Mechanical Interlocking of Macrocycles in Different Sequences
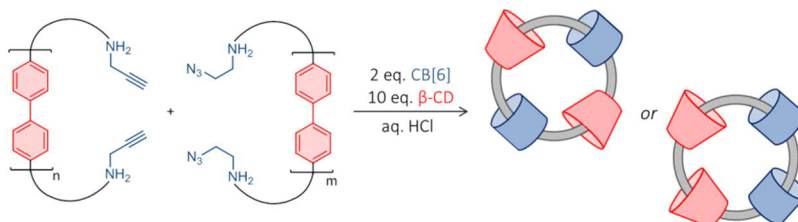
Ho Yu Au-Yeung*
Antony Wing Hung Ng

Department of Chemistry, The University of Hong Kong,
Pokfulam Road, Hong Kong, P. R. China

* indicates the main/corresponding author.

hoyuay@hku.hk

Click here to insert a dedication.

❖ one step, high yield (>80%) synthesis of [5]catenanes
❖ isomeric sequences of mechanically bonded macrocycles
❖ sequence-dependent properties

Abstract Sequence isomerism is fundamental to the storage, transfer and expression of information in (bio)macromolecules and artificial polymers. Realization of sequence specific properties in mechanically bonded molecules is extremely challenging due to the huge synthetic difficulty in the precise and controllable non-covalent interlocking of constitutionally different macrocycles in specific orders within a rotaxane or catenane. This Synpacts article highlights how sequence isomers of multi-component rotaxane and catenane can be obtained by novel synthetic strategies and careful building block designs.

Isomerism is a central concept in Chemistry. Isomers arise when the same group of atoms is covalently bonded in different connectivity (structural isomers) or different geometry (stereoisomers), and the chemical, physical or biological properties of a molecule are often specific to a particular isomer.

Bonding within components in a molecule is not limited to covalent bond. New types of isomerism, and new properties and applications thereof, are possible when groups of atoms are held together by interactions of different nature. In particular, isomerism could be due to mechanical bond in which the mechanically interlocked components are arranged differently in space.[1] Stereoisomerism involving different co-conformations that are interconvertible by intramolecular motions is perhaps one most important and unique feature of mechanically interlocked molecules, which is also critical to their potential applications in diverse areas such as molecular machines, switches, shuttles, actuators, sensors … etc.[2] With the rapid development in synthetic strategies to access mechanically interlocked molecules of increasing number of interlocked components and also structural and topological

complexity, realization of more different types of isomerism involving mechanical bond is to be expected.[3]

One underdeveloped type of isomerism involving mechanically bonded molecules is sequence isomerism that features macrocycles interlocked in different sequences. As in natural biomacromolecules such as DNA, RNA and proteins that contain covalently linked building blocks in a specific sequence, arranging mechanically interlocked macrocycles in specific orders could be implicated in the development of synthetic materials that are capable of storing, transferring, and processing of information,[4] not mentioning other new and unique functions and potential applications as a result of expressing sequence specific properties in the context of mechanical bond. Of note, while sequence isomers of covalent molecules are not interconvertible without breaking and re-forming of covalent bonds, sequence isomers of mechanically bonded molecules could be interconverted with all the mechanical and covalent bonds remain intact if intramolecular motions, such as ring-through-ring shuttling,[5] are permissible for exchanging positions of the interlocked macrocycles (Figure 1).
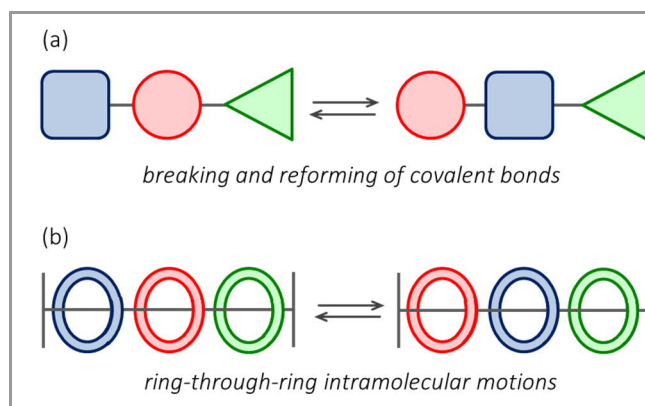

Figure 1 Sequence isomers of (a) covalently and (b) mechanically bonded molecules can interconvert through covalent bond breaking/reforming and

intramolecular motions respectively.

Synthetic challenges in interlocking multiple macrocycles of different constitution in different order are one major difficulty in realizing sequence isomerism in rotaxane and catenane (Figure 2). It is worth noting that neither hetero[n]rotaxane or hetero[n]catenane is synthetically trivial,[6] therefore the further control of macrocycle interlocking in a specific sequence is particularly difficult. In the case of rotaxane, few different strategies such as self-sorting and orthogonal template have been developed for the efficient synthesis of hetero[n]rotaxane, but almost all of these hetero[n]rotaxanes are prepared as one single isomer in one sequence, and thus no comparative analysis for studying properties due to sequence-dependent mechanically interlocking is available.[6a] There are even fewer examples of hetero[n]catenane, probably due to the extra challenge associated with macrocycle formation in catenane synthesis.[3b,6b] There are therefore only very few examples of molecular systems that feature different possible arrangements of the same set of mechanically bonded macrocycles.
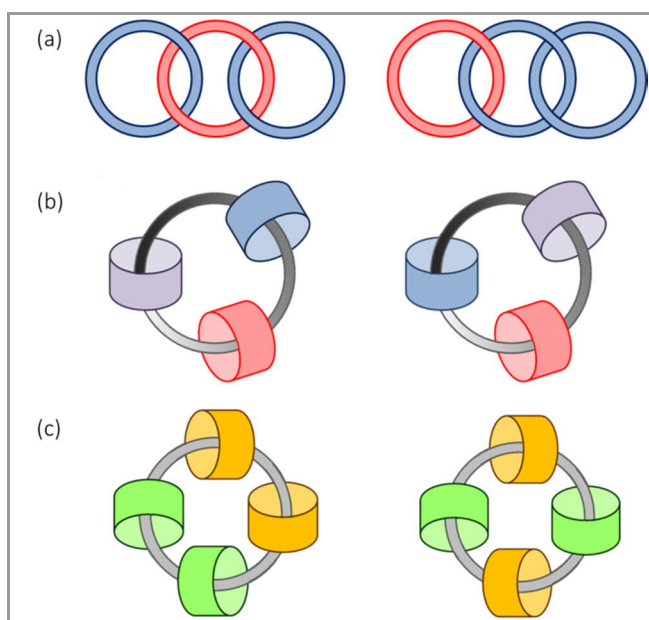

Figure 2 Examples of isomeric catenanes with the interlocked macrocycles arranged in different sequences. (a) Linear [3]catenanes with two constitutionally different macrocycles; (b) radial [4]catenanes with three constitutionally different macrocycles interlocked on a central macrocycle with directionality; (c) radial [5]catenanes with four macrocycles of two constitutions interlocked on a central macrocycle.
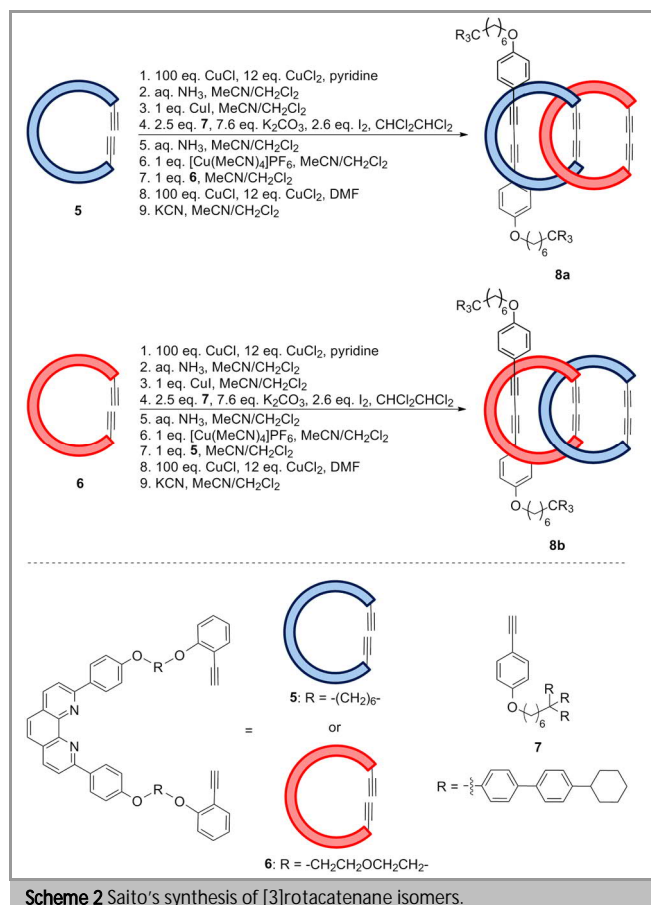
In 2010, Leigh and co-workers have reported their seminal work on the first realization of sequence isomerism in [3]rotaxanes.[7] By the strategical use of an unsymmetrical linear molecule 1 with a pyridine moiety located at one end as a dumbbell, macrocycles derived from 2,6-pyridyldiamide with different substituents were clipped onto the dumbbell via a series of Pd^{2+} preorganization, alkene metathesis, hydrogenation by 2-nitrobenzenesulfonyl hydrazide (NBSH) and demetallation using KCN (Scheme 1). Simply by introducing the different 2,6-pyridyldiamide precursors 2 or 3 in different orders, the macrocycles were mechanically interlocked in different sequences because the Pd^{2+}-preorganization has to be occurred only at the pyridine end of

the dumbbell. A pair of [3]rotaxane sequence isomer (4a and 4b) was prepared and characterized.
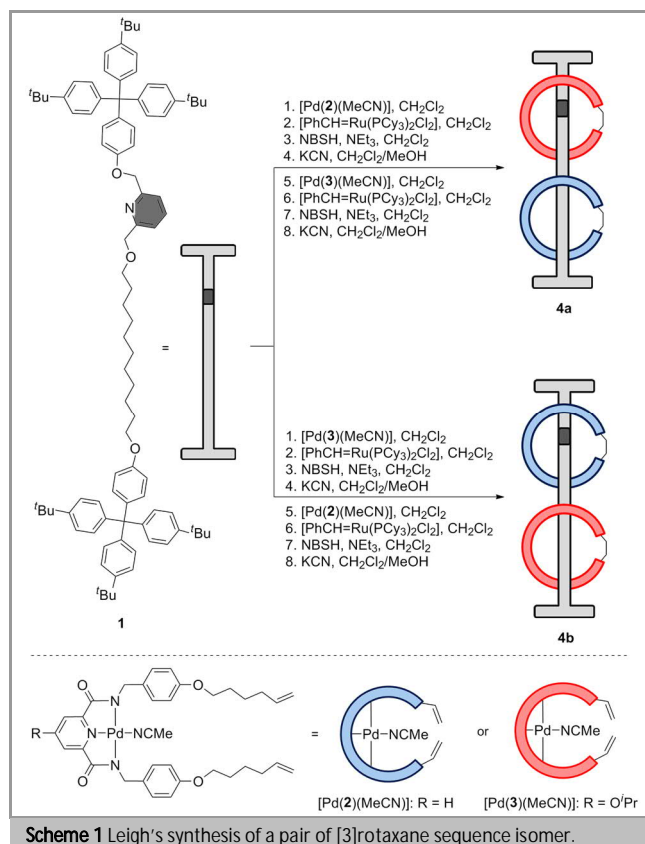

Scheme 1 Leigh's synthesis of a pair of [3]rotaxane sequence isomer.

More recently in 2016, Saito and co-workers have described the synthesis of a pair of [3]rotacatenane isomers with two macrocycles and one axle components that are interlocked in different orders.[8] Phenanthroline-derived macrocycles were first formed via an intramolecular alkyne coupling of 5 or 6. Cu^+-coordination to the phenanthroline then templated the formation of a new dumbbell inside the macrocyclic cavity upon a Cu^+-catalyzed alkyne coupling of 7 to give the corresponding [2]rotaxanes. Further Cu^+-coordination and preorganization of the macrocycle precursor and intramolecular alkyne coupling furnished the synthesis of the [3]rotacatenane isomers 8a and 8b (Scheme 2). Similar to the [3]rotaxane isomers reported by Leigh and co-workers, the different sequence of Saito's [3]rotacatenanes is a result of the different order of mechanical interlocking of the respective components.

Scheme 2 Saito's synthesis of [3]rotacatenane isomers.

Scheme 3 Catenane synthesis via CBAAC. Triazole formation is mediated inside CB[6] cavity and thus CB[6] interlocking is ensured.

Our group has been developing new strategies for the efficient synthesis of high-order, multi-component [n]catenanes.[9] One big challenge in [n]catenane synthesis is the precise spatiotemporal control of both the preorganization of a large number of precursors and the covalent reaction for forming the new macrocycles. Topological isomers containing different number of mechanically bonded macrocycles in different structures are often formed which not only lower the yield but also complicate the purification of the desired [n]catenane. To address this challenge, we have adopted the cucurbit[6]uril (CB[6])-mediated azide-alkyne cycloaddition (CBAAC) for macrocycle formation.[10] As the triazole formation is only mediated inside the CB[6] cavity in CBAAC, new macrocycle formation is to be accompanied by CB[6] interlocking and thus efficiency of catenane formation is greatly improved (Scheme 3). By designing building blocks that contain multiple binding sites to preorganizing several building blocks via orthogonal interactions, we have successfully synthesized a series of [n]catenanes and [n]rotaxane (n up to 6) in high yields.[11]
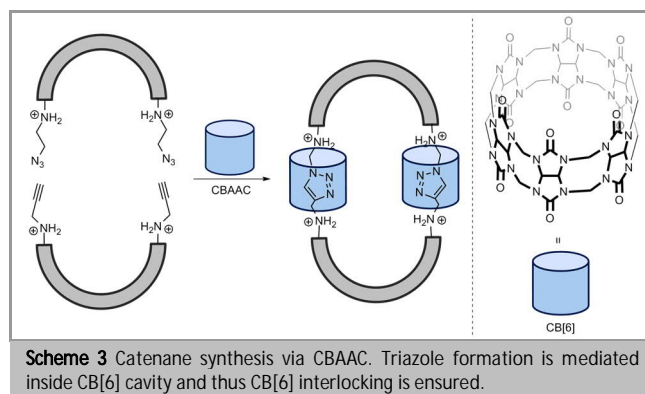
We envisaged that catenane isomers with different sequences of the interlocked macrocycles can also be easily prepared by CBAAC. In particular, two pairs of building blocks 9/10 and 11/12 have been designed with strategically positioned biphenylene units.[12] In the presence of β-cyclodextrin (β-CD) which is a well-known host for biphenylene, CBAAC of the building blocks gave two radial [5]catenane isomers (13a and 13b) with a cyclic –ABAB– or –AABB– sequence of the interlocked CB[6] and β-CD (Scheme 4). Due to the high efficiency of CBAAC, both [5]catenanes were formed in over 80% yields with no other topological isomers composed of less interlocked rings. Conceptually similar to DNA translation or ribosomal protein synthesis that rely on complementary hydrogen bonds between a sequence-encoded biopolymer and relevant biomolecules, the peripheral macrocycles in the [5]catenanes are interlocked on the central macrocycle via orthogonal non-covalent templates in a sequence that is determined by the covalent structure of the building blocks. Of note, due to the different covalent structure of the central macrocycles in 13a and 13b, the [5]catenanes are to be classified as structural isomers despite their sequences of the mechanically bonded macrocycles are also different.[7]

Interestingly, because of the remarkably difference in the strength of CB[6]-ammonium (log K ≈ 5–7) and (β-CD)-biphenylene (log K ≈ 2–3) interactions,[13] arranging the macrocycles in different sequences resulted in different properties that are unique to mechanically bonded molecules. In 13a, the two loosely bound β-CDs are separated by the tightly bound CB[6]s, shuttling motions of the two β-CDs are therefore relatively independent from each other; whereas in 13b, the two β-CDs are adjacent to each other and thus their motions are coupled. This difference in the β-CD dynamics is reflected by the temperature at which the biphenylene aromatic signals are resolved in their ^{1}H NMR spectra. Moreover, shuttling motions of the pH-insensitive β-CD was found to be facilitated by an increase in the pH of the system which removes the strong CB[6]-ammonium interactions. Notably, the transmission of a stimulus (pH change) from one mechanically bonded component (CB[6]) to another (β-CD) is rarely realized but strongly implicated in the design of complex multi-component molecular machines.
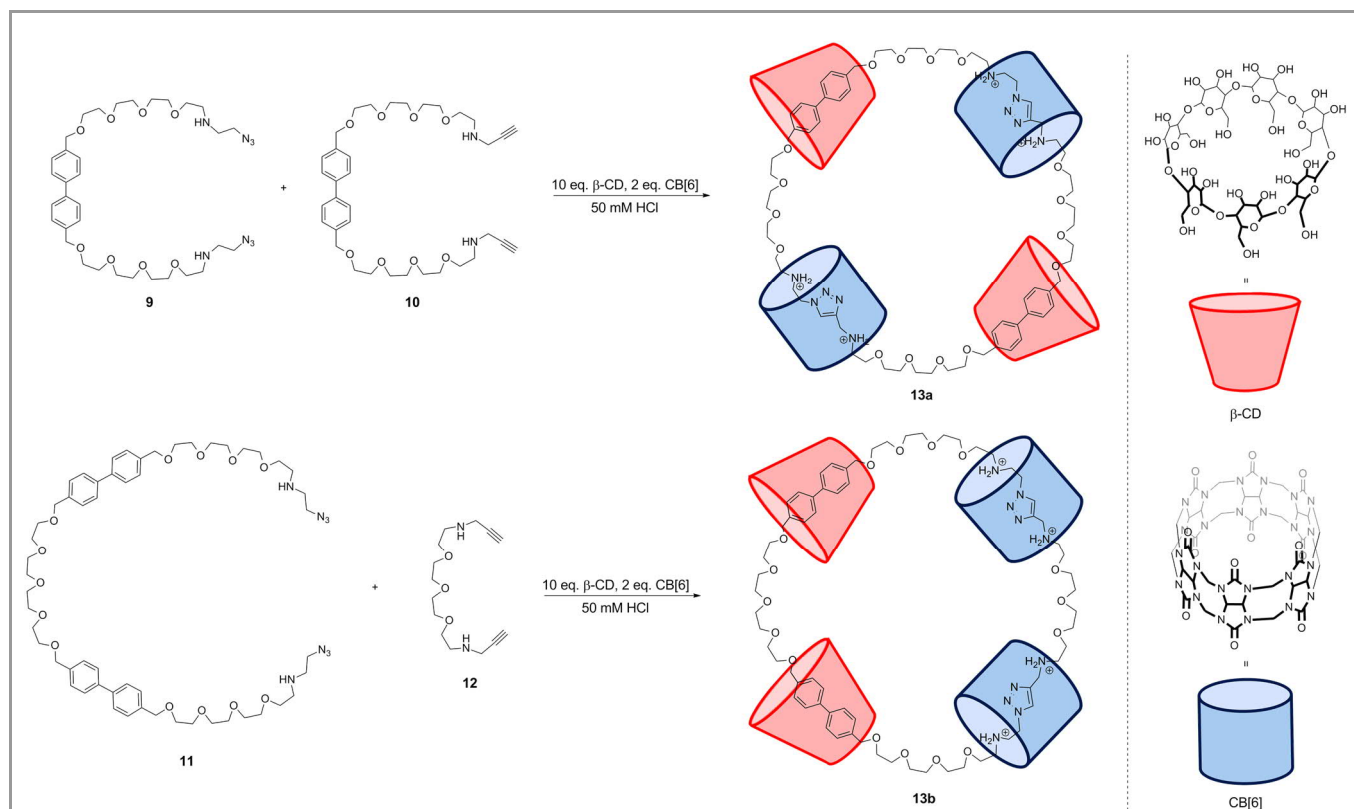
Scheme 4 Synthesis of specific radial [5]catenane isomers by CBAAC of strategically designed building blocks. Only one stereoisomer is shown for each [5]catenanes with an arbitrary orientation of the β-CD.

Sequence-specific features were also observed in the MS/MS study of the [5]catenane isomers. Upon cleavage of the central macrocycle, a pseudo[4]rotaxane fragment was resulted from 13a due to the mechanical protection by the CB[6] that prevented slippage of the β-CD. On the other hand, slippage of both β-CD from 13b gave the corresponding pseudo[3]rotaxane as the major fragment (Figure 3).
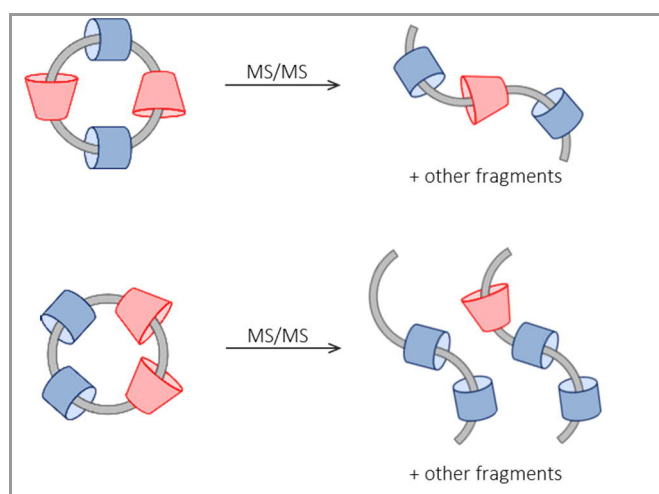

Figure 3 Distinctive MS/MS fragmentation of the [5]catenane isomers.

In conclusion, sequential preorganization and interlocking, and arranging orthogonal templates in a covalent sequence are the only two strategies available now for controlling the order of mechanically bonded macrocycles in hetero[n]rotaxanes and hetero[n]catenanes. From being structurally aesthetic objects to candidates for developing functional molecular entities, lying behind all the distinctive attributes of mechanically bonded molecules is the fundamental nature of mechanical bond. Realizing characteristics known in covalent molecules in mechanically bonded compounds not only presents interesting synthetic challenges but can also bring new properties, functions and possibilities. Mechanical interlocking macrocycles of different structures and properties in a single [n]rotaxane or [n]catenane is still very difficult. Further innovative synthetic strategies and sophisticated building block designs for tailor-making complex, multi-component mechanically bonded molecules, and the sequence specific incorporation of functional groups in these molecules to achieve new properties and functions under the context of mechanical bond, are awaited.

Funding Information

Acknowledgment

References

(1) Bruns, C. J.; Stoddart, J. F. The Nature Of The Mechanical Bond: From Molecules To Machines; John Wiley & Sons, 2016

(2) (a) Neal, E. A.; Goldup, S. M. Chem. Commun. 2014, 50, 5128. (b) Mena-Hernando, S.; Pérez, E. M. Chem. Soc. Rev. 2019, 48, 5016.

(3) For reviews on rotaxanes, catenanes and knots, see (a) Beves, J. E.; Blight, B. A.; Campbell, C. J.; Leigh, D. A.; McBurney, R. T. Angew.

Chem. Int. Ed. 2011, 50, 9260. (b) Gil-Ramírez, G.; Leigh, D. A.; Stephens, A. J. Angew. Chem., Int. Ed. 2015, 54, 6110. (c) Fielden, S. D. P.; Leigh, D. A.; Woltering, S. L. Angew. Chem., Int. Ed. 2017, 56, 11166.

(4) (a) Martens, S.; Landuyt, A.; Espeel, P.; Devreese, B.; Dawyndt, P.; Du Prez, F. Nat. Commun. 2018, 9, 4451. (b) Lutz, J. F. Macromolecules 2015, 48, 4759. (c) Szaciłowski, K. Chem. Rev. 2008, 108, 3481.

(5) Zhu, K.; Baggi, G.; Loeb, S. J. Nat. Chem. 2018, 10, 625.

(6) (a) Wang, X.-Q.; Li, W.-J.; Wang, W.; Yang, H.-B. Chem. Commun. 2018, 54, 13303. (b) Au-Yeung, H. Y.; Yee, C.-C.; Ng, A. W. H.; Hu, K. Inorg. Chem. 2018, 57, 3475.

(7) Fuller, A. M. L.; Leigh, D. A.; Lusby, P. J. J. Am. Chem. Soc. 2010, 132, 4954.

(8) Hayashi, R.; Slavik, P.; Mutoh, Y.; Kasama, T.; Saito, S. J. Org. Chem. 2016, 81, 1175.

(9) (a) Yee, C.-C.; Ng, A. W. H.; Au-Yeung, H. Y. Chem. Commun. 2019, 55, 6169. (b) Ng, A. W. H.; Yee, C. C.; Wang, K.; Au-Yeung, H. Y. Beilstein J. Org. Chem. 2018, 14, 1846. (c) Tong, K. L.; Yee, C. C.; Tse, Y. C.; Au-Yeung, H. Y. Inorg. Chem. Front. 2016, 3, 348. (d) Ng, A. W. H.; Au-Yeung, H. Y. Chem. Asian J. 2019, 14, 1602.

(10) (a) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. J. Org. Chem. 1983, 48, 3619. (b) Ke, C.; Smaldone, R. A.; Kikuchi, T.; Li, H.; Davis, A. P.; Stoddart, J. F. Angew. Chem., Int. Ed. 2013, 52, 381.

(11) (a) Wang, K.; Yee, C. C.; Au-Yeung, H. Y. Chem. Sci. 2016, 7, 2787. (b) Man, J. Y. H.; Au-Yeung, H. Y. Beilstein J. Org. Chem. 2019, 15, 1829-1837.

(12) Ng, A. W. H.; Yee, C.-C.; Au-Yeung, H. Y. Angew. Chem. Int. Ed., 2019, 58, 17375.

(13) (a) Mock, W. L.; Shih, N. Y. J. Org. Chem. 1986, 51, 4440. (b) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. Angew. Chem., Int. Ed. 2005, 44, 4844. (c) Rekharsky, M. V.; Inoue, Y. Chem. Rev. 1998, 98, 1875. (d) Connors, K. A. Chem. Rev. 1997, 97, 1325.

Biosketches

Ho Yu Au-Yeung obtained his BSc (First Class) and MPhil degrees in Chemistry from The Chinese University of Hong Kong. He was awarded a Croucher Scholarship to pursue his PhD at University of Cambridge, UK with Prof. J. K. M. Sanders and later conducted his postdoctoral research at University of California, Berkeley as a Croucher Postdoctoral Fellow with Prof. C. J. Chang. In summer 2013, he joined the Department of Chemistry at The University of Hong Kong as an Assistant Professor. Current research interest in his group includes the synthesis and properties of complex [n]catenanes, and applications of mechanically bonded molecules in catalysis, sensing and materials. He has been awarded Thieme Chemistry Journals Award 2016, Croucher Innovation Award, Graeme Hanson Early Career Researcher Award and more recently an Asian Core Program Lectureship Award (Taiwan).

Checklist (have these on hand for manuscript submission in ScholarOne):

- cover letter, including a statement of the work's significance
- full mailing address, telephone and fax numbers, and e-mail address of the corresponding author
- email address for each author
- original Word file
- original graphics files zipped into one zip file
- eye-catching graphical abstract as an individual file
- 5–8 key words

Useful links:

- SYNLETT homepage
- SYNLETT information and tools for authors
- Graphical abstract samples (PDF file download)
- What is "Primary Data"?
- ScholarOne (manuscript submission)