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One-pot vinylation of azlactones: fast access to enantioenriched α-vinyl quaternary amino acids

Massimo Serra*, Eric Bernardi, Giorgio Marrubini, and Lino Colombo*

Abstract: We report a fast one-pot protocol for the direct vinylation of azlactones (oxazol-5-(4*H*)-ones) exploiting as a key step an aldol addition with 2-(phenylselenenyl)acetaldehyde followed by dehydroxyselenation. The acid hydrolysis of the oxazolone ring afforded the desired fully deprotected α-vinyl quaternary α-amino acids in almost quantitative yields. An enantioselective variant of the method was also developed by the use of catalytic chiral bases. The use of Sharpless ligand $(DHQD)_2PHAL$ produced the final quaternary amino acids in good overall yields (62–78%) and ee up to 86%. Scale-up of the optimized protocol to gram quantities did not affect yields and ee's. Moreover, we demonstrated that the vinyl moiety installed onto the oxazolone ring can be exploited as a handle for the attachment of aryl groups through a Heck coupling reaction.

Introduction

The synthesis of non-proteinogenic amino acids and their incorporation into peptides or proteins for the obtainment of chemically- and enzymatically-stable derivatives is an area of growing interest in medicinal chemistry and biology.[1] In particular, *α,α*-disubstituted (quaternary) *α*-amino acids, due to the lack of hydrogen at the *α*-position, are characterized by restricted conformational flexibility, increased lipophilicity, and stability towards racemization.[2] Quaternary amino acids are present in nature either in their free form or as constituents of many biologically active natural and unnatural compounds.[3] Among the various C^{α}-tetrasubstituted amino acids, *α*-vinyl amino acids showed irreversible inhibitory effects on a variety of PLP-dependent enzymes, particularly amino acid decarboxylases.[4] Furthermore, the straightforward conversion of the C-C double bond into a variety of different functional groups, including the impressive applications in C-C bond formation afforded by olefin metathesis and Pd–catalyzed coupling reactions, has aroused new interest in the synthesis of *α*-vinyl *α*-amino acids as versatile building blocks for the achievement of conformationally constrained or easily functionalizable peptidomimetics.

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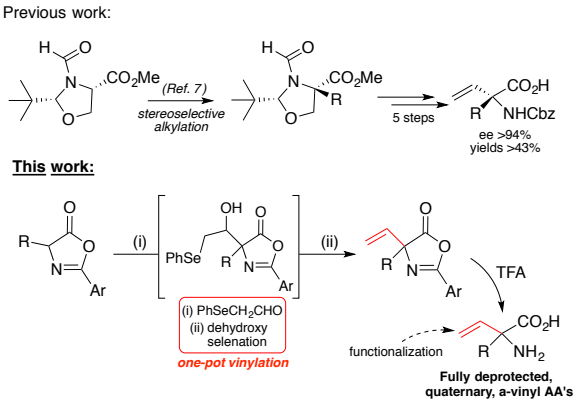
Oxazol-5-(4*H*)-ones (azlactones), readily available through cyclization-dehydration of various *N*-protected *α*-amino acids, have been proven to be excellent substrates for the synthesis of quaternary unsaturated *α*-amino acids.[5] However, to the best of our knowledge, only one example of one-pot installation of ethynyl and/or ethenyl groups at the C-4 position of the oxazolone ring has been reported in literature.[6] In their work, Nachtsheim and co-workers described an electrophilic alkynylation of oxazol-5-(4*H*)-ones using alkynyliodonium salts as the alkyne source. Even though the method itself is practical and suitable for the obtainment of a large range of *N*-benzoyl amino acids derivatives, its major limitation is the inability to convert the 4-ethynyl azlactones into the corresponding unprotected *α*-amino acids.

In a previous work we carried out the enantioselective synthesis of different *α*-vinyl quaternary amino acids exploiting a stereoselective alkylation of the Seebach's oxazolidine followed by a Wittig methylenation of the aldehyde group resulting from hydrolysis of the oxazolidine and subsequent oxidation of the primary alcohol.[7] Since this enantioselective sequence requires six steps (starting from Seebach's oxazolidine), we were in need of a more rapid synthetic protocol for the preparation of the aforementioned derivatives. In addition, this protocol should be amenable to be performed in an enantioselective fashion. In this communication we report a fast access to unprotected *α*-alkyl, *α*-vinyl *α*-amino acids, *via* one-pot vinylation of the corresponding oxazol-5-(4*H*)-ones (Scheme 1). Among the various methods able to introduce a vinyl moiety into the *α*-carbon of carbonyl compounds en route to quaternary amino acids,[4b, 8] we opted for the protocol involving the reaction of an enolate with phenylseleno acetaldehyde followed by elimination of the phenylselenyl and hydroxyl group after the conversion of the latter function into a better leaving group such as a mesylate.[9, 10]



Scheme 1. Novel route to unprotected *α*-alkyl, *α*-vinyl *α*-amino acids

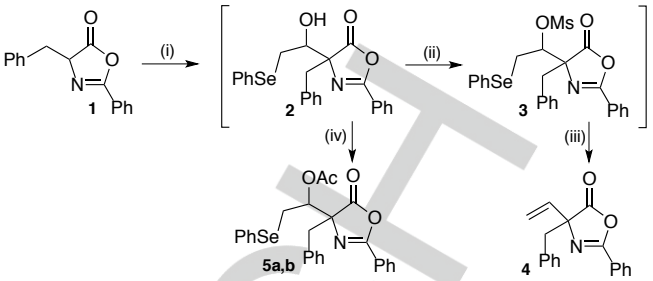
Three main considerations directed our efforts towards this choice: a) the synthetic sequence, once optimized, could be carried out one-pot; b) an enantioselective variant could be devised through the use of a chiral base; c) a literature precedent of a successful condensation between an oxazolone enolate and aldehyde en route to *β*-hydroxy-*α*-aminoacids.[11] In addition, the vinyl moiety is more versatile than substituted alkenyl groups if the terminal carbon is designed as point of attachment for further functionalization or modification as, for example, in the case of Heck reaction or alkene/alkyne metathesis. In a paradigmatic example, a Heck reaction of a quaternary amino acid carrying both a *α*-vinyl and a 1-methyl-2-butenyl substituents involves only the former group.[8f]

Results and Discussion

We started our investigations using the phenylalanine derived-azlactone **1** (Scheme 2), which was treated with 2-(phenylseleno)acetaldehyde in the presence of triethylamine. The aldol reaction proceeded smoothly at RT to give the diastereoisomeric aldol adducts, which were converted *in situ* to the corresponding mesylates **3** by treatment with methanesulfonyl chloride. After 24 hours, we isolated the desired vinyl azlactone **4**, although in low (20%) overall yield. The monitoring of the reaction by TLC analysis showed the rapid formation of the aldol adducts, while the obtainment of the mesylate derivatives and, more significantly, the final elimination step turned out to be slower. In order to get some insight on the stereoselection of the relevant newly formed stereocenter adjacent to the carbonyl function, we attempted to separate the diastereoisomeric alcohols **2** by flash chromatography, but a retro-aldol reaction promoted by silica gel chromatography was observed. On the other hand, the chromatographic separation of stable mesylates **3** was troublesome, giving in all cases diastereoisomeric mixtures. Eventually we found that *in situ* acetylation with acetic anhydride of the aldol adducts allowed an easy separation of the two diastereoisomers **5a** and **5b**.

In anticipation of the feasible enantioselective variant of the reaction, we tested catalytic amounts of a limited number of chiral bases derived by cinchona alkaloids and found in some cases a significant increase in the **5a**/**5b** diastereomeric ratio.[12] For example, the use of 20% of $(DHQD)_2PHAL$ raised the diastereoisomeric excess from 24% to 80% and, more importantly, the enantiomeric excess of both diastereoisomers, determined by HPLC using a chiral stationary phase, was found to be 64% for the minor diastereoisomer **5a**, and slightly lower for the major one **5b**.

By assuming that the yield of the dehydroxyselenation reaction might be increased by the use of a stronger nucleophile than the chloride ion, which could be able to more efficiently attack the selenium atom, we thought to employ tetrabutylammonium iodide as a source of iodide anions. In fact, adding a stoichiometric amount of quaternary ammonium salt, yield was raised to 46% (Table 1, entry 4). Experimentation showed that increasing the amount of tetrabutyl ammonium iodide the yields remained almost unchanged (entry 5), while its use in



Scheme 2. One-pot vinylation of phenylalanine-derived azlactone **1.** Reagents and conditions: (i) $PhSeCH_2CHO$, Et_3N; (ii) MsCl, Et_3N; (iii) Bu_4NI, Δ; (iv) Ac_2O, DMAP.

Table 1. One-pot vinylation of azlactones: preliminary studies[a]

Entry [a]	Base (equiv)	Aldol/DHSe temp	Bu_4NI (equiv)	**4** (%)[d]
1 [b]	1.5	RT / RT	-	20
2	1.05	0°C / RT	-	27
3	1.05	–10°C / RT	-	24
4	1.05	0°C / RT	1	46
5	1.05	0°C / RT	2	45
6	1.05	0°C / RT	0.5	36
7	1.05	0°C / Reflux	1	54
8	0.5	0°C / Reflux	1	56
9 [c]	0.5	0°C / Reflux	1	42

[a] Reactions were performed in DCM on a 0.075–0.15 mmol scale (0.1 M), using 1.0 equiv of oxazolone and 1.05 equiv of aldhehyde. The mesylation step was performed with MsCl (4.5 equiv added in 3 portions, followed by an equimolar amount of Et_3N), The reaction mixture was reacted for 24 h. [b] Reaction performed with 1.5 equiv of aldehyde. [c] The reaction time was 12 h. [d] Yield of isolated product **4** over 3 steps.

sub-stoichiometric ratio (0.5 equiv) had a detrimental effect (entry 6). Heating the reaction mixture at reflux we observed a further increase in the reaction yields, whose relative values remained the same also by lowering the amount of base to 0.5 eq (entries 7 and 8). Attempts to shorten the reaction time, keeping the other parameters unchanged, proved to be ineffective (entry 9). Encouraged by these initial results, we further proceeded to optimize the reaction conditions in order to enhance, if possible, both the yield and the rate of the reaction (Table 2). For this purpose, we decided to explore the use of microwave-assisted heating in the dehydroxyselenation step.

The first attempts, performed applying a simple microwave transfer protocol (2 h at 80°C vs. 24 h at reflux), gave the desired vinyl azlactone **4** in quite low yields (Table 2, entry 1). As shown by the results summarized in Table 2, the yields have been considerably improved by increasing the temperature and

Table 2. Screening of the optimal reaction conditions[a]

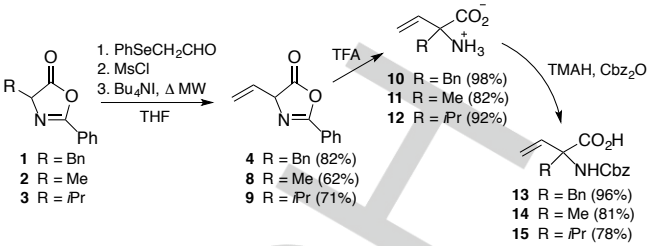
Entry	Solvent	Base	MW heating temp (°C)	Time (min)	**4** (%)[d]
1	DCM	TEA	80	120	23
2	DCM	TEA	120	15	57
3	DCE	TEA	150	12	17
4	MeCN	TEA	120	15	13
5	THF	TEA	110	10	82
6	THF	TEA	150	10	60
7	THF	DIEA	110	10	21
8	THF	DBU	110	10	0
9[b]	THF	TEA	110	10	20
10	$PhCH_3$	TEA	110	10	75
11[c]	THF	TEA	Reflux	1440	80

[a] Reactions were executed on a 0.075–0.15 mmol scale (0.1 M) starting from azlactone **1**. The mesylation step was performed with MsCl (4.5 equiv added in 3 portions, followed by an equimolar amount of Et_3N), and the elimination step was accomplished in the presence of 1.0 equiv of Bu_4NI applying microwave heating. [b] Reaction performed without Bu_4NI. [c] Reaction performed applying conventional heating. [d] Yield of isolated product **4** over 3 steps.

concurrent shortening the reaction time, reaching, in a few minutes of MW heating, the same values obtained by conventional heating (entry 2).

Switching the solvent to tetrahydrofuran the overall yield reached a satisfactory 82% value (entry 5). Comparable results were obtained working in toluene (entry 10), whereas the use of acetonitrile gave low yields. With regard to the base, triethylamine was superior to diisopropylethylamine and stronger bases such as DBU. Finally control experiments were performed as we have wondered whether the use of THF with conventional heating would give the same or worse results with respect to microwave heating. The obtainment of vinyl azlactone **4** in almost the same yield (entry 11) clearly pointed out that MW heating affects only the reaction rate.

With the optimized one-pot protocol for the direct vinylation of phenylalanine-derived azlactone in our hands, we proceeded for a further investigation of the reaction substrate scope (Scheme 2). Azlactones derived from alanine **6** and valine **7** reacted smoothly to give the corresponding vinyl azlactones **8** and **9** in 62% and 71% yields, respectively. To obtain free *α*-vinyl *α*-amino acids, that may find useful applications in peptide synthesis, we tried to open the oxazolone ring under acidic conditions. Both the use of 6N HCl and trifluoroacetic acid (TFA) worked well, although the latter gave the desired fully deprotected quaternary amino acids in higher yields. For the sake of completeness, we demonstrated that the free amino acids could be easily converted into *N*-protected derivatives, such as *N*-Cbz α-vinyl quaternary amino acids **13**–**15** (Scheme 3).



Scheme 3. Substrate scope and obtainment of fully deprotected and *N*-protected α-vinyl quaternary amino acids

Since a fast method for the obtainment of easy-to-functionalize quaternary amino acids in an enantiopure fashion would be highly desirable, we decided to perform a study on enantioselective variant of this synthetic protocol, focusing our attention on the use of chiral bases in the enolate formation step For this purpose we thought to exploit the reactivity of the commercially available *Cinchona* alkaloids **I**–**VI**,[13] the thiourea-based catalyst of Takemoto and co-workers **VII**,[14] and the chiral guanidines **VIII**–**XI** reported to catalyze a direct asymmetric aldol reaction between 5*H*-oxazol-4-ones and aldehydes[15] (Figure 1).

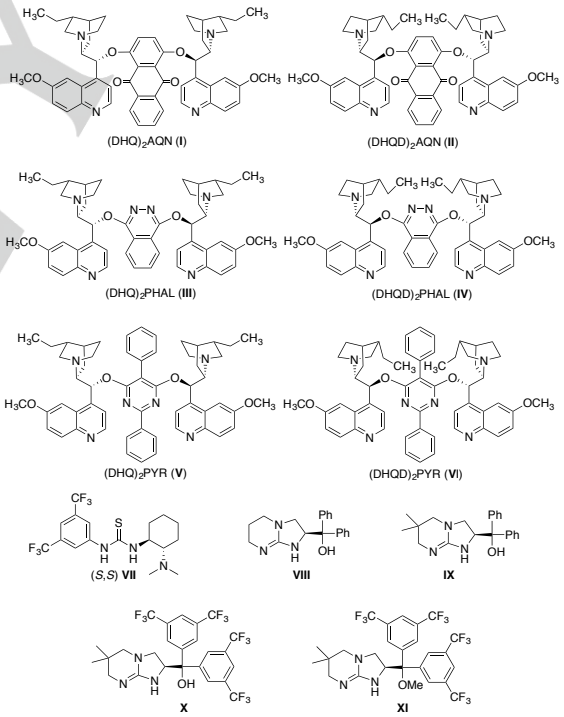


Figure 1. Chiral bases

When 2-phenyl-4-benzyl-5-oxazolone **1** was treated with 0.1 equivalents of the Sharpless ligand $(DHQD)_2PHAL$ (**IV**), the vinylated product **4** was obtained in moderate enantioselectivity (73% enantiomeric excess (ee)) and good overall yields (Table 3, entry 1).

Table 3. Chiral protocol

Entry	R =	Solvent	Base	Base equiv	Aldol temp	y[a] %	ee[b] %
1	Bn	THF	IV	0.1	0 °C	51	73
2	Bn	THF	IV	0.025	0 °C	20	71
3	Bn	THF	IV	0.6	0 °C	66	64
4	Bn	THF	VI	0.1	0 °C	50	55
5	Bn	THF	II	0.1	0 °C	34	41
6	Bn	THF	III	0.1	0 °C	59	16
7	Bn	THF	V	0.1	0 °C	60	–18
8	Bn	THF	I	0.1	0 °C	64	–10
9	Bn	$PhCH_3$	IV	0.1	0 °C	75	74
10	Bn	$PhCH_3$	IV	0.1	-10 °C	78	86
11	Bn	$PhCH_3$	IV	0.1	-30 °C	62	75
12	Bn	$PhCH_3$	IV	0.1	-78 °C	54	31
13	Bn	Xylene	IV	0.1	-10 °C	63	78
14	Bn	DCM	IV	0.1	-10 °C	36	54
15	Bn	$PhCH_3$	VII	0.1	-10 °C	76	19
16	Bn	$PhCH_3$	VIII	0.1	-10 °C	25	0
17	Bn	$PhCH_3$	IX	0.1	-10 °C	12	79
18	Bn	$PhCH_3$	X	0.1	-10 °C	20	30
19	Bn	$PhCH_3$	XI	0.1	-10 °C	25	0
20	Me	THF	IV	0.1	-10 °C	35	46
21	Me	$PhCH_3$	IV	0.1	-10 °C	69	55
22	Me	THF	VI	0.1	-10 °C	32	43
23	Me	$PhCH_3$	II	0.1	-10 °C	29	49
24	Me	$PhCH_3$	VII	0.1	-10 °C	46	30
25	Me	$PhCH_3$	IX	0.1	-10 °C	3	7
26	*i*Pr	$PhCH_3$	IV	0.1	-10 °C	62	45
27	*i*Pr	$PhCH_3$	VI	0.1	-10 °C	36	8
28	*i*Pr	THF	II	0.1	-10 °C	64	31
29	*i*Pr	$PhCH_3$	VII	0.1	-10 °C	52	13
30	*i*Pr	$PhCH_3$	IX	0.1	-10 °C	4	0

[a] Yield of isolated azlactones **4**, **8**, and **9** over 3 steps. [b] The ee's were determined by chiral HPLC under constant flow rate of 1 mL/min in isocratic mode using 100% *n*-heptane as mobile phase. The absolute configurations of the major enantiomers were determined to be *S* by converting azlactones **4**, **8**, and **9** into the corresponding zwitterionic amino acids **10**,[8c] **11**,[16] and **12**,[8c] and comparing the optical rotations with literature values.

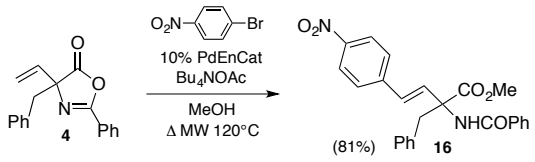
It is worth mentioning that even if an efficient enantioselective organocatalyzed aldol reaction between (4-substituted)-oxazol-5-one enolates and aliphatic aldehydes was recently reported,[11] to the best of our knowledge, herein we describe the first example of this asymmetric transformation in the presence of an α-functionalized aldehyde.

A decrease in the amount of base marginally affected the enantioselectivity but brought about a substantial decrease in the yield (entry 2), whereas the use of greater amounts of base afforded the desired product in higher yields but in lower enantiomeric ratio (entry 3). The dihydroquinidine-derived ligands $(DHQD)_2AQN$ (**II**) and $(DHQD)_2PYR$ (**VI**) were shown to be less efficient and afforded the vinyl azlactone with lower enantioselectivity (ee 41–55%), while when we used the pseudoenantiomers of the Sharpless catalysts the enantioselectivities dropped dramatically (entries 6–8). Furthermore, opposite sense of enantioselection was observed with $(DHQD)_2PYR$ (**V**) and $(DHD)_2AQN$ (**I**) (entries 7 and 8). Switching the solvent to toluene the ee remained almost unchanged, but we observed a considerable increase of the overall yield (entry 9). Gratifyingly, the use of $(DHQD)_2PHAL$ at –10°C afforded the final vinyl oxazolone **3** in very good yield (78%) and a satisfactory 86% ee (entry 10). Unfortunately, the enantioselectivity did not improve upon a further decrease in the temperature. The use of other aromatic solvents such as xylene also gave comparable results in terms of yield and enantioselectivity (entry 13), while employing chlorinated solvents both the yield and the ee dropped down (entry 14). The optimized conditions (toluene, $(DHQD)_2PHAL$, –10°C) were then applied in subsequent experiments in order to study the reactivity of the commercially available Takemoto thiourea **VII**, and the chiral guanidines **VIII**–**XI,** which were synthesized following the reported procedures.[15] Among these, only the guanidine-based ligand **IX** furnished the desired product **4** in good enantiomeric excess, albeit in low yield (entry 17). To further examine the substrate scope of the reaction, the experimentation was extended to alanine- and valine-derived azlactones **6** and **7**. The phthalazine-based ligand $(DHQD)_2PHAL$ showed to be the only one capable of inducing an acceptable level of enantioselectivity, giving the vinyl azlactones **8** and **9** with 55% (entry 21) and 45% (entry 26) ee's respectively.

A preliminary scale-up study of the vinylation reaction was performed on the phenylalanine-derived azlactone **4** firstly quadrupling, then increasing tenfold (up to 1 gram) the standard amount of starting material. In both cases, we obtained the desired products in very similar yields and ee's. Comparable results were obtained with alanine- and valine-derived azlactones.

As a final proof of concept, we demonstrated that this novel vinylation method could be used for the preparation of further functionalizable quaternary amino acids with potential applications in *de novo* peptide design and engineering; therefore, a brief investigation on the reactivity of the installed vinyl group was planned. By performing a Heck reaction in the

presence of 1-bromo-4-nitrobenzene and PdEnCat 30 (a polyurea-encapsulated $Pd(OAc)_2$ catalyst),[17] the azlactone **4** was easily converted into the N- and C-protected quaternary amino acid **16** (Scheme 4), achieving at the same time the opening of the oxazolone ring, the protection of the carboxylic function, and the derivatization of the double bond.



Scheme 4. Functionalization of the vinyl moiety

Conclusions

In conclusion we have developed an efficient protocol for the synthesis of quaternary α-vinyl-α-amino acids, exploiting a direct one-pot vinylation of different azlactones. The key step is an aldol addition with phenylseleno acetaldehyde, followed by a dehydroxyselenation reaction. The final quaternary amino acids were obtained in enantioenriched form (up to 86% ee) and good overall yields (62–78%) by the use of catalytic Sharpless ligand $(DHQD)_2PHAL$ in the aldol condensation step. It is worth to mention that the optimized synthetic protocol can be performed in gram-scale giving the final products in almost unchanged yields and ee's. Moreover, we demonstrated that the vinyl moiety installed onto the oxazolone ring could be exploited for the obtainment of further functionalized quaternary amino acids.

Experimental Section

General Remarks

All chemicals were of reagent grade and were used without further purification. Solvents were purified according to the guidelines in Purification of Laboratory Chemicals[18]. All solvents were freshly distilled from the appropriate drying agent. THF and toluene were distilled from sodium/benzophenone ketyl; TEA and DCM from CaH_2. Reactions requiring anhydrous conditions were performed under N_2. Yields were calculated for compounds purified by flash chromatography and judged homogeneous by thin-layer chromatography, NMR, and mass spectrometry. Thin layer chromatography was performed on Kieselgel 60 F_{254} (Merck) glass plate eluting with solvents indicated, visualized by a 254 nm UV lamp, and stained with aqueous ceric molybdate solution or iodine and a solution of 4,4'-methylenebis-*N,N*-dimethylaniline, ninhydrin, and KI in an aqueous ethanolic solution of AcOH. Flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Optical rotations $[\alpha]_D$ were measured in a cell of 5 cm path length and 1 mL capacity with a Jasco DIP-1000 polarimeter. Infrared spectra were recorded on a Perkin–Elmer ATR-FTIR 1600 series spectrometer using neat samples. Mass spectra were acquired with an APEX II FT-ICR mass spectrometer (Bruker Daltonics, Billerica, MA) equipped with a 4.7 tesla superconducting magnet (Magnex Scientific, Oxford, England). Glassware for all reactions was oven-dried at 110 °C and cooled in a desiccator, or flame-dried and cooled under inert atmosphere prior to use. Liquid reagents and solvents were introduced by oven-dried syringes through septa-sealed flasks under an inert atmosphere.

NMR spectroscopic methods

Nuclear magnetic resonance spectra were acquired at 400 MHz for 1H and 100 MHz for 13C, using a Bruker Avance 400 MHz spectrometer equipped with Bruker's TopSpin 1.3 software package. The abbreviatons s, d, t, q, br s, and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, broad singlet, and multiplet, respectively. In the peak listing of 13C spectra abbreviations s and t refer to zero and two protons attached to the carbons, as determined by DEPT-135 experiments. Sample temperatures were controlled with the variable-temperature unit of the instrument.

Chiral HPLC methods

For details on the chiral HPLC separations see Supporting Information.

General procedure for the synthesis of oxazolones 1, 6, and 7

N-benzoyl amino acid was added portion-wise over 20 minutes to a stirred solution of DCC (1 equiv) in dry DCM (0.3 M) under nitrogen atmosphere at 0°C. Reaction completion was monitored by TLC analysis. While keeping the reaction mixture at 0°C, a vacuum filtration with Gooch apparatus was performed. The residue was washed with Et_2O and the solvent was evaporated in vacuo. Oxazolones **1**, **6**, and **7** were matched with their reported data [19].

*4-benzyl-2-phenyloxazol-5(4H)-one (**1**).* The title compound was prepared from *N*-benzoylphenylalanine (1 g, 3,71 mmol) according to the general procedure. The crude mixture was purified by crystallization with light petroleum ether to obtain **1** as white solid (746 mg, 80%).

*4-methyl-2-phenyloxazol-5(4H)-one (**6**).* The title compound was prepared from *N*-benzoylalanine (1 g, 5,17 mmol) according to the general procedure. The crude mixture was purified by Kugelrohr distillation (150°C, 0.01 mmHg) to obtain **6** as a white solid (680 mg, 75%).

*4-isopropyl-2-phenyloxazol-5(4H)-one (**7**).* The title compound was prepared from *N*-benzoylvaline (1 g, 4,52 mmol) according to the general procedure. The product was purified by Kugelrohr distillation (165°C, 0.01 mmHg) to obtain **7** as a white solid (790 mg, 86%)

Synthesis of 4-methyl-2-phenyl-4-vinyloxazol-5(4*H*)-one (8)

To a solution of 4-methyl-2-phenyloxazol-5(4H)-one (**6**) (100 mg, 0.57 mmol) in dry THF (0.95 mL, 0.60 M) under nitrogen atmosphere, Et_3N (40 µL, 0.29 mmol) was added and the reaction mixture was cooled at –10°C. A solution of 2-(phenylselenyl)acetaldehyde (119 mg, 0.60 mmol) in dry THF (1 mL, 0.60 M) was added and the reaction mixture was stirred for 0.5 h. Formation of the aldol adducts was monitored by TLC analysis, R_f

= 0.36 and R_f = 0.29 (hexane/AcOEt 85:15). Afterwards, methanesulfonyl chloride (66 µL, 0.86 mmol) and Et_3N (80 µL, 0.57 mmol) were added in three portions at 10 minute intervals. After each addition, the pH was monitored with litmus paper and, if necessary, Et_3N was added to maintain a basic pH during the reaction. Formation of the mesylates was monitored by TLC analysis, R_f = 0.23 and R_f = 0.19 (hexane/AcOEt 80:20). After 10 minute from the last addition, tetrabutylammonium iodide (207 mg, 0.57 mmol) was added and the reaction mixture was heated in a microwave oven at 110°C for 10 minute in sealed vessel. The reaction temperature was monitored by external surface sensor. After reaction completion was monitored by TLC analysis, the mixture was washed with phosphate buffer saturated with NaCl. The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo. The crude mixture was purified by flash chromatography (SiO_2; hexane/AcOEt 95:05) to obtain **8** as a yellow oil (71 mg, 62 %).

Chiral procedure: **(**$(DHQD)_2$PHAL (0.1 equiv) was used in the aldol condensation step in place of Et_3N (79 mg, 69 %). R_f = 0.63 (hexane/AcOEt 95:5); IR (neat, cm-1) 3077, 2977, 2921, 2845, 1823, 1651, 1580, 1448; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66 (s, 3H), 5.29 (d, *J* = 10.5 Hz, 1H), 5.47 (d, *J* = 17.2 Hz, 1H), 6.02 (dd, *J* = 10.5, 17.2 Hz, 1H), 7.51 (app t, *J* = 7.5 Hz, 2H), 7.60 (app t, *J* = 7.5 Hz, 1H), 7.51 (app d, *J* = 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 24.7, 70.6 (s), 117.2 (t), 126.3 (s), 128.4, 129.2, 133.3, 135.8, 160.7 (s), 178.9 (s); HRMS (ESI) calculated for $C_{12}H_{11}NNaO_2$ $[M+Na]^+$ 224.06820, found 224.06869 (Δ = 2.2 ppm).

Synthesis of 4-isopropyl-2-phenyl-4-vinyloxazol-5(4*H*)-one (9)

To a solution of 4-isopropyl-2-phenyloxazol-5(4H)-one (**7**) (100 mg, 0.49 mmol) in dry THF (0.82 mL, 0.60 M) under nitrogen atmosphere, Et_3N (34 µL, 0.25 mmol) was added and the reaction mixture was cooled at –10°C. A solution of 2-(phenylselenyl)acetaldehyde (103 mg, 0.52 mmol) in dry THF (0.87 mL, 0.60 M) was added and the reaction mixture was stirred for 0.5 h. Formation of the aldol adducts was monitored by TLC analysis, R_f = 0.36 and R_f = 0.29 (hexane/AcOEt 85:15). Afterwards, methanesulfonyl chloride (57 µL, 0.74 mmol) and Et_3N (68 µL, 0.49 mmol) were added in three portions at 10 minute intervals. After each addition, the pH was monitored with litmus paper and, if necessary, Et_3N was added to maintain a basic pH during the reaction. Formation of the mesylates was monitored with TLC analysis, R_f = 0.32 and R_f = 0.40 (hexane/AcOEt 80:20). After 10 minute from the last addition, tetrabutylammonium iodide (179 mg, 0.49 mmol) was added and the reaction mixture was heated in a microwave oven at 110°C for 10 minute in sealed vessel. The reaction temperature was monitored by external surface sensor. After reaction completion, monitored by TLC analysis, the mixture was washed with phosphate buffer saturated with NaCl. The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo. The crude mixture was purified by flash chromatography (SiO_2; hexane/AcOEt 95:05) to obtain **9** as a yellow oil (81 mg, 71 %).

Chiral procedure: **(**$(DHQD)_2$PHAL (0.10 equiv) was used in the aldol condensation step in place of Et_3N (71 mg, 62 %). R_f = 0.63 (hexane/AcOEt 95:05); IR (neat, cm^{-1}) 3062, 2969, 2934, 2876, 1822, 1806, 1654, 1580, 1451; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 2.28 (septuplet, *J* = 6.8 Hz, 1H), 5.32 (dd, *J* = 0.8, 10.5 Hz, 1H), 5.44 (dd, *J* = 0.8, 17.2 Hz, 1H), 6.01 (dd, *J* = 10.5, 17.2 Hz, 1H), 7.52 (app t, *J* = 7.8 Hz, 2H), 7.61 (app t, *J* = 7.5 Hz, 1H), 8.08 (app d, *J* = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 17.1, 17.3, 36.3, 78.0 (s), 118.0 (t), 126.3 8 (s), 128.4, 129.2, 133.1, 135.1, 160.6 (s), 178.7 (s); HRMS (ESI) calculated for $C_{14}H_{15}NNaO_2$ $[M+Na]^+$ 252.09950, found 252.09999 (Δ = 1.9 ppm).

Synthesis of 4-benzyl-2-phenyl-4-vinyloxazol-5(4*H*)-one (4)

To a solution of 4-benzyl-2-phenyloxazol-5(4H)-one (**1**) (100 mg, 0.40 mmol) in dry THF (0.67 mL, 0.6 M) under nitrogen atmosphere, Et_3N (28 µL, 0.20 mmol) was added and the reaction mixture was cooled at –10°C. A solution of 2-(phenylselenyl)acetaldehyde (83 mg, 0.42 mmol) in dry THF (0.70 mL, 0.60 M) was added and the reaction mixture was stirred for 0.5 h. Formation of the aldol adducts was monitored by TLC analysis, R_f = 0.36 and R_f = 0.29 (hexane/AcOEt 85:15). Afterwards, methanesulfonyl chloride (46 µL, 0.60 mmol) and Et_3N (56 µL, 0.40 mmol) were added in three portions at 10 minute intervals. After each addition, the pH was monitored with litmus paper and, if necessary, Et_3N was added to basify the solution. Formation of mesylates was monitored with TLC analysis, R_f = 0.28 and R_f = 0.23 (hexane/AcOEt 80:20). After 10 minute from the last addition, tetrabutylammonium iodide (145 mg, 0.40 mmol) was added and the reaction mixture was heated in a microwave oven at 110°C for 10 minute in sealed vessel. The reaction temperature was monitored by external surface sensor. After reaction completion, monitored by TLC analysis, the mixture was washed with phosphate buffer saturated with NaCl. The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo. The crude mixture was purified by flash chromatography (SiO_2; hexane/AcOEt 95:05) to obtain **4** as a yellow oil (89 mg, 82 %).

Chiral procedure: **(**$(DHQD)_2$PHAL (0.10 equiv) was used in the aldol condensation step in place of Et_3N (87 mg, 78 %). R_f = 0.63 (hexane/AcOEt 95:05); IR (neat, cm^{-1}) 3031, 2917, 2848, 1815, 1654, 1580, 1450; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.29 (s, 2H), 5.35 (d, *J* = 10.7 Hz, 1H), 5.55 (d, *J* = 17.2 Hz, 1H), 6.14 (dd, *J* = 10.5, 17.2 Hz, 1H), 7.14–7.25 (m, 5H), 7.45 (app t, *J* = 7.8 Hz, 2H), 7.56 (app t, *J* = 7.5 Hz, 1H), 7.91 (app d, *J* = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 44.6 (t), 75.7 (s), 117.9 (t), 126.1 (s), 127.7, 128.3, 128.6, 129.1, 130.7, 133.1, 134.4 (s), 135.0, 160.5 (s), 177.8 (s); HRMS (ESI) calculated for $C_{18}H_{15}NNaO_2$ $[M+Na]^+$ 300.09950, found 300.10005 (Δ = 1.8 ppm).

Synthesis of 1-(4-benzyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)-2-(phenylselanyl)ethyl acetates (5)

To a solution of 4-benzyl-2-phenyloxazol-5(4H)-one (**1**) (100 mg, 0.40 mmol) in dry solvent (0.67 mL, 0.60 M) under nitrogen atmosphere, Et_3N (28 µL, 0.20 mmol) was added and the reaction mixture was cooled at -10°C. A solution of 2-(phenylselenyl)acetaldehyde (71 mg, 0.36 mmol) in dry toluene (0.60 mL, 0.60 M) was added and the reaction mixture was stirred for 0.5 h. Formation of alcohol intermediates **2** was monitored by TLC analysis, R_f = 0.36 and R_f = 0.29 (hexane/AcOEt 85:15). Afterwards acetic anhydride (226 µL, 2.40 mmol) and catalytic 4-dimethylaminopyridine were added. The reaction mixture was allowed to warm to room temperature. After reaction completion was monitored by TLC analysis, a $NaHCO_3$ saturated solution was added and the mixture was extracted three times with DCM. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo. The crude mixture was purified by flash chromatography (SiO_2; hexane/AcOEt 90:10) to obtain diastereoisomers **5**.

Diastereoisomer 5a

Colorless oil (59 mg, 30 %). R_f = 0.35 (hexane/AcOEt 90:10); IR (neat, cm-1) 3058, 2925, 2845, 1818, 1738, 1648, 1578, 1451, 1208, 1050; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98 (s, 3H), 3.15 (d, *J* = 13.1 Hz, 1H), 3.27 (d, *J* = 13.1 Hz, 1H), 3.27–3.45 (m, 2H), 5.69 (dd, J_1 = 3.1 Hz, J_2 = 9.2 Hz, 1H), 7.08–7.20 (m, 5H), 7.26–7.35 (m, 3H), 7.46 (app t, *J* = 7.6 Hz, 2H),

7.53–7.64 (m, 3H), 7.87 (app d, *J* = 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 21.1, 28.5 (t), 40.5 (t), 74.4, 78.0 (s), 125.8 (s), 127.9, 128.0, 128.4, 128.7, 129.1, 129.6, 130.0 (s), 130.6, 133.3 (s), 133.4, 133.8, 161.7 (s), 170.0 (s), 177.0 (s);; HRMS (ESI) calculated for $C_{26}H_{23}NNaO_4Se$ $[M+Na]^+$ 516.07005, found 516.06925 (Δ = 1.6 ppm).

Diastereoisomer 5b

Colorless oil (63 mg, 32%). R_f = 0.33 (hexane/AcOEt 90:10); IR (neat, cm-1) 3060, 2961, 2923, 2850, 1806, 1746, 1651, 1577, 1451, 1217, 1045 ; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.96 (s, 3H), 3.15 (d, *J* = 13.3 Hz, 1H), 3.24 (d, *J* = 13.3 Hz, 1H), 3.25 (dd, J_1 = 3.4 Hz, J_2 = 13.4 Hz, 1H), 3.35 (dd, J_1 = 10.3 Hz, J_2 = 13.4 Hz, 1H), 5.61 (dd, J_1 = 3.4 Hz, J_2 = 10.3 Hz, 1H), 7.12–7.17 (m, 5H), 7.26–7.31 (m, 3H), 7.43 (app t, *J* = 7.6 Hz, 2H), 7.52–7.59 (m, 3H), 7.81–7.86 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 21.0, 27.5 (t), 39.7 (t), 74.2, 77.2 (s), 125.5 (s), 127.9, 128.0, 128.4, 128.7, 129.2, 129.5 (s), 129.7, 130.6, 133.4, 133.5 (s), 133.7, 161.9 (s), 170.1 (s), 177.0 (s); HRMS (ESI) calculated for $C_{26}H_{23}NNaO_4Se$ $[M+Na]^+$ 516.07005, found 516.06934 (Δ = 1.4 ppm).

General procedure for the synthesis of unprotected α-amino acids (10–12)

4-vinyloxazol-5(4*H*)-one was dissolved in TFA/water 90:10 (0.05 M) and heated to 100 °C for 12h. After reaction completion, the solvent was evaporated in vacuo, the residue was recovered with water and washed three times with DCM. The aqueous phase was evaporated in vacuo. Amino acids **10, 11,** and **12** were matched with their reported data [8c, 16].

*2-ammonio-2-benzylbut-3-enoate (**10**).* The title compound was prepared from 4-benzyl-2-phenyl-4-vinyloxazol-5(4*H*)-one **4** (100 mg, 0.36 mmol) according to the general procedure. The crude mixture was purified by ion-exchange chromatography with AMBERLITE IR-120(PLUS)® resin as stationary phase. After the crude mixture was loaded onto the column, the resin was washed with H_2O until the eluted solution turned neutral, then eluted with NH_3 10% aqueous solution. The fractions containing the product were evaporated in vacuo to afford **10** as a white solid (66 mg, 95%).

*2-ammonio-2-methylbut-3-enoate (**11**).* The title compound was prepared from 4-methyl-2-phenyl-4-vinyloxazol-5(4*H*)-one **8** (100 mg, 0.50 mmol) according to the general procedure. The crude mixture was purified by ion-exchange chromatography with AMBERLITE IR-120(PLUS)® resin as stationary phase. After the crude mixture was loaded onto the column, the resin was washed with H_2O until the eluted solution turned neutral, then eluted with NH_3 10% aqueous solution. The fractions containing the product were evaporated in vacuo to afford **11** as a white solid (47 mg, 81%).

*2-ammonio-2-isopropylbut-3-enoate (**12**).* The title compound was prepared from 4-isopropyl-2-phenyl-4-vinyloxazol-5(4*H*)-one **9** (100 mg, 0.44 mmol) according to the general procedure. The crude mixture was purified by ion-exchange chromatography with AMBERLITE IR-120(PLUS)® resin as stationary phase. After the crude mixture was loaded onto the column, the resin was washed with H_2O until the eluted solution turned neutral, then eluted with NH_3 10% aqueous solution. The fractions containing the product were evaporated in vacuo to afford **12** as a white solid (57 mg, 91%).

General procedure for the synthesis of *N*-Cbz-protected amino acids (13–15).

To a solution of quaternary amino acid in dry CH_3CN (0.10 M) under nitrogen atmosphere, tetramethyl ammonium hydroxide monohydrate (2 equiv) was added. The reaction mixture was stirred for 45 minutes, then Cbz_2O (2 equiv) was added. Formation of the *N*-protected derivative was monitored by TLC analysis. After reaction completion, the solvent was evaporated in vacuo. The residue was recovered with a saturated aqueous solution of Na_2CO_3 and washed three times with AcOEt. The pH of the aqueous phase was adjusted to 1 with a HCl 1N solution, and extracted three times with AcOEt. The organic layers were collected, dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo. Amino acids **13,** and **14** were matched with their reported data [7].

*2-benzyl-2-(((benzyloxy)carbonyl)amino)but-3-enoic acid (**13**).* The title compound was prepared from 2-ammonio-2-benzylbut-3-enoate **10** (100 mg, 0.52 mmol) according to the general procedure. The crude mixture was purified by Kugelrohr distillation (110°C, 0.01 mmHg) to obtain **13** as a yellow oil (162 mg, 96%). R_f = 0.53 (DCM/MeOH 90:10 with 1% AcOH).

*2-(((benzyloxy)carbonyl)amino)-2-methylbut-3-enoic acid (**14**).* The title compound was prepared from 2-ammonio-2-methylbut-3-enoate **11** (100 mg, 0.87 mmol) according to the general procedure. The crude mixture was purified by Kugelrohr distillation (110°C, 0.01 mmHg) to obtain **14** as a yellow oil (176 mg, 81 %).

Synthesis of 2-(((benzyloxy)carbonyl)amino)-2-isopropylbut-3-enoic acid (15)

The title compound was prepared from 2-ammonio-2-isopropylbut-3-enoate **12** (100 mg, 0.70 mmol) according to the general procedure. The crude mixture was purified by Kugelrohr distillation (110°C, 0.01 mmHg) to obtain **15** as a yellow oil (151 mg, 78%). R_f = 0.49 (DCM/MeOH 90:10 with 1% AcOH). IR (neat, cm-1) 3315, 3033, 2966, 2925, 2854, 1708, 1661, 1498, 1409, 1258, 1067; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.8 hz, 3H), 2.26 (m, 1H), 4.44–4.97 (br, 1H, exchanges with D_2O), 5.11 (d, *J* = 12.2 Hz, 1H), 5.15 (d, *J* = 12.2 Hz, 1H) 5.22 (d, *J* = 17.4 Hz, 1H), 5.29 (br s, 1H), 5.34 (d, *J* = 10.8 Hz, 1H), 6.26 (dd, J_1 = 10.8 Hz, J_2 = 17.4 Hz, 1H), 7.32–7.43 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ16.7, 17.3, 35.0, 67.0 (s), 67.1, 115.7 (t), 128.2 (2C), 128.5, 133.4, 135.9 (s), 155.4 (s), 175.5 (s); HRMS (ESI) calculated for $C_{15}H_{18}NO_4$ $[M]^-$ 276.12413, found 276.12368 (Δ = 1.6 ppm).

*Synthesis methyl (E)-2-benzamido-2-benzyl-4-(4-nitrophenyl)but-3-enoate (**16**).* To a solution of 4-benzyl-2-phenyl-4-vinyloxazol-5(4*H*)-one **4** (100 mg, 0.36 mmol) in dry MeOH (3.6 mL, 0.10 M) under nitrogen atmosphere, 1-bromo-4-nitrobenzene (80 mg, 0.40 mmol), tetrabutylammonium acetate (326 mg, 1.08 mmol) and Pd EnCat® (90 mg, 0.036 mmol) were added. The reaction mixture was heated in a microwave oven at 120°C for 45 minute. Reaction completion was monitored by TLC analysis, R_f = 0.39 (hexane/AcOEt 70:30). The reaction mixture was filtered with Gooch funnel to remove Pd EnCat®. The solvent was evaporated in vacuo, and the residue was recovered with AcOEt and washed two times with water. The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo. The crude mixture was purified by flash chromatography (SiO_2; hexane/AcOEt 75:25) to obtain **16** as a yellow oil (126 mg, 81%). The product was matched with its reported data [20].

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Keywords: • *α,α*-disubstituted amino acids • aldol condensation • quaternary stereocenter • oxazolones • one-pot vinylation

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Quaternary amino acids

Massimo Serra, Eric Bernardi, Giorgio Marrubini, and Lino Colombo**

Page No. – Page No.

One-pot vinylation of azlactones: fast access to enantioenriched α-vinyl quaternary amino acids

Here we report an efficient protocol for the synthesis of quaternary α-vinyl-α-amino acids, exploiting a direct one-pot vinylation of different azlactones. The key step is an aldol addition with phenylseleno acetaldehyde, followed by a dehydroxyselenation reaction. The final quaternary amino acids were obtained in enantioenriched form (up to 86% ee) and good overall yields (62–78%) by the use of catalytic Sharpless ligand $(DHQD)_2PHAL$ in the aldol addition step.