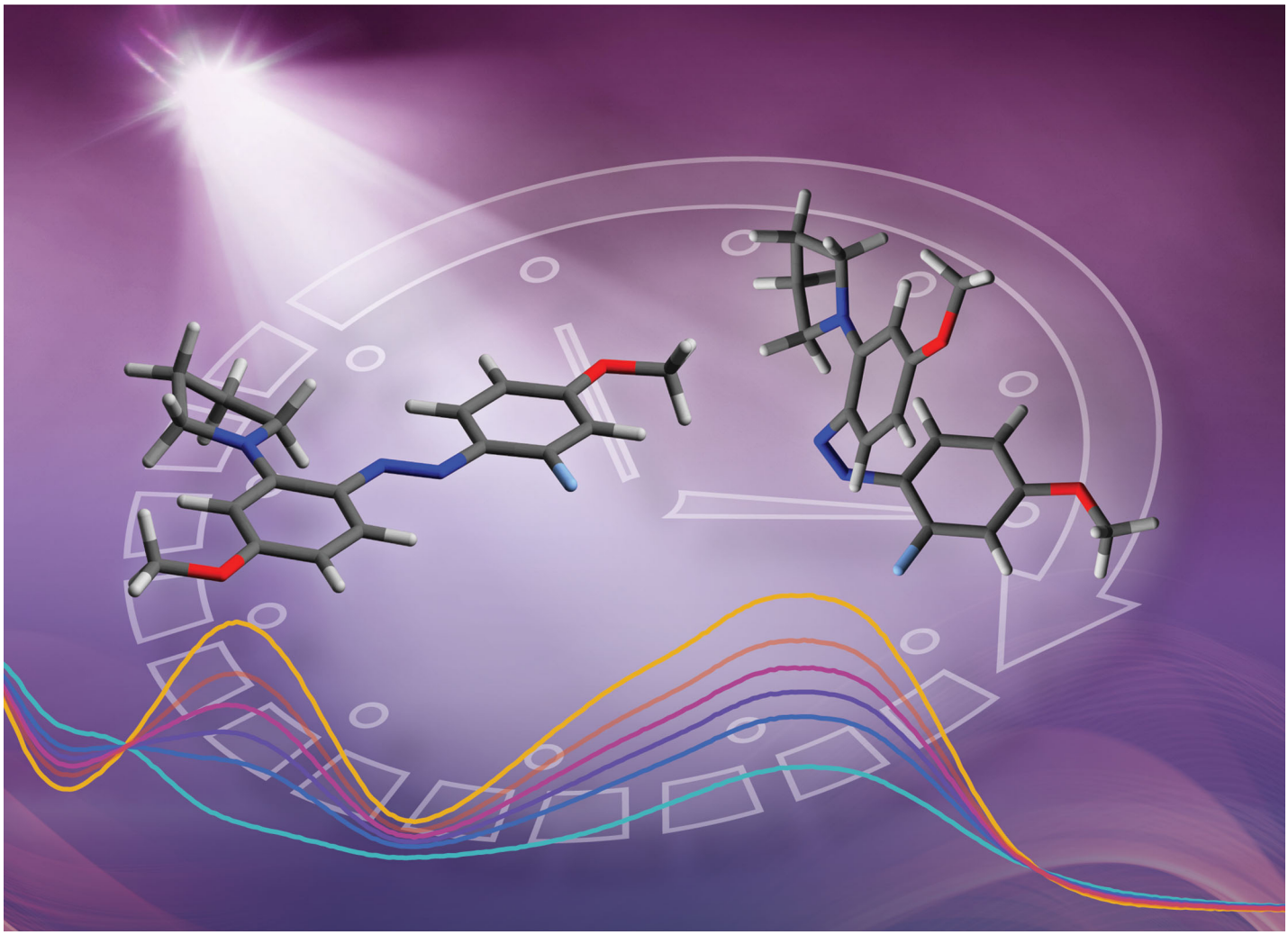
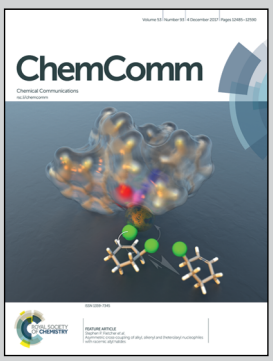


Showcasing research from the Smart Photonic Materials Group of Prof. Arri Priimagi at the Laboratory of Chemistry and Bioengineering, Tampere University of Technology, Finland.

Controlling azobenzene photoswitching through combined *ortho*-fluorination and -amination

In azobenzene photoswitches, *ortho*-fluorination can be used to control the *cis*-lifetime while *ortho*-amination allows for boosting visible-light absorption. The combination of these two yields strongly visible-absorbing azobenzenes with *cis*-lifetimes ranging from one second up to three days, depending on the substitution pattern.

As featured in:



See A. Priimagi *et al.*, *Chem. Commun.*, 2017, **53**, 12520.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Registered charity number: 207890

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2017, 53, 12520

Received 18th September 2017,
Accepted 9th October 2017

DOI: 10.1039/c7cc07308a

rsc.li/chemcomm

Controlling azobenzene photoswitching through combined *ortho*-fluorination and -amination†

Z. Ahmed, ‡ A. Siiskonen, ‡ M. Virkki and A. Priimagi *

We present a series of visible-light-absorbing azobenzene photoswitches with *cis*-lifetimes ranging from one second to three days. We combine *ortho*-fluorination to control the *cis*-lifetimes, and *ortho*-amination to boost the visible-light absorption. The synthesis is accomplished by selectively replacing one or more *ortho*-fluorines with amines in the *ortho*-fluoroazobenzene precursors.

Photoswitchable azobenzene derivatives have gained increased utility in devising materials whose properties and functions can be remotely controlled with light.[1] Their attractiveness is based on their synthetic versatility, high isomerization quantum yields, change in dipole moment upon photoisomerization, and fatigue resistance.[2] Equally importantly, their activation wavelengths as well as the photoisomerization dynamics can be significantly altered by simple structural modifications. As a result, azobenzenes have been employed in a variety of applications, including photopharmocology,[3] photocontrollable catalysis,[4] solar light harvesting,[5] and optical-to-mechanical energy conversion.[6] Generally, visible-light-switchable azobenzenes are preferred over their UV-switchable counterparts, ideally combined with strong absorptivity to enable switching with low-intensity irradiation. However, the desired switching dynamics may drastically depend on the application. For example, fast bidirectional switching may be required for liquid-crystal photonics,[7] whereas in photobiology,[3b] a bistable system may be more beneficial. Therefore, methods to selectively control the *cis*-lifetimes of azobenzenes, while maintaining strong visible-light absorption, are of great importance in different fields of research.

The activation wavelength as well as the switching dynamics of azobenzenes can be controlled through *ortho*-substitution. For example, *ortho*-fluorination significantly increases the *cis*-lifetime and separates the n–π* transitions of the *trans* and *cis* isomers, enabling quantitative and bidirectional photoswitching.[8] The *ortho*-fluorinated azobenzenes have therefore found use in photoactuators,[9] metal–organic frameworks,[10] and crystal engineering.[11] However, due to their low molar absorption coefficients in the visible region, relatively intense irradiation is required for fast photoswitching, which may be a significant drawback especially in biological systems.

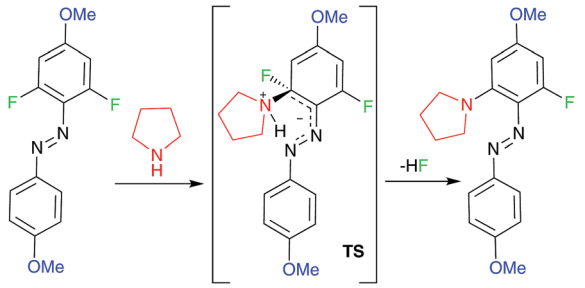
ortho-Amination, on the other hand, significantly increases the molar absorptivity in the visible range, yet at the same time decreases the *cis*-lifetime.[12] *ortho*-Methoxylation increases both the *cis*-lifetime and the molar absorption coefficient, but the latter only moderately.[13] Although *ortho*-methoxylated azobenzenes have been employed in photobiology,[14] they are quite rapidly reduced with glutathione, which may limit their use in biological applications. *ortho*-Aminated azobenzenes, in turn, are not reduced with glutathione, but as a drawback, the described synthetic route suffers from low reaction yields (2–24%) and does not allow for the synthesis of asymmetric azobenzenes with different substituents at the aromatic rings.[12] Although different types of *ortho*-substituents yield very distinct spectral and photochemical properties, they have not been systematically combined into the same photoswitch. Through rationally designed combination of different *ortho*-substituents, a versatile control over the photoswitching properties can be achieved.

Herein, we report the design, synthesis and characterization of azobenzene photoswitches that combine *ortho*-fluorination to increase the *cis*-lifetimes, and *ortho*-amination to increase the visible-light absorption. Since the azo group activates vicinal halogens towards nucleophilic aromatic substitution in *ortho*-halogenated azobenzenes,[15] and fluoride is an excellent leaving group, we reasoned that the *ortho*-amino groups could be conveniently introduced by replacing *ortho*-fluorines with amines in the easily synthesized *ortho*-fluoroazobenzenes[8] (Scheme 1). Density functional theory (DFT) calculations on the mechanism of the amination reaction showed that in azobenzenes with two *ortho*-fluorines, the energy barrier for the first amination is several kilocalories per mole lower than for the second

Laboratory of Chemistry and Bioengineering, Tampere University of Technology, P.O. Box 541, FI-33101, Tampere, Finland. E-mail: arri.priimagi@tut.fi

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7cc07308a

‡ These authors contributed equally to this work.

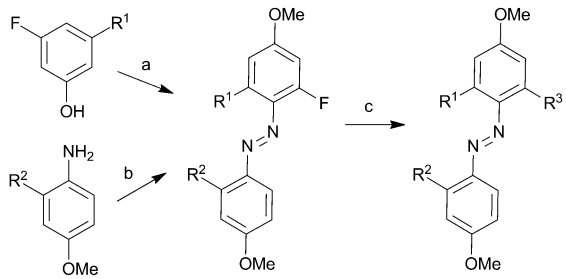


Scheme 1 Selective amination of the *ortho*-fluorinated azobenzene precursor, showing the transition state (TS) and the mono-aminated product.

amination (ESI†). Hence, by controlling the reaction conditions, it should be possible to selectively replace only one of the fluorines.

As precursors, we used three *ortho*-fluorinated azobenzenes, **1**, **2** and **3**, containing only one fluorine, one fluorine on each ring, and two fluorines on one ring, respectively. The asymmetric azobenzene precursors **1** and **3** were obtained *via* a one-pot diazonium coupling reaction of the corresponding phenols with 4-methoxyphenyldiazonium tetrafluoroborate, followed by methylation, whereas the symmetrical *ortho*-fluorinated precursor **2** was synthesized by oxidation of the corresponding aniline as shown in Scheme 2.[8a,16] The precursors were designed to carry methoxy groups at the *para* positions, to provide a possibility towards further functionalization with, *e.g.*, biocompatible units or polymerizable groups. Pyrrolidine was chosen as the amine (unless otherwise stated) since it red-shifts the absorption maxima and enhances the molar absorption coefficient in the visible region.[12]

Treatment of the monofluorinated precursor **1** with pyrrolidine at room temperature afforded the *ortho*-aminated azobenzene **4** in excellent yield (90%). As expected, replacing the fluorine with pyrrolidine decreases the *cis*-lifetime dramatically (41.8 h → 15.2 s; Fig. S22 and S27, ESI†), at the same time significantly enhancing



1: R^1, R^2 = H
2: R^1 = H, R^2 = F
3: R^1 = F, R^2 = H

4: R^1, R^2 = H, R^3 = pyr
5: R^1, R^2 = H, R^3 = pip
6: R^1 = H, R^2 = F, R^3 = pyr
7: R^1= H, R^2, R^3 = pyr
8: R^1, R^3 = pyr, R^2 = H
9: R^1 = F, R^2 = H, R^3 = pyr

(a) i) 4-methoxyphenyldiazonium tetrafluoroborate, K_2CO_3, MeCN, RT, 30 min. ii) MeI, RT, 20 h; (b) $KMnO_4$, $FeSO_4{\cdot}7H_2O$, CH_2Cl_2, reflux; (c) pyrrolidine or piperidine, RT or heat; pyr = pyrrolidine, pip = piperidine

Scheme 2 Synthesis of *ortho*-aminated azobenzenes.

visible-light absorption (Fig. 1a, Table 1). In addition, **4** can be switched back and forth between the *trans*- and *cis*-forms using 435 nm and 595 nm light over several cycles without any sign of fatigue (Fig. S28, ESI†). The fluorine could also be replaced with piperidine under gentle heating (55 °C), to afford **5** in excellent yield (96%). Also in this case the absorption in the visible range was significantly increased, while the *cis*-lifetime was much less affected (41.8 h → 9.1 h; Fig. S30, ESI†). Therefore, by using the same fluorinated precursor and two different amines, a great variability in the *cis*-lifetimes (15.2 s for **4** *vs.* 9.1 h for **5**) was obtained, while maintaining relatively strong absorption in the visible region. We envision that the reaction can be extended to various amines to control other properties, such as water solubility.

Next, the selectivity of the amination was tested by reacting the symmetrical difluoro precursor **2** with pyrrolidine. By carrying out the reaction at room temperature, the mono-aminated product **6** was obtained in high yield (81%), along with a minor amount of the bis-aminated product **7** (15%). The two products were easily separated by chromatography. By performing the reaction at 55 °C, the yields were reversed and the bis-aminated product **7** was obtained in 74% yield (along with **6** in 20% yield). Thus, as predicted by the DFT calculations (ESI†), the reactivity difference of the first and second amination is large enough to enable mono-amination in good selectivity. In other words, depending on the reaction temperature, we could replace either one or both of the *ortho*-fluorines with pyrrolidine, thereby controlling the selectivity of the reaction and obtaining either symmetric (**7**) or asymmetric (**6**) amination of **2**.

Compounds **6** and **7** showed a substantial difference in their absorption profile and photoswitching behavior. Compound **7** exhibits an absorption maximum at 488 nm, with a pronounced low-energy shoulder at 514 nm, yet with moderate molar absorption coefficient of $<4\ 000\ M^{-1}\ cm^{-1}$. Compound **6**, in turn, displays a comparable absorption maximum wavelength (479 nm) accompanied with a significant increase in the molar absorption coefficient ($>15\,000\ M^{-1}\ cm^{-1}$). In addition to the four-fold enhancement in the absorption coefficient, the *cis*-lifetime of **6** was increased from 1.2 s to 258 seconds (Table 1, Fig. S32 and S33, ESI†), *i.e.*, by more than a factor of 200. This can be attributed to the presence of the *ortho*-fluorine, pinpointing the benefit of our design concept of simultaneous *ortho*-fluorination and *ortho*-amination.

Finally, we studied the selective amination of **3**, bearing two *ortho*-fluorines on the same phenyl ring. Performing the reaction in neat pyrrolidine afforded the bis-aminated product **8** which was highly unstable and therefore not studied further. However, conducting the reaction in acetonitrile, with pyrrolidine only as a reagent, the mono-aminated product **9** was obtained in excellent yield (92%). It has very attractive properties, combining strong molar absorptivity in the visible range and an exceptionally long *cis*-lifetime of 72 h at 25 °C (Fig. 1c, Table 1, Fig. S35, ESI†). This lifetime is substantially longer than for any other *ortho*-aminated azobenzene reported up to date. The *trans–cis* and *cis–trans* photoswitching of **9** can be triggered by 405 nm and 595 nm irradiation, respectively, with no sign of photodegradation over repeated switching cycles (Fig. S36, ESI†). We used

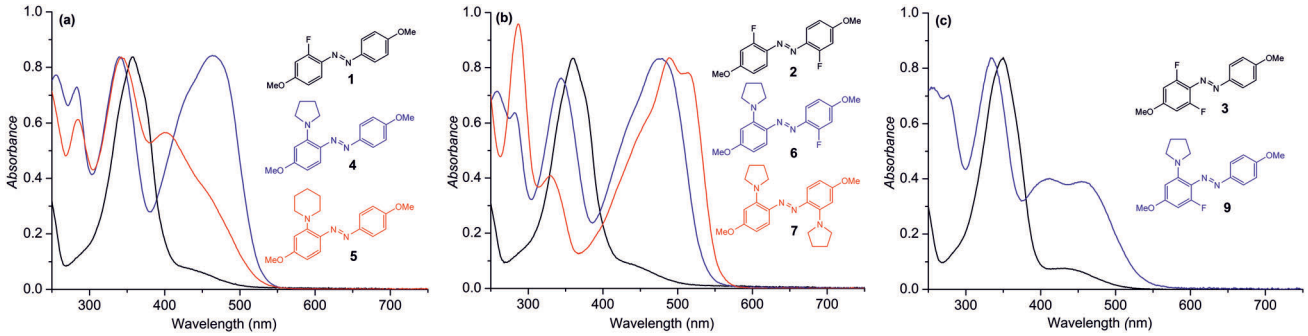


Fig. 1 Normalized UV/Vis spectra, measured from 0.03–0.05 mM acetonitrile solution of (a) mono-fluorinated precursor **1** and its aminated derivatives **4** and **5**; (b) bis-fluorinated precursor **2** and its selectively aminated derivatives **6** and **7**; (c) bis-fluorinated precursor **3** and its selectively aminated derivative **9**.

Table 1 Spectral and photochemical properties of **1**–**9** in acetonitrile, including the wavelengths of absorption maxima (λ_{max}), the corresponding molar absorption coefficients ε, as well as the *cis* lifetimes τ at 25 °C, and the fractions of the *cis*-isomers in the photostationary state

Compd	λ_{max} (nm)	ε (M^{-1} cm^{-1})	τ (s h^{-1})	*cis*-% at PSS[c]
1	357/432	29110/3608	41.8 ± 1.3 h[a]	93
2	359/432	25810/3185	60.2 ± 0.5 h[a]	93
3	350/432	24652/2286	430 ± 150 h[ab]	94
4	340/462	12693/12749	15.2 ± 0.1 s	73
5	341/402	14924/10075	9.1 ± 0.3 h	75
6	344/479	13777/15042	258 ± 30 s	71
7	488/514	3701/3456	1.21 ± 0.01 s	62
9	335/411/454	16739/8006/7792	72 ± 8 h[a]	80

[a] Lifetimes measured at 50, 60, and 70 °C, and extrapolated to 25 °C using the Arrhenius equation. [b] The long measurement time resulted in slight solvent evaporation during the experiment, which increased the error margin. [c] Estimated fractions of the *cis*-isomers at the photostationary state.

^{1}H NMR spectra, obtained before and after irradiation with the visible light (405 nm), to estimate the *cis*-fraction of **9**, concluding that >80% of the azobenzenes exist in the *cis*-form in the photostationary state (Fig. S37, ESI†).

Fig. 2 illustrates the pronouncedly different *cis*-lifetimes achievable through our molecular design, ranging from one second (compound **7**; the red curve) up to several days (compound **9**; the blue curve). This is a highly attractive feature, enabling the use of our synthetic pathway to rationally design visible-absorbing azobenzenes with optimized isomerization dynamics for a multitude of applications.

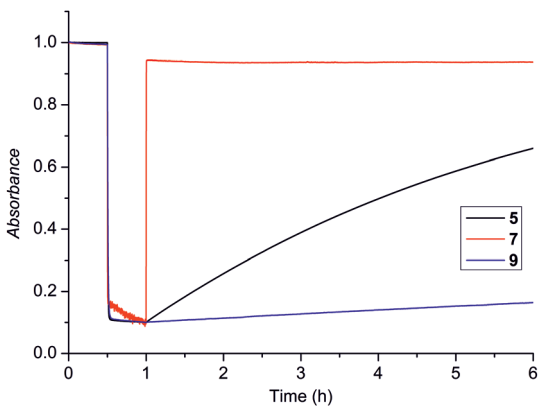


Fig. 2 Normalized *cis*–*trans* thermal back relaxation for compounds **5**, **7**, **9**. The irradiation was switched on at 30 min and ceased at 60 min.

In summary, we describe a novel approach for controlling the *cis*-lifetimes and absorption coefficients of azobenzenes by combining *ortho*-fluoro- and *ortho*-amino-functionalities in the same photoswitch. This combination stabilizes the *cis*-isomer and at the same time increases the absorption in the visible region. The attained control over the *cis*-lifetimes and broad coverage of absorption spectrum makes the studied compounds promising candidates for a variety of applications such as sunlight harvesting and photobiology. The synthetic route allows for selective replacement of one or more fluorines with an amine in the fluorinated azobenzenes in good to excellent yields. The presence of methoxy groups in the *para* positions leaves a possibility to attach the photoswitches with different polymers/systems, according to the field of application. We envision that the design concept of including different types of *ortho*-substituents to control the spectral and photochemical properties of azobenzenes can be expanded to other functionalities besides fluorines and amines, to obtain photoswitchable compounds with even a wider range of properties.

We thank the financial support of the European Research Council (Grant Agreement No. 679646). Computing resources provided by the CSC – IT Center for Science Ltd are gratefully acknowledged.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 M. M. Russew and S. Hecht, *Adv. Mater.*, 2010, **22**, 3348–3360.
2 (*a*) H. M. Bandara and S. C. Burdette, *Chem. Soc. Rev.*, 2012, **41**, 1809–1825; (*b*) A. A. Beharry and G. A. Woolley, *Chem. Soc. Rev.*, 2011, **40**, 4422–4437; (*c*) R. Klajn, *Pure Appl. Chem.*, 2010, **82**, 2247–2279.
3 (*a*) J. Broichhagen, J. A. Frank and D. Trauner, *Acc. Chem. Res.*, 2015, **48**, 1947–1960; (*b*) M. M. Lerch, M. J. Hansen, G. M. van Dam, W. Szymanski and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2016, **55**, 10978–10999.

4 (*a*) R. S. Stoll and S. Hecht, *Angew. Chem., Int. Ed.*, 2010, **49**, 5054–5075; (*b*) R. Gostle, A. Senf and S. Hecht, *Chem. Soc. Rev.*, 2014, **43**, 1982–1996.
5 (*a*) A. K. Saydjari, P. Weis and S. Wu, *Adv. Energy Mater.*, 2017, **7**, 1601622; (*b*) A. M. Kolpak and J. C. Grossman, *Nano Lett.*, 2011, **11**, 3156–3162; (*c*) A. Lennartson, A. Roffey and K. Moth-Poulsen, *Tetrahedron Lett.*, 2015, **56**, 1457–1465.
6 (*a*) O. S. Bushuyev, M. Aizawa, A. Shishido and C. J. Barrett, *Macromol. Rapid Commun.*, 2017, 1700253; (*b*) T. Ube and T. Ikeda, *Angew. Chem., Int. Ed.*, 2014, **53**, 10290–10299; (*c*) T. J. White, *Photomechanical Materials, Composites, and Systems: Wireless Transduction of Light into Work*, John Wiley & Sons, 2017.
7 U. A. Hrozhyk, S. V. Serak, N. V. Tabiryan, L. Hoke, D. M. Steeves and B. R. Kimball, *Opt. Express*, 2010, **18**, 8697–8704; L. De Sio, N. Tabiryan, T. J. Bunning, B. R. Kimball and C. Umeton, *Prog. Opt.*, 2013, **58**, 1–64.
8 (*a*) C. Knie, M. Utecht, F. Zhao, H. Kulla, S. Kovalenko, A. M. Brouwer, P. Saalfrank, S. Hecht and D. Bleger, *Chem. – Eur. J.*, 2014, **20**, 16492–16501; (*b*) D. Bleger, J. Schwarz, A. M. Brouwer and S. Hecht, *J. Am. Chem. Soc.*, 2012, **134**, 20597–20600; (*c*) D. Bleger and S. Hecht, *Angew. Chem., Int. Ed.*, 2015, **54**, 11338–11349; (*d*) M. J. Hansen, M. M. Lerch, W. Szymanski and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2016, **55**, 13514–13518.
9 (*a*) S. Iamsaard, E. Anger, S. J. Asshoff, A. Depauw, S. P. Fletcher and N. Katsonis, *Angew. Chem., Int. Ed.*, 2016, **55**, 9908–9912; (*b*) K. Kumar, C. Knie, D. Bleger, M. A. Peletier, H. Friedrich, S. Hecht, D. J. Broer, M. G. Debije and A. P. Schenning, *Nat. Commun.*, 2016, **7**, 11975.
10 (*a*) K. Mueller, A. Knebel, F. Zhao, D. Bleger, J. Caro and L. Heinke, *Chem. – Eur. J.*, 2017, **23**, 5434–5438; (*b*) S. Castellanos, A. Goulet-Hanssens, F. Zhao, A. Dikhtiarenko, A. Pustovarenko, S. Hecht, J. Gascon, F. Kapteijn and D. Bleger, *Chem. – Eur. J.*, 2016, **22**, 746–752.
11 (*a*) O. S. Bushuyev, A. Tomberg, T. Friscic and C. J. Barrett, *J. Am. Chem. Soc.*, 2013, **135**, 12556–12559; (*b*) O. S. Bushuyev, T. C. Corkery, C. J. Barrett and T. Friscic, *Chem. Sci.*, 2014, **5**, 3158–3164; (*c*) S. K. Rastogi, R. A. Rogers, J. Shi, C. Gao, P. L. Rinaldi and W. J. Brittain, *J. Org. Chem.*, 2015, **80**, 11486–11490; (*d*) M. Saccone, A. Siiskonen, F. Fernandez-Palacio, A. Priimagi, G. Terraneo, G. Resnati and P. Metrangolo, *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.*, 2017, **73**, 227–233.
12 O. Sadovski, A. A. Beharry, F. Zhang and G. A. Woolley, *Angew. Chem., Int. Ed.*, 2009, **48**, 1484–1486.
13 A. A. Beharry, O. Sadovski and G. A. Woolley, *J. Am. Chem. Soc.*, 2011, **133**, 19684–19687.
14 S. Samanta, A. A. Beharry, O. Sadovski, T. M. McCormick, A. Babalhavaeji, V. Tropepe and G. A. Woolley, *J. Am. Chem. Soc.*, 2013, **135**, 9777–9784.
15 (*a*) G. M. Badger, J. W. Cook, W. P. Vidal, H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 1947, 1109; (*b*) J. T. Manka, V. C. Mckenzie and P. Kaszynski, *J. Org. Chem.*, 2004, **69**, 1967–1971; (*c*) J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, New York, 1968.
16 E. Merino, *Chem. Soc. Rev.*, 2011, **40**, 3835–3853.