


 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†

 Emad Elramadi,[‡] Sohom Kundu,[‡] Debabrata Mondal and Michael Schmittl[‡] *

When the basic ligand **3** was added to the heteroleptic three-component slider-on-deck $[Ag_3(1)(2)]^{3+}$ (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 $[Ag_3(1)(2)(3)]^{3+}$, 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 $[Ag_3(1)(2)(3)]^{3+}$ 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 $[Ag_3(1)(2)(3)]^{3+}$, 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.

Center of Micro and Nanochemistry and (Bio)Technology, Organische Chemie I, School of Science and Technology, University of Siegen, Adolf-Reichwein-Str. 2, Siegen D-57068, Germany. E-mail: schmittl@chemie.uni-siegen.de;

Tel: +49(0) 2717404356

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

‡ Emad Elramadi and Sohom Kundu contributed equally.



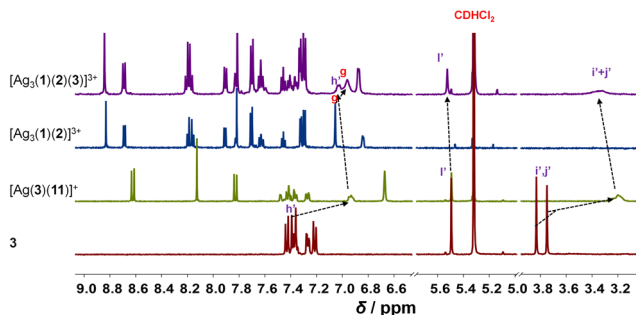


Fig. 2 Comparison of partial ^1H -NMR spectra (600 MHz, CD_2Cl_2 , 298 K) of **3**, silver(I) phenanthroline complex $[\text{Ag}(\mathbf{3})(\mathbf{11})]^+$, three-component slider-on-deck $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$, and four-component slider-on-deck $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$.

both slider-on-deck systems, one can deduce that $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ is also in motion despite the addition of ligand **3**. By comparison of the shifts of proton signals i' , j' -H in **3** ($\delta_{i',j'} = 3.75, 3.83$ ppm), $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ ($\delta_{i',j'} = 3.33$ ppm) and reference $[\text{Ag}(\mathbf{3})(\mathbf{11})]^+$ ($\delta_{i',j'} = 3.21$ 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 $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ shows a shift that lies in between those of free **3** and $[\text{Ag}(\mathbf{3})(\mathbf{11})]^+$, 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 $[\text{Ag}_3(\mathbf{1})(\mathbf{2})]^{3+}$, 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 $\Delta H^\ddagger = 45.8$ kJ mol $^{-1}$, $\Delta S^\ddagger = 0.7$ J mol $^{-1}$ K $^{-1}$ and $\Delta G_{298}^\ddagger = 45.6$ kJ mol $^{-1}$ as well as the exchange rate $k_{298} = 57$ kHz. Contrastingly, in the four-component slider-on-deck $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$, the proton 4-H signal split already at -40 °C. The kinetic analysis afforded $k_{298} = 45$ kHz along with the activation data $\Delta H^\ddagger = 47.8$ kJ mol $^{-1}$, $\Delta S^\ddagger = 5.4$ J mol $^{-1}$ K $^{-1}$ and $\Delta G_{298}^\ddagger = 46.3$ kJ mol $^{-1}$. As a result of the addition of **3** to $[\text{Ag}_3(\mathbf{1})(\mathbf{2})]^{3+}$, 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 (CD_2Cl_2 , 600 MHz) of (a) $[\text{Ag}_3(\mathbf{1})(\mathbf{2})]^{3+}$ and (b) of $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$.

Table 2 Product yield in both concurrent and sequential reactions catalyzed by $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$

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 $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ 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 $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ are simultaneously active we tested for concurrent base and silver(I) catalysis. Thus, the slider-on-deck $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ and reactants **4**, **5**, and **7** were combined (1 : 30 : 30 : 30) in CD_2Cl_2 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 $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$ and reactants **4** & **9** (1 : 30 : 30) were mixed in CD_2Cl_2 . 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

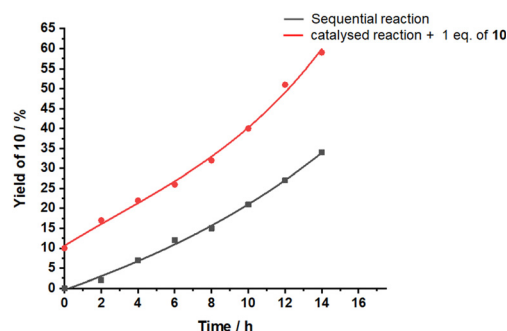


Fig. 4 Yield of **10** with time in the tandem reaction catalysed by $[\text{Ag}_3(\mathbf{1})(\mathbf{2})(\mathbf{3})]^{3+}$.



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.

Notes and references

- 1 Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051–15053.

- 2 J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001–1020.
- 3 P. Ojeda-May, A. U. Mushtaq, P. Rogne, A. Verma, V. Ovchinnikov, C. Grundström, B. Dulko-Smith, U. H. Sauer, M. Wolf-Watz and K. Nam, *Biochemistry*, 2021, **60**, 2246–2258.
- 4 M. J. Wiester, P. A. Ulmann and C. A. Mirkin, *Angew. Chem., Int. Ed.*, 2011, **50**, 114–137.
- 5 K. A. Henzler-Wildman, V. Thai, M. Lei, M. Ott, M. Wolf-Watz, T. Fenn, E. Pozharski, M. A. Wilson, G. A. Petsko, M. Karplus, C. G. Hübner and D. Kern, *Nature*, 2007, **450**, 838–844.
- 6 P. Neupane, S. Bhujju, N. Thapa and H. K. Bhattarai, *Biomol. Concepts*, 2019, **10**, 1–10.
- 7 (a) Z. Dong, Q. Luo and J. Liu, *Chem. Soc. Rev.*, 2012, **41**, 7890–7908; (b) M. Raynal, P. Ballester, A. Vidal-Ferran and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2014, **43**, 1734–1787; (c) D. Zhang, T. K. Ronson and J. R. Nitschke, *Acc. Chem. Res.*, 2018, **51**, 2423–2436; (d) N. Mittal, M. S. Özer and M. Schmittel, *Inorg. Chem.*, 2018, **57**, 3579–3586; (e) F. J. Rizzuto, L. K. S. von Krbek and J. R. Nitschke, *Nat. Rev. Chem.*, 2019, **3**, 204–222; (f) G. Olivo, G. Capocasa, D. Del Giudice, O. Lanzalunga and S. Di Stefano, *Chem. Soc. Rev.*, 2021, **50**, 7681–7724; (g) P. Howlader and M. Schmittel, *Beilstein J. Org. Chem.*, 2022, **18**, 597–630; (h) A. W. Heard, J. M. Suárez and S. M. Goldup, *Nat. Rev. Chem.*, 2022, **6**, 182–196; (i) R. Saha, B. Mondal and P. S. Mukherjee, *Chem. Rev.*, 2022, **122**, 12244–12307.
- 8 *Supramolecular Catalysis: New Directions and Developments*, ed. P. W. N. M. van Leeuwen and M. Raynal, Wiley-VCH GmbH, Weinheim, 1st edn, 2022, ISBN: 9783527349029.
- 9 (a) N. Mittal, S. Pramanik, I. Paul, S. De and M. Schmittel, *J. Am. Chem. Soc.*, 2017, **139**, 4270–4273; (b) Y. Li, X. Caumes, M. Raynal and L. Bouteiller, *Chem. Commun.*, 2019, **55**, 2162–2165; (c) E. Iniesta and A. Vidal-Ferran, *Chem. Commun.*, 2020, **56**, 6364–6367.
- 10 L. van Dijk, M. J. Tilby, R. Szpera, O. A. Smith, H. A. P. Bunce and S. P. Fletcher, *Nat. Rev. Chem.*, 2018, **2**, 1–18.
- 11 V. V. Rajasekaran, A. Ghosh, S. Kundu, D. Mondal, T. Paululat and M. Schmittel, *Angew. Chem., Int. Ed.*, 2022, **61**, e2022124.
- 12 I. Paul, A. Goswami, N. Mittal and M. Schmittel, *Angew. Chem., Int. Ed.*, 2018, **57**, 354–358.
- 13 P. K. Biswas, S. Saha, T. Paululat and M. Schmittel, *J. Am. Chem. Soc.*, 2018, **140**(29), 9038–9041.
- 14 S. Gaikwad, A. Goswami, S. De and M. Schmittel, *Angew. Chem., Int. Ed.*, 2016, **55**, 10512–10517.
- 15 S. De, S. Pramanik and M. Schmittel, *Angew. Chem., Int. Ed.*, 2014, **53**, 14255–14259.
- 16 E. Elramadi, A. Ghosh, I. Valiyev, P. K. Biswas, T. Paululat and M. Schmittel, *Chem. Commun.*, 2022, **58**, 8073–8076.
- 17 U. Kaya, P. Chauhan, K. Deckers, R. Puttreddy, K. Rissanen, G. Raabe and D. Enders, *Synthesis*, 2016, 3207–3216.
- 18 H. J. Reich, *NMR Spectrum Calculations: WinDNMR, Version 7.1.13*, Department of Chemistry, University of Wisconsin.
- 19 L. Zhou and L. Liu, *Chem. Commun.*, 2021, **57**, 5690–5693.

