Isocyanide Chemistry

Stereoselective Synthesis of Functionalized Bicyclic Scaffolds by Passerini 3-Center-2-Component Reactions of Cyclic Ketoacids


Abstract: We report the use of bifunctional starting materials (ketoacids) in a diastereoselective Passerini three-center-two-component reaction. Study of the reaction scope revealed the required structural features for stereoselectivity in the isocyanide addition. In this system, an interesting isomerization of the primary Passerini product – the α-carboxamido lactone – into an atypical product, an α-hydroxy imide, was found to occur under acidic conditions. Furthermore, enantioenriched Passerini products can be generated from an enantioenriched ketoacid obtained by chemoenzymatic synthesis.

Introduction

Isocyanide-based multicomponent reactions (IMCRs) are essential tools in combinatorial and diversity-oriented synthesis. Based on the unique reactivity of the formally divalent isocyanide carbon atom, this chemistry facilitates the efficient exploration of chemical space, rapidly generating complexity from simple starting materials. Importantly, the primary MCR (multicomponent reaction) products provide numerous opportunities for further synthetic elaboration, for instance into planar heterocycles as well as sp³-rich structures.[1] The first discovered IMCR, the Passerini reaction, in which an aldehyde (or ketone), a carboxylic acid, and an isocyanide are combined,[2] still represents one of the most widely used IMCRs in various applications[3] owing to its many advantages (convergence, atom economy, simple operation, broad scope).[4] However, its most important limitation, the poor control over the stereochemistry of the newly formed stereocenter, is also well recognized in the multicomponent reaction community.[5] Despite the great efforts that have been made to address this issue, successful asymmetric Passerini reactions are still limited to just a few examples of catalytic enantioselective variants[6] and diastereoselective reactions (with chiral isocyanides,[7] chiral carboxylic acids,[8] or chiral aldehydes/ketones,[9] respectively). Some representative examples of diastereoselective Passerini reactions are shown in Scheme 1. A relatively simple strategy to improve the modest stereocontrol involves the use of bifunctional starting materials (oxoacids), as the (partially) intramolecular reaction benefits

![Scheme 1. Diastereoselective Passerini reactions. PMP = p-methoxyphenyl; Boc = tert-butoxycarbonyl.](image)

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from a more sterically constrained transition state for the isocyanide addition. The bifunctional nature of oxoacid components has been strategically exploited in isocyanide chemistry to create a broad spectrum of heterocycles through the Ugi reaction (Scheme 2). However, similar examples of the Passerini reaction are scarce (Scheme 1D and E).

In this paper, we report a new diastereoselective Passerini reaction using simple cyclic oxoacids as starting materials. The reaction proceeds through a fused bicyclic transition state with additional steric constraints, thus leading to improved stereoselectivity. Furthermore, we report the unusual rearrangement of these Passerini products to give unprecedented \( \alpha \)-hydroxy bicyclic imides.

Results and Discussion

We began our investigation with the reaction between 2-(2-oxocyclohexyl)acetic acid (1a) and tert-butyl isocyanide (2a; 1.5 equiv.). Under standard Passerini conditions (CH\(_2\)Cl\(_2\), room temp.), the reaction proceeded smoothly to give the desired product with already good diastereoselectivity (85:15) in favor of the \( \text{trans} \)-fused isomer (Table 1, entry 1). The stereochemistry corresponds to an axial attack of the isocyanide (expected for a non-sterically-demanding nucleophile) to yield a \( \text{cis} \)-fused \( O \)-acyl imidate \( \alpha \)-adduct, which, upon Mumm rearrangement, gives \( \text{trans} \)-fused bicyclic lactone 3a (see also Scheme 3). This structure was unambiguously confirmed by X-ray diffraction analysis, as shown in Figure 1.

Encouraged by this initial result, we attempted to improve the diastereomeric ratio of the isocyanide addition by varying the solvent. The reaction was found to proceed in most of the solvents investigated (toluene, dimethyl carbonate, tert-butanol, methanol, and even water) but with lower stereoselectivity. We then resorted to Lewis acid catalysis with the hypothesis that coordination of both carbonyl groups (and possibly the isocyanide as well) to a metal center would lead to a more rigid transition state. A small screening identified Zn(OTf)_2 as a promising candidate for improved diastereoselectivity (Table 1, entry 3). Since the Lewis acid also led to an increase in the reaction rate, we repeated the solvent screening and focused on the solvent with the slowest background (uncatalyzed) reaction. Thus, the reaction with Zn(OTf)_2 (20 mol-%) in dimethylcarbonate (DMC) gave complete conversion and a 9:1 diastereomeric ratio (Table 1, entry 9). Carrying out the reaction at 0 °C was detrimental to both the yield and the selectivity (possibly due to the insolubility of the catalyst), but we observed that we could significantly decrease both the catalyst loading (to 10 mol-%) and the reaction time (to 2 h) without adverse effects. These conditions turned out to be optimal, as any further
decrease in the amount of isocyanide (Table 1, entry 14) or in the catalyst loading (entry 15) did not lead to improved results.

Having established this optimal protocol, we went on to investigate the scope of the reaction in terms of the isocyanide component. Gratifyingly, all classes of isocyanides are accepted in this reaction (Table 2): aliphatic (tertiary [products 3a, 3b], secondary [products 3c, 3d], primary [products 3e, 3f]), aromatic (including the bulky 2,6-dimethylphenyl derivative [product 3h]), and α-acidic (products 3i, 3j). In general, the diastereoisomers of the products were readily separated by flash chromatography, and the isolated yields of the pure trans-fused Passerini products 3a–3j were moderate to high. As expected for relatively small linear nucleophiles like isocyanides, the diastereoselectivity was well conserved across the series (ca. 9:1, as in the parent example 3a).

Table 2. Scope of the reaction in terms of isocyanides.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ketoacid</th>
<th>R</th>
<th>Time [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3k</td>
<td>1b</td>
<td>tBu</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>3l</td>
<td>1c</td>
<td>tBu</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>3m</td>
<td>1c</td>
<td>TsCH₂</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>3n</td>
<td>1d</td>
<td>tBu</td>
<td>2</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>3o</td>
<td>1d</td>
<td>TsCH₂</td>
<td>2</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>3p</td>
<td>1e</td>
<td>tBu</td>
<td>24</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>3q</td>
<td>1f</td>
<td>tBu</td>
<td>24</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>3r</td>
<td>1g</td>
<td>tBu</td>
<td>2</td>
<td>11[d] = 1:1</td>
</tr>
<tr>
<td>9</td>
<td>3s</td>
<td>1g</td>
<td>TsCH₂</td>
<td>24</td>
<td>82[g] = 1:1</td>
</tr>
<tr>
<td>10</td>
<td>3t</td>
<td>1h</td>
<td>tBu</td>
<td>24</td>
<td>95[k] = 1:1</td>
</tr>
<tr>
<td>11</td>
<td>3t</td>
<td>1h</td>
<td>tBu</td>
<td>24</td>
<td>50[f]</td>
</tr>
</tbody>
</table>

[a] Standard conditions: ketoacid 1a (1.0 mmol) and isocyanide 2 (1.5 mmol, 1.5 equiv.) in DMC (2 mL) with Zn(OTf)₂ (10 mol-%) at room temperature for 2 h; yields refer to isolated yields of the pure major diastereoisomer after flash chromatography.

Next, we sought to extend this intramolecular Passerini reaction to other oxoacids in order to rationalize the structural features required for high diastereoselectivity. In this context, we focused on the ring size, the distance between the ketone and carboxylic acid, and the conformational flexibility of the oxoacid 1.

First, the introduction of a carbamate group into the cyclohexanone ring (starting material 1b) led to a drastic decrease in the reaction rate (Table 3, entry 1), possibly due to a preferential binding of the Zn ions to this additional coordinating group. A starting material with the keto and carboxylic groups in a 1,5-relationship reacted somewhat more slowly (the imidate α-aduct is a seven-membered ring in this case) but still gave the products 3l and 3m in reasonable yield under the standard conditions (with tBuNC and TsCH₂NC, Table 3, entries 2 and 3). The diastereoselectivity was found to be lower (3:1), but the direction of isocyanide attack was preserved (trans-fused products predominated). Unfortunately, we found that the reaction

Table 3. Scope of the reaction in terms of ketoacids.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ketoacid</th>
<th>R</th>
<th>Time [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3k</td>
<td>1b</td>
<td>tBu</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>3l</td>
<td>1c</td>
<td>tBu</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>3m</td>
<td>1c</td>
<td>TsCH₂</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>3n</td>
<td>1d</td>
<td>tBu</td>
<td>2</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>3o</td>
<td>1d</td>
<td>TsCH₂</td>
<td>2</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>3p</td>
<td>1e</td>
<td>tBu</td>
<td>24</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>3q</td>
<td>1f</td>
<td>tBu</td>
<td>24</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>3r</td>
<td>1g</td>
<td>tBu</td>
<td>2</td>
<td>11[d] = 1:1</td>
</tr>
<tr>
<td>9</td>
<td>3s</td>
<td>1g</td>
<td>TsCH₂</td>
<td>24</td>
<td>82[g] = 1:1</td>
</tr>
<tr>
<td>10</td>
<td>3t</td>
<td>1h</td>
<td>tBu</td>
<td>24</td>
<td>95[k] = 1:1</td>
</tr>
<tr>
<td>11</td>
<td>3t</td>
<td>1h</td>
<td>tBu</td>
<td>24</td>
<td>50[f]</td>
</tr>
</tbody>
</table>

[a] Standard conditions: ketoacid 1 (1 mmol) and isocyanide 2 (1.5 mmol, 1.5 equiv.) in DMC (2 mL) with Zn(OTf)₂ (10 mol-%) at room temperature for the indicated time. [b] Isolated yield of the major diastereoisomer unless indicated otherwise. [c] Based on NMR spectroscopic analysis of the crude product. [d] Combined yield of diastereomers. [e] With cyclohexanone and acetic acid as reactants. [f] Crude yield with mesitylene as internal standard. [g] Without catalyst.
is not tolerant of variation in the nature of the cyclic ketone; starting materials based on a cyclopentanone (1d), cycloheptanone (1e), or tetralone (1f) motif gave slow conversions and side reactions (Table 3, entries 4–7). Due to ring strain, the carbonyl group is particularly reactive in the cyclohexanone system compared to the C_5 and C_7 homologs; conjugation with the aromatic ring drastically decreases the reactivity of 1f. Furthermore, side reactions (e.g., multiple isocyanide addition) may take place as a result of conformational/strain effects disfavoring the formation of the usual reaction intermediates. Indeed, for starting material 1d, a more ionic mechanism (i.e., isocyanide addition to generate a nitrilium ion followed by addition of the carboxylate) can be expected, since the nucleophilic attack would presumably take place from the least hindered dia-stereotopic face of the carbonyl group leading to a strained trans-fused α-adduct. This adduct may be difficult to form, and may not evolve cleanly into a single product. Additionally, intermolecular reactions can take place if the transition state for the intramolecular condensation is not favorable. Evidence for these side reactions was obtained in the reaction of 1d with tBuNC under the standard conditions: a complex mixture of products was observed (Table 3, entry 10). Moreover, in the case of the less reactive isocyanide TsCH_2NC, the conversion was low, and product formation could not be confirmed. In the case of the seven-membered homolog 1e, HRMS analysis indicated the formation of the desired product 3p, but we were unable to isolate it from the complex product mixture. A similar outcome was observed for tetralone-based acid 1f. On the other hand, the simple cyclic derivative 1g reacted cleanly, albeit slowly and with no stereoselectivity (Table 3, entry 8). Extending the reaction time to 24 h allowed the isolation of the expected Passerini product of 1g and TsCH_2NC in 82 % yield (Table 3, entry 9), but for this scaffold the diastereoisomers could not be separated. As a control experiment, the Passerini reaction of tBuNC, AcOH, and cyclohexanone proceeded to completion within 24 h, even in the absence of a Lewis acid catalyst (Table 3, entry 10). This result confirms the particularly high electrophilicity of cyclohexanone. Remarkably, the addition of catalytic Zn(OTf)_2 gave a much lower yield (ca. 50 %; Table 3, entry 10). This result confirms the particularly high electrophilicity of cyclohexanone.

Figure 2. X-ray structure of 4j (some H atoms omitted for clarity).

Nevertheless, this transformation is general in the series of Passerini products 3a–3j and can be pushed to near completion over 24 h (Table 4). The tertiary derivatives 3a and 3b represent a special case as they undergo dealkylation under these conditions: for 3a, the conversion was slow, and led to a mixture of products, whereas for the tert-octyl derivative 3b the corresponding free α-hydroxy imide (4b, R = H) could be isolated in reasonable yield (Table 4, entry 2). We hypothesize that ring strain plays an important role in this rearrangement, which corresponds to a formal 1,3(O–N) acyl transfer in the Passerini α-adduct instead of acyl migration to the OH group. The thermodynamic driving force for this isomerization is most probably the release of strain in moving from the trans-fused [4.3.0] bicyclic system to the more relaxed cis-hexahydroisoquinoline scaffold. This premise is supported by negative control experiments: the minor diastereoisomer 3h′ was stable under the rearrangement conditions, whereas homolog 3m and monocyclic lactone 3r gave at best low conversions over 24 h (Scheme 3).

Table 4. Rearrangement of Passerini products to α-hydroxyimides.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>3</th>
<th>R</th>
<th>Time</th>
<th>Yield [%]</th>
<th>4/3[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>tBu</td>
<td>24</td>
<td>n.d.[d]</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>tOct</td>
<td>7</td>
<td>60[16]</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>cHex</td>
<td>24</td>
<td>89</td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>iPr</td>
<td>24</td>
<td>96</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>n-pentyl</td>
<td>2</td>
<td>75</td>
<td>94:6</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>benzyl</td>
<td>4</td>
<td>93</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>2-naphthyl</td>
<td>24</td>
<td>64[9]</td>
<td>91:9</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>2,6-Me_2C_6H_4</td>
<td>3</td>
<td>99</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>TsCH_2</td>
<td>4</td>
<td>83</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>10</td>
<td>3j</td>
<td>MeO_2CCH_2</td>
<td>3</td>
<td>76[1]</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

Table 4. Rearrangement of Passerini products to α-hydroxyimides.

Entry 3 R Time Yield 4/3
1 3a tBu 24 n.d.[d] n.d.
2 3b tOct 7 60[16] >95:5
3 3c cHex 24 89 94:6
4 3d iPr 24 96 95:5
5 3e n-pentyl 2 75 94:6
6 3f benzyl 4 93 >95:5
7 3g 2-naphthyl 24 64[9] 91:9
8 3h 2,6-Me_2C_6H_4 3 99 >95:5
9 3i TsCH_2 1 83 >95:5
10 3j MeO_2CCH_2 3 76[1] >95:5

[a] Standard conditions: Passerini product (0.1 mmol) and MeSO_3H (1 equiv.) in CHCl_3 (0.3 mL) at 80 °C for the indicated time. [b] Isolated yield of 4 with minor amount of 3. [c] Based on the NMR spectrum of the crude product mixture. [d] Complex product mixture. [e] Free imide (4b, R = H) isolated after column chromatography. [f] Minor impurity observed.

Finally, we attempted to control not only the diastereoselectivity, but also the absolute stereochemistry during our intramolecular Passerini reaction. Thus, asymmetric bioreduction of unsaturated keto ester 5 with the nicotinamide-dependent...
ene-reductase NCR from Zymomonas mobilis\textsuperscript{(19)} and subsequent hydrogenolysis delivered (R)-1a.\textsuperscript{(20)} This can then react with isocyanides to give enantioenriched Passerini products,\textsuperscript{(21)} as exemplified for 3a (Scheme 4). This result underlines the fruitful complementarity of biocatalysis and multicomponent reactions in the asymmetric synthesis of valuable small molecules.\textsuperscript{(22)}

![Scheme 3. Negative control experiments in the formal 1,3(O–N) Mumm rearrangement of scaffold 3.](image)

In conclusion, we report a new diastereoselective intramolecular Passerini reaction with cyclic ketoacids leading to interesting sp\textsuperscript{3}-rich bicyclic lactones. The structural features required for high stereoselectivity in the isocyanide addition were identified and discussed. Interestingly, these Passerini products can isomerize to \(\alpha\)-hydroxy imide derivatives as formal 1,3(O–N) Mumm rearrangement products of the \(\alpha\)-adducts. Furthermore, complete stereocontrol can be achieved by combining this diastereoselective isocyanide addition with a chemoenzymatic preparation of the nonracemic ketoacid building block.

**Experimental Section**

**General Information:** Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Melting points were recorded with a Büchi M-565 melting-point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker Avance 500 (125.78 MHz for \(^{13}\)C) or Bruker Avance 400 (100.62 MHz for \(^{13}\)C) instrument with the residual solvent as an internal standard (\(^{1}H\): \(\delta = 7.26 \text{ ppm} \), \(^{13}\)C\(^{(1)}H\): \(\delta = 77.16 \text{ ppm} \) for CDCl\(_3\); \(^{1}H\): \(\delta = 2.50 \text{ ppm} \), \(^{13}\)C\(^{(1)}H\): \(\delta = 39.52 \text{ ppm} \) for \((D)\text{DMSO})\). Chemical shifts (\(\delta\)) are given in ppm, and coupling constants (\(J\)) are quoted in Hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sep (septet), br. (broad singlet), and m (multiplet) or combinations thereof. Infrared (IR) spectra were recorded neat by using a Shimadzu FTIR-8400s spectrophotometer, and data are reported in wave-numbers (cm\(^{-1}\)). Electrospray ionization (ESI) high-resolution mass spectrometry (HRMS) was carried out by using a Bruker microTOF-Q instrument in positive-ion mode (capillary potential of 4500 V). Chiral GC analysis was carried out with a Shimadzu GC-2010 Plus chromatograph. Flash chromatography was carried out on Silicycle Silia-P flash silica gel (particle size 40–63 \(\mu\)m, pore diameter 60 Å) or a silica gel 60 (70–230 mesh) column (particle size 0.063–0.2 mm, pore diameter 60 Å). Melting points were recorded with a Büchi M-565 melting-point apparatus. Commercially available reagents were used as purchased. Melting points were determined with an Agilent Supernova diffractometer equipped with a Cu microsource, mirror monochromator, and Atlas CCD detector. Omega scans were used at liquid-nitrogen temperatures. Additional experimental details can be found in the CIFs in the Supporting Information. The ketoacids 1a and 1c–1f are known compounds, and were prepared according to literature procedures: 1a,\textsuperscript{(23)} 1c,\textsuperscript{(24)} 1d,\textsuperscript{(25)} 1e,\textsuperscript{(26)} 1f.\textsuperscript{(26)} Compound 1g is commercially available.

**General Optimization Procedure:** Zn(OTf)\(_{2}\) (0.05 mmol, 0.1 equiv.) and isocyanide 2a (0.75 mmol, 1.5 equiv.) were added to a solution of ketoacid 1a (0.5 mmol, 1 equiv.) in solvent (1 mL). The solution was stirred at room temperature for 2–20 h. Then the mixture was diluted with CH\(_{2}\)Cl\(_{2}\) and quenched with a saturated NaHCO\(_{3}\) solution. The organic layer was separated, and the aqueous layer was extracted again with CH\(_{2}\)Cl\(_{2}\). The combined organic layers were dried with Na\(_{2}\)SO\(_{4}\), and concentrated in vacuo. The crude yield of 3a and the ratio 3a/3'a were determined by NMR spectroscopic analysis with mesitylene as an internal standard.

**Procedure A – Intramolecular Passerini Reaction:** Zn(OTf)\(_{2}\) (0.1 mmol, 0.1 equiv.) and isocyanide 2 (1.5 mmol, 1.5 equiv.) were added to a solution of ketoacid 1 (1 mmol, 1 equiv.) in dimethyl carbonate (2 mL). The solution was stirred at room temperature for 2 h. Then the mixture was diluted with CH\(_{2}\)Cl\(_{2}\) and quenched with a saturated NaHCO\(_{3}\) solution. The organic layer was separated, and the aqeous layer was extracted again with CH\(_{2}\)Cl\(_{2}\). The combined organic layers were dried with Na\(_{2}\)SO\(_{4}\), and concentrated in vacuo. The crude product 3 was purified by column chromatography on silica gel.

**Procedure B – Rearrangement of Passerini Products:** Passerini product 3 (0.1 mmol) was dissolved in CHCl\(_{3}\), and CH\(_{3}\)SO\(_{4}\)H (0.1 mmol, 1 equiv.) was added. The solution was heated at 80 °C in a sealed vial for 1–24 h (conversion monitored by TLC). The solution was then diluted with CH\(_{2}\)Cl\(_{2}\), and quenched with a saturated NaHCO\(_{3}\) solution. The organic layer was separated, and the aqueous layer was extracted again with CH\(_{2}\)Cl\(_{2}\). The combined organic layers were dried with Na\(_{2}\)SO\(_{4}\), and concentrated in vacuo. The yield and the ratio 4/3 were determined by NMR spectroscopic analysis.

**Conclusions**

In conclusion, we report a new diastereoselective intramolecular Passerini reaction with cyclic ketoacids leading to interesting sp\textsuperscript{3}-rich bicyclic lactones. The structural features required for high stereoselectivity in the isocyanide addition were identified and discussed. Interestingly, these Passerini products can isomerize to \(\alpha\)-hydroxy imide derivatives as formal 1,3(O–N) Mumm rearrangement products of the \(\alpha\)-adducts. Furthermore, complete stereocorrol can be achieved by combining this diastereoselective isocyanide addition with a chemoenzymatic preparation of the nonracemic ketoacid building block.

![Scheme 4. Chemoenzymatic preparation of enantioenriched 3a. NADH = nicotinamide adenine dinucleotide.](image)
N-(tert-Butyl)-2-oxohydrobenzofuran-7a(2H)-carboxamide (3a/3a’): Prepared from 2-(2-oxocyclohexyl)acetic acid (1a; 156 mg, 1 mmol, 1 equiv.) and tert-butyl isocyanide (170 μL, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1); the diastereoisomers could be separated (Rf = 0.5 (major) and Rf = 0.34 (minor)).

Data for major diastereoisomer 3a (trans): Isolated as a white crystals (182 mg, 0.76 mmol, 76%). M.p. 50–54 °C. 1H NMR (500 MHz, CDCl3): δ = 6.08 (br. s, 1 H), 2.52 (qd, J = 13.5 Hz, J = 3.5 Hz, 1 H), 2.46–2.34 (m, 2 H), 2.18–2.06 (m, 2 H), 2.01–1.87 (m, 2 H), 1.78 (d, J = 13.0 Hz, 1 H), 1.76–1.66 (m, 1 H), 1.47–1.37 (m, 1 H), 1.35 (s, 9 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 175.9 (C), 170.2 (C), 86.5 (C), 51.6 (CH), 48.5 (CH3), 34.8 (CH2), 28.7 (CH3), 25.3 (CH2), 24.0 (CH2), 22.1 (CH3) ppm. IR (neat): ν = 3396 (m), 2924 (w), 2868 (w), 1790 (s), 1665 (s), 1452 (m), 1210 (s), 1180 (s), 1127 (s), 1012 (s), 881 (m), 883 (m), 694 (s), 538 (m) cm–1. HRMS (ESI): calcd. for C15H30NO3 [M + H]+ 296.2215; found 296.2215.

N-Isopropyl-2-oxohydrobenzofuran-7a(2H)-carboxamide (3d): Prepared from 2-(2-oxocyclohexyl)acetic acid (1a; 156 mg, 1 mmol, 1 equiv.) and isopropyl isocyanide (141 μL, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 3:1); the diastereoisomers could be separated (Rf = 0.5 (major) and Rf = 0.25 (minor)).

The major diastereoisomer 3d (trans) was isolated as a white solid (124 mg, 0.55 mmol, 55%). M.p. 84–86 °C. 1H NMR (500 MHz, CDCl3): δ = 6.19 (d, J = 12.0 Hz, 1 H), 4.04–3.96 (m, 1 H), 2.49 (qd, J = 12.6, J = 3.8 Hz, 1 H, 2.44–2.30 (m, 2 H), 2.16–2.07 (m, 2 H), 1.98–1.84 (m, 2 H), 1.80–1.65 (m, 3 H), 1.43–1.31 (m, 1 H), 1.11 (d, J = 6.5 Hz, 6 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 175.6 (C), 169.5 (C), 86.1 (C), 48.1 (CH), 41.1 (CH), 34.1 (CH2), 24.9 (CH3), 23.6 (CH2), 22.4 (CH2), 22.1 (CH3) ppm. IR (neat): ν = 3310 (w), 2927 (m), 1784 (s), 1645 (s), 1521 (s), 1450 (m), 1196 (m), 1026 (s), 906 (m), 883 (m), 698 (s) cm–1. HRMS (ESI): calcd. for C9H14NO3 [M + H]+ 226.1438; found 226.1437.

N-Pentyl-2-oxohydrobenzofuran-7a(2H)-carboxamide (3e): Prepared from 2-(2-oxocyclohexyl)acetic acid (1a; 156 mg, 1 mmol, 1 equiv.) and n-pentyl isocyanide (188 μL, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 5:1); the diastereoisomers could be separated [Rf = 0.30 (major)]. The major diastereoisomer 3e (trans) was isolated as a white solid (177 mg, 0.70 mmol, 70%). M.p. 55–57 °C. 1H NMR (500 MHz, CDCl3): δ = 6.33 (br. s, 1 H), 3.25–3.14 (m, 2 H), 2.50 (qd, J = 12.6, J = 3.9 Hz, 1 H, 2.44–2.29 (m, 2 H), 2.18–2.09 (m, 2 H), 1.99–1.83 (m, 2 H), 1.81–1.64 (m, 3 H), 1.50–1.33 (m, 3 H), 1.32–1.19 (m, 4 H), 0.87 (t, J = 6.9 Hz, 3 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 175.7 (C), 170.5 (C), 86.5 (C), 48.4 (CH), 39.1 (CH3), 34.3 (CH3), 33.5 (CH2), 29.0 (CH2), 28.9 (CH2), 25.1 (CH3), 23.7 (CH2), 22.7 (CH2), 21.8 (CH3) ppm. IR (neat): ν = 3312 (w), 2928 (m), 2866 (w), 1788 (s), 1651 (s), 1533 (s), 1439 (m), 1194 (m), 1184 (m), 1026 (s), 943 (m), 881 (m), 704 (m) cm–1. HRMS (ESI): calcd. for C13H22NO3 [M + H]+ 254.1751.1751; found 254.1745.

N-Benzyl-2-oxohydrobenzofuran-7a(2H)-carboxamide (3f): Prepared from 2-(2-oxocyclohexyl)acetic acid (1a; 156 mg, 1 mmol, 1 equiv.) and benzyl isocyanide (188 μL, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 5:1); the diastereoisomers could be separated [Rf = 0.5 (major) and Rf = 0.3 (minor)]. The major diastereoisomer 3f (trans) was isolated as a yellowish solid (200 mg, 0.73 mmol, 73%). M.p. 56–66 °C. 1H NMR (500 MHz, CDCl3): δ = 7.32–7.29 (m, 2 H), 7.27–7.25 (m, 1 H), 7.20 (d, J = 7.3 Hz, 2 H), 6.78 (br. s, 1 H), 4.33 (dd, J = 14.8, J = 5.5 Hz, 1 H), 4.45 (dd, J = 14.8, J = 6.1 Hz, 1 H), 2.51 (dq, J = 12.7, J = 4.0 Hz, 1 H), 2.44–2.34 (m, 2 H), 2.17–2.10 (m, 2 H), 1.98–1.88 (m, 2 H), 1.80–1.78 (m, 2 H), 1.74–1.69 (m, 2 H), 1.42–1.35 (m, 1 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 175.6 (C), 170.5 (C), 137.7 (C), 128.7 (CH), 127.5 (CH), 127.3 (CH), 86.5 (C), 48.3 (CH), 34.2 (CH2), 33.5 (CH2), 29.6 (CH2), 25.0 (CH2), 23.7 (CH2), 21.8 (CH3) ppm. IR (neat): ν = 3315 (w), 2930 (m), 1782 (s), 1653 (s), 1522 (s), 1452 (m), 1194 (m), 1183 (m), 1021 (s), 938 (m), 885 (m), 733 (s), 693 (s), 557 (s) cm–1. HRMS (ESI): calcd. for C15H24NO3 [M + H]+ 274.2215; found 274.2135.
as a white solid (77 mg, 0.25 mmol, 50%). M.p. 115–129 °C (dec).

1H NMR (500 MHz, CDCl3): δ = 8.23 (br, 1 H), 8.22 (d, J = 13.5 Hz, 1 H), 7.78 (t, J = 8.0 Hz, 3 H), 7.46 (t, J = 8.0 Hz, 1 H), 7.42 (t, J = 7.0 Hz, 2 H), 2.65 (q, J = 13.0, J = 4.2 Hz, 1 H), 2.54–2.46 (m, 2 H), 2.37–2.29 (m, 1 H), 2.28–2.17 (m, 1 H), 2.07–1.92 (m, 2 H), 1.91–1.75 (m, 3 H), 1.52–1.40 (m, 1 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 175.5 (C), 169.2 (C), 134.5 (C), 133.8 (C), 131.0 (C), 129.0 (CH), 127.8 (CH), 126.7 (CH), 125.6 (CH), 120.2 (C), 117.2 (CH), 86.7 (C), 48.5 (CH), 34.4 (CH3), 33.7 (CH2), 25.2 (CH3), 23.9 (CH2) ppm. IR (neat): = 3332 (w), 2937 (w), 1772 (s), 1684 (s), 1540 (m), 1223 (m), 1021 (s), 810 (m) cm−1. HRMS (ESI): calcd. for C20H23NNaO6S [M+Na]+ 406.1295; found 406.1341.

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(N-tert-Butyl)-2,3-dimethyl-5-oxotetrahydronaphthalen-2-carboxamide (3r): Prepared from 3-methyl-4-oxopentanoic acid (1g; 130 mg, 1 mmol, 1 equiv.) and tert-butyl isocyanide (170 µL, 1.5 mmol, 1.5 equiv.) according to Procedure A (reaction time 2 h). The diastereoisomers were not separated by chromatographic purification. Isolated as a colorless oil (24 mg, 0.11 mmol, 11 %). In the NMR spectroscopic data, D1 and D2 denote the two diastereomers.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3/\text{[D}_6\text{]}\text{DMSO): } \delta = 7.67 (d, J = 8.0 Hz, 2 H), 6.49 (br, 1 H, D2), 5.97 (t, J = 6.6 Hz, 1 H, D1/D2), 7.69 (t, J = 7.0 Hz, 1 H, D1/D2), 7.30 (d, J = 8.0 Hz, 2 H, D1, 2 H, D2), 4.73–4.53 (m, 2 H, D1/D2), 2.80 (dd, J = 17.0, J = 9.0 Hz, 1 H, D1), 2.57 (dd, J = 17.0, J = 9.0 Hz, 1 H, D1), 2.50–2.38 (m, 1 H, 1 H, D1, 1 H, D2), 2.37 (s, 3 H, D1), 2.37 (s, 3 H, D2), 2.23–2.14 (m, 1 H, 1 H, D1, 1 H, D2), 1.40 (s, 3 H, D3), 1.26 (s, 3 H, D3), 1.00 (d, J = 7.5 Hz, 3 H, D1, 1 H, D3), 0.81 (d, J = 7.5 Hz, 3 H, D2) ppm. \]^13C NMR (125 MHz, CDCl\textsubscript{3}): \delta = 174.9 (C, D2), 174.6 (C, D1), 171.9 (C, D1), 170.1 (C, D2), 145.4 (C, D1), 133.9 (C, D1), 129.9 (CH, D1), 129.8 (CH, D2), 129.0 (CH, D1), 129.0 (CH, D2), 88.4 (C, D3), 87.3 (C, D1), 59.9 (CH\textsubscript{3}, D1), 59.8 (CH\textsubscript{3}, D2), 38.5 (CH\textsubscript{2}, D1), 37.1 (CH, D1), 36.2 (CH\textsubscript{2}, D2), 35.6 (CH\textsubscript{2}, D1), 23.9 (CH\textsubscript{3}, D1), 21.7 (CH\textsubscript{3}, D2), 18.2 (CH\textsubscript{3}, D2/D1), 15.9 (CH\textsubscript{2}, D2), 14.3 (CH\textsubscript{3}, D1) ppm. IR (neat): \( \tilde{\nu} = 3354 \) (w), 1784 (s), 1676 (s), 1518 (s), 1294 (s), 1220 (m), 1148 (s), 1088 (t), 1053 (m), 926 (m), 750 (cm\textsuperscript{-1}). HRMS (ESI): calcd. for C\textsubscript{4}H\textsubscript{12}N\textsubscript{2}NaO\textsubscript{4} [M + MeOH + Na]\textsuperscript{+} 380.1178; found 380.1178.

8a-Hydroxyhexahydroisoquinoline-1,3-(2H,4H)-dione (4b): Prepared from 3b (6 mg, 0.02 mmol) according to Procedure B (reaction time 7 h). Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1, to cyclohexane/ethyl acetate, 2:1, R\textsubscript{t} = 0.13). Isolated as a white solid (22 mg, 0.12 mmol, 60 %). M.p. 150–158 °C.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3/\text{D}_2\text{MSO-d}_6): } \delta = 9.32 (br, 1 H, 1 H), 4.73 (br, 1 H), 2.76 (d, J = 16.6 Hz, 1 H), 2.20 (d, J = 16.6 Hz, 1 H), 2.11–1.97 (m, 1 H, 1 H), 1.95–1.84 (m, 1 H, 1 H), 1.67–1.45 (m, 2 H, 2 H), 1.43–1.31 (m, 1 H, 1 H), 1.28–0.95 (m, 4 H) ppm. \]^13C NMR (125 MHz, CDCl\textsubscript{3}/D\textsubscript{2}\text{MSO-d}_6): \delta = 172.5 (C), 71.4 (C), 37.5 (CH\textsubscript{2}), 34.4 (CH\textsubscript{2}), 32.8 (CH\textsubscript{2}), 29.5 (CH\textsubscript{2}), 22.6 (CH\textsubscript{2}), 22.2 (CH\textsubscript{2}) ppm. IR (neat): \( \tilde{\nu} = 3166 \) (w), 2923 (s), 1668 (s), 1358 (s), 1209 (s), 1068 (s), 1041 (m), 840 (m), 732 (m) cm\textsuperscript{-1}. HRMS (ESI): calcd. for C\textsubscript{2}H\textsubscript{12}N\textsubscript{2}NaO\textsubscript{3} [M + Na]\textsuperscript{+} 206.0788; found 206.0786.
1 H), 2.41 (sex, J = 4.0 Hz, 1 H), 2.16 (t, J = 11.0 Hz, 1 H), 2.10–2.01 (m, 1 H), 1.92–1.80 (m, 1 H), 1.71–1.44 (m, 6 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 171.9 (C), 133.5 (C), 133.2 (C), 123.2 (C), 129.4 (CH), 128.2 (CH), 128.0 (CH), 127.4 (CH), 127.0 (CH), 126.7 (CH), 125.8 (CH), 72.8 (C), 34.8 (CH), 34.7 (CH2), 32.7 (CH2), 26.0 (CH2), 21.2 (CH2), 20.7 (CH2) ppm. IR (neat): ν = 3446 (w), 2936 (w), 1734 (m), 1680 (s), 1511 (s), 1304 (s), 1288 (s), 1138 (s), 1043 (m), 927 (m), 820 (m), 735 (m) cm–1. HRMS: calcd. for C27H22NaNO5 [M + Na]+ 374.1025; found 374.1024. Crystals for single-crystal X-ray diffraction were grown by slow evaporation of an ethanolic solution.

2-(2,6-Dimethylphenyl)-8a-hydroxyhexahydroisoquinoline-1,3-(2H,4H)-dione (4H): Prepared from 3h (29 mg, 0.1 mmol) according to Procedure B (reaction time 3 h). Isolated as a colorless oil (29 mg, 76%). M.p. 122–126 °C. 1H NMR (500 MHz, CDCl3): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.34 (d, J = 7.5 Hz, 2 H), 5.26 (s, 2 H), 3.08 (br, 1 H), 2.99 (dd, J = 18.5, J = 5.0 Hz, 1 H), 2.65 (dd, J = 18.5, J = 7.0 Hz, 1 H), 2.21–2.12 (m, 2 H), 1.94–1.64 (m, 2 H, 1.65–1.27 (m, 5 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 170.3 (C), 145.4 (C), 136.0 (C), 130.0 (CH), 128.6 (CH), 72.7 (C), 59.4 (CH2), 35.7 (CH), 34.5 (CH3), 33.5 (CH3), 32.1 (CH3), 21.9 (CH) ppm. IR (neat): ν = 3440 (w), 2930 (m), 1734 (m), 1651 (s), 1453 (m), 1300 (s), 1298 (s), 1223 (s), 1207 (s), 1186 (s), 1132 (m), 1003 (m), 768 (m), 725 (m) cm–1. HRMS (ESI): calcd. for C17H21NNaO5S [M + Na]+ 278.0992; found 278.0992.

2-Tosylmethyl-8a-hydroxyhexahydroisoquinoline-1,3-(2H,4H)-dione (4i): Prepared from 3i (29 mg, 0.1 mmol) according to Procedure B (reaction time 3 h). Isolated as a white solid (24 mg, 0.083 mmol, 83 %). M.p. 149–163 °C. 1H NMR (500 MHz, CDCl3): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.34 (d, J = 7.5 Hz, 2 H), 5.26 (s, 2 H), 3.08 (br, 1 H), 2.99 (dd, J = 18.5, J = 5.0 Hz, 1 H), 2.65 (dd, J = 18.5, J = 7.0 Hz, 1 H), 2.21–2.12 (m, 2 H), 1.94–1.64 (m, 2 H, 1.65–1.27 (m, 5 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 170.3 (C), 145.4 (C), 136.0 (C), 130.0 (CH), 128.6 (CH), 72.7 (C), 59.4 (CH2), 35.7 (CH), 34.5 (CH3), 33.5 (CH3), 32.1 (CH3), 21.9 (CH) ppm. IR (neat): ν = 3420 (w), 2934 (m), 1734 (m), 1676 (s), 1304 (s), 1288 (s), 1138 (s), 1043 (m), 927 (m), 725 (m) cm–1. HRMS (ESI): calcd. for C17H17TOSNaO5 [M + Na]+ 374.1033; found 374.1033.

Methyl 2-(8a-Hydroxy-1,3-dioxo-octahydroquinolin-2(1H)-yl)acetate (4j): Prepared from 3j (26 mg, 0.1 mmol) according to Procedure B (reaction time 3 h). Isolated as a white solid (24 mg, 0.083 mmol, 83 %). M.p. 122–126 °C. 1H NMR (500 MHz, CDCl3): δ = 4.57 (d, J = 16.5 Hz, 1 H), 4.52 (d, J = 16.5 Hz, 1 H), 3.72 (s, 3 H), 2.96 (dd, J = 19.0, J = 5.5 Hz, 1 H), 2.80 (br, 1 H), 2.75 (d, J = 19.0, J = 8.0 Hz, 1 H), 2.28–2.19 (m, 1 H), 2.16–2.05 (m, 1 H), 1.98–1.88 (m, 1 H), 1.86–1.75 (m, 1 H), 1.64–1.40 (m, 5 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 171.3 (C), 168.5 (C), 72.4 (C), 52.5 (CH2), 40.8 (CH2), 35.6 (CH), 34.5 (CH3), 33.3 (CH3), 26.7 (CH2), 21.7 (CH), 21.7 (CH2) ppm. IR (neat): ν = 3404 (w), 2948 (w), 1753 (s), 1720 (m), 1664 (s), 1380 (s), 1329 (s), 1218 (s), 1173 (s), 1130 (s), 1070 (s), 1022 (s), 940 (m), 744 (m) cm–1. HRMS (ESI): calcd. for C17H21NNaO5 [M + Na]+ 278.0999; found 278.0989. Crystals for single-crystal X-ray diffraction were grown by slow evaporation of an ethanol solution.

Aromatic substitution on silica gel (cyclhexane/ethyl acetate, 6:1) to give (3aR,7aS)-3a (18 mg, 0.075 mmol, 68 %). The spectroscopic data are in accordance with racemic 3a. The enantiomeric ratio was determined by chiral GC on the chiral phase ChiraSil Dex CB (25 m × 0.25 μm); temperature program 130 °C, hold for 60 min. Retention times: tR(S) = 23.5 min, tR(R) = 25.6 min; er = 928. [α]D20 = −54 (c = 0.67, CH3Cl).

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Keywords: Multicomponent reactions · Cyclization · Ketoacids · Diastereoselectivity · Lactones · Rearrangement

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[13] Other Lewis acids such as BF₃·Et₂O and Sc(OTf)₃ were explored, but gave lower conversions and stereoselectivities.


[16] In Ugi reactions, ketoacid 1d does indeed preferentially (3:1 ratio) give the cis-bicyclic lactam corresponding to an anti addition, see ref.[10c]

[17] Crystal packing forces may be relevant in the transformation of 3j into 4j during crystallization.

[18] For a recent example of the use of enzymes to prepare optically pure precursors for Passerini reactions, see ref.[10c]


[21] Chiral oxoacid 1a was observed to racemize slowly upon prolonged storage.


[27] Due to cyclohexane ring flipping, some peaks in the 13C NMR spectra of compounds 4 appear broad and have low intensities.

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