JOC The Journal of Organic Chemistry

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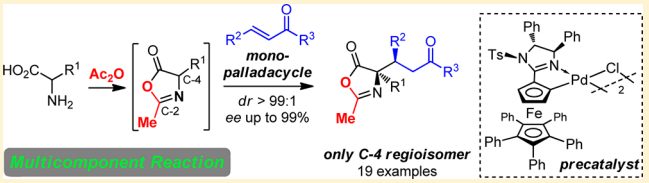
Pd(II)-Catalyzed Regio-, Enantio-, and Diastereoselective 1,4-Addition of Azlactones Formed in Situ From Racemic Unprotected Amino Acids and Acetic Anhydride

Manuel Weber and René Peters*

Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

Supporting Information

ABSTRACT: A multicomponent reaction is reported generating highly enantioenriched and diastereomerically pure quaternary amino acid derivatives via 1,4-addition of azlactones to enones. The azlactone intermediates are generated in situ from unprotected α-amino acids and acetic anhydride. Previous attempts using bis-palladacycle catalysts required the use of a large excess of benzoic anhydride (which is very difficult to remove from the products), since acetic anhydride provided regioisomeric product mixtures. Key for the high regioselectivity is a pentaphenylferrocene monopalladacycle catalyst.



INTRODUCTION

Azlactones (oxazol-5-(4*H*)-ones) have been reported as very versatile masked and activated amino acid equivalents for a diversity oriented access to natural and unnatural α-amino acid derivatives.[1] Their broad utility is mainly explained by two reasons: (1) the relatively high tendency to enolize forming an aromatic heterocycle with a nucleophilic site at the C-4 position and (2) the masked cyclic anhydride type structure, which allows for ring-opening reactions with various nucleophiles under mild conditions. The sequential combination of these two orthogonal reactivities has been shown to be particularly valuable for the asymmetric synthesis of enantioenriched biologically interesting[2] α,α-disubstituted (quaternary) α-amino acids.[1,3,4] In this context, we have recently reported the first catalytic asymmetric 1,4-additions[5] of azlactones to enones, and we have demonstrated the value of the addition products for a divergent access to a number of different classes of biologically interesting quaternary amino acid derivatives including bicyclic dipeptides.[6,7] In these previous studies, we have found that the azlactone substrates can be generated in situ from either racemic *N*-benzoylated[6a,c] or unprotected amino acids[6b,c] using a planar chiral bis-palladacycle catalyst. In that way the sometimes tedious preparation (2−4 steps) and isolation of the azlactone substrates could be avoided.

The in situ generation of the azlactones starting from *N*-benzoylated amino acids **1** could be accomplished by the use of an excess of acetic anhydride (Scheme 1, first row).[6a,c] Unprotected amino acids required the use of a large excess of benzoic anhydride (in combination with benzoic acid) for the regioselective formation of the C-4 addition product, whereas azlactones bearing a 2-methyl substituent, introduced by *N*-acetylation of the unprotected amino acid with Ac_2O, provided mixtures of the C-4 and the undesired C-2 addition products (Scheme 1, third and second row, respectively). The C-4/C-2 azlactone regioselectivity issue has been reported in several other cases for catalytic asymmetric 1,4-additions.[7c,f,g]

For practical reasons, the use of acetic anhydride/acid is considered to be much more convenient for the 1,4-addition to enones than that of benzoic acid/anhydride, because acetic acid/anhydride can be readily evaporated, whereas removal of a large excess of the solid benzoic anhydride proved to be tedious and required two sequential column chromatographies.[6b,c] Moreover, regeneration of the amino group by hydrolysis of the amide protecting group might be more effective for acetamides (e.g., enzymatically) compared to benzamides.

Herein we report that the monopalladacycle catalyst **7a**[8−10] is capable to regioselectively form the azlactone-C-4 Michael addition products with high enantio- and diastereoselectivity in a single step starting from racemic unprotected amino acids, enones and acetic anhydride (Scheme 1, bottom). This efficiency was surprising, because in the above-mentioned studies using the azlactones **2-Ph** (with a 2-phenyl substituent), this and other related monopalladacycles generally provided the product in poor yields and with only low to moderate enantioselectivity, and a bimetallic catalyst system was essential for synthetically attractive results. However, the situation completely changes upon using azlactones **2-Me** with a 2-methyl substituent.

RESULTS AND DISCUSSION

Application of reaction conditions initially investigated for the bimetallic precatalyst to the model reaction of racemic alanine (**3a**) and enone **4a** formed the C-4 addition product **5a** in 57% yield with 99% *ee* (Table 1, entry 1),[11] while the C-2 addition product could not be detected.[12]

Received: October 4, 2012
Published: November 29, 2012

Scheme 1. Cooperative Influence of the Azlactone C-2 Substituent and the Catalyst Type on the Regioselectivity

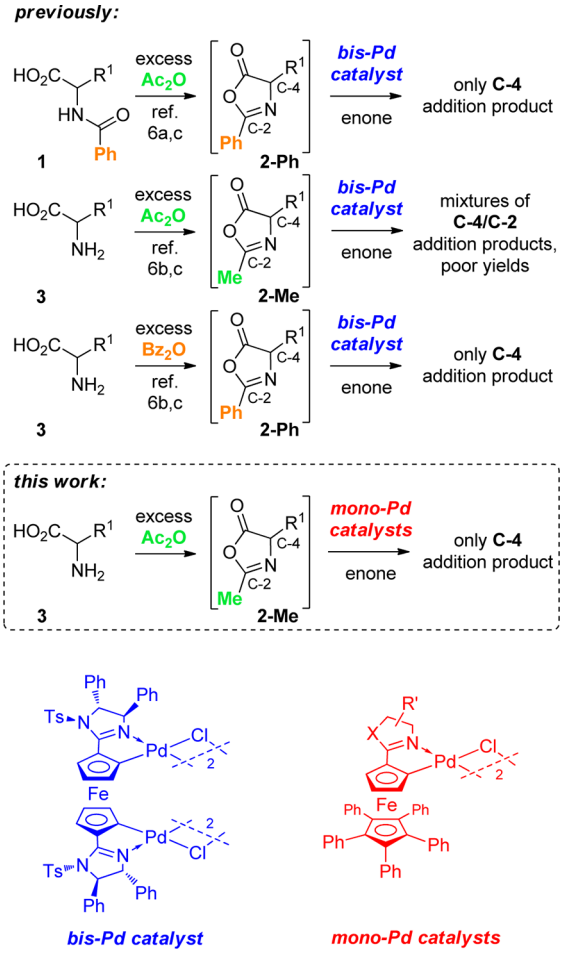
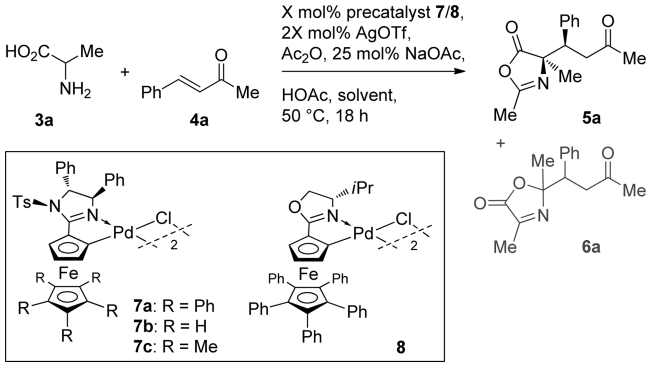


Table 1. Investigation of the Reaction Conditions Using Racemic Alanine (3a), Enone 4a and Acetic Anhydride



#	7/8	X	solvent	5a/6a[a]	yield 5a (%)[b]	dr 5a[a]	ee 5a (%)[c]
1	7a	3		>50:1	57	>99:1	99
2	7b	3		4:1	59	>99:1	55
3	7c	3		6:1	51	>99:1	96
4	8	3		>50:1	68	>99:1	98
5[d]	7a	3		>50:1	38	>99:1	99
6	7a	5		>50:1	58	>99:1	99
7[e]	7a	3		33:1	56	>99:1	99
8	7a	3	acetone	21:1	55	>99:1	99
9	7a	3	diglyme	n.d.[f]	54	>99:1	99
10	7a	3	THF	15:1	59	>99:1	99
11	7a	3	CH_2Cl_2	>50:1	69	>99:1	99
12	7a	3	toluene	>50:1	48	>99:1	99
13	7a	3	hexane	45:1	54	>99:1	99
14	8	3	CH_2Cl_2	6:1	71	>99:1	98

[a]Determined by ^{1}H NMR of the crude product. [b]Determined by ^{1}H NMR analysis of the crude product using mesitylene as an internal standard. [c]Determined by HPLC. [d]No NaOAc was used. [e]The precatalyst was activated by 12 mol % AgOTf. [f]Not determined, since diglyme signals overlay the relevant product signals.

The steric demand of the pentaphenyl-Cp moiety of precatalyst **7a** is a key factor for high enantio- and regioselectivity as demonstrated by entry 2, in which catalyst **7b** was used lacking the five phenyl rings on the spectator Cp ligand. With this catalyst the product was formed with only moderate enantioselectivity (*ee* = 55%) and regioselectivity (4:1). Accordingly, the sterically more demanding pentamethylferrocene derivative **7c** provided both better C-4 selectivity and an excellent enantioselectivity (entry 3). The pentaphenylferrocene oxazoline palladacycle **8** performed similar to the related imidazoline **7a** (entry 4). Entry 5 shows that the product yield is significantly reduced by the absence of NaOAc. We therefore assume that the azlactone coordinated to (and acidified by) the Pd-center is deprotonated by acetate to form an enolate as reactive intermediate under the acidic reaction conditions. An increased precatalyst loading of 5 mol % (entry 6) or oxidation of the catalyst to the corresponding Pd(III) species[13] (entry 7) had almost no impact on the reaction outcome.

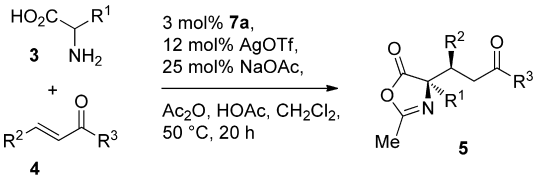
Catalyst **7a** provided product **5a** with excellent enantioselectivity (*ee* = 99%) in solvents of widely variable polarities such as acetone, diglyme, THF, CH_2Cl_2, toluene and *n*-hexane in comparable yields (entries 8−13). By using CH_2Cl_2 or toluene as solvent, the undesired C-2 regioisomer **6a** was not detectable by ^{1}H NMR (entries 11−12). Product **5a** was obtained in a yield of 69% (determined by ^{1}H NMR via an internal standard) by this multicomponent reaction in CH_2Cl_2 as solvent (entry 11). A similar yield (71%) was also obtained in this solvent with catalyst **8**, but with a significant amount of the regioisomer as side product (ratio **5a**/**6a** = 6:1, entry 14).

The investigation of a number of amino acids **3** and enones **4** (Table 2) was performed under the best conditions found (Table 1, entry 11).[14] Product **5a** of the model reaction could be isolated in a yield of 50% after silica gel column chromatography. This yield is somewhat lower than determined via ^{1}H NMR (using an internal standard) and can be attributed to partial hydrolysis of the azlactone moiety during workup and on silica gel. As a general trend, the isolated yield increased with a growing length of an unbranched alkyl amino acid residue R^1 (compare entries 1−4). This might reflect the higher product stability toward hydrolysis based on steric effects. On the other hand, the enantioselectivity gradually slightly decreased from alanine via ethylglycine and norvaline to norleucine from 99 to 92% *ee*. Branched α-residues like in leucine (entry 5) and phenylalanine (entry 6) resulted in a lower substrate reactivity and enantioselectivity.[15] Gratifyingly, functionalized amino acids like glutamic acid 5-methyl ester (entry 7) and tryptophan (entry 8) are also well tolerated.

The enone scope was investigated with racemic norvaline. Unfortunately, increasing the size of the enone substituent R^3 from methyl to isopropyl resulted in a low product yield as a result of a reduced reactivity, but stereoselectivity was still very high (entry 9). π-Donors (entries 10−11) as well σ- (entries 12 and 14) and π-acceptors (entry 15) in 4-position of an aryl

dx.doi.org/10.1021/jo302177t | J. Org. Chem. 2012, 77, 10846−10855

Table 2. Investigation of the Substrate Scope



#	5	R^1	R^2	R^3	5 / 6	yield 5 (%)[a]	*dr* 5 [b]	*ee* 5 (%)[c]
1	**5a**	Me	Ph	Me	> 50:1	50	>99:1	99
2	**5b**	Et	Ph	Me	> 50:1	55	>99:1	98
3	**5c**	*n*-Pr	Ph	Me	> 50:1	64	>99:1	93
4	**5d**	*n*-Bu	Ph	Me	> 50:1	72	>99:1	92
5	**5e**	*i*-Bu	Ph	Me	> 50:1	42	>99:1	79
6	**5f**	CH_2Ph	Ph	Me	> 50:1	49	>99:1	82
7	**5g**	$(CH_2)_2CO_2Me$	Ph	Me	> 50:1	56	>99:1	95
8	**5h**		Ph	Me	> 50:1	66	>99:1	87
9	**5i**	*n*-Pr	Ph	*i*-Pr	> 50:1	16	>99:1	96
10	**5j**	*n*-Pr	4-MeO-C_6H_4	Me	> 50:1	41	>99:1	99
11	**5k**	*n*-Pr	3,4-MeO-C_6H_3	Me	> 50:1	56	>99:1	86
12	**5l**	*n*-Pr	4-Cl-C_6H_4	Me	> 50:1	59	>99:1	93
13	**5m**	*n*-Pr	2-Cl-C_6H_4	Me	> 50:1	37	>99:1	92
14	**5n**	*n*-Pr	4-Br-C_6H_4	Me	> 50:1	63	>99:1	94
15	**5o**	*n*-Pr	4-O_2N-C_6H_4	Me	> 50:1	41	>99:1	97
16	**5p**	*n*-Pr	2-furyl	Me	> 50:1	58	>99:1	84
17	**5q**	*n*-Pr	Me	Et	> 50:1	70	>99:1	86
18	**5r**	*n*-Pr	*n*-Pr	Me	> 50:1	52	>99:1	78
19	**5s**	*n*-Pr	*i*-Pr	Me	> 50:1	26	>99:1	62

[a]Yield of isolated product **5**. [b]Determined by ^{1}H NMR. [c]Determined by HPLC.

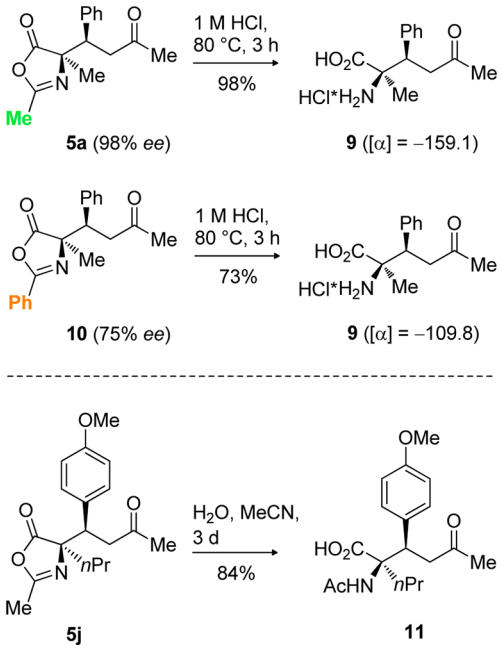
residue R^2 were all tolerated and permitted useful product yields and high stereoselectivity. Similar results were attained with enones carrying heteroaromatic (entry 16) or aliphatic residues R^2 (entries 17−18), albeit branched alkyl substituents R^2 like *i*-Pr did not result in useful yield and enantioselectivity (entry 19).[16]

The absolute configuration was determined by chemical correlation (Scheme 2, *top*). Hydrolysis of **5a** (*ee* = 98%) and the known compound **10** (*ee* = 75%)[6a,c] with 1 M HCl at 80 °C provided the known quaternary amino acid **9** (as hydrochloride salt) without partial epimerization.[6a,c] Since the sign of the specific optical rotation is negative in both cases, the absolute configuration of **5a** and **10** is identical. The hydrolysis of **5a** proceeded quantitatively, whereas hydrolysis of **10** was less efficient. Under less forcing conditions, acetyl protected amino acids like, e.g., **11**, can also be readily prepared (Scheme 2, *bottom*). Because of the considerable electrophilicity of the azlactone moiety, hydrolysis proceeded already under neutral aqueous conditions. Also in that case partial epimerization has not been observed.

The reasons for the complementarity of the bis-Pd-catalysts reported earlier and mono-Pd-catalysts reported in this study are not yet fully understood. Whereas the use of bis-Pd-catalysts was found to be essential for high efficiency in terms of high enantioselectivity and reactivity using azlactones carrying a 2-Ph substituent, the pentaphenyl ferrocene based mono-Pd-catalysts performed significantly better for azlactones carrying a 2-Me substituent, because the undesired C-4 addition regioisomer is not formed, which is the major side product for the bimetallic catalyst. A possible reason for the superiority of the bimetallic catalyst using 2-Ph-substituted azlactones might be a lower inherent nucleophilicity of the corresponding enolates as compared to the 2-Me-substituted analogues owing to a more widespread π-system of the former resulting in a lower energy of the HOMO. This might lead to a situation in which a simultaneous activation of the enone is essential to efficiently trigger the C−C-bond formation. In contrast, the higher nucleophilicity of the 2-methyl substituted derivative might already be sufficient for a nucleophilic attack at the enone without additional activation of the Michael acceptor by the catalyst explaining the good reactivity with the monopalladacycle in this specific case. For the bis-Pd-catalyst this would mean that a monometallic pathway might compete with the bimetallic pathway for 2-methylazlactones, but not for 2-phenylazlactones.

dx.doi.org/10.1021/jo302177t | J. Org. Chem. 2012, 77, 10846−10855

Scheme 2. (*Top*) Determination of the Absolute Configuration by Hydrolysis of 5a via Chemical Correlation; (*Bottom*) Partial Hydrolysis toward the *N*-Acetyl Protected Amino Acid 11



Quantum mechanical computations were used to survey our hypothesis. By the DFT/B3LYP/6-31G* method the equilibrium conformers of the azlactone sodium enolates **12** and **13** were identified and used for more detailed considerations. Figure 1 shows the calculated HOMOs of both enolates as well as the HOMO densities. The phenyl-π-system of **13** displays some participation to the HOMO, and as a consequence of the delocalization, the HOMO of **13** is ca. 4.2 kcal/mol (17.6 kJ/mol) lower in energy than that of **12**. Since the higher HOMO energy corresponds to a more reactive molecule in reactions with an electrophile,[17] enolate **12** can be considered more nucleophilic by electronic effects.

The fact that the regioselectivity is poor for 2-methyl-azlactones using the bimetallic catalyst[18] might, e.g., reflect two competing reactive conformations **IIa** and **IIb** for a bimetallic pathway in which either the 2-methyl substituent or the C-4-substituent R^1 adopt an *exo* orientation with regard to the catalyst core (Figure 2). In comparison, using the 2-Ph-azlactone the reactive conformer **I** with an *exo* orientation of the Ph moiety might be strongly preferred for steric reasons to minimize repulsive interactions of the Ph group with the catalyst core. Only the nucleophilic azlactone atom (either C-2 or C-4) in *endo* position would be in close spatial proximity to the enone for such a bimetallic reaction pathway.

For the monometallic catalyst, we think that the preferred reacting intermediate might be species **III**, in which the 2-methyl group points toward the sterically demanding pentaphenylcyclopentadienide spectator ligand, because the fragment CH_3−C(2)−O is less bulky compared to R^1−C(4)−C(5)−$ONa_{(solv)}$ (Figure 3, *left*). If **III** is the reactive confomer, C-2 (in *endo*-position relative to the ferrocene core and shielded by C_5Ph_5) is less accessible than C-4 in *exo*-position. Since the *Si*-face of the enolate is shielded by the pentaphenyl ferrocene moiety (Figure 3, *middle* and *right*), the *Re*-face should selectively attack the enone, thus explaining the good enantioselectivity.

Like for the 2-Ph substrates[6a,c] the high diastereoselectivity might be the consequence of a transition state with a staggered conformation around the generating C−C-bond. The frontier molecular orbitals were calculated for enone **4a** (LUMO) and Na-enolate **12a** (HOMO) by DFT computations (B3LYP/6-31G*) in vacuum (Figure 4). Our model suggests a maximum molecular orbital overlap in a transition state leading to the observed diastereomer. Next to the orbital overlap at the azlactone C-4 atom and the 4-position of the enone resulting in the C−C bond formation, we suggest a secondary molecular orbital interaction of the azlactone C-2 atom and the 2-position

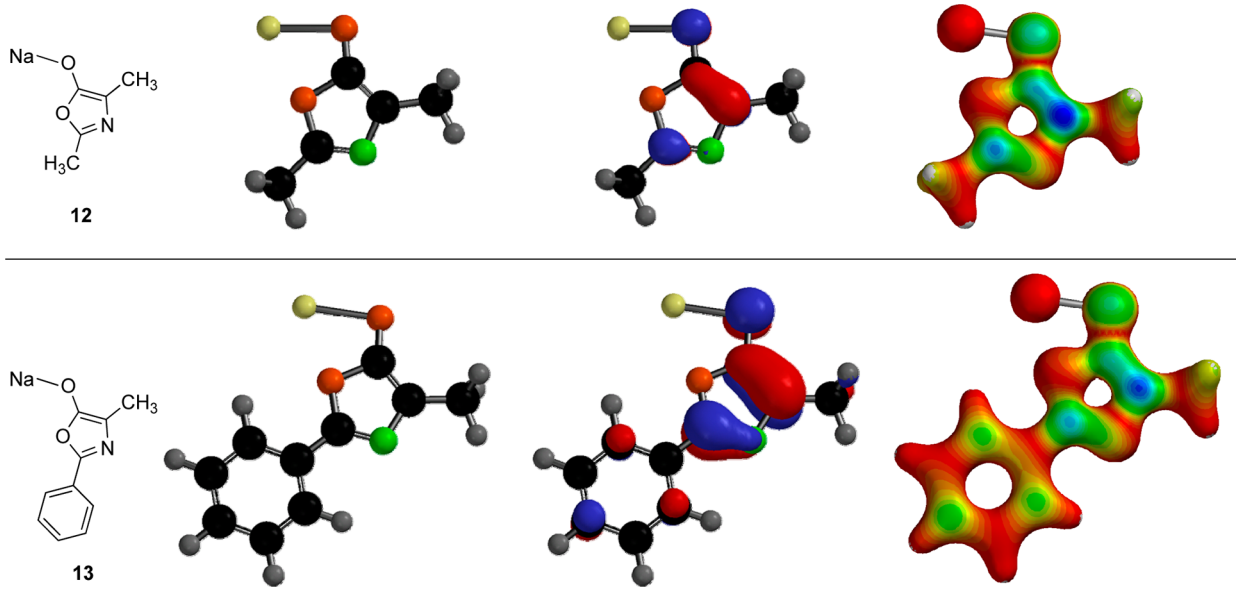


Figure 1. Comparison of sodium enolates **12** (*top*) and **13** (*bottom*) by quantum mechanical computations (DFT/B3LYP/6-31G*). (*Left*) representation of the equilibrium conformers; (*middle*) representation of the HOMOs of the enolates; (*right*) HOMO densities (blue color indicates high electron density; red color means low electron density).

dx.doi.org/10.1021/jo302177t | J. Org. Chem. 2012, 77, 10846−10855

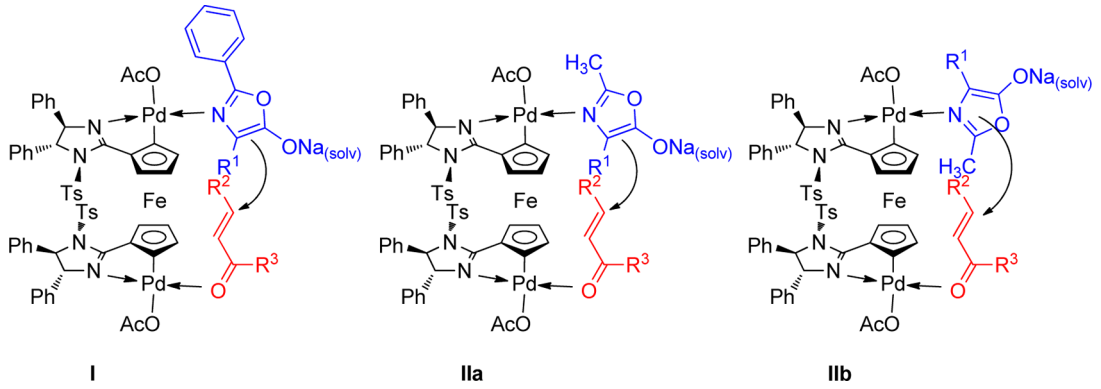


Figure 2. Representation of the assumed reactive intermediates to form a C−C bond to explain the exclusive regioselectivity with 2-Ph azlactones and the poor regioselectivity with 2-Me azlactones using a bis-Pd catalyst.

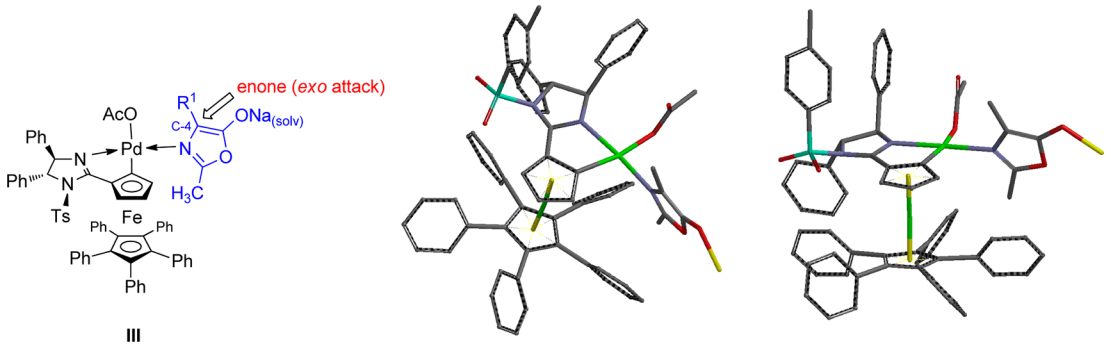


Figure 3. Representations of the assumed reactive intermediate using the mono-Pd catalyst to explain (a) the exclusive regioselectivity with 2-Me azlactones by the preference of the *exo*-attack (left formula) and (b) the high enantioselectivity (middle and right). The latter 3D-models (two different views) show that the *Si*-face at C-4 is shielded by the pentaphenylferrocene core, whereas th *Re*-face is considerably more accessible.

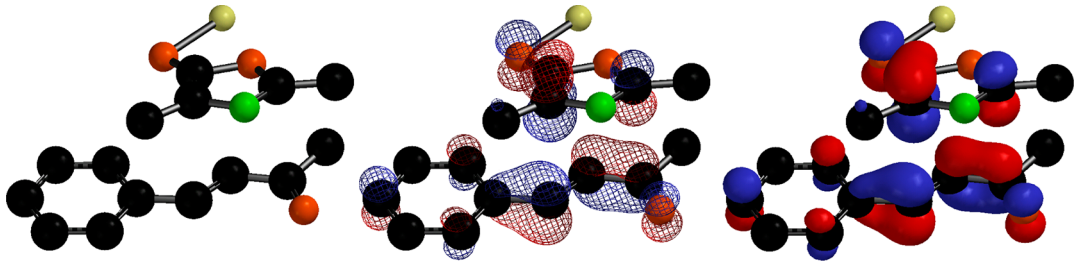


Figure 4. Rationale for the observed high diastereoselectivity by a secondary molecular orbital interaction of the azlactone C-2 atom and the 2-position of the enone.

of the enone to explain the inherent diastereoselectivity of the title reaction.

CONCLUSION

In conclusion, we have presented an enantio- and diastereoselective 1,4-addition of azlactones generated in situ from racemic unprotected amino acids and acetic anhydride that proceeds regioselectively forming exclusively the azlactone C-4 regioisomer. In contrast, previous attempts with unprotected amino acids required the use of a large excess of benzoic anhydride (via the azlactone intermediate **2-Ph**), whereas the use of acetic anhydride had provided regioisomeric mixtures of the azlactone C-2/C-4 addition products. The use of acetic anhydride offers a significant practical advantage: it can be conveniently removed due to its volatility, whereas removal of a large excess of the solid benzoic anhydride as previously described[6b,c] proved to be tedious and required two sequential column chromatographies. The new development was allowed by the use of a pentaphenylferrocene monopalladacycle catalyst. The observed complementarity of mono- and bis-palladacycle catalysts might at least be partly explained by a higher nucleophilicity of the enolates derived from 2-methyl azlactones, which could allow for a monometallic reaction pathway in which the enone does not need to be activated by the catalyst, whereas the less nucleophilic 2-phenyl azlactones might prefer a bimetallic pathway in which both the azlactone and enone should be activated to achieve a sufficient reactivity.

EXPERIMENTAL SECTION

General Procedure for the Activation of the Precatalyst [PPFIP-Cl]$_2$ (GP1). [**PPFIP-Cl**]$_2$ (1 equiv) and the silver salt (2 equiv) were dissolved/suspended in acetonitrile (1 mL per 5 mg of [**PPFIP-Cl**]$_2$) and stirred overnight at room temperature. The reaction flask was covered with aluminum foil to shield from light during that period. After the activation was complete, the mixture was filtered through Celite, and then free acetonitrile was removed under

dx.doi.org/10.1021/jo302177t | J. Org. Chem. 2012, 77, 10846−10855

reduced pressure (ca. 5 min at 15 mbar and room temperature). A stock solution was subsequently prepared.

General Procedure for the Catalytic Asymmetric Synthesis of α,α-Disubstituted α-Amino Acid Derivatives Using Unprotected Amino Acids (GP2). The corresponding racemic amino acid (**3**, 1.00 equiv, 0.30 mmol), the corresponding enone (**4**, 6.00 equiv, 1.80 mmol) and NaOAc (0.25 equiv, 75.0 μmol, 6.2 mg) were successively charged into a vial. To this mixture was added the activated catalyst (prepared from 0.03 equiv of [**PPFIP-Cl**]$_2$, 9.00 μmol, 19.5 mg; see **GP1**) as a stock solution in AcOH/Ac_2O (4/1, 900 μL) and CH_2Cl_2 (900 μL). The resulting slurry was heated to 50 °C for 18 h. After this time, the mixture was cooled to room temperature and was then directly used for silica gel column chromatography to isolate the targeted products. To completely remove residual traces of catalyst, the material was dried under reduced pressure (0.1 mbar) and was then extracted several times with *n*-pentane.

General Procedure for the Synthesis of the Racemic α,α-Disubstituted α-Amino Acid Derivatives (GP3). The syntheses were carried out like described in **GP2** but using a ca. 1:1 mixture of both catalyst enantiomers and applying a smaller scale: the corresponding racemic amino acid (**3**, 1.00 equiv, 0.05 mmol), the corresponding enone (**4**, 6.00 equiv, 0.30 mmol) and NaOAc (0.25 equiv, 12.0 μmol, 1 mg) were successively charged into a vial. To this mixture was added the activated, nearly racemic catalyst mixture (prepared from a mixture of 0.015 equiv of S_p-[**PPFIP-Cl**]$_2$ and 0.015 equiv of R_p-[**PPFIP-Cl**]$_2$, each 0.75 μmol, 1.63 mg, see **GP1**) as a stock solution in AcOH/Ac_2O (4/1, 150 μL) and CH_2Cl_2 (150 μL). The resulting slurry was heated to 50 °C for 18 h. After this time, the mixture was cooled to room temperature and was then directly used for silica gel column chromatography to isolate the racemic products **rac-5**.

Activated Catalysts. *{[η^5-(4′R,5′R)-(S_p)-2-(2′-4′,5′-Dihydro-4′,5′-diphenyl-1′-tosyl-1′H-imid-azolyl)cyclopentadienyl,1-C, 3′-N)(η^5-pentaphenylcyclopentadienyl)-iron(II)]palladium(II)}-triflate acetonitrile complex (PPFIP-OTf).* The catalyst precursor [**PPFIP-Cl**]$_2$ (1.0 equiv, 6.93 μmol, 15 mg) was activated according to **GP1** using AgOTf (2 equiv, 13.9 μmol, 3.56 mg). **PPFIP-OTf** was isolated as a crystalline purple-red solid (13.6 μmol, 16.8 mg, 98%).

$C_{65}H_{50}F_3FeN_3O_5PdS_2$: MW 1236.50; mp >250 °C (decomp.); $[\alpha]_D^{23}$ −853.3 (*c* = 0.00656, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55 (*d*, *J* = 8.2, 2 H), 7.33 (*d*, *J* = 7.9, 2 H), 7.25−6.95 (*m*, 31 H), 6.46 (*d*, *J* = 7.8, 2 H), 6.33 (*d*, *J* = 7.4, 2 H), 5.81 (*d*, *J* = 1.5, 1 H), 4.77 (*t*, *J* = 2.0, 1 H), 4.65 (*d*, *J* = 1.0, 1 H), 4.55−4.42 (*m*, 2 H), 2.52 (*s*, 3 H), 2.42 (*s*, 3 H), 1.94 (*s*); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.5, 146.4, 140.0, 138.4, 134.6, 134.2, 132.7, 132.4, 131.7, 130.5, 129.3, 129.0, 128.7, 128.2, 127.8, 127.2, 127.0, 126.9, 126.7, 126.3, 125.7, 122.6, 118.5, 89.7, 79.8, 79.4, 75.5, 75.4, 73.2, 21.7, 3.7, 1.9; ^{19}F NMR (235 MHz, $CDCl_3$) δ = −78.33; IR (in $CDCl_3$) ν = 3059, 2932, 2322, 2250, 1599, 1543, 1503, 1453, 1383, 1280, 1255, 1224, 1172, 1078, 1030, 972, 911, 739, 699, 670, 659, 638, 603, 570, 543; MS (ESI) *m*/*z* 1045.17 (100%, [M − MeCN − OTf]$^+$); HRMS (ESI) *m*/*z* calculated for $C_{62}H_{47}FeN_2O_2PdS$ (M − MeCN − OTf) 1045.1759, found 1045.1743.

{[η^5-(4′R,5′R)-(S_p)-2-(2′-4′,5′-Dihydro-4′,5′-diphenyl-1′-tosyl-1′H-imid-azolyl)cyclopentadienyl,1-C, 3′-N)(η^5 pentaphenylcyclopentadienyl)-iron(II)]palladium(II)}-acetate acetonitrile complex (PPFIP-OAc). The catalyst precursor [**PPFIP-Cl**]$_2$ (1.0 equiv, 6.93 μmol, 15 mg) was activated according to **GP1** using AgOAc (2 equiv, 13.9 μmol, 2.31 mg). **PPFIP-OAc** was isolated as a crystalline purple-red solid (13.2 μmol, 15.1 mg, 95%).

$C_{66}H_{53}FeN_3O_4PdS$: MW 1146.47; mp >250 °C (decomp.); $[\alpha]_D^{23}$ −845.7 (*c* = 0.01313, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56 (*d*, *J* = 8.3, 2 H), 7.42−7.17 (*m*, 12 H), 7.17−6.93 (*m*, 21 H), 6.48 (*d*, *J* = 7.7, 2 H), 6.43 (*d*, *J* = 7.5, 2 H), 5.72 (*d*, *J* = 1.9, 1 H), 4.88 (*d*, *J* = 1.2, 1 H), 4.65 (*t*, *J* = 2.3, 1 H), 4.49 (*d*, *J* = 7.7, 1 H), 4.46 (*d*, *J* = 7.8, 1 H), 2.50 (*s*, 3 H), 2.00 (*s*, 3 H), 1.97 (*s*, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ = 171.1, 145.8, 139.9, 139.0, 134.9, 133.1, 132.7, 132.2, 130.4, 129.1, 128.9, 128.6, 128.0, 127.9, 127.1, 126.5, 126.2, 99.2, 89.3, 88.9, 79.4, 77.9, 75.7, 75.5, 74.7, 72.6, 24.4, 21.7, 14.1, 1.9; IR (in $CDCl_3$) ν = 3056, 2243, 1597, 1541, 1502, 1444, 1407, 1380, 1328, 1286, 1171, 1155, 1076, 1045, 1027, 969, 907, 814, 801, 784, 729, 696, 670, 659, 647, 601, 568, 543, 531; MS (ESI) *m*/*z* 1045.17 (100%, [M − MeCN − OAc]$^+$); HRMS (ESI) *m*/*z* calculated for $C_{62}H_{47}FeN_2O_2PdS$ (M − MeCN − OAc) 1045.1759, found 1045.1743.

Asymmetric Synthesis of the α,α-Disubstituted Amino Acid Derivatives (5). *(R)-2,4-Dimethyl-4-((R)-3-oxo-1-phenylbutyl)-oxazol-5(4H)-one (**5a**).* D,L-Alanine (26.7 mg) was treated with *trans*-4-phenyl-but-3-en-2-one (263 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 0/1) yielded **5a** as a colorless oil (150 μmol, 38.8 mg, 50%; *dr* > 99:1, *ee* = 99%).

$C_{15}H_{17}NO_3$: MW 259.30; $[\alpha]_D^{23}$ +3.8 (*c* = 1.60, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.21−7.13 (*m*, 2 H), 7.06−6.93 (2 × *m*, 3 H), 3.83 (*t*, *J* = 7.0, 1 H), 2.73 (*d*, *J* = 6.8, 2 H), 1.51 (*s*, 3 H), 1.44 (*s*, 3 H), 1.18 (*s*, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.1, 179.6, 161.2, 139.0, 129.6, 128.2, 127.7, 72.3, 46.6, 43.7, 29.7, 21.8, 14.3; IR (in C_6D_6) ν = 3032, 2978, 2937, 1821, 1801, 1715, 1685, 1493, 1454, 1431, 1382, 1244, 1166, 1062, 1046, 1020, 903, 703, 667, 620; MS (ESI) *m*/*z* 282.1 (25%, [M + Na]$^+$), 254.1 (10%), 241.1 (100%), 213.1 (12%), 197.1 (10%), 170.1 (8%); HRMS (ESI) *m*/*z* calculated for $C_{15}H_{17}NO_3$ + Na 282.1101, found 282.1129.

*(R)-4-Ethyl-2-methyl-4-((R)-3-oxo-1-phenylbutyl)oxazol-5(4H)-one (**5b**).* D,L-Ethyl glycine (30.9 mg) was treated with *trans*-4-phenyl-but-3-en-2-one (263 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/10) yielded **5b** as a colorless oil (166 μmol, 45.3 mg, 55%; *dr* > 99:1, *ee* = 98%).

$C_{16}H_{19}NO_3$: MW 273.33; $[\alpha]_D^{23}$ −6.2 (*c* = 0.95, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.24−7.17 (*m*, 2 H), 7.02−6.94 (2 × *m*, 3 H), 3.88 (*t*, *J* = 6.8, 1 H), 2.82−2.66 (*m*, 2 H), 1.83−1.67 (*m*, 1 H), 1.66−1.52 (*m*, 1 H), 1.51 (*s*, 3 H), 1.48 (*s*, 3 H), 0.66 (*t*, *J* = 7.2, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.1, 178.9, 161.7, 139.1, 129.7, 128.2, 127.7, 77.1, 46.4, 44.0, 29.7, 28.3, 14.1, 8.2; IR (in C_6D_6) ν = 3031, 2973, 2935, 2882, 1814, 1716, 1683, 1455, 1433, 1357, 1243, 1165, 1067, 967, 900, 755, 735, 703, 670, 620, 528; MS (ESI) *m*/*z* 274.1 (5%, [M + H]$^+$), 246.1 (5%), 204.1 (5%), 187.1 (100%); HRMS (ESI) *m*/*z* calculated for $C_{16}H_{19}NO_3$ + H 274.1438, found 274.1428.

*(R)-2-Methyl-4-((R)-3-oxo-1-phenylbutyl)-4-propyloxazol-5(4H)-one (**5c**).* D,L-Norvaline (35.1 mg) was treated with *trans*-4-phenyl-but-3-en-2-one (263 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/7) yielded **5c** as a colorless oil (192 μmol, 54.8 mg, 64%; *dr* > 99:1, *ee* = 93%).

$C_{17}H_{21}NO_3$: MW 287.35; $[\alpha]_D^{23}$ +4.8 (*c* = 1.60, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.25−7.18 (*m*, 2 H), 7.08−6.94 (2 × *m*, 3 H), 3.87 (*dd*, *J* = 8.5, 5.3, 1 H), 2.82 (*dd*, *J* = 17.1, 8.4, 1 H), 2.73 (*dd*, *J* = 17.2, 5.3, 1 H), 1.82−1.69 (*m*, 1 H), 1.69−1.55 (*m*, 1 H), 1.52 (*s*, 3 H), 1.49 (*s*, 3 H), 1.20−1.01 (*m*, 2 H), 0.69 (*t*, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.1, 179.0, 161.6, 138.9, 129.7, 128.2, 127.7, 76.6, 46.7, 44.0, 37.3, 29.8, 17.7, 14.2, 13.9; IR (in C_6D_6) ν = 3032, 2962, 2933, 2875, 2279, 1818, 1716, 1683, 1494, 1455, 1432, 1381, 1358, 1244, 1201, 1164, 1068, 901, 811, 750, 733, 703, 671, 619, 535; MS (ESI) *m*/*z* 310.1 (15%, [M + H]$^+$), 282.1 (5%), 269.1 (100%), 241.1 (5%), 225.1 (10%), 170.1 (5%); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{21}NO_3$ + Na 310.1414, found 310.1429.

*(R)-4-Butyl-2-methyl-4-((R)-3-oxo-1-phenylbutyl)oxazol-5(4H)-one (**5d**).* D,L-Norleucine (39.4 mg) was treated with *trans*-4-phenyl-but-3-en-2-one (263 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/3) yielded **5d** as a colorless oil (216 μmol, 65.0 mg, 72%; *dr* > 99:1, *ee* = 92%).

$C_{18}H_{23}NO_3$: MW 301.38; $[\alpha]_D^{23}$ −8.7 (*c* = 1.01, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.26−7.18 (*m*, 2 H), 7.08−6.95 (2 × *m*, 3 H), 3.89 (*dd*, *J* = 8.4, 5.7, 1 H), 2.83 (*dd*, *J* = 17.2, 8.4, 1 H), 2.76 (*dd*, *J* = 17.2, 5.5, 1 H), 1.92−1.75 (*m*, 1 H), 1.75−1.61 (*m*, 1 H), 1.52 (*s*, 3 H), 1.49 (*s*), 1.20−1.03 (*m*, 4 H), 0.73 (*t*, *J* = 6.9); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.2, 179.1, 161.6, 138.9, 129.7, 128.2, 127.7, 76.6, 46.8, 44.0, 35.0, 29.8, 26.4, 22.8, 14.2, 13.9; IR (in C_6D_6) ν = 3032, 2958, 2930, 2872, 1818, 1716, 1683, 1494, 1455, 1382, 1357, 1243, 1198, 1164, 1063, 1020, 970, 900, 742, 702, 670, 536; MS (ESI) *m*/*z* 302.2 (5%, [M + H]$^+$, 274.2 (5%), 232.2 (5%), 215.1 (100%); HRMS (ESI) *m*/*z* calculated for $C_{18}H_{23}NO_3$ + H 302.1751, found 302.1743.

*(R)-4-Isobutyl-2-methyl-4-((R)-3-oxo-1-phenylbutyl)oxazol-5(4H)-one (**5e**).* D,L-Leucine (39.4 mg) was treated with *trans*-4-phenyl-but-3-

en-2-one (263 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/3) yielded **5e** as a colorless oil (126 μmol, 37.7 mg, 42%; *dr* > 99:1, *ee* = 79%).

$C_{18}H_{23}NO_3$: MW 301.38; $[\alpha]_D^{23}$ +12.2 (*c* = 1.31, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.22−7.17 (*m*, 2 H), 7.07−6.94 (2 × *m*, 3 H), 3.83 (*dd*, *J* = 8.4, 5.3, 1 H), 2.82 (*dd*, *J* = 17.3, 8.5, 1 H), 2.74 (*dd*, *J* = 17.2, 5.2, 1 H), 1.80 (*dd*, *J* = 13.9, 5.8, 1 H), 1.72 (*dd*, *J* = 14.2, 6.3, 1 H), 1.51 (*s*, 3 H), 1.50 (*s*, 3 H), 1.33−1.20 (*m*, 1 H), 0.79 (*d*, *J* = 6.6, 6 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.1, 179.5, 161.4, 138.7, 129.8, 128.2, 127.8, 76.4, 47.7, 44.2, 43.8, 29.8, 25.5, 24.0, 23.6, 14.3; IR (in C_6D_6) ν = 3032, 2958, 2873, 1817, 1717, 1683, 1494, 1469, 1455, 1431, 1382, 1358, 1283, 1244, 1165, 1070, 900, 764, 740, 703, 672, 619, 604; MS (ESI) *m*/*z* 302.2 (10%, $[M + H]^+$), 274.2 (10%), 232.2 (5%), 215.1 (100%); HRMS (ESI) *m*/*z* calculated for $C_{18}H_{23}NO_3$ + H 302.1751, found 302.1735.

*(R)-4-Benzyl-2-methyl-4-((R)-3-oxo-1-phenylbutyl)oxazol-5(4H)-one (**5f**)*. D,L-Phenyl alanine (49.6 mg) was treated with *trans*-4-phenyl-but-3-en-2-one (263 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/2) yielded **5f** as a colorless solid (147 μmol, 48.9 mg, 49%; *dr* > 99:1, *ee* = 82%).

$C_{21}H_{21}NO_3$: MW 335.40; mp 117.2 − 117.7 °C; $[\alpha]_D^{23}$ −61.8 (*c* = 0.73, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.29−7.23 (*m*, 2 H), 7.19−7.16 (*m*, 2 H), 7.08−6.93 (*m*, 6 H), 4.03 (*t*, *J* = 6.9, 1 H), 3.04−2.89 (*m*, 2 H), 2.86 (*s*, 1 H), 2.84 (*s*, 1 H), 1.55 (*s*, 3 H), 1.26 (*s*, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.0, 178.1, 161.7, 139.0, 134.9, 130.8, 129.8, 128.31, 128.27, 127.7, 127.4, 77.8, 46.6, 44.2, 41.6, 29.8, 13.9; IR (in C_6D_6) ν = 3062, 2929, 1817, 1716, 1684, 1603, 1494, 1455, 1431, 1382, 1358, 1244, 1162, 1100, 1061, 1030, 984, 902, 749, 701, 670, 642, 620, 602, 583; MS (ESI) *m*/*z* 336.2 (15%, $[M + H]^+$), 308.2 (20%), 290.1 (4%), 266.2 (25%), 249.1 (100%), 190.1 (2%); HRMS (ESI) *m*/*z* calculated for $C_{21}H_{21}NO_3$ + Na 358.1414, found 358.1405.

*Methyl 3-((R)-2-methyl-5-oxo-4-((R)-3-oxo-1-phenylbutyl)-4,5-dihydrooxazol-4-yl)propanoate (**5g**)*. D,L-Glutamic acid γ-methyl ester (48.4 mg) was treated with *trans*-4-phenyl-but-3-en-2-one (263 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/6) yielded **5g** as a colorless oil (168 μmol, 55.5 mg, 56%; *dr* > 99:1, *ee* = 95%).

$C_{18}H_{21}NO_5$: MW 331.36; $[\alpha]_D^{23}$ −2.55 (*c* = 0.98, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.20−7.13 (*m*, 2 H), 7.06−6.94 (*m*, 3 H), 3.84 (*t*, *J* = 7.0, 1 H), 3.29 (*s*, 3 H), 2.76 (*d*, *J* = 6.9, 2 H), 2.28−2.04 (*m*, 4 H), 1.51 (*s*, 3 H), 1.47 (*s*, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.03, 204.02, 178.7, 172.0, 162.4, 138.6, 129.7, 128.2, 127.8, 75.69, 75.68, 51.3, 46.3, 43.8, 30.3, 29.7, 29.1, 14.2; IR (in C_6D_6) ν = 2953, 1817, 1736, 1717, 1683, 1494, 1454, 1436, 1381, 1296, 1243, 1202, 1164, 1109, 1062, 1022, 901, 761, 739, 704, 669, 643, 620; MS (ESI) *m*/*z* 332.1 (20%, $[M + H]^+$), 304.2 (22%), 286.1 (23%), 262.1 (24%), 245.1 (100%), 230.1 (15%), 212.1 (15%), 171.1 (35%); HRMS (ESI) *m*/*z* calculated for $C_{18}H_{21}NO_5$ + Na 354.1312, found 354.1310.

*(R)-4-((1H-Indol-3-yl)methyl)-2-methyl-4-((R)-3-oxo-1-phenylbutyl)oxazol-5(4H)-one (**5h**)*. D,L-Tryptophan (61.3 mg) was treated with *trans*-4-phenyl-but-3-en-2-one (263 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/5) yielded **5h** as a colorless solid (198 μmol, 73.8 mg, 66%; *dr* > 99:1, *ee* = 87%).

$C_{23}H_{22}N_2O_3$: MW 374.43; mp 63.5 − 63.9 °C; $[\alpha]_D^{23}$ −265.3 (*c* = 0.81, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.96−7.87 (*m*, 1 H), 7.35−7.27 (*m*, 2 H), 7.23−7.13 (*m*, 2 H), 7.09−6.93 (*m*, 5 H), 6.68 (*d*, *J* = 2.5, 1 H), 4.12 (*dd*, *J* = 7.7, 5.9, 1 H), 3.29 (*d*, *J* = 13.9, 1 H), 3.20 (*d*, *J* = 13.9, 1 H), 3.05−2.87 (*m*, 2 H), 1.58 (*s*, 3 H), 1.12 (*s*, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.6, 179.0, 161.9, 139.3, 136.3, 129.7, 128.3, 128.1, 124.5, 122.0, 120.4, 119.6, 111.4, 109.0, 79.1, 46.5, 44.3, 32.0, 29.9, 13.9; IR (in C_6D_6) ν = 3412, 3059, 2921, 2279, 1816, 1713, 1685, 1547, 1493, 1456, 1426, 1381, 1357, 1340, 1242, 1163, 1100, 1062, 1011, 984, 904, 743, 703, 670, 621; MS (ESI) *m*/*z* 375.2 (35%, $[M + H]^+$), 347.2 (65%), 315.1 (75%), 246.1 (100%), 229.1 (70%), 218.1 (40%), 201.1 (35%), 171.1 (45%), 130.1 (85%); HRMS (ESI) *m*/*z* calculated for $C_{23}H_{22}N_2O_3$ + H 375.1703, found 375.1706.

*(R)-2-Methyl-4-((R)-4-methyl-3-oxo-1-phenylpentyl)-4-propyloxazol-5(4H)-one (**5i**)*. D,L-Norvaline (35.1 mg) was treated with *trans*-4-methyl-1-phenylpent-1-en-3-one (314 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/1 to 1/4) yielded **5i** as a colorless gummy solid (48.0 μmol, 15.6 mg, 16%; *dr* > 99:1, *ee* = 96%).

$C_{19}H_{25}NO_3$: MW 315.41; $[\alpha]_D^{23}$ −27.7 (*c* = 0.30, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.30−7.24 (*m*, 2 H), 7.08−6.93 (*m*, 3 H), 4.02 (*dd*, *J* = 8.7, 5.0, 1 H), 2.99 (*dd*, *J* = 17.3, 8.7, 1 H), 2.88 (*dd*, *J* = 17.3, 5.0, 1 H), 2.10 (*sep*, *J* = 6.9, 1 H), 1.88−1.74 (*m*, 1 H), 1.74−1.61 (*m*, 1 H), 1.51 (*s*, 3 H), 1.22−1.06 (*m*, 2 H), 0.82 and 0.69 (2 × *d*, 2 × *J* = 6.8, 2 × 3 H), 0.68 (*t*, *J* = 7.2, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 210.1, 179.0, 161.6, 139.2, 129.8, 128.2, 128.1, 76.7, 46.7, 41.3, 41.2, 37.4, 18.0, 17.99, 17.89, 17.7, 14.2, 13.9; IR (in C_6D_6) ν = 2965, 2932, 2874, 1818, 1712, 1683, 1494, 1455, 1433, 1382, 1244, 1201, 1150, 1067, 1035, 1009, 899, 752, 730, 702, 674, 619; MS (ESI) *m*/*z* 338.2 (1%, $[M + Na]^+$), 274.2 (5%), 229.2 (100%), 175.1 (5%); HRMS (ESI) *m*/*z* calculated for $C_{19}H_{25}NO_3$ + Na 338.1727, found 338.1709.

*(R)-4-((R)-1-(4-Methoxyphenyl)-3-oxobutyl)-2-methyl-4-propyloxazol-5(4H)-one (**5j**)*. D,L-Norvaline (35.1 mg) was treated with *trans*-4-(4-methoxyphenyl)but-3-en-2-one (317 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/3) yielded **5j** as a colorless oil (123 μmol, 38.7 mg, 41%; *dr* > 99:1, *ee* = 99%).

$C_{18}H_{23}NO_4$: MW 317.38; $[\alpha]_D^{23}$ −8.0 (*c* = 0.66, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.20−7.12 (*m*, 2 H), 6.70−6.62 (*m*, 2 H), 3.85 (*dd*, *J* = 9.2, 4.9, 1 H), 3.21 (*s*, 3 H), 2.84 (*dd*, *J* = 17.0, 9.4, 1 H), 2.72 (*dd*, *J* = 17.0, 4.8, 1 H), 1.84−1.71 (*m*, 1 H), 1.70−1.58 (*m*, 1 H), 1.56 (*s*, 3 H), 1.52 (*s*, 3 H), 1.24−1.05 (*m*, 2 H), 0.71 (*t*, *J* = 7.2, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.4, 179.2, 161.5, 159.4, 130.7, 130.6, 113.7, 76.9, 54.6, 46.2, 44.1, 37.3, 29.9, 17.7, 14.2, 14.0; IR (in C_6D_6) ν = 2962, 2934, 2875, 2838, 1817, 1715, 1684, 1611, 1513, 1463, 1432, 1381, 1360, 1247, 1180, 1165, 1068, 1034, 900, 833, 783, 670, 619, 548; MS (ESI) *m*/*z* 340.2 (20%, $[M + Na]^+$), 299.1 (100%), 255.1 (40%), 200.1 (10%), 157.1 (5%); HRMS (ESI) *m*/*z* calculated for $C_{18}H_{23}NO_4$ + Na 340.1519, found 340.1511.

*(R)-4-((R)-1-(3,4-Dimethoxyphenyl)-3-oxobutyl)-2-methyl-4-propyloxazol-5(4H)-one (**5k**)*. D,L-Norvaline (35.1 mg) was treated with *trans*-4-(3,4-dimethoxyphenyl)but-3-en-2-one (371 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/3 to 0/1) yielded **5k** as a gummy solid (168 μmol, 58.7 mg, 56%; *dr* > 99:1, *ee* = 86%).

$C_{19}H_{25}NO_5$: MW 347.41; $[\alpha]_D^{23}$ +6.1 (*c* = 0.31, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 6.84 (*s*, 1 H), 2.82 (*dd*, *J* = 9.9, 2.1, 1 H), 6.47 (*d*, *J* = 8.1, 1 H), 3.87 (*dd*, *J* = 9.2, 4.8, 1 H), 3.45 and 3.31(2 × *s*, 2 × 3 H), 2.90 (*dd*, *J* = 16.8, 9.5, 1 H), 2.75 (*dd*, *J* = 16.8, 4.7, 1 H), 1.87−1.74 (*m*, 1 H), 1.74−1.62 (*m*, 1 H), 1.60 (*s*, 3 H), 1.53 (*s*, 3 H), 1.27−1.06 (*m*, 2 H), 0.72 (*t*, *J* = 7.4, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 204.5, 179.2, 161.6, 149.59, 149.56, 131.1, 122.1, 113.8, 111.7, 77.0, 55.7, 46.5, 44.3, 37.4, 29.9, 17.7, 14.3, 14.0; IR (in C_6D_6) ν = 2961, 2935, 2875, 2836, 1817, 1715, 1684, 1606, 1590, 1516, 1464, 1423, 1381, 1359, 1260, 1242, 1157, 1144, 1069, 1027, 901, 812, 765, 677, 617; MS (ESI) *m*/*z* 370.2 (50%, $[M + Na]^+$), 342.2 (10%), 329.1 (100%), 285.1 (40%), 230.1 (15%), 187.1 (15%); HRMS (ESI) *m*/*z* calculated for $C_{19}H_{25}NO_5$ + Na 370.1625, found 370.1631.

*(R)-4-((R)-1-(4-Chlorophenyl)-3-oxobutyl)-2-methyl-4-propyloxazol-5(4H)-one (**5l**)*. D,L-Norvaline (35.1 mg) was treated with *trans*-4-(4-chlorophenyl)but-3-en-2-one (325 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/1 to 1/8) yielded **5l** as a colorless gummy solid (177 μmol, 56.5 mg, 59%; *dr* > 99:1, *ee* = 93%).

$C_{17}H_{20}ClNO_3$: MW 321.80; $[\alpha]_D^{23}$ −2.9 (*c* = 0.59, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.04−6.94 (*m*, 4 H), 3.76 (*t*, *J* = 7.1, 1 H), 2.66 (*d*, *J* = 7.0, 2 H), 1.75−1.62 (*m*, 1 H), 1.62−1.50 (*m*, 1 H), 1.52 (*s*, 3 H), 1.45 (*s*, 3 H), 1.16−0.99 (*m*, 2 H), 0.69 (*t*, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 203.8, 178.9, 161.8, 137.4, 131.1, 128.4, 76.3, 45.9, 43.7, 37.2, 29.8, 17.6, 14.1, 13.9; IR (in C_6D_6) ν = 2962, 2933, 2875, 1817, 1717, 1684, 1493, 1431, 1381, 1360, 1244, 1201, 1165, 1093, 1069, 1014, 901, 831, 782, 741, 717, 674, 619; MS (ESI) *m*/*z* 344.1 (25%, $[M + Na]^+$), 303.1 (100%), 280.1 (20%), 235.1 (100%), 204.0 (5%), 179.1 (10%); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{20}ClNO_3$ + Na 344.1024, found 344.1034.

*(R)-4-((R)-1-(2-Chlorophenyl)-3-oxobutyl)-2-methyl-4-propyloxazol-5(4H)-one (**5m**).* D,L-Norvaline (35.1 mg) was treated with *trans*-4-(2-chlorophenyl)but-3-en-2-one (325 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/1 to 1/7) yielded **5m** as a colorless oil (111 μmol, 35.6 mg, 37%; *dr* > 99:1, *ee* = 92%).

$C_{17}H_{20}ClNO_3$: MW 321.80; $[\alpha]_D^{23}$ −13.2 (*c* = 0.44, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.21−7.16 (*m*, 2 H), 6.82 (*td*, *J* = 7.7, 1.4, 1 H), 6.72−6.64 (*m*, 1 H), 4.70 (*dd*, *J* = 8.9, 5.4, 1 H), 2.75 (*dd*, *J* = 16.8, 5.3, 1 H), 2.63 (*dd*, *J* = 16.9, 9.2, 1 H), 1.81−1.69 (*m*, 2 H), 1.57 and 1.55 (2 × *s*, 2 × 3 H), 1.19−0.97 (*m*, 2 H), 0.65 (*t*, *J* = 7.1, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 203.5, 178.3, 161.9, 137.1, 136.1, 130.4, 128.7, 128.1, 126.3, 76.0, 44.9, 41.2, 37.1, 29.3, 17.5, 14.3, 13.8; IR (in C_6D_6) ν = 2963, 2933, 2875, 2279, 1821, 1717, 1683, 1475, 1432, 1382, 1360, 1330, 1245, 1199, 1166, 1059, 1037, 1010, 901, 814, 783, 755, 688, 669, 619; MS (ESI) *m*/*z* 344.1 (15%, $[M + Na]^+$), 316.1 (5%), 303.1 (100%), 275.1 (5%), 259.1 (5%), 204.0 (5%); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{20}ClNO_3$ + Na 344.1024, found 344.1018.

*(R)-4-((R)-1-(4-Bromophenyl)-3-oxobutyl)-2-methyl-4-propyloxazol-5(4H)-one (**5n**).* D,L-Norvaline (35.1 mg) was treated with *trans*-4-(4-bromophenyl)but-3-en-2-one (405 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 2/1 to 1/6) yielded **5n** as a colorless oil (189 μmol, 69.4 mg, 63%; *dr* > 99:1, *ee* = 94%).

$C_{17}H_{20}BrNO_3$: MW 366.25; $[\alpha]_D^{23}$ −4.2 (*c* = 0.93, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.20−7.13 (*m*, 2 H), 6.94−6.85 (*m*, 2 H), 3.74 (*t*, *J* = 7.1, 1 H), 2.64 (*d*, *J* = 7.0, 2 H), 1.74−1.61 (*m*, 1 H), 1.61−1.48 (*m*, 1 H), 1.51 (*s*, 3 H), 1.44 (*s*, 3 H), 1.16−0.99 (*m*, 2 H), 0.68 (*t*, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 203.8, 178.9, 161.8, 137.9, 131.4, 121.9, 76.2, 46.0, 43.7, 37.2, 29.8, 17.6, 14.1, 13.9; IR (in C_6D_6) ν = 2962, 2932, 2875, 2359, 1818, 1717, 1684, 1489, 1431, 1381, 1360, 1244, 1201, 1165, 1072, 1010, 900, 828, 781, 740, 715, 672, 619, 537; MS (ESI) *m*/*z* 390.1 (45%, $[M + Na]^+$), 347.0 (100%), 281.0 (90%), 201.0 (20%), 144.1 (50%), 129.1 (10%); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{20}BrNO_3$ + Na 390.0500, found 390.0495.

*(R)-2-Methyl-4-((R)-1-(4-nitrophenyl)-3-oxobutyl)-4-propyloxazol-5(4H)-one (**5o**).* D,L-Norvaline (35.1 mg) was treated with *trans*-4-(4-nitrophenyl)but-3-en-2-one (344 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 1/3) yielded **5o** as a colorless gummy solid (123 μmol, 41.3 mg, 41%; *dr* > 99:1, *ee* = 97%).

$C_{17}H_{20}N_2O_5$: MW 332.35; $[\alpha]_D^{23}$ −10.0 (*c* = 0.90, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 7.79−7.71 (*m*, 2 H), 7.01−6.94 (*m*, 2 H), 3.75 (*dd*, *J* = 8.0, 5.8, 1 H), 2.70−2.53 (*m*, 2 H), 1.71−1.47 (*m*, 2 H), 1.53 (*s*, 3 H), 1.45 (*s*, 3 H), 1.13−0.95 (*m*, 2 H), 0.68 (*t*, *J* = 7.2, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 203.4, 178.6, 162.0, 147.6, 145.9, 130.2, 123.2, 75.9, 46.1, 43.4, 37.2, 29.7, 17.5, 14.1, 13.9; IR (in C_6D_6) ν = 2963, 2933, 2875, 1817, 1716, 1682, 1604, 1519, 1431, 1382, 1345, 1317, 1277, 1242, 1166, 1110, 1068, 1014, 899, 854, 735, 702, 671, 618; MS (ESI) *m*/*z* 333.1 (1%, $[M + H]^+$), 263.1 (35%), 246.1 (100%); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{20}N_2O_5$ + Na 355.1264, found 355.1271.

*(R)-4-((S)-1-(Furan-2-yl)-3-oxobutyl)-2-methyl-4-propyloxazol-5(4H)-one (**5p**).* D,L-Norvaline (35.1 mg) was treated with *trans*-4-(furan-2-yl)but-3-en-2-one (245 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 2/1 to 1/2) yielded **5p** as a colorless oil (174 μmol, 48.2 mg, 58%; *dr* > 99:1, *ee* = 84%).

$C_{15}H_{19}NO_4$: MW 277.32; $[\alpha]_D^{23}$ +22.5 (*c* = 0.67, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 6.97 (*dd*, *J* = 1.9, 0.7, 1 H), 6.08 (*d*, *J* = 3.5, 1 H), 5.97 (*dd*, *J* = 3.4, 1.9, 1 H), 4.05 (*dd*, *J* = 9.5, 4.3, 1 H), 2.89 (*dd*, *J* = 17.4, 9.6, 1 H), 2.64 (*dd*, *J* = 17.4, 4.4, 1 H), 1.79−1.52 (*m*, 2 H), 1.574 and 1.571 (2 × *s*, 2 × 3 H), 1.21−0.97 (*m*, 2 H), 0.67 (*t*, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 203.8, 178.9, 161.8, 153.1, 141.9, 110.7, 108.4, 75.7, 41.9, 40.7, 36.8, 29.5, 17.5, 14.3, 13.9; IR (in C_6D_6) ν = 2963, 2934, 2876, 1818, 1717, 1683, 1503, 1432, 1382, 1361, 1277, 1243, 1163, 1148, 1071, 1012, 899, 813, 740, 653, 619, 600; MS (ESI) *m*/*z* 300.1 (100%, $[M + Na]^+$), 259.1 (12%), 191.1 (10%); HRMS (ESI) *m*/*z* calculated for $C_{15}H_{19}NO_4$ + Na 300.1206, found 300.1200.

*(R)-2-Methyl-4-((S)-2-oxoheptan-4-yl)-4-propyloxazol-5(4H)-one (**5q**).* D,L-Norvaline (35.1 mg) was treated with *trans*-hept-3-en-2-one (177 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 3/1 to 1/1) yielded **5q** as a colorless oil (210 μmol, 50.1 mg, 70%; *dr* > 99:1, *ee* = 86%).

$C_{13}H_{21}NO_3$: MW 239.31; $[\alpha]_D^{23}$ −20.4 (*c* = 1.23, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 2.75−2.61 (*m*, 1 H), 2.43 (*dd*, *J* = 16.8, 3.5, 1 H), 2.04 (*dd*, *J* = 16.9, 9.5, 1 H), 1.96−1.78 (*m*, 2 H), 1.63 (*s*, 3 H), 1.61−1.53 (*m*, 2 H), 1.21−1.00 (*m*, 2 H), 0.88 (*d*, *J* = 6.7, 3 H), 0.87 (*t*, *J* = 7.3, 3 H), 0.69 (*t*, *J* = 7.2, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 207.8, 180.0, 161.2, 75.5, 43.8, 36.6, 36.2, 35.1, 17.4, 14.9, 14.2, 14.0, 7.8; IR (in C_6D_6) ν = 2965, 2937, 2877, 1816, 1713, 1684, 1459, 1434, 1415, 1380, 1241, 1168, 1108, 1077, 1059, 1032, 982, 896, 866, 650, 620; MS (ESI) *m*/*z* 240.3 (1%, $[M + H]^+$), 170.2 (10%), 153.1 (100%); HRMS (ESI) *m*/*z* calculated for $C_{13}H_{21}NO_3$ + Na 262.1414, found 262.1415.

*(R)-2-Methyl-4-((S)-4-oxohexan-2-yl)-4-propyloxazol-5(4H)-one (**5r**).* D,L-Norvaline (35.1 mg) was treated with *trans*-hex-4-en-3-one (202 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 3/1 to 1/1) yielded **5r** as a colorless oil (156 μmol, 39.6 mg, 52%; *dr* > 99:1, *ee* = 78%).

$C_{14}H_{23}NO_3$: MW 253.34; $[\alpha]_D^{23}$ −19.1 (*c* = 1.18, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 2.77−2.66 (*m*, 1 H), 2.60 (*dd*, *J* = 18.0, 5.5, 1 H), 1.99 (*dd*, *J* = 18.0, 5.0, 1 H), 1.78−1.38 (3 × *m*, 4 H), 1.72 (*s*, 3 H), 1.62 (*s*, 3 H), 1.22−1.00 (*m*, 4 H), 0.78 (*t*, *J* = 6.8, 3 H), 0.69 (*t*, J = 7.1, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 205.1, 180.3, 161.2, 76.0, 43.8, 39.3, 36.6, 33.3, 21.0, 17.3, 14.3, 14.2, 13.9; IR (in C_6D_6) ν = 2961, 2933, 2874, 1815, 1716, 1684, 1459, 1433, 1381, 1362, 1241, 1167, 1055, 1036, 1005, 896, 743, 701, 665, 618; MS (ESI) *m*/*z* 276.2 (10%, $[M + Na]^+$), 248.2 (8%), 235.1 (100%), 207.1 (5%), 191.1 (5%), 167.1 (10%); HRMS (ESI) *m*/*z* calculated for $C_{14}H_{23}NO_3$ + Na 276.1570, found 276.1558.

*(R)-2-Methyl-4-((S)-4-oxohexan-2-yl)-4-propyloxazol-5(4H)-one (**5s**).* D,L-Norvaline (35.1 mg) was treated with *trans*-5-methylhex-3-en-2-one (202 mg) according to **GP2**. Flash column chromatography (petrol ether/ethyl acetate = 2/1) yielded **5s** as a colorless oil (78 μmol, 19.5 mg, 26%; *dr* > 99:1, *ee* = 62%).

$C_{14}H_{23}NO_3$: MW 253.34; $[\alpha]_D^{23}$ −18.1 (*c* = 0.16, PhH); ^{1}H NMR (300 MHz, C_6D_6) δ = 2.90−2.81 (*m*, 1 H), 2.62 (*dd*, *J* = 18.5, 6.6, 1 H), 2.07 (*dd*, *J* = 18.3, 4.0, 1 H), 1.96−1.72 (*m*, 2 H), 1.71 (*s*, 3 H), 1.60 (*s*, 3 H), 1.59−1.45 (*m*, 2 H), 1.15−0.98 (*m*, 1 H), 0.77 (*d*, *J* = 6.9, 3 H), 0.69 (*d*, *J* = 7.0, 3 H), 0.66 (*t*, *J* = 7.7, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ = 205.3, 180.2, 160.9, 77.1, 44.1, 39.3, 38.0, 29.3, 29.3, 23.4, 17.8, 17.1, 14.3, 13.8, 13.7; IR (in C_6D_6) ν = 2962, 2931, 2876, 2358, 2342, 1817, 1758, 1716, 1686, 1466, 1433, 1383, 1355, 1243, 1170, 1097, 1034, 1013, 970, 945, 899; MS (ESI) *m*/*z* 254.2 (5%, $[M + H]^+$), 212.2 (100%), 166.2 (60%); HRMS (ESI) *m*/*z* calculated for $C_{14}H_{23}NO_3$ + Na 276.1570, found 276.1575.

Synthesis of the α,α-Disubstituted α-Amino Acids. *(2R,3R)-2-Amino-2-methyl-5-oxo-3-phenylhexanoic acid hydrochloride (**9**).* Synthesis starting from azlactone **10** with known configuration: According to literature,[6a] the azlactone **10** (1.00 equiv, 38.0 μmol, 12.2 mg, 75% *ee*) was stirred in aqueous HCl (1 M, 2 mL) in a preheated oil bath to 80 °C for 3 h. The mixture was cooled to room temperature and subsequently filtered through cotton. After dilution with demineralized water the filtrate was washed twice with CH_2Cl_2. All volatiles were removed under reduced pressure to yield **9** as a colorless solid (27.7 μmol, 7.5 mg, 73%); $[\alpha]_D^{23}$ −109.8 (*c* = 0.45, H_2O). All other data are in accordance with the literature.

Synthesis starting from azlactone **5a**: A mixture of the azlactone **5a** (1.00 equiv, 122 μmol, 32.4 mg, 98% *ee*) in aqueous HCl (1 M, 5 mL) was stirred in a preheated oil bath at 80 °C for 3 h. The mixture was cooled to room temperature, and after dilution with demineralized water, the mixture was washed twice with CH_2Cl_2. All volatiles were removed under reduced pressure to yield **9** as a colorless solid (120 μmol, 32.4 mg, 98%); $[\alpha]_D^{23}$ −159.1 (*c* = 1.00, H_2O).

$C_{13}H_{17}NO_3$: MW 271.74; mp 89.8 − 92.4 °C; ^{1}H NMR (300 MHz, D_2O) δ = 7.46−7.34 (*m*, 3 H), 7.34−7.22 (*m*, 2 H), 3.91 (*t*, *J* = 8.3, 1 H), 3.70 (*dd*, *J* = 20.5, 8.4, 1 H), 3.58 (*dd*, *J* = 20.5, 8.3, 1 H), 2.66 (*s*, 3 H), 1.76 (*s*, 3 H); ^{13}C NMR (75 MHz, D_2O) δ = 196.3, 171.6, 135.4,

128.9, 128.6, 127.8, 79.3, 51.8, 43.6, 21.6, 18.3; IR (ATR) ν = 3354, 2869, 2738, 1727, 1675, 1455, 1405, 1377, 1328, 1151, 1029, 921, 845, 777; MS (ESI) m/z 218.1 (6%, $[M - H_2O - HCl]^+$), 172.1 (100%), 131.1 (27%); HRMS (ESI) m/z calculated for $[C_{13}H_{16}NO_2]^+$ ($M - H_2O - HCl$) 218.1176, found 218.1170.

(2R,3R)-2-Acetamido-3-(4-methoxyphenyl)-5-oxo-2-propylhexanoic acid (11). The azlactone **5j** (1.00 equiv, 29.9 μmol, 9.5 mg, 99% *ee*) was stirred in acetonitrile/water (3 mL, 1/1) at room temperature for 64 h. After this time, all volatiles were removed under reduced pressure. The crude product was then washed with cold demineralized water (ca. 1 mL) once and dried in a vacuum to yield pure *N*-acetyl amino acid **11** as an off-white solid (25.1 mmol, 8.4 mg, 84%).

$C_{18}H_{25}NO_5$: MW 335.39; mp 72.5−73.1 °C; $[\alpha]_D^{23}$ −42.4 (*c* = 0.21, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15−7.07 (*m*, 2 H), 6.84−6.77 (*m*, 2 H), 6.42 (*s*, 1 H), 3.96 (*dd*, *J* = 8.7, 5.0, 1 H), 3.77 (*s*, 3 H), 3.37 (*dd*, *J* = 17.5, 4.7, 1 H), 2.99 (*dd*, *J* = 17.5, 4.7, 1 H), 2.44−2.29 (*m*, 1 H), 2.05 and 2.04 (2 × *s*, 2 × 3 H), 1.91−1.77 (*m*, 1 H), 1.36−1.20 (*m*, 1 H), 1.20−1.07 (*m*, 1 H), 0.89 (*t*, *J* = 7.2, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 208.3, 174.8, 170.8, 158.8, 130.9, 113.6, 68.1, 55.1, 45.5, 45.2, 34.0, 30.5, 24.2, 17.7, 14.0; IR (in $CDCl_3$) ν = 3371, 2958, 2924, 2853, 2360, 1715, 1612, 1513, 1463, 1440, 1372, 1302, 1250, 1180, 1033, 910, 834, 734, 648, 581; MS (ESI) m/z 358.2 (85%, $[M + Na]^+$), 340.2 (15%), 298.1 (75%), 270.1 (100%), 181.1 (15%); HRMS (ESI) m/z calculated for $C_{18}H_{25}NO_5$ + Na 358.1625, found 358.1636.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, NMR spectra, HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rene.peters@oc.uni-stuttgart.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG, PE 818/4-1).

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