results have been obtained in the catalytic asymmetric version of the classic classical 1,4- addition with carbon and nitrogen nucleophiles. Nevertheless, the development of an efficient and cheap procedure for this reaction still represents a challenge.[3] Among α,β-unsaturated derivatives, alkylidene malonates and acetoacetates have received

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relatively little attention, even if the presence of a second conjugated carbonyl opens access to further transformations.

The reactivity of these derivatives with nitromethane,[4] hydrazones,[5] indole,[6] lithium carbanions,[7] cuprates,[8] allenyltitanium derivatives,[9] enolates[10] and enamines[11] has been already reported.

As a follow up of our interest on the conjugate addition of hydroxylamino derivatives to α,β-unsaturated compounds,[12] we explored the conjugate addition of *N,O*-bis(trimethylsilyl)hydroxylamine to alkylidene malonates[13] and acetoacetates.[14] This protocol allows the formation of a novel C-N bond in a stereoselective manner, and affords useful intermediates for the preparation of aziridines and isoxazolines.

In this context, small heterocyclic rings can be regarded to as systems of central importance in theoretical, synthetic organic, bio-organic and medicinal chemistry. In particular, aziridines are very useful and interesting building blocks and versatile synthetic intermediates.[15] Furthermore, aziridines are present in a variety of strongly biologically active compounds such as azinomycins A and B,[16] which are potent antitumor as well as antibiotic agents against both Gram-positive and gram-negative bacteria and have been isolated from the fermentation broth of *Streptomyces griseofuscus* S42227. Moreover, the antineoplastic activity of mitomycins A, B, and C,[17] produced by *Streptomyces caespitosus*, is associated with the high reactivity of the strained heterocycle. Finally, some synthetic aziridines show strong activity as enzyme inhibitors,[18] or are versatile intermediates for bioactive compounds. The ring strain of aziridines, which amounts to 26–27 kcal/mol, renders these compounds susceptible to ring opening[19] with excellent stereo- and regiocontrol and allows their use as precursors of a variety of nitrogen containing compounds as substituted alfa, or beta-amino acids, aminoalcohols and β-lactams. On the other hand, five membered heterocycles containing nitrogen and oxygen, such as isoxazolines, isoxazolidines and isoxazolidinones have been used as scaffolds for bioactive synthetic molecules, as chiral auxiliaries and as intermediates for the preparation of amino-alcohols.[20]

As a continuation of our studies on the conjugate addition of hydroxylamino derivatives, we studied the behavior of alkylidene malonamides as substrates and their potential application in the synthesis of aziridines and isoxazolidinones. Only few examples of the reactivity of this particular class of compounds as Michael receptors have so far been presented in the literature.[21] Our synthetic protocol takes advantage of the use of the microwave technology to prepare the unsaturated starting materials by a fast, clean and high-yielding Knövenagel reaction.[22] In the last few years, microwave activation has become a very popular energy source to induce acceleration for a wide range of organic reactions.[23] The possibility to perform transformations under solvent free conditions and the tolerance of highly functionalized molecules to high temperatures for short periods, suggests the usefulness of these technique for fine chemicals industries.

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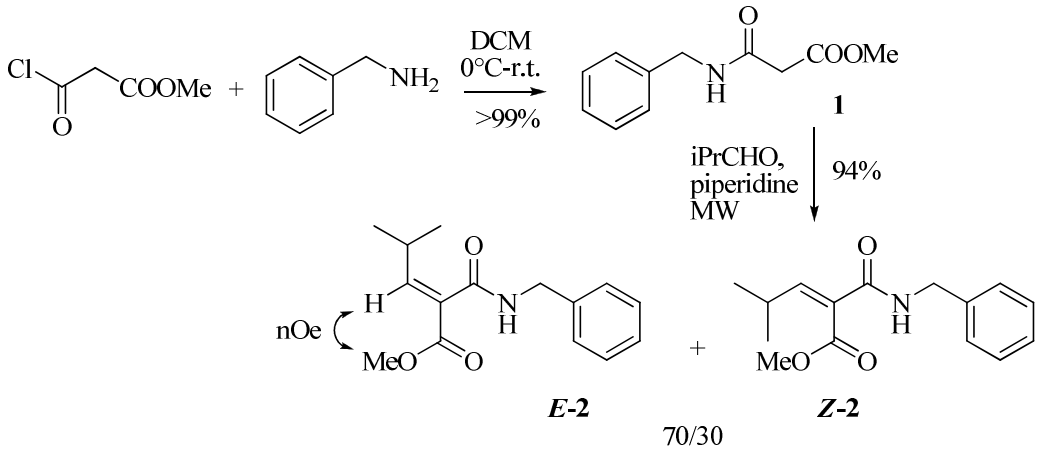
Results and Discussion

The model compound alkylidene malonamide **2** was synthesized as reported in Scheme 1. Coupling of methyl malonyl chloride with benzylamine in DCM afforded malonamide **1** in quantitative yield, as a crystalline yellow solid which was used in the following step without further purification. The Knövenagel condensation with isobutyraldehyde in the presence of 0.25 equiv. of piperidine was performed under microwave irradiation (7.5 minutes, 250 W) without any additional solvent. An excess of the volatile aldehyde (b.p.63°C) was required to reach complete conversion of the starting material. Under these conditions, the alkylidene malonamide **2** was obtained in 94% yield, as a 70/30 mixture of *Z/E* isomers. The two stereoisomers were easily separated by flash chromatography on silica gel and analyzed by nOe NMR experiment to determine the configuration of the double bond. For the major isomer, the enhancement of the vinylic proton upon irradiation of the methyl ester group and the enhancement of the isopropyl protons signals upon irradiation of the benzyl group, allowed to unambiguously attribute the *E* configuration. The same experiment performed on the minor isomer accounted for the Z configuration.



Scheme 1. Synthesis of the alkylidene malonamide **2.**

The conjugate addition of the commercially available of *N,O*-bis(trimethylsilyl)hydroxylamine to compound **2** was performed in the presence of different Lewis acid (Scheme 2). All the reactions were performed in DCM, by addition of the nucleophile to a stirred solution of the alkylidene derivative and in the presence of 5% amount of the catalyst. Diastereoselectivities and yields were determined by NMR/HPLC analysis of the crude reaction mixtures, since any attempt to purify **3** and **4** by flash chromatography failed, due to their degradation both on silica gel or alumina. Some selected results are summarized in Table 1.

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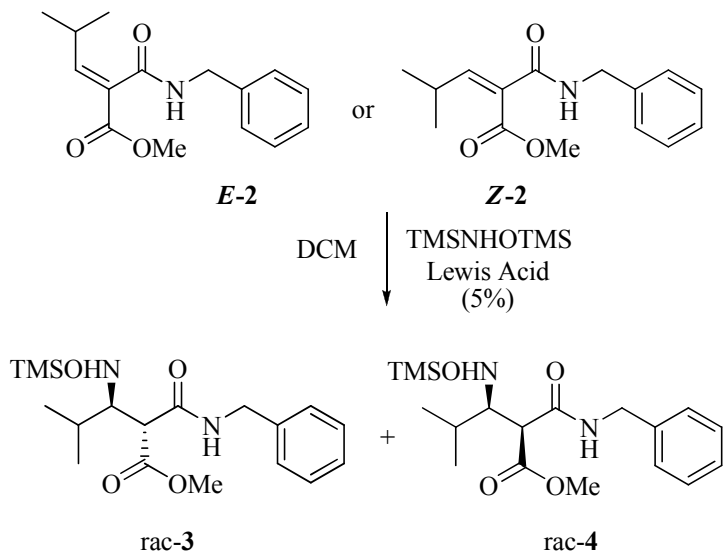

Scheme2. Synthesis of rac-*anti*-**3** and rac-*syn*-**4** by conjugate addition of *N,O*-bis(trimethylsilyl) hydroxylamine to **2**.

Table 1. Lewis acid catalyzed conjugate addition of *N,O*-bis(trimethylsilyl)hydroxylamine to **2**

Entry	**2**	Lewis acid	T (°C)	Time (h)	Yield (%)	d.r. [a]	e.e[b]
1	*E*	/	0	1	83	70/30	/
2	*E*+*Z*	/	0	2	90	70/30	/
3	*E*	$Cu(OTf)_2$	0	1	80	70/30	/
4	*Z*	$Mg(OTf)_2$	0	1	82	60/40	/
5	*Z*	$Mg(ClO_4)_2$	0	0.5	35	65/35	/
6	*Z*	$Mg(ClO_4)_2$	-20	2	94	80/20	/
7	*Z*	$Mg(ClO_4)_2$	-40	3	70	85/15	/
8	*E*	$Sc(OTf)_3$	0	1	/	/	/
9	*E*	$Sc(OTf)_3$	-40	0.5	44	90/10	/
10	*E*+*Z*	$Sc(OTf)_3$	-40	0.5	75	90/10	/
11	*Z*	$Sc(OTf)_3$	-40	1	>99	80/20	/
12	*Z*	$Sc(OTf)_3$	-78	1	88	88/12	/
13	*E*	$Sc(OTf)_3$-**A**	-40	0.5	95	92/8	0
14	*E*	$Sc(OTf)_3$-**A**	-40	0.5	>99	92/8	15
15	*E*	$Sc(OTf)_3$-**A**	-78	0.5	85	95/5	20
16	*E*	$Cu(OTf)_2$-**B**	-40	0.5	/	/	/
17	*E*	$Mg(ClO_4)_2$-**B**	-40	5	92	95/5	3

[a] Calculated on the basis of ^{1}H NMR signals integration in the spectra of the crude reactions. [b] Determined by HPLC on chiral column (Chiralcel OD, isocratic 98/2 hexane/isopropanol, flow 1.0 mL/min).

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The reaction was initially tested without any catalyst at 0°C. Under these conditions good yield could be observed, both starting from the pure *E-2* or from a mixture of *E* and *Z* isomers. In either case, rac-*anti*-**3** and rac-*syn*-**4** could be obtained as 70/30 diastereomeric mixtures (Table 1, entries 1 and 2). The use of $Cu(OTf)_2$, $Mg(OTf)_2$ or $Mg(ClO_4)_2$ as catalysts did not afford better results (entries 3,4 and 5), and similar or lower diastereoselectivities were observed. Since a fast conversion of the starting material to the products took place also in the absence of Lewis acid at 0°C, we performed the reaction at lower temperatures in order to decrease the competitive uncatalyzed process. To this purpose, the reaction catalyzed by $Mg(ClO_4)_2$ was repeated at -20°C and -40°C (Table 1, entries 6 and 7). As expected, the slower reaction led to better diastereomeric ratios (up to 85/15). When the reaction was performed in the presence of $Sc(OTf)_3$, a strong increase in reactivity was observed and only malonamide **1** and trimethyloxyme were isolated at 0°C, as products arising from a retroaldolic rearrangement of the conjugate addition derivatives (entry 8). On the basis of this result, the reaction was repeated at -40°C, either on pure *E* or *Z* isomers or on their mixture (entries 9, 10, 11). The reactions were monitored by thin layer chromatography and were stopped at the appearance of the retroaldolic products. The 1,4-addition on the *E* isomer was then quenched after only thirty minutes when the adducts were formed in a low yield (44%), but with a very good **3/4** distereomeric ratio (90/10). The treatment of the *E*+*Z* mixture under the above reported conditions afforded similar diastereomeric ratios but in a better yield (75%, Table 1, entry 9). When the same protocol was applied to pure *Z* isomer, no trace of the degradation products could be observed after one hour, when complete conversion was achieved. Nevertheless, a decrease in the stereoselectivity was observed since **3** and **4** were obtained in 80/20 ratio. By performing the reaction at -78°C, lower yield was achieved in one hour but an increase in diastereoselectivity was observed (88/12, Table 1, entry 12). Some further attempt were carried out to perform the enantioselective addition in the presence of chiral Lewis acids. The use of (*S,S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine **A** (Figure 1) as ligand for scandium triflate allowed obtaining the adducts in a fast and diastereoselective way, but only with a modest enantiomeric excess. Indeed, no enantioselectivity could be observed when the reaction was performed under the usual conditions. By the same token, only 20% enantiomeric excess was observed when molecular sieves were added to the reaction mixture (Table 1, entries 13,14,15). The reaction catalyzed by copper triflate and (*S*)-(−)-2,2'-isopropylidenebis(4-benzyl-2-oxazoline) **B** (Figure 1) did not afford any product since a retroaldolic rearrangement took place (Table 1, entry 17). On the other hand, by changing the catalyst to magnesium perchlorate, a sluggish conversion of the starting material occurred, giving the products in good yield and diastereoselectivity but without any enantioselectivity (Table 1, entry 17). Enantiomeric excess was determined by HPLC on chiral stationary phase (Chiralcel OD isocratic 98/2 hexane/isopropanol, flow 1.0 mL/min).

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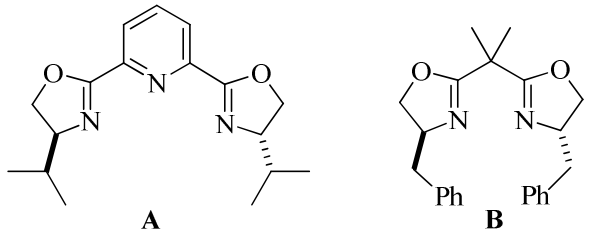
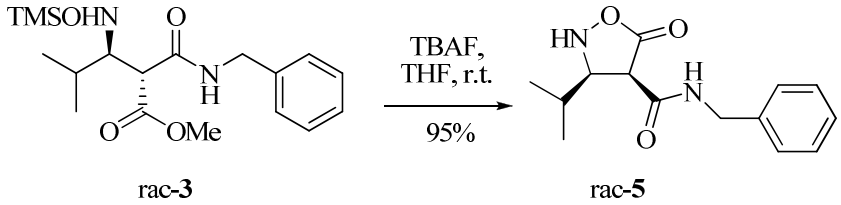


Figure 1. Ligands **A** and **B**.

The 1,4-adducts can be exploited as useful intermediate for the synthesis of heterocyclic compounds, due to the presence of functional groups that may be submitted to further transformations. For instance, a common synthetic route to isoxazolidin-5-ones,[24] involves conjugate addition of hydroxylamino derivatives to unsaturated carbonyl compounds, followed by intramolecular cyclization. This protocol has been investigated in detail by several research groups[25] and has been already applied by us to the transformation of alkylidene malonate adducts.[13a] On these premises, the removal of the trimethylsilyl group was carried out by treatment of **3** with tetrabutylammonium fluoride in THF at room temperature, inducing the cyclization to isoxazolidin-5-one **5** (Yield 95%, Scheme 3). Indeed, the attack of fluoride on silicon leads to the formation of tetrabutylammonium hydroxylamino salt, that promotes the attack on the methyl ester group. The same transformation took place spontaneously when compound **3** was left standing at room temperature for five days. The ^{1}H NMR coupling constant of 5.4 Hz between two protons at 3,4-positions in **5** is consistent with the *cis* configuration,[26] thus confirming the stereochemistry assigned to the adduct **3**.



Scheme 3. Cyclization of **3** to isoxazolidin-5-one **5**.

A most interesting reactivity feature of the silylated adduct is illustrated by its conversion to aziridine dicarboxylate.

Indeed, compound **3** can be considered a precursor of aziridine since the hydroxylamine moiety acts as electrophile during the cyclization to aziridine.[13b,27] Thus, the OTMS group, behaves as a good leaving group, when adjacent to an enolizable position. Moreover, TMSOK acts as a base to induce the cyclization, making it possible to use a sub-stechiometric amount of base.

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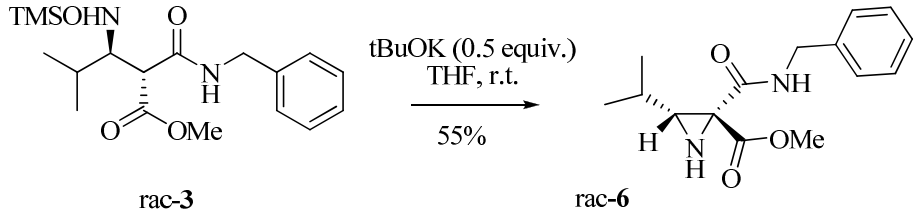
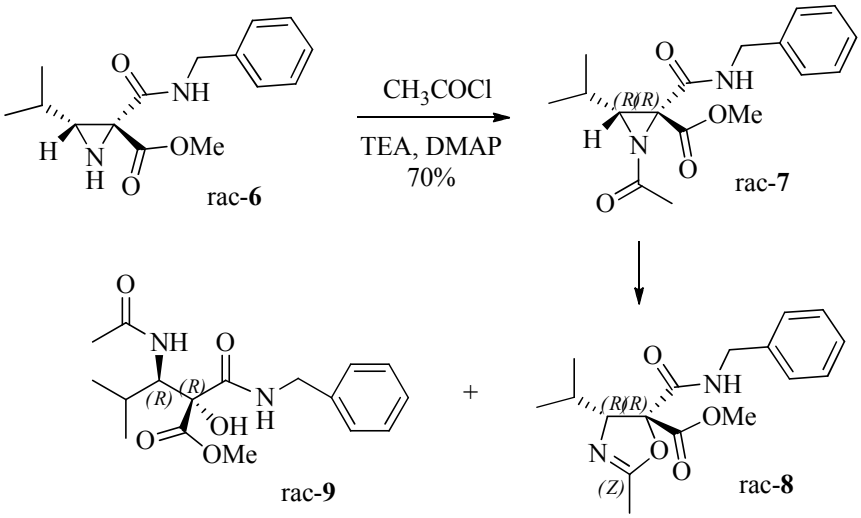


Scheme 4. Cyclization of **3** to aziridine **6**.

Thus, by treatment of **3** with 0.5 equivalents of potassium *tert*-butoxyde in THF, racemic *trans* aziridine **6** was obtained in 55% yield. Several attempts to optimize the reaction conditions (different bases and solvents, higher temperature, microwave activation) did not afford any increase in the yield of isolated aziridine. The relative stereochemistry of *rac*-**6** was assigned on the basis of nOe experiments, showing an enhancement of the methyl ester signal upon irradiation of the hydrogen in position 3. This polyfunctionalized molecule is very stable but may be activated by introducing an electron-withdrawing acyl group at the nitrogen. The ring expansion of acylaziridine to oxazoline is a well known reaction that occurs with retention of configuration of the stereogenic centres, as shown by chemical evidence and ab initio calculations.[28] To this purpose, acetylation with acetyl chloride, TEA and DMAP was carried out and aziridine **7** was isolated in 70% yield after purification by flash chromatography on silica gel (Scheme 5, table 2). Spontaneous rearrangement to oxazoline **8**[29] was be observed in chloroform after one week (Table 2, entry 1). Nevertheless, a faster transformation could be induced by a Lewis acid such as $BF_3 \cdot Et_2O$ both at room temperature or under microwave assisted conditions (Table 2, entries 2 and 3). This rearrangement induces the formation of a crowded quaternary centre and for this reason partial hydrolysis of **8** to the corresponding *N*-acetyl-α-hydroxy-β-amino derivative **9** could not be avoided in the presence of moisture.



Scheme 5. Acylation of **6** , ring expansion to **8** and hydrolysis to **9**.

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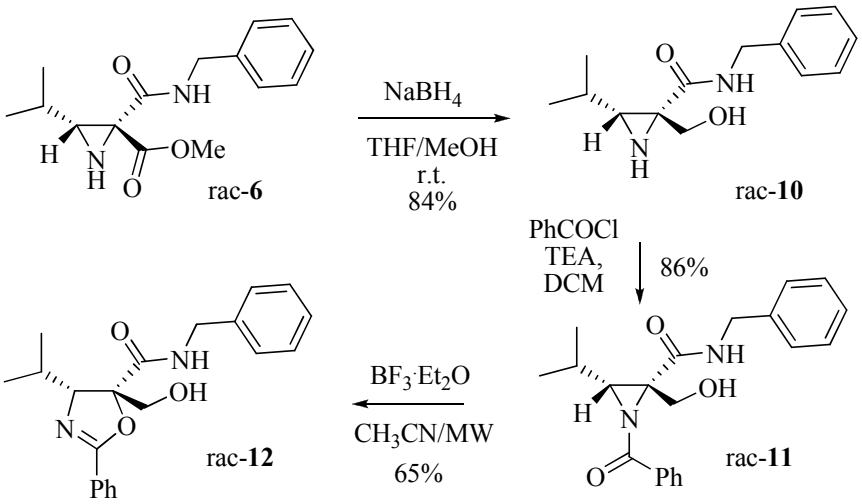
Table 2. Ring expansion of N-acetyl-aziridine **7** to oxazoline **8** and *N*-acetyl-α-hydroxy-β-amino derivative **9**

Entry	Solvent	Catalysis	time	**8**(%)	**9** (%)
1	$CHCl_3$	/	7 days	66	22
2	CH_3CN	$BF_3{\cdot}Et_2O$	1 day	42	40
3	CH_3CN	$BF_3{\cdot}Et_2O$/MW	10 minutes	63	26

To further explore the reactivity of aziridine **6**, we treated it with $NaBH_4$ in 8:2 THF/MeOH at 0 °C. Under these conditions complete reduction of the methyl ester group to primary alcohol occurred and derivative **10** was isolated by flash chromatography on silica gel in 84% yield. Activation of the aziridine ring by acylation of the nitrogen, followed by further treatment with $BF_3{\cdot}Et_2O$ under microwave assisted conditions, induced the ring expansion to oxazoline **12**, isolated in 65% yield (Scheme 6).



Scheme 6. Synthesis of aziridine-alcohol **10** and ring expansion to **12**.

Conclusions

The behavior of alkylidene malonamides in the conjugate addition of *N,O*-bis(trimethylsilyl)hydroxylamine has been investigated under different reaction conditions. Thanks to the presence of several different functionalities that may be selectively transformed, the obtained adducts represent versatile building blocks. Some representative transformations to isoxazolidinones, aziridines, oxazolines or highly functionalized β-amino-acid derivatives have been successfully performed. These novel molecules possessing unusual backbones may be exploited as scaffolds in the preparation of bioactive molecules. Work is in progress to introduce such unusual bioactive structures.

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Experimental Section

General. All chemicals were purchased from commercial suppliers and used without further purification. Anhydrous solvents were purchased in sure seal bottles over molecular sieves and used without further drying. Flash chromatography was performed on silica gel (230-400 mesh). DOWEX® 50WX2-200(H) ion exchange resin was used for purification of free amino acids. NMR Spectra were recorded with Varian Gemini 200, Gemini 300, Mercury Plus 400 or Unity Inova 600 MHz spectrometers. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of $CDCl_3$ set at δ = 7.27 (^{1}H NMR) or δ = 77.0 (^{13}C NMR), CD_3OD set at δ = 3.31 (1H NMR) or δ = 49.0 (^{13}C NMR), D_2O set at δ = 4.79 (1H NMR). Coupling constants are given in Hz. The enantiomeric excesses of products were determined by HPLC analyses performed on an HP1100 instrument with UV-VIS detector. LC-MS analyses was performed on a HP1100 liquid chromatograph coupled with an electrospray ionization-mass spectrometer (LC-ESI-MS), using H_2O/CH_3CN as solvent at 25 °C (positive scan 100-500 m/z, fragmentor 70V). Microwave-assisted reactions were performed with a Milestone Mycrosynth multimode apparatus, keeping irradiation power fixed and monitoring internal reaction temperature with a built-in ATC-FO advanced fiber optic automatic temperature control. The reactions were performed in an open vessel, equipped with a refrigerator connected to a fume hood.

Methyl 3-(benzylamino)-3-oxopropanoate (1). To a stirred solution of methylmalonyl chloride (10 mmol, 1.1 mL) in dry DCM (10 mL) at 0 °C, benzylamine (2 equiv., 20 mmol, 2.18 mL) was added dropwise. After 1.5h, the reaction was diluted with DCM (10 mL) and then washed twice with acidic water (0.1 M solution of HCl, 10 ml). The organic layers were dried with Na_2SO_4 and solvent was removed under reduced pressure. Amide **1** was obtained in quantitative yield as a yellow solid. After crystallization from diethyl ether, a white crystalline powder was isolated in 82% yield.

1. ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 3.38 (2H, s, CO-C*H*$_2$-CO), 3.75 (3H, s, OC*H*$_3$), 4.49 (2H, d, $^3J_{HH}$ = 5.6 Hz, C*H*$_2$Ph), 7.28-7.35 (5H, m, Ph), 7.45 (1H, bs, NH). ^{13}C NMR (50 MHz, $CDCl_3$): 34.2, 45.1, 51.2, 126.9, 127.9, 128.5, 137.4, 166.4, 168.3. GC-MS r.t 18.2 min *m/z*: 207 [M].

Methyl 2-(benzylcarbamoyl)-4-methylpent-2-enoate (2). A mixture of amide **1** (8 mmol, 1.65 g), isobutyraldehyde (5 equiv., 40 mmol, 3.7 mL) and piperidine (0.25 equiv., 2 mmol, 0.2 mL) was submitted to microwave irradiation (7.5 minutes, 250 W). The residue was then diluted with DCM (15 mL) and washed twice with acidic water (0.1 M solution of HCl, 10 ml). The organic layers were dried with Na_2SO_4 and solvent was removed under reduced pressure. The mixture of E/Z isomers was separated by flash chromatography on silica gel (cyclohexane/ethyl acetate 8:2 as eluent).

(*E*)-**2.** White solid, 66% yield, mp 72-74 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.04 (6H, d, $^3J_{HH}$ = 6.6 Hz, C*H*$_3$-CH-C*H*$_3$), 3.30 (1H, m, CH$_3$-C*H*-CH$_3$), 3.75 (3H, s, OC*H*$_3$), 4.53 (2H, d, $^3J_{HH}$ = 5.4 Hz, C*H*$_2$Ph), 6.94 (1H, d, , $^3J_{HH}$ = 10.2 Hz, C*H*=C), 7.25-7.40 (6H, m, NH + Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 21.7 (2CH$_3$), 29.2 (CH), 43.6 (CH$_2$), 51.8 (CH$_3$), 123.6 (C), 127.0 (CH), 127.4

(CH), 128.3 (CH), 138.0 (C), 160.6 (CH), 163.1 (C), 167.9(C). LC-MS r.t 8.5 min m/z: 262 [M+1].

(*Z*)-**2.** White oil, 28% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.09 (6H, d, $^3J_{HH}$ = 6.6 Hz, C*H*$_3$-CH-C*H*$_3$), 3.08 (1H, m, CH$_3$-C*H*-CH$_3$), 3.84 (3H, s, OC*H*$_3$), 4.54 (2H, d, $^3J_{HH}$ = 5.7 Hz, C*H*$_2$Ph), 7.25-7.39 (6H, m, CH=C + Ph), 8.18 (1H, bs,NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 21.9 (2CH$_3$), 28.9 (CH), 43.4 (CH$_2$), 52.3 (CH$_3$), 125.7 (C), 127.3 (CH), 127.6 (CH), 128.6 (CH), 138.0 (C), 160.0 (CH), 164.2 (C), 166.5(C). LC-MS r.t 7.4 min *m/z*: 262 [M+1].

General procedure for the 1,4 addition of N,O-bis(trimethylsilyl)hydroxylamine to compound (2)

Lewis acid (0.25 mmol) was added to a stirred solution of isopropylidene malonamide 2 (5 mmol, 1.3 g) in dry DCM (25 mL) at the temperature of choice. After ten minutes, *N,O*-bis(trimethylsilyl)hydroxylamine (2.2 equiv., 11 mmol, 2.35 mL) was added dropwise and the solution was monitored by TLC and quenched with water (20 mL) at appearance of degradation products. After washing twice with water (20 mL), the organic layer was dried with Na_2SO_4 and solvent was removed under reduced pressure. Compounds **3** and **4** were obtained as yellow oil with the yield reported in Table 1 and were used in the following step without further purification.

(**3**+**4**). White oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.13 (9H, s, (CH$_3$)$_3$Si), 0.99 (3H, d, $^3J_{HH}$ = 6.6 Hz, C*H*$_3$-CH-CH$_3$), 1.00 (3H, d, $^3J_{HH}$ = 6.6 Hz, CH$_3$-CH-C*H*$_3$), 1.89 (1H, m, CH$_3$-C*H*-CH$_3$), 3.32 (1H, s, C*H*-NHO), 3.65 (1H, d, $^3J_{HH}$ = 4.6 Hz, CO-C*H*-CO isomer **4**), 3.76 (3H, s, OC*H*$_3$), 3.82 (1H, d, $^3J_{HH}$ = 5.7 Hz, CO-C*H*-CO isomer **3**), 4.49 (2H, m , C*H*$_2$Ph), 5.80 (1H, bd, NH), 7.29-7.37 (5H, m, Ph), 7.86 (1H, bt, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C -1.5 (3CH$_3$), 17.2 (CH$_3$),19.9 (CH$_3$), 28.3 (CH), 42.8 (CH$_2$), 51.4 (CH$_3$), 52.5 (CH), 67.6 (CH), 126.6 (CH), 126.8 (CH), 127.8 (CH), 137.6 (C), 167.3 (CH), 171.2(C). LC-MS r.t. 11.0 min (isomer **3**), 11.3 min (isomer **4**) *m/z*: 367 [M+1], 755 [2M+Na]. HPLC on chiral column: Chiralcel OD of isomer **3**, isocratic 98/2 hexane/isopropanol, flow 1.0 mL/min, r.t. 10.1 min – 16.7 min.

Cis-N-benzyl-3-isopropyl-5-oxoisoxazolidine-4-carboxamide (5). Tetrabutylammonium fluoride (2 equiv., 1.5 g) was added to a solution of 3 (3 mmol, 0.92 g) in THF at room temperature. The solution was stirred overnight and then the solvent was removed under reduced pressure. The residue was diluted with diethyl ether (10 mL) and washed twice with water (10 ml). The organic layers were dried with Na_2SO_4 and solvent was removed under reduced pressure. Isoxazolidinone **5** was obtained in 95% yield after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 8:2).

5. White oil, 95% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.99 (3H, d, $^3J_{HH}$ = 6.9 Hz, C*H*$_3$-CH-CH$_3$), 1.02 (3H, d, $^3J_{HH}$ = 6.9 Hz, CH$_3$-CH-C*H*$_3$), 1.89 (1H, m, CH$_3$-C*H*-CH$_3$), 3.41 (1H, d, $^3J_{HH}$ = 5.4 Hz CO-C*H*-CO), 3.97 (1H, m, C*H*-NHO), 4.45 (2H,d, $^3J_{HH}$ = 5.7 Hz, C*H*$_2$-Ph), 6.92 (1H,bs, NH), 7.24-7.36 (6H, m, NH + Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 19.5, 19.7, 25.4, 41.1, 43.1, 51.9, 126.9, 127.0, 128.2, 137.7, 165.3, 169.0. HPLC on chiral column: Chiralcel OD, isocratic 90/10 hexane/isopropanol, flow 0.8 mL/min, r.t. 18.0 min – 26.9 min

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Trans-Methyl 2-(benzylcarbamoyl)-3-isopropylaziridine-2-carboxylate (6). To a stirred solution of **3** (3 mmol, 0.92 g) in dry THF (15 mL) at room temperature, potassium terbutoxyde (0.5 equiv., 1.5 mmol, 173 mg) was added in one portion. After 3h, the solvent was removed under reduced pressure and the residue was diluted with diethyl ether (10 mL) and then washed twice with water (10 ml). The organic layers were dried with Na_2SO_4 and solvent was removed under reduced pressure. Aziridine **6** was obtained in 55% yield after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 7:3).

6. White oil, 55% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.92 (3H, d, $^3J_{HH}$ = 6.9 Hz, C*H*$_3$-CH-CH$_3$), 1.12 (3H, d, $^3J_{HH}$ = 6.9 Hz, CH$_3$-CH-C*H*$_3$), 1.36 (1H, m, CH$_3$-C*H*-CH$_3$), 2.18 (1H, d, $^3J_{HH}$ = 9.3 Hz C*H*-NH-C), 2.40 (1H, bs, NH), 3.81 (3H, s, OC*H*$_3$), 4.47 (1H,dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 5.7 Hz, C*H*$_2$-Ph), 4.57 (1H,dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 6.3 Hz, C*H*$_2$-Ph), 7.27-7.39 (5H, m, Ph), 8.51 (1H, bt, NH). ^{13}C NMR (100 MHz, $CDCl_3$)): δ_C 19.3 (CH$_3$), 20.8 (CH$_3$), 28.8 (CH), 44.3 (CH$_2$), 52.9 (CH$_3$), 53.7 (CH), 60.2 (CH), 127.5 (3CH), 128.7 (CH), 137.6 (C), 166.3 (CH), 171.1(C). LC-MS r.t. 7.39 min *m/z*: 277 [M+1], 575 [2M+Na].

Methyl 1-acetyl-2-(benzylcarbamoyl)-3-isopropylaziridine-2-carboxylate (7). Acetyl chloride (1.5 equiv., 1.5 mmol, 0.106 mL), TEA (1.5 equiv., 1.5 mmol, 0.210 mL) and a catalytic amount of DMAP (0.1 mmol, 0.122 g) were added to a stirred solution of **6** (1 mmol, 0.276 g) in dry DCM (10 mL). After 3h, the reaction was quenched by addition of water (10 mL) and diluted with DCM (10 mL) The organic layer was washed twice with water (10 mL), dried with Na_2SO_4 and solvent was removed under reduced pressure. Aziridine **7** was obtained in 70% yield after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 8:2).

7. Yellow oil, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.97 (3H, d, $^3J_{HH}$ = 6.8 Hz, C*H*$_3$-CH-CH$_3$), 1.12 (3H, d, $^3J_{HH}$ = 6.8 Hz, CH$_3$-CH-C*H*$_3$), 1.43 (1H, m, CH$_3$-C*H*-CH$_3$), 2.15 (3H, s, CO-CH$_3$), 2.85 (1H, d, $^3J_{HH}$ = 9.6 Hz C*H*-N-CO), 3.84 (3H, s, OC*H*$_3$), 4.46 (1H,dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 5.6 Hz, C*H*$_2$-Ph), 4.54 (1H,dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 6.0 Hz, C*H*$_2$-Ph), 7.26-7.37 (5H, m, Ph), 8.17 (1H, bt, NH). LC-MS r.t. 7.47 min m/z: 319 [M+1], 341 [M+Na], 659 [2M+Na].

Procedure for the microwave assisted ring expansion of aziridine (7). To a stirred solution of 7 (1 mmol, 0.318 g) in acetonitrile (5 mL), $BF_3 \cdot Et_2O$ (1 equiv., 1 mmol, 0.125 mL) was added in one portion. The mixture was submitted to microwave irradiation (250 W, 10 minutes) and then was diluted with EtOAc (10 mL). The organic layer was washed twice with water (10 mL), dried with Na_2SO_4 and solvent was removed under reduced pressure. Oxazoline **8** and compound **9** were separated by flash chromatography on silica gel (cyclohexane/EtOAc, 8:2).

Methyl 5-(benzylcarbamoyl)-4-isopropyl-2-methyl-4,5-dihydrooxazole-5-carboxylate (8). (Yellow oil, 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.03 (3H, d, $^3J_{HH}$ = 6.6 Hz, C*H*$_3$-CH-CH$_3$), 1.15 (3H, d, $^3J_{HH}$ = 6.6 Hz, CH$_3$-CH-C*H*$_3$), 1.70 (1H, m, CH$_3$-C*H*-CH$_3$), 2.06 (3H, s, OC-CH$_3$), 3.73 (3H, s, OC*H*$_3$), 4.48 (2H, m, C*H*$_2$-Ph), 5.18 (1H, d, $^3J_{HH}$ = 7.0 Hz C*H*-N=C), 7.28-7.34 (5H, m, Ph), 9.10 (1H, bt, NH). LC-MS r.t. 10.1 min *m/z*: 319 [M+1], 341 [M+Na], 659 [2M+Na].

Methyl 3-acetamido-2-(benzylcarbamoyl)-2-hydroxy-4-methylpentanoate (9). Yellow oil, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.97 (3H, d, $^3J_{HH}$ = 7.0 Hz, C*H*$_3$-CH-CH$_3$), 1.15 (3H,

d, $^3J_{HH}$ = 7.0 Hz, CH_3-CH-C*H*$_3$), 1.40 (1H, m, CH_3-C*H*-CH_3), 2.19 (3H, s, OC-CH_3), 3.84 (3H, s, OC*H*$_3$), 4.47 (2H, m, C*H*$_2$-Ph), 4.96 (1H, m, C*H*-NH-CO), 6.92 (d, $^3J_{HH}$ = 6.2 Hz, NH) 1H, 7.26-7.35 (5H, m, Ph), 8.19 (1H, bt, NH). ^{13}C NMR (100 MHz, $CDCl_3$)): δ_C 22.6 (2CH_3), 23.8 (CH), 43.9 (CH_2), 53.1 (CH_3), 56.7 (CH), 90.2 (C), 127.1 (3CH), 127.5 (CH), 128.7 (CH), 137.2 (C), 164.9 (C), 168.3 (C), 171.3 (C). LC-MS r.t. 8.1 min *m/z*: 337 [M+1].

***N*-Benzyl-2-(hydroxymethyl)-3-isopropylaziridine-2-carboxamide (10).** Aziridine **6** (1 mmol, 0.276 mg) was added to a solution of $NaBH_4$ (1.5 equiv., 56 mg) in THF/MeOH (10 mL, 8/2) at 0 °C. The mixture was left stirring at room temperature for 2h and then THf was removed under reduced pressure. The residue was diluted with EtOAc (10 mL) and washed twice with water (10 mL), After drying with Na_2SO_4, solvent was removed under reduced pressure. Purification by flash chromatography on silica gel afforded **10** in 84% yield.

10. Yellow oil, 84% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.04 (3H, d, $^3J_{HH}$ = 6.6 Hz, C*H*$_3$-CH-CH_3), 1.09 (3H, d, $^3J_{HH}$ = 6.6 Hz, CH_3-CH-C*H*$_3$), 1.39 (1H, m, CH_3-C*H*-CH_3), 2.03 (1H, d, $^3J_{HH}$ = 9.6 Hz C*H*-N-CO), 3.77 (1H,d, $^2J_{HH}$ = 12.0 Hz, C*H*$_2$-OH), 3.96 (1H,d, $^2J_{HH}$ = 12.0 Hz, C*H*$_2$-OH), 4.46 (1H,dd, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 5.7 Hz, C*H*$_2$-Ph), 4.54 (1H,dd, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 5.7 Hz, C*H*$_2$-Ph), 7.28-7.39 (5H, m, Ph), 7.80 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.4 (CH_3), 21.1 (CH_3), 28.3 (CH), 43.2 (C), 43.7 (CH_2), 50.0 (CH), 61.2 (CH_2), 127.4 (3CH), 128.7 (2CH), 137.9 (C), 172.2(C). LC-MS r.t. 5.52 min *m/z*: 249 [M+1], 519 [2M+Na].

1-Benzoyl-*N*-benzyl-2-(hydroxymethyl)-3-isopropylaziridine-2-carboxamide (11). Benzoyl chloride (1.5 equiv., 1.5 mmol, 0.174 mL) and TEA (1.5 equiv., 1.5 mmol, 0.210 mL) were added to a stirred solution of **10** (1mmol, 0.248 g) in dry DCM (10 mL). After 3h, the reaction was quenched by addition of water (10 mL) and diluted with DCM (10 mL) The organic layer was washed twice with water (10 mL), dried with Na_2SO_4 and solvent was removed under reduced pressure. Aziridine **11** was obtained in 86% yield after purification by flash chromatography on silica gel (cyclohexane/EtOAc, 9:1).

11. Yellow oil, 86% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.05 (3H, d, $^3J_{HH}$ = 6.6 Hz, C*H*$_3$-CH-CH_3), 1.18 (3H, d, $^3J_{HH}$ = 6.6 Hz, CH_3-CH-C*H*$_3$), 1.62 (1H, m, CH_3-C*H*-CH_3), 2.92 (1H, d, $^3J_{HH}$ = 9.9 Hz C*H*-N-CO), 4.10 (1H,d, $^2J_{HH}$ = 11.7 Hz, C*H*$_2$-OH), 4.14 (1H,dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 5.1 Hz, C*H*$_2$-Ph), 4.22 (1H,d, $^2J_{HH}$ = 11.7 Hz, C*H*$_2$-OH), 4.40 (1H,dd, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 6.3 Hz, C*H*$_2$-Ph), 6.92 (1H, m, Ph), 7.20-7.62 (7H, m, Ph), 7.83 (1H, bs, NH), 7.91-7.94 (2H, m, Ph).

N-benzyl-5-(hydroxymethyl)-4-isopropyl-2-phenyl-4,5-dihydrooxazole-5-carboxamide (12). To a stirred solution of 11 (1 mmol, 0.354 g) in acetonitrile (5 mL), $BF_3{\cdot}Et_2O$ (1 equiv., 1 mmol, 0.125 mL) was added in one portion. The mixture was submitted to microwave irradiation (250 W, 10 minutes) and then was diluted with EtOAc (10 mL). The organic layer was washed twice with water (10 mL), dried with Na_2SO_4 and solvent was removed under reduced pressure. Oxazoline **12** was obtained in 65% by flash chromatography on silica gel (cyclohexane/EtOAc, 9:1).

12. Yellow oil, 65% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.75 (3H, d, $^3J_{HH}$ = 7.0 Hz, C*H*$_3$-CH-CH_3), 1.17 (3H, d, $^3J_{HH}$ = 7.0 Hz, CH_3-CH-C*H*$_3$), 2.30 (1H, m, CH_3-C*H*-CH_3), 3.30 (1H, bs,

OH), 3.82 (1H, d, $^2J_{HH}$ = 11.6 Hz CH_2-OH), 3.97 (1H,d, $^2J_{HH}$ = 11.6 Hz,), 4.19 (1H, d, $^3J_{HH}$ = 5.1 Hz, CH-N), 4.51 (2H,m, CH_2-Ph), 6.97 (1H, bt, NH), 7.20-7.60 (8H, m, Ph), 7.90-7.98 (2H, m, Ph).

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