Organocatalytic Asymmetric Synthesis of Functionalized 1,3,5-Triarylpyrroli-
din-2-ones via an Aza-Michael/Aldol Domino Reaction

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Abstract: The organocatalytic asymmetric synthesis of functionalized 1,3,5-triarylpyrrolidin-2-ones bearing three contiguous stereocenters through an aza-Michael/aldol domino reaction of α-ketoamides with α,β-unsaturated aldehydes is described. The domino products were further derivatized by aldehyde olefination under one-pot conditions. The reaction proceeds with excellent diastereoselectivities (>20:1) and good to excellent enantioselectivities (60–96% ee).

Key words: organocatalysis, domino reactions, asymmetric synthesis, pyrrolidin-2-ones, aza-Michael addition

The polysubstituted pyrrolidin-2-one or γ-lactam core is a crucial structural feature of numerous pharmaceuticals and natural products of diverse complexity possessing various biological activities (Figure 1). Prominent examples are lactacystin (A), isolated from Streptomyces and acting against multiple cancer cell lines as a proteasome inhibitor; clausenamide (B), known as an anti-inflammatory and antidepressant agent; and cotinine (D), a metabolite of nicotine also used as an antidepressant. Even closer to the title compounds, 3,5-diarylpyrrolidin-2-ones E have shown activity as neurokinin-1 (NK1) antagonists or as endothelin receptor antagonists. As a result, multiple synthetic pathways have been developed in order to access these nitrogen-containing five-membered heterocycles. Various diastereoselective syntheses of these polysubstituted pyrrolidin-2-ones have already been reported, whereas enantioselective methods are less developed.

The rapidly growing field of asymmetric organocatalysis has proved to be a powerful tool for the synthesis of chiral molecules and it has been widely applied in synthesis. Particularly, organocatalyzed domino reactions have shown their efficiency when it comes to the one-pot formation of several bonds yielding highly substituted compounds with excellent diastereo- and enantioselectivities. Secondary amine catalysts working via iminium or enamine activation of carbonyl compounds have been efficiently used in simple, triple, and quadruple cascade reactions.

The organocatalyzed aza-Michael addition has been frequently used in the asymmetric synthesis of nitrogen-containing molecules. Domino reactions with substrates that bear a nucleophilic nitrogen atom and electrophilic centers have been used to achieve the synthesis of heterocycles. α-Ketoamides have already been employed in organocatalysis, although the nucleophilicity of their nitrogen atom has not been exploited yet in an aza-Michael addition. Furthermore, these molecules also possess two electrophilic centers that make them ideal partners for the design of new cascade reactions.

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We began by investigating the reaction of 2-oxo-N,N',2-di-phenylacetamide (1a), cinnamaldehyde (2a), and 20 mol% of the diphenylprolinol trimethylsilyl ether catalyst (S)-3a (Table 1). Although chloroform, dichloromethane, and toluene yielded mainly the condensation product 7 and its isomerized equivalent 8 (entries 1–3), ethanol, methanol, and dimethyl sulfoxide appeared to furnish the desired product 4. We realized that the domino product itself was not suitable for purification and analysis due to its relative instability. As a consequence, the aldehyde 4 was trapped in a one-pot fashion with 1.5 equivalents of the stabilized Wittig reagent 5 converting it into the more stable α,β-unsaturated ester 6.

### Table 1  Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time <strong>(h)</strong></th>
<th>Ratio 1a:2a</th>
<th>Yield (% of 6a)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>CH₂Cl₂</td>
<td>4.5</td>
<td>1:1</td>
<td>–d</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>CHCl₃</td>
<td>4.5</td>
<td>1:1</td>
<td>–d</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>toluene</td>
<td>4.5</td>
<td>1:1</td>
<td>–d</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>DMSO</td>
<td>4.5</td>
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<tr>
<td>5</td>
<td>3a</td>
<td>MeOH</td>
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<td>1:1</td>
<td>51</td>
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<tr>
<td>6</td>
<td>3a</td>
<td>EtOH</td>
<td>4.5</td>
<td>1:1</td>
<td>50</td>
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<td>7</td>
<td>3b</td>
<td>EtOH</td>
<td>4.5</td>
<td>1:1</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>3c</td>
<td>EtOH</td>
<td>4.5</td>
<td>1:1</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>3d</td>
<td>EtOH</td>
<td>4.5</td>
<td>1:1</td>
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</tr>
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<td>8</td>
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<td>46</td>
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<tr>
<td>12</td>
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<td>–d</td>
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<tr>
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<td>4.5</td>
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<td>–</td>
</tr>
<tr>
<td>14</td>
<td>3a</td>
<td>EtOH</td>
<td>4.5</td>
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<td>15</td>
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<td>EtOH</td>
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**a** Unless otherwise noted, all reactions were performed on a 0.33-mmol scale using the indicated ratio of 1a:2a, catalyst (20 mol%), solvent (1.5 mL), r.t., for the indicated time, followed by addition of the Wittig reagent (1.5 equiv) with reaction overnight.

**b** Time for the domino reaction before the introduction of the Wittig reagent.

**c** Isolated yield.

**d** A mixture of 7 and 8 was obtained.
After performing a short catalyst screening and an evaluation of the optimum reaction conditions, we concluded that the best results were obtained using 1.5 equivalents of the α-ketoamide 1a, 1 equivalent of the cinnamaldehyde 2a and 20 mol% of the catalyst 3a. The reaction was performed in 1.5 mL of ethanol for 4.5 hours at room temperature before the addition of 1.5 equivalents of the Wittig reagent (entry 15). A decrease in the catalyst loading gave lower yields, while increasing it gave no significant improvement; using a longer reaction time before the addition of the Wittig reagent also did not improve the outcome of the reaction (entry 11). Performing the reaction overnight yielded almost exclusively dehydrated products 7 and 8 (entry 12).

With the optimized conditions in hand, we explored the scope of the reaction. Initially we varied the α,β-unsaturated aldehyde moiety 2 (Table 2). Although the yields show high variations (between 20 and 73%), the reaction tolerates electron-withdrawing as well as electron-donating groups giving products 6a–i with good to excellent enantioselectivities (entries 1–9). Heteroaryl substituents are also well accepted giving 6h,i, although a lower asymmetric induction was observed with the furyl derivative 6h (entries 8 and 9). Aliphatic residues did not lead to any satisfactory results.

The extension of the scope regarding the α-ketoamide substrate was also investigated. For this purpose we synthesized derivatives bearing different groups on both aromatic rings (R1, R2), and performed the cascade reactions using the optimum conditions (entries 10–13). The yields of 6j–m as well as the enantioselectivities were in accordance with the results obtained previously. Other α-ketoamide derivatives bearing nonaromatic residues were also tested in the cascade reaction, however these did not react in the desired fashion, with the exception of the 2-oxo-2-phenyl-N-tosylacetamide (1f), which gave the desired pyrrolidin-2-one 6n in very good yield with excellent enantioselectivity (entry 14).

In the present transformation we assume that the reaction is initiated by an aza-Michael addition of the nucleophilic

Table 2 Reaction of α-Ketoamides 1 with α,β-Unsaturated Aldehydes 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R1</th>
<th>R2</th>
<th>2</th>
<th>R3</th>
<th>Product</th>
<th>T1 (h)b</th>
<th>T2 (h)c</th>
<th>Yieldd (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Ph</td>
<td>Ph</td>
<td>2a</td>
<td>Ph</td>
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<td>16</td>
<td>65</td>
<td>87 (91)f</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Ph</td>
<td>Ph</td>
<td>2b</td>
<td>4-MeOC6H4</td>
<td>6b</td>
<td>4.5</td>
<td>2</td>
<td>54</td>
<td>95 (93)f</td>
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<tr>
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<td>Ph</td>
<td>Ph</td>
<td>2c</td>
<td>4-ClC6H4</td>
<td>6c</td>
<td>5 (4.5)f</td>
<td>1 (16)f</td>
<td>58 (34)f</td>
<td>90 (96)f</td>
</tr>
<tr>
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<td>1a</td>
<td>Ph</td>
<td>Ph</td>
<td>2d</td>
<td>4-Me2NC6H4</td>
<td>6d</td>
<td>5</td>
<td>2</td>
<td>20</td>
<td>89 (90)f</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>Ph</td>
<td>Ph</td>
<td>2e</td>
<td>4-O2NC6H4</td>
<td>6e</td>
<td>5.5 (16)f</td>
<td>1 (2)f</td>
<td>21 (25)f</td>
<td>86 (83)f</td>
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<td>Ph</td>
<td>2f</td>
<td>3,4,5-(BnO)3C6H3</td>
<td>6f</td>
<td>16</td>
<td>2</td>
<td>52 (61)f</td>
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<td>Ph</td>
<td>2g</td>
<td>3,4-(OCH2O)C6H3</td>
<td>6g</td>
<td>16</td>
<td>2</td>
<td>56 (51)f</td>
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<td>Ph</td>
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<td>Ph</td>
<td>2i</td>
<td>1-Boc-1H-indol-3-yl</td>
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<td>81 (88)f</td>
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<td>Ph</td>
<td>6j</td>
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<td>6l</td>
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<td>6m</td>
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<td>6n</td>
<td>5</td>
<td>2</td>
<td>33</td>
<td>96</td>
</tr>
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</table>

a All the reactions were run on a 0.33-mmol scale with α-ketoamide (1.5 equiv), α,β-unsaturated aldehyde (1 equiv), 3a (20 mol%), EtOH (1.5 mL), r.t. All the products were obtained as a single diastereomer.

b Time for the domino reaction before the addition of the Wittig reagent 5 (1.5 equiv).
c Time for the olefination.
d Yield of the isolated product 6a–n after flash column chromatography.
e Determined by HPLC on a chiral stationary phase.
f Values in parentheses correspond to the results obtained with the catalyst (R)-3a.
nitrogen of the α-ketoamide to the iminium-activated α,β-
unsaturated aldehyde 9. This yields the acyclic interme-
diate 10 that undergoes an aldol addition cyclization due to
the enamine activation providing the intermediate
11, and the product 4a after hydrolysis and return of the catalyst
(Scheme 2). The expected transition states for the imini-
um [Scheme 3 (a)] as well as for the enamine activation
[Scheme 3 (b)] allowed us to predict the relative and ab-
solute configuration of the products. They were confirmed
by NOESY experiments on 6l [Scheme 3 (c)].

In conclusion, we have developed a new convenient or-
ganocatalytic method for the asymmetric synthesis of
functionalized 1,3,5-triarylpyrrolidin-2-ones in good
yields, virtually complete diastereoselectivities, and very
good enantioselectivities via an aza-Michael/aldol addi-
tion domino reaction between α-ketoamides and α,β-un-
saturated aldehydes. As the pyrrolidin-2-one substructure
is widely present in a large number of biologically active
molecules, our protocol could provide a new approach for
these γ-lactams. The applications of the method described
here are currently being investigated.

Unless otherwise noted, all commercially available compounds
were used without further purification. Preparative column chroma-
tography SIL G-25 UV252 from Macherey & Nagel, particle size
0.040–0.063 mm (230–240 mesh, flash). Visualization of the devel-
opped TLC plates was performed with UV irradiation (254 nm) and
by staining with vanillin stain. Optical rotations were measured on
a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a
Finnigan SSQ7000 (EI 70 eV) spectrometer and HRMS on a Ther-
mo Fisher Scientific Orbitrap XL spectrometer. IR spectra were re-
corded on a Perkin-Elmer FT-IR Spectrum 100 using ATR-Unit. 1H
and 13C spectra were recorded at r.t. on Varian Mercury 600 or Ino-
va 400 instruments with TMS as an internal standard. Analytical
HPLC was performed on a Hewlett-Packard 1100 Series instrument
using chiral stationary phases (Daicel AD, Daicel AS, Daicel IA,
Daicel OD, Diacel OJ, or Chiralpak IC). α-Ketoamide 1d was pre-
pared from ethyl 2-(2,4-dimethoxyphenyl)-2-oxoacetate via 2-(2,4-
dimethoxyphenyl)-2-oxoacetic acid; α-ketoamide 1e was prepared
from o-methylmandelic acid via 2-methylphenylglyoxylic acid.

α-Ketoamides: General Procedure
To a solution of phenylglyoxylic acid (1.774 g, 12 mmol, 1 equiv)
in N,N-dimethylacetamide (30 mL) cooled to –15 °C, SOCl2 (1.0
mL, 13.8 mmol, 1.15 equiv) was added dropwise. After stirring
for 1 h at this temperature, aniline (1.5 mL, 16.7 mmol, 1.4 equiv) was
added and the mixture was stirred for 3 h at temperatures between
–10 °C and 0 °C, then poured onto a mixture of ice and H2O and
stirred at r.t. overnight. The solid formed was dissolved in Et3O (50
mL) and extracted with Et3O (3 × 20 mL). The combined organic
layers were washed with H2O and brine, dried (Na2SO4), and con-
centrated in vacuo before purification by flash column chromatog-
raphy.
Following the general procedure using aniline (1.5 mL, 16.7 mmol, 1.4 equiv) and phenylglyoxylic acid (1.774 g, 12 mmol, 1 equiv) with purification of the crude product by flash column chromatography (n-pentane–EtOAc, 3:1) gave 1a (2.69 g, 99%) as a yellow solid; bp 85–90 °C, Rf = 0.5 (n-pentane–EtOAc, 4:1).

Following the general procedure using aniline (0.37 g, 4.0 mmol, 1.4 equiv) and phenylglyoxylic acid (0.69 g, 12 mmol, 1 equiv) with purification of the crude product by flash column chromatography (n-pentane–EtOAc, 6:1) gave 1b (0.84 g, 54%) as a yellow solid; mp 147 °C; IR (ATR): 3478, 3371, 3039, 1784, 1662, 1457, 1421, 1366, 1150, 1067, 735, 690, 656, 636 cm⁻¹.

To a solution of 1,3-dimethoxybenzene (1.31 mL, 10 mmol, 1 equiv) in anhyd CH₂Cl₂ (20 mL) cooled to 0 °C under argon SnCl₄ was carefully added (1.4 mL, 12 mmol, 1.2 equiv) and the solution was stirred for 30 min at r.t. After cooling to 0 °C, ethyl oxalyl chloride (3.36 mL, 30 mmol, 3 equiv) was added dropwise, followed by MeNO₂ (15 mL). The resulting dark purple solution was stirred for 1 h at r.t. The reaction was quenched by the careful addition of sat. aq NaHCO₃ (10 mL), the pH was brought to 10 by the addition of 25% NaOH (10 mL) and the mixture was stirred at r.t. for 1 h. The crude product was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with H₂O, dried (MgSO₄), and evaporated in vacuo. Flash column chromatography (n-pentane–EtO₂:1:1) of the residue gave the product (1.133 g, 47.5%) as a colorless oil, Rf = 0.26 (n-pentane–EtO₂: 1:1).

IR (ATR): 3098, 2980, 2846, 1739, 1661, 1594, 1464, 1374, 1302, 1208, 1177, 1024, 919, 836, 754, 673, 583, 515 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 1.39 (t, J = 7.2 Hz, 3 H, CH₂(CH₃)₂), 3.85 (s, 3 H, OCH₃), 3.88 (s, 3 H, OCH₃), 4.37 (q, J = 7.2 Hz, 2 H, CH₂), 6.43 (d, J = 1.8 Hz, 1 H, CHAr), 6.60 (dd, J = 1.8, 9.1 Hz, 1 H, CHAr), 7.91 (d, J = 9.1 Hz, 1 H, CHAr).

13C NMR (150 MHz, CDCl₃): δ = 114.2 (CH₂), 55.7 (OCH₃), 56.0 (CH₃), 61.6 (CH₃), 98.2 (CH₂), 106.7 (CH₂), 116.0 (C), 132.9 (CH₂), 162.3 (C), 165.9 (C), 166.7 (C), 185.0 (C).

MS (ESI): m/z (%): 261 (100, [M + Na]+), 239 (55, [M + H]+).

Anal. Calcld for C₁₂H₁₄O₅: C, 60.50; H, 5.92. Found: C, 60.30; H, 5.79.

(2,4-Dimethoxyphenyl)-2-oxo-2-phenylacetamide (1d)

Following the general procedure using aniline (0.37 g, 4.0 mmol, 1.4 equiv) and 2-(4,4-dimethoxy-2-phenylacetamide (0.6 g, 2.85 mmol, 1 equiv) with purification of the crude product by flash column chromatography (n-pentane–EtO₂: 1:2) gave 1d (0.79 g, 94%) as a colorless solid; mp 91–93 °C; Rf = 0.4 (n-pentane–EtO₂: 1:2).

IR (ATR): 3278, 3144, 3092, 1672, 1593, 1493, 1447, 1280, 1207, 1124, 874, 836, 745, 690 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 3.85 (s, 3 H, OCH₃), 3.88 (s, 3 H, OCH₃), 6.49 (d, J = 9 Hz, 1 H, CH₂), 7.17 (t, J = 7.2 Hz, 1 H, CHAr), 7.38 (t, J = 7.8 Hz, 2 H, CH₂), 7.67 (d, J = 7.8 Hz, 2 H, CH₂), 7.92 (dd, J = 1.8, 7.8 Hz, 1 H, CHAr).

13C NMR (150 MHz, CDCl₃): δ = 55.7 (OCH₃), 56.1 (CH₃), 98.3 (CH₃), 106.9 (CH₂), 115.3 (C), 133.3 (CH₂), 162.7 (C), 167.1 (C), 167.1 (COOH), 183.7 (CO).


(2-(4-Methoxyphenyl)-2-oxo-2-phenylacetamide (1c)

Following the general procedure using p-anisidine (343 mg, 3.5 mmol, 1.4 equiv) and phenylglyoxylic acid (376 mg, 2.5 mmol, 1 equiv) with purification of the crude product by flash column chromatography (n-pentane–EtO₂: 2:1) gave 1c (495 mg, 76%) as a yellow solid; mp 103 °C; Rf = 0.43 (n-pentane–EtO₂: 2:1).

1H NMR (600 MHz, CDCl₃): δ = 3.82 (s, 3 H, CH₃), 6.92 (d, J = 8.4 Hz, 2 H, CH₂), 7.50 (t, J = 7.8 Hz, 2 H, CH₂), 6.74 (m, 3 H, CH₂), 8.41 (d, J = 7.8 Hz, 2 H, CH₂), 8.89 (br s, 1 H, NH).

13C NMR (150 MHz, CDCl₃): δ = 55.5 (OCH₃), 124.4 (CH₂), 128.5 (CH₂), 129.8 (C), 131.4 (CH₃), 133.2 (C), 134.5 (CH₂), 157.1 (COCH₃), 158.7 (NCO), 187.6 (CO).

Ethyl 2-(2,4-Dimethoxyphenyl)-2-oxoacetate

To a solution of 1,3-dimethoxybenzene (1.31 mL, 10 mmol, 1 equiv) in anhyd CH₂Cl₂ (20 mL) cooled to 0 °C under argon SnCl₄ was carefully added (1.4 mL, 12 mmol, 1.2 equiv), and the solution was stirred for 30 min at r.t. After cooling to 0 °C, ethyl oxalyl chloride (3.36 mL, 30 mmol, 3 equiv) was added dropwise, followed by MeNO₂ (15 mL). The resulting dark purple solution was stirred for
**o-Methylandellic Acid**

To a solution of 2-methylbenzaldehyde (12 g, 100 mmol, 1 equiv) and 

\[ \text{BnEtNCI} (1.23 \, g, 5 \, \text{mmol}, 0.05 \, \text{equiv}) \] in 

\[ \text{CHCl}_3 (16 \, \text{mL}) \] was added carefully \( \text{aq} \) \( \text{NaOH} \) (1 g/mL) (25 mL). The resulting orange slurry was refluxed for 1 h and then cooled to r.t. H\(_2\)O was added carefully aq NaOH (1 g/mL) (25 mL) and the mixture was extracted with Et\(_2\)O (2 \times 100 mL). The resulting aqueous layer was acidified with conc HCl until the solution became colorless; \( R_f = 0.27 \) (n-pentane–EtO, 1:1).

1H NMR (600 MHz, CDC\(_3\)): \( \delta = 2.35 \) (s, 3 H, CH\(_3\)), 5.19 (s, 1 H, C=OH), 7.15–7.27 (m, 4 H, CH\(_{\text{Ar}}\)).

13C NMR (150 MHz, CDC\(_3\)): \( \delta = 213.4 \) (CH\(_{\text{Ar}}\)), 123.6 (CH\(_{\text{Ar}}\)), 121.0 (CH\(_{\text{Ar}}\)), 129.1 (CH\(_{\text{Ar}}\)), 112.3 (CH\(_{\text{Ar}}\)), 136.3 (C), 172.1 (COOH).

MS (EI, 70 eV): m/z \( = 326 \) (100, [M + Na\(^+\)]).

HRMS: m/z \( = 326 \) [M + Na\(^+\)] calculated for C\(_{15}\)H\(_{13}\)NO\(_4\)NaS: 326.0457; found: 326.0457.

**Ethyl (E)-3-(2S,3S,4R)-4-Hydroxy-5-oxo-1,2,4-triphenylpyrrolidin-3-yl]acetate (6a)**

Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 6a as a colorless solid; yield: 91 mg (65%); mp 165–170 °C; 87% ee [chiral stationary phase HPLC (Daicel AS)]; \( R_f = 0.46 \) (n-pentane–EtOAc, 3:1); \([\alpha]_\text{D}^{22} +109.0 \) (c 0.51, CHCl\(_3\)).

IR (ATR): 3363, 3054, 2984, 1606, 1601, 1538, 1495, 1449, 1374, 1276, 1174, 1033, 979, 871, 749, 693 cm\(^{-1}\).

IR (ATR): 3360, 3054, 2984, 1666, 1656, 1595, 1533, 1494, 1439, 1375, 1281, 1150, 1053, 973, 894, 825, 744, 680 cm\(^{-1}\).

**2-Oxo-2-phenyl-2-(2-tolyl)acetamide (1e)**

Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 1e as a colorless solid; yield: 91 mg (65%); mp 165–170 °C; 87% ee [chiral stationary phase HPLC (Daicel AS)]; \( R_f = 0.46 \) (n-pentane–EtOAc, 3:1); \([\alpha]_\text{D}^{22} +109.0 \) (c 0.51, CHCl\(_3\)).

**1f**

**2-Oxo-2-phenyl-2-(2-tolyl)acetamide (1f)**

Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 1f as a colorless solid; yield: 91 mg (65%); mp 165–170 °C; 87% ee [chiral stationary phase HPLC (Daicel AS)]; \( R_f = 0.46 \) (n-pentane–EtOAc, 3:1); \([\alpha]_\text{D}^{22} +109.0 \) (c 0.51, CHCl\(_3\)).

**Ethyl (E)-3-(2S,3S,4R)-4-Hydroxy-5-oxo-1,2,4-triphenylpyrrolidin-3-yl]acetate (6b)**

Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 6b as a colorless solid; yield: 91 mg (65%); mp 165–170 °C; 87% ee [chiral stationary phase HPLC (Daicel AS)]; \( R_f = 0.46 \) (n-pentane–EtOAc, 3:1); \([\alpha]_\text{D}^{22} +109.0 \) (c 0.51, CHCl\(_3\)).

**1g**

**2-Oxo-2-phenyl-2-(2-tolyl)acetamide (1g)**

Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 1g as a colorless solid; yield: 91 mg (65%); mp 165–170 °C; 87% ee [chiral stationary phase HPLC (Daicel AS)]; \( R_f = 0.46 \) (n-pentane–EtOAc, 3:1); \([\alpha]_\text{D}^{22} +109.0 \) (c 0.51, CHCl\(_3\)).

**1h**

**2-Oxo-2-phenyl-2-(2-tolyl)acetamide (1h)**

Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 1h as a colorless solid; yield: 91 mg (65%); mp 165–170 °C; 87% ee [chiral stationary phase HPLC (Daicel AS)]; \( R_f = 0.46 \) (n-pentane–EtOAc, 3:1); \([\alpha]_\text{D}^{22} +109.0 \) (c 0.51, CHCl\(_3\)).

**1i**

**2-Oxo-2-phenyl-2-(2-tolyl)acetamide (1i)**

Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 1i as a colorless solid; yield: 91 mg (65%); mp 165–170 °C; 87% ee [chiral stationary phase HPLC (Daicel AS)]; \( R_f = 0.46 \) (n-pentane–EtOAc, 3:1); \([\alpha]_\text{D}^{22} +109.0 \) (c 0.51, CHCl\(_3\)).
yield: 31 mg (20%); mp 89–91 °C; 89% ee [chiral stationary phase
MS (EI, 70 eV):
(2 C, C), 165.6 (COOEt), 173.8 (NCO).

IR (ATR): 3356, 2981, 2919, 2805, 1699, 1611, 1522, 1451, 1364,
1027, 981, 832, 797, 749, 692 cm–1.

1H NMR (600 MHz, CDCl3): δ = 1.24 (t, J = 7.2 Hz, 3 H, CH3), 2.86 (t, J = 8.8 Hz, 1 H, NCHC6H5), 3.59 (br s, 1 H, OH), 4.14 (q, J = 7.2 Hz, 2 H, CH2), 5.22 (d, J = 8.4 Hz, 1 H, NCH), 5.35 (d, J = 16 Hz, 1 H, CH2), 7.00 (s, 1 H, CH Ar), 7.18 (dd, J = 9.0, 15.6 Hz, 1 H, CH Ar), 7.48 (d, J = 8.4 Hz, 1 H, CHAr), 7.80 (s, 1 H, CHAr), 7.81 (d, J = 9, 16.2 Hz, 1 H, CH = CHCOOEt), 7.22–7.33 (m, 5 H, CHAr), 7.39 (t, J = 7.8 Hz, 2 H, CH2), 7.48 (d, J = 8.4 Hz, 2 H, CH2).

13C NMR (150 MHz, CDCl3): δ = 14.1 (CH3), 126.1 (CH2), 126.7 (CH(OOEt)), 128.2 (CH2), 128.4 (2 C, CH2), 128.5 (2 C, CH2), 128.8 (2 C, CH2), 129.1 (2 C, CH2), 129.4 (2 C, CH2), 130.4 (C), 135.8 (C), 136.8 (C), 139.3 (CH=CH(OOEt)), 140.2 (C), 165.4 (COOEt), 173.8 (NCO).

HRMS: m/z [M + H]+ caleld for C27H25NO4Cl: 462.1467; found: 462.1467.

Ethyl (E)-3-[2(S,3,4R,5)-4-(4-Chlorophenyl)-4-hydroxy-5-oxo-1,4-diphenylpyrroli din-3-yl]acetate (6c)
Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 6c as a colorless solid; yield: 144 mg (52%); mp 55–57 °C; 82% ee [chiral stationary phase HPLC (Daicel AS)]; Rf = 0.3 (n-pentane–EtOAc, 3:1); [α]D22 +94.5 (c 1.0, CHCl3).

IR (ATR): 3365, 3063, 3032, 1702, 1592, 1497, 1441, 1372, 1309, 1242, 1216, 1166, 1013, 929, 988, 836, 792, 739, 693 cm–1.

1H NMR (600 MHz, DMSO-d6): δ = 1.26 (t, J = 7.2 Hz, 3 H, CH2), 2.90 (t, J = 8.4 Hz, 1 H, NCHC6H5), 4.04 (q, J = 7.2 Hz, 2 H, CH2CH3), 4.77 (m, 2 H, CH2CH2Ph), 4.95 (d, J = 12 Hz, 2 H, CH2Ph), 5.05 (d, J = 12.6 Hz, 2 H, CH2Ph), 5.26 (d, J = 15.6 Hz, 1 H, CH=CH(OOEt)), 5.36 (d, J = 16.2 Hz, 1 H, NCHPh), 6.75 (s, 2 H, CH2), 6.81 (s, 1 H, CH3), 7.00 (dd, J = 8.4, 15.6 Hz, 1 H, CH=CH(OOEt)), 7.10 (m, 1 H, CHAr), 7.20–7.49 (m, 23 H, CHAr).

13C NMR (150 MHz, DMSO-d6): δ = 14.4 (CH3), 59.3 (NCHC6H5), 60.4 (CH3), 64.9 (NCHPh), 80.9 (COCH3), 112.3 (2 C, CH2), 124.1 (2 C, CH2), 125.8 (CH2), 125.9 (2 C, CH2), 126.1 (CH(OOEt)), 128.0 (2 C, CH2), 128.1 (2 C, CH2), 128.4 (2 C, CH2), 128.5 (CH2), 137.2 (2 C, CH), 140.7 (CH=CH(OOEt)), 140.9 (2 C, CH), 165.6 (COOEt), 173.8 (NCO).

MS (El, 70 eV): m/z (%) = 746 (18), 546 (10), 391 (18), 390 (100), 636 (68), 282 (15), 241 (11), 227 (55), 181 (34).
IR (ATR): 3363, 2898, 1702, 1596, 1494, 1447, 1373, 1304, 1245, 1175, 1116, 1034, 981, 927, 895, 785, 749, 693 cm⁻¹.

¹³C NMR (600 MHz, DMSO-d₆): δ = 14.4 (CH₃), 28.0 (3 C, CH₂), 56.2 (NCH₃), 57.4 (NCH₉), 60.4 (CH), 80.5 (CO), 84.7 (CH₂), 115.6 (CH₃), 116.7 (C), 120.0 (CH₂), 123.4 (CH), 124.2 (2 C, CH₂), 124.9 (CH₉), 125.5 (CHCOOE), 125.9 (CH₉), 126.1 (CH₂), 126.7 (2 C, CH₉), 126.9 (C), 127.9 (CH), 128.4 (2 C, CH₂), 128.6 (2 C, CH₉), 135.4 (C), 137.8 (C), 141.6 (C), 142.2 (CH=CHCOOE), 149.2 (COOR), 165.2 (COOE), 172.9 (NCO).

MS (EI, 70 eV): m/z (%) = 566 (43), 466 (29), 449 (23), 448 (100), 249 (21), 220 (16).

HRMS: m/z [M + H⁺] calculated for C₂₃H₃₉NO₅: 567.2489; found: 567.2488.

Ethyl (E)-[1]-(2S,3R,4R)-2-(Furan-2-yl)-4-hydroxy-5-oxo-1,4-diphenylpyrroolidin-3-yl]acetate (6b)
Following the general procedure with purification by flash chromatography (n-pentane–EtOAc, 3:1) gave 6b as a colorless solid; yield: 148 mg (44%); mp 70–72 °C; 84% ee (95%) [chiral stationary phase HPLC (Daicel AS)]; [α]D = 0.35 (n-pentane–EtOAc, 3:1); [α]D = +2.8° (c 1.0, CHCl₃).

IR (ATR): 3366, 2980, 2176, 2113, 1707, 1581, 1470, 1373, 1306, 1252, 1174, 1119, 1029, 980, 913, 869, 803, 748, 699 cm⁻¹.

¹³C NMR (600 MHz, DMSO-d₆): δ = 111.1 (t, J = 2.7 Hz, 3 C, CH₃), 3.39 (t, J = 8.4 Hz, 1 H, NCH₉), 3.72 (s, 3 H, CH₃), 6.94 (d, J = 8.4 Hz, 1 H, CH=CHCOOEt), 7.26–7.47 (m, 9 H, CHAr).
IR (ATR): 3413, 2982, 2307, 2173, 1716, 1656, 1597, 1492, 1453, 1365, 1308, 1170, 1087, 1034, 980, 868, 803, 751, 700, 662 cm⁻¹.

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Supporting Information

For this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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