A copper-templated, bifunctional organocatalyst: a strongly cooperative dynamic system for the aldol reaction.

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The study of novel metal-templated dynamic organocatalytic systems has led to the identification of CuSO₄ as the most efficient template to assemble monofunctional prolinamide- and thiourea-modified pyridine ligands. The structural and electronic requirements to assemble an efficient catalyst have been disclosed: both pyridine ligands must bear a 1,3-substitution pattern, and the thiourea ligand serves as reducing agent to copper(II) as well. Eventually, the cooperative effects achieved with such a simple system deliver high reaction rates and stereoselectivities at room temperature in the asymmetric aldol reaction, requiring only 1 mol% of copper salt.

Introduction

Within the broad field of self-assembled organocatalysis,¹⁻⁴ metal-templated organocatalysis has emerged as a powerful way of assembling the catalytic functions around a metal center that solely provides the correct geometry for catalysis. Such supramolecular catalysts have been known for some time, although their use is not widespread yet maybe because their preparation, isolation and characterization are not trivial. Chiral ligands but also chirality at metal exclusively have been exploited to achieve highly stereoselective reactions.⁵⁻⁶ Nevertheless several exciting examples that make use of octahedral geometries are known in the literature: cobalt⁷⁻¹² and iridium¹³⁻¹⁸ have been successfully used to generate octahedral complexes able to perform asymmetric organocatalytic reactions through their coordination sphere. Remarkable examples include those of Gong, Meggers and co-workers, who have disclosed a series of iridium-templated catalysts with exclusive chirality at the metal center that were able to carry out Michael additions and conjugate reductions, aza-Henry reactions, α -amination and Friedel-Craft alkylations in high yields and stereoselectivities.¹³⁻¹⁸ Catalysis took place through hydrogen bonding interactions from the ligands without any participation of the metal center. In turn, previous work by Belokon and co-workers had made use of Co(III) complexes comprising both chirality at metal and chiral hemisalen ligands to achieve high ee's in the alkylation of enolates under phase transfer conditions or the epoxidation of enones.⁷⁻¹⁰ Chiral Co(III) complexes with octahedral geometry

Scheme 1 The original dynamic catalytic mixture of ZnCl₂, P3 and T3, and reaction conditions for the asymmetric direct aldol reaction.

that combine chirality at the metal center and chiral ligands have been used by Gladysz *et al.* for asymmetric Michael additions as well.¹¹⁻¹²

The following recent example also shows the potential of metal-bound organocatalytic ligands: Mirkin *et al.* have demonstrated how Pt complexes bearing amino-squaramide P,S-ligands can be allosterically regulated by HCl in the non-asymmetric Michael addition of nitroethane to nitrostyrene.¹⁹ In the context of our program aimed at understanding and developing water-tolerant organocatalysts²⁰⁻²⁴ and dynamic systems able to recognize organic molecules in aqueous environment,²⁵⁻²⁶ we have recently developed a metal-templated, dynamic approach wherein ligands and metal salts

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were simply mixed together to generate efficient organocatalytic asymmetric systems. Catalysis was carried out solely through the ligands, which upon binding to the metal center generate a new bifunctional, efficient catalyst in the asymmetric aldol reaction (Scheme 1).²⁷

This approach avoids the tedious preparative steps, and libraries of ligands and metal salts can be thus easily constructed and screened. In particular, we found that pyridine-based prolinamide and thiourea ligands assembled on zinc chloride to generate a highly active catalytic species, among other catalytic entities of lower activity. Such monodentate ligands required a 1,3-substitution pattern and were termed **P3** and **T3** respectively (Scheme 1). Notably, the addition of controlled amounts of water (3 equiv.) was crucial to ensure the full solubility of the catalytic system and achieve high yields and stereoselectivities. We proposed that a tetrahedral geometry achieved by a $\text{ZnCl}_2 \cdot \text{P3} \cdot \text{T3}$ complex was responsible for the enhanced catalytic activity towards the asymmetric aldol reaction of cyclohexanone with aromatic aldehydes at -20°C (Scheme 1).²⁷

It is noteworthy that complexes of the Zn(II) -prolinamide²⁸⁻³² and Cu(II) -pyridinylamine³³⁻³⁴ type have been proposed to work as single catalysts through a Lewis acid/Lewis base mechanism. Other Lewis acids have been successfully used in combination with organocatalysts too.³⁵⁻³⁶ Nevertheless, the high reaction acceleration achieved by our $\text{ZnCl}_2 \cdot \text{P3} \cdot \text{T3}$ system in combination with careful control experiments clearly indicated the presence of a metal-templated assembly delivering a remarkable cooperative catalysis. Hence, the only role of the metal center was to provide the assembly point for the organocatalytic ligands.²⁷

In this article we want to give a full account of our subsequent research that has led to the identification of an improved Cu-templated catalyst containing **P3** and **T3** ligands. An even stronger cooperative effect between **P3** and **T3** has been discovered in the presence of CuSO_4 , rendering an extremely efficient catalytic system under milder reaction conditions. We also provide evidence on the nature of the catalytic species, which shows that a Cu(I) sulfate complex is responsible for the observed catalytic activity.

Results and discussion

After the optimization of the ZnCl_2 -templated dynamic organocatalytic system, we turned our attention back to the role of the metal center, which must be a key parameter in defining the structure of the self-assembled catalyst. The screening of zinc and other metal salts at room temperature suggested a new direction to further improve the dynamic catalytic system (Table 1). Most Zn(II) salts in the presence of prolinamide **P3** and thiourea **T3** provided high conversion and reasonable ee for the aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde at room temperature (Entries 1-7, Table 1). Other metal salts tested were deceiving (Entries 8-10, Table 1). The very high stereoselectivity obtained with CuCl_2 , though, (d.r. 95/5 and 98% ee, Entry 11) encouraged us to work further

Table 1 Effect of the metal salt in the asymmetric aldol reaction.

Entry	Metal salt	Conv. [%] ^[a]	d.r. (anti/syn) ^[a]	ee [%] ^[b]
1	$\text{Zn(OAc)}_2 \cdot 2\text{H}_2\text{O}$	89	71/29	67
2	Zn(OTf)_2	45	68/32	73
3	$\text{Zn(ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	60	72/28	79
4	ZnI_2	89	83/17	62
5	ZnBr_2	100	85/15	59
6	ZnCl_2	99	87/13	79
7 ^[c]	$\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$	52	76/24	72
8	CdCl_2	38	75/25	61
9	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	3	76/24	n. d.
10	$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$	59	70/30	68
11	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	17	95/5	98

[a] Determined by ^1H NMR on crude mixtures. [b] Determined by HPLC on a chiral stationary phase. [c] No water added. N. d., not determined.

in a new, copper-based catalytic system despite its initial low conversion.

We therefore turned our attention to copper and undertook an screening of Cu(I) and Cu(II) salts using several solvents and variable amounts of water at rt (1-3 equiv. water with respect to *p*-nitrobenzaldehyde, Table 2). It must be noted that copper salts and ligands were mixed together for 1 hour prior to the addition of the rest of the reactants to ensure a good solubility and the formation of the putative catalysts.

First, Cu(I) salts were studied (Entries 1-6, Table 2). In THF, conversion increased when moving from CuCl and CuBr to CuI (67% conversion) but diastereo- and enantioselectivity decreased: from 92% ee for CuCl to 85% ee for CuBr and 78% ee for CuI (Entries 2, 5 and 6, Table 2). The addition of a small amount of water to CuCl did not lead to any significant improvement (Entry 1), and neither the use of DMF or acetonitrile as solvents (Entries 3 and 4, Table 2). High ee's and d.r. were already achieved, although conversion was still modest.

Then, we performed an screening of Cu(II) salts (Entries 7-18, Table 2). Copper(II) chloride (Entry 7) rendered high stereoselectivity but low conversion, similarly to CuCl (Entry 7). These results were not surpassed by copper(II) bromide (Entry 8). Basic copper(II) carbonate and copper(II) perchlorate performed poorly in all aspects (Entries 9 and 10). However, copper(II) sulfate turned out to make the catalytic system very active and stereoselective, furnishing the aldol product in >96% conversion and up to 95% ee. The presence of water in THF was moderately important (20 mol% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ already supplies the system with 1 equiv. of water) and best conditions were achieved when 2-3 equiv. of total water were present (Entries 11-14, Table 2). Other solvents were tested as well,

Table 2 Effect of copper salts in the asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde.

	Copper salt	Solvent	Conv. [%] ^[a]	d.r. (anti/syn) ^[a]	ee [%] ^[b]
1	CuCl	THF ^[c]	14	96/4	92
2	CuCl	THF	43	90/10	92
3	CuCl	CH ₃ CN	10	82/18	93
4	CuCl	DMF	17	79/21	86
5	CuBr	THF	32	86/14	85
6	CuI	THF	67	77/23	78
7	CuCl ₂ ·2H ₂ O	THF ^[c]	17	95/5	98
8	CuBr ₂	THF	7	90/10	93
9	CuCO ₃ ·Cu(OH) ₂	THF	30	75/25	76
10	Cu(ClO ₄) ₂ ·6H ₂ O	THF	4	50/50	n. d.
11	CuSO ₄ ·5H ₂ O	THF	96	91/9	93
12	CuSO₄·5H₂O	THF^[e]	98	93/7	95
13	CuSO₄·5H₂O	THF^[d]	98	93/7	95
14	CuSO ₄ ·5H ₂ O	THF ^[c]	96	91/9	95
15	CuSO ₄ ·5H ₂ O	MeOH	12	88/12	90
16	CuSO ₄ ·5H ₂ O	Dioxane ^[c]	95	93/7	95
17	CuSO ₄ ·5H ₂ O	DMF	35	91/9	n. d.
18	CuSO ₄ ·5H ₂ O	DMF ^[d]	45	94/6	99

[a] Determined by ¹H NMR on crude mixtures. [b] Determined by HPLC on a chiral stationary phase. [c] In the presence of 3 equiv. of added water. [d] In the presence of 2 equiv. of added water. [e] In the presence of 1 equiv. of added water. N. d., not determined.

but except dioxane, which furnished similar results to THF, MeOH and DMF were clearly inferior (Entries 15–18, Table 2). After this screening, we moved on to further understand the copper sulfate-based catalytic system. First, the amount of copper was studied because its dissolution into the system had proven difficult: solubility depended on the amount of copper and its ratio with respect to **P3** and **T3** ligands. For example, CuSO₄ was still not fully soluble at 5 mol% loading and 20 mol% **P3** and **T3**, and no difference in catalytic output was observed with respect to the original 20 mol% loading (Compare Entry 6 in Table 3 with Entry 13 in Table 2). Using 1 mol% CuSO₄ and decreasing amounts of ligands **P3** and **T3** from 20 down to 2 mol% led to a concomitant decrease in conversion, diastereo- and enantioselectivity (Entries 5 and 3–1, Table 3). This decrease in efficiency can be associated to a decrease in the solubility of CuSO₄ in the system as well. Optimal results were thus set for a 1:20:20 CuSO₄:**P3**:**T3** molar ratio, wherein all CuSO₄ was dissolved within one hour. It must be noted that under these conditions a clear pale yellow solution was obtained after 1 hour of pre-mixing with the ligands. Additionally, a 10 mol% of **P3** and **T3** ligands can be used provided that the system is left 4 hours pre-mixing before adding the reactants (Entry 4, Table 3). These results show the role of the ligands in solubilizing copper sulfate, which saturates the reacting solution at ca. 1 mol%.

Table 3 Effect of the amount of CuSO₄ and ligands in the asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde.

	CuSO ₄ [mol%]	P3 , T3 [mol%]	Conv. [%] ^[a]	d.r. (anti/syn) ^[a]	ee [%] ^[b]
1	1 ^[d] [e]	2	9	80/20	78
2	1 ^[d] [e]	5	40	86/14	86
3	1 ^[d] [e]	10	79	88/12	91
4	1 ^[c]	10	91	92/8	93
5	1 ^[e]	20	100	92/8	94
6	5 ^[d] [e]	20	99	93/7	95

[a] Determined by ¹H NMR on crude mixtures. [b] Determined by HPLC on a chiral stationary phase. [c] After 4 hours premixing CuSO₄ and ligands. [d] CuSO₄ was partially soluble. [e] After 1 hour pre-mixing CuSO₄ and ligands.

A deeper analysis of this system (1 mol% CuSO₄ plus 20 mol% **P3** and 20 mol% **T3**) was embraced to ascertain the nature of the catalytic species and the origin of activity and stereoselectivity. Several control reactions were sampled to construct conversion vs. time plots (Figure 1).

Free ligand **P3** (20 mol%) showed poor catalytic activity, reaching ca. 40% conversion after 21 hours at rt. The combination of **P3** and **T3** (both at 20 mol% loading) led to a slight enhancement, likely due to hydrogen bonding activation of the aldehyde. We had previously observed this effect too. In contrast, the addition of 1 mol% of CuSO₄ to **P3** produced a small decrease of the catalytic activity compared to the free **P3**. This negative result is important because it demonstrates that there is no Lewis acid enhancement at all for this system. Finally, the CuSO₄·**P3**·**T3** system (1 mol% Cu and 20 mol% **P3** and **T3**) was analyzed. A very important rate enhancement was

Figure 1 Conversion vs. time plots for the asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde using 1 mol% of CuSO₄ and 20 mol% of ligands, in THF plus 2 equiv. of water at rt. CuSO₄·**P3**·**T3**, circles; **P3**·**T3**, triangles; **P3**, diamonds; CuSO₄·**P3**, squares; CuSO₄·**P3**·**U3**, stars and dotted line.

observed, and full conversion was reached after *ca.* 10–12 hours (Figure 1).

The importance of the thiourea ligand **T3** in this reaction was made evident by running an analogous reaction using the urea derivative (1-(3,5-bis(trifluoromethyl)phenyl)-3-(pyridin-3-yl) urea, **U3**): a clearly lower rate was recorded (Figure 1).

Regarding enantioselectivity, the new copper-templated catalytic system exhibited an important enhancement as well: the aldol product was obtained in 94% ee, whereas free **P3** only reached 72% ee. No improvement was observed upon addition of hydrated CuSO_4 to **P3** (71% ee) and only a small improvement up to 80% ee was detected in the **P3** plus **T3** mixture. The use of the urea ligand (**U3**) led to significantly poorer result as well (83% ee). Altogether, a clear cooperative effect emerges from the CuSO_4 ·**P3**·**T3** system that clearly surpasses simple organocatalysis and Lewis acid or hydrogen bonding enhancements. A Cu-templated system is thus suggested (Figure 1).

At this point, it is also worth highlighting that the absolute configuration of the major aldol product corresponds in all cases to (S)-2-((R)-hydroxy(4-nitrophenyl)methyl) cyclohexanone, as determined by its specific optical rotation and the elution order in the chiral HPLC traces (See SI). This is valid for the free prolinamide ligands and our previous Zn(II)-based catalytic system as well. Therefore the chiral prolinamide ligand determines the absolute configuration of the aldol product.

To assess the regiochemical pattern in the pyridine ligands, new conversion vs. time plots were constructed using 1,2- and 1,4-substituted pyridine-prolinamide ligands, which we termed **P2** and **P4**, respectively (Figure 2). In the presence of 1 mol% CuSO_4 , the **P3**·**T3** combination was clearly superior to the **P2**·**T3** mixture, and still more efficient than the **P4**·**T3** system. Differences were even more striking in terms of ee: The slower **P2**·**T3** combination reached a moderate 85% ee of the aldol product, whereas the faster reacting **P4**·**T3** system only reached 72% ee. In contrast, the matched **P3**·**T3** system not only was the fastest, but also the most enantioselective catalytic system for the aldol reaction studied (94% ee, Figure 2).

An additional experiment was carried out with a combination of CuSO_4 , **P3** and a thiourea analog **T** containing a phenyl ring instead of the 3-pyridinyl moiety (Figure 2). The observed reaction rate falls compared to the optimum CuSO_4 ·**P3**·**T3** system, eventually obtaining a lower ee as well (89% vs. 94% ee). The need of a pyridine-type ligand for copper is thus evident. These results also show the importance of generating a particular geometry in the assembled catalytic system to achieve cooperativity. This will ultimately lead to the highest conversion and stereoselectivity.

The fast color change of the CuSO_4 ·**P3**·**T3** system from bright blue to pale yellow upon dissolution and the similarity between CuCl and CuCl_2 in terms of catalytic output (Table 2, entries 1 and 7) prompted us to examine the oxidation state of copper. In fact, after EPR analysis of several samples we concluded that a fast reduction of paramagnetic Cu(II) to diamagnetic Cu(I) was taking place in the presence of **T3**.

Figure 2 Conversion vs. time plots for the asymmetric aldol reaction of cyclohexanone and p-nitrobenzaldehyde using 1 mol% of CuSO_4 and 20 mol% of ligands, in THF plus 2 equiv. of water at rt. CuSO_4 ·**P3**·**T3**, circles; CuSO_4 ·**P4**·**T3**, squares; CuSO_4 ·**P2**·**T3**, diamonds; CuSO_4 ·**P3**·**T**, stars and dotted line.

Coordination of **P3** to Cu(II) was observed through the signal shift and the generation of a fine structure in the EPR spectrum. However, upon addition of **T3**, all paramagnetic species disappeared in less than 10 minutes (Figure 3).

The reduction of CuSO_4 and other copper salts by thiourea (H_2NCSNH_2) is indeed well known in the literature.^{37–40} We must notice that each thiourea group can reduce one Cu(II) atom.⁴¹ Moreover, ureas (like **U3**) do not participate of this reactivity, and therefore its poor performance observed in Figure 1 makes full sense.

Finally, it must be added that all the experiments carried out in this piece of work were actually carried out under fully reducing conditions to Cu(I) and an excess of **P3** and **T3** ligands.

Figure 3 Superimposed EPR spectra of CuSO_4 with the **P3** and **T3** ligands. $[\text{CuSO}_4] = 2$ mM, $[\text{P3}] = [\text{T3}] = 40$ mM in THF/ water mixtures.

Figure 4 UV-Vis spectra of $\text{CuSO}_4\cdot\text{P3}\cdot\text{T3}$ (black line), $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (blue line), **T3** (orange line) and **P3** (red line). $[\text{CuSO}_4] = 84 \text{ mM}$. $[\text{P3}] = [\text{T3}] = 840 \text{ mM}$.

UV-Vis spectrophotometry also showed that the absorption band of an aqueous solution of CuSO_4 centered at 805 nm was not present in the $\text{CuSO}_4\cdot\text{P3}\cdot\text{T3}$ system (which in this case contains a ten-fold amount of ligands compared to copper). In this latter case, the strong absorption at $< 500 \text{ nm}$ is a contribution of the absorption of both **P3** and **T3**, but no trace of the spectral characteristics of aqueous CuSO_4 is maintained (Figure 4). This result also suggests a full reaction of the copper salt to furnish new Cu(I) complexes. Detailed UV-Vis spectra for **P3**, **T3**, and $\text{CuSO}_4\cdot\text{P3}\cdot\text{T3}$ can be found in the SI, where it can also be appreciated that the spectrum of $\text{CuSO}_4\cdot\text{P3}\cdot\text{T3}$ corresponds roughly to the sum of **P3** and **T3**.

In turn, MALDI provided evidence for the formation of Cu(I) complexes containing the catalytically active ligands. In positive mode, $[\text{CuSO}_4(\text{H}_2\text{O})_3(\text{P3H})(\text{P3})+\text{Na}]^+$ ($m/z = 619.1$) and $[\text{CuSO}_4(\text{H}_2\text{O})_3(\text{P3H})(\text{T3})+\text{Na}]^+$ ($m/z = 793.0$) were detected, whereas in negative mode $[\text{CuSO}_4(\text{H}_2\text{O})_3(\text{P3})(\text{T3})+\text{Na-H}]^-$ ($m/z = 791.0$) and $[\text{CuSO}_4(\text{H}_2\text{O})_2(\text{THF})(\text{P3})(\text{T3})]^-$ ($m/z = 823.0$) were identified. In all cases, intense and easily identifiable peaks were observed. The isotopic distribution patterns observed fitted the proposed structures as well (See SI).

Further characterization of the $\text{CuSO}_4\cdot\text{P3}\cdot\text{T3}$ organocatalytic system was then carried out by ^1H NMR. A mixture of **P3** and **T3** in THF-d^8 (16 mM each) was titrated with CuSO_4 ensuring a constant concentration of ligands (Figure 5). Signal broadening and shifting was observed for most peaks. Since no paramagnetic species are present in solution, this is indicative of a dynamic system in fast exchange at room temperature. No new signals appeared either. In Figure 5 the spectral region corresponding to the aromatic and NH signals (7–11 ppm) has been expanded. The full ^1H NMR spectra with the assignment of the ligand peaks can be found in the SI. It is also noteworthy that under realistic reaction conditions (Ligands to copper ratio of *ca.* 20/1) signal broadening and shifting are already evident (Figure 5, spectrum (d)).

All the spectroscopic evidence showed above leads to the conclusion that a dynamic $\text{Cu(I)}\cdot\text{P3}\cdot\text{T3}$ system is responsible for the catalysis.

Figure 5 ^1H NMR titration of **P3** and **T3** with CuSO_4 (From bottom to top). Expansion of the pyridine signals region (6.90–10.40 ppm). Performed in THF-d^8 at 25°C at 400 MHz.

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Accordingly, it is very difficult to propose a specific catalyst structure due to the very dynamic nature of the system itself. It is even possible that several catalytic species do coexist. Several additional details are important to help streamline this catalytic system in the absence of crystallographic information: First, a related NMR experiment consisting of the titration of **P3** with paramagnetic Cu(II) shows a significantly higher peak broadening for the signals of the pyridine region compared to the pyrrolidine region (see SI). A preferable coordination of the pyridine vs. pyrrolidine moieties in **P3** is thus suggested (Solomon equation), at least for Cu(II).⁴²

Second, Cu(I) complexes have d^{10} electronic configuration, the same as Zn(II) from our previous catalytic system.²⁷ Therefore a tetrahedral geometry is likely for the catalytically active complex.

Third, the existence of other geometries cannot be discarded, though, as the detection by MS of six-coordinated Cu(I) aqua complexes might suggest.

Fourth, it could be argued that **T3** could bind to copper through the sulfur atom, as it is actually well established with thiourea ligands. However, in the case of pyridine-thiourea ligands, only the 1,2-substituted pyridines (like **T2**) are known to bind in a bidentate fashion leading to discrete Cu(I) complexes.^{43–44} 1,3- and 1,4-pyridine-thiourea ligands yield coordination networks with Cu(I) instead.⁴⁴ In this respect we have shown in Figure 2 how both the pyridine and thiourea moieties of **T3** ligand (1,3 substitution) are necessary and clearly superior to a pyridine-free analogue, which highlights the requirement of the pyridine moiety. The bidentate chelate of this **T3** ligand is nevertheless unlikely due to geometric reasons, and the large excess of ligands **P3** and **T3** compared to Cu(I) would prevent the formation of coordination networks. Therefore a discrete, pyridine-bound coordination complex is suggested.

Fifth, the requirement of a sulfate counter ion for an efficient catalysis is clear. In this respect, the importance of the sulfate ion in accelerating the reaction is evident with the following experiment: When CuCl (which renders a poor conversion, see Table 2, entries 1 and 2) is treated with Ag_2SO_4 , it becomes catalytically active and furnishes full conversion and high stereoselectivity in the aldol reaction. Indeed, these results are

in practice identical to those obtained with CuSO_4 (Scheme 2). A sulfate ion bridging two Cu(I) atoms is plausible, but again the large excess of **T3** and **P3** ligands makes this scenario unlikely.

Sixth, In view of these results, the experiment in Figure 1 with **P3** and an urea ligand (**U3**) should be carried out now using a Cu(I)-sulfate metal template. Accordingly, the above CuCl/ Ag_2SO_4 system was used. The asymmetric aldol reaction proceeded in moderate yield (63%) and ee (78% ee). This is in agreement with the higher hydrogen-bonding donor ability of thioureas vs. ureas. The full conversion vs. time plots can be found in the SI.

Seventh, the absence on non-linear effects (NLE) suggests the presence of one **P3** ligand in the catalytic complex as well (See SI).

Eight, it could be even argued that a protonated pyridine-prolinamide arising from acid coming from the oxidation of the thiourea ligand could be the responsible for catalysis. An example working under different reaction conditions is known wherein a 1,2-substituted pyridine is required, though.⁴⁵ A heterogeneous system comprising dodecylsulfonic acid and pyridine-prolinamide proved to be catalytically efficient.⁴⁶ However that micellar system in water is far different from our homogeneous system in organic medium as well. Furthermore, control experiments with pyridine-prolinamide ligands and acid in our previous communication discarded that possibility.²⁷

Altogether, in combination with the conversion vs. time plots of the catalytic system and other control experiments (Figures 1 and 2) it is strongly suggested that cooperative catalysis in this dynamic system must arise from a Cu(I) complex containing both **P3** and **T3**. A tentative model that can predict the observed stereoselectivity is shown in Scheme 3. The aldehyde binds in such a way that steric repulsion from the inner coordination shell is minimized.

At this point it is also worth mentioning that although 20 mol% of ligands **P3** and **T3** is used, the catalytically active species cannot represent more than 1 mol% (the amount of CuSO_4). This fact tells in favor of the high performance of the self-assembled, catalytically active species. We attribute the comparatively high amount of **P3** and **T3** ligands required to the dynamic nature of the catalytic system and the low solubility of CuSO_4 .

Finally, we proceeded to test the performance of the Cu-**P3-T3** system with a variety of substrates. The aldol reaction of cyclohexanone with aromatic aldehydes took place from good to excellent yields, high diastereo- and high enantioselectivities in the range of 90–94% ee (Table 4, entries 1–6). Aldehydes with electron-withdrawing groups afforded

Scheme 2 Effect of sulfate ion in the asymmetric aldol reaction catalyzed by Cu(I)-**P3-T3**.

X = H₂O, THF, SO₄²⁻

Scheme 3. Predictive model for the CuSO₄·P3·T3 catalytic system.

Table 4. The asymmetric aldol reaction catalyzed by CuSO₄ and P3 and T3.

	Product	Yield [%] ^[a]	d.r. (anti/syn) ^[b]	ee [%] ^[c]
1		95	92/8	94
2		23 ^[d]	87/13	90
3		83	93/7	92
4		45	93/7	93
5		82	98/2	94
6		68	93/7	94
7		90	24/76	61 ^[e]
8		95	-	55

[a] Isolated yield after flash chromatography on silica gel. [b] d.r. determined by ¹H-NMR. [c] ee determined by HPLC on a chiral stationary phase. [d] Not isolated. [e] 20% ee of the *syn* isomer.

better yields than benzaldehyde, though (Entry 2). High aldol yield was isolated for cyclopentanone and acetone too, although with lower stereoselectivity (Table 4, Entries 7 and 8). Remarkably, reactions took place at room temperature in 15-

24 hours, which represents faster and more practical conditions than the previous ZnCl₂-based system at -20 °C.

Conclusions

Metal-templated bifunctional organocatalytic systems provide a fast platform for the development of asymmetric reactions. Within the complexity of the dynamic mixture of metal salt, ligands and solvents, the generation of a self-assembled species leading to the emergence of strong cooperative catalysis will overcome all other side reactions. These secondary reactions might include single ligand organocatalysis and Lewis acid catalysis combined with organocatalysis. However, once a metal-templated species is able to deliver cooperative catalysis, this will become the predominant reaction mechanism.

We have found that inexpensive CuSO₄·5H₂O renders the most active metal-templated organocatalytic system to date, surpassing our previously described ZnCl₂-based system. Cross aldol reactions can now be performed at room temperature in 15-24 hours instead of -20 °C in 24-48 h with excellent yields and stereoselectivities. Furthermore, only 1 mol% of CuSO₄·5H₂O is necessary, which means that the real copper-templated catalyst is indeed at very low concentration. Further research aimed at extending the use of metal-templated organocatalytic systems to other reactions is underway in our laboratory.

Conflicts of interest

The authors declare no conflicts of interest.

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TOC Graphic:

A copper-templated bifunctional organocatalyst
delivers aldol adducts in high yields and
stereoselectivities