EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Palladium-Catalyzed Asymmetric Decarboxylative Allylation of Azlactone Enol Carbonates: Fast Access to Enantioenriched α-Allyl Quaternary Amino Acids

Authors: Massimo Serra, Eric Bernardi, Giorgio Marrubini, Ersilia De Lorenzi, and Lino Colombo

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801363

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801363

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201801363

WILEY-VCH

Palladium-Catalyzed Asymmetric Decarboxylative Allylation of Azlactone Enol Carbonates: Fast Access to Enantioenriched α-Allyl Quaternary Amino Acids

Massimo Serra*, Eric Bernardi, Giorgio Marrubini, Ersilia De Lorenzi and Lino Colombo*

Abstract: We report a fast protocol for the synthesis of enantioenriched quaternary 4-allyl oxazol-5-ones. The key step is a Pd-catalyzed enantioselective Tsuji allylation of azlactone allyl enol carbonates, which can be easily prepared starting from racemic α-amino acids. The use of (*R*,*R*)-DACH-phenyl Trost chiral ligand allowed the attainment of the allylated derivatives in very good yields (83–98%) and with *ee* up to 85%. Scaling up the allylation protocol to gram quantities did not affect the yields end *ee* values. The produced 4-allyl azlactones can be converted into the corresponding quaternary amino acids or submitted to further synthetic elaborations exploiting the allyl moiety as a handle for the attachment of alkyl and aryl groups. After hydrolysis of the azlactone ring, the zwitterionic amino acids can be attained in enantiopure or nearly optically pure form through only one recrystallization step.

Introduction

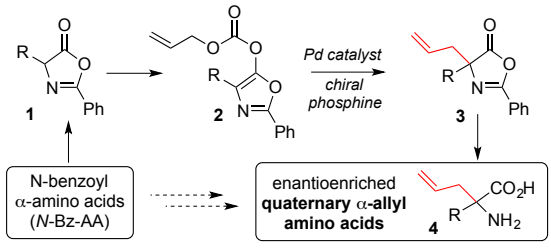
During the last decade the deeper understanding of peptides and peptidomimetics structural properties and the advances in peptide synthesis, prompted the development of a wide range of peptidic drug candidates. To date, more than 80 peptide drugs have reached the market, approximately 140 novel therapeutic peptides are being evaluated in clinical trials, and 400 are in advanced preclinical stages,[1] with a global peptide market value approaching U.S. $21B in 2015 and an expected valuation of $46B by 2024.[2]

The use of peptides as drugs has certain advantages, such as their high biological activity, high specificity and low toxicity, but suffers from some drawbacks, *e.g.* the lack of oral bioavailability and the low stability under physiological conditions, which are the major obstacles preventing peptides from becoming active pharmaceutical ingredients. The development of chemical interventions to stabilize the bioactive structure of peptides in order to increase their bioavailability and bioactivity remains an active area of research.[3] The impact of unnatural amino acids in this field continues to grow at an impressive pace; in particular, quaternary amino acids have been widely used as building blocks for the synthesis of peptides and peptidomimetics thanks to their ability to prevent racemization and ensure higher metabolic stability of the structures in which they are incorporated.[2a,4] Moreover, the substitution at the alpha-carbon of alpha-amino acids can dramatically change their steric features and, as a consequence, affect the conformation of the peptide framework, which plays a predominant role in determining the biological effects of peptides and their analogues.[5] The incorporation of quaternary amino acids carrying a double bond containing moiety at C^{α} not only allows the attainment of biologically active cyclic[6] and stapled peptides,[3,7] but also would make it possible to explore new routes beyond traditional peptide design. Examples of such approaches are site-selective peptide modifications[8] and the preparation of multifunctional peptides, cell penetrating peptides and peptide-drug/polymer conjugates.[1a,9] This gave rise to new attention in the synthesis of α-allyl amino acids as versatile building blocks for the attainment of therapeutic peptides.

Within this line of research, we became interested to the use of 5-alkyl-oxazol-5-(4H)-ones, easily accessible via cyclodehydration of *N*-protected α-amino acids, as substrates for the asymmetric synthesis of α,α-disubstituted (quaternary) α-amino acids.[10] In a previous work we reported the gram scale Pd-catalyzed synthesis of α-allyl-phenylalanine exploiting the synthetic strategy depicted in Scheme 1.[11] The phenylalanine-derived azlactone **1** (R = CH_2Ph) was converted to the corresponding allyl enol carbonate **2**, and submitted to a Tsuji decarboxylative allylation[12] in the presence of a Pd/diphosphine 1:4 complex composed by $Pd_2(dba)_3$ and 1,2-bis(diphenylphosphino)ethane (dppe) to give the 4-allyl azlactone **3**. The rapid, quantitative attainment of the free quaternary α-amino acid **4**, together with the use of readily accessible and cheap starting materials, encouraged us to both extend the substrate scope, and study an enantioselective variant of this transformation.

[a] Dr. M. Serra, Dr. E. Bernardi, Dr. G. Marrubini, Prof. E. De Lorenzi and Prof. L. Colombo
Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section
University of Pavia
Viale Taramelli 12, 27100 Pavia, Italy
E-mail: massimo.serra@unipv.it
http://dipsf.unipv.eu/site/home.html

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))



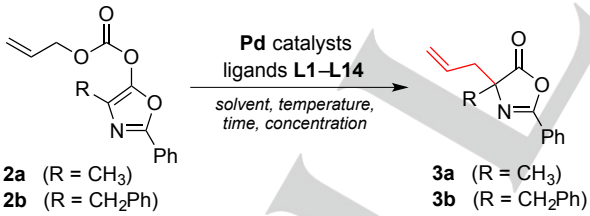
Scheme 1. Asymmetric approach for the synthesis of quaternary α-allyl amino acids.

Here we want to describe an efficient synthetic protocol for the fast conversion of racemic α-amino acids into the corresponding enantioenriched quaternary α-allylated derivatives via decarboxylative allylation of intermediate azlactone allyl enol carbonates.

Results and Discussion

The electrophilic asymmetric allylation at C4 position of the oxazolone ring was firstly reported by Trost et al., which exploited an intermolecular allylic alkylation reaction in the presence of a chiral palladium catalyst to directly install the allyl moiety.[13] High levels of *ee*'s (≥90%) were obtained only with substituted allyl derivatives, while the use of allyl acetate afforded the desired 4-alkyl-4-allyl oxazolones with *ee*'s not higher than 40%. A different strategy made use of a chiral base to deprotonate various oxazolones, followed by allylation of the resulting enolates with allyl bromide to give enantioenriched quaternary allyl oxazolones. Using *Cinchona*-derived dimeric ammonium salts, Tarí et al. performed the allylation of 4-benzyl azlactone with 80% *ee*, whereas 4-methyl, 4-ehtyl, and 4-isobuthyl oxazolones gave allylated products with lower *ee*'s (53–62%). The desired products were obtained in poor to moderate 35–65% yields determined by ^{1}H-NMR.[14] In a similar manner, using tetraaminophosphonium salts as chiral phase-transfer organocatalysts, Uraguchi et al. performed the allylation reaction on phenylalanine- and leucine-derived azlactones with 91% and 83% *ee*, respectively.[15]

The catalytic enantioselective Tsuji allylation of oxazol-5-(4H)-ones has remained essentially unexplored,[16] the only example being the preparation of 4-allyl-4-methyl-oxazol-5-one in a very low 2% *ee* in the presence of (*S*)-*t*-Bu-phosphinooxazoline **L1** as chiral ligand.[17] Starting from these literature data, we decided to perform an extensive study of the various reaction parameters in order to gain higher levels of enantioselectivity (Scheme 2).



Scheme 2. Study of the reaction parameters.

The allyl enol carbonate **2a** can be prepared from racemic alanine in 89% isolated yield without the need of intermediate purifications. The synthetic procedure involves a three-step sequence comprising a Schotten-Baumann benzoylation, a DCC-promoted cyclodehydration, and the final conversion of the obtained oxazolone into the corresponding allyl enol carbonate by prior formation of the enolate and subsequent treatment with allyl chloroformate. It is worth mentioning that the derivative **2a** and the other allyl enol carbonates prepared in this work showed to be much more stable than the related oxazolones towards flash chromatography. Moreover, they can be stored for months at –4 °C without any noticeable loss in titer and purity.

In our initial experiments we planned to explore the reactivity of the most representative chiral ligands usually employed in Pd-catalyzed enantioselective allylations such as 2,4-bis-(diphenylphosphine)pentane (bdpp) **L5**, BINAP **L13**, pyridine bisoxazoline (PyBOX) **L14**, phosphinooxazolines (PHOX) **L1**–**L4**, ferrocenylphosphine **L6**-**L8**, and Trost ligands **L9**–**L12** (Figure 1).[18]

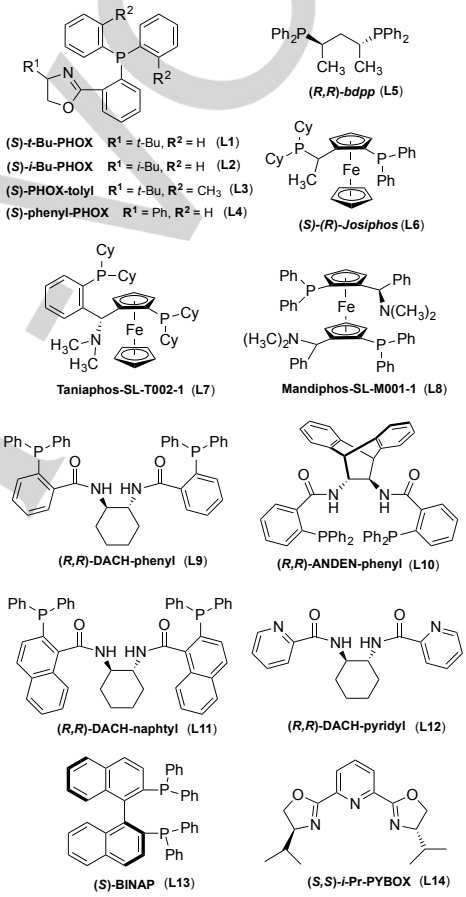


Figure 1. Chiral ligands.

Applying the reaction conditions reported in literature,[17] *i.e.* the use of THF as solvent and a $Pd_2(dba)_3$/phosphine 1:2.5 ratio, only (*R*,*R*)-DACH-phenyl Trost **L9** afforded the allylated product **3a** with some degree of enantioselectivity (24% *ee*), while the other chiral ligands gave *ee* ranging from 0 to 10%.[19] Interestingly, (*R*,*R*)-ANDEN **L10**, which was found to be optimal in the Pd-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) of a wide range of cyclic and acyclic ketones,[20] gave the desired product in low 4% *ee*. Differently from what stated by Trost et al.,[20] using toluene or dioxane, the solvents of choice in DAAA, the yield and *ee* dropped down (Table 1, entry 4 and 9). Similar results were obtained with dimethoxyethane (entry 8),

while in protic solvents such as methanol no reaction occurred (entry 7). The best performing solvent was shown to be acetonitrile, which provided a significant increase in enantioselectivity with only a slight decrease in the allylation yield (entry 6).

Table 1. Solvent screening.

Entry	Solvent	Yield of **3a**[a] [%]	*ee*[b] [%]
1	THF	98	24
2	Et_2O	86	25
3	DCM	49	28
4	Toluene	68	10
5	DMSO	63	30
6	ACN	92	40
7	MeOH	n.r.	-
8	DME	45	2
9	1,4-Dioxane	37	2

[a] Yield of isolated azlactone **3a**. [b] The *ee* values were determined by chiral HPLC with a constant flow rate of 1 mL/min using hexane/isopropyl alcohol 99.75:0.25 as the mobile phase.

Having in our hands grams of 4-benzyl-azlactone **2b**, a key building block for other research projects under study in our lab, we decided to further investigate reaction parameters exploiting **2b** as starting material in the presence of **L9** as chiral ligand (Table 2). Working at standard 0.1 M concentration in ACN, *ee* and yield were only marginally affected by the variation of both the reaction time and temperature (entry 3 and 4). By increasing the $Pd_2(dba)_3$/phosphine ratio to 1:4 and lowering the concentration to 0.01 M we observed an increase in the *ee* (entry 6). The reaction time can be shortened to 30 min without any loss in yield and enantioselectivity (entry 7), which reached a value of 59% when azlactone **2b** was slowly added to the reaction mixture by the use of a syringe pump (entry 9). By raising the reaction temperature up to 50°C (entry 10) and increasing the catalyst/phosphine ratio to 1:6 (entry 11) the enantioselectivity remained unchanged, while the slow addition of the catalyst to a solution of the 4-methyl-oxazol-5-one resulted in almost complete loss of enantioselectivity (entry 12). Finally, warned by a recent report by Lloyd-Jones and coworkers, which showed that the oligomerisation of the substrate-catalyst complex erodes enantioselectivity during Pd-catalysed allylic alkylation mediated by the Trost modular ligand **L9**,[21] we decided to investigate the effect of the catalyst loading on the outcome of the reaction. By doubling the amount of the chiral catalyst, and keeping the Pd/diphosphine ratio unchanged, we observed a significant decrease in the *ee* (entry 13). The best results were conversely obtained lowering the $Pd_2(dba)_3$ amount

Table 2. Screening of the optimal reaction conditions

Entry	Time	Temp (°C)	Conc [M]	Cat[a] (mol%)	**L9** (mol%)	Yield of **3b**[b] [%]	*ee*[c] [%]
1	1 h	rt	0.1	2.5	6.25	94	41
2	1 h	rt	0.1	2.5	7.5	98	43
3	6 h	rt	0.1	2.5	7.5	98	40
4	1 h	0 °C	0.1	2.5	7.5	95	38
5	1 h	rt	0.1	2.5	10	98	47
6	1 h	rt	0.01	2.5	10	96	52
7	30 min	rt	0.01	2.5	10	97	52
8	5 min	rt	0.01	2.5	10	92	50
9[d]	30 min	rt	0.01	2.5	10	98	59
10[d]	30 min	50 °C	0.01	2.5	10	96	58
11[d]	30 min	rt	0.01	2.5	15	96	59
12[e]	30 min	rt	0.01	2.5	10	91	4
13[d]	30 min	rt	0.01	5	20	98	40
14[d]	30 min	rt	0.01	1.0	4.0	98	58
15[d]	30 min	rt	0.01	0.5	2	98	64
16[d]	30 min	rt	0.01	0.1	0.4	98	1

[a] $Pd_2(dba)_3$. [b] Yield of isolated azlactone **3b**. [c] The *ee* values were determined by chiral HPLC with a constant flow rate of 1 mL/min using hexane/isopropyl alcohol 99.75:0.25 as the mobile phase. [d] The oxazolone **1** was slowly added to the reaction mixture by the use of a syringe pump. [e] The chiral catalyst was slowly added to a solution of the oxazolone **1** through a syringe pump

to 0.5 mol% (entry 15), while by further decreasing the catalyst loading we attained an almost racemic mixture of the desired 4-allyl azlactones **3b** (entry 16).

The reaction conditions described in entry 15 were then selected to perform a screening of different palladium sources (Table 3, entries 1–5). The use of $Pd(OAc)_2$ and $PdCl_2$ afforded the allylated derivatives as racemates (entry 4) and in low 18% *ee* (entry 2), while all the examined dimeric Pd-catalysts gave comparable results in terms of yields and enantioselectivities. The best one proved to be allylpalladium (II) chloride dimer, which allowed the attainment of the desired allylated derivative in 66% *ee* and nearly quantitative yield (entry 5). Also in this case the optimization of the catalyst loading turned out to be a suitable strategy to further increase the enantiomeric excess, which reached 70% when 1.0 mol% of $[PdCl(allyl)]_2$ was used (entry 6).

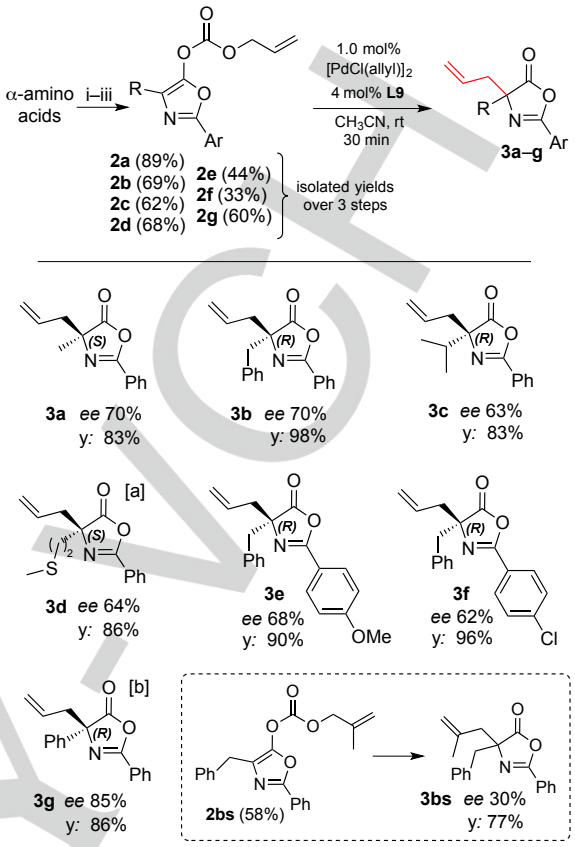
Table 3. Screening of the palladium source.

Entry	Pd Catalyst	Pd catalyst (mol%)	**L9** (mol%)	Yield of **3b**[b] [%]	*ee*[a] [%]
1	$Pd_2(dba)_3$	0.5	2.0	98	64
2	$PdCl_2$	1.0	2.0	92	18
3	$[(Cinnamyl)PdCl]_2$	0.5	2.0	93	62
4	$Pd(OAc)_2$	1.0	2.0	97	0
5	$[PdCl(allyl)]_2$	0.5	2.0	98	66
6	$[PdCl(allyl)]_2$	1.0	4.0	98	70
7	$[PdCl(allyl)]_2$	2.5	10.0	98	62
8	$[PdCl(allyl)]_2$	5.0	20.0	98	53
9	$[PdCl(allyl)]_2$	0.1	0.4	98	30
10	$[PdCl(allyl)]_2$	1.0	2.5	98	64

[a] The *ee* values were determined by chiral HPLC with a constant flow rate of 1 mL/min using hexane/isopropyl alcohol 99.75:0.25 as the mobile phase. [b] Yield of isolated azlactone **3b**.

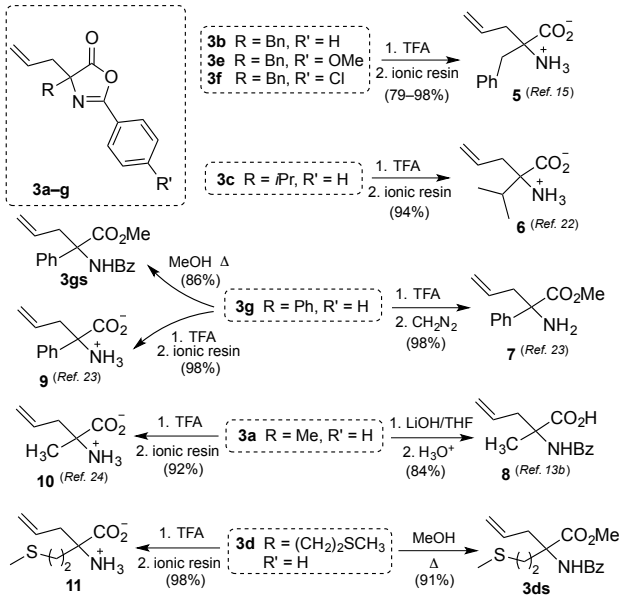
To further examine the substrate scope, the optimized conditions, *i.e.* acetonitrile as a solvent, 1.0 mol% of $[PdCl(allyl)]_2$ in 1:4 ratio with the chiral ligand **L9**, and 0.01M as final substrate concentration, were then applied to the synthesis of 4-allyl azlactones reported in Scheme 3. The allyl enol carbonates **2** were synthesized starting from the corresponding α-amino acids in three-step with yields ranging from 33% (**2f**) to 89% (**2a**), by avoiding intermediate purification processes. The allylation protocol showed to be very efficient, allowing the preparation of the allylated derivatives in high yields with enantiomeric excesses ranging from 62 to 85% ee. The best level of enantioselection (85% ee) was achieved with the sterically demanding α-phenylglycine-derived allyl enol carbonate **2g**. In the presence of an alkyl or benzyl group at C4 as in **2a** and **2b** the *ee* reached a satisfactory 70%. The introduction of a 4-methoxy substituent on the C2 aryl moiety did not affect significantly the outcome of the reaction (**3e**), while an electron withdrawing chlorine atom in the same position led to a slightly decreased *ee* in the product (**3f**). Similar results can be observed in the presence of a branched or a heteroatom-containing C4 alkyl chain. In fact, allyl enol carbonates derived from valine (**2c**) and methionine (**2d**) reacted smoothly to give the corresponding allylated azlactone with 63% and 64% *ee*, respectively. On the contrary, the presence of a substituted allyl moiety, as in the case of enol carbonate **2bs**, resulted in a significant loss of enantioselectivity.

In a preliminary scale-up study, the optimized asymmetric allylation protocol was carried out on the phenylalanine-derived allyl enol carbonate **2b** by increasing tenfold the amount of starting material (up to 1 g). The 4-allyl azlactone **3b** was isolated without any loss in yield and with very similar *ee* value.



Scheme 3. Substrate scope. (i) PhCOCl, 3N NaOH, 0 °C; (ii) DCC, CH_2Cl_2, 0 °C; (iii) allyl chloroformate, Et_3N, THF, 0 °C then rt. [a] The *ee* value was determined on the corresponding N-Bz quaternary amino ester **3ds** (see scheme 4). [b] The *ee* value was determined both, on **3g** and on the corresponding N-Bz quaternary amino ester **3gs** in order to ascertain that the opening of the oxazolone ring occurs without racemization. For details see Supporting Information.

The lack of any literature data about the stereochemistry of the allylated azlactones required the assignment of the absolute configuration of the major enantiomers by correlation with known compounds. For this purpose, we exploited the ring-opening of the azlactone ring under acidic conditions to convert the phenylalanine-derived 4-allyl oxazolones **3b**, **3e**, and **3f** into the corresponding zwitterionic amino acid **5**[15] (Scheme 4). The aforementioned reaction allowed the attainment of the zwitterionic α-allyl valine **6**[22] starting from the parent allylated azlactone **3c**, though the α-allyl phenylglycine methylester **7**[23] was prepared through ring-opening of **3g** followed by diazomethane esterification of the obtained quaternary amino acid. The known N-benzoyl alanine derivative **8**[13b] was synthesized by performing a basic hydrolysis of **3a**, while the methionine-derived azlactone **3d** was transformed into the corresponding N-Bz quaternary amino ester **3ds** through methanolysis of the azlactone ring.



Scheme 4. Preparation of fully deprotected and protected quaternary α-allyl amino acids.

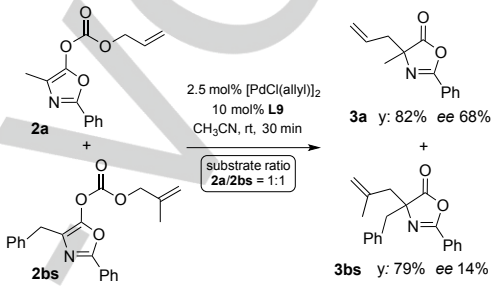
The absolute configuration of the obtained quaternary amino acid derivatives **5**–**8** was determined by comparing their optical rotations with literature values, whereas in the case of the methionine-derived compound **3ds** the configuration was determined by the order of elution of the enantiomers in chiral HPLC in relation to **3gs**.

The synthesis of zwitterionic derivatives **5**, **6** and **9**–**11** was accomplished since we wondered if this methodology could have been applied to the preparation of enantiopure fully deprotected quaternary amino acids. Recrystallization afforded optically pure (*R*)-α-allyl phenylglycine **9**[23], and (*S*)-α-allyl alanine **10**[24], while (*R*)-α-allyl phenylalanine **5**[15] was recovered in estimated 99% *ee* (by comparison with reported specific rotation data). The same procedure allowed attaining the previously unreported methionine derivative **11** in almost enantiopure form, as indicated by comparison of its measured and predicted specific optical rotations. Finally, recrystallized valine derivative **6**[22] showed remarkable increased optical rotation and an estimated *ee* value of 91%.

The synthesis of the methylallyl enol carbonate **2bs** was planned also with the aim to perform a crossover experiment (Scheme 5), as we were curious to ascertain if this decarboxylative allylation proceeded via a tight-ion-pair-type process involving a Pd^{II}-π-allyl complex strictly linked with the nucleophile, or a separate Pd^{II}-π-allyl complex and an enolate species.

To date, the mechanism of bond formation and the origin of enantioselectivity behind these transformations are still quite debated.[25,16b] In one of their initial reports, Trost and coworkers reported minimal cross-over between allyl and crotyl carbonates in palladium catalyzed DAAA using (*R,R*)-ANDEN **L10** as chiral ligand.[26] Conversely, Stoltz's group observed scrambling of allyl termini and complete cross-over when deuterated allyl enol carbonates were reacted in the presence of *t*-Bu-PHOX ligand **L1**.[27] In a subsequent study, Stoltz and Goddard reported a theoretical calculation on the mechanism of Pd-catalyzed DAAA in the presence of the aforementioned ligand **L1**;[17] the computational results were in agreement with an inner-sphere mechanism of the Tsuji allylation reaction. On the other hand, in an extensive experimental work performed by employing various modular ligands, Trost concluded that the C–C bond formation is "more likely an outer-sphere S_N2 substitution than the alternative inner-sphere reductive elimination of the palladium enolate".[20]

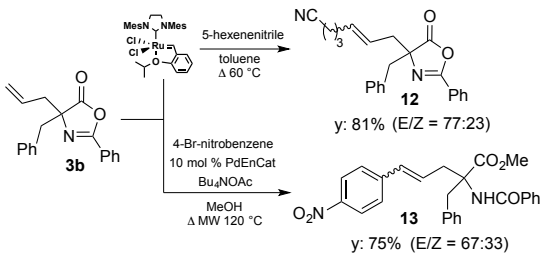
When a 1:1 mixture of allyl enol carbonates **2a** and **2bs** were reacted in the presence of our chiral catalytic system, we



Scheme 5. Crossover experimentation: decarboxylative allylation of an equimolar mixture of **2a** and **2bs**.

isolated only an equimolar amount of the enantioenriched allylated **3a** and methallylated **3bs** compounds**,** with the lack of any scrambling products (Scheme 5). This evidence supports the hypothesis that the allylation proceeds via a tight ion pair intramolecular process.[28]

Finally, we demonstrated that the newly introduced allyl moiety could be manipulated to attain modified azlactones and quaternary amino acids with potential applications in modern peptide synthesis. By reacting racemic **3b** with 5-hexenenitrile in the presence of Hoveyda-Grubbs catalyst, the versatile nitrile functionality was easily introduced on the azlactone quaternary stereocenter to give **12** as a 77:23 mixture of (*E*)/(*Z*) stereoisomers (Scheme 6). Moreover, exploiting a Heck reaction with 1-bromo-4-nitrobenzene in the presence of a polyurea-encapsulated Palladium(II) acetate catalyst (PdEnCAt 30), the allylated oxazolone **3b** was one-pot converted to the corresponding derivatized N- and C-protected quaternary amino acid **13** as a 67:33 mixture of (*E*)/(*Z*) stereoisomers.



Scheme 6. Functionalization of the allyl moiety.

Conclusions

We have developed a fast synthetic protocol for the preparation of enantioenriched quaternary 4-allyl oxazol-5-ones, which can give access to the corresponding quaternary amino acids through opening of the azlactone ring. The starting substrates, *i.e.* the azlactone allyl enol carbonates, can be prepared from racemic α-amino acids without the need of intermediate purifications, and showed to be much more stable than the parent oxazolones. The key Pd-catalyzed enantioselective Tsuji allylation, using (*R*,*R*)-DACH-phenyl Trost as chiral ligand, allowed the attainment of the allylated derivatives in very good yields (83–98%) and with *ee* up to 85%. The quaternary zwitterionic amino acids resulting from hydrolysis of the azlactone ring can be recovered in their enantiopure form or in high optical purity after a simple recrystallization step. Finally, we demonstrated that the allyl moiety installed onto the oxazolone ring could be exploited as a handle for the introduction of alkyl and aryl groups, thus allowing the synthesis 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.[29] 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. High-resolution mass spectra (HRMS) were acquired with an APEX IITM Bruker mass spectrometer (4.7 Tesla) & Xmass software (Bruker Daltonics). 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 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 the allyl enol carbonates 2a–2g

The amino acid derivative (1.0 equiv.) was dissolved in a 3 N aqueous solution of NaOH (0.10 M) at 0 °C and benzoylated under Schotten-Baumann conditions by performing three sequential additions of benzoyl chloride (1.0 eq) and 6 N aqueous NaOH (3.0 eq) at 30 minutes intervals. Afterwards, the reaction mixture was stirred for 1 hour at 0 °C and filtered through a Gooch apparatus. The solid residue was washed with cold water and dried in vacuo for 12 hours. The *N*-benzoyl amino acid (1 equiv.) was added portionwise over 20 min to a stirred solution of DCC (1 equiv.) in dry CH_2Cl_2 (0.30 M) under a nitrogen atmosphere at 0 °C. The progress of the reaction was monitored by TLC analysis. While the reaction mixture was kept at 0°C, a vacuum filtration with a Gooch apparatus was performed. The solvent from the filtrate was evaporated in vacuo to obtain the desired azlactones as white amorphous solids. To a solution of crude oxazolone (1.0 equiv.) in dry THF (0.10 M) under nitrogen atmosphere at 0°C, NEt_3 (1.1 equiv.) and allyl chloroformate (1.1 equiv.) were added. Afterwards, the reaction mixture was warmed to room temperature and the formation of the product was monitored by TLC analysis. After 12 hours, H_2O was added, the organic solvent was evaporated in vacuo and the aqueous layer was extracted three times with Et_2O. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated in vacuo.

Allyl (4-methyl-2-phenyloxazol-5-yl) carbonate (2a)

The title compound was prepared from L-alanine (1.00 g, 11.2 mmol) according to the general procedure. The product was purified by flash chromatography to give **2a** as a white amorphous solid (2.60 g, 89% over three steps). The spectroscopic data of compound **2a** were matched with literature values.[30]

Allyl (4-benzyl-2-phenyloxazol-5-yl) carbonate (2b)

The title compound was prepared from L-phenylalanine (1.00 g, 6.05 mmol) according to the general procedure. The product was purified by flash chromatography to give **2b** as a pale yellow amorphous solid (1.40 g, 69% over three steps). The spectroscopic data of compound **2b** were matched with literature values.[11]

Allyl (4-isopropyl-2-phenyloxazol-5-yl) carbonate (2c)

The title compound was prepared from L-valine (1.00 g, 8.54 mmol) according to the general procedure. The product was purified by flash

chromatography to give **2c** as a colourless oil (1.52 g, 62% over three steps). R_f = 0.24 (hexane/AcOEt 90:10); IR (neat, cm^{-1}) 3062, 2968, 2875, 1783, 1654, 1198; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, *J* = 6.9 Hz, 6 H), 2.92 (septuplet, *J* = 6.9 Hz, 1 H), 4.81 (dt, *J* = 1.3, 5.9 Hz, 2 H), 5.39 (dq, *J* = 1.3, 10.4 Hz, 1 H), 5.48 (dq, *J* = 1.3, 17.1 Hz, 1 H), 6.02 (ddt, *J* = 5.9, 10.4, 17.1 Hz, 1 H), 7.41–7.47 (m, 3 H), 7.95–8.02 (m, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 21.4, 25.8, 70.8 (t), 120.7 (t), 126.4, 127.7 (s), 129.0, 129.9 (s), 130.5, 130.7, 144.9 (s), 152.1 (s), 155.2 (s) HRMS (ESI) calcd. for $C_{16}H_{18}NO_4$ $[M + H]^+$ 288.1236; found 288.1225 (Δ = –3.8 ppm).

Allyl (4-(2-(methylthio)ethyl)-2-phenyloxazol-5-yl) carbonate (2d)

The title compound was prepared from L-methionine (1.00 g, 6.70 mmol) according to the general procedure. The product was purified by flash chromatography to give **2d** as a pale yellow amorphous solid (1.46 g, 68% over three steps). R_f = 0.29 (hexane/AcOEt 90:10); IR (neat, cm^{-1}) 3074, 2916, 1785, 1664, 1243, 1209; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3 H), 2.77–2.89 (m, 4 H), 4.81 (d, *J* = 5.9 Hz, 2 H), 5.39 (d, *J* = 10.4 Hz, 1 H), 5.48 (d, *J* = 17.1 Hz, 1 H), 6.01 (ddt, *J* =5.9, 10.4, 17.1 Hz, 1 H), 7.40–7.48 (m, 3 H), 7.92–7.99 (m, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 15.9, 25.6 (t), 32.7 (t), 71.0 (t), 120.9 (t), 123.3 (s), 126.3, 127.4 (s), 129.1, 130.6, 130.8, 146.6 (s),151.7 (s), 155.5 (s); HRMS (ESI) calcd. for $C_{16}H_{17}NO_4SNa$ $[M + Na]^+$ 342.0776; found 342.0778 (Δ = 0.6 ppm).

Allyl (4-benzyl-2-(4-methoxyphenyl)oxazol-5-yl) carbonate (2e)

The title compound was prepared from L-phenylalanine (1.00 g, 6.05 mmol) according to the general procedure. The product was purified by flash chromatography to give **2e** as pale yellow amorphous solid (0.98 g, 44% over three steps). R_f = 0.33 (hexane/AcOEt 85:15); IR (neat, cm^{-1}) 3063, 2944, 2839, 1782, 1663, 1206, 1166; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.87 (s, 3H), 3.88 (s, 2 H), 4.71 (dt, *J* = 1.3, 5.9 Hz, 2 H), 5.38 (dq, *J* = 1.2, 10.4 Hz, 1 H), 5.44 (dq, *J* = 1.3, 17.2 Hz, 1 H), 5.95 (ddt, *J* = 5.9, 10.4, 17.2 Hz, 1 H), 6.95 (d, *J* = 8.9 Hz, 2 H), 7.24 (m, 1 H), 7.30–7.33 (m, 4 H), 7.90 (d, *J* = 8.9 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 31.9 (t), 55.8, 70.8 (t), 114.5, 120.2 (s), 120.8 8t), 123.4 (s), 126.9, 128.1, 128.8, 129.3, 130.6, 138.0 (s), 146.3 (s), 151.7 (s), 155.7 (s), 161.7 (s); HRMS (ESI) calcd. for $C_{21}H_{19}NO_5Na$ $[M + Na]^+$ 388.1161; found 388.1165 (Δ = 1.0 ppm).

Allyl (4-benzyl-2-(4-chlorophenyl)oxazol-5-yl) carbonate (2f)

The title compound was prepared from L-phenylalanine (1.00 g, 6.05 mmol) according to the general procedure. The product was purified by flash chromatography to give **2f** as a yellow amorphous solid (0.74 g, 33% over three steps). R_f = 0.27 (hexane/AcOEt 90:10); IR (neat, cm^{-1}): 3060, 2927, 2902, 1780, 1668, 1206, 1166, 1093; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.89 (s, 2 H), 4.72 (dt, *J* = 1.1, 6.0 Hz, 2 H), 5.39 (dq, *J* = 1.1, 10.4 Hz, 1 H), 5.45 (dq, *J* = 1.3, 17.2 Hz, 1 H), 5.96 (ddt, *J* = 5.9, 10.4, 17.2 Hz, 1 H), 7.25 (m, 1 H), 7.30–7.36 (m, 4 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.90 (d, *J* = 8.7 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 31.8 (t), 70.9 (t), 120.9 (t), 124.1 (s), 126.0 (s), 127.0, 127.7, 128.9, 129.2, 129.4, 130.5, 136.8 (s), 137.8 (s), 146.8 (s), 151.6 (s), 154.6 (s); HRMS (ESI) calcd. for $C_{20}H_{16}NO_4NaCl$ $[M + Na]^+$ 392.0666; found 392.0674 (Δ = 2.0 ppm).

Allyl (2,4-diphenyloxazol-5-yl) carbonate (2g)

The title compound was prepared from L-α-phenylglycine (1.00 g, 8.68 mmol) according to the general procedure. The product was purified by flash chromatography to give **2g** as a pale yellow amorphous solid (1.68 g, 60% over three steps). R_f = 0.27 (hexane/AcOEt 97:03); IR (neat, cm^{-1}) 3031, 2950, 1781, 1752, 1649, 1201; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.85 (dt, *J* = 1.3, 5.9 Hz, 2 H), 5.42 (dq, *J* = 1.2, 10.4 Hz, 1 H), 5.50 (dq, *J* = 1.3, 17.2 Hz, 1 H), 6.03 (ddt, *J* = 5.9, 10.4, 17.2 Hz, 1 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 7.43–7.52 (m, 5 H), 7.85 (d, *J* = 7.3 Hz, 2 H), 8.05–8.11 (m, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 71.2 (t), 121.0 (t), 124.1 (s), 126.3, 126.6, 127.4 (s), 128.4, 129.1, 129.2, 130.2 (s), 130.5, 130.9, 145.6 (s), 151.5 (s), 155.6 (s); HRMS (ESI) calcd. for $C_{19}H_{15}NO_4Na$ $[M + Na]^+$ 344.0899; found 344.0900 (Δ = 0.3 ppm).

4-benzyl-2-phenyloxazol-5-yl (2-methylallyl) carbonate (2bs)

2-Methylprop-2-en-1-ol (172 mg, 2.39 mmol) was dissolved in dry toluene (3.0 ml, 0.80 M) at 0 ºC, under a nitrogen atmosphere, and K_2CO_3 (396 mg, 2.87 mmol) was added to the reaction mixture. Then, a solution of triphosgene (508 mg, 1.71 mmol) in dry toluene (1.8 ml, 0.66 M) was added drop-wise. After 2 h the reaction was bubbled with nitrogen to remove the excess of phosgene, and was transferred via cannula into a round-bottom flask containing 4-benzyl-2-phenyloxazol-5(4H)-one[10c] (300 mg, 1.19 mmol) and Et_3N (0.500 ml, 3.74 mmol) in dry THF (5.42 ml, 0.22 M) cooled at 0 °C. After 12 hours, H_2O was added, the organic solvent was evaporated in vacuo and the aqueous layer was extracted three times with Et_2O. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated in vacuo. The crude mixture was purified by flash chromatography to give a white amorphous solid (242 mg, 58%). R_f = 0.26 (hexane/AcOEt 95:05); IR (neat, cm^{-1}): 3030, 2944, 2926, 1778, 1665, 1209; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.80–1.83 (m, 3 H), 3.91 (s, 2 H), 4.63–4.65 (m, 2 H), 5.05 (m, 1 H), 5.09 (quintuplet, *J* = 1.1 Hz, 1 H), 7.25 (m, 1 H), 7.30–7.34 (m, 4 H), 7.42–7.47 (m, 3 H), 7.94–8.00 (m, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 19.7, 31.9 (t), 73.6 (t), 115.5 (t), 126.4, 126.9, 127.5 (s), 128.9, 129.1, 129.2, 130.7, 137.9 (s), 138.5 (s), 146.7 (s), 151.7 (s), 155.5 (s); HRMS (ESI) calcd. for $C_{21}H_{19}NO_4Na$ $[M + Na]^+$ 372.1212; found 372.1212 (Δ = 0.0 ppm).

General procedure for the asymmetric Tsuji decarboxylative allylation

To a solution of Pd catalyst (0.01 eq) and chiral phosphine (0.04 eq) in dry CH_3CN (0.015 M), a solution of allyl enol carbonate (1.0 eq) in dry CH_3CN (0.03 M) was added over 5 minutes by using a syringe-pump. After 30 minutes, phosphate buffer (pH 7.4) was added and the organic solvent was evaporated at reduced pressure. The aqueous layer was extracted with DCM and the organic phases were collected, dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo.

4-allyl-4-methyl-2-phenyloxazol-5(4*H*)-one (3a)

The title compound was prepared from **2a** (50 mg, 0.19 mmol) according to the general procedure. The product was purified by flash chromatography to give **3a** as a colourless oil (34 mg, 83%). The

spectroscopic data of compound **3a** were matched with literature values.[17]

4-allyl-4-benzyl-2-phenyloxazol-5(4*H*)-one (3b)

The title compound was prepared from **2b** (1.0 g, 2.98 mmol) according to the general procedure. The product was purified by flash chromatography to give **3b** as a colourless oil (851 mg, 98%). The spectroscopic data of compound **3b** were matched with literature values.[11]

4-allyl-4-isopropyl-2-phenyloxazol-5(4*H*)-one (3c)

The title compound was prepared from **2c** (50 mg, 0.17 mmol) according to the general procedure. The product was purified by flash chromatography to give **3c** as a colourless oil (34 mg, 83%). The spectroscopic data of compound **3c** were matched with literature values.[31]

4-allyl-4-(2-(methylthio)ethyl)-2-phenyloxazol-5(4*H*)-one (3d)

The title compound was prepared from **2d** (50 g, 0.16 mmol) according to the general procedure. The product was purified by flash chromatography to give **3d** as a colourless oil (38 g, 86%). R_f = 0.30 (hexane/AcOEt 90:10); $[\alpha]_D^{22}$ –23.5 (c = 1.0, $CDCl_3$); IR (neat, cm^{-1}) 3076, 2917, 2852, 1813, 1651, 1290; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3 H), 2.23–2.29 (m, 2 H), 2.40 (m, 1 H), 2.50 (m, 1 H), 2.59 (ddt, *J* = 0.9, 7.8, 13.6 Hz, 1 H), 2.67 (ddt, *J* = 1.1, 6.9, 13.6 Hz, 1 H), 5.14 (dq, *J* = 0.9, 10.1 Hz, 1 H), 5.20 (dq, *J* = 1.2, 17.1 Hz, 1 H), 5.67 (dddd, *J* = 6.9, 7.8, 10.1, 17.1 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 7.60 (tt, *J* = 1.3, 7.5 Hz, 1 H), 7.99–8.05 (m, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 15.6, 29.1 (t), 36.3 (t), 42.3 (t), 73,1 (s), 121.3 (t), 126.1 (s), 128.4, 129.2, 130.6, 132.2, 161.0 (s), 180.0 (s); HRMS (ESI) calcd. for $C_{15}H_{17}NO_2NaS$ $[M + Na]^+$ 298.0878; found 298.0883 (Δ = 1.7 ppm).

4-allyl-4-benzyl-2-(4-methoxyphenyl)oxazol-5(4*H*)-one (3e)

The title compound was prepared from **2e** (50 mg, 0.14 mmol) according to the general procedure. The product was purified by flash chromatography to give **3e** as a colourless oil (41 mg, 90%). The spectroscopic data of compound **3e** were matched with literature values.[14]

4-allyl-4-benzyl-2-(4-chlorophenyl)oxazol-5(4*H*)-one (3f)

The title compound was prepared from **2f** (50 mg, 0.14 mmol) according to the general procedure. The product was purified by flash chromatography to give **3f** as a colourless oil (44 g, 96%). The spectroscopic data of compound **3f** were matched with literature values.[14]

4-allyl-2,4-diphenyloxazol-5(4*H*)-one (3g)

The title compound was prepared from **2g** (50 mg, 0.16 mmol) according to the general procedure. The product was purified by flash chromatography to give **3g** as a colourless oil (38 mg, 86%). The spectroscopic data of compound **3g** were matched with literature values.[31]

4-benzyl-4-(2-methylallyl)-2-phenyloxazol-5(4*H*)-one (3bs)

The title compound was prepared from **2bs** (50 mg, 0.14 mmol) according to the general procedure. The product was purified by flash chromatography to give **3bs** as a colourless oil (28 mg, 64%). R_f = 0.33 (hexane/AcOEt 97:03); IR (neat, cm^{-1}): 3063, 2923, 2854, 1815, 1652, 1290, 1096; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.77 (s, 3 H), 2.73 (d, *J* = 13.4 Hz, 1 H), 2.79 (d, *J* = 13.4 Hz, 1 H), 3.19 (d, *J* = 13.4 Hz, 1 H), 3.26 (d, *J* = 13.4 Hz, 1 H), 4.86 (s, 2 H), 7.12–7.22 (m, 5 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.85 (d, *J* = 7.5 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 24.6, 44.2 (t), 45.3 (t), 75.9 (s), 116.4 (t), 126.2 (s), 127.6, 128.2, 128.5, 129.1, 130.6, 132.8, 134.7 (s), 140.3 (s), 160.1 (s), 179.7 (s); HRMS (ESI) calcd. for $C_{20}H_{19}NO_2Na$ $[M + Na]^+$ 328.1313; found 328.1309 (Δ = –1.2 ppm).

Synthesis of methyl 2-benzamido-2-(2-(methylthio)ethyl)pent-4-enoate (3ds)

Compound **3d** (50 mg, 0.18 mmol) was dissolved in dry MeOH (1.8 ml, 0.10 M) and a saturated HCl methanolic solution (50 µl) was added. Afterwards the reaction mixture was heated at 120 °C for 1.5 hours by microwave irradiation. The solvent was evaporated in vacuo and the crude mixture was purified by flash chromatography to give compound **3ds** as a colorless oil (50 mg, 91%). R_f = 0.27 (hexane/AcOEt 80:20); IR (neat, cm^{-1}) 3407, 3321, 3063, 2950, 2917, 1735, 1643, 1226; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3 H), 2.19–2.36 (m, 2 H), 2.51 (m, 1 H), 2.60 (dd, *J* = 7.5, 13.8 Hz, 1 H), 3.02 (m, 1 H), 3.41 (dd, *J* = 7.3, 13.8 Hz, 1 H), 3.84 (s, 3 H), 5.04–5.15 (m, 2 H), 5.63 (ddt, *J* = 7.4, 10.1, 17.4 Hz, 1 H), 7.26 (s, 1 H), 7.64 (t, *J* = 7.4 Hz, 2 H), 7.54 (t, *J* = 7.3 Hz, 1 H), 7.81 (d, *J* = 7.3 Hz, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 16.0, 29.5 (t), 34.6 (t), 40.0 (t), 53.4, 64.9 (s), 119.8 (t), 127.3, 129.0, 132.0, 132.3, 135.1 (s), 166.7 (s), 174.4 (s); HRMS (ESI) calcd. for $C_{16}H_{21}NO_3NaS$ $[M + Na]^+$ 330.1140; found 330.1143 (Δ = 0.9 ppm).

Synthesis of methyl 2-benzamido-2-phenylpent-4-enoate (3gs)

Compound **3g** (50 mg, 0.18 mmol) was dissolved in dry MeOH (1.8 ml, 0.10 M) and a saturated HCl methanolic solution (50 µl) was added. Afterwards the reaction mixture was heated at 120 °C for 1.5 hours by microwave irradiation. The solvent was evaporated in vacuo and the crude mixture was purified by flash chromatography to give compound **3gs** as a colorless oil (48 mg, 86%). R_f = 0.31 (hexane/AcOEt 85:15); IR (neat, cm^{-1}): 3413, 3062, 2952, 1731, 1667, 1480, 1230; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.32 (dd, *J* = 7.6, 13.6 Hz, 1 H), 3.76 (s, 3 H), 3.84 (dd, *J* = 6.9, 13.6 Hz, 1 H), 5.15 (dd, *J* = 1.7, 10.2 Hz, 1 H), 5.21 (dd, *J* = 1.7, 17.1 Hz, 1 H), 5.73 (dddd, *J* = 6.9, 7.6, 10.2, 17.1 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.39 (t, *J* = 7.1 Hz, 2 H), 7.47 (t, *J* = 7.2 Hz, 2 H), 7.50–7.57 (m, 3 H), 7.74 (s, 1 H), 7.85 (d, *J* = 7.1 Hz, 1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 37.6 (t), 53.8, 66.2 (s), 120.1 (t), 126.4, 127.4, 128.4, 129.0 (2C),

132.1, 132.7, 135.0 (s), 139.5 (s), 166.0 (s), 173.6 (s); HRMS (ESI) calcd. for $C_{19}H_{19}NO_3Na$ $[M + Na]^+$ 332.1263; found 332.1270 (Δ = 2.1 ppm).

General procedure for the ring-opening of azlactone ring under acidic conditions

The allyl oxazolone (1.0 eq) was dissolved in TFA/water 90:10 (0.1 M), and the solution was heated at 100 °C for 12 h. After evaporation of the solvent under reduced pressure, water was added to the residue, and the mixture was washed three times with DCM. The aqueous phase was evaporated in vacuo to give the fully deprotected quaternary amino acid.

2-ammonio-2-benzylpent-4-enoate (5)

The title compound was prepared from compound **3b** (152 mg, 0.521 mmol), **3e** (36 mg, 0.19 mmol) and **3f** (34 mg, 0.10 mmol) according to the general procedure for the ring-opening of azlactone ring under acidic conditions. The crude mixture was purified by ion-exchange chromatography with Amberlite IR-120 (Plus)® resin as the 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 it was eluted with NH_3 (10% aqueous solution). The fractions containing the product were evaporated in vacuo to give **5** (105 mg, 98% starting from **3b**; 34 mg, 87% starting from **3e**; 17 mg, 79 % starting from **3f**) as a white solid. The quaternary amino acid deriving from acid hydrolysis of **3b** was crystalized from MeOH to afford racemic compound **5** (33 mg, 32%). The mother liquors were evaporated in vacuo to attain the desired (*R*)-enantiomer in estimated 99% *ee* (71 mg, 68%).[11] The spectroscopic data of compound **5** were matched with literature values.[11] $[\alpha]_D^{22}$ = -13.1 (1.0 c, H_2O, before crystallization), $[\alpha]_D^{22}$ = -24.9 (1.0 c, H_2O, after crystallization). Melting point: 188-190 °C.

2-ammonio-2-isopropylpent-4-enoate (6)

The title compound was prepared from compound **3c** (160 mg, 0.658 mmol) according to the general procedure for the ring-opening of azlactone ring under acidic conditions. The crude mixture was purified by ion-exchange chromatography with Amberlite IR-120 (Plus)® resin as the 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 it was eluted with NH_3 (10% aqueous solution). The fractions containing the product were evaporated in vacuo to give **10** (97 mg, 94%) as a white solid. The product was crystalized from *i*PrOH/H_2O (10:2) to afford the desired (*R*)-enantiomer in estimated 91% *ee* (59 mg, 61%). The spectroscopic data of compound **6** were matched with literature values.[22] $[\alpha]_D^{22}$ = -22.6 (0.5 c, H_2O, before crystallization), $[\alpha]_D^{22}$ = -30.3 (0.5 c, H_2O, after crystallization). Melting point: 225-228 °C.

Methyl 2-ammonio-2-phenylpent-4-enoate (7)

The title compound was prepared from compound **3g** (80 mg, 0.28 mmol) according to the general procedure for the ring-opening of azlactone ring under acidic conditions. The crude mixture was dissolved in dry methanol (2.8 ml, 0.10 M) and, afterwards, a 0.30 M solution of diazomethane in Et_2O (0.93 ml, 0.28 mmol) was added. After 3 hours, the solvent was evaporated in vacuo and the residue was recovered with a 1.0 M solution of HCl. The aqueous layer was washed with DCM, basified to pH 12 with a 3.0 M aqueous solution of NaOH and extracted three times with AcOEt. The organic phases were collected, dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo to afford compound 7 was obtained as a pale yellow oil. The spectroscopic data of compound **7** were matched with literature values.[23]

Synthesis of 2-benzamido-2-methylpent-4-enoic acid (8)

To a solution of **3a** (22 mg, 0,10 mmol) in dry THF (1.0 mL, 0.10 M), a 1.6 M aqueous solution of LiOH was added (5.0 µL, 1.2 mmol). After 2 h the organic solvent was evaporated in vacuo and the residue was washed two times with DCM. Then, the aqueous phase was acidified to pH 1 with a 6 M aqueous solution of HCl and was extracted three times with DCM. The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated in vacuo to give **8** as a yellow solid (20 mg, 84%) without the need of further purifications. The spectroscopic data of compound **8** were matched with literature values.[13b]

2-ammonio-2-phenylpent-4-enoate (9)

The title compound was prepared from compound **3g** (142 mg, 0.512 mmol) according to the general procedure for the ring-opening of azlactone ring under acidic conditions. The crude mixture was purified by ion-exchange chromatography with Amberlite IR-120 (Plus)® resin as the 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 it was eluted with NH_3 (10 % aqueous solution). The fractions containing the product were evaporated in vacuo to give **9** (96 mg, 98%) as a white solid. The spectroscopic data of compound **9** were matched with literature values.[23a] The product was crystalized from EtOH/H_2O (10:1.5) to afford racemic **9** (23 mg, 24%). The mother liquors were evaporated in vacuo to attain the desired optically pure (*R*)-enantiomer (73 mg, 76%). $[\alpha]_D^{22}$ = -15.3 (0.5 c, 1 N HCl), Lit. (*S*)-enantiomer[23b] $[\alpha]_D^{22}$ = +12.6 (0.5 c, 1 N HCl). Melting point: 188-190 °C. The optical purity was further confirmed by comparing the $[\alpha]_D^{22}$ values in H_2O before and after the crystallization process, -23.7 (0.5 c, H_2O) and -27.0 (0.5 c, H_2O), respectively.

2-ammonio-2-methylpent-4-enoate (10)

The title compound was prepared from compound **3a** (153 mg, 0.711 mmol) according to the general procedure for the ring-opening of azlactone ring under acidic conditions. The crude mixture was purified by ion-exchange chromatography with Amberlite IR-120 (Plus)® resin as the 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 it was eluted with NH_3 (10% aqueous solution). The fractions containing the product were evaporated in vacuo to give **10** (84 mg, 92%) as a white solid. The spectroscopic data of compound **10** were matched with literature values.[22] The product was crystalized from EtOH/H_2O (10:1) to afford the optically pure (*S*)-enantiomer (54 mg, 64%).[24] $[\alpha]_D^{22}$ = -28.8 (0.5 c, H_2O), Lit.[24] $[\alpha]_D^{22}$ = -28.5 (0.5 c, H_2O). Melting point: 269-271 °C.

2-ammonio-2-((methylthio)methyl)pent-4-enoate (11)

The title compound was prepared from compound **3d** (163 mg, 0.592 mmol) according to the general procedure for the ring-opening of azlactone ring under acidic conditions. The crude mixture was purified by ion-exchange chromatography with Amberlite IR-120 (Plus)® resin as the 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 it was eluted with NH_3 (10% aqueous solution). The fractions containing the product were evaporated in vacuo to give **11** (110 mg, 98%) as a white solid. The product was crystalized from EtOH/H_2O (10:1.5) to afford the estimated optically pure (*S*)-enantiomer (65 mg, 59 %). $[\alpha]_D^{22}$ = -4.1 (0.5 c, H_2O, before crystallization), $[\alpha]_D^{22}$ = -6.6 (0.5 c, H_2O, after crystallization). Melting point: 175-178 °C. IR (neat, cm^{-1}): 3075, 2975, 2916, 1591, 1518, 1439, 1384, 1310; ^1H NMR (D_2O, 400 MHz) δ 1.99 (m, 1H), 2.05 (s, 3H), 2.13 (m, 1H), 2.37–2.47 (m, 2H), 2.48–2.68 (m, 2H), 5.17–5.28 (m, 2H), 5.58 (m, 1H); $^{13}C\{^1H\}$ NMR (D_2O, 50 °C, 100 MHz) δ 14.8, 28.1 (t), 35.8 (t), 41.0 (t), 65.0 (s), 122.3 (t), 131.0, 175.1 (s); HRMS (ESI) calcd. for $C_8H_{16}NO_2S$ $[M + H]^+$ 190.0902; found 190.0904 (Δ = 1.1 ppm).

Synthesis of (*E*)-7-(4-benzyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)hept-5-enenitrile (12)

Compound **3b** (50 mg, 0,17 mmol) and 5-hexenenitrile (49 mg, 0.51 mmol) were dissolved in dry toluene (1.7 mL, 0.10 M) under nitrogen atmosphere. Afterward, Hoveyda-Grubbs II generation catalyst (11 mg, 10% mol) was added and the reaction mixture was heated at 60 °C. Reaction completion was monitored by TLC analysis, R_f = 0.25 (hexane/AcOEt 80:20). After 5 hours the solvent was evaporated in vacuo and the crude mixture was purified by flash chromatography to give **9b** as a pale yellow oil (50 mg, 81%). R_f = 0.19 (hexane/AcOEt 80:20); IR (neat, cm-1): 3031, 2922, 2851, 2246, 1814, 1654; ^1H NMR ($CDCl_3$, 400 MHz, mixture of E/Z diastereoisomers). The integral of the isolated quartet at 2.19 ppm, belonging to the major diastereoisomer, was arbitrarily assigned the value of two protons: δ 1.63 (quintuplet, *J* = 7.1 Hz, 2 H), 1.72 (quintuplet, *J* = 7.2 Hz, 0.6 H), 2.11 (q, *J* = 7.1 Hz, 2 H), 2.19 (t, *J* = 7.1 Hz, 2 H), 2.26 (q, *J* = 7.2 Hz, 0.6 H), 2.34 (t, *J* = 7.2 Hz, 0.6 H), 2.65–2.87 (m, 2.6 H), 3.12–3.32 (m, 2.6 H), 5.37–5.50 (m, 1.6 H), 5.55 (dt, *J* = 7.0, 15.2 Hz, 1 H), 7.14–7.23 (m, 6.5 H), 7.42–7.49 (m, 2.6 H), 7.52–7.58 (m, 1.3 H), 7.84–7.90 (m, 2.6 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, mixture of E/Z diastereoisomers) δ 16.4 (t), 16.9 (t), 25.1 (t), 25.5 (t), 26.7 (t), 31.5 (t), 35.3 (t), 40.7 (t), 43.5 (t), 43.7 (t), 75.2 (s), 75.3 (s), 119.7 (s), 119.9 (s), 123.9, 124.9, 125.7 (s), 125.8 (s), 127.7, 128.2, 128.6, 129.1, 129.2, 130.5, 132.9, 133.1, 133.2, 134.5, 134.6 (2C), 160.5 (s, 2C), 179.2 (s), 179.4 (s); HRMS (ESI) calcd. for $C_{23}H_{22}N_2O_2Na$ $[M + Na]^+$ 381.1579; found 381.1581 (Δ = 0.5 ppm).

Synthesis of methyl 2-benzamido-2-benzyl-5-(4-nitrophenyl)pent-4-enoate (13)

To a solution of **3b** (50 mg, 0,17 mmol) in dry MeOH (1.7 mL, 0.10 M) under nitrogen atmosphere, 1-bromo-4-nitrobenzene (38 mg, 0.19 mmol), tetrabutylammonium acetate (0.16 g, 0.52 mmol) and Pd EnCat 30® (43 mg, 10% mmol) were added. The reaction mixture was heated at 120°C for 15 minute by microwave irradiation. Reaction completion was monitored by TLC analysis, R_f = 0.26 (hexane/AcOEt 80:20). The reaction mixture was filtered with a Gooch apparatus to remove Pd EnCat 30®. 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 to give **10b** as a yellow solid (57 mg, 75%). R_f = 0.20 (hexane/AcOEt 80:20); IR (neat, cm^{-1}): 3030, 2951, 2854, 1734, 1660, 1512, 1338, 1221; ^1H NMR ($CDCl_3$, 400 MHz, mixture of E/Z diastereoisomers). The integral of the isolated signal at 6.22 ppm, belonging to the major diastereoisomer, was arbitrarily assigned the value of one proton: δ 2.98 (dd, *J* = 7.5, 14.1 Hz, 1 H), 3.10 (ddd, *J* = 1.3, 8.1, 15.1 Hz, 0.5 H), 3.18 (d, *J* = 13.5 Hz, 0.5 H), 3.27 (d, *J* = 13.5 Hz, 1 H), 3.72 (s, 1.5 H), 3.81–3.94 (m, 4.5 H), 3.98 (d, *J* = 13.5 Hz, 0.5 H), 4.03 (d, *J* = 13.5 Hz, 1 H), 5.75 (ddd, *J* = 6.6, 8.1, 11.9 Hz, 0.5 H), 6.22 (dt, *J* = 7.6, 15.4 Hz, 1 H), 6.54–6.61 (m, 1.5 H), 6.97–7.03 (m, 2.5 H), 7.05–7.10 (m, 2 H), 7.17–7.25 (m, 4.5 H), 7.36–7.47 (m, 6 H), 7.49–7.56 (m, 1.5 H), 7.65–7.72 (m, 3 H), 8.12 (d, *J* = 8.8 Hz, 2 H), 8.22 (d, *J* = 8.8 Hz, 1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, mixture of E/Z diastereoisomers) δ 34.5 (t), 39.3 (t), 40.8 (t), 41.1 (t), 53.2, 53.4, 66.5 (s), 67.0 (s), 124.0, 124.3, 127.1, 127.2 (2C), 127.5, 127.6, 128.7, 128.8, 129.0, 129.1, 129.3, 129.6, 129.8, 129.9, 130.0, 130.8, 132.1 (2C), 132.6, 135.2 (s), 135.5 (s), 136.1 (s), 136.2 (s), 143.8 (s), 144.0 (s), 147.3 (s), 167.2 (s), 167.5 (s), 173.5 (s); HRMS (ESI) calcd. for $C_{26}H_{24}N_2O_5Na$ $[M + Na]^+$ 467.1583; found 467.1586 (Δ = 0.6 ppm).

Acknowledgements

Financial support from Italian Ministry of Education, University and Research (MIUR) is gratefully acknowledged (PRIN2015 prot. 20157WW5EH). The authors thank Enrico Torregrossa, Francesco Zerilli and Nicola Ranalli for their valuable contributes.

Keywords: • quaternary amino acids • asymmetric synthesis• allylation • asymmetric catalysis • palladium

[1] (a) Fosgerau, K.; Hoffmann T. *Drug Discovery Today* **2015**, *20*, 122–128; (b) Therapeutic peptides: Albericio, F.; Kruger, H. G. *Future Med Chem.* 2012, *4*, 1527–1531.

[2] (a) Schwieter, K. E.; Johnston, J. N. *J. Am. Chem. Soc.*, **2016**, *138*, 14160−14169; (b) *Peptide Therapeutics Market - Global Industry Analysis, Size, Share, Growth, Trends, and Forecast 2016–2024*; Transparency Market Research, 2017.

[3] Walensky, L.D.; Bird, G. H. J. *Med. Chem.* **2014**, *57*, 6275–6288.

[4] (a) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152. (b) Paradìs-Bas, M.; Tulla-Puche, J.; Albericio, F. *Chem. Soc. Rev.*, **2016**, *45*, 631–654.

[5] Bock, J. E.; Gavenonis, J.; Kritzer, J. A. *ACS Chem Biol.* 2**013**, *8*, 488–499.

[6] (a) Roxin, A.; Zheng, G. *Future Med. Chem.* **2012**, *4*, 1601–1618. (b) White, C. J.; Yudin, A. K. *Nature Chemistry* **2011**, *3*, 509–524. (c) Cardote, T. A. F.; Ciulli, A. *ChemMedChem* **2016**, *11*, 787–794. (d) For ring-closing metathesis reactions applied to the synthesis of cyclic peptides see: Gleeson, E. C.; Jackson, W. R.; Robinson, A. J. Tetrahedron Letters 2016, 57, 4325–4333.

[7] Lau, Y. H.; de Andrade, P.; Wu, Y.; Spring, D. R. *Chem. Soc. Rev.* **2015**, *44*, 91–102.

[8] (a) Chalker, J. M.; Bernardes, G. J. L.; Davis, B. G. *Acc Chem Res.* **2011**, *44*, 730–741. (b) Antos, J. M.; Francis, M. B. *Curr Opin Chem Biol.* **2006**, *10*, 253–262.

[9] (a) Dehn, S.; Chapman, R.; Jolliffe, K. A.; Perrier, S. *Polym Rev.* **2011**, *51*, 214–234. (b) Hamley, I. W. *Biomacromolecules* **2014**, *15*, 1543–1559.

[10] (a) Di Giacomo, M.; Serra, M.; Brusasca, M.; Colombo, L. *J. Org. Chem.* **2011**, *76*, 5247–5257. (b) Serra. M.; Tambini, S. M.; Di Giacomo, M.; Peviani, E. G.; Belvisi, L.; Colombo, L. *Eur. J. Org. Chem.* **2015**, 7557–7570. (c) Serra, M.; Bernardi, E.; Marrubini, G.; Colombo, L. *Eur. J. Org. Chem.* **2017**, *20*, 2964–2970. (d) Di Giacomo, M.; V. Vinci, V.; Serra, M.; Colombo, L. *Tetrahedron: Asymmetry*, 2008, **19**, 247–257.

[11] Serra, M.; Peviani, E. G.; Bernardi, E.; Colombo, L. *J. Org. Chem.* **2017**, *82*, 11091–11101.

[12] Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140–145.

[13] (a) Trost, B. M.; Piquer, J. A. PCT International Application WO 9846578 A1 19981022, Application: WO 98-GB1076 19980414. Priority: US 97–832713 19970411, **1998**, p. 26; *Chem. Abstr.* 129, 316549. (b) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999,** *121,* 10727–10737.

[14] Tarí, S.; Avila, A.; Chinchilla, R.; Nájera, C. *Tetrahedron: Asymmetry* **2012**, *23*, 176–180.

[15] Uraguchi, D.; Asai, Y.; Seto, Y.; Ooi, T. *Synlett* **2009**, *4*, 658–660.

[16] (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2007**, *2*, 1476–1491.

[17] Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

[18] Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; *Angew. Chem.* **2007**, *120*, 264–303.

[19] Results of the chiral phosphine screening and details about the reaction conditions were reported in Supporting Information (Table S1).

[20] Trost, B.M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357.

[21] Racys, D. T.; Eastoe, J.; Norrby, P.; Grillo, I.; Rogers, S. E.; Lloyd-Jones G. C. *Chem. Sci.* **2015**, *6,* 5793–5801.

[22] Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999,** *121,* 2460–2470.

[23] (a) Reyes Rangel, G.; Bandala, Y.; García Flores, F.; Juaristi, E. *Chirality* **2013**, *25*, 529–540. (b) Hartwig, W.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, 1952–1970.

[24] Belokon, Y. N.; Bakhmutov, V. I.; Chernoglazova, N. I.; Kochetkov, K. A.; Vitt, S. V.; Garbalinskaya, N. S.; Belikov, V. M. *J. Chem. Soc. Perkin Trans. 1*, **1998**, *2*, 305–312.

[25] Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6952–6955; *Angew. Chem.* **2006**, *118*, 7106–7109.

[26] Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847.

[27] Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927; *Angew. Chem.* **2005**, *117*, 7084–7087.

[28] A similar result was recently reported in the catalytic enantioselective decarboxylative allylation of enol carbonates towards the synthesis of Folicanthine, see: Ghosh, S.; Chaudhuri, S.; Bisai, A. *Chem. Eur. J.* **2015**, *21*, 17478–17484.

[29] Armarego, W. L. F.; Chai, C. L. L. in *Purification of Laboratory Chemicals*, *7th ed.*, Butterworth–Heinemann, Oxford, UK, **2013**.

[30] Tokunaga, M.; Kiyosu, J.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4481–4486.

[31] Jenny, C.; Heimgartner, H. *Helv. Chim. Acta* **1989**, *72*, 1639–1646.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Text for Table of Contents

((Insert TOC Graphic here: max. width: 5.5 cm; max. height: 5.0 cm; NOTE: the final letter height should not be less than 2 mm.))

Key Topic*

*Author(s), Corresponding Author(s)**

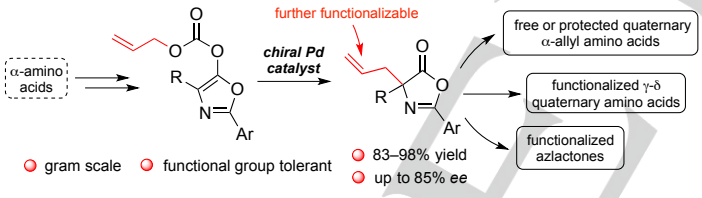
Page No. – Page No.

Title

*one or two words that highlight the emphasis of the paper or the field of the study

Layout 2:

FULL PAPER



We developed a practical synthetic protocol for the preparation of enantioenriched 4-allyl oxazol-5-ones. The key Pd-catalyzed decarboxylative allylation allowed the attainment of the allylated derivatives in very good yields (83–98%) and with *ee* up to 85%. The corresponding quaternary amino acids can be recovered in their enantiopure form or in high optical purity after a single recrystallization step.

Quaternary amino acids

Massimo Serra, Eric Bernardi, Giorgio Marrubini, Ersilia De Lorenzi, and Lino Colombo**

Page No. – Page No.

Palladium-Catalyzed Asymmetric Decarboxylative Allylation of Azlactone Enol Carbonates: Fast Access to Enantioenriched α-Allyl Quaternary Amino Acids