

Metal Cation-Driven Dynamic Covalent Formation of Imine and Hydrazone Ligands Displaying Synergistic Co-catalysis and Auxiliary Amine Effects

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Abstract: Optimizing C=N bond formation and C/N component exchange has major significance in Dynamic Covalent Chemistry (DCC). Imine and hydrazone generation from their aldehyde, amine and hydrazine components showed large accelerations in presence of AgOTf or $Zn(OTf)_2$, up to 10^4 for the Zn(II)-(*p*-anisidine)imine complex. $Zn(OTf)_2$ and auxiliary *p*-anisidine together accelerated 630 times the formation of the Zn(II)-hydrazone complex, revealing a strong synergistic effect, traced to very fast initial formation of the reactive Zn(II)-imine complex presenting a C=N bond metallo-acti-

Introduction

Simultaneous application of two or more chemical agents to assist a chemical reaction may result in a synergistic effect to a level unreachable for a single agent:^[1] i) increasing the reactivity of the reactants, thus significantly accelerating the reaction rate and decreasing the reaction time; ii) increasing reaction selectivity so as to generate cleaner outputs by way of more inputs; iii) increasing reaction yield and efficiency of product delivery. Similar behaviour manifests itself also in biological processes.^[2] The main challenges for such synergistic effects lie in ensuring the compatibility of the different agents and in analysing the kinetics of the key intermediate formation.^[3] For example, catalysis using a Lewis acid and a Lewis base together may be prevented by their mutual interaction resulting in selfguenching.^[4] Such a detrimental outcome can be circumvented by preventing the interaction as is the case in the frustrated Lewis acid-base pairs.^[5]

Reversible covalent reactions have been extensively explored in recent years in view of their importance for the development of dynamic covalent chemistry (DCC)^[6] and of its potential to lead to numerous applications in a wide range of fields. For example, a variety of responsive materials,^[7] biological applications such as drug delivery,^[8] dynamic receptors and inhibitors^[9] have been developed based on reversible reactions. Dynamic covalent libraries (DCLs) and networks,^[6,10]

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202100662 vated towards reaction with the hydrazine component. Reactions involving more entities showed kinetically faster and thermodynamically simpler outputs due to dynamic competition within a mixture of higher complexity. Catalytic amounts of metal salts and auxiliary amine gave similar marked rate accelerations and turnover, indicating true catalysis. The synergistic effect achieved by combining metallo- and organo-catalysis points to a powerful co-catalysis strategy of bond-formation in DCC through interconnected chemical transformations.

have been established which are responsive to external effectors by adaptation of the constitution of their members. As a consequence, much interest and many efforts have been devoted to the catalysis of the formation of dynamic covalent bonds in order to accelerate component exchange and constituent adaptation in systems based on imine^[11] or disulphide bonds,^[12] metathesis,^[13] transamination and transimination,^[14] and enamine exchange^[15] either in aqueous or in organic phase.

The typical two-step imine C=N formation^[6e,11,16] and component exchange reactions cover a large range of rates depending on differences in structural features and electronic properties of both carbonyl and amino partners, such as nucleophilic reactivity and basicity of amines.^[17] Hydrazone, acylhydrazone and oxime formation and exchange are much slower than those of imines.^[18] Thus, many catalysts, such as aniline and some aniline derivatives,^[19] protonic acid,^[20] molecular sieves,^[21] metal oxides and salts^[22] have been developed to accelerate the rates of these condensations. Metal cations especially of metal triflates^[23] play an important role in organic synthesis, not only serving as Lewis acids to facilitate nucleophilic attack on bound ligands, but also acting as a template^[24] by coordination of the intermediates or products in the reaction.

We report here investigations on the ability of metal cations to drive C=N imine and hydrazone bond formation as well as on the synergistic operation of metal salts and an auxiliary amine on hydrazone formation between 6-phenyl pyridine-2carboxaldehyde (A1) and two amino compounds *p*-anisidine (B1) or N-methyl pyridine hydrazine (B2). Similar results obtained for the 6-methyl (A2) and 6-bromo (A3) pyridine-2carboxaldehydes as well as the experimental procedures for data acquisition on rates and amounts of product formation are given in the SI. The reactions were performed in stoichiometric

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conditions in order to achieve highest efficiencies. However, reactions conducted in sub-stoichiometric amounts of metal cations and auxiliary amine indicated that the processes were of true catalytic nature.

Results and Discussion

The C=N formation in presence of metal salts

Imine formation driven by metal salts

To evaluate the efficiency of metal salts as Lewis acids in C=N formation, we first studied the condensation between A1 and B1, leading to the formation of the imine A1B1 (Figure 1a) both in absence and presence of AgOTf or $Zn(OTf)_2$. The evolution of

the reactions was followed by ¹H NMR spectroscopy at 25 °C in CD_3CN and the data obtained are plotted in Figure 1 and Table 1.

The results indicated that the formation of **A1B1** from the condensation of **A1** with **B1** was very slow (92%, 250 h; Figures 1b and S1), as characterized by an initial rate constant k_1 being 1.1×10^{-3} M⁻¹s⁻¹ (entry 1 in Table 1; Figures 1c and S2). This low reactivity is a reflection of the weak reactivity of the aromatic amine **B1** compared with aliphatic amines. In strong contrast, in presence of 0.5 equiv. of AgOTf, the complex [Ag(A1B1)₂]⁺ was obtained much more rapidly (95%, 45 h; Figures 1b and S3) meaning that the metal cation greatly accelerates the **A1**+**B1** condensation to give the imine ligand in its coordinated form. The initial rate k_{15} of formation in presence of AgOTf is ~18 times faster than that in absence of AgOTf (entries 1 and 2 in Table 1; Figures 1c and S4). Interest-



Figure 1. a) Imine and d) hydrazone formation from A1 and B1 or B2 in absence and in presence of metal salts [AgOTf or Zn(OTf)₂]; kinetic plots of the evolution of the corresponding b) imine and e) hydrazone formation as a function of time as obtained from integration of the imine CH=N proton signal in the 500 MHz ¹H NMR spectra (10 mM each, CD₃CN, 25 °C); Values of the initial rate constants (*k*) for the corresponding c) imine and f) hydrazone formation process calculated from a fit to a second-order reaction over the first 10% of the reaction (error of about 5% in integration of the imine proton signal). The numbers above the columns correspond to $10^3 k$ for ease of comparison. All the reactions also generated one molecule of water.

Table 1. Kin absence and	netic features of the d in presence of meta	reactions between 6-phe l salts.	enyl pyridine-2-carbo	oxaldehyde (A	1) and <i>p</i> -anision	dine (B1) or N-methyl	pyridine hydrazine (B2) in
Entry ^[a]	Reaction	Catalyst 0.5 equiv.	Product	$t_{50}[h]^{[c]}$	t ₁₀ [h] ^[d]	<i>k</i> ^[e] /10 ⁻³ M ⁻¹ s ⁻¹	Acceleration Factor
1	A1+B1	_[b]	A1B1	23	3	1.1	n.a. ^[f]
2	A1+B1+Ag(I)	Ag(I)	[Ag(A1B1) ₂] ⁺	1.4	0.5	20	18
3	A1+B1+Zn(II)	Zn(II)	[Zn(A1B1) ₂] ²⁺	\leq 0.08	\leq 0.08	\geq 18200	\geq 16500
4	A1+B2	_[b]	A1B2	21	1.94	0.97	n.a. ^[f]
5	A1+B2+Ag(I)	Ag(I)	[Ag(A1B2) ₂] ⁺	2.4	0.35	14	14
6	A1+B2+Zn(II)	Zn(II)	[Zn(A1B2) ₂] ²⁺	4	0.55	7.5	8

[a] In all these entries, aldehyde (10 mM), amine (10 mM), AgOTf or $Zn(OTf)_2$ (5 mM), at 25 °C, in CD₃CN, monitored by ¹H NMR. [b] No catalyst was added. [c] Time for 50% completion of the reaction. [d] Time for 10% completion of the reaction. [e] The rate constant *k* has been calculated from a fit to a second-order reaction over the first 10% of the reaction (error of about 5% in integration of the imine proton signal). The values are listed as 10³ *k* for ease of comparison. [f] Not applicable.

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ingly, the formation of A1B1 in presence of Zn(OTf)₂ (entry 3 in Table 1; Figures 1b and S5) is even more strongly accelerated, being completed within 5 minutes, compared to its formation in absence of metal cations or in presence of AgOTf (Figure 1; Table 1) amounting to an acceleration of about 1.65 $\times 10^4$ compared with that in absence of Zn(II) (Figures 1c and S6). This strong facilitation of the reaction by Zn(OTf)₂ may have a double origin: being doubly charged and a strong Lewis acid the cation binds and activates the pyridyl aldehyde towards attack by the amine and it may also enhance the rate of elimination of water from the hemiaminal. Titration experiments of A1 + B1 with $Zn(OTf)_2$ (Figure 2) showed that, on addition of only 0.05 equiv. of Zn(OTf)₂, within 4 minutes, the imine had formed almost fully both as free A1B1 (90%) and the remainder as its [Zn(A1B1)₂]²⁺ complex, identified by their ¹H NMR imine signals. On increasing progressively the amounts of zinc added up to 0.5 equiv., the $[Zn(A1B1)_2]^{2+}$ complex was fully formed. This result also indicated that the effect of the metal ion is catalytic (see also below). By adding more zinc, the spectrum did not change any more. Low temperature (-35 °C) ¹H NMR spectra were measured for the mixture obtained by adding either 1/2 equiv. or 1/3 equiv. of Zn(OTf)₂ to the preformed ligand A1B1. In the latter case [A1B1 to Zn(OTf)₂ ratio=3:1], two peaks were observed in the imine region (at 8.95 and 8.65 ppm) due to the complex $[Zn(A1B1)_2]^{2+}$ and free ligand A1B1 respectively (as independently shown) in the ratio 2:1, confirming the stoichiometry of the complex (Figure S7). It was verified by its single-crystal structure further [Zn-(A1B1)₂(CF₃SO₃)₂] (with deposition number 2052560 in CCDC) where Zn(II) is coordinated by the two A1B1 ligands and two triflate anions (Figures S8 and S9).

Similarly, reactivities were found using A2 and A3 instead of A1 (see Figures S10–S22 in Supporting Information). In all three cases, the metal cations may serve as Lewis acids to activate the aldehyde group driving the formation of the imine ligand.





Hydrazone formation driven by metal salts

In earlier studies, hydrazones were found to form much more slowly in organic solvent than imines.^[18] In order to verify whether metal ions could also drive hydrazone formation, the following reactions were conducted (entries 4 to 6 in Table 1). Aldehyde A1 and hydrazine B2 were reacted in absence as well as in presence of metal ions (Figure 1d). The hydrazone complex $[Ag(A1B2)_2]^+$ formed faster from A1 + B2 + 0.5 equiv. AgOTf (95%, 18 h, Figures 1e, S25-S26, entry 5 in Table 1) than the ligand A1B2 itself from A1+B2 (95%, 162 h, Figures 1e, S23-S24, entry 4 in Table 1). The corresponding rate constants are $k_{2s} = 14 \times 10^{-3} \text{ M}^{-1} \text{s}^{-1}$ and $k_2 = 0.97 \times 10^{-3} \text{ M}^{-1} \text{s}^{-1}$ in presence and in absence of AgOTf respectively, with an acceleration factor of 14 due to the presence of AgOTf (Figure 1f). While in presence of $Zn(OTf)_2$, the hydrazone complex $[Zn(A1B2)_2]^{2+}$ also formed faster by a factor of 6 from A1 + B2 + 0.5 equiv. Zn(OTf)₂ (99%, 62 h, $k_{2z} = 7.5 \times 10^{-3} \text{ M}^{-1} \text{s}^{-1}$; Figures 1e–1f, S27–S28, entry 6 in Table 1) than its ligand A1B2 itself from A1 + B2.

Similarly, results were obtained for the aldehydes A2 and A3 (see Figures S29–S41 in Supporting Information).

The results above indicate that metal salts efficiently drive both imine and hydrazone formation, the effect being larger on imine formation than on hydrazone formation. Taking into account the fact that aniline derivatives significantly increase the rate of hydrazone formation by acting as nucleophilic catalysts^[19] and on the other hand, that metal ions accelerate the formation of hydrazone ligands in the course of concomitant cation complexation, it is worth investigating whether the simultaneous application of a metal ion and the auxiliary amine *p*-anisidine would exert a synergistic effect and increase even further the rate of hydrazone formation. To this end a series of five experiments were performed. The corresponding evolutions in time of the compounds in these five dynamic mixtures are shown in the curves displayed in Figure 3.

Synergistic effects of metal salts and an auxiliary amine on hydrazone formation

Experiments involving four entities

To evaluate such a synergistic effect, the reaction of a mixture of the two components A1 + B2 (10 mM each) was followed by ¹H NMR (Figure 3a) on addition of i) amine B1 (1.0 equiv.) or ii) a metal salt (0.5 equiv.) or iii) both amine B1 and a metal salt (see entries 1 to 5 in Table 2).

In presence of only amine **B1**, **A1B2** was fully formed 3 times faster (k_{2a} Figure 3a; entry 1 in Table 2, Figures 3b–3c; Figures S42–S43) than in the reaction **A1** + **B2** in absence of the amine (entry 4 in Table 1, Figures 1e–1f). Separate experiments in presence of AgOTf or Zn(OTf)₂ gave an acceleration of the same reaction by a factor of 14 and 8 (see rate constants in entries 5 and 6 in Table 1; 18 h and 70 h, Figure 1f).

The addition of the amine **B1** to the reaction in presence of AgOTf had no visible effect (entry 2 in Table 2; Figures S44–S45). In contrast, a strong effect is observed when **B1** is

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Figure 3. a) Hydrazone formation from A1 and B2 in the presence of (i) B1 alone or together with either (ii) AgOTf or (iii) Zn(OTf)₂ as well as hydrazone formation from (iv) A1B1 and B2 and (v) $[Zn(A1B2)_2]^{2+}$ formation from $[Zn(A1B1)_2]^{2+}$ and B2. k_{2ar} , k_{2ar} , k_{3z} , k_{3z} are the initial corresponding rate constants calculated from the formation of 10% product using a second order kinetic equation. For the structures of A1B1 and $[Zn(A1B1)_2]^{2+}$ see Scheme 1 below; b) Kinetic curves obtained as a function of time from integration of the imine CH=N proton signal in the 500 MHz ¹H NMR spectra (10 mM each, CD₃CN, 25 °C); c) initial rate constants (*k*) calculated from a fit to a second-order reaction over the first 10% of the reaction for the hydrazone formation process between A1 and B2 (Figure 1) in absence of catalyst and in presence of B1 or a metal salt, AgOTf or Zn(OTf)₂ separately, as well as B1 and AgOTf or B1 and Zn(OTf)₂ together as co-catalysts along with the additional control reactions of A1B1 with B2 and $[Zn(A1B1)_2]^{2+}$ with B2. Note that the curves for A1 + B2 + B1 + Zn(II) and for $[Zn(A1B1)_2]^{2+}$ + B2 are superimposed (error of about 5% in integration of the imine proton signal). The numbers above the columns correspond to $10^3 k$ for ease of comparison.

Table 2. Kinetic features of the reactions between 6-phenyl pyridine-2-carboxaldehyde (A1) and N-methyl pyridine hydrazine (B2) in presence of metal ions separately as well as in presence of both *p*-anisidine (B1) and metal ions together and control reactions of $[Zn(A1B1)]_2^{2+}$ with B2 and A1B1 with B2.

Entry ^[a]	Reaction	Catalyst 0.5 equiv.	Product	$t_{50}[h]^{[c]}$	$t_{10}[h]^{[d]}$	$k^{\rm [e]}/10^{-3}{\rm M}^{-1}{ m s}^{-1}$	Acceleration Factor
1	A1+B2+B1	B1 (1.0 equiv.)	A1B2	8.8	0.97	2.4	3
2	A1 + B2 + B1 + Ag(I)	B1 (1.0 equiv.) + Ag(l)	[Ag(A1B2) ₂] ⁺	2.7	0.44	16	16
3	A1 + B2 + B1 + Zn(II)	B1 (1.0 equiv.) + Zn(II)	[Zn(A1B2) ₂] ²⁺	0.15	\leq 0.08	<u>≥</u> 610	630
4	[Zn(A1B1) ₂] ²⁺ +B2	_[b]	[Zn(A1B2) ₂] ²⁺	0.16	\leq 0.08	≥640	\geq 660 ^[b]
5	A1B1+B2	_ ^[b]	A1B2	1.0	0.08	39	40 ^[b]

[a] In all entries, aldehyde (10 mM), amine or hydrazine (10 mM), AgOTf or $Zn(OTf)_2$ (5 mM), at 25 °C, in CD_3CN , monitored by ¹H NMR. [b] Transimination experiments; no catalyst added; the acceleration factors correspond to the reaction of **B2** with the imine **A1B1** free (entry 5) or complexed (entry 4) compared to the reaction of **B2** with the aldehyde **A1** (entry 1). [c] Time for 50% completion of the reaction. [d] Time for 10% completion of the reaction. [e] The rate constant *k* has been calculated from a fit to a second-order reaction over the first 10% of the reaction (error of about 5% in integration of the imine proton signal). The values are listed as $10^3 k$ for ease of comparison.

combined with Zn(OTf)₂ (entry 3 in Table 2; Figures S46–S47). Indeed after just 4 minutes, the mixture contained about 25% of free A1B1, 29% of free A1, 70% of free B1 and 64% B2 in its coordinated form (Figures S48-S49) together with 26% [Zn- $(A1B2)_2$ ²⁺; the remainder consisting of combinations of A1, B1, B2 and zinc salt gave other signals in the spectrum but the corresponding species could not be identified. The components thereafter underwent recombination and after about 2 hours, the zinc complex $[Zn(A1B2)_2]^{2+}$ was fully formed leaving free B1 in the solution (Figures 3b and S46). Thus, the formation of $[Zn(A1B2)_2]^{2+}$ (k_{2az} Figures 3c and S47; 98%, 2 h, entry 3 in Table 2) was markedly increased when both metal cation and amine were added simultaneously to the reaction of A1 with B2, with an acceleration factor of 630 compared to the formation of A1B2 from A1+B2 alone. Further information about the kinetic evolution of the reaction was obtained by performing low temperature ¹H NMR experiments from -35°C to +25 °C in steps of 10 degrees (for details see SI; Figure S50). The results indicated that $[Zn(A1B1)_2]^{2+}$ formed in the very beginning as activated species which reacted with B2 to form $[Zn(A1B2)_2]^{2+}$. They revealed that metal ions and auxiliary amine together strongly enhance the hydrazone formation.

In order to gather more information about the mechanism of such a synergistic catalysis effect, a number of control experiments were conducted, in particular by modifying the order of addition of the reagents: i) adding **B2** to preformed **A1B1**; ii) adding Zn(II) to preformed **A1B1** followed by **B2**; iii) and iv) adding Zn(II) together with **B1** to the (**A1** + **B2**) mixture. The results are given in the Supporting Information (Figures S51–S56).

They confirmed the very marked synergistic co-catalytic effect on addition of Zn(II) and **B1** to the **A1** + **B2** mixture which leads to a much faster formation of the $[Zn(A1B2)_2]^{2+}$ complex than when either Zn(II) or **B1** is added separately (2 h versus 62 h or versus 50 h respectively; see entry 4 in Table 1 and entries 1 and 3 in Table 2).

In order to establish the mechanism of such co-catalysis, the features of the experiments conducted above taken together can be summarized in the following basic facts:

1) The formation of the imine **A1B1** from **A1**+**B1** is very slow (entry 1 in Table 1, $k_1 = 1.1 \times 10^{-3} \text{ M}^{-1} \text{s}^{-1}$, Figure 1c).

- 2) The formation of the hydrazone **A1B2** is very slow but increases along the sequence: i) **A1** + **B2** (entry 4 in Table 1, $k_2 = 0.97 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$, Figure 3c); ii) **A1** + **B2** + **B1** (entry 1 in Table 2, $k_{2a} = 2.4 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$, Figure 3c) a little faster with no **A1B1** observed; iii) **A1B1** + **B2** (entry 5 in Table 2, $k_3 = 3.9 \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}$, Figure 3c).
- 3) The formation of the imine-based complex $[Zn(A1B1)_2]^{2+}$ from A1+B1+Zn(II) (entry 3 in Table 1, k_{1z} =18.2 M⁻¹s⁻¹, Figure 1c) is much faster than that of the imine A1B1 in absence of Zn(II), being completed when the first spectrum is measured (about 5 min; >90%) giving an acceleration factor at least 1.65×10⁴.
- 4) The formation of the hydrazone-based zinc complex [Zn- $(A1B2)_2$]²⁺ from A1+B2+Zn(II) (entry 6 in Table 1, k_{2z} = 7.5×10⁻³ M⁻¹s⁻¹, Figure 1f) is comparable to that of the hydrazone A1B2 from A1+B2+B1 (2ii above), both being faster (about 8 times and 3 times) than that of the hydrazone A1B2 from A1+B2 (see 2i).
- 5) The formation of the ligand A1B2 from A1+B2 is accelerated by a factor of 3 by the addition of B1 (see 2i and 2ii) whereas the formation of the complex $[Zn(A1B2)_2]^{2+}$ is accelerated by a factor of 8 by addition of Zn(II), see 4) above.
- 6) The formation of $[Zn(A1B2)_2]^{2+}$ from $[Zn(A1B1)_2]^{2+} + B2$ is very fast (entry 4 in Table 2, $k_{32} = 0.64 \text{ M}^{-1}\text{s}^{-1}$, Figures S53–S54).
- 7) The formation of the hydrazone-based zinc complex [Zn- $(A1B2)_2$]²⁺ from A1+B2+B1+Zn(II) is very fast (entry 3 in Table 2, k_{2az} =0.61 M⁻¹s⁻¹, Figures 3b-3c, Figures S46-S47).

These facts indicate that i) the formation of the imine complex $[Zn(A1B1)_2]^{2+}$ is by far the fastest reaction of all; ii) B1 and Zn(II) exert independently a moderate effect on the

formation of respectively the ligand A1B2 itself and of its complex $[Zn(A1B2)_2]^{2+}$; iii) when BOTH are present together, they exert a very strong synergistic catalysis effect towards the formation of this same complex.

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It means that i) complex $[Zn(A1B1)_2]^{2+}$ is the active species in the process; ii) the C=N bond of imine A1B1 is more activated than the C=O group of aldehyde A1 by Zn(II) binding; iii) the N of imine A1B1 is a better binding site for Zn(II) than the O of C=O in A1.

Therefore, from these experiments and facts, the proposed mechanism (Scheme 1) contains two main steps: 1) Zn(II) strongly catalyses the formation of the imine-based two ligand zinc complex $[Zn(A1B1)_2]^{2+}$, characterized by its single crystal structure (see above and Figures S8); 2) **B2** reacts with the activated C=N bonds in this complex $[Zn(A1B1)_2]^{2+}$ to form $[Zn(A1B2)_2]^{2+}$ and release the free **B1**. Furthermore, whatever the different transient species forming in the two-component mixture on addition of Zn(II) and **B1**, the observed overall behaviour reveals reactional output from a mixture of higher complexity (four entities: an interesting case of more efficient, "simpler" and "faster" three molecular components A1 + B2 + B1 and one metal ion), in line with the notion that an increase in complexity may results in a simpler output, in simplexity.^[10f,25]

Similar results as for A1 were obtained for reactions run with A2 or A3: (A2 + B2) or (A3 + B2) in presence of B1 alone (Figures S57–S60), 1.0 equiv. B1 and 0.5 equiv. of either AgOTf (Figures S61–S64) or $Zn(OTf)_2$ (Figures S65–S68). The corresponding kinetic curves and rate constants are shown in Figures S69–S70, Table S1 and Figures S71–S72, Table S2.



Scheme 1. Proposed schematic mechanism for the formation of the zinc complex $[Zn(A1B2)_2]^{2+}$ from A1 + B2 in presence of both $Zn(OTf)_2$ and B1 via the intermediate formation of the $[Zn(A1B1)_2]^{2+}$ complex with $Zn(OTf)_2$ and B1 acting in a synergistic co-catalysis pathway. a) Overall reaction of $[Zn(A1B2)_2]^{2+}$ formation; b) Stepwise mechanism of $[Zn(A1B2)_2]^{2+}$ formation (see text section 2.1). The formation of $[Zn(A1B2)_2]^{2+}$ may proceed via an intermediate mixed-ligand complex.

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Experiments involving five entities

When the same reaction A1 + B2 (10 mM each) was run in presence of the three co-factors, B1 (10 mM) together with both AgOTf (5 mM) and Zn(OTf)₂ (5 mM), the silver complex [Ag-(A1B1)₂]⁺ of the imine A1B1 was already formed (95%) after only 10 minutes together with a similar amount of the Zn(II) complex of **B2**, $[Zn(B2)_2]^{2+}$ in strong contrast to the very slow formation of A1B1 in absence of metal cations. Thereafter, the set rearranged by component exchange to form the zinc complex $[Zn(A1B2)_2]^{2+}$, giving the final distribution of 8% $[Ag(A1B1)_2]^+$, 92% $[Zn(A1B2)_2]^{2+}$ and free B1 (4 h; Figure S73). Thus, in presence of both silver and zinc cations and of B1, the silver complex of A1B1, $[Ag(A1B1)_2]^+$ is the kinetic product and then the set slowly changes (38 hours) to the zinc complex of A1B2, $[Zn(A1B2)_2]^{2+}$ as thermodynamic product (Scheme 2). These results display a striking example of a faster and simpler kinetic output (the silver complex) resulting from competition within a mixture of higher complexity (five entities: three molecular components A1 + B2 + B1 and two metal ions), thus extending to the kinetic arena the behaviour simplification noted above on the thermodynamic scene.

The conversion of $[Ag(A1B1)_2]^+$ into $[Zn(A1B2)_2]^{2+}$ amounts to a kinetic switching process reminiscent of the network switching reported earlier.^[18b]

Control experiments involving five entities

A number of other control experiments involving various combinations of altogether five components and of addition sequences were performed in order to obtain more information on the reaction mechanism in the multicomponent mixture [A1 + B1 + B2 + AgOTf + Zn(OTf)_2]. They are described in the Supporting Information (Figures S74–S80). For instance, the fact that the reaction of (A1 + B1) with [B2 + AgOTf + Zn(OTf)_2] gives first the [Ag(A1B1)_2]⁺ complex whereas the reaction of (A1 + B1) with [AgOTf + Zn(OTf)_2] gives the [Zn(A1B1)_2]²⁺ complex at about the same rate, indicates that Zn(OTf)_2 is first bound by B2 which reduces its reactivity.

Experiments performed for the two sets of three components A2 + B2 and A3 + B2 in presence of both B1 and two metal cations [AgOTf and Zn(OTf)₂] gave similar results (see Figures S81–S82).

Catalysis of imine and hydrazone formation by metal salts and acid

The large accelerations observed for the formation of imine and hydrazone ligands by stoichiometric amounts of metal salts, prompted us to explore the effect of catalytic amounts of the salts (Figures 4 and S83). To this end the kinetics of the imine **A1B1** and hydrazone **A1B2** formation were investigated in the presence of only 0.05 equiv. (5 mol%) of AgOTf, $Zn(OTf)_2$, Sc(OTf)₃ and CF₃COOD (Table 3; Figure 4). Several parameters



Scheme 2. Proposed sequential mechanism for the formation of the zinc complex $[Zn(A1B2)_2]^{2+}$ from A1 + B2 in presence of the auxiliary amine B1 and both metal salts AgOTf and Zn(OTf)₂ via the initial fast formation of the intermediate complex $[Ag(A1B1)_2]^+$, which then reacts much more slowly with the complex $[Zn(B2)_2]^{2+}$ (see text section 2.2).

Table 3. Kinetic features of the reactions between 6-phenyl	pyridine-2-carboxaldehyde (A1	I) and <i>p</i> -anisidine (B1) or N-me	ethyl pyridine hydrazine (B2) in
absence and in presence of catalysts.			

Entry ^[a]	Reaction	Catalyst 0.05 equiv.	t ₅₀ [h] ^[c]	t ₁₀ [h] ^[d]	k ^[e] /M ⁻¹ s ⁻¹	Acceleration Factor	TOF/h^{-1}
1	A1+B1	_[b]	23	3	1.1×10^{-3}	1	n.a. ^[f]
2	A1+B1	Ag(I)	35	2.2	1.6×10^{-3}	1.5	0.005
3	A1+B1	Zn(II)	< 3 min	< 3 min	> 5.0	4.5×10^{3}	430
4	A1+B1	Sc(III)	< 3 min	< 3 min	> 4.8	4.4×10^{3}	410
5	A1+B1	CF ₃ COOD	<2 min	< 2 min	>29	2.6×10^4	>986
6	A1+B2	_[b]	21	1.9	0.97×10 ⁻³	1	n.a. ^[f]
7	A1+B2	Ag(I)	6.2	1.5	3.1×10^{-3}	3.2	0.98
8	A1+B2	Zn(II)	6.4	1.7	3.2×10 ⁻³	3.3	0.54
9	A1+B2	Sc(III)	0.15	<4 min	> 0.15	>155	6.5
10	A1+B2	CF ₃ COOD	0.17	<4 min	> 0.12	>124	3.5
11	A1+B2	Zn(II) + p-anisidine	7.7	1.5	4.4×10^{-3}	4.5	0.60

[a] Conditions for all these entries: aldehyde (10 mM), amine or hydrazine (10 mM), catalyst (0.5 mM), at 25 °C, in CD₃CN, monitored by ¹H NMR. [b] No catalyst was added. [c] Time for 50% completion of the reaction. [d] Time for 10% completion of the reaction. [e] The rate constant *k* has been calculated from a fit to a second-order reaction over the first 10% of the reaction (error of about 5% in integration of the imine proton signal). [f] Not applicable.

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Figure 4. Kinetic plots of the evolution of: a) imine A1B1 formation from a mixture of equal amounts of components A1 + B1 in absence of catalyst or in presence of catalysts as indicated; b) zoom of a); c) hydrazone A1B2 formation from a mixture of equal amounts of components A1 + B2 in absence of catalyst or in presence of catalysts as indicated; d) zoom of c). Data obtained as a function of time from integration of the CH=N proton signal in the 500 MHz ¹H NMR spectra (10 mM each, CD₃CN, 25 °C).

were determined including the initial rate constant, the turnover frequency (TOF) and the acceleration factor.

On addition of 0.05 eq. of Aq(I), the formation of A1B1 from its components A1 and B1 was accelerated by only a factor of 1.5 compared to the rate in the absence of the salt (entries 1 and 2 in Table 3, Figures S84–S85), indicating that Ag(I) displayed a very weak catalytic effect on imine formation. In the presence of the same amount of Zn(II), the formation of A1B1 was greatly accelerated by a factor of 4.5×10^3 (entry 3 in Table 3, Figures S86-S87). The highest rates were found in the presence of 0.05 equiv. of CF₃COOD (entry 5 in Table 3, Figures S88–S89), with a rate enhancement by a factor of $2.6 \times$ 10⁴ over that in absence of added acid. The presence of 0.05 eq. of Sc(III) triflate also displayed a remarkable catalytic effect on A1B1 formation with an acceleration factor of 4.4×10^3 (entry 4 in Table 3; Figures S90-S91). These results are in line with a study of the effect of different metal ions on the transamination reaction.[14f]

A similar set of experiments were conducted for the formation of hydrazone A1B2. Addition of 0.05 eq. of Ag(I) to A1+B2 produced a catalytic effect with an acceleration by a factor of 3.2 compared to the reaction in absence of salt

(entries 6 and 7 in Table 3; Figures S92–S93), an effect similar to that observed on imine formation. In presence of 0.05 eq. of Zn(II), a similar rate enhancement of 3.3 was obtained (entry 8 in Table 3; Figures S94–S95). On changing the aldehyde to A2, the initial reaction rate was faster while the reaction conversion time did not change much (Figures S96–S98). As in the case of imine formation, Sc(III) or CF₃COOD gave the hydrazone with a significant acceleration by a factor of 155 and 124 respectively (entries 9 and 10 in Table 3; Figures S99–S102). Finally, the combined addition of both 0.05 equiv. of Zn(II) and of **B1** made only a very minor (if any) difference (entries 8 and 11 in Table 3, Figures S103–S104), indicating that **B1** had no significant effect when present in just catalytic amount.

Taken together, the present results indicated that the addition of a catalytic amount of Ag(I), Zn(II), Sc(III) metal salts or of CF₃COOD result in catalysis of both imine and hydrazone formation. The effect displayed by these catalysts was much more pronounced on the formation of imine than that of hydrazone. It further demonstrated that the facilitation of the hydrazone formation by the synergistic operation of both Zn(II) and the auxiliary amine is due to a very fast initial imine formation catalysed by Zn(II).



Conclusion

The results described herein demonstrate the marked enhancement of the efficiency of imine and hydrazone formation by metal cations in stoichiometric conditions as well as the catalytic nature of the process. Moreover, simultaneous addition of both a metal salt and an aniline derivative as auxiliary amine to the reacting components of a DCL induced a strong acceleration of the formation of the complex of the hydrazone ligand by a synergistic fashion. Such effects are of much interest for DCC systems based on chemical bond formation by reversible reactions with differences in formation rates and thermodynamic stabilities. In particular, simultaneous addition of an auxiliary aniline as well as both a silver salt and a zinc salt resulted in a synergistic co-catalysis whereby the DCC system undergoes a switching from a kinetic product (the silver complex of an imine) to the thermodynamic product (the zinc complex of a hydrazone). This mode of co-catalysis, which combines metallo- and organo-catalysis, represents a step in the implementation in DCC of two or more catalytic species acting together in a dynamic network through synergistic interconnected chemical transformations. Such behaviours point out that increasing system complexity may result in kinetically faster and thermodynamically simpler outputs. Thus, an increase in complexity leads to simplexity $^{\left[10f,25\right] }$ on both thermodynamic and kinetic levels through advanced features such as competition, feedback and synergy in constitutional dynamic systems.

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Conflict of Interest

The authors declare no conflict of interest.

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