EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Prolinamides of aminouracils, organocatalyst modifiable by complementary modules

Authors: Karen M. Ruíz-Pérez, Beatriz Quiroz-García, and Marcos Hernández-Rodríguez

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800886

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800886

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201800886

WILEY-VCH

Prolinamides of aminouracils, organocatalyst modifiable by complementary modules

Karen M. Ruíz-Pérez[a], Beatriz Quiroz-García[a], Marcos Hernández Rodríguez*[a]

Abstract: We report the synthesis and evaluation of prolinamide organocatalysts that incorporate aminouracils. The features of these catalysts are enhanced NH acidity of the amide because of the electron withdrawing nature of the heterocycle, additional hydrogen bond donor at the α or β positions of this functional group (using 6-aminouracil or 5,6-diaminouracil respectively), and it can be recovered due to its low solubility and used again without losing enantioselectivity. A unique feature of these systems is that the self-assembly capability with complementary modules by Watson-Crick interactions. These supramolecular adducts behave differently from the catalyst alone, some of them have lower performance but others improve the selectivity of the product. Therefore, this approach avoids the synthesis of many catalysts.

Introduction

Organocatalysis is an established toolkit to build chiral molecules.[1] Among these methods, aminocatalysis is used to activate aldehydes or ketones by primary or secondary amines trough enamine or iminium species.[2] Prolinamide aminocatalysts induce enantioselectivity through the cyclic Houk-List model. Consequently, the hydrogen bonding properties of the NH donor of the amide is crucial in this TS.[3] The substitution of the carboxylic functional group of proline **A** to amide **B** allows a higher solubility of the catalyst, lower catalyst loading, avoid stationary resting states and overall higher selectivity. Studies with prolinamides have found that higher NH acidity or another hydrogen bond (HB) donor group, **C** and **D** respectively, enhance the selectivity of the catalyst.[4] In this manuscript, we studied prolinamides of aminouracils[5] under the hypothesis that the electron withdrawing properties of the uracil in aminocatalyst **1** would provide good HB donor properties to the NH moiety. Besides, the substitution pattern in the uracil allows the possibility of an additional hydrogen bond donor as shown in structures **2** and **3** at a different distance from the aforementioned NH. Another interesting feature of the proposed aminocatalyst (AC) is the possibility to self-assemble to other molecules by HB to form supramolecular adducts **E**. The different scaffolds that have been developed to pair with uracil[6] can be exploited to create with the developed systems diverse supramolecules. In principle, each adduct can be a catalyst with a different steric environment with the potential to improve the stereoselectivity.[7,8] This approach opens the option of a tunable system that avoids the synthesis of many catalysts[9] (Figure 1).

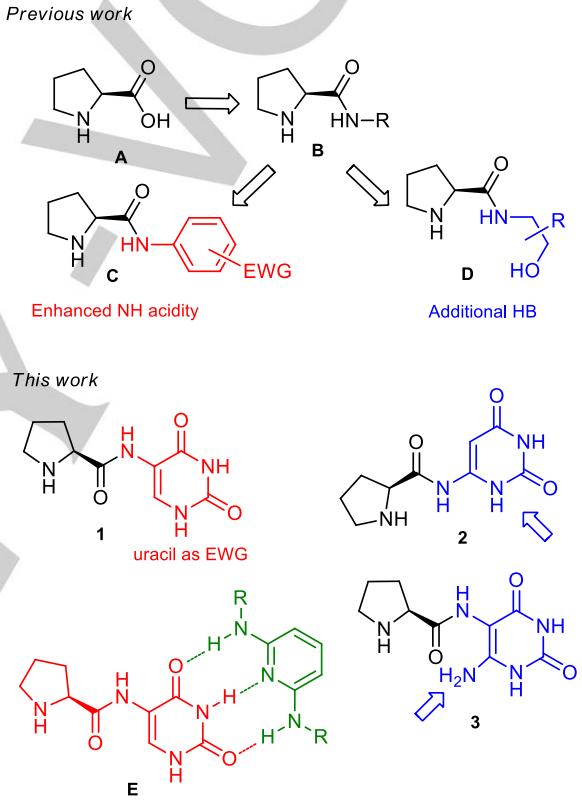


Figure 1. Hypothesis for the catalyst in this work.

Results and Discussion

Besides catalyst **1** and **2** mentioned above, we studied diamino uracil **3a** and the dimethylated analog **3b**. Other systems that are not prolinamides but incorporate uracil or guanine, **4** and **5** respectively, were also aimed in this study and the phenylalanine amide **6** (Figure 2).

[a] Instituto de Química, Universidad Nacional Autónoma de México. Circuito Exterior, Ciudad Universitaria, Del. Coyoacán, C.P. 04510 México, Cd. Mx., México.
E-mail: marcoshr@unam.mx
https://www.iquimica.unam.mx/departamentos/qorg/95-deps/qo/138-drmarcoshernandeziq-alias

Supporting information for this article are available on the WWW under https://doi.org/

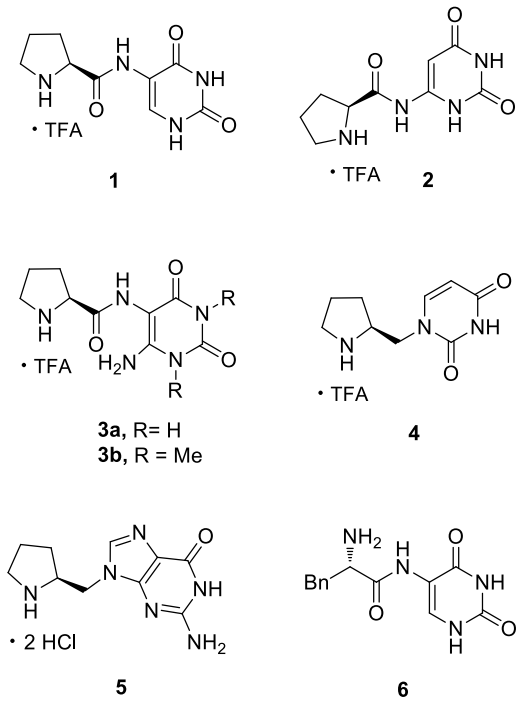
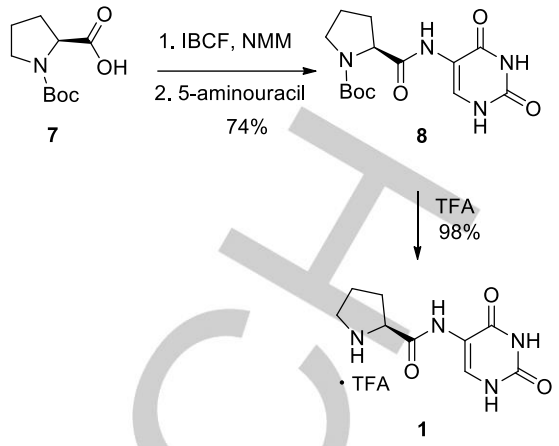


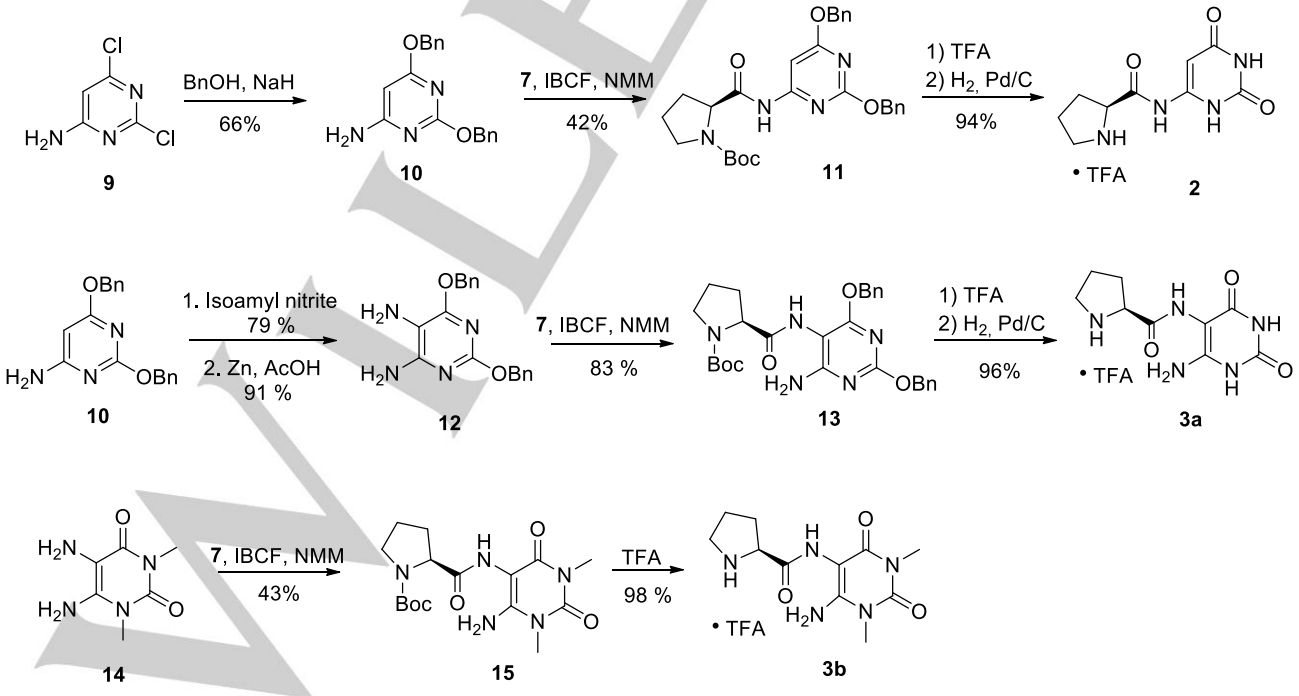
Figure 2. New catalyst examined in this work.

The overall synthetic approach to obtain the ACs was to couple *N*-Boc protected proline **7** activated by isobutyl chloroformate (IBCF) and add the corresponding commercially available aminouracil. With this method, 5-aminouracil was attached and obtained **8**, which after removal of the protecting group afforded **1** (Scheme 1). Compound **6** was made by the same procedure employing *N*-Cbz-phenylalanine as starting material (not shown).

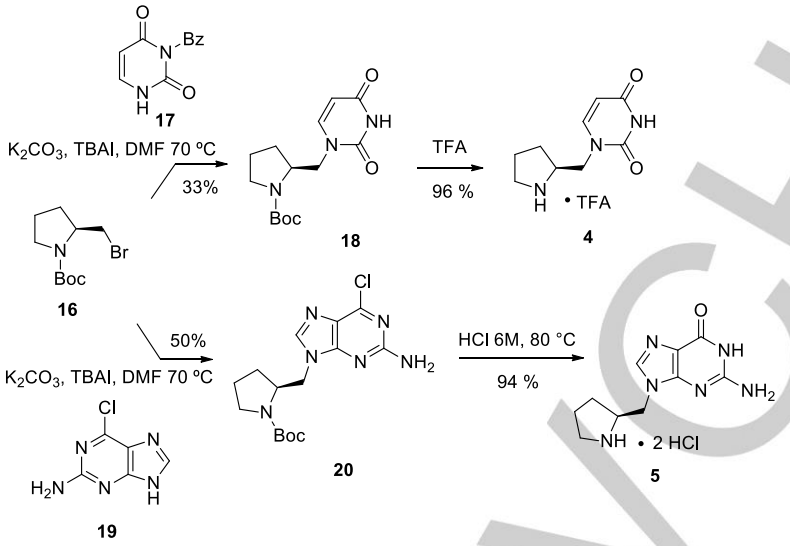


Scheme 1. Synthesis of AC **1**.

The 6-aminouracil showed lower reactivity and scarce solubility, so the prolinamide couldn't be obtained by a variety of activating agents and conditions. We solved this issue employing an oxygen protected analog (4-amino-2,6-dibenzyloxypyrimidine, **10**) which reacted with the activated proline and after removal of protecting groups of **11** AC **2** was obtained. The 5,6-diaminouracil it is reported to be prone to dimerize by oxidation by air exposure.[10] Therefore, we used the same strategy employing pyrimidine **10** as starting material. The amino group was introduced by nitrosation and further reduced to the desired compound **12**. The coupling of diaminopyrimidine **12** with *N*-Boc-proline yielded **13** and the removal of protecting groups led us to catalyst **3a**. With commercially available 1,3-dimethyl-5,6-diaminouracil **14** was synthesized **3b** using the same conditions. In both cases, the connectivity to the 5-amino group was correlated through NMR experiments (Scheme 2).



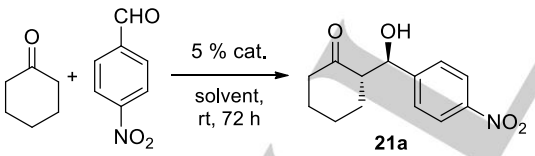
Scheme 2. Synthesis of AC **2**, **3a-b**.



Scheme 3. Synthesis of AC **4** and **5**.

To study catalysts without the NH of the amide, we considered other ACs with uracil and guanine **4** and **5** respectively. We reduced the carboxyl group of proline and transformed to the bromoalkyl compound **16**. This compound reacted with *N*^{3}-Bz uracil **17** to obtain compound **18** in 33 % along with the *N*^{3}-Bz analog in 48 %. The removal of the Boc group, afforded AC **4**. The direct nucleophilic substitution of **16** with guanine failed. We employed chloropurine **19** as a substrate, and not only it was successfully attached, but also the desired regioisomer **20** was the major product. The acidic hydrolysis led to AC **5** (Scheme 3).

The aldol reaction between ketones and aldehydes is the archetypical reaction to study the new ACs.[11] We chose cyclohexanone and 4-nitrobenzaldehyde as reactants to examine the performance of these compounds (Scheme 4).



Scheme 4. Aldol reaction between cyclohexanone and 4-nitrobenzaldehyde.

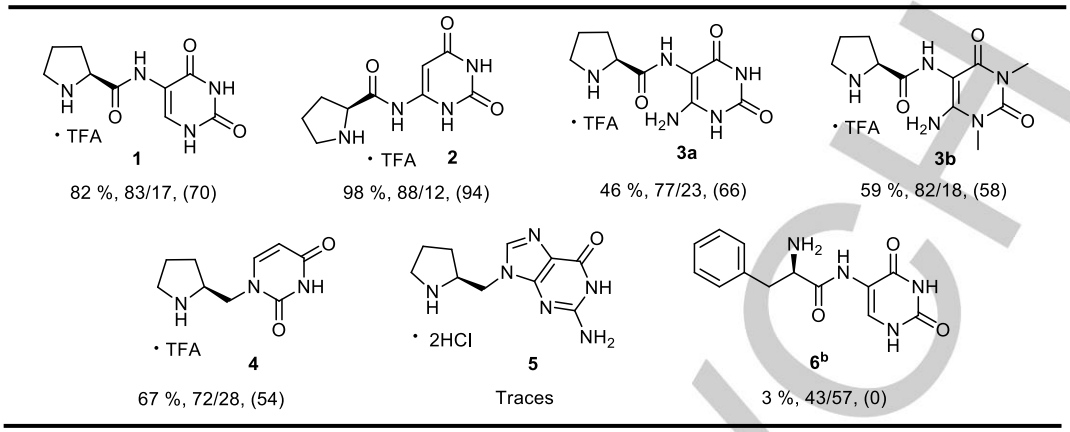
Catalyst **1** was studied in common organic solvents. We observed that in non-polar media, such as chloroform, no product was found whereas increasing the polarity of the solvent some aldol compound was formed (Table 1, entries 1-4). If the reaction was done without solvent a similar result in yield was obtained (Table 1, entry 5). The reason for this low activity is the low solubility of the catalyst in common solvents. A mixture chloroform/methanol at room temperature slightly increased the yield and at higher temperature moderate yield with loss of selectivity was the outcome (Table 1, entries 6-7). Next, we examined very polar solvents in which the catalyst was completely soluble. In DMF or DMSO (Table 1, entries 8-9) the aldol compound can be obtained. Particularly, in DMF a good yield and acceptable 85:15 enantiomeric ratio (70 % ee) was attained. With a mixture DMF/chloroform or NMP the product was obtained but lower yield compared to pure DMF (Table 1, entries 10-11). Other conditions for the reaction optimization can be found in the ESI.

Table 1. Screening of solvents of the model aldol reaction between cyclohexanone and 4-nitrobenzaldehyde with catalyst **1**.[a]

Entry	Solvent	Yield (%)[b]	d.r. *anti/syn*	*ee* (%)[c]
1	$CHCl_3$	Traces	-	-
2	THF	9	84/16	50
3	Dioxane	11	84/16	56
4	MeOH	19	92/8	92
5	Neat	12	83/17	88
6	$CHCl_3$/MeOH 2:1	30	88/12	84
7	$CHCl_3$/MeOH 2:1 50 °C	54	55/45	34
8	DMF[d]	82	83/17	70
9	DMSO[d]	59	84/16	70
10	DMF/$CHCl_3$ 1:2[d]	24	91/9	72
11	NMP[d]	59	81/19	78

[a] Reaction conditions: cyclohexanone (1.5 mmol), 4-nitrobenzaldehyde (0.3 mmol) and catalyst (5 mol%), 0.5 M, room temperature, 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Concentration 0.88 M.

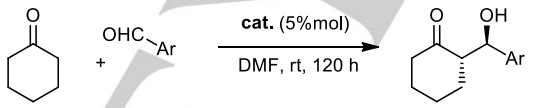
Table 2. Evaluation of the new AC in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde.[a] It is shown yield, d.r. and ee in parenthesis for each experiment.

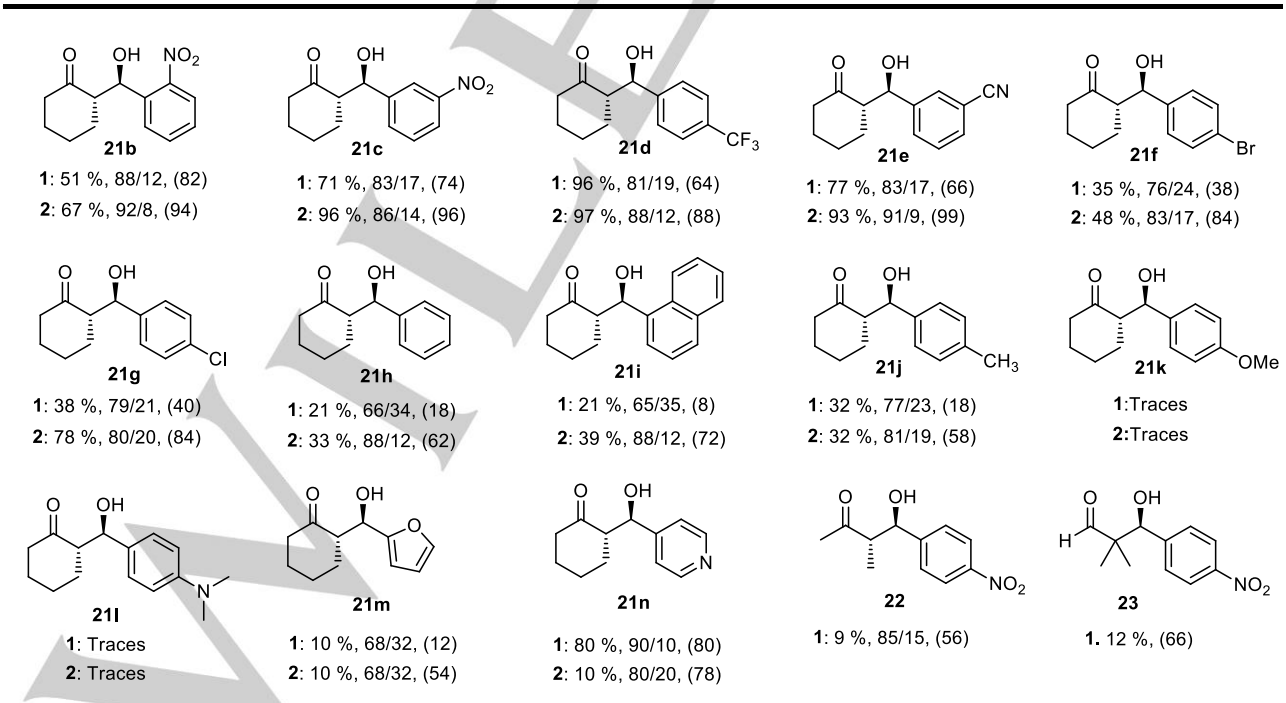


[a] Reaction conditions: cyclohexanone (1.5 mmol), 4-nitrobenzaldehyde (0.3 mmol) and catalyst (5 mol%), DMF, 0.88 M, 72 h. [b] It was studied the free amino and the TFA salt, on both experiments little product was found.

We choose DMF as the solvent to study all the catalysts so the solubility would not be an issue and therefore a clear evaluation of their features can be achieved. Table 2 shows the results with the synthesized catalysts. The 6-aminouracil in system **2** was the most stereoselective. Diaminouracils **3a** and **3b** with the hydrogen bond donor in β position presented lower selectivity compared to **1** or **2**. It was not surprising that compound **4** could not get good diastereo or enantioselectivity due to the lack of the hydrogen bond donor. The ACs with guanine **5** or phenylalanine **6** instead of proline did not promote the reaction.

Table 3. Substrate scope of aldehydes with catalysts **1** and **2**.[a] It is shown yield, d.r. and ee in parenthesis for each experiment.

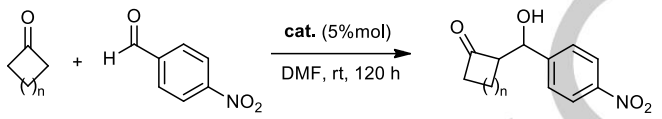




[a] Reaction conditions: cyclohexanone (1.5 mmol), aldehyde (0.3 mmol) and catalyst (5 mol%), DMF, 0.88 M, 120 h.

A further comparison between catalyst **1** and **2** with different aldehydes showed a better performance of the latter over the former. The reaction showed a strong dependence on the electrophilic character of the aldehyde. It was obtained good yield and selectivity with aromatic aldehydes with electron withdrawing groups (Table 3, **21b**-**g**). Benzaldehyde, 1-naphthaldehyde and *p*-tolualdehyde showed moderate to low yield and selectivity (Table 3, **21h**-**j**). Aromatic aldehydes with electron donating groups no reactivity was found (Table 3, **21k**-**l**). Aldehydes attached to heterocyclic rings have also a dependency on the ring character. Therefore, the aldehyde containing electron rich furan a low reactivity was found whereas with pyridine a similar behavior as the phenyl with electronwithdrawing groups was obtained (Table 3, **21m**-**n**). It was found that employing acyclic ketones the reaction was sluggish and with enolizable aldehydes further condensation of the product prevents isolation in good yield like in the aldol **23**.

Table 4. Substrate scope of cyclic ketones.[a] It is shown yield, d.r. and ee in parenthesis for each experiment.

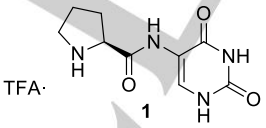


24	**25**	**21a**	**26**
1: 16%, 56/44, (46) *anti* (28) *syn*	**1**: 62%, 31/69, (51) *anti* (44) *syn*	**1**: 82%, 83/17, (70) *anti* (16) *syn*	**1**: 84%, 89/11, (74) *anti* (20) *syn*
2: 50%, 49/51, (80) *anti* (65) *syn*	**2**: 60%, 30/70, (77) *anti* (82) *syn*	**2**: 98%, 88/12, (94) *anti* (4) *syn*	**2**: 91%, 86/14, (96) *anti* (40) *syn*

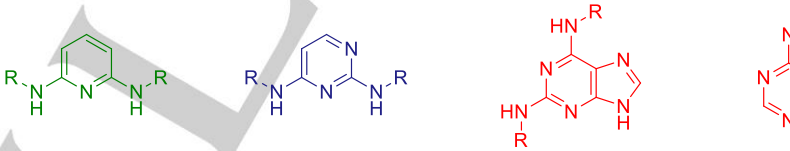
[a] Reaction conditions: cyclohexanone (1.5 mmol), aldehyde (0.3 mmol) and catalyst (5 mol%), DMF, 0.88 M, 120 h.

Other cyclic ketones were studied as pronucleophiles in the aldol reaction. Again, in all experiments compound **2** outperforms catalyst **1**. Four and five-membered ring ketones favor the *syn* diastereomer, whereas six and seven-membered cyclic ketones the *anti* diastereomer was obtained with high ee employing catalyst **2** (Table 4).

Next, we studied the effect of the complementary modules in the model reaction between cyclohexanone and 4-nitrobenzaldehyde. We first employed catalyst **1** due to the possibility to improve the moderate selectivity of this system. The examined complementary modules that bind to uracil by Watson-Crick pairing, some are commercially available or already reported the synthesis.



82 %, 83/17, (70)



	Py-a	**PyMD-a**	**DP-a**	**A-a**
a, R = H	75 %, 86/14, (91)	55 %, 82/18, (78)	70 %, 92/8, (84)	91 %, 89/11, (84)
b, R = Ac	**Py-b** 67 %, 80/20, (64)	**PyMD-b** 80 %, 84/16, (73)	**DP-b** 71 %, 80/20, (74)	
c, R= Bz	**Py-c** 78 %, 79/21, (64)	**PyMD-c** 90 %, 84/16, (74)	**DP-c** 74 %, 81/19, (70)	
d, R = Bn	**Py-d** 80 %, 82/18, (78)	**PyMD-d** 91 %, 85/15, (78)	**DP-d*** 84 %, 91/9, (80)	
e, R = Ph	**Py-e** 73 %, 69/31, (72)	**PyMD-e** 72 %, 65/35, (74)	**DP-e** 69 %, 81/19, (64)	

Figure 3. Effect of the complementary modules in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde with catalyst **1**. It is shown yield, d.r. (ee) of each experiment. *With *i-Pr* at *N*[9]. Reaction conditions: cyclohexanone (1.5 mmol), aldehyde (0.3 mmol), 5 % 1, 5% module, DMF, 0.88 M, 120 h.

The 2,6-diaminopyridines (**Py**), 2,4-diaminopyrimidines (**PyMD**), 2,6-diaminopurines (**DP**) and adenine (**A**) were modified in the amino group with acyl derivatives to enhance the NH hydrogen bond donor properties and with benzyl and phenyl to provide a different steric environment of the module. Comparing the results with and without additive we found the designed effect. Some of the examined molecules diminished the ee (acyl derivatives) whereas the unsubstituted diaminopyridine (**Py-a**) notably improved the outcome of the reaction being almost as selective as catalyst **2**.[12] We also observed that unsubstituted diaminopurine and adenine increased the selectivity of the reaction (Figure 3).

We also explored the effect of **Py-a** on the performance of catalyst **2** through the Watson-Crick pairing between these compounds (green, Figure 4). It was found that in all cases the supramolecular adduct showed a positive effect on the yield and selectivity of the reaction compared to the result with catalyst **2** solely.

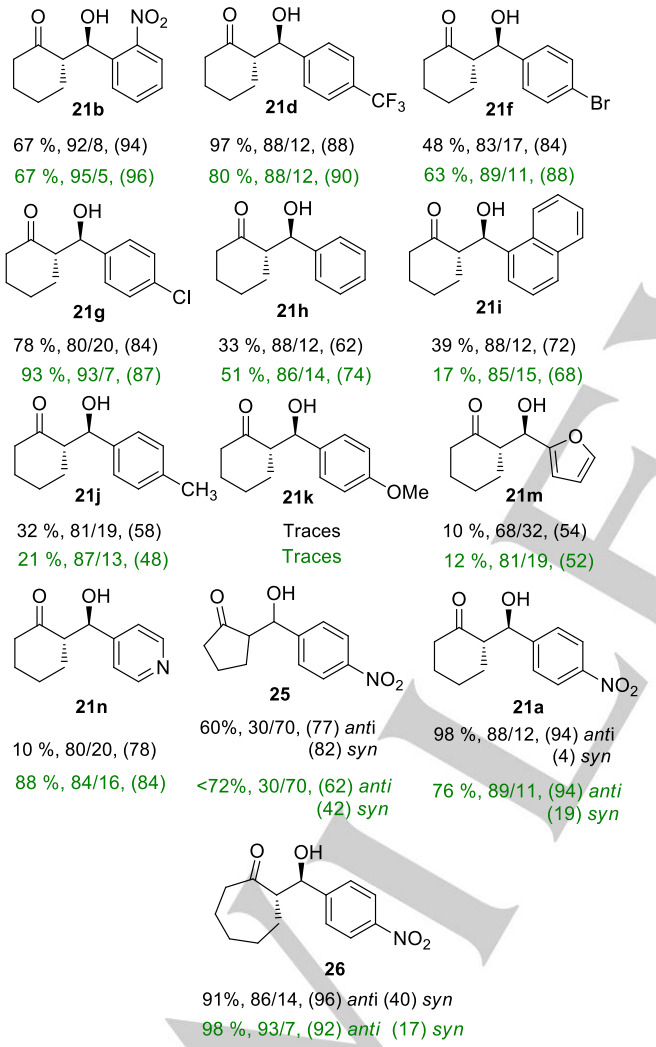
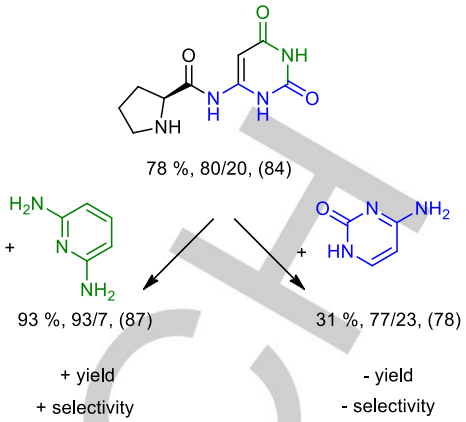


Figure 4. Effect of the complementary modules in the aldol reaction employing catalyst **2** (1st row, black) and **2** + **Py-a** (2nd row, green). It is shown yield, d.r. (*ee*) of each experiment. Reaction conditions: cyclohexanone (1.5 mmol), aldehyde (0.3 mmol), 5 % 1, 5 % module, DMF, 0.88 M, 120 h.



Scheme 5. Effect of two different complementary modules on the performance of catalyst **2**. It is shown yield, d.r. (*ee*) of each experiment. Reaction conditions: cyclohexanone (1.5 mmol), aldehyde (0.3 mmol), 5 % 1, 5% module, DMF, 0.88 M, 120 h.

We used cytosine to test the importance of the NH in the prolinamide on the reaction to obtain **21g**. The self-assemble hinders the prolinamide NH (together with N^1H and C^2=O) and as expected a drop in the yield and selectivity (31 % yield) was found. This drop in yield was more pronounced with aldol **25** where no reaction occurs. The addition of cytosine could be a strategy to change the amino catalyst from a hydrogen bond donor to only steric effect on the reaction without planning a new synthesis (Scheme 5).

We further provide insights on the binding between 5-aminouracil and **Py-a** by studying the stoichiometry and the binding between these compounds in a polar media with H-Bond acceptor capacity. The stoichiometry was addressed by Job's continuous variation method[13] using compound **8** and **Py-a** showed the expected 1:1 ratio between these species (Figure 5). We also used DOSY experiments in DMSO-*d*6 to study the hydrodynamic radius (r_H) of these compounds and mixtures **8**/**Py-a** (1:1 and 1:2) (See Figures S3-S6 in the ESI). The experiment showed that there is dissociated species in equilibrium with associated species with an increment of the r_H of the catalyst in the mixture of compounds.

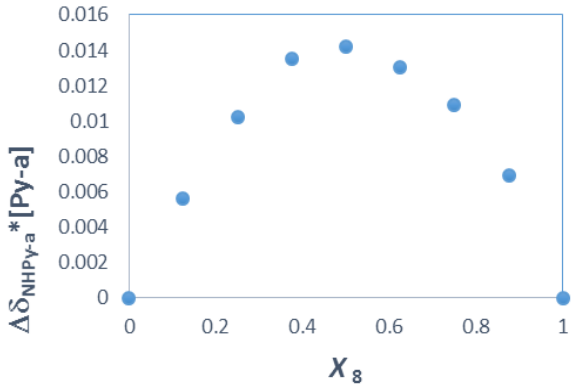
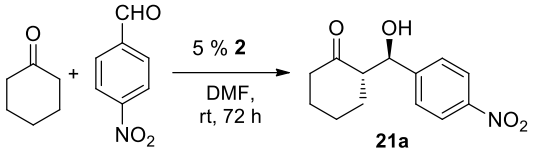


Figure 5. Job's plot analysis between **8** and **Py-a.**

On the other hand, the low solubility of catalyst **2** can be an advantage. In a 1.5 mmol scale of the model aldol reaction the catalyst can be precipitated with EtOAc at the end, recovered and used in another reaction. It was found that indeed the recovered catalyst can be used and recovered in two further experiments without loss in the enantioselectivity, albeit some erosion of the yield (Scheme 6).



Scheme 6. Scale up and recycling of catalyst **2**. It is shown yield, d.r. (*ee*) of each experiment.

Conclusion

We found that aminocatalysts that incorporate aminouracils can promote the aldol reaction in polar media. Among them, catalyst **2** with 6-aminouracil was very selective with aldehydes with electronwithdrawing groups. It was also shown the possibility to have a variety of catalyst by the assembly of complementary modules in solution through Watson-Crick pairing being the result with system **1**+**Py-a** almost as selective as catalyst **2**. Besides, the low solubility of the catalysts makes the recovery and recycle of the catalyst for 3 consecutive reactions.

Experimental section

General: All starting materials were purchased from Aldrich and used as received. THF, toluene, diethyl ether were distilled from sodium benzophenone ketyl. Flash column chromatography was carried out with silica gel 60 (70-230 mesh, 63-200 μm), TLC was performed with silica gel F254 plates. Melting points are uncorrected. 1H and 13C NMR were recorded at 300 MHz and 75 MHz respectively. Chemical shifts (δ) were reported in ppm downfield from TMS, and coupling constants were reported in Hertz. Mass spectra and HRMS (DART) were measured with a quadrupole and TOF mass spectrometers. CSP-HPLC analyses were performed using the indicated chiral column and UV detector. With hexane HPLC Fermont, EtOH-HPLC Fermont and isopropanol-HPLC Fermont.

General procedure for coupling of N-Boc-L-proline with aminouracils and aminopyrimidines. Synthesis of compounds 8, 11, 13, 15: *N*-Boc-L-proline (500 mg, 2.32 mmol, 1.0 equiv) was dissolved in 15 mL of CH_2Cl_2 under N_2 atmosphere. It was cooled to 0 °C and added *N*-methylmorpholine (NMM) (0.33 mL, 3.0 mmol, 1.3 equiv) and after 5 min, isobutyl chloroformate (0.4 mL, 2.8 mmol, 1.2 equiv) was slowly added. The reaction mixture was stirred 1 h at 0 °C, then NMM (0.33 mL, 3.0 mmol, 1.3 equiv) and a suspension of the corresponding aminouracil (2.32 mmol, 1.0 equiv) in 10 ml of DMF were added. The reaction was kept at 0°C for 2 h and at room temperature overnight. The solvent was evaporated and the residue purified by column chromatography with a mixture of solvents indicated in each compound.

(S)-1-tert-Butoxycarbonyl-2-((2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)carbamoyl)pyrrolidine (8): Purified by column chromatography (CH_2Cl_2/MeOH, 97:3). Obtained (557 mg, 74 %) of **8** as a white solid, mp 145 - 150 °C, $[\alpha]_D^{25}$ = -74.8 (*c* 0.22, MeOH), R_f = 0.48 (CH_2Cl_2/MeOH, 9:1). **^{1}H NMR** (300 MHz, DMSO-d_6, mixture of rotamers): δ 11.45 (br, 1H, Ura-NH^3), 10.61 (br, 1H, Ura-NH^1), 9.06 (s, 1H, CONH), 8.06 (s, 1H, Ura-H^6), 4.40 (br, 1H, C*H), 3.41-3.24 (m, 2H, CH_2N), 2.17-1.68 (m, 4H, CH_2CH_2), 1.39-1.29 (m, 9H, $(CH_3)_3$) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6, mixture of rotamers): δ 171.76/171.07 (CONH), 160.52 (Ura-C^4), 153.85/153.20 ($CO_2C(CH_3)_3$), 149.53(Ura-C^2), 128.78/128.33 (Ura-C^6), 113.18 (Ura-C^5), 78.88/78.64 ($C(CH_3)_3$), 59.62 (C*H), 46.75/46.55 (CH_2N), 30.87/28.76 (CH_2C*HNH), 28.09/27.92 ($(CH_3)_3$), 23.89/23.30 (NCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3283, 2829, 1680, 1656, 1244, 1201, 1173, 1128, 833, 717, 555, 520, 435 cm^{-1}. **MS-DART** (positive): *m/z* (%) 325 (25) [M + H]$^+$, 225(100), 269 (50). **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_{14}H_{21}N_4O_5$ 325.1506; found 325.1510.

(S)-1-tert-Butoxycarbonyl-2-((2,6-bisbenzyloxypyrimidyl-4-yl)carbamoyl)pyrrolidine (11): A small modification of the general procedure. Pyrimidine **10** was dissolved in CH_2Cl_2 instead of DMF. Purified by column chromatography (Hexane/EtOAc 4:1). Obtained (538 mg, 46 %) of **11** as a white solid, mp 53 – 55 °C, $[\alpha]_D^{25}$ = -33.2 (*c* 0.34, MeOH), R_f = 0.32 (Hexane/EtOAc 4:1 x2). **^{1}H NMR** (300 MHz, $CDCl_3$ mixture of rotamers): δ 9.38 (br, 0.5H, CONH), 8.39 (br, 0.5H, CONH), 7.45-7.30 (m, 11H, Ph-H, PyMD-H^5), 5.40 (s, 2H, OCH_2Ph), 5.36 (s, 2H, OCH_2Ph), 4.63-4.17 (m, 1H, C*H), 3.71-3.22 (m, 2H, CH_2N), 2.49-1.87 (m, 4H, CH_2CH_2), 1.47 (m, 9H, $(CH_3)_3$). **^{13}C NMR** (75 MHz, $CDCl_3$ mixture of rotamers): δ 172.82 (PyMD-C^2), 172.02/171.52 (CONH), 163.82 (PyMD-C^6), 158.77 (PyMD-C^4), 156.25/154.50 ($CO_2C(CH_3)_3$), 136.48 (*ipso*-Ph), 136.34 (*ipso*-Ph), 128.64 (Ph), 128.56 (Ph), 128.18 (Ph), 127.98 (Ph), 89.40 (PyMD-C^5), 81.26 ($C(CH_3)_3$), 69.30 (OCH_2Ph), 68.64 (OCH_2Ph), 62.11/61.20 (C*H), 47.33 (CH_2N), 30.97/29.81 (CH_2C*HN), 28.44 ($(CH_3)_3$), 24.59/24.10 (NCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3332-2879, 1670, 1574, 1511, 1397, 1333, 1161, 1117, 736, 695 cm^{-1}. **MS-DART** (positive): *m/z* (%) 505 (48) [M + H]$^+$, (308) 100. **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_{28}H_{33}N_4O_5$ 505.2445; found 505.2456.

(S)-1-tert-Butoxycarbonyl-2-((4-amino-2,6-bisbenzyloxypyrimidyl-5-yl)carbamoyl)pyrrolidine (13): A small modification of the general procedure. Pyrimidine **12** was dissolved in CH_2Cl_2 instead of DMF. Purified by column chromatography (CH_2Cl_2/MeOH, 97:3). Obtained (1000 mg, 83 %) of **13** as a pale yellow solid, mp 64 - 65 °C, $[\alpha]_D^{25}$ = -47.4 (*c* 0.27, MeOH), R_f = 0.4 (CH_2Cl_2/MeOH, 95:5). **^{1}H NMR** (300 MHz, $CDCl_3$ mixture of rotamers): δ 7.57-7.25 (m, 10H, Ph-H), 5.40-5.28 (m, 4H, OCH_2-Ph), 4.35-4.24(m, 1H, C*H), 3.45-3.34 (m, 2H, CH_2N), 2.26-1.56 (m, 4H, CH_2CH_2), 1.42 (s, 9H, $(CH_3)_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$ mixture of rotamers): δ 171.75 (CONH), 165.24 (PyMD-C^2), 162.13 (PyMD-C^6), 161.76 (PyMD-C^4), 155.86 ($CO_2C(CH_3)_3$), 137.03 (*ipso*-Ph), 128.52 (Ph), 128.43 (Ph), 128.07 (Ph), 127.89 (Ph), 93.92 (PyMD-C^5), 80.89 ($C(CH_3)_3$), 68.96/68.37 (OCH_2Ph), 60.77 (C*H), 47.31(CH_2N), 29.79/29.30 (CH_2C*HN), 28.45 ($(CH_3)_3$), 24.70 (NCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3435, 3291, 3148, 2958, 1692, 1640, 1577, 1514, 1419, 1350, 1240, 1138, 1042, 961, 727, 692, 438 cm^{-1}. **MS-DART** (Positive): *m/z* (%) 520 (100) [M + H]$^+$. **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_{28}H_{34}N_5O_5$ 520.2554; found 520.2552.

(S)-1-tert-Butoxycarbonyl-2-((2,4-dioxo-1,3-dimethyl-1,2,3,4-tetrahydro-pyrimidin-5-yl)carbamoyl)pyrrolidine (15): Purified by column chromatography (CH_2Cl_2/MeOH, 100-0 to 97:3). Obtained (367 mg, 43 %) of **15** as a pale yellow foam, mp 130 - 133 °C, $[\alpha]_D^{25}$ = -0.73 (*c* 0.27, $CHCl_3$), R_f = 0.5 (CH_2Cl_2/MeOH, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 (s, 1H, CONH), 5.75 (s, 2H, Ura-NH_2), 4.24-4.20 (m, 1H, C*H), 3.58-3.48(m, 2H, CH_2N), 3.41 (s, 3H, Ura-N$^1CH_3$), 3.28 (s, 3H, Ura-N$^3CH_3$), 2.31-1.82 (m, 4H, CH_2CH_2), 1.43 (s, 9H, $(CH_3)_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.78 (CONH), 160.58 (Ura-C^4), 155.68 ($CO_2C(CH_3)_3$), 151.33 (Ura-C^6), 150.90 (Ura-C^2), 88.37(Ura-C^5), 80.84($C(CH_3)_3$), 61.20 (C*H), 47.54 (CH_2N), 30.22 (CH_2C*HN), 29.66 (Ura-N$^1CH_3$), 28.53($(CH_3)_3$), 28.27 (Ura-N$^3CH_3$), 24.77 (NCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3324-2881, 1622, 1588, 1504, 1403, 1160, 755, 495 cm^{-1}. **MS-DART** (Positive): *m/z* (%) 368 (100) [M + H]$^+$. **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_{16}H_{26}N_5O_5$ 368.1928; found 368.1938.

General procedure for the Boc removal. Catalysts 1, 3b and 4: *N*-Boc-proline derivative (2.36 mmol, 1.0 equiv) was dissolved in 4 mL of CH_2Cl_2

and added 2.3 mL (30.1 mmol, 13 equiv) of trifluoroacetic acid. The reaction was stirred for 2 - 3 h. The reaction mixture was concentrated and the solid washed with EtOAc to obtain the pure catalysts **1**, **3b**, **4**.

(S)-N-(2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-prolinamide trifluoroacetate (1): Obtained (776 mg, 97 %) of **1** as a white solid, mp 230 - 234 °C, $[\alpha]_D^{25}$ = -33.3 (*c* 0.20, MeOH), R_f = 0.39 (MeOH/*i*-PrOH/NH_4OH (3:7:1). **^{1}H NMR** (300 MHz, DMSO-d_6): δ 11.49 (s, 1H, Ura-NH^3), 10.88 (br, 1H, Ura-NH^1), 9.90 (s, 1H, CONH), 9.18 (br, 2H, N^+H_2), 8.04 (s, 1H, Ura-H^6) 4.49-4.45 (m, 1H, C*H), 3.28-3.18 (m, 2H, CH_2NH), 2.37-2,29 (m, 1H, CH_2C*HNH), 1.98-1.72 (m, 3H, CH_2CH_2) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ 167.49 (CONH), 160.57 (Ura-C^4), 158.56 (q, *J* = 31.3 Hz, F_3CCO), 149.76 (Ura-C^2), 131.41 (Ura-C^6), 117.21 (q, J =299.2 Hz, F_3C), 112.33 (Ura-C^5), 59.20 (C*H), 45.87 (CH_2NH), 29.90 (CH_2C*HNH), 23.58 (NHCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3283-2829, 1651, 1556, 1201, 1173, 1128, 833, 717, 555, 520, 435 cm^{-1}. **MS-DART** (positive): *m/z* (%) 225 (35) [M + H]$^+$, 115 (100), 116 (40). **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_9H_{13}N_4O_3$ 225.0982; found 225.0988.

(S)-2-((2,4-Dioxo-1,3-dimethyl-1,2,3,4-tetrahydro-pyrimidin-5-yl)carbamoyl)pyrrolidine trifluoroacetate (3b): Obtained (873 mg, 97%) of **3b** as a beige solid, mp 144 - 146 °C, $[\alpha]_D^{25}$ = +1.21 (*c* 0.66, MeOH), R_f = 0.3 (MeOH/*i*-PrOH/NH_4OH (3:7:1). **^{1}H NMR** (300 MHz, DMSO-d_6): δ 9.04 (s, 2H, NH), 6.82 (s, 1H, CONH), 4.35-4.31 (m, 1H, C*H), 3.32 (s, 3H, Ura-N^1CH_3), 3.26-3.22 (m, 2H, CH_2NH), 3.11 (s, 3H, Ura-N^3CH_3), 2.38-2.29 (m, 1H, CH_2C*HNH), 2.10-1.90 (m, 3H, CH_2CH_2) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ 169.34 (CONH), 159.02 (Ura-C^4), 152.28 (Ura-C^6), 150.59 (Ura-C^2), 86.02 (Ura-C^5), 59.25 (C*H), 45.92 (CH_2NH), 30.08 (Ura-N^1CH_3), 29.58 (CH_2C*HNH), 27.52 (Ura-N^3CH_3), 23.62 (NHCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3195, 1672, 1589, 1507, 1196, 1176, 1125, 833, 799, 757, 719, 496 cm^{-1}. **MS-DART** (Positive): *m/z* (%) 268 (100) [M + H]$^+$. **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_{11}H_{18}N_5O_3$ 268.1404; found 268.1409.

(S)-1-(2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)methylpyrrolidine trifluoroacetate (4): Obtained (864 mg, 96 %) of **4** as a white solid mp 180 -182 °C, $[\alpha]_D^{25}$ = -9.6 (*c* 0.23, MeOH), R_f = 0.3 (MeOH/*i*-PrOH/NH_4OH (3:7:1). **^{1}H NMR** (300 MHz, MeOH-d_4): δ 7.60 (d, *J* = 7.9Hz, 1H, Ura-C^6), 5.69 (d, *J* = 7.9 Hz, Ura-C^5), 4.17 (dd, *J* = 15.1, 8.8 Hz, 1H, C*HCH_2N), 4.01 (dd, *J* = 15.1, 3.5 Hz, 1H, C*HCH_2N), 3.85-3.76 (m, 1H, C*H), 3.45-3.36 (m, 1H, CH_2NH), 3.30-3.21 (m, 1H, CH_2NH), 2.30-2.20 (m, 1H, CH_2C*H), 2.13-1.97(m, 2H, CH_2CH_2C*H), 1.83-1.70 (m, 1H, CH_2C*H). **^{13}C NMR** (75 MHz, MeOH-d_4): δ 166.42 (Ura-C^4), 153.68 (Ura-C^2), 146.87 (Ura-C^6), 103.16 (Ura-C^5), 61.75 (C*H), 50.31 (C*HCH_2N), 46.62 (CH_2NH), 28.51 (CH_2C*HNH), 23.48 (NHCH_2CH_2). **IR** (KBr): $\tilde{\nu}$ = 3029, 1689, 1662, 1179, 1135, 834, 800, 719, 521, 423 cm^{-1}. **MS-DART** (positive): *m/z* (%) 196 (100) [M + H]$^+$. **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_9H_{14}N_3O_2$ 196.1080; found 196.1085.

General procedure for the Boc and OBn removal. Catalysts 2 and 3a: Prolinamide (2.38 mmol, 1 equiv) was dissolved in CH_2Cl_2 (4.5 mL). Trifluoroacetic acid (26.18 mmol, 11 equiv) was added and the reaction was stirred for 2 h. The solvent was evaporated, and the solid was dissolved in MeOH (30 mL). It was added Pd/C (10%) and the reaction was stirred for 3 h under H_2 atmosphere. The reaction mixture was filtered through Celite, washed with CH_2Cl_2-MeOH 1:1 (150 mL) and the solvent was evaporated. The product was washed with EtOAc to obtain the pure catalysts **2**, **3a**.

(S)-N-(2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-6-yl)-prolinamide trifluoroacetate (2): Obtained (745 mg, 92 %) of a **2** as a white solid, mp 260 °C decomp., $[\alpha]_D^{25}$ = -16.1 (*c* 0.23, MeOH), R_f = 0.5 (MeOH/iPrOH/NH_4OH 3:7:1 x2). **^{1}H NMR** (300 MHz, DMSO-d_6): δ 10.31 (br, 5H, NH), 5.84(s, 1H, Ura-C^5), 4.37-4.32 (m, 1H, C*H), 3.25-3.20 (m, 2H, CH_2NH), 2.37-2.28 (m, 1H, CH_2C*HNH), 2.01-1.87 (m, 3H, CH_2CH_2) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ 169.27 (CONH), 164.53 (Ura-C^4), 158.56 (q, *J* = 31.3 Hz, F_3CCO), 150.32 (Ura-C^2), 147.09 (Ura-C^6), 117.21 (q, J = 299.2 Hz, F_3C), 86.35 (Ura-C^5), 60.01 (C*H), 46.00 (CH_2NH), 29.20 (CH_2C*HNH), 23.61 (NHCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 2966-2794, 1660, 1569, 1200, 1132, 832, 720, 535, 417 cm^{-1}. **MS-DART** (positive): *m/z* (%) 225 (100) [M + H]$^+$. **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_9H_{13}N_4O_3$ 225.0982; found 225.0987.

(S)-2-((2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)carbamoyl)pyrrolidine trifluoroacetate (3a): Obtained (799 mg, 95 %) of a **3a** as a white solid, mp 220°C decom., $[\alpha]_D^{25}$ = +1.11 (*c* 0.27, MeOH), R_f = 0.2 (MeOH/*i*-PrOH/NH_4OH, 3:7:1). **^{1}H NMR** (300 MHz, DMSO-d_6): δ 10.51 (br, 1H, NH), 10.37 (s, 1H, NH), 9.20 (br, 1H,NH), 8.91 (s, 1H, NH), 6.40 (s, 1H, CONH), 4.28-4.23 (m, 1H, C*H), 3.24-3.20 (m, 2H, CH_2NH), 2.39-2.28 (m, 1H, CH_2C*HNH), 2.07-1.82 (m, 3H, CH_2CH_2) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ 168.85 (CONH), 161.18 (Ura-C^4), 151.88 (Ura-C^6), 149.82 (Ura-C^2), 85.41 (Ura-C^5), 59.24 (C*H), 45.86 (CH_2NH), 29.45 (CH_2C*HNH), 23.64 (NHCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3174-2984, 1671, 1607, 1196, 1130, 798, 763, 720, 531 cm^{-1}. **MS-DART** (Positive): *m/z* (%) 240 (90) [M + H]$^+$, 116 (100), 89 (60). **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_9H_{14}N_5O_3$ 240.1091; found 240.1099.

Synthesis of pyrimidines 10 and 12. 4-amino-2,6-dibenzyloxy-pyrimidine (10): A suspension of 460 mg (11.6 mmol, 4.5 equiv) of sodium hydride (60% wt, previously washed with anhydrous Et_2O) in 30 mL of anhydrous toluene was slowly added 2 mL (19.0 mmol, 7.3 equiv) of benzyl alcohol. When the hydrogen evolution stopped, it was added 800 mg (2.6 mmol, 1.0 equiv) of 6-amino-2,4-dichloropyrimidine (**9**). The reaction mixture was refluxed for 16 h under nitrogen atmosphere. It was cooled to room temperature, neutralized with AcOH and the solvent was evaporated. The product was purified by column chromatography (Hexane/EtOAc 4:1). A white solid was obtained (995 mg, 66%), mp 95 - 96, lit.[14] 74 - 76 °C, R_f = 0.23 (Hexane/EtOAc 4:1 x2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47-7.31 (m, 10H, Ph-H), 5.51 (s, 1H, PyMD-H^5), 5.37-5.36 (m, 4H, OCH_2Ph), 5.05 (br, 2H, NH_2) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.32 (PyMD-C^2), 166.05 (PyMD-C^6), 164.59 (PyMD-C^4), 136.97 (*ipso*-Ph), 136.75 (*ipso*-Ph), 128.46 (Ph-H), 128.33 (Ph-H), 127.95 (Ph-H), 127.90 (Ph-H), 127.89 (Ph-H), 127.77 (Ph-H), 81.44 (PyMD-C^5), 68.51 (OCH_2Ph), 67.81 (OCH_2Ph) ppm. **IR** (KBr): $\tilde{\nu}$ = 3480, 3291, 3156, 1629, 1566, 1407, 1344, 1202, 796, 739, 690 cm^{-1}. **MS-DART** (positive): *m/z* (%) 308 (100) [M + H]$^+$. **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_{18}H_{18}N_3O_2$ 308.1393; found 308.1399.

4,5-diamino-2,6-bis(benzyloxy)pyrimidine (12): Pyrimidine **10** (500 mg, 1.63 mmol, 1.0 equiv) was dissolved in DMSO (4 mL) and isoamyl nitrite[15] (230 mg, 1.95 mmol, 1.2 equiv) was added. The reaction mixture was stirred for 4 h. Water (8 mL) was added and the suspension was stirred for a further 2 h. The blue solid was filtered and washed with water. It was dissolved in CH_2Cl_2, dried over Na_2SO_4, and concentrated to dryness. The 4-amino-2,6-bisbenzyloxy-5-nitrosopyrimidine was purified by column chromatography (CH_2Cl_2). A blue solid was obtained (435 mg, 79%), mp 136 - 138 °C, lit.[16] 140 - 142 °C, R_f = 0.5 (CH_2Cl_2/MeOH 97:3). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.13 (br, 1H, NH_2), 7.55-7.32 (m, 10H, Ph-H), 6.04 (br, 1H, NH_2), 5.76 (s, 2H, OCH_2Ph), 5.45 (s, 2H, OCH_2Ph) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.30 (PyMD-C^2), 165.90 (PyMD-C^6), 149.76 (PyMD-C^4), 140.82 (PyMD-C^5), 135.54 (*ipso*-Ph), 135.49 (*ipso*-Ph), 128.77 (Ph), 128.63 (Ph), 128.58 (Ph), 128.36 (Ph), 128.29 (Ph), 70.53 (CH_2), 70.10 (CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3359-2956, 1625, 1522, 1353, 1307, 1202, 1157, 955, 794, 744, 693, 661 cm^{-1}. **MS-DART** (Positive): *m/z* (%) 337 (100) [M + H]$^+$. **HRMS** (DART/TOF): m/z [M+H]$^+$ calcd for $C_{18}H_{17}N_4O_3$ 337.1295; found 337.1305. The nitroso compound was reduced adapting a literature procedure.[17] Zinc powder (193.4 mg, 2.95 mmol, 5.0 equiv) was added to a solution of 4-amino-2,6-bisbenzyloxy-5-nitrosopyrimidine (200 mg, 0.59 mmol, 1.0 equiv) in acetic acid (4 mL), the suspension was stirred for 20 min. A change in color from blue to yellow was observed. The reaction mixture was filtered over Celite and washed with EtOAc (20 mL). The product was concentrated to dryness and purified by column chromatography (CH_2Cl_2/MeOH 95:5). A yellow solid was obtained (175 mg, 91%), mp 78 - 80 °C, R_f = 0.39 (CH_2Cl_2/MeOH 97:3). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43-7-25 (m, 10H, Ph-H), 5.36 (s, 2H, CH_2), 5.29 (s, 2H, CH_2) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 160.75 (PyMD-C^2), 158.50 (PyMD-C^6), 158.40 (PyMD-C^4), 137.43 (*ipso*-Ph), 137.04 (*ipso*-Ph), 128.61 (Ph), 128.41 (Ph), 128.15 (Ph), 127.98 (Ph), 127.78 (Ph), 102.53 (PyMD-C^5), 68.63 (CH_2), 68.30 (CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3325, 3174, 1654, 1582, 1451, 1405, 1340, 1322, 1200, 1030, 880, 739, 689, 589 cm^{-1}. **MS-DART**

(Positive): *m/z* (%) 323 (100) $[M + H]^+$. **HRMS** (DART/TOF): m/z $[M+H]^+$ calcd for $C_{18}H_{19}N_4O_2$ 323.1502; found 323.1510.

Synthesis of precursor 18. (S)-1-tert-Butoxycarbonyl-2-bromomethyl-pyrrolidine. (16): *N*-Boc-OTs prolinol (7.1 g, 20 mmol, 1 equiv) and LiBr (5.16 g, 30 mmol, 3.0 equiv) were dissolved in 40 mL of acetone. The reaction mixture was refluxed for 6 h (it was observed the formation of a precipitate). It was cooled and concentrated. The residue was dissolved in 40 mL of DCM and 40 mL of water and the aqueous phase was washed with DCM (30 mL x 2) The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4 anh) and concentrated. The product was purified by column chromatography by a mixture Hexane/EtOAc 9:1 obtaining 5.0 g (95 % yield) of a colorless oil, $[\alpha]_D^{25}$ = -35.3 (*c* 0.32, DCM), lit.[18] $[\alpha]_D^{25}$ = -40.5 (*c* 0.80, $CHCl_3$), R_f = 0.66 (Hexane/EtOAc, 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$ mixture of rotamers): δ 4.03-3.96 (m, 1H, C*H), 3.65-3.52 (m, 1H, CH_2N), 3.43-3.23 (m, 3H, CH_2N, CH_2Br), 1.98-1.77 (m, 4H, CH_2CH_2), 1.45 (s, 9H, $(CH_3)_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$ mixture of rotamers): δ 154.59 ($NCO_2C(CH_3)_3$), 80.02/79.71 ($C(CH_3)_3$), 58.01/57.88 (C*H), 47.45/46.99 (CH_2N), 34.95 (CH_2Br), 30.15/29.43 (CH_2C*HN), 28.58 ($(CH_3)_3$), 23.65/22.87 (NCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 2973, 1757, 1689, 1386, 1167, 110, 771, 649, 549 cm^{-1}. **MS-DART** (positive): *m/z* (%) 264 (54) $[M + H]^+$, 266 (53), 206 (100), 207 (99). **HRMS** (DART/TOF): m/z $[M+H]^+$ calcd for $C_{10}H_{19}BrNO_2$ 264.0593; found 264.0595.

3-Benzoyluracil (17): Uracil (500 mg, 4.46 mmol, 1 equiv), benzoyl chloride (1.2 ml, 10.3 mmol, 2.3 equiv), dry acetonitrile (4.5 mL, 86 mmol, 19.3 equiv) y dry pyridine (1.78 mL, 22.1 mmol, 5.0 equiv) were stirred together at room temperature. After 24h, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (25 mL) and water (25 mL) was added. The organic layer was separated and evaporated. The residue was dissolved in a mixture of aqueous K_2CO_3 (0.5 M, 5 mL) and dioxane (10 mL). After 30 min, the pH is adjusted to 5 with addition of acetic acid. The solvent was evaporated and the residue was allowed to stir with saturated solution $NaHCO_3$ (25 mL). After 1 h, the product was filtered and washed with cold water (2.5 mL x 3). The product was recrystallized from water-acetone. A white solid was obtained (645 mg, 70 %), mp 174 - 176 °C, lit.[19] 173.5 - 175.8 °C, R_f = 0.46 (CH_2Cl_2/MeOH, 9:1). **^{1}H NMR** (300 MHz, DMSO-d_6): δ 11.63 (br, 1H, Ura-NH), 7.97 (m, 2H, Ph-H, Ura-C^6), 7.78 (m, 1H, Ph-H) 7.67-7.58 (m, 3H, Ph-H), 5.74 (d, *J* = 7.7 Hz, 1H, Ura-C^5) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ 169.99 (COPh), 162.91 (Ura-C^4), 150.05 (Ura-C^2), 143.28 (Ura-C^6), 135.36 (Ph), 131.33 (*ipso*-Ph), 130.17 (Ph), 129.47 (Ph), 100.07 (Ura-C^5) ppm. **IR** (KBr): $\tilde{\nu}$ = 3271-2965, 1745, 1702, 1649, 1595, 1413, 1229, 1180, 932, 783, 677, 531, 450 cm^{-1}. **MS-DART** (positive): *m/z* (%) 217 (72) $[M + H]^+$, 105 (100), 218 (10) **HRMS** (DART/TOF): m/z $[M+H]^+$ calcd for $C_{11}H_9N_2O_3$ 217.0607; found 217.0612.

(S)-1-tert-Butoxycarbonyl-2-((2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-1-yl)methyl)pyrrolidine (18): It was adapted from a literature procedure.[20] Pyrrolidine **16** (1186 mg, 4.48 mmol, 0.8 equiv), uracil **17** (1213 mg, 5.61 mmol, 1.0 equiv), K_2CO_3 (775.3 mg, 5.61 mmol, 1.0 equiv) and TBAI (207 mg, 0.56 mmol, 0.1 equiv) were dissolved in dry DMF (15 mL). The reaction mixture was allowed to stir at 70-80 °C for 24 h. The reaction crude was concentrate to dryness. The product was purified by two column chromatographies (CH_2Cl_2/MeOH, 95:5 and Hexane/EtOAc, 1:1). The unprotected product **18** (440 mg, 33 %) and the protected product **30** (859 mg, 48 %) were obtained as white solid. mp 95 - 96 °C, $[\alpha]_D^{25}$ = + 90.8 (*c* 0.25, MeOH) R_f = 0.6 (CH_2Cl_2/MeOH, 95:5 x2) or 0.33 (EtOAc). **^{1}H NMR** (300 MHz, DMSO-d_6 mixture of rotamers): δ 11.18 (br, 1H, Ura-NH), 7.50-7.44 (m, 1H, Ura-H^6), 5.52-5.42 (m, 1H, Ura-H^5), 4.10 (m, 1H, C*H), 3.83-3.75 (m, 1H, CH_2N), 3.43-3.36 (m, 1H, CH_2N), 3.26-3.25 (m, 2H, C*HCH_2N), 1.98-1.55 (m, 4H, CH_2CH_2) 1.31-1.29 (m, 9H, $C(CH_3)_3$) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6 mixture of rotamers): δ 163.99 (Ura-C^4), 153.97/153.70 ($CO_2C(CH_3)_3$), 151.30/151.13 (Ura-C^2), 146.16/145.72 (Ura-C^6), 100.31 (Ura-C^5), 78.61/78.46 ($C(CH_3)_3$), 55.05/54.35 (C*H), 50.55 (CH_2N), 45.95/45.36 (C*HCH_2N), 28.05/27.91 ($(CH_3)_3$), 27.35 (C*HCH_2), 23.05/22.00 (NCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3176-2879, 1749, 1669, 1389, 1168, 764, 548, 422 cm^{-1}. **MS-DART** (positive): *m/z* (%) 296 (15) $[M + H]^+$, 240 (38), 88 (50), 196 (100). **HRMS** (DART/TOF): m/z $[M+H]^+$ calcd for $C_{14}H_{22}N_3O_4$; 296.3416 found 296.1604.

Synthesis of AC 5. (S)-1-tert-Butoxycarbonyl-2-(2-amino-6-chloro-purine-9-yl) methylpyrrolidine (20): The bromopyrrolidine **16** (947 mg, 3.6 mmol, 2 equiv) was dissolved in anhydrous DMF (30 mL). It was added 2-amino-6-chloropurine **19** (300 mg, 1.8 mmol, 1 equiv) and K_2CO_3 (746 mg, 5.4 mmol, 3 equiv). The reaction mixture was stirred at 70-80 ° C for 6 h. The reaction crude was concentrate to dryness and was dissolved in DCM (100 mL), washed with water (40 mL), dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (CH_2Cl_2/MeOH 100:0 to 99:1). A white solid was obtained (318 mg, 50 %), mp 75 - 78 °C, $[\alpha]_D^{25}$ = -85.2 (*c*, 0.27, DCM), R_f = 0.48 (CH_2Cl_2/MeOH 97:3 x2). **^{1}H NMR** (300 MHz, $CDCl_3$ mixture of rotamers): δ 7.69 (s, 1H, Pur-H^8), 5.25 (br, 2H, NH_2), 4.41-4.09 (m, 3H, C*H, PurN^9-CH_2), 3.29-3.18 (m, 2H, CH_2N), 1.97-1.59 (m, 4H, CH_2CH_2), 1.45 (s, 9H, $(CH_3)_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$ mixture of rotamers): δ 159.29 (Pur-C^2), 155.01 (CO), 154.40 (Pur-C^6), 151.40 (Pur-C^4), 143.17/142.70 (Pur-C^8), 125.19 (Pur-C^5), 80.23 ($C(CH_3)_3$), 57.25 (C*H), 47.15/46.43 (NCH_2), 45.16 (PurN^9-CH_2), 29.21 (C*HCH_2), 28.53 ($CH_3)_3$), 23.67/22.92 (NCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ =3325, 3208, 2972-2881, 1679, 1608, 1558, 1392, 1159, 1102, 908, 771 cm^{-1}. **MS-DART** (positive): *m/z* (%) 353 (100) $[M + H]^+$. **HRMS** (DART/TOF): m/z $[M+H]^+$ calcd for $C_{15}H_{22}ClN_6O_2$ 353.1487; found 353.1497.

(S)-2-(2-amino-6-oxo-1H-purin-6(1H)-one-9-yl)methylpyrrolidine hydrochloride (5): Compound **20** (300 mg, 0.8 mmol, 1.0 equiv) was dissolved in 6 M HCl (1.5 mL) and heated to 70-80 °C with stirring for 2 h. The solvent was evaporated and the residue was washed with EtOAc. The hydrochloride salt was obtained as a white solid (204 mg, 83 %), mp 203 - 207 °C, $[\alpha]_D^{25}$ = +31.9 (c 0.37, MeOH), R_f = 0.33 (MeOH/*i*PrOH/NH_4OH 3:7:1 x 2). **^{1}H NMR** (300 MHz, DMSO-d_6): δ 11.91 (br, 1H, Pur-H^1), 10.83 (br, 1H), 9.96 (br, 2H, N^+H_2), 9.22 (s, 1H, Pur-H^8), 7.49 (br, 2H, NH_2), 4.73-4.65 (m, 1H, NCH_2C*H), 4.49-4.43 (m, 1H, CH_2C*H), 3.98 (m, 1H, C*H), 3.26-3.13 (m, 2H, CH_2NH), 2.14-1.66 (m, 4H, CH_2CH_2) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ.155.69 (Pur-C^6), 153.48 (Pur-C^2), 149.90 (Pur-C^4), 137.19 (Pur-C^8), 108.29 (Pur-C^5), 57.72 (C*H), 44.86 (C*HCH_2N), 44.42 (CH_2N), 27.57 (C*HCH_2), 22.84 (NCH_2CH_2) ppm. **IR** (KBr): $\tilde{\nu}$ = 3335-2491, 1680, 1629, 1596, 1360, 1176, 1064, 843, 663, 543, 501 cm^{-1}. **MS-DART** (positive): *m/z* (%) 235 (100) $[M + H]^+$. **HRMS** (DART/TOF): m/z $[M+H]^+$ calcd for $C_{10}H_{15}N_6O$ 235.1301; found 235.1306.

Synthesis of AC 6. (S)-N-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-2-amino-3-phenylpropionamide (6): *N*-Cbz-L-phenylalanine (1.0 g, 3.34 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 ml) at 0°C under N_2 atmosphere. NMM (0.5 mL, 4.35 mmol, 1.3 equiv) was added, and after 5 min, isobutyl chroroformate (0.52 mL, 4.0 mmol, 1.2 equiv) was slowly added. The reaction mixture was stirred for 1 h at 0 °C. Again, NMM (0.6 mL, 5.3 mmol, 1.6 equiv) and a suspension of uracil (427 mg, 3.34 mmol, 1.0 equiv) in DMF (10 mL) were added. The reaction was stirred at 0 °C for 2 h and at room temperature overnight. The solvent was evaporated and filtered through a short silica column with CH_2Cl_2/MeOH (8:2). The fraction with R_f = 0.34 (CH_2Cl_2/ MeOH 97:3 x2) was concentrated and used in the next reaction. The coupled product was dissolved in MeOH-DMF 1:1 (40 ml), 10 percent Pd/C (98 mg) was added. The reaction was stirred at room temperature under hydrogen atmosphere. After 24h, the reaction mixture was filtered through Celite, washed with CH_2Cl_2/MeOH 1:1 (30 mL), and concentrated under vacuum. The product was recrystallized of EtOH/MeOH. A beige solid was obtained (68 %, 448 mg), mp > 270 °C, $[\alpha]_D^{25}$ = +66.3 (c 0.19, MeOH), R_f = 0.55 (MeOH). **^{1}H NMR** (300 MHz, DMSO-d_6): δ 11.46 (br, 1H, Ura-NH^6), 10.89 (br, 1H, Ura-NH^1), 9.82 (s, 1H, CONH), 8.48 (br, 2H, NH_2), 8.02 (s, 1H, Ura-H^6), 7.32-7.24 (m, 5H, Ph-H), 4.43-4.39 (m, 1H, C*H), 3.16-3.02 (m, 2H, $PhCH_2$) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ 167.23 (CONH), 160.38 (Ura-C^4), 149.55 (Ura-C^2), 134.88 (*ipso*-Ph), 130.39 (Ura-C^6), 129.57 (Ph), 128.45 (Ph), 127.12 (Ph), 112.36 (Ura-C^5), 53.29 (C*H), 37.03 ($PhCH_2$) ppm. **IR** (KBr) $\tilde{\nu}$ = 3320-2912, 1722, 1670, 1542, 1454, 1236, 833, 750, 702, 539 cm^{-1}. **MS-DART** (positive): m/z (%) 275 (100) $[M + H]$+, **HRMS** (DART/TOF): m/z $[M+H]$+ calcd for $C_{13}H_{15}N_4O_3$ 275.1138; found 275.1147.

General procedures for the aldol reaction: In a screw-thread vial catalyst (0.015 mmol, 0.05 equiv) was disolved in DMF (0.19 mL). It was added cyclohexanone (0.15 mL, 1.5 mmol, 5 equiv) and stirred 5 min.

Aldehyde (0.3 mmol, 1.0 equiv) was added and the reaction mixture was stirred 72 h (Tables 1-2, Figure 3 and Scheme 6) or 120 h (Tables 3-4, Figure 4 and Scheme 5) at room temperature. It was concentrated to dryness and purified by column chromatography Hexane/EtOAc (8:2). For the complementary modules evaluation it was added the diaminocompound **Py**, **PyMD**, **Pur** or **A** (0.015 mmol, 0.05 equiv) and stirred 1h prior the addition of the aldehyde.

Acknowledgments

We thank DGAPA-UNAM (grant IN207318) and CONACyT (grant 254014) for financial support. K. M. R.-P. gratefully acknowledge CONACyT/México for Ph.D. scholarship (No. 273441). We also thank L. C Márquez, E. García and L. M. Ríos for HPLC analysis, F. J. Pérez, L. Velasco, M. C. García for mass analysis and, M. A. Peña, E. Huerta, H. Ríos, R. Gaviño for recording NMR experiments, R. Patiño and M. P. Orta for IR and optical rotation measurements. DOSY studies made use of UNAM´s NMR lab: LURMN at IQ-UNAM, which is funded by CONACyT Mexico (Project: 0224747), and UNAM.

Keywords: Organocatalysis • Self-assembly • Aldol reaction • Supramolecular catalyst • Pyrimidines.

[1] D.W.C. MacMillan, *Nature*, **2008**, *455*, 304–308.

[2] M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.,* **2011**, *47*, 632–649.

[3] (a) A. Armstrong, R. A. Boto, P. Dingwall, J. Contreras-García, M. J. Harvey, N. J.; Mason, H. S. Rzepa, *Chem. Sci.*, **2014**, 5, 2057–2071. (b) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc*, **2003**, *125*, 2475–2479.

[4] R. Rios, *Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes*, John Wiley & Sons: New Jersey, 2013.

[5] (a) G. K. Mittapalli, Y. M. Osornio, M. A. Guerrero, K. R. Reddy, R. Krishnamurthy, A. Eschenmoser, *Angew. Chem. Int. Ed.* **2007**, *46*, 2478–2484. (b) M. Hernández-Rodríguez, J. Xie, Y. M. Osornio, R. Krishnamurthy, *Chem. Asian J.* **2011**, *6*, 1252– 1262.

[6] (a) J. Chiba, M. Inouye, *Chem. Biodiversity*, **2010**, 7, 259–282. (b) R. Krishnamurthy *Acc. Chem. Res.*, **2012**, *45*, 2035–2044.

[7] (a) M. L. Clarke, J. A Fuentes, *Angew. Chem. Int. Ed*., **2007**, *46*, 930–933. (b) T. Mandal, C.-G. Zhao, *Angew. Chem. Int. Ed.*, **2008**, *47*, 7714-7717. (c) A. Demir, S. Eymur, *Tetrahedron: Asymmetry,* **2010**, *21*, 112-115. (d) J. A. Fuentes, T. Lebl, A. M.Z. Slawin, M. L. Clarke, *Chem. Sci.,* **2011**, *2*, 1997–2005. (c) S. Muramulla, C.-G. Zhao, *Tetrahedron Lett.*, **2011**, 52, 3905–3908. (d) N. K. Rana, H. Huang, J. C.-G. Zhao, *Angew. Chem. Int. Ed.,* **2014**, 53, 7619–7623.

[8] (a) M. Vaquero, L. Rovira, A. Vidal-Feran, *Chem. Commun.,* **2016**, *52*, 11038-11051. (b) L. Hong W. Sun, D. Yang, G. Li, R. Wang, *Chem. Rev.,* **2016**, *116*, 4006–4123.

[9] S. Piovesana, D. M. Scarpino, M. Bella, *Angew. Chem. Int. Ed.* **2011**, *50*, 6216–6232.

[10] (a) Jr. E.C. Taylor, H. M. Loux, E. A. Falco, G. H. Hitchings, *J. Am. Chem. Soc*., **1995**, *77*, 2243–2248. (b) E. Procházková, P. Jansa, A. Březinová, L. Čechová, H. Mertlíková-Kaiserová, A. Holý, M. Dračínský, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 20, 6405–6409.

[11] (a) M. Orlandi, M. Benaglia, L. Raimondi, G. Celentano, *Eur. J. Org. Chem*. **2013**, 2346-2354. (b) L. Zheng-Yi, C. Yuan, Z. Chong-Quian, Y. Yue, W. Liang, S. Xiao-Qiang, *Tetrahedron*, **2017**, *73*, 78–85. (c) B. Trost, C. Brindle, *Chem. Soc. Rev*.; **2010**, 39, 1600–1632. (d) T. Naresh, T. Pavan, K. Haribabu, S. Chandrasekhar, *Tetrahedron: Asymmetry*, **2014**, *25*, 1340–1345.

[12] This may be attributable to the more basic character of pyrimidine than the others species.

[13] L. Fielding, *Tetrahedron*, **2000**, *56*, 6151.

[14] A. Marchal, M. Nogueras, A. Sánchez, J. Low, L. Naesens, E. De Clercq, M. Melguizo, *Eur. J. Org. Chem*. **2010**, *20*, 3823–3830.

[15] Isoamyl nitrite was synthesized following the methodology described by P. Canning, K. McCrudden, H. Maskill, B. Sexton, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 2735–2740.

[16] A. Marchal, M. Melguizo, M. Nogueras, A. Sánchez, J. Low, *Synlett*., **2002**, *2*, 255–258.

[17] B. Carbain, D. Paterson, E. Anscombe, A. Campbell, C. Cano, A. Echalier, J. Endicott, B. Golding, K. Haggety, I. Hardcastle, P. Jewsbury, D. Newell, M. Noble, C. Roche, L. Wang, R. Griffin, *J. Med. Chem.* **2014**, *57*, 56–70.

[18] D-Z. Xu, Y. Liu S. Shi, Y. Wang, *Tetrahedron: Asymmetry*, **2010**, *21*, 2530–2534.

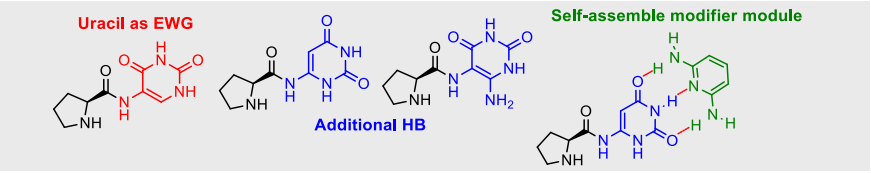
[19] M. Frieden, M. Giraud, C. Reese, Q. Song, *J. Chem. Soc., Perkin Trans, 1*. **1998**, *0*, 2827–2832.

[20] X. Mejías, L. Feliu, M. Planas, E. Bardají, *Tetrahedron Lett.* **2006**, *47*, 8069–8071.

10.1002/ejoc.201800886

WILEY-VCH

FULL PAPER



Prolinamide organocatalysts with aminouracils have the features of enhanced NH acidity, additional hydrogen bond donor and the self-assembly with complementary modules by Watson-Crick pairing. Each module affects the selectivity on the reaction and particularly 2,6-diaminopyridine is beneficial to the selectivity in the reaction.

Supramolecular catalyst

*Karen M. Ruíz-Pérez, Beatriz Quiroz-García, Marcos Hernández Rodríguez**

Page No. – Page No.

Prolinamides of aminouracils, organocatalyst modifiable by complementary modules.