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Modular urea-based catalytic platforms bearing flexible pyridylmethylamine and rigid pyridyl-imidazolidine fragments

Olivier Colin, Hamza Boufroura, Christine Thomassigny, Serge Perato, Anne Gaucher, Jérôme Marrot, and Damien Prim *[a]

Abstract: The selective and concise synthesis of new urea-based catalytic platforms is described. Each platform associates an urea or thiourea motif to a pyridylmethylamine or a pyridyl-imidazolidine fragment. These modular catalytic platforms efficiently organo-promote Michael additions. Moreover, the corresponding Cu complexes successfully catalyze Henry-type reactions.

Introduction

Since its artificial synthesis in 1828 by German chemist Friedrich Wöhler,[1] urea is an ubiquitous pattern in modern organic chemistry. The H-bonding properties as well as the unique templating or organization abilities of urea and their derivatives have inspired the scientific community towards thriving developments in various domains. As examples, urea-based materials have been successfully used as polymerization[2] or corrosion[3] process inhibitors, gel propellants,[4] gelators,[5] adhesives,[6] antibacterial agents,[7] graphene exfoliation promoters,[8] nanoparticle stabilization agents,[9] supramolecular recognition agents[10] anion sensors[11] or transporters.[12]

As one of these advances, urea-based homogeneous catalysis is a rapidly expanding area of research. Within this context, H-bonding properties of urea derivatives and flexibility *vs* rigidity of the catalytic platform play a central role in selective activation processes. The modulation of the strength of H-bonds can be achieved by several ways including the switch from urea to thiourea, the modification of the substitution pattern of urea nitrogen atoms and the installation of specific fluorinated fragments at various sites of the platform.[13] The control of chiral information transfer in urea-promoted catalytic transformations is mostly obtained from the installation of chiral substituents at nitrogen neighbouring positions.[13]

Combination of urea H-bond donor fragments with a chiral scaffold and secondary or tertiary amines distributed at a single catalytic platform recently emerged as a pillar in organic synthesis.[14] In the main catalytic platforms developed to date (figure 1) urea is associated with cyclohexyldiamine, diphenylethylenediamine, binaphtylamine and cinchona derivatives. Such catalytic platforms revealed performant in a wide range of asymmetric organocatalysed transformations including (hetero)-Michael additions, Huisgen cycloadditions, reduction of ketones, alkylation of heterocycles, Horner-Wadsworth-Emmons, aza-Henry, Mannich or Conia-ene reactions and kinetic resolutions for examples.[14,15]

As part of a research program devoted to the development of pyridylmethylamine(pma)-based catalytic systems, we found that the pma fragment was not only able to accommodate various metallic species in metallo-catalysed reactions,[16] but also to act as a base or a H-bond acceptor in organocatalysis.[17] In the context of this work, these results prompted us to investigate the preparation new urea derivatives bearing a chiral diaminocyclohexyl scaffold decorated with an H-bond acceptor pma unit (family 1). During the course of our study, attempts to switch from a cyclic to an acyclic chiral scaffold led to the preparation of a second family of platform comprising the urea motif associated to a rigid pyridyl-imidazolidine system (family 2)

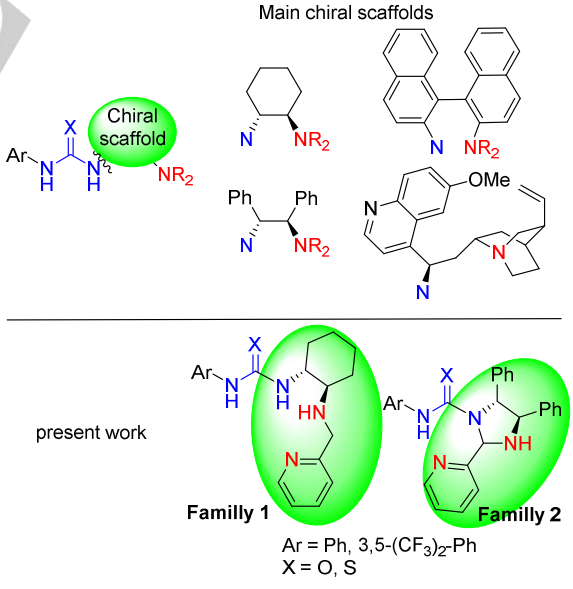

Figure 1. Design of new catalytic platforms.

In this paper, we describe the preparation of both families of catalytic platforms **1** and **2** using the same strategy and the evaluation of their catalytic properties in Michael addition and nitroaldol reactions.

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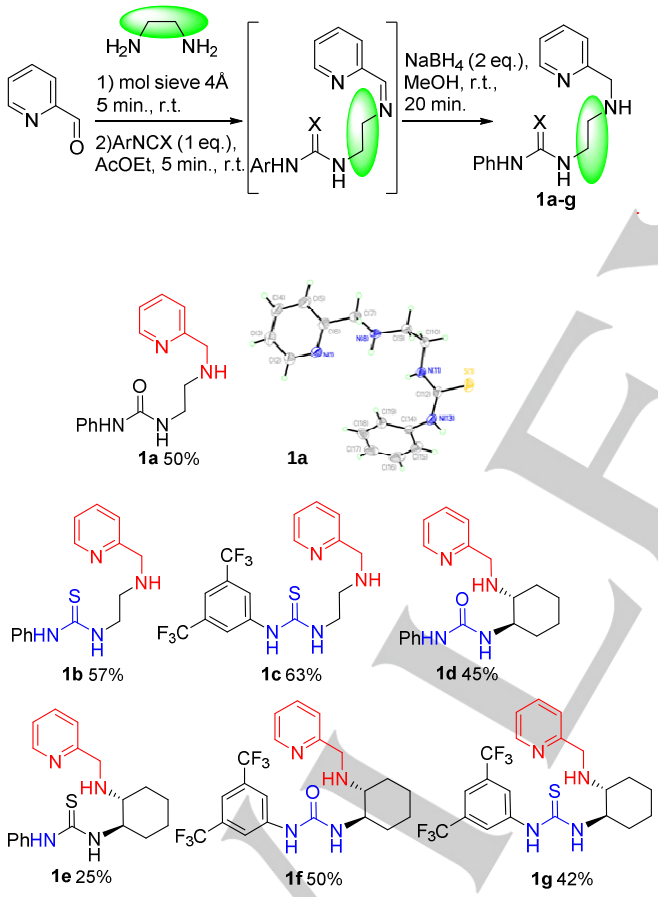
Results and Discussion

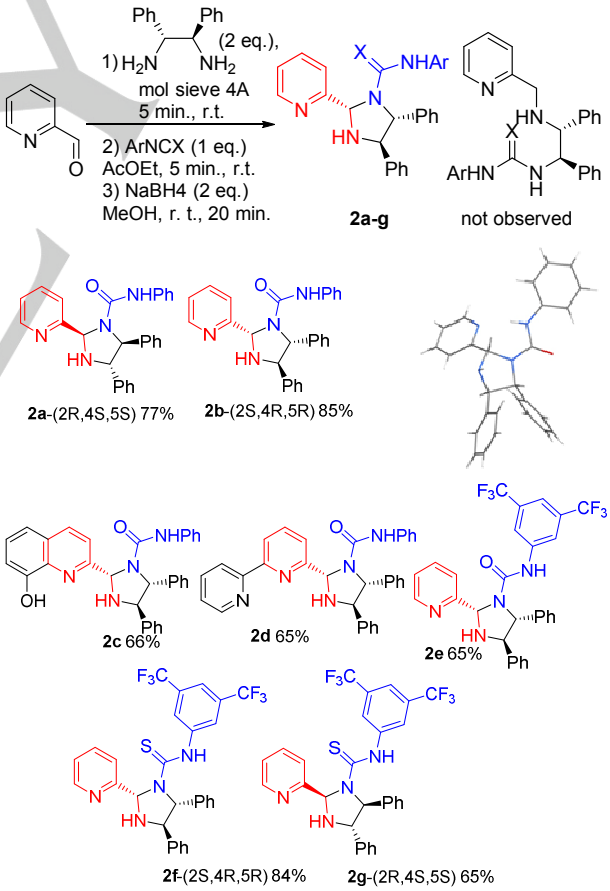
We first focused on the preparation of platform **1a** from ethylene diamine, pyridylcarboxaldehyde and phenylisocyanate. Our objective was to avoid the formation of bisimine adduct and imidazolidine intermediates originated from the condensation of ethylene diamine and pyridylcarboxaldehyde.[18] Gratifyingly, we found that pyridylcarboxaldehyde cleanly reacted with 2 eq. of ethylenediamine at room temperature in the presence of crushed 4Å molecular sieve without any solvent (scheme 1). Within 5 min., pyridylcarboxaldehyde was fully consumed. Filtration of the reaction mixture over Celite followed by quick removal of the excess of ethylenediamine *in vacuo* and further addition of PhNCO in AcOEt for an additional 5 min. gave the imine-urea intermediate. The latter was not isolated and further reduced through addition of MeOH and $NaBH_4$ (2eq.) into the expected platform **1a** in an overall 50% yield for three steps.



Scheme 1. Strategy towards the one-pot preparation of platforms **1**.

Our pseudo-sequential one-pot methodology requires one filtration during the process and selectively afforded **1a** in ca. 30 minutes. Single crystals suitable for X-ray analysis were obtained by slow evaporation of DCM solution of **1a** (scheme 1).[19] As shown, the molecular structure of **1a** has been unequivocally confirmed, evidencing the joint presence of both the vicinal pyridylmethylamine fragment and urea motif. We further took advantage of the one-pot sequence to prepare thio analogues **1b** and **1c** in yields ranging from 57 to 63% by using PhNCS and 3,5-$(CF_3)_2$-PhNCS respectively instead of phenylisocyanate.

Chiral non racemic cyclohexyldiamine was next successfully installed at the parent pyridine. Indeed, compounds **1d**-**1g** were isolated using the same one pot procedure, albeit in modest yields.[20] Attempts to install diphenylethylenediamine instead of ethylenediamine or cyclohexyldiamine led to a different issue. Under the aforementioned reaction conditions, diphenylethylenediamine cleanly did not afford the expected platform **1** but urea-pyridine-imidazolidine platform **2** (scheme 2). It is worthy to note that the presence of the pyridine ring induces the selective formation of the imidazolidine ring as evidenced by crude product ^{1}H NMR study (ESI-1).[18] Neither the bis imine nor the mono imine adduct could be observed. Further addition of isocyanate derivatives led to platforms **2a-g** in yields ranging from 65 to 85%.[21] In this sequence, the addition of $NaBH_4$ allowed reducing the unreacted residual isocyanates and revealed essential to avoid the formation of bisurea adducts.



Scheme 2. One-pot access to platforms **2**.

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Relative as well as absolute configurations have been unequivocally assigned by X-ray analysis [22] of the platform **2b** (scheme 2) and the corresponding Pd complex (ESI-2). X-ray analysis confirmed the selective installation of urea motives in full agreement with recent Arai's observations in the mono *N*-alkylated pyridyl-imidazolidine series. [23]

Our next objective was to evaluate the catalytic properties of platforms **1** and **2** on two model reactions: the organo-catalysed Michael addition of isobutyraldehyde to *N*-phenylmaleimide and Cu-promoted nitroaldol reaction.

We first started to evaluate platforms **1** and **2** as the catalyst for Michael addition of isobutyraldehyde to *N*-phenymaleimide (table 1).

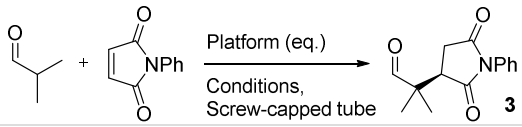


Table 1. Michael addition pormoted by platforms **1** and **2**

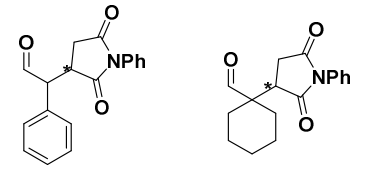
Entry	Platform (eq.)	Conditions[a]	Yield (%) [c]	e.e.(%)
1	**1g** (0.1)	A	72	57 (*R*)
2	**1g** (0.05)	A	30	62 (*R*)
3	**1g** (0.1)	B	91	58 (*R*)
4	**1g** (0.2)	C	74	42 (*R*)
5	**1g** (0.05)	D	59	52 (*R*)
6	**1d** (0.1)	B	91	74 (*R*)
7	**1d** (0.1)	A	72	32 (*R*)
8	**1e** (0.1)	B	70	48 (*R*)
9	**1f** (0.1)	B	80	72 (*R*)
10	**2a-(*2R,4S,5S*)** (0.2)	B	49	94 (*R*)
11	**2b-(*2S,4R,5R*)** (0.2)	B	49	93 (*S*)
12	**2c** (0.2)	B	46	96 (*R*)
13	**2d** (0.2)	B	50	96 (*R*)
14	**2e** (0.2)	B	68	98 (*R*)
15	**2f-(*2S,4R,5R*)** (0.2)	B	89	97 (*R*)
16	**2g-(*2R,4S,5S*)** (0.2)	B	56	72 (*S*)

[a] Condition A : DCM, 40°C, 72h. Condition B : DCE, 85°C, 28h. Condition C : DCE, 85°C, 15h. Condition D: DCE, 85°C, 72h.

1g, combining a 3,5-bis(trifluoromethyl)phenyl thiourea group and a cyclohexyldiamine chiral unit, was chosen as the model platform to set best conditions to promote Michael addition. In fact, best catalytic compromise was obtained using 0.1 eq. of platform **1g**, 1 eq. of *iso*butyraldehyde at 85°C in DCE for 28h. Under condition B, adduct **3** was isolated in 91% yield and 58% ee (compare entry 3 with entries 1, 2 and 4). As expected the decrease of platform loading to 0.05 eq. even after prolonged reaction time showed erosion of both yield and ee (entry 5). In the case of platform **1d**, conditions B were again found superior to condition A (compare entries 6 and 7) affording the best results within this series of platforms. Indeed, **1e** and **1f** were both less effective under identical reaction conditions.

The further step was to compare the efficiency of ligand **1d** and cyclic analogues **2a-2g**. Under the aforementioned conditions, **2a-2g** (0.2 eq.) revealed highly selective and Michael adduct **3** was obtained in high ees ranging from 72 to 98% (compare entries10-16). Decrease of catalytic loading to 0.1 eq. revealed detrimental to conversion albeit without erosion of selectivity. 89% yield and 97% ee were obtained using ligand **2f** (entry 15), which represented the best results within the pyridyl imidazoline series. Interestingly, *R* and *S* adducts can be independently obtained from platforms **2a** and **2f** to **2b** and **2g** respectively. In fact, we have two reliable catalytic platforms: (i) a flexible acyclic platform **1d**, composed by a pyridylmethyl, a cyclohexyldiamine and a H-bonding donor phenylurea leading to the Michael adduct in 91% yield and 74% ee for a 0.1 eq. of catalytic loading (ii) a rigid cyclic platform **2f**, composed by a pyridyl-imidazoline core decorated by a strong H-bonding donor thiourea motif leading to the Michael adduct in 89% yield and 97% ee for a 0.2 eq. of catalytic loading.

Platform **2a-(*2R,4S,5S*)** (0.2 eq.) was next used under conditions B (table 1) for the Michael addition of *N*-phenylmaleimide to phenylacetaldehyde and cyclohexylcarboxaldehyde. If adduct **4b** could be isolated in 78% ee under these conditions, **4a** could not be obtained even after prolonged reaction course (96h).



4a no reaction **4b** 15%, ee 79% (*R*)

Figure 2. Michael adducts using phenylacetaldehyde and cyclohexylcarboxaldehyde as substrates.

We next focused on metal-catalysed transformations, to evidence that the present platforms are not only able to organo-promoted but also metal-promoted reactions. In this context, Cu-promoted nitroaldol reaction is a benchmarck reaction of current interest.[24] Taking into account the aforementioned catalytic results, platforms **1d** and **2f** were first tested (Table 2). To this end, Cu salt and the ligand were mixed for 24h in order to generate the corresponding Cu complexes prior to the addition of nitroaldol reagents. The formation of adduct **4**, was strongly depending on the nature of the Cu salt. Indeed, reactants

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remained unchanged by using a combination of ligand **2f**-(*2S,4R,5R*) with $CuCl_2$ (entry 1). In contrast, switch of the Cu source to $Cu(OAc)_2$ resulted in the formation of the expected nitro adduct in fair 40% yield and 44% ee (entry 2). As shown in entries 3-5, no conversion was observed when the control reaction was realized without the catalytic system, without the ligand or the copper salt clearly indicating that the $Cu(OAc)_2$-ligand combination is mandatory to catalyze the Henry reaction. Attempts to improve both yields and selectivities using ligands **1d** or even **1g** were next realized but led to disappointing results (entries 6, 7) such as 7 and 15% yields of the corresponding nitroaldol adduct respectively. The use of Et_3N as an additive to $Cu(OAc)_2$-**1g** catalytic system led to an impressive increase of yield to 80% but a poor 15% ee (entry 8). A clear improvement was observed when pyridyl-imidazoline **2e** was used leading to 54% yield and 44% ee (entry 9) by comparison with analogue **2f**. Tridentate (*O*,*N*,*N*) **2c** based on a quinoline core afforded modest yields and ee (24 and 44% respectively). Finally, **2a** incorporating an urea motive voided of CF_3 groups, represented the best compromise, leading to 60% yield and 61% ee (entry 11). As already observed by us, the use of Et_3N as an additive was shown beneficial to the yield but detrimental to the ee (entry 12).

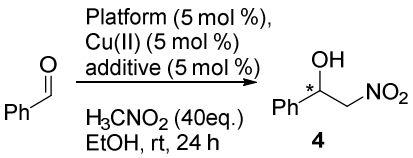

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Table 2. Cu-promoted Nitroaldol reaction

Entry	Platform	Cu(II)/additive	Yield (%) [c]	e.e.(*R*,%)
1	**2f-(*2S,4R,5R*)**	$CuCl_2$	0	
2	**2f-(*2S,4R,5R*)**	$Cu(OAc)_2$	40	44
3	**-**	-	0	
4	**2f-(*2S,4R,5R*)**	-	0	
5	**-**	$Cu(OAc)_2$	0	
6	**1d**	$Cu(OAc)_2$	7	[a]
7	**1g**	$Cu(OAc)_2$	15	[a]
8	**1g**	$Cu(OAc)_2$ / Et_3N	80	15
9	**2e**	$Cu(OAc)_2$	54	44
10	**2e**	$Cu(OAc)_2$	25	24
11	**2a-(*2S,4R,5R*)**	$Cu(OAc)_2$	60	61
12	**2a-(*2S,4R,5R*)**	$Cu(OAc)_2$ / Et_3N	87	23

[a] e.e were not determined.

Conclusions

The preparation of two new families of urea-based catalytic platforms has been described. Pyridylmethylamine fragments completed the urea and thiourea core of the acyclic flexible familly **1**. We were also able to prepare (thio)urea decorated by rigid pyridyl-imidazolidines motives as well. Both families can be easily obtained through one pot sequences within minutes.

In a second part of our paper, we have shown that catalytic platforms designed from a pyridylmethylamine or pyridyl-imidazolidine core in association with urea fragments are able to independently promote both Michael-type addition and nitroaldol reaction under organo- and metallo-assisted conditions respectively. Micheal-type adducts were obtained in high yields and ee's up to 91 and 98% respectively. In combination with Cu salt, pyridyl-imidazolidine-Cu complexes successfully catalyzed Henry-type additions.

Experimental Section

General remarks:

Solvents and reagents were purchased and used without further purification except for DCM who was freshly distilled from calcium hydride and stored under Ar. Reaction progress was carried out using silica gel 60 F245 precoated aluminum plates (0.25 mm), which were visualized by UV fluorescence quenching or vanillin staining. Silica gel 60 (40-63 µm) was used for flash chromatography. ^{1}H NMR spectra were recorded at 300 MHz and 298 K, referenced to TMS signal and were calibrated using residual $CHCl_3$ (δ = 7.26 ppm), DMSO-d^6 (δ = 2.50 ppm) or MeOD (δ = 3.31 ppm). ^{19}F NMR spectra were recorded at 300 MHz and 298 K, and were calibrated using $CFCl_3$ (δ = 0.00 ppm). ^{13}C NMR spectra were recorded at 75 MHz and 298 K, and were calibrated using $CDCl_3$ (δ = 77.16 ppm) DMSO-d^6 (δ = 39.52 ppm) or MeOD (δ = 49.00 ppm). ^{1}H NMR spectroscopic data are reported as follow: chemical shift δ [ppm] (multiplicity, coupling constant [Hz], integration). Multiplicities are reported as follow: s = singlet, d = doublet, t = triplet, q = quadruplet, sext = sextuplet, hept = heptuplet, dd = doublet of doublet, td = triplet of doublet, tt = triplet of triplet, ddd = doublet of doublet of doublet, m = multiplet. ^{13}C NMR spectroscopic data are reported in terms of chemical shifts δ [ppm] and when it was necessary, multiplicity and coupling constant [Hz]. IR spectra are reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were obtained with a QTOF instrument with an electrospray ionization source (ESI^+), using enkephaline leucine as internal calibrant. UPLC/ESI^+ analyses were performed on a QTOF instrument with ESI^+ detector and the achiral stationary-phase UPLC C_{18}. The eluent is: solvent A - H_2O + 0.1 % HCOOH, solvent B - ACN + 0.1 % HCOOH, A/B 95/5 during 0.5 min then gradient A/B 95/5 to 0/100 during 4.5 min, 0.450 $mL.min^{-1}$. Optical rotations were measured by using sodium D radiation (589 nm) or mercury radiation (578 nm) at 25 °C and are reported as follow $[\alpha]_\lambda$ (*c* in g/100 mL, solvent). HPLC analyses were performed with a UV detector and a chiral stationary-phase column and reported as follow (column, solvent, flow, temperature, λ UV detector).

General procedure for the preparation of platforms 1 and 2. The diamine (1 equiv., 0.3 $mol.L^{-1}$) was dissolved in AcOEt in a round bottom flask with molecular sieves 4 Å crush. The aldehyde (1 equiv.) was added, and the reaction mixture was stirred at room temperature for 5 minutes. Further aromatic(thio)isocyanate (1 equiv.) was added. The reaction mixture was stirred at room temperature for 5 minutes, then was

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transferred to a $NaBH_4$/MeOH suspension (2 equiv., 0,2 mol.L^{-1}). The reaction mixture was stirred at room temperature for 20 minutes, and then was filtered through a pad of Celite, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (DCM/MeOH/NH_3(30 % in water) 100/0.1/2) to give the expected product.

General procedure for the Michael addition. Isobutyraldehyde (1 equiv., 0.2 mol.L^{-1}), *N*-phenylmaleimide (1 equiv.) and the catalyst (20 mol %) in DCE were mixed in a screw-capped tube. The mixture was kept for 17 h at 85 °C, and then the solvent was removed *in vacuo*. The residue was purified by flash chromatography (pentane/AcOEt 4/1) to give the expected product.

General procedure for the Henry reaction. To a solution of $Cu(OAc)_2.H_2O$ (5 mol %) dissolved in dry DCM (1.10^{-2} mol.L^{-1}) was the added ligand (5 mol %). The solution was stirred under argon at room temperature for 17 h. The solvent was removed under reduced pressure. Next, the residue was dissolved in EtOH ($2.5x10^{-2}$ mol.L^{-1}). To the mixture was added nitromethane (40 equiv.) and benzaldehyde (1 equiv.) under argon. After stirring for 24 h at room temperature, the solvent was removed *in vacuo*. The residue was purified by flash chromatography (pentane/AcOEt 9/1) to give the expected product.

1-phenyl-3-(2-((pyridin-2-ylmethyl)amino)ethyl)urea **1a**. Following *general procedure for the preparation of platforms*, the compound **1a** was obtained as yellow oil with a yield of 50 %. R_f = 0.46 (DCM/MeOH/NH_3(30 % in water) 100/10/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.50 (d, *J* = 4.8 Hz, 1H), 8.05 (s, 1H), 7.59 (td, *J* = 7.7 and 1.8 Hz, 1H), 7.28-7.13 (m, 6H), 6.97 (t, *J* = 7.1 Hz, 1H), 6.02 (d, *J* = 5.0 Hz, 1H), 3.87 (s, 2H), 3.32 (q, *J* = 5.4 Hz, 2H), 2.78 (t, *J* = 5.5 Hz, 2H), 2.28 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1 (C), 156.8 (C), 149.4 (CH), 139.4 (C), 139.5 (CH), 136.8 (CH), 129.1 (CH), 122.8 (CH), 122.6 (CH), 122.3 (CH), 120.0 (CH), 54.7 (CH_2), 49.4 (CH_2), 40.4 (CH_2). IR: 3306, 3051, 2929, 2839, 1656, 1593, 1547, 1497, 1435, 1309, 1231, 751, 693 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{15}H_{19}N_4O$ [M + H]$^+$: 271.1559; found: 271.1562.

1-phenyl-3-(2-((pyridin-2-ylmethyl)amino)ethyl)thiourea **1b.** Following *general procedure for the preparation of platforms*, the compound **1b** was obtained as white needles with a yield of 57 %. R_f = 0.53 (DCM/MeOH/NH_3(30 % in water) 100/10/2). Mp = 85- 86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.67 (s, 1H), 8.38 (d, *J* = 4.0 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.28-7.04 (m, 8H), 3.79 (s, 2H), 3.66 (s, 2H), 2.81 (t, *J* = 5.2 Hz, 2H), 2.16 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.1 (C), 159.2 (C), 149.2 (CH), 139.7 (C), 136.5 (CH), 129.7 (CH), 126.4 (CH), 125.5 (CH), 124.6 (CH), 122.2 (CH), 54.2 (CH_2), 47.4 (CH_2), 44.8 (CH_2). IR: 3158, 3012, 2942, 2844, 1594, 1514, 1424, 1310, 1300, 1240, 1168, 1041, 845, 754, 729, 690, 609 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{15}H_{19}N_4S$ [M + H]$^+$: 287.1330; found: 287.1336.

1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-((pyridin-2-ylmethyl)amino)-ethyl)thiourea **1c**. Following *general procedure for the preparation of platforms*, the compound **1c** was obtained as a brown oil with a yield of 63 % under multiple rotamers form. R_f = 0.49 (DCM/MeOH/NH_3(30 % in water) 100/10/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.40 (m, 2H), 8.12-7.74 (m, 3H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.45 (s, 1H), 7.13 (d, *J* = 7.4 Hz, 2H), 3.93 (s, 2H), 3.82 (m, 1H), 3.41 (m, 1H), 2.97 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.9 (C), 181.2 (C), 157.5 (C),156.5 (C),149.3 (CH), 141.8 (C),140.4 (C),136.9 (CH), 131.4 (q, *J* = 34 Hz, C), 123.1 (q, *J* = 273 Hz, C), 54.1 (CH_2), 51.0 (CH_2), 48.0 (CH_2), 45.8 (CH_2). ^{19}F NMR (188 MHz, $CDCl_3$/CHF_3) δ = -63.42. IR: 3236, 3045, 2929, 2847, 1594, 1544, 1472, 1381, 1273, 1168, 1121, 1106, 882, 847, 755, 727, 699, 680 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{17}H_{17}F_6N_4S$ [M + H]$^+$: 423.1078; found: 423.1082.

1-phenyl-3-((1R,2R)-2-((pyridin-2-ylmethyl)amino)cyclohexyl)urea **1d.** Following *general procedure for the preparation of platforms*, the compound **1d** was obtained as a yellow oil with a yield of 45 %. R_f = 0.27 (DCM/MeOH/NH_3(30 % in water) 100/10/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.84 (s, 1H), 8.54 (d, *J* = 4.7 Hz, 1H), 7.62 (td, *J* = 7.7 and 1.7 Hz, 1H), 7.33-7.18 (m, 6H), 7.00 (t, *J* = 7.1 Hz, 1H), 5.53 (s, 1H), 4.09 (d, *J* = 14.2 Hz, 1H), 3.96 (d, *J* = 14.2 Hz, 1H), 3.49 (s, 1H), 2.98 (s, 1H), 2.38 (td, *J* = 10.3 and 4.0 Hz, 1H), 2.09 (t, *J* = 11.8 Hz, 2H), 1.73 (t, *J* = 1.73 Hz, 2H), 1.34-1.11 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1 (C), 157.1 (C), 149.1 (CH), 139.7 (C), 136.9 (CH), 128.9 (CH), 122.9 (CH), 122.4 (CH), 122.3 (CH), 119.5 (CH), 62.2 (CH), 56.0 (CH), 52.7 (CH_2), 33.2 (CH_2), 32.1 (CH_2), 24.9 (CH_2). IR: 3307, 3051, 2927, 2854, 1650, 1594, 1546, 1498, 1438, 1314, 1224, 749, 729, 693, 631 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{19}H_{25}N_4O$ [M + H]$^+$: 325.2028; found: 325.2029. $[\alpha]_D^{25}$ -7.4 (c 1.0, $CHCl_3$); $[\alpha]_{578}^{25}$ -7.9 (c 1.0, $CHCl_3$).

1-phenyl-3-((1R,2R)-2-((pyridin-2-ylmethyl)amino)cyclohexyl)-thiourea **1e.** Following *general procedure for the preparation of platforms* the compound **1e** was obtained as a yellow oil with a yield of 25 % yield under multiple rotamers form. R_f = 0.53 (DCM/MeOH/NH_3(30 % in water) 100/10/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.52-8.32 (m, 2H), 7.55 (td, *J* = 7.7,and 1.6 Hz, 1H), 7.26-7.16 (m, 6H), 6.51 (s, 1H), 4.03-3.91 (m, 2H), 2.61 (s, 1H), 2.38 (s, 1H), 2.03 (d, *J* = 11.7 Hz, 1H), 1.70 (d, *J* = 10.6 Hz, 2H), 1.27-1.13 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.2 (C), 159.9 (C), 158.9 (C), 157.1 (C), 149.1 (CH), 139.8 (CH), 136.9 (CH), 128.9 (CH), 122.9 (CH), 122.3 (CH), 119.4 (CH), 63.9 (CH), 55.7 (CH), 52.3 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 25.0 (CH_2). IR: 3208, 3045, 2926, 2854, 1526, 1496, 1317, 1258, 750, 716, 692 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{19}H_{25}N_4S$ [M + H]$^+$: 341.1800; found: 341.1797. $[\alpha]_D^{25}$ +47.5 (c 1.0, $CHCl_3$); $[\alpha]_{578}^{25}$ +48.6 (c 1.0, $CHCl_3$).

1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,2R)-2-((pyridin-2-ylmethyl)amino)cyclohexyl)-urea **1f**. Following *general procedure for the preparation of platforms*, the compound **1f** was obtained as a yellow oil with a yield of 50 % under multiple rotamers form. R_f = 0.39 (DCM/MeOH/NH_3 (30 % in water) 100/10/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.47 (d, *J* = 4.1 Hz, 1H), 7.66 (s, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 7.16-7.11 (m, 2H), 4.10 (d, *J* = 14.0 Hz, 1H), 3.95 (d, *J* = 14.9 Hz, 1H), 3.68-3.28 (m, 2H), 2.52-2.42 (m, 1H), 2.20-1.96 (m, 2H), 1.82-1.60 (m, 2H), 1.39-1.03 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.5 (C), 149.2 (CH), 141.6 (C), 137.0 (CH), 131.7 (q, *J* = 33 Hz, C), 123.3 (q, *J* = 273 Hz, C),122.8 (CH), 118.2 (CH), 114.9 (CH), 63.1 (CH), 56.5 (CH), 55.0 (CH_2), 33.2 (CH_2), 32.0 (CH_2), 24.9 (CH_2). ^{19}F NMR (188 MHz, $CDCl_3$/CHF_3) δ = -63.44. IR: 3296, 2934, 2859, 1663, 1560, 1473, 1436, 1386, 1274, 1169, 1122, 1027, 999, 879, 755, 730, 702, 681 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{21}H_{23}F_6N_4O$ [M + H]$^+$: 461.1776; found: 461.1776. $[\alpha]_D^{25}$ +7.9 (c 1.0, $CHCl_3$); $[\alpha]_{578}^{25}$ +7.1 (c 1.0, $CHCl_3$).

1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,2R)-2-((pyridin-2-ylmethyl)amino)cyclohexyl)-thiourea **1g.** Following *general procedure for the preparation of platforms*, the compound **1g** was obtained as a white powder with a yield of 42 % under multiple rotamers form. R_f = 0.79 (DCM/MeOH/NH_3(30 % in water) 100/10/2). Mp = 64.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.55 (s, 1H), 7.68 (s, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.21-7.15 (m, 2H), 6.40 (s, 1H), 4.12-4.01 (m, 2H), 3.50 (s, 1H), 2.42 (s, 1H), 2.10 (s, 2H), 1.80 (s, 2H), 1.37-1.22 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.3 (C), 156.9 (C), 149.9 (CH), 137.0 (CH), 131.3 (q, *J* = 35 Hz, C), 123.0 (CH), 123.1 (q, *J* = 272 Hz, C), 122.6 (CH), 122.4 (CH), 121.4 (C), 64.7 (CH), 62.6 (CH), 54.4 (CH_2), 32.6 (CH_2), 24.9 (CH_2), 24.7 (CH_2). ^{19}F NMR (188 MHz, $CDCl_3$/CHF_3) δ = -63.32. IR: 3219, 3013, 2933, 2858, 1594, 1542, 1473, 1383, 1274, 1169, 1122, 881, 755, 730, 700, 680, 645 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{21}H_{23}F_6N_4S$ [M + H]$^+$: 477.1548; found: 477.1552; $[\alpha]_D^{25}$ +31.8 (c 1.0, $CHCl_3$); $[\alpha]_{578}^{25}$ +32.2 (c 1.0, $CHCl_3$).

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***(2R,4S,5S)*-N'*,4,5-triphenyl-2-(pyridin-2-yl)imidazolidine-1-carboxamide* 2a-(*2R,4S,5S*).** Following *general procedure for the preparation of platforms*, the compound **2a-(*2R,4S,5S*)** was obtained as a white powder with a yield of 77 %. R_f = 0.75 (AcOEt). Mp = 103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.83 (s, 1H), 8.74 (d, *J* = 4.8 Hz, 1H), 7.90-7.85 (m, 2H), 7.39-7.32 (m, 8H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.19-7.13 (m, 3H), 7.02-6.93 (m, 3H), 6.22 (s, 1H), 5.07 (d, *J* = 8.6 Hz, 1H), 4.38 (d, *J* = 8.6 Hz, 1H), 3.30 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.7 (C), 155.7 (C), 149.0 (CH), 140.1 (C), 139.9 (C), 137.9 (CH), 137.9 (C), 128.9 (CH), 128.7 (CH), 128.5 (CH), 127.6 (CH), 127.4 (CH), 126.8 (CH), 123.3 (CH), 122.4 (CH), 120.8 (CH), 119.1 (CH), 76.8 (CH), 70.7 (CH), 69.7 (CH). IR: 3294, 3059, 3021, 2898, 1666, 1593, 1553, 1498, 1444, 1321, 1254, 1135, 1002, 904, 748, 695, 618, 533, 506 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{27}H_{25}N_4O$ [M + H]$^+$: 421.2028; found: 421.2022. $[\alpha]_D$ -181 (*c* 0.9, $CHCl_3$). $[\alpha]_{578}$ -186 (*c* 0.9, $CHCl_3$).

***(2S,4R,5R)*-N'*,4,5-triphenyl-2-(pyridin-2-yl)imidazolidine-1-carboxamide* 2b-(*2S,4R,5R*).** Following *general procedure for the preparation of platforms*, the compound **2b-(*2S,4R,5R*)** was obtained as a white powder with a yield of 85 %. R_f = 0.75 (AcOEt). Mp = 103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.94 (s, 1H), 8.75 (d, *J* = 4.6 Hz, 1H), 7.90-7.85 (m, 2H), 7.44-7.33 (m, 8H), 7.25 (t, *J* = 6.1 Hz, 2H), 7.17-7.13 (m, 3H), 7.00-6.97 (m, 3H), 6.21 (s, 1H), 5.07 (d, *J* = 8.7 Hz, 1H), 4.38 (d, *J* = 8.4 Hz, 1H), 3.31 (s, 1H). ^{1}H NMR (300 MHz, DMSO-d^6) δ = 10.67 (s, 1H), 8.88 (d, *J* = 4.5 Hz, 1H), 8.00 (t, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.52-7.48 (m, 3H), 7.40-7.36 (m, 5H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.12-7.10 (m, 3H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.80-6.83 (m, 2H), 6.16 (d, *J* = 7.4 Hz, 1H), 4.91 (d, *J* = 8.9 Hz, 1H), 4.61 (dd, *J* = 12.5 and 7.5 Hz, 1H), 4.18 (dd, *J* = 12.3 and 9.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.7 (C), 155.7 (C), 149.0 (CH), 140.1 (C), 139.9 (C), 137.9 (CH), 137.8 (C), 128.9 (CH), 128.7 (CH), 128.5 (CH), 127.6 (CH), 127.4 (CH), 126.7 (CH), 123.3 (CH), 122.4 (CH), 120.7 (CH), 119.1 (CH), 76.7 (CH), 70.7 (CH), 69.6 (CH). ^{13}C NMR (75 MHz, DMSO-d^6) δ = 160.8 (C), 154.9 (C), 149.0 (CH), 141.0 (C), 140.2 (C), 138.3 (CH), 137.9 (C), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.6 (CH), 126.8 (CH), 126.2 (CH), 123.3 (CH), 121.7 (CH), 120.0 (CH), 118.4 (CH), 76.8 (CH), 70.6 (CH), 69.0 (CH). IR: 3307, 3022, 2908, 2844, 2806, 1670, 1622, 1593, 1561, 1498, 1446, 1364, 1330, 1257, 1133, 1005, 911, 748, 690, 556, 507 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{27}H_{25}N_4O$ [M + H]$^+$: 421.2028; found: 421.2024. $[\alpha]_D$ +178 (*c* 1.1, $CHCl_3$). $[\alpha]_{578}$ +186 (*c* 1.1, $CHCl_3$).

***(2S,4R,5R)*-2-(8-hydroxyquinolin-2-yl)-N,*4,5-triphenylimidazolidine-1-carboxamide* 2c.** Following *general procedure for the preparation of platforms*,the compound **2c** was obtained as a white powder with a yield of 66 %. R_f = 0.71 (AcOEt). Mp = 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.36-6.37 (m, 20H), 6.55 (s, 1H), 6.37 (s, 1H), 4.81 (d, *J* = 7.4 Hz, 1H), 4.43 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.8 (C), 155.0 (C), 152.1 (C), 138.7 (C), 138.5 (C), 138.2 (C), 137.7 (CH), 137.4 (C), 129.5 (CH), 128.9 (CH), 127.3 (CH), 127.1 (CH), 119.5 (CH), 118.2 (CH), 111.0 (CH), 76.3 (CH), 71.2 (CH),70.1 (CH) ppm. IR: 3395, 3291, 3053, 3028, 2892, 1651, 1596, 1529, 1498, 1441, 1318, 1237, 1156, 1084, 1028, 896, 837, 748, 691, 533, 502 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{31}H_{27}N_4O_2$ [M + H]$^+$: 487.2134; found: 487.2139. $[\alpha]_D$ +185 (*c* 1.5, $CHCl_3$). $[\alpha]_{578}$ +190 (*c* 1.5, $CHCl_3$).

***(2S,4R,5R)*-2-([2,2'-bipyridin]-6-yl)-N'*,4,5-triphenylimidazolidine-1-carboxamide* 2d**. Following *general procedure for the preparation of platforms*, the compound **2d** was obtained as a white powder with a yield of 65 %. R_f = 0.72 (AcOEt). Mp = 171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.75 (s, 1H), 8.43 (d, *J* = 7.6 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.01-7.91 (m, 2H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.38 (s, 6H), 7.28-7.10 (m, 10H), 6.95 (t, *J* = 7.1 Hz, 1H), 6.30 (s, 1H), 5.09 (d, *J* = 8.2 Hz, 1H), 4.46 (d, *J* = 8.0 Hz, 1H), 3.50 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.0 (C), 155.8 (C), 155.5 (C), 149.6 (CH), 139.9 (C), 139.4 (C), 138.8 (CH), 138.1 (C), 137.3 (C), 129.0 (CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 126.9 (CH), 124.2 (CH), 122.7 (CH), 121.6 (CH), 121.1 (CH), 119.3 (CH), 76.9 (CH), 70.9 (CH), 69.8 (CH). IR: 3288, 3240, 3056, 3029, 2892, 1665, 1596, 1581, 1536, 1498, 1442, 1428, 1318, 1245, 1146, 1072, 992, 903, 748, 695, 632, 618, 554, 532, 506 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{32}H_{28}N_5O$ [M + H]$^+$: 498.2294; found: 498.2291.

***(2S,4R,5R)*-N'*-(3,5-bis(trifluoromethyl)phenyl)-4,5-diphenyl-2-(pyridin-2-yl)imidazolidine-1-carboxamide* 2e**. Following *general procedure for the preparation of platforms*, the compound **2e** was obtained as a white powder with 65 % yield. R_f = 0.44 (AcOEt/pentane 1/4). Mp = 112 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.49 (s, 1H), 8.80 (d, *J* = 3.4 Hz, 1H), 7.96-7.89 (m, 4H), 7.45 (s, 2H), 7.38-7.33 (m, 5H), 7.13 (d, *J* = 3.0 Hz, 3H), 6.86 (s, 2H), 6.24 (s, 1H), 5.11 (d, *J* = 9.0 Hz, 1H), 4.32 (d, *J* = 8.4 Hz, 1H), 3.22 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.4 (C), 155.4 (C), 149.0 (CH), 141.7 (C), 139.7 (C), 138.5 (CH), 137.1 (C), 132.1 (q, *J* = 33 Hz, C), 129.1 (CH), 128.8 (CH), 128.7 (CH), 127.6 (CH), 127.4 (CH), 126.4 (CH), 123.7 (CH), 123.5 (q, *J* = 271 Hz, C), 120.3 (CH), 118.9 (CH), 115.3 (CH), 76.9 (CH), 70.8 (CH), 69.6 (CH). ^{19}F NMR (188 MHz, $CDCl_3$/CHF_3) δ = -63.45. IR: 3304, 3064, 3032, 2905, 1676, 1588, 1473, 1447, 1337, 1318, 1275, 1170, 1124, 946, 879, 843, 754, 697, 681, 619 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{29}H_{23}F_6N_4O$ [M + H]$^+$: 557.1776; found: 557.1774. $[\alpha]_D$ +161 (*c* 1.0, $CHCl_3$). $[\alpha]_{578}$ +169 (*c* 1.0, $CHCl_3$).

***(2S,4R,5R)*-N'*-(3,5-bis(trifluoromethyl)phenyl)-4,5-diphenyl-2-(pyridin-2-yl)imidazolidine-1-carbothioamide* 2f-(*2S,4R,5R*).** Following *general procedure for the preparation of platforms*, the compound **2f-(*2S,4R,5R*)** was obtained as a white powder with a yield of 84 %. R_f = 0.50 (AcOEt/pentane 1/4). Mp = 143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.91 (s, 1H), 8.82 (d, *J* = 4.5 Hz, 1H), 8.23 (s, 2H), 7.99-7.94 (m, 2H), 7.55 (s, 1H), 7.49 (t, *J* = 5.8 Hz, 1H), 7.41 (s, 5H), 7.13 (s, 1H), 7.12 (s, 1H), 7.11 (s, 1H), 6.77 (s, 1H), 6.76 (s, 1H), 6.56 (d, *J* = 6.7 Hz, 1H), 5.63 (d, *J* = 9.1 Hz, 1H), 4.44 (t, *J* = 9.6 Hz, 1H), 3.42 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.1 (C), 159.3 (C), 148.6 (CH), 142.0 (C), 139.6 (CH), 138.9 (CH), 136.8 (C), 131.4 (q, *J* = 33 Hz, C), 129.1 (CH), 128.8 (CH), 128.4 (CH), 127.5 (CH), 127.1 (CH), 126.7 (CH), 123.9 (CH), 123.4 (q, *J* = 275 Hz, C), 122.4 (CH), 121.0 (CH), 116.8 (CH), 80.4 (CH), 72.7 (CH), 70.9 (CH). ^{19}F NMR (188 MHz, $CDCl_3$/CHF_3) δ = -63.41. IR: 3270, 3247, 3034, 2914, 1588, 1471, 1456, 1369, 1339, 1273, 1173, 1128, 1008, 977, 899, 882, 759, 740, 697, 680, 629, 529 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{29}H_{23}F_6N_4S$ [M + H]$^+$: 573.1548; found: 573.1542. $[\alpha]_D$ +326 (*c* 1.0, $CHCl_3$). $[\alpha]_{578}$ +342 (*c* 1.0, $CHCl_3$).

***(2R,4S,5S)*-N'*-(3,5-bis(trifluoromethyl)phenyl)-4,5-diphenyl-2-(pyridin-2-yl)imidazolidine-1-carbothioamide* 2g-(*2R,4S,5S*).** Following *general procedure for the preparation of platforms*, the compound **2g-(*2R,4S,5S*)** was obtained as a white powder with a yield of 65 %. R_f = 0.50 (AcOEt/pentane 1/4). Mp = 149 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.85 (s, 1H), 8.82 (d, *J* = 4.7 Hz, 1H), 8.21 (s, 2H), 7.98-7.94 (m, 2H), 7.55 (s, 1H), 7.49 (t, *J* = 5.5 Hz, 1H), 7.40 (s, 5H), 7.12 (s, 1H), 7.11 (s, 1H), 7.10 (s, 1H), 6.75 (s, 1H), 6.74 (s, 1H), 6.55 (s, 1H), 5.62 (d, *J* = 9.1 Hz, 1H), 4.42 (s, 1H), 3.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.2 (C), 159.4 (C), 148.7 (CH), 142.1 (C), 139.6 (CH), 138.9 (CH), 136.9 (C), 131.3 (q, *J* = 33 Hz, C), 129.1 (CH), 128.8 (CH), 128.4 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 124.0 (CH), 123.4 (q, *J* = 271 Hz, C), 122.6 (CH), 121.1 (CH), 116.9 (CH), 80.4 (CH), 72.7 (CH), 71.0 (CH). ^{19}F NMR (188 MHz, $CDCl_3$/CHF_3) δ -63.40. IR: 3260, 3061, 3033, 2896, 1591, 1471, 1456, 1367, 1342, 1272, 1169, 1127, 1026, 1007, 977, 882, 845, 758, 740, 697, 680, 641, 552, 529 cm^{-1}. HRMS (ESI$^+$) *m/z* calcd. for $C_{29}H_{23}F_6N_4S$ [M + H]$^+$: 573.1548; found: 573.1550.

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***2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal* 3.** Following *Michael addition procedure* with isobutyraldehyde, the compound **3** was obtained as a yellow oil. R_f = 0.15 (AcOEt/pentane 1/4). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 9.51 (s, 1H), 7.48-7.38 (m, 3H), 7.27 (dd, *J* = 8.3 and 1.7 Hz, 2H), 3.15 (dd, *J* = 9.4 and 5.3 Hz, 1 H), 2.97 (dd, *J* = 18.0 and 9.4 Hz, 1H), 2.61 (dd, *J* = 18.0 and 5.3 Hz, 1H), 1.32 (s, 3 H), 1.28 (s, 3H). HPLC (Venusil Chiral OD-H column, heptane/2-propanol 75/25, 0.9 mL.min^{-1}, 30 °C, 230 nm) t_r(*S*) = 16.8 min, t_r(*R*) = 18.1 min. Data were in concordance with the literature. [25]

***2-nitro-1-phenylethanol* 4.** Following *Henry reaction procedure*, the compound **4** was obtained as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.40-7.26 (m, 5H), 5.47 (dd, *J* = 9.0 and 3.4 Hz, 1H), 4.67-4.45 (m, 2H), 2.96 (s, 1H). HPLC (Venusil Chiral OD-H column, heptane/2-propanol 85/15, 1 mL.min^{-1}, 30 °C, 230 nm) t_r(*S*) = 8.2 min, t_r(*R*) = 9.2 min. Data were in concordance with the literature.[24h]

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Keywords: Urea • Thiourea • Pyridinemethylamine• Michael addition • nitroaldol reaction

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[19] Platform **1a**: CCDC 1442858.

[20] Analysis of crude ^{1}H NMR spectra (see ESI-1) revealed the presence of both mono imine and bis imine adducts in a ratio of almost 1/1 as evidenced by characteristic chemical shifts of their respective H(6) protons that might explain somewhat lower yields obtained.

[21] Pyridylcarboxaldehyde derivatives are commercially available. Only 2-bipyridine-6-carboxaldehyde precursor was prepared according to recent literature. See ref. [16b].

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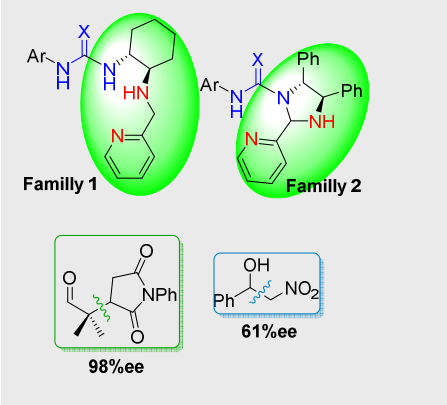

Urea-based catalytic platforms

*Olivier Colin, Hamza Boufroura, Christine Thomassigny, Serge Perato, Anne Gaucher, Jérôme Marrot, and Damien Prim**

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