Trapping Carbamates of α-Amino Acids: One-Pot and Catalyst-Free Synthesis of 5-Aryl-2-Oxazolidinonyl Derivatives

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Abstract.

Carbonation of natural α-amino acids in water and subsequent cyclization with (2-bromo-1-arylethyl)dimethylsulfonium bromides led selectively to a family of 2-oxazolidinonyl derivatives, which were isolated without the needing of purification. Analogous conjugation of the 2-oxazolidinone skeleton with amino acids was previously realized by complicated and narrow-scope routes, whereby the amino acid core is built stepwise. Deprotonation of some of the products afforded the corresponding water-soluble carboxylates, while a straightforward, *proof of concept*

esterification reaction of the carboxylic acid group yielded a menthol-alanine-oxazolidinone conjugate.

Introduction

2-Oxazolidinones constitute a valuable family of five-membered cyclic carbamates, which exhibit interesting biological properties and are employed as important key intermediates in organic synthesis [1–3]. Several strategies involving CO_2-fixation have been extensively explored with the aim of developing environmentally benign synthetic routes to 2-oxazolidinone rings. In particular, unsaturated amines [4–6], halo-amines [7], aziridines [1,8,9] and amino-alcohols [10] have been investigated for their direct coupling with carbon dioxide, and also different three-component reaction systems are successful [7,11–14]. In general, a catalyst is needed to promote the CO_2 activation, and in addition high temperature and/or pressurized conditions might be required to achieve satisfying conversions. Beside to the construction of the oxazolidinone core, there is a current interest in discovering new synthetic routes to modify the nitrogen substituent on the external section of the ring, in order to tune the properties of the molecule [15].

On the other side, α-amino acids are ubiquitous natural compounds with several appealing characteristics, e.g. their water solubility, relative non-toxicity, structural diversity provided by the side chain, and the presence of a chiral center. Therefore, their use as precursors of valued-added chemicals has witnessed a highly growing interest [16–22]. In particular, “tailor-made” α-amino acids have been regarded as essential components of modern medicinal chemistry, and indeed a significant fraction of small molecular drugs comprise amino-acidic residues [16,23]. However, despite the reactivity of α-amino acids has been the subject of a long-time investigation, there is still space for the exciting and extremely worthy discovery of new reaction types [24–27]. It is well established that α-amino acids ($aaNH_2$) in aqueous solutions reversibly and easily add carbon dioxide to generate the corresponding ammonium carbamates, Equation 1 [28,29]. This reactivity is involved in various biological phenomena and, besides, has been extensively exploited for the development of CO_2-sequestration/storage technologies [30,31].

$$2\ aaNH_2 + CO_2 \rightleftharpoons [aaNH_3][aaNHCO_2] \qquad (1)$$

Amino acid carbamates have been utilized for synthetic purposes, and in particular their incorporation as a robust function in the molecular structure of biologically active compounds is a promising approach [32–34].

Herein, we report the unprecedented use of a range of natural α-amino acids, including some bearing a hetero-function in the side chain, for the synthesis of oxazolidinonyl derivatives through a three-component reaction via CO_2 fixation, which works under ambient conditions. This synthetic approach exploits the atmospheric pressure carbamation of the amino-function belonging to the α-amino acid core, and the subsequent, straightforward coupling with a convenient C_2-synthon.

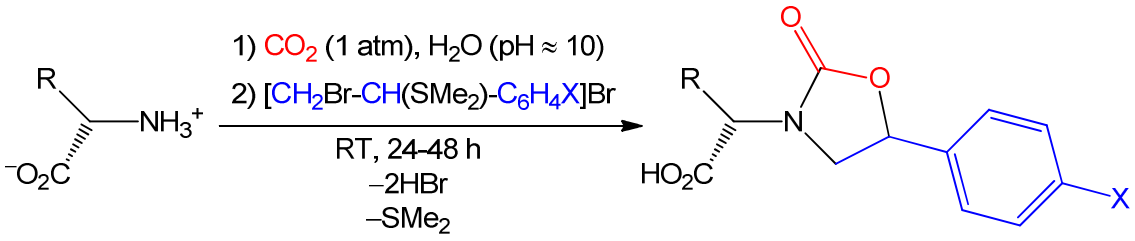
Results and discussion

Carbonation of the α-amino acids was conducted in water at ambient temperature and atmospheric pressure of CO_2, using the simple, safe and low-energy balloon technique; potassium carbonate was used as a base to fix the pH within the optimal range of 9.9-10.5, in accordance with the literature [28,29,35]. Then, the addition of (2-bromo-1-arylethyl)dimethylsulfonium bromide salts resulted in the regiospecific cyclization to 5-aryl-2-oxazolidinones (Scheme 1). Note that such versatile sulfonium reagents [36] are easily accessible in a multigram scale [37,38]. Products **1**-**4** were extracted with ethyl acetate from the acidified aqueous phase, and isolated as solid/oily materials upon removal of the solvent under vacuum (no purification needed).

In general, the amino acid was used in approximately 3:1 molar ratio with respect to the sulfonium salt, and in this condition the reactions proceeded with excellent selectivity and moderate to high conversion of the sulfonium over 48 hours. Indeed, a ^1H NMR experiment on D_2O reaction mixtures affording **1-Gly** and **1-Pha** highlighted the absence of any by-product. The observed limited conversion is reasonably imputable to the intrinsically limited degree of the α-amino acid carbonation which is usually encountered working under atmospheric pressure [39]. In selected cases, the use of a larger excess (ca. 10 equivalents) of amino acid significantly increased the

conversion of the sulfonium leading to higher yields of **1-Pha**, **1-Val** and **1-Try**; compounds **2-Try** and **3-Try** were conveniently obtained with this method.

However, the residual aqueous phase containing the larger excess of L-phenylalanine was recycled twice by basification and addition of further sulfonium salt, yielding two additional crops of the product **1-PhA** (see Supporting Information for details). This fact points out that the employed excess of amino acid reactant, required to achieve a satisfying conversion of the sulfonium reagent, may be re-utilized for the same reaction allowing to reduce the waste.



R	***X***	***Yield*[a]**	
H	H	74%	**1-Gly**
Me	H	70%	**1-Ala**
CH_2CHMe_2	H	49%	**1-Leu**
CH_2CH_2SMe	H	42%	**1-Met**
CH_2Ph	H	73% [b]	**1-Pha**
$CH(Me)CH_2Me$	H	35%	**1-Iso**
$CHMe_2$	H	62% [b]	**1-Val**
$CH_2(C_8H_5N)$	H	69% [b]	**1-Try**
H	Me	72%	**2-Gly**
Me	Me	62%	**2-Ala**
CH_2CHMe_2	Me	48%	**2-Leu**
CH_2CH_2SMe	Me	41%	**2-Met**
$CH_2(C_8H_5N)$	Me	55% [b]	**2-Try**
H	Cl	78%	**3-Gly**
Me	Cl	61%	**3-Ala**
CH_2CHMe_2	Cl	46%	**3-Leu**
CH_2CH_2SMe	Cl	43%	**3-Met**
$CH_2(C_8H_5N)$	Cl	59% [b]	**3-Try**
H	F	72%	**4-Gly**
CH_3	F	45%	**4-Ala**
CH_2CHMe_2	F	42%	**4-Leu**
CH_2CH_2SMe	F	41%	**4-Met**

Scheme 1. Synthesis of oxazolidinonyl derivatives of natural α-amino acids. Selectivity >99% in every case (^{1}H NMR). [a]Yields referred to ca. 3:1 amino acid/sulfonium molar ratio, unless otherwise specified. [b]Amino acid/sulfonium molar ratio = 10.

Compounds **1-4** are poorly soluble in water, and well soluble in acetone and methanol. They were characterized by analytical and spectroscopic methods (Supporting Information). The IR spectra (in the solid state) display one intense absorption at ca. 1740 cm^{-1}, ascribable to the carbamato function, and another one in the range 1683-1705 cm^{-1}, related to the carboxylic acid group. In general, the NMR spectra consist of two sets of resonances in ca. 1:1 ratio, except for the glycine derivatives existing as single species (**1-Gly**, **2-Gly**, **3-Gly**, **4-Gly**). The two sets are related to the diastereomeric forms *SR* and *SS*, corresponding to the two different spatial orientations of the aryl unit bonded to a quaternary ring carbon (the original *S* configuration of the α-amino acid is retained). Note that the absence of stereoselectivity in the formation of 5-aryl-2-oxazolidinones is common to the majority of the previously reported CO_2 fixation methods, unless enantiopure precursors are employed in the synthesis [1,8,40,41]. Salient NMR features (acetone-d_6 solutions) are represented by the resonances of the carbon atoms belonging to the five-membered cycle, occurring around 76 ppm (CH), 50 ppm (CH_2) and 159 ppm (C=O), i.e. close to the values available in the literature for other 5-aryl-2-oxazolidinones. The ^{13}C NMR signal accounting for the carboxylic acid was detected in the range 169.4-173.0 ppm.

The molecular structures of **1-Gly**, **2-Leu**, **3-Gly**, **3-Ala** and **3-Leu** were confirmed by X-ray diffraction studies. A view of the representative structure of **3-Ala** is given in Figure 1, and relevant bonding parameters are listed in the caption. The remaining structures and related bonding parameters (including H-bonds) are shown in the Supporting Information. Coherently with the NMR features, a 1:1 mixture of the two *R* and *S* configurations on C(1) is present within the unit cells. The C(4) center of **2-Leu**, **3-Ala** and **3-Leu** displays the *S* configuration as in the parent amino acid.

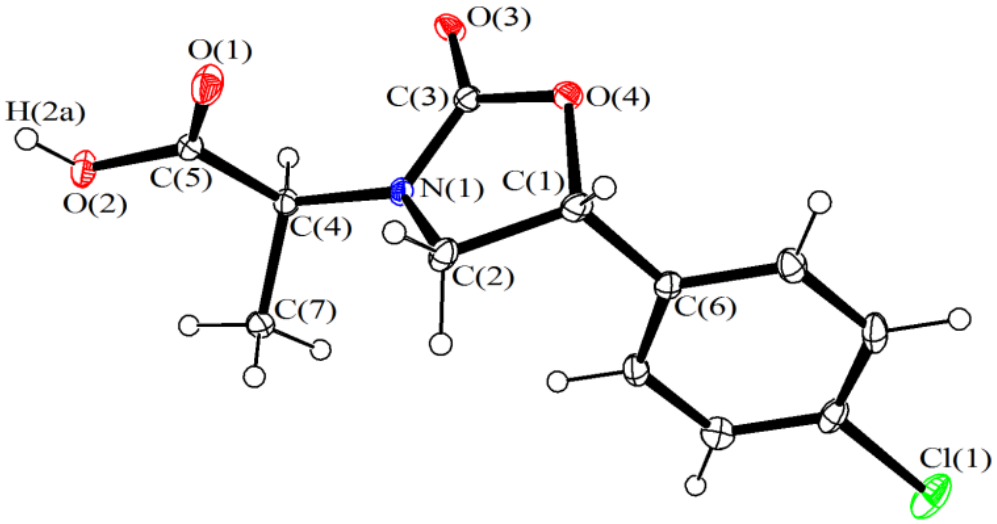
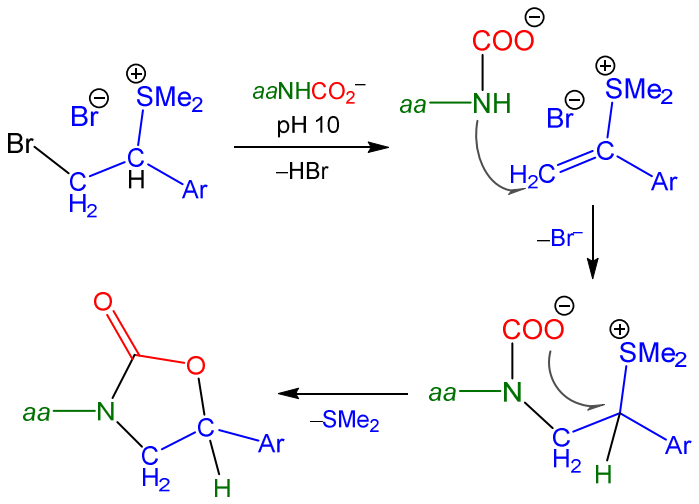


Figure 1. ORTEP drawing of **3-Ala**, with key atoms labelled. Displacement ellipsoids are at 30% probability level. Selected bond lengths (Å) and angles (deg): C(1)-C(2) 1.538(3), N(1)-C(2) 1.456(2), N(1)-C(3) 1.343(2), C(3)-O(3) 1.216(2), C(3)-O(4) 1.347(2), C(1)-O(4) 1.468(2), C(4)-N(1) 1.452(2), C(4)-C(5) 1.519(2), C(5)-O(1) 1.198(2), C(5)-O(2) 1.327(2), O(1)-C(5)-O(2) 124.58(17), O(1)-C(5)-C(4) 124.43(16), O(2)-C(5)-C(4) 110.97(15), C(5)-C(4)-N(1) 110.30(14), C(4)-N(1)-C(3) 121.14(14), C(4)-N(1)-C(2) 124.38(14), C(3)-N(1)-C(2) 111.06(15), N(1)-C(3)-O(4) 120.93(16), C(3)-O(4)-C(1) 109.00(13), N(1)-C(2)-C(1) 100.79(13), C(2)-C(1)-O(4) 103.13(13).

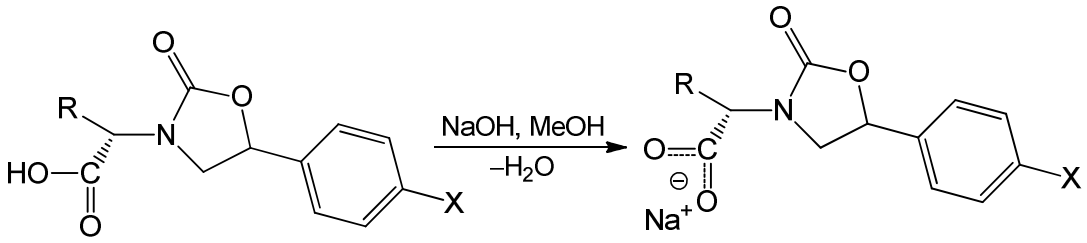
The synthesis of **1-4** proceeds through a presumable pathway which is depicted in Scheme 2. First, the sulfonium reagents are expected to undergo HBr elimination in a basic environment [38,42], and this feature was confirmed by a ^{1}H NMR experiment in the case of [$CH_2BrCH(SMe_2)(4\text{-}C_6H_4F)$]Br, which cleanly converted into [$CH_2{=}C(SMe_2)(4\text{-}C_6H_4F)$]Br upon treatment with 0.1 M K_2CO_3 in dimethylsulfoxide solution [43]. Then, nucleophilic attack from the pre-formed carbamato nitrogen to the alkenic moiety is preliminary to the generation of the five-membered cycle, whose closing is achieved by C−O bond formation via release of dimethylsulfide, accordingly to the recently described formation of 5-aryl-2-oxazolidinones from carbamates of primary amines [14].



Scheme 2. Proposed mechanism for the construction of an oxazolidinone ring via CO_2 fixation on an α-amino acid function.

Compounds **1-4** constitute a substantially novel class of five-membered cyclic carbamates, generated through the incorporation in the cycle of the original amine function belonging to pre-existing natural α-amino acids. To the best of our knowledge, only the simplest member of the series reported in Scheme 1, i.e. **1-Gly**, was previously prepared, using a three-step procedure from 2-amino-1-phenylethanol [44]. In general, the N-glycination of the 2-oxazolidinone skeleton has been achieved through the stepwise modification of the latter, and thus not employing the amino acid as a convenient building block [45,46]. The same concept was applied to the construction of alanine, {$(CO_2H)CH(Me)N$} [47], and methionine, {$(CO_2H)CH(CH_2CH_2SMe)N$} [48], fragments on either 4-phenyl-2-oxazolidinone or 4,5-diphenyl-2-oxazolidinone rings: in these cases, even more elaborated multi-step protocols are required, making use of various hazardous chemicals including toxic metal based ones.

In order to obtain water soluble derivatives, the deprotonation of a series of compounds belonging to the series **1-4** was performed in methanol solution with one equivalent of sodium hydroxide. The respective sodium carboxylates were obtained as hygroscopic microcrystalline solids in good to excellent yields (Scheme 3). They are well soluble in water and methanol and not soluble in acetone, except **Na-1-Try** and **Na-3-Try** which are slightly soluble in acetone.

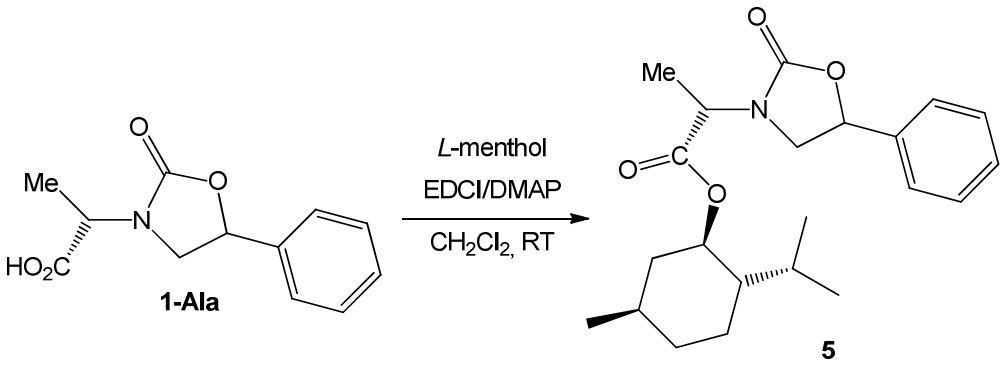


R	*X*	*Yield*	
Me	H	87%	**Na-1-Ala**
CH_2CH_2SMe	H	66%	**Na-1-Met**
CH_2Ph	H	85%	**Na-1-Pha**
$CH(Me)CH_2Me$	H	84%	**Na-1-Iso**
$CH_2(C_8H_5N)$	H	94%	**Na-1-Try**
H	Me	87%	**Na-2-Gly**
$CH_2(C_8H_5N)$	Cl	59%	**Na-3-Try**
CH_2CH_2SMe	F	95%	**Na-4-Met**

Scheme 3. Synthesis of sodium carboxylates of oxazolidinonyl derivatives.

The conversion of the carboxylic acid function into carboxylate is evident based on the IR (solid state) and NMR spectra (CD_3OD). In particular, the IR band due to the carboxylate is found at 1591-1618 cm^{-1}, while the related ^{13}C NMR resonance is significantly downfield shifted, compared to the corresponding signal in the parent carboxylic acids (e.g. at 177.1 and 177.0 ppm for **Na-1Met**, 173.5 ppm for **1-Met**). Compounds **1-Pha** and **1-Met** were quantitatively recovered from their ionic counterparts **Na-1-Pha** and **Na-1-Met** upon HCl addition in water solution and subsequent extraction with ethyl acetate.

Further, we investigated the potential of the new compounds **1-4** to undergo esterification of the carboxylic acid function: **1-Ala** and *L*-menthol - a bioactive, naturally occurring alcohol widely used in synthetic chemistry [49–51] - were selected for this purpose. The reaction was accomplished using the EDCI-DMAP protocol in dichloromethane and led to the isolation of **5** in 65% yield (Scheme 4); the product was fully characterized by elemental analysis, IR and NMR spectroscopy (see ESI), and represents an unusual example of molecular scaffold containing three biologically relevant units, i.e. L-menthol, L-alanine and the oxazolidinone ring.



Scheme 4. Esterification of carboxylic acid function with L-menthol.

Compound **5** contains five chiral centers and is obtained as a diastereomeric mixture of two isomers, i.e. *R* and *S* with reference to the orientation of the phenyl group; interestingly, a careful chromatographic separation allowed to isolate a fraction of one of the two.

Conclusions

The straightforward conjugation of two molecular structures of large interest in organic chemistry, i.e. the 2-oxazolidinone ring on the one side and naturally occurring α-amino acids on the other side, has been realized through the construction of the five-membered cycle on the original amino group. Remarkably, among known applications of amino acids, this approach was never envisioned and explored to date. The synthetic strategy is simple, general to afford 5-aryl-substituted products, tolerant to various function on the amino acidic side chain, and with a significant degree of sustainability, in that it is based on the catalyst-free one-pot reaction in water between easily available precursors. The latter include carbon dioxide, which is activated at atmospheric pressure. The reactions are featured by excellent selectivity, thus avoiding purification procedures and, as demonstrated in one model case, allowing the recycle of the employed excess of amino acid. The subsequent deprotonation reaction provides water solubility, thus taking full advantage of the inclusion of the natural fragment. Moreover, we demonstrate that the carboxylic acid function is susceptible to facile esterification allowing to grow the molecular structure with an additional

bioactive group. The substantial advance provided by the synthetic method presented here is suggested by the fact that analogous oxazolidinonyl-amino acid conjugates were previously obtained by means of elaborated, non-green and narrow-scope routes, based on the opposite approach, i.e. the stepwise growing of the amino acid like fragment usually on a pre-existing oxazolidinone ring.

Experimental section

General details. CO_2 (99.99%) was purchased from Rivoira, while other reactants and organic solvents were commercial products (Merck, TCI Europe or Strem) of the highest purity available, which were stored under N_2 atmosphere as received. Reactions were carried out in air, except Steglich esterification [52] which was performed under N_2 using standard Schlenk techniques and CH_2Cl_2 dried with the solvent purification system mBraun MB SPS5. Compounds [$Me_2SCH(4\text{-}C_6H_4X)CH_2Br$]Br were prepared according to the literature [37,38]. Infrared spectra were recorded at 298 K on an FTIR-Perkin Elmer Spectrometer, equipped with UATR sampling accessory (4000-400 cm^{-1} range). IR spectra were processed with Spectragryph software [53]. NMR spectra were recorded at 298 K on a Bruker Avance II DRX400 instrument equipped with a BBFO broadband probe. Chemical shifts (expressed in parts per million) are referenced to the residual solvent peaks (^1H, ^{13}C) [54] or to external standard (^{19}F, $CFCl_3$). NMR spectra were assigned with the assistance of ^1H-^{13}C (*gs*-HSQC and *gs*-HMBC) correlation experiments [55]. Elemental analyses were performed on an Elementar Vario MICRO cube instrument.

Synthesis of neutral compounds

General procedure. The selected α-amino acid was dissolved into a solution of K_2CO_3 in H_2O (0.50 M, 50 mL), in a 250 mL round-bottom flask. The measured pH of the resulting solution was in the range 9.9 to 10.5. The flask was evacuated by a vacuum pump and then filled with CO_2; the vacuum/CO_2 sequence was repeated twice. The mixture was stirred under CO_2 atmosphere (from a

balloon) for 24 hours at ambient temperature. Afterwards, the appropriate sulfonium salt was added to the solution under a stream of CO_2, and this mixture was stirred for 48 hours under CO_2 atmosphere from a balloon. The final solution was poured into a separatory funnel, and concentrated aqueous HCl was added dropwise until pH 1. The product was extracted with ethyl acetate (3 x 20 mL), then the volatiles were removed under vacuum affording a solid/oil material. Yields are referred to the sulfonium salt.

Synthesis of sodium salts

General procedure. A methanol solution (ca 15 mL) of the selected oxazolidinone was treated with 1 eq. of NaOH. The mixture was stirred at ambient temperature for 3 hours, then the solvent was removed under reduced pressure. The oily residue was washed with acetone (2 x 5 mL), thus allowing the precipitation of a microcrystalline solid, which was isolated and dried under vacuum.

Formation of neutral oxazolidinones from the corresponding sodium salts

The regeneration of neutral oxazolidinones was evaluated from **Na-1-Pha** and **Na-1-Met**. To a water solution (ca. 5 mL) of the sodium salt (ca. 50 mg), concentrated HCl was added until pH 1. The mixture was extracted with ethyl acetate (3 x 5 mL), and the collected organic phases were anhydrified with anhydrous $MgSO_4$. Then the solvent was removed under vacuum, affording pure oxazolidinone in almost quantitative yield (98% for **1-Pha**, 96% for **1-Met**).

Synthesis of 5

In a 50 mL round bottom flask, **1-Ala** (124 mg, 0.53 mmol) and *L*-menthol (100 mg, 0.64 mmol) were dissolved in dichloromethane (15 mL) and then treated with DMAP (3.00 mg, 0.02 mmol) and EDCI·HCl (152 mg, 0.79 mmol). The mixture was stirred at room temperature for 16 hours. The obtained solution was washed with water (3 x 10 mL) and the organic phase was evaporated under reduced pressure. Product **5** was obtained as a colorless oil after purification by silica column

using a mixture of ethyl acetate and hexane (1:2 v/v) as eluent. Yield: 128 mg, 65%. A subsequent, careful chromatography (eluent ethyl acetate/hexane 1:4 v/v) allowed to separate a fraction (ca. 30 mg) of enantiopure compound.

X-ray crystallography

Crystal data and collection details for **1-Gly**, **2-Leu**, **3-Gly**, **3-Ala** and **3-Leu** are reported in Table S1. Data were recorded on a Bruker APEX II diffractometer equipped with a PHOTON2 detector using Mo–Kα radiation. Data were corrected for Lorentz polarization and absorption effects (empirical absorption correction SADABS) [56]. The structures were solved by direct methods and refined by full-matrix least-squares based on all data using F^2 [57]. Hydrogen atoms were fixed at calculated positions and refined by a riding model. All non-hydrogen atoms were refined with anisotropic displacement parameters. **1-Gly** and **3-Gly** crystallize in centrosymmetric space groups and contain racemic mixtures of enantiomers. **2-Leu**, **3-Ala** and **3-Leu** crystallize in chiral space groups and contain mixtures of diastereoisomers which differ for the orientation of the aryl groups at C(5). The crystals of **1-Gly** appeared to be nonmerohedrally twinned. The TwinRotMat routine of PLATON [58] was used to determine the twinning matrix and to write the reflection data file (.hkl) containing the two twin components. Refinement was performed using the instruction HKLF 5 in SHELXL and one BASF parameter, which refined as 0.267(8).

Conflicts of interest

There are no conflicts to declare.

Supporting Information

Characterization and recycling reactions, crystal data, IR and NMR spectra of products. CCDC reference numbers CCDC 2043019-2043023 (**1-Gly**, **2-Leu**, **3-Gly**, **3-Ala**, **3-Leu**) contain the supplementary crystallographic data for the X-ray studies reported in this paper. These data can be

obtained free of charge at https://www.ccdc.cam.ac.uk/structures/ (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

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