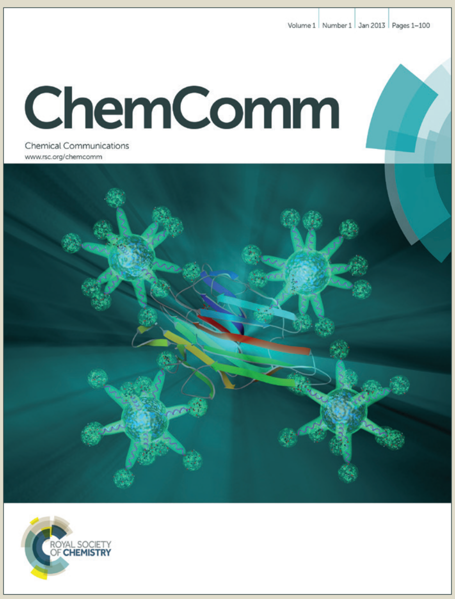
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Diastereoselective Synthesis of Novel Aza-diketopiperazines via a Domino Cyclohydrocarbonylation/Addition Process

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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 cyclohydro-carbonylation 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.[1] However, the corresponding aza-DKP platform remains underexplored.[2] This class of heterocycles can be viewed as a constrained dipeptidomimetic DKP analogue (Figure 1). As reported for aza-peptides,[3] the replacement of one C_{α}-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.

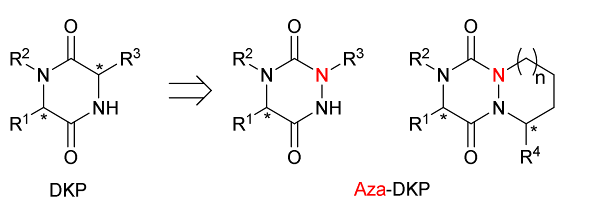
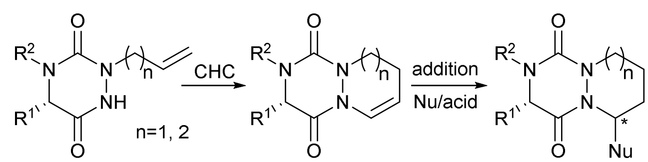


Figure 1 General structure of diketopiperazines (DKP) and aza-diketopiperazines (aza-DKP).

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



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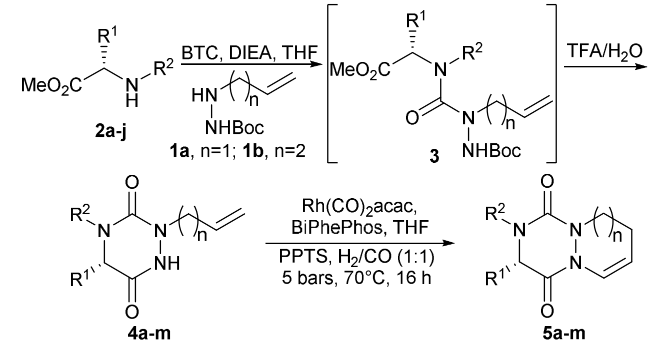
Scheme 1 Strategy towards novel *N*-heterocyclic aza-DKP scaffolds **6**.

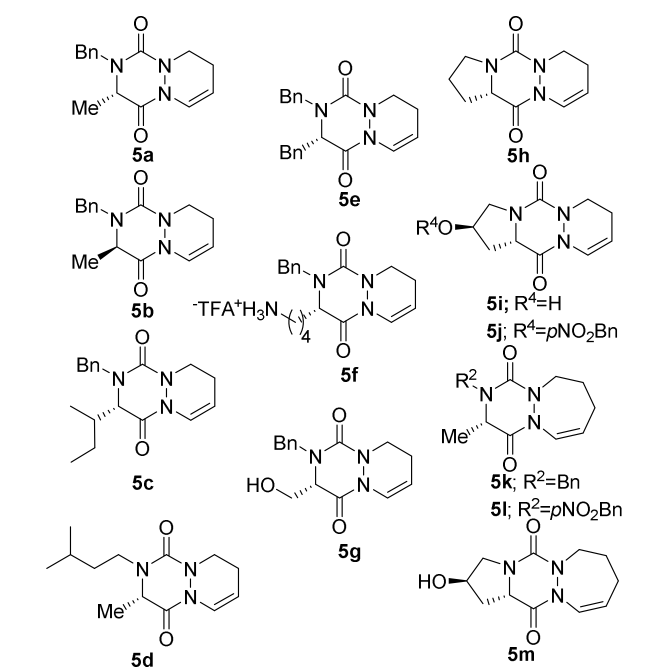
To investigate the applicability of the CHC reaction on aza-DKP systems, we initially prepared a set of allyl-substituted precursors **4a-g** and **4k,l** according to our previously described procedure.[2b] The amino acids were converted into amino esters which were alkylated by reductive amination. The resulting secondary amines **2a-g** and **2k,l** as well as the proline derivatives **2h-j** and **2m** were reacted with bis(trichloromethyl)carbonate (BTC) and allyl or homoallyl t-butyl carbazate **1a** or **1b**, obtained in one step from commercially available t-butyl carbazate (see supporting information for 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 **4a-m**, in 27% to 77% yields from amines **2a-j**, the lower yields

Table 1 CHC-based strategy towards novel bicyclic and tricyclic aza-DKP scaffolds **5a-m**.



entry	amino acid	R^1	R^2	n	yield **4** (%)[b]	yield **5** (%)[b]
1	L -Ala	(*S*)-Me	Bn	1	**4a**(70)[c]	**5a**(81)
2	D-Ala	(*R*)-Me	Bn	1	**4b**(68)[c]	**5b**(79)
3	L -Ile	(*S*)-*sec*-Bu	Bn	1	**4c**(31)	**5c**(81)
4	L-Ala	(*S*)-Me	*i*Pe[a]	1	**4d**(31)	**5d**(78)
5	L-Phe	(*S*)-Bn	Bn	1	**4e**(49)	**5e**(77)
6	L-Lys(Boc)	(*S*)-$H_2N(CH_2)_4$	Bn	1	**4f**(51)	**5f**(43)
7	L-Ser(^{t}Bu)	(*S*)-$HOCH_2$	Bn	1	**4g**(45)[d]	**5g**(57)
8	L -Pro	(*S*)-$(CH_2)_3$		1	**4h** (38)[c]	**5h**(69)
9	L-Pro(OBn)	R^5O– **4i**: R^5=Bn; **5i**: R^5=H		1	**4i**(29)[c,e]	**5i**(73)
10	L-Pro (O*p*NO_2Bn)	*p*NO_2BnO–		1	**4j**(39)	**5j**(62)
11	L -Ala	(*S*)-Me	Bn	2	**4k**(77)[c]	**5k**(72)[f]
12	L -Ala	(*S*)-Me	*p*NO_2-Bn	2	**4l**(54)	**5l**(81)
13	L-Pro(OBn)	R^5O– **4m**: R^5=Bn; **5m**: R^5=H		2	**4m**(27)[c,e]	**5m**(61)[f]

[a] *i*Pe = isopentyl. [b] Isolated yields. [c] Semicarbazide **3** was obtained in THF/CH_2Cl_2. [d] Compound **4g** was obtained in TFA/water/triisopropylsilane (95/2.5/2.5, v/v/v). [e] Cleavage of the benzyl protecting group was performed prior to CHC. [f] CSA instead of PPTS.



being obtained with the most sterically hindered R^1 and R^2 substituents (Table 1, entries 3 and 4). Noteworthy, 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 (H_2/CO) in the presence of a Rh(I) catalyst.[5] BiPhePhos was selected as metal chelating agent to ensure formation of linear rather than branched aldehydes.[6] 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 82% 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).

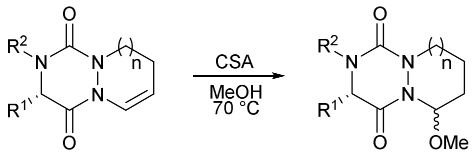
Next, the scope and limitations of the reaction were evaluated on allylic aza-DKP **4b**-**m**. In all cases, the expected cyclized compounds **5** were isolated in yields ranging from 43 to 81% (Table 1), thus demonstrating the efficiency of the method, regardless of the nature of R^1 and R^2 (Table 1, entries 3-5) or of the configuration of the starting amino-acid (Table 1, entry 2). Noteworthy, CHC still occurred in reasonable yields with compounds **4f** and **4g** encompassing nucleophiles groups at R^3, which could possibly compete as ligand for the metal (Table 1, entries 6 and 7).[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, 9 and 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.[8]

These promising results for the synthesis of six-membered rings prompted us to evaluate CHC as an entry to aza-DKP fused to 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 (Figure 2). This result combined with the axial position of the methoxy group indicate that the nucleophilic attack of the acyl imminium intermediate is likely under stereoelectronic control.[9] 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.[10]

Table 2 Diastereoselective acid-catalyzed addition of MeOH on enamide **5**.



5a-d, f, h, j-l → **6a-d, f, h, j-l**

entry	R^1	R^2	n	yield (%)[b]	dr (trans/cis)[c]
1	(*S*)-Me	Bn	1	**6a** (86)	93:7
2	(*R*)-Me	Bn	1	**6b** (83)	92:8
3	(*S*)-*sec*-Bu	Bn	1	**6c** (65)	>99:1
4	(*S*)-Me	*i*Pe[a]	1	**6d** (74)	97:3
5	(*S*)-$H_2N(CH_2)_4$	Bn	1	**6f** (61)	96:4
6	(*S*)-$(CH_2)_3$		1	**6h** (65)	4:96
7	*p*NO_2BnO–		1	**6j** (59)	4:96
8	(*S*)-Me	Bn	2	**6k** (62)	37:63
9	(*S*)-Me	*p*NO_2Bn	2	**6l** (55)	37:63

[a] *i*Pe = isopentyl. [b] Isolated yields. [c] Diastereomeric ratio were determined by ^{1}H NMR or HPLC analysis of the crude reaction mixtures.

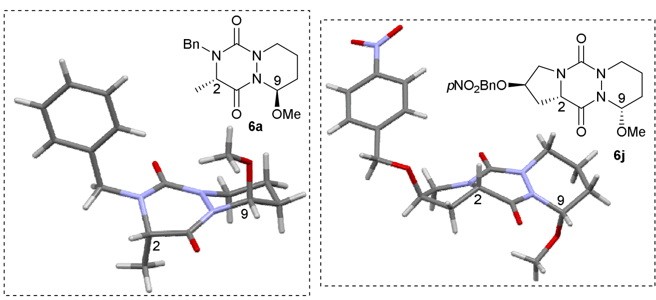
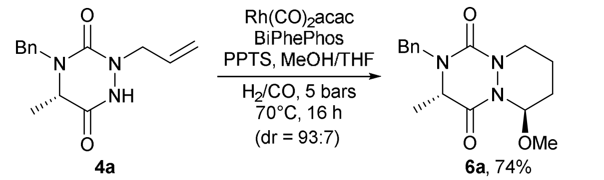


Figure 2 X-ray structures of compounds **6a** and **6j**.

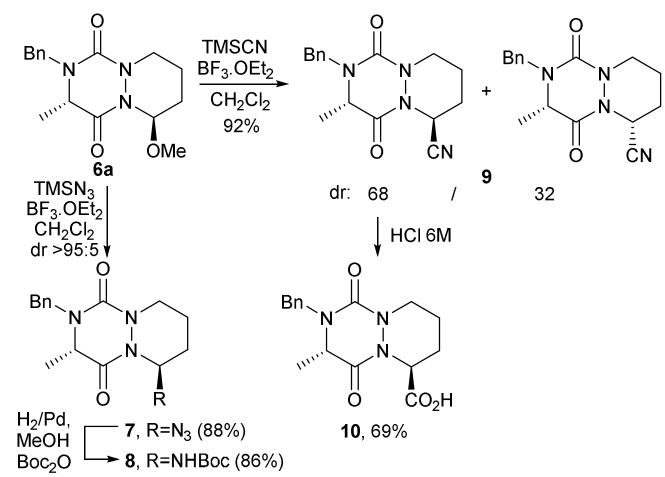
The diastereoselective addition reaction was then extended to various enamides. As shown in Table 2, the expected compound was obtained whatever the absolute configuration at C_α(Table 2, entry 2).The steric hindrance at R^2 was found to impact the selectivity (Table 2, entry 4). In contrast, when a hindered group was introduced at R^1, only one diastereomer was detected by ^{1}H NMR and HPLC analysis of the crude material (Table 2, entry 3). The diastereoselective addition was also found compatible with the presence of a nucleophilic primary amine at R^1 (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 (4:96), as demonstrated by X-ray diffraction analysis of **6j** (Figure 2). The inversion of dr for proline-based substrates compared to other aminoacids was previously reported for the 2,5-diketopiperazine system.[11,12] Finaly, the addition performed on seven-membered rings **5k** and **5l** led to the corresponding hemiaminals **6k** and **6l** in still good yields (62 and 55%, respectively) but with a lower dr (37:63), likely due to greater flexibility of the seven-membered ring.[13] As aforementioned for **6h** and **6j**, the X-ray diffraction analysis of **6l** revealed that the major isomer was the C9-C2 *cis*-isomer.

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).[14] 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.



Scheme 2 Domino Cyclohydrocarbonylation/Addition Reaction.

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 $TMSN_3$ or with TMSCN, both in presence of $BF_3.OEt_2$ (Scheme 3).[15] 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, Supporting Information).



Scheme 3 Diastereoselective functionalization of aza-diketo-piperazine **6a**.

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 H_2/Pd in presence of di-*tert*-butyl dicarbonate to provide *t*Boc-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.[16]

Conclusions

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

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Electronic Supplementary Information (ESI) available: Detailed experimental procedures and analytical data for all the compounds. Crystal structures for **5a**, **5i**, **5k**, **6a**, **7**, *trans*-isomer of **9** and *cis*-isomers of **6l** and **6j**. See DOI: 10.1039/c000000x/

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