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Controlled self-sorting in self-assembled cage complexes

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In this frontier article we highlight recent advances in subcomponent self-sorting in self-assembled metal–ligand cage complexes, with a focus on selective discrimination between ligands that contain highly similar metal-coordinating groups. Effects such as varying ligand length, coordination angle and backbone flexibility, as well as the introduction of secondary weak forces such as hydrogen bonds can be exploited to favor either narcissistic or social self-sorting. We highlight these creative solutions, and emphasize the challenges that remain in the development of functional self-assembled heterocomplexes.

Introduction

The construction of complex molecular machines, switches and functional devices requires a high level of control in subcomponent self-assembly.[1,2] Nature uses exquisitely selective methods to construct complex biomolecular machines, often exploiting multiple small interactions to direct the outcome.[3] A popular method of mimicking complex biomacromolecular constructs exploits multicomponent metal–ligand-based assembly.[4–6] There are many different types of molecular polygons and cage polyhedra that can now be accessed *via* this strategy, and a wide variety of functions are possible, from biomimicking catalysis,[7–9] to molecular recognition,[10,11] structural switching[12–14] and drug delivery.[15] One of the major remaining challenges is to selectively control the incorporation of multiple different ligand types into a single cage complex, which requires selective self-sorting between the ligands. This is simple if the coordinating groups on the ligands are different (similar to the possibilities in heterocomplex formation *via* H-bonding mediated assembly, either in Nature[16] or with synthetic equivalents[17]), but far more complex if the coordinating groups are identical. Despite this challenge, there has recently been some highly imaginative work in the area of selective self-sorting in multicomponent cage assembly.[18]

When attempting to combine two (or more) different ligand types into a self-assembled cage, the possible self-sorting behaviour can be divided into two specific subsets: narcissistic self-sorting, and social (or integrative[19]) self-sorting, as shown in Fig. 1. Narcissistic self-sorting consists of the homo-selective assembly of the individual components, forming multiple homocomplexes in the reaction mixture. Social self-sorting is less common, and requires the incorporation of multiple different ligands into the final assembly. A further subset of these sorting types is enantioselective self-sorting, which we will not discuss here. The reader is directed to a comprehensive recent review on that topic.[20] Here we will describe recent efforts to control the sorting of highly similar ligands into discrete self-assembled cage complexes, and identify the challenges that yet remain.

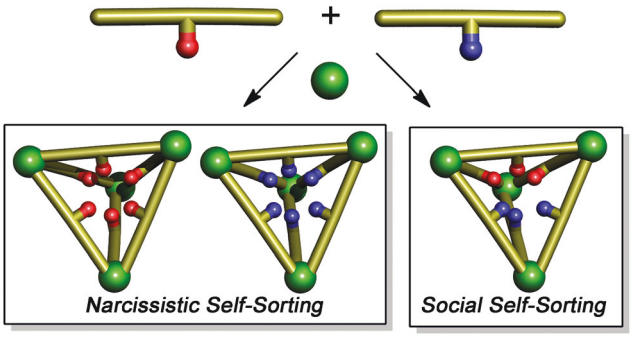

Fig. 1 Different types of self-sorting behaviour possible when combining two similar ligands into a metal–ligand cage assembly.

There are a variety of methods that can be used to control self-sorting behaviour: varying the ligand size or angle, changing the denticity or nature of the coordinating motif, introducing secondary interactions into the ligand backbone, or relying on templating effects with bound guests. Obviously, the greater the differences between the individual ligands, the more effective the self-sorting becomes. These differences can be additive: selecting between different ligands that form assemblies of different stoichiometries (*e.g.* M_2L_3 *vs.* M_4L_6, *etc.*) is common, as the entropic differences between cages of different stoichiometry are often large. Similarly, using ligands with different coordinating groups allows their selective assembly, if designed properly, but this adds an extra layer of

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synthetic complexity to the process. As with all supramolecular assemblies, inspiration can be found in Nature: multiple secondary weak forces, each of which is small by itself, but collectively add up, can be exploited to allow selective sorting between ligands of similar shape, size and coordinating motif.

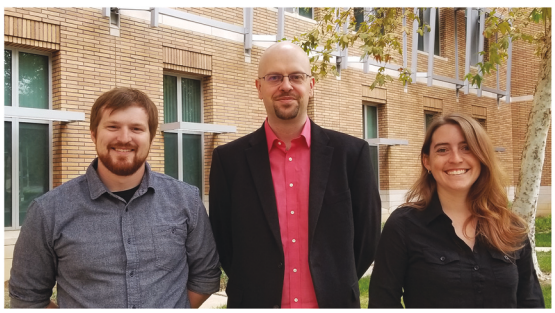
Discussion

Narcissistic self-sorting

The first examples of self-sorting exploited identical metal coordinating groups in ligands of different lengths. This sorting is applicable to assemblies utilizing either bidentate or monodentate M–L contacts. By varying the length of the spacer between different bis-catechol-based ligands, narcissistic self-sorting could be achieved in the formation of M_2L_3 helicates with Ga^{3+} ions.[21] More recently, bis-phenanthroline ligands with variably sized allenoacetylene spacers showed length-based narcissistic self-sorting, as well as impressive homochiral selectivity.[22] This concept can also be applied to selective sorting between ligands of different length *via* Pt-phosphine-based assembly.[23] Varying the lengths of rigid linear acetylenyl-Pt ligands along with the phosphine end "clips" also allows narcissistic self-sorting. The subtle differences in length precludes the accommodation of different ligands within the assembly, and based on the angle of the clip, the assembly can form either triangular or square polygons. Most recently, the concept has been extended to organometallic self-assembled systems. Tripodal N-heterocyclic carbene (NHC) ligands containing various spacers between the NHC and the central tripodal core are capable of length-selective narcissistic self-sorting when complexed with Ag^+ or Au^+ ions, forming molecular M_3L_3 cylinders of varying sizes with high selectivity.[24]

Narcissistic discrimination can also be achieved by varying the coordination angle as well as modifying the length of the ligand. Changing the coordination angle increases the overall differences between the ligands significantly. When the ligand angle changes (from linear to v-shaped, for example), the length almost always changes as well, and often confers a different stoichiometry on the assembly as a whole (*e.g.* M_2L_3 *vs.* M_4L_6). The large changes in overall energetics between assemblies of two different stoichiometries unsurprisingly leads to selective self-sorting between the components.[25] However, it is also possible to confer selective sorting between ligands of varying coordination angle that form cages of identical stoichiometry.[26] Fig. 2a shows an example using Ln-mediated assembly with bis-salicylhydrazone ligands. Linear ligand **3** is easily differentiated from bent ligands **1** and **2** upon treatment with Ln^{3+} ions, as the overall stoichiometries of assembly are different. However, ligands **2** and **3** also show complete narcissistic self-sorting, even though the differences between the ligands are considerably smaller. Highly effective narcissistic sorting has also been shown between bipodal and tripodal Ln coordinating ligands (as well as impressive enantioselectivity in assembly of the homochiral components).[27] Despite the presence of identical coordinating groups, selective discrimination between ligands was possible, allowing controlled formation of either Eu_4L_4 or Eu_4L_6 cages.

The greatest challenge is to confer self-sorting between ligands that are extremely similar in size, angle and the nature of the metal coordinating group, varying in only internal substitution. In certain cases, extremely small differences can be distinguished in the assembly processes. Fig. 2b shows how small those differences need to be: ligands **2**, **4** and **5** display identical lengths, rigidities, coordination angles and donor ability, and form helicate complexes of identical stoichiometry. Despite this, complete narcissistic self-sorting is observed



From left to right in the picture – Paul M. Bogie, Richard J. Hooley, Lauren R. Holloway

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Richard Hooley obtained his undergraduate degrees in Natural Sciences from Emmanuel College, Cambridge University (1999), before moving to Princeton University where he received his Ph.D. in 2004 in the laboratory of Prof. Martin F. Semmelhack. In 2004, he joined the lab of Prof. Julius Rebek Jr. at The Scripps Research Institute in La Jolla, CA as a Skaggs Postdoctoral Fellow. In 2008, Richard began his independent career in the Department of Chemistry at the University of California – Riverside. The Hooley group works on various aspects of organic, inorganic and supramolecular chemistry, with a focus on the synthesis and applications of biomimetic self-assembled cages and hosts, and their functions in supramolecular catalysis, molecular recognition and biosensing.

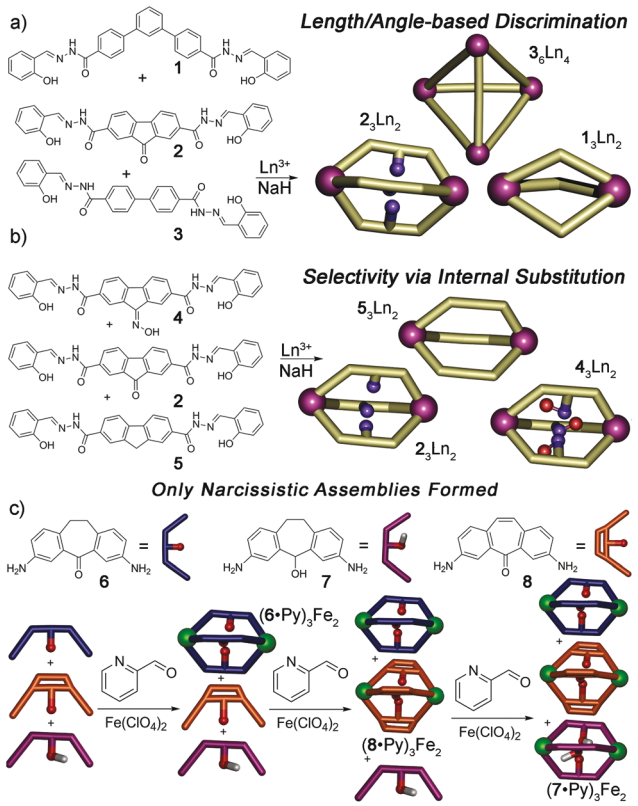

Fig. 2 Narcissistic self-sorting driven by: (a) varying ligand angles, (b) varying internal steric bulk;[26] (c) hybridization and ligand deformation upon multicomponent assembly.[28]

when the ligands are combined with a variety of different Ln^{3+} ions. Discrimination between ligands varying only by the presence of a C=O group *vs.* a CH_2 group on the interior is possible. The reason for this impressive discrimination highlights the limitations of this system, however: the Ln_2L_3 helicates have essentially no cavity, and the internal groups directly interact with each other. While the selectivity is impressive, its applicability to larger complexes with guest-binding cavities is unclear.

Fortunately, the concept of structural control *via* introducing small variables to ligand backbones is applicable to other, more varied systems with larger cavity sizes. Fig. 2c shows how the introduction of hydrogen bonding groups and changes in backbone hybridization can control the assembly process.[28] The diaminodibenzosuberyl scaffolds **6–8** are forced to bend somewhat upon multicomponent self-assembly with 2-formylpyridine (PyCHO) and Fe^{2+} salts. The variable deformation energies between the ligands, which vary minimally in structure, control the favourability of the process. The amount of ligand distortion required to form a *meso*-helicate assembly is inversely related to the order of stability of the homocomplexes. Not only do ligands **6–8** display high fidelity narcissistic self-sorting, but stepwise homoleptic cage formation can be observed from a complex mixture of 33 components in the same pot through the sequential addition of metal and PyCHO. In addition, the presence of hydrogen bonding groups on the interior can control the stereoselectivity of the process,[29] and large aromatic ligand surfaces can direct assembly *via* π-stacking effects.[30]

Social self-sorting

Narcissistic self-sorting is less studied than social (or integrative) self-sorting, probably due to the fact that social selectivity is simply more useful when constructing functional assemblies. Incorporating multiple different ligands (and their concomitant functions) into an assembly provides a method for introducing unique functions to the system. As such, there have been many attempts to confer this type of sorting in the formation of catenanes, knots and molecular machines, and the reader is directed to some recent reviews on the topic.[18,31,32] The overarching strategy used in many of these systems is to vary the coordinating group in each ligand. This is obviously the most effective way of ensuring the presence of multiple different functions in the assembly, but introduces synthetic complexity to the systems. An alternate strategy is to employ dynamic combinatorial libraries, where varying degrees of energetic biases and social sorting can be found and exploited to create functional assemblies.[33–36] Our focus here is strongly selective sorting between ligands with highly similar coordinating groups, however, and that area of research is far less developed. The reader is directed to an excellent recent review that covers many of these possibilities.[19]

The challenge in selective social self-sorting is that ligand matching cannot be exploited: self-complementary ligands by definition favour narcissistic sorting. One creative solution to the problem is to apply post-assembly ligand displacement (Fig. 3a).[37] This solution is simple and elegant, in that the use of coordinating groups that vary only slightly in electron donating ability can lead to the predictable formation of heterocomplexes in a reliable manner. This concept does require cage complexes with low barriers to ligand displacement, such as Pd-pyridyl M_2L_4 cages. If electron rich amine-decorated ligand **12** is added to the preformed $[Pd_2\mathbf{11}_4]^{4+}$ complex, the *cis*-heteroleptic cage $[Pd_2\mathbf{11}_2\mathbf{12}_2]^{4+}$ can be formed selectively. The presence of the hydrogen-bonding amine groups close to the coordinating site prevents further displacement of undecorated ligands to form the homocomplex. Density functional theory calculations suggested the *cis* product was the most stable product, and that the heteroleptic cages are kinetically metastable intermediates rather than the thermodynamic product. Three other heteroleptic cages with different *exo* and *endo* functionalities were readily assembled, which indicates that this displacement method could be applied to synthesize a range of other heteroleptic complexes. These M_2L_4 paddlewheel complexes are sensitive to internal substitution, and a certain degree of social self-sorting is possible by packing the interior of the cage with a suitable sized group.[38] Ligand **10** is functionalized with a medium-sized trifluoroacetamido group on the interior, and is incapable of self-assembly with Pd^{II} ions due to steric repulsion. However, if combined with the unfunctionalized equivalent **9**, the $[Pd_2\mathbf{9}_3\mathbf{10}]^{4+}$ complex forms selectively, albeit in the presence of the more favourable

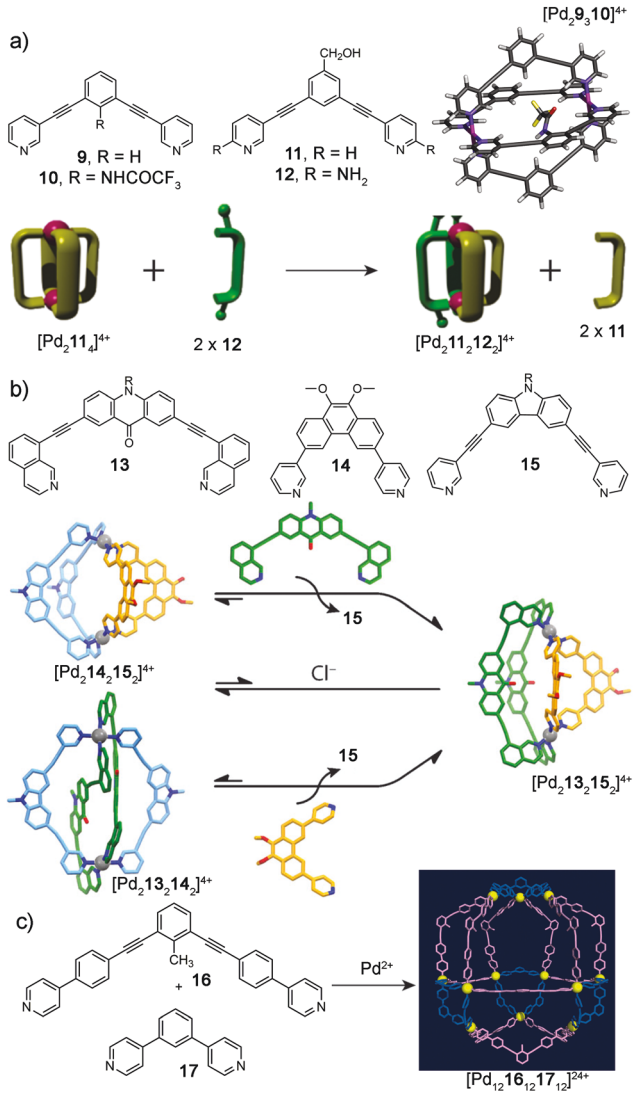

Fig. 3 Social self-sorting driven by: (a) internal[38] or external substitution and postsynthetic ligand displacement;[37] (b) complementary angle[39,40] and (c) ligand bridging length ratios.[41] Reproduced from ref. 37, copyright 2016 American Chemical Society and from ref. 41, copyright 2014 Wiley-VCH Verlag GmbH & Co.

$[Pd_2\mathbf{9}_4]^{4+}$ complex. This effect is size-dependent: small internal NH_2 groups conferred no sorting, and larger benzamido groups prevented any assembly at all.

The most effective method to reliably create socially self-sorting systems exploits small changes in the coordinating angle of the ligands. By varying the size and shape of the internal ligand cores, as well as the coordination angle of pyridine-based ligands, heteroleptic complexes can be favoured upon assembly with Pd^{2+} salts.[39] The key to this control lies in choosing ligands that form strained homocomplexes. Acridone based ligand **13** has a bite angle of 120° and forms a $[Pd_2\mathbf{13}_4]^{4+}$ bent helical structure while **14** (60° angle) forms a $[Pd_4\mathbf{14}_8]^{8+}$ cube, but both of these complexes are of limited stability. As such, when a mixture of these two ligands was combined with Pd^{2+} salts, their complementary shapes lead to the formation of a $[Pd_2\mathbf{13}_2\mathbf{14}_2]^{4+}$ complex possessing a significantly lower energy barrier to formation than the individual homocomplexes. In a second study, a third ligand (**15**) with an intermediate bite angle of 75° was employed as a "missing link". Two additional heterocomplexes could be accessed and the relative favourability of the complexes was studied.[40] In each of these cases, the stereochemistry of the heteroleptic assemblies was also controlled, with only the *cis* isomers being observed. Designing socially self-sorted cages in this manner requires careful planning so that the strained homocomplexes form, yet are less stable than the more favoured heterocomplexes.

Careful ligand design can be used to create very large heterocomplexes.[41] A unique cantellated tetrahedron $[Pd_{12}\mathbf{16}_{12}\mathbf{17}_{12}]^{24+}$ (Fig. 3c) was synthesized *via* the incorporation of two different ligands that display identical coordination angles. In this case, it was discovered that as the ratio of the bridging lengths of the two ligands increased, the sorting behaviour of the self-assembly critically switches from a dynamic library to the well-defined cantellated tetrahedron. However, when two ligands with a smaller bridging length ratio were mixed, statistical incorporation into a narcissistic self-sorted system occurs.[42] It was concluded that bridging length ratio values in the range of 1–1.6 will lead to the formation of a statistical dynamic library of complexes. However, when the bridging length ratio is increased to >2.0, a critical switch in behaviour is observed and the system forms a defined social self-sorted heterocomplex. These cases illustrate that there is a "goldilocks zone" of ligand coordination types that can be exploited for the design of functional heterocomplexes.

Conclusion and outlook

The synthesis of self-assembled cage complexes is now a mature field, but there are still many challenges in their application as functional devices and biomimetic catalysts. Controlled self-sorting between ligands with similar (or identical) coordinating groups is challenging, yet highly desirable, as it simplifies ligands synthesis and allows modular strategies to be used to incorporate functionality to the complexes. While coordinative strategies such as varying the ligand angle, length or steric bulk of the ligand are most common, sorting can also be driven by other small and often overlooked factors such as secondary self-complementary weak forces, and control of ligand distortion upon metal complexation. These strategies have mainly been successful in favouring narcissistic self-sorting, while social self-sorting can be achieved by meticulous design of ligands with just the right lengths and angles for controlled heterocomplex assembly.

These advances are an important step towards making self-assembled cages capable of effective biomimetic catalysis: by incorporating both acidic and basic groups on the interior of a cage capable of guest recognition, species that mimic peptidase activity are in reach. This requires more robust assemblies, and the extension of this sorting technology to metal–

ligand cages that exploit bidentate coordinating groups. This is still a challenge, as control of ligand coordination angle is more difficult than with monodentate pyridyl coordinators, and the slower ligand exchange rate limits the possibilities for postsynthetic ligand exchange. Still, the controlled self-sorting shown recently opens up a variety of possibilities in the creation of functional machines and switches from self-assembled cage complexes.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 M. D. Ward and P. R. Raithby, *Chem. Soc. Rev.*, 2013, **42**, 1619.
2 R. W. Saalfrank, H. Maid and A. Scheurer, *Angew. Chem., Int. Ed.*, 2008, **47**, 8794.
3 G. Wei, W. Xi, R. Nussinov and B. Ma, *Chem. Rev.*, 2016, **116**, 6516.
4 Y. Tu, F. Peng, A. Adawy, Y. Men, L. K. E. A. Abdelmohsen and D. A. Wilson, *Chem. Rev.*, 2016, **116**, 2023.
5 M. Fujita, M. Tominaga, A. Hori and B. Therrien, *Acc. Chem. Res.*, 2005, **38**, 369.
6 T. R. Cook and P. J. Stang, *Chem. Rev.*, 2015, **115**, 7001.
7 C. J. Brown, F. D. Toste, R. G. Bergman and K. N. Raymond, *Chem. Rev.*, 2015, **115**, 3012.
8 Y. Ueda, H. Ito, D. Fujita and M. Fujita, *J. Am. Chem. Soc.*, 2017, **139**, 6090.
9 C. J. Hastings, M. D. Pluth, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2010, **132**, 6938.
10 T. K. Ronson, C. Giri, N. K. Beyeh, A. Minkkinen, F. Topic, J. J. Holstein, K. Rissanen and J. R. Nitschke, *Chem. – Eur. J.*, 2013, **19**, 3374.
11 C.-L. Liu, L.-P. Zhou, D. Tripathy and Q.-F. Sun, *Chem. Commun.*, 2017, **53**, 2459.
12 S. Erbas-Cakmak, D. A. Leigh, C. T. McTernan and A. L. Nussbaumer, *Chem. Rev.*, 2015, **115**, 10081.
13 E. R. Kay and D. A. Leigh, *Angew. Chem., Int. Ed.*, 2015, **54**, 10080.
14 L. R. Holloway, H. H. McGarraugh, M. C. Young, W. Sontising, G. J. O. Beran and R. J. Hooley, *Chem. Sci.*, 2016, **7**, 4423.
15 S. K. Samanta, D. Moncelet, V. Briken and L. Isaacs, *J. Am. Chem. Soc.*, 2016, **138**, 14488.
16 B. J. G. E. Pieters, M. B. van Eldijk, R. J. M. Nolte and J. Mecinović, *Chem. Soc. Rev.*, 2016, **45**, 24.
17 P. Mukhopadhyay, A. Wu and L. Isaacs, *J. Org. Chem.*, 2004, **69**, 6157.
18 M. M. Safont-Sempere, G. Fernandez and F. Wurthner, *Chem. Rev.*, 2011, **111**, 5784.
19 W. M. Bloch and G. H. Clever, *Chem. Commun.*, 2017, **53**, 8506.
20 H. Jędrzejewska and A. Szumna, *Chem. Rev.*, 2017, **117**, 4863.
21 D. L. Caulder and K. N. Raymond, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1440.
22 O. Gidron, M. Jirásek, N. Trapp, M.-O. Ebert, X. Zhang and F. Diederich, *J. Am. Chem. Soc.*, 2015, **137**, 12502.
23 Y.-R. Zheng, H.-B. Yang, B. H. Northrop, K. Ghosh and P. J. Stang, *Inorg. Chem.*, 2008, **47**, 4706.
24 N. Sinha, T. T. Y. Tan, E. Peris and F. E. Hahn, *Angew. Chem., Int. Ed.*, 2017, **56**, 739.
25 S. M. Jansze, G. Cecot, M. D. Wise, K. O. Zhurov, T. K. Ronson, A. M. Castilla, A. Finelli, P. Pattison, E. Solari, R. Scopelliti, G. E. Zelinskii, A. V. Vologzhanina, Y. Z. Voloshin, J. R. Nitschke and K. Severin, *J. Am. Chem. Soc.*, 2016, **138**, 2046.
26 A. M. Johnson, C. A. Wiley, M. C. Young, X. Zhang, Y. Lyon, R. R. Julian and R. J. Hooley, *Angew. Chem., Int. Ed.*, 2015, **54**, 5641.
27 L.-L. Yan, C.-H. Tan, G.-L. Zhang, L.-P. Zhou, J.-C. Bünzli and Q.-F. Sun, *J. Am. Chem. Soc.*, 2015, **137**, 8550.
28 L. R. Holloway, M. C. Young, G. J. O. Beran and R. J. Hooley, *Chem. Sci.*, 2015, **6**, 4801.
29 M. C. Young, L. R. Holloway, A. M. Johnson and R. J. Hooley, *Angew. Chem., Int. Ed.*, 2014, **53**, 9832.
30 S. P. Black, D. M. Wood, F. B. Schwarz, T. K. Ronson, J. J. Holstein, A. R. Stefankiewicz, C. A. Schalley, J. K. M. Sanders and J. R. Nitschke, *Chem. Sci.*, 2016, **7**, 2614.
31 M. Schmittel and K. Mahata, *Chem. Commun.*, 2010, **46**, 4163.
32 S. De, K. Mahata and M. Schmittel, *Chem. Soc. Rev.*, 2010, **39**, 1555.
33 I. Saur, R. Scopelliti and K. Severin, *Chem. – Eur. J.*, 2006, **12**, 1058.
34 K. E. Allen, R. A. Faulkner, L. P. Harding, C. R. Rice, T. Riss-Johannessen, M. L. Voss and M. Whitehead, *Angew. Chem., Int. Ed.*, 2010, **49**, 6655.
35 B. Brusilowskij and C. A. Schalley, *Eur. J. Org. Chem.*, 2011, 469.
36 J. J. Henkelis, J. Fisher, S. L. Warriner and M. J. Hardie, *Chem. – Eur. J.*, 2014, **20**, 4117.
37 D. Preston, J. E. Barnsley, K. C. Gordon and J. D. Crowley, *J. Am. Chem. Soc.*, 2016, **138**, 10578.
38 A. M. Johnson and R. J. Hooley, *Inorg. Chem.*, 2011, **50**, 4671.
39 W. M. Bloch, Y. Abe, J. J. Holstein, C. M. Wandtke, B. Dittrich and G. H. Clever, *J. Am. Chem. Soc.*, 2016, **138**, 13750.
40 W. M. Bloch, J. J. Holstein, W. Hiller and G. H. Clever, *Angew. Chem., Int. Ed.*, 2017, **56**, 8285.
41 Q.-F. Sun, S. Sato and M. Fujita, *Angew. Chem., Int. Ed.*, 2014, **53**, 13510.
42 Q.-F. Sun, J. Iwasa, D. Ogawa, Y. Ishido, S. Sato, T. Ozeki, Y. Sei, K. Yamaguchi and M. Fujita, *Science*, 2010, **328**, 1144.