Switching Between Anion-Binding Catalysis and Aminocatalysis with a Rotaxane Dual-Function Catalyst

DOI:
10.1021/jacs.7b04955

Document Version
Accepted author manuscript

Article

Switching Between Anion-Binding Catalysis and Amino-catalysis with a Rotaxane Dual-Function Catalyst

Katarzyna Eichstaedt, Javier Jaramillo-Garcia, David A. Leigh, Vanesa Marcos, Simone Pisano, and Thomas A. Singleton

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b04955 • Publication Date (Web): 19 Jun 2017

Switching Between Anion-Binding Catalysis and Aminocatalysis with a Rotaxane Dual-Function Catalyst

Katarzyna Eichstaedt, Javier Jaramillo-Garcia, David A. Leigh,* Vanesa Marcos, Simone Pisano, Thomas A. Singleton

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK

KEYWORDS: Rotaxane, Molecular Machines, Switchable Catalyst, Anion-Binding Catalysis, Aminocatalysis, Tandem Reactions

ABSTRACT: The 'off' state for aminocatalysis by a switchable [2]rotaxane is shown to correspond to an 'on' state for anion-binding catalysis. Conversely, the aminocatalysis 'on' state of the dual-function rotaxane is inactive in anion-binding catalysis. Switching between the different states is achieved through the stimuli-induced change of position of the macrocycle on the rotaxane thread. The anion-binding catalysis results from a pair of triazolium groups that act together to CH-hydrogen bond to halide anions when the macrocycle is located on an alternative (ammonium) binding site, stabilizing the *in situ* generation of benzhydryl cation and oxonium ion intermediates from activated alkyl halides. The aminocatalysis and anion-binding catalysis sites of the dual-function rotaxane catalyst can be sequentially concealed or revealed, enabling catalysis of both steps of a tandem reaction process.

1. INTRODUCTION

Biology uses molecular machines in a broad range of molecular construction processes, from the ribosome[1] to allosterically-regulated[2] enzymes. The latter is inspiring the development of 'smart' artificial catalysts[3] in which a stimulus is used to significantly alter the rate, or stereo- or regioselective outcome, of a chemical reaction.[4] However, systems that can switch between different catalytic groups that promote different chemical transformations remain scarce.[5,6] We previously described[7] a rotaxane-based[8] switchable aminocatalyst[9] (**1** 'on' state/**1**-H^+ 'off' state) that modulates the rate of a range of organocatalyzed reactions *via* diverse activation pathways,[7b] including iminium-ion, enamine and trienamine, and even tandem iminium-enamine processes (Figure 1). Here we show that the 'off' state of the aminocatalyst also corresponds to an 'on' state for anion-binding catalysis,[10] promoted by the presence of two triazolium groups on the rotaxane axle[11] that work together to bind anions[12,13] when the rotaxane macrocycle is located on the central ammonium group of the thread (Figure 2).

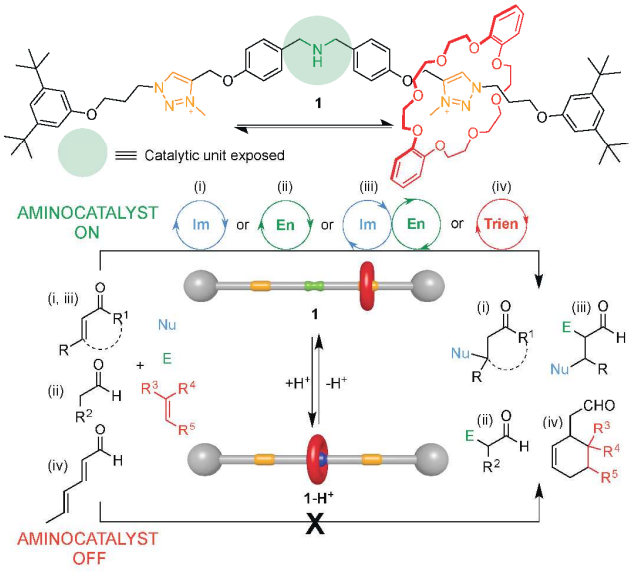


Figure 1. Acid-base switching of the position of the macrocycle in rotaxane **1** ('on' state)/**1**-H^+ ('off' state) for controlling the rate of aminocatalysis *via* different activation pathways: (i) iminium-ion (Im); (ii) enamine (En); (iii) tandem iminium-enamine (Im-En); and (iv) trienamine (Trien).[7]

In the last few years, hydrogen bonding catalysis has emerged as a powerful tool for synthesis.[14-16] The hydrogen bonding activation of neutral electrophiles, such as carbonyl or imine moieties, is well established,[15] and hydrogen bonding activation of electrophilic ionic substrates by coordination to their counter anions is increas-

ingly being exploited.[15] Anion-binding catalysis generally utilizes catalysts based on strongly-polarized N–H bonds, such as those in ureas, thioureas[16] and thiophosphoramides.[17] However, structures based on strong O–H bonds,[18] and even the cooperative action of less polarized C–H[19] or C–X[20] bonds, have also proved effective. Accordingly, we investigated whether the two triazolium groups of rotaxane **1-H**$^+$ could act as an anion-binding catalyst for the *in-situ* generation of ionic intermediates, such as benzhydryl cations and oxonium ions *via* halide abstraction (Figure 2a). If so, the 'off' state of aminocatalyst (**1-H**$^+$) would also be an 'on' state for anion-binding catalysis, and the 'on' state for aminocatalysis (**1**) would be an 'off' state for anion-binding catalysis. The two different catalytic modes could, in principle, be activated in sequence, allowing the rotaxane-based molecular switch to promote tandem anion-binding/amino-catalyzed processes (Figure 2b).

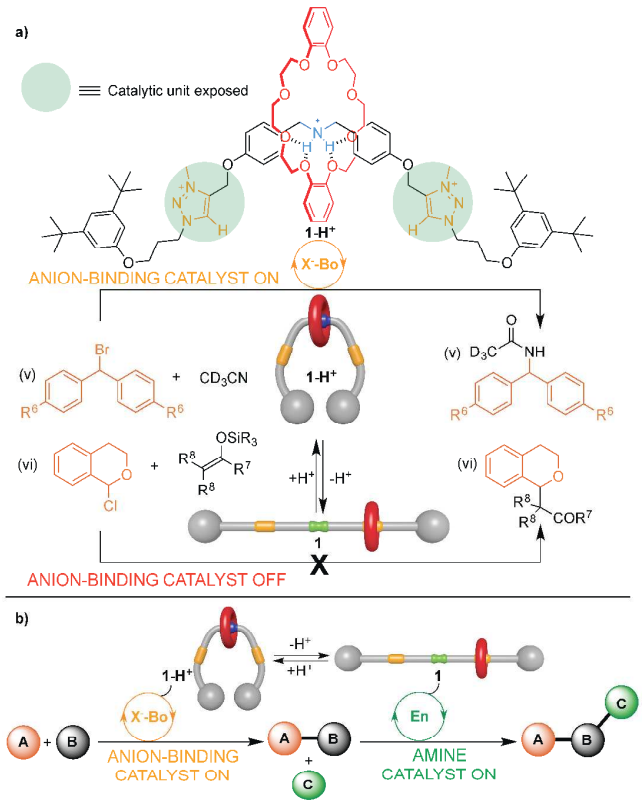


Figure 2. Acid-base switching of the position of the macrocycle in rotaxane **1-H**$^+$/**1**: (a) for controlling the rate of anion-binding-catalyzed reactions (X^--Bo); (b) for promoting tandem processes; an anion-binding-catalyzed reaction followed by an enamine-catalyzed reaction.

2. RESULTS AND DISCUSSION

Switchable rotaxane catalyst **1-H**$^+$/**1** consists of a dibenzo-24-crown-8 macrocycle locked onto a thread bearing a dibenzylamine/ammonium moiety and two triazolium rings,[11] and was prepared according to a previously established synthetic route.[7] The bromide and chloride anion binding properties of rotaxanes **1-H**$^+$ and **1** in CD_3CN were investigated through ^{1}H NMR spectroscopy and titration experiments using the corresponding tetrabutylammonium halide salts (see Supporting Information). With rotaxane **1-H**$^+$, significant shifts in the resonances of the triazolium protons upon addition of Bu_4NCl or Bu_4NBr was observed by ^{1}H NMR spectroscopy. Titration experiments showed that rotaxane **1-H**$^+$ forms 1:1 complexes with both bromide and chloride, with association constants (K_a) in CD_3CN of 200 M^{-1} in each case (see Supporting Information).[21] In contrast, ^{1}H NMR spectroscopy showed little or no interaction between halide salts and the triazolium protons of rotaxane **1** (Supporting Information, Fig. S9 and S10).

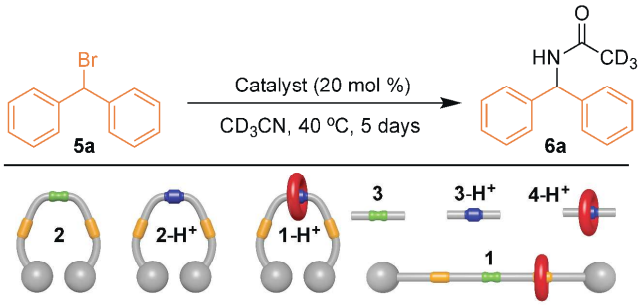
Having established the halide-binding properties of the protonated rotaxane (**1-H**$^+$) and confirmed that halide binding is switched 'off' by changing the position of the macrocycle (i.e. in **1**), we investigated the efficacy of the anion-binding state of the rotaxane as an anion-binding catalyst.

The Ritter reaction of bromodiarylmethane compounds and deuterated acetonitrile (CD_3CN)[20c–e] was chosen for the investigation of the *in situ* generation of benzhydryl carbocation derivatives (Ar_2CH^+) formed through the rotaxane **1-H**$^+$-promoted cleavage of a carbon-bromide bond (Table 1). We first confirmed that the reaction of **5a** with CD_3CN does not proceed in the absence of the catalyst (Table 1, entry 1), and then carried out a series of experiments involving different potential reaction-promoting species (Table 1). Dibenzylamine (**3**), protonated dibenzylamine (**3-H**$^+$) and pseudorotaxane **4-H**$^+$ (Table 1, entries 2–4) did not promote the Ritter reaction over 7 days at 40 °C. Under the same reaction conditions, the threads in both protonated and deprotonated forms (**2** and **2-H**$^+$, respectively) catalyzed the reaction equally effectively after 5 days (Table 1, entries 5 and 6). The bis-triazolium-based catalyst contained in the protonated rotaxane, **1-H**$^+$, catalyzed the reaction as effectively as the bis-triazolium-based unit of the threads (**2** and **2-H**$^+$) affording **6a** with good conversion (Table 1, entry 7). However, the deprotonated form of the rotaxane, **1**, did not afford any product (Table 1, entry 8). This demonstrates that the inhibition of anion-binding catalysis by the rotaxane is caused by the macrocycle position in **1**, which blocks the ability of the two triazolium groups to bind halide ions.

The progress of the Ritter reaction could also be controlled through *in situ* switching of the position of the macrocycle in the rotaxane catalyst (Table 1, entries 9–12). After 3 days of stirring **5a** in the presence of 20 mol % rotaxane in its inactive, deprotonated state (**1**), no conversion of Ph_2CHBr to the acetamide product **6a** was observed. Upon addition of CF_3CO_2H (20 mol %), the rotaxane catalyst was switched 'on', affording **6a** in 60 % yield within 5 days (Table 1, entry 9). The activity of protonated rotaxane catalyst **1-H**$^+$ could also be switched 'off' *in situ* by adding NaOMe (20 mol %) to the reaction mixture (Table 1, entry 11). Control experiments, reactions carried out with NaOMe (20 mol %) or CF_3CO_2H (20 mol %) in the absence of the rotaxanes, also confirmed that product formation requires the presence of the rotaxane organocatalyst (Table 1, entries 10 and 12).

Under similar reaction conditions with other bromodiarylmethane derivatives (**5b**,**c**), the use of protonated rotaxane **1**-H$^+$ (anion-binding catalysis 'on') afforded the corresponding acetamide products (**6b**,**c**) in comparable conversions to that found for Ph_2CHBr (Table 2, entries 1 and 3). In contrast, the use of deprotonated rotaxane **1** (anion-binding catalysis 'off') did not produce any products in these reactions (Table 2, entries 2 and 4).

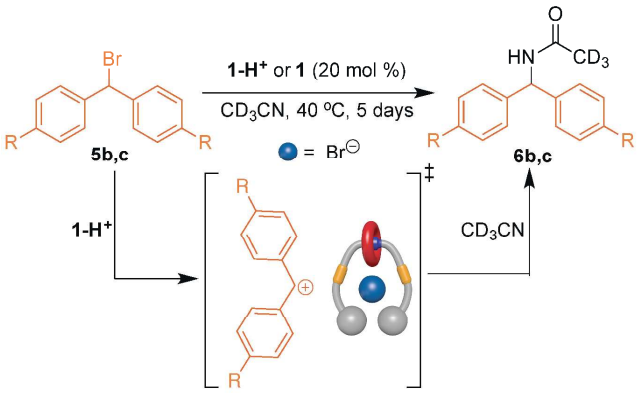
Table 1. Investigation of the anion-binding-catalyzed Ritter reaction of bromodiphenylmethane with various potential catalysts and *in situ* switching of the catalytic activity.[a]



Entry	Catalyst	Conversion (%)[b]
1	–	<1
2	**3**	<1
3	**3**-H$^+$	<1
4	**4**-H$^+$	<1
5	**2**	54
6	**2**-H$^+$	55
7	**1**-H$^+$	69
8	**1**	<1
9	**1**+ CF_3CO_2H (20 mol%)	60[c]
10	CF_3CO_2H (20 mol%)	<1[c]
11	**1**-H$^+$+ NaOMe (20 mol%)	<1[d]
12	NaOMe (20 mol%)	<1[d]

[a] Reaction conditions: 36 μmol of **5a**, and 7.2 μmol of catalyst (20 mol%) in 400 μL of CD_3CN at 40 °C. [b] Conversions determined after 5 days by ^{1}H NMR. [c] Addition of CF_3CO_2H (20 mol%) to the reaction mixture. [d] Addition of NaOMe (20 mol%) to the reaction mixture.

Table 2. Scope of the anion-binding-catalyzed Ritter reaction of bromodiarylmethane derivatives (5b,c) using rotaxanes 1-H$^+$ and 1.[a]

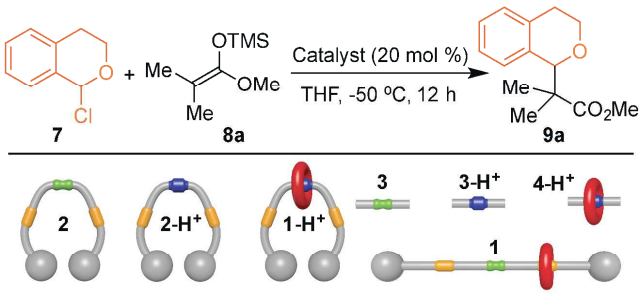


Entry	R	Catalyst	Conversion (%)[b]
1	OMe	**1**-H$^+$	52
2	OMe	**1**	<1
3	Me	**1**-H$^+$	48
4	Me	**1**	<1

[a] Reaction conditions: 36 μmol of **5b–c**, and 7.2 μmol of catalyst (**1** or **1**-H$^+$, 20 mol%) in 400 μL of CD_3CN at 40 °C. [b] Conversions determined after 5 days by ^{1}H NMR.

In order to further evaluate the effectiveness of the bis-triazolium halide-binding groups in rotaxane **1**-H$^+$ in catalysis, we investigated its performance for the *in situ* generation of oxonium ions *via* carbon-chlorine bond cleavage.[22] The catalytic activity of both rotaxanes (**1**-H$^+$ and **1**), and other potential reaction-promoting species, were studied in the reaction between 1-chloroisochroman (**7**) and the silyl ketene acetal **8a** (Table 3). Other than the protonated rotaxane **1**-H$^+$, or the protonated or non-protonated non-interlocked thread **2**-H$^+$ and **2**, none of the other potential reaction-promoting species (Table 3, entries 2-4) catalyzed the formation of product **9a**. In contrast, both threads **2** and **2**-H$^+$ catalyzed the reaction with excellent conversion (Table 3, entries 5 and 6). As before, the reaction promoted with the protonated rotaxane **1**-H$^+$ (anion-binding catalysis 'on' state) is equally effective. In contrast, no reaction was observed using rotaxane **1** (anion-binding catalysis 'off' state).

Table 3. Investigation of the anion-binding-catalyzed reaction of 1-chloroisochroman (7) and the ketene silyl acetal (8a) with various potential catalysts. [a]

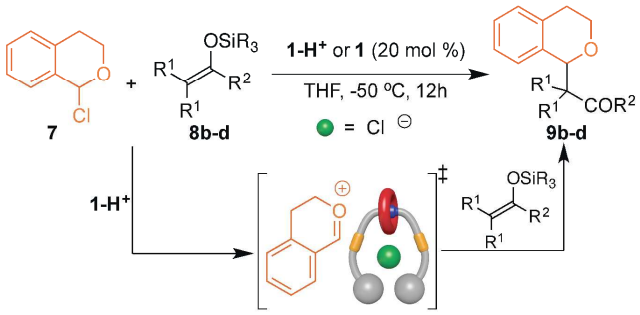


Entry	Catalyst	Conversion (%)[b]
1	–	<1
2	**3**	<1
3	**3**-H$^+$	<1
4	**4**-H$^+$	<1
5	**2**	81
6	**2**-H$^+$	72
7	**1**-H$^+$	76
8	**1**	<1

[a] Reaction conditions: 36 μmol of **7**, 54 μmol of **8a** and 7.2 μmol of catalyst (20 mol%) in 750 μL of THF at -50 °C. [b] After 12 hours, the reaction was quenched by addition of NaOMe and the conversion determined by ^{1}H NMR.

The generality of rotaxane **1**-H$^+$/**1** as a switchable anion-binding catalyst was studied with diverse silyl ether nucleophiles (**8b**,**d**; Table 4). Protonated rotaxane **1**-H$^+$ ('on' catalyst) promoted the reaction between **7** and α-unsubstituted silyl ether nucleophiles (**8b** and **8d**) with high conversions (Table 4, entries 1 and 3). However, hindered α-disubstituted silyl enol ether **8c** (Table 4, entry 5) afforded the corresponding aldehyde derivative in a poor yield. The change of the position of the macrocycle on the rotaxane allows for total control over the rate of the reactions, as the 'off' state of the system (**1**) does not exhibit any observable catalytic activity at all (Table 4, entries 2, 4 and 6).

Table 4. Scope of the anion-binding-catalyzed reaction between 1-chloroisochroman (7) and 8b–d with rotaxanes 1-H$^+$ and 1. [a]



Entry	R^1	R^2	R^3	Catalyst	Conv. (%)[b]
1	H	OMe	TBS	**1**-H$^+$	84 (**9b**)
2	H	OMe	TBS	**1**	<1
3	Me	H	TMS	**1**-H$^+$	20 (**9c**)
4	Me	H	TMS	**1**	<1
5	H	H	TMS	**1**-H$^+$	70 (**9d**)
6	H	H	TMS	**1**	<1

[a] Reaction conditions: 36.0 μmol of **7**, 54.0 μmol of **8b–d** and 7.2 μmol of catalyst (**1** and **1**-H$^+$, 20 mol %) in 750 μL of THF at -50 °C. [b] After 12 hours, the reaction was quenched by addition of NaOMe and the conversions determined by ^{1}H NMR.

Finally, the ability of rotaxane **1**-H$^+$/**1** to switch *in situ* between the two catalytic states (anion-binding catalyst and aminocatalyst), each promoting a different chemical transformation, was exploited to bring about a tandem reaction. The process consists first of an anion-binding-catalyzed alkylation reaction between **7** and **8d**, followed by a nucleophilic addition of **10** *via* enamine activation of the intermediate aldehyde **9d** (Scheme 1). An equimolar mixture of **7** and **8d** (72 μmol) in the presence of 20 mol % of protonated rotaxane **1**-H$^+$ (anion-binding catalyst 'on') was stirred in THF at -50 °C, affording the alkylated product **9d** with 70 % conversion after 12 h. After this time, NaOMe was added to quench the remaining excess of silyl enol ether and to switch 'on' the aminocatalyst state of the rotaxane (**1**) *in situ*. Subsequent addition of vinyl bissulfone **10** afforded compound **11** (50 % conversion after 48 h at r.t.) through enamine activation of **9d** (see Supporting Information for experimental details). By controlling the order in which catalytic sites are revealed and concealed, dual-function switchable rotaxane catalyst **1**-H$^+$/**1** is able to control the outcome of a tandem process, creating two new C–C bonds, the first by anion-binding catalysis and the second by aminocatalysis *via* enamine activation.

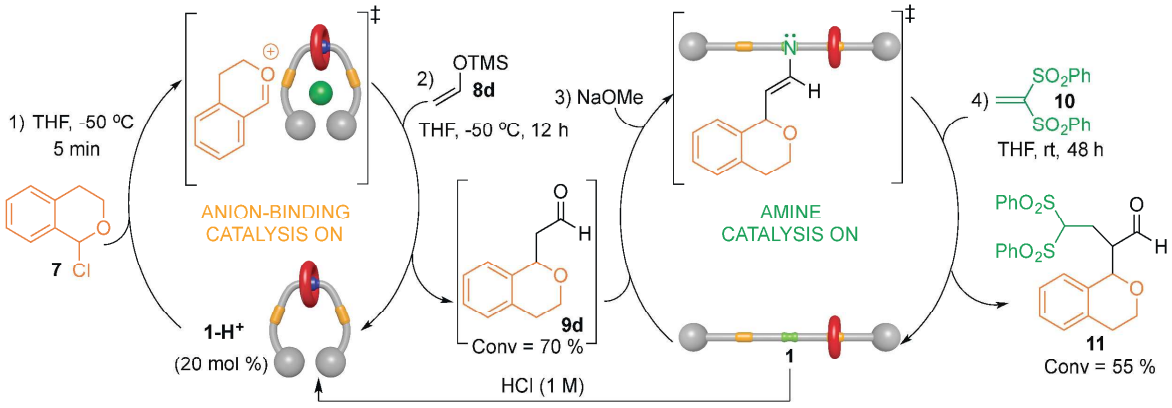
3. CONCLUSIONS

A rotaxane that selectively masks or exposes a bis-triazolium-based catalytic unit in response to acid/base acts as an effective switchable anion-binding catalyst. The

rotaxane can effectively control the rate of Ritter and alkylation reactions by C–Br or C–Cl bond cleavage, respectively, either by adding the catalyst in its active form or by *in situ* switching. To the best of our knowledge these are the first examples of anion-binding catalysis of these reactions. The two catalytic functions of the system, an anion-binding catalyst and an aminocatalyst, can be selectively concealed or revealed and their activities switched on or off, enabling control over the product outcome of a tandem anion-binding-enamine catalytic reaction sequence.

Controlling the order in which catalytic sites are revealed and concealed by molecular machine multifunction catalysts represents a 'bio-like' strategy for molecular construction.[3e] Turning 'on' and 'off' different catalyst activities in response to a specific stimulus or analyte may be useful for promoting alternative reactions and product outcomes from mixtures of building blocks.[5a]

Scheme 1. Controlling the product outcome of a tandem reaction using switchable dual-function rotaxane 1-H$^+$/1: Switching *in situ* between the two catalytic units, anion-binding catalyst 1-H$^+$ and aminocatalyst 1.[a]



[a] See Supporting Information for experimental details.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures, spectral data for new compounds and ^{1}H NMR data for catalytic experiments and binding studies. This material is available free of charge *via* the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

david.leigh@manchester.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was funded by the European Research Council (Advanced grant no. 339019) and the European Union's seventh Framework Program (FP7-PEOPLE-2013-ITN-607602 'Hierarchical Self Assembly of Polymeric Soft Systems' SASSYPOL). We thank the Royal Society for a Newton International Fellowship (to TS) and a Research Professorship (to DAL).

REFERENCES

(1) (a) Yonath, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 4340. (b) Ramakrishnan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 4355. (c) Steitz, T. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 4381.

(2) Traut, T. W. *Allosteric Regulatory Enzymes*, Springer, New York, **2008**.

(3) (a) Lüning, U. *Angew. Chem., Int. Ed.* **2012**, *51*, 8163. (b) Leigh, D. A.; Marcos, V.; Wilson, M. R. *ACS Catal.* **2014**, *4*, 4490. (c) Neal, E. A.; Goldup, S. M. *Chem. Commun.* **2014**, *50*, 5128. (d) Erbas-Cakmak, S.; Leigh, D. A.; McTernan, C. T.; Nussbaumer, A. L. *Chem. Rev.* **2015**, *115*, 10081. (e) Blanco, V.; Leigh D. A.; Marcos, V. *Chem. Soc. Rev.* **2015**, *44*, 5341. (f) Pan T.; Liu, J. *ChemPhysChem* **2016**, *17*, 1752. (g) Lewis, J. E. M.; Galli M.; Goldup, S. M. *Chem. Commun.* **2017**, *53*, 298.

(4) For representative examples of artificial catalysts that can be switched 'on' and 'off' by a specific stimulus, see: (a) Würthner, F.; Rebek Jr., J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 446. (b) Yoon, H. J.; Kuwabara, J.; Kim, J.-H.; Mirkin, C. A. *Science* **2010**, *330*, 66. (c) Sohtome, Y.; Tanaka, S.; Takada, K.; Yamaguchi, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 9254. (d) Berryman, O. B.; Sather, A. C.; Lledó, A.; Rebek Jr., J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9400. (e) Wang, J.; Feringa, B. L. *Science* **2011**, *331*, 1429. (f) Mortezaei, S.; Catarineu, N. R.; Canary, J. W. *J. Am. Chem. Soc.* **2012**, *134*, 8054. (g) Neilson, B. M.; Bielawski, C. W. *J. Am. Chem. Soc.* **2012**, *134*, 12693. (h) Schmittel, M.; De, S.; Pramanik, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3832. (i) Schmittel, M.; Pramanik, S.; De, S. *Chem. Commun.* **2012**, *48*, 11730. (j) Wilson, D.; Branda, N. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 5431. (k) Viehmann, P.; Hecht, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1825. (l) Neilson, B. M.; Bielawski, C. W. *Chem. Commun.* **2013**, *49*, 5453. (m) Neilson, B. M.; Bielawski, C. W. *Organometallics* **2013**, *32*, 3121. (n) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericás, M. A. *Org. Lett.* **2014**, *16*, 1704. (o) McGuirk, C. M.; Stern, C. L.; Mirkin, C. A. *J. Am. Chem. Soc.* **2014**, *136*, 4689. (p) Blanco, V.; Leigh, D. A.; Marcos, V.; Morales-Serna, J. A.; Nussbaumer, A. L. *J. Am. Chem. Soc.* **2014**,

136, 4905. (q) Vlatković, M.; Bernardi, L.; Otten, E.; Feringa, B. L. *Chem. Commun.* **2014**, *50*, 7773. (r) Galli, M.; Lewis, J. E. M.; Goldup, S. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 13545. (s) Martinez-Cuezva, A.; Saura-Sanmartin, A.; Nicolas-García, T.; Navarro, C.; Orenes, R.-A.; Alajarin, M.; Berná, J. *Chem. Sci.* **2017**, *8*, 3775.

(5) For switching to unmask different catalytic sites within a molecule, see: (a) Beswick, J.; Blanco, V.; De Bo, G.; Leigh, D. A.; Lewandowska, U.; Lewandowski, B.; Mishiro, K. *Chem. Sci.* **2015**, *6*, 140. (b) Kwan, C.-S.; Chan, A. S. C.; Leung, K. C.-F. *Org. Lett.* **2016**, *18*, 976. For switching that unmasks different catalysts in multi-component systems, see: (c) De, S.; Pramanik S.; Schmittel, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 14255. (d) Mittal, N.; Pramanik, S.; Paul, I.; De, S.; Schmittel, M. *J. Am. Chem. Soc.* **2017**, *139*, 4270.

(6) For orthogonal catalytic states of a single active-site, see: (a) Biernesser, A. B.; Delle Chiaie, K. R.; Curley, J. B.; Byers, J. A. *Angew. Chem., Int. Ed.* **2016**, 55, 5251. (b) Teator, A. J.; Shao, H.; Lu, G.; Liu, P.; Bielawski, C. W. *Organometallics* **2017**, *36*, 490. (c) Semwal, S.; Choudhury, J. *Angew. Chem., Int. Ed.* **2017**, *56*, 5556.

(7) (a) Blanco, V.; Carlone, A.; Hänni, K. D.; Leigh, D. A.; Lewandowski, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 5166. (b) Blanco, V.; Leigh, D. A.; Lewandowska, U.; Lewandowski, B.; Marcos, V. *J. Am. Chem. Soc.* **2014**, *136*, 15775.

(8) For rotaxanes incorporating catalytic centers, see: (a) Thordarson, P.; Bijsterveld, E. J. A.; Rowan, A. E.; Nolte, R. J. M. *Nature* **2003**, *424*, 915. (b) Tachibana, Y.; Kihara, N.; Takata, T. *J. Am. Chem. Soc.* **2004**, *126*, 3438. (c) Hattori, G.; Hori, T.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12930. (d) Li, Y.; Feng, Y.; He, Y.-M.; Chen, F.; Pan, J.; Fan, Q.-H. *Tetrahedron Lett.* **2008**, *49*, 2878. (e) Miyagawa, N.; Watanabe, M.; Matsuyama, T.; Koyama, Y.; Moriuchi, T.; Hirao, T.; Furusho, Y.; Takata, T. *Chem. Commun.* **2010**, *46*, 1920. (f) Berná, J.; Alajarín, M.; Orenes, R.-A. *J. Am. Chem. Soc.* **2010**, *132*, 10741. (g) Suzaki, Y.; Shimada, K.; Chihara, E.; Saito, T.; Tsuchido, Y.; Osakada, K. *Org. Lett.* **2011**, *13*, 3774. (h) Hoekman, S.; Kitching, M. O.; Leigh, D. A.; Papmeyer, M.; Roke, D. *J. Am. Chem. Soc.* **2015**, *137*, 7656. (i) Cakmak, Y.; Erbas-Cakmak, S.; Leigh, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 1749. (j) Xu, K.; Nakazono, K.; Takata, T. *Chem. Lett.* **2016**, *45*, 1274. (k) Martinez-Cuezva, A.; Lopez-Leonardo, C.; Bautista, D.; Alajarin, M.; Berná, J. *J. Am. Chem. Soc.* **2016**, *138*, 8726.

(9) For some representative reviews on aminocatalysis, see: (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (b) Mielgo, A.; Palomo, C. *Chem.-Asian J.* **2008**, *3*, 922. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (d) Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1360. (e) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (f) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (g) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138. (h) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042. (i) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632. (j) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. (k) Parra, A.; Reboredo, S.; Alemán, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9734. (l) Meninno, S.; Lattanzi, A. *Chem. Commun.* **2013**, *49*, 3821. (m) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287. (n) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774. (o) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869. (p) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Chem.-Eur. J.* **2014**, *20*, 358. (q) Matos Paz, B.; Jiang, H.; Jørgensen, K. A. *Chem.-Eur. J.* **2015**, *21*, 1846. (r) Zhang, L.; Fu, N.; Luo, S. *Acc. Chem. Res.* **2015**, *48*, 986. (s) Halskov, K. S.; Donslund, B. S.; Matos Paz, B.; Jørgensen, K. A. *Acc. Chem. Res.* **2016**, *49*, 974.

(t) Dzięgielewski, M.; Pięta, J.; Kamińska, E.; Albrecht, Ł. *Eur. J. Org. Chem.* **2015**, 677. (u) Marcos, V.; Alemán, J. *Chem. Soc. Rev.* **2016**, *45*, 6812. (v) Łągiewka, B.; Albrecht, Ł. *Asian J. Chem.* **2017**, 10.1002/ajoc.201600616.

(10) For some representative reviews of anion-binding catalysis, see: (a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (b) Beckendorf, S.; Asmus, S.; García Mancheño, O. *ChemCatChem* **2012**, *4*, 926. (c) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534. (d) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603. (e) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. (f) Seidel, D. *Synlett* **2014**, *25*, 783.

(11) (a) Coutrot, F.; Busseron, E. *Chem.-Eur. J.* **2008**, *14*, 4784. (b) Coutrot, F.; Romuald, C.; Busseron, E. *Org. Lett.* **2008**, *10*, 3741. (c) Clavel, C.; Romuald, C.; Brabet, E.; Coutrot, F. *Chem.-Eur. J.* **2013**, *19*, 2982. (d) Chao, S.; Romuald, C.; Fournel-Marotte, K.; Clavel, C.; Coutrot, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 6914. (e) Coutrot, F. *ChemistryOpen* **2015**, *4*, 556.

(12) For representative examples of anion-binding interlocked molecules, see: (a) Sambrook, M. R.; Beer, P. D.; Wisner, J. A.; Paul, R. L.; Cowley, A. R. *J. Am. Chem. Soc.* **2004**, *126*, 15364. (b) Lankshear, M. D.; Beer, P. D. *Coord. Chem. Rev.* **2006**, *250*, 3142. (c) Sambrook, M. R.; Beer, P. D.; Lankshear, M. D.; Ludlow, R. F.; Wisner, J. A. *Org. Biomol. Chem.* **2006**, *4*, 1529. (d) Lankshear, M. D.; Beer, P. D. *Acc. Chem. Res.* **2007**, *40*, 657. (e) Mullen, K. M.; Beer, P. D. *Chem. Soc. Rev.* **2009**, *38*, 1701. (f) Ayme, J.-F.; Beves, J. E.; Leigh, D. A.; McBurney, R. T.; Rissanen, K.; Schultz, D. *Nature Chem.* **2012**, *4*, 15. (g) Ayme, J.-F.; Beves, J. E.; Leigh, D. A.; McBurney, R. T.; Rissanen, K.; Schultz, D. *J. Am. Chem. Soc.* **2012**, *134*, 9488. (h) White, N. G.; Colaço, A. R.; Marques, I.; Félix, V.; Beer, P. D. *Org. Biomol. Chem.* **2014**, *12*, 4924. (i) Leigh, D. A.; Pritchard, R. G.; Stephens, A. J. *Nat. Chem.* **2014**, *6*, 978. (j) Cornes, S. P.; Davies, C. H.; Blyghton, D.; Sambrook, M. R.; Beer, P. D. *Org. Biomol. Chem.* **2015**, *13*, 2582. (k) Langton, M. J.; Marques, I.; Robinson, S. W.; Félix, V.; Beer, P. D. *Chem.-Eur. J.* **2016**, *22*, 185. (l) Brown, A.; Beer, P. D. *Chem. Commun.* **2016**, *52*, 8645. (m) Gilday, L. C.; White, N. G.; Beer, P. D. *Supramol. Chem.* **2016**, *28*, 62. (n) Danon, J. J.; Krüger, A.; Leigh, D. A.; Lemonnier, J.-F.; Stephens, A. J.; Vitorica-Yrezabal, I. J.; Woltering, S. L. *Science*, **2017**, *355*, 159.

(13) For examples of shuttling induced by anion binding in rotaxanes, see: (a) Keaveney, C. M.; Leigh, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1222. (b) Lin, C.-F.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Chem.-Eur. J.* **2007**, *13*, 4350. (c) Huang, Y.-L.; Hung, W.-C.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6629. (d) Ng, K.-Y.; Félix, V.; Santos, S. M.; Rees, N. H.; Beer, P. D. *Chem. Commun.* **2008**, 1281. (e) Barrell, M. J.; Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 8036. (f) Gassensmith, J. J.; Matthys, S.; Lee, J.-J.; Wojcik, A.; Kamat, P. V.; Smith, B. D. *Chem.-Eur. J.* **2010**, *16*, 2916. (g) Serpell, C. J.; Chall, R.; Thompson, A. L.; Beer, P. D. *Dalton Trans.* **2011**, *40*, 12052. (h) Caballero, A.; Swan, L.; Zapata, F.; Beer, P. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11854.

(14) Pihko, P. M. *Hydrogen Bonding in Organic Chemistry*, Wiley-VCH, Weinheim, **2009**.

(15) For some representative reviews on hydrogen bonding catalysis, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (c) Taylor, S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (e) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678.

(16) For examples of (thio)ureas-based catalysts, see: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686. (c) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (d) De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538. (e) Ford, D. D.; Lehnherr, D.; Kennedy, C. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 7860.
(17) Borovika, A.; Tang, P.-I.; Klapman, S.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, 52, 13424.
(18) (a) Schafer, A. G.; Wieting, J. M.; Fisher, T. J.; Mattson, A. E. *Angew. Chem., Int. Ed.* **2013**, 52, 11321. (b) Beletskiy, E. V.; Schmidt, J.; Wang, X.-B.; Kass, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 18534. (c) Diemoz, K. M.; Wilson, S. O. Franz, A. K. *Chem.-Eur. J.* **2016**, *22*, 18349.
(19) (a) Beckendorf, S.; Asmus, S.; Mück-Lichtenfeld, C.; García Mancheño, O. *Chem.-Eur. J.* **2013**, *19*, 1581. (b) Zurro, M.; Asmus, S.; Beckendorf, S.; Mück-Lichtenfeld, C.; García Mancheño, O. *J. Am. Chem. Soc.* **2014**, *136*, 13999. (c) García Mancheño, O.; Asmus, S.; Zurro, M.; Fischer, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 8823. (d) Zurro, M.; Asmus, S.; Bamberger, J.; Beckendorf, S.; García Mancheño, O. *Chem.-Eur. J.* **2016**, *22*, 3785. (e) Fischer, T.; Bamberger, J.; García Mancheño, O. *Org. Biomol. Chem.* **2016**, *14*, 5794. (f) Marcos, V.; Stephens, A. J.; Jaramillo-Garcia, J.; Nussbaumer, A. L.; Woltering, S. L.; Valero, A.; Lemonnier, J.-F.; Vitorica-Yrezabal, I. J.; Leigh, D. A. *Science* **2016**, *352*, 1555. (g) Fischer, T.; Duong, Q.-N.; García Mancheño, O. *Chem.-Eur. J.* **2017**, *23*, 5983. (h) Zurro, M.; García Mancheño, O. *Chem. Rec.* **2017**, *17*, 485.
(20) (a) Kniep, F.; Jungbauer, S. H.; Zhang, Q.; Walter, S. M.; Schindler, S.; Schnapperelle, I.; Herdtweck, E.; Huber, S. M. *Angew. Chem., Int. Ed.* **2013**, 52, 7028. (b) Jungbauer, S. H.; Huber, S. M. *J. Am. Chem. Soc.* **2015**, *137*, 12110. For C–X based activated reagents, see: (c) Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem., Int. Ed.* **2011**, 50, 7187. (d) Kniep, F.; Walter, S. M.; Herdtweck, E.; Huber, S. M. *Chem.-Eur. J.* **2012**, *18*, 1306. (e) Kniep, F.; Rout, L.; Walter, S. M.; Bensch, H. K. V.; Jungbauer, S. H.; Herdtweck, E.; Huber, S. M. *Chem. Commun.* **2012**, *48*, 9299.
(21) Using OriginPro 8.51 from OriginLab©, see Supporting Information.
(22) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.

Table of Contents artwork