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Interplay between *anti–anti* and *syn–anti* conformations of thiourea modulating ON–OFF catalysis†

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The design, synthesis and operation of a readily accessible two-state switch are demonstrated. The switch initially exists in an intramolecularly hydrogen-bonded self-locked state, as evidenced by the solution-state NMR and solid-state structure. The switch can be reversibly altered between *anti–anti* and *syn–anti* conformations by adding and removing Cu^{+} ions, as evidenced by the NMR and crystallographic study. The *anti–anti* form was found to be catalytically active in the Michael addition reaction, whereas the *syn–anti* form was catalytically inactive.

Introduction

Majority of the enzymatic processes are tuned *via* allosteric regulation,[1] which is a major inspiration behind the development of "smart" synthetic catalysts[2] whose efficacy in altering the rate[3] or regio/stereo-selectivity[4] of diverse chemical transformations can be modulated by external stimuli. Understanding the principles and behaviour of these synthetic switchable catalysts will not only help mimic the biological counterparts where several reactions occur in parallel without interfering with each other but also aid in identifying their potential applications in sustainable chemistry and green synthesis. A traditional catalyst generally can catalyse one reaction; however, switchable catalysts can control multiple reactions from several states,[5] and they can selectively react with specific components.[6] Moreover, they are the basis of artificial signal transduction.[7] This approach minimises waste generation, reduces energy consumption, and improves overall process efficiency by selectively activating catalysts only when needed. Moreover, the capability to control catalytic reactions in real time enables adaptive and responsive chemical processes, paving the way for dynamic and programmable chemistry with promising prospects. Therefore, discovering multiple switchable catalysts is essential. In this regard, several switchable catalysts have been reported that can control one reaction,[8] multiple reactions,[9] tandem reactions[10] *etc*. However, most switchable catalysts synthesised to date involve multi-steps (more than ten steps in general), thus limiting their use. Herein, we report a two-step synthesis of a switchable catalyst that can switch between two states by adding and removing copper ions and regulating Michael addition[11] reactions between the 1,3-dicarbonyl compound and *trans*-beta nitro styrene in an ON/OFF manner.

Design

The design of the switch combines thiourea, a known organocatalyst,[12] and an unshielded phenanthroline in such a way that the thiourea moiety is locked with the phenanthroline unit *via* intramolecular hydrogen bonding, as shown in Fig. 1. Thus, we expect the thiourea moiety to be unavailable in the solution for catalysing the Michael addition reaction between the 1,3-dicarbonyl compound and β-nitrostyrene. However, adding one equivalent of copper-loaded shielded phenanthroline would form a HETPHEN-type[13] complex that will disrupt the intramolecular hydrogen bond, and N–H will be available in solution for catalysing the Michael addition reaction. Adding a better complexing agent, such as KCN/cyclam,[14] will abstract Cu^{+}, resetting the switch to its initial locked state and thus switching off the reaction.

Results and discussion

The desired switch was synthesised in two steps from commercially available compounds. First, 2-bromo[1,10]phenanthroline was subjected to a Suzuki coupling reaction with 2-aminophenyl boronic acid in the presence of Pd(0) as a catalyst to yield compound **2** which upon further treatment with 3,5-

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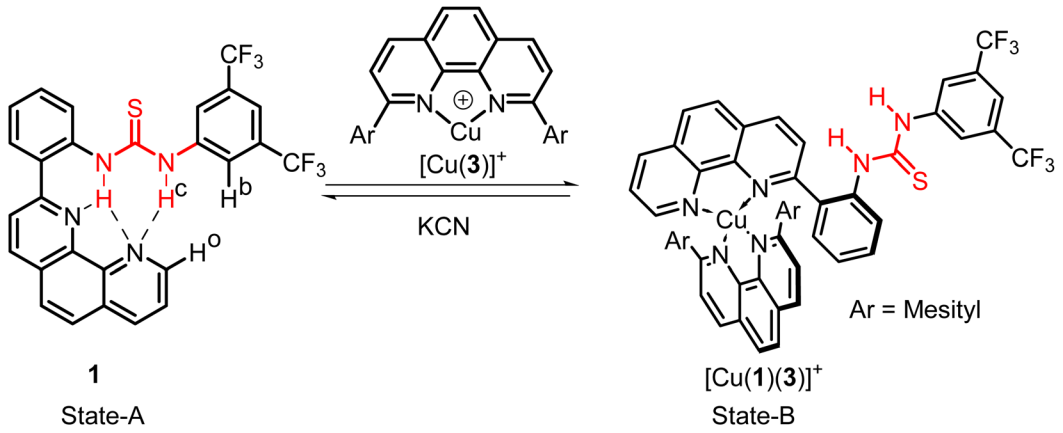

Fig. 1 Blueprint and switching between the open and closed state of the switch.

bistrifluoromethylphenylthiocyanate afforded switch **1** (Fig. 2a). The intermediate and switch **1** were unequivocally characterised by ^{1}H (Fig. S2 and S6†) and ^{13}C NMR (Fig. S3 and S8†), as well as ESI-MS. For example, the formation of switch **1** was confirmed by the appearance of a peak centred at *m*/*z* 543.1072 (Fig. S10†) in the ESI mass spectrum, which corresponds to $[\mathbf{1} + H]^+$ with a matching isotopic distribution pattern between experimental and theoretical spectra. The formation of **1** was further confirmed by NMR spectroscopy. The appearance of the sharp N–H protons of the switch at a very downfield region (16.6 and 10.92 ppm) in the ^{1}H NMR spectrum indicates hydrogen bonding with the phenanthroline nitrogen (Fig. S6†). The concentration-independent ^{1}H NMR spectrum further supports intramolecular hydrogen bonding (Fig. S21†). The correlation of c-H (10.92 ppm) with o-H (8.38 ppm) and b-H (8.04 ppm) in the NOESY spectrum further supports the self-locked conformation (Fig. S12†). The conformation of switch **1** has also been unveiled by single-crystal X-ray crystallography, which shows that the switch exists in a self-locked state (Fig. 2c) where the N–Hs are intramolecularly hydrogen bonded with phenanthroline nitrogen (1.898 (d-H and N1) and 2.148 (c-H and N10) Å). In summary, all the experimental data demonstrate **1** to be intramolecularly hydrogen-bonded as expected.

With **1** in our hand, we first focused on switching from state A to state B by adding $[Cu(CH_3CN)_4]PF_6$ as a stimulus. Indeed, when copper-loaded phenanthroline was added to a solution of switch **1**, the yellow colour turned immediately red

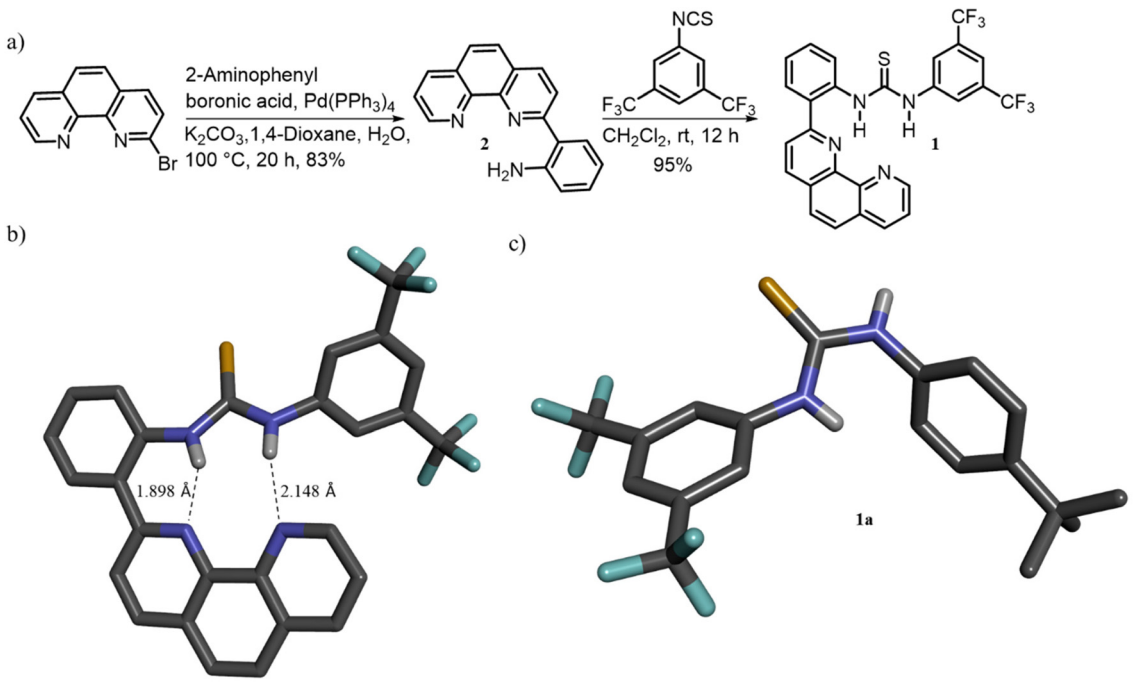

Fig. 2 (a) Synthetic scheme of the switch; crystal structure of (b) **1** and (c) **1a**.

(MLCT), indicating the formation of the copper complex. The formation of the HETPHEN-type complex in solution was further established from its ^{1}H NMR spectrum, which showed a significant upfield shift of the mesityl protons from 6.96 ppm to 6.13 and 6.27 ppm (Fig. 4) due to shielding by the ring currents from the switch. Moreover, the ESI mass spectrometry of the complex revealed the expected peak for the heteroleptic complex at *m*/*z* 1021.2537 Da (Fig. S17†) with a isotopic splitting pattern matching with the theoretical one. The HETPHEN type complex was further established by the appearance of the MLCT band at 433 nm in UV-vis spectroscopy (Fig. S23†).

The ^{1}H NMR spectroscopy results supported the coordination-induced conformational change of the switch. The upfield shifts of N–H protons of the switch from 16.6 and 10.92 ppm to 8.11 and 7.31 ppm (Fig. S13†) signify the disruption of intramolecular hydrogen bonding, probably due to the formation of state B. Moreover, the NOESY spectrum of the complex does not show the correlation between c-H (7.96 ppm) and o-H (8.63 ppm) (Fig. 4a), signifying the change of conformation. The switch can be brought back to its initial state by treating the complex with either KCN or cyclam. As anticipated, adding KCN extracted Cu^+ from [Cu(**1**)(**3**)]PF_6, thereby regenerating the switch in its initial state as evidenced by the appearance of N–H protons at 16.6 and 10.92 ppm and the disappearance of mesityl protons from 6.13 and 6.27 ppm (Fig. 4). Reversible switching between the two states of the switch by adding and removing Cu^+ was performed for up to three cycles without any noticeable degradation (Fig. S20†).

Having established the reversible switching between the two states of the switch by addition and removal of copper ions, we investigated the efficacy of the switch and the copper complex of the switch to promote Michael addition of 1,3-dicarbonyl nucleophiles to *trans*-β-nitrostyrene (**4**). We first established that the Michael addition reaction between **4** and **5a** does not proceed without the catalyst (Fig. S24†). We then carried out the Michael addition reaction in the presence of switch **1**. To our surprise, when a mixture of **4**, **5a**, and Et_3N (in a 100 : 1000 : 1 ratio) was stirred in the presence of five mol% of switch **1** in $CDCl_3$ at room temperature, the Michael addition product **6** was obtained (~40% conversion after 25 h), as evidenced by ^{1}H NMR spectroscopy (Fig. S25†). In contrast, the use of the copper complex of the switch does not induce the formation of any product under similar conditions (Fig. S26†). Similarly, switch **1** can catalyse the Michael addition reactions of **4** with various Michael donors (**5b**, **5c**, **5d** and **5e**), whereas the above reactions did not proceed in the presence of [Cu(**1**)(**3**)]PF_6 (Scheme S4 and Fig. S31–S38†).

Initially, we expected that the catalytic activity in the closed state would be less compared to that in the open state. To investigate this unexpected OFF state of the complex, we tried to grow the crystals of the copper complex to get complete confirmation. Fortunately, after several trials, we could grow the crystals of the copper complex. The complex's crystal structure showed that the thiourea conformation is *syn–anti* instead of *anti–anti* (Fig. 3a). A literature survey also confirmed that thiourea can exist in the *syn–anti* conformation.[15] Therefore, state-B will not be able to sufficiently increase the electrophili-

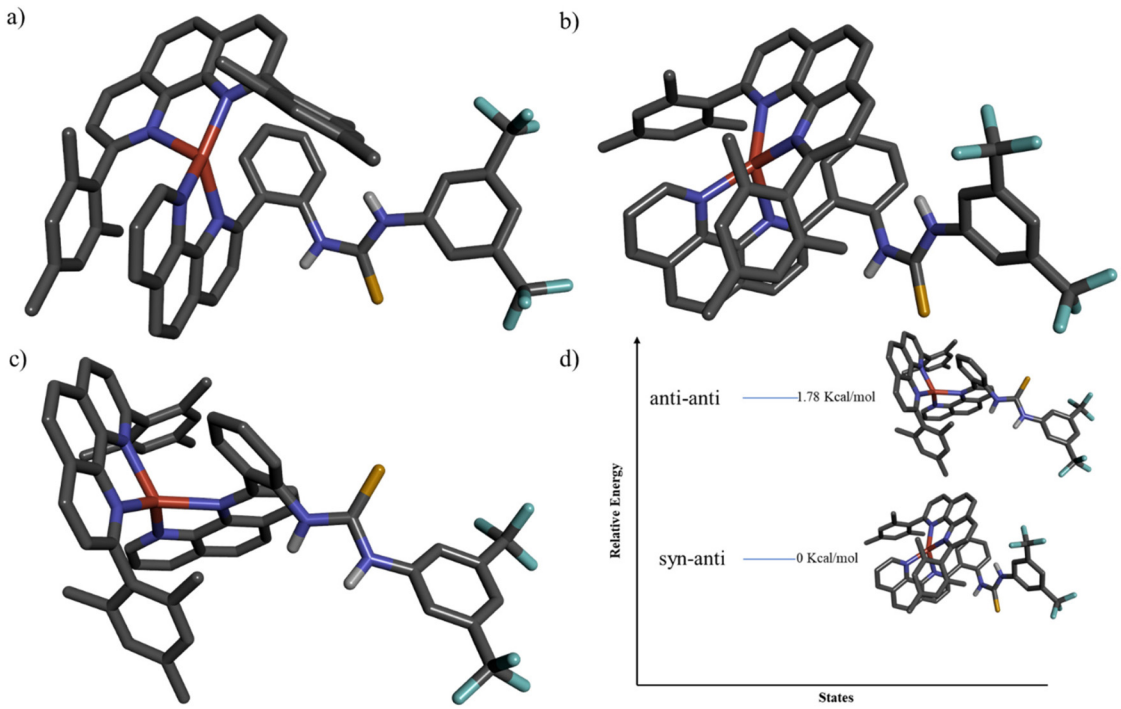

Fig. 3 (a) Crystal structure of [Cu(**1**)(**3**)]$^+$; geometry optimized structure of (b) the *syn–anti* conformation and (c) the *anti–anti* conformation of [Cu (**1**)(**3**)]$^+$ at the 6-311G(d,p) basis set on C, H, N, F, S and the LANL2DZ ECP basis set on Cu. (d) Relative energies of optimised geometries of different configurations of [Cu (**1**)(**3**)]$^+$. It was found that the *syn–anti* conformation is more stable compared to *anti–anti* conformation.

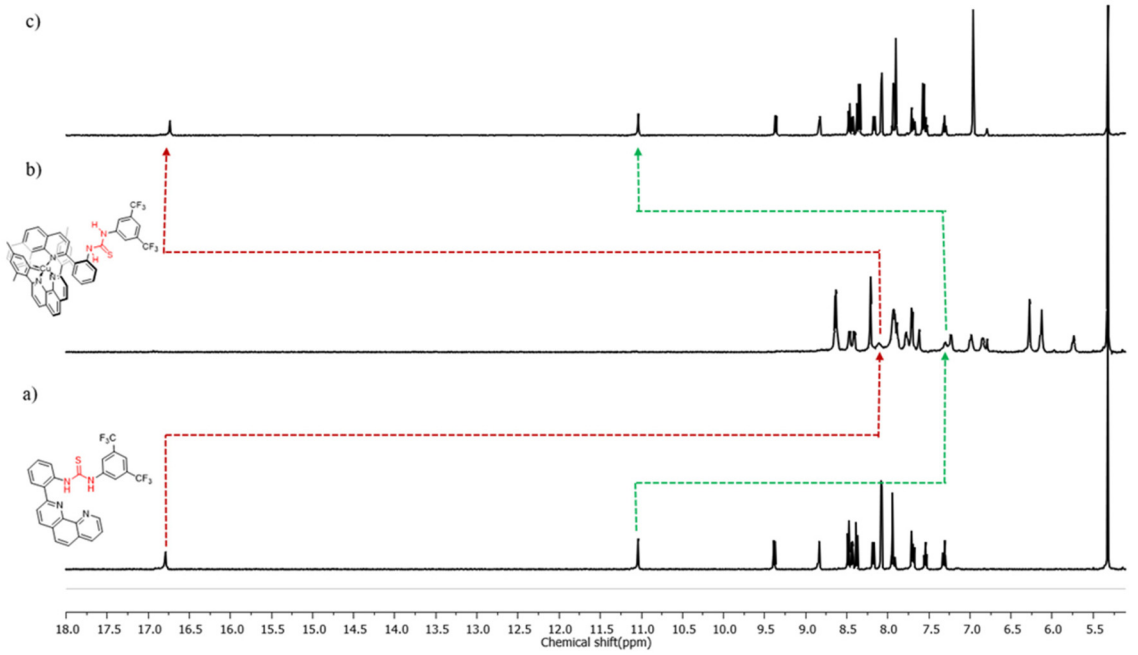

Fig. 4 ^{1}H NMR (CD_2Cl_2, 298 K, 500 MHz) spectra of (a) switch **1** (10 mM); (b) [Cu(**1**)(**3**)]PF_6; and (c) [Cu(**1**)(**3**)]PF_6 + excess aqueous KCN.

city of β-nitrostyrene (due to the availability of only one N–H) and does not catalyse the Michael addition reaction. In contrast, the closed state is probably broken in the presence of β-nitrostyrene, a competitive hydrogen bond acceptor. As a result, the electrophilicity of β-nitrostyrene and the reaction rate increase. To understand the solution state structure of the complex, we carried out geometry optimisation of both *anti–anti* and *syn–anti* conformations using 6-311G(d,p) as the basis

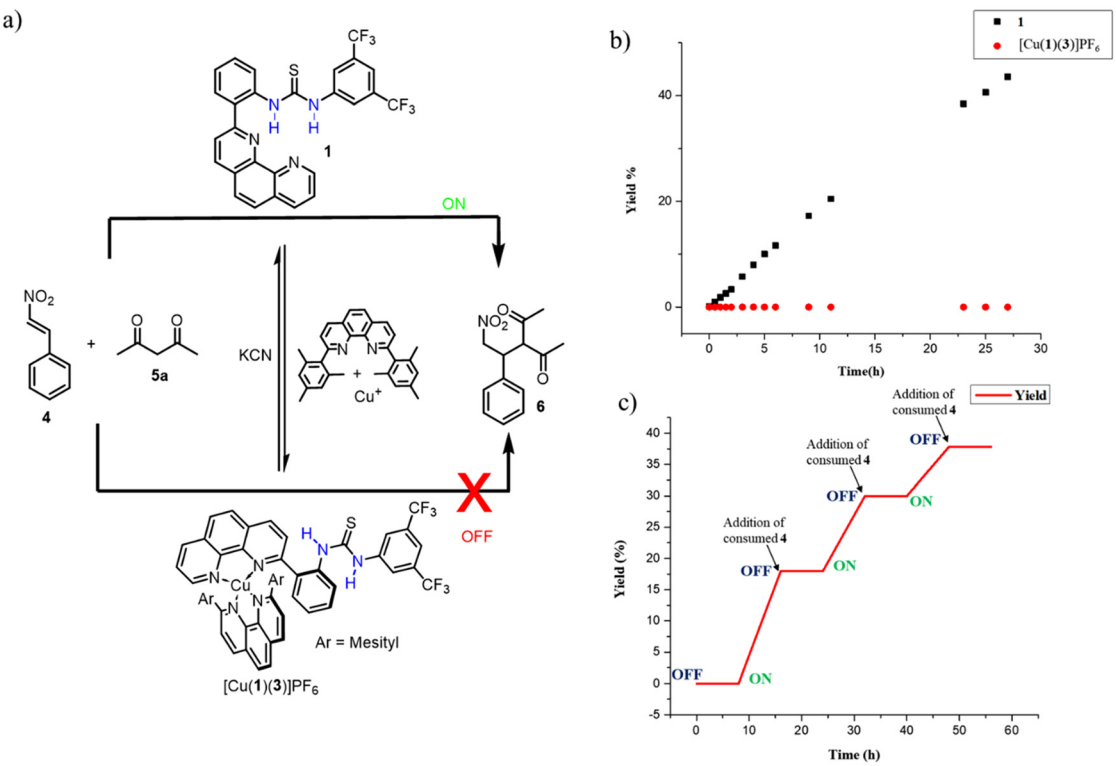

Fig. 5 (a) Schematic representation of the catalytic activity of the molecular switch **1** in the ON and OFF states; (b) comparison of the yield of catalytic reactions with switch **1** (five mol%) and [Cu(**1**)(**3**)]PF_6; and (c) *in situ* changes of the catalytic reaction by the removal and addition of Cu^{+}.

set. It was found that the *syn–anti*-conformation is more stable than the *anti–anti*-conformation.

Additionally, we synthesised a model catalyst (**1a**) resembling compound **1** but lacking a phenanthroline moiety (Fig. 2c). Under analogous conditions, treating **4** (33.5 μmol) with **5a** (335 μmol) in the presence of **1a** and triethylamine resulted in a lower yield of the Michael addition product compared to switch **1** (Fig. S29 and S30†). The crystal structure analysis of **1a** indicated a prevailing *syn–anti* conformation in the solid state, akin to that observed in [Cu(**1**)(**3**)]PF_6. This observation accounts for the reduced reactivity of the model catalyst. Importantly, these data indirectly imply that the OFF state of [Cu(**1**)(**3**)]PF_6 is attributed to its *syn–anti* conformation.

Furthermore, we evaluated the effectiveness of the switch to catalyse Michael addition reactions by *in situ* alteration between the catalytic states. Hence, the treatment of **4** (33.5 μmol), **5a** (335 μmol) and Et_3N (one mol%) in the presence of five mol% of copper-complex, [Cu (**1**)(**3**)]PF_6, under similar conditions did not give any products. However, when the same mixture was stirred for 8 h after adding KCN, the product was obtained in 18% yield. In contrast, Michael addition was shut down when Cu^+ was added to the above mixture. The ON–OFF *in situ* switching of catalysis was performed for up to three cycles (Fig. 5c).

Conclusion

In conclusion, we have demonstrated a very short synthesis of a switchable catalyst fully characterised by NMR spectroscopy, ESI-MS and X-ray crystallography. Both ^1H NMR spectra and crystal structure analysis showed that the initial state is self-locked with intramolecular hydrogen bonding, whereas the copper complex existed in the *syn–anti* conformation. The *anti–anti* conformation of the switch can catalyse the Michael addition reaction by increasing the Michael acceptor's electrophilicity *via* hydrogen bonding, whereas the *syn–anti* conformation obtained by the addition of copper-loaded phenanthroline was catalytically inactive as only one N–H is available for hydrogen-bonding with a Michael acceptor. This interplay of thiorurea's conformation between *syn–syn* and *syn–anti* by allosteric regulation for ON–OFF catalysis can open a new direction for switchable catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

1 (*a*) N. M. Goodey and S. J. Benkovic, *Nat. Chem. Biol.*, 2008, **4**, 474–482; (*b*) K. Reiss, V. S. Batista and J. P. Loria, *Biochemistry*, 2020, **59**, 1711–1712.

2 (*a*) U. Lüning, *Angew. Chem., Int. Ed.*, 2012, **51**, 8163–8165; (*b*) V. Blanco, D. A. Leigh and V. Marcos, *Chem. Soc. Rev.*, 2015, **44**, 5341–5370; (*c*) R. Dorel and B. L. Feringa, *Chem. Commun.*, 2019, **5**, 6477–6486; (*d*) J. Choudhury, *Tetrahedron Lett.*, 2018, **59**, 487–495; (*e*) A. Ghorbani-Choghamarani and Z. Taherinia, *RSC Adv.*, 2022, **12**, 23595–23617.

3 (*a*) C. M. McGuirk, C. L. Stern and C. A. Mirkin, *J. Am. Chem. Soc.*, 2014, **136**, 4689–4696; (*b*) T. Imahori, R. Yamaguchi and S. Kurihara, *Chem. – Eur. J.*, 2012, **18**, 10802–10807; (*c*) V. Blanco, A. Carlone, K. D. Hänni, D. A. Leigh and B. Lewandowski, *Angew. Chem., Int. Ed.*, 2012, **51**, 5166–5169; (*d*) E. Deck, H. E. Wagner, J. Paradies and F. Breher, *Chem. Commun.*, 2019, **55**, 5323–5326; (*e*) S. Semwal and J. Choudhury, *ACS Catal.*, 2016, **6**, 2424–2428.

4 (*a*) J. Wang and B. L. Feringa, *Science*, 2011, **331**, 1429–1432; (*b*) Y. Cakmak, S. Erbas-Cakmak and D. A. Leigh, *J. Am. Chem. Soc.*, 2016, **138**, 1749–1751.

5 (*a*) S. De, S. Pramanik and M. Schmittel, *Angew. Chem., Int. Ed.*, 2014, **53**, 14255–14259; (*b*) K. Eichstaedt, J. Jaramillo-Garcia, D. A. Leigh, V. Marcos, S. Pisano and T. A. Singleton, *J. Am. Chem. Soc.*, 2017, **139**, 9376–9381; (*c*) A. Goswami, T. Paululat and M. Schmittel, *J. Am. Chem. Soc.*, 2019, **141**, 15656–15663; (*d*) S. Kundu, D. Mondal, V. V. Rajasekaran, A. Goswami and M. Schmittel, *Inorg. Chem.*, 2022, **61**, 17007–17011; (*e*) S. Semwal and J. Choudhury, *Angew. Chem., Int. Ed.*, 2017, **56**, 5556–5560.

6 Y. Shen, S. M. Shepard, C. J. Reed and P. L. Diaconescu, *Chem. Commun.*, 2019, **55**, 5587–5590.

7 (*a*) H. Kai, S. Nara, K. Kinbara and T. Aida, *J. Am. Chem. Soc.*, 2008, **130**, 6725–6727; (*b*) T. Muraoka, K. Kinbara and T. Aida, *Nature*, 2006, **440**, 512–515; (*c*) S. Pramanik, S. De and M. Schmittel, *Chem. Commun.*, 2014, **50**, 13254–13257; (*d*) P. Remon, D. González, M. A. Romero, N. Basílio and U. Pischel, *Chem. Commun.*, 2020, **56**, 3737–3740; (*e*) P. Remón and U. Pischel, *ChemPhysChem*, 2017, **5**, 1667–1677.

8 (*a*) M. Schmittel, S. De and S. Pramanik, *Angew. Chem., Int. Ed.*, 2012, **51**, 3832–3836; (*b*) M. Schmittel, S. Pramanik and S. De, *Chem. Commun.*, 2012, **48**, 11730–11732; (*c*) S. De, S. Pramanik and M. Schmittel, *Dalton Trans.*, 2014, **43**, 10977–10982; (*d*) M. V. Peters, R. S. Stoll, A. Kühn and S. Hecht, *Angew. Chem., Int. Ed.*, 2008, **47**, 5968–5972; (*e*) B. Majia and J. Choudhury, *Chem. Commun.*, 2019, **55**,

4574–4577; (*f*) M. Szewczyk, G. Sobczak and V. Sashuk, *ACS Catal.*, 2018, **8**, 2810–2814; (*g*) V. Sashuk and O. Danylyuk, *Chem. – Eur. J.*, 2016, **22**, 6528–6531.

9 (*a*) K. Eichstaedt, J. Jaramillo-Garcia, D. A. Leigh, V. Marcos, S. Pisano and T. A. Singleton, *J. Am. Chem. Soc.*, 2017, **139**, 9376–9381; (*b*) A. Goswami, T. Paululat and M. Schmittel, *J. Am. Chem. Soc.*, 2019, **141**, 15656–15663.

10 S. Gaikwad, A. Goswami, S. De and M. Schmittel, *Angew. Chem., Int. Ed.*, 2016, **55**, 10512–10517.

11 (*a*) T. Inokuma, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2006, **128**, 9413–9419; (*b*) S. Hoekman, M. O. Kitching, D. A. Leigh, M. Papmeyer and D. Roke, *J. Am. Chem. Soc.*, 2015, **137**, 7656–7659.

12 (*a*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289–296; (*b*) T. Parvin, R. Yadav and L. H. Choudhury, *Org. Biomol. Chem.*, 2020, **18**, 5513–5532; (*c*) S. J. Connon, *Chem. – Eur. J.*, 2006, **12**, 5418–5427.

13 (*a*) M. Schmittel and A. Ganz, *Chem. Commun.*, 1997, 999–1000; (*b*) S. De, K. Mahata and M. Schittel, *Chem. Soc. Rev.*, 2010, **39**, 1555–1575.

14 (*a*) C. O. Dietrich-Buchecker, J.-P. Sauvage and J. M. Kern, *J. Am. Chem. Soc.*, 1984, **106**, 3043–3045; (*b*) J. D. Megiatto Jr. and D. I. Schuster, *Org. Lett.*, 2011, **13**, 1808–1811.

15 (*a*) S. T. Tuncel, S. E. Gunal, M. Ekizoglu, N. G. Kelekci, S. S. Erdem, E. Bulak, W. Frey and I. Dogan, *J. Mol. Struct.*, 2019, **1179**, 40–56; (*b*) A. Tarai and J. B. Baruah, *ACS Omega*, 2017, **2**, 6991–7001; (*c*) A. A. Ehrhard, L. Gunkel, S. Jäger, A. C. Sell, Y. Nagata and J. Hunger, *ACS Catal.*, 2022, **12**, 12689–12700.