Herein, we report an unprecedented, short and diastereo-selective synthesis of newly reported aza-diketopiperazine (aza-DKP) scaffolds starting from amino acids. The strategy is based on a Rh(I)-catalyzed hydroformylative cyclohydrocarbonylation of allyl-substituted aza-DKP, followed by a diastereoselective functionalization of the platform. This methodology allows the synthesis of novel bicyclic and tricyclic aza-DKP scaffolds incorporating six- or seven-membered rings, with potential applications in medicinal chemistry.

The diketopiperazine (DKP) moiety found in several natural products has been extensively studied in medicinal chemistry. However, the corresponding aza-DKP platform remains underexplored. This class of heterocycles can be viewed as a constrained dipeptidomimetic DKP analogue (Fig. 1). As reported for aza-peptides, the replacement of one Cα-stereogenic center by a planar nitrogen atom could have a profound impact on both the chemical and biological properties of DKP and could offer new potential for drug discovery and chemical biology.

Recently, we have described a convenient access to original 2,4,5-trisubstituted-1,2,4-triazine-3,6-diones, both in solution and in the solid-phase. In the present work, we report a diversity-oriented, efficient and stereoselective synthesis of novel bicyclic and tricyclic scaffolds derived from aza-DKP. To access such structures, we have explored a strategy based on cyclohydrocarbonylation (CHC) of allyl aza-DKP, followed by an acid-catalyzed diastereoselective nucleophilic addition on the resulting enamide (Scheme 1). This strategy involves for the first time the catalytic hydroformylation of a newly reported 1,2,4-triazine-3,6-dione system. The scope, limitations and diastereoselectivity of the approach have been carefully studied, resulting in the preparation of enantiomerically pure scaffolds with potential applications in medicinal chemistry.

To investigate the applicability of the CHC reaction to aza-DKP systems, we initially prepared a set of allyl-substituted precursors and according to our previously described procedure. The amino acids were converted into amino esters which were alkylated by reductive amination. The resulting secondary amines and as well as the proline derivatives were reacted with bis(trichloromethyl)carbamate (BTC) and allyl or homoallyl t-butyl carbazate obtained in one step from commercially available t-butyl carbazate (see ESI† for a detailed procedure). The crude semicarbazides 3a–m were then treated in TFA/water (95:5) for 1 h, resulting in the consecutive semi-carbazide deprotection and cyclization. This led to allyl derivatives in 27% to 77% yields from amines 2a–j, the lower yields being obtained with the most sterically hindered R1 and R2 substituents (Table 1, entries 3 and 4). Noteworthily, the preparation of aza-DKP 4i and 4m (from l-hydroxyproline) required hydroxy protection prior to semicarbazide cyclization (Table 1, entries 9 and 12).
with compounds 4a–m in hand, we explored the CHC using syngas (H₂/CO) in the presence of a Rh(i) catalyst. BiPhePhos was selected as a metal chelating agent to ensure the formation of linear rather than branched aldehydes. All reactions were performed under acid catalysis (pyridinium p-toluenesulfonate: PPTS or camphorsulfonic acid: CSA) to promote cyclization, if any, into enamide 5 in the same reactor.

In our first attempt, we were pleased to obtain cyclized compound 5a in an excellent 81% yield from allyl compound 4a, thus validating the CHC as a convenient and high yielding method for bicyclic aza-DKP synthesis (Table 1, entry 1).

Next, the scope and limitations of the reaction were evaluated on allylic aza-DKP 4b–m. In all cases, the expected cyclized compounds 5 were isolated in yields ranging from 43 to 81% (Table 1), thus demonstrating the efficiency of the method, regardless of the nature of R¹ and R² (Table 1, entries 3–5) or of the configuration of the starting amino acid (Table 1, entry 2). Noteworthily, CHC still occurred in reasonable yields with compounds 4f and 4g encompassing nucleophile groups at R³, which could possibly compete as a ligand for the metal (Table 1, entries 6 and 7).

Interestingly, CHC also gave access to tricyclic L-proline-based aza-DKP 5h, 5i and 5j in good 69%, 73% and 62% yields, respectively (Table 1, entries 8–10). This scaffold is particularly appealing for medicinal chemistry as the corresponding DKP is embedded in the core of several natural product classes used in targeted cancer therapy.

These promising results for the synthesis of six-membered rings prompted us to evaluate CHC as an entry to aza-DKP fused to a seven-membered ring. Thus, with homoallylic derivative 4k, the CHC reaction proceeded smoothly and 5k was obtained in moderate yield (34%). Then, we switched from PPTS to the more acidic CSA, which drives the reaction to completion and dramatically improves the yield (72%). This optimized procedure was also applied to the synthesis of tricyclic L-hydroxyproline-based aza-DPK 5m obtained in 61% yield.

With all these novel structures in hand, we decided to investigate the functionalization of the diaza-cyclohexene and diaza-cycloheptene rings in order to extend the molecular diversity of these novel scaffolds. A first experiment was carried out by subjecting compound 5a to a CSA acid-catalyzed addition of MeOH which led to hemiaminal 6a with a high 86% yield and a good diastereoisomeric ratio (dr) of 93:7 (Table 2, entry 1). The major isomer was readily isolated by preparative HPLC and was shown to be the C9–C2 trans-isomer by X-ray diffraction analysis (Fig. 2). This result combined with the axial position of the methoxy group indicate that the nucleophilic attack of the acyl iminium intermediate is likely under stereo-electronic control. The out-of-plane substituents associated with the presence of stereocenters make the aza-DKP scaffold a promising platform to increase receptor–ligand interactions and to develop potentially active and selective compounds.

The diastereoselective addition reaction was then extended to various enamides. As shown in Table 2, the expected compound was obtained whatever the absolute configuration at C₉ (Table 2, entry 2). The steric hindrance at R² was found to impact the selectivity (Table 2, entry 4). In contrast, when a
hindered group was introduced at R¹, only one diastereomer was detected by ¹H NMR and HPLC analyses of the crude material (Table 2, entry 3). The diastereoselective addition was also found compatible with the presence of a nucleophilic primary amine at R¹ (Table 2, entry 5). Interestingly, when the addition was performed on tricyclic proline derivatives 5h and 5j (Table 2, entries 6 and 7), desired hemiaminals 6h and 6j were also obtained in good yields (65% and 59%, respectively) but with an inverted dr in favor of the cis-isomer. ¹H NMR or HPLC analysis of the crude reaction mixtures.

Table 2	Diastereoselective acid-catalyzed addition of MeOH on enamide

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>n</th>
<th>Yield (%)</th>
<th>dr (trans/cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-Me</td>
<td>Bn</td>
<td>1</td>
<td>6a (86)</td>
<td>93:7</td>
</tr>
<tr>
<td>2</td>
<td>(R)-Me</td>
<td>Bn</td>
<td>1</td>
<td>6b (83)</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td>(S)-sec-Bu</td>
<td>Bn</td>
<td>1</td>
<td>6c (65)</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>(S)-Me</td>
<td>iPe</td>
<td>1</td>
<td>6d (74)</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>(S)-H₂N(CH₂)₃</td>
<td>Bn</td>
<td>1</td>
<td>6f (61)</td>
<td>96:4</td>
</tr>
<tr>
<td>6</td>
<td>(S)-H₂N(CH₂)₃</td>
<td>Bn</td>
<td>1</td>
<td>6h (65)</td>
<td>4:96</td>
</tr>
<tr>
<td>7</td>
<td>pNO₂Bn</td>
<td>Bn</td>
<td>1</td>
<td>6i (59)</td>
<td>4:96</td>
</tr>
<tr>
<td>8</td>
<td>(S)-Me</td>
<td>Bn</td>
<td>2</td>
<td>6k (62)</td>
<td>37:63</td>
</tr>
<tr>
<td>9</td>
<td>(S)-Me</td>
<td>pNO₂Bn</td>
<td>2</td>
<td>6l (55)</td>
<td>37:63</td>
</tr>
</tbody>
</table>

a iPe = isopentyl. b Isolated yields. c Diastereomeric ratio was determined by ¹H NMR or HPLC analysis of the crude reaction mixtures.

Looking for a further improvement in the access to novel aza-DKP platforms, a domino CHC/acid-catalyzed MeOH addition sequence was envisaged (Scheme 2). To this end, N-allyl substituted triazinedione 4a was submitted to a CHC reaction in the presence of PPTS in MeOH/THF (10:1) and led to compound 6a in 74% yield and a good stereoselectivity (93:7). Thus, compound 6a is readily attainable in a three-step process only from simple N-benzyl amino ester 2a in a 52% overall yield. This result highlights the efficiency of our strategy to provide a rapid access to novel N-heterocyclic scaffolds.

Finally, to further enlarge the molecular diversity of novel aza-DKP platforms and access to diversity-oriented chemical libraries, we envisaged the incorporation at C9 of functional groups able to react with commercially available building blocks. Hence, trans-isomer 6a was reacted either with TMSN₃ or with TMSCN, both in the presence of BF₃·OEt₂ (Scheme 3). Thus, azide 7 was obtained in good yield (88%) and dr (>95:5). Nitrile 9 was also isolated in excellent yield (92%) but with a lower dr (68:32). Again, for both compounds, the major isomer was shown to be the C9-C2 trans-isomer (X-ray structure analysis, ESI†).

Besides, hydrolysis of the major isomer under acidic conditions led to carboxylic acid 10, able to react with amino building-blocks. Azide 7 was reduced with H₂/Pd in the presence of di-tert-butyl dicarbonate to provide tBoc-protected compound 8 (86%). To further extend the chemical diversity of aza-diketopiperazines, compound 7 could also be engaged in Cu(i)-catalyzed azide–alkyne cycloaddition reactions. Starting from the amino acid pool, we have developed a diastereoselective approach for the preparation of a diverse range of N-heterocyclic scaffolds derived from aza-DKP. Indeed, this rapid and flexible method enables the efficient conversion of N-allyl substituted aza-DKP into newly reported bicyclic or tricyclic scaffolds containing six- or seven-membered rings by a
domino CHC/addition sequence. A subsequent substitution at C-9 of the aza-DKP allows the diastereoselective incorporation of cyano and azido groups readily amenable, respectively, to amino or carboxylic functions which paves the way to the preparation of diversity-oriented libraries.

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Notes and references


