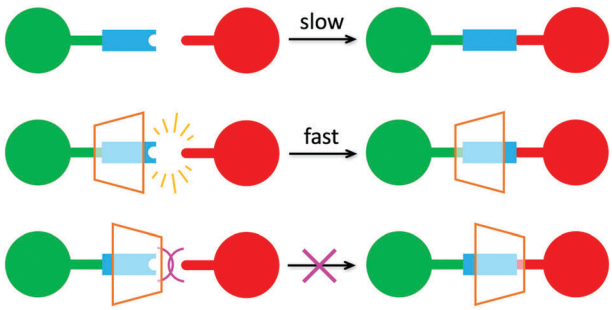
Covalent capture of oriented calix[6]arene rotaxanes by a metal-free active template approach

Chemical Communications

c7cc02859h

We have presented the Graphical Abstract text and image for your article below. This brief summary of your work will appear in the contents pages of the issue in which your article appears.



Covalent capture of oriented calix[6]arene rotaxanes by a metal-free active template approach

Guido Orlandini, Giulio Ragazzon, Valeria Zanichelli, Andrea Secchi, Serena Silvi, Margherita Venturi, Arturo Arduini* and Alberto Credi*

A rotaxane with predetermined orientation of its nonsymmetric components is obtained by a rim-selective active template effect exerted by a calix[6]arene.

Q1

Please check this proof carefully. **Our staff will not read it in detail after you have returned it.**

Proof corrections must be returned as a single set of corrections, approved by all co-authors. No further corrections can be made after you have submitted your proof corrections as we will publish your article online as soon as possible after they are received.

Please ensure that:

- The spelling and format of all author names and affiliations are checked carefully. Names will be indexed and cited as shown on the proof, so these must be correct.
- Any funding bodies have been acknowledged appropriately.
- All of the editor's queries are answered.
- Any necessary attachments, such as updated images or ESI files, are provided.

Translation errors between word-processor files and typesetting systems can occur so the whole proof needs to be read. Please pay particular attention to: tables; equations; numerical data; figures and graphics; and references.

Please send your corrections preferably as a copy of the proof PDF with electronic notes attached or alternatively as a list of corrections – do not change the text within the PDF file or send a revised manuscript. Corrections at this stage should be minor and not involve extensive changes.

Please return your **final** corrections, where possible within **48 hours** of receipt, by e-mail to: chemcomm@rsc.org. If you require more time, please notify us by email.

Funder information

Providing accurate funding information will enable us to help you comply with your funders' reporting mandates. Clear acknowledgement of funder support is an important consideration in funding evaluation and can increase your chances of securing funding in the future. We work closely with Crossref to make your research discoverable through the Funding Data search tool (http://search.crossref.org/fundref).

Further information on how to acknowledge your funders can be found on our webpage (http://rsc.li/funding-info).

What is Funding Data?

Funding Data (http://www.crossref.org/fundingdata/) provides a reliable way to track the impact of the work that funders support. We collect funding information from our authors and match this information to funders listed in the Open Funder Registry. Once an article has been matched to its funders, it is discoverable through Crossref's search interface.

PubMed Central

Accurate funder information will also help us identify articles that are mandated to be deposited in PubMed Central (PMC) and deposit these on your behalf.

Providing funder information

We have included the funder information you gave us on submission in the table below. The 'Funder name' shown and their associated 'Funder ID' number is written as listed in the Open Funder Registry. **Please check that the information in the table is correct.** The funder information should match your acknowledgements. This table will not be included in your final PDF but we will share the data with Crossref so that your article can be found *via* the Funding Data search tool.

Funder name	Funder ID	Award/grant/contract number
Università di Bologna	501100005969	FARB SLaMM project

If a funding organisation you included on submission of your article is not currently listed in the registry it will not appear in the table above. We can only deposit data if funders are already listed in the Open Funder Registry, but we will pass all funding information on to Crossref so that additional funders can be included in future.

Researcher information

If any authors have ORCID or ResearcherID details that are not listed below, please provide these with your proof corrections. Please check that the ORCID and ResearcherID details listed below have been assigned to the correct author. Please use this space to add your own unique ORCID iDs and not another researcher's, as errors will delay publication.

Please also update your account on our online manuscript submission system to add your ORCID details, which will then be automatically included in all future submissions. See here for step-by-step instructions and more information on author identifiers.

First (given) name(s)	Last (family) name(s)	ResearcherID	ORCID
Guido	Orlandini		0000-0003-1937-3758
Giulio	Ragazzon		
Valeria	Zanichelli		0000-0003-2642-1578
Andrea	Secchi	G-2554-2012	0000-0003-4045-961X
Serena	Silvi		
Margherita	Venturi		
Arturo	Arduini		0000-0003-2774-0095
Alberto	Credi	H-4450-2011	0000-0003-2546-9801

Queries for the attention of the authors

Journal: **ChemComm**

Paper: **c7cc02859h**

Title: **Covalent capture of oriented calix[6]arene rotaxanes by a metal-free active template approach**

For your information: You can cite this article before you receive notification of the page numbers by using the following format: (authors), Chem. Commun., (year), DOI: 10.1039/c7cc02859h.

Editor's queries are marked on your proof like this Q1, Q2, etc. and for your convenience line numbers are indicated like this 5, 10, 15, ...

Please ensure that all queries are answered when returning your proof corrections so that publication of your article is not delayed.

Query reference	Query	Remarks
Q1	Please carefully check the spelling of all author names. This is important for the correct indexing and future citation of your article. No late corrections can be made.	
Q2	Do you wish to add an e-mail address for the corresponding author? If so, please provide the relevant information.	arturo.arduini@unipr.it

ChemComm

COMMUNICATION

Covalent capture of oriented calix[6]arene rotaxanes by a metal-free active template approach†

Cite this: DOI: 10.1039/c7cc02859h

Received 13th April 2017,
Accepted 11th May 2017

DOI: 10.1039/c7cc02859h

rsc.li/chemcomm

Guido Orlandini,[a] Giulio Ragazzon,[b] Valeria Zanichelli,[a] Andrea Secchi,[a] Serena Silvi,[b] Margherita Venturi,[bc] Arturo Arduini *[a] and Alberto Credi *[cd]

We describe the active template effect of a calix[6]arene host towards the alkylation of a complexed pyridylpyridinium guest. The acceleration of the reaction within the cavity is significant and rim-selective, enabling the efficient preparation of rotaxanes with full control of the mutual orientation of their nonsymmetric components.

Mechanically interlocked molecules (MIMs) such as rotaxanes, catenanes and related species, initially developed as laboratory curiosities, have been revealed to be appealing for a variety of applications in materials science, information technology, nanoscience, catalysis and medicine.[1,2] The growing interest in these species is strictly related to the development of simple and efficient synthetic methodologies that rely on template-directed effects.[1a,3] Sauvage and co-workers pioneered the use of metal ions as templates[4] to entwine appropriately designed ligands in such a way that the subsequent formation of covalent bonds leads to mechanical interlocking of the molecular components.[1a,3] In these cases the metal ion has been referred to as a passive template,[1a,5] because it provides the correct spatial arrangement of the precursors but it does not play a role in the successive interlocking reaction.

More recently, Leigh and coworkers developed an active metal template strategy[5] in which the metal ion not only acts as a template to preorganise the reactants but also promotes the formation of the covalent bonds that lead to the final MIMs. This procedure, which can be carried out by using either stoichiometric or catalytic amounts of the template, has enabled the efficient synthesis of rotaxanes and catenanes with attractive structural and dynamic features.[6] Although chemical reactions can be kinetically affected within the cavity of a macrocycle,[1a,7] all active template syntheses of MIMs reported to date involve the use of metals.

Here we describe a system in which a calix[6]arene-type host exerts an active template effect in the formation of rotaxanes by both keeping the precursor inside its cavity and accelerating the alkylation reaction that forms the axle component. The process does not require metals and is inherently stoichiometric, because the template is a component of the final MIM and not an external species.

The present investigation stems from the ability of the π-rich tris(*N*-phenylureido)calix[6]arene **1** (Scheme 1) to form inclusion complexes with π-acceptors such as 1,1′-dialkyl-4,4′-bipyridinium guests, which enabled us to prepare a variety of rotaxanes and catenanes over the past decade.[1b,8] In particular, we have been able to exploit the different chemical nature of the two rims of the calixarene to control the threading direction of molecular axles[9] and make oriented rotaxane isomers.[10]

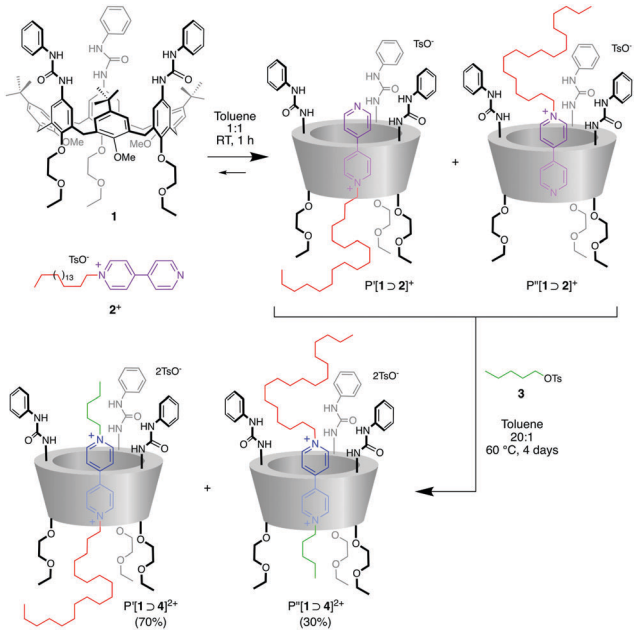
Upon addition of calixarene **1** to a colorless suspension of the pyridylpyridinium species $\mathbf{2}^+$ in toluene at room temperature, the mixture became rapidly homogeneous and orange coloured, suggesting that a complex is formed. A ^{1}H NMR analysis of the solution revealed that $\mathbf{2}^+$ is included into the cavity of **1**, as witnessed by the presence of four signals at very high fields (from 0 to 1 ppm), consistent with the threading of the octadecyl chain of the guest through the macrocycle.† The broadness of the NMR signals suggests that the solution contains several species – namely, free molecular components and two pseudorotaxane isomers $\mathrm{P}'[\mathbf{1}\supset\mathbf{2}]^+$ and $\mathrm{P}''[\mathbf{1}\supset\mathbf{2}]^+$ that differ for the relative orientation of their nonsymmetric components (Scheme 1). The apparent stability constant of the 1 : 1 complex, determined by UV-visible titrations in toluene at 60 °C, is $8.1 \times 10^4\ \mathrm{M}^{-1}$.†

In order to assess whether the reactivity of the pyridylpyridinium guest is affected by complexation, $\mathbf{2}^+$ was alkylated by adding 20 equivalents of *n*-pentyl tosylate (**3**) in the presence of one equivalent of **1** at 60 °C to afford the 1-pentyl-1′-octadecyl-4,4′-bipyridinium species $\mathbf{4}^{2+}$ (Scheme 1).

The formation of $\mathbf{4}^{2+}$ inside the calixarene wheel (Scheme 1) was confirmed by ^{1}H NMR spectra, and observed as a function

[a] Dipartimento di Scienze Chimiche, Della Vita e della Sostenibilità Ambientale, Università di Parma, Parco Area delle Scienze 17/A, I-43124 Parma, Italy
[b] Dipartimento di Chimica "G. Ciamician", Università di Bologna, via Selmi 2, 40126 Bologna, Italy
[c] Istituto per la Sintesi Organica e la Fotoreattività, Consiglio Nazionale delle Ricerche, via Gobetti 101, 40129 Bologna, Italy
[d] Dipartimento di Scienze e Tecnologie Agro-alimentari, Università di Bologna, viale Fanin 50, 40127 Bologna, Italy

† Electronic supplementary information (ESI) available: Synthetic procedures, NMR spectra and UV/Vis titration data. See DOI: 10.1039/c7cc02859h



Scheme 1

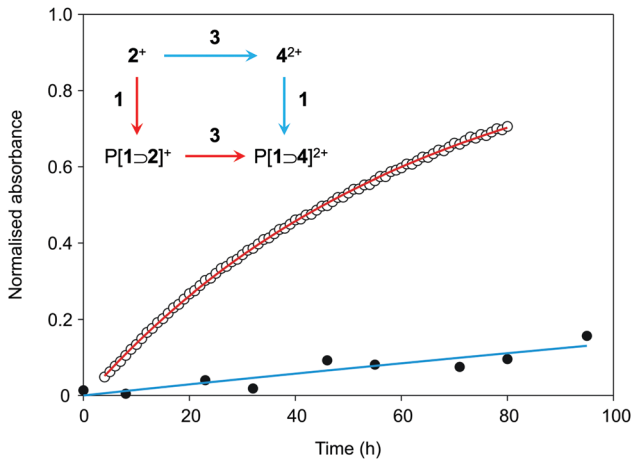


Fig. 1 Normalised absorption changes observed at 470 nm as a function of time upon treating a 1 : 1 mixture of **1** and $\mathbf{2}^+$ with 20 equivalents of **3** (empty circles). Solid circles show the absorption changes observed when $\mathbf{2}^+$ alone is reacted with **3** and the product is detected through its complexation with **1**. The full lines are the fitting according to a second-order rate law. Conditions: toluene, 60 °C, 1.6 mM $\mathbf{2}^+$.

of time by monitoring the intensity of the charge-transfer absorption band at $\lambda = 470$ nm, typical of pseudorotaxanes composed of **1** and bipyridinium guests (Fig. 1). The time-dependent absorption data could be fitted according to a S_N2 mechanism, yielding a rate constant of 1.4×10^{-4} M^{-1} s^{-1} in toluene at 60 °C.

The reaction between $\mathbf{2}^+$ and **3** was investigated in the absence of the calixarene host under the same conditions of the previous experiment. The formation of the product, however, could not be monitored directly because $\mathbf{4}^{2+}$ is insoluble in toluene. Hence, we set up distinct alkylation experiments which were stopped at different times; in each of these experiments the amount of $\mathbf{4}^{2+}$ formed was evaluated by measuring the absorbance at 470 nm upon addition of **1** to the reaction mixture. From the fitting of the absorption data a second-order rate constant of 8.6×10^{-6} M^{-1} s^{-1} was determined (Fig. 1). Thus, under the examined conditions (toluene, 60 °C) the alkylation of $\mathbf{2}^+$ is 16 times faster when the calixarene is present.

The ^{1}H NMR spectra of the reaction mixture in the presence of **1** show that the pseudorotaxane isomer P′$[\mathbf{1}\supset\mathbf{4}]^{2+}$ is obtained preferentially (70%) over P″$[\mathbf{1}\supset\mathbf{4}]^{2+}$ (30%) (Scheme 1). Interestingly, the formation of P′$[\mathbf{1}\supset\mathbf{4}]^{2+}$ is kinetically disfavoured with respect to P″$[\mathbf{1}\supset\mathbf{4}]^{2+}$ upon threading of pre-formed $\mathbf{4}^{2+}$ into **1** in toluene. Indeed, only P″$[\mathbf{1}\supset\mathbf{4}]^{2+}$ is afforded at room temperature, and a P′$[\mathbf{1}\supset\mathbf{4}]^{2+}$/P″$[\mathbf{1}\supset\mathbf{4}]^{2+}$ ratio of 30 : 70 is reached after 10 days under reflux.[9]

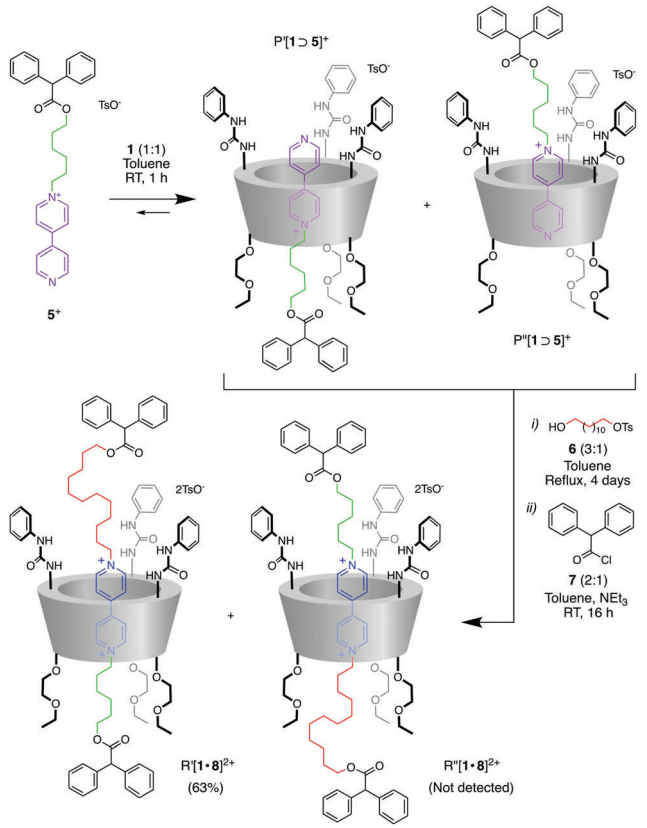
These observations, on the one hand, unequivocally prove that the alkylation of $\mathbf{2}^+$ in the presence of **1** occurs on guest molecules accommodated inside the calixarene cavity. On the other hand, they suggest that the reaction takes place preferentially on P′$[\mathbf{1}\supset\mathbf{2}]^+$, because it may be more populated and/or more reactive than P″$[\mathbf{1}\supset\mathbf{2}]^+$. In fact, we cannot exclude that P′$[\mathbf{1}\supset\mathbf{4}]^{2+}$ is the sole alkylation product and that subsequently, under the reaction conditions, its components dethread and rethread to afford the kinetic product of the threading process, that is, P″$[\mathbf{1}\supset\mathbf{4}]^{2+}$.‡

To gain a deeper mechanistic understanding and enhance the active template effect of **1** on the distribution of the orientational isomers, we limited the scrambling of the wheel and axle components by introducing a bulky substituent on the alkyl extremity of the pyridylpyridinium guest. Thus, we performed a new alkylation experiment using the stoppered axle $\mathbf{5}^+$ (Scheme 2). As already observed for $\mathbf{2}^+$, the complete solubilisation of the guest and the appearance of an orange colour upon addition of **1** revealed the formation of a complex. The ^{1}H NMR spectra of the solution are consistent with the presence of the two pseudorotaxane isomers, P′$[\mathbf{1}\supset\mathbf{5}]^+$ and P″$[\mathbf{1}\supset\mathbf{5}]^+$, and the free molecular components (Scheme 2).

The detection of both orientational isomers when a stoppered axle is employed shows unequivocally that the pyridylpyridinium guest can pierce the calixarene through either the upper (urea-decorated) or the lower (alkoxy-decorated) rim. This observation is in contrast to the behaviour of bipyridinium axles, which in nonpolar solvents can enter the wheel only by passing through the upper rim.[11] Presumably, the role of the urea moieties in driving the threading/dethreading of a dicationic bipyridinium species through the upper rim is less significant when the guest bears only one positive charge, as in the case of $\mathbf{5}^+$ (or $\mathbf{2}^+$).

The complexity of the NMR spectra prevented us from assessing the exact amount of the P′$[\mathbf{1}\supset\mathbf{5}]^+$ and P″$[\mathbf{1}\supset\mathbf{5}]^+$ isomers in solution. Therefore, we covalently captured the corresponding oriented rotaxanes by alkylation and subsequent stoppering. To this aim, the solution containing the pseudorotaxanes was reacted with an excess of 12-hydroxy-*n*-dodecyl tosylate (**6**) in refluxing toluene for 4 days (Scheme 2), enabling the formation of the corresponding dicationic semirotaxanes.

The mixture was then directly treated with diphenylacetyl chloride (**7**) at room temperature to obtain the two rotaxane



Scheme 2

isomers R′[**1**·**8**]$^{2+}$ and R″[**1**·**8**]$^{2+}$ (Scheme 2). Indeed, only R′[**1**·**8**]$^{2+}$ was isolated in 63% yield after chromatographic separation; no trace of R″[**1**·**8**]$^{2+}$ was found. The ^{1}H NMR spectrum of the product, interpreted with the aid of the spectra of known symmetric rotaxanes bearing, respectively, C6 and C12 alkyl chains linking the bipyridinium unit and the stoppers, unequivocally confirmed the arrangement of the axle **8**$^{2+}$ with respect to the calixarene wheel in R′[**1**·**8**]$^{2+}$.†

The fact that R′[**1**·**8**]$^{2+}$ is the sole product indicates unequivocally§ that under the conditions employed only P′[**1**⊃**5**]$^{+}$ undergoes an accelerated alkylation; that is, the active template action of **1** takes place only when the pyridyl nitrogen is oriented towards the upper rim of the calixarene. Such an observation may be rationalized considering that (i) the pyridine nitrogen is more exposed to the bulk when facing the upper rim, (ii) the deep encapsulation of the pyridinium charge into the electron rich cavity of **1** could result in an enhanced nucleophilicity of the pyridyl nitrogen, and (iii) the proximity of the urea moieties to the reaction site could stabilize the transition state by binding the incipient, strongly coordinating tosylate anion.

In summary, we have shown that calixarene **1** plays the role of an active template in the formation of (pseudo)rotaxanes by accelerating the alkylation of a pyridylpyridinium substrate inside the cavity of the host. At present, this is a unique example of metal-free active template synthesis of MIMs. Moreover, the template effect takes place selectively at the upper rim of the calixarene, thereby enabling the synthesis of rotaxanes containing oriented components arranged in a predetermined manner, in significantly higher yields and much shorter reaction times with respect to sequential threading–capping procedures.[10] We are interested in MIMs of this kind for the development of novel molecular machines capable of stimuli-induced directionally controlled movements.[12] Experiments aimed at unravelling the reaction mechanism are also underway in our laboratories.

This work was supported by Università di Bologna (FARB SLaMM project) and Università di Parma (Centro Interdipartimentale di Misure).

Notes and references

‡ It cannot even be excluded that the P″[**1**⊃**4**]$^{2+}$ results obtained from the *exo*-cavity reaction of **2**$^{+}$ with **3** to yield **4**$^{2+}$, which threads **1** from the upper rim with its pentyl chain, as previously observed.[9]
§ If the alkylation occurred on free **5**$^{+}$, the resulting dicationic monostoppered compound would thread **1** from the upper rim,[11] affording R″[**1**·**8**]$^{2+}$. On the other hand, both the direct alkylation of P″[**1**⊃**5**]$^{+}$ and the isomerization of the dicationic semirotaxane resulting from the alkylation of P′[**1**⊃**5**]$^{+}$ have to be excluded, as they would also lead, after the attachment of the second stopper, to the formation of R″[**1**·**8**]$^{2+}$.

1 (*a*) C. J. Bruns and J. F. Stoddart, *The nature of the mechanical bond: from molecules to machines*, Wiley & Sons, Hoboken, 2017; (*b*) A. Arduini, G. Orlandini, A. Secchi, A. Credi, S. Silvi and M. Venturi, in *Calixarenes and Beyond*, ed. P. Neri, J. L. Sessler and M.-X. Wang, Springer, Cham, 2016, pp. 761–781; (*c*) *From Non-Covalent Assemblies to Molecular Machines*, ed. J. -P. Sauvage and P. Gaspard, Wiley-VCH, Weinheim, 2010; (*d*) V. Balzani, A. Credi and M. Venturi, *Molecular devices and machines – concepts and perspectives for the nanoworld*, Wiley-VCH, Weinheim, 2008.
2 (*a*) J. E. M. Lewis, M. Galli and S. M. Goldup, *Chem. Commun.*, 2017, **53**, 298–312; (*b*) C. J. Bruns and J. F. Stoddart, *Acc. Chem. Res.*, 2014, **47**, 2186–2199; (*c*) M. Xue, Y. Yang, X. Chi, X. Yan and F. Huang, *Chem. Rev.*, 2015, **115**, 7398–7501; (*d*) S. Erbas-Cakmak, D. A. Leigh, C. T. McTernan and A. L. Nussbaumer, *Chem. Rev.*, 2015, **115**, 10081–10206; (*e*) Y.-W. Yang, Y.-L. Sun and N. Song, *Acc. Chem. Res.*, 2014, **47**, 1950–1960; (*f*) M. J. Langton and P. D. Beer, *Acc. Chem. Res.*, 2014, **47**, 1935–1949.
3 R. S. Forgan, J.-P. Sauvage and J. F. Stoddart, *Chem. Rev.*, 2011, **111**, 5434–5464.
4 C. O. Dietrich-Buchecker, J.-P. Sauvage and J. P. Kintzinger, *Tetrahedron Lett.*, 1983, **24**, 5095–5098.
5 J. D. Crowley, S. M. Goldup, A.-L. Lee, D. A. Leigh and R. T. McBurney, *Chem. Soc. Rev.*, 2009, **38**, 1530–1541.
6 See, *e.g.*: (*a*) J. E. M. Lewis, J. Winn, L. Cera and S. M. Goldup, *J. Am. Chem. Soc.*, 2016, **138**, 16329–16336; (*b*) J. J. Danon, D. A. Leigh, P. R. McGonigal, J. W. Ward and J. Wu, *J. Am. Chem. Soc.*, 2016, **138**, 12643–12647.
7 See, *e.g.*: (*a*) W. L. Mock, T. A. Irra, J. P. Wepsiec and T. L. Manimaran, *J. Org. Chem.*, 1983, **48**, 3619–3620; (*b*) W. Herrmann, M. Schneider and G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2511–2514; (*c*) A. Martinez-Cuezva, C. Lopez-Leonardo, D. Bautista, M. Alajarin and J. Berna, *J. Am. Chem. Soc.*, 2016, **138**, 8726–8729; (*d*) X. Hou, C. Ke and J. F. Stoddart, *Chem. Soc. Rev.*, 2016, **45**, 3766–3780.
8 (*a*) A. Arduini, R. Bussolati, A. Credi, G. Faimani, S. Garaudée, A. Pochini, A. Secchi, M. Semeraro, S. Silvi and M. Venturi, *Chem. – Eur. J.*, 2009, **15**, 3230–3242; (*b*) G. Orlandini, V. Zanichelli, A. Secchi, A. Arduini, G. Ragazzon, A. Credi, M. Venturi and S. Silvi, *Supramol. Chem.*, 2016, **28**, 427–435.
9 A. Arduini, R. Bussolati, A. Credi, A. Secchi, S. Silvi, M. Semeraro and M. Venturi, *J. Am. Chem. Soc.*, 2013, **135**, 9924–9930.
10 V. Zanichelli, G. Ragazzon, A. Arduini, A. Credi, P. Franchi, G. Orlandini, M. Venturi, M. Lucarini, A. Secchi and S. Silvi, *Eur. J. Org. Chem.*, 2016, 1033–1042.
11 A. Arduini, F. Calzavacca, A. Pochini and A. Secchi, *Chem. – Eur. J.*, 2003, **9**, 793–799.
12 (*a*) A. Arduini, R. Bussolati, A. Credi, S. Monaco, A. Secchi, S. Silvi and M. Venturi, *Chem. – Eur. J.*, 2012, **18**, 16203–16213; (*b*) G. Ragazzon, M. Baroncini, S. Silvi, M. Venturi and A. Credi, *Nat. Nanotechnol.*, 2015, **10**, 70–75; (*c*) C. Cheng, P. R. McGonigal, S. T. Schneebeli, H. Li, N. A. Vermeulen, C. Ke and J. F. Stoddart, *Nat. Nanotechnol.*, 2015, **10**, 547–553.