nature chemistry

ARTICLES

PUBLISHED ONLINE: 11 AUGUST 2014 | DOI: 10.1038/NCHEM.2023

Triazolinediones enable ultrafast and reversible click chemistry for the design of dynamic polymer systems

Stijn Billiet[1], Kevin De Bruycker[1], Frank Driessen[1], Hannelore Goossens[2], Veronique Van Speybroeck[2], Johan M. Winne[1]* and Filip E. Du Prez[1]*

With its focus on synthetic reactions that are highly specific and reliable, 'click' chemistry has become a valuable tool for many scientific research areas and applications. Combining the modular, covalently bonded nature of click-chemistry linkages with an ability to reverse these linkages and reuse the constituent reactants in another click reaction, however, is a feature that is not found in most click reactions. Here we show that triazolinedione compounds can be used in click-chemistry applications. We present examples of simple and ultrafast macromolecular functionalization, polymer–polymer linking and polymer crosslinking under ambient conditions without the need for a catalyst. Moreover, when triazolinediones are combined with indole reaction partners, the reverse reaction can also be induced at elevated temperatures, and the triazolinedione reacted with a different reaction partner, reversibly or irreversibly dependent on its exact nature. We have used this 'transclick' reaction to introduce thermoreversible links into polyurethane and polymethacrylate materials, which allows dynamic polymer-network healing, reshaping and recycling.

The concept of click chemistry was introduced by Sharpless and co-workers not much more than a decade ago[1], and the reactions it advocates have rapidly found their way into the standard toolbox of many research disciplines, even outside the chemical sciences[2,3]. The search for suitable combinations of modular reagents (and catalysts) that can result in a very efficient and reliable covalent coupling is an important objective of ongoing fundamental chemical research[4–6]. Some subdivisions have even become more strict with regard to which reaction characteristics are desirable for click-chemistry applications, as was proposed recently for the polymer community[7]. Many alternative systems for the archetypical copper-catalysed azide–alkyne cycloaddition have been suggested in recent years[3,6,8,9], each with their advantages and disadvantages. However, the quest for a truly versatile system still continues. In the ideal case, such a system, besides having all the characteristics associated with the click concept, should also offer a choice between irreversible and reversible connections. For example, in the case of polymer chemistry applications, dynamic or reversible covalent bonds are highly desired nowadays as they can be used to elicit unique material properties, such as self-healing, recycling and network malleability.

To the best of our knowledge, no general click-chemistry system has been reported that can be tuned for either reversible or completely irreversible covalent linking within useful temperature ranges. Here we introduce such a versatile click-chemistry platform based on the reactivity of a 1,2,4-triazoline-3,5-dione (TAD) component (Fig. 1a). TAD molecules are heterocyclic compounds with an azo moiety connected to two carbonyl functionalities[10]. This electronic conjugation stabilizes the azo function but the electron-withdrawing carbonyls and the symmetry of the electronic system also give it a very particular orbital-controlled electrophilic reactivity, similar to that of carbenes or singlet oxygen, which are highly reactive but unstable reagents with very short lifetimes[11]. Indeed, TAD molecules have a very similar reactivity profile to that of singlet oxygen, and favour ultrafast Diels–Alder and ene-type reactions (Fig. 1a). These reaction types are known for their inherent orthogonality and reversibility, although most systems (such as the well-known Diels–Alder reaction of furans and maleimides) do not meet all click-chemistry requirements[8,12,13]. Conversely, TAD compounds offer a range of selective and predictable covalent linking reactions that are high yielding under equimolar conditions at low temperature (<20 °C), without the need for a catalyst[11,14–16]. Although TADs can undergo a very wide range of reactions with many different functional groups (Supplementary Fig. 1), these reactions are usually not observed in the presence of suitable Diels–Alder or ene reaction partners and, moreover, TAD compounds show high kinetic preferences for electron-rich π systems, which allows for good selectivity between alternatively substituted (di)enes. Additionally, the resulting urazole-type adducts (Fig. 1a) are robust heterocyclic scaffolds, compatible with a large number of solvents, reaction conditions and applications. An additional benefit of these reactions is the intense colour of TAD compounds, which provides a visual feedback system, as most of the corresponding urazoles are colourless[17].

The reactivity of TADs in Diels–Alder and ene reactions has been studied extensively using the commercially available 4-phenyl-1,2,4-triazoline-3,5-dione with components of low molecular weight in organic synthesis[10,15,17,18], in pharmaceutical applications[19,20] and in orthogonal peptide labelling[21–24]. In some of these cases, an efficient reaction has even been performed at room temperature in water[22,23]. TADs have also been used in polymer science, mostly in stepwise Diels–Alder and ene-type polymerizations[25,26]. However, these TAD-based linking methods have, so far, been considered mainly as 'curiosities' or as instances of well-fitted niche applications.

---

[1]Department of Organic Chemistry, Polymer Chemistry Research Group and Laboratory for Organic Synthesis, Ghent University, Krijgslaan 281 S4-bis, B-9000 Ghent, Belgium, [2]Center for Molecular Modeling, Ghent University, Technologiepark 903, B-9052 Zwijnaarde, Belgium.
*e-mail: filip.duprez@ugent.be; johan.winne@ugent.be

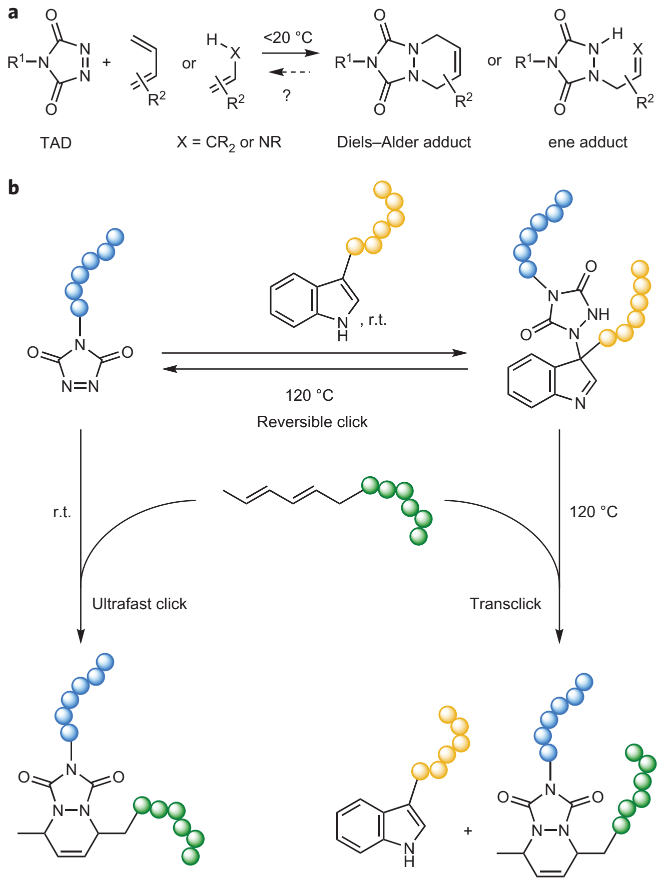

Figure 1 | Summary of applied TAD chemistry for click and transclick reactions. a, Generic reaction scheme for ultrafast triazolinedione-based Diels–Alder and ene click reactions. **b**, Overview of TAD-based click reactions reported herein, in which a transclick reaction is a combination of a reversible click reaction (between TAD and indoles) and an ultrafast irreversible click reaction (between TAD and dienes). This concept is applied to both low-molecular-weight compounds and polymers, and results in applications such as reversible polymer conjugation and both healable and reshapable polymeric materials. r.t., room temperature.

Our continued interest in evaluating and developing promising click chemistries for the controlled synthesis of challenging macromolecular architectures[27–30] prompted the work reported herein. In particular, the combination of catalyst-free, room-temperature reactivity of TADs with the possibility of reversible bond formation led us to envisage functional applications beyond the current scope of the click-chemistry toolbox, such as dynamic bond formation or the thermal exchange of a clickable group between two distinct moieties. For the latter, we introduce here the term 'transclick' reaction in analogy with well-known chemical processes such as transesterifications or transalkylations[31]. In other words, a transclick reaction can be defined as any covalent linking process that subsequently can be triggered to form a new bond with an alternative or orthogonal reaction partner, and at the same time release one of the original binding partners, in which both bond-forming steps meet the usual requirements for click reactions.

An overview of the possibilities and key aspects of TAD-based chemistry reported here is given in Fig. 1b, which is subdivided between reversible and irreversible TAD chemistry with model compounds (left) and macromolecular materials (right).

Results and discussion

Model reactions. To evaluate the reactions of TAD reagents as versatile click-chemistry tools in a macromolecular context, we first performed a series of model reactions with compounds of low molecular weight. The aim of these experiments was to establish reaction conditions, functional group tolerances and, importantly, the temperature and conditions required for possible reversible click reactions and/or the envisaged dynamic exchange reactions ('transclick' reactions).

A wide range of TAD reagents can be prepared easily in a large scale from the corresponding, readily available isocyanates in three high-yielding steps (overall yield up to 95%) that do not require purification (see Supplementary Section 3.2). Thus, 4-butyl-1,2,4-triazoline-3,5-dione (**BuTAD**) was prepared and reacted at room temperature with 2,4-hexadien-1-ol (HDEO), an abundant diene building block (Supplementary Fig. 2). This resulted in an almost instantaneous and completely chemo- and stereoselective conversion into the expected Diels–Alder adduct, accompanied by a sudden colour change from deep red to transparent (Fig. 2a and Supplementary Movie 1). Similarly, **BuTAD** was found to give very efficient and selective click-type reactions with a range of alternative dienes and enes, such as 2,3-dimethyl-2-butene (DMB) (Supplementary Figs 3–5 and Supplementary Table 1 for orthogonality[32]). To check the reversible or dynamic nature of this efficient linking reaction, the resulting urazole products were mixed with a competitive reactant for TAD moieties (2,4-hexadiene-1,6-diol (HDD)) and heated in dimethylsulfoxide (DMSO) in a pressurized vessel up to 250 °C for a prolonged period (more than one hour). The **TAD–HDEO** adduct proved to be thermally stable as it was fully recovered from these reactions and no trace of the possibly transclicked **TAD–HDD** cycloadducts was observed. These experiments were repeated with a number of alternative simple diene and ene reaction partners for **BuTAD**, which gave very similar results (Supplementary Figs 6 and 7). Thus, the expected reversed reaction (Fig. 1a) does not occur within a useful temperature range for most organic materials, and these TAD-based click reactions can be considered as completely irreversible for most applications.

Although the retroreaction of TAD Diels–Alder adducts has found quite a few applications in organic synthesis, such as a protecting group for dienes[33], most of these require pyrolysis conditions (>300 °C) and/or an irreversible hydrolysis of the TAD moiety[33]. During our investigations of the relevant literature, we were thus intrigued by a report from Baran *et al.*[34], wherein indole compounds were regenerated from their ene-type adducts with 4-methyl-1,2,4-triazoline-3,5-dione (**MeTAD**) by simply heating the neat compounds *in vacuo* at 100–150 °C, which removes the volatile **MeTAD** (Fig. 2b). This reported reversible TAD-based chemistry, which was described as a protecting-group strategy for indoles, made us consider indoles as reaction partners for the reversible formation of TAD adducts.

Indeed, indoles are basic heterocyclic scaffolds that can be prepared easily in high yields from inexpensive starting materials via various straightforward routes. Furthermore, although indoles are mostly used as fine chemicals in the pharmaceutical and fragrance industry, they are also applied as bulk additives in high-volume polymers, such as polyvinyl chloride (PVC)[35]. From the work of Baran *et al.*[34], we surmised that some specific structural characteristics for an indole building block would assure a reversible adduct formation at a reasonable temperature (Supplementary Fig. 8). Thus, the commercially available 2-*t*-butylindole (1) was identified as a suitable starting material, which gave access to a wide range of functionalized indoles (2–5 (Fig. 2c)) in a single step through a straightforward reductive alkylation with various aldehydes (Supplementary Fig. 9).

The reactions of equimolar amounts of indole 5 with **BuTAD** resulted in a fast and clean conversion into the expected ene-type adduct (Fig. 3a). To facilitate straightforward monitoring of the reaction reversibility, an equivalent of HDEO was added to a

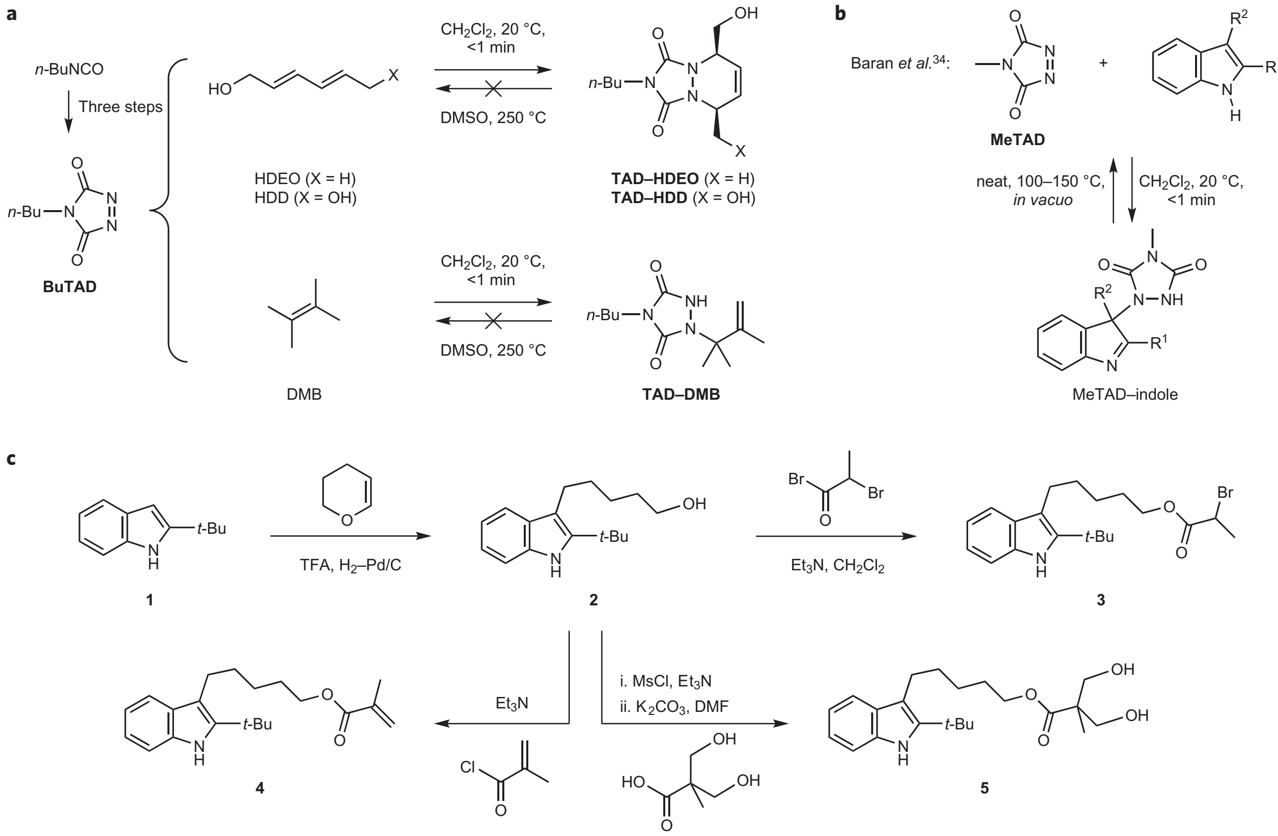

Figure 2 | Model reactions and synthesis of indole components. **a**, Reactions of TAD reagents with functionalized dienes (HDEO and HDD) and enes (DMB) are irreversible below 250 °C. **b**, Known reversible reaction of **MeTAD** with indoles as reported by Baran and colleagues[34]. **c**, Synthesis of functionalized indole building blocks 2–5. Ms, methane sulfonyl; TFA, trifluoroacetic acid.

solution of these ene adducts in DMSO-d_6. NMR spectroscopy allowed the direct monitoring of the reaction progress after heating multiple samples to different temperatures. From these NMR spectra, a clean conversion of the **TAD–indole** adduct in to the **TAD–HDEO** adduct was observed (Supplementary Fig. 10), together with the quantitative regeneration of the parent indole compound. Significant **BuTAD** transfer was observed, starting from a reaction temperature of about 100 °C, and a complete conversion was achieved by heating the mixture for 15 minutes at 150 °C. This first promising result was the starting point for the development of transclick reactions.

Essentially, the same results were obtained with indole 2 and a non-functionalized reference indole (2-*t*-butyl-3-isopentylindole), which showed that this dynamic behaviour and the efficiency of the **BuTAD** transfer was not affected by the presence of hydroxyl or ester functional groups (Supplementary Fig. 11). Moreover, no side reactions or by-products were observed by NMR spectroscopy or liquid chromatography (LC)–mass spectroscopy analysis (Supplementary Figs 10 and 12). Thus, a highly promising, reversible and orthogonal click reaction between indoles and TAD compounds was demonstrated, which allows a 'programmed' transclick reaction of a TAD compound from one partner to another. Although heating of TAD compounds, in bulk or in the presence of small amounts of mild nucleophiles such as water or alcohols, rapidly results in complex decompositions[11], we found that TAD–indole adducts can be heated to a high temperature and retain the inherent selectivity for the typical TAD-conjugation reactions with reaction partners such as conjugated dienes. This unexpectedly clean dynamic behaviour of the TAD–indole click reaction in condensed phases indicates that, although TAD reagents are highly reactive and 'spring-loaded' for a thermodynamically favoured single-reaction trajectory, these reactions are also characterized by very low energy barriers in comparison to all other reaction pathways available for TAD compounds, such as dimerization, hydrolysis and alcoholysis (Supplementary Fig. 1).

Theoretical rationalization. In light of the promising results described above, we investigated the mechanism of the TAD-based click reactions by means of density functional theory (DFT) calculations (Fig. 3b) to better understand the factors that influence the barriers of forward and reverse reactions and to help the design of suitable polymer building blocks and materials.

The ene reaction of **BuTAD** with 2-*t*-butyl-3-methylindole (as a simplified model) was found to follow a stepwise route via an iminium–urazolide zwitterionic intermediate (IZ, $\Delta G^{\ddagger} = 70.3$ kJ mol^{-1} (Fig. 3b, red lines)). This intermediate zwitterion is readily converted into the reaction product by a simple proton transfer. As expected, the Diels–Alder reaction of **BuTAD** with HDEO proceeds via a concerted mechanism ($\Delta G^{\ddagger} = 33.6$ kJ mol^{-1} (black lines)). The calculated relative product stabilities and the associated barriers for the reverse reactions, regenerating the TAD reagent and the initial reaction partner, are in good agreement with the experimental observations that the click reactions with HDEO are irreversible (barriers for reverse reactions exceed 200 kJ mol^{-1}), while the TAD–indole click reaction is reversible at elevated temperatures. The energy profile for the TAD–ene reaction with a simple olefin (pent-3-en-1-ol), as well as more details concerning the mechanism thereof, are given in Supplementary Section 4.

Polymer conjugation. In a second stage of evaluating the versatility of the TAD-based click reactions, and their use in practical applications, reversible and irreversible binary linking of

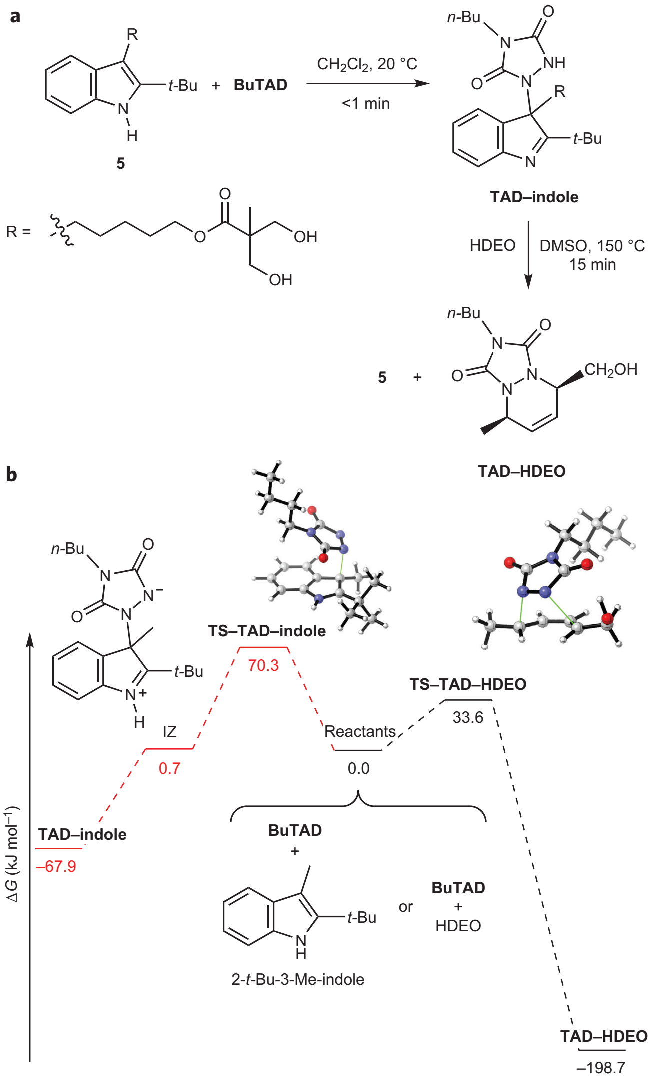

Figure 3 | Transclick study and theoretical rationalization of TAD reactions. a, Click reaction of indole 5 with **BuTAD** and the thermal transclick reaction of the indole-bound TAD reagent to HDEO, with complete formation of the **TAD-HDEO** Diels–Alder adduct and regeneration of the indole. **b**, Gibbs free energy profiles for the reactions of HDEO and 2-*t*-Bu-3-Me-indole with **BuTAD** (polarizable continuum model ($\varepsilon = 8.93$) M06-2X/6-31 + G(d,p)). DMSO, dimethyl sulfoxide; IZ, iminium-urazolide zwitterionic intermediate; TS, transition state.

macromolecules with either small molecules or other linear polymers was investigated in detail.

For this purpose, suitable end-group functionalized linear polymers were synthesized and reacted with a low-molecular-weight TAD compound (**BuTAD**). Using a procedure developed by Barner-Kowollik and co-workers[36], a polyisobornylacrylate (PIBA) with a terminal cyclopentadiene (Cp) moiety, one of the most reactive dienes in Diels–Alder reactions, was prepared. This diene-functionalized polymer, PIBA–Cp (number average molecular weight (M_n) = 3.5 kg mol^{-1} and dispersity ($Đ$) = 1.19), was dissolved in THF and mixed in a 1:1 molar ratio with **BuTAD** (Supplementary Figs 13–17). The reaction was completed within five seconds, as judged by the disappearance of the distinctive colour of the BuTAD reagent. The resulting polymer was characterized by ^{1}H NMR spectroscopy, size-exclusion chromatography (SEC) (M_n = 3.74 kg mol^{-1}, $Đ$ = 1.20) and matrix-assisted laser desorption/ionization–time-of-flight mass spectroscopy (Supplementary Figs 18–20). These analyses showed a complete conversion into the **BuTAD** Diels–Alder adduct with no sign of side reactions. The same results were obtained when a polystyrene backbone was used (PS–Cp, M_n = 4.2 kg mol^{-1}, $Đ$ = 1.1, Supplementary Figs 21–33). Furthermore, an HDEO-derived moiety was introduced as an end group onto the same polymer backbones and the reactions with **BuTAD** were found to proceed with the same efficiency (Supplementary Figs 34–53).

Then, to test the reversible click and transclick reactions in a macromolecular context, an indole-functionalized poly(methylmethacrylate) (PMMA) sample was synthesized using the indole-containing initiator 3 in a Cu-mediated polymerization (indole–PMMA, M_n = 8.3 kg mol^{-1}, $Đ$ = 1.32). This polymer was reacted with **BuTAD** to give a clean conversion into the indole–TAD–ene adduct (as shown by ^{1}H NMR spectroscopy and SEC (Supplementary Figs 54 and 55)). The resulting TAD–indole–PMMA was then dissolved in DMSO with an excess of HDEO. This mixture was heated for 30 minutes at 120 °C, which resulted in the parent indole–PMMA, along with detectable amounts of the **TAD–HDEO** adduct. Similarly, both PIBA- and PS-derived indole-functionalized polymers were clicked with **BuTAD**, followed by a thermal transclick reaction to HDEO (Supplementary Figs 56–63).

After having demonstrated an efficient clicking and transclicking of a small TAD molecule on and off polymer substrates, we next investigated the synthesis of block copolymers through irreversible and reversible TAD-based click reactions. To obtain a TAD-functionalized polymer, a urazole-derived initiator was prepared (see Supplementary Section 3.2) for the Cu-mediated radical polymerization of butylacrylate. This urazole-end-capped poly(butylacrylate) (PBA–urazole, M_n = 20 kg mol^{-1}, $Đ$ = 1.38) was then oxidized to give the corresponding polymer-bound TAD reagent (PBA–TAD). As expected, this polymer showed the same distinctive colour as the other TAD components (Supplementary Fig. 64). After dissolving PBA–TAD and PS–Cp (*vide supra*) in THF, the distinctive red colour disappeared in a matter of seconds, which indicated an ultrafast, quantitative polymer–polymer conjugation reaction in an additive-free way under ambient conditions. The obtained reaction mixture was analysed by LC-SEC (Fig. 4) and ^{1}H NMR analysis (Supplementary Fig. 65), all of which revealed a single distribution related to the expected block copolymer (Fig. 4).

The clicking and transclicking of a macromolecular chain on and off another polymer chain was investigated by mixing PS with an indole end group (M_n = 1.4 kg mol^{-1}, $Đ$ = 1.17) and PBA–TAD in THF. This gave the anticipated block copolymer formation within 30 minutes, as judged by the observed colour change and further confirmed by ^{1}H NMR analysis (Supplementary Fig. 66). LC-SEC analysis was somewhat hampered by a much higher detector response for the PS-based polymers (Fig. 5, left). The elugram after the reaction (Fig. 5, centre) also showed the presence of a residual amount of PS–indole. Furthermore, the larger difference in molecular weight for the two blocks (1.4 kg mol^{-1} compared to 20 kg mol^{-1} for the PBA block) does not result in a significant change in elution time or elution volumes relative to the PBA homopolymer. However, when the block copolymer was treated with an excess of HDEO and heated to 120 °C in *N*,*N*-dimethylformamide (DMF) for two hours, the relative intensities in the resulting elugram (Fig. 5, right) revealed the recovery of the original homopolymer distributions (see Fig. 5, left), which indicates that a selective transclick of one of the two initially clicked polymers had occurred.

Polymer networks. As a final demonstration of the possibilities of TAD-based click and transclick reactions in macromolecular systems, the synthesis of polymer networks was sought by using a bifunctional TAD compound as the crosslinking reagent. Thus, two diol monomers were used to incorporate suitable reaction partners for TAD reagents in polymer backbones, HDD and the

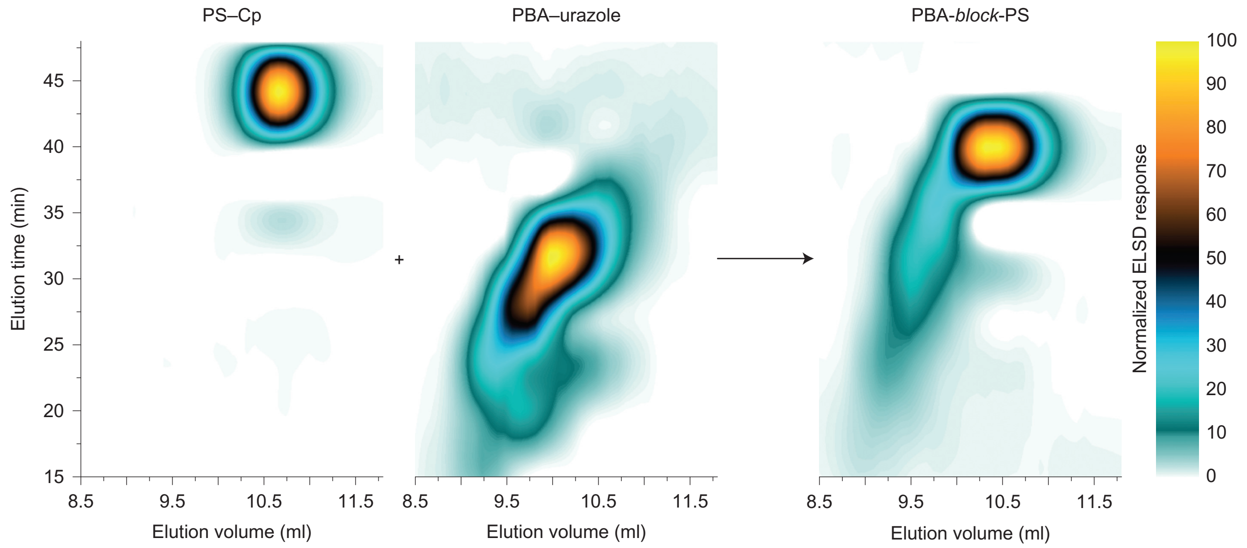

Figure 4 | Irreversible polymer conjugation. LC-SEC analysis of separate polymers (PS–Cp and PBA–urazole) and the obtained block copolymer. In each elugram, the *y* axis shows a separation on the first (LC) dimension, whereas the *x* axis depicts the separation of collected fractions according to the hydrodynamic volume (SEC) in the second dimension. After linking the homopolymers, a new signal is visible, which represents the newly formed block copolymer, characterized by an altered behaviour in both hydrophobicity and hydrodynamic volume. The small tailing in the corresponding elugram is ascribed to a small deviation from equimolarity because of the dispersity of both polymers.

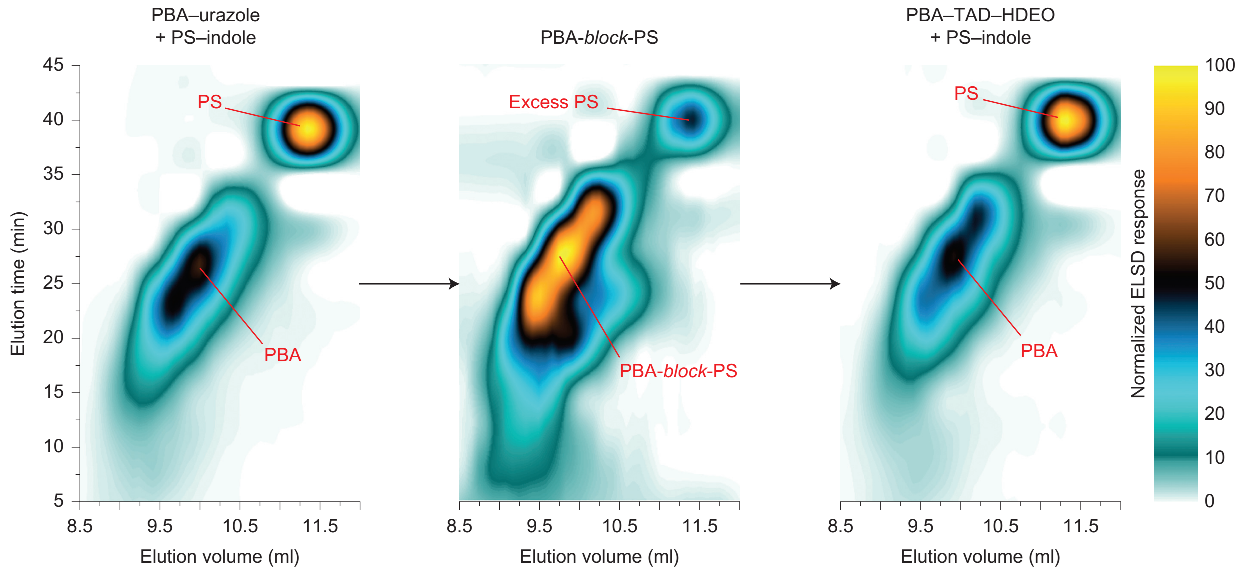

Figure 5 | Reversible polymer conjugation. Left: LC-SEC analysis of an equimolar amount of two separate polymers (PBA–urazole and PS–indole) before coupling. Centre: LC-SEC analysis of the block copolymer after coupling, which is characterized by very similar physical behaviour compared to the PBA homopolymer as a result of the large difference in molecular weight of the two blocks. However, the higher detector response for the PS block allows us to conclude a successful linking, and the slight excess of PS–indole can be ascribed to a deviation from equimolarity because of the dispersity of both polymers. Right: LC-SEC analysis after heating (120 °C for two hours in DMF) in the presence of excess HDEO shows the recovery of the original polymer blend.

indole diol 5 (Fig. 2c). Linear polyurethanes (PUs) were prepared from either of these monomers in combination with hexamethylene diisocyanate (HDI) and polypropylene oxide (PPO) (for the synthesis, see Supplementary Section 3.2). Treatment of solutions of these PU chains in DMF with a bifunctional TAD reagent resulted in gelation within seconds, and in a complete curing within minutes, as evidenced by the gradual disappearance of the red colour (Supplementary Fig. 67 and Supplementary Movie 2). The obtained materials were completely insoluble in refluxing DMF, although the indole-based material did show plasticity on heating in DMF. When HDEO was added to the solvent, within minutes the indole-based material dissolved completely in DMF at 150 °C. However, the HDD-derived crosslinked material remained completely insoluble, even when heated at 200 °C in a pressurized vessel.

As a preliminary exploration of the possibilities of TAD-based click and dynamic transclick chemistries in functional materials, a number of qualitative tests were conducted with the materials obtained above. In a first test, a macroscopic scratch was made in the rubbery TAD-crosslinked PU networks. After heating the sample at 120 °C for one hour, the indole-derived sample was visibly healed, and it broke elsewhere after the application of

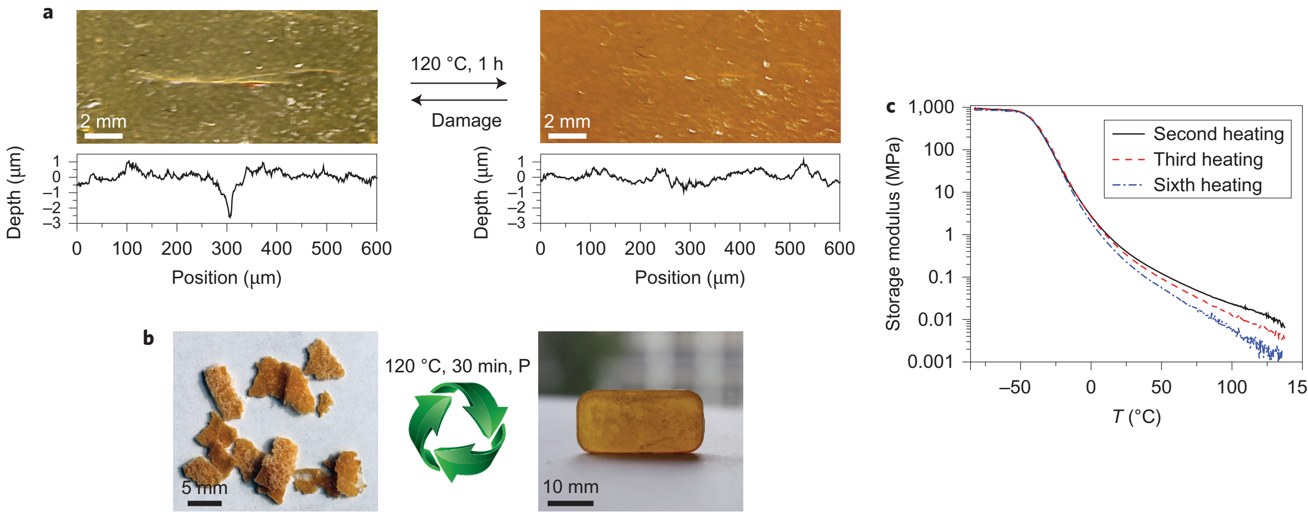

Figure 6 | Dynamic properties of TAD-based materials. a, Image of a manually damaged PU sample (left) and the healed sample after heating for one hour at 120 °C (right) and measured profiles for a 3 μm deep scratch on another sample of an identical material. **b**, Image of crosslinked PU sample that was broken into smaller pieces (left) and the same sample after being put into a mould under pressure (P) for 30 minutes at 120 °C (right). Owing to stress relaxation caused by dynamic behaviour at elevated temperature, the pressure is only necessary to keep the mould closed. **c**, Dynamic mechanical thermal analysis thermograms (storage modulus versus temperature) for these PU networks after the second, third and sixth heating.

stress. This result was further confirmed using a profilometer on the same material in which a scratch with a depth of 3 μm had been applied (Fig. 6a). As expected, the HDD-derived PU network did not show this healing ability. In another test, the materials were broken into smaller pieces and put into a mould under pressure for 30 minutes at 120 °C. For the indole-derived material, a pristine sample was retrieved from the mould after cooling (Fig. 6b). This last test was repeated seven times, and each time resulted in a similar behaviour of the storage modulus (Fig. 6c). For the HDD-derived PU rubber, only the original pieces of the material were retrieved from the heated moulds, even at moulding temperatures up to 200 °C. Finally, this thermally assisted polymer-network reshaping, moulding and recycling was also demonstrated on a network derived from a PMMA copolymer with a high glass-transition temperature ($T_g = 101$ °C), which was prepared from the copolymerization of MMA with an indole-functionalized methacrylate comonomer 4 (Fig. 2c and Supplementary Section 3.2). This stiff material could be moulded thermally and reprocessed in the same way as the PU rubbers. Moreover, it could also be powdered and moulded into a homogeneous material by extrusion above 110 °C (Supplementary Fig. 68).

Conclusions

The core principle of the click-chemistry concept is its focus on the modular production of new functional molecules and associated properties using reliable synthetic reactions between simple chemical building blocks. Without any doubt, ultrafast covalent linking on the one hand and dynamic properties on the other hand are highly desirable for many functional applications. We have shown that both of these features are united in the unique reactivity of TAD reagents. Indeed, TAD groups can be reliably clicked onto a range of olefinic reaction partners (enes and dienes). Moreover, when indole-containing substrates are reacted with TAD, the resulting click reaction is efficient enough to link macromolecular chains at room temperature within minutes without the use of a catalyst, and the resulting indole–TAD adduct can be exchanged dynamically above 100 °C. Also, the addition of a diene reaction partner to this reversible adduct results in a new and irreversible click reaction with the formation of a new Diels–Alder adduct.

The versatile TAD-based click and transclick reactions described herein thus enable the design and production of molecular systems with unique, modular and tunable dynamic properties. This was demonstrated for the field of polymer science, and exemplified with thermal reshaping, recycling and healing of reversible networks, but we strongly believe that the TAD-based click/transclick reactions will become useful for many other applications beyond the current scope of the click-chemistry toolbox.

Methods

General procedure for polymer–polymer conjugation. Polymer (50 mg) with a Cp/indole end group was dissolved in 0.5 ml THF and 1 equiv. TAD–polymer (in 0.5 ml THF) added at room temperature. The solution was allowed to stir until the red colour disappeared. The obtained (block) copolymer was precipitated from an appropriate solvent, filtrated, washed thoroughly and dried overnight in a vacuum oven at 40 °C.

Direct synthesis of the reversible polyurethane network. To a solution of 0.805 g indole diol (2.14 mmol, 0.68 equiv.) in 3 ml DMF was added 0.194 g 4,4′-(4,4′-diphenylmethylene)-bis(1,2,4-triazoline-3,5-dione) (0.536 mmol, 0.17 equiv.). After the reaction had reached completion (less than one minute), the solution was mixed with 2.00 g PPO (1.00 mmol, 0.32 equiv.) and 0.529 g HDI (3.15 mmol, 1 equiv.) in a 50 ml flask. Then 29 μl dibutyltin dilaurate was added and the mixture was stirred well. This reactive mixture was injected between two glass plates separated by a silicone spacer, and placed in an oven at 70 °C for six hours. The obtained network was dried overnight in a vacuum oven at 40 °C.

LC–SEC analysis. For two-dimensional LC, sample fractions from the first dimension were transferred to the second-dimension column via an electronically controlled eight-port valve system (VICI Valco instruments), equipped with two 200 μl sample loops. The second dimension consisted of an Agilent Infinity 1260 isocratic pump and a PSS SDV LIN M 5 μm column. Detection in the second dimension was accomplished by using an evaporative light-scattering detector (ELSD). Nitrogen was used as the carrier gas in the ELSD at a flow rate of 2.5 l min^{-1}. Spray chamber, drift tube and optical cell temperatures were set at 30 °C, 80 °C and 70 °C, respectively. The flow rates used in the first and second dimensions were 0.05 ml min^{-1} and 5 ml min^{-1}, respectively. Sample concentrations were between 0.25 and 2.0 mg ml^{-1}. THF was used as the solvent for the second dimension analysis. Data were recorded using PSS WinGPC Unichrom software.

Received 16 February 2014; accepted 26 June 2014;
published online 11 August 2014; corrected after print
11 August 2014

References

1. Kolb, H. C., Finn, M. G. & Sharpless, K. B. Click chemistry: diverse chemical function from a few good reactions. *Angew. Chem. Int. Ed.* **40,** 2004–2021 (2001).

2. Moses, J. E. & Moorhouse, A. D. The growing applications of click chemistry. *Chem. Soc. Rev.* **36,** 1249–1262 (2007).
3. Xi, W., Scott, T. F., Kloxin, C. J. & Bowman, C. N. Click chemistry in materials science. *Adv. Funct. Mater.* **24,** 2572–2590 (2014).
4. Golas, P. L. & Matyjaszewski, K. Marrying click chemistry with polymerization: expanding the scope of polymeric materials. *Chem. Soc. Rev.* **39,** 1338–1354 (2010).
5. Tasdelen, M. A. & Yagci, Y. Light-induced click reactions. *Angew. Chem. Int. Ed.* **52,** 5930–5938 (2013).
6. Pauloehrl, T. *et al.* Adding spatial control to click chemistry: phototriggered Diels–Alder surface (bio)functionalization at ambient temperature. *Angew. Chem. Int. Ed.* **51,** 1071–1074 (2012).
7. Barner-Kowollik, C. *et al.* 'Clicking' polymers or just efficient linking: what is the difference? *Angew. Chem. Int. Ed.* **50,** 60–62 (2011).
8. Tasdelen, M. A. Diels–Alder 'click' reactions: recent applications in polymer and material science. *Polym. Chem.* **2,** 2133–2145 (2011).
9. Mather, B. D., Viswanathan, K., Miller, K. M. & Long, T. E. Michael addition reactions in macromolecular design for emerging technologies. *Prog. Polym. Sci.* **31,** 487–531 (2006).
10. Cookson, R. C., Gilani, S. S. H. & Stevens, I. D. R. 4-Phenyl-1,2,4-triazolin-3,5-dione: a powerful dienophile. *Tetrahedron Lett.* **3,** 615–618 (1962).
11. Radl S. in *Advances in Heterocyclic Chemistry* Vol. 67 (ed. Katritzky, A. R.) 119–208 (Elsevier, 1997).
12. Funel, J-A. & Abele, S. Industrial applications of the Diels–Alder reaction. *Angew. Chem. Int. Ed.* **52,** 3822–3863 (2013).
13. Nicolaou, K. C., Snyder, S. A., Montagnon, T. & Vassilikogiannakis, G. The Diels–Alder reaction in total synthesis. *Angew. Chem. Int. Ed.* **41,** 1668–1698 (2002).
14. Novikov, R. A., Korolev, V. A. & Tomilov, Y. V. Reactions of 4-phenyl-1,2,4-triazoline-3,5-dione with 2-pyrazolines. *Russ. Chem. Bull.* **60,** 1685–1693 (2011).
15. Gillis B. T. & Hagarty J. D. The reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with conjugated dienes. *J. Org. Chem.* **32,** 330–333 (1966).
16. Syrgiannis, Z., Koutsianopoulos, F., Muir, K. W. & Elemes, Y. Reaction of a triazolinedione with simple alkenes. Isolation and characterization of hydration products. *Tetrahedron Lett.* **50,** 277–280 (2009).
17. Korobitsyna, I. K., Khalikova, A. V., Rodina, L. L. & Shusherina, N. P. 4-Phenyl-1,2,4-triazoline-3,5-dione in organic synthesis (review). *Chem. Heterocycl. Compd* **19,** 117–136 (1983).
18. Jensen, F. & Foote, C. S. Reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with substituted butadienes. A nonconcerted Diels–Alder reaction. *J. Am. Chem. Soc.* **109,** 6376–6385 (1987).
19. Higashi, T., Shibayama, Y., Fuji, M. & Shimada, K. Liquid chromatography–tandem mass spectrometric method for the determination of salivary 25-hydroxyvitamin D_3: a noninvasive tool for the assessment of vitamin D status. *Anal. Bioanal. Chem.* **391,** 229–238 (2008).
20. Aronov, P. A., Hall, L. M., Dettmer, K., Stephensen, C. B. & Hammock, B. D. Metabolic profiling of major vitamin D metabolites using Diels–Alder derivatization and ultra-performance liquid chromatography–tandem mass spectrometry. *Anal. Bioanal. Chem.* **391,** 1917–1930 (2008).
21. Hoogewijs, K., Buyst, D., Winne, J. M., Martins, J. C. & Madder, A. Exploiting furan's versatile reactivity in reversible and irreversible orthogonal peptide labeling. *Chem. Commun.* **49,** 2927–2929 (2013).
22. Ban, H., Gavrilyuk, J. & Barbas, C. F. Tyrosine bioconjugation through aqueous ene-type reactions: a click-like reaction for tyrosine. *J. Am. Chem. Soc.* **132,** 1523–1525 (2010).
23. Ban, H. *et al.* Facile and stabile linkages through tyrosine: bioconjugation strategies with the tyrosine-click reaction. *Bioconjugate Chem.* **24,** 520–532 (2013).
24. Pieken, W. *et al.* Method for solution phase synthesis of oligonucleotides. World patent WO98/47910 (1998).
25. Chen, T. C. S. & Butler, G. B. Chemical reactions on polymers. 111. Modification of diene polymers via the ene reaction with 4-substituted-1,2,4-triazoline-3,5-diones. *J. Macromol. Sci. Pure Appl. Chem.* **16,** 757–768 (1981).
26. Butler, G. B. Triazolinedione modified polydienes. *Ind. Eng. Chem. Prod. Res. Dev.* **19,** 512–528 (1980).
27. Kaufmann, T. *et al.* 'Sandwich' microcontact printing as a mild route towards monodisperse Janus particles with tailored bifunctionality. *Adv. Mater.* **23,** 79–83 (2011).
28. Espeel, P. *et al.* Multifunctionalized sequence-defined oligomers from a single building block. *Angew. Chem. Int. Ed.* **125,** 13503–13506 (2013).
29. Stamenovic, M. M. *et al.* Straightforward synthesis of functionalized cyclic polymers in high yield via RAFT and thiolactone–disulfide chemistry. *Polym. Chem.* **4,** 184–193 (2013).
30. Hansell, C. F. *et al.* Additive-free clicking for polymer functionalization and coupling by tetrazine–norbornene chemistry. *J. Am. Chem. Soc.* **133,** 13828–13831 (2011).
31. Kricheldorf H. R. & Denchev Z. in *Transreactions in Condensation Polymers* (ed. Favirov, S.) Ch. 8, 319–389 (Wiley-VCH, 1999).
32. Collins, K. D. & Glorius, F. A robustness screen for the rapid assessment of chemical reactions. *Nature Chem.* **5,** 597–601 (2013).
33. Rickborn, B. The retro-Diels–Alder reaction Part II. Dienophiles with one or more heteroatom (*Organic Reactions* **53,** John Wiley, 2004).
34. Baran, P. S., Guerrero, C. A. & Corey, E. J. The first method for protection-deprotection of the indole 2,3-π bond. *Org. Lett.* **5,** 1999–2001 (2003).
35. Zweifel H., Maier R. D. & Schiller M. *Plastics Additives Handbook* (Hanser, 2009).
36. Inglis, A. J., Paulöhrl, T. & Barner-Kowollik, C. Ambient temperature synthesis of a versatile macromolecular building block: cyclopentadienyl-capped polymers. *Macromolecules* **43,** 33–36 (2009).

Acknowledgements

B. De Meyer is acknowledged for the measurements of the LC-SEC samples. S.B. and F.D. thank the Agency for Innovation by Science and Technology in Flanders for PhD scholarships. K.D.B. thanks the Research Foundation-Flanders (FWO) for the funding of his fellowship. H.G., F.D.P. and V.V.S. acknowledge the FWO (Vlaanderen), the Research Board of Ghent University and the Belgian Science Policy Office Interuniversity Attraction Poles (IAP) programme in the frame of IAP 7/05 for financial support. Computational resources and services used in this work were provided by Ghent University (Stevin Supercomputer Infrastructure).

Author contributions

S.B, K.D.B., F.D. and H.G. performed the experiments. S.B., K.D.B., J.M.W. and F.D.P. conceived and designed the experiments. H.G. and V.V.S. were responsible for the theoretical calculations. S.B., J.M.W. and F.D.P wrote the paper. K.D.B prepared all the figures. All the authors discussed the results and commented on the manuscript at all stages.

Additional information

Supplementary information is available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to J.M.W. and F.E.D.P.

Competing financial interests

The authors declare no competing financial interests.

ERRATUM

Triazolinediones enable ultrafast and reversible click chemistry for the design of dynamic polymer systems

Stijn Billiet, Kevin De Bruycker, Frank Driessen, Hannelore Goossens, Veronique Van Speybroec, Johan M. Winne and Filip E. Du Prez

Nature Chemistry **6,** 815–821 (2014); published online 11 August 2014; corrected after print 11 August 2014.

Technical issues with our online publication processes resulted in this Article being published the day after that referred to in the print version. The official date of publication is 11 August 2014.