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Dynamic assembly of a zinc-templated bifunctional organocatalyst in the presence of water for the asymmetric aldol reaction.

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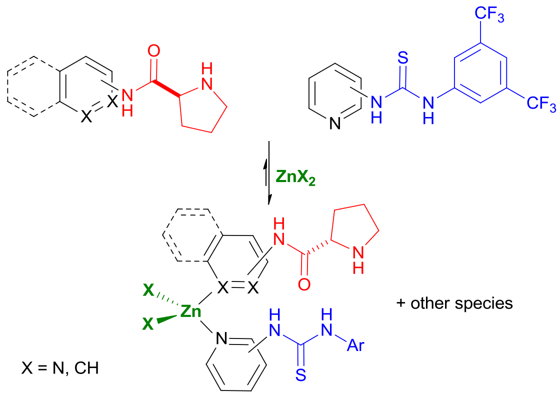
A bifunctional organocatalytic system consisting of simple pyridine ligands containing the separate catalytic functionalities was assembled using $ZnCl_2$. This novel metal-templated catalyst furnished high yields and stereoselectivities towards the aldol reaction. The addition of controlled amounts of water turned out crucial to dissolve the system and achieve optimal results.

Among the growing types of supramolecular catalysts and strategies for their preparation,[1-3] metal-templating has emerged as a powerful tool for the design of new asymmetric organocatalysts.[4, 5] In these entities, the catalytic function is carried out solely by the cooperative action of the ligands, and the metal center participates as assembly point, providing the correct geometry for catalysis. The vast majority of metal-templated organocatalysts consist of octahedral complexes where chirality at the metal is often encountered, thus leading to diastereomeric complexes that must be isolated and tested separately. A remarkable example of an iridium-templated enantioselective α-amination of aldehydes through an enamine/H-bonding bifunctional catalyst has been described recently. The octahedral geometry of the metal center was the exclusive source of chirality.[6] Simpler yet still efficient systems are known, but they might not be considered true organocatalysts: the now classical Zn-prolinate system[7-11] and recent Cu-pyridinylamine complexes[12] are proposed to work under dual Lewis acid-Lewis base catalysis.

In this Communication we present as proof-of-concept a method in which simple *monodentate* pyridine ligands containing separate thiourea and prolinamide functionalities assemble on Zn salts generating a highly stereoselective organocatalyst from a dynamic mixture (Scheme 1).[13-16] The simplicity of these ligands made their preparation trivial (See ESI), and therefore libraries of ligands could be generated very fast. Catalysts were generated and tested just by mixing the



Scheme 1. Zn-templated formation of thiourea-prolinamide bifunctional organocatalysts.

three components (two ligands and a zinc salt) in a one-pot reaction, thus facilitating the screening. Zinc was chosen as templating agent because it binds pyridines strongly and generates tetrahedral complexes[17] that would ensure a close contact between the ligands around it and avoid the formation of configurational isomers. Of course, several complexes can arise from these dynamic mixtures of ligands and metals. At least an statistical 1:2:1 mixture of MA_2:MAB:MB_2 complexes could be expected, if no higher coordination numbers appear, together with free ligands. Still, we were aware that whenever a catalytically active species was formed in sufficient amount from such a complex dynamic system, isolation of the putative catalysts would not be necessary and catalysis (and stereoselectivity) would be easily recorded.[18]

Our initial experiments were aimed at determining the optimal ligands structure, zinc salt, and reaction conditions for catalysis to take place. The asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde was used as test reaction. After synthesizing a library of pyridines, quinolines and isoquinolines with different substitution patterns bonded either to a prolinamide or a 3,5-bis(trifluoromethyl)phenylthiourea moieties, we concluded that simple pyridine ligands were unsurpassed by the other nitrogen ligands and that $ZnCl_2$ was the metal source of choice (see ESI for the full

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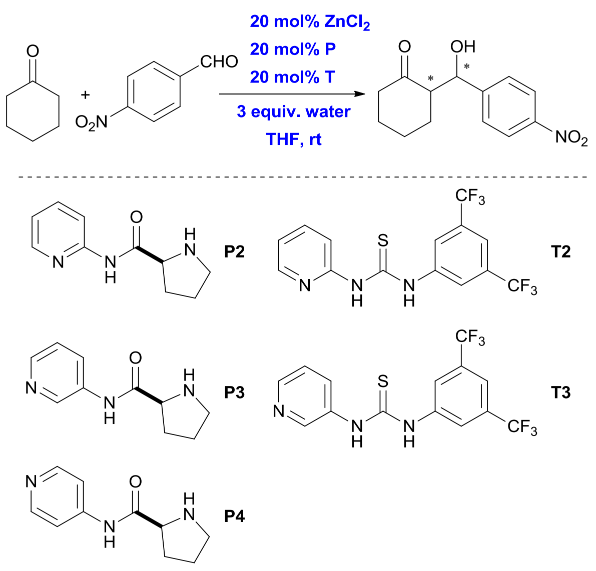
screening of ligands, zinc salts and other metal sources). The effect of the zinc counterion in zinc-prolinate catalysts had been found to be indeed remarkable, being chloride and acetate the most convenient salts.[19] Further experimentation led to the observation that the $ZnCl_2$ - pyridine ligands mixtures were not fully soluble in organic solvents. Nevertheless, the addition of a small amount of water to THF produced a fast dissolution of the system and an enhancement of the catalytic activity and specially stereoselectivity (Table 1, entries 1-2 and 5-7). Other solvents were tested as well, but poorer results were always obtained (See ESI).

Under these conditions (THF plus 3 equivalents of water respect to *p*-nitrobenzaldehyde), a deep effect of the substitution pattern in the pyridine ligands was observed, showing that best results were achieved when both 1,3-substituted prolinamide and thiourea ligands were used (Table 1, entries 5 and 6). When the temperature was decreased to -20 °C, the d.r. could be increased to 95/5 and the ee up to 92%

Table 1. Effect of the isomeric substitution at the pyridine ligands and the addition of water in the benchmark aldol reaction.



Entry	P	T	Conv.[%][a]	d.r. *anti/syn*[a]	ee [%][b]
1	P2	T2	52	69/31	76
2[c]	P2	T2	33	76/24	56
3	P2	T3	24	77/23	74
4	P3	T2	99	91/9	48
5	**P3**	**T3**	**99**	**87/13**	**79**
6[d]	**P3**	**T3**	**81**	**95/5**	**92**
7[c]	P3	T3	97	84/16	14
8	P4	T2	0	-	-
9	P4	T3	10	90/10	nd

[a] Determined by ^1H NMR. [b] ee of the *anti* diastereomer. Determined by HPLC on a chiral statiorary phase. [c] Reaction run without added water in anhydrous THF. [d] Reaction run at -20 °C.

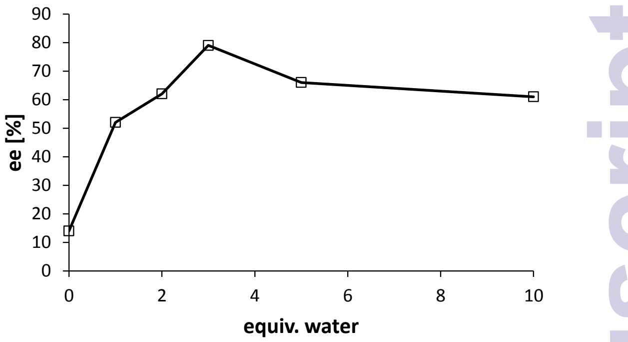


Figure 1. Effect of the amount of water in the benchmark aldol reaction catalyzed by 20 mol% $ZnCl_2$, **P3** and **T3** in THF at rt.

and still keeping a high level of conversion (Entry 6, Table 1). It is worth highlighting how the combination of these two ligands, **P3** and **T3**, led to such a high level of reactivity *and* stereoselectivity compared to the other possible combinations of ligands. A strong cooperative effect and bifunctional catalysis was thus suggested.

Several zinc-prolinate complexes that catalyze aldol reactions have been shown to be water-compatible.[7-11, 20-23] However, in our zinc-pyridine ligands example presented herein, *water is necessary* to achieve higher stereoselectivity (Entries 5 and 7, Table 1). Furthermore, the amount of water must be carefully controlled to achieve optimal results. In Figure 1, the dramatic effect on enantioselectivity of the amount of water for the aldol addition of cyclohexanone to *p*-nitrobenzaldehyde is shown, being 3 equivalents of water (respect to *p*-nitrobenzaldehyde) ideal for this reaction. Therefore, we suggest that the role of water is more complex than just dissolving the catalytic system, and likely actively participates in the mechanistic scenario.[24]

While addressing the structural features of the putative catalyst, no single crystals suitable for X-rays diffraction could be obtained, but solution NMR of the $ZnCl_2$:**P3**:**T3** mixture at variable temperature showed several species in fast exchange in the pyridine region. This result was confirmed by NMR titration of the $ZnCl_2$:**P3**:**T3** mixture with **P3** ligand. Moreover, MS (MALDI-TOF) allowed us to identify $ZnCl_2$(**P3**)$_2H^+$ and $ZnCl(H_2O)$(**P3**)(**T3**)$^+$ complexes in the catalytic mixture. Finally, UV-Vis spectroscopy showed small changes in the $ZnCl_2$:**P3**:**T3** absorption spectrum that did not correspond to a full overlapping of the independent species spectra, suggesting the formation of a new complex (See ESI for details). Altogether, the presence of a dynamic mixture of zinc complexes with exchange of pyridine ligands was suggested, in accordance to our working hypothesis.

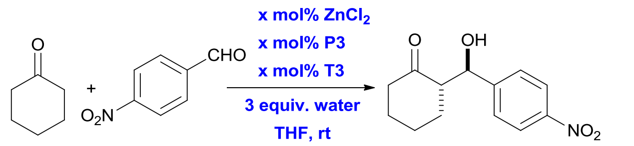
Then, a series of control experiments were carried out to clarify the nature of the catalytic species present in the reaction medium (Table 2). Ligand **P3** alone showed little catalytic activity and poor d.r. and ee (Entry 3, Table 2). The addition of ligand **T3** enhanced the reactivity but kept the same poor stereoselectivity, likely due to an activating effect of the thiourea on the aldehyde (Entry 4, Table 2). Still, $ZnCl_2$ and ligands **P3** and **T3** (Entries 1 and 2, Table 2) is the combination that clearly led to higher conversion and stereoselectivity. The mixture of $ZnCl_2$ and ligand **P3** (Entries 7 and 9, Table 2), potentially leading to Lewis acid-Lewis base catalysis, proved to be very active as well at rt, but clearly providing lower ee's. Nevertheless, at -20 °C, a mixture of $ZnCl_2$:**P3** led to lower conversion (36%) and ee (77% ee) than the active $ZnCl_2$:**P3**:**T3** mixture (entry 8, Table 2). Finally, the presence of protonated catalytic species arising from adventitious acid due to the hydrolysis of $ZnCl_2$ was discarded by adding controlled amounts of HCl to the mixture of ligands **P3** and **T3** (entries 5 and 6, Table 2). Very low conversion and poor ee's were found, but even more importantly, diastereoselectivities were the opposite and the *syn* diastereomer predominated.

In Figure 2, a conversion *vs.* time plot for the $ZnCl_2$:**P3**:**T3** and $ZnCl_2$:**P3** mixture is shown, demonstrating the rate enhancement achieved when **T3** is present. Therefore it can be concluded that several species with potential catalytic activity might be present in the dynamic mixture of $ZnCl_2$ and ligands, ranging from free ligands to $ZnCl_2$:**P3** complexes, but predominant catalysis and stereoselectivity must arise from a bifunctional zinc complex coordinated by **P3** and **T3** ligands.

From these data, a simple model for catalysis can be tentatively inferred (Scheme 2): Ligands **P3** and **T3** would bind to a zinc complex in a tetrahedral fashion, and once the enamine is formed, the aldehyde would bind the thiourea and dispose in such a way that steric crowding from the inner coordination shell (the zinc-pyridines region) would be minimized. The stereochemistry of the major aldol can be predicted correctly from this model.

Finally, with the optimized conditions in hand (20 mol% catalyst loading, THF and 3 equiv. water at -20 °C), a small set of substrates were tested in the asymmetric aldol reaction to determine the scope of the catalyst (Table 3). Although

Table 2. Blank aldol reactions indicating the formation of a 1:1:1 Zn:P3:T3 catalytic complex.



Entry	$ZnCl_2$ [%]	P3 [%]	T3 [%]	Conv. [%][a]	d.r. *anti/syn*[a]	ee [%][b]
1	20	20	20	99	87/13	79
2[e]	**20**	**20**	**20**	**81**	**95/5**	**92**
3	0	20	0	21	69/31	50
4	0	20	20	77	71/28	50
5[c]	0	20	20	9	30/70	5
6[d]	0	20	20	17	14/86	47
7	20	20	0	98	85/15	63
8[e]	20	20	0	36	94/6	77
9	20	40	0	98	83/17	54

[a] Determined by ^1H NMR. [b] Determined by HPLC on a chiral stationary phase. [c] 20 mol% of HCl (4 M in dioxane) added. [d] 40 mol% of HCl (4 M in dioxane) added. [e] Reaction run at -20 °C.

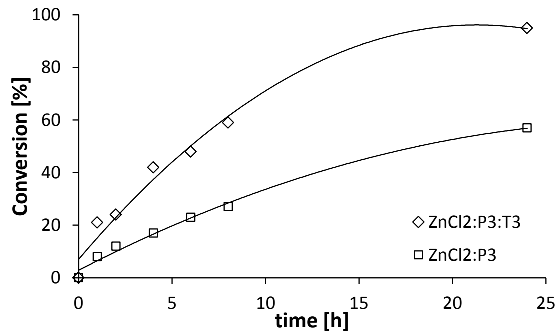
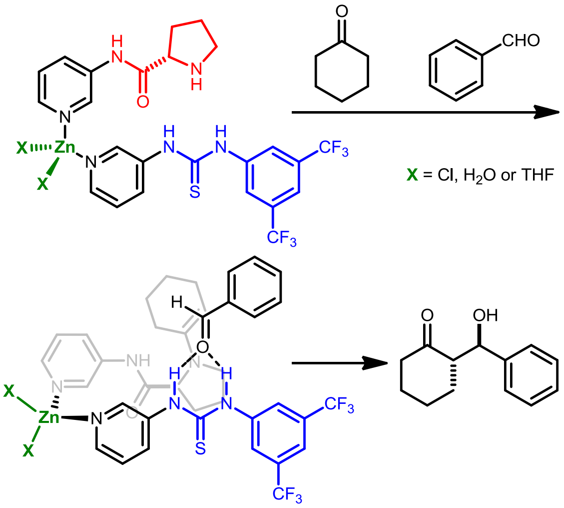


Figure 2. Conversion *vs.* time profiles in the aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde for the $ZnCl_2$:**P3**:**T3** (diamonds) and $ZnCl_2$:**P3** (squares) mixtures.

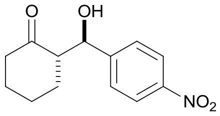
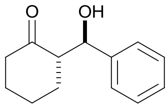
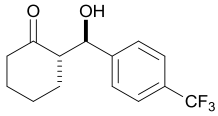
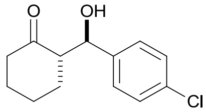
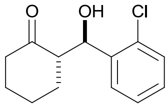
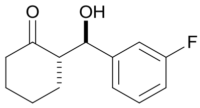
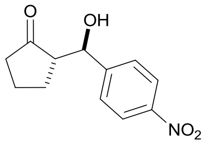
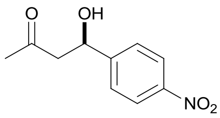


Scheme 2. Model of a $ZnCl_2$:**P3**:**T3** complex leading to the observed major stereoselectivity.

stereoselectivity (d.r. and ee) was high in the reaction of cyclohexanone with benzaldehyde (Table 3, entry 2), yield was low, and other aldehydes with electron donating groups were not tested.[25] However, aromatic aldehydes with electron withdrawing groups furnished the desired aldol adducts of cyclohexanone with good yields and excellent ee's (ranging from 88 to 97% ee) and d.r. (Table 3, entries 1 and 3-6). Cyclopentanone aldol derivatives could also be isolated in good yields but reversed d.r. (the *syn* diastereomer predominated), although the ee was modest. (Table 3, entry 7). Finally, the adduct of acetone and *p*-nitrobenzaldehyde was also prepared using our catalyst with excellent yield but modest ee (Table, 3, entry 8).

In conclusion, we have developed a bifunctional $ZnCl_2$:**P3**:**T3** catalyst suitable for the asymmetric aldol reaction with separate catalytic functions (prolinamide and thiourea) in each ligand from a dynamic mixture, using very simple monodentate 3-aminopyridine ligand derivatives. The catalyst was formed *in situ*, and experimental evidence suggested that $ZnCl_2$ templates the assembly of the pyridine ligands towards the catalytically active species, among other species that present lower catalytic activity and stereoselectivity. The

Table 3. Substrate scope of the $ZnCl_2$:**P3**:**T3** catalyst in the asymmetric aldol reaction at -20 °C for 24 h.

Entry	Product	Yield[a] [%]	d.r.[b] *anti/syn*	ee[c] [%]
1		75	95/5	92
2		18	91/9	90
3[d]		71	98/2	93
4		58	94/6	97
5		73	>99/1	88
6[d]		40	97/3	97
7[d]		90	33/67	43/73
8		97	-	62

[a] Isolated yield after flash chromatography. [b] Determined by ^1H NMR. [c] ee of the major diastereomer. Determined by HPLC on chiral stationary phases. [d] Reacted for 48 h.

addition of 3 equivalents of water was essential for the total dissolution of the system and to provide an enhanced enantioselectivity. To our knowledge, this is the first example of a metal-templated organocatalyst of this type furnishing high yields and stereoselectivities for a variety of substrates in the aldol reaction. The potential applications of this type of catalysis are huge, ranging from the fast generation and screening of tailor-made asymmetric catalysts for particular substrates to the mechanistic understanding of the separate catalytic functions and comparison with biological systems. Our on-going research in this field will be reported at due course.

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Notes and references

1 M. Raynal, P. Ballester, A. Vidal-Ferran and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2014, **43**, 1660-1733.
2 M. Raynal, P. Ballester, A. Vidal-Ferran and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2014, **43**, 1734-1787.
3 P. W. N. M. van Leeuwen, *Supramolecular Catalysis*, Wiley-VCH, Weinheim, 2008.
4 L. Gong, L.-A. Chen and E. Meggers, *Angew. Chem. Int. Ed.*, 2014, **53**, 10868-10874.
5 J. Ma, X. Ding, Y. Hu, Y. Huang, L. Gong and E. Meggers, *Nature Commun.*, 2014, **5**.
6 H. Huo, C. Fu, C. Wang, K. Harms and E. Meggers, *Chem. Commun.*, 2014, **50**, 10409-10411.
7 T. Darbre and M. Machuqueiro, *Chem. Commun.*, 2003, 1090-1091.
8 R. Fernandez-Lopez, J. Kofoed, M. Machuqueiro and T. Darbre, *Eur. J. Org. Chem.*, 2005, 5268-5276.
9 J. Kofoed, T. Darbre and J. L. Reymond, *Chem. Commun.*, 2006, 1482-1484.
10 J. Kofoed, M. Machuqueiro, J. L. Reymond and T. Darbre, *Chem. Commun.*, 2004, 1540-1541.
11 J. Kofoed, J. L. Reymond and T. Darbre, *Org. Biomol. Chem.*, 2005, **3**, 1850-1855.
12 P. Daka, Z. Xu, A. Alexa and H. Wang, *Chem. Commun.*, 2011, **47**, 224-226.
13 J. Atcher and I. Alfonso, *RSC Adv.*, 2013, **3**, 25605-25608.
14 J. Atcher, A. Moure and I. Alfonso, *Chem. Commun.*, 2013, **49**, 487-489.
15 J. Atcher, A. Moure, J. Bujons and I. Alfonso, *Chem. Eur. J.*, 2015, **21**, 6869-6878.
16 J. Sola, M. Lafuente, J. Atcher and I. Alfonso, *Chem. Commun.*, 2014, **50**, 4564-4566.
17 N. S. Gill and R. S. Nyholm, *J. Inorg. Nucl. Chem.*, 1961, **18**, 88-97.
18 M. Matsumoto, D. Estes and K. M. Nicholas, *Eur. J. Inorg. Chem.*, 2010, 1847-1852.
19 C. Andreu, F. Sanz and G. Asensio, *Eur. J. Org. Chem.*, 2012, 4185-4191.
20 C. Andreu and G. Asensio, *Tetrahedron*, 2011, **67**, 7050-705.
21 C. Andreu, T. Varea and G. Asensio, *Tetrahedron*, 2011, **67**, 8705-8709.
22 M. Penhoat, D. Barbry and C. Rolando, *Tetrahedron Lett.*, 2011, **52**, 159-162.
23 J. Paradowska, M. Stodulski and J. Mlynarski, *Adv. Synth. Catal.*, 2007, **349**, 1041-1046.
24 N. Zotova, A. Franzke, A. Armstrong and D. G. Blackmond, *J. Am. Chem. Soc.*, 2007, **129**, 15100-+.
25 A. M. Valdivielso, A. Catot, I. Alfonso and C. Jimeno, *RSC Adv.*, 2015, **5**, 62331-62335.