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Intramolecular Palladium-Catalyzed Aminocarboxylation of Olefins as a Direct Route to Bicyclic Oxazolidinones

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Abstract: An efficient, direct synthesis of oxazolidinones fused to six-membered heterocyclic rings starting from carbamate-protected aminoalkenes has been developed. This procedure is based on an oxidative palladium(II)-catalyzed reaction performed in the presence of stoichiometric copper chloride, which is determinant to promote the formation of the bicyclic product and prevent the isolation of the monocyclic amination product. Oxazolidinone compounds arise from a domino aminocarboxylation process through the direct intervention of the carbamate oxygen after the initial palladium-promoted transfer of the nitrogen atom on the C=C double bond.

Keywords: amination; carboxylation; domino reactions; nitrogen heterocycles; palladium

Introduction

Nitrogen-containing heterocycles are widely present in natural and synthetic compounds endowed with biological and pharmaceutical properties.[1] As a consequence, the development of synthetic procedures for the construction of mono- and polycyclic skeletons containing one or more nitrogen atoms represents a continuous goal in organic synthesis. Among the most investigated approaches that rely on amination reactions, palladium-catalyzed processes occupy a prominent role.[2] For instance, the Pd-catalyzed coupling of aryl halides with various amines, pioneered by the groups of both Buchwald and Hartwig,[3] have been broadly exploited to synthesize different kinds of pharmaceutical compounds.[4] On the other hand, oxidative Pd-catalyzed reactions, which enable direct amination of C=C double bonds, have been the main focus in recent years.[5] In this latter field, notwithstanding their rarity in the literature, particularly appealing are the domino processes such as carboaminations,[6] diaminations,[7] oxoaminations[8] and aminohalogenations[9] of alkenes, that allow an easy access to (poly)functionalized compounds or to bicyclic ring systems.

Over the last decade, studies in our laboratory have been concentrated on the synthesis of complex heteropolycyclic nitrogen-containing compounds by means of intramolecular Pd-catalyzed procedures,[10] involving also reactions in oxidative conditions onto multiple carbon-carbon bonds.[11] Herein, we report a direct, one-step synthesis of oxazolidinones fused to six-membered heterocyclic rings by a domino aminocarboxylation reaction on allylamides of *N*-alkoxycarbonyl-protected α-amino acids under oxidative conditions.

Our work plan relies on the use of a carbamate group as oxygen source to build directly a carbon-oxygen bond in Pd-catalyzed reactions. This is predictably reasonable according to (i) the well known behaviour of the carbonyl oxygen as nucleophile in such reactions[12] and (ii) the Au-catalyzed procedures aimed at the synthesis of oxazolidinones involving *tert*-butyl carbamates, already described in the literature.[13] In our case, the carbonyl group would have to intervene on a σ-alkyl-palladium complex generated *in situ* subsequently to direct amination of an alkene (Figure 1).

The oxazolidinone skeleton is found in several drug-like molecules (Figure 2).[14] Moreover, it also deserves interest from the synthetic point of view, being able to act as a precursor of 1,2-amino alcohols,[15] which in turn are prevalent motifs in a diverse range of important natural and pharmaceutical prod-

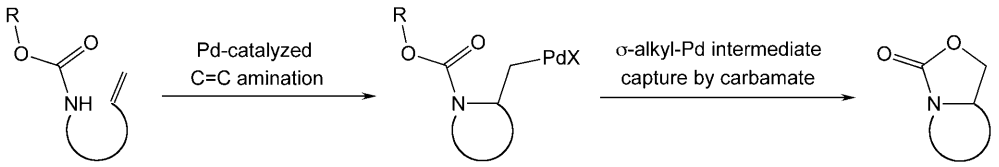


Figure 1. Approach to a Pd-catalyzed synthesis of bicyclic oxazolidinones involving a carbamate group.

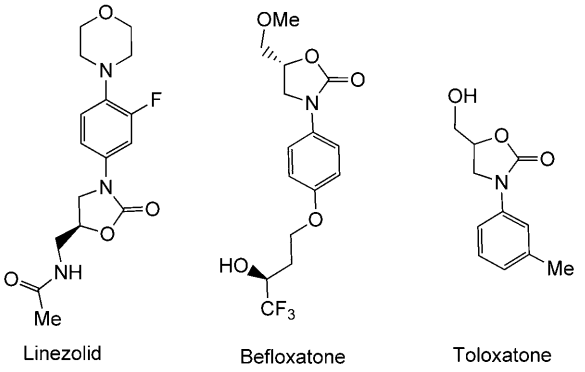
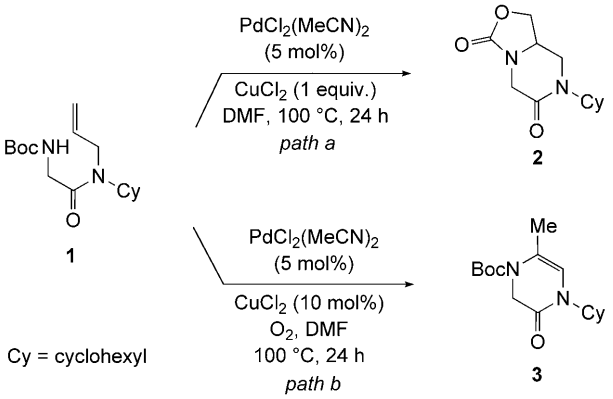


Figure 2. Examples of biologically active compounds containing oxazolidinone skeleton.



Scheme 1. Aminocarboxylation *vs.* amination process.

ucts. Several procedures for the formation of oxazolidinones have been already reported,[16] some of which featuring an intramolecular Pd-catalyzed amination of *O*-allyl or *O*-homoallyl carbamates.[8a,9a,b,15a,17] Conversely, our approach allows the construction of the oxazolidinone ring from easily accessible carbamate-protected aminoalkenes, with the simultaneous formation of a fused-heterocycle ring.

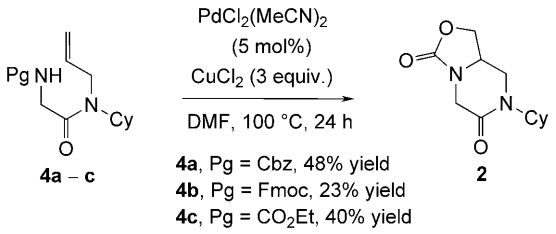
Results and Discussion

In order to evaluate the feasibility of the aminocarboxylation reaction, we selected Boc-glycine *N*-allyl-*N*-cyclohexyl-amide (**1**) as a model substrate, on which a survey of the activity of different catalysts and oxidants was undertaken. At the outset of our screening, we tested two different catalytic systems based on the use of $PdCl_2(MeCN)_2$ as catalyst coupled with $CuCl_2$, which revealed a remarkable role as oxidant. Indeed, $CuCl_2$ was able to promote the divergent formation of two cyclization products, depending solely on its amount, catalytic *vs.* stoichiometric. In particular, compound **2** was obtained using $PdCl_2(MeCN)_2$ (5 mol%) and a stoichiometric amount of $CuCl_2$ in DMF at 100 °C (Scheme 1, *path a*); i.e., the domino product was obtained through the planned aminocarboxylative process based on an initial carbon-nitrogen bond formation, followed by an intramolecular carboxylation reaction, involving the *tert*-butoxycarbonyl group.

Conversely, treatment of the allylamide **1** with $PdCl_2(MeCN)_2$ (5 mol%) and $CuCl_2$ (10 mol%)/O_2 as the oxidant system in DMF at 100 °C resulted in the dihydropyrazinone derivative **3**, arising from a 6-*exo*-trig cyclization, followed by a β-hydride elimination from the Pd(II) intermediate, and double bond isomerization of the *exo*-methylene product (Scheme 1, *path b*). This result represents an alternative route to the already reported Pd-catalyzed procedures to access the piperazine ring.[18]

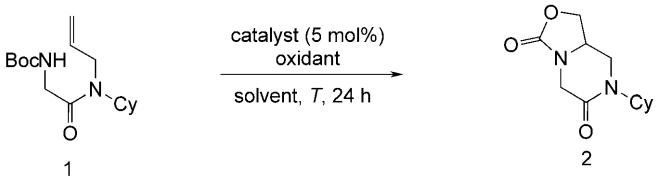
Gratified by the effective conversion of **1** into bicyclic oxazolidin-2-one **2**, which represents a much more valuable result than the simple amination process, we then focused our efforts to optimize the conditions for the aminocarboxylation process.

As apparent from Table 1, an excess of $CuCl_2$ yielded **2** in higher amounts (entry 2 *vs.* 1). Both palladium and cupric chloride were required, since the conversion of **1** was precluded by the removal of $PdCl_2(MeCN)_2$ as well as by the use of other oxidants



Scheme 2. Aminocarboxylation of different carbamates.

Table 1. Optimization of the aminocarboxylation reaction conditions.



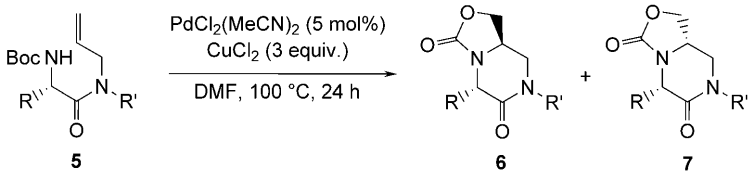
Entry	Catalyst	Oxidant (equiv.)	Solvent	T [°C]	Yield [%][a]
1	$PdCl_2(MeCN)_2$	$CuCl_2$ (1)	DMF	100	69
2	$PdCl_2(MeCN)_2$	$CuCl_2$ (3)	DMF	100	81
3	–	$CuCl_2$ (3)	DMF	100	n.r.
4	$PdCl_2(MeCN)_2$	$Cu(OAc)_2$ (3)	DMF	100	n.r.
5	$PdCl_2(MeCN)_2$	1,4-BQ (2)	DMF	100	n.r.
6	$PdCl_2(MeCN)_2$	$PhI(OAc)_2$ (3)	DMF	100	traces
7	$PdCl_2(MeCN)_2$	$CuCl_2$ (3)	DMF	r.t.	64
8	$PdCl_2(MeCN)_2$	$CuCl_2$ (3)	THF	reflux	40
9	$PdCl_2(MeCN)_2$	$CuCl_2$ (3)	CH_2Cl_2	reflux	26
10	$PdCl_2(MeCN)_2$	$CuCl_2$ (3)	Toluene	80	n.r.
11	$Pd(OAc)_2$	$Cu(OAc)_2$ (3)	DMF	100	n.r.
12	$Pd(OAc)_2$	1,4-BQ (2)	DMF	100	n.r.

[a] Isolated yield.

such as $Cu(OAc)_2$, 1,4-benzoquinone, or $PhI(OAc)_2$ (entries 3–6). Similar yields were obtained by running the reaction in an open vessel or under a nitrogen atmosphere. The reaction occurred also at room temperature, but the yield of **2** was somehow lower (entry 7). Further screening of different solvents proved to be unfruitful to improve the yields or to gain milder conditions (entries 8–10). When using other typical catalyst systems based on a different source of palladium, namely $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$ or 1,4-benzoquinone, no conversion took place (entries 11 and 12). It is worth mentioning that the formation of the intramolecular amination product **3** was never observed using $CuCl_2$ in stoichiometric or excess amounts.

Then, we investigated the feasibility of this domino reaction on allylamides of α-amino acids bearing different *N*-alkoxycarbonyl groups. As depicted in Scheme 2, the oxazolidin-2-one **2** is accessible also from a variety of alkenyl carbamates. In fact, when Cbz-, Fmoc- and ethoxycarbonyl-glycine amides **4a–c** were subjected to the optimized reaction conditions

Table 2. Scope of the aminocarboxylation reaction.



Entry	R	R′	*dr* (**6**/**7**)[a]	Isolated product (yield)	
1	isopropyl	cyclohexyl	70:30	**6a** (56%)	**7a** (23%)
2	isopropyl	cyclopentyl	75:25	**6b** (48%)	**7b** (18%)
3	isopropyl	benzyl	85:15	**6c** (67%)	**7c** (10%)
4	isobutyl	cyclohexyl	80:20	**6d** (62%)	**7d** (15%)
5	isobutyl	cyclopentyl	80:20	**6e** (62%)	**7e** (9%)
6	isobutyl	benzyl	80:20	**6f** (64%)	**7f** (19%)
7	benzyl	cyclohexyl	75:25	**6g** (41%)	**7g** (13%)
8	benzyl	cyclopentyl	70:30	**6h** (57%)	**7h** (25%)
9	methyl	cyclohexyl	80:20	**6i** (55%)	
10	methyl	cyclopentyl	80:20	**6j** (49%)	

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.

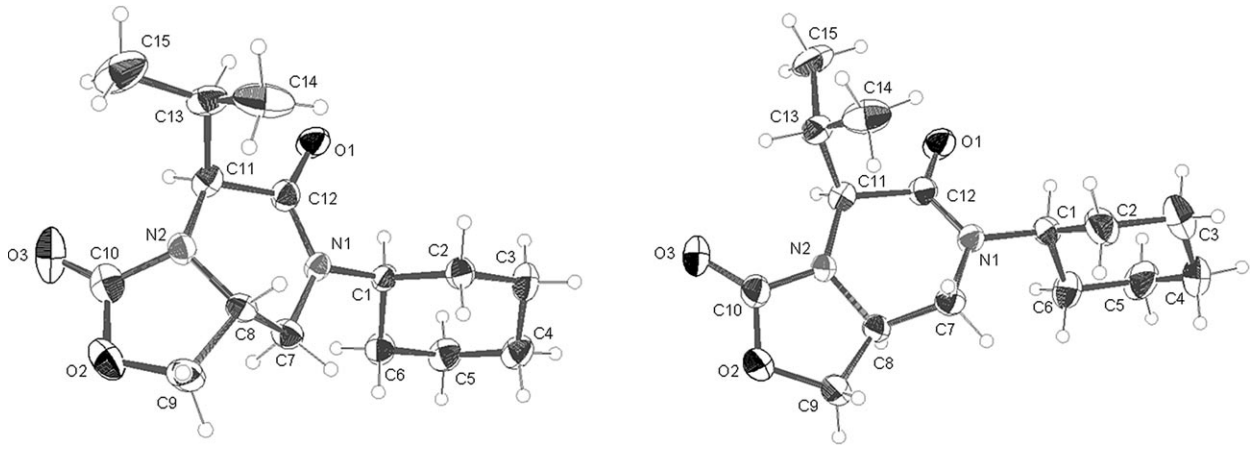


Figure 3. ORTEP representation, at 30% probability level, of the molecular structure in compound **6b** (*left*) and **7b** (*right*).

(entry 2, Table 1), the conversion to product **2** was obtained, although in lower yields (48%, 23% and 40%, respectively, *vs.* 81% of the corresponding Boc derivative).

The scope of this transformation was then explored, examining the behaviour of the easily obtained allylamides **5a–h**, and the results are summarized in Table 2. In the cases of amides arising from L-valine, L-leucine and L-phenylalanine, the reactions provided the desired oxazolo[3,4-*a*]pyrazine derivatives as a separable mixture of two diastereoisomers, while in the case of L-alanine allylamides we were unable to isolate the two products. The relative configurations of the major and minor products, namely *trans* and *cis*, were identified by single-crystal X-ray analysis, performed on compounds **6b** and **7b** (Figure 3).[19]

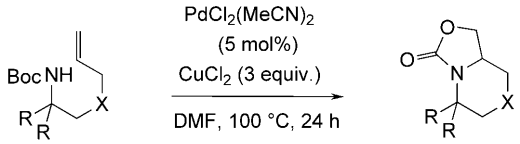
It should be stressed that the amination products (Scheme 1, *path b*) were never isolated or detected in the NMR spectra of the crude reaction mixtures under these conditions.

On the other hand, the dihydropyrazinone derivatives **8** resulted as the sole products when a number of allylamides **5** were treated with $CuCl_2$ (10 mol%)/O_2 as the oxidant. This confirms the selectivity of these procedures which depends only on the amount of $CuCl_2$ (Table 3).

The domino process was then extended to other carbamate-protected aminoalkenes, to further increase the scope of this methodology: Boc-amino allyl ethers **9a** and **9b** as well as *N*′-allyl-*N*′-tosyl-*N*-Boc-ethylenediamine **9c**, having a more flexible tether between the reacting centres, were submitted to the aminocarboxylation conditions. To our delight, all the substrates gave the bicyclic morpholino and piperazino derivatives **10a–c** in good yields (Scheme 3).

Two more reactions were studied to have a better insight into this domino aminocarboxylative process.

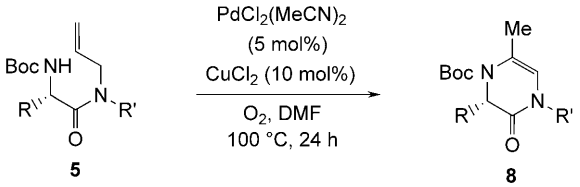
In a first instance, allylamide **1** was reacted using $CuCl_2$ (10 mol%)/O_2 as oxidant in the presence of excess LiCl (5 equiv.), leading only to **3** in low yield (14%). Subsequently, the cyclization of the acetylglycine amide **11**, lacking the carbamate group, was investigated in the aminocarboxylative conditions. Also



10a, X = O, R = H, 75% yield
10b, X = O, R = Me, 82% yield
10c, X = NTs, R = H, 72% yield

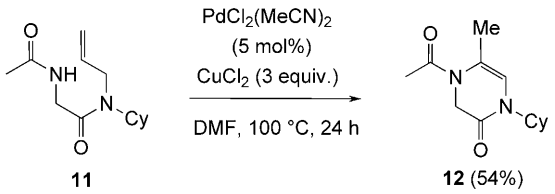
Scheme 3. Aminocarboxylation processe on different Boc-aminoalkenes.

Table 3. Scope of the the amination reaction.



Entry	R	R′	Product (Yield)[a]
1	isopropyl	cyclohexyl	**8a** (82%)
2	isopropyl	methyl	**8b** (55%)
3	isobutyl	cyclohexyl	**8c** (82%)
4	isobutyl	methyl	**8d** (72%)
5	benzyl	cyclohexyl	**8e** (71%)
6	benzyl	methyl	**8f** (65%)
7	methyl	cyclohexyl	**8g** (83%)
8	methyl	methyl	**8h** (70%)

[a] Isolated yield.



Scheme 4. Cyclization under aminocarboxylative conditions of acetylglycine allylamide.

in this case, the substrate underwent the amination/β-hydride elimination/isomerization sequence affording **12** (Scheme 4). In both reactions, the putatively stable 5-chloromethyl piperazinone,[9b] resulting from a nucleophilic substitution of the Pd(II) moiety by a chloride anion, was never detected among the reaction products.

A possible rationalization of the aminocarboxylative reaction consists in an oxidative $CuCl_2$-assisted Pd-elimination from the σ-alkylpalladium complex **A**, in turn arising from the initial aminopalladation (Figure 4). In this case, a $PdCl^+$ species behaves as a leaving group in the intramolecular nucleophilic attack of the carbamate oxygen, generating the intermediate **B**. $CuCl_2$ would inhibit the more straightforward palladium β-hydride elimination through a transient palladium oxidation[7f,20] or by formation of a heterobimetallic σ-Pd/Cu complex.[21] An alternative pathway may involve an initial alkene aminochlorination, followed by intramolecular displacement of the chlorine, although the presence of chlorinated intermediates was never observed.[9c] Finally, **B** can evolve to the product **2** by loss of isobutene (in the case of *tert*-butoxycarbonyl protecting group),[13b,c] or through the intervention of a nucleophile such as the chloride anion or water present in the reaction medium (on different carbamates).

In summary, a general and highly efficient methodology for the synthesis of bicyclic oxazolidinones has been developed starting from easily available allylamides of *N*-alkoxycarbonyl-protected α-amino acids. The cyclization has been performed in oxidative Pd(II)-catalyzed conditions, where the key role is played by $CuCl_2$ as oxidant agent. Depending on its amount, more specifically catalytic *vs.* stoichiometric, a divergent route to simple amination or domino aminocarboxylation reaction can be selected.

Experimental Section

General Remarks

Melting points were measured with a Büchi B-540 apparatus and are uncorrected. Optical rotations (Na D line) were measured on a Jasco P-1010 polarimeter. IR spectra were recorded on a FT-IR spectrophotometer. Column chromatography was performed on a Merck silica gel 60 (mesh size 63–200 μm). Nuclear magnetic resonance spectra were acquired at 400 MHz for ^1H and 100 MHz for ^{13}C on a Bruker AVANCE 400 spectrometer. Chemical shifts (δ) for proton nuclear magnetic resonance (^1H NMR) spectra are reported in parts per million downfield relative to the centre-line of the $CDCl_3$ singlet at 7.25 ppm. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the centre-line of the $CDCl_3$ triplet at 77.23 ppm. ^{13}C spectra are ^1H decoupled and multiplicities were determined by the APT pulse sequence. Mass spectra were determined on an HPLC-MS LCQ-Advantage Thermo Finnigan instrument. Elemental analyses were executed on a Perkin–Elmer CHN Analyzer Series II 2400.

Detailed procedures for the preparation of allylamides and allylethers as well as a general procedure for the amination of allylamides and details on the X-ray diffraction measurements and analyses are available as Supporting Information.

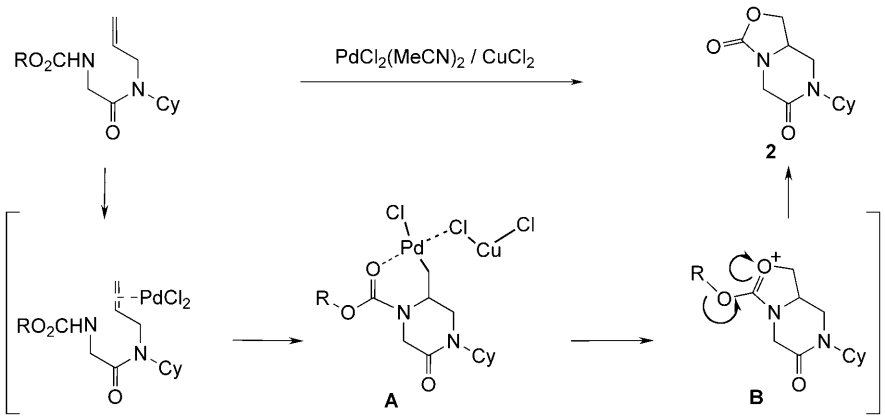


Figure 4. Proposed mechanistic key-steps for the Pd(II)/$CuCl_2$-mediated aminocarboxylation reaction.

General Procedure for the Aminocarboxylation Reactions

A solution of alkene (1 mmol) in anhydrous DMF (10 mL) was added to a solution of $CuCl_2$ (3 mmol) and Pd-$(MeCN)_2Cl_2$ (0.05 mmol) in anhydrous DMF (10 mL). The reaction mixture was heated at 100 °C for 24 h. Brine was added and the mixture was extracted with CH_2Cl_2 (3× 10 mL). The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude was purified by silica gel column chromatography.

7-Cyclohexyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6-(5*H*,7*H*)-dione (2): Yield: 81% (from **1**), 48% (from **4a**), 23% (from **4b**), 40% (from **4c**); yellow solid; mp 121–124 °C; IR: ν = 1751, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00–1.95 (m, 10H), 3.26 (dd, *J* = 12.1, 10.9 Hz, 1H), 3.39 (dd, *J* = 12.1, 4.0 Hz, 1H), 3.89, 4.36 (AB system, *J* = 14.0 Hz, 2H), 3.98–4.05 (m, 1H), 4.11 (dd, *J* = 9.1, 3.5 Hz, 1H), 4.48–4.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (t), 25.4 (t), 25.5 (t), 29.3 (t), 29.7 (t), 44.2 (t), 45.0 (t), 50.6 (d), 52.6 (d), 65.2 (t), 156.4 (s), 163.4 (s); MS: *m*/*z* = 238 (M^+); anal. calcd. for $C_{12}H_{18}N_2O_3$: C 60.49, H 7.61, N 11.76; found: C 60.35, H 7.70, N 11.92.

(5*S*,8a*R*)-7-Cyclohexyl-5-isopropyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6a): Yield: 56%; red solid; mp 119–120 °C; $[\alpha]_D^{23}$: +20.4 (*c* 1.73, $CHCl_3$); IR: ν = 1757, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8 Hz, 3H), 0.99 (dd, *J* = 6.8, 1.2 Hz, 3H), 1.15–1.80 (m, 10H), 2.57–2.70 (m, 1H), 3.19 (dd, *J* = 11.9, 11.3 Hz, 1H), 3.30 (dd, *J* = 11.9, 4.2 Hz, 1H), 3.97–4.06 (m, 2H), 4.13–4.17 (m, 1H), 4.40–4.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (q), 19.5 (q), 25.3 (t), 25.4 (t), 25.5 (t), 29.4 (t), 29.6 (t), 32.3 (d), 44.4 (t), 51.2 (d), 52.7 (d), 60.6 (d), 64.8 (t), 157.8 (s), 166.0 (s); MS: *m*/*z* = 280 (M^+); anal. calcd. for $C_{15}H_{24}N_2O_3$: C 64.26, H 8.63, N 9.99; found: C 64.31, H 8.90, N 9.76.

(5*S*,8a*S*)-7-Cyclohexyl-5-isopropyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (7a): Yield: 23%; orange solid; mp 137–139 °C; $[\alpha]_D^{23}$: −57.8 (*c* 1.54, $CHCl_3$); IR: ν = 1755, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 7.4 Hz, 3H), 1.01–1.90 (m, 10H), 1.17 (d, *J* = 7.4 Hz, 3H), 2.86 (dqq, *J* = 3.4, 7.4, 7.4 Hz, 1H,), 3.20 (dd, *J* = 12.0, 9.9 Hz, 1H), 3.45 (dd, *J* = 12.0, 2.6 Hz, 1H), 3.88–3.98 (m, 2H), 4.11 (d, *J* = 3.4 Hz, 1H), 4.43–4.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 (q), 19.8 (q), 25.2 (t), 25.4 (t), 25.6 (t), 29.1 (t), 29.5 (d), 30.3 (t), 43.6 (t), 53.0 (d), 53.2 (d), 62.2 (d), 65.4 (t), 155.7 (s), 165.3 (s); MS: *m*/*z* = 280 (M^+); anal. calcd. for $C_{15}H_{24}N_2O_3$: C 64.26, H 8.63, N 9.99; found: C 64.50, H 8.75, N 9.81.

(5*S*,8a*R*)-7-Cyclopentyl-5-isopropyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6b): Yield: 48%; red solid; mp 139–142 °C; $[\alpha]_D^{23}$: +66.9 (*c* 1.05, $CHCl_3$); IR: ν = 1750, 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.30–1.88 (m, 8H), 2.66 (dqq, *J* = 3.2, 7.0, 7.0 Hz, 1H), 3.21–3.31 (m, 2H), 3.99–4.05 (m, 1H), 4.08 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.17 (d, *J* = 3.2 Hz, 1H), 4.44–4.49 (m, 1H), 4.95–5.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (q), 19.5 (q), 23.9 (t), 24.2 (t), 27.4 (t), 28.7 (t), 32.3 (d), 44.6 (t), 51.2 (d), 54.6 (d), 60.7 (d), 64.8 (t), 157.8 (s), 166.5 (s); MS: *m*/*z* = 266 (M^+); anal. calcd. for $C_{14}H_{22}N_2O_3$: C 63.13, H 8.33, N 10.52; found: C 63.22, H 8.55, N 10.41.

(5*S*,8a*S*)-7-Cyclopentyl-5-isopropyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (7b): Yield: 18%; yellow solid; mp 118–120 °C; $[\alpha]_D^{23}$: −13.8 (*c* 1.42, $CHCl_3$); IR: ν = 1749, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.20–1.95 (m, 8H), 2.85 (dqq, *J* = 3.0, 7.0, 7.0 Hz, 1H), 3.27 (dd, *J* = 12.0, 10.0 Hz, 1H), 3.36 (dd, *J* = 12.0, 2.6 Hz, 1H), 3.95–3.98 (2H, m), 4.12 (d, *J* = 3.0 Hz, 1H), 4.44–4.47 (m, 1H), 4.90–4.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 (q), 19.8 (q), 24.0 (t), 24.1 (t), 28.2 (t), 28.3 (t), 29.3 (d), 43.8 (t), 53.1 (d), 54.6 (d), 62.4 (d), 64.7 (t), 155.6 (s), 165.8 (s); MS: *m*/*z* = 266 (M^+); anal. calcd. for $C_{14}H_{22}N_2O_3$: C 63.13, H 8.33, N 10.52; found: C 62.87, H 8.45, N 10.31.

(5*S*,8a*R*)-7-Benzyl-5-isopropyl-8,8a-dihydro-1*H*-oxazolo-[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6c): Yield: 67%; red oil; $[\alpha]_D^{23}$: +28.7 (*c* 0.42, $CHCl_3$); IR: ν = 1748, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 2.71–2.73 (m, 1H), 3.21 (dd, *J* = 4.3, 12.0 Hz, 1H), 3.36 (t, *J* = 11.4 Hz, 1H), 3.97 (d, *J* = 9.3 Hz, 1H), 4.03–4.07 (m, 1H), 4.29–4.33 (m, 2H), 4.37–4.42 (m, 1H), 4.95 (d, *J* = 14.6 Hz, 1H), 7.22–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (q), 19.6 (q), 32.3 (d), 49.2 (t), 50.6 (t), 50.7 (d), 60.7 (d), 64.6 (t), 128.0 (d), 128.1 (d), 128.9 (d), 136.0 (s), 157.4 (s), 166.9 (s); MS: *m*/*z* = 288 (M^+); anal. calcd. for $C_{16}H_{20}N_2O_3$: C 66.65, H 6.99, N 9.72; found: C 66.76, H 6.87, N 9.84.

(5*S*,8a*S*)-7-Benzyl-5-isopropyl-8,8a-dihydro-1*H*-oxazolo-[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (7c): Yield: 10%; yellow oil; $[\alpha]_D^{23}$: −50.3 (*c* 0.10, $CHCl_3$); IR: ν = 1745, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 2.91–2.97 (m, 1H), 3.29–3.35 (m, 2H), 3.85–3.96 (m, 2H), 4.20 (d, *J* = 3.1 Hz, 1H), 4.36 (t, *J* = 6.7 Hz, 1H), 4.53 (d, *J* = 14.4 Hz, 1H), 4.75 (d, *J* = 14.4 Hz, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2 (q), 19.8 (q), 29.5 (d), 48.2 (t), 50.7 (t), 52.8 (d), 62.3 (d), 65.2 (t), 128.1 (d), 128.5 (d), 128.9 (d), 135.9 (s), 155.7 (s), 166.1 (s); MS: *m*/*z* = 288 (M^+); anal. calcd. for $C_{16}H_{20}N_2O_3$: C 66.65, H 6.99, N 9.72; found: C 66.51, H 7.09, N 9.61.

(5*S*,8a*R*)-7-Cyclohexyl-5-isobutyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6d): Yield: 62%; yellow solid; mp 118–119 °C; $[\alpha]_D^{23}$: +18.8 (*c* 2.20, $CHCl_3$); IR: ν = 1750, 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 1.25–1.85 (m, 13H), 3.23 (dd, *J* = 11.9, 10.9 Hz, 1H), 3.31 (dd, *J* = 11.9, 4.5 Hz, 1H), 3.99–4.02 (m, 1H), 4.07 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.32 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.40–4.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (q), 23.3 (q), 24.7 (d), 25.4 (t), 25.5 (t), 25.6 (t), 29.4 (t), 29.5 (t), 41.6 (t), 44.4 (t), 48.2 (d), 52.7 (d), 53.9 (d), 65.2 (t), 156.6 (s), 167.0 (s); MS: *m*/*z* = 294 (M^+); anal. calcd. for $C_{16}H_{26}N_2O_3$: C 65.28, H 8.90, N 9.52; found: C 65.32, H 9.11, N 9.38.

(5*S*,8a*S*)-7-Cyclohexyl-5-isobutyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (7d): Yield: 15%; red solid; mp 135–136 °C; $[\alpha]_D^{23}$: −36.5 (*c* 2.23, $CHCl_3$); IR: ν = 1754, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.80–1.02 (m, 6H), 1.05–2.16 (m, 13H), 3.22 (dd, *J* = 12.0, 10.0 Hz, 1H), 3.48 (dd, *J* = 12.0, 2.3 Hz, 1H), 3.92–3.97 (m, 2H), 4.17–4.21 (m, 1H), 4.40–4.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (q), 23.7 (q), 24.5 (d), 25.3 (t), 25.4 (t), 25.5 (t), 29.2 (t), 29.7 (t), 39.3 (t), 43.8 (t), 53.0 (d), 53.1 (d), 56.3 (d), 65.4 (t), 155.6 (s), 167.3 (s); MS: *m*/*z* = 294

(M$^+$); anal. calcd. for $C_{16}H_{26}N_2O_3$: C 65.28, H 8.90, N 9.52; found: C 65.43, H 9.12, N, 9.41.

(5*S*,8a*R*)-7-Cyclopentyl-5-isobutyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6e): Yield: 62%; yellow solid; mp 120–121 °C; $[\alpha]_D^{23}$: +29.3 (*c* 2.36, $CHCl_3$); IR: ν = 1751, 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 1.31–1.87 (m, 11H), 3.22–3.32 (m, 2H), 3.99–4.05 (m, 1H), 4.09 (dd, *J* = 9.2, 1.5 Hz, 1H), 4.31 (dd, *J* = 10.7, 3.0 Hz, 1H), 4.42 (dd, *J* = 9.2, 8.2 Hz, 1H), 4.90–4.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (q), 23.4 (q), 23.9 (t), 24.2 (t), 24.7 (d), 27.4 (t), 28.4 (t), 41.7 (t), 44.4 (t), 48.2 (d), 53.9 (d), 54.6 (d), 65.2 (t), 156.6 (s), 167.5 (s); MS: *m*/*z* = 280 (M$^+$); anal. calcd. for $C_{15}H_{24}N_2O_3$: C 64.26, H 8.63, N 9.99; found: C 64.33, H 8.82, N 9.91.

(5*S*,8a*S*)-7-Cyclopentyl-5-isobutyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (7e): Yield: 9%; brown solid; mp 101–102 °C; $[\alpha]_D^{23}$: −8.3 (*c* 1.72, $CHCl_3$); IR: ν = 1760, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–1.00 (m, 6H), 1.20–2.17 (m, 11H), 3.28 (dd, *J* = 12.0, 9.4 Hz, 1H), 3.40 (dd, *J* = 12.0, 1.2 Hz, 1H), 3.94–4.09 (m, 2H), 4.20 (dd, *J* = 7.1, 3.5 Hz, 1H), 4.46–4.50 (m, 1H), 4.91–4.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (q),23.7 (q), 24.0 (t), 24.2 (t), 24.4 (d), 27.8 (t), 28.3 (t), 39.3 (t), 44.0 (t), 53.0 (d), 54.7 (d), 56.4 (d), 65.4 (t), 155.5 (s), 167.8 (s); MS: *m*/*z* = 280 (M$^+$); anal. calcd. for $C_{15}H_{24}N_2O_3$: C 64.26, H 8.63, N 9.99; found: C 64.09, H, 8.50, N 10.24.

(5*S*,8a*R*)-7-Benzyl-5-isobutyl-8,8a-dihydro-1*H*-oxazolo-[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6f): Yield: 64%; red oil; $[\alpha]_D^{23}$: +29.2 (*c* 0.79, $CHCl_3$); IR: ν = 1753, 1629 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 1.64–1.67 (m, 2H), 1.80–1.83 (m, 1H), 3.19–3.27 (m, 2H), 3.90–4.00 (m, 2H), 4.27–4.35 (m, 3H), 4.67 (d, *J* = 14.6 Hz, 1H), 7.13–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (q), 23.4 (q), 24.6 (d), 41.4 (t), 47.4 (d), 49.3 (t), 50.4 (t), 53.7 (d), 65.1 (t), 127.9 (d), 128.0 (d), 128.8 (d), 135.9 (s), 156.6 (s), 167.8 (s); MS: *m*/*z* = 302 (M$^+$); anal. calcd. for $C_{17}H_{22}N_2O_3$: C 67.53, H 7.33, N 9.26; found: C 67.66, H 7.25, N 9.12.

(5*S*,8a*S*)-7-Benzyl-5-isobutyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (7f): Yield: 19%; yellow oil; $[\alpha]_D^{23}$: −29.3 (*c* 0.42, $CHCl_3$); IR: ν = 1758, 1636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–0.98 (m, 6H), 1.83–1.98 (m, 1H), 2.10–2.15 (m, 2H), 3.33 (d, *J* = 7.1 Hz, 2H), 3.82–3.87 (m, 1H), 3.93–3.99 (m, 1H), 4.24 (t, *J* = 5.3 Hz, 1H), 4.36 (t, *J* = 7.5 Hz, 1H), 4.49 (d, *J* = 14.6 Hz, 1H), 4.74 (d, *J* = 14.6 Hz, 1H), 7.22–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (q), 23.5 (q), 24.5 (d), 39.2 (t), 48.4 (t), 50.8 (t), 52.7 (d), 56.3 (d), 65.3 (t), 128.1 (d), 128.3 (d), 128.9 (d), 135.8 (s), 155.7 (s), 167.9 (s); MS: *m*/*z* = 302 (M$^+$); anal. calcd. for $C_{17}H_{22}N_2O_3$: C 67.53, H 7.33, N 9.26; found: C 67.28, H 7.51, N 9.38.

(5*S*,8a*R*)-5-Benzyl-7-cyclohexyl-8,8a-dihydro-1*H*-oxazolo-[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6g): Yield: 41%; yellow solid; mp 170–171 °C; $[\alpha]_D^{23}$: −6.6 (*c* 1.76, $CHCl_3$); IR: ν = 1758, 1627 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82–1.79 (m, 10H), 2.75–2.83 (m, 1H), 3.01–3.08 (m, 3H), 3.57 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.85 (dd, *J* = 8.9, 3.6 Hz, 1H), 4.17 (dd, *J* = 8.9, 8.4 Hz, 1H), 4.47–4.58 (m, 2H), 7.16–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3 (t), 25.4 (t), 25.5 (t), 29.3 (t), 29.5 (t), 37.9 (t), 44.7 (t), 49.5 (d), 52.9 (d), 55.8 (d), 65.0 (t), 127.1 (d), 128.4 (d), 129.9 (d), 136.7 (s), 156.4 (s), 165.4 (s); MS: *m*/*z* = 328 (M$^+$); anal. calcd. for $C_{19}H_{24}N_2O_3$: C 69.49, H 7.37, N 8.53; found: C 69.41, H 7.53, N 8.72.

(5*S*,8a*S*)-5-Benzyl-7-cyclohexyl-8,8a-dihydro-1*H*-oxazolo-[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (7g): Yield: 13%; yellow solid; mp 141–142 °C; $[\alpha]_D^{23}$: −88.3 (*c* 2.05, $CHCl_3$); IR: ν = 1755, 1629 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–1.80 (m, 11H), 2.95 (dd, *J* = 8.5, 3.5 Hz, 1H), 3.24 (dd, *J* = 13.6, 2.3 Hz, 1H), 3.64 (dd, *J* = 10.5, 8.5 Hz, 1H), 3.80–3.90 (m, 2H), 4.32–4.52 (m, 3H), 7.16–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2 (t), 25.3 (t), 25.5 (t), 29.3 (t), 29.4 (t), 35.2 (t), 42.4 (t), 52.1 (d), 52.8 (d), 57.5 (d), 65.5 (t), 127.2 (d), 128.2 (d), 130.4 (d), 135.8 (s), 155.6 (s), 166.2 (s); MS: *m*/*z* = 328 (M$^+$); anal. calcd. for $C_{19}H_{24}N_2O_3$: C 69.49, H 7.37, N 8.53; found: C 69.32, H 7.61, N 8.38.

(5*S*,8a*R*)-5-Benzyl-7-cyclopentyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6h): Yield: 57%; yellow solid; mp 83–86 °C; $[\alpha]_D^{23}$: +10.1 (*c* 2.22, $CHCl_3$); IR: ν = 1751, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07–1.90 (m, 8H), 2.78–2.82 (m, 1H), 2.92–3.14 (m, 3H), 3.50 (d, *J* = 13.1 Hz, 1H), 3.84 (d, *J* = 6.4 Hz, 1H), 4.11–4.15 (m, 1H), 4.51 (br s, 1H), 4.93–4.99 (m, 1H), 7.10–7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9 (t), 24.2 (t), 27.3 (t), 28.5 (t), 38.0 (t), 44.8 (t), 49.5 (d), 54.7 (d), 55.9 (d), 65.0 (t), 127.1 (d), 128.4 (d), 129.9 (d), 136.8 (s), 156.4 (s), 166.0 (s); MS: *m*/*z* = 314 (M$^+$); anal. calcd. for $C_{18}H_{22}N_2O_3$: C 68.77, H 7.05, N 8.91; found: C 68.50, H 7.20, N 8.88.

(5*S*,8a*S*)-5-Benzyl-7-cyclopentyl-8,8a-dihydro-1*H*-oxazolo-[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (7h): Yield: 25%; orange solid; mp 159–161 °C; $[\alpha]_D^{23}$: −8.9 (*c* 2.57, $CHCl_3$); IR: ν = 1750, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95–1.95 (m, 9H), 2.83 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.22 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.64 (dd, *J* = 10.6, 8.4 Hz, 1H), 3.82–3.88 (m, 2H), 4.35 (dd, *J* = 8.4, 7.8 Hz, 1H), 4.51 (dd, *J* = 4.9, 2.7 Hz, 1H), 4.94–4.99 (m, 1H), 7.12–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0 (t), 24.2 (t), 27.4 (t), 28.3 (t), 35.3 (t), 42.4 (t), 51.9 (d), 54.2 (d), 57.6 (d), 65.6 (t), 127.2 (d), 128.2 (d), 130.3 (d), 135.9 (s), 155.5 (s), 166.7 (s); MS: *m*/*z* = 314 (M$^+$); anal. calcd. for $C_{18}H_{22}N_2O_3$: C 68.77, H 7.05, N 8.91; found: C 68.60, H 7.20, N 8.68.

(5*S*,8a*R*)-7-Cyclohexyl-5-methyl-8,8a-dihydro-1*H*-oxazolo-[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6i): Yield: 55%; yellow solid; mp 121–122 °C; $[\alpha]_D^{23}$: +27.2 (*c* 3.11, $CHCl_3$); IR: ν = 1747, 1632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98–1.08 (m, 1H), 1.20–1.45 (m, 4H), 1.46 (d, *J* = 7.1, 3H), 1.55–1.80 (m, 5H), 3.22 (dd, *J* = 11.9, 10.6 Hz, 1H), 3.36 (dd, *J* = 11.9, 3.9 Hz, 1H), 3.99–4.08 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 1H), 4.40–4.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3 (q), 25.4 (t), 25.5 (t), 29.2 (t), 29.4 (t), 29.6 (t), 45.0 (t), 48.3 (d), 51.0 (d), 52.8 (d), 65.2 (t), 156.1 (s), 167.1 (s); MS: *m*/*z* = 252 (M$^+$); anal. calcd. for $C_{13}H_{20}N_2O_3$: C 61.88, H 7.99, N 11.10; found: C 61.70, H 8.26, N 11.01.

(5*S*,8a*R*)-7-Cyclopentyl-5-methyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyrazine-3,6(5*H*,7*H*)-dione (6j): Yield: 49%; red solid; mp 137–138 °C; $[\alpha]_D^{23}$: +37.2 (*c* 1.64, $CHCl_3$); IR: ν = 1749, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.87 (m, 8H), 1.46 (d, *J* = 7.1 Hz, 3H), 3.28–3.30 (m, 2H), 4.00–4.09 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 1H), 4.43–4.48 (dd, *J* = 8.6, 8.1 Hz, 1H), 4.90–4.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (q), 23.9 (t), 24.2 (t), 27.5 (t), 28.4 (t), 45.0 (t), 48.3 (d), 51.0 (d), 54.6 (d), 65.3 (t), 156.1 (s), 167.4 (s); MS: *m*/*z* = 238 (M$^+$); anal. calcd. for $C_{12}H_{18}N_2O_3$: C 60.49, H 7.61, N 11.76; found: C 60.55, H 8.51, N 11.58.

5,6,8,8a-Tetrahydrooxazolo[4,3-*c*][1,4]oxazin-3(1*H*)-one (10a): Yield: 75%; colourless oil; IR: $\nu = 1745\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.17–3.33$ (m, 2H), 3.45 (ddd, $J = 11.8$, 11.7, 3.0 Hz, 1H), 3.72 (dd, $J = 13.3$, 3.0 Hz, 1H), 3.87–3.97 (m, 4H), 4.40 (dd, $J = 8.0$, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 41.3$ (t), 52.3 (d), 64.2 (t), 66.1 (t), 69.8 (t), 156.6 (s); MS: $m/z = 143$ (M^+); anal. calcd. for $C_6H_9NO_3$: C 50.35, H 6.34, N 9.79; found: C 50.54, H 6.49, N 9.58.

5,5-Dimethyl-5,6,8,8a-tetrahydrooxazolo[4,3-*c*]-[1,4]oxazin-3(1*H*)-one (10b): Yield: 82%; colourless oil; IR: $\nu = 1740\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (s, 3H), 1.51 (s, 3H), 3.16–3.26 (m, 2H), 3.47 (d, $J = 12.6$ Hz, 1H), 3.68–3.72 (m, 1H), 3.92–4.00 (m, 1H), 4.04 (dd, $J = 10.4$, 3.6 Hz, 1H), 4.29 (dd, $J = 8.1$, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.5$ (q), 22.5 (q), 50.8 (d), 53.1 (s), 63.9 (t), 70.1 (t), 76.5 (t), 155.9 (s); MS: $m/z = 171$ (M^+); anal. calcd. for $C_8H_{13}NO_3$: C 56.13, H 7.65, N 8.18; found: C 56.31, H 7.56, N 8.04.

7-Tosyl-1,5,6,7,8,8a-hexahydrooxazolo[3,4-*a*]pyrazine 3-one (10c): Yield: 72%; colourless oil; IR: $\nu = 1738\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3H), 3.16–3.25 (m, 2H), 3.73 (d, $J = 3.7$, 1H), 3.76 (d, $J = 3.7$ Hz, 1H), 3.84 (d, $J = 3.7$ Hz, 1H), 3.88 (dd, $J = 2.4$, 3.7 Hz, 1H), 3.90–3.92 (m, 1H), 3.94–4.02 (m, 1H), 4.42 (dd, $J = 8.4$, 8.5 Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$ (q), 40.5 (t), 45.1 (t), 49.2 (t), 52.7 (d), 64.9 (t), 127.6 (d), 130.3 (d), 132.3 (s), 144.5 (s), 156.4 (s); MS: $m/z = 296$ (M^+); anal. calcd. for $C_{13}H_{16}N_2O_4S$: C 52.69, H 5.44, N 9.45; found: C 52.78, H 5.22, N 9.28.

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