



Cite this: *Org. Biomol. Chem.*, 2018, **16**, 8559

Received 2nd August 2018,
Accepted 4th October 2018

DOI: 10.1039/c8ob02428f

rsc.li/obc

Introduction

Reversibly photoisomerizable diarylethene (DAE) units have been inserted in countless molecules and systems, whose properties and functions can be controlled with light.¹ DAEs undergo pericyclic transformations under irradiation with UV or visible light (Fig. 1). The “open” and “closed” photoforms are stable at ambient temperatures that makes them attractive for numerous applications, especially in biology and medicine.^{1*i,j,m,o*}

One of the popular synthetic approaches utilizes functionalized DAE-derived reagents (“building blocks”) for modular construction of photocontrollable molecules. For example, bis-diethynyl-substituted diarylethene **1** (Fig. 2) has been proposed as an entry to new photochromic DAE materials through palladium-catalyzed Sonogashira cross-coupling reaction² or for Cu-catalysed cycloaddition to azides (a “click”-reaction) involving its triple bonds.³

We were interested in **1** and similar compounds because they could be used for cross-linking the azide-substituted side chains in biologically active peptides in order to stabilize their

conformation *via* so-called “stapling”. This could be done, for example, using a two-component strategy, employing the click-reaction.⁴ Stapling can increase the biostability, improve binding affinities and pharmacokinetic properties of peptides,⁵ and photoisomerizable cross-linkers can additionally make their bioactivities photocontrollable – a feature which is attracting much interest due to potential applications in biotechnology and medicine.^{1*i,j,o*}

Cross-linking of peptides with azobenzene-derived, mainly thiol-reactive photoisomerizable cross-linkers was extensively studied since the beginning of 2000th. Efficient photocontrol of peptide conformation,^{6*a–i*} folding,^{6*j,k*} and affinity of binding to DNA^{6*l,m*} was documented. It was demonstrated that biologically relevant processes like protein–protein interaction (PPI)^{6*n–q*} and insulin secretion^{6*r*} could be “switched on” and “switched off” reversibly with the use of the azobenzene-derived cross-linked peptides. Photoisomerizable spirobopyrane^{6*s*} and rhodopsin-like fragments^{6*t*} were also utilized in peptide cross-linkers to enable the photocontrol of peptide conformation and properties. These studies have laid the ground for the development of practically useful photocontrollable biologically active compounds for biotechnology and *in vivo* applications.^{1*i*}

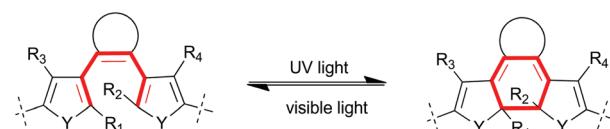


Fig. 1 Diarylethene fragment used in photocontrollable molecules and systems, $R_1, R_2 = \text{alkyl}$; $R_3, R_4 = \text{H, alkyl, aryl}$; $Y = \text{S, O or N}$. The core unit undergoing photoinduced pericyclic transformations is highlighted in red.

^aUniversity Chemical Laboratory, University of Cambridge, Lensfield Road, CB2 1EW Cambridge, UK. E-mail: spring@ch.cam.ac.uk

^bEnamine Ltd., Vul. Chervonotkatska 78, 02094 Kyiv, Ukraine

^cInstitute of Biological Interfaces (IBG-2), Karlsruhe Institute of Technology (KIT), POB 3640, 76021 Karlsruhe, Germany

^dInstitute of Organic Chemistry (IOC), KIT, Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany

^eTaras Shevchenko National University of Kyiv, Institute of High Technologies, Vul. Volodymyrska 64/13, 01601 Kyiv, Ukraine. E-mail: ik214@yahoo.com

^fLumobiotics GmbH, Auer Str. 2, 76227 Karlsruhe, Germany

† Electronic supplementary information (ESI) available: Synthetic procedures, analytical data for novel compounds & details of the calculations. See DOI: 10.1039/c8ob02428f



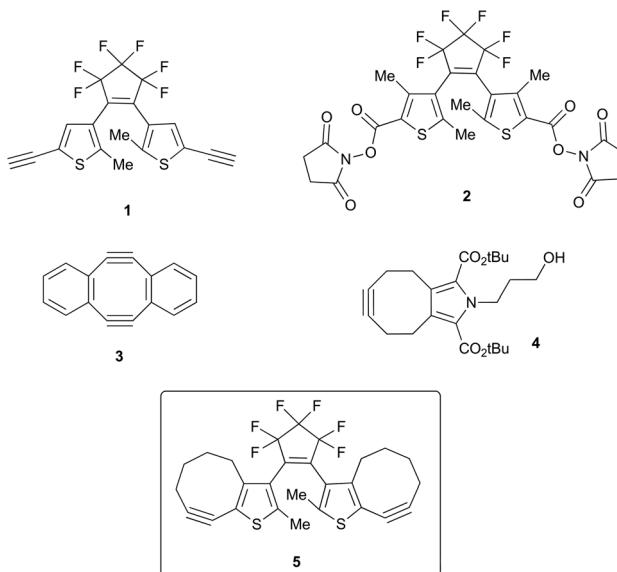


Fig. 2 The cross-linking reagents (1–3), a pyrrole-containing cyclooctyne (4) described in the literature and the new reagent developed in this work (5).

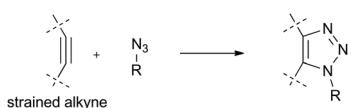


Fig. 3 Strain-promoted azide–alkyne cycloaddition (SPAAC) reaction.

DAE-derived peptide cross-linkers are much less studied. The only proof-of-principle experiment demonstrating successful photocontrol of peptides stapled by the DAE building block 2 have been reported for DNA-binding peptides (Fig. 2).^{6a} The activated carboxylic groups in 2 reacted with the amino groups of ornithine side chains to form amide bonds in the stapled peptides. To the best of our knowledge, no DAE building blocks equipped for a click-reaction have been used so far for peptide stapling. In this paper, we report on the design and synthesis of such a building block, and its validation for peptide stapling applications.

Of particular interest for applications are bio-orthogonal cross-linking reagents utilizing the strain-promoted azide–alkyne cycloaddition (SPAAC) as the click-reaction, which avoids toxic Cu-catalysts (Fig. 3).⁷ SPAAC has already been successfully used for peptide stapling: a cyclooctadiyne derivative 3 (Fig. 2) was employed as the stapling reagent and demonstrated excellent performance.⁸ Here, we aimed at developing a DAE-based cross-linking building block suitable for the Cu-free SPAAC.

Results and discussion

Design of the target compound

The utility of SPAAC in biological systems critically depends on the reactivity of the strained alkynes involved in the reaction:

more reactive reagents can address faster biological processes and can react with the azide-modified biomolecules even if they are present at low concentrations in living systems. After the pioneering work describing relatively slow-reacting cyclooctynes,^{7a} much effort was put into the development of stable, but more reactive fluoro- and difluoro-substituted analogues,^{7b} heteroatom-containing cyclooctynes,^{7c} dibenzo-annulated cyclooctadiynes⁹ and twisted systems¹⁰ (see a recent review¹¹).

When designing our DAE-based building block, we were inspired by a recent report demonstrating that the addition of one mole of azide to dibenzo[a,e]cyclooctadiyne 3 made the second triple bond 500-fold more reactive.^{12a} This can be attributed to additional strain imposed on the medium-sized carbocycle by the annulation of the five-membered triazole ring, resulting in the enhanced reactivity of the remaining triple bond. An exceptionally high reactivity was also reported for compound 4, a cyclooctyne mono-annulated to a five-membered pyrrole ring.^{12b} Taking into account these findings and aiming at enhanced reactivity of our reagent, we targeted structure 5 (Fig. 2), in which two cyclooctyne residues are symmetrically annulated to the five-membered thiophene rings of the DAE fragment. Comparing to the known DAE-derived building block 2, compound 5 will form less conformationally flexible cross-linker (due to the presence of two additional cycles) which might help to better convey its structural changes to the cross-linked molecular unit upon photoisomerization.

Synthesis

The key intermediate in our synthesis of 5 was the cycloheptanone derivative 6 (Fig. 4). This compound is easily available through the technically simple 1,1,1,3,3,3-hexafluoro-2-propanol-promoted intramolecular Friedel–Crafts acylation reaction of 7, as described for its non-methyl-substituted analogue.¹³ Compound 7 was obtained in good yield starting from 2-methyl-4-bromothiophene 8, following the procedures first described more than half a century ago.¹⁴ All the synthetic sequence can be scaled up to multigram quantities of the compound 6, which can be prepared in a reasonable time (1–2 weeks).

Easy synthetic availability of 6 prompted us to explore the cyclooctyne ring construction first using this compound as a model, and then applying the elaborated procedure to the more complex and expensive DAE-derived bis-cyclooctyne precursor of 5, which could also be synthesized from 6.

The exocyclic alkene 9 was obtained from 6 in excellent yield using the Wittig reaction. Rearrangement of 9 to the corresponding cyclooctanone 10 proceeded smoothly under action of hydroxy(tosyloxy)iodobenzene followed by aqueous-methanol work-up, a procedure reported recently for β -benzocycloalkenones.¹⁵ Formation of the enol triflate 11 followed by elimination completed the synthesis of the model cyclooctyne 12, in overall 18% yield.

We were pleased to find that compound 12 was highly reactive in SPAAC, yet stable enough to allow performing the reaction with azides *in situ* at ambient temperature. Although attempts at isolating of pure 12 failed in our hands due to



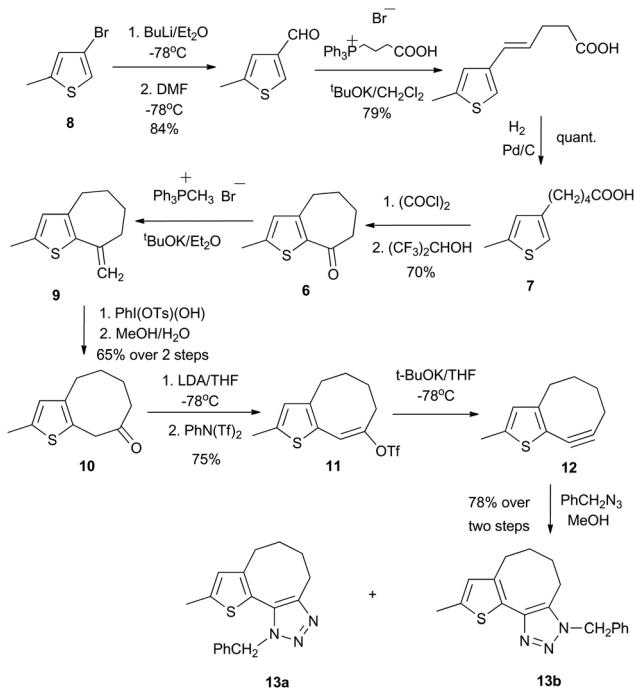


Fig. 4 Synthesis of the model cyclooctyne 12 and its reaction with benzyl azide.

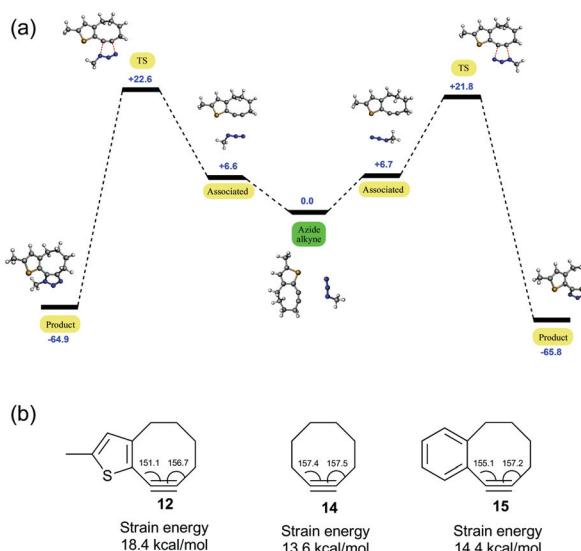


Fig. 5 (a) Energy level diagram depicting SPAAC between 12 and methyl azide in methanol (energy in kcal mol⁻¹). (b) Calculated strain energies and alkyne bond angles of 12, cyclooctyne 14, and benzofused cyclooctyne 15.

compound decomposition, storage of this compound at -20°C in the solution after preparation preserved the compound almost not degraded for several days. Reaction of 12 with benzyl azide proceeded completely in less than 30 minutes at 1 mM concentration and 0 $^{\circ}\text{C}$ giving isomeric

13a and 13b (*syn* : *anti* 24 : 76). Both triazole isomers were separated by preparative HPLC and their structure was assigned through series of HMBC and NOESY 2D-NMR experiments (see ESI†).

DFT calculations of the structure of 12 and its reaction with methyl azide confirmed that the high reactivity of this compound stems from the additional strain imposed by the five-membered heterocycle fused to the cyclooctyne ring (Fig. 5).

Transition state activation barriers for SPAAC between 12 and methyl azide were calculated using Gaussian 09¹⁶ with the B3LYP density functional and the 6-31 G(d) basis set within the CPCM model for methanol as solvent at standard conditions (see ESI† for full computational details). We found that the activation barrier for the formation of the *anti*-regioisomer (21.8 kcal mol⁻¹) was lower than for the *syn*-regioisomer (22.6 kcal mol⁻¹), which is consistent with the experimental observation of the *anti*-isomer being the predominant product (Fig. 5a). Furthermore, the activation barrier for SPAAC with 12 (21.8 kcal mol⁻¹) was found to be lower than the activation barrier reported for both cyclooctyne 14 and benzocyclooctyne

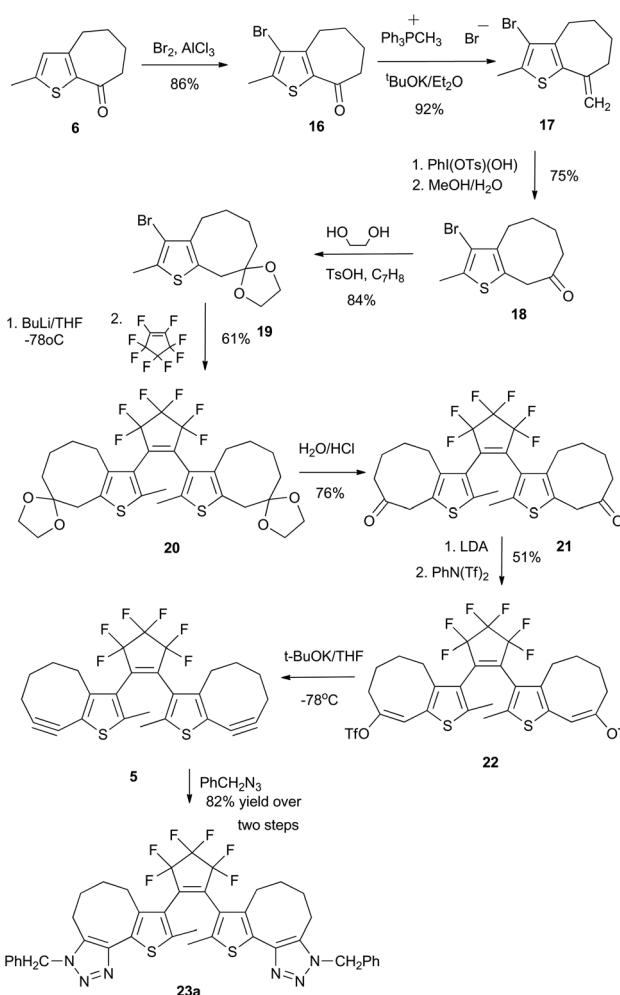


Fig. 6 Synthesis of the target compound 5 and its SPAAC with benzyl azide.

15 (24.9 kcal mol⁻¹),¹⁷ suggesting an increased reactivity. We also calculated the strain energy for **12** (18.4 kcal mol⁻¹) which was found to be higher than the calculated strain energy of cyclooctyne **14** (13.6 kcal mol⁻¹) and benzocyclooctyne **15** (14.4 kcal mol⁻¹), implying an increased reactivity due to the fusion of the five-membered thiophene ring (Fig. 5b). This increase in the ring strain due to the fused five-membered thiophene ring was also reflected by the decreased alkyne bond angles in **12** (151.1°, 156.7°) compared to **14** (157.4°, 157.5°) and **15** (155.1°, 157.2°).

With these encouraging results at hands, we performed the synthesis of the target DAE-derived bis-cyclooctyne **5**, also starting from **6**. The corresponding synthetic route is shown in Fig. 6.

The cycloheptanone **6** was brominated, and the obtained bromo-derivative **16** was converted (through alkene **17**) into the cyclooctanone **18**, similarly to the transformation of **6** to **10** described above. The carbonyl group in **18** was protected to allow synthesizing the DAE derivative **20** using the procedure reported previously by Irie *et al.*¹⁸ Then the carbonyl groups were liberated (forming compound **21**). Formation of the enol triflate (compound **22**) followed by the HOTf elimination completed the synthesis of the DAE building block **5** in about 10% overall yield, calculating on **6**.

As expected, the bis-cyclooctyne **5** was as reactive as **12** towards benzyl azide, a colourless **23a** was formed as a major

product in its SPAAC with benzyl azide (the storage of **12** after the preparation should be done at -20 °C due to its relative instability). Compound **23a** was isolated in the open form and fully characterized. Blue-coloured **23a(closed)** was prepared from the colourless **23a(open)** by irradiation with UV light (256 nm) and characterized; **23a(closed)** could, in turn, be transformed back to **23a(open)** by irradiation with visible light (590 nm). Both transformations proceeded in quantitative yield, demonstrating a high efficiency of the photoconversion. Notably, the conversion of **23a(closed)** to **23a(open)** can be achieved by red light: the low-energy absorption band of the closed isomer is intense enough at 630–650 nm (see the UV-VIS absorption spectrum in Fig. 7a). This feature is important for the application of the DAE-derived compounds *in vivo*, because red light penetrates deeply into live tissues. Hence, photocontrol of biologically active derivatives of **23** should be feasible non-invasively as deep as 1–2 cm beneath the tissue surface.¹⁹

The photoisomerization of **23a(closed)** to **23a(open)** proceeded within minutes (Fig. 7b), which is typical for DAEs.^{1a–d} Observation of a perfect isosbestic point (298 nm) confirmed that no other chemical processes other than the photo-isomerization took place during irradiation.

Finally, to check the utility of the new building block **5** for peptide stapling, we prepared a stapled version of a peptide that originally stemmed from the PDI sequence

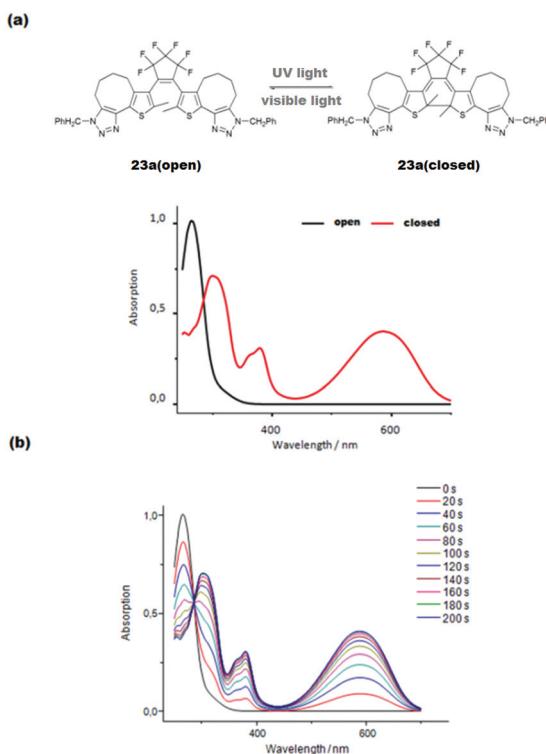


Fig. 7 (a) Photoisomerization of **23** and UV-VIS absorption spectra of both photoforms; (b) kinetics of the photoconversion of **23a(closed)** to **23a(open)** (MeOH solution, $C = 1 \times 10^{-5}$ M, 25 °C) by irradiation with UV light (256 nm) at ~10 mW cm⁻².

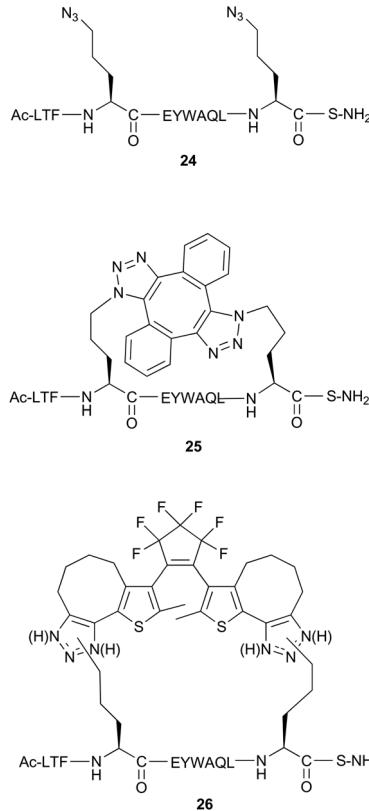


Fig. 8 Linear peptide used for stapling with **3** (ref. 8) and **5** (this work) and its SPAAC products **25** and **26**.



(LTFEHYWAQLTS), which had been identified by phage display as an efficient inhibitor of p53/MDM2 and p53/MDMX protein–protein interactions.²⁰ These interactions are known as important targets for anti-cancer drug candidates.²¹ Peptide inhibitors of p53/MDM2 and p53/MDMX are among the most promising compounds currently under investigation and development.²² Recently, PDI analogues stapled by SPAAC employing the cyclooctadiyne 3 as a linker have been prepared.⁸ For one of the most potent MDM2 binders identified, the linear precursor 24 bearing two azide-substituted side-chains in positions (*i*,*i* + 7) was used to prepare a stapled peptide 25 (Fig. 8). In this work, we also used precursor 24 to prepare the DAE-modified stapled peptides.

SPAAC between 24 and the cross-linker 5 was performed at 1 mM concentration of both reactants and was found to be complete within less than one hour (methanol, 25 °C, LCMS monitoring of the reaction mixture). Three different stapled peptide isomers (of the general formula 26, Fig. 8) were easily separated by preparative HPLC using standard chromatographic approaches (see the ESI† for the details).

Conclusions

A novel DAE-derived bis-cyclooctyne 5 was synthesized for use as a cross-linking reagent by SPAAC. The stable compound was shown to be highly reactive towards azides due to additional strain imposed on the cyclooctyne rings by the fused thiophene rings. The high azide reactivity of 5 makes it a useful building block for azide cross-linking, *e.g.* for obtaining stapled peptides, as demonstrated on a peptide inhibitor of the p53/MDM2 and p53/MDMX protein–protein interactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors acknowledge EU funding by the EU H2020-MSCA-RISE-2015 through the PELICO project (grant 690973). DRS acknowledges support from the Engineering and Physical Sciences Research Council (EP/P020291/1) and Royal Society (Wolfson Research Merit Award). K. S. would like to thank Trinity College, Cambridge Trust, Cambridge Nehru Trust and the Cambridge Philosophical Society for providing fellowships. Part of this work was performed using the Darwin Supercomputer of the University of Cambridge High Performance Computing Service (<http://www.hpc.cam.ac.uk/>), provided by Dell Inc. using Strategic Research Infrastructure Funding from the Higher Education Funding Council for England and funding from the Science and Technology Facilities Council. ASU and SA thank the DFG for supporting GRK 2039, ASU and OB acknowledge the BMBF for VIP-PLUS funding. IVK acknowledges the Alexander von Humboldt

Foundation (Germany) for financial support as a recipient of the Georg Forster Research Prize.

Notes and references

- (a) *Photochromism: molecules and systems*, ed. H. Dürr and H. Bouas-Laurent, Elsevier, Amsterdam, 1990; (b) M. Irie, *Chem. Rev.*, 2000, **100**, 1685–1716; (c) Y. Yokoyama and M. Kose, *J. Photochem. Photobiol. A*, 2004, **166**, 9–18; (d) K. Matsuda and M. Irie, *J. Photochem. Photobiol. C*, 2004, **5**, 169–182; (e) C. Yun, J. You, J. Kim, J. Huh and E. Kim, *J. Photochem. Photobiol. C*, 2009, **10**, 111–129; (f) D. Wandera, S. R. Wickramasinghe and S. M. Husson, *J. Membr. Sci.*, 2010, **357**, 6–35; (g) N. Tamaoki and T. Kamei, *J. Photochem. Photobiol. C*, 2010, **11**, 47–61; (h) C. Brieke, F. Rohrbach, A. Gottschalk, G. Mayer and A. Heckel, *Angew. Chem., Int. Ed.*, 2012, **51**, 8446–8476; (i) W. Szymański, J. M. Beierle, H. A. V. Kistemaker, W. A. Velema and B. L. Feringa, *Chem. Rev.*, 2013, **113**, 6114–6178; (j) W. A. Velema, W. Szymanski and B. L. Feringa, *J. Am. Chem. Soc.*, 2014, **136**, 2178–2191; (k) M. Irie, T. Fukaminato, K. Matsuda and S. Kobatake, *Chem. Rev.*, 2014, **114**, 12174–12277; (l) D.-H. Qu, Q.-C. Wang, Q.-W. Zhang, X. Ma and H. Tian, *Chem. Rev.*, 2015, **115**, 7543–7588; (m) M. M. Lerch, M. J. Hansen, G. M. van Dam, W. Szymanski and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2016, **55**, 10978–10999; (n) M. Vlatkovic, B. S. L. Collins and B. L. Feringa, *Chem. – Eur. J.*, 2016, **22**, 17080–17111; (o) I. V. Komarov, S. Afonin, O. Babii, T. Schober and A. S. Ulrich, *Chem. – Eur. J.*, 2018, **24**, 11245–11254.
- A. Osuka, D. Fujikane, H. Shinmori, S. Kobatake and M. Irie, *J. Org. Chem.*, 2001, **66**, 3913–3923.
- (a) O. Tosic and J. Mattay, *Eur. J. Org. Chem.*, 2011, 371–376; (b) J. Ma, X. Cui, F. Wang, X. Wu, J. Zhao and X. Li, *J. Org. Chem.*, 2014, **79**, 10855–10866.
- (a) Y. H. Lau, P. de Andrade, S.-T. Quah, M. Rossmann, L. Laraia, N. Sköld, T. J. Sum, P. J. E. Rowling, T. L. Joseph, C. Verma, M. Hyvönen, L. S. Itzhaki, A. R. Venkitaraman, C. J. Brown, D. P. Lane and D. R. Spring, *Chem. Sci.*, 2014, **5**, 1804–1809; (b) Y. H. Lau, P. de Andrade, Y. Wu and D. R. Spring, *Chem. Soc. Rev.*, 2015, **44**, 91–102.
- P. M. Cromm, J. Spiegel and T. N. Grossmann, *ACS Chem. Biol.*, 2015, **10**, 1362–1375.
- (a) J. R. Kumita, O. S. Smart and G. A. Woolley, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 3803–3808; (b) D. G. Flint, J. R. Kumita, O. S. Smart and G. A. Woolley, *Chem. Biol.*, 2002, **9**, 391–397; (c) Z. Zhang, D. C. Burns, J. R. Kumita, O. S. Smart and G. A. Woolley, *Bioconjugate Chem.*, 2003, **14**, 824–829; (d) D. C. Burns, D. G. Flint, J. R. Kumita, H. J. Feldman, L. Serrano, Z. Zhang, O. S. Smart and G. A. Woolley, *Biochemistry*, 2004, **43**, 15329–15338; (e) V. Borisenko and G. A. Woolley, *J. Photochem. Photobiol. A*, 2005, **173**, 21–28; (f) A. A. Beharry, O. Sadovski and G. A. Woolley, *Org. Biomol. Chem.*, 2008, **6**, 4323–4332;



(g) C. Hoppmann, R. Kühne and M. Beyermann, *Beilstein J. Org. Chem.*, 2012, **8**, 884–889; (h) R. J. Mart and R. K. Allemann, *Chem. Commun.*, 2016, **52**, 12262–12277; (i) C. Renner and L. Moroder, *ChemBioChem*, 2006, **7**, 868–878; (j) E. Chen, J. R. Kumita, G. A. Woolley and D. S. Klier, *J. Am. Chem. Soc.*, 2003, **125**, 12443–12449; (k) S.-H. Xia, G. Cui, W.-H. Fang and W. Thiel, *Angew. Chem., Int. Ed.*, 2016, **55**, 2067–2072; (l) L. Guerrero, O. S. Smart, C. J. Weston, D. C. Burns, G. A. Woolley and R. K. Allemann, *Angew. Chem., Int. Ed.*, 2005, **44**, 7778–7782; (m) G. A. Woolley, A. S. I. Jaikaran, M. Berezovski, J. P. Calarco, S. N. Krylov, O. S. Smart and J. R. Kumita, *Biochemistry*, 2006, **45**, 6075–6084; (n) S. Kneissl, E. J. Loveridge, C. Williams, M. P. Crump and R. K. Allemann, *ChemBioChem*, 2008, **9**, 3046–3054; (o) P. Wysoczanski, R. J. Mart, E. J. Loveridge, C. Williams, S. B.-M. Whittaker, M. P. Crump and R. K. Allemann, *J. Am. Chem. Soc.*, 2012, **134**, 7644–7647; (p) L. Nevola, A. Martín-Quirós, K. Eckelt, N. Camarero, S. Tosi, A. Llobet, E. Giralt and P. Gorostiza, *Angew. Chem., Int. Ed.*, 2013, **52**, 7704–7708; (q) L. Nevola, A. Martín-Quirós, K. Eckelt, S. Madurga, P. Gorostiza and E. Giralt, *Chem. Biol.*, 2015, **22**, 31–37; (r) J. Broichhagen, T. Podewin, H. Meyer-Berg, Y. von Ohlen, N. R. Johnston, B. J. Jones, S. R. Bloom, G. A. Rutter, A. Hoffmann-Röder, D. J. Hodson and D. Trauner, *Angew. Chem., Int. Ed.*, 2015, **54**, 15565–15569; (s) K. Fujimoto, M. Amano, Y. Horibe and M. Inouye, *Org. Lett.*, 2006, **8**, 285–287; (t) M. Blanco-Lomas, S. Samanta, P. J. Campos, G. A. Woolley and D. Sampedro, *J. Am. Chem. Soc.*, 2012, **134**, 6960–6963; (u) K. Fujimoto, M. Kajino, I. Sakaguchi and M. Inouye, *Chem. – Eur. J.*, 2012, **18**, 9834–9840.

7 (a) N. J. Agard, J. A. Prescher and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2004, **126**, 15046–15047; (b) J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli and C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 16793–16797; (c) J. C. Jewetta and C. R. Bertozzi, *Chem. Soc. Rev.*, 2010, **39**, 1272–1279; (d) M. F. Debets, C. W. J. van der Doelen, F. P. J. T. Rutjes and F. L. van Delft, *ChemBioChem*, 2010, **11**, 1168–1184; (e) R. Ni, N. Mitsuda, T. Kashiwagi, K. Igawa and K. Tomooka, *Angew. Chem., Int. Ed.*, 2015, **54**, 1190–1194.

8 Y. H. Lau, Y. Wu, M. Rossmann, B. X. Tan, P. de Andrade, Y. S. Tan, C. Verma, G. J. McKenzie, A. R. Venkitaraman, M. Hyvönen and D. R. Spring, *Angew. Chem., Int. Ed.*, 2015, **54**, 15410–15413.

9 L. Kii, A. Shiraishi, T. Hiramatsu, T. Matsushita, H. Uekusa, S. Yoshida, M. Yamamoto, A. Kudo, M. Hagiwara and T. Hosoya, *Org. Biomol. Chem.*, 2010, **8**, 4051–4055.

10 T. Harris, G. dos Passos Gomes, S. Ayad, R. J. Clark, V. V. Lobodin, M. Tuscan, K. Hanson and I. V. Alabugin, *Chem.*, 2017, **3**, 1–12.

11 J. Dommerholt, F. P. J. T. Rutjes and F. L. van Delft, *Top. Curr. Chem. (Z)*, 2016, **374**, 1–20.

12 (a) D. A. Sutton and V. V. Popik, *J. Org. Chem.*, 2016, **81**, 8850–8857; (b) C. Gröst and T. Berg, *Org. Biomol. Chem.*, 2015, **13**, 3866–3870.

13 H. F. Motiwala, R. H. Vekariya and J. Aubé, *Org. Lett.*, 2015, **17**, 5484–5487.

14 Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein and B. V. Lopatin, *J. Gen. Chem. USSR*, 1964, **34**, 961–961.

15 M. W. Justik and G. F. Koser, *Molecules*, 2005, **10**, 217–225.

16 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, *Gaussian 09 Rev. D.01*, Wallingford, CT, 2013.

17 K. Chenoweth, D. Chenoweth and W. A. Goddard III, *Org. Biomol. Chem.*, 2009, **7**, 5255–5258.

18 K. Higashiguchi, K. Matsuda, Y. Asano, A. Murakami, S. Nakamura and M. Irie, *Eur. J. Org. Chem.*, 2005, 91–97.

19 O. Babii, S. Afonin, L. V. Garmanchuk, V. V. Nikulina, T. V. Nikolaienko, O. V. Storozhuk, D. V. Shelest, O. I. Dasyukevich, L. I. Ostapchenko, V. Iurchenko, S. Zozulya, A. S. Ulrich and I. V. Komarov, *Angew. Chem., Int. Ed.*, 2016, **55**, 5493–5496.

20 B. Hu, D. M. Gilkes and J. Chen, *Cancer Res.*, 2007, **67**, 8810–8817.

21 C. J. Brown, S. Lain, C. S. Verma, A. R. Fersht and D. P. Lane, *Nat. Rev. Cancer*, 2009, **9**, 862–873.

22 (a) C. Zhan and W. Lu, *Curr. Pharm. Des.*, 2011, **17**, 603–609; (b) Y. S. Chang, B. Graves, V. Guerlavais, C. Tovar, K. Packman, K.-H. To, K. A. Olson, K. Kesavan, P. Gangurde, A. Mukherjee, T. Baker, K. Darlak, C. Elkin, Z. Filipovic, F. Z. Qureshi, H. Cai, P. Berry, E. Feyfant, X. E. Shi, J. Horstick, D. A. Annis, A. M. Manning, N. Fotouhi, H. Nash, L. T. Vassilev and T. K. Sawyer, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, **110**, E3445–E3454.

