



Cite this: *Chem. Commun.*, 2023, 59, 4915

Received 11th February 2023,
Accepted 27th March 2023

DOI: 10.1039/d3cc00637a

rsc.li/chemcomm

Concurrent tandem catalysis enabled by nanomechanical motion in heteroleptic four-component dual-catalyst machinery†

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When the basic ligand **3** was added to the heteroleptic three-component slider-on-deck $[\text{Ag}_3(1)(2)]^{3+}$ (sliding frequency $k_{298} = 57$ kHz), it operated as a moderate brake pad ($k_{298} = 45$ kHz). Due to motion in the resulting four-component slider-on-deck $[\text{Ag}_3(1)(2)(3)]^{3+}$, both ligand **3** and silver(I) were continuously exposed and became catalytically active in a concurrent tandem Michael addition/hydroalkoxylation.

Inside multicellular organisms, enzymes catalyze a gamut of reactions, ranging from simple to cascaded¹ and concurrent tandem reactions.² In many cases, enzymatic activity critically depends on protein mobility, *e.g.*, for substrate binding or product release.³ If enzymes with multiple components are concerned, then mobility may even involve cooperative motions of distinct parts for achieving rate and efficiency increase,^{4,5} as convincingly demonstrated by the ATP synthase.⁶

Only recently, chemists have been able to mimic such spectacular enzyme capabilities by developing multicomponent catalysts,^{7–9} but few have succeeded to connect catalytic function with intrinsic motion.¹⁰ Herein, we illustrate the suitability of four-component machinery to act as a dual catalytic effector for concurrent tandem catalysis with both processes occurring in one solution. Dual catalytic activity of a single slider-on-deck – instigated only by its dynamics – has not yet been realized.¹¹

In earlier work, we demonstrated that the superior action of nanorotors and slider-on-deck systems as catalysts in both base-¹² or metal-catalyzed¹³ reactions depended crucially on their motional speed. Notably, the speed correlated with the ability of the machinery to free the catalyst¹² or product¹³ (reducing product inhibition). Such effect is conceptually

different from static liberation of a catalyst as used in switchable catalysis.^{14,15}

In detail, the four-component slider-on-deck was constructed from deck **1**,¹⁶ biped **2**, silver(I) ions and the chelating base **3** as shown in Scheme 1 (for synthesis, see ESI,[†] Chapter 1). The resulting catalytic machinery $[\text{Ag}_3(1)(2)(3)]^{3+}$ exhibited a stochastic sliding motion that in parallel liberated the silver(I) sites and base **3** for catalysis. The resulting dual-catalyst machinery proved to be



Scheme 1 (a) Chemical structure of ligands **1–3**. (b) Transformation of the three- into the four-component dual-catalyst machinery. Both organobase **3** and the silver(I) centers are liberated due to the sliding motion in $[\text{Ag}_3(1)(2)(3)]^{3+}$, which enables concurrent tandem catalysis. A & B represent the substrates, C denotes the intermediate product and D the final product of the concurrent tandem reaction.

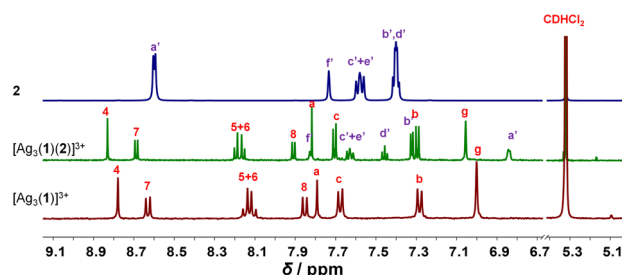
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† Electronic supplementary information (ESI) available: Experimental procedures, characterization, VT-NMR, spectral data. See DOI: <https://doi.org/10.1039/d3cc00637a>

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Scheme 2 (a) Parallel one-pot base-catalyzed Michael addition and silver(I)-catalyzed cyclization. For catalyst(s), see Tables 1 and 2. (b) Sequential Michael addition/hydroalkoxylation reaction (for mechanism, see ESI,† Scheme S4).¹⁷ (c) Further ligands used in this study.

Before designing the main system, model studies were required to warrant the operation of the catalytic machinery. Thus, the chelating amine **3** and AgBF_4 were mixed in 1:1 and 2:1 ratio to investigate their combined catalytic activity. At a ratio of 1:1, ^1H NMR spectroscopy showed formation of complex $[\text{Ag}(\mathbf{3})]^+$. In case of a 2:1 ratio, the bishomoleptic complex $[\text{Ag}(\mathbf{3})_2]^+$ was furnished (ESI,† Fig. S16).

To check the potential of both silver complexes to concurrently perform the base-catalyzed Michael addition $4 + 5 \rightarrow 6$ and the silver(i)-catalyzed cyclization of $7 \rightarrow 8$ (Scheme 2), we mixed **4**, **5** and **7** in CD_2Cl_2 in presence of the silver(i) complex (either $[\text{Ag}(\text{3})]^+$ or $[\text{Ag}(\text{3})_2]^+$) at a ratio 10:10:10:1. At room temperature (for time, see Table 1) the Michael addition catalyzed by base **3** afforded only small amounts of **6**. The yields (11% vs. 13%) were similar although in $[\text{Ag}(\text{3})_2]^+$ the base concentration formally was 2-fold the one in $[\text{Ag}(\text{3})]^+$. In contrast, the yield of the silver(i)-catalyzed reaction was high with $[\text{Ag}(\text{3})]^+$ and *ca.* 8-fold less with $[\text{Ag}(\text{3})_2]^+$ (Table 1).

Further investigation with $[\text{Ag}(\text{3})]^+$ or $[\text{Ag}(\text{3})_2]^+$ as catalyst toward the concurrent tandem reaction of **4** and **9** (in a ratio 1:10:10) affording **10** (Scheme 2b and Table 1) revealed 4% and 11% yield of **10** after 14 h, respectively, and in case of $[\text{Ag}(\text{3})_2]^+$ only a minor increase of the yield after 40 h, *i.e.*, to 17% (ESI,† Fig. S32–S35). Thus, high dual catalytic activity cannot be realized by simply combining chelating base **3** and silver ions.

We carried out further model studies to predict the catalytic strength of the final assembly $[\text{Ag}_3(\mathbf{1})(2)(3)]^{3+}$, if it were static! Thus, benzyl amine **3**, AgBF_4 , 2,9-dimesitylphenanthroline (**11**) and 4-iodopyridine (**12**) were mixed in a 1:3:3:2 ratio to furnish $2 \times [\text{Ag}(\mathbf{11})(\mathbf{12})]^+ + [\text{Ag}(\mathbf{3})(\mathbf{11})]^+$, reflecting the three coordination units in the assembly $[\text{Ag}_3(\mathbf{1})(2)(3)]^{3+}$. While silver catalysis was ON, base catalysis was completely OFF (ESI,[†] Table S1). Apparently, base **3** remains strongly bound to $[\text{Ag}(\mathbf{11})]^+$ as the binding constant is $\log K = 5.96$ (see ESI,[†] Fig. S45). Hence, the question emerged, whether the motion of bipyridine **2** in the slider-on-deck $[\text{Ag}_3(\mathbf{1})(2)(3)]^{3+}$ would lead to a steady exposure of both the base and silver(I)-ions thus setting up a dual-catalyst machinery for concurrent tandem reactions.

Upon mixing **1**, **2** and silver(I) in 1:1:3 ratio at room temperature in CD_2Cl_2 , the three-component slider-on-deck immediately self-assembled in quantitative yield, as evidenced by NMR and mass spectroscopy. The ^1H NMR of $[\text{Ag}_3(\mathbf{1})(\mathbf{2})]^{3+}$ shows a single signal set as both pyridine feet of biped **2** are sliding across all three silver(I) phenanthroline units of deck $[\text{Ag}_3(\mathbf{1})]^{3+}$. Since the pyridine feet of **2** are placed between the shielding phenanthroline's aryl groups, diagnostic upfield shifts are seen for proton signals a'-H and b'-H from 8.62 and 7.38 ppm in **2** to 6.84 and 7.32 ppm, respectively, despite their binding to the silver(I) ions. In contrast to the inner deck's proton signals, *i.e.*, a-, b- and c-H, that remained constant, most phenanthroline signals are slightly shifted downfield when compared to those in $[\text{Ag}_3(\mathbf{1})]^{3+}$ (Fig. 1). Such finding suggests that the positive charge at the silver(I) is less neutralized by the BF_4^- counter anion in $[\text{Ag}_3(\mathbf{1})(\mathbf{2})]^{3+}$ than in $[\text{Ag}_3(\mathbf{1})]^{3+}$, because motion in the former impedes close ion pairing.

Upon addition of **3** to $[\text{Ag}_3(\mathbf{1})(\mathbf{2})]^{3+}$, the four-component slider-on-deck $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ was afforded as a stand-alone nano-assembly, as seen in the ^1H NMR (Fig. 2) and ESI-MS (ESI,[†] Fig. S25). Since the proton signals of the phenanthroline core, 3-H, 4-H, 5-H, 6-H, 7-H and 8-H, exhibit identical shifts for

Table 1 Yield of **6**, **8** and **10** furnished in presence of $[\text{Ag}(\mathbf{3})]^+$ and $[\text{Ag}(\mathbf{3})_2]^+$

	Yield with [Ag(3)] ⁺			Yield with [Ag(3) ₂] ⁺		
Time (h)	Of 8 (Ag ⁺ cat.) (%)	Of 6 (base cat.) (%)	Of 10 (%)	Of 8 (Ag ⁺ cat.) (%)	Of 6 (base cat.) (%)	Of 10 (%)
2	6	<1	1	0	<1	1
7	38	6	2	2	7	7
14	68	11	4	9	13	11



Fig. 2 Comparison of partial ¹H-NMR spectra (600 MHz, CD₂Cl₂, 298 K) of **3**, silver(I) phenanthroline complex [Ag₃(1)(2)(3)]³⁺, three-component slider-on-deck [Ag₃(1)(2)]³⁺, and four-component slider-on-deck [Ag₃(1)(2)(3)]³⁺.

both slider-on-deck systems, one can deduce that [Ag₃(1)(2)(3)]³⁺ is also in motion despite the addition of ligand **3**. By comparison of the shifts of proton signals i', j'-H in **3** (δ_{i',j'} = 3.75, 3.83 ppm), [Ag₃(1)(2)(3)]³⁺ (δ_{i',j'} = 3.33 ppm) and reference [Ag(3)(11)]⁺ (δ_{i',j'} = 3.21 ppm), similar upfield shifts were observed for both complexes attesting that **3** is situated in the shielding pocket of the silver(I) phenanthroline sites (Fig. 2). As expected from product liberation in moving rotors,¹³ ligand **3** in [Ag₃(1)(2)(3)]³⁺ shows a shift that lies in between those of free **3** and [Ag(3)(11)]⁺, indicating that some is liberated by the motion in the four-component slider-on-deck.

By means of variable temperature (VT) ¹H NMR spectroscopy, we determined the exchange frequency of both slider-on-deck assemblies. In case of the three-component [Ag₃(1)(2)]³⁺, the 4-H proton signal split at -60 °C into two peaks (ratio 2 : 1) due to freezing the sliding of biped 2 across deck 1 on the NMR time scale (Fig. 3). Using WinDNMR,¹⁸ the ¹H NMR traces were simulated over a large temperature range, providing the activation data as ΔH[‡] = 45.8 kJ mol⁻¹, ΔS[‡] = 0.7 J mol⁻¹ K⁻¹ and ΔG₂₉₈[‡] = 45.6 kJ mol⁻¹ as well as the exchange rate k₂₉₈ = 57 kHz. Contrastingly, in the four-component slider-on-deck [Ag₃(1)(2)(3)]³⁺, the proton 4-H signal split already at -40 °C. The kinetic analysis afforded k₂₉₈ = 45 kHz along with the activation data ΔH[‡] = 47.8 kJ mol⁻¹, ΔS[‡] = 5.4 J mol⁻¹ K⁻¹ and ΔG₂₉₈[‡] = 46.3 kJ mol⁻¹. As a result of the addition of **3** to [Ag₃(1)(2)]³⁺, the motion thus slowed down by 21% at room temperature and even more at lower temperature. This trend is



Fig. 3 Experimental (left) and simulated (right) partial VT ¹H NMR spectra (CD₂Cl₂, 600 MHz) of (a) [Ag₃(1)(2)]³⁺ and (b) of [Ag₃(1)(2)(3)]³⁺.

Table 2 Product yield in both concurrent and sequential reactions catalyzed by [Ag₃(1)(2)(3)]³⁺

Time (h)	Yield of 6 (base cat.) (%)	Yield of 8 (Ag ⁺ cat.) (%)	Yield of 10 (dual seq. cat.) (%)
0	0	0	0
2	7	17	2
4	18	35	7
6	25	47	12
8	29	53	15
10	33	61	21
12	35	64	27
14	38	67	34

a result of the higher positive activation entropy of [Ag₃(1)(2)(3)]³⁺ that is increased due to the liberation of **3** into solution in the rate-determining step. As in the rate-limiting step the biped must depart from one silver(I) binding site to kick out the base **3**, both the silver(I) and **3** are temporarily available for catalysis.

To investigate whether both catalytic units in [Ag₃(1)(2)(3)]³⁺ are simultaneously active we tested for concurrent base and silver(I) catalysis. Thus, the slider-on-deck [Ag₃(1)(2)(3)]³⁺ and reactants **4**, **5**, and **7** were combined (1:30:30:30) in CD₂Cl₂ for running both transformations parallel (Scheme 2a). The reactions were monitored by ¹H NMR over 14 h at room temperature, showing formation of the silver(I)-catalyzed product **8** (67%) and base-catalyzed product **6** (38%) as displayed in Table 2. The data demonstrate that the base-catalyzed formation of **6** is slower than the silver-catalyzed reaction affording **8**.

Since dual activity of this slider-on-deck is increased in comparison with the static model compounds, we probed a concurrent tandem catalysis consisting of a Michael addition followed by hydroalkoxylation (see Scheme 2b). Hence, the slider-on-deck [Ag₃(1)(2)(3)]³⁺ and reactants **4** & **9** (1:30:30) were mixed in CD₂Cl₂. The kinetic profile of this reaction was monitored at room temperature by ¹H NMR over 14 h at 2 h intervals. ¹H NMR spectra showed 34% of **10** after 14 h (black curve in Fig. 4).

Closer inspection revealed several surprising features. Initially, the base catalyzed reaction is the rate-determining step in the tandem reaction to **10**, because intermediate **10'** created by



Fig. 4 Yield of **10** with time in the tandem reaction catalysed by [Ag₃(1)(2)(3)]³⁺.

base catalysis does not show up in the ^1H NMR. Only, when product **10** of the tandem base- and silver(i) catalysis had formed to more than 15%, then intermediate **10'** (Scheme 2b) became visible. Furthermore, the kinetic profile of the tandem reaction showed an increasing rate the more product **10** had formed (Fig. 4), indicative of some autocatalytic effect. To check whether it is the final product **10** that impacts on the rate, the slider-on-deck $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$, reactants **4**, **9** and product **10** were mixed in a 1:30:30:3 ratio in CD_2Cl_2 . Now 59% of **10** (49% after subtracting 10% of the initially added **10**) was afforded after 14 h with higher rate (initial rate at $t = 0$: $\nu_0 = 2.8 \mu\text{M s}^{-1}$) than in absence of product **10** ($\nu_0 = 2.1 \mu\text{M s}^{-1}$) (Fig. 4). This effect is attributed to the competitive displacement of base **3** at the silver(i)-loaded phenanthroline by product **10** as it may act as ligand as well. Thus, in presence of sliding motion and 1 equiv. of **10**, more base **3** is released.

In conclusion, we report a three-component slider-on-deck assembly $[\text{Ag}_3(\mathbf{1})(\mathbf{2})]^{3+}$ with a sliding speed of $k_{298} = 57 \text{ kHz}$. Addition of amine **3** to the slider-on-deck converted it into a four-component dual-catalyst machinery $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ with a reduced sliding speed ($k_{298} = 45 \text{ kHz}$). The sliding motion in the machinery instigated two simultaneous events that enabled concurrent tandem catalysis: (a) liberation of base **3**, and (b) exposure of the silver(i) sites, so that they could act synergistically¹⁹ as dual catalyst in the two-step synthesis of **10**. Thus, the present system portrays a lucid example of unleashing multiple catalytic functions instigated by a single nanomechanical motion within artificial catalytic machinery.

We thank the DFG (Schm 647/22-1, no. 491092614) and the Univ. of Siegen for continued support. Moreover, we are indebted to Dr Paululat (Siegen) for the VT- ^1H NMR measurements.

Conflicts of interest

There are no conflicts to declare.

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